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Meta-Analysis
Trauma

Biodegradable versus titanium osteosynthesis 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 osteosynthesis 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 or morbidity between biodegradable and titanium osteosynthesis. The risk of perioperative screw breakage was significantly higher (risk ratio 17.13, 95% confidence interval 2.19–34.18) and the symptomatic plate removal rate lower in the biodegradable group (risk ratio 0.11, 95% confidence interval 0.02–0.57), which was confirmed by the trial sequential analysis. The quality of evidence ranged from very low to moderate. Based on the narrative review and meta-analyses, current evidence shows that biodegradable osteosynthesis is a viable alternative to titanium osteosynthesis 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 group compared to the titanium group.

Key words: biodegradable; titanium; fixation; craniofacial; trauma; osteosynthesis; plates.

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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 osteosynthesis include palpability[2], sensitivity to temperature changes[1], stress shielding of the underlying bone[3], growth restriction[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 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 accompanying 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 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 osteosynthesis have been published, but the results of these solitary studies remain controversial[2,11,13,14]. A previous randomized controlled trial (RCT) by the present authors' research group, showed an unexpected higher symptomatic plate removal rate in the biodegradable group than in the titanium group after trauma and orthognathic surgery[2]. To place these results in the context of the literature, systematic reviews addressing the efficacy and morbidity of these interventions were sought. The most recent systematic review comparing the two 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 remains the 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 that 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-analysis and trial sequential analysis, of RCTs, 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 osteosynthesis 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]. The study protocol was registered in the PROSPERO database prior to the systematic literature search (registration number CRD42018086477).

Study identification

A systematic literature search of three electronic databases was conducted: MEDLINE (1964–2019), Embase (1947–2019), and the Cochrane Central Register of Controlled Trials (CENTRAL; inception to 2019). The sensitive search strategy consisted of medical subject heading terms and free-text words (Supplementary Material Table S1). The search strategy also included orthognathic populations, as some studies included both populations in a single study. The data of trauma patients were obtained 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 April 20, 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 that should have been included in this review. No restriction on language or year of publication was applied.

Study selection

The inclusion criteria were formulated using the PICOS format. The population (P) included all 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 the 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, maximum mouth opening (MMO), Mandibular Function Impairment Questionnaire score (MFIQ; lower score equals better function), temporomandibular joint dysfunction (TMJ dysfunction), infection, swelling, wound dehiscence, plate exposure, palpability of plates and/or screws, patient satisfaction with the surgery performed, 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) were evaluated for both groups. The study types (S) included were 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 study, while the latter two designs are useful for the assessment of adverse events. The follow-up of each corresponding endpoint is described below (see Data collection).

Exclusion criteria were 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, expert 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 to make a decision on inclusion, or in the case of any doubt, the article was included for full text assessment. The full-text articles of studies included by title and abstract were independently assessed by the same two reviewers for final inclusion using the inclusion and exclusion criteria listed above. Any disagreement was resolved by discussion. If consensus could not be reached, a third reviewer (PUD) was asked to make a final decision.

After each selection stage, the inter-observer agreement was expressed as Cohen's kappa and the 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 included studies was independently assessed by two reviewers (BG and NBvB). Trials performed by the authors' research group were assessed by two independent researchers not involved in those studies (PUD and SJvdG; see Acknowledgements) to avoid any conflict of interest.

RCTs were assessed using the Cochrane Collaboration tool for assessing risk of bias[20], including seven 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 risk of bias of non-randomized studies was assessed using the Methodological Index for Non-Randomized Studies (MINORS)[21]. MINORS is a valid and reliable instrument for quality assessment[21]. It includes eight items that are applicable to all non-randomized studies, and an additional four 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 were extracted using a standardized, pre-defined form. Initially, two reviewers (BG and NBvB) extracted data from a sample (10%) of the eligible studies. If an agreement of $\geq$80% was achieved, the remainder of the data were to be extracted by one reviewer (BG). The data collected included: first author and year of publication, country in which the study was conducted, study design, number of patients, sex, age, tobacco and alcohol usage, surgical procedures, types of osteosynthesis system used, intraoperative switching to another osteosynthesis system, osteosynthesis principle, duration of maxillomandibular fixation (MMF), duration of follow-up, and conflicts of interest. The endpoints were collated for five time periods: perioperative, short-term follow-up (i.e., 0–4 weeks; soft tissue healing), intermediate follow-up (i.e., 6–12 weeks; bone healing), long-term follow-up (i.e., >12 weeks; degradation effects), and overall follow-up (i.e., the endpoints of the longest follow-up; Supplementary Material Table S2).

If the relevant data could not be extracted, the authors of the studies were contacted by email; this was done from May to November 2018 and April to 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 version 23 (IBM Corp., Armonk, NY, USA). Regarding binary variables, the events and totals were used to calculate the risk ratio (RR) and 95% confidence interval (CI). The standardized mean difference (SMD) with 95% CI was calculated for continuous variables. Statistical heterogeneity was regarded as substantial if $I^2 > 50\%$[20]. The meta-analysis was performed in R package 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 different study designs. A summary effect estimate was calculated if two or more studies with the same study design could be pooled. Also, a subgroup analysis of low risk versus high risk of 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. The plate removal rate was also analysed according to the follow-up of the included studies, i.e., $\leq$1 year of follow-up and >1 year of follow-up. 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 random-effects model was used to evaluate 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 $\leq$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 Fig. S1 in the Supplementary Material. 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, Copenhagen, Denmark)[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 (Fig. 1). The percentage of

