Multicenter Randomized Clinical Trial: Early Loading of Implants in Maxillary Bone

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ABSTRACT

Purpose: The aim of this study was to show prognostic equivalence between implant loading in the maxilla after 12 weeks versus 4 weeks.

Materials and Methods: One hundred four patients, from four centers in this open-labeled randomized multicenter prospective controlled clinical trial, were assigned to either 12 weeks or 4 weeks of unloaded healing. Two hundred sixty-nine implants (sand blasted large-grid, acid etched [SLA] surface, ≥4.1 mm diameter; ≥10 mm length) were inserted and evaluated during an individual 5-year follow-up. Primary outcome was implant success after 12 months; prognostic equivalence was characterized by a maximum difference of ±5% in implant failure rates.

Results: Implant-wise 1-year failure rates were estimated 3.1% (5/163 implants) in the 4 weeks group versus 3.6% (4/112 implants) in the 12 weeks group (95% confidence interval [CI] for the difference −3.2 – +4.2%); implant-wise evaluation demonstrated statistically significant prognostic equivalence of 4 and 12 weeks loading. Patient-wise 1-year failure rates were estimated 6.7% ($n = 4$ patients) in the 4 weeks group versus 5.1% ($n = 2$ patients) in the 12 weeks group (95% CI for the difference −9.6 – +6.5%). All implant failures occurred within the first 3 months of the individual observation period. Prior bone augmentation, underdimensioned drilling, bone quality, implant type, implant length, implant diameter, residual teeth, and fixing of the restoration did not reveal associations with the implant outcome: trial site, posterior jaw region, and splinting were associated with a higher failure rate. Resonance frequency analysis did not serve as a predictor of implant failures at the time of implant insertion.

Conclusion: Loading of standard SLA implants in the maxilla 4 weeks versus 12 weeks after insertion resulted in statistically equivalent failure patterns within a 1-year follow-up period; nevertheless, the observed patient-wise failure patterns of the interim analysis requires further understanding of patient-individual aspects of the early loading concept.

KEY WORDS: bone density, clinical study, early loading, maxilla, RCT, resonance frequency analysis

INTRODUCTION

Implant supported rehabilitations have well documented 5-year success rates of above 95%.[1] The original concepts supported an unloaded healing time of 3 months in the mandible and 6 months in the maxilla.[2] Other concepts started early to promote immediate loading of implants in the lower jaw.[3] The currently accepted definitions for implant loading distinguish between immediate loading

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Conflict of interests statement: Financial grants (study organization, study nurse, data management, and statistical evaluation) for this investigator initiated study were received from the International Team for Implantology (Code: ITI 173/2000).

DOI 10.1111/j.1708-8208.2011.00427.x

and immediate restoration within the first 72 hours compared with early loading within 3 months and conventional loading concepts (3–6 months).[4] Regarding immediate or early loading of implants in mandibular "high quality bone," a number of prospective clinical studies are found supporting this concept including two prospective, randomized studies indicating a survival rate for machined or rough implants of more than 97%.[5,6] In a classical multicenter study in the posterior region of the upper and lower jaw in 133 patients with a good bone quality (class I–III), a healing time of 6 weeks for implants with a blasted and etched surface is well documented, whereas in soft bone (class IV), a healing time of 12 weeks is recommended.[7] Similar results are found by other groups for early loading in the edentulous maxilla and posterior jaw area with survival rates >99%.[8] Other investigations with limited patient numbers document 6 weeks healing time for etched and blasted implants.[9–11] It should be kept in mind that most authors recommend a modified drilling protocol in the soft bone of the posterior maxilla to enhance primary stability.[12]

In superior bone quality of the lower jaw, 2 weeks versus 6 weeks healing time has been studied with good outcome results.[13] However, the authors report on spinning implants at the time of loading, which are left for an extended healing period of 12 weeks. For anodically oxidized implants in the maxilla, a study on single-tooth restorations compares early loading at 6 weeks with conventional loading, revealing no difference between the two groups.[14] Using implants with chemically modified surfaces in mandibular bone of partly edentate patients, promising results for 2 to 4 weeks healing time are reported in a prospective study.[15] Whereas in fully edentulous patients, using a different implant type, higher implant failure rate was reported after 2 weeks of unloaded healing.[16] A recent Cochrane Review[17] concluded that it is possible to successfully load dental implants immediately or early after their placement in selected patients. The role of primary implant stability (high value of insertion torque) is emphasized. It is also stated that not all clinicians may achieve optimal results, which gives the need for more well-designed randomized controlled trials.

