Does Bilateral Internal Mammary Artery Grafting Better Suit Patients With Diabetes?
— Two Different Ways to Explore Outcomes —

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**Background:** This analysis compared short-term mortality, sternal wound infection (SWI), and long-term survival outcomes in diabetic patients who underwent coronary artery bypass grafting (CABG) with bilateral (BIMA) vs. single (SIMA) internal mammary artery, as well as in diabetic vs. non-diabetic patients undergoing BIMA grafting.

**Methods and Results:** Nineteen studies were included in the study, covering 21,143 different patients. Of these patients, 6,464 underwent CABG with BIMA, 10,264 underwent CABG with SIMA, 11,584 had diabetes, and 6,717 did not. Compared with SIMA, BIMA had a significantly lower risk of in-hospital mortality (odds ratio [OR] 0.73, P=0.02), but a significantly higher risk of SWI (OR 1.30, P=0.04). However, compared with non-diabetic patients who underwent CABG with BIMA, diabetic patients with BIMA grafting did not have significantly higher risks of either mortality (OR 1.22, P=0.53) or SWI (OR 1.10, P=0.72). No significant differences were detected with different harvesting techniques. Longer term, BIMA was associated with a significantly higher rate of survival than SIMA (hazard ratio [HR] 0.76, P<0.001).

**Conclusions:** Results from the 2 types of comparisons indicate that BIMA is a preferable option for diabetic patients, even though it has a higher risk of infection. CABG with BIMA is also associated with a long-term survival benefit.

**Key Words:** Bilateral internal mammary artery; Coronary artery bypass grafting; Diabetes; Single internal mammary artery
Does BIMA Grafting Better Suit Diabetics?

The full text of all potentially eligible trials was reviewed. Disagreements were resolved by discussion with the senior author (J.L.).

Data Collection and Quality Assessment

The following data were independently collected for all studies by 3 authors (C.W., P.L., Q.K.): authors, year of publication, study type, matching method, sample size, basic demographic and preoperative data, harvest method, 30-day mortality rate, infection rate, long-term survival data, and other important information.

Quality assessment was performed thoroughly and independently using consensus criteria by 3 authors (C.W., P.L., Q.K.). The Cochrane risk of bias tool (http://handbook-5-1.cochrane.org/chapter_8/8_5_the_cochrane_collaborations_tool_for_assessing_risk_of_bias.htm) was used to examine randomized control trials (RCTs) and the Newcastle-Ottawa Scale (http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf) was used to examine observational studies. Publication bias was evaluated by visual inspection of funnel plots and an Egger linear regression test.

Data Acquisition and Statistical Analysis

All data were derived directly from the selected studies. The 30-day mortality rates, infection rates, and long-term survival rates were directly reported in most studies, whereas other survival data were acquired from Kaplan-Meier survival curves or the actuarial survival curves using Engauge Digitizer software (http://markummitchell.github.io/engauge-digitizer/), according to standard approaches.

databases were searched automatically and manually, including the Cochrane Library, Embase, Medline, and the ISI Web of Science. Initial searches identified studies published from January 2000 to September 2019 using the key words “bilateral internal mammary artery”, “single internal mammary artery”, “diabetes mellitus”, and “survival”. There was no restriction on the language of publication. The references of selected articles and conference proceedings were also screened. Titles and abstracts were filtered and duplicate studies were deleted. This research was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Inclusion and Exclusion Criteria

To be eligible for inclusion in this review, trials had to meet the following criteria: (1) report on comparisons between BIMA and SIMA in diabetic patients or comparisons of outcomes between diabetic and non-diabetic patients following BIMA grafting; (2) clearly describe CABG surgical techniques; (3) provide preoperative data (including age, sex, hypertension, hyperlipidemia, and other relative risk factors); (4) report 30-day postoperative mortality and SWI rate (including both superficial and deep SWIs); (5) clearly describe long-term results; and (6) provide Kaplan-Meier survival curves.

Trials those without control groups, with irrelevant comparison groups (e.g., BIMA vs. other types of surgeries), without early postoperative results, long-term survival data, or survival curves, and those with other irrelevant characteristics were excluded from the review.

