

EDITORIAL COMMENT

Do We Need a Trial of DES Versus CABG Surgery in Diabetic Patients With ACS?*



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The comparative effectiveness of percutaneous coronary intervention (PCI) versus coronary artery bypass graft (CABG) surgery for patients with multivessel disease (MVD) who

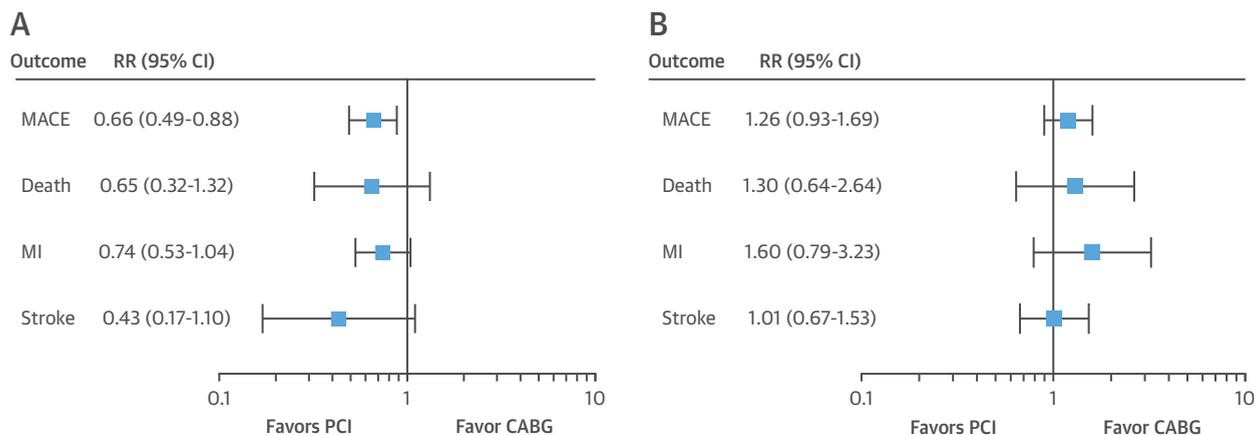
require revascularization has been a matter of debate over the last 4 decades. With every iteration of PCI (plain old balloon angioplasty, bare-metal stents, and first-generation drug-eluting stents [DES]), randomized trials and observational registries have attempted to answer this question. Over the long term, these randomized trials have shown that when compared with PCI, CABG has: 1) reduced risk of repeat revascularization (most trials); 2) reduced risk of myocardial infarction (MI) (some trials); and 3) reduced risk of death (in a few trials). Over the short term (in hospital or 30 days), however, these randomized trials have also shown that when compared with PCI, CABG has an increased risk of periprocedural events (e.g., death, MI, stroke, renal failure, bleeding or need for transfusion, infection, prolonged intubation, prolonged recovery). As such, a balanced approach is to weigh the short-term risk of CABG with the long-term risk of PCI, taking into consideration patient preferences. However, are the results of these trials applicable to contemporary practice?

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From an interventionalist's perspective, prior clinical trials used stents that are no longer in clinical practice and the PCI technique resulted in subpar rates of complete revascularization, potentially leading to worse long-term outcomes with PCI. A number of clinical trials, large registries, and meta-analyses have shown superior efficacy and safety of second-generation DES over first-generation DES or bare-metal stents at reducing not only the softer endpoint of restenosis, but also reductions in stent thrombosis, MI, and death in patients with or without diabetes (1-4). Moreover, the equipment and technique for complex PCI (e.g., chronic total occlusions) have vastly expanded, with success rates for chronic total occlusion PCI exceeding 80% in contemporary practice. As such, the potential for complete revascularization with PCI has improved. From a surgeon's perspective, prior

FIGURE 1 Short- and Long-Term Risk of PCI With Second-Generation DES Versus CABG



(A) Short-term risk and (B) long-term risk results from a meta-analysis of 3 randomized trials of PCI with second-generation drug eluting stents (DES) versus coronary artery bypass grafting (CABG) (BEST [Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease], EXCEL [Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization], and NOBLE [Nordic-Baltic-British left main revascularisation] trials). CI = confidence interval; MACE = major adverse cardiac event(s); MI = myocardial infarction; RR = relative risk.

