Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

Sandhya Mehta, PhD; Sabyasachi Ghosh, BPharm, MS; Stephen Sander, PharmD; Effie Kuti, PharmD; and William K. Mountford, PhD

ABSTRACT

BACKGROUND: Multiple studies have reported that type 2 diabetes mellitus (T2DM) is a major risk factor for cardiovascular diseases (CVD), and presence of T2DM and CVD increases risk of death. There is growing interest in examining the effects of antidiabetic treatments on the reduction of cardiovascular events in T2DM adults with a history of CVD and thus at higher risk of cardiovascular events.

OBJECTIVE: To estimate the incremental all-cause health care utilization and costs among adults with T2DM and a history of CVD compared with adults without a history of CVD, using a national linked electronic medical records (EMR) and claims database.

METHODS: Adults aged ≥ 18 years with evidence of at least 1 T2DM-related diagnosis code or antidiabetic medication (date of earliest occurrence was defined as the index date) in calendar year 2012 were identified. The population was divided into 2 cohorts (with and without a history of CVD) and followed until the end of their enrollment coverage, death, or 12 months, whichever came first. Multivariable generalized linear models were used to assess differences in health care utilization and per patient per month (PPPM) total costs (plan- and patient-paid amount for health care services) between the 2 groups during the post-index year, while adjusting for an a priori list of demographic and clinical characteristics.

RESULTS: A total of 138,018 adults with T2DM was identified, of which 16,547 (12%) had a history of CVD. The unadjusted resource utilization (outpatient: 27.5 vs. 17.8; emergency room [ER]: 0.8 vs. 0.4; inpatient: 0.4 vs. 0.2 days; and total unique drug prescriptions: 10.1 vs. 8.3) and PPPM total health care costs (\$2,655.1 vs. \$1,435.0) were significantly higher in T2DM adults with a history of CVD versus T2DM adults without a history of CVD. The adjusted models revealed that T2DM adults with a history of CVD had a 31% higher number of ER visits (rate ratio [RR]=1.31, 95% CI=1.25-1.37); 27% more inpatient visits (RR=1.27, 95% CI=1.21-1.34); 15% longer mean inpatient length of stay (RR=1.15, 95% CI=1.06-1.25); and 11% more outpatient visits (RR=1.11, 95% CI=1.09-1.13) compared with T2DM adults without a history of CVD. Furthermore, the difference in total PPPM health care cost was found to be 16% (\$200) higher in adults with a history of CVD (RR=1.16, 95% CI=1.13-1.19). PPPM costs associated with outpatient and ER visits were approximately 21% and 19% higher among adults with a history of CVD, respectively ($P<0.0001$), while costs for inpatient visits were similar between the 2 groups. In addition, a subgroup analysis revealed that adjusted differences in PPPM total cost was larger in the younger age group (56% higher cost in those aged <45 years) and diminished in the older age group (only 2% higher in those aged ≥ 65 years).

CONCLUSIONS: Study findings showed that resource utilization and costs remains significantly higher in T2DM patients with a history of CVD compared with patients without a history of CVD even after controlling for significant patient comorbid and demographic characteristics. Also, younger age groups had higher differences in outcomes compared with older age

groups. This study underscores the importance of cost-effective interventions that may reduce economic burden in this T2DM population with a history of CVD.

J Manag Care Spec Pharm. 2018;24(3):280-90

Copyright©2018, Academy of Managed Care Pharmacy. All rights reserved.

What is already known about this subject

- Patients with type 2 diabetes mellitus (T2DM) have a higher risk of a cardiovascular disease (CVD) event compared with patients with no history of T2DM or CVD.
- Medical claims contribute to the escalating economic burden of diabetes, with hospital inpatient care as the major driver.
- A study based on a single-payer database reported higher costs for adults with T2DM and comorbid CVD.

What this study adds

- Results from this real-world study indicated that the total all-cause health care costs per patient per month in T2DM patients with a history of CVD was 16% higher than T2DM patients without a history of CVD.
- Among adults with T2DM and a history of CVD, the health care cost disparity was larger in the younger age group (aged <45 years and 45-64 years) and diminished in the older age group (aged ≥ 65 years).
- Among different racial groups, the highest disparity was observed in blacks (33% higher cost in diabetes patients with a history of CVD compared with diabetes patients without a history of CVD) and lowest in Asians (5% higher costs in patients with a history of CVD).

Type 2 diabetes mellitus (T2DM) accounts for 90%-95% of all diabetes cases and is characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both.¹ According to 2012 estimates, 29.1 million people in the United States were diagnosed with diabetes, up 11% from 2010.² Furthermore, it was estimated that the overall prevalence will continue to grow, and that by 2050, 1 in 5 to 1 in 3 adults will have diabetes.³

T2DM is a major risk factor for cardiovascular disease (CVD), and the presence of both is a major cause of mortality.⁵⁻⁷ Approximately 70% of deaths in individuals with diabetes can be attributed to CVD, making it the leading cause of death in this patient population.⁸ Diabetes patients have a 1.8- to 6-fold increased risk of stroke and have a 2 to 4 times greater risk of mortality from CVD.⁹ Adults with T2DM also have a higher rate of certain comorbid conditions, such as hypertension and dyslipidemia, which further elevate the risk of CVD.^{10,11} Other behavioral risk factors for CVD, such as cigarette smoking and obesity, continue to act as independent contributors to CVD in diabetes patients.¹¹⁻¹⁵ In addition, evidence that lowering glucose with antidiabetic treatments reduces the rate of cardiovascular events and death is inconclusive,¹⁶ although modest cardiovascular benefits may be observed with prolonged treatment.¹⁷ Currently, there is a growing interest in establishing the cardiovascular safety benefits of glucose-lowering agents, with few medications recommended by recent American Diabetes Association guidelines to consider for adults with T2DM and established CVD to reduce the risk of mortality.¹⁸ In order to properly evaluate the cost-benefit of such interventions in preventing CVD events and costs, it is pertinent for decision makers to understand the effect of CVD on health care utilization and costs in adults with T2DM.

The prevalence of CVD in adults with T2DM and its incremental effect on subsequent health care utilization and cost is not well known. Previous studies have examined health care resource utilization or costs in adults with T2DM with multiple comorbid conditions, including CVD.¹⁹⁻²⁶ However, the majority of these studies compared patients with diabetes and CVD to patients without diabetes.²⁰⁻²⁵ Previous studies that have evaluated the cost differential associated with CVD among T2DM patients have done so using administrative data from single-payer settings.^{19,26} None of these studies have examined the differences in health care resource utilization driving those costs.

