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Improving Outcome Over Time of Percutaneous Coronary Interventions in Unstable Angina

Mandeep Singh, MD,* Charanjit S. Rihal, MD, FACC,* Peter B. Berger, MD, FACC,* Malcolm R. Bell, MB, BS,* Diane E. Grill, MS,† Kirk N. Garratt, MD, FACC,* Gregory W. Barseness, MD, FACC,* David R. Holmes, Jr., MD, FACC*

Rochester, Minnesota

OBJECTIVE This study was performed to evaluate the recent changes in the outcome of coronary interventions in patients with unstable angina (UA).

BACKGROUND An early invasive strategy has not been shown to be superior to conservative treatment in patients with UA. Earlier studies had utilized older technology. Interventional approaches have changed in the recent past, but to our knowledge, no large studies have addressed the impact of these changes on the outcome of coronary interventions.

METHODS We analyzed the in-hospital and intermediate-term outcome in 7,632 patients with UA who underwent coronary interventions in the last two decades. The study population was divided into three groups: group 1, n = 2,209 who had coronary intervention from 1979 to 1989; group 2, n = 2,212 with interventions from 1990 to 1993; and group 3, n = 3,211 treated from 1994 to 1998.

RESULTS Group 2 and 3 patients were older and sicker compared with group 1 patients. The clinical success improved significantly in group 3 (94.1%) compared with group 2 (87%) and group 1 (76.5%) ($p < 0.001$). There was a significant reduction in in-hospital mortality, Q-wave myocardial infarction and need for emergency bypass surgery in group 3 compared with the earlier groups. One-year event-free survival was also significantly higher in the recent group compared with the earlier groups: 77% in group 3, 70% in group 2 and 74% in group 1 ($p < 0.001$). With the use of multivariate models to adjust for clinical and angiographic variables, treatment during the most recent era was found to be independently associated with improved in-hospital and intermediate-term outcomes.

CONCLUSIONS There has been significant improvement in the in-hospital and intermediate-term outcome of coronary interventions in patients with UA in recent years; newer trials comparing conservative and invasive strategies are therefore needed. (J Am Coll Cardiol 2000;36: 674–8) © 2000 by the American College of Cardiology

An early aggressive approach for the treatment of unstable angina (UA) has not been found to be superior to a conservative strategy (1–3). However, interventional approaches have changed significantly in the recent years. Use of glycoprotein IIb/IIIa inhibitors has improved the outcome of angioplasty in patients with UA (4–6), and placement of stents has reduced the frequency of in-hospital adverse events as well as improved the restenosis rates (7,8). These two advances have significantly improved the outcome of coronary interventions in patients with UA, rendering previous conclusions of the relative roles of an aggressive versus conservative approach less applicable to today's practice. In addition, new interventional devices and adjunctive medical therapies have come into practice in the recent years. To our knowledge, no large studies have addressed the issue of the changing technology on the outcome of coronary interventions in patients with UA.

From the *Division of Internal Medicine and Cardiovascular Diseases, and the †Section of Biostatistics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
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Our principal objective was to evaluate changes in the early- and intermediate-term outcomes of patients with UA undergoing coronary intervention over two decades.

METHODS

Study patients. Patients undergoing percutaneous revascularization at the Mayo Clinic have been followed up prospectively since 1979 in accord with an Institutional Review Board approved protocol. A total of 7,632 patients who underwent coronary intervention with the diagnosis of UA in the last 20 years were included in this study. Patients were divided into three groups. Group 1 comprised 2,209 patients who underwent coronary intervention from 1979 to 1989. In this era, the technology of percutaneous transluminal coronary angioplasty was evolving and operator experience in coronary interventions was increasing. Group 2 consisted of 2,212 patients who underwent coronary interventions from 1990 to 1993. In this transition period, the operator experience was greater, but stents were available only on an investigational basis and were used infrequently. Group 3 consisted of 3,211 patients treated from 1994 to 1998. In this recent era, there was more frequent use of

Abbreviations and Acronyms

CI	=	confidence interval
ECG	=	electrocardiogram
MI	=	myocardial infarction
UA	=	unstable angina

stents and glycoprotein IIb/IIIa inhibitors as well as much greater operator experience.

