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International Variability of Renal and Cardiovascular Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus in Europe

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Abstract
Introduction: Type 2 diabetes and its complications represent a huge burden to public health. With this prospective, observational cohort study, we aimed to estimate and to compare the incidence rate (IR) of renal and cardiovascular outcomes and all-cause mortality in patients with type 2 diabetes in different European countries. ***Methods:*** The renal endpoint was a composite of a sustained decline in estimated GFR of at least 40%, a sustained increase in albuminuria of at least 30% including a transition in albuminuria class, progression to kidney failure with replacement therapy, or death from renal causes. The cardiovascular endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. ***Results:*** 3,131 participants from four European countries (Austria, Hungary, The Netherlands, and Scotland) with a median follow-up time of 4.4 years were included. IRs were adjusted for several risk factors including sex, age, estimated GFR, albuminuria, HbA_{1c}, blood pressure, and duration of type 2 diabetes. Across countries, the adjusted IR for the renal endpoint was significantly higher in Hungary and Austria, and the adjusted IR for the cardiovascular endpoint was significantly higher in Scotland and Austria. All-cause mortality was significantly higher in Scotland compared to all other countries. ***Conclusion:*** Our findings show how the longitudinal outcome of patients with type 2 diabetes varies significantly across European countries even after accounting for the distribution of underlying risk factors.

Introduction

Diabetes mellitus is a rapidly evolving global health problem that increasingly assumes epidemic proportions. Throughout the past 20 years, the global prevalence has more than tripled, with type 2 diabetes (T2DM)

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accounting for the vast majority. By 2045, about 700 million people will be affected worldwide [1].

Throughout the course of disease, about 40% of patients with T2DM develop diabetic kidney disease (DKD), a detrimental microvascular complication that usually manifests about 10–20 years after diabetes onset and is often present by the time of diagnosis of diabetes [2]. Over the past 30 years, DKD has become the single most frequent cause for kidney failure with replacement therapy (KFRT) in both, developed and developing countries, thereby representing a huge burden to public health [3]. Even in early stages, the presence of DKD is associated with a significant increase of mortality, mostly attributable to cardiovascular disease. In fact, although noncardiovascular mortality is also increased, the majority of patients with DKD die from cardiovascular causes before reaching KFRT [4]. Despite the major impact of T2DM and DKD on health care systems and societies, only a comparatively small number of studies examine the natural course of disease in Europe and no large-scale databases are available reporting the exact incidence rate (IR) of renal and cardiovascular outcomes and mortality in these patients [5].

We sought to estimate and to compare the IR of renal and cardiovascular endpoints and all-cause mortality using data collected at the primary level of healthcare in four European countries. Additionally, we aimed to identify risk factors in this less selected cohort receiving routine medical care compared to interventional studies.

Materials and Methods

The prospective study for validation of biomarkers in diabetic kidney disease (PROVALID) is a member of the ISN International Network of Chronic Kidney Disease (iNET-CKD) cohort studies. The study was approved by the local Institutional Review Board in each participating country. Signing an informed consent was a prerequisite for study participation at each site.

Population

PROVALID is a prospective, multinational, non-interventional cohort study that recruited 4,000 patients with incident or prevalent T2DM, irrespective of the presence of chronic kidney disease (CKD). Study participants were recruited by general practitioners or other facilities involved in the primary level of healthcare in five European countries (Austria, Hungary, The Netherlands, Scotland, and Poland). Details regarding the trial design and the recruitment in each country have been described previously [6]. In brief, 4,000 adults with incident or prevalent T2DM were recruited between 2011 and 2014. In-person follow-up visits were performed annually. At each follow-up visit, clinical and laboratory data as well as information on medication and potential trial outcomes were collected. Only participants with active malignancy requiring chemotherapy were excluded.

The presence of T2DM was defined according to the American Diabetes Association (ADA) guidelines, or as current treatment with hypoglycemic agents. The presence of DKD was defined as a urinary albumin-to-creatinine ratio greater than 30 mg/g and/or an estimated glomerular filtration rate (eGFR) of less than 60 mL/min/1.73 m^2 in the absence of other known kidney pathologies.

In each country, participants were treated according to local practice and patient management was not affected by participation in the PROVALID study. Next to estimating the IR of renal and cardiovascular outcomes and all-cause mortality, the primary objective of the PROVALID study was to compare the longitudinal outcome of patients with T2DM treated at the primary level of healthcare in different European countries.

