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Randomized multicenter comparison of two coatings of intramobile cylinder implants in 313 partially edentulous mandibles followed up for 5 years

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Abstract: Intramobile cylinder (IMZ) implants with either of two coatings, hydroxyapatite (HA) or titanium plasma-flame (TPF), as distal abutments for combined tooth implant-supported restorations, were compared in 313 partially edentulous mandibles with respect to postprosthetical failure patterns and complication frequencies in a randomized multicenter clinical trial. Within the treatment protocols, the two coatings do not show evidence of different efficacy with respect to occurrence of postprosthetical integration deficiency (ID) or functional deficiency (FD). Statistical equivalence for an absolute effect of ±15% in event-free survival could only be demonstrated for FD, not for ID, however. Intent-to-treat and per-protocol population analyses gave consistent results. Hazards of occurrence of ID and FD, adjusted for years of follow-up, were estimated for ID as 7% per year (95%CI 4-10% per year) with HA and 5% per year (95%CI 3-7% per year) with TPF, and for FD as 5% per year (95%CI 3-7% per year) with HA and 4% per year (95%CI 2-6% per year) with TPF. The 5-year cumulative success rates for no ID were 69.5% (95%CI 58-81%) with HA and 82.2% (95%CI 74-91%) with TPF. With respect to frequencies of complications, there was no relevant statistically significant difference between the two coatings.

Osseointegrated implants have been used successfully over the years in partially edentulous patients as an alternative to conventional fixed or removable dentures. In most of the literature references, the outcome has been based on the experience with implants*ad modum* Brånemark. The cumulative 5-year implant survival rates as reported in several (prospective or retrospective) studies, vary from 88 to 97.3% (Ellegaard et al. 1997, Jemt & Lekholm 1993, Lekholm et al. 1994, Olsson et al. 1995, Parein et al. 1997, Quirynen et al. 1992a; Wyatt & Zarb 1998).

Osseointegration was defined as structural and functional connection between ordered and living bone and the surface of load carrying implant (Albrektsson et al. 1981). Hydroxyapatite-coated implants were expected to have a higher interfacial strength due to a direct chemical interaction at the bone-implant interface, but due to the absorption of HA coating, the long-term success of HA-coated implants has remained a concern.

The aim of this clinical study was to compare two different coatings of intramobile cylinder implants (IMZ, Koch 1976) – hydroxyapatite (HA) and titanium plasma-flame (TPF) – between-patients and prospectively with a minimum of 3 years and an average follow-up of 5 years. IMZ implants were chosen as a vehicle for convenience because the two coatings

were already on the market, and sufficient practical experience with this system was considered an advantage.

In 1987, a group of five clinical centers began to admit patients to three randomized trials on different indications, one of which was partially edentulous mandibles restored with a fixed bridge on the distal tooth of the residual dentition and one posterior implant. The main criteria of comparison are the durations of no integration deficiency (Table 1) and of no functional deficiency (Table 1) after placement of prosthesis, and frequencies of complications. The success criteria concern not only absolute implant survival, but also bony alteration according to radiographs and the parameters in terms of implant mobility as well.

Adequate experimental and statistical methodology is required in order to eliminate biasing confounders: Though double-blinding is not feasible in dental implantology, one may still use a comparative and random design, and take duration of follow-up into account using survival analysis due to Kaplan & Meier (1958) and Cox (1972).

Material and methods

Patient population

Patients with a shortened dental arch on one or both sides of the mandible (Kennedy Class I or II), who were at least 20 years old, were eligible when the terminal first or second premolar could be used for a combined implant tooth-supported bridge, and the last extraction at implantation sites was at least 8 months ago.

Patients with a history of dental implants, limited ability to communicate (for lingual or neurological reasons) or to cooperate (i.e. adhere to examinations schedule or comply with hygiene recommendations), with any diseases or therapeutical treatments that might have an impact on healing period or outcome (systemic corticosteroidal, local radiological, immunosuppressive, or anti-coagulative therapy, acute infection at the implantation site), or patients who had an insufficient bone height over mandibular canal of less than 11 mm, were excluded from the study.

Table 1. **Success criteria of no integration deficiency (no ID) and of no functional deficiency (no FD) of an implant after loading**

	no ID	no FD
In situ	yes	yes
Bone loss	max. 4 mm	≤ 1/2 implant length
Periotest value	≤ 10	-
Manual mobility grade		
of implant	0	≤ I
of abutment tooth	-	≤ II

Treatment protocols

The test regimen used hydroxyapatite-coated intramobile cylinder (IMZ) implants (HA) of type DH with a diameter of 3.3 mm, while the control regimen used titanium plasma-flame-coated IMZ implants (TPF) with the same design (Friatec, Mannheim, Germany).

Common surgical procedures for insertion of HA-coated and TPF-coated cylinder implants included the general dental examination, a visual and tactile inspection of the edentulous area, and presurgical radiographs to determine bone height in order to choose implants of an adequate length. After flap removal, the width of bone was measured at a distance of 3 and 6 mm from the most coronal point of the alveolar crest. As surgical procedure, a two-stage technique was used: implants were inserted according to the standard protocol for the IMZ implant system (Kirsch & Mentag 1986), and second stage surgery took place approximately 3 months after implant placement. The treatment was discontinued when the actual bone situation did not allow implant insertion or other surgical complications occurred, such as insufficient primary stability, inadequate bone quality, or fracture of surrounding bone walls. Six months after the implants were uncovered, bridge constructions were planned. The bridges were supported by one natural tooth (first or second premolar) and one implant placed in the molar region. The connection between implants and teeth was rigid, using an individual screw-retained attachment to allow for retrievability of the implant-supported part of the bridge.

Examination protocols

After pretreatment assessment prior to randomization, parameters and procedures were documented after surgery, after completion of prosthetic treatment and then every 6 months during subsequent follow-up. Radiographs were planned to be taken immediately after implant placement and then once per year of follow-up. Intrasurgery recordings included width of the alveolar crest at 3 mm and 6 mm, usable bone height, buccal width of keratinized mucosa, thickness of bone wall buccally and lingually, uncovered implant neck buccally and lingually, and vestibulum depth after wound covering. Follow-up examinations included the following clinical parameters, measured at the buccal surfaces of the implants:

