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Original article

Cardiovascular outcome according to renal status in Finnish patients with type 2 diabetes

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ABSTRACT

Background: : Type 2 diabetes (T2DM) increases the risk for chronic kidney disease (CKD). The objective of this study was to describe the characteristics of patients with T2DM and assess their cardiovascular (CV) and renal outcomes as well as survival in a real-life setting in Finland. The study aimed to map the use of diagnostic and monitoring measures in the management of T2DM patients in clinical practice and to assess the proportion of patients that could benefit from SGLT2 inhibitor treatment.

Methods: : This retrospective registry study included 29,628 adult T2DM patients gathered from national registries in Finland between 2012 and 2018. Patients were included from primary and specialized care. From all patients, all available health care data, including laboratory results, degree of albuminuria, and eGFR data, was gathered. The occurrence of CV events and end-stage kidney disease (ESKD) was assessed using a multivariable Cox proportional hazards model. All-cause and CV deaths were visualized using Kaplan-Meier plots.

Results: : Overall, patients were more frequently male (54%), and their mean age was 66 (SD = ±12.4) years. eGFR status was available for 21,889 patients, and among these patients CKD stage 3–5 was observed in 3,945 (13.3%) patients. Data on albuminuria was available in less than half (45.5%) of the cohort. In patients with available urinary albumin measurement, increased albumin excretion was present in 12% of patients with CKD class 1–2, of whom 1.6% had severe albuminuria. Of all comorbidities, atrial fibrillation was independently associated with the risk of CV events and ESKD.

Conclusions: : This large real-world study confirms that CV morbidity and mortality are substantial within T2DM patients, and that age, prior kidney function, albuminuria and prior diagnosis of AF were associated with the risk of CV events, including death, and progression to ESKD. Despite guideline recommendations, monitoring and treatment of T2DM was suboptimal leaving patients at risk of inadequate treatment.

1. Introduction

Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease (CKD) in patients starting renal replacement therapy (RRT) and is associated with increased cardiovascular mortality [1–4]. DKD is defined by the sustained presence of albuminuria and/or decreased glomerular filtration rate (GFR, less than 60 ml/min/1.73 m^2). Previous studies have shown an increased incidence of both albuminuria and decreased estimated GFR (eGFR) in type 2 diabetes (T2DM) patients: in the UKS Prospective Diabetes Study (UKPDS), the incidence of increased albuminuria was 2.0% per year with 25% prevalence 10 years after T2DM diagnosis [5–7]. Thus, decreased eGFR without concomitant albuminuria is also common within the T2DM patient group. Among patients starting RRT, the incidence of DKD doubled between the years 1991–2001 according to a survey by the United States Renal Data System (USRDS) [8]. Although improvements in diagnostics and prevention have slowed down the incidence of DKD, the screening and management of DKD, regardless of international guidelines, have remained suboptimal [7,9].

Poor glycemic control and kidney function are both associated with increased risk of atrial fibrillation (AF), which, is a common condition in patients with T2DM and/or CKD [10–12]. AF has been associated with excess mortality and cardiovascular morbidity in both CKD and T2DM patients, highlighting the clinical significance of AF

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diagnosis and treatment in these patients [13,14]. Interestingly, a recent large meta-analysis showed that sodium -glucose cotransporter-2 (SGLT2) inhibitors might be associated with a decreased risk of incident AF in patients with and without T2DM, underscoring the need for assessing the prevalence of AF in the contemporary T2DM patient population [10,15].

Clinical trials have shown that SGLT2 inhibitors reduce the risk of cardiovascular events in T2DM, which has expanded their use within the T2DM patient population. Recently, further evidence has been emerging on the renoprotective effect of SGLT2 inhibitors. Dapagliflozin and canagliflozin randomized controlled trials (RCT) have demonstrated favorable effects on renal outcomes in patients with T2DM and DKD with concomitant albuminuria [16–18].

Although these RCTs undeniably demonstrated the benefit of SGLT2 inhibitors in T2DM patients, the proportion of patients with similar clinical presentation of reduced kidney function and albuminuria corresponding to the participants in the RCTs [16,17] within the T2DM patient population remains unknown. The aim of this retrospective registry study was to describe the characteristics of patients with T2DM and assess their cardiovascular (CV) and renal outcomes as well as survival for the first time in a real-world cohort from both primary care and specialized care in Finland. Furthermore, this study aimed to map the use of routine diagnostic and monitoring measures in the management of T2DM patients in contemporary clinical practice and to assess the proportion of patients that could benefit from SGLT2 inhibitor treatment.

