Frequency of Early Occlusion and Stenosis in a Left Internal Mammary Artery to Left Anterior Descending Artery Bypass Graft After Surgery Through a Median Sternotomy on Conventional Bypass

Benchmark for Minimally Invasive Direct Coronary Artery Bypass

Peter B. Berger, MD; Edwin L. Alderman, MD; Andrea Nadel, PhD; Hartzell V. Schaff, MD; for the International Multicenter Aprotinin Graft Patency Experience (IMAGE) Investigators

Background—Uncertainty exists regarding the frequency of early occlusion when the left internal mammary artery (LIMA) is anastomosed to the left anterior descending artery (LAD) through a sternotomy with conventional coronary artery bypass grafting (CABG). The issue has gained importance for comparison with less invasive surgical approaches in which operative exposure may be limited and graft anastomosis more difficult.

Methods and Results—Data were analyzed from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial in which 617 patients underwent conventional CABG of the LAD with a LIMA between April 1993 and May 1995. Coronary angiography was performed a mean of 10.8 days postoperatively. Patients were randomized to receive intraoperative aprotinin, an inhibitor of several serine proteinases, or placebo. Because no differences existed in patency rates of LIMA grafts between patients who received aprotinin and placebo, both groups were analyzed collectively. On coronary angiography, the LIMA was widely patent (<50% stenosis) in 561 patients (91%), had ≥50% and <99% stenosis in 48 patients (7.8%), and was occluded in 8 patients (1.3%). Therefore, the LIMA was patent in 609 patients (98.7%).

Conclusions—In the IMAGE trial, the largest and most contemporary early angiographic analysis of CABG available, early patency of the LIMA was >98% when anastomosed to the LAD. These data provide an important benchmark for less invasive surgical approaches in which the LIMA is anastomosed to the LAD. (Circulation. 1999;100:2353-2358.)

Key Words: cardiopulmonary bypass ■ angiography ■ trials ■ coronary disease ■ revascularization

Uncertainty exists regarding the frequency of early occlusion and subtotal stenosis when the left internal mammary artery (LIMA) is anastomosed to the left anterior descending artery (LAD) through a sternotomy with conventional coronary artery bypass grafting (CABG). In prospective angiographic studies, early patency rates of the LIMA have ranged from 95% to 99%, with wide confidence intervals due to the small size of these studies.1–3

The true frequency of early patency after a LIMA is anastomosed to the LAD through a sternotomy with conventional CABG is important for comparison with less invasive surgical approaches, such as minimally invasive direct coronary artery bypass (MIDCAB). With MIDCAB, the operation is performed through a smaller incision than a conventional sternotomy and without cardiopulmonary bypass. Harvest of the LIMA, exposure and stabilization of the LAD, and control of blood flow through the LAD are more difficult, in general, with MIDCAB than with the conventional operation, and these potential problems may increase the risk of early graft occlusion. Few studies of MIDCAB have reported early patency rates, and routine postoperative angiographic follow-up has been obtained in only a minority of cases.4–7

We performed this analysis to determine the frequency of early patency and subtotal stenosis when a LIMA is anastomosed to the LAD through a sternotomy with conventional CABG.

Methods

Patient Population

We analyzed data from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) Trial, a double-blind, placebo-controlled trial in which 870 patients undergoing CABG between April 1993 and May 1995 were randomized to receive aprotinin or placebo.8 Aprotinin is a single-chain polypeptide inhibitor of serine proteases.
proteinases, including plasmin and plasmin and tissue kallikrein, trypsin, and plasmin. Aprotinin reduces postoperative bleeding and the need for red blood cell and platelet transfusions, but whether its antifibrinolytic effect may also increase the frequency of early closure of vein grafts is unknown.13 Accordingly, the IMAGE trial was performed to determine whether the frequency of vein graft closure was greater with aprotinin than placebo. The study was approved by the Institutional Review Board at each participating center.

Patients were eligible if they required elective myocardial revascularization and did not require noncoronary procedures, such as aneurysm resection or valve repair or replacement. The trial had no upper age limit. Exclusion criteria included known or suspected allergy to aprotinin or contrast media, a known bleeding disorder or hematologic abnormality, refusal to use allogenic blood products, predonation of autologous blood, or a preoperative red blood cell mass so low that homologous blood would be required in the prime fluid for cardiopulmonary bypass. Additional exclusion criteria included a previous median sternotomy, diabetes mellitus with a serum creatinine level >1.5 mg/dL, nondiabetics with a serum creatinine level >1.9 mg/dL, inadequate vascular access for postoperative angiography, treatment with an investigational drug within the preceding 30 days, and known or suspected pregnancy.

