ESC European Society of Cardiology
European Heart Journal (2019) **40**, 2441–2443
doi:10.1093/eurheartj/ehz263

EDITORIAL

The optimal antithrombotic regimen to prevent post-CABG adverse events: an ongoing controversy

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Online publish-ahead-of-print 30 May 2019

This editorial refers to 'Randomized trial of ticagrelor vs. aspirin in patients after coronary artery bypass grafting: the TiCAB trial'†, by H. Schunkert *et al.*, on page 2432.

The occurrence of major adverse cardiovascular events (MACE) and graft failure following coronary artery bypass grafting (CABG) poses significant challenges. Saphenous vein grafts (SVGs) remain the most widely used conduits, but are associated with 10–25% rates of failure within 1 year.[1] However, there is controversy surrounding the relationship between graft failure and MACE, with most of the evidence supporting a relationship to MACE following LAD graft occlusion.[2] The lack of a consistent link between graft failure and MACE is multifactorial in aetiology, with one mechanism being grafting beyond non-critical stenoses. SVG failure within 1 month has been attributed to thrombosis, beyond 1 month to the development of intimal hyperplasia, and beyond 1 year to arteriosclerosis. Less is known of the pathophysiology of arterial graft failure that may fail due to competitive flow. In addition, graft failure has been associated with diabetes, young age, female gender, and other pre-existing risk factors such as hypercoagulability, inflammation, and oxidative stress (*Figure 1*).[1,2]

Antiplatelet therapy is a major strategy used to prevent post-CABG failure and MACE. Routine aspirin monotherapy is recommended based on improved 60-day to 1-year SVG patency compared with placebo in small angiographic studies conducted in the 1980s employing pre-operative aspirin and a ≥325 mg daily dose. Importantly, there have been no dedicated large-scale studies in the CABG population to support post-operative dual antiplatelet therapy (DAPT). DAPT has been recommended in patients undergoing CABG following acute coronary syndromes (ACS) and coronary stenting,[3] the latter was based on analyses of randomized trials of antiplatelet therapy in ACS. The limited evidence base to support DAPT in stable ischaemic heart disease (SIHD) patients after CABG has been reflected in the recent European guidelines where there is a Class IIb recommendation with level C evidence for off-pump procedures.[3]

In a recent meta-analysis of 20 315 patients, DAPT vs. single antiplatelet therapy was associated with reduced cardiovascular mortality in observational studies, but not in randomized trials or in patients with SIHD. DAPT was associated with reduced SVG failure that was offset by increased risk for major bleeding.[4] In a network meta-analysis of randomized controlled trials including 3133 patients with 4490 SVGs and 1226 internal mammary artery grafts, a significantly improved all-graft patency was observed with aspirin monotherapy or DAPT vs. placebo, but only a trend for better outcomes with DAPT vs. aspirin.[5]

The recent Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) trial (~70% off-pump surgery) assessed the effect of ticagrelor plus aspirin, vs. ticagrelor alone and vs. aspirin alone in 500 patients with 1360 grafts in elective CABG. Treatment was started within 24 h post-CABG, and 1 year SVG patency was assessed by multislice computed tomographic (CT) angiography or coronary angiography. The DAPT arm was associated with greater 1-year graft patency than aspirin monotherapy (89% vs. 77%, RR = 0.48, $P < 0.001$). Although there was no difference in patency between aspirin and ticagrelor monotherapy (77% vs. 83%, $P = 0.10$), there were numerically similar rates of graft patency observed between the two ticagrelor-treated groups (89% vs. 83%, respectively). The study was not powered to evaluate the relationship between graft failure and clinical outcomes.[6] In the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial, pre-operative aspirin therapy vs. placebo did not reduce 1-year post-CABG thrombotic complications or death (4.1% in the aspirin group and 3.5% in the placebo group, RR = 1.17; P =0.48). A recent updated meta-analysis suggested that perioperative aspirin vs. placebo up to 1 year after surgery might reduce the rate of myocardial infarction (MI), but not overall MACE.[7]

Thus far, the evidence available suggests that: (i) a relationship between graft failure and post-CABG MACE is not definitive, with LAD

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

† doi:10.1093/eurheartj/ehz185.

