

## REVIEW ARTICLE

# Improving the residual risk of renal and cardiovascular outcomes in diabetic kidney disease: A review of pathophysiology, mechanisms, and evidence from recent trials

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## Abstract

Based on global estimates, almost 10% of adults have diabetes, of whom 40% are estimated to also have chronic kidney disease (CKD). Almost 2 decades ago, treatments targeting the renin-angiotensin system (RAS) were shown to slow the progression of kidney disease. More recently, studies have reported the additive benefits of antihyperglycaemic sodium-glucose co-transporter-2 inhibitors in combination with RAS inhibitors on both CKD progression and cardiovascular outcomes. However, these recent data also showed that patients continue to progress to kidney failure or die from kidney- or cardiovascular-related causes. Therefore, new agents are needed to address this continuing risk. Overactivation of the mineralocorticoid (MR) receptor contributes to kidney inflammation and fibrosis, suggesting that it is an appropriate treatment target in patients with diabetes and CKD. Novel, selective non-steroidal MR antagonists are being studied in these patients, and the results of two large recently completed clinical trials have shown that one such treatment, finerenone, significantly reduces CKD progression and cardiovascular events compared with standard of care. This review summarizes the pathogenic mechanisms of CKD in type 2 diabetes and examines the potential benefit of novel disease-modifying agents that target inflammatory and fibrotic factors in these patients.

## KEYWORDS

albuminuria, diabetes mellitus, diabetic nephropathies, glomerular filtration rate, mineralocorticoid receptor antagonist, renal insufficiency, chronic, renin-angiotensin system, sodium-glucose co-transporter-2 inhibitors

## 1 | INTRODUCTION

Type 2 diabetes (T2D) exacts a significant toll on healthcare systems throughout the world, with almost one in 10 adults diagnosed with the disease.<sup>1</sup> Current estimates suggest that 37% of patients with diabetes also have chronic kidney disease (CKD) stages 1 through 4 and that 38% of end-stage kidney disease cases are attributable to diabetes.<sup>2,3</sup>

In the Third National Health and Nutrition Examination Survey, examination of 10-year cumulative mortality in patients with T2D showed that the risk of all-cause and cardiovascular (CV)-related death is significantly elevated compared with patients without diabetes and that these risks are approximately 3-fold higher in patients with T2D and CKD than in patients with T2D alone.<sup>4</sup>

In addition, patients with T2D and CKD are more probable to die from other causes than progress to kidney failure.<sup>5</sup> This risk is

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particularly higher in older adults with CKD, who are 13-fold more probable to die from any cause and 6-fold more probable to die from CV causes than progress to kidney failure.<sup>6</sup> Although progress has been achieved in the past 3 decades in reducing the risk of CV events (e.g. myocardial infarction [MI], stroke), patients with diabetes still remain at high continuing risk for progression of CKD and additional CV events.<sup>7</sup>

Current treatment targets for slowing progressive kidney disease and reducing CV risk in patients with T2D focus on improving glycaemic control, reducing blood pressure (BP), managing lipids, and addressing obesity.<sup>8,9</sup>

Despite current guideline recommendations, incident rates of kidney failure in patients with T2D and CKD did not change from 2007 to 2017.<sup>10</sup> Thus, it appears that these treatment strategies have reached the limits of their benefit and that new treatment targets are needed. This review summarizes our current understanding of the pathogenic mechanisms of CKD in T2D and provides an overview of mechanisms for explaining the positive findings of recent trials that have led to the approval of the first new drugs (sodium-glucose co-transporter-2 inhibitors [SGLT2is] and finerenone) for the treatment of CKD in 20 years. These agents reduce the residual risk of adverse renal and CV outcomes that exist with current guideline-based therapy and target two different pathways that are involved in the pathogenesis of diabetic kidney disease (DKD).

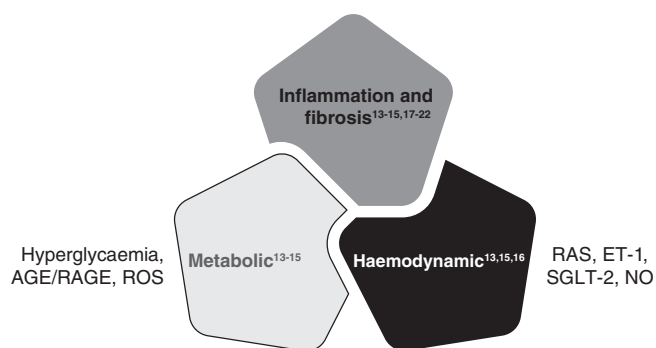
## 2 | EFFECT OF OBESITY ON CKD

Obesity is a powerful risk factor for kidney disease.<sup>11</sup> Several population-based studies have reported an association between measures of obesity and both the development and the progression of CKD.<sup>12</sup> In those affected by obesity, a compensatory mechanism of hyperfiltration is probably triggered to meet the enhanced metabolic burden of increased body weight. Raised intraglomerular pressure can result in kidney damage and increase the long-term risk of developing CKD. Obesity can cause kidney injury directly through induced synthesis of various adipose tissue cytokines with nephrotoxic potential, as well as indirectly by increasing the risk of developing diabetes and hypertension.<sup>12</sup> Lifestyle modifications and pharmacological interventions have shown modest benefits in secondary analysis of clinical trials, while bariatric surgery has been shown to improve kidney-related outcomes in observational studies.<sup>11</sup> The effect of loss of muscle mass on creatinine and calculated glomerular filtration rate (GFR) are limitations of these studies and therefore further investigations are needed to clarify the independent effect of weight loss on CKD outcomes.

