

Glycoprotein inhibitors in patients on chronic anticoagulation: Safe enough or too much risk?

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The optimal antithrombotic treatment of patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) is unclear, especially for those currently taking oral anticoagulation. There are no large randomised trials exploring the best antithrombotic regimen in these patients, and thus the management of this patient population is controversial (1, 2). Moreover, current guidelines do not adequately address this issue (3, 4).

A few observational studies have shown that the overall efficacy of triple antithrombotic therapy (aspirin, clopidogrel and coumarin) may be superior to other strategies adopted in the prevention of cardiovascular events (5, 6). However, long-term maintenance with triple therapy (warfarin, clopidogrel and aspirin) seems to be associated with an increased bleeding risk (7). Importantly, major bleeding has been strongly associated with increased rates of in-hospital and late mortality, myocardial infarction, and repeat revascularisation procedures after PCI (8, 9).

Glycoprotein IIb/IIIa on the platelet surface is the final common pathway of platelet aggregation, regardless of the initiating stimulus, and thus this glycoprotein IIb/IIIa has become the target of another family of antiplatelet drugs (10). For high-risk patients undergoing PCI, adding a gly-

coprotein IIb/IIIa inhibitor (GPI) reduces the risk of procedure-related thrombotic complications (11). However, the benefit/risk profile of GP inhibitors is substantially uncertain for patients with acute coronary syndromes who are not routinely scheduled for early revascularisation. Moreover, in stable patients undergoing elective PCI, pre-treatment with 600 mg of clopidogrel seems to provide platelet inhibition sufficient to enable a safe procedure without the need for GPI (12).

There are few data about the use and importance of GPI drugs in anticoagulated patients in clinical practice. What about bleeding risk? Is this therapeutic approach safe enough? In the December 2009 issue of *Thrombosis and Haemostasis*, Lahtela et al. reported on a retrospective multicenter registry, showing a wide inter-hospital variation in GPI use (13). These drugs were mainly used – as expected – in acute coronary syndromes. Importantly, GPI use and advanced age remained as the only independent predictors of major bleeding. In the GPI group, major bleeding was not predicted by international normalised ratio (INR) levels.

Due to the increased bleeding risk and the lack of established recommendations in this field, warfarin-treated patients are usually less frequently treated with GPI (5). There is also wide inter-centre variability in the use of these drugs (14). Nonetheless, patients with AF undergoing PCI constitute a high-risk population due to age, comorbidities and stroke risk factors. Indeed, these patients have a high mortality rate, with an increased risk of both thrombotic and haemorrhagic complications (6). Hence, the consistent increase in bleeding risk associated with GPI use has been seen in non-selected patient populations (15, 16), is also observed in anticoagulated patients (17, 18), and confirmed now by Lahtela et al. (13). Although a propensity

score was used in this recent study, some important differences remained between patients with and without use of GPI. For example, diabetes, bridging therapy with low-molecular-weight heparin, warfarin interruption, radial artery access or the indication for PCI, are all established risk factors for major bleeding (17, 19, 20). A strict evaluation for both thrombotic and haemorrhagic risk should be performed before coronary stenting in order to determine the best antithrombotic treatment option. Large registries and prospective clinical studies are necessary in order to assess the optimum management of these patients.

The timely publication of a Consensus Document of the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association (EHRA) and the European Association of Percutaneous Cardiovascular Interventions (EAPCI) gives recommendations on antithrombotic therapy for patients with AF presenting with acute coronary syndrome and/or undergoing percutaneous coronary intervention/stenting (21). The consensus document states that GPI seem to increase major bleeding events irrespective of periprocedural INR levels and should be used with caution in these patients, and probably avoided unless in a 'bail out' situation, perhaps due to intraluminal coronary thrombi. Thus, GPI use should be avoided in anticoagulated patients. These drugs add little benefit in patients with stable angina or troponin-negative acute coronary syndrome. In acute coronary syndromes, other suggested options could perhaps be mechanical thrombus aspiration (22) or bivalirudin use (23). Whilst bivalirudin could reduce bleeding risk, comparing to heparin and GPI, there are limited data in anticoagulated AF patients (24). Clearly, more information on the optimal management strategy for such patients is needed.

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