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ORIGINAL ARTICLE

Comparing CKD populations with T1D and T2D: a perspective based on the FINE-ONE and FIDELITY populations

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ABSTRACT

Chronic kidney disease (CKD) is a common comorbidity of both type 1 diabetes (T1D) and type 2 diabetes (T2D) and is associated with increased mortality, end-stage kidney disease and cardiovascular disease risk. Despite standard-of-care treatment with renin–angiotensin system inhibitors added to blood pressure and glycaemic control, people with CKD and T1D have a residual risk of CKD progression. Advances in therapeutic management have been limited over the past 3 decades, especially compared with CKD in T2D, for which new treatment options have emerged in the last 5 years. In this review article we discuss the similarities and differences between T1D and T2D populations with CKD, including epidemiology, pathophysiology and clinical findings. Additionally, we explore the use of albuminuria as a potential bridging biomarker to extrapolate clinical evidence from one population to the other. This concept could offer a promising strategy to narrow the gap in treatment availability between these populations and address the unmet therapeutic need in people with CKD and T1D. The FINE-ONE trial is investigating the non-steroidal mineralocorticoid receptor antagonist finerenone in a population with CKD and T1D using the change in urine albumin:creatinine ratio from baseline over 6 months as its primary endpoint and bridging biomarker. Similarities between the populations from FINE-ONE trial and FIDELITY (a pooled dataset of individuals with CKD and T2D included in two large phase 3 clinical trials of finerenone) may inform the translation of clinical evidence on finerenone from people with CKD and T2D to those with CKD and T1D.

Keywords: chronic kidney disease, finerenone, type 1 diabetes, type 2 diabetes, urine albumin:creatinine ratio

INTRODUCTION

The International Diabetes Federation estimates that 588.7 million people worldwide had diabetes in 2024 [1]. Of these, 9.2 million had type 1 diabetes (T1D). Chronic kidney disease (CKD) is a common complication of diabetes, developing in ≈30% of people with T1D and 40% of people with type 2 diabetes (T2D) [2, 3]. Both CKD and T1D or T2D are associated with an increased risk of kidney failure, cardiovascular (CV) disease and mortality, affirming the high disease burden driven by CKD [4, 5]. While new therapies have become available for the management of CKD progression in people with T2D, similar innovations for people with T1D lag behind. Landmark clinical trials conducted >30 years ago demonstrated that improved glycaemic control and treatment with the angiotensin-converting enzyme inhibitor (ACEi) capto-

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pril reduced both estimated glomerular filtration rate (eGFR) decline and the risk of progression to kidney failure in people with T1D and CKD [6, 7]. Since then, no new drugs to slow the progression of CKD have become available and people with T1D remain at high residual risk. A registry study of 591 people with T1D who had CKD onset between January 2000 and December 2020 reported that the cohort continued to lose kidney function and the risks of kidney and CV events remained high despite 73% receiving renin–angiotensin system (RAS) inhibitor therapy [8]. Thus there is an unmet need for novel therapies.

Clinical trials using validated surrogate outcomes can accelerate new therapy development, given that these are smaller and have shorter follow-ups than clinical outcome trials. This is particularly relevant for T1D, where it is challenging to recruit large cohorts of participants to record sufficient clinical kidney outcomes that would enable robust assessment of drug efficacy. In these settings, a surrogate outcome can serve as a bridging biomarker to translate evidence from one population to another. In the case of CKD in T1D and T2D, albuminuria is common in both conditions and is a major driver of CKD progression [9]. As such, changes in albuminuria, typically measured by the urine albumin:creatinine ratio (UACR), could be used to extrapolate clinical evidence from one patient population to the other. Here we describe the use of UACR as a bridging biomarker to translate evidence of the efficacy and safety of the non-steroidal mineralocorticoid receptor antagonist (nsMRA) finerenone from populations with CKD in T2D to those with CKD in T1D. We compare the FINE-ONE trial (NCT05901831) population (patients with CKD and T1D) with a CKD and T2D population {FIDELITY; a prespecified pooled analysis of two large phase 3 clinical trials [FIDELIO-DKD (NCT02540993) and [FIGARO-DKD (NCT02545049)]} receiving optimized doses of ACEi or angiotensin receptor blocker (ARB) therapy in which finerenone has demonstrated significant reductions in CKD progression and CV events with a manageable safety profile.

CKD IN PEOPLE WITH T1D

Prevalence and risk factors

Several new studies have recently been published, providing details on the prevalence of CKD in people with T1D. Among these, a study of >23 000 individuals with T1D in a US clinical registry reported that 27.1% had CKD [3]. Higher risks of developing CKD were noted among females, older adults, people in certain ethnic and racial groups (such as African Americans, Asians and Pacific Islanders) and people with underlying CV disease [3]. Additionally, a study based on data from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications cohort showed that in people with T1D, higher long-term cumulative glycaemic exposure [as measured by updated mean glycated haemoglobin (HbA1c)] and male sex were independently associated with incident macroalbuminuria [10]. Furthermore, an analysis from the US National Health and Nutrition Examination Survey concluded that CKD is common in people with T1D, with a conservative estimated prevalence of 21.5% (weighted to reflect the population distribution in the USA) [11].