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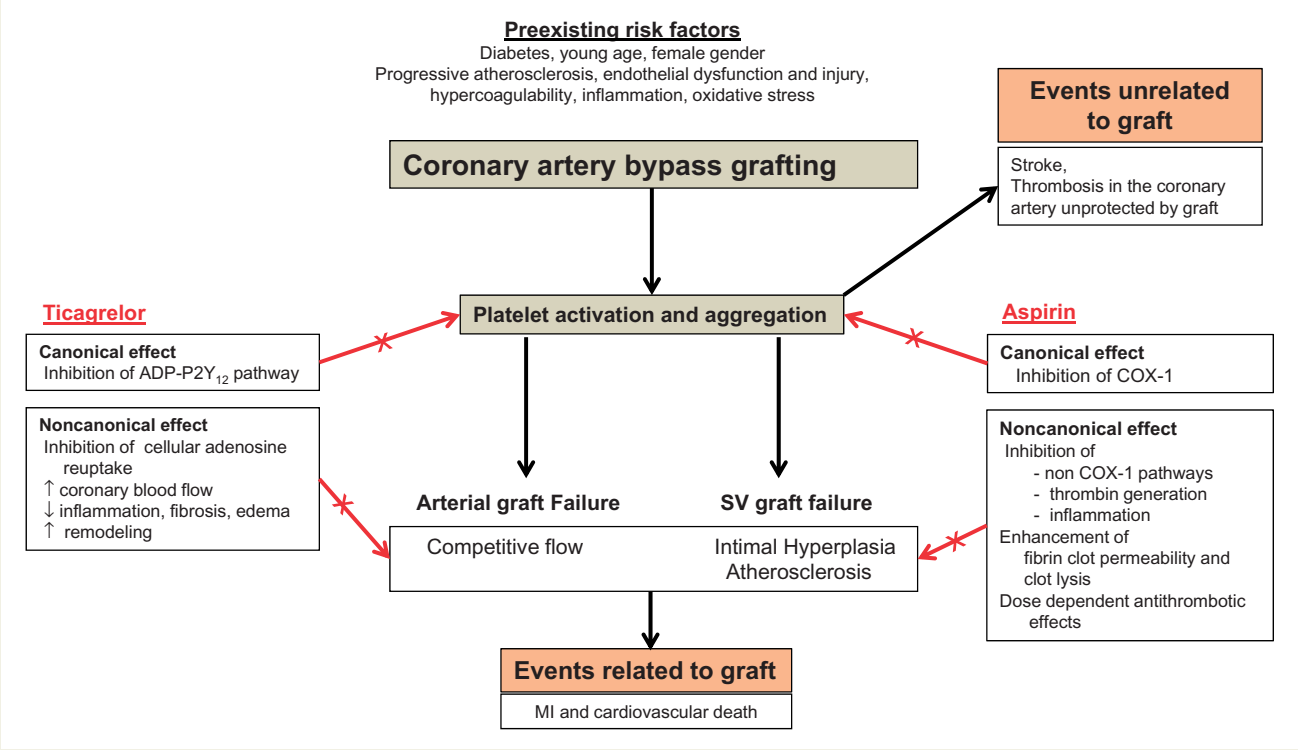

Figure 1 Major cardiovascular event occurrence following coronary artery bypass grafting (CABG) is both graft related and unrelated. In the presence of pre-existing risk factors during CABG, platelet activation and aggregation play important roles in the occurrence of early graft thrombosis and graft-unrelated events. Vein grafts are susceptible to intimal hyperplasia and arteriosclerosis that play important roles in later graft failure, whereas arterial grafts may fail due to competitive flow. Antiplatelet therapy with aspirin inhibits the COX-1 enzyme and with ticagrelor inhibits the ADP–$P2Y_{12}$ interaction. Both aspirin and ticagrelor exhibit non-canonical effects that may influence major adverse cardiovascular events (MACE) in addition to canonical effects. Greater antithrombotic effects have been reported with higher doses of aspirin than low dose. ADP, adenosine diphosphate; COX-1, cyclooxygenase; SV, saphenous vein.

graft failure most associated with MACE;[2] (ii) aspirin is more effective than placebo in reducing all-graft failure[5] and, despite its routine use, as many as ~30% of patients have at least one occluded SVG 1 year after CABG surgery;[1] (iii) a DAPT-based strategy was more effective than aspirin monotherapy in reducing SVG failure at the expense of more bleeding, but its effectiveness in reducing MACE is not clearly established;[4] and (iv) the efficacy of DAPT after CABG in patients with SIHD is uncertain.[3]

DAPT with ticagrelor as compared with DAPT with clopidogrel was effective in reducing total and cadiovascular mortality without excess risk of CABG-related bleeding in the subanalysis of the PLATO trial.[8] The antiplatelet effect of aspirin is primarily attributed to irreversible inhibition of platelet cyclooxygenase-1 (COX-1) enzyme and subsequent inhibition of thromboxane A_2 generation and platelet aggregation. In addition, non-canonical effects of aspirin have been attributed to dose-dependent inhibition of non-COX-1 pathways, inhibition of thrombin generation and inflammation, and enhancement of fibrin clot permeability and clot lysis.[9] Although these are undeniable effects associated with aspirin, early vein graft failure is predominantly mediated by thrombosis and occurs despite aspirin treatment, which calls into question whether aspirin is effective and sufficient. In addition to its strong inhibitory effect on ADP-induced platelet aggregation, ticagrelor has been shown to inhibit cellular adenosine reuptake that might enhance coronary blood flow and tissue remodelling.[10] Recently it has been argued that a strategy of monotherapy with a potent antiplatelet agent such as ticagrelor only might offer better net outcomes than DAPT with aspirin.[11] Therefore, it is not unreasonable to assume that ticagrelor monotherapy would provide a beneficial influence on graft patency and MACE following CABG with an acceptable bleeding risk.