2. Methods

2.1. Study design and data

This was a retrospective registry study utilizing electronic patient record data collected from both primary and specialized care units in South-West Finland. The formation of the study cohort is presented in **Fig. 1**. The cohort was formed according to diabetes drug purchase and reimbursement records of the Social Insurance Institution of Finland. All patients aged ≥18 years in the hospital district of South-West Finland (HDSWF) with prevalent or incident reimbursement number for the treatment of diabetes between Jan 2012 and Dec 2018 were included in the study. Patients with type 1 diabetes or with diagnosed sepsis were excluded from the cohort. The data on reimbursement numbers were complemented with patient records using the specialized care electronic patient registry of HDSWF, and national registries: Social Insurance Institution (SII), National Institute for Health and Welfare (THL) and Statistics Finland. For all analyses, the index date, i.e., the date from which patient data was analyzed onwards, was set to 1.1.2012 for prevalent patients or to the date of first reimbursement of diabetes medication for incident patients. The patients were followed from the index until the end of reimbursement, the initiation of SGLT2 inhibitor medication, death, or the end of study. STROBE checklist was used in study design and reporting.

To assess the proportion of patients with an indication for SGLT2 inhibitor use, data on patients age (>30 years), gHbA1c (6.5–12%), eGFR (less than 89 ml/min/1.73 m^2), and increased albuminuria were collected. The criteria were selected based on previous clinical trial criteria [16,17].

The patients were stratified according to CKD stage and albuminuria classes based on data at index. Patients were stratified to mutually exclusive subgroups using data ± 1 year around the index. For patients with multiple records, the data point closest to index was used. eGFR values were computed from plasma creatinine measures using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and CKD was categorized according to KDIGO CKD stages (CKD1: eGFR ≥ 90 ml/min/1.73 m^2; CKD2: eGFR 60–89 ml/min/1.73 m^2; CKD3: eGFR 30–59 ml/min/1.73 m^2; CKD4: eGFR 15–29 ml/min/1.73 m^2; CKD5: eGFR < 15 ml/min/1.73 m^2, dialysis, kidney transplant or diagnosis of end-stage kidney disease (ESKD)) (9,10). To define the albuminuria classes, all possible laboratory measures (spot urine albumin to creatinine ratio (UACR), first morning urine albumin, and 24-hour urine albumin) for urine albumin were utilized and the category of albuminuria (normal, moderate, severe; exact definitions are presented in the **Supplemental Table S1**) was determined according to KDIGO staging system [19]. The permission to use patient data was granted by the register holders.

2.2. Statistical analysis

Patient characteristics were described with mean ± standard deviation (SD) or median (inter-quartile range [IQR]) in the case of normally distributed or skewed continuous variables, respectively, and with absolute and relative (percentage) frequencies in the case of categorical variables. Groupwise comparisons for normally distributed and skewed continuous variables were performed using the ANOVA and Kruskall-Wallis test, respectively. For the categorical variables, the Chi squared test or Fisher's exact test was used as appropriate.

