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

The ESTEEM trial was a phase II study evaluating the efficacy and safety of treatment with the first available oral direct thrombin inhibitor ximelagatran together with aspirin, when compared with aspirin only, after a recent myocardial infarction. In a subgroup of 518 (out of 1883) patients, we measured markers of coagulation activity, i.e. prothrombin fragment 1 + 2 (F 1 + 2) and D-dimer, in serial samples obtained during and after study treatment. Ximelagatran persistently decreased these markers of thrombin generation and fibrin turnover. At follow-up after cessation of study treatment, the levels of coagulation activity in the ximelagatran group had increased and were no longer different from the aspirin only group, although the levels of D-dimer in the ximelagatran group were slightly but significantly lower than those at randomization.

As pointed out in the letter by Testa and co-workers, the aim of the recently published results from the ESTEEM substudy was to evaluate whether the coagulation activity was related to clinical outcome. 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 antithrombotic treatment after acute myocardial infarction.

References

Letters to the Editor 1783

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Surmey et al. used virtual histology-intravascular ultrasound to characterize coronary plaque in patients with acute coronary syndrome (ACS) and stable angina. Although VH-IVUS is a promising 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 image quality of plaque borders or grey-scale IVUS. Unfortunately, the authors do not describe their method of thrombus border detection nor their measurement variability.