Temporal trends in cardiovascular outcomes and costs among patients with type 2 diabetes

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Background Type 2 diabetes (T2D) is a strong risk factor for cardiovascular (CV) disease. CV outcomes in T2D have generally been improving over time but recent data from the US suggest attenuation of trends in older adults with reversal of trends in younger adults. However, published data are only reported through 2015.

Objectives To quantify trends over time in CV outcomes from 2001 to 2018, and describe changes over time in health care costs in T2D.

Methods This retrospective cohort study incorporated data from a regional health insurance plan. Study outcomes included acute myocardial infarction (AMI), ischemic stroke, hemorrhagic stroke, heart failure hospitalization (HFH), percutaneous coronary intervention, coronary artery bypass surgery, and all-cause mortality. Poisson regression estimated rate ratios across the entire 17-year study period (RR^{17}).

Results Among 79,392 T2D members tracked on average 4.1 years, overall trends in AMI ($RR^{17} = 0.69$; 95% CI: 0.64, 0.74), HFH ($RR^{17} = 0.82$; 0.79, 0.86), and all-cause mortality ($RR^{17} = 0.87$; 0.84, 0.91) improved while ischemic stroke ($RR^{17} = 2.36$; 2.16, 2.57) worsened. For AMI, HFH, and all-cause mortality, trends in older age groups were significantly better than in younger age groups (interaction *P*-values $< .001$). Health care costs related to pharmaceuticals (+15%/year) and emergency department (ED) visits (>15%/year) increased at faster rates than other utilization metrics (+10%/year).

Conclusions In T2D, overall trends in most CV outcomes improved but smaller improvements or worsening trends were observed in younger patients. Health care costs accelerated at faster rates for medications and ED visits. (Am Heart J 2023;265:161–169.)

Type 2 diabetes (T2D) affects nearly 15% of United States (US) adults, and with the growing obesity epidemic the absolute number of people with T2D and its associated complications are expected to rise.[1-4] T2D associates with multiple risk factors for cardiovascular disease (CVD) which accelerate the development and progression of atherosclerotic CVD (ASCVD).[5] As such, T2D increases by 2-fold the risk of ASCVD-related events including myocardial infarction (MI), ischemic stroke, and cardiovascular (CV) death.[5-12] Notably, better control of ASCVD risk factors through either lifestyle or pharmacologic means is strongly associated with improved CV outcomes in T2D.[5,13-16]

Over the last few decades, ASCVD event and all-cause mortality rates in T2D have generally been improving in the US and elsewhere.[9,17-22] However, in the US, an attenuation of trends was observed in older adults while in younger adults (<65 years) trend reversals were observed including for acute MI and stroke but only through 2015.[19] Furthermore, ASCVD risk factor control in T2D has been stagnating or worsening in recent years following an extended period of improving control.[1,23-25] In addition, 2 new classes of glucose-lowering therapy—the glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i)—have recently shown cardioprotective effects in randomized trials and uptake of these classes has been rising.[5,13,23,26,27-29] The collective effect of these changes on population-level ASCVD outcome rates in T2D is uncertain, and the heterogeneous trends by age observed in prior studies require confirmation. Lastly, the effects of changes in outcomes and treatments on health care costs in T2D have not been

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recently examined. Accordingly, the present study utilized a regional insurance claims database to achieve the following goals: (1) quantify changes over time in cardiovascular outcomes among T2D patients from 2001 to 2018; (2) evaluate historical trends and contemporary uptake of novel and established diabetes medications; and (3) quantify changes over time in health care costs in an unselected T2D cohort.

Methods

This retrospective cohort study incorporated insurance claims data from the Geisinger Health Plan (GHP), a regional health insurance plan serving members in Pennsylvania and surrounding states. Study-eligible members were required to have at least 1 continuous GHP enrollment period of >2 years between 1999 and 2020. T2D patients were identified through the appropriate International Classification of Diseases 10th edition (ICD-10) codes documented at either 1 inpatient or 2 separate outpatient encounters. Member-level study intervals were defined by the time period beginning on the first outpatient visit after inclusion criteria were met and ending on the disenrollment date or December 31, 2020.

