Clinical Kidney Journal, 2023, vol. 16, no. 11, 2032–2040

https://doi.org/10.1093/ckj/sfad194
Advance Access Publication Date: 1 September 2023
Original Article

ORIGINAL ARTICLE

Cardiovascular risk due to diabetes mellitus in patients with chronic kidney disease—prospective data from the German Chronic Kidney Disease cohort

Johannes Ruhe[1], Jennifer Nadal[2], Barbara Bärthlein[3], Heike Meiselbach[4], Ulla T. Schultheiss[5,6], Fruzsina Kotsis[5,6], Helena Stockmann[7], Vera Krane[8], Claudia Sommerer[9], Ivonne Löffler[1], Turgay Saritas[10], Jan T. Kielstein[11], Thomas Sitter[12], Markus P. Schneider[4], Matthias Schmid[2], Christoph Wanner[8], Kai-Uwe Eckardt[4,7], Gunter Wolf[1] and Martin Busch[1]

[1]Department of Internal Medicine III, Nephrology, University Hospital Jena – Friedrich Schiller University, Jena, Germany, [2]Department of Medical Biometry, Informatics, and Epidemiology, University Hospital Bonn, Bonn, Germany, [3]Medical Centre for Information and Communication Technology, University Hospital Erlangen, Erlangen, Germany, [4]Department of Nephrology and Hypertension, University Hospital Erlangen, Friedrich-Alexander University Erlangen-Nürnberg, Erlangen, Germany, [5]Institute of Genetic Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, [6]Department of Medicine IV-Nephrology and Primary Care, Faculty of Medicine and Medical Center, University of Freiburg, Freiburg, Germany, [7]Department of Nephrology and Medical Intensive Care, Charité-Universitätsmedizin Berlin, Berlin, Germany, [8]Division of Nephrology, Department of Medicine I, University Hospital Würzburg, Würzburg, Germany, [9]Nephrology Unit, University Hospital Heidelberg, Heidelberg, Germany, [10]Division of Nephrology and Clinical Immunology, University Hospital RWTH Aachen, Aachen, Germany, [11]Medical Clinic V Nephrology, Rheumatology, Blood Purification – Academic Teaching Hospital Braunschweig, Braunschweig, Germany and [12]Department of Medicine, Ludwig-Maximilians-University Hospital Munich, Munich, Germany

Correspondence to: Martin Busch; E-mail: martin.busch@med.uni-jena.de

ABSTRACT

Background. Diabetes mellitus (DM) and chronic kidney disease (CKD) are well-known cardiovascular and mortality risk factors. To what extent they act in an additive manner and whether the etiology of CKD modifies the risk is uncertain.
Methods. The multicenter, prospective, observational German Chronic Kidney Disease study comprises 5217 participants (1868 with DM) with a baseline mean estimated glomerular filtration rate of 30–60 mL/min/1.73 m^2 and/or proteinuria >0.5 g/day. We categorized patients whose CKD was caused by cardiovascular or metabolic diseases (CKDcvm) with and without DM, as opposed to genuine CKD (CKDgen) with and without DM. Recorded outcomes were first events of non-cardiovascular and cardiovascular death, 4-point major adverse cardiovascular events (4-point MACE) and hospitalization for heart failure (HHF).

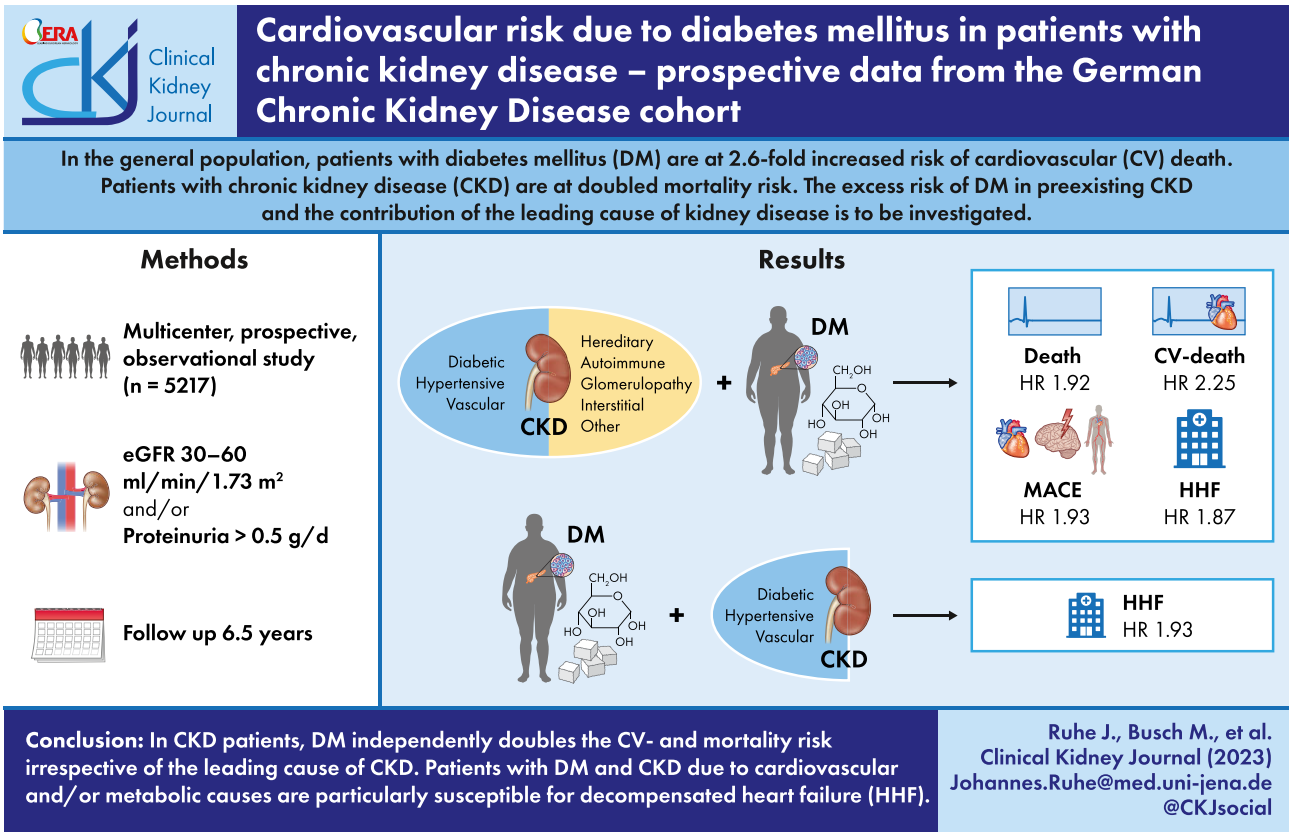
Received: 31.5.2023; Editorial decision: 3.7.2023

