Descriptive Analysis of Long- and Intermediate-Acting Insulin and Key Safety Outcomes in Adults with Type 2 Diabetes Mellitus

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ABSTRACT

BACKGROUND: As new biosimilar and follow-on insulins enter the market, more data are needed on safety, effectiveness, and patterns of use for these products to inform prescriber and patient decision-making regarding treatment. Additionally, data are needed regarding real-world patterns of use to inform future studies comparing the safety and effectiveness of biosimilars to already approved agents for diabetes treatment.

OBJECTIVE: To analyze the medication use patterns, adverse events, and availability of glycated hemoglobin (A1c) values for adult patients with type 2 diabetes mellitus (T2DM) who use long-acting insulin (LAI) or neutral protamine Hagedorn (NPH), an intermediate-acting insulin.

METHODS: We used the Biologics and Biosimilars Collective Intelligence Consortium's (BBCIC) distributed research network (DRN) for this descriptive analysis. The analysis time frame was January 1, 2011, to September 30, 2015, and included patients continuously insured for at least 183 days before the first date of a filled prescription for LAI or NPH insulin alone or with rapid- or short-acting insulin or sulfonylureas, whether newly starting insulin or switching to a different product. Insulin exposure episodes were the unit of analysis, and patients were classified in cohorts according to treatment. We followed patients until end of health plan enrollment or the end of the study period. We used occurrence of a study outcome, switch to another medication regimen, discontinuation of the current medication, or study end date to mark the end of an insulin episode. We describe demographics and availability of A1c values for analysis. Study outcomes included severe hypoglycemic events and major adverse cardiac events (MACE).

RESULTS: We identified 103,951 patients with T2DM from a database of 39.1 million patients with commercial or Medicare Advantage pharmacy and medical benefits, who contributed 279,533 unique insulin exposure episodes. Most episodes (89%) included patients using LAI, and 52% of patients contributed data to 2 or more exposure cohorts. Insulin episodes lasted an average of 3.5 months, and patients had an average follow-up of 8.6 months. The unadjusted rate of severe hypoglycemic events requiring medical attention was 96.9 per 10,000 patient-years at risk (10kPYR). The unadjusted incident MACE rate was 676.9 events per 10kPYR. 38,330 T2DM patients in the BBCIC DRN had a baseline A1c available, and of those, less than 50% had a follow-up A1c result.

CONCLUSIONS: Among patients with T2DM, our observed insulin patterns of use and rates of severe hypoglycemic outcomes and MACE are consistent with other studies. We noted a paucity of A1c results available, which implies that additional data sources may be needed to augment the BBCIC DRN.

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What is already known about this subject

- Patients with type 2 diabetes mellitus (T2DM) may use multiple medications, and characterizing patterns of use is often difficult because of this heterogeneity.
- Patients with T2DM benefit from using insulin, and such patients may adopt follow-on insulins in the future.
- Identification of potential data sources to monitor insulin use and patient outcomes is needed to better understand future uptake and patient outcomes when using follow-on insulins.

What this study adds

- With the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) distributed research network (DRN), we described insulin exposures and insulin-related outcomes for patients with T2DM in a large, commercially insured population of patients.
- The insulin use, baseline covariates, and insulin-related outcomes we observed in the BBCIC DRN are similar to previous studies among patients with T2DM.

An estimated 29 million people in the United States have type 2 diabetes mellitus (T2DM), representing 9% of the total population.¹ Approximately 6 million patients with T2DM use insulin replacement to manage their diabetes.¹ The patent expiration of long-acting insulin (LAI) or intermediate-acting insulin products, such as neutral protamine Hagedorn (NPH) insulin, has increased therapeutic options for patients with diabetes. The U.S. Food and Drug Administration (FDA) approved Basaglar (insulin glargine injection) and Admelog (insulin lispro injection) in 2017-2018, and review of new biosimilar insulins and innovative insulin products is ongoing.² The FDA's accelerated approval processes for biosimilars and follow-on biologics require only comparative safety and efficacy data to the originator product, reducing lengthy clinical trial time frames. Patients and providers are interested in assurances regarding safety and effectiveness of biosimilar products when used in clinical practice.³⁻⁶ Real-world evidence is one potential source of information that addresses these concerns. There is a paucity of research regarding the real-world comparative

safety and effectiveness of biosimilars and follow-on biologics and their reference biologics, including insulins. In an initial effort to begin to fill this research gap, we have conducted a descriptive analysis to evaluate the fitness and robustness of a potential data source that can be used for future comparative analyses of biosimilars.

