Bilateral Versus Unilateral Internal Mammary Revascularization in Patients With Diabetes

Masahiro Endo, MD; Yasuko Tomizawa, MD; Hiroshi Nishida, MD

Background—This historical cohort study evaluated the benefit of bilateral internal mammary artery (BIMA) grafts in coronary bypass grafting (CABG) for patients with diabetes.

Methods and Results—We performed elective, isolated, primary, multiple CABG using skeletonized internal mammary artery (IMA) grafts for multivessel disease in 1131 patients, 467 (41.3%) of whom had type 2 diabetes mellitus. The early and long-term results were compared between 277 patients with diabetes using single IMA (SIMA) grafts and 190 using BIMA grafts (median follow-up, 8.1 years). Hospital mortality was similar in both groups. Early patency rate of all grafts was significantly higher using BIMA than using SIMA (97.7% versus 93.8%, P=0.0012). Survival rates were not significantly different between SIMA and BIMA groups. Late cardiac mortality was significantly higher in patients with low ejection fraction (0.4 or lower) compared with preserved ejection fraction (higher than 0.4) (P=0.0001). In patients with preserved ejection fraction, 10-year survival rate was significantly higher using BIMA than using SIMA (87.8±3.5% versus 75.2±3.4%, P=0.04), and 10-year all death–free or repeat CABG or recurrent myocardial infarction–free rate was significantly higher using BIMA than using SIMA (86.6±3.6% versus 69.0±3.7%, P=0.0086).

Conclusions—Skeletonized BIMA grafts are beneficial in coronary revascularization for diabetic patients with preserved ejection fraction but have limited survival benefit for those with reduced ejection fraction attributable to high cardiac mortality. (Circulation. 2003;108:1343-1349.)

Key Words: follow-up studies ■ revascularization ■ surgery ■ coronary disease

Diabetes,1–4 older age,2,3,5 reduced ejection fraction (EF),2,3,5 and chronic hemodialysis6 are significant independent predictors of poor outcome in long-term survival after elective coronary artery bypass grafting (CABG). Diabetes mellitus is an established risk factor for mortality, whereas low EF and chronic dialysis are the worst predictors.

In the United States, patients with diabetes mellitus represent roughly 25% of the nearly 1.5 million surgical and percutaneous coronary revascularization procedures performed annually.7 Recently, the population of diabetics in Japan has reached 6.9 million, and 10% of Japanese people older than 40 years of age are diabetic. In patients with diabetes, cardiovascular disease is the leading cause of death, and almost 80% of all deaths result from ischemic heart disease.8 Type 2 (non-insulin–dependent) diabetes increases the risk of coronary artery disease and is the predominant type among diabetic patients with acute myocardial infarction (MI).9

The aim of this historical cohort study was to evaluate the benefit of using skeletonized bilateral internal mammary artery (BIMA) grafts in patients with diabetes mellitus who underwent CABG.

Methods

This historical cohort study was a retrospective review of medical records after the patients were discharged from the hospital and is a subset analysis based on the first general study.3

Patients

From April 1985 to March 1998, 1827 patients underwent isolated CABG at the Heart Institute of Japan, Tokyo Women’s Medical University. Of the 1572 patients who received internal mammary artery (IMA) grafts, 1355 had multiple CABG for multivessel disease. From this group, we extracted 1131 patients who underwent elective, primary, isolated, multiple CABG with IMA grafts, excluding those who had chronic dialysis, emergency surgery, or repeat CABG. Among them, 467 (41.3%) patients had diabetes mellitus and 664 (58.7%) patients were nondiabetic. Diabetes was defined as fasting plasma glucose (FPG) higher than 126 mg/dL in at least 2 morning measurements, stressed glucose higher than 200 mg/dL, or hemoglobin A1c greater than 6.0%. Of 467 diabetic patients, 295 were treated with diet therapy, 122 with oral hypoglycemic therapy, and 50 with insulin.

