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Original Article

Cardiovascular medication use and cardiovascular disease in children and adolescents with type 1 diabetes: a population-based cohort study

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Objectives: To investigate the 5-yr prevalence and incidence rates of cardiovascular medication and cardiovascular disease before and after onset of type 1 diabetes (T1D) in children and adolescents.
Methods: Children and adolescents (<19 yr) with T1D (n = 925), defined as those who received at least two insulin prescriptions, and a four times larger reference cohort (n = 3591) with the same age and gender in the Dutch PHARMO Record Linkage System (RLS) were studied in a retrospective cohort study between 1999 and 2009. The date of first insulin dispensing was selected as the index date.
Results: The overall prevalence rate of cardiovascular medication use was substantially higher in the T1D cohort before (2.2 vs. 1.0%, $p < 0.001$) and after (9.2 vs. 3.2%, $p < 0.001$) the index date. After the index date angiotensin-converting enzyme inhibitors (2.0%) and statins (1.5%) were the most prevalent cardiovascular medications in the T1D cohort. The highest incidence rate of cardiovascular medication use was observed in the first year after the index date [28.1 per 1000 person years (PY)]. Furthermore, three type 1 diabetic patients were hospitalized due to cardiomyopathy (n = 2) and heart failure (n = 1) and one child from the reference group was hospitalized due to cardiomyopathy in the 5 yr after the index date.
Conclusions: Children with T1D were more likely to use cardiovascular medications in the years before and after the onset of diabetes. Our study emphasizes the importance of routine screening tests and timely treatment of CVD risk factors in the pediatric population with diabetes.

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It is well established that type 1 diabetes (T1D) in children is associated with an increased risk of cardiovascular disease (CVD) that manifests as early as in childhood (1). CVD risk factors such as hyperlipidemia, hypertension, and diabetes cause damage to arterial vessels due to atherosclerosis. This is a process that develops over many years, starting in childhood and manifesting as coronary artery disease and stroke in adulthood (2). Children and adolescents with T1D have a higher prevalence of CVD risk factors such as hypertension and hyperlipidemia compared with children without diabetes (3–7). In line with this, they have a higher risk of cardiovascular (CV) abnormalities such as vascular endothelial and smooth

muscle dysfunction, arterial stiffness, and increased carotid intima media thickness (8–11). Furthermore, they have a sixfold higher risk of prolonged heart rate corrected QT interval (≥450 ms) (12–15).

The available guidelines (16, 17) advise to start the treatment in diabetic patients with CVD risk factors, however there is a lack of longitudinal data on efficacy of CV drugs in children with T1D (18). Previous studies have shown beneficial effects of angiotensin-converting enzyme (ACE) inhibitors in adolescents with microalbuminuria (18–22), but data on cholesterol lowering therapy in this population are limited (23, 24). The results of the adolescent T1D cardio-renal intervention trial (AdDIT) which is an ongoing multicenter, randomized, double-blind, placebo-controlled trial provide important data on the potential renal and CV protective effects of ACEI and statins in high-risk adolescents (25, 26).

Given this situation, it is of interest to study the use of CV medication and disease in type 1 diabetic children in daily clinical practice. Therefore, the aim of our study was to calculate the prevalence and incidence rates of CV medication use and the incidence rates of hospital admissions for CVD in children and adolescents with T1D before and after the diagnosis of diabetes and to compare these rates with a group of age- and sex-matched diabetes-free children and adolescents in the Netherlands.

Methods

Setting

Data for this retrospective cohort study was obtained from the Dutch PHARMO Record Linkage System (RLS) (http://www.pharmo.nl). PHARMO RLS is a population-based patient centric data network including high quality and complete information linked on a patient level of, among other data, patient demographics, drug dispensing records from community pharmacies, and hospital discharge records of more than four million individuals throughout the Netherlands (approximately 24% of the Dutch population) (27, 28). The drug-dispensing database contains detailed information on the dispensed drug, the type of prescriber, the dispensing date, the amount dispensed, and the written dose instructions. The hospital records are obtained from the Dutch National Medical Register (LMR), which comprises all hospital admissions in the Netherlands. Date of hospital admissions and discharges, together with primary and secondary diagnoses, are documented in the hospital records. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) (http://icd9cm.chrisendres.com), whereas the drugs are coded according to the Anatomical Therapeutic Chemical codes (ATC codes) (http://www.whocc.no/atc_ddd_index).