Results. During the 6.5-year follow-up 603 (12%) non-cardiovascular and 209 (4%) cardiovascular deaths, 645 (12%) 4-point MACE, and 398 (8%) HHF were observed, most frequently in patients with DM having CKDcvm. DM increased the risk of non-cardiovascular [hazard ratio (HR) 1.92; 95% confidence interval (CI) 1.59–2.32] and cardiovascular (HR 2.25; 95% CI 1.62–3.12) deaths, 4-point MACE (HR 1.93; 95% CI 1.62–2.31) and HHF (HR 1.87; 95% CI 1.48–2.36). Mortality risks were elevated by DM to a similar extent in CKDcvm and CKDgen, but for HHF in CKDcvm only (HR 2.07; 95% CI 1.55–2.77). In patients with DM, CKDcvm (versus CKDgen) only increased the risk for HHF (HR 1.93; 95% CI 1.15–3.22).
Conclusions. DM contributes to cardiovascular and mortality excess risk in patients with moderate to severe CKD in both, CKDcvm and CKDgen. Patients with DM and CKDcvm are particularly susceptible to HHF.

LAY SUMMARY

Chronic kidney disease (CKD) and diabetes mellitus (DM) are frequent comorbidities. DM increases both cardiovascular and mortality risk, however the level of additional risk in patients with preexisting CKD is controversial. In this large multicenter, prospective, observational study of patients with moderate to severe CKD, DM doubled the cardiovascular and non-cardiovascular mortality risk, and furthermore increased the risk for major adverse cardiac events and symptomatic heart failure requiring hospitalization. The additional risk of DM on investigated mortality endpoints in CKD patients is similar to that in patients without CKD according to previously published data. Moreover, diabetic patients with CKD due to cardiovascular and/or metabolic causes (e.g. diabetes or hypertension-related CKD) were particularly susceptible for hospitalization for heart failure.

GRAPHICAL ABSTRACT



Keywords: cardiometabolic kidney disease, cardiovascular risk, chronic kidney disease, diabetes mellitus, diabetic kidney disease

INTRODUCTION

Environmental and demographic changes have led to an increasing number of patients with diabetes mellitus (DM) [1]. In parallel, the global prevalence of patients with chronic kidney disease (CKD) is also rising, with estimates among adults currently already at 10%–13% [2]. Diabetic kidney disease (DKD), i.e. CKD caused by DM, represents one of the main complications of DM and is currently the leading cause of kidney failure [3–5].

Patients with CKD are more likely to develop concomitant cardiovascular diseases (65% versus 32%) [6] and have a doubled mortality risk [7]. Likewise, adults with DM have an up to 6-fold increased relative risk for cardiovascular-associated morbidity and the death rates attributed to cardiovascular disease are up to 2.6-times higher [8–11]. DM complicated by CKD was found to be associated with higher rates of myocardial infarction (MI) and all-cause mortality compared with DM alone [12]. In contrast, no significant affection of the all-cause mortality could be detected when CKD patients with DM were compared with CKD patients with equal estimated glomerular filtration rate (eGFR) or albuminuria without DM [13]. It remains uncertain to what extent CKD and DM confer additive risks for cardiovascular disease, as they are frequent comorbidities.

This study aims to describe the impact of DM on the increased risk of cardiovascular disease and mortality observed in patients with moderate to severe CKD [14]. In order to elucidate the influence of the etiology of CKD, further analyses were performed separately for patients whose leading causes of CKD are cardiovascular or metabolic disorders including diabetes (CKDcvm) as opposed to genuine causes of CKD such as autoimmune or genetic diseases (CKDgen).

MATERIALS AND METHODS

Study population and design

The German Chronic Kidney Disease (GCKD) study is a prospective, multicenter, observational cohort study of participants with moderate to severe CKD. The study design and baseline were described previously [14, 15]. Local ethics committees approved the study and registered in the national registry of clinical studies (DRKS 00003971). Written informed consent was obtained from all participants. Briefly, the study included 5217 participants under regular nephrological care aged 18–74 years with an eGFR of 30–60 mL/min/1.73 m^2 (according to the 4-variable Modification of Diet in Renal Disease formula) and/or proteinuria >0.5 g/day (or equivalent measures). Main exclusion criteria were non-Caucasian ethnicity, the presence of active malignant disease, New York Heart Association IV stage heart failure, and a history of organ transplantation.

In a structured baseline interview (2010–12), each patient provided details regarding concomitant diseases, previous cardiovascular events and any medications. The participants' nephrologists added detailed information on the medical history. DM was defined according to American Diabetes Association criteria when a hemoglobin A1c (HbA1c) >6.5% was present and/or if a patient received antidiabetic medication [16].

Regular follow-up visits were conducted to assess predefined incidents and events that occurred over time. For the current analysis data extraction from the main database was performed in February 2021. To this point, 311 (5.9%) participants had left the study, and 188 participants (2.3%) had been lost to follow-up.

Outcomes and definitions

The clinical endpoints were (i) non-cardiovascular death; (ii) cardiovascular death (including death following MI or coronary heart disease, decompensated heart failure, death following cerebrovascular or peripheral vascular events, sudden cardiac death, or death following valvular heart disease); (iii) 4-point major adverse cardiovascular events (4-point MACE; including non-fatal MI, stroke, non-fatal peripheral artery disease events); and (iv) hospitalization for heart failure (HHF). Endpoints were regarded as competing risk events; the time to the first event was considered.

The primary cause of kidney disease was determined by consultation with the treating physician or by kidney biopsy, if available. We stratified participants according to the etiology of their kidney disease into two groups. A first group comprised participants with CKD clearly not induced by cardiovascular or metabolic disorders, with diagnoses including assured primary glomerulopathy ($n = 978$), autoimmune systemic disease ($n = 418$), interstitial nephropathy ($n = 225$), hereditary kidney disease ($n = 215$), single kidney ($n = 137$), CKD following acute kidney injury ($n = 127$), or postrenal/obstructive nephropathy ($n = 65$) (CKDgen). A second group of participants with cardiovascular or metabolic causes of CKD like DM or arterial hypertension included all participants with DKD or vascular kidney disease (including nephrosclerosis, renal artery stenosis or kidney infarction, all associated with arterial hypertension) as the leading causes of CKD (CKDcvm). Participants with undetermined nephropathy in which the treating physician noted that, while they may not be the leading causes, DM and/or hypertension were likely to have largely contributed to this condition were also stratified as CKDcvm. Both CKDgen and CKDcvm included participants with and without DM, resulting in four subgroups that were analyzed separately (Fig. 1). We chose to focus on this clinical compound classification due to a low rate of kidney biopsies of patients with CKDcvm (6%); of note, DM can induce vascular damage even at its early stages and also in the absence of proteinuria [17]. Participants for whom the leading cause of kidney disease remained unclear were excluded from this analysis ($n = 470$; 9%).