CKD and diabetes independently increase the risk of CV disease outcomes [12]. Although this is well recognized in T2D, registry studies showed that CV disease rates are similarly high in adults with T1D. For example, a Scandinavian observational study including ≈540 000 individuals found similarly high rates of CV disease in T1D and T2D across different age ranges [13]. Interestingly, a French study of ≈500 000 hospitalized individuals reported a lower crude prevalent burden of CV diseases in those with T1D compared with T2D; however, rates for both T1D and T2D increased with advancing age, and at middle to older ages the risk of incident CV diseases was higher in individuals with T1D [14]. This was also reported in a prospective cohort study of ≈19 000 middle-aged and older adults with diabetes in the UK, where those with T1D had a higher incidence of cardio-kidney outcomes than those with T2D [15].

Pathophysiology: differences and similarities versus T2D

Hyperglycaemia and hypertension are key risk factors for CKD development and progression in both T1D and T2D [2]. Together, these factors contribute to driving inflammation and fibrosis, leading to cellular hypertrophy and proliferation, extracellular matrix expansion, glomerulosclerosis, tubulo-interstitial damage and albuminuria [16]. MR overactivation is a key part of this process, because it upregulates expression of genes associated with inflammation and fibrosis in the kidney and heart [17, 18]. An overview of these processes at the cellular and tissue levels is shown in Fig. 1.

While there are clinical similarities between CKD in T1D and T2D, the morphology of the lesions that impact kidney function may differ. In T1D, the glomeruli are predominantly affected, resulting in thickening of the glomerular basement membrane and mesangial expansion [19]. Podocyte loss and tubulo-interstitial damage are also frequently observed, along with changes in the arterioles, which are associated with glomerulosclerosis [19]. The degree of structural lesions and kidney tissue abnormalities vary within and between patients. In patients with T2D, the same tissue structure alterations can be involved in the disease pathophysiology, but with a higher level of complexity. Biopsy studies have demonstrated a greater heterogeneity in the underlying kidney pathophysiology in people with T2D compared with the typical patterns of CKD often associated with T1D [19]. Indeed, when comparing T1D and T2D populations with similar CKD characteristics, disease duration is often much longer in T1D than T2D. This suggests either a different rate of kidney damage or involvement of other factors such as inflammation associated with T2D or higher blood pressure [20]. Nevertheless, irrespective of the precise pathophysiology of kidney disease in T1D and T2D, albuminuria remains a hallmark of the disease and a strong risk marker of adverse kidney and CV outcomes in both T1D and T2D [9].

Albuminuria: a common manifestation of CKD in T1D and T2D

Albuminuria is a common manifestation of kidney disease in people with diabetes. Current guidelines recommend screening and monitoring of UACR to identify CKD early, and treatments that reduce UACR should be initiated to slow CKD progression [5]. The cause of albuminuria in CKD is probably multifactorial and appears to be the same in T1D and T2D. The glycocalyx, an important part of the vascular permeability barrier, is damaged by hyperglycaemia, leading to albumin leakage across the glomerular capillaries and subsequently into the urine [21]. Tubulo-interstitial damage (resulting from fibrotic and inflammatory processes; Fig. 1) reduces the capacity for albumin reabsorption in the proximal tubule [22]. Additionally, exposure to albumin is toxic to proximal tubular epithelial cells, exacerbating