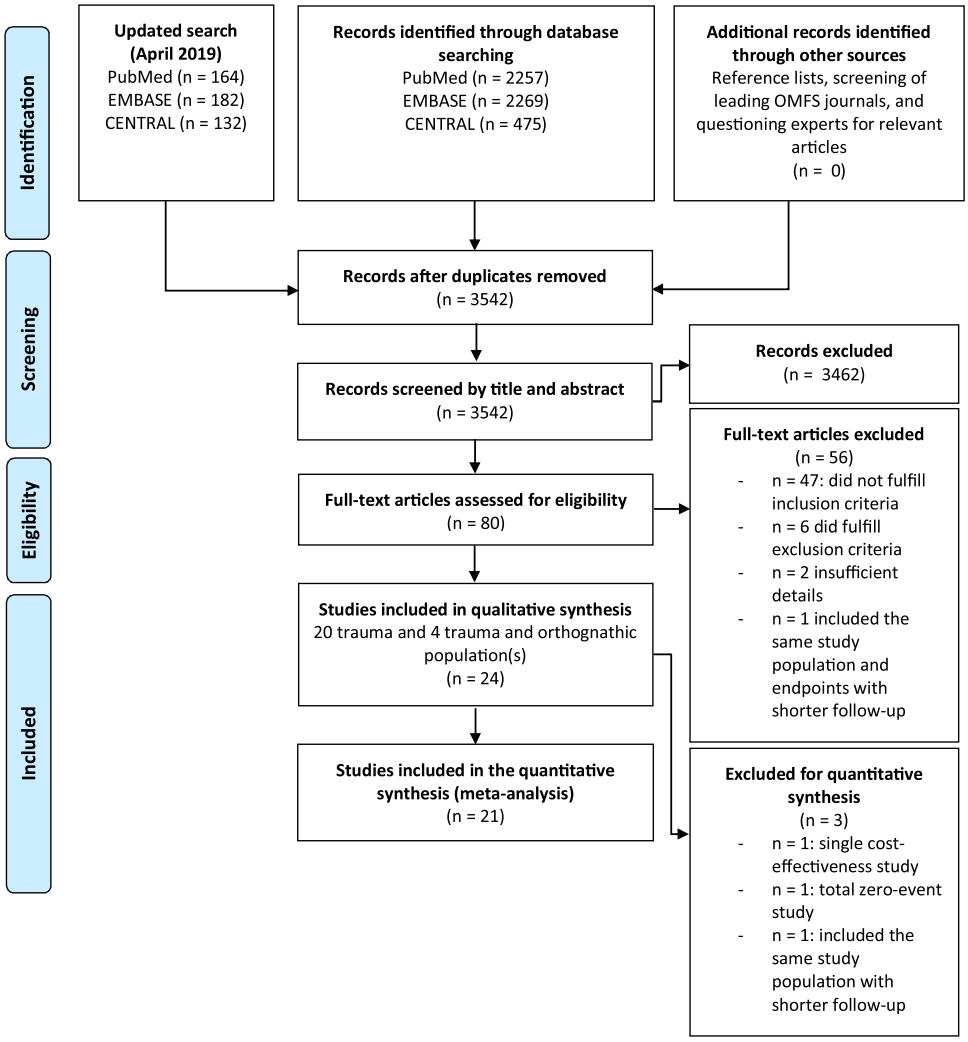

Fig. 1. Flowchart of the study identification and selection process.

agreement and kappa were 99% and 0.91, respectively. The full-text articles 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 follow-up ($n = 1$) (Supplementary Material 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 seven publications of RCTs[2,14,33–37] (of which four were publications of a single RCT, each with a different follow-up[2,33,35,36]), four prospective cohort studies[11,13,38,39], and 13 retrospective cohort studies[8,40–51]. A low risk of bias was observed in the 'random sequence generation' domain for all but one of the included RCTs (Table 1). A high risk of performance and detection bias was observed in all the included RCTs. 'Other sources of bias' were assessed as high risk in the four publications of a single RCT, due to the fact that there was a switch perioperatively from the biodegradable to the titanium system whenever the surgeon deemed this to be necessary. 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 studies.

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 of the remaining studies declared no funding or conflict of interest.

Patient characteristics

The number of patients in the studies ranged from 12 to 1122, resulting in a total of 2450 patients (Supplementary Material Table S4). Of these, 1639 patients received titanium osteosynthesis systems 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]. Age ranged from 4 to 83 years. Two studies only included paediatric patients[48,49]. The most common types of fractures were mandibular, zygomatic,

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

	Cochrane Collaboration 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	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
Randomized controlled trials																			
Bhatt et al. (2010)[14]	Low	Unclear	High	High	Unclear	Low	Low												
Buijs et al. (2012)[33]	Low	Low	High	High	Low	Low	High												
Ahmed et al. (2013)[34]	Low	Unclear	High	High	Unclear	Low	Low												
van Bakelen et al. (2013)[35]	Low	Low	High	High	High	Low	High												
van Bakelen et al. (2015)[36]	Low	Low	High	High	High	Low	High												
Sukegawa et al. (2016)[37]	Unclear	Unclear	High	High	Low	Low	Low												
Gareb et al. (2017)[2]	Low	Low	High	High	High	Low	High												
Prospective cohort studies																			
Leonhardt et al. (2008)[11]								2	1	2	2	0	1	1	0	2	2	1	0
Qiu (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 and Kindsfater (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 and Choudhury (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
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
Taylan 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. High: high risk of bias; Low: low risk of bias; Unclear: unclear risk of bias; 0: not reported; 1: reported but inadequate; 2: reported and adequate. Empty cells: not applicable.

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[2,13,14,33–36,38,39,41–44,46,47,50], while two studies did not exclude this fracture type[8,45]. The remaining six studies did not report specific inclusion or exclusion criteria regarding comminuted fractures[11,37,40,48,49,51]. Four studies included both orthognathic and trauma patients, but only the trauma patient data were 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 the Supplementary Material. 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]. Thirteen studies reported details regarding the sizes of the titanium plates and screws[2,8,11,13,14,33,35–38,40,43,47]. The screw diameter ranged from 1.3 mm 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 Bio-Sorb FX (self-reinforced 70/30 PLLA/PDLLA)[38,41,42,46,51] (Supplementary Material Table S4). The screw diameters ranged from 1.5 mm to 2.5 mm; these were generally larger compared to the titanium systems for similar fracture types. Five articles reported intraoperative switches from a biodegradable to a titanium osteosynthesis system[2,14,33,35,36]. Of these, one RCT[14]

