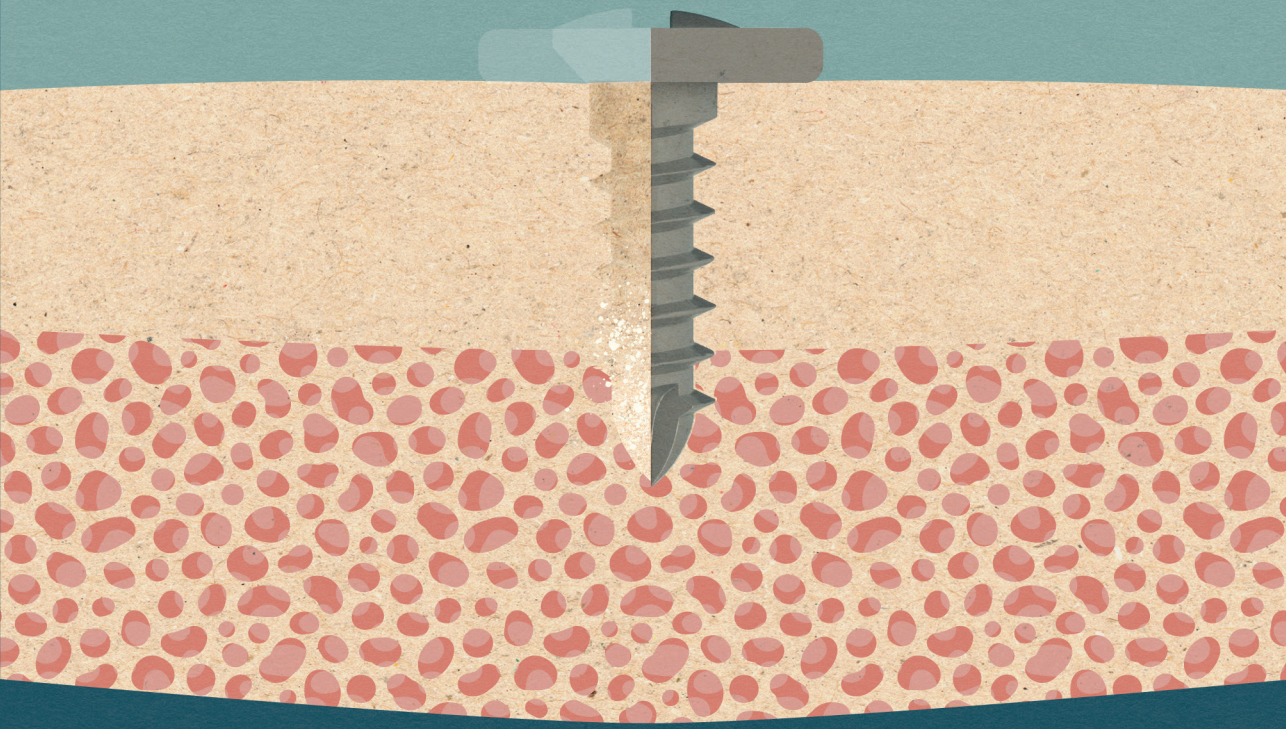
Biodegradable and titanium osteosynthesis in maxillofacial surgery

In vitro and *in vivo* performances



Barzi Gareb

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Voor pappa en mamma,
die alles riskeerden
om ons
alles te kunnen geven

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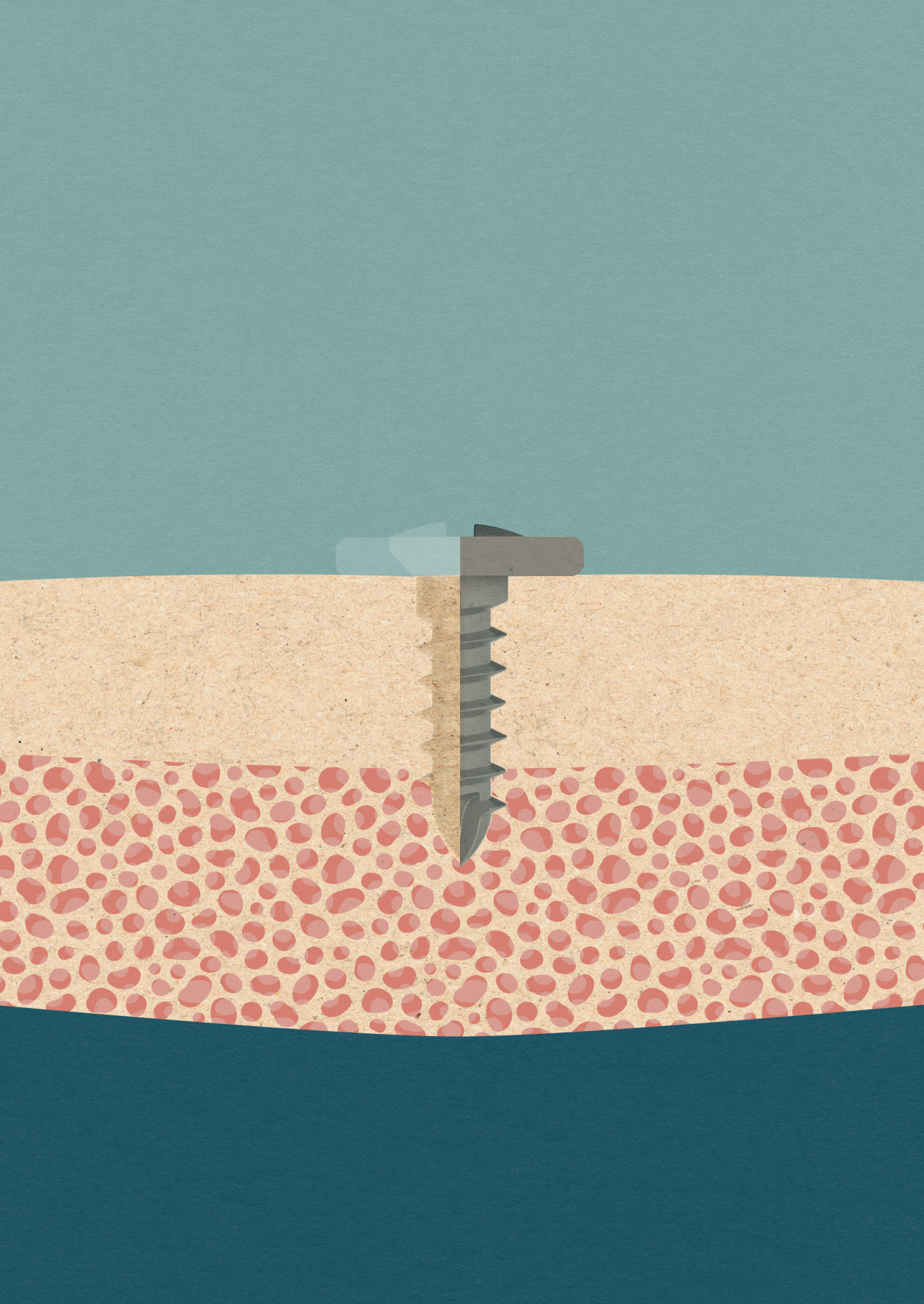

Chapter 1

General introduction

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Introduction

Osteosynthesis systems consist of plates and screws to fixate bone segments by various medical disciplines, including oral and maxillofacial surgery (OMF-surgery). Within OMF-surgery, these systems are commonly used for maxillofacial trauma (e.g., fixation of bone segments after anatomical reduction of dislocated or mobile fractures), and orthognathic and reconstructive surgery. Orthognathic surgery consists of the surgical manipulation of osteotomy segments of the facial skeleton to restore stable and functional occlusion, and to restore the aesthetics in patients with dentofacial deformities[1]. The osteotomy segments are fixated in a predetermined position using osteosynthesis systems. It is indicated when the dentofacial deformity requires more than orthodontic treatment (dental discrepancies) or maxillofacial orthopaedics (skeletal discrepancies). Orthognathic surgery is usually accompanied by pre- and post-operative orthodontic treatment[2]. In reconstructive surgery, congenital deformities or anatomical defects, following injuries or diseases (e.g., after oncological resection), are reconstructed to restore function and aesthetics. Bone defects are usually reconstructed with osteosynthesis systems. Since traumatology, orthognathic surgery, and reconstructive surgery are main aspects of OMF-surgery, these systems are widely used by OMF-surgeons[2]. In the United States, 73% of all the craniomaxillofacial devices used by OMF-surgeons are osteosynthesis systems[3]. This thesis will focus on the two main applications of osteosynthesis systems: maxillofacial traumatology and orthognathic surgery.

Historically, ligature wires, and plates and screws of osteosynthesis systems consisted of stainless steel. However, research showed that titanium was more biocompatible than stainless steel[4] and was introduced in 1968 within maxillofacial systems[5]. Since then, the osteosynthesis systems have been improved further, e.g., by changing the composition of the plates and screws (from titanium to titanium alloys), the screw applications (from bicortical to monocortical systems), by improving the topography and surfaces of plates and screws (e.g., from non-contoured to well-contoured shapes), and by improving the peri-operative handling of the systems (e.g., the screw heads and the stiffness of the plate to make plate adaption easier)[6–8]. Titanium osteosynthesis systems are currently considered the gold standard for maxillofacial fracture treatment and orthognathic surgery. Monocortical titanium osteosynthesis systems are able to provide an environment for undisturbed fracture or osteotomy healing that can withstand the strains created during non-loaded movements without the need for rigid maxillomandibular fixation (MMF)[9–14].

Osteosynthesis systems are available in various sizes and are named according to the external diameter of the screws that are used to fixate the plate to the underlying bone. Originally, the different system names described the complete systems (i.e., differences in plates as well as in screws) rather than only the external diameter of the screw. With increasing screw diameters, the corresponding plate dimensions (i.e., length [L], width [W], and thickness [T]) also increase substantially (e.g., a titanium four-hole 1.5 mm plate: 18.5x3.5x0.6 mm; a titanium four-hole 2.0 mm plate: 25.5x5.0x1.0 mm)[15]. Nowadays, some manufacturers provide different plate profiles with the same screw diameter[16].

Epidemiology

The global age-standardised incidence of facial fractures is estimated to be 98 per 100,000 individuals per year[17]. In the Netherlands, the incidence is 137 people per 100,000 per year[17]. Both globally and nationally, the incidence is highest in patients aged 14-29 and >40 years[17,18]. The most common causes of maxillofacial trauma are motor vehicle accidents, falls, assaults and sport injuries[17–20]. Although the sex-ratio of all trauma patients is estimated to be 1:1, the male to female maxillofacial trauma ratio is estimated to be 3.9:1[17,21]. Maxillofacial trauma leads to a major burden on society due to morbidity and associated costs (e.g., medical costs and absence from work). The estimated cost in the United States is $1 billion per year[19]. Population growth and an increase in traffic, means of transport (e.g., introduction of the electric bicycle), industrialization and violence are expected to be important causes that will amplify the incidence of (maxillofacial) trauma in the coming years[22].

The aetiology of dentofacial deformities is multifactorial, including genetic and environment factors acting on the craniofacial complex[23]. In the United Kingdom, the age- and sex-standardised incidence of orthognathic procedures is estimated to be 6 per 100,000 individuals per year[24]. The majority (60%) of orthognathic surgery patients are female[25] with the average being 26 years of age[26,27]. In patients with dentofacial deformities, orthognathic surgery leads to a significant improvement in the quality of life in the emotional, psychological, oral function and social domains[28,29]. Both single and two jaw surgery have been shown to be cost-effective with an estimated cost of £954 and £840 per quality-adjusted life year, respectively[24].

Biomechanics of the craniomaxillofacial skeleton

Historically, a MMF of 6 to 8 weeks was used to prevent strains on the osteosynthesis systems created during mastication. However, MMF is uncomfortable for the patient and immobilizing the temporomandibular joints can result in cartilage degeneration and atrophy of the masticatory musculature[30]. Therefore, efforts have been made to develop osteosynthesis systems that can withstand the non-loaded movements, while maintaining device dimensions within clinically acceptable limits and, thus, obviating the need for rigid MMFs. Monocortical micro- (i.e., osteosynthesis systems with 1.0 mm and 1.5 mm screw diameters) and miniplate osteosynthesis systems (i.e., osteosynthesis systems with 2.0 mm screw diameters) are able to provide an environment for undisturbed fracture or osteotomy healing that can withstand the strains created during non-loaded functions without the need for rigid MMF[9–14]. To achieve such an environment, knowledge about the biomechanics of the craniomaxillofacial skeleton (CMF-skeleton) is essential[9].

Midface biomechanics

The CMF-skeleton provides a framework to protect the soft organs, e.g., the eyes and brain[31,32]. The midface consists of shell-like thin bones, reinforced by areas with strong and thick bones called buttresses, that form air-containing cavities which function as crumple zones to protect vulnerable cranial structures such as the brain. The two major horizontal buttresses include the inferior buttress consisting of the inferior orbital rim and the zygomaticomaxillary complex, and the superior buttress consisting of the superior orbital rims and the frontal bone[32]. The vertical buttresses include the nasomaxillary (anterior), zygomaticomaxillary (anterior) and pterygomaxillary (posterior) buttresses[31]. During mastication, the midface occlusal surfaces are exposed to loads of equal magnitude and in opposite directions to those of the mandible[31]. Maximum bite forces in participants with healthy teeth range from 200 to 300 N in the incisor region, 300 to 500 N in the canine and premolar region, and 500-700 N in the molar region[9,14,31,33]. Since the buttresses, in particular the vertical buttresses, can deform the least compared to other areas of the CMF-skeleton, these are exposed to the gross of these mastication forces[9]. The forces exerted on the midface are complex and three-dimensional, and lead in particular to bending and torsion stresses[9].

Mandible biomechanics

The mandible behaves as a curved beam in the axial plane that is supported by the pterygo-masseteric sling at each end. It is loaded at the superior surface on contacting

the midface via the teeth or dentures[9,31]. All curved beams are exposed to tension and compression stresses when load is applied[31]. Physiological muscle coordination results in tension forces at the superior border and compressive forces at the inferior border of the mandible[9]. Furthermore, mandibular osteosynthesis systems fixating the osteotomy are also exposed to side bending forces[34]. Since there is no muscle support at the midline during loading, torsion forces are exerted on the mandible between both canines (Figure 1).

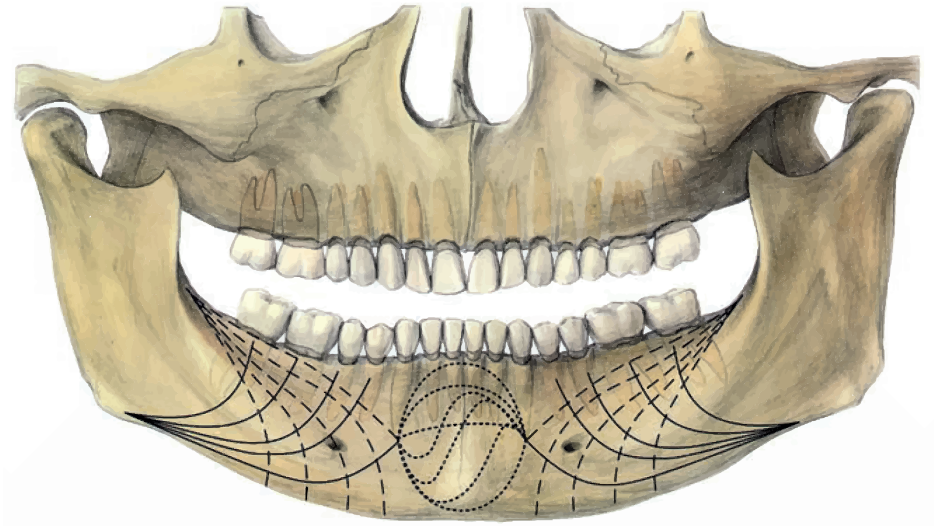

Figure 1. *The different forces acting on the mandible due to biting forces (from angle to incisor region). Tensions forces are shown by the dashed lines, compression forces by the solid lines, and torsion forces by the dotted lines. Source: Haerle, F., Champy, M. & Terry, B.C. Atlas of Craniomaxillofacial Osteosynthesis. Stuttgart: Thieme, 2000 (www.thieme.com). Reprinted with permission.*

The moment of tension, compression, and torsion can be described by the following formula[9]:

$$E = F \times L/d$$

Where E is the state of constraints, F is the masticatory force, L the distance from the chin to a point of interest, and d the distance from the point of interest (e.g., an osteosynthesis plate) to the inferior border of the mandible. This formula demonstrates that the strain exerted on the point of interest is inversely related to the distance between the point of interest and the inferior border of the mandible. This is particularly important in cases of advanced atrophy of the mandible since the tension and compression strains are then

concentrated in a narrow bundle and thus demand a lot from the applied osteosynthesis system, leading to an increased risk of complications during fracture healing[9].

Osteosynthesis

Load-sharing versus load-bearing are two essential concepts of osteosynthesis. The former allows sharing of the load between bone segments and the osteosynthesis system (e.g., fractures with interfragmentary stability) whereas in the latter, the complete load at the fracture site is carried by the osteosynthesis system without interfragmentary stability (e.g., in an osteotomy, a comminuted fracture, an atrophic mandible, or a reconstruction)[9,31]. In a load-bearing situation, the osteosynthesis system is exposed to substantially higher loads and, thus, the biomechanical requirements for an optimal osteosynthesis system are higher compared to load-sharing osteosyntheses[15,35].

Osteosynthesis goals and requirements in maxillofacial traumatology

The main goals in trauma surgery are: (1) anatomical reduction and the re-establishment of a previous occlusion, (2) complete and stable fixation that allows non-loaded mobilization of the operated region, and (3) maintenance of the blood supply in the fragments and surrounding tissues[9]. These goals are required to achieve functional and painless union of the bone segments with adequate and undisturbed bone healing[9,31].

An osteosynthesis is considered stable when no movement or distraction is visible between the bone fragments, the osteosynthesis system neutralizes any harmful distraction strains (e.g., the tensile strains of the mandible), and there is restoration of the self-compression strains from the masticatory forces to ensure interfragmentary stability (e.g., at the inferior border of the mandible) and the friction forces between the contacting fracture surfaces[9,36].

The biomechanical requirements for an optimal osteosynthesis system include: (1) sufficient mechanical properties to withstand the various tensile, compression, side bending and torsional stresses for a particular case, (2) minimal plate dimensions to ensure minimum fracture exposure as well as stress-free closure of the incision, and (3) that the plates are malleable enough for adaptation to the bone surface[9,31]. Since the mandible is exposed to considerably higher biomechanical forces compared to the maxilla, the osteosynthesis systems used to fixate bone segments in the mandible are larger (e.g., 2.0 mm screw diameter) compared to those in the midface (e.g., 1.5 mm screw diameter)[9,31]. Furthermore, if the interfragmentary stability is poor or absent

(i.e., in load-bearing osteosyntheses), the friction forces between the bone fragments are low due to the small contact area between the bone fragments, or are absent. In such cases, the required mechanical properties of the osteosynthesis systems are much higher compared to when interfragmentary stability is present (i.e., in load-sharing osteosyntheses)[9]. This will inevitably necessitate more or larger plates and screws. Consequently, both will lead to more difficult closure of the incision, and larger dimensions also lead to more difficult and time-consuming plate adaptation. Therefore, knowledge of its mechanical properties is important when selecting an appropriate osteosynthesis system, and depends on the type and location of the fracture as well as the applied osteosynthesis concept.

Besides properties of the osteosynthesis system, the amount of torque applied to the screws by OMF-surgeons also contributes to the primary stability by generating compression and friction between the osteosynthesis system and the underlying bone[37,38]. This leads to shear forces that counteract screw motion due to forces derived from the surrounding musculature[39]. Insufficient screw torque may lead to mobility of the bone segments, loosening of screws and disturbed fracture healing[39]. Applying excessive torque can cause loose screws due to bone stripping, screw damage and/or screw breakage[39]. Currently, applying a suitable torque to the osteosynthesis screws is based on the surgeon's "feeling". A recent systematic review showed that, on average, 26% of all the inserted osteosynthesis screws are irreparably damaged or have stripped screw holes, that the awareness of any stripping is poor, and that the variability between surgeons is high[39]. Currently, manufacturers only state the maximum allowed torque before screw breakage occurs, but there is no reference torque interval for maxillofacial osteosynthesis screws, i.e., a minimum and maximum torque value, for safe and adequate bone fixation.

Osteosynthesis principles of mandibular fractures

From a historical perspective, there are two conflicting osteosynthesis principles for the mandible: the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) principle and Champy's principle[9,31]. Although both principles agree that mandibular fractures in the (para)symphysis region have to be fixated with two 2.0 mm osteosynthesis plates due to the torsion forces exerted on the mandible between the canines, the principles differ in terms of plate location and in the dimensions of the osteosynthesis systems used for mandibular body and angle fractures[9,31].

Originally, the AO/ASIF principle advised using bicortical screws in combination with an arch bar for load-bearing fixation of mandibular body and angle fractures with a large compression plate (e.g., a 2.4 mm system) in the compression zone (Figure 2A). After studying the biomechanics of the mandible, Champy and colleagues (1975) proposed a load-sharing fixation method using monocortical fixation with a single 2.0 mm miniplate in the tension zone of the mandible that did not need MMF (Figure 2B)[9]. With growing biomechanical evidence, Champy's principle of fixation became invaluable[9]. Since the volume and quantity of implanted material should be as low as possible[9], and the empirical evidence showed no differences regarding the effectiveness of both principles[40–42], the usage of Champy's principle has gained interest among OMF-surgeons over the last few decades. An international survey of OMF-surgeons in Europe and North-America showed that, even in AO faculties, Champy's principle is currently the preferred method, provided that load-sharing osteosynthesis is biomechanically feasible[43]. If load-bearing osteosynthesis is necessary, both principles advise reconstruction plates (e.g., 2.3 or 2.7 mm screw diameters) although Champy's principle offers an alternative using two plates with a 2.0 mm screw diameter[9].

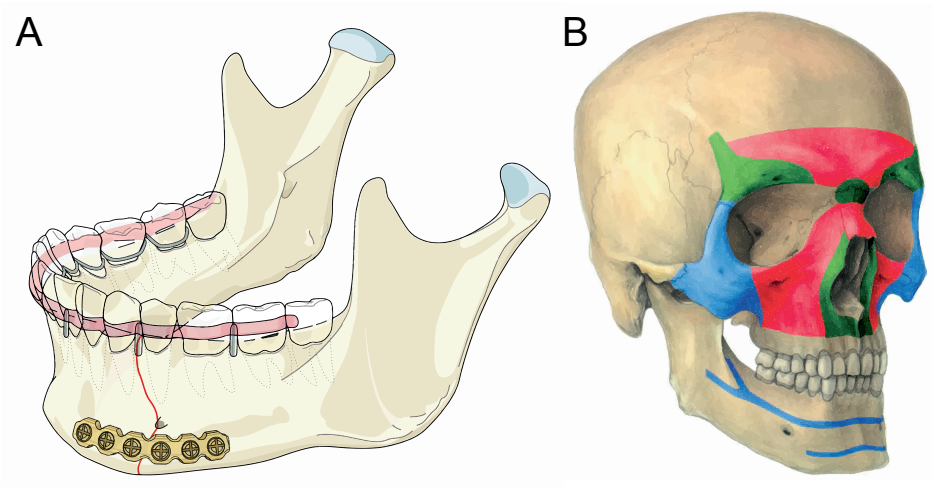

Figure 2. *The original AO/ASIF (A): a compression plate with 2.4 mm bicortical screws in the compression zone combined with an arch bar[31]. Champy's principle for load-sharing osteosynthesis (B): the blue lines on the mandible indicate the ideal osteosynthesis line(s) following Champy's principle[9]. The favourable regions for 2.0 mm miniplate osteosynthesis and 1.5 mm microplates are indicated by the blue and red areas, respectively. The green regions indicate the areas where micro- or miniplates can be used. Sources: Ehrenfeld M., Manson P. & Prein J. Principles of Internal Fixation of the Craniomaxillofacial Skeleton – Trauma and Orthognathic Surgery. Stuttgart: Thieme, 2012 (www.thieme.com); Haerle, F., Champy, M. & Terry, B.C. Atlas of Craniomaxillofacial Osteosynthesis. Stuttgart: Thieme, 2000. Reprinted with permission.*

Osteosynthesis goals and requirements in orthognathic surgery

Before orthognathic surgery can be performed, preoperative orthodontic treatment is usually needed to position the teeth according to a preoperatively drafted plan. The main objective during preoperative orthodontic treatment is the levelling and alignment of the teeth over the basal bone[44]. Further specific goals include reversing the dental compensation, establishing proper incisor inclination and/or arch width, and maintenance of the dental midline[44]. These preoperative goals allow for optimal skeletal correction during orthognathic surgery[45].

The main goals of orthognathic surgery are: (1) establishment of the intended occlusion, i.e., an occlusion according to a preoperatively drafted plan so that the orthodontist can align the teeth into a position with proper intercuspation within a reasonable time[45], (2) semi-stable fixation that allows undisturbed bone healing, and (3) maintenance of the blood supply in the fragments and surrounding tissues[9].

An osteosynthesis is semi-stable when no movement or distraction is visible between the bone fragments and the osteosynthesis system neutralizes harmful distraction strains (e.g., tensile strains of the mandible)[9,36]. Since the fixated bone segments are semi-stable after an osteotomy (i.e., there is no interfragmentary contact and there is no proper intercuspation of teeth), soft-guiding elastics (6-8 weeks) and a soft diet (4-6 weeks) are necessary to ensure the bone segments are immobilized during the bone healing process[2]. Furthermore, as interfragmentary stability is, by definition, absent in osteotomies, the osteosyntheses on the osteotomy segments are load-bearing. Regarding midface osteotomies (e.g., a Le Fort I osteotomy), this translates to applying four 4-hole titanium osteosynthesis plates (i.e., two on each side) with 1.5 mm diameter monocortical screws. Regarding mandibular osteotomies (e.g., a bilateral sagittal split osteotomy), this translates to using two 4-hole titanium osteosynthesis plates (i.e., one on each side) with 2.0 mm diameter monocortical screws, or six 2.0 mm bicortical screws (i.e., three on each side)[2]. Similar to osteosyntheses in trauma surgery, the amount of torque applied to the screws by OMF-surgeons also contributes to the primary stability.

Titanium osteosynthesis systems

Titanium osteosynthesis systems are considered the gold standard for maxillofacial fracture treatment and orthognathic surgery. The titanium plate and screw combination has excellent mechanical and handling properties, providing adequate bone stability with clinically acceptable plate and screw dimensions[46]. However, the disadvantages of titanium osteosyntheses include palpability[46], sensitivity to temperature changes[46],

stress shielding of the underlying bone[47], growth restrictions[48], interference with radiographic imaging and radiotherapy[47,49,50], and possible mutagenic effects[46]. Furthermore, although titanium is believed to be completely bioinert, small titanium particles (i.e., 7.9 to 31.8 µg/gram of dry tissue) have been observed in the regional soft tissue and lymph nodes[51] as well as in the lymphatic system after implanting titanium osteosynthesis systems[52]. Finally, the continued presence of the plates and screws in the body after the system has fulfilled its function (i.e., undisturbed bone healing) is a commonly reported complaint by patients[53].

Postoperative complications and symptoms due to the osteosynthesis systems (e.g., infection, palpability, etc.), that can also occur later on, are valid reasons for plate and screw removal[54–57]. Symptomatic titanium plates and screws are removed in a second operation in 5-40% of cases with the associated burdens, costs, and risk of complications[54,55,58–61]. The main causes of symptomatic plates and screws removal are infection, exposed plates, and thermal sensitivity[61]. In the twentieth century, routine removal of all the inserted titanium osteosynthesis systems was common after consolidation of the osteotomy or fractured bone segments[53,62]. Nowadays, elective removal of the osteosynthesis systems in adults is discouraged from a medical point of view as any secondary surgical procedure has an additional risk of complications[55,56,63,64]. However, a second operation for elective osteosynthesis removal is performed in 17-80% of the patients after demanding it due to their awareness of the presence of a foreign body[53,65,66]. In paediatric maxillofacial fracture treatment, specific stages of facial and dentition development have to be taken into account. Special attention should be given to the presence of unerupted tooth buds, mixed dentition, ongoing skeletal growth, and the relative inability to tolerate rigid MMF because children are less instructive and predictable[67]. Improperly treated fractures during childhood may result in facial asymmetry, malocclusion, and poor aesthetic outcomes that result in higher incidence of orthognathic surgery at a later age[68–70]. Although titanium osteosynthesis is still regarded the gold standard in paediatric fracture treatment, growth restriction[48] and implant migration (i.e., due to bone overgrowth) are detrimental in children[67]. This translates to high rates of removal of titanium plates and screws (87-100%) in the paediatric population[67,71,72].

Biodegradable osteosynthesis systems

Biodegradable devices include natural and synthethic polymers[8]. Biodegradable synthethic polymers, such as poly(L-lactic acid) (PLLA), are widely used in different medical disciplines including orthopaedic, trauma and maxillofacial surgery (e.g., in

osteosynthesis systems)[8,73], cardiology and thoracic surgery (e.g., in cardiovascular stents)[8], and neurosurgery (e.g., in temporary intracranial pressure, pH and temperature sensors)[8,74]. Since their degradation kinetics and mechanical properties can be easily modulated by using, e.g., L- and D-chirality of lactic acid or by copolymerization with different homopolymer ratios, researchers as well as clinicians have been increasingly interested in such biodegradable polymers over the last few decades[8,75,76].

Biodegradable osteosynthesis systems have the ability to degrade in the human body which, ideally, could reduce or even eliminate implant removal during a second operation. The other advantages of biodegradable osteosyntheses are: no sensitivity to temperature changes, no (late) palpability of systems, no interference with radiographic imaging and radiotherapy, no growth disturbances, and a more gradual stress transfer to the healing bone[48,77–79]. However, biodegradable systems also have limitations including less favourable mechanical properties compared to titanium systems, the need to tap the screw hole before inserting the screws in most systems, and tissue reactions to the prolonged presence of foreign materials[8,80].

The most commonly used (co)polymers in biodegradable osteosynthesis systems are PLLA, poly(D,L-lactic acid) (PDLLA), poly(lactic-*co*-glycolic acid) (PLGA), or poly(L-*co*-D,L-lactic acid-*co*-trimethylene carbonate) (P(LLA-*co*-DLLA-*co*-TMC))[8]. These poly(α-esters) degrade in two phases to eventually form CO_2 and H_2O as final products: early degradation via hydrolysis of ester bonds can produce crystalline intermediate products that undergo secondary hydrolysis[75]. Secondary hydrolysis is the rate-limiting step and depends highly on the crystallinity and hydrophobicity of the intermediate products. Biodegradable systems should, preferably, be completely resorbed within 12 months[76]. In practice, prolonged presence of the polymers and degradation products may cause foreign body reactions. These foreign body reactions may be expressed as sterile abscess formation, even years after implantation[81,82]. Factors that are known to influence foreign-body reactions are implant related (e.g., polymer composition, crystallinity, geometry, surface topology), recipient related (e.g., blood supply, tissue/implant dynamics), and plate location related (e.g., epiperiosteal versus subperiosteal)[8,83,84]. The reported foreign body reactions occur predominately with biodegradable osteosyntheses with a high proportion (i.e., >70%) of PLLA[8,15,85,86] or poly(glycolic acid) (PGA)[8]. More amorphous copolymers such as PDLLA (e.g., 50LLA/50DLA ratio) and PLGA (e.g., 70LLA/30GA ratio) are more hydrophilic, and degrade and resorb more quickly[87].

Several studies have assessed tissue responses to biodegradable osteosynthesis systems composed of as-polymerized PLLA[85], amorphous PLLA[88], PDLLA[89–91], PLGA[87,90,92–95], and

P(LLA-*co*-DLLA-*co*-TMC)[96,97], with follow-ups ranging from 6 weeks to 2 years[87,89–95,97–99]. Although most of these studies still found residual polymeric particles at the final follow-up, several studies concluded that the systems had been resorbed completely by the 1 to 2-year follow-ups[89,90,93]. However, these conclusions were only based on *in vivo* assessments of degradation using light microscopy while the polymeric fragment dimensions, which can induce foreign-body reactions, can be smaller than the light microscopy resolution[85]. Furthermore, degradation of these polymers leads to increasing crystallinity and even to the formation of crystalline oligomeric stereo-complexes over time[100,101] that are more stable and resistant to further hydrolytic degradation and resorption than amorphous fragments[8,76,85,102]. Therefore, evidence of complete resorption of polymeric biodegradable systems (i.e., at a nanoscale level) with appropriate follow-ups (i.e, >2 years) is still lacking. Thus, there remains a need for an assessment of the degradation of different polymeric biodegradable osteosynthesis systems at nanoscale levels with a long-term follow-up, as this is essential for biocompatibility evaluations as well as to gain knowledge of the development of foreign body reactions to such biodegradable polymers.

Mechanical properties

The presumed less favourable mechanical properties of biodegradable compared to titanium osteosynthesis systems retricts the use of most biodegradable systems for midface or non-load bearing mandibular fracture fixation. Both titanium and biodegradable osteosynthesis systems are constantly being improved. Improvements to the titanium systems include an adjusted screw head to get a better grip on the screws. Furthermore, an adjusted production process has been introduced to lower the stiffness of these systems thereby reducing stress shielding of the underlying bone and improving perioperative handling of the systems[6,7]. An example of an improved biodegradable system is the SonicWeld xG system (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)[8]. This system uses thermoplastic biodegradable pins instead of screws which are inserted into the burr hole using an ultrasound probe, resulting in a flow of the biodegradable polymer into the cancellous bone. This technique obviates the need to tap the burr hole and results in fusion of the pin with the plate that leads to a stable three-dimensional system[8,79]. Furthermore, biodegradable copolymeric systems consisting of biocomposites with osteoconductive properties have been introduced[8].

Currently, over 12 different titanium and over 36 different biodegradable osteosynthesis systems (without taking the different sizes of each system into account) are available for OMF-surgery[8]. Since the improvements in both types of systems are recent, there

is a lack of studies comparing these systems which means it is still unclear to surgeons which titanium and biodegradable osteosynthesis systems are suitable and preferable to treat fractures and for osteomy fixation.

Titanium or biodegradable osteosynthesis?

Studies comparing biodegradable versus titanium osteosyntheses after orthognathic and trauma surgery have been performed, but the results are controversial. Some report higher plate removal rates after titanium osteosyntheses[103–105], while others show higher rates of symptomatic plate removal after biodegradable osteosyntheses[106,107]. This controversy also applies to other clinically assessed endpoints such as infection[108], wound dehiscence[108,109], skeletal stability[103,110,111] and pain[103,105]. These comparative studies' follow-ups ranged from 8 weeks to 2 years. Although the results are of importance, well-designed studies focusing on long-term outcomes (i.e., >5 years) are needed since host response and full degradation and resorption of implants can take up to 6 years[73,80,96,112,113]. Additionally, removal of titanium plates and screws five years after surgery has been reported[54,55].

Therefore, in 2006, our research group started a randomised controlled trial (RCT) comparing a titanium (KLS Martin CrossDrive) and a biodegradable osteosynthesis system (Inion CPS) in orthognathic and trauma surgery[35,60]. The short-term (i.e., 8 weeks) healing outcomes (e.g., undisturbed bone healing) were similar in both groups[35]. However, the risk of symptomatic removal of biodegradable systems within the first 2 postoperative years was 2.2 times higher compared to the titanium systems[60]. As symptomatic implant removal of both types continues, an assessment of the >5 year follow-up outcomes is required to judge the need to remove both systems.

To gain insight into the behaviour of both types of osteosyntheses, primary studies as well as systematic reviews with and without meta-analysis comparing titanium and biodegradable osteosynthesis in trauma[114] and orthognathic surgery[115] have been undertaken. A systematic review focusing on the efficacy and safety of these interventions in maxillofacial traumatology was published in 2009, but could not include any studies because none met the inclusion criteria[114]. It was concluded that there was insufficient evidence to support or refute the use of biodegradable osteosynthesis. In 2018, a systematic review comparing osteosynthesis systems for orthognathic surgery was published[115], but focused on skeletal stability only and failed to account for clinical (e.g., inclusion of patients with cleft lip and palate) and methodological heterogeneity

(e.g., they pooled the data from different study designs). Thus, to guide evidence based decisions, the need remains for a systematic review that adequately assesses the efficacy and morbidity of biodegradable versus titanium osteosyntheses in patients undergoing trauma and orthognathic surgery, including all the relevant clinical endpoints, and which takes methodological and clinical heterogeneity of the studies into account.

Aims of this thesis

To guide evidence-based selection of osteosynthesis systems, the **overall aim** of the research described in this thesis was to compare the *in vitro* and *in vivo* performances of different biodegradable osteosynthesis systems as well as to compare the (clinical) performance of biodegradable and titanium osteosynthesis systems. The **specific aims** were:

1. To systematically review and analyse the efficacy and morbidity of biodegradable and titanium osteosyntheses in patients with maxillofacial fractures treated with open reduction and internal fixation (**Chapter 2**).
2. To systematically review and analyse the efficacy and morbidity of biodegradable and titanium osteosyntheses in patients with dentofacial deformities treated with orthognathic surgery (**Chapter 3, Chapter 4**).
3. To compare the long-term clinical performance of a titanium and biodegradable osteosynthesis system following the fixation of Le Fort-I, zygomatic and mandibular fractures, and Le Fort-I and/or bilateral sagittal split osteotomies (**Chapter 5**).
4. To assess and compare the histological responses, and the molecular and thermal properties of four commonly used copolymeric biodegradable osteosynthesis systems and a negative control (i.e., an area without invasive treatment) in a goat model (**Chapter 6**).
5. To determine and compare the mechanical properties of commonly used biodegradable and titanium osteosynthesis systems in OMF-surgery (**Chapter 7**).
6. To assess the test-retest and intra-individual reliabilities of the torque applied by residents and experienced OMF-surgeons, to define a reference torque interval for the commonly used 1.5 mm and 2.0 mm osteosynthesis screws, and to compare the compliance to the reference torque interval between OMF-surgeons and residents with varying years of experience (**Chapter 8**).

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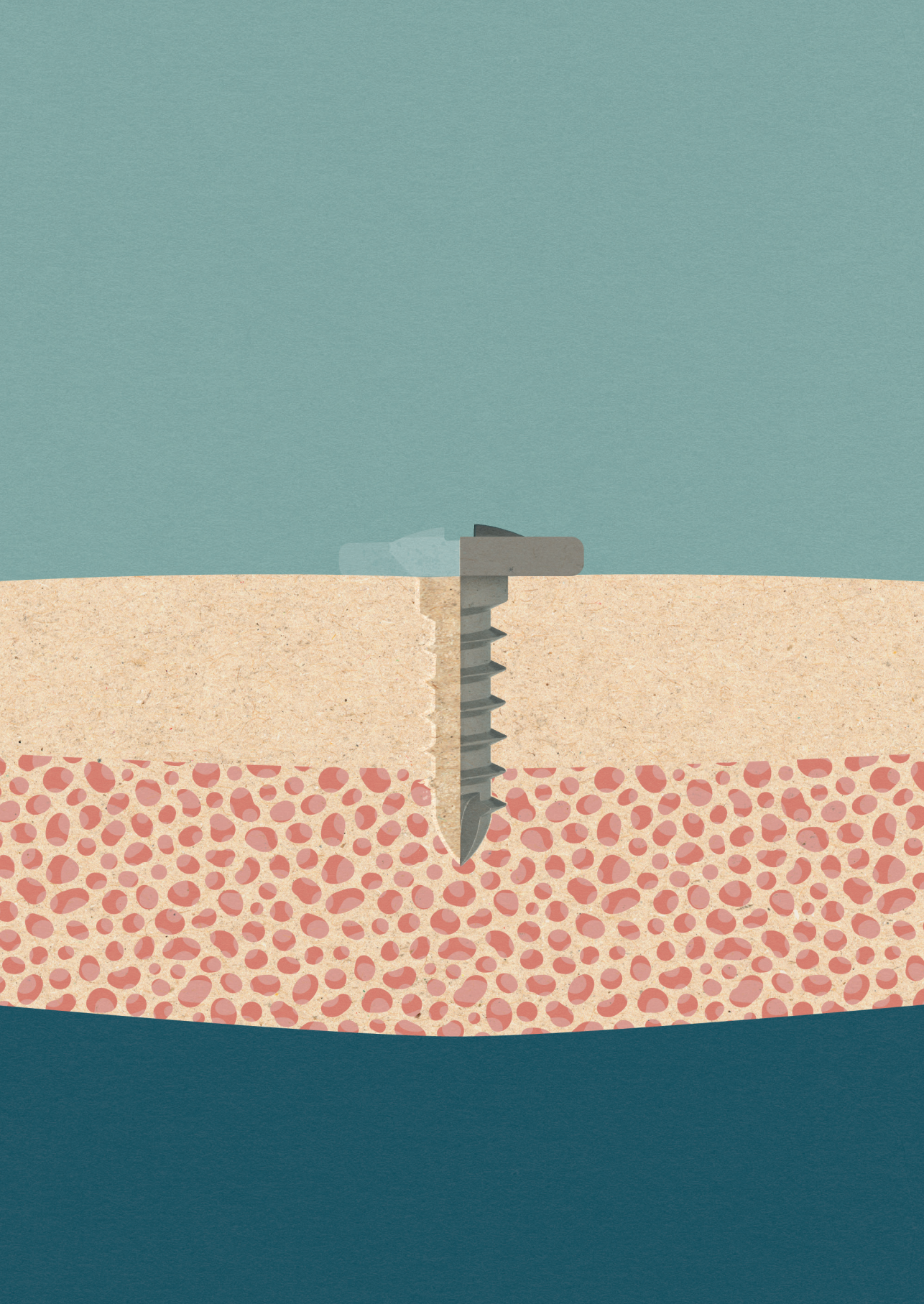

Chapter 2

Biodegradable versus titanium osteosyntheses in maxillofacial traumatology

a systematic review with meta-analysis and trial sequential analysis

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Abstract

Titanium osteosynthesis is currently the fixation system of choice in maxillofacial traumatology. Biodegradable osteosynthesis systems have the ability to degrade in the human body. The aim of this study was to conduct a systematic review, with meta- and trial sequential analyses, to assess the efficacy and morbidity of biodegradable versus titanium osteosyntheses after maxillofacial trauma. MEDLINE, EMBASE, and CENTRAL were searched for randomized controlled trials, and prospective and retrospective controlled studies. Five time periods were studied: perioperative, short-term (0-4 weeks), intermediate (6-12 weeks), long-term (>12 weeks) and overall follow-up. After screening 3542 records, 24 were included. All had a high risk of performance and detection bias due to the nature of the interventions. Meta-analysis showed no differences in efficacy and morbidity between biodegradable and titanium osteosyntheses. Risk of perioperative screw breakage was significantly higher (RR 17.13, 95% CI: 2.19;34.18) and the symptomatic plate removal rate lower in the biodegradable group (RR 0.11; 95% CI 0.02;0.57), which was confirmed by the trial sequential analysis. The quality of evidence ranged from very low to moderate. Based on both narrative review and meta-analyses, current evidence shows that biodegradable osteosyntheses are a viable alternative to titanium osteosyntheses when applied in the treatment of maxillofacial trauma with similar efficacy but significantly lower symptomatic plate removal rates. Perioperative screw breakage occurred significantly more often in the biodegradable compared to the titanium group.

Introduction

Titanium osteosynthesis systems are considered the gold standard in maxillofacial fracture treatment and orthognathic surgery. Titanium plates and screws combine excellent mechanical and handling properties, providing adequate bone stability[1]. The disadvantages of titanium osteosyntheses include palpability[2], sensitivity to temperature changes[1], stress shielding of the underlying bone[3], growth restrictions[4], interference with radiographic imaging and radiotherapy[3,5,6], titanium particles in the soft tissue and regional lymph nodes[7], and possible mutagenic effects[1]. As a consequence, titanium plates and screws are removed in a second operation in 0-33% of the cases with the associated burdens and costs[2,8].

Currently, the most commonly used biodegradable osteosynthesis systems are made of resorbable polymers (e.g., poly-DL-lactic acid), whose properties might eliminate the need to remove implants in a second operation, thereby avoiding the accompanied additional risks, costs, and burdens of a second operation. Additionally, the other disadvantages associated with titanium osteosynthesis are avoided. The limitations of biodegradable osteosynthesis systems include less favourable mechanical properties[9], which could potentially lead to mobility or malunion of bone segments, and possible adverse tissue reactions[10]. Biodegradable implants have to be removed in 0-17% of the cases[2,11].

A systematic review focusing on the efficacy and safety of these interventions in maxillofacial traumatology was published in 2009, but could not include any studies because none met the inclusion criteria[12]. It was concluded that there was insufficient evidence to support or refute the use of biodegradable osteosynthesis. Since then, many studies comparing biodegradable versus titanium osteosyntheses have been published, but the results of these solitary studies remain controversial[2,11,13,14]. Our randomized controlled trial showed an unexpected higher symptomatic plate removal rate in the biodegradable compared to the titanium group after trauma and orthognathic surgery[2]. To place these results in the literature context, we looked for systematic reviews addressing efficacy and morbidity of these interventions. The most recent systematic review comparing both systems in maxillofacial surgery was published in 2013[15]. However, it only focused on complications and failed to account for clinical or methodological heterogeneity. Therefore, there is still a need for a systematic review that adequately assesses the efficacy and safety of biodegradable versus titanium systems in trauma patients, including all the relevant endpoints for clinicians, and which takes the methodological heterogeneity of the studies into account, thereby enabling well informed and evidence based decisions.

The aim of this study was to conduct a systematic review, with meta- and trial sequential analyses, of randomized controlled trials, prospective controlled cohort studies, and retrospective controlled cohort studies examining the efficacy (i.e., bone healing and occlusion) and morbidity of biodegradable (i.e., composed of (co-)polymers) versus titanium osteosyntheses in patients with maxillofacial fractures.

Materials and methods

This systematic review and meta-analysis was conducted following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions, Risk Of Bias In Systematic Reviews tool* (ROBIS) and *A Measurement Tool to Assess Systematic Reviews 2 (AMSTAR 2)*, and is reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement to ensure quality and completeness[16–19]. This study's protocol was registered in PROSPERO prior to the systematic literature search (registration number CRD42018086477).

Study identification

A systematic literature search of three electronic databases (MEDLINE (1964-2019), EMBASE (1947-2019), and the Cochrane Central Register of Controlled Trials (CENTRAL; inception to 2019) was conducted. The sensitive search strategy consisted of medical subject heading terms and free-text words (Table S1). The search strategy also included orthognathic populations as some studies include both populations in a single study. Data of trauma patients were derived from the authors of those studies and were included while data of orthognathic patients were excluded. The complete search was performed in January 2018 and was updated on 20 April, 2019. Additionally, the reference lists of the included studies and leading oral and maxillofacial journals were screened for relevant studies and maxillofacial surgery experts in biodegradable and titanium osteosynthesis (RRMB and NBvB) were asked if any relevant studies were missing which should have been included in this review. No language or period restrictions were applied.

Study selection

The inclusion criteria were formulated using the PICOS format. The population (P) included all the patients who had been treated for maxillofacial fractures, i.e., Le Fort I, Le Fort II, Le Fort III, cranial, zygomaticomaxillary complex and mandibular fractures. The intervention group (I) was treated surgically with biodegradable fixation (i.e., plates

and/or screws/pins) that consisted of (co-)polymers. The control group (C) received surgical treatment with titanium fixation (i.e., plates and/or screws). The primary outcomes (O) were efficacy of the fixation method, i.e., adequate bone healing with the absence of malunion of bone segments, clinical mobility of bone segments, and objective and subjective malocclusion. Secondary outcomes were related to morbidity, i.e., symptomatic plate removal rate (i.e., routinely removed asymptomatic plates were excluded), pain, analgesia usage, maximal mouth opening (MMO), mandibular function impairment questionnaire (MFIQ; lower score equals better function), temporomandibular joint dysfunction (TMJ-dysfunction), infection, swelling, wound dehiscence, plate exposure, palpability of plates and/or screws, the patient's satisfaction with the performed surgery, and revision surgery (e.g., abscess incision and drainage; plate removal was excluded). Additionally, the handling of the osteosynthesis systems by the surgeons, plate and screw breakage, and total costs (i.e., direct and indirect costs) of both groups were evaluated. The included study types (S) were randomized controlled trials (RCTs), prospective studies with a control group, and retrospective studies with a control group. The RCT is the highest quality of evidence of an original manuscript, while the latter two designs are useful for adverse events assessment. The follow-up (FU) of each corresponding endpoint is described below (see Data collection).

Exclusion criteria consisted of patients with syndromic disorder(s), patients with cleft lip or palate, multiple publications of the same study and endpoints, case reports, case series with fewer than 10 cases, experts' opinions, letters to the editor, review articles, and conference abstracts.

Two reviewers (BG and NBvB) independently assessed the titles and abstracts for eligibility for inclusion. If the title and abstract provided insufficient information or in case of any doubt, they were included for full text assessment. The full text articles of included titles and abstracts were independently assessed by the same two reviewers for final inclusion using the above mentioned in- and exclusion criteria. Any disagreement was resolved by a discussion. If no consensus was found, a third reviewer (PUD) was asked to give a final decision.

After each selection stage, the inter-observer agreement was expressed as Cohen's kappa and percentage of agreement. Studies written in languages that the observers were not competent in were translated by researchers fluent in both that language and English. Subsequently, these translated studies underwent the same review process.

Assessment of methodological quality

The risk of bias of all the included studies was independently assessed by two reviewers (BG and NBvB). Trials performed by the author's research group were assessed by two independent researchers not involved in those studies (PUD and SJvdG; see acknowledgement) to avoid conflict of interests.

Randomized controlled trials were assessed using the *The Cochrane Collaboration's tool for assessing risk of bias*[20], including 7 domains: sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues'. The domains were graded low risk, unclear risk or high risk of bias.

The nonrandomized studies' risk of bias was assessed using The Methodological Index for Non-Randomized Studies (MINORS)[21]. The MINORS is a valid and reliable instrument for quality assessment[21]. It includes 8 items which are applicable to all nonrandomized studies, and an additional 4 applicable to comparative studies. Each item was scored either 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

The quality of the body of evidence for each outcome was graded by two independent reviewers (BG and NBvB) as high, moderate, low, or very low quality using the *Grades of Recommendation, Assessment, Development and Evaluation Working Group system* (GRADE system). The grades can be increased or decreased based on the underlying methodology depending on the presence of certain factors (e.g., downgrading studies with a high risk of bias)[22].

Data collection

The data was extracted using a standardised, pre-defined form. Two reviewers (BG and NBvB) extracted data from a sample (10%) of eligible studies. If an agreement of ≥80% was achieved, the remainder of the data was extracted by one reviewer (BG). The collected data included: first author and year of publication, country in which the study was conducted, study design, number of patients, gender, age, tobacco and alcohol usage, surgical procedures, types of osteosynthesis systems used, intra-operative switching to another osteosynthesis system, osteosynthesis principle, duration of maxillomandibular fixation (MMF), duration of FU, and conflict of interests. The endpoints were collated for 5 time periods: perioperative, short-term FU (i.e., 0-4 weeks; soft tissue healing), intermediate FU (i.e., 6-12 weeks; bone healing), long-term FU (i.e., >12 weeks; degradation effects), and overall FU (i.e., the endpoints of the longest FU; Table S2).

If the relevant data could not be extracted, the authors of the studies were contacted by e-mail from May - November 2018 and April – July 2019. Data were not included in the analyses if the authors could not provide the relevant data or did not respond despite a minimum of three email attempts.

Statistical analysis

The inter-observer agreement was calculated using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA). Regarding binary variables, the events and totals were used to calculate the risk ratio (RR) and 95% confidence intervals (CI). The standardised mean difference (SMD), with 95% CI, was calculated for continuous variables. Statistical heterogeneity was regarded substantial if $I^2 > 50\%$[20]. The meta-analysis was performed in R-*meta*[23], version 3.5.3, using a random-effects model because of clinical heterogeneity (e.g., different polymer compositions).

Separate analyses were conducted for the study designs. A summary effect estimate was calculated if ≥2 studies with the same study design could be pooled. Also, a subgroup analysis of low risk versus high risk bias RCTs was performed as well as subgroup analyses of the primary endpoints and plate removal rate of paediatric patients (<16 years) versus adults, and mandibular versus other fractures. Plate removal rate was also analysed according to the FU of the included studies, i.e., ≤1 year FU and >1 year FU. A narrative synthesis was performed if only a single study per study design or subgroup was available.

Since a conventional meta-analysis excludes studies with zero events in both treatment groups, a sensitivity analysis was performed, including those studies with a reciprocal continuity correction of the opposite arm[24]. A meta-regression analysis with a random-effects model evaluated the effect of the study design and items of methodological quality on each primary endpoint and plate removal. Reporting bias was assessed through funnel plots if >10 studies were available per endpoint and study design, and did not have clinical heterogeneity[16]. Funnel plots with ≤10 studies are underpowered and the presence of clinical or statistical heterogeneity results in inconclusive funnel plots[16,25–27]. $P<0.05$ was considered statistically significant. The meta-regression was conducted using Comprehensive Meta-Analysis, version 3 (Biostat, Englewood, NJ, USA).

As traditional meta-analyses are prone to type-I errors (i.e., false positive findings) due to random error and repeated significance testing after each additional trial is published[28,29], trial sequential analyses (TSA), including RCTs, were performed for each endpoint. TSA reduces the risk of type-I errors by combining information size

estimations with trial sequential monitoring boundaries [28] and provides information on how many patients are required in the meta-analysis to sufficiently support the conclusions (i.e., equivalent to a sample size calculation in RCTs)[29–31]. An explanation of TSA, with an example and the interpretation of the data, is shown in Figure S1. The TSA, which included the random-effects (DerSimonian-Laird) model based on the observed relative risk reduction (RRR) and diversity (D^2) of RCTs, and an overall type I error (α) of 0.05 and a type II error (β) of 0.20[32], was performed using Trial Sequential Analysis Viewer, version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet)[32].

Results

Study identification and selection

The search resulted in 5479 potentially eligible papers. After excluding duplicates, 3542 papers were screened by title and abstract (Figure 1). The percentage of agreement and kappa were 99% and 0.91, respectively. The full text manuscripts of the remaining 80 papers were screened for inclusion. Fifty-six studies were excluded due to not fulfilling the inclusion criteria (n=47), fulfilling the exclusion criteria (n=6), providing insufficient details (n=2), or due to including the same study population and endpoints with a shorter FU (n=1) (Table S3). The percentages of agreement and kappa were 100% and 1.0, respectively. The remaining 24 publications were included in the qualitative synthesis of this review, and 21 of them were included in the quantitative synthesis. There was no need to consult the third reviewer in any phase of the identification and selection of a study.

Assessment of methodological quality

The included studies consisted of 7 publications of RCTs[2,14,33–37], of which 4 were publications of a single RCT, each with a different FU[2,33,35,36], 4 prospective cohort studies[11,13,38,39], and 13 retrospective cohort studies[8,40,49–51,41–48]. Low risk of bias was observed in the 'random sequence generation' domain in all but one of the included RCTs (Table 1). High risk of performance and detection bias was observed in all the included RCTs. 'Other sources of bias' were assessed as high risk in four publications of a single RCT due to the fact that, whenever the surgeon deemed it necessary, the surgeon chose to switch perioperatively from biodegradable to titanium systems. As none of the included RCTs were assessed as low risk of bias, no subgroup analyses could be performed between high and low risk of bias.

None of the cohort studies had undertaken an adequate unbiased assessment of the study endpoints (Table 1). All of them had an adequate control group as this was one of the inclusion criteria. Seventy-five percent of the included studies had adequate contemporary groups.

Two studies declared funding from research programmes[34,51] and one from the armed forces[43]. Six studies did not mention funding or conflict of interest[11,14,40–42,48]. All the remaining studies declared no funding or conflict of interest.

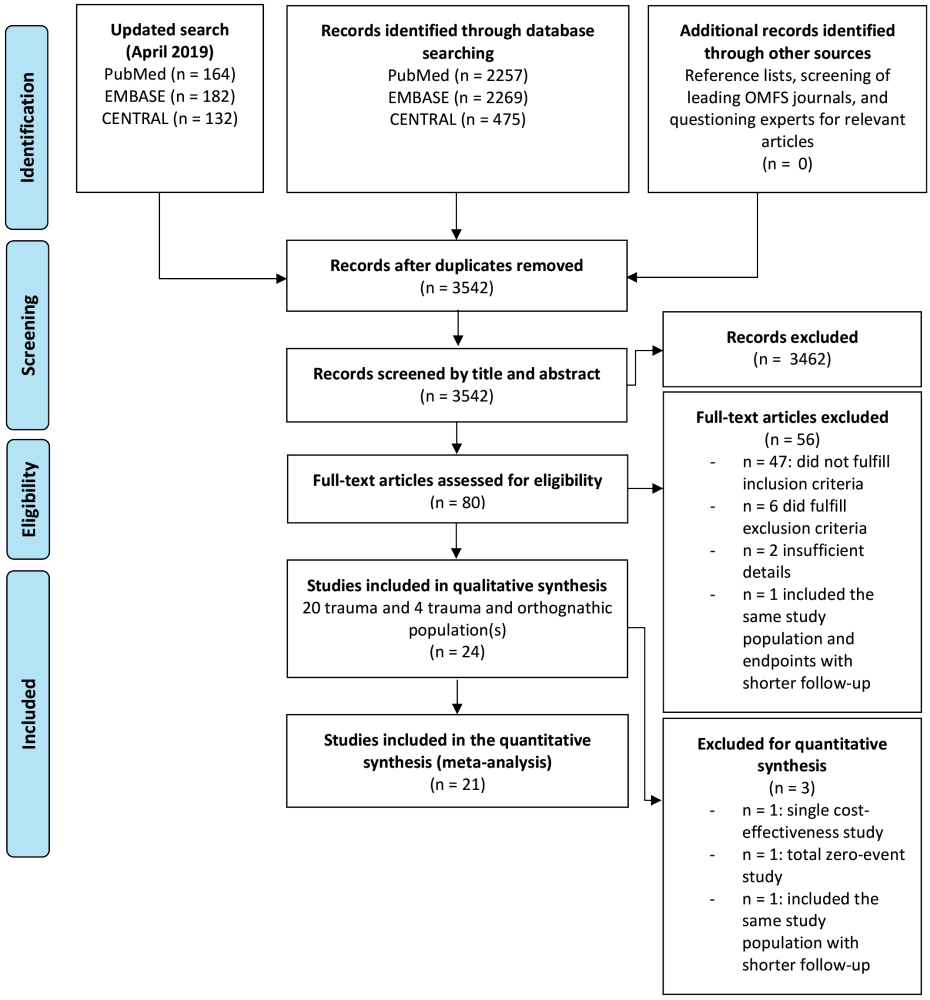


Figure 1. Flowchart of study identification and selection progress.

Table 1. Risk of bias assessment of all included studies.

	Cochrane Collaboration's tool for assessing risk of bias							MINORS									
Study name (year)	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and researchers (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	FolL-up period appropriate to the aim of the study	Loss to folL up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses
Randomized controlled trials																			
Bhatt et al. (2010)[14]	L	U	H	H	U	L	L												
Buijs et al. (2012)[33]	L	L	H	H	L	L	H												
Ahmed et al. (2013)[34]	L	U	H	H	U	L	L												
Bakelen et al. (2013)[35]	L	L	H	H	H	L	H												
Bakelen et al. (2015)[36]	L	L	H	H	H	L	H												
Sukegawa et al. (2016)[37]	U	U	H	H	L	L	L												
Gareb et al. (2017)[2]	L	L	H	H	H	L	H												
Prospective cohort studies																			
Leonhardt et al. (2008)[11]								2	1	2	2	0	1	1	0	2	2	1	0
Qiu et al. (2015)[38]								2	1	1	2	0	2	2	0	2	2	2	2
Mahmoud et al. (2016)[39]								2	2	2	2	0	2	2	0	2	2	1	1
Leno et al. (2017)[13]								2	2	2	2	0	2	0	0	2	2	1	2
Retrospective cohort studies																			
Bell et al. (2006)[40]								2	2	0	1	0	1	0	0	2	2	1	0
Wittwer et al. (2006)[41]								1	1	1	1	0	2	2	0	2	1	1	1
Lee et al. (2010)[42]								2	1	0	1	0	2	0	0	2	2	0	0
Park et al. (2011)[51]								1	1	0	1	0	1	0	0	2	2	1	0
Menon et al. (2012)[43]								2	0	0	0	0	2	2	0	2	0	1	0
Tripathi et al. (2013)[44]								2	1	0	1	0	1	0	0	2	0	0	0
Kang et al. (2014)[45]								2	2	0	1	0	2	2	1	2	2	2	1

Table 1. *(continued)*

	Cochrane Collaboration's tool for assessing risk of bias							MINORS										
Study name (year)	**Random sequence generation (selection bias)**	**Allocation concealment (selection bias)**	**Blinding of participants and researchers (performance bias)**	**Blinding of outcome assessment (detection bias)**	**Incomplete outcome data (attrition bias)**	**Selective reporting (reporting bias)**	**Other bias**	**A clearly stated aim**	**Inclusion of consecutive patients**	**Prospective collection of data**	**Endpoints appropriate to the aim of the study**	**Unbiased assessment of the study endpoint**	**FolL-up period appropriate to the aim of the study**	**Loss to folL up less than 5%**	**Prospective calculation of the study size**	**An adequate control group**	**Contemporary groups**	**Baseline equivalence of groups**	**Adequate statistical analyses**
Lim et al. (2014)[46]								2	1	0	1	0	1	0	0	2	2	1	1
Bhatt et al. (2015)[47]								2	1	0	2	0	1	0	0	2	2	2	2
Burlini et al. (2015)[48]								1	2	0	1	0	2	1	0	2	2	1	1
Filinte et al. (2015)[49]								2	0	0	1	0	1	0	0	2	0	1	0
Wu et al. (2017)[50]								2	2	0	2	0	1	2	0	2	2	1	1
Kim et al. (2018)[8]								2	2	0	2	0	1	2	0	2	2	2	2

MINORS: Methodological index for non-randomized studies. H: high risk of bias; L: low risk of bias; U: unclear risk of bias; 0: not reported; 1: reported but inadequate; 2: reported and adequate. Empty cells: not applicable

Patient characteristics

The number of patients in the studies ranged from 12 to 1122, resulting in a total of 2450 patients (Table S4). Of these, 1639 patients received titanium and 811 patients received biodegradable osteosynthesis systems. The majority of patients were male. Four studies just had male patients in the biodegradable group [2,33,35,36]. Ages ranged from 4 to 83 years. Two studies only included paediatric patients[48,49]. The most common types of fractures were mandibular, zygomatic and maxillary fractures. Ten studies solely included patients with mandibular fractures[8,11,13,14,34,38,42,46,47,49], while six studies included patients with only zygomatic fractures[37,39,41,43,44,50]. The remaining studies included various types of fractures (e.g., Le Fort or orbital fractures)[2,33,35,36,40,45,48,51]. Comminuted fractures were excluded in 16 studies[13,14,43,44,46,47,50,33–36,38,39,41,42], while two studies did not exclude these type of fractures[8,45]. The remaining six studies did not

report specific in- or exclusion criteria regarding comminuted fractures[11,37,40,48,49,51]. Four studies included both orthognathic and trauma patients, but only the trauma patients' data have been included in this review[2,33,35,36]. None of the included studies reported information regarding tobacco or alcohol usage by the patients.

Procedural characteristics

The procedural characteristics of the included studies are presented in Table S4. In one study, the procedure was endoscopically assisted[8]. The most commonly used titanium osteosynthesis systems were manufactured by KLS Martin[2,11,33,35,36,41], Synthes[14,37,40,42,47], and Stryker[13,43]. Twelve studies reported details regarding the size of the titanium plates and the screws[2,8,40,43,47,11,13,14,33,35–38]. The screw diameter ranged from 1.3 to 2.0 mm with corresponding plates, depending on the location of the fracture.

The most frequently used biodegradable osteosynthesis systems were the Inion CPS (79/15/6 poly-L-lactic acid (PLLA)/poly-DL-lactic acid (PDLLA)/trimethylene carbonate)[2,11,14,33,35,36,44,46,47] and the BioSorb FX (self-reinforced 70/30 PLLA/PDLLA)[38,41,42,46,51] (Table S4). The screw diameters ranged from 1.5 to 2.5 mm, being generally larger compared to the titanium systems for similar fracture types. Five articles reported intra-operative switches from a biodegradable to a titanium osteosynthesis system[2,14,33,35,36]. Of these, one RCT[14] reported 1 intra-operative switch (5%). The other 4 articles were publications of the same RCT with different FUs[2,33,35,36] and reported 4 intra-operative switches (40%) in the trauma patients. The main reason for switching material was inadequate fixation due to non-grip screws or inadequate stability of the bone segments after fixation of the osteosynthesis plates[52].

Nine studies followed Champy's principle[2,11,14,33,35,36,42,46,47] and one the Association for Osteosynthesis/Association for the Study of Internal Fixation (AO/ASIF) principle[40] for osteosynthesis of mandibular fractures. Six studies did not report the osteosynthesis principle[8,13,34,38,48,49]. MMF was used in 14 studies, of which 5 studies used soft guiding elastics in both groups[2,8,33,35,36], 3 studies used rigid MMF in both groups[34,42,46], 2 studies just used MMF in the biodegradable group[13,14], and 3 studies only used MMF whenever this was deemed necessary[37,40,49], although no details regarding this clinical decision were reported (Table S4).

Primary endpoints

All the pooled endpoints are reported as RR or SMD (95% CI), with the quality of the evidence. A total of 16 studies reported data regarding malunion (Table S5)[8,11,43–

[47,49,13,33,34,37,38,40–42]. In 14 of these studies, no malunion was found in either the titanium or the biodegradable groups. Malunion, assessed after 6-12 weeks FU, was present in two retrospective studies and pooling of the data showed no significant differences between both groups (RR 0.93 (0.15;5.75), very low quality, Figure 2A).

The mobility of bone segments was assessed in 5 of the studies after 6-12 weeks FU[14,33,34,38,49]. Two studies reported no mobility of bone segments[33,49]. One prospective study assessed that 4% and 13% of the patients had mobile bone segments after biodegradable and titanium osteosyntheses, respectively[38]. Data derived from two RCTs showed no significant differences between both groups (RR 2.11 (0.32;13.79), very low quality, Figure 2B). No subgroup analysis could be performed.

Malocclusion within 4 weeks FU was assessed in 7 studies[11,13,14,38,44,47,49]. Three of them reported zero events in both groups[13,38,44]. One RCT found similar rates of short-term objective malocclusion in both groups (24%)[14]. One prospective study reported objective malocclusion in 41% and 21% of the cases in the biodegradable and titanium group, respectively[11]. Data derived from two retrospective studies showed no significant difference in objective malocclusion between both groups (RR 0.51 (0.06;4.68), very low quality, Figure 2C). Both of these two retrospective studies only included patients with mandibular fractures. Subgroup analysis between paediatric patients and adults showed no significant difference in the estimate between both subgroups (adults: RR 0.91 (0.29;2.83); paediatric: RR 1.83 (0.81;4.11), very low quality, Figure S2).

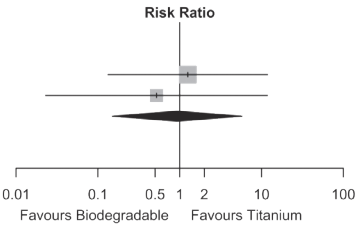
Eight studies documented malocclusion after 6-12 weeks FU[11,13,14,33,34,38,47,48]. Three of these studies reported no objective malocclusion in both groups[13,38,47]. Pooling of the data from the RCTs showed no significant differences between both groups (RR 1.01 (0.21;4.81), very low quality, Figure 2D). One prospective study mentioned 3% and 7% of the patients had objective malocclusion[11], while one retrospective study found subjective malocclusion in 17% and 10% of the cases in the biodegradable and titanium groups, respectively[48]. No subgroup analysis could be performed.

Six studies assessed malocclusion after >12 weeks FU[2,11,13,35,38,41]. One RCT reported one case (13%) of objective malocclusion in the titanium group after 1-year of FU[35]. Another RCT with >5 years FU reported two cases (50%) of subjective malocclusion[2] (Table S5). Both these RCTs included the same study population with different FU moments. No subgroup analysis could be performed.

A

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
Retrosp. CS						
Bell et al. (2006)	1	59	3	222	1.25	[0.13; 11.84]
Filinte et al. (2015)	0	12	1	19	0.52	[0.02; 11.79]
Random effects model		**71**		**241**	**0.93**	**[0.15; 5.75]**

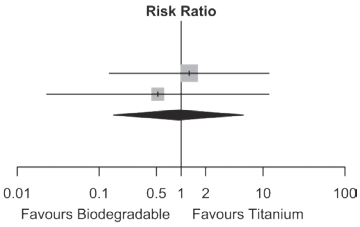
Heterogeneity: I^2 = 0%, p = 0.65
Test for effect in subgroup: p = 0.94
Test for subgroup differences: χ^2_0 = 0.00, df = 0 (p = NA)



B

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
Retrosp. CS						
Bell et al. (2006)	1	59	3	222	1.25	[0.13; 11.84]
Filinte et al. (2015)	0	12	1	19	0.52	[0.02; 11.79]
Random effects model		**71**		**241**	**0.93**	**[0.15; 5.75]**

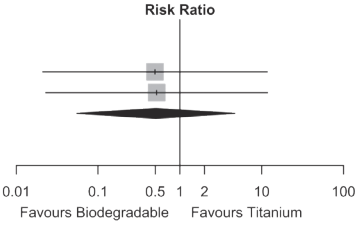
Heterogeneity: I^2 = 0%, p = 0.65
Test for effect in subgroup: p = 0.94
Test for subgroup differences: χ^2_0 = 0.00, df = 0 (p = NA)



C

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
Retrosp. CS						
Bhatt et al. (2015)	0	24	1	36	0.50	[0.02; 11.70]
Filinte et al. (2015)	0	12	1	19	0.52	[0.02; 11.79]
Random effects model		**36**		**55**	**0.51**	**[0.06; 4.68]**

Heterogeneity: I^2 = 0%, p = 0.98
Test for effect in subgroup: p = 0.55
Test for subgroup differences: χ^2_0 = 0.00, df = 0 (p = NA)



D

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
RCT						
Bhatt et al. (2010)	2	18	1	13	1.44	[0.15; 14.29]
Buijs et al. (2012)	0	8	2	9	0.22	[0.01; 4.03]
Ahmed et al. (2013)	1	34	0	35	3.09	[0.13; 73.21]
Random effects model		**60**		**57**	**1.01**	**[0.21; 4.81]**

Heterogeneity: I^2 = 0%, p = 0.44
Test for effect in subgroup: p = 0.99
Test for subgroup differences: χ^2_0 = 0.00, df = 0 (p = NA)

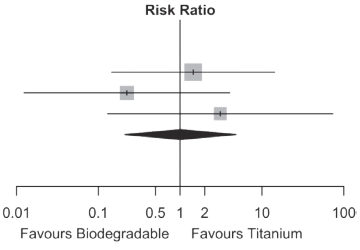


Figure 2. Forest plots of the primary endpoints: (A) malunion (6-12 weeks follow-up); (B) mobility of bone segments (6-12 weeks follow-up); (C) malocclusion (<4 weeks follow-up); (D) malocclusion (6-12 weeks follow-up), stratified by study design. *Retrosp. CS, retrospective cohort studies; RCT, randomised controlled trials; RR, risk ratio; 95% CI, 95% confidence interval; NA, not applicable.*

Secondary endpoints

Focusing on perioperative endpoints, the occurrence of plate breakage ranged from 0 to 6% and 0 to 2% plates in the biodegradable and titanium groups, respectively (Table S5). Breakage of screws occurred in 0-7% of the biodegradable screws, while only one study reported a single broken titanium screw[48]. The RCTs showed that biodegradable screws broke more often compared to titanium screws (RR 17.13 (2.19;134.18), moderate quality) while the retrospective studies showed no significant difference between both groups (Figure S3). The mean operative time in the biodegradable and titanium groups ranged between 119-169 and 94-127 minutes, respectively. Data derived from the retrospective studies did not result in a significant difference in operation time between both groups (SMD 0.72 (-0.17;1.61), very low quality, Figure S4). Plate and screw handling, as assessed by surgeons, was only reported in one RCT and was similar for both groups[33].

Infection within 4 weeks FU occurred in 0-8% and 0-10% in the biodegradable and titanium groups, respectively, and did not differ significantly between both groups in all the study designs (RCTs: RR 0.26 (0.03;2.26), very low quality, Figure 3A). Short-term swelling was assessed in one RCT[37], one prospective study [11], and two retrospective studies[41,44]. One of the retrospective studies reported swelling in all the included patients after 1 week FU[44]. Therefore, it was not possible to pool this study's data. Abscess formation at short-term FU was assessed in one study and was not present in either group[33]. Pain within 4 weeks FU ranged from 10-71% in the biodegradable group, while 0-65% of the patients treated with titanium presented with pain. No study reported analgesic usage. MMO was assessed in three studies. One study reported a similar postoperative MMO in both groups[39] while another study reported a higher postoperative MMO in the biodegradable group [50]. One study only gave bar graphs and could not provide numbers for the data synthesis[13]. Dehiscence ranged between 0-37% and 0-38% in the biodegradable and titanium groups, respectively. The RCTs and retrospective studies did not show statistical differences between both groups (RCTs: RR 1.68 (0.56;5.00), very low quality; Figure S5). Finally, plate exposure after short-term FU did not differ significantly on pooling the retrospective studies' data (RR 0.79 (0.23;2.71), very low quality, Figure S6).

Secondary endpoint data from 6-12 weeks FU were scarce (Table S5). Pain was reported in two RCTs but the studies measured pain differently[14,33]. MMO was only presented as bar graphs in one study[13], while another study reported similar postoperative MMOs in both groups[39]. TMJ-dysfunction was assessed in two studies and occurred in 7-8% and 7-16% of the patients after biodegradable and titanium osteosynthesis, respectively[8,38].

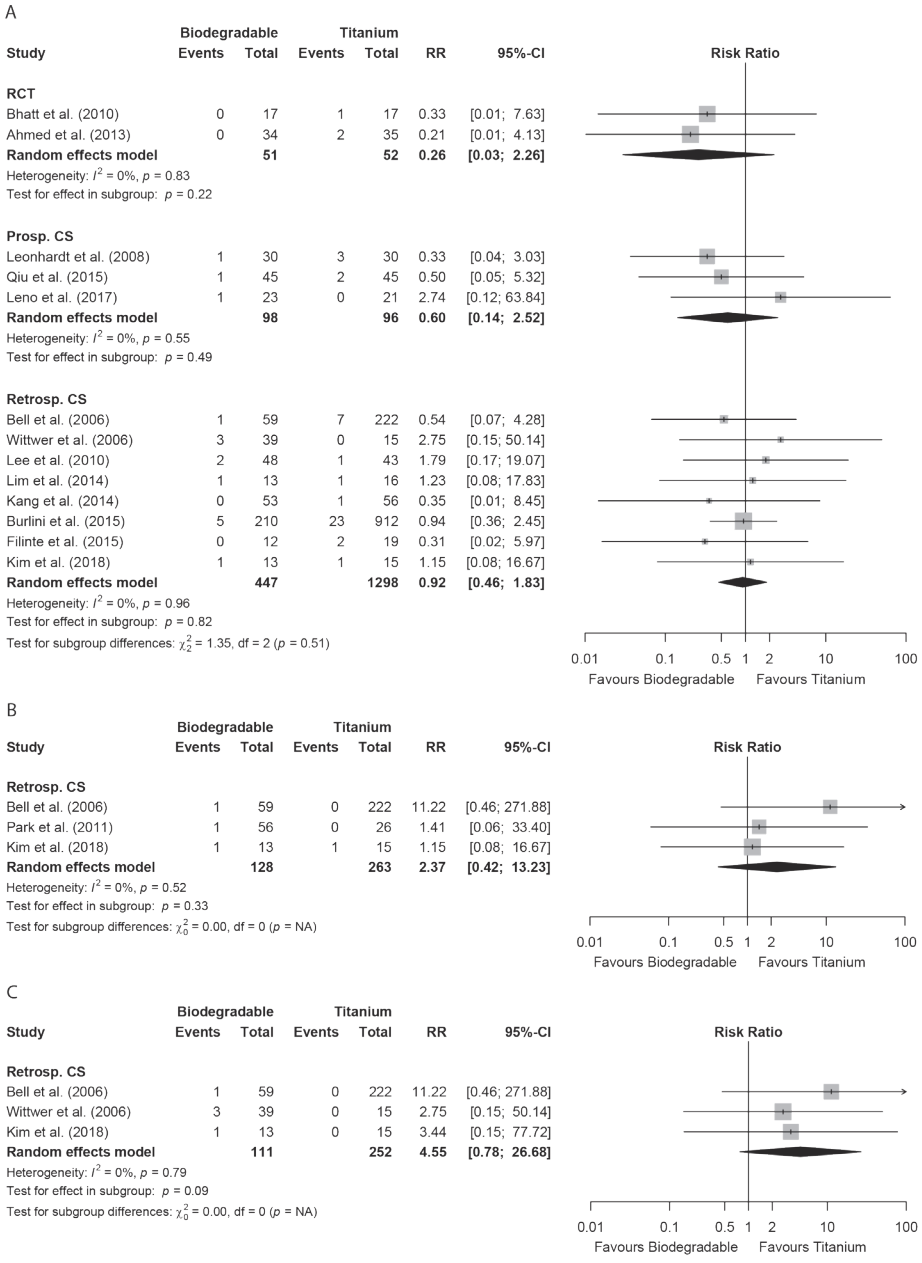
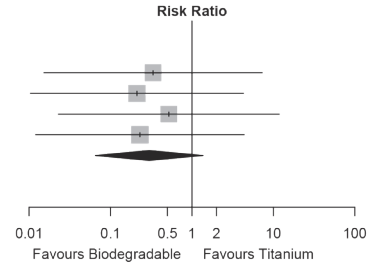


Figure 3. Forest plots of the secondary endpoints: (A) infection (<4 weeks follow-up); (B) abscess (>12 weeks follow-up); (C) swelling (>12 weeks follow-up); (D) palpability of plates/screws (>12 weeks follow-up); (E) satistifaction (>12 weeks follow-up); (F) symptomatic plate removal (overall follow-up), stratified by study design. *RCT, randomised controlled trials; Prosp. CS, prospective cohort studies; Retrosp. CS, retrospective cohort studies; RR, risk ratio; SMD, standardised mean difference; 95% CI, 95% confidence interval.*

D

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
Retrosp. CS						
Tripathi et al. (2013)	0	10	1	10	0.33	[0.02; 7.28]
Kang et al. (2014)	0	53	2	56	0.21	[0.01; 4.30]
Filinte et al. (2015)	0	12	1	19	0.52	[0.02; 11.79]
Kim et al. (2018)	0	13	2	15	0.23	[0.01; 4.38]
Random effects model		**88**		**100**	**0.30**	**[0.07; 1.37]**

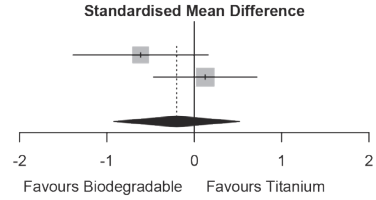
Heterogeneity: I^2 = 0%, p = 0.98
Test for effect in subgroup: p = 0.12
Test for subgroup differences: χ^2_0 = 0.00, df = 0 (p = NA)



E

Study	Biodegradable Total	Titanium Total	SMD	95%-CI
Mahmoud et al. (2016)	14	13	-0.61	[-1.39; 0.16]
Leno et al. (2017)	23	21	0.13	[-0.47; 0.72]
Random effects model	**37**	**34**	**-0.20**	**[-0.92; 0.52]**

Heterogeneity: I^2 = 55%, p = 0.14
Test for overall effect: p = 0.58



F

Study	Biodegradable Events	Biodegradable Total	Titanium Events	Titanium Total	RR	95%-CI
RCT						
Bhatt et al. (2010)	0	18	5	13	0.07	[0.00; 1.10]
Ahmed et al. (2013)	0	34	4	35	0.11	[0.01; 2.04]
Gareb et al. (2017)	0	8	3	10	0.18	[0.01; 2.97]
Random effects model		**60**		**58**	**0.11**	**[0.02; 0.57]**
Heterogeneity: I^2 = 0%, p = 0.89						
Test for effect in subgroup: p < 0.01						
Prosp. CS						
Leonhardt et al. (2008)	5	30	4	30	1.25	[0.37; 4.21]
Leno et al. (2017)	2	21	0	20	4.77	[0.24; 93.44]
Random effects model		**51**		**50**	**1.51**	**[0.49; 4.65]**
Heterogeneity: I^2 = 0%, p = 0.41						
Test for effect in subgroup: p = 0.47						
Retrosp. CS						
Wittwer et al. (2006)	3	39	2	15	0.58	[0.11; 3.12]
Park et al. (2011)	3	56	0	26	3.28	[0.18; 61.30]
Kang et al. (2014)	0	53	5	56	0.10	[0.01; 1.69]
Bhatt et al. (2015)	0	24	5	36	0.14	[0.01; 2.34]
Filinte et al. (2015)	0	12	1	19	0.52	[0.02; 11.79]
Kim et al. (2018)	0	13	3	15	0.16	[0.01; 2.90]
Random effects model		**197**		**167**	**0.39**	**[0.14; 1.11]**
Heterogeneity: I^2 = 0%, p = 0.53						
Test for effect in subgroup: p = 0.08						
Test for subgroup differences: χ^2_2 = 7.20, df = 2 (p = 0.03)						

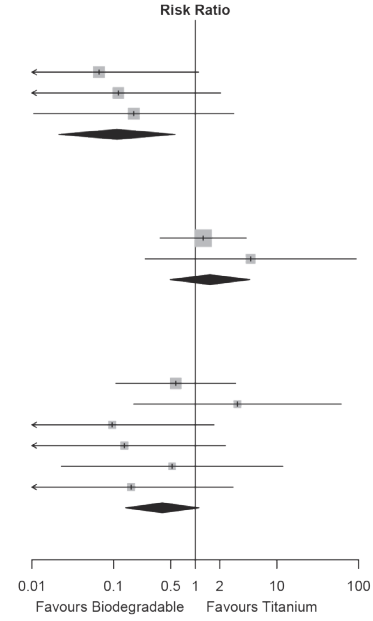


Figure 3 (cont.). Forest plots of the secondary endpoints: (A) infection (<4 weeks follow-up); (B) abscess (>12 weeks follow-up); (C) swelling (>12 weeks follow-up); (D) palpability of plates/screws (>12 weeks follow-up); (E) satistifaction (>12 weeks follow-up); (F) symptomatic plate removal (overall follow-up), stratified by study design. *RCT, randomised controlled trials; Prosp. CS, prospective cohort studies; Retrosp. CS, retrospective cohort studies; RR, risk ratio; SMD, standardised mean difference; 95% CI, 95% confidence interval.*

At long-term FU, the presence of pain was scarce in both groups (Table S5). Pooling of the retrospective data did not result in significant differences between both groups (RR 0.40 (0.10;1.68), very low quality, Figure S7). TMJ-dysfunction was assessed in one study with a FU of 1 year[8]. MFIQ was assessed in two publications of one RCT[2,35]. The MFIQ was better after >5 years FU in the biodegradable compared to the titanium group (17 (interquartile range 17-17) and 35 (21-41), respectively)[2]. Three retrospective studies reported abscess formation after 1-year[8,51] and 2-years FU[40]. No significant difference between both treatment groups was found (RR 2.37 (0.42;13.23), very low quality, Figure 3B). Long-term swelling assessment was generally scarce. One RCT with a FU >5 years reported 20% (1/5) and 25% (1/4) of cases with swelling in the biodegradable and titanium groups, respectively[2]. The retrospective studies showed no significant differences between both groups regarding long-term swelling (RR 4.55 (0.78;26.68), very low quality; Figure 3C). Palpability of plates and screws after long-term FU occurred only in the titanium group, but did not differ between both groups based on the data derived from the retrospective studies (RR 0.30 (0.07;1.37), very low quality, Figure 3D). Both groups' patients were similarly satisfied with the result after 1-year (prosp. CS: SMD -0.20 (-0.92;0.52), very low quality, Figure 3E; [13,39]) and >5-years FU[2].

Symptomatic titanium and biodegradable plate removal rates ranged from 0-39% and 0-17%, respectively (Table S5). The FU ranged from 8 weeks to >5 years (Table S4). The main reason for plate removal was chronic infection or disturbed wound healing. The data of one study was not included in the analysis as the authors could not provide the symptomatic plate removal rates and all the titanium plates were removed after 6-8 months due to possible growth disturbances[48]. Although the RCTs data showed a significant difference in plate removal rate in favour of the biodegradable group (RR 0.11 (0.02;0.57), moderate quality), the prospective and retrospective studies did not demonstrate any significant differences (Figure 3F). Subgroup analyses showed that the symptomatic plate removal rate did not differ significantly between the paediatric titanium and biodegradable groups (RR 1.11 (0.36;3.45). However, all the titanium plates were eventually removed from the paediatric patients due to possible growth disturbances, while only symptomatic biodegradable plates were removed in both studies which included paediatric patients. In adult patients, the symptomatic plate removal rate was significantly lower in the biodegradable group (RR 0.33 (0.13;0.84), Figure S8). Subgroup analyses of plate removal rates comparing mandibular versus other fractures showed no differences (mandibular fractures: RR 0.41 (0.13;1.34); other fractures: RR 0.56 (0.11;2.96), Figure S9). Comparing plate removal rates between ≤1

year and >1 year FU did not display any significant differences between different FU and treatment groups (Figure S10).

One RCT assessed total costs (i.e., direct and indirect costs) after 2 years FU, and found mean costs of 6137 ± 2980 and 8128 ± 5453 euros after biodegradable and titanium osteosynthesis, respectively[36]. The higher total costs in the titanium group was mainly due to a second operation for symptomatic plate removal. Finally, revision surgery (i.e., no plate removal) was performed in 0-8% and 0-7% of the patients after biodegradable and titanium osteosynthesis, respectively (retrospective studies: RR 1.16 (0.33;4.06), very low quality, Figure S11). The FU ranged from 8 weeks up to 74 months and the most common indication for revision surgery was abscess formation. The summary of the findings, including the quality of evidence of all the endpoints, is shown in Table 2.

Additional analyses

The results of a sensitivity analysis, including both-armed zero event studies, were not significantly different than the above mentioned analyses (available via the corresponding author). In the meta-regression analysis, study design had no effect on malocclusion in the intermediate FU (P>0.05) but had an effect on the reported risk ratios of plate removal (P=0.03). The prospective cohort studies had a significantly higher log risk ratio (2.61), whereas the retrospective studies did not (1.27) compared to the RCTs (-2.21; Table S6). No other meta-regression analyses could be performed. No funnel plots were constructed as none of the endpoints included >10 studies per study design.

The TSA showed that the required information size (RIS) for the infection and mobility of bone segment endpoints were not achieved and no boundaries were crossed (Table S7). Thus, based on the currently available evidence, TSA could not support the conclusions derived of conventional meta-analyses for these endpoints. Regarding the endpoints dehiscence and malocclusion at intermediate FU, the included patients made up <5% of the RIS and therefore a TSA could not be performed. The RIS for plate removal was achieved and the conventional test and the O'Brien-Fleming test boundary for benefit were crossed. Therefore, the provided evidence suggests that less symptomatic plate removal of biodegradable osteosynthesis occurred (Table S7). TSA could not be performed on all the other endpoints as these endpoints were assessed in no or in only a single randomized controlled trial, or were only assessed in total zero-event trials.

Table 2. Summary of findings with quality of evidence assessment.

Outcome	Randomized controlled trials					Prospective cohort studies					Retrospective cohort studies				
	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)
Perioperative endpoints															
Plate breakage[a]	Two studies, of which 1 had zero events (see Table S5)					Single study (see Table S5)					Four studies, of which 3 had zero events (see Table S5)				
Screw breakage[a]	718 (2)	17.13 (2.19; 134.18)	0 per 1000	NA	Moderate[1,3,5]	No studies					748 (3)	5.67 (0.98; 32.65)	0 per 1000	NA	Very low[1,3,4]
Operation time[b]	Single study (see Table S5)					Single study (see Table S5)					165 (3)	+0.72 (-0.17; 1.61)	NA	NA	Very low[1,3,4]
Handling by surgeon[b]	Single study (see Table S5)					No studies					No studies				
Short-term follow-up															
Malocclusion[a]	Single study (see Table S5)					Three studies of which 2 had zero events (see Table S5)					91 (2)	0.51 (0.06; 4.68)	36 per 1000	18 per 1000 (2;168)	Very low[1,3,4]
Infection[a]	103 (2)	0.26 (0.03;2.26)	58 per 1000	15 per 1000 (2;131)	Very low[1,3,4]	194 (3)	0.60 (0.14; 2.52)	52 per 1000	31 per 1000 (7;131)	Very low[1-4]	1745 (8)	0.92 (0.46; 1.83)	28 per 1000	26 per 1000 (13;51)	Very low[1,2,4]
Swelling[a]	Single zero-event study (see Table S5)					No studies					Two studies, of which one had 100% event rate in both groups (see Table S5)				
Abscess[a]	Single study (see Table S5)					No studies					No studies				
Pain[a]	Single study (see Table S5)					No studies					Single study (see Table S5)				
Analgesics used[a]	No studies					No studies					No studies				
MMO[b]	No studies					Two studies, of which one only reported postoperative MMO (see Table S5)					Single study (see Table S5)				

Table 2. *(continued)*

Outcome	Randomized controlled trials					Prospective cohort studies					Retrospective cohort studies				
	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)
Dehiscence[a]	126 (2)	1.68 (0.56;5.00)	75 per 1000	126 per 1000 (42;375)	Very low[1,3,4]	Four studies, of which 3 had zero events (see Table S5)					123 (3)	0.58 (0.18;1.84)	157 per 1000	91 per 1000 (28;289)	Very low[1-4]
Plate exposure[a]	Single zero-event study (see Table S5)					Single study (see Table S5)					1313 (3)	0.79 (0.23;2.71)	13 per 1000	10 per 1000 (3;35)	Very Low[1-4]
Intermediate follow-up															
Malunion[a]	Three zero-event studies (see Table S5)					Three zero-event studies (see Table S5)					312 (2)	0.93 (0.15; 5.75)	17 per 1000	16 per 1000 (3;98)	Very low[1,2,4]
Mobility bone segments[a]	100 (2)	2.11 (0.32;13.79)	21 per 1000	44 per 1000 (7;290)	Very low[1,3,4]	Single study (see Table S5)					Single zero-event study (see Table S5)				
Malocclusion[a]	117 (3)	1.01 (0.21;4.81)	53 per 1000	54 per 1000 (11;257)	Very low[1-4]	Three studies of which 2 had zero-events (see Table S5)					Two studies of which 1 had zero-events (see Table S5)				
Pain[a]	Two studies, different outcome measures (see Table S5)					No studies					No studies				
MMO[b]	No study					Two studies, of which one only reported postoperative MMO (see Table S5)					No studies				
TMJ-dysfunction[a]	No studies					Single study (see Table S5)					Single study (see Table S5)				

Table 2. *(continued)*

Outcome	Randomized controlled trials					Prospective cohort studies					Retrospective cohort studies				
	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)
Long-term follow-up															
Malocclusion[a]	Two studies with the same study population (see Table S5)					Three zero-event studies (see Table S5)					Single zero-event study (see Table S5)				
Pain[a]	Two zero-event studies with the same study population (see Table S5)					No studies					194 (3)	0.40 (0.10; 1.68)	44 per 1000	18 per 1000 (4;74)	Very low[1,3,4]
MMO[b]	No studies					Two studies, of which one only reported postoperative MMO (see Table S5)					Single study with only postoperative data (see Table S5)				
TMJ-dysfunction[a]	No studies					No studies					Single study (see Table S5)				
MFIQ[b]	Two studies with the same study population (see Table S5)					No studies					No studies				
Abscess[a]	Single study (see Table S5)					No studies					391 (3)	2.37 (0.42; 13.23)	4 per 1000	9 per 1000 (2;53)	Very low[1,4]
Swelling[a]	Two studies with the same study population (see Table S5)					No studies					363 (3)	4.55 (0.78;26.68)	0 per 1000	NA	Very low[1,4]
Palpability plate/screws[a]	Three studies, of which two had the same study population and one had zero events (see Table S5)					Single zero-event study (see Table S5)					188 (4)	0.30 (0.07;1.37)	60 per 1000	18 per 1000 (4;82)	Very low[1,3,4]
Satisfaction[b]	No studies					71 (2)	-0.20 (-0.92 ;0.52)	NA	NA	Very low[1-4]	Single study (see Table S5)				

Table 2. *(continued)*

Outcome	Randomized controlled trials					Prospective cohort studies					Retrospective cohort studies				
	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)
Overall follow-up															
Symptomatic plate removal[a]	118 (3)	0.11 (0.02;0.57)	207 per 1000	23 per 1000 (4;118)	Moderate[1,3,5]	104 (2)	1.51 (0.49; 4.65)	80 per 1000	121 per 1000 (39;372)	Very low[1,3,4]	364 (6)	0.39 (0.14; 1.11)	96 per 1000	37 per 1000 (13;107)	Very low[1-4]
Total costs[b]	Single study (see Table S5)					No studies					No studies				
Revision surgery (not plate removal)[a]	Three studies of which two had zero-events (see Table S5)					Single zero-event study (see Table S5)					1544 (5)	1.16 (0.33; 4.06)	13 per 1000	15 per 1000 (4;53)	Very low[1,2,4]

[a]: binary variable; [b]: continuous variable; GRADE, Grades of Recommendation, Assessment, Development and Evaluation Working Group system; Bio, biodegradable osteosynthesis; Tit, titanium osteosynthesis; RR, risk ratio (binary variables); SMD, standardised mean difference (continuous variables). NA, not applicable. [1]Downgraded one level due to high risks of bias identified across studies: the majority of studies had high or unclear risk of bias in at least two of the domains assessed; [2]Downgraded one level for inconsistency: substantial methodological or clinical heterogeneity that could not be accounted for in analyses; [3]Downgraded one lever for indirectness: the evidence of the original manuscripts were more restrictive than the review question; [4]Downgraded one level for imprecision: limits of effect estimate confidence interval are not consistent (i.e., cover both benefit and harm); [5]Upgraded one level due to large effect (i.e. RR<0.5 or RR>2.0, or SMD<-0.8 or SMD>+0.8).

Discussion

The present meta-analysis shows that the performance of biodegradable osteosynthesis is similar to titanium osteosynthesis regarding malunion, mobility of bone segments, and malocclusion after fixation of non-comminuted maxillofacial fractures. Additionally, no differences were found between both types of osteosyntheses regarding infection, dehiscence, plate exposure, pain, abscess formation, swelling, palpability of plates and/or screws, satisfaction, operative time, and revision surgery (i.e., no plate removal) at the predefined follow-up moments. The TSA showed that the required information size was not reached and thus the data remain inconclusive for these endpoints (i.e., may be false neutral). However, perioperative screw breakage during application occurred significantly more often in the biodegradable group compared to the titanium group. The symptomatic plate removal rate was significantly lower (i.e., 89% risk difference) in the biodegradable compared the titanium group. The TSA confirmed a true positive effect regarding plate removal, although only high risk of biased RCTs could be included. Finally, the meta-regression analysis showed that prospective cohort studies had significantly higher effect estimates of plate removal rate (i.e., in favour of the titanium group) compared to the RCTs and retrospective cohort studies.

Malunion was scarce in both intervention groups. Since pooled data derived from total zero-event studies is not available, the data from the RCTs and prospective cohort studies could not be synthesized. These outcomes, accompanied with the data on low mobility of bone segments and objective malocclusion, emphasise that both interventions are adequate for the fixation of maxillofacial fractures. This review focused on the objective and subjective malocclusion assessments by healthcare professionals or patients themselves, respectively. Although objective assessment of malocclusion is preferred over subjective ones for literature comparison purposes, we also feel that the patient's opinion regarding occlusion is of high importance. Three studies assessed subjective malocclusion[2,11,41], of which one small RCT assessed subjective malocclusion after >5-years FU[2]. In this latter study, subjective malocclusion was present in 50% of the titanium group compared to 0% in the biodegradable group. Also, the former group had worse mandibular function, as assessed by the MFIQ, even though these patients were not assessed as having an objective malocclusion at the 2 year FU[35]. Researchers should therefore also focus on long-term (i.e., >5-years FU) objective and subjective assessments of malocclusion and mandibular function as there may be discrepancy between both assessments and after long-term follow-up.

