

Percutaneous and Surgical Interventions for In-Stent Restenosis: Long-Term Outcomes and Effect of Diabetes Mellitus

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- OBJECTIVE** We examined long-term outcomes of patients with in-stent restenosis (ISR) who underwent different percutaneous interventions at the discretion of individual operators: balloon angioplasty (BA), repeat stent or rotational atherectomy (RA). We also examined long-term outcomes of patients with ISR who underwent coronary artery bypass surgery (CABG).
- BACKGROUND** In-stent restenosis remains a challenging problem, and its optimal management is still unknown.
- METHODS** Symptomatic patients (n = 510) with ISR were identified using cardiac catheterization laboratory data. Management for ISR included BA (169 patients), repeat stenting (117 patients), RA (107 patients) or CABG (117 patients). Clinical outcome events of interest included death, myocardial infarction, target vessel revascularization (TVR) and a combined end point of these major adverse cardiovascular events (MACE). Mean follow-up was 19 ± 12 months (range = 6 to 61 months).
- RESULTS** Patients with ISR treated with repeat stent had significantly larger average post-procedure minimal lumen diameter compared with BA or RA (3.3 ± 0.4 mm vs. 3.0 ± 0.4 vs. 2.9 ± 0.5 , respectively, $p < 0.05$). Incidence of TVR and MACE were similar in the BA, stent and RA groups (39%, 40%, 33% for TVR and 43%, 40%, 33% for MACE, $p = \text{NS}$). Patients with diabetes who underwent RA had similar outcomes as patients without diabetes, while patients with diabetes who underwent BA or stent had worse outcomes than patients without diabetes. Patients who underwent CABG for ISR, mainly because of the presence of multivessel disease, had significantly better outcomes than any percutaneous treatment (8% for TVR and 23% for MACE).
- CONCLUSIONS** In this large cohort of patients with ISR and in the subset of patients without diabetes, long-term outcomes were similar in the BA, repeat stent and RA groups. Tissue debulking with RA yielded better results only in diabetic patients. Bypass surgery for patients with multivessel disease and ISR provided the best outcomes. (J Am Coll Cardiol 2001;37:1877-82) © 2001 by the American College of Cardiology

Intracoronary stenting has been shown to have superior short- and long-term outcomes compared with conventional balloon angioplasty (1-3). Consequently, stenting is the procedure of choice in most percutaneous coronary interventions. However, angiographic and clinical restenosis after stenting develops in 15% to 45% of the cases and constitutes a major limitation to the effectiveness of this technique (1-4). Treatment of in-stent restenosis (ISR) has, therefore, become an important clinical problem. Several studies have shown variable results using balloon angioplasty (BA) alone (5-10), repeat stenting (11,12), rotational atherectomy (RA) (13-16) or directional atherectomy (17,18), excimer laser angioplasty (19,20) and, more recently, intracoronary radiation therapy (21-23). Other stud-

ies have compared these different techniques (24-31), and it is still unclear which one, if any, will provide the most favorable outcomes. The goal of this study was to compare the long-term outcomes of symptomatic patients with angiographically proven ISR who underwent either BA, repeat stenting or RA or those patients who underwent coronary artery bypass graft surgery (CABG).

METHODS

Patients. We reviewed the cardiac catheterization laboratory records from both Memorial Hermann Hospital and St. Luke's Episcopal Hospital in Houston, Texas. Between January 1995 and July 1999, a total of 630 consecutive patients with no prior history of CABG underwent coronary angiography for chest pain syndromes and had angiographically documented first occurrence of ISR of native coronary vessels ($\geq 70\%$ diameter stenosis at the stented region). Of those, 120 patients received medical treatment

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Abbreviations and Acronyms

BA	=	balloon angioplasty
CABG	=	coronary artery bypass graft surgery
ISR	=	in-stent restenosis
LAD	=	left anterior descending artery
MACE	=	major adverse cardiovascular events
MI	=	myocardial infarction
MLD	=	minimal lumen diameter
RA	=	rotational atherectomy
TVR	=	target vessel revascularization

only and were excluded from our study. The remaining patients (n = 510) underwent revascularization for in-stent restenosis, including BA (169 patients), repeat stenting (117 patients), RA (107 patients) or CABG (117 patients). The choice of revascularization procedure was at the discretion of the operator, and all procedures were done according to standard techniques. None of the study patients received medications or radiation specifically to prevent restenosis.

Demographic and clinical characteristics. At both institutions, demographic and clinical characteristics were recorded on standard forms. Angiographic and procedural data were recorded by trained cardiac catheterization laboratory personnel. Postprocedural events were monitored and recorded using standard protocols in each hospital.

Follow-up. Information was collected primarily using a mailed standardized questionnaire. Additional information was obtained using telephone contacts or review of medical records during outpatient visits and hospitalizations.

