A Comparison of Internal Mammary Artery and Saphenous Vein Grafts After Coronary Artery Bypass Surgery

No Difference in 1-Year Occlusion Rates and Clinical Outcome

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Background Superior patency rates for internal mammary artery (IMA) grafts compared with vein coronary bypass grafts have been demonstrated by retrospective studies. This difference may have been affected by selection bias of patients and coronary arteries for IMA grafting.

Methods and Results To estimate the difference between IMA and vein grafts, we analyzed graft patency data of 912 patients who entered a randomized clinical trial. In this trial, 494 patients received both IMA and vein grafts (group 1) and 418 only vein grafts (group 2). Occlusion rates of IMA grafts and IMA plus vein grafts in group 1 were compared with those of vein grafts in group 2. Multivariate analysis was used to compare occlusion rates of IMA and vein grafts while other variables related to graft patency were controlled for. In addition, 1-year clinical outcome was assessed by the incidence of myocardial infarction, thrombosis, major bleeding, and death. Occlusion rates of distal anastomoses in group 1 versus group 2 were 5.4% (IMA grafts) versus 12.7% (vein grafts) (P<.0001) and 10.4% (IMA plus vein grafts) versus 12.7% (vein grafts) (P=.14). There was no difference in adjusted risk of occlusion between IMA grafts and vein grafts (P=.089). Type and location of distal anastomosis and lumen diameter of the graft coronary artery were shown to be predictors of occlusion. Clinical events occurred in 17.8% (group 1) and 16.0% (group 2) of patients (P=.53).

Conclusions The observed difference in 1-year occlusion rates between IMA and vein grafts can be explained by a maldistribution of graft characteristics by selection of coronary arteries for IMA grafting rather than being ascribed to graft material. One-year clinical outcome is not improved by IMA grafting. (Circulation. 1994;90:2367-2374.)

Key Words • arteries • veins • bypass • clinical trials

In patients who undergo coronary artery bypass surgery, the internal mammary artery (IMA) is considered to be the bypass conduit of choice. Superior long-term patency rates have been reported for IMA grafts compared with saphenous vein grafts. At the end of the first 10 postoperative years, 69% to 83% of IMA grafts versus 41% to 63% of vein grafts were still patent.1-4 The longevity of IMA grafts has been related to improved survival and a lower incidence of recurrent angina and cardiac events.1,5-7

Several studies comparing long-term patency of IMA grafts and vein grafts consistently showed a benefit for IMA grafts.1,3,6,8-13 However, a number of limitations of these retrospective studies may have biased the observed differences, at least in part. These include (1) a selection of patients for IMA grafting; (2) a selection of patients in whom coronary angiography after surgery was performed; and (3) a comparison of IMA grafts that were placed exclusively or mainly to the left anterior descending coronary artery either versus vein grafts to the remaining coronary arteries in the same group of patients or versus all vein grafts in a control group of patients who had not received IMA grafts. Moreover, previous studies reflect coronary artery bypass surgery over a period of 2 to 13 years starting between 1968 and 1978. As the population of patients who undergo surgery and surgical technique has changed and the clinical course of patients receiving vein grafts has improved over time, it is questionable whether the results of previous studies still represent today's surgery.2,4,14

A more appropriate assessment of graft patency after IMA and vein coronary bypass grafting can be obtained by the following methods, provided that patients are similar with respect to baseline characteristics and revascularization: (1) patients with only IMA grafts are
compared with patients with only vein grafts and (2)
overall patency rates are compared in patients with both
IMA and vein grafts versus those who received only vein
grafts. These methods do not allow risk-adjusted com-
parisons, a limitation that can be overcome by means of
a multivariate statistical analysis. We applied the latter
approach to the data obtained in a randomized clinical
trial, the Prevention of Coronary Artery Bypass Graft
 Occlusion by Aspirin, Dipyridamole, and Aceno-
coumarol/Phenprocoumon Study (CABADAS).15 This
 trial was designed to compare the effects of a low dose
of aspirin, alone or in combination with dipyridamole,
and oral anticoagulants on vein graft occlusion during
the first year after coronary artery bypass surgery. Since
half of the patients studied also received IMA grafts,
this trial allowed a comparison of 1-year patency and
clinical outcome with patients versus those without
IMA grafts.

