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Commentary: Yin and Yang: Antiplatelet and lipid-lowering therapies to prevent vein graft thrombosis and atherosclerosis after coronary artery bypass graft surgery

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The saphenous vein (SV) continues to be routinely used during coronary artery bypass graft (CABG) surgery because of its ease of use and ready availability.¹ While convenient as a conduit, the SV remains limited by the eventual development of vein graft disease, featuring the pathologically linked processes of thrombosis and atherosclerosis.^{2,3} Early thrombosis can be a major cause of vein graft attrition. Even when preformed under optimal conditions, the harvesting of venous conduits can lead to focal endothelial disruption, resulting in the accumulation of fibrin and platelets on the luminal surface.⁴ Grafts that survive this early period frequently develop a progressive thickening of the media, forming a template for the development of atherosclerotic changes.² By 10 years after surgery, most SV grafts have occluded or have developed significant stenosis.^{1,2}

As a result of graft and native vessel attrition, patients undergoing CABG are at high risk for subsequent ischemic events,³ highlighting the importance of secondary preventive therapies after surgery.^{1,5} The yin and yang of postoperative therapies, antiplatelet agents and lipid-lowering medications, continue to be the mainstay of secondary prevention, targeting different and yet complementary pathways to prevent SV graft occlusion after CABG.

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CENTRAL MESSAGE

Antiplatelet and lipid-lowering therapies are the mainstay of secondary prevention after CABG and are critical for the prevention of vein graft thrombosis and atherosclerosis.

Antiplatelet therapies help prevent platelet aggregation and graft thrombosis and have been found to be particularly beneficial if administered in the early postoperative period following CABG.^{1,5} Focusing on the burden of atherosclerosis, lipid-lowering therapies (such as statins) reduce low-density lipoprotein (LDL) levels, inhibit SV neointimal formation, and reduce late SV occlusion.^{6,7} Both therapies play key roles in the prevention of adverse cardiovascular outcomes after CABG and are strongly recommended postoperatively in contemporary guideline statements.^{5,8}

In the current issue of the *Journal*, Zhu and colleagues⁹ performed a post hoc analysis of the Different Antiplatelet Therapy Strategy After Coronary Artery Bypass Graft Surgery (DACAB) trial that enrolled 500 patients undergoing elective CABG (75.8% off-pump). Subjects were randomized to either ticagrelor plus aspirin, ticagrelor alone, or aspirin alone, starting within 24 hours after surgery, for the duration of 1 year. In the landmark paper published in 2018,¹⁰ the authors reported that the combination of ticagrelor plus aspirin significantly improved SV patency compared with aspirin alone, confirming the critical importance of dual antiplatelet therapy when CABG is performed using off-pump techniques.^{5,11,12} In the current paper, the DACAB group explored the impact of baseline LDL levels on SV patency 1 year after surgery. Patients were stratified into 2 groups based on preoperative LDL level greater or lesser than 1.8 mmol/L (70 mg/dL). In this post hoc evaluation, the authors noted that baseline LDL levels did not influence 1-year graft occlusion, noting similar patency rates

for the 2 subgroups (83.8% vs 82.3%, LDL-low vs LDL-high, $P = .86$). Moreover, for both LDL subgroups, the 1-year graft patency rates were greater with ticagrelor and aspirin, compared with aspirin alone.⁹

The authors are to be congratulated for performing the DACAB trial and making a major contribution to the field of secondary prevention after CABG. Nevertheless, the results of this DACAB post hoc analysis should be interpreted within the context of the study design. DACAB was a randomized open-label, antiplatelet trial that was not originally designed as a lipid study, and patients were not randomized to either of the 2 LDL groups. Moreover, the original trial enrolled mainly off-pump patients undergoing surgery in China, and therefore the results may not necessarily apply to other CABG populations or those having on-pump surgery, which is more common in many parts of the world. Second, of importance in this post hoc analysis, information regarding the statin type and dose were not prospectively recorded during the trial, limiting any analysis of association between statin use and SV patency. Since the majority of trial subjects had baseline LDL levels great than 1.8 mmol/L (70 mg/dL), it is unclear how many patients were treated with guideline-recommended^{5,8} high-intensity statins in the perioperative period and if any were treated with ezetimibe or PCSK9 inhibitors.

Despite these limitations, an important take-home message is readily apparent in the current study. As noted by the authors, the process of graft thrombosis, which is prevented with antiplatelet therapy, appears to be the dominant factor causing early SV disease. Vein graft atherosclerosis is generally a long-term process contributing to late SV failure, which is possibly the reason why the authors did not find a significant relationship between LDL levels and 1-year SV patency. Similarly, in the recent Aggressive Cholesterol Therapy to Inhibit Vein Graft Events (ACTIVE) trial, randomization to high-intensity statin treatment did not significantly reduce vein graft occlusion 1 year after CABG, and neither baseline LDL nor mean LDL during the trial was associated with SV occlusion.¹³ As noted by the authors in the current study, the influence of LDL and the impact lipid-lowering therapies may take longer than 1 year to yield significant improvements in SV graft patency.^{6,7}

Despite the emergence of new clinical trials, for many years now, antiplatelet and lipid-lowering therapies have cemented their roles as the yin and yang of secondary

prevention, helping to avert SV graft thrombosis and atherosclerosis after CABG. In the future, the cardiovascular community can look forward to follow-up studies from the ACTIVE and DACAB research groups, which should provide contemporary data and interesting analysis evaluating the impact of lipids levels on SV atherosclerosis and late graft occlusion.

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