Real-World Outcomes Analysis of Cardiac Events Among Medicare Beneficiaries Utilizing Insulin to Treat Type 2 Diabetes Mellitus: A Retrospective Analysis of a US Claims Database

Kendall Smith, BS; Wenxuan Cai, PhD, PharmD; Agata Siwak, PharmD; Marleen Wickizer, PharmD, AE-C, CDCES; Kevin Look, PhD, PharmD; Brett Gadow, PharmD

School of Pharmacy
UNIVERSITY OF WISCONSIN-MADISON

BACKGROUND

- Type 2 Diabetes Mellitus (T2DM) is a chronic disease that is difficult to manage and a major risk factor for atherosclerotic cardiovascular disease (ASCVD).[1] Nonadherence to medication therapy is a critical barrier for disease control and is often associated with financial concerns.
- Insulin is a potent antidiabetic medication class and is effective at managing patients with poor glycemic control.[2] However, 25% of patients were observed to have cost-related insulin underuse leading to hyperglycemia.[3]
- Glucagon-like peptide-1 receptor agonists (GLP-1 RA) have shown efficacy in treating patients with T2DM and high cardiovascular risk, and studies have shown the combination with insulin helps reduce total daily insulin use while lowering A1C levels and providing cardiac protection not seen with insulin monotherapy.[4,5] However, adding an additional expensive medication can further intensify financial burdens for these patients.
- The Inflation Reduction Act has capped out-of-pocket insulin costs for Medicare beneficiaries to help make it a more affordable treatment option. However, there are emerging T2DM treatment options, such as GLP-1 RA, that provide additional ASCVD benefits which may lead to them being utilized more than insulin despite now being lower in cost. Currently, there are few studies utilizing real-world claims data to evaluate the correlation between GLP-1 RA utilization and ASCVD events among insulin-dependent T2DM patients.

OBJECTIVES

- Determine GLP-1 RA utilization and the correlation with cardiovascular outcomes among Medicare beneficiaries with a T2DM diagnosis and using insulin.
- Analyze current costs associated with insulin and GLP-1 RA for T2DM treatment using pharmacy claims for Medicare beneficiaries.

METHODS

DESIGN

- A pharmacy benefit manager (PBM) led retrospective claims analysis was conducted over a two-year period from January 1, 2020 to December 31, 2022, among beneficiaries with T2DM utilizing insulin.
- The distribution of beneficiaries prescribed insulin monotherapy or in combination with a GLP-1 RA was compared between the beneficiaries with an ASCVD event and without an ASCVD event.
- Statistical analysis was performed using Fisher's exact test and multivariable logistic regression, adjusting for age and the use of other cardio-protective medications (i.e., statin, renin-angiotensin system antagonist, sodium-glucose cotransporter-2 (SGLT2) inhibitor, or P2Y12 inhibitor) and accounting for confounding effects for the likelihood of an ASCVD event.
- A follow-up review on the financial burden was performed by comparing the percentage of member and plan spend on insulin and GLP-1 RA in the case population.

STUDY POPULATION

- Medicare beneficiaries were included in the case population if they had a diagnosis of T2DM, pharmacy claims for insulin monotherapy or in combination with a GLP-1 RA from 2020 to 2021, and medical claims for an ASCVD event from 2021 to 2022.
- Medicare beneficiaries utilizing insulin for the treatment of Type 1 Diabetes Mellitus and beneficiaries with T2DM younger than 45 years old and older than 85 years old were excluded from this study.
- The control population consisted of the same inclusion criteria as the case population but without a medical claim for an ASCVD event from 2021 to 2022.
- An ASCVD event was defined by the 2018 AHA/ACC Multi-society Guideline on the Management of Blood Cholesterol[6] (Figure 1).

OUTCOMES:

- The outcomes of interest were ICD-10 coded ASCVD events from 2021 to 2022, and the exposure of interest was being prescribed a GLP-1 RA in addition to insulin from 2020 to 2021 prior to having an ICD-10 coded ASCVD event.

RESULTS

- A total of 6,514 Medicare beneficiaries diagnosed with T2DM and utilizing insulin for glycemic control were included in the analysis. The case population had 94 beneficiaries and the control population (patients without medical claim data for an ASCVD event) had 6,420 beneficiaries (Figure 1, Table 1).
- In the case population (patients with medical claim data indicative of ASCVD event), most were prescribed insulin monotherapy compared to combination therapy with a GLP-1 RA (66% versus 34%). Similar proportions were seen in the control population (59% versus 41%) (Table 2).
- The analysis revealed that the odds of being prescribed a GLP-1 RA was lower by 27% among beneficiaries with T2DM utilizing insulin who experienced an ASCVD event in the subsequent year compared to beneficiaries with T2DM who did not experience an ASCVD event. However, the result was not statistically significant (odds ratio (OR) = 0.73; p-value = 0.15) (Table 4).
- After adjusting for potential confounders, including age, the use of statins, renin-angiotensin system antagonist, SGLT2 inhibitor, and P2Y12 inhibitor, the OR = 0.67 (p-value = 0.07), not statistically significant (Table 4).