Methods

Patients

From July 1987 through August 1990, 948 patients who
underwent elective aortocoronary bypass surgery with saphe-
nous vein grafts for disabling angina were entered into the trial
by 10 participating centers. Of these, 494 received IMA grafts
in addition to vein grafts. Exclusion criteria were age >70
years; unstable angina or myocardial infarction < 2 and < 7
days before surgery, respectively; previous or concurrent car-
diac surgery; need for continued antithrombotic drug therapy;
an increased risk of bleeding; impaired renal or hepatic
function; concomitant severe disease; and the inability to
repeat coronary angiography due to allergy to contrast agent.
The prior use of antiplatelet drugs or oral anticoagulants had
to be discontinued at least 14 and 5 days before surgery,
respectively. Informed written consent was obtained. The
protocol was approved by the ethics committee of each par-
ticipating hospital.

Patients were assigned randomly to treatment with either
aspirin, aspirin plus dipyridamole, or oral anticoagulants
(acenocoumarol or phenprocoumon). They were stratified by
center. Treatment was started before (dipyridamole, oral
anticoagulants) or after (aspirin) surgery. Dipyridamole was
administered perioperatively by intravenous infusion (5
mg: kg⁻¹·24 h⁻¹) and continued orally in a slow release form
(200 mg BID). Aspirin was given in a dose of 50 mg/d. The
dose of oral anticoagulants was adjusted to prothrombin
time measurements at a target range of international normalized
ratio between 2.8 and 4.8. Antiplatelet drugs, unless assigned,
were not allowed. Acetaminophen was provided as a substitute
for aspirin as analgesic.

Saphenous vein and IMA grafts were implanted according to
the routine techniques of each participating hospital. The
decision to use IMA grafts was made by the surgeon. The
lumen of the donor coronary artery was measured by cali-
bred probes at the arteriotomy site and as distally as
possible. Coronary endarterectomy was performed in diffusely
diseased native arteries at the discretion of the surgeon.
Heparin, administered during operation, was antagonized by
protamine sulfate at the end of the procedure unless it was
continued because of the introduction of an intra-aortic bal-
loon pump. Total postoperative blood loss through chest tubes
and required blood transfusions were recorded.

After discharge from the hospital, follow-up visits were
scheduled at 3-month intervals, and coronary angiography was
performed 1 year after surgery. At follow-up visits, clinical and
laboratory data were collected and an ECG was recorded. A
questionnaire was addressed to the cardiologist 1 year after
surgery to complete clinical data if a patient had been with-
drawn from the trial. Coronary angiography was not repeated
if it had been obtained for medical reasons >9 months after
surgery or if an earlier angiogram already showed vein graft
occlusion according to the protocol of the original vein graft
patency study.

Angiographic End Points

Grafts were visualized by selective injection. If the origin of
a vein graft could not be visualized selectively, aorto root
angiography was performed. A vein graft was defined as
occluded (1) if the occluded origin was visualized selectively,
(2) if the origin could not be visualized selectively and the
contrast agent failed to flow through the graft into the(
grafted artery on aort root angiography, or (3) if one or more
distal anastomoses appeared to be occluded. An arterial graft
was defined as occluded if occlusion was visualized at selective
injection. A distal anastomosis was defined as occluded if
contrast agent failed to flow from the graft into the
mechanical artery. If the graft was occluded at its origin, all
associated distal anastomoses were considered occluded unless
a retrograde flow of contrast agent from the graft was
3 demonstrated. An arterial graft was classified as
unoccluded if selective injection failed for technical reasons and
no retrograde filling of the graft with contrast agent
at coronary angiography was demonstrated.

Angiograms were reviewed by independent experienced
cardiologists, members of the Angiography Classification
Committee, and a consensus was reached.

Clinical End Points

Primary clinical end points were myocardial infarction,
thromboembolism, major bleeding, and death. Myocardial
infarction was diagnosed according to ECG criteria. Throm-
boembolic events included ischemic stroke, transient ischemic
attacks, deep vein thrombosis, and pulmonary embolism.
Bleeding was defined as major if life-threatening or fatal and
if blood transfusion or (re) surgery was necessary. Secondary
clinical end points were residual or recurrent angina, heart
failure, and symptomatic arrhythmias. Criteria for clinical end
points and review procedures have been described more
extensively previously.15

Statistics

The primary aim of statistical analysis was a proper com-
parison of IMA grafts versus vein grafts with respect to the
incidence of graft occlusion. In addition, clinical outcome
was compared in patients with both IMA and vein grafts versus
patients with only vein grafts.

