Background—The prevalence of diabetes mellitus is increasing at an unprecedented rate, affecting nearly 8% of the population. Previous studies have demonstrated a potential benefit for surgical over interventional revascularization in this group of patients. Similarly, studies have shown the superiority of bilateral internal mammary artery (BIMA) grafting over single internal mammary artery (SIMA) grafting in select populations. However, concerns about sternal wound infection have discouraged the use of BIMA grafting in diabetics. Therefore, we studied the long-term results of BIMA versus SIMA grafting in a large population of diabetic patients in whom BIMA grafting was broadly applied.

Methods and Results—Between February 1972 and May 1994, 1107 consecutive diabetic patients underwent coronary artery bypass grafting with either SIMA (n=646) or BIMA (n=461) grafting. Optimal matching with the propensity score was used to create matched SIMA (n=414) and BIMA (n=414) cohorts. Cross-sectional follow-up (6 weeks to 30.1 years; mean, 8.9 years) determined long-term survival. There was no difference in operative mortality, sternal wound infection, or total complications between matched SIMA and BIMA groups (operative mortality, 10 of 414 [2.4%] versus 13 of 414 [3.1%]; P=0.279; sternal wound infection, 7 of 414 [1.7%] versus 13 of 414 [3.1%]; P=0.179); total complications, 71 of 414 [17.1%] versus 71 of 414 [17.1%]; P=1.000). Late survival was significantly enhanced with the use of BIMA grafting (median survival: SIMA, 9.8 years versus BIMA, 13.1 years; P=0.001). Use of BIMA was found to be associated with late survival on Cox regression (P=0.003).

Conclusion—Compared with SIMA grafting, BIMA grafting in propensity score–matched patients provides diabetics with enhanced survival without any increase in perioperative morbidity or mortality. 

Key Words: coronary artery bypass ■ coronary artery disease ■ diabetes mellitus ■ follow-up studies ■ survival analysis

Diabetes mellitus currently afflicts 25.8 million people in this country, ≈8.3% of the US population. The prevalence has more than doubled in the past decade,1 and current estimates predict an incidence between 1 in 5 and 1 in 3 Americans by 2050.² The burden of disease associated with diabetes mellitus is dramatic: Adults with diabetes mellitus are 2 to 4 times more likely to have cardiovascular disease than those without it, and at least 65% will die of it.³ The national burden of cardiovascular disease caused by diabetes mellitus is increasing at an unprecedented rate.⁴ The nature of cardiovascular disease in diabetics is clinically challenging because it tends to be extensive with multivessel involvement.⁵ ⁶ Perhaps it is for this reason that surgical revascularization has been reported to be well suited for the diabetic patient.⁷ ⁸ Numerous clinical trials have demonstrated a survival benefit for bilateral (BIMA) compared with single (SIMA) internal mammary artery bypass grafting for patients with multivessel disease.⁹ ¹¹ However, there remains considerable reluctance to use this surgical approach in diabetic patients because of concerns about the risk of deep sternal wound infection (SWI).¹² We therefore studied the results of a 30-year follow-up of unmatched and propensity score–matched diabetic patients who underwent SIMA or BIMA grafting in a cohort in whom BIMA grafting was extensively applied.

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Clinical Perspective on p 2942

Methods

Patient Population
From February 1972 through May 1994, 1107 consecutive diabetic patients underwent isolated coronary artery bypass grafting (CABG)
with either an SIMA (n=646) or a BIMA (n=461). Diabetic patients in the study included those who were treated with either hypoglycemic agents or insulin. Excluded from the study group were patients with concomitant cardiovascular procedures and those in whom only 1 distal graft was performed. This study was presented at the Institutional Review Board, and a waiver of the requirement for informed patient consent was granted.

The coronary and perioperative risk factors and preoperative angiographic findings for unmatched and propensity score–matched diabetic patients are summarized in Table 1. Although SIMA and BIMA patients had markedly different risk factor profiles, there were no significant differences in any of the risk factors in the propensity score–matched groups.

### Operative Data

Details of the operative technique used in the present series, including IMA mobilization, orientation, and reconstruction in BIMA grafting, have been previously discussed.13 The IMA is dissected as an isolated pedicle from the chest wall free from surrounding muscle and fascia. The vein is initially dissected but subsequently removed to allow maximal length and versatility. All side branches are cauterized carefully or clipped as necessary. Since 1989, combined antegrade and retrograde infusion methods of cardioplegia were implemented to enhance myocardial protection during the operation. Cardiopulmonary bypass was used in all operations. The left IMA, as either a sequential or an isolated graft, was preferentially anastomosed to the left anterior descending coronary artery. The right IMA was used for grafting either the right or left system, as previously discussed in detail.13 The coronary and perioperative risk factors and preoperative angiographic findings for unmatched and propensity score–matched diabetic patients are summarized in Table 1. Although SIMA and BIMA patients had markedly different risk factor profiles, there were no significant differences in any of the risk factors in the propensity score–matched groups.