The IMAGE trial enrolled 870 patients at 10 US sites and 3 additional sites within Israel (2) and Denmark (1). Patients were randomized by clinical center using a computer-generated randomization code (Bayer Corporation): 436 were given aprotinin and 434, placebo. The 10 US sites randomized 471 patients (54%; range, 2 to 95 patients per site), and the 3 sites within Israel and Denmark randomized 126 (14.5%), 168 (19.3%), and 105 (12.1%) patients. In addition, randomization was stratified on the basis of whether or not patients received aspirin within 5 days preoperatively or a nonsteroidal anti-inflammatory drug within 3 serum half-lives preoperatively. The study was approved by the Institutional Review Board at each participating center.

No differences existed in the patency of the LIMA in aprotinin-versus placebo-treated patients. Therefore, both groups were analyzed collectively.

Operative Procedures
Anesthesia, cardiopulmonary bypass, and postoperative intensive care procedures were performed according to standard protocols at each study site. Each center endeavored to adhere to the same procedures and regimens for all patients. The heparin loading dose for cardiopulmonary bypass was ≤350 IU/kg, which included the heparin administered before aortic cannulation and that added to the prime volume of the cardiopulmonary bypass circuit. Additional doses of heparin were given as needed to maintain an activated clotting time above 400 s and to maintain whole-blood heparin levels ≥2.7 U/mL, as determined using a heparin-protamine titration test. Patients in the aprotinin group received a loading dose of 2 000 000 KIU followed by continuous infusion at a rate of 500 000 KIU/h. In addition, aprotinin (2 000 000 KIU) was added to the prime volume of the cardiopulmonary bypass circuit. Postoperatively, all patients received 325 mg of aspirin daily. The first dose was administered via a nasogastric tube 6 hours postoperatively. During the operation, the surgeon assessed the quality of the distal vessel and the diameter of the distal vessel and graft.

Follow-up Angiography
Repeat coronary angiography, which was required by the protocol to be performed within 90 days postoperatively, was performed a mean of 10.8 days postoperatively (median, 7 days). If serum creatinine levels were >1.9 mg/dL within the preceding 2 days, angiography was postponed. Among patients who had postoperative angiography, 85% underwent angiography within 2 weeks. Nonionic contrast was used, and sublingual nitroglycerin (0.6 mg) was given before angiography unless contraindicated.

Angiographic Analysis
Cineangiograms were interpreted both at the Central Radiographic Laboratory at Stanford University and at the clinical sites. The Central Radiographic Laboratory review used the same criteria as the clinical sites, but the review was blinded to clinical site and site interpretations. The Central Radiographic Laboratory and site readings were then compared to identify discrepancies. Discrepancies were referred to an independent reader for adjudication.

Dynamic kinks and anastomotic stenoses were not considered stenoses unless a thrombus obstructing ≥50% of the lumen diameter was clearly evident within the graft at these sites; in these cases, they were considered to be obstructing stenoses. Smooth, tubular stenoses within the graft that narrowed the lumen by ≥50% and that had the appearance of spasm, nonetheless, also were considered to represent obstructing stenoses if they did not resolve when additional nitroglycerin was administered. If thrombus was present within the graft at the site of a stenosis >50%, the graft was considered occluded, even if some antegrade blood flow was present beyond the obstruction.

Detection of Myocardial Infarction
A standard 12-lead ECG was acquired preoperatively and postoperatively on days 3, 5, and 7 or hospital discharge. In patients experiencing a suspected ischemic cardiac event outside the protocol window, the ECG associated with that event was examined. Myocardial infarction was diagnosed on a blinded basis by the Core ECG Laboratory at St Louis University Medical Center. All ECGs were classified according to the Minnesota Code. The diagnosis of definite myocardial infarction was based on the new development of a 2-step worsening Minnesota code Q-wave change, the new development of persistent left bundle branch block patterns, and the presence of acute necrosis at autopsy.

Results
Baseline Clinical Characteristics
Baseline clinical characteristics can be seen in Table 1. The median age of the patients was 62 years. Eighty-seven percent of the patients were male, 62% had New York Heart Association class III or IV angina. 28% had an ejection fraction <50%, and 34% had taken aspirin or a nonsteroidal anti-inflammatory agent within 2 days preoperatively.

