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BIODEGRADABLE VERSUS TITANIUM PLATES AND SCREWS IN MAXILLOFACIAL SURGERY

Thesis

Nico van Bakelen

rijksuniversiteit groningen

Biodegradable versus Titanium Plates and Screws in Maxillofacial Surgery

Proefschrift

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Nicolaas Bernardus van Bakelen

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CONTENTS

GENERAL INTRODUCTION

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Maxillofacial fractures and dentofacial anomalies comprise a considerable portion of the field of contemporary oral and maxillofacial (OMF) surgery. Anatomically and aesthetically restoration of form and function of the maxillofacial hard and soft tissues is crucial in these cases. Due to population growth, increase of traffic, industrialization, violence and sport, traumatology has considerably increased worldwide [1]. The introduction and perfection of anaesthetics, imaging techniques, antibiotics, specially designed instruments, new surgical techniques and biomaterials have allowed OMF surgeons to improve treatment outcomes [2]. In orthognathic surgery the bilateral sagittal split osteotomy (BSSO), the Le Fort-I osteotomy, and the genioplasty have become common procedures to solve a wide range of clinical problems [3]. These procedures are usually combined with orthodontics for the most optimal result.

The main goal in orthognathic and trauma surgery is to achieve a predictable, fast, anatomical, safe and painless functional union of bone segments that results in adequate and undisturbed bone healing. Essential prerequisites for primary bone healing of fractures and osteotomies are sufficient blood supply, anatomical reduction (fractures) or positioning of bone segments as intended (osteotomies), and immobilization of bone segments. The optimum end point is a situation with good aesthetics and good oral functions, such as chewing, swallowing, laughing, and speaking, which can be maintained over time [4,5].

Current state of the art

To achieve this main goal the treatment of nearly all maxillofacial fractures and osteotomies is currently performed by 'open reduction and internal fixation' (ORIF). ORIF involves the following steps:
- exposure of fracture/osteotomy site
- reduction/aimed positioning of the fragments
- internal fixation
- meticulous wound closure

Currently, internal fixation is obtained (depending on the situation) by using plates or mesh and/or screws or pins. With these systems (semi) rigid internal fixation and uncomplicated bone healing can be achieved without the necessity to apply maxillomandibular fixation (MMF) post-operatively [6]. The use of MMF during the healing period of 6-8 weeks is very uncomfortable. In addition, it immobilizes the temporomandibular joints resulting in cartilage degeneration [7]. MMF is still used intra-operatively to establish or preserve the occlusal relationship of the upper and lower jaw in orthognathic surgery and facial trauma. Due to the discontinuation of MMF, patients can open their mouths, and carefully load their masticatory system directly following surgery. Guiding elastics for functional training are usually recommended to achieve neuromuscular adaptation. Continuation of post-surgical MMF would be a step back in history.

Titanium versus biodegradable osteosynthesis: pros and cons

Titanium is currently regarded as the "golden standard" for internal fixation of fractures and osteotomies. Titanium screws can be inserted directly after drilling a pilot hole (self-tapping screw) or even without drilling a pilot hole (drill-free screw). Titanium fixation systems can be used safely and (cost)effectively, (at least the miniplates) are easily adaptable, and the intrinsic mechanical properties guarantee adequate bone healing and ensure that the device dimensions are kept within clinically acceptable limits. Titanium can be used for a wide variety of indications in traumatology and orthognathic surgery. It appears to be the most "bio-inert" metal suitable for osteosynthesis [8]. However, titanium still has several potential adverse effects:
(1) corrosion and metal release from the implants [9];
(2) inflammatory response and infection [10];
(3) sensitivity to hot and cold stimuli [11];
(4) palpability (and sometimes visibility) of the plates through the soft tissues;
(5) possible growth disturbance or mutagenic effects [12,13]; and
(6) interference with imaging or radio-therapeutic irradiation techniques [14,15].

The continued presence of plates and screws in the human body after the material has fulfilled its function, *i.e.*, undisturbed bone healing, is a disadvantage. Despite its good biocompatibility, titanium should still be regarded as a foreign body to the human organism. Titanium plates and screws are removed following bone healing in a second operation in 5-40% of the cases [16-21] .

There is a continuous search for the ideal osteosynthesis. In literature it is stated that the ideal material should be completely removed by the human body itself as soon as it has fulfilled its function [22]. Biodegradable osteosynthesis material, degrading after healing time and with gradual transfer of functional forces to the healing bone during disintegration of the biodegradable devices, potentially is a suitable alternative and seems to be the perfect solution for most of the above-mentioned potential disadvantages. A reduction or even a complete deletion of the problems associated with titanium systems is desirable from the viewpoint of cost-effectiveness, patient comfort, healthcare quality, and risk of complications due to plate removal. This could benefit patients in OMF surgery [23-25], but can also have implications for patients in other medical fields that use biodegradable plates/mesh and/or screws/pins for fixation, *e.g.*, orthopedic [26-29] or plastic (reconstructive) surgery [30-32], otolaryngology [33,34], cardiothoracic surgery [35-38], obstetrics and gynaecology [39,40], urology [41], neurosurgery [42] and craniofacial surgery [43,44]. Furthermore, biodegradable osteofixation devices are compatible with diagnostic (CT and MRI) and therapeutic radiation.

However, biodegradable fixation systems may also have their limitations. The mechanical properties are less favourable [45-47] showing perhaps inferior bone healing. To compensate for these inferior mechanical properties, the manufacturers have made the biodegradable materials more bulky. Therefore, biodegradable plates may initially be even more palpable than titanium plates. Bulkiness can also be a disadvantage for the ap-

plication of the material in the limited surgical field of OMF surgery, and can lead to problems with tension-free wound closure. As a consequence, an intra-operative switch from biodegradable to titanium plates and screws could occur, if the intention was to use biodegradable plates [48]. Regarding disintegration, in literature there is no evidence of total *in vivo* resorption, at least on an electron microscopic level, of any biodegradable osteosynthesis material. Additionally, adverse tissue reactions to degradation products have been reported [49,50]. According to the literature biodegradable osteosynthesis materials have to be removed in a second operation in 0-31% of the cases [51,52] .

Worldwide application of biodegradables? Why not?
Despite the supposed advantages of biodegradable osteofixation devices, these systems have not replaced the titanium systems and are currently applied in only limited numbers. The major drawback for general use of biodegradable devices is the lack of clinical evidence for well-defined indications [53]. Numerous *in vitro*, *animal*, and *clinical* studies have been published reporting positive [54-62] as well as negative results [49,63-65]. Only few of the available studies in the literature are randomized controlled trials (RCTs), while most of them are not appropriately powered. There is some evidence available from RCTs to support the conclusion that there is no significant difference between biodegradable and titanium osteofixation devices with regard to short-term clinical outcome, and complication rate in the area of orthognathic surgery [53,66]. A definitive conclusion regarding the fixation of fractured and osteotomized bone segments with respect to the long-term performance in OMF surgery cannot be drawn.

Another significant factor of the limited use is the resistance by surgeons to modify their conventional, familiar, and well experienced, treatment techniques [67]. Improvements in intra-operative application, particularly in plate adaptation and screw insertion, are needed before their use becomes more widespread [68]. Most biodegradable plates are not malleable at room temperature, but require pre-heating (in a heating bath) to be shaped. The only exceptions are the self-reinforced plates. These plates are easily bendable at room temperature [69]. Moreover, biodegradable screws can be inserted only after pre-drilling and pre-tapping. Regarding the difficulty of the intra-operative application, authors disagree: Jain *et al.* (2006) stated that contouring resorbable plates is easier than metallic plates [70]. With few extra tools (*i.e.*, heating bath) resorbable plate systems could be easily handled and adapted [71]. Bos (2005) stated that biodegradable plate bending and screw insertion are more time consuming and far more complicated compared with titanium [72].

At present, biodegradable fixation systems are more expensive than titanium plates and screws. This is a potential threat for the general use of biodegradable systems. In order to become truly more cost-effective than titanium, the costs of the biodegradable systems have to be reduced while clinical outcomes need to be superior to titanium. In the literature no data are available regarding the cost-effectiveness of biodegradable plates and screws in OMF surgery.

Since the introduction of biodegradable devices in 1966 [73] the ideal (biodegradable) osteosynthesis is still to be found or valued.

Multicenter RCT
Given the above, starting a randomized controlled clinical trial in which a biodegradable system is compared to an established titanium system is the most logical step. Such a study has to be sufficiently powered, be of high-quality, have well defined indications, and has to be appropriately reported [53].
First of all the effectiveness, *i.e.*, bone healing 8 weeks after surgery, should be tested. Bone healing is the primary function of the osteosynthesis material. Although, the rationale for using biodegradable devices is to prevent a second operation to remove the material, one simply cannot draw conclusions on plate removal rates, when it is unknown if the material has fulfilled its primary function. We chose bone healing as primary outcome measure for this reason. The bone healing performance of conventional titanium fixation systems is very high [25,53,74-78]. Bone healing with the biodegradable system should at least be as effective as with titanium. Therefore, a non-inferiority design should be chosen. If the biodegradable system proves to be non-inferior regarding bone healing after 8 weeks, a longer follow-up is necessary as the supposed advantage, *i.e.*, less plate removals, and the associated costs and cost-effectiveness, will become clear over time. Secondary outcome measures such as costs and cost-effectiveness analyses should include the hospital admission costs, surgical costs (material), plate removal costs, and the costs associated with sick leave of the patients. Last but not least, the post-operative relapse should be tested. This is probably the most important issue after primary bone healing, even more important than the risk of plate removal and cost-effectiveness. Whatever the outcomes of the plate removal percentages and the cost-effectiveness of both systems, the system with the least relapse, is (probably) most favorable for clinical use. This implies that if the biodegradable system proves to have less plate removals and is more cost-effective, but has significantly more relapse, one should nevertheless still choose a titanium system. The reverse scenario is also possible. The last possibility is that there will be no significant difference in relapse between both groups. In that case, the preferred system would be the system with the least plate removals and/or highest cost-effectiveness.

AIMS OF THIS THESIS

The general **aim** of this thesis was to establish (1) short-term effectiveness and safety, (2) long-term clinical performance, (3) cost-effectiveness, and (4) relapse of biodegradable plates and screws used for fixation of bone segments in the maxillofacial skeleton as a potential alternative to titanium plates and screws.
More specifically, the aims of this research project were:
- to investigate the bone healing after 8 weeks, the handling characteristics, and safety of biodegradable plates and screws used for fixation of fractures and osteotomies

in the maxillofacial skeleton compared to conventional titanium plates and screws (chapter 2);

- to investigate the 1 and 2 years post-operative clinical performance of the biodegradable system as a potential alternative to the titanium system regarding fixation of fractures and osteotomies in the maxillofacial skeleton (chapter 4);

- to investigate the cost-effectiveness of bone healing and plate removal of biodegradable plates and screws as a potential alternative to titanium plates and screws regarding treatment of fractures and osteotomies in the maxillofacial skeleton (chapter 5);

- to investigate the relapse of biodegradable plates and screws as a potential alternative to titanium plates and screws regarding treatment of osteotomies in the maxillofacial skeleton (chapter 6).

In the design of the study intra-operative switches from the biodegradable to the conventional titanium system were unexpected, and initially not an outcome measurement. Retrospectively, the reasons for the intra-operative switches were analyzed in order to find predictor variables that may be helpful in deciding in advance whether to use biodegradable devices or not (chapter 3).

A RANDOMIZED CLINICAL TRIAL OF BIODEGRADABLE AND TITANIUM FIXATION SYSTEMS IN MAXILLOFACIAL SURGERY

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ABSTRACT

Background - Biodegradable fixation systems could reduce or delete the problems associated with metallic systems, since removal is not necessary.

Aim - The aim of this study was to establish the effectiveness and safety of biodegradable plates and screws as potential alternatives to metallic ones.

Materials & Methods - This multicenter randomized controlled trial was conducted from December 2006 to July 2009. Included were patients who underwent mandibular- and/or Le Fort-I osteotomies and those with fractures of the mandible, maxilla, and zygoma. The patients were assigned to a titanium control group (KLS Martin) or to a biodegradable test group (Inion CPS). The primary outcome measure was 'bone healing 8 wks post-operatively'.

Results - The Intention-To-Treat (ITT) analysis of 113 patients in the titanium group and 117 patients in the biodegradable group revealed that biodegradable plates and screws performed inferiorly to titanium plates and screws ($p<0.001$), whereas the Treatment-Received (TR) analysis revealed that biodegradable plates and screws did not perform inferiorly regarding bone healing after 8 wks ($p=0.15$). In 25 patients ('switchers') who were randomized to the biodegradable group, the maxillofacial surgeon made the decision to switch to the titanium system intra-operatively. In the ITT analysis, the switches were assessed as failures for the primary outcome measure.

Conclusion & Discussion - The relatively many intra-operative 'switches' were primarily responsible for the inferior primary outcome result. Despite this 'inferior' result, biodegradable plates and screws could be safely used when it was possible to apply them. The benefits of using biodegradable systems (fewer plate removal operations) should be confirmed during a follow-up of minimally 5 years (http://controlled-trials.com; ISRCTN 44212338).

Keywords: Effectiveness, non-inferior, safety, bone-healing, maxillofacial, efficacy.

INTRODUCTION

Essential prerequisites for the bone healing of fractures and osteotomies include sufficient vascularization, anatomical reduction, and immobilization of bone segments. At present, immobilization of bone fragments is obtained with metallic plates and screws without MaxilloMandibular Fixation (MMF) [79]. This allows patients to load their masticatory system functionally immediately following surgery. The currently available metal plating systems have the advantage of combining excellent mechanical and handling properties. A disadvantage of metallic plates and screws is their long life remain *in situ*, resulting in several potential adverse effects, such as:

(1) inflammatory response and infection [10];
(2) sensitivity to hot and cold stimuli [11];
(3) palpability of the plates;
(4) possible growth disturbance or mutagenic effects [12,13]; and
(5) interference with imaging or radio-therapeutic irradiation techniques [14,15].

As a consequence, the implants are removed following bone healing in a second operation in 5-40% of the cases [16,17]. Biodegradable plates and screws degrade in the human body, reducing or eliminating the problems associated with metallic systems. This is desirable from the viewpoint of cost-effectiveness, patient comfort, healthcare quality, and risk of complications due to plate removal. However, adverse tissue reactions to degradation products have been reported [49,50,63,65]. Moreover, biodegradable systems are mechanically less favourable than metallic systems, which can result in insufficient bone healing. A few controlled trials have been published on this subject [24,25,75,80], which have previously been summarized and analyzed in a systematic review [53]. Since the results were inconclusive, mainly because of the lack of sufficiently powered and appropriately designed trials and heterogeneity among the included studies, there is a need for well-designed randomized controlled trials of sufficient size.

The aim of this study was to establish the effectiveness and safety of biodegradable plates and screws as an alternative to metallic ones. Therefore, we tested the null hypothesis that the performance of the Inion CPS biodegradable system is inferior to that of a titanium system in terms of bone healing following treatments of mandibular, maxillary (Le Fort-I), zygomatic fractures, and bilateral sagittal split osteotomies (BSSO's) and/or Le Fort-I osteotomies.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria:

- patients scheduled for 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 parents or responsible persons if necessary) who signed the *informed consent* form.

Exclusion criteria:

- patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);
- patients presented with heavily comminuted fractures of the facial skeleton;
- patients who experienced compromised bone healing in the past;
- patients who were pregnant;
- patients who could/would not participate in a 1-year follow-up (reasons);
- patients who would not agree with an *at random* assignment to one of the treatment groups, or one of the methods or treatment administered in the study;
- patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);
- patients who experienced cleft lip and palate surgery in the past;
- patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);
- patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.

MATERIALS & METHODS

This RCT has been described according to the CONSORT statement 2010 (http://www.consort-statement.org/).

Patients
This prospective randomized controlled trial was conducted from December 2006 to July 2009. The source population consisted of patients who were treated at the departments of Oral and Maxillofacial (OMF) Surgery in the Netherlands of the: (1) University Medical Centre Groningen (UMCG), (2) Rijnstate Hospital Arnhem (RHA), (3) Amphia Hospital Breda (AHB), and (4) Medical Centre Leeuwarden (MCL).

Patients meeting the inclusion criteria were eligible for this study (Table 1). All patients were informed regarding the treatment options prior to surgery and were required to provide written informed consent to participate in the study. The surgeons recruited the participants and assigned them randomly to two treatment groups a day before (osteotomies) or immediately prior to (fractures) the operation. A statistician generated the randomization sequences using a computerized randomization program. The randomization was performed using an IVRS (Interactive Voice Response System) (block size 10), which was available 24-hours a day to conceal the randomization sequence until the interventions were assigned. Randomization was stratified by hospital to ensure that the two treatment options were equally divided over the participating hospitals. The study was approved by the Medical Ethical Committees of the participating hospitals.

Interventions
The patients were assigned to a titanium control group (KLS Martin, Gebrüder Martin GmbH&Co., Tuttlingen, Germany) or to a biodegradable test group (Inion CPS, Inion Ltd., Tampere, Finland). Neither prior to nor after surgery were the patients aware of the system that had been used.

All plates and screws were applied according to the instructions of the manufacturers. The screw holes were pre-drilled for both titanium and biodegradable screws, and pre-tapped for biodegradable screws. For fixation of mandibular osteotomies and fractures, 2.5-mm biodegradable or 2.0-mm titanium plates and screws were used, whereas 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used for fixation of zygoma 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 screws and pre-heating the plates, and to get used to the different dimensions. These 'test-surgeries' were not included in the study. Post-operatively, the patients did not receive MMF, but soft guiding elastics, and they were instructed to eat a soft diet for 5 wks.

Outcome measures
The primary outcome measure was 'bone healing 8 weeks after surgery', which was defined as follows:

(1) absence of clinical mobility of the bone segments assessed by bi-manual traction on the distal and proximal bone segments, and;

(2) absence of radiographic signs of disturbed bone healing assessed on an orthopantomogram (OPT; all indications), a lateral cephalogram (osteotomies), an occipito-mental radiograph (zygoma fractures), and a fronto-suboccipital radiograph (mandible fracture).

The following secondary outcome measures were assessed:

(1) clinical: correct occlusion (yes/no), palpability of plates/screws (yes/no), wound dehiscence (yes/no), and signs of inflammation (rubor, calor, dolor, tumor, or functio leasa: yes/no);

(2) radiographic: correct position of the bone segments (yes/no; position of teeth, path

Assessed for eligibility (n= 834)

Enrolment

Excluded (n= 604)
- Not meeting in- exclusion criteria (n= 105)
- Refused to participate (n= 499)

Patients randomized (n= 230)

BIODEGRADABLE GROUP

Allocated to biodegradable group (n = 117)

Allocation

TITANIUM GROUP

Allocated to titanium group (n=113)

Analyzed (ITT) in biodegradable group (n = 117)

ITT analyses

Analyzed (ITT) in titanium group (n = 113)

Protocol violations (n = 5)
- after randomisation it turned out patients had cleft lip and palate (n = 3);
- after randomisation it turned out patient had a psychiatric disorder (n = 1);
- randomized to the wrong centre (n = 1)

Protocol violations (n = 2)
- after randomisation it turned out patient had cleft lip and palate (n = 1)
- randomized to the wrong centre (n =1)

Switched to titanium (n = 25)

Treatment Received (n = 87)

Treatment Received violations (n = 0)

Treatment Received (n = 136)

Treatment Received violations (n = 2)
- stable position zygomatic fracture achieved without osteosynthesis (n = 1);
- fixation mandibular fracture with lag screws without titanium plate (n = 1).

Operated with Inion CPS (n=87)

Operated with titanium (n=134)

Lost-to-follow-up (n=3)

Follow-up

Lost-to-follow-up (n=1)

Analyzed (TR) (n = 84)

TR analyses

Analyzed (TR) (n = 133)

Figure 1. *Flow diagram of patient's progress though the phases of RCT*

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of mandibular canal, and contour of cortical structures);

(3) patient-related (self-evaluation): pain reported on a Visual Analogue Scale (VAS; ranging 1-100) and mandibular function evaluated by the 17 questions on the Mandibular Function Impairment Questionnaire (MFIQ) [81]; range 17-85: a higher score means worse function; and

(4) handling characteristics (plate adaptation, drilling/tapping, screw insertion, and wound closure; scale 1-10).

Post-operative interventions, such as wound irrigation with saline, use of antibiotics, abscess incision and drainage, or removal of plates/screws within 8 wks, were reported separately. The primary and the secondary outcome measures were evaluated 8 wks following surgery by a colleague of the OMF surgeon who performed the surgery.

Statistical analysis

Hypothesis testing was conducted following the principles of non-inferiority analysis (one-tailed test). Based on an expected percentage of bone healing of 95% with a titanium system and a maximum acceptable difference of 5% between the two groups in terms of the primary outcome measure, two groups of 109 patients were necessary to demonstrate non-inferiority with a power of 80% at a significance level of 5%. When patients violating the study protocol were taken into account, 115 patients were included in each group.

The Statistical Package for Social Sciences (SPSS, version 18.0) was used for data analysis. The means and standard deviations of normally distributed variables were calculated and analyzed by the independent-samples t test. Dichotomous variables were analyzed by the Chi-squared or the Fischer's exact test. No interim analyses were performed during the study period.

RESULTS

Fig. 1 represents the flow of 230 randomized patients during the phases of the study regarding the Intention-To-Treat (ITT) analysis and Treatment-Received (TR) analysis. The inclusion of the different centres UMCG, RHA, AHB, and MCL resulted in 103, 78, 44, and 5 patients, respectively. The randomization procedure resulted in an ITT population of 113 patients in the titanium group and 117 patients in the biodegradable group. Inclusion errors were made for seven patients; four patients did not complete the follow-up. The outcome data for these patients were 'imputed', *i.e.*, adequate bone healing, according to the strategies of the Cochrane Collaboration (http://www.cochrane-net.org). In 25 patients ('switchers') who were randomized to the biodegradable group, the OMF surgeon made the decision to switch to the titanium system intra-operatively. The main reasons for switching were material failures, including non-grip screws (n=6), inadequate stability after the first fixation (n=3), and after re-positioning (n=4), inadequate plate adaptation (n=2), dimension of plate too big (n=1), and plate fracture during fixation

Table 2. *Baseline characteristics for ITT analysis*

Description	Titanium group (n)	Biodegradable group (n)	Total (n)
Surgical procedures	113	117	230
BSSO	72 (63.7%)	70 (59.8%)	142
Le Fort-I osteotomy	8 (7.1%)	8 (6.8%)	16
Bimaxillary osteotomy	24 (21.2%)	21 (17.9%)	45
Mandibular fracture	2 (1.8%)	9 (7.7%)	11
Le Fort-I fracture	1 (0.9%)	0	1
Zygoma fracture	4 (3.5%)	4 (3.4%)	8
Protocol violations	2 (1.8%)	5 (4.3%)	7
Gender/age distribution			*p* value
Male	44 (38.9%)	56 (47.9%)	0.17
Female	69 (61.1%)	61 (52.1%)	
Age (mean +/- s.d. in yrs)	31 +/- 11	31 +/- 12	0.59
(range in yrs)	16-60	14-59	

Abbreviations: BSSO = bilateral sagittal split osteotomy, ITT = Intention-To-Treat, s.d. = standard deviation.

Table 3. *Baseline characteristics for TR analysis*

Description	Titanium group (n)	Biodegradable group (n)	Total (n)
Surgical procedures	133	84	217
BSSO	87 (65.4%)	52 (61.9%)	139
Le Fort-I osteotomy	8 (6.0%)	8 (9.5%)	16
Bimaxillary osteotomy	29 (21.8%)	16 (19.0%)	45
Mandibular fracture	5 (3.8%)	4 (4.8%)	9
Le Fort-I fracture	1 (0.8%)	0	1
Zygoma fracture	3 (2.3%)	4 (4.8%)	7
Gender/age distribution			*p* value
Male	54 (40.6%)	42 (50%)	0.18
Female	79 (59.4%)	42 (50%)	
Age (mean +/- s.d. in yrs)	31 +/- 11	31 +/- 12	0.8
(range in yrs)	16-60	14:59	

Abbreviations: BSSO = bilateral sagittal split osteotomy, s.d. = standard deviation, TR = Treatment-Received.

(n=1). Other reasons were logistical problems (n=3), 'bad split' (n=1), and 'unknown' (n=4). In the ITT analysis, the switches were assessed as failures for the primary outcome measure. Regarding the TR analysis, the seven 'inclusion error' patients and the four 'lost to follow-up' patients were excluded. Additionally, the 25'switchers' were added to the titanium control group. This resulted in a TR analyses of 133 patients and 84 patients in the titanium group and biodegradable group, respectively.

None of the baseline characteristics differed significantly between the biodegradable and titanium group for the ITT and TR analysis (Tables 2 and 3).

Inadequate bone healing of 2 patients in the biodegradable group was reported. One patient had a mobile maxilla one day after surgery and was re-operated with the titanium system. The second patient had a mobile maxilla after 8 wks that healed without intervention. Following the ITT analysis, 27 patients in the biodegradable group (25 'switchers' and the two above-mentioned patients) and no patients in the titanium group showed inadequate bone healing, resulting in a significant difference (*p*<0.001). Regarding the TR analysis the two above-mentioned patients in the biodegradable group and no patients in the titanium group showed inadequate bone healing, resulting in a non-significant difference (*p*=0.15). The ITT analysis showed significant differences regarding dehiscence of the plate/screws, palpability of the plate/screws, and inflammatory reactions. There were no significant differences regarding incorrect occlusion and position of the bone fragments 8 wks after surgery. Self-evaluation of pain revealed VAS scores lower than 10 for

both groups, whereas the MFIQ showed nearly equal scores for the mandibular function. The post-operative interventions, wound irrigation with saline, use of antibiotics, abscess incision and drainage, and removal of plate/screws after 8 wks, did not significantly differ between both groups. The handling characteristics revealed significant lower scores for the biodegradable system for plate adaptation, drilling/tapping, and screw insertion. Wound closure and mean operation time did not reveal a significant difference, despite the variation in handling characteristics. The results of the ITT and TR analyses for the primary and secondary outcome measures are summarized in Tables 4 and 5.

An ancillary analysis revealed that there was no 'center effect' with regard to bone healing. Analysis of the various surgeries did not differ significantly between the groups [*p*=0.31 (ITT); *p*=0.74 (TR)].

DISCUSSION

The ITT analysis revealed that biodegradable plates and screws performed inferiorly to titanium plates and screws, whereas the TR analysis revealed that biodegradable plates and screws did not perform inferiorly regarding bone healing after 8 wks. The relatively many intra-operative 'switches' (21%) were primarily responsible for the inferior outcome result. These results imply that the biodegradable system is inferior to titanium plates and screws, but that the system could be successfully used without MMF when it is possible

Table 4. *Primary and secondary outcome measures for ITT analysis*

Description	Titanium group (n)	Biodegradable group (n)	p value
*Primary outcome measure**			
Inadequate bone healing	0	27 (23.1%)	< 0.001
Secondary outcome measures†			
Clinical assessments			
Non-correct occlusion	10 (8.8%)	13 (11.1%)	0.48
Palpability plate/screws	43 (38.1%)	59 (50.4%)	0.021
Dehiscence	0	5 (4.3%)	0.028
Abscess formation	4 (3.5%)	11 (9.4%)	0.065
Inflammatory reactions	8 (7.1%)	20 (17.1%)	0.013
Radiographic assessment			
Changed position bone segments	0	3 (2.6%)	0.12
Self-evaluation of patient			
Pain VAS (mean +/- s.d.)	6 +/- 12	6 +/- 11	0.75
MFIQ (mean +/- s.d.)	36 +/- 16	35 +/- 14	0.43
Postoperative interventions			
Irrigation with saline	0	1 (0.9%)	0.50
Antibiotics	4 (3.5%)	9 (7.7%)	0.16
Abscess incision and drainage	0	1 (0.9%)	0.50
Removal of plate/screws	2 (1.8%)	1 (0.9%)	> 0.99
Handling characteristics			
Plate adaptation (mean +/- s.d.)	8.6 +/- 0.6	7.5 +/- 1.6	< 0.001
Drilling/tapping (mean +/- s.d.)	8.8 +/- 0.6	7.3 +/- 1.6	< 0.001
Screw insertion (mean +/- s.d.)	8.7 +/- 0.8	7.2 +/- 1.8	< 0.001
Wound closure (mean +/- s.d.)	8.8 +/- 0.7	8.5 +/- 1.2	0.058
Operation time (h:m)	2:11	2:18	0.42

*Tested one-sided
†Tested two-tailed
Abbreviations: h = hours, ITT = Intention-To-Treat, m = minutes, MFIQ = Mandibular Function Impairment Question-naire (range 17-85), n = number, s.d. = standard deviation, VAS = Visual Analogue Scale (range 1-100).