Study population

A population-based cohort study was conducted within PHARMO RLS. The T1D cohort consisted of children and adolescents younger than 19 yr who received at least two insulin prescriptions [based on the ATC codes for insulin preparations (A10A)] between 1999 and 2009 (29). The date of the first insulin dispensing was selected as the cohort entry date (index date). Up to four diabetes-free children and adolescents from the PHARMO RLS without any prescription of glucose lowering medications (ATC code: A10) or hospitalization for diabetes (ICD-9-CM code: 250) during the study period were matched to each child in the T1D cohort by gender, age, and calendar time distribution (reference cohort). Patients in both cohorts were eligible for inclusion in the study if they had at least 12 months of exposure history before and at least 12 months follow up after the index date. Patients in the T1D cohort were excluded in case of any use of oral anti-diabetic agents or use of glucagon prior to insulin.

Glucagon is mainly used to treat diabetic patients for the management of hypoglycemia. Therefore the index date was not clear for those patients who had a prescription of glucagon before starting insulin therapy.

For both cohorts, data for a maximum of 5 yr before and after the index date were retrieved.

CV medication use and hospital admissions due to CVD

For both cohorts, exposure to CV medication was defined as a recorded receipt of a prescription for CV medication categorized into the following groups: cardiac drugs (C01), anti-hypertensive drugs (C02) [including (diuretics (C03), peripheral vasodilators (C04), beta-blocking agents (C07), calcium channel blockers (C08), agents acting on the renin–angiotensin system (C09)], lipid modifying agents (C10), and antithrombotic agents (B01) as listed in Table S1, Supporting Information. Children and adolescents who received at least one prescription for CV medication during the study period were defined as CV medication users. All hospital admissions due to CVD were extracted from the database using ICD-9-CM codes as listed in Table S2.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of both cohorts. Overall prevalence rates

of CV medication use in the period before and after the index date were calculated for both cohorts. Prevalence rate ratios (PRRs) were calculated by dividing the prevalence rates in children with T1D by the prevalence rates in the reference cohort. Annual prevalence rates of CV medication use in each cohort were calculated by dividing the number of CV medication users in a specific year by the total number of children and adolescents in the same year. In subgroup analyses, prevalence rates of CV medication use stratified by gender and age categories (using age bands: 0–4, 5–9, 10–14, and 15–18 yr) were compared using the ordinal chi-square test. Annual incidence rates of CV medication use and hospital admission for CVD in each cohort were defined as the number of incident CV medication users and incident hospitalized CVD cases during a given time period divided by the person time at risk. For calculating annual incidence rates, to exclude prevalent cases in each year, subjects were required to have at least 12 months prior history (either a drug prescription or the occurrence of a hospital admission due to CVD) in the database. Incidence rate ratios (IRRs) were calculated to compare the incidence rates between different cohorts by dividing incidence rates in the T1D cohort by the rates in the reference cohort. Data analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL, USA).

Results

A total of 925 children and adolescents with T1D(the T1D cohort) were identified from PHARMO RLS in the period 1999 to 2009 and compared with a group of 3591 diabetes-free children and adolescents in the reference cohort. At the index date, almost 49% of the study participants were girls with a median age of 10 yr [interquartile range (IQR) 7–14 yr] (Table 1).