For this research, we used the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) distributed research network (DRN) to determine data availability, describe potential study populations, and define rates of severe adverse events among patients with T2DM and insulin exposure. The BBCIC is a nonprofit public service initiative formed to provide scientific evidence on the comparative safety and effectiveness of biosimilars and innovator biologics. The BBCIC DRN is composed of commercial and Medicare Advantage health insurance providers and leverages the FDA Sentinel data structure and analytical tools for its research purposes.^{7,8} More information on the BBCIC is available at www.bbcic.org.

In this study, we identified and described the patient cohorts of interest, described patterns of medication use, and evaluated outcomes among adult patients (aged 18 years and over) with T2DM. We focused on LAI and NPH insulin products to give a comprehensive description of background insulin use in this population and described the potential users of biosimilars and follow-on insulins. We also reported patient outcomes by (a) use of oral second-generation sulfonylureas (SU) and rapid-acting insulin (R) in conjunction with LAI or NPH insulin; (b) the frequency of preexisting cardiovascular, renal, neurologic, and retinal conditions; and (c) the percentage of patients with a history of hypoglycemic events. We then evaluated the outcomes of serious hypoglycemic events, major adverse cardiac events (MACE), and availability of hemoglobin A1c (A1c) values.

Methods

The BBCIC DRN leverages the FDA Sentinel Common Data Model (SCDM; V6 used in this analysis) and includes commercial and Medicare Advantage administrative claims data from 2 national health insurers (Aetna and Healthcore [Anthem]) and 3 regional health insurers (Kaiser Permanente of Washington, Harvard Pilgrim Health Care, and HealthPartners).^{9,10} Each health plan participates in the FDA Sentinel initiative.^{7,8}

Study Design and Population

We used the BBCIC DRN for this descriptive cohort study. The study period was January 1, 2011, to September 30, 2015, which included a baseline lookback period of 183 days before an insulin exposure episode. The lookback was to ensure that no outcomes of interest occurred during that period that could be attributed to a cause other than insulin exposure, thus establishing the incidence of an outcome. This is the typical baseline period used by the FDA Sentinel initiative analyses.¹¹

Patients could contribute multiple exposure episodes to this study, provided they met all inclusion and exclusion criteria, including 6 months with no occurrence of outcomes of interest. Both new (e.g., incident) and current (e.g., prevalent) users of insulin were included, but the lookback period allowed for identification of new (incident) primary outcomes.

The study population included adults aged 18 years or over with commercial or Medicare Advantage medical and pharmacy insurance, a diagnosis of T2DM, and a dispensed LAI or NPH insulin product within the study period. We defined T2DM as at least 1 medical claim with a T2DM (250.x0 or 250.x2) *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis code observed at any time in the claims history.

Similar to exclusion criteria often used in clinical trials,¹²⁻¹⁴ we used the modified Klompas algorithm to exclude patients with health insurance claims for T1DM and T2DM diagnoses, as well as claims for insulin pumps or related supplies, gestational diabetes, liver disease, dialysis, end-stage renal disease, amputations, hemoglobinopathy, hemolytic anemia, sickle cell anemia, and blood transfusion. We excluded any patients with an emergency department (ED) visit for hypoglycemia or an ED visit or hospitalization for a cardiovascular event in their claims 183 days before the index insulin episode date. We also truncated exposure episodes if any insulins except those listed below were dispensed, unless such insulins were used in combination with LAI or NPH insulin. Patients could switch between LAI or NPH insulin cohorts. All codes used in this analysis can be found at www.bbcic.org.

