Response to Letter by Tourmousoglou et al

Response:

In the response to our article entitled “Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting,” Dr Tourmousoglou and colleagues mention important issues concerning the applicability/generalizability of the randomized clinical trials of less invasive surgery. I would add that learning curve/surgical skill and ability to mask patients and surgeons are 2 important methodological issues that can potentially limit the generalizability of the results found in this evidence synthesis and surgical evidence in general.

Surgeons cut and sew heart chambers and coronary vessels. It is not a surprise that surgical skill is a critical contributor to good outcomes. There is a long learning curve to achieve excellence in off-pump coronary bypass surgery (CABG), and it has a great impact on the outcomes of this procedure. It is therefore understandable that trials of this new way of operating are hotly debated. But there is a good solution to this problem when conducting clinical trials: consider embarking on a clinical trial of less invasive surgery only after mastering this procedure. Not many investigators of off-pump surgery adopted this strategy. As we illustrated in our report, in larger trials there was little or no difference between off-pump and traditional CABG in terms of the number of grafts implanted (a proxy for learning curve). Although this is a limitation, it should not serve as a justification for not adopting the technique. If it is possible to achieve excellence with this technique and have better outcomes, then efforts should be made to develop curricula for surgical training in off-pump surgery.

To diminish the effect of inability to mask (blind) patients and surgeons, one can use good methods of allocation concealment. As an example, one can use a centralized telephone system rather than sealed envelopes and thus separate the person who performs the allocation concealment from the surgeon who recruits the patients. Furthermore, one can announce the allocation in the operating room just before the start of the surgery, with both pump and off-pump instruments ready to be used. This will help to reduce patients’ and surgeons’ interference in the allocation process after randomization is announced. In our evidence syntheses we found that few trials used these strategies to cancel the allocation. We hope that reporting of this finding will help them to conduct better studies in the future.

Dr Tourmousoglou and colleagues state that many trials of off-pump surgery are quite small. This is not unique to off-pump surgery. The benefit of evidence synthesis is that underpowered clinical trials can be combined to inform decision-making in the absence of a large definitive trial. Whereas in theory there is a potential that some imbalance can occur in individual studies attributable to small sample size, systematic review and metaanalysis have the potential to overcome this limitation by the inclusion of many trials. It is unlikely that imbalance will systematically favor one group or another, as these imbalances should cancel out when combining many underpowered trials. It is interesting that off-pump surgery is one of the most studied operations in surgery, and yet it did not get adopted by cardiothoracic surgeons as fast as many other minimally invasive or less invasive surgeries that had much less evidence behind them. Some surgeons suggest that there might be a generational issue among surgeons, with the new generation eager to learn this new technique.

The use of various definitions for the events in the trials is also not a phenomenon unique to off-pump surgery. Within each study, definitions were applied to study groups in the same fashion. Thus, this is it not likely to substantially bias results unless the evidence of benefits or harms is found only in trials with “loose” definitions (limited to less serious events) but generalized to all definitions. This clearly was not the case in off-pump studies.

Inclusion of less severely ill patients in the trials of off-pump CABG does affect the generalizability of the results. It certainly would be hard to apply this evidence to much sicker groups of patients, and it would be important to study these groups in future trials. However, I would mention that a number of observational studies of off-pump surgery in “real life” practice reported reassuring results.

Certainly, the concern about the long-term problems with off-pump surgery, such as the need for reintervention, appears to be valid, even though this adverse outcome is less likely to occur in experienced centers. We agree that large trials can be helpful when conducted with the highest methodological rigor and incorporating the methodological issues discussed above. But we would like to add a note of caution for surgeons seeking absolute certainty: such a thing will hardly exist even after extensive research, and we should learn to make decisions under uncertainty. In the development of evidence-based medicine, we have witnessed too many instances of missed opportunities to save lives: the case of delayed recommendations for thrombolytic therapy or β-blocker therapy after myocardial infarctions is a vivid reminder from the past.

Disclosures

Dr Artyom Sedrakyan is employed by the Agency for Healthcare Research and Quality (AHRQ). The author of this article is responsible for its contents. No statement in this article should be construed as an official position of the Agency for Healthcare Research and Quality or the US Department of Health and Human Services.

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References

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