C-reactive protein and albuminuria
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**Introduction**

**Background**

Cardiovascular disease continues to be the leading cause of death in industrialised countries, despite the annual decline in cardiovascular mortality.\(^1\) The incidence of end-stage renal disease in the population is low, however rising due to the increasing incidence of diabetes and prolonged survival after a first cardiovascular event.\(^2\) In contrast to the low incidence of end-stage renal disease, the prevalence of mild to moderate renal insufficiency is high. The National Health and Nutritional Examination Survey estimates the prevalence of renal insufficiency (glomerular filtration rate <60 ml/min/1.73 m\(^2\)) around 10% among citizens of the United States.\(^3,4\) The incidence of mild renal disease is unknown, but may be high as well.

The assessment of cardiovascular risk in primary prevention involves the determination of blood pressure, blood levels of lipids and glucose, and smoking status. In order to prevent renal disease progression, the evaluation of blood pressure, level of urinary protein excretion, serum lipids, plasma glucose and smoking status is advocated. Aside from their importance in diabetic nephropathy and primary renal disease progression, these risk factors also appear to be major determinants of kidney function in the general population as well. This has been shown for diabetes, hypertension, isolated systolic hypertension, smoking, obesity and physical inactivity in long-term population-based studies.\(^5-8\) Importantly, there seems to be a great overlap in the use of classical risk factors in renal and cardiovascular risk assessment.

Unfortunately, much cardiovascular and renal risk remains unexplained with the use of classical risk factors. Therefore, the search for easy to obtain risk factors other than the conventional ones has recently gained much interest. A variety of novel biochemical risk markers have been proposed in order to identify subjects at increased risk. It is important to recognise that these risk markers are indirectly related to the presence of disease, whereas risk factors are assumed to be causally involved in disease progression. This thesis specifically focuses on two emerging risk markers, namely C-reactive protein and albuminuria.

How can we view the implementation of these markers in risk assessment? First, these risk markers may provide additive prognostic information about disease risk. Second, the prognostic information may be equal or better than provided by conventional risk factors. In other words, these risk markers add prognostic information beyond the information obtained by classical risk assessment. Third, as also occurred with blood pressure and lipids decades ago, treatment may be specifically targeted to the level of a specific risk marker in order to prevent disease.

All proposed risk markers, including C-reactive protein and albuminuria, have been suggested to indicate putative pathophysiological mechanisms of atherosclerotic vascular disease.
C-reactive protein, a member of the pentraxin family of proteins, is an acute-phase protein. C-reactive protein is a sensitive, however non-specific marker of inflammation. It is secreted by the liver upon stimulation by cytokines, mainly interleukin-6. Its serum levels rise in case of tissue damage, infection and other inflammatory conditions. Since the half-life of this molecule is dictated by its production rate by the liver, and not by other body kinetics, elevated C-reactive protein represents a chronic low-grade inflammatory state. Slightly elevated C-reactive protein levels have been shown to increase the risk of cardiovascular disease. It is generally assumed that slightly elevated C-reactive protein levels are indicative of the inflammatory process within the atherosclerotic vessel wall. This hypothesis derives from the observation that inflammation plays a pivotal role in the initiation and progression of atherosclerosis. Thus, the role of C-reactive protein seems quite convincing for cardiovascular disease progression. However, its role in renal disease progression is less well known.

Albuminuria, even at levels considered to be normal, predicts cardiovascular mortality in diabetes, but also in apparently healthy subjects. Whether albuminuria is an indicator of cardiovascular disease in the general population is unknown. It is generally accepted that albuminuria reflects a generalised endothelial dysfunction leading to atherothrombotic events. With respect to renal disease progression, albuminuria is a real classical risk marker, and probably even a risk factor. Slightly elevated levels of albuminuria, so-called microalbuminuria (i.e. albuminuria of 30-300 mg/24 hours), predict the development of macroproteinuria and renal functional disease progression in diabetes and hypertension. One important concept implies the deterioration of renal function after a period of relative hyperfiltration. Renal hyperfiltration is a compensatory mechanism by which intact nephrons try to maintain glomerular filtration rate after one or more renal insults. In this case, albuminuria is a result of renal hyperfiltration due to altered hemodynamic forces and increased fractional clearance of albumin. As renal disease progresses, renal function falls with a rise of urinary albumin. In non-diabetic subjects, we recently found evidence of this trend also: microalbuminuria related to hyperfiltration, whereas macroalbuminuria related to renal insufficiency. Thus, albuminuria plays an important role in renal and cardiovascular mortality, whereas its role in cardiovascular morbidity in the population is less well known.