Definitions. Unstable angina was defined as new onset of chest pain at rest or progression of stable angina to an increased class (Canadian Heart Classification) within two months of coronary intervention, the last episode of pain occurring within one week of the procedure. Any ischemic pain after myocardial infarction (MI) was also considered to represent UA. Clinical success was defined as a reduction of residual luminal diameter stenosis to <50% on the basis of visual assessment of orthogonal views without in-hospital death, Q-wave MI or need for emergency coronary artery bypass surgery. In-hospital mortality was defined as death from any cause occurring during the same hospitalization as that in which the coronary intervention was performed.

Periprocedural MI was defined as chest pain with development of new Q-wave on electrocardiogram (ECG). Myocardial infarction on follow-up was defined as chest pain with either increase in creatine kinase concentration to at least two times the upper limit of normal with a positive MB fraction or new Q waves on the ECG after angioplasty. Three-vessel disease was defined as diameter stenosis of ≥70% in all three epicardial coronary arteries or major branches thereof. Repeat revascularization was defined as any subsequent revascularization following coronary intervention in any vessel.

Follow-up. Research coordinators contacted all patients after hospital discharge at six months and annually thereafter. The Mayo Clinic hospital records of patients who suffered an event during follow-up were reviewed. The medical records of patients suffering adverse events at other hospitals were also obtained and reviewed.

Statistical analysis. The univariate associations between discrete baseline and complication data were tested for overall group. One-way analysis of variance was used to test for differences in continuous variables. Stepwise logistic regression was used to develop multivariate models for in-hospital mortality and for the composite end point of in-hospital death, MI or repeat revascularization. A dichotomous variable for each of the last named two time periods was added to the model. Results are presented as odds ratio with 95% confidence intervals (CIs). Cox proportional hazards models were developed for patients who had successful interventions, for the end point of postdischarge death, death or MI, and the composite end point of death, MI or repeat revascularization. The variables representing the year groups were forced into the model. Results are presented as relative risk ratios with corresponding CIs. Estimated event-free survival curves were calculated from these models for each of the end points. All covariates, with the exception of the year group variables, were fixed at their mean value; the year group was set to represent each of the time periods.

RESULTS

Baseline characteristics. Clinical and baseline characteristics of the three groups are shown in Table 1. The mean age of group 2 and 3 patients was significantly older than that of group 1. The prevalence of other adverse cardiovascular risk factors, including diabetes and hypertension at presentation and prior coronary artery bypass surgery, was significantly higher in the recent time period as compared with earlier time periods ($p < 0.001$). Three-vessel disease was equally prevalent in all three groups.

Procedural practice. The use of balloon angioplasty alone in the treatment of UA decreased by 60% across the three time periods and the use of stents increased from zero before 1990 to 51.4% of all the procedures in the last four years (Table 2). Atherectomy was used in 62 (2.8%) patients (3 transluminal extraction catheter, 59 directional coronary

Table 1. Baseline Characteristics

Variable	Group 1 (1979–1989) n = 2,209 (%)	Group 2 (1990–1993) n = 2,212 (%)	Group 3 (1994–1998) n = 3,211 (%)	p Value
Age, yr (mean ± SD)	62.1 ± 11.1	64.8 ± 11.2	64.6 ± 12.0	< 0.001
Male	1,572 (71.2)	1,569 (70.9)	2,222 (69.2)	0.2
Diabetes mellitus	292 (13.3)	440 (19.9)	661 (20.6)	< 0.001
Hypertension	1,008 (45.9)	1,076 (49)	1,835 (57.8)	< 0.001
Prior CABG	280 (12.7)	500 (22.6)	671 (20.9)	< 0.001
Three-vessel disease	627 (29)	629 (29.2)	903 (29.5)	0.9
CHF (ever occurred)	203 (9.2)	248 (11.3)	376 (11.9)	0.009
Thrombus	661 (29.9)	908 (41.1)	1099 (34.2)	0.001
LVEF ≤40%	154 (6.9)	70 (3.1)	251 (7.8)	0.001
CHC 3 or more	1,938 (87.7)	1,884 (85.2)	2,266 (70.6)	0.001
MI 1–7 d	326 (14.8)	366 (16.6)	489 (15.2)	0.2
MI <24 h	305 (13.8)	301 (13.6)	356 (11.1)	0.003

CABG = coronary artery bypass grafting; CHC = Canadian heart classification; CHF = congestive heart failure; LVEF = left ventricular ejection fraction; MI = myocardial infarction.

