Linking Kidney and Cardiovascular Complications in Diabetes—Impact on Prognostication and Treatment: The 2019 Edwin Bierman Award Lecture

Peter Rossing,[1,2] Frederik Persson,[1] Marie Frimodt-Møller,[1] and Tine Willum Hansen[1]

Diabetes 2021;70:39–50 | https://doi.org/10.2337/dbi19-0038

In diabetes, increasing albuminuria and decreasing glomerular filtration rate are hallmarks of chronic kidney disease in diabetes and increase the risk of atherosclerotic cardiovascular events and mortality as well as the risk for end-stage kidney disease. For two decades, standard of care has been controlling risk factors, such as glucose, blood pressure, lipids, and lifestyle factors, and specifically use of agents blocking the renin-angiotensin system. This has improved outcome, but a large unmet need has been obvious. After many failed attempts to advance the therapeutic options, the past few years have provided several new promising treatment options such as sodium–glucose cotransporter 2 inhibitors, endothelin receptor antagonists, glucagon-like peptide 1 agonists, and nonsteroidal mineralocorticoid receptor antagonists. The benefits and side effects of these agents demonstrate the link between kidney and heart; some have beneficial effects on both, whereas for other potentially renoprotective agents, development of heart failure has been a limiting factor. They work on different pathways such as hemodynamic, metabolic, inflammatory, and fibrotic targets. We propose that treatment may be personalized if biomarkers or physiological investigations assessing activity in these pathways are applied. This could potentially pave the way for precision medicine, where treatment is optimized for maximal benefit and minimal adverse outcomes. At least it may help prioritizing agents for an individual subject.

The global burden of diabetes is currently estimated to affect 463 million individuals, or 1 in 11, according to the International Diabetes Federation, and projections suggest a 48% increase in the prevalence to 700 million people by 2045 (1). Diabetes is associated with a two- to fourfold increased risk for atherosclerotic cardiovascular disease (CVD) compared with the background population, and 30–40% with diabetes are affected by chronic kidney disease characterized by increased albuminuria or decreased glomerular filtration rate (GFR) (or diabetic kidney disease [DKD]). The presence of kidney disease increases the risk of CVD, and the combination is a deadly cocktail. Increasing albuminuria or decreasing GFR increases the risk of CVD and mortality (2) (see Fig. 1) as well as the risk for end-stage kidney disease. Furthermore, albuminuria and GFR levels form the basis on which chronic kidney disease is staged according to the Kidney Disease Improving Global Outcomes (KDIGO) guidelines (3). Early-onset DKD may shorten life expectancy by 14–16 years (4), and excess mortality in diabetes is primarily due to mortality in DKD (5), with a 6-fold increased risk for mortality with albuminuria and 15-fold increased risk with albuminuria and reduced GFR (5).

The aim of this review is to discuss the link between kidney and heart in diabetes, as it is important to understand for optimal treatment and prevention of late complications. Deckert et al. (6) formulated the Steno hypothesis, suggesting that albuminuria reflects widespread vascular damage and proposing a linkage between DKD and CVD. Here, we will discuss recent investigations of functional links showing connections between kidney and heart damage. We will evaluate biomarkers ranging from albuminuria to omics, which could pave the way to a personalized medicine approach in kidney and heart diseases. Finally, we will describe how these biomarkers can be used when applying new therapies such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like

[1]Steno Diabetes Center Copenhagen, Gentofte, Denmark
[2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Corresponding author: Peter Rossing, peter.rossing@regionh.dk

The 2019 Edwin Bierman Award Lecture was presented at the American Diabetes Association's 79th Scientific Sessions, San Francisco, CA, 10 June 2019.

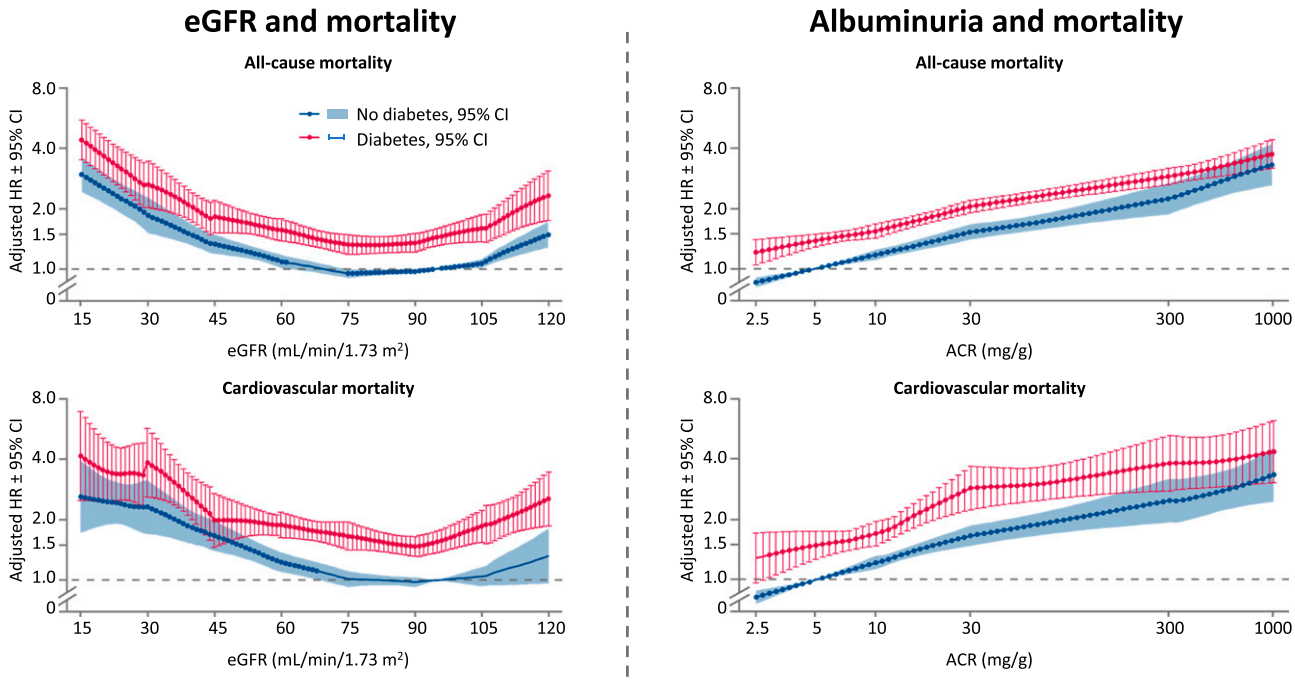

Figure 1—Declining eGFR and increasing albuminuria are associated with mortality in individuals with diabetes. ACR, albumin-to-creatinine ratio (2).

peptide 1 receptor agonists (GLP-1RA), and mineralocorticoid receptor antagonists. These agents have different mechanisms of action, and the biomarkers can help tailoring treatment to the pathophysiology. The cardio-renal link is stressed by the fact that some of these agents may work on the kidney to "save" the heart and others protect the kidney but with a risk for heart failure.

Investigations of Functional Links—Connections Between the Kidney and Heart

A chronic cardio-renal syndrome has been described where impaired renal function with retention of uremic solutes, hypertension, fluid retention, and anemia affect the heart. On the other hand, a failing heart with low cardiac output with hypoperfusion and atherosclerosis has detrimental impact on renal function (7). In diabetes, the coexistence of microvascular and macrovascular complications increases mortality, and we aimed to investigate the associations between albuminuria and vascular and ventricular function of the heart.

