

The Incidence and Costs of Hypoglycemia in Type 2 Diabetes

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Hypoglycemia can occur during therapy with antidiabetic drug agents and has the potential to lead to serious complications, including morbidity and mortality. While these agents are effective in treating hyperglycemia, optimal glycemic control can be more difficult to attain. The risk of hypoglycemia remains a serious adverse effect of diabetic pharmacotherapy and a potential limit to aggressive treatment.

While hypoglycemia has been well-researched in patients with type 1 diabetes, previous studies in persons with type 2 diabetes have focused on populations with limited demographics,¹⁻³ persons using insulin in type 2 diabetes,⁴ or specific oral medications,⁵ or were conducted outside of the United States.⁶ Furthermore, the incidence of hypoglycemia is often measured in clinical trials and may not approximate true rates in more real-world populations. Published incidence rates (IRs) of hypoglycemia in type 2 diabetes vary from 0.02 to 0.35 events/patient/year, but differences in study design, sample populations, and definitions of hypoglycemia make direct comparisons between studies problematic.⁷

Research indicates that hypoglycemia places an economic burden on healthcare payers, but estimates of the magnitude of that burden differ considerably. While several non-US-based cost studies of hypoglycemia have been published, broad differences in payer systems make these analyses less generalizable to the US healthcare system.⁸⁻¹² Over the past 10 years, several US studies have evaluated the medical costs of hypoglycemia.¹³⁻¹⁵ Curkendall et al evaluated costs associated with development of hypoglycemia during an inpatient hospital stay,¹³ while Rhoads et al evaluated the costs of hypoglycemia in patients taking insulin.¹⁴ An additional study by Pelletier and colleagues¹⁵ assessed allowed health plan costs in a large sample of patients with type 2 diabetes who experienced at least 1 diabetes-related medical complication during the study. Within this study, 0.2% of the population had a hypoglycemic event in the first year, with a mean annual allowed charge for hypoglycemia of \$345 (2007 US dollars). While several studies have assessed costs associated with hypoglycemia, none have comprehensively evaluated these costs in a population of patients with type 2 diabetes taking oral antidiabetic drugs (OADs).

While 1 in 10 US adults currently have diabetes, the Centers for Disease Control and Prevention estimate that 1 in 3 adults will have the disease by 2050.¹⁶ The management of diabetes complications such as hypoglycemia and resulting costs to the healthcare system will be of greater

Objectives: To estimate the rate and costs of hypoglycemia in patients with type 2 diabetes.

Study Design: We used a retrospective cohort design to assess the rate and costs of hypoglycemia among working-age patients with type 2 diabetes in the 2004 to 2008 MarketScan database.

Methods: We followed patients from cohort entry to the first instance of hypoglycemia requiring medical intervention (inpatient, emergency department [ED], or outpatient) and calculated incidence rates (IRs), stratifying these estimates by age (18-34, 35-49, 50-64, and 65+ years) and gender. We calculated inflation-adjusted total and mean direct costs of medical visits for hypoglycemia, other diabetes-related visits, and all other medical visits.

Results: The cohort was composed of 536,581 members with approximately 1.21 million person-years (p-yrs) of follow-up. The IR of hypoglycemic events leading to an inpatient admission, ED, or outpatient visit was 153.8/10,000 p-yrs. The IRs of hypoglycemic events were highest in adults aged 18 to 34 years (218.8/10,000 p-yrs). Regardless of age group, rates of hypoglycemia were greater in women than in men ($P < .001$). Total hypoglycemia costs were \$52,223,675 over the study period and accounted for 1.0% of all inpatient costs, 2.7% of ED costs, and 0.3% of outpatient costs. The mean costs for hypoglycemia visits were \$17,564 for an inpatient admission, \$1387 for an ED visit, and \$394 for an outpatient visit.

Conclusions: The overall incidence of visits for hypoglycemia was considerable in this large database, and was associated with high per-episode costs. Continued vigilance and the development of strategies to decrease potentially avoidable hypoglycemic episodes requiring medical intervention are needed.

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Take-Away Points

Our analyses evaluate the incidence and costs of hypoglycemia in a large working-age population with type 2 diabetes.