## 3 | PATHOGENESIS OF CKD IN T2D

Progression of CKD is driven by three inter-related pathophysiological processes: metabolic, haemodynamic, and inflammation and fibrosis (Figure 1).<sup>13-22</sup> These processes promote structural changes in the nephron and are often associated with albuminuria, hypertension,

Angiopoietin-2, CKD273 proteins, CTGF, CXCL-16, FGF-23, fibrinogen, galectin-3, ICAM-1, KRIS proteins including TNF-R1/2, IL-1, IL-6, IL-18, MCP1, TNF- $\alpha$ , TGF- $\beta$ , SAA, VCAM-1, VEGFA



**FIGURE 1** Three interconnected processes contribute to the development and progression of chronic kidney disease in patients with type 2 diabetes. AGE, advanced glycation end product; CTGF, connective tissue growth factor; CXCL-16, C-X-C motif chemokine ligand-16; ET-1, endothelin-1; FGF-23, fibroblast growth factor 23; ICAM-1, intercellular adhesion molecule-1; IL, interleukin; KRIS, kidney risk inflammatory signature; NO, nitric oxide; MCP-1, monocyte chemoattractant protein-1; RAGE, receptor for advanced glycation end products; RAS, renin-angiotensin system; ROS, reactive oxygen species; SAA, serum amyloid A; SGLT-2, sodium-glucose co-transporter-2; TGF- $\beta$ , transforming growth factor beta; TNF- $\alpha$ , tumour necrosis factor alpha; TNF-R1/2, tumour necrosis factor receptor 1/2; VCAM-1, vascular cell adhesion molecule-1; VEGFA, vascular endothelial growth factor A

reduced GFR, increased CV events, and CV death.<sup>23</sup> The development and progression of CKD in T2D is complex and not completely understood; however, multiple pathways, multiple cell types, and epigenetic alterations have all been implicated in the progression of CKD.<sup>24</sup>

It is well recognized that hyperglycaemia is a key initiating event in the development and subsequent progression of T2D.<sup>13</sup> This initial pathophysiological event leads to increased reabsorption of glucose and sodium via the SGLT2 in the proximal tubules of the kidney and activation of the renin-angiotensin system (RAS).<sup>23</sup> Hyperglycaemia directly and indirectly (via haemodynamic changes) contributes to pro-inflammatory signalling. Pro-inflammatory cytokines can be activated via increased intraglomerular wall tension and shear stress,<sup>7</sup> whereas at the cellular level, hyperglycaemia independently causes endothelial dysfunction and structural damage to the glomerulus by promoting oxidative stress through increased reactive oxygen species (ROS) production in endothelial cells and activates pro-inflammatory signalling pathways via increased protein kinase C, nuclear factor (NF)- $\kappa$ B, and advanced glycation end products (AGEs). Furthermore, hyperglycaemia directly inactivates two important antiatherosclerotic enzymes, eNOS and prostacyclin synthase.<sup>23,25</sup>

Oxidative stress is inextricably linked to inflammation and fibrosis via the activation of transcription factors (e.g. NF- $\kappa$ B) and signalling pathways (e.g. Janus kinase signal transducer and activator of transcription) that promote the generation of pro-inflammatory cytokines (e.g. interleukin [IL]-1 $\beta$ , IL-6, tumour necrosis factor- $\alpha$ ) and pro-fibrotic factors (e.g. transforming growth factor [TGF]- $\beta$ , connective tissue

growth factor, osteopontin).<sup>17,26</sup> Activation of pro-inflammatory pathways in the presence of elevated intracellular ROS causes epigenetic changes and the expression of pro-inflammatory genes that persist after glycaemia is normalized.<sup>25</sup> Inflammation is not only a consequence of hyperglycaemia and haemodynamics, but also develops because of a chronically activated innate immune system and low-grade inflammatory state.<sup>27,28</sup> Renal ischaemia further enhances inflammation via increased infiltration of neutrophils and macrophages, whereas activated complement facilitates the recruitment of leukocytes and mast cells in the kidney.<sup>23</sup> Activation of the RAS is also implicated in the promotion of kidney fibrosis. RAS activation appears to be either an indirect effect via macula densa-mediated feedback mechanisms or through activation of G protein-coupled receptor GPR91, a succinate receptor located in the kidney.<sup>29</sup> Both hyperglycaemia and AGEs activate the RAS via ROS and GPR91,<sup>30,31</sup> which promotes kidney fibrosis via angiotensin II.<sup>32</sup> Aldosterone has an equally important role, including the upregulation of pro-fibrotic growth factors and adhesion molecules, as well as activation of the innate and adaptive immune systems.<sup>33</sup> Aldosterone has been implicated in the downregulation of regulatory T cells, increased polarization of cluster of differentiation (CD)4+ T cells into T-helper cells (Th17 and Th1), activation of dendritic cells and CD8+ T cells, and recruitment of B lymphocytes.<sup>33</sup> Although many of these effects of aldosterone do not require elevated serum aldosterone levels,<sup>33</sup> recent studies have shown that the majority of patients with hypertension have high aldosterone levels.<sup>34</sup>

## 4 | GUIDELINE-RECOMMENDED STANDARD OF CARE FOR CKD IN PATIENTS WITH T2D

The American Diabetes Association and Kidney Disease Improving Global Outcomes (KDIGO) guidelines (both published in 2020) recommend a multifactorial risk-reduction strategy for patients with T2D and CKD to delay decline in kidney function and reduce the risk of CV complications.<sup>8,9</sup> Evidence from the multicentre Nephropathy in Diabetes type 2 (NID-2) study has shown that simultaneous management of CV risk factors by implementing an intensified multifactorial treatment approach has early and long-lasting benefits in reducing the risk of major CV events and all-cause mortality in patients with DKD.<sup>35</sup> Current kidney-protective recommendations include reduction of BP and optimization of glycaemic control.<sup>8,9</sup> Recommended treatments for reducing BP in patients with T2D and CKD are angiotensin-converting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs).<sup>9</sup> The KDIGO guidelines also indicate that ACEis/ARBs may be considered in normotensive patients with T2D and CKD.<sup>8</sup> Both drug classes have also been shown to reduce, but not completely prevent, worsening kidney function.<sup>9</sup> Importantly, combinations of ACEis plus ARBs should not be used, as combinations of RAS inhibitors have not shown renal protection and have been associated with acute kidney injury or hyperkalaemia.<sup>5,8,9</sup> The guidelines also recommend the use of glucose-lowering drugs such as SGLT2is (canagliflozin and dapagliflozin) and glucagon-like peptide-1 receptor

agonists (GLP-1 RAs; liraglutide and semaglutide) to slow the progression of kidney disease.<sup>9</sup> SGLT2is and GLP-1 RAs have also shown benefits on reduced CV risk, particularly for heart failure (HF) in the case of SGLT2is and atherosclerotic CV disease in the case of GLP-1 RAs.<sup>36-38</sup> Updated guidelines now state clinicians should consider an SGLT2i in patients with T2D and CV disease or CKD (estimated [e]GFR  $\geq 30$  mL/min/1.73 m<sup>2</sup> and particularly  $>300$  mg/g albuminuria), irrespective of HbA1c levels, to reduce the risk of kidney disease progression, CV events, or both, or the use of a GLP-1 RA in patients with T2D and CVD, to reduce the risk of CV events, progression of albuminuria, or both.<sup>9</sup>