Aim of the thesis

The introduction of cardiovascular risk factors into clinical practice, as exemplified by blood pressure and cholesterol, has taken decades of basic and epidemiological research. Before
introducing novel risk markers into practice, the same road has to be pursued. This thesis places C-reactive protein and albuminuria into perspective as novel risk markers. From the pathophysiological perspective, both markers reflect intimately related components of the atherosclerotic disease process as described in the latter paragraphs. Therefore, it is interesting to study the associations and interrelationship of both markers with each other, relative to other risk factors and relative to disease outcome and mortality. From an epidemiological perspective, this thesis evaluates whether both markers (independently) add to the risk of renal and cardiovascular morbidity and mortality and whether they are explained by other factors. This approach paves the way for 1) a better understanding of the interrelation between these risk markers and their relative contribution to disease and 2) risk assessment.

Chapter 2 considers the associations between cardiovascular risk factors and C-reactive protein. The influence of albuminuria on these associations will be evaluated in order to assess whether these associations include a mechanistic pathway in which albuminuria is involved. Further, we recently showed that cardiovascular risk factors are differently associated with albuminuria in men and women. We also questioned whether the relationship between risk factors and C-reactive protein differs between the genders.

Blood pressure is the main determinant of microalbuminuria in basic and epidemiological studies. C-reactive protein is modestly associated with microalbuminuria at the epidemiological level. Regarding the overlap of both markers in atherosclerosis, we hypothesised that some effect-modifier obscures a stronger relationship. Therefore, we questioned whether C-reactive protein modifies the association between blood pressure and microalbuminuria in Chapter 3.

Whereas the relation between C-reactive protein and cardiovascular outcome is corroborated in a number of studies, it is unknown whether elevated C-reactive protein levels increase the risk of renal function abnormalities, i.e. diminished renal filtration as a marker of renal insufficiency and a relatively elevated filtration as a marker of renal hyperfiltration. In Chapter 4 therefore, we questioned whether elevated C-reactive protein levels are associated with these renal function abnormalities in the non-diabetic population. We also questioned whether this relation was additive to the risk held by albuminuria and other renal risk factors.

In Chapter 5 we further describe the relationship of C-reactive protein, albuminuria and vascular disease in the heart, kidney and peripheral arteries. We questioned whether both markers independently add to the risk of disease in these vascular domains or whether they are similar markers.

Classical risk factors are currently being used in risk tables in the setting of primary prevention. Chapter 6 describes the value of C-reactive protein and albuminuria with respect to cardiovascular and non-cardiovascular mortality in the general population. This chapter also
evaluates whether both markers add to risk of mortality beyond the risk held by classical and other risk factors. If both markers add to the risk of mortality, this may have implications in the use of these markers in primary prevention. In future, primary prevention studies may then be developed specifically targeted to the level of C-reactive protein and/or albuminuria. Further, different pathophysiological pathways may be involved by which both markers increase the risk of mortality.

Chapter 7 is a review of the current literature concerning risk markers in general and their place in renal and cardiovascular risk prediction. It discusses the overlap in renal and cardiovascular risk factors and risk markers with respect to classical risk factors, C-reactive protein, albuminuria and many other novel markers. This review also gives an overview of the current evidence concerning drug effects aimed at reducing the level of a specific risk marker, in order to target treatment in future.

All investigations in this thesis have been performed within the scope of the Prevention of Renal and Vascular Endstage Disease (PREVEND) study in Groningen, the Netherlands.
References


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