**LETTERS TO THE EDITOR**

**Drug-Eluting Stents for Saphenous Vein Graft Lesions**

Wiisanen et al. (1) performed a meta-analysis of 23 studies comparing drug-eluting stents (DES) with bare-metal stents for saphenous vein graft lesions, and they demonstrated the superiority of DES in reducing death, myocardial infarction, and target vessel revascularization. Eleven meta-analyses have been published thus far on the same subject in a little over 1 year, whereas the number of primary studies has remained more or less the same (29 studies involving 7,994 patients) (2). All these meta-analyses have yielded similar results showing that DES reduced the risk of major adverse cardiac events predominantly driven by a lower target lesion revascularization. So how does the meta-analysis by Wiisanen et al. (1) add new information? Specifically, the investigators have included “duplicate” data. They have included 4 randomized controlled trials. In reality, there are only 2 randomized comparisons of DES with bare-metal stents for saphenous vein graft lesions—the SOS (Stenting of Saphenous Vein Grafts) and RRISC (Reduction of Restenosis In Saphenous Vein Grafts With Cypher Sirolimus-Eluting Stent) trials. Wiisanen et al. (1) have included both short- and long-term outcome studies for the RRISC trial (same patient population counted twice). The third included randomized controlled trial is a subgroup analysis from the BASKET (Basal Stent Cost-Effectiveness Trial) and not a randomized comparison. Analyzing the data on the same patients more than once may lead to significantly biased estimates of efficacy and safety (3).

We identified 11 meta-analyses (and perhaps a few more in the pipeline) with more than 8 published in <6 months by different investigators (Online Table 1). Is there any “novelty” in terms of incremental scientific value of these publications or are they just redundant? Which of these 11 papers should be cited and what would be the criteria? Is the criterion the number of studies and included patients? Publication date? Quality of the meta-analysis? Or the reputation of the journal? These issues and their potential negative impact have been raised by a few reports (3–5). It might be a consequence of multiple cardiology journals with rapid review turnaround times, online publication ahead of print, and so forth, so we believe reorganizing the process in which meta-analyses are conceived, designed, executed, and reviewed could help address some of these issues (4,5). Authors should be required to submit their proposals in a central registry like clinicaltrials.gov or others recently proposed (5). Submitted meta-analysis should be rigorously evaluated for accuracy of data and careful scrutiny to avoid issues such as overlapping/redundant data. Further evaluation of statistical methods by a dedicated statistician (as mandated by a few journals) would also be helpful. Journals should lay out comprehensive guidelines for meta-analysis in their “Instructions for Authors” section.

*Abdul Hakeem, MD
Tarek Helmy, MD

**REFERENCES**


**APPENDIX**

To see a table with the details of the 11 meta-analyses referred to in the text, please see the online version of this paper.

**Drug-Eluting Stents for Saphenous Vein Graft Interventions**

I read with interest the meta-analysis by Wiisanen et al. (1) regarding stents in saphenous vein graft interventions. I was surprised to see that the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) trial is counted twice in the analysis of the randomized controlled trials. This study included 38 patients in the drug eluting stents (DES) and 37 in the bare-metal stents categories. The initial publication reports the 6-month outcome (2), whereas the second publication reports long-term outcome of the same patients (3). Counting these patients twice is obviously wrong. Unfortunately, this error leads to wrong conclusions such as, for example, the conclusion from the correct analysis of mortality in
randomized controlled trials should be that DES are associated with increased mortality (17 deaths of 113 DES and 4 deaths of 89 bare-metal stents; p = 0.027). This is in contradiction to the main conclusion of this manuscript that “DES use was associated with improved mortality.” It is hard, if not impossible, to justify such a conclusion even if it is supported by nonrandomized cohort trials data when the randomized controlled trials data are contradictory. I believe the message to the readers from this manuscript is misleading, therefore, I believe the entire manuscript should be rewritten with the correct analysis and conclusions.

*Yeoseph Rozenman, MD

**E. Wolfson Medical Center
Department of Cardiology
POB 5
Holon 58100
Israel
E-mail: yeosephr@post.tau.ac.il

doi:10.1016/j.jcin.2011.02.007

REFERENCES


Reply

We would like to thank the authors of the letters for their interest in our paper (1). We agree that the RRISC (Reduction of Restenosis In Saphenous vein grafts with Cypher sirolimus-eluting stent) and DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction of Restenosis In Saphenous vein grafts with Cypher stent) trials included the same patients (2,3). On the basis of the pre-specified criteria for the meta-analysis, we included all published trials on the use of drug-eluting stents (DES) versus bare-metal stents (BMS) in vein graft percutaneous coronary intervention (PCI). Because the included studies were weighted on the basis of study size, and because this particular study was small in size (only 75 patients), we did not anticipate any significant impact of this strategy on the overall conclusions. We analyzed the data with and without inclusion of the short-term RRISC data and found no significant differences in the conclusions. Drug-eluting stent use was associated with reduced mortality when early and delayed RRISC data were included (odds ratio [OR]: 0.72; 95% confidence interval [CI]: 0.58 to 0.89), and there was no significant difference when the early RRISC data were excluded (OR: 0.72; 95% CI: 0.58 to 0.89) (Fig. 1A). Similarly, DES use—including early RRISC data—led to reduced target vessel revascularization (OR: 0.56; 95% CI: 0.40 to 0.77). Excluding these data, there was no significant change in the estimated benefit of DES on target vessel revascularization (OR: 0.58; 95% CI: 0.42 to 0.77) (Fig. 1B). Identical conclusions were made when other adverse outcomes were analyzed with and without inclusion of early RRISC events.

Despite the statistically significant reduction in mortality associated with DES in our overall analysis, we clearly stated in the discussion that this is possibly caused by selection bias. We emphasized that this finding was primarily noted in the cohort trials and not in randomized trials, hence reinforcing the notion that it might have been driven by interventional operators selecting healthier patients to implant DES. We referenced the work by Shishehbor et al. (4), who made similar observations. Because of that concern, we opted not to state that mortality benefit in our final conclusions paragraph in the published paper (1). The meta-analysis of the body of literature supports the fact that DES use in vein graft PCI is safe and not associated with increased risk of adverse events or mortality, despite the limitations and as noted in the conclusions paragraph. This remains our conclusion and that of others who performed similar meta-analyses (5–9).

We agree with the criticism of the multiplicity of meta-analyses performed on the same subject. We believe this is the effect of the publication and peer-review process as it works today. It is likely that—given the time it takes from writing the manuscript to submission, review, and response to editorial revisions—most of these manuscripts were making their way through the process at different journals at the same time, thus making it difficult to know that each of these papers was in press. As stated, this can be avoided with the creation of a central repository of systematic reviews and meta-analyses for authors to submit to as well as be aware of similar projects in development. Given the number of independent journals dedicated to cardiology and its subspecialties, this might not be an easy task.

*Khaled M. Ziada, MD
Ahmed Abdel-Latif, MD
Matthew E. Wiisanen, MD

*Division of Cardiovascular Medicine
Gill Heart Institute
University of Kentucky
900 South Limestone Street
326 Charles T. Wethington Building
Lexington, Kentucky 40536-0200
E-mail: khaled.ziada@uky.edu

doi:10.1016/j.jcin.2011.03.007