Table 2. Procedural and Adjunctive Therapy

	Group 1 (1979–1989) (n) (%)	Group 2 (1990–1994) (n) (%)	Group 3 (1994–1998) (n) (%)
Total procedures	2,209 (28.9)	2,212 (29.0)	3,211 (42.1)
PTCA alone	2,117 (95.8)	1,796 (81.2)	1,184 (36.9)
Atherectomy ± PTCA	62 (2.8)	180 (8.1)	344 (10.7)
Laser ± PTCA	29 (1.3)	105 (4.7)	15 (0.5)
Stent implantation	1	121 (5.5)	1,649 (51.4)
Combined procedure	0 (0.0)	25 (1.1)	188 (5.9)
Abciximab use	NA	NA	1,082 (34.5)

NA = not available; PTCA = percutaneous transluminal coronary angioplasty.

atherectomy) in group 1; 180 (8.1%) patients in group 2 (160 directional coronary atherectomy, 16 rotational atherectomy, 4 transluminal extraction catheter); and 344 (10.7%) in group 3 (245 rotational atherectomy, 66 directional coronary atherectomy, 35 transluminal extraction catheter procedures). The use of the glycoprotein IIb/IIIa inhibitor, abciximab, increased over the last few years; it was used in 34.5% of patients in the most recent cohort.

In-hospital outcome. Procedural outcomes significantly improved with time (Table 3). Clinical success rates in the most recent era were significantly higher. The clinical success in group 3 was 94.1% compared with 87% in group 2 and 76.5% in group 1 ($p < 0.001$). A significant reduction in mortality was observed in patients with UA treated with coronary interventions in the last four years compared with earlier time periods. Mortality was 3% in group 1, 2.4% in group 2 and 1.8% in group 3 ($p = 0.009$). There was also a significant reduction in the incidence of Q-wave MI and the need for emergency coronary artery bypass surgery in group 3 as compared with groups 1 and 2.

The correlates of in-hospital mortality and composite end points on multivariate logistic regression analysis are presented in Table 4. After adjustment for these baseline and angiographic variables, patients treated in the recent time period had a significantly lower in-hospital mortality compared with early groups (odds ratio, 0.5; 95% CI, 0.3 to 0.7; $p < 0.001$) (Table 4). Similarly, treatment era was correlated with a lower incidence of in-hospital death, MI, coronary artery bypass surgery or need of repeat coronary angioplasty. Group 3 demonstrated significant improvement in the composite end points in comparison with group 1 (odds ratio, 0.34; 95% CI, 0.28 to 0.41; $p < 0.001$) (Table 5).

Event-free survival after hospital discharge. Follow-up was complete in 100% of group 1 and 2 patients and 93% of group 3 patients. Follow-up data were analyzed for patients who had a successful coronary intervention. The mean follow-up was 9.4 ± 3.6 years for group 1 patients, 5.2 ± 1.8 years for group 2 patients and 1.7 ± 1.2 years for group 3 patients. After adjustment for the other significant factors, the risk of death for the 1994 to 1998 cohort (group 3) relative to the 1979 to 1989 cohort (group 1) was 0.67 (0.54 to 0.84, $p < 0.001$), and the risk for the 1990 to 1993 cohort (group 2) relative to the 1979 to 1989 cohort (group 1) was 0.87 (0.74 to 1.02, $p = 0.08$). These results are displayed in Figure 1. Estimated one-year event-free survival curves for death and MI based on the Cox proportional hazards model are shown in Figure 2. The risk of death or MI for group 3 relative to group 1 was 0.82 (0.70 to 0.97, $p = 0.02$), and for group 2 compared with group 1, 0.96 (0.84 to 1.09, $p = 0.53$). Figure 3 shows the estimated event-free survival curves for death, MI, coronary artery bypass surgery or repeat revascularization. Estimated event-free survival for group 3 relative to group 1 was 0.85 (0.76 to 0.94, $p = 0.002$). Similar estimated event-free survival for group 2 relative to group 1 was 1.07 (0.97 to 1.17, $p = 0.14$).