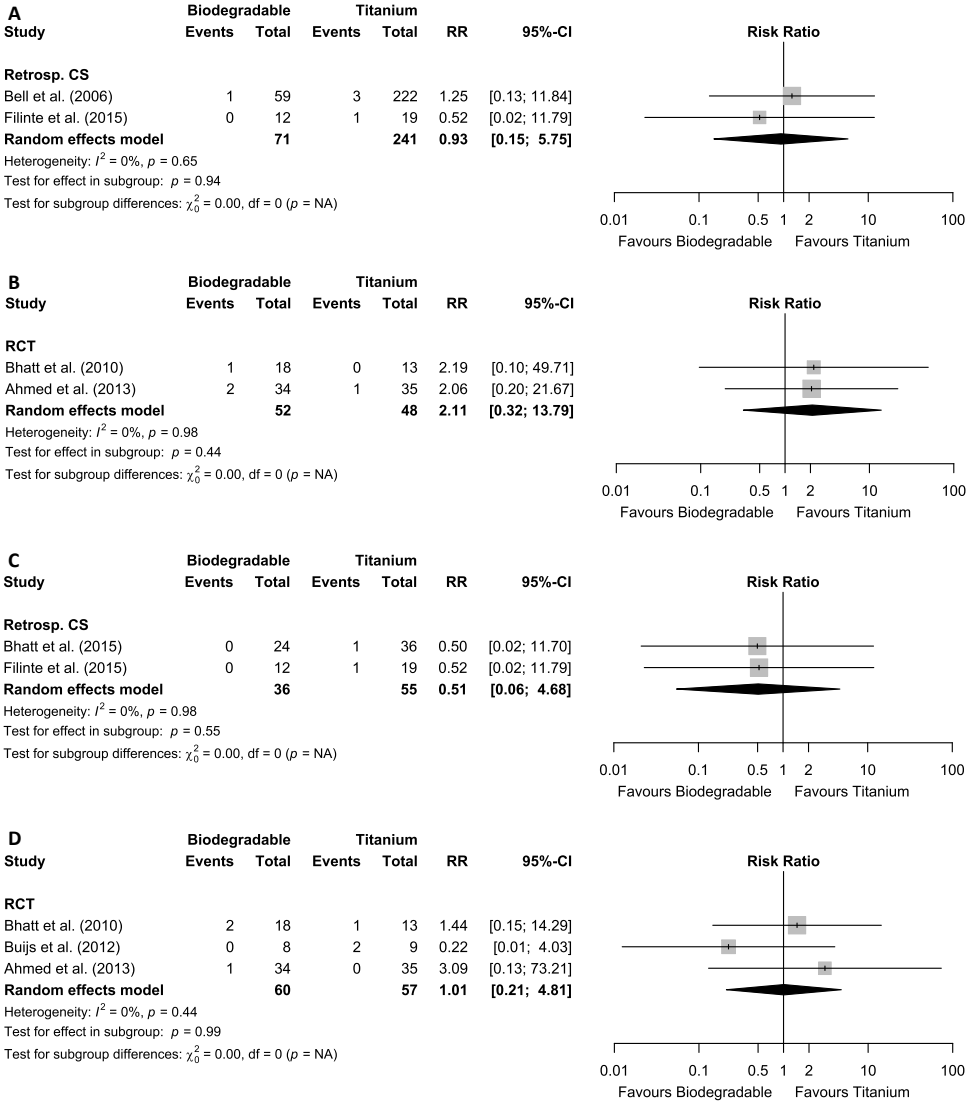

Fig. 2. Forest plots of the primary endpoints: (A) malunion (6–12 weeks follow-up); (B) mobility of bone segments (6–12 weeks follow-up); (C) malocclusion (<4 weeks follow-up); (D) malocclusion (6–12 weeks follow-up), stratified by study design. (Retrosp. CS, retrospective cohort studies; RCT, randomized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

reported one intraoperative switch (5%). The other four articles were publications of the same RCT with different follow-up periods[2,33,35,36] and reported four intraoperative 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 five used soft guiding elastics in both groups[2,8,33,35,36], three studies used rigid MMF in both groups[34,42,46], two studies just used MMF in the biodegradable group[13,14], and three studies only used MMF whenever this was deemed necessary[37,40,49], although no details regarding this clinical decision were reported (Supplementary Material Table S4). One study reported the usage of MMF in both treatment groups but did not specify whether soft guiding elastics or rigid MMF was used.[38]

Primary endpoints

All of the pooled endpoints are reported as the RR or SMD (95% CI), with the quality of the evidence. A total of 16 studies reported data regarding malunion (Supplementary Material Table S5)[8,11,13,33,34,37,38,40–47,49]. In 14 of these studies, no malunion was found in either the titanium group or the biodegradable group. Malunion assessed after 6–12 weeks of follow-up was present in two retrospective studies; pooling of the data showed no significant difference between the two groups (RR 0.93, 95% CI 0.15–5.75, very low quality; Fig. 2A).

The mobility of bone segments was assessed in five of the studies after 6–12 weeks of follow-up[14,33,34,38,49]. Two studies reported no mobility of bone segments[33,49]. One prospective study found that 4% of the patients had mobile bone

segments after biodegradable osteosynthesis and 13% of the patients after titanium osteosynthesis[38]. Data derived from two RCTs showed no significant difference between the two groups (RR 2.11, 95% CI 0.32–13.79, very low quality; Fig. 2B). No subgroup analysis could be performed.

Malocclusion within 4 weeks of follow-up was assessed in seven 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% of the cases in the biodegradable group and 21% of the cases in the titanium group[11]. Data derived from two retrospective studies showed no significant difference in objective malocclusion between the two groups (RR 0.51, 95% CI 0.06–4.68, very low quality; Fig. 2C). Both of these retrospective studies included only patients with mandibular fractures. Subgroup analysis between paediatric patients and adults showed no significant difference in the estimate between the two subgroups (adults: RR 0.91, 95% CI 0.29–2.83; paediatric: RR 1.83, 95% CI 0.81–4.11, very low quality; Supplementary Material Fig. S2).

Eight studies documented malocclusion after 6–12 weeks of follow-up[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 the two groups (RR 1.01, 95% CI 0.21–4.81, very low quality; Fig. 2D). One prospective study mentioned that 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 group and titanium group, respectively[48]. No subgroup analysis could be performed.