Outcomes

The primary endpoint was a composite of a sustained decline in the eGFR of at least 40%, a sustained increase in albuminuria of at least 30% including a transition in albuminuria class (e.g., from stage A1 [normal to mildly increased] to A2 [moderately increased] or A3 [severely increased], or from stage A2 to A3), progression to KFRT, and death from renal causes. A decline in eGFR and an increase in albuminuria were considered as sustained, if they persisted over a least two consecutive follow-ups. EGFR was estimated based on the MDRD equation [7]. The secondary endpoint was a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. As tertiary endpoint, we determined the all-cause mortality. Clinical endpoints such as myocardial infarction and stroke were adjudicated by the treating general practitioners.

Statistical Analysis

Patient characteristics are described at baseline. Continuous variables are, due to non-normality, skewness, or limited range of the data, described using median and 1st and 3rd quartiles. For discrete variables, we present absolute and relative frequencies.

To provide a descriptive epidemiological overview for every country as well as to serve as a basis for a comparison between countries, crude IRs were estimated as the ratio of the number of events and the person-time at risk from baseline. IRs are measured in events per 1,000 person-years. Under the assumption of relatively rare events in large samples, respective exact Poisson rate confidence intervals (CI) are presented [8]. By employing person-time as an offset variable, comparable adjusted IRs are estimated with quasi-Poisson regression models [9, 10] to guard also against biased standard errors due to potential overdispersion. Resulting in ceteris paribus comparisons between countries, the risk factors used to adjust the IRs were centered on the whole population level; i.e., adjusted IRs resemble estimates at the international population mean of all risk factors. For each endpoint, risk factors commonly known from the literature or clinical practice were selected as adjustment variables. All regression models were adjusted for age, sex, duration of T2DM, duration of hypertension, eGFR, albuminuria, HbA_{1c}, and blood pressure. The regression models for the renal and cardiovascular endpoint were additionally adjusted for low-density lipoprotein (LDL) and high-density lipoprotein (HDL). The regression models for the cardiovascular and mortality

endpoint were additionally adjusted for cardiovascular and renal comorbidities such as the presence of coronary artery disease (CAD), peripheral artery disease (PAD), cerebrovascular disease (CD), heart failure and DKD.

Given the structure of missingness in the data, to not introduce additional distorting variation to subsequent estimates by applying imputation strategies and thereby endanger the validity of subsequent inference, a complete case analysis was conducted. As participants with missing values were excluded, the regression analysis for the renal, cardiovascular, and mortality outcome was computed based on 2,584, 2,584, and 2,894 observations, respectively. A comparison of the characteristics of patients with and without missing values is provided in the supplemental material (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000528438) and does not show any concerning differences hinting toward a potential selection bias.

The estimates' standard errors derived from bootstrapped covariance matrices [11] were used to compute Wald-type CIs for the adjusted IRs of the country subcohorts and for the incidence rate ratios of the risk factors. Differences in the main study outcomes between countries were assessed by Wald tests. We allow for a type 1 error of 5% in all analyses. All analyses were performed using R 3.6.3 [12].

Results

In total, 4,000 participants from five European countries were recruited. Participants from Poland (n = 539) were excluded due to incomplete follow-up data. Additional 330 participants did not return for the first follow-up visit, leaving four countries and 3,131 participants for analysis.

Of the 3,131 participants, 20% were Austrian, 39% Hungarian, 27% Dutch, and 14% Scottish. At baseline, participants had a median age of 65 years, a median eGFR of 79 mL/min/1.73 m^2, and a median albuminuria of 8.2 mg/g. The median duration of T2DM at study inclusion was 8 years. Twenty-eight percent of patients had DKD at baseline. The total follow-up time was 13,000 person-years; the median follow-up time was 4.4 years (1st, 3rd quartile: 3.1, 5.7). At baseline, 67% of patients were treated with an ACE inhibitor or angiotensin receptor blocker (RASi), 57% were treated with blood pressure-lowering agents (including calcium antagonists, alpha receptor blockers, thiazide diuretics, loop diuretics), 67% were treated with lipid-lowering agents, and 26% received treatment with acetylsalicylic acid. As described previously, therapeutic practice patterns were highly heterogeneous among countries [13]. Table 1 shows the baseline characteristics for the overall study population and for each country separately.