Table 5. *Primary and secondary outcome measures for TR analysis*

Description	Titanium group (n)	Biodegradable group (n)	p value
*Primary outcome measure**			
Inadequate bone healing	0	2 (2.4%)	0.15
Secondary outcome measures†			
Clinical assessments			
Non-correct occlusion	16 (12.0%)	7 (8.3%)	0.44
Palpability plate/screws	49 (36.8%)	53 (63.1%)	< 0.001
Dehiscence	2 (1.5%)	3 (3.6%)	0.38
Abscess formation	6 (4.5%)	9 (10.7%)	0.08
Inflammatory reactions	11 (8.3%)	17 (20.2%)	0.009
Radiographic assessment			
Changed position bone segments	3 (2.3%)	0	0.29
Self-evaluation of patient			
Pain VAS (mean +/- s.d.)	7 +/- 14	6 +/- 11	0.60
MFIQ (mean +/- s.d.)	37 +/- 17	33 +/- 12	0.028
Postoperative interventions			
Irrigation with saline	0	1 (1.2%)	0.38
Antibiotics	8 (6.0%)	5 (6.0%)	> 0.99
Abscess incision and drainage	1 (0.8%)	0	> 0.99
Removal of plate/screws	2 (1.5%)	1 (1.2%)	> 0.99
Handling characteristics			
Operation time (h:m)	2:16	2:13	0.74

*Tested one-sided
†Tested two-tailed
Abbreviations: h = hours, m = minutes, MFIQ = Mandibular Function Impairment Questionnaire (range 17-85), n = number, s.d. = standard deviation, TR = Treatment-Received, VAS = Visual Analogue Scale (range 1-100).

to apply them. Concerning the secondary outcome measures, the biodegradable system did not perform significantly different from the titanium system, except for palpability of the system and inflammatory reactions. These differences could be expected at the 8-week follow-up and did not result in more plate removal operations. Up to 8 wks, the biodegradable plates and screws are safe to apply. The handling characteristics showed a

remarkable difference between both systems, whereby biodegradable plates and screws were more difficult to use as compared with titanium plates and screws.

Other studies [24,25,75,80], as discussed in a systematic review [53], did not demonstrate a significant difference regarding clinical morbidity and stability. However, they did not use bone healing as the primary outcome measure. The primary outcome measure 'bone healing after 8 wks' used in the present study was chosen since the mechanical characteristics of biodegradable plates and screws were less favourable compared with titanium ones [45-47]. This may result in insufficient and delayed bone healing percentages. In

addition, the reviewed studies included limited numbers of patients. Titanium plates and screws show high success rates (95%) according to the opinions of clinical experts and in large patient series [17,82]. Taking these results into account, it is a prerequisite to obtain 'non inferior' bone healing when using biodegradable plates and screws. Until now, there is no thorough scientific evidence that biodegradable plates and screws will result in more incomplete or delayed bone healing. A remarkable difference is that the systematically reviewed studies did not report any switches, in contrast to the present study.

Regarding the ITT analysis, the outcome data for the seven 'inclusion error' patients and the four 'lost to follow-up' patients were 'imputed' to remain an ITT population. Counting these patients as failures does not seem to be reasonable, given the overall low failure rate and also the fact that most patients with problems would be more likely to return than not. By contrast, the 'switchers' to the titanium group were defined as failures of the biodegradable system. The vast majority of these failures were related to material failures (see Results). If the system could not be applied initially, the system failed to obtain bone healing 8 wks after surgery. The 'switchers' were excluded from further analyses. Inexperience and lack of confidence in a still 'unknown and new' biodegradable system, handling differences, and having a sense of certainty and confidence regarding the titanium system may have contributed to the relatively high number of switches. The primary outcome measure was not stratified for indication, since it could be expected that the bone segments would be healed after 8 wks, independent of the indication. The *post-hoc* analysis provided a non-significant result between the groups. However, the relatively low number of Le Fort-I fractures impedes the power of the results for this indication. By contrast, the high number of inclusions of the other indications implies good eloquence of the results. In the Materials & Methods section, it is stated that the evaluation of outcome measures was planned to be performed by a colleague of the OMF surgeon who performed the surgery. Despite the intended protocol, in too many cases this was not practical. This phenomenon may have introduced observer bias. The study was performed in 4 hospitals, and different surgeons did the operations. This implies good generalizability. In contrast, several surgeons could imply diminished power of the study as a result of a possible learning curve factor. However, it appeared that the switches from the biodegradable to the titanium system took place over the entire study. Moreover, the switches were made by all participating surgeons and at all centres. It can therefore be expected that the performance of the Inion CPS biodegradable system in other hospitals will be similar to that found in our study.

Regarding the choice for Inion CPS: there were (and still are) several biodegradable systems available on the market, each with its own composition and mechanical properties. The BioSorb FX 2.0mm, LactoSorb 2.0mm, and Inion CPS 2.5mm systems appeared to be the strongest and most rigid biodegradable materials [45,46]. Most manufacturers discourage the use of their biodegradable system in the mandible unless in conjunction with 6 weeks of rigid MMF. Inion CPS 2.5mm is the only biodegradable system that allows the use of fixation of fractures and osteotomies of the mandible without using MMF ac-

cording to the manufacturer. Therefore, Inion CPS 2.5mm plates and screws were chosen to use in the RCT. The co-polymer Inion CPS, which is CE marked and FDA approved for human use, consists of the following monomers: D-lactide (16%), L-lactide (78%), and trimethylene carbonate (TMC, 6%) [83].

In summary, it is concluded that, in terms of bone healing after 8 wks, the performance of the Inion CPS biodegradable system is inferior compared with that of the titanium system for the treatment of mandibular fractures, zygoma fractures, and BSSO's, and/or Le Fort-I osteotomies. Despite this 'inferior' primary outcome result, biodegradable plates and screws could be safely used without MMF in selected cases. The benefits of using biodegradable systems (fewer plate removal operations) should be confirmed during a follow-up of minimally 5 yrs. The presented results are part of a longer-running follow-up study.

DECISION–MAKING CONSIDERATIONS IN APPLICATION OF BIODEGRADABLE FIXATION SYSTEMS IN MAXILLOFACIAL SURGERY: A RETROSPECTIVE COHORT STUDY

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ABSTRACT

Background - In a recent RCT comparing biodegradable (Inion CPS) with titanium (KLS Martin) plates and screws for fixation of osteotomies or fractures, we found that in 21% of the cases the surgeon decided intra-operatively to switch from biodegradable to titanium.

Aim - The aim of the current retrospective cohort study was to analyse the reasons for these switches in order to find predictor variables that may be helpful in the decision to use biodegradable devices or not. The surgeons' opinion about the biodegradable system, and if there was a learning curve in the application of the biodegradable system were also investigated.

Materials & Methods - All variables were assessed during the original RCT by using a questionnaire that was completed by the OMF surgeon directly post-operatively. For the outcome variable "surgeons' opinion" a separate questionnaire was used.

Results - Regarding the predictor variables a mandibular fracture had a higher risk of switching compared to a BSSO. However, looking at the reasons for these switches no firm conclusions can be drawn. There was a subjective learning curve to acquire the application-skills for the biodegradable system. There were no changes in isolated Le-Fort-I osteotomies despite the fact that the biodegradable system seems more difficult to apply in the midface. Inadequate stability was the main reason for switching. This can be material-related, or related to inexperience with or lack of confidence in the system, or impatience of the surgeon.

Conclusion & Discussion - A learning curve and personal preferences probably play an important role in the decision to switch. We think that with more patience and more experience it should be possible to increase both user comfort and confidence in the biodegradable system of Inion CPS, which likely will decrease the number of intra-operative switches.

Keywords: Intra-operative switches, predictor variables, learning curve, handling characteristics, surgeons' opinion, osteosynthesis

INTRODUCTION

There seems to be a learning curve to acquire the application-skills needed to use biodegradable plates and screws [84]. When application of biodegradable plates and screws fails, this will result into an intra-operative switch to commonly used titanium plates and screws. Recently, this has also been shown in the study of Buijs *et al.* [23]. In this study, patients were included who underwent bilateral sagittal split osteotomies (BSSO), Le Fort-I or bimaxillary osteotomies and patients with fractures of the mandible, maxilla, or zygoma. In the Intention-To-Treat (ITT) analysis, there were 117 patients in the biodegradable test group and 113 patients in the titanium control group. In the biodegradable-randomized group, there were 25 patients (21%) with an intra-operative switch to the titanium fixation system. Despite the intra-operative switch, all the patients showed uncomplicated bone healing post-operatively. There were no switches from the titanium to the biodegradable system.

The purposes of this study were: (1) to identify factors associated with surgeons' decisions to switch from one system to the other, and (2) to determine if there was a learning curve in the use of the biodegradable fixation system. The investigators hypothesize that there are factors associated with the decision to switch, and that there is a learning curve. Patient variables, the type of surgical procedure and individual preferences/experience of the Oral and Maxillofacial (OMF) surgeons were investigated.

MATERIALS & METHODS

Study design
This retrospective cohort study was derived from a previous performed Randomized Controlled Trial (RCT) of Buijs *et al.* (2012) [23], and has been described according to the STROBE statement (http://www.strobe-statement.org/).

Patients
To be included in the cohort study sample, patients had to be enrolled in the original RCT and randomized to biodegradable fixation. In the original RCT 117 patients were randomized to the biodegradable system, and 113 patients to the titanium system. Five patients in the biodegradable group and 2 patients in the titanium group were protocol violators and were excluded from further analyses.

The original RCT was conducted from December 2006 to July 2009. The patients were treated at four different departments of OMF Surgery in the Netherlands (University Medical Centre Groningen, Rijnstate Hospital Arnhem, Amphia Hospital Breda, and Medical Centre Leeuwarden). The inclusion and exclusion criteria of the original RCT are summarized in Table 1. All patients were informed regarding the treatment options prior to surgery and had to provide written informed consent to participate in the study. Patients meeting the inclusion criteria were randomly assigned to two treatment groups. A

Table 1. *Inclusion and exclusion criteria of the original prospective multicenter RCT*

Inclusion criteria:

-	patients scheduled for 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 parents or responsible persons if necessary) who signed the *informed consent* form.

Exclusion criteria:

-	patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);
-	patients presented with heavily comminuted fractures of the facial skeleton;
-	patients who experienced compromised bone healing in the past;
-	patients who were pregnant;
-	patients who could/would not participate in a 1-year follow-up (reasons);
-	patients who would not agree with an *at random* assignment to one of the treatment groups, or one of the methods or treatment administered in the study;
-	patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);
-	patients who experienced cleft lip and palate surgery in the past;
-	patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);
-	patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.

statistician generated the randomization sequences using a computerized randomization program. The randomization was performed using an IVRS (Interactive Voice Response System) (block size 10), which was available 24-hours a day to conceal the randomization sequence until the interventions were assigned. The study was approved by the Medical Ethical Committees of the participating hospitals.

Interventions
In the original RCT patients were assigned to a titanium control group (KLS Martin, Gebrüder Martin GmbH&Co., Tuttlingen, Germany) or to a biodegradable test group (Inion CPS, Inion Ltd., Tampere, Finland).
All plates and screws were applied according to the instructions of the manufacturers. For fixation of mandibular osteotomies and fractures 2.5-mm biodegradable or 2.0-mm titanium plates and screws were used, whereas 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used for fixation of zygoma fractures, Le Fort-I fractures, and Le
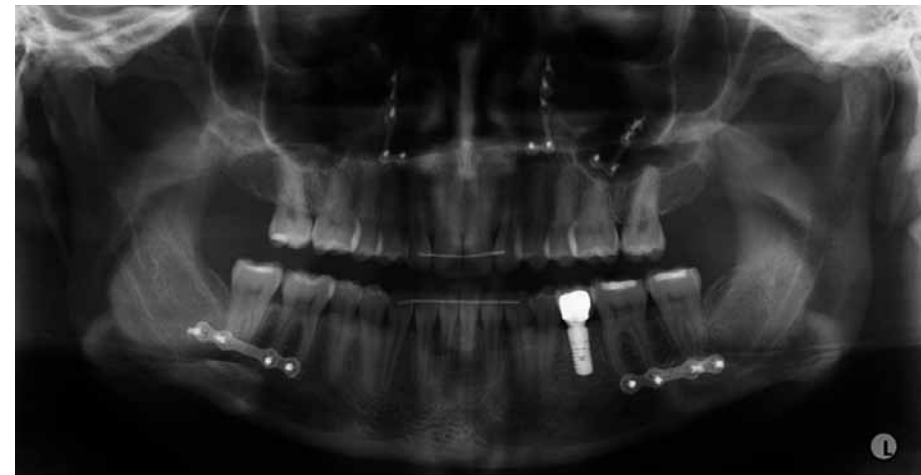
Figure 1. *Orthopantomograph showing the position of the plates and screws in a titanium bimaxillary case. Biodegradable plates and screws in 'biodegradable-cases' were placed in a similar manner, but would not be visible on the X-ray.*

Fort-I osteotomies. The way mandibles and maxilla's were stabilized can be seen in Fig. 1. Each participating OMF surgeon performed 2 'test-surgeries' using the biodegradable system to acquire the different application-skills, *i.e.*, pre-tapping the screws and pre-heating the plates, and to get used to the different dimensions. These 'test-surgeries' were not included in the study. The patients did not receive rigid maxillomandibular fixation, but soft guiding elastics post-operatively, and they were instructed to use a soft diet.

Outcome measures
The most important outcome variable in the current study was the decision to switch from the biodegradable to the titanium system (yes/no).
Predictor variables that possibly influenced switching:
(1)	demographic: female sex, age;
(2)	type of surgical procedure: BSSO, Le Fort-I osteotomy, bimaxillary osteotomy, fracture of the mandible, maxilla, or zygoma; and
(3)	Number of operations performed by a surgeon with the biodegradable system;
There were three other outcome measures:
(1)	The "learning curve", *i.e.*, the more operations performed by a surgeon the better the handling characteristics (plate adaptation, drilling/tapping, screw insertion, and wound closure (scale of 1-10));
(2)	The differences in handling characteristics (scale 1-10), and reasons for switching (inadequate fixation versus 'other reason') between the types of surgical procedure;
(3)	Surgeons' opinion.

Table 2. *Questionnaire used to evaluate the surgeons' opinion*

- Indicate what you think of the user comfort, and confidence in the system for Inion CPS as well as for KLS Martin titanium (scale 1-10);
- Are there important aspects for OMF surgeons who are planning to use Inion CPS? If so, please specify;
- Is there a difference in using Inion CPS between the different surgical procedures?;
- What problems have you encountered when using Inion CPS? And if so, is there a difference between the different types of surgical procedure?

All variables were assessed during the original RCT by using a questionnaire that was completed by the OMF surgeon directly post-operative. For the outcome variable "surgeons' opinion" an extra questionnaire (Table 2) was also used. The questionnaire was sent to all participating OMF surgeons (n=11) who performed more than 5 operations (n=5) with the biodegradable system.

Statistical analysis
The Statistical Package of Social Sciences (SPSS, version 18.0) was used to analyze the data. Differences between the groups with regard to normally distributed variables were analyzed by the independent-samples t test. For dichotomous variables Chi-squared/ Fisher's exact tests were used. To identify predictor variables for switching, potential influencing factors were tested univariately in a logistic regression analysis. To ensure broad inclusion of possible determinants, α was set at .15 for the univariate analyses. All significant variables were then submitted for multiple logistic regression analysis. Regarding the type of surgical procedure, as predictor variable for switching, dummy variables were made. Regarding the number of operations performed by a surgeon with the biodegradable system, as predictor variable for switching, all surgeries received a rank number, *i.e.*, the first operations by each surgeon all received the number '1', the second operations the number '2', etc. The 'learning curve' for the handling characteristics was tested in a linear regression analysis. The outcome variables for the learning curve were the intra-operative handling characteristics. The predictor variable was the rank number of operation performed by each surgeon. The difference in handling characteristics, and reasons for switching between the types of surgical procedure were tested with a One-way ANOVA and Fisher's exact test respectively. p-values less than .05 were considered statistically significant.

Table 3. *Gender/age distribution, and surgical procedures of the biodegradable randomized group obtained from the original RCT (n=112*)*

Description	Non-switches† (n=87)	Switches† (n=25)	p value
Gender/age distribution			
Male (n)	43 (49.4%)	12 (48%)	> 0.99
Female (n)	44 (50.6%)	13 (52%)	
Age (mean +/- s.d. in yrs)	31 +/- 12	30 +/- 11	0.66
(range in yrs)	14-59	18-49	
Surgical procedures			0.076
BSSO (n)	55 (78.6%)	15 (21.4%)	
Le Fort-I osteotomy (n)	8 (100%)	0	
Bimaxillary osteotomy (n)	16 (76.2%)	5 (23.8%)	
Mandibular fracture (n)	4 (44.4%)	5 (55.6%)	
Zygoma fracture (n)	4 (100%)	0	

*The 5 biodegradable-randomized protocol violators are not included. Protocol violation: after randomization it turned out the patient met an exclusion criteria (see Chapter 2: Fig. 1 (Buijs *et al.* 2012) [23])
†Switches and non-switches are biodegradable-randomized patients where the OMF surgeon decided to switch to the titanium system intra-operatively, and in whom the biodegradable application was successful, respectively.
Abbreviations: BSSO = bilateral sagittal split osteotomy, n = number, s.d. = standard deviation.

RESULTS

Baseline characteristics
The 25 'switch patients' had a mean age of 30 years (s.d. 11 yrs), and 13 (52%) were females (Table 3). The 87 'non-switch patients' had a mean age of 31 years (s.d. 12 yrs), and 44 (50.6%) were females. In 15 of the 70 patients (21.4%) who were treated with a BSSO, in 5 of the 9 (55.6%) mandible fractures, and in 5 of the 21 bimaxillary osteotomies (23.8%) there was a switch intra-operatively. There were no switches in patients treated with a solitary Le Fort-I osteotomy or in patients treated for a zygomatic fracture. Both age, sex, and types of surgical procedure did not significantly differ between both groups (p-values: 0.66; >0.99; and 0.076). There were 11 OMF surgeons who performed between 1 and 5 operations with the biodegradable system (Fig. 2). In 5 of the 11 'first operations' (45%) there was a switch to titanium. There were only 5 surgeons who performed more than 5 'biodegradable-operations'. They decided to switch to titanium in 9-62% of their cases. There was one OMF surgeon who had significantly more switches (8 of his 13 operations (62%); 32% of the total amount of 25 switches) than the other surgeons (p=0.025).

Surgeon

Surgeon (Operations performed)	No. of switches (%)
No.1 (n=41)	7 (17%)
No.2 (n=22)	2 (9%)
No.3 (n=14)	2 (14%)
No.4 (n=13)	8 (62%)
No.5 (n=8)	2 (25%)
No.6 (n=4)	1 (25%)
No.7 (n=3)	1 (33%)
No.8 (n=3)	1 (33%)
No.9 (n=2)	0
No.10 (n=1)	1 (100%)
No.11 (n=1)	0
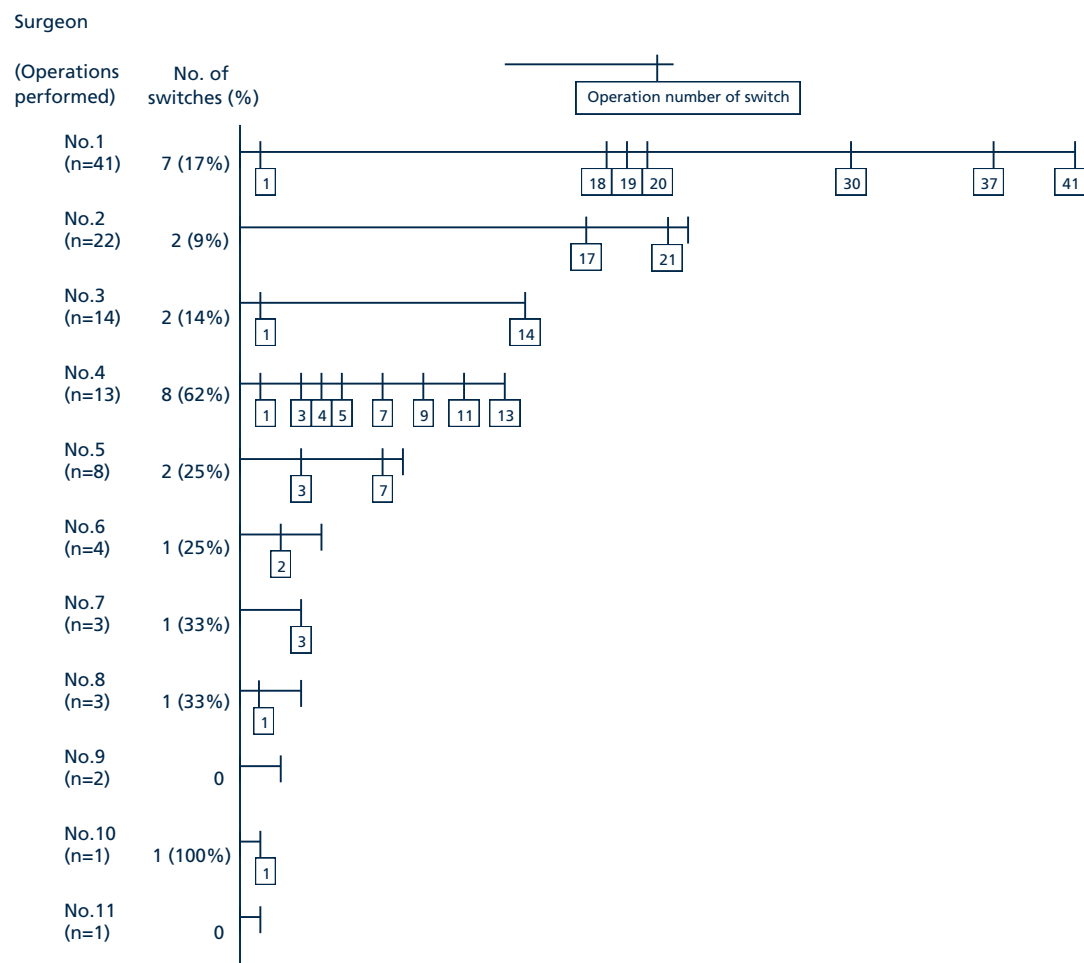
Figure 2. *There were 11 OMF surgeons who performed at least one operation with the biodegradable system. Surgeon no.1 performed a total of 41 operations with the biodegradable system. In 7 of his cases (17%) there was an intra-operative switch to titanium. These switches took place during the 1st, 18th, 19th, 20th, 30th, 37th, and 41st operation that surgeon no.1 performed. Surgeon no.4 had significantly more switches (8 of his 13 operations (62%)) than the other surgeons (p=0.025). In total it seems that there was no less switching as the number of operations performed by a surgeon increased.*

Predictor variables

Age (*p*=0.66; OR 0.99; 95%CI 0.96-1.03), female sex (*p*=0.9; OR 1.1; 95%CI 0.4-2.6), and the number of 'biodegradable-operations' performed by a surgeon (*p*=0.71; OR 0.99; 95%CI 0.95-1.04) were not statistically associated with an intra-operative change to titanium in the univariate analyses. A mandibular fracture had a higher risk of switching compared to a BSSO (*p*=0.037; OR 4.6; 95%CI 1.1-19.2). A multiple logistic analysis was not performed, because this was the only significant variable in the univariate analyses.

Learning curves

The rank number of the operation performed by the surgeons was not statistically associated with better intra-operative handling characteristics in a linear regression (*p*-values: 0.56; 0.48; 0.27; and 0.56 for plate adaptation, drilling/tapping, screw insertion, and wound closure respectively).

Differences between the types of surgical procedure

Handling characteristics

As far as the handling characteristics between the surgical procedures are concerned, there was a significant difference between the operation types for screw insertion (*p*=0.023) and wound closure (*p*=0.022) (Table 4). The Bonferroni Posthoc Analysis revealed that for screw insertion this difference could be explained by the bimaxillary osteotomy versus the zygomatic fracture (6.7 vs. 9.5; *p*=0.04), and for wound closure this difference could be explained by the BSSO versus the bimaxillary osteotomy (8.6 vs. 7.8; *p*=0.025).

Reasons for switches

Inadequate fixation (n=17), especially non-grip of the screws (n=6), was the main overall reason for switching, and for each type of surgical procedure separately (Table 5). There were no significant differences between the types of surgical procedure regarding the reasons for switching (*p*=0.72).

Surgeons' opinion

The extra questionnaire was answered by all OMF surgeons (n=5) who performed more than 5 'biodegradable-operations'. This showed that the user comfort of and confidence in the biodegradable system was significantly less compared to the titanium system (5.6 versus 8.6, *p*=0.001; and 6.6 versus 9.2, *p*=0.023 respectively). All our surgeons agree that there was a learning curve to acquire the different application-skills for the biodegradable system. They also agree that in regions with thin overlying skin, *i.e.*, the infra-orbital rim, and in regions with thin bone, *i.e.*, the maxilla/mid-face, the Inion CPS 2.0-mm plate is relatively "bulky", and in the mid- face area the screws are more difficult to apply. They noticed that there is no difference in using Inion CPS in trauma and orthognathic cases, and that screws need to be fixed 'finger tight' only.

Table 4. *Handling characteristics listed by the type of surgical procedure*

Description	BSSO	Le Fort-I osteotomy	Bimaxillary osteotomy	Mandibular fracture	Zygomatic fracture	Total
	(n=70)	(n=8)	(n=21)	(n=9)	(n=4)	(n=112)*
Handling characteristics						
Plate adaptation						
(mean +/- s.d.)	7.7 +/- 1.4	6.9 +/- 1.6	6.9 +/- 1.9	8.0 +/- 1.4	8.8 +/- 1.0	7.5 +/- 1.6
Drilling/tapping						
(mean +/- s.d.)	7.3 +/- 1.4	7.1 +/- 1.5	7.0 +/- 2.2	7.9 +/- 2.1	8.8 +/- 1.0	7.3 +/- 1.6
Screw insertion						
(mean +/- s.d.)†	7.2 +/- 1.7	6.5 +/- 0.9	6.7 +/- 2.1	8.0 +/- 1.9	9.5 +/- 1.0	7.2 +/- 1.8
Wound closure						
(mean +/- s.d.)‡	8.6 +/- 0.7	8.9 +/- 0.6	7.8 +/- 2.2	8.8 +/- 0.8	9.0 +/- 1.2	8.5 +/- 1.2

*The 5 biodegradable-randomized protocol violators are not included. Protocol violation: after randomization it turned out the patient met an exclusion criteria (see Chapter 2: Fig. 1 (Buijs et al. 2012) [23]).
†One-way ANOVA p=0.023 > Bonferroni posthoc: screw insertion bimaxillary osteotomy versus zygomatic fracture: 6.7 versus 9.5, p=0.04.
‡One-way ANOVA p=0.022 > Bonferroni posthoc: wound closure BSSO versus bimaxillary osteotomy: 8.6 versus 7.8, p=0.025.
Abbreviations: BSSO = bilateral sagittal split osteotomy, n = number, s.d. = standard deviation.