We used the following medication subgroups to categorize patients based on insulin exposure:

1. LAI: Long-acting insulin, including insulin detemir and glargine.
2. LAI+R: Long-acting insulin plus rapid- or short-acting insulin, including detemir or glargine plus regular, lispro, glulisine, or aspart insulin and combinations such as aspart protamine human/aspart, as well as aspart protamine human/aspart plus regular pork, beef, or human or lispro/lispro-protamine combinations.
3. LAI+SU: Long-acting insulin plus second-generation SU agent, including insulin detemir and glargine with glimepiride, glipizide, glipizide/metformin, glyburide, or glyburide/metformin.
4. NPH: Intermediate-acting insulin, including Humulin, Novolin, isophane pork, beef, or human.
5. NPH+R: NPH insulin plus rapid- or short-acting insulin, including Humulin, Novolin, mixed isophane pork, beef, or human and regular as well as isophane pork, beef, or human plus regular pork, beef, or human.
6. NPH+SU: NPH insulin plus second-generation SU agent, including Humulin, Novolin, isophane pork, beef, or

FIGURE 1 Example of Insulin Exposure

^aAn episode can end due to the timeline illustrated here or earlier if a study outcome or other truncation event occurs.

human with glimepiride, glipizide, glipizide/metformin, glyburide, or glyburide/metformin.

Exposure to metformin was allowed within each of the 6 groups; however, an episode was truncated if a patient filled a prescription for oral antidiabetes agents other than those included in the exposure cohorts, including first-generation SUs (e.g., chlorpropamide, tolazamide); thiazolidinediones (TZD; e.g., pioglitazone, rosiglitazone); dipeptidyl peptidase-4 inhibitors (DPP-4; e.g., sitagliptin, saxagliptin); glucagon-like peptide-1 agonists (GLP-1; e.g., exenatide, liraglutide); and sodium glucose cotransporter 2 inhibitors (SGLT2; e.g., empagliflozin, canagliflozin).

Unit of Analysis and Medication Exposure

Insulin exposure episode was the unit of analysis for primary outcomes, with the insulin dispensing date as the index date of an exposure episode. An exposure episode began on the date of prescription fill for LAI or NPH and extended for the prescribed insulin days supply with a grace period of 60 days added to the end to account for imperfect adherence and changes to insulin dosage. Continuous medical and prescription drug insurance coverage was required, with a 45-day enrollment gap permitted. We analyzed the LAI and NPH cohorts with “+R” (long-acting plus rapid-acting insulin) or “+SU” (long-acting

insulin plus oral SU) to describe patterns of care and characteristics of patients who may use LAI biosimilars, and outcomes for patients who are at increased risk of hypoglycemia and cardiovascular events.¹⁵⁻¹⁸ To be categorized in a combination cohort (e.g., LAI+R) for an episode, patients could fill these concomitant medications on the same day as LAI or NPH, or within 90 days following the LAI or NPH fill date. When a second agent was filled within this window, the episode was categorized in the combination cohort. For these groups, the dispensing date of the second agent (R or SU) defined the episode index date.

Exposure episode length was determined by days supplied reported from the pharmacy claim with a 60-day grace period to account for adherence and dosing variability. Following the FDA Sentinel analytic standard, an episode began at the index date and continued as long as there was no gap in insulin or other medication exposure of 60 days or greater observed. We ended the exposure episode if a patient's claims reflected 61 days or longer without a filled prescription for any of the medications. The next prescription filled for the patient began a new medication episode.

Time at risk was defined as the sum of all episode time. Patients stopped contributing time at risk at the point when an episode was either truncated or ended but could resume contributing time at risk at the start of the next episode.

FIGURE 2 CONSORT Diagram for Study Cohort Selection

^aIncludes any insulin claim during the study period.

^bIncludes insulin exposure during the study period after the 183-day lookback period.

BBCIC DRN = Biologics and Biosimilars Collective Intelligence Consortium's distributed research network; LAI = long-acting insulin; NPH = neutral protamine Hagedorn, an intermediate-acting insulin; R = rapid-acting insulin; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Patients could contribute more than 1 episode with different index dates if they met all inclusion criteria at the time of each new exposure; those who switched medications during the study period were assigned to the cohort for the new medication. Patients were further stratified into those who contributed to 1 medication cohort versus those in multiple cohort types (i.e., LAI/NPH only vs. LAI/NPH as well as LAI/NPH+SU).

We truncated a medication exposure episode for the following reasons: subject loss to follow-up (e.g., end of insurance enrollment), medication regimen change during an exposure, study outcome attainment, or end of study observation period. Medication regimen changes that resulted in truncation include (a) use of an insulin in a category different from the initial exposure insulin; (b) use of oral antidiabetes medications including first-generation SU agents; or (c) use of DPP-4, GLP-1, SGLT-2, or TZD medications alone or in combination with insulin. After a truncated insulin exposure episode, the

patient could have another episode with a new 183-day look-back baseline period (Figure 1).

