

Clinical and Angiographic Follow-Up After Primary Stenting in Acute Myocardial Infarction

The Primary Angioplasty in Myocardial Infarction (PAMI) Stent Pilot Trial

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Background—Restenosis has been reported in as many as 50% of patients within 6 months after PTCA in acute myocardial infarction (AMI), which necessitates repeat target-vessel revascularization (TVR) in $\approx 20\%$ of patients during this time period. Routine (primary) stent implantation after PTCA has the potential to further improve late outcomes.

Methods and Results—Primary stenting was performed as part of a prospective study in 236 consecutive patients without contraindications who presented with AMI of <12 hours' duration at 9 international centers. A mean of 1.4 ± 0.7 stents were implanted per patient (97% Palmaz-Schatz) at 17.3 ± 2.4 atm. During a clinical follow-up period of 7.4 ± 2.6 months, death occurred in 4 patients (1.7%), reinfarction occurred in 5 patients (2.1%), and TVR was required in 26 patients (11.1%). By Cox regression analysis, small reference-vessel diameter and the number of stents implanted were the strongest determinants of TVR. Angiographic restenosis occurred in 27.5% of lesions. By multiple logistic regression analysis, the number of stents implanted and the absence of thrombus on the baseline angiogram were independent determinants of binary restenosis.

Conclusions—A strategy of routine stent implantation during mechanical reperfusion of AMI is safe and is associated with favorable event-free survival and low rates of restenosis compared with primary PTCA alone. (*Circulation*. 1999;99:1548-1554.)

Key Words: angioplasty ■ restenosis ■ myocardial infarction ■ revascularization ■ stents

Although the 30-day rates of death, reinfarction, and stroke are improved after primary PTCA compared with thrombolytic therapy,¹ angiographic restenosis occurs in up to 50% of patients, which necessitates target-vessel revascularization (TVR) of the infarct artery with either repeat percutaneous intervention or CABG in $\approx 20\%$ of patients within this time frame.²⁻⁶ Compared with balloon angioplasty in patients undergoing elective coronary intervention, the implantation of coronary stents has been shown to reduce the angiographic rate of restenosis and improve late outcomes. Scant long-term data exist, however, on late outcomes after stenting during acute myocardial infarction (AMI).

The Primary Angioplasty in Myocardial Infarction (PAMI) Stent Pilot Trial was a prospective, controlled, multicenter study designed to investigate the feasibility, safety, and

long-term outcomes of a routine (primary) stent strategy in AMI in a large, consecutive series of patients.⁷ With 236 patients stented, this trial represents the largest experience with AMI stenting to date. The present report describes the major end points of this study, which were the late clinical and angiographic outcomes.

Methods

Patients and Clinical Centers

The methodology has been described previously in detail.⁷ Nine clinical sites in the United States, Europe, and South America participated in this prospective study, which was approved by the investigational review boards of the participating hospitals. Consecutive patients of any age with symptom duration ≤ 12 hours with any ECG pattern of AMI were enrolled. Patients were excluded for cardiogenic shock; for absolute contraindications to heparin, aspirin,

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or ticlopidine; and for prior use of thrombolytic therapy during the same hospitalization. All patients provided informed, written consent before enrollment.

Study Protocol

After receiving aspirin, ticlopidine, and heparin in the emergency room, patients were transferred to the catheterization laboratory, and primary PTCA was performed as previously described.⁷ After restoration of flow, stent implantation was attempted in all eligible lesions. Stenting was deferred if the reference segment was visually <3.0 or >4.0 mm in diameter, if the lesion would require ≥ 3 stents for coverage, if stenting would compromise a major side branch, if the infarct lesion was a true ostial left anterior descending coronary or left circumflex artery lesion, or if excessive proximal tortuosity or lesion calcification was present. Stenting was routinely performed directly into small or moderate amounts of thrombus but was deferred in 5 patients (1.6%) for large thrombus burden refractory to PTCA or pharmacological treatment.

Postprocedure medications consisted of oral aspirin 325 mg/d PO indefinitely, ticlopidine 250 mg PO BID for 4 weeks, and a 60-hour tapering heparin regimen (48 hours of full dose after sheath removal to keep the activated partial thromboplastin time at 55 to 80 seconds, followed by 12 hours of half dose, a schedule empirically derived to offset the frequently present rebound hypercoagulable state⁸). Clinical follow-up visits were scheduled at 1 and 6 months. Protocol follow-up angiography was planned after the 6-month visit in all surviving patients in whom CABG was not performed before hospital discharge, provided that restenosis had not already been documented.

