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A Randomized Comparison of Repeat Stenting With Balloon Angioplasty in Patients With In-Stent Restenosis

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OBJECTIVES This randomized trial compared repeat stenting with balloon angioplasty (BA) in patients with in-stent restenosis (ISR).

BACKGROUND Stent restenosis constitutes a therapeutic challenge. Repeat coronary interventions are currently used in this setting, but the recurrence risk remains high.

METHODS We randomly assigned 450 patients with ISR to elective stent implantation (224 patients) or conventional BA (226 patients). Primary end point was recurrent restenosis rate at six months. Secondary end points included minimal lumen diameter (MLD), prespecified subgroup analyses, and a composite of major adverse events.

RESULTS Procedural success was similar in both groups, but in-hospital complications were more frequent in the balloon group. After the procedure MLD was larger in the stent group (2.77 ± 0.4 vs. 2.25 ± 0.5 mm, $p < 0.001$). At follow-up, MLD was larger after stenting when the in-lesion site was considered (1.69 ± 0.8 vs. 1.54 ± 0.7 mm, $p = 0.046$). However, the binary restenosis rate (38% stent group, 39% balloon group) was similar with the two strategies. One-year event-free survival (follow-up 100%) was also similar in both groups (77% stent vs. 71% balloon, $p = 0.19$). Nevertheless, in the prespecified subgroup of patients with large vessels (≥3 mm) the restenosis rate (27% vs. 49%, $p = 0.007$) and the event-free survival (84% vs. 62%, $p = 0.002$) were better after repeat stenting.

CONCLUSIONS In patients with ISR, repeat coronary stenting provided better initial angiographic results but failed to improve restenosis rate and clinical outcome when compared with BA. However, in patients with large vessels coronary stenting improved the long-term clinical and angiographic outcome. (J Am Coll Cardiol 2003;42:796–805) © 2003 by the American College of Cardiology Foundation

Coronary stenting is increasingly used during coronary interventions (1–3). Treatment of in-stent restenosis (ISR), however, represents a technical and clinical challenge (4–11). Satisfactory initial results are usually obtained with conventional balloon angioplasty (BA), but the risk of recurrent restenosis remains high (4–11). Therefore, the use of alternative mechanical approaches, such as debulking techniques, has been advocated (12–14). However, a recent randomized study (13) failed to demonstrate benefits of rotational atherectomy in these patients. Angiographic and intravascular ultrasound studies suggest that repeated coronary interventions do not obtain the same results that were achieved during initial stent implantation (4,7,11). Accordingly, suboptimal procedural results could explain the unsatisfactory course of some patients. In addition, although the effectiveness of coronary brachytherapy has been clearly demonstrated in this setting, it is not widely available and it has inherent problems and limitations (15–18). There is, therefore, still a need to determine which mechanical intervention is best suited for patients with ISR, a problem affecting up to 150,000 patients annually in the U.S. alone (18).

In some patients treated for ISR, a new "unplanned" stent implantation is eventually required to achieve a satisfactory final angiographic result (19–22). Preliminary reports (21,22) have suggested the potential value of "elective" stenting (used as the primary strategy) in these patients. Nevertheless, the outcome of patients with ISR electively treated by the implantation of a new stent remains largely unknown.

We hypothesized that repeat coronary stenting could improve the initial angiographic results of patients with ISR and that this might translate into better long-term clinical and angiographic outcomes. Therefore, we conducted a multicenter randomized trial to compare elective coronary stenting with conventional BA in these patients.

METHODS

Patient selection and study design. Patients with angina or objective evidence of myocardial ischemia undergoing

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Abbreviations and Acronyms

BA = balloon angioplasty
ECG = electrocardiogram
ISR = in-stent restenosis
MI = myocardial infarction
MLD = minimal lumen diameter

repeat coronary interventions for ISR (>50% stenosis on visual estimation) were eligible if they had lesions amenable to both interventional strategies. The target lesion had to be a first ISR that could be spanned by a single stent (≤32 mm in length) and had to be located in a vessel >2.5 mm in diameter. Lesions located in severely tortuous or calcified vessels and those presenting as total occlusions were excluded. Patients with prior stent implantation within the previous month, severe concomitant systemic illness, and conditions likely to preclude follow-up angiography were not included. The study was carried out following the principles of the Declaration of Helsinki regarding investigations with human subjects (23) and the recommendations for conducting/reporting randomized trials (24). Written informed consent was obtained from all patients. Randomization was performed by telephone, using a computer-generated code, and was stratified according to restenosis length.

At the coordinating center, data were verified by consistency checks, and double data set entry and queries about any missing or inconsistent data were sent back to the sites. Summaries of clinical records from all patients with potential events were also reviewed at the coordinating center. Subsequently, all events were classified and adjudicated by an independent clinical events committee unaware of the assigned treatment.