The aim of this randomized multicenter study therefore was to investigate, whether a reduced healing time of 4 weeks in the cancellous bone of the maxilla results in similar implant success patterns as expectable for the conventional healing time of 12 weeks.

MATERIALS AND METHODS

Study Design and Protocol

The study was designed as a nonblinded multicenter prospective randomized trial testing for prognostic equivalence of an early (test group: 4 weeks) versus a standard (control group: 12 weeks) loading regimen within a parallel group comparison of 400 implant insertions. Four oral and maxillofacial surgery departments hosted at three university hospitals and one medical teaching hospital in Germany participated in the trial (Mainz, Erlangen, Stuttgart, and Muenster). The implants were considered as observational units with all implants standing at a distance of ≥3 mm. This investigator-initiated study was performed according to Good Clinical Practice (International Conference of Harmonisation-GCP) criteria and was financially granted by the International Team for Implantology, a nonprofit foundation. The trial protocol including its statistical analysis plan was agreed by all investigators prior to the study. The local ethical committees accepted the protocol. On-site monitoring was done by the financial sponsor (Mrs. Francoise Peters).

The study design intended the overall documentation of 400 implant insertions (see below for sample size considerations), where each trial participant was supplied with one to four implants, respectively. After surgery, an individual 5-year follow-up was intended to both estimate intermediate and long-term implant prognosis pattern.

Outcome Criteria

The primary outcome criterion was defined as an implant's 12 months success defined by "absence of mobility, persistent pain, parestesia, persistent inflammation or radiologic periimplant radiolucency."[1] Secondary outcome criteria were implant survival (in situ/removed) during an individual 5-year follow-up period as well as resonance frequency analysis (RFA).

Implant Insertion

The surgical procedures were performed according to the manufacturer's recommendations. Standard panoramic x-rays were used for planning the surgery. In case of either insufficient bone at time of implant insertion or visible lack of primary stability, the patient would not be eligible for randomization. In all centers, implant insertion was done in the operation theater under aseptic

conditions. In accordance to the guidelines for the specific implant, tapping was not recommended in D IV bone. All changes to the standard protocol during implant cavity preparation were documented (e.g., bone condensation). Implants used in this study were standard custom Straumann sand blasted large-grid, acid etched (SLA) implants (Straumann, Basel, Switzerland) with 4.1 mm or 4.8 mm diameter and a length of 10–14 mm. Bone quality was graded into the established categories D I – D IV.[18] At this time point, implants with visible lateral or rotational mobility (lack of primary stability) were excluded. The implants were allowed for either trans- or subgingival healing. Perioperative medication (antibiotic, disinfectant, and analgesics) were applied as necessary. A postoperative panoramic x-ray was mandatory.

Randomization

After the surgical procedure, during which visible primary stability as the last inclusion criterion was checked, a fax-based treatment allocation was communicated to the clinical investigator based on an external randomization list. For all trial sites, the randomization procedure and group allocation was performed by the Coordination Center for Clinical Trials at the University of Mainz, Germany. The randomization scheme stratified for trial sites and was generated by means of the software SAS® (release 10.0 for Windows®; SAS Institute Inc., Cary, NC, USA) to the centers according to a permutation algorithm. Test group was 4 weeks, control group was 12 weeks of unloaded healing. To adjust for possible protocol violations due to late loading in the test group, a patient-wise 60:40 randomization was done favoring the test group.

Change of Abutment/Start of Loading

The change of abutment and, where necessary, second-stage surgery was done after 4 weeks (28th–34th day) in the test group and after 12 weeks (84th–90th day) in the control group. At the time of abutment change, transversal mobility was tested by two opposing instruments and rotational mobility with a manual wrench to a torque of 15 Ncm. Pain profiles during change of abutment were documented. Peri-implant mucosa was rated as "fixed," "movable," and "moving"; bleeding was documented as well. Prosthetic loading either definitively or provisionally had to be started immediately or at maximum of 14 days after change of abutment; otherwise a formal protocol violation was ascertained for the respective patient's trial course (note that this trial is based on an equivalence design, which implies primarily concentration on the "per protocol" trial population and therefore crucially calls for formal consideration of "delayed 4 weeks" and "premature 12 weeks" loading). Finally, the type of restoration ("splinted/unsplinted") ("fixed/removable") was documented.

