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LEADER-6: Baseline renal function and associated factors in a high cardiovascular risk type 2 diabetes population

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ABSTRACT

Aims: To examine the prevalence of chronic kidney disease (CKD) and its associated factors in a multinational population with type 2 diabetes mellitus (T2DM) and prior cardiovascular disease (CVD).
Methods: The LEADER trial randomized 9340 participants—81.3% with prior CVD at baseline. CKD was defined as estimated GFR <60 ml/min/1.73 m^2 and/or an albumin-to-creatinine ratio ≥3.0 mg/mmol.
Results: At baseline, 51.9% of participants with prior CVD had CKD. CKD prevalence was highest in Asia (75.8%) and lowest in Europe (43.7%) and the Middle East (43.4%). Baseline factors associated with increased CKD prevalence included increased age, HbA_{1c}, diabetes duration, systolic blood pressure or triglyceride levels; greater number of antihypertensive medications; living in Asia, the Americas or Africa versus Europe; being male; and not receiving oral antidiabetic drugs (most receiving insulin), beta-blockers or ACE inhibitors. Factors associated with decreased CKD prevalence included increased diastolic blood pressure, no diuretic treatment and prior myocardial infarction, angina or stroke.
Conclusions: CKD prevalence is high among patients with T2DM and prior CVD. Advanced age, long diabetes duration, poor glycemic control, comorbidities and medications used are associated with CKD. Our results strengthen the rationale for early screening and interventions for CKD in patients with T2DM and prior CVD.

Clinical trial registration: ClinicalTrials.gov, NCT01179048.

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1. Introduction

Type 2 diabetes mellitus (T2DM) increases the risk of microvascular complications (Stratton et al., 2000), confers an approximately two-fold excess risk of cardiovascular events (Emerging Risk Factors Collaboration et al., 2010) and is increasing in prevalence throughout the world (International Diabetes Federation, 2015).

Chronic kidney disease (CKD) is defined by albuminuria and/or reduced estimated glomerular filtration rate (eGFR) and has increased in prevalence from 1988 to 1994 and 1999 to 2004 in the National Health and Nutrition Examination Survey (NHANES) population (Coresh, Astor, Greene, Eknoyan, & Levey, 2003; Coresh et al., 2007).

In European guidelines on cardiovascular disease (CVD) prevention, CKD is acknowledged as a CVD risk equivalent (Graham et al., 2007). Similarly, in patients with T2DM, albuminuria and reduced eGFR are established risk factors for cardiovascular and renal events (Gerstein et al., 2001; Ninomiya et al., 2009). However, the relationship between CVD and CKD in T2DM is incompletely understood.

Several publications have highlighted the potential influence of race and geographical location on the occurrence and progression of CKD in patients with diabetes (Chandie Shaw et al., 2002; Parsa et al., 2013; Samanta, Burden, & Jagger, 1991). For example, diabetic nephropathy is more common among Asian than White individuals in the UK and the Netherlands (Chandie Shaw et al., 2002; Samanta et al., 1991). In addition, Black patients in the USA have approximately twice the risk of end-stage renal disease (ESRD) compared with White patients, despite a similar prevalence of early stage CKD (Parsa et al., 2013).

The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial was designed to assess the cardiovascular safety of liraglutide versus placebo in patients with T2DM and high cardiovascular risk (Marso et al., 2013). Several features of its design allow for further study of the interplay between CVD, CKD and other factors.

Here, we examined baseline data from the LEADER trial to evaluate the factors associated with CKD prevalence in a global T2DM population with established CVD.

2. Materials and methods

The LEADER trial design, inclusion and exclusion criteria, and several clinical characteristics of the full LEADER cohort have been previously described (Marso et al., 2013). People with T2DM, either drug-naïve or treated with oral antidiabetic drugs (OADs) and/or selected insulin regimens (human neutral protamine Hagedorn [NPH], long-acting analogue or premixed), and at elevated cardiovascular risk, were randomized double-blind to receive either liraglutide ≤1.8 mg once daily or placebo as add-on to standard of care. In total, 9430 participants were enrolled at 410 centers across 32 countries. All participants gave informed consent. The trial was approved by local ethical committees and institutional review boards, and was conducted in accordance with the Declaration of Helsinki.

2.1. Participants

Two groups of participants were recruited. The prior CVD group ($n = 7592$, 81.3% of total cohort) comprised participants ≥50 years old with prior myocardial infarction (MI); ischemic heart disease; stroke; transient ischemic attack; arterial revascularization; >50% stenosis of coronary, carotid or lower extremity arteries; history of symptomatic chronic heart disease; asymptomatic cardiac ischemia; chronic heart failure (New York Heart Association [NYHA] classes II–III); or chronic renal failure (assessed by GFR <60 ml/min/1.73 m^2 using Modification of Diet in Renal Disease [eGFR-MDRD] or Cockcroft–Gault formula). The second group ($n = 1748$, 18.7% of total cohort) included participants ≥60 years old without prior CVD, who had one or more of the following cardiovascular risk factors: microalbuminuria, proteinuria, hypertension and left ventricular hypertrophy, left ventricular dysfunction or ankle brachial index <0.9. The protocol stipulated target enrollment of ≥400 individuals with eGFR-MDRD 30–59 ml/min/1.73 m^2) and 200 with eGFR-MDRD <30 ml/min/1.73 m^2. Only the prior CVD group enrolled participants with eGFR <60 ml/min/1.73 m^2 (Marso et al., 2013). Therefore, only the baseline data (i.e., prior to initiation of trial drug) from the prior CVD group were evaluated here as this was the population of interest.

