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EXPEDITED REVIEWS

Prospective, Randomized Evaluation of Thrombectomy Prior to Percutaneous Intervention in Diseased Saphenous Vein Grafts and Thrombus-Containing Coronary Arteries

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OBJECTIVES We sought to determine whether routine thrombectomy prior to stent implantation in diseased saphenous vein grafts (SVGs) and thrombus-containing native coronary arteries would reduce peri-procedural myonecrosis and subsequently enhance event-free survival.

BACKGROUND Percutaneous coronary intervention in diseased SVGs and thrombotic native coronary arteries is complicated by a high rate of peri-procedural myocardial infarction (MI). Thrombectomy prior to intervention may enhance the safety of intervention and improve early and late outcomes in these high-risk patients.

METHODS At 60 centers in the U.S. and Canada, 797 patients with 839 diseased SVGs or thrombus-containing native coronary arteries were prospectively randomized to stent implantation with versus without prior thrombectomy with the X-SIZER device (ev3, Plymouth, Minnesota).

RESULTS Peri-procedural MI occurred in 15.8% of patients assigned to the X-SIZER device compared with 16.6% of control patients ($p = 0.77$), although the rate of large MI (pre-specified as the development of new pathologic Q waves or creatine phosphokinase-MB isoenzyme elevation $>8 \times$ upper limits of normal) was reduced with X-SIZER device use from 9.6% to 5.5% (multivariate risk ratio 0.35 [95% confidence interval 0.18 to 0.66], $p = 0.002$). Major adverse cardiac events (cardiac death, MI, or repeat target vessel revascularization) occurred in 16.8% of X-SIZER patients versus 17.1% of control patients at 30 days ($p = 0.92$), and in 31.3% of X-SIZER patients versus 28.2% of control patients at 1 year ($p = 0.35$).

CONCLUSIONS Thrombectomy with the X-SIZER device prior to stent implantation in high-risk diseased SVGs and thrombus-containing native coronary arteries may reduce the extent, but not the occurrence, of myonecrosis. Early and late event-free survival, however, were not improved by routine thrombectomy with this device. (J Am Coll Cardiol 2003;42:2007–13) © 2003 by the American College of Cardiology Foundation

The introduction of coronary stents and adjunctive pharmacologic agents including thienopyridines and glycoprotein (GP) IIb/IIIa receptor inhibitors have improved the safety profile of percutaneous coronary intervention (PCI) (1–5). Despite contemporary approaches, however, the rate of peri-procedural complications remains excessively high after PCI in friable lesions prone to embolization, including native coronary arteries with thrombus and diseased saphenous vein grafts (SVGs) (6–8). Mechanical extraction of soft atherothrombotic material prior to stent implantation may further enhance the safety and efficacy of PCI in high-risk lesions. Therefore, we performed a large-scale, multicenter, prospective, randomized trial to determine the utility of thrombectomy with the X-SIZER device (ev3, Plymouth, Minnesota) during PCI.

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METHODS

Study population and study protocol. Angiographic inclusion criteria required the presence of ≥1 lesion in a native coronary artery or SVG with a reference vessel diameter

Abbreviations and Acronyms

CPK = creatine phosphokinase
GP = glycoprotein
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
SVG = saphenous vein graft
TIMI = Thrombolysis In Myocardial Infarction
TVR = target vessel revascularization
ULN = upper limit of normal
X-TRACT = X-SIZER for Treatment of Thrombus and Atherosclerosis in Coronary Interventions Trial

≥3.0 mm and a diameter stenosis >50% but <100%; totally occluded SVG lesions could be enrolled if successfully crossed with a guidewire. The presence of angiographic thrombus as assessed by the investigator was also mandatory for inclusion of native coronary artery lesions, although *not* for SVGs. Patients with multiple lesions in the same or different vessels were eligible if all lesions met enrollment criteria. Clinical and angiographic exclusion criteria included: recent (<24 h) or acute myocardial infarction (MI) or elevated creatine phosphokinase (CPK)-MB isoenzyme on the day of the procedure; left ventricular ejection fraction <30% or cardiogenic shock; target lesion was either an isolated ostial lesion, at the distal SVG anastomosis, within a SVG <6 months old or an arterial bypass graft conduit, or within a previously stented segment; excessive vessel or lesion tortuosity or calcification; prior unsuccessful or complicated PCI within 6 months; and current participation in other investigational protocols. The study was approved by the institutional review board at each participating center, and consecutive, eligible patients signed informed, written consent.