Baseline Characteristics

We described the following clinical and demographic characteristics for patients: age (18-49, 50-64, 65-79, and 80+ years); gender; insulin type; health service utilization (e.g., number of hospitalizations, ED, and ambulatory visits); medication measures (i.e., use of metformin and other antidiabetes medications); and specific comorbidities incorporated into a combined comorbidity index (includes conditions found in the Romano adoption of the Charlson Comorbidity Index and the Elixhauser Comorbidity Index, including complicated diabetes, cardiac, renal, or neurological comorbidities).^{19,20} We accounted for level of illness by combined comorbidity index along with ED use, inpatient hospitalization, and metformin use in the 183 days before each insulin episode in the study period.²¹

TABLE 1 Baseline Characteristics, Insulin Episodes, and Dispensing Patterns Among All Patients with a Recorded Use of LAI or NPH Insulin

Insulin Episodes							
Unique patients with at least 1 episode	N = 103,951						
Total number of episodes	N = 279,533						
	LAI	LAI + R	LAI + SU	NPH	NPH + R	NPH + SU	
Insulin episodes, n	128,686	68,074	50,682	14,540	12,197	5,354	
Episodes per patient, mean (SD)	1.67 (1.2)	1.74 (1.3)	1.57 (1.1)	1.55 (1.2)	1.61 (1.2)	1.48 (1.0)	
Months per episode, mean (SD)	2.28 (4.3)	3.84 (5.3)	3.36 (5.3)	4.56 (8.4)	4.92 (6.6)	6.96 (9.5)	
Months of follow-up, ^a mean (SD)	3.72 (6.6)	6.72 (8.8)	5.40 (7.9)	6.96 (11.9)	7.92 (10.4)	10.32 (13.2)	
Dispensing per patient, mean (SD)	2.91 (4.0)	3.79 (5.1)	3.10 (4.0)	4.00 (5.9)	4.33 (6.1)	3.99 (5.0)	
Dispensing per episode, mean (SD)	1.75 (2.8)	2.18 (3.4)	1.97 (2.7)	2.58 (4.5)	2.70 (4.4)	2.69 (3.6)	
Days supplied per patient, mean (SD)	75.8 (142.8)	116.4 (180.1)	98.5 (170.3)	157.9 (290.1)	146.8 (225.8)	217.3 (323.1)	
Days supplied per episode, mean (SD)	45.5 (102.4)	67.0 (122.2)	62.6 (125.4)	101.8 (220.2)	91.5 (160.8)	146.8 (250.5)	
Patient Characteristics by Insulin Episode							
Female, ^b n (%)	59,201 (46)	32,004 (47)	22,735 (45)	7,586 (52)	6,314 (52)	2,628 (49)	
Age groups in years, ^c n (%)							
18-49	39,004 (30)	19,202 (28)	12,232 (24)	3,983 (27)	3,307 (27)	1,099 (21)	
50-64	69,004 (54)	37,462 (55)	27,872 (55)	6,739 (46)	5,722 (47)	2,523 (47)	
65-79	17,603 (14)	9,790 (14)	9,130 (18)	3,154 (22)	2,583 (21)	1,441 (27)	
80+	3,075 (2)	1,620 (2)	1,448 (3)	664 (5)	585 (5)	291 (5)	
Clinical Characteristics							
	Any LAI			Any NPH			
Mean age, years (SD)	55.1 (11.5)			57.1 (12.6)			
Combined comorbidity index, mean (SD)	0.2 (1.3)			0.5 (1.4)			
Gastroparesis, %	0.3			0.3			
Hyperlipidemia, %	41.9			31.7			
Hypertension, %	53.7			47.6			
Nephropathy and CKD, %	4.1			8.1			
Obesity and abnormal weight gain, %	11.8			13.6			
Peripheral neuropathy, %	6.4			13.5			
Retinopathy, %	7.2			11.0			
Health Service Utilization							
Ambulatory visits, mean (SD)	5.2 (6.2)			5.1 (6.3)			
Emergency department visits, mean (SD)	0.2 (0.5)			0.1 (0.5)			
Inpatient hospital stays, mean (SD)	0.1 (0.3)			0.1 (0.3)			
Other ambulatory visits, mean (SD)	1.7 (4.5)			4.4 (6.0)			
Prescriptions dispensed, mean (SD)	16.1 (14.3)			15.4 (13.3)			
Generic prescriptions dispensed, mean (SD)	6.5 (4.3)			7.0 (4.4)			
Unique drug classes, mean (SD)	6.1 (4.1)			6.7 (4.2)			
Metformin use, %	46.8			50.7			

Note: Results are based on episodes, and each patient may contribute multiple episodes across insulin exposures.

