PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Medicine. The paper was subsequently accepted for publication at BMJ Medicine.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Multinational Patterns of Second-line Anti-hyperglycemic Drug Initiation Across Cardiovascular Risk Groups: A Federated Pharmacoepidemiologic Evaluation in LEGEND-T2DM
AUTHORS	Khera, Rohan; Dhingra, Lovedeep Singh; Aminorroaya, Arya; Li, Kelly; Zhou, Jin J.; Arshad, Faaizah; Blacketer, Clair; Bowring, Mary; Bu, Fan; Cook, Michael; Dorr, David; Duarte-Salles, Talita; DuVall, Scott; Falconer, Thomas; French, Tina; Hanchrow, Elizabeth; Horban, Scott; Lau, Wallis; Li, Jing; Liu, Yuntian; Lu, Yuan; Man, Kenneth; Matheny, Michael; Mathioudakis, Nestoras; McLemore, Michael; Minty, Evan; Morales, Daniel; Nagy, Paul; Nishimura, Akihiko; Ostropolets, Anna; Pistillo, Andrea; Posada, Jose; Pratt, Nicole; Reyes, Carlen; Ross, Joseph; Seager, Sarah; Shah, Nigam; Simon, Katherine; Wan, Eric; Yang, Jianxiao; Yin, Can; You, Seng; Schuemie, Martijn; Ryan, Patrick; Hripcsak, George; Krumholz, Harlan; Suchard, Marc

VERSION 1 - REVIEW

REVIEWER 1	Reviewer 1
REVIEW RETURNED	20-Mar-2023

GENERAL COMMENTS	I read the article by Rohan and colleagues with great interest. The article is well written, addresses a clinically interesting topic, and the study is well executed. However, there may be potential opportunities to clarify / improve the manuscript. Clinical guidelines use the presence of CVD as the basis for recommending specific second-line therapies, but often bifurcate CVD along the phenotypic lines of ASCVD and HF, recommending SGLT2i for HF patients, and either SGLT2i or GLP-1RA for patients with ASCVD. However, the current definition for established CVD – while aligned with CVOTs – is representative of ASCVD. Accordingly, it would be very useful to show results for the subgroup of patients with HF, though I concede this might be difficult to implement in non-US data due to limited sample size. Perhaps one way to circumvent this would be to report biennial results for non-US data or expanding the current CVD definition to include HF codes as sensitivity analyses. While historically metformin has been avoided in HF patients due to concerns of higher risk of lactic acidosis in this population, this should no longer be the case. Similarly, it would be informative to break down findings by CKD status, though this might prove to be even more challenging given the lack of information on CKD stage and greater hesitancy to prescribe metformin in this population. Given

	there are several prior studies on this topic (see next comment), the inclusion of a HF group at the very least would add to the novelty of the study findings. Prior studies – which include some of the source data used in this investigation – have reported similar findings, though the inclusion of multinational databases adds novelty to the current investigation. That being said, please consider incorporating some recent publications (e.g., PMID: 35015080) into your discussion; more specifically, please comment on the differences in study populations and the observed findings. A major study strength is the use of multiple (and multinational) data, which provides a more comprehensive and global context on the uptake of 2nd line glucose lowering therapies. There is some overlap among the data sources, though this is appropriately acknowledged. Of note, 4.6 out of the 4.8 million patients included in the study are from the US, though this is not a concern given that results are not pooled across data. I am less familiar with the non-US data included (except THIN), but I do have some concerns regarding study generalizability. First, some data such as FLPD and SIDIAP appear to be more representative of general practitioners, which could explain the lower use of GLP-1RAs (as these agents historically have been preferentially prescribed by endocrinologists). Second, there exist differences in the uptake of these therapeutics in academic vs non-academic centers (as is also evident in the US data). Some non-US data (e.g., HK data) are primarily derived from academic centers. These are not major concerns in the context of drug safety or effectiveness studies, but may warrant a more circumspect interpretation of study findings in the setting of descriptive designs where the generalizability of the data are an important consideration. Minor comments: For the regression model examining the annualized changes in the incidence rate of SGLT2i and GLP-1RA, please consider adjusting for the effects of age and sex (and perhaps include this analysis in the supplement). Figures 4-7 are hard to read. Please consider truncating the Y axis to 50-60%.

REVIEWER 2	Philip Home; Newcastle University. Competing Interest: I or institutions with which I am associated have received funding for my educational, research and/or advisory activities from most major suppliers of glucose-lowering medications includiing AstraZenaca, Biocon, Boehringer Ingelheim, Eli Lilly, Gan & Lee, GlaxoSmithKline, Merck (MSD), Janssen (J$J), Novo Nordisk, and Sanofi
REVIEW RETURNED	20-Mar-2023

GENERAL COMMENTS	Summary: 1. The authors show that in an area of new class introductions of two series of medications, both the subject of accumulating and different evidence bases and thus guidelines and licensed indications, prescribing is increasing at different rates according to different clinical databases globally. Such is expected, but not explained by the data.

	2. They also show that in two distinct populations (prior cardiovascular disease or not) prescription rates are increasing but seemingly faster in the population without CV disease. This is contrary to the evidence base that has emerged from outcome trials, but quite consistent with the primary licensed indication for these medications (ie glucose-lowering) and evidence of improved tolerability profile (body weight and hypoglycaemia). However the data presented do not serve to explain the difference. Major comment 3. SGLT2 inhibitors (channel blockers) were first licensed in the EU in 2012, and the US in 2013. Since that time a series of outcome studies have been published, with findings that were a surprise (and in one instance rogue), leading to further confirmatory outcome studies (in heart failure and kidney disease areas) leading to indication changes approved by the regulators, as recently in the EU as December 2022. Along the line we have happily seen an updated series of meta-analyses, and legitimate debates about different components of adverse CV outcomes (see below) and applicability in people without CV disease (some studies included these but most did not, and the meaning of prior status interaction with outcome is debated). Major guidelines, and valid consensus statements globally used in diabetes care, have thus continued to evolve, and can be expect to evolve further. Funding-based guidelines, often behind the evidence-based curve (see the VA curve), have been similarly unstable. Accordingly prescribing practice has not only been changing over that time but still is – note the rising lines between the last two years (2020 and 2021) of the authors figures 4-7. The authors then document the changing uptake in different prescribing areas (mostly US, but also Europe, and dipping into a untypical database from Asia), the main message being that these differ. 4. GLP-1RAs have a longer history (2005), but a very unstable one. The interest took off in 2010 with the introduction of liraglutide, but further with its outcome study in 2016, the first of a series of positive class studies, and unlike SGLT2i's across all MACE components but not beyond. But this field is still evolving quite strongly, and thus unstable in terms of prescribing, notably with the advent in the last years of the more effective (glucose and weight surrogates) weekly agents, an oral preparation, a combination peptide of greater efficacy, and even licences for obesity outside of diabetes. Again the authors document the changing landscape in different prescribing areas, but the reviewer can find no useful meaning in their very non-steady state data (apart from the VA and FLPD lags). 5. The authors note, an interesting finding but one likely to have explanations, that uptake of the newer agents is proportionately lower in the people they identify as having CV disease rather than the populations with no such record (note the confusion of the figure presentations as noted below point 13, but the data seems secure according to the vertical axis labels). This is a large difference, and essentially independent of global database source. While the arguments over CV vs non-CV patients differ for SGLT2i's and GLP-1RAs, the same difference is seen, and in both cases is the opposite of what would be crudely expected from the evidence-base. The answer this reviewer would suggest is that the non-CV population is nearly entirely in the hands of diabetes services, who have welcomed these medications because of their strong advantages in body weight control and lack of hypoglycaemia, together unavailable for the competitor medication classes. Further GLP-1RAs are now recommended rather than

