Journal of the Society for Cardiovascular Angiography & Interventions 4 (2025) 102502

JSCAI

The official journal of the Society for Cardiovascular Angiography & Interventions

Original Research

Cardiovascular Event Prevalence in Type 1 Versus Type 2 Diabetes: Veradigm Metabolic Registry Insights

Andrew M. Goldsweig, MD, MS [a,b,c,*], Alexander Knee, MS [d,e], Hyo Jung Tak, PhD [f], Nihar R. Desai, MD, MPH [g,h], Steven M. Bradley, MD, MPH [i,j], Amir S. Lotfi, MD [a,b], John A. Spertus, MD, MPH [k], Bracha K. Goldsweig, MD [l]

[a] *Department of Cardiovascular Medicine, Baystate Medical Center, Springfield, Massachusetts;* [b] *Division of Cardiovascular Medicine, University of Massachusetts-Baystate, Springfield, Massachusetts;* [c] *Division of Cardiovascular Medicine, University of Nebraska Medical Center, Omaha, Nebraska;* [d] *Epidemiology and Biostatistics Research Core, Baystate Medical Center, Springfield, Massachusetts;* [e] *Department of Medicine, University of Massachusetts-Baystate, Springfield, Massachusetts;* [f] *College of Public Health, Department of Health Services Research & Administration, University of Nebraska Medical Center, Omaha, Nebraska;* [g] *Section of Cardiovascular Medicine, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut;* [h] *Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut;* [i] *Allina Health Minneapolis Heart Institute, Minneapolis, Minnesota;* [j] *Minneapolis Heart Institute Foundation, Minneapolis, Minnesota;* [k] *St. Luke's Mid America Heart Institute, Kansas City, Missouri;* [l] *Division of Pediatric Endocrinology, Baystate Medical Center, Springfield, Massachusetts*

ABSTRACT

Background: Diabetes mellitus type 1 (DM1) and type 2 (DM2) are well-established risk factors for cardiovascular disease but differ pathophysiologically in that DM1 results from insulin deficiency, whereas DM2 results from insulin insensitivity. The association between DM1 and DM2 and cardiovascular events remains undetermined.

Methods: For DM1 or DM2 patients aged 46 to 75 years receiving care at outpatient facilities with primary care and/or endocrinology enrolled in the National Cardiovascular Data Registry Veradigm Metabolic Registry 2017-2022, we compared the prevalence of incident cardiovascular events including myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, stroke, carotid revascularization, limb ischemia, and peripheral revascularization.

Results: The study population included 5823 DM1 patients (3.59%) and 156,204 DM2 patients (95.41%) with a total of 758,643 visits. DM1 patients were younger and had fewer comorbidities. A total of 11,096 incident cardiovascular events occurred with a prevalence ratio (PR) of 0.63 (95% CI, 0.55-0.71) for fewer events associated with DM1 than DM2. After adjustment for age, the PR was 0.66 (95% CI, 0.58-0.74). When analyzed by separate cardiovascular events, DM1 was associated with less myocardial infarction, percutaneous coronary intervention, stroke, and limb ischemia than DM2. Overall cardiovascular event probability was lower in DM1 than in DM2 across all 10-year age categories, in both female and male patients, before and during/after the coronavirus disease 2019 pandemic, and after adjustment for comorbidities, hemoglobin A1c, and serum creatinine.

Conclusions: DM1 was associated with a lower probability of incident cardiovascular events than DM2. Although DM1 may carry a lower risk of incident cardiovascular events than DM2, the pathophysiology, prevention, and treatment of cardiovascular disease in DM1 remain poorly understood.

Introduction

Diabetes mellitus type 1 (DM1) and type 2 (DM2) are both well-established risk factors for cardiovascular disease. Numerous metabolic abnormalities, which vary between DM1 and DM2, result in increased atherogenesis: hyperglycemia, insulin resistance, dyslipidemia, inflammation, reactive oxygen species, endothelial dysfunction, hypercoagulability, and vascular calcification.[1] As a result, diabetic patients exhibit greater arterial plaque volumes and smaller arterial lumen diameters than nondiabetics.[2]

However, DM1 and DM2 are fundamentally different in that DM1 results from insulin deficiency, whereas DM2 results from insulin

Abbreviations: CABG, coronary artery bypass grafting; CAD, coronary artery disease; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; HbA1c, hemoglobin A1c; MI, myocardial infarction; PAD, peripheral artery disease; PR, prevalence ratio; Q, calendar quarter; VMR, Veradigm Metabolic Registry.

Keywords: cardiovascular event; diabetes; diabetes mellitus type 2; diabetes mellitus type 1; myocardial infarction; stroke.

* Corresponding author: goldsa04@nyu.edu (A.M. Goldsweig).

https://doi.org/10.1016/j.jscai.2024.102502
Received 11 October 2024; Received in revised form 27 November 2024; Accepted 2 December 2024; Available online 12 February 2025

insensitivity. The medical literature remains shockingly deficient in granular data on the association with cardiovascular events in these 2 distinct disease entities. Do patients receiving care for DM1 and DM2 have different risks of developing coronary artery disease (CAD), stroke, or peripheral artery disease (PAD) and requiring revascularization procedures?

Diabetes mellitus type 1 has long been neglected in cardiovascular outcomes research, as highlighted in a joint statement from the American Heart Association and the American Diabetes Association.[3] DM1-associated cardiovascular disease is frequently managed by extrapolating from studies of patients with DM2. However, these 2 diseases are fundamentally separate entities with distinctly different courses.

Among patients with DM1 or DM2 without a history of a cardiovascular event receiving outpatient care at facilities with primary care and/or endocrinology and enrolled in the National Cardiovascular Data Registry Veradigm Metabolic Registry (VMR), we compared the association of composite cardiovascular events as well as each individual

