Journal of the American Heart Association

ORIGINAL RESEARCH

National Trends in Use of Sodium-Glucose Cotransporter-2 Inhibitors and Glucagon-like Peptide-1 Receptor Agonists by Cardiologists and Other Specialties, 2015 to 2020

Rishav Adhikari, BS; Kunal Jha, MD; Zeina Dardari, MS; James Heyward, MPH; Roger S. Blumenthal, MD; Robert H. Eckel, MD; G. Caleb Alexander, MD, MS; Michael J. Blaha, MD, MPH

BACKGROUND: Sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs) mitigate cardiovascular risk in individuals with type 2 diabetes, but most eligible patients do not receive them. We characterized temporal trends in SGLT2i and GLP-1RA use by cardiologists compared with other groups of clinicians.

METHODS AND RESULTS: We conducted a descriptive analysis of serial, cross-sectional data derived from IQVIA's National Prescription Audit, a comprehensive audit capturing ≈90% of US retail prescription dispensing and projected to population-level data, to estimate monthly SGLT2is and GLP-1RAs dispensed from January 2015 to December 2020, stratified by prescriber specialty and molecule. We also used the American Medical Association's Physician Masterfile to calculate average annual SGLT2is and GLP-1RAs dispensed per physician. Between January 2015 and December 2020, a total of 63.2 million SGLT2i and 63.4 million GLP-1RA prescriptions were dispensed in the United States. Monthly prescriptions from cardiologists increased 12-fold for SGLT2is (from 2228 to 25 815) and 4-fold for GLP-1RAs (from 1927 to 6981). Nonetheless, cardiologists represented only 1.5% of SGLT2i prescriptions and 0.4% of GLP-1RA prescriptions in 2020, while total use was predominated by primary care physicians/internists (57% of 2020 SGLT2is and 52% of GLP-1RAs). Endocrinologists led in terms of prescriptions dispensed per physician in 2020 (272 SGLT2is and 405 GLP-1RAs). Cardiologists, but not noncardiologists, increasingly used SGLT2is over GLP-1RAs, with accelerated uptake of empagliflozin and dapagliflozin coinciding with their landmark cardiovascular outcomes trials and subsequent US Food and Drug Administration label expansions.

CONCLUSIONS: While use of SGLT2is and GLP-1RAs by cardiologists in the United States increased substantially over a 6-year period, cardiologists still account for a very small proportion of all use, contributing to marked undertreatment of individuals with type 2 diabetes at high cardiovascular risk.

Key Words: cardiometabolic health ■ GLP-1 receptor agonists ■ prescribing patterns ■ risk reduction ■ SGLT2 inhibitors ■ type 2 diabetes

Cardiovascular disease (CVD) is the leading cause of death and disability among individuals with type 2 diabetes (T2D).[1,2] Of the 34 million Americans with T2D,[3] over one-third also have CVD, and half will eventually die of heart disease or stroke.[4] Patients with T2D and CVD face an alarming 4-fold risk of heart disease or stroke mortality,[5] yet only 21% of individuals with diabetes achieve basic risk factor goals

Correspondence to: Michael J. Blaha, MD, MPH, Johns Hopkins Ciccarone Center for the Prevention of Cardiovascular Disease, The Johns Hopkins Hospital, Blalock 524D1, 600 North Wolfe St, Baltimore, MD 21287. Email: mblaha1@jhmi.edu

Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.023811

For Sources of Funding and Disclosures, see page 12.

© 2022 The Authors. Published on behalf of the American Heart Association, Inc., by Wiley. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The role cardiologists have played relative to other clinicians in disseminating cardioprotective sodium-glucose cotransporter-2 inhibitor (SGLT2i) and glucagon-like peptide-1 receptor agonist (GLP-1RA) medications has not been well characterized.
- This analysis of a near–census-level audit of the US retail prescriptions shows that since 2015, cardiologists have increased use of SGLT2is and GLP-1RAs 12-fold and 4-fold, respectively.
- Nonetheless, cardiologists accounted for <2% of all SGLT2i and GLP-1RA use in 2020.

What Are the Clinical Implications?

- The marginal role of cardiologists in deploying cardioprotective SGLT2is/GLP-1RAs may be contributing to the undertreatment of patients with diabetes and cardiovascular disease.
- Deploying SGLT2i and GLP-1RA medications to these patients will require a focused and coordinated effort across all the medical specialties that treat patients with diabetes, with an enhanced role for the cardiologist.
- Further research is needed to understand the persistent barriers among clinicians to increased adoption of these evidence-based therapies, particularly how these barriers might differ by specialty (ie, cardiology).

Nonstandard Abbreviations and Acronyms

FDA	US Food and Drug Administration
GLP-1RA	glucagon-like peptide-1 receptor agonist
NPA	National Prescription Audit
PIONEER-6	Peptide Innovation for Early Diabetes Treatment
SGLT2i	sodium-glucose cotransporter-2 inhibitor
T2D	type 2 diabetes

for blood pressure, blood glucose, and low-density lipoprotein.[6,7] As the prevalence of diabetes continues to surge globally,[8] therapies that effectively mitigate the cardiovascular risks associated with T2D have the potential to transform the landscape of diabetes care and improve health outcomes for millions of patients.

Two such treatments, sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), are already broadly available in the United States. Over a dozen cardiovascular outcomes trials have shown that these antihyperglycemic drugs are also robust cardioprotective agents[9]; meta-analyses indicate that among patients with T2D, SGLT2is reduce cardiovascular mortality or hospitalization for heart failure by ≈23%,[10] while GLP-1RAs reduce a composite of cardiovascular death, stroke, or myocardial infarction by ≈12%.[11] Additional data point toward a role for SGLT2is and GLP-1RAs in slowing progression of diabetic kidney disease,[12] while multiple large trials now indicate that SGLT2is are effective treatments to manage heart failure and chronic kidney disease, regardless of whether patients have diabetes.[13–16] Thus, SGLT2i and GLP-1RA drugs have been heralded as paradigm-shifting cardiometabolic therapies to curtail the chronic cardiovascular and renal consequences of T2D. Reflecting this evidence, since 2016 the US Food and Drug Administration (FDA) has approved label expansion of many SGLT2is and GLP-1RAs to incorporate cardiovascular risk reduction indications, and recent clinical guidelines[17–20] now strongly recommend the use of an SGLT2i or GLP-1RA in patients with T2D who have established CVD or additional cardiovascular risk factors.

Despite the promise of SGLT2is and GLP-1RAs, most individuals who are eligible for these treatments do not receive them. Estimates from multiple cross-sectional analyses of large T2D cohorts suggest that only 2% to 10% and 3% to 8% of patients with T2D and CVD are receiving an SGLT2i or GLP-1RA, respectively.[21–26] Meanwhile, over a third of patients with T2D have concomitant CVD,[4,21,24] making them strong candidates for an SGLT2i or GLP-1RA. Because cardiologists outnumber most other specialists that regularly manage the microvascular and macrovascular consequences of T2D[27] and have more frequent encounters than other specialists with high-risk patients with T2D with comorbid CVD,[28] they may be well positioned to deploy these treatments. However, limited available data from individual academic medical centers and 1 pharmacy benefits manager before 2019 suggest that cardiologists may be playing a limited role in prescribing these drugs.[29–32] Many landmark cardiovascular outcomes trials occurred after this period,[9] and prominent clinical guidelines and awareness campaigns have since specifically called upon cardiologists to take a leading role in deploying these drugs.[17–20] Therefore, we used a large, nationally representative data set to characterize prescribing patterns of cardiologists compared with noncardiologists, as well as to understand how these patterns have evolved in response to key events from 2015 to 2020.

METHODS

The data that support the findings of this study are available from the corresponding author upon

reasonable request. This study was exempt from the Johns Hopkins University School of Medicine institutional review board, as it did not constitute human subjects research.

Data Sources

We analyzed IQVIA's National Prescription Audit (NPA) from January 2015 to December 2020. The NPA represents a gold-standard source of information about retail pharmacy transactions and provides dispensing estimates based on a sample of ≈90% of all retail prescriptions dispensed in the United States, including 90% of retail pharmacies, 80% of nursing home pharmacies, and 70% of mail-service pharmacies.[33,34] This sample is then weighted, using projection factors such as distance between sample and nonsample stores, to estimate 100% of retail transactions in the United States. IQVIA links the NPA to the American Medical Association's Physician Masterfile and other professional organization records to confirm the primary specialty of prescribers. We also combined the NPA-generated projections of total dispensed prescription volume with aggregate physician census data for each specialty from the American Medical Association's Physician Masterfile[35] and the American Osteopathic Association's Osteopathic Medical Profession Report[36] to estimate the average number of dispensed prescriptions per clinician in 2020 within each specialty.

For our analysis, we categorized physician assistants and nurse practitioners as advanced practice providers, while grouping a cluster of general practitioners as primary care physicians (PCP)/internists. This latter category includes family practice, general practice, general preventive medicine, geriatrics, internal medicine, internal medicine/pediatrics, osteopathic medicine, and pediatrics, and is based on prior publications that reported specialty-specific data from the NPA.[33]

From the NPA, we extracted monthly dispensed prescriptions, prescriber specialty, and brand names of the drugs used among all patients, regardless of their diabetes status. All SGLT2is and GLP-1RAs were included, except for Saxenda, a liraglutide dose marketed for weight loss and not indicated for T2D or cardiovascular risk reduction. We examined total, new, and refill prescriptions in our initial analyses; these analyses each yielded substantively similar findings, and only total prescriptions are reported herein. Thus, use of the term *prescriptions* throughout the article refers to total dispensed prescriptions.