### Data Sources

Perioperative data were entered prospectively in a standardized manner into a clinical database according to the guidelines of the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Follow-up information was obtained through comprehensive questionnaires and by telephone interview with surviving patients, family members, or the patient’s personal physician and entered into the follow-up component of the database.

### Statistical Analysis

Demographic and clinical data are presented as frequency distributions and simple percentages. Values of continuous variables are expressed as mean±SD. In unmatched patient cohorts, univariate analysis of selected preoperative and postoperative discrete variables was accomplished by the χ² test with the appropriate degrees of freedom.
freedom or the Fisher exact test to assess the equality of proportions. Two-sample $t$ tests were used to test for the equality of means in continuous variables. To assess differences in matched cohorts, the McNemar test was used to test categorical variables, and paired $t$ tests were used for continuous variables.

To control for measured potential confounders in the data set, a Cox proportional hazards regression model was used to discern the influence of multiple clinical variables on late survival for patients discharged from the hospital in unmatched and propensity score–matched diabetic patient groups (Table III in the online-only Data Supplement). The final logistic regression model included 4 covariates. Conditional logistic regression was used to determine the independent effects of selected demographic/clinical variables on hospital mortality in propensity score–matched patients.

To identify variables associated with hospital mortality in unmatched patients, an initial logistic regression model was developed with 21 preoperative and intraoperative demographic/clinical preoperative covariates as independent variables with treatment type (SIMA versus BIMA) as a binary dependent variable (Table I in the online-only Data Supplement). The resulting propensity score represented the probability that a patient underwent BIMA grafting in CABG. BIMA patients were then matched to SIMA patients in a 1:1 ratio with the use of a Rosenbaum optimal matching algorithm.14,15 This approach minimized the overall distance between observations and was conducted with Mahalanobis distance within propensity score calipers (no matches outside the calipers). The quality of the match was assessed by comparing selected baseline characteristics in propensity score–matched patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unmatched Diabetic Patients</th>
<th>Propensity Score–Matched Diabetic Patient Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIMA</td>
<td>BIMA</td>
</tr>
<tr>
<td>Patients, n (%)</td>
<td>646</td>
<td>461</td>
</tr>
<tr>
<td>Total grafts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distal coronary artery grafts, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD, n</td>
<td>2036</td>
<td>1551</td>
</tr>
<tr>
<td>Range, n</td>
<td>3–6</td>
<td>3–6</td>
</tr>
<tr>
<td>Cardiopulmonary bypass time, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>119.9±45.9</td>
<td>118.6±45.2</td>
</tr>
<tr>
<td>Range</td>
<td>30–504</td>
<td>40–391</td>
</tr>
<tr>
<td>Aortic cross-clamp time, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>68.5±23.9</td>
<td>74.8±24.1</td>
</tr>
</tbody>
</table>

SIMA indicates single internal mammary artery; BIMA, bilateral internal mammary artery; and CAD, coronary artery disease.

Results

Hospital Morbidity

The overall incidence of postoperative morbidity for the 2 unmatched diabetic groups was low. No complications were experienced in 79.3% (512 of 646) of the SIMA patients or in 83.1% (383 of 461) in the BIMA group ($P=0.111$). The number of complications was similar in the propensity score–matched groups, with 82.9% (343 of 414) of each group being free of complications (Table 3). A between-group comparison revealed that the prevalence of deep SWI was not affected by the type of IMA grafting used in unmatched patients ($P=0.144$) or in propensity score–matched diabetic patients ($P=0.174$).

Hospital Mortality

Hospital mortality rate was defined as death that occurred during the operation or the hospitalization in which the procedure was performed or after discharge from the hospital but within 30 days of the surgical procedure, unless the cause was unrelated to the operation. The overall hospital mortality rate for all diabetic patients was 4.4% (49 of 1107). The hospital mortality rate for unmatched SIMA patients was 5.4% (35 of 646) and 3.0% (14 of 461) for BIMA patients (odds ratio = 1.79; 95% CI, 0.95–3.51; $P=0.058$). This difference approached statistical significance. The hospital mortality rate for propensity score–matched SIMA patients was 4.6% (19/414) and 3.1% (13/414) for BIMA patients ($P=0.279$). The McNemar test for comparison of paired proportions in hospital mortality confirmed no significant differences between groups (odds ratio = 1.545; 95% CI, 0.68–3.65; $P=0.257$).

