Treatment of Saphenous Vein Bypass Grafts With Ultrasound Thrombolysis
A Randomized Study (ATLAS)

Mandeep Singh, MD; Uri Rosenschein, MD; Kalon K.L. Ho, MD; Peter B. Berger, MD; Richard Kuntz, MD; David R. Holmes, Jr, MD

Background—Percutaneous coronary interventions (PCIs) in saphenous vein grafts (SVGs) with thrombus have a high frequency of distal embolization. Acolysis (therapeutic ultrasound) can break up thrombus in vitro in animal models and humans. Whether this is beneficial during percutaneous SVG interventions is unknown.

Methods and Results—We performed a trial of coronary ultrasound thrombolysis in which patients with an acute coronary syndrome undergoing PCI in SVGs were randomly assigned to receive acolysis or abciximab. The primary end point was a successful procedure, defined as final luminal diameter stenosis 30% or less with Thrombolysis In Myocardial Infarction grade 3 flow and freedom from major adverse cardiac events (composite of death, Q-wave, and non-Q-wave myocardial infarction [MI], emergency bypass procedure, disabling stroke, and target lesion revascularization). Of 181 enrolled, 92 received acolysis and 89 abciximab. Angiographic procedural success was achieved in 63% of acolysis patients and 82% of abciximab patients (P=0.008). Incidence of major adverse cardiac events at 30 days was 25% with acolysis and 12% with abciximab (P=0.036), attributable mainly to a greater frequency of non-Q-wave MI with acolysis (19.6% versus 7.9%, P=0.03). The incidence of Q-wave MI was also higher with acolysis (5.4% versus 2.2%, P=nonsignificant). The primary end point was achieved in 53.8% of acolysis patients and 73.1% of abciximab patients (P=0.014).

Conclusions—Use of therapeutic ultrasound in vein graft lesions in patients with acute coronary syndrome had poor angiographic outcome and increased the incidence of acute ischemic complications. (Circulation. 2003;107:2331-2336.)

Key Words: angioplasty • thrombolysis • ultrasonics

Approximately 33% of saphenous vein grafts (SVGs) become occluded by 10 years, and another 33% have significant atherosclerosis.1 Percutaneous coronary interventions (PCIs) in diseased SVGs are associated with frequent procedural complications, including distal embolization. Distal embolization during SVG interventions is associated with a high frequency of major adverse cardiac events, including death and myocardial infarction (MI),2 regardless of whether percutaneous transluminal coronary angioplasty, directional coronary atherectomy, or transluminal extraction atherectomy is used.3,4 The outcome of vein graft interventions when stents are used has improved; however, there are no data suggesting that stents reduce the high frequency of distal embolization in such cases.5,6 Only 2 devices used as adjuncts to balloon angioplasty and stenting in thrombus-containing lesions in the SVG appear promising: rheolytic thrombectomy (with AngioJet, Possis Medical, Inc) and distal protection (with PercuSurge, Medtronic, Inc).7,8 Studies of glycoprotein IIb/IIIa inhibitors during PCI generally have not suggested benefit during vein graft interventions.9–12

There are data to suggest that percutaneous coronary ultrasound thrombolysis (CUT) is beneficial in patients with diseased SVGs. With CUT, the acolysis probe (Angiosonics, Inc) delivers a therapeutic level of ultrasound at the treatment site. This produces a cavitation effect, resulting in a vortex that pulls thrombus toward the catheter tip, where it is lysed or liquefied to subcapillary size. Initial results with this device in patients with acute MI and those undergoing vein graft interventions were promising.13,14 Therefore, we performed this randomized, multicenter trial to test the hypothesis that among patients undergoing a vein graft intervention, pretreatment with acolysis followed by balloon angioplasty or stenting would be associated with an equivalent if not superior outcome to administration of abciximab during balloon angioplasty or stenting.
Patient Selection
This study, ATLAS (Acolysis During Treatment of Lesions Affecting Saphenous Vein Bypass Grafts), was a multicenter, randomized, controlled trial comparing acolysis and abciximab. Patients with prior coronary bypass grafting and de novo lesions in a vein graft who presented with either acute coronary syndrome or angiographic or clinical evidence of thrombus were considered for enrollment. Inclusion criteria were the following: (1) unstable angina, ischemic ST changes on resting electrocardiography, recent MI within 24 hours before intended treatment, or a positive stress test; (2) an SVG with 1 or 2 lesions requiring treatment that had not been treated in the prior 30 days and in which no other intervention was planned in the next 30 days; (3) left ventricular ejection fraction 25% or more; (4) creatine kinase and creatine kinase–MB levels within normal range at the time of the procedure; (5) angiographic evidence of thrombus or, in cases of an occluded graft, clinical symptoms within the past 30 days suggestive of recent clot in the target vessel; and (6) 60% or more stenosis in a graft 2.0 mm or larger in diameter. Exclusion criteria included the following: (1) thrombolysis by the prior 7 days; (2) hypersensitivity to aspirin, heparin, or abciximab; (3) a major gastrointestinal bleed within 6 months, major operation within 6 weeks, or stroke within the prior 2 years; (4) severe uncontrolled hypertension (blood pressure >180/110 mm Hg); (5) planned treatment at more than 2 sites in one graft or planned treatment in more than 1 target vessel; and (6) inability to cross a total occlusion with a guidewire. At each site, the institutional review board approved the protocol.