	insulin as first injectable, displacing the huge basal insulin starter market, and quite independent of CV protection. Many of the 'CV' patients might already have a heavy medication burden, and/or judged as having short life expectancy – a reason for less intensive glucose-lowering therapy in the guidelines. 6. However this finding (CV vs non-CV uptake) does not need the bulk of data in this paper – data from the last year (as indeed the authors give for geographic scenario in Figures 1-3) would suffice. 7. However, the authors need to be careful with the word 'cardiovascular'. SGLT2i's do not reduce stroke, and it is wrong then to say they offer CV protection. Protection against MI is about 10 %, small and perhaps contaminated by the robust HF protection (30-40 %). But it has not been usual to include HF in the usual meaning of CV outcomes in major studies (HF was an incidental finding in the first studies). Further SGLT2i's have a major protective affect against progression to renal disease – this also ought to be driving prescribing in non-CV groups, though the diabetes community has yet to work out how to implement this effectively. 8. Given the emphasis on findings in prior CV groups one might expect to see robust criteria for these given in the Methods. Instead we find the vague 'A team of clinicians verified the covariates included for presentation in the study to focus on those relevant to the management of diabetes, spanning domains of cardiovascular risk factors, established CVD, and kidney disease.' There is in supplementary material page 50 a list of conditions apparently used for such mapping. Unfortunately these use many terms which do not map to the criteria used in participant selection for the studies, and which would not be regards as extant CV disease by prescribers in diabetes care. The present study findings in this area then seem non-generalizable. 9. Some of the data in the databases is very questionable. For example the hypertension prevalence in HIC, SIDIAP, and IMRD is obviously wrong. Given ischaemic heart disease would include prior MI, prior ACS, and prevalent angina (or use of anti-anginals), the absence of these in the characteristics' tables (Table S4 et seq) and the very very low prevalence of 'coronary atherosclerosis' is puzzling at best. ALPD participants appear to lack sex identity in a variable but large minority. These observations create marked concerns over validity of either or both of data content and extraction. 10 But if the individual cohort characteristics are valid (Tables S4 et seq) then these are very different populations in the different databases (as would be expected a priori) and comparisons between them are fairly meaningless without understanding the context of the coverage of the populations concerned (primary care, specialist care, HMOs, admissions, funding types and the like). Other points 11. It is untrue (end of Introduction) that there is no evidence-base for cardioprotection from sulfonylureas. In the extension phase (randomized cohorts) of the UKPDS both MI and indeed all cause death were significantly reduced, the cohort being mainly people randomized to sulfonylureas. Metformin did show positive outcomes, and in other studies sulfonylureas did not perform any worse than metformin (eg ADOPT, RECORD). What differs here is that glucose lowering effects take 8 or more years to manifest, while the HF gains from SGLT2i's and MACE protective effects of GLP-1RAs are pretty much immediate. 12. The clinical problem preventing more extensive use of PPAR-

	gamma agonists is not heart failure and bladder cancer, but rather weight gain (in obese and struggling populations) and fluid retention. Only pioglitazone has a signal for bladder cancer. 13. The reviewer notes some careless errors in manuscript preparation: in Figures 5 and 6 the graphics appears to have been swopped, so that the SGLT2-i data is shown in Figure 5 and vice versa. The reviewer is not happy – some time was spent trying to understand why some of the data on the panels currently shown on Figure 6 was above zero in 2012 seemingly before approvals of the drug referred to in the Figure title on the page, before raising the magnification of the page revealed the graphics were for a GLP-1RA available from the previous decade. The graphic labelling is anyway too small to read on a 13-inch laptop screen (which delayed this review). 14. The reviewer would suggest many figure panels could be further amalgamated onto one page. Eg combined figures 1-3, 4-5, and 6-7. This would anyway aid interpretation and comparison by the reader. It would also reduce waste on repetitive material in figure legends. Common sense would suggest that abbreviations for the funders/databases (as used in the keys) is kept to the same order as the keys, and kept separate from the drug class names (but see below). 15. The authors might note that in the diabetes literature (where backward medical journal editors allow) the 'GLP-1 receptor agonist' class is referred to as such now, and not as 'glucagon-like peptide-1'. This has arisen because the action of these drugs is not at all 'glucagon-like', something that, unsurprisingly, confused the prescribing fraternity. British National Formulary for example refers to these drugs as 'GLP-1 (glucagon-like peptide-1)' in contrast to 'sodium-glucose co-transporter 2 (SGLT2)' [and, yes, the disconnect with 'L' for 'linked' is unspoken]. 16. There is seemingly a rather obvious typo on the first line of page 51 in the supplementary section. 17. One wonders if for the Hong Kong database the participants ought to exit (and indeed not enter) the study if an alpha-glucosidase medication is used. These are commonly prescribed in China, but I am not sure about HK. 18. References are generally well prepared but there are some formatting errors (eg 25), while others now in print are shown as 'On line first' (39, 45).

VERSION 1 – AUTHOR RESPONSE

Reviewer #1

I read the article by Rohan and colleagues with great interest. The article is well written, addresses a clinically interesting topic, and the study is well executed. However, there may be potential opportunities to clarify / improve the manuscript.

Comment 1: Clinical guidelines use the presence of CVD as the basis for recommending specific second-line therapies, but often bifurcate CVD along the phenotypic lines of ASCVD and HF, recommending SGLT2i for HF patients, and either SGLT2i or GLP-1RA for patients with ASCVD. However, the current definition for established CVD – while aligned with CVOTs – is representative of ASCVD. Accordingly, it would be very useful to show results for the subgroup of patients with HF, though I concede this might be difficult to implement in non-US data due to limited sample size. Perhaps one way to circumvent this would be to report

biennial results for non-US data or expanding the current CVD definition to include HF codes as sensitivity analyses. While historically metformin has been avoided in HF patients due to concerns of higher risk of lactic acidosis in this population, this should no longer be the case. Similarly, it would be informative to break down findings by CKD status, though this might prove to be even more challenging given the lack of information on CKD stage and greater hesitancy to prescribe metformin in this population. Given there are several prior studies on this topic (see next comment), the inclusion of a HF group at the very least would add to the novelty of the study findings.

Response: We appreciate the thoughtful comment by the reviewer. We agree that exploring the uptake of SGLT2is with respect to heart failure and chronic kidney disease would be valuable. As the reviewer highlighted, atherosclerotic cardiovascular disease is the common indication for both SGLT2is and GLP-1 RAs, whereas heart failure and chronic kidney disease are specific indications for SGLT2is alone. Therefore, we had opted to not incorporate these aspects into the current study to maintain the overall focus and coherence. Our goal is to address similar questions as part of the LEGEND-T2DM initiative in future studies.[3]

We have not revised the manuscript in response to this comment.

Comment 2: Prior studies – which include some of the source data used in this investigation – have reported similar findings, though the inclusion of multinational databases adds novelty to the current investigation. That being said, please consider incorporating some recent publications (e.g., PMID: 35015080) into your discussion; more specifically, please comment on the differences in study populations and the observed findings.

Response: We appreciate the comment. We agree that the consistently defined populations and evaluations allow a clearer assessment of the observed patterns in data. We appreciate the reference, which we have now added and discussed. Briefly, the study reported the uptake of GLP-1 RAs and SGLT2is among patients with T2DM and established CVD across VA facilities in 2020. On the other hand, our study more comprehensively defines patterns of all second-line drug initiation among patients with and without established CVD who initiated a second-line antihyperglycemic agent after metformin monotherapy. Additionally, we reported data from the VA healthcare system from 2011 through 2021 as a serial cross-sectional study (Supplemental Table S3), therefore, spanning the 2020 data presented in the abovementioned study. We have now cited this study in the revised Discussion section.

(Discussion, Page 17, Paragraph 2)

> “These prior studies focused on the overall **prevalent** use of cardioprotective therapy **in select years** and found that at most 10%-15% of individuals with compelling indications use cardioprotective medications. The current study adds to the literature by focusing on new initiators of second-line therapy **who are currently using metformin alone**, therefore,

assessing initiation of these agents exclusively in individuals who likely required clinical escalation of antihyperglycemic therapy **as recommended by the ADA. The study further covers 11 years of data enabling us to evaluate the trends, which offers additional qualitative information on the trajectory of the uptake of antihyperglycemic agents.** Moreover, **the study** represents the first assessment contrasting the trends observed in the US with those in other countries and demonstrating the large uptake of SGLT2is that has occurred in many countries in Europe and Asia, during a period when the use has been relatively limited in the US."

