Commentary: Is the era of bilateral internal thoracic artery coming for diabetic patients? Yes, 取决于你问谁 [depends who you ask]

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Approximately 50% of patients undergoing coronary artery bypass grafting (CABG) have diabetes.¹ Survival after CABG in patients with diabetes is worse² because of the severity of coronary disease, extent of associated atherosclerotic vascular disease, and peripheral organ complications of diabetes. On the other hand, it has been shown that patients with diabetes may have the most to gain from bilateral internal thoracic artery (BITA) grafting, because they usually have a more severe, diffuse, and distal coronary disease, and BITA grafts possess well-documented unique histologic and physiologic properties³ superior to the radial artery (RA) and saphenous vein grafts (SVGs), which can ameliorate the diabetic-induced coronary endothelial dysfunction and accelerated atherosclerotic disease process. There have been numerous recent investigations seeking to define the preferred treatment in this sharply increasing subgroup of patients. The perceived higher risk of deep sternal wound infection (DSWI) related to BITA grafting and morbidity and the financial penalties of the complication have precluded the use of the best conduits (internal thoracic artery [ITA]) for diabetic patients.

In this issue of the *Journal*, Zhuo and colleagues⁴ present a large and comprehensive meta-analysis including 1 randomized controlled trial and 17 observational studies of 129,871 diabetic patients who underwent isolated CABG. Of those, 124,233 patients were operated on with the use of single internal thoracic artery (SITA) grafting and 5638 with the use of BITA grafting; 1128 received a BITA graft harvest with the skeletonized technique. The important findings of this investigation are that the skeletonized ITA harvest technique completely mitigated the difference between the SITA and BITA groups in terms of risk of DSWI rates (2.46% vs 2.48%, respectively), and in-hospital mortality rate was similar in both groups. BITA grafting significantly improved long-term overall survival

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Central Message

In patients with diabetes undergoing CABG, skeletonized BITA grafting seems to be the most important factor to increase longevity.

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(hazard ratio [HR], 1.41, $P < .001$) and long-term cardiac mortality-free survival compared with SITA (HR, 3.15; $P < .001$).

The strength of this report is the overall large cohort of diabetic patients, the use of propensity matching, and the subset analysis of patients undergoing the skeletonized ITA harvest technique. The authors also stratified the studies by insulin- versus non-insulin-treated patients and assessed the quality of the included observational studies by the appropriate scales and guidelines. Analysis of the 3 most important clinical implications of SITA versus BITA in diabetic patients showed the DSWI rate in skeletonized versus pedicled ITA harvest techniques, early and long-term survival differences, and cardiac-related mortality, and those provide an important adjunct to the current literature.

There are some obvious weaknesses to this study. First, most of the included studies were of a retrospective nature, many without matched cohorts. Second, we do not have data on preoperative blood glucose level control as reflected by the level of glycated hemoglobin (HbA1C). It is now recognized that HbA1C has a major impact on the long-term results of CABG in diabetic patients,⁵ and this was included in only 2 studies of this meta-analysis. The authors should be commended for emphasizing the lack of these important data in previous studies.

The use of the skeletonized ITA harvest technique is mandatory when using BITA grafts in general, but especially in diabetic patients, to preserve an adequate blood supply to the sternum and prevent DSWI.⁶ Many studies reported results on diabetic patients without stratifying or analyzing outcomes of the cohorts by the ITA harvest technique.⁷ Benedetto and colleagues,⁸ in their report of outcomes from the ART trial, have clearly shown that by using a skeletonized ITA harvesting technique, the risk of sternal wound infection with BITA grafting was similar to the risk of sternal wound infection after standard pedicled SITA harvesting, even in patients at higher risk, such as insulin-dependent diabetic patients, women, and those with increased body mass index. This correlates well with the findings of the current meta-analysis and with numerous previous studies.^{9,10} Unfortunately, the skeletonized ITA harvest technique is not universally accepted because of the learning curve and anticipated additional time required. A recent editorial has described the current barriers to multiarterial grafting, the proposed solutions, and the responsible parties in an outstanding informative table,¹¹ and the authors also referred to their recent report showing similar perioperative and long-term outcomes of RA and right ITA grafting in patients with diabetes,¹² but emphasized their preference to first use BITA grafting in diabetic patients. Raja and colleagues¹³ showed that BITA did not increase the operative risk, including DSWI rate, improved long-term outcomes, and improved overall survival, when compared with SITA/RA. This advantage appeared to be greater among diabetic and obese patients. Notably, Goldstone and colleagues,¹⁴ in their recent large report of 59,000 patients undergoing isolated CABG in California, did not stratify the diabetic cohort as a distinct subgroup or report the BITA harvest technique of skeletonized versus pedicled; thus, their conclusion of overall increased risk of sternal wound infection associated with the right ITA should be interpreted cautiously.