During the observation period, 318 (10%) participants reached the renal composite endpoint, 221 (7%) participants reached the cardiovascular composite endpoint, and 234 (7.5%) participants died. Of the investigated risk factors, age, male sex, HbA_{1c}, systolic blood pressure values >140 mmHg, albuminuria, eGFR, and the duration of hypertension were associated with a significantly increased risk of reaching the renal composite endpoint. For the cardiovascular composite endpoint, the same applied to the risk factors age, male sex, HbA_{1c}, albuminuria, the presence of CAD, PAD, and CD, while age, male sex, HbA_{1c}, the presence of DKD, albuminuria, CAD, and PAD were associated with a significantly increased risk for all-cause mortality. The IRR of analyzed risk factors for each composite endpoint are shown in Figure 1.

The overall adjusted IR for the renal and cardiovascular composite endpoint was 21.1 (95% CI, 18.3–24.3) and 15.5 (95% CI, 12.8–18.7) per 1,000 person-years, respectively. The overall adjusted IR of all-cause mortality was 13.0 (95% CI, 10.9–15.6) per 1,000 person-years (Table 2).

Hungary (IR, 26.7; 95% CI, 22.1–32.2) and Austria (IR 23.3; 95% CI, 18.3–29.7) were the countries with the highest adjusted IRs for the composite renal endpoint. Both IRs were significantly higher as compared to the IRs in Scotland (IR, 15.1; 95% CI, 9.5–23.9) and the Netherlands (IR, 15.5; 95% CI, 11.2–21.5) ($p < 0.05$) (Table 2).

Adjusted IRs for the cardiovascular endpoint were highest in Scotland (IR, 24.3; 95% CI, 17.2–34.5) and Austria (IR, 19.6; 95% CI, 15.1–25.4). Both IRs were significantly higher as compared to the IRs in the Netherlands (IR, 9.3; 95% CI, 5.3–16.2) and Hungary (IR, 8.3; 95% CI, 6.2–11.2) ($p < 0.05$) (Table 2).

The highest incidence for all-cause mortality is found in Scotland (IR, 19.2; 95% CI, 13.7–26.9), followed by Hungary (IR, 12.1; 95% CI, 9.5–15.4) and Austria (IR, 11.5; 95% CI, 8.5–15.7). The Netherlands has the lowest IR for all-cause mortality (IR, 5.8; 95% CI, 3.3–10.1). All-cause mortality was significantly higher in Scotland as compared to all other countries ($p < 0.05$) (Table 2). To show how the single components contributed to the composite endpoints, unadjusted IRs for the composite endpoints and their components are shown in Figure 2.

Discussion

This multinational cohort study in 3,131 individuals provides an overall IR for renal and cardiovascular

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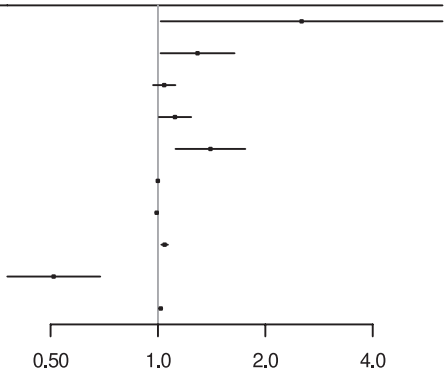
Table 1. Baseline characteristics