Statistical Analysis

We used descriptive statistics to perform our analyses, with main outcomes including monthly/yearly prescriptions for each drug, monthly/yearly change in prescription volumes, monthly shifts in market share of each medication within its drug class, and annual prescriptions dispensed per physician within each specialty. We plotted these outcomes over time to assess for notable trends and inflection points, then used the Wald test for structural breaks[37] to determine whether key clinical trial e-publications and FDA drug label expansions coincided with statistically significant inflections in our data. We analyzed the data using Stata 15 (StataCorp, College Station, TX) and Microsoft Excel (Microsoft, Redmond, Washington).

RESULTS

Growth in Prescribing of SGLT2is and GLP-1RAs

From January 2015 to December 2020, ≈63.2 million SGLT2i and 63.4 million GLP-1RA medications were dispensed in the United States (Table and Table S1). Annual prescriptions doubled for SGLT2is and tripled for GLP-1RAs from 2015 to 2020. The average annual growth rate during this 6-year period was 15.6% for SGLT2is and 25.2% for GLP-1RAs.

Among cardiologists, monthly dispensed prescriptions increased ≈12-fold for SGLT2is (2228 in January 2015 to 25 815 in December 2020) and 4-fold for GLP-1RAs (from 1927 to 6981) (Figure 1). Compared with the annual trend among all prescribers, cardiologists outpaced the overall increase for SGLT2is (532% increase among cardiologists versus 101% overall) but slightly lagged the overall increase for GLP-1RAs (160% versus 207%) (Table). This observed increase in prescription volumes was largely not explained by an increase in the number of cardiologists in the United States, which grew 15% from 2015 to 2020.[35] While cardiologists increased prescribing for these medications, they represented a marginal fraction of national monthly totals (SGLT2is: 0.5% in January 2015 versus 1.9% in December 2020; GLP-1RAs: 0.5% versus 0.4%) (Figure 1).

Relative Prescription Volumes Across Specialties

Most prescriptions for both SGLT2is and GLP-1RAs were provided by PCPs/internists (Figure 2). In 2020, this group accounted for 57% and 52% of national SGLT2i and GLP-1RA prescriptions, respectively, followed by advanced practice providers (24% and 26%), endocrinologists (15% and 19%), cardiologists (1.5% and 0.4%), and nephrologists (0.5% and 0.3%). Using a different metric, average number of dispensed prescriptions per physician in 2020 within each specialty, endocrinologists prescribed more than other clinicians (272 SGLT2is and 405 GLP-1RAs), with cardiologists (6 SGLT2is and 2 GLP-1RAs) again lower (Figure 3).

Table. SGLT2i and GLP-1RA Prescriptions Dispensed and Year-Over-Year Growth by Specialty

SGLT2i	2015	2016	2017	2018	2019	2020	Total from 2015–2020
Cardiology	35 136	48 759 (+39%)	61 883 (+27%)	87 883 (+42%)	135 476 (+54%)	221 948 (+64%)	591 085 (+532%)
Nephrology	14 616	21 105 (+44%)	24 597 (+17%)	28 350 (+15%)	40 031 (+41%)	69 507 (+74%)	198 206 (+376%)
Endocrinology	1 332 436	1 623 451 (+22%)	1 656 326 (+2%)	1 786 542 (+8%)	1 971 564 (+10%)	2 220 876 (+13%)	10 591 195 (+67%)
PCP/Internist	4 505 408	5 666 536 (+26%)	5 835 253 (+3%)	6 190 060 (+6%)	6 954 341 (+12%)	8 281 097 (+19%)	37 432 695 (+84%)
APP	1 198 857	1 685 227 (+41%)	1 906 972 (+13%)	2 218 806 (+16%)	2 723 749 (+23%)	3 452 394 (+27%)	13 186 005 (+188%)
Other	147 671	181 212 (+23%)	171 557 (–5%)	186 469 (+9%)	210 610 (+13%)	310 215 (+47%)	1 207 734 (+110%)
Total SGLT2i	7 234 124	9 226 290 (+28%)	9 656 588 (+5%)	10 498 110 (+9%)	12 035 771 (+15%)	14 556 037 (+21%)	63 206 920 (+101%)
GLP-1RA	**2015**	**2016**	**2017**	**2018**	**2019**	**2020**	**Total from 2015–2020**
Cardiology	26 897	33 671 (+25%)	34 867 (+4%)	40 571 (+16%)	52 229 (+29%)	70 055 (+34%)	258 290 (+160%)
Nephrology	19 835	24 378 (+23%)	27 699 (+14%)	31 942 (+15%)	40 010 (+25%)	51 719 (+29%)	195 583 (+161%)
Endocrinology	1 336 023	1 735 004 (+30%)	1 895 542 (+9%)	2 276 274 (+20%)	2 793 210 (+23%)	3 314 692 (+19%)	13 350 745 (+148%)
PCP/Internist	3 226 871	4 034 407 (+25%)	4 495 686 (+11%)	5 649 762 (+26%)	7 215 560 (+28%)	9 004 492 (+25%)	33 626 778 (+179%)
APP	946 889	1 395 344 (+47%)	1 736 788 (+24%)	2 411 028 (+39%)	3 421 990 (+42%)	4 602 282 (+34%)	14 514 321 (+386%)
Other	130 963	165 942 (+27%)	185 324 (+12%)	239 404 (+29%)	303 255 (+27%)	441 287 (+46%)	1 466 175 (+237%)
Total GLP-1RA	5 687 478	7 388 746 (+30%)	8 375 906 (+13%)	10 648 981 (+27%)	13 826 254 (+30%)	17 484 527 (+26%)	63 411 892 (+207%)

Values for each year are absolute number of prescriptions dispensed that year, with percentages in parentheses indicating change in prescription volumes from the prior year. The rightmost column displays the total number of prescriptions dispensed over the study period and the total percentage increase from 2015 compared with 2020. APP indicates advanced practice providers; GLP-1RA, glucagon-like peptide-1 receptor agonist; PCP, primary care physician; and SGLT2i, Sodium-glucose cotransporter-2 inhibitor.

Source: IQVIA National Prescription Audit, 2015–2020.

Drug Choice Among Cardiologists versus Noncardiology Clinicians

While both cardiologists and noncardiology clinicians used SGLT2is and GLP-1RAs in approximately equal ratios in 2015, cardiologists increasingly used SGLT2is over the course of the study (Figure 4A). The ratio of SGLT2i prescriptions to GLP-1RA prescriptions among cardiologists was 1.2:1 in January 2015. By December 2020, this ratio had shifted to 3.7:1. In contrast, noncardiologists trended slightly in the opposite direction (Figure 4B), starting the study at 1.1:1 in January 2015 and ending at 0.8:1 in December 2020.

SGLT2i Trends

The predominance of SGLT2is over GLP-1RAs among cardiologists began in late 2015 and early 2016, mainly consisting of accelerated use of the SGLT2i empagliflozin (Figure 4A). Empagliflozin eventually became the most widely used SGLT2i among cardiologists and noncardiologists, accounting for 67% and 58%, respectively, of SGLT2is dispensed in 2020, although its growth was more rapid and pronounced among cardiologists (Figure 4A versus Figure 4B). The timing of empagliflozin's early rise coincided with publication of the results from the EMPA-REG OUTCOME (BI 10773 [Empagliflozin] Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) trial[38] and the FDA expansion of empagliflozin's drug label[39] to reflect a cardiovascular risk reduction indication in T2D (Figure 4A).

The average monthly change in empagliflozin's share of SGLT2i prescriptions among cardiologists was 1.6 times higher in the 6 months following publication of its trial than the 6 months prior, and 3.8 times higher in the 6 months following FDA indication expansion than the 6 months prior. The Wald test for structural breaks, which can be used to detect abrupt changes in time-series data, showed a

