Long-Term Follow-Up after Deferring Angioplasty in Asymptomatic Patients with Moderate Noncritical In-Stent Restenosis

JAE-HWAN LEE, M.D., CHEOL WHAN LEE, M.D., SEONG-WOOK PARK, M.D., PH.D., MYEONG-KI HONG, M.D., PH.D.,
JAE-JOONG KIM, M.D., PH.D., KYOUNG SUK RHEE, M.D., SEUNG-JUNG PARK, M.D., PH.D.

Department of Medicine, Asan Medical Center, University of Ulsan, Seoul, Korea

Summary

Background: Many patients with in-stent restenosis (ISR) are angina-free, but the optimal treatment for these patients remains uncertain.

Hypothesis: In cases with asymptomatic moderate noncritical ISR, deferral of the intervention may be safe and associated with favorable clinical outcome.

Methods: We evaluated the long-term clinical outcome of asymptomatic patients (Group 1, $n = 98$) with moderate noncritical ISR ($< 70\%$ diameter stenosis) after intervention was deferred, and compared it with that of patients (Group 2, $n = 655$) without restenosis. After repeat angioplasty was deferred, all patients were treated medically and later underwent angioplasty only in the case of clinical recurrence.

Results: Baseline characteristics were similar between the two groups. Clinical follow-up was available in all patients at 26.3 ± 15.9 months. Twenty patients died during the follow-up: 1 in Group 1 and 19 in Group 2. Target lesion revascularization was performed in 3 patients in Group 1 and 11 patients in Group 2 during follow-up ($p = \text{NS}$), and new lesion revascularization in 2 patients in Group 1 and 27 patients in Group 2 ($p = \text{NS}$). Event-free survival rate (cardiac death, nonfatal myocardial infarction, repeat revascularization) was $86.7 \pm 6.1\%$ in Group 1 and $84.8 \pm 2.2\%$ in Group 2 at the end of follow-up ($p = \text{NS}$). Major adverse cardiac events were only associated with the presence of diabetic mellitus (hazards ratio 2.65, 95%

confidence interval [CI] 1.48–4.73, $p < 0.01$). The percentage of patients receiving antianginal medication was similar between the two groups at the end of the study ($p = \text{NS}$).

Conclusions: Asymptomatic patients with moderate noncritical ISR have a good prognosis and similar clinical outcome as those without ISR, suggesting that it may be safe to defer repeat angioplasty in these patients until angina recurrence.

Key words: stent, restenosis, prognosis

Introduction

In-stent restenosis (ISR) remains a major limitation of stent technology and represents a technical challenge to the interventional cardiologist.^{1–5} In order to identify patients with ISR, some physicians routinely perform follow-up functional testing or coronary angiography. Until now, follow-up angiography has been considered to be the standard of reference for the documentation of ISR because noninvasive evaluation is limited by its poor positive predictive value.^{6–8} However, the dilemma of whether to reintervene in a patient who is asymptomatic but has angiographic evidence of ISR often arises. Many patients with ISR have recurrence of their symptoms, whereas others are angina free. The optimal treatment of these patients remains uncertain because the long-term significance has not been determined.^{9–11} Recently, it was reported that a thinning of in-stent neointima occurs and increases the luminal diameter in the later phase.^{12,13} We therefore assumed that deferral of the intervention in asymptomatic patients with moderate noncritical ISR may be safe and associated with favorable clinical outcome. To test this hypothesis, we evaluated the long-term clinical outcome of asymptomatic patients with moderate noncritical ISR after intervention was deferred and compared it with that of patients without restenosis.

Materials and Methods

Study Patients

Between June 1993 and July 1998, a total of 1,424 consecutive patients (age ≤ 70) underwent single-vessel stenting in a major epicardial vessel at our institution. During this period,

This study was supported by a grant from the Asan Institute for Life Science (#97-060).

Address for reprints:

Seung-Jung Park, M.D., Ph.D.
Department of Medicine
Asan Medical Center
University of Ulsan
388-1 Pungnap-dong, Songpa-gu
Seoul, 138-736, Korea

Received: May 10, 2000

Accepted with revision: December 7, 2000

897 patients (63% angiographic follow-up rate) received routine follow-up angiography at 6 months, and angiographic restenosis (> 50% diameter stenosis by quantitative coronary angiography) was documented in 242 patients (26.9%): severe ISR ($\geq 70\%$ diameter stenosis, $n = 68$) and moderate noncritical ISR ($< 70\%$ diameter stenosis, $n = 174$). Of these, 98 patients with moderate noncritical ISR were deferred for repeat revascularization due to the absence of symptoms. The long-term outcome of these patients (Group 1, $n = 98$) was compared with that of patients (Group 2, $n = 655$) without restenosis ($\leq 50\%$ diameter stenosis). Patients were excluded if they had significant left main coronary artery disease, previous coronary bypass graft surgery, multivessel angioplasty, or left ventricular dysfunction (ejection fraction $< 35\%$).