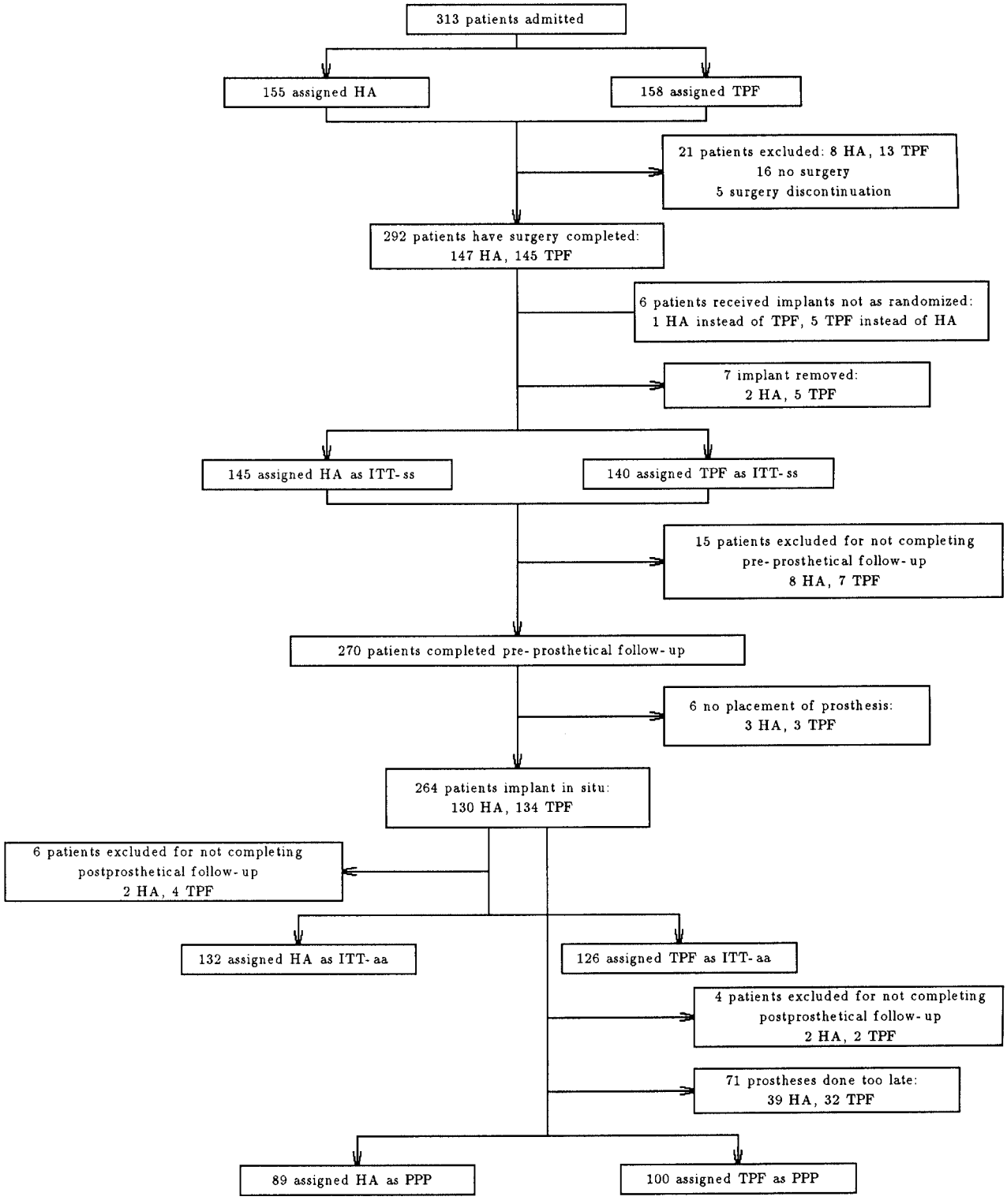
- plaque index (Silness & Löe 1964);
- gingival index (Löe & Silness 1963);
- probing depth; Periotest value (Schulte 1986);
- manually assessed mobility (graded as either 0 = no mobility, I = slight, just perceptible mobility, II = visible mobility or III = mobile under pressure of lip and tongue and/or manually mobile in axial direction, cf.Tetsch et al. 1985).

For changes in alveolar bone level, panoramic radiographs were analyzed with respect to the immediate postoperative radiograph as the reference (Gomez-Roman et al. 1995).

Trial design and statistical analysis

Five German clinical centers (Aachen, Berlin, Duesseldorf, Mainz and Tuebingen) began to recruit patients in January 1987 and follow-up was terminated on 31 December 1996. Patients with an indication for a single implantation were assigned to either TPF-coated IMZ implants as control or HA-coated IMZ implants as test. For patients with an indication for symmetrical implantations, one of the two sides was chosen at random for treatment assignment and the between-patient comparison on which the trial had been based statistically. A balanced central-telephone random assignment technique stratified by center was used. The enrolled patients had been informed about and consented to both treatment modalities prior to communication of the assigned protocol. Patients could withdraw their cooperation at any time. Criteria for patient drop-out as specified in the trial protocol were:

- discontinuation of surgery for any of the reasons mentioned above;
- patient's wish to remove the implants or to withdraw from the trial for any reason;
- exogenous injury implying implant loss;



ITT = intention-to-treat
ITT-ss = intention-to-treat strictu sensu
ITT-aa = intention-to-treat as available
PPP = per-protocol population
HA = IMZ implant with hydroxyapatite coating
TPF = IMZ implant with titanium plasma-flame coating

Fig. 1. Trial flow diagram for efficacy analyses.

Table 2a. **Sample sizes and demographic data of *ITT* and *PPP* patients**

	Assigned treatment			Test	
	HA	TPF	Total	z	*P*
Number of total randomized patients					
Total randomized	155	158	313		
no surgery done	6	10	16		
surgery discontinued	2	3	5		
surgery completed	147	145	292		
Deviations from randomized system					
TPF instead of HA	5	–	5		
HA instead of TPF	–	1	1		
Number of patients without preprosthetical follow-up					
no completed preprosthetical follow-up	8	7	15		
preprosthetical explantation	2	5	7		
Number of preprosthetical patients					
ITT-aa	137	133	270		
PPP	133	137	270		
Number of patients without postprosthetical follow-up					
no placement of prosthesis	3	3	6		
ITT-aa no postprosthetical follow-up	2	4	6		
PPP no postprosthetical follow-up	2	2	4		
prosthesis done too late	39	32	71		
Number of postprosthetical patients					
ITT-aa	132	126	258		
PPP	89	100	189		
Gender(no. of men : no. of women)					
ITT-aa	51:81	63:63	114:144	3.375	0.066
PPP	36:53	53:47	89:100	2.977	0.084
Age in years (mean ± (SD))					
ITT-aa	44.6 (12.1)	44.1 (11.3)	44.3 (11.7)	- .469	0.639
PPP	44.8 (12.1)	44.1 (11.2)	44.5 (11.6)	0.557	0.578

HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
ITT = intent-to-treat.
PPP = per-protocol population.
z values are approximate chi-square values, 1 df, for the common chi-square test of 2-by-2 contingency tables for gender, and approximate standard-normal values of the Wilcoxon U-test, for age, *P* values are not adjusted for multiple testing.

- lack of adherence to recall appointments according to the examinations protocol.