Statistical analysis

Baseline characteristics are stated using means ± standard deviation (SD) for normally distributed variables, and median values with interquartile ranges for variables that are non-normally distributed. Categorical variables are presented as frequency distributions with percentages.

Multivariable Cox proportional hazards models were used to examine the adjusted risk associated with DM both for the total cohort and separately for participants diagnosed with CKDcvm and CKDgen. These models were also used to assess the effects of CKDcvm on the aforementioned clinical endpoints in participants with DM at baseline. Estimates obtained from Cox regression models are presented as cause-specific hazard ratios (HRs) with 95% confidence intervals (CIs). Adjustment was made for gender (reference: female), age (in years), eGFR (mL/min/1.73 m^2), urinary albumin/creatinine ratio (UACR; per 10 mg/g creatinine), low-density lipoprotein (LDL, mg/dL), systolic and diastolic blood pressure (mmHg), previous cardiovascular disease (reference: no), active smoking (reference: no), body mass index (BMI; kg/m^2), C-reactive protein (CRP; per 10 mg/L) and cardiovascular/metabolic kidney disease (CKDcvm) (reference: CKDgen). HbA1c (%) was only included when throughout patients with DM were analyzed. As most participants (88%) received inhibitors of the renin–angiotensin system (RASi) we refrained from using RASi as covariable [14].

Censoring was performed at the time of the last follow-up visit for participants who did not complete the total 6.5-year follow-up period (e.g. participants who left the study because they did not want to participate in any more follow-up visits, or were lost to follow-up). The hazard estimates obtained from

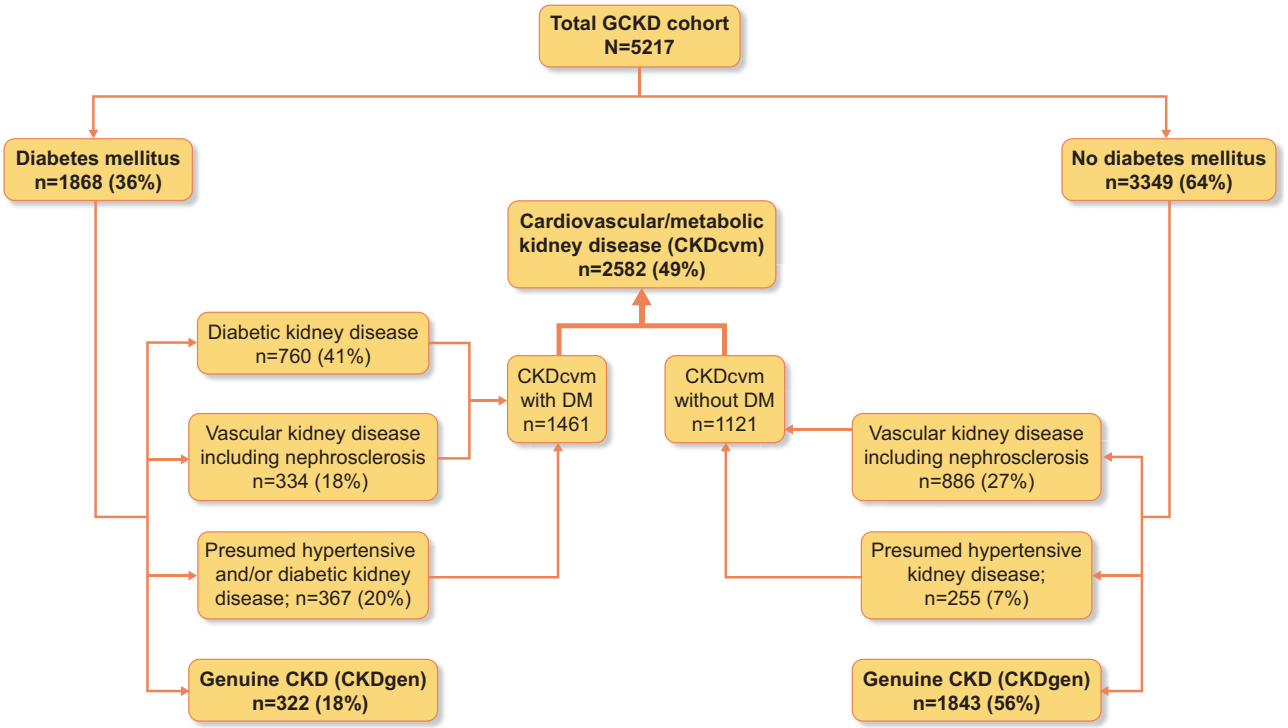


Figure 1: Distribution of the study cohort participants including those with and without DM and stratified by cardiovascular/metabolic versus genuine leading causes of CKD (CKDcvm versus CKDgen). CKDgen included primary glomerulopathy (45%), autoimmune systemic disease (19%), interstitial nephropathy (10%), hereditary kidney disease (10%), single kidney (6%), CKD following acute kidney injury (6%) or postrenal/obstructive nephropathy (3%). In 470 participants (9%) including 85 with DM (18%) and 385 without DM (82%), the cause of kidney disease remained unknown leading to exclusion from further analysis.

our models were cause-specific, as participants were censored at death if the latter event was not included in the definition of the outcome of interest. Statistical analyses were performed with SAS 9.4 Copyright © 2002–2012 by SAS Institute Inc., Cary, NC, USA.

RESULTS

Patient characteristics

The GCKD study enrolled 5217 participants. Of these, 1868 (36%) were diagnosed with DM. Overall, 2582 (49%) of all participants fulfilled our criteria of CKDcvm, of whom 1461 (57%) had DM. A detailed overview of all subgroups is shown in Fig. 1 using available data for the leading cause of CKD for 1783 participants (34%) with and 2964 (57%) participants without DM (missing data for $n = 470$; 9%).

Baseline characteristics of the total GCKD patient cohort and each subgroup, which included participants with and without DM and according to their leading cause of CKD, are summarized in Table 1. Participants with CKDcvm were predominantly male, had a lower eGFR and were more likely to present with cardiovascular disease at baseline. The UACRs reported in participants with CKDcvm without DM were lower than those in the other subgroups. Participants with CKDgen without DM were significantly younger ($P < .001$) and had the highest eGFR in subgroup comparison ($P < .001$). Furthermore, the frequency of renal biopsies was notably lower in participants with CKDcvm (6%) compared with CKDgen (55%), especially among participants with CKDcvm and DM (4%).

