The Interplay Between Diabetes, Cardiovascular Disease, and Kidney Disease

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Burden of Diabetes and Associated Cardiorenal Disorders

The Global Burden of Disease Study estimates that there are currently 476 million patients with diabetes worldwide, the large majority of whom suffer from type 2 diabetes. In the United States, the prevalence of type 2 diabetes is 32.6 million, or ~1 in 10 people. These numbers are expected to continue to rise (139).

The metabolic system is closely interrelated with the cardiac and renal systems, and these three systems share a symbiotic relationship that helps maintain homeostasis. The heart is one of the most metabolically demanding organs and is sensitive to changes in energy and volume status. Thus, it relies on the liver, pancreas, and fat for optimal energy metabolism and on the kidneys for volume maintenance. Similarly, the kidneys rely on the heart for adequate perfusion and on the metabolic system for the appropriate hormonal milieu, both of which are necessary to maintain their function. The metabolic system depends on functioning heart and kidneys to prevent neurohormonal activation, which keeps metabolic derangements such as insulin resistance, glucose dysregulation, and dyslipidemias at bay (140).

Given the close-knit physiology of the metabolic, cardiac, and renal systems, it is not surprising that type 2 diabetes frequently coexists with cardiovascular disease (CVD) and chronic kidney disease (CKD). A 2018 study of >500,000 adults living with type 2 diabetes in the United States demonstrated that <10% had isolated type 2 diabetes with no associated cardiovascular or kidney disorder (141). CVD and CKD in the presence of type 2 diabetes worsen each other, leading to an increase in morbidity and mortality (142). This article focuses on the epidemiology and pathophysiology of CVD and CKD in relation to diabetes and provides an overview of current management.

Effect of Diabetes on a Molecular and Cellular Level

The mechanism behind the clinical manifestations of type 2 diabetes and its complications are rooted in molecular and cellular derangements.

Oxidative Stress

Oxidative stress is a state in which the generation of reactive oxygen species (ROS) exceeds the capacity of the antioxidants to neutralize them. In hyperglycemic states, the increased flux of glucose increases ROS production in mitochondria. Oxidative stress–induced cellular injury plays a central role in the pathology of diabetes-related CVD and CKD, as discussed in more detail in the subsequent sections (143).

Advanced Glycation End Products

Oxidative stress and hyperglycemia drive a nonenzymatic reaction that causes excessive covalent binding between glucose and substrates such as proteins, lipids, and nucleic acid, a process known as nonenzymatic glycation. The resulting compounds are termed advanced glycation end products (AGEs). AGEs can increase the production of ROS, causing increased intracellular oxidative stress. This increased oxidative stress, in turn, promotes the formation of more AGEs, thus resulting in a vicious cycle. AGEs and associated oxidative stress can result in inflammation, cellular dysfunction, and cell death. In the context of CVD and CKD, the effect of AGEs on the endothelium of blood vessels is important (143).

Endothelial Dysfunction

Endothelial dysfunction in patients with type 2 diabetes results from nonenzymatic glycation of the endothelium and oxidative damage. Endothelial dysfunction subsequently drives the development of microvascular and macrovascular disease. Hypertension, a common comorbidity in patients with type 2 diabetes, is also a potent risk factor for endothelial dysfunction (143).

Hypercoagulability

The first line of defense against a thrombotic event is an intact and functioning vascular endothelium. The endothelium releases antithrombotic factors and prevents contact of blood with collagen, which has a prothrombotic effect. Diabetes results in endothelial dysfunction and enhanced activation of both platelets and coagulation factors. On the other hand, anticoagulation mechanisms are relatively diminished in patients with diabetes. A hypercoagulable state inevitably increases the risk of thrombotic events such as myocardial infarction and stroke (143).

Diabetes and Complications of the Cardiovascular System

The link between type 2 diabetes and CVD has been known for decades. Compared to patients without diabetes, those with type 2 diabetes are two to four times more likely to experience cardiovascular events and are more likely to have worse outcomes after these events (144,145). About half of all diabetes-related fatalities can be attributed to cardiovascular causes (145).