2.2. Renal parameters

Serum and urine creatinine concentrations were determined by the modified kinetic Jaffe reaction and all other parameters by an enzymatic colorimetric assay (Roche Diagnostics, Mannheim, Germany) and performed centrally (ICON PLC, Dublin, Ireland).

GFR was estimated using the standard MDRD equation (Levey et al., 1999) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (Levey et al., 2009).

Participants were asked to bring first morning urine to their randomization visit, which was sent to a central laboratory for albumin-to-creatinine ratio (ACR) assessment.

2.3. Definitions

eGFR levels were categorized as follows: stage 1 (≥90 ml/min/1.73 m^2), stage 2 (60–89 ml/min/1.73 m^2), stage 3 (30–59 ml/min/1.73 m^2; 3a, 45–59 ml/min/1.73 m^2; 3b, 30–44 ml/min/1.73 m^2), or stage 4/5 (<30 ml/min/1.73 m^2) (Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013; Kidney Disease: Improving Global Outcomes CKD Work Group, 2013).

Urine ACR levels were categorized as follows: normal (normoalbuminuria <3.0 mg/mmol [approximate equivalent <30 mg/g]), mildly to moderately increased (microalbuminuria 3.0–30.0 mg/mmol [30–300 mg/g]) and severely increased (macroalbuminuria >30.0 mg/mmol [>300 mg/g]).

CKD was defined as presence of eGFR-MDRD <60 ml/min/1.73 m^2 and/or urine ACR ≥3.0 mg/mmol (Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

Target HbA_{1c} was defined as ≤7% (53 mmol/mol) in this analysis. Blood pressure (BP) was recorded at screening, usually as an average of two BP measurements. Hypertension was defined in this analysis as systolic BP (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥80 mm Hg. Intensively treated hypertension was defined as prescription of ≥3 antihypertensive medications, including ACE inhibitors (ACE-Is), angiotensin receptor blockers (ARBs), calcium channel blockers, diuretics and others.

The primary eGFR-MDRD model was defined as an eGFR <60 ml/min/1.73 m^2 and/or ACR ≥3.0 mg/mmol; the four other models (sensitivity analyses) included reduced eGFR-CKD-EPI and/or increased ACR, reduced eGFR-MDRD, reduced eGFR-CKD-EPI, or increased ACR.

2.4. Statistical analysis

Distributions of continuous variables are described by mean (SD), and median (interquartile range [IQR]). Categorical variables are listed as numbers and percentages. Comparisons of continuous or categorical variables were performed by t-test or χ^2 test. A P-value <0.05 was considered statistically significant.

Factors potentially associated with the prevalence of CKD in the prior CVD group were investigated using multivariate logistic regression analyses and expressed as adjusted ORs with 95% CIs. As previously described, the primary model was eGFR-MDRD <60 ml/min/1.73 m^2 and/or ACR ≥3.0 mg/mmol, and results from four other models (sensitivity analyses) are also presented. All analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC, USA) and data available at the time, prior to the end of the study.

3. Results

3.1. Baseline demographic and laboratory characteristics

Baseline demographic and laboratory characteristics of the subset of LEADER participants with prior CVD are presented by gender in Table 1. Nearly two-thirds of participants were male (66.5%), mean age was 64 years, mean diabetes duration was 12.8 years and mean HbA_{1c} was 8.7% (71 mmol/mol). Within the male and female populations, there were comparable proportions of participants with CKD. Among the population with prior CVD, 93.2% had hypertension, and 20.9% had intensively treated hypertension (Table 2). Most of the population with prior CVD (78.7%) were White, 9.9% were Asian, 7.0% were Black and 4.3% were of another race (Table 2).

3.2. Renal function

The prevalence of CKD in the subset of LEADER participants with prior CVD was 51.9%.

The proportions of participants with stage 1–5 eGFR-MDRD are shown in Table 1 (data for stage 4 and 5 categories are combined). The CKD-EPI equation identified more people with normal or severely reduced eGFR and fewer with mild-to-moderately reduced eGFR (Table 1), but there was a strong correlation between the results of the two methods ($r = 0.937$, $P < 0.0001$).

The prevalence of normal, mildly-to-moderately increased and markedly increased ACR was 50.2%, 33.6% and 16.3%, respectively (Table 1).

3.3. Renal function by gender and race

Fig. 1 shows eGFR-MDRD by gender and race. In Black individuals of both genders and women of 'other' race, eGFR revealed an asymmetric distribution with a curve shifted to the left. In Asian women, eGFR peaked at approximately 100 ml/min/1.73 m^2. In all other groups, eGFR showed a normal distribution with a peak at approximately 80 ml/min/1.73 m^2. Distributions of renal function defined by eGFR-MDRD categories were broadly similar among races and between genders (Supplementary Fig. 1).

3.4. Renal function by region

Fig. 2 shows CKD prevalence by region. CKD was highest in participants from Asia (75.8%) and lowest in participants from Europe (43.7%) or the Middle East (43.4%).

3.5. Baseline characteristics of participants with or without CKD

Baseline characteristics of participants with and without CKD are shown in Table 2. We observed an increase in age and diabetes duration in patients with CKD (Table 2). CKD was more common in the underweight (BMI ≤18.5 kg/m^2), normal-weight (BMI 18.5–25 kg/m^2) and morbidly obese (BMI >40 kg/m^2) groups than in the overweight or other obese groups (BMI 25–40 kg/m^2) (Table 2). Both hypertension and intensively treated hypertension, as defined by use of antihypertensive drugs, were more common in patients with CKD (Table 2). Compared to patients without CKD, more patients with CKD were treated with insulin only or insulin plus OADs, ARBs and diuretics. Fewer patients in the CKD group were treated with ACE-Is or acetyl salicylic acid (ASA) (Table 2). In the full population with prior CVD, 49.1% and 28.9% of patients were treated with either ACE-Is or ARBs, respectively, and only 2.8% of patients were treated with both (Supplementary Table 1).