Follow-Up Visits

At 3 and 6 months as well as at 1, 2, 3, 4, and 5 years after abutment change respective follow-up visits were scheduled. The same criteria as mentioned above were tested allowing for the evaluation of long-term implant success. In addition, 1, 3, and 5 years after change of abutment a panoramic x-ray was obtained. The images were either primary digital or were digitalized using a scanner. Resonance frequency analysis was measured at time of implant insertion, change of abutment, and 6 months follow-up. For the follow-up visits, splinted and removable supraconstructions were unscrewed to test each implant individually.

Confirmatory Analysis and Sample Size Calculation

The primary clinical end point of this investigation was defined as implant success 12 months after insertion (see above); the trial intended to prove prognostic equivalence of the 4 weeks and the 12 weeks loading concepts in terms of this prognostic end point. Prognostic equivalence was characterized by a maximum difference of ±5% between the treatment groups' respective 1 year failure rates. Accordingly, the confirmatory analysis of the trial intended to compare the confidence interval of the failure rates' difference with a ±5% tolerability interval for the latter: according to the interval inclusion test method[19] prognostic equivalence at a 5% significance level would be established, if the estimated two-sided confidence interval for the failure rates' difference turned out completely covered by the assumed ±5% tolerance interval. The confidence interval for the failure rate difference was to be computed exactly based on binomial distribution estimates, which were derived by means of the statistics software SAS (release 10.0 for Windows).

For this purpose, the confirmatory analysis of the trial intended an implant-wise evaluation of patient failure times. Additional secondary analyses intended a "worst case" patient-wise evaluation by consideration of the smallest observed failure time among each patient's

implants as well as a multivariate implant-wise evaluation based on generalized estimation equations by taking account for the interdependence of several implants in one patient. In both settings, the primary analysis of the trial concentrated on the "per protocol" population at hand (see above) with respect to the underlying equivalence hypothesis of the investigation.

According to the binary nature of its primary end point, the sample size calculation assumed nonrelevant inferiority of the new therapy when the expected 12 months failure rate of 5% for the standard loading regime was not raised to more than 10% in the experimental 4 weeks loading sample. However, admitting and taking account for in fact rather imprecise a priori knowledge on the expectable failure rates, the trial was not designed in terms of a noninferiority investigation but rather in terms of a two-sided trial on therapeutic/prognostic equivalence. Assuming a two-sided tolerance of ±5% for the deviation between the actual 12 months failure rates as well as a statistical power of 80% and a significance level of 5% for the confidence interval inclusion test sketched out above, the overall investigation intended the documentation of at least 400 implant documentations per treatment group. Assuming an asymmetric drop out rate of 30% (due to possibly inevitably frequent protocol violations caused by delayed loading in patients, which were initially randomized onto the 4 weeks regime and by untimely loading in patients initially randomized onto the 12 weeks regime due to logistic circumstances), a total recruitment of twice 520 implant documentations was intended. Assuming a mean number of 1.25–1.30 implants per patient, this would have corresponded to a total sample size of twice 400 trial participants. During the planning phase of the trial, the sample size calculation was based on binomial simulations according to the suggestions by Newcombe[20] and recently confirmed by means of NQuery Advisor® (release 7.0; Statistical Solutions, Cork, Ireland).

Exploratory Analyses and Secondary End Point Evaluation

Data description was based on medians and quartiles for continuous end points, on absolute and appropriate relative frequencies for categorical end points and on Kaplan/Meier estimates for time-to-event data. Exploratory association analysis between secondary end points and the primary clinical end point "implant failure during 12 months after insertion" was based on exact Fisher tests for binary end points and on two sample Wilcoxon tests for continuous variates. Results of these exploratory analyses were summarized in terms of p values. Exploratory analyses were performed by means of SPSS® (release 15.0 for Windows®; SPSS Inc., Chicago, IL, USA).

