Antiplatelet therapy after coronary bypass surgery: “Broken portions” and “uncertainty” in the search for “absolute truth”

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Central Message

One year of DAPT after CABG surgery may be associated with improved long-term outcomes.

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There have been dramatic improvements in early survival and short-term outcomes after coronary artery bypass grafting (CABG), with considerable focus on surgical techniques, the ideal grafting strategy, and conduit use.¹⁻³ However, there is now increasing emphasis on improving long-term outcomes, including survival, functional status, and repeat revascularization after CABG.^{4,5} The great Canadian physician William Osler once stated that “Medicine is a science of uncertainty and an art of probability.”⁶ This philosophy arguably heralded the start of evidence-based medicine. The optimal secondary prevention strategies after CABG remain uncertain,⁷ and in this edition of the *Journal*, the CASCADE investigators seek further evidence for the optimal antiplatelet strategy.⁸ They report an 8-year follow-up of their original trial to evaluate long-term outcomes of the addition of clopidogrel to aspirin during the first year after CABG, versus aspirin plus placebo. Their findings are provocative and potentially important, but they acknowledge the “science of uncertainty.”

In the original CASCADE study, 113 patients undergoing CABG were randomized to receive clopidogrel or placebo in addition to aspirin for 1 year postoperatively.⁹ The study demonstrated that compared with aspirin monotherapy, the combination of aspirin plus clopidogrel did not significantly reduce the process of saphenous vein graft (SVG) intimal hyperplasia at 1 year after CABG. In this subsequent study, the authors evaluate the 8-year follow-up of the initial CASCADE cohort with respect to survival, functional status, and major adverse cardiac or cerebrovascular events including revascularization (MACCE/R). Graft patency and native coronary artery disease progression were also assessed using coronary computed tomography angiography (CCTA) and compared with the conventional coronary angiograms from the CASCADE study. They achieved a

100% clinical follow-up of the 99 surviving patients, as well as obtaining mortality and MACCE/R information for all patients. However, with 38 of 51 patients in the aspirin-clopidogrel group and 23 of 48 patients in the aspirin-placebo group ($P = .008$) undergoing CCTA, these data were both incomplete and unbalanced. The overall survival in the entire cohort of $85.5\% \pm 3.8\%$ was excellent. No difference in functional status or freedom from angina was observed between the 2 groups, but there was an apparent trend toward enhanced freedom from all-cause death or MACCE/R in the aspirin-clopidogrel group ($P = .11$). Long-term SVG patency was also excellent in both groups at a median follow-up of 7.6 years (89.11% in the aspirin-clopidogrel group and 91.23% in the aspirin-placebo group). The authors found that treatment with dual antiplatelet therapy (DAPT) for the first year only after CABG is associated with a lower incidence of long-term moderate to severe native coronary disease progression than with aspirin alone, regardless of the antiplatelet therapy the patients received after the first year (7/122 vs 13/78 coronary segments studied respectively, $P < .02$). No differences in bleeding complications were observed between the groups; however, with relatively small patient numbers and crossover in terms of DAPT use after the first year, it is difficult to draw conclusions regarding safety of DAPT.

The authors⁸ clearly identify and acknowledge the limitations of the study. It was not an a priori planned long-term analysis of the CASCADE trial, and therefore neither designed nor powered for this purpose. Although the authors succeeded in obtaining a 100% clinical follow-up, the CCTA follow-up was both incomplete and unbalanced. In addition, more patients in the aspirin-placebo group had hypertension at long-term follow-up, even though this was not the case at the time of surgery. Of note, at long-term follow-up, 20% of the original aspirin-placebo group were taking DAPT compared with 10% of the original aspirin-clopidogrel group. This was not statistically significant. Furthermore, although again not statistically significant, bilateral internal thoracic arteries (BITAs) were used in 28.9% of the aspirin-clopidogrel undergoing CCTA versus 13.0% of the aspirin-placebo group. The authors conclude that any differences in BITA use did not affect subsequent MACCE/R events or mortality at 7.6 years in this study, and they suggest that BITA use may only affect survival in the even longer term. Of course, the excellent SVG patency observed at CCTA might also be an important factor in the long-term clinical outcomes. Finally, the authors acknowledge that more pronounced P2Y12 antagonists may have more beneficial effects than clopidogrel and are themselves investigating the effect of ticagrelor in the TARGET trial ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02053909) Identifier: NCT02053909).

Some strategies that have been proposed to improve long-term survival and outcomes after CABG, such as intricate arterial revascularisation techniques, are both complex and challenging.^{1,10} However, this study investigates a simple, universal therapy that could have important clinical effects. The outcomes achieved in all patients were outstanding, with high graft patency rates and freedom from death and MACCE/R, and are a reflection of the surgical standards of the authors' units as well as subsequent adherence to secondary prevention measures by their patients. Ironically, this made assessment for differences between the aspirin-clopidogrel and the aspirin-placebo groups more difficult to detect. The need to investigate bleeding complications¹¹ more thoroughly, as well as personalized responses of individual patients to antiplatelet therapy,¹² will be important for future research.

William Osler also stated that "In seeking absolute truth we aim at the unattainable and must be content with broken portions."¹³ The conclusion of the CASCADE investigators,⁸ from Montreal and Ottawa, that DAPT for 1 year post-CABG may result in long-term benefits with a lower incidence of progression of native coronary artery disease and a trend toward higher freedom from MACCE/R or death is indeed provocative. They admit this is a hypothesis-generating study, but it could be a further "broken portion" in our search for the best therapy to which their illustrious Canadian predecessor eluded.

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