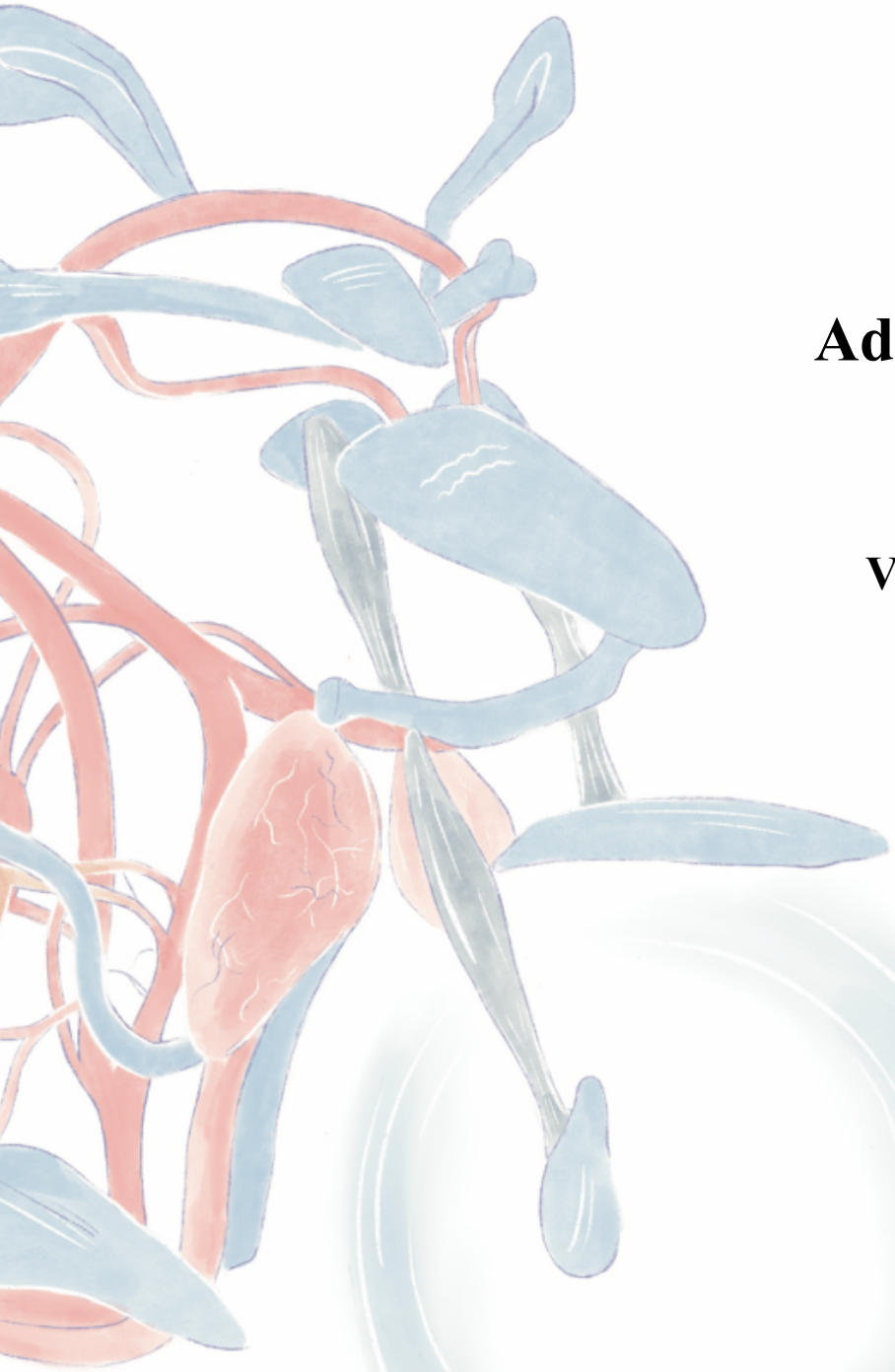
Oral anticoagulants as double-edged swords



Addendum

Valorisation

In this chapter I discuss possible opportunities for valorisation of knowledge based on the findings described in this thesis. Valorisation is about the impact created by the transfer of scientific knowledge. This is not limited to money, but can also result in spin-off companies, patents or updates in medial guidelines. Research can be split into basic and clinical research. Here, we present translational research with focus on increasing basic knowledge to have a direct impact on medical care. Knowledge obtained via basic translational research by providing mechanistic insight, clinical research can be better and more specifically conducted. This interplay is crucial for further improving our medical care.