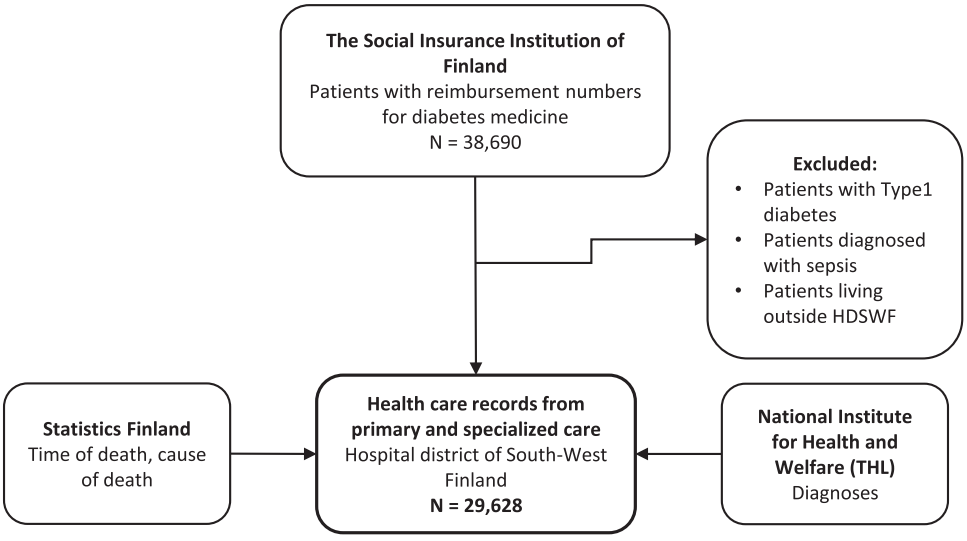

Fig. 1. Cohort formation.

Overall survival (OS) and CV deaths were analyzed using Kaplan-Meier estimates and the difference in survival between strata was tested using the log-rank test. For OS, the patients were followed from index to death (event) or end of study (censoring event). For CV mortality, the outcome was defined as CVD related death (event), death by other cause (censoring), or end of study (censoring event). A death recorded with any of the I20-I79 diagnosis codes (ICD-10) as a main or immediate cause of death, was classified as a CV death.

The effect of predetermined variables of interest on the occurrence of CV events and ESKD were assessed in a multivariable Cox proportional hazards model using age, sex, CKD and albuminuria classes, prior CV events (including any previous event of myocardial infarction, ischemic stroke, or unstable angina pectoris; see **Supplemental Table S2** for details), and AF as covariates. Age was assessed as a continuous variable, whereas sex and previous CV events were assessed as binary variables, and CKD stages, albuminuria stages and AF as time-varying categorical variables. For occurrence of CV events, the outcome was defined as non-fatal CV event (event), death related to CVD, non-CVD death (censoring), or end of study (censoring). For occurrence of ESKD, the outcome was defined as ESKD diagnosis (defined as diagnosis of N18.0, eGFR<15 ml/min/1.73 m^2, dialysis, or kidney transplant; event), death (censoring), or end of study (censoring). Additionally, SGLT2 initiation and end of reimbursement were considered as censoring events in all time-to-event analyses.

Due to the retrospective nature of this study, missing and incomplete data was expected in some of the medical records. Patients' records were not excluded due to missing data and missing data was not imputed. Proportion of missingness was reported for the patient characteristics. A significance level of $p<0.05$ was used in all statistical testing and all tests were two-sided. All analyses were conducted using R (version 4.0.2) [20].

3. Results

3.1. Cohort formation and patient characteristic

Overall, 38,690 T2DM patients were extracted from the Hospital district of South-West Finland based on the reimbursement numbers for diabetes medication in the registry of social insurance institution of Finland (Kela). Of these patients, 29,628 (76.6%) were eligible for the study according to the set inclusion criteria (**Fig. 1**). Patients were more frequently male (54%) and their mean age was 66 years (SD = ±12.4) (**Table 1**). Altogether, 67% of the patients were on angiotensin converting enzyme inhibitors (ACEi) or angiotensin II receptor blockers (ARB).

Patients in the missing CKD class, n = 7739 (26.12%), i.e., lacking the eGFR measurement, formed a substantial group in this study. The characteristics of these patients resembled those with CKD1−2. HbA1c was measured in 65% of patients and less than half (46%) of patients had documentation of measured albuminuria (**Fig. 2**). Thus, a substantial proportion of patients were left without eGFR and albuminuria measurements.

Altogether, 13.3% of the patients had eGFR <60 ml/min/1.73 m^3 (**Table 1**). The median eGFR for all patients with eGFR data available was 82 ml/min/1.73 m^2 (IQR 66−94 ml/min/1.73 m^2), indicating at least minor kidney dysfunction in half of the T2DM patient population. Most patients had CKD1 (n = 7791, 26.3%) or CKD2 (n = 10,153, 34.3%). Patients with CKD3−5 (13.3%) were older compared to those with CKD1 or CKD2 and had slightly higher gHbA1c values. For all patients, the median HbA1c was 6.5% (IQR 6.0−7.2%) (47.5 mmol/mol). The patients with an indication for SGLT2 inhibitors were summarized in **Fig. 2**.