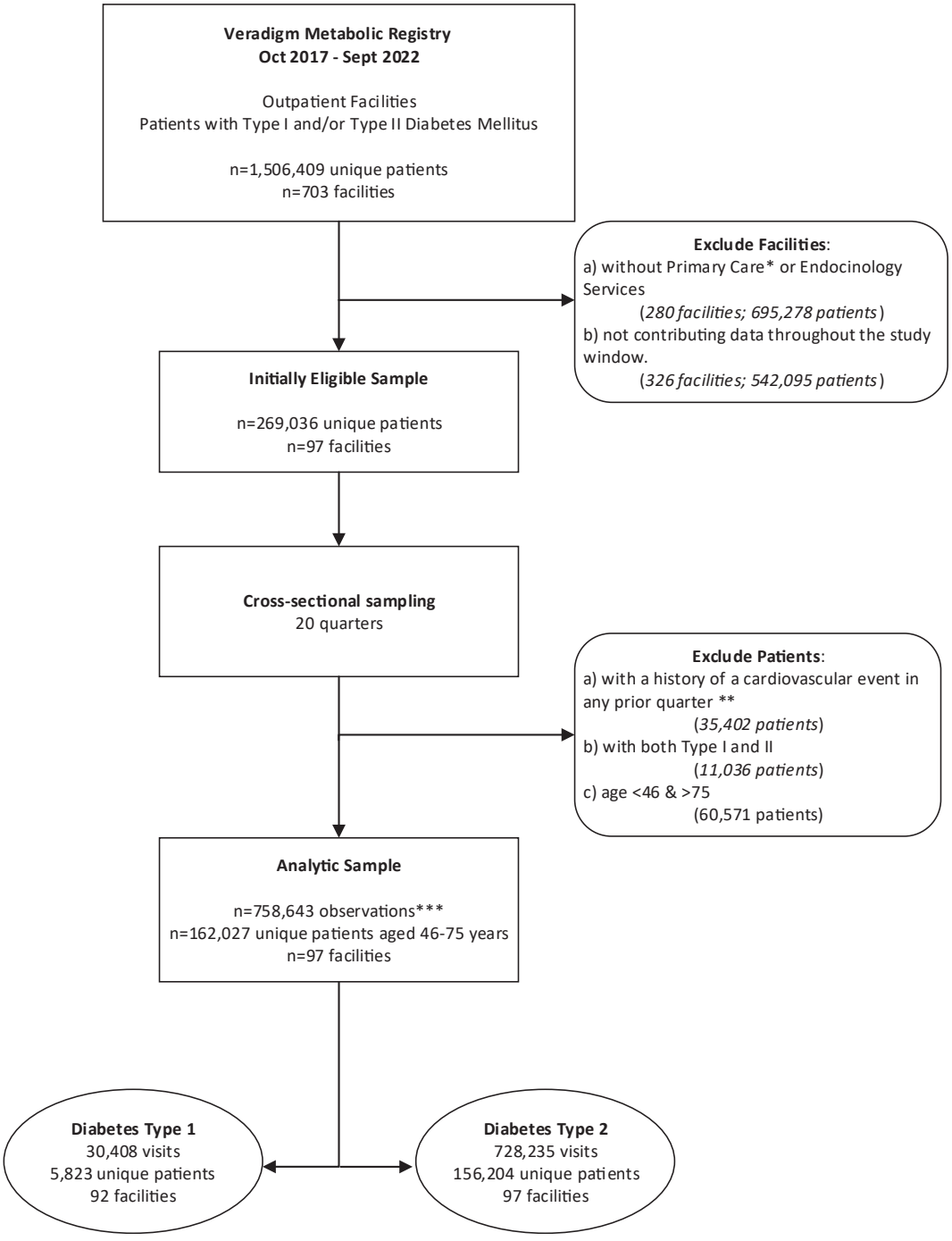


Figure 1.

Flow diagram showing identification of the study population and cohorts, Veradigm Metabolic Registry (October 2017 to September 2022). *Primary care services include primary care unspecified, family practice and internal medicine. **Cardiovascular events include myocardial infarction, stroke, percutaneous coronary intervention, carotid revascularization, coronary artery bypass grafting, peripheral bypass/intervention, or limb ischemia in the quarter prior to being sampled. Exclusion counts listed here refer to patients never eligible for inclusion in any quarter. ***Median (IQR) number of quarters each patient was sampled = 3 (1-7).

Table 1. Facility characteristics, Veradigm Metabolic Registry (October 2017 to September 2022), adults (aged 46-75 years) with type 1 or type 2 diabetes.

	Total organizations (N = 97)
Total patients per facility/system	2116 (674-4045)
Total visits per facility/system	12,955 (5757-29,067)
Total number of specialties at facility/system	2 (1-3)
Facility/system services (mutually exclusive)	
Ever primary care[a]	85 (87.6%)
Only primary care[a]	24 (24.7%)
Only diabetes or endocrinology	12 (12.4%)
Ever primary care[a] and cardiology and endocrinology	5 (5.2%)
Facility/system services (not mutually exclusive)	
Cardiology	21 (21.6%)
Diabetes or endocrinology	19 (19.6%)
Primary care unspecified	29 (29.9%)
Family practice	60 (61.9%)
Internal medicine	56 (57.7%)
Obstetrics and gynecology	7 (7.2%)
Other[b]	22 (22.7%)

Values are median (IQR) or n (%).

[a] Primary care includes unspecified primary care, family practice, and internal medicine. [b] Other specialties include pediatrics, orthopedics, rheumatology, gastroenterology, surgical, dermatology, physical rehabilitation, podiatry, urgent care, nephrology, pulmonary, etc.

event type in stratified and adjusted analyses. An understanding of the association of cardiovascular events with these 2 diseases may help guide appropriate prognosis and management for patients with DM1, the long-term cardiovascular sequelae of which remain poorly characterized.

Methods

Data source

The VMR is a clinical registry designed to improve the quality of diabetes and cardiometabolic care across outpatient primary care and specialty care in the United States. Administered by the American College of Cardiology, American College of Physicians, American Diabetes Association, American Association of Clinical Endocrinologists, and Joslin Diabetes Center, the VMR longitudinally follows more than 1.5 million patients receiving care at more than 700 facilities in the United States. Participating facilities range from individual practices to health systems. This study uses a convenience sample of visits from this data set.

Study design and sampling

We utilized a cross-sectional panel sampling design to include unique patients with an eligible visit within the 20 calendar quarters between October 2017 through September 2022. To be eligible, facilities had to provide primary care or endocrinology services (although they may have also provided other services) in each of the 20 quarters within the sampling frame. Many of these facilities also provided cardiology, obstetrics and gynecology, and other specialty care services. We did not include cardiology-only facilities as such facilities may induce an association between the exposure (diabetes type) and outcome (cardiovascular events) through collider-stratification bias. Primary care included unspecified primary care, internal medicine, and family practice. These criteria were instituted to focus the investigation on patients who may be receiving care for diabetes and also to minimize variability and potential selection bias across facilities. Patient eligibility, evaluated quarterly, included unique adult patients aged 46 to 75 years with either DM1 or DM2. Age criteria and age-stratified analyses were implemented to reduce the influence of age on the prevalence of cardiovascular events. We excluded patient visits with simultaneous DM1 and DM2 diagnoses coded as well as those with diagnoses of cardiovascular events in a prior quarter so that our analysis would capture new incident events.

Study outcomes and covariates

The primary outcome was a composite of incident cardiovascular events during each calendar quarter for a unique patient with an eligible facility visit. Cardiovascular events included myocardial infarction (MI, defined by the VMR Data Dictionary per the Fourth Universal Definition[4]), percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), stroke, carotid revascularization (endarterectomy or stent), limb ischemia, and peripheral revascularization (bypass or endovascular intervention). Secondary outcomes included individual cardiovascular event types.

