Drug-Induced Changes in Risk/Biomarkers and Their Relationship with Renal and Cardiovascular Long-Term Outcome in Patients with Diabetes

Yan Miao,1† Paul A. Smink,1† Dick de Zeeuw,1 and Hiddo J. Lambers Heerspink1*

BACKGROUND: Optimal renal and cardiovascular risk management in diabetic patients includes optimal maintenance of blood pressure and control of glucose and lipids. Although the optimal control of these risk factors or “risk/biomarkers” has proven to be effective, it often is difficult to achieve. Consequently, the risk for renal and cardiovascular complications remains devastatingly high. Many risk/biomarkers have been discovered that accurately predict long-term renal and cardiovascular outcome. However, the aim of measuring risk/biomarkers may not be only to determine an individual’s risk, but also to use the risk/biomarker level to guide therapy and thereby improve long-term clinical outcome.

CONTENT: This review describes the effects of various drugs on novel risk/biomarkers and the relationship between (drug induced) short-term changes in risk/biomarkers and long-term renal and cardiovascular outcome in patients with diabetes.

SUMMARY: In post hoc analyses of large trials, the short-term reductions in albuminuria, transforming growth factor-β, and N-terminal pro-B–type natriuretic peptide (NT-proBNP) induced by inhibitors of the renin-angiotensin-aldosterone system were associated with a decreased likelihood of long-term adverse renal and cardiovascular outcomes. However, the few studies that systematically investigated the utility of prospectively targeting novel risk/biomarkers such as hemoglobin or NT-proBNP failed to demonstrate long-term cardiovascular protection. The latter examples suggest that although a risk/biomarker may have superior prognostic ability, therapeutically changing such a risk/biomarker does not necessarily improve long-term outcome. Thus, to establish the clinical utility of other novel risk/biomarkers, clinical trials must be performed to prospectively examine the effects of therapeutically-induced changes in single or multiple risk/biomarkers on long-term risk management of patients with diabetes.

Patients with diabetes mellitus are prone to develop a broad range of complications. The most common of these are renal and cardiovascular (CV)2 complications that are associated with a large burden of social dysfunction and with high risk of premature death.

Several modifiable risk factors are associated with poor renal and CV outcome, including blood pressure, plasma glucose and lipid concentrations, smoking, and body weight. In this review we distinguish between modifiable risk factors and biomarkers in the following way: A modifiable risk factor or risk marker (hereinafter called risk factor or risk marker) is a biological characteristic that is causally correlated to a clinical endpoint, and its intervention-induced change should predict outcome; the risk factor differs from a biomarker in that the latter is a biological characteristic indicating a normal biologic process, a pathogenic process, or an effect of treatment on such a process (1). Biomarkers are often used as surrogate endpoints in clinical studies. In such studies the biomarker is used to substitute for a clinical endpoint. It is hoped that the biomarker will directly reflect the disease process under

2 Nonstandard abbreviations: CV, cardiovascular; RAAS, renin-angiotensin-aldosterone system; RENAAAL, Reduction of Endpoints in NIDDM (non–insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan; ARB, angiotensin-receptor blocker; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation; ACEi, angiotensin-converting–enzyme inhibitor; RENI, Ramipril Efficacy in Nephropathy; VDRA, vitamin D–receptor activators; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint; TGF-β1, transforming growth factor-β1; GFR, glomerular filtration rate; ESA, erythropoiesis-stimulating agents; TREAT, Trial to Reduce Cardiovascular Events with Aranesp Therapy; hs-CRP, high-sensitivity C-reactive protein; JUPITER, Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; NT-proBNP, amino-terminal pro-B–type natriuretic peptide; BNP, brain natriuretic peptide; SGLT2, sodium-glucose cotransporter.

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Effects of Drugs on Renal and CV Risk/Biomarkers

Reviews

Investigation, but the biomarker could be indirectly related. It is therefore possible that changes in the biomarker will not directly correlate to the treatment or desired outcome.