### 4.1 | Putative renoprotective mechanisms of SGLT2is and GLP-1 RAs

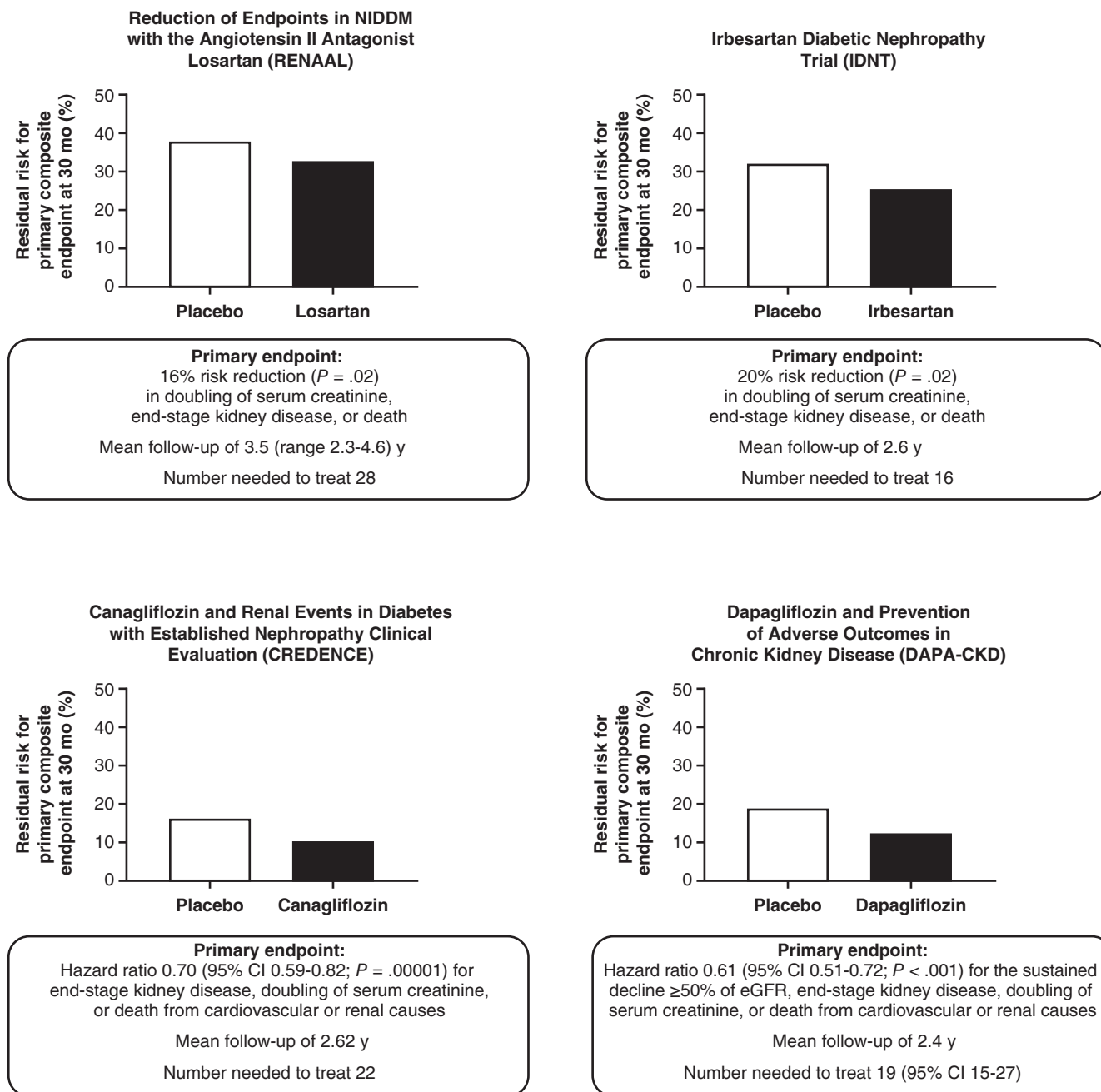
In addition to their benefits on glycaemic control and weight, SGLT2is exert a natriuretic effect that lowers plasma volume, improves endothelial function, and lowers arterial stiffness, which in turn reduce BP and CV risk.<sup>7</sup> The restoration of sodium to physiological levels in the macula densa increases afferent tone and decreases renal perfusion to normal rates (via tubuloglomerular feedback), while avoiding overcompensation.<sup>8</sup> However, anti-inflammatory and antifibrotic effects appear to be an indirect downstream effect of SGLT2is. Although currently unknown, putative mechanisms include reduction of intraglomerular pressure, wall tension, and shear stress, as well as possible inhibition of pro-inflammatory or pro-fibrotic signalling and reduced renal oxygen consumption and protection against renal hypoxia.<sup>39</sup>

The mechanism of the renoprotective effects of GLP-1 RAs is less clear, although benefits on weight loss and BP reduction may play a role. They also appear to have natriuretic effects, possibly via vasoactive mediators (atrial natriuretic peptide, brain natriuretic peptide, cyclic guanyl monophosphate, and cyclic adenylyl monophosphate) and by reducing plasma concentrations of angiotensinogen, renin, and angiotensin II.<sup>40</sup>

### 4.2 | Residual risk of CKD progression and CV events persists despite guideline-recommended medical therapy

Despite the shown benefits of currently recommended treatments (ACEis/ARBs, SGLT2is, and GLP-1 RAs) for preventing the progression of CKD, patients with T2D have a continuing risk of progression of CKD (Figure 2).<sup>38</sup>

The Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan Diabetic Nephropathy Trial (IDNT) were the first studies to show that ARBs could slow the progression of CKD in patients with T2D.<sup>41,42</sup> Despite the significant benefits observed on kidney disease progression, 43.5% (RENAAL) and 32.6% (IDNT) of patients receiving an ARB experienced a primary endpoint.<sup>41,42</sup> Neither study showed a benefit of ARBs on the composite CV endpoints (CV death, MI,



**FIGURE 2** Residual risk for the primary composite endpoint at 30 months in RENAAL, IDNT, CREDENCE, and DAPA-CKD. CI, confidence interval; eGFR, estimated glomerular filtration rate

hospitalization for HF, stroke, hospitalization for angina [RENAAL], or lower limb amputation above the ankle [IDNT]).<sup>41,42</sup>