Comment 3: A major study strength is the use of multiple (and multinational) data, which provides a more comprehensive and global context on the uptake of 2nd line glucose lowering therapies. There is some overlap among the data sources, though this is appropriately acknowledged. Of note, 4.6 out of the 4.8 million patients included in the study are from the US, though this is not a concern given that results are not pooled across data. I am less familiar with the non-US data included (except THIN), but I do have some concerns regarding study generalizability. First, some data such as FLPD and SIDIAP appear to be more representative of general practitioners, which could explain the lower use of GLP-1RAs (as these agents historically have been preferentially prescribed by endocrinologists). Second, there exist differences in the uptake of these therapeutics in academic vs non-academic centers (as is also evident in the US data). Some non-US data (e.g., HK data) are primarily derived from academic centers. These are not major concerns in the context of drug safety or effectiveness studies, but may warrant a more circumspect interpretation of study findings in the setting of descriptive designs where the generalizability of the data are an important consideration.

Response: We thank the reviewer for the comment. We acknowledge that the study findings may not fully represent national or subnational populations due to their derivation from administrative claims or EHR databases. While this is a study limitation, we presented the data from the various sources separately without combining them, as the reviewer has suggested. We believe that this approach can serve as a benchmark for monitoring the uptake of antihyperglycemic agents in response to changes in regional guidelines, insurance coverage, and contemporary evidence rather than aiming to infer generalizable estimates of the use of antihyperglycemic agents.

We have now underscored this limitation in the revised Discussion section. The revisions are included as an excerpt in our response to comment #6 of the Editors.

Comment 4: For the regression model examining the annualized changes in the incidence rate of SGLT2i and GLP-1RA, please consider adjusting for the effects of age and sex (and perhaps include this analysis in the supplement).

Response: This is an interesting suggestion. Due to the federated nature of our international data sources and to protect patient privacy and rights, we are unable to collect age and sex information for some specific years and, in some smaller data sources, as individual patients begin to become identifiable.

Therefore, we calculated the age- and sex-standardized incident use of GLP-1 RAs, SGLT2is, DPP-4is, and SUs across data from 2016 through 2021 using direct standardization, using the world standard population as the reference.[4] Subsequently, we compared the age- and sex-standardized slope for GLP-1 RAs, SGLT2is, DPP-4is, and SUs between patients with and without CVD across data sources. We found that the age- and sex-standardized incident use of GLP-1 RAs and SGLT2is increased more among patients without CVD than patients with CVD in several data sources, consistent with the unadjusted rates. Importantly, these analyses did not find a higher uptake of GLP-1 RAs or SGLT2is uptake in patients with vs without CVD in any population. Therefore, the non-selective uptake of cardioprotective antihyperglycemic agents was observed even after age- and sex-standardizing. We included these analyses in the Online Supplement.

(Online Supplement, Supplemental Tables S12, S13, S16, S17)

Supplemental Table S12 | Annualized Change in the Age- and Sex-Standardized Incident Use of Glucagon-like Peptide-1 Receptor Agonists for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	1.53% (0.94 to 2.12)	4.78% (3.21 to 6.36)	0.001
MDCD	0.99% (0.58 to 1.41)	1.41% (1.19 to 1.62)	0.03
MDCR	0.71% (0.11 to 1.31)	0.39% (-1.46 to 2.24)	0.658
OCEDM	1.95% (1.19 to 2.71)	4.27% (3.25 to 5.3)	0.001
OEHR	1.55% (0.76 to 2.33)	6.86% (3.25 to 10.46)	0.004
USOC	1.3% (0.52 to 2.07)	4.56% (1.67 to 7.46)	0.016
US Health System Databases			
CUIMC	1.3% (0.79 to 1.81)	3.44% (1.34 to 5.53)	0.025
JHM	0.6% (0.1 to 1.1)	2.22% (1.01 to 3.43)	0.009
STARR	0.77% (0.37 to 1.18)	1.41% (-0.23 to 3.05)	0.328
VA	0.67% (0.17 to 1.17)	1.58% (0.37 to 2.78)	0.089
Non-US Databases			
ALPD	-0.36% (-0.93 to 0.22)	-0.52% (-1.03 to -0.01)	0.574
FLPD	0.35% (0.06 to 0.64)	1.07% (0.28 to 1.86)	0.045
GDA	0.45% (-0.05 to 0.96)	1.17% (0.04 to 2.29)	0.147

HIC	0.03% (-0.12 to 0.18)	0.62% (-0.08 to 1.32)	0.05
HKHA	NA	NA	NA
IMRD	0.28% (-0.2 to 0.76)	1.27% (-1.63 to 4.17)	0.22
SIDIAP	0.21% (-0.09 to 0.5)	0.83% (0.03 to 1.63)	0.075

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S13 | Annualized Change in the Age- and Sex-Standardized Incident Use of Sodium-Glucose Cotransporter 2 Inhibitors for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	1.18% (0.52 to 1.83)	1.91% (0.24 to 3.58)	0.29
MDCD	1.58% (1.16 to 2)	1.38% (0.17 to 2.58)	0.633
MDCR	0.16% (-1.15 to 1.47)	-0.3% (-3.17 to 2.58)	0.7
OCEDM	2.15% (1.17 to 3.13)	2.74% (1.77 to 3.7)	0.275
OEHR	1.99% (1.16 to 2.81)	4.04% (2.8 to 5.28)	0.005
USOC	1.58% (0.73 to 2.43)	3.13% (1.07 to 5.19)	0.09
US Health System Databases			
CUIMC	1.76% (0.94 to 2.57)	2.26% (1.08 to 3.45)	0.357
JHM	0.83% (0.65 to 1.02)	1.86% (1.21 to 2.5)	0.003
STARR	0.74% (0.39 to 1.09)	1.68% (0.64 to 2.73)	0.044
VA	2.95% (1.56 to 4.33)	4.9% (2.79 to 7)	0.064
Non-US Databases			
ALPD	-1.92% (-6.25 to 2.41)	-4.68% (-14.23 to 4.87)	0.486
FLPD	0.11% (-0.03 to 0.26)	0.55% (-0.05 to 1.15)	0.082
GDA	2.56% (0.95 to 4.17)	4.05% (1.01 to 7.1)	0.264
HIC	0.71% (0.39 to 1.03)	2.58% (1.38 to 3.79)	0.003
HKHA	NA	NA	NA
IMRD	1.12% (0.08 to 2.16)	2.92% (-3.55 to 9.39)	0.303
SIDIAP	1.62% (0.97 to 2.28)	2.18% (0.6 to 3.76)	0.393

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data

Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S16 | Annualized Change in the Age- and Sex-Standardized Incident Use of Dipeptidyl Peptidase-4 Inhibitors for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.62% (-0.92 to -0.33)	-1.59% (-2.44 to -0.74)	0.017
MDCD	-0.38% (-0.75 to -0.01)	-1.86% (-2.86 to -0.86)	0.004
MDCR	-2.05% (-4.54 to 0.45)	-2.24% (-4.51 to 0.04)	0.881
OCEDM	-0.17% (-0.38 to 0.04)	-1.07% (-1.7 to -0.44)	0.005
OEHR	0.5% (0.24 to 0.75)	1.17% (0.8 to 1.54)	0.003
USOC	-0.33% (-0.5 to -0.16)	-0.73% (-1.38 to -0.09)	0.129
US Health System Databases			
CUIMC	0.1% (-0.26 to 0.45)	-0.39% (-1.14 to 0.37)	0.145
JHM	0.28% (-0.35 to 0.91)	1.02% (-1.89 to 3.93)	0.511
STARR	-0.03% (-0.29 to 0.23)	0.05% (-0.34 to 0.45)	0.629
VA	2.15% (1.6 to 2.71)	3.69% (2.03 to 5.35)	0.04
Non-US Databases			
ALPD	-2.67% (-5.9 to 0.56)	-5.13% (-10.68 to 0.42)	0.319
FLPD	0.62% (0.32 to 0.91)	1.02% (0.44 to 1.6)	0.121
GDA	1.5% (0.72 to 2.29)	3% (1.41 to 4.59)	0.047
HIC	-0.6% (-1.25 to 0.06)	-1.43% (-3.15 to 0.28)	0.243
HKHA	NA	NA	NA
IMRD	-0.11% (-0.61 to 0.4)	0.41% (-3.94 to 4.76)	0.64
SIDIAP	-0.06% (-0.43 to 0.3)	-0.06% (-0.97 to 0.84)	0.997