Because a facility could contribute data from more than 1 medical specialty, we identified facilities as ever vs only primary care, ever vs only endocrinology, or ever cardiology. In addition, we captured covariates on the patient-quarter level including age (continuous and in 10-year categories), sex, race, ethnicity, insurance status (4 mutually exclusive statuses defined as Medicaid only, Medicare [regardless of concurrent Medicaid], private [regardless of concurrent Medicaid or Medicare], or none), body mass index (BMI; obesity defined as BMI $\geq$30 kg/m^2), tobacco use, hemoglobin A1c (HbA1c), and serum creatinine. Comorbidities included CAD, atrial fibrillation, stable angina, heart failure, dyslipidemia, hypertension, PAD, lower extremity osteomyelitis, foot/leg cellulitis, and claudication. Because HbA1c and serum creatinine had extensive missing data, we used the highest value recorded closest to the quarter sampled but no more than 4 quarters prior to the visit.

Data analysis

Facility characteristics and baseline characteristics of visits across the DM1 and DM2 cohorts are reported using mean $\pm$ SD or median (IQR) for continuous variables and frequency (percentage) for categorical variables. The primary analysis focused on the description of incident cardiovascular events within the same quarter as the visit to a facility with primary care or endocrinology services. Event probabilities were compared between patients with DM1 vs DM2 using prevalence ratios (PR) and 95% CI. Estimates were calculated using generalized estimating equations with a Poisson family and log link and an exchangeable correlation structure. As patients could be sampled in multiple quarters, models were clustered at the patient level using robust standard errors. PR are presented as unadjusted and age-stratified, as well as by individual cardiovascular events. In subgroup analyses, we evaluated how the overall association varied across patient or facility characteristics including sex, the onset of the coronavirus disease 2019 (COVID-19) pandemic (calendar quarters prior vs subsequent to March 2020), combinations of comorbidities, and by the types of medical services offered at each facility. As initial age-stratified estimates were relatively consistent, we utilized age-adjusted models in our subgroup analysis. PR were not estimated if there were fewer than 10 events. In sensitivity analyses, we explored additional adjustments for sex and comorbidities. We also explored how estimates varied when adjusted for BMI, smoking status, HbA1c, and serum creatinine, restricting the sample for these analyses to patients with data available for these parameters given frequently missing data. Our power analysis, assuming a sample size of 750,000 visits and 2-tailed alpha of 0.05, suggested over 95% power to detect a difference as small as 0.1% vs 0.2% (a PR of 2.0 or

Table 2. Patient visit characteristics in the DM1 and DM2 cohorts, Veradigm Metabolic Registry (October 2017 to September 2022), adults (aged 46-75 years) with DM1 or DM2.

	Overall (N = 758,643)	Type 1 visits (n = 30,408)	Type 2 visits (n = 728,235)
Age, y	62.6 ± 7.9	59.4 ± 8.3	62.7 ± 7.8
46-55 y	163,483 (21.5%)	11,146 (36.7%)	152,337 (20.9%)
56-65 y	284,463 (37.5%)	10,971 (36.1%)	273,492 (37.6%)
66-75 y	310,697 (41.0%)	8291 (27.3%)	302,406 (41.5%)
Sex			
Female	401,765 (53.0%)	15,941 (52.4%)	385,824 (53.0%)
Male	356,867 (47.0%)	14,467 (47.6%)	342,400 (47.0%)
Missing	11 (0.0%)	0 (0.0%)	11 (0.0%)
Race			
African American	15,887 (2.1%)	231 (0.8%)	15,656 (2.1%)
Asian	104,986 (13.8%)	1332 (4.4%)	103,654 (14.2%)
Caucasian	448,595 (59.1%)	22,266 (73.2%)	426,329 (58.5%)
Other	4997 (0.7%)	107 (0.4%)	4890 (0.7%)
Missing	184,178 (24.3%)	6472 (21.3%)	177,706 (24.4%)
Hispanic			
No	545,384 (71.9%)	23,290 (76.6%)	522,094 (71.7%)
Yes	49,236 (6.5%)	990 (3.3%)	48,246 (6.6%)
Missing	164,023 (21.6%)	6128 (20.2%)	157,895 (21.7%)
Insurance			
Medicaid	2552 (0.3%)	121 (0.4%)	2431 (0.3%)
Medicare	76,265 (10.1%)	1521 (5.0%)	74,744 (10.3%)
Private	478,761 (63.1%)	22,847 (75.1%)	455,914 (62.6%)
None	3955 (0.5%)	27 (0.1%)	3928 (0.5%)
Missing	197,110 (26.0%)	5892 (19.4%)	191,218 (26.3%)
Body mass index, kg/m^2	33.6 ± 7.4	28.4 ± 5.9	33.8 ± 7.4
Missing	298,511 (39.3%)	17,399 (57.2%)	281,112 (38.6%)
Obese (BMI ≥ 30 kg/m^2)			
No	155,236 (20.5%)	8658 (28.5%)	146,578 (20.1%)
Yes	304,896 (40.2%)	4351 (14.3%)	300,545 (41.3%)
Missing	298,511 (39.3%)	17,399 (57.2%)	281,112 (38.6%)
Tobacco use			
Never	293,550 (38.7%)	14,619 (48.1%)	278,931 (38.3%)
Current	190,166 (25.1%)	5893 (19.4%)	184,273 (25.3%)
Former	60,266 (7.9%)	2186 (7.2%)	58,080 (8.0%)
Missing	214,661 (28.3%)	7710 (25.4%)	206,951 (28.4%)
Comorbidities			
Coronary artery disease	88,597 (11.7%)	2302 (7.6%)	86,295 (11.8%)
Atrial fibrillation	33,705 (4.4%)	392 (1.3%)	33,313 (4.6%)
Stable angina	13,877 (1.8%)	206 (0.7%)	13,671 (1.9%)
Heart failure	32,883 (4.3%)	303 (1.0%)	32,580 (4.5%)
Dyslipidemia	546,865 (72.1%)	20,269 (66.7%)	526,596 (72.3%)
Hypertension	590,002 (77.8%)	15,572 (51.2%)	574,430 (78.9%)
Peripheral artery disease	16,930 (2.2%)	304 (1.0%)	16,626 (2.3%)
Lower extremity osteomyelitis	703 (0.1%)	49 (0.2%)	654 (0.1%)
Foot/leg cellulitis	26,605 (3.5%)	292 (1.0%)	26,313 (3.6%)
Claudication	3491 (0.5%)	85 (0.3%)	3406 (0.5%)
Hemoglobin A1c, %	7.0 (6.3-8.1)	7.4 (6.8-8.2)	7.0 (6.3-8.1)
Missing	328,638 (43.3%)	11,481 (37.8%)	317,157 (43.6%)
Hemoglobin A1c category			
<7	201,358 (26.5%)	6071 (20.0%)	195,287 (26.8%)
≥7	228,647 (30.1%)	12,856 (42.3%)	215,791 (29.6%)
Serum creatinine, mg/dL	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Missing	332,185 (43.8%)	11,467 (37.7%)	320,718 (44.0%)
Facility services (nonmutually exclusive)			
Endocrinology	377,389 (49.7%)	27,410 (90.1%)	349,979 (48.1%)
Primary care unspecified	246,178 (32.4%)	3289 (10.8%)	242,889 (33.4%)
Family practice	390,330 (51.5%)	4046 (13.3%)	386,284 (53.0%)
Internal medicine	294,133 (38.8%)	4000 (13.2%)	290,133 (39.8%)
Cardiology	129,955 (17.1%)	2146 (7.1%)	127,809 (17.6%)
Obstetrics and gynecology	80,200 (10.6%)	735 (2.4%)	79,465 (10.9%)
Other	173,512 (22.9%)	2199 (7.2%)	171,313 (23.5%)
Facility services (mutually exclusive)			
Ever primary care[a]	468,560 (61.8%)	5120 (16.8%)	463,440 (63.6%)
Only primary care[a]	97,081 (12.8%)	774 (2.5%)	96,307 (13.2%)
Only diabetes or endocrinology	290,083 (38.2%)	25,288 (83.2%)	264,795 (36.4%)
Ever primary care[a] and cardiology and endocrinology	65,357 (8.6%)	1220 (4.0%)	64,137 (8.8%)