More recently, the effects of SGLT2is on a background of standard of care (SOC; either an ACEi or an ARB) have been explored in the Canagliflozin and Renal Events in Diabetes with Established Nephropathy–Clinical Evaluation (CREDENCE) study<sup>38</sup> and the Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD) study.<sup>43</sup> Canagliflozin plus SOC significantly reduced the risk of several renal endpoints compared with placebo plus SOC<sup>38</sup>; however, 11.1% of patients receiving canagliflozin

experienced a primary endpoint. A continuing risk of CV events was also evident in 12.4% of patients who received canagliflozin plus SOC after a median follow-up of 2.6 years.<sup>38</sup> Dapagliflozin on a background of SOC (either an ACEi or an ARB)<sup>43</sup> significantly reduced the risk of progressive CKD or renal/CV death; however, 9.2% of patients experienced a primary outcome, which was similar to that seen in CREDENCE. The continuing risk for the composite CV endpoint (hospitalization for HF or CV death) was 6.6%.<sup>43</sup>

These data highlight the need for new therapies that target alternative pathways, such as those directly involved in inflammation or

fibrosis, to further reduce the continuing risk of CKD progression in patients with T2D.

## 5 | THE EVOLUTION OF THERAPIES TARGETING INFLAMMATION AND FIBROSIS

Several different classes of drugs targeting oxidative stress and inflammation in CKD with T2D have been investigated in clinical trials, and these include pronatriuretics (neprilysin inhibitors), antifibrotics (pirfenidone, anti-TGF antibodies), anti-AGEs (pyridoxamine, aminoguanidine), uric acid-lowering agents (allopurinol), endothelin receptor antagonists (atrasentan, avosentan), and antioxidants/anti-inflammatory agents (bardoxolone, baricitinib, pentoxifylline, CCL2 antagonists). Some of these drugs have shown potential in protecting renal function in patients with T2D at high risk of developing end-stage kidney disease. For example, in the SONAR study, atrasentan reduced the risk of renal events in a patient population with diabetes and CKD who were selected as being probable to benefit from the therapy and have a reduced risk of adverse effects.<sup>44</sup> However, because of a lack of efficacy versus control groups in terms of renoprotection (eGFR decline, reduced serum creatinine, or albuminuria) and/or safety concerns, many are no longer under development.

Pathways that influence inflammation and fibrosis in the heart and kidney are complex, but a key trigger is overactivation of the mineralocorticoid receptor (MR).<sup>17,45</sup> Thus, some of the most promising agents being investigated target the MR.

### 5.1 | MR overactivation is a key trigger of inflammation and fibrosis in the kidney

MR is a steroid hormone receptor, a subfamily of nuclear receptors that activate intracellular receptors and nuclear transcription factors.<sup>46</sup> The binding of cortisol or aldosterone (ligands of the MR) leads to recruitment of at least 22 known co-factors that mediate the effects of the MR in a cell-specific manner.<sup>46</sup> The MR is expressed on a variety of cells, including cardiomyocytes, fibroblasts, vascular (endothelial and smooth muscle) cells, immune cells, and subcutaneous adipocytes.<sup>17,47</sup> The MR has pleiotropic effects but is primarily involved in tissue repair and remodelling, electrolyte balance, and BP regulation.<sup>17,45</sup> Cell specificity is conferred by the expression of 11 $\beta$ -hydroxysteroid dehydrogenase type 2, which inactivates 11-hydroxy steroids, thus protecting the non-selective MR from activation by glucocorticoids.<sup>48,49</sup>

Under conditions of disease or pathology (e.g. hyperglycaemia, heart and kidney disease, oxidative stress, and salt loading), increased MR activation 'switches' its principal activity from homeostatic regulator to pathophysiological mediator by promoting inflammation and fibrosis in tissues where it is expressed.<sup>45,50</sup> MR overactivation leads to the production of factors that mediate the production of pro-inflammatory cytokines (e.g. IL-1 $\beta$ , IL-6) and pro-fibrotic proteins

(e.g. TGF- $\beta$ , fibronectin, osteopontin) and increased expression of signalling proteins (e.g. Rac1; Figure 3).<sup>17,51-58</sup>

In diabetes, increased aldosterone activity in the kidney results in increased hypertension, glomerular injury, renal vasoconstriction, and proteinuria.<sup>7</sup> Increased plasma aldosterone levels (known as aldosterone breakthrough) have been reported following chronic RAS inhibition with ACEis/ARBs in patients with congestive HF, CKD, or hypertension, although their clinical significance is not yet understood.<sup>59</sup> Aldosterone breakthrough occurring during blockade of the renin-angiotensin-aldosterone system with RAS inhibitors in diabetic nephropathy has been associated with enhanced decline in glomerular filtration rate. However, MR overactivation may also be mediated by a variety of mechanisms independent of serum aldosterone.<sup>49</sup> The hypothesized mechanisms include increased MR expression in target tissues, elevated tissue levels of MR steroid hormone agonists (aldosterone and cortisol), and increased expression of non-classical MR activator Rac1.<sup>47,60</sup> Overactivation of the MR may also elevate CV and renal risks via haemodynamic and metabolic pathways.<sup>61,62</sup> Glomerular hyperfiltration is also rapidly corrected with MR antagonism, either with or without an aldosterone excess.<sup>63</sup> This is reflected in an initial decrease in eGFR, possibly as a result of increased tubuloglomerular feedback, which predicts a later favourable influence on renal function.<sup>63,64</sup>