The purpose of this study was to estimate differences in all-cause costs and utilization in adults with T2DM with and without a history of CVD, using a large nationally representative sample and driving data from patient electronic medication records (EMR) with rich clinical information and their administrative claims from a multipayer setting. The estimated health care utilization and costs information may help policy-makers and other health care professionals to identify the most cost-effective interventions for better disease management and prevention of adverse outcomes in diabetes populations.

Methods

Data Source

This study used IQVIA's electronic medical records (Q-EMR) database, which is linked to administrative claims from the Truven Health MarketScan database. The linked databases provided the opportunity to use available components of the

EMR records, such as additional clinical history, in conjunction with claims data, which captures health care resource use and costs. The Q-EMR database is obtained from a national network of outpatient offices whose providers allow their deidentified patient-level data to be used for research. The MarketScan database contains health care claims for inpatient and outpatient services and outpatient prescription drugs for patients with commercial and Medicare supplemental insurance. The algorithm for linkage between the Q-EMR clinical data and the claims-based reimbursement data is provided elsewhere.²⁷

Study Design and Sample

A retrospective cohort study was conducted using the EMR-linked claims databases spanning calendar years 2011 through 2013. Adults aged ≥ 18 years with evidence of at least 1 T2DM-related *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code or antidiabetic medication prescription from January 1, 2012, through December 31, 2012, were identified, and the earliest occurrence of a claim related to T2DM was defined as the index date. To be included in the study, patients were required to have coverage in the administrative claims database for the 12-month pre-index time period, as well as at least 30 days of coverage after the index date. Adults with pregnancy or gestational diabetes (ICD-9-CM codes 648.0 and 648.8) or type 1 diabetes (ICD-9-CM code 250.x1 or 250.x3) during the 12-month pre- and post-index periods were excluded from the study.

Identified patients were further stratified into mutually exclusive cohorts based on their history of CVD (yes/no), which was assessed using ICD-9-CM diagnosis and procedure codes in any position in the EMR and claims databases during the 12-month pre-index period. Previous observational studies have used varied definitions of CVD, including a narrow or broad number of CV events, depending on the study.¹⁹⁻²⁶ This study defined CVD as the presence of a diagnosis of stroke, transient ischemic attack, myocardial infarction, unstable angina, or coronary revascularization, since these conditions have been identified as major complications of diabetes and are the leading causes of morbidity and mortality in the diabetes population.^{2,28,29} The presence of any of these events is likely to affect prospective risk of health care resource utilizations. The ICD-9-CM diagnosis and procedure codes used to identify individuals with a history of CVD are available from the authors upon request.

Study Measures

T2DM adults with and without CVD history were followed for a minimum of 30 days and a maximum of 12 months after the index date. They were followed until the earliest of the following: (a) end of continuous enrollment, (b) death, or (c) end of the 12-month period after the index date. A sensitivity analysis of all outcomes was also performed with

a fixed follow-up time period among all adults who had 12 months of continuous enrollment in the post-index period.

To examine overall economic burden, all-cause health care utilization was measured during the follow-up period using claims data only for all patients by service type, which included (a) outpatient visits, (b) emergency room (ER) visits, (c) inpatient hospital visits, (d) total length of stay for all inpatient visits, and (e) total number of filled prescriptions for unique drugs (i.e., same medication refilled multiple times was counted only once).

All-cause health care costs based on plan- and patient-paid amounts for medical and pharmacy claims were measured by service type during the follow-up period for all patients using claims data and included (a) outpatient visit costs, defined as the total per-patient-per-month (PPPM) cost related to all outpatient visits (any nonfacility care including office visit, laboratory, diagnostic services, home health, physical therapy, and hospice care); (b) ER visit costs, defined as the total PPPM cost related to all ER visits; (c) inpatient hospital visit costs, defined as the total PPPM cost related to all inpatient stays; (d) pharmacy costs, defined as the total PPPM prescription-related costs; and (e) total health care costs, defined as the summation of all outpatient, ER, inpatient, and pharmacy costs. The calculated costs represent total cost incurred by health plan payers and patient out-of-pocket costs. Health care cost was standardized to 2013 U.S. dollar value after adjusting for inflation using the Consumer Price Index for medical care, provided by the U.S. Bureau of Labor Statistics.³⁰

Statistical Analyses

The health care utilization and cost outcomes were summarized in a descriptive manner separately for each cohort. Statistically significant differences in mean values for each outcome were evaluated using two-sample t-tests. The differences in baseline characteristics (demographics, comorbidities, and concomitant medications) between the cohorts were also examined. Categorical variables were summarized using frequency and percentages, while continuous variables were summarized using means, standard deviations (SDs), and medians. The chi-square test was used for categorical variables, and two-sample t-tests were used for continuous variables to examine the differences between the cohorts.

Baseline characteristics included in this study were (a) *demographics* (age, gender, race, and insurance type); (b) *other comorbid conditions* (Charlson comorbidities [acquired immunodeficiency syndrome, malignancy, chronic pulmonary heart disease, cerebrovascular disease, congestive heart failure, dementia, metastatic solid tumor, hemiplegia or paraplegia, mild liver disease, moderate to severe liver disease, peptic ulcers, peripheral vascular disease, renal disease, rheumatologic disease³¹], hyperlipidemia, hypertriglyceridemia, hypertension, obesity, depressive disorders, alcohol

dependence/abuse, hyperthyroidism, cardiomyopathy, chronic obstructive pulmonary disease, asthma, other respiratory disorders, chronic kidney disease, arthritis, osteoporosis, open heart surgery, lower knee amputations, and skin problems); and (c) *use of concomitant medications* (angiotensin-converting-enzyme inhibitors, angiotensin-receptor blockers, aspirin, vasodilators, anti-arrhythmic agents, fibrates, statins, anti-obesity agents, antiplatelet agents, nonsteroidal anti-inflammatory drugs, antithrombotic agents, and immunomodulating drugs). The clinical characteristics were selected based on previous literature (identified as common comorbid conditions observed in the diabetes population), clinical recommendations, and availability in the database.³²⁻³⁴

Health care utilization data were analyzed using Poisson regression models with log link function to determine the expected health care service use difference between the 2 cohorts. PPPM was calculated for each patient and modeled to obtain differences in adjusted cost estimates between the cohorts. To model cost outcomes, generalized linear models with log-link function and gamma distribution were used. All multivariable regression models included demographics and clinical characteristics that were significant in the descriptive analysis, after examining for multicollinearity bias and small cell counts. In addition, the differences in utilization and costs estimates between the cohorts were examined among different demographic (age, gender, and race) subgroups, after adjusting for all other factors. All analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

There was a total of 246,753 individuals with evidence of T2DM in the database during 2012. After applying inclusion/exclusion criteria, 138,018 individuals with T2DM were included in the study (Appendix A, available in online article). Baseline continuous enrollment was a major driver for attrition during cohort selection. Of the total study population, 16,547 individuals (12.0%) had a history of CVD, and 121,471 individuals (88.0%) did not have a history of CVD based on baseline medical history derived from claims and EMR data.