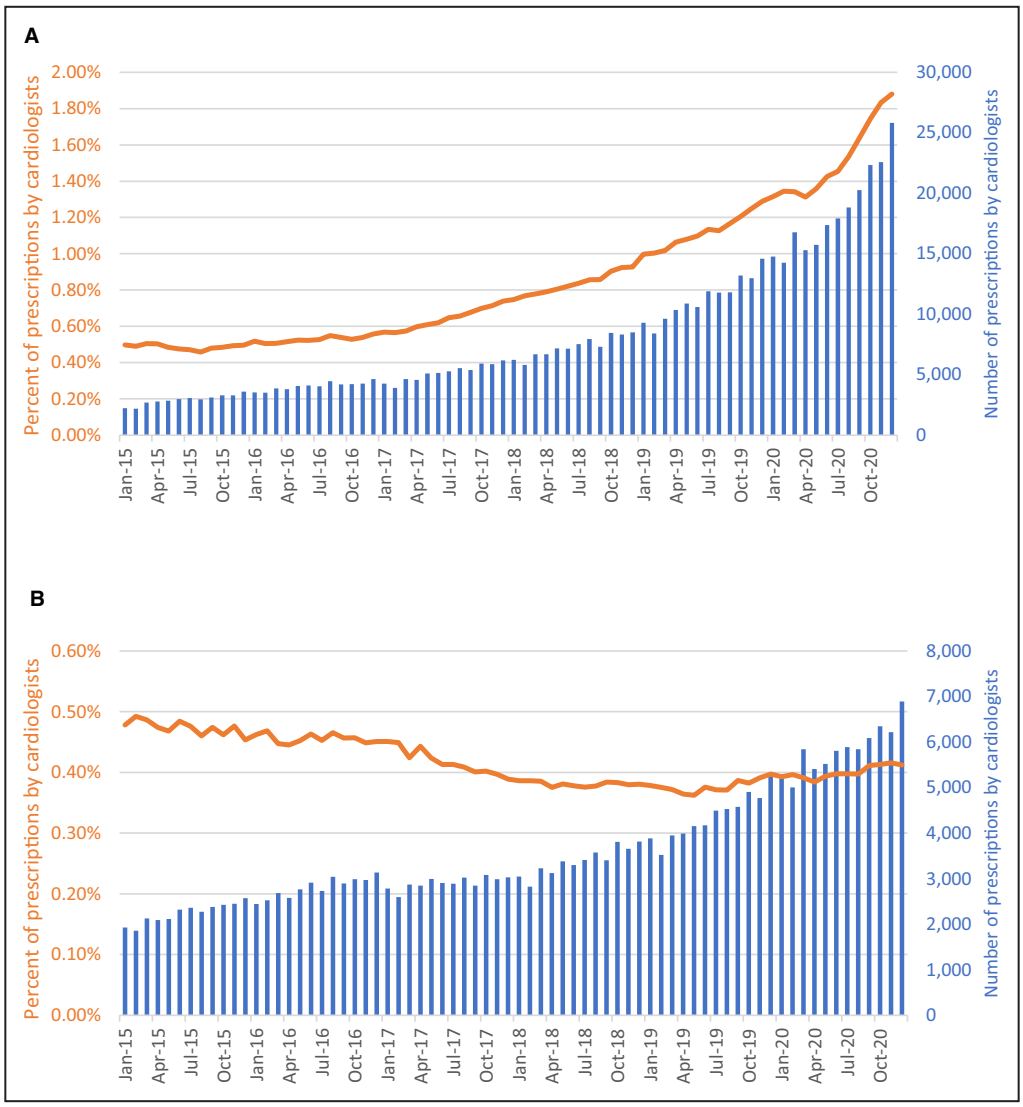


Figure 1. Cardiologist contribution to use of SGLT2is and GLP-1RAs.
SGLT2i **(A)** and GLP-1RA **(B)** prescriptions by cardiologists. The primary axis in orange shows the percentage of overall monthly dispensed prescriptions for each drug class that are attributed to cardiologists; the secondary axis in blue shows the absolute number of dispensed prescriptions by cardiologists each month. While cardiologists have substantially increased absolute numbers of prescriptions, they continue to account for a very small proportion of overall use. GLP-1RA indicates glucagon-like peptide-1 receptor agonists; and SGLT2i, sodium-glucose cotransporter-2 inhibitor. Source: IQVIA National Prescription Audit, 2015–2020.

statistically significant structural break in December 2016 ($P<0.001$), when the FDA expanded empagliflozin's indications but not in September 2015 ($P=0.16$), when EMPA-REG OUTCOME results were published online. While noncardiology clinicians also increased their empagliflozin use following this FDA activity, the shift was less pronounced (Figure 4B and Figure 5B; $P=0.41$ in September 2015 after EMPA-REG OUTCOME and $P=0.043$ in December 2016 after the FDA activity).

During the study period, there was a declining trend in the relative use of canagliflozin, from a maximum of 65% of all SGLT2i prescriptions in the first month of the study to a nadir of 3.0% in the most recent month (Figure 4). Our analysis did not detect any structural breaks in this trend coinciding with FDA communications regarding potential amputation risks with this medication (Figure S1).[40–42]

From September 2019 to December 2020, dapagliflozin's share of SGLT2i prescriptions among cardiologists increased 23%, following a decrease since 2015 (Figure 5A), while empagliflozin's share declined 18%, following an increase since 2015 (Figure 5B). This shift from empagliflozin to dapagliflozin among cardiologists was not observed among noncardiologists, for whom

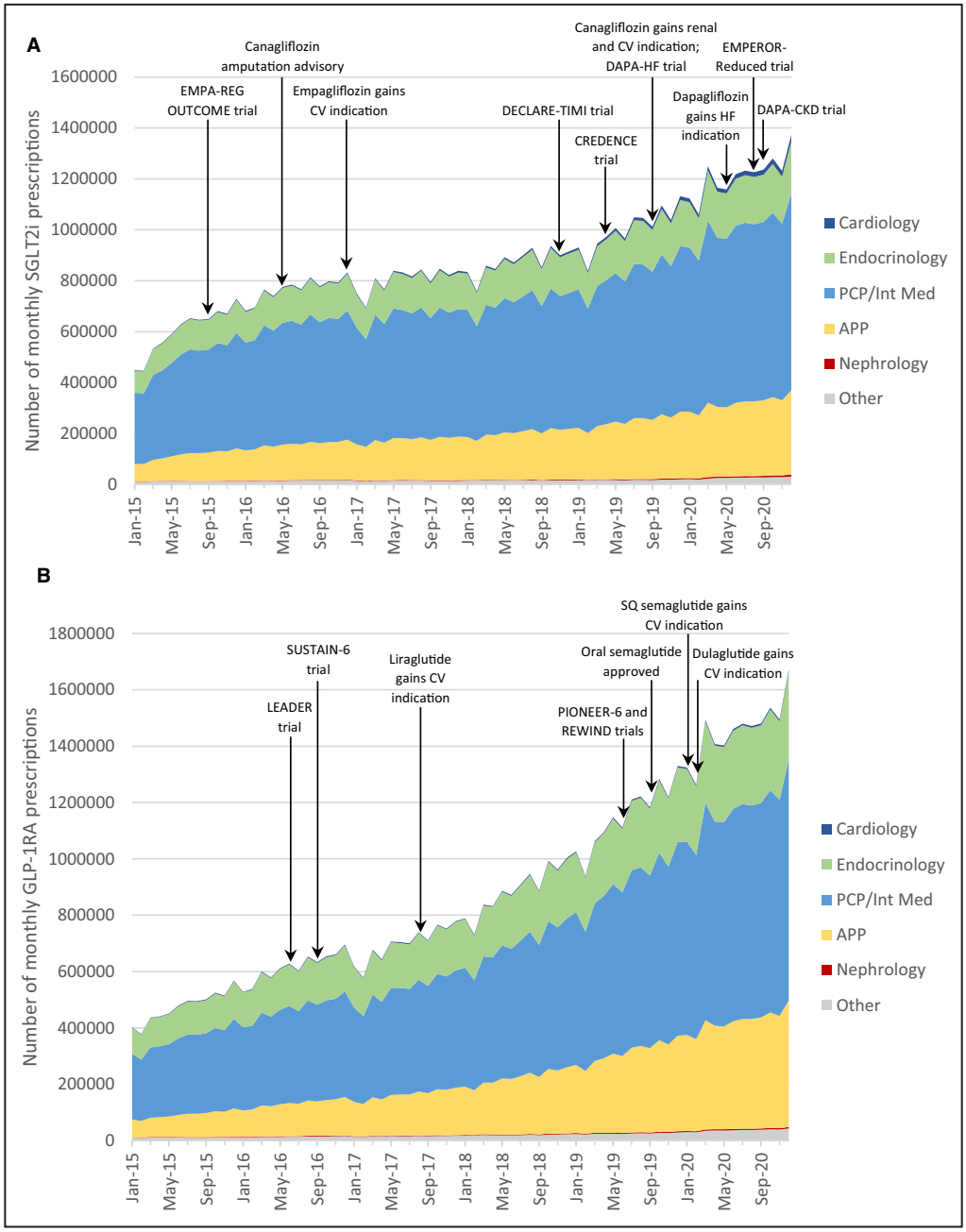


Figure 2. SGLT2i and GLP-1RA use across clinician specialties.
Monthly SGLT2i **(A)** and GLP-1RA **(B)** dispensed prescriptions by specialty of the prescriber. PCP/internist prescribers accounted for the majority of dispensed prescriptions. Arrows delineate a subset of relevant clinical trial publications and key regulatory actions. APP indicates advanced practice provider; CREDENCE, Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; CV, cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DECLARE-TIMI, Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PCP/Int Med, primary care physicians and internists; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SQ, subcutaneous; and SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes 6. Source: IQVIA National Prescription Audit, 2015–2020.