Graft occlusion rates were analyzed in several different
ways, all of which take into account that grafts (distal anasto-
moses) within the same patient act in a dependent way with
respect to the occurrence of occlusion.16 We used the cluster
sampling approach for estimation of occlusion rates by distal
anastomosis16 and also compared the proportions of patients
with at least one occluded graft. With both these approaches,
we made two comparisons in patients with both IMA and vein
grafts: (group 1) and patients who had received only vein grafts
(group 2): (1) a comparison of IMA grafts in group 1 versus
vein grafts in group 2 in conformity with previous studies and
(2) a comparison of both IMA and vein grafts (group 1) versus
vein grafts (group 2) representing the overall results of these
bypass grafting procedures. With these two approaches, it
is not possible to take into account graft-specific information. To
do this, we used the random-effects logistic regression analysis
(Mauritsen RH, Logistic Regression With Random Effects,
PhD thesis, University of Washington, 1984). This method
takes into account that occlusion or patency of grafts within
the same patient are dependent events (see Appendix). Oc-
clusion of a distal anastomosis was considered the binary
dependent variable. Patient- and graft-specific characteristics
were the independent variables. We used the Epidemiologic
Graphics, Estimation, and Testing (EGERET) package (Statistics
and Epidemiology Research Corp) for computations. The risk of graft occlusion is described by the odds ratio and its 95% confidence interval.

Clinical outcome was analyzed by comparison of (1) the incidence of individual clinical end points, (2) the proportion of patients who experienced at least one primary clinical end point, and (3) the proportion of patients with any primary or secondary clinical end point.

The groups were compared by the \( \chi^2 \) test or the Fisher's exact test for qualitative variables. Student's \( t \) test or the Mann-Whitney \( U \) test were used for quantitative variables. Continuous variables, unless indicated otherwise, are expressed as mean±SD. A two-tailed value of \( P<.05 \) was considered to indicate statistical significance.

Analysis included all patients conforming to the protocol of the original vein graft patency study. Patients who withdrew their consent before the start of trial medication or in whom the surgeon decided during operation to use only arterial grafts were excluded accordingly.

### Results

#### Patients

Of 948 patients who entered into the trial, 912 were eligible for analysis. Exclusion was due to withdrawal of consent before the start of assigned drug therapy in 7 and to only arterial grafting in 29 patients. Both IMA and vein grafts were applied in 494 patients (group 1); the remaining 418 patients received vein grafts only (group 2). Clinical baseline characteristics were equally distributed among the two groups (Table 1). Graft characteristics are summarized in Table 2. Distal anastomoses averaged 3.9 per patient in group 1 (IMA, 1.4 and vein, 2.5) and 3.6 per patient in group 2. Single grafts represented 57% and 36% of arterial and all distal anastomoses, respectively, in group 1 and 39% of distal anastomoses in group 2. Of IMA grafts, 68% were placed to the left anterior descending coronary artery versus 22% of vein grafts in group 2 (\( P<.001 \)). The lumen diameter of the recipient coronary artery was >1.5 mm in 56% of IMA grafts compared with 31% of vein grafts in group 2 (\( P<.001 \)). If all grafts in group 1 were considered, 26% were placed to the left anterior descending coronary artery (\( P=.026 \), versus group 2) and 45% to large vessels (\( P<.001 \), versus group 2). Clinical and angiographic baseline characteristics showed no differences for subgroups defined by assigned drug therapy (data not mentioned).

Repeat angiography was performed in 786 patients (86%), equally distributed among groups 1 and 2, after a median time from surgery of 372 and 370 days, respectively. Grafts were classified to be undefined in 8.9% of IMA grafts and 0.9% of vein grafts. This difference was due to a larger number of technical failures in visualizing IMA grafts by selective injection of contrast agent.

### Graft Patency

Occlusion rates by distal anastomosis and the proportion of patients with one or more occluded grafts are summarized in Table 3. These data represent the results obtained from 741 single (395 IMA) and 494 sequential (148 IMA) grafts in group 1 (in total, 1927 distal anastomoses, of which 692 were arterial) and 585 single and 334 sequential grafts in group 2 (in total, 1505 distal anastomoses). Table 4 shows the occlusion rates for subgroups defined by type of graft, type of distal anastomosis, location of distal anastomosis, and lumen diameter of the recipient coronary artery. Endarterectomy was performed in 76 vessels, representing 1.2% of both IMA and vein distal sites in group 1 and 3.6% of distal sites in group 2. The results were not affected.

