Thrombosis and cardiovascular disease: Exciting perspectives in cardiovascular prevention and therapy

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This second part of the *Thrombosis and Haemostasis* theme issue “Hot topics in Cardiovascular Cell and Pharmacotherapy” contains a further collection of manuscripts that address various concepts of therapeutic interventions in thrombosis and its prevention, in relation to cardiovascular disease.

Starting with the concept of “treating” high homocysteine levels that seems to be sound in experimental model systems but which is not supported by clinical studies. The major limitations of current thrombolytic treatment of pulmonary embolism (PE) and stroke are also covered. This theme issue further contains data on novel anticoagulant developments and limitations of anti-platelet therapy. Finally, the theme issue addresses problems of haemostasis at the forefront of cardiovascular therapy, in the application of cardiac assist devices and total artificial hearts.

The association between homocysteine levels in blood, thrombosis and cardiovascular disease has been the focus of many experimental as well as clinical studies. A review and a large scale epidemiological study in this theme issue describe interesting perspectives on potential pathophysiological mechanisms and provide clinical recommendations in this controversially discussed area.

Schroecknagel et al. (1) investigated circulating homocysteine. The association between homocysteine and CAD. The authors found a correlation between homocysteine level and CAD. They describe several determinants of homocysteine levels including age, renal impairment and heart failure. Interestingly, the authors demonstrate that low vitamin B availability, inflammatory status and homocysteine levels seem to be closely related indicating a pathophysiological connection of inflammation and circulating homocysteine.

Di Minno et al. (2) also present a thorough review on the role of homocysteine in thrombosis, including experimental studies on potential pathomechanisms and large scale epidemiological as well as interventional studies. Notably, results from the latter have been quite disappointing. Despite a reduction in homocysteine plasma levels by vitamin supplementation (vitamin B6, B12, and folic acid) there was no significant reduction in cardiovascular risk. Also, despite an increase in homocysteine plasma levels by some lipid-lowering drugs there is no associated increase in cardiovascular risk. Therefore, the final conclusion of this review contains a clear message that the data presently available do not provide support for routine screening and treatment of elevated homocysteine to prevent cardiovascular disease.

Although thrombosis as well as bleeding are major problems in patients with ventricular assist devices or total artificial hearts, studies towards the understanding of the underlying pathophysiological mechanisms are rare. Nevertheless, they are pivotal for the adequate choice of concomitant medication and the design of assist devices and total artificial hearts. More recently, changes in platelet function (Leoffler et al. [3]) and in this issue changes in humeral coagulation (Heilmann et al. [4]) have been investigated. The first describes that despite a high rotational speed in the Jarvik 2000 assist device, platelets are not activated. The latter paper describes a potential pathophysiological mechanism of bleeding. Patient on a ventricular assist device developed von Willebrand syndrome, whereas those with total artificial hearts with less tubing do not. These observations are clearly important examples demonstrating the importance of haemostatic evaluations of new assist or heart replacement devices.

An important clinical question is addressed in the paper in this issue by Lankeit et al. (5): Which patients with pulmonary embolism (PE) should receive thrombolytic treatment? The relevance of this question is given by the fact that the rate of intracranial/fatal haemorrhage in patients with thrombolysis for PE is reported to be up to 4 % in retrospective cohort studies/registries. This high complication rate is particularly troublesome since the development and clinical trialling of further fibrinolytic agents is nearly halted as many large-scale trials testing novel fibrinolytics in myocardial infarction did not demonstrate major benefits of new developments. Thus, it is important to clearly define the patients in whom bleeding risk is outweighed by the reduction in PE-induced death. Clearly, the group of patients who are haemodynamically compromised, would probably benefit most from thrombolysis. However, there is an ‘intermediate risk’ group of PE patients who potentially benefit from fibrinolytic treatment. These are probably patients in whom right ventricle-dysfunction (e.g. diagnosed in echocardiography) and myocardial injury (increased troponins) are also present. An ongoing large scale trial, will hopefully help to define the optimal therapy: Thrombolysis or sole anticoagulation.

An area in which novel fibrinolytics are clearly needed and in which a few new agents are still developed and tested in clinical trials is in relation to thrombolysis in patients with stroke. The only fibrino-
lytic reagent so far approved for this indication is recombinant tissue-type plasminogen activator (rt-PA). However, the time after onset of symptoms in which the benefits outweigh the risks, in particular fatal intra-cerebral bleeding, is restricted. In addition to its fibrinolytic effects, rt-PA seems to have additional unfavourable effects in the ischaemic brain. Thus, it makes sense to develop fibrinolytics with other modes of action than rt-PA. Microplasmin (μPli) is such a promising agent that acts as a direct fibrinolytic agent. Using a rat stroke model, in a systematic comparison with rt-PA and tenecteplase (TNK), microplasmin indeed reduced the volume of ischaemic lesion and reduced markers of microvascular damage (Burggraf et al. in this issue [6]). Interestingly, TNK, which is a recombinant variant of rt-PA did even worse than rt-PA. These findings indicate that novel fibrinolytic agents might indeed provide major improvements for patients with stroke, hopefully reducing the debilitating effects of this frequent disease.

In a prospective observational study with 623 patients, Harmsze et al. (7) investigated a potential interaction between the metabolism of clopidogrel and calcium channel blockers. They found clopidogrel poor response (less platelet inhibition) when the calcium channel blocker amloidipine was administered concomitantly. Interestingly several other calcium channel blockers did not cause inhibition of clopidogrel response in platelets. This finding warrants prospective, randomised studies to define recommendations in regards to concomitant therapy of clopidogrel and specific calcium channel blockers. As long as clear-cut clinical consequences of platelet function test results are not established, these studies have to assess clinical outcome as primary endpoint.

Van Walderveen et al. (8) investigated a novel anticoagulant, a covalently fused complex of anti-thrombin and heparin (ATH), which has previously been shown to strongly inhibit thrombin, even if bound to fibrin and to demonstrate minimal unspecific binding to plasma proteins and endothelial cells. Also, the plasma half-life could be substantially prolonged in comparison to heparin. In addition to these effects the authors of the manuscript published in this second part of the theme issue demonstrate that ATH is beneficial in regards to protein C activation and the efficiency of activated protein C. These findings therefore demonstrate the therapeutic potential of fine-tuned anticoagulant approaches.

Clearly, the field is moving quickly. We hope that the both parts of this open theme issue (part 1 published in March 2010) have highlighted some of the exciting and expanding themes in relation to thrombosis in cardiovascular disease.

References