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data

Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

Supplemental Table S17 | Annualized Change in the Age- and Sex-Standardized Incident Use of Sulfonylureas for Patients with Established Cardiovascular Disease and Patients without Established Cardiovascular Disease

Data Source	Age- and Sex-Standardized Slope for Patients with CVD	Age- and Sex-Standardized Slope for Patients without CVD	P-value for Slope Difference
US National Databases			
CCAE	-0.25% (-0.77 to 0.28)	0.55% (-0.52 to 1.62)	0.099
MDCD	-0.53% (-1.17 to 0.1)	-3.12% (-4.08 to -2.15)	<0.001
MDCR	-1.21% (-2.79 to 0.38)	-1.08% (-3.44 to 1.28)	0.905
OCEDM	0.39% (-0.03 to 0.81)	-0.63% (-3.56 to 2.3)	0.368
OEHR	0.74% (0.52 to 0.95)	-0.81% (-3.04 to 1.42)	0.091
USOC	0.06% (-0.33 to 0.46)	-0.45% (-1.07 to 0.17)	0.09
US Health System Databases			
CUIMC	-0.22% (-0.71 to 0.28)	-0.68% (-1.41 to 0.06)	0.186
JHM	0.37% (-0.52 to 1.25)	1.17% (-3.14 to 5.49)	0.624
STARR	-0.18% (-0.66 to 0.31)	-0.86% (-1.73 to 0.02)	0.097
VA	-0.1% (-0.75 to 0.54)	0.16% (-3 to 3.31)	0.829
Non-US Databases			
ALPD	-0.38% (-1.15 to 0.38)	-1.27% (-2.54 to 0)	0.135
FLPD	0.03% (-0.12 to 0.18)	0.24% (-0.38 to 0.87)	0.384
GDA	0.09% (-0.25 to 0.43)	0.2% (-0.22 to 0.62)	0.578
HIC	-0.28% (-0.54 to -0.02)	-0.66% (-0.96 to -0.35)	0.031
HKHA	NA	NA	NA
IMRD	-0.15% (-0.37 to 0.06)	0.54% (-1.24 to 2.33)	0.169
SIDIAP	-0.1% (-0.31 to 0.11)	-1.1% (-1.87 to -0.33)	0.008

Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data

Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System

In the main text, we also point readers to this supplementary analysis:

(Materials and Methods, Statistical Analysis, Page 10, Paragraph 1)

> "We compared the annual changes between patients with and without CVD for each second-line agent using the interaction term of CVD status and year in analysis of covariance (ANCOVA) models. **Additionally, to account for the differences in the age and sex distribution between patients with and without CVD, we calculated the age- and sex-standardized incident use of GLP-1 RAs, SGLT2is, DPP-4is, and SUs across data sources from 2016 to 2021 using direct standardization to the world standard population. Subsequently, we compared the age- and sex-standardized slope for GLP-1 RAs, SGLT2is, DPP-4is, and SUs between patients with and without CVD across data sources similarly.**"

(Results, Second-Line Antihyperglycemic Drug Use Across Cardiovascular Risk Groups, Page 16, Paragraph 1)

> "Although Australia, UK, Scotland, and some US databases showed greater increases in the uptake of SGLT2is among patients without CVD compared with patients with CVD from 2016 to 2021, trends of the uptake of SGLT2is were not different between these populations in other databases **(Table 2)**. **These patterns were consistent even after age- and sex-standardization of the data across sources (Supplemental Tables S12 and S13).** The uptake trends of DPP-4is and SUs were inconsistent **(Supplemental Tables S14-S17).**"

Comment 5: Figures 4-7 are hard to read. Please consider truncating the Y axis to 50-60%.

Response: Thank you for the suggestion. To enhance interpretability, we have truncated the Y-axis in the Figures to 0.6 accordingly.

> The revisions are included as an excerpt in our response to comment #14 of reviewer #2.

Reviewer #2

Comment 1: The authors show that in an area of new class introductions of two series of medications, both the subject of accumulating and different evidence bases and thus guidelines and licensed indications, prescribing is increasing at different rates according to different clinical databases globally. Such is expected, but not explained by the data. They also show that in two distinct populations (prior cardiovascular disease or not) prescription rates are increasing but seemingly faster in the population without CV disease. This is contrary to the evidence base that has emerged from outcome trials, but quite consistent with the primary licensed indication for these medications (ie glucose-lowering) and evidence of improved tolerability profile (body weight and hypoglycaemia). However the data presented do not serve to explain the difference.

Response: We appreciate the comments by the reviewer. The primary objective of this study was to describe the trends in the uptake of GLP-1 RAs, SGLT2is, DPP-4is, and SUs across various multinational data sources over the past decade. Consequently, we reported these trends and attempted to interpret them within the context of regional regulations. Although these data alone cannot explain the mechanisms behind the observed differences, they reveal insightful patterns that can potentially be attributed to variations in guideline recommendations and insurance coverage. For instance, the lower use of SGLT2is observed in the FLPD database can be attributed to the French National guidelines recommendations. The lower use of GLP-1 RAs observed in the VA can similarly be attributed to the lower coverage of GLP-1 RAs.

Additionally, we noted a higher uptake of cardioprotective antihyperglycemic agents among patients without established CVD compared with those with established CVD, contrary to initial expectations. While these differences cannot be explained by the available data or regional regulations, it is a data signal that merits an evaluation of widespread non-selective uptake.

While we acknowledge the study's limitations, we believe there are several key additions to the literature, including comparison across multiple US databases, evaluation at large medical centers in the US, and multinational comparison between US and non-US databases. We have further emphasized the value of studying these patterns in the revised manuscript. The revisions are included as an excerpt in our response to comment #2 of the Editors.

Comment 2: SGLT2 inhibitors (channel blockers) were first licensed in the EU in 2012, and the US in 2013. Since that time a series of outcome studies have been published, with findings that were a surprise (and in one instance rogue), leading to further confirmatory outcome studies (in heart failure and kidney disease areas) leading to indication changes approved by the regulators, as recently in the EU as December 2022. Along the line we have happily seen an updated series of meta-analyses, and legitimate debates about different components of adverse CV outcomes (see below) and applicability in people without CV disease (some studies included these but most did not, and the meaning of prior status interaction with outcome is debated). Major guidelines, and valid consensus statements globally used in diabetes care, have thus continued to evolve, and can be expect to evolve further. Funding-based guidelines, often behind the evidence-based curve (see the VA curve), have been similarly unstable. Accordingly prescribing practice has not only been changing over that time but still is – note the rising lines between the last two years (2020 and 2021) of the

authors figures 4-7. The authors then document the changing uptake in different prescribing areas (mostly US, but also Europe, and dipping into a untypical database from Asia), the main message being that these differ. GLP-1RAs have a longer history (2005), but a very unstable one. The interest took off in 2010 with the introduction of liraglutide, but further with its outcome study in 2016, the first of a series of positive class studies, and unlike SGLT2i's across all MACE components but not beyond. But this field is still evolving quite strongly, and thus unstable in terms of prescribing, notably with the advent in the last years of the more effective (glucose and weight surrogates) weekly agents, an oral preparation, a combination peptide of greater efficacy, and even licences for obesity outside of diabetes. Again the authors document the changing landscape in different prescribing areas, but the reviewer can find no useful meaning in their very non-steady state data (apart from the VA and FLPD lags).