Coronary interventions. All patients were pretreated with aspirin, and 100 IU/kg of heparin was given as a bolus at the beginning of the procedure. Balloon size was selected with the aim of achieving a final balloon-to-artery ratio of 1.1/1. Relatively high pressures (>12 atm) were recommended in both arms. In patients allocated to repeat stenting the stent was deployed after a previous balloon dilation of the lesion. Because the strategy of repeated stenting (rather than the value of any specific stent design) was under investigation, three different noncoil stent designs were selected for the study: the NIR stent (Boston Scientific, Maple Grow, Minnesota) (106 patients), the Crown stent (Cordis, Johnson and Johnson, Warren, New Jersey) (46 patients), and the Bestent (Medtronic-AVE, Santa Rosa, California) (45 patients). However, in 24 patients other noncoil stent types were eventually implanted for logistic reasons or operator preferences. Crossover to the other treatment method was strongly discouraged. In all cases repeated prolonged balloon inflations had to be attempted before crossover to stent deployment. Crossover was allowed only in patients with persistent stenosis >50%, major coronary dissections (National Heart, Lung, and Blood Institute types D-F), or dissections associated with ischemia.

Creatine kinase levels (with myocardial isoenzymes if abnormal) and 12-lead electrocardiograms (ECGs) were obtained before the procedure and every eight hours afterwards for 24 h. Personnel blinded to the assigned treatment reviewed the ECGs. Procedural success was defined as angiographic success (residual stenosis <50%) in the absence of major complications. Myocardial infarction (MI) was considered in the presence of two of the following: prolonged (>30 min) chest pain, new Q-waves (>0.04 s), and increase in the creatine kinase level more than twice the upper normal value (with a MB fraction >10% of the total value). All patients received aspirin indefinitely, whereas patients treated with repeated stenting also received ticlopidine (500 mg daily) for one month. Patients were followed up at one, six, and seven months and at one year. An exercise test was recommended immediately before the follow-up angiography. Angiographic follow-up was obtained routinely at six months or earlier if clinically indicated. Follow-up angiographic data obtained <3 months after the index procedure were excluded unless restenosis was documented; otherwise, the patient was asked to undergo the scheduled angiogram at six months.

Objectives. The primary end point was the recurrent restenosis rate "per segment." Secondary end points included: 1) the analysis of the influence of 10 prespecified relevant variables on the restenosis rate according to the assigned treatment (age, gender, diabetes, unstable angina, time to restenosis, left anterior descending coronary artery location, reference vessel ≥3 mm, diffuse [≥10 mm] restenosis, stent type, and balloon/artery ratio); 2) comparison of minimal lumen diameters (MLDs) at follow-up; 3) comparison of angiographic findings confined to the "in-lesion" analysis; and 4) assessment of a combined clinical end point at one year follow-up.

Angiographic analysis. Multiple coronary views were obtained after the administration of intracoronary nitroglycerin (0.2 mg). All cine films or CDs were analyzed at the centralized angiographic core laboratory and reviewed by experienced personnel blind to the assigned treatment (25). Special care was taken in trying to identify the site of initial stent deployment—before the injection of contrast material—and subsequently the relative location of the lesion. Detailed drawings of these two sites (requested on the case report forms) were also reviewed. Quantitative coronary angiographic analysis was carried out using a validated, automatic edge-detection algorithm (MEDIS, CMS 4.0, Leiden, the Netherlands) (26). Matched angiographic views were reviewed before, after intervention and at follow-up. A first analysis was confined at the lesion site "in-lesion analysis" (site showing the initial narrowing), and a second analysis considered "the segment" that encompassed the lesion site, the treated region, and the adjacent 5 mm of the

