Biochemical risk markers: a novel area for better prediction of renal risk?

Introduction

Prevention of end-stage renal disease (ESRD) by early detection and treatment is an important tool to stop the growing need for renal replacement therapy. The last decade has brought forward strong reasons for such an approach. The incidence of ESRD has increased dramatically, which is mostly attributed to type 2 diabetes\(^1\) and improved survival from atherosclerotic vascular disease.\(^2\) This increased rate of ESRD further augments the already high burden on the patient and doctor, as well as on health care economics. Indeed, patients entering renal replacements program are fifteen times more likely to die relative to subjects in the general population.

The target population for prevention still needs to be defined. There is no doubt that prevention in patients with glomerulonephritis, pyelo- and interstitial nephritis and diabetic renal disease is feasible. For non-diabetic subjects, logical steps are to identify those who are also at risk for the consequences of progressive renal disease, such as subjects with (undiagnosed) slight renal dysfunction. Only recently, the high prevalence (~10%) of mild to moderate renal insufficiency (glomerular filtration rate, GFR < 60 ml/min/1.73 m\(^2\)) in the population has been recognized.\(^3,4\)

In mild renal insufficiency, (pre)diabetes, hypertension and other risk factors are already highly prevalent.\(^5,6\) Moreover, renal insufficiency itself appears to be a major predictor of cardiovascular mortality, in the general population as well as in subjects with cardiovascular disease.\(^7,8\) Considering the high burden of mild renal impairment, this group of patients may be an eligible one in the primary prevention of disease and mortality. To identify those individuals at high risk we need a minimal set of essential risk factors.

The progression of renal function loss is dictated by several classical risk factors such as hypertension, proteinuria, obesity, smoking, and hyper- or dyslipidemia, all of which are potentially modifiable. Elevations in blood pressure are a strong independent risk factor for ESRD.\(^9\) Proteinuria has been more recently established as a key risk marker (and likely a factor)\(^10\) of renal function decline in subjects with primary renal disease and nephropathy from type 1 or 2 diabetes. A proportion of diabetic and hypertensive subjects with even lower amounts of urinary protein or albumin excretion (microalbuminuria) will eventually progress to proteinuria and subsequent renal function decline.\(^11,12\) Obesity is a risk factor for the development of ESRD in the population.\(^13\) Recent evidence suggests that obesity-related glomerulosclerosis is a serious clinical condition with an adverse long-term renal outcome.\(^14\) The incidence of this obesity-related glomerulopathy has increased tenfold over the last fifteen years in the population. Furthermore, Praga et al underlined the impact of obesity by showing that initially healthy obese subjects (BMI > 30 kg/m\(^2\)) were at high risk for developing proteinuria and loss of renal function after unilateral nephrectomy as compared to lean subjects.\(^15\) Smoking has also been demonstrated to be a risk factor for progressive renal
function loss. Epidemiological data reveal that smoking has deleterious effects on the kidney in populations with as well as without primary renal disease. In the general population and in subjects with essential hypertension, smoking is dose-dependently related to albuminuria and decreased glomerular filtration rate. Smoking also increases the risk of renal failure in the general (male) population. Hyperlipidemia has been shown to determine decline of renal function and to predict the onset of microalbuminuria. A dyslipidemic lipid profile, namely low high-density lipoprotein and elevated low-density lipoprotein / triglyceride levels, has also been shown to be related to microalbuminuria and renal function decline. Intervention studies for all (or most) of the above risk markers/factors, including proteinuria, hypertension, obesity and hyperlipidemia, show indirect or direct evidence for renal protection through a change in intermediate and hard renal endpoints.

Interestingly, global cardiovascular (CV) risk assessment involves the same classical risk markers and risk factors as for renal risk assessment. There is a host of evidence for blood pressure, obesity, smoking, and hyperlipidemia as predictors of CV outcome. For CV outcome, intervention in each of these factors has proven clear benefit. In addition, there is increasing evidence that (micro)albuminuria is also a risk marker for CV disease and mortality in the population. Nevertheless, much of the total risk still remains to be explained and optimal intervention still leaves a substantial amount of risk. This has stimulated the search for novel, easy to obtain CV risk markers or factors, recently resulting in a host of biochemical markers indicative of putative pathophysiological mechanisms for CV disease such as inflammation, vascular dysfunction, dysregulation of the coagulation and fibrinolysis system, and others. As will be discussed, these markers add independent prognostic information about risk in various patient groups. These novel markers often show high risk estimates, often higher than classical risk factors. Table 1 shows these risk markers and the relative evidence for their role in predicting CV and renal disease risk. For example, high-sensitive C-reactive protein (CRP), a sensitive marker of inflammation, has been proposed as a novel predictor of CV outcome: it has been proposed a stronger CV risk predictor than low-density lipoprotein cholesterol in many studies. It predicts risk in absence of hyperlipidemia or elevated blood pressure, and CRP adds prognostic information in risk scoring systems. This has had already such a strong impact that a large intervention trial was undertaken to alter the natural course of CV disease by lowering of a biochemical parameter like CRP by a cholesterol-lowering drug (JUPITER). This would be by analogy with the observation that some antihypertensive drugs such as those intervening in the renin-angiotensin-aldosterone system, reduce CV risk beyond their effect on blood pressure lowering (e.g. LIFE trial). Novel risk markers are expected to add to the existing classical repertoire as a possible target for treatment.
Table 1. Novel risk markers and their significance in the prediction of cardiovascular and renal outcome: an update.