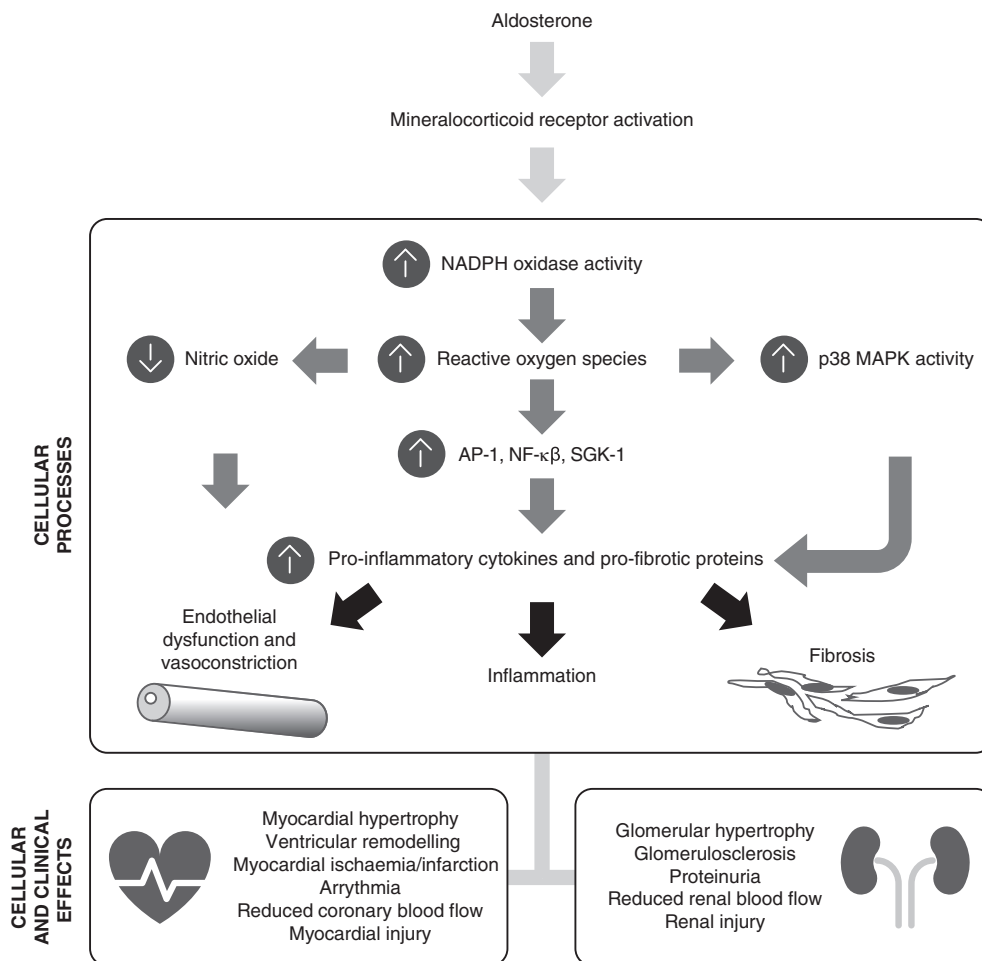
### 5.2 | The evolution of MR antagonists in the management of CKD in T2D

Over the past 2 decades, several randomized controlled trials have reported antiproteinuric and potentially renoprotective effects of MR antagonists (MRAs) in CKD. The steroidal MRAs spironolactone and eplerenone exert their therapeutic effects by lowering BP and, in patients with reduced left ventricular ejection fraction (LVEF), show BP-independent anti-inflammatory and antifibrotic effects, lowering both CV morbidity and mortality.<sup>62</sup> However, their use in clinical practice is limited because of their safety profiles and labelling precautions (hyperkalaemia and worsening kidney function).<sup>62</sup>

#### 5.2.1 | Non-steroidal MRAs

To overcome the limitations of steroidal MRAs, several non-steroidal MRAs have been developed with improved efficacy and tolerability compared with their steroidal predecessors. Of these, finerenone (BAY94-8862) was recently approved to reduce the risk of kidney function decline, kidney failure, CV death, non-fatal heart attacks, and hospitalization for HF in adults with CKD associated with T2D; and of the others, apararenone (MT-3995) and esaxerenone (CS-3150) are furthest along in their clinical development.

Finerenone, which currently has the most available evidence,<sup>55-69</sup> differs from steroidal MRAs in several important ways, including balanced distribution to the heart and kidneys, a comparatively short half-life, lack of active metabolites, and a bulkier molecular structure



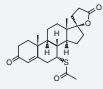
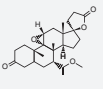

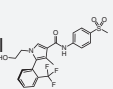





















**FIGURE 3** Pathophysiological mechanisms involved in the deleterious effects of mineralocorticoid receptor activation in the heart and kidneys. AP-1, activator protein-1; MAPK, mitogen-activated protein kinase; NADPH, nicotinamide adenine dinucleotide phosphate; NF- $\kappa$ B, nuclear factor- $\kappa$ B; SGK-1, serum- and glucocorticoid-induced protein kinase-1

(Figure 4).<sup>46,60,70-72</sup> These differences result in differential effects, including diminished effects on potassium levels and BP. The bulkier structure of finerenone also influences co-factor recruitment within the nucleus, leading to differential gene expression in different tissues<sup>60</sup> and more potent antifibrotic and anti-inflammatory effects compared with steroidal MRAs.<sup>46,73-76</sup> The direct effects of finerenone on fibrosis and inflammation are independent of BP lowering and differ from the indirect effects of SGLT2is.

### 5.2.2 | Clinical evidence of cardiorenal protection with non-steroidal MRAs

Limited phase 2 data suggesting that apararenone and esaxerenone may offer cardiorenal protection have been published; however, findings from completed or ongoing phase 3 studies are not yet available (Table 1).<sup>77,78</sup> By contrast, five phase 2 studies of finerenone have been published: mineralocorticoid Receptor antagonist Tolerability Study (ARTS), ARTS-Diabetic Nephropathy (DN), ARTS-DN Japan, ARTS-Heart Failure (HF), and ARTS-HF Japan; and more recently, two phase 3 studies, Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease (FIDELIO-DKD),<sup>68,79-81,84</sup> and Efficacy and Safety of Finerenone in Subjects With

Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease (FIGARO-DKD), have also been completed (Table 1).<sup>82,83</sup> Both the phase 3 studies enrolled adult patients with T2D and CKD receiving an ACEi or an ARB that was optimized to the maximum tolerated dose (in accordance with the manufacturer's label). In FIDELIO-DKD, patients were predominantly enrolled with stage 3 to 4 CKD with severely elevated albuminuria and T2D, a population with high risk of kidney disease. FIGARO-DKD was conducted in patients with stage 2 to 4 CKD and moderately elevated albuminuria or stage 1 to 2 CKD with severely increased albuminuria, a population at high CV risk that was excluded from or understudied in FIDELIO-DKD.<sup>82</sup> Both FIDELIO-DKD and FIGARO-DKD share the same primary and secondary composite endpoints: time to onset of kidney failure, a sustained decrease of eGFR of 40% or more from baseline, or renal death (primary in FIDELIO-DKD,<sup>82</sup> secondary in FIGARO-DKD<sup>83</sup>), and time to CV death, non-fatal MI, non-fatal stroke, or hospitalization for HF (primary in FIGARO-DKD, secondary in FIDELIO-DKD). Additional endpoints include all-cause hospitalization, all-cause mortality, change in urine albumin-creatinine ratio (UACR), and a composite endpoint of onset of kidney failure, decreased eGFR, or renal death. The combined FIDELIO-DKD and FIGARO-DKD programme (N = 13 171) is the largest to date to examine the effects of a non-steroidal MRA on CV and kidney outcomes in patients with T2D and CKD.