Definitions

The primary end point of the study was the 6-month rate of adverse clinical events (death, reinfarction, and TVR); angiographic restenosis was a secondary end point. Reinfarction was defined as recurrent ischemic symptoms or ECG changes, with any creatine kinase-MB reelevation. TVR was defined as the performance of repeat percutaneous intervention or CABG of the infarct vessel after the index procedure. Thrombus was defined by the core laboratory as the presence of discrete intraluminal filling defects or lucency outlined by contrast material or of a convex leading edge with staining or haziness if the vessel was occluded. Binary restenosis was defined as present when the diameter stenosis within the axial length of the stent was >50%.

Data Collection and Statistical Analysis

Detailed in-hospital, 1-month, and 6-month follow-up case report forms were prospectively completed for each patient. Clinical events were confirmed and adjudicated at the coordinating center by separate review of all catheterization reports, ECGs, laboratory tests, and discharge summaries. Quantitative coronary analysis of all index and follow-up films was performed by an independent core angiographic laboratory at the Washington Hospital Center using previously validated methodology.⁹

Clinical and angiographic data were entered into a computerized database, and statistical analysis was performed

TABLE 1. Adverse Clinical Outcomes in 236 Stented Patients With AMI at a Mean Follow-Up Duration of 7.4 ± 2.6 Months

Event	In-Hospital	After Discharge	Cumulative
Death	2 (0.8%)	4 (1.7%)	6 (2.5%)
Reinfarction	4 (1.7%)	5 (2.1%)	9 (3.8%)
(Re)percutaneous intervention	13 (5.5%)	41 (17.5%)	51 (21.6%)
Target vessel	5 (2.1%)	20 (8.5%)	24 (10.2%)
Nontarget vessel	9 (3.8%)	24 (10.3%)	31 (13.1%)
CABG	6 (2.5%)	10 (4.3%)	16 (6.8%)
TVR	10 (4.2%)	26 (11.1%)	35 (14.8%)
Stroke	1 (0.4%)	1 (0.4%)	2 (0.8%)
Death, reinfarction, or TVR	13 (5.5%)	30 (12.8%)	41 (17.4%)
Death, reinfarction, TVR, or stroke	14 (5.9%)	30 (12.8%)	42 (17.8%)

with commercially available software (JMP 3.1, SAS Institute). Categorical variables were compared with χ^2 or Fisher's exact tests, whereas continuous variables were compared with paired or unpaired Student *t* tests. Follow-up clinical events were analyzed with actuarial methods, and Kaplan-Meier curves were constructed. The influence of 25 baseline demographic and angiographic variables on late clinical events during the follow-up period was assessed with the log rank test. Cox proportional hazard regression was then used to determine the independent predictors of late adverse events.

Baseline, postprocedural, and follow-up angiographic core laboratory measures were displayed as a cumulative frequency distribution function. The independent correlates of angiographic binary restenosis were evaluated by multiple

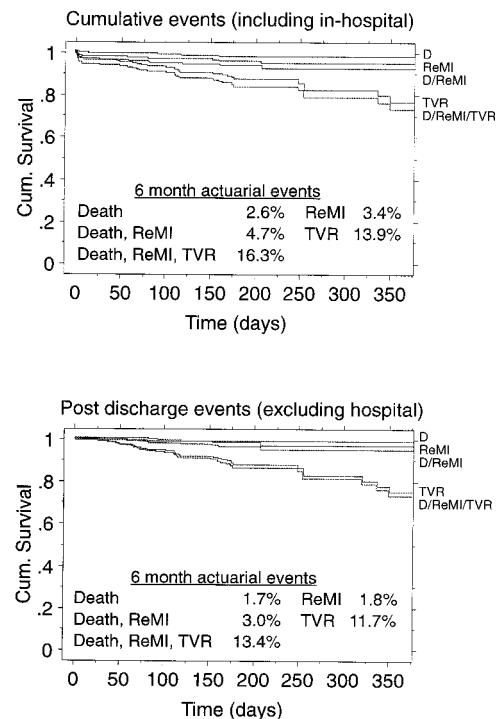


Figure 1. Actuarial event curves for death (D), reinfarction (ReMI), TVR, and the composite of death, reinfarction, and TVR. Upper graph represents cumulative (Cum.) events, including in-hospital outcomes in 236 patients; lower graph displays follow-up events only after hospital discharge.