^aFollow-up is defined as time from index insulin dispensing date to end of insulin episode. End of episode can be because of insurance disenrollment, death, end of data, or end of dispensed days of insulin plus 60 days extension.

^bNumber of episodes observed for female patients contributing time to the exposure category.

^cNumber of episodes observed for patients in each age category contributing time to the exposure category.

CKD=chronic kidney disease; LAI=long-acting insulin; NPH=neutral protamine Hagedorn (NPH), an intermediate-acting insulin; R=rapid-acting insulin; SD=standard deviation; SU=sulfonylurea.

Primary Outcomes

Because addition of regular insulin and an SU has been shown to increase hypoglycemic and cardiovascular risk, primary outcomes were stratified by 3 combined insulin cohorts: (a) LAI and NPH, (b) LAI+R and NPH+R, and

(c) LAI+SU and NPH+SU.¹⁵⁻¹⁸ Hypoglycemic and MACE outcomes were identified using diagnosis codes and procedure codes.²² We included the first qualifying hypoglycemic event and the first qualifying MACE following the index insulin dispensing for each patient. In other words, among the

prevalent (new and existing) users of insulin, we identified incident (new) events. For patients with multiple events, we classified an event by the exposure in the episode when the event occurred.

Hypoglycemia was defined using the following ICD-9-CM codes with the modified Ginde algorithm: (a) an ED visit with at least 1 diagnosis code of 250.0, 250.1, 250.2, 270.3, 775.0, or 775.6; or (b) ED visit with a diagnosis code of 250.8x, without the following codes: 251.0, 251.1, 251.2, 270.3, 775.0, 775.6, 259.8, 272.7, 681.xx, 682.xx, 686.9x, 707.x, 709.3, 730.0-730.2, or 731.8.²³ MACE is a composite endpoint of hospitalization or ED visit for stroke, acute myocardial infarction (AMI) or unstable angina (including occlusion without infarction or coronary insufficiency), cardiac or carotid revascularization procedure, or other heart disease (including heart failure) defined using a combination of ICD-9-CM and Healthcare Common Procedural Coding System codes.²⁴⁻²⁶

Secondary Outcomes

We measured the availability of A1c values and created 3 categories: no A1c results available, any baseline A1c (i.e., within 183 days of index date), and any study period A1c (baseline or exposure period). Of the 5 data partners participating in this study, 3 contributed laboratory values to the BBCIC DRN. FDA Sentinel tools classify laboratory values in categories, so our analysis was limited to observing counts rather than analyzing A1c as a continuous variable. A1c values were categorized as A1c less than or equal to 6.5, between 6.5 and 7.0, between 7.0 and 8.0, and greater than 8.0.

Statistical Methods

We described continuous measures with means and standard deviations and categorical measures with counts, frequencies, and percentages. This study used a distributed analytic approach in which each site maintained data locally. Only aggregate data, and no individual patient-level data, were shared outside the study sites. Measures that involved patient-level data, such as the calculation of means and standard deviations, were performed by ad hoc programs with only final aggregated results provided to BBCIC. The BBCIC Coordinating Center at the Harvard Pilgrim Health Care Institute (HPHCI) used publicly available Sentinel analytic tools to create analytic code that was securely sent to each local site to create the study cohort. The HPHCI Institutional Review Board (IRB) and each data partner site IRB reviewed the protocol and determined it did not meet the definition for human subject research.