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

Secondary endpoints

Focusing on perioperative endpoints, the occurrence of plate breakage ranged from 0 to 6% of plates in the biodegradable group and from 0 to 2% of plates in the titanium group (Supplementary Material 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 than titanium screws (RR 17.13, 95% CI 2.19–134.18, moderate quality), while the retrospective studies showed no significant difference between the two groups (Supplementary Material Fig. S3). The mean operative time ranged between 119 and 169 minutes in the biodegradable group and between 94 and 127 minutes in the titanium group. Data derived from the retrospective studies did not result in a significant difference in operation time between the two groups (SMD 0.72, 95% CI −0.17 to 1.61, very low quality; Supplementary Material Fig. S4). Plate and screw handling, as assessed by the surgeons, was only reported in one RCT and was similar in both groups[33].

Infection within 4 weeks of follow-up occurred in 0–8% of patients in the biodegradable group and 0–10% of patients in the titanium group, and did not differ significantly between the two groups in studies of all designs (RCTs: RR 0.26, 95% CI 0.03–2.26, very low quality; Fig. 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 included patients after 1 week of follow-up[44]. Therefore, it was not possible to pool the data from this study. Abscess formation at short-term follow-up was assessed in one study and was not present in either group[33]. Pain within 4 weeks of follow-up ranged from 10% to 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 and 37% in the biodegradable group and between 0 and 38% in the titanium group. The RCTs and retrospective studies did not show any statistically significant difference between the two groups (RCTs: RR 1.68, 95% CI 0.56–5.00, very low quality; Supplementary Material Fig. S5). Finally, plate exposure after short-term follow-up did not differ significantly on pooling the data from the retrospective studies (RR 0.79, 95% CI 0.23–2.71, very low quality; Supplementary Material Fig. S6).

Secondary endpoint data for follow-up at 6–12 weeks were scarce (Supplementary Material Table S5). Pain was reported in two RCTs, but the studies measured pain differently[14,33]. MMO was only presented in bar graphs in one study[13], while another study reported similar postoperative MMO 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].

At long-term follow-up, the presence of pain was scarce in both groups (Supplementary Material Table S5). Pooling of the retrospective data did not result in any statistically significant difference between the two groups (RR 0.40, 95% CI 0.10–1.68, very low quality; Supplementary Material Fig. S7). TMJ dysfunction was assessed in one study with a follow-up of 1 year[8]. The MFIQ was assessed in two publications of one RCT[2,35]. The MFIQ was better after >5 years of follow-up in the biodegradable group than in the titanium group (median score 17 (interquartile range 17–17) and median score 35 (interquartile range 21–41), respectively)[2]. Three retrospective studies reported abscess formation after 1 year[8,51] and 2 years of follow-up[40]. No significant difference was found between the two treatment groups (RR 2.37, 95% CI 0.42–13.23, very low quality, Fig. 3B). Long-term assessment of swelling was generally scarce. One RCT with follow-up of >5 years reported 20% (1/5) and 25% (1/4) of cases with swelling in the biodegradable group and titanium group, respectively[2]. The retrospective studies showed no significant difference in long-term swelling between the two groups (RR 4.55, 95% CI 0.78–26.68, very low quality; Fig. 3C). Palpability of plates and screws after long-term follow-up occurred only in the titanium group, but did not differ between the two groups based on the data derived from the retrospective studies (RR 0.30, 95% CI 0.07–1.37, very low quality; Fig. 3D). Patients in both groups were similarly satisfied with the result after 1 year of follow-up (prospective cohort studies[13,39]: SMD −0.20, 95% CI −0.92 to 0.52, very low quality; Fig. 3E) and at >5 years of follow-up[2].

Symptomatic titanium and biodegradable plate removal rates ranged from 0 to 39% and from 0 to 17%, respectively (Supplementary Material Table S5). Follow-up ranged from 8 weeks to >5 years (Supplementary Material Table S4). The main reason for plate removal was chronic