Procedural Characteristics
Procedural characteristics are shown in Table 2. Patients received a median of 3.0 graft insertions. The segment of the LAD to which the LIMA was anastomosed was ≤1.5 mm in 43% of cases. In a separate analysis of vessel quality, the segment of LAD to which the LIMA was anastomosed was characterized as being of fair or poor quality in 53% of cases.

Comparison of Patients Who Did and Did Not Undergo Follow-Up Angiography
The primary reason for follow-up angiography not being obtained was patient refusal. However, the baseline clinical
and procedural characteristics of patients who did and did not undergo follow-up angiography of the LIMA were compared to determine if evidence existed that the LIMA patency rate may have been lower in patients who did not undergo follow-up angiography. Patients who did not undergo follow-up angiography were older (64 versus 61 years; \( P = 0.007 \)), received less total protamine (316 versus 338 mg; \( P = 0.021 \)), and had lower preoperative hemoglobin levels (13.7 versus 14.1 g/dL; \( P = 0.006 \)). However, no significant differences existed between the 2 groups in any of the other clinical or procedural characteristics listed in Tables 1 or 2.

**Clinical Outcome**

One death (0.2%) occurred among the 617 patients in the study. Fifteen patients (2.5%) suffered a definite myocardial infarction. Seven deaths occurred within 8 days, and the remainder occurred between 15 and 50 days after surgery. Therefore, the overall mortality among the 733 patients who received a single LIMA graft to the LAD was 1.6%.

Among the 116 patients without follow-up angiography, 111 had an evaluable postoperative ECG, and 9 of these (8%) showed evidence of myocardial infarction.

**Patency Rates**

The LIMA was patent, without \( \geq 50\% \) stenosis anywhere in the graft or distal anastomosis in 561 of 617 patients (91%). In 48 patients (7.8%), the LIMA was patent, but a stenosis \( \geq 50\% \) but \(< 99\% \) was present. The LIMA was occluded (\( \geq 99\% \) stenosis) in 8 patients (1.3%). Therefore, the LIMA was patent in 609 patients (98.7%), although a \( \geq 50\% \) stenosis was present in 7.8% of them. No differences existed in LIMA patency between aprotinin-treated patients (98.2%) and placebo-treated patients (99.0%).

The sites of the \( \geq 50\% \) stenoses included the distal anastomosis, fixed kinks within the graft, and smooth tubular stenoses within the graft that had the appearance of spasm but were refractory to nitroglycerin. In the 48 patients with a patent LIMA with a \( \geq 50\% \) stenosis, the mean stenosis was 60% by quantitative analysis. The severity of stenoses in these 48 patients ranged from 50% in 13 (27%) to 75% in 1 patient.

**Potential Impact of Early Mortality on the Analysis**

Some early deaths before the performance of angiography may have been the result of graft failure, particularly of the LIMA graft. In some patients, death seemed to result from the failure of other organ systems. However, even if all 11 patients who did not undergo follow-up angiography and died had an occluded LIMA, the overall patency rate among the 733 patients with a single LIMA graft to the LAD would still be 97.4%.

**Comparison of Occluded and Nonoccluded LIMAs**

To determine why the LIMA was occluded in some patients and remained patent in others, we compared clinical and procedural characteristics in the patients with occluded and patent grafts (Figure). Although differences in clinical and procedural characteristics were seen, few reached statistical significance due to the small number of patients with an occluded LIMA. Although an ejection fraction \(< 50\% \), a distal vessel \( \leq 1.5 \) mm, and a distal vessel that was qualitatively fair or poor tended to be more frequent in patients whose LIMA was occluded at follow-up angiography, most patients with these characteristics had a patent LIMA on follow-up angiography. There were 158 patients (26%) with