Table 1 shows differences in baseline demographics and clinical characteristics between T2DM individuals with and without a history of CVD. The median length of follow-up in both cohorts was 12 months, and average length of follow-up was slightly higher in the group without CVD history (10.99 [SD±2.49] vs. 10.92 [SD±2.59]). The average age of individuals with T2DM who had a history of CVD was statistically significantly higher (67.0 [SD±11.8] years) than T2DM individuals who did not have a history of CVD (58.1 [SD±13.0] years). More than half of T2DM individuals with a history of CVD were male (55.7%), and less than half in the group without a history of CVD were male (46.8%). The majority of individuals were of white race/ethnicity in both cohorts (over

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

TABLE 1 Demographic and Baseline Clinical Characteristics of T2DM Adults with and Without CVD History

	With CVD History ^a		Without CVD History		P Value ^b
Characteristics	n = 16,547		n = 121,471		
Length of follow-up, months					
Mean (±SD)	10.92	(±2.59)	10.99	(±2.49)	0.0027 ^c
Median	12		12		
Follow-up groups, n (%)					
1 month	230	(1.39)	1,483	(1.22)	0.0004 ^c
2 months	255	(1.54)	1,816	(1.50)	
3 months	310	(1.87)	1,761	(1.45)	
4-6 months	724	(4.38)	5,151	(4.24)	
7-9 months	863	(5.22)	6,506	(5.36)	
10-12 months	14,165	(85.6)	104,754	(86.24)	
Age, years, mean (±SD)	67.0	(±11.8)	58.1	(±13.0)	<0.0001 ^c
Age groups, n (%)					
<45 years	432	(2.6)	16,707	(13.8)	<0.0001 ^c
45-64 years	7,147	(43.2)	73,045	(60.1)	
65+ years	8,968	(54.2)	31,719	(26.1)	
Gender, n (%)					
Male	9,211	(55.7)	56,783	(46.8)	<0.0001 ^c
Female	7,336	(44.3)	64,688	(53.3)	
Race, n (%)					
White	11,206	(67.7)	76,836	(63.3)	<0.0001 ^c
Black	1,156	(7.0)	12,155	(10.0)	
Hispanic	183	(1.1)	2,116	(1.7)	
Asian	164	(1.0)	1,948	(1.6)	
Other	137	(0.8)	1,457	(1.2)	
Unknown	3,701	(22.4)	26,959	(22.2)	
Region, n (%) ^d					
Northeast	6,174	(37.3)	41,849	(34.5)	<0.0001 ^c
South	6,227	(37.6)	47,963	(39.5)	
Midwest	2,615	(15.8)	18,696	(15.4)	
West	1,443	(8.7)	12,425	(10.2)	
Unknown	88	(0.5)	538	(0.4)	
Insurance, n (%)					
Commercial	3,485	(21.1)	41,021	(33.8)	<0.0001 ^c
Medicare	7,822	(47.3)	28,965	(23.9)	
Other	159	(1.0)	1,111	(0.9)	
Unknown	5,081	(30.7)	50,374	(41.5)	
Charlson comorbidities, n (%) ^e					
AIDS	23	(0.1)	211	(0.2)	0.3087
Any primary malignancy	2,291	(13.9)	10,727	(8.8)	<0.0001 ^c
Chronic pulmonary heart disease	4,527	(27.4)	17,663	(14.5)	<0.0001 ^c
Cerebrovascular disease	10,108	(61.1)	1,832	(1.5)	<0.0001 ^c
Congestive heart failure	3,734	(22.6)	5,882	(4.8)	<0.0001 ^c
Dementia	247	(1.5)	444	(0.4)	<0.0001 ^c
Metastatic solid tumor	266	(1.6)	1,155	(0.9)	<0.0001 ^c
Hemiplegia or paraplegia	423	(2.6)	343	(0.3)	<0.0001 ^c
Mild liver disease	1,118	(6.8)	6,721	(5.5)	<0.0001 ^c
Moderate or severe liver disease	97	(0.6)	444	(0.4)	<0.0001 ^c
Peptic ulcer disease	367	(2.2)	978	(0.8)	<0.0001 ^c
Peripheral vascular disease	4,174	(25.2)	6,664	(5.5)	<0.0001 ^c
Renal disease	2,543	(15.4)	7,426	(6.1)	<0.0001 ^c
Rheumatologic disease	771	(4.7)	3,430	(2.8)	<0.0001 ^c
Diabetes without chronic complications	15,447	(93.4)	106,905	(88.0)	<0.0001 ^c
Diabetes with chronic complications	3,418	(20.7)	15,587	(12.8)	<0.0001 ^c

continued on next page

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

TABLE 1 Demographic and Baseline Clinical Characteristics of T2DM Adults with and Without CVD History (continued)