Before the catheterization procedure, patients received chewable aspirin 325 mg and clopidogrel 300 mg. The decision to use procedural GP IIb/IIIa inhibitors was left to

Table 1. Baseline Clinical and Angiographic Characteristics

	X-SIZER Prior to Stent	Stent Alone	p Value
Demographic features			
Number of patients	400	397	
Age (yrs)	66.4 ± 10.3	65.4 ± 12.1	0.54
Range	31–88	30–88	–
Male gender (%)	78.5	79.1	0.86
Diabetes mellitus (%)	31.6	29.5	0.54
Hypertension (%)	68.9	67.5	0.70
Hyperlipidemia (%)	72.4	69.4	0.39
Current cigarette use (%)	19.6	22.6	0.33
Prior myocardial infarction (%)	66.2	62.4	0.29
Prior coronary bypass surgery (%)	77.0	73.6	0.29
Peripheral vascular disease (%)	16.8	17.0	0.99
Cerebrovascular disease (%)	8.6	11.4	0.19
Unstable angina (%)	85.5	88.9	0.17
Left ventricular ejection fraction (%)	49.4 ± 11.8	50.7 ± 11.1	0.15
Angiographic features			
Number of target vessels	420	419	
Single-vessel disease (%)	22.3	24.9	0.40
Double-vessel disease (%)	18.5	19.5	0.79
Triple-vessel disease (%)	59.1	55.6	0.32
Target lesion			
Left anterior descending artery (%)	6.1	9.6	0.07
Left circumflex artery (%)	3.5	3.0	0.69
Right coronary artery (%)	15.7	15.6	0.99
Saphenous vein graft (%)	74.7	71.9	0.38
Core laboratory analysis			
TIMI flow (%)			
0/1	12.9	10.5	0.46
2	13.4	10.9	0.33
3	73.7	78.6	0.11
Thrombus (%)	70.1	57.7	< 0.001
Eccentric lesion (%)	36.5	41.0	0.19
ACC/AHA lesion class B_2/C (%)	69.1	70.6	0.94
Reference vessel diameter (mm)	3.33 ± 0.74	3.30 ± 0.66	0.94
Minimal luminal diameter (mm)	1.01 ± 0.68	1.10 ± 0.69	0.07
Diameter stenosis (%)	69.9 ± 18.8	66.8 ± 19.2	0.01
Lesion length (mm)	15.1 ± 10.4	15.2 ± 10.0	0.88

ACC = American College of Cardiology; AHA = American Heart Association; TIMI = Thrombolysis In Myocardial Infarction.

Table 2. Procedural Results

	X-SIZER Prior to Stent (n = 400)	Stent Alone (n = 397)	p Value
GP IIb/IIIa inhibitor pre-intervention (%)	75.9	76.6	0.80
Stent implanted (%)	98.0	97.2	0.50
Total stent length (mm)	32.1 ± 21.8	31.1 ± 21.4	0.77
Stent implantation pressure (atms)	13.7 ± 3.8	13.8 ± 3.5	0.53
Intra-procedural events			
GP IIb/IIIa inhibitor for "bail-out" (%)	0.8	2.3	0.09
GP IIb/IIIa inhibitor for "bail-out" in patients not pre-treated with GP IIb/IIIa (%)	3.1	9.8	0.06
Atherothrombectomy for "bail-out" (%)	1.5	2.5	0.33
GP IIb/IIIa inhibitor or atherothrombectomy for "bail-out" (%)	2.3	4.8	0.056
Perforation (%)	0.3	1.3	0.12
Acute closure (%)	1.0	0.8	0.99
Post-procedure core angiographic analysis			
TIMI flow (%)			
0/1	1.8	2.5	0.72
2	2.8	2.4	0.83
3	95.4	95.0	0.87
TIMI flow improvement (baseline to post-intervention)	0.4 ± 1.0	0.3 ± 1.0	0.17
Residual thrombus (%)	3.3	4.0	0.71
Distal emboli (%)	1.0	1.2	0.99
No reflow (%)	0.5	1.2	0.45
Dissection (%)	1.3	0.2	0.12
Minimal luminal diameter (mm)	2.70 ± 0.71	2.73 ± 0.76	0.41
Diameter stenosis (%)	19.8 ± 15.0	18.7 ± 15.6	0.15

GP = glycoprotein; TIMI = Thrombolysis In Myocardial Infarction.

the discretion of the operator. Unfractionated heparin was administered to attain an activated clotting time of ≥300 s, or 200 to 300 s if a GP IIb/IIIa inhibitor was administered. All patients meeting the angiographic enrollment criteria were randomized after successful wire-crossing of the first lesion. Randomization was stratified by planned procedural GP IIb/IIIa inhibitor use to assure balanced distribution of this variable.

