Early decrease in coagulation activity after myocardial infarction is associated with lower risk of new ischaemic events: observations from the ESTEEM trial

We have carefully read the interesting article focusing on the pivotal issue of risk stratification and prognosis in patients recovering from an acute myocardial infarction (AMI). Analysing data from a cohort of patients enrolled in the ESTEEM trial, the authors aimed at evaluating whether markers for thrombin generation, fibrin turnover, and activated thromboplastin time (APTT) were related to clinical outcomes and whether change in the level of these markers could predict the risk of new ischaemic events or bleeding. The authors concluded that in patients with recent AMI a reduction of an initially elevated coagulation activity identifies those at a decreased risk of new ischaemic events, regardless of whether this reduction occurs spontaneously or is induced by pharmacological treatment. In addition, they purported that patients with higher initial coagulation activity may benefit the most from long-term treatment with ximelagatran. Some issues, in our opinion, deserve attention and need a deeper examination in order to avoid possibly misleading conclusions.

Briefly, there were no significant differences in prothrombin fragment 1 + 2 (F1 + 2) and D-dimer levels between the ximelagatran and the placebo groups at randomization. After a week of treatment, in the ximelagatran treated patients, 76% had decreased F1 + 2 level and 72% had decreased D-dimer level, compared with 39% and 40%, respectively, in the placebo group (P < 0.001). Patients with reduction vs. no reduction of F1 + 2 tended to have fewer ischaemic events during the period of randomized treatment (10 vs. 14%), while the group of patients without ischaemic events showed a significantly larger reduction of D-dimer levels than patients with ischaemic events. However, there was no significant interaction (interaction P > 0.05) between changes in coagulation activity and study treatment. Within the cohort of patients with reduced levels of F1 + 2 or D-dimer after 1 week, the frequency of ischaemic events 'did not significantly differ' between the ximelagatran group (10 and 8%, P = 0.5) and placebo group (13 and 11%, P = 0.5). At cessation of study treatment (after 6 months) or at premature discontinuation, the median levels for F1 + 2 and D-dimer in the ximelagatran group were still significantly reduced when compared with the placebo group (P < 0.001). However, at follow-up, 2 weeks after cessation of study treatment, the median levels of F1 + 2 and D-dimer had increased in the ximelagatran group and at this time point no significant difference was evident between the ximelagatran and the placebo group.

Given these findings, we agree with the authors when they underline that a reduction of the coagulation markers 'regardless whether it occurred spontaneously or by ximelagatran treatment' is associated with a better outcome, in particular at 1-week time point, and that F1 + 2, which reflects thrombin generation, is unlikely to be an useful prognostic marker. On the other hand, D-dimer, reflecting fibrin generation and degradation, appears to be a reliable prognostic marker.

So at odds with the conclusions of the authors, it is conceivable, but 'not proven' on the basis of these data, that the addition of ximelagatran on top of the currently available therapies may provide additional benefit in terms of reduction of the coagulation markers: this point is crucial.

At the end of the study, the levels of coagulation markers increased in the ximelagatran group, and we wonder if this increase is significant with respect to the end of the study and to the randomization. Moreover, and this point is completely neglected by the authors, the long-term administration of ximelagatran is bared by prohibitive hepatic toxicity, measured as the rate of alanine aminotransferase (ALT) elevation greater than three times above the upper normal limit.

We have conducted and recently published a non-biased/non-funded systematic review and a meta-analysis on this topic showing that ximelagatran treatment >3 months was associated with an OR for hepatic toxicity of 6.73 (95% CI: 5.01–9.05) compared with placebo (P < 0.001). In absolute terms, for prolonged treatments, the incidence of hepatic toxicity rose from 1.1 to 7.1%, with a number needed to harm of 17.5. We think that stating that 'ximelagatran, effectively reduced coagulation activity, and reduced the risk of new ischaemic events in patients with high initial coagulation activity', could be misleading if not weighted against the risk of serious hepatic injury. Indeed, such risk led the FDA to deny approval for ximelagatran in the USA, the EMEA to allow only short-term administration and the manufacturer (AstraZeneca), after a further fatality in a post-marketing study, to withdraw the drug.6–8 In our opinion, even if the aim of the study by Christersson et al. was different, they should have reported, or at least mentioned, possible adverse events related to the study drug.

This study clearly suggests D-dimer as a useful prognostic marker in post-AMI patients, but all the conclusions have to be balanced in a context in which the study drug has been judged unsafe.

References

We found that early reduction of initially high coagulation activity, as measured by the D-dimer levels, identified patients with decreased risk of the composite of death, myocardial re-infarction, severe recurrent ischaemia, or stroke (9% vs. 16%, \( P = 0.03 \)), regardless of whether the reduction occurred spontaneously or was induced by pharmacological means. Patients with higher initial coagulation activity seemed to benefit most from long-term treatment with ximelagatran.

Long-term treatment with oral anticoagulants, e.g. warfarin, has in several studies of myocardial infarction patients been shown superior to aspirin. The use of warfarin has several drawbacks including frequent INR controls and increased bleeding risk, thereby indicating a need for the development of new anticoagulants such as direct thrombin inhibitors. In the ESTEEM study, treatment with the first oral direct thrombin inhibitor ximelagatran reduced major cardiovascular events during 6 months, without a significant increase in major bleedings. However, as pointed out already in the original ESTEEM publication, 6.5% on the lowest and 12.2–13.0% on the higher ximelagatran doses developed increased levels of alanine transaminase. Owing to the concern for hepatotoxicity in ESTEEM and other long-term ximelagatran trials, this drug was withdrawn from the market in February 2006.

New oral direct thrombin inhibitors, hopefully without adverse effects on liver function tests, and other anticoagulants are currently evaluated in clinical trials. We believe that the ESTEEM trial and our recently published substudy have provided important knowledge and hope for the future. Prolonged treatment with an oral direct thrombin inhibitor after a myocardial infarction can reduce the risk of new ischaemic events without increased risk of major bleedings. Furthermore, markers for coagulation activity, preferably D-dimer, might be an additional tool for tailoring of anti-thrombotic treatment after acute myocardial infarction.

References

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Limitations to the use of virtual histology-intravascular ultrasound to detect vulnerable plaque

Surmely et al.\(^1\) used virtual histology-intravascular ultrasound (VH-IVUS) to characterize coronary plaque in patients with acute coronary syndrome (ACS) and stable angina. Although VH-IVUS is a promising plaque- imaging platform, we believe that significant methodological issues must be resolved before VH-IVUS is used to detect vulnerable plaque, let alone direct therapy. First, in thrombus-laden arteries, VH-IVUS does not enhance the precise detection of plaque borders by grey-scale IVUS. Unfortunately, the authors do not describe their method of thrombus border detection nor their measurement variability.

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