Impact of DM in the total cohort ($n = 5217$)

During the 6.5-year follow-up, 603 participants (12%) succumbed to non-cardiovascular death and 209 (4%) to cardiovascular death. In addition, 645 (12%) participants had 4-point MACE and 398 (8%) reported first admissions to a hospital for symptomatic heart failure (HHF). All endpoints occurred more frequently in participants with DM (non-cardiovascular death: 20% versus 7%; cardiovascular death: 7% versus 2%; 4-point MACE: 21% versus 7%; HHF: 14% versus 4%). This observation held true for both participants with CKDcvm and those with CKDgen (Table 2). The 1461 participants with DM and CKDcvm reached the clinical endpoints most frequently in 8%–22% (Table 2).

In Cox regression analyses DM was an independent risk factor for all outcomes in the total CKD cohort (included in final model, $n = 4995$). DM led to an approximate doubling of the HRs (1.87–2.25) in multivariable-adjusted Cox regression analyses (**Fig. 2**; Supplementary data, Table S1). For participants with CKDcvm (included, $n = 2455$) as well as with CKDgen (included, $n = 2088$), DM contributed to the increased risk of 4-point MACE, cardiovascular and non-cardiovascular death (Supplementary data, Table S1). Of interest, the mortality hazard associated with DM was similar for both CKD subgroups, CKDcvm and CKDgen (Fig. 2). Our results also revealed that the DM-associated hazard for HHF increased about 2-fold among the participants with CKDcvm.

Male gender, higher age, lower eGFR, higher UACR, lower diastolic blood pressure, higher CRP levels, current smoking and the presence of cardiovascular disease at baseline were associated with increased HRs for all described endpoints among participants in the full study cohort (Supplementary data, Table S1).

Table 1: Baseline characteristics of the GCKD patient cohort ($n = 5217$) that included patients with ($n = 1868$) and without ($n = 3349$) DM with subgroups according to the leading cause of CKD and presence of DM.

	Total	CKDgen with DM	CKDgen without DM	CKDcvm with DM	CKDcvm without DM	Missing (*n*, %)
Number of patients	5217	322	1843	1461	1121	
Male gender (*n*, %)	3132 (60%)	189 (59%)	976 (53%)	1007 (69%)	697 (62%)	
Age (years)	60 ± 12	62 ± 10	53 ± 14	65 ± 8	64 ± 9	
eGFR (mL/min/1.73 m²)	49 ± 18	50 ± 20	54 ± 21	45 ± 15	46 ± 14	57 (1%)
Stages of CKD (*n*, %)						
>90 mL/min/1.73 m² (G1)	234 (5%)	18 (6%)	160 (9%)	28 (2%)	10 (0.1%)	
60–90 mL/min/1.73 m² (G2)	883 (17%)	59 (18%)	395 (21%)	176 (12%)	161 (14%)	
45–59 mL/min/1.73 m² (G3a)	1717 (33%)	98 (30%)	569 (31%)	483 (33%)	403 (36%)	
30–44 mL/min/1.73 m² (G3b)	1865 (36%)	104 (32%)	572 (31%)	587 (40%)	446 (40%)	
<30 mL/min/1.73 m²	461 (9%)	34 (11%)	135 (7%)	167 (11%)	91 (8%)	
UACR (mg/g creatinine)	51 (382)	115 (667)	133 (657)	45 (321)	18 (107)	89 (2%)
Stages of CKD (*n*, %)						
<30 mg/g creatinine (A1)	2188 (43%)	107 (33%)	556 (30%)	646 (44%)	635 (57%)	
30–300 mg/g creatinine (A2)	1495 (29%)	99 (31%)	564 (31%)	405 (28%)	294 (26%)	
>300 mg/g creatinine (A3)	1445 (28%)	112 (35%)	697 (38%)	374 (26%)	173 (15%)	
Previous cardiovascular disease (*n*, %)	1591 (30%)	75 (23%)	258 (30%)	723 (49%)	419 (30%)	
HbA1c (%)	6 (0.9)	6.7 (0.9)	5.8 (0.5)	7.2 (1.4)	5.9 (0.4)	120 (2%)
Antidiabetic treatment (*n*, %)						
Dietary	406 (22%)	138 (43%)		228 (16%)		
Oral antidiabetic drugs	525 (28%)	95 (30%)		411 (28%)		
Insulin	937 (50%)	89 (28%)		822 (56%)		
BMI (kg/m²)	29.8 ± 6	31.2 ± 6	27.6 ± 5	32.8 ± 6	29.4 ± 5.2	54 (1%)
Systolic blood pressure (mmHg)	139 ± 20	138 ± 20	136 ± 18	143 ± 21	142 ± 21	34 (1%)
Diastolic blood pressure (mmHg)	79 ± 12	79 ± 12	82 ± 11	76 ± 12	80 ± 12	34 (1%)
LDL levels (mg/dL)	114 (54)	115 (58)	125 (52)	99 (48)	114 (51)	67 (1%)
Statin use	2319 (44%)	171 (53%)	668 (36%)	936 (64%)	544 (49%)	
Anti-aggregant use	1682 (32%)	113 (35%)	312 (17%)	777 (53%)	480 (43%)	
Current smokers (*n*, %)	828 (16%)	60 (19%)	330 (18%)	205 (14%)	158 (14%)	
CRP levels (mg/L)	2.3 (4)	2.7 (4.5)	1.7 (3.1)	3.0 (4.9)	2.4 (3.8)	55 (1%)
Renal biopsy performed (*n*, %)	1369 (26%)	178 (55%)	1001 (54%)	60 (4%)	99 (9%)	

Data are presented as *n* (%), mean ± standard deviation or median (interquartile range).
Subgroup data were missing due to indeterminable leading cause of kidney disease in 470 participants (9%), including 85 with DM (18%) and 385 without DM (82%).

Table 2: Frequency of reached cardiovascular and mortality endpoints (first events) for the total GCKD cohort and subgroups according to the leading cause of CKD and presence of DM.

	Total	CKDgen with DM	CKDgen without DM	CKDcvm with DM	CKDcvm without DM
Number of patients	5217	322	1843	1461	1121
Non-cardiovascular death (*n*, %)	603 (12%)	50 (16%)	87 (5%)	305 (21%)	112 (10%)
Cardiovascular death (*n*, %)	209 (4%)	15 (5%)	18 (1%)	122 (8%)	36 (3%)
4-point MACE (n, %)	645 (12%)	45 (14%)	101 (5%)	323 (22%)	125 (11%)
HHF (*n*, %)	398 (8%)	18 (6%)	48 (3%)	231 (16%)	72 (6%)

Data are presented as *n* (%) referred to each subgroup.
Subgroup data were missing due to indeterminable leading cause of kidney disease in 470 participants (9%), including 85 with DM (18%) and 385 without DM (82%).