3.6. Factors associated with CKD: primary model

A multivariable logistic regression model was used to investigate the association of different baseline factors with the prevalence of CKD (Table 3, Supplementary Table 2). Factors associated with an increase in the likelihood of CKD were as follows: more advanced age, male, longer diabetes duration, higher HbA_{1c}, higher SBP, higher heart rate, higher triglycerides, greater number of antihypertensive medications, being a current smoker, having an abnormal ECG (determined by the investigator), living in Asia, Australia, North America, Africa or South America (but not Middle East) versus living in Europe, type of diabetes treatment (treatment with basal insulin versus no insulin; treatment with no OAD [mostly treatment with insulin, or dietary intervention with no OAD] versus >2 OADs) and concomitant medications (not being on a beta-blocker, ASA or ACE-I). Factors associated with a decrease in the

Table 1
Demographic and laboratory characteristics of the prior CVD group by gender.

Parameters[a]	Full ($n = 7592$)	Female ($n = 2544$)	Male ($n = 5048$)
Age, y	63.9 (7.6); 64.0 (11.0)	64.0 (7.7); 63.0 (11.0)	63.9 (7.5); 64.0 (11.0)
Body weight, kg	92.3 (20.9); 90.1 (26.9)	85.5 (19.6); 83.1 (25.2)	95.7 (20.7); 93.3 (26.3)
BMI, kg/m^2	32.5 (6.3); 31.7 (8.0)	33.8 (6.9); 33.0 (9.0)	31.9 (5.9); 31.2 (7.4)
Waist circumference, cm	110.1 (16.1); 108.5 (19.0)	107.9 (15.7); 107.0 (19.3)	111.2 (16.1); 109.2 (19.3)
HbA_{1c}, % (mmol/mol)	8.67 (1.51); 8.30 (1.80)	8.77 (1.56); 8.40 (2.00)	8.61 (1.48); 8.20 (1.80)
	71.2 (16.5); 67.2 (19.7)	72.4 (17.1); 68.3 (21.9)	70.6 (16.2); 66.1 (19.7)
Duration of diabetes, y	12.8 (8.1); 11.4 (10.3)	13.6 (8.6); 12.0 (11.3)	12.4 (7.9); 11.1 (10.2)
SBP, mm Hg	137.1 (18.8); 136.0 (23.0)	138.5 (19.6); 137.5 (24.5)	136.4 (18.3); 135.0 (23.0)
DBP, mm Hg	77.5 (10.6); 78.0 (14.5)	77.6 (10.9); 78.5 (14.5)	77.5 (10.4); 78.0 (14.3)
Heart rate, beats/min	72.7 (11.3); 72.0 (16.0)	73.9 (10.9); 73.0 (14.0)	72.0 (11.5); 72.0 (16.0)
Creatinine, μmol/l	89.5 (39.6); 80.0 (37.0)	78.6 (37.6); 68.0 (34.5)	95.1 (39.3); 85.0 (37.0)
Renal function category (based on eGFR ml/min per 1.73 m^2 by MDRD; and CKD-EPI equations), %			
Normal (≥90)	34.5; 39.3	32.7; 39.3	35.4; 39.2
Mild (60–89)	38.8; 35.6	36.8; 32.8	39.8; 37.0
Moderate (30–59)	24.4; 22.6	27.5; 24.8	22.9; 21.5
Severe (<30)	2.3; 2.6	3.0; 3.2	2.0; 2.3
ACR (mg/mmol; $n = 6189$; male: 4247, female: 1942), %			
Normal (<3.0)	50.2	52.2	49.2
Mild-moderately elevated (3.0–30.0)	33.6	31.3	34.6
Markedly elevated (>30.0)	16.3	16.6	16.2
Lipids, mmol/l			
LDL cholesterol	2.28 (0.92); 2.12 (1.14)	2.51 (0.98); 2.36 (1.25)	2.16 (0.86); 2.01 (1.03)
HDL cholesterol	1.16 (0.31); 1.11 (0.37)	1.29 (0.33); 1.25 (0.40)	1.09 (0.29); 1.06 (0.33)
Triglycerides	2.07 (1.59); 1.71 (1.25)	2.02 (1.31); 1.73 (1.16)	2.10 (1.72); 1.70 (1.29)

ACR, urinary albumin-to-creatinine ratio; BMI, body mass index; BP, blood pressure; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; DBP, diastolic blood pressure; eGFR, estimated GFR; IQR, interquartile range; MDRD, Modification of Diet in Renal Disease study; SBP, systolic blood pressure; SD, standard deviation.

[a] Data are given as mean (SD); median (IQR) unless otherwise indicated.