Although all risk markers can be considered biomarkers, it is likely that only a subset of biomarkers will achieve risk-marker status. Blood pressure is a clear example of a risk marker because it is causally related to CV disease and the reduction in blood pressure induced by an antihypertensive agent is related to the degree of CV risk reduction (2). Angiotensin is an example of a biomarker because high angiotensin concentrations are a reflection of renal disease and therapy-induced changes in angiotensin concentrations may reflect the efficacy of the therapy, without a direct causal relationship between angiotensin and renal disease. There are also examples for which the boundaries between risk marker and biomarker are overlapping. For example, albuminuria is a reflection of renal damage. As such it is a biomarker of renal disease state. On the other hand, albuminuria is also believed to be a causal factor in progressive loss of renal function. Treatments that lower albuminuria lower the risk for renal and CV disease. In this respect albuminuria is also a risk factor/marker. Thus the differentiation between a risk marker and a biomarker is not always well defined. Throughout this review we use the term risk/biomarker, a designation that indicates the potential differential relationship.

In clinical practice there are several risk/biomarkers that can be used as targets to improve renal and CV protection. However, optimal control of these risk/biomarkers seems to be difficult to achieve. This difficulty is illustrated by the results of the multifactorial intervention trial of the Steno Diabetes Center, Steno-2. In this study only a small proportion of patients achieved optimal risk/biomarker control despite intensive renal and CV protective therapy (3). Consequently, a substantial proportion of patients remain at a high renal and CV risk (4).

A host of reports on novel risk/biomarkers are currently being published. Many of these publications intend to show that the novel risk/biomarkers at hand enable the more accurate identification of patients with diabetes who are at risk for the development of renal and CV diseases (5, 6). Although this may be true, one has to realize that the goal of measuring risk/biomarkers is not only to determine an individual’s risk but also to use the risk assessment to guide appropriate therapy and thereby to improve long-term clinical outcome. It is therefore important to obtain insight into the effects of therapeutic approaches on short-term changes (observed within the first months after initiation of therapy) in these new risk/biomarkers, and to delineate whether these short-term drug-induced risk/biomarker changes are associated with long-term reductions in risk for renal and CV outcomes in ensuing years. Such information will allow the doctor and patient to use the risk/biomarker to estimate risk as well as therapy success. In this review we discuss the impact of treatment on novel renal and CV risk/biomarkers (excluding traditional risk factors such as blood pressure, glucose, lipids, body weight, and smoking), and delineate whether short-term treatment-induced changes in single or a panel of multiple risk/biomarkers predict changes in risk for long-term renal and CV outcomes.

Targeting Single Risk/Biomarkers

Albininuria

Albuminuria, a marker of generalized vascular dysfunction, is one of the most frequently evaluated risk/biomarkers in patients with diabetes. Large observational studies in patients with diabetes have shown that albuminuria is a valuable marker in predicting the risk for renal and CV disease (7–9). In addition, various drugs are known to decrease albuminuria, such as the well-known renin-angiotensin-aldosterone system (RAAS) inhibitors. These agents decrease albuminuria by approximately 40% (10). The (short-term) reduction in albuminuria achieved with RAAS inhibitors may be a critical step in achieving long-term protection against renal events (defined throughout this review as the need for chronic dialysis or renal transplantation) and CV events. Post hoc analyses from the Reduction of Endpoints in NIDDM (non–insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan Study (RENAAL) trial in patients with diabetes illustrated that each 50% reduction in albuminuria induced by treatment with an angiotensin-receptor blocker (ARB) during the first months of therapy was associated with 45% and 18% risk reduction for renal and CV events, respectively, during the ensuing 3.4 years of follow-up (Table 1 and Fig. 1) (11, 12). Similar results were observed in the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial. The ADVANCE trial illustrated that each halving of albuminuria during follow-up, achieved with combination therapy consisting of an angiotensin-converting-enzyme inhibitor (ACEI) and diuretic, resulted in 20% risk reduction for CV events (7).