Table 5. *Reasons switches listed by the type of surgical procedure*

Description	BSSO	Le Fort-I osteotomy	Bimaxillary osteotomy	Mandibular fracture	Zygomatic fracture	Total
	(n=70)	(n=8)	(n=21)	(n=9)	(n=4)	(n=112)*
Number of switches	(n =15)	(n=0)	(n=5)	(n=5)	(n=0)	(n=25)
	21%	-	24%	56%	-	21%
Reasons switching						
Inadequate fixation	**11**	**-**	**3**	**3**	**-**	**17**
Non-grip screws (n)	1	-	3†	2	-	6
Inadequate stability after first fixation attempt (n)	2	-	0	1	-	3
Inadequate stability after more fixation attempts (n)	4	-	0	0	-	4
Inadequate plate adaptation (n)	2	-	0	0	-	2
Dimension of plate too big (n)	1	-	0	0	-	1
Plate fracture (n)	1	-	0	0	-	1
Other	**4**	**-**	**2**	**2**	**-**	**8**
Logistical problem (n)	1	-	1	1	-	3
'Bad split' (n)	1	-	0	0	-	1
Unknown (n)	2	-	1	0	-	4

*The 5 biodegradable-randomized protocol violators are not included. Protocol violation: after randomization it turned out the patient met an exclusion criteria (see Chapter 2: Fig. 1 (Buijs et al. 2012) [23]).
†Two times non-grip screw on the maxilla, 1 time non-grip screw on the mandible
Abbreviations: BSSO = bilateral sagittal split osteotomy, n = number, s.d. = standard deviation.

DISCUSSION

In this study we found that a mandibular fracture had a higher risk of switching from the biodegradable plates and screws of Inion CPS to the titanium plates and screws of KLS Martin compared to a BSSO. However, firm conclusions cannot be drawn, because one switch of the total of 5 switches seen in mandibular fractures was due to logistical problems and for another switch the reason was unknown. There was a subjective learning curve in the use of the biodegradable fixation system, which could not be objectified with statistical analysis.

It is remarkable that there was one surgeon who statistic significantly switched to titanium more often than the other surgeons. Unfortunately there is an inconsistency in the number of operations performed with the biodegradable system by each surgeon. This resulted in a large spread of switching percentages, which makes it hard to extract proper data to support firm conclusions. In retrospect the 2 test-surgeries may have been a too small an amount. Personal preferences probably also play an important role. In total it seems that there was similar switching as the number of operations performed by a surgeon increased (Fig. 2).

In contrast to our expectations switches were mainly seen in the mandible, and only in a small percentage in the maxilla. All switches in the maxilla were during bimaxillary cases. In solitary Le Fort-I osteotomies no switches were observed at all.

Singh et al. (2011) in a study that included 14 patients with zygomatic fractures treated with Inion reported no intra-operative switches [84]. This is in conjunction with our results since we also found no switches in patients treated for zygomatic fractures. They noticed no plate fracture during manipulation, but 2 cases of screw head fracture occurred while tightening. To prevent this they stated that screws need to be fixed 'finger tight' only, and care must be taken while placing them, especially in thin bones. The surgeons in our study agree on these items. Furthermore, Singh et al. stated that the angulation and the pressure at the time of drilling and tapping are important factors in this technique-sensitive system, and that inadequate drilling or tapping length could be a reason for screw head fracture. When screw fractures occur, a new hole can be drilled through the broken screw, and after re-tapping, a new (emergency) screw may be inserted [4,85]. We found that plate fracture was a reason to switch to titanium, screw fractures were not. In the current study inadequate fixation, especially non-grip of the screws, was the main overall reason for switching. For sufficient screw grip there has to be sufficient cortical bone. Removing too much bone, i.e., drilling too broadly, or tapping too roughly, or when screw insertion is performed too roughly (with subsequent breaking of the thread), results in non-grip of screws. The reasons for inadequate fixation can be material-related, but can also be related to inexperience or impatience of surgeons. Less confidence in the system could be another reason for switching. In our study the confidence in the biodegradable system was significantly less when compared to the titanium system. Singh et al. (2011) agree that there was a learning curve to acquire the different application-skills for the Inion biodegradable system.

Choi et al. (2011) evaluated the post-surgical relapse in maxillary surgery in 20 patients. They also used the resorbable plates of Inion CPS. In contrast to our study they did not report any intra-operative switches [86].

Paeng et al. (2011) reported on a comparative study of skeletal stability after mandibular setback between Inion CPS and a titanium system with 25 patients in both groups. They did not report any intra-operative switches, but they used bicortical screw fixation instead of the monocortical plate/screw-fixation that was used in our study [87].

Bayat et al. (2010) in a study that included 19 patients with mandibular angle fractures treated with Inion CPS also did not report any intra-operative switches [85].

Many authors that use different other kinds of biodegradable systems also did not report any intra-operative switches [25,80,88,89].

Wittwer et al. (2005) evaluated the clinical application of three different biodegradable fixation systems for treatment of zygomatic fractures [48]. In this study in 23 (24.5%) of the 94 fracture sites there was a switch to titanium plates and screws. Non-stable fixation (n=7) and fixation of small fragments (n=16) were the reasons for switching. They stated that biodegradable materials were frequently unfeasible for use at the infra-orbital rim and in the zygomaticomaxillary/anterior sinus wall area, probably because the biodegradable plates are too bulky in these areas. Although the surgeons in our study agree on this item in the questionnaires, the number of zygomatic fractures in our series is too small (n=4) to substantiate these findings.

Unlike the study of Buijs et al. [23], Jain et al. (2006) stated that contouring resorbable plates is easier than metallic plates [70]. It has been stated that with few extra tools (i.e., heating bath, bending templates) biodegradable plates can be easily handled and adapted [71]. In our study the user comfort of the biodegradable system was significantly less when compared to the titanium system. Contouring of the plates was not always easy and in a few cases inadequate plate adaptation was a reason to switch to titanium. Bos (2005) mentioned that biodegradable plate bending, pre-tapping and screw insertion are very time consuming and far more complicated than titanium [72]. In our original RCT it is described that an operation with the biodegradable system takes 7 minutes longer on average than an operation with the titanium system [23].

The extra questionnaire for the OMF surgeons who performed more than 5 'biodegradable-operations' is non-validated and limited by potential recall bias, i.e., a surgeon who decided to switch systems more often may be more apt to recall technical difficulties with instrumentation.

We could not objectify the subjective learning curve, probably because the numbers are too small. Several OMF residents performed (parts of the) surgeries for their training program. This may have resulted in lower scores and failure to identify a learning curve. There probably would have been fewer switches when all the surgeries were performed by a smaller number of skilled and experienced surgeons, but this was practically unfeasible in OMF Training Clinics. In daily practice without residents the usage of Inion CPS may therefore be easier and may result in fewer switches.

CONCLUSION

In summary, it is concluded that analysis of the intra-operative switches showed that a mandibular fracture had a higher risk of switching compared to a BSSO. However, looking at the reasons for these switches no firm conclusions can be drawn. We found no other statistically significant predictor variables that could aid in deciding in advance whether to use the biodegradable plates and screws of Inion CPS or not.

There is a subjective learning curve to acquire the application-skills for the biodegradable system of Inion CPS. A learning curve and personal preferences probably play a crucial role in the decision making process of switching. The results presented are part of a longer running follow-up study. The potential incentive to use this biodegradable fixation system, *i.e.*, less plate removals, should be determined after at least five years of follow-up. This will be described elsewhere.

COMPARISON OF A BIODEGRADABLE AND A TITANIUM FIXATION SYSTEM IN MAXILLOFACIAL SURGERY: A TWO-YEAR MULTICENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background - Biodegradable osteosynthesis could reduce/delete the problems associated with titanium plate removal.

Aim - The aim of the present study was to compare the clinical performance in the first 2 post-operative years between a biodegradable and a titanium system in oral and maxillofacial surgery.

Materials & Methods - The multicenter randomized controlled trial (RCT) was performed in the Netherlands from December 2006-July 2009. Included were 230 patients who underwent a bilateral sagittal split osteotomy (BSSO) , a Le Fort-I osteotomy, or a bimaxillary osteotomy and those treated for fractures of the mandible, maxilla, or zygoma. The patients were randomly assigned to a titanium group (KLS Martin) or to a biodegradable group (Inion CPS).

Results - Plate removal was necessary in 16 of the 134 patients (11.9%) treated with titanium and in 21 of the 87 patients (24.1%) treated with the biodegradable system within the first 2 post-operative years [p=0.016, Hazard Ratio (HR) biodegradable (95%CI) = 2.2 (1.1-4.2), HR titanium = 1].

Occlusion, VAS- and MFIQ-scores showed that both groups had a good mandibular function and were (almost) free of pain one and two years post-operatively.

Conclusion & Discussion - In terms of plate removal within the first 2 post-operative years, the performance of the biodegradable system was inferior compared with that of the titanium system for fixation of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies, and bimaxillary osteotomies. Given the rates of plate removal and the intra-operative switches (Chapter 3) from the biodegradable system to the titanium system, there seems to be no place for the clinical usage of Inion CPS in treatment of these surgical situations. To put the usage into a broader perspective, it is also necessary to take relapse and cost-effectiveness into account.

Trial registration: http://www.controlled-trials.com; ISRCTN 44212338.

Keywords: Surgical fixation devices, oral surgery, oral surgical procedures, maxillofacial injuries, treatment outcome, safety.

INTRODUCTION

Titanium is regarded as the "golden standard" for osteosynthesis. Because of sequelae, titanium must be removed following bone healing, in a second operation, in 5-40% of the cases [16,19].

Biodegradable plates and screws have been developed to dissolve in the human body, to reduce or even eliminate the problems associated with titanium.

Biodegradable fixation systems may also have their limitations. Adverse tissue reactions to degradation products have been reported [49,50]. According to the literature, biodegradable fixation devices must be removed in a second operation in 0-31% of the cases [51,52]. Most studies reported in the literature comparing biodegradable and titanium osteofixation devices are not randomized controlled trials (RCTs), and the RCTs that are available have a relatively short follow-up [53]. We therefore conducted a randomized controlled clinical trial comparing titanium *vs.* a biodegradable fixation system with a long follow-up period. The trial design and short-term outcomes after 8 wks of healing have been previously published [23]. Briefly, short-term healing outcomes were similar between biodegradable and titanium fixation, although, in a significant proportion (25/117) of patients randomized to the biodegradable fixation system, the operating surgeons decided intra-operatively to switch to the titanium system, due to either technical complications such as non-grip of the screws or for other reasons. Details regarding these switches have been described elsewhere [90].

The aim of the present paper was to compare the clinical performance between the biodegradable and the titanium fixation systems after 24 mos of follow-up regarding fixation of mandibular, Le Fort-I, and zygomatic fractures, and bilateral sagittal split osteotomies (BSSO), Le Fort-I osteotomies, and bimaxillary osteotomies.

MATERIALS & METHODS

This RCT has been described according to the CONSORT statement 2010 (http://www.consort-statement.org/).

Study population
Recruitment for this RCT was performed from December 2006 to July 2009. Two hundred thirty patients were treated at 4 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 inclusion and exclusion criteria are summarized in Table 1. All patients provided written informed consent prior to enrollment. Details regarding the randomization procedure have been described in detail elsewhere [23]. The study was approved by the Medical Ethical Committees of the participating hospitals.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria:

- patients scheduled for 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 parents or responsible persons if necessary) who signed the *informed consent* form.

Exclusion criteria:

- patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);
- patients presented with heavily comminuted fractures of the facial skeleton;
- patients who experienced compromised bone healing in the past;
- patients who were pregnant;
- patients who could/would not participate in a 1-year follow-up (reasons);
- patients who would not agree with an *at random* assignment to one of the treatment groups, or one of the methods or treatment administered in the study;
- patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);
- patients who experienced cleft lip and palate surgery in the past;
- patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);
- patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.

Interventions

The patients were assigned to a titanium control group (KLS Martin, Gebrüder Martin GmbH&Co., Tuttlingen, Germany) or to a biodegradable test group (Inion CPS, Inion Ltd., Tampere, Finland). Neither prior to nor after surgery were the patients informed of the system that had been used.

All plates and screws were applied according to the instructions of the manufacturers. For fixation of mandibular osteotomies and fractures, 2.5-mm biodegradable or 2.0-mm titanium plates and screws were used, while 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used for fixation of zygoma 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 getting used to the different dimensions of the material. These 'test-surgeries' were not included in the study. Post-operatively, the

patients did not receive rigid maxillomandibular fixation, but soft guiding elastics, and were instructed to eat a soft diet for five wks. In the design of the RCT, it was agreed that routine removal of asymptomatic plates would not be performed.

Outcome measures

The most important outcome variable in the current study was the removal of the plates/screws (yes/no) (on a patient level) within the first 2 post-operative yrs after treatment with the biodegradable or the titanium system, with the time of removal, *i.e.*, survival time, taken into account. The 25 intra-operative switches from the biodegradable to the titanium system possibly influenced plate removal.

The following other outcome measures were assessed:

(1) reasons for plate/screws removal;

(2) clinical: correct occlusion (yes/no), palpability of plates/screws (yes/no), wound dehiscence (yes/no), abscess formation (yes/no), and signs of inflammation (rubor, calor, dolor, tumor, or functio leasa: yes/no);

(3) radiographic: correct position of the bone segments (yes/no; position of teeth, path of mandibular canal, and contour of cortical structures);

(4) patient-related (self-evaluation): pain reported on a Visual Analogue Scale (VAS; range 1-100) and mandibular function evaluated by the 17 questions on the Mandibular Function Impairment Questionnaire (MFIQ) [81]; ranging 17-85: a higher score means worse function; and

(5) interventions within the first and second post-operative yrs: wound irrigation with saline (yes/no), use of antibiotics (yes/no), abscess incision and drainage (yes/no).

The outcome measures were evaluated 1 and 2 yrs post-operatively by a colleague of the surgeon performing OMF surgery and recorded on Case Report Forms. The following radiographs were taken during these outpatient visits: an orthopantomogram (OPT; all indications), a lateral cephalogram (osteotomies), an occipito-mental radiograph (zygomatic fracture), and a fronto-suboccipital radiograph (mandible fracture). Data from unplanned intermediate outpatient visits – such as time-to-event data, *i.e.*, plate removals – were recorded on Case Report Forms.

Statistical analysis

Inclusion of the 230 patients was based on power analysis with the outcome measure 'bone healing after 8 weeks', and has been described in detail elsewhere [23]. The Statistical Package of Social Sciences (SPSS, version 20.0) was used for data analysis. The means and standard deviations of normally distributed variables were calculated and analyzed by the independent-samples *t* test. Skewed variables were either transformed to obtain normally distributed variables, or (if this could not be achieved) analyzed by non-parametric tests. Dichotomous variables were analyzed using the Chi-squared or the Fisher's exact test. The survival of plate removal between the biodegradable and the titanium groups was analyzed by the Logrank test (or Cox regression when the 'intra-
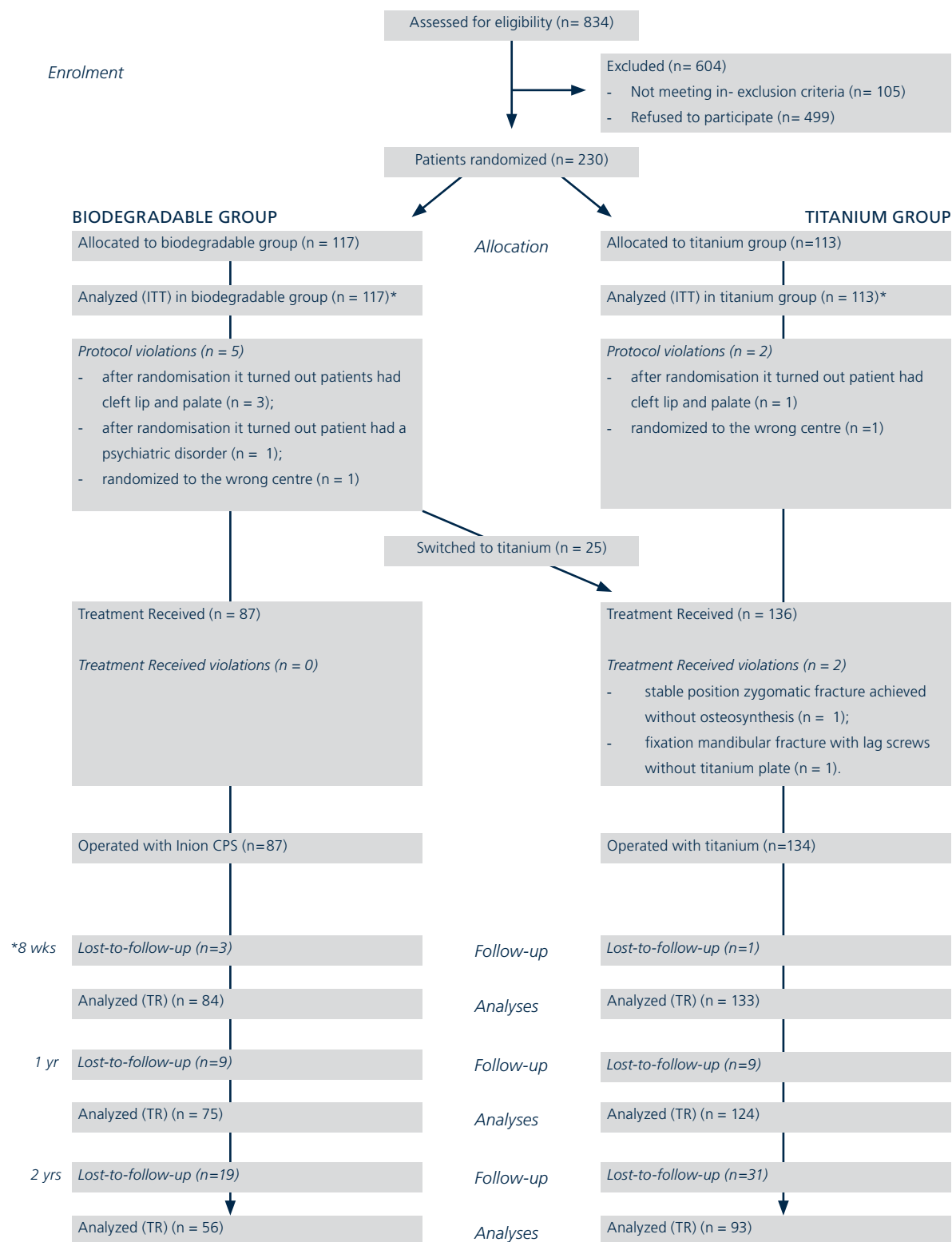
Figure 1 — Flow diagram

Assessed for eligibility (n= 834)

Enrolment

Excluded (n= 604)
- Not meeting in- exclusion criteria (n= 105)
- Refused to participate (n= 499)

Patients randomized (n= 230)

BIODEGRADABLE GROUP

Allocated to biodegradable group (n = 117)

Allocation

TITANIUM GROUP

Allocated to titanium group (n=113)

Analyzed (ITT) in biodegradable group (n = 117)*

Analyzed (ITT) in titanium group (n = 113)*

Protocol violations (n = 5)
- after randomisation it turned out patients had cleft lip and palate (n = 3);
- after randomisation it turned out patient had a psychiatric disorder (n = 1);
- randomized to the wrong centre (n = 1)

Protocol violations (n = 2)
- after randomisation it turned out patient had cleft lip and palate (n = 1)
- randomized to the wrong centre (n =1)

Switched to titanium (n = 25)

Treatment Received (n = 87)

Treatment Received violations (n = 0)

Treatment Received (n = 136)

Treatment Received violations (n = 2)
- stable position zygomatic fracture achieved without osteosynthesis (n = 1);
- fixation mandibular fracture with lag screws without titanium plate (n = 1).

Operated with Inion CPS (n=87)

Operated with titanium (n=134)

*8 wks — Lost-to-follow-up (n=3) | Follow-up | Lost-to-follow-up (n=1)

Analyzed (TR) (n = 84) | Analyses | Analyzed (TR) (n = 133)

1 yr — Lost-to-follow-up (n=9) | Follow-up | Lost-to-follow-up (n=9)

Analyzed (TR) (n = 75) | Analyses | Analyzed (TR) (n = 124)

2 yrs — Lost-to-follow-up (n=19) | Follow-up | Lost-to-follow-up (n=31)

Analyzed (TR) (n = 56) | Analyses | Analyzed (TR) (n = 93)

Figure 1. *Flow diagram of patient's progress though the phases of RCT*
*The 8 wks post-operative analyses have been described in detail elsewhere (Buijs et al. 2012).

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operative switches' appeared to contribute significantly to plate removal according to a separate Logrank test, for which α was set at <0.10). The Hazard ratio was calculated by Cox regression. The Hazard ratio and a Kaplan-Meier curve were described only when the Logrank/Cox regression for plate removal revealed a significant difference. The estimated plate removal rate was calculated by dividing the number of events (plate removal) by the total plate exposure time. The total exposure time was calculated by taking the sum of:

(1) the exposure time up to plate removal of plates that were removed during the observation time;
(2) the exposure time of plates that were not removed and could be followed for the entire observation period; these patients were censored at 2 yrs in the survival analysis;
(3) the exposure time up to the end of the observation of plates that were not removed and where patients did not complete the entire observation period as a result of reasons such as missed appointments or refusal to participate in follow-up visits (lost to follow-up). Patients in this category were contacted by telephone, and were asked if their plates had been removed during the lost-to-follow-up period. We also viewed their (digital) records. If their records showed no plate removal, no matter if they could be reached by telephone, these patients were also censored at 2 yrs.

The other *post-operative interventions* were analyzed in the same way.

Any *p* values less than .05 were considered statistically significant.

RESULTS

Fig. 1 represents the flow of the 230 randomized patients during the phases of the research project. Eight wks post-operatively, there were 133 patients in the titanium group and 84 patients in the biodegradable group [23]. This is the starting point of the present study. There were 18 'lost-to-follow-up' patients from 8 wks to 1 yr post-operatively. This resulted in an analysis of 124 patients in the titanium group and 75 patients in the biodegradable group after 1 yr. Another 50 patients did not complete the follow-up after 2 yrs. This resulted in 93 patients in the titanium group and 56 patients in the biodegradable group. There were significant more men lost to follow-up and more plate removals in the lost-to-follow-up patients (Appendix Table).

All baseline characteristics did not differ significantly between the biodegradable and titanium groups after 1 and 2 yrs (Table 2).

Regarding the removal of the plate/screws within the first 2 post-operative yrs, there were 16 of the 134 patients (11.9%) who received titanium and 21 of the 87 patients (24.1%) who received the biodegradable system who needed a second operation to remove the plates/screws (Table 3; Fig. 2). Thirteen of these removals were seen in the 72 patients who did not complete the entire observation period of 2 yrs. Viewing the records of the other 59 lost-to-follow-up patients revealed 3 extra plate removals, and no other post-operative interventions. Forty of the other 56 patients could be contacted by telephone. This revealed no extra interventions. The 'intra-operative switches' did not

Table 2. *Baseline characteristics after 1 year and 2 years**

Description	1 Year			2 Years		
	Titanium (n)	Biodegradable (n)	p value	Titanium (n)	Biodegradable (n)	p value
Surgical procedures	124	75		93	56	
BSSO	83 (66.9%)	46 (61.3%)	0.62	61 (65.6%)	37 (66.1%)	0.21
Le Fort-I osteotomy	7 (5.6%)	7 (9.3%)		5 (5.4%)	6 (10.7%)	
Bimaxillary osteotomy	26 (21.0%)	14 (18.7%)		24 (25.8%)	10 (17.9%)	
Mandibular fracture	4 (3.2%)	4 (5.3%)		3 (3.2%)	1 (1.8%)	
Le Fort-I fracture	1 (0.8%)	0		0	0	
Zygoma fracture	3 (2.4%)	4 (5.3%)		0	2 (3.6%)	
Gender/age distribution						
Male	51 (41.1%)	36 (48%)	0.38	35 (37.6%)	23 (41.1%)	0.73
Female	73 (58.9%)	39 (52%)		58 (62.4%)	33 (58.9%)	
Age (mean +/- s.d. in years)	31 +/- 11	31 +/- 12	0.92	31 +/- 11	33 +/- 12	0.37
(range in years)	16-60	15-59		16-59	15-59	

*Analyses performed without the Protocol violations, the Treatment-Received violations, and lost-to-follow-up patients (see Fig. 1).
Abbreviations: BSSO = bilateral sagittal split osteotomy, n = number, s.d. = standard deviation.
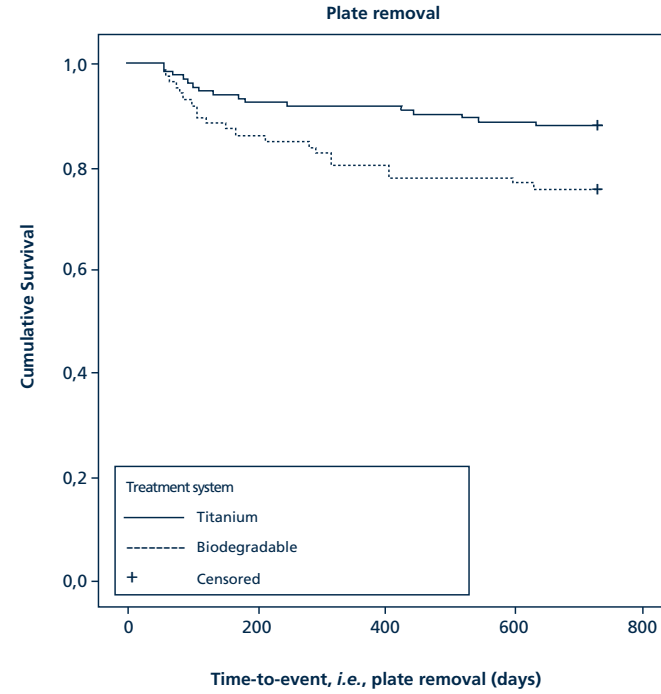
Figure 2. *Kaplan-Meier curve of plate removal for the first 2 post-operative yrs on total Treatment-Received group (n=221: titanium n=134, biodegradable n=87). Hazard Ratio (HR) biodegradable = 2.2 (95%CI: 1.1-4.2), HR titanium = 1; p=0.016.*

contribute significantly to plate removal (*p*=0.59), nor did they contribute to any of the other post-operative interventions (data not shown). Therefore, the treatment variable, *i.e.*, biodegradable or titanium, was tested (univariately) in the plate removal analysis by the Logrank: *p*=0.016 [hazard ratio (HR) biodegradable (95%CI) = 2.2 (1.1-4.2), HR titanium = 1].

In the biodegradable group, all 21 removals were due to clinical problems located in the mandible and were seen in the 79 patients (26.6%) treated with an osteotomy. In the titanium group, 2 of the 16 removals (12.5%) were at the request of mandibular fracture patients with clinically asymptomatic plates/screws. All the other removals (87.5%) were due to clinical problems and, with one exception, were seen only in patients who had undergone an osteotomy.