Safety Monitoring

In terms of safety surveillance of the overall trial, regular data steering board meetings were implemented to become aware of unexpected failure occurrence pattern within or between the respective treatment samples. During one of this board meetings, the trial board decided to cancel further recruitment because of two observations: on the one hand, the actual absolute failure rates did not show the order as expected during the planning phase (it exceeds, the trial might undergo a severe loss in statistical power) and on the other hand, all observed implant failures occurred during a rather early period after change of abutment, so that the derivation of causal differences between the underlying loading regimes became reconsidered. In summary, the overall trial's patient recruitment ended in a total of 104 patients.

Patient Sample

The investigation's inclusion and exclusion criteria are shown in Table 1. After individual information on the trial's intentions and content, patients were required to give their informed consent prior to implant insertion. Between 03/2001 and 03/2003, a total of $n = 146$ patients were screened; 119 patients gave their informed consent and were enrolled into the study. The treatment allocation figures are summarized in Figure 1 in accordance to the Consolidated Standards of Reporting Trials criteria.[21,22] The 104 patients received a total of 269 implants, which were primary stable and therefore underwent randomized allocation. A total of 15 patients were not randomized, three of them because of having received a different implant type or size, two of them because of being subject to early loading,, and 10 of them because of withdrawal of their initially ascertained informed consent to the trial. No patient was excluded because of missing primary stability. In the early loading sample, a total of nine implants were not loaded within the maximum admissible time period (see above) and were therefore rated as conventionally loaded (but withdrawn from the per protocol population).

TABLE 1 Inclusion and Exclusion Criteria

Inclusion criteria:

- Written informed consent of the patient available
- Indication for a rehabilitation of at least one tooth by an implant
- Planned implant in the maxilla (either local or augmented bone)
- In case of augmentation: time from augmentation to implant insertion minimum of 3 months
- Sufficient horizontal and vertical bone quantity to insert a dental implant

Exclusion criteria

- Female subject who is pregnant or lactating at the time of any surgical procedures within the scope of this study
- Known addiction to drugs
- Known unavailability of subject for individual follow up visit(s)
- Psychiatric disease or disturbance altering the ability to give an informed consent
- No comedication that affects bone physiology (e.g., steroids, bisphosphonates)
- Decompensated general diseases altering the general medical status (e.g., diabetes without therapy)
- Visible intraoperative mobility of the implant (missing primary stability)

RESULTS

The treatment groups of 4 versus 12 weeks loading time did not differ concerning age or gender distribution: mean age was 48.6 years, 50 male and 54 female patients. The implant-wise 12 months failure rates were estimated 3.1% (5/163 implants) in the 4 weeks loading group versus 3.6% (4/112 implants) in the 12 weeks loading group (95% confidence interval for the failure rates' difference −3.2 – +4.2%). According to this interim analysis confidence interval test, the implant-wise evaluation demonstrated statistically significant prognostic equivalence of the 4 and 12 weeks loading concepts at the 5% significance level. All implants were lost prior to loading. The secondary patient-wise 1 year failure evaluation, however, estimated patient-wise failure rates of 6.7% ($n = 4$ patients) in the 4 weeks loading group versus 5.1% ($n = 2$ patients) in the 12 weeks loading group (95% confidence interval for the patient-wise failure rates' difference −9.6 – +6.5%); as a consequence, the patient-wise evaluation failed to demonstrate statistically significant prognostic equivalence of the respective loading concepts, but rather suggested a tendency toward prognostic inferiority of the earlier loading.

Table 2 lists important descriptive parameters of the control and test groups. There were two dominating recruitment centers (73 vs 93 implants containing 3 versus 6 1 year failures, respectively), whereas the other trial sites recruited at a moderate level (36 and 58 implants, no failures observed). Nevertheless, the failure rate increase (8%) observed in the second trial site could not be related to putatively asymmetric cofactor patterns among trial sites by multivariate evaluations due to the rather small effective sample size and absolute failure counts.

Table 2 also demonstrates a tendency for increased failure risk in the posterior versus to the anterior region (5% vs 1%). Prior augmentation procedures, drilling protocol, bone quality, implants type, implant diameter, and implant length as "surgical" process parameters did not show a statistically significant association with the 12 months implant outcome. Indication, splinting, and fixing of restoration were recorded as "prosthetic" parameters, with more implant failures losses being observed in the splinted group (see Table 2).

