See Article page 1093.

Commentary: Isn't evidence a prerequisite for evidence-based medicine?

Ana Karen Velez, MD, and Jennifer S. Lawton, MD

Properly blinded and unbiased randomized controlled trials provide the greatest level of evidence to inform clinical care. Such trials comparing the use of multiarterial grafting (MAG) with the use of single arterial grafting (SAG) for coronary artery bypass grafting (CABG) in women have not been conducted. Robinson and colleagues¹ provide a meta-analysis of 6 propensity-matched observational studies published between 2005 and 2020 that included outcomes following CABG reported by sex and stratified into MAG versus SAG strategies. In 32,793 female patients, the rate of MAG use ranged between 14% and 35%. There was a low incidence of diabetes (41%-53%), and no patient had obesity, both of which are felt by some surgeons to be contraindications to bilateral internal mammary artery (BIMA) use. The authors found that in contrast to women who received SAG, women with MAG had lower long-term mortality and spontaneous myocardial infarction, with no difference in operative mortality and stroke. The lack of difference in operative mortality is not surprising, as the benefit of MAG is seen in the long term, although the authors found no difference in long-term mortality when comparing studies with <5 or >5 years' follow-up.

From the Division of Cardiac Surgery, Department of Surgery, Johns Hopkins School of Medicine, Baltimore, Md.

Disclosures: The authors 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.

Received for publication Aug 12, 2021; revisions received Aug 12, 2021; accepted for publication Aug 13, 2021; available ahead of print Aug 19, 2021.

Address for reprints: Jennifer S. Lawton, MD, Division of Cardiac Surgery, Department of Surgery, Johns Hopkins School of Medicine, 1800 Orleans St, Zayed 7107, Baltimore, MD 21287 (E-mail: jlawton4@jhmi.edu).

J Thorac Cardiovasc Surg 2023;165:1099-101

0022-5223/\$36.00

Copyright © 2021 by The American Association for Thoracic Surgery

<https://doi.org/10.1016/j.jtcvs.2021.08.030>

CENTRAL MESSAGE

Randomized controlled trials are needed to determine if multiarterial grafting improves long-term survival compared to single arterial grafting in women undergoing coronary artery bypass grafting.

An important finding noted by the authors was that the treatment effect was inversely correlated to the sample size. When they included only the 3 largest series, there was no difference in survival between MAG versus SAG. Interestingly, the smaller studies were also the oldest, had the greatest percentage of MAG use, and included studies with 100% radial use (no BIMA) (Table 1).²⁻⁷

- The 3 smallest studies had an average MAG use of 31%, whereas the 3 largest had an average use of 24%. A greater use of MAG use (with only radial) suggests surgeons may have been dedicated coronary surgeons and experience with arterial grafting.
- More contemporary studies may have had better surgical techniques and guideline-directed medical therapy.
- The diversity of propensity matching strategies between studies, and specifically, the introduction of BIMA grafting (in the 2 larger studies), similar to the Arterial Revascularization Trial (ART),⁸ may have introduced the variable of surgeon experience with BIMA grafting.^{8,9}

Despite differences in the propensity-matched studies summarized in this meta-analysis, Robinson and colleagues¹ have provided surgeons with the best data currently available to address the question of potential benefits derived in women who receive MAG rather than SAG

TABLE 1. Studies included in meta-analysis by Robinson and colleagues¹ in order of date of publication

Study	% MAG use	% Radial	PS matching
Lawton et al, 2005 ²	35 (301/862)	100	Women with SVG vs women with radial
Schwann et al, 2012 ⁴	33 (656/1971)	100	Women with SVG vs women with radial
Dimitrova et al, 2013 ⁶	25 (332/1339)	100	Women with SVG vs women with radial
Pullan et al, 2015 ⁷	30 (728/2459)	100	Women with SVG vs women with radial
Gaudino et al, 2020 ³	14 (2101/15,247)	14	Women with SAG vs women with MAG*
Tam et al, 2021 ⁵	27 (2961/10,915)	62	Women with SAG vs women with MAG*

Date is date of publication. %MAG = N MAG/Overall N. MAG, Multiarterial grafting; PS, propensity score; SVG, saphenous vein graft; SAG, single arterial grafting. *Bilateral internal mammary artery or radial included.

during CABG. The authors appropriately note the need for randomized trials in women and enrollment of more women in clinical trials.

Women remain underrepresented in cardiovascular clinical trials (Figure 1). In more than 230,000 patients enrolled in cardiovascular trials, Preventza and colleagues¹⁰ noted that women made up only 28% of participants. The female patient participation-to-prevalence ratio was low (0.64, well below what is considered equivalent enrollment) in 85 cardiovascular trials pertaining to CABG and decreased between 2008 and 2012.¹⁰ Similarly, women have been underrepresented in clinical trials evaluating cardiovascular devices, and, thus, strategies have been developed to increase the participation of women (including Rigor and Reproducibility mandates by National Institutes of Health).¹¹⁻¹³

Several challenges contribute to the slow progress in enrolling more women in clinical trials, including a lower percentage of women undergo CABG compared with men, the fact that women are less likely to receive arterial grafting, and women are underrepresented as

Principal Investigators of clinical trials. Women comprise approximately 25% of patients undergoing isolated CABG and they are less likely to receive MAG compared with men.^{2,14-19} This may be somewhat of a vicious cycle, as there is a perception that there is no strong evidence to support the use of MAG in women, there may be treatment bias, or there may be a perception that there are more contraindications to MAG use in women. In addition, Nguyen and colleagues²⁰ note that women are underrepresented as Principal Investigators of cardiac surgery clinical trials and that this may affect equitable recruitment and retention of female patients.