#### Comparison of IMA Grafts (Group 1) and Vein Grafts (Group 2)

Occlusion rates per distal anastomosis were 5.4% for IMA grafts and 12.7% for vein grafts (\( P<.0001 \)). If patients were considered, 5.9% of the patients had at least one occluded IMA graft versus 30.7% of the patients in whom one or more vein grafts were occluded (\( P<.00001 \)). Subgroups showed consistently lower occlusion rates of IMA grafts, but differences were not significant for grafts to the left anterior descending coronary artery (\( P=.31 \)) and for grafts to arteries with a lumen diameter of >1.5 mm (\( P=.10 \)).

#### Comparison of IMA Plus Vein Grafts (Group 1) and Vein Grafts (Group 2)

Overall occlusion rates in group 1 and group 2 were 10.4% versus 12.7% (distal anastomoses) and 26.7%...
Multivariate analysis selected type of distal anastomosis (end-to-side or side-to-side), location of distal anastomosis, and lumen diameter of the recipient coronary artery as graft characteristics that were independent predictors of graft occlusion (Table 5). The adjusted risk of graft occlusion showed no difference between IMA and vein grafts. Diabetes mellitus and baseline serum HDL cholesterol level were other predictors of graft occlusion, as were cardiopulmonary bypass time, administration of protamine sulfate at the end of surgery, and postoperative values of hematocrit and number of platelets. A center-related effect and a significant within-patient dependence were also demonstrated (not shown in Table 5).

### Table 2. Baseline Graft Characteristics of 912 Patients

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2 (Vein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>494</td>
<td>418</td>
</tr>
<tr>
<td>Single grafts per patient, n</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Sequential grafts per patient, n</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>Distal anastomoses per patient, n</td>
<td>1.4</td>
<td>3.6</td>
</tr>
<tr>
<td>Location of distal anastomosis, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>68</td>
<td>22</td>
</tr>
<tr>
<td>D</td>
<td>24</td>
<td>18</td>
</tr>
<tr>
<td>Cx</td>
<td>7</td>
<td>35</td>
</tr>
<tr>
<td>RCA</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>Diameter of recipient artery, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤ 1.0 mm</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>1.1-1.5 mm</td>
<td>39</td>
<td>56</td>
</tr>
<tr>
<td>1.6-2.0 mm</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td>&gt; 2.0 mm</td>
<td>14</td>
<td>10</td>
</tr>
</tbody>
</table>

IMA indicates internal mammary artery; LAD, left anterior descending coronary artery; D, diagonal coronary artery; Cx, circumflex coronary artery; and RCA, right coronary artery. Group 1 received IMA plus vein grafts, group 2 only vein grafts. IMA grafts (group 1) were compared with vein grafts (group 2) and IMA plus vein grafts (group 1) with vein grafts (group 2).

versus 30.7% (patients). These differences were not significant. A similar trend to improved patency in patients with IMA grafts was observed for subgroups. A significant difference was demonstrated only for end-to-side distal anastomoses (P = .031).

### Multivariate Logistic Regression Analysis

Univariate analysis of 72 baseline, surgical, and graft-specific characteristics and assigned antithrombotic drug therapy showed that the risk of graft occlusion was related to graft material (IMA or vein), number of distal anastomoses per graft, type of distal anastomosis (end-to-side or side-to-side), location of distal anastomosis, and lumen diameter of the recipient coronary artery. An association was also demonstrated for a number of baseline characteristics (diabetes mellitus, blood pressure, and HDL cholesterol) and surgical characteristics (cardiopulmonary bypass time, administration of protamine sulfate, transfusion requirement, postoperative hematocrit, and postoperative number of platelets). Finally, occlusion rates showed differences between the participating centers.

### Table 3. Frequency of Graft Occlusion

<table>
<thead>
<tr>
<th>Unit of Analysis</th>
<th>Group 1</th>
<th>Group 2 (Vein)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal anastomoses</td>
<td>5.4 (551)</td>
<td>10.4 (1516)</td>
<td>12.7 (1251)</td>
</tr>
<tr>
<td>Patients</td>
<td>5.9 (389)</td>
<td>26.7 (389)</td>
<td>30.7 (348)</td>
</tr>
</tbody>
</table>

IMA indicates internal mammary artery. Group 1 received IMA plus vein grafts; group 2, only vein grafts. Values represent percentage occluded and, in parentheses, total number.

*IMA grafts (group 1) vs vein grafts (group 2).