FIGURE 1: BENEFICIARY POPULATION INCLUSION/EXCLUSION FLOWCHART

1. Conducted primary and secondary literature searches on PubMed and Cochrane Library.
   - Reviewed ASCVD event criteria
   - Search terms: GLP-1 RA, insulin, cardiac OR CVD outcomes, ASCVD
2. Determined ICD-10 carrier codes used to identify ASCVD events.
   - ASCVD events: non-ST elevated myocardial infarction, ST elevated myocardial infarction, unstable/stable angina, peripheral artery disease, percutaneous coronary intervention, general ASCVD, stroke, coronary artery bypass graft, transient ischemic attack, cerebral infarction without residual effects
3. Utilized the medical claims analyzer to determine population with ASCVD ICD-10 codes.
   - Total ASCVD Population: 1,711 members
   - Medicare Employer Group: 9 groups
4. Utilized pharmacy claim data to establish case population: T2DM patients with ASCVD events who utilized insulins and identify control population.
   - Case population: 94 members
   - Control population: 6,420 members
   - Exclusion Criteria: Type 1 Diabetes Mellitus ICD-10 coded diagnosis; age younger than 45 y/o or older than 85 y/o
5. Utilized pharmacy claims to compare GLP-1 RA utilization between the case and control population and conduct statistical analysis.
   - Statistical Analysis: Fisher's exact test; logistic regression
   - Odds ratio: 95% CI interval

TABLE 1: POPULATION DEMOGRAPHICS (N=6514)

	Case Population (ASCVD, n = 94)	Control Population (No ASCVD, n = 6420)
Age (45-85 y/o)		
< 50 y/o, n(%)	1 (1%)	337 (5%)
50-59 y/o, n(%)	18 (19%)	1499 (23%)
60-69 y/o, n(%)	38 (40%)	2525 (39%)
70-79 y/o, n(%)	31 (33%)	1505 (23%)
>/= 80 y/o, n(%)	6 (6%)	554 (9%)
Average age (standard deviation)	67 (9)	65 (10)
Gender		
Female, n(%)	41 (43%)	3404 (53%)
Male, n(%)	53 (57%)	3016 (47%)
Medicare Employer Group		
Group 1, n(%)	2 (2%)	113 (2%)
Group 2, n(%)	0 (0%)	78 (1%)
Group 3, n(%)	0 (0%)	3 (0.0005%)
Group 4, n(%)	46 (49%)	3264 (51%)
Group 5, n(%)	0 (0%)	392 (6%)
Group 6, n(%)	0 (0%)	111 (2%)
Group 7, n(%)	7 (7%)	94 (2%)
Group 8, n(%)	34 (36%)	1962 (31%)
Group 9, n(%)	5 (5%)	403 (6%)

TABLE 2: PRESCRIBING PREVALENCE OF INSULIN AND GLP-1 RAS

	Case Population (ASCVD)	Control Population (No ASCVD)
Medication Type		
Insulin Monotherapy, n%	62 (66%)	3765 (59%)
Insulin + GLP-1 RA, n%	32 (34%)	2655 (41%)

TABLE 3: STUDY POPULATION ADDITIONAL CARDIO-PROTECTIVE MEDICATION USE

	Case Population (Insulin only) n = 62	Case Population (Insulin and GLP-1 RA) n = 32	Control Population (Insulin only) n = 3765	Control Population (Insulin and GLP-1 RA) n = 2655
Medication Class				
Glucagon-Like Peptide-1 receptor agonist (GLP-1 RA), n(%)	0 (0%)	32 (34%)	0 (0%)	2655 (41%)
Statin, n(%)	57 (92%)	31 (97%)	3023 (80%)	2372 (89%)
Sodium Glucose Cotransporter-2 inhibitor (SGLT2i), n(%)	10 (16%)	10 (31%)	567 (15%)	733 (28%)
Angiotensin-Converting Enzyme inhibitor/Angiotensin Receptor Blocker (ACEI/ARB), n(%)	43 (69%)	27 (84%)	2341 (62%)	1935 (73%)
P2Y12 inhibitor, n(%)	26 (42%)	20 (63%)	465 (12%)	333 (13%)

FIGURE 2: PREVALENCE OF CARDIO-PROTECTIVE MEDICATION USE, CASE POPULATION

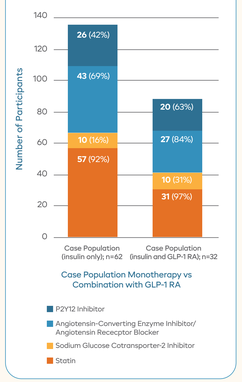


FIGURE 3: PREVALENCE OF CARDIO-PROTECTIVE MEDICATION USE, CONTROL POPULATION

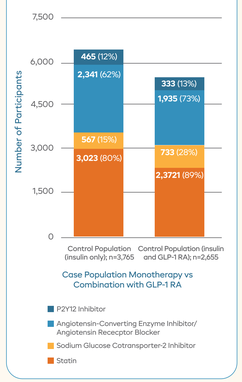


TABLE 4: STATISTICAL ANALYSIS FOR THE ODDS OF GLP-1 RA UTILIZATION AMONG THE CASE POPULATION (ASCVD)

