EDITORIAL

Right for the Wrong Reasons: Implications of Data Insufficiency in Bilateral Versus Single Internal Thoracic Artery Grafting Analysis

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Coronary artery bypass grafting (CABG) is a major success story in modern medicine, providing improved quality of life and survival to millions around the world since its inception. Although the incident rate of CABG procedures has declined in recent years with improvements in medical therapy and percutaneous coronary intervention, recent evidence from randomized controlled trials has reconfirmed the impact of CABG in increasing the event-free survival of individuals with advanced coronary artery disease, and nearly 400 000 CABG procedures are still performed annually in the United States alone.[1–4] Further, outcomes for CABG have continued to improve, with observed mortality rates for isolated CABG improving from 2.4% to 1.9% at Society of Thoracic Surgeons database reporting institutions between 2000 and 2009. This improvement has occurred despite an increasing number of comorbidities in the population undergoing the operation during that time.[5]

Improvements in the long-term efficacy of CABG remain limited by (saphenous) vein graft failure and progression of native artery atherosclerosis.[6] Nearly 50% of coronary bypass vein grafts will have failed after 10 years, compared with the >90% patency rate exhibited by left internal thoracic artery (LITA) grafts, contributing to long-term mortality and morbidity in patients undergoing CABG as angina recurrence, myocardial infarction, and repeat revascularization.[6,7]

Given these limitations of the use of venous coronary bypass grafts, an inflection point in the history of surgical coronary revascularization occurred in 1986 with the definitive demonstration of a significant survival benefit with the use of LITA compared with saphenous vein grafts to the left anterior descending coronary artery (LAD).[8] Later studies suggested a lower rate of cardiac events and death from any cause starting as early as 3 to 4 years after surgery.[9] Since that discovery, the use of LITA-LAD grafts has steadily increased to >95% in the United States and carries a class I recommendation in published guidelines.[5,10,11]

Because of the demonstrated superiority of LITA-LAD grafting and the biological evidence supporting the superiority of arterial grafts in general, a long-standing interest has been developed in finding other opportunities to use arterial conduits for coronary bypass grafting. The use of bilateral internal thoracic artery (BITA) grafts has been at the center of these efforts for many years and has engendered considerable debate as to whether or not what is "good for the LAD" (use of the internal thoracic artery to provide an arterial bypass conduit) may also be beneficial for bypassing other coronary territories.

Initial retrospective investigations examining the use of BITA compared with single internal thoracic artery (SITA) coronary bypass (as a component of multivessel bypass) consistently demonstrated a significant mortality benefit with BITA grafting, with pooled data analyses suggesting separation of the survival curves only beginning somewhere between 5 and 10 years postoperatively, with 20% fewer deaths at 10 years and continued divergence of outcomes at 15 and 20 years.[7,12–14] Patients receiving BITA grafts in the majority of these studies tended to be younger and healthier than their comparators in the SITA (ie, LITA plus saphenous vein graft) groups, but statistical adjustments used to account for these differences supported the survival benefit of BITA versus SITA, and guidelines developed on the basis of these data recommended use of a second internal thoracic artery graft in appropriate CABG patients (class IIb and IIa recommendations in the United States and Europe, respectively).[6,10,11] Despite these recommendations, the use of secondary internal thoracic grafts remains limited. BITA utilization accounts for only <5% of CABG procedures in the United States and <10% of procedures in other Western countries in the latest available reports.[15,16]

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There are many likely reasons for the discrepancy between the recommended and actual use of BITA in CABG procedures. These include surgeon reticence to use BITAs because of the relatively greater technical complexity and length of the procedure associated with the harvest of a second internal thoracic artery graft, the increased risks of surgical infection and other complications associated with bilateral thoracic artery use, and the prolonged interval before survival benefits are derived from BITA utilization. Likewise, it has been argued that a second arterial conduit to a non-LAD target has less potential to affect overall survival than the single LITA to the LAD. Perhaps more significantly, though, a nagging excuse regarding the quality and validity of BITA versus SITA study data remains a major contributor to the persistently limited use of BITA grafting.