Macrovascular and Microvascular Complications

Macrovascular complications such as coronary artery disease (CAD), stroke, and peripheral vascular disease are largely a consequence of atherosclerosis. Several diabetes-specific factors

promote atherosclerosis. Dysfunctional endothelial cells within large arteries are a fertile ground for the initiation of atherosclerosis (143). Dyslipidemia is prevalent in ~80% of patients with type 2 diabetes and is associated with atherosclerosis. Insulin deficiency and insulin resistance activate the enzyme hormone-sensitive lipase, which releases free fatty acids (FFAs) into the blood. This release leads to increased lipoprotein generation and release by the liver and, ultimately, increased circulating levels of triglycerides and LDL cholesterol. Lipoprotein lipase, the enzyme that clears LDL cholesterol, is downregulated, which aggravates dyslipidemia. HDL cholesterol levels are decreased in diabetes (143).

Diabetes also affects the microvasculature. Microvascular damage can lead to complications such as nephropathy, retinopathy, and neuropathy. Microvascular damage is often initiated by nonenzymatic glycation of endothelial cells. This process leads to formation of glycated proteins that trigger a range of effects on surrounding tissues, the most prominent ones being, *1*) thickening of endothelium and collagen, leading to local ischemia; *2*) overproduction of endothelial growth factors and pathologic angiogenesis; and *3*) vascular inflammation and generation of ROS (146). In tandem, these changes increase the risk of endothelial cell apoptosis, vascular remodeling, capillary blockage, capillary hemorrhage, and formation of microthrombosis (146). Depending on the site of involvement, these changes can lead to organ dysfunction and failure. The vascular remodeling and endothelial cell damage increase arterial stiffness and also lead to the loss of local nitric oxide, a potent vasodilator released by the endothelium (143), leaving the vasculature in a predominantly constricted state. Type 2 diabetes contributes to the development of hypertension by this major mechanism. Damage to microvasculature of the kidney can lead to CKD. Hypervolemia secondary to CKD is also an important mechanism by which type 2 diabetes leads to hypertension.

Damage to microvasculature of autonomic nerves (vasa nervorum) is responsible for the characteristic autonomic neuropathy of type 2 diabetes. Autonomic neuropathy further impairs autoregulation of blood flow in the vascular beds of a variety of organs, including the heart. Patients with diabetic autonomic neuropathy lack the normal cardiac flow reserve recruited in conditions that require increased myocardial perfusion. This could, in part, explain the increased rates of sudden cardiac death and overall cardiovascular mortality seen in patients with diabetic autonomic neuropathy (143). Autonomic neuropathy also predisposes patients with diabetes to fatal arrhythmias and sudden cardiac death (147).

Heart Failure

The prevalence of heart failure (HF) in patients with diabetes is ~15–20%, which is multiple-fold higher than the prevalence in age- and sex-matched control subjects without type 2 diabetes (4.5%) (148). The converse is concerning as well, with the prevalence of diabetes ranging from 40–50% in patients with HF. Moreover, in patients with HF, mortality is higher in those with versus those without concomitant diabetes (148).

HF with preserved ejection fraction (HFpEF) is emerging as an especially significant problem among patients with type 2 diabetes. Many of these patients have asymptomatic diastolic dysfunction, and HFpEF, a disease without known mortality-modifying therapies, is the predominant form of HF in type 2 diabetes (143,149). It is important to note that type 2 diabetes has distinct myocardial effects in HFpEF and in patients with HF and reduced ejection fraction (HFrEF), with different biomarker profiles. In HFpEF, the systemic inflammation is associated with higher serum levels of inflammatory biomarkers such as soluble interleukin-1 receptor-like 1 and C-reactive protein; biomarkers of myocardial injury and stretch such as troponins and natriuretic peptides are higher in HFrEF than in HFpEF.

In patients with type 2 diabetes, HF can occur as a result of ischemia or a thrombotic event secondary to CAD. In many cases, however, pathophysiological factors unrelated to CAD are at play. Cardiac disease in patients with type 2 diabetes that is not be attributed to any other known CVD such as CAD or hypertension is sometimes labeled as "diabetic cardiomyopathy," although the exact mechanism and identity of this entity is not fully understood (150). The mechanism behind diabetic cardiomyopathy is attributed to two-pronged abnormalities involving metabolic derangements and microvascular injury (143).

Analysis of the UK Prospective Diabetes Study demonstrated that every 1% increase in A1C was associated with a 12% increase in the risk of HF (43). In states of chronic hyperglycemia and insulin deficiency/insulin resistance, cardiac glucose metabolism is impaired, and the heart in patients with type 2 diabetes switches to FFA oxidation. As discussed earlier, hyperglycemia also induces generation of ROS. FFA oxidation also contributes to oxidative stress. Increased ROS-mediated cell death may drive cardiac remodeling and subsequent morphological and functional abnormalities. In addition, hyperglycemia-induced nonenzymatic glycation of cardiac tissue is another factor that can contribute to myocardial cell damage and remodeling (143).