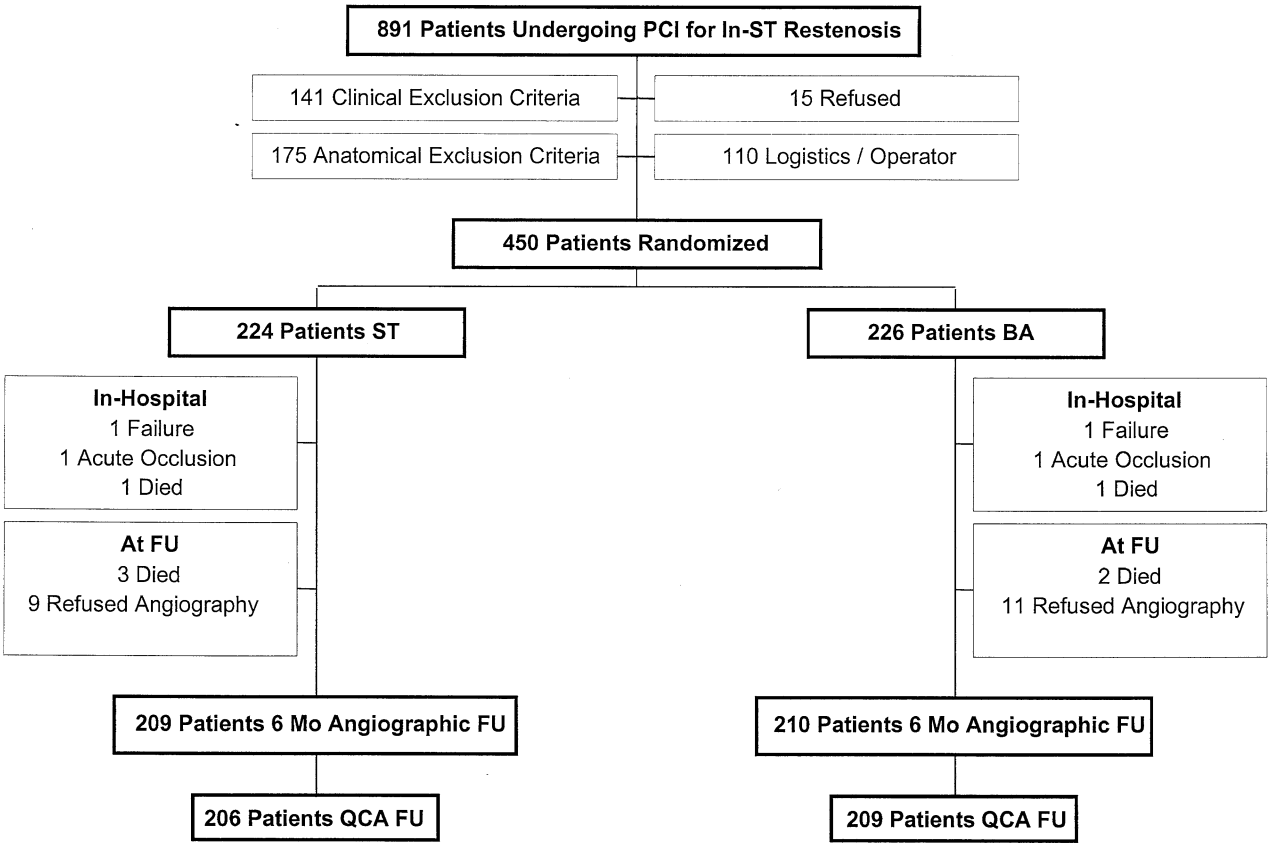

Figure 1. Trial profile. Of 891 consecutive patients undergoing repeat coronary interventions for in-stent restenosis during the study period, 450 (51%) were included in the trial. BA = balloon angioplasty arm; FU = follow-up; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; ST = stent arm.

vessel on each side. This methodology has been used in previous controlled trials (18,27). A binary definition for restenosis (stenosis >50% at follow-up) was used.

Statistical analysis. On the basis of data from a previous *pilot study* of repeated stenting for ISR (21) and prior studies of BA in this setting (7) (2/3 of patients presenting diffuse ISR), a recurrent restenosis rate of 30% and 45% was estimated in the stent and balloon groups respectively. Given these assumptions we required 185 in each group to be able to detect a 30% reduction in the restenosis rate with repeat stenting with a power (1-beta) of 90% and a type I error (alpha) of 5%. To compensate for non-evaluable patients at follow-up (10% expected, because of patient refusal or poor-quality angiograms), the sample size was increased to a total number of 450 patients. Comparisons were performed according to the intention-to-treat principle. Categorical data were compared with the chi-square test or Fisher exact test (when expected values were <5). For the comparison of continuous variables a two-tailed Student *t* test (normally distributed data) or Wilcoxon rank-sum nonparametric test were used. Rates of event-free survival were studied with Kaplan-Meier analysis and compared with the log-rank test. Cox proportional hazards models were also used to assess events. The 10 prespecified subgroups, were examined for interactions (28,29) using a logistic regression model. The p value of the interaction terms was corrected with the Bonferroni test. Analyses were performed using the SPSS package (version 10.0). A p value <0.05 was considered statistically significant.

RESULTS

Hospital results. Between December 1997 and December 1999, 450 patients were enrolled at 24 investigational sites from Spain and Portugal; 224 patients were assigned to repeat stent implantation and 226 to balloon treatment (Fig. 1). Baseline demographic, clinical, and angiographic data (Table 1) were well matched in the two groups. Procedural characteristics were also similar, although higher inflation pressures and shorter total balloon inflation times were used in the stent arm (Table 1).

Angiographic success (448 patients, 99%) was obtained in all but one patient in each group. Procedural success was similar in both groups (98% stent group, 95% balloon group, p = 0.11). Crossover to the other strategy was required in only 16 patients, 13 (5.7%) in the balloon group and 3 (1.3%) in the stent group (p = 0.02). All but 11 patients (5%) in the stent group were treated with single stents (mean stented length 19 ± 6 mm). During hospitalization 2 patients died, 11 developed MI (Q-wave in 1), and 1

Table 1. Baseline Clinical, Angiographic, and Procedural Characteristics

Characteristic	Stent Group (n = 224)	Balloon Group (n = 226)
Age (yrs)	61 ± 11	61 ± 11
Female gender, no. (%)	59 (26)	42 (19)
Risk factors, no. (%)		
Diabetes mellitus	60 (27)	58 (26)
Hyperlipidemia	132 (59)	117 (53)
Hypertension	131 (59)	116 (51)
Ever smoked	122 (55)	136 (60)
Clinical features, no. (%)		
Unstable angina	102 (45)	92 (41)
Stable angina	105 (47)	119 (53)
Silent ischemia*	17 (8)	15 (6)
Previous myocardial infarction	98 (44)	95 (42)
Previous bypass surgery*	9 (4)	10 (4)
Time to restenosis, days†	180 (132–230)	180 (124–228)
Target artery, no. (%)		
Left anterior descending	105 (47)	130 (57)
Left circumflex	50 (22)	38 (17)
Right coronary	65 (29)	53 (24)
Saphenous vein graft*	4 (2)	5 (2)
Multivessel disease	108 (48)	92 (41)
Ejection fraction (%)	65 ± 12	64 ± 12
Procedural characteristics		
Maximal pressure (atm)	13.5 ± 2.2	12.6 ± 2.8‡
Total inflation time (s)	131 ± 86	176 ± 120§
Final balloon diameter (mm)	3.14 ± 0.4	3.09 ± 0.4
IIb/IIIa inhibitors	4 (2%)	8 (4%)

*Fisher exact test. †Median and interquartile range (25th to 75th percentile) (Wilcoxon test). ‡$p < 0.001$, §$p < 0.01$. Plus-minus values are means ± SD.

patient (with initial angiographic failure) required elective surgery before discharge (Table 2). Two patients experienced subacute vessel occlusion during admission and required repeat interventions (one fulfilled the study criteria of MI). Altogether there were fewer hospital complications in the stent group (Table 2).