	Odds ratio	*p*-value	Confidence Interval (95%)
Statistical Test			
Fisher's exact test	0.74	0.17	0.46 – 1.14
Logistic regression without adjustment	0.73	0.15	0.48 – 1.12
Logistic regression with adjustment[1]	0.74	0.17	0.48 – 1.14
Logistic regression with adjustment[2]	0.67	0.07	0.44 – 1.04

[1] Adjusted by age
[2] Adjusted by age and the use of statin, renin-angiotensin system antagonist, SGLT2 inhibitor and P2Y12 inhibitor

FIGURE 4: PERCENT COST PAID BY THE BENEFICIARIES IN THE CASE POPULATION (ASCVD) PER MEDICATION IN 2020

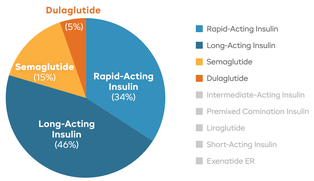
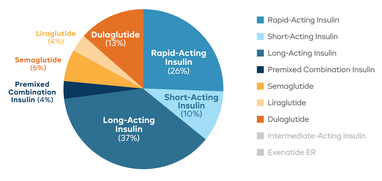


FIGURE 5: PERCENT COST PAID BY THE PLAN FOR THE CASE POPULATION (ASCVD) PER MEDICATION IN 2020



LIMITATIONS

- Inclusion was based on 1 paid pharmacy claim for insulin monotherapy or combination therapy with a GLP-1 RA. This does not account for treatment failure, discontinuation, or nonadherence contributing to the likelihood of an ASCVD event.
- All events rely on accurate ICD-10 coding; inaccurate coding may skew the study's results.
- The timeframe of the study may not have been an adequate length to capture an appropriate number of ASCVD events. A longer study timeframe may have captured more ASCVD events to appropriately power the study.

CONCLUSIONS

- Beneficiaries who experienced an ASCVD event were less likely to be prescribed a GLP-1 RA when already utilizing insulin for T2DM treatment compared to beneficiaries with T2DM who did not experience an ASCVD event.
- Continued health outcomes research is warranted to investigate GLP-1 RA-associated cardiac outcomes and cost compared to insulin once the Inflation Reduction Act is more broadly implemented.
- In analyzing the cost of insulin and GLP1-RA for the case population, the plan as well as members were spending more annually on insulin compared to GLP-1 RA with long-acting insulin being the drug class with highest spending.

DISCLOSURE

This research was conducted by Navitus Health Solutions, LLC in Madison, WI and the University of Wisconsin-Madison School of Pharmacy without external funding.

REFERENCES

1. Evans M, Engberg S, Faurby M, Fernandes JDDR, Hudson P, Polonsky W. Adherence to And Persistence With Antidiabetic Medications And Associations With Clinical And Economic Outcomes in People With Type 2 Diabetes Mellitus: A Systematic Literature Review. *Diabetes Obes Metab.* 2022;24(3):377-390. doi:10.1111/dom.14603
2. ElSayed NA, Aleppo G, Aroda VR, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2023. *Diabetes Care.* 2023;46(Suppl 1):S140-S157. doi:10.2337/dc23-S009
3. Herkert D, Vijayakumar P, Luo J, et al. Cost-Related Insulin Underuse Among Patients With Diabetes. *JAMA Intern Med.* 2019;179(1):112-114. doi:10.1001/jamainternmed.2018.5008
4. Meyer J, Dreischmeier E, Lehmann M, Phelan J. The Effects of Adding Semaglutide to High Daily Dose Insulin Regimens in Patients With Type 2 Diabetes. *Ann Pharmacother.* 2023;57(3):241-250. doi:10.1177/10600280221107381
5. Retnakaran R, Pu J, Ye C, Emery A, Kramer CK, Zinman B. The Vascular Function Effects of Adding Exenatide or Meal Insulin to Basal Insulin Therapy in Early Type 2 Diabetes. *Cardiovasc Diabetol.* 2023;22(1):50. Published 2023 Mar 9. doi:10.1186/s12933-023-01781-z
6. Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in J Am Coll Cardiol. 2019 Jun 25;73(24):3234-3237]. *J Am Coll Cardiol.* 2019;73(24):3168-3209. doi:10.1016/j.jacc.2018.11.002

© 2023 Navitus Health Solutions, LLC. All rights reserved. 5762-0923PO