Meta-analysis of the messenger: The price of small trials diverting our attention from the real target

Fraser Rubens, MD, MSc, FACS, FRCSC

From the Department of Surgery, University of Ottawa Heart Institute, Ottawa, Ontario, Canada.

Disclosures: Author has nothing to disclose with regard to commercial support.

Received for publication Aug 17, 2015; accepted for publication Aug 18, 2015; available ahead of print Sept 15, 2015.

Address for reprints: Fraser Rubens, MD, MSc, FACS, FRCSC, Professor of Surgery, University of Ottawa Heart Institute, 40 Ruskin St, Ottawa, Ontario K1Y 4W7 (E-mail: frubens@ottawaheart.ca).

J Thorac Cardiovasc Surg 2016;151:78-9

0022-5223/\$36.00

Copyright © 2016 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2015.08.057>

The meta-analysis of Kowalewski and colleagues¹ appearing in this issue of the *Journal* has presented a thorough comparison of on- and off-pump coronary artery bypass grafting with regard to 3 perioperative outcomes: death, myocardial infarction, and stroke. Data were presented to confirm that there was no selection bias in the articles, and Forest plot analyses were performed to provide the reader with confidence that the trials were relatively homogeneous as the confidence intervals generally overlapped. Kowalewski and colleagues¹ concluded that there is no definitive evidence of clinical superiority of either strategy relative to the other with regard to the first 2 outcomes; however, there was a significant association between on-pump surgery and the risk of stroke.

Meta-analyses were originally designed to address the complex issue of combining underpowered studies to derive a more precise estimation of a treatment effect. Some believe that in the hierarchy of evidence, meta-analyses trump randomized, controlled trials if the latter are small, and in fact the meta-analysis is currently the most frequently cited form of clinical research.² The assumption that a meta-analysis uniformly represents the final viewpoint of an area of research is not necessarily warranted, however, and readers should be wary. Meta-analyses are limited in their validity, because the pooled results incorporate the biases of the individual trials as well as prejudice resulting from trial heterogeneity.³ In fact, meta-analyses may inaccurately predict the outcomes of subsequent large randomized, controlled trials on the same topic in as many as 35% of cases.³ The fallibility of meta-analyses has been highlighted by cases in which they were contradicted by a single well-designed large randomized, controlled trial.^{4,5}

So where does that leave the surgeon in terms of advocacy for the patient for the best approach? Do we have confidence that the results of this meta-analysis in particular should influence one's practice such that we should routinely advocate for an off-pump strategy?

First of all, I think we can lay the question of perioperative myocardial infarction and 30-day mortality safely to

Fraser Rubens, MD, MSc, FACS, FRCSC

Central Message

Meta-analysis is a valuable statistical technique to increase the precision of estimated treatment effects, but it has limitations.

See Article page 60.

See Editorial page 4.

bed. The answer that one can take away from this study is quite definitive; there is no evidence to support a benefit of off-pump surgery in terms of early all-cause mortality or perioperative myocardial infarction. That does not mean that there isn't a benefit of course, but it implies that if there is a benefit, it is so small that one would need a huge sample size to prove it, thus making it of questionable clinical relevance.

Addressing the stroke question, however, does require a detailed look at the results. Specifically, Kowalewski and colleagues¹ stated that the risk of stroke was diminished by 28% and the number needed to treat with the off-pump strategy to prevent a single stroke was 152. But what is the effect of the wide variability in trial sizes in this outcome? Although attempts are made to control for trial quality, one is skeptical of clinical results coming from relatively small randomized trials. Specifically, many of these trials have likely not undergone the scrutiny of peer-review and a priori statistical assessment, and by extension they may suffer from compromised trial methodology. In the largest randomized trials (which accounted for the majority of patients in the sample), there was certainly no difference in stroke.⁶⁻⁸ Excluding trials with fewer

than 200 patients per group, one still ends up analyzing more than 5400 patients per group with stroke rates of 1.4% in the off-pump group and 1.6% in the on-pump group, an absolute risk reduction of 0.2%. This translates to a number needed to treat to prevent a single stroke of 500 patients and the sample size required to prove this difference would exceed 58,000 patients per group. One must therefore assimilate this information with the worrisome evidence that off-pump surgery is associated with an increased incidence of incomplete revascularization,^{9,10} which is likely related to the subsequent increased need for repeated revascularization.¹¹

Barring the advent of some new dramatic technical evolution for off-pump surgery, I therefore believe that this question has been answered, and we can lay it to rest and stop it from distracting us from the more pressing strategic questions. Specifically, we need to focus our attention on the targets of greatest value to our patients: long-term survival, repeated revascularization, and angina-free survival. And the strategy with the greatest yield that is in the grasp of every cardiac surgeon is multiple arterial revascularization. We are doing a disservice to patients when we exhaust our resources to graft a single internal thoracic artery and veins with an off-pump approach when we should be grafting a minimum of 2 arterial grafts with the most reliable and safe strategy in our hands, be that off pump or on pump. Off-pump surgery is a means to an end. It is the messenger, not the message.

References

1. Kowalewski M, Pawliszak W, Malvindi PG, Bokszanski MP, Perlinski D, Raffa GM, et al. Off-pump coronary artery bypass grafting improves short-term outcomes in high-risk patients as compared to on-pump coronary artery bypass grafting: meta-analysis. *J Thorac Cardiovasc Surg.* 2016;151:60-77.e58.
2. Patsopoulos NA, Analatos AA, Ioannidis JP. Relative citation impact of various study designs in the health sciences. *JAMA.* 2005;293:2362-6.
3. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. *N Engl J Med.* 1997;337:536-42.
4. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med.* 2007;356:2457-71. Erratum in: *N Engl J Med.* 2007;357:100.
5. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, et al. Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet.* 2009;373:2125-35.
6. Diegeler A, Börgermann J, Kappert U, Breuer M, Böning A, Ursulescu A, et al; GOPCABE Study Group. Off-pump versus on-pump coronary-artery bypass grafting in elderly patients. *N Engl J Med.* 2013;368:1189-98.
7. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al; CORONARY Investigators. Off-pump or on-pump coronary-artery bypass grafting at 30 days. *N Engl J Med.* 2012;366:1489-97.
8. Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, et al. Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med.* 2009;361:1827-37.
9. Synnnergren MJ, Ekroth R, Odén A, Rexius H, Wiklund L. Incomplete revascularization reduces survival benefit of coronary artery bypass grafting: role of off-pump surgery. *J Thorac Cardiovasc Surg.* 2008;136:29-36.
10. Robertson MW, Buth KJ, Stewart KM, Wood JR, Sullivan JA, Hirsch GM, et al. Complete revascularization is compromised in off-pump coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 2013;145:992-8.
11. Lamy A, Devereaux PJ, Prabhakaran D, Taggart DP, Hu S, Paolasso E, et al; CORONARY Investigators. Effects of off-pump and on-pump coronary-artery bypass grafting at 1 year. *N Engl J Med.* 2013;368:1179-88.