Table 2
Baseline variables in the LEADER prior CVD population with or without CKD.[a]

Parameters, %	Full prior CVD (n = 7592)	No CKD (n = 3650)	CKD (n = 3942)
Categorical variables[b]			
Gender			
Female, *n* (%)	2544 (33.5)	1236 (33.9)	1308 (33.2)
Male, *n* (%)	5048 (66.5)	2414 (66.1)	2634 (66.8)
Age group, y			
50–59, *n* (%)	2295 (30.2)	1331 (36.5)	964 (24.5) [42.0][c]
60–69, *n* (%)	3502 (46.1)	1664 (45.6)	1838 (46.6) [52.5][c]
70–79, *n* (%)	1618 (21.3)	616 (16.9)	1002 (25.4) [61.9][c]
≥80, *n* (%)	173 (2.3)	39 (1.1)	138 (3.5) [78.0][c]
BMI group, kg/m^2			
≤18.5, *n* (%)	7 (0.1)	1 (0.0)	6 (0.2) [85.7][c]
>18.5, ≤25, *n* (%)	686 (9.0)	274 (7.5)	412 (10.5) [60.1][c]
>25, ≤30, *n* (%)	2151 (28.3)	1053 (28.8)	1098 (27.9) [51.0][c]
>30, ≤35, *n* (%)	2452 (32.3)	1196 (32.8)	1256 (31.9) [51.2][c]
>35, ≤40, *n* (%)	1405 (18.5)	714 (19.6)	691 (17.5) [49.2][c]
>40, *n* (%)	882 (11.6)	407 (11.2)	475 (12.0) [53.9][c]
Diabetes duration, y			
≤5, *n* (%)	1178 (15.5)	716 (19.6)	462 (11.7) [39.2][c]
>5, ≤10, *n* (%)	1934 (25.5)	1032 (28.3)	902 (22.9) [46.6][c]
>10, ≤15, *n* (%)	1847 (24.3)	911 (25.0)	936 (23.7) [50.7][c]
>10, ≤20, *n* (%)	1244 (16.4)	498 (13.6)	746 (18.9) [60.0][c]
>20, *n* (%)	1385 (18.2)	492 (13.5)	893 (22.7) [64.5][c]
Race			
Asian, *n* (%)	753 (9.9)	218 (6.0)	535 (13.6)
Black, *n* (%)	535 (7.0)	227 (6.2)	308 (7.8)
White, *n* (%)	5974 (78.7)	3041 (83.3)	2933 (74.4)
Other, *n* (%)	330 (4.3)	164 (4.5)	166 (4.2)
Region			
Europe, *n* (%)	2929 (38.6)	1649 (45.2)	1280 (32.5)
North America, *n* (%)	2342 (30.8)	1038 (28.4)	1304 (33.1)
South America, *n* (%)	868 (11.4)	383 (10.5)	485 (12.3)
Middle East, *n* (%)	422 (5.6)	239 (6.5)	183 (4.6)
Asia, *n* (%)	592 (7.8)	143 (3.9)	449 (11.4)
Africa, *n* (%)	244 (3.2)	116 (3.2)	128 (3.2)
Australia, *n* (%)	195 (2.6)	82 (2.2)	113 (2.9)
Smoking			
Current smoker, *n* (%)	927 (12.2)	449 (12.3)	478 (12.1)
Previous smoker, *n* (%)	3670 (48.3)	1806 (49.5)	1864 (47.3)
Never smoked, *n* (%)	2995 (39.4)	1395 (38.2)	1600 (40.6)
Use of antihypertensive drugs			
Yes, *n* (%)	7077 (93.2)	3363 (92.1)	3714 (94.2)
No, *n* (%)	515 (6.8)	287 (7.9)	228 (5.8)
Intensively treated HT (prescribed ≥3 antihypertensive drugs)			
Yes, *n* (%)	1583 (20.9)	608 (16.7)	975 (24.7)
No, *n* (%)	6009 (79.1)	3042 (83.3)	2967 (75.3)
ECG			
Missing *n* (%)	32 (0.4)	15 (0.4)	17 (0.4)
Normal *n* (%)	2877 (37.9)	1496 (40.3)	1381 (35.6)
Abnormal *n* (%)	4683 (61.7)	2203 (59.5)	2480 (64.0)
Previous diabetes treatment			
None/diet, *n* (%)	405 (5.3)	163 (4.5)	242 (6.1)
Insulin only, *n* (%)	596 (7.9)	163 (4.5)	433 (11.0)
OAD only, *n* (%)	3927 (51.7)	2100 (57.5)	1827 (46.3)
Insulin + OADs, *n* (%)	2664 (35.1)	1224 (33.5)	1440 (36.5)
Number of OADs ('OAD only')			
1 OAD, *n* (%)	1539 (39.2)	860 (41.0)	679 (37.2)
2 OADs *n* (%)	2131 (54.3)	1120 (53.3)	1011 (55.3)
>2 OADs, *n* (%)	257 (6.5)	120 (5.7)	137 (7.5)
Type of insulin ('insulin only' plus 'insulin + OADs')			
Basal, *n* (%)	2622 (80.4)	1135 (81.8)	1487 (79.4)
Premixed, *n* (%)	599 (18.4)	234 (16.9)	365 (19.5)
Basal + premixed, *n* (%)	39 (1.2)	18 (1.3)	21 (1.1)
HbA_{1c} on target (<7% [53 mmol/mol]), *n* (%)	580 (7.6)	305 (8.4)	275 (7.0)
Antihypertensive drugs			
ACE-I, *n* (%)	3935 (51.8)	1986 (54.4)	1949 (49.4)
ARB, *n* (%)	2404 (31.7)	982 (26.9)	1422 (36.1)
Diuretic, *n* (%)	3350 (44.1)	1408 (38.6)	1942 (49.3)
Other concomitant medications			
Statins, *n* (%)	6000 (79.0)	2879 (78.9)	3121 (79.2)
Other lipid-lowering, *n* (%)	163 (2.1)	80 (2.2)	83 (2.1)
ASA, *n* (%)	5103 (67.2)	2542 (69.6)	2561 (65.0)
NSAID, *n* (%)	80 (1.1)	44 (1.2)	36 (0.9)
Previous comorbidities (%)			
MI, *n* (%)	1471 (19.4)	754 (20.7)	717 (18.2)
Angina, *n* (%)	2572 (33.9)	1453 (39.8)	1119 (28.4)