Of all patients, 1976 (6.5%) had moderate (N = 1651) or severe (N = 325) albuminuria (**Table 2**). As expected, albuminuria was mostly absent in patients with normal kidney function or CKD 1−2 and, conversely, most (61.1%) of patients with CKD 5 were observed with albuminuria. However, a significant proportion of patients presenting moderate or severe albuminuria had normal or only slightly decreased eGFR. In patients with available albumin measurement, albuminuria was present in 12.2% of patients with CKD class 1−2, of whom 1.6% had severe albuminuria. Accordingly, of the patients with available data on both eGFR and urinary albuminuria (N = 13 152), 25.4% of patients had either eGFR less than 60 ml/min/1.73 m^3 or increased albuminuria, thus concluding in DKD. In patients with CKD 3−5, urinary albumin was increased in 29% of patients.

Most common baseline co-morbidities are presented in the **Supplemental Table S3**. A substantial proportion of the patients had been diagnosed with CV diseases: chronic ischemic heart disease (11.7%), AF (10.8%) or heart failure (HF) (6.1%). CV diseases at baseline were more frequent in later stages of CKD, with AF prevalence increasing from 6% in CKD 1 to 32% in CKD 4 and HF increasing from 3% to 33%, respectively.

3.2. Predictors of end stage kidney disease and cardiovascular events

Results from the multivariable Cox proportional hazards models predicting CV events are presented in **Table 3A**. Overall, the risk for CV events was higher in men and increased with increasing age and the occurrence of severe albuminuria (HR 2.25 [95% CI 2.02, 2.50], $p <$ 0.001) or ESKD (HR 2.40 [95% CI 1.97, 2.93], $p < 0.001$). Accordingly, the risk increased with advancing CKD, where patients with CDK 4 or CKD 5 had 1.69- and 2.4-fold risk for CV events compared to CKD 1, respectively ($p<0.001$). Moreover, any previous CV event (e.g., myocardial infarction, ischemic stroke, or unstable angina pectoris) and AF were independently associated with higher risk for CV events.

The results of the multivariable Cox proportional hazards model for incident ESKD are summarized in **Table 3B**. The risk of progression to ESKD was associated with lowered baseline kidney function, being 4.41- and 22.61-fold for CKD 3 and CKD 4 compared to CKD 1, respectively. Furthermore, the risk for ESKD was increased with moderate to severe albuminuria. However, previous CV events (myocardial infarction, ischemic stroke or unstable angina pectoris) were not whereas prior diagnosis of AF was (HR 1.35 [95% CI 1.17, 1.56], $p <$ 0.001) associated with ESKD risk. The association between AF and ESKD progression remained independent of CKD class or albuminuria.

3.3. All-cause mortality and CV mortality

Overall, the 7-year survival was 77% and the probability of dying due to a CV event during the follow-up was 13% (**Fig. 3A**). Impaired kidney function increased the risk of mortality and the patients with CKD 4 and CKD5 had the poorest survival (**Fig. 3B**). All-cause median survival was 3.3 and 3.2 years for CKD4 and CKD5 patients (**Fig. 3B**), respectively, whereas the corresponding time to CV death was 5.1 and 6.8 years (**Fig. 3C**).

4. Discussion

This was the first large real-world registry study describing the T2DM patient population in Finland. As the data was gathered from both primary and specialized care, the patient cohort was considered to be a good representation of the Finnish T2DM patient population. CV morbidity and mortality were substantial in this study. Furthermore, age, prior kidney function, albuminuria and prior diagnosis of AF were associated with the risk of CV events and progression to ESKD, both. However, the prevalence of monitoring data on T2DM patients during the study time frame was disappointing as every fourth patient lacked a measurement of eGFR and less than half were observed with a documented measurement of albuminuria.

T2DM in association with CKD has been linked to increased CV morbidity and mortality. Furthermore, CKD has been suggested as one of the most important contributors to mortality in the T2DM

Table 1
Baseline characteristics of patients with T2DM stratified by CKD classes.

