The good, the bad, and the ugly: triple therapy after PCI in patients requiring chronic anticoagulation

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This editorial refers to 'Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting'† by P. Karjalainen et al., on page 726

A percutaneous coronary intervention presents unique challenges to the antithrombotic management of patients requiring chronic anticoagulation. Warfarin is often discontinued several days before a percutaneous intervention, exposing patients to the risk of potentially life-threatening thrombo-embolic complications. In contrast, bridging the period after the intervention until a therapeutic INR is reached again often requires additional anticoagulation with heparin, greatly increasing the risk of in-hospital bleeding complications. One solution to this problem is to consider a transradial approach, which not only obviates the need for temporarily discontinuation of anticoagulation therapy, but also avoids having to administer additional heparin while restarting warfarin in patients already receiving dual antiplatelet therapy. Finding the ideal chronic antithrombotic combination after hospital discharge appears to be an even more challenging problem. Triple therapy, i.e. dual antiplatelet therapy and warfarin, appears to be the ideal approach after PCI in patients requiring chronic anticoagulation: aspirin plus clopidogrel avoids stent thrombosis, whereas warfarin prevents thrombo-embolism. Unfortunately, this combination clearly increases the risk of bleeding complications during follow-up after stenting. To date, it remains unclear whether we have good alternative antithrombotic strategies for this growing patient population to a large extent because of the absence of the study data. All boils down to finding a perfect balance between risk of stent thrombosis and thrombo-embolic complications and the risk of major bleeding. Unfortunately, the present study by Karjalainen et al. indicates that this balance is very delicate and requires treading a very thin line dictated by careful weighing of all risk factors in each individual patient.

Before the advent of thienopyridines, aspirin plus oral anticoagulation was the standard antithrombotic regimen after stenting. This combination is still often used after stenting in patients requiring chronic anticoagulation. A recent meta-analysis, nevertheless, indicates that the combination of warfarin and aspirin after PCI is associated not only with a higher risk of stent thrombosis or myocardial infarction, but also with a higher incidence of serious bleeding complications. Can aspirin plus clopidogrel then be considered as an alternative regimen? Dual antiplatelet therapy is undoubtedly current evidence-based practice for the prevention of in-stent thrombosis, but does not adequately protect against thrombo-embolic complications. Nevertheless, not all patients requiring chronic anticoagulation have a similar risk of thrombo-embolic complications. Patients with a recent venous thrombo-embolic event or with mechanical prosthetic heart valves, especially tilting-disc aortic valves and valves in the mitral position, are at very high risk for thrombo-embolism. In contrast, the thrombo-embolic risk is probably somewhat less in most patients with atrial fibrillation or dilated left ventricle or an aortic prosthetic valve, depending on age and co-morbidities. Consequently, it appears to be reasonable to adjust the need or extent of anticoagulation to the perceived thrombo-embolic risk in patients after coronary stenting. More frequent lab analyses might also be helpful to ensure international normalized ratio (INR) values well within recommended evidence-based ranges. Likewise, chronic aspirin doses should also be kept within the 75–100 mg range as recommended by the ESC guidelines.

To date, only a handful of small retrospective studies have addressed the safety of triple therapy. Unsurprisingly, most find an increased bleeding risk. One study in elderly patients undergoing PCI found a 1.9 times higher risk of bleeding with triple therapy (95% CI 1.3–2.9). Another study assessing triple therapy after primary PCI for ST-elevation myocardial infarction even reported an unacceptably high transfusion rate of 21% at 1-year follow-up. However, major bleeding complications remain a serious concern. Even nuisance bleedings during long-term follow-up can result in a catastrophe, because patients or their physician might be tempted to stop aspirin, clopidogrel, or the anticoagulant. Permanent discontinuation of either aspirin or clopidogrel after a short and usually innocent episode of bleeding will undeniably increase the risk of stent thrombosis.