Response: Thank you for the thoughtful perspective on the temporal patterns of use of GLP-1 RAs and SGLT2is. We agree with the reviewer that the trends in the uptake of these agents are expected to differ across various data sources, given the evolving evidence base and indications. Nonetheless, that was the primary motivation behind assessing their trends in a multinational study. We believe that providing a comprehensive description is the first step towards improving clinical care by properly spotting the challenges. It should be noted that without the federated design of this multinational study, we were not able to identify the unique patterns in the VA and FLPD, which, in the authors' opinion, are crucial in terms of developing future regional guidelines and expanding insurance coverage.

We have not revised our manuscript in response to this comment.

Comment 3: The authors note, an interesting finding but one likely to have explanations, that uptake of the newer agents is proportionately lower in the people they identify as having CV disease rather than the populations with no such record (note the confusion of the figure presentations as noted below point 13, but the data seems secure according to the vertical axis labels). This is a large difference, and essentially independent of global database source. While the arguments over CV vs non-CV patients differ for SGLT2i's and GLP-1RAs, the same difference is seen, and in both cases is the opposite of what would be crudely expected from the evidence-base. The answer this reviewer would suggest is that the non-CV population is nearly entirely in the hands of diabetes services, who have welcomed these medications because of their strong advantages in body weight control and lack of hypoglycaemia, together unavailable for the competitor medication classes. Further GLP-1RAs are now recommended rather than insulin as first injectable, displacing the huge basal insulin starter market, and quite independent of CV protection. Many of the 'CV' patients might already have a heavy medication burden, and/or judged as having short life expectancy – a reason for less intensive glucose-lowering therapy in the guidelines.

Response: We appreciate the comment. We have now discussed the potential underlying factors contributing to the non-selective uptake of GLP-1 RAs and SGLT2is, such as prescription by endocrinologists compared with other providers, per the reviewer's recommendation.

(Discussion, Page 18, Paragraph 3)

> "*We noted a greater increase in the uptake of GLP-1 RAs and SGLT2is among patients without CVD compared with those with established CVD between 2016 and 2021. Nevertheless, the latter group represents the only group with robust recommendations for the use of these medications in clinical practice guidelines. The non-selective uptake of cardioprotective agents may potentially be attributed to the fact that cardiologists contribute to less than 2% of prescribed GLP-1 RAs and SGLT2is. In contrast, more than two-thirds of these agents are prescribed by primary care physicians, internists, and endocrinologists. As a result, patients with T2DM and CVD who are often treated by cardiologists may be less likely to receive cardioprotective antihyperglycemic agents compared with those with T2DM but without CVD who are probably managed by non-cardiologists.*"

Comment 6: However this finding (CV vs non-CV uptake) does not need the bulk of data in this paper – data from the last year (as indeed the authors give for geographic scenario in Figures 1-3) would suffice.

Response: We appreciate the comment. While we can compare the uptake of antihyperglycemic agents cross-sectionally in recent years, the evaluation of trends offers additional qualitative information on the trajectory of uptake. Hence, we would prefer the analyses related to the differential uptake of cardioprotective antihyperglycemic agents over time in the manuscript unless the Editors feel strongly otherwise.

We have not revised the manuscript in response to this comment.

Comment 7: However, the authors need to be careful with the word 'cardiovascular'. SGLT2i's do not reduce stroke, and it is wrong then to say they offer CV protection. Protection against MI is about 10 %, small and perhaps contaminated by the robust HF protection (30-40 %). But it has not been usual to include HF in the usual meaning of CV outcomes in major studies (HF was an incidental finding in the first studies). Further SGLT2i's have a major protective affect against progression to renal disease – this also ought to be driving prescribing in non-CV groups, though the diabetes community has yet to work out how to implement this effectively.

Response: Thank you for the comment. As the reviewer mentioned, SGLT2is have not been shown to reduce the risk of stroke. However, they have been shown to reduce a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.[5,6] Hence, they are being considered cardioprotective. We decided not to incorporate this distinction in the manuscript to maintain the overall focus of the results.

Comment 8: Given the emphasis on findings in prior CV groups one might expect to see robust criteria for these given in the Methods. Instead we find the vague 'A team of clinicians verified the covariates included for presentation in the study to focus on those relevant to the management of diabetes, spanning domains of cardiovascular risk factors, established CVD, and kidney disease.' There is in supplementary material page 50 a list of conditions apparently used for such mapping. Unfortunately these use many terms which do not map to the criteria used in participant selection for the studies, and which would not be regards as extant CV disease by prescribers in diabetes care. The present study findings in this area then seem non-generalizable.

Response: We thank the reviewer for the comment. We followed prior studies using diagnosis codes to define ASCVD. In our study, we adhered to these criteria to appropriately define "established CVD" by including concepts related to acute and chronic ischemic heart disease, acute and chronic cerebrovascular disease, and acute and chronic peripheral vascular disease, which would represent a comprehensive definition of ASCVD, consistent with how it was defined in ADA guidelines.[7] We acknowledge that individual clinical entities within the broad definition of ASCVD will often vary in sensitivity and specificity. Still, the broader definition is likely to be most sensitive to the definition of ASCVD. Of note, the same definition was used in prior studies of SGLT2is.[8,9] Therefore, we believe the study's definition of ASCVD represents the population indicated to receive GLP-1 RAs and SGLT2is according to the ADA guidelines.[7]

We have not revised the manuscript in response to this comment.

Comment 9: Some of the data in the databases is very questionable. For example the hypertension prevalence in HIC, SIDIAP, and IMRD is obviously wrong. Given ischaemic heart disease would include prior MI, prior ACS, and prevalent angina (or use of anti-anginals), the absence of these in the characteristics' tables (Table S4 et seq) and the very very low prevalence of 'coronary atherosclerosis' is puzzling at best. ALPD participants appear to lack sex identity in a variable but large minority. These observations create marked concerns over validity of either or both of data content and extraction.

Response: We appreciate the potential confusion that Supplementary Tables S8-S11 may have caused readers, and we have now clarified some important differences between data sources that could lead to this confusion. A major strength of our present work is its characterization of second-line treatment initiation in patients with and without established CVD across various healthcare settings internationally. We believe this global aggregation helps to increase the generalizability of our findings. How patient information is collected and can be shared differs across healthcare settings and be differing requirements. Our use of the well-established Observational Medical Outcomes Partnership (OMOP) common data model and its associated medical vocabularies standardizes medical terms across data sources. Nonetheless, HIC, SIDIAP, and IMRD record primarily incident health conditions, as opposed for example to insurance claims data sources that often return multiple records of prevalent conditions. For consistency across all data sources, our Supplementary Tables of patient characteristics report recorded health conditions within 365 days of treatment initiation. As such, the reported percentages are correct. We now note this point in the manuscript:

(Materials and Methods, Data Sources, Page 9, Paragraph 2)

> "The study was designed at a data source level and followed federated analytic principles, so the same patients may be represented in more than one data source, particularly in the US. **It should be noted that some non-US databases, including Health Informatics Centre at the University of Dundee (HIC), Information System for Research in Primary Care (SIDIAP), and UK-IQVIA Medical Research Data (IMRD), record primarily incident health conditions, as opposed to other data sources that often return multiple records of prevalent conditions.**"

We have updated the table captions as well:

(Caption of Supplemental Tables S4-S11)

> "* *The table reports clinical covariates within 365 days of treatment initiation.*"

Importantly, please note that this difference between incident and prevalent encoding only impacts the supplementary patient characterization tables and not the primary results of our study that rely on identifying patients with incident second-line treatment use with prevalent T2DM and with and without prevalent established CVD. We achieve prevalent T2DM and established CVD across all data sources by considering records all time (not just 365 days) prior to initiation.

Finally, we have added a "Unknown" percentage row to cover limited sex identity in ALPD as differential sharing requirements mask this information in about approximately 40% of the total patients in the data source.

