Editorial

Ticagrelor and aspirin increased vein graft patency after coronary artery bypass grafting but does it matter?

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Saphenous vein graft is commonly used for coronary artery bypass grafting (CABG) surgery. The most frequent complication is the occlusion of the venous graft despite preventive antiplatelet therapy based on aspirin (1,2), so much so that 10% to 25% of them occlude within one year of CABG (3). The "Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB)" trial aimed at comparing two original postoperative antiplatelet strategies involving ticagrelor with the classic low-dose aspirin recommended by the guidelines (4,5).

Ticagrelor, a direct-acting antiplatelet agent, provides faster, greater and more consistent platelet inhibition in comparison with other $P2Y_{12}$ antagonists (6,7). Since the publication of the PLATO trial, ticagrelor is recommended in association with aspirin as the first line therapy in patients with acute coronary syndromes (7). It was therefore logical to hypothesize that ticagrelor could be useful in the prevention of graft thrombosis. The DACAB trial confirms this hypothesis after comparing the effects of three antiplatelet strategies: a combination of ticagrelor and aspirin, ticagrelor alone, or aspirin alone, on saphenous vein graft patency at one year after CABG. The observed rates of saphenous vein graft patency after a one-year follow-up were 88.7%, 82.8% and 76.5% in the ticagrelor plus aspirin, ticagrelor alone and aspirin alone groups respectively, one year after CABG. The difference between ticagrelor plus aspirin *versus* aspirin alone on saphenous vein graft patency rates after a one-year follow-up was statistically significant [12.2% (95% CI: 5.2–19.2%; P<0.001)]. Unfortunately, the difference between ticagrelor group and aspirin group was not significant, but, according to the authors, the study was likely underpowered to draw any strong conclusion regarding ticagrelor alone.

The choice of ticagrelor to challenge aspirin in such context is appealing for several reasons. Early vein graft failure is predominantly mediated by platelet activation and thrombosis and occurs despite aspirin treatment, which calls into question whether aspirin is effective and sufficient. First, laboratory investigations reported that aspirin does not always induce the expected inhibition of platelet function. This effect is called "aspirin resistance" (8). Moreover, in a review published in the *European Journal of Cardio-thoracic Surgery*, Zimmermann *et al.* explains that patients with graft thrombosis are often resistant to aspirin compared with patients without thrombotic events supporting the use of other antiplatelet agents for patients with aspirin resistance (8). Furthermore, occurrence of graft thrombosis in patients with good response to aspirin suggests that a more potent antiplatelet treatment may be beneficial. On this basis, an alternative antiplatelet therapy, achieving a greater platelet inhibition through a different mechanism of action may be more efficient than aspirin to

reduce the risk of graft thrombosis. Ticagrelor is indeed a good option. This potent antiplatelet agent is a selective and reversibly binding $P2Y_{12}$ receptor antagonist and is direct-acting, in contrast to thienopyridines, including clopidogrel, which action depends on variable and genetically determined metabolic activation (9). Interestingly, in addition to potent and consistent antiplatelet effects, ticagrelor has adenosine-associated pleiotropic effects. It inhibits adenosine cellular uptake, thus increases plasma levels of adenosine, which has been proposed to have cardiovascular protective effect (10,11). Adenosine regulates coronary vasodilation and decreases inflammatory responses to a various stressful setting. Moreover, adenosine may reduce microvascular spasm and prevent endothelial injury of coronary microcirculation. Adenosine can also prevent ischemia/reperfusion injury according to the PLEIO trial (11). Therefore, this unique mechanism may contribute to additional benefits of ticagrelor after CABG compared to other antiplatelet agents, and ticagrelor alone may be as effective as associated to aspirin. Unfortunately, the low statistical power of the trial affects conclusions and only opens the debate.

All antiplatelet agents are associated with an increased risk of perioperative and spontaneous bleeding complications, but ticagrelor seems to be particularly at risk. This is an important point highlighted by this study. Actually, a total of five major bleeding events occurred during the follow-up period: 3 in the ticagrelor plus aspirin group, 2 in the group receiving ticagrelor only, none in the aspirin-treated group. Although bleeding episodes were numerically more common in patients treated with combination therapy, which is coherent with previous studies of dual antiplatelet therapy in a variety of indications, the DACAB trial lacked sufficient statistical power to assess safety and to characterize the bleeding risk. Ticagrelor, like prasugrel, provides a more consistent platelet inhibition than clopidogrel. However, the bleeding risk does not seem to be similar (12). In the PLATO trial, which demonstrates the superiority of ticagrelor plus aspirin on dual aspirin-clopidogrel therapy to prevent cardiovascular events and mortality in patients with acute coronary syndrome, there was no significant increase of major bleeding (11.6% *versus* 11.2%, P=0.43), either fatal or life-threatening, associated with ticagrelor. Major bleeding with no relation to CABG (gastro intestinal or intracranial hemorrhages), accounting for 1/3 of major bleedings, were more frequent with ticagrelor than with clopidogrel (1.2% *versus* 2.9%, P<0.001) (7). The bleeding risk of ticagrelor seems to be comparable to that of aspirin, when used in monotherapy. In the SOCRATE trial, there was no increase in major bleeding, intracranial and life-threatening hemorrhage, among 13,199 patients treated in monotherapy with ticagrelor or aspirin for a non-severe ischemic stroke or high-risk transient ischemic attack (13). Major bleeding occurred in 0.5% of patients treated with ticagrelor and in 0.6% of patients treated with aspirin, intracranial hemorrhage in 0.2% and 0.3% respectively, and fatal bleeding in 0.1%. Although data from other trials on ticagrelor are reassuring, in the DACAB trial, the safety issues remain unanswered.

The DACAB trial demonstrated that the association of ticagrelor and aspirin was superior to aspirin alone to maintain vein graft patency at one year after CABG surgery. Unfortunately, this study was not designed to assess whether this positive effect in graft patency translates into a meaningful improvement in robust clinical outcomes. The statistical power of the DACAB study is not sufficient to show a significant effect on the incidence of major adverse cardiovascular events or major bleeding events. Moreover, the association between graft failure and adverse clinical outcomes is not clearly established: different studies report discordant results and several cohorts do not show association between graft failure and myocardial infarction or death (14). The DACAB trial raises more questions than it answers and, eventually, the clinical impact of ticagrelor and aspirin remains unknown. Additional studies are needed before changing our practice of antiplatelet therapy. We are waiting for results of the TiCAB trial (NCT01755520), a randomized, double blind phase III multicenter study of ticagrelor compared with aspirin for prevention of vascular events in patients undergoing CABG, to define the right place of ticagrelor (15).

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Footnote

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

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outcomes after coronary artery bypass surgery. Circulation 2012;125:749-56.
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