Incidence and Prevalence of Microvascular and Macrovascular Diseases and All-cause Mortality in Type 2 Diabetes Mellitus: A 10-year Study in a US Commercially Insured and Medicare Advantage Population

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ABSTRACT

Purpose: The relationship between type 2 diabetes mellitus (T2DM) and increased microvascular and macrovascular disease and mortality is well established; however, data for the broad US T2DM population, especially by age, are limited. To help address this issue, we conducted a cohort study in a large national US commercially insured/Medicare Advantage population that incorporated a broad range of different age groups, including a large subset of younger individuals, during a 10-year study period.

Methods: This longitudinal study combined health plan claims and mortality data to identify incident T2DM patients and 1:1 directly matched non-DM controls. T2DM individuals (n = 13,883) were identified by a medical claim with a T2DM diagnosis or T2DM medication pharmacy claim in 2007; non-DM controls had no DM medical or pharmacy claims over the entire study period (January 1, 2006 to December 31, 2015). The outcomes assessed were incidence, prevalence, time to vascular disease and all-cause mortality, as well as age-stratified incidence and mortality based on Centers of Disease Control and Prevention–defined age strata.

Findings: Individuals with T2DM developed vascular disease at twice the rate as non-DM controls, 197 versus 98 per 1000 person-years, respectively. Vascular disease (composite) rates increased by age in T2DM/non-DM groups, 107.1/28.2 (18–44 years), 166.3/70.3 (45–64 years), and 391.0/199.7 (≥65 years) per 1000 person-years. The largest rate ratio was observed in younger individuals. All-cause mortality over follow-up was higher in T2DM individuals (27.5%) than in non-DM controls (19.6%). The largest increases in vascular disease prevalence and mortality among T2DM individuals were observed in the first year of follow-up.

Implications: T2DM has a substantial effect on microvascular and macrovascular disease and all-cause mortality rates in all age groups. These outcomes appear to occur early after T2DM diagnosis, and have more pronounced, nearly fourfold, relative impact on younger individuals with T2DM compared to matched non-DM controls. (*Clin Ther*. 2019;41:1522–1536)

Key words: complications, prevalence, macrovascular disease, microvascular disease, prevalence, time to first disease type 2 diabetes mellitus.

Accepted for publication May 13, 2019
https://doi.org/10.1016/j.clinthera.2019.05.012
0149-2918/$ - see front matter

INTRODUCTION

Type 2 diabetes mellitus (T2DM) continues to present a significant burden to individuals and society despite advances in understanding and managing the disease.[1–3] Individuals with T2DM made up approximately 90% to 95% of the 30.3 million Americans with diabetes in 2015, and 1.5 million new cases are diagnosed each year in the United States. Diabetes was identified as the underlying cause in 79,535 deaths in 2015, ranking as the seventh leading cause of US deaths.[4,5] Annual expenditure on diabetes care is approximately US $245 billion—$176 billion in direct medical expenses and $69 billion for indirect costs.[3–5] Rowley et al[2] projected that between the years 2015 and 2030 prevalence will increase by 54%, total diabetes-attributable deaths will increase by 38% per year, and annual total costs will rise by 53% to >$622 billion.

If uncontrolled, the long-term course of this complex chronic disease can lead to serious macrovascular diseases (cardiovascular disease, peripheral vascular disease and cerebrovascular disease) and microvascular diseases (nephropathy, neuropathy, and retinopathy).[6,7] Hyperglycemia linked to T2DM is believed to cause injury to small and large blood vessels, leading to the development of the aforementioned vascular diseases.[7] Vascular diseases are also associated with risk factors other than T2DM, including aging,[8] elevated weight,[9] and atherosclerosis.[10] Long-term microvascular and macrovascular diseases are associated with increased morbidity (eg, kidney failure, amputation, and blindness) and mortality risks that worsen over time.[7,11] Overall, microvascular and macrovascular diseases are burdensome to patients and the health care system.[12,13]

Only limited information, mainly on older individuals, is available on the progression of microvascular and macrovascular disease states and mortality in individuals with DM, and on their associated clinical burden in the United States.[6,14–16] Drawing from a large national sample representing a wide range of age groups, including a large subset of younger individuals, our study aimed to compare incidence and prevalence rates of microvascular and macrovascular diseases, and all-cause mortality, among individuals with T2DM and matched non-DM controls over a >10-year study period.

MATERIALS AND METHODS

Data Source and Study Design

Pharmacy and medical claims data for individuals with and without T2DM were accessed for this retrospective, matched-cohort study from the HealthCore Integrated Research Database and linked to mortality data from the Social Security Administration Death Master File for the study period of January 1, 2006, through December 31, 2015. Enrollee data from 14 geographically diverse Anthem health plans are curated within the HealthCore Integrated Research Database, which is representative of US National Census data,[17] and incorporates a variety of commercial health insurance models along with Medicare Advantage and Part D plans. The study design is shown in Supplemental Figure S1 (see the online version at https://doi.org/10.1016/j.clinthera.2019.05.012). The management of all study data complied with pertinent state and federal regulations, and Health Insurance Portability and Accountability Act Standards were applied strictly to preserve the privacy and security of identifiable personal health information of all individuals included in the study. A limited data set, delineated in the Health Insurance Portability and Accountability Act Privacy Rule, was used because access to direct patient identifiers was not necessary for this observational study.

Incident T2DM Cohort

Inclusion required continuous eligibility for medical and pharmacy benefits from January 1, 2006, until date of death or December 31, 2015, whichever was earlier. We identified the individuals with DM as having ≥2 medical claims with a DM diagnosis (ICD-9-CM code 250.xx) or ≥1 pharmacy claim for diabetes medication (Generic Product Indicator code starting with 27x, excluding 2730x) between January 1, 2007, and December 31, 2007. Among individuals identified with DM, we excluded individuals with type 1 diabetes mellitus (T1DM) during the same time period. The presence of T1DM was defined as ≥2 medical claims with a T1DM diagnosis, ≥1 pharmacy claim for insulin (Generic Product Indicator code 2710x) or ≥1 medical claim for

insulin pumps (Current Procedural Terminology codes E0784 and J1817; ICD-9-CM code V53.91) and no pharmacy claims for noninsulin diabetes medications except metformin. Among individuals without T1DM, we identified individuals with T2DM between January 1, 2006, and December 31, 2007, defined as having ≥2 medical claims with a T2DM diagnosis (ICD-9-CM codes 250.x0 and 250.x2) or a combination of ≥1 medical claim with a T2DM diagnosis and ≥1 pharmacy claim for a diabetes medication. Among individuals with T2DM, the first medical or pharmacy claim defining T2DM in 2007 was set as the *index date*, with the *baseline period* defined as the 1-year prior to index date. To identify individuals with incident (new) T2DM, those with any medical claims for DM or diabetes medication (Generic Product Indicator code starting with 27x) between January 1, 2006, and the index date were excluded.