Comment 10: But if the individual cohort characteristics are valid (Tables S4 et seq) then these are very different populations in the different databases (as would be expected a priori) and comparisons between them are fairly meaningless without understanding the context of the coverage of the populations concerned (primary care, specialist care, HMOs, admissions, funding types and the like).

Response: Supplemental Table S1 represents a brief description of each data source from the Observational Health Data Sciences and Informatics Network included in the study. For instance, (1) SIDIAP is a primary care records database that covers approximately 80% of the population of Catalonia, North-East Spain; (2) HIC covers approximately 1.2 million people from the Tayside and Fife regions of Scotland, provided by the Health Informatics Centre (HIC) at the University of Dundee; etc.

We acknowledge that the included populations are heterogenous, as can be expected from a multinational study, and is mentioned by the reviewer. However, we analyzed and presented the data from the various sources separately without combining them. We acknowledge that the data cannot be generalized to obtain national or regional estimates and have underscored this limitation in the revised Discussion section. The revisions are included as an excerpt in our response to the Editor's comment #6.

Comment 11: It is untrue (end of Introduction) that there is no evidence-base for cardioprotection from sulfonylureas. In the extension phase (randomized cohorts) of the UKPDS both MI and indeed all cause death were significantly reduced, the cohort being mainly people randomized to sulfonylureas. Metformin did show positive outcomes, and in other studies sulfonylureas did not perform any worse than metformin (eg ADOPT, RECORD). What differs here is that glucose lowering effects take 8 or more years to manifest, while the HF gains from SGLT2i's and MACE protective effects of GLP-1RAs are pretty much immediate.

Response: We thank the reviewer for the comment. We appreciate that other antihyperglycemic agents have some evidence for decreased cardiovascular risk by improving glycemic control and reducing macrovascular dysfunction in patients with T2DM. However, the cardioprotective effects of GLP-1 RAs and SGLT2is appear independent of glycemic control and manifest in the short term compared with sulfonylureas. Moreover, the guidelines endorse only these agents as cardioprotective and, therefore, was the terminology we used in the study. We have now revised the Introduction section to convey this message more clearly.

(Introduction, Page 8, Paragraph 1)

> "This is particularly relevant as an assessment of their initiation relative to other second-line agents, namely, dipeptidyl peptidase-4 inhibitors (DPP-4is) and sulfonylureas (SUs) that have been available for longer, but lack cardioprotective or renoprotective effects **in the short term**."

Comment 12: The clinical problem preventing more extensive use of PPAR-gamma agonists is not heart failure and bladder cancer, but rather weight gain (in obese and struggling populations) and fluid retention. Only pioglitazone has a signal for bladder cancer.

Response: We acknowledge that weight gain is a common side effect of thiazolidinediones, which we have now included in the revised manuscript.

(Materials and Methods, Study Population, Page 10, Paragraph 1)

"We did not consider thiazolidinediones given their known association with a risk of heart failure**, weight gain,** and bladder cancer."

Comment 13: The reviewer notes some careless errors in manuscript preparation: in Figures 5 and 6 the graphics appears to have been swopped, so that the SGLT2-i data is shown in Figure 5 and vice versa. The reviewer is not happy – some time was spent trying to understand why some of the data on the panels currently shown on Figure 6 was above zero in 2012 seemingly before approvals of the drug referred to in the Figure title on the page, before raising the magnification of the page revealed the graphics were for a GLP-1RA available from the previous decade. The graphic labelling is anyway too small to read on a 13-inch laptop screen (which delayed this review).

Response: We sincerely apologize for the inconvenience and thank the reviewer for their meticulous examination of our work. We have revised the figures based on the feedback. The revisions are included as an excerpt in our response to the reviewer's comment #14.

Comment 14: The reviewer would suggest many figure panels could be further amalgamated onto one page. Eg combined figures 1-3, 4-5, and 6-7. This would anyway aid interpretation and comparison by the reader. It would also reduce waste on repetitive material in figure legends. Common sense would suggest that abbreviations for the funders/databases (as used in the keys) is kept to the same order as the keys, and kept separate from the drug class names (but see below).

Response: Thanks for the suggestion. We combined figures 1-3, 4-5, and 6-7 as recommended to avoid redundancy and improve interpretability. We also edited the manuscript to reflect these changes.

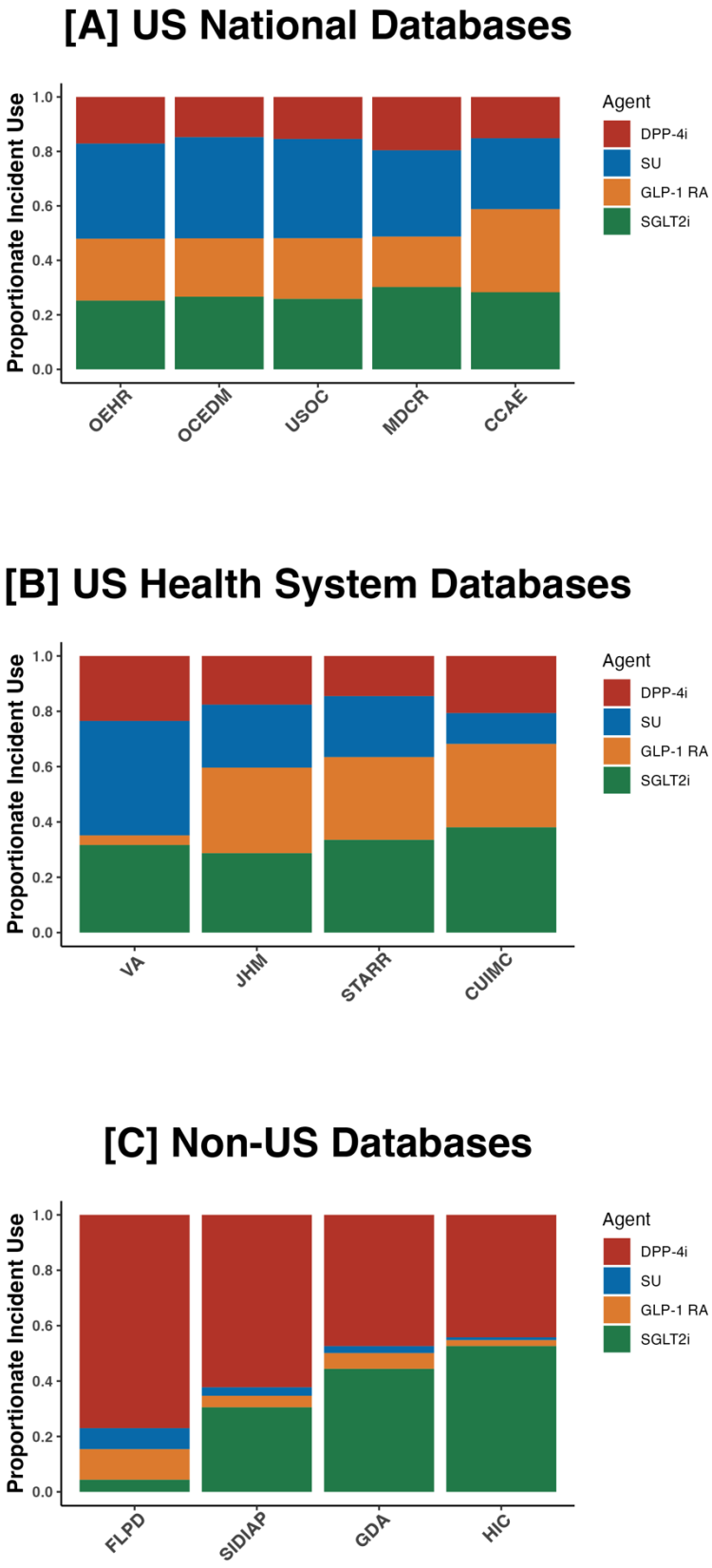
We appreciate the reviewer's suggestion regarding the order of abbreviations. We believe that maintaining them in alphabetical order would facilitate efficient reference for our readers. Hence, we have decided to retain the alphabetical arrangement.