The nine failing implants did not differ from the successful ones concerning implant stability quotient (ISQ) values at implant insertion: median ISQ values at implant insertion were 55 for the 4 weeks loading group versus 55 for the 12 weeks loading group (Figure 2). Median intraindividual ISQ changes from insertion to clinical loading in successful implants were −1 after 4 weeks loading versus 0 after 12 weeks loading (Figure 3).

All observed implant failures contributed to implant losses (Table 3). There were no implants with persistent pain, inflammation, or radiolucency. Figure 4 displays the Kaplan/Meier survival estimates for the respective treatment groups for the 12 months period, which constituted the primary end point. The implant-wise survival rates did not differ significantly between the two loading samples (Logrank $p = .786$). In the further individual follow–up, no additional implant failures occurred.

DISCUSSION

The above implant success rates of 96% versus 97% range within the (implant-wise) findings of other investigators.[8,9,12–14,23–25] In accordance to a recent

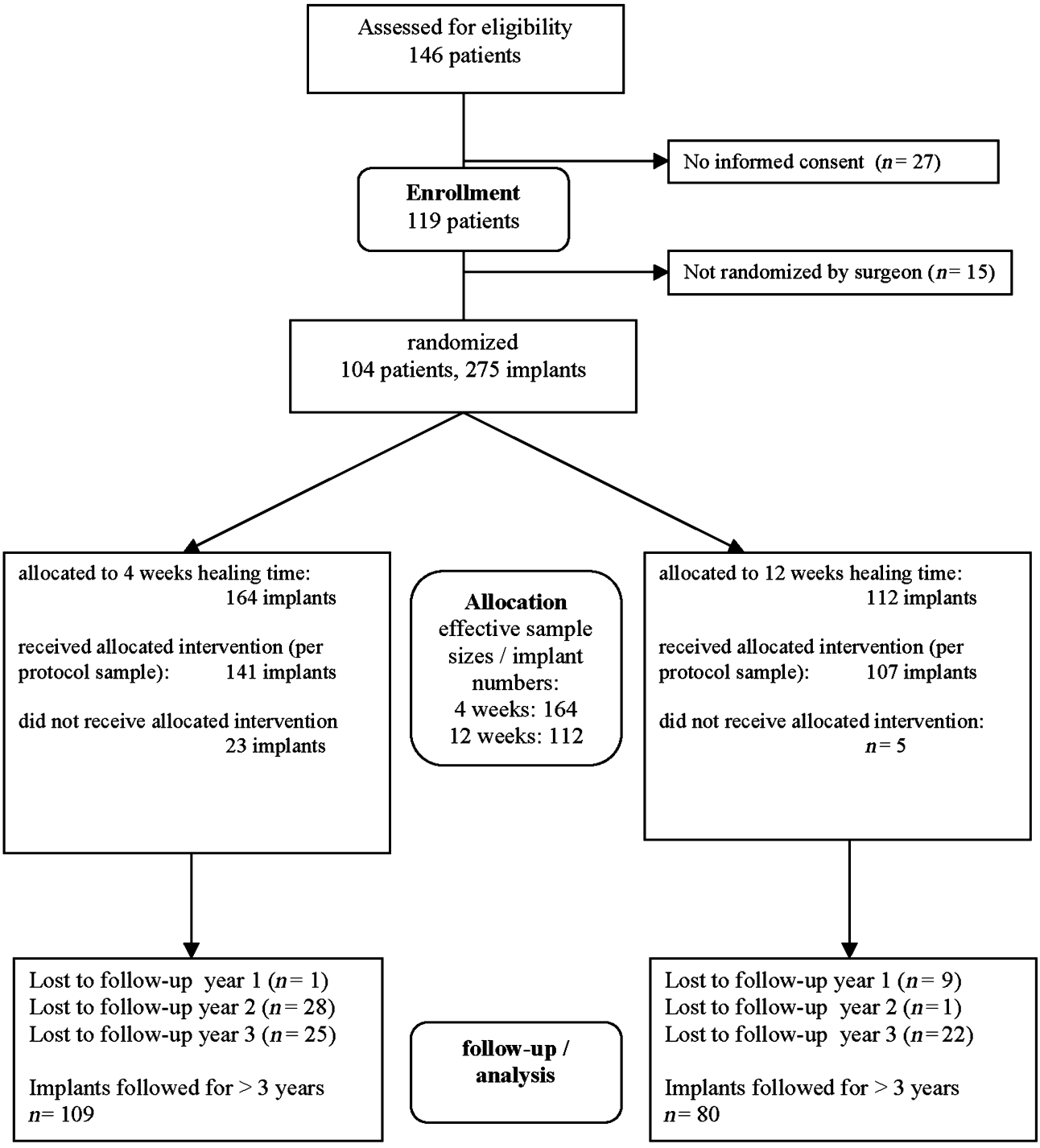

Figure 1 Patient screening, recruitment, and allocation chart according to the Consolidated Standards of Reporting Trials (CONSORT) criteria.

systematic review, most failures occurred within the first months of loading.[24] As a consequence, the investigation at hand comprises representative data by means of a GCP concordant trial implementation; its research hypothesis equivalent failure rates after 4 versus 12 weeks loading was confirmed.

Nevertheless, it must be mentioned that this initial research must be reconsidered from a rather critical point of view: although the presumed therapeutic/prognostic equivalence between earlier and later loading could be formally established based on 5 versus 4 1 year failures, this formally significant result becomes