In the Ticagrelor in CABG (TiCAB) trial published in this issue of the *European Heart Journal*, it was hypothesized that ticagrelor monotherapy as compared with aspirin monotherapy results in less 1-year post-CABG cardiovascular death, MI, stroke, and repeat revascularization.[12] The investigators should be commended for their effort to address this important clinically relevant concern in a large-scale international study. Although planned to administer therapy pre-CABG, there was slow recruitment, necessitating a change in protocol to within the first 24 h after CABG. Unfortunately, the study was prematurely discontinued after interim analysis of approximately half of the patients showed lower than expected event rates that were higher in the ticagrelor arm and lack of further funding support from the sponsor. The planned analysis was for 3760 patients; the study stopped after 1893 patients were enrolled. The majority of patients (69%) had stable angina and nearly 97% underwent on-pump CABG. There was a high frequency of arterial grafts: ~53% of patients received ≥2 arterial grafts whereas ~28% of patients received ≥2 SVGs. Overall, this study provides conflicting results. Between

ticagrelor and aspirin, there was no difference in occurrence of the composite primary endpoint [9.7% vs. 8.2%, hazard ratio (HR) = 1.19, $P = 0.28$] and in BARC ≥3 bleeding (3.7% vs. 3.3%, HR = 1.17, $P = 0.53$). Ticagrelor therapy was associated with a numerical reduction in MI (HR = 0.63, $P = 0.12$), no cardiovascular mortality benefit (HR = 0.85, $P = 0.68$), but numerically greater repeat revascularization (HR = 1.28, $P = 0.28$) and stroke (HR = 1.21, $P = 0.49$). With respect to subgroups, there was a trend to support ticagrelor therapy in patients <60 years old (P for homogeneity = 0.08) and in patients treated with ≥2 arterial grafts (P for homogeneity = 0.06). Importantly, there was no assessment of graft patency. The study was not powered to assess the primary endpoint, and the above results should be considered hypothesis generating.[12]

What is the take-home message from this study? Although underpowered, ticagrelor monotherapy was no better than long-used aspirin in reducing 1-year post-CABG MACE. It was also no worse with respect to bleeding. Recent trials of long-term ticagrelor monotherapy have also failed to show significant benefits over the comparator in percutaneous coronary intervention (vs. aspirin), peripheral arterial disease (vs. clopidogrel), and stroke (vs. aspirin).[13] These findings support the concept that an enhanced antithrombotic effect of ticagrelor requires concomitant aspirin.[14] More convincing adequately powered studies for MACE are definitley needed before considering aspirin deletion. Post-CABG MACE is also heterogeneous with respect to cause. Some mechanisms may be platelet dependent whereas others may not be influenced by any antiplatelet therapy. Moreover, the effect of antiplatelet therapy on events will probably be affected by the type of graft used (arterial vs. venous) and the setting in which the surgery took place (ACS vs. stable disease). In the current study, the high implementation of evidence-based medications such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins is likely to have influenced the lower than anticipated event rate. Ongoing studies may provide more evidence for or against alternative antiplatelet strategies compared with aspirin following CABG. The Ticagrelor Antiplatelet Therapy to Reduce Graft Events and Thrombosis (TARGET) trial ($n = 300$ patients) is evaluating the effects of ticagrelor vs. aspirin on vein graft failure assessed by CT angiography 1 year after CABG (NCT02053909). In another study planned in 720 patients, ticagrelor plus aspirin is being compared with aspirin alone for reduction of SVG failure assessed by CT angiography at 1 year (NCT02352402). At this time, aspirin is the mainstay to prevent post-CABG MACE in elective patients. However, the optimal aspirin dose still is an unresolved issue, with no adequately powered trial evaluating the comparative efficacy of low vs. moderate dose aspirin. It is important to note that there are dose-related enhanced antithrombotic effects of aspirin.[15] A higher aspirin dose may have yielded different results in the current study.

Conflict of interest: P.A.G. reports receiving grants from the National Institutes of Health, Bayer, Medicure, Instrumentation labs, Haemonetics, Amgen, Idorsia, Ionis, Janssen, and Merck; receiving honoraria and payment for lectures; and consultations including service on speakers' bureaus from Bayer, Janssen, Merck, UptoDate, and Medicure. U.S.T. reports receiving honoraria from Astra Zeneca, UptoDate, and Medicure. E.P.N. has received grants from Amgen, Inc and fees for lectures/service on speakers bureaus from AstraZeneca, Sanofi, Regeneron, and Amgen Inc.

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