An essential aspect of biodegradable osteosynthesis is its ability to degrade and be resorbed in the human body, which may eliminate the need to remove implants in a second operation. Second plate removal operations are accompanied with an additional risk of complications[11]. The present review shows that biodegradable osteosyntheses are removed significantly less often compared to titanium ones due to symptoms. Although the subgroup analysis shows that symptomatic plate removal did not differ significantly between both interventions in paediatric patients, all the titanium plates were eventually removed (i.e., 100% of plates) due to possible growth disturbances, while only symptomatic biodegradable plates were removed from those patients (i.e., 12% of plates; Figure S9). Thus, titanium osteosyntheses will also eventually result in more re-operations compared to biodegradable osteosyntheses in paediatric patients. The present review also performed a subgroup analysis of plate removal rate between mandibular and other fractures. The biomechanical forces acting on the mandible are considerably higher compared to fractures elsewhere hence, this could result in loosening of the screws and subsequently to inflammation[2]. Only three of all the biodegradable osteosynthesis systems used in the included studies are certified to be used in the mandible, namely the Inion CPS (Inion Oy, Tampere, Finland), GrandFix (Gunze, Kyoto, Japan), and OsteotransMX (Teijin Medical Corp., Osaka, Japan)[53–55]. All the instructions for the other biodegradable systems explicitly state that these are contraindicated for use in load-bearing areas in adults, including the mandible[56–58] and yet, several studies implanted biodegradable osteosyntheses off-label[13,34,38,42]. Furthermore, the morphology and lesser vascularization of the mandible could negatively influence fixation and degradation of biodegradable osteosyntheses[2]. These factors have been suggested to contribute to higher symptomatic plate removal rate in the mandible compared to other facial fractures in both biodegradable and titanium osteosyntheses[2]. The current meta-analysis did not find significant differences between both osteosynthesis systems regarding symptomatic plate removal rate when mandibular and other fractures were compared separately. Finally, most of the included studies note a FU of up to 1 to 2 years. However, different studies have reported titanium and biodegradable plate removal rates, during maxillofacial surgery, of up to 19% after a 5-year FU[2,45], while no plates were removed between 1- and 5-years FU[59]. Therefore, future research should extend the FU beyond 2-years in order to assess the plate removal rate adequately in both intervention groups.

Foreign-body reactions after implantation of biodegradable osteosynthesis systems have been reported and remain a concern in the usage of such systems[2,9,10]. The present review did not find any differences, regarding the presence of swelling or abscess

formation, between both interventions after short- and long-term FUs, although it must be noted that only two studies had included patients with >3 years follow-up[2,40]. Also, revision surgery (i.e., non-plate removal) was scarce and there was no difference between both groups. The factors that are known to influence foreign-body reactions are implant related (i.e., polymer composition, plate size and shape, surface texture), recipient related (i.e., blood supply, temperature), and related to the location of plate placement (i.e., subcutaneous, epiperiosteal, subperiosteal). Of these factors, polymer composition has been studied the most[60–62]. The reported foreign body reactions occur predominately in biodegradable osteosyntheses with high proportion of PLLA (i.e., >70%) composition[2,9,10,63]. PLLA degrades in two phases to eventually form CO_2 and H_2O as final products: early degradation via hydrolysis produces crystalline structures which undergo secondary hydrolysis. Secondary hydrolysis is the rate-limiting step and depends highly on the crystallinity and hydrophobicity of the intermediate products. L-isomers form crystalline products that are highly hydrophobic and therefore more resistant to degradation and resorption compared to D-isomers[60]. PLLA crystalline particles have been identified intra-cellularly up to 5.7 years after fixation of zygomatic fractures in patients[10]. Only one of the included studies reported sterile abscess formation which was incised and drained during a second operation[40]. That study used a 70%-30% PLLA/PDLLA biodegradable osteosynthesis system. More amorphous (co-)polymer compositions such as polyglycolide (PGA), poly(lactic-co-glycolic acid) (PLGA), or PDLLA are more hydrophilic and undergo degradation and resorption more quickly[60]. Tissue response to PLLA has been extensively studied in animals and patients, with a long-term follow-up (i.e., up to 6 years), whereas no long term data is currently available for PGA, PLGA, or PDLLA (co-)polymer compositions. Current *in vivo* studies including these biodegradable systems have been performed with a follow-up up to 18 months[60,62,64]. Long-term *in vivo* degradation of these (co-)polymer compositions are currently being investigated by our research group and the results are eagerly being awaited. Additionally, future research should preferably incorporate the other factors that contribute to foreign-body reactions.

Data about analgesia usage, MMO, MFIQ, TMJ-dysfunction, handling of osteosynthesis systems by surgeons, perioperative plate breakage, and total costs could not be synthesised due to a lack of studies which had (adequately) assessed these endpoints. Analgesia usage was not assessed in any of the included studies and TMJ-dysfunction was only noted in one recent study[8]. Data of (postoperative) MMO could not be synthesized on account of only a few studies reporting MMO or because the authors could not provide the data. MFIQ was only assessed in two publications consisting of the same study

population[2,35]. Thus, there is currently insufficient evidence to provide conclusions regarding mandibular and TMJ-function after both interventions. Although pre-operative endpoint data are preferred in order to assess the effect of the osteosynthesis system on these endpoints, the patients presenting with maxillofacial fractures often have restricted MMO and impaired mandibular function as a consequence of the trauma. It is unlikely that any data will be at hand regarding mandibular function before the fracture. Therefore, future researchers should collect post-operative data regarding TMJ-function and MMO or use validated questionnaires (e.g., MFIQ) to make adequate assessments of mandibular function and to enable comparisons with healthy subjects.

Total costs were assessed in only one small RCT and titanium osteosyntheses were associated with higher costs compared to biodegradable ones, mainly due to the additional costs of a second operation for symptomatic plate removal[36]. Finally, only a small RCT reported the handling of osteosynthesis systems by surgeons[33]. The differences between both systems were small and the authors report that more exposure to biodegradable systems by surgeons could diminish this difference.

The meta-regression analysis showed that the effect estimates of plate removal rates by prospective studies were significantly higher compared to randomized controlled trials and retrospective studies. One of the prospective studies included in this analysis allowed the patients to voluntarily choose the fixation material[13]. The patient's choice is always dependent on the provided information, and therefore dependent on the healthcare professional. The other study could not randomize the patients due to the occasional unavailability of the required plating systems[11]. Both studies are therefore prone to selection bias. Selection bias has been shown to exaggerate effect estimates[16] and, thus, this could explain the difference in the effect estimates between the different study designs.

Comparison to other systematic reviews

A systematic review in 2013, comparing complications after fracture fixation between five studies, showed that biodegradable osteosyntheses had lower overall complication rates compared to titanium osteosyntheses (RR 0.71, 95% CI 0.52;0.97)[15]. A subgroup analysis of these complications indicated that only the palpability of the plates remained significantly lower in the biodegradable group (RR 0.38, 95% CI 0.22;0.68). However, that review used a fixed-effects model, while methodological and clinical heterogeneity was clearly present (e.g., different study designs, composition of biodegradable plates), and it did not perform an assessment of the endpoints in relation to follow-up. Additionally, the difference in palpability was based on a single small retrospective study[65]. The

results of the present review show that, according to current evidence, there is no significant difference in complications between both interventions. In particular, there is no difference in long-term palpability between both interventions. Furthermore, the aforementioned review concluded that no publication bias was present by using funnel plots, although only five studies were included and the endpoints were only assessed based on one (e.g., palpability) to four studies (e.g., infection). Funnel plots with ≤10 studies are underpowered and inconclusive, and thus, their usage is discouraged if insufficient studies could be included for a meta-analysis[16,25–27]. Finally, the authors do not provide any data regarding inter-observer agreement and do not incorporate risk of bias in the interpretation of the results. We therefore express our concerns about the conclusions drawn in that particular review.

Quality of the evidence

All the studies considered had two or more domains assessed as high risk of bias owing to the nature of the intervention. Biodegradable plates and screws are easily distinguished by surgeons (i.e., no blinding possible) and are not visible on radiographs while titanium osteosyntheses are visible (i.e., no blinding of the outcome assessment is possible). Therefore, these two domains do not result in differences in quality between the included studies.

The evidence was of very low or moderate quality as assessed by the GRADE system. The main reasons of downgrading the quality of evidence was high risk of bias, indirectness, and imprecision of the data. Moderate quality evidence was found for perioperative screw breakage and plate removal rate. Infection (<4 weeks FU), dehiscence (<4 weeks FU), mobility of bone segments (6-12 weeks FU), and malocclusion (6-12 weeks FU) were assessed as very low quality. The quality of evidence of the endpoints malunion and pain (6-12 weeks FU), and MFIQ, swelling, and palpability of plates/screws (>12 weeks FU) could not be assessed due to zero event studies, different outcome measures, or studies that consisted of the same study population with different follow-up moments. Also, the RCTs data regarding revision surgery could not be pooled due to zero event studies.

The data derived from the prospective and retrospective cohort studies were assessed as very low quality. Endpoints based on very low quality evidence cannot be used to make recommendations to surgeons and should therefore be interpreted with caution[16].

Strengths and limitations

The strengths of the current meta-analysis are: the transparent and robust methodology used, based on a pre-specified protocol, the PRISMA statement, and the Cochrane Handbook. Also, a comprehensive and up-to-date literature search was performed without language or period restrictions. A range of relevant endpoints with predefined follow-up moments were included. Furthermore, study eligibility, data-extraction, and risk of bias assessment were performed independently by two reviewers with excellent inter-observer agreement. Also, we used TSA to increase the reliability of our data and to determine the required information size of each endpoint. Finally, certainty of evidence was assessed in duplicate using GRADE.

The limitations of this review include the low quality of the studies due to high risk of bias. Therefore, we cannot exclude a biased effect estimate. Additionally, clinical heterogeneity could not be excluded due to the inclusion of studies with different biodegradable and titanium systems (i.e., different compositions), different sized osteosynthesis systems, and the differences in the application and duration of the MMF. Subgroup analysis (i.e., mandibular versus other fractures) of the primary endpoints could not be performed due to a lack of studies. Finally, some data could not be retrieved from the authors of the original manuscripts despite multiple efforts and could therefore not be included in this review.

Implications for future research

This review shows that the quality of the current evidence ranges from very low to moderate and high quality research is therefore necessary. The main reason for downgrading the evidence was the high risk of bias in all of the included studies. Although blinding the surgeons and the outcome assessors is not possible due to the nature of the intervention, and thus contributes substantially to the risk of bias, none of the studies could be assessed as low risk of bias when these two domains of blinding were excluded. We, therefore, suggest that future RCTs should be performed with long-term follow-up using pre-specified and well-defined protocols. The pre-specified protocol should pay particular interest to: (i) well-defined endpoints to minimize reporting bias, (ii) adequate follow-up of the corresponding endpoints to minimize attrition bias, and (iii) well-defined indications for plate removal to minimize detection bias. Also, more patient reported outcomes (e.g., subjective malocclusion, MFIQ) are preferred. Additionally, the reporting of patient characteristics, surgical procedures, and outcomes should be improved. In particular, researchers should include details regarding the osteosynthesis systems used (i.e., composition, sizes, osteosynthesis principle), alcohol and tobacco usage, as these factors are known to compromise wound

healing and decrease vascularization intra-orally which may affect degradation and resorption rates, and the use of, reasons for, and duration of, the MMF. We advocate that future studies should comply with the CONSORT guidelines to ensure high quality reporting of all aspects of the methodology and results[66]. This enables appraisal, interpretation, and pooling of future data. Finally, future studies should focus on the cost-effectiveness of biodegradable systems, including direct (i.e., perioperative costs) and indirect costs (e.g., second operations, absence from work).

Conclusions

Based on all currently available evidence after both narrative review and meta-analyses, biodegradable and titanium osteosyntheses are similar regarding the efficacy and morbidity of fixation of non-comminuted maxillofacial fractures. However, perioperative screw breakage occurred significantly more often in the biodegradable compared to the titanium group. The symptomatic plate removal rate was significantly lower after biodegradable compared to titanium fixation in this population. Combining these aspects, current available evidence shows that biodegradable osteosynthesis is a viable alternative to titanium osteosynthesis after maxillofacial trauma. Due to the low to moderate quality of the included studies, the results of this systematic review should be interpreted with caution.

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Conflict of interests

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Supplementary data

Supplementary tables:

Table S1: Electronic databases with the corresponding search details.

Table S2: Endpoints divided into five time units.

Table S3: Excluded articles with reasons for exclusion after full-text screening.

Table S4: Characteristics of the included studies.

Table S5: All assessed endpoints of the included studies.

Table S6: Results of meta-regression analysis to determine the effect of study design to the log risk ratio of plate removal using a random effects model.

Table S7: Input and results of the trial sequential analyses using the random-effects (DerSimonian-Laird) model with the corresponding interpretations.

Supplementary figures:

Figure S1: Example graph with explanation of the trial sequential analysis stratified by study design.

Figure S2: Forest plot of the endpoint malocclusion (<4 weeks follow-up) of studies including pediatric patients versus adult patients.

Figure S3: Forest plot of the endpoint perioperative screw breakage stratified by study design.

Figure S4: Forest plot of the endpoint operative time stratified by study design.

Figure S5: Forest plot of the endpoint dehiscence (<4 weeks follow-up) stratified by study design.

Figure S6: Forest plot of the endpoint plate exposure (<4 weeks follow-up) stratified by study design.

Figure S7: Forest plot of the endpoint pain (>12 weeks follow-up) stratified by study design.

Figure S8: Forest plot of the endpoint plate removal (overall follow-up) of studies including pediatric patients versus adult patients.

Figure S9: Forest plot of the endpoint plate removal (overall follow-up) of studies including patients with mandibular fractures versus non-mandibular fractures.

Figure S10: Forest plot of the endpoint plate removal (overall follow-up) stratified by ≤1-year and >1-year follow-up.

Figure S11: Forest plot of the endpoint revision surgery (overall follow-up) stratified by study design.

Table S1. Electronic databases with the corresponding search details.

Database	Search terms	Date	Hits	Updated search date	Additional hits after update
PubMed	("Orthognathic Surgery"[Mesh] OR "Orthognathic Surgical Procedures"[Mesh] OR "Osteotomy, Le Fort"[Mesh] OR "Osteotomy, Sagittal Split Ramus"[Mesh] OR "Mandibular Advancement"[Mesh] OR "Facial Bones/surgery"[Mesh] OR "Facial Injuries"[Mesh:NoExp] OR "Maxillofacial Injuries"[Mesh] OR "Maxillofacial Abnormalities"[Mesh] OR "Malocclusion/surgery"[Mesh] OR maxill*[tiab] OR mandib*[tiab] OR jaw[tiab] OR orthognat*[tiab] OR craniofac*[tiab] OR craniomaxil*[tiab] OR retrognat*[tiab] OR orthodont*[tiab] OR zygom*[tiab] OR split ramus[tiab] OR "Facial injuries"[MeSH] OR ((orbit*[tiab] OR facial[tiab] OR face[tiab] OR nose[tiab] OR nasal[tiab]) AND (fract*[tiab] OR injur*[tiab] OR reconstruct*[tiab]))) AND ("Absorbable Implants"[Mesh] OR "Internal Fixators"[Mesh] OR "Fracture Fixation, Internal"[Mesh] OR plate*[tiab] OR screw*[tiab] OR miniscrew*[tiab] OR miniplate*[tiab] OR implant*[tiab] OR osteosynth*[tiab] OR osseointegrat*[tiab] OR osteofixat*[tiab] OR osteotom*[tiab] OR fixat*[tiab]) AND ("Absorbable Implants"[Mesh] OR bioresorb*[tiab] OR biodegrad*[tiab] OR bioabsorb*[tiab] OR bioadsorb*[tiab] OR absorb*[tiab] OR resorb*[tiab] OR adsorb*[tiab] OR "Lactic acid"[MeSH] OR lactic acid[tiab] OR "Polyglycolic acid"[MeSH] OR polyglycolic acid[tiab] OR "Hydroxyapatites"[MeSH] OR hydroxyapatite[tiab] OR biologically inert[tiab]) NOT ("Case Reports" [Publication Type] OR "Review" [Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	29 January 2018	2257	20 April 2019	164
EMBASE	('craniofacial surgery'/de OR 'cranioplasty'/exp OR 'face surgery'/de OR 'maxillofacial surgery'/exp OR 'nose surgery'/exp OR 'orthognathic surgery'/exp OR 'orbit reconstruction'/exp OR 'maxillofacial injury'/de OR 'skull injury'/exp OR 'skull'/exp OR 'face fracture'/exp OR 'skull malformation'/exp/dm_su OR 'craniofacial malformation'/exp OR 'face malformation'/dm_su OR 'malocclusion'/exp/dm_su OR (maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR zygom* OR 'split ramus' OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct*))):ab,ti)	31 January 2018	2269	20 April 2019	182

Table S1. *(continued)*

Database	Search terms	Date	Hits	Updated search date	Additional hits after update
EMBASE	AND ('bone plate'/exp OR 'bone screw'/exp OR 'internal fixator'/exp OR 'fracture fixation'/exp OR 'bioabsorbable screw'/exp OR 'biodegradable screw'/exp OR 'biodegradable implant'/exp OR 'orthopedic fixation device'/de OR (plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*):ab,ti) AND ('biodegradable implant'/exp OR 'bioabsorbable screw'/exp OR 'biodegradable screw'/exp OR 'lactic acid'/exp/mj OR 'polyglycolic acid'/exp/mj OR 'hydroxyapatite'/exp/mj OR 'biosorbent'/exp OR (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR 'lactic acid' OR 'polyglycolic acid' OR hydroxyapatite OR 'biologically inert'):ab,ti) NOT (('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('review'/exp OR 'case report'/exp OR 'conference abstract'/it)	31 January 2018	2269	20 April 2019	182
Cochrane Central Register of Controlled Trials	(maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND (plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*) AND (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert")	30 January 2018	475	20 April 2019	132

Table S2. Endpoints divided into five time units.

Time unit	Endpoints
Perioperative	Plate and/or screw breakage, operation time, and handling by surgeon
Short-term (0-4 weeks; soft tissue healing)	Infection, dehiscence, malocclusion, pain, swelling, plate exposure, MMO, abscess, and analgesics used
Intermediate follow-up (6 – 12 weeks; bone healing)	Malunion, mobility of bone segments, malocclusion, MMO, TMJ-dysfunction, and pain
Long-term follow-up (>12 weeks; degradation effects)	Palpability of plate and screws, malocclusion, pain, swelling, satisfaction, TMJ-dysfunction, MMO, abscess, and MFIQ
Overall	Symptomatic plate removal, additional surgery (not plate removal), and total costs

MMO: maximal mouth opening; TMJ-dysfunction: temporomandibular joint dysfunction; MFIQ: Mandibular Function Impairment Questionnaire

Table S3. Excluded articles with reasons for exclusion after full-text screening.

#	Author (year)	Reason for exclusion	Reference
1	Ahn et al. (2010)	Surgical procedure not relevant for this review	[1]
2	Bakelen et al. (2014)	Surgical procedure not relevant for this review	[2]
3	Ballon et al. (2012)	Surgical procedure not relevant for this review	[3]
4	Blakey et al. (2014)	Surgical procedure not relevant for this review	[4]
5	Bohm et al. (1998)	Insufficient details reported	[5]
6	Bouletreau et al. (2005)	Both groups consist of biodegradable and titanium osteosynthesis	[6]
7	Champy et al. (1992)	No control group	[7]
8	Cheung et al. (2004)	Surgical procedure not relevant for this review	[8]
9	Cheung et al. (2008)	Surgical procedure not relevant for this review	[9]
10	Costa et al. (2006)	Surgical procedure not relevant for this review	[10]
11	Dhol et al. (2008)	Surgical procedure not relevant for this review	[11]
12	Ferrretti et al. (2002)	Surgical procedure not relevant for this review	[12]
13	Fuente del Campo et al. (1996)	No control group; Biodegradable plates with titanium screws used	[13]
14	Harada et al. (1997)	Surgical procedure not relevant for this review	[14]
15	Hashiba et al. (2007)	No relevant endpoints for this review	[15]
16	Ho et al. (2011)	No pure biodegradable group, only titanium or mixed groups	[16]
17	Hwang et al. (2017)	No pure biodegradable group, only titanium or mixed groups	[17]
18	Iatrou et al. (2010)	Insufficient details regarding comparison of both interventions	[18]
19	Illi et al. (1989)	Children with syndromic disorders included	[19]
20	Imola et al. (2002)	Review paper	[20]
21	Janickova et al. (2018)	All data are reported by fracture-level. Authors were not able to provide data by patient-level.	[21]
22	Kallela et al. (1999)	Review paper	[22]
23	Kobayashi et al. (2004)	No control group	[23]
24	Kretschmer et al. (2011)	Surgical procedure not relevant for this review	[24]
25	Landes et al. (2006)	Surgical procedure not relevant for this review	[25]
26	Landes et al. (2007)	Surgical procedure not relevant for this review	[26]
27	Landes et al. (2014)	Patients with cleft lip and palate included	[27]
28	Landes et al. (2015)	No control group	[28]
29	Lee et al. (2014)	Surgical procedure not relevant for this review	[29]
30	Lee et al. (2014)	Surgical procedure not relevant for this review	[30]
31	Lee et al. (2014)	Surgical procedure not relevant for this review	[31]
32	Liu et al. (2016)	Surgical procedure not relevant for this review	[32]
33	Matthews et al. (2003)	Surgical procedure not relevant for this review	[33]
34	Menon et al. (2007)	Same population as Menon et al. (2012), with shorter follow-up	[34]
35	Norholt et al. (2004)	Surgical procedure not relevant for this review	[35]
36	Obwegeser et al. (1994)	No biodegradable osteosynthesis used, only resorbable sutures	[36]
37	Paeng et al. (2012)	Surgical procedure not relevant for this review	[37]

Table S3. *(continued)*

#	Author (year)	Reason for exclusion	Reference
38	Park et al. (2010)	Surgical procedure not relevant for this review	[38]
39	Pistner et al. (1991)	Review paper	[39]
40	Stockmann et al. (2010)	Surgical procedure not relevant for this review	[40]
41	Stuck et al. (2011)	Review paper	[41]
42	Tan et al. (2011)	Surgical procedure not relevant for this review	[42]
43	Tuovinen et al. (2010)	Surgical procedure not relevant for this review	[43]
44	Turvey et al. (2006)	Surgical procedure not relevant for this review	[44]
45	Ueki et al. (2005)	Surgical procedure not relevant for this review	[45]
46	Ueki et al. (2006)	Surgical procedure not relevant for this review	[46]
47	Ueki et al. (2009)	Surgical procedure not relevant for this review	[47]
48	Ueki et al. (2011a)	Surgical procedure not relevant for this review	[48]
49	Ueki et al. (2011b)	Surgical procedure not relevant for this review	[49]
50	Ueki et al. (2012)	Surgical procedure not relevant for this review	[50]
51	Ueki et al. (2015a)	Surgical procedure not relevant for this review	[51]
52	Ueki et al. (2015b)	Surgical procedure not relevant for this review	[52]
53	Ueki et al. (2017)	Surgical procedure not relevant for this review	[53]
54	Yoshioka et al. (2012)	Surgical procedure not relevant for this review	[54]
55	Yu et al. (2014)	Surgical procedure not relevant for this review	[55]
56	Zheng et al. (2001)	No control group	[56]

Table S4. Characteristics of the included studies.

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Fractures included (n)		Intra-operative switches (B to T, n)	Osteo-synthesis principle	Duration of MMF		Follow-up	
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*			*T*	*B*	*T*	*B*
Randomized controlled trials																
Bhatt et al. (2010)[57]	21	19	20/1	18/1	28.7 (range 18-48)	26.6 (range 18-46)	Synthes (2.0)	Inion CPS[a] (2.5)	21 mandible	19 mandible	1	Champy's principle[k]	No	2 wks	1 and 2 mos	
Buijs et al. (2012)[58]	10	8	8/2	8/0	37±12	35±16	KLS Martin (mandible 2.0; zygoma & Le Fort I: 1.5)	Inion CPS[a] (mandible 2.5; zygoma & Le Fort I: 2.0)	6 mandible, 3 zygoma, and 1 Le Fort I	4 mandible, 4 zygoma	4	Champy's principle[k]	Soft guiding elastics; up to 2wks		8 wks	
Ahmed et al. (2013)[59]	35	34	31/4	31/3	34.3±10.7	31.3±11.1	True-dynamic	Bonaplates[b]	Mandible, unknown number				1 wks rigid		89± 6 dys	90± 4 dys
Bakelen et al. (2013)[60]	10	8	8/2	8/0	37±12	35±16	KLS Martin (mandible 2.0; zygoma & Le Fort I: 1.5)	Inion CPS[a] (mandible 2.5; zygoma & Le Fort I: 2.0)	6 mandible, 3 zygoma, and 1 Le Fort I	4 mandible, 4 zygoma	4	Champy's principle[k]	Soft guiding elastics; up to 2wks		1 and 2 yr	
Bakelen et al. (2015)[61]	10	8	8/2	8/0	37±12	35±16	KLS Martin (mandible 2.0; zygoma & Le Fort I: 1.5)	Inion CPS[a] (mandible 2.5; zygoma & Le Fort I: 2.0)	6 mandible, 3 zygoma, and 1 Le Fort I	4 mandible, 4 zygoma	4	Champy's principle[k]	Soft guiding elastics; up to 2wks		8 wks and 1 yr	
Sukegawa et al. (2016)[62]	6	6	5/1	4/2	48.0	53.2	Synthes (1.55)	GrandFix (2.2)[c]	Zygoma			NA	Soft guiding elastics when appropriate		'Every 2 months'	

Table S4. *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Fractures included (n)		Intra-operative switches (B to T, n)	Osteo-synthesis principle	Duration of MMF		Follow-up	
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*			*T*	*B*	*T*	*B*
Gareb et al. (2017)[63]	10	8	8/2	8/0	37±12	35±16	KLS Martin (mandible 2.0; zygoma & Le Fort I: 1.5)	Inion CPS[a] (mandible 2.5; zygoma & Le Fort I: 2.0)	6 mandible, 3 zygoma, and 1 Le Fort I	4 mandible, 4 zygoma	4	Champy's principle[k]	Soft guiding elastics; up to 2wks		95 (77-111) mos	98 (80-111) mos
Prospective cohort studies																
Leonhardt et al. (2008)[64]	30	30	28/2	24/3	32 (range 15-75)	24 (range 15-45)	KLS Martin (2.0)	Inion CPS[a] (2.0 and 2.5)	44 mandible	37 mandible		Champy's principle[k]	No		1 and 6 wk, and 6 mos	
Qiu et al. (2015)[65]	45	45	31/14	33/12	28.1±3.4 (range 19-52)	27.0±3.2 (range 20-54)	Bang Xi (2.0)	BioSorb FX[d] (2.0)	Mandible, unknown number				Yes		3 mos	
Mahmoud et al. (2016)[66]	13	14	9/4	9/5	34.1±16.1	29.2±11.2		Bonaplates[b]	13 zygoma	14 zygoma		NA	NA		1 yr	
Leno et al. (2017)[67]	20	21	15/5	15/6	27.3±10	26.2±9.7	Stryker (symphysis, parasymphysis, and body fracture: 2.3; angle fracture: 2.0)	Bonaplates[b] (2.5)	21 mandible	23 mandible			No	Soft guiding elastics; 2wks	2, 4, and 6 wks & 3, 6, and 12 mos	

Table S4. *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Fractures included (n)		Intra-operative switches (B to T, n)	Osteo-synthesis principle	Duration of MMF		Follow-up	
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*			*T*	*B*	*T*	*B*
Retrospective cohort studies																
Bell et al. (2006)[68]	222	59	203/62		29.1 (range 2-92)		Synthes (1.3, 1.5, or 2.0)	Synthes[e] (1.5 or 2.0)	14 Le Fort I, 7 Le Fort II, 15 Le Fort III, 73 ZMC, 20 orbit, 14 frontal sinus, 138 mandible	5 Le Fort I, 1 Le Fort II, 1 Le Fort III, 33 ZMC, 6 orbit, 7 frontal sinus, 7 mandible	NA	AO/ASIF principle[l]	Condyle fracture: 2 wks; Soft guiding elastics when appropriate		3 wks to 3 ys	
Wittwer et al. (2006)[69]	15	39	12/3	37/12	35.5±14.8 (range 17-71)	34.6±14.8 (range 17-71)	KLS Martin	LactoSorb[f] (1.5), BioSorb FX[d] (1.5), or Delta[g] (1.7)	ZMC fractures, unknown number of fractures		NA	NA	NA		6, 12, and 24 mos	
Lee et al. (2010)[70]	43	48	65/26		28.4 (range 11-69)		Synthes	BioSorb FX[d]	44 mandible	47 mandible	NA	Champy principle's[k]	7.4 dy rigid		1, 3, 6, 12 mos	
Park et al. (2011)[71]	26	56	24/2	48/8	36.4 (range 16-83)		Solco Intermed	BioSorb FX[d]	Maxillary, maxillozygomatic fractures without orbital wall, skull base, Le Fort and orbital wall fractures.		NA	NA	NA		12 mos	
Menon et al. (2012)[72]	20	20	16/4	17/3	31.3 (range 21-51)	30.5 (range 20-41)	Stryker (2.0)	Delta[g] (2.2)	ZMC fractures, unknown number of fractures		NA	NA	NA		3, 6, and 12 mos	
Tripathi et al. (2013)[73]	10	10	17/3		range 17-50		1.7	Inion CPS[a] (1.5)	ZMC fractures, unknown number of fractures		NA	NA	NA		3 and 6 mos	

Table S4. *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Fractures included (n)		Intra-operative switches (B to T, n)	Osteo-synthesis principle	Duration of MMF		Follow-up	
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*			*T*	*B*	*T*	*B*
Kang et al. (2014)[74]	56	53	46/10	40/13	34.6±9.9	37.5±16.2		Conmed ` Linvatec[h]	28 ZMC, 16 Le Fort I, 5 frontal sinus, 2 nasoethmoidal, 5 complex fractures	23 ZMC, 17 Le Fort I, 8 frontal sinus, 1 nasoethmoidal, 4 complex fractures	NA	NA	NA		39.4±14.5 mos	34.4±9.9 mos
Lim et al. (2014)[75]	16	13	15/1	12/1	28.3±12.9	24.2±6.9	Osteo-fit and Synthes	Inion CPS[a] and BioSorb FX[d]	"Combined mandibular symphysis and angle fractures", unknown number		NA	Champy's principle[k]	2.38 dy rigid	2.56 dy rigid	1 and 2 wks & 1 and 3 mos	
Bhatt et al. (2015)[76]	20	24	19/1	21/3	26.4±10.1	26.9±8.6	Synthes (2.0)	Inion CPS[a] (2.5)	97 mandible		NA	Champy's principle[k]	No		>6 mos	
Burlini et al. (2015)[77]	912	210	536/382	126/84	8.6±0.3	7.7±0.2		KLS Martin[i] (1.6 and 2.1)	581 mandible, 165 orbit, 163 maxilla	52 Le Fort I, 34 Le Fort II, 11 Le Fort III, 49 orbit, 35 mandible, 29 others	NA		No		1, 6, 12 and 24 mos	
Filinte et al. (2015)[78]	19	12			9.2 (4-14 yr)	6.9 (range 20 mo-11 yr)		LactoSorb[f] (2.0)	27 mandible	16 mandible	NA		No	No, unless problems in stability	41 (11-74) mos	22 (8-35) mos

Table S4. *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Fractures included (n)		Intra-operative switches (B to T, n)	Osteo-synthesis principle	Duration of MMF		Follow-up	
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*			*T*	*B*	*T*	*B*
Wu et al. (2017)[79]	55	53	30/25	28/25	30	33		Bonaplates[b] (2.5)	55 ZMC	53 ZMC	NA	NA	NA		8.6±3.2 mos	10.6± 4.3 mos
Kim et al. (2018)[80]	15	13	12/3	11/2	32.5±15.0	33.8±15.3	Jeil Lefort system (2.0)	Takiron Osteotrans MX[j] (2.0)	21 mandible	18 mandible	NA		Soft guiding elastics; 2wks		6.7±4.1 mos	16.9±9.0 mos

[a]: Inion CPS (79/15/6 PLLA/PDLLA/TMC); [b]: Bonaplates (90/10 PLLA/PDLLA); [c]: GrandFix (100 PLLA); [d]: BioSorb FX (self-reinforced 70/30 PLLA/PDLLA); [e]: Synthes (70/30 PLLA/PDLLA); [f]: LactoSorb (82/18 PLLA/PGA); [g]: Delta (85/5/10 PLLA/PDLA/PGA); [h]: Conmed Linvatec (self-reinforced PLLA/PDLLA); [i]: KLS Martin (different copolymer compositions possible, details not reported in original manuscript); [j]: Takiron Osteotrans MX (40/60 uHA/PLLA); [k]: Champy's principle for osteosynthesis of the mandible, i.e. osteosynthesis plates should be fixated in the tensile zone (upper border) of the mandible; [l]: the AO/ASIF principle for osteosynthesis of the mandible, i.e. osteosynthesis plates should be fixated in the compression zone (lower border) of the mandible. *T, titanium osteosynthesis; B, biodegradable osteosynthesis; SD, standard deviation; IQR, interquartile range; M, male; F, female; yrs, years; mos, months; wks, weeks; MMF, maxillomandibular fixation; ZMC, zygomaticomaxillary complex. PLLA, poly-L-lactic acid; PDLLA, poly-D,L-lactic acid; TMC, trimethylene carbonate; PGA, polyglycolic acid; uHA, unsintered hydroxyapatite; AO/ASIF: Association for Osteosynthesis/Association for the Study of Internal Fixation. Empty cells: not reported.*

Table S5. All assessed endpoints of the included studies.

Study name (year)	Osteosynthesis system	Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; meadin, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
		Perioperative endpoints				Short-term follow-up								Intermediate follow-up						Long-term follow-up										Overall follow-up		
Randomized controlled trials																																
Bhatt (2010)[57]	**B**	0	1.8			23.5 (O)	0		52.2		20.0[f]				5.6	11.1 (O)	37.5												0		0
	T	0	0			23.5 (O)	5.9		45.8		9.4[f]				0	7.7 (O)	10.5												38.5		0
Buijs (2012)[58]	**B**			130 ± 85	7 (6-8)				0		0	0[d]		0	0	0 (O)	0.6 ±1.8[a]												0		0
	T			111 ± 92	8 (7-8)				0		0	0[d]		0	0	22.2 (O)	13.2 ± 23.6[a]												0		0
Ahmed (2013)[59]	**B**	5.7	7.4				0				5.9[f]			0	5.9	2.9 (O)													0		
	T	0	0				5.7				5.7[f]			0	2.9	0 (O)													11.4		

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; meadin, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
		Perioperative endpoints				Short-term follow-up										Intermediate follow-up				Long-term follow-up										Overall follow-up		
Bakelen (2013)[c,60]	**B**																			0 & 0 (O)	7.6 ± 21.6 & 0.0 ± 0.0[a]			17 (17-18) & 17 (17-17)	0 & 0	0 & 66.7	62.5 & 100		0		0
	T																			12.5 & 0 (O)	0.0 ± 0.0 (both)			20 (18-27) & 22 (19-27)	0 & 0	0 & 0	50.0 & 33.3		30.0		0
Bakelen (2015)[61]	**B**																													6137± 2980	
	T																													8128± 5453	
Sukegawa (2016)[62]	**B**						0	0					0	0													0				
	T						0	0					0	0													0				
Gareb (2017)[63]	**B**																			0 (S)	0.0 ± 0.0[a]			17 (17-17)		20.0	0	100	0		
	T																			50.0 (S)	0.0 ± 0.0[a]			35 (21-41)		25.0	25.0	100	30.0		

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; meadin, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
		Perioperative endpoints				Short-term follow-up										Intermediate follow-up				Long-term follow-up										Overall follow-up		
Prospective cohort studies																																
Leonhardt (2008)[64]	**B**					41.4 (O) & 44.8 (S)	3.3	100				36.7		0		3.4 (O) & 6.9 (S)				0 (O & S)					13.3			16.7		
	T					20.7 (O) & 24.1 (S)	10.0	100				40.0		0		6.9 (O) & 13.8 (S)				0 (O & S)					NNA			13.3		
Qiu (2015)[65]	**B**					0 (O)	2.2						0	0	4.4	0 (O)			6.7	0 (O)										0
	T					0 (O)	4.4						0	0	13.3	0 (O)			15.6	0 (O)										0
Mahmoud (2016)[66]	**B**	0	169 ± 84				0				36.5 ± 9.7	0	0[d]					40.6 ± 8.6			47.0 ± 8.8						99.5 ± 0.8[a]				
	T	0	115 ± 38				0				34.4 ± 8.0	0	0[d]					38.2 ± 11.3			48.0 ± 5.7						96.5 ± 7.0[a]				

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Perioperative endpoints				Short-term follow-up								Intermediate follow-up						Long-term follow-up										Overall follow-up		
		Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; meadin, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
Leno (2017)[67]	**B**	4.2				0 (O)	4.3				NNA	0	0[d]	0		0 (O)		NNA		0 (O)		NNA					0	99.2[a]	9.5		
	T	0				0 (O)	0				NNA	0	0[d]	0		0 (O)		NNA		0 (O)		NNA					0	99.4[a]	0		
Retrospecitve cohort studies																																
Bell (2006)[68]	**B**						1.7			10.3				1.7											1.7	1.7					3.4
	T						3.2			0				1.4											0	0					0
Wittwer (2006)[69]	**B**						7.7	12.8				7.7		0		0 (S)	5.1									7.7			7.7		
	T						0	0				6.7		0		0 (S)	13.3									0			13.3		
Lee (2010)[70]	**B**	0	0				4.2							0																	
	T	2.3	0				2.3							0																	
Park (2011)[71]	**B**						0						3.6												1.8				5.4	0	
	T						0						0												0				0	3.8	
Menon (2012)[72]	**B**	0	2.5	100								0	0[d]	0																	
	T	0	0	75								15.0	NNA	0																	
Tripathi (2013)[73]	**B**		2.5			0 (O)	0	100					0	0												0	0				
	T		0			0 (O)	0	100					0	0												0	10.0				
Kang (2014)[74]	**B**						0							0			0										0		0		
	T						1.8							0			1.8										3.6		8.9		

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Perioperative endpoints			Short-term follow-up									Intermediate follow-up			Long-term follow-up							Overall follow-up
		Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; median, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
Lim (2014)[75]	**B**	0	1.3	119			7.7					15.4		0														0		0
	T	0	0	113			6.3					25.0		0														0		0
Bhatt (2015)[76]	**B**					0 (O)								0		0 (O)												0		
	T					2.8 (O)								0		0 (O)												13.9		
Burlini (2015)[77]	**B**	0	0				2.4						1.0			15.7 (S)											96.7	0		1.0
	T	0	1/ TU				2.5						1.3			9,9 (S)											95.0			1.3
Filinte (2015)[78]	**B**					0 (O)	0							0	0					0							0	0		8.3
	T					5.3 (O)	10.5							5.3	0					5.3							5.3	5.3		5.3

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)*	Screw breakage (%)#	Operation time in minutes (mean±SD)	Handling by surgeon (0: worst; 10: excellent; meadin, IQR)	Malocclusion (%)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (mean±SD)[b]	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	Malocclusion (%)	Pain (% or mean±SD)	MMO (mean±SD)[b]	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate removal (%)	Costs (direct and indirect; mean±SD)	Revision surgery (not plate removal; %)
		Perioperative endpoints				Short-term follow-up								Intermediate follow-up						Long-term follow-up										Overall follow-up		
Wu (2017)[79]	**B**	136 ± 38									42											46.0							NNA	0		
	T	94 ± 16									36											46.0							NNA	0		
Kim (2018)[80]	**B**	129 ± 29				7.7								0					7.7				7.7		7.7	7.7	0		0		7.7
	T	127 ± 25				6.7								0					6.7				6.7		6.7	0	13.3		20.0		6.7

*All data are given in percentages, unless stated otherwise. All unit of analysis was number of patients, unless stated otherwise. *Unit of analysis was plates. #Unit of analysis was screws. †Unit of analysis was fracture site. [a]Data given in mean±standard deviation. [b]Maximal mouth opening was only assessed postoperatively, no data regarding pre-operative maximal mouth opening reported. [c]Two follow-up moments: 1- and 2-year follow-up, respectively. [d]If no wound dehiscence was present, plate exposure was also assessed as not present. B, biodegradable; T, titanium; SD, standard deviation; IQR, interquartile range; O, objectively assessed; S, subjectively assessed; NNA, numbers not available. MMO, maximal mouth opening; TMJ-dysfunction, temporomandibular joint dysfunction; MFIQ, Mandibular Function Impairment Questionnaire; TU, total number unknown. Empty cells: not reported. Note that (i) analgesic usage after short-term follow-up is not mentioned in this table as this endpoint was not assessed in any of the included studies and (ii) that certain continuous variables are shown without standard deviations because these were not reported in the original manuscripts.*

Table S6. Results of meta-regression analysis to analyze the effect of study design on the log risk ratio of plate removal using a random effects model.

Study designs	Regression coefficient	95% CI (lower to upper border)	P-value	Interpretation
Prospective cohort studies	2.61	0.63 to 4.60	0.001	Significantly higher effect estimate of symptomatic plate removal rate in the included studies (i.e., in favor of titanium osteosyntheses)
Retrospective cohort studies	1.27	-0.66 to 3.22	0.197	Not significantly related to effect estimate of symptomatic plate removal rate in the included studies

95% CI, 95% confidence interval. Reference study design were randomized controlled trials. Statistical heterogeneity: $Tau^2 = 0.31$, $I^2 = 17.35\%$, $p = 0.279$. The meta-regression analysis shows that prospective cohort studies have significantly higher effect estimates of plate removal rate (i.e., in favor of the titanium group) compared to randomized controlled trials and retrospective cohort studies.

Table S7. Input and results of the trial sequential analyses using the random-effects (DerSimonian-Laird) model with the corresponding interpretations.

Endpoint	Control event proportion (titanium)[a]	Relative risk (95% CI)[a]	Diversity (D^2)[a]	Total N/RIS	Crossed conventional test boundary	Crossed O'Brien-Fleming boundary	Crossed futility boundary	Interpretation
Perioperative endpoints								
Screw breakage	0.0%	17.12 (2.19-134.07)	TSA could not be performed due to a control event proportion of 0.0%					
Short-term follow-up								
Infection	5.8%	0.26 (0.03-2.26)	0.0	115/601	No	No	No	Inconclusive, potentially false neutral
Dehiscence	7.5%	1.68 (0.56-5.00)	0.0	144/6112	Not estimatable due to <5% of RIS achieved			Inconclusive, potentially false neutral
Intermediate follow-up								
Mobility bone segments	2.1%	2.11 (0.32-13.85)	0.0	100/468	No	No	No	Inconclusive, potentially false neutral
Malocclusion	5.3%	1.01 (0.21-4.82)	0.0	118/6331150[b]	Not estimatable due to <5% of RIS achieved			Inconclusive, potentially false neutral
Overall follow-up								
Symptomatic plate removal	20.7%	0.11 (0.02-0.57)	0.0	118/94	Yes (benefit)	Yes (benefit)	No	**Biodegradable osteosyntheses is superior to titanium osteosyntheses**

RIS, required information size. [a]*According to the observed relative risk and diversity of the present meta-analysis including randomized controlled trials only.* [b]*RIS is very high due to a very small relative risk reduction. Outcomes that are not mentioned were assessed in no or a single randomized controlled trials, or were only assessed in total zero-event trials.*

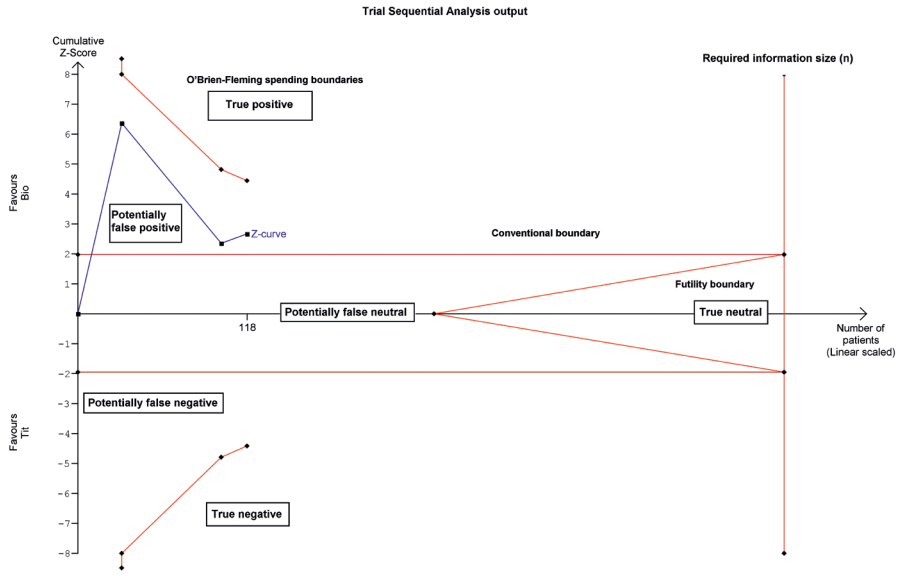

Figure S1. Example graph with explanation of the trial sequential analysis. The y-axis represents the cumulative Z-score and the x-axis the number of patients of included trials. A Z-score of +/- 1.96 corresponds to α = 0.05 (conventional boundaries). The required information size is the number of patients needed to draw a definite conclusion and this number is comparable to a sample size calculation in randomized controlled trials. The O'Brien-Fleming spending boundaries are trial sequential adjusted boundaries; the fewer patients are randomized, the wider these borders are due to increased chance of random errors. Crossing the futility boundary indicates that the intervention is unlikely to have the anticipated effect. The interpretation of each area is presented as textboxes in the graph. Thus, TSA provides three borders: conventional test boundaries (α = 0.05; Z = +/- 1.96; i.e., crossing boundary means potentially false positive or negative), O'Brien-Fleming spending boundaries (i.e., crossing boundary means true positive or negative effect), and futility boundaries (crossing boundary means true neutral effect). If no boundaries are crossed, the evidence remain inconclusive (i.e., potentially false neutral).

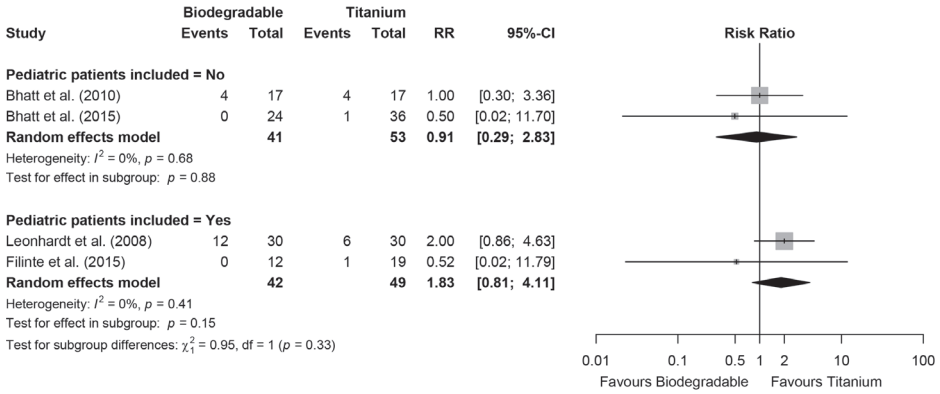

Figure S2. Forest plot of the endpoint malocclusion (<4 weeks follow-up) of studies including pediatric patients versus adult patients. *RR, risk ratio; 95%-CI, 95% confidence interval.*

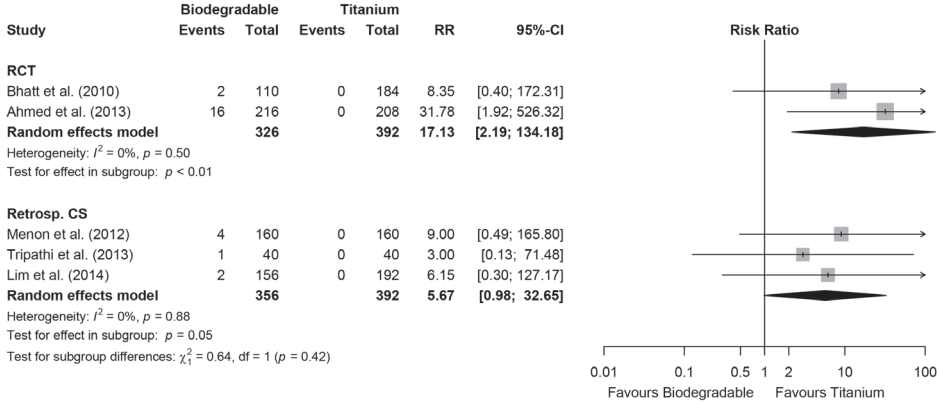

Figure S3. Forest plot of the endpoint perioperative screw breakage stratified by study design. *RCT, randomized controlled trials; Retrosp. CS, retrospective cohort studies; RR, risk ratio; 95%-CI, 95% confidence interval.*

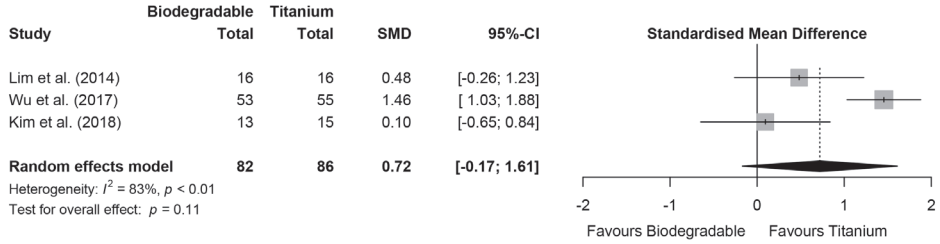

Figure S4. Forest plot of the endpoint operative time derived from retrospective cohort studies. *SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

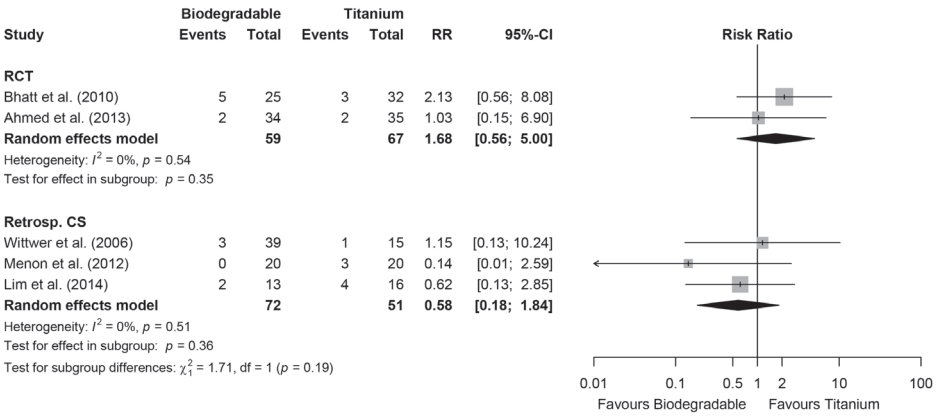

Figure S5. Forest plot of the endpoint dehiscence (<4 weeks follow-up) stratified by study design. *RCT, randomized controlled trials; Retrosp. CS, Retrospective cohort studies, RR, risk ratio; 95%-CI, 95% confidence interval.*

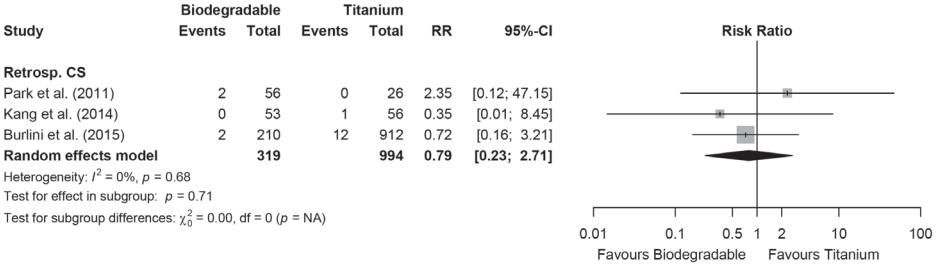

Figure S6. Forest plot of the endpoint plate exposure (<4 weeks follow-up) stratified by study design. *Retrosp. CS, Retrospective cohort studies, RR, risk ratio; 95%-CI, 95% confidence interval, NA, not applicable.*

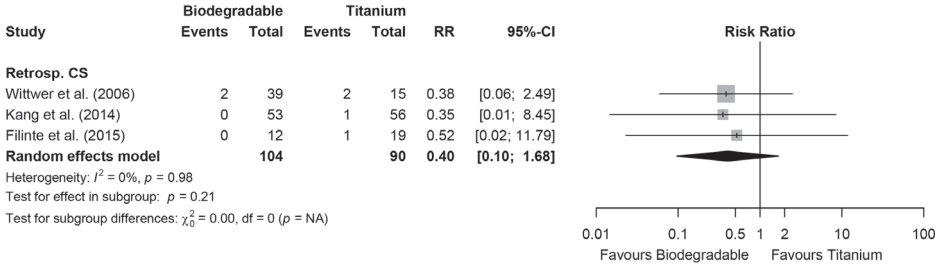

Figure S7. Forest plot of the endpoint pain (>12 weeks follow-up) stratified by study design. *Retrosp. CS, Retrospective cohort studies, RR, risk ratio; 95%-CI, 95% confidence interval; NA, not applicable.*

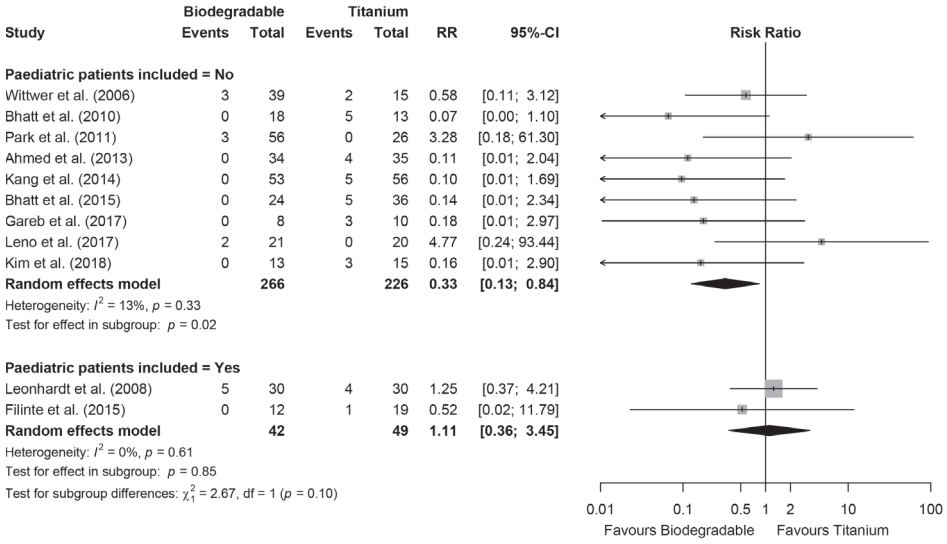

Figure S8. Forest plot of the endpoint plate removal (overall follow-up) of studies including pediatric patients versus adult patients. *RR, risk ratio; 95%-CI, 95% confidence interval.*

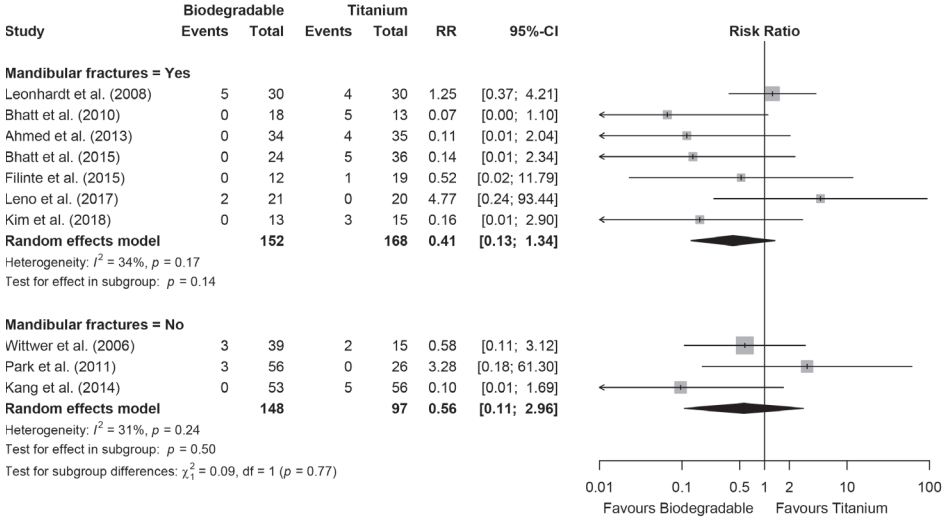

Figure S9. Forest plot of the endpoint plate removal (overall follow-up) of studies including patients with mandibular fractures versus other fractures. *RR, risk ratio; 95%-CI, 95% confidence interval.*

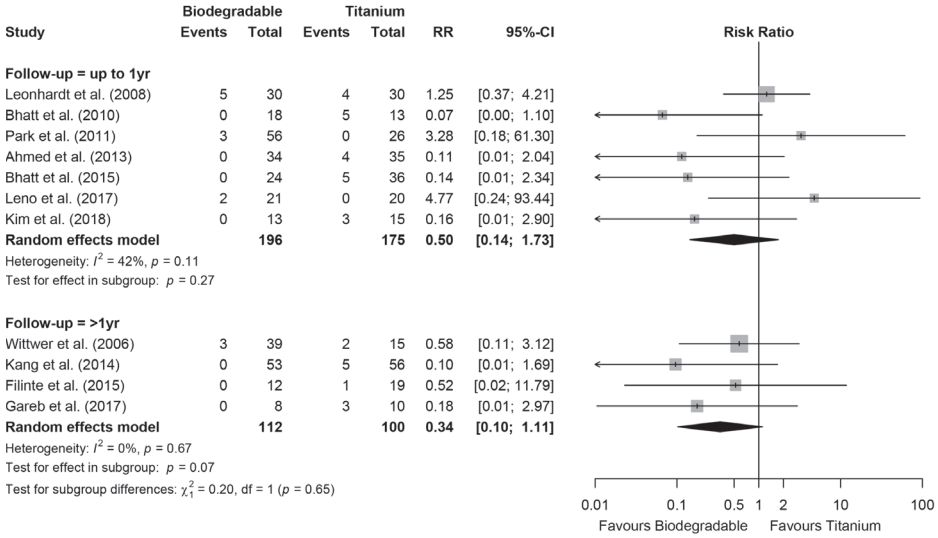

Figure S10. Forest plot of the endpoint plate removal (overall follow-up) stratified by ≤1-year and >1-year follow-up. *RR, risk ratio; 95%-CI, 95% confidence interval.*

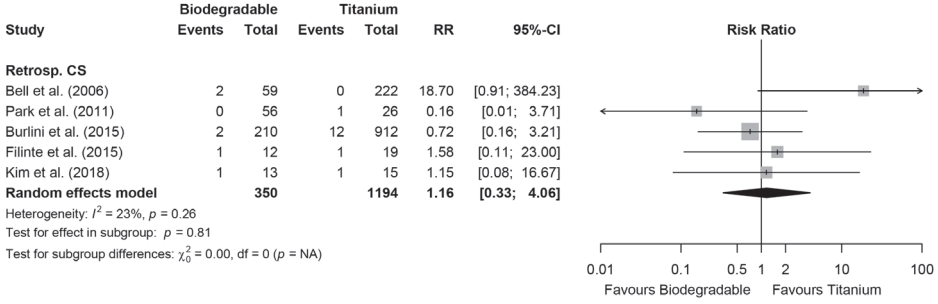

Figure S11. Forest plot of the endpoint revision surgery (overall follow-up) stratified by study design. *Retrosp. CS, Retrospective cohort studies, RR, risk ratio; 95%-CI, 95% confidence interval, NA, not applicable.*

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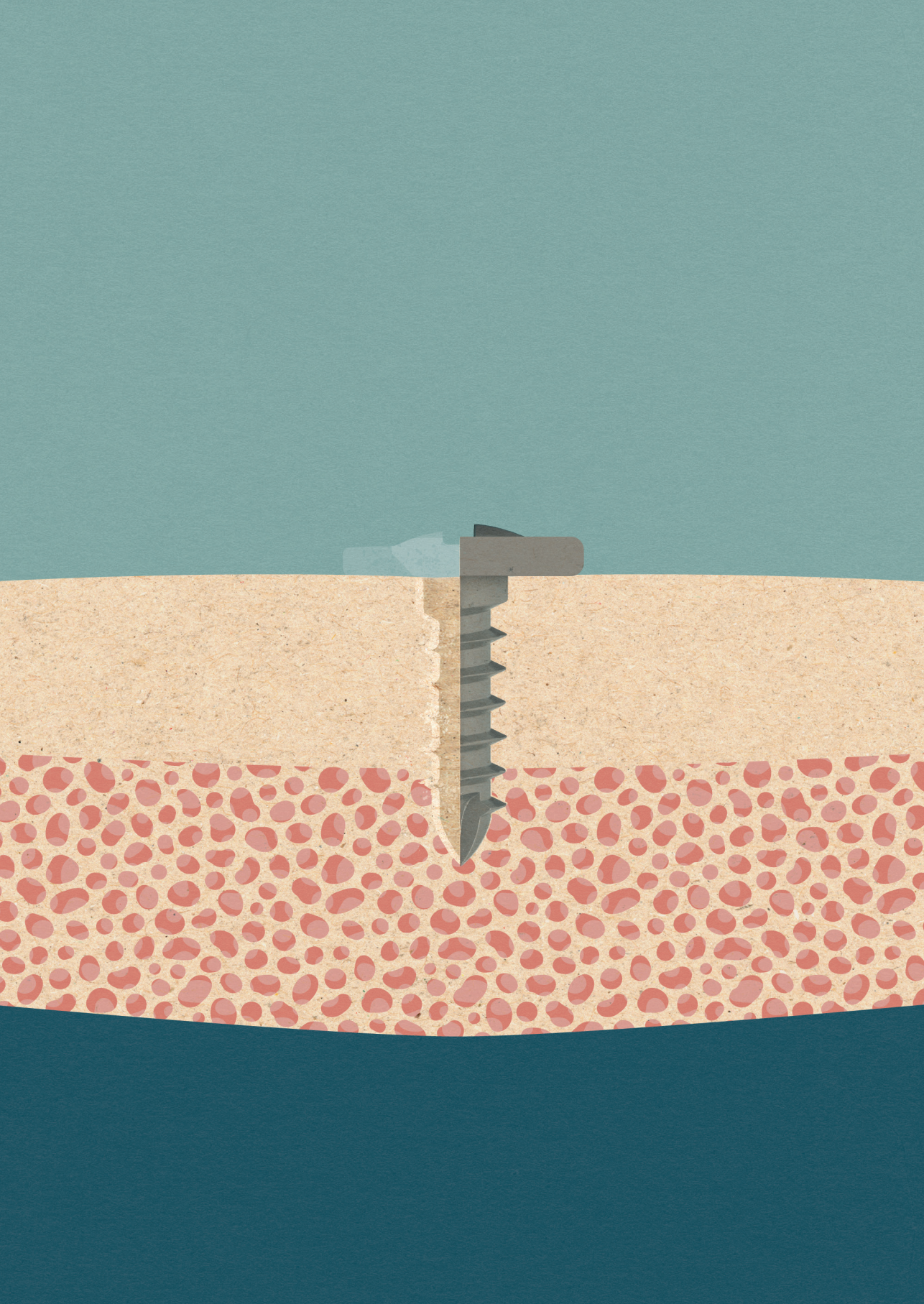

Chapter 3

Efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery

a systematic review with meta-analysis and trial sequential analysis

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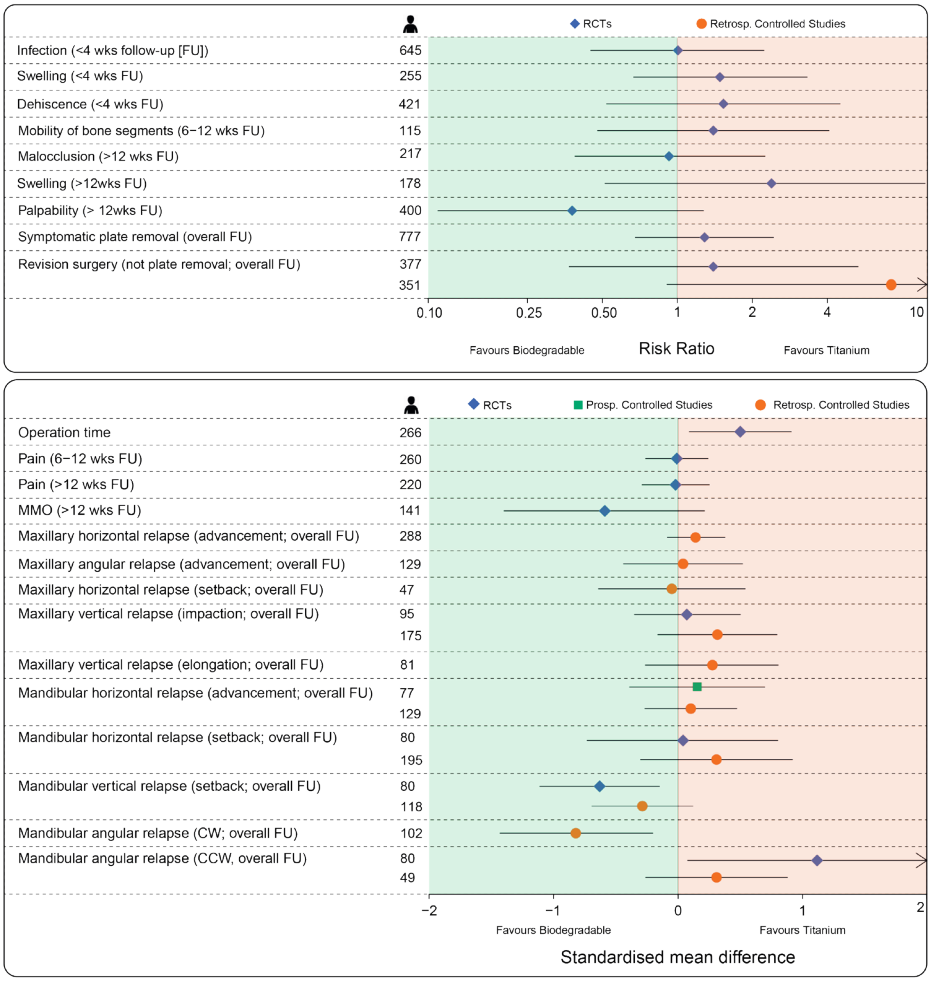
Abstract

Titanium osteosynthesis is currently the gold standard in orthognathic surgery. Biodegradable osteosynthesis' properties avoid removal of plates/screws in a second operation. This systematic review aimed to assess the efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery (PROSPERO CRD42018086477). Patients with syndromic disorder(s) and/or cleft lip/palate were excluded. Randomised, prospective and retrospective controlled studies were searched for in nine databases (February 2021). The time periods perioperative, short-term, intermediate, long-term and overall follow-up were studied. Meta-analyses were performed using random-effects models. A total of 9073 records was assessed, of which 33 were included (N=2551). Seven RCTs had 'some concerns' while another seven RCTs had high risk-of-bias (Cochrane-RoB2). No differences in malunion (qualitative analyses), mobility of bone segments (RR 1.37 [0.47;3.99]), and malocclusion (RR 0.93 [0.39;2.26]) were found. The operative time was longer in the biodegradable group (SMD 0.50 [0.09;0.91]). Symptomatic plate/screw removal was comparable among both groups (RR 1.29 [0.68;2.44]). Skeletal stability was similar in most types of surgery. Biodegradable osteosyntheses is a valid alternative to titanium osteosyntheses for orthognathic surgery, but with longer operation times. Since the quality of evidence varied from very low to moderate, high quality research is necessary to elucidate the potential of biodegradable osteosyntheses.

Graphical abstract

Efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery: a systematic review with meta-analysis and trial sequential analysis



Introduction

Titanium osteosynthesis systems are currently the fixation system of choice in orthognathic surgery. The disadvantages, though, include temperature sensitivity[1], tactile sensation of plates and screws[2], growth restrictions[3], hampering of imaging and radiotherapy[4–6], presence of titanium particles in lymph nodes[7], extreme stiffness causing stress shielding of the underlying bone[4], and potential mutagenicity[1]. Hence, titanium systems are removed in up to 33% of the cases with accompanied costs and burdens[2,8].

Biodegradable plates and screws are composed of degradable polymers (e.g., poly-L-lactic or polyglycolic acid) and may reduce removal rates of these osteosynthesis systems in a second operation while also avoiding the disadvantages of titanium osteosyntheses. Biodegradable systems have, however, their own limitations including lower strength and stiffness[9] that could lead to higher malunion rates and less skeletal stability after orthognathic surgery, palpability due to bulkiness[10], and possible foreign body reactions[11]. As a consequence, biodegradable implants are removed in up to 17% of the cases in a second operation[2,10,12].

Studies comparing biodegradable versus titanium osteosyntheses after orthognathic surgery have been performed, but the results are controversial. Some studies report higher plate removal rates after titanium osteosyntheses[13–16], while other studies[2,17,18] show higher rates of symptomatic plate removal after biodegradable osteosyntheses. This controversy also applies to other clinically assessed endpoints such as skeletal stability[14,19,20] and pain[2,14]. In 2017, a systematic review focussed on the safety and efficacy of biodegradable versus titanium systems[21] and included two randomised controlled trials (RCTs) but could not perform a meta-analysis. The authors concluded that there was insufficient evidence as to which osteosynthesis system is superior[21,22]. However, certain RCTs that were available at the time of writing were, for unknown reasons, not included in the review. In 2018, a systematic review comparing osteosynthesis systems for orthognathic surgery was published[23] but focused on skeletal stability only and failed to account for clinical (e.g., inclusion of patients with cleft lip and palate) and methodological heterogeneity (e.g., they pooled the data from different study designs). Thus, to guide evidence based decisions, the need remains for a systematic review of the current literature that assesses the efficacy and morbidity of biodegradable versus titanium osteosyntheses in patients undergoing orthognathic surgery adequately, including all relevant clinical endpoints (i.e., not only restricted to skeletal stability) and which takes methodological and clinical heterogeneity of the studies into account.

This systematic review with meta-analysis and trial sequential analysis was performed to analyse the efficacy (i.e., bone healing, (mal)occlusion, skeletal stability) and morbidity of biodegradable (i.e., consisting of synthetic polymers) against titanium osteosyntheses in patients with dentofacial deformities treated with orthognathic surgery.

Materials and methods

This systematic review and meta-analysis was conducted following the recommendations of the *Cochrane Handbook for Systematic Reviews of Interventions* and reported according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* statement[24,25]. The study protocol was registered in PROSPERO prior to the systematic literature search (registration number CRD42018086477). A systematic review of biodegradable versus titanium osteosyntheses in trauma patients, using the same approach, was published separately[10].

Study identification

A systematic literature search of nine electronic databases (PubMed, EMBASE, the Cochrane Central Register of Controlled Trials [CENTRAL], Web of Science, EBSCOhost, Scopus, African Journals Online, OpenGrey and ClinicalTrials.gov was conducted [all: inception to 2021]). The sensitive search strategy consisted of medical subject heading terms and free-text words (Table S1). The search strategy also included maxillofacial trauma populations as some studies include both populations in a single study. Data of patients treated with orthognathic surgery were derived from the authors of those studies and included while the trauma patients' data were excluded for this paper but were recently published separately[10]. The initial search was performed on January 29, 2018, and was updated on February 11, 2021. Additionally, the reference lists of the included studies and leading oral and maxillofacial journals were screened for relevant studies. Maxillofacial surgery experts in biodegradable and titanium osteosynthesis (RRMB and NBvB) were asked if any relevant studies were missing. No language or period restrictions were applied.

Study selection

Inclusion criteria were formulated using the PICOS format. The population (P) included patients with dentofacial deformities treated with orthognathic surgery i.e., Le Fort I, Le Fort II, Le Fort III, (bilateral) sagittal split (BSSO) and intraoral vertical ramus osteotomies (IVRO), with and without concurrent genioplasty. The intervention group

(I) was treated surgically with biodegradable fixation (i.e., plates and/or screws/pins) that consisted of (co-)polymers. The control group (C) was surgically treated with titanium fixation (i.e., plates and/or screws). The primary outcome (O) was efficacy of the fixation method, i.e., adequate bone healing with the absence of malunion of bone segments at 12 weeks follow-up. The secondary outcomes were related to morbidity, i.e., clinical mobility of bone segments, objective and subjective malocclusion, symptomatic osteosynthesis device removal rate (i.e., routinely removed asymptomatic plates were excluded), skeletal stability (i.e., skeletal relapse) assessed by lateral cephalograms or three dimensional imaging, pain, analgesic usage, maximal mouth opening (MMO), mandibular function impairment questionnaire (MFIQ; lower score equals better function), temporomandibular joint dysfunction (TMJ-dysfunction), infection, swelling, wound dehiscence, plate exposure, palpability of plates and/or screws, the patient's satisfaction with the performed surgery, and revision surgery other than device removal (e.g., abscess incision and drainage). Additionally, the handling of the osteosynthesis systems by the surgeons, plate and screw breakage, operative time, and total costs (i.e., direct and indirect costs) of both groups were evaluated[10]. The included study types (S) were RCTs, prospective studies with a control group, and retrospective studies with a control group. RCTs are the highest quality of evidence of an original study, while the latter two designs are valuable for, e.g., the assessment of adverse events. The follow-up (FU) of each corresponding endpoint is described below (see Data collection)[10].

Exclusion criteria consisted of patients with syndromic disorder(s), patients with cleft lip or palate, multiple publications of the same study and endpoints, case reports, case series with fewer than 10 cases, experts' opinions, letters to the editor, review articles, and conference abstracts[10].

Two reviewers (BG and NBvB) independently assessed titles and abstracts for inclusion eligibility. If the title and abstract provided insufficient information, or in case of any doubt, full text assessment followed. The full text of the included titles and abstracts were independently assessed by the same two reviewers for final inclusion using the above mentioned in- and exclusion criteria. Any disagreement was resolved by a discussion. If no consensus could be reached, a third reviewer (PUD) was available to make a final decision. After each selection stage, inter-observer reliability was expressed as Cohen's kappa and percentage of agreement. Studies written in languages that the observers were not competent in were translated to English by researchers fluent in both that language and English. Subsequently, these translated studies underwent the same review process[10].

Data collection

The data were extracted using a standardised, pre-defined form[10]. Two reviewers (BG and NBvB) extracted data from a sample (10%) of eligible studies. If agreement was ≥80%, the remainder of the data were extracted by one reviewer (BG). The collected data included: first author and year of publication, country in which the study was conducted, study design, number of patients, gender, age, tobacco and alcohol usage, surgical procedures, types of osteosynthesis systems used, intra-operative switching to another osteosynthesis system, duration of postoperative maxillomandibular fixation (MMF), duration of orthodontic treatment, postoperative dietary restrictions, duration of FU, and conflict of interests. The endpoints were collated for 5 time periods: perioperative, short-term FU (i.e., 0-4 weeks; soft tissue healing), intermediate FU (i.e., 6-12 weeks; bone healing), long-term FU (i.e., >12 weeks; degradation effects), and overall FU (i.e., the endpoints of the longest FU; Table S2)[10]. If an identical endpoint was assessed in multiple articles of the same study (e.g., same RCT) at different follow-ups, the article with the longest follow-up was included in the analyses of that specific endpoint.

Lateral cephalograms and three dimensional imaging were used to assess skeletal stability. The landmarks used for maxillary horizontal and vertical relapse were, in order of priority: point A, anterior nasal spine (ANS) and the anterior implant (AI). Maxillary angular relapse was assessed using the angle sella-nasion-point A (SNA). The landmarks used for mandibular horizontal and vertical relapse were, in order of priority: point B, pogonion (Pg) and menton (Me). Mandibular angular relapse was assessed using the angle articulare-gonion-gnathion.

The skeletal stability data were included if the first postoperative cephalogram was performed within one month after surgery. The amount of relapse was assessed by calculating the difference between the measurements of the longest follow-up cephalogram and the first postoperative cephalogram. Whenever the differences in measurements were not presented in the manuscript, but the data of those two time points (i.e., first postoperative and latest cephalogram) were given as means and standard deviations, the mean and standard deviation of the difference was calculated assuming a normal distribution of data. Data presented as medians with (interquartile) ranges were excluded. All the skeletal stability data were converted to absolute values for statistical analyses.

Whenever two or more studies included an identical control group, the means and standard deviations of both intervention groups were pooled and analysed as a single

pairwise comparison with that specific control group, assuming normal distribution of data, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions*[25].

If the relevant data could not be extracted, the authors of the studies were contacted by e-mail from May - November 2018 and April - July 2019. Data were not included in the analyses if the authors did not respond despite three email attempts (Table S3)[10].

Risk of bias assessment

The risk of bias of all the included studies was independently assessed by the two reviewers (BG and NBvB). Trials performed by the author's research group were assessed by two independent researchers not involved in those studies (PUD and SJvdG; see acknowledgement) to avoid conflict of interests[10].

Randomised controlled trials were assessed using *The Revised Cochrane risk-of-bias tool (RoB 2)*[26]. The domains were graded low risk, some concerns or high risk of bias. The nonrandomised studies' risk of bias was assessed using The Methodological Index for Non-Randomized Studies (MINORS)[27]. The MINORS is a valid and reliable instrument for bias assessment[27]. Each item was scored either 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate).

The quality of the body of evidence for each outcome was graded by the two independent reviewers (BG and NBvB) as high, moderate, low, or very low quality using the *Grades of Recommendation, Assessment, Development and Evaluation Working Group system* (GRADE system)[28].

Statistical analysis

The inter-observer agreement was calculated using IBM SPSS Statistics 23 (SPSS, Chicago, IL, USA). Regarding binary variables, the events and totals were used to calculate the risk ratio (RR) and 95% confidence intervals (CI). The standardised mean difference (SMD), with 95% CI, was calculated for the continuous variables. Statistical heterogeneity was regarded substantial if I^2>50%[25]. Separate analyses were conducted of the study designs. A summary effect estimate was calculated if ≥2 studies with the same study design could be pooled, unless these studies were total zero-event studies[25]. The meta-analysis was performed in R-*meta* (R v4.0.2, *meta*-package v4.15-1), using a random-effects model, with the DerSimonian-Laird estimator, due to the presence of clinical heterogeneity[25,29].

The following *a priori* defined subgroup analyses of the primary outcome, malocclusion, and device removal rate were performed using random-effects model with the DerSimonian-Laird estimator: low versus high risk bias RCTs, paediatric patients (<16 years) versus adults, osteosyntheses with plates and screws/pins versus only screws/pins, ≤8 mm versus >8 mm mandibular advancement, and mandibular versus maxillary osteotomies. Device removal rate was also analysed according to the FU of the included studies, i.e., ≤1 year FU and >1 year FU. Additionally, subgroup analyses of the skeletal stability following osteosyntheses with plates and screws/pins versus only screws/pins and ≤8 mm versus >8 mm mandibular advancement were performed.

Since conventional meta-analyses exclude studies with zero events in both treatment groups, a sensitivity analysis was performed, including those studies with a reciprocal continuity correction of the opposite arm[30]. Furthermore, a sensitivity analysis comparing the effect estimates of all included RCTs versus non-high-risk-of-bias RCTs was performed. A meta-regression analysis with a random-effects model with the DerSimonian-Laird estimator evaluated the effect of the study design and the risk of bias items for the primary endpoint, mobility of bone segments, malocclusion, and symptomatic device removal. The meta-regression was conducted using R-*meta*. Reporting bias was assessed through funnel plots if >10 studies were available per endpoint and study design, and did not have clinical heterogeneity[10,25,31–33].

As traditional meta-analyses are prone to type-I errors (i.e., false positive findings) due to random error and repeated significance testing after each additional trial is published[34,35], trial sequential analyses (TSA), including RCTs, were performed for each binary endpoint. An explanation of the TSA, with an example and interpretation of the data, is shown in Figure S1. The TSA, which included the random-effects (DerSimonian-Laird estimator) model based on the observed relative risk reduction (RRR) and diversity (D^2) of RCTs, and an overall type I error (α) of 0.05 and a type II error (β) of 0.20[36], was performed using Trial Sequential Analysis Viewer, version 0.9.5.10 beta (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet)[10,36].

In all analyses, $P<0.05$ (two-tailed) was considered statistically significant.

Results

Study identification and selection

The initial search was updated on February 11, 2021, and yielded 24349 potentially eligible papers. A total of 9073 titles and abstracts was screened after eliminating duplicate records (Figure 1 and Table S4, kappa 0.91, agreement 99.7%). Eighty-eight full-text manuscripts were screened, and 33 and 27 articles were included in the qualitative and quantitative synthesis, respectively (agreement 100%, kappa 1.0). Of the screened full-text manuscripts, two were written in the Korean[20,37] and one in the Japanese language[38]. The third reviewer was not consulted.

Patient characteristics

In total 2551 patients (N=33 studies), of which 1391 received titanium and 1160 received biodegradable osteosynthesis systems, were included (range 18 – 272; Table 1). The majority of patients were female. Ages ranged from 16 to 57 years. No study included only paediatric patients. Sixteen studies included patients with class III[14,18–20,37,39–49], six studies with class II[15,16,50–53], and 10 studies with both class II and class III malocclusion patients[2,13,54–61]. One study did not specify the malocclusion of the included patients[17]. Five studies included both orthognathic and trauma patients[2,52,55–57]. Tobacco and alcohol usages by patients was reported in one study[17].

Procedural characteristics

The characteristics of all included procedures are presented in Table 1. The titanium screw diameters varied from 1.5 to 2.0mm whenever osteosynthesis plates were used, while the screw diameters varied from 2.0 to 2.7mm whenever osteosyntheses was performed solely with screws.

BioSorb FX (self-reinforced 70/30 PLLA/PDLLA) and Inion CPS (79/15/6 poly-L-lactic acid (PLLA)/poly-DL-lactic acid (PDLLA)/trimethylene carbonate) were the biodegradable osteosynthesis systems that were most frequently used (Table 1). The biodegradable screw diameters varied from 2.0 to 3.5mm. Perioperative switching from biodegradable to titanium osteosyntheses was reported in four articles[2,55–57]. Main reasons for switching was non-grips screws resulting in inadequate fixation or a lack of stability of the fixated bone segments[62].

The most commonly performed surgical procedures were Le Fort I and bilateral sagittal split osteotomies. Only one study reported duration of the pre- and postoperative

orthodontic treatment[43] while one study only reported duration of postoperative orthodontic treatment[51]. Postoperative MMF duration ranged from 1 week to 8 weeks and most of the studies used soft guiding elastics for MMF. Four studies only used rigid MMF[37,43,46,47] while five studies used a combination of rigid and soft guiding elastics for MMF[19,39,41,48,49]. Ten studies reported on postoperative dietary restrictions, a soft or pureed diet for 4 to 6 weeks[2,51,52,54–59,61].

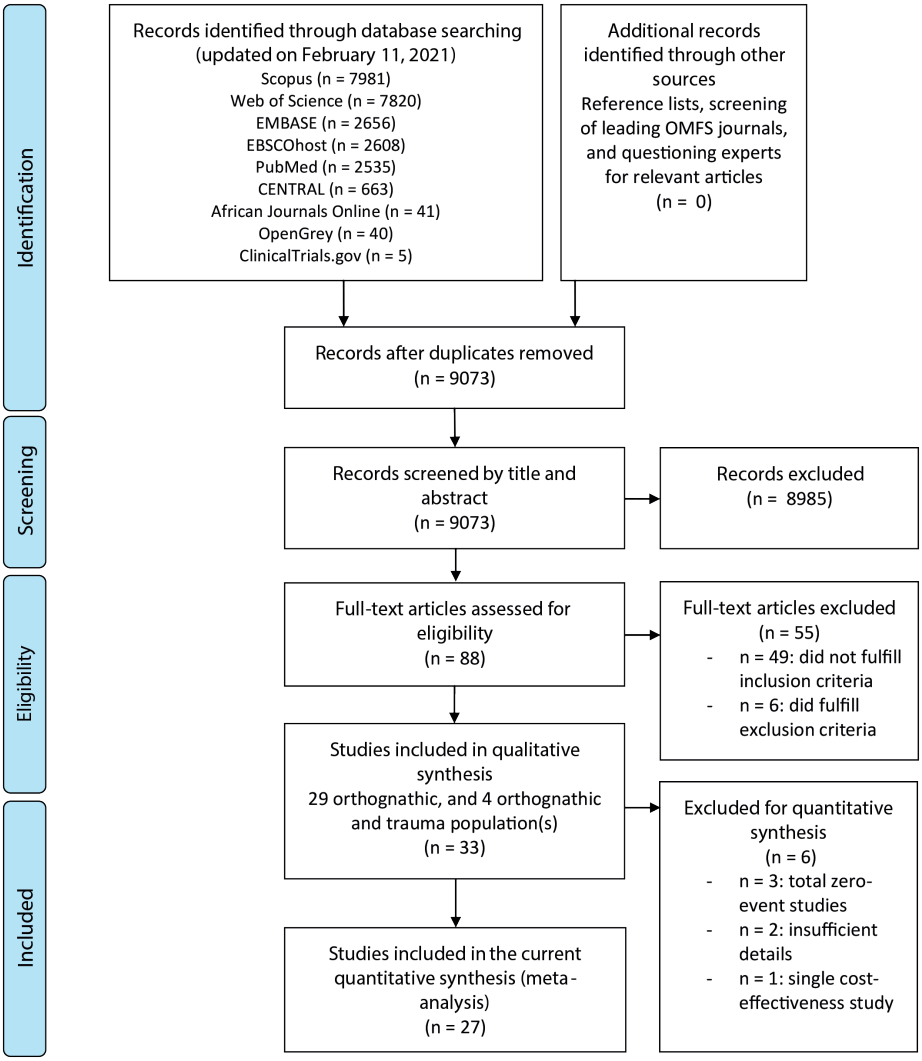


Figure 1. Flowchart of study identification and selection progress.

Table 1: Characteristics of the included studies.

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Randomised controlled trials																		
Matthews et al. (2003)[50]	11	11	0/11	0/11	32 (range 18-46)	29 (range 21-44)	NM*		Biofix[a,*] (3.5)		BSSO advancement	0	Pre- and postoperative; durations NM		Soft guiding elastics; 4-5 wks		1 yr	
Norholt et al. (2004)[14]	30	30	10/20	12/18	22 (range 17-50)	23 (range 17-48)	W. Lorenz (2.0)		LactoSorb[b] (2.0)		Le Fort I advancement ± impaction	0	Postoperative; preoperative and durations NM		Soft guiding elastics; 2-4 wks		2 and 6 wks, 6 and 12 mos	
Cheung et al. (2004)[17]	30	30	9/21	9/21	22.9 (range 16-37)		Mathys Compact 2.0 (2.0)		Biosorb FX[c] (2.0 and 2.4)		Le Fort I, maxillary subapical, mandibular subapical, mandibular body, sagittal split, and genioplasty	0	Preoperative; postoperative and durations NM				2 and 6 wks, 3 and 6 mos, 1 and 2 yrs	
Ueki et al. (2005)[19]	20	20					Würzburg (2.0)		Fixorb-MX[d] (2.0)		BSSO setback	0			Rigid, 2 wks; soft guiding elastics, duration NM		1, 3, 6, and 12 mos	
Cheung et al. (2008)[54]	20	20	17/23		24± 8.4	22± 5.5	Synthes		Inion CPS[e] (2.0)		Le Fort I advancement/ setback/ impaction/ elongation	0	Preoperative; postoperative and durations NM				2 wks, and 3, 6, 12 mos	Soft diet; 6 wks

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Park et al. (2010)[20]	10	30	4/6	17/13	22.8± 2.0	23.4± 2.9	M3 Visidisk	BioSorb FX[c]	Le Fort I advancement ± impaction and BSSO setback		0					6 mos		
Stock-mann et al. (2010)[13]	33	33			27.0± 7.1	27.0± 5.4	Stryker[a] (2.7)	Isosorb[f,a] (3.5)	BSSO advancement and setback		0	Postoperative; preoperative and durations NM		Soft guiding elastics; 2-3 dys		1, 2, and 6 wks, 3 and 6 mos, and 1, 2, 3, 4, and 8 yrs		
Tuovinen et al. (2010)[15]	50	51	14/36	18/33	33.5		Stryker (max: 2.0; mand[a]: 2.0)	BioSorb FX[c] (max: 2.4; mand[a]: 2.8)	Le Fort I advancement ± impaction and/or BSSO advancement		0	Postoperative; preoperative and durations NM		Soft guiding elastics; duration NM		6.8 yrs (range 4.8-7.5)		
Buijs et al. (2012)[55]	124	76	47/77	34/42	30.5± 11.1	30.0± 11.9	KLS Martin (max: 1.5; mand: 2.0)	Inion CPS[e] (max: 2.0; mand: 2.5)	Le Fort I, BSSO, or Le Fort I + BSSO		21	Postoperative; preoperative and durations NM		Soft guiding elastics; 6-8 wks		8 wks		Soft diet; 5 wks
Yoshioka et al. (2012)[18]	90	110	24/66	43/67	20 (range 18-37)	20 (18-45)	Stryker (2.0)	Neofix[g] (2.2)	BSSO setback		0	Preoperative; postoperative and durations NM		7 dys; details NM		3 and 6 mos, and 1, 2, and 3 yrs		

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Bakelen et al. (2013)[56]	124	79	47/77	35/44	30.5± 11.1	30.0± 11.9	KLS Martin (max: 1.5; mand: 2.0)	Inion CPS[e] (max: 2.0; mand: 2.5)	Le Fort I, BSSO, or Le Fort I + BSSO		21	Preoperative; postoperative and durations NM		Soft guiding elastics; 6-8 wks		1 and 2 yr		Soft diet; 5 wks
Yu et al. (2014)[16]	51	50	23/28	12/38	33.5± 14.3	31.2± 14.2	Stryker[*]	Inion CPS[e,*]	BSSO advancement		0			Soft guiding elastics; 41.2%	Soft guiding elastics; 96%	8.06 ± 9.24 mos	10.53 ± 7.33 mos	
Bakelen et al. (2015)[57]	124	79	47/77	35/44	30.5± 11.1	30.0± 11.9	KLS Martin (max: 1.5; mand: 2.0)	Inion CPS[e] (max: 2.0; mand: 2.5)	Le Fort I, BSSO, or Le Fort I + BSSO		21	Preoperative; postoperative and durations NM		Soft guiding elastics; 6-8 wks		8 wks and 2 yrs		Soft diet; 5 wks
Gareb et al. (2017)[2]	124	79	47/77	35/44	30.5± 11.1	30.0± 11.9	KLS Martin (max: 1.5; mand: 2.0)	Inion CPS[e] (max: 2.0; mand: 2.5)	Le Fort I, BSSO, or Le Fort I + BSSO		21	Preoperative; postoperative and durations NM		Soft guiding elastics; 6-8 wks		95 mos (range 77-111)	98 mos (range 80-11)	Soft diet; 5 wks
Prospective cohort studies																		
Ferrretti et al. (2002)[51]	20	20					NM (2.0)[*]	Lactosorb[b,*] (2.5)	BSSO advancement			Preoperative duration NM; postoperative 4 wks		Soft guiding elastics; duration NM		1 and 6 wks, and 3, 6, and 12 mos		Pureed diet; 4 wks

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Dhol et al. (2008)[45]	25	25	8/17	5/20	22.9± 1.6	23.3± 2.0		Lactosorb[b] (2.0)	Le Fort I impaction							1 and 6 wks, and 3, 6, and 12 mos		
Bakelen et al. (2014)[52]	22	15	6/16	7/8	35±11	35±12	KLS Martin (2.0)	Inion CPS[e] (2.5)	BSSO advancement			Pre- and postoperative; durations NM		Soft guiding elastics; 6-8 wks		Mean 27 mos	Mean 25 mos	Soft diet; 5 wks
Retrospective cohort studies																		
Harada et al. (1997)[46]	10	10	4/6	3/7	23.0 (range 18-30)	22.4 (range 20-31)	OSW Leibinger[a] (2.7)	Takiron[h,a] (2.7)	BSSO setback			Pre- and postoperative; durations NM		Rigid; 9.4 dys	Rigid; 14.6 dys	2 and 3 dys, and 3, 6 and 12 mos		
Costa et al. (2006)[47]	12	10			27.8± 5.9	26.9± 7.1		Lactosorb[b] (2.0)	Le Fort I advancement ± impaction and BSSO setback					Rigid; 1 wk		1 and 8 wks, and 1 yr		
Landes et al. (2006)[58]	30	30	23/37		25 (range 16-57)		Stryker (2.0)	MacroSorb[i] and PolyMax[j] (2.0)	Le Fort I advancement/ setback ± BSSO advancement/ setback					Soft guiding elastics; 2-4 wks		3 dys and 1 yr		Soft diet; 6wks
Turvey et al. (2006)[53]	35	34	16/18	11/24	26.8± 11.2	27.5± 13.0	NM[a] (2.0)	BioSorb FX[c,a] (2.0)	BSSO advancement ± genioplasty			Pre- and postoperative; durations NM		Soft guiding elastics; duration NM		3 and 5 wks, and 1 yr		

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Ueki et al. (2006a and b)[#48]	a: 12, b: 14	a: 12, b: 9	8/39		a: 21.8 (range 16-34), b: 26.5 (range 17-34)	a: 21.6 (range 17-32), b: 21.1 (range 19-25)	Würzburg (2.0)	Fixorb-MX[d] (2.0)	a: Le Fort advancement + BSSO setback, b: Le Fort I advancement + IVRO without fixation			Pre- and postoperative; durations NM		a: rigid, 'several days' + soft guiding elastics, duration NM; b: rigid, 1-3 wks + soft guiding elastics, duration NM		1, 3, 6, and 12 mos		
Landes et al. (2007)[59]	30	15	23/22		27 (range 18-46)		Stryker (2.0)	LactoSorb[b] (2.0) and RapidSorb[k] (2.0)	Le Fort I advancement/ setback ± BSSO advancement/ setback					Soft guiding elastics; 2-4 wks		3 dys and 1 yr		Soft diet; 6wks
Ueki et al. (2009)[49]	12	11	3/20		25.1±7.3		Stryker (2.0)	Fixorb-MX[d] (2.0)	BSSO setback			Pre- and postoperative; durations NM		Rigid, 1 wk; soft guiding elastics, duration NM		1 yr		
Ahn et al. (2010)[60]	152	120	126/146		23			BioSorb FX[e] (max: 2.0; mand: 2.4; genioplasty: 2.0)	BSSO ± Le Fort I ± genioplasty							follow-up examinations on a regular basis'		

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Choi et al. (2010)[37]	15	15	9/6	7/8	21.8 (range 17-32)	21 (range 17-31)	Stryker (2.0)	Inion CPS[e] (2.0)	BSSO setback			Pre- and postoperative; durations NM		Rigid 3 dys		14.5 mos		
Ueki et al. (2011)[39]	20	20[1]; 20[4]	10/10	5/15[12]; 10/10[4]	21.7± 5.6	29.1± 11.2[12]; 23.5± 5.9[4]	Würzburg (2.0)	Super-Fixsorb-MX[l] (2.0); Fixorb-MX[d] (2.0)	BSSO setback					Rigid, 'few days' + soft guiding elastics, duration NM		1, 3, and 12 mos		
Ballon et al. (2012)[61]	43	41	22/21	20/21	25 (range 16-57)	24 (range 16-46)	Stryker-Leibinger (2.0)	Inion CPS[e] (max : 2.0 ; mand : 2.5)	Le Fort I ± BSSO or BSSO	Le Fort I ± BSSO				Soft guiding elastics; 2-6 wks		35 (6-113) mos	13 (7-27) mos	Soft diet; 6wks
Paeng et al. (2012)[40]	25	25	13/12	11/14	25.3± 4.1	22.6± 2.9	Le Forte system[*] (2.4)	Inion CPS[e,*] (2.5)	BSSO setback					Soft guiding elastics; duration NM		3 dys, and 2, 6, and 12 mos		
Ueki et al. (2012)[41]	20	20[1]; 20[4]	4/16	9/11[12]; 4/16[4]	21.6± 4.4	26.4± 8.6[12]; 23.8± 6.4[4]	Würzburg (2.0)	Super-Fixsorb-MX[l] (2.0); Fixorb-MX[d] (2.0)	Le Fort I advancement ± impaction + BSSO setback			Pre- and postoperative; durations NM		Rigid, 'few days' + soft guiding elastics, duration NM		1, 3, and 12 mos		
Blakey et al. (2014)[42]	30	27	14/16	7/20	20.8± 6.4	19.7± 5.5	Leibinger or Stryker (2.0)	Inion CPS[e] or BioSorb FX[c] (2.0)	Le Fort I advancement			Pre- and postoperative; durations NM		Soft guiding elastics; 6 wks		1 yr		

Table 1: *(continued)*

Study (first author, year)	Number of patients		Gender (M/F)		Age (mean±SD or median (IQR) in yrs)		Osteosynthesis system (outer screw diameter in millimeters)		Type of osteotomy (n)		Operative switches (B to T, n)	Orthodontic treatment		Duration of postoperative MMF		Follow-up		Postoperative dietary restrictions
	T	*B*	*T*	*B*	*T*	*B*	*T*	*B*	*T*	*B*		*T*	*B*	*T*	*B*	*T*	*B*	*T and B*
Lee et al. (2014)[†43]	10	8					Le Forte system	BioSorb FX[c]	BSSO setback			Pre-operative 2.75±1.82 mos; post-operative, duration NM	Pre-operative 2.34±1.89 mos; post-operative, duration NM	Rigid; 2-3 wks		6 mos		
Ueki et al. (2015)[°44]	13	35					Stryker (2.0)	Fixorb-MX[d] (2.0)	BSSO setback ± Le Fort I advancement			Pre- and postoperative; durations NM		Soft guiding elastics; duration NM		1 yr		

Osteosyntheses were performed using plates and screws, unless stated otherwise. [a]Biofix (self-reinforced PLLA); [b]Lactosorb (82/18 PLLA/PGA); [c]BioSorb FX (self-reinforced 70/30 PLLA/PDLLA); [d]Fixorb-MX (100 PLLA); [e]Inion CPS (79/15/6 PDLLA/PDLA/TMC); [f]Isosorb (80/20 (90/10 PLLA/PDLLA) /(50/50 PLLA/PDLA)); [g]Neofix (100 PLLA); [h]Takiron (100 PLLA); [i]MacroSorb (70/30 PLLA/PDLLA); [j]PolyMax (70/30 PLLA/PDLLA); [k]RapidSorb (85/15 PLLA/PGA); [l]Super-Fixsorb-MX (40/60 uHA/PLLA); [*]Osteosyntheses performed with screws only; [#]Identical study, but different comparisons: (a) Le Fort I + BSSO or (b) Le Fort I + IVRO without osteosyntheses; [†]Only subgroup 2 and 3 of the original manuscript are relevant for the present review. The distribution of gender and age are not given for each subgroup; [°]Only subgroup 1-3 of the original manuscript are relevant for the present review. The distribution of gender and age are not given for each subgroup. *T, titanium osteosynthesis; B, biodegradable osteosynthesis; M, male; F, female; max, maxilla; mand, mandible; yrs, years; mos, months; wks, weeks; PLLA, poly-L-lactic acid; PDLLA, poly-D,L-lactic acid; PDLA, poly-D-lactic acid; TMC, trimethylene carbonate; PGA, polyglycolic acid; uHA, unsintered hydroxyapatite; MMF, maxillomandibular fixation; BSSO, bilateral sagittal split osteotomy; IVRO, intraoral vertical ramus osteotomy; NM, not mentioned. Empty cells: not reported.*

Risk of bias assessment

Of all included articles, 14 were publications of RCTs[2,13–20,50,54–57], of which 4 were from the same RCT with different FU[2,55–57]; 3 prospective cohort studies[45,51,52]; and 16 retrospective cohort studies[37,39–44,46–49,53,58–61]. Seven publications of RCTs were assessed having 'some concerns' regarding risk of bias. All other RCTs had high risk of bias (Table 2). Of all included cohort studies, none were assessed as having an unbiased assessment of study endpoints while 42% of the included studies had adequate contemporary groups (i.e., biodegradable and titanium groups; Table 2).