Angiographic findings. Angiographic data before and immediately after the procedure are summarized in Table 3

Table 2. In-Hospital and One Year Clinical Events

Event	Stent Group (n = 224)	Balloon Group (n = 226)	p Value	Relative Risk (95% CI)
Hospital events, no. (%)				
Death	1 (0.4)	1 (0.4)	1	1 (0.06–16.03)
Myocardial infarction	2 (0.9)	9 (4)	0.06	0.22 (0.05–1.03)
Target vessel revascularization	1 (0.4)	2 (0.9)	1	0.50 (0.046–5.52)
Coronary angioplasty	1 (0.4)	1 (0.4)	1	1 (0.06–16.03)
Coronary surgery	0 (0)	1 (0.4)		
Any major hospital event	3 (1.3)	11 (4.9)	0.039	0.27 (0.078–0.97)
Events at 7 months, no. (%)				
Death	5 (2.2)	4 (1.8)	0.75	1.26 (0.34–4.64)
Myocardial infarction	5 (2.2)	12 (5.3)	0.13	0.42 (0.15–1.17)
Target vessel revascularization	37 (16.5)	39 (17.3)	0.9	0.96 (0.63–1.44)
Coronary angioplasty	27 (12)	29 (12.8)	0.89	0.94 (0.57–1.53)
Coronary surgery	12 (5.4)	11 (4.9)	0.83	1.10 (0.49–2.44)
Any major event at 7 months	42 (19)	47 (21)	0.64	0.90 (0.62–1.31)
Events at 1 yr, no. (%)				
Death	8 (4)	7 (3)	0.8	1.15 (0.42–3.12)
Myocardial infarction	6 (2.7)	13 (5.8)	0.15	0.46 (0.18–1.20)
Target vessel revascularization	44 (19.6)	55 (24.3)	0.25	0.81 (0.57–1.14)
Coronary angioplasty	32 (14)	43 (19)	0.20	0.75 (0.49–1.14)
Coronary surgery	14 (6.3)	13 (5.8)	0.84	1.08 (0.52–2.26)
Any major event at 1 yr (+)	52 (23)	65 (29)	0.19	0.81 (0.58–1.10)

Patients with more than one event are counted only once for the composite clinical end points, although each event is listed separately in the corresponding category.

CI = confidence interval; (+) = a prespecified secondary study end point (p values from Cox analysis).

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Table 3. Initial and Follow-Up Angiographic Results

Variable	Stent Group	Balloon Group	p Value
Before the procedure	(n = 224)	(n = 226)	
Reference vessel diameter (mm)	2.87 ± 0.5	2.83 ± 0.5	0.24
Minimal lumen diameter (mm)	0.68 ± 0.4	0.67 ± 0.4	0.79
Stenosis (% of lumen diameter)	76 ± 12	76 ± 12	0.95
Lesion length (mm)	12.7 ± 6	13.0 ± 7	0.62
Diffuse lesions (>10 mm), no. (%)	132 (60)	130 (59)	1
After the procedure	(n = 224)	(n = 226)	
Reference vessel diameter (mm)	3.12 ± 0.4	2.92 ± 0.5	< 0.001
Minimal lumen diameter (mm)	2.77 ± 0.4	2.25 ± 0.5	< 0.001
Stenosis (% of lumen diameter)	12 ± 10	23 ± 10	< 0.001
Acute gain (mm)	2.08 ± 0.5	1.58 ± 0.5	< 0.001
At follow-up ("per segment" analysis)	(n = 206)	(n = 209)	
Reference vessel diameter (mm)	2.91 ± 0.5	2.82 ± 0.5	0.042
Minimal lumen diameter (mm)	1.63 ± 0.8	1.52 ± 0.7	0.17
Stenosis (% of lumen diameter)	45 ± 25	46 ± 23	0.82
Restenosis, no (%)	79 (38)	82 (39)	0.92
Late loss (mm)	1.12 ± 0.8	0.73 ± 0.7	< 0.001
Loss index	0.55 ± 0.4	0.42 ± 0.5	0.004
Net gain (mm)	0.95 ± 0.8	0.84 ± 0.7	0.13
At follow-up ("in lesion" analysis)	(n = 206)	(n = 209)	
Reference vessel diameter (mm)	2.91 ± 0.5	2.82 ± 0.5	0.03
Minimal lumen diameter (mm)	1.69 ± 0.8	1.54 ± 0.7	0.046
Stenosis (% of lumen diameter)	43 ± 24	45 ± 23	0.31
Restenosis, no. (%)	69 (33)	80 (38)	0.36
Late loss (mm)	1.06 ± 0.7	0.72 ± 0.7	< 0.001
Loss index	0.52 ± 0.4	0.42 ± 0.5	0.02
Net gain (mm)	1.01 ± 0.8	0.85 ± 0.68	0.03

and Figure 2. Of the 262 lesions with diffuse restenosis, 99 had a proliferative pattern (14). Reference vessel size and MLD before intervention were similar in the two groups. After the procedure, however, angiographic results were significantly better in the stent group. Patients in the stent group obtained a larger final MLD and had a larger acute gain and a lower residual diameter stenosis compared with those in the balloon group.