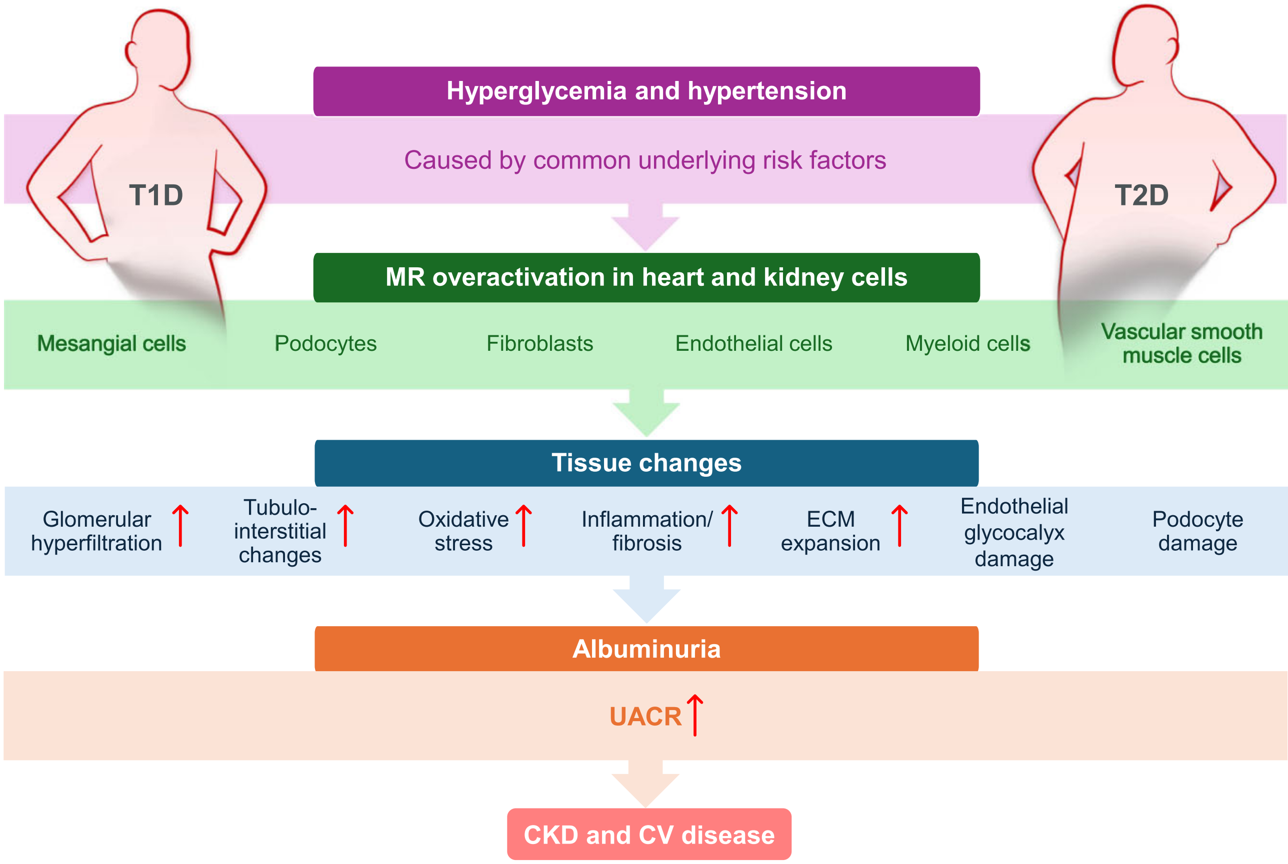

Figure 1: Role of MRA activation in the pathophysiology of CKD in T1D and T2D. ECM: extracellular matrix. Figure based on Heerspink HJL et al. *Diabetes Res Clin Pract* 2023;204:110908. https://creativecommons.org/licenses/by/4.0/. [27].

tubulo-interstitial fibrosis [23], further reducing kidney function. Thus albuminuria predicts CKD progression and does so in a similar fashion in both T1D and T2D.

TREATMENT OF CKD IN T1D AND T2D

There has been significant progress in the management of CKD in people with T2D, with three new drug classes shown to reduce cardio-kidney risk. These include nsMRAs, sodium–glucose co-transporter-2 inhibitors (SGLT-2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs). Over the past 5 years the clinical benefits of these agents have been demonstrated on top of existing treatments, including RAS inhibitors [4, 5, 24].

The nsMRA finerenone significantly reduced adverse kidney and CV outcomes compared with placebo in FIDELITY [25]. The relative risk reduction of the composite kidney outcome (time to first onset of kidney failure, sustained ≥57% eGFR decline from baseline over ≥4 weeks or kidney-related death) was 24%; components of kidney failure including end-stage kidney disease (ESKD; chronic dialysis for ≥90 days) or kidney transplantation and sustained eGFR decline to <15 ml/min/1.73 m^2 were significantly lower with finerenone than placebo. The composite CV outcome (time to CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for heart failure) was reduced by 14% [25]. Furthermore, finerenone lowered UACR from baseline to 4 months by 32% versus placebo, an improvement that persisted throughout the trials [25]. Subsequent analyses revealed that the reduction in albuminuria explained 84–87% of the benefit of finerenone in reducing the risk of the kidney composite outcomes and 37% of its effect on the CV composite outcome, suggesting early reduction in albuminuria as an important indicator of the long-term benefit of finerenone [26, 27].

Regarding SGLT-2is and GLP-1RAs, similar kidney and CV benefits in people with CKD and T2D were also reported in clinical trials. In the CREDENCE trial (NCT02065791), canagliflozin reduced the risk of the primary composite kidney endpoint (ESKD, sustained doubling of serum creatinine from baseline for ≥30 days or death from renal or CV disease) by 30% versus placebo in participants with CKD and T2D [28]. In the DAPA-CKD trial (NCT03036150), where 68% of participants had CKD and T2D, dapagliflozin reduced the composite cardio-kidney endpoint (sustained ≥50% eGFR decline, ESKD or kidney/CV death) by 36% in this subpopulation [29]. In EMPA-KIDNEY trial (NCT03594110), there was a 28% reduction in the risk of kidney disease progression or CV death with empagliflozin in people with CKD, 44% of whom had T2D [30]. More recently, the FLOW trial (NCT03819153) found that the GLP-1RA semaglutide reduced the primary composite outcome (onset of kidney failure, sustained ≥50% reduction in eGFR from baseline or death from kidney or CV causes) by 24% in people with T2D and CKD [24].

Despite recent findings in the CKD population, the lack of new therapies for people with T1D contrasts sharply with innovations in clinical management for people with T2D. No new drugs to slow CKD progression in T1D have become available since the landmark Collaborative Study Group Captopril Trial, which demonstrated that improved glycaemic control and treatment with captopril reduced both eGFR decline and the risk of progression to kidney failure [6]. Since then, few trials have focused on therapeutic advancements for this population, with the most recent trial, Preventing Early Renal Function Loss, demonstrating no benefit for allopurinol treatment on kidney outcomes in people with CKD and T1D [31]. Neither SGLT-2is nor GLP-1RAs are currently recommended for use in people with T1D for glucose lowering, and neither class has been thoroughly tested in the T1D population for CV or kidney outcomes. Although SGLT-2is are indicated in the USA for treatment of CKD irrespective of diabetes status, they are not currently recommended for glucose lowering in T1D due to safety concerns [32, 33]. As a result, RAS blockade and glycaemic control with insulin (along with risk factor optimization) remain the only recommended medical strategies for reducing the risk of adverse kidney events. However, additional risk remains, particularly among individuals with persistently high albuminuria [8, 34], highlighting the need for new trials and therapies to reduce the risk of kidney disease progression in people with CKD and T1D.