Major advances in noninvasive imaging enable the investigation of new aspects of the cardiac microcirculation. Among these methods is quantitative cardiac positron emission tomography (PET), which allows measurement of myocardial blood flow at rest and during pharmacologically induced hyperemic conditions. The ratio between flow in the two situations is termed the myocardial flow reserve and mirrors the function of the large epicardial arteries and the microcirculation of the myocardium. Thus, in individuals without epicardial coronary stenosis, cardiac PET can be used to assess the function of the microcirculation, including the combined function of cells in the vascular smooth muscle and endothelial cells. A higher myocardial flow reserve represents enhanced ability to increase the myocardial blood flow under stress.

A hybrid scanner can combine cardiac PET with computed tomography (CT), enabling the simultaneous estimation of the coronary artery calcium score. A high coronary artery calcium score can identify asymptomatic individuals who are at higher risk of coronary heart disease and mortality (8) and is a specific marker of atherosclerosis, independent of its etiology.

In the past, clinical use of cardiac PET/CT was limited by the requirement of an expensive PET/CT scanner and an on-site cyclotron for radioisotope production. The development of less expensive PET/CT scanners has resulted in a wider clinical application of cardiac PET/CT. Moreover, rubidium-82 (^{82}Rb) is a PET myocardial perfusion tracer produced with a strontium-82 (^{82}Sr)/^{82}Rb generator and therefore can be used in centers without immediate access to an on-site cyclotron. PET myocardial perfusion imaging with ^{82}Rb has several other advantages including high image quality and low radiation dose as well as rapid examination time. Therefore, cardiac ^{82}Rb PET/CT has replaced the classical myocardial scintigraphy with single-photon emission CT as routine examination for individuals with suspected cardiac ischemia.

Taking advantage of cardiac ^{82}Rb PET/CT, we have conducted two cross-sectional studies. We aimed to gain information on the prevalence of reduced myocardial flow reserve and increased coronary artery calcium score in

individuals with type 1 diabetes and type 2 diabetes (with or without albuminuria as a measure of renal and microvascular damage) while comparing them with healthy control subjects. Moreover, we wanted to examine the association between the myocardial flow reserve and the coronary artery calcium score.

The first study included 60 individuals with type 2 diabetes, but free of overt CVD, stratified by presence/history of albuminuria (≥30 mg/24 h) ($n = 30$) or normoalbuminuria (<30 mg/24 h) ($n = 30$), and 30 age- and sex-matched healthy control subjects (9). The second study comprised 60 individuals with type 1 diabetes stratified by presence/history of macroalbuminuria (≥300 mg/g; $n = 30$) or normoalbuminuria (<30 mg/g; $n = 30$) (10). Different cutoff values to define reduced myocardial flow reserve have been applied depending on the characteristic of the study population, and a cutoff of 2.5 has been suggested in individuals without obstructive coronary artery disease (11). We therefore prespecified a cutoff of 2.5. An elevated coronary artery calcium score was defined as an Agatston score >300.

Cardiac PET/CT in Control Subjects and in Participants With Type 1 or Type 2 Diabetes Stratified by Urinary Albumin Excretion

Table 1 summarizes the sex, age, level of albuminuria, and main results from the cardiac PET/CT scans in the participants, grouped into control subjects and individuals with type 1 or type 2 diabetes (stratified by urinary albumin excretion level).

The main findings in type 1 diabetes were as follows:

1) Myocardial microvascular function was comparable in the healthy control subjects and the individuals with type 1 diabetes and normoalbuminuria but impaired in the presence of macroalbuminuria (see Fig. 2). This indicates that there is a separate microvascular injury in the heart of individuals with type 1 diabetes and albuminuria compared with normoalbuminuria.
2) Coronary calcification was higher in individuals with type 1 diabetes compared with healthy control subjects.
3) Coronary calcification was comparable in normo- and macroalbuminuric individuals with type 1 diabetes; however, when coronary artery calcium score was dichotomized, the frequency of elevated coronary artery calcium score (>300) was higher in individuals with macro- compared with normoalbuminuria. Therefore, it might be that there is an association between coronary artery calcium score and albuminuria in type 1 diabetes, but that we had limited power to detect it because of a skewed distribution of the coronary artery calcium scores.

The main findings in type 2 diabetes were as follows:

1) Myocardial microvascular function was impaired in individuals with type 2 diabetes and normoalbuminuria compared with healthy control subjects.
2) Myocardial microvascular function was impaired in the presence of albuminuria compared with normoalbuminuria, and 83% of individuals with albuminuria had impaired myocardial flow reserve (<2.5) compared with 40% with normoalbuminuria.
3) Coronary calcification was higher in individuals with type 2 diabetes compared with healthy control subjects and in individuals with type 2 diabetes and albuminuria compared with normoalbuminuria.

The Relationship Between Cardiac Vascular Function and Atherosclerosis

For both type 1 and type 2 diabetes, we demonstrated a significant, but modest, negative correlation between myocardial flow reserve and coronary artery calcium score ($R^2 = 0.20$, $P < 0.001$ [10], and $R^2 = 0.24$, $P < 0.001$ [9], respectively). Thus, the relationship between functional changes (myocardial flow reserve) and anatomical features of atherosclerosis (coronary artery calcium score) may not be straightforward and these measures might expose different pathophysiological processes and differences in time course. This implies that a coronary artery calcium score of 0 cannot solely be used as a gatekeeper, as we measured myocardial flow reserves ranging from 1.8 to 4.9 in individuals with a coronary artery calcium score of 0 (9).

The Relationship Between Cardiac Vascular Function and Cardiac Autonomic Dysfunction

Cardiac autonomic neuropathy is a severe and often overlooked complication in diabetes associated with kidney disease, increased mortality, and silent myocardial ischemia. Cardiac autonomic dysfunction, including loss of cardiac sympathetic integrity, may contribute to impaired myocardial blood flow regulation.

The cardiac autonomic function can be evaluated with simple bedside tests using heart rate variability indices or response in heart rate to standing, slow breathing, or the Valsalva maneuver (cardiovascular autonomic reflex tests). These indirect tests can reveal altered sympathetic and parasympathetic activity. Cardiac radionuclide imaging using the nonmetabolized norepinephrine analog metaiodobenzylguanidine (MIBG) allows a direct assessment of the integrity of the adrenergic cardiac innervation and may be more reliable for evaluation of cardiac autonomic function and might also diagnose cardiovascular autonomic neuropathy in early clinical stages before it can be detected by the indirect tests.

In the two cross-sectional studies described above, we evaluated the association between the cardiac autonomic function and the cardiac vascular function (assessed as the myocardial flow reserve). The cardiac autonomic function was evaluated with use of cardiac MIBG imaging, heart rate variability indices, and cardiovascular autonomic reflex tests (12,13).