(continued on next column)

Table 2. (*continued*)

Values are mean ± SD, n (%), or median (IQR). DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2.

[a] Primary care includes unspecified primary care, family practice, or internal medicine.

0.50), however power is influenced by clustering as well as multivariable adjustment and is further limited in subgroup analyses.

Ethics statement

This research involved only retrospective, deidentified registry data. The project was approved by the Baystate Medical Center Institutional Review Board. Patient consent was not required.

Results

Facility and patient visit characteristics

From calendar quarter (Q)4 2017 through Q3 2022, the VMR captured data on 1,506,409 patients with DM1 or DM2 at 703 facilities (Figure 1). After applying eligibility criteria, we identified a study population of 162,027 unique patients with 758,643 visits to 97 facilities reporting data to the VMR. This population included a DM1 cohort of 5823 patients (3.59%) with 30,408 visits and a DM2 cohort of 156,204 patients (95.41%) with 728,235 visits.

The included facilities saw a median of 2116 patients (IQR, 674-4045) with 12,955 visits (IQR, 5757-29,067). A total of 87.6% provided primary care, 19.6% provided endocrinology, 21.6% provided cardiology, 7.2% provided obstetrics and gynecology, and 22.7% provided other services (Table 1).

Because the DM1 cohort was much smaller than the DM2 cohort, overall study population characteristics matched the DM2 cohort (Table 2). Among DM1 visits, more than two-thirds of patients (72.8%) were between 46 and 65 years of age, 52.4% were female, and the mean BMI was 28.4 kg/m^2 (SD, 5.9 kg/m^2). Among DM2 visits, more than three-quarters (79.1%) were between 56 and 75 years of age, 53.0% were female, and the mean BMI was 33.8 kg/m^2 (SD, 7.4 kg/m^2). DM1 visits had a lower prevalence of comorbidities compared to DM2 visits including CAD (7.6% vs 11.8%), dyslipidemia (66.7% vs 72.3%), and hypertension (51.2% vs 78.9%). HbA1c was missing in 37.8% of DM1 visits and 43.6% of DM2 visits; however, among those with data, median HbA1c was higher in DM1 (7.4%) vs DM2 (7.0%). Serum creatinine was missing in 37.7% of DM1 visits and 44.0% of DM2 visits; however, among those with data, median creatinine was similar (median, 0.9; IQR, 0.8-1.1 for both DM1 and DM2). DM1 patient visits primarily occurred at facilities with diabetes or endocrinology services (90.1%) compared to DM2 patient visits, which primarily occurred at facilities with primary care (63.6%).

Cardiovascular events

A total of 11,096 incident cardiovascular events occurred in the study population. Among patients with an event, 45.3% had a stroke, 19.5% had limb ischemia, 17.1% had CABG, 17.5% had an MI, 9.3% had PCI, 3.8% had peripheral revascularization (including 125 of the 2166 patients with limb ischemia [5.8%] plus 291 additional patients), and 1.1% had carotid revascularization. The proportions of cardiovascular events were relatively stable across all 20 study quarters (Supplemental Figure S1). When comparing the probability of any cardiovascular event among patients with DM1 (0.9%) vs DM2 (1.5%), we observed an unadjusted PR of 0.63 (95% CI, 0.55-0.71) for fewer events associated with DM1 (Central Illustration, Table 3, Figure 2). This relative difference persisted among patients aged 46-55 (PR, 0.64; 95% CI, 0.52-0.80), aged 56 to 65 (PR, 0.69; 95% CI, 0.57-0.83), and aged 66-75 (PR, 0.62; 95% CI, 0.50-0.78) years. Among individual cardiovascular events, DM1 was associated with a lower probability of MI (PR, 0.56), PCI (PR 0.43), stroke (PR, 0.64), and limb ischemia (PR, 0.57) than DM2. Risks of CABG, carotid revascularization, and peripheral revascularization were not clinically or statistically different between the DM1 and DM2 cohorts.

After adjustment for age, the overall PR for any cardiovascular event was 0.66 (95% CI, 0.58-0.74) (Table 4, Figure 3). In subgroup analyses, the magnitude of the PR varied by comorbidities and facility services, but not by sex nor by timing with respect to the March 2020 onset of the COVID-19 pandemic. In terms of facility services, among patients who went to a facility with endocrinology, the cardiovascular event probability was lower in DM1 than in DM2; however, this phenomenon did not hold true among patients visiting a facility with primary care or cardiology services, where the DM1 probability was higher. Composite age-adjusted cardiovascular event PR varied over time, with the greatest prevalence differences (PR approaching 0.30) observed in quarter 3 of 2018 and quarters 1 and 3 of 2021 and negligible effects in quarter 4 of 2017 and quarter 3 of 2020 (PR, approximately 1.0) (Supplemental Figure S2). In sensitivity analyses (Supplemental Table S1), the PR continued to demonstrate fewer cardiovascular events in DM1 than in DM2 after adjustment for age, sex, comorbidities, HbA1c, serum creatinine BMI, and smoking status. However, there was a large amount of missing data (~ 65%) in this complete-case analysis, restricting the analysis sample to a smaller subgroup with complete data.