Impact of the leading cause of CKD in patients with DM

Unadjusted HRs for CKDcvm versus CKDgen in participants with DM ($n = 1783$) were increased for all endpoints with 1.47 (95% CI 1.09–1.98) for non-cardiovascular death, 1.95 (95% CI 1.14–3.34) for cardiovascular death, 1.80 (95% CI 1.32–2.46) for 4-point MACE and 3.22 (95% CI 2.00–5.21) for HHF. However, in multivariable Cox regression CKDcvm was associated with an increased adjusted HR only for HHF (1.93; 95% CI 1.15–3.22, Fig. 3) compared with CKDgen (included, $n = 1663$). The etiology of CKD was not found to be associated with 4-point MACE or mortality hazards in fully adjusted Cox regression models (Supplementary data, Table S2).

DISCUSSION

In this GCKD cohort study with a large fraction of CKD participants with concomitant DM (36%), cardiovascular and mortality endpoints were reached in 4%–12%, however more often by participants with DM and particularly if they had CKDcvm. This suggests a different cardiovascular risk of CKD patients with and without DM, which is also dependent on their etiology of CKD.

DM led to a nearly 2-fold increased non-cardiovascular mortality risk and even higher cardiovascular mortality risk (HR 2.3) in patients with moderate to severe CKD. This is astonishingly similar to the general population's DM-related mortality risk (e.g. HR for all-cause death 1.9; cause-specific cardiovascular

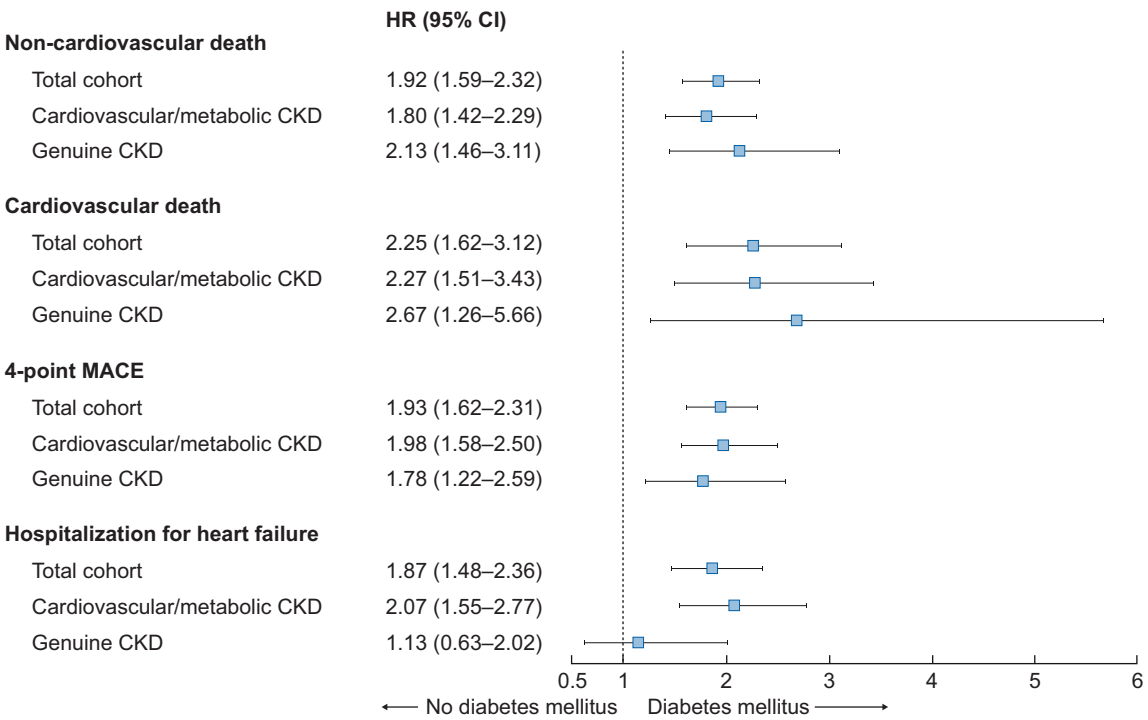


Figure 2: HRs and 95% CIs of diabetes mellitus for four clinical endpoints: non-cardiovascular death, cardiovascular death, 4-point MACE and HHF. Data reflect outcomes from the total patient cohort ($n = 4995$ of 5217 included in final Cox model), as well as those with cardiovascular/metabolic (CKDcvm; $n = 2455$ of 2582 included in final Cox model) and genuine leading causes of CKD (CKDgen; $n = 2088$ of 2165 included in final Cox model).

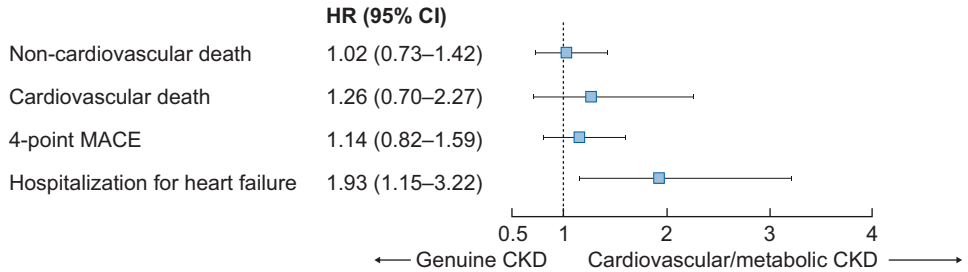


Figure 3: HRs and 95% CIs for CKD due to cardiovascular/metabolic (CKDcvm) versus genuine leading causes of CKD (CKDgen) for four clinical endpoints: non-cardiovascular death, cardiovascular death, 4-point MACE and HHF in the subgroup of patients with DM who were included in the final Cox regression model ($n = 1663$ of 1868).

mortality HRs 1.4–2.6) [10, 11]. Moreover, the hazards for cardiovascular events (4-point MACE and HHF) were nearly doubled and are thus of clinical relevance. This is consistent with the results of a large meta-analysis of prospective studies in patients without pre-existing vascular diseases irrespective of CKD, in which DM was assessed as a risk factor for the occurrence of cardiovascular events (e.g. HR for non-fatal myocardial infarction 1.8; HR for ischemic stroke 2.3) [8].