The primary efficacy endpoint has been defined *a priori* as the time from functional loading until first occurrence of an integration deficiency (ID) among the inserted implants. Implant ID was used as a synonym for lack of successful integration of a single implant. Integration deficiency was *a priori* defined (Table 1) as any of the following:

- implant loss;
- bone loss since the operation of at least 4 mm at the mesial or distal aspect;
- Periotest value of at least 10;
- manual mobility graded >0.
- manual implant mobility of implant >I;
- manual mobility of abutment tooth >II.

The safety endpoint was prespecified as occurrences of any complications.

The trial was sized to determine an absolute difference in population 'no ID' success rates between the test and the control regimen of 0.15 pertaining to an average of 5 years of follow-up after functional loading, at a significance level of 5% with a power of at least 80%. This implied at least 340 patients for analysis. With an anticipated proportion of drop-outs of 10-15%, total recruitment goal had been set to 380 randomized patients.

Five interim analyses were conducted during the first years of patient recruitment, one per year, and each at a significance level of 0.0005 in the primary endpoint, which leaves a nominal significance level of 0.0475 for the final comparison. No adjustments for multiple testing were foreseen in the trial protocol, and we therefore used a conservative Bonferroni-type adjustment on the secondary endpoints of 0.0119=0.0475/4 for each.

Case-record forms were mailed and queried regularly, and monitored on site in a latter stage of the trial. After visual screening, raw data were entered consecutively into an electronic database, using independent double-data entry by two persons into screen masks with automatic plausibility and data-identity checking. Radiographs were reevaluated after completion of data collection in joint sessions to achieve a common standard across the five centers. Interim analyses were conducted at the data center and results communicated in a partially masked form, otherwise no interim data were released. Prior to the final analysis, all ambiguous records were reviewed without disclosing the assigned treatment.

The logrank test for grouped and right-censored data is used to compare the two experimental groups in the primary endpoint, according to trial protocol, with adjustments for structural heterogeneities in the baseline parameters using a Cox 1972) proportional-hazards regression model. The null hypothesis against which one compares the distributions of time until first ID of the two hazard functions λ_{HA} and λ_{TPF} is $\lambda_{HA} = \lambda_{TPF}$. Survival functions are estimated according to Kaplan & Meier (1958).

Occurrence-exposure rates of events (ID

Three secondary efficacy endpoints had also been specified *a priori* in the trial protocol:

1. time from functional loading until first occurrence of a functional deficiency (FD),

2. occurrence of functional deficiency (FD) of the implant system within 3 years after functional loading, and

3. Periotest value at 3-6 months after surgery.

Functional deficiency was *a priori* defined (Table 1) as any of the following:

- implant loss;
- bone loss since insertion more than half of the implant length either mesial or distal or both;

Table 2b. **Baseline data of 258 postprosthetical *ITT-aa* and 189 *PPP* patients**

	Assigned treatment			Test	
	HA	TPF	Total	z	*P*
Width of alveolar crest at 3 mm (mean ± (SD))					
ITT-aa	7.19 (2.2)	7.27 (2.0)	7.23 (2.1)	0.800	0.424
PPP	7.33 (2.3)	7.31 (1.9)	7.32 (2.1)	- .551	0.582
Width of alveolar crest at 6 mm (mean ± (SD))					
ITT-aa	9.79 (2.5)	10.02 (2.3)	9.91 (2.4)	1.038	0.299
PPP	9.84 (2.2)	9.97 (2.1)	9.91 (2.2)	- .565	0.572
Usable bone height in mm (mean ± (SD))					
ITT-aa	14.00 (2.4)	14.08 (2.1)	14.04 (2.2)	0.263	0.793
PPP	14.17 (2.4)	13.96 (2.2)	14.06 (2.3)	0.449	0.653
Keratinized mucosa buccally in mm (mean ± (SD))					
ITT-aa	3.57 (2.3)	3.82 (2.6)	3.69 (2.5)	0.598	0.550
PPP	3.92 (2.6)	3.95 (2.7)	3.94 (2.6)	- .061	0.952
Implant length in mm (mean ± (SD))					
ITT-aa	12.03 (1.8)	12.10 (1.6)	12.07 (1.7)	0.374	0.709
PPP	12.04 (1.8)	12.00 (1.7)	12.02 (1.7)	0.205	0.838
Thickness of bone wall buccally in mm (mean ± (SD))					
ITT-aa	1.95 (1.6)	1.92 (1.4)	1.93 (1.5)	0.265	0.791
PPP	2.01 (1.6)	1.97 (1.4)	1.99 (1.5)	- .222	0.824
Thickness of bone wall lingually in mm (mean ± (SD))					
ITT-aa	1.66 (1.0)	1.73 (1.0)	1.69 (1.0)	0.774	0.439
PPP	1.64 (0.9)	1.73 (0.9)	1.69 (0.9)	- .706	0.480
Vestibulum depth after wound coverage in mm (mean ± (SD))					
ITT-aa	3.47 (2.7)	3.46 (2.7)	3.47 (2.7)	- .183	0.855
PPP	3.64 (2.8)	3.54 (2.9)	3.59 (2.8)	0.485	0.628
Uncovered implant neck buccally in mm (mean ± (SD))					
ITT-aa	0.98 (1.6)	0.92 (0.9)	0.95 (1.3)	0.604	0.546
PPP	0.93 (1.0)	0.91 (0.9)	0.92 (1.0)	- .241	0.810
Uncovered implant neck lingually in mm (mean ± (SD))					
ITT-aa	0.27 (0.7)	0.36 (0.7)	0.31 (0.7)	1.400	0.162
PPP	0.32 (0.8)	0.34 (0.6)	0.33 (0.7)	- .818	0.413
Primary stability (no. of primary stable : no. of primary unstable)					
ITT-aa	124 : 8	116 : 10	240 : 18	0.350	0.554
PPP	86 : 3	93 : 7	179 : 10	1.238	0.266
Osteoplasty(no. of done : no. of not done)					
ITT-aa	17 : 115	16 : 110	33 : 225	0.002	0.965
PPP	13 : 76	14 : 86	27 : 162	0.014	0.905

HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
ITT = intent-to-treat.
PPP = per-protocol population.
z values are approximate standard-normal values of the Wilcoxon U-test for respective variables, or chisquare values, were applicable.
P-values are not adjusted for multiple testing.

or FD) use the exponential-distribution constant-hazard estimator, with approximate 95% confidence intervals, to adjust for different follow-up times. Occurrences that relate to fixed time intervals are analyzed with a chi-square contingency-table test. For a statistical comparison of occurrence of complications, an adjustment was made for the number of recall inspections per patient: an exposure concept, analogous to the standard total-time-on-test concept in industrial reliability testing, was based on the total number of implant inspections.

Data was processed with the Statistical Analysis System (SAS)® of versions 5.1-6.12 consistently on different platforms since 1987, most recently under OS/2 Warp on PC and under AIX 4.3 on RS/6000 systems (SAS Institute Inc., 1989).