Abscess formation was the main reason for plate removal in both groups: 12 of the 21 removals (57.1%) in the biodegradable group, and 10 of the 16 removals (62.5%) in the titanium group.

Table 3. *Outcome measures after 1 year and 2 years*

Description	1 Year Titanium (n)	1 Year Biodegradable (n)	1 Year p value*	2 Years Titanium (n)	2 Years Biodegradable (n)	2 Years p value*
Post-operative interventions‡						
Removal plate/screws (n (%))	13/134 (9.7%)	19/87 (21.8%)		16/134 (11.9%)	21/87 (24.1%)	0.016
Removals surgical procedures						0.62
Removals osteotomies	10/124 (8.1%)	19/79 (24.1%)		13/124 (10.5%)	21/79 (26.6%)	
BSSO	7/87 (8.0%)	15/55 (27.3%)		9/87 (10.3%)	17/55 (30.1%)	
Le Fort-I osteotomy	0/8	0/8		0/8	0/8	
Bimaxillary osteotomy	3/29 (10.3%)	4/16 (25%)		4/29 (13.8%)¶	4/16 (25%)#	
Removals fractures	3/10 (30%)	0/8		3/10 (30%)	0/8	
Mandibular fracture	2/6 (33.3%)||	0/4		2/6 (33.3%)||	0/4	
Le Fort-I fracture	0/1	0/0		0/1	0/0	
Zygoma fracture	1/3 (33.3%)	0/4		1/3 (33.3%)	0/4	
Irrigation with saline (n (%))	0	2 (2.3%)		1 (0.7%)	2 (2.3%)	0.33
Antibiotics (n (%))	10 (7.5%)	7 (8.0%)		11 (8.2%)	8 (9.1%)	0.78
Abscess incision & drainage (n (%))	1 (0.7%)	0		2 (1.5%)	2 (2.3%)	0.66
Clinical assessments†						
Non-correct occlusion	15 (12.1%)	5 (6.7%)	0.33	11 (11.8%)	6 (10.7%)	> 0.99
Palpability plate/screws●	44 (38.9%)	39 (69.6%)	< 0.001	44 (51.2%)	28 (68.3%)	0.085
Dehiscence	1 (0.8%)	1 (1.3%)	> 0.99	0	0	-
Abscess formation	3 (2.4%)	2 (2.7%)	> 0.99	0	1 (1.8%)	0.37
Inflammatory reactions	4 (3.2%)	6 (8.0%)	0.18	0	5 (8.9%)	0.006
Radiographic assessment†						
Changed position bone segments	1 (0.8%)	0	> 0.99	0	0	-
Self-evaluation of patient†						
Pain VAS (mean +/- s.d.)	1 +/- 7	2 +/- 9	0.45	2 +/- 9	2 +/- 6	0.93
MFIQ (median)**	21	17	0.006	19	17	0.001
(range)	17-39	17-44		17-42	17-44	

Legend Table 3

*Tested two-tailed.
‡Percentages (%) on total Treatment-Received group of 221 patients: 134 patients in the titanium group, and 87 patients in the biodegradable group. The numbers (and percentages) given at '2 Years' include the numbers after '1 Year'. There were five biodegradable-randomized patients with an intra-operative switch to the titanium fixation system, who needed plate removal within the first post-operative year. For analysis, these 'switches' were added to the titanium group. There were no titanium-randomized patients with an intra-operative switch to the biodegradable system. The 'intra-operative switches' did not significantly contribute to plate removal (p=0.59), or to any of the other post-operative interventions (data not shown). Therefore, the treatment variable, i.e., biodegradable or titanium, was tested (univariately) in the analyses of the post-operative interventions using the Logrank (p=0.016). A separate Logrank test showed no significant difference in plate removal percentages between the surgical procedures (p=0.62).
¶Removal of plate/screws in the mandible as well as the maxilla.
#Removal of plate/screws only in the mandible.
||These 2 removals of plates/screws were at patients' request for asymptomatic plates/screws. All the other removals in Table 3 were due to clinical problems, i.e., swelling, dehiscence, infection, abscess formation, screw loosening, irritation/pain.
†Analyses performed without the Protocol violations, the Treatment-Received violations, and lost-to-follow-up patients (see Fig. 1).
●The patients in whom the plates/screws were removed were not included in the analysis.
**The mandibular function was evaluated by the 17 questions on the MFIQ [81]; range 17-85; a higher score means worse function.
Abbreviations: BSSO = bilateral sagittal split osteotomy, MFIQ = Mandibular Function Impairment Questionnaire (range 17-85), n = number, s.d. = standard deviation, VAS = Visual Analogue Scale (range 1-100).

The analysis after 1 yr showed significant differences regarding palpability (titanium 38.9% *vs.* biodegradable 69.6%; p<0.001), and MFIQ [titanium: median 21 (17-39) *vs.* biodegradable: median 17 (17-44); p=0.006]. There were no significant differences regarding occlusion, dehiscence, inflammatory reactions, and position of the bone fragments 52 wks post-operatively. Self-evaluation of pain revealed VAS scores near zero for both groups. The post-operative interventions 'wound irrigation with saline', 'use of antibiotics', and 'abscess-incision-and-drainage' within the first post-operative year, did not differ significantly between groups. Analysis after 2 yrs revealed significant differences regarding inflammatory reactions [titanium 0/93 *vs.* biodegradable 5/56 (8.9%); p=0.006], and MFIQ [titanium: median 19 (17-42) *vs.* biodegradable: median 17 (17-44); p=0.001].

DISCUSSION

Analysis revealed that the biodegradable system (Inion CPS) performed inferiorly to the titanium system (KLS Martin) in terms of plate removal. The risk for removal when biodegradable plates and screws were used was 2.2 times higher than that when titanium was used, within the first 2 post-operative yrs.
In the biodegradable group all plate removals and in the titanium group nearly all removals were due to clinical problems located in the mandible, due mainly to abscess formation. This is possibly related to the morphology of the bone and the lesser vascularization of the mandible as compared with other parts of the facial skeleton. In the biodegradable group, there were no removals in patients who were treated for a fracture, probably because of the relatively low number of fractures included in this study.

Despite the RCT protocol prescribing non-removal of asymptomatic plates, in the titanium group there were 2 removals of clinically asymptomatic plates/screws on the patients' request.

The reasons for inflammatory reactions/abscess formations are unclear. Bacterial cultures were taken in only a few (three) patients with biodegradable plate removal. These cultures showed sterile inflammatory reactions. We speculate that these inflammatory reactions are due to the degradation phase. As long as the biodegradable material is solid (in the early stages), only a fibrous capsule is formed. At the moment that small particles, which can undergo phagocytosis, have developed (at later stages), a foreign body reaction develops [49]. A low pH, caused by lactid acid (degradation product) may contribute [91,92].

Occlusion, VAS- and MFIQ-scores showed that the patients in both groups had good mandibular function and were (almost) free of pain 1 and 2 yrs post-operatively. We believe that the small difference in MFIQ is not clinically relevant.

One yr post-operatively, there were more patients in the biodegradable group in whom the plates/screws were palpable. After 2 yrs, there were no significant differences in palpability. According to the manufacturer, this can be expected, since full resorption of Inion CPS should take place within 2 to 4 yrs [83].

Many other studies have reported plate removal in OMF surgery. Titanium plate removal in trauma surgery (5-40%) [16,18] and in orthognathic surgery (7-19%) has been described [19,20]. For biodegradable systems, these percentages are 0% to 31% [51,93] and 0% to 3% [52,94,95], respectively. None of these studies was a RCT, so no firm conclusion can be drawn.

There are few RCTs that compared Inion with titanium plate removal. Bhatt *et al.* (2010) reported 0% biodegradable *vs.* 31% titanium (Synthes) plate removal in 40 patients treated for mandibular fractures [96]. These percentages are similar to the removal percentages for mandibular fractures in our study. Their follow-up period was only 8 post-operative wks, while in our study most removals occurred beyond that period. Leonhardt *et al.* (2008) also compared Inion with the KLS Martin titanium system in the treatment of mandibular fractures [97]. They reported removal of clinically symptomatic plates in five of the 30 patients (16.6%) in the biodegradable group, and in four of the 30 patients (13.3%) in the titanium group in the first 6 post-operative mos. In this study, on occasion, unavailability of the required plating system obscured randomization. In our study, there were no removals of clinically symptomatic plates/screws in patients treated for a mandibular fracture.

The (disturbing) intra-operative switches from the biodegradable to the titanium system are not compensated by the titanium plate removals. In fact, there were even more plate removals in the biodegradable group.

It is unclear why significantly more men were lost to follow-up. We believe that this did not influence the outcome of the post-operative interventions, *i.e.*, plate removal, because we viewed the patients' records and contacted them by telephone. Theoretically, for the patients who could not be contacted by telephone, it could be possible that a plate was removed in a hospital other than that in which the patients' surgery was performed, but this is highly unlikely.

The study was performed in 4 different hospitals, and no center effect for plate removal could be identified (data not shown). It can therefore be expected that the results of the use of the Inion CPS biodegradable system in other hospitals will be similar to those in our study.

In conclusion, in terms of plate removal within the first 2 post-operative years, the performance of the Inion CPS biodegradable system was inferior compared with that of the titanium KLS Martin system for fixation of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies, and bimaxillary osteotomies. Given the rates of plate removal and the intra-operative switches from the biodegradable system to the titanium system, there seems to be no place for the clinical usage of Inion CPS in treatment of these surgical situations. To put the usage into a broader perspective, it is also necessary to take relapse and cost-effectiveness into account.

Acknowledgements

Appendix Table. *Baseline characteristics and outcome measures after 1 year of patients lost to follow-up after 2 years and patients not lost to follow-up*

Description	LTFU	Not LTFU	p value*
Baseline characteristics†			
Surgical procedures	72	149	
BSSO	44 (61.1%)	98 (65.8%)	0.06
Le Fort-I osteotomy	5 (6.9%)	11 (7.4%)	
Bimaxillary osteotomy	11 (15.3%)	34 (22.8%)	
Mandibular fracture	6 (8.3%)	4 (2.7%)	
Le Fort-I fracture	1 (1.4%)	0	
Zygoma fracture	5 (6.9%)	2 (1.3%)	
Gender/age distribution			
Male	40 (55.6%)	58 (38.9%)	0.02
Female	32 (44.4%)	91 (61.1%)	
Age (mean +/- s.d. in yrs)	30 +/- 12	32 +/- 12	0.26
(range in yrs)	14-60	15-59	
Outcome measures‡			
Post-operative interventions			
Removal plate/screws (n (%))	16 (22.2%)	16 (10.7%)	0.001
Irrigation with saline (n (%))	0	2 (1.3%)	0.34
Antibiotics (n (%))	4 (5.6%)	13 (8.7%)	0.50
Abscess incision & drainage (n (%))	0	1 (0.7%)	0.50
Clinical assessments			
Non-correct occlusion	6 (12%)	14 (9.4%)	0.58
Palpability plate/screws•	11 (28.9%)	72 (55%)	0.006
Dehiscence	1 (2%)	1 (0.7%)	0.45
Abscess formation	1 (2%)	4 (2.7%)	> 0.99
Inflammatory reactions	3 (6%)	2 (1.3%)	0.72
Radiographic assessment			
Changed position bone segments	0	1 (0.7%)	> 0.99
Self-evaluation of patient			
Pain VAS (mean +/- s.d.)	4 +/- 12	1 +/- 5	0.15
MFIQ (median)**	19	20	0.94
(range)	17-57	17-61	

Legend Appendix Table

*Two-tailed test.

†Analyses performed on the total Treatment-Received group of 221 patients, *i.e.*, without the Protocol violations and the Treatment-Received violations (see Fig. 1).

‡There were 22 patients who were lost to follow-up before their one-year appointment. The outcome data 1 year post-operative of these patients is unknown. Therefore, the one-year analyses were performed on the other 50 patients who were lost to follow-up at 2 years, but who were still present at 1 year. The *post-operative interventions* were performed on the total 72 lost-to-follow-up patients. We collected the data of the *post-operative interventions* of the 22 patients who were lost to follow-up before their one-year appointment by telephoning them and by viewing their records. For readability, the plate removal rates *per* surgical procedure (see Table 3) were not described.

•The patients in whom the plates/screws were removed were not included in the analysis.

**The mandibular function was evaluated by the 17 questions on the MFIQ [81]; range 17-85; a higher score means worse function.

The reasons for lost to follow-up were missed appointments (n=36), refusal to participate in follow-up visits (n=19), unattainability (n=16), and death due to a T4 liver tumor (n=1).

Abbreviations: BSSO = bilateral sagittal split osteotomy, LTFU = Lost-to-follow-up, MFIQ = Mandibular Function Impairment Questionnaire (range 17-85), n = number, s.d. = standard deviation, VAS = Visual Analogue Scale (range 1-100).

COST–EFFECTIVENESS OF A BIODEGRADABLE COMPARED TO A TITANIUM FIXATION SYSTEM IN MAXILLOFACIAL SURGERY: A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background - Biodegradable fixation systems could reduce/delete the problems associated with titanium plate removal. This means less surgical discomfort, and a reduction in costs.

Aim - The aim of the present study was to compare the cost-effectiveness between a biodegradable and a titanium system in maxillofacial surgery.

Materials & Methods - This multicenter RCT was performed in the Netherlands from December 2006 to July 2009. Included were 230 patients who underwent a bilateral sagittal split osteotomy (BSSO), a Le Fort-I osteotomy, or a bimaxillary osteotomy and those treated for fractures of the mandible, maxilla, or zygoma. The patients were randomly assigned to a titanium group (KLS Martin) or to a biodegradable group (Inion CPS). Costs were assessed from a societal perspective. Health outcomes in the incremental cost-effectiveness ratio (ICER) were bone healing (8 weeks) and plate removal (2 years).

Results - In 25 out of the 117 patients who were randomized to the biodegradable group, the maxillofacial surgeon made the decision to switch to the titanium system intra-operatively. This resulted in an Intention-To-Treat (ITT) analysis and a Treatment-Received (TR) analysis. Both analyses indicated that operations performed with titanium plates and screws had better health outcomes. In the TR analysis the costs were lower in the biodegradable group, in the ITT analysis costs were lower in the titanium group.

Conclusion & Discussion – The difference in costs between the ITT and the TR analyses can be explained by the intra-operative switches: In the TR analysis the switches were analyzed in the titanium group. In the ITT analysis they were analyzed in the biodegradable group.

Considering the cost-effectiveness the titanium system is preferable to the biodegradable system in the regular treatment spectrum of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies and bimaxillary osteotomies.

Keywords: Bone healing, plate removal, costs, economics, osteosynthesis, oral and maxillofacial surgery.

INTRODUCTION

Titanium is regarded as the "golden standard" for osteosynthesis. It appears to be necessary that titanium is removed following bone healing in a second operation in 5-40% of the cases [16,19].

Biodegradable fixation systems have been developed to dissolve in the human body in order to reduce or even delete the problems associated with titanium plate removal. According to prevailing literature biodegradable systems are removed in a second operation in 0-31% of the cases [51,52]. Less removal operations imply less surgical discomfort for the patients. It may also benefit society, as less removal operations will put less pressure on the operation room capacity and the specialists, and ensures less sick leave of patients. The present study is part of a longer running research project. The trial design and short-term outcomes after 8 weeks of healing have been previously published [23]. Briefly, short-term healing outcomes were similar between biodegradable and titanium fixation, although in a significant proportion (25/117) of biodegradable-randomized patients, the operating surgeons decided intra-operatively to switch to the titanium system, due to either technical complications such as non-grip of the screws or other reasons. Details regarding these switches have been described elsewhere [90]. In the literature no data is available regarding the cost-effectiveness of biodegradable plates and screws in maxillofacial surgery. Therefore, the aim of the present study was to establish the cost-effectiveness of bone healing and plate removal of biodegradable plates and screws as a potential alternative to titanium regarding fixation of mandibular-, Le Fort-I-, and zygoma fractures, and bilateral sagittal split osteotomies (BSSO), Le Fort-I osteotomies, and bimaxillary osteotomies. An important sub-question is how do the costs of the intra-operative switches relate to the costs of the expected higher plate removal of titanium?

MATERIALS & METHODS

This RCT has been described according to the CONSORT statement 2010 (http://www.consort-statement.org/).

Ethics Statement
All patients provided written informed consent prior to enrollment and to publication of the work. The study was approved by the Medical Ethical Committees of the 4 participating hospitals in the Netherlands (University Medical Centre Groningen, Rijnstate Hospital Arnhem, Amphia Hospital Breda, and Medical Centre Leeuwarden). This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Table 1. *Inclusion and exclusion criteria*

Inclusion criteria:

- patients scheduled for 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 parents or responsible persons if necessary) who signed the *informed consent* form.

Exclusion criteria:

- patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);
- patients presented with heavily comminuted fractures of the facial skeleton;
- patients who experienced compromised bone healing in the past;
- patients who were pregnant;
- patients who could/would not participate in a 1-year follow-up (reasons);
- patients who would not agree with an *at random* assignment to one of the treatment groups, or one of the methods or treatment administered in the study;
- patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);
- patients who experienced cleft lip and palate surgery in the past;
- patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);
- patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.

Study population

Recruitment of the RCT was performed from December 28, 2006 to July 22, 2009. Two hundred and thirty trauma and orthognathic patients were treated at the departments of maxillofacial surgery of the participating hospitals.

The inclusion and exclusion criteria are summarized in Table 1. The surgeons recruited the participants and assigned them randomly to one of the two treatment groups a day before (osteotomies) or immediately prior to (fractures) the operation. A statistician generated the randomization sequences using a computerized randomization program. The randomization was performed using an IVRS (Interactive Voice Response System) (block size 10), which was available 24-hours a day to conceal the randomization sequence until the interventions were assigned. Randomization was stratified by hospital to ensure that the two treatment options were equally divided over the participating hospitals. The randomization procedure resulted in an ITT population of 113 patients in the titanium group and 117 patients in the biodegradable group [23]. Inclusion errors were made with 7 patients. In 25

patients who were randomized to the biodegradable group, the operating surgeon made the decision to switch to the titanium system intra-operatively. Regarding the TR analysis, the 7 'inclusion error'-patients were excluded, and the 25 switches were added to the titanium group. Additionally, 2 Treatment-Received violations were excluded. This resulted in TR groups of 134 patients (titanium) and 87 patients (biodegradable), respectively.

Interventions

The patients were assigned to a titanium control group (KLS Martin, Gebrüder Martin GmbH&Co., Tuttlingen, Germany) or to a biodegradable test group (Inion CPS, Inion Ltd., Tampere, Finland). Neither prior to nor after surgery were the patients aware of the system that had been used.

All plates and screws were applied according to the instructions of the manufacturers. For fixation of mandibular osteotomies and fractures 2.5-mm biodegradable or 2.0-mm titanium plates and screws were used, whereas 2.0-mm biodegradable or 1.5-mm titanium plates and screws were used for fixation of zygoma fractures, Le Fort-I fractures, and Le Fort-I osteotomies. Each participating maxillofacial 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 dimensions of the material. These 'test-surgeries' were not included in the study. The patients did not receive rigid maxillomandibular fixation, but soft guiding elastics post-operatively, and were instructed to maintain a soft diet for five weeks. In the design of the RCT it was agreed that routine removals of asymptomatic plates would not be performed.

Outcome measures

Cost-effectiveness was assessed from a societal perspective over a time horizon of 8 weeks and 2 years: direct medical, direct non-medical, and the indirect non-medical costs were included in the analyses (Table 2). Estimates of unit costs were based on the Dutch guidelines for cost studies [98]. Duration of the primary operation was registered per minute, and costs were based on the time invested by the different care givers, accrued with costs for materials, housing and overhead. Costs for materials (plates and screws) were actual cost prices derived from the manufacturer. Duration of plate removal surgery and abscess incision & drainage was set on 30 min, based on the mean duration of these interventions, as estimated by the surgeons (expert opinion). Costs of the medications were based on the listed prices, obtained from the website of the Dutch Health Insurance Board (www.medicijnkosten.nl). Travel costs were based on the number of visits to the hospital, the mean distance to a hospital in the Netherlands of 7.0 km (14.0 km/visit), and under the assumption that people travelled by private car. The costs per km amounted to €0.20, and parking costs were estimated at €3.00/visit [98]. Costs of productivity loss were based on the overall mean productivity costs (per hour) for men and women. Multiplying the volumes of resource use with the associated cost prices resulted in the total costs.

Table 2. *Types of costs, determinations, units and unit prices*

Types of costs	Determination/unit included	Unit	Unit price (€)
Direct medical			
Primary surgery	(1) Personnel and overhead (2) Material†	(1) Minute (2) Plates and screws	(1) 5.25* (2) Variable†
Hospital admission	Number of admission days based on standard price	Day	€598*
Plate removal surgery‡	Personnel and overhead	Minute	€2.27*
Abscess incision & drainage‡	Personnel and overhead	Minute	€2.27*
Outpatient visits	Number of visits based on standard price	Visit	€134*
Radiologic diagnostics	Quantity of radiological diagnostic procedures such as orthopantomogram	Test	Variable§
Antibiotics	Quantities of medication and unit prices	Prescription	Variable¶
Direct nonmedical			
Travelling expenses#	(1) Costs per km of €0.20 (2) Parking costs	Visit (14 km)	(1) €2.80* (2) €3.00*
Indirect nonmedical			
Absence from work	Time investment, mean income Dutch population costs	Hour	€37.82*

*Cost manual Hakkaart-van Roijen [98].
†E-mail correspondence manufacturer: titanium: plate 1.5mm €68, plate 2.0mm €34.50, screw €9. Biodegradable: plate 2.0mm €80, plate 2.5mm €88, screw €24.
‡Plate removal surgery and Abscess incision & drainage 30 min.
§Tariffs (www.nza.nl).
¶www.medicijnkosten.nl.
#Travel costs were based on the mean distance to a hospital in the Netherlands of 7.0 km (14.0 km/visit), and under the assumption that people travelled by private car.

The clinical measures of effect in the cost-effectiveness ratio were (1) bone healing (8 weeks), and (2) plate removal (2 years):

(1) 'bone healing 8 wks after surgery' (yes/no): 1. absence of clinical mobility of the bone segments assessed by bi-manual traction on the distal and proximal bone segments, and 2. absence of radiographic signs of disturbed bone healing assessed on an orthopantomogram (OPT; all indications), a lateral cephalogram (osteotomies), an occipito-mental radiograph (zygoma fractures), and a fronto-suboccipital radiograph (mandible fracture);

(2) removal of plates/screws within the first 2 post-operative years (yes/no).

The outcome measures were evaluated 8 wks (February 28, 2007 to September 21, 2009) and 2 yrs (February 3, 2009 to August 10, 2011) post-operatively and recorded on Case Report Forms, and partly by using a cost questionnaire (absence from work). Data from unplanned intermediate outpatient visits, *e.g.*, plate removals or additional radiographs, were also recorded on Case Report Forms.

Statistical analysis

Inclusion of the 230 patients was based on power analysis on the outcome measure 'bone healing after 8 weeks', and is described in detail elsewhere [23]. The Statistical Package of Social Sciences (SPSS, version 20.0) and Microsoft Office Excel (2007) were used to analyze the data. The means and standard deviations of normally distributed variables were calculated and analyzed using the independent-samples *t* test . Skewed variables were either transformed to obtain normally distributed variables, or (if this could not be achieved) analyzed using non-parametric tests. Dichotomous variables were analyzed using the Chi-squared or the Fisher's exact test. Removal of plate/screws was analyzed using the Logrank test. The Hazard ratio was calculated by Cox regression. Any *p* values less than .05 were considered statistically significant.

In the ITT analysis, the outcome data of bone healing and plate/screws removal for the inclusion errors was 'imputed' as 'adequate bone healing' and 'no plate/screws removal', according to the strategies of the Cochrane Collaboration (http://www.cochrane-net.org). Additionally, the switches were assessed as failures for bone healing. Lost-to-follow-up patients (both analyses) were contacted by telephone, and were asked if their plates/screws had been removed during the lost-to-follow-up period. We also viewed their (digital) records. If the records showed no plate/screws removal, no matter if they could be reached by telephone, these patients were 'scored' as 'no plate/screws removal'. The same was done for bone healing.

The mean costs per patient and differences in costs between the two groups were calculated. If a patient did not make use of a specific cost type costs of €0 were applied when calculating group means. If information was missing, *i.e.*, patient was lost-to-follow-up, we viewed their records for additional costs. In the cost-effectiveness analysis, costs were linked to the clinical outcomes 'bone healing' and 'plate removal' to construct an incremental cost-effectiveness ratio (ICER). Point estimates for ICER were computed on

complete cost-effect pairs by dividing the incremental societal costs by the incremental effects, *i.e.*, bone healing and plate removal. The formula used for calculating the ICER with bone healing as the incremental effect is presented below.

$$\text{ICER} = \frac{(C_{\text{Biodegradable}} - C_{\text{Titanium}})}{(BH_{\text{Biodegradable}} - BH_{\text{Titanium}})}$$

$C_{\text{Biodegradable}}$ = mean costs in the Biodegradable group
C_{Titanium} = mean costs in the Titanium group
$BH_{\text{Biodegradable}}$ = number of patients with adequate bone healing in the Biodegradable group
BH_{Titanium} = number of patients with adequate bone healing in the Titanium group

In the formula used for calculating the ICER with plate removal as the incremental effect the inadequate bone healing (BH) in the denominator is replaced by the number of plate re-movals. We estimated uncertainty around the ICERs using bootstrapping, generating 5000 replications of the original dataset, thereby creating alternative confidence intervals (2.5th and 97.5th percentile) [99]. The simulated values of the mean estimates for the cost and outcome differences were added to the cost-effectiveness plane [100,101].

The percentage of patients who fell into each of the four quadrants of the cost-effectiveness plane was determined. In the northwest quadrant the biodegradable plates and screws are less effective, and there are additional costs involved. In the southwest quadrant the bio-degradable plates and screws are less effective with less additional costs. In the northeast quadrant the biodegradable plates and screws are more effective with additional costs. In the southeast quadrant the biodegradable plates and screws are more effective with less additional costs. In the case of plate removal, the costs of plate removal operations were not accounted for in the numerator to avoid overestimating the ICER. Again bootstrapping was used to estimate the alternative confidence intervals, and cost-effectiveness planes were constructed to visually display the ICERS from the bootstrap replications.

RESULTS

Patients
Fig. 1 represents the flow of 230 randomized patients during the phases of the study. 217 and 149 patients completed the 8 weeks and 2 years post-operative follow-up, re-spectively. Missing data was 'imputed' as described in the Materials and Methods section.