Cumulative death, reinfarction or TVR

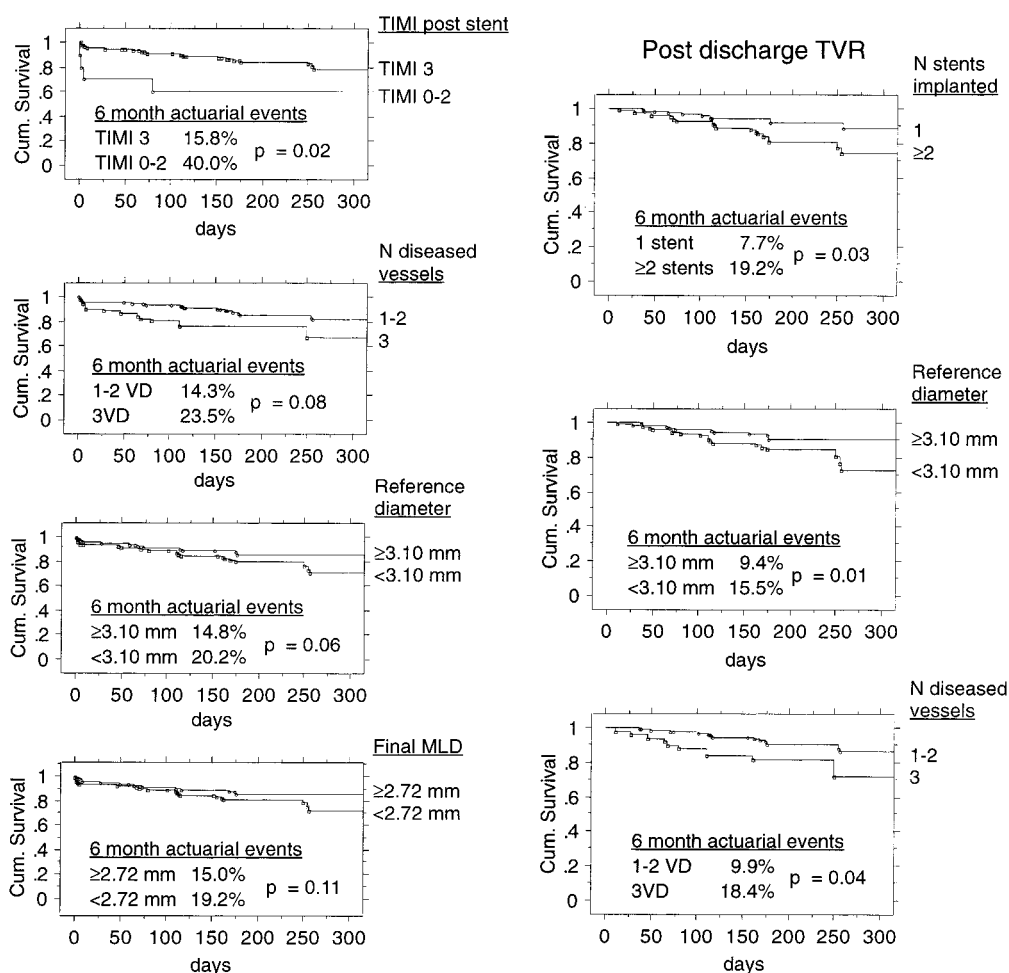


Figure 2. Univariate predictors of cumulative (Cum.) in-hospital or follow-up adverse cardiac events (death, reinfarction, or TVR) (left) and of TVR after hospital discharge (right) after primary stenting in AMI. VD indicates vessel disease; MLD, minimal lumen diameter.

logistic regression analysis. The independent predictors of the follow-up diameter stenosis considered as a continuous variable were determined by stepwise forward regression analysis. A P value of <0.05 was required for statistical significance.