	With CVD History ^a		Without CVD History		P Value ^b
Characteristics	n = 16,547		n = 121,471		
Charlson score					
Mean (±SD)	3.9	(±2.3)	1.9	(±1.7)	<0.0001 ^c
Median	3		1		
Interquartile range (p25-p75)	(2-5)		(1-3)		
Other comorbidities, n (%) ^c					
Hyperlipidemia	12,285	(74.2)	73,043	(60.1)	<0.0001 ^c
Hypertriglyceridemia	364	(2.2)	3,001	(2.5)	0.0341 ^c
Hypertension	14,057	(85.0)	78,321	(64.5)	<0.0001 ^c
Obesity	2,385	(14.4)	16,326	(13.4)	0.0006 ^c
Depressive disorders	2,404	(14.5)	14,449	(11.9)	<0.0001 ^c
Alcohol dependence/abuse	152	(0.9)	657	(0.5)	<0.0001 ^c
Hyperthyroidism	248	(1.5)	1,518	(1.3)	0.0075 ^c
Cardiomyopathy	1,315	(8.0)	2,293	(1.9)	<0.0001 ^c
COPD	3,288	(19.7)	10,133	(8.3)	<0.0001 ^c
Asthma	1,822	(11.0)	9,660	(8.0)	<0.0001 ^c
Other respiratory disorders	3,523	(21.3)	16,559	(13.6)	<0.0001 ^c
Chronic kidney disease	2,407	(14.6)	6,959	(5.7)	<0.0001 ^c
Arthritis	4,245	(25.7)	21,600	(17.8)	<0.0001 ^c
Osteoporosis	896	(5.4)	3,656	(3.0)	<0.0001 ^c
Open heart surgery	177	(1.1)	102	(0.1)	<0.0001 ^c
Lower knee amputations	5	(0.0)	22	(0.0)	0.2962
Skin problems	2,454	(14.8)	11,024	(9.1)	<0.0001 ^c
Prescriptions for concomitant therapies, ^c n (%)					
ACE inhibitors	5,838	(35.3)	35,805	(29.5)	<0.0001 ^c
ACE inhibitors combination	1,191	(7.2)	11,157	(9.2)	<0.0001 ^c
Angiotensin-receptor blockers	2,840	(17.2)	15,178	(12.5)	<0.0001 ^c
Angiotensin-receptor blockers combination	1,641	(9.9)	12,175	(10.0)	0.6707
Aspirin	510	(3.1)	1,970	(1.6)	<0.0001 ^c
Vasodilators	416	(2.5)	1,047	(0.9)	<0.0001 ^c
Vasodilators combination	12	(0.1)	24	(0.0)	<0.0001 ^c
Anti-arrhythmic agents	767	(4.6)	2,066	(1.7)	<0.0001 ^c
Fibrates	1,667	(10.1)	10,270	(8.5)	<0.0001 ^c
HMG-CoA reductase inhibitors (statins)	10,411	(62.9)	59,882	(49.3)	<0.0001 ^c
HMG-CoA reductase inhibitor (statin) combination	406	(2.5)	2,352	(1.9)	<0.0001 ^c
Anti-obesity agents	6	(0.0)	52	(0.0)	0.6998
Antiplatelet agents	4,539	(27.4)	4,750	(3.9)	<0.0001 ^c
Antiplatelet agent combination	252	(1.5)	223	(0.2)	<0.0001 ^c
Nonsteroidal anti-inflammatory drugs	3,271	(19.8)	27,620	(22.7)	<0.0001 ^c
Nonsteroidal anti-inflammatory drug combination	93	(0.6)	621	(0.5)	0.3928
Antithrombotytic agents	2,184	(13.2)	6,056	(5.0)	<0.0001 ^c
Immunomodulating drugs	232	(1.4)	1,223	(1.0)	<0.0001 ^c

Data source: Linked IQVIA EMR and Truven Health MarketScan databases.

^aCVD history is defined as evidence of myocardial infarction, nonfatal stroke, unstable angina, transient ischemic attack, or coronary revascularization procedures in pre-index period.

^bP values were obtained from chi-square tests for categorical variables and t-tests for continuous variables.

^cSignificant at P value ≤0.05.

^dNortheast=New England, Mid-Atlantic states; Midwest=East North Central, West North Central states; South=South Atlantic, East South Central, West South Central states; and West=Mountain, Pacific states.

^eComorbidities and concomitant medications observed in the 12-month pre-index period.

ACE=angiotensin-converting enzyme; AIDS=acquired immunodeficiency syndrome; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; EMR=electronic medical record; SD=standard deviation; T2DM=type 2 diabetes mellitus.

60%), and the highest percentage of individuals were from the South (39.3% overall).

The prevalence of comorbidities was significantly higher in T2DM individuals who had a history of CVD compared with the T2DM individuals who did not have a history of CVD. The average Charlson comorbidity score in the cohort with CVD history was almost double than that of the cohort without CVD history (3.9 [SD±2.3] vs. 1.9 [SD±1.7]). The most prevalent clinical conditions were hyperlipidemia (74.2% vs. 60.1% for individuals with and without CVD history, respectively) and hypertension (85.0% vs. 64.5%, respectively). The use of different concomitant medications in the pre-index period was also statistically significantly higher in T2DM adults with a history of CVD compared with T2DM adults without a history of CVD, with the exception of nonsteroidal anti-inflammatory drugs (19.8% vs. 22.7%).

Table 2 shows the unadjusted differences in health care utilization and costs between the cohorts during the follow-up period. T2DM individuals with a history of CVD had consistently higher outpatient visits, ER visits, inpatient visits, and total number of medications used in the follow-up period compared with T2DM adults without a history of CVD ($P<0.0001$). Mean days spent in the hospital was also higher in T2DM adults with a history of CVD ($P<0.0001$). The average total health care costs PPPM for individuals with a history of CVD was almost double than that of those without a history of CVD (\$2,655 [SD±\$5,757] vs. \$1,435 [SD±\$3,793], $P<0.0001$). In addition, the cost for total outpatient visits, ER visits, inpatient visits, and pharmacy were statistically significantly higher in the cohort with a history of CVD.

Table 3 also provides adjusted least square mean values for health care utilization and costs outcomes. The multivariable Poisson regression model, controlling for demographics and clinical characteristics (significant in unadjusted comparisons), revealed that individuals with a history of CVD had 31% more ER visits (rate ratio [RR]=1.31, 95% confidence interval [CI]=1.25-1.37); 27% more inpatient visits (RR=1.27, 95% CI=1.21-1.34); a 15% longer mean length of inpatient hospital stay (RR=1.15, 95% CI=1.06-1.25); and 11% more outpatient visits (RR=1.11, 95% CI=1.09-1.13). The total number of unique prescriptions was found to be higher in T2DM individuals without a history of CVD.

Least square means estimates from the multivariable generalized linear model with log-link function and gamma distribution revealed that total health care costs for T2DM individuals with CVD history was 16% higher, or an additional \$200 PPPM ($P<0.0001$; Table 3). The costs associated with outpatient visits and ER visits were approximately 21% and 19% higher in adults with a history of CVD, respectively ($P<0.0001$). The costs associated with medication use were found to be higher in adults without a history of CVD compared with adults with a history of CVD. No significant difference was observed in hospitalization cost between groups.