			CKD stages*															
	Overall		**Stage 1**		**Stage 2**		**Stage 3**		**Stage 4**		**Stage 5**		**Missing CKD class****		**p-value**		**Missing (%)**	
N,%	29,628	100	7791	26.3	10,153	34.3	3498	11.8	338	1.1	109	0.4	7739	26.1				
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**	**Mean**	**SD**				
Age, years	65.8	12.4	57.77	10.25	69.88	9.97	77.13	8.97	81.2	8.51	72.26	10.31	62.65	12.05	<0.001		0	
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**				
eGFR, ml/min/1.73m2	82	[66.00, 94.00]	98	[93.00, 105.00]	77	[69.00, 84.00]	49	[42.00, 55.00]	25	[22.00, 27.00]	17	[10.00, 42.00]	-	-	<0.001		26.1	
HbA1c,%	6.5	[6.00, 7.20]	6.5	[6.00, 7.40]	6.4	[6.00, 6.90]	6.6	[6.10, 7.30]	7	[6.30, 7.90]	6.65	[6.10, 7.40]	6.4	[5.90, 7.10]	<0.001		34.9	
HbA1c, mmol/mol	47.5	[42.10, 55.20]	47.5	[42.10, 57.40]	46.5	[42.00, 52.00]	48.6	[43.20, 56.30]	52.85	[45.40, 62.80]	49.15	[43.20, 57.40]	46.5	[41.00, 54.10]	<0.001		34.9	
UACR, mg/mmol	0.4	[0.30, 1.20]	0.4	[0.30, 1.00]	0.3	[0.30, 1.10]	0.6	[0.30, 3.00]	1.7	[0.70, 11.10]	11.55	[0.95, 24.28]	0.3	[0.30, 0.90]	<0.001		55.2	
			N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**		
Gender	**Male**		16,002	54	4665	59.9	5202	51.2	1504	43	128	37.9	66	60.6	4437	57.3	<0.001	0
	Female		13,625	46	3126	40.1	4951	48.8	1994	57	210	62.1	43	39.4	3301	42.7		
Medication	**ACEi**		10,525	35.5	2688	34.5	3804	37.5	1467	41.9	133	39.3	33	30.3	2400	31	<0.001	
	ARB		10,396	35.1	2417	31	3627	35.7	1425	40.7	133	39.3	39	35.8	2755	35.6	<0.001	
	ACEi/ARB		19,888	67.1	4857	62.3	7069	69.6	2727	78.0	255	75.4	69	63.3	4911	63.5	<0.001	
	Diabetes medication																	
	Insulins, all		5399	18.2	1607	20.6	1542	15.2	998	28.5	190	56.2	59	54.1	1003	13	<0.001	
	Biguanides		24,515	82.7	6860	88.1	8720	85.9	2144	61.3	78	23.1	23	21.1	6690	86.4	<0.001	
	Sulfonamides		4004	13.5	953	12.2	1440	14.2	629	18	55	16.3	10	9.2	917	11.8	<0.001	
	DPP-4 inhibitors		9214	31.1	2481	31.8	2896	28.5	1677	47.9	167	49.4	44	40.4	1949	25.2	<0.001	
	GLP-1 analogues		47	0.2	23	0.3	10	0.1	6	0.2	0	0	0	0	8	0.1	0.033	

* CKD stages have been stratified according to the clinical guidelines by K-DIGO (9). ** Missing CKD class depicts the patients without reported eGFR measurement. UACR, urine albumin to creatinine ratio. Data were assessed +/- 1 year from index for laboratory values and medication. ACEi = ACE inhibitors, ARB = Angiotensin Receptor Blockers.

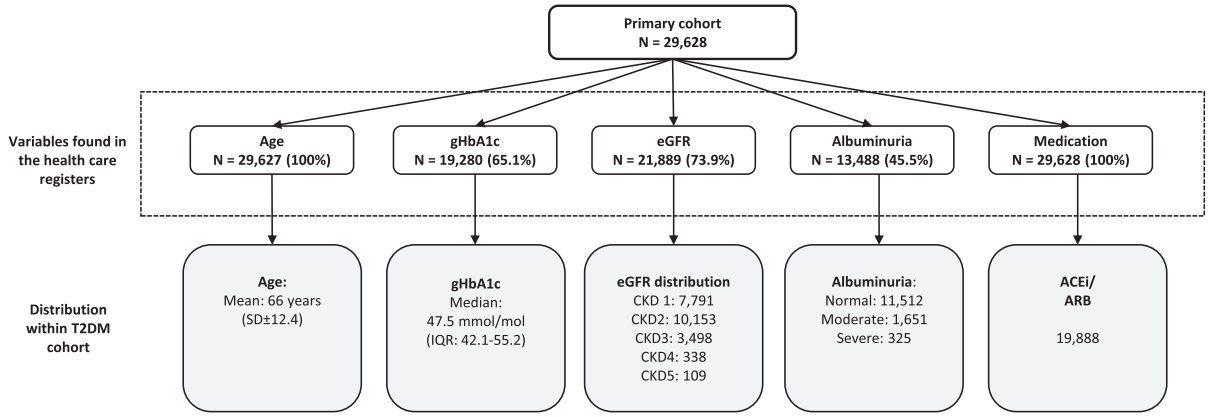

Fig. 2. Variables found for the study cohort patients from the health care registry.