clinical trials did not routinely use panarterial grafts, minimally invasive CABG, or off-pump surgery. However, these techniques are used in a minority of patients in contemporary practice and the superiority of even panarterial grafts over conventional surgery has not been systematically proven in a well-powered randomized trial. From a cardiologist’s perspective, these trials did not use contemporary medical therapy, which is a changing landscape with novel lipid-lowering strategies (ezetimibe, proprotein convertase subtilisin/kexin type 9 inhibitors), antiplatelets (ticagrelor, prasugrel), oral anticoagulants (very low-dose rivoraxaban), antidiabetic agents (sodium glucose cotransporter 2 inhibitors, glucagon-like peptide 1 agonists), and other drugs proven to reduce the risk of cardiovascular events when compared with conventional therapy. In the absence of contemporary randomized trials, observational studies provide insights into real-world outcomes.

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In this issue of the *Journal*, Ramanathan et al. (5), using a large population-based database from British Columbia, provide valuable insights into the outcomes of diabetic patients with MVD who underwent CABG or PCI (first- or second-generation DES). Among 4,661 diabetic patients included in the study, over long-term follow-up (median 3.3 years), CABG was associated with lower major adverse cardiac events

(MACE) (composite of death, MI, stroke), death, MI, and repeat revascularization when compared with PCI, with concordant results in the acute coronary syndrome (ACS) and stable ischemic heart disease cohorts. However, the study found a significant interaction by ACS status for 30-day outcomes, such that the results surprisingly favored CABG over PCI for MACE and MI with numerically lower death in those with ACS, but not in those with stable ischemic heart disease. The results were consistently seen in a number of sensitivity analyses. Ramanathan et al. (5) concluded that “a well-powered randomized trial of CABG versus PCI in the ACS population is warranted because these patients have been largely excluded from prior trials.” Of note, the study excluded patients presenting with an ST-segment elevation MI within 72 h and the characteristics (non-ST-segment elevation myocardial infarction vs. unstable angina) of this ACS cohort were not well defined. This is important because the majority of patients with ACS in the United States undergo PCI. Moreover, the limitations of this observational study were well acknowledged by the authors including the lack of patient-level data on the type of DES and potential selection and ascertainment bias.

How do these results compare with that of other registries and randomized trials? In an analysis of >16,000 patients with diabetes and MVD from New York state who underwent PCI using second-generation DES versus CABG, in contrast to the

findings of the British Columbia registry, short-term results favored PCI with a lower risk of death and stroke, whereas in the long term, PCI was associated with lower risk of stroke and higher risk of repeat revascularization with similar risk of death (6). ACS patients were included except for those with MI within 24 h preceding the index procedure (6). The study had approximately 3.5 times the sample size of the British Columbia registry and included only patients who underwent PCI with second-generation DES (everolimus-eluting stent). Three randomized trials (the BEST [Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients with Multivessel Coronary Artery Disease], EXCEL [Evaluation of XIENCE versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization trial], and NOBLE [Nordic-Baltic-British left main revascularisation study]) (7-9) with 3,969 patients have compared CABG versus PCI using second-generation DES. These trials also included a variable proportion of patients with ACS (18% to 53%). A meta-analysis of these 3 trials showed that PCI with second-generation DES was associated with significant reduction in MACE due to numerically lower death, MI, and stroke at short-term follow up (30-day outcome) (Figure 1A), consistent with the results from the New York state registries and consistent with prior trials of CABG versus PCI. Over the long-term

(follow-up 3 to 5 years), the results from the meta-analysis of randomized trials showed outcomes that are similar between PCI and CABG (Figure 1B). Diabetes was not an effect modifier in metaregression analyses for any of the outcomes.

The short-term lower risk with CABG when compared with PCI seen in the British Columbia registry is possibly due to residual confounding. Although the superiority of CABG over PCI over short-term follow-up in the ACS cohort is difficult to explain, it is possible that inability to identify the true culprit lesion in diabetic non-ST-segment elevation myocardial infarction patients undergoing PCI results in less protection against recurrent ischemic events than does complete revascularization with CABG. Regardless, the long-term outcomes should be tested in a randomized trial. The relative merits of CABG and PCI have been debated since the days of the BARI (Bypass Angioplasty Revascularization Investigation) trial and will continue to be debated in individual patients for the foreseeable future.

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