Since protocol violations occurred, separate analyses were required for patients by intent-to-treat (*ITT*), i.e. as randomized, and for the subset of patients who complied with the trial protocol, i.e. who adhered to eligibility criteria and treatment and examination protocols. Analysis on the latter subset of patients is referred to as per-protocol population (*PPP*) analysis. Since follow-up is incomplete in a substantial number of patients, separate *ITT* analyses were done, one based on different assumptions about missing values in order to include all patients (*ITT strictu sensu*) and another one on the *ITT* patients with their available data only (*ITT* 'as available', *ITT-aa*).

Results

Comparability analysis: actual trial population and randomization

In all, 313 admitted patients, who met the inclusion criteria, were enrolled in this study, among them 133 (42.5%) men and 180 (57.5%) women. Of these, 155 (49.5%) patients were randomized to HA-coated IMZ implants as test and 158 (50.5%) patients were randomized to TPF-coated IMZ implants as control.

Twenty-one patients did not enter the protocol because surgery was either not done ($n = 16$) or discontinued ($n = 5$). Six patients received the wrong implant system, i.e. HA instead of TPF or *vice versa*. Implants were removed in another seven patients (Fig. 1 and Table 2a), because of inflammation and/or implant mobility ($n = 6$) or of withdrawn consent without complication ($n = 1$). Thus, for the *ITT-strictu sensu* analysis, there were 285 eligible patients, 145 (50.9%) in the HA group and 140 (49.1%) in the TPF group.

A further 15 and six patients did not complete the preprosthetical and postprosthetical follow-up, respectively. Six patients did not receive prosthesis. The remaining 258 patients, 132 (51.2%) in the HA group and 126 (48.8%) in the TPF group, were eligible for primary endpoint and secondary endpoints analyses by intention-to-treat 'as available' (*ITT-aa*): The postprosthetical *ITT-aa* sample thus consisted of all admitted and randomized patients, irrespective of their consistency or compliance with, or adherence to the protocol specifications, who completed preprosthetical follow-up, and in whom a prosthesis was placed. It does not include six patients, two in the HA and four in the TPF group, without any postprosthetical follow-up. Similarly for postprosthetical *PPP* analyses, four patients were excluded because of no postprosthetical follow-up, two in HA and two in TPF group. A further

***Table 3. ITT-strictu sensu* analysis of the primary endpoint (ID) in three scenarios for inclusion of patients lost from protocol after insertion of implant: (i) worst-case assumption: all lost to follow-up are ID, (ii) best-case assumption: all lost to follow-up are no ID, (iii) mixed-case assumption: HA lost to follow-up are ID, TPF lost to follow-up are no ID**

	Assigned treatment			Test	
	HA	TPF	Total	z	*P*
Randomized	155	158	313		
Not completed surgery	8	13	21		
Preprosthetical explantation	2	5	7		
Total lost from postprosthetical protocol	13	14	27		
no preprosthetical follow-up	8	7	15		
no placement of prosthesis	3	3	6		
no postprosthetical follow-up	2	4	6		
Completed postprosthetical follow-up	132	126	258		
Occurrence of ID					
no ID in postprosthetical follow-up	104	100	204		
In postprosthetical follow-up	28	26	54		
Total	132	126	258		
Lost from protocol	13	14	27		
3 scenarios for primary endpoint analysis in *ITT-strictu sensu* sample					
Scenario 1: worst-case assumption					
good outcome	104	100	204		
bad outcome	41	40	81		
Total	145	140	285	0.043	0.956
Scenario 2: best-case assumption					
good outcome	117	114	231		
bad outcome	28	26	54		
Total	145	140	285	0.025	0.874
Scenario 3: mixed worst/best-case assumption					
good outcome	104	114	218		
bad outcome	41	26	67		
Total	145	140	285	3.730	0.053

good outcome with respect to primary endpoint is no integration deficiency (ID) during postprosthetical follow-up.
bad outcome is occurrence of an integration deficiency (ID) during postprosthetical follow-up.
HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
ITT = intent-to-treat.
z values are approximate chi-square values, 1 df , for the common chi-square test of 2-by-2 contingency tables with unadjusted observed.
P values ($P < 0.0475$ is significant according to trial protocol).

71 patients were excluded for *PPP* analyses because of receiving a prosthesis too late, leaving 189 patients, 89 (47.1%) in the HA group and 100 (52.9%) in the TPF group: The postprosthetical *PPP* sample thus consists of all admitted and randomized patients whose baseline characteristics are consistent with the protocol population, i.e. with the inclusion and exclusion criteria of the protocol, and who complied to the treatment protocol, but irrespective of their adherence to the exact protocol schedule of follow-up examinations (cf. Material and methods, above).

The comparisons of the two randomized treatment groups with respect to the *PPP* baseline values are summarized inTable 2a for a patient-wise and in Table 2b for an implant-wise comparison. Homogeneity analysis did not indicate any statistically significant differences in any of the baseline variables between the two groups.

Efficacy analysis: Intent-to-treat '*strictu sensu*'

For the *ITT-strictu sensu* analysis of the primary endpoint (postprosthetical time until first ID of implant), one has to use an appropriate binary endpoint in order to include assumptions about missing assessments of those patients who were not available for analysis: occurrence of ID (failure) or no occurrence of ID (success) during follow-up of any length was chosen for simplicity. There are then three possibilities to include patients into an analysis who were not assessed according to the protocol:

i. by a 'worst-case' assumption, i.e. patients who were not assessed are considered as treatment failures,

ii. by a 'best-case' assumption, i.e. patients who were not assessed are considered as treatment successes, and

iii. by a mixed worst/best-case assumption, i.e. patients who were not assessed are considered as treatment failures if assigned to the test treatment (HA), and as treatment successes if assigned to the control treatment (TPF).

Assumption (iii) may also be called the least favorable assumption for HA group.

This scenario analysis of the primary endpoint is shown for all *ITT* patients in Table 3. No statistically significant differences in percentages under either of the three scenarios are found.

Efficacy analysis: Intent-to-treat 'as available'

Because of the small discrepancy of the *ITT-aa* cohort from the *PPP* cohort, the analogous analysis of every endpoint with the former yields practically negligible differences in numerical results. The pertaining statistical data has been collected in Tables 4a and 4b, though, in order to provide a complete account. Here, priority is given to a description of results of *PPP* analyses.

Efficacy analysis: Per-protocol population

Postprosthetical occurrence of first ID of implant (primary endpoint) was reported for 24 patients in the HA group and for 21 patients in the TPF group. Differences of 6% in proportion, unadjusted for different times of loading, and of 1.7% per year of loading in occurrence rates, are not statistically significant ($P > 0.0475$) for the appropriate tests (Table 4b). Survival-type analyses yield 1-year and 5-year survival estimates for ID of 93.1% (95%CI 87.8-98.4%) and 69.5% (95%CI 58.3-80.7%), respectively, for HA, and of 95.0% (95%CI 90.6-99.3%) and 82.2% (95%CI 74.2-90.6%), respectively, for TPF. Kaplan-Meier curves in Fig. 2 do not show a statistically significant difference (log rank test chi-square of 1 df is 0.9609, $P = 0.3270$).