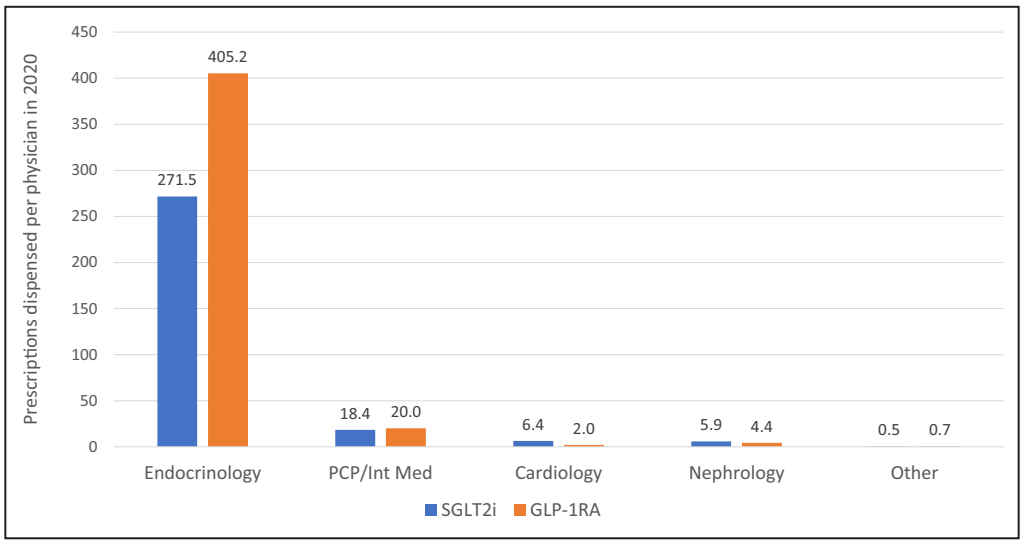


Figure 3. Prescriptions per physician in 2020.
Estimated average SGLT2i and GLP1-RA prescriptions dispensed per physician by specialty from January to December 2020. Endocrinologists outpace all other physician specialties in per-physician use. GLP-1RA indicates glucagon-like peptide-1 receptor agonists; PCP/Int Med primary care physicians and internists; and SGLT2i, sodium-glucose cotransporter-2 inhibitor. Source: IQVIA National Prescription Audit, 2015–2020.

empagliflozin's share of SGLT2i prescriptions continued to increase and dapagliflozin's share remained flat. This swing in prescribing trends among cardiologists coincided with the publication of the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial[13] in September 2019 ($P<0.001$), followed in May 2020 ($P<0.001$) by FDA drug label expansion for the treatment of heart failure in adults with and without T2D.[43]

GLP-1RA Trends

Among the GLP-1RA medications, we did not observe similar shifts in prescription choice following publication of trial results, including LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; liraglutide), SUSTAIN-6 (Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes; subcutaneous semaglutide), PIONEER-6 (Peptide Innovation for Early Diabetes Treatment; oral semaglutide), and REWIND (Researching Cardiovascular Events With a Weekly Incretin in Diabetes; dulaglutide), or their associated FDA drug label changes (Figure 4). We did observe a marked decline in the share of daily injection GLP-1RAs (76% in January 2015 to 19% in December 2020), along with a reciprocal increase toward weekly injection GLP-1RAs (Figure 6). Among both cardiologists and noncardiologists, the most dispensed GLP-1RAs in 2020 were dulaglutide (39% of cardiology GLP-1RAs and 45% of noncardiology GLP-1RAs) followed by semaglutide (37% of cardiology GLP-1RAs and 28% of noncardiology GLP-1RAs), both of which are weekly injections. We did not detect any pronounced change in trends for the prescribing of semaglutide following approval of its oral formulation[44] in September 2019 as the only GLP-1RA available as an oral medication (Figure 4). However, the growth in oral semaglutide prescriptions has consistently exceeded the growth of the GLP-1RA category since entrance into the market (Figure S2).

DISCUSSION

Despite the cardiovascular benefits of SGLT2is and GLP-1RAs, these therapies have not reached the majority of patients for whom they are guideline recommended.[21–26,45] We analyzed a comprehensive audit of the US retail prescription drug market to examine use of SGLT2is and GLP-1RAs across medical specialties between 2015 and 2020. Total use of both drug classes increased substantially during this 6-year period, including among cardiologists, whose monthly prescribing of SGLT2is increased 12-fold and prescribing of GLP-1RAs increased 4-fold. Over the 6-year study period, the relative ratio of SGLT2i to GLP-1RA use increased for cardiologists but not noncardiologists, with accelerated uptake of empagliflozin and dapagliflozin coinciding with their landmark cardiovascular outcomes trials and resulting FDA label expansions. However, cardiologists accounted for <2% of prescriptions for these drugs in 2020. Rather, PCPs/internists accounted for the majority of prescriptions in that year (57% of SGLT2is and 52% of GLP-1RAs), while endocrinologists far outpaced other

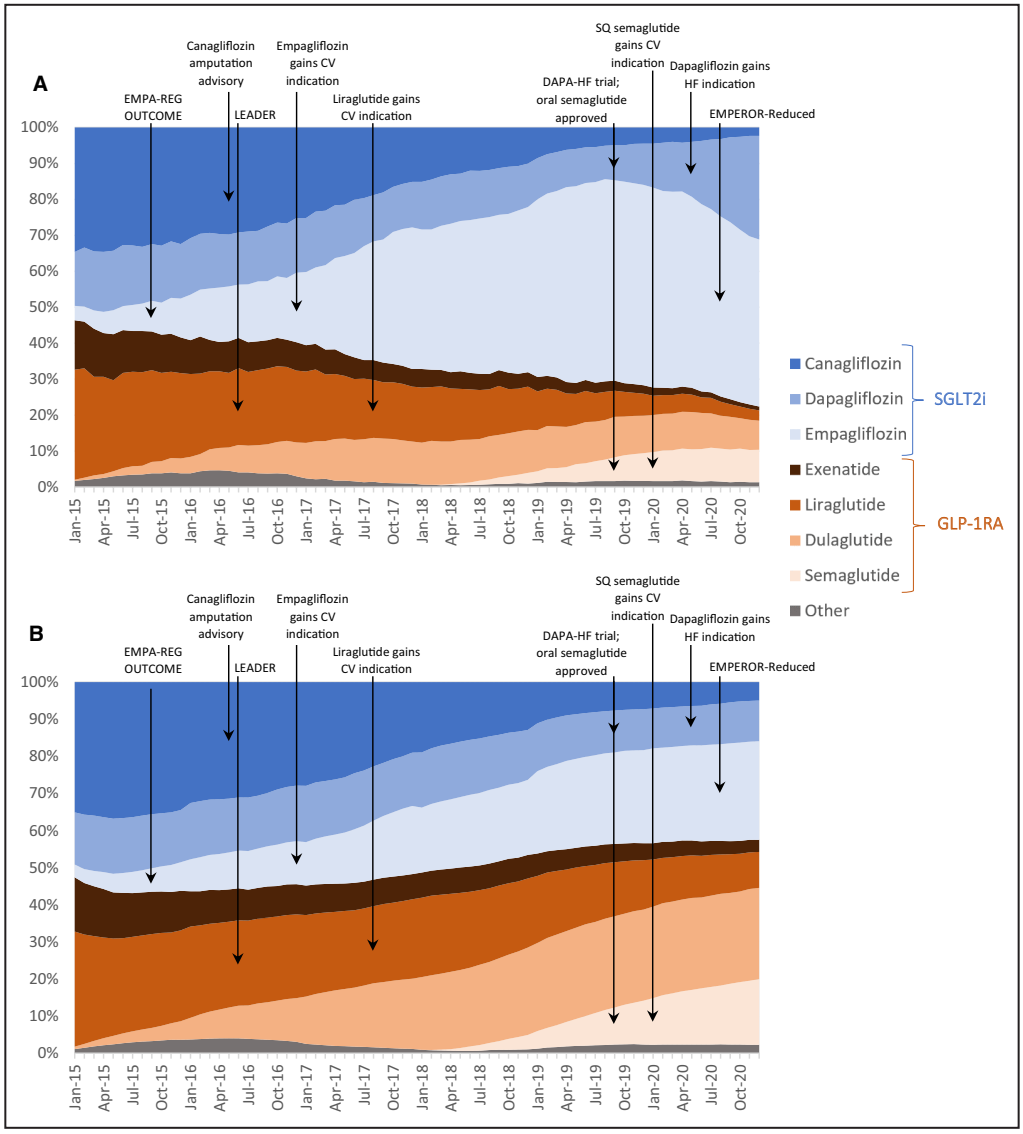


Figure 4. Drug choice among cardiologists and noncardiologists.
Proportion of monthly SGLT2i/GLP-1RA dispensed prescriptions from cardiologists **(A)** or noncardiology clinicians **(B)** attributed to each molecule in the 2 drug classes. Within each graph, SGLT2i drugs are shaded in blue hues, while GLP-1RA drugs are shaded in brown hues. The gray series (other) corresponds to ertugliflozin and albiglutide, which each accounted for <1% of the total prescriptions. Arrows delineate a subset of relevant clinical trial publications and key regulatory actions. CV indicates cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; PCP/Int Med, primary care physicians and internists; SGLT2i, sodium-glucose cotransporter-2 inhibitor; and SQ, subcutaneous. Source: IQVIA National Prescription Audit, 2015–2020.

specialties in prescriptions per physician. In light of prior estimates showing that 40% to 70% of patients with T2D and CVD see a cardiologist each year,[24,45] that an individual with T2D and CVD is equally as likely to encounter a PCP and 4 times less likely to encounter an endocrinologist as they are a cardiologist in a given year,[28,45] and that one-third of the patients that cardiologists manage have diabetes,[46] our results demonstrating a limited role of cardiologists in disseminating SGLT2i and GLP-1RA therapies present an opportunity to optimize access to these cardiometabolic therapies.

Comparison to Prior Studies

The results of our analysis build upon prior investigations of cardiologist prescribing of SGLT2is/GLP-1RAs.

