Cardiovascular and Renal Disease Burden in Type 1 Compared With Type 2 Diabetes: A Two-Country Nationwide Observational Study

Robin Kristófi,[1] Johan Bodegard,[2] Anna Norhammar,[3,4] Marcus Thuresson,[5] David Nathanson,[6] Thomas Nyström,[7] Kåre I. Birkeland,[8] Jan W. Eriksson[1]

OBJECTIVE

Type 1 diabetes (T1D) and type 2 diabetes (T2D) increase risks of cardiovascular and renal disease (CVRD) compared with diabetes-free populations. Direct comparisons between T1D and T2D are scarce. We examined this by pooling full-population cohorts in Sweden and Norway.

RESEARCH DESIGN AND METHODS

A total of 59,331 patients with T1D and 484,241 patients with T2D, aged 18–84 years, were followed over a mean period of 2.6 years from 31 December 2013. Patients were identified in nationwide prescribed drug and hospital registries in Norway and Sweden. Prevalence and event rates of myocardial infarction (MI), heart failure (HF), stroke, chronic kidney disease (CKD), all-cause death, and cardiovascular (CV) death were assessed following age stratification in 5-year intervals. Cox regression analyses were used to estimate risk.

RESULTS

The prevalence of CV disease was similar in T1D and T2D across age strata, whereas CKD was more common in T1D. Age-adjusted event rates comparing T1D versus T2D showed that HF risk was increased between ages 65 and 79 years, MI between 55 and 79 years, and stroke between 40 and 54 years (1.3–1.4-fold, 1.3–1.8-fold, and 1.4–1.7-fold, respectively). CKD risk was 1.4–3.0-fold higher in T1D at all ages. The all-cause death risk was 1.2–1.5-fold higher in T1D at age >50 years, with a similar trend for CV death.

CONCLUSIONS

Adult patients with T1D compared with those with T2D had an overall greater risk of cardiorenal disease (HF and CKD) across ages, MI and all-cause death at middle-older ages, and stroke at younger ages. The total age-adjusted CVRD burden and risks were greater among patients with T1D compared with those with T2D, highlighting their need for improved prevention strategies.

[1]Department of Medical Sciences, Clinical Diabetes and Metabolism, Uppsala University, Uppsala, Sweden
[2]AstraZeneca, Oslo, Norway
[3]Cardiology Unit, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden
[4]Capio Saint Göran Hospital, Stockholm, Sweden
[5]Statisticon AB, Uppsala, Sweden
[6]Department of Medicine, Huddinge, Karolinska Institutet, Stockholm, Sweden
[7]Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden
[8]University of Oslo and Oslo University Hospital, Oslo, Norway

Corresponding author: Johan Bodegard, johan.bodegard@astrazeneca.com

In 2019, an estimated 463 million people worldwide were living with diabetes, and the global prevalence is projected to increase by ~50% by the year 2045 (1). The majority have type 2 diabetes (T2D), while 5–10% of patients with diabetes suffer from type 1 (T1D). The highest incidence rates of T1D can be found in the Scandinavian countries, with onset often at a young age and, hence, a long lifetime with

the disease (2). Globally, cardiovascular (CV) diseases remain the leading cause of death (3), and it has been shown that both T1D and T2D are associated with markedly increased CV risk compared with populations without diabetes (4–7). In addition to disturbed glucose metabolism, T2D is linked to the metabolic syndrome, including obesity, insulin resistance, hypertension, and dyslipidemia. These factors are considered to contribute to the accelerated atherosclerotic CV and renal disease (CVRD) development and increased rates that are seen in T2D (8), especially represented by cardiorenal disease defined by heart failure (HF) and/or chronic kidney disease (CKD) (9). In contrast, these risk factors are not as common in patients with T1D, and their increased CVRD risk has traditionally been explained by the degree and duration of hyperglycemia per se and nephropathy (10). However, there is a paucity of studies directly comparing the frequency of CVRD between the two major forms of diabetes, so it is not known whether the risk differs significantly between these diabetes forms (11,12).

We aimed to directly compare the prevalence and incidence of CVRD in patients with T1D and T2D in large, full-population registries in Sweden and Norway. Furthermore, the presence of CKD, besides being an important microvascular diabetes complication, also in itself is an important risk factor for CV morbidity and mortality.

RESEARCH DESIGN AND METHODS
Data Sources
The present work is part of a large-scale initiative to acquire an understanding of diabetes and its treatment, and it is based on the Diabetes Swedish Full Population Study (DAISY) and Diabetes Norwegian Full Population Study (DAPH-NE) studies (13–16). Both Sweden and Norway have comprehensive, nationwide public health care systems. All citizens have a unique personal identification number, which is mandatory for administrative purposes, including any contact with the health care system as well as prescribed drug dispensaries, thus providing comprehensive medical information about the whole population. Individual patient-level data from the prescribed drug, cause

of death, and national patient registries covering all hospitalizations and all outpatient hospital visits, were linked using the personal identification number but in a pseudonymized manner. Database management and study protocols are described in the Supplementary Material.