Postprosthetical occurrence of first FD of implant (*1st secondary endpoint*) was reported for 18 patients in the HA group and 19 patients in the TPF group. Differences of 1.2% in proportions, unadjusted for different times after loading, and of 0.4% per year after loading in occurrence rates, are not statistically significant ($P > 0.0119$) for the appropriate tests (Table 4b). Survival-type

Table 4a. **Efficacy analysis in *ITT* patients, with numbers of patients as available (*ITT-aa*) for primary and secondary endpoints analyses, failure rates (hazard estimates) adjusted for length of follow-up**

	Assigned treatment			Test	
	HA	TPF	Total	z	*P*
Primary endpoint analysis in*ITT-aa* sample					
Occurrence of first ID during postprosthetical follow-up					
no ID	104	100	204		
ID	28	26	54		
Total number at risk	132	126	258	0.013	0.909
Total time on test (in years)	528.74	525.46	1054.20		
Hazard estimate (% per year)	5.30	4.95	5.12	0.249	0.803
95% confidence interval (% per year)	3.33-7.26	3.05-6.85	3.76-6.49		
Secondary endpoint analyses in *ITT-aa* sample					
Occurrence of first FD during postprosthetical follow-up					
no FD	110	104	214		
FD	22	22	44		
Total number at risk	132	126	258	0.029	0.865
Total time on test (in years)	551.16	561.15	1112.31		
Hazard estimate (% per year)	3.99	3.92	3.96	0.060	0.953
95% confidence interval (% per year)	2.32-5.66	2.28-5.56	2.79-5.12		
Occurrence of first FD within 3 years of postprosthetical follow-up					
FD within 3 years FU	12	5	17		
no FD w/ FU > 3 years	95	95	190		
Subtotal	107	100	207	2.649	0.104
no FD w/ FU < 3 years	25	26	51		
Total	132	126	258		
Periotest values at 3-6 months after surgery					
Mean	3.22	3.69	3.45	0.821	0.412
SD	3.92	4.15	4.03		
Number of implants	130	124	254		

ID = integration deficiency (Table 1).
FD = functional deficiency (Table 1).
HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
ITT = intent-to-treat.
z values are approximate chisquare values, 1*df* , for the common chi-square test of 2-by-2 contingency tables with unadjusted observed.
P values ($P < 0.0475$ is significant according to trial protocol for primary endpoint analysis, and $P < 0.0119$ for secondary endpoint analysis), and approximately standard-normal deviates for the comparison of hazard estimates.

analyses yield 1-year and 5-year survival estimates for FD of 100% and 76.7% (95%CI 66.3-87.2%), respectively, for HA, and of 98.0% (95%CI 95.2-100%) and 81.4% (95%CI 72.4-90.5%), respectively, for TPF. Kaplan-Meier curves in Fig. 3 do not indicate a statistically singnificant difference (log rank test chi-square of 1 df is 0.1286, $P = 0.7199$).

Postprosthetical occurrence of first FD of implant within 3 years after placement of prosthesis (2nd secondary endpoint) was reported for nine patients (11.8%, 95%CI 5.6-21.3%) in the HA group of 76 assessable patients, and for six patients (7.5%, 95%CI 2.8-15.6%) in the TPF group of 80 assessable patients. Difference in proportions is not statistically significant.

The mean values of Periotest scores 3-6 months after insertion of implant (3rd secondary endpoint) were 3.7 (SD 4.3) in 178 HA-coated implants, and 3.6 (SD4.2) in 200 TPF-coated implants (difference not statistically significant).

Safety analysis

For the safety endpoints, there are $n=91$ and $n=102$ assessable implants in the HA and the TPF group, respectively; a synopsis of results is given in Table 5. As an abbreviation, *pii* denotes 'per inspection of an implant' as 'inspection of an implant' was chosen as the unit reference of rates of occurrence.

Bleeding from the mandibular canal was the most common intraoperative complication and was documented in 1.1%*pii* for the HA group and in 1.96%*pii* in the TPF group. Flap dehiscence (2.2%*pii* in the HA group, 6.9%*pii* in the TPF group) and hematoma (2.2%*pii* in the HA group, 4.9%*pii* in the TPF group) were the most frequent postoperative complications. During the healing period, recession of marginal soft tissue occurred at rates of 11.0%*pii* in HA and 3.9%*pii* in TPF group (difference not statistically significant, $P = 0.077$). After placement of prosthesis, infections and fractures of intramobile element were the most common complications, occurring at about 2% and 3%*pii*, respectively, without any statistically significant differences in occurrence rates.

Discussion

Up to the present, most comparisons of different coatings reported in the literature and other empirical comparisons are compromised by methodological drawbacks, such as retrospective data (Wheeler 1996) or uncontrolled confounding factors, such as different implant systems (Kemppainen et al. 1997). Jones et al. (1999) have compared the hydroxyapatite-coated (HA) and titanium plasma-sprayed (TPS) cylinder implants in a randomized controlled trial, which reported a higher overall failure rate in terms of implant *in situ* by 8% for the TPS implants; this failure rate was not, however, statistically significant.

Haas et al. (1996) reported long-term overall survival rates of 89.9% after 60 months and 83.2% after 100 months for IMZ implants. When considering studies which include the peri-implant bone loss in their definition of success, our findings of 5-year cumulative success rates for integration of 70% for HA and 82% for TPF implants are in agreement with the literature. Ellegaard et al. (1997) estimated a 5-year success probability of 79.2% under application of the criterion 'first occurrence of bone loss ≥ 3.5 mm' for ITI implants. Watson et al. (1998) estimated an overall survival rate over 6 years of 92% for HA-coated cylindrical implants, and in terms of 'cervical bone loss more than 4 mm', the 6-year cumulative success rate would fall to 39%. The IMZ implants have become known for significant bone loss when this trial was about mid-way (Quirynen et al. 1992b; Dietrich & Wagner 1992, cf. also Albrektsson 1993, for a discussion), but this would not compromise the randomized comparison of the two coatings. Since comparisons between survival curves are done in terms of failures ('death') and not in terms of censored cases ('sur-

Table 4b. **Efficacy analysis in *PPP* patients, with numbers of patients for primary and secondary endpoints analyses, failure rates (hazard estimates) adjusted for length of follow-up**