Clinical outcomes
None of the baseline characteristics differed significantly between the biodegradable and titanium group for the ITT and TR analysis after 8 weeks and 2 years (Tables 3 and 4). Inadequate bone healing of two patients in the biodegradable group was reported. Fol-

Table 3. *Baseline characteristics after 8 weeks and 2 years for ITT analysis*

Description	8 weeks			2 Years		
	Titanium (n)	Biodegradable (n)	*p* value	Titanium (n)	Biodegradable (n)	*p* value
Surgical procedures	113	117	0.33	76	74	0.77
BSSO	72 (63.7%)	70 (59.8%)		50 (65.8%)	48 (64.9%)	
Le Fort-I osteotomy	8 (7.1%)	8 (6.8%)		5 (6.6%)	6 (8.1%)	
Bimaxillary osteotomy	24 (21.2%)	21 (17.9%)		19 (25%)	15 (20.3%)	
Mandibular fracture	2 (1.8%)	9 (7.7%)		1 (1.3%)	3 (4.1%)	
Le Fort-I fracture	1 (0.9%)	0		0	0	
Zygoma fracture	4 (3.5%)	4 (3.4%)		1 (1.3%)	2 (2.7%)	
Protocol violations	2 (1.8%)	5 (4.3%)				
Gender/age distribution						
Male	44 (38.9%)	56 (47.9%)	0.17	28 (36.8%)	30 (40.5%)	0.74
Female	69 (61.1%)	61 (52.1%)		48 (63.2%)	44 (59.5%)	
Age (mean +/- s.d. in yrs)	31 +/- 11	31 +/- 12	0.59	31 +/- 11	32 +/- 12	0.72
(range in yrs)	16-60	14-59		16-59	15-59	

Abbreviations: BSSO = bilateral sagittal split osteotomy, ITT = Intention-To-Treat, n = number, s.d. = standard deviation.

Assessed for eligibility (n= 834)

Excluded (n= 604)
- Not meeting in- exclusion criteria (n= 105)
- Refused to participate (n= 499)

Patients randomized (n= 230)

BIODEGRADABLE GROUP

Allocated to biodegradable group (n = 117)

Allocation

Analyzed (ITT) in biodegradable group (n = 117)

ITT analyses†

Protocol violations (n = 5)
- after randomisation it turned out patients had cleft lip and palate (n = 3);
- after randomisation it turned out patient had a psychiatric disorder (n = 1);
- randomized to the wrong centre (n = 1)

Switched to titanium (n = 25)

Treatment Received (n = 87)

Treatment Received violations (n = 0)

Operated with Inion CPS (n=87)

TR analyses†

*8 wks Lost-to-follow-up (n=3)

Available for follow-up (TR) (n = 84)

‡2 yrs Lost-to-follow-up (n=19)

Available for follow-up (TR) (n = 56)

TITANIUM GROUP

Allocated to titanium group (n=113)

Analyzed (ITT) in titanium group (n = 113)

Protocol violations (n = 2)
- after randomisation it turned out patient had cleft lip and palate (n = 1)
- randomized to the wrong centre (n =1)

Treatment Received (n = 136)

Treatment Received violations (n = 2)
- stable position zygomatic fracture achieved without osteosynthesis (n = 1);
- fixation mandibular fracture with lag screws without titanium plate (n = 1).

Operated with titanium (n=134)

Lost-to-follow-up (n=1)

Available for follow-up (TR) (n = 133)

Lost-to-follow-up (n=31)

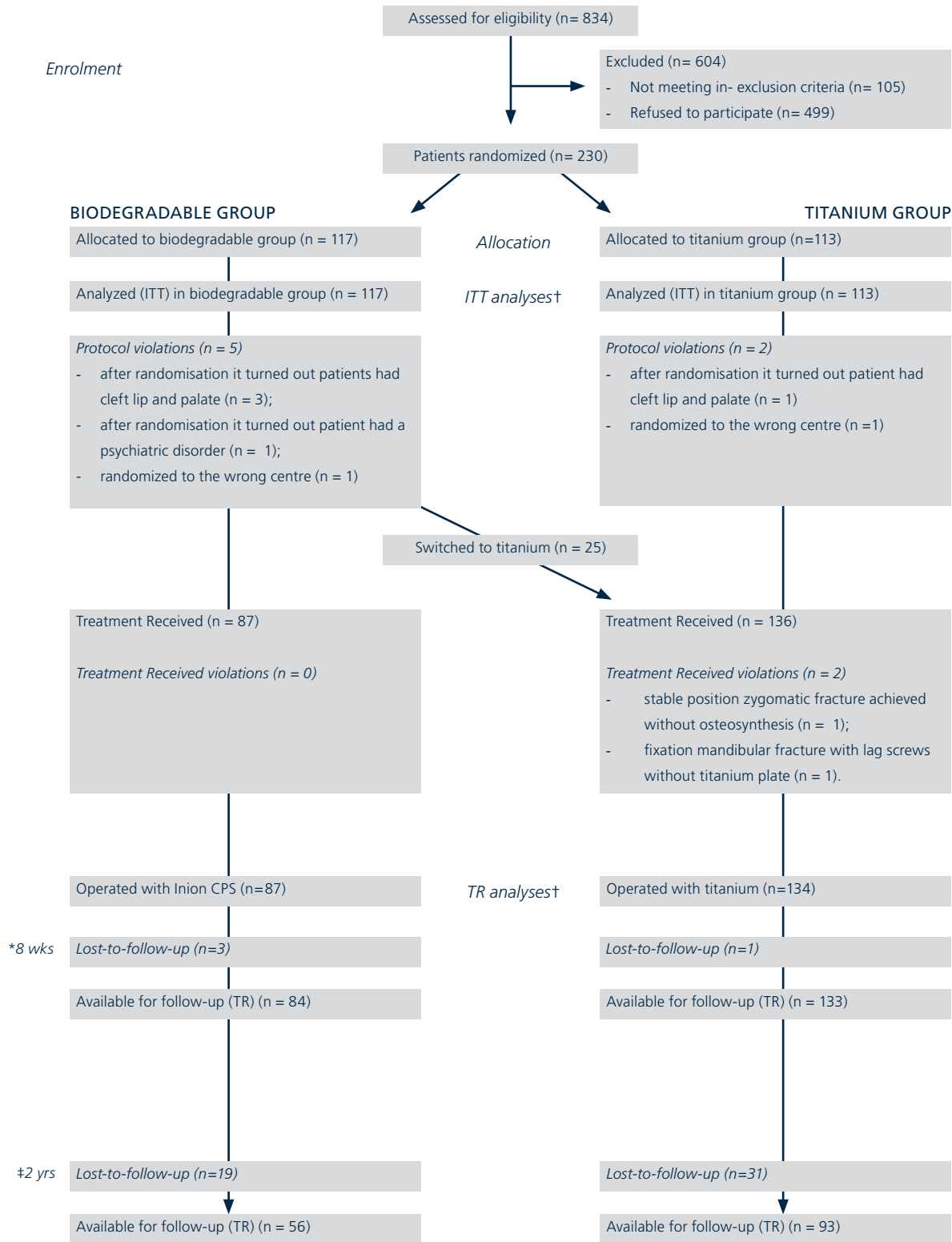Available for follow-up (TR) (n = 93)

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Figure 1. *Flow diagram of patient's progress though the phases of RCT*

*The 8 wks post-operative analyses have been described in detail in Chapter 2 (Buijs *et al.* 2012) [23].
†The cost-effectiveness analyses were performed on the total Intention-To-Treat group of 230 patients (titanium 113 patients vs. biodegradable 117 patients) and on the total Treatment-Received group of 221 patients (titanium 134 patients vs. biodegradable 87 patients). In the ITT analysis, the outcome data of bone healing and plate/screws removal for the inclusion errors was 'imputed' as adequate bone healing and no plate/screws removal, according to the strategies of the Cochrane Collaboration (http://www.cochrane-net.org). Additionally, the switches were assessed as failures for bone healing. Lost-to-follow-up patients (both analyses) were contacted by telephone, and were asked if their plates/screws had been removed during the lost-to-follow-up period. We also viewed their (digital) records. If the records showed no plate/screws removal, no matter if they could be reached by telephone, these patients were 'scored' as 'no plate/screws removal'. The same was done for bone healing.
‡The 2 yrs post-operative clinical results have been described in detail in Chapter 4 (Van Bakelen *et al.* 2013) [103].

lowing the ITT analysis, 27 patients in the biodegradable group (25 'switchers' and the two abovementioned patients) and non of the patients in the titanium group showed inadequate bone healing, resulting in a significant difference (*p*< 0.001) (Table 5). Regarding the TR analysis, the two abovementioned patients in the biodegradable group and non of the patients in the titanium group showed inadequate bone healing, resulting in a non-significant difference (*p*=0.15) (Table 6). Viewing the records and telephoning the 4 patients that were lost-to-follow-up after 8 weeks did not reveal any inadequate bone healing.

Regarding the removal of the plate/screws within the first 2 post-operative years in the TR analysis, 16 of the 134 patients (11.9%) who were treated with the titanium system and 21 of the 87 patients (24.1%) who were treated with the biodegradable system needed a second operation to remove the plates/screws (*p*=0.016, HR biodegradable (95%CI) = 2.2 (1.1-4.2), HR titanium = 1) (Table 6). 13 of these removals were seen in the 72 patients that did not complete the entire observation period of 2 years. Viewing the records of the other 59 lost-to-follow-up patients revealed 3 extra plate removals. 40 of the remaining 56 patients could be contacted by telephone. This revealed no extra interventions. The characteristics of the lost-to-follow-up patients can be seen in the Appendix Table of chapter 4. The plate/screws removal per surgical procedure are presented in Table 7. In the titanium group plate/screws removal was seen in patients treated with a BSSO: 9/87 (10.3%), bimaxillary osteotomy: 4/29 (13.8%), mandibular fracture: 2/6 (33.3%), and zygomatic fracture: 1/3 (33.3%). There was no removal in Le Fort-I fractures or -osteotomies. In the biodegradable group removal of plate/screws was seen in patients treated with a BSSO: 17/55 (30.1%), and bimaxillary osteotomy: 4/16 (25%). In this group there was no removal in patients who were treated for a fracture or with a Le Fort-I osteotomy. There were two removals on request of the patient of clinically asymptomatic titanium plates/screws. Both patients were treated for a mandibular fracture. All the other removals in both groups were due to clinical problems. The differences between the surgical procedures were not statistically significant (*p*=0.62), even if the 2 removals on request would not have been performed. The ITT analysis showed similar results. No centre effect for plate removal could be identified.

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Table 4. *Baseline characteristics after 8 weeks and 2 years for TR analysis*

Description	8 Weeks			2 Years		
	Titanium (n)	Biodegradable (n)	p value	Titanium (n)	Biodegradable (n)	p value
	133	84		93	56	
Surgical procedures						
BSSO	87 (65.4%)	52 (61.9%)	0.74	61 (65.6%)	37 (66.1%)	0.21
Le Fort-I osteotomy	8 (6.0%)	8 (9.5%)		5 (5.4%)	6 (10.7%)	
Bimaxillary osteotomy	29 (21.8%)	16 (19%)		24 (25.8%)	10 (17.9%)	
Mandibular fracture	5 (3.8%)	4 (4.8%)		3 (3.2%)	1 (1.8%)	
Le Fort-I fracture	1 (0.8%)	0		0	0	
Zygoma fracture	3 (2.3%)	4 (4.8%)		0	2 (3.6%)	
Gender/age distribution						
Male	54 (40.6%)	42 (50%)	0.18	35 (37.6%)	23 (41.1%)	0.73
Female	79 (59.4%)	42 (50%)		58 (62.4%)	33 (58.9%)	
Age (mean +/- s.d. in yrs)	31 +/- 11	31 +/- 12	0.8	31 +/- 11	33 +/- 12	0.37
(range in yrs)	16-60	14-59		16-59	15-59	

Abbreviations: BSSO = bilateral sagittal split osteotomy, n = number, s.d. = standard deviation, TR = Treatment-Received.

Table 5. *Outcome measures and costs after 8 weeks and 2 years for ITT analysis*

Description	8 weeks			2 Years		
	Titanium (n)	Biodegradable (n)	p value	Titanium (n)	Biodegradable (n)	p value
*Clinical assessments**						
Inadequate bone healing	0	27 (23.1%)	< 0.001	NA	NA	NA
Removal plate/screws	2 (1.8%)	1 (0.9%)		11 (9.7%)	26 (22.2%)	0.009
Handling						
Operation time (h:m)	2:11	2:18	0.42			
Costs‡			Difference (95%CI)			Difference (95%CI)
Direct medical						
Primary surgery	926	1310	384 (349 to 772)	926	1310	384 (349 to 772)
Hospital admission	1196	1207	11 (0 to 44)	1196	1207	11 (0 to 44)
Plate removal surgery	1.23	0.62	-0.60 (-3.45 to 1.68)	6.14	15	8.86 (-4.98 to 9.92)
Abscess incision & drainage	0	0.62	0.62 (0 to 2.52)	0.62	1.87	1.26 (-1.20 to 6.95)
Outpatient visits	599	660	61 (-6.72 to 126)	1003	1148	145 (-11.63 to 331)
Diagnostics	147	158	10.47 (-1.86 to 22.18)	299	323	24 (6.09 to 77)
Antibiotics	0.18	0.56	0.33 (-0.11 to 0.92)	0.61	1.75	1.14 (-0.61 to 2.87)
Direct nonmedical						
Travelling expenses	38	40	2.77 (-0.14 to 5.70)	52	59	6.33 (0.04 to 12.68)
Indirect nonmedical						
Absence from work	2556	2621	65 (-965 to 1066)	2967	2945	-21.89 (-1340 to 1267)
Total costs	5463	5997	534 (-580 to 1638)	6451	7010	560 (-905 to 1942)

*Percentages (%) on total Intention-To-Treat group of 230 patients: 113 patients in the titanium group, and 117 patients in the biodegradable group. The outcome data of bone healing and plate/screws removal for the inclusion errors was 'imputed' as adequate bone healing and no plate/screws removal, according to the strategies of the Cochrane Collaboration (http://www.cochrane-net.org). The switches were assessed as failures for bone healing. The lost-to-follow-up patients were contacted by telephone, and were asked if their plates/screws had been removed during the lost-to-follow-up period. We also viewed their (digital) records. If the records showed no plate/screws removal, no matter if they could be reached by telephone, these patients were 'scored' as 'no plate/screws removal'. The same was done for bone healing. Bone healing was tested one-sided. All the other outcome measures in Table 5 were tested two-tailed.
†What has actually been invested. This does not correspond to the agreements on costs between hospitals and health insurers. The costs given at 2 Years' include the costs after '8 Weeks'. Viewing the records of the lost-to-follow-up patients did not reveal additional costs in their lost-to-follow-up period.
Abbreviations: h:m = hours:minutes, ITT = Intention-To-Treat, MFIQ = Mandibular Function Impairment Questionnaire (range 17-85), n = number, NA = not applicable, s.d. = standard deviation, VAS = Visual Analogue Scale (range 1-100).

Table 6. *Outcome measures and costs after 8 weeks and 2 years for TR analysis*

Description	8 Weeks			Difference (95%CI)	2 Years			Difference (95%CI)
	Titanium (n)	Biodegradable (n)	p value		Titanium (n)	Biodegradable (n)	p value	
Clinical assessments*								
Inadequate bone healing	0	2 (2.4%)	0.15		NA	NA	NA	
Removal plate/screws	2 (1.5%)	1 (1.2%)			16/134 (11.9%)	21/87 (24.1%)	0.016	
Handling								
Operation time (h:m)	2:16	2:13	0.74					
Costs†				Difference (95%CI)				Difference (95%CI)
Direct medical								
Primary surgery	1052	1236		184 (-348 to 360)	1052	1236		184 (-3.48 to 360)
Hospital admission	1196	1210		14 (0 to 44)	1196	1210		14 (0 to 44)
Plate removal surgery	1.00	0.81		-0.20 (-2.59 to 2.50)	7.11	16.21		9.10 (1.38 to 17)
Abscess incision & drainage	0.50	0		-0.50 (-1.72 to 0)	2.03	1.62		-0.41 (-2.59 to 3.36)
Outpatient visits	623	637		14 (-54 to 82)	1061	1104		43 (-89 to 173)
Diagnostics	152	154		1.69 (-11 to 13)	306	322		16 (-15 to 46)
Antibiotics	0.25	0.55		0.29 (-0.23 to 0.86)	0.83	1.74		0.91 (-0.67 to 2.68)
Direct nonmedical								
Travelling expenses	39	39		0.66 (-2.30 to 3.59)	55	57		2.45 (-4.16 to 8.63)
Indirect nonmedical								
Absence from work	2708	2429		-279 (-1298 to 731)	3208	2597		-611 (-1893 to 599)
Total costs	5772	5707		-65 (-1154 to 1001)	6887	6546		-341 (-1748 to 1816)

*Percentages (%) on total Treatment-Received group of 221 patients: 134 patients in the titanium group, and 87 patients in the biodegradable group. The lost-to-follow-up patients were contacted by telephone, and were asked if their plates/screws had been removed during the lost-to-follow-up period. We also viewed their (digital) records. If the records showed no plate/screws removal, no matter if they could be reached by telephone, these patients were 'scored' as 'no plate/screws removal'. The same was done for bone healing. Bone healing was tested one-sided. All the other outcome measures in Table 6 were tested two-tailed.
†What has actually been invested. This does not correspond to the agreements on costs between hospitals and health insurers. The costs given at '2 Years' include the costs after '8 Weeks'. Viewing the records of the lost-to-follow-up patients did not reveal additional costs in their lost-to-follow-up period.
Abbreviations: h:m = hours:minutes, MFIQ = Mandibular Function Impairment Questionnaire (range 17-85), n = number, NA = not applicable, s.d. = standard deviation, TR = Treatment-Received, VAS = Visual Analogue Scale (range 1-100).

Table 7. *Removal of plates and screws per surgical procedure (TR analysis)*

Description	Titanium Removal (n(%))	Biodegradable Removal (n(%))
Surgical procedures*		
Total osteotomies	13/124 (10.5%)	21/79 (26.6%)
BSSO	9/87 (10.3%)	17/55 (30.1%)
Le Fort-I osteotomy	0/8	0/8
Bimaxillary osteotomy	4/29 (13.8%)†	4/16 (25%)‡
Total Fractures	3/10 (30%)	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
Total removals	16/134 (11.9%)	21/87 (24.1%)

*A Logrank test showed no significant difference in plate removal percentages between the surgical procedures (*p*=0.62).
†Removal of plate/screws in the mandible as well as the maxilla.
‡Removal of plate/screws only in the mandible.
§These 2 removals of plates/screws were on patients' request of asymptomatic plates/screws. All the other removals in table 7 were due to clinical problems, *i.e.*, swelling, dehiscence, infection, abscess formation, screw loosening, irritation/pain.
Abbreviations: BSSO = bilateral sagittal split osteotomy; TR = Treatment-Received.

Costs and cost effectiveness

The various medical and nonmedical costs generated by both groups during the first 2 years post-operatively are presented in tables 5 and 6. Viewing the records of the lost-to-follow-up patients did not reveal additional costs in their lost-to-follow-up period. The mean total costs after 8 weeks and 2 years post-operatively in the ITT analysis for the titanium group were €5463 and €6451, respectively. In the biodegradable group these costs were €5997 and €7010. The mean total costs after 8 weeks and 2 years post-operative in the TR analysis for the titanium group were €5772 and €6887, respectively. In the biodegradable group these costs were €5707 and €6546.

Results of the cost-effectiveness analyses are displayed in figures 2-5. The point estimate of the ICER for bone healing at 8 weeks was -€22 (95% CI -€62 to €15) for the ITT analysis. This means that per percent loss of patients with adequate bone healing, additional cost of €22 are invested if titanium plates and screws are replaced by biodegradables. For bone healing at 8 weeks in the TR analysis the point estimate is €27 (95% CI -€59562 to €64478). In this analysis, both the effect as well as the costs are lower in de biodegradable group.

The ICER for the 2 year ITT analysis with plate removal as health outcome was -€43 (95% CI -€228 to €56). This means an investment of €43 while the percentage of biodegradable plate removal increases with 1% if titanium plates and screws are replaced by
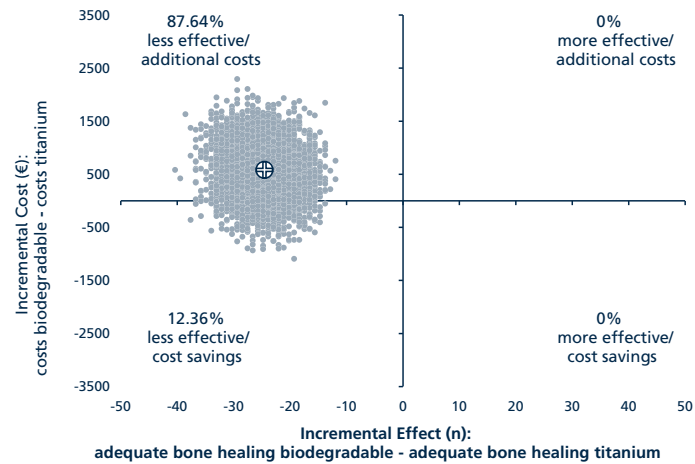
Figure 2. *Results of the cost-effectiveness in the ITT analysis with bone healing as outcome measure*

ICERs were calculated for 5000 bootstrap iterations and simulated values of the mean estimates for the costs (€548) and bone healing (-24.8) differences are presented in the cost-effectiveness plane. The point estimate of the ICER for bone healing at 8 weeks was -€22 (95% CI -€62 to €15).. This means that per percent loss of patients with adequate bone healing, additional cost of €22 are invested if titanium plates and screws are replaced by biodegradables.
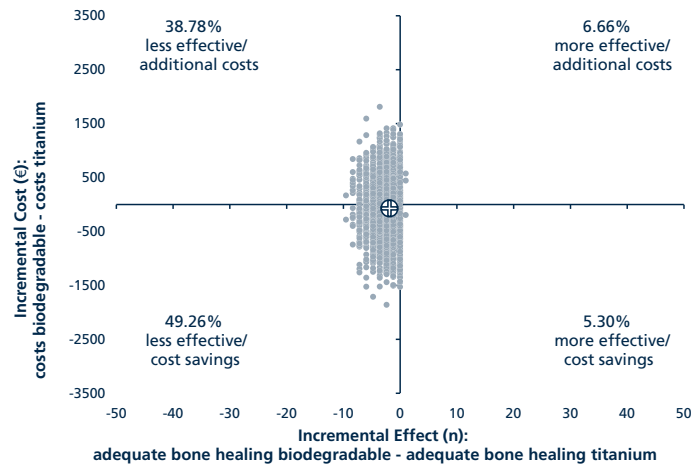

Figure 3. *Results of the cost-effectiveness in the TR analysis with bone healing as outcome measure*

ICERs were calculated for 5000 bootstrap iterations and simulated values of the mean estimates for the costs (-€65) and bone healing (-2.4) differences are presented in the cost-effectiveness plane. For bone healing at 8 weeks the point estimate is € 27 (95% CI -€59562 to € 64478). In this analysis, both the effect as well as the costs are lower in de biodegradable group, causing a positive ICER indicating that per percent loss of adequate bone healing, €27 is saved if titanium plates and screws are replaced by biodegradables.. In 700 of the 5000 bootstraps the incremental effect was zero, because bone healing was 100% adequate in both groups. In these cases the incremental effects of 0.01 and -0.01 (alternating) were applied, causing a wide confidence interval and a flattened scatter plot.
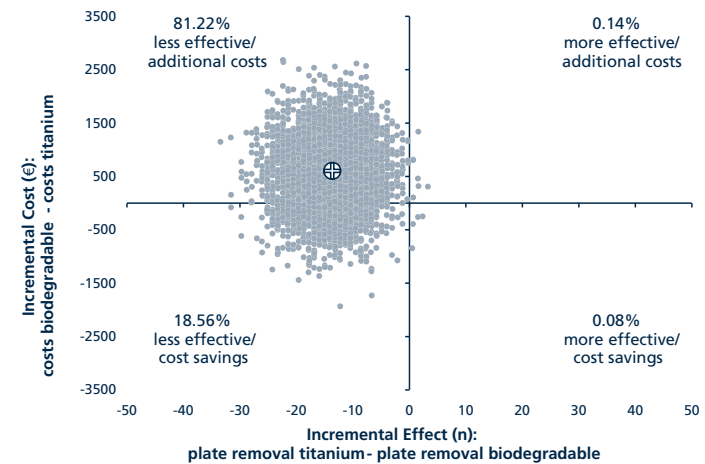

Figure 4. *Results of the cost-effectiveness in the ITT analysis with plate removal as outcome measure*

ICERs were calculated for 5000 bootstrap iterations and simulated values of the mean estimates for the costs (€566) and plate removal (-13.2) differences are presented in the cost-effectiveness plane. The point estimate of the ICER for plate removal within the first 2 years post-operative was -€43 (95% CI -€228 to €56). This means an investment of €43 while the percentage of biodegradable plate removal increases with 1% if titanium plates and screws are replaced by biodegradables.
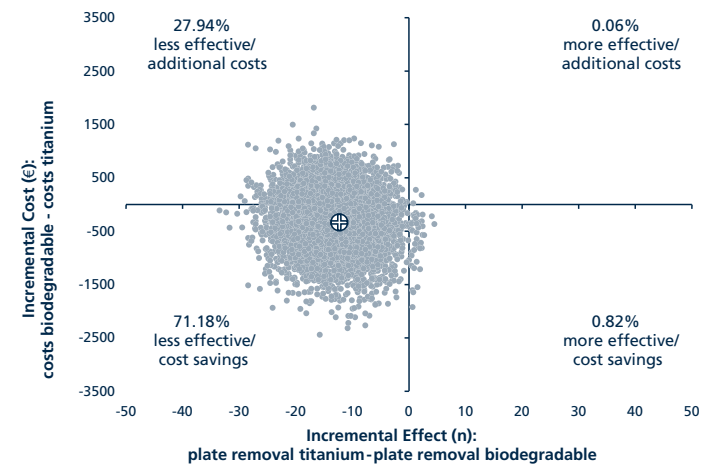

Figure 5. *Results of the cost-effectiveness in the TR analysis with plate removal as outcome measure*

ICERs were calculated for 5000 bootstrap iterations and simulated values of the mean estimates for the costs (-€350) and plate removal (-13.4) differences are presented in the cost-effectiveness plane. The point estimate of the ICER for plate removal within the first 2 years post-operative was €26 (95% CI -€73 to €206), indicating €26 is saved while the percentage of patients with plate removal increases with 1% if titanium plates and screws are replaced by biodegradables.

biodegradables. The TR analysis showed a positive ICER of €26 (95% CI -€73 to €206), indicating €26 is saved while the percentage of patients with plate removal increases with 1% if titanium plates and screws are replaced by biodegradables.

DISCUSSION

The results of the cost-effectiveness in the ITT analyses indicate that operations performed with titanium plates and screws had lower costs and better health outcomes: Mean total costs in the first 8 weeks and 2 years post-operative in the titanium group were €5463 and €6451, respectively. In the biodegradable group these costs were €5997 and €7010, respectively. Results of bone healing after 8 wks and plate removal within the first 2 post-operative yrs were more positive for the titanium group in the ITT analyses. The relatively many intra-operative 'switches' (21%) were primarily responsible for the inferior bone healing in the biodegradable group. The TR analyses indicate that costs were lower in the biodegradable group, but the titanium group had better health outcomes. Mean total costs in the first 8 weeks and 2 years post-operative in the titanium group were €5772 and €6887, respectively. In the biodegradable group these costs were €5707 and €6546, respectively. In the biodegradable group, from a clinical perspective, bone healing was not inferior, but there were more plate removals (24.1% in the biodegradable group *vs.* 11.9% in the titanium group). In summary, in the ITT analysis the mean total costs were higher in the biodegradable group, while in the TR analysis these costs were higher in the titanium group. This discrepancy between both analyses can only be explained by the intra-operative switches, because these switches are the only difference between both analyses: In the ITT analysis the switches were analyzed in the biodegradable group. In the TR analysis they were analyzed in the titanium group. Apparently these switches impose a greater burden on the healthcare system, in particular the costs due to 'absence from work'. The reason for this is not entirely clear, but the mandibular function on average was slightly less (higher MFIQ-score [81]) for these switches when compared to the non-switches (data not shown). Possibly these patients stay at home more often, because they have more complaints. We could not identify predictor variables for intra-operative switching that may be helpful in deciding in advance whether to use biodegradable devices or not [90]. Certainly, surgeons are familiar with and have confidence in titanium systems. To gain comparable familiarity with and confidence in biodegradable systems would probably have taken more time to minimize cognitive bias. The limited number of 2 test-surgeries and personal preferences/appreciation/dedication have probably played an important role in the decision to switch. Anyway, (the costs of) the (disturbing) intra-operative switches from the biodegradable to the titanium system are not compensated by the titanium plate removals. In fact, there were even more plate removals in the biodegradable group.