Cohort Without T2DM (Controls)

The control cohort included individuals with continuous health plan eligibility who had no evidence of DM between January 1, 2006, and December 31, 2015, or death, whichever was earlier.

Matching

Individuals with T2DM were matched to controls using 1:1 exact attribute matching with no replacement on age, index date, sex, health plan type (health maintenance organization, consumer-driven health plans, and preferred provider organization), geographic region of residence and type of health insurance as of index date (commercial insurance, and Medicare Advantage). Individuals with T2DM were matched to controls on age and insurance type at baseline, but were free to modify or change their type of insurance at any time during follow-up. Each control was assigned an index date equal to the index date of the matched case.

Follow-up

Incident T2DM individuals and their controls were followed from the index date until the earlier of December 31, 2015, or date of death. The presence of a comorbid condition of interest was defined as ≥1 claim with a diagnosis code for the comorbid condition during the baseline year.

Outcomes

Each microvascular and macrovascular disease was identified by the presence of ≥1 claim(s) with a set of mutually exclusive ICD-9-CM or ICD-10-CM diagnosis codes for neuropathy, nephropathy (including renal dialysis), retinopathy, peripheral vascular disease, cardiovascular disease, and cerebrovascular disease at any time during the study period (January 1, 2006, to December 31, 2015). The use of diagnosis claims to ascertain microvascular and macrovascular disease in outcomes research studies is well established. One prior study has shown that both the number and severity of diabetes complications (constituents of the Diabetes Complications Severity Index as determined by the presence of ICD diagnosis codes)[18,19] were independently associated with increased risk for mortality and hospitalization in a population-based sample of primary care patients with diabetes,[20] and have been relied on to estimate costs, and in other types of analyses.[21,22] A composite outcome (≥1 claim for any microvascular or macrovascular disease between January 1, 2006, to earlier of December 31, 2015, or death) was also created.

Incidence Rates

Incidence rates of new microvascular or macrovascular diseases and all-cause mortality were computed for each of the cohorts over follow-up. Individuals with incident microvascular and macrovascular diseases were defined as those with no claims with a diagnosis for the microvascular and macrovascular diseases of interest between January 1,2006, and 1 day prior to the index date. *Incidence rate* was defined as the total number of patients with new disease divided by the number of person-years at risk for developing new disease from the index date to the end of the study period. *Mortality* was defined as the total number of patients who died during the study period divided by the number of person-years that patients were alive during the measurement period. Age-stratified incidence rates were computed as per-age strata defined by the Centers for Disease Control Diabetes Surveillance System Atlas for patient age groups 18 to 44 years, 45 to 64 years, and ≥65 years.[23,24]

Time to First Occurrence

The time to the first occurrence of each microvascular and macrovascular disease was measured in the subset of patients that had no claim for the microvascular and macrovascular diseases of interest during the baseline period. Time to the first occurrence and time to death were calculated for individuals with T2DM and matched controls who died prior to or on December 31, 2015, and defined as the number of days between index date and the first observed claim for the microvascular and macrovascular disease of interest or date of death.

Period Prevalence

The period prevalence rates for each microvascular and macrovascular disease were computed separately from the start of the baseline to the end of each of the 8 years of follow-up. *Period prevalence* was defined as the number of individuals with ≥1 claim for a disease of interest between the beginning of the baseline year and the end of the measurement year (with matched counterpart individual with T2DM and control also alive at the beginning of measurement year), divided by the total number of individuals alive at the beginning of the measurement year.

Statistical Analysis

Descriptive statistics were calculated for baseline characteristics and presented as means (SD) and relative frequencies for continuous and categorical variables, respectively. Incidence rate ratios (IRRs) were estimated using generalized linear models with a Poisson distribution and log link function to compare individuals with incident T2DM and matched non-DM controls. Cox proportional hazards regression was used to compare time to microvascular and macrovascular disease and survival between incident T2DM patients and matched controls. Median times to the occurrence of the first vascular disease were computed for all individuals with the incident microvascular or macrovascular diseases during follow-up. Median survival times were computed for individuals who died during the study follow-up. For the analysis of time to microvascular and macrovascular disease, patients who did not experience microvascular and macrovascular disease were right censored on the earlier of date of death or December 31, /2015. for the analysis of survival, patients who did not die were censored at December 31, 2015.

RESULTS

Study Population

Of the 1.5 million eligible individuals identified during the study period, 115,070 met the inclusion criteria for T2DM in the year 2007, and of those, 12% (n = 14,151) had incident T2DM. Most (98%) of the eligible individuals with T2DM were matched to controls, resulting in 13,883 matches for a total study sample of 27,776 individuals (see Supplemental Table S1 in the online version at https://doi.org/10.1016/j.clinthera.2019.05.012).

Baseline Demographics and Comorbidities

Overall, the mean (SD) age of individuals in the 2 cohorts was 63.6 (15.36) years; median, 65 years. Individuals aged ≥65 years constituted the largest age group (51.4%). Post-match, the study sample had slightly more males (50.5%). Eligible individuals were located mostly in the Midwest (30.7%) and the South (28.7%), followed by the Northeast (18.8%) and the West (17.5%) as shown in Table. A large percentage (51.8%) of the study population was enrolled in Medicare Advantage, while 48.2% were members of commercial health plans (data not shown). The most frequently occurring baseline comorbidities were hypertension (63.5% and 42.2%) and dyslipidemia (52.6% and 38.6%) for individuals with T2DM and non-DM controls, respectively.