Patient selection for single internal mammary artery (SIMA) or BIMA grafts was not random but was decided from the in situ graft size on preoperative angiography, as described previously.3 The use of small grafts was avoided. Diabetes mellitus (insulin-treated or non-treated) did not constitute hesitation for using BIMA grafts in elective CABG. The patients received either SIMA grafts with 1 or
TABLE 1. Clinical Characteristics of the Patient Population at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Patients (n=664)</th>
<th>Diabetic Patients (n=467)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall or SIMA (n=411)</td>
<td>BIMA (n=253)</td>
</tr>
<tr>
<td>Median age, y</td>
<td>62</td>
<td>...</td>
</tr>
<tr>
<td>Overall</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>62</td>
</tr>
<tr>
<td>Median EF</td>
<td>56</td>
<td>...</td>
</tr>
<tr>
<td>Overall</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>55</td>
</tr>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>82 (12.3%)</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>64 (12.3%)</td>
</tr>
<tr>
<td>No. of lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVD</td>
<td>22.0%</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>21.9%</td>
</tr>
<tr>
<td>TVD</td>
<td>55.6%</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>55.0%</td>
</tr>
<tr>
<td>LMD</td>
<td>22.4%</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>23.1%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>64.0%</td>
<td>...</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>9.6%</td>
<td>...</td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;25 kg/m²</td>
<td>45.2%</td>
<td>...</td>
</tr>
<tr>
<td>&gt;35 kg/m²</td>
<td>0.15%</td>
<td>...</td>
</tr>
<tr>
<td>Hypertension</td>
<td>64.9%</td>
<td>...</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>68.5%</td>
<td>...</td>
</tr>
<tr>
<td>Smoker</td>
<td>72.6%</td>
<td>...</td>
</tr>
<tr>
<td>CCS class III or IV</td>
<td>60.2%</td>
<td>...</td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treated DM</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Diet therapy</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>SIMA or BIMA patients</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

DM indicates diabetes mellitus; DVD, double vessel disease; TVD, triple vessel disease; LMD, left main disease; CVD, cerebral vascular disease; BMI, body mass index (kg/m²); and CCS, Canadian Cardiovascular Society.

more supplemental grafts or BIMA grafts with or without supplemental grafts. The nondiabetic group had 411 SIMA and 253 BIMA grafts. The diabetic group had 277 SIMA and 190 BIMA grafts.

For other coronary risk factors, we defined hypertension as systolic blood pressure higher than 140 mm Hg or diastolic blood pressure higher than 90 mm Hg. Hyperlipidemia was total cholesterol higher than 220 mg/dL, LDL cholesterol higher than 140 mg/dL, triglyceride higher than 150 mg/dL, or HDL cholesterol lower than 42 mg/dL for men and 50 mg/dL for women. Hyperuricemia was uric acid higher than 7.0 mg/dL. Mild obesity was body mass index greater than 25 kg/m² and severe obesity greater than 35 kg/m². Smoking status referred to former or current smoking.

Comparing the baseline patient characteristics (Table 1), the median age was similar in the diabetic and nondiabetic groups (P=0.33). Compared with the nondiabetic group, the diabetic group had a significantly lower median left ventricular EF (P=0.003), higher proportion of women (P=0.0005), and higher frequency of triple vessel disease (P=0.004). Mild obesity was significantly more prevalent in the diabetic group (P=0.023), but severe obesity was not significantly different (P=0.31). The proportions of prior MI, prior cerebrovascular disease, smoking, hypertension, and hyperlipidemia were not significantly different between the 2 groups.

Among the diabetic patients, the BIMA subgroup had significantly more treated diabetic patients (P=0.05) and fewer women (P=0.011) than the SIMA subgroup. Among the nondiabetic pa-
tients, there were fewer women in the BIMA than in the SIMA subgroup ($P=0.0013$).

**Surgical Procedures**
The skeletonization technique was routinely used in the dissection of the IMA. After surgery, blood glucose level was controlled rigorously during the intensive care unit stay.

The mean number of patent distal anastomoses per patient and the proportions of IMA grafts were similar in the diabetic and nondiabetic groups (Table 2). However, the mean numbers of distal anastomoses were higher using BIMA than using SIMA in both diabetic ($P=0.012$) and nondiabetic ($P=0.0002$) patients. More gastroepiploic arteries ($P=0.005$) and radial arteries ($P=0.006$) were used as grafts in patients with diabetes, whereas more saphenous vein grafts ($P=0.005$) were used in patients without diabetes. Arterial grafts were used more frequently in the BIMA subgroup than in the SIMA subgroup both in patients with (91.1% versus 61.4%, $P=0.0001$) and without (89.5% versus 55.6%, $P=0.0001$) diabetes.

**Early Result Assessment**
Hospital death and perioperative morbidity including cardiac events and wound complications were assessed. Postoperative graft angiogram was performed routinely approximately 2 weeks after surgery, and 1083 patients (95.8% of all patients) underwent coronary angiography. Early graft patency was assessed on the angiograms. All the anastomoses on cine films were reviewed for coronary stenosis by cardiologists in our institute as previously described.

The mean number of distal anastomoses per patient times the patency rate was calculated.

