



# Beneficial Agents for Patients With Type 2 Diabetes and Cardiovascular Disease or Obesity: Utilization in an Era of Accumulating Evidence

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This study was an analysis of a national sample of U.S. medical office visits from 2014 to 2016, a period when evidence of effectiveness was emerging for a variety of beneficial type 2 diabetes agents with regard to potential reduction in diabetes comorbidities. Ideal therapy was defined as an American Diabetes Association–identified beneficial agent plus metformin. The associations between atherosclerotic cardiovascular disease or obesity and use of these agents were explored.

Accumulating evidence (1–7) about antidiabetic agents that are beneficial in patients with atherosclerotic cardiovascular disease (ASCVD) or obesity, including selected sodium–glucose cotransporter 2 (SGLT2) inhibitors and glucagon-like peptide 1 (GLP-1) receptor agonists, was reflected in recently published guidelines (8,9). Adoption of such new therapeutic approaches may depend on factors such as patient attributes rather than on guideline promulgation alone (10,11). Information about adoption of new therapies is needed to inform educational efforts and future analyses of treatment trends. The present exploratory and hypothesis-generating study was conducted to assess the rate and predictors of use of beneficial agents for ASCVD and obesity during a time period when evidence of their effectiveness was emerging, but guidelines for their use had not yet been published.

## Design and Methods

### Data Source and Sample

Data were obtained from the National Ambulatory Medical Care Survey (NAMCS), an annual, nationally

representative (12) and widely used (13) assessment of U.S. office-based physician visits sampled using a complex multistage design (14). Data for the survey are collected from medical records using automated, laptop-based tools (14). Collected data elements used in this study included BMI, up to five diagnoses associated with the visit, and indicators of chronic conditions (e.g., asthma, coronary artery disease [CAD], cerebrovascular disease [CEBVD], chronic kidney disease [CKD], and end-stage renal disease [ESRD]), collected for all patients regardless of visit-related diagnoses (14). Also used were indicators of up to 20 prescribed medications coded with the Lexicon Plus classification system licensed for the NAMCS by Cerner Multum (14).

The sample included visits made during the 2014–2016 period by patients who were  $\geq 18$  years of age and had either type 2 or unspecified type diabetes and at least one prescribed antidiabetic drug (Supplementary Appendix 1). Excluded were patients with type 1 diabetes and visits resulting in emergency or inpatient care.

### Outcomes and Predictors

The primary outcome was prescribed ideal therapy, defined as metformin plus an agent identified in the guidelines (8,9) as beneficial (Supplementary Appendix 1). A secondary outcome was a prescribed beneficial agent without metformin. Key independent variables of interest were ASCVD (i.e., CAD, CEBVD, peripheral arterial disease, or history of myocardial infarction or stroke) and obesity (i.e., BMI  $\geq 30$  kg/m<sup>2</sup>

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**TABLE 1** Percentage of Patients Receiving Ideal Therapy or Beneficial Agent Only, by Type of Therapy and Patient Characteristics

	CV Benefit		Weight Loss Benefit	
	Ideal Therapy*	Beneficial Agent Only†	Ideal Therapy*	Beneficial Agent Only†
All patients, unweighted <i>N</i>	146	97	218	128
Estimated total nationally, <i>N</i>	6,258,665	4,109,148	8,573,702	5,655,308
Estimated total nationally, %	3.4	2.2	4.7	3.1
Sex, %				
Male	3.6	2.0	4.8	2.9
Female	3.2	2.5	4.6	3.3
Race, %				
White	3.3	2.8	4.8	3.8
Nonwhite	3.8‡	NR	4.4	0.5‡
Age-group, %				
18–54 years	5.6§	2.9	7.3§	3.5
55–74 years	3.5§	2.6	5.0§	3.8
≥75 years	1.0‡§	0.6‡	1.2‡§	1.0‡
Specialty, %				
Not CV	3.5	2.4	4.8	3.3
CV	2.2‡	0.6‡	3.0‡	0.8‡
Number of unique drugs (all), %				
2–6	3.2‡	2.1‡	4.1	3.0
7–9	4.0	1.4‡	6.3	1.6‡
≥10	3.5	2.5	4.5	3.2
Comorbidities, %				
Hypertension	3.1	2.2	4.4	3.0
Hyperlipidemia	4.0	2.2	5.2	2.9
Kidney disease¶	0.5‡*	1.2‡	1.1‡#	2.8‡
Retinopathy	4.2‡	1.3‡	4.7‡	2.6‡
Kidney disease¶ or retinopathy#	1.2‡#	1.2‡	1.8‡#	2.5‡
CCI score, %				
1	4.7#	2.7	6.3§	3.8
2	1.5‡#	2.2	2.0§	2.3
3 or 4	2.2‡#	1.2	3.3§	2.0‡
≥5	0.0‡#	1.0‡	2.0‡§	2.2‡
ASCVD status, %				
No	4.1§	2.4	5.4§	3.2
Yes	1.1‡§	1.8‡	2.2§	2.7
Obesity status, %**				
No	1.8§	1.5	2.7§	2.3‡
Yes	5.1§	3.0	6.8§	4.0