Randomized patients were equally assigned to either pre-interventional thrombectomy using the X-SIZER device, followed by PCI (with stent implantation if possible), or to PCI and stent implantation without thrombectomy. The X-SIZER thrombectomy system has been previously described (9,10). In brief, the X-SIZER device consists of a helical cutter enclosed within a protective housing attached to a dual bore catheter shaft containing guidewire and vacuum/extraction lumens. Activation of the handheld controller simultaneously rotates the helical cutter at ~2,100 rpm, which entrains and macerates soft atherosclerotic plaque and thrombus, and opens a channel to a 250 ml vacuum collection bottle to permit material aspiration. The device is available with 1.5, 2.0, and 2.3 mm diameter cutters for vessels of different sizes, and is compatible with commercial 0.014-inch guidewires. Multiple slow passes across the lesion are performed until maximal angiographic improvement is obtained. Upsizing to a larger diameter catheter was permitted for persistent residual thrombus or grummous material after use of an undersized device.

Stent selection and decisions regarding pre- and post-dilation were at the judgment of the operator. "Bail-out" GP IIb/IIIa inhibitors in patients not pre-treated and non-study mechanical atherothrombectomy devices were allowed only in failed cases or for procedural complications. Distal protection devices were not available during the enrollment period of this study. Following the procedure, serial CPK-MB isoenzymes were drawn at least every 8 h over 24 h. Patients were maintained on aspirin 325 mg daily, and clopidogrel 75 mg daily for four weeks. Follow-up was scheduled at 1, 6, and 12 months after discharge.

Data collection and management. Clinical data were prospectively collected by dedicated research nurses and verified on-site by independent study monitors. All primary end point events were adjudicated by an independent committee blinded to treatment allocation after review of the original source documentation. A Data Safety and Monitoring Committee reviewed blinded data after 100, 350, and 550 patients were randomized, each time recommending the study continue without modification. Independent core angiographic laboratory analysis was performed as previously described (11) by technicians blinded to clinical outcomes.

Statistical methods and definitions. Major adverse cardiac events (MACE) were defined as the composite incidence of cardiac death, MI, or repeat target vessel revascularization (TVR). Myocardial infarction was defined as any post-procedural CPK-MB rise >3 × upper limits of normal (ULN), and was classified as either Q-wave or non–Q-wave based on whether new pathological Q waves developed in

≥2 contiguous leads. "Large" MI was pre-specified in the protocol as the development of Q waves or CPK-MB elevation to >8 × ULN. An additional pre-specified end point was the ability of the X-SIZER device to prevent intra-procedural complications as evidenced by a reduced need for "bail-out" use of GP IIb/IIIa inhibitors or approved atherothrombectomy devices.

The sample size was selected to demonstrate a reduction in the 30-day MACE end point from 16% in the control group to 9% in the treatment group. Using a two-sided test of binomial proportions, total alpha was 0.05, and allowing for two interim analyses using an O'Brien-Fleming boundary analysis, 765 randomized patients afforded the study 80% power. Recruitment of approximately 800 patients was thus planned to accommodate incomplete data ascertainment or follow-up. The nominal significant level alpha for each test for the primary end point was 0.014 (@350 patients), 0.021 (@550 patients), and 0.030 (@800 patients).

Categorical variables were compared with the likelihood ratio chi-square test or the Fisher exact test. Continuous variables are presented as the mean ± SD and were compared with the Wilcoxon two-sample test. The influence of baseline demographic and angiographic variables on 30-day clinical outcomes was evaluated with logistic regression using the Wald chi-square test, and the results were expressed as odds ratios with 95% confidence intervals. All analyses were by intention to treat unless otherwise stated, and all p values were two-sided.