Study Population
All patients with diabetes in Sweden and all patients >18 years of age in Norway were identified by using the prescribed drug and national patient registries. Subjects between the ages of 18 and 84 years at the index date were included in the study population. T1D was defined as having received at least one prescription of short-acting insulin from treatment start or within 6 months after start of basal insulin treatment and having a hospital diagnosis of T1D. To validate our definition of T1D, we compared our Swedish T1D cohort with data from the Swedish National Diabetes Registry (NDR) (17) and from a previous Swedish registry-based study (18) regarding prevalence, incidence, age distribution, and age at onset for subjects with T1D. We found strong agreements between our cohort and previous data sets in this regard, thus lending support for a valid classification tool (see Supplementary Fig. 1A–D for details).

T2D was defined as having any prescribed blood glucose–lowering drug dispensed by a pharmacy, except for subjects defined as having T1D and those diagnosed with gestational diabetes mellitus or polycystic ovary syndrome according to their respective diagnosis codes in the national patient registries. Subjects were followed in the national patient and cause of death registries until the end of the follow-up period or death.

Baseline and Follow-up
The index date was 31 December 2013 for both countries, and the follow-up period was 3 years for Sweden (until 31 December 2016) and 2 years for Norway (until 31 December 31 2015). This amounted to a mean follow-up of 2.6 years and 1.0 million person-years. Baseline comorbidities were searched in the national patient registries before the index date, and baseline drug

treatment was searched in the prescribed drug registries 1 year before the index date (presented in detail in Supplementary Tables 2 and 3).

Age-stratified CV and CKD event rates were calculated during the follow-up period in each country separately, and results were then pooled. Because the effect of disease duration in T1D is known to have a substantial impact on the risk of complications (6), we calculated disease duration for Swedish patients with T1D and analyzed the impact of duration on the various outcomes. Because of registry structure and limited follow-back time, complete data on duration of T2D could not be obtained.

Outcomes
Outcomes were retrieved from in- and outpatient hospital records. In cases of inpatient care, diagnoses at the end of the hospital visit were obtained after completion of clinical and laboratory investigations. Codes from the ICD-10 were used, and only the first position as main diagnosis was considered (for ICD codes of outcomes, see Supplementary Table 4). As a sensitivity analysis, all registered diagnosis codes (i.e., also beyond the first position) were searched. The following outcomes were assessed: all-cause death, myocardial infarction (MI), HF, stroke, CKD, any CVRD, and CV and all-cause death. MI was identified according to the diagnosis code of MI. Stroke included both ischemic and hemorrhagic stroke. HF included both hypertensive and other HF. CKD was defined by a first-position diagnosis of diabetic nephropathy, CKD, or renal failure (hypertensive, acute, chronic, or unspecified). CV death was defined as death as a result of stroke or MI, and any CVRD was defined as any of HF, MI, stroke, CV death, and CKD. Cardiorenal disease was defined as at least one of HF or CKD because these often appear together or sequentially. For subgroup analysis of patients with and without previous CVRD at baseline (see below), CKD was defined as described above, and CV disease was defined as MI, HF, or stroke.

Statistical Analyses
Baseline characteristics were calculated separately for each country and then

pooled. Event rates of the outcomes were calculated by dividing the number of incident cases by the duration of follow-up in person-years and expressed as incident cases/1,000 person-years.

Duration of T1D was calculated by retrieving the age at first insulin prescription or first diagnosis registration (whichever came first) available in the national patient and prescribed drug registries and calculating the time difference to age at the index date. For T2D, this was not possible since in most cases, there is not a hospital diagnosis but mainly in primary care where no national registry data are available.

Cox regression models were applied to determine the hazard ratio (HR) and 95% CI for each outcome according to type of diabetes. The effect of age was assessed by interaction analysis and was found to have a significant interaction effect on most outcomes (data not shown). Thus, age-adjusted HRs were calculated within each age category separately. Additionally, we performed analyses in patients who at baseline were free from previous CVRD and in patients who had a history of previous CVRD. This was done to explore whether previous occurrence of a CV or renal event would affect the risk in T1D versus T2D for new or recurring events, respectively.

RESULTS

Baseline Data

A total of 59,331 patients with T1D and 484,241 patients with T2D were included (Fig. 1). Data from both countries were pooled because results for the separate country cohorts were comparable. Baseline data are presented in Table 1. At baseline, 87.5% of patients with T2D were on any glucose-lowering drug, with the remaining patients having previously filled at least one prescription but stopped the treatment before the baseline date. Patients with T1D were younger than those with T2D (mean age 45.8 vs. 64.1 years) and had a lower overall prevalence of CV disease (13.3% vs. 26.2%); a similar proportion had CKD (4.3% vs. 3.3%) but more frequent microvascular complications (71.6% vs. 27.8%), mainly driven by an increased occurrence of retinopathy (58.6% vs. 13.9%) (Supplementary Table 2). A higher use of CV preventive drugs was observed in T2D versus T1D, possibly because of the higher average age. Following age stratification at baseline, the prevalence of CV disease was similar in both cohorts, with a clear increase from age ≥40 years in both T1D and T2D. For MI, HF, and stroke, there were no apparent differences in any age-groups, as shown in Fig. 2. In contrast, the age-dependent increase in prevalence of CKD appeared earlier in T1D than in T2D, and it remained consistently higher in T1D across all age-groups. The prevalence of all CV diseases combined was slightly higher in T1D compared with T2D (Supplementary Fig. 2).