Quantitative Coronary Angiography

Angiograms were reviewed by an experienced angiographer blinded to the clinical findings. Percent diameter stenosis, minimal lumen diameter, and reference diameter using an on-line quantitative angiographic analysis system (Ancor V2.0, Siemens AG, Munich, Germany) were measured at follow-up. Angiographic measurements were made during diastole after intracoronary nitroglycerin administration using the guiding catheter for magnification calibration. Single matched views with the worst diameter stenosis were compared. The reference diameter was averaged from 10 mm long angiographically normal segments proximal and distal to the lesion; when a normal proximal segment could be identified, only a distal segment was analyzed.

Clinical Follow-Up and Definitions

Follow-up information was obtained by hospital chart review and telephone interview. After repeat angioplasty was deferred, patients were treated medically and later underwent angioplasty only in case of clinical recurrence. Major adverse cardiac events were defined as the occurrence of cardiac death, nonfatal myocardial infarction, and need for repeat revascularization after the 6-month angiographic follow-up. Deaths were classified as either cardiac or noncardiac. Deaths that could not be classified were considered cardiac. Myocardial infarction was diagnosed when cardiac enzyme (creatinine kinase-MB) was elevated > 3 -fold with chest pain ≥ 30 min or with the appearance of new electrocardiographic (ECG) or echocardiographic changes.

Statistical Analysis

Statistical analysis was performed using SPSS 7.5 for Windows. Data were expressed as mean $\pm$ standard deviation for continuous variables, and frequencies for categorical variables. Continuous variables were compared by unpaired Student's *t*-test and categorical variables by chi-square test. Survival and event-free survival (freedom from cardiac death, nonfatal myocardial infarction, and repeat revascularization) distribution was estimated according to the Kaplan-Meier method, and the overall incidence of major adverse cardiac

events was tested using the log-rank test. Logistic regression analysis was used to determine predictors of major adverse cardiac events. A two-sided value of $p < 0.05$ was required for statistical significance.

Results

Clinical Characteristics

The clinical characteristics of the study patients are listed in Table I. There were no significant differences in age, gender, or coronary risk factors between the two groups.

Angiographic Characteristics

The angiographic characteristics are summarized in Table II. Reference diameter at follow-up was similar between the two groups; however, percent diameter stenosis and minimal lumen diameter were significantly lower in Group 1 than in Group 2 ($p < 0.01$). The majority of the stents used for the treatment of original lesions were Palmaz-Schatz stent ($n = 142$, Cordis, a Johnson & Johnson Corp., Miami, Fla., USA), NIR stent ($n = 133$, Boston Scientific Corp., Boston, Mass., USA), tantalum Cordis stent ($n = 90$, Cordis, a Johnson & Johnson Corp.), GFX stent ($n = 155$, Arterial Vascular Engineering, Inc., Santa Rosa, Calif., USA), and CrossFlex stent ($n = 132$, Cordis, a Johnson & Johnson Corp.). A total of 234 other stent types was used in the remaining 31.1%.

Long-Term Clinical Outcomes

Patients were followed for > 6 months, and clinical follow-up data were available in all patients for a mean duration of 26.3 ± 15.9 months after the 6-month angiographic follow-up. Data on all events at last follow-up are shown in Table III.

Twenty patients died during the follow-up: 1 in Group 1 (cardiac origin) and 19 in Group 2 (cardiac origin: 12, non-cardiac origin: 7). The probability of target lesion revascular-

TABLE I Baseline clinical characteristics

	Group 1 ($n = 98$)	Group 2 ($n = 655$)
Age, years	59.1 ± 8.7	57.3 ± 8.8
Male/female	68/30	472/183
Risk factors		
Systemic hypertension (%)	30 (30.6)	231 (35.3)
Diabetes mellitus (%)	12 (12.2)	108 (16.5)
Total cholesterol (> 240 mg/dl) (%)	8 (8.2)	60 (9.2)
Smoking (%)	50 (51.0)	327 (49.9)
Acute myocardial infarction (%) ^a	4 (4.1)	42 (6.4)
Unstable angina (%) ^a	58 (59.2)	337 (51.5)
Multi-vessel disease (≥ 2) (%)	30 (30.6)	221 (32.3)
Left ventricular ejection fraction (%)	62.6 ± 7.9	60.9 ± 10.1

^a Clinical presentation at the time of coronary stenting.