RESULTS

Patient population and baseline characteristics. Between March 2000 and April 2002, 797 patients with 839 vessels at 60 sites in the U.S. and Canada were randomized and treated with either the X-SIZER device prior to stent implantation or stent implantation alone. Baseline demographic features were well matched between the two groups (Table 1). The study cohort was elderly, had a high frequency of diabetes mellitus and prior MI, and predominantly consisted of patients with unstable angina. Approximately 73% of the lesions were in SVGs, whereas 27% were in native coronary arteries. Baseline Thrombolysis In Myocardial Infarction (TIMI) flow was abnormal in 24% of vessels. By core laboratory analysis, thrombus was present in approximately two-thirds of cases and was more frequent in X-SIZER randomized patients. Baseline lesion severity was also slightly greater among patients assigned to the X-SIZER device.

Procedural results. As seen in Table 2, in patients randomized to the X-SIZER device, a mean of 1.1 ± 0.1 catheters per case were used (with the 1.5, 2.0, and 2.3 mm diameter catheters selected in 53%, 46%, and 1% of patients, respectively). GP IIb/IIIa inhibitors were used prophylactically in three-quarters of patients in both groups, and stents were implanted in nearly all patients. In patients in whom GP IIb/IIIa inhibitors were not administered upfront, bail-out GP IIb/IIIa inhibitors were required more commonly in the control arm than in patients pre-treated with thrombectomy prior to PCI for the development of intra-procedural complications. The composite requirement for the "bail-out" usage of either an approved atherothrombectomy device or a GP IIb/IIIa inhibitor was also reduced in X-SIZER–assigned patients. The rates of final no reflow and distal thromboemboli were similar between the two groups, as were the final rates of TIMI-3 flow (Table 2).

Table 3. 30-Day and 1-Year Clinical Outcomes

	X-SIZER Prior to Stent (n = 400)	Stent Alone (n = 397)	p Value
30-day events (%)			
Death (all cause)	1.0	0.3	0.37
Cardiac death	1.0	0.3	0.37
MI	15.8	16.6	0.77
Q-wave	1.0	1.3	0.75
Non–Q-wave	14.8	15.4	0.84
CPK-MB >8 × ULN	4.5	8.3	0.03
CPK-MB >3 to <8 × ULN	10.3	7.1	0.11
Large MI*	5.5	9.6	0.03
Death or large MI*	6.3	9.8	0.07
TLR	0.8	1.3	0.99
TVR not involving the target lesion	0.8	0	0.99
Composite MACE	16.8	17.1	0.92
In saphenous vein grafts	19.6	19.3	0.99
In thrombotic native coronary arteries	9.0	9.3	0.99
1-year events (%)			
Death (all cause)	6.5	4.3	0.17
Cardiac death	5.0	3.5	0.38
MI	19.3	18.9	0.93
Q-wave	1.5	1.5	0.99
Non–Q-wave	17.8	17.4	0.93
CPK-MB >8 × ULN†	4.5	8.1	0.04
CPK-MB >3 to <8 × ULN†	11.3	8.1	0.15
Large MI	6.0	9.6	0.065
Death or large MI	10.3	12.8	0.27
TLR	11.8	8.3	0.13
TVR not involving the target lesion	4.0	1.8	0.09
Composite MACE	31.3	28.2	0.35

*Large MI = Q-wave or CPK-MB >8 × ULN; †MB values not present in all patients at 1-year.

CPK-MB = creatine phosphokinase-MB isoenzyme; MACE = major adverse cardiac events; MI = myocardial infarction; TLR = target lesion revascularization; TVR = target vessel revascularization; ULN = upper limits of normal.

30-day outcomes. Composite MACE rates at 30 days were similar between the two groups, as were the individual components of the composite end point (Table 3). Although the absolute occurrence of any degree of periprocedural myonecrosis was not reduced with thrombectomy, X-SIZER device use before PCI tended to reduce the extent of MI at all levels, as seen in Figure 1. When examined categorically, the pre-specified rate of large MI was reduced by 43% after thrombectomy with the X-SIZER device, and a strong univariate trend was present for a reduction in the combined rate of death or large MI. When differences in baseline characteristics were corrected for by multivariate analysis, randomization to the X-SIZER device prior to PCI was an independent predictor of both freedom