\*Indicates receipt of beneficial agent plus metformin, regardless of other drugs prescribed. †Indicates receipt of beneficial agent, but no metformin, regardless of other drugs prescribed. ‡Estimate does not meet one or more criteria for statistical reliability; interpret results cautiously. § $P < 0.01$ : Pearson  $\chi^2$  tests adjusted for complex sampling design; dependent variable was ideal versus nonideal therapy. ||One drug not shown because, by definition, no patient with only one drug could have ideal therapy. ¶Diagnosis code indicating glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup> or chronic condition indicator for CKD or ESRD. # $P < 0.05$ : Pearson  $\chi^2$  tests adjusted for complex sampling design; dependent variable was ideal versus nonideal therapy. \*\*BMI  $\geq 30$  kg/m<sup>2</sup> or, for patients with missing BMI, obesity indicator recorded by data collectors.

or, when BMI was missing, an obesity indicator recorded by data collectors).

Covariates were based on previously reported predictors of medication use among older adults and patients with diabetes and included female sex; residence in the

southern region of the United States; nonwhite race; age-group; presence of hypertension, hyperlipidemia, CKD, and retinopathy or poor health measured using the Charlson Comorbidity Index (CCI; Supplementary Appendix 2); and total unique medication count (15–18).

## Statistical Analyses

In bivariate analyses, Pearson  $\chi^2$  statistics assessed the significance of the associations of ASCVD, obesity, and covariates with the primary and secondary outcomes. Logistic regression analyses controlled for patient characteristics. To reduce the number of predictors in the regression models, only those covariates that were significant in bivariate analyses were included. Because of conceptual overlap of the CCI and drug counts, only the CCI was included. All analyses were performed with a critical *P* value of 0.05 and assessed for statistical reliability (19) using the SPSS version 25.0 (IBM Corp.) complex sample procedures to adjust for the multistage sampling design (12,14).

## Results

Of 10,174 sampled visits made by adults with type 2 or unspecified type diabetes in the 2014–2016 period, 5,425 included the prescribing of at least one antidiabetic medication. The final sample included 5,408 visits, representing 182.7 million nationwide. Of these, 3.4 and 4.7%, respectively, included prescribed ideal pharmacotherapy for cardiovascular (CV) benefit and weight benefit (Table 1). Receipt of ideal pharmacotherapy was less likely for patients with ASCVD than for those without (1.1 vs. 4.1%, respectively) but more likely for patients with obesity than for those without (6.8 vs. 2.7%; both *P* < 0.001). Significant negative covariate predictors in both analyses included advancing age, CKD, retinopathy, and number of comorbidities.

In adjusted analyses (Figure 1), age of  $\geq 75$  years (reference: 18–74 years) was associated with reduced odds of ideal therapy, both for CV benefit (odds ratio [OR] 0.300, 95% CI 0.094–0.963) and for weight loss benefit (OR 0.276, 95% CI 0.106–0.718). CCI score of 2 (reference: 1) was also associated with decreased odds of ideal therapy (CV benefit OR 0.362, 95% CI 0.174–0.754; weight loss benefit OR 0.325, 95% CI 0.175–0.606). CCI score  $\geq 3$  was not significantly associated with receiving ideal therapy.