| Characteristic                   | Spirolactone <sup>60</sup>   | Eplerenone <sup>60</sup>   | Finerenone <sup>60</sup>  | Esaxerenone <sup>70-72</sup>  |
|----------------------------------|--|--|---|---|
| Mineralocorticoid receptor class | Steroidal   | Steroidal   | Non-steroidal    | Non-steroidal          |
| Potency                          | <br>High  | <br>Low   | <br>High  | <br>High               |
| Selectivity                      | <br>Low   | <br>Medium  | <br>High  | <br>High               |
| Metabolites                      | Multiple Active  | No active  | No active   | Multiple Activity unknown   |
| Half-life                        |  <br>Healthy volunteers Patients |  <br>Healthy volunteers Patients |  <br>Healthy volunteers Patients | <br>Healthy volunteers |
| Tissue distribution in rodents   |                                  |                                  |                                  | Unknown   |

**FIGURE 4** Key pharmacological differences between steroidal and non-steroidal mineralocorticoid receptor antagonists

The ARTS programme established the proof of concept that finerenone may offer cardiorenal protection (Table 1).<sup>68,79-81,84</sup> ARTS showed that finerenone, compared with spironolactone, was associated with significantly smaller ( $P < .0001$ ) mean increases in serum potassium, similar decreases in N-terminal prohormone B-type natriuretic peptide (NT-proBNP) levels, and fewer adverse kidney events and hyperkalaemia in patients with chronic HF associated with a reduced LVEF and CKD.<sup>84</sup> ARTS-DN showed that finerenone (7.5-20 mg), compared with placebo, was associated with a dose-dependent reduction in albuminuria, with a minimal change in serum potassium from baseline (~0.14-0.23 mmol/L) in patients with T2D and persistent albuminuria (UACR  $\geq 30$  mg/g) receiving a RAS blocker.<sup>79</sup> There were no differences between finerenone and placebo in terms of achieving a 30% or higher decrease in eGFR and in the incidence of adverse events. Similar findings were observed in the ARTS-DN Japan study.<sup>81</sup> ARTS-HF showed that finerenone and eplerenone induced a 30% or greater decrease in NT-proBNP levels in a similar proportion of patients who presented in emergency departments with worsening chronic HF with reduced LVEF.<sup>80</sup> Finerenone (10-20 mg) performed significantly better than eplerenone in terms of reducing the composite clinical endpoint of death from any cause, CV hospitalizations, or emergency department presentation for worsening HF until day 90<sup>80</sup> and reducing UACR.<sup>67</sup>

The findings from FIDELIO (N = 5674; mean eGFR = 44.3 mL/min/1.73m<sup>2</sup>; median UACR = 852 mg/g) definitively establish the renoprotective and cardioprotective effects of finerenone (Table 1).<sup>82</sup> Finerenone, compared with placebo, significantly

lowered the risk of the primary kidney outcome, corresponding to a number needed to treat of 29 (95% confidence interval [CI], 16-166).<sup>82</sup> The individual components of the primary kidney outcome were consistently lower with finerenone, and the effects of finerenone on the primary outcome were consistent across prespecified subgroups.<sup>82</sup> Finerenone also significantly lowered the secondary CV outcome compared with placebo, corresponding to a number needed to treat of 42 (95% CI, 22-397).<sup>82</sup> The incidences of the components of the secondary CV outcome were lower with finerenone, with the exception of non-fatal stroke, which was similar between the two groups.<sup>82</sup> Exploratory secondary analyses revealed that finerenone reduced UACR by 31% from baseline to month 4, an effect that was maintained thereafter. The prespecified secondary composite kidney event (kidney failure, a sustained decrease of  $\geq 57\%$  in eGFR from baseline, or death from renal causes) was also reduced.<sup>82</sup>

In FIDELIO, the incidence of adverse events was similar in the finerenone and placebo groups.<sup>82</sup> Finerenone was associated with a higher overall risk of hyperkalaemia than placebo (18.3% and 9.0%, respectively). Few patients were hospitalized or discontinued treatment because of hyperkalaemia, although these events were more frequent in patients treated with finerenone versus placebo (2.3% and 0.9%). Because patients with serum potassium levels of more than 4.8 mmol/L were excluded from FIDELIO, serum potassium was measured regularly, and those with levels of more than 5.5 mmol/L were discontinued from the trial, and therefore it is possible that this incidence could be amplified in real-world scenarios.<sup>85</sup>