Table 2
Cross tabulation of CKD and albuminuria classes in N (%). The percentages are proportional to the sizes of the albuminuria classes.

		Albuminuria			
		Normal	Moderate	Severe	Missing
CKD class	**Stage 1**	4359 (37.9)	506 (30.6)	66 (20.3)	2860 (17.7)
	Stage 2	5448 (47.3)	686 (41.6)	109 (33.5)	3910 (24.2)
	Stage 3	1335 (11.6)	378 (22.9)	119 (36.6)	1666 (10.3)
	Stage 4	60 (0.5)	34 (2.1)	16 (4.9)	228 (1.4)
	Stage 5	14 (0.1)	12 (0.7)	10 (3.1)	73 (0.5)
	Missing	296 (2.6)	35 (2.1)	5 (1.5)	7403 (45.9)
	Total	11,512 (100)	1651 (100)	325 (100)	16,140 (100)

Table 3
Multivariate Cox proportional hazards models predicting. A.) The occurrence of CV events in T2DM patients and B.) The occurrence of end-stage kidney disease in T2DM patients.

A. The occurrence of CV events in T2DM patients

		Patient cohort (all patients) (n=17,091)			
Covariate	**Level**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Age		1.07	1.06	1.07	**<0.001**
Gender (ref. male)	female	0.68	0.64	0.72	**<0.001**
eGFR (ref. stage 1)	stage 2	0.8	0.71	0.9	**<0.001**
	stage 3	0.99	0.87	1.13	0.86
	stage 4	1.69	1.45	1.97	**<0.001**
	stage 5	2.4	1.97	2.93	**<0.001**
Albuminuria (ref. normal)	moderate	1.65	1.54	1.77	**<0.001**
	severe	2.25	2.02	2.5	**<0.001**
Prior CV event (ref. false)	secondary prevention	1.54	1.41	1.68	**<0.001**
Atrial fibrillation (ref. false)	true	1.6	1.49	1.72	**<0.001**

B. The occurrence of end-stage kidney disease in T2DM patients

		Patient cohort (all patients) (n=17,127)			
Covariate	**Level**	**Hazard ratio**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Age		1.02	1.01	1.02	**<0.001**
Gender (ref. male)	female	0.97	0.85	1.11	0.7
eGFR (ref. stage 1)	stage 2	1.4	0.98	2	0.07
	stage 3	4.41	3.09	6.27	**<0.001**
	stage 4	22.61	15.71	32.52	**<0.001**
Albuminuria (ref. normal)	moderate	2.15	1.85	2.5	**<0.001**
	severe	4.61	3.86	5.51	**<0.001**
Prior CV event (ref. false)	true	1.03	0.86	1.25	0.72
Atrial fibrillation (ref. false)	true	1.35	1.17	1.56	**<0.001**

eGFR, Estimated Glomerular Filtration Rate; CI, Confidence Interval. Prior CV event includes any previous event of myocardial infarction, ischemic stroke, or unstable angina pectoris.

