University of Groningen

Lower risk of cardiovascular events and death associated with initiation of sodium-glucose cotransporter-2 inhibitors versus sulphonylureas

the CVD-REAL Investigators and Study Group; Goh, Su Yen; Kosiborod, Mikhail N.; Lam, Carolyn S.P.; Cavender, Matthew A.; Kohsaka, Shun; Norhammar, Anna; Birkeland, Kåre I.; Holl, Reinhard W.; Mauricio, Dídac

Published in:
Diabetes, Obesity and Metabolism

DOI:
10.1111/dom.15092

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2023

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):
the CVD-REAL Investigators and Study Group, Goh, S. Y., Kosiborod, M. N., Lam, C. S. P., Cavender, M. A., Kohsaka, S., Norhammar, A., Birkeland, K. I., Holl, R. W., Mauricio, D., Tangri, N., Shaw, J. E., Thuresson, M., Fenici, P., & Kim, D. J. (2023). Lower risk of cardiovascular events and death associated with initiation of sodium-glucose cotransporter-2 inhibitors versus sulphonylureas: Analysis from the CVD-REAL 2 study. *Diabetes, Obesity and Metabolism*, *25*(8), 2402-2409. https://doi.org/10.1111/dom.15092

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Check for updates

Received: 2 February 2023 | Revised: 6 April 2023 | Accepted: 9 April 2023

DOI: 10.1111/dom.15092

RESEARCH LETTER

WILEY

Lower risk of cardiovascular events and death associated with initiation of sodium-glucose cotransporter-2 inhibitors versus sulphonylureas: Analysis from the CVD-REAL 2 study

Su-Yen Goh MD[1] | Mikhail N. Kosiborod MD[2,3] | Carolyn S. P. Lam MD[2,4,5] | Matthew A. Cavender MD[6] | Shun Kohsaka MD[7] | Anna Norhammar MD[8] | Kåre I. Birkeland MD[9] | Reinhard W. Holl MD[10] | Dídac Mauricio MD[11] | Navdeep Tangri MD[12] | Jonathan E. Shaw MD[13] | Marcus Thuresson PhD[14] | Peter Fenici MD[15,16,17] | Dae Jung Kim MD[18] | on behalf of the CVD-REAL Investigators and Study Group

[1]Singapore General Hospital, Singapore, Singapore

[2]Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, Missouri, USA

[3]University Medical Center Groningen, Groningen, The Netherlands

[4]National Heart Center Singapore and SingHealth Duke-NUS, Singapore, Singapore

[5]The George Institute for Global Health, Sydney, New South Wales, Australia

[6]University of North Carolina, Chapel Hill, North Carolina, USA

[7]Keio University School of Medicine, Tokyo, Japan

[8]Karolinska Institutet, Stockholm, Sweden

[9]University of Oslo and Oslo University Hospital, Oslo, Norway

[10]University of Ulm, Ulm, Germany

[11]Hospital de la Santa Creu i Sant Pau, CIBERDEM, IIB Sant Pau, Barcelona, Spain

[12]University of Manitoba, Winnipeg, Manitoba, Canada

[13]Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

[14]Statisticon AB, Uppsala, Sweden

[15]Catholic University of the Sacred Heart, School of Medicine and Surgery, Rome, Italy

[16]Biomagnetism and Clinical Physiology International Center (BACPIC), Rome, Italy

[17]AstraZeneca SpA, Milan, Italy

[18]Ajou University School of Medicine, Suwon, Republic of Korea

Correspondence
Su-Yen Goh, MBBS, FRCP(Edin), Singapore General Hospital, Singapore, Singapore.
Email: goh.su.yen@singhealth.com.sg

Funding information
AstraZeneca

KEYWORDS: cardiovascular disease, real-world evidence, SGLT2 inhibitor, sulphonylureas, type 2 diabetes

1 | INTRODUCTION

Sulphonylureas (SUs) are widely used in type 2 diabetes (T2D), particularly in resource-constrained regions. Although a large outcome study suggests that a specific SU (glimepiride) is neutral for cardiovascular (CV) risk, other reports show an increased risk of CV events and mortality with SU treatment.[1,2] Conversely, sodium-glucose cotransporter-2 (SGLT2) inhibitors have robust

 © 2023 John Wiley & Sons Ltd.

clinical trial[3] and large-scale real-world data demonstrating benefit.[4,5]

In this analysis from the CVD-REAL (Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors) Study Group, we compare CV events and mortality in patients newly initiated on SGLT2 inhibitors versus SUs, using real-world data from Asia-Pacific, North America, Europe and the Middle East.

