Coagulation factor Xa as driver of cardiovascular diseases

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For decades, patients have been prescribed anticoagulants to prevent and treat thrombosis. Anticoagulants inhibit enzymes of the coagulation cascade, and thereby prevent clot formation. Heparin was one of the first anticoagulants introduced already early in the previous century. In the same period, warfarin was introduced and became the number one oral agent to prevent and treat thrombosis. After almost 70 years of warfarin treatment, it became appreciated that warfarin therapy has effects beyond prevention and treatment of thrombosis, including the calcification of large blood vessels. Although warfarin is currently still being used as an anticoagulant, new direct oral anticoagulants (DOACs), such as dabigatran and rivaroxaban (I used the latter anticoagulant extensively in my thesis to study the pleiotropic effects of coagulation), are now the preferred agents in thrombosis management. However, in the past two decades, it became evident that through administration of these anticoagulants, biological and cellular processes beyond coagulation can be modulated. Although long-term effects on biological processes in humans remain largely unknown, preclinical data suggest that DOAC treatment might have protective effects on the cardiovascular system.

Since increasing numbers of patients will be administered DOACs oftentimes lifelong, it is of significant importance to fully elucidate the pleiotropic effects of coagulation proteins and the long-term biological consequence of their inhibition.

In chapter 4 I showed that the anticoagulant drug rivaroxaban, inhibited the development of atherosclerosis, and more importantly promoted regression of highly advanced atherosclerotic lesions. I attempted to further elucidate the biological processes that explain anticoagulant-mediated atheroprotection. In doing so, I revealed that inhibition of the coagulation system by rivaroxaban modulated biology at the genetic level, thereby affecting cellular metabolism. If we can fully understand the pleiotropic actions of inhibition of the coagulation system, we can turn this knowledge into new treatment options for atherosclerosis, without the bleeding risk associated with DOACs. Recent clinical trial data supports the concept of atheroprotection by DOACs: mortality rates significantly decreased in patients with stable coronary artery disease treated with a low dose rivaroxaban (in combination with aspirin) when compared to their control receiving traditional treatment. The studies described in this thesis can help create a stronger foundation for the wider use of a low dose anticoagulant in poly vascular atherosclerotic diseased patients, provided that the benefit risk (bleeding) ratio allows it. More efficient treatment of atherosclerosis will further diminish the burden on society and cost-effectiveness studies demonstrate the potential gain in subsets of patients with atherosclerosis, when treated with the dual pathway inhibition strategy.

Coronary atherosclerosis is the main cause of most myocardial infarctions and combined with stroke, responsible for the majority of deaths in Western

society. The treatment of an acute myocardial infarction is directed towards fast restoration of blood flow to the ischemic heart, termed reperfusion. However, reperfusion is considered a double-edged sword because it further enhances the damage to the infarcted site. Chapter xx describes how inhibition of coagulation by anticoagulants can potentially protect the heart from reperfusion injury, and can thereby provide a better long-term outcome for the patients.

In 2017, treatment of coronary atherosclerotic disease accounted for 22% of the total cardiovascular expenses (and 2.6% of the total healthcare expenses) amounting to 2.3 billion euros in the Netherlands alone. Since no optimal treatment for atherosclerotic disease exists to date, and prevalence rates are expected to rise significantly, expenses can become unsustainable in the next decade. Besides improved patient care, the data from this thesis can aid in decreasing the global economic burden that atherosclerotic disease and myocardial infarction have on society by guiding future treatments strategies.

In conclusion, in the short-term this thesis supports a stronger foundation for wider use of specific anticoagulants and in the long-term it aids in guiding future treatment strategies.