The examination of total health care costs for the 2 cohorts in certain subgroups, as depicted in Figure 1, shows that disparity was larger (56% higher cost in individuals with history of CVD who were aged <45 years) in the younger age group and diminished in the older age group (only 2% higher cost in individuals with a history of CVD who were aged ≥65 years compared with individuals without a history of CVD in the same age group). Among different racial groups, the highest disparity (difference between those with and without a history of CVD) was observed in blacks (33% higher cost in individuals with a history of CVD) and lowest in Asians (5% higher cost in individuals with a history of CVD). The difference was also observed to be higher in females than in males (19% vs. 11%).

Approximately 80% of the total population had 12 months of continuous enrollment. Sensitivity analysis performed on these patients, leveraging the fixed follow-up period, ensured that the results were less likely to be biased by variable length of follow-up between the 2 cohorts. Results from the sensitivity analysis are similar to that of the overall cohort (Appendix B, available in online article).

Discussion

CVD is a leading factor in the escalating mortality and economic burden related to diabetes.^{5,35} Previous studies have reported that the presence of macrovascular complications in diabetes patients is related to higher annual health care expenditures, of which CVD events account for the largest proportion of economic burden among patients with diabetes.^{36,37} Several studies have shown that cost and utilization are notably higher in patients with diabetes and CVD compared with patients without diabetes.¹⁹⁻²⁵ However, there is little or no data on the incremental effect of CVD on prospective all-cause health care resource utilization and costs in patients with T2DM.

This study used multipayer claims and EMR data that provided robust documentation of CVD history among adults with T2DM and its effect on T2DM-related economic burden. Consistent with previous literature, T2DM adults with a history of CVD were observed to be older by almost a decade than those without CVD history.¹⁸ In addition, a significantly larger disparity in resource use was observed in the younger age group and seemed to diminish with an increase in age. Future studies should investigate this association in more detail to ascertain whether the higher cost incurred at an early age is associated with reduction or delayed onset of subsequent cardiovascular outcomes.

The comorbidity burden and concomitant medication use during the pre-index period was observed to be significantly higher in individuals with CVD history compared with individuals without CVD history. After controlling for these factors, T2DM adults with CVD history had 31% and 27% more ER and inpatient visits, respectively ($P<0.0001$); 15% longer mean inpatient hospital stay ($P<0.0007$); and 11% more

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

TABLE 2 Health Care Utilization and Cost Outcomes in T2DM Adults with and Without CVD History

	With CVD History ^a		Without CVD History		P Value ^b
Health Care Utilization	n= 16,547		n = 121,471		
Outpatient visits ^c					
Mean (±SD)	27.5	(±25.0)	17.8	(±18.6)	<0.0001 ^d
Median	21.0		12.0		
Interquartile range (p25-p75)	(11-36)		(6-23)		
ER visits ^e					
Mean (±SD)	0.8	(±1.9)	0.4	(±1.2)	<0.0001 ^d
Median	0		0		
Interquartile range (p25-p75)	(0-1)		(0-0)		
Inpatient hospital visits ^f					
Mean (±SD)	0.4	(± 0.8)	0.2	(±0.5)	<0.0001 ^d
Median	0		0		
Interquartile range (p25-p75)	(0-1)		(0-0)		
Inpatient hospital length of stay (days) ^g					
Mean (±SD)	7.8	(±13.6)	6.4	(±10.6)	<0.0001 ^d
Median	4		3		
Interquartile range (p25-p75)	(2-8)		(2-7)		
Pharmacy (total no. of unique medications) ^h					
Mean (±SD)	10.1	(±8.3)	8.3	(±7.0)	<0.0001 ^d
Median	10		8		
Interquartile range (p25-p75)	(1-15)		(2-12)		
Outpatient visit costs, \$ ⁱ					
Mean (±SD)	1,332.27	(±3,003.86)	742.42	(±2,102.59)	<0.0001 ^d
Median	551.49		269.32		
Interquartile range (p25-p75)	(232.41-1,282.73)		(100.05-690.96)		
ER visit costs, \$ ^j					
Mean (±SD)	62.61	±269.50	30.92	±148.13	<0.0001 ^d
Median	0.00		0.00		
Interquartile range (p25-p75)	(0.00-39.91)		(0.00-0.00)		
Inpatient hospital visit costs, \$ ^k					
Mean (±SD)	921.78	(±4,213.39)	401.22	(±2,595.59)	<0.0001 ^d
Median	0.00		0.00		
Interquartile range (p25-p75)	(0.00-283.49)		(0.00-0.00)		
Pharmacy costs, \$ ^l					
Mean (±SD)	338.47	(±634.61)	260.38	(±534.18)	<0.0001 ^d
Median	187.76		109.51		
Interquartile range (p25-p75)	(0.00-444.78)		(5.01-330.87)		
Total health care costs, \$ ^m					
Mean (±SD)	2,655.09	(±5,757.30)	1,435.02	(±3,792.94)	<0.0001 ^d
Median	1,067.25		544.92		
Interquartile range (p25-p75)	(473.68-2,608.75)		(220.41-1,285.30)		

Data source: Linked IQVIA EMR and Truven Health MarketScan databases.

^aCVD history is defined as evidence of myocardial infarction, nonfatal stroke, unstable angina, transient ischemic attack, or coronary revascularization procedures in the pre-index period.

^bP values were obtained from chi-square tests for categorical variables and t-tests for continuous variables.

^cOutpatient visits are defined as the total number of outpatient visits during maximum of 12 months of follow-up after index date.

^dSignificant at P≤0.05.

^eER visits are defined as the total number of ER visits during maximum of 12 months of follow-up after index date.

^fInpatient hospital visits are defined as the total number of inpatient hospital visits during maximum of 12 months of follow-up after index date.

^gTotal inpatient stay is defined as the summation of all inpatient hospital visits length of stay during maximum of 12 months of follow-up after index date.

^hPharmacy is defined as the total number of unique drug prescriptions taken during maximum of 12 months of follow-up after index date.

ⁱCosts of outpatient visits are defined as total PPPM cost related to all outpatient visits during maximum of 12 months of follow-up after index date.

^jCosts ER visits are defined as total PPPM cost related to all ER visits during maximum of 12 months of follow-up after index date.

^kCosts of inpatient hospital visits are defined as total PPPM cost related to all inpatient stays during maximum of 12 months of follow-up after index date.

^lPharmacy costs are defined as total PPPM prescription-related cost during maximum of 12 months of follow-up after index date.

^mTotal health care cost is defined as the summation of all outpatient, ER, inpatient, and pharmacy PPPM costs during maximum of 12 months of follow-up after index date.

CVD=cardiovascular disease; EMR=electronic medical record; ER=emergency room; PPPM=per patient per month; SD=standard deviation; T2DM=type 2 diabetes mellitus.