Similar to bivariate analyses, after adjusting for these factors, ASCVD was associated with decreased odds (OR 0.368, 95% CI 0.165–0.819) and obesity with increased odds (OR 2.208, 95% CI 1.386–3.517) of receiving ideal therapy. Nonwhite race was a significant negative predictor of receiving a beneficial agent only (CV benefit OR 0.132, 95% CI 0.061–0.288; weight loss benefit OR

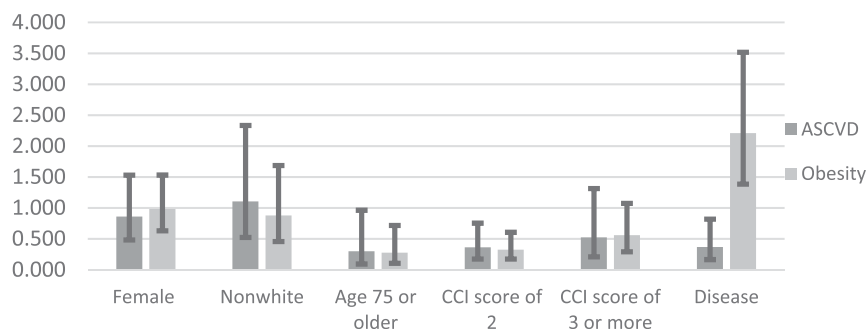
0.122, 95% CI 0.054–0.277). Neither ASCVD nor obesity was a significant predictor of beneficial agent–only pharmacotherapy. Measures of model fit and quality were suboptimal, with most coefficients not meeting standards for statistical reliability, likely because only small numbers of patients were prescribed a beneficial agent.

## Discussion and Conclusion

This exploratory, hypothesis-generating retrospective analysis of a nationally representative sample suggests that, as evidence of CV and weight loss benefits emerged, obesity was a positive predictor of ideal therapy, whereas ASCVD, older age, and comorbid conditions were negative predictors. Findings suggest that health care providers or patients may have been more aware of weight loss benefits than of CV benefits of therapies. Publication timing may have contributed to this pattern because evidence of weight loss benefits generally emerged earlier (2–4,20,21) than did evidence related to CV benefits (1,5,6). Medication cost, which is sometimes considered by physicians when making prescribing decisions (22,23), may also have affected prescribing behaviors because newer medications are relatively high in cost to payers and patients. Both these factors may help to explain the low rate of usage of beneficial pharmacotherapeutic products observed in this study.

Important limitations of this work should be noted. These include small numbers of patients using beneficial agents and no information about pharmacotherapies previously tried by patients. Confounding by unmeasured factors such as disease severity, social determinants of health, or adoption of recommended lifestyle-modification strategies (9) is also possible. Additionally, study results represent medications prescribed, not necessarily those consumed by patients. Finally, because visits included in this research took place during a period before to the issuance of ADA guidelines on the benefits of the newer medications, the rates of use described herein may not reflect current practice.

As evidence about these and other beneficial agents continues to accumulate (24), monitoring of utilization trends may be helpful to inform educational strategies. The findings of this study, a first step in that effort, suggest a hypothesis that, compared with CV benefits, weight loss benefits may be more likely to prompt use of beneficial agents. Because this study was intended to be exploratory and hypothesis-generating, further research, preferably combining insights from the fields of health psychology



**FIGURE 1** Adjusted odds of ideal therapy for patients with type 2 diabetes and ASCVD or obesity.

and pharmacy, will be needed to reassess these findings in a larger sample and to examine how patients and providers become aware of and choose beneficial pharmacotherapies.

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### DUALITY OF INTEREST

No potential conflicts of interest relevant to this article were reported.

### AUTHOR CONTRIBUTIONS

K.B. was responsible for the conception and design of the study, assisted by K.A.F. Data analysis was performed by K.A.F., assisted by K.B. K.A.F. drafted the manuscript. Both authors contributed to manuscript revision and read and approved the final manuscript. K.B. and K.A.F. are co-guarantors of the work, had full access to all the study data, and take responsibility for the integrity of the data and the accuracy of the data analysis.