**TABLE 1** Summary of phase 2/3 clinical studies of apararenone, esaxerenone, and finerenone

| Study name and reference  | Patients  | Design/treatment  | Primary endpoint(s)                 | Key results   |
|---|---|---|-------------------------------------|---|
| Apararenone (current development: Phase 3 in T2D + CKD in Japan and filed for approval in Asia) |   |   |                                     |   |
| NCT01889277<br>MT-3995-J03  | T2D + CKD receiving SOC<br>HbA1c $\leq$ 10.5%<br>Albuminuria<br>N = 51  | Phase 1/2, RCT<br>Low vs. high dose (NR) vs. PBO                          | Safety and pharmacokinetics         | Completed, no results   |
| NCT02205372<br>MT-3995-J04  | T2D + CKD receiving SOC<br>HbA1c $\leq$ 10.5%<br>Albuminuria<br>N = 31  | Phase 1/2, RCT<br>Apararenone (NR) vs. PBO                                | Safety                              | Completed, no results   |
| NCT01756703<br>MT-3995-E06  | T2D + CKD receiving SOC<br>HbA1c $\leq$ 10.5%<br>Albuminuria<br>eGFR $\geq$ 60 mL/min/1.73m <sup>2</sup><br>N = 67  | Phase 2, RCT<br>Low vs. high dose (NR) vs. PBO                            | UACR change from baseline<br>Safety | Completed, no results   |
| NCT01756716<br>MT-3995-E07  | T2D + CKD receiving SOC<br>HbA1c $\leq$ 10.5%<br>Albuminuria<br>eGFR 30 to $<$ 60 mL/min/1.73m <sup>2</sup><br>N = 49   | Phase 2, RCT<br>Low vs. high dose (NR) vs. PBO                            | UACR change from baseline<br>Safety | Completed, no results   |
| NCT02517320<br>MT-3995-J05 <sup>77</sup>  | T2D + CKD<br>HbA1c $\leq$ 10.5%<br>eGFR $\geq$ 30 mL/min/1.73m <sup>2</sup><br>UACR 50 to $<$ 300 mg/g Cr<br>DBP $<$ 100 mmHg; SBP<br>$<$ 160 mmHg<br>N = 293                       | Phase 2, RCT<br>Low vs. middle vs. high doses<br>(NR) vs. PBO             | UACR change from baseline<br>Safety | Dose-dependent decreases in UACR ( $P < .001$ vs. PBO)<br>Slight decreases in eGFR and increases in serum potassium |
| NCT02676401MT-3995-J06 <sup>77</sup>  | As for study MT-3995-J05<br>N = 241   | Open-label extension (52 wk) of MT-3995-J05                               | Safety                              | Apararenone was well tolerated  |
| Esaxerenone (current development: Phase 3 in T2D + CKD in Japan only)                           |   |   |                                     |   |
| NCT02807974<br>CS3150-A-J306  | T2D + CKD receiving SOC<br>UACR 30 to $<$ 1000 mg/g Cr<br>Sitting SBP 140 to $<$ 180 mmHg, and sitting DBP 80 to $<$ 110 mmHg<br>eGFR $\geq$ 30 mL/min/1.73m <sup>2</sup><br>N = 51 | Phase 3, open-label study<br>Esaxerenone 1.25-2.5, 5 mg                   | SBP/SBP change from baseline        | Completed, no results   |
| NCT02807987<br>CS3150-A-J305  | Sitting SBP 140 to $<$ 180 mmHg, and sitting DBP 80 to $<$ 110 mmHg<br>Receiving SOC<br>eGFR 30 to 60 mL/min/1.73m <sup>2</sup><br>N = 58   | Phase 3, open-label study<br>Esaxerenone 1.25-2.5, 5 mg                   | SBP/DBP change from baseline        | Completed, no results   |
| NCT02448628<br>CS3150-A-J206  | Sitting SBP 140 to $<$ 180 mmHg and sitting DBP 80 to $<$ 110 mmHg<br>eGFR 30 to $<$ 60 mL/min/1.73m <sup>2</sup><br>N = 33   | Phase 2, open-label study<br>Esaxerenone 1.25-2.5, 5 mg                   | SBP/DBP change from baseline        | Completed, no results   |
| NCT02345057<br>CS3150-B-J204 <sup>78</sup>  | T2D + CKD receiving SOC<br>UACR 45 to $<$ 300 mg/g Cr<br>eGFR by creatinine $\geq$ 30 mL/min/1.73m <sup>2</sup><br>N = 365  | Phase 2, RCT<br>Esaxerenone 0.625 mg, 1.25 mg, 2.5 mg, 5 mg vs. PBO + SOC | UACR change from baseline           | Dose-dependent reductions in UACR ( $P < .001$ vs. PBO)<br>Dose-dependent hyperkalaemia most common AE              |



TABLE 1 (Continued)

| Study name and reference                                      | Patients   | Design/treatment   | Primary endpoint(s)  | Key results  |
|---|--|--|--|--|
| Finerenone (current development: Phase 3 in T2D + CKD global) |  |  |  |  |
| NCT01345656<br>ARTS <sup>69</sup>                             | HF + CKD<br>LVEF $\leq$ 40%<br>N = 458   | Phase 2a, RCT<br>Part A: Mild CKD<br>Part B: Moderate CKD<br>Finerenone: 2.5 mg, 5 mg, 5 mg<br>twice-daily, 10 mg<br>Spironolactone: 25 mg, 50 mg                | Change in serum potassium  | Well tolerated; less hyperkalaemia vs. spironolactone  |
| NCT01874431<br>ARTS-DN <sup>79</sup>                          | T2D + CKD receiving SOC<br>UACR $\geq$ 30 mg/g<br>eGFR $>$ 30 mL/min/1.73m <sup>2</sup><br>Serum potassium $\leq$ 4.8 mmol/L<br>N = 823  | Phase 2b, RCT<br>Finerenone 1.25 mg, 2.5 mg, 5 mg, 10 mg, 15 mg, 25 mg vs. PBO   | PBO-corrected mean ratio 90-d UACR vs. baseline<br>Safety  | Dose-dependent UACR reduction ( $P < .01$ all doses)<br>Similar AE profile to PBO<br>Discontinuations because of hyperkalaemia were low  |
| NCT01807221<br>ARTS-HF <sup>80</sup>                          | HFrEF + CKD $\pm$ T2D<br>LVEF $\leq$ 40%<br>N = 1066   | Phase 2b, RCT<br>Finerenone uptitrated: 2.5-5 mg, 5-10 mg, 7.5-10 mg, 7.5-15 mg, 10-20 mg, 15-20 mg<br>Eplerenone uptitrated: 25 mg every second day to 25 mg QD | Proportion NT-proBNP $>$ 30% decrease vs. baseline<br>Safety                                       | Lower proportion of $>$ 30% decrease in NT-proBNP for all doses of finerenone vs. eplerenone ( $P =$ not significant)<br>Well tolerated; safety comparable with eplerenone                                     |
| NCT01968668<br>ARTS-DN Japan <sup>81</sup>                    | Japanese T2D + CKD receiving SOC<br>UACR $\geq$ 30 mg/g<br>eGFR $\geq$ 30 to $<$ 90 mL/min/1.73m <sup>2</sup><br>UACR $\geq$ 300 mg/g<br>eGFR $\geq$ 30 to $<$ 90 mL/min/1.73m <sup>2</sup><br>Serum potassium $\leq$ 4.8 mmol/L<br>N = 96 | Phase 2, RCT<br>Finerenone: 1.25 mg, 2.5 mg, 5 mg, 7.5 mg, or 10 mg<br>PBO   | Change from baseline to 90-d UACR<br>Safety  | UACR at day 90 relative to baseline for each finerenone treatment group was numerically reduced compared with PBO<br>Similar AE profile to PBO<br>No discontinuations because of hyperkalaemia                 |
| NCT01955694<br>ARTS-HF Japan <sup>68</sup>                    | Japanese hospitalized worsening HFrEF requiring emergency treatment with intravenous diuretics + T2D and/or CKD<br>LVEF $\leq$ 40%<br>N = 72   | Phase 2b, RCT<br>Finerenone uptitrated: 2.5-5 mg, 5-10 mg, 7.5-15 mg, 10-20 mg, 15-20 mg<br>Eplerenone uptitrated: 25 mg every second day to 25 mg QD            | Proportion NT-proBNP $>$ 30% decrease vs. baseline<br>Safety                                       | Proportion of NT-proBNP $>$ 30% were not significantly different between groups (all $P =$ NS)<br>Well tolerated; safety comparable with eplerenone  |
| NCT02540993<br>FIDELIO-DKD <sup>66,82</sup>                   | T2D + CKD receiving SOC<br>Serum potassium $\leq$ 4.8 mmol/L<br>UACR 30 to $<$ 300 mg/g + eGFR 25 to $<$ 60 mL/min/1.73m <sup>2</sup> or UACR $\geq$ 300 mg/g + eGFR 25 to $<$ 75 mL/min/1.73m <sup>2</sup><br>N = 5674                    | Phase 3, RCT, event-driven, Finerenone (10-20 mg once-daily) or placebo  | Composite: Kidney failure, sustained eGFR decrease (40%) over $\geq$ 4 wk or renal death<br>Safety | Primary composite: 504 (17.8%) patients vs. 600 (21.1%) patients; HR 0.82; 95% CI, 0.73-0.93; $P = .001$<br>CV composite: 367 (13.0%) patients vs. 420 (14.8%) patients; HR 0.86; 95% CI, 0.75-0.99; $P = .03$ |
| NCT02545049<br>FIGARO-DKD <sup>83</sup>                       | T2D + CKD receiving SOC<br>Serum potassium $\leq$ 4.8 mmol/L<br>UACR 30 to $<$ 300 mg/g + eGFR 25 to $<$ 90 mL/min/1.73m <sup>2</sup> or UACR $\geq$ 30 mg/g + eGFR 60 mL/min/1.73m <sup>2</sup><br>N = 7352                               | Phase 3, RCT, event-driven, Finerenone (10-20 mg once-daily) or placebo  | Composite: CV death and non-fatal CV events  | Primary composite: 458 (12.4%) patients vs. 519 (14.2%) patients; HR 0.87; 95% CI, 0.76-0.98; $P = .03$<br>Kidney composite: 350 (9.5%) patients vs. 395 (10.8%) patients; HR 0.87; 95% CI, 0.76-1.01          |