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**TABLE 1. Baseline Clinical Characteristics of the Study Population**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n=617</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>62 (55, 68)</td>
</tr>
<tr>
<td>Male/female, %</td>
<td>87/13</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82 (72, 90)</td>
</tr>
<tr>
<td>Body surface area, m²</td>
<td>2.0 (1.8, 2.1)</td>
</tr>
<tr>
<td>NYHA class III–IV, %</td>
<td>62</td>
</tr>
<tr>
<td>Myocardial infarction within 30 days, %</td>
<td>12</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>26</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;50%, %</td>
<td>28</td>
</tr>
<tr>
<td>Aspirin or NSAID within 2 days, %</td>
<td>34</td>
</tr>
<tr>
<td>Preoperative hemoglobin, g/dL</td>
<td>14.1 (13.2, 15.0)</td>
</tr>
<tr>
<td>Preoperative PTT, s</td>
<td>28 (24, 31)</td>
</tr>
<tr>
<td>Preoperative creatinine, mg/dL</td>
<td>1.1 (1.0, 1.3)</td>
</tr>
</tbody>
</table>

Data for continuous variables are presented as medians, with 25th and 75th percentiles in parentheses.

**TABLE 2. Procedural Characteristics**

<table>
<thead>
<tr>
<th>Procedural Characteristic</th>
<th>n=617</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protamine administered, mg</td>
<td>325 (250, 400)</td>
</tr>
<tr>
<td>Total heparin administered, U</td>
<td>56 500 (48 500, 68 500)</td>
</tr>
<tr>
<td>Graft insertions per patient, total (arterial and venous)</td>
<td>3.0 (3.0, 4.0)</td>
</tr>
<tr>
<td>Y or sequential vein grafts, % of grafts</td>
<td>21.4</td>
</tr>
<tr>
<td>Distal vessel &lt;1.5 mm, % of LIMA grafts</td>
<td>43</td>
</tr>
<tr>
<td>Distal vessel of good quality, % of LIMA grafts</td>
<td>47</td>
</tr>
<tr>
<td>Distal vessel of fair/poor quality, % of LIMA grafts</td>
<td>53</td>
</tr>
<tr>
<td>Large graft size, % of LIMA grafts</td>
<td>9</td>
</tr>
<tr>
<td>Normal/small graft size, % of LIMA grafts</td>
<td>91</td>
</tr>
</tbody>
</table>

Data for continuous variables are presented as medians, with 25th and 75th percentiles in parentheses.
diabetes mellitus. The occlusion rates in nondiabetics (6 of 459, 1.3%) and diabetics (2 of 158, 1.3%) were similar.

Discussion

The most important finding of this study is that in patients in whom a LIMA was anastomosed to the LAD through a sternotomy with conventional CABG, early patency of the LIMA was >98%, although 7.8% of patients had a stenosis ≥50% within the LIMA graft. The LIMA was occluded in only 1.3% of patients.

Comparison With Prior Studies

Several studies showed that patients in whom a LIMA is grafted to the LAD have better survival and freedom from recurrent infarction, severe angina, and repeat revascularization than patients in whom the LAD is bypassed with a vein graft.23–26 The duration of benefit extends for ≥10 years, and the magnitude of benefit increases in the years after surgery.23–26

Many studies evaluating early patency of the LIMA graft have been limited by their retrospective nature, biased selection of patients in whom a LIMA was placed, and incomplete angiographic follow-up. In several prospective studies of CABG, a sternotomy was performed, conventional cardiopulmonary bypass was used, and a high proportion of patients underwent early angiographic follow-up. Goldman et al1 reported the results of 224 patients in whom a LIMA was placed to the LAD; 72% of these patients underwent angiography a mean of 8 days postoperatively. The LIMA was occluded in 3 of 224 patients (1.3%). All of the occlusions were in patients who did not receive preoperative aspirin. The frequency of a significant stenosis without occlusion was not reported. A 96.4% early patency rate was reported for 494 patients in whom an internal mammary artery graft was used.2 Little information was provided about the percentage of patients undergoing follow-up angiography, the timing of angiography, the vessels to which the graft was placed, or the percentage of patients with a significant stenosis without occlusion.

Van der Meer et al3 found that 5.4% of 494 internal mammary artery grafts were occluded at 1 year. In their study, 1.4 distal anastomoses existed per internal mammary artery graft, and the distal anastomosis was to the LAD in only 68% of patients, which limits the comparability of that study with the current study. Other studies in which angiography was performed 1 year after bypass surgery have reported patency rates of 88% to 94% for the LIMA, which are generally higher than the patency rates of vein grafts in the same patients.25,27–31 These studies provide evidence of the advantages of arterial grafting.