Hyperinsulinemia plays a role in the development of HF (151). Animal studies show that excessive insulin signaling exacerbates cardiac dysfunction. Insulin use has also been shown to be independently associated with development of HF (151). Moreover, use of drugs that promote insulin signaling (e.g., thiazolidinediones) and those that increase insulin secretion is associated with increased risk of HF. In contrast, drugs that ameliorate hyperinsulinemia such as SGLT2 inhibitors and metformin demonstrate a reduced risk of HF (143,151).

Microvascular injury, particularly hyaline arteriolosclerosis and angiopathy of the small blood vessels, is a common finding in the myocardium of patients with type 2 diabetes. Microvascular disease results in local ischemia and subsequent morphological

and functional derangement. Cardiac autonomic neuropathy, also a complication of microvascular disease within nerves, correlates with systolic and diastolic dysfunction (151). Regardless of whether the mechanism of injury is via ischemia, hyperglycemia, or microvascular disease, the ultimate result is morphological and functional impairment of the heart. Under a microscope, ultrastructural changes such as myocardial injury, hypertrophy, and fibrosis are characteristic of the heart structure of patients with diabetes (152) and inevitably lead to reduced cardiac function. Metabolic derangement and abnormal energy utilization further add to the cardiac dysfunction (151).

Diabetes and Complications of the Kidney

Diabetic kidney disease (DKD) affects almost 40% of patients with diabetes (153), and its prevalence is rising in parallel to the prevalence of type 2 diabetes. DKD remains the leading cause of end-stage renal disease (ESRD) (153). Similar to diabetes-related cardiac disease, the major burden of DKD results from preceding microvascular and macrovascular injury. It is diagnosed based on estimated glomerular filtration rate (eGFR) and presence of albuminuria, along with clinical characteristics of diabetes that increase the likelihood of renal involvement, such as duration of diabetes and presence of diabetic retinopathy (140,154).

The term "DKD" is not synonymous with "diabetic nephropathy." DKD is a broad term encompassing all possible renal complications of diabetes. Diabetic nephropathy, on the other hand, is a progressive glomerular nephropathy secondary to diabetes. As such, diabetic nephropathy is one component that contributes to DKD (154). Diabetic nephropathy generally progresses in five stages, culminating in ESRD (**Table 1**).

Diabetes promotes the development of atherosclerosis. Involvement of the main renal arteries and their branches is common in patients with diffuse atherosclerosis but is frequently overlooked. Most patients with renal artery stenosis do not have the unstable or severe hypertension that is usually considered classic for the disease. Renal artery stenosis is likely underdiagnosed in patients with type 2 diabetes because of its variable presentation and a lack of clinical suspicion. Overzealous use of diuretics, ACE inhibitors, and angiotensin receptor blockers (ARBs) should be avoided in patients with renal artery stenosis (154). Apart from renal artery stenosis, other relatively rare macrovascular complications of the kidney include renal infarction and cholesterol emboli syndrome. People with diabetes are also at increased risk for upper and lower urinary tract infections (154).

Interaction Among Disease Processes

It is clear that type 2 diabetes contributes to both CVD and CKD; both of these diseases have the propensity to initiate and perpetuate each other, leading to a phenomenon termed "cardiorenal syndrome" (CRS). Ronco et al. (142) have classified CRS into five different subtypes, based on etiology (**Figure 1**).