In both studies, we demonstrated that impaired function of the cardiac autonomic system correlated with lower myocardial flow reserve. The association was strongest

Table 1—Myocardial flow rate reduced and coronary artery calcium score elevated in type 1 and type 2 diabetes subjects with albuminuria compared with subjects with normoalbuminuria or control subjects

		Type 1 diabetes (10)		Type 2 diabetes (9)	
Variable	Control subjects (n = 30)	Normoalbuminuria (n = 30)	Macroalbuminuria (n = 30)**	Normoalbuminuria (n = 30)	Albuminuria (n = 30)
Female (%)	40	40	43	40	27
Age (years)	59.8 ± 9.9	59.8 ± 9.1	58.2 ± 9.9	60.9 ± 10.1	65.6 ± 6.8[c]
Albuminuria (mg/24 h or mg/g)*	6 (5–11)	3 (3–5)[a]	121 (53–283)[b]	7 (6–14)	146 (51–298)[c]
MFR	3.0 ± 0.8	3.1 ± 0.8	2.1 ± 0.9[b]	2.6 ± 0.8[a]	2.0 ± 0.5[c]
MFR <2.5 (%)	17	23	77[b]	40[a]	83[c]
CAC score	0 (0–81)	72 (22–247)[a]	263 (23–1,315)	36 (1–325)[a]	370 (152–1,025)[c]
CAC score >300 (%)	7	17	44[b]	27	53[c]

Data are total numbers in percent, mean ± SD, or geometric mean/median (IQR). Significance ($P < 0.05$) was calculated from independent-samples t test, Mann-Whitney U test, or the χ^2 test. CAC, coronary artery calcium; MFR, myocardial flow reserve. **The classification of macroalbuminuria was based on the highest albuminuria level measured at the study visit or documented previously in two out of three consecutive urine samples within 1 year. Data presented are from study visit and reduced due to treatment with antihypertensive medication in many subjects compared with values used for classification. *Measured as urinary albumin excretion rate for control subjects and individuals with type 2 diabetes and as urinary albumin-to-creatinine ratio for individuals with type 1 diabetes. [a]Statistical difference between control subjects and individuals with normoalbuminuria. [b]Statistical difference among individuals with type 1 diabetes between those with normoalbuminuria and those with macroalbuminuria. [c]Statistical difference among individuals with type 2 diabetes between those with normoalbuminuria and those with albuminuria.

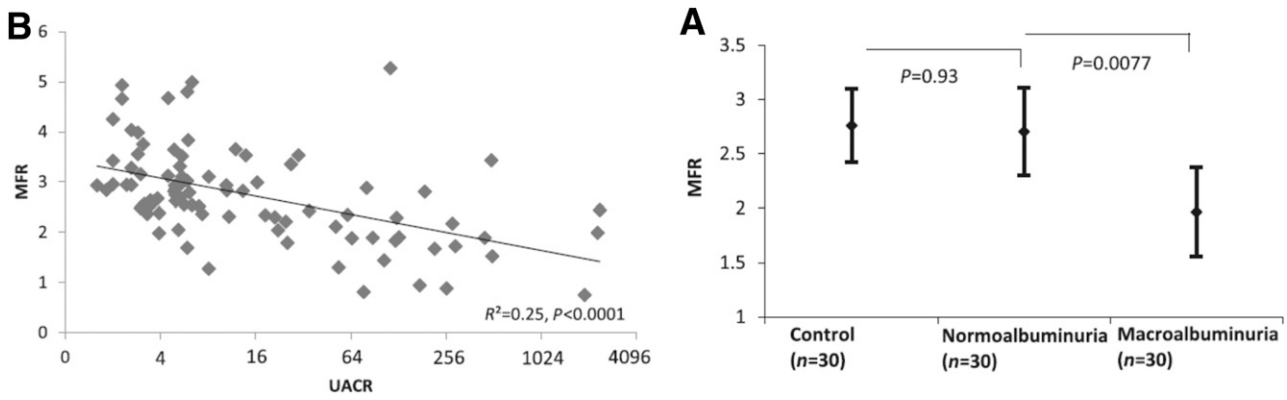

Figure 2—Myocardial flow reserve (MFR) associated with albuminuria (urinary albumin-to-creatinine ratio [UACR]) in type 1 diabetes (10).

when the cardiac autonomic function was evaluated with cardiac MIBG imaging, as it persisted after comprehensive adjustment (12,13).

Cardiac Autonomic Function in Control Subjects and in Participants With Type 1 or Type 2 Diabetes Stratified by Urinary Albumin Excretion

We demonstrated a general impaired function of the cardiac autonomic system in individuals with type 1 or type 2 diabetes and normoalbuminuria as compared with healthy control subjects (12,13). Compared with participants with normoalbuminuria, individuals with albuminuria had similar cardiac autonomic function assessed by the cardiac MIBG imaging and the heart rate variability indices in type 1 and type 2 diabetes. However, cardiac autonomic neuropathy was more frequent in the participants with albuminuria compared with in those with normoalbuminuria when evaluated by the cardiac autonomic reflex tests.

Ongoing Study: Myocardial Flow Reserve as Risk Marker

As the myocardial flow reserve estimates the microvascular function of the heart, it may provide unique risk information beyond the extent of coronary atherosclerosis, and identification of early stages of coronary microvascular disease may provide new prospects for risk stratification.

The predictive value of the myocardial flow reserve has been evaluated for mortality outcomes in individuals with diabetes (mix of type 1 and type 2) referred for cardiac ^{82}Rb PET/CT due to chest pain or dyspnea. More than 60% had previous CVD and the baseline examination was in 2006–2010, before modern multifactorial treatment, including SGLT2 inhibitors and GLP-1RA, was established (14). The study demonstrated that impaired myocardial flow reserve (<1.6) was associated with a higher rate of cardiac death (14). However, the predictive value of myocardial flow reserve for CVD and mortality in asymptomatic individuals with diabetes remains to be investigated. Therefore, we are conducting a prospective study with the primary aim of identifying subpopulations at high risk of developing CVD during follow-up, among asymptomatic individuals with type 2 diabetes, using myocardial flow reserve and coronary artery calcium score.

Heart Failure and Association With Microvascular Damage

In recent years, there has been increasing focus on heart failure in diabetes, as this is associated with a poor prognosis. Heart failure is particularly common in subjects with type 2 diabetes and kidney disease (15) but is also a concern in type 1 diabetes (16). To study whether systolic dysfunction could be detected in individuals with type 1 diabetes without known ischemic heart disease, we conducted a study with echocardiography measuring global longitudinal strain (GLS) as a sensitive measure of systolic function in 1,065 individuals with type 1 diabetes (17). Compared with 198 healthy control subjects, there was a significantly impaired systolic function (GLS) in diabetes. However, for subjects with normoalbuminuria there were no difference when compared with healthy control subjects, whereas presence of micro- or macroalbuminuria was associated with increasingly impaired GLS, again highlighting a link between the kidney (albuminuria) and heart. In evaluations after 7.5 years of follow-up, measures of systolic and diastolic function predicted cardiovascular events independently of guideline-recommended clinical risk factors alone (18).

In a cohort of 1,030 subjects with type 2 diabetes with or without previous CVD, we also found albuminuria to be related to echocardiographic abnormalities (19). When this cohort was followed for 4.8 years, a range of echocardiographic parameters predicted CVD in this cohort; however, in multivariable analyses, mean E/e′ (a measure of diastolic dysfunction) was the strongest predictor and had the highest model performance. We observed a hitherto undescribed sex interaction, as mean E/e′ performed best in men, whereas in women GLS was best (20).

Markers From Different Pathways Predict Heart and Kidney Outcomes

As an alternative description of the cardio-renal syndrome, Zannad and Rossignol described risk factors such as diabetes and hypertension, activating pathways such as inflammation, oxidative stress leading to fibrosis, and inflammation affecting both the kidney and heart (21). This model can be used for precision medicine in using biomarkers related to the different activated pathways to guide therapy (Fig. 3). After many years with renin-angiotensin system (RAS) blocking agents as the only therapy for DKD, we are currently in the fortunate situation of having a number of potential therapies for DKD that have been or are being evaluated in phase 3 studies with cardiovascular or renal primary end points. Combination therapy including all agents is probably neither feasible nor safe, and assuming pathophysiological heterogeneity between people with DKD, application of therapies based on relevant biomarkers may thus be a way forward to optimize benefit and minimize adverse events.