A relevant scientific question is whether the short-term albuminuria-lowering effects of RAAS inhibitors, registered as antihypertensive drugs, are mediated through their effect on blood pressure only, or whether they are the result of a combination of effects (including the lowering of blood pressure). Indeed, RAAS inhibitors have multiple other effects such as lowering of
albuminuria. If albuminuria reduction confers renal and CV protection independent of changes in blood pressure or other risk/biomarkers, such evidence would support the validity of albuminuria as an independent target for renal- and CV-protective therapy.

The renoprotective effects of RAAS inhibitors beyond blood pressure control were initially discovered in nondiabetic patients. The Ramipril Efficacy in Nephropathy (REIN) trial showed that ramipril lowered the risk of end-stage renal disease compared to conventional intervention reduced LDL cholesterol 0.3 mmol/L, hemoglobin A1c, 1.0%, albuminuria 32 mg/24 h, and systolic blood pressure 4 mm Hg.

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Table 1. Overview of studies performed to determine the association between drug-induced changes in risk/biomarkers and long-term changes in renal or CV risk.*

<table>
<thead>
<tr>
<th>Risk/biomarker</th>
<th>Trial</th>
<th>Intervention</th>
<th>Risk/biomarker change</th>
<th>Change of long-term renal or CV risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single risk/biomarkers</td>
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<tr>
<td>Albuminuria</td>
<td>RENAAL</td>
<td>Losartan 100 mg/day vs placebo</td>
<td>Compared to placebo, albuminuria was decreased by 32% after 6 months.</td>
<td>Each halving of albuminuria during the first 6 months was associated with a reduction in the risk of renal and CV disease of 45% and 18%, respectively, during 3.4 years follow-up.</td>
</tr>
<tr>
<td>IDNT (Irbesartan in Diabetic Nephropathy)</td>
<td>Irbesartan 300 mg/day vs Amlodipine 10 mg/day vs placebo</td>
<td>Compared to placebo, albuminuria levels were 30% lower in irbesartan-treated patients after 12 months.</td>
<td>Each halving of proteinuria during the first 12 months was associated with a risk reduction in end-stage renal disease of 56% during 2.9 years of follow-up.</td>
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<tr>
<td>TGF-β</td>
<td>Captopril trial</td>
<td>Captopril 75 mg/day vs placebo</td>
<td>Captopril caused a 25% reduction in TGF-β compared to placebo during the initial 6 months.</td>
<td>An inverse correlation was found between the change in TGF-β and the percentage change in estimated GFR over the ensuing 2 years (r = −0.45; P = 0.008).</td>
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<tr>
<td>Hemoglobin</td>
<td>TREAT</td>
<td>Darbepoetin-α vs placebo</td>
<td>Hemoglobin levels increased from 104 to 106 g/L and from 104 to 125 g/L in, respectively, patients treated with placebo or darbepoetin-α.</td>
<td>Darbepoetin-α increased hemoglobin levels but did not reduce the risk of renal or CV events.</td>
</tr>
<tr>
<td>CRP</td>
<td>JUPITER</td>
<td>Rosuvastatin 20 mg/day vs placebo</td>
<td>3573 (46%) of participants assigned to rosuvastatin had a reduction in hs-CRP more than 50%.</td>
<td>Compared to placebo, participants assigned to rosuvastatin who achieved a CRP reduction more than 50% had a 54% CV risk reduction.</td>
</tr>
<tr>
<td>NT-proBNP</td>
<td>Steno-2</td>
<td>Intensive vs conventional multifactorial intervention</td>
<td>Compared to placebo, NT-proBNP levels were 6.5 ng/L lower in intensive treatment arm after 2 years.</td>
<td>A 10 ng/L reduction in NT-proBNP during the first 2 years was associated with a significant 1% CV risk reduction during a median follow-up of 7.8 years.</td>
</tr>
<tr>
<td>Multiple risk/biomarkers</td>
<td>Steno-2</td>
<td>Intensive vs conventional multifactorial intervention</td>
<td>Compared to conventional intervention, intensive treatment reduced LDL cholesterol 0.3 mmol/L, hemoglobin A1c, 1.0%, albuminuria 32 mg/24 h, and systolic blood pressure 4 mm Hg.</td>
<td>Intensive treatment attenuated the risk of nephropathy (risk reduction 44%) retinopathy (risk reduction 55%), CV events (risk reduction 59%) and death (risk reduction 46%).</td>
</tr>
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</table>