†IMA plus vein grafts (group 1) vs vein grafts (group 2) for distal anastomoses, comparison by ratio estimate analysis.

### Blood Loss, Transfusion Requirement, and Reoperation

Blood loss by chest tubes was 1184±692 mL in group 1 and 809±560 mL in group 2 (P < .001). Median transfusion requirement for red blood cells was 1.0 (donor) unit (range, 0 to 20) and 2.0 units (range, 0 to 13), respectively (P = .11).

Cardiopulmonary bypass times were 99±32 minutes and 94±32 minutes, respectively (P = .012). The early reoperation rates (within 24 hours) were equal (4.3%). Operative mortality (within 30 days) was 0.4% in group 1 and 1.0% in group 2.

### Clinical End Points

A majority (73%) of 178 primary clinical end points occurred in the perioperative period (within 30 days after surgery). These were equally distributed among group 1 and group 2, as were the individual end points (Table 6). Mortality rate was slightly lower in group 1. Of 16 patients who died, a cardiac cause was found in 10 patients (4 in group 1 versus 6 in group 2), and death was related to bleeding in 4 patients (1 versus 3) and due to thrombosis in 2 patients (1 versus 1). The overall risk of any primary clinical end point was similar in both groups: 17.8% and 16.0%, respectively.

Angina at any time during the follow-up period was reported as 15.0% (group 1) and 19.4% (group 2). At the end of the first year, angina was found in 8.7% and 10.5% of the patients in group 1 and 2, respectively. The remaining secondary clinical outcome events revealed no differences in incidence between both groups. The overall event rate, including patients with one or more primary or secondary clinical end points, was 33.0% for group 1 and 34.9% for group 2.

### Discussion

From the results of this study, it appears likely that 1-year graft patency and clinical outcome are similar in
patients who receive both IMA grafts and vein grafts compared with patients in whom only vein grafts are applied. Moreover, IMA grafts and vein grafts with the same characteristics showed no differences in 1-year patency rates.

Occlusion rates of IMA grafts (5.4%) and vein grafts (12.7%) suggested a benefit for IMA grafts (risk reduction, 57%; 95% confidence interval, 38% to 71%; P < .0001) comparing patients with both IMA and vein grafts versus patients with only vein grafts. This finding is in agreement with the results of previous studies that revealed 1-year occlusion rates ranging from 4% to 12% and from 7% to 24%, respectively (risk reduction ranging from 35% to 51%).

We found a similar difference for subgroups defined by various graft characteristics, although it was not significant for grafts to the left anterior descending coronary artery and for grafts to large vessels (lumen diameter, > 1.5 mm). However, this estimate of the difference between IMA and vein grafts, applied in most previous studies, is biased and will result in predictable lower occlusion rates for IMA grafts. In this and previous studies, IMA grafts were used preferentially as a single graft to the left anterior descending coronary artery that commonly had a lumen diameter of > 1.5 mm. Loop et al.7 even excluded IMA grafts to other coronary arteries, as well as bilateral and sequential IMA grafts, from their analysis. In this way, graft characteristics that have been demonstrated to have lower occlusion rates for both IMA and vein grafts.1,9-12 Similarly, a difference in occlusion rates favoring IMA grafts due to an imbalance of graft characteristics may be expected if IMA grafts are compared with the remaining vein grafts in the same patients3,8-13,17 or if IMA grafts are compared with all vein grafts in separate or combined groups of patients.10,13 Furthermore, the results of previous studies have been affected by a selection bias of patients for IMA grafting and for repeat coronary angiography after surgery, in part because these studies were conducted retrospectively. Patients who received IMA grafts had a priori an improved prognosis, as suggested by a substantial mal-distribution of prognostically important variables such as age, left ventricular function, and degree of revascularization.6 In addition, coronary angiography to assess graft patency was performed mainly in patients with recurrent angina or myocardial infarction, which are related to graft occlusion.1,6,8,10,11,13 In view of the fact that grafts to the left anterior descending coronary artery and to large vessels are less prone to occlusion, it is likely that occlusion of vein grafts had to be found more frequently in these studies. Finally, these long-term follow-up studies contained patients who underwent coronary artery bypass surgery over a long period that started about 20 years ago. During this time, the results of vein coronary artery bypass surgery have been improved by changes in surgical techniques and in preservation of vein graftsand by antiplatelet drug therapy.18,19 On the other hand, the IMA grafting procedure has also changed: bilateral, sequential, and free IMA grafts are used more widely today. The effects of these modifications are probably not expressed by the results of the aforementioned studies. Thus, it is questionable whether the results of these studies represent today’s coronary bypass surgery.