Event Rates During Follow-up

Results are presented in Fig. 3. Event rates were low in age-groups <40 years, where comparisons between T1D and T2D could not be performed. For HF, event rates were significantly higher in the patients with T1D aged 65–79 years (HR 1.31–1.39), and for MI, there were similar findings in ages 55–79 years (HR 1.30–1.79). Rates of stroke, on the other hand, were significantly higher in T1D only among younger patients aged 40–54 years (HR 1.35–1.72). The incidence of CKD was greater for T1D versus T2D at all ages, similar to the baseline prevalence, although intergroup differences generally decreased with increasing age (HR 2.95 for 40–44 years to 1.53 for 80–84 years). The risk for any CVRD event was significantly higher among patients with T1D across all age-groups (HR 1.20–1.60). CV mortality rates were higher in T1D than T2D at ages 55–64 years and 70–79 years (HR 1.37–1.71) (Fig. 3) and so were total CVD events at ages 55–79 years (HR 1.14–1.42) (Supplementary Fig. 3). Except for the youngest ages of 40–49 years, all-cause mortality rates were also generally higher in the T1D group. As a further sensitivity analysis, we also included all registered diagnosis codes regardless of position (i.e., main as well as additional diagnoses). The comparisons between T1D and T2D were nearly identical to our main analyses (Supplementary Fig. 4), albeit with the expected higher overall event rates.
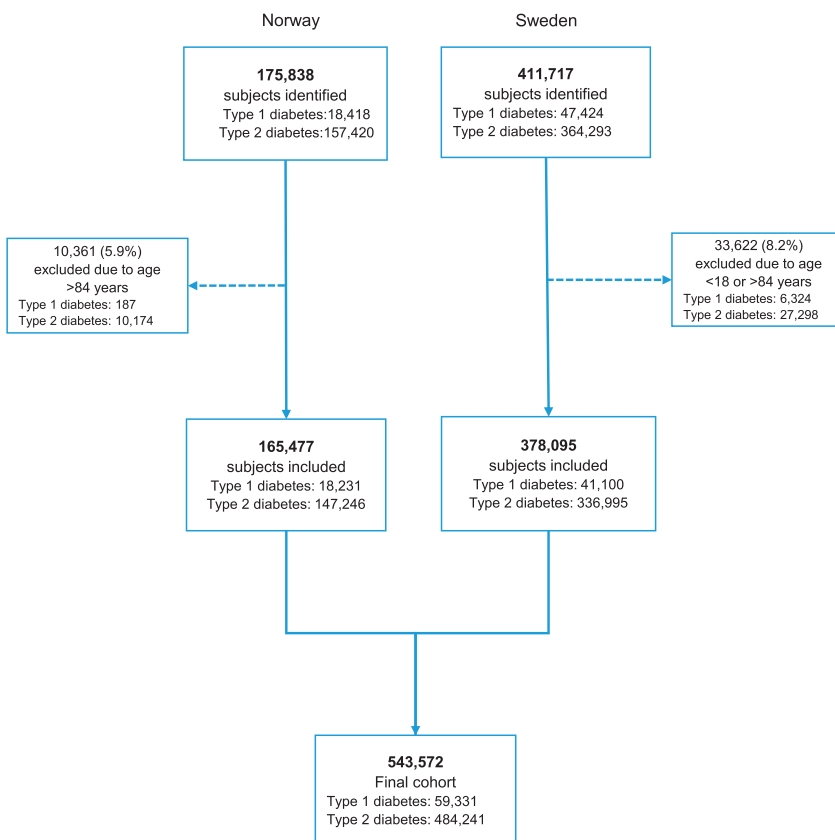
Figure 1—Flowchart of patients included in the study at the index date 31 December 2013.

Table 1—Baseline characteristics of patients with T1D and T2D in Sweden and Norway in 2013

	T1D (n = 59,331)	T2D (n = 484,241)
Age (years), mean (SD)	45.8 (16.5)	64.1 (12.4)
<50	34,405 (58.0)	64,365 (13.3)
50–75	22,978 (38.7)	315,495 (65.2)
>75	1,948 (3.3)	104,381 (21.6)
Female sex	24,911 (42.0)	208,361 (43.0)
CV disease	7,913 (13.3)	126,769 (26.2)
MI	2,476 (4.2)	41,784 (8.6)
HF	1,867 (3.1)	36,520 (7.5)
Atrial fibrillation	1,706 (2.9)	46,626 (9.6)
Stroke	2,570 (4.3)	45,074 (9.3)
Peripheral artery disease	2,987 (5.0)	28,415 (5.9)
CKD	2,530 (4.3)	15,985 (3.3)
Microvascular complications	42,452 (71.6)	134,530 (27.8)
Severe hypoglycemia	1,762 (3.0)	5,349 (1.1)
Cancer*	2,237 (3.8)	45,505 (9.4)
CV disease risk treatment	31,961 (53.9)	397,795 (82.1)
Low-dose aspirin	11,530 (19.4)	172,529 (35.6)
Statins	23,782 (40.1)	281,159 (58.1)
Antihypertensives	24,604 (41.5)	348,975 (72.1)
Diabetes medication	59,331 (100.0)	423,747 (87.5)
Metformin	2,043 (3.4)	344,651 (71.2)
Sulfonylureas	57 (0.1)	89,733 (18.5)
DPP-4 inhibitors	224 (0.4)	34,722 (7.2)
SGLT-2 inhibitors	30 (0.1)	2,021 (0.4)
GLP-1RAs	312 (0.5)	17,677 (3.7)
Insulin	59,331 (100.0)	134,350 (27.7)

Data are n (%) unless otherwise indicated. Microvascular complications include retinopathy, peripheral angiopathy, diabetic foot disease, neuropathy, and nephropathy. DPP-4, dipeptidyl peptidase 4; GLP-1RA, glucagon-like peptide 1 receptor agonist.
*Cancer diagnosis within 5 years before index date.

