

Multiarterial grafting: The answer to that question



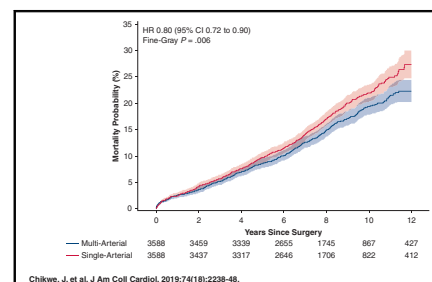
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I wish I had an answer to that because I'm tired of answering that question.

—Yogi Berra

Is there a benefit for multiarterial grafting (MAG) in patients undergoing coronary artery bypass surgery for multivessel disease? The question, which appeared to have been clearly answered on logical and evidentiary grounds, has re-emerged as unanswered. The well-established superior patency of arterial grafts compared with those constructed from saphenous veins would intuitively suggest that the goal of supplying the myocardium with improved perfusion would be better served with an arterial graft. Internal mammary artery (IMA) grafts tend to have a patency in excess of 90%, which remains relatively stable over time, whereas saphenous vein graft disease is progressive, occluding more than one third of grafts by 10 years.¹ Perhaps saphenous vein graft occlusion is subject to variations in harvesting technique² and antiplatelet and lipid-lowering therapy.^{3,4}

Early concerns regarding the patency of radial artery grafts appear to have been resolved through the appropriate selection of high-grade lesions and harvesting/management protocols, with carefully performed prospective randomized trials demonstrating superior patency compared with vein grafts.⁵ Validation of the theory would appear to reside in multiple meta-analyses demonstrating an actual survival advantage for bilateral versus single IMA grafting,⁶⁻⁹ as well as an emerging literature in support of the use of the radial artery as a second arterial conduit.¹⁰ Indeed, professional guidelines have become increasingly supportive of MAG, especially in younger patients (whose life expectancy is sufficient to realize the benefit) for patients with multivessel disease who undergo coronary artery bypass grafting (CABG) surgery.¹¹⁻¹³ And yet, as a profession, surgeons generally remain remarkably unimpressed. While the nationally representative Society of Thoracic Surgeons (STS) Adult Cardiac Surgery Database currently records a frequency of IMA usage in 99% range



10-year mortality of multiple vs single arterial grafting.

CENTRAL MESSAGE

The true value of multiarterial grafting remains an open question. Future research needs to provide more precise information regarding optimal patient selection.

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(especially since the Society added the use of an IMA for grafting of the left anterior descending artery as a quality metric in their composite measures), the frequency of bilateral internal mammary arterial (BIMA) grafting is a meager 5.7%, whereas radial artery grafting is recorded in only 6.8% of cases of isolated CABG surgery. Indeed, MAG as recorded in national databases has been relatively stable despite emerging evidence or has actually even declined over time.¹⁴

The reasons for this apparent discrepancy are multifactorial. Much of the emphasis on surgical outcome through which quality in cardiac surgery is evaluated relates to perioperative events. Mandatory state databases emphasize risk-adjusted mortality and length of stay, whereas the STS star ratings, although perhaps more circumspect, include carefully risk-adjusted mortality, complications, and process measures¹⁵—all of these metrics, although important and appropriate, focus on the immediate perioperative period. MAG tends to be more technically

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demanding, may require increased operative time, and may have specific patient-management requirements that are more challenging. BIMA grafting, especially without the more tedious skeletonized approach to harvesting, increases the risk of the dreaded complication of sternal wound infection. Indeed, even though not apparent in any of the multiple institutional retrospective studies, there may even be a slight increased risk of perioperative mortality in patients receiving a BIMA versus single internal mammary artery (SIMA), especially when performed by less-experience hands.¹⁶

Why then would a surgeon risk a more complex, time-consuming, and potentially deleterious operative approach for no recognized gain? The absence of long-term outcomes in the quality metrics is an area of active investigation, with projects to merge the STS with the Centers for Medicare & Medicaid Services and Centers for Disease Control and Prevention death registries, but these worthy projects have yet to be integrated into the metrics by which the profession assesses surgical quality.¹⁷ In addition, one cannot underestimate the technical subtleties of these techniques that are required for surgical success—nuances that reside in individual surgical practices and may not be readily known or generally integrated into all teaching programs. Lastly, until the provocative findings of the Arterial Revascularization Trial (ART), it was argued that there were no randomized control data to support the value of MAG.¹⁸ Although the criticism is valid, its application as a reason for surgical reluctance to adopt MAG is somewhat illogical, as the profession embraced the use of the IMA with arguably much less-compelling evidence. Indeed, even though virtually all guidelines support the use of a single IMA for bypass of the left anterior descending coronary artery as a Class I recommendation, the level of evidence is the same Class B as it is for MAG.