In the incident T2DM cohort with microvascular and macrovascular disease and non-DM controls, the mean (SD) age was 65.9 years (SD 14.51), and individuals who were aged ≥65 years made up the largest age group (56.3%). The most frequently occurring comorbidities were hypertension (67.0% and 45.4%) and dyslipidemia (54.4% and 40.8%) for the incident T2DM patients with vascular disease and non-DM controls, respectively.

Incidence of Microvascular and Macrovascular Diseases

Individuals with incident T2DM developed a new microvascular or macrovascular disease at twice the rate of matched controls (197 vs 98 per 1000 person-years; IRR, 2.01; $P < 0.001$), respectively, during the 8-year follow-up. A similar pattern of significantly

Table. Demographic characteristics and selected comorbidities at baseline and after index medication use.

Characteristic	All Incident T2DM (n = 13,883)	Matched Non-DM Controls (n = 13,883)
Age		
Mean (SD), y	63.6 (15.36)	63.6 (15.36)
Median (IQR), y	65 (52.0–75.0)	65 (52.0–75.0)
Group, no. (%)		
<18 y	65 (0.5)	65 (0.5)
18–34 y	303 (2.2)	303 (2.2)
35–49 y	2301 (16.6)	2301 (16.6)
50–64 y	4073 (29.3)	4073 (29.3)
65–74 y	3433 (24.7)	3433 (24.7)
≥75 y	3708 (26.7)	3708 (26.7)
Male, no. (%)	7004 (50.5)	7004 (50.5)
Residence region, no. (%)		
Midwest	4265 (30.7)	4265 (30.7)
South	3981 (28.7)	3981 (28.7)
Northeast	2609 (18.8)	2609 (18.8)
West	2424 (17.5)	2424 (17.5)
Other	604 (4.4)	604 (4.4)
Plan type, no. (%)		
PPO	10,539 (75.9)	10,539 (75.9)
HMO	3297 (23.7)	3297 (23.7)
CDHP	23 (0.2)	23 (0.2)
Other	24 (0.2)	24 (0.2)
Insurance type, n (%)		
Commercial	6691 (48.2)	6691 (48.2)
Baseline comorbid conditions, no. (%)		
Hypertension	8812 (63.5)	5859 (42.2)
Dyslipidemia	7303 (52.6)	5364 (38.6)
Congestive heart failure	1706 (12.3)	648 (4.7)
Cancer	1617 (11.6)	1335 (9.6)
Depression	1207 (8.7)	886 (6.4)
Renal disease	919 (6.6)	378 (2.7)
Liver disease	719 (5.2)	309 (2.2)
Myocardial infarction	357 (2.6)	129 (0.9)
Baseline comorbid conditions, no. (%)		
Hypertension	8812 (63.5)	5859 (42.2)
Dyslipidemia	7303 (52.6)	5364 (38.6)
Cancer	1617 (11.6)	1335 (9.6)
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Liver disease	719 (5.2)	309 (2.2)
Myocardial infarction	357 (2.6)	129 (0.9)

Table. (*Continued*)

Characteristic	All Incident T2DM (n = 13,883)	Matched Non-DM Controls (n = 13,883)
Medication use in each postindex year,* %, range		
Statins (HMG-CoA reductase inhibitors)	40.8–51.5	23.2–28.3
Biguanides	30.3–38.0	0.0–0.0
ACE inhibitors	29.3–31.0	15.3–16.2
β-blockers	29.0–31.1	17.7–19.1
Thiazide diuretics	21.9–23.1	12.9–13.4
CCBs	18.3–21.4	11.6–14.0
ARBs	17.2–22.3	8.7–11.4
Sulfonylureas	10.9–15.5	0.0–0.0
DPP-4 inhibitors	3.8–11.4	0.0–0.0
Any insulin	3.3–7.9	0.0–0.0
TZDs	2.8–6.8	0.0–0.0
GLP-1 receptor agonists	0.9–3.5	0.0–0.0
SGLT-2 Inhibitors	0.0–2.9	0.0–0.0

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blockers; CCB = calcium channel blockers; CDHP = consumer-directed health plan; DPP = dipeptidyl peptidase; GLP = glucagon-like peptide; HMG-CoA = hydroxymethylglutaryl coenzyme A; HMO = health maintenance organization; IQR = international normalized ratio; PPO = preferred provider organization; SGLT = sodium/glucose cotransporter; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones.

* Percentages of individuals with ≥1 claim for a medication of interest between year 1 and year 8 postindex, among those who were alive at the beginning of each postindex year.

higher incidence of microvascular and macrovascular diseases in individuals with incident T2DM compared with matched controls (IRR, 1.47-2.74; $P < 0.001$ for all comparisons) was seen across each of the 6 vascular diseases evaluated. Cardiovascular disease was the most frequently occurring of the incident vascular diseases in individuals with T2DM and matched controls (83 vs 54 events per 1000 person-years; IRR, 1.55; $P < 0.001$). The largest difference in microvascular incidence was for retinopathy, as individuals with incident T2DM experienced an almost threefold increase relative to matched controls (38 vs 14 events per 1000 person-years; IRR, 2.74; $P < 0.001$), as shown in Figure 1.

