Aspirin monotherapy *vs.* dual antiplatelet therapy in diabetic patients following coronary artery bypass graft (CABG): where do we stand?

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Coronary heart disease (CHD) is the most common cause of death in the United States and worldwide (1). Rupture of atherosclerotic plaque, followed by platelet aggregation and thrombus formation often leads to partial or complete occlusion of the native coronary artery, resulting in myocardial ischemia. Regardless of the revascularization modality used *vs.* medical therapy alone for patients with stable ischemic heart disease or acute coronary syndrome (ACS), antiplatelet therapy remains the standard of care.

Platelet activation and aggregation has been recognized as one of the factors responsible for venous graft occlusion following coronary artery bypass graft (CABG). Saphenous vein grafts (SVG) remain the most commonly used conduits for CABG. When compared with arterial bypass conduits, SVG are notorious for thrombotic occlusion, particularly in the first year following CABG (1,2). Aspirin (ASA) has been shown to reduce the likelihood of SVG thrombosis, reducing its incidence during the first postoperative year by nearly 50% (2,3).

Diabetic patients have higher rate of SVG occlusion following CABG compared with nondiabetics (4). Diabetes is independently associated with increased perioperative and long-term mortality in CABG patients, and may be a clinical risk factor for vein graft failure through thrombotic occlusion (5). While adding a second antiplatelet agent seems to be an attractive therapeutic option, particularly in diabetics, additional risk of bleeding and lack of conclusive evidence should also be considered.

Published in 2002, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial addressed differences in revascularization strategies in diabetics. In this trial, diabetic patients were found to have significantly reduced rates of death and myocardial infarction following CABG, compared with percutaneous coronary intervention (PCI) (6).

On January 9th 2017, a manuscript entitled "Dual antiplatelet therapy versus aspirin monotherapy in diabetics with multivessel disease undergoing CABG" was published in the *Journal of the American College of Cardiology* (7). The main objective of this paper is to assess dual antiplatelet therapy (DAPT) utilization rates and associated outcomes among post-CABG patients with diabetes, through nonrandomized post hoc secondary analysis of the FREEDOM trial. The paper included 795 diabetic patients with multivessel CAD (defined as ≥70% stenosis of 2 or more major epicardial vessels) from the FREEDOM trial who were randomized to CABG as the revascularization strategy. There were 251 patients that were defined as aspirin cohort group (those patients who were receiving

aspirin monotherapy at 30 days following CABG). Conversely, 544 patients were defined as the DAPT cohort group (those who were receiving DAPT at 30 days post-operatively). As data was extrapolated from the original FREEDOM trial, primary, secondary and safety outcomes were also the same as those identified by the FREEDOM trial. Primary outcomes included 5-year all-cause mortality, nonfatal myocardial infarction, or stroke. Secondary outcomes included vascular death, MI, and cardiovascular hospitalization (defined as unstable angina, MI, heart failure, chest pain, arrhythmia, peripheral vascular disease, or stroke or transient ischemic attack). Safety outcomes were major bleeding, blood transfusions, and bleeding hospitalization.

The paper illustrated that, at day 30 post-CABG, utilization of DAPT in patients with diabetes was high (68.4%) *vs.* aspirin monotherapy (31.6%) and, compared with aspirin monotherapy at day 30 post-CABG, no significant associations were observed with all-cause mortality, MI, or stroke at 1 year and 5 years point estimates. Additionally, no differences in outcomes were observed in bleeding, clinical indication for revascularization, complexity of coronary artery disease, completeness of revascularization, or treatment duration. The authors concluded that the routine use of DAPT in post-CABG diabetic patients warrants an adequately powered, prospective randomized clinical outcome trial.

We found that this secondary analysis of the FREEDOM trial is essential in contributing to the already scarce evidence behind the use of DAPT therapy post-CABG. The article tackled a highly controversial question in the era of modern cardiology, however it generated more questions than answers. Extensive review of the literature provided conflicting results on this topic. This review article, indeed, added more controversy, evening out the difference between the number of trials that showed benefits of DAPT post-CABG compared with those that did not (see later). Extrapolating data from FREEDOM patient population randomized to CABG yielded a modest sample size for secondary analysis (n=795) with uneven patient population subgroups (68.4% for DAPT subgroup, compared to 31.6% for aspirin monotherapy). The design of the study was confined to nonrandomized, retrospective observational analysis, decreasing its power, yet its results were consistent with most studies that addressed antiplatelet therapy post-CABG.

The authors have identified potential limitations of their secondary analysis of the FREEDOM trial. In our opinion, those limitations stem from the design of the study itself. Retrospective data analysis, as well as nonrandomization, leads to selection bias and introduction of confounding factors. Moreover, utilization of plavix plus aspirin as the only DAPT therapy, limits the potential advantages of DAPT therapy when other novel antiplatelets, such as ticagrelor are used in practice.

There are other limitations of the paper that were identified. Assessment of primary, secondary, and adverse outcome in diabetics post-CABG on either aspirin monotherapy or DAPT was based on the assumption that all patients responded equally well to antiplatelet therapy. There is a considerable variability in response to antiplatelet therapy among patients of different genomic profile. Moreover, intrapersonal variations in antiplatelet therapeutic effect can also be present in the same subject at different points in time (8). The assumption of equal response to antiplatelet therapy has been implied by both the FREEDOM trial and the current paper.

Given the inconsistency of the clinical trial data regarding utilization of DAPT post-CABG, we performed an extensive medical literature review to answer the same question. Our results were published in 2015 in the *American Journal of Cardiology* in an article entitled "Dual antiplatelet therapy after CABG in the setting of acute coronary syndrome" (9). We conducted an extensive PubMed research, using the terms aspirin, clopidogrel, DAPT, and coronary artery bypass surgery. A total of 12 trials were identified on this subject. Results varied significantly. Seven of twelve trials found significant benefit of DAPT post-CABG, in comparison to 5 trials whose results were neutral, showing no benefits of DAPT post-CABG. Currently, there is only one prospective, randomized multicenter trial, the Clopidogrel After Surgery for Coronary Artery Disease (CASCADE) Trial, published in *Circulation* in 2010. This trial concluded that the combination of aspirin plus clopidogrel, compared with aspirin monotherapy, did not significantly reduce the process of SVG intimal hyperplasia as determined by intravascular ultrasound at 1 year after CABG (10). CASCADE trial was included into our literature review, and contributed towards those trials that did not show any significant benefits of DAPT post-CABG. By concluding that there is no difference between DAPT *vs.* aspirin monotherapy group post-CABG, the current study analyzed in our editorial almost equalizes the number of contradicting trials to non-contradicting trials in our literature review.

As we illustrated above, our extensive literature review concluded that there is no clear consensus regarding the use of DAPT after CABG, and further large, multicenter, randomized clinical trials are needed to guide therapy on an evidence based basis. We correspondingly conclude that there is great need for such a clinical trial to better clarify the use of DAPT therapy post CABG, particularly in the era of novel and evolving oral antiplatelet therapy.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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