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>CV evidence</th>
<th>CV outcome in Population-based studies</th>
<th>CV outcome in High-risk patients</th>
<th>References</th>
<th>Renal evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein</td>
<td>+++ [4]</td>
<td>+++</td>
<td>See text</td>
<td>74,161,162</td>
<td>+</td>
<td>160</td>
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<tr>
<td>Fibrinogen</td>
<td>+++</td>
<td>+++</td>
<td>See text</td>
<td>68,169,179,199-203</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Tumour necrosis factor-α</td>
<td>+</td>
<td>++</td>
<td></td>
<td>44,47,57,163-168</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Interleukins (-6, 10,18)</td>
<td>++</td>
<td>+++</td>
<td>169-182</td>
<td>183</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>+++</td>
<td>+++</td>
<td>47</td>
<td>116,184</td>
<td></td>
<td></td>
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<tr>
<td>Serum amyloid A</td>
<td>+</td>
<td>?</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oxidant stress markers</td>
<td>?</td>
<td>+</td>
<td>185-187</td>
<td>188,189</td>
<td></td>
<td></td>
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<tr>
<td>Malondialdehyde</td>
<td>?</td>
<td>+</td>
<td>190,191</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Urinary) Isoprostanes</td>
<td>?</td>
<td>+</td>
<td></td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matrix metalloproteinases</td>
<td>?</td>
<td>++</td>
<td>192-194</td>
<td>188 (Urinary)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myeloperoxidases</td>
<td>?</td>
<td>++</td>
<td>196-198</td>
<td>?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endothelial markers</td>
<td>+++</td>
<td>+++</td>
<td>See text</td>
<td>201,204-206</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>++</td>
<td>+++</td>
<td>68,169,179,199-203</td>
<td>=</td>
<td>+</td>
<td>See text</td>
</tr>
<tr>
<td>Von Willebrand factor</td>
<td>++</td>
<td>+++</td>
<td></td>
<td>138,208</td>
<td>?</td>
<td>See text</td>
</tr>
<tr>
<td>Thrombomodulin b)</td>
<td>+++</td>
<td>+</td>
<td>201,204-206</td>
<td>+</td>
<td>?</td>
<td>See text</td>
</tr>
<tr>
<td>Cellular adhesion markers</td>
<td>++</td>
<td>++</td>
<td>See text</td>
<td>=</td>
<td>=</td>
<td>See text</td>
</tr>
<tr>
<td>(Soluble) ICAM-1</td>
<td>++</td>
<td>++</td>
<td>See text</td>
<td>=</td>
<td>=</td>
<td>See text</td>
</tr>
<tr>
<td>(Soluble) VCAM-1</td>
<td>++</td>
<td>++</td>
<td>See text</td>
<td>=</td>
<td>=</td>
<td>See text</td>
</tr>
<tr>
<td>MCP-1</td>
<td>=</td>
<td>+</td>
<td>138,208</td>
<td>209,210</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(E, L, P)-selectin</td>
<td>+</td>
<td>+</td>
<td>See text</td>
<td>=</td>
<td>?</td>
<td>See text</td>
</tr>
<tr>
<td>Hemostasis/Thrombosis</td>
<td>++</td>
<td>++</td>
<td>See text</td>
<td>=</td>
<td>=</td>
<td>See text</td>
</tr>
<tr>
<td>PAI-1</td>
<td>++</td>
<td>++</td>
<td>100,143,144</td>
<td>89,214</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t-PA</td>
<td>++</td>
<td>++</td>
<td>100,143,144</td>
<td>+</td>
<td>?</td>
<td>See text</td>
</tr>
<tr>
<td>D-dimer</td>
<td>++</td>
<td>+</td>
<td>51,211-213</td>
<td>+</td>
<td>?</td>
<td>214</td>
</tr>
<tr>
<td>Prothrombin fragment 1+2</td>
<td>+</td>
<td>?</td>
<td>41</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lipid-associated factors c)</td>
<td>++</td>
<td>+</td>
<td>215-222</td>
<td>?</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Small dense LDL</td>
<td>++</td>
<td>+</td>
<td></td>
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</table>
Given the clear overlap in classical risk markers between renal risk and cardiac risk prediction, one would anticipate these biochemical markers to be of use in the ‘renal arena’. Indeed, in recent years, these biochemical markers have made their entry in renal risk profiling. This review describes the (epidemiological) evidence available today with respect to the link of biochemical risk markers and renal outcome, including the associations described in CV disease. There are several (biochemical) pathways that may have an important pathophysiological role in CV risk, each having important representative markers:
1. Inflammation  
   C-reactive protein
2. Endothelial function  
   Albuminuria, von Willebrand factor
3. Other markers  
   Leukocyte adhesion molecules
   Plasminogen activator inhibitor-1

In this review, we will describe what the pathophysiological role of these pathways could be, which markers are available and how they are related to the different intermediate and hard endpoints. We will do this both for CV outcome and for renal outcome.

**Chapters**

1. Markers of inflammation
   
   1.1. C-reactive protein and CV outcome
   
   Undoubtedly, most data on novel risk markers and CV outcome in the population are available for CRP. How good is the evidence of the role of CRP in CV risk prediction? After earlier studies had shown that CRP was able to predict future coronary events in patients with both stable and unstable angina,\textsuperscript{37} large epidemiological studies showed similar results in subjects at a relatively low absolute risk of mortality. Elevated levels of CRP were associated with CV endpoints including (non)fatal myocardial infarction, stroke and peripheral artery disease. Most studies show significant associations between elevated CRP levels and these endpoint parameters in the population (Table 1),\textsuperscript{38-64} except for some studies.\textsuperscript{65-72} Most authors therefore suggest that CRP has an added value in global CV risk assessment,\textsuperscript{73} while others state that CRP does not add to absolute risk assessment according to the Framingham risk score.\textsuperscript{71} The added value of CRP usually persists after adjustment for conventional risk factors, and its ‘independent’ value in comparison with other novel risk markers (e.g. interleukin-6, fibrinogen, microalbuminuria, leptin et cetera) warrants further research. A recent meta-analysis showed that the increased risk conveyed by high serum CRP levels is about 1.5-fold when comparing the lowest tertile with the upper tertile of the CRP distribution.\textsuperscript{74} Interestingly, an earlier meta-analysis showed a risk estimate of 2-fold.\textsuperscript{50}

   In the former meta-analysis, CRP showed a risk estimate which was much lower than those risk estimates based on blood pressure and total cholesterol.\textsuperscript{74} This is in sharp contrast with reports mentioned before, which showed superiority of CRP relative to other risk factors. Possibly, some publication bias is present in earlier studies.