Vascular Damage

As discussed initially, elevated urinary albumin excretion reflects widespread vascular damage and predicts development of renal failure and cardiovascular events. In addition, treatment-induced reductions are associated with improved renal and cardiac prognosis as initially demonstrated in smaller studies (22,23) and recently documented in meta-analyses of observational (24) and intervention (25) studies. Thus, albuminuria has been an inclusion criterion in most renal outcome studies in diabetes and a surrogate outcome in many phase 2 studies. For several decades, elevated albuminuria has been clinically used as an indicator for cardioprotective therapy with RAS-blocking agents.

Troponin T has, in addition to its use in acute settings as a marker of myocardial damage, been used to demonstrate vascular, cardiac, and renal risk in both type 1 and type 2 diabetes and could be a marker of increased risk for atherosclerosis (26,27). Trimethylamine-N-oxide (TMAO), is a metabolite of phosphatidylcholine, choline, and carnitine produced by the gut microbiota from ingested animal food sources (meat, eggs, and fish). A higher level of TMAO has been suggested as an independent risk factor for renal impairment and CVD. First, simply as a biomarker of recurrent CVD in people with known CVD (28), but TMAO might be mechanistically involved in the pathogenesis of CVD, as it has been shown to be associated with higher levels of cholesterol in macrophages and it has been shown to enhance the risk of thrombosis by promoting platelet hyperactivity. We demonstrated that higher TMAO was associated with renal and cardiac events during follow-up in type 1 diabetes (29), although not independently of renal function, maybe because it is a marker of filtration or because the effect is mediated by impaired renal function. In type 2 diabetes, it was also predictive of cardiovascular damage (30).

Fibrosis

We studied, as a marker of fibrosis, serum and urine PRO-C6, a product specifically generated during collagen VI formation. We tested whether it is prognostic for adverse outcomes in individuals with type 2 diabetes and microalbuminuria. We found a doubling of serum PRO-C6 increased hazards for cardiovascular events (hazard ratio

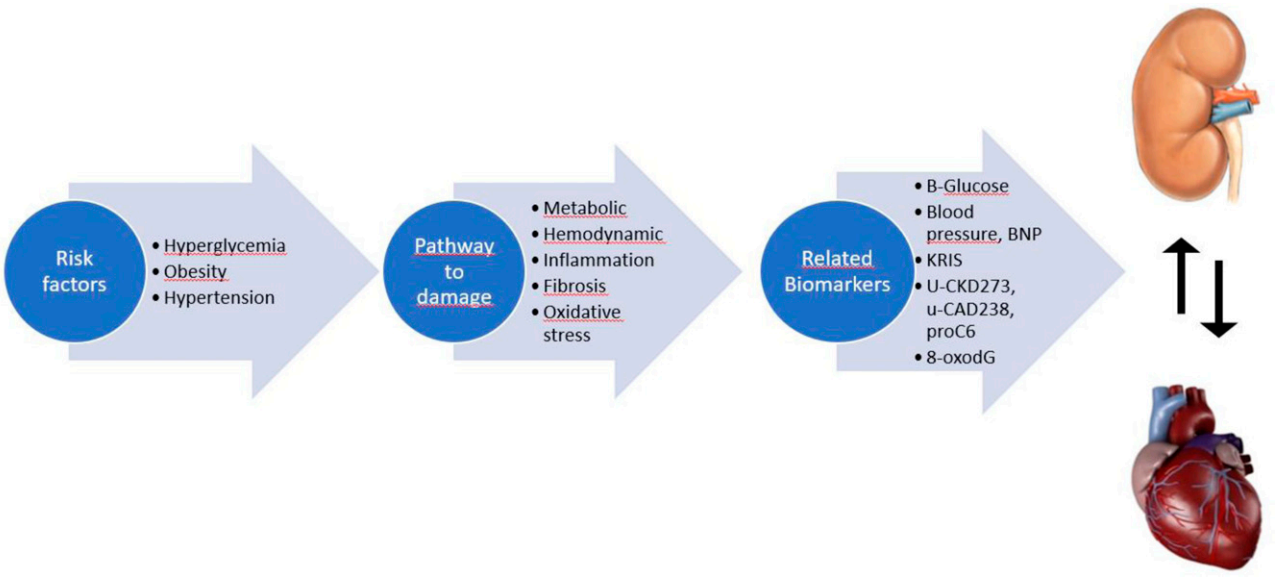

Figure 3—Potential risk factors, pathological pathways, and corresponding markers on the path to heart and kidney complications. B-Glucose, blood glucose; BNP, brain natriuretic peptide; U-CKD273, urinary proteomic marker of chronic kidney disease; u-CAD238, urinary proteomic marker of coronary heart disease; proC6, serum PRO-C6 (marker of fibrosis); 8-oxodG, 8-oxo-7,8-dihydro-2′-deoxyguanosine (see text for details).

[HR] 3.06 [95% CI 1.31–7.14]) and all-cause mortality (6.91 [2.96–16.11]) and reduction of estimated GFR (eGFR) of >30% (4.81 [1.92–12.01]) (see Fig. 4). We also tested this in type 1 diabetes and found similar results (31), although in individuals with type 1 diabetes the association with cardiovascular events was lost after adjustment for other risk factors.

Applying urinary proteomic analysis with capillary electrophoresis coupled to mass spectrometry, Good et al. (32) described a high dimensional urinary biomarker pattern composed of 273 peptides associated with overt kidney disease: CKD273. The original studies included people with chronic kidney disease on a mixed background compared with healthy control subjects. The components of CKD273 include collagen fragments and are assumed to relate to early fibrosis in the kidney. In retrospective studies, this proteomic classifier identified subjects at risk for DKD and progression in albuminuria class earlier than the indices currently used in clinical practice (33). We tested, in a prospective study including people with type 2 diabetes and normoalbuminuria, whether CKD273 was associated with development of microalbuminuria and whether progression to microalbuminuria could be prevented with the mineralocorticoid receptor antagonist (MRA) spironolactone (34) (see Fig. 5). We chose spironolactone, as this MRA had been proposed to prevent fibrosis and had been demonstrated to reduce albuminuria in DKD (35). We followed 1,775 participants; 12% ($n = 216$) had a high-risk urinary proteomic pattern, of whom 209 were included in the trial and assigned spironolactone ($n = 102$) or placebo ($n = 107$). Median follow-up time was 2.51 years. Progression to microalbuminuria was seen in 28.2% of high-risk and 8.9% of low-risk participants ($P < 0.001$) (HR 2.48 [95% CI 1.80–3.42], $P < 0.001$). There was no significant effect of spironolactone on development of microalbuminuria (HR 0.81 [95% CI 0.49–1.34] $P = 0.41$), which may reflect lack of power, or alternatively it only works in established chronic kidney disease. Based on the same urinary proteomic technology, different signatures associated with heart failure (HF1) (36) or atherosclerotic CVD (CAD238) (37) have been developed but less thoroughly evaluated.

Inflammation

Multiple markers have been investigated related to inflammation. These include fibrinogen, interleukin 6, and TNFα, which were found to be associated with risk of chronic kidney disease progression (38). Some of the most widely studied markers have been tumor necrosis factor receptor (TNFR)1 and 2. Recently, the Kidney Risk Inflammatory Signature (KRIS) was developed with 17 inflammatory markers including TNF receptor superfamily members (39). The signature was tested in two cohorts as a marker of end-stage kidney disease in both type 1 and type 2 diabetes. All components of the signature had a systemic, nonkidney source and may guide therapy to new targets. Interestingly, the signature was improved with the anti-inflammatory agent baricitinib but not with RAS blockade (39).