The current study evaluated changes over time from 2001 to 2020 in the following data domains: (1) case mix, including demographics, medical history such as the presence of concomitant CV risk factors, prior CV events and procedures, and diabetes-related complications; (2) diabetes medications; (3) cardiovascular medications; (4) new cardiovascular events and procedures ("study outcomes") including (a) acute myocardial infarction, (b) ischemic stroke, (c) hemorrhagic stroke, (d) heart failure hospitalization (HFH), (e) percutaneous coronary intervention (PCI), (f) coronary artery bypass graft (CABG) surgery, and (g) all-cause mortality; and (5) costs. Time intervals of data availability within GHP data systems varied across data domains: case mix and CV outcome/procedure data were available from 2001 to 2018, medication data from 2007 to 2020, and cost data from 2012 to 2018.

Study outcomes occurring between 2001 and 2018 within members' study intervals were identified. MI, ischemic stroke, hemorrhagic stroke, and HFH were considered study outcomes when an appropriate ICD-10 code was documented as the primary discharge diagnosis associated with a hospital admission. PCI and CABG procedures performed were identified through appropriate ICD-10 and procedure codes. Age-standardized outcome rates—standardized to the 2010 age distribution of the study cohort according to age groups <45, 45 to 54, 55 to 64, 65 to 74, 75 to 84, and ≥85—were reported per 10,000 person-years by calendar year and plotted over time. Poisson regression models were developed with calendar year as a single degree of freedom term to test for log-linear trends in outcome rates over time. Age-adjusted rate ratios (RR) with corresponding 95% confidence intervals (CI) were estimated; RRs are interpreted as the average annual relative change in outcome rates over the entire study period. RRs raised to the 17th power (RR^{17}) provide an estimate of the total relative change in outcome rates over the 17 years from the beginning (2001) to the end (2018) of the outcome-tracking study period. As a secondary analysis, age-adjusted RRs comparing a "late" time period (2014-2018) to an "early" time period (2001-2005) were also estimated. Lastly, RRs from Poisson models were also reported across age strata to evaluate trend heterogeneity across age groups and formal interaction tests were performed.

Member-level cost data were available from 2012 to 2018. Costs are defined as provider charges submitted for payment (ie, costs of providing care). Pharmaceutical costs reflect drug prices prior to application of copays, discounts, rebates, etc. Costs were identified within member-level study intervals and apportioned across calendar years (per member per year). Hypothetical trend lines denoting fixed annual cost increases of 3%, 10%, and 15% (starting from 2012 costs) were superimposed on the observed mean cost trend lines to approximate annual relative cost increases. In secondary analyses, costs were separated into various mutually exclusive categories: (1) pharmaceutical vs medical (ie, non-pharmaceutical) costs; and (2) outpatient vs inpatient vs emergency department costs.