In a large population-based study the risk of (recurrent) MI and all-cause mortality was higher due to the presence of CKD than due to DM when considering unadjusted rates [12]. Interestingly, the adjusted relative rates for first MI and all-cause mortality were similar when comparing outcomes from patients with DM (without CKD) and CKD (without DM), especially in patients with moderate or severe CKD, and highest for patients with both CKD and DM [12]. This supports our findings of DM being an independent cardiovascular- and mortality-associated risk factor in addition to the generally increased hazard level due to moderate or severe CKD. Moreover, our statistical models were consequently adjusted for several well-known DM-related risk factors. Male gender, higher age, lower eGFR, higher UACR, lower diastolic blood pressure, increased CRP levels, current smoking and preexisting cardiovascular disease were also confirmed as they were all associated with increased hazards for the investigated endpoints, particularly in patients with DM [18–25]. Higher systolic blood pressure and higher BMI were linked to increased HRs with respect to some of the cardiovascular endpoints analyzed in this study, depending on the individual outcome measure. Moreover, in patients with DM, a higher HbA1c was related to all outcomes. At baseline, patients with diabetes and CKDcvm had the lowest LDL serum levels, most likely due to the highest rate of statin use (64%) within the whole study population.

This could possibly explain why LDL could not be shown to be an independent cardiovascular or mortality risk predictor. In addition, the rate of anti-aggregant use at 53% in this group was also the highest.

Recent findings suggest that the etiology of kidney disease may modify renal and cardiovascular risk in patients with DM due to different pathomechanisms for the loss of nephron mass [26, 27]. Thus, patients with DKD, whose CKD is caused by DM due to predominant glycemic damage, often show a rapid decline in eGFR, whereas the eGFR of patients with CKD and DM but without DKD was more stable and showed a slower decline [26, 28, 29]. DM in patients with CKD other than DKD is likely to add further patterns of renal damage to those preexisting; however, renal outcomes of patients with DM and CKD stage 3b and 4 but no DKD were similar to those of patients with non-DKD [29]. Since a reduced eGFR is a well-known cardiovascular risk factor, differential progression of CKD may have a measurable impact on cardiovascular morbidity and mortality [21, 25, 30]. Variations in the severity of the accompanying organ damage, notably those in relation to microvascular changes and heart failure symptoms, are likely to be associated with changes in cardiovascular risk. Our approach to identify patients with cardiovascular or metabolic (CKDcvm) as opposed to well-described causes genuine CKD (CKDgen) is supported by various studies analyzing renal histological patterns of DKD [17, 31, 32], Furthermore, our procedure is consistent with the fact that most CKD cases worldwide are cardiometabolic in nature, i.e. CKD reported in individuals with diabetes, hypertension, or cardiovascular disease for whom screening is recommended [33].

We were able to observe elevated hazards due to DM for 4-point MACE, cardiovascular and non-cardiovascular mortality in both, patients with CKDcvm and with CKDgen to a similar extent. This suggests that the leading cause of CKD does not primarily determine the risk for these endpoints, although it would stand to reason from a clinical perspective that long-term cardiovascular and/or metabolic injury, which has already led to a renal impairment, would increase the cardiovascular risk. Similarly, no significant differences in all-cause mortality or the incidence of cardiovascular events between patients with DKD and non-DKD could be observed in a Japanese multicentric, prospective observational study [34].

However, regarding the endpoint of HHF, only patients with CKDcvm but not with CKDgen were affected by the presence of DM. In addition, analyzing exclusively patients with DM, the leading cause of CKD (CKDcvm versus CKDgen) was an independent risk factor for HHF. These findings can be easily understood, as CKDcvm likely evolved in response to long-term diabetic, vascular and/or hypertensive damage. In this setting, the renal–cardiac axis may be dysfunctional and thus lead to a higher rate of reported decompensated heart failure as an expression of both heart and kidney failure. Thus, patients with both DM and CKD will be particularly susceptible to this outcome [35]. These findings are consistent with results from a vast multinational cohort study of patients with DM in which cardiorenal disease (diagnosed as heart failure or CKD) was the most frequent first manifestation of cardiovascular or renal disease associated with an increased mortality risk [36]. Patients with DM in general have a more than 2-fold increased risk of developing heart failure [37]. In this setting, CKD patients are at particular risk for developing symptoms of heart failure also resulting from volume overload due to CKD in combination with structural cardiac remodeling (i.e. hypertensive heart disease as well as micro- or macrovascular damage pattern) [38].

The current discussion concerning the use of combined cardiorenal outcomes in future clinical trials is supported by our data, as the single endpoint HHF may be an equal reflection of both cardiac and renal damage in patients with DM [39]. Our findings may also provide an explanation for results from prospective outcome trials in which administration of sodium-glucose cotransporter 2 inhibitors reduced the risk for HHF in DM patients, including also those with CKD [40–43]. This may be related to their combined diuretic, antihypertensive, renoprotective and metabolic actions [44].

Strengths and limitations

The prospective multicenter GCKD study design provides a highly appropriate database of a homogenous cohort of participants with CKD with and without DM large enough to provide adequate statistical power for investigating cardiovascular and mortality endpoints. All participants in this study were under routine nephrological care to limit treatment variability; measurements, questionnaires and documentation were performed according to standard operational procedures by trained personnel. Clinical outcomes were centrally adjudicated based on predefined criteria by review of hospital discharge letters and death certificates. Information on the etiology of CKD was included in our assessment of cardiovascular risk factors in the statistical models. However, biopsy findings were for the most part unavailable, especially in patients with suspected CKDcvm, as this is common clinical practice. Thus, the classification of kidney disease depends on the assumptions of the treating nephrologists, which includes a degree of uncertainty. Furthermore, only 322 patients with DM were categorized as CKDgen, reducing the statistical power of our analyses concerning this subgroup. Likewise, when considering baseline findings and their relationship to endpoints evaluated during the 6.5-year follow-up, no conclusions can be drawn regarding the role of time-dependent variables, for example, a differential decrease in renal function. Finally, the design of the GCKD study precludes any evaluation of the impact of ethnic diversity.

CONCLUSIONS

DM is an important and independent risk factor for cardiovascular morbidity and mortality in patients diagnosed with moderate to severe CKD. The impact of DM on mortality affects patients with CKDcvm and CKDgen to a similar extend. CKDcvm should be taken into consideration as a risk factor for symptomatic heart failure.

SUPPLEMENTARY MATERIAL

Supplementary data are available at *ckj* online.

ACKNOWLEDGEMENTS

We are very grateful for the willingness and time given by all study participants of the GCKD study. The enormous effort of the study personnel in the regional centers is highly appreciated. We would also like to thank the large number of nephrologists who provide routine care for the patients and collaborate with the GCKD study. A list of nephrologists currently collaborating with the GCKD study is available at www.gckd.org.