Two studies reported funding from research programmes[15,42] and one from the manufacturer of biodegradable osteosyntheses[13]. Funding or conflict of interest was not reported in 20 studies[14,16–20,37,39,43–51,53,59,60]. The other studies declared no funding or conflict of interest[2,40,41,52,54–58,61].

Primary endpoint

All effect estimates of pooled endpoints are presented as RR or SMD (95% CI) including the quality of evidence. Five studies reported on malunion (Table S5)[19,44,47,49,55]. Only in one RCT malunion was present at 8 weeks FU in 3% of biodegradable osteosyntheses and 0% of titanium osteosyntheses[55]. The other four studies assessing this endpoint were total zero-event studies and, thus, pooling of data was not possible.

Secondary endpoints

Mobility of bone segments at 6-12 weeks FU was evaluated in 10 studies (Table S5) [14,17,19,41,44,47,49,54,58,59]. Mobility of bone segments was assessed as not present in seven studies[19,41,44,47,49,58,59]. No significant difference was found between the biodegradable and titanium groups (RCTs: RR 1.37 (0.47;3.99), P=0.57, n=2 studies, moderate quality, Figure 2A).

Table 2: Risk of bias assessment of all included studies.

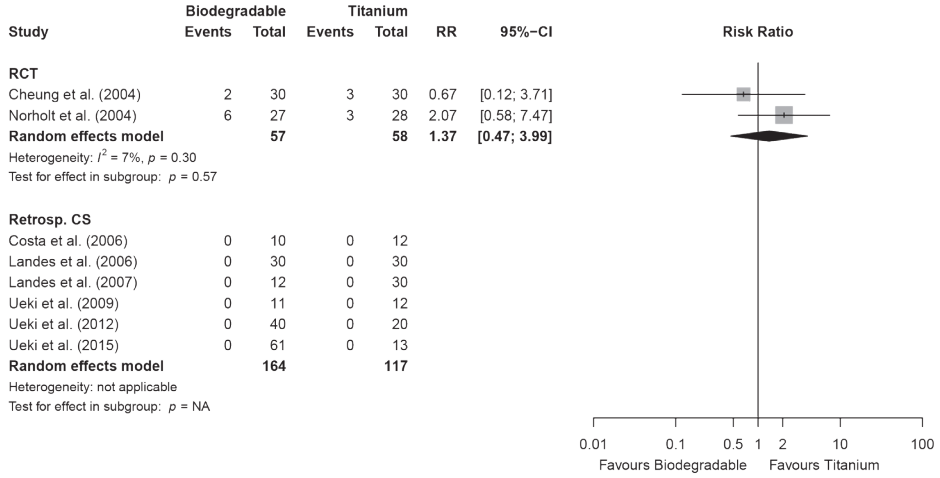
	Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)						MINORS												
Study name (year)	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall risk-of-bias	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow-up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses
Randomised controlled trials																		
Matthews et al. (2003)[50]	SC	L	L	L	L	SC												
Norholt et al. (2004)[14]	SC	L	L	L	L	SC												
Cheung et al. (2004)[17]	SC	L	SC	SC	L	SC												
Ueki et al. (2005)[19]	SC	L	L	L	L	SC												
Cheung et al. (2008)[54]	SC	L	H	L	L	H												
Park et al. (2010)[20]	SC	L	L	L	SC	SC												
Stockmann et al. (2010)[13]	SC	L	L	L	L	SC												
Tuovinen et al. (2010)[15]	SC	L	L	L	L	SC												
Buijs et al. (2012)[55]	L	H	L	L	L	H												
Yoshioka et al. (2012)[18]	SC	L	H	H	L	H												
Bakelen et al. (2013)[56]	L	H	L	L	L	H												
Yu et al. (2014)[16]	H	L	SC	L	SC	H												
Bakelen et al. (2015)[57]	L	H	L	L	L	H												
Gareb et al (2017)[2]	L	H	L	L	L	H												
Prospective cohort studies																		
Ferrretti et al. (2002)[51]							2	2	2	2	0	1	2	0	2	2	2	1
Dhol et al. (2008)[46]							2	2	2	2	0	1	2	0	2	2	2	2
Bakelen et al. (2014)[52]							2	2	2	2	1	2	0	2	2	2	2	2

Table 2: *(continued)*

	Revised Cochrane risk-of-bias tool for randomised trials (RoB 2)						MINORS										
Study name (year)	**Domain 1**	**Domain 2**	**Domain 3**	**Domain 4**	**Domain 5**	**Overall risk-of-bias**	**A clearly stated aim**	**Inclusion of consecutive patients**	**Prospective collection of data**	**Endpoints appropriate to the aim of the study**	**Unbiased assessment of the study endpoint**	**Follow-up period appropriate to the aim of the study**	**Loss to follow-up less than 5%**	**Prospective calculation of the study size**	**An adequate control group**	**Contemporary groups**	**Baseline equivalence of groups**	**Adequate statistical analyses**
Retrospective cohort studies																		
Harada et al. (1997)[46]							2	0	0	2	0	2	2	0	2	0	2	0
Costa et al. (2006)[47]							2	2	0	2	0	2	2	0	2	2	2	2
Landes et al. (2006)[58]							2	1	0	2	1	2	2	0	2	2	0	2
Turvey et al. (2006)[53]							2	1	0	2	0	2	2	0	2	1	1	0
Ueki et al. (2006)[48]							2	0	0	2	0	2	0	0	2	0	1	2
Landes et al. (2007)[59]							2	1	0	2	1	2	0	0	2	1	0	2
Ueki et al. (2009)[49]							2	0	0	2	0	2	0	0	2	0	1	2
Ahn et al. (2010)[60]							2	1	0	1	0	0	0	0	2	2	0	1
Choi et al. (2010)[37]							2	1	0	2	0	2	0	0	2	1	2	2
Ueki et al. (2011)[39]							2	0	0	2	0	2	0	0	2	0	1	2
Ballon et al. (2012)[61]							2	0	0	2	0	2	0	0	2	1	1	2
Paeng et al. (2012)[40]							2	2	0	2	0	1	2	0	2	0	2	1
Ueki et al. (2012)[41]							2	0	0	2	0	2	2	1	2	0	2	2
Blakey et al. (2014)[42]							2	0	0	2	0	2	0	0	2	2	1	2
Lee et al. (2014)[43]							2	0	0	2	1	1	2	0	2	2	1	2
Ueki et al. (2015)[44]							2	0	0	2	0	2	2	0	2	1	1	2

MINORS: Methodological index for non-randomized studies. Domain 1: Bias arising from the randomization process; Domain 2: Bias due to deviations from the intended intervention; Domain 3: Bias due to missing outcome data; Domain 4: Bias in measurement of outcome; Domain 5: Bias in selection of reported results; H: high risk of bias; L: low risk of bias; SC: some concerns; 0: not reported; 1: reported but inadequate; 2: reported and adequate. Empty cells: not applicable.

A



B

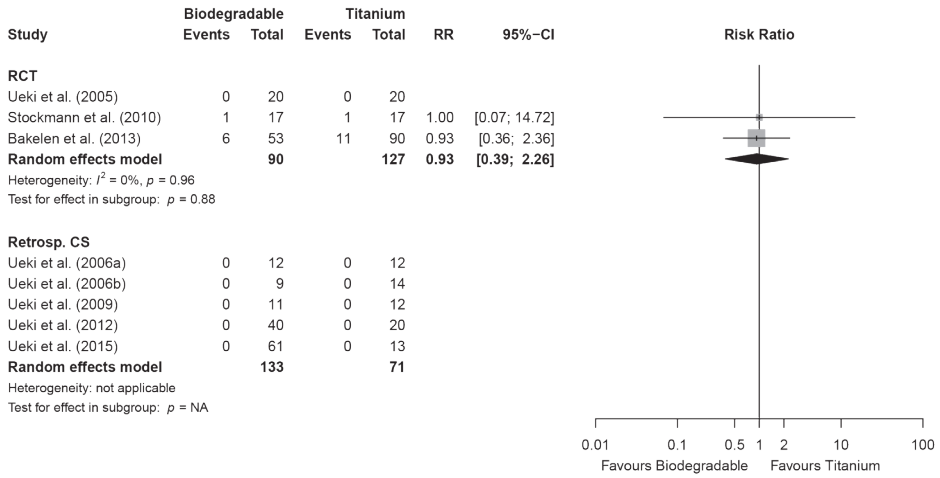


Figure 2. Forest plots of the endpoints (A) mobility of bone segments (6-12 weeks FU) and (B) malocclusion (>12 weeks FU) stratified by study design. *FU, follow-up; RCT, randomized controlled trials; RR, risk ratio; 95%-CI, 95% confidence interval, NA: not applicable.*

Malocclusion within 4 weeks FU was not reported in any of the included studies (Table S5). One RCT reported that 9% and 13% of the patients had objective malocclusion at 6-12 weeks FU in the biodegradable and titanium group, respectively (Table S5)[55]. Malocclusion after >12 weeks FU ranged from 0% to 15% (n=8 studies). All retrospective studies reporting this endpoint found no malocclusion in either treatment groups[41,44,48,49]. Pooling data from RCTs that assessed objective malocclusion did not

result in significant differences between both groups (RR 0.93 (0.39;2.26), P=0.88, n=3 studies, moderate quality, Figure 2B). One RCT with >5 years FU reported that 12% and 15% of patients in the biodegradable and titanium groups, respectively, had subjective malocclusion[2]. No subgroup analyses of objective malocclusion at short-term FU (no studies), intermediate FU (single study), and long-term FU (single studies in each of the subgroups osteosyntheses with plates/screws versus only screws) could be performed. Additionally, subgroup analyses of subjective malocclusion at any of the pre-specified follow-up moments could not be performed (single study).

Perioperative plate breakage ranged from 0 to 3% and 0% among patients in the biodegradable and titanium groups, respectively (n=4 studies, Table S5). One RCT assessed plate breakage at plate-level and reported 4% plate breakage in the biodegradable osteosyntheses group and 0% titanium plates[17]. Regarding screws, 0-12% biodegradable and 3% of the titanium screws broke (n=7 studies)[13]. Data of screw breakage in retrospective studies could not be pooled because two studies[58,59] reported the percentage of broken screws without giving the total number of included screws and these numbers could not be provided by the corresponding authors. The operative time in the RCTs was significantly longer in the biodegradable compared to the titanium group (SMD 0.50 (0.09;0.91), P=0.02, n=2 studies, moderate quality, Figure S2). Plate and screw handling was easier in the titanium compared to the biodegradable group but could not be included in the quantitative analysis (Table S5)[14,55].

Infection within 4 weeks FU was reported in 0-16% and 0-14% in the biodegradable and titanium groups (n=18 studies, Table S5), respectively, and did not differ significantly between both groups (RR 1.03 (0.46;2.28), P=0.95, n=8 studies, moderate quality, Figure 3A). Swelling within 4 weeks FU did not differ significantly between both treatment groups (RR 1.51 (0.68;3.38), P=0.31, n=2 studies, very low quality, Figure S3)[14,55]. Abscess formation was present in 12% and 5% of the patients (n=1 study) treated with biodegradable and titanium osteosyntheses, respectively[55]. Pain within short-term FU varied from 0-25% in the biodegradable and 0-30% in the titanium group (n=3 studies). MMO within 4 weeks FU was reported in one study but that study did not present exact numbers[13]. Dehiscence varied between 0-7% and 0-10% in the biodegradable and titanium groups, respectively (RCTs: RR 1.53 (0.52;4.50), P=0.44, n=5 studies, moderate quality; Figure S4 and Table S5). Plate exposure after short-term FU was reported in 0-9% and 0% in the biodegradable and titanium groups, respectively (n=8 studies).

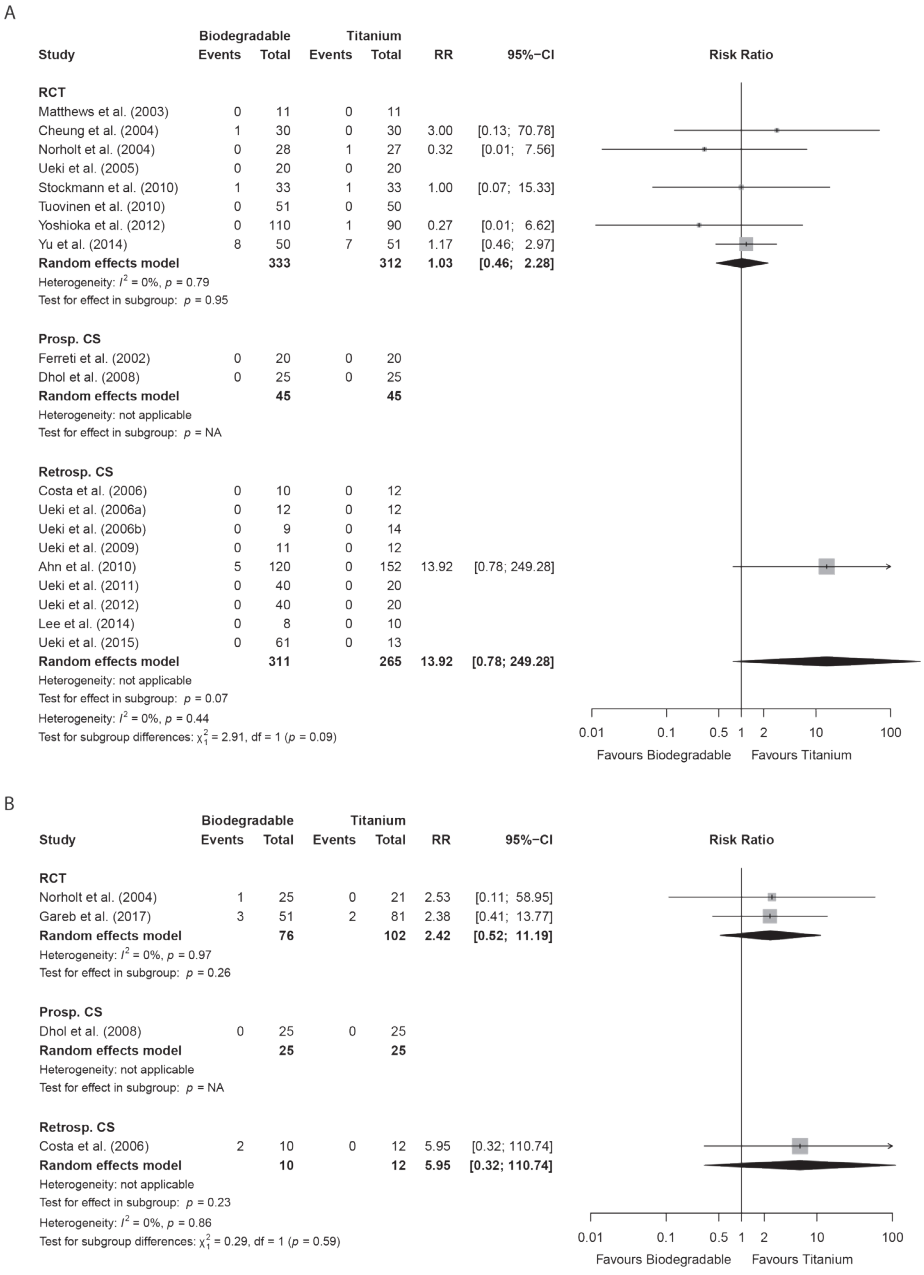


Figure 3. Forest plots of the endpoints (A) infection (<4 weeks FU) and (B) swelling (>12 weeks FU) stratified by study design. *FU, follow-up; RCT, randomized controlled trials; Prosp. CS, prospective cohort studies; Retrosp. CS, retrospective cohort studies; RR, risk ratio; 95%-CI, 95% confidence interval.*

Pain within 6-12 weeks FU was not significantly different between both treatment groups (SMD -0.1 (-0.26;0.24), P=0.93, n=2 studies, moderate quality, Figure S5 and Table S5). Two studies assessed the presence of TMJ-dysfunction after intermediate FU[46,50]. None of these included patients were diagnosed with having TMJ-dysfunction.

Regarding long-term FU, the amount of pain was generally low in both treatment groups (RCTs: SMD -0.02 (-0.29;0.25), P=0.89, n=3 studies, high quality, Figure S6 and Table S5). MMO (>12 weeks FU) was not significantly different between both groups (RCTs: SMD -0.58 (-1.39;0.22), n=2 studies, P=0.16, very low quality, Figure S7). The presence of TMJ-dysfunction ranged from 0-15% in the biodegradable and 0-25% in the titanium group (n=3 studies). MFIQ scores were similar after >5 years FU for both treatment groups (median 18 (interquartile range 17-21))[2]. A single RCT reported a similar percentage (3%) of abscesses at 1-year FU[56]. RCTs showed no significant differences between both groups regarding long-term swelling (RR 2.42 (0.52;11.19), P=0.26, n=2 studies, moderate quality; Figure 3B). Plate and screw palpability after long-term FU occurred in 2-51% and 0-42% of the biodegradable and titanium groups, respectively (RCTs: RR 0.38 (0.11;1.28), P=0.12, n=4 studies, very low quality, Figure 4A). Patients of both groups were comparable regarding satisfaction with the result after 2-years[17], 5-years[2], and 8-years FU[13] (n=3 studies, Table S5).

Secondary surgery and total costs

Symptomatic biodegradable and titanium device removal percentages varied from 0-29% and 0-15%, respectively (RCTs: RR 1.29 (0.68;2.44), P=0.44, n=7 studies, moderate quality, Figure 4B and Table S5). The FU varied from 8 weeks to 8 years (Table 1). Chronic infection and discomfort were the main reasons for symptomatic device removal. No differences were found between the maxillary versus mandibular versus bimaxillary osteotomies (maxillary: RR 0.12 (0.01;2.20), P=0.15, n=1 study; mandibular: RR 1.60 (0.76;3.34), P=0.21, n=4 studies; bimaxillary: RR 1.45 (0.64;3.27), P=0.37); P=0.09, Figure S8). A subgroup analysis of osteosyntheses using only screws versus plates and screws revealed no significant difference in symptomatic device removal rate between both subgroups (screws: RR 0.26 (0.03;2.28), P=0.22, n=2 studies; plates and screws: RR 1.86 (1.13;3.07), P=0.01, n=2 studies; P=0.08; Figure S9). A subgroup analysis of the symptomatic device removal rates at ≤1 year and >1 year FU resulted in similar symptomatic device removal rates of biodegradable and titanium osteosyntheses at ≤1 year FU (RR 0.16 (0.02;1.26), P=0.08, n=2 studies), while titanium osteosyntheses had lower symptomatic device removal rates if only studies with >1 year FU were included (RR 1.73 (1.10;2.72), P=0.02, n=5 studies; Figure S10).

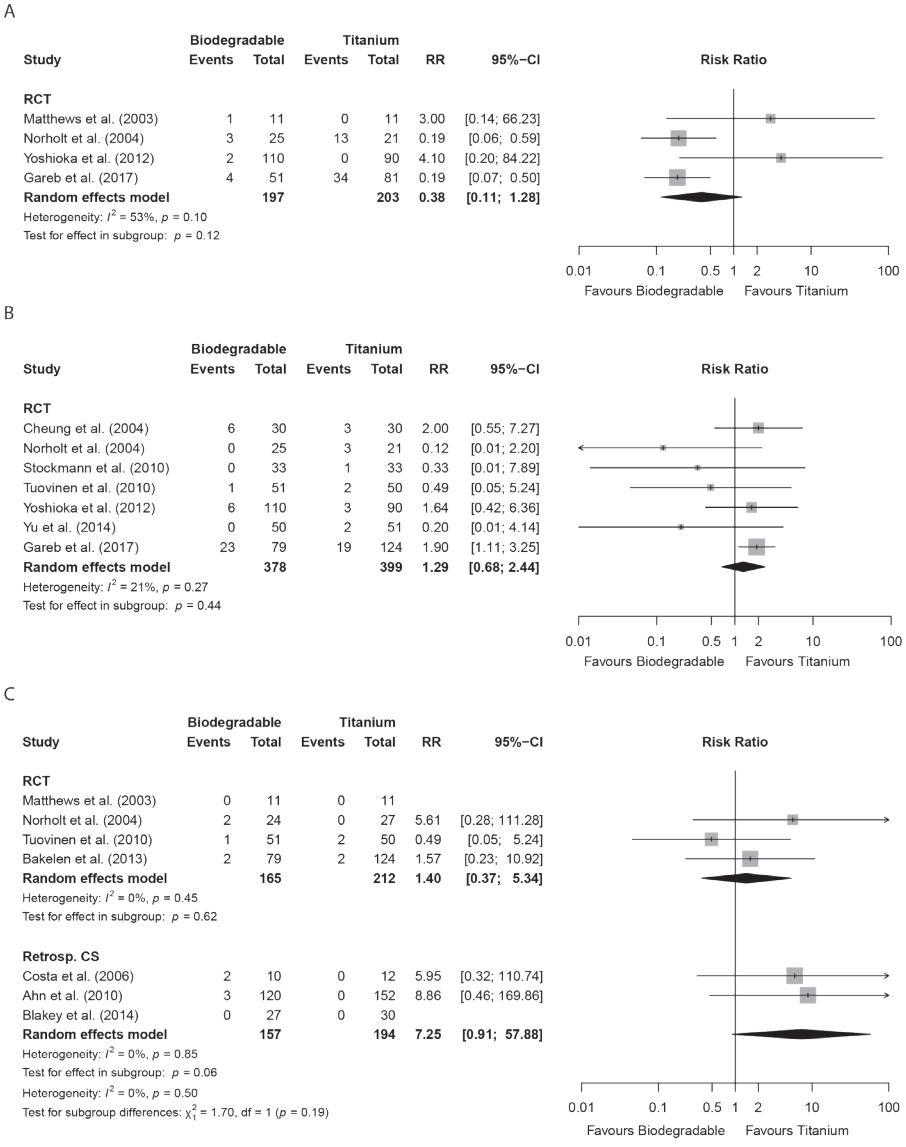


Figure 4. Forest plots of the endpoints (A) palpability of plates/screws (>12 weeks FU), (B) symptomatic device removal (overall FU), and (C) revision surgery (overall FU) stratified by study design. *FU, follow-up; RCT, randomized controlled trials; Retrosp. CS, retrospective cohort studies; RR, risk ratio; 95%-CI, 95% confidence interval.*

Total costs (i.e., indirect and direct costs) were assessed in one RCT with 2-years FU[57]. The mean costs of the biodegradable and titanium groups were 6589±3492 and 6787±5014 euros, respectively. Revision surgery (i.e., device removal not included) ranged from 0-8% and 0-4% of the patients in the biodegradable group and titanium group, respectively (RCTs: RR 1.40 (0.37;5.34), P=0.62, n=4 studies, moderate quality, Figure 4C). Chronic infection and abscess formation were the main reasons to indicate revision surgery.

Skeletal stability

The amount of operative displacement, amount of relapse with the corresponding follow-up, and the lateral reference marks used by all studies that assessed skeletal stability are presented in Table S6. Follow-up ranged from 6 weeks to 2 years. The majority of studies assessed skeletal stability after 1 year follow-up.

Horizontal relapse after a Le Fort I advancement was assessed in three RCTs[14,20,54], one prospective study[45], and seven retrospective studies[41,42,47,48,58,59,61]. RCT data could not be pooled because one study did not provide exact numbers[54] and one study reported zero variance in the amount of relapse. The retrospective studies' data showed no significant difference in the amount of relapse between biodegradable and titanium osteosyntheses (SMD 0.15 (-0.08;0.39), P=0.21, n=7 studies, very low quality, Figure S11). Angular relapse after maxillary advancement did not differ significantly between both treatment groups SMD 0.07 (-0.41;0.55), P=0.78, n=4 studies, very low quality, Figure S12). No significant difference in horizontal relapse after a Le Fort I setback between biodegradable and titanium osteosyntheses groups was found (SMD -0.02 (-0.61; 0.57), P=0.95, n=3 studies, very low quality, Figure S13).

Vertical relapse after maxillary impaction did not differ significantly between both treatment groups (SMD 0.07 (-0.35;0.50), P=0.74, n=2 studies, high quality, Figure S14). The amount of maxillary relapse after maxillary elongation was not significantly different between both types of osteosynthesis systems (SMD 0.31 (-0.23;0.84), P=0.26, n=2 studies, very low quality, Figure S15).

Horizontal relapse after mandibular advancement was not significantly different between both treatment groups (SMD 0.16 (-0.39;0.71), P=0.56, n=2 studies, very low quality, Figure S16). Two RCTs[19,20] and seven retrospective studies[37,40,43,46,58,59,61] assessed horizontal relapse after mandibular setback. Pooling of data showed no significant differences between biodegradable and titanium osteosyntheses (RCTs: SMD 0.04 (-0.73;0.80), P=0.92, n=2 studies, low quality, Figure S17). A subgroup comparison of

horizontal relapse after mandibular setback between osteosyntheses with plates and screws versus only screws resulted in no significant difference between subgroups (n=5 studies, P=0.99; Figure S18).

Data regarding vertical relapse after mandibular setback showed a significant difference in favour of biodegradable osteosyntheses opposed to titanium osteosyntheses (RCTs: SMD -0.63 (-1.11;-0.15), P=0.01, n=2 studies, low quality, Figure S19). There was no significant difference in the subgroup analysis of osteosyntheses plates and screws versus only screws (n=5 studies, P=0.58; Figure S20).

A quantitative analysis of the data of mandibular angular relapse after clockwise rotation (CW) showed significantly less relapse in the biodegradable osteosyntheses group (SMD -0.79 (-1.40;-0.17), P=0.01, n=4 studies, very low quality, Figure S21). Regarding mandibular angular relapse after counter clockwise rotation (CCW), RCTs' data showed significantly less relapse in the titanium osteosyntheses group (SMD 1.12 (0.08;2.16), P=0.03, n=2 studies, very low quality, Figure S22). All assessed endpoints with the quality of evidence are summarized in Table 3.

Additional analyses

The sensitivity analyses with total zero event studies included showed no significant differences the conventional analyses. Additionally, a post-hoc sensitivity analysis whereby one study was omitted at a time showed that excluding the study performed by Ueki et al.[19] significantly altered the overall effect estimate of vertical relapse after mandibular setback to a non-significant difference between biodegradable and titanium osteosyntheses (both sensitivity analyses are available via the corresponding author). Sensitivity analyses showed that the effect estimates of all included RCTs did not significantly differ (i.e. overlapping 95% CI) whenever compared to effect estimates of only non-high-risk-of-bias RCTs (Figures S23 and S24). A meta-regression analysis showed that all five domains and overall risk of bias did not have a significant effect on the effect estimate of symptomatic device removal (Table S7).

TSA revealed that the required information sizes (RIS) were not achieved for the outcomes swelling (short- long-term follow-up), dehiscence, mobility of bone segment, palpability of screws/plates, symptomatic device removal, and revision surgery. Also, no TSA-boundaries were surpassed (Table S8) and, hence, TSA was not able to support the findings of conventional meta-analyses for these outcomes.

Table 3: Summary of findings with quality of evidence assessment.

	Randomised controlled trials					Prospective cohort studies					Prospective cohort studies				
Outcome	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**
Perioperative endpoints															
Plate breakage[a]	482 (4)	Four studies, of which two had zero events, one assessed plate breakage at plate level, and one at patient level				No studies					No studies				
Screw breakage[a]	348 (4)	Four studies, of which two had zero events, one assessed screw breakage at screw level, and one at patient level				No studies					155 (3)	Three studies, of which two only mentioned percentages of screw breakage without the total number of screws used			
Operation time[b]	266 (2)	+0.50 (0.09; 0.91)	NA	NA	Moderate[1]	No studies					No studies				
Handling by surgeon[b]	260 (2)	Two studies, different outcome measures				No studies					No studies				
Short-term follow-up															
Malocclusion[a]	No studies					No studies					No studies				
Infection[a]	645 (8)	1.03 (0.46; 2.28)	43 per 1000	45 per 1000 (20; 98)	Moderate[4]	90 (2)	Two zero-event studies				576 (9)	Nine studies, of which eight had zero events			
Swelling[a]	255 (2)	1.51 (0.68; 3.38)	133 per 1000	201 per 1000 (91; 450)	Very low[1,2,4]	50 (1)	Single zero-event study				No studies				
Abscess[a]	200 (1)	Single study				No studies					No studies				
Pain[a]	160 (3)	Three studies, two with different outcome measures and one provided data in graphs only				50 (1)	Single zero-event study				No studies				

Outcome	Randomised controlled trials: Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Prospective cohort studies: Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)	Prospective cohort studies: Subjects, N (studies)	RR or SMD (95% CI)	Tit. event proportion	Bio. risk (95% CI)	Quality of evidence (GRADE)
Analgesics used[a]	No studies					No studies					No studies				
MMO[b]	66 (1)	Single study that provided data in graphs only				No studies					No studies				
Dehiscence[a]	421 (5)	1.53 (0.52; 4.50)	24 per 1000	37 per 1000 (13; 108)	Moderate[4]	No studies					226 (5)	Five zero-event studies			
Plate exposure[a]	182 (4)	Four studies, of which two had zero events and one did not provide sufficient details				No studies					140 (4)	Four zero-event studies			
Intermediate follow-up															
Malunion[a]	240 (2)	Two studies, of which one had zero events				No studies					93 (3)	Three zero-event studies			
Mobility bone segments[a]	115 (2)	1.37 (0.47; 3.99)	104 per 1000	143 per 1000 (49; 415)	Moderate[4]	No studies					281 (6)	Six zero-event studies			
Malocclusion[a]	200 (1)	Single study				No studies					No studies				
Pain[b]	260 (2)	-0.01 (-0.26;0.24)	NA	NA	Moderate[1]	50 (1)	Single zero-event study				No studies				
MMO[b]	66 (1)	Single study that provided data in graphs only				No studies					No studies				
TMJ-dysfunction[a]	22 (1)	Single zero-event study				No studies					60 (2)	Two zero-event studies			
Long-term follow-up															
Malocclusion[a]	217 (3)	0.93 (0.39; 2.26)	113 per 1000	105 per 1000 (44; 256)	Moderate[4]	No studies					204 (4)	Four zero-event studies			

	Randomised controlled trials					Prospective cohort studies					Prospective cohort studies				
Outcome	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**
Pain[b]	220 (3)	-0.02 (-0.29; 0.25)	NA	NA	High	50 (1)	Single zero-event study				No studies				
MMO[b]	141 (2)	-0.58 (-1.39; 0.22)	NA	NA	Very low[1,3,4]	No studies					No studies				
TMJ-dysfunction[a]	40 (1)	Single study				No studies					292 (2)	Two studies, of which one had zero events			
MFIQ[b]	203 (1)	Single study				No studies					No studies				
Abscess[a]	203 (1)	Single study				No studies					No studies				
Swelling[a]	178 (2)	2.42 (0.52; 11.19)	20 per 1000	49 per 1000 (11; 224)	Moderate[1,4,6]	50 (1)	Single zero-event study				22 (1)	Single study			
Palpability plate/screws[a]	400 (4)	0.38 (0.11; 1.28)	232 per 1000	89 per 1000 (26; 297)	Very low[1,2,4]	No studies					No studies				
Satisfaction[b]	329 (3)	Three studies, different outcome measures				No studies					No studies				
Overall follow-up															
Symptomatic device removal[a]	777 (7)	1.29 (0.68; 2.44)	83 per 1000	107 per 1000 (57; 203)	Moderate[4]	No studies					No studies				
Total costs[b]	203 (1)	Single study				No studies					No studies				
Revision surgery (not device removal)[a]	377 (4)	1.40 (0.37; 5.34)	20 per 1000	28 per 1000 (8; 107)	Moderate[4]	No studies					351 (3)	7.25 (0.91; 57.88)	0 per 1000	NA	Very low[1,4,6]

	Randomised controlled trials					Prospective cohort studies					Prospective cohort studies				
Outcome	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**
Maxillary horizontal relapse (adv)	160 (3)	Three studies, of which one provided data in graphs only and one could not be included in the meta-analysis due to zero variance in the titanium group				50 (1)	Single study				288 (7)	+0.15 (-0.08; 0.39)	NA	NA	Very low[1]
Maxillary angular relapse (adv)	100 (2)	Two studies, significant different reference points used for assessment				No studies					129 (4)	+0.07 (-0.41; 0.55)	NA	NA	Very low[1,2,4]
Maxillary horizontal relapse (sb)	No studies					No studies					47 (3)	-0.02 (-0.61; 0.57)	NA	NA	Very low[1,4]
Maxillary angle relapse (sb)	No studies					No studies					No studies				
Maxillary vertical relapse (imp)	95 (2)	+0.07 (-0.35; 0.50)	NA	NA	High	50 (1)	Single study				175 (5)	+0.35 (-0.13; 0.83)	NA	NA	Very low[1,2,4]
Maxillary vertical relapse (elong)	60 (1)	Single study				No studies					81 (3)	+0.31 (-0.23; 0.84)	NA	NA	Very low[1,4]
Mandibular horizontal relapse (adv)	80 (2)	Two studies, of which one provided data in median with interquartile range and one provided insufficient details				77 (2)	+0.16 (-0.39; 0.71)	NA	NA	Very low[1,4]	129 (4)	+0.14 (-0.23; 0.51)	NA	NA	Very low[1,4]
Mandibular horizontal relapse (sb)	80 (2)	+0.04 (-0.73; 0.80)	NA	NA	Low[2,4]	No studies					195 (7)	+0.33 (-0.25; 0.91)	NA	NA	Very low[1,2,4]

	Randomised controlled trials					Prospective cohort studies					Prospective cohort studies				
Outcome	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**	**Subjects, N (studies)**	**RR or SMD (95% CI)**	**Tit. event proportion**	**Bio. risk (95% CI)**	**Quality of evidence (GRADE)**
Mandibular vertical relapse (adv)	80 (2)	Two studies, of which one provided data in median with interquartile range and one provided insufficient details				37 (1)	Single study				69 (1)	Single study			
Mandibular vertical relapse (sb)	80 (2)	-0.63 (-1.11; -0.15)	NA	NA	Low[2,4]	No studies					118 (4)	-0.25 (-0.66; 0.16)	NA	NA	Very low[1,4]
Mandibular angular relapse (CW)	22 (1)	Single study				No studies					102 (4)	-0.79 (-1.40; -0.17)	NA	NA	Very low[1,2,4]
Mandibular angular relapse (CCW)	80 (2)	1.12 (0.08; 2.16)	NA	NA	Very low[2,3,4]	No studies					49 (3)	+0.34 (-0.23; 0.91)	NA	NA	Very low[1,4]

[a]: binary variable; [b]: continuous variable; GRADE, Grades of Recommendation, Assessment, Development and Evaluation Working Group system; Bio, biodegradable osteosynthesis; Tit, titanium osteosynthesis; RR, risk ratio (binary variables); SMD, standardised mean difference (continuous variables); adv, advancement; sb, setback; imp, impaction; elong, elongation; CW, clockwise rotation; CCW, counter clockwise rotation; NA, not applicable. [1]Downgraded one level due to high risks of bias identified across studies: majority of studies had high risk of bias; [2]Downgraded one level for inconsistency: substantial methodological or clinical heterogeneity that could not be accounted for in analyses; [3]Downgraded one level for indirectness: the evidence of the original manuscripts were more restrictive than the review question; [4]Downgraded one level for imprecision: limits of effect estimate confidence interval are not consistent (i.e., cover both benefit and harm); [5]Upgraded one level due to large effect (i.e., RR<0.5 or RR>2.0, or SMD<-0.8 or SMD>+0.8).

Discussion

This meta-analysis shows that biodegradable and titanium osteosyntheses are equivalent in malunion rates, bone segments mobility, objective and subjective malocclusion, and MMO at predefined time points after orthognathic surgery. Furthermore, we found no differences in swelling, pain, dehiscence, infection, plate exposure, plate and screw palpability, TMJ-dysfunction, symptomatic device removal, and revision surgery rates (i.e., other than removal of plates and screws). Additionally, skeletal stability was similar in most types of orthognathic surgery except when assessing mandibular vertical relapse after setback, and mandibular angular relapse after CW- (both in favour of biodegradable osteosyntheses) and CCW-rotation (in favour of titanium osteosyntheses). The operative time was significantly longer in the biodegradable compared to the titanium group.

Malunion at 6-12 weeks FU was rare in both treatment groups. One study reported that a small proportion (3%) of patients treated with biodegradable osteosyntheses demonstrated malunion[55]. All other studies reported zero events of malunion in both treatment groups. This result, together with the non-mobility of bone segments at 6-12 weeks FU in most of the studies, emphasizes that both types of osteosyntheses are adequate for the fixation of maxillofacial osteotomies. Furthermore, low rates of objective and subjective malocclusion at both intermediate and long-term FU, and similar MFIQ scores at long-term FU (i.e., >5 years) were observed with both types of osteosyntheses.

Although skeletal stability was similar among both treatment groups after most orthognathic surgeries (Table 3), even after surgical procedures which are known to exhibit a high degree of instability (e.g., maxillary setback)[63], significant differences were found between the biodegradable group and titanium group after mandibular setback (vertical relapse) and mandibular CW (angular relapse; both in favour of biodegradable osteosyntheses), and CCW rotation (angular relapse; in favour of titanium osteosyntheses) surgery. The difference in vertical relapse after mandibular setback may have been due to the higher operative displacement in the titanium group[19,20]. The sensitivity analysis showed that omitting Ueki et al.[19] (i.e., the study with the largest discrepancy in operative movement between both treatment groups; see Table S5) from the analysis diminished this significant difference between both treatment groups, indicating a non-robust effect estimate of the initial analysis. Higher operative displacement results in less skeletal stability with greater skeletal relapse, and thus may be a confounding factor[64,65]. We found no clear explanation for the difference in angular

relapse after mandibular CW rotation in favour of biodegradable osteosyntheses. Ballon et al.[61] used an outer screw diameter of 2.5mm and 2.0mm with corresponding plates in the biodegradable and titanium group, respectively. Although the mechanical properties improve significantly when larger systems are used[9], the mechanical properties of biodegradable systems remain lower than the corresponding titanium systems[9]. Skeletal stability was lower in the biodegradable group than the titanium group after CCW rotation. One of the included RCT's[19] described higher operative displacement in the biodegradable group, while another RCT reported similar operative displacement[20]. The higher operative displacement and discrepancy in duration of follow-up (ranging from 6 months to 1 year) introduces heterogeneity in the meta-analysis (I^2 = 75%). Given the confounding factors and substantial heterogeneity in these analyses, no firm conclusions regarding these differences can be drawn. Future researchers should focus on well-defined in- and exclusion criteria to minimize heterogeneity (e.g., operative displacement) and on adequate follow-up (i.e., ≥1 year) as most skeletal relapses occur in the first postoperative year[66,67]. These measures would enable adequate pooling of future data.

Biodegradable osteosyntheses have been associated with foreign-body reactions and, thus, continues to be a concern in the use of such osteosynthesis systems[2,11]. The present review finds no significant differences regarding long-term swelling and pain. A single study[56] assessed abscess formation after long-term FU and reported 2% versus 0% abscess formation in the biodegradable and titanium group, respectively. Another study assessed plate and screw palpability during a FU >5 years and reported 42% versus 8% cases after titanium and biodegradable osteosyntheses, respectively[2]. This finding is in line with the expectations given the resorbability of the latter osteosynthesis system. No significant difference was found in the symptomatic device removal rate between biodegradable and titanium osteosyntheses. The main reason for device removal in both groups was chronic infection or discomfort. A subgroup analysis comparing symptomatic device removal rates of both types of osteosyntheses according to the duration of FU (i.e., ≤1 year and >1 year FU) showed that titanium osteosynthesis systems were favourable whenever FU was longer than 1 year. Both these subgroup analyses indicate that biodegradable plates and screws, as opposed to only screws, tend to be removed after 1 year follow-up. This could be explained by the degradation process of biodegradable plates and screws which occurs in two phases, both consisting of hydrolysis[68]. Symptomatic swelling during the degradation of biodegradable osteosyntheses is in particular a concern during degradation (e.g., after >1 year FU) due to the attraction of water within the capsule surrounding the implant as

well as foreign body reactions evoked by degradation products, and is less pronounced during the initial postoperative period (i.e., <1 year FU)[68,69]. Discomfort was one of the main reasons for symptomatic device removal, especially of the biodegradable plate and screws after >1 year FU, which may have been due to their bulkiness. This effect might be less noticeable in cases where only screws or pins are used (i.e., less bulky). Therefore, future research should have at least a 1-year FU and should distinguish osteosyntheses with plates and screws versus only screws to assess the symptomatic device removal rate appropriately.

The mandible is exposed to considerably higher biomechanical forces compared to the maxilla[70,71]. Higher forces acting on the mandible may lead to loosening of screws and, thereafter, to inflammation especially in osteotomies because, unlike fractures, there is no interfragmentary stability[2]. Additionally, the lesser vascularity and morphology of the mandible could have unfavourable consequences on fixation and degradation of biodegradable osteosynthesis systems[2]. Of all included biodegradable osteosynthesis systems, three are certified to be used for mandibular osteotomies[72–74]. Instructions of all other included biodegradable systems state that usage of these systems in load-bearing areas, including mandibular osteotomies, are contraindicated. Nonetheless, these biodegradable osteosynthesis systems have been applied off-label in various studies that included patients treated with mandibular osteotomies[20,43,47,50,53,59]. A subgroup analysis comparing maxillary versus mandibular versus bimaxillary osteotomies showed no difference in symptomatic device removal between the types of osteotomies. However, this subgroup analysis showed a trend in favour of biodegradable osteosyntheses in maxillary osteotomies and titanium osteosyntheses in mandibular and bimaxillary osteotomies. Therefore, although the overall analysed symptomatic device removal rates were similar for titanium and biodegradable osteosyntheses (i.e., all patients undergoing orthognathic surgery analysed as a single group), biodegradable osteosyntheses could result in less symptomatic device removal after maxillary osteotomies and may thus be appealing for this specific subpopulation (i.e., maxillary osteotomies) due to possible lower symptomatic device removal rates compared to titanium osteosyntheses. However, the data for maxillary osteotomies in this subgroup analysis were derived from two small RCTs. Future studies should make this distinction thereby enabling a subgroup comparison with larger sample sizes.

Plate breakage occurred in none of the cases with titanium osteosyntheses while biodegradable plates broke in 0-4% of the cases. Additionally, titanium screw breakage occurred only in one study in 3% of the cases[13] while biodegradable screws

broke in 0-12% of the cases of the included studies. These less favourable handling characteristics of biodegradable osteosyntheses are also expressed by surgeons (Table S5). The perioperative material complications, accompanied with the need to tap the burr hole and to heat the biodegradable plates to facilitate bending of the plate, are the main reasons that the operation time is significantly longer for biodegradable than titanium osteosynthesis systems. Surgeons do, however, state that more exposure to biodegradable systems could diminish these differences[62,75].

None of the included studies assessed analgesic usage and angular relapse after maxillary setback. Also, data regarding abscess formation after long-term FU was rare but remains important as it could indicate a foreign-body reaction. Future studies should include this endpoint in their assessment, preferably by taking a culture to exclude an infection as a cause. Furthermore, it is hypothesized that orthognathic surgery may cause biomechanical stress at the TMJ and could induce pathophysiological remodelling processes such as degenerative joint disease[76]. In this review we found that 15% and 25% of the patients treated in one RCT[19] with biodegradable and titanium osteosyntheses, respectively, had complaints regarding TMJ-function at 1-year FU. Additionally, patients in both treatment groups still had some mandibular function impairment at >5-years FU. Therefore, to adequately assess mandibular function after orthognathic surgery as well as to make comparison with healthy subjects possible, we advocate that future research should include TMJ-function assessment and use validated questionnaires (e.g., MFIQ). Finally, a single RCT[57] assessed the total costs and reported that the titanium group's mean total costs at the 2 year FU were slightly higher. The main reason was due to 'absence of work' after the surgical procedure due to worse MFIQ scores at 8 weeks FU (i.e., indirect costs).

The most recent systematic review regarding the comparison of biodegradable versus titanium osteosyntheses for orthognathic surgery was published in 2018[23], but focused only on skeletal stability and failed to account for methodological (e.g., combining different study designs) and clinical heterogeneity (e.g. the authors included patients with cleft lip and palate). It is known that (i) the required amount of maxillary and mandibular movement is generally much larger in those patients compared to patients without a cleft[77], (ii) their osteotomies are less stable compared to non-cleft patients and therefore have more frequent and larger skeletal relapse after surgery[78], and (iii) the frequency of secondary surgical intervention increases with increasing cleft severity (i.e., cleft lip and alveolus, unilateral cleft lip and palate, and bilateral cleft lip and palate)[79].

Another recent systematic review assessed the efficacy and morbidity of biodegradable compared to titanium osteosyntheses after maxillofacial trauma in a similar way as this review[10]. It was concluded that symptomatic device removal occurred significantly less often (RR 0.11; 95% CI 0.02;0.57) and screw breakage (i.e., perioperative) significantly more often (RR 17.13, 95% CI: 2.19;34.18) after biodegradable compared to titanium osteosyntheses[10]. An essential difference between both populations is that the fixation in trauma patients is supported by interfragmentary stability while this is, by definition, absent in osteotomies. Furthermore, trauma patients' fractures are fixated into maximum occlusion whereas maximum occlusion in patients undergoing orthognathic surgery is reached after postoperative orthodontic treatment. Additionally, trauma patients are more often male using alcohol and tobacco compared to patients undergoing orthognathic surgery[80–82]. Both substances impair wound healing and reduce vascularity intra-orally and thus disturb degradation and resorption of biodegradable systems. The different conclusions of the reviews of both populations emphasize that osteosyntheses in patients undergoing open reduction with internal fixation after maxillofacial trauma and patients undergoing orthognathic surgery should be considered as two different entities. Therefore, the results of any future research of both populations should be analysed separately.

None of the included RCTs were assessed as having overall low risk of bias. The quality of evidence (i.e., using the GRADE approach) of the assessed endpoints varied from very low to high quality. Downgrading the quality of evidence was predominantly caused by the presence of high risk of bias, imprecision and inconsistency of data (e.g., due to clinical heterogeneity but with insufficient evidence available to perform subgroup analyses). Endpoints with very low quality of evidence should be interpreted with caution and should not be used to make recommendations for clinical practice[25].

This is the most comprehensive systematic review to date comparing biodegradable with titanium osteosyntheses in orthognathic surgery. The strengths of this systematic review with meta-analysis are: the robust and transparent methodology used, based on a pre-specified and -registered protocol, the Cochrane Handbook, and the PRISMA statement; a sensitive, thorough, and updated literature search without language or period restrictions; and inclusion of all relevant clinical endpoints. Furthermore, all stages of study selection and the data-extraction were independently performed by two reviewers with excellent inter-observer agreement. Additionally, the risk of bias and GRADE assessment were performed in duplicate. Finally, to increase the reliability of the conclusions drawn and to assess the required information size, TSA was performed.

The quality of studies included limits the outcomes of the current systematic review and thus biased effect estimates could not be excluded. Furthermore, clinical heterogeneity due to differences in biodegradable and titanium osteosynthesis systems used (e.g., composition and sizes), different procedures, differences in operative displacement, and differences in MMF policies were present across studies. Preferably, we would perform subgroup analyses, but there was insufficient data reported in the studies to conduct these analyses. As a result of the presences of heterogeneity, we had to downgrade the quality of evidence of several endpoints in the GRADE assessment. Finally, despite multiple attempts to contact authors of original research papers, some data could not be retrieved and, thus, not be included in this review.

Currently, the main quality of the evidence varies from very low to moderate, and thus high quality research is needed. We acknowledge the fact that blinding (i.e., by surgeons and the outcome assessment) is not possible owing to the properties of titanium and biodegradable osteosynthesis systems. However, the main reasons for increasing the risk of bias was bias due to deviations from the intended intervention and bias due to missing outcome data. This emphasizes the need of pre-specified, -registered, and well-defined protocols of future RCTs. In particular, these protocols should focus on well-defined (i) in- and exclusion criteria (e.g., separating the inclusion of maxillary and mandibular osteotomies) and (ii) endpoints to minimize reporting bias. Furthermore, (iii) appropriate follow-up is advocated to minimize attrition bias (e.g., >1 year FU for symptomatic device removal and skeletal stability) and (iv) indications for device removal should be clearly defined and followed to reduce detection bias. Additionally, since data regarding three-dimensional analysis of patients undergoing orthognathic surgery is growing, they could and should be used in the analyses of skeletal stability. Also, as the patient's opinion regarding outcomes is of high importance, patient reported outcomes (e.g., MFIQ, subjective malocclusion) should be assessed. Moreover, reporting of patient and surgical characteristics, and outcomes, including details regarding the usage of alcohol and tobacco, the used osteosynthesis systems with compositions and sizes, and the MMF, orthodontic treatment, and postoperative dietary policies, should be improved. Future studies should also include cost-effectiveness as the outcome measure, including primary (i.e., perioperative) and secondary costs (e.g., additional interventions, travelling expenses, absence of work). Finally, RCTs should adhere to the CONSORT guidelines to assure high quality reporting[83], minimize reporting bias, and enable assessment and pooling of future data.

Conclusions

Considering the qualitative review and meta-analyses, biodegradable and titanium osteosyntheses are equivalent in efficacy and morbidity of fixation after orthognathic surgery. Perioperative plate and screw breakage, however, occur more often with biodegradable relative to titanium systems, and the operative time of the former is longer. Symptomatic device removal rate is similar among both groups. Skeletal stability is similar in most types of orthognathic surgery after using both types of osteosyntheses. Biodegradable osteosyntheses can serve as a valid alternative whenever this is preferred by surgeons or patients. Due to the quality of evidence, high-quality studies are necessary to elucidate the full potential of biodegradable osteosyntheses.

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Conflict of interests

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Supplementary data

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Table S1. Electronic databases with the corresponding search details (11 February 2021).

Database	Search terms	Hits
PubMed (http://www.ncbi.nlm.nih.gov/pubmed/)	("Orthognathic Surgery"[Mesh] OR "Orthognathic Surgical Procedures"[Mesh] OR "Osteotomy, Le Fort"[Mesh] OR "Osteotomy, Sagittal Split Ramus"[Mesh] OR "Mandibular Advancement"[Mesh] OR "Facial Bones/surgery"[Mesh] OR "Facial Injuries"[Mesh:NoExp] OR "Maxillofacial Injuries"[Mesh] OR "Maxillofacial Abnormalities"[Mesh] OR "Malocclusion/surgery"[Mesh] OR maxill*[tiab] OR mandib*[tiab] OR jaw[tiab] OR orthognat*[tiab] OR craniofac*[tiab] OR craniomaxil*[tiab] OR retrognat*[tiab] OR orthodont*[tiab] OR zygom*[tiab] OR split ramus[tiab] OR "Facial injuries"[MeSH] OR ((orbit*[tiab] OR facial[tiab] OR face[tiab] OR nose[tiab] OR nasal[tiab]) AND (fract*[tiab] OR injur*[tiab] OR reconstruct*[tiab]))) AND ("Absorbable Implants"[Mesh] OR "Internal Fixators"[Mesh] OR "Fracture Fixation, Internal"[Mesh] OR plate*[tiab] OR screw*[tiab] OR miniscrew*[tiab] OR miniplate*[tiab] OR implant*[tiab] OR osteosynth*[tiab] OR osseointegrat*[tiab] OR osteofixat*[tiab] OR osteotom*[tiab] OR fixat*[tiab]) AND ("Absorbable Implants"[Mesh] OR bioresorb*[tiab] OR biodegrad*[tiab] OR bioabsorb*[tiab] OR bioadsorb*[tiab] OR absorb*[tiab] OR resorb*[tiab] OR adsorb*[tiab] OR "Lactic acid"[MeSH] OR lactic acid[tiab] OR "Polyglycolic acid"[MeSH] OR polyglycolic acid[tiab] OR "Hydroxyapatites"[MeSH] OR hydroxyapatite[tiab] OR biologically inert[tiab]) NOT ("Case Reports" [Publication Type] OR "Review" [Publication Type]) NOT ("Animals"[Mesh] NOT "Humans"[Mesh])	2535
EMBASE (http://www.embase.com/home)	('craniofacial surgery'/de OR 'cranioplasty'/exp OR 'face surgery'/de OR 'maxillofacial surgery'/exp OR 'nose surgery'/exp OR 'orthognathic surgery'/exp OR 'orbit reconstruction'/exp OR 'maxillofacial injury'/de OR 'skull injury'/exp OR 'skull'/exp OR 'face fracture'/exp OR 'skull malformation'/exp/dm_su OR 'craniofacial malformation'/exp OR 'face malformation'/dm_su OR 'malocclusion'/exp/dm_su OR (maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR zygom* OR 'split ramus' OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct*))):ab,ti) AND ('bone plate'/exp OR 'bone screw'/exp OR 'internal fixator'/exp OR 'fracture fixation'/exp OR 'bioabsorbable screw'/exp OR 'biodegradable screw'/exp OR 'biodegradable implant'/exp OR 'orthopedic fixation device'/de OR (plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*):ab,ti) AND ('biodegradable implant'/exp OR 'bioabsorbable screw'/exp OR 'biodegradable screw'/exp OR 'lactic acid'/exp/mj OR 'polyglycolic acid'/exp/mj OR 'hydroxyapatite'/exp/mj OR 'biosorbent'/exp OR (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR 'lactic acid' OR 'polyglycolic acid' OR hydroxyapatite OR 'biologically inert'):ab,ti) NOT (('animal'/exp OR 'nonhuman'/exp) NOT 'human'/exp) NOT ('review'/exp OR 'case report'/exp OR 'conference abstract'/it)	2656
Cochrane Central Register of Controlled Trials (www.thecochranelibrary.com)	(maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND (plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*) AND (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert")	663

Table S1. *(continued)*

Database	Search terms	Hits
Web of Science (www.webofknowledge.com)	TS=(maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND TS=(plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*) AND TS=(bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert") NOT DT=(review OR "meeting abstract")	7820
EBSCOhost (search.ebscohost.com) Databases: Academic search Premier, Business Source Premier, Military & Government Collection, and CINAHL	((maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND (plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*) AND (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert"))	2608
Scopus (www.scopus.com/)	TITLE-ABS-KEY(maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND TITLE-ABS-KEY(plate* OR screw* OR miniscrew* OR miniplate* OR implant* OR osteosynth* OR osseointegrat* OR osteofixat* OR osteotom* OR fixat*) AND TITLE-ABS-KEY(bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert")	7981
African Journals Online (www.ajol.info/)	(maxillary OR mandibular OR orthognathic OR craniofacial OR craniomaxillofacial) AND (bioresorbable OR biodegradable)	41
OpenGrey (www.opengrey.eu)	((maxill* OR mandib* OR jaw OR orthognat* OR craniofac* OR craniomaxil* OR retrognat* OR orthodont* OR osteotom* OR zygom* OR "split ramus" OR (malocclus* AND surg*) OR ((orbit* OR facial OR face OR nose OR nasal) AND (fract* OR injur* OR reconstruct* OR surg*))) AND (bioresorb* OR biodegrad* OR bioabsorb* OR bioadsorb* OR absorb* OR resorb* OR adsorb* OR "Lactic acid" OR "Polyglycolic acid" OR Hydroxyapatite* OR "biologically inert"))	40
ClinicalTrials.gov	Condition: (maxillary OR mandibular OR orthognathic OR craniofacial OR craniomaxillofacial) Other terms: (bioresorbable OR biodegradable)	5

Table S2. Endpoints divided into five time units.

Time unit	Endpoints
Perioperative	Plate and/or screw breakage, operation time, and handling by surgeon
Short-term (0-4 weeks; soft tissue healing)	Infection, dehiscence, malocclusion, pain, swelling, plate exposure, MMO, abscess, and analgesics used
Intermediate follow-up (6 – 12 weeks; bone healing)	Malunion, mobility of bone segments, malocclusion, MMO, TMJ-dysfunction, and pain
Long-term follow-up (>12 weeks; degradation effects)	Palpability of plate and screws, malocclusion, pain, swelling, satisfaction, TMJ-dysfunction, MMO, abscess, and MFIQ
Overall	Skeletal stability (i.e., skeletal relapse), symptomatic device removal, additional surgery (not device removal), and total costs

MMO: maximal mouth opening; TMJ-dysfunction: temporomandibular joint dysfunction; MFIQ: Mandibular Function Impairment Questionnaire.

Table S3. List with contacted authors of original articles.

Study	Dates of contact	Reasons for contact	Responses
Matthews et al. (2003)[1]	19 May 2018, 29 May 2018, and 22 August 2018.	1. Details regarding study design 2. Details regarding the distribution of data of the outcomes 'operative displacement' and 'relapse' 3. Details regarding the allocation of two patients with TMJ-dysfunction.	1. "It was a randomised study using odd/even registration numbers that are linked to concealed envelops." 2. "Unfortunately, I don't have access to the original data, it has been more than 15 years since we conducted this study." 3. "Apology, I can't remember."
Cheung et al. (2008)[2]	29 May 2018, 1 August 2018, 22 August 2018, 19 October 2018	1. All reported data are presented in figures only. No numbers are available to include in the meta-analyses.	No response
Stockmann et al. (2010)[3]	29 May 2018, 1 August 2018, 10 August 2018	1. Data not reported per treatment group 2. Definition of relapse (i.e., it currently is a binary variable).	No response
Tuovinen et al. (2010)[4]	23 August 2018, 24 August 2018, and 19 October 2018	1. Only P-values of difference between relapse of both treatment groups are reported, not the amount of relapse itself.	1. "Thank you for your interest concerning my report. I have not found my raw data yet. I'll keep on digging in my old cd-copies. My computer has been changed several times and we have been moving to three different location since that report and in the archive where the data should be I could not find it. I'll continue to look for the data." 2. "I have not found SPSS files but all handmade (written) measurements can be find, but it would be quite a job to copy and explain my notes and put them again in SPSS. Attached one example of measurements." 3. No response after asking for all the data.
Landes et al. (2006)[5]	29 May 2018, 22 August 2018, 19 October 2018	1. Details regarding the absolute number of screw and plate breakage per treatment group.	No response
Paeng et al. (2012)[6]	29 May 2018, 22 August 2018, and 19 October 2018	1. Details regarding the single patient that demonstrated infection after 7 days follow-up: which treatment group?	No response

Table S4. Excluded articles with reasons for exclusion after full-text screening.

Author (year)	Reason for exclusion	Reference
Ahmed et al. (2013)	Surgical procedure not relevant for this review	7
Arshad et al. (2019)	Surgical procedure not relevant for this review	8
Arya et al. (2020)	Surgical procedure not relevant for this review	9
Bekal et al. (2017)	Surgical procedure not relevant for this review	10
Bell et al. (2006)	Surgical procedure not relevant for this review	11
Bhatt et al. (2010)	Surgical procedure not relevant for this review	12
Bhatt et al. (2015)	Surgical procedure not relevant for this review	13
Bohm et al. (1998)	Surgical procedure not relevant for this review	14
Bouletreau et al. (2005)	Both groups consist of biodegradable and titanium osteosynthesis	15
Burlini et al. (2015)	Surgical procedure not relevant for this review	16
Champy et al. (1992)	No control group	17
Wang et al. (2013)	Surgical procedure not relevant for this review	18
Fakourand et al. (2012	Surgical procedure not relevant for this review	19
Filinte et al. (2015)	Surgical procedure not relevant for this review	20
Fuente del Campo et al. (1996)	No control group; Biodegradable plates with titanium screws used	21
Hashiba et al. (2007)	No relevant endpoints for this review	22
Ho et al. (2011)	No pure biodegradable group, only titanium or mixed groups	23
Hwang et al. (2017)	No pure biodegradable group, only titanium or mixed groups	24
Iatrou et al. (2010)	Surgical procedure not relevant for this review	25
Illi et al. (1989)	Children with syndromic disorders included	26
Imola et al. (2002)	Review paper	27
Janickova et al. (2018)	Surgical procedure not relevant for this review	28
Kallela et al. (1999)	Review paper	29
Kang et al. (2014)	Surgical procedure not relevant for this review	30
Kim et al. (2018)	Surgical procedure not relevant for this review	31
Kobayashi et al. (2004)	No control group	32
Kretschmer et al. (2011)	Surgical procedure not relevant for this review	33
Landes et al. (2014)	Patients with cleft lip and palate included	34
Landes et al. (2015)	No control group	35
Lee et al. (2010)	Surgical procedure not relevant for this review	36
Lee et al. (2014)	Surgical procedure not relevant for this review	37
Lee et al. (2014)	Endpoint not relevant for this review	38
Leno et al. (2017)	Surgical procedure not relevant for this review	39
Leonhardt et al. (2008)	Surgical procedure not relevant for this review	40
Lim et al. (2014)	Surgical procedure not relevant for this review	41
Liu et al. (2016)	Surgical procedure not relevant for this review	42
Mahmoud et al. (2016)	Surgical procedure not relevant for this review	43
Menon et al. (2007)	Surgical procedure not relevant for this review	44
Menon et al. (2012)	Surgical procedure not relevant for this review	45
Netto et al. (2013)	Surgical procedure not relevant for this review	46

Table S4. *(continued)*

Author (year)	Reason for exclusion	Reference
Obwegeser et al. (1994)	No biodegradable osteosynthesis used, only biodegradable sutures	[47]
Park et al. (2005)	Surgical procedure not relevant for this review	[48]
Park et al. (2011)	Surgical procedure not relevant for this review	[49]
Pistner et al. (1991)	Review paper	[50]
Qiu et al. (2015)	Surgical procedure not relevant for this review	[51]
Stuck et al. (2011)	Review paper	[52]
Sukegawa et al. (2016)	Surgical procedure not relevant for this review	[53]
Tan et al. (2011)	Surgical procedure not relevant for this review	[54]
Tripathi et al. (2013)	Surgical procedure not relevant for this review	[55]
Ueki et al. (2011b)	Does not fulfill inclusion criteria	[56]
Ueki et al. (2015b)	Does not fulfill inclusion criteria	[57]
Ueki et al. (2017)	Does not fulfill inclusion criteria	[58]
Wittwer et al. (2006)	Surgical procedure not relevant for this review	[59]
Wu et al. (2017)	Surgical procedure not relevant for this review	[60]
Zheng et al. (2001)	No control group	[61]

Table S5. All assessed endpoints of the included studies, except skeletal stability.

Study name (year)	Osteosynthesis system	Perioperative endpoints: Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Short-term follow-up: Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Intermediate follow-up: Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Long-term follow-up: Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Overall follow-up: Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
Randomised controlled trials																															
Matthews (2003)[1]	B	0	0			0						9.1						0								9.1				0	x
	T	0	0			0						0						0								0				0	x
Norholt (2004)[62]	B				82.1[b]	0	42.9		25		3.6	0		22.2		18.5				20					4	12		0		8.3	x
	T				100[b]	3.7	40.7		29.6		0	0		10.7		21.4				28.6					0	61.9		14.3		0	x
Cheung (2004)[63]	B	4.2[*]	10.9[#]			3.3			3.63± 2.27[a,f]		6.7			6.7		1.2± 1.35[a,f]				0.46± 1.10[a,f]							8.63± 1.44[a,f]	20			
	T	0[*]	0[#]			0			4.40± 2.29[a,f]		10			10		1.47± 1.50[a,f]				0.67± 1.13[a,f]							8.50± 1.84[a,f]	10			
Ueki (2005)[64]	B					0					0	0[c]	0	0					0 (O)	0.8± 1.8[a]	-3.40± 2.26[f]		15								x
	T					0					0	0[c]	0	0					0 (O)	1.0± 2.1[a]	-5.60± 1.86[f]		25								x
Cheung (2008)[2]	B								NNA					NNA		NNA				NNA						NNA					x
	T								NNA					NNA		NNA				NNA						NNA					x

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
		Perioperative endpoints				Short-term follow-up							Intermediate follow-up						Long-term follow-up										Overall follow-up			
Park (2010)[65]	B																														x
	T																														x
Stockmann (2010)[3]	B		9.1	+36[d]		3				NNA	3	NNA					NNA		5.9 (O)		NNA						62	0			
	T		3	NNA[d]		3				NNA	0	0[c]					NNA		5.9 (O)		NNA							3			
Tuovinen (2010)[4]	B					0																						2	2	x
	T					0																						4	4	x
Buijs (2012)[66]	B	0	0	137± 59	7.6± 0.7[a]		17.1	11.8			3.9		2.6		9.2 (O)	5.15± 8.9[a]												1.3	0		
	T	0	0	116± 64	8.5± 1.2[a]		7.3	4.8			1.6		0		12.9 (O)	4.7± 10.6[a]												1.6	0.8		
Yoshioka (2012)[67]	B	2.7				0																				1.8		5.5	0		
	T	0				1.1																				0		3.3	0		

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
		Perioperative endpoints				Short-term follow-up							Intermediate follow-up						Long-term follow-up										Overall follow-up			
Bakelen (2013)[68]**,**[e]	B														7.5 & 11.3 (O)	2±9 & 2±6						17 (17-23) & 17 (17-19)	3 & 1.9	9 & 5.7	50.7 & 47.2		24		2.5	
	T														12.1 & 12.2 (O)	1±7 & 2±9						21 (17-27) & 19 (17-23)	2.6 & 0	3.4 & 0	34.5 & 47.8		8		1.6	
Yu et al. (2014)[69]	B					16											-0.31± 6.80[f]											0			
	T					13.7											-1.86± 7.51[f]											3.9			
Bakelen (2015)[70]	B																												6589± 3492		
	T																												6787± 5014		

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
		Perioperative endpoints				Short-term follow-up							Intermediate follow-up						Long-term follow-up										Overall follow-up			
Gareb (2017)[71]	B																		11.8 (S)	7.0± 18.7[a]			18 (17-21)		5.9	7.8		29.1			
	T																		14.8 (S)	5.7± 17.6[a]			18 (17-21)		2.5	42		15.3			
Prospective cohort studies																															
Ferretti (2002)[72]	B					0																									x
	T					0																									x
Dhol (2008)[73]	B					0	0		0							0				0					0						x
	T					0	0		0							0				0					0						x
Bakelen (2014)[74]	B																														x
	T																														x
Retrospective cohort studies																															
Harada (1997)[75]	B																	0				0									x
	T																	0				0									x

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Perioperative endpoints			Short-term follow-up							Intermediate follow-up				Long-term follow-up						Overall follow-up	
		Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
Costa (2006)[76]	B				0						0	0[c]	0	0		20				20							20	x
	T				0						0	0[c]	0	0		0				0							0	x
Landes (2006)[5]	B	5[#]												0															x
	T	0[#]												0															x
Turvey (2006)[77]	B																												x
	T																												x
Ueki (2006a and b)[78]	B				a & b: 0						a & b: 0	a & b: 0[c]							a & b: 0									x
	T				a & b: 0						a & b: 0	a & b: 0[c]							a & b: 0									x
Landes (2007)[79]	B	12[#]												0															x
	T	0[#]												0															x
Ueki (2009)[80]	B				0						0	0[c]	0	0		0													
	T				0						0	0[c]	0	0		0													

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Perioperative endpoints: Plate breakage (%)	Perioperative endpoints: Screw breakage (%)	Perioperative endpoints: Operation time (mean±SD, in minutes)[a]	Perioperative endpoints: Handling by surgeon (0: worst; 10: excellent)	Short-term follow-up: Infection (%)	Short-term follow-up: Swelling (%)	Short-term follow-up: Abscess (%)	Short-term follow-up: Pain (%)	Short-term follow-up: MMO (%)	Short-term follow-up: Dehiscence (%)	Short-term follow-up: Plate exposure (%)	Intermediate follow-up: Malunion (%)	Intermediate follow-up: Mobility segments (%)	Intermediate follow-up: Malocclusion (%)	Intermediate follow-up: Pain (%)	Intermediate follow-up: MMO (mean±SD)	Intermediate follow-up: TMJ-dysfunction (%)	Long-term follow-up: Malocclusion (%)	Long-term follow-up: Pain (%)	Long-term follow-up: MMO (mean±SD)	Long-term follow-up: TMJ-dysfunction (%)	Long-term follow-up: MFIQ (median, IQR)	Long-term follow-up: Abscess (%)	Long-term follow-up: Swelling (%)	Long-term follow-up: Palpability screw/plate (%)	Long-term follow-up: Satisfaction (%)	Overall follow-up: Symptomatic plate/screw removal (%)	Overall follow-up: Costs (direct and indirect; mean±SD)[a]	Overall follow-up: Costs (direct and indirect; mean±SD)[a]	Overall follow-up: Skeletal stability assessed (yes)
Ahn (2010)[81]	B					4.2															5.8								2.5	
	T					0															6.6								0	
Choi (2010)[82]	B																														x
	T																														x
Ueki (2011)[83]	B					0												0													x
	T					0												0													x
Ballon (2012)[84]	B																														x
	T																														x
Paeng (2012)[6]	B	1.6[#]				NNA																								NNA	x
	T	0[#]				NNA																								NNA	x
Ueki (2012)[85]	B					0					0			0					0												x
	T					0					0			0					0												x

Table S5. *(continued)*

Study name (year)	Osteosynthesis system	Plate breakage (%)	Screw breakage (%)	Operation time (mean±SD, in minutes)[a]	Handling by surgeon (0: worst; 10: excellent)	Infection (%)	Swelling (%)	Abscess (%)	Pain (%)	MMO (%)	Dehiscence (%)	Plate exposure (%)	Malunion (%)	Mobility segments (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	Malocclusion (%)	Pain (%)	MMO (mean±SD)	TMJ-dysfunction (%)	MFIQ (median, IQR)	Abscess (%)	Swelling (%)	Palpability screw/plate (%)	Satisfaction (%)	Symptomatic plate/screw removal (%)	Costs (direct and indirect; mean±SD)[a]	Costs (direct and indirect; mean±SD)[a]	Skeletal stability assessed (yes)
		Perioperative endpoints				Short-term follow-up							Intermediate follow-up						Long-term follow-up										Overall follow-up		
Blakey (2014)[86]	B																												0	x
	T																												0	x
Lee (2014)[87]	B					0																								x
	T					0																								x
Ueki (2015)[88]	B					0					0	0[c]	0	0					0												
	T					0					0	0[c]	0	0					0												

All data are given in percentages, unless stated otherwise. All unit of analysis was number of patients, unless stated otherwise. [*]Unit of analysis was plates. [#]Unit of analysis was screws.[†]Data of the follow-up moment 6-12 months given. The follow-up moment 12-24 months had high proportion of participants lost to follow-up. [a]Data given in mean±standard deviation. [b]Percentage of surgeons 'satisfied' or higher with the osteosynthesis system. [c]If no wound dehiscence was present, plate exposure was also assessed as not present. [d]Only the difference in mean operative time of biodegradable compared to titanium osteosyntheses was reported. [e]Two follow-up moments: 1- and 2-year follow-up, respectively. [f]Postoperative minus preoperative MMO. B, biodegradable; T, titanium; O, objectively assessed; S, subjectively assessed; NNA, numbers not available. MMO, maximal mouth opening; TMJ-dysfunction, temporomandibular joint dysfunction; MFIQ, Mandibular Function Impairment Questionnaire; x, assessed (see Table S6). Empty cells: not reported. Note that (i) malocclusion and (ii) analgesic usage after short-term follow-up are not mentioned in this table as these endpoints were not assessed in any of the included studies, and (iii) that certain continuous variables are shown without standard deviations because these were not reported in the original manuscripts.

Table S6. Operative displacement and relapse.

Study (first author, year)	Type of displacement	Operative displacement (mean±SD or median (IQR), in mm or ° angle)		Relapse (mean±SD or median (IQR), in mm or ° angle)		Follow-up	Lateral cephalometric reference marks
		B	T	B	T		
Randomised controlled trials							
Matthews et al. (2003)[1]	Mandibular horizontal	4.0 (0.0-5.0)	4.0 (3.0-8.0)	NNA		1 yr	Go
	Mandibular vertical	4.5 (2.0-6.0)	4.5 (1.5-5.0)				Go
	Mandibular angle	4.2 (2.2-8.8)	1.5 (1.0-8.0)				Ar-Go-Gn
Norholt et al. (2004)[62]	Maxillary horizontal	2.3±2.8	2.4±2.2	0.03±0.82	0.24±1.4	6 wks	AI
	Maxillary vertical	2.1±1.6	2.2±2.2	0.58±0.60	0.56±1.9		AI
	Maxillary angle	NR	NR	3.6±2.2	0.67±2.6		OP
Ueki et al. (2005)[64]	Mandibular horizontal	2.0±3.6[a]	3.5±5.3[a]	2.4±2.89	0.7±4.99	1 yr	Pg
	Mandibular vertical	2.9±2.6[a]	4.3±3.3[a]	0.1±2.61	2.5±2.94		Pg
	Mandibular angle	8.8±2.0[a]	3.4±2.4[a]	6.7±2.53	2.6±2.33		Ar-Go-Gn
Cheung et al. (2008)[2]	Maxillary horizontal (adv)	3.43±2.03	4.0±2.45		NNA	1 yr	Point-A
	Maxillary horizontal (setb)	1.12±1.12	1.59±0.84		NNA		
	Maxillary vertical (imp)	2.65±2.05	3.27±1.84		NNA		
	Maxillary vertical (elong)	2.87±1.94	1.45±1.1		NNA		
Park et al. (2010)[65]	Maxillary horizontal	1.88±1.19	3.20±2.19	0.08±0.23	0.0±0.0	6 mos	ANS
	Maxillary vertical	1.32±1.66	2.25±1.98	0.07±0.41	0.0±0.24		ANS
	Maxillary angle	2.45±1.12	3.45±1.80	0.12±0.41	0.15±0.24		SNA
	Mandibular horizontal	8.18±5.24	8.70±8.43	0.60±1.96	1.45±2.95		Pg
	Mandibular vertical	1.05±2.89	2.00±2.16	1.26±1.52	1.85±1.73		Pg
	Mandibular angle	0.55±4.20	0.75±6.79	5.01±4.61	2.30±4.10		Ar-Go-Gn
Tuovinen et al. (2010)[4]	All	NNA	NNA	NNA	NNA		
Prospective cohort studies							
Ferretti et al. (2002)[72]	Mandibular horizontal	5.67±1.70[b]	4.80±1.33[b]	0.83±1.25	0.25±1.38	6 mos	Point-B
Dhol et al. (2008)[73]	Maxillary horizontal	2.02±0.39[c]	2.45±0.57[c]	0.20±0.43[c]	0.80±0.43[c]	≥8 mos	Point-A
	Maxillary vertical	2.46±0.71[c]	2.14±0.65[c]	0.12±0.57[c]	0.64±0.57[c]		Point-A
	Maxillary angle	0.99±0.84[c]	2.36±0.74[c]	0.04±0.69[c]	0.00±0.69[c]		Palatal plane
Bakelen et al. (2014)[74]	Mandibular horizontal	3.2±1.6	4.2±2.2	0.03±1.7	0.3±2.3	2 yrs	Point-B
	Mandibular vertical	4.8±1.8	3.2±2.4	1.1±1.5	0.9±1.6		

Table S6. *(continued)*

Study (first author, year)	Type of displacement	Operative displacement (mean±SD or median (IQR), in mm or ° angle)		Relapse (mean±SD or median (IQR), in mm or ° angle)		Follow-up	Lateral cephalometric reference marks
		B	T	B	T		
Retrospective cohort studies							
Harada et al. (1997)[75]	Mandibular horizontal	NNA		1.62±1.28	1.05±1.00	1 yr	Pg
	Mandibular vertical			0.37±1.33	0.00±0.77		
Costa et al. (2006)[76]	Maxillary horizontal	3.50±1.65	3.54±1.54	0.90±1.37	0.16±0.72	1 yr	Point-A
	Maxillary vertical	0.95±1.79	2.33±1.83	1.55±1.36	0.042±1.31		Point-A
	Maxillary angle	3.00±1.28	3.32±1.62	0.57±1.20	0.02±0.64		SNA
Landes et al. (2006)[5,d]	Maxillary horizontal (adv)	3.5±4.1	5.4±3.5	2.3±1.8	2.4±2.0	1 yr	Point-A
	Maxillary horizontal (setb)	2.8±3.7	1.9±1.8	2.3±1.9	2.5±1.7		Point-A
	Maxillary vertical (imp)	1.9±1.7	3.3±2.7	2.1±1.9	2.2±1.5		ANS
	Maxillary vertical (elong)	4.2±3.6	3.7±5.2	3.8±3.1	3.1±3.6		ANS
	Mandibular horizontal (adv)	4.6±3.6	6.3±8.8	4.9±4.3	5.1±8.2		Point-B
	Mandibular horizontal (setb)	7.5±8.3	7.2±3.2	3.0±2.0	1.7±2.0		Point-B
	Mandibular angle (CW)	11.8±9.9	7.9±6.6	6.7±8.9	8.2±9.6		Ar-Go-Gn
	Mandibular angle (CCW)	4.5±3.2	6.3±6.6	6.8±5.2	4.2±5.9		Ar-Go-Gn
Turvey et al. (2006)[77]	Mandibular horizontal	5.20±2.37	4.96±2.60	0.54±3.25	0.33±2.2	1 yr	Point-B
	Mandibular vertical	4.34±1.68	4.01±2.30	1.36±2.59	1.15±1.80		
Ueki et al. (2006a and b)[78]	Maxillary horizontal (a)	2.9±2.3[a]	3.1±2.9[a]	1.30±2.14	0.90±2.86	1 yr	Point-A
	Maxillary vertical (a)	0.8±2.0[a]	0.4±1.8[a]	2.30±2.10	0.40±1.90		Point-A
	Maxillary angle (a)	2.7±1.4[a]	3.1±1.6[a]	0.20±1.31	0.80±1.43		SNA
	Maxillary horizontal (b)	1.7±2.7[a]	2.8±1.7[a]	2.00±2.27	1.10±2.04		Point-A
	Maxillary vertical (b)	3.7±2.0[a]	0.0±1.2[a]	3.30±2.15	2.00±1.39		Point-A
	Maxillary angle (b)	2.5±2.3[a]	2.6±1.5[a]	0.40±1.92	1.10±1.61		SNA

Table S6. *(continued)*

Study (first author, year)	Type of displacement	Operative displacement (mean±SD or median (IQR), in mm or ° angle)		Relapse (mean±SD or median (IQR), in mm or ° angle)		Follow-up	Lateral cephalometric reference marks
		B	T	B	T		
Landes et al. (2007)[79,d]	Maxillary horizontal (adv)	2.5±1.0	5.4±3.5	1.2±0.8	2.4±2.0	1yr	Point-A
	Maxillary horizontal (setb)	2.2±2.4	1.9±1.8	1.8±1.9	2.5±1.7		Point-A
	Maxillary vertical (imp)	1.0±0.7	3.3±2.7	1.1±1.1	2.2±1.5		ANS
	Maxillary vertical (elong)	6.5±3.4	3.7±5.2	2.0±1.4	3.1±3.6		ANS
	Mandibular horizontal (adv)	5.5±3.7	6.3±8.8	2.6±2.7	5.1±8.2		Point-B
	Mandibular horizontal (setb)	11.2±7.7	7.2±3.2	2.7±2.6	1.7±2.0		Point-B
	Mandibular angle (CW)	7.9±2.4	7.9±6.6	2.4±2.7	8.2±9.6		Ar-Go-Gn
	Mandibular angle (CCW)	6.9±2.6	6.3±6.6	7.0±5.4	4.2±5.9		Ar-Go-Gn
Choi et al. (2010)[82]	Mandibular horizontal (setb)	7.11±2.7	5.69±1.10	1.94±0.93	1.60±0.58	14.5 mos	Point-B
	Mandibular vertical (setb)	1.58±2.73	1.81±1.44	0.08±1.38	0.10±1.10		Point-B
Ueki et al. (2011)[83]	Mandibular horizontal	5.0±7.2[e]	5.1±6.9	NNA		1 yr	Pg
	Mandibular vertical	1.5±4.0[e]	3.7±5.5				Pg
	Mandibular angle	3.2±5.4[e]	2.4±3.2				Ar-Go-Gn
Ballon et al. (2012)[84]	Maxillary horizontal (adv)	2.70±1.94	4.28±2.37	1.84±1.69	1.59±1.48	≥6 mos	Point-A
	Maxillary horizontal (setb)	3.46±2.63	3.70±2.10	2.02±1.89	1.70±1.64		Point-A
	Maxillary vertical (imp)	3.13±2.25	3.25±1.55	2.67±2.08	1.40±1.42		ANS
	Maxillary vertical (elong)	5.22±4.05	2.92±2.64	2.68±2.65	1.39±1.55		ANS
	Mandibular horizontal (adv)	4.89±3.67	4.09±2.84	3.65±3.39	2.09±1.43		Point-B
	Mandibular horizontal (setb)	9.31±5.46	8.55±4.85	4.86±2.87	1.05±1.31		Point-B
	Mandibular angle (CW)	7.75±6.18	9.57±7.13	4.55±3.52	10.63±9.47		Ar-Go-Gn
	Mandibular angle (CCW)	4.79±3.09	6.50±6.06	6.36±4.86	5.00±6.53		Ar-Go-Gn
Paeng et al. (2012)[6]	Mandibular horizontal	6.7±2.2	7.0±3.2	0.51±1.23	0.75±1.85	6 mos	Point-B
	Mandibular vertical	NNA		0.71±1.35	1.5±1.39		Me

Table S6. *(continued)*

Study (first author, year)	Type of displacement	Operative displacement (mean±SD or median (IQR), in mm or ° angle)		Relapse (mean±SD or median (IQR), in mm or ° angle)		Follow-up	Lateral cephalometric reference marks
		B	T	B	T		
Ueki et al. (2012)[85]	Maxillary horizontal	2.4±2.1[e]	2.7±2.6	0.30±1.25	0.50±1.99	1 yr	Point-A
	Maxillary vertical	1.0±4.3[e]	0.8±2.9	1.00±1.36	1.20±1.45		Point-A
	Maxillary angle	1.2±3.6[e]	2.2±2.9	0.95±0.76	0.60±1.22		SNA
Blakey et al. (2014)[86]	Maxillary horizontal	5.61±1.30	7.07±2.30	2.06±1.91	1.34±1.34	1 yr	Point-A
Lee et al. (2014)[87]	Mandibular horizontal	13.97±1.39	9.59±1.51	1.89±1.33	3.02±1.05	6 mos	Pg
	Mandibular vertical	1.7±1.68	0.65±1.6	0.83±0.53	1.51±1.56		Pg
	Mandibular angle	3.57±1.06	2.81±0.65	0.33±0.85	1.39±0.48		Ar-Pg to FH

Perioperative displacement and relapse are given in absolute values. The direction of operative displacement (e.g., setback or advancement) are only stated in this table whenever this was explicitly stated in the original manuscript. [a]Time interval values of cephalometric data (e.g., 1-year postoperative minus immediate postoperative data) were calculated based on the cephalometric data of specific time points (e.g., 1 year and immediate postoperative data), assuming normal distribution of data. [b]Discrepancy exists between data in the text and tables of the original manuscript. The authors did not respond to contact attempts. Data presented in the text of the original manuscript were used. [c]Data presented as mean ± standard error of the mean (SEM). [d]Landes et al. (2006) and Landes et al. (2007) have included the identical control groups. The means and standard deviations of both the intervention groups were pooled and analyzed as a single pair-wise comparison with that specific control group, assuming normal distribution of data. [e]The two subgroups of biodegradable osteosyntheses (i.e., uHA/PLLA and PLLA subgroups) were pooled and analyzed as a single pair-wise comparison between biodegradable and titanium osteosyntheses. a: subgroup Le Fort advancement + BSSO setback. b: subgroup Le Fort I advancement + IVRO without fixation. IQR, interquartile range; NNA, numbers not available; Go, gonion; Ar-Go-Gn, articular-gonion-gnathion angle (gonial angle); AI, anterior implant; NS, nasion-sella line; NSP, nasion-sella perpendicular line; OP, occlusal plane; Pg, pogonion; SNA, sella-nasion-A point angle; adv, advancement; setb, setback; imp, impaction; elong, elongation; ANS, anterior nasal spine; CW, clockwise rotation; CCW, counter-clockwise rotation; Me, menton; Ar-Pg, articular-pogonion; FH, Frankfurt horizontal plane; wks, weeks; mos, months; yrs, years.

Table S7. Results of univariable meta-regression analyses to analyze the effect of risk of bias items on the log risk ratio of symptomatic device removal using a random effects model.

Risk of bias item	Regression coefficient	95% CI (lower to upper border)	P-value
Domain 1 (ref. = low RoB)	0.64	-0.15 to 1.43	0.11
Some concerns	-0.56	-1.74 to 0.61	0.35
High RoB	-2.23	-5.40 to 0.94	0.35
Domain 2 (ref. = low RoB)	-0.06	-0.91 to 0.79	0.89
High RoB	0.70	-0.50 to 1.90	0.25
Domain 3 (ref. = low RoB)	-0.31	-1.68 to 1.06	0.65
Some concerns	0.34	-2.00 to 2.69	0.78
High RoB	0.80	-1.87 to 3.48	0.56
Domain 4 (ref. = low RoB)	-0.46	-1.71 to 0.79	0.47
Some concerns	1.15	-1.40 to 3.70	0.38
High RoB	0.95	-1.63 to 3.54	0.47
Domain 5 (ref. = low RoB)	0.42	-0.11 to 0.96	0.12
Some concerns	-2.01	-5.10 to 1.07	0.20
Overall RoB (ref. = some concerns)	-0.18	-1.29 to 0.93	0.75
High RoB	0.64	-0.71 to 2.00	0.35

RoB, Risk of Bias. Ref., reference item. 95% CI, 95% confidence interval. The meta-regression analysis shows none of the individual risk of bias items have a significant effect on the symptomatic device removal rate.

Table S8. Input and results of the trial sequential analyses using the random-effects (DerSimonian-Laird) model with the corresponding interpretations.

Endpoint	Control event proportion (titanium)[a]	Relative risk (95% CI)[a]	Diversity (D^2)[a]	Total N/RIS	Crossed conventional test boundary	Crossed O'Brien-Fleming boundary	Crossed futility boundary	Interpretation
Short-term follow-up								
Infection	4.3%	1.03 (0.46; 2.28)	0.0	645/780586[b]	Not estimable due to <5% of RIS achieved			Inconclusive, potentially false neutral
Swelling	13.2%	1.51 (0.68; 3.38)	0.62	255/2536	No	No	No	Inconclusive, potentially false neutral
Dehiscence	2.3%	1.53 (0.52; 4.50)	0.0	421/5865	No	No	No	Inconclusive, potentially false neutral
Intermediate follow-up								
Mobility bone segments	10.3%	1.37 (0.47; 3.99)	0.0	155/2302	No	No	No	Inconclusive, potentially false neutral
Long-term follow-up								
Malocclusion	11.2%	0.93 (0.39; 2.26)	0.0	217/49794[b]	Not estimable due to <5% of RIS achieved			Inconclusive, potentially false neutral
Swelling	2.0%	2.42 (0.52; 11.19)	0.0	178/1316	No	No	No	Inconclusive, potentially false neutral
Palpability of screws/plates	23.2%	0.38 (0.11; 1.28)	0.67	400/619	No	No	No	Inconclusive, potentially false neutral
Overall follow-up								
Symptomatic device removal	8.3%	1.29 (0.68; 2.44)	0.52	777/9717	No	No	No	Inconclusive, potentially false neutral
Revision surgery (not device removal)	2.0%	1.40 (0.37; 5.34)	0.0	377/11445	No	No	No	Inconclusive, potentially false neutral

RIS, required information size. [a]According to the observed relative risk and diversity of the present meta-analysis including randomised controlled trials only. [b]RIS is very high due to a very small relative risk reduction. Outcomes that are not mentioned were assessed in no or a single randomised controlled trials, or were only assessed in total zero-event trials.

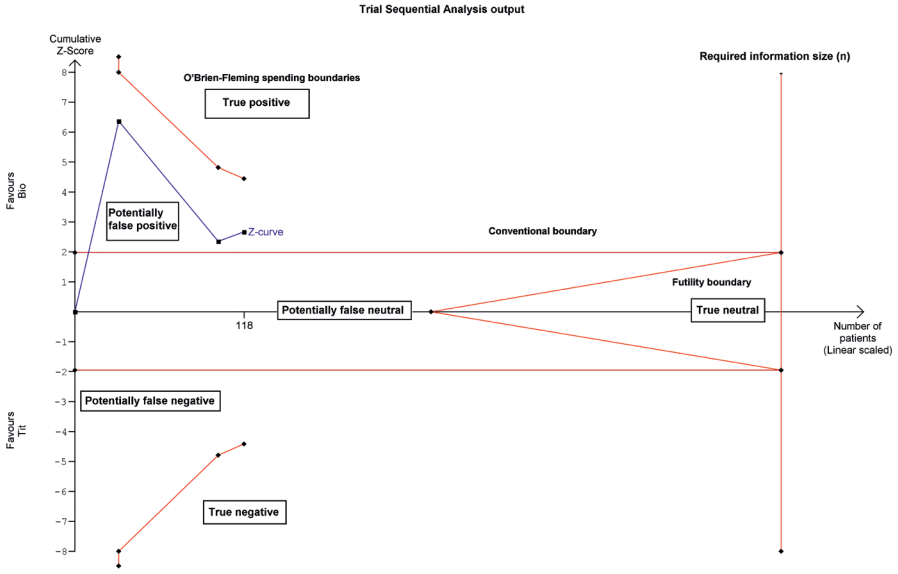

Figure S1. Example graph with explanation of the trial sequential analysis. The y-axis represents the cumulative Z-score and the x-axis the number of patients of included trials. A Z-score of ±1.96 corresponds to α = 0.05 (conventional boundaries). The required information size is the number of patients needed to draw a definite conclusion and this number is comparable to a sample size calculation in randomised controlled trials. The O'Brien-Fleming spending boundaries are trial sequential adjusted boundaries; the fewer patients are randomised, the wider these borders are due to increased chance of random errors. Crossing the futility boundary indicates that the intervention is unlikely to have the anticipated effect. The interpretation of each area is presented as textboxes in the graph. Thus, TSA provides three borders: conventional test boundaries (α = 0.05; Z = +/- 1.96; i.e., crossing boundary means potentially false positive or negative), O'Brien-Fleming spending boundaries (i.e., crossing boundary means true positive or negative effect), and futility boundaries (crossing boundary means true neutral effect). If no boundaries are crossed, the evidence remain inconclusive (i.e., potentially false neutral).