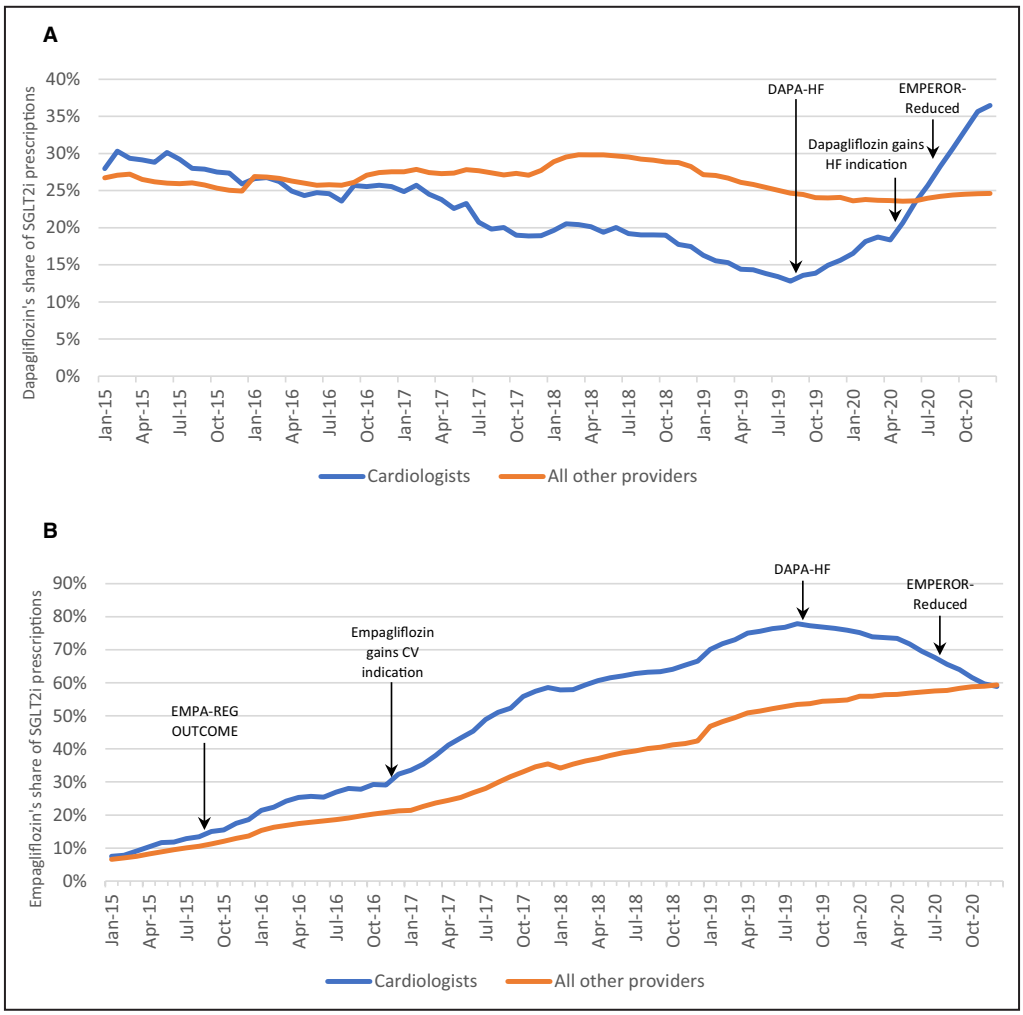


Figure 5. Share of SGLT2i prescriptions comprised by dapagliflozin and empagliflozin.
Share of monthly SGLT2i dispensing attained by dapagliflozin **(A)** and empagliflozin **(B)** among cardiologists compared with all other clinicians. Arrows delineate a selection of landmark cardiovascular outcomes trial publications and key FDA indication expansions which may have influenced prescription choice among clinicians. CV indicates cardiovascular; DAPA-HF, Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; EMPA-REG OUTCOME, BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients; EMPEROR-Reduced, Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; HF, heart failure; and SGLT2i, sodium-glucose cotransporter-2 inhibitor. Source: IQVIA National Prescription Audit, 2015–2020.

Studies within the Partners HealthCare system demonstrated that cardiologists accounted for ≈5% of total prescribing of these medications in that academic medical institution, with endocrinologists accounting for a plurality of prescriptions.[30,31] A study within the University of Mississippi Medical Center[29] as well as another study analyzing data from a pharmacy benefits manager[32] also found low relative use among cardiologists, with a majority of prescriptions originating from PCPs/internists. Our study also suggests that PCPs/internists account for most prescriptions, with the additional insight that endocrinologists lead prescribing on a per-physician basis, but account for fewer total prescriptions than PCPs/internists because of their smaller total population.

Because prior studies were restricted to prescriptions at individual academic medical centers or a single pharmacy benefits manager, their generalizability may be limited because of institutional formularies, institution-specific cultures and physician distribution across specialties, narrow patient populations, lack of all payer types, and small samples. By examining near–census-level data of total, all-payer dispensing of prescriptions each month, our analysis provides a unique opportunity to analyze highly generalizable national patterns and to compare the evolving drug choices of cardiologists to those of noncardiologists in the context of recent clinical trials and FDA announcements.

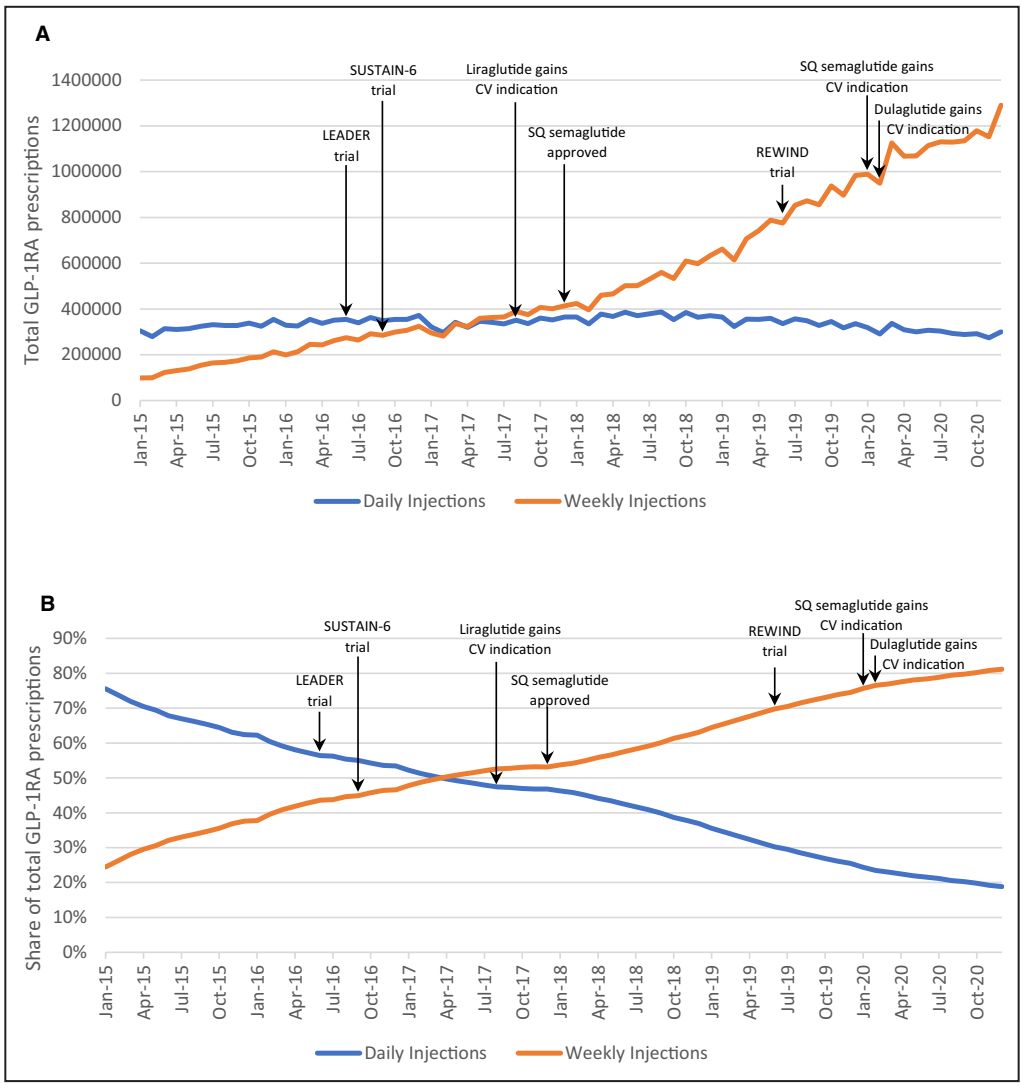


Figure 6. Prescriptions of daily vs weekly injection GLP-1RAs.
Since January 2015, the absolute number of dispensed prescriptions for daily injection GLP-1RAs has stagnated, while weekly injection GLP-1RA prescriptions have increased substantially, accounting for the majority of GLP-1RA prescriptions in 2020 (**A**). This shift from daily to weekly GLP-1RA injections is also reflected in each category's relative proportion of GLP-1RA prescriptions (**B**). Daily injection GLP-1RAs are lixisenatide, liraglutide, and short-acting exenatide (Byetta). Weekly injections are albiglutide, dulaglutide, subcutaneous semaglutide, and long-acting exenatides (Bydureon, Bydurean BCise, and Bydureon Pen). CV indicates cardiovascular; FDA, US Food and Drug Administration; GLP-1RA, glucagon-like peptide-1 receptor agonists; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SGLT2i, sodium-glucose cotransporter-2 inhibitor; SQ, subcutaneous; and SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-Term Outcomes With Semaglutide in Subjects With Type 2 Diabetes 6. Source: IQVIA National Prescription Audit, 2015–2020.