Into this somewhat-confusing arena enters the carefully performed analysis of MAG in the state of New Jersey recently published by Chikwe and colleagues.¹⁹ In reacting, one might reasonably wonder, with all of the meta-analyses of retrospective data supporting the use of MAG, do we really need confirmation from a single state registry? With the negative findings of the prospective randomized controlled ART, do we really need more retrospective data? With similar findings from other state registries, is there really any further information to glean?

The answer to each of these questions is a resounding YES. First, it should be noted that the methodologic care and sophistication with which multiple state databases were merged and data were analyzed are exemplary and, in and of itself, stand out as examples of how advanced statistical modeling can provide meaningful insight into retrospective data. To summarize, careful and successful merging of a mandatory state cardiac surgery database with 3 other mandated state databases recording all inpatient episodes, all cardiac catheterizations, and all

mortalities yielded 26,124 nonemergent, first-time isolated multivessel CABG patients, of whom 3647 (14%) underwent MAG. After thorough adjustment for baseline differences, MAG versus single arterial grafting was associated with comparable perioperative outcomes but a lower 10-year mortality in 3588 propensity-score matched pairs (15.1% vs 17.3%, $P = .01$), with lower myocardial infarction (hazard ratio [HR], 0.81, confidence interval [CI], 0.69-0.65) and reintervention (HR, 0.81, CI 0.67-0.99).

Multiple meta-analyses of BIMA versus SIMA grafting have recorded an ostensibly remarkably consistent HR around 0.80 for long-term mortality favoring the BIMA group.⁶⁻⁹ However, it should be noted that many of the actual studies (and even authors) in these analyses overlap with one another. Moreover, careful inspection of the actual studies demonstrates variability in outcome. Lastly, there is a marked difference among centers not only in individual surgical technique but also in the prevalence with which it was applied—20% in Cleveland,²⁰ 48% in Miami,²¹ and 73% in Calgary²²—suggesting marked differences in patient selection criteria. Moreover, even carefully constructed funnel plots cannot fully overcome the publication bias inherent in surgical advocacy—surgeons tend to report operative success. Individual-center data therefore tend to be more of a reflection of what can be accomplished rather than what generally is accomplished. Mandatory state registry data, in contrast, are a clearer reflection of broad spectrum of clinical reality. It is therefore not surprising to find a somewhat more moderate adjusted HR for mortality of 0.86 in the New Jersey experience.

Even if we were to accept this registry analysis as a more comprehensive reflection of clinical reality, how are we to interpret these findings in light of the negative results of the recent prospective randomized ART? Despite the generally accepted mantra that prospective randomized trials represent the greatest level of evidence, caution needs to be exercised in analyzing results. First, inclusion and exclusion criteria by design limit the interaction of potentially confounding variables and may lead to a study population that represents only a small proportion of patients who actually present for clinical care. This selection process is further confounded by variable patient consent, clinical site enrollment efficiency, and a little-recognized but potentially overwhelming feature of many surgical trials—lack of equipoise. Surgical trials tend to study techniques that require a particular area of expertise, such as MAG. To adequately evaluate the technique, the researchers must identify those surgeons sufficiently proficient to reliably perform the operation. In cases in which that technique is not necessarily standard, those surgeons who are most proficient are likely those who have become so specifically because they believe that that surgical approach is preferable. Therefore, by definition, they do not have true equipoise and may consequently be unwilling to enter into