TABLE 2 Absolute and Relative Frequencies for 12 Months Implant Success and Failure after Insertion of 269 Implants, Stratified for the Randomized Loading Time (4 versus 12 Weeks) and for Several Patient and Treatment Cofactors

		Total	Success	Failure
Treatment	4 weeks	163	158 [97%]	5 [3%]
(loading at:)	12 weeks	112	108 [96%]	4 [4%]
Trial site	1	92	89 [97%]	3 [3%]
	2	75	70 [92%]	6 [8%]
	3	49	49 [100%]	0
	4	58	58 [100%]	0
Region	Anterior	96	95 [99%]	1 [1%]
	Posterior	175	173 [95%]	8 [5%]
Augmentation	No	159	153 [96%]	6 [4%]
	Prior to implantation	112	104 [97%]	3 [3%]
Drilling	Normal drilling	200	193 [96%]	8 [4%]
	Underdimensioned	68	67 [99%]	1 [2%]
Bone quality	I	2	2 [100%]	0
	II	49	48 [98%]	1 [2%]
	III	203	195 [96%]	8 [4%]
	IV	13	13 [100%]	0
Implant type	Standard	211	202 [96%]	9 [4%]
	Plus	60	64 [100%]	0
Implant diameter	4.1	263	254 [97%]	9 [3%]
	4.8	14	12 [100%]	0
Implant length	8–10 mm	46	45 [98%]	1 [2%]
	>10 mm	229	221 [97%]	8 [4%]
Indication	Single tooth	39	37 [95%]	2 [5%]
	Partial edentulous	121	116 [96%]	5 [4%]
	Edentolous	112	113 [98%]	2 [2%]
Splinting*	Unsplinted	103	103 [100%]	0
	Splinted	138	131 [95%]	7 [5%]
Restoration	Fixed	156	151 [97%]	5 [3%]
	Removable	87	85 [98%]	2 [2%]

weakened in view of the patient-wise evaluation, which – according to the moderate sample size of 104 worst outcome implants in this analysis – suffers from a severe loss in power. Note that the patient-wise evaluation even indicates an inverse tendency in favor of the 12 weeks loading regime.

Methodological Aspects

The patient-wise analysis presented above suffers from a severe loss in statistical power of less than 10% due to the unplanned interim stopping of the overall trial. As a consequence, one cannot decide whether further recruitment and thereby gain in statistical power would have confirmed the tendency of the patient-wise evaluation or would rather have confirmed the equivalence statement of the initial implant-wise analysis. As a matter of fact, the recommendation for earlier loading must be handled with maximum care regarding the limitations of the underlying data as sketched out above.