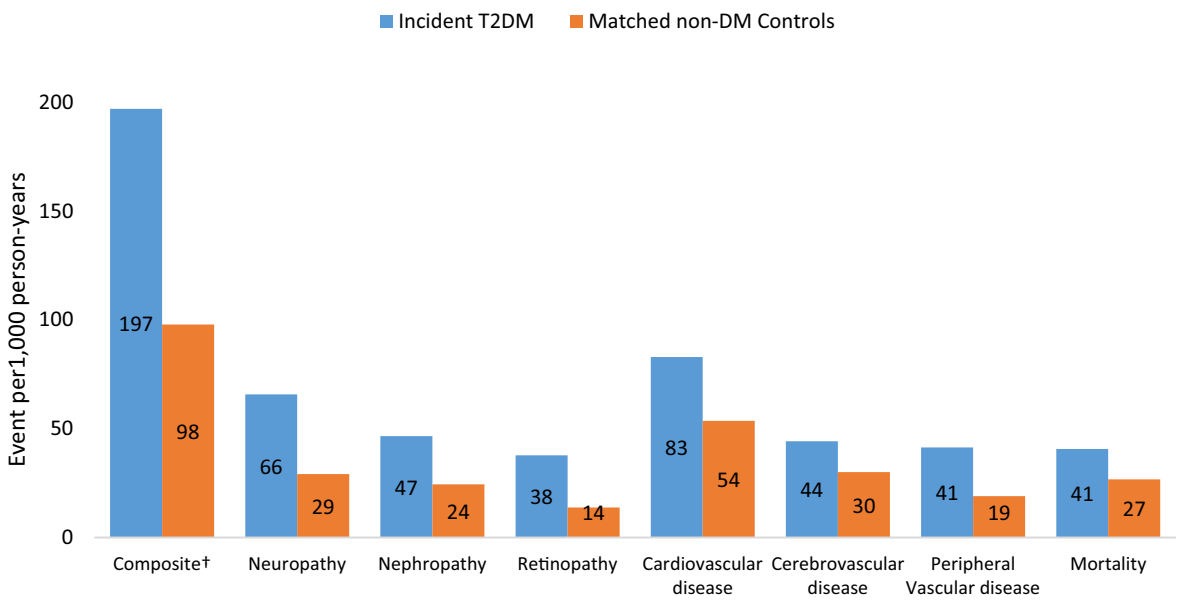
Disease Incidence by Age Stratification

The incidence rates of individual and composite microvascular and macrovascular diseases were progressively higher with increasing age across individuals with T2DM and non-DM controls. Composite vascular disease incidence by age group increased from 107.1 (18–44 years) to 166.3 (45–64 years) to 391.0 (≥65 years) per 1000 person-years in individuals with T2DM and 28.2 (18–44 years) to 70.3 (45–64 years) to 199.7 (≥65 years) per 1000 person-years in non-DM controls. The magnitude of the rate ratio in vascular disease rates between individuals with T2DM and non-DM controls for individual and composite microvascular was much greater in younger individuals (18–44 years) compared to older individuals (45–64 and ≥ 65 years) across the board for all vascular diseases. The IRR for composite vascular disease decreased from 3.80 (18–44 years) to 2.36 (45–64 years) to 1.96 (≥65 years) (all, $P < 0.001$) for individuals with T2DM relative to controls. Within each age group, there was a statistically significant higher incidence of composite and individual

incident microvascular and macrovascular diseases in individuals with T2DM compared to non-DM controls, as shown in Figure 2. For both cohorts, neuropathy was the most frequently occurring individual incident microvascular disease in the 18–44 year age group, while cardiovascular disease occurred most commonly in the 45–64 and ≥ 65 year strata. Compared to non-DM controls, individuals with T2DM had the highest relative incidence of retinopathy (IRR, 9.67 in the 18–44 age group, 3.44 in 45–64 age group; both, $P < 0.001$). Among older individuals (≥65 years), the IRRs for retinopathy (2.28; $P < 0.001$) and neuropathy (2.25; $P < 0.001$) were the highest among individual vascular conditions.

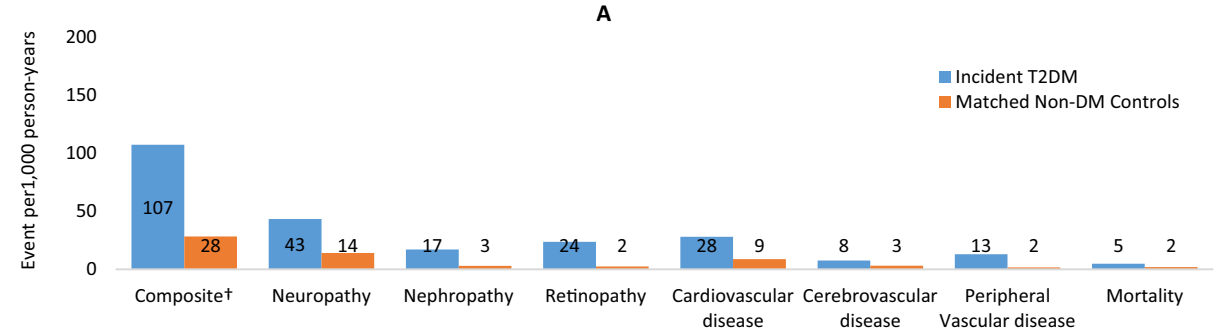
Time to First Microvascular or Macrovascular Disease

Among individuals with ≥1 incident microvascular or macrovascular disease, time to first disease manifestation was shorter for individuals with T2DM compared with non-DM controls (median times to first neuropathy diagnosis, 950 vs 1182 days; nephropathy, 957 vs 1182 days; retinopathy, 974 vs 1238 days; peripheral vascular disease, 832 vs 1081 days; cardiovascular disease, 679 vs 987 days; and cerebrovascular disease, 808 vs 1030 days). Individuals with T2DM had greater risk for composite or individual micro- or macrovascular disease states, compared to non-DM controls (data not shown graphically).

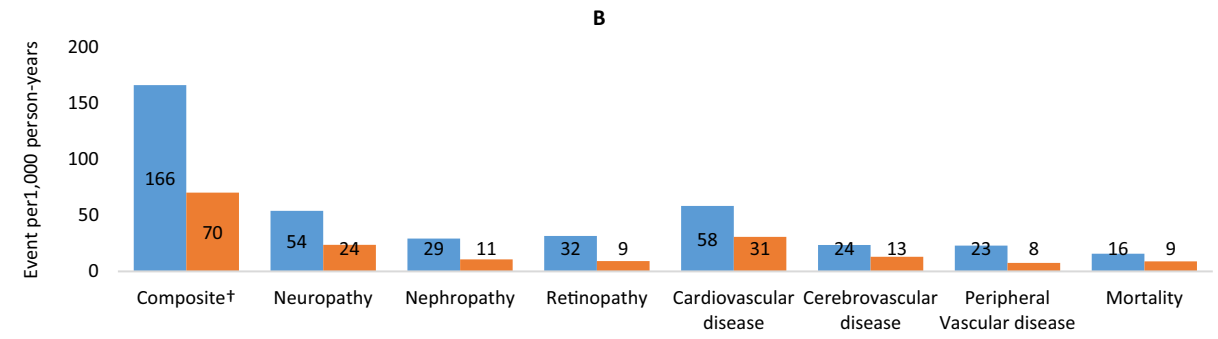


Incidence Rate Ratio* and 95% CI	2.01 (1.94,2.09)	2.26 (2.15,2.37)	1.91 (1.81,2.01)	2.74 (2.57,2.92)	1.55 (1.48,1.62)	1.47 (1.40,1.55)	2.18 (2.05,2.31)	1.52 (1.45,1.60)