Subgroup Analyses

We performed subgroup analyses among patients who were free of CVRD at baseline and those with previous CVRD (Supplementary Fig. 5A–H). In the CVRD-free group, the only significant differences between T1D and T2D were increased rates of MI for T1D in the age span 70–79 years (HR 1.41–1.70) and CV mortality at 75–79 years (HR 1.78). There were no increased risks of CKD and all-cause mortality among patients with T1D in the CVRD-free cohort compared with T2D. Among patients with previous CVRD at baseline, results showed similar patterns as the main results in the total cohort (Supplementary Fig. 6A–H). We also examined the relative impact of disease duration in the Swedish T1D cohort and found that it was an important risk factor for CV events and CKD, independent of age per se (Supplementary Fig. 7). The effect of disease duration was most marked for CKD but remained substantial for all types of CVRD events. Notably, the effect of duration on all-cause mortality was, however, much smaller.

## CONCLUSIONS

Main Findings

In this observational, longitudinal, full-population study of all patients with T1D and T2D in Sweden and Norway in 2013, we present several important findings on individuals aged 18–84 years. First, the age-adjusted incidence of CV diseases were, in general, higher for T1D than T2D, with a slightly greater stroke risk at younger ages and a greater risk of MI and HF at older ages. Also, CV mortality was greater in T1D at ages >55 years, except the age intervals 65–69 and 80–84 years. Second, CKD was more common in T1D than T2D at all ages. Third, the risk for future CVRD is modified by the presence or absence of preexisting CVRD, with an almost equal risk in T1D and T2D if CVRD free at baseline, whereas risks for T1D were increased for those with previous CVRD.

To our knowledge, this study is the first to address CV disease in full-population cohorts of both T1D and T2D in modern health care systems (from 2013 to 2016). Some studies have reported risks of CV disease (19) and death (11), but these have focused on only one outcome or performed indirect comparisons through populations without diabetes.

Previously, Juutilainen et al. (11) showed in a small long-term cohort study of 134 patients with T1D and 834 with T2D that CV mortality is similar in both groups. Subjects in this study were of similar age (45–64 years), and the age of onset was >30 years. This would suggest that CV mortality risk is similar in the two diabetes types when taking age into account. Our study was much larger and included nationwide, complete T1D and T2D cohorts, which may explain the finding of higher CV mortality in T1D over the age of 50 years.

Recently, Fang et al. (12) examined data from the U.S. National Health Interview Survey conducted in 2016 and 2017 to compare the burden of complications in young-onset T1D and T2D, defined as being diagnosed before age 40 years. They found that there were similar rates of CV disease between the two groups, which is in agreement with our results, but they also observed similar rates of renal disease, which is different from our findings. This study was purely interview based, including ~230 subjects with T1D and 1,200 subjects with T2D, and the statistical power may not have been sufficient to detect true differences between the groups. It is, however, also possible that young-onset T2D represents an aggressive diabetes phenotype with greater cardiorenal risk, as previous studies have suggested (20,21), and that this contributed to the increased risk of kidney disease among subjects with T2D in the study.