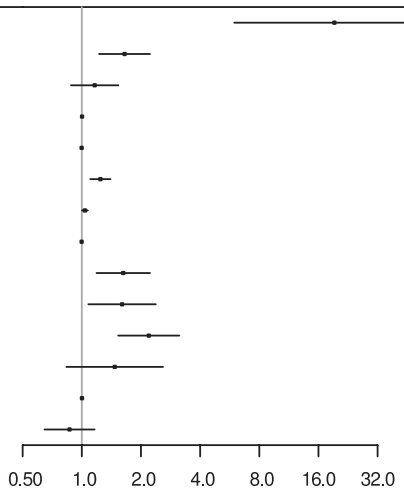
	Overall	Austria	Hungary	The Netherlands	Scotland	Missing (%)
n	3,131	610	1,232	849	440	
Maximum follow-up time, years	4.4 (3.1, 5.7)	5.0 (3.2, 6.2)	5.1 (3.4, 6.0)	4.0 (3.1, 5.0)	4.0 (2.5, 4.3)	
Female sex, *n* (%)	1,356 (43.3)	265 (43.4)	604 (49.0)	342 (40.3)	145 (33.0)	0
Age, years	65.0 (58.0, 70.0)	65.0 (58.0, 71.0)	64.0 (58.0, 70.0)	66.0 (60.0, 71.0)	62.0 (56.0, 67.0)	0
Duration of type 2 diabetes, years	8.0 (4.0, 14.0)	7.0 (3.0, 12.0)	12.0 (6.0, 19.0)	6.0 (4.0, 10.0)	6.0 (3.0, 10.0)	3.8
Diabetic retinopathy, *n* (%)	409 (13.1)	32 (5.2)	294 (23.9)	28 (3.3)	55 (12.5)	2.2
DKD, *n* (%)	904 (28.9)	226 (37.0)	414 (33.6)	168 (19.8)	96 (21.8)	2.4
Duration of hypertension, years	12.0 (7.0, 19.0)	11.0 (5.0, 15.0)	13.0 (7.0, 21.0)	5.5 (2.8, 9.0)	10.0 (7.0, 15.0)	n.a.*
History of heart failure, *n* (%)	74 (2.4)	26 (4.3)	43 (3.5)	0 (0.0)	5 (1.1)	2.7
Atherosclerotic cardiovascular disease, *n* (%)	825 (26.3)	164 (26.9)	380 (30.8)	156 (18.4)	125 (28.4)	2.6
CAD	603 (19.3)	116 (19.0)	254 (20.6)	142 (16.7)	91 (20.7)	2.6
PAD	206 (6.6)	48 (7.9)	113 (9.2)	13 (1.5)	32 (7.3)	2.7
CD	191 (6.1)	62 (10.2)	97 (7.9)	9 (1.1)	23 (5.2)	2.7
Blood pressure, mm Hg						
Systolic	135 (125, 146)	140 (130, 150)	130 (121, 140)	138 (128, 149)	137 (125, 146)	1.1
Diastolic	80 (72, 85)	80 (80, 88)	80 (70, 80)	80 (71, 84)	78 (72, 85)	
eGFR, mL/min/1.73 m^2	78.7 (63.9, 93.0)	74.1 (61.1, 90.1)	74.7 (58.6, 90.8)	81.0 (69.2, 92.8)	87.3 (75.4, 98.3)	0.4
Urinary albumin/creatinine ratio, mg/g	8.2 (4.1, 22.7)	14.0 (8.0, 28.7)	8.4 (3.8, 26.5)	5.0 (3.1, 10.2)	8.5 (5.0, 22.2)	2.1
Albuminuria, *n* (%)						
Normal to mild, A1	2,486 (79.4)	468 (76.7)	964 (78.2)	708 (83.4)	346 (78.6)	2.1
Moderate, A2	481 (15.4)	116 (19.0)	195 (15.8)	94 (11.1)	76 (17.3)	
Severe, A3	98 (3.1)	22 (3.6)	59 (4.8)	6 (0.7)	11 (2.5)	
Cholesterol, mg/dL						
Total	174 (147, 205)	194 (166, 223)	182 (151, 213)	162 (139, 186)	166 (143, 186)	0.7
LDL	94 (74, 121)	114 (89, 143)	95 (71, 123)	89 (70, 108)	85.8 (70, 105)	9.7
HDL	46 (39, 58)	49 (41, 61)	48 (40, 57)	46 (39, 54)	43 (35, 50)	1.8
Triglycerides, mg/dL	142 (98, 204)	132 (94, 187)	159 (106, 221)	125 (89, 177)	151 (106, 204)	10.3
HbA_{1c}, %	6.8 (6.3, 7.5)	6.7 (6.2, 7.3)	6.9 (6.2, 7.7)	6.7 (6.4, 7.3)	6.9 (6.3, 7.9)	1.1
HbA_{1c}, mmol/L	51 (45, 58)	50 (44, 56)	52 (44, 61)	50 (46, 56)	52 (45, 63)	
Medication, *n* (%)						
RAS inhibitors	2,107 (67.3)	374 (61.3)	979 (79.5)	492 (58.0)	262 (59.5)	
Blood pressure-lowering agents	1,770 (56.5)	287 (47.0)	888 (72.1)	382 (45.0)	213 (48.4)	
Lipid-lowering agents	2,104 (67.2)	292 (47.9)	835 (67.8)	614 (72.3)	363 (82.5)	
ASA	798 (25.5)	151 (24.8)	405 (32.9)	63 (7.4)	179 (40.7)	
Glucose-lowering agents	2,708 (86.5)	491 (80.5)	1,172 (95.1)	704 (82.9)	341 (77.5)	

RAS, renin-angiotensin system; ASA, acetylsalicylic acid. Continuous data are presented as median (1st, 3rd quartile), and categorical variables are given as absolute frequency (relative frequency). Missing values are given as relative frequency (%). *n.a., not applicable; for participants without hypertension, no values for duration of hypertension are given.