* All listed studies enrolled patients with diabetes except the JUPITER trial, which included apparently healthy individuals with high CRP.
tional antihypertensive therapy at a similar level of blood pressure control (13). These results extended to the population of patients with type 2 diabetes. The Irbesartan Diabetic Nephropathy Trial compared the effects of an ARB (irbesartan), a calcium-channel blocker (amlodipine), and placebo in patients with diabetic nephropathy (14). The rationale to include a calcium-channel blocker treatment arm in this trial was to determine blood pressure independent renoprotective effects of the ARB (15). The trial showed that irbesartan significantly lowered the risk for renal events compared to amlodipine despite similar blood pressure control. A post hoc analysis of this trial further illustrated that irbesartan’s superior renoprotective effect could be in large part attributed to its effect on proteinuria reduction (16). However, when the authors compared the renoprotective effects of irbesartan vs amlodipine at similar degrees of blood pressure and proteinuria reduction, irbesartan still provided better renoprotection. This finding indicated that the pharmacological effects of irbesartan could not be fully explained by its effects on blood pressure and proteinuria alone and implied that irbesartan’s effect on other, as yet unidentified, risk/biomarkers was involved in its long-term renoprotective effect. The results of this study argued for the simultaneous measurement of short-term changes in multiple risk/biomarkers to explain the overall pharmacological effects of an agent on long-term hard renal and CV outcomes.

Further indirect evidence supporting the validity of albuminuria as an independent target for renal- and CV-protective therapy comes from a detailed analysis by Eijkelkamp et al. (17). In this analysis of the RENAAL trial the blood pressure response to an ARB (losartan) was dissociated from the albuminuria response. The study showed that long-term renoprotection was related to the degree of albuminuria lowering and to a lesser extent to the degree of blood pressure lowering. Thus, RAAS inhibitors play a unique role in renal and CV therapy because of the protection they afford, which is mediated, at least in part, through their effect on albuminuria.

Although of interest, these post hoc analyses can be interpreted only in the context of hypothesis generation. To evaluate the monitoring and targeting of albuminuria as an effective treatment strategy, one group of patients should be assigned to frequent measurement and adjustment of medication if targets are not met, while the other group receives standard care. Such a design would isolate the role of albuminuria targeting...
by focusing on the additive effect of albuminuria monitoring compared with standard therapy, and provide a better approach to establish the clinical relevance of targeting albuminuria for renal and CV protection. Such a trial has not yet been conducted, although Hou et al. came very close with the design and results of the ROAD (Renoprotection of Optimal Antiproteinuric Doses) trial, conducted in nondiabetic patients. Hou et al. aimed to specifically target albuminuria using dosages of ACEi or ARB well above the dosage that is conventionally used for blood pressure reduction. It is known that such high dosages of ACEi or ARB confer additional antiproteinuric effects beyond their blood pressure–lowering effect (18, 19). Hou et al. reported that targeting albuminuria with optimal antiproteinuric dosages of ACEi or ARB resulted in much better renal protection than conventional antihypertensive therapy despite similar blood pressure control (20). Although these results are promising, further studies are needed to resolve the issue of whether specific lowering of albuminuria results in renal and CV protection.