ROLE OF BRIDGING BIOMARKERS

Translating evidence from clinical trials

The use of bridging biomarkers can extend the availability of therapies that have been evaluated and approved in one population to another in cases where it may be challenging to conduct large clinical trials [35]. It also addresses the ethical problem of conducting unnecessary clinical trials and delaying therapy to those who would benefit. Biomarkers can be accepted for use as drug development tools to support regulatory approval if certain conditions are met [36]. However, a bridging biomarker can only be used to extrapolate evidence between populations if it is a valid surrogate endpoint (i.e. supported by strong mechanistic evidence and correlated with patient outcomes). Furthermore, patient characteristics and expected responses to the drug must be sufficiently similar in both populations [35]. Extrapolation of therapeutic benefit from one population to another also relies on established safety of the approved treatment and a reasonable expectation that the safety profile will be similar in the target population. Ensuring comparability between populations in studies using bridging biomarkers will enable high confidence that clinical benefit can be reliably translated and justify the extrapolation of evidence.

Albuminuria as a bridging biomarker in CKD

In CKD, bridging biomarkers may be useful for translating the wealth of evidence from the T2D population to the T1D population because, once established, CKD progression is strikingly similar in both diabetes types. Analyses from observational studies and clinical trials have shown that albuminuria is a valid surrogate endpoint for future clinical trials, suggesting that it may also be a useful bridging biomarker. In a global participant-level meta-analysis of >27 million individuals in 114 cohorts, severe albuminuria was associated with kidney failure, kidney replacement therapy, CV mortality, heart failure and atrial fibrillation, and the association was evident in people with diabetes [37]. Other studies have shown that the risk relationship between albuminuria and cardio-kidney outcomes is similar in T1D and T2D. In both populations, those with macroalbuminuria had a comparable rate of loss of eGFR [38]. In people with T1D, the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study reported worsening cardio-kidney outcomes as albuminuria advanced [39]. Changes in albuminuria over time have also been associated with the risk of subsequent cardio-kidney outcomes. In a study of almost 700 000 individuals with albuminuria data (80% of whom had diabetes), increases in albuminuria over 1, 2 or 3 years were linearly associated with an increased risk of kidney failure and CV outcomes [40]. The association was similar regardless of individuals' diabetes status. Additionally, an observational analysis of >10 000 individuals with diabetes reported elevated risks of CV events, CV mortality and kidney events as UACR increased [41].

Importantly, therapeutic lowering of albuminuria is strongly associated with improved kidney outcomes in people with diabetes and CKD [42]. Among people with T1D in the Collaborative Study Group trial of captopril, treatment with captopril reduced albuminuria within 3 months of initiation and reductions were sustained throughout the trial, with significant reductions reported over 4 years [6]. In the same trial, captopril reduced the risk of kidney outcomes, including death, dialysis or transplantation, by 50%. Trials investigating RAS blockade in people with T2D and CKD reported similar results. The RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan) trial reported reductions in both proteinuria and the rate of kidney function decline with losartan compared with placebo [43], and the Irbesartan Diabetic Nephropathy Trial reported significantly reduced proteinuria compared with placebo as well as a reduced risk of kidney outcomes with irbesartan versus placebo [44]. In a meta-analysis of 41 randomized controlled clinical trials, early treatment effects on albuminuria were associated with lower risks of established kidney outcomes. The same meta-analysis also showed that therapies that reduced albuminuria by 20–30% during the first 6 months of treatment were associated with a high likelihood of reducing the risk of clinical kidney outcomes during long-term treatment [45].

However, safety is an important consideration when evaluating albuminuria as a bridging biomarker in CKD, because some therapies that improve albuminuria may have side effects in the new population that did not occur in the original population. For example, a meta-analysis of SGLT-2i use in individuals with T1D reported UACR reductions of 23% [46], which is similar to those reported in people with T2D, but increased risks of diabetic ketoacidosis, including euglycaemic ketoacidosis, have been reported in SGLT-2i trials in the T1D population [47]. For finerenone, current evidence shows that UACR reduction explains a substantial part of its benefit on kidney outcomes in T2D [26], without impacting glucose levels or inducing side effects that would pose greater risks to T1D versus T2D populations.

THE FINE-ONE TRIAL: FINERENONE FOR CKD AND T1D USING ALBUMINURIA AS A BRIDGING BIOMARKER

The FINE-ONE trial was designed to use albuminuria as a clinical trial endpoint and bridging biomarker to translate evidence from T2D to T1D. The aim is to assess the change in UACR from baseline over 6 months along with safety [27]. Adults (≥18 years of age) with CKD (UACR 200–<5000 mg/g and eGFR 25–<90 ml/min/1.73 m^2), T1D (HbA1c <10%) and serum potassium ≤4.8 mmol/l who were receiving stable ACEi or ARB therapy could participate. Eligible adults ($N = 242$) were randomized 1:1 to finerenone 10 or 20 mg once daily (participants with eGFR <60 ml/min/1.73 m^2 were initiated on the lower dose with the opportunity to up-titrate after 4 weeks) or placebo (Fig. 2) [27].