Renal Endpoint	IRR	Lower 95%CI	Upper 95%CI
Log(Age)	2.528	1.018	6.276
Male	1.291	1.017	1.639
Log(Duration T2D)	1.041	0.969	1.119
HbA1c	1.116	1.006	1.239
Systolic BP > 140 mmHg	1.403	1.120	1.757
LDL	0.999	0.996	1.003
HDL	0.992	0.983	1.001
ACR/100 mg/g	1.044	1.022	1.066
Log(eGFR)	0.510	0.378	0.689
Duration Hypertension	1.018	1.007	1.028



Cardiovascular Endpoint	IRR	Lower 95%CI	Upper 95%CI
Log(Age)	19.277	5.966	62.290
Male	1.650	1.224	2.225
Systolic BP > 140 mmHg	1.163	0.881	1.536
LDL	1.003	0.999	1.006
HDL	0.998	0.987	1.009
HbA1c	1.243	1.104	1.400
ACR/100 mg/g	1.037	1.002	1.073
eGFR	0.998	0.991	1.006
CAD	1.625	1.187	2.223
PAD	1.603	1.079	2.380
CD	2.191	1.531	3.135
Heart Failure	1.470	0.834	2.591
Duration Hypertension	1.002	0.987	1.017
Duration T2D > 10 yrs	0.866	0.646	1.162



All-cause mortality	IRR	Lower 95%CI	Upper 95%CI
Log(Age)	70.898	20.890	240.623
Male	1.754	1.319	2.333
Systolic BP > 140 mmHg	0.948	0.720	1.249
HbA1c	1.159	1.038	1.293
DKD	1.587	1.186	2.124
eGFR	1.003	0.995	1.011
ACR/100 mg/g	1.056	1.027	1.086
CAD	1.394	1.050	1.850
PAD	1.674	1.150	2.437
CD	1.269	0.826	1.949
Duration T2D	1.002	0.986	1.019
Duration Hypertension	0.997	0.983	1.010

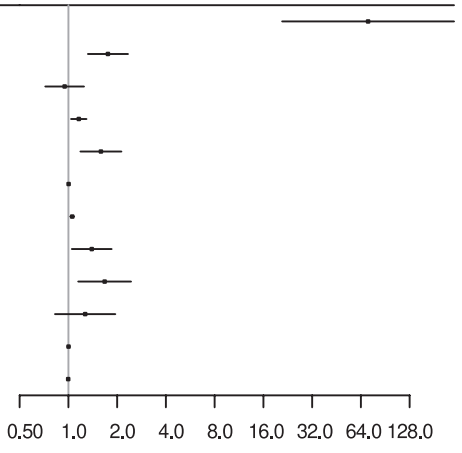


Fig. 1. IRR of risk factors for the renal, cardiovascular, and all-cause mortality outcome (on logarithmic scales).

Table 2. Adjusted IRs for the overall cohort and for each country

	No. of events	Person-years at risk	Adj. IR/1,000 pyrs (95% CI)
Renal composite endpoint			
Overall	318	12,778	21.1 (18.3–24.3)
Austria	73	2,712	23.3 (18.3–29.7)[a]
Hungary	171	5,324	26.7 (22.1–32.2)[a]
The Netherlands	48	3,211	15.5 (11.2–21.5)
Scotland	26	1,532	15.1 (9.5–23.9)
Cardiovascular composite endpoint			
Overall	221	13,219	15.5 (12.8–18.7)
Austria	79	2,752	19.6 (15.1–25.4)[b]
Hungary	56	5,686	8.3 (6.2–11.2)
The Netherlands	40	3,228	9.3 (5.3–16.2)
Scotland	46	1,553	24.3 (17.2–34.5)[b]
All-cause mortality			
Overall	234	13,714	13.0 (10.9–15.6)
Austria	51	2,936	11.5 (8.5–15.7)[c]
Hungary	101	5,803	12.1 (9.5–15.4)[c]
The Netherlands	42	3,339	5.8 (3.3–10.1)
Scotland	40	1,636	19.2 (13.7–26.9)[d]