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Results

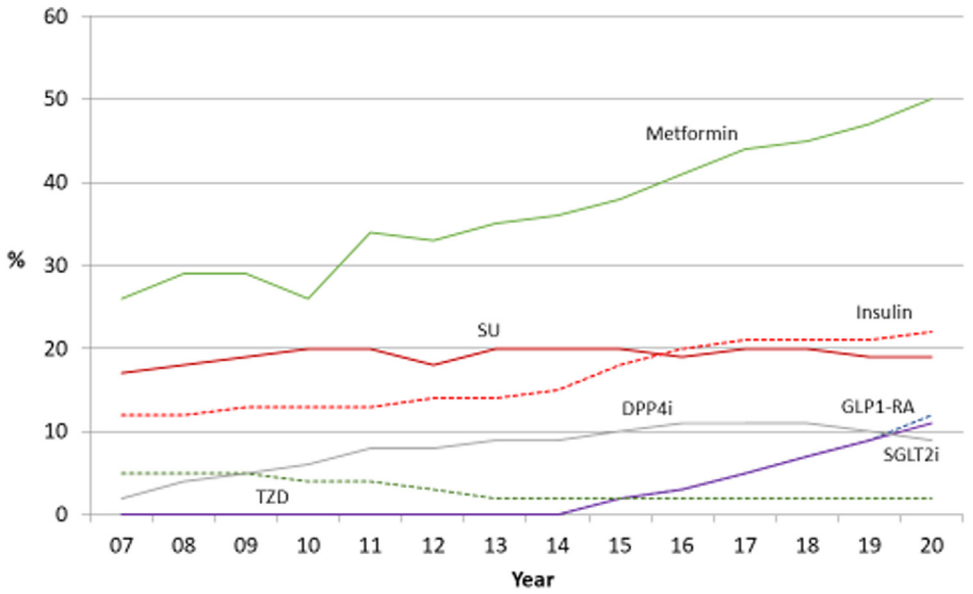
Case mix

From 2001 to 2018, 79,392 unique adult study members with T2D were tracked a total of 322,565 person-years, an average (SD) of 4.1 (4.1) years per member. The number of person-years apportioned to individual calendar years ranged from 11,075 in 2001 to 29,939 in 2018. Demographics, medical history, prior CV events and procedures, and diabetes-related complications are reported over time in eTable 1.

Diabetes and cardiovascular medications

Medication data were available for years 2007 to 2020. Over the study period, among the 8 classes of diabetes medications considered, use of metformin (26% in 2007 vs 50% in 2020), DPP4i (2% vs 9%), insulin (12% vs 22%), meglitinides (<1% vs 2%), GLP-1 RA (0% vs 12%), and

Figure 1



Diabetes Medications Over Time Among Patients with Type 2 Diabetes. DPP4i - Dipeptidyl peptidase-4 inhibitors; GLP1-RA - Glucagon-like peptide-1 receptor agonists; SGLT2i - Sodium-glucose transporter 2 inhibitors; SU - Sulfonylureas; TZD - Thiazolidinediones.

SGLT2i (0% vs 11%) increased, while sulfonylureas (17% vs 19%) and thiazolidinediones (5% vs 2%) remained steady or decreased (Figure 1; eTable 2). Since 2015, uptake of GLP-1 RAs and SGLT2is have risen sharply. Over time, the average number of diabetes medication classes used per member increased (0.63 in 2007, 1.28 in 2020—eFigure 1). Among cardiovascular medications, use of an angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) increased over time (39% in 2007 vs 60% in 2020), as did statin use (33% vs 68%) (eFigure 2; eTable 3).

Cardiovascular outcomes and procedures

Acute myocardial infarction

Between 2001 and 2018, 8,457 total MI events were documented over 322,565 person-years of observation (event rate [ER] = 262 per 10,000 person-years) [Note: person-year denominators are identical for all nonfatal study outcomes]. Within the entire study cohort, MI rates decreased over time (RR = 0.98, 95% CI: 0.97, 0.98; $RR^{17} = 0.69$ (over 17 years), 95% CI: 0.64, 0.74) (Figure 2). Comparing years 2014-2018 to 2001-2005, RR = 0.76, 95% CI: 0.67, 0.87. Across age groups, MI rates significantly decreased over time among T2D patients 65 to 74 ($RR^{17} = 0.76$, 95% CI: 0.67, 0.86), 75 to 84 ($RR^{17} = 0.68$, 95% CI: 0.60, 0.77), and ≥85 years of age ($RR^{17} = 0.63$, 95% CI: 0.53, 0.76), while no significant changes over time were observed in younger age groups (interaction $P < .001$) (Figure 3; eTable 4).