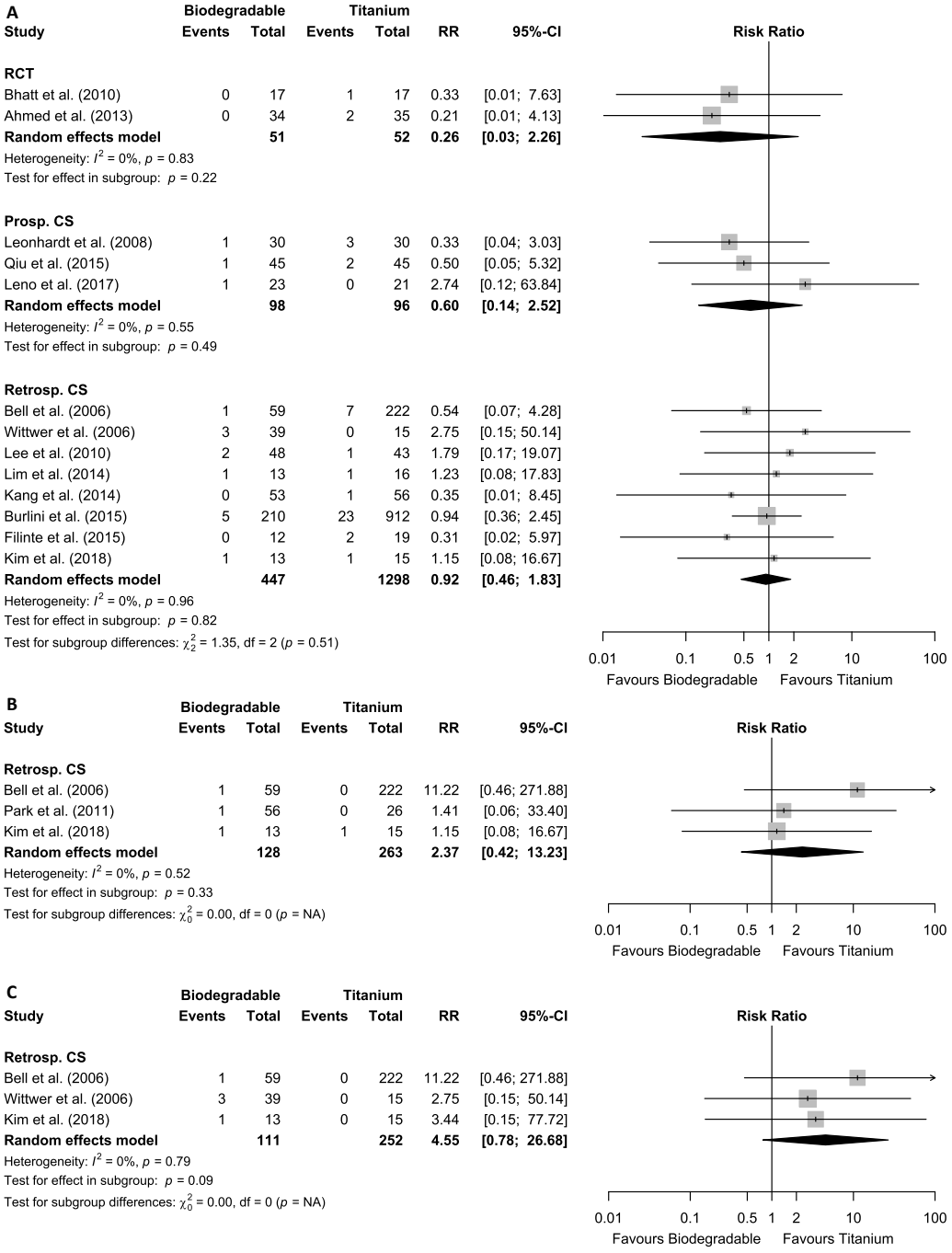

Fig. 3. Forest plots of the secondary endpoints: (A) infection (<4 weeks follow-up); (B) abscess (>12 weeks follow-up); (C) swelling (>12 weeks follow-up); (D) palpability of plates/screws (>12 weeks follow-up); (E) satisfaction (>12 weeks follow-up); (F) symptomatic plate removal (overall follow-up),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

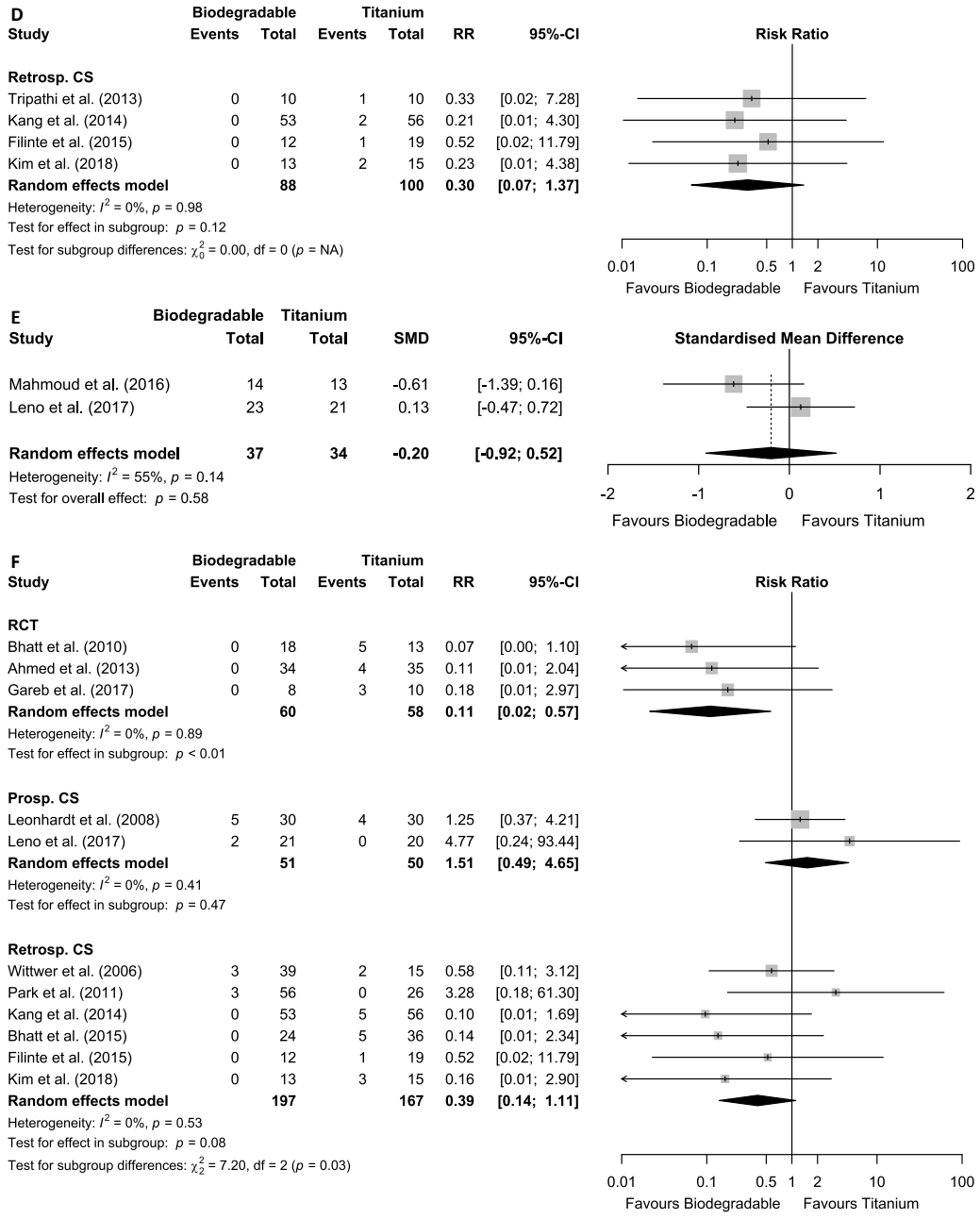

Fig. 3. (*Continued*).

infection or disturbed wound healing. The data of one study were not included in the analysis, as the authors could not provide the symptomatic plate removal rate and all titanium plates were removed after 6–8 months due to possible growth disturbances[48]. Although the RCT data showed a significant difference in plate removal rate in favour of the biodegradable group (RR 0.11, 95% CI 0.02–0.57, moderate quality), the prospective and retrospective studies did not demonstrate any significant difference (Fig. 3F). Subgroup analyses showed that the symptomatic plate removal rate did not differ significantly between the paediatric titanium and biodegradable groups (RR 1.11, 95% CI 0.36–3.45). However, all of 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 that included paediatric patients. In adult patients, the symptomatic plate removal rate was significantly lower in the biodegradable group (RR 0.33, 95% CI 0.13–0.84; Supplementary Material Fig. S8). Subgroup analyses of plate removal rates comparing mandibular versus other fractures showed no differences (mandibular fractures: RR 0.41, 95% CI 0.13–1.34; other fractures: RR 0.56, 95% CI 0.11–2.96; Supplementary Material Fig.