- The incidence of hypoglycemia in this population was highest in the youngest (18-34 years) cohort members.
- The incidence of hypoglycemia was higher in females than in males across all age groups.
- Inpatient admissions accounted for only 4% of all medical encounters for hypoglycemia, but approximately 60% of all direct medical costs for hypoglycemia.

continuous eligibility beyond the initial 12 months of eligibility used for sample identification. The last day of the month preceding the first gap in coverage served as the end of follow-up for each member. We characterized the study population by describing the demographics and estimated the prevalence of antidiabetic medication use, and micro- and macrovascular complications of diabetes. To identify medications taken within 90

concern in upcoming years, and comprehensive analyses are needed to measure hypoglycemia in the US population. Our objectives in this study were: 1) to estimate the incidence of hypoglycemia in a large sample of working-age patients with type 2 diabetes; and 2) to estimate the corresponding direct medical costs of hypoglycemia.

days of cohort entry, we evaluated pharmacy claims for prescription fills of oral and injectable antidiabetic agents. To estimate the baseline prevalence of diabetes-related complications, we used methods employed in other studies,¹⁹ and assessed inpatient and outpatient medical claims within 90 days of cohort entry.

RESEARCH DESIGN AND METHODS

Data Source

The data source was the Medstat MarketScan database, including pharmacy and medical (inpatient and outpatient) claims data for the years 2004 to 2008. The Medstat MarketScan database comprises more than 4 billion patient records, 69 million covered lives, 77 contributing employers, and 12 contributing health plans.¹⁷ The Medstat MarketScan database compiles claims from work-based insurance plans including data from currently enrolled employees, early retirees, former employees covered by COBRA, and their dependents.¹⁸ Unlike many healthcare databases, the MarketScan database provides a near-complete capture of a member's healthcare as it contains information on inpatient and outpatient medical visits, pharmacy claims, and carved-out services.¹⁸

Study Population

We conducted a retrospective cohort study of patients with type 2 diabetes and identified all persons with 2 or more inpatient and/or outpatient claims for diabetes (*International Classification of Diseases [ICD]-9 250.XX*) during the study period. As hypoglycemia may be the result of diabetes medications, we excluded from this eligible sample persons who were not taking at least 1 OAD. We further excluded participants who did not have at least 12 months of continuous eligibility within a non-capitated health plan following the first fill date of an OAD. Finally, we excluded persons with at least 1 medical claim (inpatient or outpatient) for type 1 (*ICD-9 250.X1* or *250.X3*) or gestational diabetes (*648.0X*) during the study period.

For each cohort member, we initiated follow-up on the first date of fill for an OAD agent and identified the first lapse in

Hypoglycemic Event Characterization

We followed all cohort patients from their respective index dates to the end of their follow-up to identify instances of hypoglycemia requiring medical intervention (inpatient, emergency department [ED], and/or outpatient). To identify hypoglycemic episodes, we used the algorithm proposed by Ginde and colleagues.²⁰ We identified the inpatient and outpatient claims for hypoglycemia using *ICD-9* codes: 251.0, 251.1, 251.2, 270.3, and 962.3. In addition, we identified claims for *ICD-9* code 250.8 in the absence of other contributing diagnoses (*ICD-9 259.8, 272.7, 681.XX, 682.XX, 686.9X, 707.1-707.9, 709.3, 730.0-730.2, or 731.8*). Our primary end point was the first medical encounter for hypoglycemia (inpatient, emergency department, or outpatient). We repeated similar procedures to look at the incidence for each of the 3 settings separately: the first inpatient admission, the first ED visit, or the first outpatient visit.

Cost Analyses Estimation

To estimate the direct medical costs associated with hypoglycemic events, we used the total gross payment to all providers associated with an admission in the inpatient claims database and the total gross payment to a provider for a specific service in the outpatient claims database. The cost estimates included all payments made to the provider by the patient including copayments, coinsurance, and deductibles. In addition to overall measures of cost, we calculated costs for 3 mutually exclusive groups of claims for all cohort members: 1) those related to hypoglycemia (identified using the Ginde algorithm²⁰); 2) other diabetes-related claims (primary *ICD-9 250.XX*); and 3) all other claims. To capture episodes of care in the outpatient and ED settings, we summed costs associated

with claims on the same service date as 1 episode of care. The MarketScan data already provide summary costs associated with a particular inpatient admission within the database.¹⁸ In instances where ED visits resulted in inpatient hospitalization, the collective costs for both the ED visit and the resulting inpatient hospitalization were captured within the inpatient hospitalization. All cost variables from inpatient, ED, and outpatient claims were inflated to 2008 equivalents using the regional Consumer Price Index medical care expenditure category to allow for a proper comparison of costs across years.²¹ Lastly, we calculated per-member-per-month (PMPM) costs by dividing total costs for each category of care by the number of person-months in the study sample.