Current GCKD Investigators and Collaborators with the GCKD study are:

University of Erlangen-Nürnberg: Kai-Uwe Eckardt, Heike Meiselbach, Markus P. Schneider, Mario Schiffer, Hans-Ulrich Prokosch, Barbara Bärthlein, Andreas Beck, André Reis, Arif B. Ekici, Susanne Becker, Ulrike Alberth-Schmidt, Anke Weigel, Eugenia Schefler, Sabine Marschall; University of Freiburg: Gerd Walz, Anna Köttgen, Ulla T. Schultheiß, Fruzsina Kotsis, Simone Meder, Erna Mitsch, Ursula Reinhard; RWTH Aachen University: Jürgen Floege, Turgay Saritas; Alice Groß; Charité, University Medicine Berlin: Elke Schaeffner, Seema Baid-Agrawal, Kerstin Theisen; Hannover Medical School: Kai Schmidt-Ott; University of Heidelberg: Martin Zeier, Claudia Sommerer, Mehtap Aykac; University of Jena: Gunter Wolf, Martin Busch, Johannes Ruhe, Andy Steiner; Ludwig-Maximilians University of München: Thomas Sitter; University of Würzburg: Christoph Wanner, Vera Krane, Antje Börner-Klein, Britta Bauer; Medical University of Innsbruck, Institute of Genetic Epidemiology: Florian Kronenberg, Julia Raschenberger, Barbara Kollerits, Lukas Forer, Sebastian Schönherr, Hansi Weissensteiner; University of Regensburg, Institute of Functional Genomics: Peter Oefner, Wolfram Gronwald; University of Bonn, Institute of Medical Biometry, Informatics and Epidemiology, Medical Faculty: Matthias Schmid, Jennifer Nadal.

FUNDING

The GCKD study was/is funded by grants from the German Ministry of Education and Research (BMBF, grant number 01ER0804, and for the authors F.K. and U.T.S. 01ZX1912B), the KfH Foundation for Preventive Medicine, Innovative Medicines Initiative 2 Joint Undertaking (BEAt-DKD, grant number 115974) and corporate sponsors (www.gckd.de). It is conducted under the auspices of the German Society of Nephrology (DGfN) (http://www.dgfn.eu).

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors J.N., F.K., H.S., V.K., C.S., I.L., T.Saritas, T.Sitter, M.P.S., M.S. and G.W. have no competing conflict of interest to declare. J.R. reports receiving support for attending meetings including travel support by Vifor and Alexion, and receiving lecture honoraria from Novartis. B.B. and H.M. report receiving study grants by the BEAt DKD Consortium. U.T.S. reports receiving travel support grant from German Ministry of Education and Research (BMBF, grant number 01ZX1912B) within the framework of the e:Med junior consortium CKDNapp entailed travel support. J.T.K. reports receiving honoraria from Vifor, FMC, ExThera Medical, AstraZeneca and Takeda, and stock from BAYER, Quanteryx and Synlab. C.W. reports receiving institutional grants from Idorsia, Sanofi and Boehringer Ingelheim; consulting fees from AstraZeneca, Boehringer Ingelheim, Idorsia, Bayer, GILEAD, GSK and MSD; and honoraria from Boehringer Ingelheim, AstraZeneca, FMC, Chiesi, Lilly and Vifor; and participation on a data safety monitoring board of Sanofi and Australasian Kidney Trials Network and on a leadership of the European Renal Association. K.-U.E. reports receiving grants, fees from consultancy and/or lecture fees from Akebia, Amgen, AstraZeneca, Bayer, Evotec, Otsuka, Retrophin and Vifor; and participation on data safety monitoring boards of Akebia, Bayer and Travere. M.B. reports receiving consulting fees from Boehringer Ingelheim, GSK, Novartis and Oksuka thereby participating in the (local) advisory boards; honoraria from Boehringer Ingelheim, AstraZeneca, Vifor, Pfizer, Bristol Myers Squibb and Novartis; support for attending meetings from Lilly, AstraZeneca and Hexal; and being an unpaid board member in the Thuringian Society of Internal Medicine.

REFERENCES

1. Saeedi P, Petersohn I, Salpea P *et al.* Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Res Clin Pract* 2019;**157**:107843. https://doi.org/10.1016/j.diabres.2019.107843
2. Levin A, Tonelli M, Bonventre J *et al.* Global kidney health 2017 and beyond: a roadmap for closing gaps in care, research, and policy. *Lancet North Am Ed* 2017;**390**:1888–917. https://doi.org/10.1016/S0140-6736(17)30788-2
3. Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. *Clin J Am Soc Nephrol* 2017;**12**:2032–45. https://doi.org/10.2215/CJN.11491116
4. Bolignano D, Mattace-Raso F, Sijbrands EJ *et al.* The aging kidney revisited: a systematic review. *Ageing Res Rev* 2014;**14**:65–80. https://doi.org/10.1016/j.arr.2014.02.003
5. van Dieren S, Beulens JW, van der Schouw YT *et al.* The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil* 2010;**17**:S3–8.
6. United States Renal Data System. *2018 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2018.
7. Li X, Lindholm B. Cardiovascular risk prediction in chronic kidney disease. *Am J Nephrol* 2022;**53**:730–9. https://doi.org/10.1159/000528560
8. Emerging Risk Factors Collaboration, Sarwar N, Gao P *et al.* Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010;**375**:2215–22.
9. Rivellese AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. *Nutr Metab Cardiovasc Dis* 2010;**20**:474–80. https://doi.org/10.1016/j.numecd.2010.01.008
10. Leon BM, Maddox TM. Diabetes and cardiovascular disease: epidemiology, biological mechanisms, treatment recommendations and future research. *World J Diabetes* 2015;**6**:1246–58. https://doi.org/10.4239/wjd.v6.i13.1246
11. Yang JJ, Yu D, Wen W *et al.* Association of diabetes with all-cause and cause-specific mortality in Asia: a pooled analysis of more than 1 million participants. *JAMA Netw Open* 2019;**2**:e192696. https://doi.org/10.1001/jamanetworkopen.2019.2696
12. Tonelli M, Muntner P, Lloyd A *et al.* Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. *Lancet North Am Ed* 2012;**380**:807–14. https://doi.org/10.1016/S0140-6736(12)60572-8
13. Fox CS, Matsushita K, Woodward M *et al.* Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. *Lancet North Am Ed* 2012;**380**:1662–73. https://doi.org/10.1016/S0140-6736(12)61350-6
14. Titze S, Schmid M, Kottgen A *et al.* Disease burden and risk profile in referred patients with moderate chronic kidney