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

TABLE 3 Health Care Utilization and Cost Summary: Adjusted Rate Ratios and Means in T2DM Adults with and Without CVD History^a

	With CVD History (n = 16,547)	Without CVD History (n = 121,471)			
Health Care Services	LS Means ^b	LS Means ^b	Rate Ratio	95% CI	P Value
Health care utilization					
Outpatient visits	23.60	21.27	1.11	1.09-1.13	<0.0001 ^c
ER visits	0.59	0.45	1.31	1.25-1.37	<0.0001 ^c
Inpatient hospital visits	0.19	0.15	1.27	1.21-1.34	<0.0001 ^c
Inpatient hospital length of stay (days)	0.75	0.65	1.15	1.06-1.25	0.0007 ^c
Pharmacy (total no. of unique prescriptions)	6.95	7.13	0.97	0.96-0.99	0.0021 ^c
Health care costs (PPPM), \$					
Total health care	1,419.97	1,222.63	1.16	1.13-1.19	<0.0001 ^c
Outpatient visits	760.85	630.92	1.21	1.17-1.24	<0.0001 ^c
ER visits	187.56	157.65	1.19	1.14-1.24	<0.0001 ^c
Inpatient hospital visits	3,174.96	3,203.81	0.99	0.94-1.04	0.7142
Pharmacy	270.61	282.06	0.96	0.93-0.99	0.0052 ^c

Data source: Linked IQVIA EMR and Truven Health MarketScan databases.

^aCVD history is defined as evidence of myocardial infarction, nonfatal stroke, unstable angina, transient ischemic attack, or coronary revascularization procedures in pre-index period.

^bLSMeans=least square means was calculated for main independent variable (T2DM adults with and without CVD history) after adjusting for all covariates in the model (statistically significant in bivariate association as shown in Table 1).

^cSignificant at $P < 0.05$.

CVD = cardiovascular disease; CI = confidence interval; EMR = electronic medical record; PPPM = per patient per month; T2DM = type 2 diabetes mellitus.

outpatient visits ($P < 0.0001$) than T2DM adults without CVD history. Subsequently, a 16% higher total health care cost was observed in T2DM adults with CVD history (\$1,419.97 PPPM vs. \$1,222.63 PPPM, $P < 0.001$). A consistently higher total health care cost was also observed when looking at certain subgroups of patients, after adjusting for important confounding variables that included clinical conditions such as hyperlipidemia, hypertension, obesity, cerebrovascular disease, and concomitant medications use of antihypertensives, statins, and other factors.

A study examining the effect of cardiovascular comorbidity on total health care costs using 2001-2002 West Virginia Medicaid data for T2DM adults showed significantly higher all-cause total health care costs, as well as ER and outpatient costs, compared with T2DM adults without this comorbidity.²⁶ Total health care costs for patients with a CVD comorbidity were found to be 38.9% higher (\$12,550 vs. \$9,031 annual cost, $P < 0.05$), after controlling for demographics and other clinical conditions (presence of hypertension/hyperlipidemia, cerebrovascular conditions, peripheral vascular conditions, and number of other comorbid conditions). Another study, conducted with 16,180 health maintenance organization patients after controlling for age and gender, estimated that all-cause total health care costs were \$4,402 per person per year (\$367 PPPM) among diabetes patients without CVD and \$10,172 (\$848 PPPM) among diabetes patients with CVD in 1999 dollars

(defined as presence of chronic ischemic heart disease, unstable angina, acute myocardial infarction, old myocardial infarction, angina pectoris, heart failure, bypass and angioplasty procedures, cardiac arrhythmias, Stokes-Adams attack, acute myocarditis, other diseases of pericardium, other diseases of an endocardium, cardiomyopathy, or ill-defined descriptions and complications of heart disease).¹⁹

Using a national representative sample, our study found that total all-cause health care costs were approximately \$200 (16%, $P < 0.001$) higher for T2DM adults with CVD history than for T2DM adults without CVD history after adjusting for demographics and other clinical conditions. Compared with previous studies, the lower difference in adjusted total health care costs observed in this study can be attributed to differences in sample selection criteria, definition of CVD history, the population examined, and adjustment of important confounding factors, such as prescriptions for reduction of CVD risk factors that included hypertension and hyperlipidemia. In addition, this study accessed clinical information of the study population from EMR and claims data. Therefore, this study potentially reduced the misclassification of individual CVD history, providing a more robust estimate of incremental resource use and costs.

In this study, the CVD cohort was associated with slightly lower rates of total number of unique prescriptions filled ($RR = 0.97$, 95% $CI = 0.96-0.99$) and pharmacy cost ($RR = 0.96$,

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

FIGURE 1 Average Adjusted PPM Total Health Care Costs in T2DM Adults with and Without CVD History by Demographic Subgroups

Note: Δ% = percentage increase in PPM total health care costs for patients with CVD history compared with patients without CVD history.

^aDifferences within subgroups are statistically significant at $P < 0.05$.

CVD = cardiovascular disease; EMR = electronic medical record; PPM = per patient per month; T2DM = type 2 diabetes mellitus.

95% CI=0.93-0.99). Sensitivity analysis showed that the CVD cohort with 12-month continuous enrollment also had slightly lower rates of prescriptions filled and pharmacy cost. This result had minimal effect size but was statistically significant, warranting further investigation to confirm the findings and understand the factors that resulted in higher medical but lower pharmacy costs in T2DM patients with CVD history. Our model controlled for the effect of highly prevalent comorbid conditions, such as hypertension/hyperlipidemia, as well concomitant baseline use of other medications, such as antihypertensives/antihyperlipidemics, which may have led to underestimation of the CVD effect on prescription use and costs. Another previous study also observed that CVD comorbidity was not a significant predictor of diabetes-related prescription costs.²⁶ Several clinical trials and retrospective studies have demonstrated that intensified intervention involving antidiabetic drugs and treatments to control for comorbid hypertension and hyperlipidemia reduces risk of CVD and related resource use in the long term.^{38,39}

The costs associated with outpatient and ER visits were approximately 21%-19% higher in the CVD history group, respectively ($P < 0.0001$). Although limited to the West Virginia Medicaid population, a previous study observed

significantly higher probability of outpatient and ER visits costs.^{19,26} Therefore, the observed higher costs and service use for T2DM patients with CVD history likely reflects the combination of a higher incidence of subsequent cardiovascular events and other complications observed in this population compared with patients without CVD history.