Soluble urokinase plasminogen activator receptor (suPAR) is considered an important inflammatory marker implicated in endothelial and podocyte dysfunction. We tested suPAR in type 1 diabetes and found it to be an independent risk marker of cardiovascular events, kidney function decline, and mortality. We observed an adjusted HR per doubling of suPAR for cardiovascular events ($n = 94$), progression in albuminuria ($n = 36$), eGFR decline ($n = 93$), end-stage kidney disease ($n = 23$), and mortality ($n = 58$)

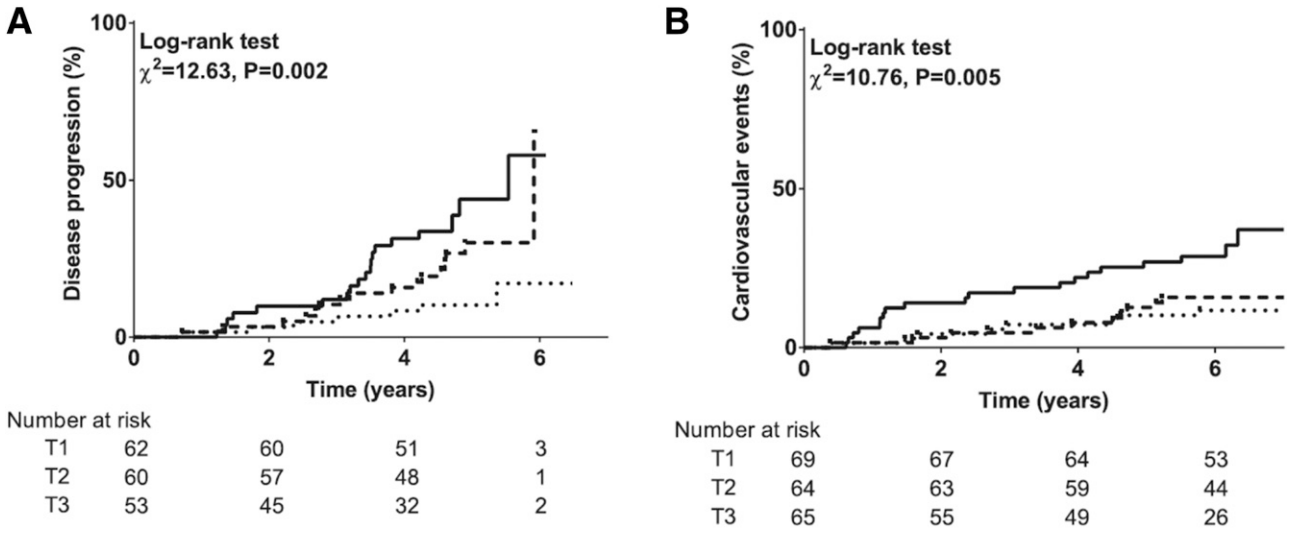

Figure 4—Serum PRO-C6 (marker of fibrosis) associated with kidney disease progression (defined as a decline of eGFR of >30% from baseline) (*A*) and cardiovascular events (cardiovascular mortality, stroke, ischemic CVD, and heart failure) (*B*) in subjects with type 2 diabetes ($n = 200$) (60). Dotted line, tertile 1 (T1); dashed line, tertile 2 (T2); solid line, tertile 3 (T3).

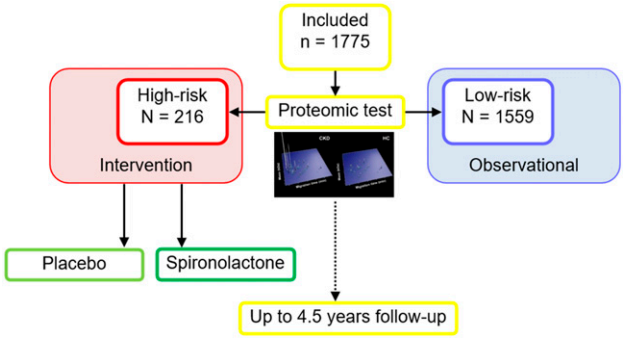

Figure 5—Design of the PRIORITY study, testing a urinary proteomic biomarker, CKD273, of risk for DKD and the potential for mitigating risk for progression to microalbuminuria in normoalbuminuric subjects with type 2 diabetes with spironolactone (34).

of 3.13 (95% CI 1.96–5.45), 1.27 (0.51–3.19), 2.93 (1.68–5.11), 2.82 (0.73–11.9), and 4.13 (1.96–8.69), respectively.

Oxidative Stress

It has been proposed that elevated levels of uric acid induce vascular and kidney damage, hypertension, and atherosclerosis due to inflammation and oxidative stress. We, and others, demonstrated elevated uric acid levels to be associated with cardiovascular events and progression of renal disease in type 1 diabetes (40). In the Prevention of Early RenaL function loss study (PERL), we tested whether lowering of uric acid with allopurinol in people with type 1 diabetes and early DKD with albuminuria or declining eGFR could prevent loss of measured GFR over 3 years. Mean serum urate level decreased from 6.1 to 3.9 mg/dL with allopurinol and remained at 6.1 mg/dL with placebo. Despite this, we found no evidence of a kidney-protective effect on albuminuria or decline in GFR (41). Although this suggests uric acid is not a target, in line with a Mendelian randomization study in type 1 diabetes (42), a study was presented in 2019 with larger reduction of uric acid in a small group of individuals with type 2 diabetes followed for 24 weeks with a urate reabsorption inhibitor, verinurad, and feboxustat in combination, giving a 49% reduction in urine albumin-to-creatinine ratio compared with placebo (43).

Other markers of oxidative stress are oxidatively modified guanine nucleosides 8-oxo-7,8-dihydro-2′-deoxyguanosine and 8-oxo-7,8-dihydroguanosine (8-oxoGuo) excreted in the urine. The level of 8-oxoGuo was associated with mortality and CVD in type 2 diabetes (44).

For clarification of whether the different markers from the diverse pathways are useful to guide selection of therapy, post hoc analyses of randomized controlled studies are useful, but ideally, there is a need for prospective studies designed to test the hypothesis that biomarker-guided therapy is better than standard of care. We have started investigating whether subjects with type 1 and type 2 diabetes have different responses to different interventions and whether these differences can be predicted by the biomarkers. Thus, participants are in random order receiving four different treatments targeting different pathways to test response and association with biomarkers before treatment.

New Treatment Options for Cardio-Renal Complications in Diabetes and Ideas for Personalized Selection of Agents

For more than 20 years, standard of care in people with diabetes and kidney disease has included treatment with RAS-blocking agents, either ACE inhibitors or angiotensin receptor blockers, in addition to control of lifestyle factors, blood glucose, lipids, and blood pressure (45). Thus, selecting treatment to protect the kidney was not complicated. Although this improved prognosis for people with DKD, there was a large unmet need. The effect on renal end points was significant but modest (HR 0.80), and for the heart there was benefit of controlling blood pressure and reducing heart failure, but RAS blockade did not provide benefit on mortality or CVD in these studies. New agents either increasing blockade of RAS or targeting other pathogenetic pathways were needed. Many strategies have been tested and failed during the past 20 years either due to side effects or due to lack of effects, such as ACE inhibitors plus angiotensin receptor blockers, renin inhibition, erythropoetin, avosentan, and bardoxolone. During the past couple of years, we have seen significant progress, with new agents showing benefit on renal and/or CVD end points in people with type 2 diabetes and chronic kidney disease. For most tested agents, the effects on heart and kidney have been linked but in different ways. For some, there were benefits on the kidney but side effects like heart failure; for others, there were benefits on kidney and heart. Although not all agents are on the market yet, we need to find out how to choose the best agent, or combination of agents, for an individual to provide optimal benefit for heart and kidney and minimal risk for side effects. We believe that the discussed physiological tests and biomarkers may be helpful in selecting between agents, although it should be stressed that this remains to be tested.

