Targeting the vessel wall in cardiovascular prevention
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General introduction
and outline of thesis
INTRODUCTION

Cardiovascular disease is the leading cause of death globally

Cardiovascular disease (CVD) is the leading cause of death in the world. With an estimated number of 18 million per year, it represents 30% of all global deaths (1). In the Netherlands alone, cardiovascular disease accounts for almost 47,000 of 142,000 deaths and over 300,000 hospital admissions annually, adding up to a healthcare expenditure of € 5.3 billion (2, 3). Cardiovascular disease is not only a problem in developed countries, but also increasingly in developing countries (4, 5). This is illustrated by the fact that over 80% of all CVD deaths take place in low- and middle-income countries. Especially in places with quick urbanization, CVD spreads almost epidemically. Moreover, whereas cardiovascular mortality in Europe is slowly declining, a rise is expected in less prosperous regions.

The process of atherosclerosis underlies most cases of cardiovascular disease

Over 80% of cases of CVD represent clinical manifestations of atherosclerosis, such as coronary artery disease, cerebrovascular disease, aortic aneurysms, and peripheral artery disease (1). Besides those, atherosclerosis may also contribute to the development of dementia, which substantially adds to the disease burden in aging populations (6). Atherosclerosis is the lifelong process of gradually clogging of arteries. This process is already apparent in adolescence (7). The development of clinical manifest atherosclerosis depends on the combination of genetic predisposition, lifestyle and environment. Well known risk factors are male gender, a positive family history, smoking, diabetes, hypertension, dyslipidemia, psychosocial factors, abdominal obesity and a sedentary lifestyle (5). More recently, inflammatory activity was added to this list (8). Research efforts are mainly focused on those risk factors that can be modified, preferentially by medication, as bad habits seem hard to break.

The vessel wall is central in the pathogenesis of atherosclerosis

If we zoom in on the vessel wall, the current hypothesis describes atherosclerosis as interplay of the endothelium, cholesterol and the immune system (9). The earliest changes that precede the formation of atherosclerotic lesions take place in the endothelium. These changes include increased endothelial permeability to low density lipoprotein (LDL)-cholesterol and other plasma constituents as well as upregulation of adhesion molecules, which facilitate transendothelial migration of immune cells (e.g. monocytes, macrophages and T lymphocytes). Subsequently, monocytes and macrophages oxidize and scavenge LDL-cholesterol particles in the vessel wall (10). This facilitates the intracellular accumulation of cholesterol esters and results in the formation of so called foam cells. These cells together with T lymphocytes form fatty streaks in the arteries. As autopsy studies have shown, fatty streaks are already present in adolescence (7). Later in the atherosclerotic process smooth muscle cells also migrate to the lesion. As the lesion progresses, a fibrous cap is formed to fence the lesion from the...
lumen. This cap covers the mixture of lipid, inflammatory cells and debris. Clinical manifestations often result from rupture of the fibrous cap, subsequent thrombus formation and occlusion of the artery. Although the entire vasculature is exposed to systemic risk factors, such as dyslipidemia and inflammation, atherosclerotic lesions only form at specific regions of the arterial tree. These are mainly branching points with disturbed blood flow and low endothelial shear stress (11).

**Key challenges are to identify individuals at high risk of cardiovascular disease and to lower it**

The two major challenges in the prevention of the occurrence (primary prevention) and re-occurrence (secondary prevention) of CVD are first of all, to identify individuals at high risk and subsequently, to reduce risk. By gaining further inside in the pathogenesis of atherosclerosis, researchers hope to identify new risk markers as well as novel targets for therapy.

Predicting who is and who is not likely to suffer from a myocardial infarction or stroke, would open the way for more targeted preventive treatment. Current risk markers, such as cholesterol levels, predict risk at a population level, but have limited predictive value on an individual level. This is illustrated by the fact that the vast majority of cardiovascular events occur in people with normal cholesterol levels and/or low risk estimates (12). However, in current clinical practice, risk estimations such as the Framingham Risk Score and SCORE, although relatively insensitive, largely determine the decision to prescribe preventive drug treatment (13-15).