Current novel antihyperglycemic treatments are tested in distinct clinical trials to evaluate their cardioprotective effects, and with favorable results, providers might have options to better manage T2DM adults with CVD history. Nonetheless, recent guidelines from the American Diabetes Association recommend the consideration of few oral antihyperglycemic medications in T2DM adults with CVD history to prevent risk of mortality in these population.¹⁸ Given the growing importance of such interventions, our study findings may provide relevant data to assess their cost-benefit in larger populations specifically aimed at delaying or preventing diabetes-related CVD complications.

Limitations

This study has limitations that should be considered. There may be data coding errors and errors in patient records because of the use of standardized coding systems for identification of diseases, procedures, and medications. There also may have

been a confounding effect on the estimates, since claims data do not capture information regarding socioeconomic status and lab values. It may be possible that some patients with CVD history who had no records in the year before diagnosis of T2DM were categorized in the cohort without CVD history, leading to misclassification bias and the underestimation of the prevalence of CVD among T2DM patients.

This study did not include all conditions from the atherosclerotic cardiovascular disease definition that is in the guidelines from the American College of Cardiology/American Heart Association, which may have led to misclassification of CVD compared with these guidelines. There may be patients who had interactions with health care providers outside of the EMR network or used another payment method not captured in the claims database. It is possible that some statistically significant differences may not be clinically relevant and may be related to the large sample size, which is common in a large retrospective cohort study.

This study measured all-cause utilization and costs outcomes as opposed to disease-specific outcomes, so the estimated effect of costs and utilization specific to CVD may be inflated. However, our utilization outcomes are aligned with current literature that is based on research using administrative claims data, and we did control for significant comorbid conditions in the multivariable models.

Despite these limitations, this study was based on a rigorous design and included a robust sample of patients with known CVD status leveraging EMR and claims data. The results can be generalizable to a wider diabetes population, since the findings are derived from a large sample, and several patient characteristics were controlled for in the multivariable regression models. Although a conservative definition was used to identify patients with a history of CVD, a statistically significant difference was observed in costs and utilization of health care resources between the groups with and without a history of CVD. This study also draws strength from using regression modeling while adjusting for known covariates in order to assess the association between CVD history status and health care costs.

Conclusions

The findings of this study highlight the association between CVD and all-cause health care resource utilization and costs among adults with T2DM. CVD also disproportionately affects overall utilization and costs in younger adults with T2DM. Given the increasing prevalence of adults with T2DM, this study underscores the importance of cost-effective interventions that may reduce economic burden among patients with diabetes.

Authors

SANDHYA MEHTA, PhD, and WILLIAM K. MOUNTFORD, PhD, IQVIA, Cambridge, Massachusetts. SABYASACHI GHOSH, BPharm, MS; STEPHEN SANDER, PharmD; and EFFIE KUTI, PharmD, Boehringer Ingelheim, Ridgefield, Connecticut.

AUTHOR CORRESPONDENCE: William K. Mountford, PhD, Director of Epidemiology, Allergan, 602 Arjean Dr., Wilmington, NC 28411. Tel.: 910.232.9942; E-mail: Kenne.Mountford@Allergan.com.

DISCLOSURES

This study was funded by Boehringer Ingelheim. At the time of this study, Mehta and Mountford were employed by IQVIA, which received funding from Boehringer Ingelheim to conduct this study. Mountford is employed by Allergan, which has no connection with this study. Ghosh, Sander, and Kuti are employed by Boehringer Ingelheim.

Study concept and design were contributed by Mountford, Mehta, and Ghosh, along with Sander and Kuti. Mountford and Mehta collected the data, and data interpretation was performed by all the authors. The manuscript was written by Sander and Kuti, along with the other authors, and revised by Mehta and Ghosh, along with the other authors.

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2012;35(Suppl 1):S64-S71. Available at: http://care.diabetesjournals.org/content/35/Supplement_1/S64.full.pdf+html. Accessed January 31, 2018.
2. American Diabetes Association. Statistics about diabetes. 2014. Available at: <http://www.diabetes.org/diabetes-basics/statistics/>. Accessed January 31, 2018.
3. Boyle JP, Thompson TJ, Gregg EW, Barker LE, Williamson DF. Projection of the year 2050 burden of diabetes in the US adult population: dynamic modeling of incidence, mortality, and prediabetes prevalence. *Popul Health Metr*. 2010;8:29.
4. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care*. 2013;36(4):1033-46.
5. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet*. 2010;375(9733):2215-22.
6. Beckman JA, Creager MA, Libby P. Diabetes and atherosclerosis: epidemiology, pathophysiology, and management. *JAMA*. 2002;287(19):2570-81.
7. Di Angelantonio E, Kaptoge S, Wormser D, et al. Association of Cardiometabolic multimorbidity with mortality. *JAMA*. 2015;314(1):52-60.
8. Bennett KE, Williams D, Feely J. Under-prescribing of cardiovascular therapies for diabetes in primary care. *Eur J Clin Pharmacol*. 2003;58(12):835-41.
9. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics-2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292.
10. Sowers JR, Epstein M, Frohlich ED. Diabetes, hypertension, and cardiovascular disease: an update. *Hypertension*. 2001;37(4):1053-59.
11. Grundy SM, Benjamin IJ, Burke GL, et al. Diabetes and cardiovascular disease: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1999;100(10):1134-46.
12. Eckel RH. Obesity and heart disease: a statement for healthcare professionals from the Nutrition Committee, American Heart Association. *Circulation*. 1997;96(9):3248-50.