Statistical Analyses

To describe the baseline characteristics of our study sample, we calculated frequencies for categorical variables and means for continuous covariates. To estimate the incidence of hypoglycemia resulting in an inpatient admission, ED, or outpatient visit, we conducted descriptive analyses. For each eligible member, we estimated person-years (p-yrs) of follow-up as the interval from the participant's index date to the date of the first of the following events: a hypoglycemic episode; the end of continuous eligibility; or December 31, 2008. We calculated the IR by dividing the number of hypoglycemic events by the total p-yrs of follow-up and constructed 95% confidence intervals (CIs) around the estimated IRs. The final IRs and corresponding 95% CI are presented per 10,000 p-yrs. We further stratified these estimates by age (18-34, 35-49, 50-64, or 65+ years), gender, and age and gender. Unadjusted Poisson regression models were used to conduct between-group comparisons of IRs (across age and gender) and *t* tests were calculated to compare mean total gross payments across cost categories (eg, hypoglycemia-related encounters, other diabetes-related encounters, and all other encounters). All analyses were performed using SAS Software (version 9.2; SAS Institute Inc, Cary, North Carolina).

RESULTS

Study Population

Within the database, there were 2,913,422 persons with inpatient and/or outpatient claims for diabetes during 2004 to 2008. Of these, 2,629,476 (93.3%) had 2 or more claims for diabetes during the study period. We then excluded 1,302,342 persons (49.5%) who were not taking at least 1 OAD; 663,424 participants (25.2%) who did not have at least 12 months of continuous eligibility within a non-capitated health plan following the first fill date of an

OAD; and 127,129 persons (4.8%) with at least 1 medical claim (inpatient or outpatient) for type 1 or gestational diabetes (648.0X) during the study period. Our final sample for analyses was 536,581.

Demographic and Clinical Characteristics

As presented in **Table 1**, the largest percentage of the population was between the ages of 50 and 64 years (70.8%), with an additional 25.7% aged 35 to 49 years. Only 3.3% of the study population was between the ages of 18 and 34 years and 0.1% were ≥ 65 years of age. The population had a slightly greater percentage of men (53.9%) versus women (46.1%). Within 90 days of cohort entry, 51.3% of the population had only 1 class of antidiabetic medication filled (referred to as monotherapy) while 48.7% had prescription fills for more than 1 class of antidiabetic drug therapy in the same 90-day period (combination therapy). The most common classes of OADs were metformin (75.7%), sulfonylureas (42.3%), and thiazolidinediones (33.3%). Insulin use in addition to OAD use was relatively infrequent, such that only 6.0% of the study population had a prescription for insulin filled in the baseline 90-day period. Overall, 7.0% of the study population had at least 1 macrovascular complication and 4.3% had at least 1 microvascular complication of diabetes. The prevalence of individual micro- and macrovascular complications of diabetes was relatively rare in the study population at baseline ($<1.0\%$), with the exception of coronary artery disease (4.9%) and retinopathy (2.1%).

Incidence of Hypoglycemia

Overall, 3.5% ($n = 18,657$) of the study sample had at least 1 inpatient, ED, or outpatient visit for hypoglycemia. In **Table 2**, the overall IR of a medical encounter for hypoglycemia was 153.8 per 10,000 p-yrs. The IR was highest in the youngest study members (18-34 years; 218.8 per 10,000 p-yrs) followed by the ≥ 65 year cohort members (193.2 per 10,000 p-yrs). The rate of hypoglycemia was higher for women (168.7 per 10,000 p-yrs) than for men (141.0 per 10,000 p-yrs; $P < .001$), a trend consistent across all age categories. Women 18 to 34 years of age had an IR of 267.0 per 10,000 p-yrs compared with an IR of 159.8 per 10,000 p-yrs in men of the same age ($P < .001$). Statistically significant differences in IR also occurred when comparing men and women in the 35 to 49 year age category ($P < .001$) and the 50 to 64 year age category ($P < .001$). Within the 65+ year age category, the IR did not differ statistically between men and women ($P = .833$).