To assess a benefit of IMA grafting, we compared overall occlusion rates in patients in whom vein grafts

<table>
<thead>
<tr>
<th>Table 4. Frequency of Graft Occlusion According to Type of Graft and Distal Anastomosis, Location of Distal Anastomosis, and Coronary Artery Lumen Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1</strong></td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Single grafts</td>
</tr>
<tr>
<td>Sequential grafts</td>
</tr>
<tr>
<td>Distal anastomoses</td>
</tr>
<tr>
<td>End to side</td>
</tr>
<tr>
<td>Side to side</td>
</tr>
<tr>
<td>Location of distal anastomosis</td>
</tr>
<tr>
<td>LAD</td>
</tr>
<tr>
<td>D</td>
</tr>
<tr>
<td>Cx</td>
</tr>
<tr>
<td>RCA</td>
</tr>
<tr>
<td>Lumen diameter, mm</td>
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<tr>
<td>≤ 1.0</td>
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<tr>
<td>1.1-1.5</td>
</tr>
<tr>
<td>1.6-2.0</td>
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<tr>
<td>&gt; 2.0</td>
</tr>
</tbody>
</table>

IMA indicates internal mammary artery; LAD, left anterior descending coronary artery; D, diagonal coronary artery; Cx, circumflex coronary artery; and RCA, right coronary artery. Group 1 received IMA plus vein grafts; group 2, only vein grafts. Values represent percentage occluded and, in parentheses, total number.

*IMA grafts (group 1) vs vein grafts (group 2).
†IMA plus vein grafts (group 1) vs vein grafts (group 2).
were required in addition to IMA grafts versus patients who received only vein grafts. Overall occlusion rates were 10.4% and 12.7%, respectively. Single grafts and the related end-to-side distal anastomoses showed a more pronounced difference. Although the observed trend to improved graft patency might suggest a potential benefit of IMA grafting, it seems more likely that this was due to significant differences in extension of revascularization and distribution of graft characteristics between the two groups of patients. This explanation is supported by the results of multivariate analyses, which revealed no significant differences in risk of occlusion between IMA and vein grafts. Our findings are in agreement with the results of another study that showed no difference in 1-year patency of IMA and vein grafts to the left anterior descending coronary artery. In our study, 32% of IMA grafts were placed to other coronary arteries, mainly a diagonal coronary artery. These also showed no differences in occlusion rates compared with vein grafts.

The observed equivalence in patency of IMA grafts and vein grafts might be attributed to the antithrombotic drug therapy used. Early vein graft occlusion is mainly due to thrombosis. It has been demonstrated that antiplatelet drugs reduce 1-year occlusion rates of vein grafts, in contrast to IMA grafts. Oral anticoagulants have been found to be as effective as antiplatelet drugs with respect to the prevention of graft occlusion. Therefore, the intrinsic benefit of IMA grafts may have been nullified by an improved patency of vein grafts due to antithrombotic drugs. However, there is no evidence that these drugs reduce the incidence of long-term graft occlusion. Late graft occlusion results mainly from progressive atherosclerosis, which seems to affect vein grafts more than arterial conduits and be-