Gaudino and colleagues,¹⁵ in their patient-level report comparing the RA with SVG in CABG surgery, did not present any significant benefit by the use of the RA compared with SVG ($P = .35$) in the subgroup and interaction term analysis in the diabetic subgroup of patients included in the RADIAL project for the primary composite outcome of death, myocardial infarction, and repeat revascularization. In a study analyzing the outcome of patients undergoing CABG with the use of 1, 2, or 3 arterial grafts (of those, the RA [96%] and right ITA [4%] were the additional arterial grafts to the left ITA), Schwann and colleagues¹⁶ found that among the 4377 diabetic patients included, the survival advantage of using 2 arteries versus 1 artery was nonsignificant, whereas it was significant for 3 arteries versus 1 artery (HR, 0.74).

A benchmark study in the *Journal*¹⁷ analyzing the outcomes of approximately 12,000 consecutive diabetic

patients undergoing CABG concluded that the most important impact on 20-year survival was achieved by the use of BITA grafting. In another important report, Raza and colleagues¹⁸ showed that graft patency was not inferior in diabetic patients over 20 years follow-up and the patency rate of BITA remained greater than 90%, outperforming the SVG patency rate of 40%, and those rates were similar both in diabetic persons and in nondiabetic persons.¹⁸ Although the cohorts were not stratified by the type of diabetes and late coronary angiography was mostly symptom driven, these findings strongly support the use of skeletonized BITA in diabetic patients. Thus, on the basis of additional recent large national¹⁹ and international reports,²⁰ which show a clear survival advantage with BITA grafting in diabetic patients, it seems that the era of skeletonized BITA is coming for diabetic patients.

Moreover, one could argue that it may be unjustified to financially penalize for DSWI in CABG with BITA performed on patients with diabetes, when our goal is to provide the best conduit available to extend their survival. This approach could have been waived by defining skeletonized BITA grafting as a quality metric in CABG in general, and especially in diabetic patients, that should have been incentivized by payers, especially when substantial data exist that survival is not jeopardized even in the rare occasion of DSWI. The benefit of skeletonized BITA grafting seems to clearly outweigh the risk of DSWI in nondiabetic and diabetic patients.

We at the Mayo Clinic recently analyzed our data with a cohort of approximately 4000 consecutive diabetic patients requiring myocardial revascularization for multivessel coronary artery disease over 20 years of follow-up. The impact of multiarterial grafting on long-term survival was impressive compared with all other myocardial revascularization methods provided in diabetic patients,²¹ but when we further stratified the multiarterial grafting group into the BITA versus the SITA/RA subgroups, we found a significant long-term outcome difference between the 2 groups, with BITA grafting being significantly superior (soon to be published). Thus, in our practice, in diabetic patients with a reasonable life expectancy, skeletonized BITA grafting is used in preference to SITA/RA or SITA/SVG strategies unless a combination of increased clinical risk factors for DSWI clearly exist, for example, patient of female gender, morbidly obese, insulin-treated diabetes, uncontrolled preoperative blood glucose levels as reflected by an HbA1C level greater than 7%, and severe clinically apparent chronic obstructive pulmonary disease. We previously showed that extending BITA grafting to higher-risk patients in our practice, including to diabetic patients, benefited those subgroups with a significant long-term survival advantage.²² Notably, at our clinic, the ITA is routinely harvested almost exclusively by using the skeletonized harvest technique.²³

Our goal in every CABG operation and especially in diabetic patients should be the appropriate selection and harvest of conduits based on patient risk factors, clinical characteristics, predicted longevity, and the completeness of revascularization. Protocol-driven perioperative management and strict blood glucose level control are critically important. Future investigations are required to better define the ways we are treating the diabetic population. For this, the following are recommended: (1) standardization of our reports to include the most relevant and important risk factors (eg, HbA1C, insulin vs oral treatment, type 1 vs 2 diabetes); (2) stratification by the surgical ITA harvest techniques of skeletonized versus pedicled (mainly in retrospective analyses); (3) evidence-based requirement for the standard use of skeletonized ITA harvest technique in future designed prospective randomized trials; (4) accurate report of the non-left anterior descending coronary targets grafted including the severity of coronary stenoses; and (5) standardization of definition of DSWI.

The conduction of well-designed and carefully tailored randomized controlled trials (eg, the ART trial,²⁴ notwithstanding the puzzling outcome difference between the “intention to treat” and “as treated” cohorts) and the adoption of advanced medical treatments,²⁵ as well as newer surgical techniques, may be prudent to benefit this important and fast growing subgroup of patients.

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