In the literature no data are available regarding the cost-effectiveness of biodegradable plates and screws in maxillofacial surgery. Therefore, our study definitely adds scientific information to the available evidence. Böstman *et al.* (1991) reported on the impact of the use of biodegradable fixation of fractures of the extremities [102]. They assumed that the hospital resources consumed and indirect costs in the form of lost earnings due to absence from work were identical for biodegradable and metallic osteosyntheses. They stated that the ultimate cost-benefit balance between the use of biodegradable and metallic implants is totally determined by the hardware removal rate. Our study showed that there was indeed a difference in indirect costs due to absence from work between the biodegradable and titanium group, and that plate removal surgery was only a small percentage of the total costs. Even if all patients would have had plate removal, these costs would not outweigh the costs of the primary surgery, hospital admission, the outpatient visits, and absence from work.

Many studies reported titanium and/or biodegradable plate removal in maxillofacial surgery [16,18-20,51,52,93-95]. None of these studies are RCTs, so no definite conclusion can be drawn.

There are a few RCTs that compared Inion to titanium plate removal. Bhatt *et al.* (2010) reported 0% biodegradable (Inion) versus 31% titanium (Synthes) plate removal in 40 patients treated for mandibular fractures [96]. These percentages are similar to the removal percentages for mandibular fractures in our study. Their follow-up period was only 8 weeks post-operative, while in our study most removals occurred after that period. Leonhardt *et al.* (2008) also compared Inion with the KLS Martin titanium system in the treatment of mandibular fractures [97]. They reported removal of clinically symptomatic plates in 5 of the 30 patients (16.6%) in the biodegradable group, and in 4 of the 30 patients (13.3%) in the titanium group in the first six post-operative months. In this study on occasion, unavailability of the required plating system obscured randomization. In our study there was no removal of clinically symptomatic plates/screws in patients treated for a mandibular fracture. As far as we know there is no RCT, including the current one, with a power analysis based on 'plate removal', so again no firm conclusion can be drawn. A post-hoc power analysis for our multicenter RCT was performed on the outcome variable plate removal. This showed that the power of the conclusion that there were more plate removals in the biodegradable group within the first 2 post-operative years was 96%.

With the exception of two removals on request in titanium fracture patients, all the other removals were due to clinical problems. When these two removals on request would not have been performed, the results would be even more positive for titanium.

Theoretically, for the patients that could not be contacted by telephone, it could be possible that a plate was removed in another hospital than where a patient was operated, but this is highly unlikely.

There were no significant differences in bone healing and plate removal percentages between the different types of surgical procedure. Therefore, the results of bone healing, plate removal and cost-effectiveness can be applied to all types of surgical procedure in the RCT.

The generalizability of the results of the bone healing performance of Inion CPS is limited

to the biodegradable systems of BioSorb FX and LactoSorb. These systems represent comparable mechanical characteristics [45,46]. With respect to the biocompatibility, *i.e.*, plate/screws removal, the generalizability of Inion CPS plates and screws is difficult as a result of the various co-polymer compositions, and different arrangement of the molecules, used to manufacture the different biodegradable plates and screws.

CONCLUSIONS

Considering the cost-effectiveness of the biodegradable plates and screws of Inion CPS compared to the titanium plates and screws of KLS Martin, the titanium system is preferable to the biodegradable system in the regular treatment spectrum of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies and bimaxillary osteotomies.

COMPARISON OF THE RELAPSE BETWEEN A BIODEGRADABLE AND A TITANIUM FIXATION SYSTEM FOLLOWING BSSO ADVANCEMENT: A COHORT STUDY BASED ON A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Background - Biodegradable fixation systems could reduce/delete the problems associated with titanium plate removal.

A multicenter RCT was performed in the Netherlands from December 2006-July 2009. Originally 230 trauma and orthognathic patients were included. The patients were randomly assigned to either a titanium control group (KLS Martin) or to a biodegradable test group (Inion CPS).

Aim - The aim of the present study was to compare the relapse of advancement bilateral sagittal split osteotomies (BSSO's) between a biodegradable system and a titanium system.

Materials & Methods - In the current study only patients of the original RCT of at least 18 years old who underwent a BSSO advancement osteotomy were included. Simultaneous Le Fort-I osteotomy or genioplasty were excluded. Point B and point Pg were chosen as most important relapse-indicating variable. Analysis of relapse was performed by digitally tracing lateral cephalograms.

Results - Relapse at point B and Pg in BSSO advancements was not statistically different between patients treated with biodegradable plates and screws and those treated with titanium plates and screws.

Conclusion & discussion - Given the comparable amount of relapse, the general usage of Inion CPS in the treatment of BSSO's needs not to be discouraged. On the basis of other properties a total picture of the clinical usage can be obtained: the bone healing performance (Chapter 2) [23], the intra-operative switches (Chapter 3) [90], the plate removal percentages (Chapter 4) [103], and the cost-effectiveness (Chapter 5).
Trial registration of original RCT: http://www.controlled-trials.com; ISRCTN 44212338.

Keywords: Inion, KLS Martin, long-term skeletal stability, treatment outcome, surgical fixation devices, oral surgery.

INTRODUCTION

Titanium osteosynthesis is regarded as the "the golden standard". Titanium is removed following bone healing in a second operation in 5-40% of the cases [16,19]. Biodegradable fixation systems have been developed in order to reduce or even delete the problems associated with titanium plate removal. Less removal operations implies less surgical discomfort for the patients. It may also benefit society, as less removal operations will put less pressure on the healthcare system capacity, and provides patients continuing contribution to the employment process. There is an ongoing search for the ideal fixation system.

The present study is part of a running research project. The 8 weeks post-operative results were described in detail elsewhere [23]. Briefly, short-term healing outcomes were similar between biodegradable and titanium fixation, although, in a significant proportion (25/117) of patients randomized to the biodegradable fixation system, the operating surgeons decided intra-operatively to switch to the titanium system, due to either technical complications such as non-grip of the screws or for other reasons. Details regarding these switches have been described elsewhere [90]. The aim of the present study was to establish the relapse of a biodegradable system as a potential alternative to titanium for fixation of advancement bilateral sagittal split osteotomies (BSSO).

MATERIALS & METHODS

Study design
This prospective cohort study is derived from a Randomized Controlled Trial (RCT) of Buijs *et al.* [23], and has been described according to the STROBE statement (http://www.strobe-statement.org/).

Study population
In the cohort study only patients of the original RCT who underwent a BSSO advancement osteotomy were included, and should be at least 18 years old. Patients who underwent simultaneous genioplasty or a Le Fort I-osteotomy were excluded.

In the original RCT 230 trauma and orthognathic patients were included. They were treated from December 2006 to July 2009 at four different departments of Oral and Maxillofacial Surgery in the Netherlands. The inclusion and exclusion criteria of the original RCT are summarized in Table 1. All patients provided written informed consent prior to enrollment and to publication of the work. Details regarding the randomization procedure were described elsewhere [23]. The study was approved by the Medical Ethical Committees of the participating hospitals.

Interventions
In the original RCT patients were assigned to a titanium control group (KLS Martin, Ge-

Table 1. *Inclusion and exclusion criteria of the original prospective multicenter RCT*

Inclusion criteria:

- patients scheduled for 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 parents or responsible persons if necessary) who signed the *informed consent* form.

Exclusion criteria:

- patients who were younger than 18 years old (trauma), or patients who were younger than 14 years (osteotomies);

- patients presented with heavily comminuted fractures of the facial skeleton;

- patients who experienced compromised bone healing in the past;

- patients who were pregnant;

- patients who could/would not participate in a 1-year follow-up (reasons);

- patients who would not agree with an *at random* assignment to one of the treatment groups, or one of the methods or treatment administered in the study;

- patients who were diagnosed with a psychiatric disorder (diagnosed by a psychiatrist);

- patients who experienced cleft lip and palate surgery in the past;

- patients where fracture reduction and fixation was delayed for more than 7 days (after day of trauma);

- patients of whom the general health and/or medication could affect bone healing, as determined by the oral and maxillofacial surgeon.

brüder Martin GmbH&Co., Tuttlingen, Germany) or to a biodegradable test group (Inion CPS, Inion Ltd., Tampere, Finland). The mandibular osteotomies were fixated with 2.5-mm biodegradable or 2.0-mm titanium plates and screws (Fig. 1). The patients did not receive rigid maxillomandibular fixation, but only soft guiding elastics post-operatively, and they were instructed to use a soft diet for five weeks. All patients underwent pre- and postsurgical orthodontic treatment. In all patients a surgical splint was used to achieve proper occlusion.

Outcome measures
The most important outcome variable in the current study was the 2 years post-operative relapse after treatment with biodegradable or titanium plates and screws. Relapse is the difference between certain cephalometric variables as measured at the final follow-up visit (T2) and directly post-operative (T1). According to Joss *et al.* (2009) point B and point Pg were chosen as most important relapse-indicating variables [104]. Analysis was

Figure 1. *Orthopantomogram showing the position of the plates and screws in a titanium BSSO case. Biodegradable plates and screws in 'biodegradable-cases' were placed in a similar manner, but would not be visible on the X-ray.*

performed by digitally tracing the lateral cephalograms. Extra analyses were performed to investigate if there was a difference in relapse between the biodegradable and titanium group in advancements (overjet reduction) ≤8mm and advancements >8mm. The cut-off point of 8mm was chosen according to Ferretti and Reyneke [24,105].

In addition, the relationship between the amount of relapse (mm) and other variables that possibly influenced this amount (predictor variables) was studied for point B and Pg. As possible predictor variables were included:

(1) demographic: female sex, age;

(2) amount of advancement: difference between the position of point B (or Pg) directly post-operative (T1) and at baseline (T0) (mm);

(3) mandibular length: distance between Articulare midpoint (Arm) and Menton (Me) at T0 (mm);

(4) body length: distance between Gonion (Go) and Menton (Me) at T0 (mm);

(5) mandibular plane angle: angle between the mandibular plane (Steiner) and SN-line at T0 (degrees).

The last cephalogram before surgery (titanium 84 days *vs.* biodegradable 90 days (mean)) was selected as T0, the second (T1) cephalogram was taken at the first post-operative outpatient visit (titanium 8 days *vs.* biodegradable 8 days (mean)), and the third one 2 years after surgery (T2) (titanium 27 months *vs.* biodegradable 25 months (mean)).

Cephalometric analysis
All digital lateral cephalograms were made using each participating hospital's own cepha-

lostat with the mandible in the most retruded position (centric relation) and the lips in a relaxed position. The "mirror position" was used in order to get a reproducible position of the head.

A predefined trace-protocol (Table 4; Appendix Table; Fig. 2) was designed [106] and all tracings were performed using Viewbox 3.1.1.6 (dHal software. Kifissia, Greece). Seventeen landmarks were identified on the lateral cephalograms. Vertical distances were measured in millimeters from the landmark perpendicular to SN; horizontal distances from the landmark perpendicular to SN-perp (line perpendicular to SN through S). As a first step, all cephalograms were converted to values of life size using the 'centimetre-indication' incorporated on each cephalogram. Next, for sagittal and vertical measurements, superimposition of the 3 cephalograms was performed on the anterior contour of the sella turcica and the line sella-nasion (SN) [107]. In order to further reduce the error of measurements, the coordinates of sella and nasion were, after superimposition, transferred from the baseline to the follow-up cephalograms in order to obtain exactly the same coordinates on all 3 cephalograms. To determine inter-observer reliability, all baseline cephalograms were traced by two different observers (NBvB and BDAB). Next, all cephalograms were traced by one observer (NBvB).

Statistical analysis

Inclusion of the 230 patients was based on power analysis using the primary outcome measure 'bone healing after 8 weeks', and was described in detail elsewhere [23]. The Statistical Package of Social Sciences (SPSS, version 20.0) was used to analyze the data. To assess inter-observer reliability of the tracings, the intra-class correlation coefficient (ICC) was calculated for each variable. ICCs <0.4 were considered poor, ICCs of 0.4 to 0.75 were considered fair to good, and those >0.75 were considered excellent [108].

For the continues cephalometric measures, 'between groups' effect sizes are reported as Cohen's *d*, based on the mean difference between the groups divided by the standard deviation of the control-group (titanium). Cohen's *d* effect sizes are interpreted as small (0.20), medium (0.50), or large (>0.80) [109]. Cohen's *d* was only calculated when analysis revealed a significant difference in relapse (or advancement) between both groups.

Inspection (eyeball) and the Kolmogorov-Smirnov tests revealed a normal distribution for all continuous data. Therefore, the means and standard deviations of the continuous variables were calculated, and analyzed using the independent-samples *t* test. Dichotomous variables were analyzed using the Chi-squared test.

To identify predictor variables for relapse, potential influencing factors were tested univariately in a linear regression analysis. To ensure broad inclusion of possible determinants, α was set at .15 for the univariate analyses. All significant variables were then submitted for multiple regression analysis. Female sex, as predictor variable for relapse, was tested using an independent-samples *t* test [110].

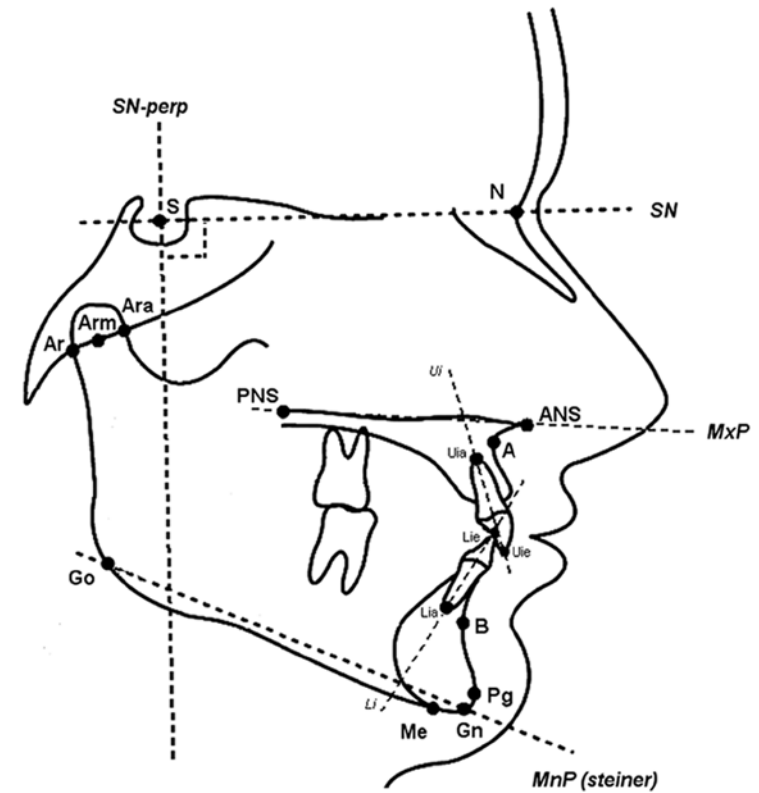Any *p* values less than .05 were considered statistically significant.

Figure 2. *Cephalometric landmarks and reference lines traced on lateral cephalograms*

The following 17 reference points were identified on lateral cephalograms: A (point A: the deepest midline concavity on the anterior maxilla), ans (anterior nasal spine: the tip of the median, sharp bony process of the maxilla at the lower margin of the anterior nasal opening), Ara (anterior articulare: the point of intersection of the inferior cranial base surface and the averaged anterior surfaces of the mandibular condyles), Arm (articulare midpoint: the midpoint of the line between Ara–Ar), Ar (articulare; the point of intersection of the inferior cranial base surface and the averaged posterior surfaces of the mandibular condyles), B (point B: the deepest midline concavity on the mandibular symphysis), Gn (gnathion: the most anteriorinferior point on the contour on the bony chin symphysis. determined by bisecting the angle formed by the mandibular plane and a line through pogonion and nasion), Go (gonion: the constructed point of the intersection of the ramus plane and the tangent to the body of the mandible), Lia (lower incisor apex), Lie (lower incisor edge: the incisal tip of the mandibular central incisor), Me (menton: the intersection of the bony inferior symphysis with the inferior margin of the mandibular body), N (nasion: the most anterior point on the frontonasal suture), Pg (pogonion: the most anterior point on the contour of the bony chin determined by a tangent through nasion), pns (posterior nasal spine: the intersection of a continuation of the anterior wall of the pterygopalatine fossa and the floor of the nose, marking the dorsal limit of the maxilla), S (sella; the midpoint of the pituitary fossa), Uia (upper incisor apex), Uie (upper incisor edge: the incisal tip of the maxillary central incisor).

The following six reference lines were identified on lateral cephalograms: Li (lower incisor line: the line through the lower incisor apex and the lower incisor incisal edge), MnP (mandibular plane according to Steiner: the line through gonion and gnathion), MxP (maxillary plane: the line through the posterior nasal spine (pns) and the anterior nasal spine (ans)), SN (sella-nasion line: the line through sella and nasion), SN-perp (SN-perpendicular: the line through Sella (S) perpendicular on line SN), Ui (upper incisor line: the line through the upper incisor apex and the upper incisor incisal edge).

Vertical distances were measured in millimeters from the landmark perpendicular to SN; horizontal distances were measured in millimeters from the landmark perpendicular to SN-perp.

Table 2. *Baseline characteristics*

Gender/age distribution	Titanium group (n)	Biodegradable group (n)	p value/Mean difference (95%CI)
Total group	**n=22**	**n=15**	
Male	6 (27%)	7 (47%)	
Female	16 (73%)	8 (53%)	p=0.30
Age (mean +/- s.d. in years)	35 +/- 11	35 +/- 12	-0.4* (-8.3 to 7.5)
(range in years)	19-59	18-59	p=0.91
Subgroups			
Advancement ≤8mm†	**n=20**	**n=15**	
Male	6 (30%)	7 (46.7%)	
Female	14 (70%)	8 (53.3%)	p=0.48
Age (mean +/- s.d. in years)	34 +/- 12	35 +/- 12	-0.5 (-8.8 to 7.7)
(range in years)	19-59	18-59	p=0.90
Advancement >8mm†	**n=2**	**n=0**	
Male	-	-	
Female	2 (100%)	-	-
Age (mean)	36	-	
(range in years)	20-41	-	-

*The minus sign indicates that the age in the biodegradable group is higher.
†The cut-off point of 8mm was chosen according to Ferretti and Reyneke (2002) [24]: advancements larger than 9 to 10 mm are considered particularly unstable (Will and West, 1989) [105], and an overjet reduction during surgery of 7mm is about the upper limit of the average advancement.

RESULTS

Patients

149 of the originally 230 randomized patients completed the 2 years post-operative follow-up [103]. Excluded from the relapse-analysis were fracture patients (n=6), Le Fort-I osteotomies (n=11), bimaxillary cases (n=34), genioplasty simultaneously (n=14), BSSO setbacks (n=6), age <18 years (n=5), lateral cephalograms not taken at all 3 time intervals (n=16), and lateral cephalograms of poor quality/not taken in centric relation (n=20). This resulted in a relapse-analysis of 15 patients in the biodegradable group, and 22 patients in the titanium group.

Baseline

Both age and sex did not significantly differ between the biodegradable and titanium group (Table 2).

Reliability

An "excellent" agreement between both examiners was found for all cephalometric variables (Table 3), except for ANB (angle), which demonstrated "fair to good" agreement [108].

Outcome measures

Relapse of biodegradable vs. titanium fixation

The horizontal relapse at point B for the biodegradable group was 0.03mm (s.d. 1.7mm), and 0.3mm (s.d. 2.3mm) for the titanium group (mean difference -0.3mm (95%CI -1.7 to 1.1); p=0.71) (Table 4). The vertical relapse at point B was 1.1mm (s.d. 1.5mm) for the biodegradable group, and 0.9mm (s.d. 1.6mm) for the titanium group (mean difference 0.2mm (95%CI -0.9 to 1.2); p=0.41).The horizontal relapse at point Pg for the biodegradable group was 0.1mm (s.d. 2.0mm), and 0.3mm (s.d. 2.6mm) for the titanium group (mean difference -0.2 (95%CI -1.8 to 1.4); p=0.45). The vertical relapse at point Pg for the biodegradable group was 1.7mm (s.d. 1.5mm), and 0.6mm (s.d. 1.7mm) for the titanium group (mean difference 1.1mm (95%CI <0.001 to 2.2); p=0.05).

There were no significant differences between both groups in relapse variables pertaining the base of the skull, the maxilla, the intermaxillary relationships, and facial height (Appendix Table).

Analyses of BSSO advancements ≤8mm showed no significant difference in relapse between patients treated with the biodegradable or the titanium system (Table 4). Analysis of advancements >8mm was not performed, because group sizes were too small.

Relapse predictor variables

The horizontal amount of advancement at point B was statistically associated with more horizontal relapse at point B in the univariate regression analysis (regression coefficient (B) -0.4 (95%CI -0.8 to -0.1); p=0.008). The same applies to the horizontal relapse at point Pg (B= -0.4 (95%CI -0.7 to -0.1; p=0.007)), the vertical relapse at point B (B= -0.3 (95%CI -0.5 to -0.1); p=0.002) and vertical relapse at point Pg (B= -0.5 (95%CI -0.7 to -0.2); p=0.001) (Table 5). Age, female sex, mandibular length, mandibular body length, and mandibular plane angle were not statistically associated with more horizontal and vertical relapse at point B and Pg.

"α was set at .15 for the univariate analyses" (see M&M). Therefore, a multiple linear regression analysis was performed for the horizontal relapse at point B for the combination of the predictor variables 'female sex' and 'horizontal advancement at point B'. In this analysis only the horizontal amount of advancement at point B was statistically associated with more horizontal relapse at point B (B= -0.4 (95%CI -0.7 to -0.1); p=0.03). The same is true for the horizontal (B= -0.4 (95%CI -0.7 to -0.05); p=0.03) amount of relapse at point Pg, i.e., only the amount of advancement was statistically associated with more relapse. In this regression analysis predictor variables were a combination of 'female sex' and 'horizontal advancement'.

Table 3. *Inter-observer reliability for tracings from all baseline cephalograms (n=37).*

Variable	ICC*	95% CI
Base of skull		
SN-length; distance between S and N (mm)	0.99	0.98 – 0.99
Maxilla		
Point A-hor; shortest distance from point A to line SN-perp through S (mm)	0.84	0.71 – 0.92
Point A-ver; shortest distance from point A to line SN (mm)	0.75	0.18 – 0.90
SNA (degrees)	0.85	0.73 – 0.92
Ui-MxP; angle between the upper incisor line and maxillary plane (degrees)	0.87	0.77 – 0.93
Maxillary length; distance between ans and pns	0.88	0.64 – 0.95
Mandible		
Point B-hor; shortest distance from point B to line SN-perp through S (mm)	0.95	0.90 – 0.97
Point B-ver; shortest distance from point B to line SN (mm)	0.98	0.94 – 0.99
Point Pg-hor; shortest distance from point Pg to line SN-perp through S (mm)	0.96	0.92 – 0.98
Point Pg-ver; shortest distance from point Pg to line SN (mm)	0.98	0.94 – 0.99
SNB (degrees)	0.96	0.91 – 0.98
Li-MnP; angle between the lower incisor line and mandibular plane (degrees)	0.84	0.32 – 0.94
MnP-SN; angle between the mandibular plane and SN-line (degrees)	0.97	0.95 – 0.99
'Bonwill'-SN; the angle between the line Arm-Li(tip) and the line S-N	0.94	0.88 – 0.97
Ramus length; distance between Arm and Go (mm)	0.94	0.89 – 0.97
Body length; distance between Go and Me (mm)	0.76	0.33 – 0.90
Mandibular length; distance between Arm and Me (mm)	0.95	0.82 – 0.98
Me-hor; shortest distance from Me to line SN-perp (mm)	0.93	0.87 – 0.96
Me-ver; shortest distance from Me to line SN (mm)	0.98	0.97 – 0.99
Arm-Go-Me; the angle between the lines Arm-Go and Go-Me (degrees)	0.90	0.68 – 0.96

Variable	ICC*	95% CI
Intermaxillary relationships		
ANB; angle between the lines NA and NB (degrees)	0.55	0.28 – 0.74
Ui-Li (interincisal angle); angle between the lines Ui and Li (degrees)	0.79	0.11 – 0.93
Overbite; lineair dimension measured from the most mesial point of the upper central incisor edge to the perpendicular projection on the buccal surface of the lower central incisor (mm)	0.88	0.63 – 0.95
Overjet; linear distance measured from the buccal surface of the lower central incisor edge to the projected point of the incisal edge of the upper central incisor (mm)	0.92	0.75 – 0.97
Facial height		
Lower anterior facial height; distance between MnP and MxP along line N-Me (mm)	0.98	0.95 – 0.99
Total anterior facial height; distance between N and Me (mm)	0.99	0.98 – 1.00
Lower posterior facial height; distance between MxP and Go along line S-Go (mm)	0.91	0.83 – 0.95
Total posterior facial height; distance between S and Go (mm)	0.97	0.93 – 0.98
Facial height ratio; ratio between the total posterior facial height and the total anterior facial height (percent)	0.92	0.55 – 0.97

*ICCs <0.4 were considered poor, ICCs of 0.4 to 0.75 were considered fair to good, and those >0.75 were considered excellent.
Abbreviations: ICC = Interclass Correlation Coefficient, 95% CI = 95% Confidence Interval.