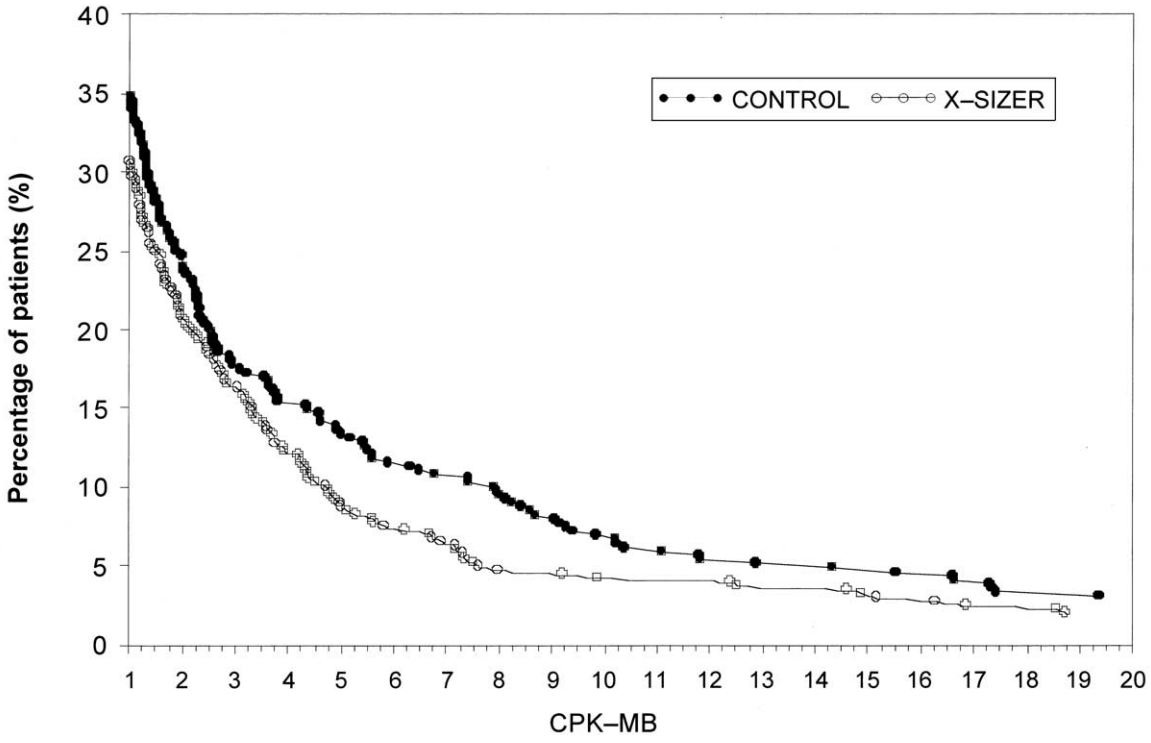

Figure 1. Cumulative frequency distribution curves of peak post-procedural creatine phosphokinase (CPK)-MB isoenzyme for patients randomized to thrombectomy with the X-SIZER device **(open circles)** versus control **(closed circles)**. Each **curve** shows the percentage of patients whose CPK-MB elevation (expressed as a multiple of institutional upper limit of normal) exceeds the value on the x-axis.

from large MI and survival free from large MI (Table 4). The protective effect of thrombectomy was present in both SVGs and native coronary arteries, in patients pre-treated or not pre-treated with GP IIb/IIIa inhibitors, and was especially evident in patients with core laboratory confirmed angiographic evidence of thrombus (Fig. 2).

Outcomes in thrombotic lesions. In thrombotic lesions, X-SIZER device use reduced the mean post-procedural peak CPK (160 ± 248 vs. 216 ± 330, p = 0.021) and peak CPK-MB (13 ± 26 vs. 25 ± 80, p = 0.067). Any CPK-MB elevation occurred in 24.7% of patients with thrombotic lesions treated with the X-SIZER device versus 32.5% of controls (p = 0.05). The occurrence of death or large MI by 30 days in patients with thrombotic lesions was reduced by 53% with X-SIZER device use before PCI (4.7% vs. 9.9%, p = 0.04).