Results

Patients and Catheterization Laboratory Course

Between June 1995 and July 1996, stenting was considered feasible and was attempted in 240 (77%) of 312 consecutive patients undergoing primary PTCA at 9 clinical centers; as previously described, the most common reasons for not stenting (72 lesions) were small vessels, excessive lesion length, proximal tortuosity, and major side-branch involvement.⁷ Stents were successfully implanted in 236 patients (98%), who constitute the study cohort for long-term analysis. The baseline demographic, clinical, and angiographic features of the patient population have been described previously.⁷ A mean of 1.4 ± 0.7 stents (range, 1 to 7) were implanted per patient (97% JJIS, 1% AVE, 1% Cook, and 1% Schneider). The median balloon size used for post-stent-

implantation expansion was 3.4 ± 0.5 mm (mean balloon-to-artery ratio 1.10 ± 0.17) at 17.3 ± 2.4 atm.

In-Hospital and Follow-Up Clinical Events

Two patients (0.8%) died before hospital discharge, 1 after a reinfarction 7 days after stenting and 1 of left ventricular failure on hospital day 4 despite angiographically successful stenting. Of 234 stented patients who were discharged from the hospital alive, clinical follow-up was available in 100% at a mean time of 7.4 ± 2.6 months. Adverse clinical events are summarized in Table 1, and actuarial event-free survival curves are displayed in Figure 1. Of note, TVR was performed in 34 of 35 patients for clinical symptoms or recurrent ischemia; in only 1 case was TVR performed in an asymptomatic patient on the basis of the findings of protocol follow-up angiography (the "oculo-stenotic reflex").

By univariate analysis, the presence of triple-vessel disease, reference-vessel diameter < 3.1 mm, postprocedural minimal lumen diameter < 2.72 mm, and the inability to restore TIMI-3 flow correlated with the occurrence of the composite end point of in-hospital or late death, reinfarction, or TVR after stenting in AMI (Figure 2, left). By Cox

TABLE 2. Baseline Characteristics, Initial Angiographic Results, and Clinical Outcomes in 229 Patients Surviving to Hospital Discharge Without Bypass Surgery, Stratified by Follow-Up Angiography

	Follow-Up Angiography		<i>P</i>
	Performed (n=176)	Not Performed (n=53)	
Baseline features			
Age, y	60.2±12.2	60.7±12.9	0.77
Female gender, n	48 (27.3%)	11 (20.8%)	0.34
Diabetes, n	33 (18.7%)	3 (5.7%)	0.02
Triple-vessel disease, n	37 (21.0%)	10 (18.9%)	0.73
LAD infarct artery, n	64 (36.4%)	19 (35.8%)	0.95
LVEF, %	47±12	48±13	0.72
Stents implanted, n	1.4±0.7	1.6±0.8	0.13
Maximal balloon size, mm	3.4±0.4	3.5±0.5	0.27
Initial core laboratory angiographic results			
Reference-vessel diameter, mm	3.19±0.54	3.10±0.56	0.33
Final MLD, mm	2.82±0.50	2.78±0.43	0.63
Final diameter stenosis, %	11.1±12.3	9.0±12.3	0.33
Final TIMI flow, grade	2.96±0.23	2.92±0.35	0.32
Clinical outcomes			
In-hospital death, reMI, TVR, or stroke, n	4 (2.3%)	3 (5.7%)	0.21

LAD indicates left anterior descending coronary artery; LVEF, left ventricular ejection fraction; MLD, minimal lumen diameter; and reMI, recurrent myocardial infarction.

multivariate regression analysis, only restoration of TIMI-3 flow was independently predictive of event-free survival (OR [95% CI]=3.2 [1.1, 9.0]; $P=0.02$). Three univariate correlates of postdischarge TVR (ie, clinical restenosis) were identified: the number of stents implanted, the reference-segment diameter, and the presence of triple-vessel disease (Figure 2, right). By Cox regression analysis, the only independent determinant for the occurrence of TVR after hospital discharge was smaller reference-vessel diameter (OR=2.2 [1.1, 4.6]; $P=0.03$); the number of stents implanted

TABLE 3. Quantitative Coronary Analysis in 142 Eligible Lesions With Paired Acute and Follow-Up Angiograms

Reference-vessel diameter, mm	
Before procedure	3.21±0.57
Final	3.23±0.53
Follow-up	3.10±0.57
Minimal luminal diameter, mm	
Before procedure	0.29±0.48
Final	2.85±0.52
Follow-up	1.98±0.93
Diameter stenosis, %	
Before procedure	90.4%±15.3
Final	10.9%±12.9
Follow-up	36.7%±27.5
Acute gain, mm	2.55±0.67
Late loss, mm	0.88±0.92
Net gain, mm	1.66±1.03
Loss index	0.35±0.39

retained borderline statistical significance in this model (OR=2.0 [0.9, 4.8]; $P=0.08$), whereas triple-vessel disease was no longer predictive of TVR (OR=1.7 [0.7, 3.4]; $P=0.15$).

