Redemption by RE-DEEM?

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This editorial refers to ‘Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial’†, by J. Oldgren et al., on page 2781

Blood coagulation is essential for survival because it prevents loss of the liquid organ blood from the organism. The present human gene pool is the result of a selection process that has favoured effective coagulation since prehistoric times. However, blood coagulation has become a double-edged sword. In the last two centuries, with an ageing population and the advance of atherosclerosis, an overly active coagulation system has become a liability for the older individual because it can lead to thrombotic complications that affect life expectancy as well as quality of life. In contrast to bleeding disorders, hypercoagulation is unlikely to be unbalanced by evolutionary selection in the future, because these events routinely occur after the reproductive phase of life. Therefore, for fine-tuning of the coagulation system we will have to rely on drugs for the foreseeable future.

Anticoagulatory drugs shift the balance towards less thrombus formation at the cost of increased bleeding. The clinical usefulness of an anticoagulant depends on its efficacy to prevent thrombus formation in relation to its effect to induce bleeding projected on the background of the absolute thrombo-embolic risk of the underlying disease for which it is intended. Importantly, the mechanism of thrombus formation differs between natural arterial and venous disease, and particular aspects have to be taken into account after intra-arterial interventions.

According to contemporary guidelines, standard antithrombotic therapy for secondary prevention of ischaemic events after myocardial infarction (MI) treated interventionally or conservatively consists of double antiplatelet therapy, namely aspirin combined with a P2Y12 receptor antagonist for 1 year. In the past, vitamin K antagonists (VKAs) have been investigated alone or in combination with aspirin to prevent recurrent ischaemic events. This strategy has proven effective in reducing ischaemic events—given that the target for the international normalized ratio (INR) was >2—however, at the cost of increased bleeding. Overall mortality was not affected. In the era of intervenational treatment of MI, VKAs have been used in patients with atrial fibrillation and stent implantation on the background of double antiplatelet therapy. This has resulted in excessive bleeding (triple therapy). Thus, long-term anticoagulation therapy for secondary prevention after MI has proven problematic.

With the advent of the new direct factor Ila and Xa inhibitors the question of added anticoagulatory therapy needs to be readdressed (Figure 1).

Oldgren et al. have reported the results of the RE-DEEM trial in which the oral direct factor Ila inhibitor dabigatran was given twice daily in a dose escalation phase II trial for secondary prevention after MI. Six month treatment was associated with a dose-related 2- to 4-fold increased risk of bleeding for patients receiving dual antiplatelet treatment. While dabigatran significantly reduced coagulation activity measured by a surrogate laboratory endpoint, there was no clear signal for a reduction of ischaemic clinical events. This is remarkable because, compared with guideline-recommended thorough revascularization for MI, the therapeutic strategy in RE-DEEM was relatively conservative. This may indeed have favoured an additional antithrombotic regimen given on top of aspirin and thienopyridine, but, even so, there was no further reduction in ischaemic endpoints. The net clinical benefit balancing the potential reduction of thrombo-embolic events vs. the shown increased risk of bleeding can only be appropriately evaluated in an adequately powered phase III study, as acknowledged by the RE-DEEM authors.

Two phase II studies with oral direct factor Xa antagonists supplement our knowledge about the interaction of oral anticoagulation and double antiplatelet treatment. The APPRAISE trial testing apixaban was prematurely stopped due to excessive bleeding in the higher dose apixaban study arms. ATLAS TIMI 46 investigated rivaroxaban in subjects stratified according to mono- or dual antiplatelet therapy. Especially in the invasively treated patients with dual antiplatelet therapy, rivaroxaban led to a dose-dependent increase in bleeding events with a non-significant reduction in the number of ischaemic events. The two lower doses are currently being tested in the phase III ATLAS II TIMI 51 trial which is adequately powered to assess if the antithrombotic benefit is large enough to outweigh anticipated increased bleeding rates.

Although the data presented by Oldgren et al. do not support the general use of antithrombins for secondary prevention of recurrent ischaemic events after MI, the information gained by RE-DEEM is still important and the authors are to be congratulated for an invaluable contribution to our knowledge in the field. Patients with atrial
fibrillation, who also receive a coronary stent, may have the indication for double antiplatelet therapy to prevent stent thrombosis and additionally for anticoagulation therapy to prevent thrombo-embolic events associated with atrial fibrillation. Triple therapy including VKAs and double antiplatelet therapy has been used with reluctance because of the substantially elevated bleeding risk reported. The RE-DEEM data will help to characterize the bleeding risk of triple therapy involving dabigatran which has proven superior to VKAs in RELY. Further studies will have to show whether there is indeed an indication for dabigatran in triple therapy.

In summary phase II studies for the prevention of recurrent thrombotic events after acute coronary syndrome with novel anticoagulants added to double antiplatelet therapy have shown marginal or no benefit at the cost of signals for increased bleeding. The much larger ATLAS II TIMI 51 phase III trial will provide us with a more definitive answer about the clinical usefulness of anti-Xa agents in this context. Whether we will see phase III data for dabigatran in this indication is not known. Therefore, we will have to wait a little longer for redemption.

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References

Figure 1: Overview of recent trials involving direct oral anticoagulants. * = study ongoing. ### = phase II study terminated early because of excessive bleeding. # = study terminated early because of superior efficacy of apixaban vs. aspirin. AF = atrial fibrillation; ACS = secondary prevention in acute coronary syndrome.