   1.2. CRP: mechanisms of CV outcome
   
   Before implementing a risk factor (or marker) into clinical practice, concepts concerning its role
CRP levels are generally higher in subjects with more severe atherosclerosis, e.g. unstable angina. However, other studies suggest that the risk held by CRP is independent of atherosclerosis. For instance, it has been shown that CRP adds to risk of...
stroke and myocardial infarction beyond the risk held by atherosclerosis (intima-media thickness) measured at level of the carotid artery.\textsuperscript{59,63}

Second, since a causal role of CRP is suggested in epidemiological research, it may be that CRP itself is involved in vascular injury. In this case, CRP may be viewed as a risk factor rather than a risk marker. Table 2 lists the proposed biological and pathophysiological properties of the CRP molecule. Considering these properties, a causal role of the molecule may be more apparent in acute situations (myocardial necrosis, plaque instability et cetera),\textsuperscript{77,78} rather than at the population level. At the population level, CRP predicts mortality over an extended period up to 20 years with a constant hazard.\textsuperscript{39} Therefore, this makes a direct role of CRP less unlikely in the population setting.

A third possibility by which CRP may be related to an increased risk of CV events is CRP as an epiphenomenon. Elevated CRP levels may either reflect inflammation elsewhere in the body or inflammation in association with other putative CV risk factors. Notably, the positive association of CRP with body mass index (BMI) is very strong, and may even be stronger in abdominal obesity.\textsuperscript{79} In children, in whom atherosclerosis is absent, BMI is by far the strongest correlate of CRP.\textsuperscript{80} These associations may in part be due to the fact that adipocytes secrete interleukin-6 and tumor necrosis factor-\(\alpha\) in high quantities, the former being the main stimulator of hepatic CRP production. In conjunction to the association with abdominal obesity, CRP levels strongly correlate with features of the metabolic syndrome and insulin sensitivity.\textsuperscript{81} Weight loss and concomitant improvement of insulin resistance clearly lowers CRP.\textsuperscript{82,83} Thus, CRP may reflect an abnormal metabolic profile, which leads to an increased risk of atherothrombotic events. This is further strengthened by the fact that CRP predicts the incidence of type 2 diabetes.\textsuperscript{84}

1.3. CRP: mechanisms in renal outcome

What can be the mechanisms behind the association between low-grade inflammation and renal disease? Again, atherosclerosis may be a key element. Interestingly, it has been postulated that the renal analogue of the inflammatory process observed in atherosclerosis is glomerulosclerosis,\textsuperscript{75} the final common pathway of kidney damage as found in proteinuria, hypertension, obesity and the age-related decline of renal function. Glomerulosclerotic lesions disclose epithelial- and endothelial-cell injury and dysfunction with glomerular influx of inflammatory cells like monocytes (foam cells) and lymphocytes, and mesangial expansion as paralleled by smooth muscle cell proliferation in atherosclerosis.\textsuperscript{75,85}

Second, risk factors like obesity, hypertension and smoking may enhance a decline in kidney function through inflammation. Stengel et al showed independent effects of physical inactivity, obesity and smoking as risk factors for the incidence of ESRD.\textsuperscript{13} Unfortunately, these studies relating risk factors to the incidence of ESRD did not include measurements of inflammatory markers.
Finally, tubulointerstitial inflammation and fibrosis are the most constant features of renal function decline in various animal models (diabetes, hypertension, ischemia, renal ablation and proteinuria). This inflammation is accompanied by influx of immune cells like macrophages and monocytes. The cell influx enhances proinflammatory cascades in the diseased kidney like superoxide formation, activation of the angiotensin system and others. Interestingly, the concept of renal inflammation in progressive kidney disease intertwines with the concept of hemodynamically induced renal injury. Only recently, it has been shown that dual intervention on renal hemodynamics (angiotensin-converting enzyme inhibitor) and inflammation (mycophenolate mofetil) maximised renoprotection in animals. Whether renal (tubulointerstitial) inflammation induces CRP production by the liver is not known.

1.4. CRP as a predictor of renal outcome – GFR

Some epidemiological studies have focussed on the relation between inflammatory markers and renal disease outcome.

**General population**

Regarding the similarities between atherosclerosis and glomerulosclerosis on the one hand and inflammation and CV events on the other hand, we and others recently found evidence of a link between CRP and a decreased glomerular filtration rate (GFR) in the general population. We found that CRP was related to a diminished GFR, but also with renal hyperfiltration, the latter being explained by increased body fat. Possibly, early inflammatory processes related to high body fat may predispose the kidney to hyperfiltration-related renal function decline. Shlipak et al similarly showed that CRP, interleukin-6 and fibrinogen were elevated in a dose-dependent fashion across levels of decreased kidney function in the population either in the presence or absence of manifest atherosclerosis. These associations were found independent of conventional renal risk factors. Thus, inflammation seems to be present in early renal disease in the general population. From these cross-sectional data however, no conclusions can be drawn whether inflammation was cause or consequence of the decreased renal function.

**Chronic kidney disease**

In predialytic patients with kidney disease comprising of a variety of aetiologies, CRP and interleukin-6 levels were inversely correlated with creatinine clearance as shown in two cross-sectional studies. In another heterogeneous patient group with chronic kidney diseases (diabetic and non-diabetic), the investigators of the Modification of Diet in Renal Disease Study prospectively found a relation between transferrin, a negative acute-phase protein, and the
decline of renal function. In a later report however, they did not prospectively find a relationship between CRP and progression of kidney disease.

_Diabetes_

Whether inflammatory parameters are associated with levels of GFR or deterioration of GFR over time in patients with type 1 or 2 diabetes is as yet unknown.