Table 1. Baseline characteristics in the T1D and the reference cohorts

		T1D cohort (N = 925)	Reference cohort (N = 3591)
Sex, N (%)	Male	469 (50.7)	1817 (50.6)
	Female	456 (49.3)	1774 (49.4)
Age at diagnosis (index date), N (%)	0–4 yr	132 (14.3)	537 (15.0)
	5–9 yr	269 (29.1)	1043 (29.0)
	10–14 yr	338 (36.5)	1295 (36.1)
	15–18 yr	186 (20.1)	716 (19.9)
Age (median, IQR), yr		10 (7–14)	10 (7–14)
Follow-up before the index date (median, IQR), yr		2.7 (1.8–3.7)	2.9 (1.9–3.9)
Follow-up after the index date (median, IQR), yr		3.0 (2.0–4.0)	3.0 (2.0–4.0)

T1D, type 1 diabetes; IQR, interquartile ratio.

Prevalence rates of CV medication use

The overall prevalence rate of CV medication use before the index date in the T1D cohort [2.2%, 95% confidence interval (CI), 1.3–3.5] was two times higher than in the diabetes-free cohort (1.0%, 95% CI, 0.7–1.4). For the period after the index date the prevalence rate in the T1D cohort (9.2% , 95% CI, 7.4–11.4) was almost three times higher than in the reference cohort (3.2%, 95% CI, 2.6–3.8) (Table 2). The annual prevalence rates showed that the statistically significant higher consumption of CV medication in the T1D cohort compared with the reference cohort started from 1 yr before the index date (1.3%, 95% CI, 0.7–2.3 vs. 0.5%, 95% CI, 0.3–0.7) and continued in the 5 yr after the index date. There was an increasing trend and the highest prevalence rate appeared in patients with T1D in the period of 4–5 yr after the index date with a prevalence rate of 5.1% (95% CI, 3.6–7.2) vs. 1.2% (95% CI, 0.8–1.7) in the reference cohort (Fig. 1 and Table S3).

Children and adolescents in the T1D cohort had a four times higher prevalence rate of CV medication use in the period after the onset of diabetes compared with the years before. The same pattern was observed in the reference cohort.

There was no statistically significant difference between boys and girls in the prevalence rates of CV medication use in both cohorts. As shown in Fig. 2, the number of CV prescriptions increased with increasing age. Diabetic adolescents aged 15–18 yr used CV medication more frequently in the period 5 yr after the index date (5.4%, 95% CI, 4.2–7.0) compared with the reference cohort (1.2%, 95% CI, 0.9–1.6).

In the period after the index date, ACE inhibitors were the most commonly used CV medications in patients with T1D with a prevalence rate of 2.0%, 95% CI, 1.2–3.2 compared with the reference cohort (0.2%, 95% CI, 0.1–0.4). Statins (1.5 vs. 0.1%; $p < 0.001$), heparin (1.3 vs. 0.5%; $p = 0.02$), diuretics and potassium sparing agents (1.1% vs. 0.1%; $p < 0.001$), and selective beta-blocking agents (1.0% vs. 0.2%; $p < 0.001$) were also significantly more often prescribed in diabetic patients compared with the reference cohort.

Incidence rates of CV medication use

Annual incidence rates of CV medication use during the 5 yr before and after the index date are presented in Fig. 3. The highest annual incidence rate of CV

Table 2. Overall prevalence rates of CV medication use in the T1D and the reference cohorts

	Cohort	Total population	CV medication users	Prevalence rate (%), 95% CI	PRR, 95% CI
5 yr before the index date	T1D	737	16	2.2 (1.3–3.5)	2.2 (1.2–4.1)
	Reference	2875	28	1.0 (0.7–1.4)	
5 yr after the index date	T1D	794	73	9.2 (7.4–11.4)	2.9 (2.2–3.9)
	Reference	3068	97	3.2 (2.6–3.8)	

CV, cardiovascular; T1D, type 1 diabetes; PRR, prevalence rate ratio.