The IR of the renal composite endpoint is adjusted for age, sex, duration of type 2 diabetes, HbA_{1c}, blood pressure, LDL, HDL, urinary albumin-to-creatinine ratio (ACR), eGFR, and duration of hypertension. The IR of the cardiovascular composite endpoint is adjusted for age, sex, blood pressure, LDL, HDL, HbA_{1c}, ACR, eGFR, CAD, PAD, CD, heart failure, duration of hypertension, and duration of type 2 diabetes. The IR of all-cause mortality is adjusted for age, sex, blood pressure, HbA_{1c}, diabetic kidney disease, eGFR, ACR, CAD, PAD, CD, duration of type 2 diabetes, and duration of hypertension. [a]Significantly higher compared to the Netherlands and Scotland ($p < 0.05$). [b]Significantly higher compared to the Netherlands and Hungary ($p < 0.05$). [c]Significantly higher compared to the Netherlands ($p < 0.05$). [d]Significantly higher compared to all other countries ($p < 0.05$).

outcomes and mortality in patients with T2DM, and in subcohorts of four European countries. For the first time, PROVALID draws the attention to a significant international variation in the longitudinal outcome of people with diabetes receiving routine medical care in four European countries. We identified risk factors with significant impact on the main study outcomes emphasizing the clinical importance of well-known, modifiable risk factors in the context of T2DM.

Analysis of Risk Factors

In line with existing literature [14–17], our study shows that HbA_{1c} and albuminuria represent key modifiable risk factors in the context of T2DM. Both variables show a significant impact on all study outcomes, especially on cardiovascular events and all-cause mortality.

According to the ADA guidelines, patients with T2DM and hypertension should, at a minimum, reach a blood pressure target of <140/90 mm Hg to reduce macro- and microvascular complications [18]. In the present study, a systolic blood pressure above 140 mm Hg was strongly associated with the renal, but not with the cardiovascular and all-cause mortality endpoint. This could be due to multicollinearity, as hypertension is often related to risk factors such as the presence of CAD, PAD, and CD, which show significant associations with the respective outcomes. With an up to twofold increased risk of death, the presence of DKD shows a substantial impact on mortality in diabetic patients.

Differences in Baseline Characteristics and Study Outcome between Countries

When looking at the baseline characteristics of each country, differences in the distribution of most risk factors are striking. To some extent, these differences may explain the variability in study outcome; however, even after accounting for their distribution, significant differences between countries remain evident.

For instance, we find the highest IR for the renal outcome in Hungary and Austria. Notably, the duration of T2DM in Hungary is almost twice as high as in every other country, suggesting a more advanced stage of disease in these participants. Accordingly, Hungarian