Because RAAS inhibition forms the mainstay therapy for renal and CV protective therapy, the albuminuria-lowering effects of novel agents are now tested on top of RAAS inhibition. Thiazolidinediones, oral glucose-lowering drugs, act through stimulation of the peroxisome proliferator activated receptor γ. These drugs have been shown to significantly lower albuminuria in patients with diabetes (21, 22). Another target has been the vitamin D receptor. Studies have indicated that vitamin D–receptor activators (VDRA) exert albuminuria-lowering effects through suppression of the RAAS and antiinflammatory effects (23, 24). Apart from VDRA therapy, HMG-CoA (3-hydroxy-3 methyl glutaryl coenzyme A) reductase inhibitors (statins) also lowered albuminuria, but this seems to be a specific drug effect because not all statins uniformly lowered albuminuria (25, 26). Another target to lower albuminuria has been blocking the endothelin type A receptor in the endothelin system, which seems to play a role in the pathogenesis of albuminuria. Several studies have shown that blocking the endothelin type A receptor significantly reduced albuminuria up to 40% in patients with type 2 diabetes and nephropathy beyond optimal RAAS blockade (27, 28). Although effective, the side effects of endothelin antagonists, particularly fluid overload, have been a cause of concern and may blunt the CV protective effects of albuminuria lowering. To date, no hard end-point trial has been completed with either VDRAs, statins, or endothelin antagonists. Thus, it is not known whether short-term reductions in albuminuria during either VDRA, statin, or endothelin-antagonist therapy are related to reductions in the risk for hard renal and CV events.

The utility of (changes in) albuminuria as a risk/biomarker for renal and CV disease have been debated extensively. Critics have focused on at least 3 issues: variability of the albuminuria within an individual, absence of albuminuria in patients with renal or CV function loss, and results of large trials that did not confirm the importance of albuminuria as a predictor or a target for treatment. First, studies have shown that the variability in albuminuria is large, and as such albuminuria would not be a good risk/biomarker. Indeed, large, random, day-to-day fluctuations in any risk/biomarker hamper the accuracy and precision of predictions of changes in renal and CV risk. When examined at the individual level, albuminuria has been found to vary from day to day (29). However, when examined at the group level, the variability in albuminuria was equal to the variability in other risk/biomarkers (27).

Second, studies have shown that patients without albuminuria can have progressive loss of renal function. This finding is no surprise, because albuminuria is just like other risk/biomarkers and is one of many contributors to renal and CV disease. Obviously, other factors likely play a role in disease progression (30). Importantly, the available evidence clearly has shown that the presence of increased levels of urine albumin is an excellent predictor of later renal and CV problems in patients with and without diabetes (31). Third, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint (ONTARGET) trial showed that despite additional albuminuria reduction, combination therapy with ACEi and ARB did not confer CV protection, and even increased the risk of renal disease (32, 33). This result led to lively discussions about the validity of albuminuria as a risk/biomarker of renal disease and recommendations to dismiss albuminuria as a surrogate endpoint for renal and CV protection. Intriguingly, the discussion focused on albuminuria, although blood pressure was also further reduced in the combination arm. Because the combination arm showed no further protection in long-term outcomes, it would have been equally valid to consider dismissing blood pressure as a valid risk/biomarker! With regard to albuminuria in the ONTARGET trial, a recent analysis provided ample evidence that both baseline albuminuria as well as changes in albuminuria during the first years predicted the risk for renal and CV events in the following years (34). This result was in contrast with the earlier ONTARGET renal report, which gave the impression that albuminuria was not a valid renal risk predictor. Thus, the recent ONTARGET analysis further substantiates numerous previous studies with results demonstrating that in individual patients changes in albu-
minuria are an excellent predictor for changes in future renal and CV risk.

TRANSFORMING GROWTH FACTOR-β
Transforming growth factor-β (TGF-β) has a key role in the processes that lead to an increase in matrix components, infiltration of macrophages in renal tissue, and loss of nephrons, eventually leading to diabetic nephropathy. Therefore, it is not surprising that the presence of TGF-β has been shown to predict the onset of end-stage renal disease.