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

Outcome	Randomized controlled trials				
	Subjects, *n* (studies)	RR or SMD (95% CI)	Titanium osteosynthesis event proportion	Biodegradable osteosynthesis risk (95% CI)	Quality of evidence (GRADE)
Perioperative endpoints					
Plate breakage[a]	Two studies, of which one had zero events (see Table S5)				
Screw breakage[a]	718 (2)	17.13 (2.19–134.18)	0 per 1000	NA	Moderate[1,3,4]
Operation time[b]	Single study (see Table S5)				
Handling by surgeon[b]	Single study (see Table S5)				
Short-term follow-up					
Malocclusion[a]	Single study (see Table S5)				
Infection[a]	103 (2)	0.26 (0.03–2.26)	58 per 1000	15 per 1000 (2–131)	Very low[1,3,4]
Swelling[a]	Single zero-event study (see Table S5)				
Abscess[a]	Single study (see Table S5)				
Pain[a]	Single study (see Table S5)				
Analgesics used[a]	No studies				
MMO[b]	No studies				
Dehiscence[a]	126 (2)	1.68 (0.56–5.00)	75 per 1000	126 per 1000 (42–375)	Very low[1,3,4]
Plate exposure[a]	Single zero-event study (see Table S5)				
Intermediate follow-up					
Malunion[a]	Three zero-event studies (see Table S5)				
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]
Malocclusion[a]	117 (3)	1.01 (0.21–4.81)	53 per 1000	54 per 1000 (11–257)	Very low[1,2,3,4]
Pain[a]	Two studies, different outcome measures (see Table S5)				
MMO[b]	No studies				
TMJ dysfunction[a]	No studies				
Long-term follow-up					
Malocclusion[a]	Two studies with the same study population (see Table S5)				
Pain[a]	Two zero-event studies with the same study population (see Table S5)				
MMO[b]	No studies				
TMJ dysfunction[a]	No studies				
MFIQ[b]	Two studies with the same study population (see Table S5)				
Abscess[a]	Single study (see Table S5)				
Swelling[a]	Two studies with the same study population (see Table S5)				
Palpability plate/screws[a]	Three studies, of which two had the same study population and one had zero events (see Table S5)				
Satisfaction[b]	No studies				
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]
Total costs[b]	Single study (see Table S5)				
Revision surgery (not plate removal)[a]	Three studies of which two had zero-events (see Table S5)				

Outcome	Prospective cohort studies				
	Subjects, *n* (studies)	RR or SMD (95% CI)	Titanium osteosynthesis event proportion	Biodegradable osteosynthesis risk (95% CI)	Quality of evidence (GRADE)
Perioperative endpoints					
Plate breakage[a]	Single study (see Table S5)				
Screw breakage[a]	No studies				
Operation time[b]	Single study (see Table S5)				
Handling by surgeon[b]	No studies				

Table 2 (*Continued*)

Outcome	Prospective cohort studies				
	Subjects, *n* (studies)	RR or SMD (95% CI)	Titanium osteosynthesis event proportion	Biodegradable osteosynthesis risk (95% CI)	Quality of evidence (GRADE)
Short-term follow-up					
Malocclusion[a]	Three studies of which two had zero events (see Table S5)				
Infection[a]	194 (3)	0.60 (0.14–2.52)	52 per 1000	31 per 1000 (7–131)	Very low[1,2,3,4]
Swelling[a]	No studies				
Abscess[a]	No studies				
Pain[a]	No studies				
Analgesics used[a]	No studies				
MMO[b]	Two studies, of which one only reported postoperative MMO (see Table S5)				
Dehiscence[a]	Four studies, of which three had zero events (see Table S5)				
Plate exposure[a]	Single study (see Table S5)				
Intermediate follow-up					
Malunion[a]	Three zero-event studies (see Table S5)				
Mobility bone segments[a]	Single study (see Table S5)				
Malocclusion[a]	Three studies of which two had zero-events (see Table S5)				
Pain[a]	No studies				
MMO[b]	Two studies, of which one only reported postoperative MMO (see Table S5)				
TMJ dysfunction[a]	Single study (see Table S5)				
Long-term follow-up					
Malocclusion[a]	Three zero-event studies (see Table S5)				
Pain[a]	No studies				
MMO[b]	Two studies, of which one only reported postoperative MMO (see Table S5)				
TMJ dysfunction[a]	No studies				
MFIQ[b]	No studies				
Abscess[a]	No studies				
Swelling[a]	No studies				
Palpability plate/screws[a]	Single zero-event study (see Table S5)				
Satisfaction[b]	71 (2)	−0.20 (−0.92 to 0.52)	NA	NA	Very low[1,2,3,4]
Overall follow-up					
Symptomatic plate removal[a]	104 (2)	1.51 (0.49–4.65)	80 per 1000	121 per 1000 (39–372)	Very low[1,3,4]
Total costs[b]	No studies				
Revision surgery (not plate removal)[a]	Single zero-event study (see Table S5)				

Outcome	Retrospective cohort studies				
	Subjects, *n* (studies)	RR or SMD (95% CI)	Titanium osteosynthesis event proportion	Biodegradable osteosynthesis risk (95% CI)	Quality of evidence (GRADE)
Perioperative endpoints					
Plate breakage[a]	Four studies, of which three had zero events (see Table S5)				
Screw breakage[a]	748 (3)	5.67 (0.98–32.65)	0 per 1000	NA	Very low[1,3,4]
Operation time[b]	165 (3)	+0.72 (−0.17 to 1.61)	NA	NA	Very low[1,3,4]
Handling by surgeon[b]	No studies				
Short-term follow-up					
Malocclusion[a]	91 (2)	0.51 (0.06–4.68)	36 per 1000	18 per 1000 (2–168)	Very low[1,3,4]
Infection[a]	1745 (8)	0.92 (0.46–1.83)	28 per 1000	26 per 1000 (13–51)	Very low[1,2,4]
Swelling[a]	Two studies, of which one had 100% event rate in both groups (see Table S5)				
Abscess[a]	No studies				