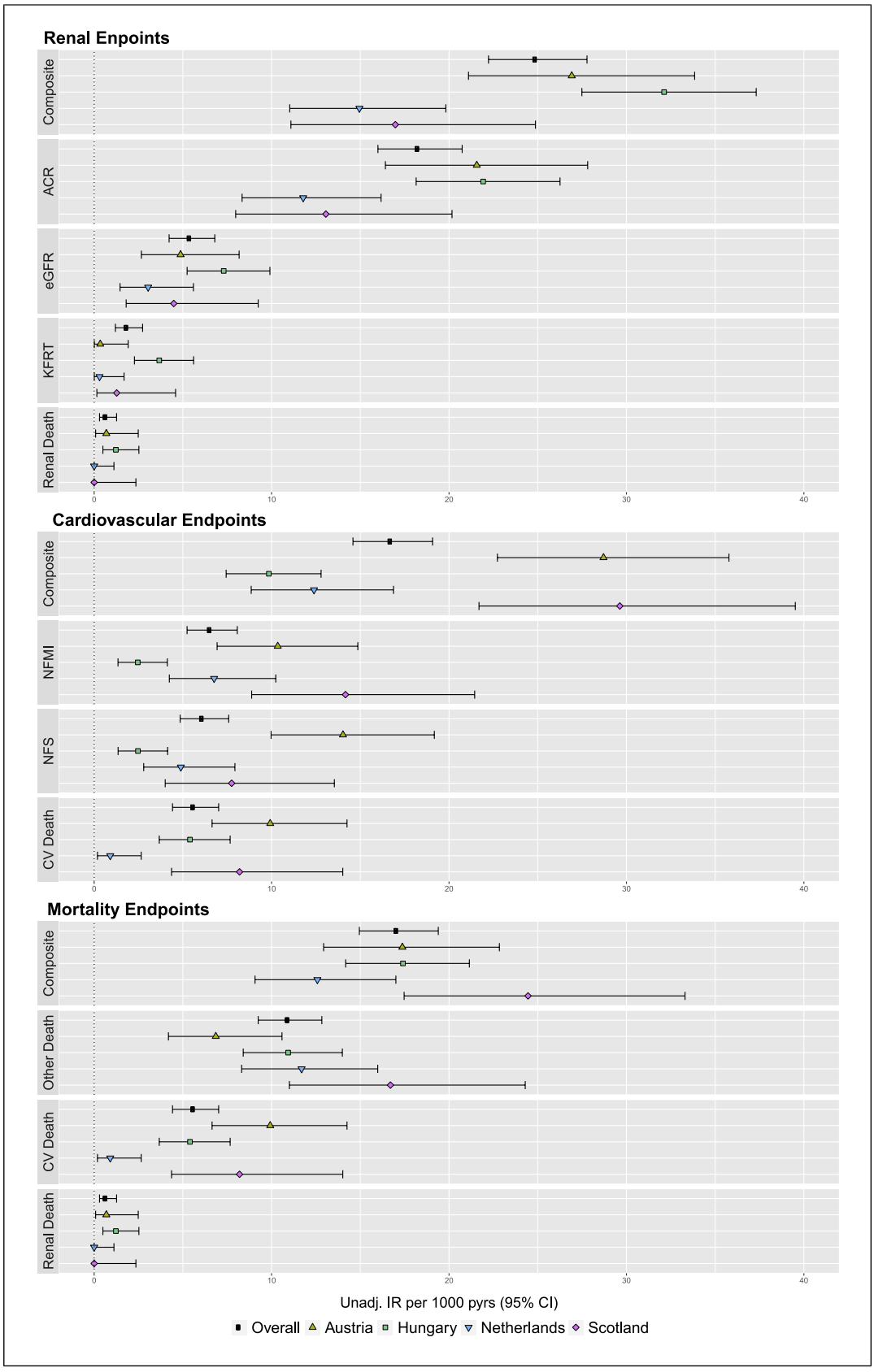


Fig. 2. Unadjusted IR of the composite endpoints and single components.

study participants have the highest prevalence of diabetic retinopathy (23.9%) and arteriosclerotic cardiovascular disease (30.8%). In Austria however, despite a significantly shorter duration of disease, more participants meet the criteria for DKD (37.0% vs. 33.6%) and have moderately increased albuminuria (19.0% vs. 15.8% in Hungary). In addition, systolic blood pressure levels tend to be higher in Austria as compared to every other country. In agreement with the latter, the Austrian IR of the renal endpoint is mainly driven by the progression of albuminuria. In fact, the IR for the progression of albuminuria in Austria is just as high as in Hungary. In this context, it is noticeable that 80% of Hungarian participants receive treatment with RASi, while this only applies to 61% of Austrian participants (Table 1).

Despite the longer duration of T2DM, Hungary is the country with the lowest IR for the cardiovascular outcome. This is remarkable considering that diabetes-related complications and comorbidities accumulate and the risk of mortality increases over time. Moreover, even subclinical stages of DKD are associated with a significant increase in cardiovascular morbidity and mortality [2, 19]. Austria, on the other hand, along with Scotland, has a significantly higher IR of the cardiovascular outcome compared to Hungary and the Netherlands. Looking at the distribution of cardiovascular comorbidities and risk factors between countries, the prevalence of CAD was similar in Scotland (20.7%) and Hungary (20.6%). The prevalence of PAD was significantly higher in Hungary (9.2%), whereas the prevalence of CD was significantly higher in Austria (10.2%). Patients from Scotland were more likely to be of male sex and, along with Hungary, tended to have higher HbA_{1c} levels. As described above, the risk factors moderately increased albuminuria and hypertension were predominant in Austria; in addition, median LDL levels were significantly higher in Austrian participants. Again it is noteworthy, that treatment patterns aiming at cardiovascular disease differ widely between these countries; while Scotland has the highest proportion of patients treated with lipid-lowering drugs and acetylsalicylic acid followed by Hungary, Austria is among the countries with the lowest proportion of participants treated with respective agents (Table 1). Finally, the highest all-cause mortality is found in Scotland. This supports current evidence that the excess risk of mortality in T2DM is mainly due to cardiovascular events [20, 21].