Results

Over 39.1 million patients met the study inclusion criteria of at least 183 days of medical and drug coverage during the study period; 82% (32.1 million) were adults aged 18 years or over (Figure 2). Within each of these exposure cohorts,

TABLE 2 Insulin Episodes and Dispensing Patterns Among All Patients with Recorded Use of LAI or NPH Insulin Contributing Either 1 Insulin Episode Only or 2 or More Insulin Episodes

Insulin Episodes			
Unique patients with at least 1 episode	N = 103,951		
Total number of episodes ^a	N = 279,337		
	Any Exposure, ^b 1 Cohort Only	Any Exposure, ^b 2 or More Cohorts	
Patients contributing to episodes, n	49,704	54,247	
Insulin episodes, n	77,538	201,799	
Episodes per patient, mean (SD)	1.56 (1.2)	3.72 (2.5)	
Months per episode, mean (SD)	4.44 (6.7)	2.64 (4.7)	
Months of follow-up, ^a mean (SD)	6.96 (9.7)	10.08 (11.2)	
Dispensing per patient, mean (SD)	4.09 (5.8)	6.53 (6.1)	
Dispensing per episode, mean (SD)	2.62 (4.3)	1.75 (2.5)	
Days supplied per patient, mean (SD)	134.81 (219.4)	189.32 (239.0)	
Days supplied per episode, mean (SD)	86.41 (165.5)	50.85 (109.8)	

^aThe total number of exposures observed is slightly less than those defined by insulin cohort because of rounding when calculating the combined cohorts.

^bIncludes all exposure cohorts: LAI, LAI+R, LAI+SU, NPH, NPH+R, and NPH+SU.

LAI = long-acting insulin; NPH = neutral protamine Hagedorn (NPH), an intermediate-acting insulin; R = rapid-acting insulin; SD = standard deviation; SU = sulfonylurea.

55%-76% were excluded because of a diagnosis of T1DM in claims, clinical exclusions (e.g., history of myocardial infarction), or observation of an outcome in the baseline period. These exclusions yielded final counts of 77,197 patients contributing to the LAI cohort, 39,167 patients contributing to the LAI+R cohort, 32,216 patients contributing to the LAI+SU cohort, 9,374 patients contributing to the NPH cohort, 7,598 patients contributing to the NPH+R cohort, and 3,617 patients contributing to the NPH+SU cohort.

A total of 103,951 patients contributed at least 1 insulin exposure episode and met study criteria for inclusion. A total of 279,337 insulin episodes were included in this analysis. Table 1 shows insulin exposures, dispensings, and patient characteristics for each insulin cohort. There were 128,686 episodes in the LAI cohort, 68,074 episodes in the LAI+R cohort, 50,682 episodes in the LAI+SU cohort, 14,540 episodes in the NPH cohort, 12,197 episodes in the NPH+R cohort, and 5,354 episodes in the NPH+SU cohort during the study period. Patients could be included in more than 1 group because of changing treatment regimens over time. Overall, insulin episodes lasted an average of 3.5 months, and patients had an average follow-up of 8.6 months. The average episode duration ranged from 2.3 to 3.8 months in the LAI cohorts and from 4.6 to 7.0 months in the NPH cohorts. Follow-up time in the LAI cohorts ranged from 3.7 to 6.7 months and 7.0 to 10.3 months in the NPH cohorts.

TABLE 3 Outcomes Among Patients with T2DM by Type of Insulin Used

Hypoglycemia				
Unique patients evaluated for outcomes	N = 102,960 ^a			
	LAI or NPH	(LAI or NPH) + R	(LAI or NPH) + SU	Any Exposure ^b
Insulin episodes	139,756	77,870	55,278	272,904
Episodes with events	304	309	156	769
Patients with events	302	306	156	721
Patients with events per 10kPYR	102.6	111.5	88.8	96.9
Episodes per patient with events, mean (SD)	1.94 (1.2)	2.08 (1.5)	1.89 (1.3)	2.10 (1.5)
Episodes with events per 10kPYR	103.3	112.6	88.9	103.4
MACE				
Episodes with events	2,061	2,234	1,231	5,526
Patients with events	2,020	2,166	1,205	5,036
Patients with events per 10kPYR	702.1	811.5	703.5	676.9
Episodes per patient with events, mean (SD)	1.83 (1.4)	1.94 (1.4)	1.73 (1.2)	1.98 (1.5)
Episodes with events per 10kPYR	716.3	837.0	718.7	742.8

Note: Results are based on insulin episodes and each patient may contribute multiple episodes across insulin exposures.

^aTotal number of patients contributing data to the outcomes analysis.

^bIndividual patients could contribute events to multiple exposure categories.