Ischemic stroke

For ischemic stroke, 6,731 events were documented over the study period (ER = 209 per 10,000 person-years). In the entire study cohort, ischemic stroke rates increased over time (RR = 1.05, 95% CI: 1.05, 1.06; $RR^{17} = 2.36$, 95% CI: 2.16, 2.57) (Figure 2). Comparing years 2014-2018 to 2001-2005, RR = 2.00, 95% CI: 1.71, 2.35. Ischemic stroke rates increased significantly within all age groups (interaction $P = .36$) (Figure 3; eTable 5).

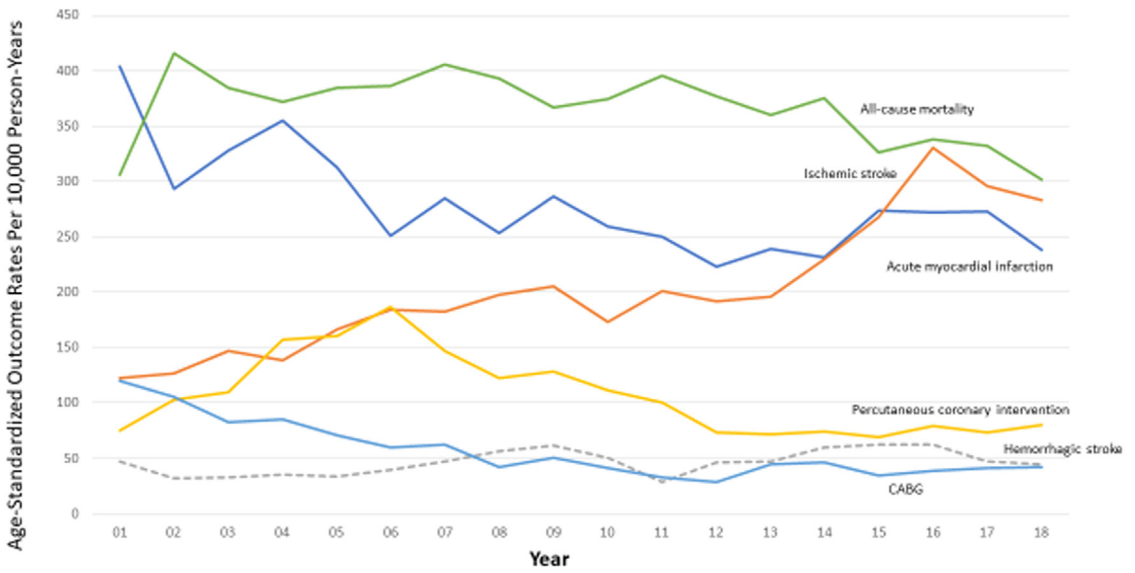
Hemorrhagic stroke

For hemorrhagic stroke, 1,479 events were documented over the study period (ER=46 per 10,000 person-years). For the entire study cohort, hemorrhagic stroke rates increased over time (RR = 1.02, 95% CI: 1.01, 1.03; $RR^{17} = 1.50$, 95% CI: 1.26, 1.79). Comparing years 2014-2018 to 2001-2005, RR = 1.54, 95% CI: 1.11, 2.15. Across age groups a significantly increasing trend was observed only in the ≥85 group ($RR^{17} = 1.89$, 95% CI: 1.26, 2.84) (interaction $P = .12$) (Figure 2; Figure 3; eTable 6).

Heart failure hospitalization

For heart failure hospitalization, 32,114 events were observed over the study period (ER = 996 per 10,000 person-years). For the entire study cohort, HFH rates decreased over time (RR = 0.99, 95% CI: 0.99, 0.99; $RR^{17} = 0.82$, 95% CI: 0.79, 0.86). Comparing years 2014-

Figure 2



Age-standardized cardiovascular outcome rates over time among patients with type 2 diabetes.