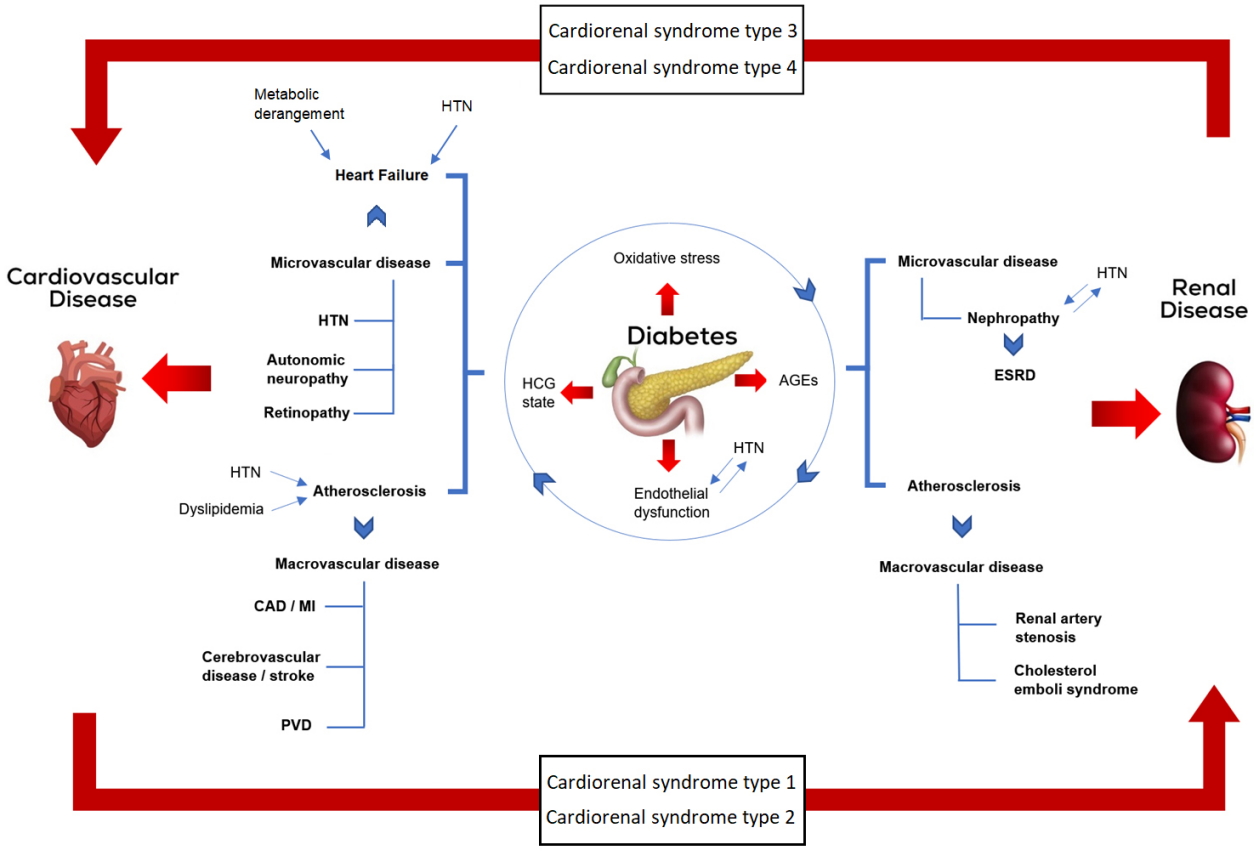
Type 1 CRS is characterized by acute cardiac dysfunction–related kidney dysfunction. Acute cardiac dysfunction may be the result of ischemia or HF, both of which are prevalent in diabetes, resulting in acute hypoperfusion, kidney ischemia, and subsequent necrosis/apoptosis of renal tubular cells. Type 1 CRS may further accelerate cardiovascular injury via activation of neurohormonal and inflammatory pathways (142).

Type 2 CRS is defined as chronic cardiac dysfunction leading to CKD. HF leads to chronic hypoperfusion of the kidney, resulting

TABLE 1 Stages of Diabetic Nephropathy

Stage	Onset (Time After Diabetes Diagnosis)	Key Microscopic Features	Clinical Features	Notes
1 (hyperfiltration)	At diagnosis	▸ Glomerular hypertrophy	▸ Increased GFR	▸ This stage is at least partially reversible.
2 (silent)	2–5 years	▸ Glomerular basement membrane hypertrophy	▸ Increased GFR and intermittent microalbuminuria	▸ Microalbuminuria is only seen when blood glucose is uncontrolled. A large proportion of people with diabetes stay in this stage throughout their life.
3 (incipient)	5–15 years	▸ Mesangial expansion, glomerular basement membrane thickening, and arteriolar hyalinosis	▸ Normal or supranormal GFR, progressive microalbuminuria, and hypertension	▸ This stage heralds the eventual onset of overt diabetic nephropathy.
4 (overt)	>25 years	▸ Mesangial nodules (Kimmelstiel-Wilson lesions) and tubulointerstitial fibrosis	▸ Progressively declining GFR and overt proteinuria (>0.5 g/24 hours)	▸ The decrease in GFR in this stage is particularly steep when comorbid hypertension is not treated.
5 (ESRD)	>25 years	▸ Global glomerular sclerosis in >50% of glomeruli	▸ GFR <15 mL/min/1.73 m^2, uremia, anemia, and other renal failure complications	▸ Renal replacement therapy is essential at this stage.

