Comeback for glycoprotein IIb/IIIa inhibitors during percutaneous coronary interventions for saphenous vein bypass grafts: may be for distal protection with filter-based devices?

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This editorial refers to ‘Platelet glycoprotein IIb/IIIa receptor inhibition as adjunctive treatment during saphenous vein graft stenting: differential effects after randomization to occlusion or filter-based embolic protection’ by M. Jonas et al., on page 920

Long-term outcome of coronary bypass surgery (CABG) is limited by progressive and significant narrowing of vein grafts in about half the patients within 10 to 15 years after operation. Despite a reduced world-wide trend for bypass operations and more widespread utilization of arterial conduits during CABG, treatment of symptomatic patients with degenerated aorto-coronary bypass vein grafts will remain a challenge of interventional cardiology. Bare metal coronary stents have improved long-term outcome after percutaneous coronary intervention (PCI) for saphenous vein grafts (SVG), by reducing restenosis after balloon angioplasty, whereas many devices such as sevoflurane stents have failed to show additional benefit. Stent placement in SVG, however, carries up to 20% incidence of procedure-related complications mainly because of distal embolization, especially in old, diffusely diseased vein grafts. Because of an even greater risk associated with surgical re-intervention, PCI is a tempting alternative for revascularization in the majority of patients with vein graft disease. Preliminary long-term results with increased utilization of drug eluting stents during vein graft PCI are encouraging.

The SAFER trial demonstrated that acute atherothrombotic, embolic complications associated with vein graft PCI can be roughly halved by the use of distal protection based on balloon occlusion and aspiration system, even in a cost-effective way. Even though risk of adverse major cardiac events (MACE) is increased in diffusely diseased vessels and bulkier SVG lesions, significant benefit with distal protection appears to be achievable across all levels of lesions. Recent observations suggest that comparable distal protection of SVG can be achieved by using either filter-based catheters or flush extraction devices during PCI. Because of technical limitations, vein graft disease may prevent successful delivery of these devices or their protection is not ‘complete’. Thus, even with appropriate use of distal protection devices, acute MACE rate after old vein graft PCI may exceed 10%, mainly due to ‘no-reflow’ phenomenon resulting in Q or non-Q wave myocardial infarction.

Adjunctive glycoprotein IIb/IIIa inhibitors have shown their effect when used during PCI procedures of native coronary vessels, especially among patients with acute coronary syndromes (ACS). Data supporting widespread use of glycoprotein IIb/IIIa inhibitors for vein graft PCI, however, is lacking; a pooled analysis of five randomised trials (EPIC, EPILOG, EPISTENT, IMPACT II, and PURSUIT) even suggested worse 30-day outcome in terms of MACE among patients receiving glycoprotein inhibitors compared with placebo (16.5 vs. 12.9%). These trials, however, included a mixed patient population in terms of clinical presentation. Some preliminary results suggest that vein graft PCI with adjunctive glycoprotein IIb/IIIa inhibitors might result in better immediate outcome in ACS patients with elevated troponin levels and critically stenosed vein grafts.

Michael Jonas et al. report differential effects of adjunctive use of glycoprotein IIb/IIIa inhibitors during SVG stenting in patients assigned to two different distal embolic protection devices. The study represents results of a prespecified subgroup analysis of the FIRE trial, where 651 patients undergoing SVG stenting were randomized to either filter-based FilterWire EX, or balloon occlusion and aspiration GuardWire embolic protection devices. GuardWire assigned patients treated with glycoprotein IIb/IIIa inhibitors showed a higher 30-day MACE rate, when compared with those not receiving adjunctive medication (16.0 vs. 6.3%; \( P = 0.007 \)). In contrast, high risk FilterWire patients assigned to adjunctive glycoprotein IIb/IIIa inhibitors had similar MACE rates when compared with their low-risk counterparts, who did not receive glycoprotein inhibitors (9.9 vs. 9.5%; \( P = 0.89 \)). It should be noted that...
the use of glycoprotein IIb/IIIa inhibitors was at the discretion of the investigator and not randomly assigned. However, this therapeutic effect was evaluated within each device subgroup. The authors, therefore, correctly conclude that adjunctive glycoprotein IIb/IIIa inhibitors may improve short-term procedural outcome of SVG stenting in those high-risk patients treated with filter-based protection catheters, but not in those treated with balloon occlusion and aspiration device.