TABLE II Angiographic characteristics

Characteristics	Group 1 (n = 98)	Group 2 (n = 655)
Target artery		
Left anterior descending coronary (%)	61 (62.2)	360 (55.0)
Left circumflex (%)	10 (10.2)	96 (14.7)
Right coronary (%)	27 (27.6)	199 (30.4)
ACC/AHA lesion type ^a		
B2, C (%)	66 (69.5)	429 (65.5)
Restenotic lesion ^a (%)	4 (4.1)	23 (3.5)
Infarct-related artery ^a (%)	13 (13.3)	110 (16.8)
QCA at 6-months follow-up		
Reference diameter, mm	3.3 ± 0.4	3.4 ± 0.5
Minimal lumen diameter, mm	1.3 ± 0.2	2.5 ± 0.62 ^b
Diameter stenosis, %	60.0 ± 5.2	26.4 ± 14.2 ^b
Long stents (>20mm) (%)	25 (25.5)	122 (18.6)
Types of stents		
Coil design (%)	33 (33.7)	233 (35.6)
Hybrid design (%)	27 (27.6)	132 (20.2)
Slotted tube (%)	38 (38.8)	290 (44.3)

^a Lesion characteristics at the time of coronary stenting.^b $p < 0.01$.

Abbreviations: QCA = quantitative coronary angiography, ACC/AHA = American College of Cardiology/American Heart Association.

ization was similar between the two groups (98.0 ± 1.4 vs. $99.2 \pm 0.3\%$ at 1 year, 95.7 ± 2.6 vs. $98.0 \pm 0.6\%$ at 3 years, and 95.7 ± 2.6 vs. $96.3 \pm 1.4\%$ at 5 years, respectively (Fig. 1, $p = \text{NS}$). New lesion revascularization was required in 29 patients during the follow-up: 2 in Group 1 and 27 in Group 2. Five patients in Group 2, but no patients in Group 1 had an acute myocardial infarction at a mean follow-up time of 10.0 months (range, 5–19 months).

Major adverse cardiac events had occurred in 31 patients after a mean of 16.9 ± 12.2 months (range, 1–45 months) with no differences between the two groups ($p = \text{NS}$). As shown in Figure 1, the cumulative probability of event-free survival in Group 1 was 98.0 ± 1.4 , 86.7 ± 6.1 , and $86.7 \pm 6.1\%$ at 1, 3,

TABLE III Clinical events at last follow-up

Clinical events	Group 1 (n = 98)	Group 2 (n = 655)
Average follow-up (months)	26.5 ± 14.1	26.2 ± 16.1
Death (%)	1 (1.0)	19 (2.9)
Cardiac (%)	1 (1.0)	12 (1.8)
Noncardiac (%)	0 (0)	7 (1.1)
Nonfatal myocardial infarction (%)	0 (0)	5 (0.8)
Repeat revascularization (%)	5 (5.1)	38 (5.8)
Target lesion revascularization (%)	3 (3.1)	11 (1.7)
New lesion revascularization (%)	2 (2.0)	27 (4.1)
Major adverse cardiac events (%)	6 (6.1)	55 (8.4)

No differences between the two groups.

and 5 years, respectively. In Group 2, the probability of event-free survival was 95.8 ± 0.8 , 88.1 ± 1.7 , and $84.8 \pm 2.3\%$ at 1, 3, and 5 years, respectively. The presence of diabetes mellitus was the only independent predictor of major adverse cardiac event (hazards ratio 2.65, 95% CI 1.48–4.73, $p < 0.01$). However, other clinical and angiographic variables were not associated with major adverse cardiac events. The percentage of patients receiving antianginal medication was similar in the treatment groups at the end of the study (Table IV).

Discussion

The major findings of this study are that (1) asymptomatic moderate noncritical ISR was associated with a good prognosis, and (2) these patients had a clinical outcome similar to those without restenosis. These results may provide the rationale for the management of asymptomatic patients with moderate noncritical ISR, suggesting that it may be safe to defer repeat angioplasty in these patients until angina recurrence.

Treatment of In-Stent Restenosis

Stent use has risen dramatically in recent years, and today stents are a ubiquitous routine in interventional cardiology. Without question, stents have contributed to progress in the

Fig. 1 Cumulative probability of survival free from cardiac death (A), target lesion revascularization (TLR, B), and event-free survival (C). There were no differences between the two groups.