Figure 3

	Acute MI	Isch Stroke	Hem Stroke	HF hosp	PCI	CABG	Death
All	↓	↑	↑	↓	↓	↓	↓
<45	○	↑	○	↑	↓	○	↑
45-54	○	↑	○	↑	↓	↓	↑
55-64	○	↑	○	○	↓	↓	○
65-74	↓	↑	○	↓	↓	↓	↓
75-84	↓	↑	○	↓	↓	↓	↓
≥85	↓	↑	↑	↓	↓	↓	↓

↑ : Outcome rates significantly increasing over time

○ : Outcome rates not significantly changing over time

↓ : Outcome rates significantly decreasing over time

Cardiovascular outcome trends among patients with type 2 diabetes stratified by age group.

2018 to 2001-2005, RR=0.86, 95% CI: 0.81, 0.92. However, there was heterogeneity of trends across age groups (interaction $P < .001$). HFH rates significantly decreased in older age groups (eg, age ≥85: $RR^{17} = 0.77$, 95% CI: 0.71, 0.83), but significantly increased in younger age groups (eg, age 45-54: RR^{17}=2.02, 95% CI: 1.57, 2.59) (eTable 7).

Revascularization procedures

PCI (ER=106 per 10,000 person-years) and CABG (ER = 53 per 10,000 person-years) rates declined consistently both overall (PCI: $RR^{17} = 0.54$, 95% CI: 0.48, 0.60; CABG: $RR^{17} = 0.29$, 95% CI: 0.24, 0.34) and across most age groups (Figure 2; Figure 3; eTable 8; eTable 9). For PCI, comparing years 2014-2018 to 2001-2005, RR = 0.62, 95% CI: 0.49, 0.77. For CABG, comparing years 2014-2018 to 2001-2005, RR = 0.44, 95% CI: 0.33, 0.58.