trial those patients whom they feel would most benefit from their preferred approach. They chose rather to enter only those patients who have a more marginal perceived benefit, thereby biasing the study toward the null. One possible solution was adopted by the CORONARY²³ investigators, who randomized patients to on- versus off-pump CABG in centers with surgeons accomplished in both techniques; after randomization, patients were then assigned to the surgeon most experienced in that approach, thereby eliminating surgical bias at the point of study entry. Unfortunately, such an approach was not adopted by the ART investigators, and the study reports do not disclose what percentage of potentially eligible patients were actually enrolled. What did emerge clearly from this trial, however, is the inherent challenge of studying surgical approach—technique and competence is not uniform across sites; indeed, 13.9% of patients did not receive the treatment assigned, with huge variability among sites as to actual performance of BIMA grafting, with worse outcomes for those sites with greater crossover. Because radial artery grafting was permitted as per-surgeon preference, 21.8% of SIMA patients actually received a radial artery graft; as-treated analysis of patients receiving MAG versus single arterial grafting actually supported the survival benefit for MAG (adjusted HR, 0.81). In contrast to older historical data, adjunctive medical therapy compliance was quite high in the ART (75%-90%), perhaps ameliorating the survival differences between groups, as medication compliance has been shown to have a potentially dramatic impact on the long-term outcomes of CABG surgery.²⁴ Of note the 10 difference in survival noted in the New Jersey study was only 2.2%—ART (powered for a 5% absolute and 20% relative difference) was underpowered for such a finding. In fact, a similar state registry study emerging from New York, which included some of the same authors as the New Jersey study, reported similar benefits for MAG with a 7-year composite outcome of mortality, acute myocardial infarction, and stroke versus single arterial grafting of 20.2% versus 22.8%, adjusted HR, 0.88 (CI, 0.83-0.93).²⁵ This combined end point is nearly identical to the 0.90 HR for the same end point in the ART trial; however, with a sample less than one third that of the registry data, the conclusion from the ART data was the reverse. The impact of patient selection and the importance of balancing registry data with randomized trials is further emphasized by careful examination of the considerable difference in patient characteristics between the ART patients and those found in the New Jersey study: body mass index 28 versus 34, prevalence of diabetes 24% versus 47%, hypertension 77% versus 92%, peripheral vascular disease 7% versus 17%, previous stroke 3% versus 8%, previous percutaneous coronary intervention 16% versus 24%. We will spare the reader the dramatic *P* values, but one can readily begin to recognize that the New Jersey patients

are much closer to what we find in our clinical practices. Although the enthusiasm and tenacity of the ROMA investigators is to be greatly admired,²⁶ as there will likely be extremely valuable information that will emerge, those findings will nonetheless need to be evaluated through the familiar compass of patient selection and sample size.

Lastly one might wonder, with data available from California,²⁷ New York State,²⁵ and the province of Ontario²⁸ and British Columbia,²⁹ all of which have mandatory data-entry requirements, what additional information might be gleaned from yet another state registry report. The first point of interest is, despite reasonably similar study time periods, the variability in use of MAG: 9.9% in California, 14.0% in New Jersey, 19.9% in New York, 22.5% in Ontario, and 27.8% in British Columbia. None of these registries reported a difference in operative mortality after risk adjustment; however, all reported a long-term survival benefit that varied between an adjusted HR of 0.84 and 0.86 in New Jersey and New York and 0.79, 0.80, 0.79 in California, Ontario, and British Columbia, the latter 3 of which are remarkably similar to what has reported in multiple meta-analysis of retrospective surgical series. Subtle differences in patient selection, clinical practice patterns, possible impact of public reporting, and variations in analytical approach (all of which were carefully constructed in these studies) may account for the differences in reported treatment effect. However, if we adopt the relatively conservative estimate of Chikwe and colleagues of a 2.2% survival benefit at 10 years among patients who surgeons tend to find potentially appropriate for MAG—with a number needed to treat of nearly 40, the major challenge is no longer whether MAG is superior to single arterial grafting, but rather, who specifically are those patients who will be most likely to derive benefit. The Chikwe study clearly sets us along this path with their findings that no survival benefit was observed in patients >70 years of age, nor those with ejection fraction ≤30%. Issues of conduit selection, surgical technique, myocardium at risk, patient frailty, patient self-care, and support are all difficult to tease out from large registry data. However, the fact that reliable information regarding actual surgical practice in a large patient population can be analyzed so skillfully as was performed by these authors certainly provides valuable information to inform further more precise investigation. Perhaps future merger of registry with direct clinical data in an artificial intelligent environment will help to support more granular insight into patient selection. Unlike our hapless prophet of the baseball lore, I am not yet tired of trying to answer this question.

Conflict of Interest Statement

The author reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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