Randomization
Patients were randomized either to acolysis followed by percutaneous transluminal coronary angioplasty or stent implantation or to abciximab followed by balloon dilation and stent implantation. The coordinating center was the Cardiovascular Data Analysis Center, Boston, Mass. After informed consent was obtained, the randomization center was contacted by telephone for treatment assignment.

Revascularization Procedures
Use of a guide catheter 7F or larger and a 0.014-inch extra support guidewire was recommended. All patients received 325 mg aspirin for at least 1 day before the procedure. In the acolysis group, weight-adjusted heparin was given to maintain activated clotting time longer than 300 seconds. In the abciximab group, the target activated clotting time was 200 to 300 seconds. Ticlopidine (250 mg twice a day) was administered beginning the day before the procedure, or a loading dose of 500 mg was given on the day of the procedure. Other medications were given at the discretion of the operator. For the acolysis group, the acolysis probe was flushed and then advanced to the lesion and positioned at the proximal end of the clot or at the treatment site, the probe was held stationary for the first 60 seconds and then moved back and forth with an amplitude of approximately 3 mm for the remainder of the procedure. Sonication was performed at 60-second intervals up to a maximum of 6 minutes per lesion. Lesions were not crossed mechanically with the probe before reestablishment of flow to minimize the risk of distal embolization. Definitive treatment was completed with standard balloon angioplasty and stenting.

For the abciximab group, abciximab was administered as an intravenous bolus (0.25 mg/kg) followed by an infusion (0.125 \(\mu\)g/kg per minute to a maximum of 10 \(\mu\)g/min) for 12 hours. The bolus was given at least 10 minutes (but not longer than 1 hour) before initial balloon inflation.

Definitions Used
MI was defined on the basis of ischemic electrocardiographic changes and creatine kinase–MB enzyme levels. Distal embolization was defined as angiographic evidence of migration of a filling defect or thrombus distally to occlude the target vessel or one of its branches or a new abrupt cutoff of distal vessels and branches.

End Points
The primary end point was the frequency of successful procedures, defined as a final diameter stenosis of 30% or less by quantitative coronary angiography, achievement of Thrombolysis In Myocardial Infarction (TIMI) 3 flow (by quantitative coronary angiography), and freedom from major adverse cardiac events (MACE) (a composite of cardiac death, Q-wave and non–Q-wave MI, emergency bypass, repeat target lesion revascularization, and disabling stroke) within 30 days of treatment.

Sample Size Estimates and Statistical Considerations
This was an equivalency study; the study planned to enroll 540 patients (270 in each arm), not including the roll-in and training phase at each site. Sample size was based on a primary end point rate of 70% for patients treated with abciximab, as described in this protocol. The null hypothesis was that the primary end point would occur less often with acolysis therapy. The allowable rate difference was 10% with an \(\alpha\) of 0.05 and power of 0.80. The primary end point was analyzed on an intention-to-treat basis. Data are presented as mean±SD for continuous variables and frequencies or percentages for binary variables. Comparisons were performed with \(t\) tests and Fisher exact tests; a 2-sided \(P<0.05\) was required for statistical significance. All analyses were performed with SAS for Windows version 6.12 and 8.0 (SAS Institute).