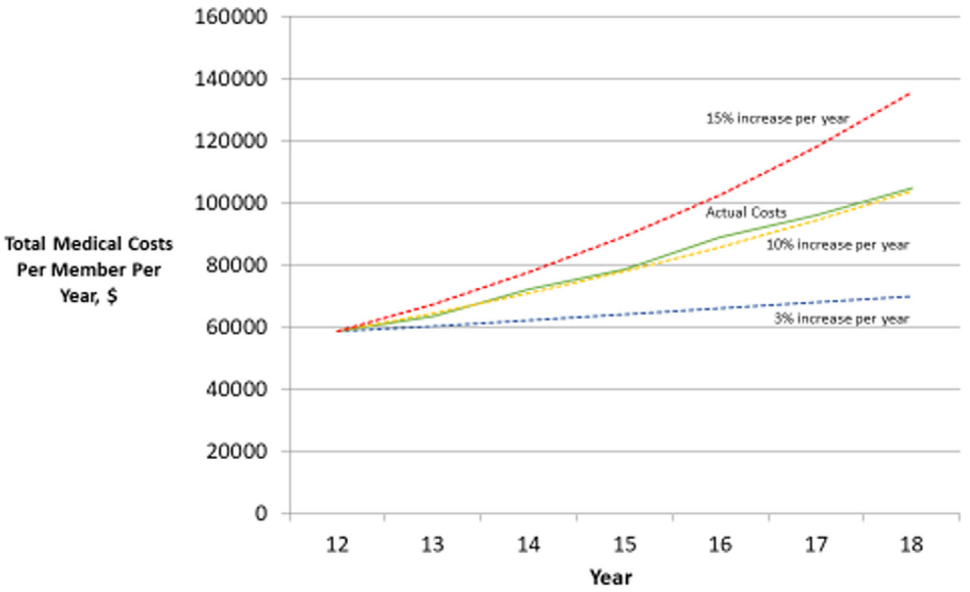
Mortality

For all-cause mortality, 21,334 deaths occurred over the study period (ER = 354 per 10,000 person-years). Across the entire study cohort, the age-standardized death rate decreased over time (RR = 0.99, 95% CI: 0.99, 0.99; $RR^{17} = 0.87$, 95% CI: 0.84, 0.91) but with heterogeneity across age groups (interaction $P < .001$) (Figure 2; Figure 3; eTable 10). Comparing years 2014-2018 to 2001-2005, RR = 0.90, 95% CI: 0.83, 0.98. Among older age groups, death rates significantly decreased over time (age 65-74: $RR^{17} = 0.78$, 95% CI: 0.71, 0.86; age 75-84: $RR^{17} = 0.79$, 95% CI: 0.74, 0.86; age ≥ 85: $RR^{17} = 0.74$, 95% CI: 0.67, 0.80), while death rates significantly increased over time in younger age groups (age <45: $RR^{17} = 2.86$, 95% CI: 1.57, 5.21; age 45-54: $RR^{17} = 1.48$, 95% CI: 1.11, 1.98). In the 55 to 64 age group there was no significant (linear) change in death rates over time ($RR^{17} = 1.03$, 95% CI: 0.87, 1.21).

Costs

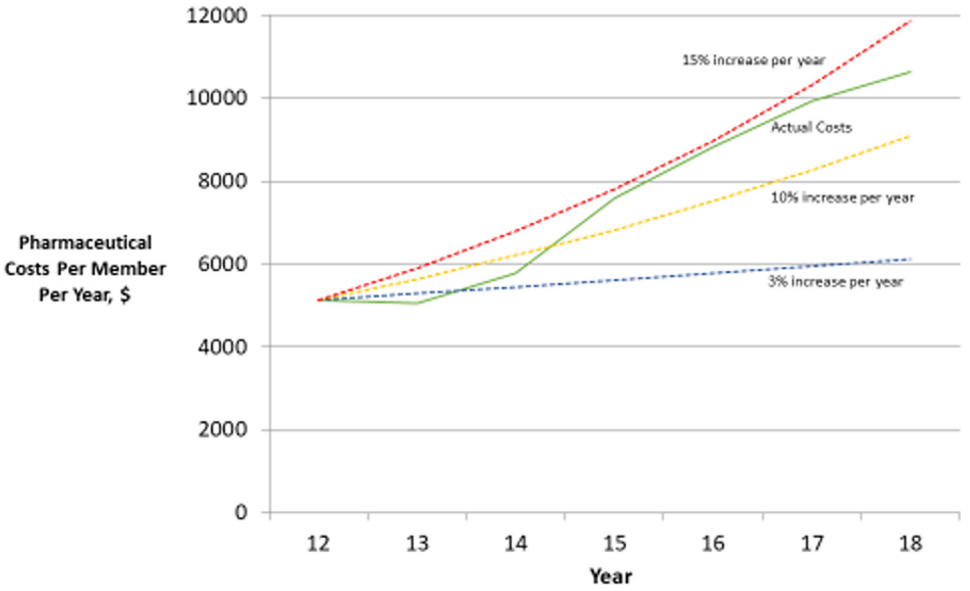
Total per member per year mean costs increased at an annual rate of approximately 10% per year (eFigure 3; eTable 11). Whereas annual increases in mean medical (ie, nonpharmaceutical) costs remained around 10% per

Figure 4



Medical costs over time among patients with type 2 diabetes.

Figure 5



Pharmaceutical costs over time among patients with type 2 diabetes.

year over the study period, mean pharmaceutical costs increased sharply starting in 2015 such that the average annual increase was ~15% per year over the study period (Figure 4; Figure 5). In 2018, pharmaceutical costs accounted for 9.2% of total costs, increasing from 8.0% in 2012. Mean outpatient and inpatient costs increased 10% per year, but annual increases in emergency department (ED) costs exceeded 15% per year (eFigure 4; eFigure 5; eFigure 6). The fraction of total medical costs attributed to ED utilization increased from 5.3% in 2012 to 7.8% in

2018. Furthermore, in 2018, hospitalizations accounted for 46.9% of total medical costs while outpatient costs accounted for 45.3%.