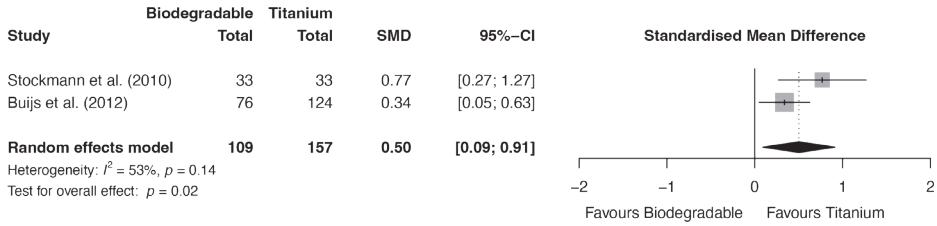

Figure S2. Forest plot of the endpoint operative time in minutes. *SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

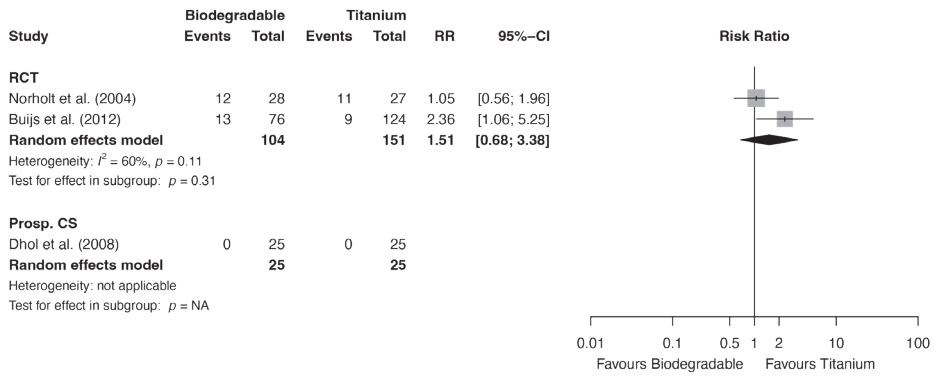

Figure S3. Forest plot of the endpoint swelling (<4 weeks follow-up) stratified by study design. *RCT, randomised controlled trials; Prosp. CS, prospective cohort studies; RR, risk ratio; 95%-CI, 95% confidence interval.*

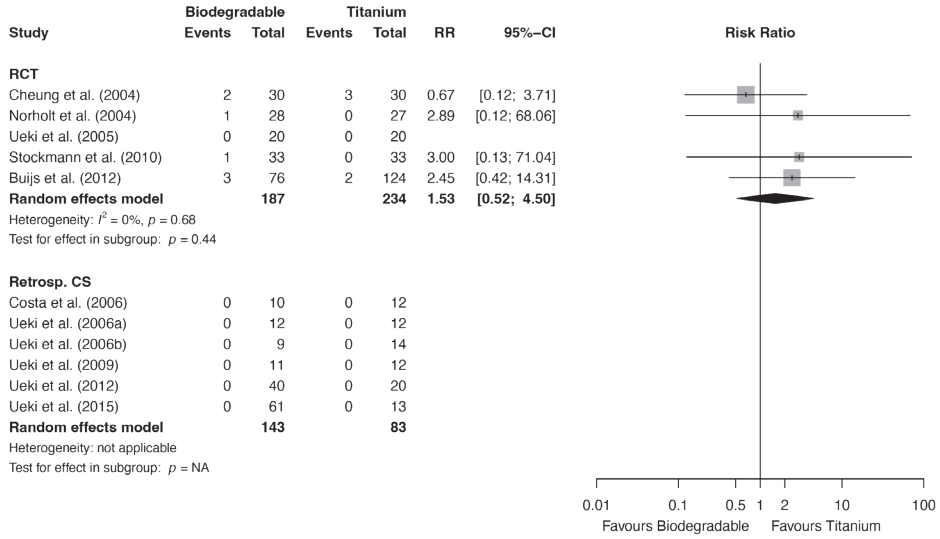

Figure S4. Forest plot of the endpoint dehiscence (<4 weeks follow-up) stratified by study design. *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; RR, risk ratio; 95%-CI, 95% confidence interval.*

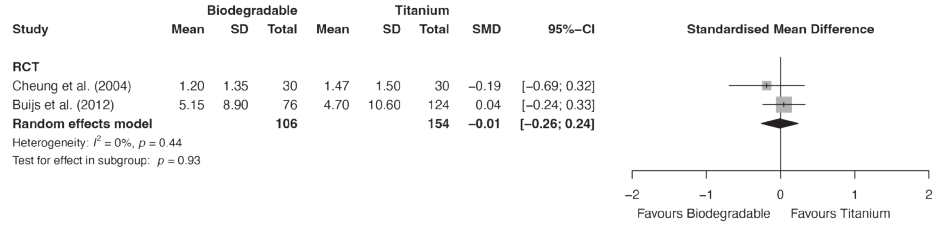

Figure S5. Forest plot of the endpoint pain (6-12 weeks follow-up) stratified by study design. *RCT, randomised controlled trials; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

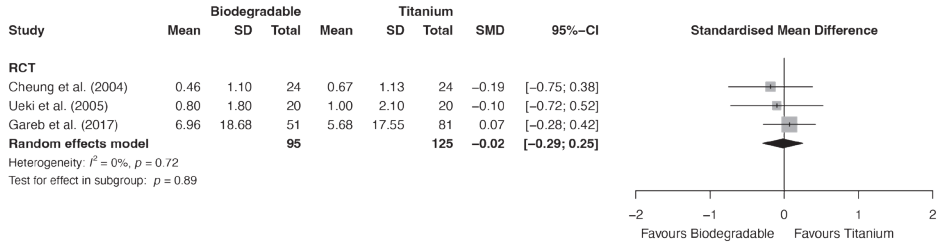

Figure S6. Forest plot of the endpoint pain (>12 weeks follow-up) stratified by study design. *RCT, randomised controlled trials; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

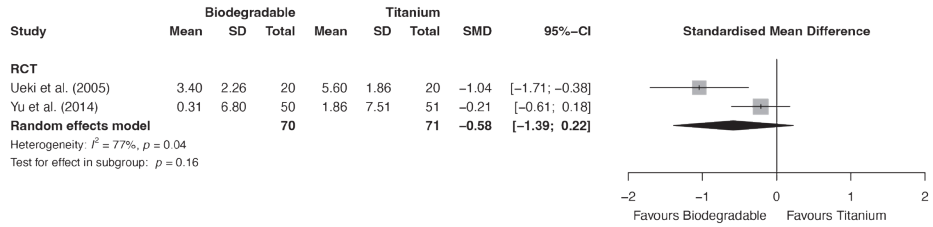

Figure S7.: Forest plot of the endpoint maximum mouth opening (>12 weeks follow-up) stratified by study design. *RCT, randomised controlled trials; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

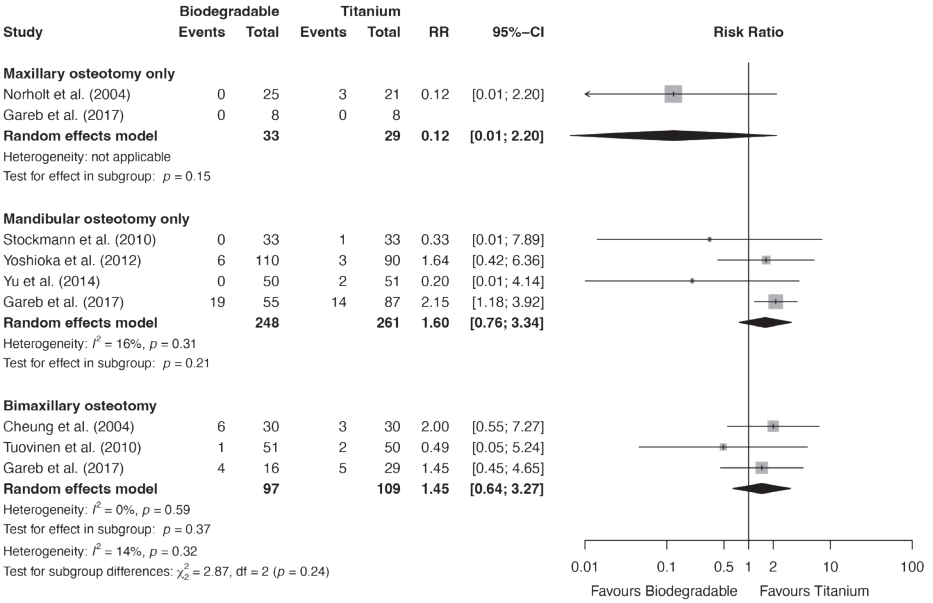

Figure S8. Forest plot of the endpoint symptomatic device removal (overall follow-up) of studies stratified maxillary, mandibular, and bimaxillary osteotomies. *RR, risk ratio; 95%-CI, 95% confidence interval.*

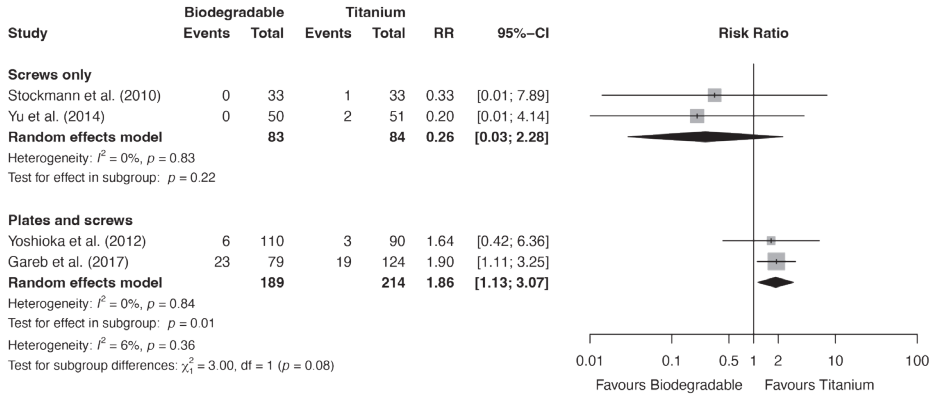

Figure S9. Forest plot of the endpoint symptomatic device removal (overall follow-up) of studies including osteosynthesis by plates and screws versus only screws. *RR, risk ratio; 95%-CI, 95% confidence interval.*

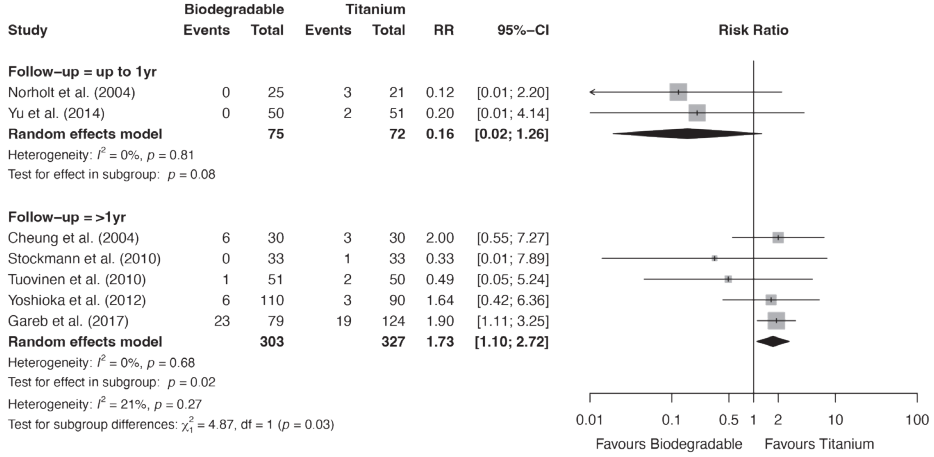

Figure S10. Forest plot of the endpoint symptomatic device removal (overall follow-up) stratified by ≤1-year and >1-year follow-up. *RR, risk ratio; 95%-CI, 95% confidence interval.*

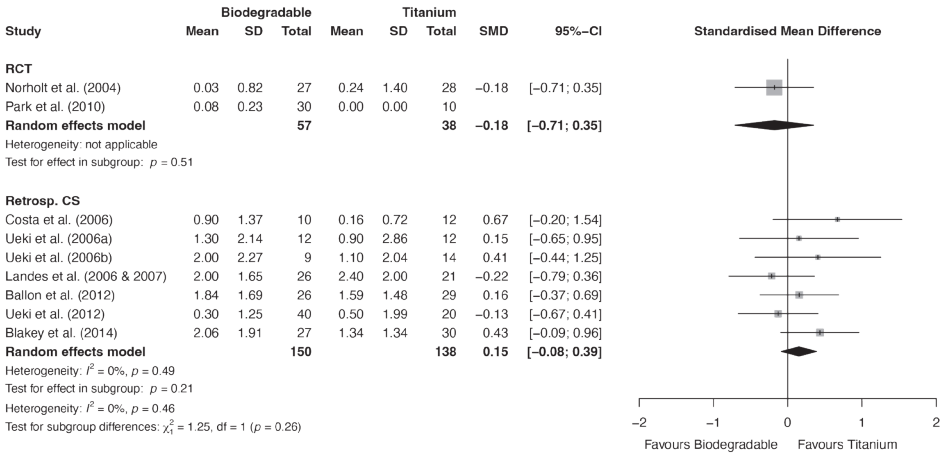

Figure S11. Forest plot of the endpoint maxillary horizontal relapse after maxillary advancement stratified by study design (overall follow-up). *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

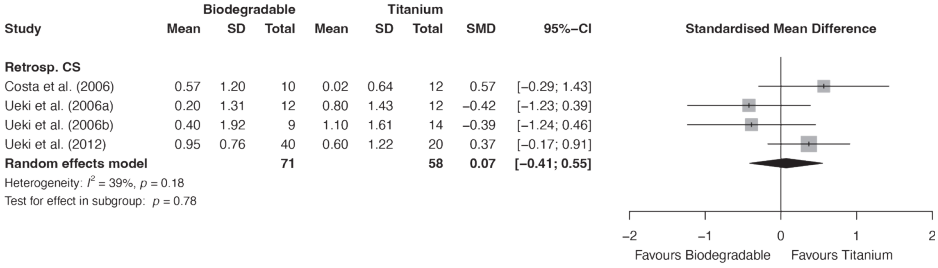

Figure S12. Forest plot of the endpoint maxillary angular relapse after maxillary advancement stratified by study design (overall follow-up). *Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

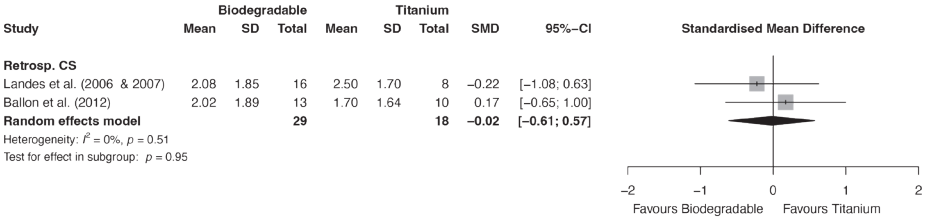

Figure S13. Forest plot of the endpoint maxillary horizontal relapse after maxillary setback stratified by study design (overall follow-up). *Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

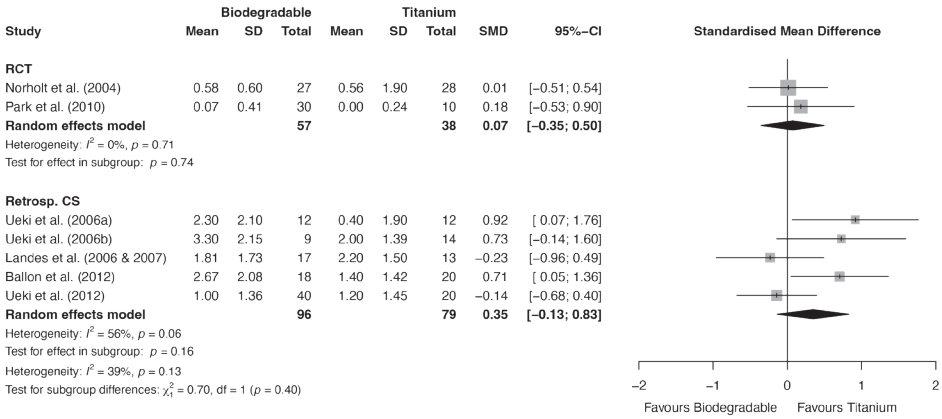

Figure S14. Forest plot of the endpoint maxillary vertical relapse after maxillary impaction stratified by study design (overall follow-up). *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

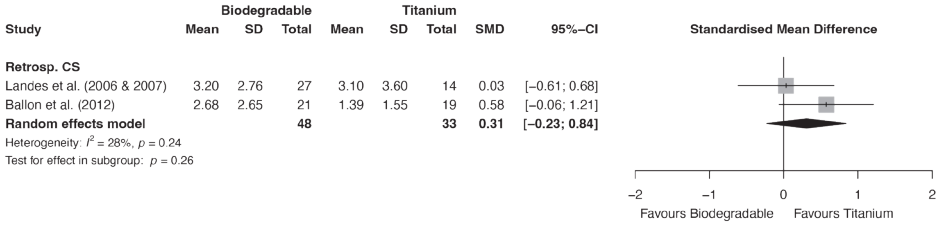

Figure S15. Forest plot of the endpoint maxillary vertical relapse after maxillary elongation stratified by study design (overall follow-up). *Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

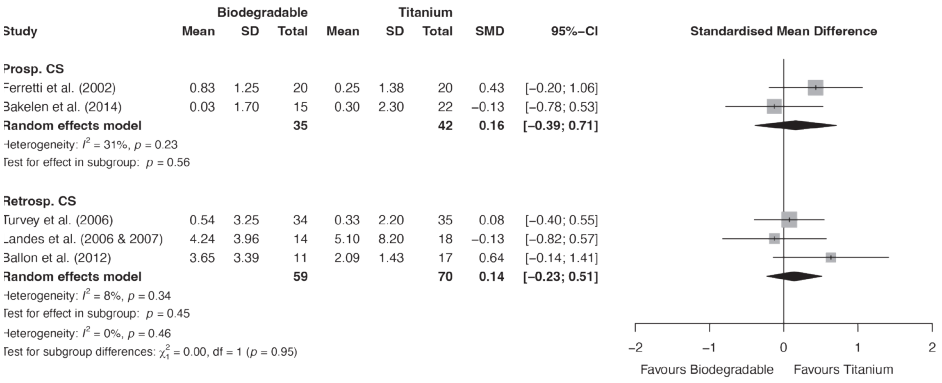

Figure S16. Forest plot of the endpoint mandibular horizontal relapse after mandibular advancement stratified by study design (overall follow-up). *Prosp. CS, prospective cohort studies; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

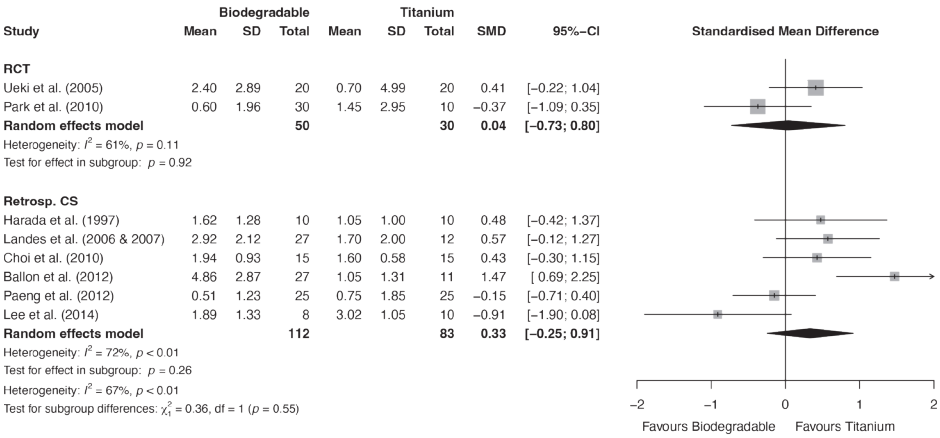

Figure S17. Forest plot of the endpoint mandibular horizontal relapse after mandibular setback stratified by study design (overall follow-up). *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

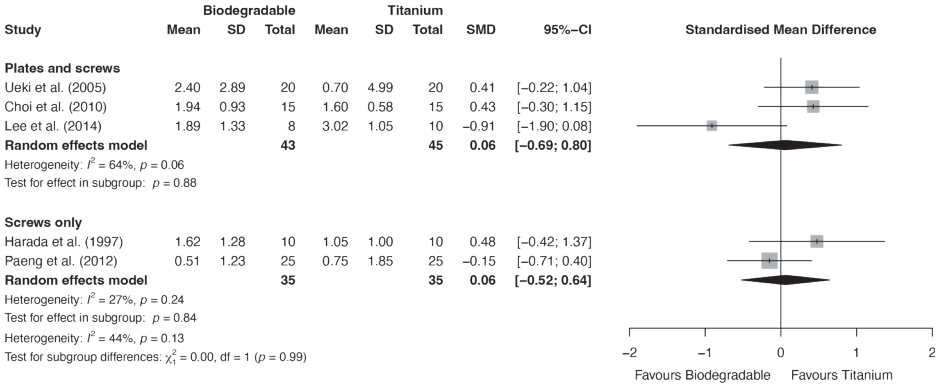

Figure S18. Forest plot of the endpoint mandibular horizontal relapse after mandibular setback of studies including osteosynthesis by plates and screws versus only screws (overall follow-up). *SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

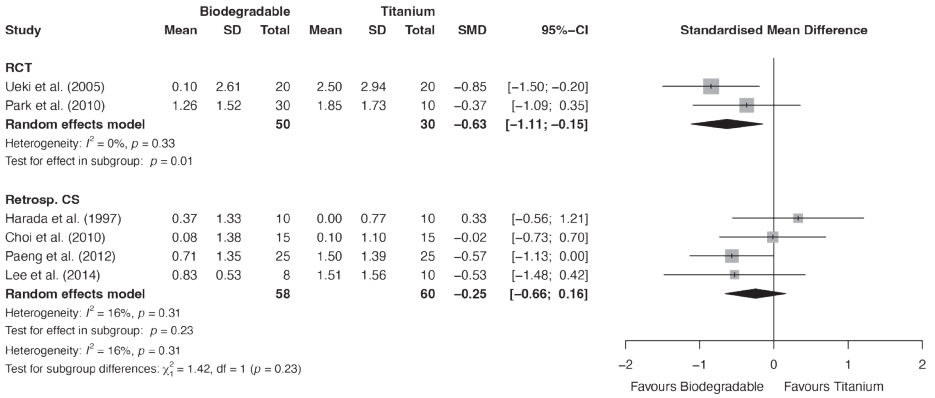

Figure S19. Forest plot of the endpoint mandibular vertical relapse after mandibular setback stratified by study design (overall follow-up). *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

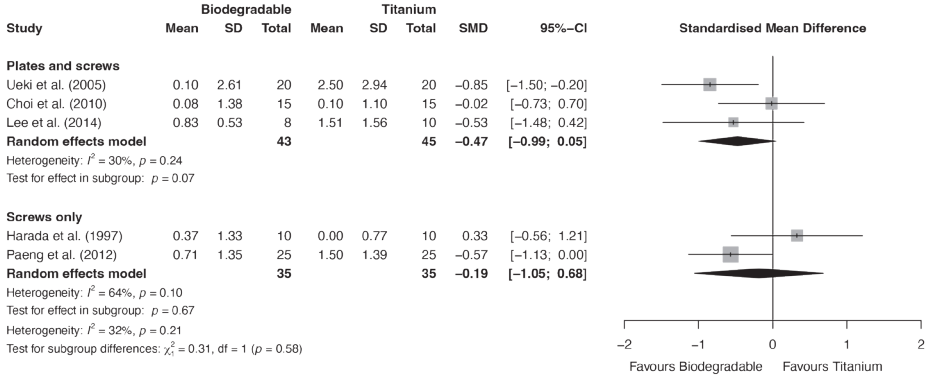

Figure S20. Forest plot of the endpoint mandibular vertical relapse after mandibular setback of studies including osteosynthesis by plates and screws versus only screws (overall follow-up). *SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

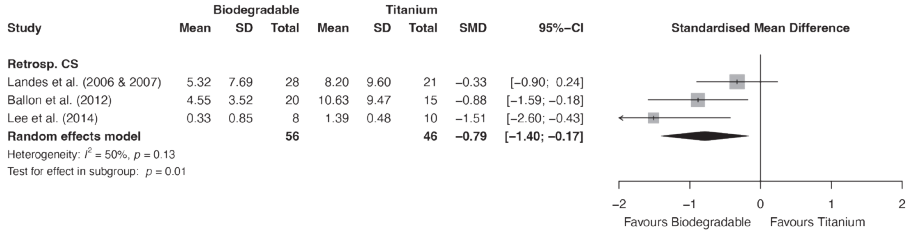

Figure S21. Forest plot of the endpoint mandibular angular relapse after mandibular clockwise rotation stratified by study design (overall follow-up). *Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

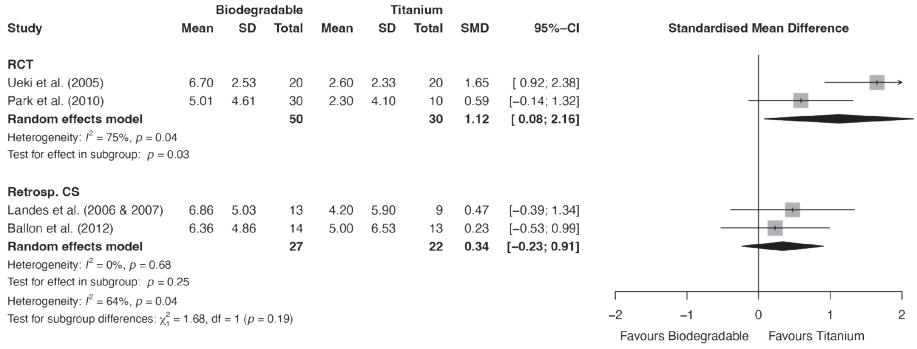

Figure S22. Forest plot of the endpoint mandibular angular relapse after mandibular counter clockwise rotation stratified by study design (overall follow-up). *RCT, randomised controlled trials; Retrosp. CS, retrospective cohort studies; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

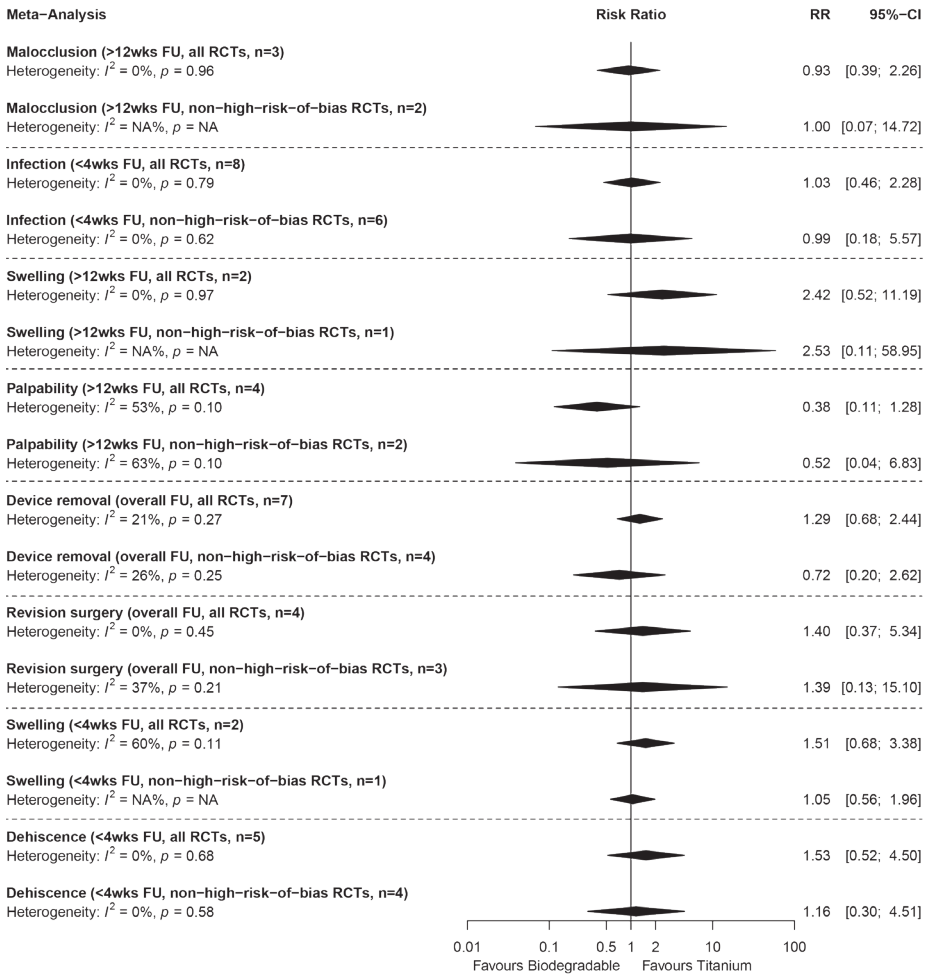

Figure S23. Sensitivity analysis with summary risk ratios for all pooled outcomes according to the inclusion of all randomized controlled trials and non-high-risk-of-bias RCTs only. *RCT, randomised controlled trials; RR, risk ratio; 95%-CI, 95% confidence interval.*

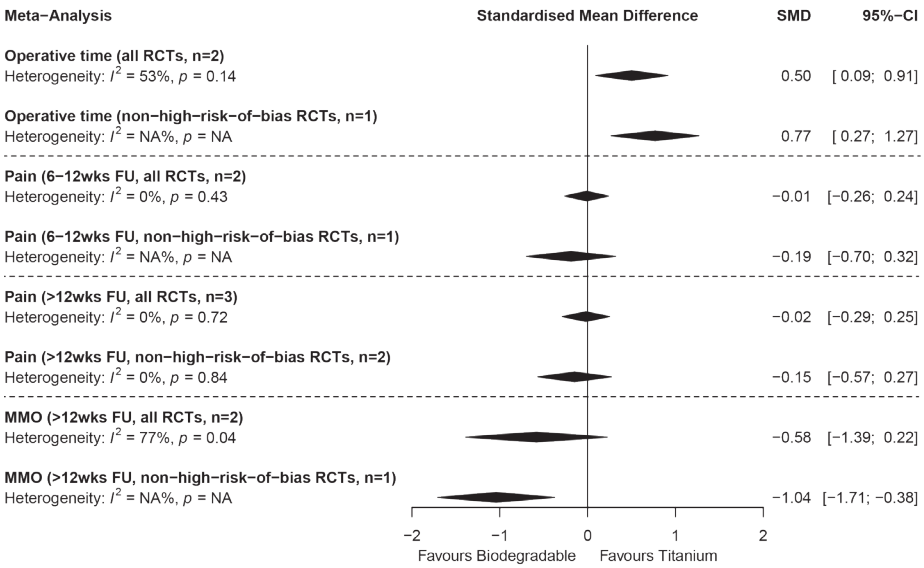

Figure S24. Sensitivity analysis with summary standardized mean differences for all pooled outcomes according to the inclusion of all randomized controlled trials and non-high-risk-of-bias RCTs only. *RCT, randomised controlled trials; SMD, standardised mean difference; 95%-CI, 95% confidence interval.*

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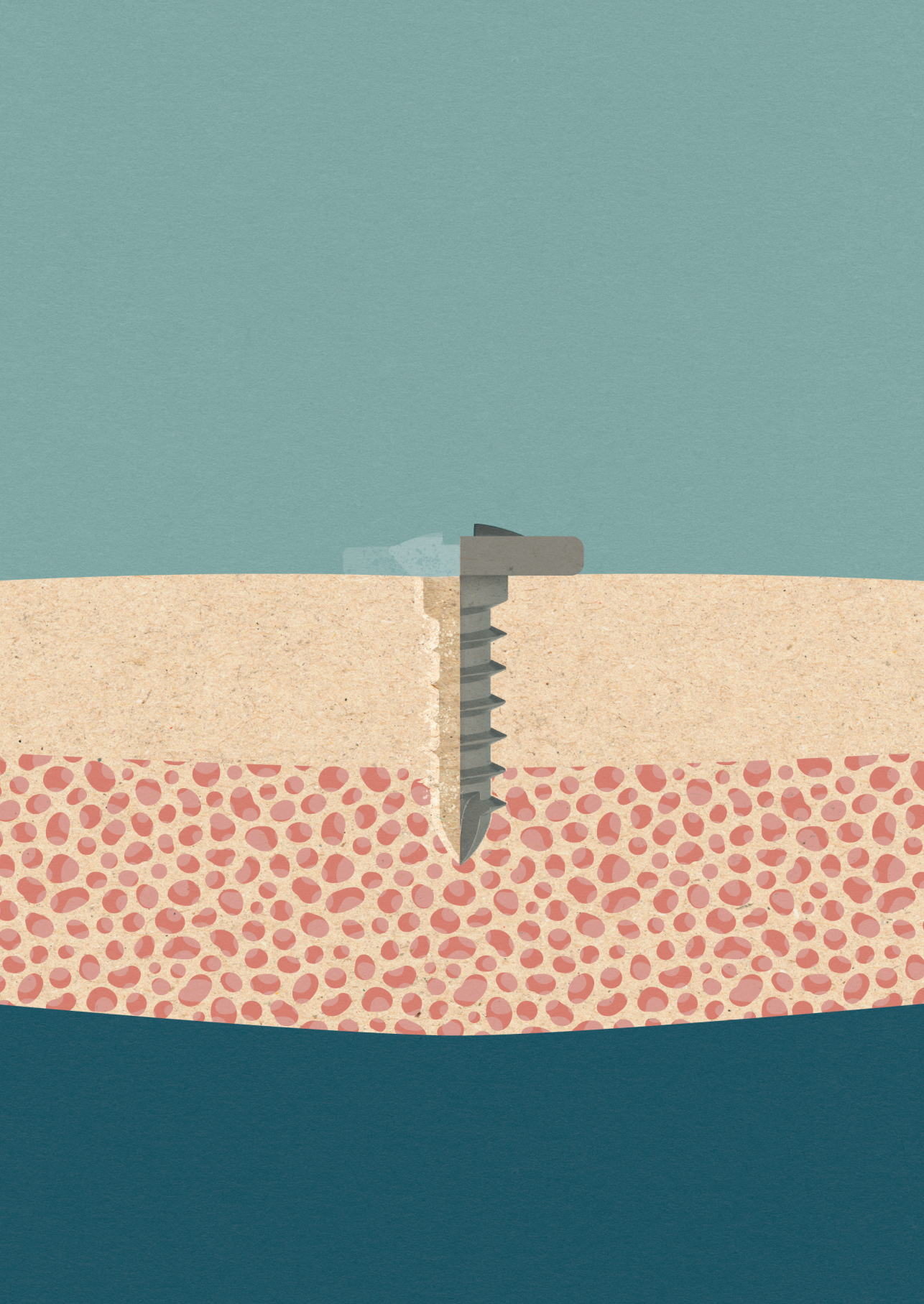

Chapter 4

Trust, but verify:

response to “Titanium plate removal in orthognathic surgery prevalence, causes and risk factors. A systematic literature review and meta-analysis”

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Dear Editor,

We read with great interest the work of Gómez-Barrachina et al.[1]. Their systematic review covers prevalence, causes and risk factors of titanium plate removal in orthognathic surgery. We have some concerns, however, regarding the completeness of the review due to their search strategy and interpretation of funnel plots.

Systematic reviews aim to identify all available evidence that fits pre-specified criteria to answer a specific research question, while minimizing bias[2]. Although substantial evidence was reported, at least three randomized controlled trials[3–5] were not included. These trials should have been included when applying their prespecified in- and exclusion criteria.

A thorough look at their methodology showed that some aspects of a sensitive search strategy were missing. This gap in methodology might have resulted in missing identification of relevant studies. Their search string for PubMed lacks Medical Subject Headings (MeSH) terms (e.g., *"Osteotomy, Le Fort"[MeSH]*). Inappropriate use or not using MeSH terms at all may result in missing studies and, thus, in incompleteness of a systematic review[2]. This common error in search strategies occurs in 44% of systematic reviews[6]. Furthermore, no explosion of terms (e.g., *'orthognathic surgery'/exp*) and no truncations were used in the PubMed, Scopus and Embase search strategy (e.g., *osteosynth**). Explosion of terms searches for specific terms underneath a specific heading. Truncations are used to search variants of spellings of a term. Excluding both results in less sensitive search strategies with the potential of missing evidence[6]. Finally, their search string for the PubMed, Scopus and Embase are identical, while each database needs a search string tailored to that database. This error occurs in 21% of systematic reviews[6]. As a result of such incompleteness, the guidelines for systematic reviews emphasize that authors should work closely with information specialists, preferably from the start of protocol writing, to ensure an appropriate and sensitive search strategy[2]. How complete and reliable is a systematic review when eligible literature is not included? Hence, trust your search strategy, but have it verified by an experienced information specialist.

The three missed studies report prevalence rates of titanium plate removal in patients of 3.3%[3], 0% (Le Fort I osteotomies)[4] and 15.3%[5]. Furthermore, these studies report data regarding location of plate placement. One study also provides data regarding the cause of plate removal[3]. Including these studies would have lowered the estimated plate removal prevalence, provided valuable information regarding the causes and risk

factors for plate removal, and increased the power of analyses performed by Gómez-Barrachina et al.[1].

Funnel plots are useful to assess publication bias but may result in false-positive test results when substantial between-study heterogeneity exists; in such cases, they are discouraged[2]. The authors constructed funnel plots passing clinical (e.g., different procedures) and methodological (e.g., different study designs) between-study heterogeneity. Furthermore, they report that their funnel plots of the prevalence of plate removal were symmetrical, and that trim and fill methods showed no significant difference between observed and imputed studies. Thus, they concluded that there was no publication bias. However, the results of statistical tests for funnel plot asymmetry should always be interpreted in combination of visual inspection of funnel plots[2]. The trim and fill test has low power in case of substantial heterogeneity, and, thus, even when this test does not provide evidence of funnel plot asymmetry, bias cannot be excluded[2]. We observed asymmetry in their funnel plots when visually inspected, i.e., smaller studies with statistically significant higher prevalence of titanium plate removal are less often observed than expected. Therefore, based on between-study heterogeneity and visually observed funnel plot asymmetry, the authors cannot exclude presence of publication bias. Hence, we advocate to trusting the statistical tests, but verifying the conclusions by critically inspecting the funnel plots.

Conflict of interests

The authors state that they have no conflict of interests.

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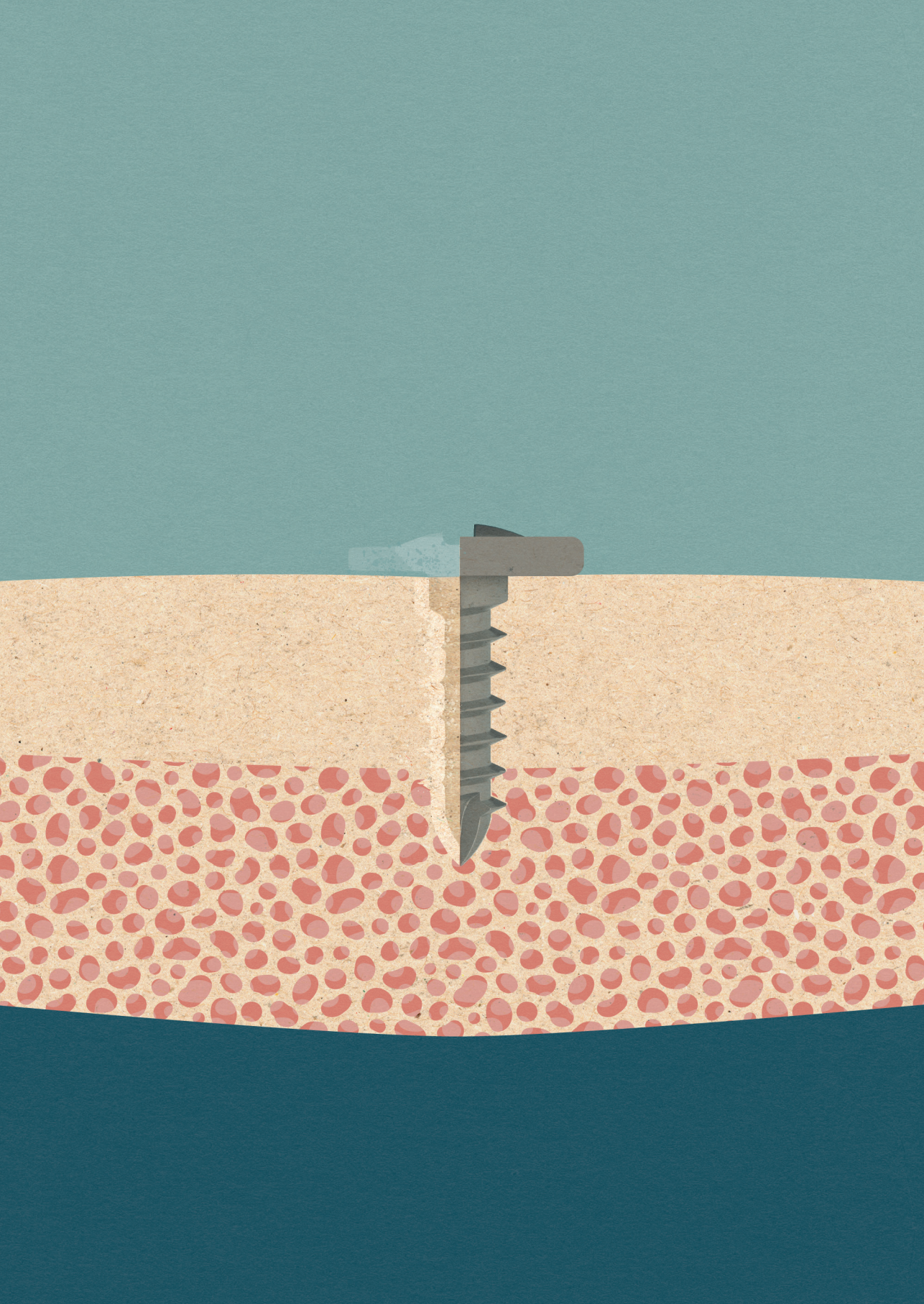

Chapter 5

Comparison of the long-term clinical performance of a biodegradable and a titanium fixation system in maxillofacial surgery

A multicentre randomised controlled trial

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Abstract

Biodegradable fixation systems could reduce or eliminate problems associated with removing titanium implants in a second operation. The aim of this study was to compare the long-term (i.e., >5 years postoperatively) clinical performance of a titanium and a biodegradable osteosynthesis system in oral and maxillofacial surgery. The present multi-centre randomized controlled trial was performed in four hospitals in the Netherlands. Patients treated with a bilateral sagittal split osteotomy (BSSO) and/or a Le Fort-I osteotomy, and those treated for fractures of the mandible, maxilla, or zygoma, were included from December 2006 to July 2009. The patients were randomly assigned to either a titanium (KLS Martin) or a biodegradable (Inion CPS) group. After >5 years postoperatively, plates had been removed from 22 of the 134 (16.4%) patients treated with titanium and from 23 of the 87 (26.4%) patients treated with the biodegradable system (P=0.036, hazard ratio (HR) biodegradable/titanium (95% CI) = 2.0 (1.05 – 3.8). The occlusion, VAS pain score, and MFIQ results showed good and (almost) pain free mandibular function in both groups. In conclusion, the performance of the maxillofacial Inion CPS biodegradable osteosynthesis system was inferior compared to the KLS Martin titanium system regarding plate/screws removal.

Trial registration: ISRCTN44212338.

Introduction

Titanium osteosynthesis is currently the fixation system of choice in maxillofacial traumatology and orthognathic surgery. According to the literature, titanium osteosynthesis material is removed from 5-40% of the cases in a second operation following adequate bone healing because of infections or other clinical symptoms[1–5].

Biodegradable osteofixation systems have the ability to degrade in the human body which, ideally, could reduce or even eliminate implant removal during a second operation[6]. However, adverse tissue reactions against the degradation products have been reported[7–9]. Consequently, biodegradable implants are removed in a second operation in 0-31% of the cases[4,10,11].

Most studies in the literature comparing titanium versus biodegradable osteofixation systems lack a control group, or their follow-up is inadequate[12]. In 2006, we started a randomized controlled trial comparing titanium vs. biodegradable plates and screws in maxillofacial surgery[3]. The short-term (i.e., 8 weeks) healing outcomes were similar in both groups[3]. However, the risk of biodegradable plate and screw removal was 2.2 times higher than for titanium implants within the first 2 postoperative years[4]. Although these results are of importance, studies focusing on long-term outcomes (i.e., >5 years) are needed since the host response, as well as full implant degradation and resorption, can take up to 4 or 5 years[9,13–16]. Additionally, titanium plate and screw removal has been reported three to five years after surgery[1,17]. The present study is part of the abovementioned randomized controlled trial[3].

The aim of the present study was to compare the long-term (i.e., >5 years postoperatively) clinical performance (i.e., removal of the plate/screws) of the titanium and the biodegradable systems following the fixation of mandibular, Le Fort-I, and zygomatic fractures, bilateral sagittal split osteotomies (BSSO) and/or Le Fort-I osteotomies.

Materials and methods

This randomised controlled trial (RCT) has been described according to the CONSORT statement 2010 (http://www.consort-statement.org/). The trial registration date and number are: 28 December 2006, ISRCTN44212338 (http://controlled-trials.com). The authors confirm that all ongoing trials related to this drug/intervention have been registered.

Study population

The recruitment start date of the RCT was October 2006. Patients were included from December 2006 to July 2009. During this period, 230 patients were treated at four different departments of Oral and Maxillofacial (OMF) Surgery in the Netherlands (University Medical Centre Groningen, Rijnstate Hospital Arnhem, Amphia Hospital Breda, and Medical Centre Leeuwarden). The in- and exclusion criteria are summarized in Table 1. Participants were recruited by OMF surgeons and were randomly assigned to either the titanium or biodegradable treatment group. Randomization occurred a day before (osteotomies) or immediately prior to the operation (fractures). Randomization sequences were generated by a statistician using a computerized randomization program and randomization was performed using an Interactive Voice Response System (IVRS) with block size 10, which was available 24-hours a day to conceal the randomization sequence until the interventions had been assigned. Randomization was stratified by the hospitals to ensure that both treatment options were equally divided over the participating hospitals. All the patients provided written informed consent prior to enrolment and publication of the work. The study was approved on 1 May 2006 by the Medical Ethical Committees of the participating hospitals in the Netherlands (University Medical Centre Groningen, Rijnstate Hospital Arnhem, Amphia Hospital Breda, and Medical Centre Leeuwarden).

Table 1. Inclusion and Exclusion Criteria

Inclusion criteria
Patients with a Le Fort-I fracture, and/or a solitary or multiple (maximum 2) mandibular fracture(s), and/or a zygoma fracture
Patients scheduled for a Le Fort-I osteotomy, and/or a Bilateral Sagittal Split Osteotomy (BSSO)
Patients (also, if needed, parents or guardians) who signed the *informed consent* form
Exclusion criteria
Patients younger than 18 years of age (trauma), or patients younger than 14 years of age (osteotomies)
Patients presenting with heavily comminuted fractures of the facial skeleton
Patients who had experienced compromised bone healing in the past
Patients who were pregnant
Patients who could/would not participate in a 1-year follow-up (with reasons)
Patients who would not agree to random assignment to one of the treatment groups, or one of the methods or treatment administered in the study
Patients diagnosed with a psychiatric disorder (diagnosed by a psychiatrist)
Patients who had undergone cleft lip and palate surgery in the past
Patients whose fracture reduction and fixation had been delayed for more than 7 days (after the day of the trauma)
Patients whose general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon

Interventions

Patients were assigned to either the titanium control-group (KLS Martin, Gebrüder Martin GmbH&Co. Tuttlingen, Germany) or to the biodegradable test-group (Inion CPS, Inion Ltd. Tampere, Finland). Prior to surgery, the patients were blinded for the used system. All the plates and screws were applied according to the manufacturers' instructions.

Mandibular osteotomies and fractures were fixated with 2.5-mm biodegradable or 2.0-mm titanium plates and screws, while 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used to fixate zygomatic fractures, Le Fort-I fractures, and Le Fort-I osteotomies. Each participating OMF surgeon performed 2 'test-surgeries' using the biodegradable system to acquire the different application-skills, i.e. pre-tapping the screw holes and pre-heating the plates, and to get used to the different material dimensions. These 'test-surgeries' were not included in the study. None of the study patients underwent rigid maxillomandibular fixation, but received soft guiding elastics post-operatively, and were instructed to use a soft diet for five weeks. It was agreed that routine removal of asymptomatic plates would not be performed.

Outcome measures

The most important outcome variable in the present study was plate/screws removal (yes/no) during the long-term follow-up (i.e., >5 years postoperatively) after the biodegradable or titanium system treatment, taken the time from the moment of implantation to removal into account.

The following other outcome measures were assessed:

1. reasons for plate/screws removal;
2. patient-related (self-evaluation): correct occlusion (yes/no); plate/screws palpability (yes/no); signs of swelling in the operation area at the follow-up (yes/no); pain reported on a Visual Analogue Scale (VAS; ranging 1-100); and mandibular function evaluated by the 17 questions of the Mandibular Function Impairment Questionnaire (MFIQ[18]; ranging from 17-85: a higher score means worse function);
3. patients were also asked whether they would have agreed to the surgery if they had known all the implications of the operation in advance (yes/no).

All the patients were contacted by telephone >5 years postoperatively to evaluate the outcome measures. In addition, their (electronic) medical records were evaluated for plate/screws removal. The complete date range of the patient inclusion until the final follow-up was December 2006 to June 2016. The outcome measures were recorded on Case-Report-Forms.

Statistical analysis

Inclusion of the 230 patients was based on a power analysis using the outcome measure 'bone healing after 8 weeks', which is described in detail elsewhere[3]. All the normally distributed variables were presented as means and standard deviations (SD). The mean values of both treatment groups were compared using the independent-samples t-test. Not normally distributed continuous data were presented as medians and ranges, and compared using the Mann-Whitney U test. All the nominal or categorical variables were described as frequencies and percentages. Both groups' variables were compared with the Fisher's exact test or Chi-squared test.

The difference in plate survival between the biodegradable and the titanium group was presented using a Kaplan-Meier estimator plot and analysed by the Logrank test. The intra-operative switches from the biodegradable to the titanium system may have influenced plate removal[19]. Therefore, the hazard ratio of the used treatment systems was calculated using a Cox regression analysis, which was adjusted for 'intra-operative switches'. The estimated plate removal rate was calculated by dividing the number of events (plate removal) by the plate's total in situ time. The total in situ time was calculated by taking the sum of:

- the *in situ* time up to plate removal during the observation period;
- the *in situ* time of the plates that were not removed and could be followed for the entire observation period. These patients were censored at the day of medical record evaluation in the survival analysis;
- the *in situ* time up to the end of the observation of the plates that were not removed from patients who did not complete the entire observation period. We also viewed the (electronic) medical records and if they showed no plate removal, these patients were also censored at the medical record evaluation day.

P-values less than 0.05 were considered statistically significant. All the analyses were performed in Statistical Package of Social Sciences (SPSS) 22 (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.).

Results

The flow of the 230 originally included randomized patients is shown in Figure 1. Seven patients (five in the biodegradable and two in the titanium group) were excluded due to protocol violations. In 25 patients who were randomized to the biodegradable group, the OMF surgeon decided to switch to the titanium system intra-operatively[3]. There were

2 titanium treatment received violations. Consequently, the titanium group consisted of 134 patients and the biodegradable group consisted of 87 patients ('Total included patients'; Table 2). In the course of the present study, 49 (36.5%) and 31 (35.6%) patients were lost to follow-up (LTFU) from the titanium and biodegradable groups, respectively. These patients could not be reached by telephone. This resulted in 85 patients in the titanium group and 56 patients in the biodegradable group ('Contacted patients'; Table 2). There were no significant differences in performed surgical procedures, gender and age distribution, and removal of plates/screws between the LTFU and not LTFU patients (Table S1).

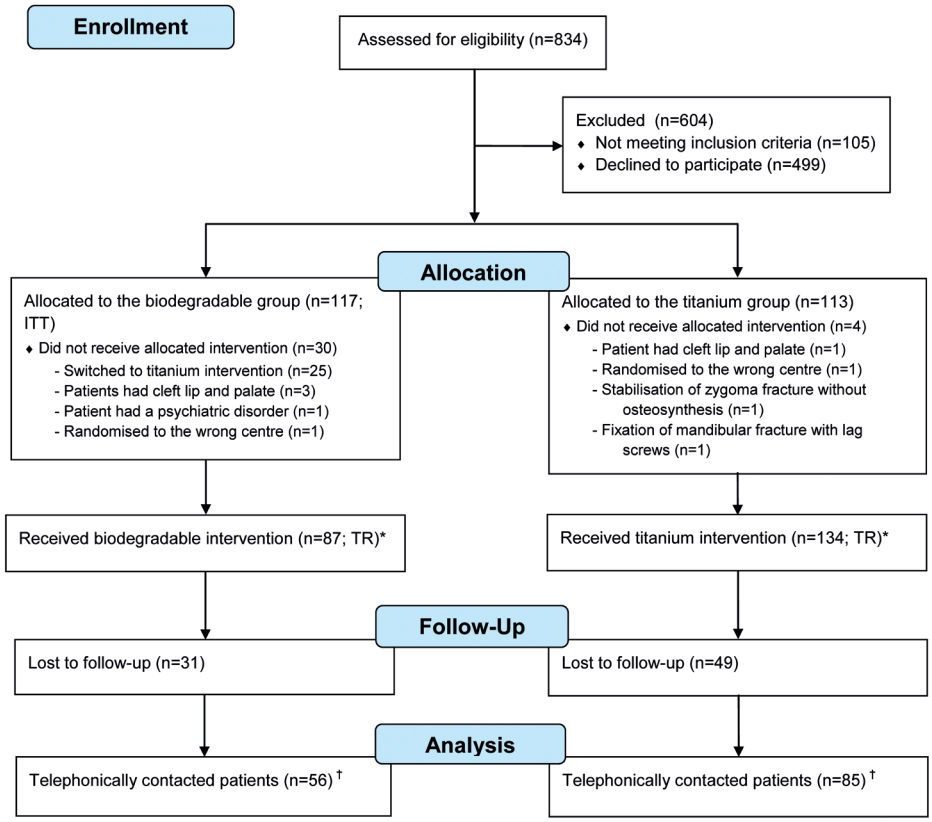

Figure 1. Flow diagram of patients' progress through the RCT phases. *Plate removal analyses. †Analyses of the other variables. ITT = intention-to-treat, n = number.

Table 2. Baseline characteristics of the total included and telephonically contacted patients.

Description	Total included patients*			Contacted patients‡		
	Titanium (n)	Biodegradable (n)	P-value†	Titanium (n)	Biodegradable (n)	P-value†
Surgical procedures	134	87		85	56	
BSSO	87 (64.9%)	55 (66.3%)	0.795	59 (69.4%)	35 (62.5%)	0.165
Le Fort-I osteotomy	8 (6.0%)	8 (9.2%)		3 (3.5%)	5 (8.9%)	
Bi-maxillary osteotomy	29 (21.6%)	16 (18.4%)		19 (22.4%)	11 (19.6%)	
Mandibular fracture	6 (4.5%)	4 (4.6%)		4 (4.7%)	2 (3.6%)	
Le Fort-I fracture	1 (0.7%)	0		0	0	
Zygoma fracture	3 (2.2%)	4 (4.6%)		0	3 (5.4%)	
Gender/age distribution						
Male	55 (41%)	43 (49.4%)	0.268	37 (43.5%)	28 (50%)	0.492
Female	79 (59%)	44 (50.6%)		48 (56.5%)	28 (50%)	
Age (median (range) in years)	29 (16-60)	28 (14-59)	0.786	30 (16-60)	30 (15-59)	0.993

*Analyses performed on all the included patients except the Protocol violation and the Treatment Received violation patients (see Fig 1), n=221: titanium n=134, biodegradable n=87. †Two-tailed test. ‡Analyses performed on all telephonically contacted patients for the long-term follow-up (i.e., >5 years postoperatively), n=141: titanium n=85, biodegradable n=56. Abbreviations: BSSO = bilateral-sagittal-split osteotomy, n = number.

All the titanium and biodegradable groups' baseline characteristics among both the 'total included patients' and 'contacted patients' did not differ significantly (Table 2). The median (range) follow-up was 95 (77-111) and 98 (80-111) months for the titanium and biodegradable groups, respectively (Table 3). Twenty two patients (16.4%) with a titanium system and 23 patients (26.4%) with a biodegradable system needed a second operation for plate/screws removal during the follow-up period (Table 3; Fig 2). Univariable plate removal analysis showed no significant difference between both groups (P=0.070). However, in six of the 25 (24%) intra-operative switch patients, a second operation was needed to remove the plates/screws. Therefore, the treatment variable, i.e. titanium or biodegradable, was analysed using a Cox regression analysis, adjusting for 'intra-operative switches' (Figure 2; P=0.036, hazard ratio (HR) biodegradable/titanium (95% CI) = 2.0 (1.05 – 3.8)). This states that the risk of biodegradable plate and screws removal is 2.0 times higher compared to titanium plates and screws during the long-term follow-up.

All 23 removals from the biodegradable group were due to clinical problems in the mandible and were only seen after an osteotomy. In the titanium group, 2 of the 22 removals (9.1%) were from mandible fracture patients. All the other titanium removals, except one, were due to clinical problems after an osteotomy in the mandible. The main reason for plate/screws removal was abscess formation: 15 patients (65.2%) in the biodegradable and 12 patients (50.1%) in the titanium group.

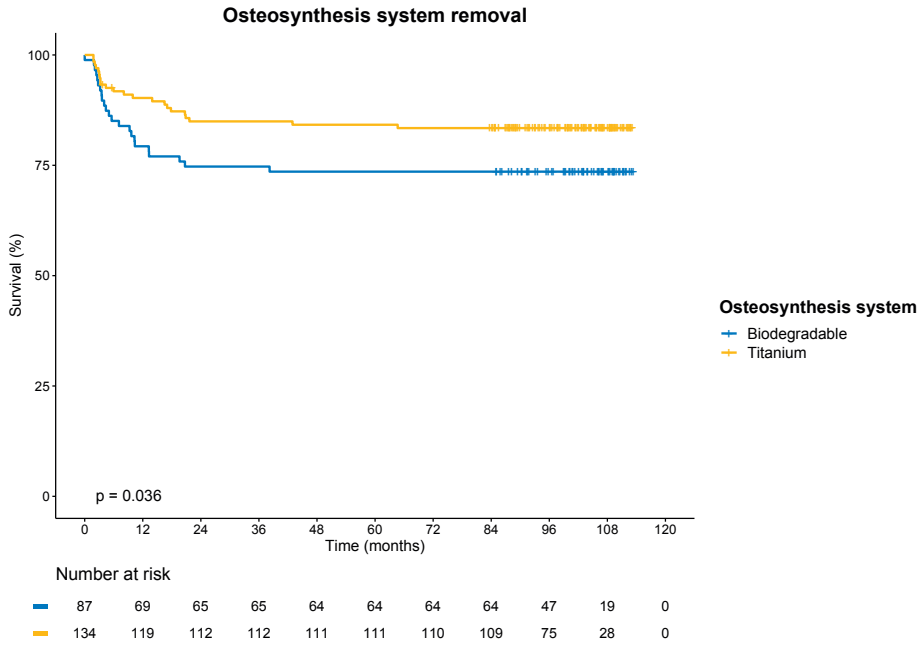

Figure 2. Kaplan-Meier curve of plate removal at the long-term follow-up of all the included patients (n=221: titanium n=134, biodegradable n=87). Adjusted hazard ratio (HR) biodegradable = 2.0 (95% CI: 1.05 – 3.8), HR titanium = 1; p=0.036.

Table 3. Outcome measures at the long-term follow-up (i.e., >5 years post-operatively).

Description	Titanium (n)	Biodegradable (n)	P-value*
Removal of plate/screws (n (%))†	22/134 (16.4%)	23/87 (26.4%)	0.036‡
Removal from surgical procedure patients			0.318
Removal from osteotomy patients	19/124 (15.3%)	23/79 (29.1%)	
BSSO	14/87 (16.1%)	19/55 (34.5%)	
Le Fort-I osteotomy	0/8	0/8	
Bi-maxillary osteotomy	5/29 (17.2%)	4/16 (25%)	
Removal from fracture patients	3/10 (30.0%)	0/8	
Mandibular fracture	2/6 (33.3%)	0/4	
Le Fort-I fracture	0/1	0/0	
Zygoma fracture	1/3 (33.3%)	0/4	
Patient self-evaluation¶			
Incorrect occlusion	14 (16.5%)	6 (10.7%)	0.461
Palpability of plate/screws#	34 (41.5%)	4 (7.8%)	< 0.001
Swelling	3 (3.5%)	4 (7.1%)	0.436
Permanent	2 (2.4%)	3 (5.4%)	
Fluctuating	1 (1.2%)	1 (1.8%)	
Pain VAS (median (range))	0 (0-80)	0 (0-80)	0.736
MFIQ (median (range)) ‖	18 (17-64)	17 (17-71)	0.110
Satisfied with the surgical procedure	81 (95.3%)	51 (91.1%)	0.483
Follow-up time (median (range) in months)•	95 (77-111)	98 (80-111)	0.458

*Two-tailed test. †Analyses performed on all the included patients except the Protocol violation and the Treatment Received violation patients (see Fig 1; n=221: titanium n=134, biodegradable n=87). ‡ After adjusting for intra-operative switches. Univariable plate removal analysis showed no significant difference between both subgroups (P=0.070). ¶ Analyses performed on all the telephonically contacted patients during the long-term follow-up (i.e., >5 years postoperatively), (n=141: titanium n=85, biodegradable n=56). #The patients whose plates/screws had been removed were not included in the analysis. ‖Mandibular function was evaluated by the 17 MFIQ questions; range 17-85; a higher score means worse function. • All the telephonically contacted patients' follow-ups. The follow-up period of all the included patients was 98 (78-113) months. Abbreviations: BSSO = bilateral-sagittal-split osteotomy, MFIQ = Mandibular Function Impairment Questionnaire, n=number, VAS=Visual Analogue Scale (range 0-100).

The titanium group showed significantly higher plate/screws palpability (41.5%) compared to the biodegradable group (7.8%; P<0.001). No significant differences were found regarding occlusion, swelling, VAS pain scores, and MFIQ between both groups (Table 3). Additionally, no significant difference was found in terms of satisfaction with the performed surgical procedure. The main reason for dissatisfaction among the nine unsatisfied patients was insufficient occlusion (44.4%). Adjusting for the baseline characteristics (i.e., age, gender, and surgical procedure) did not contribute significantly to the other outcome variables (e.g., palpability, MFIQ, etc.; data not shown).

There were no significant differences between the intention-to-treat (ITT) and treatment received (TR) analyses. In addition, no 'centre-effect' was found with respect to plate removal (data not shown).

Discussion

This study shows that the biodegradable fixation system (Inion CPS) was removed significantly more often compared to the titanium fixation system (KLS Martin) during the study period. The risk of biodegradable plate and screws removal was 2.0 times higher than titanium plates and screws removal within a median follow-up of 99 months after surgery.

All the biodegradable, and nearly all the titanium plate/screws removals, were due to clinical problems related to the mandible. This could have been caused by the considerable forces acting on the plates/screws mounted in the mandible. This applies in particular to osteotomies of the mandible because interfragmentary stability is not possible, whereas it is for fractures of the mandible. Consequently, screws may loosen which could result in an inflammation. Additionally, it could be due to the morphology of the mandible and the lesser vascularization compared to other parts of the facial skeleton. Although the 8 patients with fractures in the biodegradable group did not have any hardware removed, the total number of fracture patients included in this study was small so no firm conclusion regarding these surgical procedures can be drawn.

The main reason for plate and screws removal in both groups was abscess formation, which corresponds to the literature[20]. The causes of abscess formation are still unclear. During this trial, bacterial cultures from the three biodegradable group patients with abscess formation showed it was sterile inflammation[4]. A recent study reported similar results[21]. These inflammatory reactions could be a result of the degradation phase of the biodegradable systems, which could trigger a foreign body reaction[8]. Additionally, during degradation, lactic acid is formed, causing a low pH which may contribute to an inflammatory reaction[22].

The differences regarding occlusion, swelling, VAS pain scores, MFIQ, and satisfaction with the performed surgical procedure, were not significant. Almost every contacted patient was pain-free and reported good mandibular function. The titanium group showed higher plate/screws palpability compared to the biodegradable group. This was expected as the vast majority of the biodegradable systems should have dissolved by that time in the human body. Nevertheless, it must be noted that in almost 8% of the contacted

biodegradable group patients, the plate/screws were still palpable. This could, in theory, still have been the biodegradable fixation system. On the other hand, it is possible that the patients were palpating the remodelled bone rather than the plates and screws.

Occlusion was assessed from the patients' self-evaluations. Although the assessment of occlusion by patients themselves is subjective and may differ from an assessment by a professional, we feel that the patient's opinion regarding occlusion is of great importance. The discrepancy between a healthcare professional's judgement of occlusion and the patient's perception of their occlusion is therefore secondary.

Several observational studies have reported on plate removal in OMF surgery. Titanium systems were removed from 5-40% patients after trauma surgery[2,23] and from 7-27.5% patients after orthognathic surgery[1,24,25]. Biodegradable hardware was removed from 0-31%[10,26] and 0-3% of the patients[11,27,28], respectively. Randomized controlled trials that compare biodegradable with titanium fixation systems are scarce. One study showed 0% biodegradable and 31% titanium plate/screws removal after mandibular fractures[29]. Our study has similar results, i.e. 0% biodegradable vs. 33.3% titanium plate removal in patients treated for mandibular fractures. A recent meta-analysis showed 7.9% (21/267) biodegradable vs. 5.4% (22/404) titanium plate removal after orthognathic surgery[5]. The follow-up periods of the included studies were 8 weeks[3], up to 1 year[30], and up to 2 years[4,31]. Follow-up period discrepancies may have led to different plate removal rates compared to our study.

The study described herein was a multicentre randomised controlled trial involving four different hospitals. We found no centre-effect for plate removal. Therefore, it may be assumed that our results could be applied to other hospitals using Inion CPS biodegradable and KLS Martin titanium systems.

Despite the RCT protocol declaring that asymptomatic plates would not be removed, 2 patients from the titanium group requested the removal of their asymptomatic plates/screws. We analysed these patients as non-removals and censored them at the moment of the plate removal in the survival analysis. Furthermore, 80 patients (36%) were lost to long-term follow-up. However, since our most important outcome measure was plate/screws removal, we could also evaluate the medical records of all the included patients for this outcome measure. Theoretically, it is possible that patients who could not be contacted by telephone had their plate/screws removed in a hospital other than the one in which the patient's primary surgery had been performed, though this is highly unlikely. A post-hoc power analysis showed that, to detect a difference of 5%

fewer biodegradable plate removals with a power of 80% or 90%, 140 or 180 patients were needed in total, respectively. We included a total of 221 patients, which, in theory, makes the present study overpowered. Finally, the intra-operative switches could have influenced the plate removal rate. To minimalize this effect, we adjusted for these intra-operative switches in our survival analysis.

Conclusions

In conclusion, regarding plate/screws removal after >5 years follow-up, the performance of the Inion CPS biodegradable system was inferior compared to the KLS Martin titanium system following fixation of mandibular, Le Fort-I, and zygomatic fractures, bilateral sagittal split osteotomies (BSSO) and/or Le Fort-I osteotomies. However, due to the small number of included fracture patients in this study, no firm conclusion regarding these surgical procedures could be drawn. Finally, the intra-operative switches due to material failure of the biodegradable system[3] and the preferable cost-effectiveness of the titanium system[32] also argue against the use of Inion CPS in the abovementioned surgical procedures.

Conflict of interests

The authors state that they have no conflict of interests.

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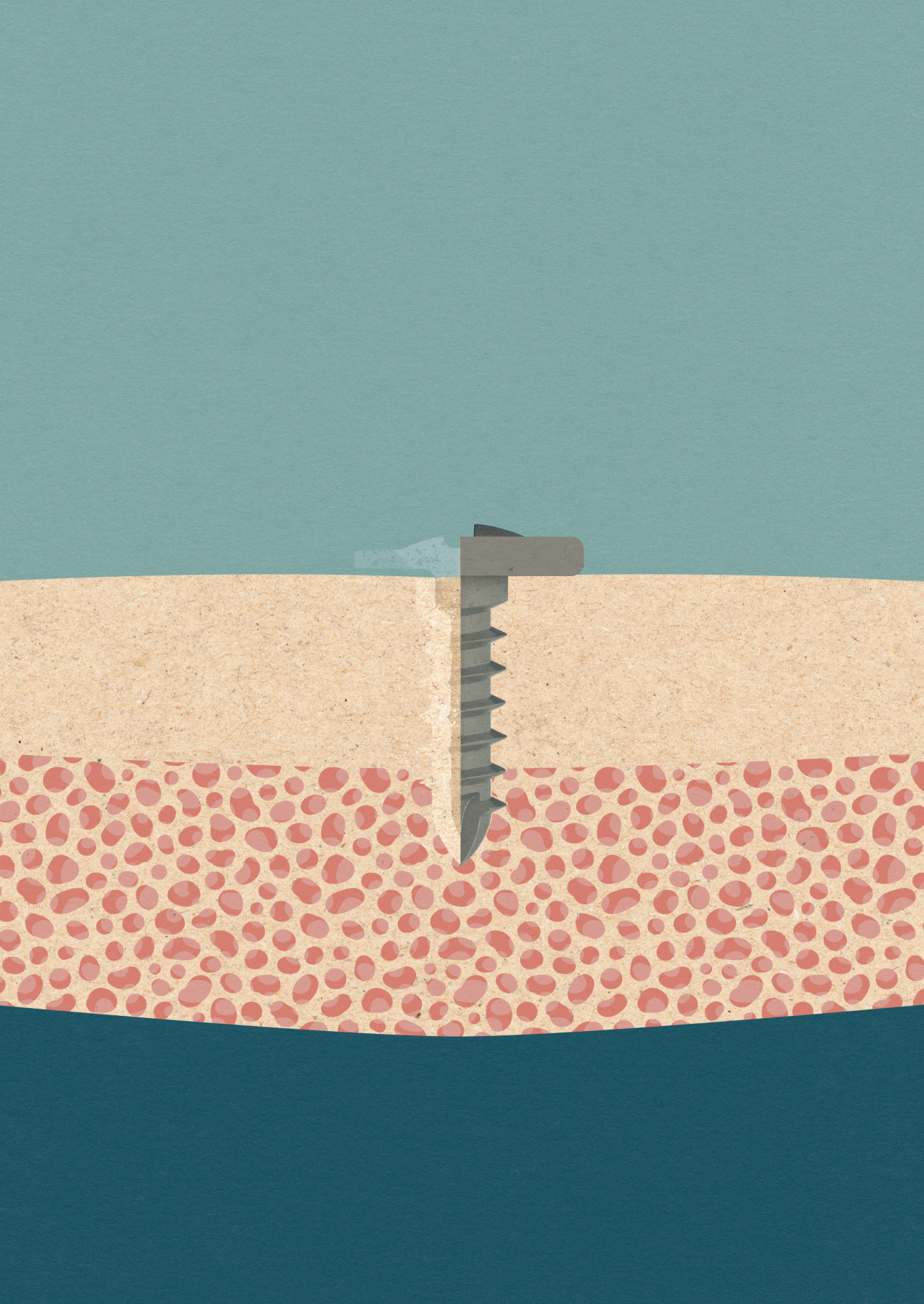
Supplementary data

Table S1. Baseline characteristics and outcome measures of patients lost to long-term follow-up (i.e. >5 years) and patients not lost to long-term follow-up*

Description	LTFU	Not LTFU	P-value†
	Baseline characteristics		
Surgical procedures	80	141	
BSSO	48 (60%)	94 (66.7%)	0.402
Le Fort-I osteotomy	8 (10%)	8 (5.7%)	
Bi-maxillary osteotomy	15 (18.8%)	30 (21.3%)	
Mandibular fracture	4 (5.0%)	6 (4.3%)	
Le Fort-I fracture	1 (1.3%)	0	
Zygoma fracture	4 (5.0%)	3 (2.1%)	
Gender/age distribution			
Male	33 (41.3%)	65 (46.1%)	0.573
Female	47 (58.8%)	76 (53.9%)	
Age (median (range) in years)	25 (14-60)	30 (15-59)	0.050
	Outcome measure		
Removal plate/screws (n (%))	19/80 (23.8%)	26/141 (18.4%)	0.386



Chapter 6

Biocompatibility and degradation comparisons of four biodegradable copolymeric osteosynthesis systems used in maxillofacial surgery

a goat model with four years follow-up

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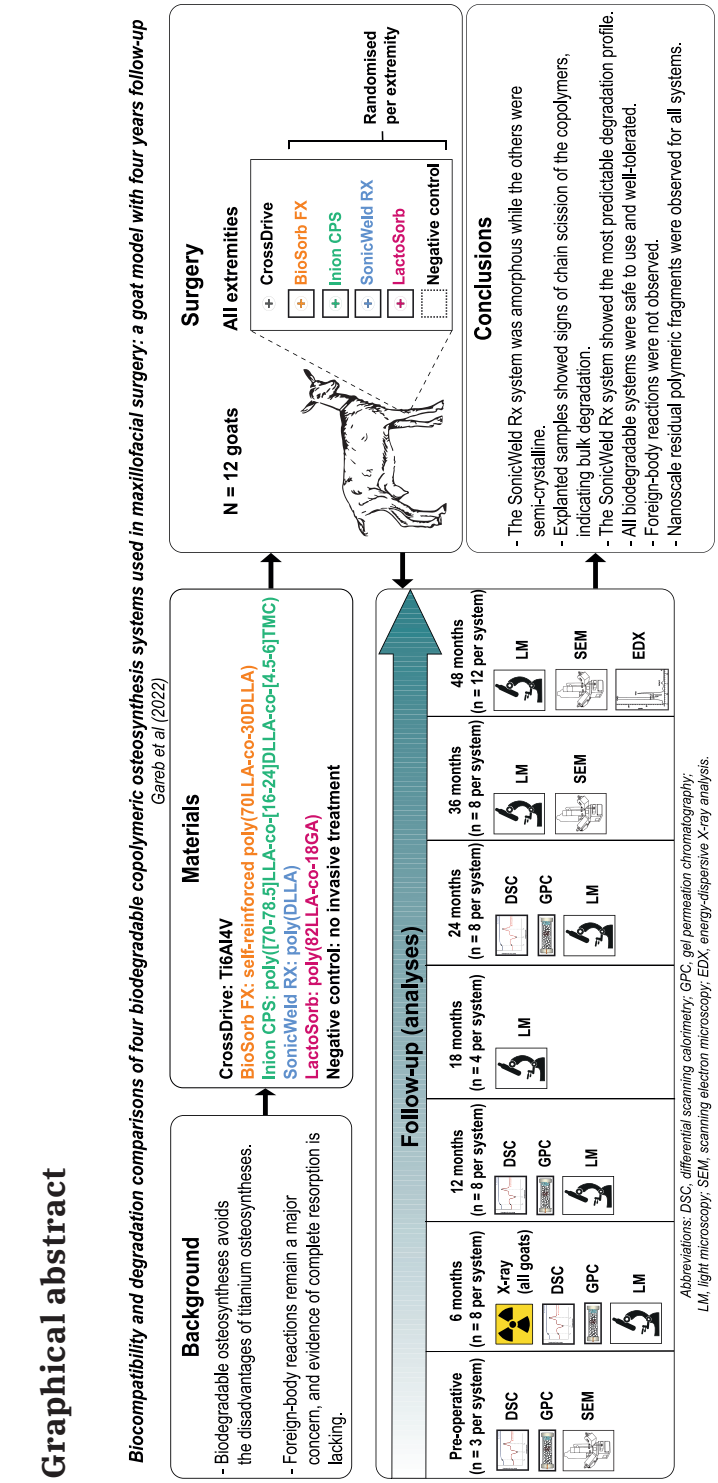
Abstract

Applying biodegradable osteosyntheses avoids the disadvantages of titanium osteosyntheses. However, foreign-body reactions remain a major concern and evidence of complete resorption is lacking. This study compared the physico-chemical properties, histological response and radiographs of four copolymeric biodegradable osteosynthesis systems in a goat model with 48-months follow-up. The systems were implanted subperiosteally in both tibia and radius of 12 Dutch White goats. The BioSorb FX [poly(70LLA-*co*-30DLLA)], Inion CPS [poly([70-78.5]LLA-*co*-[16-24]DLLA-*co*-4TMC)], SonicWeld Rx [poly(DLLA)], LactoSorb [poly(82LLA-*co*-18GA)] systems and a negative control were randomly implanted in each extremity. Samples were assessed at 6-, 12-, 18-, 24-, 36-, and 48-month follow-up. Surface topography was performed using scanning electron microscopy (SEM). Differential scanning calorimetry and gel permeation chromatography were performed on initial and explanted samples. Histological sections were systematically assessed by two blinded researchers using (polarized) light microscopy, SEM and energy-dispersive X-ray analysis. The SonicWeld Rx system was amorphous while the others were semi-crystalline. Foreign-body reactions were not observed during the complete follow-up. The SonicWeld Rx and LactoSorb systems reached bone percentages of negative controls after 18 months while the BioSorb Fx and Inion CPS systems reached these levels after 36 months. The SonicWeld Rx system showed the most predictable degradation profile. All the biodegradable systems were safe to use and well-tolerated (i.e., complete implant replacement by bone, no clinical or histological foreign body reactions, no [sterile] abscess formation, no re-interventions needed), but nanoscale residual polymeric fragments were observed at every system's assessment.

Graphical abstract



Introduction

Biodegradable materials, mainly consisting of polymers, are used as temporary implantable medical devices[1]. Biodegradable polymers, such as poly(L-lactic acid) (PLLA), are widely used in different medical disciplines including orthopaedic, trauma and maxillofacial surgery (e.g., in osteosynthesis systems)[1–3], cardiology and thoracic surgery (e.g., in cardiovascular stents)[1], and neurosurgery (e.g., in temporary intracranial pressure, pH and temperature sensors)[1,4]. Since their degradation kinetics and mechanical properties can be easily modulated by using, for example, L- and D-chirality of lactic acid or by copolymerization with different homopolymer ratios, researchers as well as clinicians have been increasingly interested in such biodegradable polymers over the last few decades[1,5,6].

Currently, titanium osteosynthesis systems are considered the gold standard to fixate bone segments in oral and maxillofacial surgery (OMF-surgery)[7,8], and orthopedics and trauma surgery[9]. However, the disadvantages of titanium systems include temperature sensitivity[10], tactile sensations of the plates and screws[11], growth restrictions[12], hampering of imaging and radiotherapy[13–15], presence of titanium particles in lymph nodes[16], extreme stiffness causing stress shielding of the underlying bone[2] and increased risk of medication-related osteonecrosis of the jaws[6,17]. Consequently, titanium systems are removed in a second operation in up to 40% of cases, resulting in accompanying costs and burdens[7,11,18].

The removal rate of polymeric biodegradable osteosynthesis systems in OMF-surgery is less and the disadvantages of titanium osteosyntheses are avoided[7,8]. Biodegradable systems should, preferably, be completely resorbed after 3 to 12 months[6]. However, sterile abscess formation due to foreign-body reactions remain a major concern, even after >5-years follow-up[7,11,19,20]. Factors that are known to influence foreign-body reactions are implant related (e.g., polymer composition), recipient related (e.g., blood supply), and plate location related (e.g., supraperiosteal versus subperiosteal)[1,21,22].

The most commonly used (co)polymers in biodegradable osteosynthesis systems are PLLA, poly(D,L-lactic acid) (PDLLA), poly(lactic-*co*-glycolic acid) (PLGA), or poly(L-*co*-D,L-lactic acid-*co*-trimethylene carbonate) (P(LLA-*co*-DLLA-*co*-TMC))[2,7]. These (co) polymers degrade in two phases to eventually form CO_2 and H_2O as final products: early degradation via hydrolysis of ester bonds can produce crystalline intermediate products that undergo secondary hydrolysis[5]. Secondary hydrolysis is the rate-limiting step and depends highly on the crystallinity and hydrophobicity of the intermediate products.

The reported foreign body reactions (FBR) occur predominately with biodegradable osteosyntheses with a high proportion (i.e., >70%) of PLLA[1,11,23–25] or poly(glycolic acid) (PGA)[1]. More amorphous copolymers such as PDLLA (e.g., 50LLA/50DLA ratio) and PLGA (e.g., 70LLA/30GA ratio) are more hydrophilic, and degrade and resorb more quickly[26].

Several studies have assessed tissue responses to biodegradable osteosynthesis systems composed of as-polymerized PLLA[23], amorphous PLLA[27], PDLLA[28–30], PLGA[26,29,31–34], and P(LLA-*co*-DLLA-*co*-TMC)[35,36], with follow-ups ranging from 6 weeks to 2 years[26,28–34,36–38]. Although most of these studies still found residual polymeric particles at the final follow-up, several studies concluded these systems had been resorbed completely by the 1 to 2-year follow-ups[28,29,32]. However, these conclusions were only based on *in vivo* assessments of degradation using light microscopy while the polymeric fragment dimensions which can induce foreign-body reactions can be smaller than the resolution of light microscopy[23]. Furthermore, degradation of these polymers leads to increasing crystallinity and even to the formation of crystalline oligomeric stereo-complexes over time[39,40] that are more stable and resistant to further hydrolytic degradation and resorption than amorphous fragments[1,6,23,41]. Therefore, evidence of complete resorption of polymeric biodegradable systems (i.e., at a nanoscale level) with appropriate follow-up (i.e, >2 years) is still lacking. Moreover, a comparison of biodegradable systems composed of different copolymers in the same model have not been performed and, thus, only indirect comparisons of degradation profiles of biodegradable osteosyntheses are currently available. Hence, there remains a need for an assessment of the degradation of different polymeric biodegradable osteosynthesis systems at nanoscale levels with a long-term follow-up, as this is essential for biocompatibility evaluations as well as to gain knowledge of the development of FBR to such biodegradable polymers.

This study aimed to assess and compare the histological responses (i.e., at macro, micro- and nanoscale levels) of four commonly used copolymeric biodegradable osteosynthesis systems in a goat model from a six-month up to a four-year follow-up. Additionally, the molecular and thermal properties of these systems at different time points were analysed to assess *in vivo* fragmentation and crystallinity, respectively, of the (residual) copolymers with time.

Materials and methods

This study was conducted following the International Organization for Standardization (ISO) standards[42] and is reported according to the 'Animal Research: Reporting of In Vivo

Experiments' (ARRIVE) guidelines[43]. The study is fully in agreement with the National Laws and Regulations for Animal Experiments, National Institutes of Health guide for the care and use of Laboratory animals[44], and was approved by the Institutional Animal Care and Use Committee of the University of Groningen (UG)/University Medical Center Groningen (UMCG; DEC 5642A).

Osteosynthesis systems

Four different copolymeric biodegradable osteosynthesis systems commonly used in OMF-surgery were included[7], viz. BioSorb FX 2.0x7 mm (self-reinforced poly(70LLA-*co*-30DLLA) stereo-copolymer; ConMed Linvatec Biomaterials Ltd., Tampere, Finland), Inion CPS 2.0x7 mm (poly([70-78.5]LLA-*co*-[16-24]DLLA-*co*-4TMC); Inion Oy, Tampere, Finland), SonicWeld Rx 2.1x7 mm (poly(DLLA) stereo-copolymer; KLS Martin Group, Gebrüder Martin GmbH & Co., Tuttlingen, Germany), and LactoSorb 2.0x7 mm (poly(82LLA-*co*-18GA) copolymer; Biomet Microfixation, Jacksonville, Florida, USA)[2]. Proton nuclear magnetic resonance analyses (^{1}H-NMR; Bruker Avance III 400 MHz NMR spectrometer using $CDCl_3$ as a solvent at 25 ºC) of the materials confirmed that the composition of the polymers was in agreement with the manufacturer's specifications (data not shown). All the systems consisted of a 1-hole plate with a corresponding biodegradable screw or pin[2]. Additionally, a CrossDrive 2.0x6 mm screw (90/6/4% titanium/aluminum/vanadium [Ti6Al4V]; KLS Martin Group) were used as a non-degradable reference marker (i.e., to localise the biodegradable implants after complete fragmentation and resorption). As a negative control, an area where no invasive treatment was performed was assessed (Figure 1). The sizes of plates and screws are given in Table S1. The minimal distance between implants was ≥1 cm. All the osteosynthesis systems underwent the manufacturer's sterilization process (i.e., the BioSorb FX, Inion CPS, and SonicWeld Rx systems were sterilized with γ-irradiation at a dose level of 25 kGy and the LactSorb system with two 2-hour ethylene oxide (EtO) half cycles with 100% EtO gas at 38 to 43 ºC), were implanted before the expiration date, and were applied according to the manufacturer's instructions. Assessment of surface topography of all materials was performed with chromium coating using scanning electron microscopy (SEM; Zeiss Supra55 SEM at 3 kV)[45,46].

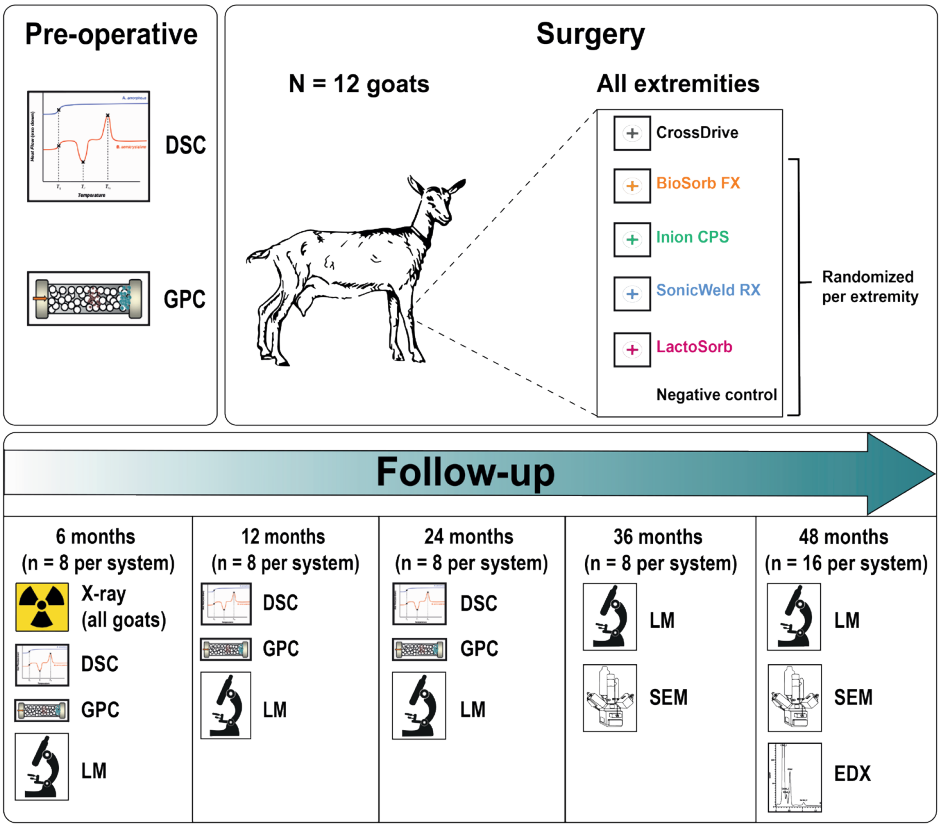


Figure 1. Study design. Note that the study protocol (i.e., assessment at 6, 12, 24, 36, and 48 months [n=8 per system] with two extra goats [n=8 per system]) differed from the actual execution as presented here: the goat that died prematurely was assessed at 18 months follow-up (n=4 per system), one of the extra goats was used to replace the goat that died prematurely, and the other extra goat was sacrificed at the 48-month follow-up (n=12 per system). *Ti6Al4V, 90/6/4% titanium/aluminum/vanadium; LLA, L-lactic acid; DLLA, D,L-lactic acid; TMC, trimethylene carbonate; GA, glycolic acid; DSC, differential scanning calorimetry; GPC, gel permeation chromatography; LM, light microscopy; SEM, scanning electron microscopy; EDX, Energy-dispersive X-ray analysis.*

Animals and surgical procedure

Twelve skeletally mature female Dutch White goats (16-18 months old and 72-79 kg) were selected (Figure 1). Skeletally mature goats have similar osseous macro- and microarchitecture, physiology, biomechanical properties, bone composition, and remodelling rates as humans, and are able to generate a FBR to copolymeric biomaterials[47]. Therefore, goats are a suitable and recommended large animal model for preclinical assessment of biomaterials for bone reconstruction[48–52]. Since this was

the first study comparing different copolymeric osteosynthesis in a long-term animal model, and since pilot data was not available, sample size calculation was performed using the Fermi approximation method[53]. All systems were implanted in both tibia and radius of each goat. Thus, each goat had a total of 16 biodegradable 1-hole plates with screws/pins (i.e., four of each biodegradable system) and four Ti6Al4V screws implanted (a total of 20 implants per animal). Two goats were planned to be sacrificed at 6, 12, 24, 36 and 48 months follow-up resulting in 8 samples from each biodegradable system per time point. Two extra goats were included for the premature death of a goat so that 8 samples could be studied at each time point. This ensured sufficient samples for reliable histological and molecular analyses[42] while also reducing the number of animals used for scientific research[1,42]. The positions of the biodegradable systems and the negative control were randomised using a computer random number generator by a researcher (LD) who was not involved in the outcome assessment or in the statistical analyses. Prior to surgery, all the goats were acclimatized for two weeks with daily cycles of 12 hours light/dark and were fed twice daily with hay and grain. A veterinarian ensured good health by performing complete health assessments. All the goats were housed on a farm specialized in animal research (Overasselt, the Netherlands) and had not been used in previous research.

The surgical procedures were performed by a senior OMF-surgeon (RRMB) and a researcher (NBB) at the Central Animal Laboratory of the UMCG under standard aseptic conditions. General anaesthesia was induced by an intravenous injection of thiopental (15 mg/kg body weight). The goats were intubated and received a stomach probe. Anaesthesia was maintained with a mixture of sevoflurane/30% oxygen through a constant volume ventilator. Vital signs (i.e., heart rate, body temperature, oxygen saturation, and respiration monitoring) were monitored during surgery. The incision sites were disinfected using a diluted betadine solution and saline. Buprenorphine (10 µg/kg body weight) was administered intravenously to reduce postoperative pain. A skin incision was made anterior of the tibia and radius. The skin and underlying soft tissues were transected and reflected from the bone. Using a drilling guide with the titanium screw as a reference, the screw holes were drilled with the prescribed drills (Table S1) and tapped with the prescribed taps while cooled with sterile saline. After subperiosteal fixation of osteosynthesis systems, the periosteum and soft tissues were closed tension-free in three layers with Vicryl® 3-0. An additional intramuscular injection of buprenorphine (10 µg/kg body weight) was administered ten hours after the surgical procedure. The goats' general behaviour, vital signs, wound inflammation,

macroscopic swelling, mobility, appetite and defecation were checked daily post-operatively by a veterinarian.

Specimen retrieval and processing

After 6 months, all the animals underwent an X-ray of the surgical sites. The goats were euthanized with an overdose of intravenously injected pentobarbital. Two randomly selected samples of each biodegradable system were retrieved after 6, 12, and 24 months for planned analyses with differential scanning calorimetry (DSC, n=1) and gel permeation chromatography (GPC, n=1). However, the DSC analyses of explanted materials could not be performed due to insufficient amounts of remaining material at 6, 12 and 48-months follow-up. The GPC analyses of explanted materials could only be performed of the BioSorb FX system. The remaining amounts of materials of the other three biodegradable systems were also insufficient for GPC analyses. The remaining samples of each biodegradable system were planned to be retrieved for histological processing, i.e., at 6, 12, and 24 months: n=6 per system; at 36 and 48 months: n=8 per system. The pH of all the implant sites was measured and noted at every assessment moment.

The histological processing of the samples involved fixating in 4% phosphate-buffered formalin solution for 5 days, decalcifying with 10% aqueous ethylenediaminetetraacetic acid (EDTA) solutions, and dehydration in ascending ethanol concentrations (70-100%). The samples were embedded in poly(glycidyl methacrylate). Poly(methyl methacrylate) was deliberately avoided as it dissolves the polymers of the biodegradable systems and thus would interfere with the study's results (Table S2)[54].

Longitudinal histological sections of ~5 µm thickness were prepared for (polarized) light microscopy (LM) assessment using a rotational microtome (Leica RM 2155) and subsequently stained with haematoxylin and eosin (HE) and Safranin O-fast green (SafO)[54]. The SafO-stained sections were used to verify any occurrence of endochondral ossification. The histological sections were recoded by one researcher (LD) so that both assessors (BG and PB) were blinded.

Histological sections of ~1 µm thickness were cut for SEM using an ultramicrotome and glass knife, collected on a wet slide, dried and finally sputter-coated with gold. These histological sections were prepared from the ≥36 month follow-up samples without and with observable birefringent fragments. Elemental mapping using energy-dispersive X-ray analysis (EDX) was performed on the samples with birefringent fragments to verify the origin of these fragments. EDX was performed on similar samples but with

carbon coating using a X-Max 150 EDX detector (Oxford Instruments) mounted on a Zeiss Supra55 SEM operated at 10 kV, as described previously[45,46].

Differential scanning calorimetry

DSC was performed on the initial samples as well as on the 6, 12, and 24 month follow-up explanted samples. The DSC setup consisted of a Perkin Elmer Pyris 1 Differential Scanning Calorimeter (Fremont, CA, USA) and was performed under an inert atmosphere of ultra-high purity N_2. Indium was used for calibration. The 8-11 mg samples were cooled to 0 ºC at 300 ºC/min, held for 1 min and then heated to 200 ºC at 10 ºC/min. The glass transition temperature (T_g; onset and midpoint), melting temperature (T_m; onset and midpoint), and melting enthalpy (ΔH_m) were determined using OriginPro 2019b (OriginLab Corporation, Northampton, MA, USA). The degree of crystallinity was calculated using the following formula[55]:

(1) $$X_c = (\Delta H_m/\Delta H^*) / \Phi_{PLLA} * 100\%$$

where X_c is the degree of crystallinity (%), ΔH_m the determined melting enthalpy of the copolymer (J/g), ΔH^* the melting enthalpy of 100% crystalline PLLA (J/g), and Φ_{PLLA} the weight fraction of LLA segments in the copolymer. The melting enthalpy of 100% crystalline PLLA is 93 J/g[56].

Gel permeation chromatography

The weight averaged molecular weight (Mw) and the number averaged molecular weight (Mn), the polydispersity index (PDI), and intrinsic viscosity of the copolymers were determined with GPC. GPC was performed on the initial samples as well as on the 6, 12, and 24 month the explanted samples. The GPC setup consisted of a Viscotek GPCmax VE-2001 GPC solvent/sample module (Malvern, Worcestershire, United Kingdom), a series of ViscoGEL I columns, and a TDA 302 triple detector array consisting of a light scattering detector (i.e., Right Angle Light Scattering and Low Angle Light Scattering), a differential refractive index detector, and a four-capillary differential viscometer. A polystyrene standard (Mn = 64000 g/mol) with a narrow molecular weight distribution was used for calibration. Tetrahydrofuran was used as the eluent.

Histology and histomorphometry

The histological sections were independently assessed by two blinded researchers (BG and PB) using a systematic and validated approach[42]. Each histological section was divided into two pre-defined regions of interest: the supraosseous zone, which

is the side of the implant that was not covered by bone at the time of insertion (t=0) at the periosteal side (i.e., the head of the screw/pin and plate), and the intraosseous zone, which is the side of the implant that was covered by bone at the time of insertion, towards the endosteum (i.e., the shaft of the screw/pin).

Both zones of each histological section were assessed using a semi-quantitative scoring system based on (polarized) light microscopy (Zeiss Axioplan 2, Carl Zeiss Microscopy GmbH)[42,57]. The complete list with scoring-items and their definitions are presented in Table S3. Briefly, the scoring items consisted of: implant fragmentation, implant resorption at implant site, type of bone formation, fibrous capsule thickness, necrosis, active remodelling, periosteal or endosteal reaction, birefringent particles in non-implant sites, and the location of any birefringent particles in the non-implant sites. Non-implant site was defined as not being the original site of the implant but was in the same histological section. Additionally, cell responses were scored from the implant and bone interfaces (cells per field at 100x magnification). The scored cells included multinucleated giant cells (MNGCs), polymorphonuclear leukocytes (PMNs), eosinophils, macrophages, lymphocytes, and adipocytes. Likewise, distant cell responses (i.e., not at the implant site but in the same histological section) to birefringence particles were scored. In addition to the above-mentioned cell types, distant osteocytes with birefringence particles were also scored. The percentage of new bone formation per zone, and the total in each histological section, was quantitatively analysed with the aid of the image processing software ImageJ Fiji (version 2.1.0/1.53c)[58]. Any score disagreements between the two blinded researchers was resolved by a discussion.

Statistical analysis

Ordinal data were presented as medians with 25th to 75th percentiles. Nominal data were presented as the number of samples with the corresponding percentage. Continuous data were presented as means ± standard error of the mean (SEM). Univariable statistical comparisons of the ordinal, nominal and continuous data between osteosynthesis systems were performed by applying the Friedman test, Cochran's Q test, or the repeated measure analysis of variance (ANOVA) test, respectively. The inter-rater reliability of the nominal and ordinal data was assessed by calculating the unweighted and quadratic weighted Cohen's kappa, respectively, as well as by calculating the percentage of agreement[59].

Multilevel models were fitted to assess the effect of the different osteosynthesis systems on all the scored items. The fixed effects of the models included the type

of osteosynthesis system and follow-up in months. The interaction between the osteosynthesis system and follow-up (system*follow-up) or a quadratic term of follow-up (follow-up^2) were only included if such a relation was visually observed and if the term improved the model. Model improvement was tested using likelihood-ratio tests. The included random effects were the subjects. All the models yielded an estimated regression coefficient (β) with corresponding 95% confidence intervals (95% CI). In addition, odds ratios were calculated for the nominal and ordinal outcome variables.

P≤0.05 (two-tailed) was considered statistically significant. The Bonferroni correction was applied to all the pairwise comparisons to correct for multiple testing. All the analyses were performed in R, version 4.0.5 of, using the *lme4*-package[60].

Results

Postoperative care and follow-up

The surgical procedures were performed without any complications. All the osteosynthesis systems were implanted according to the pre-specified protocol. The surgical procedures were well tolerated by all 12 goats. None of the goats showed any deviations in general behaviour, vital signs, appetite and defecation. Mild swelling was noted directly post-operatively around the surgical site, which disappeared without further treatment. During the complete follow-up, no wound inflammation was observed.

At the 18-month follow-up, one goat showed signs of an aching back, most probably due to a previous epileptic seizure, and therefore Carprofen (1.4 mg/kg body weight) was administered subcutaneously. Initially, the goat recovered but after two weeks it showed signs of another epileptic seizure and subsequently died prematurely. An independent veterinarian concluded that the goat's epileptic seizures were not related to the experimental procedures. Specimens were retrieved from this goat and analysed as an 18-month follow-up. No other premature deaths occurred. One of the extra goats was used to replace the goat that died prematurely, the other goat was sacrificed at the 48-month follow-up (samples: at 6, 12, 24 and 36 months: n=8 per system; at 18 months: n=4 per system; at 48 months: n=12 per system; Figure 1).

Differential scanning calorimetry

The calorimetric properties of the included systems are presented in Table 1. The initial samples showed that the glass transition temperature (midpoint) ranged from 55.3 (Inion CPS plate) to 58.2 ºC (BioSorb FX plate). The Inion CPS plate and screw had evident melting peaks at ~136 ºC with ΔH_{m1} of 20-26 J/g, corresponding to a crystallinity of 27.6 to 40.8% related to PLLA. The LactoSorb screw also showed melting peaks at ~136 ºC with ΔH_{m1} of 14.6 J/g, corresponding to a crystallinity of 19.1%. The melting peaks of the LactoSorb and BioSorb FX plates were minimal. The SonicWeld Rx plate and pin did not show any melting peaks. DSC of the explanted samples from all the systems could not be performed at the 6, 12, and 24 month follow-ups due to insufficient amount remaining material.