Pain[a]	Single study (see Table S5)				
Analgesics used[a]	No studies				
MMO[b]	Single study (see Table S5)				
Dehiscence[a]	123 (3)	0.58 (0.18–1.84)	157 per 1000	91 per 1000 (28–289)	Very low[1,2,3,4]
Plate exposure[a]	1313 (3)	0.79 (0.23–2.71)	13 per 1000	10 per 1000 (3–35)	Very Low[1,2,3,4]
Intermediate follow-up					
Malunion[a]	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]	Single zero-event study (see Table S5)				
Malocclusion[a]	Two studies of which one had zero events (see Table S5)				
Pain[a]	No studies				
MMO[b]	No studies				
TMJ dysfunction[a]	Single study (see Table S5)				
Long-term follow-up					
Malocclusion[a]	Single zero-event study (see Table S5)				
Pain[a]	194 (3)	0.40 (0.10–1.68)	44 per 1000	18 per 1000 (4–74)	Very low[1,3,4]
MMO[b]	Single study with only postoperative data (see Table S5)				
TMJ dysfunction[a]	Single study (see Table S5)				
MFIQ[b]	No studies				
Abscess[a]	391 (3)	2.37 (0.42–13.23)	4 per 1000	9 per 1000 (2–53)	Very low[1,4]
Swelling[a]	363 (3)	4.55 (0.78–26.68)	0 per 1000	NA	Very low[1,4]
Palpability plate/screws[a]	188 (4)	0.30 (0.07–1.37)	60 per 1000	18 per 1000 (4–82)	Very low[1,3,4]
Satisfaction[b]	Single study (see Table S5)				
Overall follow-up					
Symptomatic plate removal[a]	364 (6)	0.39 (0.14–1.11)	96 per 1000	37 per 1000 (13–107)	Very low[1,2,3,4]
Total costs[b]	No studies				
Revision surgery (not plate removal)[a]	1544 (5)	1.16 (0.33–4.06)	13 per 1000	15 per 1000 (4–53)	Very low[1,2,4]

CI, confidence interval; GRADE, Grades of Recommendation, Assessment, Development and Evaluation Working Group system; MFIQ, Mandibular Function Impairment Questionnaire; MMO, maximum mouth opening; NA, not applicable; RR, risk ratio (binary variables); SMD, standardized mean difference (continuous variables); TMJ, temporomandibular joint.

[1] Downgraded one level due to high risks of bias identified across studies: the majority of studies had a 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 level for indirectness: the evidence of the original manuscripts was 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 $> +0.8$).

[a] Binary variable.

[b] Continuous variable.

S9). Comparing plate removal rates between ≤1 year and >1 year follow-up did not display any significant difference between the different follow-up and treatment groups (Supplementary Material Fig. S10).

One RCT assessed total costs (i.e., direct and indirect costs) after 2 years of follow-up and found mean costs of 6137 ± 2980 euros for biodegradable osteosynthesis and 8128 ± 5453 euros for titanium osteosynthesis[36]. The higher total cost 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, 95% CI 0.33–4.06, very low quality; Supplementary Material Fig. S11). Follow-up ranged from 8 weeks to 74 months and the most common indication for revision surgery was abscess formation.

A summary of the findings, including the quality of evidence for all of the endpoints, is shown in Table 2.

Additional analyses

The results of sensitivity analyses, including both-armed zero-event studies, did not differ significantly from the analyses mentioned above (available from the corresponding author). In the meta-regression analysis, study design had no effect on malocclusion in the intermediate follow-up ($P > 0.05$), but had an effect on the reported RR of plate removal ($P = 0.03$). The prospective cohort studies had a significantly higher log RR (2.61), whereas the retrospective studies did not (1.27) compared to the RCTs (−2.21; Supplementary Material 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 (Supplementary Material Table S7). Thus, based on the currently available evidence, TSA could not support the conclusions derived from conventional meta-analyses for these endpoints. Regarding the endpoints dehiscence and malocclusion at intermediate follow-up, 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 evidence provided suggests that less symptomatic plate removal of biodegradable osteosynthesis occurred (Supplementary Material Table S7). TSA could not be performed on any of the other endpoints as these endpoints were assessed in no RCT or in only a single RCT, or were only assessed in total zero-event trials.

Discussion

The meta-analysis in this study showed that the performance of biodegradable osteosynthesis was similar to that of titanium osteosynthesis regarding malunion, mobility of bone segments, and malocclusion after fixation of non-comminuted maxillofacial fractures. Additionally, no differences were found between the two types of osteosynthesis 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 time points. 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 than in the titanium group. The symptomatic plate removal rate was significantly lower (i.e., 89% risk difference) in the biodegradable group than in the titanium group. The TSA confirmed a true-positive effect regarding plate removal, although only RCTs with a high risk of bias could be included. Finally, the meta-regression analysis showed that prospective cohort studies had significantly higher effect estimates of the 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 were not available, the data from the RCTs and prospective cohort studies could not be synthesized. These outcomes, accompanied by the data on low mobility of bone segments and objective malocclusion, emphasize that both interventions are adequate for the fixation of maxillofacial fractures. This review focused on objective malocclusion assessments by healthcare professionals and subjective malocclusion assessments by the patients themselves. Although objective assessment of malocclusion is preferred over subjective assessment for literature comparison purposes, we 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 of follow-up[2]. In this latter study, subjective malocclusion was present in 50% of the titanium group compared to 0% of the biodegradable group. Also, the former group had worse mandibular function, as assessed by MFIQ, even though these patients were not assessed as having an objective malocclusion at the 2-year follow-up[35]. Researchers should therefore also focus on long-term (i.e., >5 years of follow-up) objective and subjective assessments of malocclusion and mandibular function, as there may be discrepancies between the two 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 by an additional risk of complications[11]. The present review showed that biodegradable osteosynthesis material was removed significantly less often than titanium osteosynthesis material due to symptoms. Although the subgroup analysis showed that symptomatic plate removal did not differ significantly between the two interventions in paediatric patients, all titanium plates were eventually removed (i.e., 100% of plates) due to possible growth disturbances, while only symptomatic biodegradable plates were removed from these patients (i.e., 12% of plates; Supplementary Material Fig. S8). Thus, titanium osteosynthesis will also eventually result in more re-operations compared to biodegradable osteosynthesis in paediatric patients.