Discussion

In this retrospective study of patients with type 2 diabetes enrolled in a regional health insurance plan, age-standardized rates of all-cause mortality, acute myocardial infarction, heart failure hospitalization, percutaneous coronary intervention, and coronary bypass graft surgery improved over time from 2001 to 2018, while rates of ischemic and hemorrhagic stroke worsened. Outcome trends were generally more favorable in older than younger T2D patients; indeed, for all-cause mortality and HFH, event rates significantly worsened over time in younger age groups yet improved in older groups. Over time, T2D members were increasingly more likely to be diagnosed with diabetes-related microvascular conditions and received a greater number of glucose-lowering medications. Total health care costs among T2D members increased approximately 10% per year from 2012 to 2018, while pharmaceutical costs increased approximately 15% per year starting in 2015. Among health care utilization metrics considered, costs related to emergency department visits increased at a relatively faster rate than costs related to hospitalizations and outpatient visits, though hospitalizations and outpatient visits each accounted for >40% of total costs.

After an extended period of decreasing all-cause mortality and CV-related event rates in T2D over time in the US and elsewhere, a recent study[19] has cast doubt on this progress reporting an attenuation of trends in older adults and concerning trend reversals in younger adults under 65 years of age through 2015.[7,9,17,19-22,30-32] Our results generally support these findings in a large though geographically confined T2D patient population enrolled in a regional health insurance plan. This study extends previous findings by tracking an expanded collection of CV outcomes through 2018. In particular, we observed consistent decreases over time in all-cause mortality, acute MI, heart failure hospitalization, and coronary revascularization procedures performed. A notable exception was observed for ischemic stroke whose occurrence rate consistently increased over the study period such that its estimated overall increase from 2001 to 2018 was over 2-fold. Cautious interpretation of this observation is warranted however as no obvious explanation can be provided for the diverging trends. However, in agreement with our findings, a study from Spain examining trends in multiple CV outcomes from 2002 to 2014 reported a similar, though less extreme, discordance of trends between stroke and other CV outcomes.[33] Also consistent with the recent study by Gregg et al,[19] our study observed trend heterogeneity by age across multiple study outcomes, whereby flat or worsening trends were observed in younger age groups while improving trends were observed in older age groups.[17-19] Explanations for this heterogeneity are speculative. Notably, a relative increase in the number of younger T2D patients was observed during the latter years of our study. This may reflect increased diagnostic screening in the clinical environment, thereby uncovering a greater number of younger T2D patients—a group more likely to go undiagnosed.[1] Indeed, a recent study revealed that the fraction of undiagnosed T2D cases has been declining faster among younger than older individuals.[34] Coupled with the observation that T2D in younger patients typically follows a more aggressive clinical course, an explanation for the worsening trends in younger T2D patients can be hypothesized.[35]

In parallel with the temporal changes in CV outcomes observed in this study, multiple changes in the risk profile and applied therapeutic strategies occurred which may have impacted outcome rates in T2D. In particular, multiple lines of evidence suggest that disease severity has been worsening over time among T2D patients. Our study reported significant increases over time in the prevalence of coexisting microvascular disorders—conditions strongly associated with poor glycemic control. We caution, however, that the large observed increases may be partially attributable to nonphysiologic factors such as increased diagnostic testing, recognition, and upcoding. Furthermore, an electronic health record-(EHR-) based study from the study institution and other recent population-based studies from the US have reported worsening glycemic control among T2D patients in recent years.[1,23,24] Worsening glycemic control has been observed despite an increasing number of T2D medications being used over time.[23,24,36] Our study reported a near doubling in the average number of T2D medications used per member over the period of available data (2007-2020). This increase in T2D medication use has been observed worldwide as part of the evolving medical management of T2D with increasing use of metformin, insulin, GLP-1 RA, and SGLT2i.[37-40] The increased uptake of GLP-1 RAs and SGLT2is to >10% of T2D patients in 2020 is especially noteworthy in the current study's context as these are the only diabetes medication classes convincingly shown to reduce CV outcomes in randomized trials.[26]

