Summary of Symposium

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Low-molecular-weight heparins (LMWHs) represent an important advance in the anti-thrombotic therapy of the past two decades. Their potential advantages as antithrombotic agents are based on their half-life in plasma, which is two to four times longer than that for standard heparin (SH) at therapeutic doses, and on their 90-98% bioavailability after subcutaneous administration, producing not only a predictable anticoagulant response but also permitting once-daily injection. Furthermore, for an equivalent antithrombotic effect, LMWHs have been shown to cause less disturbance of haemostasis than SH in experimental models and this has been assumed to represent a reduced risk of serious haemorrhage.

Earlier, several randomized clinical trials had shown LMWHs to be effective in preventing post-operative venous thromboembolism and this has been the subject of a number of previous symposia. Recent studies have evaluated the safety and effectiveness of LMWHs in treating various syndromes of arterial occlusion and in the treatment of venous thromboembolism. This symposium was organized to review the possible role of LMWHs as antithrombotic agents in the management of unstable coronary syndromes and acute myocardial infarction (MI), and the special predisposition of the cancer patient to thrombotic complications.

Coronary artery thrombosis is now recognized to be a critical event in the evolution of not just stable coronary atherosclerotic disease and acute MI but also unstable coronary syndromes.

In the past, studies have primarily emphasized the value of traditional risk factors, for example hyperlipidaemia, cigarette consumption, blood pressure and diabetes, which predict < 50% of all future cardiovascular events.

Dr Paul Ridker reviewed the value of novel haemostatic and thrombotic markers, such as intrinsic fibrinolysis and systemic micro-inflammation, for the prediction of the risk of arterial thrombotic disease. Abnormal levels of fibrinolytic parameters have been shown to predict future cardiovascular events and tissue-type plasminogen activator appears to be the most useful of these markers. Most striking has been the observation that elevated levels of C-reactive protein, a marker of low grade chronic inflammation, can predict the future risk of both MI and stroke.

Dr James Chesebro summarized the current understanding of the pathological processes that underlie the thrombotic and clini-

cal events responsible for unstable coronary syndromes and acute MI. Coronary artery thrombosis appears to be initiated by atherosclerotic plaque rupture. The resultant

thrombus is typically platelet-rich, containing varying amounts of fibrin, erythrocytes and leucocytes. The determinants of the extent and rate of development of thrombosis in response to plaque rupture are not well characterized but there is considerable evidence that thrombin generation is a critical determinant of the progression of thrombosis. In the setting of acute MI, thrombosis appears to progress rapidly until there is total coronary artery occlusion. Dr Chesebro emphasized that platelet-rich thrombosis appears to be dependent on a dynamic interaction among several factors that promote platelet adhesion, aggregation and secretion and the tissue-factor-mediated activation of the coagulation system. Thrombosis appears to be a critical mediator of the extent of arterial thrombosis but the extent of local shear forces also plays an important role in the progression of a thrombotic lesion.

The combination of SH and aspirin is the current treatment of choice for patients suffering from unstable coronary syndromes. Dr Alexander Turpie reported that SH given intravenously in therapeutic doses has been shown to be more effective than aspirin in reducing the risk of death or MI in such patients. A number of LMWHs have been evaluated in unstable angina and there is accumulating evidence that LMWHs are safe and effective alternatives to SH in unstable coronary artery syndromes, and may have practical and therapeutic advantages.

Although thrombolysis is of undoubted benefit in appropriately selected patients suffering from acute MI, a considerable proportion do not receive such therapy for a number of reasons. In general, these patients receive aspirin in addition to a variety of other therapies, including nitrates, angiotensin-converting enzyme inhibitors and beta-blockers. Additionally, high-risk patients, including those who have sustained large anterior infarctions, are given intravenous SH in an attempt to prevent early coronary re-occlusion, infarct extension and re-infarction, and the complications associated with left ventricular (LV) mural thrombosis.

As mentioned above, a number of studies have evaluated the efficacy and safety of LMWHs in unstable coronary artery syndromes. Workers at this institute have organized a study with the aim of evaluating the efficacy/safety profile of long-term treatment (days 4-30) with a LMWH (dalteparin) in a placebo-controlled study of acute MI patients of < 85 years of age, who were not candidates for thrombolysis, presenting within 24 h of the onset of chest pain. All patients entering the study received an adjusted LMWH dose administered subcutaneously on days 1-3 inclusive. On day 4, the patients were randomized to receive LMWH in a fixed dose or placebo during days 4-30. In addition, both groups received daily oral aspirin commencing on day 1 and continuing for the duration of the study. The primary efficacy variables assessed included the prevalence of total cardiac events (death, re-infarction/infarct extension, post-infarction angina, requirement for emergency revascularization and clinically diagnosed heart failure) during days 4-30 post-infarction.

Secondary endpoints included: the incidence of death, re-infarction and angina occurring between day 30 and 3-month follow-up; the combined incidence of thromboembolic events, including the presence of LV mural thrombus, embolic stroke, peripheral arterial occlusion and venous thromboembolic events occurring during days 1-30 and at 3-month follow-up; and ischaemia during exercise testing and an LV function of $\leq$ 40%,

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as assessed by echocardiography, both performed on day 30.

Safety was evaluated on the basis of the prevalence of major and minor bleeding episodes (including total and haemorrhagic strokes, categorized according to standard criteria during days 4-30); allergic reactions; and thrombocytopenia. The study population size was based upon the literature from previous international multicentre trials which reported an overall 30% incidence of cardiac events. If a 30% incidence of cardiac events is assumed in the placebo arm of the study then, in order to detect a 25% absolute reduction in the LMWH group, 1,000 randomized patients are required in order to have a 90% power of detecting this difference at the 5% level. Recruitment into the study has now been completed and the results are currently being analysed. These will be reported in the near future.

A prothrombotic state is believed to occur in association with malignant disease and its assessment may provide an insight into therapeutic intervention as well as helping to understand the pathological mechanism. Dr Mannucci reported that although coagulation activation markers are often elevated, the results available so far do not indicate that they are useful in the clinical management of individual cancer patients.

Dr Ajay Kakkar reported that the principal interventions in patients with cancer are surgery, chemotherapy and venous catheterization, and these interventions heighten the risk of a venous thrombosis. SH is currently the most widely used and best researched pharmacological thromboprophylactic in oncology patients. LMWHs may offer significant advantages to cancer patients because of their safety and ease of use.

Dr Mark Levine stressed the fact that cancer patients with an established venous thromboembolism are more likely to develop recurrent episodes during treatment with oral anticoagulants. The treatment of acute thrombosis in such patients consists of at least 5 days of SH, followed by administration of oral anticoagulants. LMWHs have been shown to be as effective and safe as SH for treating acute venous thrombosis. Dr Levine also reported that recent meta-analyses have revealed lower mortality rates with LMWH than with SH, indicating that LMWH may exert an inhibitory effect on tumour growth that is not observed with SH.

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