1.5. **CRP as a predictor of renal outcome – Albuminuria**

_The general population_

Other data supportive of a role of inflammation in renal disease come from studies regarding another marker of (incipient) renal disease, namely microalbuminuria. Festa et al showed a link between inflammatory markers and microalbuminuria in non-diabetic subjects from the general population. In non-diabetic subjects from a Dutch population, Jager et al prospectively showed that CRP was related to the incidence of microalbuminuria. Such a link was also provided in premenopausal obese women. Recently, we showed that CRP modified the relation between blood pressure and microalbuminuria. We hypothesised that inflammation 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 glomerulus.

_Chronic kidney disease_

Whether albuminuria in chronic kidney disease is related to CRP or other inflammatory markers is unknown. However, asymptomatic proteinuric patients have higher CRP levels as compared to healthy subjects.

_Diabetes_

The participation of inflammation in the pathogenesis of early nephropathy was also hypothesised by Navarro et al, who showed a dose-dependent rise in micro- and macroalbuminuria in type 2 diabetic patients with increasing serum CRP and tumour necrosis factor-α levels. These correlations were remarkably high ($r=0.68$). Urinary TNF-α was correlated with albuminuria to the same extent, however, urinary TNF-α was unrelated to serum TNF levels. This observation suggests that local inflammatory activity in the kidney results in albuminuria, which is independent of systemic inflammation. Further, the incidence of microalbuminuria is increased in type 2 diabetic subjects with elevated levels of CRP. The development of albuminuria in the latter patient group was determined by the gradual and concomitant rise with CRP over time.
Altogether, these data provide evidence of involvement of inflammation in the pathogenesis of early nephropathy in type 2 diabetes.

Elevated levels of inflammatory markers in type 1 diabetes yield an increased risk for urinary albumin losses in the range of micro- to macroalbuminuria in cross-sectional studies, but this has not yet been studied in prospective studies.

**Conclusion.** In line with the abundant evidence of CRP as a marker of CV outcome, recent evidence suggests that this molecule may also serve as an early predictor of renal function decline and early nephropathy.

### 2. Markers of endothelial function

#### 2.1 Microalbuminuria

**2.1.1. Albuminuria and CV outcome**

Aside from the fact that albuminuria is a renal outcome parameter as described in previous paragraphs, microalbuminuria itself is also regarded as a marker of CV risk. An important concept is that generalised endothelial damage along the vascular tree is being disclosed by traces of urinary albumin loss. In line with the homogeneity between renal and CV risk factors, we have recently shown that elevated levels of urinary albumin excretion independently predicted all-cause and CV mortality in the general population. This was confirmed in a Norwegian population based study. For each doubling of albuminuria, subjects faced a 29% increased relative risk of CV death. Interestingly, the risk held by albuminuria was independent of conventional risk factors and comparable across strata of well-known risk factors. Romundstad et al found that the relationship between albuminuria and the risk of all-cause mortality was generally stronger in men than in women, especially in hypertensive subjects. These results extended earlier results found in elderly and hypertensive populations as well as in diabetes. Thus, it may well be that albuminuria can be used as an additive tool in absolute CV risk assessment in the general population, like CRP.

**2.1.2. Albuminuria: mechanisms of CV outcome**

The pathophysiological role and mechanisms of albuminuria in diabetic and hypertensive renal disease, but also in the general population have been reviewed elsewhere. Thus, here we only discuss the role of albuminuria as a parameter in CV outcome. The relation between albuminuria and CV outcome could be explained by systemic effects of a mildly injured kidney in blood pressure and salt regulation, in which glomerular autoregulation is impaired. Alternatively,
albuminuria could represent a more generalised endothelial dysfunction, thus allowing a vascular origin for CV risk. Finally, albuminuria could be a sign of the metabolic syndrome, this by itself causing increased CV risk.

Microalbuminuria may be viewed as a pressure-related phenomenon. It could appear when glomerular autoregulation is impaired. This may be the reason why systemic blood pressure is most strongly associated with albuminuria in the population and in diabetes. Both increased and decreased effective circulating volume, the latter due to efferent vasoconstriction resulting in an elevated filtration fraction, are associated with albuminuria. Increased salt intake is also a well-known determinant of an increase in urinary albumin. Conceptually, every (risk) factor that alters glomerular autoregulation may enhance the development of albuminuria. It is however unknown whether proxy markers of volume/salt status can explain the risk of death which is attributed to (micro)albuminuria.

Microalbuminuria can also be regarded as a marker of underlying generalised endothelial or vascular dysfunction. The fact that the risk of death held by albuminuria is more related to death from CV causes than from non-CV causes strengthens the concept of a generalised vascular involvement. On the other hand, while some authors found an increased transcapillary escape rate of albumin in microalbuminuric subjects, others failed to show such a relation. Furthermore, the correlation of albuminuria with the extent of atherosclerosis seems limited at the population level. Recent evidence also indicate that other markers of endothelial dysfunction, such as von Willebrand factor and leukocyte adhesion molecules cannot explain the risk of death held by albuminuria.

Lastly, albuminuria could also be a compound factor associated with the metabolic syndrome. This is certainly possible, since albuminuria is related to hyperinsulinemia and insulin resistance, and it also predicts the onset of type 2 diabetes in the population. Further, microalbuminuria is associated with almost all components of the metabolic syndrome, especially blood pressure. Kuusisto et al, for instance, showed that the simultaneous occurrence of hyperinsulinemia and albuminuria identified a patient group with an inexorably high risk of CV death. On the other hand, parameters of the metabolic syndrome such as blood pressure, obesity and hyperlipidemia, usually cannot explain the excess CV risk held by albuminuria itself. Smoking, an other important risk factor for the development of albuminuria, cannot explain the excess risk in albuminuric subjects either.