The use or nonuse of BIMA grafting was not found to be associated with hospital mortality in unmatched patients (Table 4). Moreover, conditional logistic regression analysis for propensity score–matched patients confirmed the inser-
tion of the intra-aortic balloon pump preoperatively or intraoperatively to be associated with an increased risk of hospital mortality (odds ratio = 5.33; 95% CI, 2.55–11.15; \( P < 0.001 \)).

### Long-Term Follow-Up

Follow-up data for the unmatched patient groups were collected on 94.6% of SIMA (611 of 646) and 97.0% of BIMA patients. Comparison of the survival distribution for the 2 unmatched patient groups demonstrated a significant difference (\( P = 0.001 \)). These results provide further evidence of the survival benefits from BIMA grafting, unmatched patients were stratified into those <65 or \( \geq 65 \) years of age at the time of surgery. In SIMA patients <65 years of age, the median survival time was 13.2 years (95% CI, 10.98–15.42) compared with 17.6 years (95% CI, 14.67–18.99) for BIMA patients. The equality of survival distribution for these 2 groups of propensity score–matched diabetic patients demonstrated a significant difference (\( P < 0.001 \)).

The coronary artery disease-related surgical complications in the unmatched groups are listed in Table 3. Comparison of the hospital complications for unmatched and propensity score–matched diabetic patient groups

#### Table 3. Comparison of Hospital Complications for Unmatched and Propensity Score–Matched Diabetic Patient Groups

<table>
<thead>
<tr>
<th>Complication</th>
<th>Unmatched (n = 1107)</th>
<th>Propensity Score–Matched (n = 828)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIMA/BIMA Diabetic</td>
<td>SIMA/BIMA Diabetic</td>
</tr>
<tr>
<td></td>
<td>Patients, n (%)</td>
<td>Patients, n (%)</td>
</tr>
<tr>
<td></td>
<td>SIMA</td>
<td>BIMA</td>
</tr>
<tr>
<td>Patients</td>
<td>646 (100.0)</td>
<td>461 (100.0)</td>
</tr>
<tr>
<td>Reoperation for bleeding</td>
<td>19 (2.9)</td>
<td>10 (2.2)</td>
</tr>
<tr>
<td>Pulmonary insufficiency</td>
<td>63 (9.8)</td>
<td>26 (5.6)</td>
</tr>
<tr>
<td>Cerebral vascular accident</td>
<td>13 (2.0)</td>
<td>8 (1.7)</td>
</tr>
<tr>
<td>Perioperative myocardial infarction</td>
<td>31 (4.8)</td>
<td>20 (4.3)</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>35 (5.4)</td>
<td>13 (2.8)</td>
</tr>
<tr>
<td>Low cardiac output</td>
<td>20 (3.1)</td>
<td>12 (2.6)</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>22 (3.4)</td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>13 (2.0)</td>
<td>9 (2.0)</td>
</tr>
<tr>
<td>Deep sternal infection</td>
<td>10 (1.5)</td>
<td>13 (2.8)</td>
</tr>
</tbody>
</table>

SIMA indicates single internal mammary artery; BIMA, bilateral internal mammary artery.

To discern the influence of age on the survival benefits from BIMA grafting, unmatched patients were stratified into those <65 or \( \geq 65 \) years of age at the time of surgery. In SIMA patients <65 years of age, the median survival time was 13.2 years (95% CI, 10.98–15.42) compared with 17.6 years (95% CI, 14.67–18.99) for BIMA patients. The equality of survival distribution for patients <65 years of age demonstrated a significant survival advantage for BIMA patients (\( P = 0.006 \); Figure 2A). In patients \( \geq 65 \) years of age, the median survival time for SIMA patients was 8.1 years (95% CI, 7.32–9.26) compared with 10.6 years (95% CI, 9.43–12.16) for BIMA patients. A comparison of the survival distribution for these 2 groups of patients demonstrated a
significant survival advantage for BIMA patients \( (P = 0.014; \text{Figure 2B}) \).

### Discussion

Despite consistently favorable reports on the long-term benefits of BIMA grafting,9–11 the Society of Thoracic Surgeons National Database reports that <4% of patients undergoing CABG surgery currently receive the benefits of BIMA grafting.16 Surgical reluctance to use BIMA grafting has been particularly noteworthy among diabetic patients because of concerns about an increased risk of SWI.15 Here, we report an enhanced long-term survival advantage for BIMA grafting in a large cohort of consecutive multigraft diabetic CABG patients in whom BIMA grafting was liberally applied.