### REFERENCES

- Schnell O, Rydén L, Standl E, Ceriello A; D&CVD EASD Study Group. Current perspectives on cardiovascular outcome trials in diabetes. *Cardiovasc Diabetol* 2016;15:139
- Robinson LE, Holt TA, Rees K, Randeve HS, O'Hare JP. Effects of exenatide and liraglutide on heart rate, blood pressure and body weight: systematic review and meta-analysis. *BMJ Open* 2013;3:e001986
- Häring HU, Merker L, Seewaldt-Becker E, et al.; EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2013;36:3396–3404
- Rosenstock J, Jelaska A, Frappin G, et al.; EMPA-REG MDI Trial Investigators. Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes. *Diabetes Care* 2014;37:1815–1823
- Inzucchi SE, Zinman B, Wanner C, et al. SGLT-2 inhibitors and cardiovascular risk: proposed pathways and review of ongoing outcome trials. *Diab Vasc Dis Res* 2015;12:90–100
- Marso SP, Bain SC, Consoli A, et al.; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016;375:1834–1844
- Häring HU, Merker L, Seewaldt-Becker E, et al.; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. *Diabetes Care* 2014;37:1650–1659
- Cosentino F, Grant PJ, Aboyans V, et al.; ESC Scientific Document Group. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. *Eur Heart J* 2020;41:255–323
- American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: *Standards of Medical Care in Diabetes—2020*. *Diabetes Care* 2020;43(Suppl. 1):S98–S110
- Lublóy Á. Factors affecting the uptake of new medicines: a systematic literature review. *BMC Health Serv Res* 2014;14:469
- Rodríguez F, Lin S, Maron DJ, Knowles JW, Virani SS, Heidenreich PA. Use of high-intensity statins for patients with atherosclerotic cardiovascular disease in the Veterans Affairs Health System: practice impact of the new cholesterol guidelines. *Am Heart J* 2016;182:97–102
- Centers for Disease Control and Prevention, National Center for Health Statistics. NAMCS scope and sample design. Available from [https://www.cdc.gov/nchs/ahcd/ahcd\\_scope.htm](https://www.cdc.gov/nchs/ahcd/ahcd_scope.htm). Accessed 31 July 2019
- Centers for Disease Control and Prevention, National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). List of publications (1/11/2019). Available from [https://www.cdc.gov/nchs/data/ahcd/namcs\\_nhamcs\\_publication\\_list.pdf](https://www.cdc.gov/nchs/data/ahcd/namcs_nhamcs_publication_list.pdf). Accessed 31 July 2019
- Centers for Disease Control and Prevention, National Center for Health Statistics. 2016 NAMCS micro-data file documentation. Available from [https://www.cdc.gov/nchs/ahcd/datasets\\_documentation\\_related.htm](https://www.cdc.gov/nchs/ahcd/datasets_documentation_related.htm). Accessed 31 July 2019
- Qato DM, Trivedi AN. Receipt of high risk medications among elderly enrollees in Medicare Advantage plans. *J Gen Intern Med* 2013;28:546–553

16. Gentile S, Strollo F, Viazzi F, et al.; The Amd-Annals Study Group. Five-year predictors of insulin initiation in people with type 2 diabetes under real-life conditions. *J Diabetes Res* 2018;2018: 7153087
17. Cooper AL, Dore DD, Kazis LE, Mor V, Trivedi AN. Predictors of high-risk prescribing among elderly Medicare Advantage beneficiaries. *Am J Manag Care* 2014;20:e469–e478
18. 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;173:676–682
19. Parker JD, Talih M, Malec DJ, et al. National Center for Health Statistics data presentation standards for proportions. *Vital Health Stat 2* 2017;175:1–22
20. Bailey CJ, Gross JL, Hennicken D, Iqbal N, Mansfield TA, List JF. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Med* 2013;11:43
21. Ladenheim EE. Liraglutide and obesity: a review of the data so far. *Drug Des Devel Ther* 2015;9:1867–1875
22. Tamblyn R, Winslade N, Qian CJ, Moraga T, Huang A. What is in your wallet? A cluster randomized trial of the effects of showing comparative patient out-of-pocket costs on primary care prescribing for uncomplicated hypertension. *Implement Sci* 2018;13:7
23. Hunter WG, Hesson A, Davis JK, et al. Patient-physician discussions about costs: definitions and impact on cost conversation incidence estimates. *BMC Health Serv Res* 2016; 16:108
24. Gerstein HC, Colhoun HM, Dagenais GR, et al.; REWIND Investigators. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 2019;394:121–130