Clinical trials with a larger representation of women are needed to test the hypothesis generated—that MAG provides long-term survival in women compared with SAG—by Robinson and colleagues. Ultimately, high-quality evidence from randomized controlled trials will answer these important questions, provide evidence for evidence-based medicine, and guide us to make the best decisions for all of our patients.

Multiarterial Grafting Clinical Trials

FIGURE 1. Women are underrepresented in clinical trials involving coronary artery bypass grafting.

References

1. Robinson NB, Lia H, Rahouma M, Audisio K, Soletti GJ, Demetres M, et al. Coronary artery bypass with single versus multiple arterial grafts in women: a meta-analysis. *J Thorac Cardiovasc Surg*. 2023;165:1093-8.
2. Lawton JS, Barner HB, Bailey MS, Guthrie TJ, Moazami N, Pasque MK, et al. Radial artery grafts in women: utilization and results. *Ann Thorac Surg*. 2005; 80:559-63.
3. Gaudino M, Samadashvili Z, Hameed I, Chikwe J, Girardi LN, Hannan EL. Differences in long-term outcomes after coronary artery bypass grafting using single vs multiple arterial grafts and the association with sex. *JAMA Cardiol*. 2020;6: 401-9.
4. Schwann TA, Engoren M, Bonnell M, Clancy C, Habib RH. Comparison of late coronary artery bypass graft survival effects of radial artery versus saphenous vein grafting in male and female patients. *Ann Thorac Surg*. 2012;94:1485-91.
5. Tam DY, Rocha RV, Fang J, Ouzounian M, Chikwe J, Lawton J, et al. Multiple arterial coronary bypass grafting is associated with greater survival in women. *Heart*. 2021;107:888-94.
6. Dimitrova KR, Hoffman DM, Geller CM, Ko W, Lucido DJ, Dincheva GR, et al. Radial artery grafting in women improves 15-year survival. *J Thorac Cardiovasc Surg*. 2013;146:1467-73.
7. Pullan M, Kirmani BH, Conley T, Oo A, Shaw M, McShane J, et al. The effect of patient sex on survival in patients undergoing isolated coronary artery bypass surgery receiving a radial artery. *Eur J Cardiothorac Surg*. 2015;47:324-30.
8. Taggart DP, Benedetto U, Gerry S, Altman DG, Gray AM, Lees B, et al. Bilateral versus single internal-thoracic-artery grafts at 10 years. *N Engl J Med*. 2019;380: 437-46.
9. Benedetto U, Altman DG, Flather M, Gerry S, Gray A, Lees B, et al; Arterial Revascularization Trial Investigators. Incidence and clinical implications of intraoperative bilateral internal thoracic artery graft conversion: insights from the Arterial Revascularization Trial. *J Thorac Cardiovasc Surg*. 2018;155: 2346-55.e6.
10. Preventza O, Critsinelis A, Simpson K, Olive JK, LeMaire SA, Cornwell LD, et al. Sex, racial, and ethnic disparities in U.S. cardiovascular trials in more than 230,000 patients. *Ann Thorac Surg*. 2021;112:726-35.
11. National Institutes of Health. Guidance: Rigor and Reproducibility in Grant Applications. Available at: <https://grants.nih.gov/policy/reproducibility/guidance.htm>. Accessed July 26, 2021.
12. Ghare MI, Chandrasekhar J, Mehran R, Ng V, Grines C, Lansky A. Sex disparities in cardiovascular device evaluations: strategies for recruitment and retention of female patients in clinical device trials. *JACC Cardiovasc Interv*. 2019;12: 301-8.
13. Kuehn BM. Boosting women's participation in cardiovascular trials: more work needed to match real-world epidemiology for heart failure, coronary artery disease, and acute coronary syndrome. *Circulation*. 2018;138:1366-7.
14. Mickleborough LL, Carson S, Ivanov J. Gender differences in quality of distal vessels: effect on results of coronary artery bypass grafting. *J Thorac Cardiovasc Surg*. 2003;126:950-8.
15. Aldea GS, Gaudiani JM, Shapira OM, Jacobs AK, Weinberg J, Cupples AL, et al. Effect of gender on postoperative outcomes and hospital stays after coronary artery bypass grafting. *Ann Thorac Surg*. 1999;67:1097-103.
16. Parolari A, Dainese L, Naliato M, Polvani G, Loardi C, Trezzi M, et al. Do women currently receive the same standard of care in coronary artery bypass graft procedures as men? A propensity analysis. *Ann Thorac Surg*. 2008;85: 885-90.
17. Attia T, Koch CG, Houghtaling PL, Blackstone EH, Sabik EM, Sabik JF. Does a similar procedure result in similar survival for women and men undergoing isolated coronary artery bypass grafting? *J Thorac Cardiovasc Surg*. 2017;153: 571-9.
18. Jabagi H, Tran DT, Hessian R, Glineur D, Rubens FD. Impact of gender on arterial revascularization strategies for coronary artery bypass grafting. *Ann Thorac Surg*. 2018;105:62-8.
19. Jawitz OK, Lawton JS, Thibault D, O'Brien S, Higgins RSD, Schena S, et al. Sex differences in coronary artery bypass grafting techniques: a STS database analysis. *Ann Thorac Surg*. July 16, 2021 [Epub ahead of print].
20. Nguyen Q, Luc JGY, Lawton JS, Chikwe J, Cornwell LD, Simpson K, et al. Gender representation among Principal Investigators in cardiac surgery clinical trials in the United States: the glass ceiling and room for improvement. *Ann Surg*. June 2, 2021 [Epub ahead of print].