In South Korea, Lee et al. (22) followed a population of 20.4 million individuals from 2009 to 2016, of whom ~1.9 million had T2D and 9,400 had T1D. In agreement with our results, they found a significantly higher risk of MI, HF hospitalization, atrial fibrillation, and mortality among the subjects with T1D compared with those with T2D during a mean follow-up of 4.6 years. Furthermore, we show that individuals with T1D who already have established
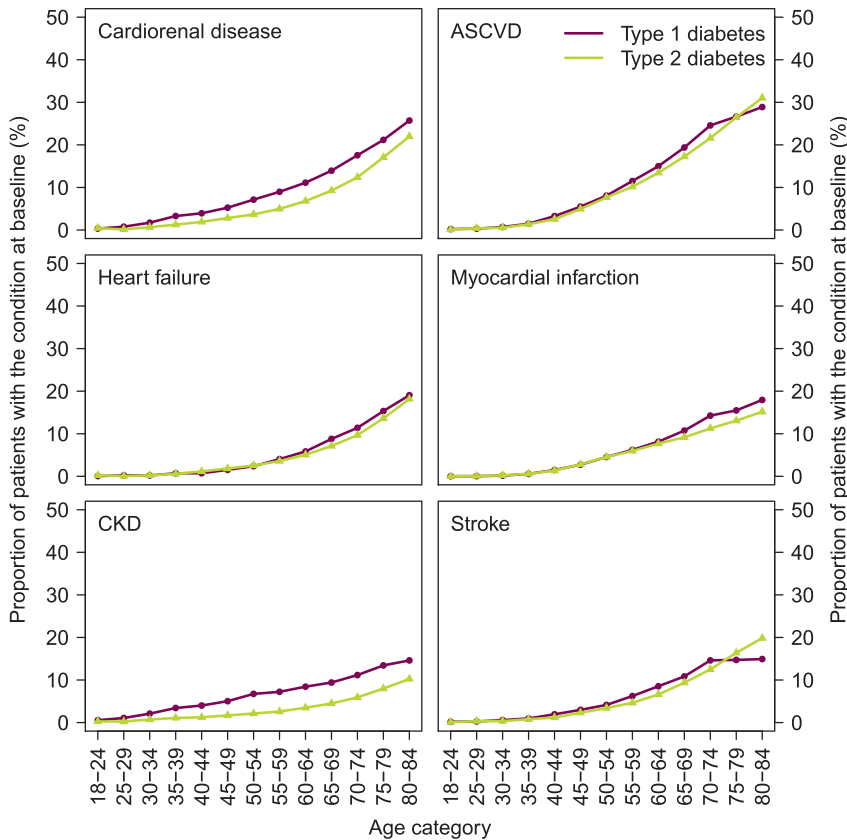
Figure 2—Age-stratified baseline prevalence of CKD, HF, cardiorenal disease (HF or CKD), stroke, MI, and atherosclerotic CV disease (ASCVD) (MI or stroke).

CVRD are at a higher risk of further CVRD events, which suggests that patients with T1D will benefit from a more intensive strategy for both primary and, in particular, secondary prevention of CVRD.

Possible Explanations for Higher CVRD Risk in T1D

Several factors could explain the high risk of CV disease in individuals with T1D. Previous studies have established the importance of albuminuria and CKD in increasing the risk of mortality and CV disease in T1D (23,24). We did not have access to laboratory assessments and, therefore, could not adjust for the degree of renal impairment, but our results indicate that both prevalent and incident CKD are more common in T1D than in T2D, and this could contribute to the higher rates of CV disease in T1D found in several age-groups. We did not have complete data on T2D duration, but microvascular complications, including diabetic nephropathy, often progressing to manifest CKD, are known to be associated with disease

duration (25), and it is likely that the earlier age of onset of T1D and, hence, longer average duration, would lead to a greater risk of microvascular complications in later life. Hyperglycemia is another risk factor, and higher mean HbA$_{1c}$ levels and long-term glycemic exposure are associated with increased mortality (5) and greater risk of macro- and microvascular complications (26,27). A study that was based on Swedish NDR data explored the prognostic significance of various risk factors among subjects with T1D and found HbA$_{1c}$ and albuminuria to be the most important predictors for mortality and CV disease (28). However, other conventional risk factors such as LDL cholesterol and systolic blood pressure were also strongly associated with adverse CV outcomes.

Interestingly, there was an excess risk in the CVRD-free T1D versus T2D cohorts only of MI and CV death in some age strata but not of other CV events and CKD. The reasons for this are not readily apparent. It is possible that these cohorts were more homogenous,

with relatively low risks overall. However, it is worth noting that previous studies have shown that excess mortality in T1D is largely accounted for by nephropathy (24,29), which may explain the finding of a relatively lower risk elevation in T1D versus T2D in the CVRD-free cohorts. In T1D, aggressive nephropathy leading to advanced CKD typically has an early onset, and there is seldom development of nephropathy leading to end-stage renal disease after 15 years of T1D (24,30,31). Notably, among patients with T2D, those with onset at younger ages have a relatively higher risk of serious nephropathy (21,30). Taken together, these findings are compatible with an increased CKD risk in T1D across age strata. However, a similar risk for CKD events in previously CVRD-free patients with T1D versus T2D is somewhat surprising and warrants further detailed investigations.