The reasons for significant differences in outcome across European countries may be manifold. Previous studies have reported geographic variation in the prevalence of CKD and incidence of KFRT in Europe [22], USA [23], Japan [24], and China [25]. The authors of the respective studies discuss many potential reasons for their findings, like heterogeneity of study design and study population, genetic factors, human and environmental factors as well as factors related to the public health system. Similar to our findings, Orlandi et al. [26] found great heterogeneity of CKD progression rates, KFRT, all-cause mortality, and cardiovascular events among CKD cohorts from different countries. However, their analysis is based on several cohorts from different studies. Thus, differences in study protocols and inclusion criteria may have been responsible for geographical differences in study outcomes. In addition, as cohorts across the globe are included, part of the observed heterogeneity may also be attributable to differences in ethnicity. An advantage of PROVALID as a multinational study lies in the fact that the same study protocol and therefore the same recruitment strategy and inclusion criteria were applied to cohorts from different countries, thereby reducing sources of between-country variability. In contrast to the study by Orlandi et al. [26], the significant heterogeneity of outcome found in the present study cannot be attributed to differences in study design, inclusion criteria, or ethnicity. Nonetheless, it is possible that different health systems will generate different models of care which could affect the recruitment patterns. In addition, PROVALID lacks information of socioeconomic factors, which are known to be important drivers of health inequality [27].

PROVALID supports the hypothesis that differences in underlying risk factors do exist but are not exclusively responsible for geographical differences in outcome in these patients. Among many possible causes, differences in treatment patterns and adherence to guidelines need to be considered. PROVALID, along with other studies, has shown that there is substantial variability in treatment patterns of patients with T2DM, also suggesting room for improvement of guideline adherence [13, 28–30]. Further analysis of why significant differences in treatment patterns exist and how they affect study outcome is crucial to uncover and to address potential shortcomings in medical care provision. The study by Rawshani et al. [31] clearly shows how poor control of risk factors dramatically worsens outcome in this highly vulnerable population.

As data are collected at the primary level of healthcare, IRs derived from PROVALID reflect the natural course of disease in diabetics exposed to routine medical care in real-life conditions. In contrast to national registries, this recruitment strategy allows a more granular insight into the treatment and outcomes as well as the national healthcare provision of these patients.

A multinational cohort study is the design of choice for the assessment of IRs and the identification of risk factors and provides a valuable contribution to identify shortcomings in

healthcare provision. Due to the broad inclusion criteria and only one exclusion criterion, estimates provided by this study have to be considered externally valid for the European diabetic population.

Along with these strengths, PROVALID has also some limitations. First, participants lost to follow-up may have led to selection and attrition bias. Second, we evaluate the risk factor status at a single point in time. Although accounting for risk-factor changes over time certainly has advantages, the approach we use minimizes the risk of reverse causation and strengthens the interpretation of our results. Third, PROVALID does not account for socioeconomic factors. We also acknowledge that neither confounding nor reverse causation can be fully overcome. Since observational studies do not necessarily allow a conclusion on cause and effect, further studies are needed to investigate why the longitudinal outcome of patients with T2DM varies significantly across European countries.

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Statement of Ethics

This study protocol was reviewed and approved by the local Institutional Review Board in each participating country: West of Scotland Research Ethics Service (approval number: 12/WS/0005). Ethics Committee of Medical University of Silesia (approval number: KNW/0022/KB1/78/11). Ethics Committee of University Medical Center Groningen (approval number: NL35350.042.11). Ethics Committee of Semmelweis Universit Budapest (approval number: 12656-0/2011-EKU [421/PI/11.]). Ethics Committee of the Province of Upper Austria Study (approval number: I-1-11 [2.1.10 – Register]). Ethics Committee of the Medical University of Innsbruck (approval number: IRB00002662-U). Signing an informed consent was a prerequisite for study participation at each site.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Stefanie Thöni wrote the first draft of the manuscript. Felix Keller, Sara Denicolò, Susanne Eder, Lukas Buchwinkler, Laszlo Rosivall, Andrzej Wiecek, Patrick B. Mark, Peter Rossing, Hiddo L. Heerspink, and Gert Mayer critically reviewed and edited the manuscript. Felix Keller conceived and conducted the statistical analyses. Felix Keller and Stefanie Thöni analyzed and visualized the results. Stefanie Thöni, Felix Keller, and Gert Mayer are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors reviewed and approved the final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author. The data underlying this article will be shared on reasonable request to the corresponding author.

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