Pathophysiology of distal embolization during vein graft PCI is multi-factorial, including plaque embolization, thrombus formation, and vasospasm. As platelet aggregation plays a significant role, it would be logical to assume that adjunctive glycoprotein IIb/IIIa inhibitors might provide additional benefit during vein graft PCI. In the FIRE trial, not surprisingly, patients pre-selected to GP IIb/IIIa inhibitors appeared to have more complex vein graft disease. Among all patient subgroups, patients receiving glycoprotein IIb/IIIa inhibitors and assigned to GuardWire appeared to have the worst 30-day outcome (MACE rate 16.0%), mainly because of a high rate of non-Q-wave myocardial infarctions. This observation, actually in agreement with findings from the SAFER trial, is most likely because of selection of a higher risk cohort (more advanced vein graft disease), and not because of adverse effects of glycoprotein inhibition. Curiously, a significantly higher bleeding complication rate at 30-days requiring blood transfusion was observed in those high risk patients assigned to GuardWire (9.1 vs. 2.1%) but not to FilterWire (5.8 vs. 5.1%) and those receiving glycoprotein IIa/IIb inhibitors compared with their respective low-risk subgroups.

What could explain the important observation of the FIRE trial, that is, a differential benefit of adjunctive glycoprotein IIb/IIIa inhibition limited to those patients assigned to filter catheter distal protection. As the authors conclude, mechanical conditions are different when these devices are used. During balloon occlusion, use of glycoprotein IIb/IIIa inhibitors is unlikely to have beneficial effect as embolic retrieval is facilitated with occlusion and aspiration of the bypass vein graft. In contrast, filter catheters allow, or actually require, ante-grade perfusion during the PCI procedure. Thus, favourable effects of adjunctive glycoprotein inhibition observed during filter catheter protection might well be explained by reduced platelet aggregation and deposition, during the vein graft intervention. Interestingly, those higher risk patients treated with FilterWire receiving adjunctive glycoprotein IIa/IIb inhibitors appeared to have a trend towards lower procedural MACE rate when compared with those not receiving glycoprotein inhibitors (3 vs. 7.6%). Thus, on the basis of the findings from the FIRE trial, not using glycoprotein inhibitors might even paradoxically prevent optimal performance of FilterWire during SVG procedure. Even though the FIRE trial was not powered to capture late differences in MACE, higher risk patients in the GuardWire group treated with glycoprotein IIb/IIIa inhibitors appeared to have an increased mortality trend at 6 months. This trend was not observed in the high-risk FilterWire subgroup.

Of course, because of the sample size limitation and non-randomized allocation to glycoprotein IIb/IIIa inhibitors, the observations from the FIRE trial need to be validated in a randomized trial. Nevertheless, these interesting findings reported by Michael Jonas et al. cannot be neglected. The FIRE trial is suggesting a need for adjunctive glycoprotein IIb/IIIa inhibition for optimal performance of Filter-Wire for the distal embolic vein graft protection. No such benefit was observed during utilization of GuardWire, which may well be due to different mechanical conditions during distal SVG protection. Whether patients with vein bypass graft disease presenting with non-ST-elevation ACS and elevated troponin levels, indicative of platelet microembolization, might derive additional benefit from such a tailored therapeutic approach would be of interest to study. Perhaps, there really is a comeback for adjunctive glycoprotein IIb/IIIa inhibition during vein bypass graft interventions in selected higher risk patient subgroups, at least when treated with filter-based distal embolic protection devices.

Conflict of interest: none declared.

References