Possible Influence by Key Events

While both cardiologists and noncardiologists started the study period with approximately equal use of SGLT2is versus GLP-1RAs, there were prominent increases in SGLT2i use relative to GLP-1RA use among cardiologists. This shift was driven primarily by an accelerated uptake of empagliflozin and may have been influenced by publication in 2015 of the EMPA-REG OUTCOME trial,[38] the first cardiovascular outcomes trial to demonstrate cardiovascular benefit of an SGLT2i, and the FDA's addition of an indication for cardiovascular risk reduction in T2D in 2016.[39] While later trials (CANVAS [Canagliflozin Cardiovascular Assessment Study], DECLARE-TIMI [Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events], etc) demonstrated cardioprotective benefits for other SGLT2is,[9] we did not

observe any inflections in our data corresponding to those trials.

In September 2019, the DAPA-HF trial demonstrated for the first time that an SGLT2i, dapagliflozin, could be effective not just in the primary prevention of heart failure in T2D, but also in secondary prevention as a treatment for heart failure with reduced ejection fraction, regardless of a patient's diabetes status.[13] This marked expansion in the population of patients who may benefit from an SGLT2i is reflected in our time-series data after publication of this trial, with use of dapagliflozin accelerating and reducing empagliflozin's market share among cardiologists. Although the EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction) trial later showed a similar heart failure result for empagliflozin, the impact of this is not yet reflected in our data. As with the prior shift toward empagliflozin, this prominent shift toward dapagliflozin was observed among cardiologists, but not among noncardiology prescribers.

Insights Into Barriers to Uptake

All major American and European clinical guidelines for cardiovascular management in diabetes now strongly recommend an SGLT2i or GLP-1RA for patients with T2D who have a history of or high risk for CVD.[17–19] However, only a fraction of these patients receive these medications.[21–24] Such shortcomings are the result of many potential barriers, including traditional boundaries in diabetes care between medical specialties, cost, clinical inertia, lack of clinician familiarity with the evidence base and potential adverse effects, and, in the case of GLP-1RAs, concerns and preferences on the part of patients to avoid injected therapies.[47–49] While our study cannot directly evaluate the relative importance of each factor, it does provide some important insight.

The growth in dapagliflozin use among cardiologists coinciding with the DAPA-HF trial, the first cardiovascular outcomes trial to demonstrate the effectiveness of an SGLT2i outside of T2D, suggests that one possible factor holding back cardiologist uptake of these drugs could be the perception that diabetes care is beyond their specialty's purview.[48] Second, the lagging use of GLP-1RAs relative to SGLT2is among cardiologists, despite the opposite trend among noncardiologists, may be consistent with the hypotheses that a preference to avoid needles or concerns regarding the potential gastrointestinal side effects of GLP-1RAs are hindering use by cardiologists.[49] Future initiatives to foster uptake among cardiologists should specifically consider these 2 potential barriers. These efforts to increase use by cardiologists might include conducting clinical trials to assess the effectiveness of additional SGLT2is/GLP-1RAs for a growing number of applications outside the context of T2D,[50] investigating the cardiovascular benefits of oral GLP-1RA formulations,[51] and avoiding reference to SGLT2is and GLP-1RAs solely as antihyperglycemic or "diabetes" drugs, but rather promoting cross-disciplinary, coordinated models of care that extend across multiple medical specialties.

Study Limitations

While the NPA provides robust, all-payer national dispensing estimates from US outpatient retail pharmacies, it excludes nonretail channels such as hospital pharmacies or dispensing physicians. This registry captures data on drug dispensing by pharmacies, rather than clinician prescribing, and the 2 metrics may be slightly discordant.[52,53] Additionally, the NPA does not include any demographic or diagnostic information about individuals, nor does it include CIs for its projections, although the audit provides a near census of the US retail market. Furthermore, because the NPA categorizes both newly initiated therapy as well as a newly written prescription to continue existing therapy after a patient is completely out of refills as new prescriptions, it was not possible to fully limit our analysis to only those prescriptions that are confirmed new initiations. In addition, the COVID-19 pandemic overlapped with the final 10 months of our study period and may have had additional impacts on prescribing that are not reflected in our analysis (reduced doctor or pharmacy visits, shifts to mail-order dispensing, etc).[54] Finally, although our analyses suggest inflection points in the use of certain medications that coincided with important clinical trials or regulatory actions, our study was not designed to determine whether a particular event was directly responsible for these inflections. Other simultaneous events, such as increased physician marketing, knowledge dissemination at conferences, changes in preferred drug formularies, or lightening of prior authorization requirements, may influence prescribing patterns.

CONCLUSIONS

Our study demonstrates that while prescriptions from cardiologists for SGLT2i and GLP-1RA medications have increased many-fold since 2015, they continue to account for a very small share of the use of these therapies. Most prescriptions were provided by PCPs/internists, while endocrinologists accounted for the most prescriptions per provider. Favorable results from landmark SGLT2i cardiovascular outcomes trials and the subsequent FDA drug indication expansions coincided with evolving

prescribing preferences, especially among cardiologists. Reaching the millions of individuals whose quality and duration of life could be significantly improved with these treatments will require a concerted and coordinated effort across a diverse range of clinicians as well as a reimagining of the traditional boundaries between medical specialties.

ARTICLE INFORMATION

Received September 3, 2021; accepted March 28, 2022.

Affiliations

Ciccarone Center for the Prevention of Cardiovascular Disease, Johns Hopkins School of Medicine, Baltimore, MD (R.A., K.J., Z.D., R.S.B., M.J.B.); Department of Epidemiology (J.H., G.C.A., M.J.B.) and Center for Drug Safety and Effectiveness (J.H., G.C.A.), Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; and Division of Endocrinology, Metabolism & Diabetes, University of Colorado Anschutz Medical Campus, Aurora, CO (R.H.E.).

Acknowledgments

The statements, findings, conclusions, views, and opinions contained and expressed in this article are based in part on data obtained under license from the following IQVIA information service: Formulary Impact Analyzer, IQVIA. All Rights Reserved. The statements, findings, conclusions, views, and opinions contained and expressed herein are not necessarily those of IQVIA Inc. or any of its affiliated or subsidiary entities.

Sources of Funding

None.

Disclosures

Dr Alexander is past chair and a current member of the FDA Peripheral and Central Nervous System Advisory Committee; has served as a paid advisor to IQVIA; is a cofounding principal and equity holder in Monument Analytics, a health care consultancy whose clients include the life sciences industry as well as plaintiffs in opioid litigation; and is a member of OptumRx's National P&T Committee. Dr Blaha has received research/grant support from the National Institutes of Health, FDA, American Heart Association, Aetna Foundation, Amgen, and Novo Nordisk and has served on advisory boards for Amgen, Sanofi, Regeneron, Novartis, Novo Nordisk, Bayer, Akcea, 89Bio, Kaleido, Inozyme, and Kowa. These arrangements have been reviewed and approved by Johns Hopkins University in accordance with its conflict-of-interest policies. The remaining authors have no disclosures to report.