Quantitative coronary angiographic follow-up data (Table 3, Fig. 2) were obtained in 415 of 439 (95%) eligible patients (median 188 days, similar in both groups) (Fig. 1). Although MLD at follow-up ("per-segment" analysis) was larger in the stent group, this difference was no longer significant ($p = 0.17$). However, when the more stringent "in-lesion" analysis was used, patients in the stent group obtained a significantly better MLD at follow-up ($p = 0.046$) and a larger net gain (Table 3). The binary restenosis rate per segment analysis was similar in the two groups (38% stent group vs. 39% balloon group). Restenosis rates for patients with focal (27% vs. 26%), diffuse (39% vs. 43%) and proliferative (58% vs. 59%) ISR were similar with the two techniques. In addition, the restenosis rate using the "in-lesion" analysis was also similar (33% stent arm vs. 38% balloon arm, $p = 0.36$) (Table 3). The "per-protocol" angiographic analysis did not differ from the primary intention to treat analysis. In the stent arm no differences could be identified among the three stents used (p for interaction 0.29). Finally, the influence of the 10 prespecified variables on treatment effect is summarized in Figure 3. On logistic regression analysis there was a significant vessel-size/treatment-effect interaction ($p = 0.001$, $p = 0.01$ after the Bonferroni correction). In patients with large vessels (reference diameter ≥3 mm), the binary restenosis rate was significantly reduced after stenting (27% vs. 49%, $p = 0.007$; risk ratio 0.55, 95% confidence interval 0.35 to 0.85). In clinical terms, four patients with ISR in large vessels would need to be treated by repeat stenting to prevent one episode of recurrent restenosis. Conversely, in patients with small vessels (<2.6 mm, lower tercile) the restenosis rate (59% vs. 41%, $p = 0.053$) tended to be higher in the stent group.

Clinical follow-up. All 450 patients were followed up for one year with no patient lost to follow-up (Table 2). Of the 99 patients undergoing target vessel revascularization during follow-up, 96 (97%) had angina or documented ischemia (as required by protocol), but in 3 patients (1 stent group, 2 balloon group) only an "anatomic indication" led to repeat intervention. Although the clinical outcome was similar in the two groups a nonsignificant trend ($p = 0.19$) was found for a poorer event-free survival in the balloon group (Fig. 4), mainly because a larger number or patients required target vessel revascularization. In patients with large vessels, however, the one-year event-free survival was significantly better in the stent group (Fig. 4). This difference was largely determined by a reduced need for repeat interventions (13% vs. 34%, $p = 0.002$).