Table 2 (*continued*)

Parameters, %	Full prior CVD ($n = 7592$)	No CKD ($n = 3650$)	CKD ($n = 3942$)
Stroke, *n* (%)	1097 (14.4)	563 (15.4)	534 (13.5)
Gallstones, *n* (%)	889 (11.7)	403 (11.0)	486 (12.3)
Continuous variables[d]			
HbA_{1c} (%)	8.67 (1.51); 8.3 (1.8)	8.50 (1.37); 8.1 (1.7)	8.82 (1.61); 8.4 (2.1)
HbAc (mmol/mol)	71.3 (16.50); 67.2 (19.6)	69.4 (14.97); 65.0 (18.5)	72.9 (17.60); 68.3 (22.9)
Lipids (mmol/l)			
Triglycerides	2.07 (1.59); 1.71 (1.25)	1.99 (1.44); 1.64 (1.19)	2.15 (1.72); 1.76 (1.29)
HDL cholesterol	1.16 (0.31); 1.11 (0.37)	1.17 (0.31); 1.11 (0.36)	1.15 (0.31); 1.11 (0.38)
LDL cholesterol	2.28 (0.92); 2.12 (1.14)	2.26 (0.90); 2.12 (1.12)	2.29 (0.93); 2.11 (1.15)

ACE-I, ACE-inhibitor; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CKD, chronic kidney disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; ECG, electrocardiogram; eGFR, estimated GFR; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein; HT, hypertension; IQR, interquartile range; LDL, low-density lipoprotein; MDRD, Modification of Diet in Renal Disease study; MI, myocardial infarction; NSAID, non-steroid anti-inflammatory drug; OAD, oral antidiabetic drug; SD, standard deviation.

[a] CKD defined as eGFR <60 ml/min per 1.73 m^2 using the MDRD equation and/or ACR ≥3.0 mg/mmol.

[b] Each factor, such as previous diabetes treatment, contains different categories that are exhaustive and mutually exclusive.

[c] CKD prevalence in square brackets calculated from patients (n) per group.

[d] Data are given as mean (SD); median (IQR).

probability of having CKD were increased DBP, not being on a diuretic treatment and history of MI, angina or stroke (Supplementary Table 2).

3.7. Factors associated with CKD: sensitivity analyses

Results of multivariable logistic regression model sensitivity analyses are summarized in Supplementary Table 2 and presented in detail in Supplementary Tables 3–6.

Briefly, the present study identified several factors associated with CKD in patients with T2DM and prior CVD, using five different models. Baseline factors associated with higher prevalence of CKD across all models were: more advanced age; longer diabetes duration; higher SBP; higher triglycerides; greater number of antihypertensive medications; living in North America, South America or Asia versus living in Europe; no OAD treatment (mostly insulin treatment) versus >2 OADs; treatment with basal insulin versus no insulin; and not being on a beta-blocker or ACE-I.

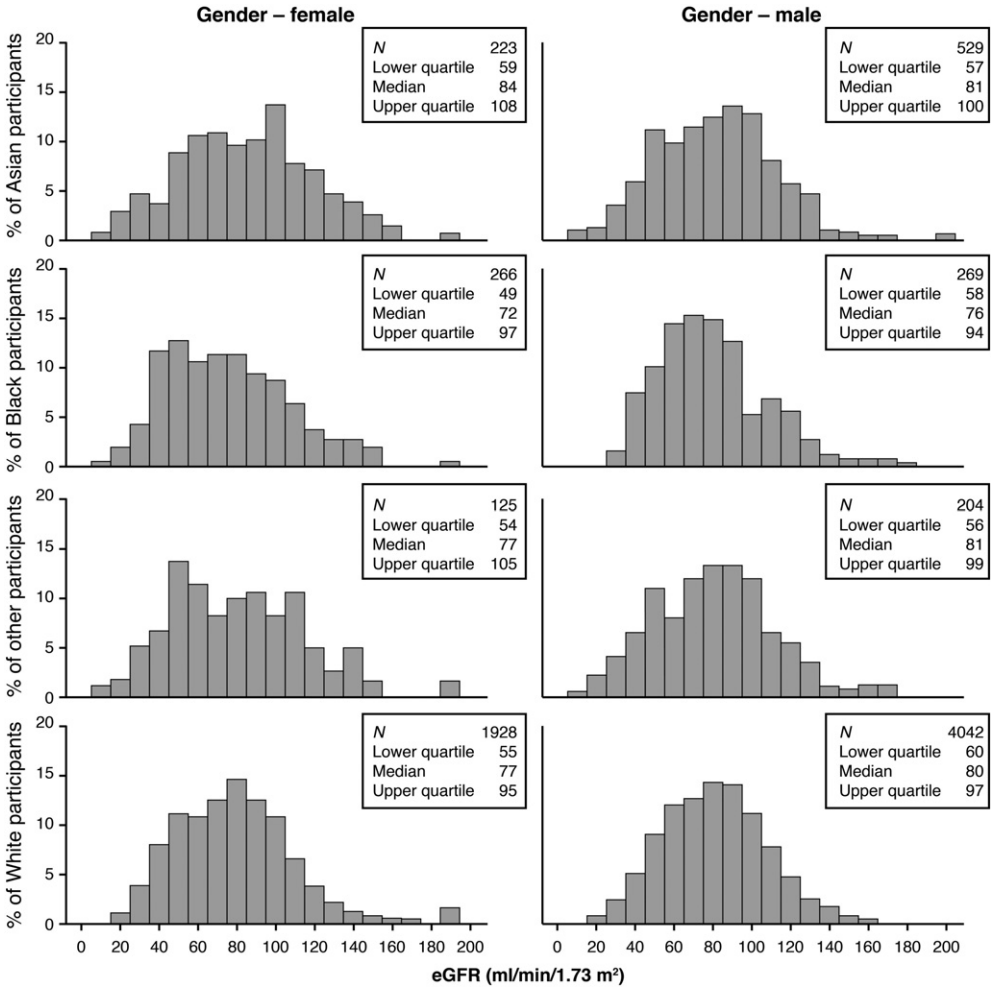

Fig. 1. eGFR-MDRD in LEADER participants with prior CVD at baseline by race and gender. Race information was collected using the following categories: Asian, Black, White or other. CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease study.