Gel permeation chromatography

The results of the GPC are presented in Table 2. An analysis of the initial samples showed that the Mn ranged from 25.6 (LactoSorb plate) to 64.3 kDa (SonicWeld Rx plate), while the Mw ranged from 62.5 (LactoSorb plate) to 100.2 kDa (SonicWeld Rx plate). The PDI of the initial samples ranged from 1.5 (Inion CPS plate) to 2.5 (LactoSorb screw), indicating substantial differences between systems in the breadths of molecular weight distribution. The intrinsic viscosity ranged from 0.88 (SonicWeld Rx pin) to 1.31 dl/g (BioSorb FX screw). GPC could only be performed on the 6-month follow-up explanted BioSorb FX plate and screw samples as there was insufficient amount of explanted material available from the other systems to perform the analyses. After 6-months, the Mn, Mw, and intrinsic viscosity of the BioSorb plate and screw decreased, while the PDIs of both parts increased.

Surface topography

The scanning electron micrographs of the initial samples of the four biodegra-dable implants are shown in Figure 2. The BioSorb FX and Inion CPS systems had rough and irregular surfaces while the SonicWeld Rx and LactoSorb systems had smooth and homogenous surfaces. Polymeric fibres could be observed at the surface of the BioSorb FX implant. None of the implants was porous.

X-ray radiographs

The 6-month follow-up X-ray radiographs of the surgical sites (Figure S1) showed that all the osteosynthesis screw holes were still visible. The volume occupied by each osteosynthesis plate was also visible.

Table 1. Differential scanning calorimetry results of the initial and explanted materials.

			Initial materials						Explanted materials				
									6-, 12-, and 24-months follow-up				
Brand name of system	**Part**	**Copolymer composition**	**Tg (onset) (°C)**	**Tg (midpoint) (°C)**	**Tm (onset) (°C)**	**Tm (midpoint) (°C)**	**ΔHm (J/g)**	**Xc (%)**	**Tg (midpoint) (°C)**	**Tm (onset) (°C)**	**Tm (midpoint) (°C)**	**ΔHm (J/g)**	**Xc (%)**
BioSorb FX	Plate	SR poly(70LLA-*co*-30DLLA)	56.6	58.2	-	-	1.87	2.9	Insufficient amounts of remaining material to perform analyses				
	Screw	SR poly(70LLA-*co*-30DLLA)	53.1	55.6	-	-	-	0.0					
Inion CPS	Plate	Poly([70-78.5]LLA-*co*-[16-24] DLLA-*co*-4TMC)	52.4	55.3	128.8	136.4	26.59	36.4 to 40.8					
	Screw	Poly([70-78.5]LLA-*co*-[16-24] DLLA-*co*-4TMC)	53.8	57.2	124.4	136.2	20.12	27.6 to 30.9					
SonicWeld Rx	Plate	Poly(DLLA)	54.8	55.3	-	-	-	0.0					
	Pin	Poly(DLLA)	55.0	55.9	-	-	-	0.0					
LactoSorb	Plate	Poly(82LLA-*co*-18GA)	56.4	57.2	-	-	0.93	1.2					
	Screw	Poly(82LLA-*co*-18GA)	52.0	54.3	125.8	135.5	14.55	19.1					

Abbreviations: Tg, glass transition temperature; C, Celcius; Tm, melting temperature; ΔHm, melting enthalpy; Xc, degree of crystallinity assuming crystallization of PLLA segments only; SR, self-reinforced; LLA, L-lactic acid; DLLA, D,L-lactic acid; TMC, trimethylene carbonate; GA, glycolic acid.

Table 2. Gel permeation chromatography results of the initial and explanted materials.

			Initial materials				Explanted materials				
							6-months follow-up				12- and 24-months follow-up
Brand name of system	**Part**	**Copolymer composition**	**Mn (kg/mol)**	**Mw (kg/mol)**	**Poly-dispersity index**	**Intrinsic viscosity (dl/g)**	**Mn (kg/mol)**	**Mw (kg/mol)**	**Poly-dispersity index**	**Intrinsic viscosity (dl/g)**	
BioSorbFX	Plate	SR poly(70LLA-*co*-30DLLA)	39.9	85.7	2.2	1.14	26.4	61.5	2.3	0.91	Insufficient amounts of remaining material to perform analyses
	Screw	SR poly(70LLA-*co*-30DLLA)	42.3	83.6	2.0	1.31	33.8	77.7	2.3	1.07	
Inion CPS	Plate	Poly([70-78.5]LLA-*co*-[16-24]DLLA-*co*-4TMC)	61.1	92.5	1.5	1.30	Insufficient amounts of remaining material to perform analyses				
	Screw	Poly([70-78.5]LLA-*co*-[16-24]DLLA-*co*-4TMC)	52.4	97.1	1.9	1.15					
SonicWeld Rx	Plate	Poly(DLLA)	64.3	100.2	1.6	1.05					
	Pin	Poly(DLLA)	49.2	81.6	1.7	0.88					
LactoSorb	Plate	Poly(82LLA-*co*-18GA)	25.6	62.5	2.4	0.93					
	Screw	Poly(82LLA-*co*-18GA)	28.0	68.7	2.5	0.96					

Abbreviations: Mn, number averaged molecular weight; Mw, weight averaged molecular weight; kg/mol, 10^3 g per mol; dl, deciliter; g, gram; SR, self-reinforced; LLA, L-lactic acid; DLLA, D,L-lactic acid; TMC, trimethylene carbonate; GA, glycolic acid.

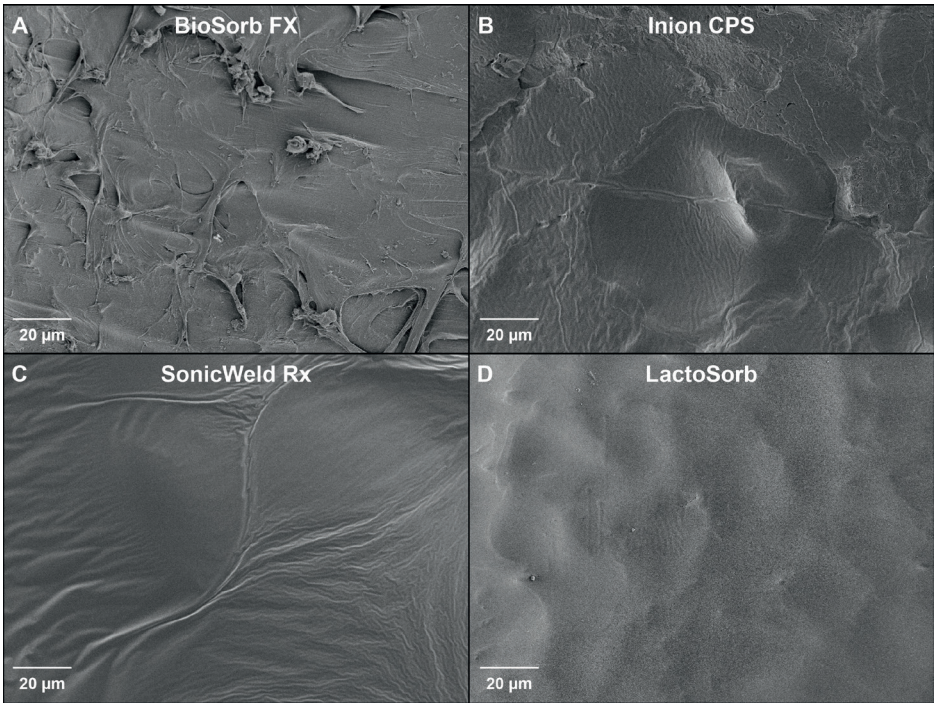


Figure 2. Scanning electron micrographs of the BioSorb FX (A), Inion CPS (B), SonicWeld Rx (C), and LactoSorb (D) surfaces of initial samples at 1500x magnification.

Histology and histomorphometry

The inter-rater reliability and percentage of agreement between both assessors of the histological sections ranged from 0.66 to 1.00 and 93.7 to 100%, respectively (Table S4).

The pH of the implant sites could not be measured as all the implants were overgrown with bone at every assessment moment. An overview of the histological sections assessed with polarized light microscopy (LM-pol) of each osteosynthesis system over time is shown in Figure 3. At the 6-month follow-up, remnants of the BioSorb FX, Inion CPS and LactoSorb osteosynthesis systems were clearly visible using LM-pol while remnants of the SonicWeld Rx system were not visible. At the 12- and 18-month follow-ups, fragments of the BioSorb FX and Inion CPS systems were still visible but not of the SonicWeld Rx and LactoSorb systems. At the 24-month follow-up, no remnants of any system could be observed at the implant sites using LM-pol. All the implant areas were replaced by bone with time. The overview shows signs of bulk degradation as well as surface erosion of all the included systems (Figure 3).

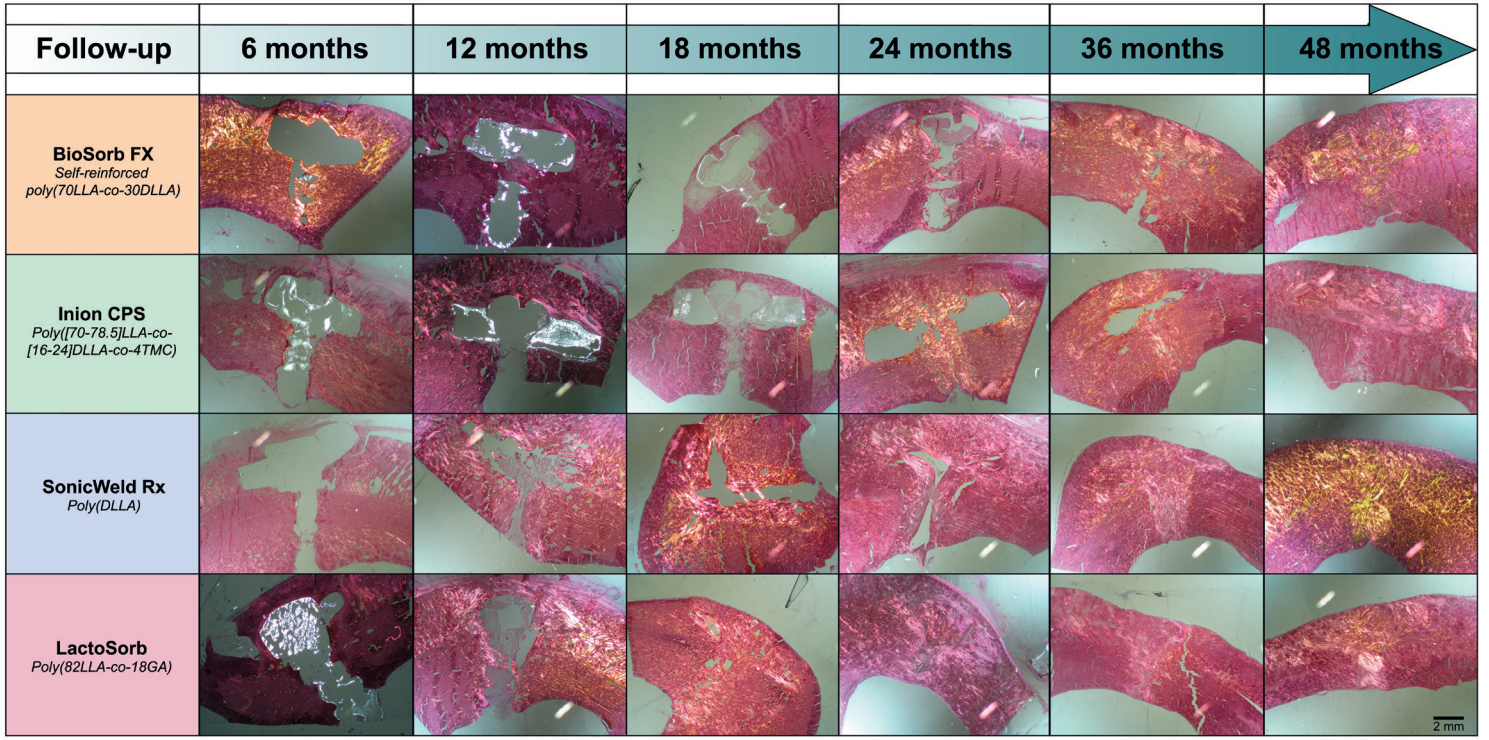


Figure 3. Overview of histological HE-sections assessed with polarized light microscopy (LM-pol) of each osteosynthesis system over time at 12.5x magnification. *HE, hematoxylin and eosin; LLA, L-lactic acid; DLLA, D,L-lactic acid; TMC, trimethylene carbonate; GA, glycolic acid.*

The scores of all the semi-quantitative scoring items of both zones over the 6 to 18 month and 24 to 48 month follow-ups, with univariable analyses at each follow-up point between the different systems, are shown in Tables S5 and S6, respectively. Visual presentations of the scoring items are shown in Figures 3-6. Adipocytes with birefringent particles at interface (both zones), necrosis (both zones), eosinophils at interface (intraosseous zone), and distant PMNs, eosinophils and lymphocytes with birefringent particles were not observed in any of the histological sections. The multilevel models with estimates, odds ratios (OR) and P-values are presented in Tables S7 and S8.

The fragmentation and resorption scores were similar between the supra- and intraosseous zones (Figures 4A-B and 4C-D, respectively). At the 6-month follow-up, the SonicWeld Rx was completely absent in all the histological sections while the other three systems showed observable implant fragments up to the 24-month follow-up (Figures 8A-B). The multilevel model of both the supra- and intraosseous zones showed that follow-up (i.e., the effect of time) was significantly associated with fragmentation and resorption of the implant ($P<0.001$). On adjusting for the effect of time, the LM(-pol) assessment of the SonicWeld Rx indicated that it was significantly more fragmented and resorbed compared to the other three systems (both $P<0.001$; Table S7 and S8).

The course of new bone formation at the supra- and intraosseous zones of the SonicWeld Rx system and at the supraosseous zone of the LactoSorb system increased constantly up to the 18 month follow-up while the trajectory of new bone formation with the BioSorb FX (both zones), Inion CPS (both zones), and LactoSorb (intraosseous zone) systems showed a deviation at the 12-month follow-up (Figure 4E-F). The multilevel model showed that the BioSorb FX and Inion CPS systems had significantly lower new bone formation in both zones compared to the SonicWeld Rx and LactoSorb systems (both $P=0.001$). In the supraosseous zones, woven bone was observed in the histological section after 6 months (SonicWeld Rx) and 18 months (BioSorb FX) while woven bone was not observed in the intraosseous zones (Figure 4G-H). The multilevel model demonstrated a significant effect of time (OR 1.11 [1.06;1.16] per month; $P<0.001$) as well as a significant difference in the odds of having new bone formation in the supraosseous zone between the Inion CPS system (OR 0.29 [0.09;0.99]) and the LactoSorb system (OR 1.0 [reference category]; $P=0.049$; Figure 4G). New lamellar type bone was observed in all the histological sections after 24 months in the supraosseous and after 18 months in the intraosseous zones. The SafO-stained sections confirmed the occurrence of endochondral ossification (Figures 8C-D). The percentage of total new bone formation (i.e., at the complete implant site) with the SonicWeld Rx and LactoSorb systems reached

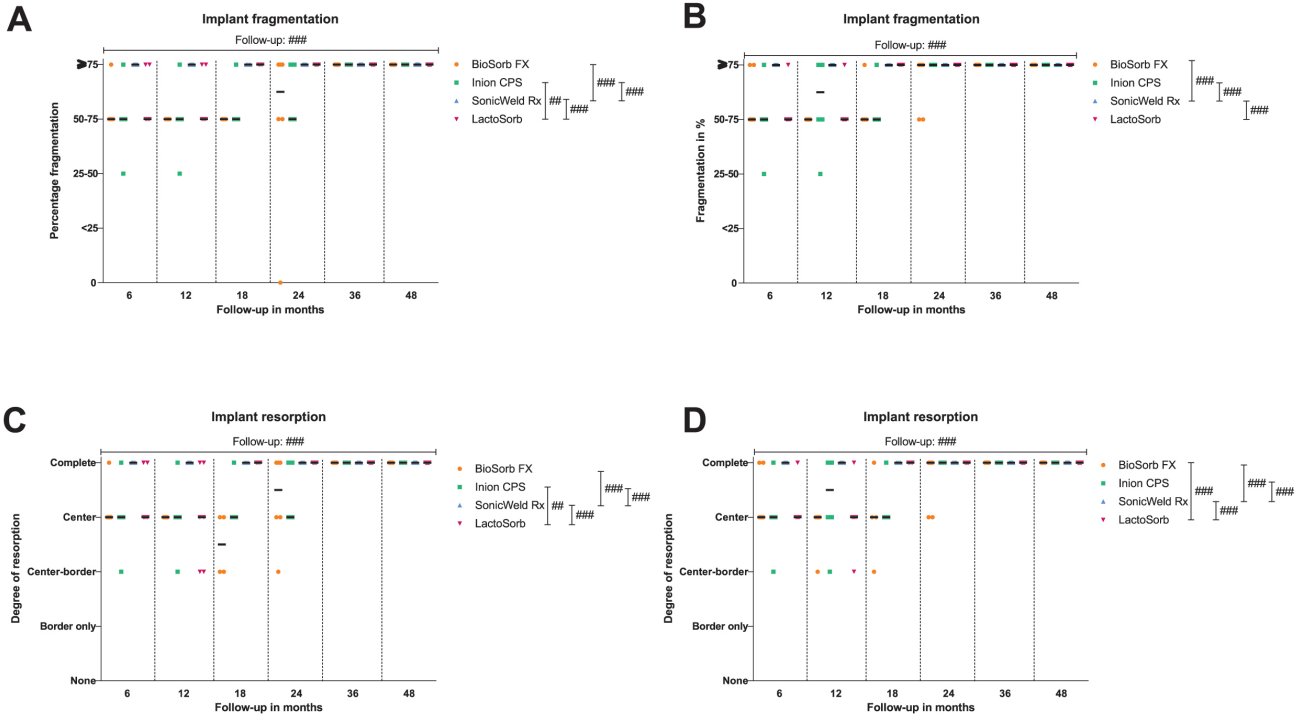
the same level as the negative control after 18 months while the BioSorb Fx and Inion CPS systems eached similar levels after 36-months (P<0.001 in favour of SonicWeld Rx and LactoSorb; Table 3; Figure 7B).

The fibrous capsule in the intraosseous zones was generally thinner from the 12- to 24-month follow-ups compared to the supraosseous zones (Figures 5A-B). In the multilevel model, there was a significant reduction in thickness with time (supraosseous: OR 0.90 [0.87;0.92] per month; intraosseous: OR 0.90 [0.88;0.92] per month; both P<0.001). No significant differences could be detected between the systems when adjusting for follow-up duration (supraosseous: P=0.232, intraosseous: P=0.093). The number of MNGCs at the supra- and intraosseous zone interfaces was comparable (Figures 5C-D). MNGCs were observed in the implant sites of all the systems and were absent from all the sections after the 36-month follow-up (Figures 8E-F). The multilevel model revealed that increasing follow-up resulted in fewer MNGCs at both zones' interfaces (both P<0.001) and that this effect was smaller for the BioSorb FX system (OR 0.96 [0.70;1.32] per month) at the supraosseous zone compared to the LactoSorb system (0.82 [0.69;0.98] per month; P=0.023). The number of PMNs (Figure 9A), eosinophils, macrophages and lymphocytes at the interface did not differ significantly between all the systems (Figures 5E-H and 6A-D). Remarkably, macrophages were present at the interface of the supraosseous zone in sections of the Inion CPS, SonicWeld Rx, and LactoSorb systems at the 12-, 18-, and 24-month follow-ups (i.e., up to >10 cells per field; Figure 6A) while macrophages were only observed in a single section of the intraosseous zone of the Inion CPS system at the 18-month follow-up (i.e., 6-10 cells per field) (Figure 6B). The number of distant MNGCs, macrophages, adipocytes, macrophages and osteocytes with birefringence fragments were not significantly different between the included biodegradable systems (Figure 7C-F). These distant cells were absent in all negative control sections.

Although the longer follow-up showed lower odds of the presence of active remodelling in both the supra- and intraosseous zones, bone remodelling was still occurring at 48-months in the supraosseous zones of both the BioSorb FX and Inion CPS sections and the intraosseous zones of both the Inion CPS and SonicWeld Rx sections while this was not observed in any of the negative control sections (Figures 6E-F). The BioSorb FX and Inion CPS sections' intraosseous zone bone remodelling was less compared to that in the LactoSorb sections (Table S7). The Inion CPS system resulted in significantly more periosteal apposition compared to the LactoSorb system (OR 2.82 [1.07;7.40]; P=0.036). The BioSorb FX, SonicWeld Rx, and the negative control showed similar periosteal reaction. Endosteal reaction was observed in all the systems' sections from the different

Supraosseous

Intraosseous



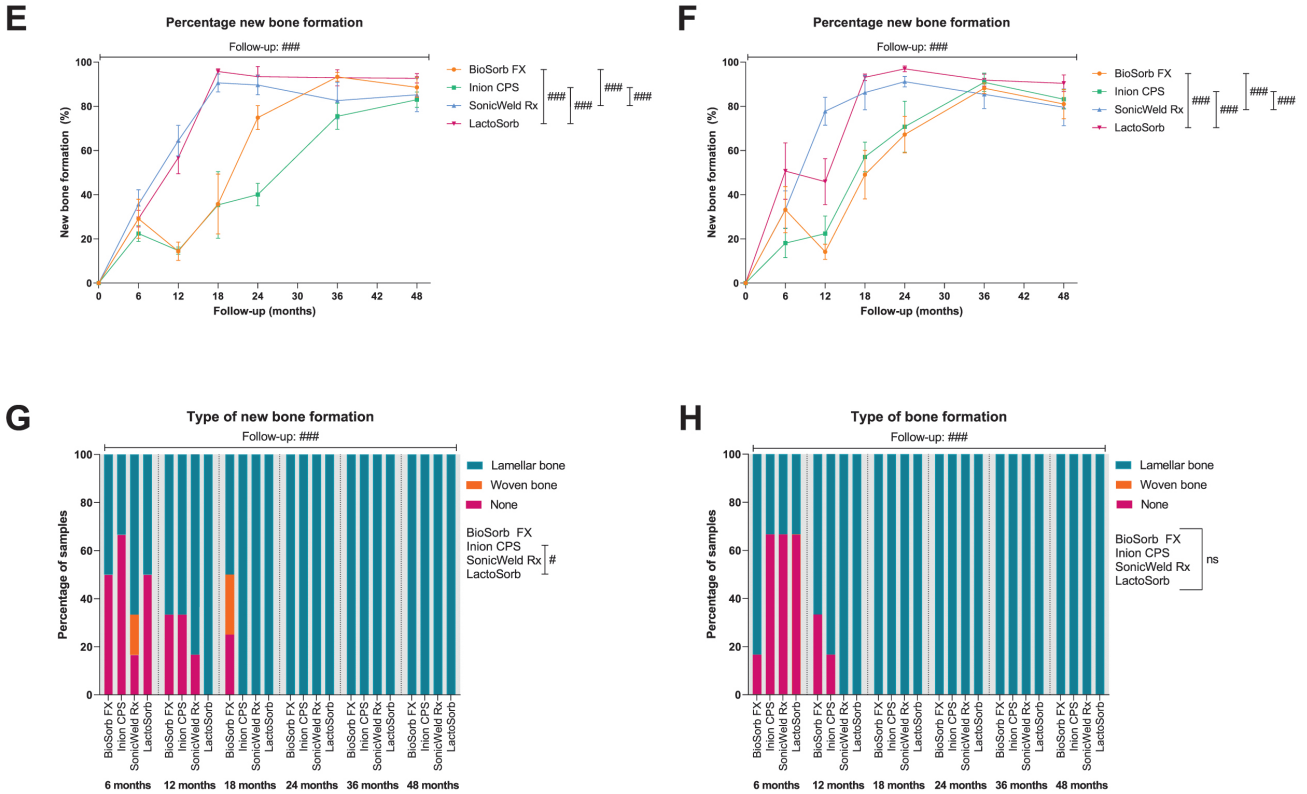
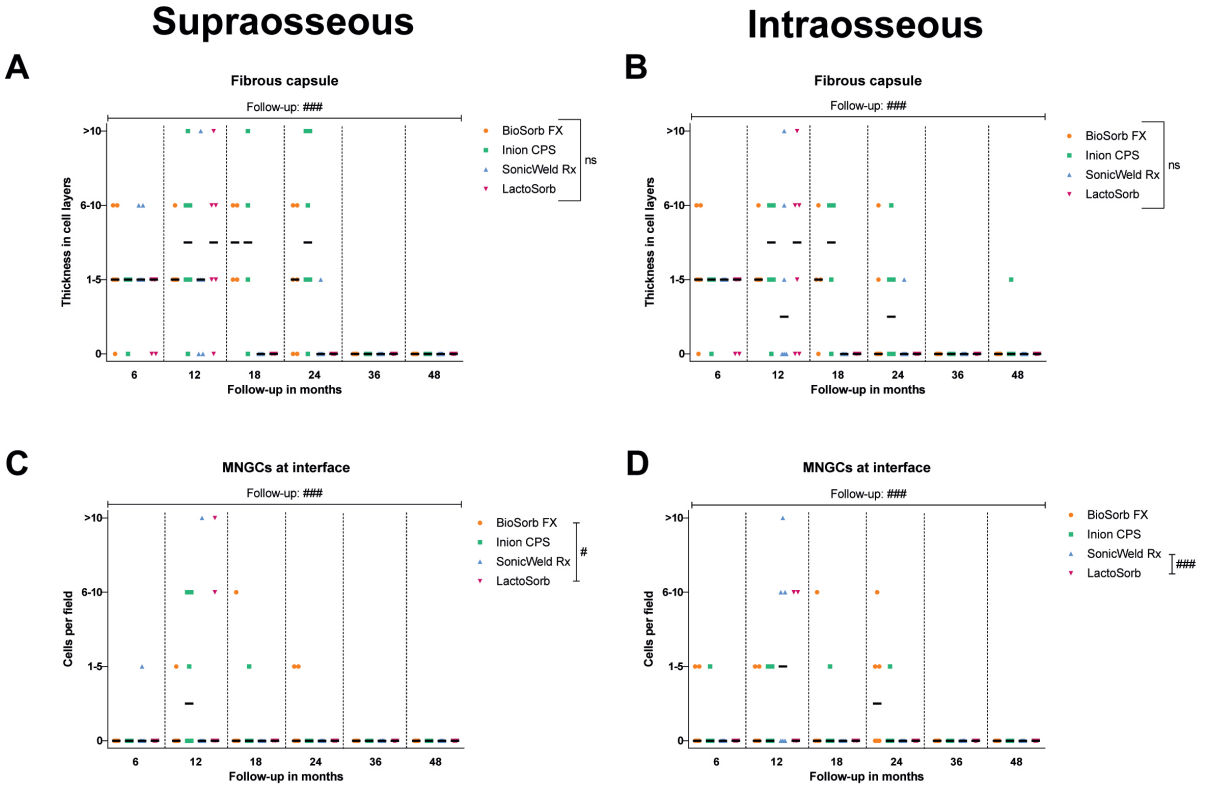


Figure 4. Implant fragmentation at the supraosseous and intraosseous zones (A and B, resp.). Implant resorption at the supraosseous and intraosseous zones (C and D, resp.). Percentage of new bone formation at the supraosseous and intraosseous zones (E and F, resp.). Type of bone formation at the supraosseous and intraosseous zones (G and H, resp.). *Samples: at 6, 12, and 24 months: n=6 per system; at 18 months: n=4 per system; at 36 months: n=8 per system; and at 48 months: n=12 per system. Black bars represent median values (Fig. A-D). Symbols with error bars represent mean±SEM (Fig. E-F). #, ##, and ### represent P<0.05, P<0.01, and P<0.001, respectively, in the multilevel model analyses including all follow-up data. Ns, non-significant; SEM, standard error of the mean.*


Supraosseous
Intraosseous
A
B
C
D
Fibrous capsule
MNGCs at interface
Follow-up: ###
Thickness in cell layers
Cells per field
>10
6-10
1-5
0
6
12
18
24
36
48
Follow-up in months
BioSorb FX
Inion CPS
SonicWeld Rx
LactoSorb
ns
#
###

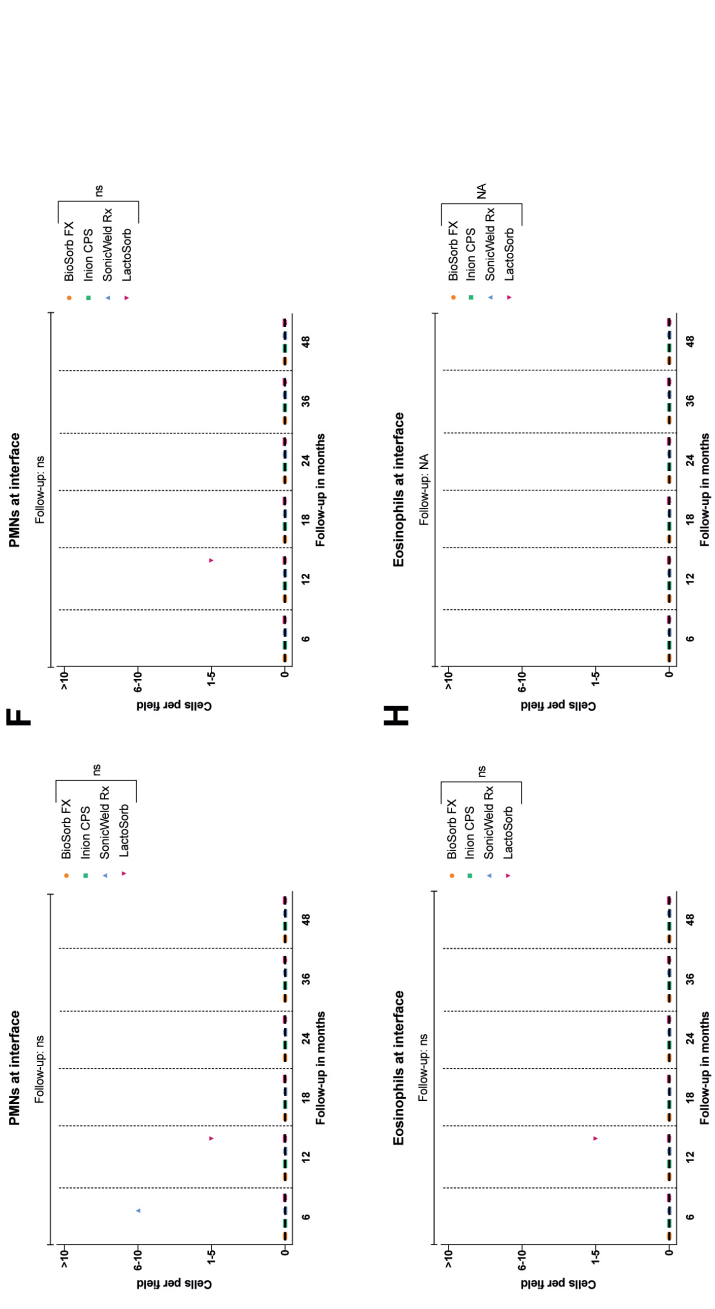
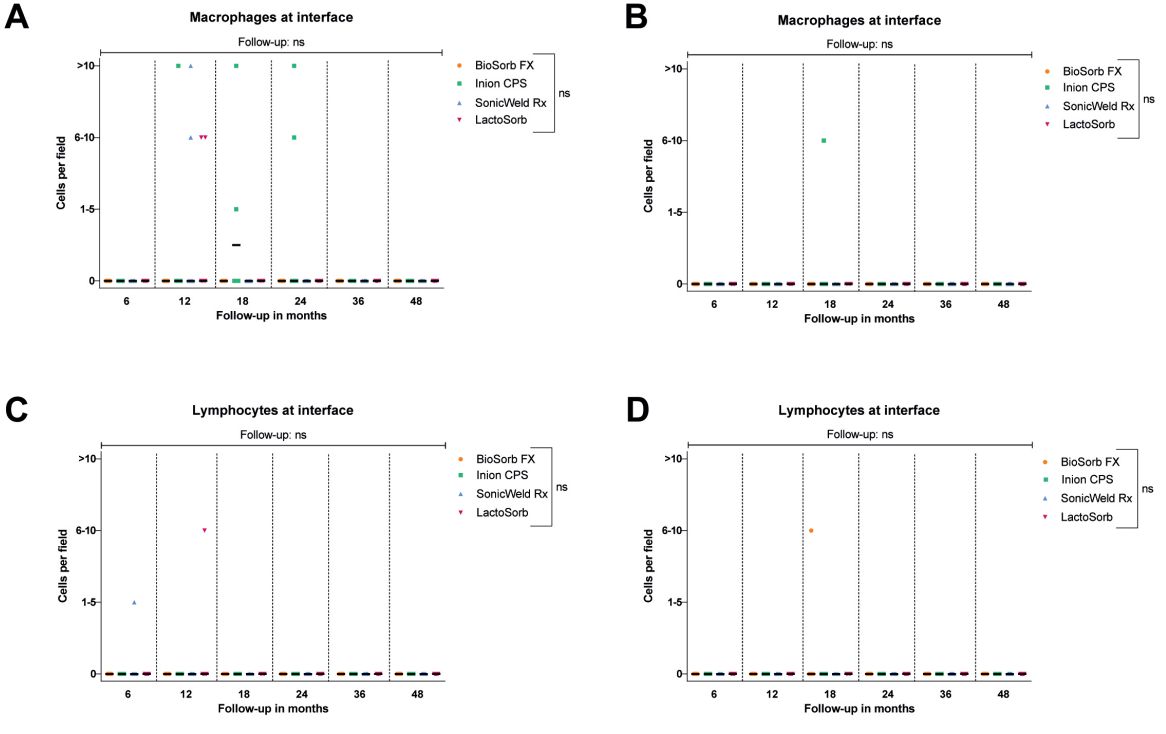


Figure 5. Fibrous capsule at the supraosseous and intraosseous zones (A and B, resp.). Presence of MNGCs at the supraosseous and intraosseous zones with 100x magnification (C and D, resp.). Presence of PMNs at interface at the supraosseous and intraosseous zones with 100x magnification (E and F, resp.). Presence of eosinophils at the supraosseous and intraosseous zones with 100x magnification (G and H, resp.). *Samples: at 6, 12, and 24 months: n=6 per system; at 18 months: n=4 per system; at 36 months: n=8 per system; and at 48 months: n=12 per system. Black bars represent median values. #, ##, and ### represent P<0.05, P<0.01, and P<0.001, respectively, in the multilevel model analyses including all follow-up data. Ns, non-significant; MNGCs, multinucleated giant cells.*

Supraosseous

Intraosseous



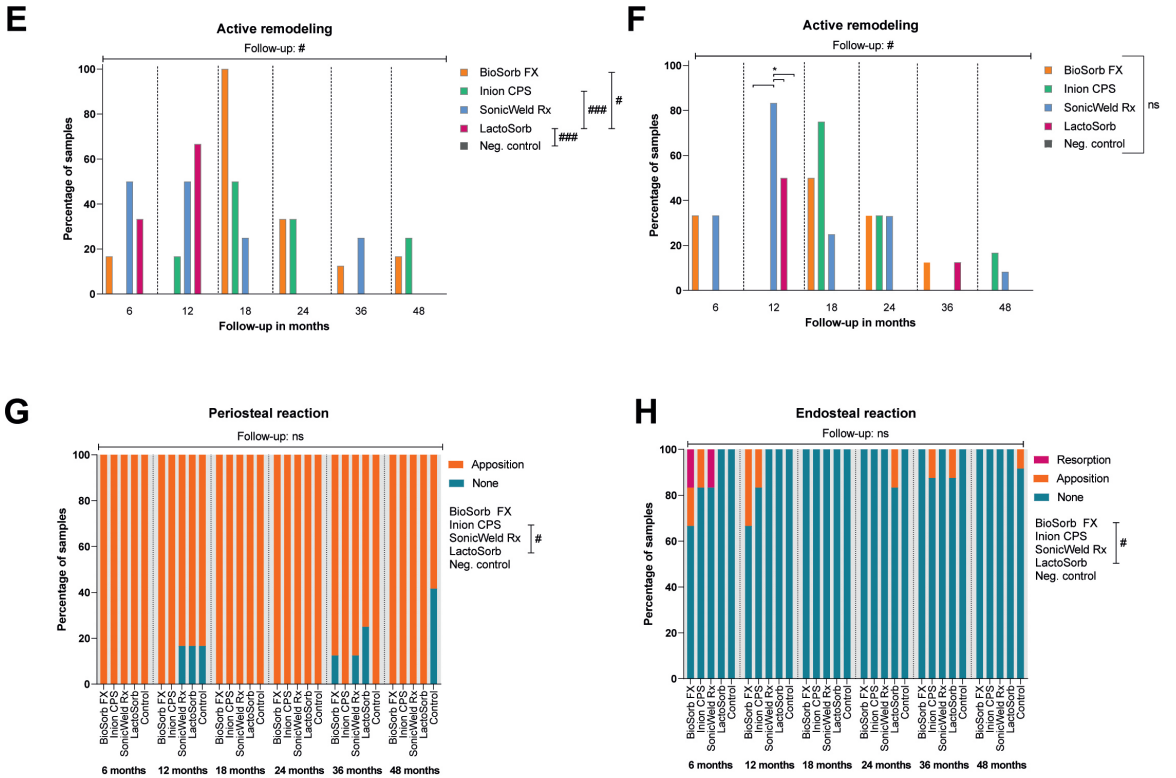
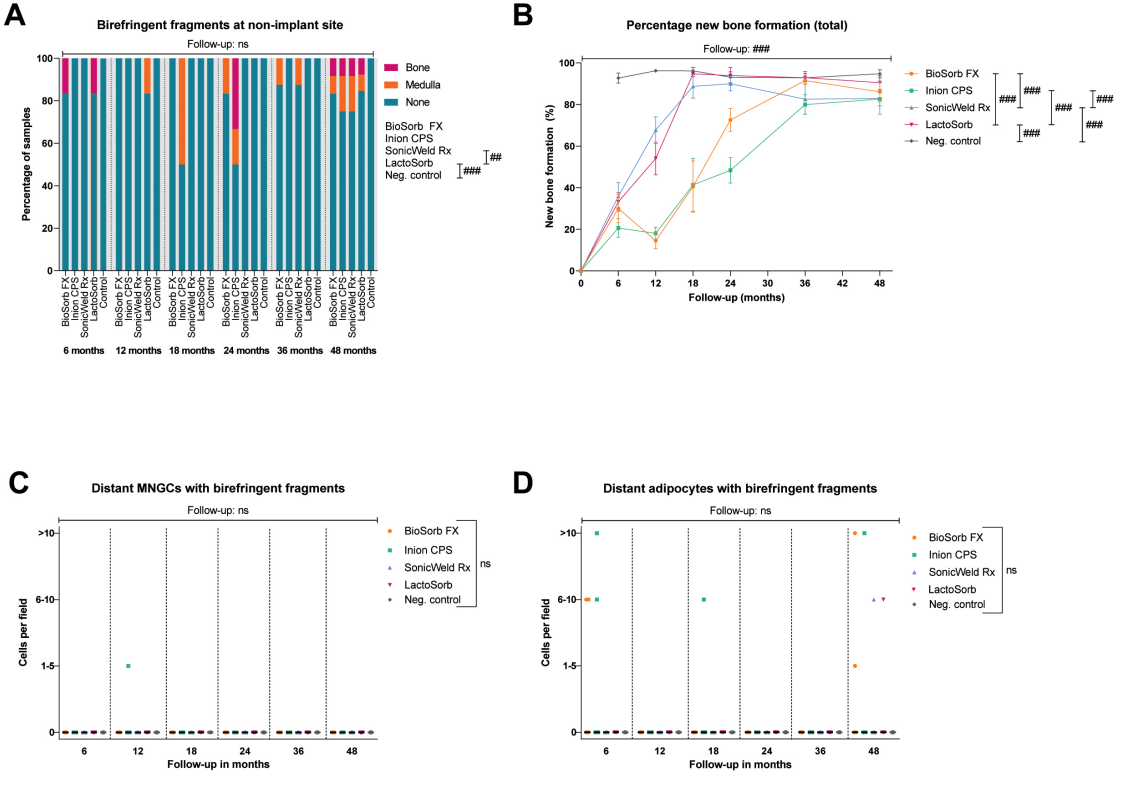


Figure 6. Presence of macrophages at interface at the supraosseous and intraosseous zones with 100x magnification (A and B, resp.). Presence of lymphocytes at the supraosseous and intraosseous zones with 100x magnification (C and D, resp.). Active remodelling at the supraosseous and intraosseous zones (E and F, resp.; the absence of bars represent 0% of samples). Presence of periosteal (G) and endosteal reaction (H). *Samples: at 6, 12, and 24 months: n=6 per system; at 18 months: n=4 per system; at 36 months: n=8 per system; and at 48 months: n=12 per system. Black bars represent median values (Fig. A-D). #, ##, and ### represent P<0.05, P<0.01, and P<0.001, respectively, in the multilevel model analyses including all follow-up data. Ns, non-significant.*


A
Birefringent fragments at non-implant site
Follow-up: ns
Percentage of samples
Bone
Medulla
None
BioSorb FX
Inion CPS
SonicWeld Rx
LactoSorb
Neg. control
##
###
6 months
12 months
18 months
24 months
36 months
48 months
B
Percentage new bone formation (total)
Follow-up: ###
New bone formation (%)
Follow-up (months)
BioSorb FX
Inion CPS
SonicWeld Rx
LactoSorb
Neg. control
###
C
Distant MNGCs with birefringent fragments
Follow-up: ns
Cells per field
>10
6-10
1-5
0
Follow-up in months
ns
D
Distant adipocytes with birefringent fragments
Follow-up: ns
Cells per field
Follow-up in months
ns

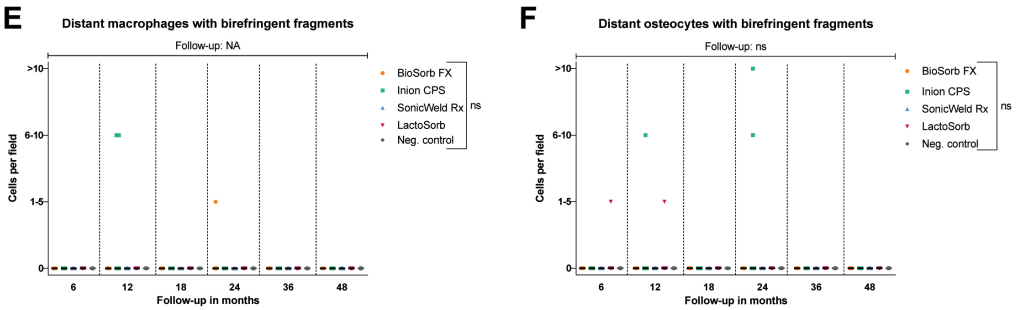


Figure 7. Presence of birefringent fragments at non-implant site (A), percentage of total new bone formation (B), and presence of distant MNGCs (C), distant adipocytes (D), distant macrophages (E), and distant osteocytes (F) with birefringent fragments with 100x magnification. *Samples: at 6, 12, and 24 months: n=6 per system; at 18 months: n=4 per system; at 36 months: n=8 per system; and at 48 months: n=12 per system. Symbols with error bars represent mean±SEM (Fig. B). Black bars represent median values (Fig. C-F). #, ##, and ### represent P<0.05, P<0.01, and P<0.001, respectively, in the multilevel model analyses including all follow-up data. Ns, non-significant; SEM, standard error of the mean; MNGCs, multinucleated giant cells.*

Table 3. Multilevel model of percentage new bone formation at the implant site (n=210).

Model variables	β (95% CI)	P-value
Intercept	24.31 (11.00;37.60)	**<0.001**
Osteosynthesis system (ref. = LactoSorb)		**<0.001**
Negative control	46.46 (32.45;60.46)	**<0.001**
BioSorb FX	-32.27 (-46.28;-18.27)	**<0.001**
Inion CPS	-39.60 (-53.61;-25.60)	**<0.001**
SonicWeld Rx	7.50 (-6.51;21.50)	0.292
Follow-up (months)	3.45 (2.54;4.37)	**<0.001**
Osteosynthesis system * Follow-up		**<0.001**
Negative control	-1.09 (-1.52;-0.65)	**<0.001**
BioSorb FX	0.58 (0.15;1.01)	**0.009**
Inion CPS	0.58 (0.14;1.01)	**0.009**
SonicWeld Rx	-0.37 (-0.80;0.07)	0.095
Follow-up^2 (months^2)	-0.04 (-0.06;-0.03)	**<0.001**

Bold P-values represent statistical significant values. Example: the estimated percentage of new bone formation at the implant site of the BioSorb FX system at 24 month follow-up is estimated to be: 24.31 - 32.27 + (3.45*24) + (0.58*24) – (0.04*24*24) = 65.7%.
Abbreviations: β, estimated coefficient; CI, confidence interval; Ref, reference group.

follow-ups (Figures 6H and 9B). The rate at which the endosteal reaction decreased was highest in the BioSorb FX sections (OR 0.91 [0.84;0.99] per month; P=0.024). The endosteal reaction of the other three biodegradable systems were comparable with the negative control (Table S8).

Birefringent fragments were observed at the implant sites of all the osteosynthesis systems, from 6 to 48 months (Figure 7A). Most of the birefringent fragments were observed as intracellular accumulation of fragments in adipocytes of the medulla (Figures 7C-F and 9C-D; Tables S5 and S6). Birefringent fragments were also observed intravascularly after 6-months with the BioSorb FX system (Figures 9E-F).

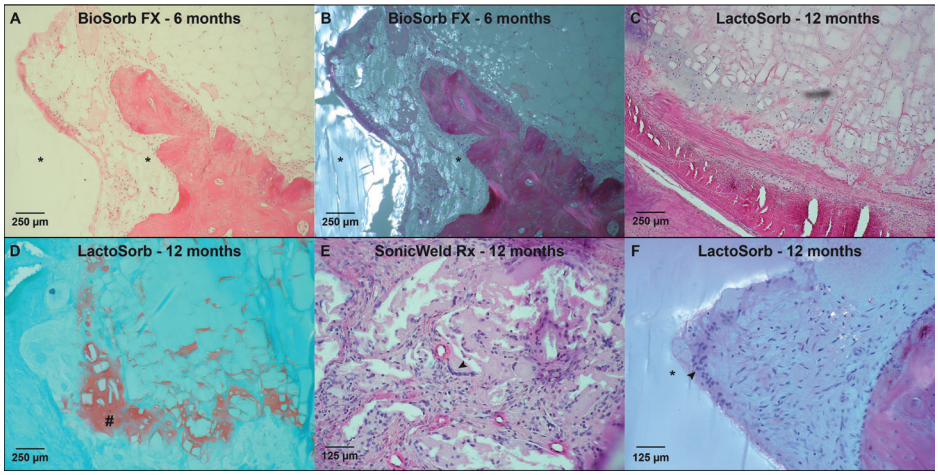


Figure 8. (A & B) HE-sections of the BioSorb FX system at 6-months follow-up under LM and LM-pol, resp., with observable polymer fragments (*). (C & D) HE- and SafO-section of the LactoSorb system at 12-months follow-up, showing the presence of cartilage (D: orange area; #) indicating endochondral ossification. (E) HE-section under LM showing the presence of MNGCs (black arrowhead) at the supraosseous zone of the SonicWeld Rx system at 12-months follow-up. (F) HE-section under LM-pol showing the presence of MNGCs (black arrowhead) at the interface of the LactoSorb system (*) at 12-months follow-up. *HE, hematoxylin and eosin; LM, light microscopy; LM-pol, polarized light microscopy; resp., respectively; SafO, Safranin O-fast green, MNGCs, multinucleated giant cells.*

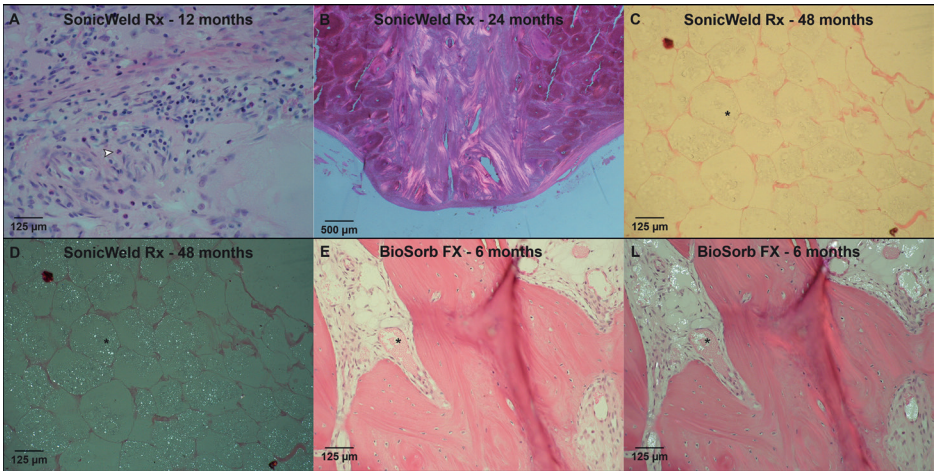


Figure 9. (A) HE-section under LM showing PMNs (white arrowhead) at the interface of the SonicWeld Rx system at 12-months follow-up. (B) HE-section under LM-pol showing endosteal apposition of the SonicWeld Rx system at 24-months follow-up, in which the distinction between newly formed (light red/purple) and old bone (dark red/purple) is also visible. (C & D) HE-section under LM and LM-pol, resp., of the SonicWeld Rx system at 48-months follow-up with intracellular birefringent fragments (*) in adipocytes at the medulla of bone. (E & F) HE-section under LM and LM-pol, resp., of the BioSorb FX system at 6-months follow-up showing intravascular birefringent fragments (*). *HE, hematoxylin and eosin; LM, light microscopy; LM-pol, polarized light microscopy; resp., respectively; PMNs, polymorphonuclear leukocytes.*

SEM and EDX

At the 48-month follow-up, birefringent fragments were observable in all the osteosynthesis systems' LM-pol, SEM, and EDX samples (Figure 10). The fragments were encapsulated by bone or present in the bone medulla. EDX mapping showed that these birefringent fragments mainly consisted of carbon and oxygen while being nitrogen-free, corresponding with the absence of nitrogen in the implanted materials. Furthermore, birefringent fragments were not observed in any of the control sections. Both aspects substantiated that the crystalline fragments are of polymeric origin (Figure 10). The 36-month follow-up SEMs also showed typical nanoscale crystalline needle-like structures in the randomly selected vacuoles within the BioSorb FX systems' implant sites' medulla (Figure S2), without being observable with LM(-pol). None of the other osteosynthesis systems had typical crystalline needle-like structures when analysing locations without birefringent fragments.

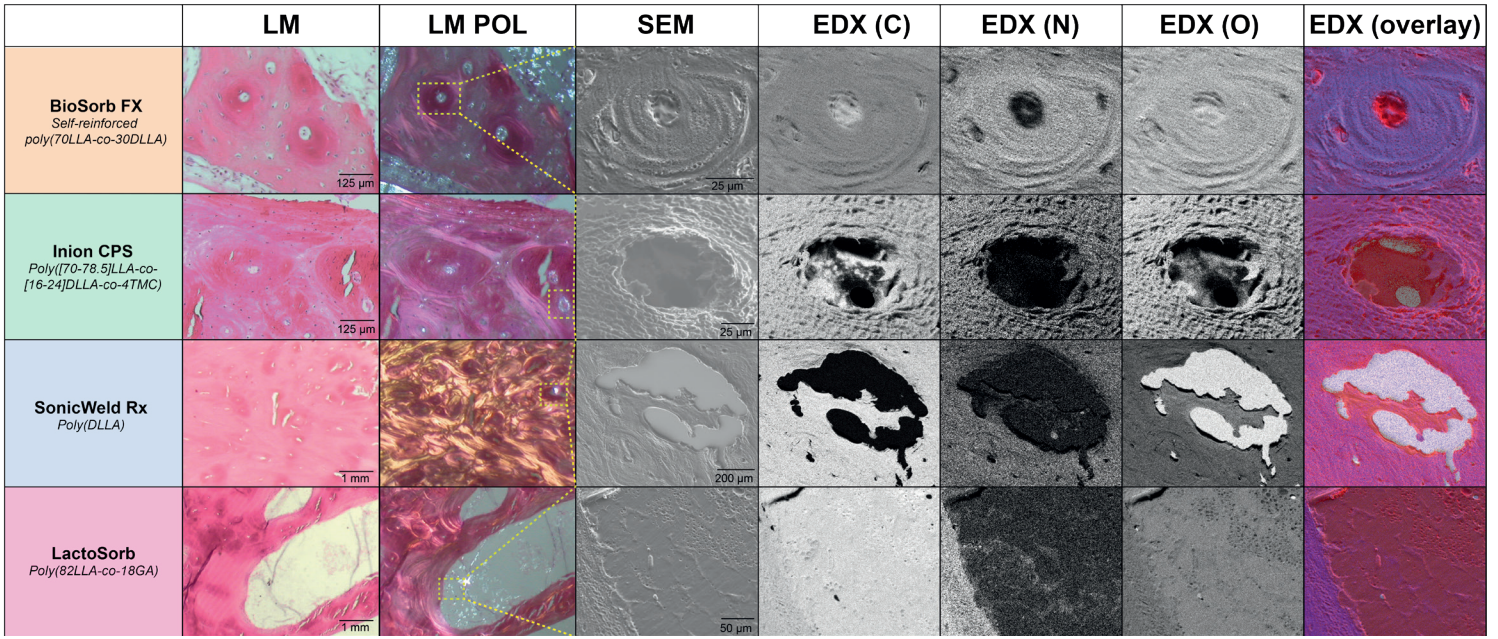


Figure 10. HE-sections (LM and LM-pol), SEM, and EDX by element and with overlay (red: carbon, and blue: nitrogen) of birefringent polymeric residual fragments of every osteosynthesis system at 48-months follow-up. *HE, hematoxylin and eosin; LM, light microscopy; LM-pol, polarized light microscopy; SEM, scanning electron microscopy; EDX, energy-dispersive X-ray analysis; C, carbon; N, nitrogen; O, oxygen*

Discussion

Foreign-body reactions to polymeric biodegradable materials remain a major concern in the usage of biomaterials. Currently, comparisons of degradation profiles of different biodegradable copolymers in the same large animal model, as well as evidence of complete resorption of biomaterials, are still lacking. To the best of our knowledge, this is the first study to assess and compare the long-term (i.e., up to 4-years) micro- and nanoscale histological responses to four commonly used copolymeric biodegradable osteosynthesis systems. Additionally, the molecular and thermal properties, and the surface topography of these systems were assessed. A DSC of the initial samples showed that only the SonicWeld Rx plate and pins were completely amorphous while the Inion CPS plate and screws, the LactoSorb screws, and the BioSorb FX plate were clearly semi-crystalline in nature. The differences in PDI and intrinsic viscosity of the initial samples indicated substantial differences between the systems in molecular weight distribution. During the 4-year follow-up, there were no signs of clinical foreign-body reactions and there was no need for re-interventions. Differences in complete implant replacement by bone were observed, viz. the percentage of bone 18 months after implanting the SonicWeld Rx and LactoSorb systems reached the same level as the negative control (i.e., an area where no invasive treatment was performed) while the BioSorb Fx and Inion CPS systems reached similar levels after 36-months. Although all the biodegradable systems were clinically safe to use and were well-tolerated, nanoscale polymeric fragments were observed at every follow-up assessment of all four copolymeric systems, up to 4-years of follow-up.

Biodegradable implants evoke an initial host response after implantation that includes inflammation, proliferation and remodelling of tissue remodelling, and is affected by the degradation products[1]. This host response is mediated by both the innate and adaptive immune systems. Macrophages are the most important innate immune cells during the host response and they play a main role in the outcome of biodegradable implants[1]. The phenotype of macrophages ranges from pro-inflammatory M1 macrophages to anti-inflammatory M2 macrophages[61,62]. After tissue injury, M1 macrophages secrete several inflammatory mediators such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) to initiate the healing process[1,63]. After the initial inflammatory phase, macrophages switch to a wound-healing phenotype (M2a), secreting growth factors (e.g., platelet-derived growth factor) that promote angiogenesis and cell proliferation[63,64]. Subsequently, macrophages switch to an anti-inflammatory phenotype (M2c) and

produce anti-inflammatory cytokines (e.g., IL-10) that leads to the inhibition of the inflammatory response[65].

The adaptive immune system is also involved in the host response to biodegradable implants. Through antigen presentation, macrophages and dendritic cells can activate $CD4^+$ T-cells of the adaptive immune system. T helper 1 (T_H1) cells can induce M1 macrophages by producing interferon-γ and IL-2[66]. Subsequently, M1 macrophages can produce cytokines and chemokines (e.g., IL-12, CXC-chemokine ligand 9) that intensify the T_H1 response by recruiting additional T_H1 cells[1]. In contrast to T_H1 cells, T_H2 cells produce anti-inflammatory cytokines (e.g., IL-4 and IL-10) that induce polarization of macrophages towards M2 macrophages. M2 macrophages in turn secrete cytokines (e.g., CC-chemokine ligand 17) that recruit additional T_H2 cells that tempers the inflammatory response[66]. Imbalances of M1 over M2 macrophages or prominent presence of M1 macrophages may lead to FBR[1]. Therefore, it is essential for a biodegradable implant that a well-controlled and timely switch of M1 to M2 macrophages occurs as this then leads to controlled implant degradation and tissue remodelling, to eventually replace the implant by host tissue (e.g., bone)[1]. Our results show that macrophages at interface were still present up to 24 months follow-up, predominately at the supraosseous zone. The results suggest that the equilibrium between M1 and M2 macrophages at the supraosseous zone is present up to 24 months after implantation, after which macrophage are absent up to 48 months after implantation. On the other hand, apart from one histological section at 18 months follow-up, macrophages at the interface of the intraosseous zone were absent. Together, these results suggest that macrophage activity is particularly located at the supraosseous zone rather than the intraosseous zone in the long-term.

Polymeric biodegradable osteosynthesis systems, including the systems assessed in this study, consist of poly(α-esters) such as PLA, PGA, TMC and their copolymers[1]. Extracellular degradation of poly(α-esters) occur through hydrolysis, enzymatic degradation, and oxidation. During hydrolysis, cleavage of the ester bonds by water results in oligomers and monomers such as lactic acid and glycolic acid[67,68], that can enter the tricarboxylic-acid cycle and are then eliminated as carbon dioxide and water. Furthermore, enzymes secreted by macrophages and derived from blood can contribute to hydrolysis through extracellular hydrolysis[1]. In addition, M1 macrophages can phagocytise biomaterial particles. Inflammatory cells (e.g., macrophages, neutrophils) can induce depolymerisation of polymers by oxidation via the release of reactive oxygen species[69]. Macrophages can also undergo fusion to improve their efficiency and form

MNGCs[70]. Although the phagocytosis capacity of MNGCs is reduced compared to M1 macrophages, the capacity of extracellular degradation is substantially increased by secreting higher concentrations of enzymes and reactive oxygen species into the interface between the macrophage and implant[70]. In this study, macrophages at the interface were predominately present during 12-24 months follow-up accompanied by the presence of MNGCs at interface. Also, some histological sections showed distant macrophages and MNGCs with intracellular birefringent fragments derived from phagocytised polymeric particles. These results show that MNGCs remain present up to 24 months follow-up, and that phagocytosis of polymeric fragments by inflammatory cells also can take up to 24 months. Future research focussing on degradation and biocompatibility of copolymers included in this study should therefore have a follow-up of ≥24 months so that a proper degradation assessment can be performed.

The progression of the initial host response is affected by the acidic degradation products of poly(α-esters) as they alter the microenvironment in different ways. The lowering of pH intensifies the inflammatory response that results in fibrous encapsulation of the implant[71,72]. Furthermore, the acidic degradation products are autocatalytic resulting in progressive degradation of the remaining polymers and an increase of the inflammatory response. Additionally, bulk degradation leads to fragmentation of the polymer that may result in phagocytized particles within the fibrous tissue[1]. Demineralization of surrounding bone can occur whenever the degradation occurs too quickly and the surrounding tissue fails to eliminate the degradation products[73]. The possibility to induce a FBR (e.g., a sterile abscess formation) is dependent on an equilibrium between the levels of degradation products, the degree of fibrous encapsulation, and the ability of the host to eliminate the degradation products[1]. Short-term FBR are mainly caused by fast-degrading polymers (e.g., PGA)[3] while delayed FBR are often associated with slow-degrading (e.g., PLLA) with high crystallinity and crystalline degradation fragments[23,25,74]. We observed increasing fibrous capsules thicknesses from 6 to 24 months follow-up. Although fibrous encapsulation was present in all system's assessment up to 12 months follow-up, the fibrous capsule remained present at 18 and 24 months follow-up in the BioSorb FX and Inion CPS only. Even though we did not observe a clinical or histological FBR (e.g., sterile abscess formation), these results also emphasize that a follow-up of ≥24 months is essential for assessment of FBR since the degree of fibrous encapsulation is an important factor to induce FBR[1].

Sterile abscess formation due to FBR are presumed to be the main reason for biodegradable plate and screw removal[7,11] and, thus, remain a major concern in the

usage of such systems[7,11,23]. Currently, two main hypotheses regarding the aetiology of FBR to these polymeric biomaterials are given. After implantation, the biodegradable polymers are encapsulated by fibrous tissue that acts as a semi-permeable membrane[21]. The first hypothesis is that as the polymer degradation continues over time, the size of the polymeric fragments decreases while the number of particles increases. These particles cannot pass the semi-permeable membrane. Subsequently, the osmotic pressure within the area surrounded by the fibrous layer increases and this results in a clinically observable swelling that, without an intervention, remains *in situ*[11,23]. In this study, no persistent swelling was observed at any implant site during the entire follow-up period. An alternative hypothesis is that, eventually, the acidic polymeric fragments become small enough to pass the membrane. This results in a decrease in pH of the surrounding tissues which then causes an excessive sterile inflammation[75,76] accompanied by phagocytosis of any residual fragments[21]. However, since crystalline fragments are stable and more resistant to further hydrolytic degradation, these residual fragments accumulate in the macrophages and MNGCs, and then remain *in situ*. Besides, extra- and intracellular residual fragments can lead to the accumulation of crystalline oligomeric lactide stereo-complexes over time that are resistant to further hydrolytic degradation[1,39]. These hypotheses could also succeed each other over time.

Our study observed MNGCs at the interface up to the 24-month follow-up. Intracellular accumulation of polymeric fragments was only observed in a few MNGCs in one single histological section of the Inion CPS system. Despite the presence of MNGCs, we did not observe clinical or histological FBR to the implanted copolymeric biomaterials. Previously, MNGCs were characterized as foreign body giant cells and only associated with biomaterial rejection and FBR[77]. Recent research has demonstrated that MNGCs can have both pro-inflammatory and wound-healing aspects[77–79]. MNGCs with a pro-inflammatory character are needed for complete degradation of the polymeric biomaterials while MNGCs with wound-healing aspects are essential for the physiological wound healing process[80]. However, the long-term effect of the presence of MNGCs, and the possibility to induce a FBR, is dependent on a foreign body equilibrium between the presence of the foreign body and presence of MNGCs with degradation capabilities[81]. Whenever intracellular residual polymeric fragments cannot be degraded further, e.g., due to their crystalline nature, this equilibrium is disturbed resulting in an excessive activation of macrophages and subsequent fusion into many more MNGCs than before that may, in turn, lead to bone resorption and/or sterile abscess formation[21,81]. This phenomenon was not observed in our study. In previous research, FBR to poly(70LLA-*co*-30DLLA) was observed in a similar goat model with 12 month follow-up, indicating that

the used goat model is capable of generation such a reaction[47]. A possible explanation for not observing FBR in our study could be that all the implants' volumes were too low to induce such a reaction. However, FBR have also been observed in PLLA facial fillers which were of a similar volume as this study's implanted systems[82], so the volume of biomaterial used in this study is not expected to be a limiting factor in inducing FBR.

The DSC-analyses showed that the LactoSorb screw (poly[82LLA-*co*-18GA]) and Inion CPS plate and screws (poly([70-78.5]LLA-*co*-[16-24]DLLA-*co*-4TMC)) were semi-crystalline. According to the manufacturer of the LactoSorb system, the used copolymers have both amorphous and crystalline characteristics[83] which is in line with our analyses. However, the manufacturer of the Inion CPS system states that the copolymers are completely amorphous[84], while the current DSC-analysis indicates a crystallinity of 27 to 41%. These crystalline regions are more stable and resistant to hydrolytic degradation and resorption than the amorphous regions[23,41]. Furthermore, the amorphous regions degrade faster than the crystalline regions, resulting in inadequate degradation and prolonged presence of crystalline residual fragments, that in turn, may induce FBR[1]. Although this study did not observe FBR, accumulation of residual crystalline fragments was observed up to the 4-year follow-up. Therefore, it is highly preferred to have completely amorphous (co)polymers so that the degradation *in vivo* is predictable[1]. Of the included biodegradable systems, only the SonicWeld Rx (poly[DLLA]) system was completely amorphous and, correspondingly, this system showed the most predictable implant fragmentation and resorption profile as well as new bone formation.

Although it would have been preferable to analyse the explanted samples with DSC and GPC, the limited amount or even lack of explanted materials shows that all four degradable copolymers had been degraded to such an extent that these analyses could not be performed. This was also substantiated by histological assessments at these follow-up moments, that showed advanced fragmentation and resorption in all the histological samples. The Mn, Mw, and intrinsic viscosity of the BioSorb FX plate and screw explanted at 6-months had decreased, indicating chain scission of the copolymer. These findings fit the nature of biodegradable implants with bulk degradation[1].

The birefringent fragments in the 6- and 24-month follow-up non-implant sites may have been from the local distribution of incomplete but ongoing implant fragmentation and resorption. For example, the BioSorb FX and Inion CPS systems had not been completely fragmented and resorbed at the 24-month follow-up (Figure 4A-D) and birefringent fragments were also observed in the non-implant sites at these assessment moments (Figure 7A). However, all the systems were absent from the implant sites at the 36- and

48-month follow-ups (Figure 4A-D) whereas birefringent fragments were increasingly obvious in the non-implant sites. Birefringent fragments were particularly not observed in the non-implant site of the SonicWeld Rx system until the 24-month follow-up but were increasingly present at the 36- and 48-month follow-ups even though implant fragmentation and resorption of this system in the implant site was already completed by the 6-month follow-up (Figure 4A-D). We observed remarkable accumulations of polymeric birefringent fragments in all the systems' adipocytes within the medullary bone cavity, even at the 4-year follow-up (Figure 9C-D). Both the intermediate degradation products of the included copolymers as well as the crystalline oligomeric stereo-complexes that can be formed during degradation over time are hydrophobic[6]. This could explain why these hydrophobic fragments were particularly observed in the adipocytes. It is unlikely that the residual particles were distributed between implant sites, e.g. by circulation or local distribution, since no polymeric fragments were observed in any of the negative control samples despite that the positions of the biodegradable systems and negative control were randomised.

Birefringent fragments derived from as-polymerized PLLA have been observed in previous research with 5-year follow-up[23,27,85], and clinical studies have shown that these PLLA-derived crystalline fragments can induce FBR up to 5.7 years after implantation[23,86]. Since this is the first study that assessed and compared the histological responses of PDLLA, PLGA, and/or P(LLA-*co*-DLLA-*co*-TMC) implants with long-term follow-up, it remains unknown whether the birefringent fragments observed in this study can also induce such a clinical FBR. To the best of our knowledge, the accumulation of polymeric residuals in adipocytes after degradation of PDLLA, PLGA, and/or P(LLA-*co*-DLLA-*co*-TMC) has not been described in the literature before.

Several studies reported complete resorption of the studied systems after 1 to 2-years[29,35,36,87]. However, these conclusions were based on *in vivo* degradation assessments of polymeric fragments using light microscopy whereas polymeric fragment dimensions that induce FBR can be smaller than the light microscopy resolution[23]. This was also shown by our study, viz., fragments were not observable with LM(-pol) but SEM revealed typical nanoscale crystalline needle-like structures in vacuoles from the medulla. Thus, one cannot exclude the presence of residual polymeric fragments if (birefringent) fragments are not observed with light microscopy. Other studies have assessed histological responses to biodegradable osteosyntheses using transmission electronic microscopy (TEM)[23,27]. However, those studies used acetone and/or methyl methacrylate while processing the histological samples. As we have shown

in the present study, both dissolve polymeric components of the assessed copolymer biodegradable systems and thus interfere with proper assessment of the polymer in these samples. Therefore, the absence of polymeric residuals in those studies could also be due to the histological specimen processing rather than *in vivo* resorption of these residual fragments.

In addition to polymer composition, the mechanical properties and geometry are also important factors affecting the host reponse[1]. A mismatch between the mechanical properties of an implant can cause micromotions between the implant and host tissue that can lead to FBR[88]. Therefore, it is important that the mechanical properties of biodegradable implants matches with the mechanical properties of the target tissue (e.g., bone). Previous research showed that all assessed systems meet the required mechanical properties for stable fixation of load-sharing maxillofacial fractures and osteotomies[2]. The SonicWeld Rx and BioSorb FX systems showed the most favourable mechanical properties based on tensile, side bending and torsion tests[2]. Since loadings on biodegradable biomaterials can affect degradation and resorption, it is noteworthy that the stress patterns in the tibia and radius are different than that of the maxilla and mandible. However, these differences in stress patterns are particularly important when bridging bone defects (i.e., if the biomaterials are exposed to substantial loads that would otherwise be beared by the bone)[1,89,90]. As we did not create bone defects that had to be bridged by the biomaterials, it is unlikely that stress patterns affected the degradation profile of the assessed biomaterials. Furthermore, studies have shown that geometry and surface topography of the implant also affects the host response. A smooth, well-contoured shape without acute angles induced macrophage polarization towards M2 macrophages (i.e., towards wound repair and an immune regulatory phenotype) whereas implants with acute angles and non-contoured shapes increases the risk of FBR to biomaterials[91,92]. The shape of screws (e.g., of the LactoSorb, BioSorb FX and Inion CPS systems) is by definition different from a ultra-sound welded pin (e.g., from the SonicWeld Rx system). Screws possess acute angles while welded pins are smooth and do not contain acute angles[1]. Furthermore, surface topography analysis showed a smoother surface of the SonicWeld Rx and LactoSorb systems compared to the BioSorb FX and Inion CPS surfaces. Combining both characteristics (i.e., welded pins with smooth surfaces) may explain the favourable degradation profile of the SonicWeld Rx system compared to the other three biodegradable systems[1,93,94]. Since the SonicWeld Rx system is less bulky (i.e., -14% in volume of a 4-hole plate) and the degradation profile is more favourable compared to the BioSorb FX system, we believe the SonicWeld Rx system has the greatest potential as a safe biodegradable copolymeric osteosynthesis

system with favourable geometry and mechanical properties for fixation of load-sharing maxillofacial fractures and osteotomies.

Sterilization methods can also alter the physicochemical material properties and may influence biocompatibility[95]. The LactoSorb system was EtO-sterilized while the other three systems were sterilized by γ-irradiation. Although EtO is approved for sterilization of (co)polymeric biomaterials, its usage in recent years has been limited due to its toxicity for humans (i.e., carcinogenic and mutagenic) and environment[95]. An important disadvantage of EtO sterilization is that residues can remain inside the (co)polymer and be leached from the implant *in vivo* up to 3 months after implantation, reacting with proteins of the surrounding tissues[95]. Furthermore, EtO can lead to changes in (co)polymers structures (e.g., loss of orientation), molecular weight loss, and increase in crystallisation of PLLA that, in turn, affects cell adhesion and proliferation[95]. *In vitro* material comparisons (i.e., inherent viscosity, Tg, stiffness, and energy to break) of EtO-sterilized versus unsterilized LactoSorb systems showed no significant differences[96]. Similar to EtO, γ-irradiation can also result in changes in (co)polymeric properties including cross-linking and/or chain scission. Cross-linking can lead to brittleness, cracking and degradation of the polymer while chain scission results in reduction of molecular weight, decreased pore sizes and rougher surfaces[95]. However, at the irradiation dose needed for sterilization (25 kGy according to ISO standards[97]) these effects are small[95]. In line with previous research[98–105], this study did not show cytotoxicity or other biocompatibility issues during degradation of the four assessed biodegradable systems. Therefore, the effects of both approved and validated sterilization methods are considered not to interfere with the biocompatibility comparisons between the assessed systems.

Based on the results of this study, several key factors can be assigned for a predictable degradation profile. It is preferred to (1) have completely amorphous (co)polymers (e.g., poly[DLLA]), (2) low intrinsic viscosity, (3) a well-contoured shape without acute angles (e.g., by welding pins instead of using screws), (4) a smooth and homogenous surface, and (5) low implant volume but with sufficient mechanical properties for the purpose of the implant[2]. The histological assessment showed no substantial differences between the supra- and intraosseous zones of all included systems, indicating that the degradation of both zones are uniform and is a less important factor for predictable degradation.

Large animal models are the gold standard to assess long-term host response to (biodegradable) implanted devices[1,42] since skeletally mature goats have similar osseous macro- and microarchitecture, physiology, biomechanical properties, bone composition,

and remodelling rates as humans, and are able to generate a FBR to copolymeric biomaterials[47]. The model used simulates the *in vivo* degradation and host response of the assessed biomaterials in humans as closely as possible[1,52]. The host response reported in this study can therefore also be expected to be present in humans after implantation of the assessed biodegradable copolymeric osteosynthesis systems[1,42,52]. However, it is important to note that this study only assessed subperiosteally implanted biodegradable materials while in some medical disciplines biomaterials are placed supraperiosteally (e.g., in orthopaedic surgery). Supraperiosteally placed biodegradable implants tend to degrade and resorb slower compared to subperiosteally placed implants[106]. Therefore, translation of these results to copolymeric biodegradable materials that are implanted supraperiosteally should be done with caution.

One of the strengths of our work is that this is the first study to perform histological assessments (i.e., with LM, LM-pol, SEM, and EDX) of four different biodegradable copolymers with a long-term follow-up of a large animal model. Furthermore, all the sections were independently assessed by two blinded researchers using a systematic and validated approach, with good to excellent inter-rater reliability. Additionally, molecular and thermal properties were assessed at baseline, as well as of the explanted osteosynthesis systems, while X-ray radiographs were also taken at the 6-month follow-up. Finally, the animal model was optimized by carrying out extremity-level implantations enabling intra-animal comparisons at individual time-points and during follow-up, thereby increasing the reliability while reducing the number of animals used for the research.

Limitations of this study include not being able to measure the pH because all the implants were overgrown with bone. We did not try to access the implants by drilling holes in the overgrown bone to perform pH measurements because of the possibility of damaging the implant which could, in turn, interfere with the (histological) samples. Furthermore, as polymeric fragments were still present in all the implant systems' 4-year follow-up sections, extending the follow-up beyond 4-years would be of high scientific value. However, in The Netherlands, a 4-year follow-up is the maximum allowed period for animal research.

Conclusions

The present study showed no signs of FBR to the BioSorb FX, Inion CPS, SonicWeld Rx, and LactoSorb biodegradable copolymeric osteosynthesis systems during a 4-year

follow-up period. The SonicWeld Rx system showed the most predictable profile of implant fragmentation and resorption as well as new bone formation at the implant site. Although all the biodegradable systems were clinically safe to use and were well-tolerated (i.e., complete implant replacement by bone, no clinical or histological FBR, no [sterile] abscess formation, no re-interventions needed), nanoscale polymeric fragments of all four copolymeric systems were observed at every follow-up assessment up to the 4-year follow-up. These residual fragments had predominately accumulated in the adipocytes in the medullary cavity of bone. Whether these nanoparticles may be harmful on the long run (i.e., >4 years) is not clear.

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Conflict of interests

The authors state that they have no conflict of interests.

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Supplementary data

Supplementary tables:

Table S1. Specifications of the included osteosynthesis systems.

Table S2. Solubility tests of the included osteosynthesis systems in different mediums used for histological processing.

Table S3. Items scored in the assessment of the histological sections.

Table S4. Inter-rater reliability and percentage of agreement between both assessors of histological sections.

Table S5. Scores of all semi-quantitative scoring items of both zones after 6 to 18 months.

Table S6. Scores of all semi-quantitative scoring items of both zones after 24 to 48 months.

Table S7. Multilevel models of each outcome scoring item at the supraosseous zone.

Table S8. Multilevel models of each outcome scoring item at the intraosseous zone and at non-implant site.

Supplementary figures:

Figure S1. X-ray radiographs of the surgical sites at 6-months follow-up.

Figure S2. Scanning electron microscopy image of crystalline, needle-like structures of nanoscale in randomly selected vacuoles of the medulla after implantation of the BioSorb FX system at 36 months follow-up (magnification 52.860x).

Table S1. Specifications of the included osteosynthesis systems.

Brand name	Manufacturer	Plate composition	Screw/pin composition	Drill diameter (mm)	Tap diameter (mm)	Screw/pin diameter (mm)	Screw/ pin length (mm)	Plate length (mm)	Plate width (mm)	Plate thickness (mm)
Biodegradable osteosynthesis systems										
BioSorb FX 2.0mm	ConMed Linvatec Biomaterials Ltd. (Tampere, Finland)	SR poly(70LLA-co-30DLLA)	SR poly(70LLA-co-30DLLA)	1.5	2.0	2.0	7.0	6.3	5.5	1.3
Inion CPS 2.0mm	Inion Oy (Tampere, Finland)	Poly([70-78.5]LLA-co-[16-24]DLLA-co-4TMC)[1]	Poly([70-78.5]LLA-co-[16-24]DLLA-co-4TMC)[1]	1.75	2.0	2.0	7.0	7.0	7.0	1.3
SonicWeld Rx 2.1mm	KLS Martin Group (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)	Poly(DLLA)	Poly(DLLA)	1.6	None	2.1	7.0	6.5	6.0	1.0
LactoSorb 2.0mm	Biomet Microfixation (Jacksonville, Florida)	Poly(82LLA-co-18GA)	Poly(82LLA-co-18GA)	1.7	2.0	2.0	7.0	7.1	7.0	1.3
Non-degradable reference marker										
CrossDrive 2.0mm (2006)	KLS Martin Group (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)	NA	90% titanium 6% aluminium 4%vanadium (Ti6Al4V)	1.5	None	2.0	6.0	NA		

SR: self-reinforced; PLLA, poly-L-lactic acid; PDLLA, poly-D,L-lactic acid; TMC, trimethylene carbonate; PGA, poly-glycolic acid, NA, not applicable.
[1]The manufacturer does not publicly report the exact composition of the copolymers;

Table S2. Solubility tests of the included osteosynthesis systems in different mediums used for histological processing.

			Plate thickness after 24-hours of complete submersion in the specific medium									
Osteosynthesis system	**Polymer composition**	**Initial plate thickness**	**Formalin**	**Ethanol 70%**	**Ethanol 96%**	**Ethanol 100%**	**Xylene**	**Acetone**	**MMA**	**GMA**	**EDTA**	**Formic acid**
BioSorb FX	SR poly(70LLA-co-30DLLA)	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.5 mm	Dissolved	Dissolved	1.3 mm	1.3 mm	1.3 mm
Inion CPS	Poly([70-78.5]LLA-co-[16-24]DLLA-co-4TMC)[1]	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.3 mm	Dissolved	Deformed	1.3 mm	1.3 mm	1.3 mm
SonicWeld Rx	Poly(DLLA)	1.0 mm	1.0 mm	1.0 mm	1.0 mm	1.0 mm	Dissolved	Dissolved	Dissolved	1.0 mm	1.0 mm	1.0 mm
LactoSorb	Poly(82LLA-co-18GA)	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.3 mm	1.3 mm	Deformed	Dissolved	1.3 mm	1.3 mm	1.3 mm

Abbreviations: MMA, methyl methacrylate; GMA, glycidyl methacrylate; EDTA, Ethylenediaminetetraacetic acid.
[1]The manufacturer does not publicly report the exact composition of the copolymers;

Table S3. Items scored in the assessment of the histological sections.

Scoring-item	Sections scored	Possible scores
1. Fragmentation of implant	Supra- and intraosseous	0: 0% 1: <25% 2: 25-50% 3: 50-75% 4: ≥75%
2. Resorption of implant	Supra- and intraosseous	0: none (i.e., implant completely visible) 1: border only 2: center-border 3: center 4: complete (i.e. implant not visible with light microscopy)
3. Percentage new bone formation	Supra- and intraosseous, and total	Quantitatively analysed with the aid of image processing software (ImageJ Fiji).
4. Type of new bone formation	Supra- and intraosseous	None, woven or lamellar bone.
5. Fibrous capsule thickness	Supra- and intraosseous	0: 0 cell layers thickness 1: 1-5 cell layers thickness 2: 6-10 cell layers thickness 3: >10 cell layers thickness
6. Cells in interface at 100x magnification, scored per cell type a. Foreign-body giant cells b. Polymorphonuclear leukocytes c. Eosinophils d. Adipocytes with birefringent particles e. Macrophages f. Lymphocytes	Supra- and intraosseous	0: 0 cells per field 1: 1-5 cells per field 2: 6-10 cells per field 3: >10 cells per field
7. Distant cells with birefringent particles at 100x magnification, scored per cell type a. Foreign-body giant cells b. Polymorphonuclear leukocytes c. Eosinophils d. Adipocytes e. Macrophages f. Lymphocytes g. Osteocytes	Total	0: 0 cells per field 1: 1-5 cells per field 2: 6-10 cells per field 3: >10 cells per field
8. Necrosis	Supra- and intraosseous	Yes or no. <u>*Yes, if one of these criteria were observed::*</u> · *Increased eosinophilia* · *Glassy homogenous appearance* · *'Moth-eaten' appearance of cytoplasm* · *Dystrophic calcifications* · *Presence of 'mylein figures' (i.e., whorled phospholipid masses)* · *Karyolysis* · *Pyknosis* · *Karyorrhexis*

Table S3. *(continued)*

Scoring-item	Sections scored	Possible scores
9. Active remodelling	Supra- and intraosseous	Yes or no. *Defined as: osteoclasts and osteoblasts present and active at the same surface.*
10. Endosteal reaction	Intraosseous	Yes or no.
11. Periosteal reaction	Supraosseous	Yes or no.
12. Birefringent material at non-implant site		*Visible using polarized light microscopy.*
a. Present		Yes or no
b. Location	Supra- and intraosseous	Description of location.
c. Type of cells		Description of cell types.

Table S4. Inter-rater reliability and percentage of agreement between both assessors of histological sections.

Scoring item (number of possible categories)	Percentage of agreement	Cohen's kappa[a]
1. Fragmentation (4)	99.1	0.98
2. Resorption (4)	98.5	0.96
3. Type of new bone formation (3)	98.5	0.92
4. Fibrous capsule thickness (4)	93.7	0.87
5. Cells in interface (4)		
g. Foreign-body giant cells	96.7	0.94
h. Polymorphonuclear leukocytes	97.6	0.95
i. Eosinophils	97.9	0.95
j. Adipocytes with birefringent particles	98.2	0.95
k. Macrophages	97.3	0.94
l. Lymphocytes	97.6	0.94
6. Distant cells with birefringent particles (4)		
h. Foreign-body giant cells	100	1.00
i. Polymorphonuclear leukocytes	100	1.00
j. Eosinophils	100	1.00
k. Adipocytes	98.2	0.84
l. Macrophages	100	1.00
m.Lymphocytes	100	1.00
n. Osteocytes	99.4	0.89
7. Necrosis (2)	100	NA[b]
8. Active remodelling (2)	97.0	0.82
9. Endosteal reaction (2)	97.0	0.77
10. Periosteal reaction (2)	98.2	0.66
11. Birefringent material at non-implant site		
d. Present (2)	98.5	0.97
e. Location (3)	98.5	0.87
f. Type of cells (3)	98.8	0.90

NA: not applicable. [a]For categorical scoring items, the unweighted Cohen's kappa was calculated while for scoring items with ordinal categories the quadratic weighted Cohen's kappa was calculated. [b]Both observers did not observe necrosis in any of the samples, thus no Cohen's kappa could be calculated.

Table S5. Scores of all semi-quantitative scoring items of both zones after 6 to 18 months.

	6 months						12 months						18 months					
	BioSorbFX	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**
Scoring item	N=6	N=6	N=6	N=6	N=6		N=6	N=6	N=6	N=6	N=6		N=4	N=4	N=4	N=4	N=4	
Fragmentation score*																		
Supraosseous	3 (3-3.25)	3 (2.75-3.25)	4 (4-4)	3 (3-4)	NA	**0.028**	3 (3-3)	3 (2.75-3.25)	4 (4-4)	3 (3-4)	NA	**0.010**	3 (3-3)	3 (3-3.75)	4 (4-4)	4 (4-4)	NA	**0.017**
Intraosseous	3 (3-4)	3 (2.75-3.25)	4 (4-4)	3 (3-3.25)	NA	**0.017**	3 (3-3)	3.5 (2.75-4)	4 (4-4)	3 (3-3.25)	NA	**0.015**	3 (3-3.75)	3 (3-3.75)	4 (4-4)	4 (4-4)	NA	0.052
Resorption score*																		
Supraosseous	3 (3-3.25)	3 (2.75-3.25)	4 (4-4)	3 (3-4)	NA	**0.028**	3 (3-3)	3 (2.75-3.25)	4 (4-4)	3 (2-4)	NA	**0.026**	2.5 (2-3)	3 (3-3.75)	4 (4-4)	4 (4-4)	NA	**0.016**
Intraosseous	3 (3-4)	3 (2.75-3.25)	4 (4-4)	3 (3-3.25)	NA	**0.017**	3 (2.75-3)	3.5 (2.75-4)	4 (4-4)	3 (2.75-3.25)	NA	**0.015**	3 (2.25-3.75)	3 (3-3.75)	4 (4-4)	4 (4-4)	NA	0.056
New bone formation#, %																		
Supraosseous	29.1 ±8.8	22.4 ±3.6	35.6 ±6.6	29.2 ±3.7	NA	0.592	14.4 ±4.2	14.7 ±1.6[a]	64.4 ±6.9[a]	56.7 ±7.3	NA	**0.004**	35.8 ±13.6	35.3 ±15.1	90.6 ±4.1	95.8 ±1.2	NA	**0.016**
Intraosseous	33.2 ±10.4	18.1 ± 6.6	33.3 ± 8.4	39.0 ±10.5		0.546	14.1 ±3.4[b]	22.3 ±8.0	77.7 ±6.3[b]	45.9 ±10.4		**<0.001**	49.1 ±11.0	57.1 ±6.7	86.2 ±7.8	93.1 ±1.5		**0.036**
Total	30.0 ±6.7[c]	20.6 ±4.4[d]	35.9 ±6.5[e]	33.2 ±4.4[f]	92.7 ±2.4[c-f]	**<0.001**	14.5 ±3.8[g,h]	18.0 ±2.9[i,j]	67.7 ±6.4[g,i]	54.1 ±7.9[k]	96.3 ±0.9[h,j,k]	**<0.001**	40.5 ±12.4	41.4 ±12.7	88.7 ±5.7	94.8 ±1.3	96.2 ±1.7	**0.001**

Table S5. *(continued)*

	6 months						12 months						18 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
Type of new bone formation head, n (%)																		
Supraosseous						0.533						0.695						0.200
None	3 (50)	4 (50)	1 (17)	3 (50)	NA		2 (33)	2 (33)	1 (17)	-	NA		1 (25)	-	-	-	NA	
Woven	-	-	1 (17)	-			-	-	-	-			1 (25)	-	-	-		
Lamellar	3 (50)	2 (33)	4 (67)	3 (50)			4 (67)	4 (67)	5 (83)	6 (100)			2 (50)	4 (100)	4 (100)	4 (100)		
Intraosseous						0.310						0.573						NA
None	1 (17)	4 (67)	4 (67)	4 (67)			2 (33)	1 (17)	-	-			-	-	-	-		
Woven	-	-	-	-	NA		-	-	-	-	NA		-	-	-	-	NA	
Lamellar	5 (83)	2 (33)	2 (33)	2 (33)			4 (67)	5 (83)	6 (100)	6 (100)			4 (100)	4 (100)	4 (100)	4 (100)		
Thickness of fibrous capsule, score*																		
Supraosseous	1 (0.75-2)	1 (0.75-1)	1 (1-2)	1 (0-1)	NA	0.153	1 (1-1.25)	1.5 (0.75-2.25)	1 (0-1.5)	1.5 (0.75-2.25)	NA	0.418	1.5 (1-2)	1.5 (0.25-2.75)	0 (0-0)	0 (0-0)	NA	**0.023**
Intraosseous	1 (0.75-1)	1 (0.75-1)	1 (1-1)	1 (0-1)		0.290	1 (1-1)	1 (0.75-1)	0.5 (0-1)	1 (0-1)		0.861	1 (0.25-1)	1 (0.25-1)	0 (0-0)	0 (0-0)		0.052
MNGCs at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0.25)	0 (0-0)	NA	0.392	0 (0-0.25)	0.5 (0-2)	0 (0-0.75)	0 (0-2.25)	NA	0.334	0 (0-1.5)	0 (0-0.75)	0 (0-0)	0 (0-0)	NA	0.392
Intraosseous	0 (0-1)	0 (0-0.25)	0 (0-0)	0 (0-0)		0.194	0 (0-1)	0 (0-1)	1 (0-2.25)	0 (0-2)		0.448	0 (0-1.5)	0 (0-0.75)	0 (0-0)	0 (0-0)		0.392

Table S5. *(continued)*

	6 months						12 months						18 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
PMNs at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0.5)	0 (0-0)	NA	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.25)	NA	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.25)		0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Eosinophils at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.25)	NA	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Adipocytes with birefringent particles at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Macrophages at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0.75)	0 (0-2.25)	0 (0-2)	NA	0.498	0 (0-0)	0.5 (0-2.5)	0 (0-0)	0 (0-0)	NA	0.112
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-1.5)	0 (0-0)	0 (0-0)		0.392
Lymphocytes at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0.25)	0 (0-0)	NA	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.5)	NA	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-1.5)	0 (0-0)	0 (0-0)	0 (0-0)		0.392

Table S5. *(continued)*

	6 months						12 months						18 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
Distant cells with birefringent particles																		
MNGCs, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0.25)	0 (0-0)	0 (0-0)	0 (0-0)	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
PMNs, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Eosinophils, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Adipocytes, score*	0 (0-2)	0 (0-2.25)	0 (0-0)	0 (0-0)	0 (0-0)	0.187	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-1.5)	0 (0-0)	0 (0-0)	0 (0-0)	0.392
Macrophages, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-2)	0 (0-0)	0 (0-0)	0 (0-0)	0.112	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Lymphocytes, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Osteocytes, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0.25)	0 (0-0)	0.392	0 (0-0)	0 (0-0.5)	0 (0-0)	0 (0-0.25)	0 (0-0)	0.527	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Necrosis, n (yes, %)																		
Supraosseous	-	-	-	-	-	NA	-	-	-	-	-	NA	-	-	-	-	-	NA
Intraosseous	-	-	-	-	-	NA	-	-	-	-	-	NA	-	-	-	-	-	NA
Active remodelling, n (yes, %)																		
Supraosseous	1 (17)	-	3 (50)	2 (33)	-	0.075	-	1 (17)	3 (50)	4 (67)	-	**0.038**	4 (100)	2 (50)	1 (25)	-	-	**0.037**
Intraosseous	2 (33)	-	2 (303)	-	-	0.144	-[l]	-[m]	5 (83)[l,m,n]	4 (67)	-[n]	**0.002**	2 (50)	3 (75)	1 (25)	2 (33)	-	0.147

Table S5. *(continued)*

	6 months						12 months						18 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
Periosteal reaction, n (%)						NA						>0.99						NA
None	-	-	-	-	-		-	-	1 (17)	1 (17)	1 (17)		-	-	-	-	-	
Apposition	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)		6 (100)	6 (100)	5 (83)	5 (83)	5 (83)		4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	
Resorption	-	-	-	-	-		-	-	-	-	-		-	-	-	-	-	
Endosteal reaction, n (%)																		
None	4 (67)	5 (83)	5 (83)	6 (100)	6 (100)		4 (67)	5 (83)	6 (100)	6 (100)	6 (100)		4 (100)	4 (100)	4 (100)	4 (100)	4 (100)	
Apposition	1 (17)	1 (17)	-	-	-		2 (33)	1 (17)	-	-	-		-	-	-	-	-	
Resorption	1 (17)	-	1 (17)	-	-		-	-	-	-	-		-	-	-	-	-	
Birefringent particles at non-implant site, n (yes, %)	1 (17)	-	-	1 (17)	-	0.558	-	-	-	1 (17)	-	0.406	-	2 (50)	-	-	-	0.092
Location	Bone and intravascular	NA	NA	Bone	NA		NA	NA	NA	Medulla	NA		NA	Medulla	NA	NA	NA	
Type of cells	Adipocytes	NA	NA	Osteocyte	NA		NA	NA	NA	Adipocytes	NA		NA	Adipocytes	NA	NA	NA	

* Data presented as median (25^{th}-75^{th} percentile). # Data presented as mean ± SEM. Pairwise comparison with Bonferroni correction for multiple testing: [a]P=0.012, [b]P=0.019, [c]P=0.003, [d]P<0.001, [e]P=0.001, [f]P=0.001, [g]P=0.016, [h]P<0.001, [i]P=0.013, [j]P<0.001, [k]P=0.037, [l]P=0.039, [m]P=0.039, and [n]P=0.039. Bold P-values are statistically significant (i.e. P<0.05). MNGCs, multinucleated giant cells; PMNs, polymorphonuclear leukocytes ; -: none (0.0%); NA: not applicable; SEM: standard error of the mean.

Table S6. Scores of all semi-quantitative scoring items of both zones after 24 to 48 months.