Table 4. Independent Multivariate Correlates of 30-Day Adverse Events

	Hazard Ratio (95% Confidence Interval)	p Value
Large myocardial infarction		
Age (per yr)	1.06 (1.02–1.10)	0.0003
Lesion length (per mm)	1.04 (1.02–1.06)	0.0006
Randomization to X-SIZER	0.35 (0.18–0.66)	0.002
Reference vessel diameter (mm)	1.54 (1.04–2.28)	0.03
Death or large myocardial infarction		
Age (yr)	1.06 (1.02–1.10)	0.0001
Lesion length (mm)	1.04 (1.02–1.06)	0.0001
Randomization to X-SIZER	0.45 (0.25–0.80)	0.008

1-year outcomes. At one year, the overall rates for MACE, as well as death, Q-wave MI, and TVR were similar in both groups (Table 3). Although the overall rate of non–Q-wave MI was not reduced by X-SIZER device use, the incidence of large non–Q-wave MI remained less frequent in X-SIZER–treated patients, and trends were present toward reduction in the rates of large MI and death or large MI.

DISCUSSION

Although the widespread use of stents and GP IIb/IIIa inhibitors have enhanced the safety of PCI (1–5), patients requiring intervention in diseased SVGs and thrombotic lesions in native coronary arteries remain at high risk for peri-procedural complications (6–8). As evident from the control arm of the current and recent trials, approximately 20% of patients develop an adverse ischemic event within 30 days after stenting in diseased SVGs (12), a rate that is not diminished by GP IIb/IIIa inhibitors (3). Although the occurrence of MI after SVG intervention is reduced with distal protection catheters (12,13) (which were not available during the period this study was performed), these devices cannot be applied to distal vein graft lesions; they are unable to prevent embolization into side branches of coronary arteries arising at or between the lesion and device, and their use has not yet been evaluated in the native coronary circulation. Thus, an unequivocal clinical need exists for a device that can safely improve clinical outcomes in high-risk

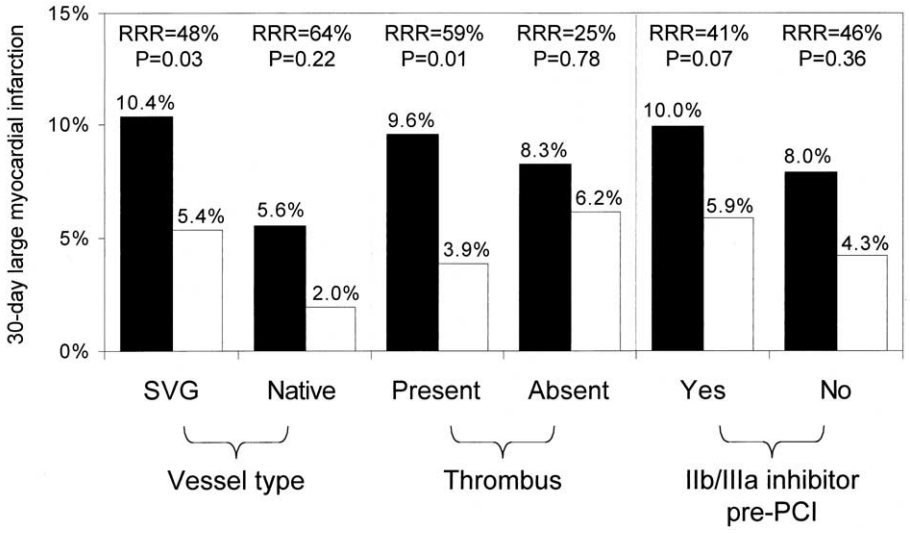

Figure 2. Incidence of large myocardial infarction at 30 days in patients randomized to thrombectomy with the X-SIZER device prior to stenting versus stenting without thrombectomy, stratified by baseline and procedural variables. **Black bars** = control; **open bars** = X-SIZER. Native = native coronary artery; PCI = percutaneous coronary intervention; RRR = relative risk reduction; SVG = saphenous vein graft.

patients with diseased SVGs and native coronary arteries containing thrombus.