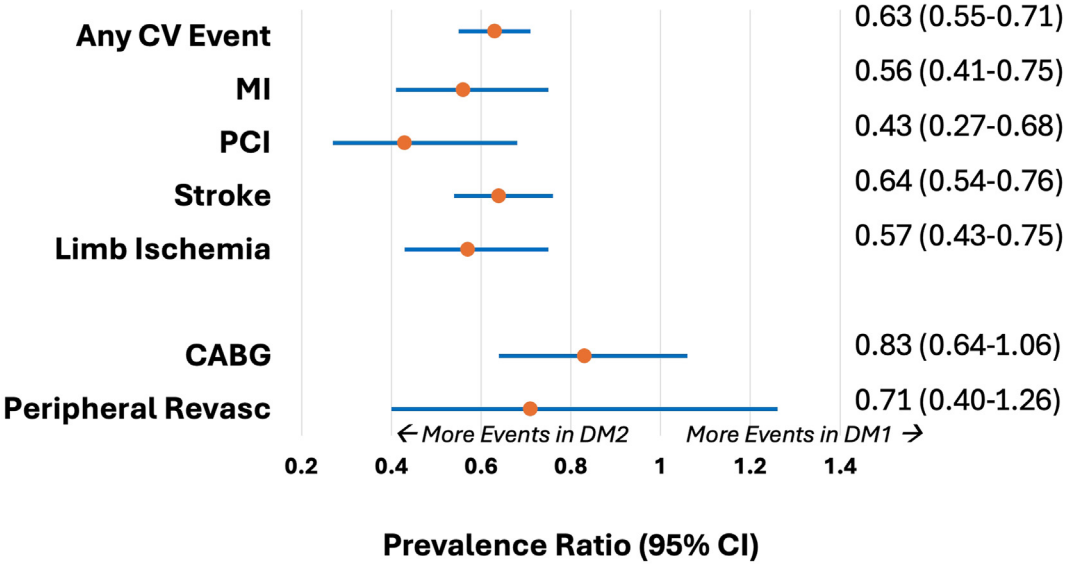
Discussion

Diabetes mellitus type 1 and DM2 may convey different cardiovascular risks. In the present descriptive study, among VMR patients aged 46-75 years receiving diabetes care, DM1 was associated with a lower risk of incident cardiovascular events than DM2. In particular, risks of MI, PCI, stroke, and limb ischemia were lower, whereas risks of CABG, carotid revascularization, and peripheral revascularization did not differ. DM1 was associated with lower cardiovascular event risk than DM2 across subgroups of age, sex, calendar quarter, comorbidities, and endocrinology care. The lower risk in DM1 persisted in subgroups adjusted for HbA1c and serum creatinine.

Different cardiovascular risks

Both DM1 and DM2 are associated with hyperglycemia and increased cardiovascular risks.[5] However, the different risks of cardiovascular events in DM1 and DM2 relate to their different pathophysiologies, not just to the greater comorbidity burden typically associated with DM2. At the cellular level, hyperglycemia may cause myocardial injury, exposing antigens and inducing cardiac autoimmunity in DM1 patients, who have a predisposition to autoimmunity as evidenced by their having developed DM1. In the Diabetes Control and Complications Trial, poor glycemic control was associated with the development of cardiac autoantibodies in DM1 but not in DM2.[6] In turn, cardiac autoantibodies were associated with increased inflammation as measured by high-sensitivity C-reactive protein, coronary artery calcification, and cardiovascular events (MI, stroke CABG, heart failure, or cardiovascular death). In fact, because cardiovascular disease in DM1 is a cascade of inflammatory processes, the traditional cardiovascular risk marker of low-density lipoprotein cholesterol may not even apply in DM1.[7]

By contrast, in DM2, insulin resistance contributes to increased free fatty acids, advanced glycation end-products, protein kinase C activation, oxidative stress, and endothelial dysfunction. The result is a stress



Central Illustration.
Overall cardiovascular (CV) event prevalence ratios (PR) in diabetes mellitus type 1 (DM1) and diabetes mellitus type 2 (DM2), Veradigm Metabolic Registry (October 2017 to September 2022). CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Table 3. Overall and age-stratified cardiovascular event PR and 95% CI comparing adults (aged 46-75 years) with DM1 to DM2 stratified by age, Veradigm Metabolic Registry (October 2017 to September 2022).

Event type	Type 1 visits	Type 2 visits	PR (95% CI)[a]
Any cardiovascular event[b]			
Overall	279 (0.92%)	10,817 (1.49%)	0.63 (0.55-0.71)
Ages 46-55 y	86 (0.77%)	1849 (1.21 %)	0.64 (0.52-0.80)
Ages 56-65 y	111 (1.01%)	4078 (1.49%)	0.69 (0.57-0.83)
Ages 66-75 y	82 (0.99%)	4890 (1.62%)	0.62 (0.50-0.78)
Myocardial infarction			
Overall	44 (0.14%)	1896 (0.26%)	0.56 (0.41-0.75)
Ages 46-55 y	17 (0.15%)	358 (0.24%)	0.65 (0.40-1.06)
Ages 56-65 y	17 (0.15%)	723 (0.26%)	0.59 (0.36-0.95)
Ages 66-75 y	10 (0.12%)	815 (0.27%)	0.45 (0.24-0.84)
PCI			
Overall	18 (0.06%)	1013 (0.14%)	0.43 (0.27-0.68)
Ages 46-55 y	5 (0.04%)	173 (0.11%)	—
Ages 56-65 y	6 (0.05%)	387 (0.14%)	—
Ages 66-75 y	7 (0.08%)	453 (0.15%)	—
CABG			
Overall	63 (0.21%)	1830 (0.25%)	0.83 (0.64-1.06)
Ages 46-55 y	14 (0.13%)	219 (0.14%)	0.88 (0.51-1.50)
Ages 56-65 y	22 (0.20%)	639 (0.23%)	0.86 (0.56-1.32)
Ages 66-75 y	27 (0.33%)	972 (0.32%)	1.02 (0.69-1.50)
Stroke			
Overall	130 (0.43%)	4892 (0.67%)	0.64 (0.54-0.76)
Ages 46-55 y	41 (0.37%)	980 (0.64%)	0.58 (0.42-0.79)
Ages 56-65 y	61 (0.56%)	1940 (0.71%)	0.79 (0.61-1.02)
Ages 66-75 y	28 (0.34%)	1972 (0.65%)	0.52 (0.36-0.76)
Carotid revascularization			
Overall	5 (0.02%)	116 (0.02%)	—
Ages 46-55 y	1 (0.01%)	14 (0.01%)	—
Ages 56-65 y	1 (0.01%)	46 (0.02%)	—
Ages 66-75 y	3 (0.04%)	56 (0.02%)	—
Limb ischemia			
Overall	50 (0.16%)	2116 (0.29%)	0.57 (0.43-0.75)
Ages 46-55 y	19 (0.17%)	277 (0.18%)	0.94 (0.59-1.50)
Ages 56-65 y	21 (0.19%)	796 (0.29%)	0.66 (0.43-1.02)
Ages 66-75 y	10 (0.12%)	1043 (0.34%)	0.35 (0.19-0.66)
Peripheral revascularization			
Overall	12 (0.04%)	404 (0.06%)	0.71 (0.40-1.26)
Ages 46-55 y	4 (0.04%)	65 (0.04%)	—
Ages 56-65 y	6 (0.05%)	152 (0.06%)	—
Ages 66-75 y	2 (0.02%)	187 (0.06%)	—

Values are n (%) unless otherwise noted. CABG, coronary artery bypass graft; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; PCI, percutaneous coronary intervention; PR, prevalence ratio.

[a] PR and 95% CI estimated using Poisson generalized estimating equations clustering on patients with robust standard errors and exchangeable correlation structure. Models are not estimated when there are fewer than 10 events.