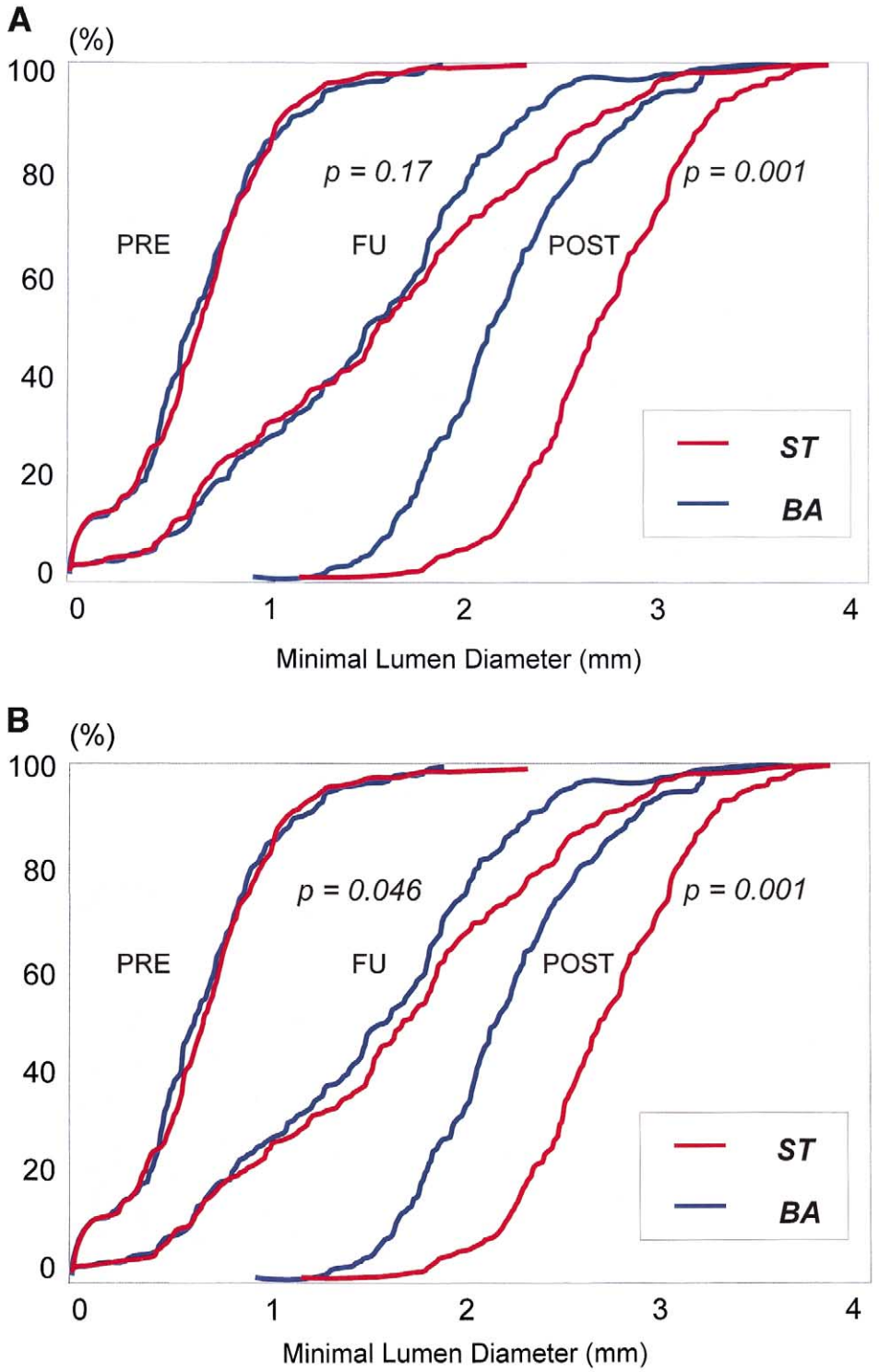

Figure 2. Cumulative frequency distribution curves of the minimal lumen diameter before the procedure (PRE), immediately after intervention (POST), and at six months follow-up (FU), in patients treated with balloon angioplasty (BA) and repeat stenting (ST). **(A)** "Per-segment" analysis. **(B)** "In-lesion" analysis. After the procedure the distribution curve in the stent group is shifted to the right (with the two analyses) indicating a larger acute gain. At follow-up the results of the stent group are better than those in the balloon group in the "in-lesion" analysis **(B)**, but not in the "per-segment" analysis **(A)**.

DISCUSSION

This study has demonstrated the value of stent implantation in patients with ISR. This technique reduced the risk of procedure-related complications and provided much better immediate angiographic results but failed to reduce the rate of recurrent restenosis compared with BA. In fact, MLD at follow-up was better after stenting only when the "in-lesion"