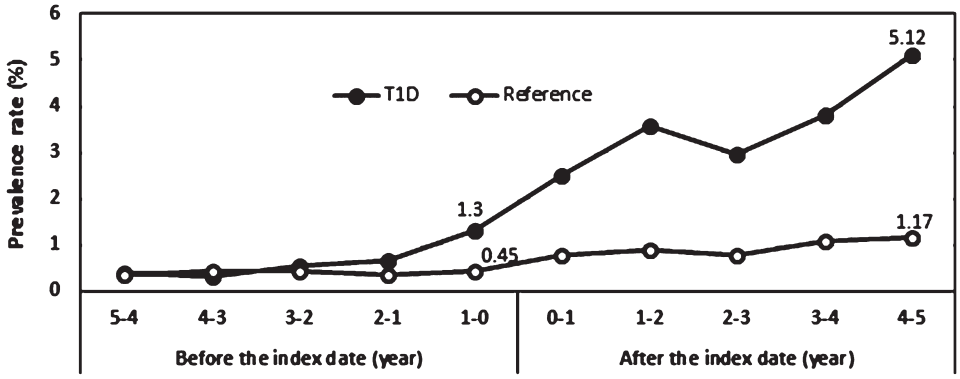

Fig. 1. Annual prevalence rates of cardiovascular (CV) medication use in the type 1 diabetes (T1D) and the reference cohorts, Index date is the date of first insulin dispensing.

medication use in the T1D cohort was observed in the first year after the index date which was 5.5 times higher than the reference cohort in the same time period with a incidence rate of 28.1 per 1000 person years (PY) (95% CI, 19.1–41.2) compared with 5.1 per 1000 PY (95% CI, 3.2–8.0) in the reference cohort. This annual incidence rate of CV medication use in the T1D cohort gradually decreased to 23.1 per 1000 PY in the second year after the index date and had a sharp decline in the third year after the index date which was followed by an increase to 23.6 per 1000 PY at the end of follow up (Table S4). Because of the low numbers it was not possible to stratify the incidence rates of CV medication use by age and gender.

Incidence rates of hospital admission due to CVD

In the T1D cohort, three patients were hospitalized due to cardiomyopathy (n = 2) and heart failure (n = 1), while in the reference group only one child was hospitalized with cardiomyopathy in the 5 yr after the index date.

Discussion

This study showed that the overall prevalence rates of CV prescriptions among type 1 diabetic children and adolescents were significantly higher than among age- and sex-matched diabetes-free individuals in the periods both before and after the onset of diabetes.

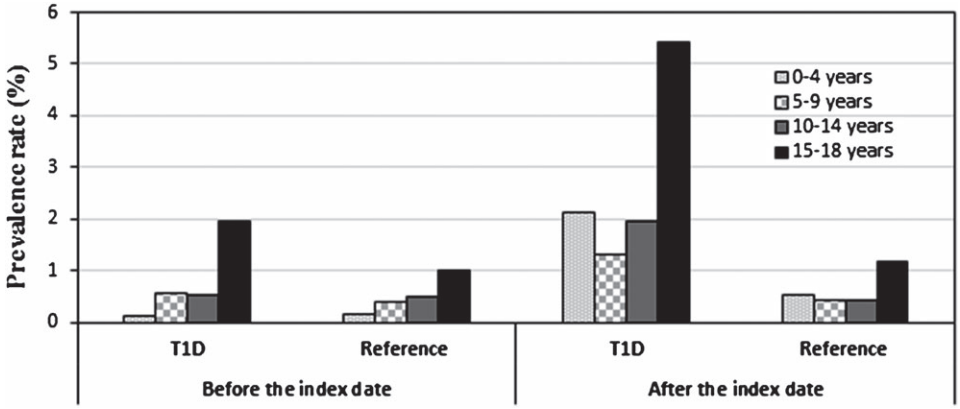

Fig. 2. Overall prevalence rate of cardiovascular (CV) medication use in the type 1 diabetes (T1D) and the reference cohorts, stratified by age, Index date is the date of first insulin dispensing.