SGLT2 Inhibitors

The first, and so far, most marked, success has been with SGLT2 inhibitors, initially tested for safety in cardiovascular outcome trials, where not only a benefit on the primary end point major adverse cardiovascular events was demonstrated with empagliflozin (HR 0.86 [95% CI 0.74–0.99], $P = 0.04$ for superiority) (46). A significant benefit on hospitalization for heart failure was also observed. In addition, a reduction in incident or worsening nephropathy occurred (HR 0.61 [95% CI 0.53–0.70]) (47). These findings were confirmed in cardiovascular outcome trials with canagliflozin and dapagliflozin. The first study with hard renal end points (end-stage kidney disease, significant loss of renal function) as the primary end point using a SGLT2 inhibitor was Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical

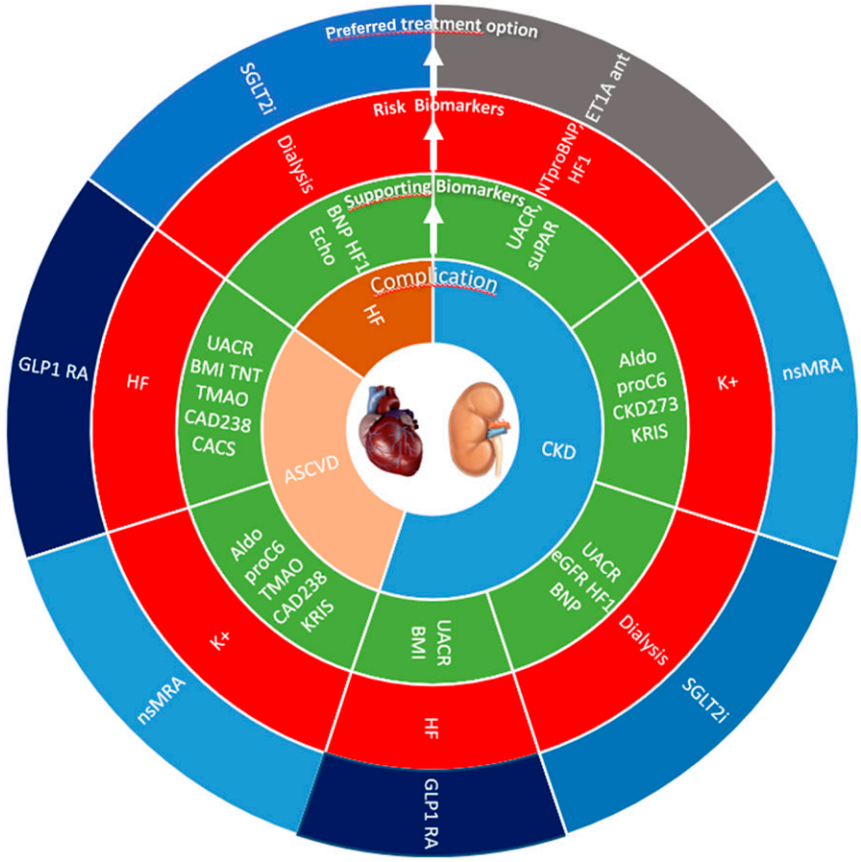

Figure 6—Biomarker-guided treatment selection. A proposal for how biomarkers could guide selection of treatment among recently tested options with a precision medicine approach in diabetic kidney and heart disease ("Complication" in inner circle). Using available "Supporting Biomarkers" (green circle) reflecting underlying pathology and "Risk Biomarkers" or contraindications (red circle) to select optimal treatment (outer circle) in patients with type 2 diabetes. Thus, as an example in CKD: elevated urinary albumin-to-creatinine ratio (UACR) or fluid retention (brain natriuretic peptide [BNP]) would suggest an SGLT2 inhibitor (SGLT2i), whereas markers of inflammation and fibrosis would suggest nonsteroidal MRA (nsMRA) (currently not available), and suPAR would suggest endothelin receptor 1A antagonist (ET1Aant) (currently not available) unless there are signs of fluid retention (elevated NTproBNP). Aldo, aldosterone; ASCVD, atherosclerotic CVD; HF, heart failure; CKD, chronic kidney disease; Echo, echocardiography; CACS, coronary artery calcium score; K+, potassium; U-CKD273, urinary proteomic marker of chronic kidney disease; u-CAD238, urinary proteomic marker of coronary heart disease; HF1, urinary proteomic marker of heart failure; proC6, serum PRO-C6 (marker of fibrosis); TNT, troponin T; suPAR, soluble urokinase plasminogen activator receptor.

Evaluation (CREDENCE), showing a major benefit not only on renal outcome but also on heart failure and major adverse cardiovascular events in people with type 2 diabetes (urine albumin-to-creatinine ratio >300 mg/g and eGFR 30–90 mL/min/1.73 m^2) (48). The primary outcome was a composite of end-stage kidney disease, a doubling of the serum creatinine level, or death from renal or cardiovascular causes. The study was stopped early showing a benefit of canagliflozin with HR 0.70 (95% CI 0.59–0.82). These data were confirmed and extended by Dapa-CKD (A Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients With Chronic Kidney Disease) including subjects with chronic kidney disease with or without diabetes (49). Whereas SGLT2 inhibitors were introduced to treat hyperglycemia, they also provide organ protection in individuals without diabetes with heart failure and/or chronic kidney disease. The explanation for the renal and cardiac benefits is not clear but may involve interaction between the organs (50). Recently, neuropathy and renal innervation were implicated (51). It is now recommended that they be added to standard of care in type 2 diabetes with chronic kidney disease (52), and in addition to patients with albuminuria and eGFR criteria, patients at risk for or with heart failure would potentially benefit the most (Fig. 6).

Atrasentan

The Study Of diabetic Nephropathy with AtRasentan (SONAR) was presented simultaneous with the presentation of CREDENCE (53). Although stopped early for concern of futility, the study eventually showed a renal benefit of the same magnitude as in CREDENCE, but with no effect on major adverse cardiovascular events and a tendency to increased risk of heart failure, which also stopped another ET1A receptor antagonist, avosentan. The mode of action may relate to an effect on inflammation, but also an effect on podocytes and glycocalyx has been proposed from experimental data (54). Thus, we

propose that suPAR is used to identify subjects who would benefit, and markers of heart failure would exclude the use of atrasentan (Fig. 6).

GLP-1RA

For some of the long-acting GLP-1RA (liraglutide, semaglutide, dulaglutide), the cardiovascular outcome trials in type 2 diabetes demonstrated cardiovascular benefits in subjects with already existing atherosclerotic CVD (52). There were renal benefits as secondary end points, mostly driven by reductions in albuminuria, but also some potential effects on eGFR. This was supported by the AWARD-7 study with dulaglutide in individuals with DKD, although the primary end point was glycemic control (55). It remains to be demonstrated whether there will be benefits on hard renal end points in addition to cardiovascular benefits; this is currently being tested in the FLOW study (clinical trial reg. no. NCT03819153, ClinicalTrials.gov). It is suggested that albuminuria and BMI as well as markers related to vascular damage, including troponin T, CAD238, TMAO, and elevated coronary calcium score on CT imaging (or ^{82}Rb PET/CT), could be used to identify relevant subjects, and as there is no impact on heart failure, heart failure was used as exclusion criteria (Fig. 6). Currently we are involved in investigations of the mode of action of the effect on atherosclerosis, and the study may provide insight into more specific markers or imaging techniques to guide therapy (clinical trial reg. no. NCT04032197, ClinicalTrials.gov).

