Introduction to this Thesis

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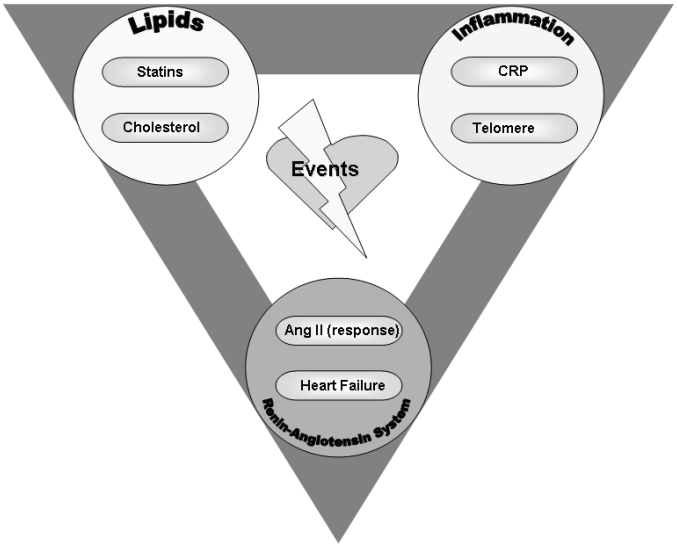
In 2004, 136,553 people in The Netherlands died. Cardiovascular disease is still the major cause of death in The Netherlands (n=45.445; 33%).[1] It is not only the leading cause of death but also the most important cause of loss of disability-adjusted life years.[2] The major contributor to the growing burden of cardiovascular disease is atherosclerotic disease, which accounts for about one third of the cardiovascular deaths. Our knowledge of the pathophysiology of atherosclerosis and its complications has greatly evolved over time.
Endothelial dysfunction and inflammation are among the earliest events in the pathogenesis of atherosclerosis.[3,4] The attachment of leukocytes to the endothelium and its migration into the intima leads to foam cell formation, lipids accumulation, formation of fatty streaks, and subsequent evolvement to an atheromatous plaque. Some new cardiovascular risk markers are emerging; most noteworthy are inflammatory markers, and markers of renal dysfunction.[5-8] From a (patho)physiological point of view, the renin-angiotensin



system plays a key role in cardiovascular pathophysiology.[9] The renin-angiotensin system is acknowledged as a major factor determining blood pressure, and fluid homeostasis. The effector molecule of the renin-angiotensin system, angiotensin II, can also be considered a pro-inflammatory and pro-oxidant stimulus, and accordingly provides a link between the mechanisms at play in hypertension and its common companion, atherosclerosis.[3,4] Stimulation of the angiotensin type 1 receptor by angiotensin II plays a central role in the cascade of signalling pathways, eventually leading to vasoconstriction, inflammation, oxidative stress and proliferation.[9,10] These are indeed key-

processes in various cardiovascular disease, including hypertension, atherosclerosis and heart failure. The evidence for interplay of the renin-angiotensin system with other cardiovascular risk factors, both potentiating each other is increasing. For example, both cholesterol and the inflammatory marker C-reactive protein have been demonstrated to upregulate the angiotensin type 1 receptor.[11,12] Elevated blood pressure is frequently associated with elevated cholesterol levels in hypertensive subjects. Increased knowledge of the interrelationships between the renin-angiotensin system with other cardiovascular risk factors in modifying vascular function is essential in the continuing fight against cardiovascular disease. Lack of profound understanding of these factors in the contribution and causation of the cardiovascular disease stands in the way of developing new therapeutic approaches aimed at treating cardiovascular disease.[13] The need exists for basic and clinical research designed to better comprehend the complex pathophysiology involved. This thesis will weave together laboratory and clinical advances to extend our knowledge on cardiovascular function and pharmacotherapy.
Several drugs proved to have anti-atherosclerotic properties and subsequent reduction of cardiovascular events. Keystone drugs in the prevention of cardiovascular disease are the 3-hydroxy-3-methylglutaryl co-enzyme-A (HMG-CoA) inhibitors (statins) and the renin-angiotensin system inhibitors.[14-17] The success of these drugs in the clinic has prompted intense investigation, in the context of vascular function and inflammation, to garner a more complete picture of the mechanism(s) of the clinical benefit observed. Of note, statin do not only inhibit cholesterol synthesis, but also block the production of isoprenoid intermediates, which play, for example, important roles in modifying small G proteins.[18] Recent evidence even suggests that intensive statin therapy, lowering cholesterol even below the current guidelines, might provide significant additional clinical benefit in high-risk patients.[19-21] Additional analysis have indicated that patients who have lower C-reactive protein levels after statin therapy have better clinical outcomes, regardless of the resultant level of cholesterol.[22,23]