TABLE IV Use of antianginal medication

	Group 1 (n = 98)	Group 2 (n = 655)
Aspirin (%)	91 (92.3)	628 (95.9)
Beta blocker (%)	54 (55.1)	342 (52.2)
Calcium-channel blocker (%)	50 (51.0)	372 (56.8)
Nitrate (%)	15 (15.3)	60 (9.2)
Lipid-lowering agent	20 (20.4)	159 (24.3)

No differences between the two groups.

field of interventional cardiology, but ISR remains the major limitation of this technology. The prevalence of ISR has been increasing along with the widespread use of stents in a variety of coronary lesions. At present, repeat balloon angioplasty with or without debulking atherectomy is commonly used for the treatment of ISR, but it is limited by an unacceptably high restenosis rate.^{3, 14, 15} However, ISR is not necessarily associated with recurrence of angina, and many patients with ISR remain angina-free. In clinical practice, some interventional cardiologists tend to perform a repeat angioplasty for these lesions even if the patient is asymptomatic. Unfortunately, repeat intervention adds the risk of another procedure and may trigger a restenotic exacerbation by activating quiescent cells in the lesion. Therefore, it remains uncertain whether repeat angioplasty is favorable or unfavorable for the treatment of ISR if the patient is asymptomatic. In this study, the prognosis of these patients was excellent, indicating that deferral of the intervention on the basis of symptoms may be safe and associated with a lower clinical event rate.

Natural History of In-Stent Restenosis Lesion

Restenosis is a time-limited reparative phenomenon that is usually restricted to the first 6 months after angioplasty.¹⁶ Recent studies have demonstrated that the luminal diameter at 3 years was significantly larger than that seen at 6 months, suggesting that there is spontaneous regression in ISR after a period of 3 years.¹³ The mechanism of luminal diameter increase in the later phase remains uncertain, but it may be associated with the decrease in cellular components.¹⁷ Previous studies have reported an incidence of asymptomatic restenosis of 25 to 50% after balloon angioplasty;^{9, 18} however, the exact incidence of asymptomatic ISR remains unknown. In our studies, it approached 40% of patients with ISR, and the long-term outcome of asymptomatic patients with noncritical ISR was similar to that of patients without restenosis. In-stent restenosis at 6 months may not always be the final outcome, and it can be improved thereafter. Our results suggest that unnecessary repeat intervention can be avoided in a subset of ISR.

Post-Stenting Evaluation

Until now, there is no standard protocol for post-stenting evaluation. Some physicians use an aggressive approach and

routinely send all their patients for functional testing or coronary angiography. Other physicians use a more conservative approach and selectively evaluate only patients with angina recurrence. Therefore, it is still unclear whether routine evaluation is the optimal strategy for patients who received stent placement. In this study, patients with severe critical ISR ($\geq 70\%$ diameter stenosis) were not included because they received repeat revascularization. It has been estimated that most lesions with $\geq 70\%$ diameter stenosis eventually cause myocardial ischemia, leading to angina recurrence. In our hospital, most patients with severe ISR ($\geq 70\%$ diameter stenosis) are treated with repeat revascularization. Therefore, our results suggest that poststenting evaluation is only necessary for selected patients with angina recurrence, indicating that a conservative approach may be reasonable for evaluation of the stented lesions compared with routine aggressive approach.

Study Limitations

Several potential limitations need to be addressed. First, this is a retrospective analysis and is, therefore, subject to the limitations pertinent to this type of clinical investigation. Second, angiographic follow-up rate was not complete and, therefore, the incidence of asymptomatic ISR may not be accurate in this study. Third, follow-up angiography was only used for documentation of ISR without functional evaluation. For these reasons, the impact of documented ischemia on the cardiac events could not be evaluated in this study. Further studies may be needed to ascertain these issues.

Conclusions

Asymptomatic patients with moderate noncritical ISR are associated with a good prognosis and have a clinical outcome similar to those without ISR, suggesting that it may be safe to defer repeat angioplasty of these patients until symptoms recur.

Acknowledgment

The authors are indebted to Dong Soon Shin, R.N. and Young-Hee Kim, R.N., for their important contribution to data collections, and to Mr. Soon Deok Jang, C.V.T., for assistance in preparing coronary angiograms.