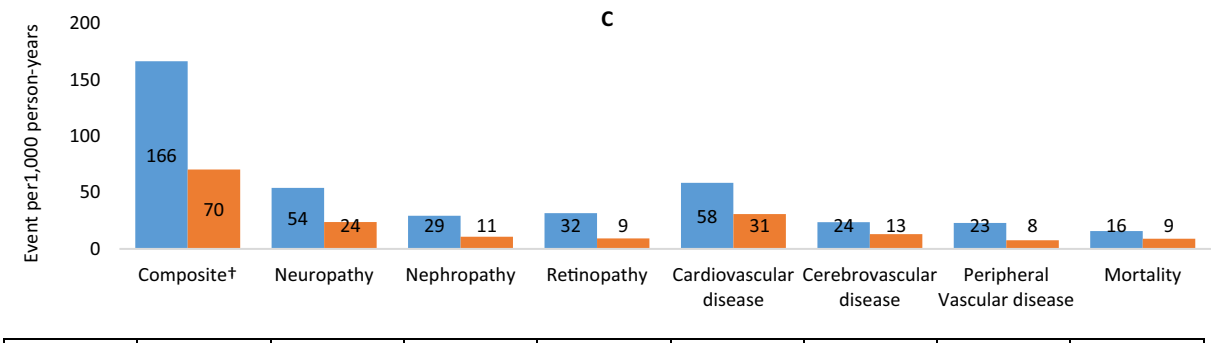
Figure 1. Incidence of microvascular disease, macrovascular disease, and all-cause mortality between the index date and the end of 8-year follow-up period. *Incident diabetes* was defined as the absence of claims with a diagnosis of diabetes mellitus (ICD-9 code 250.xx) or claims for diabetes medication between January 1, 2006, and the index date. †*Composite* was defined as the presence of a diagnosis for neuropathy, nephropathy, retinopathy, peripheral vascular disease, cardiovascular disease, or cerebrovascular disease. T2DM = type 2 diabetes mellitus. * P<0.001 for all comparisons.



Incidence Rate Ratio* and 95% CI	Composite†	Neuropathy	Nephropathy	Retinopathy	Cardiovascular disease	Cerebrovascular disease	Peripheral Vascular disease	Mortality
	3.80 (3.32,4.35)	3.09 (2.57,3.70)	5.62 (3.95,7.99)	9.67 (6.62,14.11)	3.19 (2.54,3.99)	2.45 (1.68,3.59)	7.90 (4.95,12.6)	2.51 (1.56,4.03)



Incidence Rate Ratio* and 95% CI	Composite†	Neuropathy	Nephropathy	Retinopathy	Cardiovascular disease	Cerebrovascular disease	Peripheral Vascular disease	Mortality
	2.36 (2.23,2.51)	2.27 (2.09,2.47)	2.73 (2.44,3.05)	3.44 (3.06,3.87)	1.89 (1.75,2.04)	1.81 (1.62,2.01)	3.04 (2.67,3.46)	1.75 (1.54,1.98)



Incidence Rate Ratio* and 95% CI	Composite†	Neuropathy	Nephropathy	Retinopathy	Cardiovascular disease	Cerebrovascular disease	Peripheral Vascular disease	Mortality
	1.96 (1.86,2.07)	2.25 (2.11,2.40)	1.75 (1.65,1.86)	2.28 (2.10,2.47)	1.59 (1.51,1.68)	1.51 (1.43,1.60)	2.10 (1.96,2.24)	1.54 (1.46,1.63)

Figure 2. Age-stratified incidence of microvascular disease, macrovascular disease, and all-cause mortality—index date to end of 8-year follow-up in age groups 18–44 years (A), 45-64 years (B), and ≥65 years (C). *$P < 0.001$ for all comparisons. †*Composite* was defined as the presence of a diagnosis for neuropathy, nephropathy, retinopathy, peripheral vascular disease, cardiovascular disease, or cerebrovascular disease. T2DM = type 2 diabetes mellitus.

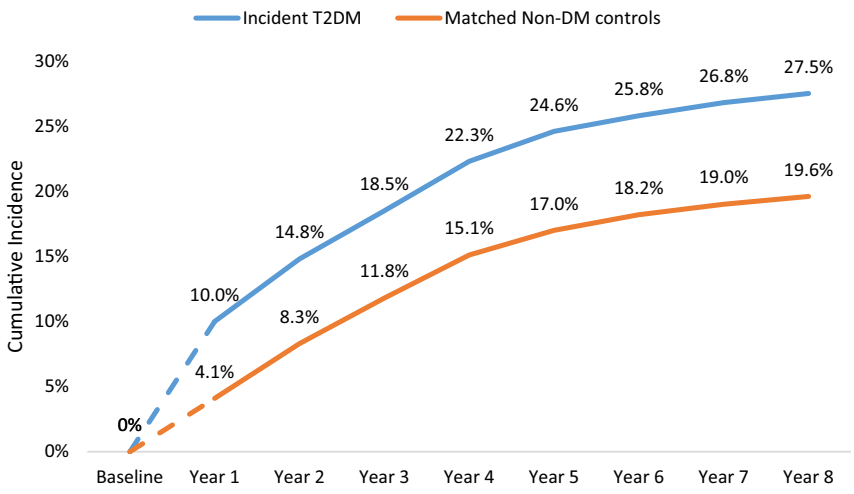


Figure 3. Cumulative all-cause mortality after each year of follow-up. T2DM = type 2 diabetes mellitus.

Mortality

Of 13,883 individuals with T2DM at the start of the study, 3819 (27.5%) died during follow-up compared to 2725 (19.6%) non-DM controls, as shown in Figure 3.