(Figure 1)

"Figure 1 | Proportional Incident Use of Second-Line Antihyperglycemic Agents in (A) United States National Databases, (B) United States Health System Databases, and (C) Non-United States Databases in 2021

Abbreviations: CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, DPP-4i - Dipeptidyl Peptidase-4 Inhibitors, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, HIC - Health Informatics Centre at the University of Dundee, JHM - Johns Hopkins Medicine, MDCR - IBM Health MarketScan®

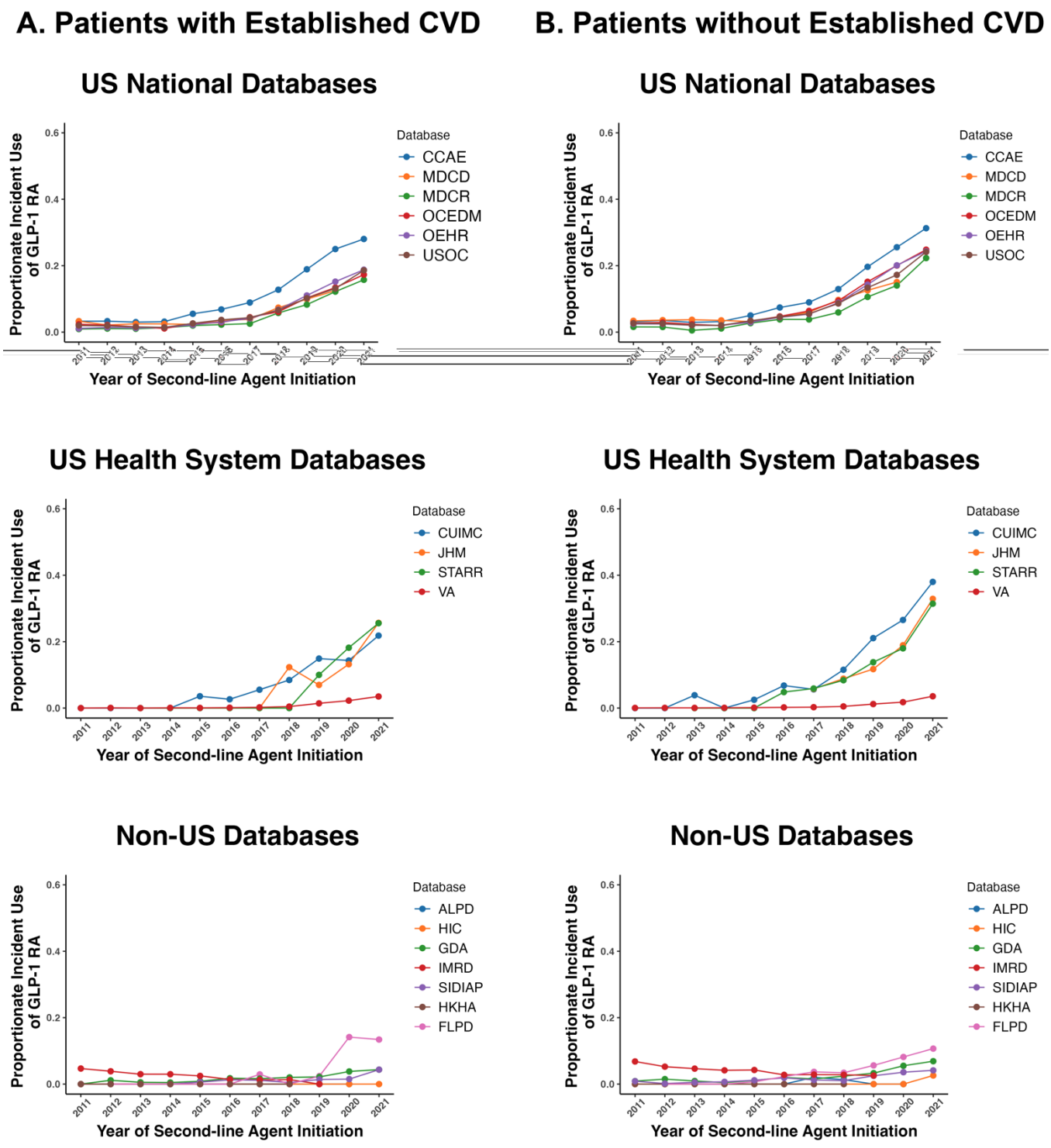
Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, SU - Sulfonylurea, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System”


[A] US National Databases
Proportionate Incident Use
1.0
0.8
0.6
0.4
0.2
0.0
OEHR
OCEDM
USOC
MDCR
CCAE
Agent
DPP-4i
SU
GLP-1 RA
SGLT2i
[B] US Health System Databases
Proportionate Incident Use
1.0
0.8
0.6
0.4
0.2
0.0
VA
JHM
STARR
CUIMC
Agent
DPP-4i
SU
GLP-1 RA
SGLT2i
[C] Non-US Databases
Proportionate Incident Use
1.0
0.8
0.6
0.4
0.2
0.0
FLPD
SIDIAP
GDA
HIC
Agent
DPP-4i
SU
GLP-1 RA
SGLT2i

(Figure 2)

“Figure 2 | Proportional First Incident Use of Glucagon-like Peptide-1 Receptor Agonists as Second-line Therapy after Metformin in (A) Patients with Established Cardiovascular Disease, and (B) Patients without Established Cardiovascular Disease

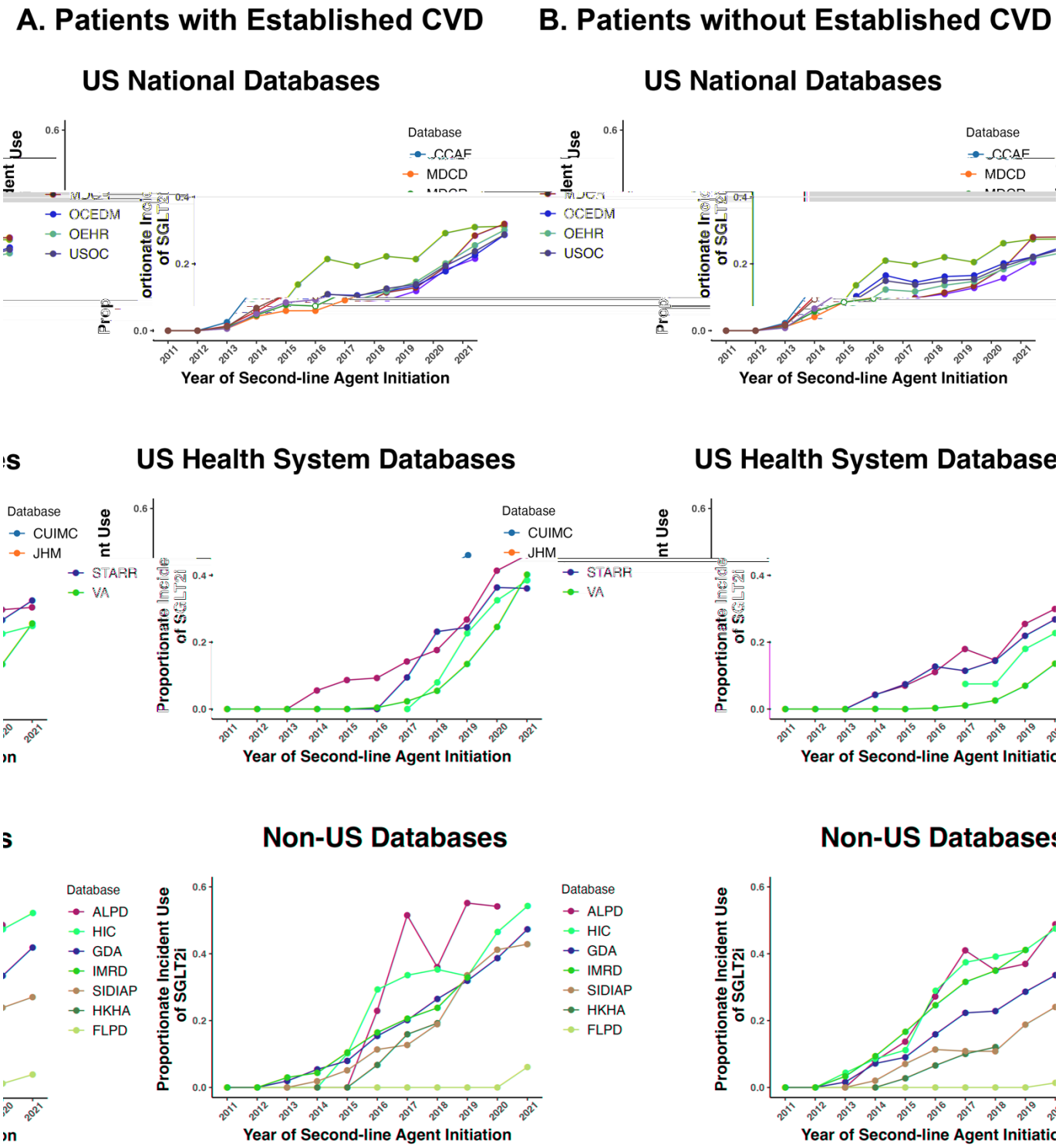
Abbreviations: ALPD - Australia Longitudinal Patient Database Practice Profile, CCAE - IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC - Columbia University Irving Medical Center, FLPD - France Longitudinal Patient Database, GDA - Germany Disease Analyser, GLP-1 RA - Glucagon-like Peptide-1 Receptor Agonist, HIC - Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD - UK-IQVIA Medical Research Data, JHM - Johns Hopkins Medicine, MDCD - IBM Health MarketScan® Multi-State Medicaid Database, MDCR - IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM - Optum Clinformatics Extended Data Mart - Date of Death (DOD), OEHR - Optum© de-identified Electronic Health Record Dataset, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System”