With respect to non–glucose-related CV risk factors and therapies, our study reported increased uptake of blood pressure- and lipid-lowering therapies over time though use remained suboptimal. In 2020, documented statin use was 68% (up from 33% in 2007) despite 87% of study patients having a dyslipidemia diagnosis. Furthermore, ACEI/ARB use was 60% in 2020 (up from 39% in 2007) despite a documented hypertension diagnosis in 87%. These results concur with prior work reporting underutilization of effective, CV-event-reducing therapies in T2D.[41-44] Though the current insurance claims-based

analysis was unable to track actual changes in blood pressure and lipids over time, a complementary study from our group using EHR data reported noticeable improvements in lipid control over time but no change in blood pressure control.[23] Two recently-published studies incorporating NHANES data reported similar findings.[1,24] Importantly, better control of CV risk factors has been associated with improved CV outcomes in both observational and randomized studies.[5,24-31] Unfortunately, maintaining control of CV risk factors in T2D has been challenging as underscored by ample data.[1,14,16,23-25,29,41,43-46] For instance, in our EHR-based study, only 41% of T2D patients had simultaneous control of 4 important risk factors (HbA1c, blood pressure, non–high-density lipoprotein cholesterol, and smoking) in 2020.[23]

The management of T2D and its complications are important drivers of health care costs.[2] Our study observed an annual increase in total health care costs of approximately 10% per year, well above average annual inflation. When breaking down total costs into mutually exclusive categories, in 2018, hospitalizations accounted for 42.6% of costs, emergency department visits for 7.1%, outpatient care (ie, nonhospital, non-ED) for 41.1%, and outpatient pharmacologic management for 9.2%. Prior work has shown that hospitalizations account for a large proportion of costs in managing T2D.[47-48] Costs related to ED visits and pharmaceuticals increased at faster rates than costs related to other utilization metrics. In particular, annual costs related to ED visits increased at a rate exceeding 15% per year, while pharmaceutical costs increased at a rate of about 15% per year. Prior studies have reported increases over time in inflation-adjusted spending for diabetes therapies related to both the number of medications prescribed and the per-claim price of popular diabetes drugs.[49-51] Furthermore, a significant fraction of the costs related to T2D is associated with the management of CVD with studies reporting that costs of managing T2D are double among those with versus without CVD.[47,48,52,53]

Limitations

Some limitations of this study should be noted. The health plan member T2D cohort was significantly older (median age ~70) than more population-based T2D cohorts (mean age ~60).[24,42] This may be partially attributed to our 2+-year enrollment criterion which may have excluded a disproportionate number of younger patients enrolled through employers. In common with all insurance claims data studies, we lacked information on important variables which may have helped explain our findings such as body mass index, smoking status, blood pressure, cholesterol, and glucose indices. Data availability varied across the different data domains which limited our ability to assess correlations between study variables. Proper interpretation of outcome trends can be obscured by artifacts including changing diagnostic criteria, coding practices, etc.[17] Notably, the primary diagnostic biomarker for T2D changed during our study period (from blood glucose to HbA1c) and this change may have affected the patient profile and observed trends. Furthermore, the observed trend in ischemic stroke may reflect unidentified artifact and this analysis should be repeated in future studies. However, that all study outcomes were operationalized through a common methodology argues against artifact as explaining the trend.

In conclusion, in T2D, overall trends in most CV outcomes improved but smaller improvements or worsening trends were observed in younger patients. Health care costs accelerated at faster rates for medications and ED visits. Opportunity remains for further improvement in CV outcomes, and future work should attempt to better understand the worsening CV outcomes in younger T2D patients.

Disclosures

Novo Nordisk was an active participant in all phases of this study and Novo Nordisk employees are listed as co-authors. JR and YMP are employees of Novo Nordisk. NK is a former employee of Novo Nordisk. JPB is on the speakers' bureau of Novo Nordisk. The remaining authors have nothing to disclose.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.07.012.

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