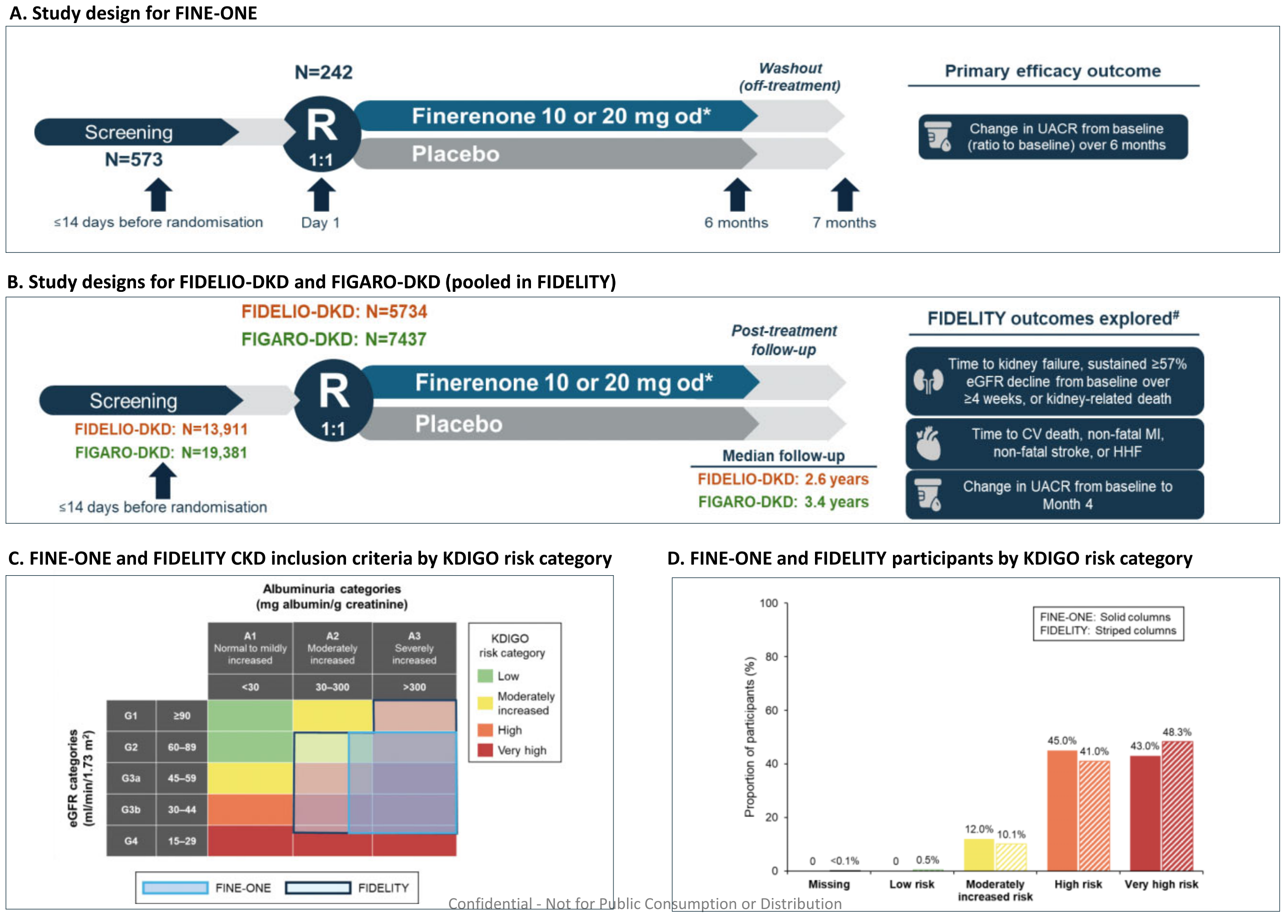

Figure 2: FINE-ONE and FIDELITY study designs and baseline KDIGO risk categories. CKD was defined as UACR 200–<5000 mg/g and eGFR 25–<90 ml/min/1.73 m^2 in FINE-ONE and UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m^2 or UACR 300–≤5000 mg/g and eGFR ≥25 ml/min/1.73 m^2 in FIDELITY. Six participants in FIDELITY had missing values (one missing eGFR only, three missing UACR only and two missing both eGFR and UACR. *Starting dose 10 mg/day for participants with eGFR ≥25–<60 ml/min/1.73 m^2 and 20 mg/day for participants with eGFR ≥60 ml/min/1.73 m^2. #Other prespecified outcomes included time to first occurrence of kidney failure, sustained ≥40% decrease in eGFR from baseline over ≥4 weeks, or kidney-related death; time to all-cause mortality; and time to all-cause hospitalization. HHF: hospitalization for heart failure; KDIGO: Kidney Disease: Improving Global Outcomes; MI: myocardial infarction; R: randomization.

Comparing FINE-ONE and FIDELITY populations at baseline

Table 1 summarizes study details of the FINE-ONE trial and FIDELITY pooled analysis. Recruitment for FINE-ONE was completed in February 2025. Participant baseline characteristics of the FINE-ONE and FIDELITY cohorts are presented in Table 2. These data show that participants in FINE-ONE and FIDELITY had comparable kidney function at baseline, as demonstrated by similar mean eGFR (58.8 and 57.6 ml/min/1.73 m^2, respectively) and median UACR (549.0 and 515.1 mg/g, respectively). The percentage of participants with moderate, high and very high cardio-kidney risk, as predicted by the Kidney Disease: Improving Global Outcomes (KDIGO) heat map [4], were similar, with most participants having high or very high risk at baseline (88.0% of FINE-ONE participants and 89.3% of FIDELITY participants) (Fig. 2). More than a quarter of participants in both the FINE-ONE and FIDELITY populations had UACR levels >1000 mg/g at baseline, indicating that a substantial proportion of both populations (CKD with T1D and T2D) were at high risk of CKD progression.