Clinical end points. Clinical end points of interest included death from any cause, target vessel revascularization (TVR), including percutaneous interventions or surgical revascularization, myocardial infarction (MI) or angina necessitating hospitalization accompanied with documented ischemia on a stress test. A combined end point of these was termed major adverse cardiovascular events (MACE). Patients were not re-entered into the study after reaching an initial end point.

STATISTICAL ANALYSIS

Continuous data are presented as mean ± SD, and discrete data are presented as frequencies. Continuous data were compared using analysis of variance, and frequencies were compared using the chi-square or Fischer exact tests. To account for different duration of follow-up, the incidence of event-free survival was compared among four groups. A multivariate analysis was performed to identify the predictors of adverse cardiovascular events in a model that included age, gender, hypertension, diabetes, hypercholesterolemia, smoking status, lesion location, lesion type and length and mode of intervention. A p value of <0.05 was considered to be significant.

RESULTS

Demographic and clinical characteristics. The demographic and clinical characteristics of the 510 patients included in the analysis are shown in Table 1. None of the values were significantly different.

Angiographic characteristics. As depicted in Table 2, patients who underwent repeat stenting had left anterior descending artery (LAD) lesions treated less often compared with patients with treated with BA, RA or CABG. They also had a shorter mean ISR lesion length and larger mean postintervention minimal lumen diameter (MLD) when compared with patients receiving BA or RA treatment. Multivessel disease was present in 20% to 25% of patients who had percutaneous interventions for ISR but was present in 85% of patients who received CABG for ISR.

Clinical end points. Adequate follow-up was obtained in 490 patients (96%), and mean follow-up duration was 19 ± 12 months (range 6 to 61 months). The incidence of different clinical end points in all four groups is shown in Table 3. No significant differences were seen in the incidence of TVR (including percutaneous interventions) or MACE between patients who underwent BA or repeat stent treatment (39% vs. 40% for TVR and 43% vs. 40% for MACE). On the other hand, patients who underwent RA

Table 1. Demographic and Clinical Characteristics of Patients With In-Stent Restenosis According to Treatment Group

	Balloon Angioplasty (n = 169)	Stent (n = 117)	Rotational Atherectomy (n = 107)	CABG (n = 117)
Age (yr)	61 ± 12	63 ± 13	60 ± 10	64 ± 12
Women (%)	34	39	35	25
Diabetes (%)	25	29	36	32
Hypertension (%)	79	79	76	76
Hypercholesterolemia (%)	64	62	77	64
Smoker (%)	56	53	55	60
Prior CHF (%)	13	14	16	12
Prior MI (%)	45	39	46	51

CABG = coronary artery bypass graft surgery; CHF = congestive heart failure; MI = myocardial infarction.

Table 2. Angiographic Characteristics in Different Treatment Groups

	Balloon Angioplasty (n = 169)	Stent (n = 117)	Rotational Atherectomy (n = 107)	CABG (n = 117)
LAD lesion (%)	47	30*	42	44
Type C lesion (%)	23	23	23	20
Lesion length (mm)	23 ± 10	18 ± 6*	21 ± 5	—
Post-treatment MLD (mm)	3.0 ± 0.4	3.3 ± 0.4*	2.9 ± 0.5	—
Multivessel disease (%)	22	25	20	85*

*p < 0.05 compared with other groups.

CABG = coronary artery bypass surgery; LAD = left anterior descending; MLD = minimal luminal diameter.

had a lower incidence of TVR and MACE when compared with patients treated with BA and repeat stent, although it did not reach statistical significance. Patients who underwent CABG had a significantly lower incidence of TVR (8%) and MACE (23%) compared with patients who underwent a percutaneous intervention. No significant differences were seen in the incidence of death or angina/MI among all four groups. The incidence of two-year event-free survival was also compared among four groups. As seen in Table 4, BA, stent and RA yielded similar outcomes. On the other hand, TVR-free and MACE-free survival were higher in the CABG group (p = 0.01 for TVR and 0.06 for MACE). After controlling for baseline variables, CABG, but not BA, stent or RA, was independently associated with lower incidences of TVR and MACE.

Effect of diabetes mellitus. Patients were grouped according to their diabetic status, and clinical outcome was assessed in different treatment groups. As shown in Table 5, the incidence of TVR and MACE was the same in patients with diabetes who underwent BA or repeat stent and was significantly higher than it was in patients without diabetes. Patients with diabetes who underwent RA had a lower incidence of TVR and MACE than patients with diabetes who underwent BA or repeat stenting, and their outcome was similar to patients without diabetes who underwent percutaneous interventions. There were no significant differences in the incidence of TVR or MACE in patients without diabetes regardless of the percutaneous intervention used. Coronary artery bypass graft surgery was superior to percutaneous interventions in both patients with and without diabetes. Mortality was similar in patients with and without diabetes regardless of which intervention was used.