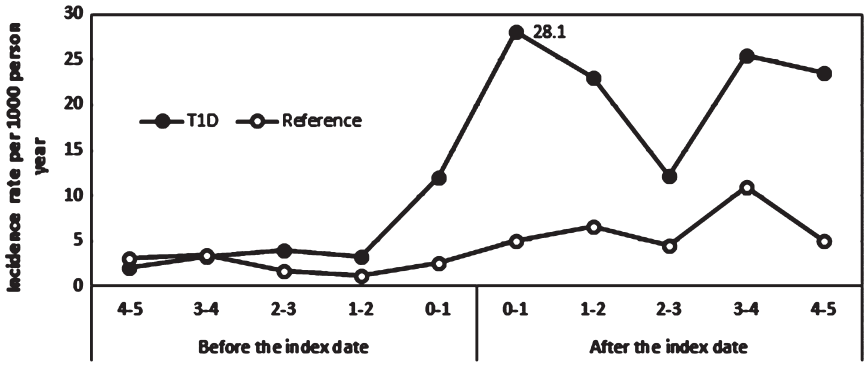

Fig. 3. Annual incidence rates of cardiovascular (CV) medication use (per 1000 PY) in the type 1 diabetes (T1D) and the reference cohorts, Index date is the date of first insulin dispensing.

The statistically significant difference between the two cohorts had already started 1 yr before the onset of diabetes and further increased during the follow up. There was no significant difference between boys and girls in the prevalence rate of CV medication use. The oldest age group (15–18 yr) had the highest prevalence rate of CV medication use (5.4%) in the T1D cohort. The highest incidence rate of CV medication use was observed for children and adolescents with T1D in the first year after the diagnosis which was 5.5 times higher than what we observed for the reference cohort. Furthermore, the number of CV hospitalizations, as expected, was low in this age category.

The use of CV medication which was already higher before the diagnosis of T1D can be explained in two ways. Firstly, it is possible that the variable asymptomatic period of beta-cell destruction prior to the clinical presentation of T1D (30) is associated with a higher occurrence of CVD risk factors. However it is not clear how these pancreatic changes could influence the occurrence of CVD risk factors. Secondly, it is clear that some of the CV drugs may trigger the clinical manifestation of T1D, for instance, beta blockers and thiazide diuretics have diabetogenic properties (31, 32). Beta blockers increase insulin resistance and thiazide diuretics reduce insulin secretion (33–35). Owing to the very low frequency of CV medication use before the onset of diabetes we could not formally test the association between drugs with diabetogenic properties and the occurrence of T1D. Further research is needed to understand the increased use of CV medication prior to the clinical onset of T1D.

The higher use of CV medication in children and adolescents with T1D compared with the reference cohort is in line with earlier findings that these patients have higher prevalence rates of CVD risk factors (3–7) and have an increased risk of carotid intima-media thickness, reduced endothelium-dependent arterial flow-mediated dilation (FMD), and increased arterial stiffness (8–11). The highest incidence rate of CV medication use in the T1D cohort in the first year after the diabetes diagnosis (28.1 per 1000 PY; IRR: 5.5) is probably caused by active screening for CVD risk factors (16, 17, 36, 37). There is an unexpected dip in the data for the second and third years, as seen in Figs. 1 and 2.

Although there was a higher consumption of CV medication among the T1D cohort, still only 9% of these patients were on CV medications during the 5 yr follow-up. Based on the published prevalence rates of hypertension and dyslipidemia in children and adolescents with T1D (ranging between 8.1–16.7% and 16.9–28.7%, respectively) (3, 5, 17), and the recommendations of the American Diabetes Association (ADA) (16) to treat these risk factors, there is probably under treatment in children with T1D in the Netherlands. Such under-treatment was shown in several other population-based studies (4–6, 23, 38). One explanation might be that there is no evidence that pharmacological treatment of hypertension and dyslipidemia in children with T1D prevents CV morbidity and mortality. Another explanation might be that clinically apparent vascular complications are rarely manifested in children and adolescents (39) and there is a general reluctance to use drug therapy to treat hypertension and lipid abnormalities in children and adolescents. Finally it is possible that the first step in first line management of these risk factors has been through lifestyle modifications.