Source: <https://clinicaltrials.gov/>.

Abbreviations: AE, adverse event; ARTS, minerAlocorticoid Receptor antagonist Tolerability Study; ARTS-DN, ARTS-Diabetic Nephropathy; ARTS-HF, ARTS-Heart Failure; CI, confidence interval; CKD, chronic kidney disease; Cr, creatinine; CV, cardiovascular; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FIDELIO-DKD, Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and Diabetic Kidney Disease; FIGARO-DKD, Efficacy and Safety of Finerenone in Subjects With Type 2 Diabetes Mellitus and the Clinical Diagnosis of Diabetic Kidney Disease; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; LVEF, left ventricular ejection fraction; NR, dose not reported; NS, not significant; NT-proBNP, N-terminal prohormone B-type natriuretic peptide; PBO, placebo; QD, daily; RCT, randomized controlled trial; SBP, systolic blood pressure; SOC, standard of care (comprising an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker); T2D, type 2 diabetes; UACR, urine albumin-creatinine ratio.

More recently, it was reported that in FIGARO (N = 7352; mean eGFR = 67.8 mL/min/1.73m<sup>2</sup>; median UACR = 308 mg/g), treatment with finerenone showed significantly improved efficacy relative to placebo in reducing the composite risk of time to first occurrence of CV death or non-fatal CV events (MI, stroke, or hospitalizations for HF).<sup>83</sup>

## 6 | FUTURE DIRECTIONS: POTENTIAL MOLECULAR PATHOGENIC TARGETS

As knowledge of the pathophysiology of CKD in T2D increases, novel target pathways are being identified, offering opportunities to further optimize treatment to slow kidney disease progression. One such target involves podocyte autophagy, a cellular recycling process that maintains kidney homeostasis and is modulated by pathogenic mechanisms, including RAS activation, insulin resistance, oxidative stress, AGEs, and hypoxia.<sup>86</sup> Activating autophagy may protect mesangial cells from apoptosis stimulated by TGF- $\beta$ 1 via its signalling pathways (TGF- $\beta$ -activated kinase 1 and phosphoinositide 3-kinase-protein kinase B/Akt) in patients with T2D and CKD,<sup>87</sup> and these may serve as potential therapeutic targets in the future. Another potential target includes the restoration of mitochondrial function and superoxide production via cyclic AMP-activated protein kinase, which has been associated with an improvement in markers of renal dysfunction in diabetes.<sup>23</sup> The breadth of novel targets ensures that significant research will continue for the foreseeable future.

## 7 | CONCLUSION

There is a continuing risk for the development and progression of CKD in patients with T2D, despite the optimal use of current guideline-based therapies. Apart from metabolic and haemodynamic factors, there is emerging evidence that inflammation and fibrosis are intrinsically involved in CKD pathogenesis and progression. Previous therapies targeting these pathways have failed to show benefits in clinical trials. Overactivation of the MR is a key driver of inflammation and fibrosis, which are associated with end-organ damage in both CKD and CV disease in patients with T2D; however, there is currently no MR-targeting therapy approved for use in this setting. The recently published results from the FIDELIO-DKD study clearly show the significant benefit of finerenone on both CKD and CV outcomes, offering for the first time a novel approach to target MR overactivation independent of haemodynamic (BP) and hyperglycaemic pathways. The results of FIGARO-DKD will probably provide additional data and, importantly, the largest dataset of patients with T2D and CKD receiving an MRA. The potential for offering a more intensive and potentially disease-modifying treatment approach using three different classes of therapeutic agent (i.e. glucose lowering [SGLT2is, GLP-1RAs], RAS inhibition [ACEis/ARBs], and MR inhibition [MRAs]) with complementary mechanisms of action may ameliorate the continuing risk of CV events and CKD progression reported with current SOC therapies.

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### AUTHOR CONTRIBUTIONS

Bayer Corporation was involved in the development of the concept for this manuscript but had no role in the selection or interpretation of articles to be included or preparation of the manuscript. All authors participated in the selection and interpretation of the articles and in the drafting, critical revision, and approval of the final version of the manuscript.

### PEER REVIEW

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### DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study

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