Comparison With MIDCAB

A paucity of early patency data exists after less invasive surgical procedures in which the LIMA is anastomosed to the LAD. In the CardioThoracic Systems registry, the qualitative patency rate was 97% among the 219 patients who had MIDCAB.4 However, this represented <15% of the >1400 patients in the registry. Furthermore, a core angiographic laboratory was not used to assess qualitative patency. Many studies have shown that angiographic analyses performed at clinical sites and core laboratories differ substantially, with site analyses invariably more “optimistic” than analyses conducted at core laboratories by investigators who are not involved with the clinical care of the patients undergoing analysis.32,33

The results of the current study provide an important benchmark for assessing the results of minimally invasive approaches to internal mammary graft placement. However, all patients in this study had multivessel disease, in contrast with MIDCAB procedures, which are usually performed in patients with single vessel disease. Indeed, patients with single vessel disease having LIMA grafting would be expected to have similar or even better patency than those in this study. With multivessel disease, some patients will be accepted for surgery who have a poor-quality LAD but other good target vessels. In contrast, all patients with single vessel disease selected for surgery should have an adequate distal LAD for bypass. Clearly, the outcome of patients undergoing LAD bypass with a LIMA using conventional techniques, including cardiopulmonary bypass, is excellent, and MIDCAB techniques should be rigorously evaluated with postoperative angiography to assess the operative results.

Limitations of the Study

Patients who had an acute myocardial infarction or who required emergency CABG surgery were not eligible for the IMAGE trial. The early patency rates observed in this study may not reflect patency rates of the LIMA in patients with these high-risk characteristics.

The patency rate of the LIMA may have been different in the 116 patients (16%) who did not undergo repeat angiography. However, no important differences in clinical or procedural characteristics were identified between patients who did and did not undergo angiography. Although the most common reason that follow-up angiography was not performed was patient refusal, the rate of myocardial infarction was higher in patients who did not undergo the procedure. The possible impact of early deaths on the observed patency rates was discussed.
Conclusions
In the IMAGE trial, the largest and most contemporary early angiographic analysis of CABG available, early patency of the LIMA was >98% when it was anastomosed to the LAD through a sternotomy with conventional bypass; 7.8% of patients had a stenosis of ≥50% but <99% within the LIMA graft. Only 1.3% of LIMAs were occluded. These data provide an important benchmark for the minimally invasive surgical approaches for anastomosis of the LIMA to the LAD.

Appendix
The IMAGE Investigators
Edwin Alderman, MD, Stanford University Medical Center, Stanford, Calif; Jerrold H. Levy, MD, Emory University School of Medicine, Atlanta, Ga; Jeff Rich, MD, Sentara Hospital, Norfolk, Va; Moshe Nili, MD, and Bernardo Vidne, MD, Bellin Memorial Medical Center, Petah-Tivka, Israel; Hartzell Schaff, MD, Mayo Clinic, Rochester, Minn; Gideon Uretzky, MD, Carmel Medical Center, Haifa, Israel; Gosta Pettersson, MD, and Jens J. Thios, MD, University Hospital of Copenhagen, Copenhagen, Denmark; Charles B. Hanterl, MD, University of Texas Health Science Center, San Antonio, Tex; Bernard Chatman, MD, St. Louis University Hospital, St. Louis, Mo; Donald B. Williams, MD, and Howard Wettels, MD, Mt Sinai Medical Center, Miami Beach, Fl; Robert A. Albus, MD, Fairfax Hospital, Annandale, Va; Jeremy R. Morton, MD, Portland, Maine; Gulshan Sethi, MD, Department of Veterans Affairs Medical Center and University of Arizona Health Science Center, Tucson, Ariz; Emery W. Dilling, MD, Cardiovascular and Thoracic Surgeons, Austin, Tex; Mark E. Comunale, MD, Beth Israel Hospital, Boston, Mass.

Acknowledgments
The authors thank the patients who participated in the IMAGE trial and John Ferril, PhD, and Bianca Ruzicka, PhD, for their invaluable editorial contributions. This study includes data from protocol D92–048 sponsored by the Bayer Corporation, Pharmaceutical Affairs Medical Center and University of Arizona Health Science Center, Phoenix, Ariz; Gregory W. Mandula, MD, Mayo Clinic, Rochester, Minn; and the IMAGE Investigators do not own stock or options in Bayer Corporation, but they have received research support from Bayer Corporation. A.N. is an employee of Bayer Corporation.

References


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Circulation. 1999;100:2353-2358
doi: 10.1161/01.CIR.100.23.2353

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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