Figure 1. Flow chart of study election.
bias scale indicated medium performance bias, and the Newcastle-Ottawa Scale summary table for 18 observational studies indicated a relatively high score (Figure 2), meaning that all studies had a low risk of bias, guaranteeing high quality for the present meta-analysis. The overall risk bias was relatively low.

Primary Endpoint of Short-Term Results
The meta-analysis of diabetic patients undergoing coronary revascularization showed that BIMA grafting was associated with a significantly lower risk of postoperative hospital all-cause mortality than was SIMA (OR 0.73, 95% CI 0.56–0.96, P=0.021, I²=0%; Figure 3A). Because of the dominance of observational studies, another meta-analysis was conducted with PSM studies and the RCT; this analysis also showed that BIMA grafting was associated with a significantly lower risk of postoperative hospital all-cause mortality (OR 0.75, 95% CI 0.56–0.98, P=0.038, I²=0%; Figure 3B). In addition, we ran meta-analyses comparing the outcomes of diabetic and non-diabetic patients within the BIMA group to investigate the relationship between DM and BIMA grafting. In this analysis, there was no significant difference in mortality between BIMA and SIMA grafting (OR 1.22, 95% CI 0.66–2.29, P=0.53, I²=0%; Figure 3C). Sensitivity analysis did not show any particular study that could largely influence the result.

Results
Study Characteristics and Quality
In all, 19 studies (Figure 1) were included in this analysis, covering 21,143 different patients. Of these patients, 6,464 underwent CABG with BIMA, 10,264 underwent CAGB with SIMA, 11,584 patients were diabetic, and 6,717 patients were non-diabetic. Eighteen studies were observational (14 were retrospective, with 10 using propensity score matching [PSM]; 3 were prospective), and 1 study was an RCT. Of these 19 studies, 18 compared the BIMA and SIMA techniques in diabetic patients, and 5 compared the outcomes of diabetic vs. non-diabetic patients following BIMA grafting. In general, the patient populations were similar between groups. A summary of the studies is provided in Supplementary Table.

The funnel plot for publication bias, shown in Supplementary Figure 1, and the Egger linear regression test both indicated low heterogeneity. The Cochrane bias scale indicated medium performance bias, and the Newcastle-Ottawa Scale summary table for 18 observational studies indicated a relatively high score (Figure 2), meaning that all studies had a low risk of bias, guaranteeing high quality for the present meta-analysis. The overall risk bias was relatively low.

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Nevertheless, BIMA grafting was associated with a significantly higher risk of postoperative SWI in diabetic patients (OR 1.30, 95% CI 1.02–1.67, P=0.037, I²=10%; Figure 4A). This results was not changed if the retrospective study without PSM was excluded from the analysis (OR 1.50, 95% CI 1.12–2.00, P=0.006, I²=15%; Figure 4B). Similarly, no significant differences were detected in SWI outcomes between diabetic and non-diabetic patients in the BIMA group (OR 1.10, 95% CI 0.66–1.82, P=0.72, I²=0%; Figure 4C). Sensitivity analysis did not show any particular study that could largely influence the result.

Subgroup analyses were conducted to determine whether different harvest methods could lead to different infection rates for diabetic patients undergoing CABG with BIMA.
Figure 3. Forest plots showing postoperative mortality comparisons for (A) diabetics undergoing coronary artery bypass grafting with bilateral (BIMA) vs. single (SIMA) internal mammary artery grafts, (B) propensity score-matched diabetics with BIMA vs. SIMA grafts, and (C) diabetic vs. non-diabetic patients with BIMA grafts. CI, confidence interval; OR, odds ratio.
Figure 4. Forest plots showing postoperative wound infection rates for (A) diabetics undergoing coronary artery bypass grafting with bilateral (BIMA) vs. single (SIMA) internal mammary artery grafts, (B) propensity score-matched diabetics with BIMA vs. SIMA grafts, and (C) diabetic vs. non-diabetic patients with BIMA grafts. CI, confidence interval; OR, odds ratio.
BIMA grafting was associated with a significantly lower risk of postoperative hospital all-cause mortality than SIMA grafting in diabetic populations, which is consistent with previous studies. The use of BIMA appeared to be advantageous in diabetic patients because of the diffuse nature of diabetic coronary lesions and the small caliber of the coronary arteries. The internal mammary arteries were proved to enhance the production of endothelium-derived nitric oxide, which may improve vascular function in diabetic patients. 