2 | METHODS

The CVD-REAL study methods have been published previously,[6] and are also described in the supplementary materials. Briefly, adult patients with T2D newly prescribed/dispensed a prescription (initial or add-on) for any SGLT2 inhibitor or SU (including fixed-dose combination) from 13 countries (South Korea, Japan, Taiwan, Singapore, Australia, United States, Canada, Denmark, Sweden, Norway, Spain, Germany and Israel) were included. Patients with type 1 or gestational diabetes were excluded. A non-parsimonious propensity score for initiating SGLT2 inhibitors was developed for each country and SGLT2 inhibitors and SU patients were matched (1:1). Outcomes investigated were hospitalization for heart failure (HHF), all-cause death (ACD), a composite of ACD and HHF, myocardial infarction (MI) and stroke in the intention-to-treat population (Table S1). The first episode of initiation of an SGLT2 inhibitor or SU for each patient was included. Cox proportional hazards models were used to assess time-to-first event for each outcome and for each country separately by independent academic/statistical groups. The hazard ratios (HRs) and 95% confidence intervals (CIs) from each country were then pooled for an overall weighted summary, in which random-effects models with inverse variance weighting for each country were implemented. Pooled meta-analyses were conducted by Statisticon AB and validated by independent academic statisticians at Saint Luke's Mid America Heart Institute.

3 | RESULTS

Between 2012 and 2017, 1 958 950 patients with T2D were started on SGLT2 inhibitors (n = 253 709) or SUs (n = 1 705 241). Before matching, patients in the SGLT2 inhibitor group were younger, more likely to be on metformin/glucagon-like peptide-1 receptor agonists/insulin, and had lower rates of comorbid heart failure, microvascular disease, stroke and chronic kidney disease (Table S2). After propensity matching, there were 192 687 new users of SGLT2 inhibitors and 192 687 new users of SUs (Figure S1). Baseline characteristics were well balanced between groups post-matching; the mean age was 57.4 years, 45% were women, and approximately 29% had established CV disease (CVD; Table 1). The distribution of specific agent use within the SGLT2 inhibitor and SU groups is shown (Table S3) and the mean follow-up time was 415 and 424 days in each treatment group, respectively (Table S4).

Initiation of SGLT2 inhibitors versus SUs was associated with a lower risk of HHF (pooled HR 0.72 [95% CI 0.64–0.81]; $P < 0.001$), ACD (pooled HR 0.53 [95% CI 0.47–0.60]; $P < 0.001$), composite of HHF or ACD (pooled HR 0.62 [95% CI 0.56–0.69]; $P < 0.001$), MI (pooled HR 0.77 [95% CI 0.66–0.90]; $P = 0.001$), and stroke (pooled HR 0.73 [95% CI 0.68–0.78]; $P < 0.001$ [Figure 1A–E]). HRs favoured SGLT2 inhibitors versus SUs in most countries for all outcomes. The summary of the associations between initiation of SGLT2 inhibitors versus SUs across countries pooled for all outcomes (Figure 1F) and the incidence rate per individual country (Table S5) is shown. An analysis within subgroups of patients with/without established CVD showed that initiation of SGLT2 inhibitors versus SUs was consistently associated with significantly lower risk for all five outcomes regardless of whether patients did or did not have established CVD (Figure S2).

4 | DISCUSSION

The role of SUs in diabetes management remains controversial. Cost, cost-effectiveness, affordability, and safety feature heavily for payers, policy makers, providers and patients, particularly considering most people with diabetes reside in low- to middle-income areas.

The focus for diabetes therapy has moved beyond mere glucose-lowering efficacy towards comprehensive cardio-renal risk reduction and improved survival. In this regard, SU agents have never been shown to provide such benefits. Despite the lack of benefit, SU use is still common, as evidenced by the approximately sevenfold higher usage of SUs versus SGLT2 inhibitors as the newly initiated agent in our cohort. SUs act on pancreatic β cells independently of serum glucose levels, resulting in an elevated risk of hypoglycaemia with potential increased risk of QT prolongation, arrhythmias and sudden cardiac death. While previous studies suggested higher risk of CV events with SUs, a recent large CV outcome trial showed neutral effects of glimepiride (vs. linagliptin) on major adverse CV events as well as risk of HHF.[1,2] However, head-to-head comparisons for SU versus SGLT2 inhibitors on CV outcomes are generally lacking.

In this cohort of >385 000 patients with T2D, initiation of SGLT2 inhibitors was associated with significantly lower risk of HHF and ACD versus initiation of SUs. A 38% lower risk was observed for the composite outcome of HHF or ACD, with SGLT2 inhibitor-associated risk reductions also observed for MI and stroke. Benefits were observed regardless of established CVD status. There were differences in point estimates across countries for outcomes, but directionality of associations was consistent despite variable patient characteristics, healthcare settings, practice patterns and specific SGLT2 inhibitor compounds used across the Asia-Pacific, North America and Europe/Israel regions.