TGF-β is an important transducer of the pathogenetic effects of angiotensin II, and its levels are controlled by the RAAS. Because of these characteristics, studies of TGF-β have investigated whether the effects of RAAS inhibitors on TGF-β could account for the renoprotective effects of RAAS inhibitors beyond decreasing blood pressure and albuminuria. To this end, the changes induced by the ACEi captopril in serum TGF-β levels at 6 months were measured and correlated to the 2-year rate of renal function decline in patients with type 1 diabetes (35). Captopril caused a significant decline in TGF-β levels compared to placebo. The degree of TGF-β reduction coincided with the degree of preservation of the glomerular filtration rate (GFR) during the ensuing 2 years of follow-up (Table 1). Thus, if TGF-β declined at 6 months, the rate of renal function decline during the subsequent 2 years of follow-up was smaller. An important question was whether the changes in TGF-β were independent of changes in albuminuria. Another study provided more insight into the independent effects of RAAS inhibition on TGF-β levels. Agarwal et al. found that 4-week treatment with the combination of an ACEi and an ARB significantly attenuated TGF-β levels. Interestingly, the reductions in TGF-β levels occurred independently of changes in 24-h urinary protein excretion or blood pressure (36). These data suggest that the effect of RAAS inhibition on TGF-β may in part explain its renal protective effect. However, the definitive answer to whether TGF-β suppression is independently associated with renoprotection should come from randomized controlled trials.

HEMOGLOBIN
Anemia is a common finding in patients with diabetes, and it has potential to negatively affect well-being and social functioning. Clear evidence is available that anemia is an independent potent risk factor for CV disease (37–39). The role of anemia as a CV risk factor appears to extend to progression of chronic kidney disease. In patients with type 2 diabetes, anemia has been documented to be an independent risk factor for doubling of serum creatinine (50% reduction in GFR) or end-stage renal disease (9).

Various drugs affect hemoglobin levels. First, ARB are known to lower hemoglobin levels (an unwanted side effect). The reductions in hemoglobin during ARB therapy appear not to affect the overall efficacy of ARB on the progression of renal disease. Toto et al. demonstrated that the long-term renoprotective effects of the ARB losartan in individuals with diabetes and nephropathy persisted in the presence of a significant reduction in hemoglobin (40). These data indicated that a reduction in hemoglobin during the initial months after the start of ARB therapy did not necessarily imply a dose reduction or discontinuation of treatment altogether.

Erythropoiesis-stimulating agents (ESA) are a class of agents that are intended to target hemoglobin levels and bring them toward reference intervals. Despite the absence of high-quality outcome data, ESA therapy has been frequently used based on the expectation that correction of anemia improves renal and CV outcomes. Data from the Trial to Reduce Cardiovascular Events with Aranesp Therapy (TREAT), however, created a dilemma: ESA therapy increased hemoglobin levels after just 3 months of therapy but did not confer long-term renal or CV protection (41). These results were remarkable because theoretically increasing oxygen delivery and improving CV hemodynamics should improve vascular outcomes (42). Although a lot of attention has centered on the hemoglobin targets used in these trials, another explanation could be that high ESA exposure itself might account for the detrimental effects. Indeed, a post hoc analysis of the TREAT trial demonstrated that patients with a poor hematopoietic response to ESA therapy (those within the lowest quartile of the 4-week hemoglobin change) were more likely to experience a CV event or die compared to responsive patients (Table 1) (43). These data underscore the importance of considering individualized therapeutic responsiveness and limiting dose escalation in those patients who are not attaining targeted hemoglobin goals. Further studies, such as the CEDOSE (Clinical Evaluation of the Dose of Erythropoietins) trial, in which the effects of fixed-dose ESA combinations are tested, should provide additional evidence as to whether the ESA dose itself or the targeted hemoglobin level mediates the increased risk of adverse renal and CV outcomes (44). Nevertheless, the lack of renal and CV protective effects despite increasing hemoglobin levels in the TREAT trial indicate that hemoglobin is a poor risk/biomarker with which to follow the response of ESA therapy.

C-REACTIVE PROTEIN
In recent years, it has been postulated that chronic low-grade tissue inflammation may play a critical role in initiation and progression of atherosclerosis and
diabetic renal and CV injury. Several studies have demonstrated that measurement of low-grade inflammatory risk/biomarkers, among them high-sensitivity C-reactive protein (hs-CRP), improves CV risk stratification, particularly in those already at intermediate or high CV risk (45–48). The predictive ability of hs-CRP goes beyond CV risk prediction. Laaksonen et al. (49) and Brantsma et al. (50) have provided evidence that the presence of increased concentrations of hs-CRP in apparently healthy individuals is associated with increased risk for de novo type 2 diabetes.

