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Trial Sequential Analysis of Drug-Eluting Stents Versus Bare-Metal Stents in Saphenous Vein Graft Intervention

Implantation of drug-eluting stent (DES) compared with bare-metal stent (BMS) has emerged as an effective treatment for native coronary artery disease (CAD), even with a single month of dual antiplatelet therapy.[1] Contrary to native CAD, the pathophysiology of saphenous vein graft (SVG) lesions is characterized by a diffuse atherosclerotic burden coupled with a more rapid progression of the disease.[2] In a recent direct meta-analysis, Patel et al[2] reported the results of DES versus BMS implantation in SVG intervention. The results showed similar efficacy in both stent types with regard to the soft and hard clinical end points, specifically major adverse cardiovascular events, all-cause mortality, cardiovascular mortality, myocardial infarction, stent thrombosis, and target vessel revascularization (all $p > 0.05$).[2] However, only a few randomized controlled trials (RCTs; n = 6) with a limited sample size (n = 1,582 patients) were included in the analysis. As a consequence, the probability of type II errors (false negative) increases with consequent possible absence of statistical significance. Therefore, we performed a trial sequential analysis (TSA) to account for the risk of "chance findings" due to the lack of statistical power and precision.[3] We applied trial sequential monitoring boundaries using TSA software, Copenhagen Trial Unit, version 0.9.5.10 Beta, similar to that performed in interim analyses for RCTs.[3]

According to the available RCTs, the incidence of major adverse cardiovascular events in the BMS group was 43.3%.[2] To provide an 80% power to detect a relative risk reduction of 25% in the DES group at a 2-sided type α-error of 0.05, we estimated a diversity (D2)-adjusted information (sample) size of 4,157 participants (vs 1,582 in the current analysis). The cumulative Z-curve did not cross either traditional or trial sequential monitoring boundaries, indicating an "absence of evidence" (Figure 1). Similar inconclusive results were noted with regard to other clinical outcomes, such as all-cause and cardiovascular mortalities, myocardial infarction, stent thrombosis, and target vessel revascularization.

Although previous studies have shown beneficial short-term effects of DES implantation in SVG lesions compared with BMS likely due to restenosis prevention, long-term outcomes including target vessel revascularization were not impressive.[4] Although newer generation DESs have demonstrated improved outcomes in native CAD, they did not show advantages over BMS in a recent RCT for SVG intervention.[5]

Our TSA raises the distinct possibility that the publication by Patel et al and Brilakis et al are underpowered to answer the question of whether DES is superior to BMS in the treatment of patients who underwent SVG interventions. For now,

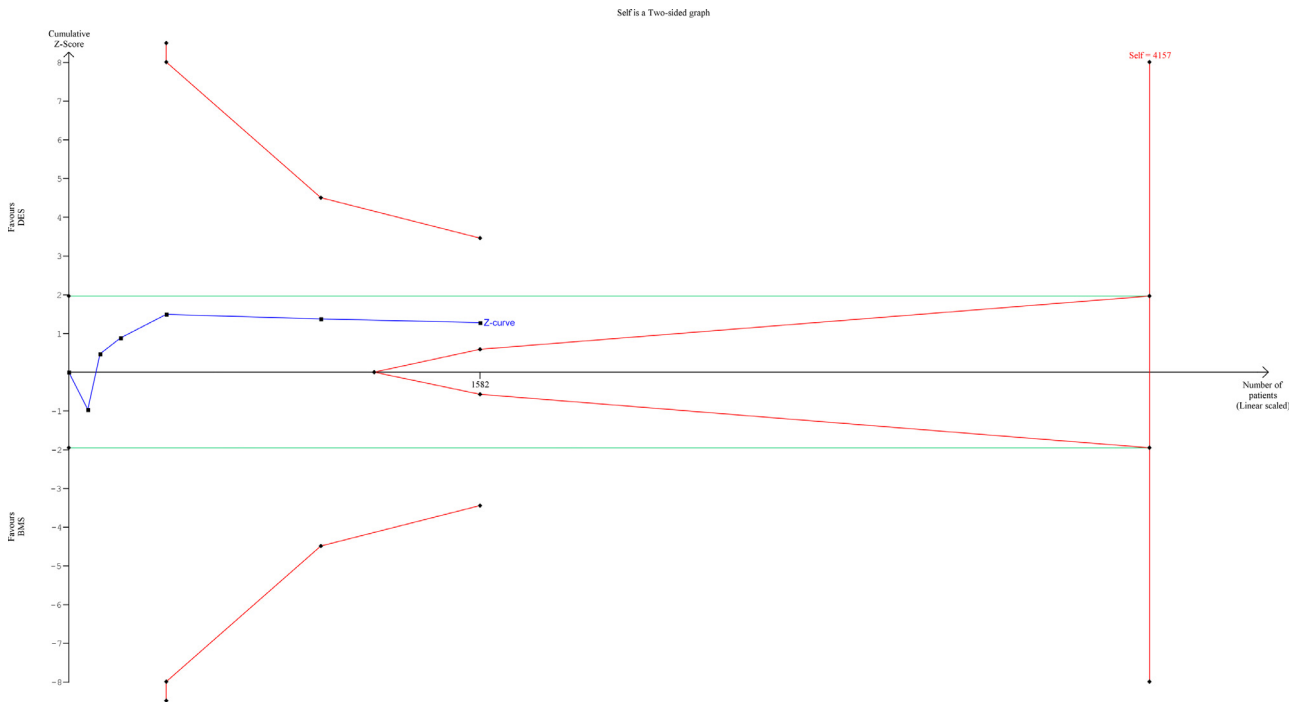

Figure 1. Trial sequential analysis for major adverse cardiovascular events. The diversity-adjusted information size equal to 4,157 (*vertical red line*). The cumulative Z-curve (*blue line* with *small black squares* representing each trial) does not cross the traditional boundary (*horizontal green line*), trial sequential monitoring boundaries (*concave red lines*), or the futility boundaries (*convex red lines*), indicating absence of evidence (inconclusive result). (Color version of figure is available online.)

our analyses suggest that the absence of benefit may be due to type II errors. To answer the question, adequately powered RCTs and novel strategies for SVG interventions are warranted.

Disclosures

The authors have no conflicts of interest to disclose.

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