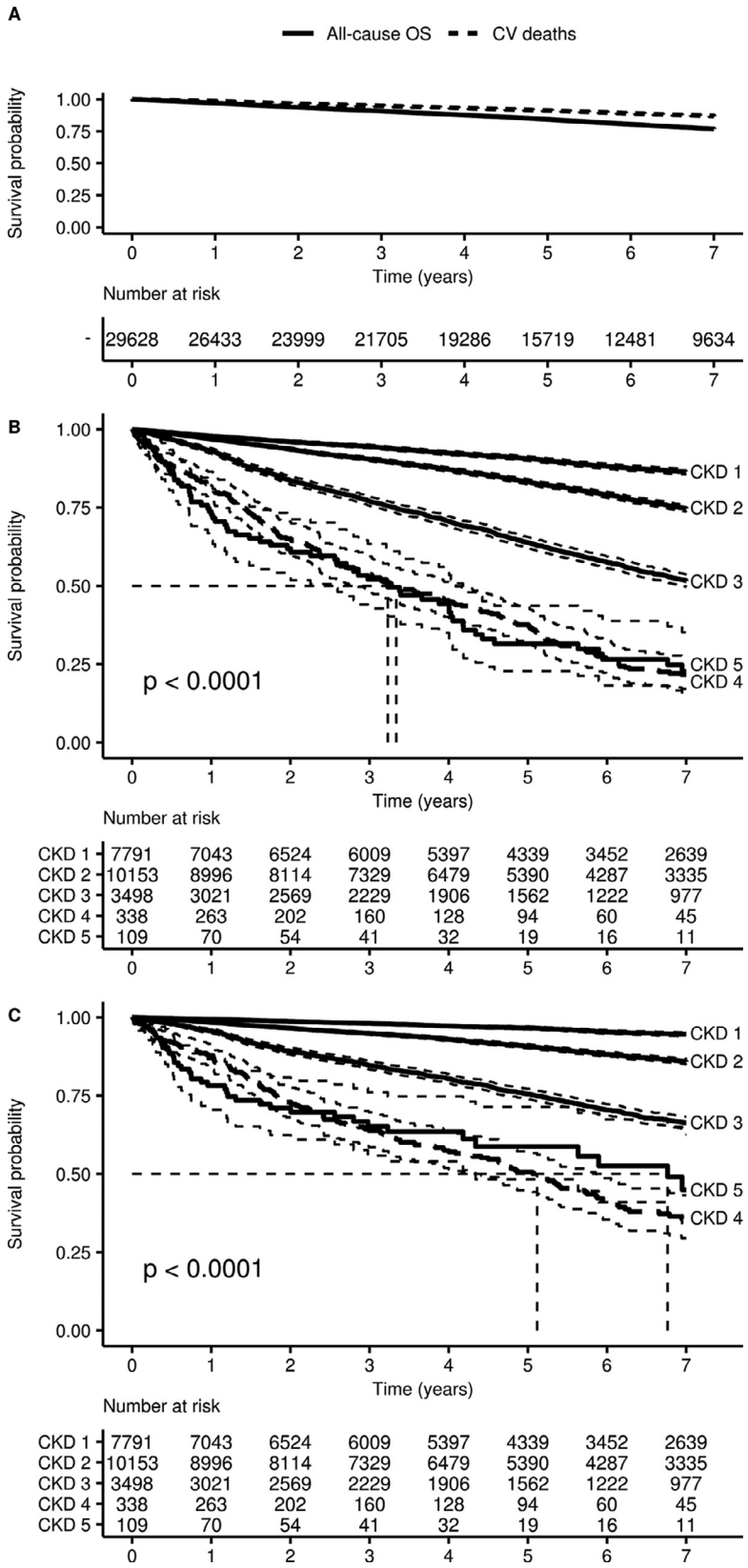

Fig. 3. All-cause and CV mortality. A) Overall survival (OS) and CV deaths in the patient cohort. B) Overall (all cause) survival in the patient cohort grouped by CKD classes. C) CV deaths in the patient cohort grouped by CKD classes.

patient population [21]. Importantly, previous smaller cross-sectional studies on T2DM patients in Finland have demonstrated a high prevalence of CKD and increased risk of CV together with low rate of SGLT2 inhibitor use. [22].

This study is the first to describe the prevalence of AF in a large real-world cohort of T2DM patients in Finland. Overall, the prevalence of AF among T2DM patients was high as every tenth patient had a prior diagnosis of AF, marking a 2.5-fold prevalence compared to recent data in an unselected patient cohort in Finland [23]. This was not a surprise as both T2DM and CKD are associated with the risk of AF [10]. In line with prior studies, AF prevalence increased substantially with increasing CKD stage (**Supplemental Table S3**) [11]. AF is the most common cardiac rhythm disturbance in CKD patients and the prevalence of AF among dialysis patients has been reported as high as 15–20% (19). Furthermore, AF was associated with, both, the risk of incident CV events and progression to ESKD. These associations have also been described in prior literature and underscore the clinical significance of AF in T2DM patients especially with concomitant CKD as both conditions share a high prevalence, several common risk factors and induce excess morbidity and mortality in the T2DM population [10,13]. The recent meta-analysis describing a beneficial association between SGLT2 inhibitors and a diminished risk of incident AF in patients with and without T2DM suggests important clinical implications in preventing cardiovascular adverse outcomes and preserving kidney function in these patients [15]. Further research on the matter is warranted.