DISCUSSION

To our knowledge, this is one of the largest studies that compare the long-term outcomes of patients who underwent BA, repeat stent or RA for ISR. This is also the first study that assesses the long-term outcomes of surgical revascularization for this problem.

Despite a better procedural outcome in the repeat stent group with a larger postprocedure MLD, the long-term outcomes of these patients were similar to those who underwent BA alone. Patients who underwent debulking with RA had a better long-term outcome than patients undergoing BA or repeat stent, although with the small number of patients, the difference did not reach statistical significance. Patients with diabetes who underwent RA had similar outcomes as patients without diabetes, while patients with diabetes who underwent BA or repeat stenting had worse outcomes than patients without diabetes. Patients who underwent CABG for ISR (mainly because of the presence of multivessel disease) had the best outcomes of all groups.

Stenting versus PTCA. Several studies have shown that stenting for de novo lesions provides better short- and long-term outcomes compared with BA alone (1-3). In the BELgian NEtherlands Stent (BENESTENT) study (1), for example, the mean postprocedure MLD was larger in the stent group compared with the BA group, and, at seven month follow-up, 20% of patients in the stent group had undergone TVR compared with 30% in the BA group. In a different study, Fischman et al. (2) showed that the immediate and six-month follow-up MLD was significantly larger and the incidence of

Table 3. Incidence of Clinical End Points in Different Treatment Groups

	Balloon Angioplasty (n = 169)	Stent (n = 117)	Rotational Atherectomy (n = 107)	CABG (n = 117)
Angina/MI (%)	32	30	27	23
PCI (%)	17	16	11	7*
TVR (%)	39	40	33	8*
Death (%)	9	6	6	5
MACE (%)	43	40	33	23*

*p < 0.05 compared with balloon angioplasty, stent or rotational atherectomy.

CABG = coronary artery bypass graft surgery; MACE = major adverse cardiovascular events; MI = myocardial infarction; PCI = percutaneous interventions; TVR = target vessel revascularization.

Table 4. Two-Year Event-Free Survival Rate in Different Treatment Groups

	Balloon Angioplasty (n = 169)	Stent (n = 117)	Rotational Atherectomy (n = 107)	CABG (n = 117)
Angina/MI (%)	65 ± 5	66 ± 5	64 ± 6	72 ± 5
TVR (%)	75 ± 4	73 ± 5	73 ± 5	90 ± 4*
Death (%)	92 ± 3	96 ± 2	93 ± 3	94 ± 3
MACE (%)	55 ± 4	57 ± 6	58 ± 6	66 ± 5

*p < 0.05 compared with balloon angioplasty, stent or rotational atherectomy.
 CABG = coronary artery bypass surgery; MACE = major adverse cardiovascular events; MI = myocardial infarction;
 TVR = target vessel revascularization.

coronary events was significantly less in the stent group compared with the BA group.

Incidence of ISR. Despite the superiority of stenting, ISR remains a major limitation to its effectiveness. The incidence of ISR is variable depending on the definition, and angiographic ISR rates up to 46% and TVR rates up to 30% have been reported in several studies (1-4).

Predictors and pathophysiology of ISR. Multiple clinical and angiographic variables have been shown to be associated with a higher risk of ISR. The most important predictors seem to be postprocedure MLD, lesion length, LAD lesion, presence of diabetes, time to ISR and use of multiple stents (32-36).

Extensive data have shown that ISR is mainly caused by intimal hyperplasia and, less importantly, by stent elastic recoil. Animal and postmortem studies reported that the process is initiated by a giant cell-based inflammatory reaction with subsequent smooth muscle cell migration and proliferation in the newly formed intimal layer (37,38). These findings have been confirmed by angiographic and intravascular ultrasound studies (24), which showed that the decrease in lumen correlated strongly with the increase in neointimal tissue rather than the decrease in-stent dimensions.

PTCA versus stenting for ISR. Several studies have compared the efficacy of different percutaneous techniques in the treatment of ISR (24-31). When compared with BA, stenting for ISR may provide better immediate procedural results. In our study, the postprocedure MLD in the stent group was significantly larger than it was in the BA group (3.3 ± 0.4 vs. 3.0 ± 0.4 mm). Other studies (24,25) have shown similar results. In the Washington Hospital Center experience (24), BA recovered only 85% of the minimal cross-section area of the original stent with 18% residual stenosis, while stent implantation, on the other hand,

appears to recover all the lumen area of the original implantation procedure.