FIGURE 1 Cardiorenal syndrome.



in subclinical inflammation, endothelial dysfunction, atherosclerosis, renal cell damage, and sclerosis/fibrosis. The reduced GFR results in salt and water retention and in activation of the renin-angiotensin-aldosterone system (RAAS), which exacerbates water retention and systemic vasoconstriction. This process results in hypertension and worsening of chronic HF, thus forming a vicious cycle (142).

Type 3 CRS is defined as acute kidney dysfunction leading to cardiac dysfunction. Patients with diabetes are prone to renal artery stenosis, which increases the risk of acute kidney injury (AKI), especially when ACE inhibitors are used. Renal infarction secondary to distal emboli and acute pyelonephritis are also potential causes of acute kidney dysfunction in diabetes. Abrupt worsening of renal function can affect the heart by fluid overload, hyperkalemia, and the negative effects of uremia on myocardial contractility (142).

Type 4 CRS is characterized by primary CKD, leading to risk of CVD. DKD often progresses to CKD; in fact, up to 23% of patients with diabetes live with CKD. Patients with CKD are 10–20 times more likely to die of cardiovascular causes. CKD can exacerbate hypertension, activate the RAAS, and cause fluid retention. Hypertension increases the incidence of CVD in patients with CKD more than in those with normal renal function. Disturbed mineral and vitamin D metabolism increases vascular calcification risk. Left ventricular hypertrophy is increased in CKD, which may partially explain the risk of sudden cardiac death in this population. Patients with CKD are often undertreated for CVD due to concerns about kidney dysfunction with medication use; also, most drugs used to treat CVD have limited data in CKD (142).

Type 5 CRS is defined as simultaneous cardiac and renal dysfunction resulting from an acute or chronic systemic disorder (e.g., sepsis, amyloidosis, and diabetes). Whereas types 1–4 CRS refer to interactions between disease processes in the heart and kidneys, type 5 CRS refers to other diseases that affect both the heart and the kidney (142).

Several diagnostic tools such as assessment of biomarkers and volume measurement techniques can be used to discriminate among the different CRS phenotypes. While cardiac biomarkers such as troponins and natriuretic peptides are routinely used in clinical practice, kidney biomarkers are being studied to aid in diagnoses. Cystatin C and albuminuria are reflective of glomerular filtration and integrity in CRS, whereas NGAL (neutrophil gelatinase-associated lipocalin) and combination of TIMP-2 (tissue inhibitor of metalloproteinase-2) and IGFBP7 (insulin-like growth factor-binding protein 7) may represent biomarkers of acute tubular injury. These novel kidney biomarkers may have negative predictive value in distinguishing creatinine fluctuations from true AKI (142).

Management Strategies

The protective effects of ACE inhibitors on the heart and kidneys of patients with type 2 diabetes are well known. Certain novel medications such as sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, and selective nonsteroidal mineralocorticoid receptor (MR) antagonists have also shown cardiac and kidney protective effects in populations with type 2 diabetes (**Figure 2**). This supports the idea of integrated multi-organ physiology and pathophysiology leading to benefits with medications across organ systems.

Prevention of Cardiovascular Disease

Blood glucose control may seem like the natural option to prevent diabetes-related cardiovascular events. However, traditional glucose-lowering agents such as metformin, sulfonylureas, and insulin have not demonstrated a convincing relationship between blood glucose control and reduction in macrovascular cardiovascular events. Furthermore, some hypoglycemic agents paradoxically have been associated with an increase in cardiovascular events (e.g., thiazolidinediones are associated with an increased risk of HF). In response to concerns of increased cardiovascular risk, the U.S. Food and Drug Administration (FDA) mandated in 2008 that cardiovascular safety be demonstrated with all new diabetes drugs (155).