A. Patients with Established CVD
B. Patients without Established CVD
US National Databases
US Health System Databases
Non-US Databases
Proportionate Incident Use of GLP-1 RA
Year of Second-line Agent Initiation
Database
CCAE
MDCD
MDCR
OCEDM
OEHR
USOC
CUIMC
JHM
STARR
VA
ALPD
HIC
GDA
IMRD
SIDIAP
HKHA
FLPD

(Figure 3)

“Figure 3 | Proportional First Incident Use of Sodium-Glucose Cotransporter 2 Inhibitors as Second-line Therapy after Metformin in (A) Patients with Established Cardiovascular Disease, and (B) Patients without Established Cardiovascular Disease

Abbreviations: ALPD – Australia Longitudinal Patient Database Practice Profile, CCAE – IBM MarketScan® Commercial Claims and Encounters Data (CCAE), CUIMC – Columbia University Irving Medical Center, FLPD – France Longitudinal Patient Database, GDA – Germany Disease Analyser, HIC – Health Informatics Centre at the University of Dundee, HKHA - Hong Kong Hospital Authority, IMRD – UK-IQVIA Medical Research Data, JHM – Johns Hopkins Medicine, MDCD – IBM Health MarketScan® Multi-State Medicaid Database, MDCR – IBM Health MarketScan® Medicare Supplemental and Coordination of Benefits Database, OCEDM – Optum Clinformatics Extended Data Mart – Date of Death (DOD), OEHR – Optum© de-identified Electronic Health Record Dataset, SGLT2i - Sodium-Glucose Cotransporter 2 Inhibitor, SIDIAP - Information System for Research in Primary Care, STARR - Stanford Medicine, USOC - United States Open Claims, VA - Department of Veterans Affairs Healthcare System”



Comment 15: The authors might note that in the diabetes literature (where backward medical journal editors allow) the 'GLP-1 receptor agonist' class is referred to as such now, and not as 'glucagon-like peptide-1'. This has arisen because the action of these drugs is not at all 'glucagon-like', something that, unsurprisingly, confused the prescribing fraternity. British National Formulary for example refers to these drugs as 'GLP-1 (glucagon-like peptide-1)' in

contrast to 'sodium-glucose co-transporter 2 (SGLT2)' [and, yes, the disconnect with 'L' for 'linked' is unspoken].

Response: We included the abbreviations based on the previous literature.[10,11] We would defer to the Editors to indicate how the names of the drug classes should be referred to. For the moment, we have not revised the manuscript in response to the comment.

Comment 16: There is seemingly a rather obvious typo on the first line of page 51 in the supplementary section.

Response: Thank you for the comment. We have edited the Online Supplement accordingly.

(Online Supplement, Supplemental Methods – Exposure Cohort Definitions, Page 10, Paragraph 1)

"The person also **exits** the cohort when encountering any of the following events:"

Comment 17: One wonders if for the Hong Kong database the participants ought to exit (and indeed not enter) the study if an alpha-glucosidase medication is used. These are commonly prescribed in China, but I am not sure about HK.

Response: Our objective was to evaluate the utilization of GLP-1 RAs, SGLT2is, DPP-4is, and SUs as second-line antihyperglycemic agents among patients with type 2 diabetes mellitus who had previously received metformin monotherapy. Consequently, participants who initiated treatment with an alpha-glucosidase inhibitor such as acarbose or miglitol were excluded from the study population across all databases, including the Hong Kong Hospital Authority database.

We have not revised the manuscript in response to this comment.

Comment 18: References are generally well prepared but there are some formatting errors (eg 25), while others now in print are shown as 'On line first' (39, 45).

Response: We have now revised references 25, 39, and 45 accordingly.

(References)

Reference 25

> "*25 Khera Rohan, Lu Yuan, Chen Ruijun, et al. Comparative cardiovascular effectiveness and safety of individual angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: a multinational participant-level assessment from LEGEND-HTN. J Am Coll Cardiol 2021;**77**:1474–1474. doi:10.1016/S0735-1097(21)02832-1*"

Previously Reference 39

> "*42 Taha MB, Valero-Elizondo J, Yahya T, et al. Cost-related medication nonadherence in adults with diabetes in the United States: The National Health Interview Survey 2013-2018. Diabetes Care 2022;**45:594–603**. doi:10.2337/dc21-1757*"

Previously Reference 45

> "*27 Recalde M, Rodríguez C, Burn E, et al. Data Resource Profile: The Information System for Research in Primary Care (SIDIAP). Int J Epidemiol 2022;**51**:e324–e336. doi:10.1093/ije/dyac068*"

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1 Nargesi AA, Clark C, Aminorroaya A, *et al.* Persistence on Novel Cardioprotective Antihyperglycemic Therapies in the United States. *Am J Cardiol* 2023;**196**:89–98.

2 Schuemie MJ, Ryan PB, Pratt N, *et al.* Large-scale evidence generation and evaluation across a network of databases (LEGEND): assessing validity using hypertension as a case study. *J Am Med Inform Assoc* 2020;**27**:1268–77.

3 Khera R, Schuemie MJ, Lu Y, *et al.* Large-scale evidence generation and evaluation across a network of databases for type 2 diabetes mellitus (LEGEND-T2DM): a protocol for a series of multinational, real-world comparative cardiovascular effectiveness and safety studies. *BMJ Open* 2022;**12**:e057977.

4 World Standard Population by Sex. Public Health Scotland. 2018.https://www.opendata.nhs.scot/dataset/standard-populations (accessed 24 May 2023).

5 Zinman B, Wanner C, Lachin JM, *et al.* Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med* 2015;**373**:2117–28.

6 Neal B, Perkovic V, Mahaffey KW, *et al.* Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med* 2017;**377**:644–57.

7 ElSayed NA, Aleppo G, Aroda VR, *et al.* 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2023. *Diabetes Care* 2022;**46**:S140–57.

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VERSION 2 – REVIEW

REVIEWER	Perera, Rafael; University of Oxford, Primary Care Health Sciences. Competing Interest: None
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GENERAL COMMENTS	The authors have replied to the editors' and reviewers' comments adequately, and I believe this version of the manuscript is suitable for publication in BMJ Medicine.