Statin therapy has greatest effects in the presence of inflammation. Several studies show that statin therapy reduces hs-CRP (51, 52). In trials of patients with coronary disease and acute coronary syndrome, the benefits of statin therapy relate at least in part to their effect on hs-CRP reduction (53, 54). The recent Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial was designed to study the effect of rosuvastatin in people with LDL concentrations within reference intervals but increased hs-CRP concentrations. The trial showed that rosuvastatin lowered LDL cholesterol and hs-CRP in the short term and markedly lowered the long-term risk for CV events (55). In this trial rosuvastatin decreased the concentrations of both LDL cholesterol and hs-CRP. Thus it could not be established whether the reductions in hs-CRP or LDL or both (or another undiscovered risk/biomarker) were the driving parameter for CV protection. A post hoc analysis recently provided further insight into this topic. This analysis demonstrated that in patients assigned to rosuvastatin who achieved LDL cholesterol of <1.8 mmol/L and hs-CRP of <2 mg/L at 1 year had a substantially lower risk for CV events compared to those who achieved neither target or only the LDL cholesterol target concentration of <1.8 mmol/L (Table 1 and Fig. 1) (56). The correlation between the achieved LDL cholesterol and hs-CRP concentrations was small, indicating that only a small part of the achieved hs-CRP concentration could be explained by the achieved LDL cholesterol concentration. These data suggest that the extent to which statins lower hs-CRP and LDL cholesterol in the short term determines the degree of long-term CV protection.

As was the case for the post hoc analyses of albuminuria trials described above, the JUPITER trial did not provide direct evidence that monitoring of hs-CRP to guide the intensity of statin therapy resulted in improved CV outcomes. An alternative to the JUPITER design in which one group of patients is assigned to intensive hs-CRP targeting while the control group receives usual care would have provided direct evidence of the value of an hs-CRP–targeted intervention approach. Until such data become available, the efficacy of improving health outcomes by using hs-CRP as a target is not proven.

**Amino-terminal pro-B-type natriuretic peptide**

Amino-terminal pro-B-type natriuretic peptide (NT-proBNP) is a risk/biomarker of the cardiac response to volume overload. In the setting of increased volume expansion, the proBNP precursor is released and subsequently converted into active brain natriuretic peptide (BNP) and inactive NT-proBNP. Studies in patients with diabetes and diabetic nephropathy have shown that NT-proBNP is an important prognostic marker for CV events and all-cause mortality. ACEi and ARB reduce plasma concentrations of NT-proBNP in post–myocardial infarction and congestive heart failure patients. Anand et al. demonstrated that the ARB valsartan caused a sustained reduction in BNP within 4 months of therapy. Individuals in whom BNP concentrations were attenuated during the first 4 months had markedly lower risk for long-term CV events than those in whom BNP rose during the first months of therapy (Fig. 1) (57). The Steno-2 trial in patients with type 2 diabetes showed that intensive targeting of multiple CV risk factors reduced NT-proBNP during follow-up compared to conventional therapy (58). Interestingly, the magnitude of NT-proBNP reduction during the first 2 years of treatment was associated with a reduction in CV risk during the subsequent 6 years of follow-up (Table 1).