Supplemental Material

Table S1
Figures S1–S2

REFERENCES

1. Rawshani A, Rawshani A, Franzén S, Eliasson B, Svensson A-M, Miftaraj M, McGuire DK, Sattar N, Rosengren A, Gudbjörnsdottir S. Mortality and cardiovascular disease in type 1 and type 2 diabetes. *N Engl J Med*. 2017;376:1407–1418. doi: 10.1056/NEJMoa1608664
2. Gregg EW, Hora I, Benoit SR. Resurgence in diabetes-related complications. *JAMA*. 2019;321:1867–1868. doi: 10.1001/jama.2019.3471
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. 2020. Accessed March 23, 2021.
4. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. *Cardiovasc Diabetol*. 2018;17:83. doi: 10.1186/s12933-018-0728-6
5. Di Angelantonio E, Kaptoge S, Wormser D, Willeit P, Butterworth AS, Bansal N, O'Keeffe LM, Gao P, Wood AM, Burgess S, et al. Association of cardiometabolic multimorbidity with mortality. *JAMA*. 2015;314:52–60. doi: 10.1001/jama.2015.7008
6. Wang L, Li X, Wang Z, Bancks MP, Carnethon MR, Greenland P, Feng Y-Q, Wang H, Zhong VW. Trends in prevalence of diabetes and control of risk factors in diabetes among US adults, 1999–2018. *JAMA*. 2021;326:1999–2018. doi: 10.1001/jama.2021.9883
7. Bittner V, Bertolet M, Barraza Felix R, Farkouh ME, Goldberg S, Ramanathan KB, Redmon JB, Sperling L, Rutter MK. Comprehensive cardiovascular risk factor control improves survival: the BARI 2D trial. *J Am Coll Cardiol*. 2015;66:765–773. doi: 10.1016/j.jacc.2015.06.019
8. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the International Diabetes Federation Diabetes Atlas, 9(th) edition. *Diabetes Res Clin Pract*. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843
9. Ferro EG, Michos ED, Bhatt DL, Lincoff AM, Elshazly MB. New decade, new FDA guidance for diabetes drug development: lessons learned and future directions. *J Am Coll Cardiol*. 2020;76:2522–2526. doi: 10.1016/j.jacc.2020.09.590
10. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, Mosenzon O, Kato ET, Cahn A, Furtado RHM, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet*. 2019;393:31–39. doi: 10.1016/s0140-6736(18)32590-x
11. Kristensen SL, Rørth R, Jhund PS, Docherty KF, Sattar N, Preiss D, Køber L, Petrie MC, McMurray JJV. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. *Lancet Diabetes Endocrinol*. 2019;7:776–785. doi: 10.1016/s2213-8587(19)30249-9
12. Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. KDIGO 2020 clinical practice guideline for diabetes management in chronic kidney disease. *Kidney Int*. 2020;98:S1–S115. doi: 10.1016/j.kint.2020.06.019
13. McMurray JJV, Solomon SD, Inzucchi SE, Køber L, Kosiborod MN, Martinez FA, Ponikowski P, Sabatine MS, Anand IS, Bělohlávek J, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med*. 2019;381:1995–2008. doi: 10.1056/NEJMoa1911303
14. Packer M, Anker SD, Butler J, Filippatos G, Pocock SJ, Carson P, Januzzi J, Verma S, Tsutsui H, Brueckmann M, et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med*. 2020;383:1413–1424. doi: 10.1056/NEJMoa2022190
15. Heerspink HJL, Stefánsson BV, Correa-Rotter R, Chertow GM, Greene T, Hou F-F, Mann JFE, McMurray JJV, Lindberg M, Rossing P, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med*. 2020;383:1436–1446. doi: 10.1056/NEJMoa2024816
16. Anker SD, Butler J, Filippatos G, Ferreira JP, Bocchi E, Böhm M, Brunner–La Rocca H-P, Choi D-J, Chopra V, Chuquiure-Valenzuela E, et al. Empagliflozin in heart failure with a preserved ejection fraction. *N Engl J Med*. 2021;385:1451–1461. doi: 10.1056/NEJMoa2107038
17. American Diabetes Association. Cardiovascular disease and risk management: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:S111–S134. doi: 10.2337/dc20-S010
18. Das SR, Everett BM, Birtcher KK, Brown JM, Januzzi JL, Kalyani RR, Kosiborod M, Magwire M, Morris PB, Neumiller JJ, et al. 2020 Expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes. *J Am Coll Cardiol*. 2020;76:1117–1145. doi: 10.1016/j.jacc.2020.05.037
19. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, Federici M, Filippatos G, Grobbee DE, Hansen TB, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the task force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD). *Eur Heart J*. 2019;41:255–323. doi: 10.1093/eurheartj/ehz486
20. Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, Palo KED, Golden SH, Sperling LS. Comprehensive management of cardiovascular risk factors for adults with type 2 diabetes: a scientific statement from the American Heart Association. *Circulation*. 2022;145:e722–e759. doi: 10.1161/CIR.0000000000001040
21. Pantalone KM, Misra-Hebert AD, Hobbs TM, Ji X, Kong SX, Milinovich A, Weng W, Bauman J, Ganguly R, Burguera B, et al. Antidiabetic treatment patterns and specialty care utilization among patients with type 2

diabetes and cardiovascular disease. *Cardiovasc Diabetol*. 2018;17:54. doi: 10.1186/s12933-018-0699-7
22. Arnold SV, Inzucchi SE, Tang F, McGuire DK, Mehta SN, Maddox TM, Goyal A, Sperling LS, Einhorn D, Wong ND, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: an NCDR® research to practice project. *Eur J Prev Cardiol*. 2017;24:1637–1645. doi: 10.1177/2047487317729252
23. Arnold SV, de Lemos JA, Rosenson RS, Ballantyne CM, Liu Y, Mues KE, Alam S, Elliott-Davey M, Bhatt DL, Cannon CP, et al. Use of guideline-recommended risk reduction strategies among patients with diabetes and atherosclerotic cardiovascular disease. *Circulation*. 2019;140:618–620. doi: 10.1161/CIRCULATIONAHA.119.041730
24. Weng W, Tian Y, Kong SX, Ganguly R, Hersloev M, Brett J, Hobbs T. The prevalence of cardiovascular disease and antidiabetes treatment characteristics among a large type 2 diabetes population in the United States. *Endocrinol Diabetes Metab*. 2019;2:e00076. doi: 10.1002/edm2.76
25. Eberly LA, Yang L, Eneanya ND, Essien U, Julien H, Nathan AS, Khatana SAM, Dayoub EJ, Fanaroff AC, Giri J, et al. Association of race/ethnicity, gender, and socioeconomic status with sodium-glucose cotransporter 2 inhibitor use among patients with diabetes in the US. *JAMA Netw Open*. 2021;4:e216139. doi: 10.1001/jamanetworkopen.2021.6139
26. Vaduganathan M, Fonarow GC, Greene SJ, DeVore AD, Kavati A, Sikirica S, Albert NM, Duffy CI, Hill CL, Patterson JH, et al. Contemporary treatment patterns and clinical outcomes of comorbid diabetes mellitus and HFrEF: the CHAMP-HF registry. *JACC Heart Fail*. 2020;8:469–480. doi: 10.1016/j.jchf.2019.12.015
27. Patel RB, Al Rifai M, McEvoy JW, Vaduganathan M. Implications of specialist density for diabetes care in the United States. *JAMA Cardiol*. 2019;4:1174–1175. doi: 10.1001/jamacardio.2019.3796
28. Gunawan F, Nassif ME, Partridge C, Ahmad T, Kosiborod M, Inzucchi SE. Relative frequency of cardiology vs. endocrinology visits by type 2 diabetes patients with cardiovascular disease in the USA: implications for implementing evidence-based use of glucose-lowering medications. *Cardiovasc Endocrinol Metab*. 2020;9:56–59. doi: 10.1097/XCE.0000000000000195
29. Hamid A, Vaduganathan M, Oshunbade AA, Ayyalasomayajula KK, Kalogeropoulos AP, Lien LF, Shafi T, Hall ME, Butler J. Antihyperglycemic therapies with expansions of US food and drug administration indications to reduce cardiovascular events: prescribing patterns within an academic medical center. *J Cardiovasc Pharmacol*. 2020;76:313–320. doi: 10.1097/fjc.0000000000000864
30. Vaduganathan M, Patel RB, Singh A, McCarthy CP, Qamar A, Januzzi JL, Scirica BM, Butler J, Cannon CP, Bhatt DL. Prescription of glucagon-like peptide-1 receptor agonists by cardiologists. *J Am Coll Cardiol*. 2019;73:1596–1598. doi: 10.1016/j.jacc.2019.01.029
31. Vaduganathan M, Sathiyakumar V, Singh A, McCarthy CP, Qamar A, Januzzi JL Jr, Scirica BM, Butler J, Cannon CP, Bhatt DL. Prescriber patterns of SGLT2i after expansions of U.S. Food and Drug Administration labeling. *J Am Coll Cardiol*. 2018;72:3370–3372. doi: 10.1016/j.jacc.2018.08.2202
32. Dave CV, Schneeweiss S, Wexler DJ, Brill G, Patorno E. Trends in clinical characteristics and prescribing preferences for SGLT2 inhibitors and GLP-1 receptor agonists, 2013–2018. *Diabetes Care*. 2020;43:921. doi: 10.2337/dc19-1943
33. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in opioid analgesic-prescribing rates by specialty, U.S., 2007–2012. *Am J Prev Med*. 2015;49:409–413. doi: 10.1016/j.amepre.2015.02.020
34. IQVIA, Inc. Prescription Information. Available at: https://www.iqvia.com/locations/united-states/solutions/commercial-operations/essential-information/prescription-information. 2021. Accessed March 1, 2021.
35. American Medical Association. Available at: AMA Physician Masterfile. https://www.ama-assn.org/about/masterfile/ama-physician-masterfile. Accessed August 2020.
36. American Osteopathic Association. 2019 Osteopathic Medical Profession Report. Available at: https://osteopathic.org/wp-content/uploads/OMP2019-Report_Web_FINAL.pdf. 2020. Accessed March 23, 2021.
37. Ditzen J, Karavias Y, Westerlund J. xtbreak: Testing for Structural Breaks in Stata. Available at: https://www.stata.com/meeting/switzerland20/slides/Switzerland20_Ditzen.pdf. 2020. Accessed March 23, 2021.
38. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373:2117–2128. doi: 10.1056/NEJMoa1504720
39. U.S. Food and Drug Administration. FDA approves Jardiance to reduce cardiovascular death in adults with type 2 diabetes. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-jardiance-reduce-cardiovascular-death-adults-type-2-diabetes. 2016. Accessed April 5, 2022.
40. U.S. Food and Drug Administration. FDA Drug Safety Communication: Interim clinical trial results find increased risk of leg and foot amputations, mostly affecting the toes, with the diabetes medicine canagliflozin (Invokana, Invokamet). Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-interim-clinical-trial-results-find-increased-risk-leg-and-foot. 2016. Accessed April 5, 2022.
41. U.S. Food and Drug Administration. FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-confirms-increased-risk-leg-and-foot-amputations-diabetes-medicine. 2017. Accessed April 5, 2022.
42. U.S. Food and Drug Administration. FDA removes Boxed Warning about risk of leg and foot amputations for the diabetes medicine canagliflozin. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-removes-boxed-warning-about-risk-leg-and-foot-amputations-diabetes-medicine-canagliflozin. 2020. Accessed April 5, 2022
43. U.S. Food and Drug Administration. FDA approves new treatment for a type of heart failure. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-type-heart-failure. 2020. Accessed April 5, 2022.
44. U.S. Food and Drug Administration. FDA approves first oral GLP-1 treatment for type 2 diabetes. Available at: https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes. 2019. Accessed April 5, 2022.
45. Nelson AJ, Ardissino M, Haynes K, Shambhu S, Eapen ZJ, McGuire DK, Carnicelli A, Lopes RD, Green JB, O'Brien EC, et al. Gaps in evidence-based therapy use in insured patients in the united states with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. *J Am Heart Assoc*. 2021;10:e016835. doi: 10.1161/jaha.120.016835
46. Bartnik M, Rydén L, Ferrari R, Malmberg K, Pyörälä K, Simoons M, Standl E, Soler-Soler J, Öhrvik J. The prevalence of abnormal glucose regulation in patients with coronary artery disease across Europe: the Euro Heart Survey on diabetes and the heart. *Eur Heart J*. 2004;25:1880–1890. doi: 10.1016/j.ehj.2004.07.027
47. Adhikari R, Rajan T, Blaha M. Unmet role of cardiologists: use of cardiometabolic drugs that lower cardiovascular risk. American College of Cardiology. Available at: https://www.acc.org/latest-in-cardiology/articles/2020/06/17/13/49/unmet-role-of-cardiologists. 2020. Accessed February 8, 2021.
48. Slater TA, Drozd M, Palin V, Bowles C, Waduud MA, Khatib R, Ajjan RA, Wheatcroft SB. Prescribing diabetes medication for cardiovascular risk reduction in patients admitted with acute coronary syndromes: a survey of cardiologists' attitudes and practice. *Eur Heart J Cardiovasc Pharmacother*. 2019. doi: 10.1093/ehjcvp/pvz058
49. Sikirica MV, Martin AA, Wood R, Leith A, Piercy J, Higgins V. Reasons for discontinuation of GLP1 receptor agonists: data from a real-world cross-sectional survey of physicians and their patients with type 2 diabetes. *Diabetes Metab Syndr Obes*. 2017;10:403–412. doi: 10.2147/DMSO.S141235
50. Ryan DH, Lingvay I, Colhoun HM, Deanfield J, Emerson SS, Kahn SE, Kushner RF, Marso S, Plutzky J, Brown-Frandsen K, et al. Semaglutide effects on cardiovascular outcomes in people with overweight or obesity (SELECT) rationale and design. *Am Heart J*. 2020;229:61–69. doi: 10.1016/j.ahj.2020.07.008
51. Nordisk N. A Heart Disease Study of Semaglutide in Patients With Type 2 Diabetes. Available at: https://ClinicalTrials.gov/show/NCT03914326. 2024. Accessed February 14, 2021.
52. Larsen BA. Prescription drugs that are not dispensed. *Tidsskr nor Laegeforen*. 2020;140. doi: 10.4045/tidsskr.19.0577
53. Lin PD, Daley MF, Boone-Heinonen J, Rifas-Shiman SL, Bailey LC, Forrest CB, Horgan CE, Sturtevant JL, Toh S, Young JG, et al. Comparing prescribing and dispensing data of the PCORnet common data model within PCORnet antibiotics and childhood growth study. *EGEMS (Wash DC)*. 2019;7:11. doi: 10.5334/egems.274
54. Alexander GC, Tajanlangit M, Heyward J, Mansour O, Qato DM, Stafford RS. Use and content of primary care office-based vs telemedicine care visits during the COVID-19 pandemic in the US. *JAMA Netw Open*. 2020;3:e2021476. doi: 10.1001/jamanetworkopen.2020.21476