	Assigned treatment			Test	
	HA	TPF	Total	z	*P*
Primary endpoint analysis in *PPP* sample					
Occurrence of first ID during postprosthetical follow-up					
no ID	65	79	144		
ID	24	21	45		
Total number at risk	89	100	189	0.924	0.336
Total time on test (in years)	350.83	406.96	757.79		
Hazard estimate (% per year)	6.84	5.16	5.94	0.937	0.349
95% confidence interval (% per year)	4.10-9.58	2.95-7.37	4.20-7.67		
Secondary endpoints analyses in *PPP* sample					
Occurrence of first FD during postprosthetical follow-up					
no FD	71	81	152		
FD	18	19	37		
Total number at risk	89	100	189	0.045	0.832
Total time on test (in years)	374.00	431.20	805.20		
Hazard estimate (% per year)	4.81	4.41	4.60	0.268	0.789
95% confidence interval (% per year)	2.59-7.04	2.43-6.39	3.11-6.08		
Occurrence of first FD within 3 years of postprosthetical follow-up					
FD within 3 years FU	9	6	15		
no FD w/ FU > 3 years	67	74	141		
Subtotal	76	80	156	0.846	0.358
no FD w/ FU < 3 years	13	20	33		
Total	89	100	189		
Periotest values at 3-6 months after surgery					
Mean	3.67	3.56	3.61	0.362	0.717
SD	4.30	4.23	4.25		
Number of implants	89	100	189		

ID = integration deficiency (Table 1).
FD = functional deficiency (Table 1).
HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
PPP = per-protocol population.
z values are approximate chisquare values, 1 df , for the common chi-square test of 2-by-2 contingency tables with unadjusted observed *P* values ($P < 0.0475$ is significant according to trial protocol for primary endpoint analysis, and $P < 0.0119$ for secondary endpoint analysis), and approximately standard-normal deviates for the comparison of hazard estimates.

vivors'), it was even advantageous, from a strictly statistical point of view, to have used a system with a high base rate of ID-occurrence as a vehicle for the comparison of two coatings.

In the present study, 313 patients aged 20-71 were enrolled and evenly randomized into two treatment groups. No heterogeneities were seen with respect to patient characteristics and baseline variables. Hence, the two treatment groups may validly be considered as structurally comparable.

To assess marginal bone level, panoramic radiographs were used in this study. The drawback of panoramic radiographs is the potential inaccuracy of measurement, especially in the anterior mandible due to the overlaying spinal column. Nevertheless, panoramic radiography has its practical value due to the high reproducibility, especially in the vertical dimension. In addition, there was a pre-analysis reevaluation of all radiographs to introduce a standardized evaluation into the trial.

The primary and secondary efficacy endpoints had been defined explicitly before admission of patients started. This permits a fair comparison, then, to be made between the two treatment groups and leads to a better interpretation of statistical results than any *post hoc* data-driven choices of variables. The comparison of failures between the two treatment groups was made first by means of proportions, i.e. the number of cases over the number of patients exposed, of ID or of FD in postprosthetical follow-up without any adjustment for different durations of follow-up. Since unadjusted calculations are typically inadequate for follow-up studies, the total time of follow-up (after loading) was taken into account, and an adjusted comparison made in terms of occurrence rates, i.e. the proportions of ID, or of FD, divided by the mean follow-up time. This concept is actually based on an *ad hoc* assumption of constant hazard during follow-up. The definitive comparison was then made in terms of ID- or FD-free times of follow-up after loading, which also admits non-constant hazards. Practically identical results were obtained under all statistical approaches for the proportions, the occurrence rates, and the actual time of event-free follow-up. Hence, the statistical results on efficacy are robust against different statistical approaches to their analysis.

As to the safety analyses, no serious adverse event was observed in this study, and no statistically significant differences were found between the two treatment groups with respect to occurrences of complications. It should be mentioned that IME (intramobile element) is an important component of IMZ implant. The occurrence of fracture of IME was included in the analysis and it was the most frequently reported complication. There was no statistical significance between the two groups, and the same is seen with the occurrence of fracture of other components. The second most commonly observed complication was the occurrence of infection and pain. They are the two main syndromes that may influence the subjective assessment of patients. The occurrences of recessions are not far from being assessed as statistically significant, $P = 0.0765$, but this may still be considered a random result.

The method adopted here to analyze complications seems to be new. Occurrences of complications were analyzed as rates per number of implant inspections instead of rates per times of follow-up. The comparison of the occurrences of complications between the two treatment groups was hence adjusted by the total number of implant inspections. Apart from the nominal difference in rates of inflammations, the results did not show any statistically significant differences between HA and TPF groups with respect to risk of complications, at any stage, i.e. during surgery, after surgery, during healing period, during placement of prosthesis, or after placement of prosthesis.

By the large number of patients not assessed, there is hence a considerable potential for confounding in the non-availability

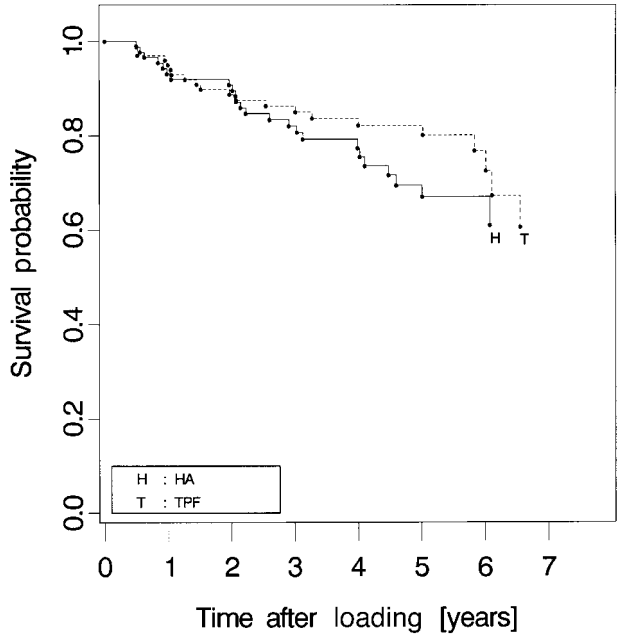


*Fig. 2.*Kaplan-Meier estimates of first occurrence of postprosthetical integration deficiency (ID) according to treatments for per-protocol population analyses.

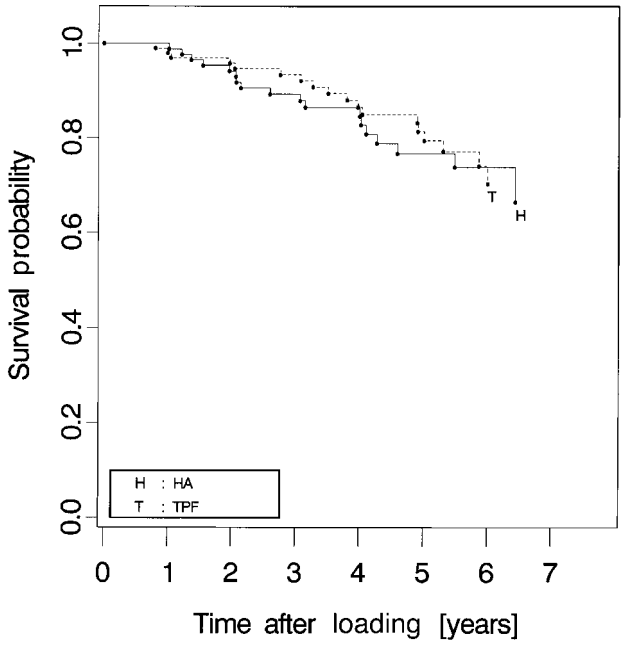


*Fig. 3.*Kaplan-Meier estimates of first occurrence of postprosthetical functional deficiency (FD) according to treatments for per-protocol population analyses.

of follow-up data. This suggested an analysis with three scenarios for the primary endpoints in the *ITT* sample: both best-case and worst-case scenarios produced no significant difference of HA group *versus* TPF group. The mixed worst/best-case is the least favorable for HA group (test treatment); this assumes that all patients from whom data was not available, were not a success when in the HA group and were a success when in the TPF group (control treatment): This scenario showed a borderline nonsignificant ($P = 0.053$) difference in the primary endpoint (postprosthetical ID).