disease: composition of the German Chronic Kidney Disease (GCKD) cohort. *Nephrol Dial Transplant* 2015;**30**:441–51. https://doi.org/10.1093/ndt/gfu294
15. Eckardt KU, Barthlein B, Baid-Agrawal S *et al*. The German Chronic Kidney Disease (GCKD) study: design and methods. *Nephrol Dial Transplant* 2012;**27**:1454–60. https://doi.org/10.1093/ndt/gfr456
16. Tuttle KR, Bakris GL, Bilous RW *et al*. Diabetic kidney disease: a report from an ADA Consensus Conference. *Am J Kidney Dis* 2014;**64**:510–33. https://doi.org/10.1053/j.ajkd.2014.08.001
17. Rodriguez-Rodriguez R, Hojs R, Trevisani F *et al*. The role of vascular lesions in diabetes across a spectrum of clinical kidney disease. *Kidney Int Rep* 2021;**6**:2392–403. https://doi.org/10.1016/j.ekir.2021.06.001
18. Adler AI, Stevens RJ, Manley SE *et al*. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int* 2003;**63**:225–32. https://doi.org/10.1046/j.1523-1755.2003.00712.x
19. Anavekar NS, Pfeffer MA. Cardiovascular risk in chronic kidney disease. *Kidney Int* 2004;**66**:S11–5. https://doi.org/10.1111/j.1523-1755.2004.09203.x
20. Benjamin EJ, Blaha MJ, Chiuve SE *et al*. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. *Circulation* 2017;**135**:e146–603. https://doi.org/10.1161/CIR.0000000000000485
21. Go AS, Chertow GM, Fan D *et al*. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;**351**:1296–305. https://doi.org/10.1056/NEJMoa041031
22. Halcox JP, Roy C, Tubach F *et al*. C-reactive protein levels in patients at cardiovascular risk: EURIKA study. *BMC Cardiovasc Disord* 2014;**14**:25. https://doi.org/10.1186/1471-2261-14-25
23. Matsushita K, Coresh J, Sang Y *et al*. Estimated glomerular filtration rate and albuminuria for prediction of cardiovascular outcomes: a collaborative meta-analysis of individual participant data. *Lancet Diabetes Endocrinol* 2015;**3**:514–25. https://doi.org/10.1016/S2213-8587(15)00040-6
24. Sharp Collaborative Group. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. *Am Heart J* 2010;**160**:785–94.e10. https://doi.org/10.1016/j.ahj.2010.08.012
25. Thomas B, Matsushita K, Abate KH *et al*. Global cardiovascular and renal outcomes of reduced GFR. *J Am Soc Nephrol* 2017;**28**:2167–79. https://doi.org/10.1681/ASN.2016050562
26. Anders HJ, Huber TB, Isermann B *et al*. CKD in diabetes: diabetic kidney disease versus nondiabetic kidney disease. *Nat Rev Nephrol* 2018;**14**:361–77. https://doi.org/10.1038/s41581-018-0001-y
27. Anguiano Gomez L, Lei Y, Kumar Devarapu S *et al*. The diabetes pandemic suggests unmet needs for 'CKD with diabetes' in addition to 'diabetic nephropathy'-implications for pre-clinical research and drug testing. *Nephrol Dial Transplant* 2018;**33**:1292–304. https://doi.org/10.1093/ndt/gfx219
28. Oshima M, Shimizu M, Yamanouchi M *et al*. Trajectories of kidney function in diabetes: a clinicopathological update. *Nat Rev Nephrol* 2021;**17**:740–50. https://doi.org/10.1038/s41581-021-00462-y
29. Iwai T, Miyazaki M, Yamada G *et al*. Diabetes mellitus as a cause or comorbidity of chronic kidney disease and its outcomes: the Gonryo study. *Clin Exp Nephrol* 2018;**22**:328–36. https://doi.org/10.1007/s10157-017-1451-4
30. Menon V, Gul A, Sarnak MJ. Cardiovascular risk factors in chronic kidney disease. *Kidney Int* 2005;**68**:1413–8. https://doi.org/10.1111/j.1523-1755.2005.00551.x
31. Caramori ML. Should all patients with diabetes have a kidney biopsy? *Nephrol Dial Transplant* 2017;**32**:3–5. https://doi.org/10.1093/ndt/gfw389
32. Klessens CQ, Woutman TD, Veraar KA *et al*. An autopsy study suggests that diabetic nephropathy is underdiagnosed. *Kidney Int* 2016;**90**:149–56. https://doi.org/10.1016/j.kint.2016.01.023
33. Shlipak MG, Tummalapalli SL, Boulware LE *et al*. The case for early identification and intervention of chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2021;**99**:34–47. https://doi.org/10.1016/j.kint.2020.10.012
34. Chen S, Chen L, Jiang H. Prognosis and risk factors of chronic kidney disease progression in patients with diabetic kidney disease and non-diabetic kidney disease: a prospective cohort CKD-ROUTE study. *Ren Fail* 2022;**44**:1310–9. https://doi.org/10.1080/0886022X.2022.2106872
35. Vijay K, Neuen BL, Lerma EV. Heart failure in patients with diabetes and chronic kidney disease: challenges and opportunities. *Cardiorenal Med* 2022;**12**:1–10. https://doi.org/10.1159/000520909
36. Birkeland KI, Bodegard J, Eriksson JW *et al*. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: a large multinational cohort study. *Diabetes Obes Metab* 2020;**22**:1607–18. https://doi.org/10.1111/dom.14074
37. Kenny HC, Abel ED. Heart failure in type 2 diabetes mellitus. *Circ Res* 2019;**124**:121–41. https://doi.org/10.1161/CIRCRESAHA.118.311371
38. Rangaswami J, Bhalla V, Blair JEA *et al*. Cardiorenal syndrome: classification, pathophysiology, diagnosis, and treatment strategies: a scientific statement from the American Heart Association. *Circulation* 2019;**139**:e840–78. https://doi.org/10.1161/CIR.0000000000000664
39. Patel RB, Ter Maaten JM, Ferreira JP *et al*. Challenges of cardio-kidney composite outcomes in large-scale clinical trials. *Circulation* 2021;**143**:949–58. https://doi.org/10.1161/CIRCULATIONAHA.120.049514
40. Neal B, Perkovic V, Mahaffey KW *et al*. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med* 2017;**377**:644–57. https://doi.org/10.1056/NEJMoa1611925
41. Perkovic V, Jardine MJ, Neal B *et al*. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N Engl J Med* 2019;**380**:2295–306. https://doi.org/10.1056/NEJMoa1811744
42. Wiviott SD, Raz I, Bonaca MP *et al*. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2019;**380**:347–57. https://doi.org/10.1056/NEJMoa1812389
43. Zinman B, Wanner C, Lachin JM *et al*. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med* 2015;**373**:2117–28. https://doi.org/10.1056/NEJMoa1504720
44. Tuttle KR, Brosius FC, III, Cavender MA *et al*. SGLT2 inhibition for CKD and cardiovascular disease in type 2 diabetes: report of a Scientific Workshop Sponsored by the National Kidney Foundation. *Am J Kidney Dis* 2021;**77**:94–109. https://doi.org/10.1053/j.ajkd.2020.08.003

Received: 31.5.2023; Editorial decision: 3.7.2023