DISCUSSION

This study demonstrated marked improvement in the in-hospital and intermediate-term outcome of coronary interventions in patients with unstable angina in the most recent era. Greater operator experience, technical improvements in angioplasty equipment and improvement in medical therapy

Table 3. Procedural Results After Coronary Intervention Stratified by Era

	Group 1 (1979–1989) n = 2,209 (n) (%)	Group 2 (1990–1993) n = 2,212 (n) (%)	Group 3 (1994–1998) n = 3,211 (n) (%)	p Value
Clinical success	1,689 (76.5)	1,925 (87)	3,020 (94.1)	< 0.001
In-hospital death	67 (3.0)	54 (2.4)	57 (1.8)	0.009
QMI	39 (1.8)	22 (1.0)	24 (0.7)	0.002
Emergency CABG	108 (4.9)	40 (1.8)	21 (0.7)	< 0.001

CABG = coronary artery bypass grafting; QMI = Q-wave myocardial infarction.

Table 4. Correlates of In-Hospital Mortality

	p Value	Odds Ratio (95% CI)
MI <24 h	< 0.001	4.7 (3.1–7.1)
Current CHF	< 0.001	2.8 (1.9–4.0)
MI within 1–7 d	< 0.001	2.2 (1.5–3.3)
Ejection fraction <0.40	< 0.001	2.5 (1.5–4.1)
Multivessel disease	< 0.001	2.4 (1.5–3.7)
Thrombus	0.002	1.8 (1.2–2.7)
Age*	< 0.001	1.8 (1.6–2.2)
CHC ≥3	0.03	2.0 (1.1–3.7)
Group 2 (1990–1993)	< 0.001	0.5 (0.3–0.7)
Group 3 (1994–1998)	< 0.001	0.5 (0.3–0.7)

*Represents the odds of a 10-year change in age.
CHC = Canadian heart classification; CHF = congestive heart failure; CI = confidence interval; MI = myocardial infarction.

likely contributed to the improved outcomes, which occurred despite a higher risk profile of the treated patients.

Comparison with previous studies. In none of the published randomized trials of an early invasive strategy had the newer treatment strategies, including glycoprotein IIb/IIIa inhibitors and intracoronary stents, been in use to a significant degree. Moreover, in the Thrombolysis in Myocardial Infarction (TIMI) IIIB trial, <10% of patients had three-vessel disease; in contrast, in the current study, 29% had triple-vessel disease. In addition, patients in the recent cohort in this study were older and sicker. Despite this, the in-hospital death and MI rates were higher in TIMI IIIB study—3.2%, compared with 2.5% in the recent group in our study. This highlights the improvement in the results of coronary interventions in this high-risk group in the recent years. The Veterans Affairs Non–Q-Wave Infarction Strategies in Hospital (VANQWISH) trial compared the invasive and the conservative strategy in patients with acute non–Q-wave MI (1). There was high mortality (11.6%) after coronary artery bypass surgery and the two revascularization strategies of bypass surgery and percutaneous revascularization were combined in this trial, and the outcome weighed in favor of conservative strategy (1). There was no mortality after coronary angioplasty in the early invasive arm. Moreover, there was no difference in the long-term event-free survival in the two groups. In the Organization to Assess Strategies for Ischemic Syndrome (OASIS) registry,

Table 5. Correlates of In-Hospital Death, MI, Coronary Artery Bypass Grafting, Repeat Percutaneous Revascularization

	p Value	Odds Ratio (95% CI)
MI < 24 h	< 0.001	2.2 (1.8–2.8)
Thrombus	< 0.001	1.7 (1.5–2.1)
Current CHF	< 0.001	1.6 (1.2–2.1)
Multivessel disease	< 0.001	1.4 (1.2–1.7)
Age*	< 0.001	1.2 (1.1–1.3)
MI 1–7 d	0.05	1.2 (1.0–1.5)
Group 2 (1990–1993)	< 0.001	0.6 (0.5–0.7)
Group 3 (1994–1998)	< 0.001	0.34 (0.28–0.41)

*Represents the odds of a 10-year change in age.
CHF = congestive heart failure; CI = confidence interval; MI = myocardial infarction.