2.1.3. Albuminuria as a predictor of renal outcome – GFR

The general population

Considering its widespread clinical use in diabetes care, microalbuminuria is undoubtedly one of the most promising parameters to be used in the general population to identify subjects at increased renal risk. Whether the presence of albuminuria in the general population will lead to renal function
decline in time is being studied at present in a large cohort in the Netherlands. We have described
the pattern of renal function abnormalities in non-diabetic subjects from the population in a cross-
sectional study. Low levels of albuminuria were associated with an elevated creatinine clearance,
suggestive of renal hyperfiltration, whereas gross albuminuria was associated with a decreased
creatinine clearance relative to subjects with normal albuminuria,\textsuperscript{118} a pattern which is similarly
observed in diabetes. A preliminary analysis of longitudinal data supports a role of albuminuria in
renal function decline in the population (Verhave \textit{et al}, Kidney Int., in press).

\textbf{Diabetes}

There is no need to built a case for albuminuria as a predictor for renal risk in chronic kidney
disease and type 1 and 2 diabetes: authoritative reviews have clearly outlined the impact of
albuminuria in (non)-diabetic nephropathy.\textsuperscript{105}

2.1.4. Baseline albuminuria as a predictor of albuminuria progression

\textit{The general population}

We recently found that subjects with albuminuria levels 15-30 mg/24 hours had the highest risk
for the incidence of microalbuminuria in the non-diabetic general population (abstract; Stuveling,
J Am Soc Nephrol 2003;14:679-80A). The risk of high-normal albuminuria was 20-fold relative to
normoalbuminuria. Other population based studies in non-diabetic subjects did not implement
the predictive value of baseline albuminuria as a determinant of incident microalbuminuria.\textsuperscript{95} In the
HOPE study, comprising of subjects with pre-existent cardiovascular disease, a high incidence of
macroalbuminuria (albuminuria >300 mg/24 hr) was found. Baseline microalbuminuria appeared
to be the most important determinant of subsequent progression to this stage of nephropathy
by far (estimated odds ratio 17.5).\textsuperscript{119}

\textbf{Diabetes}

Aside from blood pressure, smoking and glycemic control, albuminuria at baseline is one of the
most important predictors of progression of albuminuria in type 1 and 2 diabetes mellitus as
shown in several studies.\textsuperscript{120,121}

\textbf{Conclusion.} Albuminuria at a low level bears much information as a cardiovascular risk determinant
in order to identify subjects at increased CV risk. Aside from the impact of common risk factors in
the progression of early nephropathy, the presence of a relatively high level of albuminuria is an
important determinant of renal disease progression and albuminuria itself. Preliminary evidence
suggests such a role in relatively healthy subjects also.
Von Willebrand factor

2.2.1. vWF and CV outcome

A recent nested case-control study, including a meta-analysis, showed that increased von Willebrand factor (vWF) serum levels predicted incident coronary heart disease in the general population, of which the risk was twofold. vWF is also associated with an increased risk of CV mortality among diabetic and non-diabetic subjects, in whom high levels increase the risk threefold.

2.2.2. vWF: mechanisms of CV outcome

Although vWF has prothrombotic properties, it is indicated as a marker of endothelial function. vWF is released upon endothelial cell activation. Thus, in case of endothelial cell damage with degranulation of Weibel-Palade bodies, it is hypothesized that a concomitant rise of vWF will occur in blood. Its values in blood are however raised in many clinical conditions which are not necessarily due to endothelial cell damage. vWF may therefore lack specificity as a marker.

What mechanisms may be the link between increased vWF and CV outcome? First, increased levels of vWF may be indicative of a procoagulant state, eventually leading to CV events. Second, increases in vWF are often accompanied by increases in acute-phase proteins. In vitro, mediators of inflammation like complement and cytokines (IL-6, TNF-α) are potent stimulators of vWF release by endothelial cells. Not surprisingly therefore, its correlation with CRP is relatively high compared to other risk factors. Interestingly, despite this overlap of vWF and CRP, one study suggests independent effects of both markers in the prediction of mortality in type 2 diabetes. This suggests that endothelial dysfunction and inflammation represent two different pathophysiological mechanisms leading to the same disease.

2.2.3. vWF: mechanisms and predictive value in renal outcome – GFR

General population

Whether elevated vWF levels in the population predict the decline of renal function in the population is unknown. A small cross-sectional study found that vWF is inversely related to creatinine clearance, this relation however being explained by elevated homocysteine levels.

Diabetes

In microalbuminuric type 2 diabetes, subjects with elevated vWF levels had typical signs of diabetic nephropathy and retinopathy, whereas these features were absent in subjects with normal vWF levels. This observation was confirmed in the EURODIAB type 1 diabetes study, which showed that vWF was associated with albuminuria only in the presence of retinopathy.
This led to the suggestion that microalbuminuria is only indicative of diabetic kidney damage in presence of endothelial dysfunction. This concept of heterogeneity is however challenged by others, who showed that this interaction was absent with respect to CV mortality.\textsuperscript{127}

2.2.4. \textit{vWF: mechanisms and predictive value in renal outcome – Albuminuria}

\textit{General population}

In non-diabetic subjects of the general population, Jager \textit{et al} were unable to show an increased incidence of microalbuminurias across levels of vWF.\textsuperscript{95} However, in a representative sample of healthy subjects, Clausen \textit{et al} prospectively found that elevated baseline vWF levels predicted progression of albuminuria over 4 years.\textsuperscript{128}

\textit{Diabetes}

In type 2 diabetes, a cross-sectional study showed a progressive rise in serum concentration of vWF with increasing urinary albumin excretion, independent of risk factors and prevalent atherosclerosis.\textsuperscript{129} More supportive data revealed that elevated vWF levels were shown to be related to the incidence and progression of (micro)albuminuria in type 2 diabetic subjects.\textsuperscript{100} These data underscore the concept that endothelial dysfunction precedes the onset of microvascular disease and nephropathy. This has been suggested by Stehouwer \textit{et al} who found that increased vWF levels preceded the onset of microalbuminuria in type 1 diabetic subjects.\textsuperscript{130} The development of hypertension may be an important mediator of this process in type 1 diabetes.