**Late-Result Assessment**
All patients were treated with aspirin with or without low-dose warfarin (approximate target international normalized ratio, 1.5 to 2.0) and calcium antagonist or $\beta$ blockade. Supplemental medication was used for treating coronary risk factors. Smoking cessation was routine. Chronic dialysis attributable to renal failure was started postoperatively in 16 patients.

All patients were reviewed annually following a standardized protocol. Eight patients (0.7%) were lost to follow-up. The median follow-up period was 8.1 years as of August 2002.

**Statistical Analysis**
The analyses were performed with the SAS System (SAS Institute Inc.). The data are presented as frequency or mean±SD. Characteristics of the patient group were compared by $\chi^2$ test or Fisher’s exact probability test. Long-term event-free curves were estimated by the Kaplan-Meier method, and differences between curves were assessed by the log-rank test. To determine the effect of various predictors and operative methods, univariate and multivariate Cox proportional hazards models were applied. Two-tailed values of $P<0.05$ were considered to indicate statistical significance.

**Results**
Hospital mortality was not significantly different between diabetic (1.1%) and nondiabetic (0.8%) patients ($P=0.75$) and also not significantly different between the SIMA and BIMA subgroups in both diabetic (1.4% versus 0.5%) and nondiabetic (0.5% versus 1.2%) patients. The incidence of
TABLE 3. Relationships between EF and Cause of Cardiac Death

<table>
<thead>
<tr>
<th>Causes of cardiac death</th>
<th>EF &gt; 0.4</th>
<th>EF ≤ 0.4</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients</td>
<td>910</td>
<td>221</td>
<td>…</td>
</tr>
<tr>
<td>Sudden death</td>
<td>14 (1.5%)</td>
<td>15 (6.8%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Heart failure</td>
<td>20 (2.2%)</td>
<td>20 (9.0%)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16 (1.8%)</td>
<td>4 (1.8%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Total</td>
<td>50 (5.5%)</td>
<td>39 (17.6%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

depth sternal wound infections was not different between diabetic (9.0%) and nondiabetic (8.3%) patients (P=0.24) and also not significantly different between the SIMA and BIMA subgroups in both diabetic (1.1% versus 0.5%, P=0.65) and nondiabetic (0.2% versus 0.4%, P=0.99) patients.

The mean total graft patency rate was identical (95.5%) in diabetic and nondiabetic patients. However, the graft patency rates were significantly higher in the BIMA than in the SIMA subgroup both in diabetic (97.7% versus 93.8%, P=0.0012) and nondiabetic (96.8% versus 94.6%, P=0.032) patients. From calculation, the BIMA subgroup had a higher percentage of functional grafts at discharge than the SIMA subgroup both in diabetic (9.6% higher) and nondiabetic (11.3% higher) patients.

Long-Term Results

Late follow-up (median interval, 8.1 years) documented 32 repeat CABGs (8 SIMA and 1 BIMA in diabetic patients and 21 SIMA and 2 BIMA in nondiabetic patients), 150 percutaneous coronary interventions (42 SIMA and 22 BIMA in diabetic patients and 57 SIMA and 29 BIMA in nondiabetic patients), and 51 recurrent MIs (17 SIMA and 4 BIMA in diabetic patients and 23 SIMA and 7 BIMA in nondiabetic patients).

Eighty-nine cardiac deaths, including 29 sudden deaths, were documented (25 SIMA and 14 BIMA in diabetic patients and 38 SIMA and 12 BIMA in nondiabetic patients) (Table 3). When EF was classified into greater than 40% or 40% or lower, the rates of sudden death and death attributable to heart failure were significantly higher in patients with EF ≤ 40 than in those with EF > 40 (P=0.0001), but fatal MI rate did not differ significantly depending on EF (P=0.99).

A total of 148 noncardiac deaths were documented, including 59 malignancies (17 stomach, 17 lung, 5 liver, 4 bile duct or gallbladder, 3 prostate, 3 pancreas, 3 colon, 3 bladder, 2 leukemia, and 2 others), 26 strokes, 17 pneumonias, 9 respiratory failures, 10 renal failures, 7 aortic ruptures, 4 accidents, 4 suicides, 4 gastrointestinal disease, 2 sepsis, and 6 unknown causes. The death rate of the each cause of diabetes-related late death was not significantly different between diabetic and nondiabetic patients. However, the composite death rate for stroke, aortic rupture, renal failure, pneumonia, and sepsis was significantly higher in diabetic patients (7.5%) compared with nondiabetic patients (4.1%) (P=0.013).

For the 237 late deaths, the median age at operation was 64 years, and the median age at death was 70 years. Including 10 hospital deaths, 247 (21.7%) of the study population (1131) died after surgery, 76 with SIMA and 32 with BIMA grafts among diabetic patients and 99 with SIMA and 40 with BIMA grafts among nondiabetic patients.