[b] Cardiovascular event includes any myocardial infarction, PCI, CABG, stroke, carotid revascularization, limb ischemia, or peripheral revascularization.

response including leukocyte infiltration of the endothelium, macrophage proliferation, and vascular injury.[1]

Cardiovascular events

We found a lower probability of overall cardiovascular events associated with DM1 than DM2. At the patient level, previous studies have shown mixed results regarding the relative risk of cardiovascular events between these conditions. In a cohort of 824 age-matched Australian diabetics (DM1, n = 470), DM1 was associated with lower 20-year cardiovascular mortality than DM2, but no adjustment was performed for the higher rate of comorbidities in DM2.[8] However, among 2532 patients in the Hong Kong Diabetes Registry (DM1, n = 209), the association between DM1 and a lower incidence of cardiovascular disease became nonsignificant with adjustment for cardiovascular risk factors.[9]

At the population level, 4 prior studies have reported risks of cardiovascular events in DM1 than in DM2. However, these studies were conducted in populations that differ substantially from the contemporary US population in the present study.

Among patients aged 18 to 40 years in the Hungarian National Health Insurance Fund database from 2001 through 2014, compared to DM2 patients (n = 47,931), DM1 patients (n = 11,863) had similar rates of MI and stroke but higher rates of all-cause mortality (hazard ratio [HR], 2.17; 95% CI, 1.95-2.14).[10] The excess mortality in the DM1 cohort was attributed to higher rates of cancer, dialysis, hypoglycemia, and ketoacidosis, not cardiovascular events. This analysis differed from the present study by focusing on patients aged 18 to 40 years, whereas we found that the majority of cardiovascular events in both DM1 and DM2 occurred in patients older than this range.

In an aggregate of the Cohort of Swedish Men and the Swedish Mammography Cohort (DM1 n = 247, DM2 n = 2130), diabetic patients' cardiovascular event risks were compared to those of nondiabetics from 1998 through 2014.[11] MI was more strongly associated with DM1 (HR, 3.26; 95% CI, 2.47-4.30) than with DM2 (HR, 1.65; 95% CI, 1.48-1.83), and ischemic stroke exhibited a similar association that failed to meet statistical significance. The small sample size of DM1 patients resulted in low power for certain cardiovascular events and differed from the DM1 patients in the present study, having an older baseline age (mean 57.2 years) and more hypertension (35.2%); the comparator DM2 population also had markedly fewer comorbidities (hypertension, 41.3%; hypercholesterolemia, 15.8%).

An analysis of the Korean National Health Insurance Service data set from 2009 through 2016 (DM1 n = 9397, DM2 n = 1,913,503) found an adjusted HR for MI of 1.679 (95% CI, 1.490-1.893)[12] in DM1 vs DM2. In this population, the mean BMI was 25.08 and 24.13 kg/m^2, respectively, the mean systolic BP was 128.91 and 126.78 mm Hg, respectively, and the mean low-density lipoprotein was 110.81 and 106.26 mg/dL, respectively. These values suggest a population with DM2 principally resulting from genetic susceptibility, a population that differs substantially from the US population, where obesity, hypertension, and dyslipidemia are widely prevalent.

In the largest analysis to date, DM1 (n = 36,869) and DM2 (n = 457,473) patients were independently compared with propensity-matching in the Swedish National Registry from 1998 through 2014.[13] Hospitalization for acute MI was similarly associated with DM1 (HR, 1.37; 95% CI, 1.16-1.62) and DM2 (HR, 1.24; 95% CI, 1.18-1.31), as was hospitalization for stroke (DM1 HR, 1.47; 95% CI, 1.22-1.76; DM2 HR, 1.24; 95% CI, 1.18-1.31). This study included patients with prior cardiovascular events; so at least in part, the reported cardiovascular risks may represent recurrent events rather than incident events. Additionally, this study found that mortality from any cause, cardiovascular disease, and CAD were all lower in DM2 than in matched controls, raising the specter of significant bias in terms of low DM2 cohort cardiovascular event rates.

Thus, the present study, using VMR data from 2017 through 2022, provides the first large-scale comparison of cardiovascular events in DM1 and DM2 in a US population with its associated comorbidities and the availability of contemporary medical therapy. This study identified incident cardiovascular events and used granular, patient-level data to adjust for demographics and comorbidities. These advantageous study characteristics build confidence in the suggestion that DM1 may confer a lower probability of cardiovascular events than DM2 in the US.

Risk of specific cardiovascular events

Our study found that DM1 is associated with a lower prevalence of MI, PCI, stroke, and limb ischemia, whereas the prevalence of CABG, carotid revascularization, and peripheral revascularization were similar

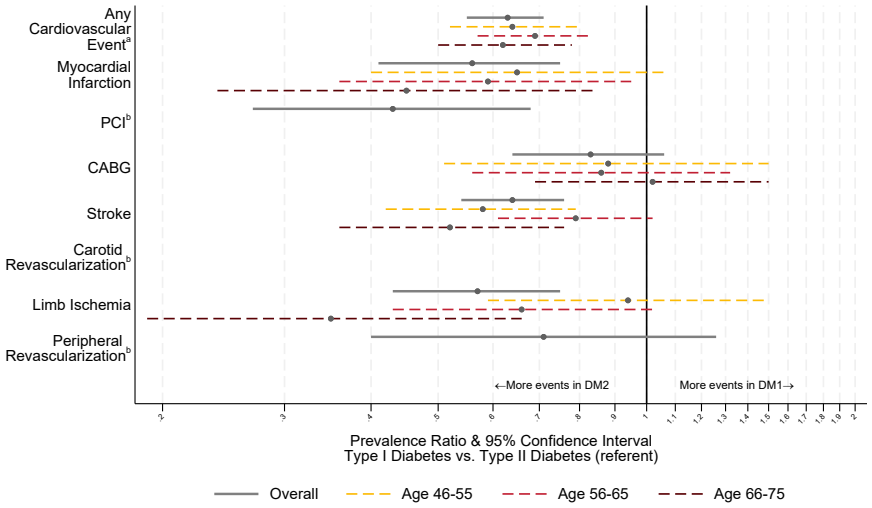


Figure 2.
Cardiovascular event prevalence ratios (PR) in diabetes mellitus type 1 (DM1) and diabetes mellitus type 2 (DM2) with age stratification, Veradigm Metabolic Registry (October 2017 to September 2022). [a]Cardiovascular event includes any myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, carotid revascularization, limb ischemia, or peripheral revascularization. [b]Estimates not calculated when fewer than 10 events.

in DM1 and DM2. The associations with MI and stroke were discussed above and compared to previous literature. However, the associations with CABG, carotid revascularization, and peripheral revascularization are novel observations, not studied previously. We hypothesize that, although DM1 patients may have lower risks of cardiovascular events, they are also a younger population with fewer comorbidities than DM2 patients; therefore, DM1 patients are more favorable procedural candidates and can safely be offered procedures more frequently than the older DM2 population with its copious comorbidities.