Drugs in the dipeptidyl peptidase 4 (DPP-4) inhibitor class in general have good cardiovascular safety from a vascular disease perspective. However, saxagliptin did raise concerns about an increased risk of hospitalization for HF (HHF). Impressively, SGLT2 inhibitors have been shown to reduce the risk of major adverse cardiovascular events (MACE) (hazard ratio [HR] 0.90, 95% CI 0.85–0.95), HHF (HR 0.68, 95% CI 0.61–0.76), and kidney outcomes (HR 0.62, 95% CI 0.56–0.70) (156). The presence or absence of atherosclerotic cardiovascular disease (ASCVD) did not modify the association for any of these outcomes. GLP-1 receptor agonists have also demonstrated improved cardiovascular outcomes, with lower rates of MACE and cardiovascular death compared to placebo. However, no consistent reductions in HF or kidney risk have been observed with agents in this class (155). Finerenone, a selective nonsteroidal MR antagonist, has also exhibited improved cardiovascular outcomes in patients with type 2 diabetes and CKD. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) trial, finerenone use (versus placebo) resulted in a significantly lower incidence of the composite endpoint of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and HHF (9).

Apart from selecting appropriate antihyperglycemic drugs, other relevant steps are required to prevent or treat CVD. Aspirin therapy is recommended as a primary prevention strategy in patients with type 2 diabetes who are at increased cardiovascular risk. Lipid levels should be measured annually, and appropriate treatment should be given to meet guideline-directed goals. Statin therapy should be initiated if the patient has a history of ASCVD or other risk factors (157). Blood pressure control is recommended for patients with comorbid hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg). The target systolic and diastolic blood pressure should be <130 and <80 mmHg, respectively. Potential therapeutic options include ACE

FIGURE 2 Medications with cardiorenal protective effects and their respective potential mechanisms and outcomes. CV, cardiovascular; MI, myocardial infarction.

Renal Outcomes	Potential Mechanisms	Medication	Potential Mechanisms	Cardiovascular Outcomes
↓ Composite of dialysis, transplant, or death due to kidney disease ↓ ESRD ↓ AKI	↑ Vasoconstriction of afferent arteriole and decreased hyperfiltration, barotrauma, and proteinuria ↓ Oxidative stress ↓ Blood pressure	**SGLT2 inhibitors**	↓ Plasma volume, arterial stiffness, and blood pressure ↓ Oxidative stress ↑ Sensitivity to diuretics and natriuretic peptides	↓ CV death ↓ MI ↓ HHF ↔ Stroke
↓ Composite of development of new onset macroalbuminuria, decline in eGFR, ESRD, or death due to kidney disease	↓ Blood pressure ↓ Weight ↓ Dyslipidemia ↓ Oxidative stress ↓ Endothelial dysfunction	**GLP-1 receptor agonists**	↓ Blood pressure ↓ Weight ↓ Dyslipidemia ↓ Oxidative stress ↓ Endothelial dysfunction	↓ CV death ↓ MI ↓ HF ↓ Stroke
↓ Composite of kidney failure, a sustained decrease of at least 40% in the eGFR from baseline, or death from renal causes	↓ Inflammation ↓ Fibrosis ↓ Blood pressure ↓ Endothelial dysfunction ↓ Tissue remodeling ↓ Proteinuria	**Selective nonsteroidal MR antagonists**	↓ Inflammation ↓ Fibrosis ↓ Blood pressure ↓ Endothelial dysfunction ↓ Tissue remodeling	↓ Composite of death from CV causes, nonfatal MI, nonfatal stroke, or HHF
↓ Onset of microalbuminuria ↓ Progression to macroalbuminuria ↓ ESRD	↓ Blood pressure ↓ Endothelial dysfunction ↓ Vasoconstriction of efferent arteriole and decreased hyperfiltration	**RAAS inhibitors**	↓ Blood pressure ↓ Vasoconstriction of coronary arteries ↓ Atherosclerosis ↓ Endothelial dysfunction ↓ Cardiac remodeling	↓ MI ↓ HHF

inhibitors, ARBs, beta-blockers, and calcium channel blockers. Most patients with type 2 diabetes eventually need combined therapy with multiple drugs for adequate blood pressure control. Importantly, lifestyle modifications play a central role in the management of type 2 diabetes and prevention of CVD. These include increased exercise, weight reduction, smoking cessation, and adherence to dietary recommendations (157).