The lower risk of stroke with SGLT2 inhibitors (vs. placebo) has been seen in the CANVAS trial (HR 0.90 [95% CI 0.71–1.15])[7] and a previous CVD-REAL analysis (HR 0.68 [95% CI 0.55–0.84]),[8] but not in EMPA-REG OUTCOME (HR 1.24 [95% CI 0.92–1.67])[9] or DECLARE-TIMI 58 (HR 1.01 [95% CI 0.84–1.21]).[10] Older data on SUs (chlorpropramide, glibenclamide)[11] indicated a potential higher risk for stroke, while newer-generation SUs (gliclazide, glimepiride) have a lower risk of CV mortality versus older SUs.[12]

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universitetsbiblioteket, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 Baseline characteristics after propensity-score matching

Characteristics	SGLT2 inhibitors (*N* = 192 687)	SUs (*N* = 192 687)	Std diff[a], %
Mean age (SD), years	57.4 (11.7)	57.4 (12.7)	1.1
Women	86 438 (44.9)	87 019 (45.2)	0.6
Cardiovascular history	55 049 (29.5)	52 843 (28.4)	2.6
Myocardial infarction	7435 (4.0)	7162 (3.8)	0.8
Unstable angina	8541 (4.6)	8123 (4.4)	1.1
Heart failure	13 429 (7.2)	12 869 (6.9)	1.2
Atrial fibrillation	8141 (4.4)	7934 (4.3)	0.5
Stroke	19 274 (10.3)	18 503 (9.9)	1.4
Peripheral artery disease	10 039 (5.4)	9719 (5.2)	0.8
Microvascular disease	80 316 (43.1)	77 276 (41.5)	3.3
Chronic kidney disease	9939 (5.3)	9446 (5.1)	1.2
Frailty: yes[b]	14 874 (8.2)	14 953 (8.3)	0.2
Metformin	151 526 (78.6)	152 272 (79.5)	2.2
DPP-4 inhibitor	74 522 (38.7)	73 604 (38.2)	1.0
Thiazolidinedione	15 725 (8.2)	14 773 (7.7)	1.8
GLP-1 receptor agonist	12 659 (6.6)	10 491 (5.4)	4.7
Insulin	42 361 (22.0)	40 434 (21.0)	2.4
Anti-hypertensive therapy	129 651 (67.3)	128 057 (66.5)	1.8
Low-ceiling diuretic	24 569 (12.8)	24 230 (12.6)	0.5
ACE inhibitor	40 303 (20.9)	40 386 (21.0)	0.1
ARB	74 849 (38.8)	74 126 (38.5)	0.8
Loop diuretic	15 903 (8.3)	15 507 (8.0)	0.8
Statin therapy	121 319 (63.0)	120 313 (62.4)	1.1
β-blocker	47 020 (24.4)	45 736 (23.7)	1.6
Aldosterone antagonist	5763 (3.0)	5737 (3.0)	0.1
Index year			
2012	40 (0.1)	8 (0.0)	3.5
2013	6335 (6.2)	6464 (6.3)	0.5
2014	30 822 (17.4)	30 094 (17.0)	1.1
2015	55 159 (31.8)	54 286 (31.3)	1.1
2016	84 182 (45.2)	84 336 (45.3)	0.2
2017	16 149 (19.0)	17 499 (20.6)	4.0

Note: Data are n (%), unless stated otherwise.
Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose cotransporter-2; Std diff, standardized difference; SU, sulphonylurea.
[a]Standardized difference >10% represents a non-negligible difference.
[b]Hospitalized for ≥3 consecutive days in year prior to index.

Our observations are consistent with the growing body of evidence on the wide range of benefits with SGLT2 inhibitors. Network and pairwise meta-analyses have reported reduced ACD (relative risk [RR] 0.63 [95% CI 0.46–0.87]) and CV mortality (RR 0.52 [95% CI 0.31–0.88]) when comparing SGLT2 inhibitors versus SUs.[13] Another analysis of a large claims database[14] showed that SGLT2 inhibitors were associated with a decreased risk of developing CVD compared with SUs (HR 0.50 [95% CI 0.45–0.55]) as well as a lower risk of HHF (HR 0.48 [95% CI 0.40–0.57]) and amputation (HR 0.74 [95% CI 0.57–0.96]). Our results expand these findings by using one of the largest, most geographically diverse cohorts of patients with T2D from real-world clinical practice. The observations from our analysis have compelling implications for prescribers, payers, policy makers and patients, which are pertinent in today's era of value-driven care looking beyond pill cost.

