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Letters

Prescription of Glucagon-Like Peptide-1 Receptor Agonists by Cardiologists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are a class of incretin mimetics with multisystem cardiometabolic effects. Six GLP-1RAs are approved for improving glycemic control by the U.S. Food and Drug Administration (FDA). Four therapies (albiglutide, dulaglutide, liraglutide, and semaglutide) have been demonstrated to reduce cardiovascular events in high-risk patients with type 2 diabetes mellitus (T2DM) in cardiovascular outcomes trials (NCT02465515, NCT01394952, NCT01179048, and NCT01720446). Subsequently, the FDA expanded the labeling of liraglutide to lower major adverse cardiovascular events in T2DM and established cardiovascular disease (CVD). While GLP-1RAs have been in clinical use for more than a decade, utilization by cardiologists is unknown. We aimed to describe specialty-specific prescription patterns of GLP-1RAs at a tertiary care hospital system.

We identified all first-time prescriptions of GLP-1RAs on formulary (albiglutide, dulaglutide, exenatide [immediate-release/extended-release], and liraglutide) across the multicenter Partners HealthCare system from April 2005 (FDA approval of first GLP-1RA) to August 2018. Two recently approved GLP-1RAs (semaglutide and lixisenatide) are not yet on formulary, and albiglutide has been withdrawn from the market. Statistical analyses were performed with STATA 14.1 (StataCorp, College Station, Texas). The Partners HealthCare Institutional Review Board approved the study.

Overall, 7,609 patients were prescribed GLP-1RAs (median age 61 years [25th to 75th percentiles: 53 to 69 years], 54% women, 76% white, 34% CVD). Most patients (64%) prescribed GLP-1RA by cardiologists had CVD, whereas rates were lower for other specialties (23% to 40%). The median number of background glucose-lowering therapies was 2 (25th to 75th percentiles: 1 to 2). Background therapy with insulin (54%) or metformin (64%) were common, whereas few patients were on sodium-glucose cotransporter 2 inhibitors (4%) or dipeptidyl peptidase-4 inhibitors (4%). From 2005 to 2015, quarterly GLP-1RA prescriptions rose steadily, followed by a decrease in the first half of 2016, and a subsequent increase from the second half of 2016 onward (**Figure 1**).

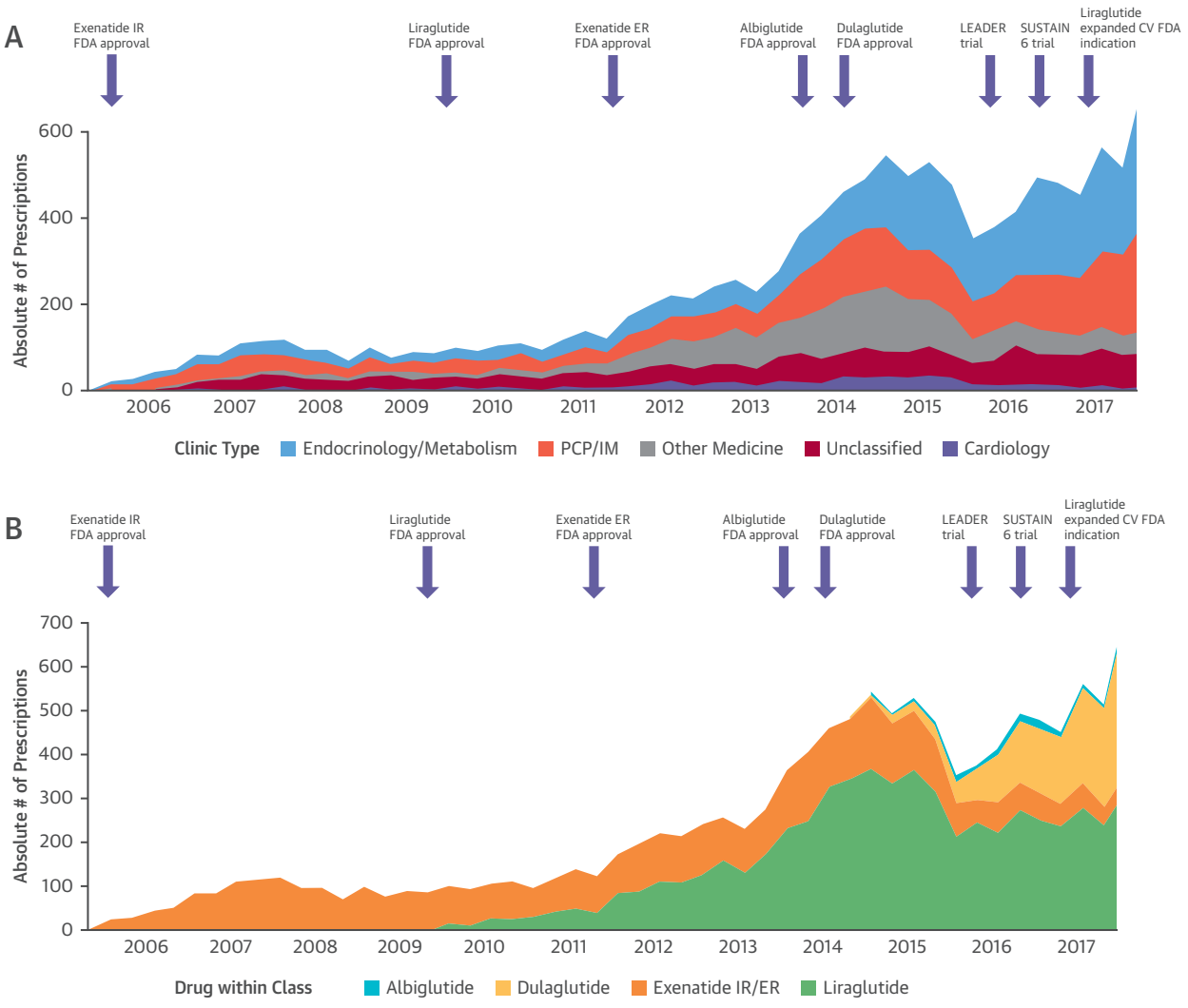
The specialty-specific prescriber rates were: endocrinology (33%), primary care (29%), other specialties (16%), cardiology (4.5%), and unclassified (17.5%) (**Figure 1A**). In the year after expansion of the FDA labeling for liraglutide, endocrinologists and primary care physicians prescribed 43% and 33%, respectively, while cardiologists accounted for 2% of prescriptions.

