Summary

Cardiovascular diseases continue to be one of the leading causes of death in general population, despite preventive measures in health care. Among subjects with renal impairment, cardiovascular mortality is up to 30 times higher than in the general population. The detection of subjects who are at risk for cardiovascular disease or deterioration of renal function is warranted. A number of classical risk factors are usually advocated to be of value in cardiovascular and renal medicine namely blood pressure, cholesterol, smoking and blood glucose levels. The thesis concerns the role of C-reactive protein and albuminuria, two novel risk markers, in the prediction of cardiovascular and renal disease progression. It has been proposed that both markers reflect putative mechanisms of atherosclerotic disease (progression), namely inflammation and endothelial dysfunction. We show that C-reactive protein and albuminuria are two independent and highly predictive risk markers for renal and cardiovascular morbidity and mortality: independently of each other and of classical risk factors. Future studies should be directed towards primary prevention in subjects who are characterised by both elevated C-reactive protein and albuminuria levels.

In chapter 2, the association between classical risk factors and C-reactive protein is described in men and women, as well as the influence of hormonal factors on C-reactive protein levels in women. It is well known that the incidence of cardiovascular disease and mortality in men is higher than in women, which is partly attributed to the fact that men have a higher prevalence of risk factors. Remarkably, the PREVEND study shows that C-reactive protein levels are higher in women than in men. Smoking and higher age were shown to be related to elevated C-reactive protein levels in men, whereas in women oral contraceptive use and (abdominal) obesity contributed most strongly to an elevated C-reactive protein level. Diabetes was associated with elevated C-reactive protein levels equally in men and women. We hypothesise that different pathways are involved by which risk factors lead to inflammation in men and women, and possibly end-organ damage. Secondly, we investigated the influence of albuminuria on the associations between risk factors and C-reactive protein. Albuminuria itself was related to C-reactive protein, but did not alter the associations between risk factors and C-reactive protein. From a mechanistic point of view, we hypothesised that the association between cardiovascular risk factors and C-reactive protein does not include a pathway in which albuminuria, as a marker of vascular dysfunction, is involved.

In subjects with diabetes and hypertension, blood pressure is most strongly associated with the presence of albuminuria. Other risk factors, which cluster within the insulin resistance syndrome (hypertension, abdominal obesity, hyperglycemia, hyperlipidemia) are also more or less associated with albuminuria. It appears from literature that the association between C-
reactive protein and albuminuria is weak. This may appear contra-intuitive, since both markers are considered established markers of vascular dysfunction. In chapter 3, we hypothesised that C-reactive protein modifies the relation between blood pressure and albuminuria. Indeed, especially in subjects with an elevated blood pressure, C-reactive protein was strongly associated with increased albuminuria (interaction or effect-modification), i.e. stronger than was expected by the additive contribution of both blood pressure and C-reactive protein alone. From a pathophysiological point of view, this is an interesting finding. Inflammation apparently increases the likelihood of increased glomerular leakage of albumin in response to blood pressure. This glomerular leakage may either involve increased transmission of systemic blood pressure or a decreased barrier function of the glomerular filter.

In chapter 4, we investigated the association between elevated C-reactive protein levels and renal function abnormalities: a decreased renal function as well as an increased renal function (hyperfiltration). This hyperfiltration is viewed as a renal compensatory mechanism by which remaining nephrons try to maintain normal renal filtration after one or more renal insults. Subjects with elevated C-reactive protein levels had an increased probability to have a decreased renal function, independent of classical renal risk markers, including albuminuria. Increased C-reactive protein levels were also related to renal hyperfiltration, however, most of this association was attributed to the presence of obesity. We hypothesised that early inflammatory processes related to high body fat may predispose the kidney to glomerular hyperfiltration-related function loss. Secondly, this study shows that the relationship between C-reactive protein and renal function abnormalities is independent of albuminuria. Probably, both risk markers are differently involved in the progression of renal disease. Because C-reactive protein, albuminuria and kidney function levels were measured at the same time we cannot conclude to a cause and effect relationship. It would be interesting to investigate whether subjects with elevated C-reactive protein levels at baseline have an enhanced decrease of renal function loss over time.

In chapter 5, we investigated the relationship between C-reactive protein and/or albuminuria with various expressions of vascular end-organ damage: coronary heart disease, renal insufficiency, and peripheral artery disease. It appears that C-reactive protein is associated with all three expressions of vascular disease. This is independent from albuminuria and classical risk factors. Albuminuria is also related to coronary artery disease, renal insufficiency, and peripheral artery disease. However, albuminuria is only independently associated with coronary artery disease, whereas age is a major confounder in the relationship between albuminuria on the one hand and renal insufficiency and peripheral artery disease on the other hand. We conclude that C-reactive protein and albuminuria contribute differently to different expressions of vascular end-organ damage. Prospective studies are needed to further evaluate these findings.
The strong and independent prognostic value of C-reactive protein and albuminuria to cardiovascular and non-cardiovascular mortality in the general population is described in chapter 6. Interestingly, it appears that both risk markers convey a better predictive performance than some established risk factors like blood pressure, hyperlipidemia, and diabetes. It also appears that some other novel risk factors strongly predict cardiovascular mortality in the general population, like decreased renal function and increased waist circumference (a measure of abdominal obesity). C-reactive protein and albuminuria are not only related to cardiovascular mortality, but also to non-cardiovascular mortality. C-reactive protein trended to be more strongly related to non-cardiovascular than to cardiovascular mortality, whereas albuminuria appears more strongly related to cardiovascular mortality. C-reactive protein apparently reflects low-grade inflammation in general rather than in the vessel wall alone.

Measurement of C-reactive protein and albuminuria levels will especially be useful if a decrease of the raised levels translates into a reduction in cardiovascular risk. Much can be learned from research in subjects with diabetes, who have increased levels of albuminuria. It has been shown that in subjects with diabetes and increased albuminuria, pharmacological intervention which results in a decrease of urinary albumin excretion, delays the onset of cardiovascular morbidity and mortality and, especially, renal failure. In the United States, subjects with elevated C-reactive protein, but normal cholesterol levels, are currently being treated with a lipid-lowering drug within the scope of the JUPITER study. This study will give an answer to the question whether it is worthwhile to treat subjects with elevated C-reactive protein levels in order to delay the onset of cardiovascular disease. In chapter 7, the role and evidence of various novel risk markers in cardiovascular and renal disease progression is described: C-reactive protein, albuminuria, von Willebrand factor, leukocyte adhesion molecules, and plasminogen activator inhibitor-1, as well as other factors. This overview also describes intervention modalities which modify the levels and presence of these novel risk markers in order to prevent renal and cardiovascular disease.

In conclusion, C-reactive protein and albuminuria are independent prognostic risk markers of renal and cardiovascular disease. Future studies should be aimed at reducing the level of these risk markers by pharmacological intervention, and test whether this will translate into a reduction of renal and cardiovascular risk.