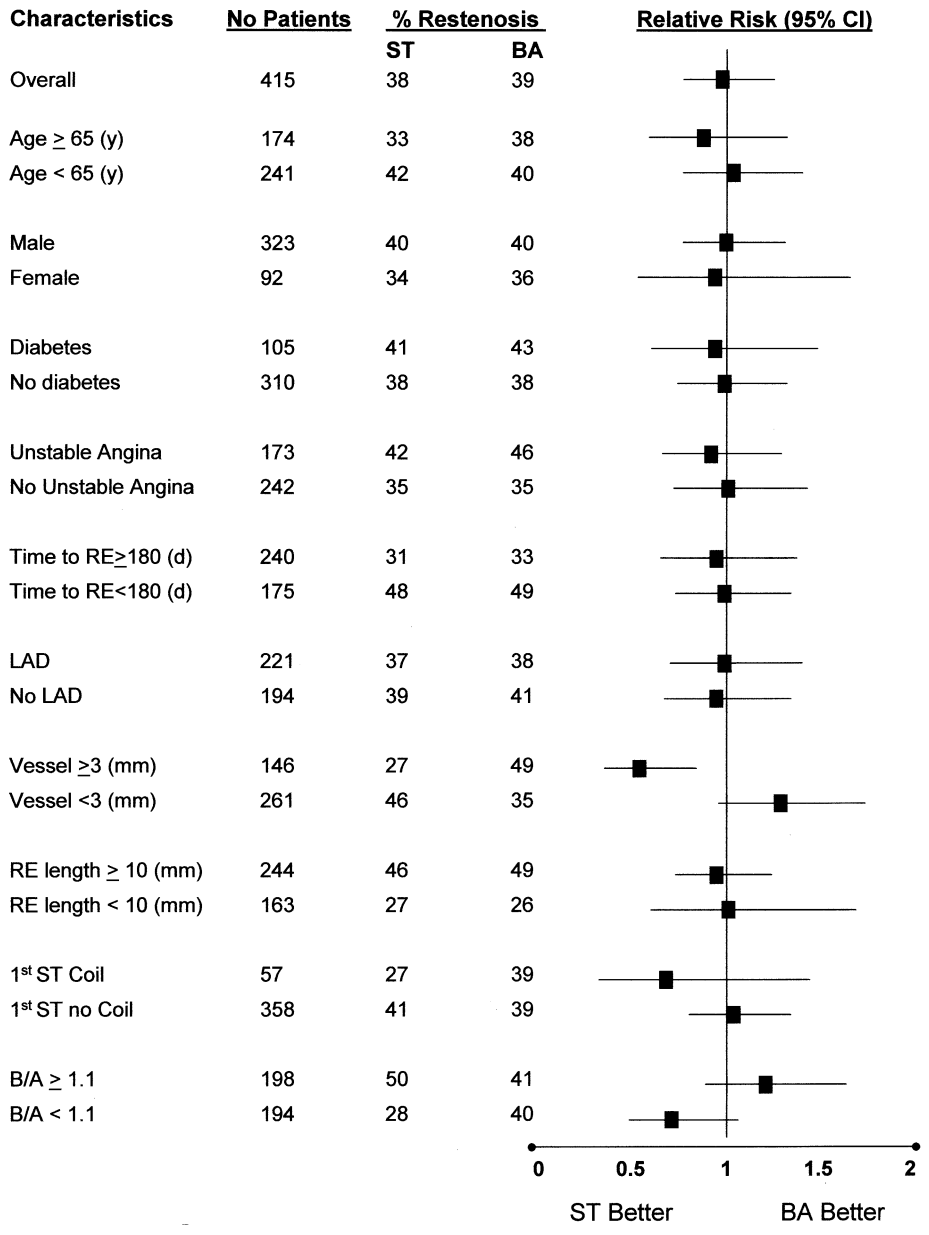

Figure 3. Rates, relative risks, and confidence intervals (CI) of restenosis according to the 10 prespecified variables. P values for the interaction (logistic regression analysis) were only significant for reference vessel size (p = 0.001). BA = balloon angioplasty; B/A = balloon to artery ratio; LAD = left anterior descending coronary artery; RE = restenosis; ST = stent.

segment was taken into consideration. The study also suggests that in patients with large vessels (≥3 mm) repeat stenting appears to have long-term clinical and angiographic benefits beyond those obtained with BA and, therefore, should be recommended.

The current study shows that repeat stenting is safe and can be readily accomplished. Indeed, the occurrence of procedure-related complications was higher in the balloon arm. A previous observational study comparing BA with repeat stenting in patients with "focal" ISR (22) suggested that patients treated with BA had a higher rate of major in-hospital complications (death, Q-wave infarction, urgent revascularization). Although procedure-related complications in patients with ISR may be the result of side-branch occlusion, this event rarely results in clinically evident myocardial necrosis (9). Some of the MIs documented in our study were the result of crossover to stenting after a complicated BA procedure. The potential implication of the antiplatelet therapy imbalance in this regard is of interest but remains speculative.

Compared with conventional BA elective restenting provided much better immediate angiographic results because of a larger acute gain. These findings confirm that repeat stenting can guarantee an excellent immediate angiographic result in these patients (20–22). Nevertheless, recurrent restenosis rates were eventually high and similar with both techniques. The greater late loss and late loss-index seen in the stent group suggest that this strategy elicits a more profound proliferative response. Although the MLD at