Differences in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

13. Harris MI. Epidemiological correlates of NIDDM in Hispanics, whites, and blacks in the U.S. population. *Diabetes Care*. 1991;14(7):639-48.
14. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2009;32(1):193-203.
15. Zinman B, Inzucchi SE, Lachin JM, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOME). *Cardiovasc Diabetol*. 2014;13:102.
16. Cobble ME, Frederich R. Saxagliptin for the treatment of type 2 diabetes mellitus: assessing cardiovascular data. *Cardiovasc Diabetol*. 2012;11:6.
17. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *New Engl J Med*. 2008;359(15):1577-89.
18. Standards of medical care in diabetes—2017: summary of revisions. *Diabetes Care*. 2017;40(Suppl 1):S4-5.
19. Nichols GA, Brown JB. The impact of cardiovascular disease on medical care costs in subjects with and without type 2 diabetes. *Diabetes Care*. 2002;25(3):482-86.
20. Ariza MA, Vimalananda VG, Rosenzweig JL. The economic consequences of diabetes and cardiovascular disease in the United States. *Rev Endocr Metab Disord*. 2010;11(1):1-10.
21. Glauber H, Brown J. Impact of cardiovascular disease on health care utilization in a defined diabetic population. *J Clin Epidemiol*. 1994;47(10):1133-42.
22. Garis RI, Shara MA, Farmer KC, Horrell JF, Arora M. The cost of diabetes in the presence of comorbid conditions. *Manag Care Interface*. 2002;15(4):48-53, 55.
23. Ramsey SD, Newton K, Blough D, McCulloch DK, Sandhu N, Wagner EH. Patient-level estimates of the cost of complications in diabetes in a managed-care population. *Pharmacoeconomics*. 1999;16(3):285-95.
24. Simpson SH, Corabian P, Jacobs P, Johnson JA. The cost of major comorbidity in people with diabetes mellitus. *CMAJ*. 2003;168(13):1661-67.
25. Williams R, Van Gaal L, Lucioni C. Assessing the impact of complications on the costs of Type II diabetes. *Diabetologia*. 2002;45(7):S13-17.
26. Mody R, Kalsekar I, Kavookjian J, Iyer S, Rajagopalan R, Pawar V. Economic impact of cardiovascular co-morbidity in patients with type 2 diabetes. *J Diabetes Complications*. 2007;21(2):75-83.
27. Huse DM. Expanding the evidence base in outcomes research: linking electronic medical records and claims data. A case study examining risk factors and costs of uncontrolled hypertension. Presented at: ISPOR 18th Annual International Meeting; May 18-22, 2013; New Orleans, LA. Available at: <https://www.ispor.org/meetings/neworleans0513/releasedpresentations/W26-Durden.pdf>. Accessed January 31, 2018.
28. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2016 update: a report from the American Heart Association. *Circulation*. 2016;133(4):e38-360.
29. Yat Wa L, Wilbert SA. Diabetes mellitus and cardiovascular disease. *J Clin Experiment Cardiol*. 2011;2(1):114. Available at: <https://www.omicsonline.org/diabetes-mellitus-and-cardiovascular-disease-2155-9880.1000114.pdf>. Accessed January 31, 2018.
30. U.S. Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Available at: <http://www.bls.gov/cpi>. Accessed January 31, 2018.
31. Quan H, Li B, Couris CM, et al. Updating and validating the Charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. *Am J Epidemiol*. 2011;173(6):676-82.
32. Piette JD, Kerr EA. The impact of comorbid chronic conditions on diabetes care. *Diabetes Care*. 2006;29(3):725-31.
33. Slater M, Perruccio AV, Badley EM. Musculoskeletal comorbidities in cardiovascular disease, diabetes and respiratory disease: the impact on activity limitations; a representative population-based study. *BMC Public Health*. 2011;11:77.
34. American Association of Clinical Endocrinologists, Diabetes Resource Center. Management of common comorbidities of diabetes. Available at: <http://outpatient.aace.com/type-2-diabetes/management-of-common-comorbidities-of-diabetes>. Accessed January 31, 2018.
35. Hogan P, Dall T, Nikolov P. Economic costs of diabetes in the U.S. in 2002. *Diabetes Care*. 2003;26(3):917-28.
36. Fu AZ, Qiu Y, Radican L, Wells BJ. Health care and productivity costs associated with diabetic patients with macrovascular comorbid conditions. *Diabetes Care*. 2009;32(12):2187-92.
37. O'Brien JA, Shomphe LA, Kavanagh PL, Raggio G, Caro JJ. Direct medical costs of complications resulting from type 2 diabetes in the U.S. *Diabetes Care*. 1998;21(7):1122-28.
38. Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. *New Engl J Med*. 2003;348(5):383-93.
39. Luft VC, Giugliani C, Harzheim E, Schmidt MI, Duncan BB. Prevalence of use and potential impact of increased use of primary care interventions to prevent cardiovascular hospitalizations in patients with diabetes. *Diabetes Res Clin Pract*. 2009;85(3):328-34.
40. Frazee T, Jiang J, Burgess J. Hospital stays for patients with diabetes, 2008. Statistical Brief #93. Healthcare Cost and Utilization Project (HCUP). August 2010. Available at: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb93.pdf>. Accessed January 31, 2018.
41. Udell JA, Cavender MA, Bhatt DL, Chatterjee S, Farkouh ME, Scirica BM. Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials. *Lancet Diabetes Endocrinol*. 2015;3(5):356-66.

Difference in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

APPENDIX A Patient Attrition Table

CVD = cardiovascular disease; T2DM = type 2 diabetes mellitus.

Difference in All-Cause Health Care Utilization and Costs in a Type 2 Diabetes Mellitus Population with and Without a History of Cardiovascular Disease

APPENDIX B Health Care Utilization and Cost Summary: Adjusted Rate Ratios and Means in T2DM Adults with and Without CVD History^a

	With CVD History (n = 13,073)	Without CVD History (n = 96,408)			
Health Care Services	LS Means ^b	LS Means ^b	Rate Ratio	95% CI	P Value
Health care utilization					
Outpatient visits	20.54	18.52	1.11	1.09-1.13	<0.0001 ^c
ER visits	0.65	0.49	1.33	1.27-1.40	<0.0001 ^c
Inpatient hospital visits	0.21	0.16	1.31	1.24-1.39	<0.0001 ^c
Inpatient hospital length of stay (days)	0.85	0.68	1.25	1.14-1.37	<0.0001 ^c
Total prescriptions	7.84	7.92	0.99	0.97-1.01	0.1972
Health care costs, \$					
Total health care	1,438.30	1,200.94	1.20	1.16-1.23	<0.0001 ^c
Outpatient visits	722.00	606.44	1.19	1.16-1.23	<0.0001 ^c
ER visits	168.98	144.58	1.17	1.12-1.22	<0.0001 ^c
Inpatient hospital visits	2,862.00	2,710.02	1.06	1.00-1.11	0.0392 ^c
Pharmacy	272.44	282.54	0.96	0.93-0.99	0.0225 ^c

Data source: Linked IQVIA EMR and Truven Health MarketScan databases.

^aAdults with 12 months of continuous enrollment.

^bLSMeans=least square means was calculated for main independent variable (T2DM adults with and without CVD history) after adjusting for all covariates in the model (statistically significant in bivariate association).

^cSignificant at P<0.05.

CVD=cardiovascular disease; CI=confidence interval; EMR=electronic medical record; ER=emergency room; T2DM=type 2 diabetes mellitus.