

Doubling up on antiplatelet therapy after CABG: changing practice ASAP after DACAB?

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Comment on: Zhao Q, Zhu Y, Xu Z, *et al.* Effect of Ticagrelor Plus Aspirin, Ticagrelor Alone, or Aspirin Alone on Saphenous Vein Graft Patency 1 Year After Coronary Artery Bypass Grafting A Randomized Clinical Trial. *JAMA* 2018;319:1677-86.

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One of the most important determinants of long-term prognosis after coronary artery bypass grafting (CABG) is graft patency. Various studies have shown that the use of arterial grafts as compared to vein grafts provides significantly better long-term patency (1,2). Nevertheless, a venous graft is still being used in the vast majority of CABG procedures (2,3).

Suboptimal venous graft patency is caused by technical problems, intimal hyperplasia and thrombosis (4). Although several techniques have been introduced to prevent endothelial damage and reduce subsequent intimal hyperplasia such as a no-touch technique for vein harvesting, secondary prevention remains a cornerstone therapy to improve graft patency (5). Timely use of platelet inhibitors is established as the standard of care to prevent early and late graft thrombosis and subsequently myocardial infarction (MI). In global registry data, the use of single antiplatelet therapy (SAPT) with aspirin within 48 hours after CABG versus no antiplatelet therapy has showed to markedly reduce in-hospital mortality (1.3% *vs.* 4.0%, $P < 0.001$, respectively) as well as the risk of the composite endpoint of cardiac, cerebral, renal and gastrointestinal ischemic events and mortality (10.6% *vs.* 18.6%, $P < 0.001$, respectively) (6). Moreover, in a meta-analysis of 12 randomized controlled trials (RCTs), rates of graft occlusion on coronary angiography 1 week to 1 year after CABG were significantly reduced with aspirin [odds ratio (OR) 0.66, 95% confidence interval (CI), 0.53–0.83]

(7). Current guidelines therefore recommend long-term SAPT as secondary prevention to decrease the risk of future morbidity and mortality in patients with coronary artery disease (CAD) (8).

In cardiology, even more aggressive dual antiplatelet therapy (DAPT) has proven to be clearly superior to SAPT with current guidelines recommending DAPT for patients with acute coronary syndrome (ACS) that undergo or do not undergo percutaneous coronary intervention (PCI) (8,9). In patients with ACS who underwent PCI DAPT has been shown to be highly effective in preventing stent thrombosis and decreases long-term risks of non-stent-related MI and stroke (10). Because of these results, DAPT is also being studied in patients who undergo CABG. Several studies suggested that graft patency improved with DAPT with clopidogrel compared to SAPT (11,12), yet this has not been uniformly confirmed by other studies (13,14). Therefore, current guidelines do not recommend the routine use of DAPT for all patients with CAD (e.g., stable CAD) who undergo CABG. On the other hand, since these studies were conducted with clopidogrel, results might have been suboptimal as approximately 30% of patients are non-responders to clopidogrel treatment (15,16). Ticagrelor, however, is a much more potent, direct-acting P2Y₁₂ inhibitor and compared to clopidogrel further decreases the risk of thrombotic complications in patients with ACS who underwent PCI (9). A subgroup analysis of the PLATO trial reported a significant reduction of mortality in patients with

ACS treated with ticagrelor (4.7%) compared to patients treated with clopidogrel (9.7%) who underwent CABG ($P < 0.01$) (17). Thus, DAPT with ticagrelor might be a better antiplatelet therapy for patients who underwent CABG.

Currently, several ongoing RCTs are evaluating the most appropriate antiplatelet strategy after CABG. The TARGET trial ($n = 300$ patients) evaluates whether vein graft failure 1 year after CABG can be prevented by treating patients with ticagrelor versus aspirin, assessed by computed tomography angiography (CT-angio) (NCT02053909) (18,19). The placebo-controlled, double-blind POPular CABG trial aims to present its data on whether the addition of ticagrelor to aspirin (e.g., DAPT) results in less saphenous vein graft (SVG) occlusion in 720 randomized patients, assessed with CT-angio 1 year after CABG (NCT02352402) (20). Finally, the TiCAB trial tests whether improved graft patency results in better clinical outcomes and hypothesizes that SAPT with ticagrelor is superior to SAPT with aspirin for the prevention of major adverse cardiac or cerebrovascular events during 1-year follow-up after CABG ($n = 3,850$ patients, NCT01755520) (21,22). These results will provide a body of evidence to conclude whether ticagrelor, as SAPT or in DAPT regime, should indeed become routine after elective CABG.

However, the first evidence from an RCT was recently reported. The DACAB trial compared the effects of SAPT, with either aspirin or ticagrelor, versus DAPT using both agents after elective CABG on the 1-year primary endpoint of vein graft patency (classified as $< 50\%$ stenosis) in 500 patients ($n = 1,460$ grafts) (23). Zhao *et al.* showed significantly increased venous graft patency at 1-year after CABG in patients treated with DAPT (88.7%, 432/487 grafts) compared to patients treated with aspirin alone [76.5%, 371/485 grafts, relative risk (RR): 0.48, 95% CI, 0.31–0.74, $P < 0.001$]. Furthermore, no difference in 1-year venous graft patency was observed between aspirin (76.5%, 371/485 grafts) and ticagrelor alone treatments (82.8%, 404/488 grafts, $P = 0.10$). Major adverse cardiac events (MACE) and major bleeding event rates were very low during the first year of follow-up in the overall population. Nevertheless, there was a significant difference in non-CABG related bleeding in the DAPT population compared to the aspirin group (21.3% absolute difference, 95% CI, 13.1–29.5). The high rate of patients completing 1-year follow-up (93.4%, $n = 467/500$) and 93.8% of all saphenous vein grafts ($n = 1,396/1,460$) assessed with multislice CT-angio or coronary angiography allowed insightful subgroup analyses which helps placing the

overall findings into context.