Termination of the Trial
The trial was stopped prematurely when the Data and Safety Monitoring Committee found a significantly higher incidence of adverse clinical outcomes in the acolysis arm. Although there was a chance of an \(\alpha\) error and it could not be determined whether the worse outcome in the acolysis arm would be maintained, there was no suggestion of benefit from the active arm of the trial, and so it was recommended that the trial be stopped.

Results
Baseline Clinical Characteristics
Enrollment in the study began April 22, 1998, and ended November 2, 2000, by which time 181 patients had been enrolled, 92 to acolysis and 89 to abciximab. Baseline characteristics are shown in Table 1. The 2 groups were well balanced. More than 90% of patients in both groups had an acute coronary syndrome at study entry.

Angiographic Characteristics
The distribution of vein graft locations, location of stenoses, and other lesion characteristics are shown in Table 2.

Procedural and In-Hospital Outcomes
Among the 92 patients in the acolysis group, 87 (95%) received 1 or more stents; in the abciximab group, 80 (90%) of 89 patients received a stent. No patient was treated with AngioJet rheolytic thrombectomy.

Clinical outcomes are shown in Table 3. Both postprocedural diameter stenosis and TIMI flow were evaluable in 80 acolysis patients and 78 abciximab patients. The postprocedural TIMI flow was 0 to 2 in 13 acolysis patients and in 5 abciximab patients, and residual diameter stenosis was greater than 30% in 24 acolysis patients and 12 abciximab patients. Thus, a diameter stenosis of 30% or less and TIMI 3 flow were achieved in 50 (62.5%) acolysis patients and 64 (82.1%) abciximab patients \(P=0.008\). MACE occurred during the first postprocedural day in 22 (23%) of 92 acolysis
TABLE 1. Baseline Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Patient Characteristic</th>
<th>Acolysis (n=92)</th>
<th>Abciximab (n=89)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean± SD</td>
<td>68.9±9.6</td>
<td>68.5±10.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Range</td>
<td>46–88</td>
<td>39–86</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Male, %</td>
<td>90.2</td>
<td>82.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>18.7</td>
<td>13.8</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>32.6</td>
<td>38.2</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>82.6</td>
<td>70.8</td>
<td>0.078</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>74.7</td>
<td>76.1</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>72.7</td>
<td>66.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Stable angina, %</td>
<td>7.7</td>
<td>8.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Worsening exertional angina, %</td>
<td>33.0</td>
<td>33.3</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rest angina, %</td>
<td>46.2</td>
<td>41.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Pain during MI, %</td>
<td>13.2</td>
<td>16.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>CCS III or IV, %</td>
<td>81.5</td>
<td>72.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total occlusion, %</td>
<td>18.5</td>
<td>18.0</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>46.2±12.0</td>
<td>47.4±13.2</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

CCS indicates Canadian Cardiovascular Society angina classification.

The cumulative incidence of MACE at 30 days was 25% in the acolysis group and 12.4% in the abciximab group (P=0.036, Table 3). The difference was mainly driven by higher rates of acute MI in the acolysis group (23.9% versus 10.1%, P=0.017). This increase in MI occurred despite a lower rate of angiographically evident distal embolization in the acolysis group (7.6% versus 11.2%, P=0.45). The rates of other MACE were similar in the 2 groups. The primary end point (postprocedural diameter stenosis ≥30% and TIMI 3 flow by quantitative coronary angiography with freedom from MACE at 30 days) was achieved in 43 (53.8%) acolysis patients and 57 (73.1%) abciximab patients (P=0.014).

Follow-Up
After 360 days of follow-up (Table 5), the cumulative frequency of MACE was 39.1% in the acolysis group and 22.5% in the abciximab group (P=0.017). The significant difference in frequency of MI in the acolysis group persisted throughout the 1-year follow-up.