10kPYR = 10,000 patient-years at risk; LAI = long-acting insulin; MACE = major adverse cardiac events; NPH = neutral protamine Hagedorn (NPH), an intermediate-acting insulin; R = rapid-acting insulin; SD = standard deviation; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Insulin Episode and Patient Characteristics

Insulin episode and patient characteristics are shown in Table 1. A total of 46% of episodes in the LAI cohort occurred in females, compared with 52% in the NPH cohort. In the LAI+R and NPH+R cohorts, 47% and 52% of episodes occurred in females, respectively, and in the LAI+SU and NPH+SU cohorts 45% and 49% of episodes occurred in females, respectively. The majority of episodes occurred in patients aged 50 to 64 years. Approximately half (47%) of LAI episodes included a metformin dispensing in the previous 183 days, while 51% of NPH episodes included a metformin dispensing.

During baseline, 54% of LAI episodes had evidence of hypertension; 42% had evidence of hyperlipidemia; 12% had evidence of obesity or abnormal weight gain; and 6% had evidence of peripheral neuropathy. In the NPH episodes, we saw evidence of hypertension in 48% of episodes, hyperlipidemia in 32%, obesity or abnormal weight gain in 14%, and peripheral neuropathy in 14% of episodes. Patients with LAI episodes had an average of 5 ambulatory visits and 16 prescriptions filled in 6 drug classes during the study period, while those with NPH episodes had an average of 5 ambulatory visits and 15 prescriptions filled in 7 drug classes in the 183 days before index insulin dispensing.

Of the 103,951 T2DM patients, 48% were categorized in only 1 type of insulin exposure cohort, accounting for 28% of insulin episodes (Table 2). The remaining 52% were categorized in multiple exposure cohorts (e.g., NPH followed by NPH+R), accounting for 72% of insulin episodes. Patients with a single episode type had 1.6 episodes per patient, an average of 4.1 insulin prescriptions dispensed, and an average of

135 days supply. As compared with patients with a single episode type, patients with multiple insulin exposure types had more episodes (3.7) and insulin prescriptions (6.5) dispensed per patient, and an average of 54 more days of insulin exposure (189 days).

Primary Outcomes

Table 3 displays the 2 primary outcomes by insulin episode group (LAI vs. NPH). The unadjusted hypoglycemic event rates for all patients with T2DM was 96.9 events per 10,000 person-years at risk (10kPYR), ranging from 88.8 for (LAI or NPH)+SU patients to 111.5 for patients using (LAI or NPH)+R. The unadjusted incident MACE rates for patients with T2DM was 676.9 per 10kPYR, ranging from 702.1 for LAI or NPH patients to 811.5 for patients using (LAI or NPH)+R.

Secondary Outcomes

A total of 38,330 patients in the BBCIC DRN had a baseline A1c value; of those, 18,507 (48%) had both baseline and study period A1c values. For those patients with a baseline A1c value, the first study period A1c after the insulin dispensing index date occurred within 2.9 months, compared with 4.2 months for patients without a baseline A1c value.

Discussion

This descriptive analysis used the BBCIC DRN to describe the demographics and medication use among adult patients with T2DM. We also characterized the insulin-related outcomes of hypoglycemic events and MACE, plus availability of A1c levels.

The baseline characteristics reported are consistent with those reported in clinical trials and observational studies. Average age for our population was comparable to those in other published observational and prospective cohort studies.²⁷⁻³¹ Our population had a high percentage of patients with preexisting cardiovascular conditions. In order of prevalence, we observed hypertension, other heart disease (including heart failure), ischemic heart disease, nephropathy/chronic kidney disease, stroke/carotid revascularization, end-stage renal disease, AMI, and coronary revascularizations as seen in other observational and clinical trials. However, unlike other studies such as LEADER, we excluded patients with a history of cardiovascular events. Metformin use was consistent with longer term persistence studies.³² The use of metformin and SU in the LAI group was consistent with that reported in the literature but was almost 3 times higher than in the NPH cohort.^{33,34}

Our results using unadjudicated events based on claims data were in the middle of published MACE rates. Our unadjusted MACE event rate of 676.9 per 10kPYR was higher than those seen in clinical trials of diabetes medications among prevalent diabetes, which varied from 278 to 528 events per 10kPYR, respectively.³⁵⁻³⁸ Our MACE composite criteria most closely resembled those of 2 trials, but overall we observed MACE outcomes generally lower than those observed in the LEADER and ORIGIN trials. The LEADER trial had T2DM MACE outcomes of 790 events per 10kPYR with transient ischemic attack, coronary revascularization, unstable angina, and congestive heart failure, which is higher than our MACE event rates except for our LAI/NPH+R group rate (837 events per 10kPYR).³⁹ For the ORIGIN trial, when primary and secondary MACE rates were included (846 events per 10kPYR), the rates were also higher than our findings.⁴⁰ In both the LEADER and ORIGIN trials, patients with previous cardiovascular disease were included in the study, whereas we excluded such patients from analysis, which likely explains our lower findings of MACE, since those with preexisting cardiovascular disease are also more predisposed to MACE.