During each subsequent year of follow-up, mortality was greater for individuals with T2DM compared to non-DM controls. All-cause cumulative mortality among individuals with T2DM increased from 10.0% at the end of follow-up year 1 to 27.5% at the end of follow-up (year 8). During the same period, all-cause mortality in the control group increased from 4.1% at the end of year 1 to 19.6%, as shown in Figure 3. All-cause mortality rate in cases was 52% greater than in controls (41 vs 27 deaths per 1000 person-years; IRR, 1.52; $P < 0.001$), as shown in Figure 1. Mortality increased in both cohorts within successively older age groups; individuals with T2DM had significantly higher mortality compared to matched controls in each age stratum, as shown in Figure 2. However, as shown with the occurrence of vascular diseases, the most pronounced difference in mortality rate ratios between individuals with T2DM and non-DM controls was observed in the younger age group.

Period Prevalence of Vascular Diseases After Each Year of Follow-up

Prevalence of microvascular and macrovascular disease increased 38% (from 43% at baseline to 81% at end of year 8) in the incident T2DM cohort and 32% (from 29% at baseline to 61% at end of year 8) for matched controls between baseline and the end of year 8, as shown in Figure 4 (composite microvascular and macrovascular disease). Prevalence of vascular disease increased the fastest for both cohorts in the first year post-baseline—with slightly less than half of the 38% increase reported for individuals with T2DM, and 9% of the 32% increase for controls. From baseline to the end of year 8, the annual period prevalence for any diabetes-related microvascular and macrovascular disease (composite) for individuals with T2DM exceeded the prevalence in the matched control group by 17% to 20%. The pattern was similar for individual microvascular and macrovascular diseases, as shown in Figure 4. From baseline to the end of follow-up, the increase in the prevalence of neuropathy, nephropathy, retinopathy, and peripheral vascular disease was greater for individuals in the T2DM cohort compared with controls. In the same period, the rate of increase in the prevalence of cardiovascular and cerebrovascular diseases was similar among individuals with T2DM and controls.

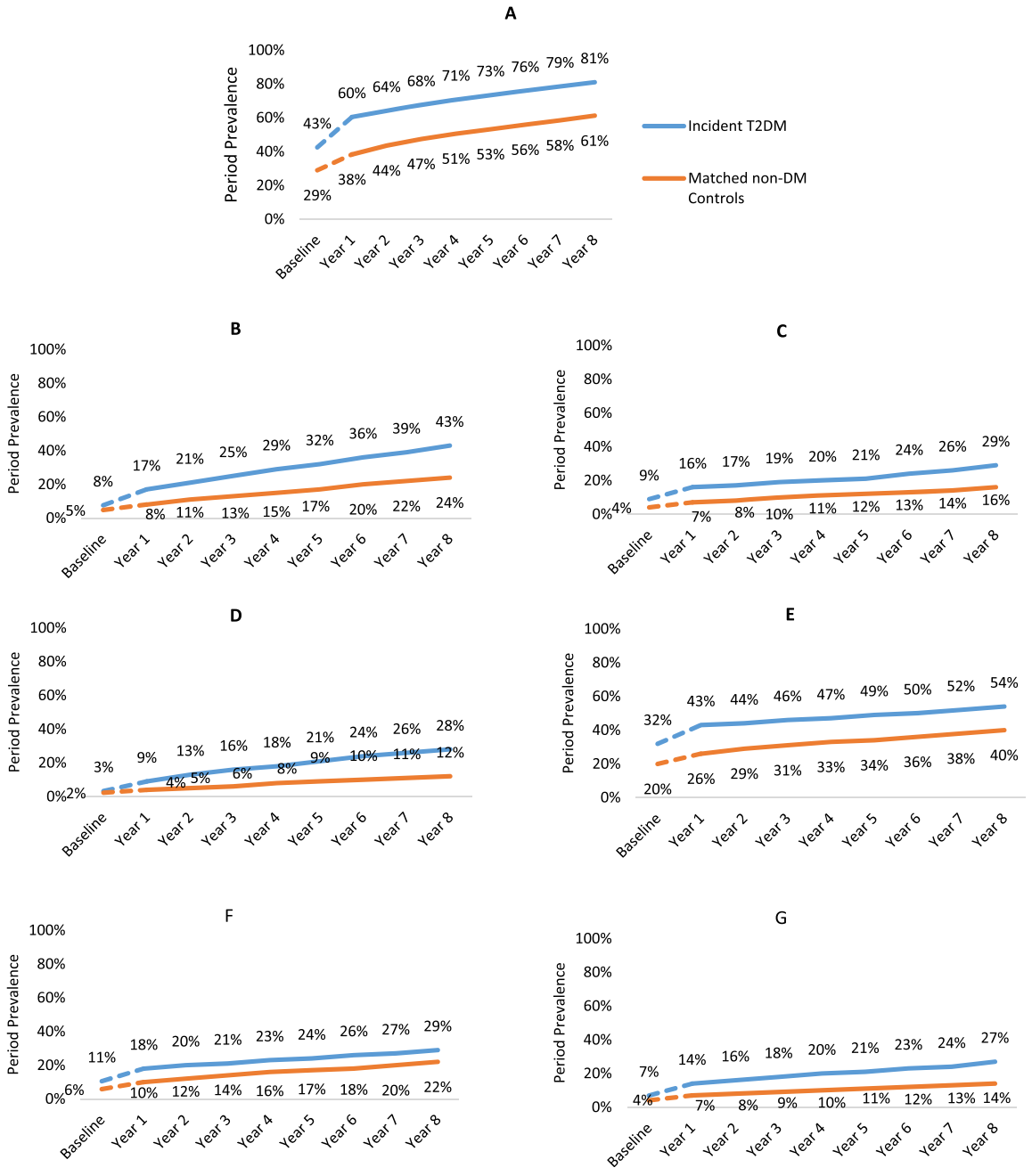


Figure 4. Period prevalence of macrovascular and macrovascular disease after each year of follow-up. A, Composite microvascular and macrovascular disease; B, neuropathy; C, nephropathy; D, retinopathy; E, cardiovascular disease, F, cerebrovascular disease; G, peripheral vascular disease. **Period prevalence* for each microvascular and macrovascular disease was computed between the start of the baseline year to the end of each incremental year of follow-up. †*Composite vascular disease* was defined as the presence of a diagnosis for neuropathy, nephropathy, retinopathy, peripheral vascular disease, cardiovascular disease, or cerebrovascular disease. T2DM = type 2 diabetes mellitus.