From 2005 to 2018, liraglutide was most commonly prescribed (50%), followed by exenatide (34%), dulaglutide (16%), and albiglutide (<1%) (**Figure 1B**). Liraglutide prescription rates rose steadily from initial FDA approval in 2010 to 2015. Subsequently, relative prescription of both liraglutide and exenatide decreased, while prescription of dulaglutide increased. By the second quarter of 2018, dulaglutide was most common (51%).

During a 13-year time span in a multicenter health system, cardiologists accounted for <5% of new prescriptions of GLP-1RAs, while endocrinologists and primary care physicians initiated >60%. In the year after regulatory broadening of the indication for liraglutide, cardiologists continued to prescribe GLP-1RAs infrequently, and use of liraglutide was relatively unchanged.

It is encouraging that use of GLP-1RAs has been increasing overall in recent years. The initial decline in prescription of GLP-1RAs in early 2016 may have been related to competing sodium-glucose cotransporter 2 inhibitor prescription, another class with established beneficial cardiovascular effects (1). However, despite these favorable trends, cardiologists infrequently prescribed either class of therapies in our health system (1). Lack of practical knowledge, concerns regarding potential adverse effects, patient fear of injections, cost/coverage issues, uncertainties about overstepping interdisciplinary boundaries, and added time to clinical care may all contribute to sluggish uptake in the cardiology community. Advances in patient-friendly injection designs (which may have contributed to recent expanded use of

FIGURE 1 **New Quarterly Glucagon-Like Peptide-1 Receptor Agonist Prescriptions By Prescriber Type and Specific Drug Within Class**



Prescriber type **(A)** and specific drug within class **(B)**. **Purple arrows** indicate key U.S. Food and Drug Administration (FDA) regulatory approvals and landmark cardiovascular outcomes trials. CV = cardiovascular; ER = extended release; IM = internal medicine; IR = immediate-release; LEADER = Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PCP = primary care physician; SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects With Type 2 Diabetes.

dulaglutide) and the prospect of an oral GLP-1RA (as the development program of oral semaglutide is nearing completion) may alleviate select barriers to uptake. However, global efforts to improve cardiologist engagement with comprehensive T2DM care are needed.

Our descriptive study is subject to limitations. We were unable to determine drug indications (obesity vs. glucose-lowering). CVD status was determined by administrative coding and may be subject to misclassification. Initial prescription outside the health system may have been missed. Despite the tertiary-care practice setting, Partners HealthCare does encompass >10 health care entities.

In current clinical practice, <5% of GLP-1RA prescriptions are initiated by cardiologists. Increased awareness and development of streamlined multidisciplinary care approaches (2) and implementation pathways (3) may improve uptake. As high-risk patients with T2DM are commonly encountered in cardiology practices, we believe cardiologists are

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uniquely positioned to participate in integration of this evidence-based but underutilized class of cardiometabolic therapies to advance comprehensive cardiovascular care.

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Administrative Billing Codes for Identifying Patients With Cardiac Arrest

Administrative data that utilize International Classification of Diseases-Ninth Revision (ICD-9) diagnosis and procedure codes are increasingly used to study patterns of care and outcomes in patients with out-of-hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). However, the validity of diagnosis and procedure codes to identify true cases of OHCA and IHCA, respectively, remains uncertain. In a recent study, we found that the sensitivity of ICD-9 procedure codes to identify confirmed cases of IHCA in a national registry was only 37.2% (1). However, an important but unanswered question in these studies is the positive predictive value (PPV) of ICD-9 codes: that is, what proportion of included patients truly have IHCA or OHCA?

To accomplish our study objective, we identified all patients (age ≥18 years) discharged from University of Iowa (UI) medical center during 2014 with ICD-9 diagnosis codes 427.5 (cardiac arrest), or 427.41 (ventricular fibrillation) that are commonly used to identify OHCA (2), and ICD-9 procedure codes 99.60 (cardiopulmonary resuscitation, not otherwise specified) or 99.63 (closed chest cardiac massage) that are commonly used to identify IHCA (3). We excluded 15