Aim of the thesis

Essentially, this thesis is divided into two parts. The aim of the first part of this thesis is to explore and understand relationships of the renin-angiotensin system with lipids and inflammation. The aim of the second part is to explore effects of the cholesterol lowering therapy with 3-hydroxy-3-methylglutaryl co-enzyme-A inhibitors (statins) in the presence of an activated renin-angiotensin system or inflammation to arrest deterioration of cardiovascular functioning.

In **Part I** of the thesis we will explore relationships of the renin-angiotensin system with lipids and inflammation (figure). We will first provide a general overview of the currently available methods to assess vascular function in humans and evaluate the role of angiotensin-converting enzyme (ACE) inhibitor and statins in modifying vascular function. We continue our exploration with a follow-up study to determine whether a locally activated renin-angiotensin system is related to future cardiovascular events. Since renal dysfunction is importantly related to an increased cardiovascular event rate[6,7], we will also take

into account the relation of the renin-angiotensin system and inflammation with renal function. We will first attempt to confirm the association between inflammatory markers and increased cardiovascular event rate in patients undergoing coronary artery bypass grafting. Thereafter, we will continue with assessment of combined effects of cholesterol and inflammation on the vascular responsiveness to angiotensin II in these coronary artery diseased patients. An additional step will be undertaken to extend our research on inflammatory parameters in patients with an activated renin-angiotensin system, namely chronic heart failure patients. Determination of the length of telomeres from circulating leukocytes might mark the number of cell-divisions of inflammatory cells and inflammatory burden, or more importantly can be considered a marker of biological age. We will determine telomere length in patients with chronic heart failure compared to healthy controls.

In **Part II**, we will explore the effects of 3-hydroxy-3-methylglutaryl co-enzyme-A inhibitors (statins) in the presence of an activated renin-angiotensin system or inflammation. We will report the results of an intervention trial comparing the effect of low and high dose statin treatment to placebo on vasomotor function. We will assess endothelial function as well as vascular responsiveness to angiotensin II. Next, we will determine whether statin induced changes on inflammation and cholesterol are lasting after withdrawal of these drugs. We will present data of patients followed for an additional 3 months after the completion of a 4 year statin intervention trial. To evaluate the effects of interplay between angiotensin II and statin intervention in more detail, we will use an animal model. In this model, we will assess vascular injury not only as vasomotor function, but also as neointimal formation after stent placement. We will test whether vascular injury and neointimal formation can be exaggerated by supraphysiological levels of angiotensin II and whether it can be modified by statin therapy. Indeed, chronic heart failure patients also have supraphysiological levels of angiotensin II and an activated renin-angiotensin system. Therefore, we will also gather the clinical evidence currently available on the efficacy of statin therapy in this specific patient category. We will perform a systematic literature review as well as summarize the potential biological mechanisms pro and contra the use of statins in these patients.