References

1. Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, Detre K, Veltri L, Ricci D, Nobuyoshi M: A randomized comparison of coronary stent placement and balloon angioplasty in the treatment of coronary artery disease Stent Restenosis Study Investigators. *N Engl J Med* 1994;331:496-501
2. Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, Emanuelsson H, Marco J, Legrand V, Materne P: A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;331:489-495

3. Dahl J, Radke PW, Haager PK, Koch KC, Kastrau F, Reffellmann T, Janssens U, Hanrath P, Klues HG: Clinical and angiographic predictors of recurrent restenosis after percutaneous transluminal rotational atherectomy for treatment of in-stent restenosis. *Am J Cardiol* 1999;83:862–867
4. Hoffmann R, Mintz GS, Popma JJ, Satler LF, Pichard AD, Kent KM, Walsh C, Mackell P, Leon MB: Chronic arterial responses to stent implantation: A serial intravascular ultrasound analysis of Palmaz-Schatz stents in native coronary arteries. *J Am Coll Cardiol* 1996;28:113–119
5. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, Kent KM, Griffin J, Leon MB: Patterns and mechanisms of in-stent restenosis: A serial intravascular ultrasound study. *Circulation* 1996;94:1247–1254
6. Hamm CW, Reimers J, Ischinger T, Rupprecht HJ, Berger J, Bleifeld W, for the German Angioplasty Bypass Surgery Investigation: A randomized study of coronary angioplasty compared with bypass surgery in patients with symptomatic multivessel coronary disease. *N Engl J Med* 1994;331:1037–1043
7. Rupprecht HJ, Espinola-Klein C, Erbel R, Nafe B, Brennecke R, Dietz U, Meyer J: Impact of routine angiographic follow-up after angioplasty. *Am Heart J* 1998;136:613–619
8. Ruygrok PN, Melkert R, Morel MA, Ormiston JA, Bar FW, Fernandez-Aviles F, Suryapranata H, Dawkins KD, Hanet C, Serruys PW, on behalf of the Benestent II Investigators: Does angiography six months after coronary intervention influence management and outcome? *J Am Coll Cardiol* 1999;34:1507–1511
9. Hernandez RA, Macaya C, Iniguez A, Alfonso F, Goicolea J, Fernandez-Ortiz A, Zarco P: Midterm outcome of patients with asymptomatic restenosis after coronary balloon angioplasty. *J Am Coll Cardiol* 1992;19:1402–1409
10. Deshpande NV, Serruys PW: Asymptomatic restenosis: Should we reintervene? An unresolved dilemma. *Am Heart J* 1999;136:576–577
11. Gordon PC, Friedrich SP, Piana RN, Kugelmass AD, Leidig GA, Gibson CM, Cohen DJ, Carrozza JP, Kuntz RE, Baim DS: Is 40% to 70% diameter narrowing at the site of previous stenting or directional coronary atherectomy clinically significant? *Am J Cardiol* 1994;74:26–32
12. Kimmura T, Yokoi N, Nakagawa Y, Tamura T, Kaburagai S, Sawada Y, Sato Y, Yokoi H, Hamasaki N, Nosaka H, Hamasaki N, Mosaka H, Nobuyoshi M: Three-year follow-up after implantation of metallic coronary-artery stents. *N Engl J Med* 1996;334:561–566
13. Asakura M, Ueda Y, Nanto S, Hirayama A, Adachi T, Kitakaze M, Hori M, Kodama K: Remodeling of in-stent neointima, which became thinner and transparent over 3 years. *Circulation* 1998;97:2003–2006
14. Sharma SK, Duvvuri S, Dangas G, Kini A, Vidhun R, Venu K, Ambrose JA, Marmur JD: Rotational atherectomy for in-stent restenosis: Acute and long-term results of the first 100 cases. *J Am Coll Cardiol* 1998;32:1358–1365
15. Lee SG, Lee CH, Hong MK, Kim JJ, Park SW, Park SJ: Immediate and long-term outcomes of rotational atherectomy versus balloon angioplasty alone for treatment of diffuse in-stent restenosis. *Am J Cardiol* 1998;82:140–143
16. Parisi AF, Folland ED, Hartigan P, on behalf of the Veterans Affairs ACME Investigators: A comparison of angioplasty with medical therapy in the treatment of single-vessel coronary artery disease. *N Engl J Med* 1999;326:10–16
17. Isner JM, Bortman S, Passeri J: Apoptosis in human atherosclerosis and restenosis. *Circulation* 1995;91:2703–2711
18. Holmes DR Jr, Vlietstra RE, Smith HC, Vetrovec GW, Kent KM, Cowley MJ, Faxon DP, Gruentzig AR, Kelsey SF, Detre KM: Restenosis after percutaneous coronary angioplasty (PTCA): A report from the PTCA Registry of the National Heart, Lung, and Blood Institute. *Am J Cardiol* 1984;53:77C–81C