The present review also performed a subgroup analysis of the 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 of the biodegradable osteosynthesis systems used in the included studies are certified for use in the mandible, namely Inion CPS (Inion Oy, Tampere, Finland), GrandFix (Gunze, Kyoto, Japan), and OsteoTrans-MX (Teijin Medical Corp., Osaka, Japan)[53–55]. All of the instructions for the other biodegradable systems explicitly state that they are contraindicated for use in load-bearing areas in adults,

including the mandible[56–58], and yet several studies implanted biodegradable osteosynthesis material off-label[13,34,38,42]. Furthermore, the morphology and lesser vascularization of the mandible could negatively influence the fixation and degradation of biodegradable osteosynthesis[2]. These factors have been suggested to contribute to higher symptomatic plate removal rates in mandible fractures compared to other facial fractures for both biodegradable and titanium osteosynthesis[2]. The current meta-analysis did not find any significant difference between the two osteosynthesis systems regarding the symptomatic plate removal rate when mandibular and other fractures were compared separately.

Most of the included studies reported a follow-up period of up to 1–2 years. However, different studies have reported titanium and biodegradable plate removal rates following maxillofacial surgery of up to 19% after 5 years of follow-up[2,45], while no plates were removed between 1 and 5 years of follow-up[59]. Therefore, future research should extend the follow-up beyond 2 years in order to assess the plate removal rate adequately in both intervention groups.

Foreign-body reactions after the implantation of biodegradable osteosynthesis systems have been reported and remain a concern in the usage of such systems[2,9,10]. This review did not find any differences regarding the presence of swelling or abscess formation between the two interventions after short- and long-term follow-up, although it must be noted that only two studies included patients with >3 years of follow-up[2,40]. Also, revision surgery (i.e., non-plate removal) was scarce and there was no difference between the two groups. 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, sub-periosteal). Of these factors, polymer composition has been studied the most[60–62].

The reported foreign body reactions have occurred predominantly in biodegradable osteosynthesis materials with a high proportion of PLLA (i.e., >70%) in their 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 that 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 are therefore more resistant to degradation and resorption than D-isomers[60]. PLLA crystalline particles have been identified intracellularly up to 5.7 years after the 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), and PDLLA are more hydrophilic and undergo degradation and resorption more quickly[60]. The tissue response to PLLA has been studied extensively in animals and patients, with long-term follow-up (i.e., up to 6 years), whereas no long-term data are currently available for PGA, PLGA, or PDLLA (co-) polymer compositions. In vivo studies on these biodegradable systems have been performed with a follow-up of up to 18 months[60,62,64]. Long-term in vivo degradation of these (co-)polymer compositions is currently being investigated by our research group and the results are eagerly awaited. Additionally, future research should preferably incorporate the other factors that contribute to foreign-body reactions.

Data on analgesia usage, MMO, MFIQ, TMJ dysfunction, handling of osteosynthesis systems by surgeons, perioperative plate breakage, and total costs could not be synthesized due to the lack of studies that 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 on (postoperative) MMO could not be synthesized on account of the limited number of studies reporting MMO or because the authors could not provide the data. The MFIQ was only assessed in two publications reporting the same study population[2,35]. Thus, there is currently insufficient evidence to provide conclusions regarding mandibular and TMJ function after both interventions. Although preoperative 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 postoperative data regarding TMJ function and MMO or use validated questionnaires (e.g., the 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 osteosynthesis was associated with higher costs compared to biodegradable osteosynthesis, 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 the two systems were small and the authors reported that more exposure to biodegradable systems by surgeons could diminish this difference.

The meta-regression analysis showed that the effect estimates of the plate removal rate in prospective studies were significantly higher than those in RCTs 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 information provided, 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]; 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 that compared complications after fracture fixation between five studies, showed that biodegradable osteosynthesis had lower overall complication rates compared to titanium osteosynthesis (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 indicate that, according to current evidence, there is no significant difference in complications between the

two interventions. In particular, there was no difference in long-term palpability between the two 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 $\leq$10 studies are underpowered and inconclusive, and thus their usage is discouraged if insufficient studies can be included for a meta-analysis[16,25–27]. Finally, the authors did not provide any data regarding inter-observer agreement and did not incorporate risk of bias in the interpretation of the results. We therefore express concerns about the conclusions drawn in that particular review.

Quality of the evidence

All of 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 is possible) and are not visible on radiographs, while titanium osteosynthesis is 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 for downgrading the quality of evidence were high risk of bias, indirectness, and imprecision of the data. Moderate quality evidence was found for perioperative screw breakage and the plate removal rate. Infection (<4 weeks follow-up), dehiscence (<4 weeks follow-up), mobility of bone segments (6–12 weeks follow-up), and malocclusion (6–12 weeks follow-up) were assessed as very low quality. The quality of evidence of the endpoints malunion and pain (6–12 weeks follow-up), and MFIQ, swelling, and palpability of plates/screws (>12 weeks follow-up) 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 time points. Also, the RCT 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

This meta-analysis has the following strengths: 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 time restriction. A range of relevant endpoints with predefined follow-up moments were included. Furthermore, study eligibility, data extraction, and the risk of bias assessment were performed independently by two reviewers with excellent inter-observer agreement. Also, TSA was used to increase the reliability of the data and to determine the RIS 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; therefore high quality research is 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, which 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: (1) well-defined endpoints to minimize reporting bias, (2) adequate follow-up of the corresponding endpoints to minimize attrition bias, and (3) 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), as well as alcohol and tobacco usage, as these factors are known to compromise wound healing and decrease vascularization intraorally, which may affect degradation and resorption rates, and the use of, reasons for, and duration of 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 would enable the appraisal, interpretation, and pooling of future data. Finally, future studies should focus on the cost-effectiveness of biodegradable systems, including direct costs (i.e., perioperative costs) and indirect costs (e.g., second operations, absence from work).

Based on all currently available evidence after both narrative review and meta-analyses, biodegradable and titanium osteosynthesis 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 group than in the titanium group. The symptomatic plate removal rate was significantly lower after biodegradable fixation 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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Competing interests

None.

Ethical approval

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Patient consent

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Appendix A. Supplementary data

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