A site/outcome interaction as found in this investigation was also observed by others and seems to be underestimated in the current discussion focusing on external evidence rather than internal evidence.[23] One aspect, which is center/surgeon dependent, is the frequency and extent of modifications to the drilling procedure. As known from ex vivo, in vivo, and as well from clinical trials, underdimensioned drilling enhances the

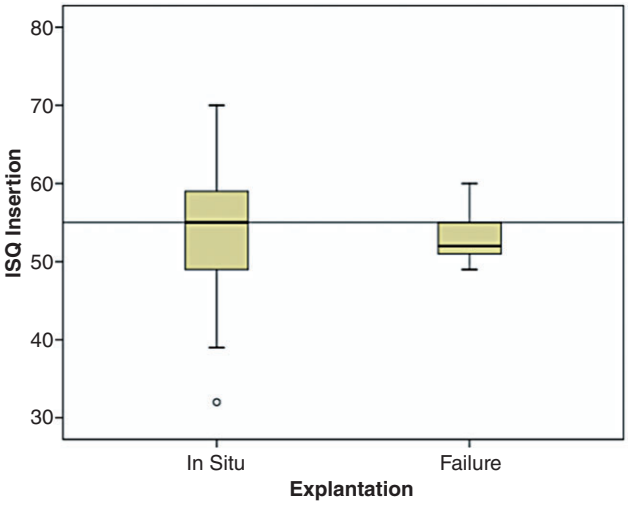

Figure 2 Box plot diagrams for the distribution of ISQ values among 269 implants at the time of insertion, stratified for the respective implants' one year success/failure status (horizontals indicate medians and quartiles, verticals indicate minimum and maximum observation values, and circles indicate statistical outliers and extreme values). ISQ = implant stability quotient.

primary stability and is used frequently.[12,26,27] On the other hand, excessive use of osteotomes seems to increase the risk for early implant failure.[26,28] In this study, underdimensioned drilling showed no significant influence on the success rate.

In accordance to other authors, critical bone quality or prior augmentation procedures do not seem to negatively affect the success rates in early loading procedures.[29–32]

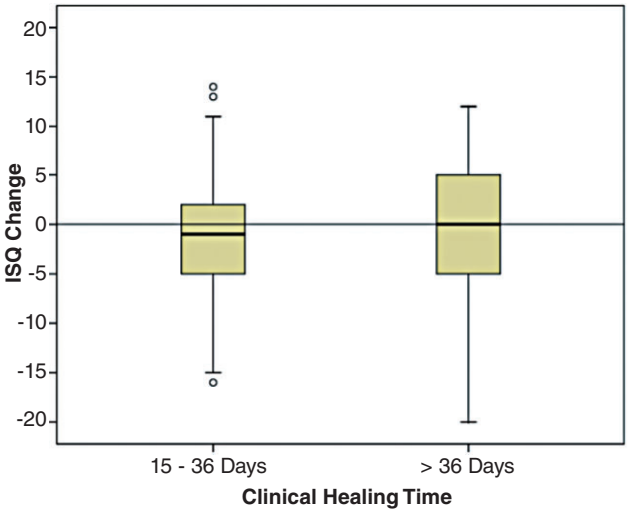

Figure 3 Box plot diagrams for the intraindividual change of ISQ values from insertion to clinical loading (horizontals indicate medians and quartiles, verticals indicate minimum and maximum observation values, and circles indicate statistical outliers and extreme values). ISQ = implant stability quotient.

Early data suggested that immediate and early loading protocols were more applicable in mandibular high density bone.[5,6,33] In more recent studies, immediate versus early loading was compared for all indications in partly edentulous patients[25,34] and in the posterior jaw area[23,35] with high survival and success rates. This is accordance with the data from our study where indication and region did not influence the success rate. The somewhat contra dictionary influence of splinting on implant success[36,37] might be explained by the reason that more critical situations were splinted resulting in a higher failure rate for splinted implants. Together with the "center effect," this shows the importance of personal experience with the respective treatment strategy. Using earlier time points (2 weeks) for loading seem to lead to more implant failures.[16] The importance of moderately rough implant surfaces for early and immediate loading has been extensively discussed in the last years.[38] Unfortunately, only very few groups have compared different modern implant surfaces using early loading.[39] There are animal models suggesting that hydrophilic surfaces[40] or fluoride modified surfaces[41] might enhance early implant healing. However, to our knowledge, a pivotal clinical study on that question is missing.