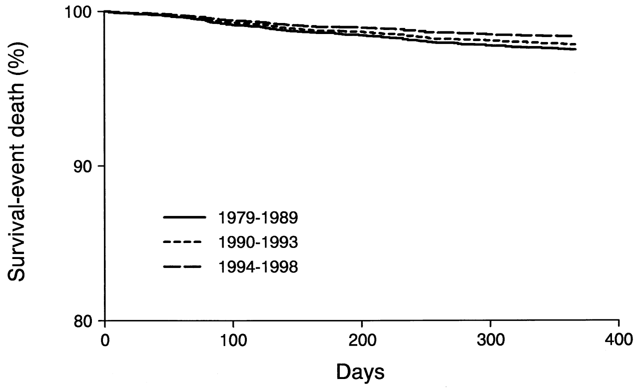

Figure 1. Estimated survival curves for mortality for each of the time periods based on the Cox proportional hazard model. Risk of 1994 to 1998 relative to 1979 to 1989 is 0.67, $p < 0.001$. Risk of 1990 to 1993 relative to 1979 to 1989 is 0.87, $p = 0.08$.

there was no significant difference in rates of cardiovascular death or MI at seven days and six months in countries with highest rates of invasive procedures (3). However, the rates of refractory angina and readmission to the hospital for UA were significantly lower in the countries with highest rates of revascularization procedures. Recently, the preliminary results of the Fast Revascularization During Instability in Coronary Artery Disease (FRISC II) study were presented which documented improved outcome in men treated with an early aggressive strategy (9).

In a 10-year follow-up study of coronary interventions in patients with UA, it was demonstrated that the early mortality in patients with UA was higher but the long-term overall and event-free survival was similar to patients in whom the diagnosis at the time of intervention was chronic stable angina (10). This highlights the importance of improvement in the clinical success and in the lowering of in-hospital complication rates associated with coronary interventions in patients with UA. The most recent group in the current study underscores the significance of the improvement in the clinical success and lowering of in-hospital complications. Improved results with coronary interventions in the last four years could be because of variety of reasons.

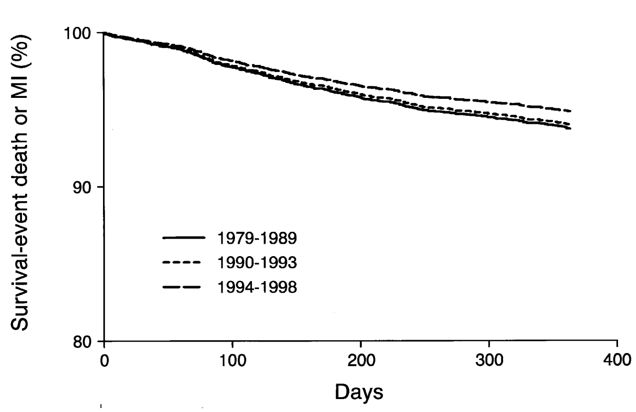

Figure 2. Estimated event-free survival curves for death and myocardial infarction *(MI)*: 1994 to 1998 relative to 1979 to 1989 is 0.82, $p = 0.02$. Risk of 1990 to 1993 relative to 1979 to 1989 is 0.96, $p = 0.53$.

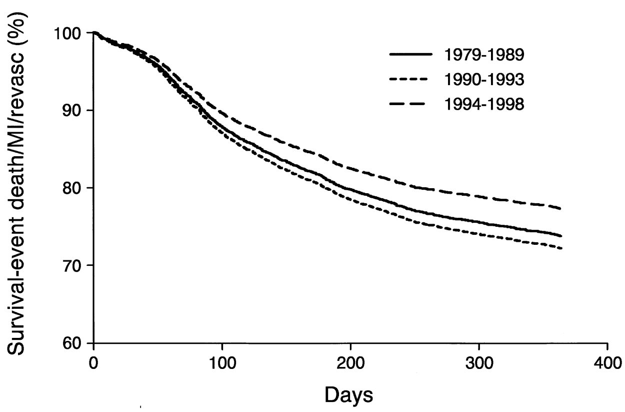

Figure 3. Estimated event-free survival curves for death, myocardial infarction (MI), coronary artery bypass surgery or repeat revascularization (revasc): 1994 to 1998 relative to 1979 to 1989 is 0.85, $p = 0.002$. Risk of 1990 to 1993 relative to 1979 to 1989 is 1.07, $p = 0.14$.

