Letters to the Editor 1783

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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 myocardial infarction. In a subgroup of 518 (out of 1883) patients, we measured markers of coagulation activity, i.e. prothrombin fragment 1 + 2 (F1 + 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

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

Surmely et al. 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 imprecise detection of plaque borders by grey-scale IVUS. Unfortunately, the authors do not describe their method of thrombus border detection nor their measurement variability.
in ACS lesions. Inaccurate detection of the borders shared by thrombus, plaque, and lumen may introduce large measurement errors of plaque composition. The site with the minimum lumen diameter may be misidentified. Thrombus may be misclassified as fibrous plaque, proportionally increasing this plaque component at the expense of the others. Thus, errors in border detection may lead to spurious conclusions about culprit plaque composition in ACS. Second, methods to define and measure coronary plaque vary widely, contributing to divergent results and conclusions. Surmely et al. do not define fixed margins for their region of interest. Moreover, they report relative plaque composition as calculated by the VH-IVUS software, a ratio of the absolute area of each plaque component to an estimated plaque area, one that excludes an estimated medial area. It is more appropriate to report relative plaque composition as the ratio of absolute area of each plaque component to the area bound by lumen and the external elastic membrane, as this utilizes direct measurements. Third, VH-IVUS-derived thin cap fibroatheroma (TCFA) is not yet a validated surrogate for plaque prone to thrombosis. VH-IVUS-derived TCFA is loosely based on the histopathological studies of necropsy specimens, which provide at least 100-fold superior spatial resolution to VH-IVUS. Complicating matters, Surmely et al. define TCFA differently from others. Larger prospective longitudinal studies, such as PROSPECT, may determine whether any VH-IVUS-derived definition of plaque phenotype has sufficient positive or negative predictive value for coronary thrombosis. Until then, it seems premature to conclude, as does the accompanying editorial, ‘that a plaque with only fibrous content by VH can be considered as stable with minimal risk of causing thrombosis.’ To advance the invasive detection of vulnerable plaque, the research community should adopt standards to measure thrombus-associated plaque, calculate plaque composition, and define vulnerable plaque. We believe that with such standards investigators will be at lower risk of experimental error.

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