As with any retrospective surgical experience, clinical decisions are based on a host of complex interacting factors. Therefore, the cohort of patients in whom SIMA grafting was selected tended to be older, more acutely ill, and associated with more preoperative comorbid conditions. However, even after propensity score matching, which controlled for each of the identifiable risk factors, a survival advantage was demonstrated in BIMA patients. These results were further confirmed by multivariable Cox regression, which clearly showed that BIMA grafting was associated with long-term survival in unmatched and propensity score–matched patients. Similar results have been previously reported in smaller groups of patients with a shorter duration of follow-up.17–19 Unlike those reports, the survival benefit observed here did not appear to be influenced by patient age at the time of surgery.20

The absence of significant difference in the SWI rate among BIMA patients may represent a type II error that could have become significant with a larger cohort of patients. However, it should be noted that the study population \( (n = 1107) \) was sufficiently robust to demonstrate a clear survival advantage for BIMA patients but not a significant difference in SWI. Moreover, previous studies have also failed to find a significant increase in SWI with BIMA grafting in diabetics.21,22 Differences reported in the literature may likely be due less to statistical variance than to surgical technique. All the IMAs in this study were harvested with a skeletonized technique, which has been demonstrated to better preserve sternal blood flow23–25 and to reduce the risk of SWI.26,27 Similarly, early reports of increased postoperative bleeding28 and pulmonary morbidity29 with BIMA grafting have not been substantiated by subsequent studies30,31 and were not evident in the present study.

Numerous studies have suggested a survival advantage for CABG over percutaneous coronary intervention for diabetic patients, presumably because of the completeness of revascularization in a milieu of extensive and diffuse coronary artery disease with which these diabetic patients present.7,8 There is no indication that revascularization was significantly more complete in the matched SIMA versus BIMA patients in this study. Certainly, the well-documented improved long-term patency of IMA versus saphenous vein grafts may have played a crucial role in providing this survival benefit. However, there may be other contributing physiological reasons. The IMA has been demonstrated to have enhanced production of endothelium-derived nitrous oxide,32–35 which may play an important role in ameliorating diabetes mellitus–induced endothelial dysfunction and susceptibility to progressive atherosclerosis and subsequent cardiac events.

Although impressive for their longevity and consistency, the results of the present study nonetheless are limited by its retrospective nature. Even though propensity score matching
is a well-described technique for “leveling the playing field” in retrospective studies and although in this study risk factors were closely matched, there remains the possibility of confounding variables not accounted for in the data set. Moreover, the use of propensity score matching limited the sample size to those patients who could be matched. The advantage of clinical registries is that they reflect aggregate surgical experience as it is practiced without the rigid selection of prospective randomized studies. However, results will nonetheless ultimately require confirmation from prospective randomized trials, which are considered the “gold standard.”36 Certain technical issues also need to be recognized. In addition to the skeletonized method of IMA harvest, this cohort made extensive use of in situ grafts (98%). Therefore, comparison with studies using free IMA and or Y and T graft configurations may not be applicable.

This long-term retrospective study includes many patients who were operated on more than 2 decades ago. Risk profiles and surgical outcomes of CABG surgery have changed dramatically since that time, with increasing patient risk and decreasing operative mortality.37 Can we be certain that the ability to apply BIMA grafting in the modern era would be equivalent to the outcomes observed in this study? Have improvements in perioperative care and medical therapy ameliorated or even eliminated the survival benefits observed? More recent studies with both on-pump19 and off-pump17 CABG suggest that these results have been replicable in today’s modern surgical era.

The limitations of the data-gathering approach did not allow us to make a more careful assessment of several potentially important factors. First, we were not able to distinguish between insulin-dependent and non–insulin-dependent patients in any of our analyses. Second, all of these patients were operated on before the routine application of careful perioperative glycemic control. Third, we have no information on the adequacy of medical therapy for these dependent patients in any of our analyses. Second, all of these patients were operated on before the routine application of careful perioperative glycemic control. Third, we have no information on the adequacy of medical therapy for these patients over the many years of follow-up. However, we have no a priori reason to suspect that any of these factors would necessarily bias the results toward 1 group or the other.

Finally, the cross-sectional nature of the follow-up did not permit accurate prospective evaluation of major adverse cardiac events. Although the historical recollection of patients alive at follow-up did not demonstrate a difference in the
occurrence of late cardiac events between groups, this information is limited to patients alive at follow-up and is unverified and therefore may not be reliable. Nonetheless, the strong historical evidence of improved event-free survival with BIMA grafting would certainly not lead us to suspect a higher incidence of major adverse cardiac events in BIMA patients.