As presented in **Table 3**, the overall rate of inpatient admissions was relatively infrequent, with a rate of 13.5 per 10,000 p-yrs. ED visits were more frequent, with an IR of 32.8 per 10,000 p-yrs. Outpatient visits occurred at the greatest rate, with 118.9 outpatient hypoglycemic encounters occur-

■ **Table 1.** Demographic and Clinical Characteristics of the Study Sample (N = 536,581)

Characteristic	n	%	
Age category (yrs)	18-34	17,862	3.3
	35-49	137,975	25.7
	50-64	380,089	70.8
	65+	655	0.1
Gender	Male	288,957	53.9
	Female	247,624	46.1
Region^a	Northeast	39,880	7.4
	Midwest	152,995	28.5
	South	273,212	50.9
	West	66,882	12.5
Antidiabetic drug therapy^b	Metformin	406,284	75.7
	Sulfonylureas	226,892	42.3
	Thiazolidinediones	178,671	33.3
	Other oral agents	23,571	4.4
	Insulin	31,928	6.0
	Other injectable agents	14,471	2.7
Antidiabetic drug regimen^b	Monotherapy	275,479	51.3
	Combination therapy	261,102	48.7
Diabetes complications: macrovascular^c	Arrhythmia	4735	0.9
	Coronary artery disease	26,085	4.9
	Heart failure	5174	1.0
	Peripheral vascular disease	5502	1.0
	Stroke	1225	0.2
Diabetes complications: microvascular^c	Acute renal failure	1472	0.3
	Amputation	141	<0.1
	Chronic renal pathophysiology	3368	0.6
	Dialysis	38	<0.1
	End-stage renal disease	70	<0.1
	Nephropathy	3579	0.7
	Retinopathy	11,038	2.1
	Ulcer	4684	0.9

^aMissing data on 3612 study participants (0.7%).

^bAntidiabetic drug therapy used in the first 90 days after cohort entry.

^cIdentified using inpatient, emergency department, and outpatient claims in the first 90 days after cohort entry.

costs. Hypoglycemia visits accounted for 1.0% of all inpatient costs, 2.7% of ED costs, and 0.3% of outpatient costs during the study period. The mean cost for inpatient hypoglycemia admissions was \$17,564.25, compared with \$13,862.03 for other diabetes-related inpatient admissions ($P < .001$) and \$19,146.25 for all other inpatient admissions ($P = .026$). The mean cost for an ED visit related to hypoglycemia was \$1386.80 relative to \$320.54 for other diabetes-related ED visits ($P < .001$) and \$632.32 for all other ED visits ($P < .001$). Mean cost for an outpatient hypoglycemia-related episode (\$393.64) was higher than the mean cost for other diabetes-related encounters (\$112.22; $P < .001$) and for non-diabetes-related encounters (\$380.15; $P = .05$) within the same setting. The sum of PMPM costs related to hypoglycemia and diabetes in all settings was \$36.98; 9.7% of all diabetes costs (\$3.58) were related to hypoglycemia treatment. PMPM costs for hypoglycemia were highest for inpatient admissions at \$2.12, which was 40.7% of all inpatient PMPM costs for diabetes care and approximately 1% of all inpatient costs.

DISCUSSION

Our study is a large retrospective cohort study assessing the incidence and costs of hypoglycemia-related medical visits in persons with type 2 diabetes and taking at least 1 OAD. To our knowledge,

our study is the first to assess the comprehensive incidence of hypoglycemia and direct medical costs in a large, real-world population of adults with type 2 diabetes. We found the risk of hypoglycemia requiring medical intervention to be 3.5%, with total costs in excess of \$52 million (2008 dollars). Our comprehensive assessment of hypoglycemia-related medical visits highlights the continued need for vigilance regarding adverse events associated with OAD therapy.

ring per 10,000 p-yrs. As with the composite measure, the incidence of hypoglycemia was typically higher in women than in men across all age groups and in all 3 settings.