Subgroup Analysis
In the 33 patients (17 randomized to acolysis and 16 to abciximab) presenting with angiographic total occlusion of the graft, MACE occurred in 23.5% in the acolysis group and 12.5% in the abciximab group (P=0.66, Table 6). The incidences of Q-wave MI (11.8% versus 0%, P=0.48) and non–Q-wave MI (11.8% versus 6.3%, P=0.1) were both higher in the acolysis group. Results at 1 year in this subgroup with total occlusion yielded results similar to the overall results, with MACE occurring more often in the acolysis group than the abciximab group (35.3% versus 12.5%, P=0.22).
Discussion

This randomized trial comparing CUT with abciximab as adjunctive treatments during balloon angioplasty, with or without stent placement, for SVG lesions demonstrated a significant increase in angiographic and clinical adverse events at 30 days with acolysis. An increase in the incidence of non–Q-wave MI, failure to achieve TIMI 3 flow, and final diameter stenosis 30% or less accounted for much of the difference in the 2 groups. This occurred despite a reduction in the frequency of angiographically evident distal embolization in the acolysis group.

Influence of Angiographic Thrombus on Outcome of PCI

The presence of thrombus during PCI is associated with higher rates of in-hospital death and MI, even in the modern era, during both native and SVG interventions.11,15 There are few data on the outcome of PCI in grafts that are occluded or contain thrombus.16,17 Most studies on vein graft interventions have only a minority of patients with angiographic evidence of thrombus.5,10 In studies by Berger et al16 and Kahn et al17 of balloon angioplasty of occluded vein grafts, the angiographic success was low at only 70%, distal embolization occurred in 11%, and event-free survival at 3 years was only 20% to 34%.

In an attempt to improve the outcome of intervention in obstructed vein grafts, many new devices have been studied. Directional coronary atherectomy was associated with higher rates of non–Q-wave MI and distal embolization than balloon angioplasty alone.3 Stents have not been specifically studied in graft lesions with large thrombus burden, although in recent years they have been used with increasing frequency in this setting. In the Vein Graft AngioJet Study (VeGAS) 2 trial, 349 patients with thrombus-containing SVG lesions were randomized to rheolytic thrombectomy with AngioJet versus intragraft administration of urokinase.18 There was no reduction in the cumulative occurrence of the primary end point at 30 days (defined as composite of death, Q-wave MI, emergency bypass procedure, target lesion revascularization, cerebrovascular accident, or stent thrombosis) in patients assigned to AngioJet versus urokinase (29.1% versus 29.2%, respectively, P=not significant). In the Saphenous Vein Graft Angioplasty Free of Emboli Randomized (SAFER) trial, 801 patients with diseased vein grafts were randomized to treatment with (n=406) or without (n=395) a distal embolic protection device (PercuSurge GuardWire Plus temporary occlusion and aspiration system).19 The frequency of death, MI, emergency coronary artery bypass grafting, and target lesion revascularization at 30 days was observed in 9.6% of patients undergoing PCI with PercuSurge and 16.5% undergoing PCI without the distal protection device.

Role of Abciximab in SVG Interventions

Although the results of PCI have improved in non–thrombus-containing lesions with the use of stents and glycoprotein IIb/IIIa inhibitors, patients with angiographic thrombus continue to have a worse outcome, even in the current era.15 Whether abciximab is beneficial during percutaneous transluminal coronary angioplasty in vein graft lesions, particularly in those with angiographic evidence of thrombus, is still uncertain. Retrospective studies and analysis of an angiographic database pooling the results from several studies

### TABLE 4. Delivery Failure and Device Malfunctions in 14 Patients Treated With Acolysis

<table>
<thead>
<tr>
<th>Failure Description</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inability to cross lesion with probe</td>
<td>3</td>
</tr>
<tr>
<td>Inability to cross lesion consistently with probe</td>
<td>1</td>
</tr>
<tr>
<td>Probe stick on guidewire</td>
<td>5</td>
</tr>
<tr>
<td>Fracture of probe</td>
<td>3</td>
</tr>
<tr>
<td>Leaking probe</td>
<td>1</td>
</tr>
<tr>
<td>Other equipment malfunction</td>
<td>3</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Acolysis terminated prematurely</td>
<td>4</td>
</tr>
<tr>
<td>Other acolysis probe used</td>
<td>4</td>
</tr>
<tr>
<td>Acolysis completed with same device</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 5. Cumulative Frequency of Major Adverse Events Through 360 Days