CV Disease Preventive Treatment

In our cohort, established drugs to prevent CV disease, such as statins and antihypertensive and antiplatelet drugs, were prescribed far less among patients with T1D compared with those with T2D, albeit this is largely explained by their overall younger age. This may have contributed to the increased cardiorenal risk in T1D. More aggressive intervention with CV disease preventive drugs should therefore be considered at an earlier disease stage, and thus at younger ages in patients with T1D, than what is currently done in routine care. Furthermore, several CV outcome trials have shown beneficial effects of sodium–glucose cotransporter 2 (SGLT2) inhibitors to prevent progression of HF and CKD in both medium- and high-risk T2D populations (32–35). SGLT2 inhibitors might be further explored regarding their risk/benefit profile in future interventional outcome studies in patients with T1D, considering their high cardiorenal risk. In patients with T2D with low-medium CVRD risk, interventional studies should also address initiation of SGLT2 inhibitors at early disease stages. Such studies are currently under way; for example, in Sweden, the SGLT2 inhibitor dapagliflozin and metformin are being compared as first-line therapy in a large randomized prospective trial (SGLT2 Inhibitor or Metformin as Standard Treatment of Early Stage Type 2 Diabetes
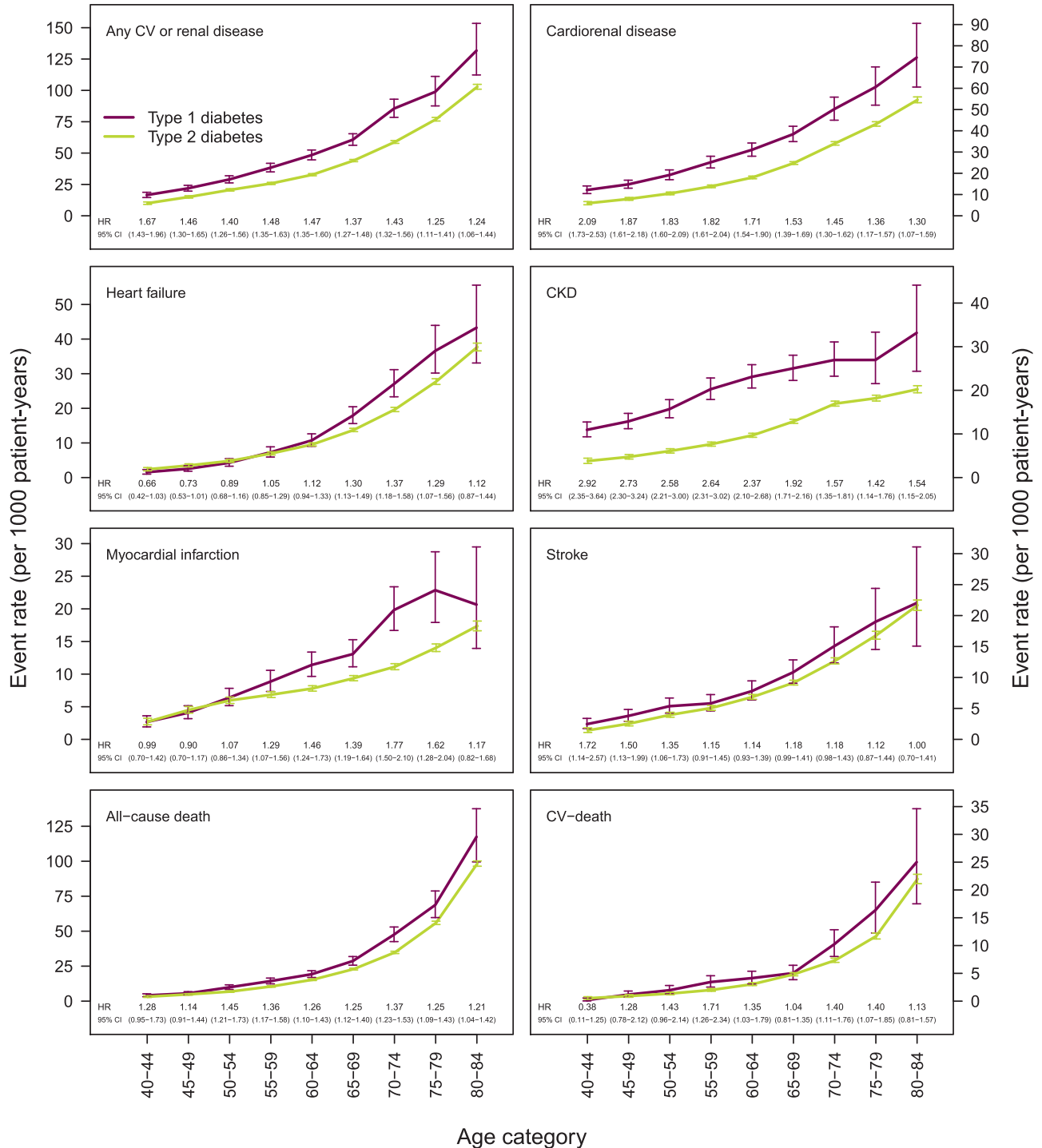
Figure 3—Age-stratified incidence of any CVRD events (including MI, stroke, HF, CKD, or CV death), cardiorenal disease (HF or CKD), HF, CKD, MI, stroke, all-cause death, and CV death.

[SMARTEST] trial, ClinicalTrials.gov identifier NCT03982381).

Strengths and Limitations
Strengths of the current study include the large population-based cohorts

from modern health care covering essentially all patients with T1D and T2D in two countries. The representative populations constitute a real-world data set and include patients of a wide age range. To our knowledge, this is the first

study in European populations to directly compare CV and renal complications in T1D and T2D in nationwide full populations. Importantly, we were also able to validate our definition of T1D and T2D by comparing our T1D cohort

(concerning prevalence and patient characteristics) with that of the Swedish NDR, showing an essentially complete overlap.