Major advances in the pharmacologic therapy were made during that period. Abciximab, a glycoprotein IIb/IIIa inhibitor, came into broad use in the last three years. The major trials of glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions in patients with UA have shown convincing benefits in terms of reduction in the composite end points including death, MI or emergency bypass surgery and the benefits were sustained at six months and three years (4–6). Stents were used in >50% of patients in group 3. The safety of stents in the presence of thrombus-containing lesions in patients with UA (generally present in patients with UA) has been a source of concern. With the advent of effective antiplatelet therapy, the risk of subacute thrombosis has been dramatically reduced in patients with UA, and even in patients with acute MI. Studies of primary angioplasty utilizing stents in patients with acute MI have shown that stents are safe even in this setting in which virtually all patients have intraluminal thrombus (7,8).

Study limitations. This study is a retrospective analysis of a study population enrolled over a period of 20 years so all the inherent limitations of a retrospective study need to be considered. It is difficult to determine the relative importance of better operator skills, improvement in technology, use of stents, improved antiplatelet and other adjunctive therapy in improving the results in the most recent period. Another limitation is that cardiac enzyme levels were not routinely measured after a clinically successful angioplasty and were measured in only clinically indicated situations. We did not subdivide the patients into categories of UA with different prognostic implications. However, we nevertheless believe that given the substantial improvement in outcome of coronary interventions in the recent era, it would be prudent to perform new trials of percutaneous coronary interventions versus medical therapy in patients with UA that include the recent advances in coronary interventions. Moreover, no comparison was made between medically and surgically treated patients who presented with UA.

CONCLUSIONS

This study documents improvement in the in-hospital and long-term outcome in patients with UA undergoing percutaneous coronary interventions since the advent of coronary angioplasty. This improvement occurred despite the fact that patients undergoing percutaneous coronary interventions in the recent years tend to be older and sicker. This demonstrable improvement in the recent time period should rekindle the debate between an early aggressive intervention and a conservative approach in the treatment of patients with UA.

Reprint requests and correspondence: Dr. David R. Holmes Jr., Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905. E-mail: dholmes@mayo.edu.

REFERENCES

1. Boden WE, O'Rourke RA, Crawford MH, et al., for the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH). Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. N Engl J Med 1998;338:1785–92.
2. The TIMI IIIB investigators. Effects of tissue plasminogen activator and a comparison of early and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB trial. Circulation 1994;89:1545–56.
3. Yusuf S, Flather M, Pogue J, et al. Variation between countries in invasive cardiac procedures and outcomes in patients with suspected unstable angina or myocardial infarction without ST elevation. Lancet 1998;352:507–14.
4. Licoff AM, Califf RM, Anderson KM, et al. Evidence for prevention of death and myocardial infarction with platelet membrane glycoprotein IIb/IIIa receptor blockade by abciximab among patients with unstable angina undergoing percutaneous coronary revascularization. J Am Coll Cardiol 1997;30:149–56.
5. The Capture investigators. Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE study. Lancet 1997;349:1429–35.
6. The EPILOG Investigators. Platelet glycoprotein IIIB/IIIa receptor blockade and low dose heparin during percutaneous coronary revascularization. N Engl J Med 1997;336:1689–96.
7. Stone GW, Brodie BR, Griffin JJ, et al. Prospective multicenter study of the safety and feasibility of primary stenting in acute myocardial infarction: in-hospital and 30-day results of the PAMI Stent Trial. J Am Coll Cardiol 1998;31:23–30.
8. Antoniucci D, Santoro GM, Bolognese L, Valenti R, Trapani M, Fazzani PF. A clinical trial comparing primary stenting of the infarct related artery with optimal primary angioplasty for acute myocardial infarction, results from the Florence Randomized Elective Stenting in Acute coronary Occlusion (FRESCO) Trial. J Am Coll Cardiol 1998;31:1234–9.
9. Wallentin L. The Fragmin during Instability in Coronary Artery Disease (FRISC) II study. Presented at the ACC 48th Annual Scientific Sessions in Late Breaking Trials in Interventional Cardiology, March 8, 1999.
10. Halon DA, Flugelman MY, Merdler A, Rennert H, Shahla J, Lewis BS. Long term (10-year) outcome in patients with unstable angina pectoris treated by coronary balloon angioplasty. J Am Coll Cardiol 1998;32:1603–9.