Gaudino and his coauthors in this issue of the *JAHA* may have thrown fuel on this fire in their report of a meta-analysis of 38 observational studies, including 174 205 total patients.[17] Their primary analysis of these studies confirms prior conclusions: "the use of BITA was associated with a statistically significant reduction of mortality at the end of follow-up (mean: 7.25 years [range: 2.1–16.3 years]) compared with SITA (IRR [incident rate ratio]: 0.74; 95% confidence interval, 0.69–0.80; $P<0.001$)." In contrast, their subanalysis of 12 propensity score matching (PSM) studies including 34 019 patients yielded an additional, potentially highly provocative finding: "the use of BITA was associated with a similar reduction [of mortality at 1 year as at the end of (7.4-year)] follow-up" (0.70 versus 0.77, respectively; $P=0.43$).[17]

Importantly, the authors suggest that this improved survival for the BITA group versus the SITA group as early as 1 year is unexpected and unexplained on the basis of benefits conferred by BITA grafting, because the saphenous graft attrition rate would not be expected to significantly affect outcomes as early as 1 year—when "the attrition rate of the SVGs [saphenous vein grafts] is still low and a survival difference attributable to a difference in graft patency is unlikely."[17] Although this supposition is countered by evidence from some studies showing saphenous vein graft failure of up to 20% at 2 years (ie, supporting even an early survival effect specifically attributable to BITA use), these data are in turn countered by evidence that the LITA-LAD conduit provides a mortality benefit regardless of secondary graft patency to other target vessels, which further suggests that factors other than BITA utilization may explain favorable outcomes seen in BITA study cohorts.

Gaudino and coauthors propose, therefore, that despite the presumed ability of PSM statistical correction to adequately account for operator bias in selecting patients for BITA versus SITA in the many retrospective studies on which conclusions about the survival benefits of BITA versus SITA have been based, such may not be the case. Instead, they argue, unmeasured confounders (other than the impact of graft patency) may account for the reported survival benefit of BITA in these observational series. This contention of unexplained confounders is supported by the lack of survival differences between BITA and SITA at early and intermediate time points in the randomized control studies exploring in this issue (in which all variables other than the use of BITA have presumably been eliminated).

What might such BITA outcome confounders be? Given that BITA procedures are, as noted, longer, technically more challenging, and associated with greater short-term risks of wound infection and other sternal complications, it is hard to argue that surgeons might not (consciously or subconsciously) select for BITA procedures those patients who are most likely to be able to avoid or withstand short-term complications and/or to garner longer term benefits compared with patients selected for SITA. In short, such patients, in measurable and perhaps unmeasurable ways, are more likely to be "healthier" or at least different from SITA patients.

Data from the study by Gaudino et al support the conclusion of group disparity in the retrospective studies on which recommendations of BITA procedures have been based: BITA patients in these studies were significantly younger, more likely to be male, and less likely to have diabetes mellitus or chronic obstructive pulmonary disease compared with SITA patients. In this context, Gaudino and colleagues argue that this 1-year data analysis suggests that when the choice of treatment is made based on physician judgment rather than randomization, nondefinable "cherry-picking" of patients makes it nearly impossible to extract and isolate the treatment effects from the already more favorable natural history of the "treated" group compared with a control group receiving current standard of care.

Propensity score–based statistical adjustment has gained widespread popularity and presumed validation as the most effective method to account for measured confounders and to adjust retrospective data to mimic randomized controlled trials. By calculating the proportional contribution of each confounder to a given patient's probability (or "propensity") for being prescribed the interventional therapy rather than standard care, propensity scoring seeks to estimate the impact on outcomes from this selection bias and subsequently remove this noise from the data.[11]

There is, however, an Achilles' heel inherent in PSM and most similar statistical methods. Propensity scoring adjusts for *measured* confounders. PSM and other such statistical corrections of retrospectively gathered data cannot capture factors that are not amenable to objective numerical measurement, such as subjective apparent quality of distal targets on preoperative coronary angiography. Gaudino et al

may have made this case that such unmeasured confounders may be the chief determinant of the survival advantage demonstrated in PSM sets comparing SITA versus BITA.

Ultimately, it is the responsibility of the individual surgeon to weigh the balance of evidence in the proper context to decide the optimal course of action for the individual patient. There is still insufficient information regarding the role of individual patient attributes such as diabetes mellitus, smoking, or patient age in the derivation of benefit from BITA grafting, and it may be specific subgroups that receive routine consideration for use of the technique in the future. Although the analysis by Gaudino and colleagues does not shed any light on this issue, it does highlight the need for good data that will provide the answer to the BITA-versus-SITA question.

The randomized control trials designed to ultimately answer the BITA-versus-SITA question have not demonstrated a survival benefit for BITA over SITA at the 5-year interim analysis time point, as originally expected given the known longer term time course of divergence of vein versus arterial graft attrition rates.[18–20] The long-sought answer to the BITA-versus-SITA question hopefully awaits the longer term outcomes of these trials.

Disclosures

None.

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