<table>
<thead>
<tr>
<th>Event</th>
<th>Acolysis (n=92)</th>
<th>Abciximab (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>4 (4.3)</td>
<td>2 (2.2)</td>
</tr>
<tr>
<td>MI</td>
<td>25 (27.2)</td>
<td>12 (13.5)</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>5 (5.4)</td>
<td>3 (3.4)</td>
</tr>
<tr>
<td>Non-Q-wave MI</td>
<td>22 (23.9)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>12 (13.0)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>PTCA</td>
<td>9 (9.8)</td>
<td>9 (10.1)</td>
</tr>
<tr>
<td>CABG</td>
<td>4 (4.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>2 (2.2)</td>
<td>2 (2.2)</td>
</tr>
</tbody>
</table>

CABG indicates coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.
failed to demonstrate an advantage of glycoprotein IIb/IIIa receptor inhibitors in native and vein graft interventions with visible thrombus at the time of percutaneous intervention.\textsuperscript{9,11,20}

The Present Study

CUT works on the principle of sonication of thrombus with low-frequency ultrasound that is not detrimental to the arterial wall. The early results of uncontrolled studies of patients undergoing primary PCI for acute MI and those undergoing vein graft interventions were promising.\textsuperscript{13,14} In the present trial, however, patients treated with acolysis had a higher incidence of both Q-wave and non–Q-wave MI, despite having less frequent angiographic evidence of distal embolization. One explanation, and the one we believe most likely, is that fragmenting the thrombus by CUT into smaller particles resulted in occlusion of the microvasculature, increasing the frequency of MI by more than 2-fold. Cavitation of thrombus seems to have reduced particle size, leading to a reduction in occlusion of visible epicardial vessels, and therefore the frequency of angiographic evidence of distal embolization was lower in the acolysis group. Another explanation is that the lesions in diseased vein grafts are a mixture of atheromatous material and thrombus layers. The mechanical introduction of a relatively stiff ultrasound probe (as evidenced by the device failures) can cause substantial embolization of the loose atheromatous material. There are important lessons from this trial. Despite apparently successful sonication of thrombus in degenerated vein grafts, substantial embolization of thrombus and atheromatous debris increased the frequency of procedural acute MI, and both procedural and clinical outcome were harmed.

Limitations

Some limitations of this trial should be kept in mind. The first and perhaps most important limitation is that the numbers of patients treated in the 2 arms are relatively small. However, the Data and Safety Monitoring Committee stopped the trial because of significant evidence of harm, and there was certainly no evidence of clinical benefit with acolysis. Also, the worse outcome associated with acolysis in this trial is possibly an artifact because of a beneficial effect from abciximab in the comparator arm, although we believe this possibility is unlikely on the basis of larger randomized placebo-controlled trials comparing abciximab and placebo. Future trials will need to determine whether and to what extent abciximab improves outcome among patients undergoing PCI in vein grafts.

Conclusions

CUT resulted in a higher incidence of procedural acute MI than abciximab when used as an adjunct to percutaneous transluminal coronary angioplasty and stenting in high-risk thrombus-containing vein grafts. Acolysis should not be used during PCI of thrombus-containing vein grafts.

References


\begin{table}
\centering
\caption{Cumulative Frequency of Major Adverse Events Among Patients With an Initially Occluded Vein Graft From Enrollment Through 30 Days}
\begin{tabular}{lccc}
\hline
Event & Acolysis (n=17) & Abciximab (n=16) & P \\
\hline
Any MACE (death, MI, emergency CABG, TLR, CVA) & 4 & 2 & 0.05 \\
Death & 0 & 0 & \\
Myocardial infarction & 4 & 1 & 0.05 \\
Q-wave MI & 2 & 1 & 0.05 \\
Non–Q-wave MI & 2 & 1 & 0.05 \\
Target lesion revascularization & 1 & 1 & \\
PTCA & 0 & 0 & \\
CABG & 0 & 0 & \\
Emergency CABG & 0 & 0 & \\
Vascular complications & 0 & 0 & \\
Cerebrovascular accident & 0 & 1 & 0.05 \\
Distal embolization & 2 & 1 & 0.05 \\
Vessel perforation & 0 & 0 & \\
\hline
\end{tabular}

CABG indicates coronary artery bypass grafting; CVA, cerebrovascular accident; PTCA, percutaneous transluminal coronary angioplasty; and TLR, target lesion revascularization.
\end{table}
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