This lower probability of index cardiovascular events refers to the populations of previously event-free DM1 and DM2 patients. Although beyond the scope of the present analysis, the outcomes of DM1 and DM2 patients who do suffer cardiovascular events may differ in the opposite direction. For example, a 2015 analysis of the SWEDEHEART Registry found that DM1 was associated with twice the 6-year post-CABG mortality of DM2.[14] Similarly, a 2020 analysis of the United State National Inpatient Sample found that DM1 patients with PAD were more likely to present with chronic limb-threatening ischemia and more likely to undergo amputation than DM2 patients with PAD.[15]

Risk trend and among population subgroups

Cardiovascular morbidity and mortality associated with both DM1 and DM2 have decreased over time, likely due to the development and increased use of therapies such as statins, angiotensin-converting enzyme inhibitors, and sodium-glucose cotransporter-2 inhibitors. Our documentation of this trend from 2017 to 2022 follows an earlier report showing a similar trend from 2000 to 2011 among over 1 million diabetics in Australia.[16] COVID-19, which reached pandemic status in Q2 2020, affected rates of medical visits, and therefore rates of diagnoses and procedures. However,

Table 4. Age-standardized overall and stratified cardiovascular event PR and 95% CI comparing adults (aged 46-75 years) with DM1 to DM2, Veradigm Metabolic Registry (October 2017 to September 2022).

Any cardiovascular event[a]	Type 1 visits	Type 2 visits	Age-standardized PR (95% CI)[b]
Overall	279 (0.92%)	10,817 (1.49%)	0.66 (0.58-0.74)
Sex			
Female	127 (0.80%)	4850 (1.26%)	0.67 (0.56-0.80)
Male	152 (1.05%)	5965 (1.74%)	0.64 (0.54-0.76)
COVID-19			
Pre-COVID-19	176 (1.01%)	6493 (1.56%)	0.69 (0.59-0.80)
During COVID-19	103 (0.80%)	4324 (1.38%)	0.61 (0.50-0.74)
Comorbidities			
Coronary artery disease	137 (5.95%)	5459 (6.33%)	0.94 (0.79-1.12)
Hypertension	194 (1.25%)	8987 (1.56%)	0.83 (0.71-0.96)
Hyperlipidemia	185 (0.91%)	6995 (1.33%)	0.73 (0.63-0.85)
Any of the above	262 (1.07%)	10,249 (1.54%)	0.73 (0.65-0.83)
None	17 (0.28%)	568 (0.88%)	0.34 (0.21-0.55)
Facility service			
Only endocrinology	126 (0.50%)	2096 (0.79%)	0.70 (0.58-0.84)
Ever endocrinology	143 (0.52%)	3552 (1.01%)	0.56 (0.48-0.67)
Only primary care	9 (1.16%)	1103 (1.15%)	—
Ever primary care	110 (3.34%)	5754 (2.37%)	1.44 (1.18-1.75)
Ever cardiology	108 (5.03%)	5033 (3.94%)	1.22 (1.00-1.48)

Values are n (%) unless otherwises noted. COVID-19, coronavirus disease 2019; DM1, diabetes mellitus type 1; DM2, diabetes mellitus type 2; PR, prevalence ratio.
[a] Cardiovascular event includes any myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft, stroke, carotid revascularization, limb ischemia, or peripheral revascularization. [b] PR and 95% CI estimated using Poisson generalized estimating equations clustering on patients with robust standard errors and exchangeable correlation structure. All model estimates are age-standardized. Models are not estimated when there are fewer than 10 events.

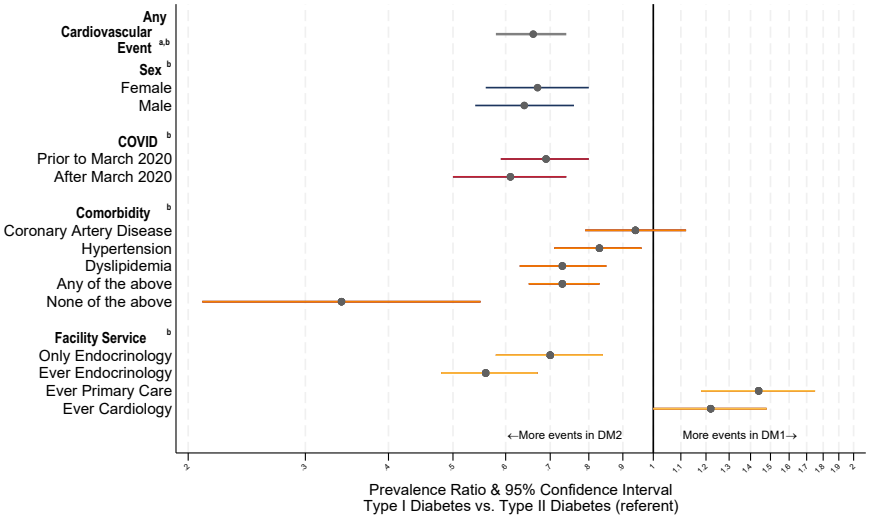


Figure 3.
Cardiovascular event age-adjusted prevalence ratios (PR) in diabetes mellitus type 1 (DM1) and diabetes mellitus type 2 (DM2) stratified by sex, onset of coronavirus disease 2019 (COVID-19) pandemic, medical provider specialty, and facility services, Veradigm Metabolic Registry (October 2017 to September 2022). [a]Cardiovascular event includes any myocardial infarction, percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), stroke, carotid revascularization, limb ischemia, or peripheral revascularization. [b]Estimates are age-adjusted.

lower rates of cardiovascular events in DM1 than in DM2 remained consistent throughout the study period.

Cardiovascular event probabilities were lower for DM1 than for DM2 in almost every subgroup when stratified by age, sex, calendar quarter, comorbidities, and endocrinology care. In patients who visited a facility with endocrinology services, DM1 carried a lower probability of cardiovascular events than DM2, but the event probability in DM1 was similar to the probability in DM2 in patients who visited a facility with primary care but no endocrinology services. This finding could suggest that specialized management of DM1 yields a more profound reduction in associated cardiovascular risk than specialized management of DM2. Regarding cardiology providers, collider-stratification bias may be at play: patients seeing cardiologists would be expected to have frequent cardiovascular events, regardless of their diabetes status.

That the lower cardiovascular risk in DM1 than in DM2 persisted after adjustment for HbA1c further supports the conclusion that this difference in cardiovascular risk may be due to the different pathophysiologies of the 2 conditions.

Future directions

Although DM1 may carry a lower risk of incident cardiovascular events than DM2, the pathophysiology, prevention, and treatment of cardiovascular disease in DM1 remains poorly understood. Both clinical trials and retrospective studies in DM1 patients are necessary to improve their care and reduce their risk of cardiovascular events.

