Descriptive analysis of the use of long- and intermediate-acting insulin, and key safety outcomes in adults with diabetes mellitus

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INTRODUCTION

Real-world safety and effectiveness is based on real-world data (RWD).

The Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) was convened by the Academy of Managed Care Pharmacy (AMCP) in 2015 to provide real-world, post-marketed evidence generation for innovator biologics and corresponding biosimilars in the US.[1,2]

BBCIC leverages the FDA Sentinel system data and analytic infrastructure: BBCIC Distributed Research Network (DRN). The BBCIC DRN uses the Sentinel Common Data Model for data standardization and Sentinel-based analytic tools for distributed analyses and examining medical product risk and benefit. [3]

Four BBCIC research teams formed to describe the biologics of the first-to-market biosimilars. The purpose was to learn about the RWD in the BBCIC DRN. Insulins was among the four descriptive analyses.

An estimated 29.1 million people in the United States have Type 1 (T1DM) or Type 2 (T2DM) diabetes, representing 9.3% of the total population.[4]

Objective
The insulin analysis objective was to describe adults with diabetes who use long-acting (LAI) or intermediate-acting (NPH) insulin, insulin episodes, diabetic outcomes, and potential confounders in the BBCIC DRN.

METHODS

This retrospective, observational study evaluated data from 6 BBCIC DRN data partners that contributed a population of over 57 million people currently covered by Commercial or Medicare-Advantage health insurance.

We identified adults with prevalent T1DM or T2DM and medical and drug coverage during **January 1, 2011 and September 30, 2015**. The population criteria included people 18 years or older, with at least one drug claim for long- or intermediate-acting insulin (LAI, NPH) alone or with either rapid/short acting insulin (R) or sulfonylurea (Sulfa), at least 183-days of medical and drug enrollment pre-insulin claim, and no claim evidence of insulin pumps or related supplies, gestational diabetes, liver disease, dialysis, end-stage renal disease, amputations, hemoglobinopathy, hemolytic anemia, sickle cell anemia, and blood transfusion, modified major adverse cardiac events (MACE), ED visit or hospitalization (excluded mortality), or hypoglycemia ED visit.

Insulin episodes was the **unit of analysis** and data was presented in either 4 subgroups: 1) T1DM w LAI 2) T1DM w NPH 3) T2DM with LAI 4) T2DM w NPH; or 6 sub-groups per diabetes type: 1) **LAI only**, 2) **LAI plus R**, 3) **LAI plus Sulfa**, 4) **NPH only**, 5) **NPH plus R**, and 6) **NPH plus Sulfa.** Episodes were followed through the earliest of: health plan disenrollment, medical-attended hypoglycemia or MACE (study outcomes), insulin regimen switch, current regimen discontinuation, or study end.

Study outcomes included medical-attended severe **hypoglycemic events**, modified- **MACE**, and hemoglobin **A1C lab results**.

Covariates included Combined Comorbidity Score (CCI) – a measure of probability of 1-year mortality, [5] 7 diagnoses, healthcare utilization, and Metformin use.

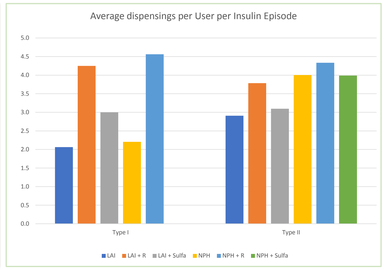
RESULTS

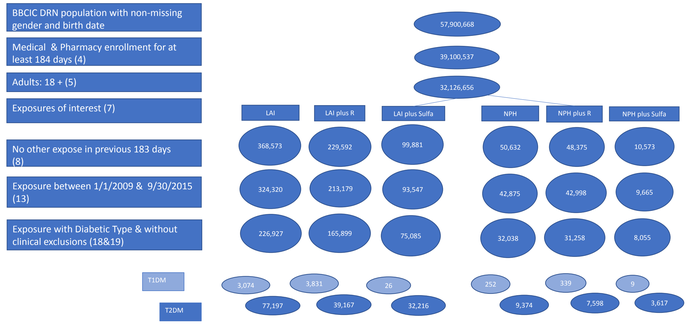
Study population. The BBCIC DRN had 4,591 T1DM and 103,951 T2DM unique patients who met the study criteria.

Insulin Episodes

T1DM. There were 3,105 T1DM patients with 4,908 LAI episodes and 297 patients with 470 NPH episodes. Over 61% had multiple insulin episodes and the average number of insulin dispensings per episode was between 2.1 and 4.6.

Demographics by diagnosis and insulin episode type	T1DM		T2DM	
Unique patients with at least one episode	4,591		103,951	
Characteristic[1]	LAI	NPH	LAI	NPH
Insulin episodes	4,908	470	84,322	16,770
Unique patients	3,105	297	53,446	11,027
Episodes per patient	1.58	1.58	1.58	1.52
Females (% based on patients)	1,149 (37%)	106 (36%)	24,570 (46%)	5,755 (52%)
Age in years, Mean (SD)	34.6 (12.3)	38.6 (13.5)	55.1 (11.5)	57.1 (12.6)
Age group: 18-49 years	4,210 (85.8%)	354 (75.3%)	27,061 (32.1%)	4,655 (27.8%)
Age group: 50-64 years	665 (13.5%)	105 (22.3%)	43,326 (51.4%)	7,872 (46.9%)
Age group: 65-79 years	31 (0.6%)	8 (1.7%)	11,639 (13.8%)	3,491 (20.8%)
Age group: 80+ years	<10 (0%)	<10 (0.6%)	2296 (2.7%)	752 (4.5%)