As expected, the LAI+R/NPH+R group experienced a higher rate of hypoglycemia events (111.5 events per 10kPYR) compared with the other studies of insulin users.⁴¹ Although direct comparisons to clinical trials are difficult given the cohorts and data available (e.g., claims documentation vs. clinical documentation), our unadjusted hypoglycemia rates were close to trial results and consistent with other claims studies.⁴²

Limitations

We note a few limitations for this study. We observed a relatively short enrollment period for available patients. The average length of enrollment across the patients in the BBCIC DRN was 17 months, which included the 183-day lookback period, and was similar to the SCDM characterization.⁴³ The

short time frame was caused by the real-world phenomena of a commercially insured population, with employment changes or employers changing health insurance carriers influencing plan enrollment, as well as Medicare Advantage patients who may have changed enrollment plans or enrolled in traditional fee-for-service Medicare.^{44,45} The insulin exposure period for the population was 7 months for T2DM patients with 1 insulin episode and 10.8 for patients with T2DM and multiple insulin episodes. Our unadjusted cardiovascular outcome events may have reflected our shorter baseline period, study time length, and the average patient enrollment.^{46,47}

Because of limitations of the FDA Sentinel tools, the results of this study were reported based on insulin episode rather than on a patient level. This can make interpretation of the results confusing and requires attention when reporting outcomes. Additionally, as these data cover the years 2011-2015, patterns of care for T2DM may have changed since that time, limiting the applicability of some of our findings.

The true treatment duration is difficult to discern from prescribed days supply with insulin use, compared with other chronic medications, because of variable dosing that is often observed to maintain blood glucose stability in patients with diabetes. We attempted to account for this variability, and the risk of lack of adherence, by including a 60-day grace period at the end of the dispensed days supply. It is likely that the true exposure period was either under- or overestimated; we cannot know which. This is an imperfect approach but reflects the inherent limitation in using claims data to evaluate drugs with variable dosing.

Finally, despite a 183-day minimum time frame, only 38,330 patients with T2DM had a baseline A1c. Only 3 of 5 research partners contributed laboratory data to this study, and the data were not complete for all patients with A1c records available. Laboratory measures are not always captured in claims, and without access to electronic medical records or other records of patient care, laboratory measures are often lacking at the level of insurance claims. Also, the FDA Sentinel tools classify laboratory values in categories, so our analysis was limited to observing counts rather than analyzing A1c as a continuous variable.

Conclusions

For this descriptive study, we used the BBCIC DRN to determine the availability of key data elements, describe relevant populations, and define rates of severe hypoglycemic events, MACE, and A1c result availability among patients with T2DM exposed to long- or intermediate-acting insulins. In this study, we found a large cohort of patients with T2DM and insulin exposure. This cohort could be used in future studies to evaluate the safety and effectiveness of biosimilars.

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DISCLOSURES

This study was coordinated and funded by the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) and represents the independent findings of the BBCIC Insulins Principal Investigator and the BBCIC Insulins Research Team. Lockhart is employed by the BBCIC and the Academy of Managed Care Pharmacy (AMCP). Eichelberger was employed by the BBCIC and AMCP at the time of this study. McMahon-Walraven is employed by Aetna, a CVS Health business. Panozzo, Marshall, and Brown are employed by Harvard Pilgrim Healthcare Institute. Aetna was reimbursed for data and analytic support from Harvard Pilgrim Healthcare Institute and the Reagan Udall Foundation for the U.S. Food and Drug Administration. Aetna receives external funding through research grants and subcontracts with Harvard Pilgrim Healthcare Institute, which are funded by the FDA, NIH, PCORI, BBCIC, Pfizer, and GSK; the Reagan-Udall Foundation for IMEDS; and PCORI for the ADAPTABLE Study.

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