General introduction
General introduction

Cardiovascular disease (CVD) poses one of the most deadliest threats to western societies and will soon become a global epidemic as the incidence is rising rapidly both in the developed and developing world. At the core of CVD lies a process which is called atherosclerosis. Atherosclerosis is a progressive disease and is characterized by the gradual accumulation of lipids and fibrous material in large arteries [1]. The development of atherosclerosis starts at an early age and has a multifactorial origin. Familial hypercholesterolemia, familial combined hyperlipidemia and familial hypoalphalipoproteinemia are some of the genetic disorders in lipoprotein metabolism which are associated with the atherosclerosis process. Traditional risk factors contributing to the development of atherosclerosis include hypercholesterolemia, smoking, hypertension, diabetes mellitus, obesity and a sedentary lifestyle [2]. Treatment and prevention of atherosclerosis has been the subject of intensive research during the last decades. Statins, which lower low-density lipoprotein cholesterol (LDL-C) by inhibiting hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, are currently the single most important drug class used to slow this process of atherosclerosis.

Recent studies have shown that some unrelated medical conditions are also associated with an increased risk of developing CVD. These include, but are not limited to, disorders such as rheumatoid arthritis, systemic lupus erythematosus, antiphospholipid syndrome [3] and human immunodeficiency virus (HIV) infection [4]. HIV infection has indeed been associated with acceleration of atherosclerosis, either by itself or through its effects on the immune system resulting in chronic immune and coagulation activation. Ironically, effectively treating these HIV-infected patients with antiretroviral therapy greatly improves HIV-related morbidity and mortality but also seems to increase the incidence of CVD [4]. This increased risk of CVD initially seemed to be confined to those patients treated with protease inhibitors [5], but more recently agents belonging to the class of nucleoside reverse transcriptase inhibitors, particularly abacavir, were also reported to be associated with increased CVD risk [6]. The risk associated with HIV protease inhibitors is plausible given the fact that protease inhibitors are known to increase plasma levels of LDL-C and triglycerides. These lipid particles are highly atherogenic. LDL-C is one of the key components contributing to the development of an atherosclerotic plaque within the vessel wall. Abacavir in contrast has been hypothesized to exert its risk by promoting inflammation. Thus, HIV-infected patients are currently surviving longer as a result of the available effective antiretroviral therapy, but are also confronted with an increased incidence of cardiovascular disease. At present, approximately 33 million people are infected with HIV worldwide [7] and although only a small proportion of these people are currently receiving effective antiretroviral treatment it is expected that the number of treated patients will rise steadily in the coming years, partly because of an in-
creased availability of low-cost antiretroviral drugs, including generics produced in developing countries themselves. The increasing number of treated patients will also lead to more patients developing dyslipidemia and requiring further treatment. How can this be dealt with effectively and more importantly, can we do anything to prevent the potential epidemic of CVD awaiting HIV-infected patients worldwide? In this thesis, we present current knowledge about the determinants of this new phenomenon in HIV-infected patients and also discuss possible treatment modalities as well as provide suggestions as to how to decrease the risk of developing CVD.

Outline of the thesis

In the first part we review the current state of surrogate markers for cardiovascular disease in general. Atherosclerosis progresses slowly over many years before becoming clinically manifest as acute cardiovascular events late in the disease process. Studies examining pharmaceutical interventions therefore require long-term follow up in large populations in order to determine clinical benefit of such interventions. In order to avoid these time consuming and expensive intervention studies, the use of surrogate markers have gained wide interest in the last decade. In chapter 1 the existing cardiovascular imaging modalities, both invasive and non-invasive, are discussed. In chapter 2 we focus on carotid intima-media thickness, a non-invasive surrogate marker, and discuss its applicability in both observational as well as in drug intervention trials.

In the second part we focus on the role of low-density lipoprotein cholesterol (LDL-C) in atherosclerosis. To substantiate the impact of LDL-C lowering, we addressed surrogate markers for atherogenesis in a group of patients characterized by genetically-determined low LDL-C levels due to a mutation in apolipoprotein B (apoB), the major protein within the LDL-C fraction: familial hypobetalipoproteinemia (FHBL). In chapter 3 we report the results of direct sequencing of the entire apoB gene in order to identify the cause of the extremely low levels of ApoB and LDL-C in subjects with FHBL. Using these same FHBL subjects we investigated the effects of extremely low levels of LDL-C on surrogate markers for atherogenesis by evaluating both carotid intima-media thickness and arterial stiffness in FHBL subjects and compared these with observations in healthy controls (chapter 4).

The majority of cardiovascular events are not prevented despite the widespread use of (high dose) statins. Recent clinical trials have raised the awareness for aggressive lowering of LDL-C showing additional clinical benefit when LDL-C goals are lowered to below 100 mcg/dL (2.6 mmol/L) [8, 9]. In chapter 5 we review the clinical experience of a novel drug which aggressively lowers LDL-C by inhibiting both cholesterol production as well as intestinal cholesterol absorption. Both efficacy as well as safety issues are discussed.
In the third part of the thesis we address the cardiovascular consequences of HIV infection. The cardiovascular risk associated with HIV infection, its treatment and possible therapeutic options are discussed.

In chapter 6 we review the available evidence in the literature linking HIV infection and its treatment with atherosclerosis and summarize the multiple mechanisms by which HIV-infected patients are at increased risk of developing cardiovascular disease. In chapter 7 we investigate the differential effects of two antiretroviral drugs on lipids and lipoproteins in neonates born to HIV-infected mothers, who have received this treatment in order to prevent transmission of HIV from mother to child. By specifically evaluating these drugs in HIV uninfected newborns, this allows for accurate evaluation of the lipid-consequences of these drugs in absence of confounding factors such as chronic inflammation.

Chapter 8. In the HIV-field, there still exists a lot of debate whether and to what extent accelerated atherogenesis can be attributed to all drugs used to treat HIV or only a subgroup of drugs (mostly protease inhibitors). To address this issue in more detail, we compared the effects on lipids and carotid intima media thickness of chronic, stable use of protease-inhibitors versus non-nucleoside reverse transcriptase inhibitors (NNRTIs). Thus, we confirmed a clear HDL-C increase in patients using NNRTIs, the mechanism of which is as yet unclear. In chapter 9 we addressed the mechanism by which Nevirapine, one of the NNRTIs, increases HDL-C. However, in order to establish optimal lowering of cardiovascular risk in HIV-1 infected patients, potent statin therapy remains treatment of first choice. However, statin therapy is often limited or even omitted, partly due to the fact that interaction between HIV-treatment drugs and statins are feared. In chapter 10 the results of a pilot study are presented in which the efficacy and safety of rosvastatin, a statin which would be expected not to have any interaction with protease inhibitors, was investigated when used to treat dyslipidemia caused by the protease inhibitor lopinavir/ritonavir (Kaletra®).
Reference List