Current treatment modalities to prevent cardiovascular disease include cholesterol lowering drugs (e.g. statins), antihypertensives (e.g. thiazides, beta-blockers, ACE-inhibitors) and anti-platelet aggregation drugs to prevent thrombus formation (e.g. aspirin) (15). Statins, in particular, have been hugely successful (16). They are the single most effective, cost effective and safest method to reduce CVD risk and have become the cornerstone of prevention of CVD. Unfortunately, the majority of cardiovascular events is not prevented. Therefore, research efforts are directed at finding additional targets for treatment. Lately, this quest has been characterized by many disappointing results. Novel compounds, such as the MTP inhibitor BMS-201038 (16), the cholesterol absorption inhibitor ezetimibe (17) and the CETP inhibitor torcetrapib (18), showed serious side effects, no beneficial or even detrimental effects.

**The long period before atherosclerosis becomes manifest complicates research**

The fact that atherosclerosis is a lifelong, complex process, which at some point may or may not lead to a clinical event, complicates research. It is difficult to mimic this entire process in a laboratory. However, aspects can be studied in for example cell cultures. Furthermore, various animal models of atherosclerosis have been developed. Especially in mice, this requires
knocking out genes often combined with feeding a high-fat, 'Western type' diet to overcome the natural protection against atherosclerosis (20). Still, the most relevant study object remains man. Small, observational studies in humans and studies of so-called accidents of natures, such as spontaneous genetic defects, often generate interesting hypotheses. For example, the study of familial hypercholesterolemia (FH) has underlined the role of cholesterol in CVD. Familial hypercholesterolemia is characterized by high LDL-cholesterol levels, caused by a defect in the LDL-receptor gene, predisposing patients to myocardial infarctions at a young age (21). Furthermore, large scale, decades long, prospective population studies, such as the Framingham Heart Study, have elucidated many risk factors for CVD (22).

New drugs travel a long way from lab bench to bedside. After initial laboratory studies and safety assessments in healthy volunteers, studies of the effect on surrogate markers of CVD, such as intima-media thickness (IMT) of the carotid artery wall, are used to get a quicker peek at drug efficacy. Finally, large randomized placebo-controlled trials, often including thousands of patients for several years, are performed to test their effect on cardiovascular morbidity and mortality.

**OUTLINE OF THESIS**

It is time to move beyond cholesterol lowering to further prevent CVD. This thesis consists of three parts. Although the subjects of each part may seem divergent, they are united in the fact that they all focus on processes in the vessel wall that may contribute to the development of atherosclerosis and overt CVD. Interestingly, the three parts also represent different stages of development in research; from hypothesis to clinical application.

Part 1 deals with the endothelial glycocalyx. The glycocalyx is a gel-like layer covering the vessel wall. It influences for instance vascular permeability and the adhesion of inflammatory cells. The idea that the endothelial glycocalyx is an important barrier against atherosclerosis is a promising and exciting concept. Our research contains mainly of small, exploratory studies in cells, mice and man that form part of the initial steps toward possible use as biomarker and potential target for therapy.

Part 2 explores the possible usefulness of myeloperoxidase (MPO) as risk marker in different study populations. Myeloperoxidase is an enzyme of the immune system, which activity is helpful in the elimination of microorganisms, but at the same time can damage the vessel wall and oxidize lipoproteins. Our research suggests that the use of MPO as a biomarker in risk assessment in primary prevention and in a non-acute setting is limited.
Finally, in part 3, I describe one of last stages of research before application in the clinic, a randomized controlled trial. On the one hand it shows the failure of the novel class of drugs intended for cardiovascular prevention, i.e. acyl coenzyme A cholesterol acyl transferase (ACAT) inhibitors. These compounds were aimed at reducing foam cell formation in the vessel wall. On the other hand it shows the power of surrogate markers, such as carotid IMT measurements, in assessing the effect of therapy on cardiovascular risk.

REFERENCES