One key difference between the FINE-ONE and FIDELITY populations was the duration of diabetes (32.0 versus 15.4 years, respectively). Nevertheless, baseline HbA1c values were similar in the two populations (7.6% in FINE-ONE versus 7.7% in FIDELITY) and similar proportions had an HbA1c >7.5% (47.6% versus 48.3%, respectively), indicating similar levels of diabetes severity and/or control. One possible cause for the difference in disease duration is that T2D progresses gradually over time, often going undiagnosed in the early stages of the disease [1]. Additionally, T1D is typically diagnosed at a young age, often in childhood, when the risk of kidney complications is lower. Over time, however, albuminuria becomes a more common finding among people with T1D. A study of registry data from almost 80 000 adults with T1D reported that approximately one-tenth of people with a diabetes duration <20 years had albuminuria, whereas approximately one-third had developed albuminuria after 40 years [48]. The prevalence of CKD in people with T1D thus remains high [3], emphasizing the need for therapies that protect the kidneys in addition to optimal glycaemic control and RAS inhibition.

A lower proportion of FINE-ONE participants had a history of CV disease at baseline compared with FIDELITY participants (24.4% versus 45.6%, respectively). This is likely due to the lower mean age in the FINE-ONE trial compared with FIDELITY. The lower prevalence of CV disease may have contributed to a lower use of CV disease–related therapies such as beta blockers,

Table 1: Study details of FINE-ONE and FIDELITY.

Characteristics	FINE-ONE (N = 242)	FIDELITY (N = 12 990)
Study design	Phase 3, randomized, double-blind, placebo-controlled, multicentre clinical trial	Pooled analysis of two phase 3, randomized, double-blind, placebo-controlled, multicentre clinical trials
Inclusion criteria	• Age ≥18 years (or legal age of consent according to local legislation) • Type 1 diabetes (continuously treated with insulin, started ≤1 year from diagnosis) • HbA1c at screening <10.0% • UACR ≥200–<5000 mg/g • eGFR ≥25–<90 ml/min/1.73 m^2 • On a stable dose of ACEi or ARB • Serum potassium level ≤4.8 mmol/l	• Age ≥18 years • Type 2 diabetes • UACR 30–<300 mg/g and eGFR 25–≤90 ml/min/1.73 m^2, or UACR 300–≤5000 mg/g and eGFR ≥25 ml/min/1.73 m^2 • Maximum tolerated dose of ACEi or ARB • Serum potassium level ≤4.8 mmol/l
Exclusion criteria	• Type 2 diabetes • Other known causes of CKD than type 1 diabetes • Kidney transplantation • Mean BP >160/100 mmHg or mean systolic BP <90 mmHg at screening • Hospitalization due to a CV event ≤4 weeks prior to screening • Symptomatic heart failure with reduced ejection fraction with class 1A indications for MRAs • Current or previous (≤8 weeks prior to screening) treatment with a SGLT-2/1i or GLP-1RA	• Non-diabetic kidney disease • Uncontrolled hypertension • HbA1c >12% • Mean BP ≥160/≥100 mmHg, or mean SBP <90 mmHg at screening • Chronic symptomatic heart failure with reduced ejection fraction • Recent CV event • Dialysis for acute kidney failure

BP: blood pressure; SGLT-2/1i: sodium–glucose co-transporter-2/-1 inhibitor.

diuretics and platelet inhibitors in the FINE-ONE trial. However, statin use was similarly high in the two populations (73.6% versus 72.3%, respectively), which may reflect broad recommendations for their use according to international treatment guidelines. The American Diabetes Association and European Association for the Study of Diabetes recommend statin use for primary prevention of CV disease in all people with diabetes >40 years of age as well as for secondary prevention of CV events in people with diabetes and established CV disease [49, 50].

MRAs are associated with an increased risk of hyperkalaemia versus placebo [51]. In the Benefits of Aldosterone Receptor Antagonism in Chronic Kidney Disease (BARACK-D) trial, for example, 8% of participants (individuals with stage 3b CKD) treated with the MRA spironolactone ($n = 677$) withdrew from treatment within 6 months for hyperkalaemia-related reasons [52]. Compared with steroidal MRAs, which are not recommended for use in CKD [4], finerenone (an nsMRA) has a higher selectivity for the MR, shorter half-life and more balanced tissue distribution in the kidneys and heart [51]. While hyperkalaemia risk remains greater with finerenone than with placebo, it is clinically manageable. In the FIDELITY analysis, potassium levels ≤4.8 mmol/l were required for inclusion in each of the trials and were monitored throughout the trials—the incidence of hyperkalaemia-related discontinuations or hospitalizations was low [25]. Safety assessment in the FINE-ONE trial includes hyperkalaemia monitoring, allowing comparison of early changes in potassium. At baseline, potassium levels were clinically similar between the FINE-ONE and FIDELITY cohorts (4.6 versus 4.4 mmol/l, respectively). Given the similarities in kidney function and baseline serum potassium levels between the FINE-ONE and FIDELITY cohorts, the overall adverse event rates by patient-years are anticipated to be comparable between the two populations. Consequently, the likelihood of new or increased adverse effects in participants with CKD and T1D is expected to be low.