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<table>
<thead>
<tr>
<th>Variable</th>
<th>$\beta$</th>
<th>SEM</th>
<th>$P$</th>
<th>Odds Ratio (95% Confidence Interval)</th>
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</thead>
<tbody>
<tr>
<td>Graft characteristics</td>
<td></td>
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<tr>
<td>IMA graft*</td>
<td>-0.490</td>
<td>0.288</td>
<td>.089</td>
<td>0.61 (0.35-1.08)</td>
</tr>
<tr>
<td>Side-to-side distal anastomosis†</td>
<td>-0.769</td>
<td>0.184</td>
<td>&lt;.001</td>
<td>0.46 (0.32-0.67)</td>
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<tr>
<td>Location of distal anastomosis‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.823</td>
<td>0.291</td>
<td>&lt;.005</td>
<td>2.28 (1.29-4.03)</td>
</tr>
<tr>
<td>Cx or RCA</td>
<td>0.906</td>
<td>0.245</td>
<td>&lt;.001</td>
<td>2.47 (1.53-4.00)</td>
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<tr>
<td>Lumen diameter, mm§</td>
<td></td>
<td></td>
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<tr>
<td>1.1-1.5</td>
<td>-0.725</td>
<td>0.240</td>
<td>.003</td>
<td>0.49 (0.30-0.78)</td>
</tr>
<tr>
<td>&gt;1.5 dial</td>
<td>-1.035</td>
<td>0.272</td>
<td>&lt;.001</td>
<td>0.36 (0.21-0.61)</td>
</tr>
<tr>
<td>Baseline characteristics</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td>0.728</td>
<td>0.309</td>
<td>.019</td>
<td>2.07 (1.13-3.80)</td>
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<tr>
<td>HDL cholesterol</td>
<td>0.958</td>
<td>0.318</td>
<td>.003</td>
<td>2.61 (1.40-4.86)</td>
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<td>Surgical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary bypass time &gt;90 min</td>
<td>0.662</td>
<td>0.207</td>
<td>.001</td>
<td>1.94 (1.29-2.91)</td>
</tr>
<tr>
<td>Protamine sulfate administration</td>
<td>-1.526</td>
<td>0.573</td>
<td>.008</td>
<td>0.22 (0.07-0.67)</td>
</tr>
<tr>
<td>Postoperative hematocrit &gt;35%</td>
<td>0.912</td>
<td>0.253</td>
<td>&lt;.001</td>
<td>2.49 (1.51-4.09)</td>
</tr>
<tr>
<td>Postoperative platelets number</td>
<td>-0.0052</td>
<td>0.0021</td>
<td>.014</td>
<td>0.99 (0.99-1.00)</td>
</tr>
</tbody>
</table>

IMA indicates internal mammary artery; D, diagonal coronary artery; Cx, circumflex coronary artery; RCA, right coronary artery; HDL, high-density lipoprotein.

*Reference, vein graft.
†Reference, end-to-side distal anastomosis.
‡Reference, distal anastomosis on left anterior descending coronary artery.
§Reference, lumen diameter ≤1.0 mm.

---

**TABLE 6. Occurrence of Primary and Secondary Clinical End Points**

<table>
<thead>
<tr>
<th>Group 1 (N=494)</th>
<th>Group 2 (N=418)</th>
<th>$P*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>8.5 (6.7)</td>
<td>8.6 (7.9)</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>2.2 (0.8)</td>
<td>2.9 (0.7)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>7.3 (5.9)</td>
<td>6.0 (5.3)</td>
</tr>
<tr>
<td>Death</td>
<td>1.2 (0.4)</td>
<td>2.4 (1.0)</td>
</tr>
<tr>
<td>Angina</td>
<td>15.0</td>
<td>19.4</td>
</tr>
<tr>
<td>Heart failure</td>
<td>2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>3.2</td>
<td>3.6</td>
</tr>
<tr>
<td>Any clinical end points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>17.8</td>
<td>16.0</td>
</tr>
<tr>
<td>Primary or secondary</td>
<td>33.0</td>
<td>34.9</td>
</tr>
</tbody>
</table>

Values represent percentage of events and, in parentheses, percentage of perioperative events. Group 1 received internal mammary artery plus vein grafts; group 2, only vein grafts.

*Comparing group 1 vs group 2.
comes relevant >5 years after surgery.\textsuperscript{2,4} Thus, it may be expected that differences in graft patency will become apparent only after the fifth postoperative year.

Clinical outcome was equal in both groups. The incidence of myocardial infarction, which occurred mostly in the perioperative period, was not different between the groups. Residual or recurrent angina tended to be more common in patients with only vein grafts. In contrast to these findings, previous studies suggested that IMA grafting improves survival and decreases the incidence of recurrent angina and cardiac events compared with vein grafting.\textsuperscript{6,7} The results of these studies may have been biased by a substantial maldistribution of variables that are associated with decreased survival.\textsuperscript{6} Nevertheless, IMA grafting remained associated with an improved survival if biased subgroups were excluded from analysis,\textsuperscript{14} and it was selected as predictor of survival by multivariate analysis.\textsuperscript{6,7} Since most studies contained coronary artery bypass procedures over a period of up to 16 years, the results might have been influenced by changes in surgical techniques and in the population of patients undergoing coronary artery bypass surgery.\textsuperscript{2,4} Comparing more recent coronary artery bypass procedures with those performed in the foregoing period, Jones et al\textsuperscript{14} found no differences in survival at a follow-up of 3 years. Sergeant et al\textsuperscript{7} identified the time period of surgery as an incremental risk factor for death, but subgroups defined by time period showed no differences in survival at a follow-up of up to 15 years.