The authors found that DAPT might be more effective in patients with more complex CAD (SYNTAX score > 23) compared to patients with less complex CAD (SYNTAX score ≤ 22 , P value for interaction = 0.04). Ozturk *et al.* found by univariate analysis that high SYNTAX scores and high logistic SYNTAX scores (24) were predictors of SVG failure assessed with coronary angiography 39.4 months after CABG. After multivariate analysis only the logistic SYNTAX score remained an independent predictor of SVG failure (25). A possible explanation could be that patients with more extensive CAD (e.g., SYNTAX score > 23) have a higher incidence of vulnerable atherosclerotic plaques, small caliber vessels with diffuse disease which often progress rapidly, and exaggerated neointimal hyperplasia increasing the likelihood of venous graft failure. Although this finding could suggest new treatment strategies in patients with more complex CAD, it needs to be confirmed in upcoming studies.

Furthermore, the study found that patients aged over 65 years seemed to have a larger benefit of DAPT on vein graft patency at 1 year (88.3%) compared to patients aged 65 years or younger (69.1%, $P < 0.001$). The interaction term of age (≤ 65 vs. > 65 years) was not significant ($P = 0.06$). However, older patients have a significantly higher risk of bleeding (26). Therefore, the balance between an increased vein graft patency and the increased risk of bleeding should be weighed, especially in the elderly patient.

Despite the impressive results, several aspects of the DACAB trial should be taken into account when interpreting these findings. First, over 75% of the patients underwent off-pump coronary artery bypass grafting (OPCAB). Therefore, the results may not directly be extrapolated to patients who undergo on-pump CABG (ONCAB). A meta-analysis comparing 3,894 OPCAB-grafts versus 4,137 ONCAB-grafts reported a significantly higher rate of overall graft failure after OPCAB versus ONCAB (RR: 1.35, 95% CI, 1.16–1.57), with an even higher effect in venous grafts specifically (RR: 1.41, 95% CI, 1.24–1.60) (27). Hence, OPCAB venous grafts, and consequently patients, might benefit most from receiving post-operative DAPT as described likewise in the 2017 EACTS guidelines on perioperative medication in adult cardiac surgery (9). The DACAB investigators showed an increased graft patency in OPCAB grafts treated with DAPT (87.7%) versus SAPT with aspirin (73.9%, $P < 0.001$). However, the treatment effect on graft patency of DAPT versus SAPT was not significantly different according to performing CABG off-pump or on-pump (P value for interaction = 0.50).

Secondly, it is remarkable that Zhao and colleagues reported very low rates of major bleeding with no difference between the aspirin alone and DAPT groups. It is generally well-accepted that additional antithrombotic treatment increases the risk of bleeding (28). Since DAPT was started shortly (e.g., <24 hours) after CABG in the DACAB trial, an increased risk of surgical bleeding would be expected. The authors may not have been able to detect bleeding differences because of the high cut-off values for bleeding that were used. Surgical bleeding was adjudicated only if patients had a transfusion of ≥ 5 units within 48 hours of the procedure and a chest-tube output >2 liters within 24 hours of the procedure. Other clinically meaningful bleedings may not have been counted as such. For example, according to the Bleeding Academic Research Consortium (BARC) definitions (29), Type 3 bleeding is clinically relevant, but is missing in the DACAB analysis. Furthermore, even the use of 1 or 2 units of perioperative packed red blood cell (PRBC) has been recognized as one of the most important determinants of increased morbidity, mortality and costs after CABG (30). Thus, a cut-off value of 5 units of transfusion in the DACAB trial leads to a severe underestimation of the actual clinically meaningful bleedings. Moreover, 30.4% (51/168) of all DAPT-treated patients experienced non-CABG-related bleedings throughout 1-year follow-up compared to 9% (15/166) of the aspirin only treated patients. Bleeding resulting in temporary discontinuation of antiplatelet therapy was 8.9% in the DAPT-treated patients versus 1.2% of the aspirin-only treated patients. These findings certainly raise concerns regarding potential adverse effects and the influence on quality of life.

Finally, the DACAB trial specifically aimed to investigate the effect of DAPT on venous graft patency and was underpowered to show any differences in clinical outcomes. Larger RCTs on DAPT versus SAPT in patients undergoing elective CABG are warranted to assess its impact on major adverse cardiac and cerebrovascular events (MACCE), MI and repeat revascularization.

To conclude, the DACAB trial has shown a significant improvement in venous graft patency at 1 year with DAPT with ticagrelor versus SAPT, when it is started within 24 hours after elective CABG. However, caution is advised when interpreting and implementing these results as concerns remain regarding the safety issues of an “aggressive” antiplatelet regime. As stated by the 2017 EACTS Guidelines on perioperative medication in adult cardiac surgery, DAPT after elective CABG may not be

beneficial for all patients, but only in a selected group of patients that undergo off-pump procedures or those with a higher complexity of CAD (SYNTAX score >23). The DACAB trial should serve as a landmark for future RCTs comparing single versus double antiplatelet therapy in CABG patients, but can currently not substantiate DAPT with ticagrelor to be the new gold standard for patients who undergo elective CABG.

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Footnote

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

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