DISCUSSION

The results of this 8-year follow-up study in a clinical practice population showed that overall the presence of T2DM was associated with a two-fold increase in the incidence of new microvascular or macrovascular disease relative to matched non-DM controls, consistent with the findings of earlier studies.[16,25–28] For each of the 6 types of vascular diseases examined, individuals with T2DM had significantly higher disease incidence relative to non-DM controls. As expected, cardiovascular disease was the most frequently occurring macrovascular condition in both cohorts,[27,29–35] however, the incidence rate was significantly greater among individuals with T2DM. In addition, the high prevalence of hypertension and dyslipidemia at baseline likely contributed to the greater incidence of cardiovascular and cerebrovascular diseases. Although hypertension and dyslipidemia occur frequently in combination with T2DM, they are also prevalent in older individuals without T2DM.[32] The threefold increase in retinopathy among individuals with T2DM represented the largest difference for microvascular diseases between the 2 cohorts, concurring with the results of earlier reported analyses.[36,37] These findings are directionally consistent with increases ranging from two-to eightfold, depending on the vascular condition investigated, that have been reported in prior studies.[16,25–28]

To our knowledge, this is the first comprehensive comparison of individuals with T2DM and non-DM controls among various age categories for specific microvascular and macrovascular conditions in a clinical practice setting. As expected, our results showed that increasing age was associated with progressively greater overall incidence rates of microvascular and macrovascular disease across both cohorts, with the rate substantially higher among individuals with T2DM.[33,35,38–42] However, for all microvascular and macrovascular diseases, the magnitude of the rate ratio between individuals with T2DM and non-DM controls decreased with increasing age, the result of individuals without T2DM developing vascular conditions independent of diabetes.[31,43] So while the overall magnitude of individuals with T2DM having microvascular and macrovascular diseases is less in younger individuals, they are at much greater risk for developing them compared to non-DM counterparts of the same age. In other words, our results show that while older individuals have higher absolute risk, younger age groups have higher relative risk.

Consistent with earlier studies,[15,25,27] our results showed that mortality rates were higher for individuals with T2DM relative to non-DM controls during follow-up overall, and after each of the 8 years of the study period. While mortality increased in both cohorts across successively older age groups, the rates were significantly higher among individuals with T2DM in each age group. Similar to the rates of microvascular and macrovascular diseases, the relative risk for mortality by age group was much greater in younger individuals than in older individuals with T2DM.

Our results also showed that the time to occurrence of the first vascular disease diagnosis was significantly shorter for individuals with T2DM versus non-DM controls among individuals with $\geq$1 incident microvascular or macrovascular disease. It appears that the time to vascular disease development is about 2 to 3 years, with a sharp increase in incidence of vascular diseases by the end of the first year post-diagnosis. In addition, deaths occurred at a high rate early and continued to escalate both in absolute and relative terms. Among the implications of such findings are the need for prompt, early T2DM management and also the need for more timely detection and diagnosis of T2DM in general. Taken together with the data showing the relative burden of T2DM in the younger population, this has significant implications as to how aggressively we should target interventions for younger patients and the potential beneficial impact of an aggressive treatment approach.

Medications known to reduce the risk for microvascular and macrovascular events such as statins and antihypertensives[44] were used more frequently in the incident T2DM cohort compared to non-DM controls. Antidiabetic medications were only used in the T2DM cohort in concordance with the study design. Rates of use of these medications reflect clinical practice usage patterns, and provide context about the population being studied and the observed pattern of vascular disease diagnoses. The proportion of the cohort using antidiabetic medications could have influenced the incidence and prevalence of vascular disease in this study population.

Another finding that has clinical and health policy management implications pertains to the prevalence of cardiovascular and cerebrovascular disease. These macrovascular conditions increased at similar rates after the first post-index year, unlike other vascular diseases where prevalence increased faster in individuals with T2DM relative to controls. This could be due to higher mortality among T2DM individuals with cardiovascular or cerebrovascular disease, which would effectively remove them from the prevalence pool. This suggests that T2DM patients may have more aggressive phenotypes of cardiovascular and cerebrovascular disease, and treatment approaches must be intensified to reduce the T2DM individual's morbidity and mortality risks from these conditions. Treatment approaches not solely focused on glycemic control but also on cardiovascular risk reduction are in line with our results. This comprehensive approach should consider use of T2DM medications with beneficial cardiovascular risk reduction data, such as empagliflozin, dapagliflozin, and canagliflozin[45] among the sodium–glucose co-transporter 2 Inhibitors,[46] and liraglutide and semaglutide among the acylated human long-acting glucagon-like peptide 1 receptor agonists.[47]

Limitations

A few limitations should be considered when evaluating our results. The status of individuals with T2DM and controls were assigned on the basis of future information, which was the absence of diabetes-related claims between 2006 and 2015. As such, at-risk individuals who developed diabetes during follow-up were not included in the non-DM control group. As a result, while the selected controls allowed the study to compare microvascular and macrovascular diseases between individuals with T2DM and non-DM controls, they may have been healthier than a cohort of general population controls. However, a previous study similar in design showed minimal differences between controls selected who could go on to develop T2DM versus a general population control cohort, and used that control group who did not ever develop T2DM for their report analyses.[28] The exposure and outcomes in our study were based on diagnoses found in medical claims, which may be prone to coding and other claims-based errors. The inherent limitations in claims data also precluded any consideration of information on diabetes-education initiatives, medication-management programs to prevent vascular disease, and clinical data such as hemoglobin A_{1c} laboratory values. In particular, microvascular and macrovascular diseases, which were established by the presence of a single diagnosis, could have been misattributed, although this would likely be similar for both cohorts in a large sample.[48] Of note, the impact of higher incidence and prevalence of microvascular and macrovascular diseases was reflected in higher mortality in incident T2DM. The association between T2DM diagnosis and vascular disease may have been influenced by cardiovascular risk factors such as presence of hypertension, heart failure, or myocardial infarction, and other covariates not adjusted for in the exact 1:1 matching of incident T2DM patients and non-DM controls. As previously mentioned, the use of medications associated with improvements in vascular disease outcomes was observed more frequently in the incident T2DM group compared to the non-DM group; nonetheless, higher rates of vascular disease were still observed in this cohort. No analysis was performed to assess the impact of medication use on vascular disease outcomes in this study, but this is certainly an area of interest for future studies. The study findings were based on a commercially managed and Medicare Advantage–enrolled US population, which limits their generalizability to other populations.