The X-SIZER is an intuitive, simple to use, low-cost device that is compatible with standard angioplasty equipment. Previous studies have shown that this device is efficient at removing thrombus and soft or grummous atherosclerotic material, but it has little effect on fibrocalcific tissue (9,10). In the current large, prospective, multicenter, randomized trial, use of the X-SIZER device prior to stent implantation in diseased SVGs and thrombus-containing native coronary arteries was safe, with no procedural increases noted in the rates of dissection, acute closure, or perforation. In addition, several early clinical and angiographic benefits of X-SIZER device use were evident, including a reduction in intra-procedural complications as evidenced by a lesser need for bail-out GP IIb/IIIa inhibitors. No final differences were noted, however, in the rates of no reflow, residual thrombus, distal thromboemboli, or TIMI-3 flow. Moreover, peri-procedural MI occurred in approximately 16% of patients in both groups, similar to the control rates from other comparable studies (12). Enzymatic quantification suggested, however, that the size of MIs occurring after PCI in diseased SVGs and thrombotic native coronary arteries might be reduced with the X-SIZER device. By multivariate analysis, thrombectomy with the X-SIZER device resulted in a 64% relative reduction in the pre-specified 30-day rate of large MI, and a 55% reduction in the composite end point of death or large MI. These findings are consistent with the fact that thrombectomy with the X-SIZER device reduces the extent but not the occurrence of post-PCI myonecrosis.

Unfortunately, despite these early salutary effects, no major clinical benefits of thrombectomy use were evident in this trial at one-year follow-up; rates of death, Q-wave MI, and TVR were similar in patients treated with and without the X-SIZER device. It might have been expected that the prevention of large MIs in these high-risk patients would have been clinically relevant, as earlier studies have demonstrated that it is the development of Q-wave and large subendocardial non–Q-wave infarcts that adversely impact survival after PCI, whereas lesser degrees of myonecrosis have minimal or no impact on late prognosis (14,15). Although one of the largest trials of its kind performed to date, however, the present trial study was underpowered to detect a late mortality difference with X-SIZER device use solely as a function of a reduction in large non–Q-wave MI. Moreover, infarct size, although pre-specified, was a secondary end point of this study. As such, the ability of the X-SIZER device to reduce infarct size and consequently improve late clinical outcomes needs to be demonstrated in additional prospective studies before such an indication can be clinically recommended.

By design, SVG lesions with and without thrombus were enrolled in X-SIZER for Treatment of Thrombus and Atherosclerosis in Coronary Intervention Trial (X-TRACT). Consistent with its mechanism of action (9,10), post-hoc angiographic analysis demonstrated that the X-SIZER device was most effective when the target lesion contained thrombus. Although cineangiography frequently underestimates the prevalence of thrombus in patients with unstable angina (16,17), angiography is relatively specific for the diagnosis of thrombus (18,19), and in this study the morphologic appearance of the lesion provided important direction into identifying patients who might benefit by adjunctive use of a thrombectomy catheter. Moreover, in patients with thrombotic lesions, X-SIZER device use prior to PCI significantly reduced the occurrence of any myonecrosis, and markedly lowered the rates of large MI and death or large MI. Subsequent trials with this device, as well as clinical use, should likely be limited to thrombotic lesions.

Clinical implications and future directions. In contrast to the X-SIZER device in the present study, both balloon occlusion/aspiration and filter-based distal protection devices during SVG intervention reduced the incidence of small as well as large MIs (12,13), and should remain the therapy of choice for eligible SVG lesions. The incidence of MACE at 30 days after SVG PCI in these trials occurred in ~10% of patients. Conversely, 30-day MACE rates after SVG intervention with thrombectomy devices such as the X-SIZER device and the AngioJet system (Possis Medical, Minneapolis, Minnesota) (20) have ranged from 19% to 23%, questioning whether the efficiency of thrombus extraction with the current devices is sufficient to prevent any degree of myonecrosis when a sensitive detector such as CPK-MB $>3 \times$ ULN is utilized. Whether thrombectomy in concert with distal protection devices might further improve outcomes after SVG intervention is of interest, but requires appropriate investigation. Moreover, despite the fact that both the X-SIZER device and AngioJet system clearly extract thrombus (10,20), neither the X-TRACT nor the Vein Graft AngioJet Study-2 (20) trials have proven whether thrombectomy devices reduce MACE in situations where distal protection is impossible (distal SVG lesions) or unproven (thrombotic native coronary arteries). Additional clinical studies are required to demonstrate whether the empirically obvious desire to remove thrombus before PCI improves event-free survival in these settings.

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APPENDIX

For a list of the names of the investigators, research coordinators, and institutions participating in X-TRACT, please see the December 3, 2003, issue of *JACC* at www.cardiosource.com/jacc.html.