\textbf{Conclusion}. Although the evidence is limited, there may be a role for \textit{vWF}, as a marker of endothelial integrity, in the prediction of the development of CV and early renal disease.

3. \textit{Other markers}

3.1 Markers of cellular leukocyte adhesion

Increased levels of circulating soluble intercellular adhesion molecules-1 and vascular cell adhesion molecules-1 (\textit{sICAM-1, sVCAM-1}) are related to an adverse CV outcome in high-risk patient groups\textsuperscript{131,132} and in relatively healthy subjects.\textsuperscript{133-137} To some extent, this also applies for different selectins, another group of adhesion molecules.\textsuperscript{135,136} Some studies however were unable to show such a relation.\textsuperscript{138,139}

Endothelial cells already express cellular adhesion molecules at a relatively early phase of the atherosclerotic process. During atherogenesis, they enhance recruitment of inflammatory
cells to sites of atheroma development. In renal disease, a similar role has been observed. In various animal models of kidney disease, the upregulation of cellular adhesion molecules plays a pivotal role in the recruitment of macrophages to the kidney, thereby inducing or amplifying the inflammatory process. ICAM-1 deficient diabetic mice are resistant to the development of diabetic nephropathy. At the epidemiological level, it is unknown whether elevated levels of sICAM-1 or sVCAM-1 predict the decline of GFR. A cross-sectional study in type 1 diabetic subjects showed that micro- and macroalbuminuric subjects had higher serum levels of sVCAM-1 and sICAM-1 as compared to normoalbuminuric subjects. The Hoorn study showed that elevated sVCAM-1 levels preceded the onset of microalbuminuria in non-diabetic subjects recruited from the population. Stehouwer et al showed that elevated levels of these markers are related to the incidence of (micro)albuminuria in type 2 diabetic subjects.

3.2 Markers of coagulation and fibrinolysis

Elevated systemic levels of plasminogen activator inhibitor-1 (PAI-1), an inhibitor of fibrinolysis, predict an adverse CV outcome in high-risk patients. Another fibrinolytic protein, namely tissue-type plasminogen activator (t-PA), also predict CV events. Thus, dysfunction of the coagulation/fibrinolysis system appears of major importance in the development of CV disease. The most frequently described CV marker of impaired fibrinolysis is PAI-1, which is produced by the vascular endothelium, but other tissues are also involved. Especially fat cells are able to produce large amounts of PAI-1: adipose PAI-1 levels highly correlate with plasma PAI-1 levels. It is therefore not surprising that PAI-1 is implicated as a core factor in insulin resistance. Dysregulation of fibrinolysis in insulin resistance may be a key mediator leading to CV events. Similarly, PAI-1 has been implicated in several renal pathologies, which include amongst others protein-overload proteinuria, hypertensive and diabetic nephropathy, ageing and glomerulosclerosis. However, it is unclear whether elevated levels of PAI-1 antigen are able to predict adverse renal outcome at the population level. In the earlier mentioned study of Shlipak et al, it was shown that a battery of procoagulant factors (factor VIIc, factor VIIIc, plasmin- antiplasmin complex and D-dimer), among which PAI-1 was not measured, were strongly related to levels of decreased kidney function. Hovind et al however did not find an association between elevated PAI-1 levels and decline of GFR over time in type 1 diabetic patients. An independent association between PAI-1 and microalbuminuria in young adults has been reported. Elevated levels of t-PA are related to the incidence and progression of (micro)albuminuria in type 2 diabetic subjects.
**Conclusion.** Many other markers of atherosclerotic vascular disease appear to be predictors of CV disease in healthy subjects. The evidence appears quite consistent with few negative reports (Table 1). Their predictive value for the development of nephropathy in the population and in diabetes remains to be established.

4. **Biochemical risk markers: do we need them all?**

The evidence that various risk markers relate to renal disease, CV disease and mortality is compelling. Meanwhile, the search for better and stronger risk markers continues. The list of risk markers mentioned in Table 1 can easily be extended and will probably be extended in the near future. The currently already important question is which of these risk markers in this comprehensive list should we use to identify subjects at increased risk? Do we need them all? Do we need combinations of markers, each marking a different aspect of disease?

As mentioned earlier, the cornerstones of CV risk prediction remain in the classical risk profile. Importantly, the discussion concerning which risk markers should be used as an additive tool in risk prediction is not closed, neither for CRP, nor for albuminuria or other markers. Let’s take CRP as an example. The majority of population-based studies relating elevated CRP levels to outcome show an additive contribution of this marker beyond the risk held by classical risk factors (see references in Table 1). In addition, CRP has been shown additive to prothrombin fragment 1+2, interleukin-6, interleukin-10, interleukin-6, atherogenic infections, macrophage inhibitory cytokine-1, coronary calcium scores, and intima-media thickness, in population-based studies, and microalbuminuria in type 2 diabetic subjects. Some investigators even state that CRP shows superior predictive performance relative to other markers.

On the other hand, the Hoorn study, the Caerphilly Prospective Heart Disease study, the Glostrup study, the Quebec Cardiovascular study, the Atherosclerosis Risk in Community (ARIC) study, the Rotterdam study, and the Health ABC study did not find a significant relation between CRP and CV outcome beyond the classical repertoire of risk factors. Others show that CRP is not superior to markers like von Willebrand factor, fibrinogen, interleukin-6, lipoprotein-associated phospholipase A2, tissue-type plasminogen activator or leptin. Thus, CRP most probably adds to the absolute risk held by classical risk factors in the population, while its contribution relative to other risk markers is less clear.