These results suggest that attenuating NT-proBNP levels in the short term improves long-term health outcomes. However, as mentioned above, such post hoc analyses do not provide direct evidence that an NT-proBNP targeted approach confers long-term renal and/or CV protection. A couple of RCTs have been conducted to test the hypothesis that an NT-proBNP targeted approach improves long-term CV outcomes. The earlier trials showed promising effects in terms of CV outcomes. However, these trials were performed in small populations and had a limited duration of follow-up (59, 60). Pfisterer et al. recently investigated an NT-proBNP guided strategy in a larger cohort of 499 heart failure patients in which approximately one third had diabetes (61). The trial failed to achieve significant differences in NT-proBNP concentrations between the 2 treatment groups, although NT-proBNP concentrations were numerically lower in the targeted group. After 18 months, no CV benefit was observed in patients assigned to NT-proBNP–targeted therapy compared to those who received conventional symptom-guided therapy. Thus, the value of specific targeting of NT-proBNP on top of symptom-guided therapy seems limited, at least in this population of patients with heart failure, despite the unquestionable
diagnostic and prognostic significance of NT-proBNP. The question of whether an NT-proBNP–targeted approach confers renal or CV protection in other populations warrants further research.

Targeting Multiple Risk/Biomarkers

Because the etiology of diabetes is multifactorial, it has been suggested that a multifactorial approach targeting the various pathways involved in the pathogenesis of diabetes simultaneously would lead to more salutary long-term outcomes. One of the few studies in which the long-term effects of a multifactorial treatment strategy in type 2 diabetes was systematically evaluated is the Steno-2 trial (3). The intensive multifactorial intervention consisted of pharmacological agents that targeted blood pressure, hemoglobin A1c, and lipid concentrations and behavioral modifications including smoking cessation and diet changes. After 4 years of follow-up, multifactorial intervention slowed the progression of nephropathy and retinopathy. In addition, the long-term follow-up data of this study demonstrated that patients assigned to intensive multifactorial intervention had a significantly lower risk for CV events and mortality, highlighting the importance of a multifactorial treatment regimen (Table 1) (62).

A new class of oral glucose-lowering agents targeting multiple risk/biomarkers is currently under development. These drugs are designed as selective inhibitors of the sodium–glucose cotransporter (SGLT2). The SGLT2 receptor mediates glucose (and sodium) reabsorption in the proximal tubule of the kidney (63). Randomized controlled trials have shown that blockade of the SGLT2 receptor increases urinary glucose excretion and decreases hemoglobin A1c (64). Intriguingly, these drugs appear to have favorable effects on other renal and CV risk/biomarker as well, including blood pressure and body weight reduction (64). Thus, multiple renal and CV risk/biomarkers are targeted with a single drug. Supposedly, these multiple favorable effects result in substantial renal and CV protection. A couple of trials are currently underway testing the efficacy and safety of SGLT2 inhibitors on renal and CV endpoints. The results of these trials are awaited.

Other Novel Risk/Biomarkers

Besides the risk/biomarkers discussed above, the effects of different pharmacological agents on other single risk/biomarkers predicting CV and renal disease have been tested. Several studies have shown that RAAS-inhibiting therapy can modify risk/biomarkers reflecting endothelial and tubular damage and inflammation (65–71). Furthermore, metformin has been reported to lower inflammation biomarkers (72). However, to the best of our knowledge, all these studies were performed in small populations with only limited duration of follow-up. Therefore, the impact of short-term treatment-induced changes in these risk/biomarkers on long-term hard renal and CV outcomes cannot be ascertained. Further studies are clearly warranted to test whether therapeutic interventions aimed at targeting these novel risk/biomarkers afford long-term protection. If so, the clinical utility of these novel risk/biomarkers in the management of diabetic renal and CV complications will increase.

Conclusions

Over the last 2 decades, a vast number of risk/biomarkers that predict renal and CV complications have been discovered. However, few studies have systematically tested whether short-term treatment-induced changes in these risk/biomarkers relate to long-term protection. Moreover, whether a targeted approach, directed at changing a panel of multiple novel risk/biomarkers, will improve long-term renal and CV outcome remains an unanswered question. The examples of targeting single novel risk/biomarkers, such as hemoglobin and NT-proBNP, have taught us that although a risk/biomarker may have superior prognostic ability, such ability does not automatically indicate that specific targeting of and changing such a risk/biomarker will improve long-term outcome. Thus, to establish the clinical utility of novel risk/biomarkers in guiding treatment intensity, specific protocols must be developed and employed to demonstrate that targeting single (or multiple) novel risk/biomarkers improves long-term health outcomes.

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