The problem of finding an objective measure for implants that are suitable for early loading remains unsolved. In this study, subjective primary stability was used. This criterion did not lead to implants that had to be excluded. Some groups suggest RFA as a tool for identification of critical implants.[42] On the other hand, animal experiments and some clinical work do not identify RFA as a suitable tool for identification of failing implants.[36,43,44] Based on the data of our study, RFA values of 55 seem to be "normal" in the maxilla for standard Straumann implants and no clear cutoff value between failing and successful implants at insertion exists.[45] It should, however, be noted that ISQ values of different implant systems are not comparable.

CONCLUSION

Loading of standard SLA implants in the maxilla 4 weeks versus 12 weeks after insertion could be shown to result in statistically equivalent failure patterns within a one year follow-up period; nevertheless, the observed patient-wise failure patterns of the interim analysis suggest sensitive consideration of the early loading concept.

TABLE 3 Listing of the Implant Failures

Patient	Center	Smoker	Indication	Randomization	Region	Bone Quality	Failure after [days]	Description	Action after Failure
005	2	Non	Edentulous	Test	27	III	27	No osseointegration; removal at second stage surgery	None
013	2	Non	Nearly edentolous	Control	15	III	83	Osseointegration at second-stage surgery; excessive manual force during removal of healing cap	Reimplantation
013	2	Non	Nearly edentolous	Control	25	III	83	Osseointegration at second-stage surgery; excessive manual force during removal of healing cap	Reimplantation
013	2	Non	Nearly edentolous	Control	26	III	83	Osseointegration at second-stage surgery; excessive manual force during removal of healing cap	Reimplantation
016	2	Non	Shortened arch	Test	16	III	32	No osseointegration, removal at second-stage surgery	Reimplantation
016	2	Non	Shortened arch	Test	26	III	122		Reimplantation
024	1	Non	Edentolous	Test	11	III	50	Insertion: persistent pain after bone condensing. No osseointegration at second-stage surgery. Removal before prosthetic restoration	None, rehabilitation on the residual five implants
028	1	Non	Single tooth	Control	15	II	18	No osseointegration before second-stage surgery	Bridge
93	1	Non	Single tooth	Test	15	III	35	No osseointegration at second-stage surgery	None

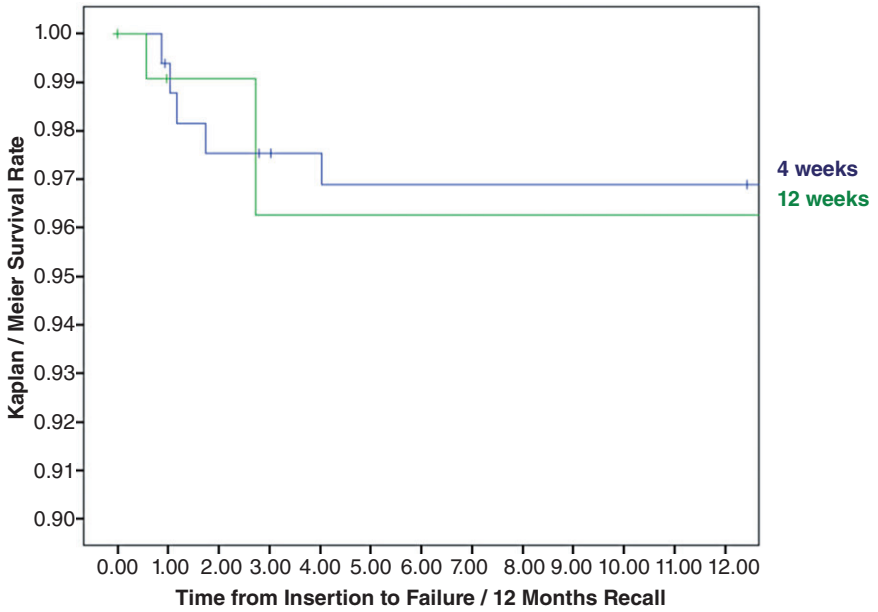

Figure 4 Kaplan/Meier survival estimates for a total of 269 implants over a maximum individual recall period of 5 years after insertion, stratified for the respective implants' randomized loading time (4 weeks versus 12 weeks).

ACKNOWLEDGMENTS

The authors are grateful to F. Peters (clinical monitoring), T. Jaberg (study initiation), J. Simpson (study plan), and C. Neugebauer (logistic trial coordination and patient interviews) for their contribution to the organization and quality assurance within this trial.

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