Limitations

The present study also includes some limitations. First, this was not a study in which patients were randomized to IMA versus vein grafts; rather, this decision was left to the discretion of the surgeon. However, it is a large study reflecting current surgical techniques regarding IMA and vein graft surgery, with more than 400 patients receiving IMA plus vein grafts and a similar number of patients receiving only vein grafts. In addition, all of these patients were scheduled prospectively for control angiography after 1 year, and most of them received it. Thus, this data set allowed a detailed comparison of variables that might influence outcome of IMA and vein grafts, respectively. Second, the follow-up of this study was limited to 1-year angiographic and clinical events. Improved survival by IMA grafting has been demonstrated only after the fifth postoperative year.\textsuperscript{7} However, the previously suggested early superiority of IMA grafts is not supported by the present report. A prolonged follow-up will be required to confirm the claim of a long-term advantage of IMA grafting over vein graft surgery with current techniques and antplatelet therapy.

Conclusions

The observed difference in 1-year occlusion rates comparing IMA and vein grafts can be explained by an uneven distribution of graft characteristics, such as type of graft, location of distal anastomosis, and lumen diameter of the recipient coronary artery. There was no difference in adjusted risk of occlusion between IMA and vein grafts. Clinical outcome after 1 year was similar in patients with both IMA and vein grafts compared with patients who received only vein grafts.

Appendix A

Estimate of Risk of Graft Occlusion Adjusted for Independent Distal Anastomosis-Specific Effects by the Random-Effects Logistic Regression Model

It has been demonstrated that occlusion or patency of distal anastomoses in the same patient is a dependent event. For this reason, the ratio estimate as applied to a cluster sampling approach is used to analyze graft patency data.\textsuperscript{16} Patients are considered to represent clusters of distal anastomoses. These clusters can contain from one distal anastomosis, in the case of a single graft, to multiple distal anastomoses, in the case of several single grafts, sequential grafts, or a combination of these different type of grafts within the same patient.

Logistic regression, as an alternative statistical approach, allows adjustment of possible imbalances of patient groups and testing of whether a particular variable contributes toward predicting graft occlusion, while also adjusting for the effects of other variables in the model. However, it assumes independence of grafts within the same patient. The percentage of distal anastomoses that becomes occluded (P) is

$$P(x_1, \ldots, x_p) = \frac{\exp(\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p)}{1 + \exp(\beta_0 + \beta_1 x_1 + \ldots + \beta_p x_p)}$$

where $\beta$ denotes model parameters and $x$, explanatory variables.

By contrast, the random-effects logistic regression model assumes that graft occlusion also depends on distal anastomosis-specific random effects. The probability of occlusion for the jth anastomosis (P) in one patient is expressed by

$$P(x_{ij}, \ldots, x_{pj}, z_{ij}, \ldots, z_{qij}) = \frac{\exp(\beta_0 + \beta_1 x_{1j} + \ldots + \beta_p x_{pj} + U_{ij} + \tau_{ij} + \ldots + \tau_{qij})}{1 + \exp(\beta_0 + \beta_1 x_{1j} + \ldots + \beta_p x_{pj} + U_{ij} + \tau_{ij} + \ldots + \tau_{qij})}$$

where U denotes a subject-specific random effect, and $x$ and $z$ are explanatory variables, and $\beta$ and $\tau$ are model parameters. As indicated by the subscript j, the covariates may be different for each distal anastomosis. The random variable U takes the same value for all distal anastomoses within one patient. EGRET assumes that U is binomially distributed with $p=\frac{1}{2}$ and n free to choose; we used n=6.

Appendix B

Committees and Centers of The CABADAS Research Group


Event and ECG Classification Committee: F.W.H.M. Bär (chairman), R.N.W. Hauer, J.W. Viersma.


Participating centers (principal investigators): Ignatius Hospital/Medical Center De Klokkenberg, Breda (M. Vuijk, P.H.J.M. Dunselman, G.J. Kostegra); University Hospital Groningen (M.J.I. de Jongste, K.I. Lie, A. Eijgelaar); Academic Medical Center, Amsterdam (R. van der Doef, B.J.M. Mulder, J. Piek, A.J. Dunning, N.G. Meyne); St Antonius Hospital, Nieuwegein (R.M. Tjon Yoe Gin, C.A.P.L. Ascoop, F.E. Vermeulen); University Hospital Basel (P. Buser, M.
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