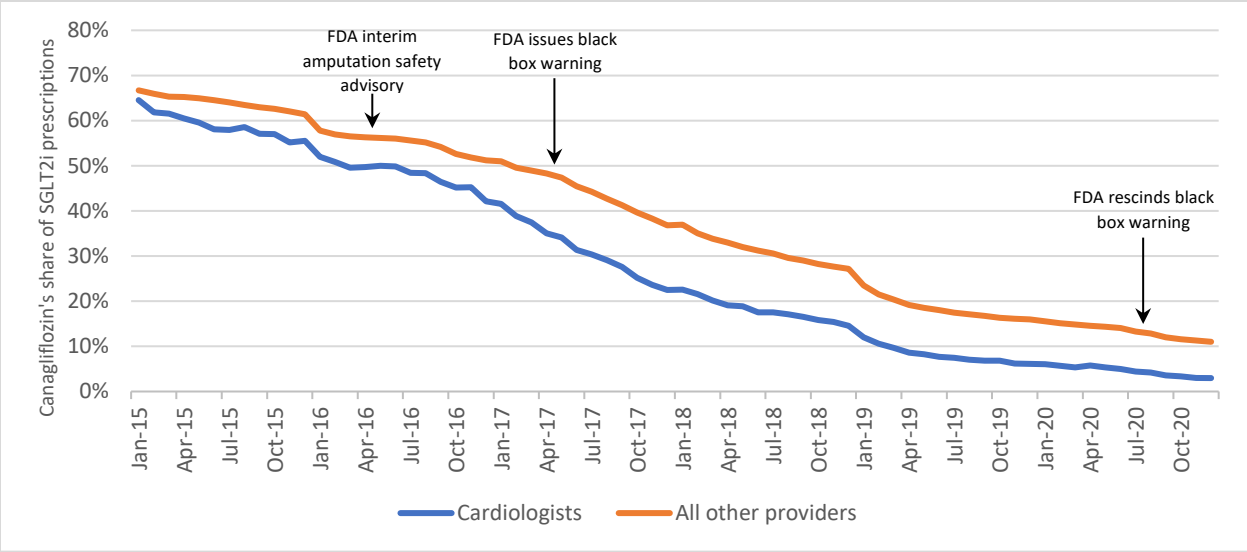
Supplemental Material

Table S1. SGLT2i and GLP-1RA Prescriptions Dispensed Annually and Cardiologist Contribution.

		2015	2016	2017	2018	2019	2020	Total from 2015-2020
SGLT2i Prescriptions	**Total**	7,234,124	9,226,290	9,656,588	10,498,110	12,035,771	14,556,037	63,206,920
	Cardiologist Prescribed	0.49%	0.53%	0.64%	0.84%	1.13%	1.52%	0.94%
GLP1-RA Prescriptions	**Total**	5,687,478	7,388,746	8,375,906	10,648,981	13,826,254	17,484,527	63,411,892
	Cardiologist Prescribed	0.47%	0.46%	0.42%	0.38%	0.38%	0.38%	0.41%

Source: IQVIA National Prescription Audit, 2015-2020

Figure S1. Share of SGLT2i Prescriptions Comprised by Canagliflozin.

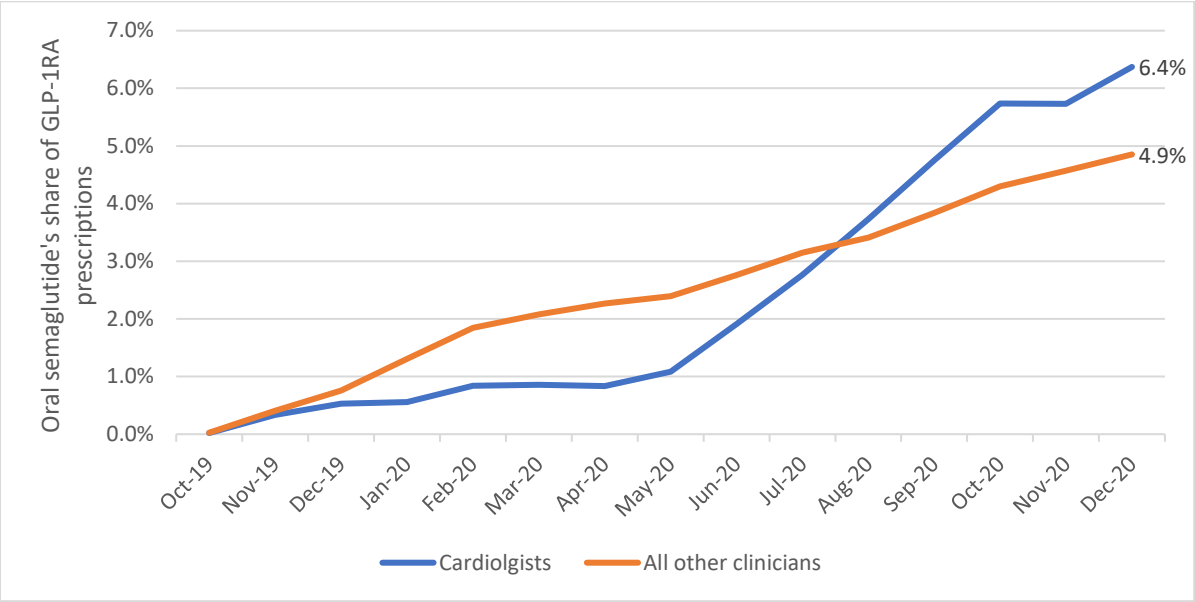


Canagliflozin's share of SGLT2i prescriptions among cardiologists compared to all other clinicians. Arrows indicate publication of key FDA safety communications related to canagliflozin. We did not observe any statistically significant structural breaks in these trends coinciding with these safety announcements.

FDA = U.S. Food and Drug Administration

Source: IQVIA National Prescription Audit, 2015-2020

Figure S2. Share of GLP-1RA Prescriptions Comprised by Oral Semaglutide.



Oral semaglutide, the first available oral formulation of a GLP-1RA, has been increasing its share of GLP-1RA prescriptions among cardiologists and non-cardiologists since it was approved by the U.S. Food and Drug Administration in September 2019.

Source: IQVIA National Prescription Audit, 2015-2020