**Actuarial Survival Rates and Long-Term Outcomes**

Long-term results followed the same pattern as short-term results. CABG with BIMA was associated with a significantly higher rate of survival than CABG with SIMA (HR = 0.76, 95% CI 0.68–0.85, P < 0.001, I² = 58%; Figure 5). Sensitivity analysis did not show any particular study that could appreciably influence the result. An actuarial estimate of the Kaplan–Meier survival curve based on the patient data just described is shown in Figure 6. This graph shows a more intuitive result of the cumulative survival rate at each time point. CABG with BIMA continued to provide diabetic patients with better survival outcomes.

**Discussion**

It has been clearly documented by numerous studies that BIMA grafting is associated with a significant reduction in mortality and cardiac-related comorbidities as well as significant long-term survival benefits compared with SIMA grafting. In addition to the well-known “gold standard” of CABG with LAD to the left internal mammary artery (LIMA), right internal mammary artery (RIMA) grafting has been proven to have a long-term patency rate similar to that of LIMA grafts. Magee et al showed that, compared with an artery graft, venous grafts had a 2.6-fold greater tendency to dysfunction, whereas the RIMA grafts had high patency (96% at 5 years, 81% after 10 years), comparable to that of the LIMA grafts (98% and 95% at 5 and 10 years, respectively).

Despite consistently favorable outcomes regarding the survival benefits of BIMA grafting, CABG in diabetic patients is associated with a higher risk of perioperative mortality and a higher risk of SWIs. Moreover, insulin therapy could be an independent risk factor for the lower survival rate. Surgeons are reluctant to use BIMA grafting in diabetic populations due to these concerns, and the use of BIMA has become an increasingly important matter of debate due to the prevalence of diabetes and the diffuse nature of diabetic coronary atherosclerosis.

In the present analysis, we found that BIMA grafting was associated with a significantly lower risk of postoperative hospital all-cause mortality than SIMA grafting in diabetic populations, which is consistent with previous studies. The use of BIMA appeared to be advantageous in diabetic patients because of the diffuse nature of diabetic coronary lesions and the small caliber of the coronary arteries. The internal mammary arteries were proved to enhance the production of endothelium-derived nitric oxide, which...
may ameliorate DM-induced endothelial dysfunction and susceptibility to progressive atherosclerosis and adverse cardiac-related events. Dorman et al revealed that, compared with SIMA grafting, diabetic patients undergoing BIMA grafting had a 23% improvement in long-term survival without differences in postoperative complications. Lytle et al demonstrated improved survival and a reduced need for repeat revascularization in diabetics with BIMA grafting; however, these authors also noted that this procedure should be avoided in patients with higher operative risks due to the prolonged cross-clamping time. Endo et al reported that the survival benefit of BIMA grafting was evident only in patients with preserved cardiac function (ejection fraction [EF] >40%), and that the benefit may be reduced with a lower EF. Toumpoulis et al demonstrated that the survival benefit of BIMA grafting was only evident in diabetic patients between 60 and 69 years of age, and that there was no survival benefit for diabetic patients aged >79 years. Similarly, Konstanty-Kalandyk et al reported higher mortality following BIMA grafting in older patients with lower EF. Conversely, Hirotani et al reported no survival benefits in diabetic patients undergoing BIMA vs. SIMA grafting, and Puskas et al did not support the routine use of BIMA in all non-insulin-dependent diabetic patients; these authors believed that survival benefits of BIMA grafting only existed in lower-risk non-insulin-dependent diabetic patients.

In this study we also compared mortality between diabetic and non-diabetic patients after BIMA grafting. No significant differences were found between groups, which is in line with some previous studies. For example, Hirotani et al did not detect any significant difference in mortality between groups, and no adverse effects of diabetes were apparent regarding survival and cardiac event–free rates. DM may not be a crucial factor when patients have poor cardiac function, with the predominant cardiac risks nullifying the survival benefits of BIMA grafts.