Reasons for these inconsistencies are numerous and may relate to differences in study design, study population (men vs women, elderly, diabetes et cetera), population size, number of events, (laboratory) assessment of risk factors, and other factors. Bias is always a main concern,
but it is difficult to extract its source. An important point to consider here is the fact that some of these risk factors show considerable variability. In the majority of studies, novel markers have only been measured once, which yields a considerable underestimation of estimated risks. Further, comparing a less reproducible parameter with a highly reproducible marker yields spurious results. The predictive performance will certainly improve if risk markers are measured more than once over time. None of these risk markers by themselves provide optimal sensitivity and specificity to identify subjects at risk. Of course, the latter arguments also hold true for blood pressure and cholesterol. Therefore, to better appreciate the (independent) role of novel risk markers relative to each other and to classical risk factors, their assessment has to be improved.

Importantly, we have to distinguish between the use of these markers in primary prevention and risk stratification in hospital. More simplified, whether a person has hypercholesterolemia does not matter in the coronary care unit and determination of cardiac tropinines will provide more useful information in this situation. In primary prevention, the determination of cholesterol levels will be more informative. Thus, each risk marker may have its specific value in risk prediction in different patient groups depending on its content and nature.

As far as the kidney is concerned, this field of research is in its developing stages and a similar process will be pursued as in CV disease prediction in general. Similar problems are at hand in research concerning renal disease progression. In diabetic renal disease, microalbuminuria is the only novel risk marker which appears to be of additional value in renal risk prediction, in prevention of renal disease progression, and even in cost-effectiveness of treatment.

In the earlier mentioned PREVEND study, we showed that both CRP and albuminuria add to the risk of CV and non-CV mortality in the general population. The estimated risks of death were comparable. Interestingly, the predictive performance of both markers was much better than classical risk factors like blood pressure and serum cholesterol, whereas smoking appeared to be of equal importance (abstract; Stuveling, J Am Soc Nephrol 2003;14:679-80A).

In conclusion, there is no consensus to which extent a combination of risk factors and markers will best predict the risk of CV and renal disease progression. Moreover, current risk scores may have to be reevaluated in future.

5. Drug effects on novel risk markers

In earlier paragraphs, we described the relative contribution of various risk markers to CV and renal outcome. Aside from their proposed role in CV risk prediction, they may be extremely useful when some intervention modifies this parameter and subsequently shows benefit on CV risk due to that
modification. Taking classical risk factors as an example first hypertension and hyperlipidemia have been shown important independent risk factors. It has been shown that blood pressure and cholesterol lowering interventions can modify these risk factors, and that the magnitude of effect on blood pressure and cholesterol by these drugs correlates with the extent of risk reduction. In primary and secondary kidney diseases, proteinuria is the best example in this context. Proteinuria is an independent risk factor for renal function decline over time, specific drugs are able to lower proteinuria beyond alterations in for example blood pressure, and the magnitude of proteinuria lowering correlates with the risk reduction in renal outcome.\textsuperscript{152} Lately, there has been growing interest in the possibility that some of the clinical benefits of certain blood pressure lowering agents and especially statins are due to so-called pleiotropic effects. It means that they have effects that are not directly related to their blood pressure and lipid lowering effects. For example, interventions in the renin-angiotensin and cholesterol synthesis system are well known because of their anti-inflammatory effects.\textsuperscript{153,154}

Table 3 lists the effects of drug interventions, which have been shown effective in CV and renal risk reduction, on various novel risk markers in humans. What can we learn from this table? The table shows that various possibilities are available to intervene on a specific marker.

\textit{C-reactive protein.} Favourable effects of angiotensin blocking agents have been shown with respect to a decrease in CRP and other proinflammatory cytokines. These effects are believed to be mainly mediated through blockade of angiotensin-I, a protein with profound proinflammatory properties. Statins and fibrates, of which the latter are known for their anti-inflammatory actions by agonism of the peroxisome proliferator-activated receptor-\(\alpha\) (PPAR-\(\alpha\)),\textsuperscript{155} seem strong modulators of CRP. With respect to statins, the reduction of CRP levels has even been shown independent of the reduction of lipid levels.\textsuperscript{156} This lipid-independent, anti-inflammatory effect is believed to be mediated through blockade of the mevalonate pathway, which eventually leads to modulation of nuclear transcription factors importantly involved in cytokine regulation and cell growth, like nuclear factor-\(\kappa\)B and others.

\textit{Albuminuria.} Any blood pressure lowering agent potentially reduces albuminuria through systemic blood pressure lowering. Indeed, the most important correlate of albuminuria is blood pressure, especially in diabetes.\textsuperscript{97} Additional renoprotection of blood pressure lowering agents are believed to be exerted by angiotensin blocking agents, due to their beneficial effects on glomerular hemodynamics. It has been shown that angiotensin blocking agents reduce albuminuria and even renal risk beyond their blood pressure lowering effects. Statins show (in)direct effects on proximate markers or even clinical measures of endothelial function and therefore, hypothetically, on albuminuria. However, the available evidence concerning beneficial effects of statins and fibrates on albuminuria (and GFR) remains inconclusive. Especially, studies performed to date are small
Table 3. Effects of pharmacological intervention on risk markers for CV disease.

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ARBs = angiotension-II-type 1 receptor blockers, ACEi = angiotension converting enzyme inhibitors, CCBs = calcium channel blockers, PPAR-γ-a = peroxisome proliferators-activated receptor agonists.
in patient numbers. The largest randomised placebo-controlled clinical trial, investigating the effects of a statin and/or an ACE-inhibitor (PREVEND-IT) on albuminuria and other endpoints (864 patients) in a low-risk population, did not show any effect of pravastatin on albuminuria during 4 years of follow-up (Asselbergs et al, Circulation 108:2723, 2003).

Von Willebrand factor. Placebo-controlled trials involving statins show a lowering of vWF in blood when compared to placebo. Mechanisms may involve improvement of endothelial function or an anti-inflammatory effect.