However, our study also has a number of important limitations. First, because of the registry structures and limited follow-back time, it was not possible to accurately determine diabetes duration for all patients with T2D. Longer duration of T2D has been linked with a greater risk of CV disease and death (36,37), and since we did not have complete information about T2D duration, we could not adjust for this. In 2013 (i.e., the time of our baseline survey), the median duration in Swedish patients with T2D was 8 years according to the 2013 NDR annual report (38) and as reported in a previous publication (4). It is clear that diabetes duration overall is longer in our T1D cohort, with a median of 14 years (range 0 to >27 years) in the Swedish patients. This undoubtedly contributes to the high CVRD risk in T1D, which for several event types overrides that of T2D, despite its metabolic components. In our cohort of Swedish patients with T1D for whom duration data were available, we found a higher risk of adverse outcomes in those with a longer age-adjusted T1D duration, which is in agreement with previous findings (39,40). Assuming similar glycemic levels in T1D and T2D and an ~10% increase in risk of CVRD for every year of diabetes duration (Supplementary Fig. 7), the longer average duration of T1D versus T2D at any given age could account for the higher risks we found. Our study did not include a control population. However, previous results comparing T2D with the general Swedish population (16) indicated an ~1.7-fold increase in the risk for MI and HF, and by extrapolation from our T2D cohort, we estimate that patients with T1D had an ~2.5-fold greater risk of MI and HF compared with the background population.

Second, no data were available regarding several important risk factors associated with increased rates of CVRD in diabetes. These include HbA$_{1c}$, blood lipids, blood pressure, and obesity (24). Furthermore, no information was available regarding socioeconomic and lifestyle risk factors, which are important for outcomes in both T1D (41) and T2D

(42). Such confounding factors should be addressed in future studies.

Third, hospital ICD codes were used, and we had no access to primary care data. This may have led to an underestimation of events in patients with T2D because the majority of them are seen in primary care. However, the main scope of the study was to address risk of major clinical CV and renal events, which almost invariably will lead to in- or outpatient hospital care. For example, early stages of CKD in T2D may be underestimated because these patients are typically found in primary care, but the overall occurrence of end-stage renal disease was clearly higher among patients with T1D versus T2D (Supplementary Table 2).

In conclusion, the CVRD burden among patients with T1D is at least as heavy as in patients with T2D following age stratification. For several CVRD events like HF and MI and clearly for CKD, T1D displays the highest risk. There is a remaining need to reinforce and evaluate additional preventive approaches, beyond glycemic control, also in patients with T1D.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 9th edition. Brussels, Belgium, International Diabetes Federation, 2019. Accessed 22 November 2020. Available from https://www.idf.org/e-library/epidemiology-research/diabetes-atlas/159-idf-diabetes-atlas-ninth-edition-2019.html
2. Katsarou A, Gudbjörnsdottir S, Rawshani A, et al. Type 1 diabetes mellitus. Nat Rev Dis Primers 2017;3:17016
3. World Health Organization. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization, 2018
4. Tancredi M, Rosengren A, Svensson AM, et al. Excess mortality among persons with type 2 diabetes. N Engl J Med 2015;373:1720–1732
5. Lind M, Svensson AM, Kosiborod M, et al. Glycemic control and excess mortality in type 1 diabetes. N Engl J Med 2014;371:1972–1982
6. Rawshani A, Sattar N, Franzén S, et al. Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study. Lancet 2018;392:477–486
7. Larsson SC, Wallin A, Håkansson N, Stackelberg O, Bäck M, Wolk A. Type 1 and type 2 diabetes mellitus and incidence of seven cardiovascular diseases. Int J Cardiol 2018;262:66–70
8. Low Wang CC, Hess CN, Hiatt WR, Goldfine AB. Clinical update: cardiovascular disease in diabetes mellitus: atherosclerotic cardiovascular disease and heart failure in type 2 diabetes mellitus - mechanisms, management, and clinical considerations. Circulation 2016;133:2459–2502
9. Birkeland KI, Bodegard J, Eriksson JW, et al. Heart failure and chronic kidney disease manifestation and mortality risk associations in type 2 diabetes: a large multinational cohort study. Diabetes Obes Metab 2020;22:1607–1618
10. de Ferranti SD, de Boer IH, Fonseca V, et al. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Diabetes Care 2014;37:2843–2863
11. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Similarity of the impact of type 1 and type 2 diabetes on cardiovascular mortality

in middle-aged subjects. Diabetes Care 2008;31:714–719

12. Fang M, Echouffo-Tcheugui JB, Selvin E. Burden of complications in U.S. Adults with young-onset type 2 or type 1 diabetes. Diabetes Care 2020;43:e47–e49

13. Lindh A, Persson F, Sobocki P, Bodegard J, Lindarck N. Nordic longitudinal data from electronic medical records and full population national registers: unique opportunities for new insights in benefit of diabetes patients (Abstract). Value Health 2015;18:A726

14. Birkeland KI, Bodegard J, Norhammar A, et al. How representative of a general type 2 diabetes population are patients included in cardiovascular outcome trials with SGLT2 inhibitors? A large European observational study. Diabetes Obes Metab 2019;21:968–974

15. Birkeland KI, Jørgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol 2017;5:709–717

16. Norhammar A, Bodegård J, Nyström T, Thuresson M, Eriksson JW, Nathanson D. Incidence, prevalence and mortality of type 2 diabetes requiring glucose-lowering treatment, and associated risks of cardiovascular complications: a nationwide study in Sweden, 2006-2013. Diabetologia 2016;59:1692–1701

17. Swedish National Diabetes Register. Swedish National Diabetes Register Annual Report 2017. Accessed 25 October 2020. Available from https://www.ndr.nu/pdfs/Arsrapport_NDR_2017.pdf

18. Rawshani A, Landin-Olsson M, Svensson AM, et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014;57:1375–1381

19. McAllister DA, Read SH, Kerssens J, et al. Incidence of hospitalization for heart failure and case-fatality among 3.25 million people with and without diabetes mellitus. Circulation 2018;138:2774–2786