Direct Medical Costs of Hypoglycemia

In **Table 4**, we present the results of the cost analyses. During the study period, costs associated with hypoglycemia visits were \$52,223,675, or 0.6% of all inpatient, ED, or outpatient

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Table 2. IRs of Composite Measure of Hypoglycemic Events (First Inpatient, ED, or Outpatient Event) Overall and Stratified by Age and Gender

		Sample Size	P-yrs of Follow-up ^a	Overall No. Office Visits ^b	Overall IR (per 10,000 p-yrs)	95% CI (per 10,000 p-yrs)
Overall	Entire Cohort	536,581	1,212,791	18,657	153.8	151.6-156.0
Age category, yrs	18-34	17,862	35,689	781	218.8	203.5-234.2
	35-49	137,975	305,048	4613	151.2	146.9-155.6
	50-64	380,089	871,433	13,251	152.1	149.5-154.6
	65+	655	621	12	193.2	83.9-302.6
Gender	Male	288,957	652,318	9200	141.0	138.2-143.9
	Female	247,624	560,473	9457	168.7	165.3-172.1
	Male 18-34	8026	16,025	256	159.8	140.2-179.3
	Female 18-34	9836	19,664	525	267.0	244.1-289.8
Gender and age, yrs	Male 35-49	74,679	164,331	2199	133.8	128.2-139.4
	Female 35-49	63,296	140,717	2414	171.5	164.7-178.4
	Male 50-64	205,905	471,632	6739	142.9	139.5-146.3
	Female 50-64	174,184	399,802	6512	162.9	158.9-166.8
	Male 65+	347	330	6	181.8	36.3-327.3
	Female 65+	308	291	6	206.2	41.2-371.2

CI indicates confidence interval; ED, emergency department; IR, incidence rate; p-yrs, person-years.

^aCalculated as the date of cohort entry until the date of first hypoglycemic event (inpatient, ED, or outpatient) or the end of continuous eligibility.

^bFor study participants with multiple hypoglycemic events during the follow-up period, only the first event was counted.

While other studies reviewed here have assessed rates of serious hypoglycemic events, direct comparison to our estimates is difficult as the sampled populations, definitions of hypoglycemia, and settings studied vary widely. In our study of hypoglycemic events warranting a medical encounter, we found an overall rate of 153.8 per 10,000 p-yrs among patients with type 2 diabetes taking 1 or more OADs. First hypoglycemia-related outpatient encounters occurred approximately 10 times more frequently as first hypoglycemia-related inpatient encounters in this cohort. A recent cohort study in England found similar rates of hypoglycemia (as diagnosed and reported by study participant's general practitioner) for nateglinide (15.71 per 1000 p-yrs) and repaglinide (20.32 per 1000 p-yrs) users, but somewhat lower rates for rosiglitazone (9.94 per 1000 p-yrs) and pioglitazone (9.64 per 1000 p-yrs) users.²² In a study of persons with type 2 diabetes, taking an oral agent with or without insulin using the General Practice Research Database (GPRD), the rate of mild/moderate (reported by general practitioner) or severe (requiring hospitalization) hypoglycemia was 60 per 100,000 p-yrs for sulfonylureas and 110 per 100,000 p-yrs for metformin with an overall risk for hypoglycemia in the study of 4.1%.²³ In a 1-year prospective cohort study, 39% of sulfonylurea users reported at least 1 hypoglycemic event compared with 51% of new insulin users (<2 years) and 64% of persons using insulin for >5 years.²⁴ Finally, 2 other studies assessed rates of hypoglycemia result-

ing in ED visits. In a 4-year (1997-2000) prospective study conducted in Germany, the highest rate of ED visits related to sulfonylurea use was in glibenclamide users (5.6 per 1000 p-yrs),²⁵ a rate comparable to our estimated rate of first ED visit (32.8 per 10,000). However, the mean age of persons with hypoglycemic events in this study was 79 years,²⁵ an age group not adequately represented in our cohort. A 12-year prospective study of ED visits in Switzerland in persons with type 2 diabetes using sulfonylureas found a lower rate of ED visits (0.92 per 1000 p-yrs).²⁶ Our study presents a more comprehensive recent assessment of instances of hypoglycemia requiring medical intervention and therefore provides new insight into the considerable impact of hypoglycemia on the rate of utilization of medical visits in the United States.