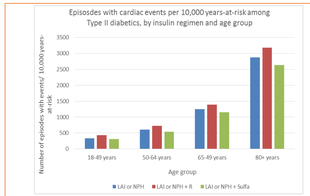
Insulin Episodes

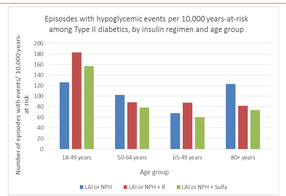
T2DM. There were 53,446 T2DM patients with 84,322 LAI episodes and 11,027 T2DM patients with 16,770 NPH episodes. 47% of patients with a LAI episode and 51% of patients with a NPH episode had a Metformin dispensing. Over 52% patients had multiple insulin episodes and the average number of insulin dispensings per episode was between 2.9 and 4.3.

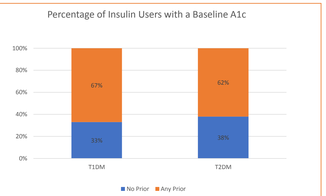
Baseline characteristics by diagnosis and episode insulin type					
		T1DM		T2DM	
Unique patients with at least one episode		4,591		103,951	
Characteristic[1]		LAI	NPH	LAI	NPH
Clinical Characteristics	Combined Comorbidity Score, Mean (SD)	0.1 (0.5)	0 (0.6)	0.2 (1.3)	0.5 (1.4)
	Gastroparesis	<10 (0.1%)	0 (0%)	266 (0.3%)	54 (0.3%)
	Hyperlipidemia	685 (14%)	74 (15.7%)	35,307 (41.9%)	5,318 (31.7%)
	Hypertension	459 (9.4%)	73 (15.5%)	45,248 (53.7%)	7,984 (47.6%)
	Metformin	137 (2.8%)	15 (3.2%)	39,462 (46.8%)	8,508 (50.7%)
	Nephropathy & Chronic Kidney Disease	19 (0.4%)	<10 (0.2%)	3,428 (4.1%)	1,364 (8.1%)
	Obesity & Abnormal Weight Gain	59 (1.2%)	<10 (1.5%)	9,935 (11.8%)	2,273 (13.6%)
	Peripheral neuropathy	68 (1.4%)	10 (2.1%)	5,381 (6.4%)	2,265 (13.5%)
	Retinopathy	195 (4%)	19 (4%)	6,107 (7.2%)	1,852 (11%)
Health Service Utilization (HSU)	Ambulatory visits	2.8 (3.7)	2.7 (4)	5.2 (6.2)	5.1 (6.3)
	Emergency room visits	0 (0.2)	0 (0.2)	0.2 (0.5)	0.1 (0.5)
	Inpatient hospital stays	0 (0.1)	0 (0.1)	0.1 (0.3)	0.1 (0.3)
	Other Ambulatory visits	0.6 (1.4)	1 (2.5)	1.7 (4.5)	4.4 (6)
	Prescriptions dispensed	8 (7)	7.3 (7.6)	16.1 (14.3)	15.4 (13.3)
	Generic prescriptions dispensed	3.6 (2.4)	3.3 (2.6)	6.5 (4.3)	7 (4.4)
	Unique drug classes	3.1 (2.3)	2.8 (2.3)	6.1 (4.1)	6.7 (4.2)

Diabetic Outcomes

- **Modified MACE.** The unadjusted MACE rates were 40.2 (T1DM) and 676.9 (T2DM) users per 10,000 patient-years at risk (10kPYR).
- **Hypoglycemia.** The unadjusted severe hypoglycemic event rates were 34.9 (T1DM) and 96.9 (T2DM) 10kPYR.
- **A1c.** Only 33% of T1DM and 38% of T2DM patients had a baseline A1C and less than 50% had a follow-up A1C result.







Covariates

T1DM. The most frequent comorbidity was hyperlipidemia and the CCI was low at 0.1 due to the clinical exclusions. Patients with a LAI episodes had 3 ambulatory visits and 8 prescriptions filled in 3 drug classes. Patients with NPH episodes had 3 ambulatory visits and 7 prescriptions filled in 3 drug classes.

T2DM. The most frequent comorbidity was hypertension, with CCI less than 1% mortality probability. For LAI episodes, patients had 5 ambulatory visits and 16 prescriptions filled in 6 drug classes. Patients with NPH episodes had 5 ambulatory visits and 15 prescriptions filled in 7 drug classes.

ACKNOWLEDGEMENTS

This study was supported by the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC).
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CONCLUSIONS

- With the BBCIC DRN we are able to reliably identify and characterize exposures, outcomes, and potential confounders for a large population of people with diabetes.
- Unadjusted MACE and severe hypoglycemic rates were consistent with other clinical and observational studies.
- The limited number of baseline and follow-up A1c values will require consistency demonstrated among data sources and de-novo programming for numeric lab values.
- Significant diabetic diagnosis inconsistency, variation in days supply and use of rapid acting insulin and sulfonylurea adherence requires additional methods development.
- Careful study design, including attention to length of episode gaps and use of algorithms to accurately identify patients with Type 1 and Type 2 diabetes, is essential in observational studies using large administrative claims data.