The main objective of this thesis is to gain further insight in the role of anticoagulants and vitamin K metabolism in cardiovascular disease, focusing on the role of vascular smooth muscle cells in this process.

Vascular calcification was long thought to be a passive process, but is now accepted as an active and highly regulated process. Vascular calcification is acknowledged as independent risk factor for cardiovascular disease and can be related to several leading cardiovascular disease resulting in death in the western world. The impact of anticoagulant treatment on calcification and cardiovascular disease is discussed in more detail in **chapter 1 and 2**.

In **Chapter 3** I have investigated the interplay between intimal calcification and coagulation. The consequence of intimal calcification is currently debated. It is currently accepted that microcalcification, or spotty calcification, worsens plaque stability and thereby increase the chance of cardiovascular risk. On the other hand, macrocalcification, or sheet-like calcification has been put forward as being beneficial and aggravating atherosclerosis. Moreover, volume and density of calcification influence cardiovascular outcome differently. Our research demonstrates that intimal calcification activates the coagulation system. Increased coagulation has been shown to worsen atherosclerosis and thereby increases cardiovascular risk. Thus, our research indicates that VKA-induced vascular calcification worsens cardiovascular outcome. These results give further insight in the role of vascular calcification in cardiovascular disease risk and encourages to investigate ways to reduce vascular calcification.

In **Chapter 4,** we investigated vitamin K supplementation as potential treatment option for intimal calcification. Currently, treatment to prevent, hold or regress vascular calcification is lacking. We identified beneficial effects of vitamin K on atherosclerosis development, likely mediated via VSMC. Moreover, we show that discontinuation of VKA treatment has beneficial outcome on atherosclerosis. Taken together, we demonstrate the importance of vitamin K for vascular health. Biomarkers of vitamin K status, such as vitamin K dependent proteins are currently being used to predict vascular calcification. The role of vitamin K in vascular disease has further led to the collaboration with companies selling vitamin K2 (Nattopharma ASA) and companies measuring vitamin K status using the vitamin K dependent matrix Gla-protein (IDS).

We demonstrate in **Chapter 5** that every anticoagulation drug has off-target effects thereby influencing cardiovascular disease differently. We compared the VKA warfarin and the NOAC dabigatran on atherogenesis. Our data suggest that patients with increased risk for arterial disease, i.e. vascular calcification, would benefit from NOACs. If translatable to the human situation, our data urge for a personalized choice of anticoagulant agent and can further help evaluate clinical decisions on the use of either VKA or NOAC treatment. Although NOAC are more expensive in direct costs, cardiovascular risk reduction will be beneficial for the health care system on the long run. Some patient groups, including patients with mechanical valve replacement and patients with end stage chronic kidney disease, are still limited to VKA treatment. Patients with end-stage chronic kidney disease are prone to develop cardiovascular disease. Our data support the development of NOAC that are not limited by clearance via the kidney. Also, novel anticoagulation therapies focusing on upstream coagulation factors XI and XII are currently being investigated to induce anticoagulation but limit bleeding risk.

In **Chapter 6** the focus lies on the role of VSMC in the initiation of vascular calcification. We show that phenotypic switching of VSMC is key in the initiation of vascular calcification. Moreover, we identified Nox5 as key-regulator of pathological VSMC oxidative stress which mediates this phenotypic switching. VSMC plays a pivotal role in many vascular diseases and therefore Nox5 is an interesting novel therapeutic target. Recently, the WHO recognized Nox inhibitors as a new therapeutic class. Nox5 is the least studied of the Nox family, probably due its absence in rodents. The Nox inhibitor Setanaxib is recognized as Nox1/4 inhibitors, however no specific targets for Nox5 are available yet.

Of note, the results described in my thesis are from experimental animal models and *in vitro* work on VSMC. Therefore, confirmation of findings in clinical trials will be important before implementation in clinical guidelines. Nevertheless, the underlying mechanistical insight creates the opportunity for novel therapeutic approaches and highlights the importance of personalized medicine. Moreover, the results will open up opportunities to limit progression of vascular calcification.