Prevention of Kidney Disease

Blood glucose control is associated with a reduced incidence of microvascular complications, including diabetic nephropathy. The target A1C level to prevent diabetic nephropathy is <7% (158). SGLT2 inhibitors have a particularly strong renoprotective effect. In the DECLARE-TIMI 58 (Dapagliflozin Effect on Cardiovascular Events–Thrombolysis in Myocardial Infarction 58) trial, patients with diabetes taking dapagliflozin had a 47% reduction compared with placebo in the relative risk of a composite renal outcome, which included ESRD, renal death, and sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) to <60 mL/min/1.73 m^2. In the CANVAS Program (Canagliflozin Cardiovascular Assessment Study), canagliflozin also demonstrated significant reduction in a similar composite renal outcome (159–162). The CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation) trial (8) targeted patients with type 2 diabetes and an eGFR ≥30 to <90 mL/min/1.73 m^2 with a urine albumin-to-creatinine ratio (UACR) >300 mg/g creatinine. Canagliflozin compared to placebo was shown to reduce the risk of a composite kidney outcome, including ESRD, doubling of serum creatinine, or death from renal or cardiovascular causes (HR 0.70, 95% CI 0.59–0.82). A recent meta-analysis of major clinical trials (159) also consolidated the above findings regarding the renoprotective effects of SGLT2 inhibitors in patients with diabetes. These findings strongly favor the idea that SGLT2 inhibitors should be routinely offered to individuals with type 2 diabetes who are at risk of progressive kidney disease.

The benefit of SGLT2 inhibitors was shown in patients with kidney disease with or without diabetes in the DAPA-CKD (Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease) trial (53). Dapagliflozin was shown to improve the primary composite kidney outcome (HR 0.61, 95% CI 0.51–0.72) in patients with an eGFR ≥25 to <75 mL/min/1.73 m^2 and a UACR ≥200 mg/g, irrespective of diabetes status. Based on this evidence, the FDA recently approved a new indication for dapagliflozin to reduce the risk of sustained eGFR decline, ESRD, cardiovascular death, and HHF in adults with CKD at risk of progression, with or without type 2 diabetes (162a). The ongoing EMPA-KIDNEY (The Study of Heart and Kidney Protection with Empagliflozin; NCT03594110) trial will investigate the effects of empagliflozin in patients with an eGFR ≥20 to <45 mL/min/1.73 m^2 irrespective of UACR or ≥45 to <90 mL/min/1.73 m^2 with UACR >200 mg/g, irrespective of diabetes status.

GLP-1 receptor agonists also have a renoprotective effect, albeit to a lesser extent than SGLT2 inhibitors (158). There is sufficient evidence that GLP-1 receptor agonists and DPP-4 inhibitors can be used safely in patients with impaired renal function (158).

Adequate blood pressure regulation also plays a key role in the primary prevention of diabetic nephropathy. Blood pressure control in type 2 diabetes is associated with a reduction in the incidence of microalbuminuria, particularly with the use of ACE inhibitors or ARBs. Agents in these two drug classes have a renoprotective effect via both reduction in blood pressure and direct effects on the kidney (158).

In the FIDELIO-DKD trial (9), treatment with finerenone resulted in lower risks of CKD progression, evaluated as a composite of kidney failure, a sustained decrease of ≥40% in eGFR from baseline, or death from renal causes.

Conclusion and Future Direction

CKD, HF, and type 2 diabetes are commonly associated with each other and lead to worse outcomes. Multidirectional relationships among all three comorbidities are well established. Data from trials of SGLT2 inhibitors, renin-angiotensin inhibitors, and selective MR antagonists provide support for the dual cardio- and renoprotective effects of these agents and the notion that the pathophysiologies of heart and renal disease are interconnected. Both SGLT2 inhibitors and MR antagonists have been shown to improve outcomes in patients with HFrEF who have diabetes (and in those without diabetes). The FIGARO-DKD (Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; NCT02545049) will provide further evidence regarding the use of finerenone in patients with type 2 diabetes and DKD. The use of SGLT2 inhibitors in patients with HFpEF is being studied in two ongoing trials: the EMPEROR-Preserved (Empaglifozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction; NCT03057951) and the DELIVER (Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; NCT03619213) trials. Although steroidal MR antagonists did not show definitive benefit in HFpEF patients in the TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial (163), a re-analysis of the trial taking into account regional differences and potential of nonadherence to trial procedures found that spironolactone use was associated with benefit in HFpEF as well (164). Finerenone is being studied in the HFpEF population in the FINEARTS (Study to Evaluate the Efficacy and Safety of Finerenone on Morbidity & Mortality in Participants With Heart Failure and Left Ventricular Ejection Fraction Greater or Equal to 40%; NCT04435626) trial. Several ongoing trials are studying this issue further.

See references starting on p. 34.

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