The follow-up duration in the FINE-ONE trial is 6 months, meaning that the trial cannot assess the long-term effect of finerenone on UACR and its impact on CV and kidney outcomes. However, as described earlier, a post hoc FIDELITY analysis showed that >80% of the kidney benefit of finerenone is explained by a UACR reduction within 4 months of treatment initiation [26]. Similar mediation results were observed in a more restricted analysis including only participants with the same inclusion criteria as the FINE-ONE trial (UACR ≥200–<5000 mg/g and eGFR 25–<90 ml/min/1.73 m^2) [27]. Notably, the American Diabetes Association guideline recommends reducing albuminuria by ≥30% in people with CKD and albuminuria levels ≥300 mg/g to slow CKD progression [5]. This recommendation is relevant for the T1D population as recruited in the FINE-ONE trial, in which 74% of participants have a UACR ≥300 mg/g at baseline. This suggests that an early UACR reduction after 6 months of finerenone treatment in FINE-ONE will likely translate into longer-term clinical benefits on kidney outcomes. Additionally, albuminuria is associated with increased CV risk, and UACR reductions have been associated with lower risks of CV events [53]. Assuming finerenone has similar albuminuria-lowering effects in T1D and T2D, the similarities evident in the FINE-ONE and FIDELITY populations at baseline support efficacy comparisons between the two populations in accordance with the bridging biomarker concept.

CONCLUSIONS AND FUTURE DIRECTIONS

While the pathophysiological mechanisms associated with CKD in T1D and T2D are similar, there is a stark difference between the availability of therapeutic options for these two populations. Given the comparable CKD pathophysiology and cardio-kidney risks, improving kidney and CV outcomes in people with CKD and T1D may require a more intensive, multifactorial therapeutic approach, similar to that recommended for T2D. This should involve

Table 2: Baseline characteristics and measurements (clinical and biochemical) in FINE-ONE and FIDELITY.

Characteristics	FINE-ONE (*N* = 242)	FIDELITY (*N* = 12 990)
Age (years), mean ± SD	51.6 ± 13.7	64.8 ± 9.5
Male, *n* (%)	158 (65.3)	9058 (69.7)
Race, *n* (%)		
White	173 (71.5)	8869 (68.3)
Black/African American	15 (6.2)	520 (4.0)
Asian	48 (19.8)	2860 (22.0)
Other[a]	6 (2.5)	741 (5.7)
Region, *n* (%)		
Europe	120 (49.6)	5862 (45.1)
North America	83 (34.3)	2049 (15.8)
Asia	39 (16.1)	3170 (24.4)
Latin America	–	1434 (11.0)
Other[b]	–	475 (3.7)
Weight (kg), mean ± SD	80.7 ± 20.8	88.1 ± 20.1
BMI (kg/m^2), mean ± SD	27.6 ± 6.0	31.3 ± 6.0
Medical history		
Duration of diabetes (years), mean ± SD	32.0 ± 14.2	15.4 ± 8.7
History of CVD[c], *n* (%)	59 (24.4)	5928 (45.6)
History of hypertension, *n* (%)	207 (85.5)	12 531 (96.5)
Medication use[d], *n* (%)		
ACEi	112 (46.3)	5076 (39.1)
ARBs	128 (52.9)	7904 (60.8)
Diuretics	87 (36.0)	6701 (51.6)
Beta blockers	66 (27.3)	6499 (50.0)
Statins	178 (73.6)	9387 (72.3)
Platelet aggregation inhibitors[e]	76 (31.4)	7296 (56.2)
Clinical measurements		
Systolic blood pressure (mmHg), mean ± SD	135.2 ± 16.7	136.8 ± 14.2
Diastolic blood pressure (mmHg), mean ± SD	77.5 ± 10.8	76.4 ± 9.6
Biochemical measurements		
HbA1c (%), mean ± SD[f]	7.6 ± 1.1	7.7 ± 1.4
HbA1c category (%), *n* (%)[f]		
≤7.5	124 (51.2)	6696 (51.5)
>7.5	116 (47.9)	6272 (48.3)
UACR (mg/g), median (IQR)	549.0 (298.8–1190.7)	515.1 (198.1–1148.3)
UACR category (mg/g) *n* (%)[g]		
<300	63 (26.0)	4311 (33.2)
≥300–1000	113 (46.7)	4871 (37.5)
>1000	66 (27.3)	3803 (29.3)
eGFR (ml/min/1.73 m^2), mean ± SD	58.8 ± 19.1	57.6 ± 21.7
eGFR category (ml/min/1.73 m^2), *n* (%)[h]		
<25	5 (2.1)	162 (1.2)
25–<45	58 (24.0)	4224 (32.5)
45–<60	62 (25.6)	3426 (26.4)
60–<90	107 (44.2)	3857 (29.7)
≥90	10 (4.1)	1318 (10.1)
Serum potassium (mmol/l), mean ± SD	4.6 ± 0.4	4.4 ± 0.4

[a] American Indian or Alaska native, Hawaiian or other Pacific Islander or not reported or multiple.
[b] Australia, New Zealand or South Africa.
[c] History of CVD was determined by the presence of one of the following in the medical history: myocardial infarction, coronary artery stenosis, cerebrovascular accident, transient ischaemic attack, peripheral arterial occlusive disease or cardiac failure.
[d] Use of SGLT-2is and GLP-1RAs was not permitted in the FINE-ONE trial.
[e] Excluding heparin.
[f] Values missing for 2 FINE-ONE and 22 FIDELITY participants.
[g] Values missing for five FIDELITY participants.
[h] Values missing for three FIDELITY participants.
BMI: body mass index; CVD: cardiovascular disease; IQR: interquartile range; SD: standard deviation.

both further research to reveal new therapeutic targets in T1D and repurposing of current drugs. Trials like FINE-ONE provide an opportunity to address CKD in the T1D population by allowing clinical findings from people with T2D to be translated to T1D.