References

1. Koek HL, Engelfriet-Rijk CJ, Bots ML. Hart-en vaatziekten in Nederland. In: Jager-Geurts MH, Peters RJ, van Dis SJ, Bots ML, eds. Hart- en vaatziekten in Nederland 2006, cijfers over ziekte en sterfte. Den Haag: Nederlandse Hartstichting; 2006.
2. Murray CJ, Lopez AD. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. Lancet 1997 May 17;349(9063):1436-42.
3. Libby P. Inflammation in atherosclerosis. Nature 2002 December 19;420(6917):868-74.
4. Ross R. Atherosclerosis--an inflammatory disease. N Engl J Med 1999 January 14;340(2):115-26.
5. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002 November 14;347(20):1557-65.
6. Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation 2000 July 11;102(2):203-10.
7. Smilde TD, Hillege HL, Voors AA, Dunselman PH, van Veldhuisen DJ. Prognostic importance of renal function in patients with early heart failure and mild left ventricular dysfunction. Am J Cardiol 2004 July 15;94(2):240-3.
8. Hillege HL, Fidler V, Diercks GF, van Gilst WH, de Zeeuw D, van Veldhuisen DJ, Gans RO, Janssen WM, Grobbee DE, de Jong PE. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. Circulation 2002 October 1;106(14):1777-82.

9. Wagenaar LJ, Voors AA, Buikema H, van Gilst WH. Angiotensin receptors in the cardiovascular system. Can J Cardiol 2002 December;18(12):1331-9.
10. van de Wal RM, van Veldhuisen DJ, van Gilst WH, Voors AA. Addition of an angiotensin receptor blocker to full-dose ACE-inhibition: controversial or common sense? Eur Heart J 2005 November;26(22):2361-7.
11. Nickenig G, Sachinidis A, Michaelsen F, Bohm M, Seewald S, Vetter H. Upregulation of vascular angiotensin II receptor gene expression by low-density lipoprotein in vascular smooth muscle cells. Circulation 1997 January 21;95(2):473-8.
12. Wang CH, Li SH, Weisel RD, Fedak PW, Dumont AS, Szmitko P, Li RK, Mickle DA, Verma S. C-reactive protein upregulates angiotensin type 1 receptors in vascular smooth muscle. Circulation 2003 April 8;107(13):1783-90.
13. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, Gordon DJ, Krauss RM, Savage PJ, Smith SC, Jr., Spertus JA, Costa F. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005 October 25;112(17):2735-52.
14. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger C, V, Orth-Gomer K, Perk J, Pyorala K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. European guidelines on cardiovascular disease prevention in clinical practice. Third Joint Task Force of European and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. Eur Heart J 2003 September;24(17):1601-10.
15. Grundy SM, Cleeman JI, Merz CNB, Brewer HB, Jr., Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr., Stone NJ, for the Coordinating Committee of the National Cholesterol Education Program, Endorsed by the National Heart LaBIACoCFaAHA. Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines. Circulation 2004 July 13;110(2):227-39.
16. Dahlof B, Devereux RB, Kjeldsen SE, Julius S, Beevers G, Faire Ud, Fyhrquist F, Ibsen H, Kristiansson K, Lederballe-Pedersen O. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. The Lancet 2002 March 23;359(9311):995-1003.
17. Oosterga M, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH, Crijns HJ, van Gilst WH. Effects of quinapril on clinical outcome after coronary artery bypass grafting (The QUO VADIS Study). QUinapril on Vascular Ace and Determinants of Ischemia. Am J Cardiol 2001 March 1;87(5):542-6.
18. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005 September 5;96(5A):24F-33F.
19. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, Joyal SV, Hill KA, Pfeffer MA, Skene AM, the Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes. N Engl J Med 2004 March 8;NEJMoa040583.
20. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, Gotto AM, Greten H, Kastelein JJ, Shepherd J, Wenger NK. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. N Engl J Med 2005 April 7;352(14):1425-35.
21. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, Crowe T, Howard G, Cooper CJ, Brodie B, Grines CL, DeMaria AN. Effect of Intensive Compared With Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: A Randomized Controlled Trial. JAMA 2004 March 3;291(9):1071-80.
22. Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, Orazem J, Magorien RD, O'Shaughnessy C, Ganz P, the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators. Statin Therapy, LDL Cholesterol, C-Reactive Protein, and Coronary Artery Disease. N Engl J Med 2005 January 6;352(1):29-38.
23. Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, Pfeffer MA, Braunwald E. C-reactive protein levels and outcomes after statin therapy. N Engl J Med 2005 January 6;352(1):20-8.