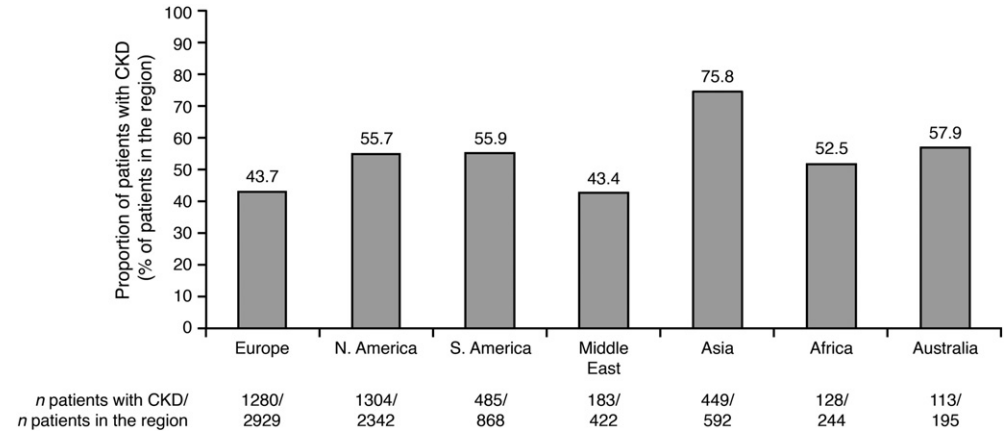

Fig. 2. The prevalence of CKD* in LEADER participants with prior CVD at baseline by region. * CKD defined as eGFR-MDRD <60 ml/min per 1.73 m^2 and/or ACR ≥3.0 mg/mmol.

4. Discussion

4.1. Study objectives and main results

We report that more than half of the LEADER population with prior CVD had some degree of CKD prior to initiation of the trial drug.

Our findings demonstrate that the duration of diabetes is a factor associated with CKD, which is consistent with several other studies (Parving et al., 2006; Yokoyama et al., 2009). Parving et al. showed that duration of diabetes was a significant ($P < 0.0001$) risk factor for micro- or macroalbuminuria (an early marker of diabetic nephropathy and leading cause of CKD), in White, Black or Asian patients with TD2M. In addition, Yokoyama et al. established that the duration of diabetes was significantly ($P = 0.037$) associated with CKD in Japanese patients with TD2M.

Putting our study into context, the prevalence of those with CKD (51.9%) is higher than those of the Renal Insufficiency And Cardiovascular Events (RIACE) study's CKD population (37.6%) (Pugliese et al., 2014), which examined a cohort of 15,773 Italian subjects with T2DM. The differences in prevalence of CKD and between the two studies may be attributable, at least in part, to the randomized trial inclusion criteria and observational study designs of LEADER and RIACE, respectively.

Increasing DBP and history of angina or stroke were associated with a decreasing prevalence of CKD across all five models. The association between higher DBP and lower CKD prevalence might appear counter to the associations between elevated SBP and increased CKD prevalence. However, a meta-analysis of people without diabetes (Jafar et al., 2003), and the Systolic Hypertension in the Elderly Program (SHEP) (Young et al., 2002), both indicated that higher SBP, but not higher DBP, is strongly associated with progression of kidney disease.

Our finding that not being on a beta-blocker or ACE-I is associated with higher prevalence of CKD is consistent with previous observations that BP-lowering interventions prevent renal adverse events (Lv et al., 2012). Increasing numbers of BP-lowering medications were also associated with increased CKD prevalence in patients with T2DM and prior CVD, suggesting that annual screening for renal impairment is even more important in people with T2DM who also have intensively treated hypertension. Moreover, studies with a beta-blocker, carvedilol demonstrated attenuated increases in albuminuria in patients with CKD with hypertension. The absence of a beta-blocker may therefore remove any renoprotection, subsequently elevating the risk of CKD (Bakris, Hart, & Ritz, 2006).

Several studies have shown that prior CVD was associated with increased CKD prevalence and risk (Elsayed et al., 2007; Rodriguez-Poncelas et al., 2013). Interestingly, in our study, having a history of angina or stroke was associated with decreased CKD prevalence across all five models.

We also found a positive correlation between more advanced age and CKD in patients with T2DM with prior CVD across all models. This aligns with data from broader populations. For example, in the NHANES, the prevalence of diabetic kidney disease was highest in those aged ≥65 years, in both the general population and those with T2DM (de Boer et al., 2011). Indeed, Coresh et al. (2003) showed that the creatinine clearance estimates demonstrated a more marked decrease with age in patients with CKD. Yokoyama et al. established that age was significantly ($P < 0.0001$) associated with CKD in Japanese patients with TD2M (Yokoyama et al., 2009). Another study, evaluating outcomes of CKD in US veterans, found that, among those with comparable levels of eGFR, older patients had higher rates of death and lower rates of ESRD than younger individuals (O'Hare et al., 2007), suggesting that age may be an important modifier in CKD. These findings challenge taking a uniform, 'age-neutral' approach to management of CKD, and underline the critical need for better prognostic tools to identify older individuals who will progress to ESRD.

