**Anticoagulation in percutaneous coronary interventions: no man’s land?**

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This editorial refers to ‘ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention’†, by S. Schulz et al., on page 2482

Since the first days of percutaneous coronary interventions (PCI), it has been a common understanding to treat patients with a combination of antiplatelet and anticoagulant drugs to prevent thrombotic complications.¹ Numerous anticoagulants have been tested during elective PCI.² Nonetheless, aspirin and unfractionated heparin (UFH) have survived more than 30 years as the standard regimen, particularly in patients with stable angina. After the introduction of stents, the antiplatelet regimen was supplemented by thienopyridines. The administration of glycoprotein IIb/IIIa antagonists did not render additional benefits in the setting of elective interventions.³ Bivalirudin as a direct antithrombin was shown to be safer and effective in patients with acute coronary syndromes.⁴ ⁵ However, the anticoagulation management during elective procedures gained only limited attention. Tradition and habits may influence the selection of anticoagulants and especially the dose of heparin.⁶ This is even more surprising, since PCI technique and material improved considerably and bleeding complications moved in our focus. Much of the data regarding heparin administration during PCI were obtained before introduction of coronary stenting and potent antiplatelet agents. Was there no need to address this question or why was there no lobby?

Unfractionated heparin is produced from animal mucosa and has various antithrombotic effects, which are not fully elucidated yet. Basically, it exerts its anticoagulant effect by potentiating the effects of antithrombin III on factor Xa and thrombin. In contrast to low-molecular-weight heparins, its individual response on coagulation is only roughly predictable and uncertain in its meaning. It is influenced by differences in body mass, the concomitant use of other drugs, and the clinical setting—particularly acute coronary syndromes, which can increase heparin resistance. However, in the current guidelines, UFH achieves class I recommendations and level of evidence C, i.e. expert opinion.⁷ ⁸ The reason for assigning a level C is that there is no alternative and/or it appears unethical to perform such studies. Despite the better pharmacological profile, low-molecular-weight heparins like enoxaparin were unable to demonstrate yet higher efficacy with respect to thrombotic complications.⁹ After fondaparinux was found in OASIS 5 to be associated with increased rates of thrombus formation, UFH was immediately reinstalled.¹⁰ There is nothing magic to UFH, but it could best adjust to the moving target in the real world of catheterization laboratories.

In the above context, it is a great achievement to investigate UFH in ISAR-REACT 3A as published in this issue. The design of this study may irritate hardliners of randomized trials. However, it appears legitimate to address such a common problem in a third controlled arm and compare this to an appropriate historic cohort. This has been done before in other trials like GABI 2¹¹ and ARTS II¹² and may serve generating new hypotheses. In the original ISAR-REACT 3 trial, the authors compared a high dose of UFH with bivalirudin in biomarker negative, clopidogrel pretreated patients and found no difference in clinical endpoints, but higher rates of bleeding complications.¹³ The authors used a dose of 140 U/kg body weight UFH, which may be more effective to achieve a target ACT, but is higher than the 100 U/kg body weight UFH bolus recommended in the current guidelines. Accordingly, it was reasonable to conduct ISAR-REACT 3A with the guideline-conform dose, which eventually levelled off the difference in bleeding without increasing thrombotic complications. Therefore, the conclusion should be rather that increasing the dose of UFH does not result in additional benefit and is only associated with higher risk of bleeding. In other words, using the standard dose of UFH and bivalirudin appears to be equally effective in stable angina patients.

Following the results of ISAR-REACT 3A, the question arises whether we now really know the optimal dose and the length of post-procedural administration of UFH or other anticoagulants? Currently, dose regimens vary widely from centre to centre and are more dictated by ‘gut feeling’. It is probably too provocative to omit UFH completely,¹⁴ but a dose <100 U/kg body weight...
seems reasonable on today’s standard background medication. Several smaller studies have shown that a standard dose of 5000 U irrespective of the body weight is safe and centres using this dose over more than a decade get safely along with this. Interestingly, several randomized studies have documented efficacy and safety of low-dose heparin during elective PCI procedures. Attractive with this low-dose regimen is further that this is identical to the 60 U/kg recommended for the combination with glycoprotein IIb/IIIa receptor inhibitors that may be given during the ongoing procedure.

Beyond that, even lower doses may be appropriate for elective low-risk PCI as demonstrated by two small trials using either a fixed dose of 2500 U or a weight-adjusted dose of 30 U/kg body weight. For the direct thrombin inhibitor bivalirudin, theoretical advantages are obvious. Monitoring its dose is accomplished using the same activated clotting time guidelines as for UFH. Thus, the question of the right dosage of bivalirudin is also not yet fully elucidated.

Regarding the present data, UFH unequivocally remains the standard anticoagulant in PCI. However, not only UFH but also the dosage for bivalirudin may be reconsidered to eventually optimize the dosing in the clinical scenario of elective coronary interventions. There is absolutely no doubt that the use of high dosage of UFH may be harmful. Indeed, it is speculative that UFH may be unessential for some stent procedures or even when glycoprotein IIb/IIIa receptor inhibitors or low-molecular-weight heparins have been administered recently. It would be rather suggestive that the dosage of heparin has to be customized at the initiation of every PCI procedure: as much as necessary, as little as possible. Patients with acute coronary syndromes, visible intracoronary thrombi, and no clopidogrel pre-treatment may require somewhat higher doses. In contrast, the stable patient pre-treated with clopidogrel, undergoing direct stenting of a short single lesion in a short procedure, may require only very little anticoagulation allowing safer sheath removal and rapid mobilization. Rules for an individually tailored management need to be established. We spend much time testing sophisticated new devices and drugs, but this ‘no man’s land’ still deserves to be cultivated.

Conflict of interest: none declared.

References