Karjalainen et al. report their retrospective study on antithrombotic strategies after coronary stenting in 239 patients requiring long-term oral anticoagulation, the largest study on triple therapy to date. Atrial fibrillation...
was the most common indication for anticoagulation. Mean INR during the procedure was 2.2 ± 0.5, with 21% undergoing a radial procedure and 26% treated with a closure device. Somewhat surprisingly, drug-eluting stents were used in 40% of patients. Triple therapy, a combination of low-dose aspirin, clopidogrel, and warfarin, was chosen upfront in almost half of the patients (48%), but the duration of clopidogrel treatment was significantly shorter than that in the dual antiplatelet only and warfarin plus clopidogrel or warfarin plus aspirin groups. Warfarin plus aspirin, warfarin plus clopidogrel, and aspirin plus clopidogrel were chosen for 15, 21, and 16% of the remaining patients, respectively.

When compared with a matched patient cohort, warfarin was found to be an independent predictor of the combined endpoint of death, myocardial infarction, target vessel revascularization, or stent thrombosis within 12 months (OR 3.4, 95% CI 1.2–9.3). Irrespective of antiplatelet co-therapy, 1-year mortality was more than five-fold higher in the warfarin group. Warfarin was also associated with a more than three-fold increased risk of major bleeding. Among warfarin-eligible patients, stent thrombosis and myocardial infarction were significantly more frequent in patients treated with only aspirin plus warfarin, with the majority of stent thromboses occurring during the first week after PCI. Only two patients in the triple therapy group had a stent thrombosis during follow-up, although one of these occurred after discontinuation of clopidogrel. Conversely, major bleeding was much more frequent with the warfarin plus clopidogrel combination, compared with triple therapy, reflecting the shorter duration of clopidogrel treatment in the triple therapy group. Finally, stroke rate was very high in warfarin-eligible patients treated with dual antiplatelet therapy only.

This study illustrates the heterogeneity in treatment strategies for warfarin-eligible patients after PCI, but it also indicates that outcome is unsatisfactory regardless of choice of antithrombotic combination. At first sight, we should not derive treatment recommendations from a retrospective study. It is, nevertheless, very tempting to speculate on the risk–benefit ratio of different treatment combinations. Triple therapy appears to be a good approach to minimize the risk of both stent thrombosis and thrombo-embolism. Furthermore, the risk of major bleeding with triple therapy is not significantly higher than that with double therapy in this analysis, probably because of the shorter duration of clopidogrel co-therapy. This implicates that triple therapy should probably be kept as short as possible. In this respect, the added benefit of using drug-eluting stents will have to be weighed against much shorter clopidogrel treatment periods with bare-metal stents in warfarin-eligible patients. Alternative combinations are aspirin plus clopidogrel, warfarin plus aspirin, or warfarin plus clopidogrel. In this study, warfarin plus aspirin was associated with an unacceptable high incidence of early stent thrombosis, whereas warfarin plus clopidogrel leads to more bleeding. Withholding anticoagulation, in contrast, exposes warfarin-eligible patients to a very high stroke risk. For practical purposes, Karjalainen’s analysis suggests that triple therapy presents the best risk–benefit ratio, provided that clopidogrel co-treatment is kept as short as possible. It also indicates that warfarin plus a short course of clopidogrel might be a safer alternative for patients with a very high risk of bleeding. This probably implies that, in general, drug-eluting stents should be avoided in these patients.

Clearly, it will take a large randomized clinical trial to answer this conundrum. Unfortunately, the heterogeneity of patients with an indication for chronic anticoagulation and the high variability in thrombo-embolic risk probably preclude the successful completion of such a trial. In this respect, however, safety data from large upcoming studies in ACS patients chronically receiving one of the new oral anticoagulants (e.g. rivaroxaban or dabigatran) on top of low-dose aspirin and clopidogrel will certainly help to solve this dilemma.

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**References**