According to regression models, the present study found no differences in the distribution of CKD between people of Asian, Black or 'other' race versus those of White race with T2DM and prior CVD, although the odds of having eGFR-CKD-EPI <60 ml/min/1.73 m^2 were elevated in people from 'other' race versus those of White race (Supplementary Table 2).

Our data revealed an increased prevalence of CKD among people with T2DM and prior CVD from outside Europe, except the Middle East. This finding supports the suggestion that rates of CKD continue to be higher in developing countries. Given the large economic and health burden of diabetes and its complications, early and frequent screening for diabetes and renal impairment is recommended, and the focus should be on disease prevention.

A significant association between higher BMI and CKD was not consistently observed across all models in the present analysis. The obesity cohort of the Framingham Heart Study had increased odds of developing stage 3 CKD relative to participants with normal BMI, but the additional risk disappeared after adjustment for known cardiovascular risk factors, suggesting the relationship between obesity and CKD may be mediated via cardiovascular risk factors (Foster et al., 2008). All patients in our study already had elevated cardiovascular risk, which could explain, in part, the inconsistent observations for higher BMI and CKD. Additionally, in a multinational population, BMI might be a good indicator for obesity.

In the present study, we used the eGFR-MDRD equation in our primary statistical model and the CKD-EPI formula in our sensitivity analyses, with a strong correlation evident between the results of the two methodologies. In the present study, however, estimation of GFR using the CKD-EPI equation identified a higher percentage of people with normal renal function and slightly more with severe renal impairment. The accuracy of these two equations in estimating renal

Table 3
Multivariable logistic regression modelling the probability of CKD (based on eGFR-MDRD <60 ml/min per 1.73 m^2 and/or urine ACR ≥3.0 mg/mmol) in the prior CVD group of LEADER.

Factor (level)	OR; 95% CI	*P*-value
Age (per SD increase, y)	1.417; 1.337–1.501	<0.0001
Male gender (ref. female)	1.242; 1.105–1.397	0.0003
BMI (per SD increase, kg/m^2)	1.028; 0.971–1.088	0.3457
Diabetes duration (per SD increase, y)	1.203; 1.137–1.272	<0.0001
HbA_{1c} (per SD increase, %)	1.259; 1.189–1.334	<0.0001
Not at HbA_{1c} target (ref. HbA_{1c} ≤7%)	0.824; 0.675–1.006	0.0574
SBP (per SD increase, mm Hg)	1.290; 1.202–1.385	<0.0001
DBP (per SD increase, mm Hg)	0.887; 0.824–0.955	0.0015
No HT (ref. ≥140/80 mm Hg)	1.011; 0.871–1.173	0.8867
Number of antihypertensives (per medication)	1.529; 1.396–1.676	<0.0001
Heart rate (per SD increase, beats per minute)	1.058; 1.003–1.1117	0.0380
Triglycerides (per SD increase, mmol/l)	1.209; 1.141–1.284	<0.0001
Current smoker (ref. never smoked)	1.271; 1.073–1.507	0.0056
Previous smoker (ref. never smoked)	1.002; 0.894–1.123	0.9752
Race (ref. White)		
Asian	1.354; 0.953–1.926	0.0905
Black	0.917; 0.743–1.134	0.4244
Other	0.856; 0.657–1.115	0.2500
Region (ref. Europe)		
North America	1.526; 1.339–1.739	<0.0001
South America	1.397; 1.159–1.683	0.0004
Middle East	1.214; 0.967–1.523	0.0939
Asia	4.357; 2.907–6.537	<0.0001
Africa	1.500; 1.098–2.050	0.0109
Australia	1.574; 1.137–2.184	0.0064
Diabetes medications		
No OAD[a] (ref. >2 OADs)	1.743; 1.317–2.306	0.0001
1 OAD (ref. >2 OADs)	1.019; 0.794–1.308	0.8798
2 OADs (ref. >2 OADs)	0.927; 0.725–1.186	0.5468
Basal and premixed insulin (ref. no insulin)	0.759; 0.382–1.518	0.4311
Basal insulin (ref. no insulin)	1.125; 1.006–1.259	0.0397
Premixed insulin (ref. no insulin)	1.099; 0.895–1.350	0.3696
Abnormal ECG (ref. normal ECG)	1.165; 1.050–1.294	0.0041
Comorbid conditions (ref. no history of the condition)		
MI	0.690; 0.597–0.797	<0.0001
Angina	0.560; 0.497–0.632	<0.0001
Stroke	0.706; 0.611–0.815	<0.0001
Gallstones	1.098; 0.937–1.287	0.2492
Concomitant medications (ref. yes)		
No beta-blocker	1.507; 1.302–1.745	<0.0001
No ASA	1.157; 1.035–1.292	0.0101
No diuretic	0.723; 0.651–0.804	<0.0001
No ACE-I	1.342; 1.148–1.569	0.0002
No ARB	1.114; 0.942–1.318	0.2091
No statin	0.943; 0.828–1.073	0.3701
No NSAID	1.507; 0.926–2.470	0.1007

ACE-I, ACE-inhibitor; ACR, urinary albumin-to-creatinine ratio; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic BP; ECG, electrocardiogram; eGFR, estimated GFR; HbA_{1c}, glycated hemoglobin; HT, hypertension; MDRD, Modification of Diet in Renal Disease study; MI, myocardial infarction; NSAID, non-steroid anti-inflammatory drug; OAD, oral antidiabetic drug; SBP, systolic blood pressure; SD, standard deviation.
[a] Mostly insulin treatment, or dietary intervention with no OAD.