	24 months						36 months						48 months					
	BioSorbFX	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**
Scoring item	N=6	N=6	N=6	N=6	N=6		N=8	N=8	N=8	N=8	N=8		N=12	N=12	N=12	N=12	N=12	
Fragmentation score*																		
Supraosseous	3.5 (2.25-4)	3 (3-4)	4 (4-4)	4 (4-4)	NA	**0.029**	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99
Intraosseous	4 (3-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	0.112	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99
Resorption score*																		
Supraosseous	3.5 (2.75-4)	3 (3-4)	4 (4-4)	4 (4-4)	NA	**0.029**	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99
Intraosseous	4 (3-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	0.112	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99	4 (4-4)	4 (4-4)	4 (4-4)	4 (4-4)	NA	>0.99
New bone formation#, %																		
Supraosseous	74.9 ±5.4[a]	40.1 ±5.1[a,b,c]	89.6 ±4.4[b]	93.4 ±4.6[c]	NA	**<0.001**	93.3 ±2.0	75.5 ±5.9	82.6 ±8.3	92.9 ±3.6	NA	0.123	88.6 ±4.6	83.0 ±3.5	85.2 ±7.6	92.7 ±2.1	NA	0.517
Intraosseous	67.2 ±8.3[d]	70.7 ±11.5	91.1 ±2.4	97.0 ±1.3[d]		**0.043**	88.2 ±2.4	90.9 ±4.2	85.4 ±6.4	91.9 ±2.7		0.724	81.0 ±6.6	83.2 ±4.2	79.5 ±8.3	90.4 ±3.8		0.606
Total	72.6 ±5.6	48.3 ±6.1[e,f,g]	90.0 ±3.4[e]	93.9 ±3.9[f]	93.1 ±2.6[g]	**<0.001**	91.5 ±1.7	80.0 ±4.7	82.6 ±7.2	92.9 ±3.0	92.9 ±2.0	0.075	86.1 ±4.9	82.7 ±3.3	83.0 ±7.6	90.5 ±3.3	94.8 ±1.9	0.339
Type of new bone formation head, n (%)																		
Supraosseous						NA						NA						NA
None	-	-	-	-			-	-	-	-			-	-	-	-		
Woven	-	-	-	-	NA		-	-	-	-	NA		-	-	-	-	NA	
Lamellar	6 (100)	6 (100)	6 (100)	6 (100)			8 (100)	8 (100)	8 (100)	8 (100)			12 (100)	12 (100)	12 (100)	12 (100)		

Table S6. *(continued)*

	24 months						36 months						48 months					
	BioSorbFX	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**
Intraosseous						NA						NA						NA
None	-	-	-	-			-	-	-	-				-	-	-		
Woven	-	-	-	-	NA		-	-	-	-	NA			-	-	-	NA	
Lamellar	6 (100)	6 (100)	6 (100)	6 (100)			8 (100)	8 (100)	8 (100)	8 (100)			12 (100)	12 (100)	12 (100)	12 (100)		
Thickness of fibrous capsule, score*																		
Supraosseous	1 (0-2)	1.5 (0.75-3)	0 (0-0.25)	0 (0-0)		**0.029**	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Intraosseous	0 (0-1.25)	0.5 (0-1.25)	0 (0-0.25)	0 (0-0)	NA	0.232	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	0.392
MNGCs at interface, score*																		
Supraosseous	0 (0-1)	0 (0-0)	0 (0-0)	0 (0-0)		0.112	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Intraosseous	0.5 (0-1.25)	0 (0-0.25)	0 (0-0)	0 (0-0)	NA	**0.043**	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
PMNs at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Eosinophils at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99

Table S6. *(continued)*

	24 months						36 months						48 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
Adipocytes with birefringent particles at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Macrophages at interface, score*																		
Supraosseous	0 (0-0)	0 (0-2.25)	0 (0-0)	0 (0-0)	NA	0.112	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Lymphocytes at interface, score*																		
Supraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	NA	>0.99
Intraosseous	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)		>0.99
Distant cells with birefringent particles																		
MNGCs, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
PMNs, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Eosinophils, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Adipocytes, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.896
Macrophages, score*	0 (0-0.25)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.392	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99

Table S6. *(continued)*

	24 months						36 months						48 months					
	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value	BioSorbFX	Inion CPS	SonicWeld Rx	LactoSorb	Negative control	P-value
Lymphocytes, score*	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Osteocytes, score*	0 (0-0)	0 (0-2.25)	0 (0-0)	0 (0-0)	0 (0-0)	0.112	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	>0.99
Necrosis, n (yes, %)																		
Supraosseous	-	-	-	-	-	NA	-	-	-	-	-	NA	-	-	-	-	-	NA
Intraosseous	-	-	-	-	-	NA	-	-	-	-	-	NA	-	-	-	-	-	NA
Active remodelling, n (yes, %)																		
Supraosseous	2 (33)	2 (33)	-	-	-	0.092	1 (12)	-	2 (25)	-	-	0.255	2 (17)	3 (25)	-	-	-	0.064
Intraosseous	2 (33)	2 (33)	2 (33)	-	-	0.199	1 (12.5)	-	-	1 (12.5)	-	0.558	-	2 (17)	1 (8)	-	-	0.255
Periosteal reaction, n (%)						NA						0.776						**0.001**
None	-	-	-	-	-		1 (12)	-	1 (12)	2 (25)	-		-	-	-	-	5 (42)	
Apposition	6 (100)	6 (100)	6 (100)	6 (100)	6 (100)		7 (88)	8 (100)	7 (88)	6 (75)	6 (100)		12 (100)	12 (100)	12 (100)	12 (100)	7 (58)	
Resorption	-	-	-	-			-	-	-	-	-		-	-	-	-		
Endosteal reaction, n (%)						>0.99						>0.99						>0.99
None	6 (100)	6 (100)	6 (100)	5 (83)	6 (100)		8 (100)	7 (88)	8 (100)	7 (88)	8 (100)		12 (100)	12 (100)	12 (100)	12 (100)	11 (92)	
Apposition	-	-	-	1 (17)	-		-	1 (12)	-	1 (12)	-		-	-	-	-	1 (8)	
Resorption	-	-	-	-	-		-	-	-	-	-		-	-	-	-	-	

Table S6. *(continued)*

	24 months						36 months						48 months					
	BioSorbFX	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**	**BioSorbFX**	**Inion CPS**	**SonicWeld Rx**	**LactoSorb**	**Negative control**	**P-value**
Birefringent particles at non-implant site, n (yes, %)	1 (17)	3 (50)	-	-	-	0.075	1 (13)	-	1 (13)	-	-	0.406	2 (17)	3 (25)	3 (25)	1 (8)	-	0.339
Location	Fibrous tissue	Bone and medulla	NA	NA	NA		Medulla	NA	Medulla	NA	NA		Bone and medulla	Bone and medulla	Bone and medulla	Bone and medulla	NA	
Type of cells	Macro-phage	Osteocytes and adipocytes	NA	NA	NA		Adipo-cytes	NA	Adipo-cytes	NA	NA		Adipo-cytes	Adipo-cytes	Adipo-cytes	Adipo-cytes	NA	

* Data presented as median (25^{th}-75^{th} percentile). # Data presented as mean±SEM. Pairwise comparison with Bonferroni correction for multiple testing: [a]P=0.050, [b]P=0.019, [c]P=0.018, [d]P=0.045, [e]P= 0.034, [f]P=0.023, and [g]P=0.004. Bold P-values are statistically significant (i.e. P<0.05). MNGCs, multinucleated giant cells; PMNs, polymorphonuclear leukocytes ; -: none (0.0%); NA: not applicable; SEM: standard error of the mean.

Table S7. Multilevel models of each outcome scoring item at the supraosseous zone.

Outcome variable	Fragmentation score (n = 168)			Resorption score (n = 168)			Percentage new bone formation at supraosseous site (n = 168)		
Model variable	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA	NA	NA	NA	19.44 (3.61;35.28)	NA	**0.016**
Osteosynthesis system (ref. = LactoSorb)			**<0.001[b]**			**<0.001[b]**			**<0.001[b]**
BioSorb FX	-1.31 (-2.62;0.01)	0.27 (0.073;1.00)[c]	0.051	-1.25 (-2.88;0.38)	0.29 (0.06;1.46)[c]	0.132	-32.47 (-48.42;-16.52)	NA	**<0.001**
Inion CPS	-1.21 (-2.10;-0.32)	0.30 (0.12;0.73)[c]	**0.008**	-1.24 (-2.29;-0.19)	0.29 (0.10;0.83)[c]	**0.021**	-41.61 (-57.57;-25.66)	NA	**<0.001**
SonicWeld Rx	4.13 (3.30;4.96)	62.08 (27.0;146.7)[c]	**<0.001**	4.31 (3.13;5.48)	74.05 (22.9;239.8)[c]	**<0.001**	7.13 (-8.82;23.08)	NA	0.379
Follow-up (months)	0.10 (0.08;0.13)	1.11 (1.08;1.14)c	**<0.001**	0.11 (0.08;0.14)	1.12 (1.08;1.15)[c]	**<0.001**	3.85 (2.72;4.98)	NA	**<0.001**
Follow-up^2 (months^2)	NA	NA	NA	NA	NA	NA	-0.05 (-0.07;-0.03)		**<0.001**
Osteosynthesis system * Follow-up			**<0.001[b]**			**<0.001[b]**			**<0.001[b]**
BioSorb FX	0.01 (-0.04;0.06)	1.01 (0.96;1.06)[c]	0.673	0.01 (-0.05;0.06)	1.01 (0.96;1.06)[c]	0.850	0.60 (0.11;1.09)	NA	**0.018**
Inion CPS	0.01 (-0.03;0.05)	1.01 (0.97;1.05)[c]	0.652	0.01 (-0.03;0.05	1.01 (0.97;1.05)[c]	0.691	0.54 (0.04;1.03)	NA	**0.033**
SonicWeld Rx	-0.10 (-0.13;-0.08)	0.90 (0.88;0.93)[c]	**<0.001**	-0.11 (-0.14;-0.08)	0.90 (0.87;0.93)[c]	**<0.001**	-0.36 (-0.86;0.13)	NA	0.149

Table S7. *(continued)*

Outcome variable	Type of new bone formation (n = 168)			Thickness of fibrous capsule (n = 168)			MNGCs at interface score (n = 168)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	0.25 (-0.90;1.40)	1.29 (0.41;4.07)[d]	0.64	NA	NA	NA	NA	NA	NA
Osteosynthesis system (ref. = LactoSorb)			**<0.001[b]**			0.232[b]			**0.006[b]**
BioSorb FX	-1.00 (-2.58;0.57)	0.37 (0.08;1.77)[d]	0.211	1.18 (-0.27;2.62)	3.35 (0.77;13.75)[c]		-1.88 (-4.49;0.73)	0.15 (0.01;2.08)[c]	0.157
Inion CPS	-1.24 (-2.47;-0.01)	0.29 (0.09;0.99)[d]	**0.049**	1.29 (-0.11;2.68)	3.62 (0.89;14.65)[c]		0.02 (-1.45;1.49)	1.02 (0.23;4.45)[c]	0.979
SonicWeld Rx	0.91 (-0.70;2.52)	2.48 (0.50;12.38)[d]	0.265	0.25 (-1.05;1.55)	1.29 (0.35;4.70)[c]		2.05 (-1.41;5.52)	7.78 (0.24;248.27)[c]	0.244
Follow-up (months)	0.10 (0.06;0.15)	1.11 (1.06;1.16)[d]	**<0.001**	-0.11 (-0.14;-0.09)	0.90 (0.87;0.92)[c]	**<0.001**	-0.20 (-0.37;-0.02)	0.82 (0.69;0.98)[c]	**<0.001**
Osteosynthesis system * Follow-up			**<0.001[b]**			NA			**<0.001[b]**
BioSorb FX	0.02 (-0.04;0.07)	1.02 (0.96;1.07)[d]	0.605	NA	NA	NA	0.16 (0.02;0.30)	1.18 (1.02;1.35)[c]	**0.023**
Inion CPS	0.03 (-0.08;0.02)	1.03 (1.00;1.07)[d]	0.080	NA	NA	NA	0.06 (-0.04;0.15)	1.06 (0.96;1.17)[c]	0.272
SonicWeld Rx	-0.03 (-0.08;0.02)	0.97 (0.92;1.02)[d]	0.188	NA	NA	NA	-0.21 (-0.46;0.04)	0.81 (0.631.04)[c]	0.094

Table S7. *(continued)*

Outcome variable	PMNs at interface score (n = 168)			Eosinophils at interface score (n = 168)			Adipocytes with birefringent particles at interface score (n = 168)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA	NA	NA	NA			
Osteosynthesis system (ref. = LactoSorb)			0.621[b]			0.473[b]			
BioSorb FX	-0.29 (-1.23;0.66)	0.75 (0.29;1.93)[c]		-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]				
Inion CPS	-0.29 (-1.23;0.66)	0.75 (0.29;1.93)[c]		-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]		**None observed in all samples**		
SonicWeld Rx	0.07 (-1.36;1.50)	1.07 (0.26;4.48)[c]		-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]				
Follow-up (months)	-0.01 (-0.04;0.01)	0.99 (0.96;1.01)[c]	0.300	-0.01 (-0.03;0.01)	0.99 (0.97;1.01)[c]	0.516			
Outcome variable	**Macrophages at interface score (n = 168)**			**Lymphocytes at interface score (n = 168)**			**Necrosis (n = 210)**		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Osteosynthesis system (ref. = LactoSorb)			**0.020[b]**			0.615[b]			
BioSorb FX	-0.56 (-1.92;0.78)	0.57 (0.15;2.21)[c]	0.413	-0.36 (-1.29;0.58)	0.70 (0.27;1.79)[c]		**None observed in all samples**		
Inion CPS	0.74 (-1.13;2.61)	2.10 (0.32;13.63)[c]	0.436	-0.36 (-1.29;0.58)	0.70 (0.27;1.79)[c]				
SonicWeld Rx	0.05 (-0.96;1.06)	1.05 (0.38;2.87)[c]	0.925	-0.07 (-1.50;1.36)	0.93 (0.22;3.89)[c]		**None observed in all samples**		
Follow-up (months)	-0.03 (0.09;-0.06)	0.97 (0.94;1.01)[c]	0.093	-0.01 (-0.04;0.01)	0.99 (0.96;1.01)[c]	0.307			

Table S7. *(continued)*

Outcome variable	Active remodelling (n = 210)			Periosteal reaction score (n = 210)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	2.21 (-0.37;4.79)	9.11 (0.69;119.97)[e]	0.093	3.07 (1.55;4.59)	21.55 (4.70;98.79)[f]	**<0.001**
Osteosynthesis system (ref. = LactoSorb)			**<0.001[b]**			**<0.001[b]**
Negative control	-18.79 (-20.87;-16.71)	0.00 (0.00;0.00)[e]	**<0.001**	-0.69 (-2.35;0.97)	0.50 (0.10;2.63)[f]	0.411
BioSorb FX	-2.96 (-5.61;-0.31)	0.05 (0.00;0.74)[e]	**0.029**	0.64 (-0.38;1.66)	1.90 (0.68;5.28)[f]	0.219
Inion CPS	-3.96 (-6.17;-1.76)	0.02 (0.00;0.17)[e]	**<0.001**	1.04 (0.07;2.00)	2.82 (1.07;7.40)[f]	**0.036**
SonicWeld Rx	-1.44 (-3.80;0.93)	0.24 (0.02;2.53)[e]	0.232	0.30 (-0.40;1.00)	1.35 (0.67;2.71)[f]	0.401
Follow-up (months)	-0.25 (-0.43;-0.08)	0.78 (0.65;0.92)	**0.027**	-0.02 (-0.05;0.01)	0.98 (0.96;1.01)[f]	0.122
Osteosynthesis system * Follow-up			**0.019[b]**			NA
Negative control	0.25 (0.09;0.41)	1.28 (1.09;1.51)[e]	**0.003**	NA	NA	NA
BioSorb FX	0.24 (0.08;0.39)	1.27 (1.09;1.47)[e]	**0.002**	NA	NA	NA
Inion CPS	0.26 (0.11;0.42)	1.30 (1.11;1.51)[e]	**0.001**	NA	NA	NA
SonicWeld Rx	0.16 (-0.02;0.33)	1.17 (0.98;1.40)[e]	0.077	NA	NA	NA

[a]Calculated in case of binary or ordinal outcome variables; [b]P-value of the complete block; [c]Odds ratio of having a higher score of that specific item; [d]Odds ratio of formation of lamellar bone compared to no new bone formation; [e]Odds ratio of the presence of active remodelling; [f]Odds ratio of the presence of periosteal reaction.
Abbreviations: β, estimated coefficient; CI, confidence interval; OR, odds ratio; NA, not applicable; Ref, reference; MNGCs, multinucleated giant cells; PMNs: polymorphonuclear leukocytes.

Table S8. Multilevel models of each outcome scoring item at the intraosseous zone and at non-implant site.

Outcome variable	**Fragmentation score (n = 168)**			**Resorption score (n = 168)**			**Percentage new bone formation at intraosseous site (n = 168)**		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA	NA	NA	NA	11.43 (-6.77;29.64)	NA	
Osteosynthesis system (ref. = LactoSorb)			**<0.001[b]**			**<0.001[b]**		NA	**<0.001[b]**
BioSorb FX	-0.41 (-1.57;0.74)	0.66 (0.21;2.10)[c]	0.482	2.18 (1.05;3.30)	8.83 (2.87;27.18)[c]	**<0.001**	-28.27 (-45.51;-11.04)	NA	**0.001**
Inion CPS	-0.23 (-1.24;0.79)	0.80 (0.29;2.20)[c]	0.660	1.21 (-1.61;4.02)	3.34 (0.20;55.73)[c]	0.399	-30.95 (-48.19;-13.72)	NA	**0.001**
SonicWeld Rx	4.71 (3.54;5.89)	111.13 (34.32;359.81)[c]	**<0.001**	24.22 (22.26;26.18)	$33*10^{9}$ ($46*10^{8}$;$23*10^{10}$)[#,c]	**<0.001**	11.36 (-5.87;28.60)	NA	0.195
Follow-up (months)	0.12 (0.08;0.16)	1.13 (1.09;1.17)c	**<0.001**	0.45 (0.25;0.64)	1.56 (1.29;1.90) [c]	**<0.001**	4.74 (3.40;6.09)	NA	**<0.001**
Follow-up^{2} (months^{2})	NA	NA	**NA**	NA	NA	NA	-0.07 (-0.09;-0.04)	NA	**<0.001**
Osteosynthesis system * Follow-up			**<0.001[b]**			**<0.001[b]**		NA	**0.001[b]**
BioSorb FX	-0.01 (-0.05;0.03)	0.99 (0.95;1.03)[c]	0.671	-0.28 (-0.45;-0.11)	0.76 (0.64;0.90)[c]	**0.001**	0.39 (-0.14;0.93)	NA	0.149
Inion CPS	-0.00 (-0.03;0.03)	1.00 (0.97;1.03)[c]	0.949	-0.15 (-0.43;0.13)	0.86 (0.65;1.14)[c]	0.286	0.54 (0.00;1.07)	NA	**0.049**
SonicWeld Rx	-0.12 (-0.16;-0.08)	0.89 (0.85;0.92)[c]	**<0.001**	-0.46 (-0.65;-0.28)	0.63 (0.52;0.76)[c]	**<0.001**	-0.48 (-1.01;0.06)	NA	0.080

Table S8. *(continued)*

Outcome variable	Type of new bone formation (n = 168)			Thickness of fibrous capsule (n = 168)			MNGCs at interface score (n = 168)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	-2.02 (-3.98;-0.06)	0.13 (0.02;0.94)	**0.043**	NA	NA	NA	NA	NA	NA
Osteosynthesis system (ref. = LactoSorb)			0.832[b]			0.093[b]			**<0.001[b]**
BioSorb FX	0.47 (-1.42;2.36)	1.59 (0.24;10.54)[d]		0.97 (0.08;1.87)	2.65 (1.09;6.46)[c]		1.60 (-0.78;3.97)	4.93 (0.46;53.16)[c]	0.187
Inion CPS	-0.42 (-2.21;1.37)	0.66 (0.11;3.95)[d]		1.13 (0.20;2.05)	3.08 (1.23;7.75)[c]		0.83 (-0.87;2.53)	2.30 (0.42;12.53)[c]	0.335
SonicWeld Rx	0.00 (-1.82;1.82)	1.00 (0.16;6.18)[d]		0.22 (-0.66;1.09)	1.24 (0.52;2.99)[c]		0.62 (0.45;0.78)	1.86 (1.58;2.19)[c]	**<0.001**
Follow-up (months)	0.32 (0.14;0.49)	1.37 (1.16;1.63)[d]	**<0.001**	-0.11 (-0.13;-0.09)	0.90 (0.88;0.92)[c]	**<0.001**	-0.10 (-0.15;-0.05)	0.90 (0.86;0.95)[c]	**<0.001**
Osteosynthesis system * Follow-up			NA			NA			NA
BioSorb FX	NA	NA	NA	NA	NA	NA	NA	NA	NA
Inion CPS	NA	NA	NA	NA	NA	NA	NA	NA	NA
SonicWeld Rx	NA	NA	NA	NA	NA	NA	NA	NA	NA

Table S8. *(continued)*

Outcome variable	PMNs at interface score (n = 168)			Eosinophils at interface score (n = 168)			Adipocytes with birefringent particles at interface score (n = 168)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA						
Osteosynthesis system (ref. = LactoSorb)			0.473[b]						
BioSorb FX	-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]							
Inion CPS	-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]		**None observed in all samples**			**None observed in all samples**		
SonicWeld Rx	-0.40 (-1.49;0.69)	0.67 (0.23;2.00)[c]							
Follow-up (months)	-0.01 (-0.03;0.01)	0.99 (0.97;1.01)[c]	0.516						
Outcome variable	**Macrophages at interface score (n = 168)**			**Lymphocytes at interface score (n = 168)**			**Necrosis (n = 210)**		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Osteosynthesis system (ref. = LactoSorb)			0.981[b]			0.477[b]			
BioSorb FX	0.00 (-2.58;2.58)	1.00 (0.08;13.16)[c]		0.40 (-0.70;1.49)	1.49 (0.50;4.45)[c]				
Inion CPS	0.40 (1.97;2.77)	1.49 (0.14;15.90)[c]		0.00 (0.00;0.00)	1.00 (1.00;1.00)[c]		**None observed in all samples**		
SonicWeld Rx	0.00 (-2.58;2.58)	1.00 (0.08;13.16)[c]		0.00 (0.00;0.00)	1.00 (1.00;1.00)[c]				
Follow-up (months)	-0.00 (-0.06;0.05)	1.00 (0.94;1.05)[c]	0.878	0.00 (-0.02;0.01)	0.97 (0.98;1.01)[c]	0.571	**None observed in all samples**		

Table S8. *(continued)*

Outcome variable	Active remodelling (n = 210)			Endosteal reaction score (n = 210)			Percentage new bone formation at complete implant site (n = 210)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA	NA	NA	NA	24.31 (11.00;37.60)	NA	**<0.001**
Osteosynthesis system (ref. = LactoSorb)			0.525[b]			**<0.001[b]**		NA	**<0.001[b]**
Negative control	-15.53 (-1915;1884)	0.00 (0.00;†)[e]		-0.90 (-2.77;0.97)	0.41 (0.06;2.63)[f]		46.46 (32.45;60.46)	NA	**<0.001**
BioSorb FX	0.42 (0.87;1.70)	1.52 (0.42;5.46)[e]		2.57 (-0.01;5.16)	13.09 (0.99;173.51)[f]		-32.27 (-46.28;-18.27)	NA	**<0.001**
Inion CPS	0.42 (0.87;1.70)	1.52 (0.42;5.46)[e]		1.67 (-0.87;4.22)	5.33 (0.42;67.85)[f]		-39.60 (-53.61;-25.60)	NA	**<0.001**
SonicWeld Rx	1.04 (-0.17;2.25)	2.83 (0.84;0.95)[e]		-0.84 (-2.73;1.06)	0.43 (0.07;2.87)[f]		7.50 (-6.51;21.50)	NA	0.292
Follow-up (months)	-0.05 (-0.08;-0.01)	0.95 (0.92;0.99)[e]	**0.011**	0.01 (-0.04;0.05)	1.01 (0.96;1.06)[f]	0.807	3.45 (2.54;4.37)	NA	**<0.001**
Follow-up^2 (months^2)	NA	NA	NA	NA	NA	NA	-0.04 (-0.06;-0.03)	NA	**<0.001**
Osteosynthesis system * Follow-up			NA			**<0.001[b]**		NA	**<0.001[b]**
Negative control				-0.01 (-0.05;0.04)	1.00 (0.95;1.05)[f]	0.843	-1.09 (-1.52;-0.65)	NA	**<0.001**
BioSorb FX	NA	NA	NA	-0.09 (-0.17;-0.01)	0.91 (0.84;0.99)[f]	**0.024**	0.58 (0.15;1.01)	NA	**0.009**
Inion CPS	NA	NA	NA	-0.05 (-0.14;0.04)	0.95 (0.87;1.04)[f]	0.252	0.58 (0.14;1.01)	NA	**0.009**
SonicWeld Rx	NA	NA	NA	-0.01 (-0.06;0.04)	0.99 (0.95;1.04)[f]	0.772	-0.37 (-0.80;0.07)	NA	0.095

Table S8. *(continued)*

Outcome variable	Distant MNGCs with birefringent particles (n = 210)			Distant PMNs with birefringent particles (n = 210)			Distant eosinophils with birefringent particles (n = 210)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Osteosynthesis system (ref. = LactoSorb)			0.995[b]						
Negative control	0.00 (-2.59;2.59)	1.00 (0.08;13.32)[c]							
BioSorb FX	0.00 (-2.59;2.59)	1.00 (0.08;13.32)[c]							
Inion CPS	0.40 (-1.99;2.78)	1.49 (0.14;16.12)[c]		**None observed in all samples**			**None observed in all samples**		
SonicWeld Rx	0.00 (-2.59;2.59)	1.00 (0.08;13.32)[c]							
Follow-up (months)	-0.01 (-0.06;0.05)	0.99 (0.95;1.05)[c]	0.828						

Outcome variable	Distant adipocytes with birefringent particles (n = 210)			Distant macrophages with birefringent particles (n = 210)			Distant lymphocytes with birefringent particles (n = 210)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Osteosynthesis system (ref. = LactoSorb)			0.437[b]			0.947[b]			
Negative control	-14.42 (-2605;2576)	0.00 (0.00;&)[c]		0.00 (-2.34;2.34)	1.00 (0.10;10.41)[c]				
BioSorb FX	1.59 (-0.74;3.92)	4.90 (0.48;50.47)[c]		0.29 (-1.91;2.49)	1.34 (0.15;12.09)[c]				
Inion CPS	1.66 (-0.66;3.98)	5.25 (0.52;53.53)[c]		0.67 (-1.39;2.73)	1.96 (0.25;15.40)[c]				
SonicWeld Rx	-0.01 (-2.91;2.89)	0.99 (0.06;18.01)[c]		0.00 (-2.34;2.34)	1.00 (0.10;10.41)[c]		**None observed in all samples**		
Follow-up (months)	-0.01 (-0.08;0.06)	0.99 (0.93;1.07)[c]	0.842	-0.01 (-0.05;0.03)	0.99 (0.95;1.03)[c]	0.630			
Osteosynthesis system * Follow-up			NA			NA			
BioSorb FX	NA	NA	NA	NA	NA	NA			
Inion CPS	NA	NA	NA	NA	NA	NA			
SonicWeld Rx	NA	NA	NA	NA	NA	NA			

Table S8. *(continued)*

Outcome variable	Distant osteocytes with birefringent particles (n = 210)			Birefringent particles at non-implant site (n = 210)		
Model variables	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**	**β (95% CI)**	**OR (95% CI)[a]**	**P-value[b]**
Intercept	NA	NA	NA	-1.75 (-3.87;0.36)	0.17 (0.02;1.44)[g]	0.104
Osteosynthesis system (ref. = LactoSorb)			0.838[b]			**<0.001[b]**
Negative control	-0.50 (-2.53;1.53)	0.61 (0.08;4.61)[c]		-15.75 (-17.77;-13.73)	0.00 (0.00;0.00)[g]	**<0.001**
BioSorb FX	-0.50 (-2.53;1.53)	0.61 (0.08;4.61)[c]		-0.78 (-4.21;2.65)	0.45 (0.02;14.18)[g]	0.655
Inion CPS	0.35 (-1.33;2.02)	1.42 (0.27;7.56)[c]		-0.13 (-3.16;2.90)	0.88 (0.04;18.16)[g]	0.933
SonicWeld Rx	-0.50 (-2.53;1.53)	0.61 (0.08;4.61)[c]		-5.10 (-8.90;-1.29)	0.01 (0.00;0.28)[g]	**0.009**
Follow-up (months)	-0.01 (-0.05;0.03)	0.99 (0.95;1.03)[c]	0.503	-0.03 (-0.05;0.11)	0.97 (0.88;1.06)[g]	0.227
Osteosynthesis system * Follow-up			NA			**0.008[b]**
Negative control	NA	NA	NA	0.03 (-0.05;0.11)	1.03 (0.95;1.12)[g]	0.457
BioSorb FX	NA	NA	NA	0.05 (-0.06;0.16)	1.05 (0.94;1.17)[g]	0.367
Inion CPS	NA	NA	NA	0.05 (-0.04;0.13)	1.05 (0.96;1.14)[g]	0.277
SonicWeld Rx	NA	NA	NA	0.15 (0.06;0.25)	1.17 (1.06;1.28)[g]	**<0.001**

[a]Calculated in case of binary or ordinal outcome variables; [b]P-value of the complete block; [c]Odds ratio of having a higher score of that specific item; [d]Odds ratio of formation of lamellar bone compared to no new bone formation; [e]Odds ratio of the presence of active remodelling; [f]Odds ratio of the presence of endosteal reaction; [g]Odds ratio of the presence of birefringent particles at non-implant site; [#]Very large coefficient and, thus, odds ratio due to that this osteosynthesis system scored 'complete resorption' in all samples (i.e., no observed variance); [†]Very large upper limit of the 95% CI due to that none of the negative control samples showed active remodeling; [&]Very large upper limit of the 95% CI due to that none of the negative control samples showed distant adipocytes with birefringent particles.
Abbreviations: β, estimated coefficient; CI, confidence interval; OR, odds ratio; Ref, reference group; NA, not applicable; MNGCs, multinucleated giant cells; PMNs, polymorphonuclear leukocytes.

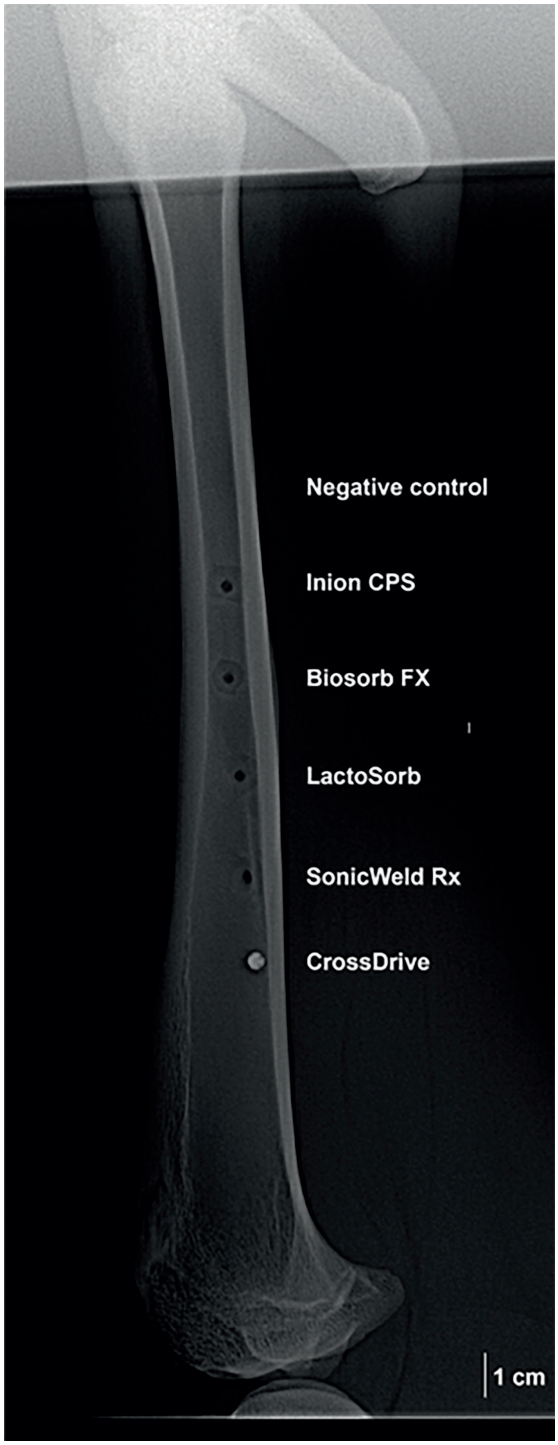


Figure S1. X-ray radiographs of the surgical sites at 6-months follow-up

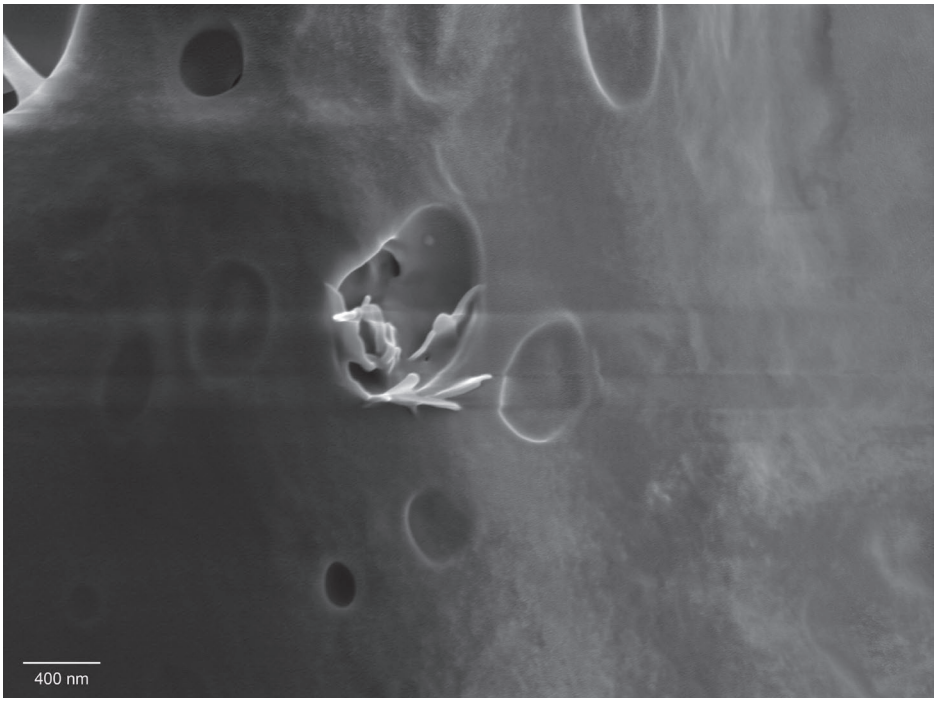
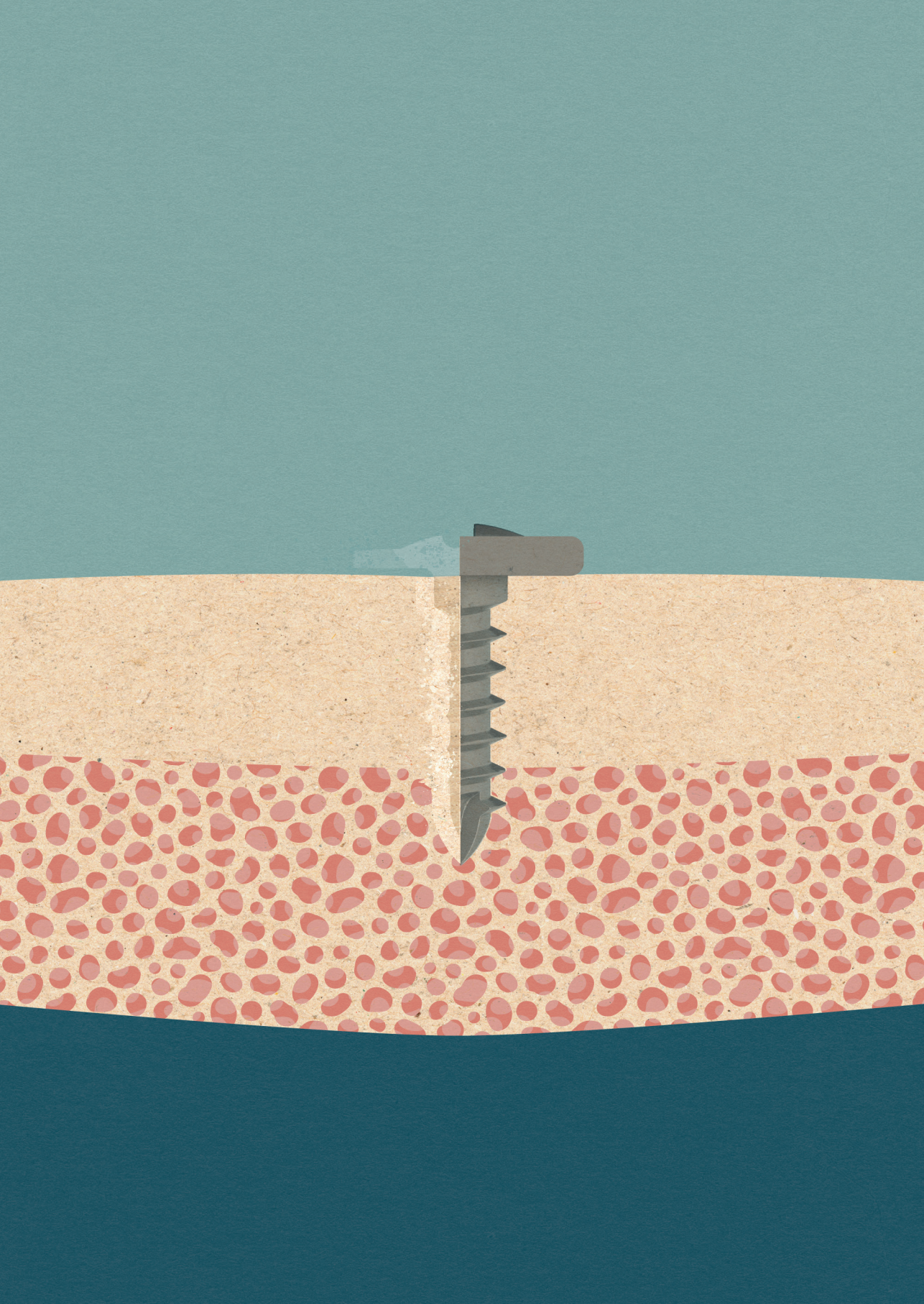


Figure S2. Scanning electron microscopy image of crystalline, needle-like structures of nanoscale in randomly selected vacuoles of the medulla after implantation of the BioSorb FX system at 36 months follow-up (magnification 52.860x).



Chapter 7

Comparison of the mechanical properties of biodegradable and titanium osteosynthesis systems used in oral and maxillofacial surgery

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Abstract

To guide the selection of osteosynthesis systems, this study compared the mechanical properties of biodegradable and titanium osteosynthesis systems. SonicPins Rx and xG were subjected to pull-out tests. Additionally, 15 biodegradable (Inion CPS 2.0 and 2.5mm; LactoSorb 2.0mm; Macropore 2.0mm; Polymax 2.0mm; BioSorb FX 2.0mm; ResorbX 2.1mm; Osteotrans-MX 2.0mm with plate thicknesses 1.0 and 1.4mm; SonicWeld Rx_{plate}/Rx_{pins}, xG_{plate}/Rx_{pins} and xG_{plate}/xG_{pins} 2.1mm without and with tapping the burr hole) and 6 titanium (CrossDrive (2006), CrossDrive (2018), MaxDrive; all 1.5 and 2.0mm) straight, 4-hole osteosynthesis systems were evaluated. All systems were subjected to tensile, bending and torsion tests. Pull-out loads of the SonicPins were comparable ($P=0.423$). Titanium systems' tensile loads were higher than biodegradable systems ($P<0.001$). CrossDrive (2018) and MaxDrive systems' tensile and torsional stiffness were lower, accompanied with higher ductility, than corresponding CrossDrive (2006) systems ($P<0.001$). Bending stiffness of 1.5mm titanium systems was comparable to, and of the 2.0mm systems higher than, all biodegradable systems ($P<0.001$). Regarding biodegradable systems, Inion CPS 2.5mm had highest tensile load and torsional stiffness, SonicWeld 2.1mm highest tensile stiffness, and BioSorbFX 2.0mm highest bending stiffness ($P<0.001$). On the basis of the results of this study, the CrossDrive (2018) and MaxDrive 1.5mm titanium systems are recommended for midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomy), and the CrossDrive (2018) and MaxDrive 2.0mm titanium systems for mandibular fractures and osteotomies when a titanium osteosynthesis system is used. When there is an indication for a biodegradable osteosynthesis system, the SonicWeld 2.1mm or BioSorbFX 2.0mm are recommended for midface fractures and osteotomies, and the Inion CPS 2.5mm biodegradable system for mandibular osteotomies and non-load bearing mandibular fractures, especially when high torsional forces are expected (e.g., mandibular symphysis fractures).

Introduction

Titanium osteosynthesis systems are currently the systems of choice in oral and maxillofacial surgery. A combination of titanium plates and screws results in excellent mechanical and handling properties, providing adequate bone stability[1]. The disadvantages of titanium osteosyntheses include: palpability[2], sensitivity to temperature changes[3], stress shielding of the underlying bone[4], growth restrictions[5], interference with radiographic imaging and radiotherapy[4,6,7], spread of titanium particles in the soft tissue and regional lymph nodes[8], and possibly mutagenic effects[3]. Consequently, titanium systems are removed in a second operation in 5-38% of cases[9].

Biodegradable osteosynthesis systems, made of resorbable (co-)polymers, significantly reduce the need to remove implants in a second operation[9]. The other advantages of biodegradable osteosyntheses are: no sensitivity to temperature changes, no interference with radiographic imaging and radiotherapy, no growth disturbances, and a more gradual transfer of stress to the healing bone[5,10–12]. Biodegradable systems have, however, limitations including less favorable mechanical properties compared to titanium systems, a need to tap the screw hole before inserting the screws, and tissue reactions to the prolonged presence of foreign materials[13,14]. These limitations result in higher perioperative screw breakage and longer operation times compared to titanium systems as well as the removal of symptomatic biodegradable systems in up to 17% of the cases[9].

Recently, new titanium osteosynthesis systems have been introduced to improve perioperative handling (e.g., adjusting the screw head to improve the grip on the screws) and to reduce stress shielding of the underlying bone by adjusting the production process to lower the stiffness of these systems[15,16]. Over 12 different titanium osteosynthesis systems (without taking the different sizes of each system into account) are used currently in oral and maxillofacial surgery (OMF-surgery)[9,17]. The biodegradable systems have also been improved to overcome the limitations of the less favourable mechanical properties, to avoid tissue reactions, and to improve perioperative handling. This was done by adjusting the copolymer composition, by using ultra-sound activated pins whereupon the pinheads fuse with the osteosynthesis plate, and by obviating the need to tap the screw hole. Currently, over 36 different biodegradable osteosynthesis systems are available on the market with different compositions and mechanical properties[13,18]. Yet, due to the presumed less favourable mechanical properties of biodegradable compared to titanium osteosynthesis systems, the use of biodegradable systems is currently restricted to midface or non-load bearing mandibular fracture fixation.

Because of the recent improvements in both types of osteosynsthesis systems and the lack of studies comparing these systems, it is still unclear for surgeons which titanium and biodegradable osteosynthesis systems are suitable and prefered for treatment of fractures and fixation of osteotomies.

Examples of improved biodegradable systems are SonicWeld Rx and the recently introduced SonicWeld xG (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)[13]. Both systems use thermoplastic biodegradable pins instead of screws. These pins are inserted into the burr hole using an ultrasound probe, resulting in a flow of the biodegradable polymer into the cancellous bone, which obviates the need to tap the burr hole. This approach has been shown to increase the mechanical properties of the biodegradable osteosynthesis systems[12,19,20]. However, when ultra-sound activated biodegradable pins are only inserted into cortical bone, their axial pull-out strenghts are significantly lower compared to biodegradable screws due to the insufficient retention properties of the smoother cortical bone[12,20]. Therefore, although the burr hole does not normally have to be tapped when applying ultra-sound activated SonicWeld systems, we hypothesized that tapping the burr hole in specific situations (i.e., when only applied in cortical bone) could strengthen the osteosynthesis systems by increasing the contact area and thereby increasing the mechanical retention of the fused pin in the cortical bone layer.

To guide OMF-surgeons and to make recommendations in the selection of osteosynthesis systems, this study aimed to determine and compare mechanical properties of commonly used biodegradable and titanium osteosynthesis systems in OMF-surgery.

Materials and methods

The most commonly used titanium and biodegradable osteosynthesis systems in OMF-surgery were selected[9,17]. The specifications of all the included osteosynthesis systems (i.e., 15 biodegradable and 6 titanium systems), including sizes and compositions, are summarized in Table 1. All the osteosynthesis systems had undergone the sterilization process of the manufacturer and were tested before the expiration date. The mechanical tests were performed six times per system and per application method which corresponds to the American Society for Testing Materials standards (ASTM D638;[21]).

Optimal tap, pull-out load and stiffness of SonicPins

Tapping the burr hole is not part of the manufacturer's standard application method for SonicPins. However, we hypothesized that tapping the burr hole whenever applied

in cortical bone only can increase the axial pull-out load by increasing the contact area and mechanical retention of the fusioned pin in the cortical bone layer. Therefore, a pilot study was conducted to determine the optimal tap diameter of SonicPins Rx in a cortical bone model. We preferred fine threaded taps over coarse threaded taps for this pilot study because fine threads increase the surface contact of the pins with the bone segments more and are tapped more easily in hard materials (i.e., bone) compared to coarse ones. Thus, four different application methods were tested, viz., (1) the method prescribed by the manufacturer, i.e., 1.6 mm diameter drill without tapping the burr hole; (2) tapping after drilling the burr hole (i.e., 1.6 mm diameter drill) with 1.7x0.20; (3) 1.8x0.20; and (4) 2.0x0.25 mm taps (diameter x pitch of taps in mm; all fine threaded taps) to increase the contact area of the pins with the smooth cortical burr holes.

The pull-out tests simulated the relatively high axial pull-out forces of *in vivo* situations (e.g., cranial reconstructions). Polymethylmethacrylate (PMMA) blocks (30.0 x 15.0 x 6.0 mm) were used to simulate bone segments[22–24]. The burr holes were drilled perpendicular to the surface of the PMMA block using the prescribed drill (i.e., 1.6mm diameter) with water cooling. After drilling and tapping / not tapping the burr hole, the burr holes were irrigated with saline to simulate *in situ* lubrication. A titanium plate (25.0 x 6.0 x 1.0 mm) were transferred directly to the pins. The thickness of the titanium plate of 1.0 mm was specifically chosen as the osteosynthesis plates corresponding to these SonicPins have the same thickness of 1.0 mm. Therefore, the test setup did not interfere with the length of the screw in the bone compared to the *in vivo* situation. The PMMA-blocks with the SonicPins Rx *in situ* were stored with a single 2.3mm hole was placed above the burr hole and the SonicPins Rx were applied, as prescribed by the manufacturer, by a single researcher (BG; Fig. 1a). The titanium plate was chosen in order to ensure that the forces for 24 hours in a water tank containing 37.1°C water to simulate SonicPins Rx relaxation at body temperature. Saline was avoided to prevent possible corrosion of the test environment. The use of water instead of saline was not expected to influence the test results[12,18]. Subsequently, the tests were performed in another tank, containing water of the same temperature, mounted on the test machine (Zwick/Roell TC-FR2, 5TS.D09, 2.5kN Test machine; force accuracy 0.2%, positioning accuracy 0.0001 mm; Zwick/Roell Nederland, Venlo, The Netherlands). All the samples were analysed in the same test machine using a standardized protocol (see the Mechanical tests and Statistical analyses described below).

Table 1. Specifications of all the included osteosynthesis systems.

Brand name	Manufacturer	Plate composition	Screw/pin composition	Drill diameter (mm)	Tap diameter (mm)	Screw/pin diameter (mm)	Screw/ pin length (mm)	Plate length (mm)	Plate width (mm)	Plate thickness (mm)
Titanium osteosynthesis systems										
CrossDrive 1.5mm (2006)	KLS Martin Group (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)	100% titanium (by stamping)	90% titanium 6% aluminium 4% vanadium (Ti6Al4V)	1.1	None	1.5	6.0	18.5	3.5	0.6
CrossDrive 2.0mm (2006)				1.5	None	2.0	6.0	25.5	5.0	1.0
CrossDrive 1.5mm (2018)		100% titanium (by milling)		1.1	None	1.5	6.0	18.5	3.5	0.6
CrossDrive 2.0mm (2018)				1.5	None	2.0	6.0	25.5	5.0	1.0
MaxDrive 1.5mm[1]			90% titanium 6% aluminium 4% vanadium (Ti6Al4V)[1]	1.1	None	1.5	6.0	18.5	3.5	0.6
MaxDrive 2.0mm[1]				1.5	None	2.0	6.0	25.5	5.0	1.0
Biodegradable osteosynthesis systems										
Inion CPS 2.0mm	Inion Oy (Tampere, Finland)	70-78.5% PLLA 16-24% PDLLA 4.5-6% TMC[2]	70-78.5% PLLA 16-24% PDLLA 4.5-6% TMC[2]	1.75	2.0	2.0	7.0	28.0	7.0	1.3
Inion CPS 2.5mm				2.25	2.5	2.5	6.0	32.0	8.5	1.6
LactoSorb 2.0mm	Biomet Microfixation (Jacksonville, Florida)	82% PLLA 18% PGA	82% PLLA 18% PGA	1.7	2.0	2.0	7.0	28.5	7.0	1.3
Macropore 2.0mm	Medtronic, Inc. (Minneapolis, USA)	70% PLLA 30% PDLLA	70% PLLA 30% PDLLA	1.5	2.0	2.0	6.0	25.0	6.7	1.2
Polymax 2.0mm	Mathys Medical Ltd. (Bettlach Switzerland)	70% PLLA 30% PDLLA	70% PLLA 30% PDLLA		2.0[3]	2.0	6.0	28.0	6.0	1.3
BioSorb FX 2.0mm	ConMed Linvatec Biomaterials Ltd. (Tampere, Finland)	SR 70% PLLA SR 30% PDLLA	SR 70% PLLA SR 30% PDLLA	1.5	2.0	2.0	6.0	25.5	5.5	1.3

Table 1. *(continued)*

Brand name	Manufacturer	Plate composition	Screw/pin composition	Drill diameter (mm)	Tap diameter (mm)	Screw/pin diameter (mm)	Screw/ pin length (mm)	Plate length (mm)	Plate width (mm)	Plate thickness (mm)
ResorbX 2.1mm	KLS Martin Group (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)	100% PDLLA	100% PDLLA	1.8	2.1	2.1	7.0	26.0	6.0	1.0
SonicWeld Rx + SonicPins Rx (Rx/Rx) 2.1mm[4]		100% PDLLA	100% PDLLA (pin)	1.6	None or 2.0	2.1	7.0	26.0	6.0	1.0
SonicWeld xG + SonicPins Rx (xG/Rx) 2.1mm[4]		85% PLLA 15% PGA	100% PDLLA (pin)	1.6	None or 2.0	2.1	7.0	26.0	6.0	1.0
SonicWeld xG + SonicPins xG (xG/xG) 2.1mm[4]		85% PLLA 15% PGA	85% PLLA 15% PGA (pin)	1.6	None or 2.0	2.1	7.0	26.0	6.0	1.0
Osteotrans-MX	Teijin Medical Technologies Co., Ltd. (Osaka, Japan)	60% PLLA 40% uHA	70% PLLA 30% uHA	1.6	2.0	2.0	8.0	28.0	4.5	1.0
Osteotrans-MX										1.4

PLLA, poly-L-lactic acid; PDLLA, poly-D,L-lactic acid; TMC, trimethylene carbonate; SR: self-reinforced; PGA, poly-glycolic acid; uHA, unsintered hydroxyapatite.
[1]The MaxDrive screws have an adjusted screw head, compared to the CrossDrive screws, to improve screw grip while the plates of corresponding MaxDrive and CrossDrive (2018) systems are identical; [2]The manufacturer does not publicly report the exact composition of the copolymers; [3]Self-drilling tap; [4]These systems were tested without tapping (as instructed by the manufacturer) and with tapping the burr holes.

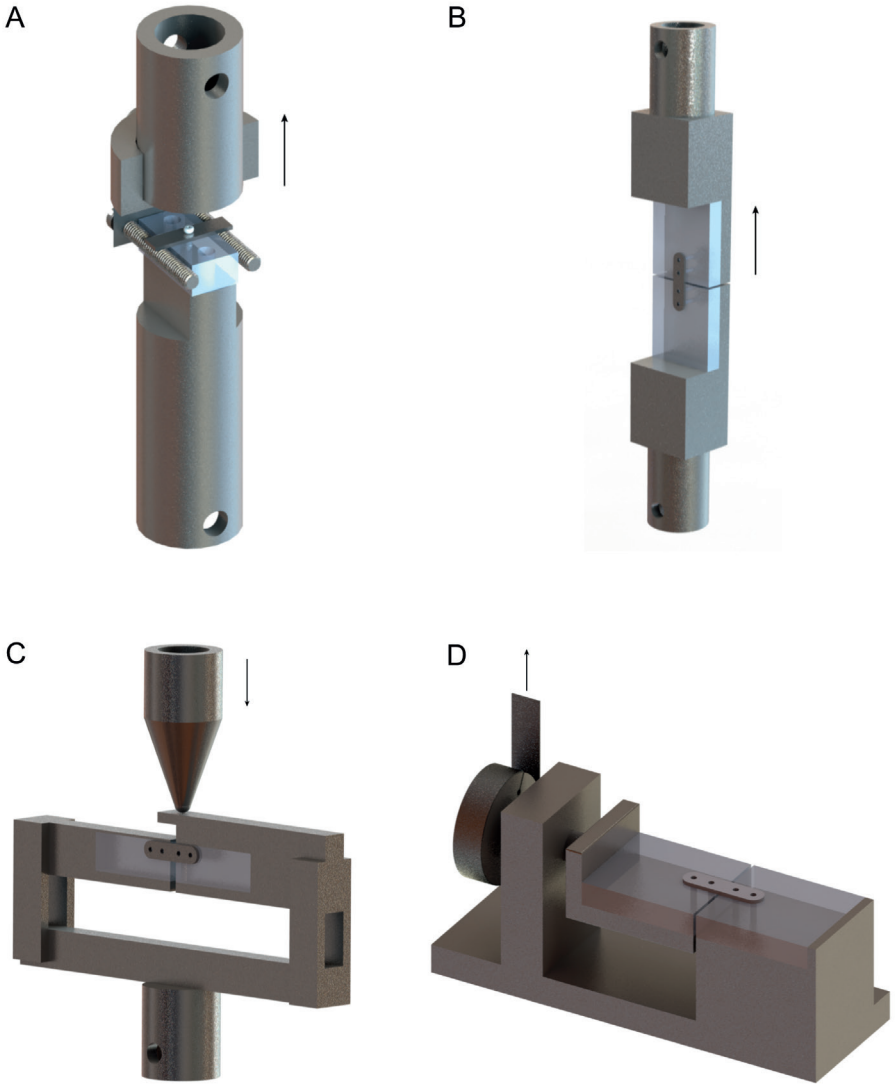

Figure 1. The pull-out (a), tensile (b), side bending (c), and torsion (d) test setups. The arrows indicate the direction of the applied force.

The SonicPins xG pins were applied using both the method prescribed by the manufacturer (i.e., without tapping the burr hole) and with a tap that yielded the highest pull-out load in the abovementioned pilot study. Subsequently, both were subjected to the pull-out tests described above.

Torque, tensile, side bending and torsion tests

All the selected osteosynthesis systems, consisting of straight 4-hole plates with intermediate spaces, underwent three different mechanical tests, i.e. tensile, three-point side bending, and torsion tests. The tensile test was a standard loading test since an osteosynthesis system is unavoidably exposed to these forces after adequate repositioning of the bone segments[25,26]. The three-point side bending tests simulated the bending forces a mandible is exposed to, e.g., after a bilateral sagittal split osteotomy (BSSO)[27]. The torsion test simulated the high torsion forces seen with, e.g., a fracture of the mandibular symphysis[28].

Once again, PMMA blocks were used to simulate bone segments. Two 40.0 x 36.0 x 6.0 mm blocks were used for the tensile and torsion tests, while two 40.0 x 15.0 x 6.0 mm blocks were used for the side bending test (Fig. 1b-1d). The size of the side bending test blocks was different to avoid premature contact of the PMMA-blocks during testing. The burr holes were drilled perpendicular to the surface of the PMMA block using the prescribed drills with cooling (Table 1). After drilling and, optionally, tapping, the burr holes were irrigated with saline to simulate *in situ* lubrication. All three SonicWeld systems were also tested using the preferred tap as determined in the abovementioned pilot study. The two PMMA-blocks were fixated using an osteosynthesis system without interfragmentary contact between the PMMA-blocks to simulate the most unfavourable situation[29]. All the osteosynthesis systems were applied according to the manufacturers' instructions, with two screws or pins in each PMMA-block (in total 4 screws/pins per plate, two at each side of the fracture; Fig. 1b-1d) and by the same researcher (BG).

The osteosynthesis screws were inserted with the prescribed screw drivers, and using the mean applied torque, by the same four experienced OMF-surgeons (RRMB, FKLS, GMR, and JJ) defined in a previous study[30]. Since the SonicWeld systems use ultrasound activated SonicPins instead of screws, no torque could be applied or measured. To standardize the application of these pins, we used a minimum of 1 sec and a maximum of 2 sec to insert each SonicPin. A fixed time was not chosen as the time needed to melt each pin varies slightly, similar to the clinical situation, and the surgeon will melt the pin until it is correctly applied. Since the MaxDrive (i.e., 1.5 and 2.0 mm) and Osteotrans-

MX systems had not been developed yet when doing the previous study[30], the same four experienced OMF-surgeons (RRMB, FKLS, GMR, and JJ)[30] were asked to participate in this study and to insert the 6 screws of both the MaxDrive and Osteotrans-MX systems into the same standardized, pre-drilled PMMA-blocks (36.0 x 36.0 x 6 mm) as they would do in the clinic (i.e., 'hand tight'). The test setup and conditions to assess the applied torque were identical to that described in the previous study[30]. Additionally, like the previous study, one researcher (BG) inserted the 6 screws of both systems until fracture occurred (i.e., torque needed for screw breakage). The torque was recorded using a torque measurement meter (Nemesis Howards Torque Gauge, Smart MT-TH 50 sensor, accuracy 2.5 Nmm, range 0-680 Nmm).

The PMMA-blocks with the osteosynthesis systems *in situ* were stored for 24 hours in a tank containing water at 37.1°C to simulate relaxation of the systems at body temperature. Subsequently, the tests were performed in another tank containing water with the same temperature. All the samples were tested in the same test machine and analysed using a standardized protocol (see Mechanical tests and Statistical analysis below).

Mechanical tests

All the mechanical tests were performed with the same machine by the same researcher (CCR). In the pull-out test, the SonicPins were subjected to axial forces with a constant speed of 5 mm/min until the SonicPins were pulled out or fractured (Fig. 1a)[21]. During the tensile tests, the osteosynthesis systems were subjected to tensile forces with a constant speed of 5 mm/min until fracture of the plate or screws/pins occurred (Fig. 1b). In the side bending tests, the PMMA-blocks were fixated at both ends and the osteosynthesis plate was loaded in the centre with a constant speed of 30 mm/min until the plate bent by 30° (Fig. 1c). The torsion test consisted of rotating the two PMMA-blocks along the long axis with a constant speed of 90°/min until 160° torsion of the plate occurred (Fig. 1d).

The applied force and displacement were measured with a frequency of 500 Hertz. These results were presented as a force-displacement graph. The pull-out and tensile tests yielded a maximum load (in N) and stiffness (in N/mm). The outcome measures for the side bending and torsion tests were stiffness (in N/mm) and torsional stiffness (Nmm/°rotation), respectively. The stiffness of the pull-out, tensile, and side bending tests were determined using the force-displacement graph. Herein, the direction coefficient of the line connecting the points of the 25% and 75% maximum force in the elastic region was determined. This excluded inaccuracies at the beginning and

end of the force-displacement graphs. The torsional stiffness was calculated using the following formulas:

(1) $T = F \times r$

(2) $k = T / \Phi$

where T is the torque (Nmm), F is the force (N), r is the radius (20 mm in this test setup), k is the torsional stiffness (Nmm/° rotation), and Φ is the angle of twist (°). The origin of failure of all tests was recorded.

In this study, all 15 biodegradable and 6 titanium osteosynthesis systems were mechanically tested. Of these, 7 biodegradable and 2 titanium systems had been tested in a previous study by the author's research group[12,18]. The test setups and environment used in the previous and current study were identical. To ensure a correct direct comparison, a biodegradable system that was tested in the previous study and that had not been altered by the manufacturer over time (i.e., KLS SonicWeld Rx_{plate}/Rx_{pins} 2.1 mm osteosynthesis system) was tested again in all three of the current study's test setups. The tensile load and tensile, side bending, and torsional stiffness were statistically compared and the force-displacement graphs were visually inspected. Direct comparability of all the mechanical tests was considered appropriate whenever the previous and current studies' outcome values did not differ statistically and the force-displacement graphs were similar.

Statistical analysis

The assumption of normal distribution of data was tested by visually examining the Q-Q plots and the Shapiro-Wilk test. All the data were presented as means with standard deviations (SD). The Levene's test was performed to check the assumption of equality of variances of data. The mean pull-out and tensile load, and pull-out, tensile, side bending and torsional stiffness of the included osteosynthesis systems were statistically compared using a one-way analysis of variance (ANOVA). To correct for multiple testing, the Tukey's or Dunett's T3 *post hoc* test was performed in case of the assumption of equal or unequal variances, respectively. P-values less than 0.05 (two-tailed) were considered statistically significant. All the analyses were performed in Statistical Package of Social Sciences (SPSS) 23 (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.).

Results

Optimal tap and pull-out load of SonicPins

The mean pull-out load and stiffness of the SonicPins Rx without tap and with 1.7, 1.8, and 2.0 mm taps are presented in Fig. 2 and Table S1. The SonicPins Rx with a tap diameter of 2.0 mm had the highest mean pull-out load compared to those with 1.7 and 1.8 mm diameter taps. Therefore, the SonicPins xG were also subjected to the pull-out test without and with tapping the burr hole with a 2.0 mm diameter tap.

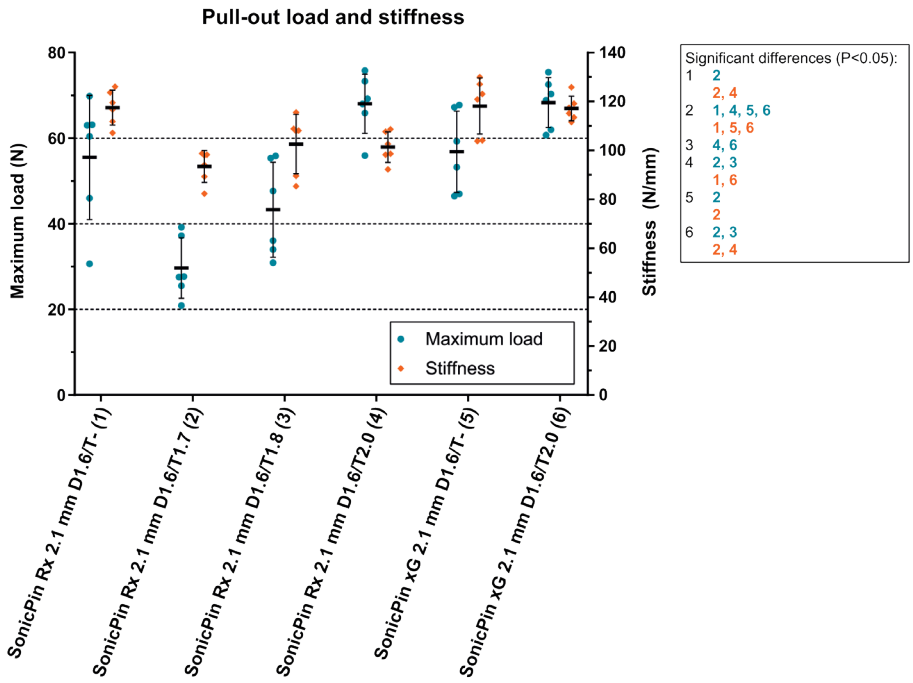

Figure 2. The pull-out load and stiffness of SonicPins Rx and xG. The characters in blue and orange represent significant differences in maximum load (N) and stiffness (N/mm). *D, drill diameter (mm); T, tap diameter (mm). Error bars: mean values ± standard deviation. All the load and stiffness values, including the P-values of the pairwise comparisons, are reported in Table S1.*

The pull-out load of the SonicPins Rx and SonicPins xG, both without tapping the burr hole, did not differ significantly (P>0.999). Tapping the burr holes with a 2.0 mm tap did not improve the pull-out loads of the SonicPins Rx and xG compared to not tapping the burr holes (Rx: 68.0 (6.94) N vs. 55.5 (14.5) N, P=0.474; xG: 68.3 (5.83) N vs. 56.8 (9.50) N, P=0.712; Fig. 2 and Table S1). Tapping the burr hole with a 1.7 mm

tap (29.7 (7.08) N) resulted in significantly lower pull-out load compared to not tapping the SonicPins Rx burr hole (P=0.001), whereas there were no significant differences in pull-out load between tapping with a 1.8 mm tap (42.5 (11.1) N) and not tapping the burr hole (P=0.474).

The pull-out stiffness of the SonicPin Rx (117 (7.14) N/mm) compared to the SonicPin xG (118 (11.4) N/mm), both without tapping the burr hole, did not differ significantly (P>0.999; Fig. 2 and Table S1). Tapping the SonicPins Rx burr hole with 2.0 mm tap significantly lowered the pull-out stiffness compared to not tapping the burr hole (101 (6.25) N/mm vs. 117 (7.14) N/mm; P=0.024). The pull-out stiffness after tapping the SonicPins xG burr hole with a 2.0 mm tap was not significantly different compared to not tapping the burr hole (117 (5.05) N/mm vs. 118 (11.4) N/mm; P>0.999).

The shaft of four of the six SonicWeld Rx pins subjected to a 1.7 mm tap failed whereas the heads of all the other SonicPins Rx and xG pins failed.

Torque of osteosynthesis screws

The mean torque applied to the KLS MaxDrive 1.5 and 2.0 mm screws by four experienced OMF-surgeons (i.e., 'hand tight') was 319 (65.3) and 407 (138) Nmm, respectively (Table S2 and Fig. S4). The mean torque applied to the same systems until screw breakage was 528 (16.9) and >680 Nmm (i.e., maximum of torque meter range achieved), respectively. Comparatively, the applied hand-tight torque of the MaxDrive 1.5 mm screws were significantly higher than the CrossDrive 1.5 mm screws (P=0.046), while the torque applied to the MaxDrive 2.0 mm screws did not differ significantly with the CrossDrive 2.0 mm screws (P>0.999). All the Osteotrans-MX 2.0 mm screw heads failed during insertion in PMMA by the OMF-surgeons, before the screws were fully in. Therefore, these osteosynthesis systems could not be tested in the setups. The mean torque applied to all the other included osteosynthesis systems (i.e., 'hand tight' and until screw breakage), as well as the statistical comparisons, are presented in Table S2 and Fig. S4. The mean torque applied to all the titanium screws with both the 'hand tight' and 'breakage' method was significantly higher than that applied to the biodegradable screws (Table S2 and Fig. S4).

Tensile, side bending and torsion tests

Firstly, to test the assumption that our previous and current studies' set-ups were identical[12,18], the KLS SonicWeld Rx/Rx 2.1 mm system was tested and compared to the results of the same system derived from our previous study[12]. The curves of the previous and current force-displacement graphs (i.e., tensile, side bending and torsion tests) were

similar (Fig. S2-4). The results of the mean tensile load (previous: 115 (8.69) vs. current: 112 (2.25) N; P=0.511) and stiffness (495 (34.0) vs. 489 (21.9) N/mm; P=0.718), and side bending (1.11 (0.09) vs. 1.08 (0.08) N/mm; P=0.656) and torsion stiffness (2.13 (0.30) vs. 2.12 (0.26) Nmm/°; P=0.932) did not differ significantly. Therefore, direct comparison of the previously and currently tested osteosynthesis systems was considered appropriate for the rest of this study.

The torque applied to the osteosynthesis screws for the tensile tests corresponded to the mean torque applied by the four experienced OMF-surgeons (Table 2). The mean tensile load and stiffness of all the systems, including statistical comparisons, are presented in Fig. 3 and Table 2. The tensile loads of all the titanium systems were significantly higher compared to the biodegradable systems. The tensile loads of the CrossDrive (2006 and 2018) and MaxDrive systems were similar. However, the tensile stiffness of the CrossDrive (2018) and MaxDrive 1.5 mm were significantly lower than the CrossDrive (2006) 1.5 mm system (P<0.001 and P=0.007, respectively). The displacement until fracture occured (i.e., in the force-displacement graph) of the CrossDrive (2018) and MaxDrive systems was significantly higher (2.11 (0.23) and 1.83 (0.11) mm, respectively) than that of the CrossDrive (2006) system (1.12 (0.07) mm; both P<0.001; Fig. S5). Similary, the stiffness of the CrossDrive (2018) and MaxDrive 2.0 mm was significantly lower compared to the CrossDrive (2006) 2.0 mm system (P=0.001 and P<0.001, respectively) and the displacement until fracture occurred was higher in the former two systems (3.05 (0.08) and 3.37 (0.10) mm, respectively) compared to the latter system (2.42 (0.11) mm; both P<0.001; Fig. S6). The higher displacement until fracture of the CrossDrive (2018) and MaxDrive systems indicates higher ductility than the CrossDrive (2006) systems (Fig. S5 and S6). Furthermore, the tensile stiffness of the SonicWeld Rx and xG systems, regardless of the method used (i.e., without or with tapping the burr hole), was significantly higher than the other biodegradable systems (Fig. 3 and Table 2). It was noted that the tensile load and stiffness of the SonicWeld Rx and xG systems were significantly higher than the Resorb X system (i.e., a system with the same composition and dimensions, but with screws instead of SonicPins). There were no significant differences in tensile load and stiffness between the SonicWeld Rx and xG systems. The Inion CPS 2.5 mm system's tensile load was the highest among all the biodegradable systems. The origin of the titanium and SonicWeld systems' failure during the tensile test was plate breakage while all the other biodegradable systems experienced screw-head shearing.

The torque applied to the osteosynthesis screws for the side bending and torsion tests corresponded to the mean torque applied by the experienced OMF-surgeons (Table 3). The side bending stiffness of the 1.5 mm titanium systems was comparable to the biodegradable systems (Fig. 4 and Table 3). The 2.0 mm titanium systems had significantly higher side bending stiffness compared to the 1.5 mm titanium and all the biodegradable systems. Of all the biodegradable systems, the BioSorb FX 2.0 mm system had the highest side bending stiffness (1.55 (0.13) N/mm). The side bending stiffness of all the included SonicWeld systems was significantly higher compared to the Resorb X system. None of the osteosynthesis systems fractured during the side bending tests.

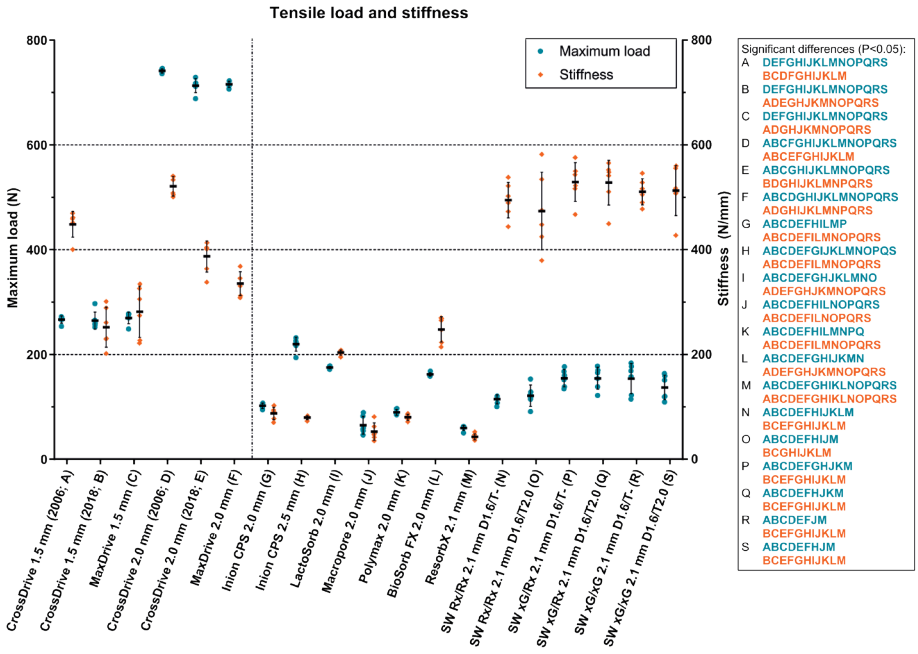

Figure 3. The tensile load and stiffness of all the included osteosynthesis systems. The characters in blue and orange represent significant differences in maximum load (N) and stiffness (N/mm). *D, drill diameter (mm); T, tap diameter (mm). Error bars: mean values ± standard deviation. The dotted line separates the titanium (left) and biodegradable systems (right). All the load and stiffness values, including the P-values of the pairwise comparisons, are reported in Table 2.*

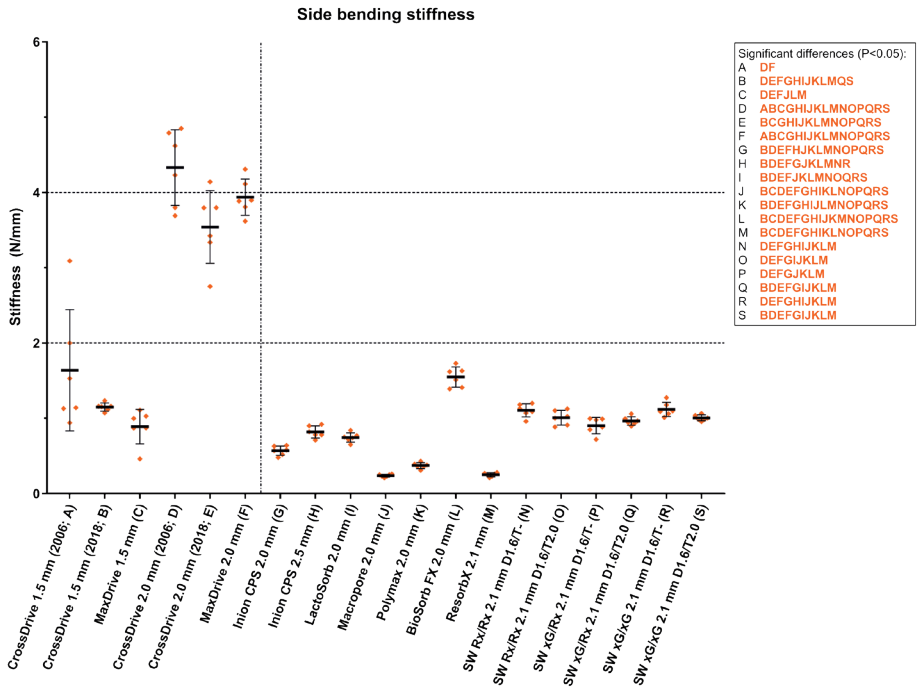

Figure 4. The side bending stiffness of all the included osteosynthesis systems. The characters in orange represent significant differences in stiffness (N/mm). *D, drill diameter (mm); T, tap diameter (mm). Error bars: mean values ± standard deviation (N/mm). The dotted line separates the titanium (left) and biodegradable systems (right). All the stiffness values, including the P-values of the pairwise comparisons, are reported in Table 3.*

The mean torsional stiffness of the titanium 2.0 mm systems was significantly higher compared to the 1.5 mm titanium systems (Fig. 5 and Table 3). Of all the biodegradable systems, the Inion CPS 2.5 mm had the highest torsional stiffness (15.8 (0.79) Nmm/°). There were no significant differences in torsional stiffness between the SonicWeld Rx and xG systems. The torsional stiffness of the SonicWeld systems was similar to the Resorb X system. None of the osteosynthesis systems fractured during the torsion tests.

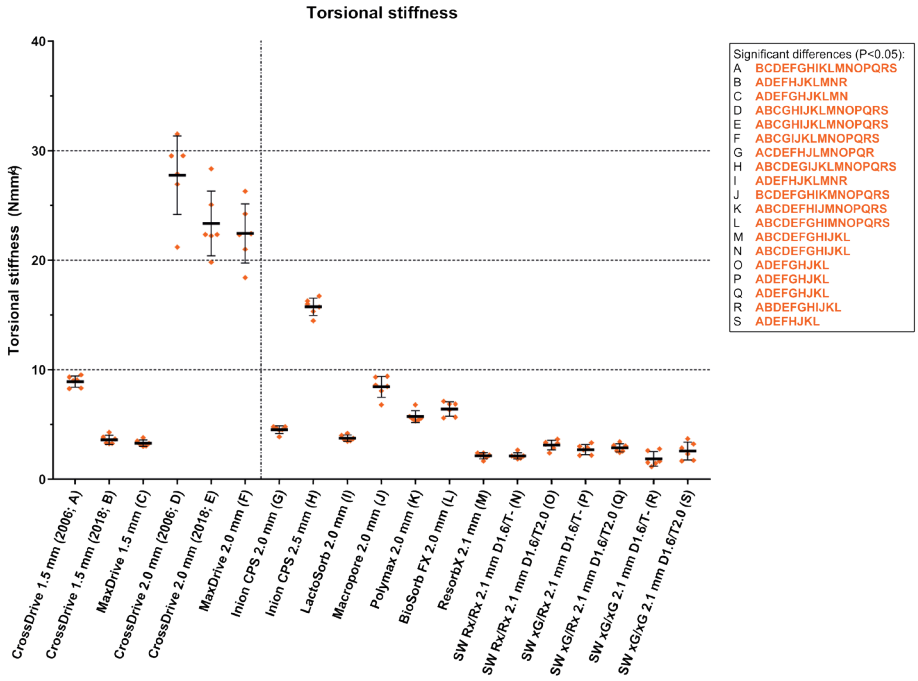

Figure 5. The torsional stiffness of all included osteosynthesis systems**.** The characters in orange represent significant differences in stiffness (Nmm/°). *D, drill diameter (mm); T, tap diameter (mm). Error bars: mean values ± standard deviation. The dotted line separates the titanium (left) and biodegradable systems (right). All the stiffness values, including the P-values of the pairwise comparisons, are reported in Table 3.*

Table 2. The tensile load and stiffness of all the included osteosynthesis systems.

Ref.	System	Mean torque applied to screws (SD) in Nmm	Mean Fmax (SD) in N	P-values (pairwise comparison)	Mean stiffness (SD) in N/mm	P-values (pairwise comparison)
A	CrossDrive 1.5 mm (2006)	251 (1.54)	267 (6.74)	B: >0.999; C: >0.999; **D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: 0.006; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: 0.001; R: 0.006; S: 0.001**	449 (24.7)	**B: <0.001; C: 0.007; D: 0.020;** E: 0.177; F: **0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: 0.679; O: >0.999; P: 0.107; Q: 0.202; R: 0.104; S: 0.563
B	CrossDrive 1.5 mm (2018)	247 (0.53)	265 (16.4)	A: >0.999; C: >0.999; **D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: 0.037; I: 0.001; J: <0.001; K: <0.001; L: 0.001; M: <0.001; N: <0.001; O: <0.001; ; P: <0.001; Q: <0.001; R: 0.003; S: <0.001**	252 (38.3)	**A: <0.001;** C: >0.999; **D: <0.001; E: 0.005;** F: 0.101; **G: 0.003; H: 0.004;** I: 0.527; **J: 0.001; K: 0.004;** L: >0.999; **M: 0.001; N: <0.001; O: 0.016; P: <0.001; Q: <0.001; R: <0.001; S: <0.00**1
C	MaxDrive 1.5 mm	320 (0.48)	270 (10.9)	A: >0.999; B: >0.999; **D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: 0.004; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: 0.004; S: <0.001**	283 (49.0)	**A: 0.007;** B: >0.999; **D: 0.001;** E: 0.099; F: 0.794; **G: 0.006; H: 0.006;** I: 0.289; **J: 0.002; K: 0.006;** L: 0.998; **M: 0.003; N: 0.001; O: 0.039; P: <0.001; Q: <0.001;R: 0.001; S: 0.001**
D	CrossDrive 2.0 mm (2006)	370 (1.09)	741 (4.08)	**A: <0.001; B: <0.001; C: <0.001;** E: 0.108; **F: 0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**	521 (18.6)	**A: 0.020; B: <0.001; C: 0.001; E: 0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: 0.992; O: 0.995; P: >0.999; Q: >0.999; R: >0.999; S: >0.999
E	CrossDrive 2.0 mm (2018)	368 (1.22)	713 (13.5)	**A: <0.001; B: <0.001; C: <0.001;** D: 0.108; F: >0.999**; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**	387 (29.5)	A: 0.177; **B: 0.005;** C: 0.099; **D: 0.001;** F: 0.326**; G: <0.001; H: <0.001; I: 0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: 0.014;** O: 0.674; **P: 0.003; Q: 0.008; R: 0.002; S: 0.033**
F	MaxDrive 2.0 mm	408 (0.34)	716 (5.91)	**A: <0.001; B: <0.001; C: <0.001; D: 0.001;** E: >0.999; **G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**	335 (22.8)	**A: 0.001;** B: 0.101; C: 0.794; **D: <0.001;** E: 0.326**; G: <0.001; H: <0.001; I: 0.001; J: <0.001; K: <0.001 L: 0.007; M: <0.001; N: 0.001;** O: 0.169; **P: <0.001; Q: 0.001; R: <0.001; S: 0.004**

Table 2. *(continued)*

Ref.	System	Mean torque applied to screws (SD) in Nmm	Mean Fmax (SD) in N	P-values (pairwise comparison)	Mean stiffness (SD) in N/mm	P-values (pairwise comparison)
G	Inion CPS 2.0 mm	74.3 (0.31)	102 (5.11)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; H: <0.001; I: <0.001;** J: 0.091; K: 0.162; **L: <0.001; M: <0.001;** N: 0.504; O: 0.847; **P: 0.015;** Q: 0.052; R: 0.193; S: 0.355	87.6 (11.7)	**A: <0.001; B: 0.003; C: 0.006; D: <0.001; E: <0.001; F: <0.001;** H: 0.992; **I: <0.001;** J: 0.140; K: 0.999; **L: <0.001; M: 0.004; ;N: <0.001; O: 0.002; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
H	Inion CPS 2.5 mm	157 (0.77)	220 (13.4)	**A: 0.006; B: 0.037; C: 0.004; D: <0.001; E: <0.001; F: <0.001; G: <0.001; I: 0.015; J: <0.001; K: <0.001; L: 0.004; M: <0.001; N: <0.001; O: <0.001; P: 0.003; Q: 0.013;** R: 0.074; **S: 0.005**	79.5 (3.74)	**A: <0.001; B: 0.004; C: 0.006; D: <0.001; E: <0.001; F: <0.001;** G: 0.992; **I: <0.001;** J: 0.284; K: >0.999; **L: <0.001; M: <0.001; N: <0.001; O: 0.002; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
I	LactoSorb 2.0 mm	98.0 (0.48)	175 (2.40)	**A: <0.001; B: 0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: 0.015; J: 0.001; K: <0.001; L: 0.002; M: <0.001; N: <0.001; O: 0.042;** P: 0.562; Q: 0.803; R: 0.969; S: 0.271	208 (4.82)	**A: <0.001;** B: 0.527; C: 0.289; **D: <0.001; E: 0.001; F: 0.001; G: <0.001; H: <0.001; J: <0.001; K: <0.001;** L: 0.186; **M: <0.001; N: <0.001; O: 0.011; P: <0.001; Q: <0.001; R: <0.001; S: 0.001**
J	Macropore 2.0 mm	62.4 (0.47)	65.1 (16.9)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001;** G: 0.091; **H: <0.001; I: 0.001;** K: 0.400; **L: 0.001;** M: >0.999; **N: 0.019; O: 0.035; P: <0.001; Q: 0.001; R: 0.013; S: 0.014**	52.9 (16.6)	**A: <0.001; B: 0.001; C: 0.002; D: <0.001; E: <0.001; F: <0.001;** G: 0.140; H: 0.284; **I: <0.001;** K: 0.276; **L: <0.001;** M: 0.999; **N: <0.001; O: 0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
K	Polymax 2.0 mm	57.1 (0.58)	89.7 (5.53)	**A: <0.001; B: <0.001; C: <0.001 ; D: <0.001; E: <0.001; F: <0.001;** G: 0.162; **H: <0.001; I: <0.001;** J: 0.400; **L: <0.001; M: <0.001; N: 0.021;** O: 0.314; **P: 0.005; Q: 0.019;** R: 0.086; S: 0.127	80.1 (5.74)	**A: <0.001; B: 0.004; C: 0.006; D: <0.001; E: <0.001; F: <0.001;** G: 0.999; H: >0.999; **I: <0.001;** J: 0.276; **L: <0.001; M: <0.001; N: <0.001; O: 0.002; P: <0.001; ;Q: <0.001 ;R: <0.001; S: <0.001**
L	BioSorb FX 2.0 mm	81.2 (0.41)	162 (3.18)	**A: <0.001; B: 0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: 0.004; I: 0.002; J: 0.001; K: <0.001; M: <0.001; N: 0.001;** O: 0.130; P: >0.999; Q: >0.999; R: >0.999; S: >0.999	248 (24.3)	**A: <0.001;** B: >0.999; C: 0.998; **D: <0.001; E: <0.001; F: 0.007; G: <0.001; H: <0.001;** I: 0.186; **J: <0.001; K: <0.001; M: <0.001; N: <0.001; O: 0.018; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
M	Resorb X 2.1 mm	56.1 (0.23)	59.9 (4.73)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001;** J: >0.999; **K: <0.001; L: <0.001; N: <0.001; O: 0.021; P: 0.001; Q: 0.003; R: 0.017; S: 0.015**	42.9 (5.82)	**A: <0.001; B: 0.001; C: 0.003; D: <0.001; E: <0.001; F: <0.001; G: 0.004; H: <0.001; I: <0.001;** J: 0.999; **K: <0.001; L: <0.001; N: <0.001; O: 0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**

Table 2. *(continued)*

Ref.	System	Mean torque applied to screws (SD) in Nmm	Mean Fmax (SD) in N	P-values (pairwise comparison)	Mean stiffness (SD) in N/mm	P-values (pairwise comparison)
N	SW Rx/ Rx 2.1 mm (D1.6/T-)	NA	115 (8.69)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001;** G: 0.504; **H: <0.001; I: <0.001; J: 0.019; K: 0.021; L: 0.001; M: <0.001;** O: >0.999; P: 0.053; Q: 0.164; R: 0.465; S: 0.879	495 (34.0)	A: 0.679; **B: <0.001;** C: **0.001;** D: 0.992; **E: 0.014; F: 0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** O: >0.999; P: 0.995; ;Q: 0.999; R: >0.999; S: >0.999
O	SW Rx/ Rx 2.1 mm (D1.6/T2.0)	NA	121 (20.2)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001;** G: 0.847; **H: <0.001; I: 0.042; J: 0.035;** K: 0.314; L: 0.130; **M: 0.021;** N: >0.999; P: 0.453; Q: 0.629; R: 0.874; S: >0.999	529 (37.0)	A: >0.999; **B: 0.016; C: 0.039;** D: 0.995; E: 0.674; F: 0.169; **G: 0.002; H: 0.002; I: 0.011; J: 0.001; K: 0.002; L: 0.018; M: 0.001;** N: >0.999; P: 0.993; Q: 0.997; R: >0.999; S: >0.999
P	SW xG/ Rx 2.1 mm (D1.6/T-)	NA	155 (16.6)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: 0.015; H: 0.003;** I: 0.562; **J: <0.001; K: 0.005;** L: >0.999; **M: 0.001;** N: 0.053; O: 0.453; Q: >0.999; R: >0.999; S: 0.999	529 (37.0)	A: 0.107; **B: <0.001; C: <0.001;** D: >0.999; **E: 0.003; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: 0.995; O: 0.993; Q: >0.999; R: >0.999; S: >0.999
Q	SW xG/ Rx 2.1 mm (D1.6/T2.0)	NA	155 (21.1)	**A: 0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001;** G: 0.052; **H: 0.013;** I: 0.803; **J: 0.001; K: 0.019;** L: >0.999; **M: 0.003;** N: 0.164; O: 0.629; P: >0.999; R: >0.999; S: >0.999	528 (42.5)	A: 0.202; **B: <0.001; C: <0.001;** D: >0.999; **E: 0.008; F: 0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: 0.999; O: 0.997; P: >0.999; R: >0.999; S: >0.999
R	SW xG/ xG 2.1 mm (D1.6/T-)	NA	154 (28.9)	**A: 0.006; B: 0.003; C: 0.004; D: <0.001; E: <0.001; F: <0.001;** G: 0.193; H: 0.074; I: 0.969; **J: 0.013** K: 0.086; L: >0.999; **M: 0.017;** N: 0.465; O: 0.874; P: >0.999; Q: >0.999; S: >0.999	511 (24.9)	A: 0.104; **B: <0.001; C: 0.001;** D: >0.999; **E: 0.002; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: >0.999; O: >0.999; P: >0.999; Q: >0.999; S: >0.999
S	SW xG/ xG 2.1 mm (D1.6/T2.0)	NA	137 (23.5)	**A: 0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001;** G: 0.355; **H: 0.005;** I: 0.271; **J: 0.014;** K: 0.127; L: 0.723; **M: 0.015;** N: 0.879; O: >0.999; P: 0.999; Q: >0.999; R: >0.999	513 (47.8)	A: 0.563; **B: <0.001; C: 0.001;** D: >0.999; **E: 0.033**; **F: 0.004; G: <0.001; H: <0.001; I: 0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001;** N: >0.999; O: >0.999; P: >0.999; Q: >0.999; R: >0.999;

Ref, reference, also used in the pairwise comparisons column and in Fig. 3; SD, standard deviation; NA, not applicable. The bold P-values represent the statistically significant values after correcting for multiple testing (P<0.05).

Table 3. The side bending and torsional stiffness of all the included osteosynthesis systems.

		Side-bending test			Torsion test		
Ref.	**System**	**Mean torque applied to screws (SD) in Nmm)**	**Mean stiffness (SD) in N/mm)**	**P-values (pairwise comparison)**	**Mean torque applied to screws (SD) in Nmm**	**Mean torsional stiffness (SD) in Nmm/°**	**P-values (pairwise comparison)**
A	CrossDrive 1.5 mm (2006)	248 (0.70)	1.64 (0.81)	B: 0.995; C: 0.877; **D: 0.007;** E: 0.064; **F: 0.026;** G: 0.468; H: 0.762; I: 0.670; J: 0.218; K: 0.297; L: >0.999; M: 0.224; N: 0.988; O: 0.948; P: 0.862; Q: 0.914; R: 0.991; S: 0.943	249 (1.36)	8.92 (0.52)	**B: <0.001; C: <0.001; D: 0.002; E: 0.002; F: 0.002; G: <0.001; H: <0.001; I: <0.001;** J: >0.999; **K: <0.001; L: 0.003; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
B	CrossDrive 1.5 mm (2018)	248 (1.43)	1.15 (0.05)	A: 0.995; ; C: 0.671; **D: 0.001; E: 0.002; F: <0.001; G: <0.001; H: 0.002; I: 0.001; J: <0.001; K: <0.001; L: 0.019; M: <0.001;** N: >0.999; O: 0.488; P: 0.075; **Q: 0.016;** R: >0.999; **S: 0.037**	248 (0.30)	3.61 (0.41)	**A: <0.001;** C: 0.999; **D: 0.001; E: 0.001; F: <0.001;** G: 0.138; **H: <0.001;** I: >0.999; **J: 0.001; K: 0.002; L: 0.001; M: 0.005; N: 0.005;** O: 0.971; P: 0.291; Q: 0.398; **R: 0.036;** S: 0.654
C	MaxDrive 1.5 mm	320 (0.16)	0.89 (0.23)	A: 0.877; B: 0.671; **D: <0.001; E: <0.001; F: <0.001;** G: 0.436; H: >0.999; I: 0.996; **J: 0.033;** K: 0.082; **L: 0.020; M: 0.035;** N: 0.895; O: >0.999; P: >0.999; Q: >0.999; R: 0.858; S: >0.999	320 (0.44)	3.30 (0.30)	**A: <0.001;** B: 0.999; **D: 0.001; E: 0.001; F: <0.001; G: 0.007; H: <0.001;** I: 0.666; **J: 0.001; K: 0.001; L: 0.001; M: 0.004; N: 0.004;** O: >0.999; P: 0.725; Q: 0.901; R: 0.097; S: 0.933
D	CrossDrive 2.0 mm (2006)	370 (1.02)	4.33 (0.50)	**A: 0.007; B: 0.001; C: <0.001;** E: 0.640; F: 0.987; **G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: 0.001; M: <0.001; N: 0.007; O: <0.001; P: <0.001; Q: 0.001; R: 0.001; S: 0.001**	368 (1.97)	27.8 (3.59)	**A: 0.002; B: 0.001; C: 0.001;** E: 0.860; F: 0.570; **G: 0.001; H: 0.013; I: 0.001; J: 0.001; K: 0.001 L: 0.001; M: <0.001; N: 0.002; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
E	CrossDrive 2.0 mm (2018)	369 (0.93)	3.54 (0.48)	A: 0.064; **B: 0.002; C: <0.001;** D: 0.640; F: 0.979; **G: 0.001; H: 0.001; I: 0.001; J: 0.001; K: 0.001; L: 0.004; M: 0.001; N: 0.002; O: 0.001; P: 0.001; Q: 0.002; R: 0.002; S: 0.002**	369 (0.80)	23.4 (2.96)	**A: 0.002; B: 0.001; C: 0.001;** D: 0.860; F: >0.999; G: **0.001;** H: **0.044;** I: **0.001;** J: **0.001;** K: **0.001;** L: **0.001;** M: <**0.001;** N: <**0.001;** O: <**0.001;** P: <**0.001;** Q: <**0.001;** R: <**0.001;** S: <**0.001**

Table 3. *(continued)*

		Side-bending test			Torsion test		
Ref.	**System**	**Mean torque applied to screws (SD) in Nmm)**	**Mean stiffness (SD) in N/mm)**	**P-values (pairwise comparison)**	**Mean torque applied to screws (SD) in Nmm**	**Mean torsional stiffness (SD) in Nmm/°**	**P-values (pairwise comparison)**
F	MaxDrive 2.0 mm	408 (0.32)	3.94 (0.24)	**A: 0.026; B: <0.001; C: <0.001;** D: 0.987; E: 0.979; **G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**	408 (0.29)	22.4 (2.69)	**A: 0.002; B: <0.001; C: <0.001;** D: 0.570; E: >0.999; **G: 0.001;** H: 0.051; **I: <0.001; J: 0.001; K: 0.001; L: 0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
G	Inion CPS 2.0 mm	74.5 (0.54)	0.57 (0.06)	A: 0.468; **B: <0.001;** C: 0.436; **D: <0.001; E: 0.001; F: <0.001; H: 0.014;** I: 0.051; **J: 0.001; K: 0.010; L: <0.001; M: 0.001; N: <0.001; O: 0.001; P: 0.014; Q: <0.001; R: <0.001; S: <0.001**	74.5 (0.83)	4.53 (0.35)	**A: <0.001;** B: 0.138; **C: 0.007; D: 0.001; E: 0.001; F: 0.001; H: <0.001;** I: 0.137; **J: 0.003;** K: 0.091; **L: 0.020; M: <0.001; N: <0.001; O: 0.013; P: 0.002; Q: 0.001; R: 0.003;** S: 0.060
H	Inion CPS 2.5 mm	157 (0.35)	0.82 (0.08)	A: 0.762; **B: 0.002;** C: >0.999; **D: <0.001; E: 0.001; F: <0.001; G: 0.014;** I: 0.988; **J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: 0.013;** O: 0.239; P: 0.999; Q: 0.252; **R: 0.013;** S: 0.062	157 (0.77)	15.8 (0.79)	**A: <0.001; B: <0.001; C: <0.001; D: 0.013; E: 0.044;** F: 0.051; **G: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**
I	LactoSorb 2.0 mm	97.6 (0.32)	0.75 (0.06)	A: 0.670; **B: <0.001;** C: 0.996; **D: <0.001; E: 0.001; F: <0.001;** G: 0.051; H: 0.988; **J: <0.001; K: <0.001; L: <0.001; M: <0.001; N: 0.002; O: 0.030;** P: 0.492; **Q: 0.007; R: 0.002; S: 0.001**	97.9 (0.56)	3.76 (0.29)	**A: <0.001;** B: >0.999; C: 0.666; **D: 0.001; E: 0.001; F: <0.001;** G: 0.137; **H: <0.001; J: 0.002; K: 0.005; L: 0.003; M: <0.001; N: <0.001;** O: 0.568; P: 0.084; Q: 0.079; **R: 0.023;** S: 0.420
J	Macropore 2.0 mm	62.2 (0.75)	0.24 (0.02)	A: 0.218; **B: <0.001; C: 0.033; D: <0.001; E: 0.001; F: <0.001; G: 0.001; H: <0.001; I: <0.001; K: 0.009; L: <0.001;** M: >0.999; **N: <0.001; O: <0.001; P: 0.001; Q: <0.001; R: <0.001; S: <0.001**	62.2 (0.45)	8.44 (0.96)	A: >0.999; **B: 0.001; C: 0.001; D: 0.001; E: 0.001; F: 0.001; G: 0.003; H: <0.001; I: 0.002; K: 0.022;** L: 0.126; **M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: <0.001**

Table 3. *(continued)*

		Side-bending test			Torsion test		
Ref.	**System**	**Mean torque applied to screws (SD) in Nmm)**	**Mean stiffness (SD) in N/mm)**	**P-values (pairwise comparison)**	**Mean torque applied to screws (SD) in Nmm**	**Mean torsional stiffness (SD) in Nmm/°**	**P-values (pairwise comparison)**
K	Polymax 2.0 mm	58.8 (0.23)	0.37 (0.04)	A: 0.297; **B: <0.001;** C: 0.082; **D: <0.001; E: 0.001; F: <0.001; G: 0.010; H: <0.001; I: <0.001; J: 0.009; L: <0.001; M: 0.014; N: <0.001; O: <0.001; P: 0.001; Q: <0.001; R: <0.001; S: <0.001**	57.5 (0.41)	5.73 (0.54)	**A: <0.001; B: 0.002; C: 0.001; D: 0.001; E: 0.001; F: 0.001;** G: 0.091; **H: <0.001; I: 0.005; J: 0.022;** L: 0.968; **M: <0.001; N: <0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: 0.003**
L	BioSorb FX 2.0 mm	81.5 (0.57)	1.55 (0.13)	A: >0.999; **B: 0.019; C: 0.020; D: 0.001; E: 0.004; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; M: <0.001; N: 0.008; O: 0.002; P: <0.001; Q: 0.002; R: 0.011; S: 0.004**	80.9 (0.43)	6.41 (0.66)	**A: 0.003; B: 0.001; C: 0.001; D: 0.001; E: 0.001; F: 0.001; G: 0.020; H: <0.001; I: 0.003;** J: 0.126; K: 0.968; **M: <0.001; N: 0.001; O: <0.001; P: <0.001; Q: <0.001; R: <0.001; S: 0.001**
M	Resorb X 2.1 mm	55.9 (0.26)	0.25 (0.03)	A: 0.224; **B: <0.001; C: 0.035; D: <0.001; E: 0.001; F: <0.001; G: 0.001; H: <0.001; I: <0.001;** J: >0.999; **K: 0.014; L: <0.001; N: <0.001; O: <0.001; P: 0.001; Q: <0.001; R: <0.001; S: <0.001**	55.9 (0.30)	2.14 (0.28)	**A: <0.001; B: 0.005; C: 0.004; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001;** N: >0.999; O: 0.090; P: 0.730; Q: 0.221; R: >0.999; S: >0.999
N	SW Rx + SP Rx 2.1 mm (D1.6/T-)	NA	1.11 (0.09)	A: 0.988; B: >0.999; C: 0.895; **D: 0.001; E: 0.002; F: <0.001; G: <0.001; H: 0.013; I: 0.002; J: <0.001; K: <0.001; L: 0.008; M: <0.001;** O: 0.987; P: 0.284; Q: 0.390; R: >0.999; S: 0.745	NA	2.13 (0.28)	**A: <0.001; B: 0.005; C: 0.004; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001; L: <0.001;** M: >0.999; O: 0.086; P: 0.711; Q: 0.211; R: >0.999; S: >0.999
O	SW Rx + SP Rx 2.1 mm (D1.6/T2.0)	NA	1.01 (0.10)	A: 0.948; B: 0.488; C: >0.999; **D: <0.001; E: 0.001; F: <0.001; G: 0.001;** H: 0.239; **I: 0.030; J: <0.001; K: <0.001; L: 0.002; M: <0.001;** N: 0.987; P: 0.989; Q: >0.999; R: 0.961; S: >0.999	NA	3.13 (0.44)	**A: <0.001;** B: 0.971; C: >0.999; **D: <0.001; E: <0.001; F: <0.001; G: 0.013; H: <0.001;** I: 0.568; **J: <0.001; K: <0.001; L: <0.001;** M: 0.090; N: 0.086; P: 0.998; Q: >0.999; R: 0.208; S: 0.999

Table 3. *(continued)*

		Side-bending test			Torsion test		
Ref.	**System**	**Mean torque applied to screws (SD) in Nmm)**	**Mean stiffness (SD) in N/mm)**	**P-values (pairwise comparison)**	**Mean torque applied to screws (SD) in Nmm**	**Mean torsional stiffness (SD) in Nmm/°**	**P-values (pairwise comparison)**
P	SW xG + SP Rx 2.1 mm (D1.6/T-)	NA	0.90 (0.11)	A: 0.862; B: 0.075; C: >0.999; **D: <0.001; E: 0.001; F: <0.001; G: 0.014;** H: 0.999; I: 0.492; **J: 0.001; K: 0.001; L: <0.001; M: 0.001;** N: 0.284; O: 0.989; Q: >0.999; R: 0.242; S: 0.884	NA	2.71 (0.46)	**A: <0.001;** B: 0.291; C: 0.725; **D: <0.001; E: <0.001; F: <0.001; G: 0.002; H: <0.001;** I: 0.084; **J: <0.001; K: <0.001; L: <0.001;** M: 0.730; N: 0.711; O: 0.998; Q: >0.999; R: 0.743; S: >0.999
Q	SW xG + SP Rx 2.1 mm (D1.6/T2.0)	NA	0.97 (0.06)	A: 0.914; **B: 0.016;** C: >0.999; **D: 0.001; E: 0.002; F: <0.001; G: <0.001;** H: 0.252; **I: 0.007; J: <0.001; K: <0.001; L: 0.002; M: <0.001;** N: 0.390; O: >0.999; P: >0.999; R: 0.346; S: 0.999	NA	2.87 (0.37)	**A: <0.001;** B: 0.398; C: 0.901; **D: <0.001; E: <0.001; F: <0.001; G: 0.001; H: <0.001;** I: 0.079; **J: <0.001; K: <0.001; L: <0.001;** M: 0.221; N: 0.211; O: >0.999; P: >0.999; R: 0.438; S: >0.999
R	SW xG + SP xG 2.1 mm (D1.6/T-)	NA	1.12 (0.09)	A: 0.991; B: >0.999; C: 0.858; **D: 0.001; E: 0.002; F: <0.001; G: <0.001; H: 0.013; I: 0.002; J: <0.001; K: <0.001; L: 0.011; M: <0.001;** N: >0.999; O: 0.961; P: 0.242; Q: 0.346; S: 0.666	NA	1.86 (0.67)	**A: <0.001; B: 0.036;** C: 0.097; **D: <0.001; E: <0.001; F: <0.001 G: 0.003; H: <0.001; I: 0.023; J: <0.001; K: <0.001; L: <0.001;** M: >0.999; N: >0.999; O: 0.208; P: 0.743; Q: 0.438; S: 0.995
S	SW xG + SP xG 2.1 mm (D1.6/T2.0)	NA	1.01 (0.04)	A: 0.943; **B: 0.037;** C: >0.999; **D: 0.001; E: 0.002; F: <0.001; G: <0.001;** H: 0.062; **I: 0.001; J: <0.001; K: <0.001; L: 0.004; M: <0.001;** N: 0.745; O: >0.999; P: 0.884; Q: 0.999; R: 0.666	NA	2.58 (0.82)	**A: <0.001;** B: 0.654; C: 0.933; **D: <0.001; E: <0.001; F: <0.001;** G: 0.060; **H: <0.001;** I: 0.420; **J: <0.001; K: 0.003; L: 0.001;** M: >0.999; N: >0.999; O: 0.999; P: >0.999; Q: >0.999; R: 0.995

Ref, reference, also used in the pairwise comparison column and in Fig. 4 and 5; SD, standard deviation; NA, not applicable. The bold P-values represent the statistically significant values after correcting for multiple testing (P<0.05).