The major concern prohibiting the wide adoption of BIMA grafting in diabetic patients is the significantly higher risk of SWI. SIMA harvesting could result in a loss of 90% of the hemisternum blood supply, whereas BIMA harvesting could devascularize the entire sternum and interfere with healing of the sternal wound, especially in diabetics with microvascular changes. DM could jeopardize the immunological response against infection; thus, the harvesting of BIMA could lead to reduced perfusion of the hemisternum during the perioperative period, resulting in decreased sternal circulation and an increased risk of SWI and dehiscence. The Arterial Revascularisation Trial (ART) demonstrated that the incidence of SWI was significantly higher in the BIMA than SIMA group (3.5% vs. 1.9%, respectively), and Savage et al reported an SWI rate of 2.8% and 1.7% in BIMA and SIMA groups, respectively. Further, Hirotani et al reported significant differences in the incidence of SWI between diabetic patients treated with insulin (11%) or not (3.9%). In the present study, we found similar outcomes, namely that BIMA was associated with a significantly higher risk of postoperative SWI in diabetic patients, but no significant difference was detected between diabetics and non-diabetics. Previously, Stevens et al reported a similar ratio of hypoperfused to total sternal area between diabetics and non-diabetics, and similar rates of SWI and reoperation for bleeding.

Some recent studies have blunted the increased risk of SWI with BIMA grafting with skeletonized harvesting. Skeletonized harvesting is defined as dissection leaving the muscle attached to the sternal wall and minimizing sternal devascularization, in contrast with pedicled harvesting, in which the accompanying endothoracic fascia, parietal pleura, and the transversus thoracis muscle are also harvested. A skeletonized conduit could lead to improved sternal perfusion compared with pedicled harvesting. Stevens et al demonstrated that skeletonized harvesting may lower the risk of deep SWI in BIMA grafting by preserving sternal blood flow. Nevertheless, in the present study, in the skeletonized subgroup, patients undergoing BIMA grafting were less likely to have SWI than those undergoing SIMA grafting, whereas in the pedicled subgroup patients with BIMA grafts were more likely to have SWI than those with SIMA grafts. However, in both cases, the differences did not reach statistical significance. We believe the non-significant results could be due to a meticulous pedicled technique. Agrifoglio et al suggested that meticulous pedicled harvesting, careful wound closure, and keeping the sternal would dry postoperatively may have helped them achieve similar SWI rates between pedicled and skeletonized harvesting. Further, both Momin et al and Saja et al used electrocautery in pedicle harvesting to reduce sternal ischemia after dissection, believing that this technique would be most beneficial in patients with poor tissue healing power. Further, Puskas et al and Raja et al reported no significant difference in sternal wound complications between diabetic and non-diabetic patients with skeletonized and pedicled BIMA harvesting respectively. Nishi et al showed that sternal microcirculation damage after pedicled and skeletonized internal mammary artery harvesting was similar, indicating that the latter technique may not be advantageous. However, we believe that preoperative selection bias remains a confounding factor in the interpretation of results associated with skeletonized harvesting and the use of BIMA grafts, and that more randomized studies are needed in the future. In addition, many previous studies also showed that perioperative control of blood glucose could lower the risk of SWI. Calafiore et al reported that insulin-treated patients had prolonged survival than diabetic patients on oral-treatment. Lev-Ran et al recommended a 48-h postoperative glucose level of ≤200 mg/dL.

The present study is the first meta-analysis with a large sample size and using 2 different ways to explore BIMA harvesting in the diabetic population. In addition to mortality and morbidity, we investigated whether the effects of harvesting techniques. However, the results still require confirmation from randomized trials. This study also has other limitations. First, risk profiles and outcomes of CABG are changing dramatically with the rapid development of technology, and so the basic preoperative profile may be different in each study included in the analysis. Second, there may be other confounders affecting the results. Third, some of the survival data were derived from survival curves in previous studies, which may lead to problems associated with rounding.

Conclusions

CABG with BIMA grafting may be a feasible option for diabetic patients. The higher risk of SWI can be reduced by a meticulous harvesting technique and tight control of glucose concentration perioperatively. Further, CABG with BIMA harvesting is associated with a long-term survival probability.
benefit in diabetic patients. However, further randomized trials are still needed.

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Conflict of Interest
None declared.

References
9. Reference points.
14. Reference points.
19. Reference points.
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**Supplementary Files**

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