Another study finding was the increased rate of hypoglycemia by younger (aged 18-34 years) and relatively older (aged 65+ years) adults in our cohort, although the number of older adults and corresponding hypoglycemic events included in our cohort was small (n = 655 with 12 events). In a study by van Staa and colleagues using the GPRD, the overall rate of hypoglycemia in sulfonylurea users at least 65 years of age was 196.7 per 10,000 p-yrs,²⁷ a rate comparable to cohort members aged at least 65 years in our study (193.2 per 10,000 p-yrs). An older study of Medicaid enrollees with type 2 diabetes estimated the rate of serious hypoglycemic events in sulfonylurea users at least 65 years of age to be 123.1 per 10,000 p-yrs.²⁸ It

■ **Table 3.** IRs of Specific Hypoglycemic Events (First Inpatient, First ED, and First Outpatient) Overall and Stratified by Age and Gender

		P-yrs of Follow-up ^a	No. of Admissions/ Visits ^b	IR (per 10,000 p-yrs)	95% CI (per 10,000 p-yrs)
Inpatient admissions (gender and age, yrs)	Overall	1,238,545	1676	13.5	12.9-14.2
	Male 18-34	16,395	13	7.9	3.6-12.2
	Female 18-34	20,440	22	10.8	6.3-15.3
	Male 35-49	167,434	129	7.7	6.4-9.0
	Female 35-49	144,269	160	11.1	9.4-12.8
	Male 50-64	480,525	702	14.6	13.5-15.7
	Female 50-64	408,853	648	15.8	14.6-17.1
	Male 65+	332	2	60.2	0-143.7
	Female 65+	296	0	0	0
ED visits (gender and age, yrs)	Overall	1,235,242	4048	32.8	31.8-33.8
	Male 18-34	16,316	74	45.4	35.0-55.7
	Female 18-34	20,372	80	39.3	30.7-47.9
	Male 35-49	167,013	458	27.4	24.9-29.9
	Female 35-49	143,894	474	32.9	30.0-35.9
	Male 50-64	479,393	1467	30.6	29.0-32.2
	Female 50-64	407,626	1494	36.7	34.8-38.5
	Male 65+	333	0	0	0
	Female 65+	295	1	33.9	0-100.3
Outpatient visits (gender and age, yrs)	Overall	1,218,398	14,491	118.9	117.0-120.9
	Male 18-34	16,124	182	112.9	96.5-129.3
	Female 18-34	19,765	447	226.2	205.2-247.1
	Male 35-49	164,941	1725	104.6	99.6-109.5
	Female 35-49	141,333	1929	136.5	130.4-142.6
	Male 50-64	473,675	5227	110.3	107.4-113.3
	Female 50-64	401,939	4972	123.7	120.3-127.1
	Male 65+	330	4	121.2	2.4-240.0
	Female 65+	292	5	171.2	21.1-321.3

CI indicates confidence interval; ED, emergency department; IR, incidence rate; p-yrs, person-years.

^aCalculated as the date of cohort entry until the date of first inpatient, ED, or outpatient hypoglycemic event or the end of continuous eligibility.

^bFor each specific type of hypoglycemic event during the follow-up period, only the first event was counted for each setting.

should be noted, however, that these studies had a broader range of older adults, whereas our population was closer to 65 years of age. We are unaware of studies that assessed rates of hypoglycemia in young adults (18-29 years). Lastly, the van Staa study also demonstrated a higher rate of hypoglycemia in women as compared with men,²⁷ a pattern that was found in our study across all age groups.

Our analyses indicate that while hypoglycemia is relatively infrequent in this large working-age population, the mean cost of medical encounters associated with hypoglycemia was up to 4 times higher than for other diabetes-related claims. Fur-

thermore, the total costs of all hypoglycemia-related inpatient admissions exceeded the costs of all hypoglycemia-related ED and outpatient visits combined. Recently, Curkendall et al found that a diagnosis of hypoglycemia in the inpatient setting was associated with over 38% higher total charges than in patients without hypoglycemia.¹³ In the same study, mean total inpatient charges for patients with hypoglycemia were approximately \$86,000, compared with approximately \$54,000 for patients without the complication.¹³ A study by Pelletier and colleagues of more than 44,000 patients with type 2 diabetes, however, found that mean direct medical charges for

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Table 4. Costs of Hypoglycemic Events, Other Diabetes-Related Events, and All Other Events Stratified by Setting