function in people with T2DM has been questioned. Highlighting the disparity between the two equations, in the RIACE cohort, those with impaired eGFR or CKD with the MDRD study equation only showed lower CVD prevalence rates and coronary heart disease risk scores. This trend was predominantly driven by female gender, younger age and shorter diabetes duration, as compared with those with both formulas; however, in contrast, the opposite trends were observed in patients in the same categories with the CKD-EPI equation only (Pugliese et al., 2014). Indeed, CKD prevalence, gender ratios, and Kidney Disease: Improving Global Outcomes (KDIGO) composite risk groupings can vary widely depending on the equation used (Kitiyakara et al., 2012). New markers, such as cystatin C, have been suggested to assess more accurately the wider ranges of GFR in multi-ethnic countries (Ho & Teo, 2010). In this regard, urine albumin concentration and ACR have been established as acceptable tests for the screening of albuminuria in Indo-Asian patients (Jafar, Chaturvedi, Hatcher, & Levey, 2007). In a study of modified equations developed in Asiatic populations, Liu et al. (2014) found limitations in such equations. Some studies, however, suggest that the CKD-EPI formula has improved accuracy, especially at higher GFRs (Stevens et al., 2010; Teo et al., 2011). Further, Teo et al. advised against using ethnic adjustment for estimating GFR in multi-ethnic Asian patients with CKD; based on these data, we did not use these adjustments in our study.

Half of our global T2DM population with prior CVD had an abnormal ACR (normal, 50%; microalbuminuria, 34%; macroalbuminuria, 16%). Our results are consistent with those from the cross-sectional DEMAND study, in which one random urinary ACR was measured in 24,151 patients with T2DM from 33 countries, and the global prevalence of normo-, micro- and macroalbuminuria was 51%, 39% and 10%, respectively (Parving et al., 2006).

Albuminuria is a marker for glomerular injury as well as endothelial dysfunction and is often an early clinical indicator of CKD (Bakris & Molitch, 2014). However, impaired GFR may be observed without substantial elevation in ACR in patients with T2DM (Coresh et al., 2003; de Boer et al., 2011). In our cohort, at baseline, nearly 60% of those with normal ACR had mild-to-moderately decreased eGFR-MDRD (Supplementary Fig. 2), confirming that nonalbuminuric renal impairment in patients with diabetes is not uncommon. This finding was supported by several studies in which diminished GFR occurred in nonalbuminuric patients (Kramer, Nguyen, Curhan, & Hsu, 2003; Pugliese et al., 2014; Retnakaran et al., 2006; Thomas et al., 2009). In terms of prevalence, in a nationally representative cohort of 3893 patients with T2DM, Thomas et al. (2009) established that of the 23.1% of individuals with T2DM who had eGFR <60 ml/min/1.73 m^2, 55% had nonalbuminuric renal impairment.

The frequent manifestation of impaired GFR supports current guidelines recommending screening for albuminuria in addition to GFR (American Diabetes Association, 2016; Canadian Diabetes Association Clinical Practice Guidelines Expert Committee, 2013; Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group, 2013).

There are also people with increased ACR, but normal GFR, as in the cohort studied here, in which approximately one-third of those with mild-to-moderately increased ACR and 16% of those with markedly increased ACR had normal eGFR-MDRD (Supplementary Fig. 2). Current guidelines from the American Diabetes Association (American Diabetes Association, 2016) and US National Kidney Foundation (National Kidney Foundation, 2012) recommend measuring albuminuria more than once, and state that two of three samples should be elevated over 3–6 months for confirmation of increased albuminuria (Tuttle et al., 2014). In LEADER, urine specimens were collected at randomization and then yearly for the duration of the trial (Marso et al., 2013).

It is clear that the relationship of ACR to ESRD and CVD risk is a continuum, starting from 'normal' levels. However, the development of microalbuminuria into progressive nephropathy is not inevitable, and glucose, BP, lipid control and use of ACE-I or ARB are crucial in delaying its progression.

The strengths of this study include using broad data, simultaneously examining ACR and eGFR in a central laboratory, and using several definitions of CKD. LEADER enrolled subjects with prior CVD and consisted of a diverse, multinational population. The large sample size permitted us to perform categorical analyses for age at 10-year intervals, for BMI from lean to morbid obesity and for diabetes duration from 5 to >20 years.

4.2. Limitations

The present study includes limitations that warrant discussion. Some of the factors associated with CKD may have a common background, e.g., more advanced age and longer diabetes duration. ACR was measured once at randomization. As this study uses baseline data, it is not possible to establish any direction of causality. It should also be noted that we cannot exclude the etiologies of CKD other than diabetes

in the population studied. Due to the large sample size, some of the associations identified may be statistically significant but not clinically relevant. For example, while a history of MI or stroke is a factor associated with a decrease in the probability of having CKD, the prevalence of acute MI or stroke is not markedly different between patients with or without CKD. LEADER specifically enrolled subjects at high cardiovascular risk, and this study included only the prior CVD group, therefore, our results are only directly applicable to patients with T2DM and CVD. Finally, the study design also dictates that the results presented apply to moderate to severe CKD, but not mild or end-stage renal disease.

5. Conclusions

CKD prevalence is high among patients with T2DM with prior CVD. Age, glycemic and BP control, diabetes treatment, comorbidities and concomitant medications used were found to be associated with CKD prevalence. Screening for CKD in patients with T2DM and prior CVD and enrolling patients at high risk of CKD into preventive programmes may be warranted.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.jdiacomp.2016.06.001.

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