Conclusions

Propensity score–matched BIMA compared with SIMA diabetic patients experienced improved long-term survival without any increase in perioperative morbidity or mortality. The magnitude of this benefit appears to be sufficient to eliminate the negative influence of diabetes mellitus on long-term survival in this cohort of patients. Given the documented benefits of CABG in diabetic patients with extensive coronary artery disease, BIMA grafting is the procedure of choice in those patients in whom the operation is technically feasible.

Acknowledgments

All authors had access to and have reviewed all of the data and agree with the conclusions presented. We would like to acknowledge the assistance of Debra Guest, EdD, for her assistance in the compilation of the manuscript.

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Disclosures

None.

References

The prevalence of diabetes mellitus is increasing at an unprecedented rate, affecting nearly 8% of the population. Previous studies have demonstrated a potential benefit for surgical over interventional revascularization in this group of patients, perhaps because of the diffuse nature of coronary atherosclerosis in this population. Similarly, multiple studies have shown the superiority of bilateral internal mammary artery (BIMA) grafting over single internal mammary artery grafting in select populations. However, concerns about sternal wound infection have discouraged the use of BIMA grafting in diabetics. Therefore, we studied the long-term results of BIMA versus single internal mammary artery grafting in a large population of diabetic patients in whom BIMA grafting was broadly applied. Because of the uncontrolled surgical selection process for single internal mammary artery versus BIMA grafting, we applied propensity score matching to create matched sets of single internal mammary artery and BIMA patients among 1107 consecutive coronary artery bypass graft patients. Although there was no difference in operative mortality, morbidity, or sternal wound infection between groups, there was a clear long-term survival benefit, even among matched patients, for BIMA over single internal mammary artery grafting. Given the increasing prevalence of diabetes mellitus, the high incidence of extensive coronary artery disease in diabetics, and the proven benefit of coronary artery bypass graft surgery as a strategy for revascularization, these findings address an issue of high clinical impact. Because the findings are compelling and radically alter current clinical practice, this research is novel and warrants serious attention from both future researchers and clinical decision makers.
Bilateral Internal Mammary Artery Grafting Enhances Survival in Diabetic Patients: A 30-Year Follow-Up of Propensity Score–Matched Cohorts
Malcolm J. Dorman, Paul A. Kurlansky, Ernest A. Traad, David L. Galbut, Melinda Zucker and George Ebra

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Supplemental Material
Supplemental Table 1: Covariates Used to Generate Propensity Score.

Preoperative variables

1. Age at operation
2. Cerebrovascular disease
3. Congestive heart failure
4. Dyslipidemia
5. Impaired ejection fraction (<0.50)
6. Family history of coronary artery disease
7. Hypertension
8. Male gender
9. Peripheral artery disease
10. Prior myocardial infarction
11. Renal dysfunction
12. Smoking history
13. 3-Vessel disease
14. Unstable angina
Supplemental Table 2: Covariates Used to Predict In-Hospital Mortality.

Preoperative variables

1. Age at operation
2. Cerebral vascular disease
3. Congestive heart failure
4. Dyslipidemia
5. Impaired ejection fraction (<0.50)
6. Family history of coronary artery disease
7. Hypertension
8. Intra-aortic balloon pump
9. Left main disease (>0.50)
10. Male gender
11. Peripheral artery disease
12. Prior myocardial infarction
13. Renal dysfunction
14. Smoking history
15. Surgical history
16. Surgical urgency
17. 3-Vessel disease
18. Unstable angina

Intraoperative variables

19. Conduit (SIMA vs. BIMA)
20. Distal grafts
21. Perfusion time (min)
Supplemental Table 3: Covariates used to predict late mortality.

Preoperative variables

1. Age at operation
2. Unstable angina
3. Congestive heart failure
4. Cerebrovascular disease
5. Dyslipidemia
6. Family history of coronary artery disease
7. Hypertension
8. Impaired ejection fraction (<0.50)
9. Intra-aortic balloon pump
10. Left main disease (>0.50)
11. Male gender
12. Peripheral artery disease
13. Prior myocardial infarction
14. Renal dysfunction
15. Smoking history
16. Surgical history
17. Surgical urgency
18. 3-Vessel disease

Intraoperative variables

19. Conduit (SIMA vs. BIMA)
20. Distal grafts
21. Perfusion time

Postoperative variables

22. Cardiac arrest
23. Deep sternal wound infection
24. Gastrointestinal disorder
25. Low cardiac output
26. Myocardial infarction
27. Pulmonary insufficiency
28. Renal insufficiency