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AUTHORS' CONTRIBUTIONS

H.J.L.H. and J.B.M. contributed to the conception, design and acquisition of data or analysis in conjunction with the sponsor and wrote the initial draft of the manuscript. All authors contributed to and were involved in the critical revision of the report for important intellectual content and assume responsibility for the integrity of the report. All authors reviewed and approved the final submitted version.

DATA AVAILABILITY STATEMENT

Availability of the data underlying this publication will be determined according to Bayer's commitment to the European Federation of Pharmaceutical Industries and Associations/Pharmaceutical Research and Manufacturers of America 'Principles for responsible clinical trial data sharing'. This pertains to scope, time point and process of data access. As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the USA and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after 1 January 2014. Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal. Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

CONFLICT OF INTEREST STATEMENT

H.J.L.H. reports consulting fees from Alexion, AstraZeneca, Bayer, Boehringer Ingelheim, BioCity Pharmaceuticals, Dimerix, Eli Lilly, Novartis, Novo Nordisk, Roche and Travere Therapeutics; research support from AstraZeneca, Boehringer Ingelheim, Janssen and Novo Nordisk; honoraria from AstraZeneca and Novo Nordisk and travel expenses from AstraZeneca and Eli Lilly. R.A. reports personal fees and non-financial support from Bayer Healthcare Pharmaceuticals during the conduct of the study and personal fees and non-financial support from Akebia Therapeutics, AstraZeneca, Bayer and Boehringer Ingelheim; he is a member of data safety monitoring committees for Chinook, Eloxx and Vertex; is a member of adjudication committees for Alnylam and Intercept Pharma; has served as Associate Editor of the *American Journal of Nephrology* and *Nephrology Dialysis Transplantation*; has been an author for *UpToDate* and has received research grants from the U.S. Veterans Administration and the National Institutes of Health. A.J.A. reports lecture fees from AstraZeneca, Eli Lilly, Medtronic, Merck, Novo Nordisk and Sanofi and travel expenses from Eli Lilly, Novo Nordisk and Sanofi. J.N.B. reports consulting fees from AstraZeneca and Bayer. D.Z.I.C. reports institutional grant funding from AstraZeneca, Boehringer Ingelheim, CSL Behring, Eli Lilly, Janssen, Merck, Novo Nordisk and Sanofi and consultancy fees and honoraria from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, CSL Behring, Eli Lilly, Gilead, Janssen, Lexicon, Maze, Merck, Mitsubishi-Tanabe, Novartis, Novo Nordisk, Otsuka, Prometic, Sanofi and Youngene Therapeutics. P.F. reports a leadership or fiduciary role in the Italian Society of Diabetes and consultancy fees and honoraria from AstraZeneca, Boehringer Ingelheim, Novo Nordisk, Eli Lilly, Enthera, Nephris, Amgen, Sanofi and Altheia Pharma. P.R. reports personal fees from Bayer during the conduct of the study; research support and personal fees from AstraZeneca and Novo Nordisk and personal fees from Abbott, Astellas, Boehringer Ingelheim, Eli Lilly, Gilead, Mundipharma, Sanofi and Vifor; all fees are given to Steno Diabetes Center Copenhagen. K.S. reports personal advisory fees from Boehringer, Novo Nordisk and Sanofi. N.M.S. reports consulting fees from Guard Therapeutics and SERB Pharmaceuticals. S.D.A. reports research support from Abbott Vascular and Vifor Pharma and personal fees from Abbott Vascular, Bayer, Boehringer Ingelheim, BRAHMS, Cardiac Dimensions, Impulse Dynamics, Novartis, Servier and Vifor Pharma. G.F. reports lecture fees and/or advisory fees and/or that he is a committee member of trials and registries sponsored by Amgen, Bayer, Boehringer Ingelheim, Medtronic, Merck, Novartis, Novo Nordisk, Servier and Vifor Pharma and has received research support from the European Union. B.P. reports consultant fees for Ardelyx, AstraZeneca, Bayer, Boehringer Ingelheim, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Phasebio, Sanofi/Lexicon, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and Vifor/Relypsa; has stock options for Ardelyx, Brainstorm Medical, Cereno Scientific, G3 Pharmaceuticals, KBP Biosciences, Sarfez, scPharmaceuticals, SQ Innovation, Tricida and Vifor/Relypsa; and holds a patent for site-specific delivery of eplerenone to the myocardium (U.S. patent 9931412) and a provisional patent for histone-acetylation-modulating agents for the treatment and prevention of organ injury (U.S. provisional patent 63/045,784). L.M.R. reports consultant fees from Bayer. R.L., M.B., J.R. and P.S. are employees of Bayer. J.B.M. reports personal fees from Bayer and MannKind and research support from Biomea, Diamyd and Lexicon.

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