Despite better procedural results, patients who undergo repeat stent seem to have similar long-term outcomes as those who undergo BA. In our series, the incidence of TVR and MACE was the same in both groups. Similarly, Waksman et al. (25) reported a subanalysis of the Washington Radiation for In-Stent Restenosis Trial (WRIST) study where the late clinical outcomes of the stent group were not different from the BA group. In a different study by Lefevre et al. (26), the seven-month incidence of TVR was less in the stent group compared with the BA group, although the difference did not reach statistical significance. A potential explanation of these findings is the phenomenon of exaggerated hyperplasia seen with repeat stenting. In fact, Mintz et al. (39) have shown, using an intravascular ultrasound study of WRIST patients, that the increase in intimal hyperplasia area was significantly greater in patients receiving repeat stent compared with other types of percutaneous interventions and that this increase can be neutralized by irradiation therapy.

RA for ISR. Since a major mechanism of ISR is intimal hyperplasia, then debulking and tissue removal with RA might provide a theoretical advantage. Animal studies have shown that intimal hyperplasia is significantly less after RA compared with BA in a porcine model of ISR (40). Human studies, on the other hand, have yielded conflicting results (27-31). In our study, patients who underwent RA tended to have a better outcome than those who underwent BA or repeat stent, although the difference was not statistically significant. Other studies (25,29,30) have shown that RA and BA are equivalent in the management of ISR. Lauer et al. (29) reported that the immediate and six-month MLD was similar in both groups, and Waksman et al. (25)

Table 5. Incidence of TVR and MACE in Different Treatment Groups According to Diabetes Status

	Patients With Diabetes				Patients Without Diabetes			
	Balloon Angioplasty (n = 36)	Stent (n = 30)	Rotational Atherectomy (n = 37)	CABG (n = 36)	Balloon Angioplasty (n = 109)	Stent (n = 76)	Rotational Atherectomy (n = 65)	CABG (n = 75)
TVR (%)	33	33	22	11	22*	18†	21	7
Death (%)	7	6	5	3	7	7	6	5
MACE (%)	53	53	32	28	40*	38†	34	29

*p < 0.05 compared with diabetics treated with balloon angioplasty; †p < 0.05 compared with diabetics treated with stent.
 CABG = coronary artery bypass graft surgery; MACE = major adverse cardiovascular events; TVR = target vessel revascularization.

reported in the WRIST study that the long-term outcomes of different percutaneous interventions are the same regardless of irradiation use. In a study by Dauerman et al. (27), 28% of patients in the RA group underwent TVR at one year follow-up compared with 46% in the BA group ($p = 0.18$). Lee et al. (28), on the other hand, showed that the incidence of clinical events at six months was significantly less in the RA group compared with the BA group (0% vs. 6.7%). Nevertheless, BA was superior to RA in the first randomized trial for management of ISR (31).

Diabetes and ISR. While acknowledging the small number of patients with diabetes in our study, several cautious observations can be made: RA may be particularly useful in patients with diabetes. Patients with diabetes who underwent RA had better outcomes than those who underwent BA or repeat stenting and had similar outcomes as patients without diabetes who underwent RA. On the other hand, patients with diabetes who underwent BA or repeat stenting had worse outcomes than patients without diabetes who had either of these procedures. This may be due to the fact that intimal hyperplasia is more exaggerated in patients with diabetes (41,42) and that tissue debulking with RA might provide a greater benefit when compared with BA or repeat stent. For example, Kornowski et al. (41) showed, using a serial intravascular ultrasound analysis, that in stented lesions the decrease in lumen area was less and the increase in intimal hyperplasia was greater in patients with diabetes compared to patients without diabetes.

CABG for ISR. Finally, patients with and without diabetes who underwent CABG for treatment of ISR (mainly because of the presence of multivessel disease) had a significantly better outcome than those who underwent percutaneous interventions, mostly in the form of lower TVR rates. These results are similar to those seen in trials comparing PTCA and CABG for de novo coronary artery disease and likely reflect the lower incidence of surgical graft restenosis.

STUDY LIMITATIONS

The main limitation of this study derives from its nonrandomized and retrospective nature. Instead, a large consecutive group of patients was studied. Classification of ISR into focal or diffuse types was not done. Angiographic follow-up was not available on all patients. Additionally, the analysis of patients with diabetes suffers from all the limitations inherent in subgroup analysis. For all these reasons, our results must be considered hypothesis-generating rather than conclusive.

CONCLUSIONS

Stenting has shown superior short- and long-term outcomes compared with BA in de novo coronary artery disease. In-stent restenosis, however, remains a challenging problem, and the optimal management is yet to be determined. Despite better procedural results with repeat stenting, the

long-term outcomes seem to be similar to BA, probably because of exaggerated intimal hyperplasia induced by the repeat stenting procedure. Tissue debulking with RA might be particularly useful in patients with diabetes where tissue intimal hyperplasia is more abundant. In patients with multiple vessel disease and ISR, CABG seems to yield the best outcomes. Randomized trials are needed to determine the best treatment strategy for ISR.

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