Acute and Follow-Up Angiography

Of 229 stented patients surviving to hospital discharge without bypass surgery, angiographic follow-up was performed in 176 (77.0%) at a mean time of 7.8 ± 3.2 months. There were no significant differences in baseline characteristics, initial angiographic results, or in-hospital outcomes between eligible patients with versus without angiographic follow-up, except for a slightly greater incidence of diabetes in patients who underwent late angiography (Table 2). The follow-up angiograms from 1 site were recorded on a CD-ROM format, which proved to be incompatible with the core laboratory digital acquisition protocols; the cases from this single site were thus excluded from further angiographic analysis (Figure 3).

The preprocedure, acute poststenting, and follow-up angiographic quantitative coronary analysis measures in 142 patients with paired core laboratory data appear in Table 3 and Figure 4. Binary restenosis was present in 27.5% of infarct arteries, including reocclusion in 6.4% of infarct vessels. The univariate and multivariate correlates of angiographic restenosis appear in Table 4. By multiple logistic regression analysis, the only independent predictors of binary restenosis were the absence of thrombus before stenting and the number of stents implanted. When considered as a continuous variable in a stepwise, forward regression analysis, the independent correlates of greater diameter stenosis at follow-up were a smaller balloon-to-artery ratio, the absence of thrombus before stenting, and the number of stents implanted. The impact of the number of stents implanted on clinical and angiographic restenosis is shown in Figure 5.

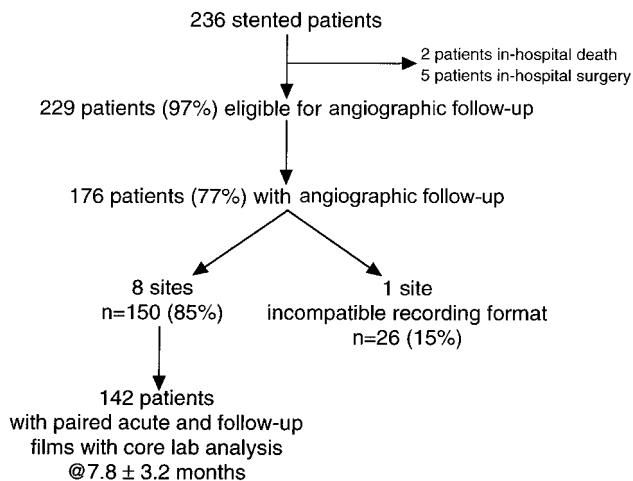


Figure 3. Eligibility and completion of angiographic follow-up after acute infarct stenting.

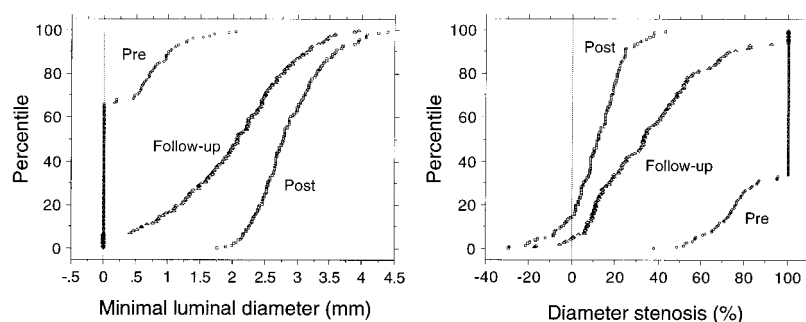


Figure 4. Minimal luminal diameters (left) and diameter stenoses (right) before procedure (Pre), immediately after procedure (Post), and at follow-up in 142 patients, with paired measures displayed as a cumulative frequency function.