Leukocyte adhesion molecules. Angiotension-II-type 1 receptor blockers are able to reduce the blood levels of sICAM and sVCAM. Again, mechanisms may involve improvement of endothelial function or an anti-inflammatory effect of this drug. Whether angiotensin-converting enzyme inhibitors and statins are able to reduce leukocyte adhesion molecules is uncertain.

Plasminogen activator inhibitor-1. Especially angiotensin-converting enzyme inhibitors are able to reduce levels of PAI-1. Besides its critical role in blood pressure and salt homeostasis, the renin-angiotensin system is also involved in fibrinolytic balance, vascular endothelial function, and vascular inflammation as explained earlier. The exact mechanisms however are unknown.

To date, there are no intervention studies available, which show that the risk reduction in CV and renal morbidity is attributed to the reduction of a novel serum marker with the exception of one indirect observation. Ridker et al showed that lovastatin therapy was even effective in subjects having a high CRP level, but a low level of cholesterol/HDL ratio. In this respect, the JUPITER trial will be an important and interesting intervention study to show whether the CV benefits of a statin can be attributed to lowering of CRP, independent of its effect on cholesterol.
When this criterion is met, CRP could serve an additive marker in global risk assessment. PPAR-γ agonists, which have not yet been shown to reduce ‘hard’ CV and renal endpoints, are a promising therapeutic option. PPAR-γ agonists are known as insulin sensitising agents and these drugs are used primarily in the treatment of type 2 diabetes. These drugs not only improve insulin sensitivity and glycemic control, but also have potentially favourable effects on other components of the metabolic syndrome. Several randomised trials show a reduction in classical risk factors (blood pressure, lipids, insulin resistance) and novel risk markers (Table 3). These effects seem profound. Interestingly, in all randomised trials performed to date, the reduction of a specific marker during intervention with a PPAR-γ agonist correlated with the improvement in insulin sensitivity. This fact underscores the role of these markers in the metabolic syndrome. The ADOPT trial will determine whether monotherapy with rosiglitazone is effective on glycemic control, improvement of other metabolic parameters (including CRP, PAI-1) and progression of diabetic nephropathy.\textsuperscript{158}

Non-pharmacological intervention is an alternative to drug intervention. For example, weight loss lowers CRP and albuminuria levels in obese subjects.\textsuperscript{82,159} Quitting smoking reduces albuminuria,\textsuperscript{117} but for CRP this is unknown. Life-style changes also have profound effects on insulin sensitivity, the fibrinolysis system and others. It is certainly possible that the improvement of surrogate markers may in part explain the benefits of lifestyle alterations with respect to CV risk.

6. Conclusions

Markers of progressive CV disease are close to come of value in clinical practice as an additive tool to the classical risk factors. These markers have been proposed from the viewpoint of plausible pathophysiological concepts in vascular disease. Although these concepts have mainly been investigated in cardiovascular disease, there is cumulating data and evidence for an important role in renal disease progression as well. Indeed, in view of the overlap between cardiovascular and renal risk factors, it is tempting to speculate that these novel risk markers will be able to predict accelerated decline of renal function in the population. In fact, some of these factors such as high-sensitive CRP and albuminuria are close to become valuable renal risk markers both for detecting the risk for disease progression as well as for the protective response to therapy.
References


Romundstad S, Holmen J, Hallan H, Kvenild K, Ellekjar H. Microalbuminuria and All-Cause Mortality


(77)  Lagrand WK, Visser CA, Hermens WT et al. C-reactive protein as a cardiovascular risk factor: more than an


(84) Freeman DJ, Norrie J, Caslake MJ et al. C-reactive protein is an independent predictor of risk for the development of diabetes in the West of Scotland Coronary Prevention Study. Diabetes. 2002;51:1596-1600.


(102) Schalkwijk CG, Poland DC, van Dijk W et al. Plasma concentration of C-reactive protein is increased in type I diabetic patients without clinical macroangiopathy and correlates with markers of endothelial dysfunction: evidence for chronic inflammation. Diabetologia. 1999;42:351-357.


(107) de Jong PE, Hillege HL, Pinto-Sietsma SJ, De Zeeuw D. Screening for microalbuminuria in the general population: a tool to detect subjects at risk for progressive renal failure in an early phase? Nephrol Dial


(151) de Maat MP, Kluft C, Gram J, Jespersen J. Angiotensin-converting enzyme inhibitor trandolapril does not
affect C-reactive protein levels in myocardial infarction patients. Circulation. 2003;108:e113.


(166) Volpato S, Guralnik JM, Ferrucci L et al. Cardiovascular disease, interleukin-6, and risk of mortality in older


(180) Reddan DN, Klassen PS, Szczech LA et al. White blood cells as a novel mortality predictor in haemodialysis


(206) Thogersen AM, Jansson JH, Boman K et al. High plasminogen activator inhibitor and tissue plasminogen activator levels in plasma precede a first acute myocardial infarction in both men and women: evidence for the fibrinolytic system as an independent primary risk factor. Circulation. 1998;98:2241-2247.


(208) Piemonti L, Calori G, Mercalli A et al. Fasting plasma leptin, tumor necrosis factor-alpha receptor 2, and monocyte chemoattracting protein 1 concentration in a population of glucose-tolerant and glucose-


(224) Danesh J, Collins R, Peto R. Lipoprotein(a) and coronary heart disease. Meta-analysis of prospective


(227) Simes RJ, Marschner IC, Hunt D et al. Relationship between lipid levels and clinical outcomes in the Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Trial: to what extent is the reduction in coronary events with pravastatin explained by on-study lipid levels? Circulation. 2002;105:1162-1169.


(239) Hanley AJ, Williams K, Stern MP, Haffner SM. Homeostasis model assessment of insulin resistance in


(346) Pedersen OD, Gram J, Jeunemaitre X, Billaud E, Jespersen J. Does long-term angiotensin converting enzyme inhibition affect the concentration of tissue-type plasminogen activator-plasminogen activator inhibitor-1 in the blood of patients with a previous myocardial infarction. Coron Artery Dis. 1997;8:283-291.