CONCLUSIONS

These results demonstrated the substantial impact of T2DM on the incidence, time to first occurrence and prevalence of microvascular and macrovascular diseases, mortality rate, and time to death in a large, clinical practice US population. These increases in microvascular and macrovascular diseases and mortality among individuals with T2DM occurred very early after diagnosis of T2DM, and were more pronounced in younger patients. The patterns of cardiovascular disease and mortality suggest that comprehensive care of the individual with T2DM is warranted. These data provide clinicians, health care payers, and policymakers with clinical practice data to better target and asses the outcomes of T2DM diagnosis and treatment interventions.

ACKNOWLEDGMENTS

Bernard B. Tulsi, MSc, senior medical writer at HealthCore Inc, provided writing and editorial support for this project.

All authors contributed substantially to the conduct of this study, and in the preparation are revisions of this manuscript. J.V. contributed to data analysis, interpretation of results, manuscript writing, manuscript review, and project management; A.R. contributed to protocol development, data analysis, interpretation of results, manuscript writing, manuscript review, and data acquisition; V.W. contributed to concept development, protocol development, interpretation of results, manuscript writing, manuscript review, and project management; D.K. contributed to concept development, protocol development, data analysis, interpretation of results, manuscript review, and project management, data acquisition; N.I. contributed to concept development, protocol development, interpretation of results, manuscript writing, manuscript review, and project management; S.K. contributed to concept development, protocol development, interpretation of results, manuscript writing, manuscript review, and project management; T.H. contributed to concept development, protocol development, interpretation of results, and manuscript review; and J.B. contributed to concept development, protocol development, interpretation of results, manuscript review, and project management.

CONFLICTS OF INTEREST

This study was sponsored by Novo Nordisk. Via its employees, who were investigators in this study and served as co-authors of the manuscript, the sponsor engaged in study conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, project administration, supervision, validation, writing, review, and editing.

S.K., N.I., T.H., and J.B. were employees of Novo Nordisk at the time of this research. D.K. was an employee of HealthCore at the time of this research, and is currently an employee of Janssen. A.R. was an employee of HealthCore at the time of the study, and is now an employee of Merck. J.V. and V.W. are employees of HealthCore, which received funding from Novo Nordisk to perform the research. J.V. is the guarantor for this submission. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Table S1. Patient attrition.

Step	Criteria	Counts	% Retained
1	Members with continuous enrollment from 1/1/2006 -12/31/2015, including those who died	1,522,005	100.00%
2	From Step 1, members with ≥1 diagnosis claims or prescription fills for DM during 1/1/2007 through 12/31/2007 (intake period)	130,947	8.60%
3	From Step 2, members without T1DM during the intake period	124,324	94.94%
4	From Step 3, members with T2DM (2 medical diagnoses or 1 medical diagnosis + 1 diabetes prescription claim) during the intake period	115,070	92.56%
5	From Step 4, members with incident T2DM	14,151	12.30%
6	From Step 5, matched pairs of an incident T2DM and a non-DM control (**main cohort of interest**)	**13,883**	98.11%

Abbreviations: DM: diabetes mellitus; T1: type 1; T2: type 2.
Note: Incident diabetes defined as absence of claims with a diagnosis as DM (ICD-9 code 250.xx) or claims for diabetes medication between 01/01/2006 and index date.

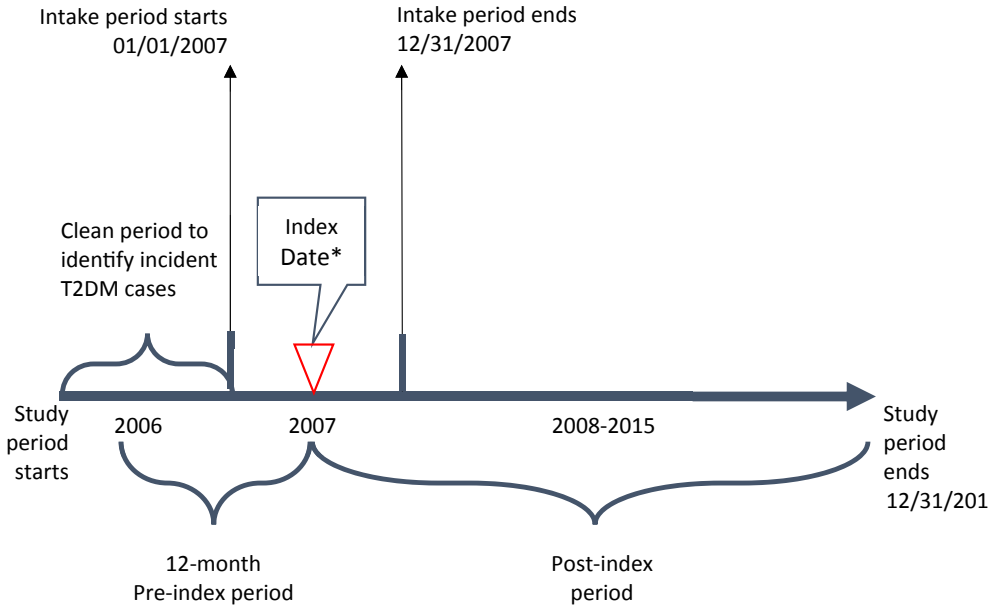

Figure S1. Study schema. Abbreviations: DM: diabetes mellitus; T2: type 2. *Index date defined as service date of first medical claim with a diagnosis for T2DM or pharmacy claim for antidiabetic medication between 1/1/2007 and 12/31/2007.