Another source of confounding is protocol violation. Separate intent-to-treat (*ITT*) and per-protocol population (*PPP*) analyses are therefore necessary. However, the *ITT*-'as available' and *PPP*-analyses actually produced similar *P* values in the four endpoints. Again, this should not be mistaken as corroborative evidence. Instead, it demonstrates a certain degree of robustness in the sense that the statistical quantifications of evidence do not depend on those patients who did not adhere to the protocol.

The lack of statistical significance in the efficacy endpoints creates the issue of considering the strength of evidence in favor of an equivalence of HA and TPF in the endpoints. Accordingly, the first issue is whether the trial had a sufficient statistical power. The 313 enrolled patients represent only 82.4% of the number of patients foreseen in the trial protocol. During follow-up, 124 patients were lost from protocol for various reasons: no surgery done, discontinuation of surgery, pre-prosthetical follow-up not completed due to explantation, delayed placement of prosthesis and no postprosthetical follow-up. In particular, for the *PPP* analyses, there were 71 patients for whom a prosthesis was inserted too late: 39 of 130 patients in HA group, and 32 of 134 patients in TPF group (the difference was not statistically significant). Hence, the trial is actually underpowered for demonstrating an absolute difference of 15% between HA and TPF in any efficacy endpoint.

When the foreseen statistical power is not achieved due to insufficient number of patients and observed effects are statistically not significant, one may investigate the strength of evidence (Mau 1988) in the data that an observed treatment effect is statistically indeed negligible within some pre-defined difference that is considered clinically irrelevant. In the trial protocol, that difference had been set at $\pm 15\%$ in terms of an absolute treatment effect in probabilities of event-free survival. In the Mau (1988) approach, which uses observed confidence calculations, the treatments under comparison may be considered 'statistically equivalent' at a level of significance of 0.05 when a critical confidence of 0.90 is passed.

For the primary efficacy endpoint (postprosthetical ID) in the *ITT-strictu sensu* analysis under the worst and best case scenarios (Table 3a), observed confidences were 0.995 and 0.999, respectively, which is clearly sufficient to declare HA and TPF statistically equivalent at $P < 0.01$. Under the mixed case scenario, however, no statis-

Table 5. **Safety endpoint analysis of PPP patients: frequencies of complications in pii (with 95%-confidence interval)**

	Assigned treatment		Test	
	HA	TPF	z	*P*
During surgery				
Bleeding from mandibular canal	1.1% (0-3.3%)	1.96% (0-4.7%)	− 0.4872	0.6261
Perforation of buccal/oral bone wall	0.6% (0-2.1%)	1.0% (0-2.9%)	− .3445	0.7305
Total number of implant inspections	91	102		
After surgery				
Hematoma	2.2% (0-5.2%)	4.9% (0.6-9.2%)	− 1.0063	0.3143
Infection	1.1% (0-3.3%)	2.9% (0-6.3%)	− .9108	0.3624
Flap dehiscence	2.2% (0-5.2%)	6.9% (1.8-12.0%)	− 5.427	0.1229
Other complications	0.6% (0-2.1%)	2.0% (0-4.7%)	− 1.8880	0.3746
Total number of implant inspections	91	102		
During healing period				
Infection	1.1% (0-3.3%)	2.9% (0-6.3%)	− .9108	0.3624
Pain	1.1% (0-3.3%)	1.0% (0-2.9%)	0.0805	0.9359
Recession of marginal soft tissue	11.0% (4.2-17.8%)	3.9% (0.1-7.8%)	17.713	0.0765
Other complications	1.1% (0-3.3%)	0.5% (0-1.9%)	0.4685	0.6394
Total number of implant inspections	91	102		
During placement of prosthesis				
Infection	1.1% (0-3.3%)	0.5% (0-1.9%)	0.4685	0.6394
Recession of marginal soft tissue	1.1% (0-3.3%)	0.5% (0-1.9%)	0.4685	0.6394
Total number of implant inspections	91	102		
After placement of prosthesis				
Infection	2.2% (1.1-3.3%)	2.0% (1.1-3.0%)	0.2230	0.8235
Pain	1.4% (0.5-2.2%)	0.8% (0.2-1.5%)	0.9982	0.3182
Recession of marginal soft tissue	0.1% (0-0.4%)	0.1% (0-0.4%)	0.0975	0.9223
Fracture of implants	0.3% (0-0.7%)	0.1% (0-0.2%)	10.144	0.3104
IME Fracture	2.9% (1.7-4.1%)	2.6% (1.5-3.7%)	0.3007	0.7637
Other complications	2.1% (1.0-3.1%)	2.9% (1.7-4.0%)	− 1.0233	0.3061
Total number of implant inspections	727	835		

HA = IMZ implant with hydroxyapatite coating (test).
TPF = IMZ implant with titanium plasma-flame coating (control).
pii = per inspection of an implant.
PPP = per-protocol population.
z values are approximate chi-square values, 1 df , for the common chi-square test of 2-by-2 contingency tables and approximate standard normal values for the comparison of complication rates per implant inspections, *P* values are not adjusted for multiple testing.

tically significant equivalence could be established with $P<0.14$. With the *ITT-aa* analysis, statistically significant equivalence within a range of ± 0.15 can be demonstrated in each composite criterion (occurrence of ID, of FD, and of FD within 3 years) with $P=0.005$, $P=0.0025$, and $P=0.01$, respectively. For the *PPP* analysis, however, only the two functional endpoints (occurrence of first FD and of first FD within 3 years of postprosthetical follow-up) achieved statistically significant equivalence with $P=0.013$ and $P=0.012$, respectively. This may mainly be due to the considerably smaller number of patients ($n=189$) in the *PPP* analysis.