Discussion

Clinical Outcomes After Primary Stenting in AMI

The principal finding from this prospective, multicenter study is that a primary stent strategy in AMI at experienced centers is safe and results in favorable intermediate-term clinical outcomes. Most events during the follow-up period consisted of repeat TVRs, with few patients dying or experiencing reinfarction. The actuarial postdischarge 6-month TVR rate of 11.7% after primary AMI stenting in this study is similar to that reported after elective stenting in the noninfarct setting^{10,11} and compares favorably to the 6-month TVR rates reported after primary PTCA for AMI (21.7% from the Primary Angioplasty Registry,⁵ 17.1% from the PAMI trial,¹² and 17.0% in the series by Hartzler et al¹³). It must be emphasized, however, that in addition to “stent-eligible” lesions, primary PTCA is also typically performed in stenoses not amenable to stenting (eg, in diffuse disease and in smaller vessels), which may have a higher restenosis rate. Thus, large-scale, multicenter randomized trials are necessary to confirm whether late event rates are indeed lower after primary stenting than after primary PTCA, as suggested from the present study.

Reference-vessel diameter and number of stents implanted were found to be the predominant determinants of freedom from late TVR (clinical restenosis) after primary stenting in AMI (Figure 2, right). Small vessel size^{14,15} and multiple stent implantation^{15,16} are also well-recognized risk factors for clinical and angiographic restenosis after elective coronary stenting. When total late composite outcomes were considered, including in-hospital death, reinfarction, and TVR, restoration of TIMI-3 flow proved to be the strongest determinant of event-free survival (Figure 2, left). The fundamental relationship between the establishment of TIMI-3 flow and reduced short-term mortality^{17,18} and reinfarction¹² after primary PTCA in AMI has been described previously and appears to be equally important after a primary stent strategy.

Angiographic Restenosis After Primary Stenting in AMI

Five prior studies (with 85 to 154 patients each) have reported the 6-month angiographic rates of restenosis and reocclusion after primary PTCA.^{5,19–22} With angiographic follow-up performed in 70% to 89% of patients in these series, restenosis was documented in 37% to 49% of vessels, including infarct artery reocclusion in 9% to 14%. In contrast, restenosis was found in 27.5% of vessels after primary stenting in the present study, including infarct artery reocclusion in 6.4%. Thus, these data support the contention that routine stenting of the infarct vessel during AMI may improve long-term vessel patency and reduce restenosis compared with primary PTCA alone. However, given differing baseline lesion characteristics and vessel eligibility between the primary stent and primary PTCA populations, randomized trials are necessary before this issue can be considered resolved.

In addition to being predictive of the need for late clinical TVR, the number of stents implanted was identified as an independent correlate of angiographic restenosis, consistent with previous studies of elective stenting.^{15,16} However, given the high percentage of patients with occluded coronary vessels, it was impossible to accurately quantify baseline lesion length in 40% of the patients in the present study. It therefore cannot be differentiated whether the number of stents implanted is truly an independent risk factor for TVR and restenosis after AMI stenting or merely represents a surrogate for lesion length. The only other variable related to restenosis was the absence of angiographically visible thrombus before intervention. To the best of our knowledge, this finding has not been described before with elective stenting (possibly because of the rarity of stenting thrombotic lesions in most prior studies). It is well known that thrombus is present in the majority of infarct-related lesions, although it is angiographically evident in only a minority of cases.²³ Although it remains speculative why angiographically visible thrombus was protective against restenosis in the present

TABLE 4. Correlates of Angiographic Binary Restenosis

	Univariate Analysis			Multivariate Analysis	
	Present	Absent	P	OR (95% CI)	P
Thrombus before PTCA*	9.7%	32.4%	0.007	4.3 (1.4,19.0)	0.02
≥2 Stents implanted	38.3%	22.1%	0.04	2.2 (1.0,4.9)	0.05
Hypertension	35.3%	20.3%	0.05	2.0 (0.9,4.3)	0.10

*Core laboratory analysis.