20. Svensson M, Sundkvist G, Arnqvist HJ, et al.; Diabetes Incidence Study in Sweden (DISS). Signs of nephropathy may occur early in young adults with diabetes despite modern diabetes management: results from the nationwide population-based Diabetes Incidence Study in Sweden (DISS). Diabetes Care 2003;26:2903–2909

21. Constantino MI, Molyneaux L, Limacher-Gisler F, et al. Long-term complications and mortality in young-onset diabetes: type 2 diabetes is more hazardous and lethal than type 1 diabetes. Diabetes Care 2013;36:3863–3869

22. Lee YB, Han K, Kim B, et al. Risk of early mortality and cardiovascular disease in type 1 diabetes: a comparison with type 2 diabetes, a nationwide study. Cardiovasc Diabetol 2019;18:157

23. Miller RG, Costacou T, Orchard TJ. Risk factor modeling for cardiovascular disease in type 1 diabetes in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study: a comparison with the Diabetes Control and Complications Trial/Epidemiology Of Diabetes Interventions and Complications study (DCCT/EDIC). Diabetes 2019;68:409–419

24. Groop PH, Thomas MC, Moran JL, et al.; FinnDiane Study Group. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009;58:1651–1658

25. Drummond KN, Kramer MS, Suissa S, et al.; International Diabetic Nephropathy Study Group. Effects of duration and age at onset of type 1 diabetes on preclinical manifestations of nephropathy. Diabetes 2003;52:1818–1824

26. Lund SS, Rossing P, Vaag AA. Follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2009;360:416–418; author reply 418

27. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study at 30 years: overview. Diabetes Care 2014;37:9–16

28. Rawshani A, Rawshani A, Sattar N, et al. Relative prognostic importance and optimal levels of risk factors for mortality and cardiovascular outcomes in type 1 diabetes mellitus. Circulation 2019;139:1900–1912

29. Orchard TJ, Secrest AM, Miller RG, Costacou T. In the absence of renal disease, 20 year mortality risk in type 1 diabetes is comparable to that of the general population: a report from the Pittsburgh Epidemiology of Diabetes Complications Study. Diabetologia 2010;53:2312–2319

30. Svensson MK, Tyrberg M, Nyström L, et al. The risk for diabetic nephropathy is low in young adults in a 17-year follow-up from the Diabetes Incidence Study in Sweden (DISS). Older age and higher BMI at diabetes onset can be important risk factors. Diabetes Metab Res Rev 2015;31:138–146

31. Helve J, Sund R, Arffman M, et al. Incidence of end-stage renal disease in patients with type 1 diabetes. Diabetes Care 2018;41:434–439

32. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128

33. Wiviott SD, Raz I, Bonaca MP, et al.; DECLARE–TIMI 58 Investigators. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–357

34. Furtado RHM, Bonaca MP, Raz I, et al. Dapagliflozin and cardiovascular outcomes in patients with type 2 diabetes mellitus and previous myocardial infarction. Circulation 2019;139:2516–2527

35. Birkeland KI, Bodegard J, Banerjee A, et al. Lower cardiorenal risk with sodium-glucose cotransporter-2 inhibitors versus dipeptidyl peptidase-4 inhibitors in patients with type 2 diabetes without cardiovascular and renal diseases: a large multinational observational study. Diabetes Obes Metab 2021;23:75–85

36. Zoungas S, Woodward M, Li Q, et al.; ADVANCE Collaborative group. Impact of age, age at diagnosis and duration of diabetes on the risk of macrovascular and microvascular complications and death in type 2 diabetes. Diabetologia 2014;57:2465–2474

37. Huo L, Magliano DJ, Rancière F, et al. Impact of age at diagnosis and duration of type 2 diabetes on mortality in Australia 1997-2011. Diabetologia 2018;61:1055–1063

38. Gudbjornsdottir S, Eliasson B, Cederholm J, Zethelius B, Svensson AM, Samuelsson P. Annual Report 2013 Results: Nationella Diabetes Registeret (NDR); 2013. Accessed 14 October 2020. Available from: https://www.ndr.nu/#/arsrapport

39. Pambianco G, Costacou T, Ellis D, Becker DJ, Klein R, Orchard TJ. The 30-year natural history of type 1 diabetes complications: the Pittsburgh Epidemiology of Diabetes Complications Study experience. Diabetes 2006;55:1463–1469

40. Soedamah-Muthu SS, Chaturvedi N, Witte DR, Stevens LK, Porta M; EURODIAB Prospective Complications Study Group. Relationship between risk factors and mortality in type 1 diabetic patients in Europe: the EURODIAB Prospective Complications Study (PCS). Diabetes Care 2008;31:1360–1366

41. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Associations between socioeconomic status and major complications in type 1 diabetes: the Pittsburgh Epidemiology of Diabetes Complication (EDC) study. Ann Epidemiol 2011;21:374–381

42. Tatulashvili S, Fagherazzi G, Dow C, Cohen R, Fosse S, Bihan H. Socioeconomic inequalities and type 2 diabetes complications: a systematic review. Diabetes Metab 2020;46:89–99