In summary, the study has compared two different coatings with otherwise identical implant characteristics on IMZ implants as vehicle. The statistical analysis was based on the randomization of patients into the two groups for comparison and done with the endpoints and the statistical methods as defined *a priori* in the trial protocol. The loss of patients from follow-up required repeated analyses under different assumptions about the outcomes in lost patients. The lack of statistically significant effects and of sufficient statistical power implied an additional assessment of the achieved strength of evidence for equivalence, which produced only a partial result: Statistically significant equivalence can be established both for risk of functional deficiency after loading within a range of ± 0.15, and for risk of integration deficiency for the *ITT-aa* analyses but not for the *PPP* analyses.

Therefore, an extensive further statistical modeling will be required to account for center effects between the five centers and for heterogeneities between the treatment groups that actually occur despite the average homogeneity produced by randomization. Any such data-driven analysis can only suggest *post hoc* explanations of patterns in the data, but it cannot replace a comparison of randomized groups by an *a priori* defined statistical test and it does not yield results under valid statistical error probabilities. Such analyses are hence postponed to a future elaborating paper.

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Résumé

Des implants cylindriques intramobiles IMZ avec l'un des deux recouvrements, soit l'hydroxyapatite (HA) ou le plasma titane (TPF) utilisés comme piliers distaux pour des restaurations implants/dents ont été comparés chez 313 édentés partiels au niveau de la mandibule en ce qui concerne les échecs post-prothétiques et les fréquences de complication dans un essai clinique multicentrique randomisé. Parmi les protocoles de traitement, les deux recouvrements ne semblaient pas être différents vis-à-vis de l'apparition de déficience d'intégration post-prothétique (ID) ou de déficiences fonctionnelles (FD). L'équivalence statistique pour un effet absolu de +/- 15 % dans la survie sans problème a seulement pû être démontrée pour FD et non pour ID. Les analyses d'intention de traiter et par protocole donnaient des résultats concrets. Les hasards de l'apparition de ID et FD ajustés pour les années de suivi ont été estimés pour ID à 7% par an (95% CI 4–10%/an) avec HA et à 5% par an (95% CI 3–7%/an) avec TPF, et pour FD à 5% par an (95% CI 3–7%/an) avec HA et à 4% par an (95% CI 2–6%/an) avec TPF. Les taux de succès cumulatifs à cinq ans pour l'absence d'ID étaient de 69,5% (95% CI 58–81%) avec HA et de 82,2% (95% CI 74–91%) avec TPF. En ce qui concerne les fréquences de complications, il n'y avait aucune véritable différence entre les deux types de recouvrement.

Zusammenfassung

Intramobile Zylinderimplantate (IMZ) mit Hydroxyapatitbeschichtung (HA) oder mit Titan Plasma Flammenbeschichtung (TPF), welche als distale Pfeiler für zahn/implantat-getragene Rekonstruktionen dienten, wurden bei 313 teilbezahnten Unterkiefern verglichen. In einem klinischen Versuch mit zufälliger Verteilung an verschiedenen Zentren wurden die prothetischen Misserfolge und

die Frequenzen der Komplikationen untersucht. Innerhalb des Behandlungsprotokolls zeigen die zwei Beschichtungen keine Unterschiede in Bezug auf das Auftreten einer postprothetischen Integrationsunzulänglichkeit (ID) oder einer funktionellen Unzulänglichkeit (FD). Statistische Aequivalenz für einen absoluten Effekt von +/-15% in ereignisfreiem Ueberleben konnte jedoch nur für FD aber nicht für ID gezeigt werden. Analysen der Behandlungsabsicht und der per-protokoll Population ergaben übereinstimmende Resultate. Zufälliges Auftreten von ID und FD, angepasst an die Anzahl Jahre Nachuntersuchung, wurde für ID als 7% pro Jahr (95%ci 4–10% pro Jahr) mit HA und 5% pro Jahr (95%ci 3–7% pro Jahr) mit TPF eingeschätzt. Für die FD betrugen die Werte 5% pro Jahr (95ci 3–7% pro Jahr) mit HA und 4% pro Jahr (95%ci 2–6% pro Jahr) mit TPF. Die kumulative Erfolgsrate über fünf Jahre ohne ID betrug 69.5% (95%ci 58–81%) mit HA und 82.2% (95%ci 74–91%) mit TPF. In Anbetracht der Frequenzen der Komplikationen bestanden keine relevanten statistisch signifikanten Unterschiede zwischen den beiden Beschichtungen

Resumen

Se compararon implantes con cilindro intramovil (IMZ) con dos coberturas, hidroxiapatita (HA) y plasma de titanio a la llama (TPF), como pilares distales para restauraciones combinadas soportadas por diente e implante, en 313 mandíbulas parcialmente edéntulas con respecto a patrones de fracaso postprostético y frecuencias de complicación en un ensayo clínico multicéntrico aleatorio. Dentro de los protocolos de tratamiento, las dos coberturas no muestran evidencias de eficacia diferente con respecto a la ocurrencia de la deficiencia de integración (ID) o deficiencia funcional (FD) postprostética. De todos modos, la equivalencia estadística por un efecto absoluto de ±15% en la supervivencia libre de eventos sólo pudo ser demostrada para FD y no para ID. Los riesgos de ocurrencia de ID y FD, ajustados durante los años de seguimiento, se estimaron para ID para 7% por año (95%ci 4–10% por año) con HA y 5% por año (95%ci-3–7% por año) con TPF, y para FD como 5% por año (95ci-3–7% por año) con HA y 4% por año (95%ci 2–6% por año) con TPF. Los índices de éxito acumulativo durante 5 años para no ID fueron del 69.5% (95%ci 58 a 81%) con HA y 82.2% (95%ci 74–91%) con TPF. Con respecto a la frecuencia de complicaciones no hubo una diferencia estadísticamente significativa relevante entre las dos coberturas.

要旨

無作為割付多施設臨床試験において、３１３名の下顎部分無歯顎にハイドロキシアパタイト（HA）かチタン・プラズマ溶射（TPF）のいずれかのコーティングを施した内部可動式シリンダーインプラント（IMZ）を、遠心支台として埋入し、天然歯と連結したインプラント補綴治療を行った後、失敗のパターンと合併症の発症率に関する比較を行った。治療プロトコール内では、２種類のコーティング間に、補綴治療後の統合の欠陥（ID）や機能的欠陥（FD）に関する有効性に差異はなかった。無病生存率における±１５％の絶対効果の統計的同等性は、FD については示されたが、ID については示されなかった。しかし全例解析とプロトコール前の母集団の分析は、一環した結果を示した。追跡期間の調整を行った後 ID と FD の発生のハザード率は、ID については HA の場合が年あたり７％（９５％ci４－１０％／年）、TPF の場合が年あたり５％（９５％ci３－７％／年）であり、FD については HA が年あたり５％（９５％ci３－７％／年）、TPF が年あたり４％（９５％ci２－６％／年）であった。ID なしの５年累積成功率は、HA が６９．５％（９５％ci５８－８１％）及び TPF が８２．２％（９５％ci７４－９１％）であった。合併症の発症率については、２種類のコーティング間に統計学的に有意な差異はなかった。

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