Discussion

The aim of this study was to be able to guide surgeons in the selection of osteosynthesis systems. We determined and compared the mechanical properties of biodegradable and titanium osteosynthesis systems used in OMF-surgery. The pull-out load of the SonicPins Rx and xG systems was comparable, irrespective of whether the burr hole was tapped or not. The CrossDrive (2018) and MaxDrive titanium systems demonstrated lower tensile and torsional stiffness accompanied with higher ductility than the corresponding CrossDrive (2006) systems. The side bending stiffness of the 1.5 mm titanium systems was comparable to, and that of the 2.0 mm systems was higher than, the biodegradable systems. Regarding the biodegradable systems, the Inion CPS 2.5 mm had the highest tensile load and torsional stiffness, all the SonicWeld 2.1 mm systems had the highest tensile stiffness, and the BioSorbFX 2.0 mm had highest side bending stiffness. On the basis of the results of this study recommendations are made and discussed below which biodegradable and titanium osteosynthesis systems are preferably used for fracture and osteotomy fixation in OMF-surgery (Table 4).

Table 4. Proposal for recommended titanium and biodegradable osteosynthesis systems for specific indications

Indications	Titanium systems	Biodegradable systems
Midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomy)	MaxDrive or CrossDrive (2018) 1.5 mm[a]	SonicWeld Rx/Rx 2.1 mm or BioSorb FX 2.0 mm
Fractures where high torsional forces are expected (e.g., mandibular symphysis fractures)	MaxDrive or CrossDrive (2018) 2.0 mm[a]	1. Inion CPS 2.5 mm[b] 2. BioSorb 2.0 mm[b]
Mandibular osteotomies (e.g. bilateral sagittal split osteotomy) and non-load bearing mandibular fractures other than symphysis fractures	MaxDrive or CrossDrive (2018) 2.0 mm[a]	Inion CPS 2.5 mm[c]

Note that the recommendations are made based on the tested osteosynthesis systems. [a]There is no clinically relevant mechanical difference between the CrossDrive (2018) and MaxDrive systems; [b]The Inion CPS 2.5 mm system has the most favourable mechanical properties, but whenever the bulkiness of this system is considered an issue, the BioSorb FX 2.0 mm is a suitable alternative (i.e., -58% in volume).[c]This is the only biodegradable system that is certified for the specific indication and that could be tested in this study (i.e., OsteotransMX mechanical properties were insufficient to be tested in this study).

The mechanical properties of osteosynthesis systems depend on several factors including composition (i.e., titanium (alloys) or (co-)polymers), the production processes of titanium systems (e.g., stamping versus laser cutting)[31–33], dimensions, self-reinforcing of polymers[34], the application method (i.e., screws or thermoplastic pins)[12],

ageing, and sterilization methods[35–37]. Self-reinforcing polymers is a manufacturing technique whereby the polymers are orientated in reinforcing units, such as fibrils or fibers, and the binding matrix has the same chemical structure[34]. This high degree of molecular orientation results in improved mechanical properties compared to identical polymers and dimensions[38].

The pull-out loads of SonicPins Rx and xG were comparable, but tapping the SonicPins Rx burr hole lowered the pull-out stiffness. This could be due to the fact that tapping the burr hole increases the volume of the burr hole, while the the pin's volume remains the same. Therefore, the density of the pin in the burr hole is lowered which then decreases the stiffness. This indicates that the volume of the SonicPin Rx in the burr hole is a limiting factor that lowers the pull-out stiffness compared to not tapping the burr hole. On the other hand, this effect did not occur with the SonicPin xG indicating that, although the volume of the SonicPin xG in the burr hole is also lowered, compared to not tapping the burr hole, the stiffness of the copolymer itself is sufficient to sustain the pull-out stiffness.

The plate and screw dimensions are important characteristics when evaluating mechanical properties of osteosynthesis systems. In particular, the tensile load and torsional stiffness increase significantly when the cross sectional area increases as shown by the results of the Inion CPS 2.0 versus 2.5 mm systems[39]. The effects of self-reinforcing polymers is demonstrated by the differences in the mechanical properties of the BioSorb FX 2.0 mm (SR 70/30 PLLA/PDLLA) and Polymax 2.0 mm (70/30 PLLA/PDLLA) systems. Furthermore, the effect of the application method (i.e., melting of thermoplastic pins in the plates compared to usage of screws) is demonstrated by the mechanical properties of the Resorb X (100% PDLLA with screws) compared to the SonicWeld Rx/Rx (100% PDLLA with thermoplastic pins) systems. Additionally, the origin of the failure of all the SonicWeld systems shows that melting the pins within the plates causes a shift of the weakest link of the complete osteosynthesis system from the screw-plate interface (i.e., all other biodegradable systems) to the plate itself (i.e., SonicWeld and titanium systems).

Several studies have assessed the mechanical forces surrounding osteosyntheses applied to maxillofacial fractures[28,40–44], osteotomies[45,46] and reconstructions[47]. After maxilofacial trauma, the reported bite force at fracture fixation increases up to 64N by the second postoperative day, 92N after 1 week, 187N after 4 weeks, and to 373N at the 3-month follow-up[40]. Other studies focusing on trauma patients showed that 100N forces were measured after 4 weeks of fixation[41,43]. The mechanical forces around maxillofacial

osteotomies have been reported to increase from 21±14N (i.e., after 1 week) to 65±43N (i.e., after 6 weeks)[42] while other studies report forces ranging from 82.5 to 132N[45,46]. The masticatory forces after mandibular reconstructions range from 28 to 186N[47]. These reported data indicate that the mechanical properties of all the titanium and most of the biodegradable osteosynthesis systems are sufficient for adequate fixation. However, the mechanical stress surrounding osteosynthesis systems is multi-factorial and is affected by the location of the fracture, differences in interfragmentary stability (i.e., of fractures), mandibulair height (i.e., following fractures, osteotomies and reconstructions), degree and direction of movement (i.e., after an osteotomy), and preoperative mastericatory forces[29,41,48]. Additionally, as bone healing progresses, the forces will be shared by the osteosynthesis system and the underlying bone. Therefore, it remains difficult to estimate the least mechanical properties an osteosynthesis system has to meet.

Although high mechanical osteosynthesis properties are sought for adequate fixation, the extreme stiffness of the titanium systems is a disadvantage due to the stress shielding of the underlying bone[4]. A remarkable reduction in tensile, side bending, and torsional stiffnesses of the CrossDrive (2018) and MaxDrive compared to the CrossDrive (2006) systems was observed, while their tensile loads were comparable. The reduction in stiffnesses is the result of an adapted production process of the newer CrossDrive (2018) and MaxDrive systems compared to the older CrossDrive (2006) system. In 2007, the production process of the KLS Martin titanium systems was altered from stamping (also known as metal pressing) to milling of plates. Differences in manufacturing processes (e.g., heat treatment during stamping of plates) are known to alter the mechanical properties of titanium[16,31,32,49–51]. The reduction in stiffness may be beneficial as this may reduce bone stress shielding and thus should be assessed *in vivo* in future research. Additionally, the CrossDrive (2018) and MaxDrive showed higher ductility compared to the CrossDrive (2006) systems. This is also preferred since it demonstrates that the CrossDrive (2018) and MaxDrive plates undergo more plastic deformation compared to the CrossDrive (2006) plates before fracturing. The CrossDrive (2018) and MaxDrive systems still meet the ASTM and ISO standard requirements for surgical titanium implants[52–55]. Additionally, this study shows that the newer CrossDrive (2018) and MaxDrive osteosynthesis systems remain to have higher mechanical properties than the tested biodegradable osteosynthesis systems. However, as clinical studies have shown that biodegradable and titanium osteosynthesis systems have similar efficacy in maxillofacial traumatology[9], both systems have mechanical properties that suffice for clinical application.

Three important aspects have to be noted before recommondations for clinical use can be made. First, it must be noted that statistical differences do not imply clinically relevant differences. Second, the stiffness of an osteosynthesis system is a more clinically relevant outcome than load since this affects adequate fixation and bone healing (i.e., malunion and non-union)[56] while tensile load is only relevant whenever the bone segments have been separated by more than a few millimeters. In the latter case, this will certainly result in compromised bone healing or malunion. Thirdly, although extreme tensile stiffness is a concern in titanium systems due to stress shielding, it is not a concern when using biodegradable systems as they undergo bulk degradation thereby decreasing their mechanical properties with time[13].

Our study aimed to guide OMF-surgeons in the selection of titanium and biodegradable osteosynthesis systems. The CrossDrive (2018) and MaxDrive 1.5 mm titanium systems are recommended for midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomy), and the CrossDrive (2018) and MaxDrive 2.0 mm titanium systems for mandibular fractures and osteotomies when a titanium osteosynthesis system is used (Table 4). The CrossDrive (2018) or MaxDrive systems are prescribed over the CrossDrive (2006) system as all tested titanium systems meet the ASTM and ISO standard requirements for surgical titanium implants while the higher ductality and lower stiffness of the CrossDrive (2018) and MaxDrive could be benificial in clinical use. The reduction in stiffness may reduce stress shielding of the underlying bone, although further *in vivo* research is necessary to prove this. There is no clinically relevant mechanical difference between the CrossDrive (2018) and MaxDrive systems. The manufacturer states that the adapted screw head of the MaxDrive system could result in better perioperative handling by surgeons, but this still has to be assessed objectively.

When there is an indication for a biodegradable osteosynthesis system, the SonicWeld Rx/Rx 2.1 mm or BioSorbFX 2.0 mm systems are recommended to fixate midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomies) due to their high tensile and side bending stiffness, respectively (Table 4)[57,58]. Both systems have their own advantages regarding perioperative handeling, viz., the possibility to adapt the BioSorb FX plate at room temperature[34] and the avoidance of tapping the burr holes when using the SonicWeld system[57]. When also considering the dimensions and volumes, and the (co-)polymer compositions of these two systems, the SonicWeld Rx/Rx system is preferred as it is less bulky (i.e., -14% in volume) and has a more favourable degradative copolymer composition[13,59]. Whenever low pull-out forces are expected, we recommend not tapping the SonicPins burr holes as this remains an

extra perioperative, time-consuming step for surgeons[9]. On the other hand, whenever high torsional forces are expected (e.g., fixating mandibular symphysis fractures[41]), the Inion CPS 2.5 mm system is recommended although it might be bulky due to the plate and screw dimensions. Whenever the bulkiness of this system is considered an issue (e.g., complicating stress free closure of the incision or due to palpability), the BioSorb FX 2.0 mm is a suitable alternative (i.e., -58% in volume; Table 4). Only two of the tested biodegradable osteosynthesis systems (i.e., Inion CPS 2.5 mm and OsteotransMX 2.0 mm with plate thickness of 1.4 mm) are certified to be used for mandibular osteotomies and non-load bearing mandibular fractures other than mandibular symphysis fractures[59,60]. Therefore, as the OsteotransMX 2.0 mm has insufficient mechanical properties to be tested in our study, we recommend the Inion CPS 2.5 mm system for fixation of mandibular osteotomies (e.g., bilateral sagittal split osteotomy) and non-load bearing mandibular fractures other than symphysis fractures (Table 4). However, it must be noted that, although the mechanical propterties of the Inion CPS 2.5 mm system are sufficient for for fixation of mandibular osteotomies, a randomized controlled trial reported a significantly higher symptomatic plate removal risk of the Inion CPS 2.5 mm compared to the CrossDrive (2018) 2.0 mm titanium system after fixation of BSSOs[2]. Therefore, when choosing an appropriate osteosynthesis system for fixation of mandibular osteotomies, we recommend OMF-surgeons to take both aspects (i.e., the mechanical properties and the risk of symptomatic plate removal) into account.

This is the most comprehensive study to date comparing various commonly used titanium and biodegradable osteosynthesis systems in OMF-surgery. Other strengths of this study are the standardized and reproducable osteosynthesis systems application methods (e.g., screws inserted using the mean applied torque by four experienced OMF-surgeons), usage of standardized test setups, and the assessment of a variety of outcomes that are relevant to clinical practice (i.e., tensile and pull-out load, and tensile, pull-out, side-bending, and torsional stiffness). Additionally, to ensure comparability, all the osteosynthesis systems were applied by one researcher (BG) while the tests were performed by another researcher (CCR). Furthermore, PMMA was chosen instead of bone blocks for all the tests because the variability in bone mineral density, in cortical and spongious bone layer thickness, and in block dimensions impede the latter's use as a standardized and reproducible model as these factors may confound the results of the mechanical tests. The mechanical properties of PMMA are similar to bone[22–24], the quality of each PMMA-block is similar (i.e., no variability in density), and blocks with identical dimensions can be easily fabricated, which ensures standardization and reproducibility of the test setups.

A limitation of this study is that the insertion of the SonicPins could not be quantified, as was done with the torque applied to the screws, because the pins are melted into the burr holes. We tried to address this by having one researcher (BG) insert the pins and by using a minimum and maximum amount of time (i.e., one and two seconds per pin, respectively) as a quantifying measure of insertion. Furthermore, the Osteotrans-MX system could not be tested due to the screw heads failing before the screws were fully screwed in. This indicates that PMMA is not suitable for testing the screws' mechanical properties. Using allo- or xenograft bone may address this limitation. However, we did not perform tests in bone due to the abovementioned limitations of bone and the fact that all the other osteosynthesis systems could be tested in PMMA, thus ensuring standardization and reproducibility of the test setups.

Conclusions

In conclusion, this study shows that the pull-out load and stiffness of SonicPinx Rx and xG are comparable and that tapping the burr hole does not improve the pull-out load and stiffness significantly. Furthermore, the KLS CrossDrive (2018) and MaxDrive titanium systems have significantly lower tensile and torsional stiffness, combined with higher ductility, than the corresponding CrossDrive (2006) titanium systems, while maintaining similar tensile load. The reduction in stiffness may reduce stress shielding of the underlying bone, although the clinical relevance of the reduction in stiffness was not investigated in this study. On the basis of the results of this study, the CrossDrive (2018) and MaxDrive 1.5 mm titanium systems are recommended for midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomy), and the CrossDrive (2018) and MaxDrive 2.0 mm titanium systems for mandibular fractures and osteotomies when a titanium osteosynthesis system is used. When there is an indication for a biodegradable osteosynthesis system, the SonicWeld 2.1 mm or BioSorbFX 2.0 mm are recommended for midface fractures and osteotomies, and the Inion CPS 2.5 mm biodegradable system for mandibular osteotomies and non-load bearing mandibular fractures, especially when high torsional forces are expected (e.g., mandibular symphysis fractures).

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Conflict of interests

The authors state that they have no conflict of interests.

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Supplementary data

Supplementary tables:

Table S1: The pull-out load and stiffness of SonicPins Rx and xG without and with tapping the burr holes.

Table S2: The torque applied until hand-tight fixation (i.e., the mean of four experienced oral and maxillofacial surgeons) and until screw breakage of all the included osteosynthesis systems.

Supplementary figures:

Figure S1: The torque applied until hand-tight fixation (i.e., the mean of four experienced oral and maxillofacial surgeons) and until screw breakage of all the included osteosynthesis systems. The characters in green and orange represent significant differences in maximum torque (Nmm) until hand-tight fixation and until breakage, respectively. *Error bars: mean values ± standard deviation. The dotted line separates the titanium (left) and biodegradable systems (right). All the values, including the P-values of the pairwise comparisons, are reported in Supplementary Table S2.*

Figure S2: Force-displacement graphs derived from the tensile test of the KLS SonicWeld Rx osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

Figure S3: Force-displacement graphs derived from the side bending test of the KLS SonicWeld Rx osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

Figure S4: Force-displacement graphs derived from the torsion test of the KLS SonicWeld Rx 2.1mm osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

Figure S5: Force-displacement graphs derived from the tensile test of the KLS MaxDrive, CrossDrive (2006), and CrossDrive (2018) 1.5 mm osteosynthesis systems, indicating higher ductility of the CrossDrive (2018) and MaxDrive systems compared to the CrossDrive (2006) system.

Figure S6: Force-displacement graphs derived from the tensile test of the KLS MaxDrive, CrossDrive (2006), and CrossDrive (2018) 2.0 mm osteosynthesis systems, indicating higher ductility of the CrossDrive (2018) and MaxDrive systems compared to the CrossDrive (2006) system.

Table S1. The pull-out load and stiffness of SonicPins Rx and xG without and with tapping the burr holes.

				Maximum load		Stiffness	
Ref	**System**	**Drill (mm)**	**Tap (mm)**	**Mean Fmax (SD) in N**	**P-values (pairwise comparison)**	**Mean stiffness (SD) in N/mm**	**P-values (pairwise comparison)**
1	SonicPin Rx 2.1mm	1.6	None	55.5 (14.5)	**2: 0.001;** 3: 0.539; 4: 0.474; 5: >0.999; 6: 0.423	117 (7.14)	**2: 0.002;** 3: 0.278; **4: 0.024;** 5: >0.999; 6: >0.999
2	SonicPin Rx 2.1mm	1.6	1.7	29.7 (7.08)	**1: 0.001;** 3: 0.304; **4: <0.001; 5: <0.001; 6: <0.001**	93.4 (6.53)	**1: 0.002;** 3: 0.774; 4: 0.468; **5: 0.020; 6: 0.0**01
3	SonicPin Rx 2.1mm	1.6	1.8	43.3 (11.1)	1: 0.539; 2: 0.304; **4: 0.002;** 5: 0.316; **6: 0.001**	103 (12.1)	1: 0.278; 2: 0.774; 4: >0.999; 5: 0.390; 6: 0.260
4	SonicPin Rx 2.1mm	1.6	2.0	68.0 (6.94)	1: 0.474; **2: 0.001; 3: 0.002;** 5: 0.793; 6: >0.999	101 (6.25)	**1: 0.024;** 2: 0.468; 3: >0.999; 5: 0.137; **6: 0.010**
5	SonicPin xG 2.1mm	1.6	None	56.8 (9.50)	1: >0.999; **2: <0.001;** 3: 0.316; 4: 0.793; 6: 0.712	118 (11.4)	1: >0.999; **2: 0.020;** 3: 0.390; 4: 0.137; 6: >0.999
6	SonicPin xG 2.1mm	1.6	2.0	68.3 (5.83)	1: 0.423; **2: <0.001; 3: 0.001;** 4: >0.999; 5: 0.712	117 (5.05)	1: >0.999; **2: 0.001;** 3: 0.260; **4: 0.010;** 5: >0.999

Ref, reference, also used in the column for pairwise comparisons and in Fig. 2; SD, standard deviation. The bold P-values represent the statistically significant values after correcting for multiple testing (P<0.05).

Table S2. The torque applied until hand-tight fixation (i.e., the mean of four experienced oral and maxillofacial surgeons) and until screw breakage of all the included osteosynthesis systems.

			Hand tight		Break
Ref.	**System**	**Mean torque (SD) in Nmm**	**P-values (pairwise comparison)**	**Mean torque (SD) in Nmm**	**P-values (pairwise comparison)**
A	CrossDrive 1.5 mm	247 (89.1)	**B: 0.046; C: 0.002; D: 0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**	396 (9.00)	**B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**
B	MaxDrive 1.5 mm	319 (65.2)	**A: 0.046;** C: 0.951; D: 0.306; **E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**	528 (16.9)	**A: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**
C	CrossDrive 2.0 mm	367 (122)	**A: 0.002;** B: 0.951; D: >0.999; **E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**	>680	A: **<0.001;** B: **<0.001;** D: **-;** E: **<0.001;** F: **<0.001;** G: **<0.001;** H: **<0.001;** I: **<0.001;** J: **<0.001;** K: **<0.001**
D	MaxDrive 2.0 mm	407 (138)	**A: 0.001;** B: 0.306; C: >0.999; **E: <0.001; F: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**	>680	A: **<0.001;** B: **<0.001;** C:-; E: **<0.001;** F: **<0.001;** G: **<0.001;** H: **<0.001;** I: **<0.001;** J: **<0.001;** K: **<0.001**
E	Inion CPS 2.0 mm	73.4 (12.2)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; F: <0.001; G: <0.001; H: 0.005; I: <0.001;** J: 0.999; **K: <0.001**	85.1 (12.3)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; F: <0.001; G: <0.001;** H: 0.950; I: >0.999; **J: <0.001;** K: 0.839
F	Inion CPS 2.5 mm	157 (18.0)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; G: <0.001; H: <0.001; I: <0.001; J: <0.001; K: <0.001**	181 (5.49)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001;** G: 0.998; **H: <0.001; I: <0.001;** J: 0.826; **K: <0.001**
G	LactoSorb 2.0 mm	96.9 (23.5)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; H: <0.001; I: <0.001;** J: 0.261; **K: <0.001**	189 (15.7)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001;** F: 0.998; **H: <0.001; I: <0.001;** J: >0.999; **K: <0.001**
H	Macropore 2.0 mm	61.7 (10.2)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: 0.005; F: <0.001; G: <0.001;** I: 0.994; **J: 0.009;** K: 0.688	77.2 (5.05)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001;** E: 0.950; **F: <0.001; G: <0.001;** I: 0.175; **J: <0.001;** K: >0.999
I	Polymax 2.0 mm	56.7 (14.3)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001;** H: 0.994; **J: 0.001;** K: >0.999	89.5 (8.92)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001;** E: >0.999; **F: <0.001; G: <0.001;** H: 0.175; **J: <0.001;** K: 0.223

Table S2. *(continued)*

			Hand tight		Break
Ref.	**System**	**Mean torque (SD) in Nmm**	**P-values (pairwise comparison)**	**Mean torque (SD) in Nmm**	**P-values (pairwise comparison)**
J	BioSorb FX 2.0 mm	80.2 (23.4)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001;** E: 0.999; **F: <0.001;** G: 0.261; **H: 0.009; I: 0.001; K: <0.001**	192 (14.2)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001;** F: 0.826; G: >0.999; **H: <0.001; I: <0.001; K: <0.001**
K	ResorbX 2.1 mm	55.4 (11.5)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001; E: <0.001; F: <0.001; G: <0.001;** H: 0.688; I: >0.999; **J: <0.001**	82.9 (11.9)	**A: <0.001; B: <0.001; C: <0.001; D: <0.001;** E: 0.839; **F: <0.001; G: <0.001;** H: >0.999; I: 0.223; **J: <0.001**

Ref, reference, also used in the pairwise comparisons column and in Fig. S1; SD, standard deviation.
The bold P-values represent statistically significant values after correcting for multiple testing (P<0.05).

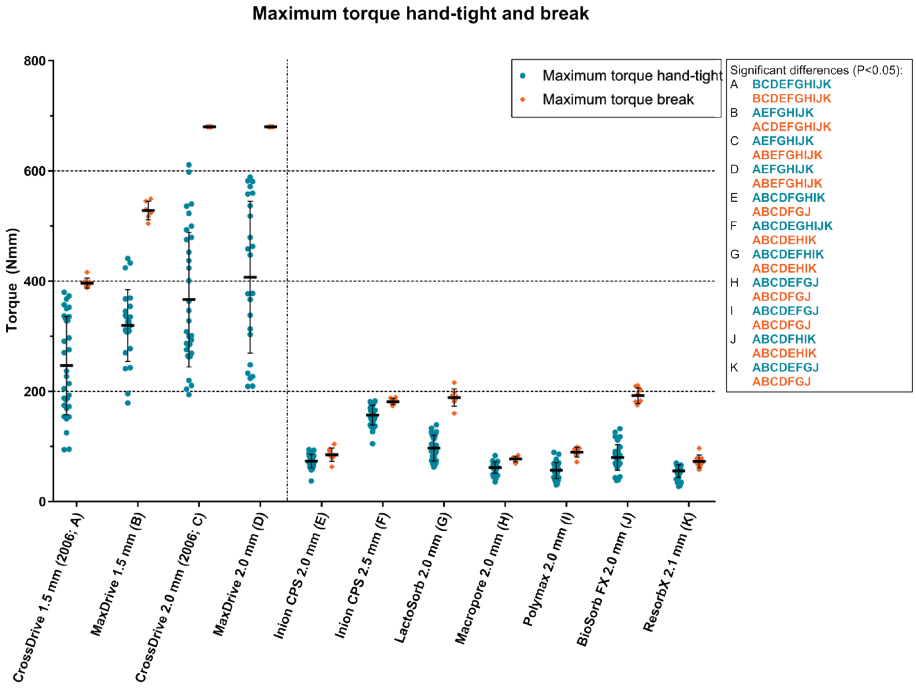


Figure S1. The torque applied until hand-tight fixation (i.e., the mean of four experienced oral and maxillofacial surgeons) and until screw breakage of all the included osteosynthesis systems. The characters in green and orange represent the significant differences in maximum torque (Nmm) until hand-tight fixation and until breakage, respectively. *Error bars: mean values ± standard deviation. The dotted line separates the titanium (left) and biodegradable systems (right). All the values, including the P-values of the pairwise comparisons, are reported in Table S2.*

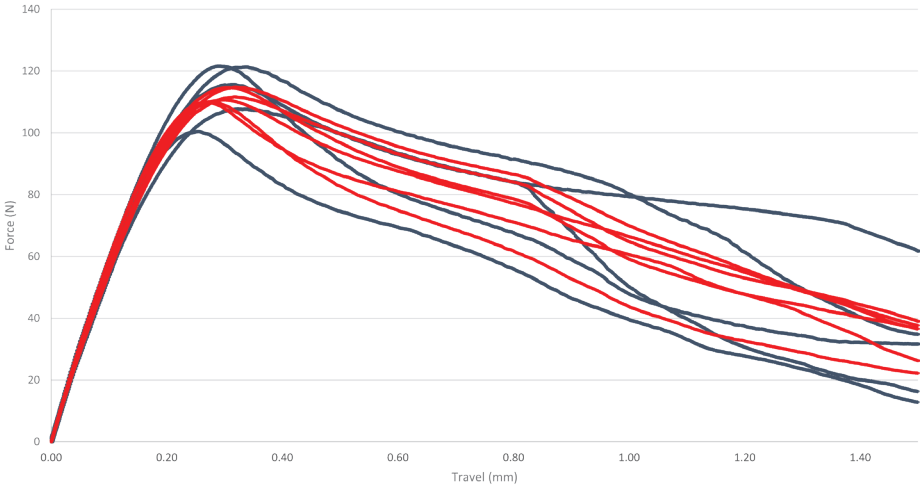


Figure S2. Force-displacement graphs derived from the tensile test of the KLS SonicWeld Rx osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

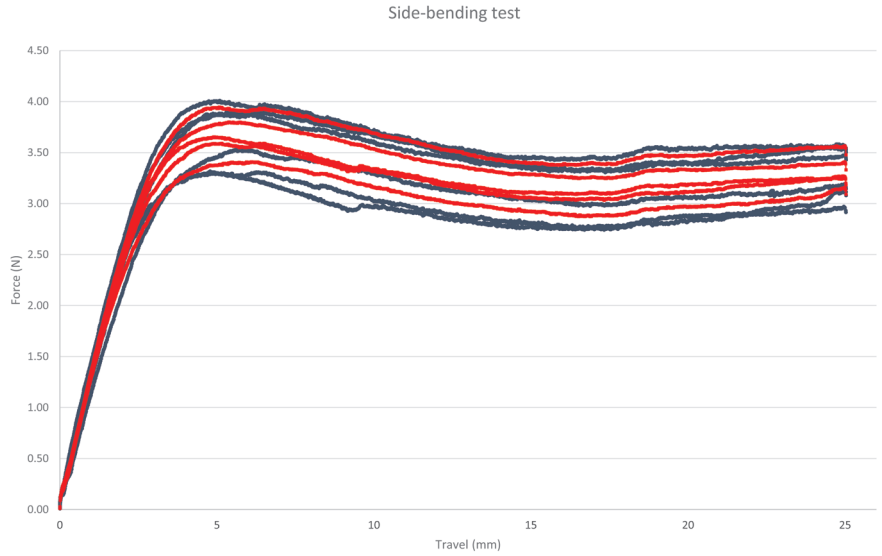


Figure S3. Force-displacement graphs derived from the side bending test of the KLS SonicWeld Rx osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

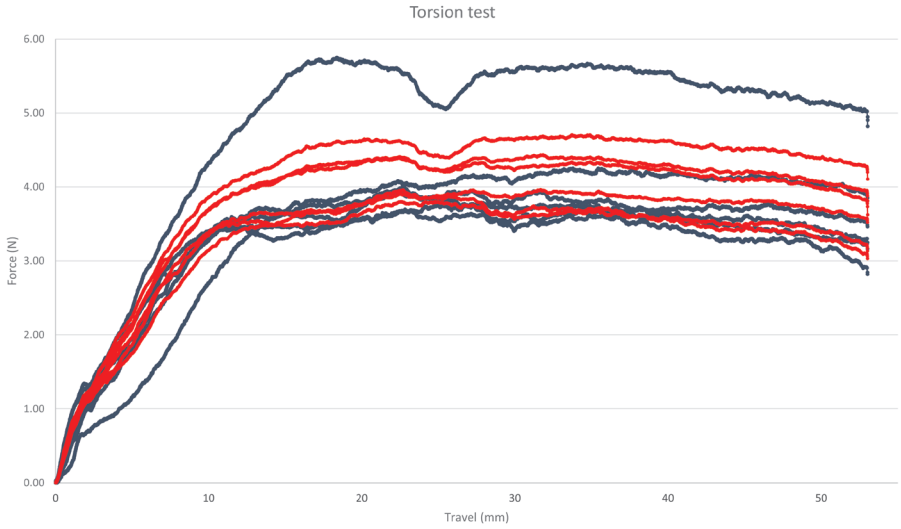


Figure S4. Force-displacement graphs derived from the torsion test of the KLS SonicWeld Rx 2.1mm osteosynthesis system. The blue (n=6) and red lines (n=6) represent the results from our previous[1] and current studies, respectively.

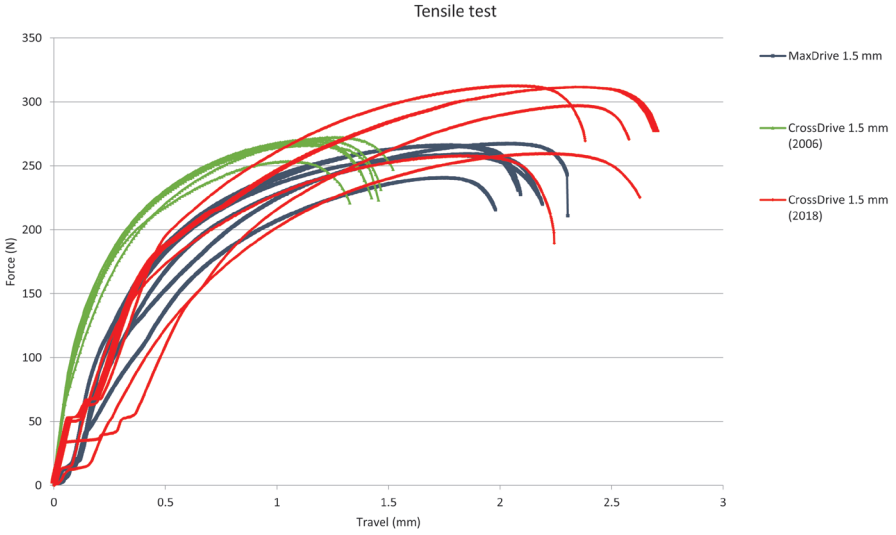


Figure S5. Force-displacement graphs derived from the tensile test of the KLS MaxDrive, CrossDrive (2006), and CrossDrive (2018) 1.5 mm osteosynthesis systems, indicating higher ductility of the CrossDrive (2018) and MaxDrive systems compared to the CrossDrive (2006) system.

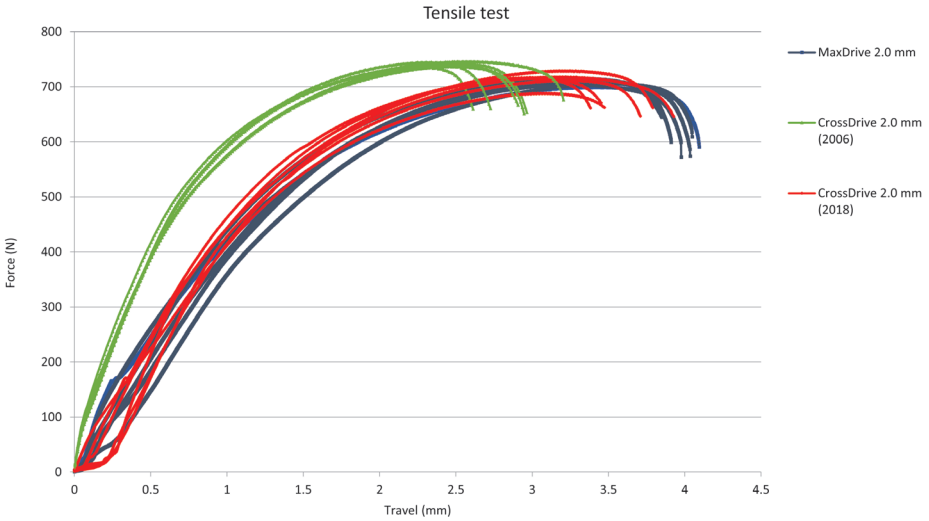
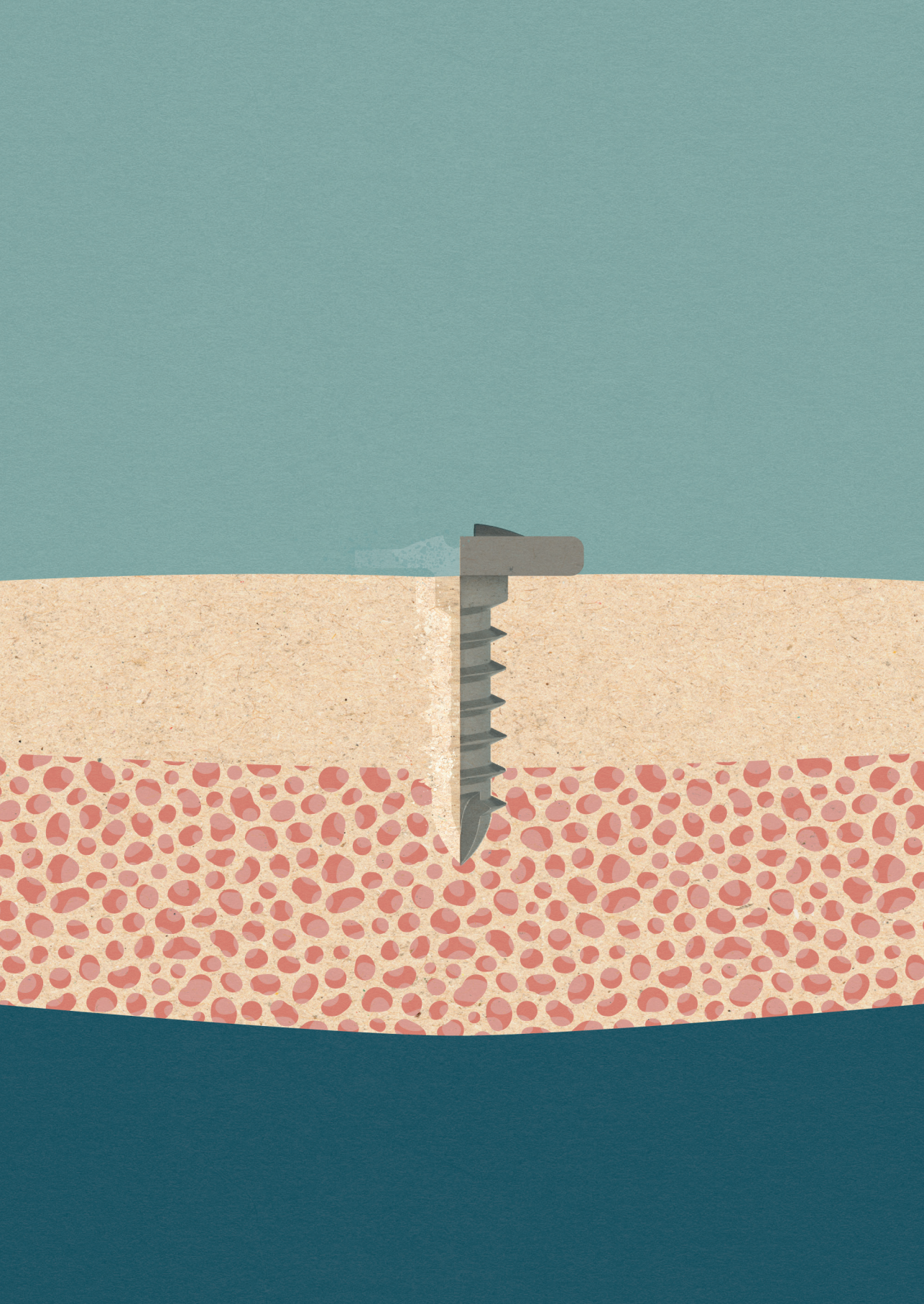


Figure S6. Force-displacement graphs derived from the tensile test of the KLS MaxDrive, CrossDrive (2006), and CrossDrive (2018) 2.0 mm osteosynthesis systems, indicating higher ductility of the CrossDrive (2018) and MaxDrive systems compared to the CrossDrive (2006) system.

Reference of supplementary data

1. Buijs, G. J., van der Houwen, E. B., Stegenga, B., Verkerke, G. J. & Bos, R. R. M. Mechanical Strength and Stiffness of the Biodegradable SonicWeld Rx Osteofixation System. *J. Oral Maxillofac. Surg.* **67**, 782–787 (2009).



Chapter 8

Reliability and accuracy of the torque applied to osteosynthesis screws by maxillofacial surgeons and residents

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Abstract

Applying the right torque to osteosynthesis screws is important for undisturbed bone healing. This study aimed to compare test-retest and intra-individual reliabilities of the torque applied to 1.5 mm and 2.0 mm osteosynthesis screws by residents and oral and maxillofacial surgeons (OMF-surgeons), to define the reference torque intervals, and to compare reference torque interval compliances. Five experienced OMF-surgeons and 20 residents, 5 of each 4 residency years, were included. Each participant inserted six 1.5x4 mm and six 2.0x6 mm screws into a preclinical model at two test moments two weeks apart (T1 and T2). Participants were blinded for the applied torque. Descriptive statistics, reference intervals, and intra-class correlation coefficients (ICC) were calculated. The OMF-surgeons complied more to the reference intervals (1.5 mm screws: 95% and 2.0 mm screws: 100%) than the residents (82% and 90%, respectively; P=0.009 and P=0.007) with the ICCs ranging between 0.85-0.95 and 0.45-0.97, respectively. The residents' accuracy and reliability were inadequate regarding the 1.5 mm screws but both measures improved at T2 for both screw types compared to T1, indicating a learning effect. Training residents and/or verifying the applied torque by experienced OMF-surgeons remains necessary to achieve high accuracy and reliability, particularly for 1.5 mm screws.

Introduction

Osteosynthesis screws are the most commonly used implants worldwide[1]. Titanium osteosynthesis systems are important for maxillofacial traumatology, orthognathic surgery and reconstructive surgery[2,3]. The amount of torque applied to the screws contributes to (primary) fracture or osteotomy stability by generating compression and friction between the osteosynthesis system and underlying bone[4,5]. Insufficient screw torque may lead to mobility of bone segments, loosening of screws and disturbed fracture healing, especially on implementing load-bearing osteosyntheses[1]. Applying excessive torque can cause loose screws due to bone stripping or screw breakage[1].

Currently, applying suitable torque to osteosynthesis screws is based on the surgeon's "feeling". Residents are instructed to insert screws with sufficient torque while minimizing the chance of stripping the screw holes or breaking the screws[6]. However, even experienced surgeons are not able to rely fully on their senses[6–9]. A recent systematic review showed that, on average, 26% of all inserted osteosynthesis screws are irreparably damaged or have stripped screw holes, that the awareness of any stripping is poor, and that the variability between surgeons is high[1]. The authors concluded that the optimum torque for different osteosynthesis screws remains unknown and that future research should focus on defining reference torque intervals and developing methods to train clinicians to apply osteosynthesis screws accurately and reliably[1]. Currently, there is no reference torque interval (i.e., a minimum and maximum torque value for safe and adequate bone fixation) for maxillofacial osteosynthesis screws. It is also unknown whether years of experience increases compliance with a predefined reference torque interval (i.e., accuracy) and reliability in the application of osteosynthesis screws.

To enable evidence-based, standardized, and reliable guidance in the application of osteosynthesis screws and to illustrate a simple and low-cost setup to train clinicians, this study aimed to: (1) assess the test-retest and intra-individual reliabilities of the torque applied by residents and experienced OMF-surgeons, (2) define a reference torque interval for the commonly used 1.5 and 2.0 mm osteosynthesis screws and, (3) compare the compliance with the reference torque interval between OMF-surgeons and residents with varying years of experience.

Materials and methods

The most commonly used titanium osteosynthesis screws in oral and maxillofacial (OMF)-surgery were selected, i.e. the 1.5x4 mm and 2.0x6 mm KLS Martin MaxDrive®

screws (Gebrüder Martin GmbH & Co., Tuttlingen, Germany)[2,3,10]. Predrilled 36x36 mm high-pressure laminate (HPL) blocks were chosen as a reproducible model, with a similar elastic modulus as cortical bone[11–13]. Predrilling was performed in a standardized manner with water cooling and using the 1.1 and 1.5 mm diameter drills provided by the manufacturer. To simulate the clinical situation, the thickness of the HPL blocks used for the 1.5 mm screws was 1.0 mm as these screws are commonly used in the midface where the bone is generally thin (e.g., the anterior wall of the maxillary sinus; Fig. 1a). The HPL blocks used for the 2.0 mm screws were 6.0 mm thick as these screws are more commonly used in thick cortical bone (e.g., in the mandible; Fig. 1b)[14].

A total of 25 participants were included: five experienced OMF-surgeons (i.e., with many years' weekly exposure to these osteosynthesis systems in the clinic) and five randomly chosen residents from each of the four residency years (i.e., a total of 20 residents) from University Medical Center Groningen (UMCG, Groningen, the Netherlands) and the Amsterdam University Medical Centers (Amsterdam UMC, the Netherlands), namely Academic Medical Center (AMC) and 'Vrije Universiteit' Medical Center (VUmc). The participants were asked to insert 6 screws of each size as they would do in the clinic ('two-finger tight') at two test moments (T1 and T2) two weeks apart (Fig. 2). The participants were blinded for the applied torque during both test moments. The burr holes were irrigated with water while inserting the screws to simulate the clinical situation. Saline was avoided to prevent possible corrosion of the test environment. The use of water instead of saline was not expected to influence the test results[10]. The applied torque was measured using a calibrated torque meter (Nemesis Howards Torque Gauge, Smart MT-TH 50 sensor; accuracy 2.5 Nmm; Fig. 1c). Screw breakage and stripped screw holes were recorded.

All the participants were asked for the amount of experience with osteosynthesis systems (also from other disciplines, e.g. orthopaedics, traumatology) and, regarding the residents, the current internship and the number of, and which, internships were completed during their residency.

All methods were carried out in accordance with relevant guidelines and regulations, including the Declaration of Helsinki. The protocol of this study was approved by the Institutional Review Board of the University Medical Center Groningen, the Netherlands. All participants provided written informed consent.

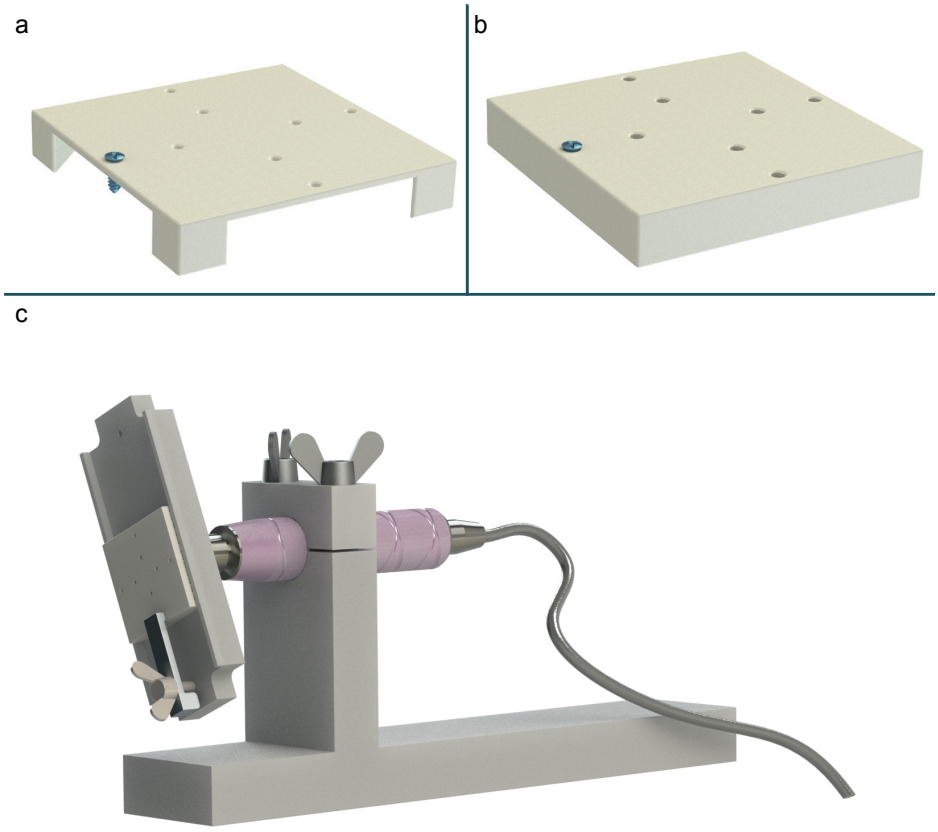

Figure 1: Example of (a) a high-pressure laminate (HPL) block with 1 mm thickness used for the 1.5 mm screws and (b) an HPL block with 6 mm thickness used for the 2.0 mm screws. Note that the screw goes through the 1 mm thick HPL plate (a), i.e. simulating a screw that goes through thin cortical bone (e.g., the anterior wall of the maxillary sinus) while the screw does not go through the 6 mm HPL block (b), i.e. simulating a bone screw in cortical bone. (c) The test setup with a torque meter with an inserted HPL block. The HPL-block was positioned in such a way that the screw hole of the HPL-block that was used to insert the screw was always aligned with the axis of the torque meter to ensure accurate torque measurement

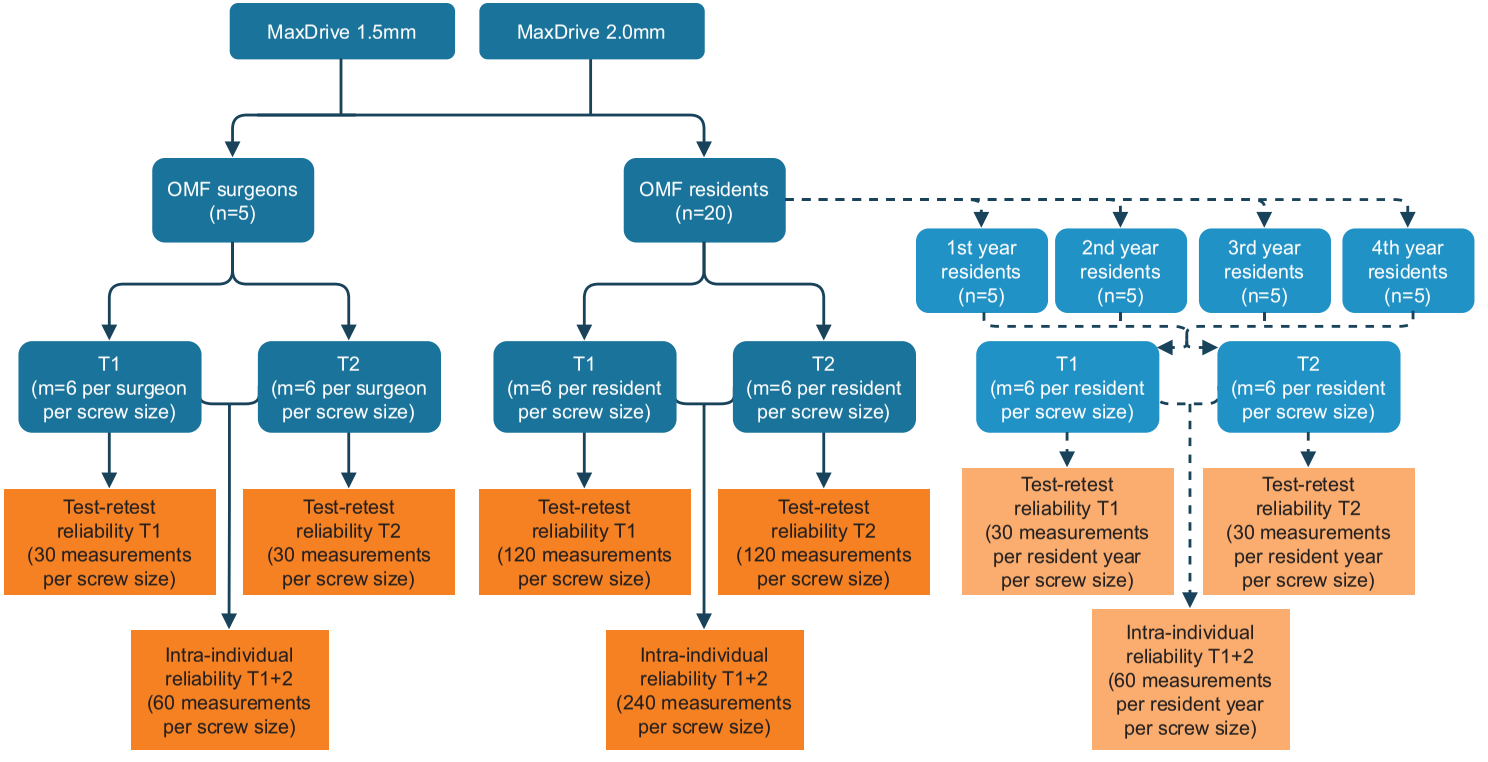

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Figure 2: Flowchart of the study procedures to assess the test-retest (at T1 and T2) and intra-individual reliability of the two main groups (i.e., oral and maxillofacial surgeons and residents) and the subgroups (i.e., the different residency years; the dashed lines and lighter colour boxes). *OMF, oral and maxillofacial; n, number of participants; m, number of measurements.* T_1*, at baseline;* T_2*, after 2 weeks.*

Sample size calculation

The number of screws of each screw size per participant and per test moment (i.e., m=6) were derived from the international standard for mechanical testing of bone screws[15]. The number of included participants was based on an *a priori* performed sample size estimation (1) for group comparisons and (2) to assess intra-individual reliability. The sample size calculation was based on data from a study that assessed differences in the torque applied by 4 OMF-surgeons to 1.5 and 2.0 mm osteosynthesis screws[16]. To provide sufficient power for both the 2.0 and 1.5 mm osteosynthesis screws, the 1.5 mm screw values were used. Using $\alpha = 0.05$, power = 0.8, effect size = 0.78, and number of groups = 5, resulted in a sample size of 25 participants (i.e., 5 per group)[16]. Regarding the reliability analyses, an expected intra-class correlation coefficient (ICC) of 0.8, and the number of repeated measurements, being 12 per screw size, also resulted in a sample size of 5 participants per group[17]. Therefore, five experienced OMF-surgeons and five randomly chosen residents from each of the four residency years participated, inserting 6 screws of each screw size at two test moments (i.e., a total of 300 measurements per screw size).

Statistical analyses

All the data were calculated and presented separately for each screw size. The assumptions of normal distribution of continuous data were tested by examining Q-Q plots and histograms, and by performing the Shapiro–Wilk test. Continuous data were presented as mean±standard deviation (SD) or median (25^{th} to 75^{th} percentile, P_{25}-P_{75}). Categorical data were reported in numbers and percentages.

Multilevel models were fitted using restricted maximum likelihood estimations that took into account variances between screws within one test moment of a certain participant, between participants within one test moment, and between test moments. A linear multilevel model was fitted for continuous outcome data while a logistic multilevel model was fitted for dichotomous outcome variables. Between-group comparisons (e.g., between OMF-surgeons and residents) were performed using a type III analysis of variance (ANOVA) test.

The test-retest reliability at T_1, the test-retest reliability at T_2, and the intra-individual reliability between T_1 and T_2 were assessed by calculating the ICC (absolute agreement using a two-way mixed model[17]) with a 95% confidence interval (CI) per group (Fig. 2). An ICC of ≤0.50, 0.50-0.75, 0.75-0.90, and ≥0.90 was considered as poor, moderate, good or excellent reliability, respectively[18]. A lower limit of the 95% CI of ICC≥0.70 was deemed

sufficient for research purposes[18]. The ICC was calculated by dividing the variance components of the participants and the interaction between the participants and the test moments by the total variance[17,19,20]. Bland-Altman plots with limits of agreement were constructed to assess systematic measurement differences[17].

Due to the lack of a gold standard for osteosynthesis screw torque, the five experienced OMF-surgeons' measurements (m=60 screws per screw size) were used to calculate the reference torque intervals for each screw size. We first checked whether the assumption that OMF-surgeons apply osteosynthesis screws consistently was met (i.e., the lower limit of the 95% CI of $ICC_{\text{intra-individual reliability}} \geq 0.70$). If this assumption was met, the 95% reference intervals of each screw size were calculated based on the experienced OMF-surgeons' multilevel model data. Here, the variance components of the fixed and random effects were summed (i.e., the total variance), the degrees of freedom were calculated based on the generalized Satterthwaite method (i.e., using the observed variances), and applying the t-values corresponding to the degrees of freedom and $\alpha = 0.05$, as appropriate[21]. The number and percentage of measurements which complied with the reference intervals were calculated per group and compared between groups.

$P \leq 0.05$ (two-tailed) was considered statistically significant. The Bonferroni correction was applied to all the pairwise comparisons to correct for multiple testing. All analyses were performed in R, version 4.0.5, using the *lme4*- and *blandr*-packages[22–24].

Results

Participants' characteristics

Of the included participants, 16 (64%) were male (all the OMF-surgeons and eleven residents (55%); Table 1). The median age (P_{25}-P_{75}) was 33.0 years (31.0-38.5; OMF-surgeons: 45.0 years (43.0-63.5); residents: 33.0 years (30.3-34.8)). The OMF-surgeons and residents experience with osteosynthesis systems was 14.8 (9.5-37.0) and 1.8 (0.2-4.0) years, respectively. Eighty-five percent of the completed internships had been followed at an academic medical centre.

Table 1. Characteristics of the included participants.

	OMF-surgeons (n=5)	All residents (n=20)	Residents			
			First year(n=5)	Second year (n=5)	Third year (n=5)	Fourth year (n=5)
Gender, n (%)						
Male	5 (100%)	11 (55%)	4 (80%)	1 (20%)	3 (60%)	3 (60%)
Age, median (P25-P75)	45.0 (43.063.5)	33.0 (30.3-34.8)	30.0 (27.0-33.0)	31.0 (27.0-32.0)	36.0 (32.5-38.5)	33.0 (32.0-35.5)
Medical Centre, n (%)						
UMCG	5 (100%)	11 (55%)	3 (60%)	4 (80%)	2 (40%)	2 (40%)
Amsterdam UMC– AMC	0	7 (35%)	2 (40%)	1 (20%)	3 (60%)	1 (20%)
Amsterdam UMC– VUmc	0	2 (10%)	0	0	0	2 (40%)
Experience with osteosynthesis systems in years, median (P_{25}-P_{75})	14.8 (9.5-37.0)	1.8 (0.2-4.0)				
Current internship, n (%)						
Outpatient clinic	NA	3 (15%)	3 (60%)	0	0	0
Dentoalveolar surgery		1 (5%)	1 (20%)	0	0	0
Trauma surgery		4 (20%)	1 (20%)	1 (20%)	1 (20%)	1 (20%)
Orthognathic surgery		5 (25%)	0	0	3 (60%)	2 (40%)
Implantology		0	0	0	0	0
Oncology		6 (30%)	0	3 (60%)	1 (20%)	2 (40%)
TMJ		1 (5%)	0	1 (20%)	0	0
Completed internships, n (%)						
Outpatient clinic	NA	14 (70%)	0	4 (80%)	5 (100%)	5 (100%)
Dentoalveolar surgery		15 (75%)	1 (20%)	4 (80%)	5 (100%)	5 (100%)
Trauma surgery		11 (55%)	0	2 (40%)	4 (80%)	4 (80%)
Orthognathic Surgery		8 (40%)	0	1 (20%)	2 (40%)	3 (60%)
Implantology		9 (45%)	0	0	4 (80%)	5 (100%)
Oncology		7 (35%)	0	0	2 (40%)	3 (60%)
TMJ		4 (20%)	0	1 (20%)	1 (20%)	2 (40%)
Internships followed at academic medical centres, $n_{academic}/N_{total}$ (%)*	NA	75/88 (85%)	6/6 (100%)	16/17 (94%)	24/28 (86%)	29/37 (78%)

Bold P-values represent statistically significant differences. *Calculated by dividing the number of internships followed at academic medical centres by the total number of internships. *OMF-surgeons: oral and maxillofacial surgeons; P_{25}-P75: 25th to 75th percentile; UMCG: University Medical Center Groningen; AMC: Academic Medical Center; VUmc: 'Vrije Universiteit' Medical Center; NA: not applicable; TMJ: temporomandibular joint.*

Torque to osteosynthesis screws

The OMF-surgeons applied 100.5±9.0 and 101.1±17.2 Nmm torque to the 1.5 mm osteosynthesis screws at T1 and T2, respectively (Table 2, Fig. 3a). The residents applied 92.4±24.6 and 92.4±16.1 Nmm torque to the 1.5 mm osteosynthesis screws at T1 and T2, respectively. The torque applied to the 1.5 mm screws by the residents at both test moments was significantly lower than that applied by the OMF-surgeons. The torque applied by the fourth-year residents at T1 was significantly lower than the first-, second- and third-year residents (Table 2).

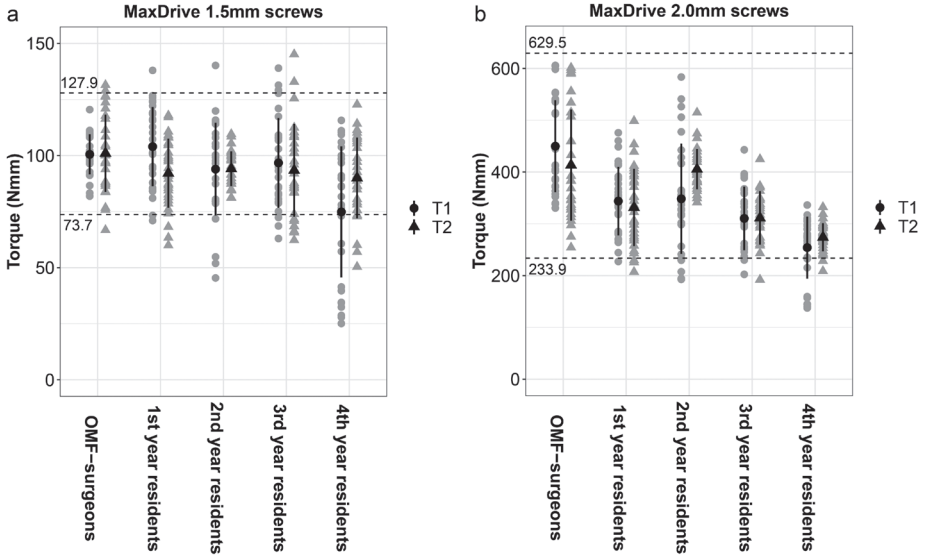

Figure 3. The applied torque to (a) 1.5mm and (b) 2.0mm osteosynthesis screws at T1 and T2. The dotted lines represent the limits of the calculated reference intervals based on the outcomes of the OMF-surgeons accompanied by the corresponding values. Black dots and triangles represent mean values at T1 and T2, respectively, with corresponding standard deviations. *OMF, oral and maxillofacial; T_1, at baseline; T_2, after 2 weeks.*

Table 2. The torque applied by experienced OMF-surgeons and residents at T1 and T2.

	OMF-surgeons	Residents	P-value*	Residents				
				1st year	2nd year	3rd year	4th year	P-value#
MaxDrive 1.5mm screws, mean±SD (Nmm)								
T1	100.5±9.0	92.4±24.6	**0.004**	104.0±17.6[c]	93.9±20.7[e]	96.8±20.0[f]	74.9±29.3[c,e,f]	**<0.001**
T2	101.1±17.2	92.4±16.1	**0.011**	92.2±15.4	94.1±7.7	93.4±20.7	90.0±18.0	0.775
MaxDrive 2.0mm screws, mean±SD (Nmm)								
T1	449.8±88.9	314.2±84.0	**<0.001**	343.9±66.2[c]	348.4±106.4[e]	310.5±61.4[f]	254.2±59.9[c,e,f]	**<0.001**
T2	413.5±107.4	330.7±69.9	**<0.001**	331.6±74.7[a,c]	405.7±38.9[a,d,e]	311.5±51.8[d,f]	274.1± 27.2[c,e,f]	**<0.001**

The bold P-values represent statistically significant differences. *Comparison between OMF-surgeons and residents. #Comparison between the residency years. Each superscript denotes significant differences in the pairwise comparisons (see P-values below): 'a' is derived from the pairwise comparison between first- and second-year residents, 'b' between first- and third-year residents, 'c' between first- and fourth-year residents, 'd' between second- and third-year residents, 'e' between second- and fourth-year residents, and 'f' between third- and fourth-year residents. 1.5 mm screws at T1: [a]P=0.502; [b]P>0.999; [c]**P<0.001**; [d]P>0.999; [e]**P=0.008**; [f]**P=0.001.** 1.5 mm screws at T2: non-significant differences between subgroups and, thus, no pairwise comparisons were performed. 2.0 mm screws at T1: [a]P>0.999; [b]P=0.551; [c]**P<0.001**; [d]P=0.335; [e]**P<0.001**; [f]**P=0.029.** 2.0 mm screws at T2: [a]**P<0.001**; [b]P=0.790; [c]**P<0.001**; [d]**P<0.001**; [e]**P<0.001**; [f]**P=0.034**. *SD: standard deviation; OMF-surgeons: oral and maxillofacial surgeons.*

The OMF-surgeons applied 449.8±88.9 and 413.5±107.4 Nmm torque to the 2.0 mm osteosynthesis screws at T1 and T2, respectively (Table 2, Fig. 3b). The residents applied 314.2±84.0 and 330.7±69.9 Nmm torque to the 2.0 mm osteosynthesis screws at T1 and T2, respectively. The torque applied to the 2.0 mm screws by the residents at both test moments was significantly lower than the torque applied by the OMF-surgeons. The torque applied by the fourth-year residents at T1 and T2 was significantly lower than the first-, second- and third-year residents.

Test-retest and intra-individual reliability

The OMF-surgeons achieved moderate to good test-retest and intra-individual reliability for the 1.5 mm screws (Table 3). The residents (i.e., as one group) achieved good to excellent test-retest and intra-individual reliability for the 1.5 mm screws. The subgroup analysis showed that the test-retest and the intra-individual reliability of the first- and second-year residents ranged from poor to moderate. In contrast, the third- and fourth-year residents achieved moderate to good reliabilities (Table 3). The Bland-Altman plot (Fig. 4a) demonstrated a systematic difference of 0.6 Nmm (limits of agreement (LOA) 38.9 to -37.7 Nmm).

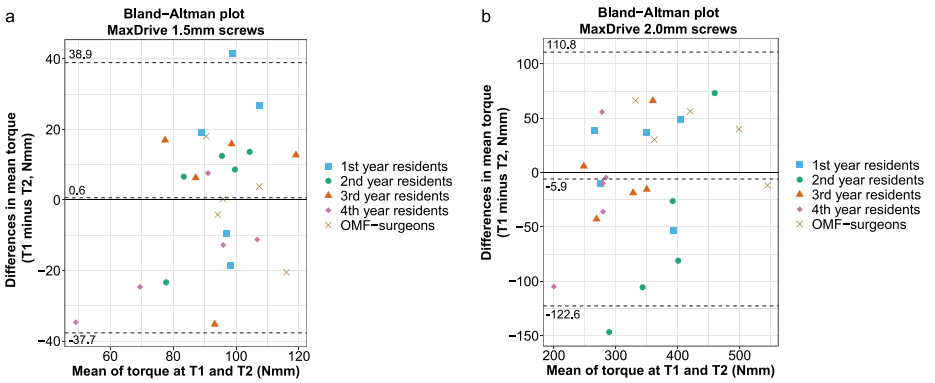

Figure 4. Bland-Altman plots of the (a) 1.5mm and (b) 2.0mm osteosynthesis screws. The dotted lines represent the lower and upper limits of agreement and the systematic difference accompanied by the corresponding values. The 95% CI of the systematic difference of the 1.5mm screws is -7.4 to 8.7 Nmm, and that of the 2.0mm screws is -30.5 to 18.7 Nmm. *OMF, oral and maxillofacial; CI, confidence interval.*

Table 3. Test-retest reliability (at T1 and T2) and intra-individual reliability between T1 and T2.

	OMF-surgeons	Residents	Residents			
			1st year	2nd year	3rd year	4th year
MaxDrive 1.5mm screws, ICC (95% CI)						
Test-retest reliability T1	0.85 (0.53;0.99)	**0.95 (0.91;0.98)**	0.89 (0.65;0.99)	0.83 (0.36;0.98)	**0.96 (0.86;0.99)**	**0.97 (0.90;0.99)**
Test-retest reliability T2	**0.95 (0.83;0.99)**	**0.91 (0.84;0.96)**	0.90 (0.67;0.99)	0.90 (0.68;0.99)	**0.92 (0.71;0.99)**	**0.96 (0.88;0.99)**
Intra-individual reliability (T1-T2)	**0.93 (0.77;0.99)**	**0.92 (0.85;0.96)**	0.45 (0.00;0.93)	0.87 (0.61;0.99)	**0.92 (0.75;0.99)**	**0.97 (0.90;0.99)**
MaxDrive 2.0mm screws, ICC (95% CI)						
Test-retest reliability T1	**0.92 (0.73;0.99)**	**0.96 (0.92;0.98)**	**0.94 (0.98;0.99)**	0.83 (0.44;0.98)	0.89 (0.62;0.99)	0.86 (0.54;0.98)
Test-retest reliability T2	**0.94 (0.81;0.99)**	**0.97 (0.94;0.99)**	**0.96 (0.87;0.99)**	**0.96 (0.87;0.99)**	**0.97 (0.90;0.99)**	**0.98 (0.93;0.99)**
Intra-individual reliability (T1 – T2)	**0.96 (0.89;0.99)**	**0.96 (0.93;0.98)**	**0.97 (0.90;0.99)**	**0.92 (0.76;0.99)**	**0.96 (0.87;0.99)**	**0.92 (0.75;0.99)**

The bold values indicate sufficient reliability (i.e., ICC≥0.7). *ICC: intra-class correlation coefficient; 95% CI: 95% confidence interval; OMF-surgeons: oral and maxillofacial surgeons.*

The OMF-surgeons achieved moderate to good test-retest and intra-individual reliability for the 2.0 mm screws. The residents achieved excellent test-retest and intra-individual reliability for the 2.0 mm screws. The subgroup analysis showed that the T_1 test-retest reliability of the second-, third-, and fourth-year residents ranged from poor to moderate. However, the T_2 test-retest reliability and intra-individual reliability of these subgroups increased to good-excellent reliability (Table 3). The Bland-Altman plot (Fig. 4b) showed a systematic difference of -5.9 Nmm (LOA 110.8 to -122.7Nmm).

Reference intervals and complications

Since the assumptions that OMF-surgeons apply osteosynthesis screws consistently were met for both the 1.5 and 2.0 mm osteosynthesis screws, reference intervals for both screw sizes could be calculated ranging from 73.7 to 127.9 Nmm for the 1.5 mm screws (Fig. 3a) and from 233.9 to 629.5 Nmm for the 2.0 mm screws (Fig. 3b).

The OMF-surgeons' compliance with the reference torque interval for the 1.5 mm screws was 57 (95%) whereas the residents' compliance was 195 (82%) (P=0.009; Table 4; Fig. 3a). The first- and second-year residents complied with the reference interval significantly more often than the third- and fourth-year residents (Table 4). The compliance to the reference interval increased from 82% at T1 to 86% at T2. Screw hole stripping with the 1.5 mm screws was similar among the OMF-surgeons and residents (Table 4). The second-year residents had the highest proportion of stripped screw holes (17%).

The OMF-surgeons complied with the reference torque interval on applying all the 2.0 mm screws (Table 4; Fig. 3b). The residents' compliance with the 2.0 mm screw reference interval was 215 (90%) (P=0.007; Table 4; Fig. 3b). Compliance with the 2.0 mm screw reference interval was similar among all the residents (Table 4). The reference interval compliance increased from 88% at T1 to 95% at T2. The OMF-surgeons and residents' screw hole stripping with the 2.0 mm screws was similar.

Table 4. The compliance with the reference intervals and the number of complications during osteosynthesis screw insertion.

	OMF-surgeons	Residents	P-value*	Residents				
				1st year	2nd year	3rd year	4th year	P-value#
MaxDrive 1.5mm screws, n (%)								
Reference interval compliance†	57 (95%)	195 (82%)	**0.009**	54 (90%)	55 (92%)[d,e]	43 (72%)[d]	43 (72%)[e]	**0.002**
Stripped screw holes	1 (2%)	14 (6%)	0.319	0 (0%)[a]	10 (17%)[a,e]	4 (7%)	0 (0%)[e]	**<0.001**
Broken screws	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
MaxDrive 2.0mm screws, n (%)								
Reference interval compliance§	60 (100%)	215 (90%)	**0.007**	56 (93%)	54 (90%)	56 (93%)	49 (82%)	0.168
Stripped screw holes	1 (2%)	0 (0%)	0.200	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA
Broken screws	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	NA

The bold P-values represent statistically significant differences. *Comparison between OMF-surgeons and residents. #Comparison between the residency years. †Reference interval 1.5 mm screws: 73.7 to 127.9 Nmm. §Reference interval 2.0mm screws: 233.9 to 629.5 Nmm. Each superscript denotes significant differences in the pairwise comparisons (see P-values below): 'a' is derived from the pairwise comparison between first- and second-year residents, 'b' between first- and third-year residents, 'c' between first- and fourth-year residents, 'd' between second- and third-year residents, 'e' between second- and fourth-year residents, and 'f' between third- and fourth-year residents. 1.5 mm screw reference interval compliance: [a]P>0.999; [b]P=0.064; [c]P=0.064; **[d]P=0.028**; **[e]P=0.028**; [f]P>0.999; stripped screw holes, **[a]P=0.008;** [b]P=0.712; [c]P=NA; [d]P=0.920; **[e]P=0.008;** [f]P=0.712; broken screws: NA. 2.0 mm screw reference interval compliance: non-significant differences between subgroups and, thus, no pairwise comparisons were performed; stripped screw holes: NA; broken screws: NA. *OMF-surgeons: oral and maxillofacial surgeons; NA: not applicable.*

Discussion

This study shows a clear effect of "learning-by-doing", with increased compliance to the reference torque intervals and reliability for both 1.5 and 2.0 mm osteosynthesis screws at T2 compared to T1. The senior residents showed higher reliability but lower compliance with the reference torque interval compared to the junior residents. Thus, despite the residency year, it is still necessary to train residents and/or to verify the applied torque by experienced OMF-surgeons remains necessary to utilize the full potential osteosynthesis systems.

A simulated learning environment is very suitable for acquiring the "feeling" of adequate screw fixation with sufficient tightness and when a screw hole will strip. This study shows that learning-by-doing increases both the test-retest reliability and compliance with the reference torque intervals for both 1.5 and 2.0 mm screws. Although first- and second-year residents showed an increase in reliability with the 1.5 mm screws at T2 compared to T1, these reliabilities were still insufficient at T2 (i.e. ICC<0.7). All the other groups with insufficient applied torque reliability at T1 increased their reliability to a sufficient level at T2. These results indicate that this test setup has a learning effect on OMF clinicians resulting in increased reliability and accuracy for both screw types. Since bone stripping and screw breakage are more likely to occur when the difference between the torque applied to the screws for adequate fixation (i.e., hand-tight) and the maximum allowed torque (i.e., torque up to screw breakage) is small[25] as well as that this setup can increase both accuracy and reliability of the applied torque, this setup is appropriate for educational purposes.

At first glance, the calculated reference intervals for both screw sizes may seem wide. The reference intervals are wide because the dispersion around the mean torque applied by the maxillofacial surgeons (i.e., the standard deviation and, thus, the variance) is relatively large. The high variability of torque applied to osteosynthesis screws between surgeons has also been reported in literature previously[1]. However, as each surgeon applied the torque consistently (i.e., the intra-individual reliability was good to excellent) and there were no signs of systematic difference between T1 and T2 in the Bland-Altman plots, the measured variability between surgeons is, thus, part of the actual application of screws. Due to the higher maximum torque needed to adequately insert the 2.0 mm screws, which in turn inevitably results in a loss in precision[16], the reference interval of the 2.0 mm screws is much wider than that of the 1.5 mm screws.

The reliability and compliance with the 2.0 mm screw reference torque interval were generally better than the 1.5 mm screws as the latter are more prone to errors (i.e., too little or much applied torque). An explanation for these differences is that the tactile feedback is higher when applying 2.0 mm screws[1,16], as shown by other studies that increasing tactile or visual feedback results in increased accuracy and the ability to predict screw hole stripping[1]. Therefore, complying with the 1.5 mm screw reference interval requires a higher degree of accuracy. Thus, although training is beneficial for both screw sizes, training of the applied torque to 1.5 mm screws is, in particular, needed.

Our study shows that this combination of compliance with the reference interval and residents' intra-individual reliability is currently inadequate for 1.5 mm screws. Although the first- and second-year residents showed higher compliance with the reference interval, the intra-individual reliability of both subgroups was poor and moderate, respectively. The third- and fourth-year residents demonstrated good intra-individual reliability but poorer compliance with the reference interval. On the other hand, regarding the 2.0 mm osteosynthesis screws, the first-, second- and third-year residents had good intra-individual reliability and high compliance with the reference interval. The fourth-year residents displayed good intra-individual reliability but applied too little torque to a substantial proportion of the screws. A post hoc analysis of the fourth-year residents' insertions showed that the torque of 10/17 (59%) of the 1.5 mm and 7/11 (64%) of the 2.0 mm screws was insufficient. A recent review also showed substantial between-surgeon variability in the application of osteosynthesis screws[1]. Therefore, regardless of the residency year, training residents (e.g., by using this test setup) and/or verification of the applied torque by experienced OMF-surgeons remains necessary when applying osteosynthesis systems.

Stripping of the screw holes only occurred on inserting the 1.5 mm screws. Interestingly, the second-year residents showed the highest proportion of stripped screw holes but with the highest compliance with the 1.5 mm reference interval. An explanation is that this was caused by the self-tapping technique for osteosynthesis screws, i.e. tightening the screws by clockwise rotation, followed by loosening the screws a bit by rotating anti-clockwise and then tightening the screws further. This technique is necessary to lower the torsional resistance when applying osteosynthesis screws as well as to remove debris that is formed on self-tapping the screw holes. However, when this technique is executed too forcefully, the screw holes get stripped without having applied excess torque[1]. All the (sub)groups' stripping rates remained lower compared to the average

stripping rate (26%) reported in the literature[1], probably because the screws used in this study were smaller, necessitating less torque.

The calculated reference intervals and the reported learning effect indicate that training clinicians (e.g., during the residency period, seminars or courses) with this simple, yet effective test setup has the potential to improve the effectivity of osteosynthesis systems. This has the potential to enhance patient care quality by increasing fracture or osteotomy stability, resulting in less compromised healing, and reducing the need for emergency screws following the stripping of bone intraoperatively, with a corresponding reduction in operation time and costs.

The osteosynthesis screws included in this study are used for fixating fractures and osteotomies in different locations of the facial skeleton, e.g., the crista zygomaticoalveolaris, anterior wall of the maxillary sinus, and mandible. These maxillofacial bones have different mechanical properties[12,13,26,27]. The HPL-blocks used in this study have mechanical properties within the known mechanical property range of maxillary and mandibular bones[11], making them a suitable bone simulation model. However, the translation of the reference intervals to the clinical setting remains uncertain due to *in vivo* variabilities in bone density and thickness. Therefore, we advocate that translation of the reference intervals to a clinical setting should not be done until *in vivo* validation of the calculated reference intervals has been performed.

Although this study focused on maxillofacial osteosynthesis systems, the results of this study also seem applicable to other disciplines that use osteosynthesis systems, e.g., orthopaedic and trauma surgery. A recent systematic review showed that, on average, 26% of all inserted osteosynthesis screws by experienced orthopaedic and trauma surgeons are irreparably damaged or have stripped screw holes[1]. Currently, it remains unknown how residents of these disciplines perform. The authors of that review indicated that there is a need for defining reference torque intervals and that future research should focus on developing methods to train clinicians to apply osteosynthesis screws accurately and reliably[1]. The test setup presented in this study can be easily adjusted by using a different torque meter (i.e., that can measure higher torque for larger screws) and different HPL-blocks, making this test setup useful for educational purposes with different sizes of osteosynthesis systems.

The strengths of this study are the simple, effective and standardized test setup, blinding all the participants to the applied torque, and the thorough study design (i.e., test-retest reliability at T_1 and T_2, and intra-individual reliability between T_1 and T_2). The presented

low-cost test setup can be easily fabricated for educational purposes. Furthermore, commonly used osteosynthesis screws were applied to a standardized bone model. A limitation of this study is that, although we used a suitable bone simulation model, translation of the reference intervals to the clinical setting remains uncertain due to *in vivo* variabilities in bone density and thickness. Moreover, bone blocks were not used because the variability in bone mineral density, cortical and spongious bone layer thickness, and block dimensions impede their use as a standardized and reproducible model since reliability assessment is then uncertain. Another limitation is the lack of a gold standard for torques applied to screws. We, therefore, determined reference intervals based on the torque values of experienced OMF-surgeons. The participating surgeons have many years of experience with osteosynthesis systems in the clinic. However, another group of OMF-surgeons might have given other reference intervals. External validation of the defined reference intervals by future research is therefore desired. Finally, since the error of the torque meter is a fixed absolute value (i.e., 2.5 Nmm), the relative error increases as the measured torque decreases. However, this study aimed to assess and compare the reliability and accuracy of maxillofacial surgeons and residents as well as to provide a simple and low-cost, yet effective, setup that can be used to train residents to increase the reliability and accuracy of the torque applied to osteosynthesis screws. The results show that the used torque meter can measure with sufficient accuracy and precision to assess the reliability, accuracy and learning-effect over time, and, thus, suits the aims of this study.

Conclusions

This study shows a learning effect on using a simple and low-cost, yet effective, setup resulting in increased compliance with the reference torque intervals and reliability regarding both 1.5 mm and 2.0 mm osteosynthesis screws. Senior residents showed higher reliability but lower compliance with the reference torque intervals compared to junior residents. The combination of high accuracy and reliability by residents was insufficient for 1.5 mm screws. Thus, despite the residency year, training and/or verification of the applied torque by experienced OMF-surgeons is still necessary for residents to utilize osteosynthesis systems to their fullest potential.

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Competing interests

The authors declare no competing interests.

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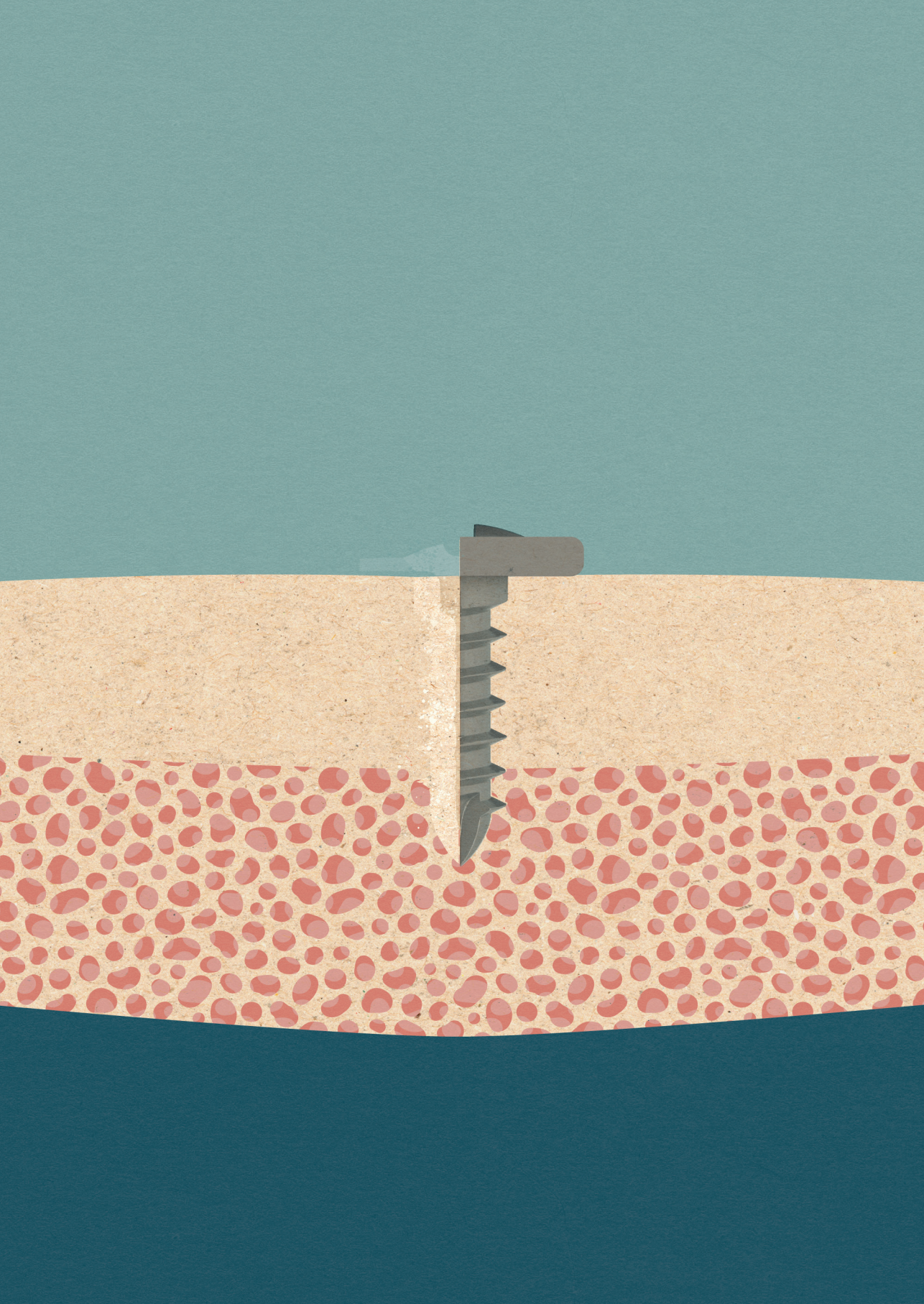

Chapter 9

General discussion

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Introduction

Most of the osteosynthesis systems applied in oral and maxillofacial surgery (OMF-surgery) consist of plates and screws. They are used to fixate bone segments in maxillofacial traumatology and orthognathic surgery. Titanium osteosynthesis systems are currently the gold standard. However, the disadvantages include temperature sensitivity[1], tactile sensation of plates and screws, possible growth restrictions[2], hampering of imaging and radiotherapy[3–5], presence of titanium particles in lymph nodes[6], extreme stiffness causing stress shielding of the underlying bone[5], and potential mutagenicity[1].

Biodegradable plates and screws are commonly composed of degradable synthetic polymers (e.g., polylactide or polyglycolide) and may reduce the removal rates of osteosynthesis systems in a second operation while also avoiding the aforementioned disadvantages of titanium osteosyntheses. Biodegradable systems have, however, their own limitations including decreased mechanical properties, palpability due to bulkiness, and possible foreign body reactions[7].

Also of importance for sufficient primary stability, besides the (mechanical) properties of the used osteosynthesis system, is the amount of torque applied to the screws by oral and maxillofacial surgeons (OMF-surgeons)[8,9].

To guide evidence-based selection of osteosynthesis systems, the aim of the research described in this thesis was to compare the *in vitro* and *in vivo* performances of different biodegradable osteosynthesis systems, as well as to compare the (clinical) performance of biodegradable and titanium osteosynthesis systems. In addition, the accuracy and reliability of the torque applied by residents and experienced OMF-surgeons to titanium osteosynthesis screws were assessed.

Titanium or biodegradable osteosyntheses?

In **Chapter 2**, the available clinical evidence from patients treated for maxillofacial fractures (i.e., Le Fort I, cranial, zygomaticomaxillary complex and mandibular fractures) with load-sharing biodegradable versus titanium osteosyntheses was systematically reviewed and analysed. The meta-analysis demonstrated similar efficacy and morbidity between the two systems but symptomatic osteosynthesis removal was significantly lower in the biodegradable compared to the titanium group. Other studies that focused on cohorts of patients who had undergone load-sharing biodegradable

fixation of midface and malar fractures[10–12], naso-orbital-ethmoid fractures[13], and mandibular body, parasymphysis and symphysis fractures[12,14,15], also showed adequate internal fixation, long-term stability, and biocompatibility with biodegradable systems. Similar results were observed in non-comparative cohorts that included adults with isolated orbital floor fractures[11] and combined orbital floor and medial wall fractures[13] treated with biodegradable mesh plates. In addition, a systematic review that focused on the composite of the complications (e.g., infection, palpability, dehiscence, material-related complications, and exposure) encountered with biodegradable versus titanium osteosynthesis of zygomatic and mandibular fractures revealed significantly fewer complications from biodegradable compared to titanium osteosyntheses, although the analysis had a risk of bias due to substantial methodological heterogeneity of the included studies[16]. Symptomatic biodegradable osteosynthesis system removal in these studies (0 to 8.6%) was comparable to that of the patients with mandibular, Le Fort I, and zygomatic fractures in the multicentre randomised controlled trial (RCT) described in **Chapter 5** (0%).

Similar to the abovementioned results, the meta-analyses comparing biodegradable versus titanium osteosyntheses in adults with dentofacial deformities treated with orthognathic surgery (i.e., Le Fort I, bilateral sagittal split (BSSO), and intraoral vertical ramus osteotomies (IVRO), with and without concurrent genioplasty) also demonstrated similar efficacy and morbidity between biodegradable and titanium osteosynthesis systems (**Chapter 3**). Non-comparative cohort studies that focused on the stability of maxillary[17–19], mandibular[17–19], or bimaxillary osteotomies[17–21], and post-operative complications[19,22,23], also showed predictable skeletal stability with post-operative complications rates similar to those reported in the literature after titanium osteosyntheses[24–26].

In contrast to the abovementioned trauma population (**Chapter 2**), a non-significant difference in symptomatic biodegradable and titanium osteosynthesis system removal was observed in the orthognathic population (**Chapter 3**). The main reasons for biodegradable osteosynthesis removal in both populations were chronic inflammation and discomfort, and this was in line with the results of the RCT described in **Chapter 5**. In-depth analyses revealed that all the removals among the biodegradable group were due to clinical problems in the mandible, and were only seen after fixation of osteotomies (**Chapter 5)**. Different reviews noted that mandibular osteotomies are associated with significantly more complications and higher symptomatic biodegradable and titanium osteosyntheses removal compared to maxillary osteotomies, and compared to fracture

fixation[16,27–29]. A large retrospective cohort study (n=685 patients) that focused on the efficacy and complications of biodegradable osteosyntheses and symptomatic removal of the systems also showed that mandibular osteotomies are associated with more complications and higher symptomatic removal rates compared to other osteotomies[30]. In addition, earlier reviews also showed more complications and symptomatic osteosynthesis removal after titanium fixation of mandibular osteotomies compared to other osteotomies[27,28]. Together, these results indicate that biodegradable osteosynthesis is a viable alternative to titanium osteosynthesis for both studied populations. However, among the studied trauma population, the symptomatic biodegradable osteosynthesis systems removal rates are lower compared to the titanium osteosyntheses group (**Chapter 2**) whereas the biodegradable and titanium osteosyntheses groups have similar symptomatic osteosyntheses removal rates after orthognathic surgery (**Chapter 3**).

Aspects of successful biodegradable osteosyntheses

An important aspect of successful biodegradable osteosyntheses (i.e., adequate bone healing and stability, and lack of foreign body reactions) is the biomechanical perspective. The biomechanical differences between fixation of fractures and osteotomies may explain the beneficial effect of biodegradable systems compared to titanium systems after fracture fixation versus osteotomy fixation. Fracture fixation with interfragmentary stability ensures friction forces between the contacting fracture surfaces and allows for load sharing between the bone segments and the osteosynthesis system (i.e., load-sharing osteosyntheses)[31,32]. In contrast, in osteotomies interfragmentary stability is, by definition, absent and thus the complete load at the osteotomy is carried by the osteosynthesis system (i.e., load-bearing osteosyntheses). Load-sharing osteosyntheses requires less mechanical properties from the osteosynthesis systems compared to load-bearing osteosyntheses[31]. Furthermore, the mandible is exposed to considerably higher biomechanical forces compared to the maxilla[31,33]. Thus, fixating mandibular fractures, especially mandibular osteotomies, requires even higher mechanical properties of the used osteosynthesis system[34,35]. Biomechanical forces that are not sufficiently counteracted can result in micromovements surrounding the osteosyntheses that may result in disturbed bone healing or foreign body reactions[31,36–41]. Animal studies have shown that these micromovements should be limited to 28-150 µm to avoid fibrosis and accompanying foreign body reactions[36–40]. Therefore, it is important that the mechanical properties of biodegradable implants are sufficient for the intended clinical application to ensure (primary) stability for adequate bone healing and to avoid micromovements and the accompanying risk of foreign body reactions.

Besides the biomechanical perspective, differences in vascularization also contribute to inducing foreign body reactions. The mandible is known to have less vascularisation compared to other parts of the facial skeleton. Sufficient vascularization is necessary for adequate bone healing but it is also essential to eliminate the acidic degradation products of the hydrolysed poly-α-esters (e.g., polylactide). Accumulation of acidic degradation products may result in decreased pH[41], bone demineralization[42], and may damage the surrounding cells such as macrophages[43–45]. Whenever micromovements are present, fibrous encapsulation can entrap the acidic degradation products, resulting in reduced elimination of the degradation products[41]. The acidic degradation products have an autocatalytic effect and cause further degradation of the remaining polymer resulting in a vicious circle that eventually leads to a more severe inflammatory reaction[41]. Since the mandible is exposed to higher forces, and has lesser vascularization, mandibular osteosyntheses are more prone to these (accumulating) effects compared to those in other parts of the facial skeleton.

Biodegradable osteosyntheses as equivalent alternative to titanium osteosyntheses

At first glance, the non-significant difference in the proportion of symptomatic removal of biodegradable and titanium osteosyntheses in orthognathic surgery seems to negate the benefits of biodegradable osteosyntheses. However, asymptomatic biodegradable osteosynthesis systems will eventually be resorbed while titanium osteosynthesis will remain *in situ* until removed surgically. Therefore, titanium osteosynthesis systems have a life-time risk of, e.g., late infection or palpability complaints. Furthermore, biodegradable osteosyntheses have other advantages, besides the most obvious benefit of less device removal compared to titanium systems, including no interference with radiographic imaging and radiotherapy, a more gradual transfer of stress to the healing bone (i.e., less stress shielding), and less system palpability in the long-term (**Chapters 2 and 5**)[2,46–49]. Whereas 17-80% of the patients undergo a second operation for elective titanium osteosynthesis removal due to their awareness of the presence of a foreign body (i.e., the titanium system)[50–52], asymptomatic biodegradable systems are generally eventually resorbed, thus forestalling such elective removals. The vast majority of patients (i.e., >95%), therefore, prefer biodegradable over titanium osteosyntheses in both maxillofacial traumatology and orthognathic surgery[53,54]. Despite the similar symptomatic removal rates in orthognathic surgery, the other benefits of biodegradable systems could also be valid reasons to choose biodegradable, and not titanium, osteosynthesis systems. All these aspects should therefore be addressed preoperatively when informing the patients to ensure well-informed decision making.