Table 4. *Cephalometric variables point B and point Pg*

Variable	Titanium (n=22) Baseline* (T0)	Bio (n=15) Baseline* (T0)	Difference (95%CI) p value†	Titanium (n=22) Advancement* (T1-T0)	Bio (n=15) Advancement* (T1-T0)	Difference (95%CI) p value† [Cohen's *d*]	Titanium (n=22) Relapse* (T2-T1)	Bio (n=15) Relapse* (T2-T1)	Difference (95%CI) p value† [Cohen's *d*]
Total group									
Point B-hor; shortest distance from point B to line SN-perp through S (mm)	45.4 +/- 5.7	44.6 +/- 6.4	0.8 (-3.3 to 4.8) p=0.71	4.2 +/- 2.2	3.2 +/- 1.6	1.0 (-0.2 to 2.3) p=0.11	-0.3 +/- 2.3	-0.03 +/- 1.7	-0.3 (-1.7 to 1.1) p=0.71
Point B-ver; shortest distance from point B to line SN (mm)	88.7 +/- 7.6	93.0 +/- 8.5	-4.3 (-9.8 to 1.1) p=0.12	3.2 +/- 2.4	4.8 +/- 1.8	-1.6 (-3.1 to -0.2) p=0.03 [0.69]	-0.9 +/- 1.6	-1.1 +/- 1.5	0.2 (-0.9 to 1.2) p=0.41
Point Pg-hor; shortest distance from point Pg to line SN-perp through S (mm)	44.2 +/- 6.3	44.3 +/- 7.5	-0.1 (-4.7 to 4.5) p=0.97	4.1 +/- 2.6	2.3 +/- 2.2	1.8 (0.1 to 3.5) p=0.04 [0.68]	-0.3 +/- 2.6	-0.1 +/- 2.0	-0.2 (-1.8 to 1.4) p=0.45
Point Pg-ver; shortest distance from point Pg to line SN (mm)	105.3 +/- 8.4	109.2 +/- 7.8	-3.9 (-9.5 to 1.6) p=0.16	3.2 +/- 1.7	4.3 +/- 1.9	-1.1 (-2.3 to 0.1) p=0.07	-0.6 +/- 1.7	-1.7 +/- 1.5	1.1 (<0.001 to 2.2) p=0.05
Advancements ≤8mm‡									
Point B-hor; shortest distance from point B to line SN-perp through S (mm)	45.8 +/- 5.7	44.6 +/- 6.4	1.2 (-3.0 to 5.4) p=0.57	4.0 +/- 2.1	3.2 +/- 1.6	0.8 (-0.6 to 2.1) p=0.25	-0.3 +/- 2.4	-0.03 +/- 1.7	-0.3 (-1.8 to 1.2) p=0.69
Point B-ver; shortest distance from point B to line SN (mm)	89.0 +/- 7.9	93.0 +/- 8.5	-4.0 (-9.7 to 1.7) p=0.16	3.0 +/- 2.3	4.9 +/- 1.8	-1.9 (-3.3 to -0.4) p=0.02 [0.83]	-0.9 +/- 1.6	-1.1 +/- 1.5	0.2 (-0.6 to 1.5) p=0.43
Point Pg-hor; shortest distance from point Pg to line SN-perp through S (mm)	44.5 +/- 6.4	44.3 +/- 7.5	0.2 (-4.6 to 5.0) p=0.94	3.9 +/- 2.6	2.3 +/- 2.2	1.6 (-0.2 to 3.2) p=0.08	-0.3 +/- 2.7	-0.1 +/- 2.0	-0.2 (-1.9 to 1.5) p=0.81
Point Pg-ver; shortest distance from point Pg to line SN (mm)	105.5 +/- 8.8	109.2 +/- 7.8	-3.7 (-9.6 to 2.1) p=0.20	3.2 +/- 1.8	4.4 +/- 1.9	-1.2 (-2.4 to 0.1) p=0.07	-0.7 +/- 1.8	-1.7 +/- 1.5	1.0 (-0.1 to 2.2) p=0.07

Table 4. *Cephalometric variables point B and point Pg*

*Means +/- standard deviations. Negative values imply a backward movement in the horizontal plane or an upward movement in the vertical plane. Positive values imply a forward movement in the horizontal plane or a downward movement in the vertical plane.
†Inspection (eyeball) and the Kolmogorov-Smirnov tests revealed a normal distribution for all continuous data. Therefore, differences between the two groups were analyzed using the independent-samples *t* test. For differences in Advancement a regression to the mean analysis for Baseline was only performed when there was a significant difference between the groups in Baseline. For differences in Relapse between the groups a regression to the mean analysis for Baseline or for Advancement was only performed when there was a significant difference between the groups in Baseline or in Advancement, respectively. When both Baseline and Advancement were significantly different between the groups, then regression was only done for Advancement. Cohen's *d* was only given when *p*<0.05. Cohen's *d* effect sizes are interpreted as small (0.20), medium (0.50), or large (>0.80). Regarding differences between the groups: negative values imply bigger dimensions or a greater displacement during surgery in the biodegradable group, or more relapse in the titanium group (and vice versa). Regarding values within the groups: positive values imply an advancement, negative values imply a relapse.
‡Analysis of advancements >8mm was not performed, because there were only 2 patients in the titanium group with an advancement >8mm and no patients available in the biodegradable group with a lateral cephalogram of good quality/in centric relation.
Abbreviations: ICC = Interclass Correlation Coefficient, 95% CI = 95% Confidence Interval.

DISCUSSION

There were no significant differences in the amount of relapse at point B and Pg after a BSSO advancement between patients treated with biodegradable plates and screws of Inion CPS and titanium plates and screws of KLS Martin. This applied to the total group of patients, as well as for advancements ≤8mm. Analysis of advancements >8mm was not performed, because group sizes were too small.

We found that the amount of horizontal advancement at point B and point Pg, was a predictor variable for the amount of horizontal relapse at point B and point Pg, respectively. The same is true for the vertical dimensions of these two points. We could not identify age, female sex, mandibular length, mandibular body length, and mandibular plane angle as predictor variables for relapse.

Many authors use different reference lines to measure relapse: surrogate Frankfurter Horizontal (FH) plane [74,87,89,111], the FH plane [112,113] or the line SN [24,25]. This could explain differences between studies.

In a systematic review on stability after BSSO advancement, Joss and Vassalli (2009) identified only one eligible prospective controlled trial that compared biodegradable osteosynthesis with titanium [104]: Ferretti and Reyneke (2002) used the same reference line, *i.e.*, line SN, as we did. They used a different biodegradable material (Lactosorb), and used bicortical screws instead of a plate with monocortical screws as in our study. They reported no statistically significant difference in stability at point B (Lactosorb 0.83 +/- 1.25mm *vs.* titanium 0.25 +/- 1.38mm). This is within the same range as the relapse measured in our study, but the follow-up of Ferretti and Reyneke was only 1 year. They concluded that Lactosorb screws were a viable alternative to titanium screws for the fixation of BSSO advancements.

Ballon *et al.* (2012) compared 84 non-randomized orthognathic patients treated with plates and screws of Inion CPS or with titanium of Stryker-Leibinger [114]. They reported

Table 5. *Predictor variables for relapse*

Description	Relapse Point B-hor (n=37) Regression coefficient (B) (95%CI) p value	Relapse Point B-ver (n=37) Regression coefficient (B) (95%CI) p value	Relapse Point Pg-hor (n=37) Regression coefficient (B) (95%CI) p value	Relapse Point Pg-ver (n=37) Regression coefficient (B) (95%CI) p value
Age	0.03 (-0.03 to 0.1) p=0.27	-0.02 (-0.1 to 0.03) p=0.39	0.05 (-0.02 to 0.1) p=0.19	-0.03 (-0.1 to 0.03) p=0.31
Amount of advancement (difference between T1 and T0)				
Point B-hor	-0.4 (-0.8 to -0.1) p=0.008*	-	-	-
Point B-ver	-	-0.3 (-0.5 to -0.1) p=0.002	-	-
Point Pg-hor	-	-	-0.4 (-0.7 to -0.1) p=0.007†	-
Point Pg-ver	-	-	-	-0.5 (-0.7 to -0.2) p=0.001
Mandibular length (Arm-Me at T0)	0.03 (-0.1 to 0.1) p=0.53	-0.01 (-0.1 to 0.1) p=0.87	0.02 (-0.1 to 0.1) p=0.72	-0.002 (-0.1 to 0.1) p=0.97
Body length (Go-Me at T0)	0.01 (-0.1 to 0.1) p=0.94	-0.02 (-0.1 to 0.1) p=0.71	0.01 (-0.1 to 0.2) p=0.93	-0.03 (-0.1 to 0.1) p=0.58
Mandibular plane angle (MnP-SN)‡	-0.03 (-0.1 to 0.1) p=0.65	0.03 (-0.1 to 0.1) p=0.44	-0.04 (-0.2 to 0.1) p=0.58	0.07 (-0.03 to 0.2) p=0.15
Sex				
Female (n=24) mean +/- s.d.	-0.6 +/- 2.0	-0.9 +/- 1.2	-0.6 +/- 2.3	-0.9 +/- 1.3
Male (n=13) mean +/- s.d.	0.7 +/- 1.9	-1.2 +/-2.0	0.7 +/- 2.2	-1.3 +/- 2.3
Mean difference relapse (95%CI)	-1.3 (-2.7 to 0.5) p=0.06*	0.3 (-0.8 to 1.4) p=0.59	-1.3 (-2.9 to 0.3) p=0.10†	0.4 (-0.8 to 1.6) p=0.55

Table 5. *Predictor variables for relapse*

*"α was set at .15 for the univariate analyses" (see M&M). Therefore, a multiple linear regression analysis was performed for the horizontal relapse at point B for the combination of the predictor variables 'sex' and 'horizontal advancement at point B'. In this analysis only the horizontal amount of advancement at point B was statistically associated with more horizontal relapse at point B (B= -0.4 (95%CI -0.7 to -0.1); p=0.03).
†A multiple linear regression analysis was performed for the horizontal relapse at point Pg for the combination of the predictor variables 'sex' and 'horizontal advancement at point Pg'. In this analysis only the horizontal amount of advancement at point Pg was statistically associated with more horizontal relapse at point Pg (B= -0.4 (95%CI -0.7 to -0.05); p=0.03).
‡MnP is the mandibular plane according to Steiner: the line through gonion and gnathion.
Abbreviations: 95%CI = 95% Confidence Interval.

a similar amount of advancement for the BSSO advancement group as in our study. Horizontal (as well as vertical) relapse at point B for both groups was far more pronounced (Inion 3.65mm, titanium 2.09mm). They used a different reference line (surrogate FH) to measure relapse, the follow-up period for the titanium group was longer (mean follow-up 35 mos *vs.* 28 mos in our study), and in many cases bimaxillary surgery was performed.

Joss and Vassalli (2009) concluded that the amount of advancement was the factor with the strongest influence on relapse after BSSO advancement, *i.e.*, the larger the surgical advancement, the larger the relapse. Our study found this same relationship.

As far as we know the study of Ballon *et al.* is the only study on relapse after treatment with Inion CPS in BSSO advancements. On top of this, Joss and Vassalli (2009) stated that "to obtain reliable scientific evidence, further short-term and long-term research into BSSO advancement with rigid internal fixation should exclude additional surgery, *i.e.*, genioplasty or maxillary surgery, and include a prospective study or randomized clinical trial design". Therefore, our study definitely adds scientific evidence to the available literature. There is a certain degree of inaccuracy in defining cephalometric points on cephalograms in general. However, our inter-observer reliability results indicate that our method was accurate.

CONCLUSIONS

The 2 years post-operative relapse after BSSO advancement was not statistically different between patients treated with biodegradable plates and screws of Inion CPS or titanium plates and screws of KLS Martin.

Given the comparable amount of relapse, the general usage of Inion CPS in the treatment of BSSO's needs not to be discouraged. On the basis of other properties a total picture on the clinical usage can be obtained: the bone healing performance (Chapter 2) [23], the intra-operative switches (Chapter 3) [90], the plate removal percentages (Chapter 4) [103], and the cost-effectiveness (Chapter 5).

Conflict of interest

None.

Appendix Table. *Cephalometric variables of the skull base, maxilla, mandible, intermaxillary relationships, and facial height*

Variable	Titanium (n=22) Baseline* (T0)	Bio (n=15) Baseline* (T0)	Difference (95%CI) p value†	Titanium (n=22) Advancement* (T1-T0)	Bio (n=15) Advancement* (T1-T0)	Difference (95%CI) p value† [Cohen's d]	Titanium (n=22) Relapse* (T2-T1)	Bio (n=15) Relapse* (T2-T1)	Difference (95%CI) p value† [Cohen's d]
Total group									
Base of skull									
SN-length; distance between S and N (mm)	68.7 +/- 3.8	70.5 +/- 3.4	-1.8 (-4.4 to 0.6) p=0.14	Same as baseline§	Same as baseline§	Same as baseline§	Same as baseline§	Same as baseline§	Same as baseline§
Maxilla									
Point A-hor; shortest distance from point A to line SN-perp through S (mm)	61.2 +/- 4.8	61.9 +/- 3.6	-0.7 (-3.6 to 2.3) p=0.66	0.2 +/- 1.0	0.2 +/- 0.9	-0.04 (-0.7 to 0.6) p=0.91	-0.3 +/- 1.2	-0.3 +/- 0.8	-0.04 (-0.8 to 0.7) p=0.91
Point A-ver; shortest distance from point A to line SN (mm)	54.3 +/- 3.6	56.8 +/- 3.6	-2.5 (-4.9 to -0.01) p=0.049	0.4 +/- 0.6	-0.1 +/- 0.9	0.5 (-0.03 to 0.9) p=0.14	0.1 +/- 1.0	-0.03 +/- 1.0	0.2 (-0.5 to 0.8) p=0.66
SNA (degrees)	82.3 +/- 3.9	81.4 +/- 3.2	0.9 (-1.6 to 3.3) p=0.46	0.3 +/- 1.0	0.2 +/- 0.9	0.1 (-0.6 to 0.7) p=0.88	-0.4 +/- 1.2	-0.3 +/- 0.9	-0.1 (-0.8 to 0.7) p=0.87
Ui-MxP; angle between the upper incisor line and maxillary plane (degrees)	110.0 +/- 5.9	109.3 +/- 6.1	0.7 (-3.4 to 4.8) p=0.73	-0.7 +/- 2.3	-0.9 +/- 2.3	0.2 (-1.4 to 1.8) p=0.8	1.3 +/- 4.4	-0.6 +/- 3.8	1.9 (-0.9 to 4.8) p=0.17
Maxillary length; distance between ans and pns	54.3 +/- 3.7	54.3 +/- 3.0	0.05 (-2.3 to 2.4) p=0.97	0.2 +/- 0.9	0.3 +/- 1.0	-0.1 (-0.7 to 0.5) p=0.75	0.2 +/- 1.2	0.4 +/- 1.7	-0.2 (-1.2 to 0.9) p=0.70
Mandible									
SNB (degrees)	75.3 +/- 3.7	74.6 +/- 3.6	0.7 (-1.7 to 3.2) p=0.55	3.0 +/- 1.4	2.5 +/- 1.01	0.5 (-0.3 to 1.3) p=0.18	-0.3 +/- 1.3	-0.2 +/- 1.0	-0.1 (-1.0 to 0.7) p=0.72
Li-MnP; angle between the lower incisor line and mandibular plane (degrees)	102.5 +/- 7.5	101.4 +/- 6.7	1.1 (-3.7 to 6.0) p=0.64	-0.8 +/- 3.1	-1.4 +/- 4.3	0.6 (-1.8 to 3.1) p=0.61	-1.1 +/- 3.8	-2.4 +/- 2.9	1.3 (-1.0 to 3.8) p=0.25
MnP-SN; angle between the mandibular plane (Steiner) and SN-line (degrees)	31.0 +/- 5.8	32.3 +/- 7.6	-1.3 (-5.8 to 3.2) p=0.56	1.1 +/- 2.1	2.9 +/- 2.5	-1.8 (-3.4 to -0.3) p=0.02 [0.86]	0.5 +/- 2.3	0.4 +/- 1.7	0.1 (-1.3 to 1.5) p=0.65
'Bonwill'-SN; the angle between the line Arm-Li(tip) and the line S-N	34.9 +/- 3.2	35.4 +/- 4.2	-0.5 (-2.9 to 2.0) p=0.69	0.1 +/- 1.6	0.8 +/- 1.5	-0.7 (-1.8 to 0.3) p=0.18	-0.4 +/- 1.3	-0.9 +/- 1.1	0.5 (-0.3 to 1.3) p=0.23
Ramus length; distance between Arm and Go (mm)	49.4 +/- 6.0	50.0 +/- 5.2	-0.6 (-4.4 to 3.3) p=0.76	-0.2 +/- 1.9	-1.3 +/- 3.3	1.1 (-0.6 to 2.9) p=0.19	-1.8 +/- 2.9	-0.9 +/- 1.3	-0.9 (-2.6 to 0.7) p=0.24
Body length; distance between Go and Me (mm)	62.0 +/- 5.8	65.6 +/- 4.0	-3.6 (-7.1 to -0.1) p=0.042	5.0 +/- 2.5	3.4 +/- 3.6	1.6 (-0.4 to 3.7) p=0.37	0.8 +/- 2.6	-1.6 +/- 3.3	2.4 (0.5 to 4.4) p=0.046 [0.95]
Mandibular length; distance between Arm and Me (mm)	95.7 +/- 7.3	99.0 +/- 5.4	-3.3 (-7.8 to 1.1) p=0.14	5.5 +/- 1.9	4.4 +/- 1.8	1.1 (-0.2 to 2.4) p=0.08	-0.9 +/- 1.9	-1.6 +/- 2.6	0.7 (-0.8 to 2.2) p=0.36
Me-hor; shortest distance from Me to line SN-perp (mm)	34.3 +/- 6.5	34.9 +/- 8.1	-0.6 (-5.5 to 4.3) p=0.81	4.1 +/- 2.6	1.7 +/- 2.2	2.4 (0.7 to 4.1) p=0.006 [0.92]	-0.1 +/- 2.5	-0.8 +/- 2.5	0.7 (-1.1 to 2.3) p=0.08
Me-ver; shortest distance from Me to line SN (mm)	108.3 +/- 8.1	112.9 +/- 7.3	-4.6 (-9.9 to 0.7) p=0.09	3.6 +/- 1.4	3.8 +/- 1.7	-0.2 (-1.3 to 0.8) p=0.66	-1.0 +/- 1.4	-1.5 +/- 1.7	0.5 (-0.6 to 1.5) p=0.38
Arm-Go-Me; the angle between the lines Arm-Go and Go-Me (degrees)	118.2 +/- 6.3	117.6 +/- 7.2	0.6 (-4.0 to 5.1) p=0.8	2.5 +/- 4.2	4.8 +/- 2.7	-2.3 (-4.8 to 0.2) p=0.07	-0.6 +/- 3.5	1.5 +/- 3.5	-2.1 (-4.4 to 0.3) p=0.09

Appendix Table. *Continued*

Variable	Titanium (n=22) Baseline* (T0)	Bio (n=15) Baseline* (T0)	Difference (95%CI) p value†	Titanium (n=22) Advancement* (T1-T0)	Bio (n=15) Advancement* (T1-T0)	Difference (95%CI) p value† [Cohen's d]	Titanium (n=22) Relapse* (T2-T1)	Bio (n=15) Relapse* (T2-T1)	Difference (95%CI) p value† [Cohen's d]
Intermaxillary relationships									
ANB; angle between the lines NA and NB (degrees)	7.0 +/- 2.0	6.9 +/- 1.5	0.1 (-1.1 to 1.4) p=0.84	-2.8 +/- 1.4	-2.3 +/- 1.4	-0.5 (-1.4 to 0.5) p=0.34	-0.03 +/- 1.4	-0.1 +/- 1.0	0.1 (-0.8 to 1.0) p=0.79
Ui-Li (interincisal angle); angle between the lines Ui and Li (degrees)	123.1 +/- 8.6	122.5 +/- 8.5	0.6 (-5.3 to 6.3) p=0.86	0.4 +/- 4.4	-0.7 +/- 5.3	1.1 (-2.1 to 4.3) p=0.5	-0.8 +/- 6.0	2.4 +/- 5.6	-3.3 (-7.1 to 0.8) p=0.12
Overbite; linear dimension measured from the most mesial point of the upper central incisor edge to the perpendicular projection on the buccal surface of the lower central incisor (mm)	2.2 +/- 2.1	2.5 +/- 1.9	-0.3 (-1.7 to 1.1) p=0.66	-1.6 +/- 2.2	-3.2 +/- 2.0	1.6 (0.1 to 3.0) p=0.03 [0.72]	0.9 +/- 1.6	2.0 +/- 1.6	-1.1 (-2.2 to -0.02) p=0.48
Overjet; linear distance measured from the buccal surface of the lower central incisor edge to the projected point of the incisal edge of the upper central incisor (mm)	7.2 +/- 2.4	7.1 +/- 1.8	0.1 (-1.4 to 1.6) p=0.9	-5.1 +/- 2.5	-5.3 +/- 1.7	0.2 (-1.3 to 1.7) p=0.78	1.0 +/- 1.4	0.6 +/- 1.2	0.4 (-0.5 to 1.3) p=0.35
Facial height									
Lower anterior facial height; distance between MnP and MxP along line N-Me (mm)	63.9 +/- 6.4	66.6 +/- 5.1	-2.7 (-6.7 to 1.3) p=0.18	2.7 +/- 1.6	3.4 +/- 1.9	-0.7 (-1.9 to 0.4) p=0.21	-1.0 +/- 1.4	-1.1 +/- 1.4	0.1 (-0.8 to 1.1) p=0.79
Total anterior facial height; distance between N and Me (mm)	113.8 +/- 8.3	118.6 +/- 8.9	-4.8 (-10.6 to 1.0) p=0.1	2.3 +/- 1.6	3.2 +/- 1.8	-0.9 (-2.0 to 0.3) p=0.13	-1.0 +/- 1.5	-1.1 +/- 1.4	0.1 (-0.8 to 1.1) p=0.79
Lower posterior facial height; distance between MxP and Go along line S-Go (mm)	35.4 +/- 5.1	34.3 +/- 5.3	1.1 (-2.4 to 4.6) p=0.52	-0.3 +/- 1.8	-1.4 +/- 3.6	1.1 (-1.0 to 3.3) p=0.28	-1.9 +/- 2.7	-1.2 +/- 1.9	-0.7 (-2.4 to 0.9) p=0.39
Total posterior facial height; distance between S and Go (mm)	76.8 +/- 7.3	78.9 +/- 5.8	-2.1 (-6.7 to 2.5) p=0.36	-0.3 +/- 1.9	-1.4 +/- 3.4	1.1 (-0.7 to 2.9) p=0.22	-1.7 +/- 2.7	-0.9 +/- 1.5	-0.8 (-2.4 to 0.7) p=0.29
Facial height ratio; ratio between the total posterior facial height and the total anterior facial height (percent)	67.6 +/- 5.2	66.7 +/- 5.5	0.9 (-2.7 to 4.5) p=0.63	-1.7 +/- 1.9	-2.9 +/- 2.9	1.2 (-0.4 to 2.8) p=0.14	-0.9 +/- 2.5	-0.2 +/- 1.6	-0.7 (-2.3 to 0.7) p=0.31

* and †See caption Table 4.
§The SN-length at baseline and follow-up were exactly the same, because the coordinates of Sella and Nasion were, after superimposition, transferred from the baseline to the follow-up cephalograms.

GENERAL DISCUSSION

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GENERAL DISCUSSION

Despite the supposed advantages of biodegradable osteofixation devices described in the General Introduction of this thesis, these devices did not replace the titanium systems, and are currently applied in only limited numbers. Lack of sufficiently powered, high quality and appropriately reported randomized controlled clinical trials was, and still is, the main reason.

In this thesis, a multicenter prospective randomized controlled clinical trial is described, which was performed in order to establish whether the biodegradable plates and screws of Inion CPS could be used safely and (cost)effectively to a large scale and fit into the current treatment protocols and guidelines in oral and maxillofacial (OMF) surgery. Clinical, cost-related, patient-related, and surgeon-related aspects were taken into account.

Summary of the principal findings
Bone healing showed comparable results in the biodegradable and the titanium group, in cases where it was possible to apply the biodegradable system. However, the handling characteristics (plate adaptation, drilling/tapping, and screw insertion) of the biodegradable system were inferior compared to the titanium system, which resulted in intra-operative switches to the titanium system in 21% of the cases. We could not identify predictor variables for intra-operative switching that may be helpful in deciding in advance whether to use biodegradable devices or not. There were significantly more plate removals in the biodegradable group within the first 2 post-operative years, and the risk of plate removal was 2.2 times higher compared to titanium. Furthermore, the biodegradable system was less cost-effective compared to the titanium system. The relapse in BSSO advancement osteotomies was not statistically different between patients treated with the biodegradable system and those treated with the titanium system.

Discussion of the findings
The Intention-To-Treat (ITT) results show that the biodegradable system performed inferiorly compared to the titanium system regarding bone healing (Chapter 2). This was mainly due to the intra-operative switches that were 'recorded' as failures for bone healing in the ITT analysis. In other words, how can something be qualified a success, when it is not even possible to apply it? It would be too rigorous to conclude that the biodegradable system was not suitable for (and should be deleted entirely from) clinical use based on only these data. Therefore, we performed an additional (Treatment-Received (TR)) analysis. This analysis showed that in cases where it was possible to apply the biodegradable system, bone healing yielded a non-significant difference between both groups without the use of maxillomandibular fixation (MMF) post-operatively.

An important question to answer was "how do the costs of the intra-operative switches relate to the costs of the expected higher plate removal of titanium?" In the cost-effectiveness analysis, costs were linked to the clinical outcomes 'bone healing' and 'plate

removal' (Chapter 5). The results of the ITT analyses and TR analyses indicate that operations performed with titanium plates and screws had better health outcomes, *i.e.*, less plate removals and less inadequate bone healing. In the ITT analysis the mean total costs were higher in the biodegradable group, while in the TR analysis these costs were higher in the titanium group. This difference can be explained by the intra-operative switches, because these switches are the only difference between both analyses. In the ITT-analysis the switches were analyzed in the biodegradable group, while in the TR-analysis the switches were analyzed in the titanium group. Apparently the switches impose a greater burden on the healthcare system, in particular the costs due to 'absence from work'. The reason for this is not clear. It was concluded that the biodegradable system was less cost-effective compared to the titanium system, and that (the costs of) the (disturbing) intra-operative switches from the biodegradable to the titanium system are not compensated by the titanium plate removals. In fact, there were even more plate removals in the biodegradable group.

There were no significant differences in bone healing and plate removal percentages between the different types of surgical procedure. Therefore, the results of bone healing, plate removal and cost-effectiveness can be applied to all types of surgical procedure in the RCT. The 'intra-operative switches' were not contributing significantly to plate removal. Occlusion, VAS- and MFIQ-scores indicated that both groups had a similar good mandibular function and had comparable pain scores one and two years post-operatively. Different plate removal percentages have been described in the literature. It is difficult to draw firm conclusions, because most studies about plate removal are not RCTs, the studies often use different biodegradable materials for different indications, and the follow-up period varies between studies and is often no longer than 1 year. Moreover, as far as we know there is no RCT, including the multicenter RCT in this thesis, with a power analysis based on 'plate removal'. One should realize that inclusion of the 230 patients was based on a power analysis using the primary outcome measure 'bone healing 8 weeks after surgery'. A post-hoc power analysis was performed on the outcome variable 'plate removal'. This showed that the power of the conclusion that there were more plate removals in the biodegradable group within the first 2 post-operative years was 96%. The total sample size required to detect a difference of 5% less biodegradable plate removals would be 140 with 80% statistical power. To detect a difference of 5% less biodegradable plate removals with 90% statistical power would require a sample size of 180. Regarding the plate removal rates, the multicenter RCT was overpowered, whether an *a priori* power of 80% or an *a priori* power of 90% was chosen. However, the difference of plate removal between biodegradable (24%) and titanium (12%) (Chapter 4) can be considered as clinically relevant. Abscess formation was the main reason for plate removal in both groups. It is unclear what the reason was for the inflammatory reactions/abscess formations.

When there would have been significant more relapse in the titanium group, surgeons should have considered to accept the risk of intra-operative switching, patients should

have considered to accept the higher risk of plate removal, and society should have considered to accept the higher costs associated with operations performed with biodegradable plates and screws. However, the relapse in BSSO advancements was not statistically different between patients treated with the biodegradable system and those treated with titanium (Chapter 6). One should realize that a post-hoc power analysis showed that the power of the relapse study was (only) 7%. However, the small difference in relapse between both groups cannot be considered as clinically relevant. Analysis of the relapse of BSSO setback osteotomies, Le Fort-I osteotomies, and bimaxillary osteotomies was not performed because both groups had not enough patients to draw firm conclusions. Theoretically, it could be possible that there is less relapse in the biodegradable group for patients in these categories.