The 10-year all death–free rates tended to be lower in diabetic patients (76.8±2.4%) than in nondiabetic patients (79.5±1.9%) (P=0.06) (Figure 1A). In diabetic patients, all death–free rates were similar up to the sixth year, but the 10-year rate tended to be higher in the BIMA than in the SIMA subgroup (80.2±3.8% versus 75.4±3.0%, P=0.46) (Figure 1B). In diabetic patients with EF > 0.4, the 10-year all death–free rates were significantly higher in the BIMA (87.8±3.5%) than in the SIMA (75.2±3.4%) subgroup (P=0.04) (Figure 1C). In diabetic patients with EF > 0.4, the 10-year rates of freedom from all death or repeat CABG or recurrent MI were significantly higher in the BIMA subgroup (86.6±3.6%) than in the SIMA (69.0±3.7%) subgroup (P=0.0086) (Figure 1D). In nondiabetic patients with EF > 0.4, the 10-year rates of freedom from all death or repeat CABG or MI were similar in the BIMA and the SIMA subgroups (P=0.3) (Figure 1E). However, the 10-year rates of freedom from cardiac death or repeat CABG or MI–free rates tended to be higher in the BIMA subgroup (92.1±2.5%) than in the SIMA (85.8±2.2%) subgroup (P=0.18) (Figure 1F).

The hazard ratios (HRs) for all death (early and late) were significantly higher for the predictive factors of poor EF and older age (Figure 2). The HR for all death in diabetic patients with EF > 0.4 tended to be lower in the BIMA subgroup than in SIMA subgroup (HR, 0.61; 95% CI, 0.36 to 1.067; P=0.08). The HR for all death, repeat CABG, or recurrent MI in diabetic patients with EF > 0.4 was significantly lower in BIMA subgroup than in the SIMA subgroup (HR, 0.53; 95% CI, 0.31 to 0.903; P=0.019).

Discussion

The advantage of BIMA grafts versus SIMA grafts has been a controversial topic, although the use of skeletonized BIMA grafts in coronary revascularization has recently been shown to produce better outcomes than use of SIMA grafts. For diabetic patients, however, the present study showed that the survival benefit was evident only in patients with preserved cardiac function (EF > 40%). Patients who received skeletonized BIMA grafts had significantly more distal anastomoses per patient than those who had pedicle BIMA. We believe that the greater the number of arterial grafts, the better the outcome, and we always aim at complete arterial grafting with exclusive use of the theoretically best conduits, namely, in situ arterial grafts, whenever anatomically possible.

Graft selection avoiding size discrepancy between the native coronary artery and the graft and choosing the best anastomotic site are 2 important surgical factors to prevent early graft occlusion. Data of superior early angiographic graft patency rate (98.0%) with exclusive use of IMA grafts for all coronary vessels and reduced patency (91.7%) when venous grafts were used indicate that superior patency of IMA graft is already evident at the time of discharge. By 10 years after CABG, 50% of saphenous vein grafts are occluded mainly because of vein graft disease, and the best way to
prevent vein graft disease is to use IMA grafts. After vein graft disease occurs in the long term, the role of the residual functioning grafts becomes more important to maintain cardiac function.

The benefits from using BIMA grafts in diabetic patients differ depending on the EF status of the patients. Survival benefit is the ultimate end point, and factors that have great effect on survival include progression of arteriosclerosis in native coronary arteries, number of functioning residual grafts after vein graft disease, and cardiac events such as heart failure and sudden death. For patients with poor cardiac function with or without diabetes, the strong cardiac risks nullify the survival benefits of BIMA grafts over SIMA grafts. In diabetic patients with preserved cardiac function,
after vein graft disease starts to manifest at 6 years, cardiac events in particular increased in the diabetic SIMA subgroup because of the characteristics of coronary artery lesions in diabetes. The diabetic SIMA subgroup has more crucial saphenous vein grafts. In nondiabetic patients with preserved cardiac function, a longer follow-up is needed to prove statistically significant survival benefits with BIMA, because this comparison requires statistical power and the number of our patients is rather small. Diabetes works synergistically in increasing the risk of survival in the SIMA subgroup.

Recently, there has been a tendency to use IMA grafts. However, previous studies comparing PTCA and CABG did not necessary evaluate arterial grafts and included only relatively mild cases. In the present study, all surgically treatable cases were included and there was no hesitation over the use of BIMA in diabetic patients (exclusion criteria were applied to match the BIMA and SIMA groups for analysis). Consequently, a reasonable number of diabetic patients were included. This cohort had a high postoperative angiography rate of 95.8%, a high follow-up rate of 99.3% for a median period of 8.1 years, and clearly identified causes of death. The findings provide useful and timely information for the choice of IMA grafts.