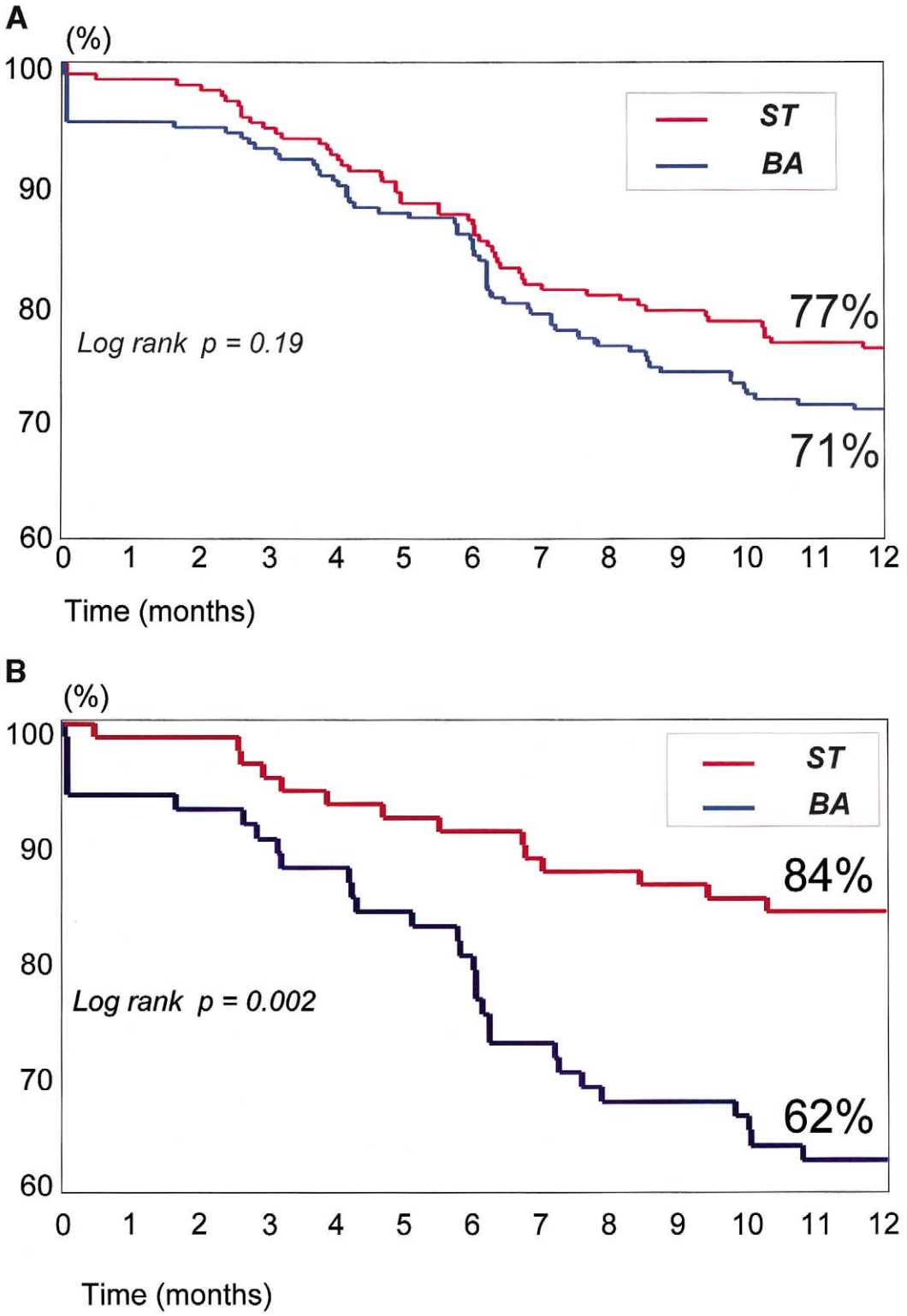

Figure 4. Kaplan-Meier estimates of the event-free survival at one year (death, myocardial infarction, or target vessel revascularization) according to treatment group. No differences were found between the two groups in the entire 450-patient population (Cox hazard ratio 0.81, 95% confidence interval [CI] 0.56 to 1.17) **(A),** but the event-free survival in patients with large vessels (≥3 mm) **(B)** was significantly greater in the stent group (Cox hazard ratio 0.31, 95% CI 0.2 to 0.73). This difference was due to the lower proportion of patients in the stent group that required target vessel revascularization. Note survival scales cut off at 60%. BA = balloon angioplasty; ST = stent.

follow-up was similar in the two groups on the "per-segment" analysis, better results were found after stenting when the analysis was focused on the "in-lesion" site. This may be relevant from the pathophysiologic point of view, suggesting that in some patients undergoing repeat stenting, a relocation of minimal lumen diameter at follow-up or "edge-effect" (27) may produce recurrent restenosis outside the site encompassed by the second stent.

The event-free survival at one year was also similar with the two techniques, with most patients having a satisfactory long-term outcome. The trend for a larger MLD at follow-up after repeat stenting could explain the associated trend toward a better long-term clinical outcome resulting from a reduction in the need for repeat interventions. In addition, the significant number of revascularization procedures after six months is of interest but also may have been driven by the requirement to demonstrate ischemia before proceeding with further revascularization. In this regard, an even longer clinical follow-up would have been of clinical relevance and this is currently planned for these patients.

Finally, an important study finding was the evidence of a major interaction between treatment effect and vessel size. In this study we prospectively predefined our subgroups of interest to determine potential interactions (28,29). In patients with large vessels (≥3 mm) elective stenting not only significantly reduced the restenosis rate compared with BA, but also improved the long-term clinical outcome. This significant "treatment effect size" (calculated power 80%) emerges from the analysis of a secondary study end point but has the inherent limitations of subgroup analyses. However, in our opinion, it is clinically relevant and may have implications for patient management. The striking difference in clinical outcomes between the stent and balloon groups in patients with large vessels was primarily due to the need for fewer repeat interventions on the target vessel. This parallels previous studies showing that the main clinical benefit of stenting in native coronary lesions occurs in large vessels as the result of a reduction in the number of reinterventions (1,2,30).

Conversely, in patients with small vessels repeat stenting was associated with a relatively high restenosis rate, and probably should be avoided. Although by design we tried to exclude patients with small vessels from this trial, one-third of our patients (with vessels >2.5 mm on visual estimation) actually had small vessels by quantitative angiography. Again, these findings mirror those found in "de novo" lesions, where the value of stenting in small vessels is, at least, controversial (31,32).

Repeat stenting, therefore, constitutes an attractive strategy for patients with ISR in large vessels. Alternatively, for most patients with small vessels and a focal pattern of restenosis BA should be preferred. Brachytherapy, however, currently remains the cornerstone of therapy for patients presenting with the vexing problem of diffuse ISR (15–18), where both angioplasty and repeat stenting are shadowed by an unacceptably high recurrence rate. Repeat stenting should not be recommended in combination with brachytherapy owing to the potential risk of late thrombosis (33).

Last, we used conventional stainless-steel stents in the present study. Our findings underscore the importance of assessing the results of restenting using the new drug-eluting stents. Because drug-coated stents prevent subsequent neointimal proliferation to a large extent (34), they appear to be ideally suited for the treatment of patients with ISR (35,36). However, the potential concern for edge effects should also be investigated with these new stents in patients with ISR.

Conclusions. Although some observational studies have suggested a potential benefit of "stenting the stent" for patients with ISR in this large multicenter randomized controlled trial repeat stenting failed to reduce the rate of recurrent restenosis when compared with BA. Nevertheless, our findings suggest that in patients with large vessels repeat stenting provides better long-term results and should be recommended.

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APPENDIX

The design and execution of the protocol as well as the analysis of the data were conducted at the coordinating center in a manner absolutely independent of the sponsors (research grants from Boston Scientific, Cordis [Johnson and Johnson], Medtronic) that had no access to the results of the trial until the analysis of the study objectives had been finalized.

The Restenosis Intra-stent: Balloon angioplasty versus elective Stenting (RIBS) Investigators, Coordinators, and Sites were the following:

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