Mineralocorticoid Receptor Antagonism

Short-term studies revealed reduction in proteinuria in DKD with the steroidal MRAs spironolactone and eplerenone (35)—an interesting strategy, as preventing overactivation of the mineralocorticoid receptor reduces inflammation and fibrosis, but due to potassium problems, diabetes and kidney disease became a contraindication for these agents. Nonsteroidal MRAs have been developed and may have the anti-inflammatory and antifibrotic effects with less potassium problems. Esaxerenone and finerenone were demonstrated to reduce microalbuminuria in type 2 diabetes (56,57). Two phase 3 trials with finerenone was started in type 2 diabetes with chronic kidney disease, and the first has been stopped and it has been announced that the primary renal and secondary cardiac outcomes were positive but not yet presented. Preclinical studies demonstrated improved effect on inflammation and fibrosis in the heart (58) and kidney (59), and thus depending on the data, nonsteroidal MRAs like finerenone may be preferred when inflammation (KRIS, TMAO) and fibrosis (CKD273, serum PRO-C6 [marker of fibrosis]) and perhaps aldosterone are elevated, whereas it remains to be seen whether potassium will be an issue (Fig. 6).

Conclusions

In diabetes, the heart and kidney are now doing better, thanks to recent advances in diagnosis and therapy. The next step is to convert this into fully individualized medicine, combining new possibilities in imaging and biomarker-based risk prediction with detailed knowledge of therapeutic avenues. This will ensure optimal treatment and prevent adverse events and unnecessary polypharmacy. A more detailed approach when choosing the right treatment for the right person may seem complicated and costly at first but has the potential to save both patients and the health care system considerable costs.

The amount of information supporting design of individualized treatment is expected to grow drastically soon. Studies of the kidney and the heart using functional MRI and kidney biopsy studies will lead to a better diagnostic discrimination. At the same time, genomics, epigenomics, and metabolomics studies increase our knowledge of physiological processes. All of this will increase the complexity of the diseases but holds promise for better understanding once we learn to interpret the large amount of data available. Hopefully, this will lead to a better prevention of renal and cardiovascular outcome in the future.

Funding. The authors were supported by the Novo Nordisk Foundation grant PROTON – PeRsOnalizing Treatment Of diabetic Nephropathy (NNF14OC0013659).

Duality of Interest. P.R. has received honoraria to Steno Diabetes Center Copenhagen from teaching and consultancy for Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, Novo Nordisk, Merck, Merck Sharp & Dohme (MSD), Mundipharma, Sanofi, and Vifor. F.P. has served as a consultant on advisory boards or as an educator for AstraZeneca, Novo Nordisk, Sanofi, Mundipharma, MSD, Boehringer Ingelheim, Novartis, and Amgen and has received research grants to his institution from Novo Nordisk, Amgen, and AstraZeneca. No other potential conflicts of interest relevant to this article were reported.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th ed. Brussels, Belgium, International Diabetes Federation, 2019
2. Fox CS, Matsushita K, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet 2012;380:1662–1673
3. Kidney-Disease-Improving-Global-Outcomes (KDIGO)-CKD-Work-Group. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl 2013;3:1–150
4. Wen CP, Chang CH, Tsai MK, et al. Diabetes with early kidney involvement may shorten life expectancy by 16 years. Kidney Int 2017;92:388–396
5. Afkarian M, Sachs MC, Kestenbaum B, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–308
6. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A. Albuminuria reflects widespread vascular damage. The Steno hypothesis. Diabetologia 1989;32:219–226
7. Ronco C, Haapio M, House AA, Anavekar N, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol 2008;52:1527–1539
8. Silverman MG, Blaha MJ, Krumholz HM, et al. Impact of coronary artery calcium on coronary heart disease events in individuals at the extremes of traditional risk factor burden: the Multi-Ethnic Study of Atherosclerosis. Eur Heart J 2014;35:2232–2241
9. von Scholten BJ, Hasbak P, Christensen TE, et al. Cardiac (82)Rb PET/CT for fast and non-invasive assessment of microvascular function and structure in asymptomatic patients with type 2 diabetes. Diabetologia 2016;59:371–378
10. Zobel EH, Winther SA, Hasbak P, et al. Myocardial flow reserve assessed by cardiac 82Rb positron emission tomography/computed tomography is associated with albumin excretion in patients with Type 1 diabetes. Eur Heart J Cardiovasc Imaging 2019;20:796–803