Similarly, after fracture fixation in paediatric patients, all the titanium systems were electively removed due to possible later growth disturbances[55,56] and plate migration[57–59], whereas only the symptomatic biodegradable systems (12%) were removed (**Chapter 2**). In a recent systematic review including paediatric upper and mid-facial fractures, the biodegradable osteosyntheses showed significantly fewer complications and symptomatic osteosynthesis system removal rates compared to titanium osteosyntheses[60]. Comparable rates were observed after applying biodegradable osteosynthesis for mandibular fracture fixation[61,62] and in craniofacial surgery[63,64] in paediatric patients. Biodegradable osteosyntheses would thus overall still result in lower osteosynthesis removal compared to titanium osteosyntheses from paediatric patients. It must be noted, though, that there is currently no conclusive evidence whether growth disturbances actually occur with titanium systems and, thus, there is controversy in the current literature regarding the elective removal of titanium osteosynthesis systems from paediatric fracture patients[57,58,65,66]. Therefore, this subject needs to be addressed by future research. OMF-surgeons should inform paediatric patients and/or their caregivers about the above preoperatively to guide the shared-decision making.

Certainty of the evidence

Although the application of biodegradable osteosynthesis in maxillofacial traumatology and orthognathic surgery is well-documented in the literature, the quality of the available evidence (i.e., the solitary studies) ranged from very low to moderate due to a high risk of bias and small sample sizes. Therefore, to guide evidence-based clinical decisions, there is still a need for large-scale and high quality randomised controlled trials based on pre-specified, pre-registered and well-defined protocols comparing biodegradable versus titanium osteosyntheses in maxillofacial traumatology and orthognathic surgery with long-term follow-ups. Furthermore, significant differences in biocompatibility and degradation profiles were observed between four copolymeric biodegradable osteosynthesis systems commonly used in maxillofacial surgery (**Chapter 6**). Also, significant mechanical property differences were observed between 15 biodegradable systems (**Chapter 7**). Therefore, future research should focus on a specific biodegradable system that has proven to be biocompatible in the long-term as well as having the most favourable mechanical properties for specific surgical indications. In addition, there is currently no evidence to support or refute the use of biodegradable osteosynthesis in load-bearing fracture fixation. Since current evidence suggests that load-sharing fixation of fractures using biodegradable osteosynthesis is feasible, the next step would be to focus on load-bearing biodegradable osteosynthesis

of fractures. Finally, systematic reviews should include tools to assess the degree of clinical heterogeneity[67], and should perform network meta-analyses to assess the most preferred biodegradable system. This would allow conclusions regarding the efficacy of specific biodegradable osteosynthesis systems based on clinical evidence.

Overcoming the disadvantages of biodegradable osteosyntheses

The systematic reviews described in **Chapters 2 and 3** reveal a significantly higher risk of perioperative screw breakage and perioperative time, respectively, in the biodegradable compared to the titanium group. Perioperative biodegradable screw breakage is a commonly reported complaint[68,69] and, together with the need to pre-tap burr holes for biodegradable screws, it is the lowest rated perioperative handling aspect of biodegradable systems by OMF-surgeons[69]. Screw breakage is more likely when the difference between the torque applied to the screws for adequate fixation (i.e., hand-tight) and the maximum allowed torque (i.e., torque up to screw breakage) is small[70,71]. As shown in **Chapter 7**, the difference between hand-tight and maximum torque is much smaller for biodegradable screws compared to titanium screws and, thus, explains the higher risk of perioperative biodegradable screw breakage. Yet, as also reported by OMF-surgeons, more exposure to biodegradable systems could diminish the differences in perioperative screw breakage[69]. Additionally, OMF-surgeons and residents could practice pre-clinically by using the training model described in **Chapter 8**, thereby increasing their awareness, reliability and accuracy of the torque applied to biodegradable screws and, possibly, decrease the risk of perioperative screw breakage.

An alternative to biodegradable screws are biodegradable pins that are inserted via ultrasonic welding (e.g., the SonicWeld systems), thereby diminishing the risk of perioperative screw breakage. This obviates the need to pre-tap the burr holes, as done for conventional biodegradable screws, which is a time-consuming extra step compared to self-tapping titanium screws, and results in longer operative times[72,73]. In craniofacial surgery, biodegradable osteosyntheses using ultrasound welding has been shown to be easy to use and reduces the time needed to apply the osteosynthesis systems by up to 50% compared to the same biodegradable system with screws[63,64,74].

Besides the advantages in perioperative handling, systems with ultrasound pin welding have significantly better mechanical properties compared to an identical system with conventional screws (**Chapter 7**)[48]. The osteosynthesis plate has to be compressed firmly onto the underlying bone to achieve primary stability[8,9] but the much lower maximum torque of biodegradable screws compared to titanium screws (**Chapter 7**) hampers firm

biodegradable plate compression onto the underlying bone. Ultrasound pin welding results in pin fusion with the plate thereby creating a three dimensional stable system that resembles a conventional locking system. Locking titanium osteosynthesis systems, for example, provide higher stability compared to non-locking systems[75]. Hence, the insufficient compression of the biodegradable plate onto the underlying bone due to the lower torque applied to biodegradable screws could be overcome with ultrasound welding, creating a more stable 'locking system'. The superior mechanical properties of ultrasound welding is also supported by the finding that the weakest link of the complete biodegradable osteosynthesis system shifts from the screw-plate interface (i.e., all other biodegradable systems) to the plate itself (i.e., similar to titanium systems).

Besides that high mechanical properties are sought for stable fixation while reducing any micromovements surrounding the osteosynthesis system, improvements in mechanical properties may also result in smaller biodegradable osteosynthesis devices thereby reducing issues regarding palpability of the system by patients, and stress free closure of the incision by OMF-surgeons. In addition, low implant volume reduces the amount of acidic degradation products and thus reduces the risk of (late) foreign body reactions[41]. Finally, studies have shown that the geometry of the implant also affects the host response. A smooth, well-contoured shape without acute angles induces macrophage polarization towards M2 macrophages (i.e., towards wound repair and an immune regulatory phenotype) whereas implants with acute angles and non-contoured shapes increase the risk of foreign body reactions to biomaterials[76,77]. Since screws possess acute angles and welded pins are smooth without acute angles, welded pins may also contribute to a more biocompatible osteosynthesis system compared to a similar system with screws[41].

In summary, using ultrasound welding of biodegradable pins may contribute to overcoming the commonly reported disadvantages of biodegradable systems by diminishing the risk of perioperative screw breakage, reducing the time needed to apply the osteosynthesis system, improving the mechanical properties and size of the system, and reducing the risk of foreign body reactions compared to a similar biodegradable system with screws. These leads should be included in future research.

Overcoming the disadvantages of titanium osteosyntheses

Titanium osteosynthesis systems have also been improved to overcome the associated disadvantages. Titanium osteosynthesis systems are commonly made of pure titanium or titanium alloys[78,79]. The most frequently used titanium alloy for

maxillofacial osteosynthesis systems consists of 90% titanium, 6% aluminium, and 4% vanadium (Ti6Al4V, also called titanium alloy grade 5)[78,80–82]. The titanium alloy production process can be altered in such a way to increase or decrease the stiffness of the titanium osteosynthesis plates[83,84]. By increasing the stiffness, the titanium plates can be thinner while maintaining sufficient mechanical properties for adequate bone healing. Another advantage of thinner systems is that it may reduce the tactile sensation of the osteosynthesis systems for patients which, in turn, could reduce symptomatic osteosynthesis removal rates. In addition, reducing the volume of the titanium osteosynthesis systems reduces imaging and radiotherapy restrictions. On the other hand, decreasing the stiffness of existing osteosynthesis plates would address the potential issue of stress shielding of the underlying bone[83,84] as well as improve the perioperative handling of the systems.

Besides the adjustments in mechanical properties, novel methods to improve biocompatibility have gained interest. Although titanium and its alloys are presumed to be completely bioinert, there is growing evidence that wearing of particles occurs that can accumulate in surrounding tissues and different organs of which the consequences are still largely unknown[78,81,85]. In a study that explanted titanium osteosynthesis plates from patients that underwent craniofacial surgery, titanium particles (7.9 to 31.8 µg/gram of dry tissue) could be detected in the regional soft tissue and lymph nodes after 24 months follow-up[6]. Similarly, a recent study showed that the tissue surrounding titanium plates after fracture and osteotomy fixation contained 1.03 and 1.09 ppm titanium particles, respectively[86]. Meningaud et al. revealed a large variation in titanium levels within the surrounding tissue (4-8000 µg/gram) after titanium fixation of osteotomies, but concluded that almost all of these particles were produced at the moment of applying the osteosynthesis system[87]. Other studies reported on presence of dark-grey pigmentation accompanied with fibrosis of the surrounding tissue and macrophages containing intra-cellular titanium particles[88–90]. Zaffe et al. have also shown presence of titanium in the surrounding tissue as well as that erythrocytes and lymphocytes contained titanium particles[91]. In addition, explanted osteosynthesis plates analysed with scanning electron microscopy showed defects and irregularities most likely due to *in vivo* substance loss[89]. Titanium debris has also been found throughout the body suggesting haematogenous dissemination, with traceable amounts of titanium particles within the liver, spleen, and lymphatic system[81,85].

To determine the effect of such titanium particles, Coen et al. assessed the cytotoxicity of Ti6Al4V particles on human fibroblast cells *in vitro*, and showed chromosomal

instability, reproductive failure and decreased clonogenic survival 10 generations postexposure[92]. Studies that analysed the periosteum surrounding titanium plates as well as blood samples in patients after mandibular fracture fixation showed redox abnormalities, and increased oxidative stress and damage[93,94]. Furthermore, an association between aluminium and the pathogenesis of Alzheimer's disease has been suggested. In addition, increased levels of circulating aluminium is associated with microcytic anaemia and osteomalacia[81,95,96]. These findings indicated that there is a need for long-term epidemiological studies that assess the effect of these particles on the long-run.

Surface modifications (e.g., oxygen plasma immersion ion implantation) have been proposed to reduce, or even eliminate, metal ion release from the implant and to decrease infection risk of titanium osteosyntheses[97]. In oxygen plasma immersion ion implantation, the implant surface is modified by targeting it with specific ions (e.g., TiO_2) to gain specific properties including reducing metal ion release from the implant[97]. In addition, surface modifications are important to reduce infection risk[81,97]. Titanium, without surface modifications, has a positively charged surface and will, therefore, tend to covalently bond to negatively charged proteins such as fibronectin[98]. Fibronectin promotes bacterial adhesion and, thus, increases the risk of infection[99]. Besides bonding to autologous proteins, most of the cell surface of bacterial species (e.g., *Staphylococcus aureus*, the most common etiological pathogen of infections surrounding osteosyntheses[100]) is negatively charged, and thus also adhere to positively charged surface such as titanium[101]. By modifying the surface charge, adhesion of various bacteria is inhibitted and, ideally, the risk of infection is reduced[97]. Different types of (hydrophobic) coatings have also been introduced to prevent bacterial adhesion to implant surfaces[39]. Other surface modifications (e,g, adjusting the nano-scale surface topography by pillars on the surface) can lead to the elimination of surrounding bacteria[102], diminishing the need for antibiotics.

Together, these novel advancements in titanium osteosynthesis systems have the potential to overcome the disavantages of currently available titanium osteosynthesis systems.

Which biodegradable osteosynthesis systems are preferred?

A biodegradable osteosynthesis system should meet two intertwined criteria to be used as an osteosynthesis system: (1) the biomaterial needs to be biocompatible with the host tissue and (2) the mechanical properties should be sufficient for stable fixation of fracture or osteotomy segments during the surgical procedure (primary stability) and during the degradation of the biomaterial, with a gradual transfer of stress to the healing bone[41].

Over the last few decades, both the titanium and biodegradable osteosynthesis systems have been improved[41,103]. Regarding the titanium systems, these include the aforementioned improvements as well as an adjusted screw head to improve the grip on the screws. Biodegradable systems have been improved by modulating the polymer composition, e.g., using L- and D-chirality of lactic acid, or by copolymerization with different homopolymer ratios, and by using ultrasound pin welding instead of screws. Furthermore, biodegradable systems consisting of biocomposites with osteoconductive properties have been introduced[41]. Currently, over 12 different titanium and over 36 different biodegradable osteosynthesis systems are available for OMF-surgery, without taking the different sizes of each system into account[41]. As the improvements to both types of systems are recent, there is a lack of studies comparing them and so it is still unclear to surgeons which titanium and biodegradable osteosynthesis systems are preferable for maxillofacial traumatology and orthognathic surgery from both the biological and biomechanical perspectives.

Biocompatibility

The most commonly used (co)polymers in biodegradable osteosynthesis systems consist of poly(α-esters) such as poly(L-lactic acid) (PLLA), poly(D,L-lactic acid) (PDLLA), poly(lactic-*co*-glycolic acid) (PLGA), or poly(L-*co*-D,L-lactic acid-co-trimethylene carbonate) (P(LLA-*co*-DLLA-*co*-TMC))[41]. Biodegradable osteosynthesis systems should, preferably, be completely resorbed within 12 months[104]. However, foreign body reactions to polymeric biodegradable materials remain a major concern, even years after implantation[39]. Factors that influence foreign-body reactions are implant related (e.g., polymer composition, crystallinity, geometry, surface topology), recipient related (e.g., blood supply), and plate location related (e.g., epiperiosteal versus subperiosteal)[41,105,106]. **Chapter 6** focused on comparing the long-term (i.e., up to 4-years follow-up) biocompatibility and degradation of four biodegradable copolymeric osteosynthesis

systems using a goat model. Although all the biodegradable systems were safe to use and well-tolerated, the SonicWeld Rx system showed the most predictable degradation profile. However, nanoscale residual polymeric fragments, predominately accumulated in adipocytes, were observed at every system's assessment. To put these results into perspective, knowledge about the degradation and host response to (co)polymeric biomaterials is essential.

Extracellular degradation of poly(α-esters) occurs through hydrolysis (two phases), enzymatic degradation, and oxidation. During hydrolysis, cleavage of the ester bonds by water results in oligomers and monomers, such as lactic acid and glycolic acid (primary hydrolysis)[107,108], that can enter the tricarboxylic-acid cycle and are then eliminated as carbon dioxide and water (secondary hydrolysis). Secondary hydrolysis is the rate-limiting step and depends highly on the crystallinity and hydrophobicity of the intermediate products[109]. Furthermore, enzymes secreted by macrophages and derived from the blood can contribute to hydrolysis through extracellular hydrolysis[41]. Macrophages can also phagocytise biomaterial particles. In addition, inflammatory cells (e.g., macrophages, neutrophils) can induce depolymerisation of polymers by oxidation via the release of reactive oxygen species[110]. Macrophages can also undergo fusion to improve their efficiency and form multinucleated giant cells[111] which can remain for up to 24 months after implantation (**Chapter 6**). Although the phagocytosis capacity of multinucleated giant cells is reduced compared to macrophages, the capacity of extracellular degradation is substantially increased by secreting higher concentrations of enzymes and reactive oxygen species into the interface between the multinucleated giant cells and implant[111].

The progression of the host response is affected by the acidic degradation products of the poly(α-esters) as they alter the microenvironment in different ways. A lowering in pH intensifies the inflammatory response that results in fibrous encapsulation of the implant[112,113]. Furthermore, the acidic degradation products are autocatalytic, resulting in progressive degradation of the remaining polymers and an increase in the inflammatory response. Additionally, bulk degradation leads to fragmentation of the polymer that may result in phagocytized particles within the fibrous tissue[41]. Demineralization of the surrounding bone can occur whenever the degradation occurs too quickly and the surrounding tissue fails to eliminate the degradation products[42]. The possibility to induce a foreign body reaction (e.g., a sterile abscess formation) is dependent on an equilibrium between the levels of degradation products, the degree of fibrous encapsulation, and the ability of the host to eliminate the degradation

products[41]. Short-term foreign body reactions are mainly caused by fast-degrading polymers (e.g., PGA)[114] while delayed foreign body reactions are often associated with slow-degrading polymers (e.g., PLLA) with high crystallinity and crystalline degradation fragments[7,115,116]. Foreign body reactions to polymeric biodegradable materials can occur to particle sizes of <2 µm, even years after the implantation[39].

Currently, two main hypotheses regarding the aetiology of foreign body reactions to these polymeric biomaterials exist. After implantation, the biodegradable polymers are encapsulated by fibrous tissue that acts as a semi-permeable membrane[105]. The first hypothesis is that, as the polymer degradation continues over time, the size of the polymeric fragments decreases while the number of particles increases. These particles cannot pass the semi-permeable membrane. Subsequently, the osmotic pressure within the area surrounded by the fibrous layer increases and this results in a clinically observable swelling that, without an intervention, remains[7]. An alternative hypothesis is that, eventually, the acidic polymeric fragments become small enough to pass the membrane. This results in a decrease in pH of the surrounding tissues which then causes excessive sterile inflammation[117,118] accompanied by phagocytosis of any residual fragments[105]. However, since crystalline fragments are stable and more resistant to further hydrolytic degradation, they accumulate in the macrophages and multinucleated giant cells, and then remain *in situ*. Furthermore, extra- and intracellular residual fragments can lead to the accumulation of crystalline oligomeric stereo-complexes over time that are resistant to further hydrolytic degradation[41,119]. These two hypotheses could also occur simultaneously.

A remarkable accumulation of polymeric birefringent fragments in adipocytes within the medullary bone cavity was observed at every system's assessment, even at the 4-year follow-up (**Chapter 6**). Since the crystalline regions of (co)polymers, the intermediate degradation products and the crystalline oligomeric stereo-complexes that can be formed *in vivo* over time are hydrophobic[104,119,120], this could explain why these fragments were particularly observed in adipocytes. The copolymer of the SonicWeld Rx system was the only one that was amorphous; all the other assessed systems were semi-crystalline. Similar birefringent fragments, derived from as-polymerised PLLA, were observed in a case report[7] and experimental studies up to the 5-year follow-up[121,122]. Such particles were found intracellular after 3 and 4.5 years of implantation, although the particles decreased in size over time[121]. Crystalline fragments derived from as-polymerised PLLA can induce foreign body reactions even up to 5.7 years after implantation[7,123]. Another clinical study that focused on the efficacy

of an osteosynthesis system composed of unsintered hydroxyapatite/PLLA composite, with a 12-month follow-up, showed that the removed symptomatic systems included up to 65% crystalline regions in the explanted polymers[12]. In a study that implanted the Resorb X osteosynthesis system (PDLLA) at the condyle of sheep mandibles, no foreign body reactions and complete bone formation were observed after 12 months [124]. Another study showed complete bone formation 18 months after implanting the LactoSorb system (poly[82LLA-co-18GA]) in the maxillofacial area of Göttingen minipigs without signs of foreign body reactions[125]. In contrast, after implanting the Inion CPS system (poly([70-78.5]LLA-co-[16-24]DLLA-co-4TMC) in sheep, the system was surrounded by a fibrous capsule with granulomatous foreign body reactions after 52 weeks[126]. In the literature, foreign body reactions have predominately been reported for biodegradable osteosyntheses with a high proportion (i.e., >70%) of PLLA[7,41,116,127] or poly(glycolic acid) (PGA)[41]. More amorphous copolymers such as PDLLA (e.g., 50LLA/50DLA ratio) are more hydrophilic, and degrade and resorb more quickly and predictably[128]. The results in **Chapter 6,** as well as those of different (pre-)clinical studies[39,41,129], emphasize that the (co)polymers used in biodegradable systems should be completely amorphous. Future research should focus on amorphous (co)polymers with a minimum follow-up of ≥24 months so that a proper degradation assessment can be performed. Also, it remains unknown whether the observed nanoparticles may be harmful in the long-run (i.e., >4 years). Since microplastics have been shown to be toxic *in vitro*, with a potential impact on human health (e.g., effects on the gastrointestinal tract, lungs, immune system, blood components)[130,131], the effects of the observed nanoparticles need further research.

Other than (co)polymer composition, the geometry and surface topography of the implanted materials also affect biocompatibility *in vivo*[129]. Thick biomaterials, especially with points and sharp edges, can increase the risk of foreign body reactions[39,132,133]. In contrast, thinner biomaterials, as well as smaller sized polymeric particles used to engineer a biomaterial, allow for quicker degradation and a lower risk of foreign body reactions[129,134,135]. A smooth well-contoured shape without acute angles induced macrophage polarization towards macrophages with an immune regulatory phenotype[76,77]. *In vivo* biocompatibility of medical devices, such as implants, can be significantly improved by tuning the spherical dimensions[129]. Furthermore, low implant volume reduces the amount of acidic degradation products and thus reduces the risk of (late) foreign body reactions[41]. The fact that screws possess acute angles, while welded pins do not, may explain the favourable degradation profile of the SonicWeld Rx system compared to the BioSorb FX, Inion CPS and LactoSorb biodegradable systems (**Chapter 6)**[41,136,137]. Novel biodegradable system development should incorporate geometry and

surface topography in the design-phase as these characteristics are tuneable and may be efficient ways to decrease foreign body reaction risk, hasten degradation, enhance quicker bone formation, and balance the degradation and regeneration equilibrium[39].

Mechanical properties

The mechanical properties of osteosynthesis systems depend on several factors including composition (i.e., titanium (alloys) or (co-)polymers), the production processes (e.g., stamping versus laser cutting of titanium systems)[138–140], dimensions, polymer self-reinforcement[141], the application method (i.e., screws or ultrasound welded pins)[48], ageing, and sterilization methods[142–144]. To guide the selection of osteosynthesis systems from a biomechanical perspective, the mechanical properties of 15 biodegradable and 6 titanium straight, four-hole osteosynthesis systems were assessed and compared (**Chapter 7**). The stiffness of an osteosynthesis system is a more clinically relevant outcome than maximum tensile load since this affects adequate fixation and bone healing (i.e., malunion and non-union)[145] while maximum tensile load is only relevant whenever the bone segments are already separated by more than a few millimeters. In the latter case, this will certainly result in compromised bone healing or malunion. Regarding the biodegradable systems, the SonicWeld Rx 2.1 mm system was recommended for midface fractures and osteotomies and the Inion CPS 2.5 mm for mandibular fractures and osteotomies. Regarding the titanium systems, the CrossDrive (2018) and MaxDrive 1.5 mm systems were recommended for midface fractures and osteotomies, and the CrossDrive (2018) and MaxDrive 2.0 mm systems for mandibular fractures and osteotomies.

Several studies assessed the mechanical forces surrounding osteosyn-theses applied to maxillofacial fractures[146–152], osteotomies[153,154] and reconstructions[155]. After maxillofacial trauma, the reported bite force increases up to 64 N by the second postoperative fracture fixation day, 92 N after 1 week, 187 N after 4 weeks, and up to 373 N at the 3-month follow-up[146]. Other studies focusing on trauma patients showed that 100 N forces were measured after 4 weeks of fixation[148,150]. The mechanical forces around maxillofacial osteotomies have been reported to increase from 21±14 N (i.e., after 1 week) to 65±43 N (i.e., after 6 weeks)[149] while other studies reported forces ranging from 82.5 to 132 N[153,154]. The masticatory forces after mandibular reconstructions ranged from 28 to 186 N[155]. However, the mechanical stress surrounding osteosynthesis systems is multi-factorial and is affected by the location of the fracture[31], differences in interfragmentary stability[31], mandibular height[31], degree and direction of movement[156], and preoperative mastericatory forces[148,157,158]. Additionally, as bone healing progresses, the forces will

be shared by the osteosynthesis system and the underlying healing bone. Therefore, it remains difficult to estimate the least mechanical properties an osteosynthesis system has to meet.

Within the limitations of finite element analyses (e.g., assumming the masticatory forces are fixed), three-dimensional analyses indicated that the biomechanical stresses surrounding (biodegradable) osteosynthesis systems remain far below the threshold of their ultimate strength [14,34,152,159]. In addition, the systematic reviews of fracture and osteotomy osteosyntheses showed that the efficacy of titanium and biodegradable osteosyntheses is similar (e.g., absence of malunion) indicating that the less favourable mechanical properties of biodegradable osteosynthesis are still sufficient to achieve similar healing outcomes (**Chapters 2 and 3**). However, as also observed from the empirical evidence, the mechanical properties of biodegradable osteosyntheses of mandibular osteotomies may be insufficient to avoid micromovements. Future research should also focus on these micromovements since they play an important role in developing foreign body reactions[39].

Finite element analyses also demonstrated that the stress surrounding conventional screws is much larger compared to those of plates, indicating that material complications may arise from the screws rather than the plates (e.g., screw loosening or fractures)[159]. The positive effect of ultrasound welding of thermoplastic pins was demonstrated by the superior mechanical properties of the SonicWeld Rx (PDLLA with thermoplastic pins) compared to the Resorb X system (PDLLA with screws). Additionally, ultrasound welding caused a shift of the weakest link of the complete osteosynthesis system from the screw-plate interface (i.e., all other biodegradable systems) to the plate itself. Therefore, ultrasound welding may reduce screw-related material complications but this has to be investigated by future research.

The comparison of the mechanical properties of 15 biodegradable and 6 titanium systems was only based on static mechanical tests of the initial materials (i.e., from the shelf; **Chapter 7**). Since the stresses on osteosynthesis systems are dynamic (e.g., due to repetitive mandibular loadings), the next step would be to perform dynamic and fatigue testing of osteosynthesis systems in relation to fractures and osteotomies. A previous study that performed fatigue testing of standardised PLLA fibers reported a decrease of -3% in the elastic modulus after only 10 cycles[160]. Furthermore, stress concentration due to long-term loading of biteforce and muscle traction on the osteosynthesis were shown to be important factors that lead to osteosynthesis system fracture[152]. In addition, since biodegradable copolymeric systems undergo bulk degradation, thereby decreasing

their mechanical properties with time[41,126], the mechanical properties of different biodegradable systems during degradation should be assessed and compared. Future research should also aim to assess the least required mechanical properties for an osteosynthesis system for specific cases. Ideally, these insights should be incorporated in a validated model in which the abovementioned osteotomy and fracture parameters can be easly adjusted (e.g., an *in silico* model).

Recent studies developed a time-dependent *in silico* model to support the design of biodegradable osteosynthesis plates[161] as well to optimize their topology[162], but both models still need to be validated in a clinical population. Although such models are currently not available for maxillofacial fractures, the rapid development of science and technology in recent years, including three-dimensional printing technologies such as stereolithography and selective laser sintering[163] means patient-specific biodegradable osteosynthesis systems are now feasible[164,165]. Patient specific osteoinductive implants made by stereolithography to repair orbital floor defects have, to date, shown promising results[165]. Constructing and validating such *in silico* models would also contribute to, and accelerate, the translation to patient-specific biodegradable osteosyntheses systems for maxillary and/or mandibular fractures and osteotomies[41].

Concluding from the results of both the biological and biomechanical perspectives, the SonicWeld Rx 2.1 mm seems to have the greatest potential as a biocompatible biodegradable copolymeric osteosynthesis system, with favourable geometry and mechanical properties.

Reliability and accuracy of the torque applied to titanium screws

Besides the properties of the osteosynthesis system, the amount of torque applied to the screws by OMF-surgeons is also an important factor to achieve primary stability by generating compression and friction between the osteosynthesis system and the underlying bone[8,9]. Therefore, the test-retest and intra-individual reliability, and the accuracy of the torque applied to titanium osteosynthesis screws by residents with varying years of experience and OMF-surgeons, were assessed (**Chapter 8**). The OMF-surgeons achieved good to excellent intra-individual reliability. Regarding the 1.5 mm screws, the first and second year residents showed sufficient accuracy with the reference interval, but insufficient reliability, while the third and fourth year residents demonstrated sufficient intra-individual reliability but poorer compliance with the

reference interval. Regarding the 2.0 mm screws, all the residents achieved sufficient reliability and accuracy.

A possible explanation could be that first and second year residents are unaware of the possible complications that may arise after applying excessive torque to the 1.5 mm screws, and thus apply excessive torque. This is supported by the findings that the first year residents applied the highest torque to the 1.5 mm screws and the second year residents showed the highest number of stripped screw holes. With increasing awareness of the complications that may arise on applying excessive torque, the third and fourth year residents became more careful – but also more reliable – at the expense of lower accuracy. Thus, training residents and/or verifying the applied torque by experienced OMF-surgeons remains necessary to achieve high accuracy and reliability with the 1.5 mm screws. Previous studies that focused on orthopaedic osteosynthesis screws demonstrated that there is a strong linear correlation between the insertion torque of osteosynthesis screws and pull-out strength in experimental settings (e.g., polyurethane foam) and in trabecular bone (R^2 0.95 to 0.98)[166]. Based on these results, accurate and reliable torque application to osteosynthesis screws in OMF-surgery can potentially increase fracture or osteotomy stability, resulting in less compromised healing, and in reducing the need for emergency screws following intraoperative bone stripping, with a corresponding reduction in operation time and costs.

Although the study described in **Chapter 8** only focused on titanium osteosynthesis screws, accurate and reliable application of the torque to biodegradable screws is even more important to avoid perioperative screw breakage. The difference between hand-tight and maximum torque is much smaller for biodegradable screws compared to titanium screws and thus biodegradable screws are more prone to screw breakage (**Chapter 7**). Therefore, OMF-surgeons and residents who want to use biodegradable systems with screws can be trained pre-clinically with the model described in **Chapter 8** to decrease the risk of perioperative screw breakage. Additionally, in orthopaedic surgery, the tapping torque was shown to be a reliable predictor of insertional torque[167]. Since the screw holes of biodegradable screws need to be pre-tapped before the actual screw insertion, the predictive value of the applied torque during tapping may also be useful for biodegradable screw insertion. Future research should assess whether the predictive value of the tapping torque is also applicable to biodegradable screws in OMF-surgery.

Future perspectives

Preclinical studies

Biocompatibility

Nanoscale residual polymeric fragments derived from the BioSorb FX, Inion CPS, SonicWeld Rx, and LactoSorb biodegradable systems could still be observed after 4 years. It is unclear whether these nanoparticles may be harmful in the long-run (**Chapter 6**). Therefore, the next essential step for biocompatibility assessments of biodegradable copolymeric osteosynthesis systems should be to investigate whether the amount of observed crystalline nanoparticles is able to induce a foreign body reaction. Since animal studies are still the gold standard for assessing host responses, future research could implant the nanoparticles in large animal models for long-term outcome data. A more ethical alternative would be to seek for new *in vitro* techniques to analyse biological responses to biomaterials, such as foreign body reactions on a chip and complex cell-culture systems mimicking *in vivo* tissue environments, without the need to sacrifice animals for scientific research. These new techniques are currently being developed but have not been validated yet[41,168–171]. At this point in time, the United States Food and Drug Administration (FDA) still recommends and demands that *in vivo* degradation should be conducted using an appropriate animal model and following the ISO10993 standards[172].

Besides the currently available biodegradable synthetic copolymeric systems (e.g., PDLLA), novel biodegradable systems composed of degradable metals (e.g., magnesium and zinc alloys)[173–175] or natural polymers (e.g., amorphous silk fibres derived from the silkworm *Bombyx mori*) are being developed[41]. Biodegradable metals are promising alternatives to polymeric osteosynthesis systems due to their mechanical properties and less harmful degradation products. Biodegradable metal degradation is driven by anodic and cathodic reactions that result in the production of oxides, hydroxides and hydrogen gas[41,174]. *In vitro* control degradation rates can be achieved by tailoring the microstructure, surface properties and coatings. However, a major challenge of biodegradable metals is the unpredictable degradation profile *in vivo* with subcutaneous emphysema due to the accumulation of hydrogen gas[41]. The correlation between the *in vitro* and *in vivo* degradation profiles is poor, e.g., because of the fibrous encapsulation that slows the degradation of the implant *in vivo*[176,177]. Therefore, although the short-term degradation profiles of biodegradable magnesium alloys look promising[178–180], research

should focus on controlling the degradation rates *in vivo* and assessing the long-term outcomes of biodegradable metal systems.

Silk is the most recent addition to biodegradable materials[41]. Silk is degraded enzymatically, e.g., by protease XIV, matrix metalloproteinase and collagenase. Silk degradation results in peptide fragments[181], and the degradation times can be tailored from minutes to years by controlling the material variables such as molecular weight, surface topography, β-sheet content, and porosity[41]. In addition, it can be easily processed into mechanically robust three-dimensional bulk materials with excellent machinability. This provides the option for patient specific silk-based biodegradable osteosynthesis systems. The preliminary fracture fixation efficacy results were comparable to the current copolymeric biodegradable systems[182]. In addition to using silk for osteosynthesis systems, it is also a promising material for drug delivery and pulsatile or delayed drug release (e.g., primer and booster vaccines)[41]. Although synthetic copolymers such as PLGA have also been proposed for drug delivery or delayed drug release, the acidic degradation products make these biomaterials incompatible with the proteins in the vaccines resulting in the denaturation of the proteins[183]. The degradation products of silk, on the other hand, are non-acidic which makes it attractive for such purposes[41,184]. However, no data are currently available on the short- and long-term effects of *in vivo* produced degradation products. Future research should focus on these aspects as well as compare the biocompatibility and safety profiles of novel biodegradable materials with other available biodegradable materials such as the copolymers assessed in this thesis.

Finally, since many of the currently available studies focused on material composition, but less on the microstructure of biomaterials, material morphology, geometry, internal structure, surface topology and porosity require more attention as these are important factors that contribute to the host response[41,185]. Surface modifications (e.g., polarity, charge) have been shown to influence cellular behaviour[186–189] and that surface coatings can have antimicrobial effects[190]. Tuning the spherical dimensions of biomaterials increases their biocompatibility[129]. Furthermore, bioactive molecules can be incorporated in biomaterials[191] which may be useful for incorporating antibiotics in osteosynthesis systems used in revision surgery following an infection. These factors may improve the next-generation (biodegradable) osteosynthesis systems so that the host responses are influenced and the risk of surgical site infections are decreased[129].

Mechanical properties

Future research should assess dynamic and fatigue testing of osteosynthesis systems, in relation to fractures and osteotomies, of both the initial materials (i.e., from the shelf) as well as during degradation. Moreover, the least required mechanical properties of an osteosynthesis system for patient-specific fractures and osteotomies should be assessed (e.g., by developing *in silico* models). In addition, three-dimensional printing technologies such as stereolithography and selective laser sintering can now be used to design patient-specific biodegradable osteosynthesis systems[163–165]. Applying such new design methods and biomechanical analyses could lead to implants with a better fit, stress resistance and dimensions[39]. Furthermore, since there seems substantial added value to ultrasound welding of pins, compared to conventional screws, regarding the mechanical properties, biocompatibility, perioperative handling and reduction in operation time, the technique should be elaborated further. Preferably, a biocompatible (synthethic) polymer that has favourable intrinisic material properties should be combined with ultrasound welding to improve both the biocompatibility and the mechanical properties of the system.

In addition to the next steps in research regarding biodegradable copolymeric osteosynthesis systems, the mechanical properties of biodegradable metal- and silk-based osteosynthesis systems should be assessed and compared to the mechanical properties of synthethic (co)polymers. Recent studies assessed the material properties of biodegradable metals[177,192,193] and silk[194], and showed that the mechanical properties of both are much closer to bone than (co)polymeric materials[41]. However, since the processing of a material into an osteosynthesis system (e.g., to achieve geometry, sterilization etc.) can alter the mechanical properties of the material, future research needs to investigate the mechancial properties of metal- and silk-based osteosynthesis systems, and compare these with the mechanical properties of available (co)polymeric osteosynthesis systems. Additionally, since the current sizes of the biodegradable osteosynthesis systems can complicate stress free closure of the incision (e.g., in mandibular osteosyntheses), different materials with more favourable properties could result in reducing the sizes of the biodegradable systems[39,41]. Since biodegradable copolymers[165], metals[195], and silk[41] can be 3D-engineered, this may even amplify these new materials further when combined with patient-specific osteosynthesis system engineering.

Reliability and accuracy of the torque applied to screws

In **Chapter 8** we described that the accuracy and reliability of the torque applied by residents to 1.5 mm titanium screws was insufficient. Since the reference intervals were based on the experienced OMF-surgeons in a single centre, the next step would be to validate the defined reference intervals externally. Despite previous studies showing that the torque applied to osteosynthesis screw contributes to primary stability[8,9], it remains unknown whether bone healing is affected by the residents' inaccuracies. Future research should determine the effect of not achieving accurate torque on the clinical outcome by, e.g., using a small animal model. In addition, since biodegradable screws are more prone to perioperative breakage (**Chapters 2 and 3**), reliability and accuracy analyses of the torque applied to biodegradable screws should also be performed. Finally, the presented simple test set-up could be used to train clinicians pre-clinically. The test set-up can be easily adjusted for other disciplines that use osteosynthesis screws. A recent systematic review showed that, on average, 25% of all the osteosynthesis screws inserted by experienced orthopaedic and trauma surgeons are irreparably damaged or have stripped screw holes[196]. Currently, it remains unknown how residents of these disciplines perform. The presented test set-up can be easily adjusted by using a different torque meter (i.e., one that can measure higher torques for larger screws) and different high pressure laminate blocks, making this test set-up useful for different sized osteosynthesis systems. If future evidence shows that not achieving an accurate torque affects the clinical outcome, a torque ratchet could be developed to achieve sufficient torque perioperatively.

Clinical studies

An important aspect when assessing efficacy, morbidity and symptomatic osteosynthesis removal is the duration of follow-up. The studies included in the systematic reviews in **Chapters 2 and 3** predominately had 2-year follow-ups. Although this is sufficient follow-up to assess efficacy (e.g., adequate bone healing), symptomatic osteosynthesis removal can occur later on (i.e., >2 years follow-up) due to osteosynthesis system palpability, thermal sensitivity or foreign body reactions (**Chapter 5**)[114,123,126,197–199]. In a cohort study with a follow-up of 67 months, 7% of the included patients underwent symptomatic biodegradable osteosynthesis removal between 24 and 67 months[11]. Additionally, microscopic polymeric remnants were observed *in vivo* at the 2- and 4-year follow-ups (**Chapter 6)**[126]. Similarly, titanium system removals due to infection and discomfort occurred after the 4-[29] and 5.5-year follow-ups[199]. Since the currently available comparative studies predominately had follow-ups of up to 2-years, future

research should also include long-term follow-up assessments (e.g., ≥5 year follow-ups) in the pre-specified protocols. The patients included in the multicentre RCT described in this thesis (**Chapter 5**) will be assessed in the future after a follow-up beyond 10 years. This will provide unique insights into the long-term outcomes of biodegradable versus titanium osteosyntheses.

In addition, the quality of the evidence should be improved. None of the currently available studies have a low risk of bias. Even if blinding of the surgeon and outcome assessor was not taken into account, current evidence is still prone to bias due to deviations from the intended intervention or missing outcome data. This emphasizes the need for pre-specified, -registered and well-defined RCT protocols. In particular, these protocols should focus on well-defined (i) in- and exclusion criteria (e.g., separating the inclusion of maxillary and mandibular fractures/osteotomies) and (ii) endpoints to minimize reporting bias. In addition, (iii) appropriate follow-up is advocated to minimize attrition bias and (iv) indications for device removal should be clearly defined and followed to reduce detection bias. Furthermore, to avoid intra-operative switching, OMF-surgeons should be extensively trained in the trial's osteosynthesis systems, prior to conducting the trial, so that surgeon-related biases are minimised[69]. Collecting high quality evidence can also reduce bias as well as leading to performing proper additional analyses (e.g., subgroup analyses per surgical procedure or biodegradable system). Finally, as also reported in the performed systematic reviews (**Chapters 2 and 3)**, some of the authors were difficult to get hold of and, when they were, some authors were not transparent or the data could not be shared. Transparency and sharing of data among researchers improves data quality and increases the power of the statistical analyses while reducing the costs and the burden of the scientific research on patients. By sharing data, individual patient data meta-analyses become possible. The aforementioned factors contribute to being able to elucidate the potential of biodegradable osteosyntheses, draw firmer conclusions for specific populations and, thus, to improving patient care quality.

Data regarding three-dimensional analysis of patients undergoing trauma and orthognathic surgery is growing. Therefore, these could and should be used in outcome analyses (e.g., malunion, skeletal stability, and aesthetic outcomes). Also, as the patient's opinion regarding outcomes is of high importance, patient reported outcomes (e.g., using the Mandibular Function Impairment Questionnaire) should be assessed. Furthermore, only a single study that focused on cost-effectiveness of both interventions could be included in both systematic reviews. Since economic evaluation is nowadays

indispensable for any intervention, and since it is expected that the health-care costs will rise constantly until 2060[200], future studies should also consider cost-effectiveness analyses, including primary (e.g., osteosynthesis system, operation time) and secondary costs (e.g., additional interventions, absence of work).

Final remarks: a broader perspective

Although not discussed in this thesis, different biodegradable materials have also been developed and used for guided bone regeneration (GBR) in oral surgery[201–205], in head and neck oncology[49], and for pulsatile or delayed drug release[41]. In GBR, collagen is currently the most frequently used resorbable barrier membrane but membrane collapse into the defect can result in restricting the volume available for bone regeneration[206]. Biodegradable PLA membranes have been successfully used for GBR of alveolar bone defects with good biocompatibility, osteogenic capabilities, and sufficient mechanical properties[203]. In addition, biodegradable PLA membranes containing zoledronic acid have been developed for enhanced and faster bone formation during GBR[207]. Besides synthetic polymers, biodegradable magnesium barrier membranes[202] and fixation screws[201] for GBR are also showing promising results as are silk fibroin/collagen blended membranes, which are biocompatible, have good mechanical properties, and show a less severe inflammatory reaction against the membrane compared to collagen membranes[204]. In head and neck oncology, a recent RCT compared titanium versus biodegradable osteosynthesis in the mandibulotomy access of patients with squamous cell carcinoma of the tongue, all of whom underwent postoperative radiotherapy[49]. The authors concluded that the biodegradable and titanium osteosyntheses showed similar efficacy and complication rates, but with significantly less scattering of the radiotherapy surrounding the biodegradable compared to the titanium osteosyntheses. Finally, biodegradable biomaterials can also be used for pulsatile and/or delayed drug release systems (e.g., single-dose primer and booster vaccines) and for biodegradable sensors[41]. A recently developed biodegradable electronic magnesium-based stent included controlled drug delivery to prevent restenosis, nanoparticles for scavenging reactive oxygen species to reduce inflammation, and biodegradable sensors to monitor temperature and blood flow[41,208]. The immense potential of using biodegradable biomaterials for health-care quality and costs have led to a substantial increase in interest in biomaterials by researchers as well as clinicians over the last years, and it is expected to increase even more in the forthcoming years[41,104,109].

Conclusions

Based on the results of the studies described in this thesis, it can be concluded that:

- Based on current evidence, biodegradable osteosynthesis is a viable alternative to titanium osteosyntheses when applied to treat maxillofacial trauma, with similar efficacy and significantly lower symptomatic osteosynthesis removal, but with higher perioperative screw breakage (**Chapter 2**).
- Based on current evidence, biodegradable osteosynthesis is a valid alternative to titanium osteosyntheses for orthognathic surgery, with similar efficacy, but with longer operation times (**Chapter 3**).
- The long-term performance of the Inion CPS biodegradable system is inferior compared to the KLS Martin titanium system regarding symptomatic osteosynthesis removal following fixation of Le Fort-I, zygomatic and mandibular fractures, and Le Fort-I and/or bilateral sagittal split osteotomies. Biodegradable osteosyntheses removal occurred only after mandibular osteotomy fixation (**Chapter 5**).
- The SonicWeld Rx biodegradable osteosynthesis system has the most predictable degradation profile compared to the BioSorb FX, Inion CPS and LactoSorb biodegradable osteosynthesis systems (**Chapter 6**).
- Of the tested biodegradable osteosynthesis systems, the SonicWeld 2.1 mm biodegradable systems have the most favourable mechanical properties for midface fracture fixation and osteotomies, and the Inion CPS 2.5 mm biodegradable system for mandibular fractures and osteotomies (**Chapter 7**).
- The residents' accuracy and reliability in applying torque to titanium osteosynthesis 1.5 mm screws are insufficient. Both accuracy and reliability can be improved using a simple preclinical training model (**Chapter 8**).

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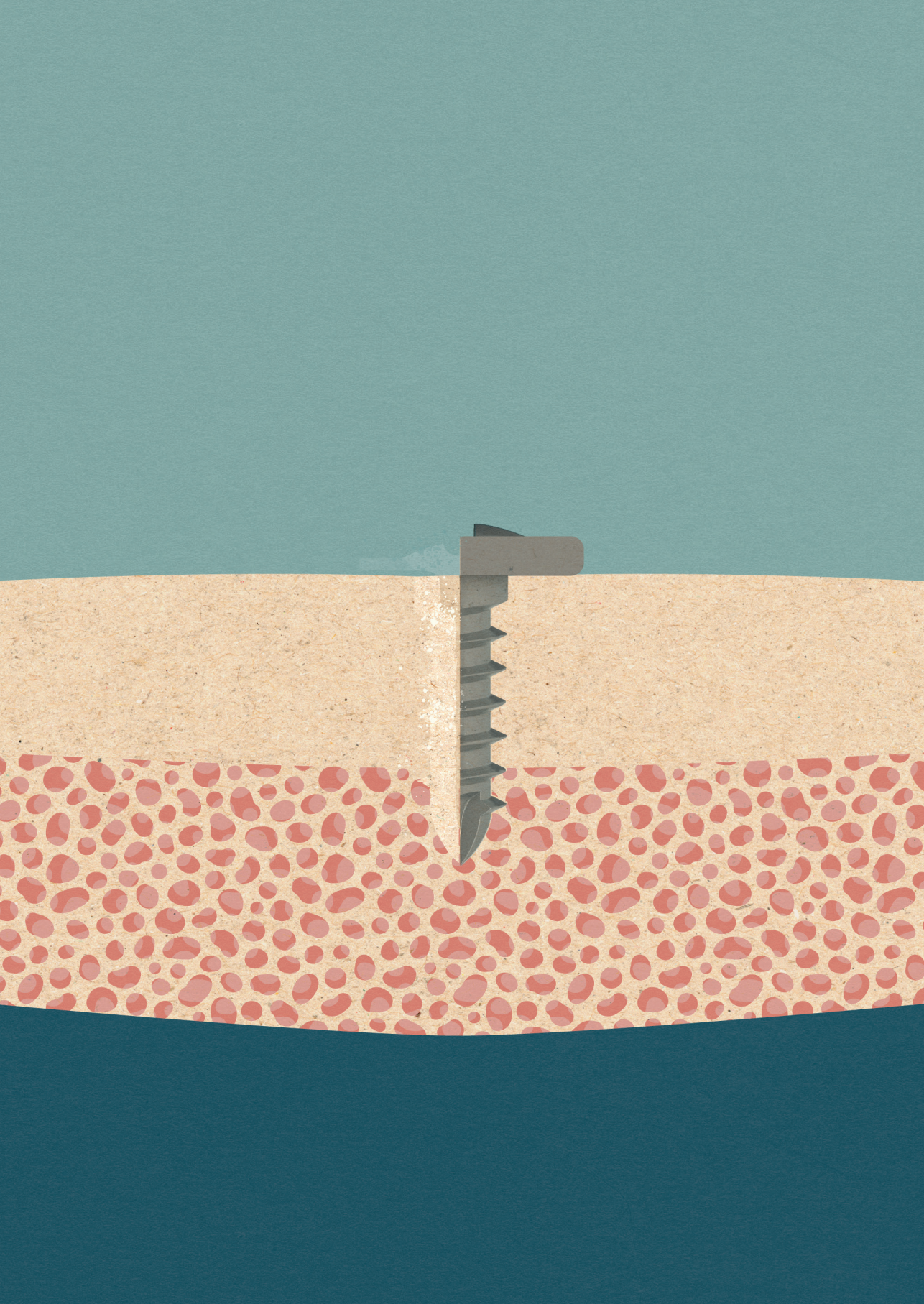

Chapter 10

Summary

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Introduction

Osteosynthesis systems, which consist of plates and screws, are applied to fixate bone segments. These systems are commonly used for maxillofacial trauma, and in orthognathic and reconstructive surgery. Titanium osteosynthesis systems are currently the gold standard. However, their disadvantages include temperature sensitivity, tactile sensation of plates and screws, possible growth restrictions, hampering of imaging and radiotherapy, presence of titanium particles in the lymph nodes, extreme stiffness resulting in stress shielding of the underlying bone, and potential mutagenicity.

Biodegradable plates and screws that are commonly composed of degradable synthetic polymers (e.g., polylactide) and may reduce removal rates in a second operation, while also avoiding the aforementioned disadvantages of titanium osteosyntheses. Biodegradable systems have, however, their own limitations including limited mechanical properties, palpability due to bulkiness, and possible foreign body reactions.

The aim of the research described in this thesis was to compare the *in vitro* and *in vivo* performances of different biodegradable osteosynthesis systems, as well as to compare the (clinical) performance of biodegradable and titanium osteosynthesis systems. In addition, since the amount of torque applied to the screws is also important to achieve primary stability of an osteosynthesis, the accuracy and reliability of the torque applied by residents and experienced OMF-surgeons to titanium osteosynthesis screws were assessed.

Key findings

The aim of the study described in **Chapter 2** was to conduct a systematic review, with meta- and trial sequential analyses, to assess the efficacy and morbidity of biodegradable versus titanium osteosyntheses after maxillofacial trauma. MEDLINE, EMBASE, and CENTRAL were searched for randomised controlled trials, and prospective and retrospective controlled studies (last search 20 April 2019). Five time periods were studied: perioperative, short-term (0-4 weeks), intermediate (6-12 weeks), long-term (>12 weeks) and overall follow-up. After screening the 3542 found records, 24 studies were included, comprising 2450 patients. All had a high risk of performance and detection bias due to the nature of the interventions. Meta-analysis showed no differences in efficacy and morbidity between biodegradable and titanium osteosyntheses. The risk of perioperative screw breakage was significantly higher (risk ratio [RR] 17.13, 95% confidence interval [CI] 2.19;34.18) in the biodegradable group but the symptomatic

plate removal rate was lower (RR 0.11, 95% CI 0.02;0.57), which was confirmed by the trial sequential analysis. However, the quality of evidence ranged from very low to moderate. The current evidence showed that biodegradable osteosyntheses are a viable alternative to titanium osteosyntheses in maxillofacial trauma treatment, with similar efficacy and significantly lower symptomatic osteosynthesis removal, but with higher perioperative screw breakage. Since the quality of the evidence varies from very low to moderate, high-quality research is necessary to elucidate the potential of biodegradable osteosyntheses.

The study described in **Chapter 3** aimed to assess the efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery. Patients with syndromic disorder(s) and/or cleft lip/palate were excluded. Randomised, prospective and retrospective controlled studies were searched for in nine databases (last search 11 February 2021). The perioperative, short-term, intermediate, long-term, and overall follow-up time periods were studied. A total of 9073 records was assessed, of which 33 were included, comprising 2551 patients. There were 'some concerns' regarding seven randomised controlled trials while another seven had 'high' risk of bias. No differences in malunion (qualitative analyses), mobility of bone segments (RR 1.37, 95% CI 0.47;3.99) and malocclusion (RR 0.93, 95% CI 0.39;2.26) were found. The operative time was significantly longer in the biodegradable group (standardised mean difference 0.50, 95% CI 0.09;0.91). Symptomatic plate/screw removal was comparable between both groups (RR 1.29, 95% CI 0.68;2.44). Skeletal stability was similar after most types of surgeries. The quality of evidence of the overwhelming majority of outcomes ranged from very low to moderate. The current evidence showed that biodegradable osteosyntheses are a valid alternative to titanium osteosyntheses for orthognathic surgery, but with longer operation times. High-quality research is necessary to elucidate the potential of biodegradable osteosyntheses.

In **Chapter 4**, we expressed our concerns regarding the completeness of a systematic review and meta-analysis that focused on the prevalence, causes and risk factors of titanium osteosynthesis removal in orthognathic surgery performed by other authors. We showed that at least three randomised controlled trials should have been included when applying their pre-specified inclusion and exclusion criteria. A thorough look at the applied methodology indicated that aspects of a sensitive search strategy were missing (e.g., lack of medical subject heading terms, explosion of terms, and truncations) and that their search strategy was not tailored to each included electronic database. In addition, we expressed our concerns regarding the interpretation of the funnel plots

and argued that, in contrast to the conclusions of the authors, publication bias could not be excluded.

In **Chapter 5**, a multicentre randomised controlled trial is described that compared the long-term (i.e., >5 years postoperatively) clinical performance of a titanium and a biodegradable system in oral and maxillofacial surgery. The study was performed in four hospitals in the Netherlands. Patients treated with a bilateral sagittal split osteotomy and/or a Le Fort-I osteotomy, and those treated for fractures of the mandible, maxilla, or zygoma, were included from December 2006 to July 2009. The patients were randomly assigned to either a titanium (KLS Martin CrossDrive) or a biodegradable group (Inion CPS). After a median follow-up of 99 (78;113) months, osteosynthesis removal was performed in 22 of the 134 (16.4%) patients treated with the titanium and in 23 of the 87 (26.4%) patients treated with the biodegradable system (hazard ratio biodegradable/titanium 2.0, 95% CI 1.1;3.8, P = 0.036). Occlusion, the visual analogue scale pain scores, and the Mandibular Function Impairment Questionnaire (MFIQ) showed good and (almost) pain free mandibular function in both groups. It was concluded that the performance of the Inion CPS biodegradable system was inferior compared to the KLS Martin CrossDrive titanium system regarding osteosynthesis removal in the abovementioned surgical procedures.

Foreign-body reactions are a major concern with biodegradable osteosyntheses and any evidence of complete resorption is lacking. Therefore, the study described in **Chapter 6** compared the physico-chemical properties, histological responses and radiographs of four copolymeric biodegradable osteosynthesis systems in a goat model with 48-months follow-up. The BioSorb FX [poly(70L-lactic acid-*co*-30DL-lactic acid)], Inion CPS [poly([70–78.5]L-lactic acid-*co*-[16–24]DL-lactic acid-*co*-4trimethylene carbonate)], SonicWeld Rx [poly(D,L-lactic acid)], and LactoSorb [poly(82L-lactic acid-*co*-18glycolic acid)] systems were randomly implanted subperiosteally in both the tibia and radius of 12 Dutch White goats. Negative controls (i.e., areas where no invasive treatment were performed) were included. Samples were assessed from the 6-, 12-, 18-, 24-, 36- and 48-month follow-ups. The surface topography was analysed with scanning electron microscopy (SEM). Differential scanning calorimetry and gel permeation chromatography were performed on the initial and explanted samples. Histological sections were systematically assessed by two blinded researchers using (polarized) light microscopy, SEM and energy-dispersive X-ray analysis. The SonicWeld Rx system was amorphous while the others were semi-crystalline. Foreign-body reactions were not observed during the complete follow-up. The new bone percentages attained with

the SonicWeld Rx and LactoSorb systems were similar to that of the negative controls after 18 months while the BioSorb Fx and Inion CPS systems reached these levels after 36 months. The SonicWeld Rx system showed the most predictable degradation profile. All the biodegradable systems were safe to use and well-tolerated (i.e., complete implant replacement by bone, no clinical or histological foreign body reactions, no [sterile] abscess formation, no re-interventions needed), but nanoscale residual polymeric fragments were observed at every system's assessment. Whether these nanoparticles may be harmful in the long run (i.e., >4 years) is not clear.

Recent improvements have led to the availability of many different biodegradable osteosynthesis systems. However, as there is a lack of studies comparing their mechanical properties, it is unclear to surgeons which biodegradable osteosynthesis systems are more suitable and preferable for fracture and osteotomy fixation from a mechanical perspective. To guide the selection, the study described in **Chapter 7** compared the mechanical properties of different biodegradable and titanium osteosynthesis systems. SonicPins Rx and xG were subjected to pull-out tests. Additionally, 15 biodegradable (Inion CPS 2.0 and 2.5 mm; LactoSorb 2.0 mm; Macropore 2.0 mm; Polymax 2.0 mm; BioSorb FX 2.0 mm; ResorbX 2.1 mm; Osteotrans-MX 2.0 mm with plate thicknesses of 1.0 and 1.4 mm; SonicWeld Rx_{plate}/Rx_{pins}, xG_{plate}/Rx_{pins} and xG_{plate}/xG_{pins} 2.1 mm without and with burr hole tapping) and six titanium (CrossDrive (2006), CrossDrive (2018), MaxDrive; all 1.5 and 2.0 mm) straight, four-hole osteosynthesis systems were evaluated. All the systems were subjected to tensile, bending and torsion tests. The pull-out loads of the SonicPins were comparable (P=0.423). The titanium systems' tensile loads were higher than those of the biodegradable systems (P<0.001). The CrossDrive (2018) and MaxDrive systems' tensile and torsional stiffness were lower, accompanied with higher ductility, than the corresponding CrossDrive (2006) systems (P<0.001). The bending stiffness of the 1.5 mm titanium systems was comparable to all the biodegradable systems (P<0.001) whereas the 2.0 mm system's bending stiffness was higher. Regarding the biodegradable systems, Inion CPS 2.5 mm had the highest tensile load and torsional stiffness, SonicWeld 2.1 mm the highest tensile stiffness, and BioSorbFX 2.0 mm the highest bending stiffness (P<0.001). On the basis of the results of the studied titanium osteosynthesis systems, we recommend the CrossDrive (2018) and MaxDrive 1.5 mm systems for midface fractures (e.g., zygomatic or maxillary fractures) and osteotomies (e.g., Le Fort I osteotomy), and the CrossDrive (2018) and MaxDrive 2.0 mm systems for mandibular fractures and osteotomies. When there is an indication for a biodegradable osteosynthesis system, we recommend the SonicWeld 2.1 mm or BioSorbFX 2.0 mm

systems for midface fractures and osteotomies, and the Inion CPS 2.5 mm system for mandibular osteotomies and non-load bearing mandibular fractures, especially when high torsional forces are expected (e.g., mandibular symphysis fractures).

Applying the right torque to osteosynthesis screws is important for stable fixation and undisturbed bone healing. The aim of the study described in **Chapter 8** was to compare test-retest and intra-individual reliabilities of the torque applied to 1.5 mm and 2.0 mm osteosynthesis screws by residents and OMF-surgeons, to define the reference torque intervals and to compare reference torque interval compliances. Five experienced OMF-surgeons and 20 residents, 5 from each of the 4 residency years, were included. Each participant inserted six 1.5x4 mm and six 2.0x6 mm screws into a preclinical model at two test moments two weeks apart (T1 and T2). The participants were blinded regarding the applied torque. Descriptive statistics, reference intervals, and intra-class correlation coefficients (ICC) were calculated. The OMF-surgeons and residents applied 100.8±13.6 Nmm and 92.4±20.7 Nmm torque to the 1.5 mm screws, respectively (P<0.001). Regarding the 2.0 mm screws, the OMF-surgeons and residents applied 431.7±99.4 Nmm and 322.5±77.5 Nmm torque, respectively (P<0.001). The reference torque intervals were 73.7 to 127.9 Nmm for the 1.5 mm screws and 233.9 to 629.5 Nmm for the 2.0 mm screws. The OMF-surgeons complied more to the reference intervals (1.5 mm screws: 95%, and 2.0 mm screws: 100%) than the residents (1.5 mm screws: 82%, and 2.0 mm screws: 90%; P=0.009 and P=0.007) with the ICCs ranging between 0.85-0.95 and 0.45-0.97, respectively. The residents' accuracy and reliability were inadequate regarding the 1.5 mm screws, but both measures had improved at T2 for both screw types compared to T1, indicating a learning effect. It was concluded that training residents and/or verifying the applied torque by experienced OMF-surgeons is necessary to achieve high accuracy and reliability, particularly for the 1.5 mm screws.

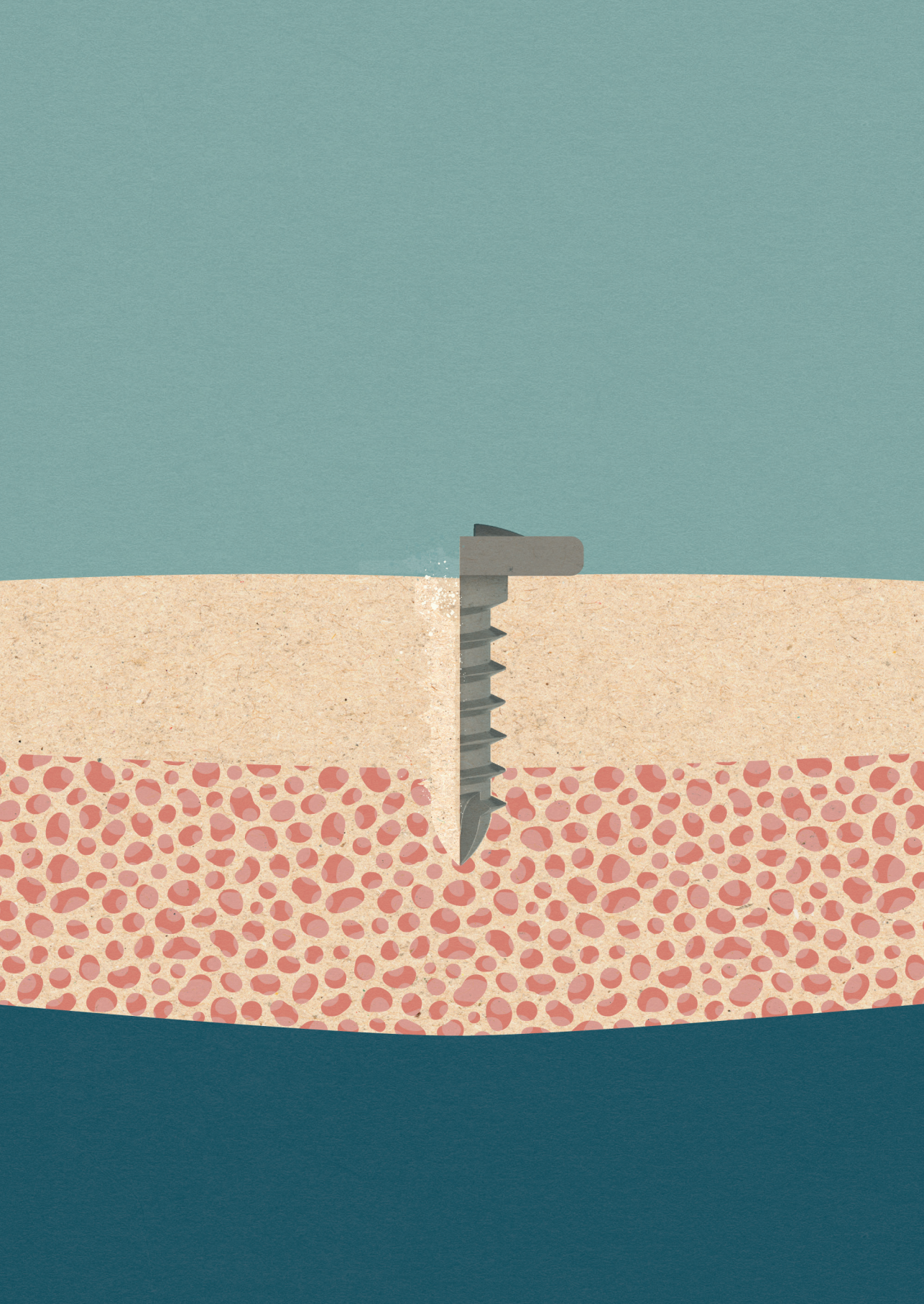
In **Chapter 9**, the results of the studies described in **Chapters 2-8** are discussed from a broader perspective and suggestions for future research are provided.

Conclusions

Based on the results of the studies described in this thesis, it can be concluded that:

- Based on current evidence, biodegradable osteosynthesis is a viable alternative to titanium osteosynthesis when applied to treat maxillofacial trauma, with similar efficacy and significantly lower symptomatic osteosynthesis removal, but with higher perioperative screw breakage (**Chapter 2**).

- Based on current evidence, biodegradable osteosynthesis is a valid alternative to titanium osteosynthesis for orthognathic surgery, with similar efficacy, but with longer operation times (**Chapter 3**).
- The long-term performance of the Inion CPS biodegradable system is inferior compared to the KLS Martin titanium system regarding symptomatic osteosynthesis removal following fixation of Le Fort-I, zygomatic and mandibular fractures, and Le Fort-I and/or bilateral sagittal split osteotomies. Biodegradable osteosyntheses removal occurred only after mandibular osteotomy fixation (**Chapter 5**).
- The SonicWeld Rx biodegradable osteosynthesis system has the most predictable degradation profile compared to the BioSorb FX, Inion CPS and LactoSorb biodegradable osteosynthesis systems (**Chapter 6**).
- Of the tested biodegradable osteosynthesis systems, the SonicWeld 2.1 mm biodegradable systems have the most favourable mechanical properties for midface fracture fixation and osteotomies, and the Inion CPS 2.5 mm biodegradable system for mandibular fractures and osteotomies (**Chapter 7**).
- The residents' accuracy and reliability in applying torque to titanium osteosynthesis 1.5 mm screws are insufficient. Both accuracy and reliability can be improved using a simple preclinical training model (**Chapter 8**).



Chapter 11

Samenvatting

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Introductie

Osteosynthesesystemen bestaan uit platen en schroeven. Deze systemen worden gebruikt om botsegmenten te fixeren en worden vaak toegepast binnen de maxillofaciale traumatologie, en de orthognatische en reconstructieve chirurgie. Titanium osteosynthesesystemen zijn op dit moment de gouden standaard. Zij hebben echter nadelen zoals temperatuurgevoeligheid, palpabiliteit van platen en schroeven, mogelijke groeibeperkingen en verstoring van radiologische beeldvorming en radiotherapie door verstrooiing van straling. Daarnaast zorgt de stijfheid van titanium systemen voor vermindering van biomechanische prikkels, waardoor de botgenezing zou kunnen vertragen. Ook zijn titanium partikels in omliggende lymfeklieren gevonden, die potentieel mutageen zijn.

De huidige biodegradeerbare osteosynthesesystemen bestaan uit bio-afbreekbare polymeren zoals polylactides. Deze systemen zouden (symptomatische) verwijdering van osteosynthesesystemen en eerdergenoemde nadelen van titanium systemen kunnen vermijden. Biodegradeerbare systemen hebben echter ook hun eigen nadelen. Eén van de belangrijkste nadelen zijn de beperktere mechanische eigenschappen waardoor de dimensies van deze systemen omvangrijker zijn. Daarnaast zijn vreemdlichaamreacties tegen biodegradeerbare systemen in de literatuur beschreven.

Het doel van het onderzoek dat beschreven is in dit proefschrift was om de *in vitro* en *in vivo* eigenschappen van verschillende biodegradeerbare osteosynthesesystemen te vergelijken. Daarnaast werden de eigenschappen van biodegradeerbare en titanium osteosynthesesystemen met elkaar vergeleken. Omdat de toegepaste torque op osteosyntheseschroeven bijdraagt aan de primaire stabiliteit van een osteosynthese werden ook de accuratesse en reproduceerbaarheid van de toegepaste torque door ervaren mond-, kaak- en aangezichtschirurgen (MKA-chirurgen) en door MKA-chirurgen in opleiding op titanium osteosyntheseschroeven gemeten.

Bevindingen

Het doel van de studie beschreven in **Hoofdstuk 2** was het uitvoeren van een systematisch literatuuronderzoek, inclusief meta-analyses en *trial sequential analyses*, om de werkzaamheid en morbiditeit van biodegradeerbare en titanium osteosyntheses bij de behandeling van aangezichtsfracturen te vergelijken. Er werd in de databases MEDLINE, EMBASE en CENTRAL gezocht naar gerandomiseerde, gecontroleerde studies en naar prospectieve en retrospectieve, gecontroleerde studies (laatste

zoekopdracht 20 april 2019). De verschillende uitkomsten werden verdeeld over vijf tijdperiodes: perioperatief, 0-4 weken, 6-12 weken, >12 weken en algehele follow-up. Vierentwintig van de 3542 artikelen werden geïncludeerd, met in totaal 2450 patiënten. Alle 24 geïncludeerde studies hadden een hoog risico op bias. De meta-analyses toonden geen verschillen in werkzaamheid en morbiditeit tussen biodegradeerbare en titanium osteosyntheses. Het risico op perioperatieve schroefbreuk was significant hoger (RR 17,13, 95% BI 2,19;34,18) en dat van symptomatische plaatverwijdering significant lager in de biodegradeerbare groep (RR 0,11; 95% BI 0,02;0,57). De significante lagere plaatverwijdering van de biodegradeerbare osteosyntheses werd bevestigd door de *trial sequential analyses*. De kwaliteit van het bewijs varieerde van zeer laag tot matig. Op basis van het beschikbare bewijs werd geconcludeerd dat biodegradeerbare osteosyntheses een valide alternatief zijn voor titanium osteosyntheses bij de behandeling van aangezichtsfracturen, met vergelijkbare werkzaamheid, maar met significant lagere symptomatische plaatverwijdering en een grotere kans op perioperatieve schroefbreuk in de biodegradeerbare groep. Aangezien de kwaliteit van het huidige bewijs varieerde van zeer laag tot matig, zijn studies van hoge kwaliteit nodig om de volledige potentie van biodegradeerbare osteosyntheses te bepalen.

Het onderzoek beschreven in **Hoofstuk 3** had als doel om de werkzaamheid en morbiditeit van biodegradeerbare en titanium osteosyntheses binnen de orthognatische chirurgie te vergelijken. Patiënten met een syndromale afwijking en/of schisis werden geëxcludeerd. Gerandomiseerde, prospectieve en retrospectieve, gecontroleerde studies werden gezocht in negen databases (laatste zoekopdracht 11 februari 2021). De verschillende uitkomsten werden verdeeld over vijf tijdperiodes: perioperatief, 0-4 weken, 6-12 weken, >12 weken en algehele follow-up. In totaal werden 9073 artikelen beoordeeld waarna 33 artikelen met in totaal 2551 patiënten werden geïncludeerd. Geen van de geïncludeerde studies had een laag risico op bias. Er werden geen verschillen gevonden in verstoorde botheling (kwalitatieve analyses), mobiliteit van botsegmenten (RR 1,37, 95% BI 0,47;3,99) en malocclusie (RR 0,93, 95% BI 0,39;2,26). De operatietijd was significant langer in de biodegradeerbare groep (SMD 0,50, 95% BI 0,09; 0,91). Symptomatische plaatverwijdering was vergelijkbaar tussen beide interventiegroepen (RR 1,29, 95% BI 0,68;2,44). Skeletale stabiliteit na verschillende orthognatische ingrepen was vergelijkbaar. Op basis van het beschikbare bewijs werd geconcludeerd dat biodegradeerbare osteosyntheses een valide alternatief zijn voor titanium osteosyntheses binnen de orthognatische chirurgie, maar met significant langere operatietijd. Aangezien de kwaliteit van het huidige bewijs varieerde van

zeer laag tot matig, zijn studies van hoge kwaliteit nodig om de volledige potentie van biodegradeerbare osteosyntheses te bepalen.

In **Hoofdstuk 4** uitten wij onze zorgen over de compleetheid en interpretatie van de trechterplots van een systematisch literatuuronderzoek met meta-analyse uitgevoerd door andere auteurs. Het systematische literatuuronderzoek richtte zich op de prevalentie, oorzaken en risicofactoren van titanium plaatverwijdering binnen de orthognatische chirurgie. We toonden aan dat er minstens drie gerandomiseerde, gecontroleerde studies ontbraken, terwijl deze wel geïncludeerd hadden moeten worden als de vooraf bepaalde in- en exclusiecriteria waren gehanteerd. Een waarschijnlijke verklaring hiervoor was dat een gevoelige zoekstrategie ontbrak (o.a., gebrek aan *medical subject heading* [MeSH] termen, explosie van termen en truncaties van termen) en dat de toegepaste zoekstrategie niet voor elk doorzochte database op maat werd gemaakt. Daarnaast uitten wij onze zorgen over de interpretatie van de gebruikte trechterplots en beargumenteerden wij dat, in tegenstelling tot de conclusies die door de auteurs worden getrokken, publicatie bias niet uitgesloten kan worden.

In **Hoofdstuk 5** werd een multicenter, gerandomiseerde, gecontroleerde studie beschreven die zich richtte op de langetermijnuitkomsten (>5 jaar follow-up) van een titanium en een biodegradeerbaar osteosynthesesysteem binnen de MKA-chirurgie. De studie werd uitgevoerd in vier Nederlandse ziekenhuizen. Patiënten met een bilaterale sagittale splijtingsosteotomie en/of een Le Fort I osteotomie en patiënten die werden behandeld voor mandibula-, maxilla- en zygomafracturen in de periode van december 2006 tot juli 2009 werden geïncludeerd. De patiënten werden via loting toegewezen aan een titanium (KLS Martin CrossDrive) of biodegradeerbare groep (Inion CPS). Na een mediane follow-up van 99 (78-113) maanden moesten osteosynthesesystemen bij 22 van de 134 (16,4%) patiënten in de titanium groep en bij 23 van de 87 (26,4%) patiënten in de biodegradeerbare groep worden verwijderd (*hazard ratio* biodegradable/titanium 2,0, 95% BI 1,1;3,8, P = 0,036). Occlusie, *visual analogue scale* pijn scores en de *Mandibular Function Impairment Questionnaire* (MFIQ) toonden goede en (vrijwel) pijnvrije mandibulaire functie in beide groepen. Er werd geconcludeerd dat, wanneer naar de noodzaak van osteosyntheseverwijdering werd gekeken bij de bovengenoemde chirurgische ingrepen, het Inion CPS biodegradeerbare systeem inferieur was ten opzichte van het KLS Martin CrossDrive titanium systeem.

Vreemdlichaamreacties kunnen ontstaan bij het gebruik van biodegradeerbare osteosynthese systemen en het bewijs van complete resorptie van deze systemen ontbreekt. Daarom werden in **Hoofdstuk 6** de fysisch-chemische eigenschappen,

de histologische respons en het röntgenologische verloop in de tijd van vier biodegradeerbare osteosynthesesystemen, allen bestaande uit copolymeren, met elkaar vergeleken. Er werd gebruik gemaakt van een geitenmodel. Deze geiten werden maximaal 48 maanden gevolgd. De BioSorb FX [poly(70L-lactide-*co*-30DL-lactide)], Inion CPS [poly([70–78.5]L-lactide-*co*-[16–24]DL-lactide-*co*-4trimethyleen carbonaat)], SonicWeld Rx [poly(DL-lactide)], LactoSorb [poly(82L-lactide-*co*-18glycolide)] systemen en een negatieve controle (een gebied waar geen invasieve behandeling werd verricht) werden willekeurig in de tibia en radius van 12 Nederlandse witte geiten geïmplanteerd. Verschillende monsters werden na 6, 12, 18, 24, 36 en 48 maanden geanalyseerd. Oppervlakte topografie van de verschillende systemen werd uitgevoerd middels rasterelektronenmicroscoop. Dynamische differentiecalorimetrie en gelpermeatiechromatografie werden gebruikt om initiële en geëxplanteerde monsters te analyseren en te vergelijken. Histologische coupes werden systematisch en in willekeurige volgorde door twee geblindeerde onderzoekers beoordeeld middels (gepolariseerde) lichtmicroscopie, rasterelektronenmicroscoop en energiedispersieve röntgenspectroscopie. Het SonicWeld Rx systeem was amorf terwijl de andere drie systemen semikristallijn waren. Vreemdlichaamreacties werden niet waargenomen gedurende de gehele follow-up periode. Op de implantatieplekken van de SonicWeld Rx en LactoSorb systemen werden na 18 maanden vergelijkbare botpercentages als de negatieve controles gevonden. Op de implantatieplekken van de BioSorb FX en Inion CPS systemen werd dit niveau na 36 maanden behaald. Het SonicWeld Rx systeem liet het meest voorspelbare degradatieprofiel zien. Alle beoordeelde biodegradeerbare systemen waren veilig en werden goed verdragen. Op elk beoordelingsmoment van elk systeem werden echter nog resterende polymeerfragmenten van nanogrootte waargenomen. Het is onduidelijk of deze nanodeeltjes op de lange termijn (>4 jaar) schadelijk kunnen zijn.

De commerciële ontwikkeling van biodegradeerbare osteosynthesesystemen heeft geresulteerd in een groot aantal op de markt verkrijgbaresystemen. Er zijn echter geen studies die de mechanische eigenschappen van deze systemen hebben vergeleken. Het is daarom voor MKA-chirurgen veelal onduidelijk welk systeem de voorkeur heeft voor het fixeren van fracturen en osteotomieën vanuit een mechanisch perspectief. In de studie beschreven in **Hoofdstuk 7** werden de mechanische eigenschappen van een aantal biodegradeerbare en titanium osteosynthesesystemen vergeleken. De SonicPins Rx en xG werden blootgesteld aan uittrekproeven. Daarnaast werden de mechanische eigenschappen van 15 biodegradeerbare (Inion CPS 2,0 en 2,5 mm; LactoSorb 2,0 mm; Macropore 2,0 mm; Polymax 2,0 mm; BioSorb FX 2,0 mm; ResorbX

2,1 mm; Osteotrans-MX 2,0 mm met plaatdiktes van 1,0 en 1,4 mm; SonicWeld Rx_{plaat}/Rx_{pinnen}, xG_{plaat}/Rx_{pinnen} and xG_{plaat}/xG_{pinnen} 2,1 mm zonder en met tappen van het boorgat) en zes titanium (CrossDrive (2006), CrossDrive (2018), MaxDrive; allen 1,5 en 2,0 mm) rechte, vier-gats osteosynthesesystemen met elkaar vergeleken. Alle systemen werden blootgesteld aan trek-, buig- en torsieproeven. De uittrekkrachten van SonicPins waren vergelijkbaar (P=0,423). De trekkrachten die de titanium systemen konden doorstaan waren hoger dan die van biodegradeerbare systemen (P<0,001). De trek- en torsiestijfheid van de CrossDrive (2018) en MaxDrive systemen waren lager, hetgeen gepaard ging met een hogere vervormbaarheid, dan de CrossDrive (2006) systemen met dezelfde afmetingen (P<0,001). De buigstijfheid van 1,5 mm titanium systemen was vergelijkbaar met die van alle biodegradeerbare systemen (P<0,001). De buigstijfheid van 2,0 mm titanium systemen was hoger dan die van alle biodegradeerbare systemen (P<0,001). Van de biodegradeerbare systemen had het Inion CPS 2,5 mm systeem de hoogste trekkracht en torsiestijfheid, de SonicWeld 2,1 mm systemen de hoogste trekstijfheid, en het BioSorb FX 2,0 mm systeem de hoogste buigstijfheid (P<0,001). Op basis van deze mechanische resultaten werd geconcludeerd dat, binnen de titanium systemen, de toepassing van CrossDrive (2018) en MaxDrive 1,5 mm systemen kunnen worden aangeraden voor middengezichtsfracturen en -osteotomieën, en de CrossDrive (2018) en MaxDrive 2,0 mm systemen voor mandibulafracturen en osteotomieën van de mandibula. Als er een indicatie is voor het gebruik van een biodegradeerbare systeem, dan worden de SonicWeld 2,1 mm systemen of het BioSorb FX 2,0 mm systeem voor middengezichtsfracturen en -osteotomieën aangeraden. Het Inion CPS 2,5 mm biodegradeerbaar systeem wordt aangeraden voor mandibulafracturen en osteotomieën van de mandibula, met name wanneer hoge torsiekrachten worden verwacht (bijvoorbeeld symfyse-fracturen van de mandibula).

Het toepassen van de correcte hoeveelheid torque op osteosyntheseschroeven is belangrijk voor stabiele fixatie en ongestoorde botheling. Het doel van de studie beschreven in **Hoofdstuk 8** was het vergelijken van de test-hertest en intra-individuele reproduceerbaarheid van torque uitgeoefend op 1,5 mm en 2,0 mm osteosyntheseschroeven tussen MKA-chirurgen in opleiding en ervaren MKA-chirurgen, het definiëren van torque referentie-intervallen en het vergelijken van de toegepaste torque door deelnemers. Vijf ervaren MKA-chirurgen en 20 MKA-chirurgen in opleiding, 5 van elk van de 4 opleidingsjaren, namen deel aan dit onderzoek. Elke deelnemer schroefde zes 1,5x4 mm en zes 2,0x6 mm schroeven op twee momenten in een preklinisch model, met een interval van twee weken (T1, T2). Alle deelnemers werden geblindeerd voor de bereikte torque. Beschrijvende statistiek, referentie-intervallen en

intra-class correlatie coëfficiënten (ICCs) werden berekend. MKA-chirurgen en MKA-chirurgen in opleiding plaatsten de 1,5 mm schroeven met respectievelijk 100,8±13,6 Nmm en 92,4±20,7 Nmm torque (P<0,001), en de 2,0 mm schroeven met 431,7±99,4 Nmm en 322,5±77,5 Nmm torque (P<0,001). Het referentie-interval betrof 73,7 tot 127,9 Nmm voor 1,5 mm schroeven en 233,9 tot 629,5 Nmm voor 2,0 mm schroeven. MKA-chirurgen voldeden vaker aan het referentie-interval (1,5 mm schroeven: 95% en 2,0 mm schroeven: 100%) dan MKA-chirurgen in opleiding (respectievelijk 82% en 90%; P=0,009 en P=0,007), met ICCs variërend tussen respectievelijk 0,85-0,95 en 0,45-0,97. Er werd geconcludeerd dat de accuratesse en reproduceerbaarheid van MKA-chirurgen in opleiding significant lager waren dan die van MKA-chirurgen. Bij beide schroefafmetingen verbeterden de accuratesse en reproduceerbaarheid op T2 ten opzichte van T1, wat duidt op een leereffect. Het trainen van MKA-chirurgen in opleiding en/of het verifiëren van de toegepaste torque door ervaren MKA-chirurgen blijft noodzakelijk om hoge accuratesse en reproduceerbaarheid te behalen, met name voor 1,5 mm schroeven.

In **Hoofdstuk 9** werden de resultaten beschreven in de **Hoofdstukken 2-8** vanuit een breder perspectief bediscussieerd en werden suggesties voor vervolgonderzoek gegeven.

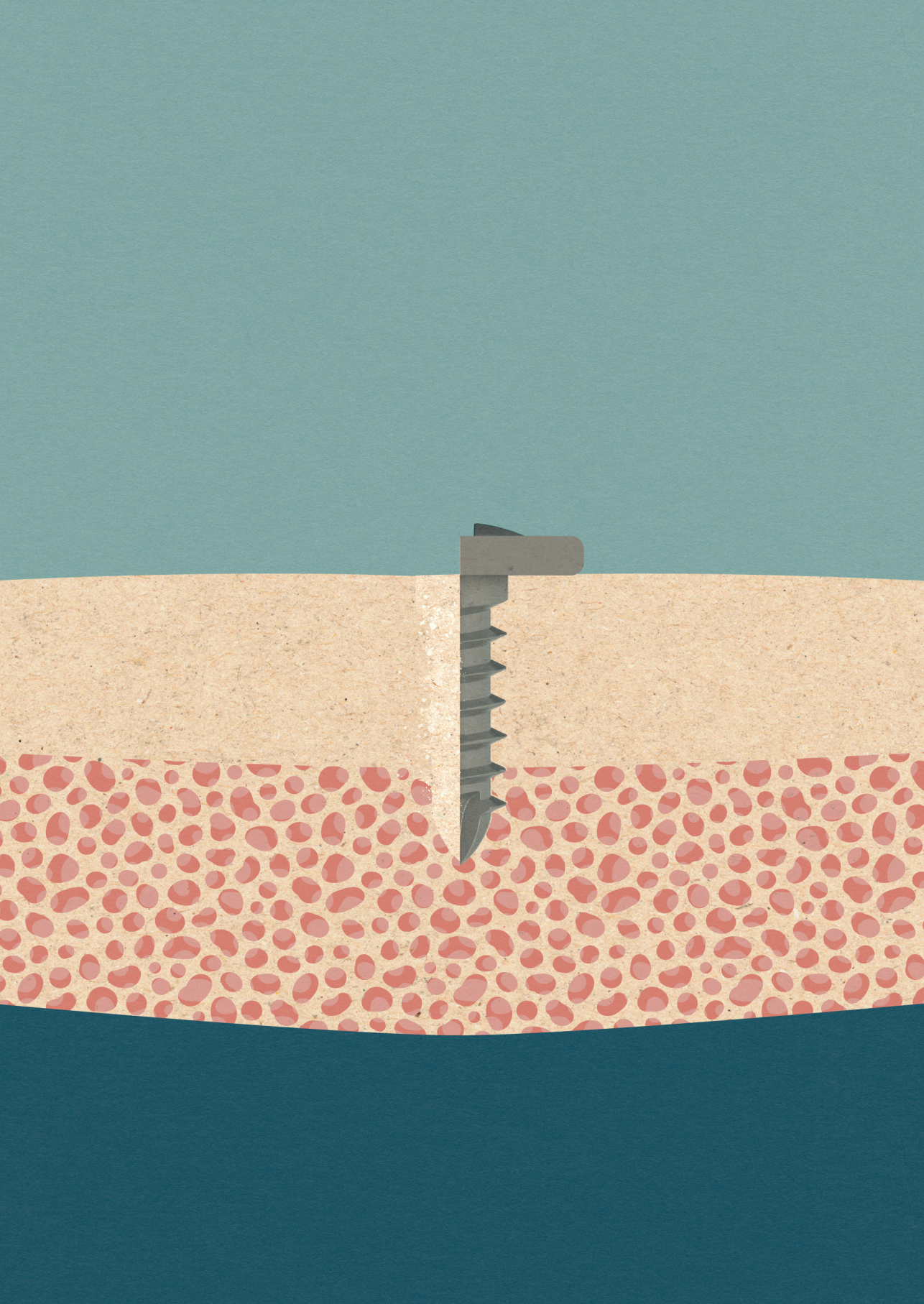
Conclusies

Op basis van de resultaten beschreven in dit proefschrift kunnen de volgende conclusies worden getrokken:

- Gebaseerd op het momenteel beschikbare bewijs lijken biodegradeerbare osteosyntheses een valide alternatief voor titanium osteosyntheses bij de behandeling van maxillofaciale trauma, met vergelijkbare werkzaamheid, maar met significant lagere symptomatische plaatverwijdering en hogere perioperatieve schroefbreuk (**Hoofdstuk 2**).
- Gebaseerd op het momenteel beschikbare bewijs lijken biodegradeerbare osteosyntheses een valide alternatief voor titanium osteosyntheses in orthognatische chirurgie, maar met een significant langere operatietijd (**Hoofdstuk 3**).
- Bij de chirurgische behandeling van Le Fort I-, zygoma- en mandibula-fracturen, en Le Fort I en/of bilaterale sagittale splijtingsosteotomieën is het Inion CPS biodegradeerbare systeem inferieur vergeleken met het KLS Martin CrossDrive titanium systeem voor wat betreft de noodzaak van osteosyntheseverwijdering op

de lange termijn. Verwijderen van biodegradeerbare osteosyntheses was alleen noodzakelijk na fixatie van bilaterale sagittale splijtingsosteotomieën (**Hoofdstuk 5**).

- Het SonicWeld Rx biodegradeerbare osteosynthesesysteem had een voorspelbaarder degradatieprofiel dan de BioSorb FX, Inion CPS en LactoSorb biodegradeerbare osteosynthesesystemen (**Hoofdstuk 6**).
- Van de geteste biodegradeerbare systemen hebben de SonicWeld 2,1 mm systemen de gunstigste mechanische eigenschappen voor fixatie van middengezichtsfracturen en -osteotomieën. Het Inion CPS 2,5 mm systeem heeft de gunstigste eigenschappen voor fixatie van fracturen en osteotomieën van de mandibula (**Hoofdstuk 7**).
- De accuratesse en reproduceerbaarheid van de toegepaste torque om 1,5 mm osteosyntheseschroeven door MKA-chirurgen in opleiding is onvoldoende. Zowel de accuratesse en reproduceerbaarheid kan worden verbeterd door het gebruik van een simpel preklinisch trainingsmodel (**Hoofdstuk 8**).



Appendices

Dankwoord

List of publications

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Dankwoord

Waarom moeilijk doen als het samen kan?

Dit avontuur begon met een korte mail naar wat later één van mijn promotoren zou worden. Wat volgde waren een aantal waanzinnige jaren waarin ik ontzettend veel heb geleerd, gelachen en genoten. Het was een voorrecht om verschillende inspirerende personen te ontmoeten, zowel nationaal als internationaal. Alhoewel mijn naam op de voorzijde van dit proefschrift staat, kan ik met zekerheid zeggen dat dit proefschrift er niet was geweest zonder hulp van verschillende sleutelfiguren. Graag wil ik de volgende personen bedanken.

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op mijn vragen en weer verder kon. Jij liet me zien dat er heel veel mogelijk is ("Proberen kan altijd, toch?"); van het regelen van osteosynthesematerialen vanuit de industrie tot het aanschrijven (en binnenhalen!) van onderzoekssubsidies. De manier waarop jij mij hebt geïntroduceerd bij verschillende toponderzoekers en -clinici heeft voor mij veel deuren geopend, waardoor ik hen later in het promotietraject zelf laagdrempelig kon benaderen. Daar ben ik je erg dankbaar voor. Jij leerde mij dat samenwerken cruciaal is en dat daardoor meer bereikt kan worden, naast dat het gewoon gezellig is! Gecombineerd met jouw enthousiasme en de aandacht voor mij en de personen om mij heen maakt voor mij dat jij een fantastische mentor bent geweest, bent en zult blijven. Dank voor jouw vertrouwen en begeleiding, en de gezelligheid tijdens alle ritjes naar Nijmegen, Amsterdam en Zwolle! Het proefschrift is af, maar ik hoop jou en Liesbeth nog regelmatig te spreken.

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Welk onderwerp voor een promotieonderzoek kies je als deel van een gezin bestaande uit een natuurkundige, scheikundige, tandarts en ziekenhuisapotheker? Juist, een onderzoek naar degradeerbare maxillofaciale osteosynthesesystemen bestaande uit polymeren. Lieve **pappa** en **mamma gian**, het – voor mij – meest relevante experiment werd ruim 31 jaar geleden uitgevoerd. Eén jaar later hebben jullie – voor ons – een cruciale keuze gemaakt die ons leven voorgoed heeft veranderd. Het feit dat jullie hele grote tegenslagen hebben weten om te buigen naar één kans die jullie volledig hebben gegrepen, is mijn levenslange motivatie. Jullie hebben bewezen dat alles mogelijk is, als je maar doorzet en een doel voor ogen hebt. Jullie zeggen altijd dat jullie trots op ons zijn, maar dat is uiteraard jullie verdienste. Dit proefschrift is voor jullie. **Chawan**, de

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List of publications

1. Tang YH, Vos LM, Tuin AJ, ..., **Gareb B**, et al.. Arthrocentesis versus non-surgical intervention as initial treatment for temporomandibular joint arthralgia: a randomized controlled trial with long-term follow-up. *Int J Oral Maxillofac Surg.* [Epub ahead of print].
2. **Gareb B**, Van Munster VDM, Dijkstra PU, et al.. Reliability and accuracy of the torque applied to osteosynthesis screws by maxillofacial surgeons and residents. *Sci Rep*. 2022 Aug 24;12(1):14411.
3. **Gareb B**, Van Bakelen NB, Vissink A, et al.. Titanium or Biodegradable Osteosynthesis in Maxillofacial Surgery? In Vitro and In Vivo Performances. *Polymers (Basel).* 2022 Jul 7;14(14):2782.
4. **Gareb B**, Van Bakelen NB, Driessen L, et al.. Biocompatibility and degradation comparisons of four biodegradable copolymeric osteosynthesis systems used in maxillofacial surgery: A goat model with four years follow-up. *Bioact Mater.* 2022 Nov;17:439-456.
5. **Gareb B**, Van Bakelen NB, Dijkstra PU, et al.. Efficacy and morbidity of biodegradable versus titanium osteosyntheses in orthognathic surgery: A systematic review with meta-analysis and trial sequential analysis. *Eur J Oral Sci.* 2021 Oct;129(5):e12800.
6. Raghoebar GM, Korfage A, Meijer HJA, ..., **Gareb B**, et al.. Linear and profilometric changes of the mucosa following soft tissue augmentation in the zone of aesthetic priority: A systematic review and meta-analysis. *Clin Oral Implants Res.* 2021 Oct;32 Suppl 21:138-156.
7. Barbateskovic M, Koster TM, Eck R, ..., **Gareb B**, et al.. A new tool to assess Clinical Diversity In Meta-analyses (CDIM) of interventions. *J. Clin. Epidemiol.* 2021 Jul;135:29-41.
8. **Gareb B**, Roossien CC, Van Bakelen NB, et al.. Comparison of the mechanical properties of biodegradable and titanium osteosynthesis systems used in oral and maxillofacial surgery. *Sci Rep*. 2020 Oct 23;10(1):18143.
9. **Gareb B**, Van Bakelen NB, Dijkstra PU, et al.. Trust, but verify: response to "Titanium plate removal in orthognathic surgery: prevalence, causes and risk factors. A systematic literature review and meta-analysis." *Int J Oral Maxillofac Surg.* 2021 May;50(5):707-708.
10. **Gareb B**, Van Bakelen NB, Dijkstra PU, et al.. Biodegradable versus titanium osteosyntheses in maxillofacial traumatology: a systematic review with meta-analysis and trial sequential analysis. *Int J Oral Maxillofac Surg.* 2020 Jul;49(7):914–931.

11. **Gareb B**, Witjes MJH. [Spontaneous numbness along with pre-existing deviations in the pigmentation of the lower lip]. *Ned Tijdschr Tandheelkd*. 2018 Oct;125(10):517-523.
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13. **Gareb B**, Van Bakelen NB, Buijs GJ, et al.. Comparison of the long-term clinical performance of a biodegradable and a titanium fixation system in maxillofacial surgery: A multicenter randomized controlled trial. *PLoS One.* 2017 May 11;12(5): e0177152.
14. De Koning ME, **Gareb B**, El Moumni M, et. al.. Subacute posttraumatic complaints and psychological distress in trauma patients with or without mild traumatic brain injury. *Injury*. 2016 Sep;47(9):2041–2047.
15. De Poorter JJ, Beunder TJ, **Gareb B**, et al.. Long-term outcomes of slipped capital femoral epiphysis treated with *in situ* pinning. *J Child Orthop.* 2016 Oct ;10(5):371–379.

About the author

Barzi Gareb was born on 10 September 1991 in Sulaymaniyya, Iraq. In 1992, he and his parents, sister and brother moved to The Netherlands. After graduation from the Augustinus College in Groningen, he studied Pharmacy from 2009-2011 at the University of Groningen (120 ECTS, *cum laude*).

He started studying Medicine in 2011 at the University of Groningen. Throughout medical school, he was involved in several extracurricular projects, including research projects that resulted in multiple publications. Furthermore, he was a member of various organizing committees. He obtained his Bachelor's degree in Medicine in 2014 (*cum laude*). Subsequently, he started with his Master's research thesis at the department of Trauma Surgery, University Medical Centre Groningen (supervisor: dr. M. el Moumni). His final internship was followed at the department of Oral and Maxillofacial Surgery at the Northwick Park Hospital, London, United Kingdom (supervisor: dr. M. Perry). In 2017, he obtained his Master's degree in Medicine (*cum laude*) and he was accepted for the Oral and Maxillofacial Surgery residency training.

In 2018, he started as a PhD-candidate to assess the *in vitro* and *in vivo* performances of biodegradable and titanium osteosynthesis systems in maxillofacial surgery, of which this thesis is the result (supervisors: prof. dr. A. Vissink, prof. dr. R.R.M. Bos, dr. B. van Minnen & dr. N.B. van Bakelen). He combined his PhD project with studying Dentistry and his registration to become a senior epidemiologist (supervisors: prof. dr. P.U. Dijkstra & prof. dr. G.H. de Bock) at the University of Groningen. He completed his Bachelor's degree in Dentistry in 2020 (*cum laude*). He presented his study results at several (inter)national conferences and was awarded, among others, the 'Strassbourg Osteosynthesis Research Group grant', 'BOOA research grant', and 'University of Groningen Excellent Student grant'. Furthermore, he is part of an international epidemiology collaboration to improve evidence-based medicine and dentistry. From 2020-2021, he was board member of the "*Symposium Experimenteel Onderzoek Heelkundige Specialismen"*. His epidemiology training (mean grade: 8.7/10) will be completed upon defending his PhD thesis. In September 2022, he started his residency in Oral and Maxillofacial Surgery at the University Medical Centre Groningen (head: prof. dr. F.K.L. Spijkervet). He will obtain his Master's degree in Dentistry (mean grade: 8.1/10) upon completing his first year of residency training.

Besides his professional career, he is interested in advancements in (digital) technology as well as in cycling, cooking and sailing. He lives together with Sofanne Ravensbergen and they recently moved into their first own house.

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