Diabetic patients without previous MI have as high a risk of MI as nondiabetic patients with previous MI, and CABG greatly reduces the risk of death after spontaneous Q-wave MI in diabetic patients. In addition, patients with diabetes are often more severely ill, advanced in age, and have high blood pressure and heart failure at baseline. Diabetic patients who are treadmill-positive often have a prevalence of silent myocardial ischemia. The BARI study reported highly significant improved survival in patients with treated diabetes and multivessel disease who underwent CABG; however, the benefits of CABG were restricted only to patients receiving at least 1 arterial conduit during CABG. Both BARI and EAST studies enrolled symptomatic patients with multivessel patients undergoing CABG, but the numbers of patients with treated diabetes were small.

The characteristics of coronary artery lesions in diabetic patients are diffuse and atherosclerotic with poor run off. In the present study, diffuse triple vessel disease was significantly more common in diabetic than in nondiabetic patients ($P=0.004$). Restenosis after intervention and appearance of new lesions tend to occur in diabetic patients, and because of the excessively narrowed lumen, stent insertion is often inappropriate. The choice of treatment is coronary revascularization with IMAs because the effect of coronary intervention is uncertain for small-diameter atherosclerotic sites and the selected treatment should reliably prolong life.

Taggart et al conducted a MEDLINE search on the effects of arterial revascularization on survival. None of the studies was randomized, and only 9 cohort studies met their inclusion criteria (more than 100 patients and longer than 4-year follow-up). The present study has certain limitations in study design, such as being a retrospective review of medical records and a nonrandomized, single-institution study with a relatively small number of patients. Another possible source of bias in our trial was differential recruitment of BIMA grafting, because the use of IMAs is becoming increasingly popular. However, we believe that the information is valuable for the choice of treatment.

There are many disagreements concerning diabetes even in well-recognized studies, and the role of glycemic control in the prevention of vascular events remains controversial. Because of the different definitions for diabetes adopted in various reports, comparison among studies is difficult. In the present study, we defined diabetes as FPG higher than 126 mg/dL, as was used in the study of Uva et al. Other studies used diverse definitions such as FPG higher than 140 mg/dL, use of oral hypoglycemic agents, and treated diabetes mellitus. In the comparison of survival between diabetic and nondiabetic patients using fasting plasma glucose as criterion, we observed a tendency of better survival in nondiabetic patients.

In the Japanese population, non-insulin–dependent diabetes mellitus is a significant risk factor for coronary heart disease, and impaired glucose tolerance itself is a risk factor for cardiovascular disease. The rate of severe obesity (body mass index greater than 35 kg/m$^2$) in patients of North America and Europe is higher than Japanese patients, and Kouchoukos et al reported 18.6% (274 of 1566) severe obesity in CABG patients at Washington University in the
United States, whereas severe obesity was only 0.4% (4 of 1131) in our study. Diabetic patients in Japan are rather thin, and this racial difference may influence the prognosis of ischemic heart disease in diabetic patients.

The use of arterial grafts in coronary revascularization was not recommended for diabetic patients in previous reports,\(^3,^4,^30\) because this method was thought to increase complications such as mediastinitis. We recommend skeletonizing the IMA graft, because we found that this method of dissecting IMA graft may lower the risk of complications.\(^5\) We strongly believe that the choice of graft for diabetic patients is in situ arterial graft to improve patency and consequently improve survival in the long term.

In conclusion, we demonstrated that skeletonized BIMA grafts were associated with minimal operative risk, high early graft patency rate, and excellent long-term survival rate in diabetic patients with EF > 0.4. In these patients, the long-term rate of freedom from all death or repeat CABG or recurrent MI was significantly higher using BIMA than using SIMA (P = 0.0086). However, in diabetic patients with EF ≤ 0.4 or lower, survival benefit is limited with BIMA grafts because of the unavoidable high cardiac death rate.

Acknowledgment

We are grateful to both Dr Teresa Nakatani for assistance in preparing the manuscript and Katsunori Shimada for assistance in data analysis.

References

Bilateral Versus Unilateral Internal Mammary Revascularization in Patients With Diabetes
Masahiro Endo, Yasuko Tomizawa and Hiroshi Nishida

*Circulation.* 2003;108:1343-1349; originally published online August 25, 2003; doi: 10.1161/01.CIR.0000085995.87982.6E
*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2003 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://circ.ahajournals.org/content/108/11/1343

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Circulation* is online at:
http://circ.ahajournals.org//subscriptions/