11. Schindler TH, Schelbert HR, Quercioli A, Dilsizian V. Cardiac PET imaging for the detection and monitoring of coronary artery disease and microvascular health. JACC Cardiovasc Imaging 2010;3:623–640
12. von Scholten BJ, Hansen CS, Hasbak P, Kjaer A, Rossing P, Hansen TW. Cardiac autonomic function is associated with the coronary microcirculatory function in patients with type 2 diabetes. Diabetes 2016;65:3129–3138
13. Zobel EH, Hasbak P, Winther SA, et al. Cardiac autonomic function is associated with myocardial flow reserve in type 1 diabetes. Diabetes 2019;68:1277–1286
14. Murthy VL, Naya M, Foster CR, et al. Association between coronary vascular dysfunction and cardiac mortality in patients with and without diabetes mellitus. Circulation 2012;126:1858–1868
15. Rosengren A, Edqvist J, Rawshani A, et al. Excess risk of hospitalisation for heart failure among people with type 2 diabetes. Diabetologia 2018;61:2300–2309
16. Lind M, Bounias I, Olsson M, Gudbjörnsdottir S, Svensson AM, Rosengren A. Glycaemic control and incidence of heart failure in 20,985 patients with type 1 diabetes: an observational study. Lancet 2011;378:140–146
17. Jensen MT, Sogaard P, Andersen HU, et al. Global longitudinal strain is not impaired in type 1 diabetes patients without albuminuria: the Thousand & 1 study. JACC Cardiovasc Imaging 2015;8:400–410
18. Jensen MT, Sogaard P, Gustafsson I, et al. Echocardiography improves prediction of major adverse cardiovascular events in a population with type 1 diabetes and without known heart disease: the Thousand & 1 Study. Diabetologia 2019;62:2354–2364
19. Jorgensen PG, Jensen MT, Mogelvang R, et al. Abnormal echocardiography in patients with type 2 diabetes and relation to symptoms and clinical characteristics. Diab Vasc Dis Res 2016;13:321–330
20. Jørgensen PG, Biering-Sørensen T, Mogelvang R, et al. Predictive value of echocardiography in type 2 diabetes. Eur Heart J Cardiovasc Imaging 2019;20:687–693
21. Zannad F, Rossignol P. Cardiorenal syndrome revisited. Circulation 2018; 138:929–944
22. Rossing P, Hommel E, Smidt UM, Parving H-H. Reduction in albuminuria predicts a beneficial effect on diminishing the progression of human diabetic nephropathy during antihypertensive treatment. Diabetologia 1994;37:511–516
23. de Zeeuw D, Remuzzi G, Parving HH, et al. Proteinuria, a target for renoprotection in patients with type 2 diabetic nephropathy: lessons from RENAAL. Kidney Int 2004;65:2309–2320
24. Coresh J, Heerspink HJL, Sang Y, et al.; Chronic Kidney Disease Prognosis Consortium and Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria and subsequent risk of end-stage kidney disease: an individual participant-level consortium meta-analysis of observational studies. Lancet Diabetes Endocrinol 2019;7:115–127
25. Heerspink HJL, Greene T, Tighiouart H, et al.; Chronic Kidney Disease Epidemiology Collaboration. Change in albuminuria as a surrogate endpoint for progression of kidney disease: a meta-analysis of treatment effects in randomised clinical trials. Lancet Diabetes Endocrinol 2019;7:128–139
26. Desai AS, Toto R, Jarolim P, et al. Association between cardiac biomarkers and the development of ESRD in patients with type 2 diabetes mellitus, anemia, and CKD. Am J Kidney Dis 2011;58:717–728
27. Galsgaard J, Persson F, Hansen TW, et al. Plasma high-sensitivity troponin T predicts end-stage renal disease and cardiovascular and all-cause mortality in patients with type 1 diabetes and diabetic nephropathy. Kidney Int 2017;92:1242–1248
28. Tang WH, Wang Z, Levison BS, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575–1584
29. Winther SA, Øllgaard JC, Tofte N, et al. Utility of plasma concentration of trimethylamine N-oxide in predicting cardiovascular and renal complications in individuals with type 1 diabetes. Diabetes Care 2019;42:1512–1520
30. Croyal M, Saulnier PJ, Aguesse A, et al. Plasma trimethylamine N-oxide and risk of cardiovascular events in patients with type 2 diabetes. J Clin Endocrinol Metab 2020;105:dgaa188
31. Pilemann-Lyberg S, Rasmussen DGK, Hansen TW, et al. Markers of collagen formation and degradation reflect renal function and predict adverse outcomes in patients with type 1 diabetes. Diabetes Care 2019;42:1760–1768
32. Good DM, Zürbig P, Argilés A, et al. Naturally occurring human urinary peptides for use in diagnosis of chronic kidney disease. Mol Cell Proteomics 2010; 9:2424–2437
33. Zürbig P, Jerums G, Hovind P, et al. Urinary proteomics for early diagnosis in diabetic nephropathy. Diabetes 2012;61:3304–3313
34. Tofte N, Lindhardt M, Adamova K, et al.; PRIORITY Investigators. Early detection of diabetic kidney disease by urinary proteomics and subsequent intervention with spironolactone to delay progression (PRIORITY): a prospective observational study and embedded randomised placebo-controlled trial. Lancet Diabetes Endocrinol 2020;8:301–312
35. Currie G, Taylor AH, Fujita T, et al. Effect of mineralocorticoid receptor antagonists on proteinuria and progression of chronic kidney disease: a systematic review and meta-analysis. BMC Nephrol 2016;17:127
36. Rossing K, Bosselmann HS, Gustafsson F, et al. Urinary proteomics pilot study for biomarker discovery and diagnosis in heart failure with reduced ejection fraction. PLoS One 2016;11:e0157167
37. Delles C, Schiffer E, von Zur Muhlen C, et al. Urinary proteomic diagnosis of coronary artery disease: identification and clinical validation in 623 individuals. J Hypertens 2010;28:2316–2322
38. Amdur RL, Feldman HI, Gupta J, et al.; CRIC Study Investigators. Inflammation and progression of CKD: the CRIC study. Clin J Am Soc Nephrol 2016;11:1546–1556
39. Niewczas MA, Pavkov ME, Skupien J, et al. A signature of circulating inflammatory proteins and development of end-stage renal disease in diabetes. Nat Med 2019;25:805–813
40. Pilemann-Lyberg S, Hansen TW, Tofte N, et al. Uric acid is an independent risk factor for decline in kidney function, cardiovascular events, and mortality in patients with type 1 diabetes. Diabetes Care 2019;42:1088–1094
41. Doria A, Galecki AT, Spino C, et al.; PERL Study Group. Serum urate lowering with allopurinol and kidney function in type 1 diabetes. N Engl J Med 2020;382: 2493–2503
42. Ahola AJ, Sandholm N, Forsblom C, Harjutsalo V, Dahlström E, Groop PH; FinnDiane Study Group. The serum uric acid concentration is not causally linked to diabetic nephropathy in type 1 diabetes. Kidney Int 2017;91:1178–1185
43. Stack AG, Dronamraju N, Parkinson J, et al. Effect of intensive urate lowering with combined verinurad and febuxostat on albuminuria in patients with type 2 diabetes: a randomized trial. Am J Kidney Dis. 29 October 2020 [Epub ahead of print]. DOI: 10.1053/j.ajkd.2020.09.009
44. Kjær LK, Cejvanovic V, Henriksen T, et al. Cardiovascular and all-cause mortality risk associated with urinary excretion of 8-oxoGuo, a biomarker for RNA oxidation, in patients with type 2 diabetes: a prospective cohort study. Diabetes Care 2017;40:1771–1778
45. National Kidney Foundation. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. Am J Kidney Dis 2012;60:850–886
46. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
47. Wanner C, Inzucchi SE, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin and progression of kidney disease in type 2 diabetes. N Engl J Med 2016;375:323–334
48. Perkovic V, Jardine MJ, Neal B, et al.; CREDENCE Trial Investigators. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295–2306
49. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al.; DAPA-CKD Trial Committees and Investigators. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020;383:1436–1446
50. Alicic RZ, Neumiller JJ, Johnson EJ, Dieter B, Tuttle KR. Sodium–glucose cotransporter 2 inhibition and diabetic kidney disease. Diabetes 2019;68:248–257
51. Wan N, Fujisawa Y, Kobara H, et al. Effects of an SGLT2 inhibitor on the salt sensitivity of blood pressure and sympathetic nerve activity in a nondiabetic rat model of chronic kidney disease. Hypertens Res 2020;43:492–499
52. Buse JB, Wexler DJ, Tsapas A, et al. 2019 update to: management of hyperglycemia in type 2 diabetes, 2018. A Consensus Report by the American

Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2020;43:487–493
53. Heerspink HJL, Parving H-H, Andress DL, et al.; SONAR Committees and Investigators. Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind, randomised, placebo-controlled trial. Lancet 2019;393:1937–1947
54. Garsen M, Lenoir O, Rops AL, et al. Endothelin-1 induces proteinuria by heparanase-mediated disruption of the glomerular glycocalyx. J Am Soc Nephrol 2016;27:3545–3551
55. Tuttle KR, Lakshmanan MC, Rayner B, et al. Dulaglutide versus insulin glargine in patients with type 2 diabetes and moderate-to-severe chronic kidney disease (AWARD-7): a multicentre, open-label, randomised trial. Lancet Diabetes Endocrinol 2018;6:605–617
56. Ito S, Shikata K, Nangaku M, Okuda Y, Sawanobori T. Efficacy and safety of esaxerenone (CS-3150) for the treatment of type 2 diabetes with microalbuminuria: a randomized, double-blind, placebo-controlled, phase II trial. Clin J Am Soc Nephrol 2019;14:1161–1172
57. Bakris GL, Agarwal R, Chan JC, et al.; Mineralocorticoid Receptor Antagonist Tolerability Study–Diabetic Nephropathy (ARTS-DN) Study Group. Effect of finerenone on albuminuria in patients with diabetic nephropathy: a randomized clinical trial. JAMA 2015;314:884–894
58. Grune J, Beyhoff N, Smeir E, et al. Selective mineralocorticoid receptor cofactor modulation as molecular basis for finerenone's antifibrotic activity. Hypertension 2018;71:599–608
59. Kolkhof P, Delbeck M, Kretschmer A, et al. Finerenone, a novel selective nonsteroidal mineralocorticoid receptor antagonist protects from rat cardiorenal injury. J Cardiovasc Pharmacol 2014;64:69–78
60. Rasmussen DGK, Hansen TW, von Scholten BJ, et al. Higher collagen VI formation is associated with all-cause mortality in patients with type 2 diabetes and microalbuminuria. Diabetes Care 2018;41:1493–1500