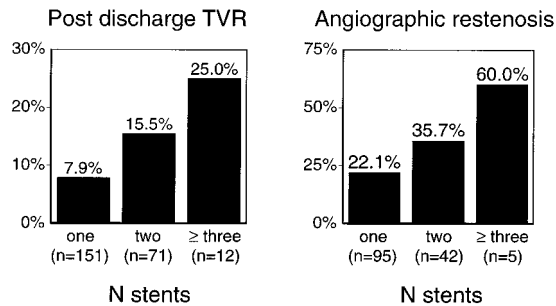


Figure 5. Impact of number of stents implanted on requirement for TVR after hospital discharge (left) and angiographic restenosis (right).

study, it is possible that the presence of abundant angiographic thrombus may signify lesser underlying plaque burden, thereby engendering greater long-term freedom from restenosis after stenting.²⁴

Comparison With Previous Primary Stent Studies

Three smaller single-center studies (72 to 124 patients each) have been published examining late clinical and angiographic outcomes after Palmaz-Schatz stenting in AMI,^{25–27} none of which were adequately powered to analyze the multivariate correlates of late TVR and restenosis. Considering only the patients in these studies treated with aspirin and ticlopidine, the 6-month reported composite rates of death, reinfarction or TVR ranged between 13.5% and 18.0%. Two of these studies^{25,26} incorporated routine angiographic follow-up at 6 months and documented restenosis rates ranging from 19.0% to 26.5% and infarct-artery reocclusion rates of 1.0% to 1.6%. Thus, the 17.4% incidence of late clinical events and 27.5% restenosis rate (including 6.4% vessel reocclusion) from the present multicenter PAMI Stent Pilot Trial are at the high end of the prior reports and probably accurately reflect the late clinical and angiographic outcomes that can be expected when primary stenting is performed by multiple operators at various institutions in a largely unselected patient population.

In contrast, the 6-month cardiac event-free rate after primary stenting in 115 patients with AMI was 95% in the recently published single-center randomized trial by Suryapranata and colleagues,²⁸ with a separately reported restenosis rate of only 11%. However, only 50% of screened patients were enrolled in that trial, compared with 77% of patients in the PAMI Stent Pilot Trial.⁷ The improved results in the study by Suryapranata et al²⁸ may therefore represent selective enrollment of a lower-risk patient cohort, as well as the possible play of chance, reemphasizing the importance of large-scale, multicenter randomized trials.

Study Limitations and Clinical Caveats

First, although the present trial, with 236 consecutive eligible patients stented, represents the largest experience to date of stenting during evolving AMI, an expanded patient population might have allowed the elucidation of other variables related to clinical and angiographic restenosis. Second, the favorable results of this study cannot be generalized to patient or lesion subtypes excluded from randomization, including patients in cardiogenic shock and infarct-related lesions

>25 mm in length or in vessels ≤ 2.5 mm in diameter. Similarly, the clinical and angiographic outcomes reported from this trial apply primarily to the balloon-expandable Palmaz-Schatz stent; whether newer, more flexible designs (without a central articulation) can surpass these event rates will require independent appraisal. Furthermore, the optimal postprocedural pharmacological regimen after primary infarct stenting has not been determined; it is unresolved, for example, whether the 60-hour tapering heparin regimen routinely used in all the recent PAMI studies is beneficial or necessary. Third, intravascular ultrasound was not routinely used to guide stent implantation in the present study. It is unknown whether the regular use of intravascular ultrasound would have identified additional predictive determinants of clinical or angiographic outcomes or would have led to improved results. Fourth, although the actual rate of completed angiographic follow-up was 77%, fewer films were available for paired acute and late angiographic core laboratory analysis. Because most of the nonexamined films were systematically not analyzable for technical reasons (despite completion of angiographic follow-up), the remainder should be representative of the entire population. Furthermore, the primary end point of the study was the incidence of late clinical adverse events, and clinical follow-up was obtained in 100% of patients; the secondary angiographic data are consistent with and support the clinical outcomes end point.

Finally, given the hazards of comparing registry experiences with historical controls and the lack of data regarding the cost-effectiveness of a primary stent approach relative to PTCA, it is prudent to currently reserve stenting during AMI for suboptimal procedural PTCA outcomes (ie, a residual stenosis >30% or dissection \geq type B), despite the encouraging results of this trial. Ongoing large-scale, international, multicenter randomized trials, including the 900-patient PAMI Stent Randomized Trial and the 2000-patient Controlled Abciximab and Device Evaluation to Lower Late Angioplasty Complications (CADILLAC) trial, should provide additional meaningful insight as to whether primary stenting indeed represents a major breakthrough in the reperfusion therapy of patients with AMI.

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