Setting	Cost Category ^a	Encounters (n)	Mean Cost per Encounter (\$)	PMPM Costs ^b	Total Costs ^c (\$)
Inpatient admissions	Hypoglycemia costs	1761	17,564.25	2.12	30,930,649
	Other diabetes costs	3253	13,862.03	3.09	45,093,191
	All other costs	165,907	19,146.25	217.59	3,176,496,569
	Total inpatient costs ^e	170,921	19,029.38	222.80	3,252,520,409
ED visits^d	Hypoglycemia costs	4764	1386.80	0.45	6,606,733
	Other diabetes costs	12,189	320.54	0.27	3,907,106
	All other costs	374,070	632.32	16.20	236,533,330
	Total ED costs ^e	391,023	631.80	16.92	247,047,170
Outpatient visits	Hypoglycemia costs	37,309	393.64	1.01	14,686,293
	Other diabetes costs	3,907,555	112.22	30.04	438,508,763
	All other costs	14,071,911	380.15	366.43	5,349,461,758
	Total outpatient costs ^e	18,016,775	322.07	397.48	5,802,656,813

ED indicates emergency department; PMPM, per-member-per-month.

^aCost category identified using *ICD-9* codes associated with the claim and creating 3 mutually exclusive groups: 1) those identified as hypoglycemia²⁰ (hypoglycemia costs); 2) those with primary *ICD-9* code 250.XX (other diabetes costs); and 3) other claims (all other costs).

^bCalculated by dividing total costs for each category of care by total number of person-months in study sample (14,598,666).

^cTotal costs rounded to nearest dollar.

^dCosts for ED visits that resulted in inpatient hospitalization were captured within the inpatient hospitalization costs and are not included in the ED costs.

^eCosts of hypoglycemic events, other diabetes-related events, and all other events may not sum to total costs due to rounding.

hypoglycemia complications were approximately \$454.¹⁵ This study reported that 12-month mean allowed amounts for hypoglycemia totaled \$345, but this analysis did not distinguish costs by setting type.¹⁵ A 1999 to 2001 study using MarketScan data found that annualized hypoglycemia-related medical costs were \$3241 for insulin users.²⁹ The absolute direct cost of medical visits for hypoglycemia was \$52 million within our sample, with potentially avoidable inpatient admissions for hypoglycemia accounting for nearly 60% of medical costs for hypoglycemia (\$30,930,649 of \$52,223,675). While per-episode costs were high, overall PMPM costs associated with hypoglycemia were relatively low. As hypoglycemic events are potentially avoidable, development of additional strategies to decrease rates of hypoglycemia that warrant medical intervention are necessary.

While our study provides several advantages over previous studies of hypoglycemia, there are several limitations that we must address. First, the data we used are from a large health-care database, generally containing workplace-sponsored insurance plans, and therefore may not be generalizable to all persons with type 2 diabetes. Notably, within our study, 4.3% and 7.0% of patients had evidence of micro- and macrovascular complications of diabetes, respectively, within 90 days of cohort entry. Another study estimated the prevalence of macrovascular complications to be 28.1% and 20.2% for microvascular complications.³⁰ Secondly, our analyses focused

on 1 direct effect of hypoglycemic episodes—medical encounters. As a result, our study does not capture minor instances of hypoglycemia and therefore underestimates the true burden of hypoglycemia, including the resulting impact on morbidity, mortality, and indirect factors (eg, lost work or productivity). Lastly, we were unable to capture medical claims for hypoglycemia that might have occurred prior to the date of cohort entry. Therefore, the incidence of hypoglycemia calculated within our study represents the first event experienced by the patient during the time period of the study, not necessarily the first episode.

CONCLUSIONS

The overall rate of hypoglycemia requiring medical intervention was 153.8 hypoglycemic episodes per 10,000 p-yrs among patients with type 2 diabetes taking at least 1 OAD. The rate of hypoglycemia was highest in youngest (18-34 years) and older (65+ years) patients and higher in women than men. The total costs associated with medical visits and hospitalizations for hypoglycemia were in excess of \$52 million (2008 dollars; \$30,930,649 for inpatient, \$6,606,733 for ED, and \$14,686,293 for outpatient visits). Further, the total costs of all hypoglycemia-related inpatient admissions exceeded the costs of all hypoglycemia-related ED and outpatient visits combined. Younger adults and women with type 2 dia-

betes may require more assistance to prevent hypoglycemic episodes. Continued vigilance for the occurrence and costs of hypoglycemia in patients with type 2 diabetes is essential. As hypoglycemia remains an important barrier to medication treatment of type 2 diabetes, strategies to decrease the incidence of hypoglycemia are needed.

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