The inferior handling characteristics of the biodegradable system resulted in intra-operative switches to titanium in a relatively high number of cases. Unfortunately, after analyzing the reasons for the switches no firm conclusions could be drawn about possible predictor variables (Chapter 3). Surgeons are familiar with and have confidence in titanium systems. To gain comparable familiarity with and confidence in biodegradable systems would probably have taken more time to minimize cognitive bias. The limited test-surgeries and personal preferences/appreciation/dedication have probably played an important role in the decision to switch. This is a threat for implementation of new techniques, and therefore a potential source of bias. It seems quite difficult to minimize/eliminate all potential sources of bias, and to (correctly) describe them [115,116]. One should realize that most surgeons are reluctant to leave the comfort of a method of surgical fixation that works well and to start using a more complex new technique. When application of biodegradable plates and screws appeared to fail to obtain adequate fixation, there was always a good alternative (*i.e.*, fixation with the conventional titanium plates and screws). In some cases maybe another attempt could have been made to apply the biodegradable plates and screws before switching to titanium. It may well be that surgeons do not want to take the risk of failing again with the application of the biodegradable system, making it more complicated to achieve adequate fixation at all, even with titanium.

It is generally accepted that the strength and stiffness of different titanium plates and screws are comparable. This is also applicable for biocompatibility as is investigated in the study of Langford in 2002 [117]. In this way, it can be concluded that the titanium plates and screws of KLS Martin, which were used in the multicenter RCT, have a good generalizability for other titanium systems. Regarding the Inion CPS biodegradable system, the generalizability of the mechanical aspects is limited to the BioSorb FX and LactoSorb system. These systems represent comparable mechanical characteristics [45,46]. With respect to the biocompatibility, the generalizability of Inion CPS plates and screws is difficult as a result of the various co-polymer compositions, and different arrangement of the molecules, used to manufacture the different biodegradable plates and screws.

Regarding the generalizability for other medical fields that use biodegradable fixation systems, *i.e.*, orthopedic [26-29] or plastic (reconstructive) surgery [30-32], otolaryngol-ogy [33,34], cardiothoracic surgery [35-38], obstetrics and gynaecology [39,40], urology [41], neurosurgery [42] and craniofacial surgery [43,44]: in other parts of the human body different magnitudes of forces and differences in blood circulation are often present. Therefore, generalizability of Inion CPS for other medical fields is not readily applicable.

General conclusions and clinical implications

Considering the relatively high number of (and disturbing) intra-operative switches, the higher plate removal percentages, the less cost-effectiveness, and the comparable relapse 2 years post-operatively of the Inion CPS biodegradable plates and screws compared to the KLS Martin titanium plates and screws, there seems to be no place for Inion CPS in the regular treatment spectrum of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies and bimaxillary osteotomies. Given the results of our multicenter RCT titanium should remain the "golden standard" for the above mentioned surgical procedures.

Future perspectives

The time-consuming pre-tapping, screw insertion, and possible screw breakage can be avoided by using biodegradable tacks or the relatively new technique of ultrasonically welding the plate and screw together. The biodegradable tacks obviously do not have the disadvantage of pre-tapping, but require thicker bone. The application of ultrasonic welding is based on a biodegradable plate and mesh system, in combination with a new special configured pin system. The pin (that replaces the screw, known from other systems) is inserted by means of an ultrasonic handpiece. Due to the ultrasonic vibrations, the pin is welded into the corticospongeous microstructure of the bone and melts with the plate. The combination of plate-pin provides a more stable complex than can be accomplished by the combination of plate and screws [47]. The thermal stress caused by the ultrasound-aided pin insertion does not result in foreign body reactions or induced necrosis [118]. Disadvantages of this technique are (1) that it is based on the mechanically inferior ResorbX® system [45,46], and (2) there exists a patent on the technique of ultrasonic welding (SonicWeld *Rx*®). Therefore, it cannot be freely used with the mechanically superior other biodegradable systems. A strong(er), more user-friendly and more biocompatible biodegradable osteofixation material can perhaps be manufactured by using (a combination of) different techniques and/or a different combination of polymers.

Final remarks

Socioeconomic and psychological advantages of biodegradable fixation systems over titanium ones make it valuable to develop them. Considering the intrinsic properties of today's polymers, it is questionable whether biodegradable polymeric fixation systems will ever fully banish metallic fixation systems from the market [119].

CHAPTER 8

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SUMMARY

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Chapter 1 describes that maxillofacial traumatology and orthognathic surgery are major fields of contemporary oral and maxillofacial (OMF) surgery. The main goal is a predictable, fast, anatomical, safe and painless functional reunion of bone segments. Essential prerequisites to achieve primary bone healing of fractures and osteotomies are sufficient blood supply, anatomical reduction and internal rigid fixation. Titanium fixation systems, *i.e.*, plates and screws, are nowadays regarded as the "golden standard" for internal rigid fixation. Titanium fixation systems can be used safely and (cost)effectively. However, titanium has several disadvantages that result in a second intervention to remove the implants in 5-40% of the cases. Biodegradable fixation systems, degrading after healing time, could be an appropriate alternative to prevent this second intervention. This is desirable from the point of view of healthcare quality, *i.e.*, patient comfort and risk of complications, and associated socio-economic costs. It has been almost 50 years since the introduction of biodegradable devices. Despite the intended benefits of biodegradable osteofixation devices these systems have not replaced the titanium fixation systems, and are these days applied in only limited numbers. The major drawback for general use of biodegradable devices is the lack of clinical evidence for well defined indications. There is some evidence available from randomized controlled trials (RCTs) to support the conclusion that there is no significant difference between biodegradable and titanium osteofixation devices with regard to short-term clinical outcome, and complication rate in the area of orthognathic surgery. A definitive conclusion regarding the fixation of fractured and osteotomized bone segments with respect to the long-term performance in OMF surgery cannot be drawn. Another significant factor of the limited use of biodegradable fixation systems is the resistance by surgeons to modify their conventional, well experienced, treatment techniques. Improvements in intra-operative application, particularly in plate adaptation and screw insertion, are needed before their use becomes more widespread. Due to the limited use of biodegradable fixation systems, the costs of the plates and screws are higher compared to the costs of titanium plates and screws. This is a potential threat for the general use of biodegradable fixation systems. In order to become truly more cost-effective than titanium, the costs of the biodegradable fixation systems have to be reduced while clinical outcomes need to be superior.

It was the general aim of this thesis to establish (1) short-term effectiveness and safety, (2) long-term clinical performance, (3) cost-effectiveness, and (4) relapse of biodegradable plates and screws used for fixation of bone segments in the maxillofacial skeleton as an alternative to titanium plates and screws.

Chapter 2 comprises a multicenter RCT regarding the short term skeletal stability (bone healing 8 weeks after surgery) without maxillomandibular fixation (MMF) post-operatively, the handling characteristics, and safety of a biodegradable and a titanium fixation system in OMF surgery. The multicenter RCT was performed in the Netherlands from December 2006-July 2009. Included were 230 patients who underwent a bilateral sagittal split osteotomy (BSSO), a Le Fort-I osteotomy, or a bimaxillary osteotomy, and

those treated for fractures of the mandible, maxilla, or zygoma. The patients were randomly assigned to a biodegradable test-group (plates and screws of Inion CPS) or to a titanium control-group (plates and screws of KLS Martin). The randomization procedure resulted in an Intention-To-Treat (ITT) population of 113 patients in the titanium group and 117 patients in the biodegradable group. At 25 biodegradable-randomized patients ('switches') the OMF surgeon made the decision to switch to the titanium fixation system intra-operatively. In the ITT analysis these switches were 'scored' as failures for the primary outcome measure 'bone healing 8 weeks after surgery'. In other words, how can something be qualified a success, when it is not even possible to apply it? This resulted in an inferior bone healing performance of the biodegradable fixation system compared to the titanium fixation system. To conclude that the biodegradable fixation system was not appropriate for (and should be deleted entirely from) clinical use on the basis of these data alone, would be too rigorous. Therefore, an extra analysis (Treatment-Received (TR) analysis) was performed: when it was possible to apply the biodegradable fixation system, bone healing (without rigid MMF post-operatively) yielded a non-significant difference between both groups. In this analysis the 25 'switches' were added to and analyzed in the titanium group.

The handling characteristics (plate adaptation, drilling/tapping, and screw insertion) of the biodegradable fixation system were inferior compared to the titanium fixation system. Other secondary outcome measures, such as occlusion, pain, and plate removal, showed no significant differences between patients treated with the titanium or the biodegradable fixation system 8 weeks post-operatively.

Chapter 3 focuses on the reasons for the intra-operative switches in order to find predictor variables that may be helpful in deciding in advance whether to use biodegradable devices or not. The surgeons' opinion about the biodegradable fixation system, and if there was a learning curve in the application of the biodegradable fixation system were also investigated.

Inadequate primary stability was the main reason for switching. This can be material-related, or related to inexperience with or lack of confidence in the system, or impatience of the surgeon. However, after analysing the reasons for the switches no firm conclusions could be drawn about possible predictor variables. The user comfort of and confidence in the biodegradable fixation system were significantly less compared to the titanium fixation system. There was also established a subjective learning curve in the application-skills for the biodegradable fixation system, which could not be objectified with statistical analysis.

It was concluded that a learning curve and personal preferences probably played an important role in the decision to switch to the titanium fixation system. With more patience and experience it should be possible to increase user comfort and confidence in the biodegradable fixation system, thereby decreasing the number of intra-operative switches.

In **chapter 4** the 1 and 2 years post-operative clinical performance of the biodegradable fixation system as an alternative to the titanium fixation system regarding fixation of fractures and osteotomies in the maxillofacial skeleton was investigated. The analyses revealed that the biodegradable fixation system performed inferiorly to the titanium fixation system regarding plate removal (24.1% vs. 11.9%). The risk for removal when operated with biodegradable plates and screws was 2.2 times higher than the risk for removal when operated with titanium within the first 2 post-operative years. In the biodegradable group all plate removals and in the titanium group nearly all removals were due to clinical problems located in the mandible. Nevertheless, there was no significant difference in plate removal percentages between the different types of surgical procedure, *i.e.*, the types of surgical procedure as predictor variable for plate removal could not be identified. The plate removals were mainly due to abscess formation. It is unclear what the reason was for the abscess formations/inflammatory reactions. Occlusion, VAS- and MFIQ-scores showed that the patients in both groups had a good mandibular function and were (almost) free of pain 1 and 2 years post-operatively.

Chapter 5 comprises the cost-effectiveness of the biodegradable fixation system as an alternative to the titanium fixation system regarding treatment of fractures and osteotomies in the maxillofacial skeleton. In the cost-effectiveness analysis, costs were linked to the clinical outcomes bone healing and plate removal. The results of the ITT analyses and TR analyses indicate that operations performed with titanium plates and screws had better health outcomes, *i.e.*, less plate removals and less inadequate bone healing. In the ITT analyses the mean total costs were higher in the biodegradable group, while in the TR analyses these costs were higher in the titanium group. This difference can be explained by the intra-operative switches, because these switches are the only difference between both analyses.

It is remarkable that plate removal surgery was only a small percentage of the total costs. Even if all patients would have had plate removal, these costs would not outweigh the costs of the primary surgery, hospital admission, the outpatient visits, and absence from work.

It was concluded that the biodegradable system was less cost-effective compared to the titanium system, and that (the costs of) the titanium plate removals do not outweigh the (disturbing) intra-operative switching from the biodegradable to the titanium system. In fact, there were even more plate removals in the biodegradable group. There were no significant differences in bone healing and plate removal percentages between the different types of surgical procedure. Therefore, the results of bone healing, plate removal and cost-effectiveness can be applied to all types of surgical procedure in the RCT.

In **chapter 6** the 2 years post-operative relapse of BSSO advancement osteotomies after treatment with the biodegradable or the titanium fixation system is presented. Point B and point Pg (Chapter 6, Figure 2) were chosen as most important relapse-indicating vari-

ables after mandibular advancement surgery. Analysis was performed by digitally tracing the lateral cephalograms. In addition, the relationship between the amount of relapse and other variables that possibly influenced this amount (predictor variables) was studied. The relapse in BSSO advancement osteotomies was not statistically different between patients treated with biodegradable plates and screws and those treated with titanium plates and screws. We found that the amount of horizontal advancement at point B and point Pg, was a predictor variable for the amount of horizontal relapse at point B and point Pg, respectively, *i.e.*, the larger the surgical advancement, the larger the relapse. The same is valid for the vertical dimensions of these two points. Age, sex, mandibular length, mandibular body length, and mandibular plane angle could not be identified as predictor variables for relapse.

Analysis of BSSO setback osteotomies, Le Fort-I osteotomies, and bimaxillary osteotomies was not performed because there was a too small number of patients in both groups to draw firm conclusions.

The main research outcomes are presented and discussed, and general conclusions are drawn in **chapter 7**. Considering the frequent (disturbing) intra-operative switches, the higher plate removal percentages, the less cost-effectiveness, and the comparable relapse 2 years post-operatively of the biodegradable plates and screws of Inion CPS compared to the titanium plates and screws of KLS Martin, there seems to be no place for the biodegradable plates and screws of Inion CPS in the regular treatment spectrum of mandibular, Le Fort-I, and zygomatic fractures, and BSSO's, Le Fort-I osteotomies and bimaxillary osteotomies. Given the results of our multicenter RCT titanium should remain the "golden standard" for the above mentioned surgical procedures.

DUTCH SUMMARY

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In hoofdstuk 1 wordt beschreven dat maxillofaciale traumatologie en orthognatische chirurgie belangrijke deelgebieden zijn binnen de Mondziekten, Kaak- en Aangezicht-schirurgie (MKA-chirurgie). Het hoofddoel is een voorspelbare, snelle, anatomisch cor-recte, veilige en functioneel pijnloze hereniging van botsegmenten. Essentiële voorwaar-den voor primaire botheling van fracturen en osteotomieën zijn voldoende bloedtoevoer, anatomische reductie en interne rigide fixatie. Titanium fixatie systemen, dat wil zeggen platen en schroeven, worden op dit moment beschouwd als de "gouden standaard" voor interne rigide fixatie. Titanium is gemakkelijk, veilig en kosteneffectief in het gebruik. Ech-ter, titanium heeft enkele nadelen die in 5-40% van de gevallen leiden tot een tweede operatie om het materiaal te verwijderen. Biodegradeerbare fixatie systemen, die oplos-sen nadat botheling heeft plaatsgevonden, zouden een geschikt alternatief kunnen zijn om deze tweede operatie te voorkomen. Dit is wenselijk vanuit het oogpunt van kwaliteit van de gezondheidszorg, dat wil zeggen patiëntencomfort en risico op complicaties, als-mede bijbehorende socio-economische kosten. Bijna 50 jaar geleden vond de introductie van de eerste biodegradeerbare fixatie systemen plaats. Ondanks de beoogde voordelen van biodegradeerbare fixatie systemen hebben deze systemen de titanium fixatie syste-men tot op heden niet vervangen, en worden ze slechts in beperkte mate toegepast. Het grootste bezwaar voor een brede toepassing van biodegradeerbare fixatie systemen is het gebrek aan wetenschappelijk bewijs voor welomschreven indicaties. Er is enig bewijs beschikbaar uit gerandomiseerde gecontroleerde studies (RCTs) dat de conclusie dat er geen significant verschil is tussen biodegradeerbare fixatie systemen en titanium fixatie systemen met betrekking tot de effectiviteit en veiligheid op het gebied van de orthogna-tische chirurgie op de korte termijn ondersteunt. Een definitieve conclusie over de fixatie van gefractureerde en geosteotomeerde botsegmenten met betrekking tot de prestaties op de lange termijn kan binnen de MKA-chirurgie niet worden getrokken. Een andere belangrijke factor voor het beperkte gebruik van biodegradeerbare fixatie systemen is de weerstand van chirurgen om hun conventionele behandelingstechnieken, waar zij veel ervaring mee hebben, te modificeren. Verbeteringen in de peroperatieve applicatie, van met name de plaatadaptatie en het aanbrengen van de schroeven, zijn nodig om groot-schalig gebruik te bewerkstelligen. Tevens is het zo dat door het gelimiteerde gebruik van biodegradeerbare platen en schroeven, de kosten hiervan hoger zijn dan de kosten van titanium platen en schroeven. Dit is een potentiële bedreiging voor een meer alge-meen gebruik van biodegradeerbare fixatie systemen. Om echt volledig kosteneffectiever dan titanium te worden, dienen de kosten van biodegradeerbare fixatie systemen te worden verminderd en dienen de klinische uitkomsten superieur te zijn.
Het doel van dit promotieonderzoek was om (1) de korte termijn effectiviteit en veilig-heid, (2) de klinische prestaties op de lange termijn, (3) de kosteneffectiviteit, en (4) de relapse van biodegradeerbare platen en schroeven vast te stellen bij het fixeren van bot-segmenten in het maxillofaciale skelet als alternatief voor titanium platen en schroeven.

Hoofdstuk 2 omvat een multicenter RCT met betrekking tot de korte termijn skeletale

stabiliteit (botheling 8 weken postoperatief) zonder postoperatieve intermaxillaire fixatie (IMF), de hanteerbaarheid en de veiligheid van een biodegradeerbaar fixatie systeem en een titanium fixatie systeem in de MKA-chirurgie. De multicenter RCT werd uitgevoerd in Nederland van december 2006 tot juli 2009. Geïncludeerd werden 230 patiënten die een bilaterale sagittale splijtingsosteotomie (BSSO), een Le Fort I-osteotomie of een bimaxil-laire osteotomie ondergingen en patiënten die behandeld werden voor een fractuur van de mandibula, maxilla of zygoma. De patiënten werden willekeurig toegewezen naar een behandeling met biodegradeerbare platen en schroeven van Inion CPS of naar een behan-deling met titanium platen en schroeven van KLS Martin. De randomisatieprocedure resul-teerde in een Intention-To-Treat (ITT) populatie van 113 patiënten in de titanium groep en 117 patiënten in de biodegradeerbare groep. Bij 25 biodegradeerbaar-gerandomiseerde patiënten ('switches') werd door de MKA-chirurg tijdens de operatie besloten om te 'swit-chen' naar het titanium fixatie systeem. Deze switches werden in de ITT analyse gescoord als 'failures' voor de primaire uitkomst 'botheling 8 weken postoperatief'. Immers, hoe kan iets gescoord worden als 'een succes', wanneer het niet eens lukt om het aan te brengen? Dit resulteerde in een inferieure botheling van het biodegradeerbare fixatie systeem ver-geleken met het titanium fixatie systeem. Om op basis van alleen die gegevens te conclu-deren dat het biodegradeerbare fixatie systeem niet geschikt is voor het klinische gebruik (en volledig geschrapt zou moeten worden uit de kliniek) is te rigoureus. Om die reden werd een extra analyse verricht, de zogenaamde Treatment-Received (TR) analyse. Deze analyse liet zien dat wanneer het tijdens de operatie gelukte om het biodegradeerbare fixatie systeem aan te brengen de botheling (zonder postoperatieve IMF) tussen beide be-handelgroepen niet significant verschillend was. In deze analyse werden de 25 'switches' toegevoegd aan en geanalyseerd in de titanium groep.
De hanteerbaarheid (plaatadaptatie, boren/tappen en schroefinsertie) van het biodegra-deerbare fixatie systeem was inferieur vergeleken met de hanteerbaarheid van het titanium fixatie systeem. Andere secundaire uitkomstmaten, zoals occlusie, pijn en plaatverwijde-ring waren 8 weken postoperatief niet significant verschillend tussen patiënten die behan-deld werden met het titanium fixatie systeem of met het biodegradeerbare fixatie systeem.

Hoofdstuk 3 richt zich op de redenen van de peroperatieve switches en beoogt variabe-len te identificeren die een hoger risico hebben op een switch (voorspellende variabelen), zodat je op voorhand zou kunnen bepalen of het biodegradeerbare fixatie systeem wel of niet gebruikt zou moeten worden. Tevens wordt in dit hoofdstuk de mening van de MKA-chirurg geëvalueerd en onderzocht of er een leercurve was in de applicatie van het biodegradeerbare fixatie systeem.
Onvoldoende primaire stabiliteit was de belangrijkste reden om te switchen. Dit kan ma-teriaal gerelateerd zijn, gerelateerd zijn aan onervarenheid, gebrek aan vertrouwen of on-geduld van de MKA-chirurg. Helaas konden na analyse van de switches geen harde con-clusies worden getrokken over mogelijke voorspellende variabelen. Het gebruikscomfort van en het vertrouwen in het biodegradeerbare fixatie systeem waren significant minder

in vergelijking met het titanium fixatie systeem. Tevens was er een subjectieve leercurve in de applicatie van het biodegradeerbare fixatie systeem, die niet geobjectiveerd kon worden door middel van statistische analyse.

Geconcludeerd werd dat een leercurve en persoonlijke voorkeuren waarschijnlijk een belangrijke rol hebben gespeeld bij de beslissing om peroperatief te switchen naar het titanium fixatie systeem. Met meer geduld en ervaring zou het mogelijk moeten zijn om het gebruikerscomfort van en het vertrouwen in het biodegradeerbare fixatie systeem te vergroten, waardoor het aantal peroperatieve switches zal kunnen afnemen.

Geëvalueerd in hoofdstuk 4 worden de 1 en 2 jaars postoperatieve klinische prestaties van het biodegradeerbare fixatie systeem als alternatief voor het titanium fixatie systeem voor behandeling van fracturen en osteotomieën in het maxillofaciale skelet. De analyse liet zien dat het biodegradeerbare fixatie systeem inferieur was vergeleken met het titanium fixatie systeem voor wat betreft plaatverwijdering (24.1% vs. 11.9%). Het risico op plaatverwijdering in de eerste 2 jaar postoperatief voor patiënten die geopereerd werden met het biodegradeerbare fixatie systeem was 2.2 keer zo hoog als het risico op plaatverwijdering voor patiënten die geopereerd werden met titanium. In de biodegradeerbare groep waren alle plaatverwijderingen en in de titanium groep waren bijna alle plaatverwijderingen het gevolg van klinische problemen in de mandibula. Toch was er geen significant verschil in plaatverwijderingspercentages tussen de verschillende soorten chirurgische procedures. Of anders gezegd, er kon geen operatietype worden geïdentificeerd waarbij het risico op plaatverwijdering verhoogd was.

De plaatverwijderingen werden hoofdzakelijk veroorzaakt door abcesformatie. Het is niet duidelijk wat de reden was voor deze abcesformaties/ontstekingsreacties. Occlusie, VAS- en MFIQ-scores lieten zien dat patiënten in beide groepen een goede mandibulaire functie hadden en (vrijwel geheel) pijnvrij waren 1 en 2 jaar postoperatief.

Hoofdstuk 5 omvat de kosteneffectiviteit van het biodegradeerbare fixatie systeem als alternatief voor het titanium fixatie systeem voor de behandeling van fracturen en osteotomieën in het aangezicht. In de kosteneffectiviteitsanalyse werden de kosten gekoppeld aan de klinische uitkomstmaten botheling en plaatverwijdering. Uit de resultaten van de ITT analyse en de TR analyse bleek dat operaties uitgevoerd met de titanium platen en schroeven betere uitkomsten hadden, dat wil zeggen minder plaatverwijderingen en minder inadequate bothelingen. In de ITT analyse waren de gemiddelde totale kosten hoger in de biodegradeerbare groep, terwijl in de TR analyse de kosten in de titanium groep hoger waren. Dit verschil kan verklaard worden door de peroperatieve switches, aangezien deze switches het enige verschil zijn tussen beide analyses.

Het is opvallend dat de kosten van de plaatverwijderingen slechts een klein percentage van de totale kosten uitmaakten. Zelfs al zouden bij alle patiënten de platen verwijderd zijn, dan nog zouden de kosten van deze plaatverwijderingen niet opwegen tegen de kosten van de primaire operatie, de kosten van de ziekenhuisopname, de kosten van de poli-

klinische bezoeken en de gederfde inkomsten ten gevolge van afwezigheid op het werk. Geconcludeerd werd dat het biodegradeerbare fixatie systeem minder kosteneffectief was vergeleken met het titanium fixatie systeem, en dat (de kosten van) de titanium plaatverwijderingen niet opwogen tegen de (storende) peroperatieve switches van het biodegradeerbare fixatie systeem naar het titanium fixatie systeem. Er waren zelfs meer plaatverwijderingen in de biodegradeerbare groep. Er waren geen significante verschillen tussen de verschillende typen operaties voor wat betreft botheling en plaatverwijdering. De resultaten van botheling, plaatverwijdering en kosteneffectiviteit kunnen dus toegepast worden op alle typen operaties die in deze RCT werden geïncludeerd.

In hoofdstuk 6 wordt de 2 jaar postoperatieve relapse van BSSO advancement osteotomieën gepresenteerd na behandeling met het biodegradeerbare fixatie systeem of met het titanium fixatie systeem. Punt B en punt Pg (Hoofdstuk 6, Figuur 2) werden gekozen als belangrijkste relapse-aangevende variabelen. Analyse werd uitgevoerd door de laterale cefalogrammen digitaal te tracen. Verder werd bestudeerd of de mate van relapse beïnvloed wordt door bepaalde andere variabelen (voorspellende variabelen).

De relapse van BSSO advancement osteotomieën was niet statistisch significant verschillend tussen patiënten die behandeld werden met het biodegradeerbare fixatie systeem en patiënten die behandeld werden met het titanium fixatie systeem. De mate van horizontale verplaatsing van punt B en punt Pg tijdens de operatie bleek een voorspellende variabele voor de mate van relapse van deze punten, namelijk hoe groter de chirurgische verplaatsing, des te groter de relapse. Hetzelfde gold voor de verticale dimensies van deze twee punten. De variabelen leeftijd, geslacht, grootte van de mandibula, grootte van de mandibular body en de zogenaamde mandibular plane angle (horizontale groeiers vs. verticale groeiers) konden niet geïdentificeerd worden als relapse-voorspellende variabelen in deze studie.

Analyse van de BSSO setback osteotomieën, Le Fort I-osteotomieën en bimaxillaire osteotomieën werd niet uitgevoerd, omdat er te weinig patiënten in beide groepen waren om harde conclusies te trekken.

De belangrijkste onderzoeksresultaten worden gepresenteerd en bediscussieerd, en algemene conclusies worden getrokken in hoofdstuk 7. Met inachtneming van de frequent optredende peroperatieve switches (en het storende karakter hiervan), de hogere plaatverwijderingspercentages, de mindere kosteneffectiviteit, en de vergelijkbare relapse 2 jaar postoperatief van de biodegradeerbare platen en schroeven van Inion CPS vergeleken met de titanium platen en schroeven van KLS Martin, lijkt er geen plaats te bestaan voor de biodegradeerbare platen en schroeven van Inion CPS in het reguliere behandelspectrum van mandibula, Le Fort-I en zygoma fracturen en van BSSO's, Le Fort I-osteotomieën en bimaxillaire osteotomieën. Gezien de resultaten van de multicenter RCT uitgevoerd in dit proefschrift dient titanium de "gouden standaard" te blijven voor de behandeling van de bovenbeschreven chirurgische procedures.

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⊕

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Curriculum Vitae

Nico van Bakelen was born on October 3rd 1979 in Nijmegen, the Netherlands. He graduated secondary school from the 'Maartens College' in Groningen, and enrolled into medical school at the University of Groningen. After obtaining his medical degree (MD) in 2006, he subsequently worked for 2 years at the department of Cardiothoracic Surgery of the University Medical Center Groningen (UMCG). Thereafter, he started his PhD research project at December 1st 2008 at the department of Oral and Maxillofacial (OMF) Surgery of the UMCG. Besides his PhD, he studied Dentistry from September 2009 to February 2013. At December 1st 2013 he became a resident in OMF Surgery in the UMCG. Nico is married to Martine van Bakelen-Knip, resident in Cardiothoracic Surgery in Oldenburg, Germany.