Importantly, this study revealed that data on albuminuria, HbA1c and eGFR, although being a significant part of the standard of care, was missing in a large proportion of the patient cohort. Albuminuria alone was screened in only 45.5% of the patients. According to the Finnish Current Care guidelines on diabetes, albuminuria should be screened for and eGFR measured annually in T2DM patients [24]. However, our results suggest that the implementation of these guidelines remains suboptimal. This may be partly explained by poor treatment compliance associated with T2DM patients [25], insufficient reporting or both. Screening of T2DM patients has been highlighted in all international guidelines and is essential in the early detection of CKD and managing the decline in kidney function. The importance of T2DM detection and DKD/CKD prevention and management is underscored by our study as our findings reinforce the link between impaired kidney function as well as albuminuria and risk of CV events and ESKD in the Finnish T2DM population. Thus, it is pivotal that T2DM patients receive appropriate DKD risk assessment in the early stages of the disease to enable the detection of albuminuria and impaired kidney function as early as possible. This is especially crucial for the less frequently monitored CKD 1–2 patients as every eight patients with CKD 1–2 and available urine measurements was observed with albuminuria, an established independent risk factor for CV events and ESKD as demonstrated in this study.

As the occurrence of T2DM has been steadily increasing all over the world, the results of this study emphasize the importance of describing risk factors affecting patient outcomes as well as mapping the prevailing clinical treatment practices. Majority of the Finnish T2DM patients in this study suffered from concomitant CV comorbidities and more than half had lowered eGFR. Two thirds of the cohort patients received ACEis or ARBs for DKD and hypertension. Empagliflozin, the first SGLT2 inhibitor, received a reimbursement status in Finland in 2016 and the use of SGLT2 inhibitors has increased and they have since become the first-line treatment of patients with DKD. SGLT2 inhibitors have rapidly changed the treatment of diabetes with encouraging results especially in patients with cardiovascular comorbidities, (and are also specifically explored for AF prevention). Importantly, the recent 2020 KDIGO guidelines on the treatment of DKD strongly recommend SGLT2 inhibitors to most patients with T2DM and CKD or DKD[19].

There are some limitations to this study. Foremost, as the data for this study was extracted from health care registries, some parts of the data may have been incompletely recorded or some parts of the data from individual patients may have been missing. As the cohort was formed using the reimbursement numbers for diabetes medications, it is possible that patients who, for some reason, did not receive reimbursement numbers have been excluded from the study. However, the sample size of the patient cohort was substantial, and the subgroups of CKD classes had enough patients to give a reliable description of the T2DM patients and prevalence of CKD among in this patient population in Finland.

5. Conclusions

In this large Finnish real-world study on T2DM patients, CV comorbidity was common and mortality substantial. Furthermore, increasing age, prior kidney function, albuminuria and AF were independently associated with both CV events and ESKD. However, every fourth and every second patient were lacking eGFR or albuminuria measurements, respectively, suggesting that the surveillance and treatment of T2DM patients remains suboptimal.

Author contributions

T.A.H, O-C.S, C.L, U.W, J.H., M.L, and K.M. participated in study conceptualization, project administration, and investigations. J.H., M.L., and J.V. participated in data analysis and visualization. O.L., T.A.H, J.V., M.L., and J.H. participated in writing the manuscript draft and editing the final version.

Role of the funding source

Mundipharma sponsored the study; contributed to the design; and participated in the collection, analysis, and interpretation of data and in the writing, reviewing, and approval of the final version. No honoraria or payments were made for authorship. The study was approved by each register holder as a scientific study with a prerequisite aim to publish the results, i.e., the decision to publish was determined at the project start.

Conflict of Interests

T.A.H. has no conflicts of interest to report; O.-C.S., U.W. are or were employees of Mundipharma; C.L. works as consultant for Mundipharma; O.L., J.V., J.H., M.I.L. are employees of Medaffcon who has received funding for the conduct of the study, K.M. has received consultancy fees from Mundipharma for participating in advisory boards.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.deman.2022.100103.

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