Limitations and strengths

Our study has several important limitations. First, in a registry-based study, incorrect or incomplete investigator-reported data and coding could lead to inaccurate data. In particular, VMR captures inpatient events reported at outpatient visits, which requires posthospitalization follow-up (~ 25% of patients were only observed once in the data set). Second, many important data points were unavailable, which can lead to unmeasured bias. Chief among these, we acknowledge the lack of information about each patient's duration of diabetes, which is not available from the VMR or any other data set; the 4 population-based studies cited above also lacked this important information. Third, the VMR has a large proportion of missing data for several important parameters including HbA1c. Multiple imputation is not a valid approach in this situation due to the extent of missing data, and we felt that propensity-matching, commonly used in causal inference methods, was inappropriate in this study of descriptive associations. Therefore, given the very large size of the data set, we performed sensitivity analyses using the population for which all the desired data points were reported. Mortality could not be studied reliably because the VMR collects data at clinic visits hence, mortality data are inconsistently reported for inclusion in the data set. Fourth, causal inference methods could not be applied to this data set; the reported PR should be interpreted as associations of prevalence. Fifth, despite statistical adjustments performed, the DM1 and DM2 patient populations are fundamentally different, especially in terms of age and comorbidities. Sixth, the analysis strategy excluded the majority of patients in the VMR. Because of its affiliation with the American College of Cardiology, the VMR includes many cardiology-only practices. We intentionally excluded these facilities because the inclusion of patients known to have both exposure (DM) and the outcome (cardiovascular event) may induce selection bias.

Despite these limitations, this study adds meaningfully to the literature as the largest study ever to compare directly cardiovascular events between DM1 and DM2, with 30,408 DM1 patient visits and 728,235 DM2 patient visits. No other data set allows such a detailed comparison between the DM1 and DM2 populations. Although the duration of diabetes was regrettably unavailable, this information is not available from any extant data set, and we are fortunate that the VMR includes detailed comorbidity and HbA1c data to allow us to explore adjusted analyses. The study also provides the first large-scale comparison of cardiovascular events in DM1 and DM2 in a United States population with its associated comorbidities and is the only population-based study since 2016, reflecting contemporary medical therapy.

Conclusion

Among VMR diabetic patients without a history of cardiovascular events receiving care at facilities with primary care and/or endocrinology, DM1 was associated with a lower probability of incident cardiovascular events than DM2. These findings were consistent across multiple types of cardiovascular events, ages 46-75, sex, calendar quarter, comorbidities, and after adjustment for HbA1c. Although these findings represent good news for DM1 patients, further research is necessary specifically in DM1 patients to prevent and treat cardiovascular events.

Peer review statement

Associate Editor Andrew M. Goldsweig had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Editor-in-Chief Alexandra J. Lansky.

Declaration of competing interest

Andrew M. Goldsweig reports consulting for Philips and Inari Medical and speaking for Philips and Edwards Lifesciences. None of the other authors report relationships with industry to disclose.

Funding sources

This study was funded by an Early Career Research Grant from the Society for Cardiovascular Angiography & Interventions and Medtronic. Medtronic had no involvement in project development, analysis, or writing.

Ethics statement and patient consent

This research involved only retrospective, deidentified registry data. The project was approved by the Baystate Medical Center Institutional Review Board. Patient consent was not required.

Supplementary material

To access the supplementary material accompanying this article, visit the online version of the *Journal of the Society for Cardiovascular Angiography & Interventions* at 10.1016/j.jscai.2024.102502.

References

1. 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(24):2459–2502. https://doi.org/10.1161/CIRCULATIONAHA.116.022194
2. Nicholls SJ, Tuzcu EM, Kalidindi S, et al. Effect of diabetes on progression of coronary atherosclerosis and arterial remodeling: a pooled analysis of 5 intravascular ultrasound trials. *J Am Coll Cardiol*. 2008;52(4):255–262. https://doi.org/10.1016/j.jacc.2008.03.051
3. 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. *Circulation*. 2014;130(13):1110–1130. https://doi.org/10.1161/CIR.0000000000000034
4. Thygesen K, Alpert JS, Jaffe AS, et al. Fourth universal definition of myocardial infarction (2018). *J Am Coll Cardiol*. 2018;72(18):2231–2264. https://doi.org/10.1016/j.jacc.2018.08.1038
5. Colom C, Rull A, Sanchez-Quesada JL, Pérez A. Cardiovascular disease in type 1 diabetes mellitus: epidemiology and management of cardiovascular risk. *J Clin Med*. 2021;10(8):1798. https://doi.org/10.3390/jcm10081798
6. Sousa GR, Pober D, Galderisi A, et al. Glycemic control, cardiac autoimmunity, and long-term risk of cardiovascular disease in type 1 diabetes mellitus. *Circulation*. 2019;139(6):730–743. https://doi.org/10.1161/CIRCULATIONAHA.118.036068
7. Hero C, Svensson AM, Gidlund P, Gudbjörnsdottir S, Eliasson B, Eeg-Olofsson K. LDL cholesterol is not a good marker of cardiovascular risk in type 1 diabetes. *Diabet Med*. 2016;33(3):316–323. https://doi.org/10.1111/dme.13007
8. 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(12):3863–3869. https://doi.org/10.2337/dc12-2455
9. Luk AOY, Lau ESH, So WY, et al. Prospective study on the incidences of cardiovascular-renal complications in Chinese patients with young-onset type 1 and type 2 diabetes. *Diabetes Care*. 2014;37(1):149–157. https://doi.org/10.2337/dc13-1336
10. Kiss Z, Rokszin G, Abonyi-Tóth Z, et al. Young adult patients with type 1 diabetes have a higher risk of mortality than those of similar age with type 2 diabetes: a nationwide analysis in Hungary. *Diabetes Metab Res Rev*. 2019;35(8):e3190. https://doi.org/10.1002/dmrr.3190
11. 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. https://doi.org/10.1016/j.ijcard.2018.03.099
12. 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(1):157. https://doi.org/10.1186/s12933-019-0953-7
13. Rawshani A, Rawshani A, Franzén S, et al. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376(15):1407–1418. https://doi.org/10.1056/NEJMoa1608664
14. Holzmann MJ, Rathsman B, Eliasson B, et al. Long-term prognosis in patients with type 1 and 2 diabetes mellitus after coronary artery bypass grafting. *J Am Coll Cardiol*. 2015;65(16):1644–1652. https://doi.org/10.1016/j.jacc.2015.02.052
15. Jain N, Agarwal MA, Jalal D, Dokun AO. Individuals with peripheral artery disease (PAD) and type 1 diabetes are more likely to undergo limb amputation than those with PAD and type 2 diabetes. *J Clin Med*. 2020;9(9):2809. https://doi.org/10.3390/jcm9092809
16. Harding JL, Shaw JE, Peeters A, Davidson S, Magliano DJ. Age-specific trends from 2000-2011 in all-cause and cause-specific mortality in type 1 and type 2 diabetes: a cohort study of more than one million people. *Diabetes Care*. 2016;39(6):1018–1026. https://doi.org/10.2337/dc15-2308