During recent years guidelines have been published with detailed recommendations for the management of diabetes and related complications including CVD risk factors. Accordingly, more attention should be given to early treatment of CVD risk factors to reduce long-term morbidity and mortality from diabetes complications (16, 17, 40, 41).

The relatively high prevalence rate of ACE inhibitor use is in accordance with the guideline for diabetes in children and adolescents (www.ispad.org/forums/2014-consensus-guidelines). ADA and American Heart Association (AHA) (17) prescribe ACE inhibitors or angiotensin II receptor blockers (ARB)

in young children. Daniels et al. showed that 36% of children with T1D used ACEI/ARB medications for microalbuminuria (42).

The observed higher consumption of heparin as a third most prevalent CV medication in T1D compared to the reference cohort was unexpected. It is not directly clear why children with T1D have more (or increased risk for) thromboembolic events.

A main strength of our study is that we used PHARMO RLS which is a large, population-based data set (including almost 24% of the Dutch population) providing accurate data on medications being dispensed and hospital admissions that is representative of the general population (27, 28, 43). As all children and adolescents with T1D are treated with insulin we are sure that all of them living in the catchment area of PHARMO will be included in the database. Routinely collected, detailed data on medication use reduces the probability of information bias and recall bias. Insulin prescriptions can be used as a proxy for T1D because hyperglycemia is the only indication for insulin (29, 44, 45) and other types of diabetes in which insulin is indicated, e.g., mitochondrial diabetes have low prevalence rates compared with T1D (46, 47). An important limitation of our study is that the reference cohort was randomly captured from the PHARMO RLS which only includes individuals who have obtained at least one prescription from the community pharmacy. Children and adolescents for whom medication was never prescribed (varying between 28 and 58% for different age categories) are not in this database, compromising the representativeness of our reference cohort. Therefore, the gap in CV medication use between the two cohorts will be even larger than observed in our study. Another limitation in this study might be ascertainment bias of CVD risk factors due to increased screening in patients with T1D compared to the general population. We did not have information on the indication for prescribing CV medication which might lead to some misclassification of the pharmacological treatment of CV risk factors. For instance, our study included adolescents who might use beta blockers for test anxiety before school exams or driving tests (48). There is also a lack of correction for multiple comparisons in our study. Finally, in our database we missed information on important CVD risk factors such as body mass index (BMI), genetic-related risk factors, and family history of CVD which might also influence the choice for pharmacological treatment.

In summary, our results showed that there is an increased risk for CV medication use in children and adolescents with T1D compared with the age- and gender-matched diabetes-free population both before and after the onset of diabetes. More comprehensive data is needed to completely address and draw conclusions about under-treatment of CVD risk factors in children and adolescents with T1D. Furthermore, our study emphasizes the need to pay more attention to screening for risk factors and to start programs that implement prevention strategies to lower CVD risk in the pediatric population with diabetes. Future observational studies are needed to study the long term CVD outcomes in diabetic children and adolescents, and also the influence of the use of CV medication early in life on these outcomes.

Author contributions

F. A. contributed to the study design, analyzed the data, wrote the manuscript, and approved the final manuscript as submitted. S. F. F., P. C. S., M. M. J. v. d. V., A. d. B. and A. H. M.-v. d. Z. contributed to the study design, the discussion and edited the manuscript, and approved the final manuscript as submitted. A.H.M.-v.d.Z. has complete access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Codes used to identify cardiovascular (CV) medications.

Table S2. Codes used to identify cardiovascular diseases (CVD).

Table S3. Annual prevalence rate of cardiovascular (CV) medication use.

Table S4. Annual incidence rate of cardiovascular (CV) medication use.

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