Recent guidance from the American Diabetes Association advocates for selection of medical therapy based on treatment goals, and although both SGLT2 inhibitors and SUs are listed as appropriate treatment options to achieve glycaemic control, only SGLT2 inhibitors are emphasized for cardiorenal risk reduction, especially in high-risk individuals.[15] This approach, however, is dependent on prior detection of cardiorenal disease (or recognition of multiple risk factors for

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universiteitsbibliotheek, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

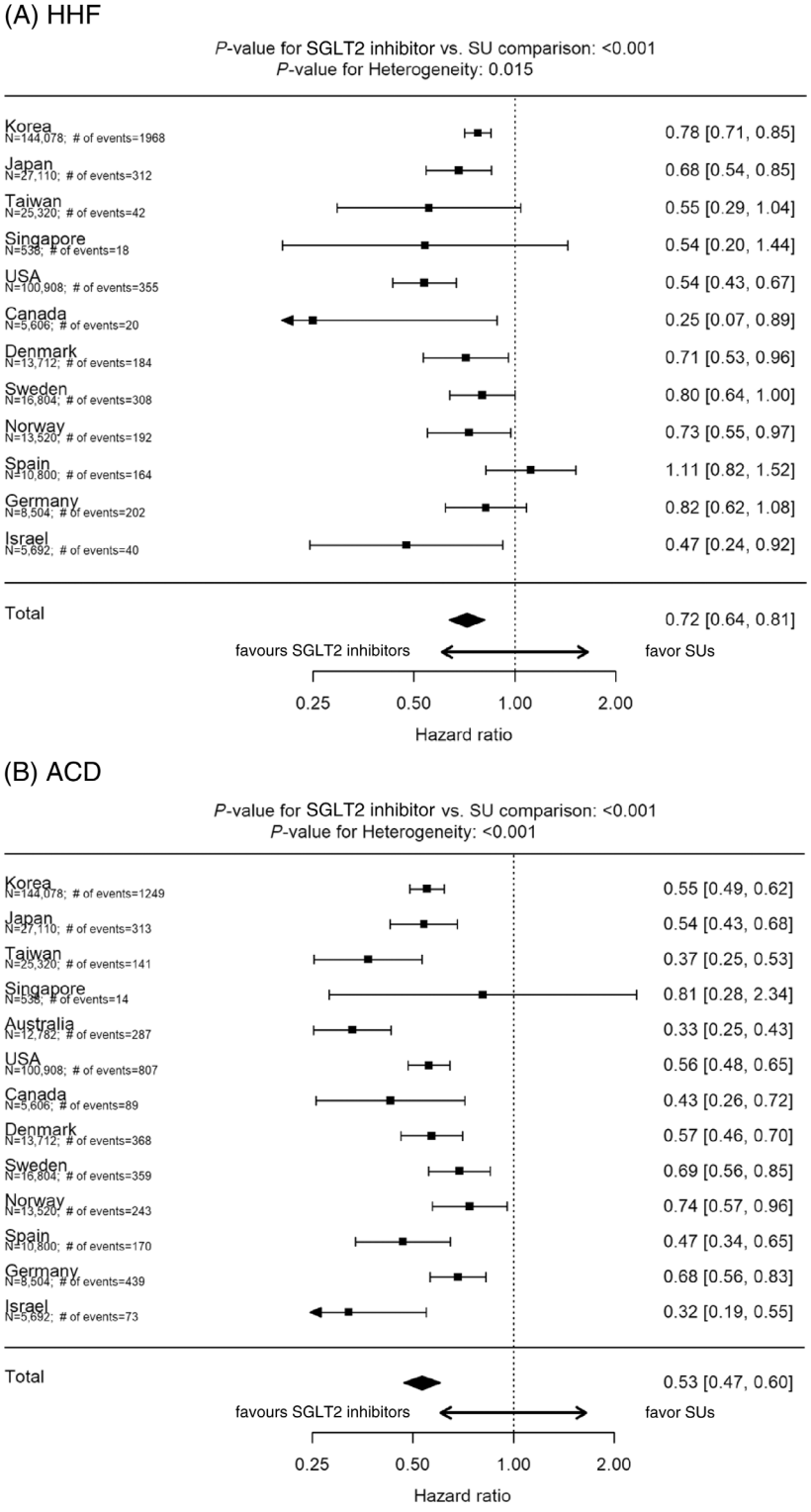

FIGURE 1 Pooled hazard ratios for the outcomes of (A) hospitalization for heart failure (HHF), (B) all-cause death (ACD), (C) composite of HHF or ACD, (D) myocardial infarction (MI), (E) stroke and (F) all five outcomes. Outcomes were defined as primary discharge diagnosis codes (Table S1). In Japan and Singapore, for the outcome of ACD, only information on deaths occurring in hospital were available, however it is noted that the majority of fatal events in those countries occur in hospital. In Australia, only data for ACD were available for inclusion in these analyses. In Sweden, Norway and Denmark, HHF was defined by any hospital visit with a registered primary diagnosis of heart failure (using the diagnosis codes for heart failure events and validated independently in each country). PY, person-years; SGLT2, sodium-glucose cotransporter-2; SU, sulphonylurea

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universiteitsbibliotheek, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

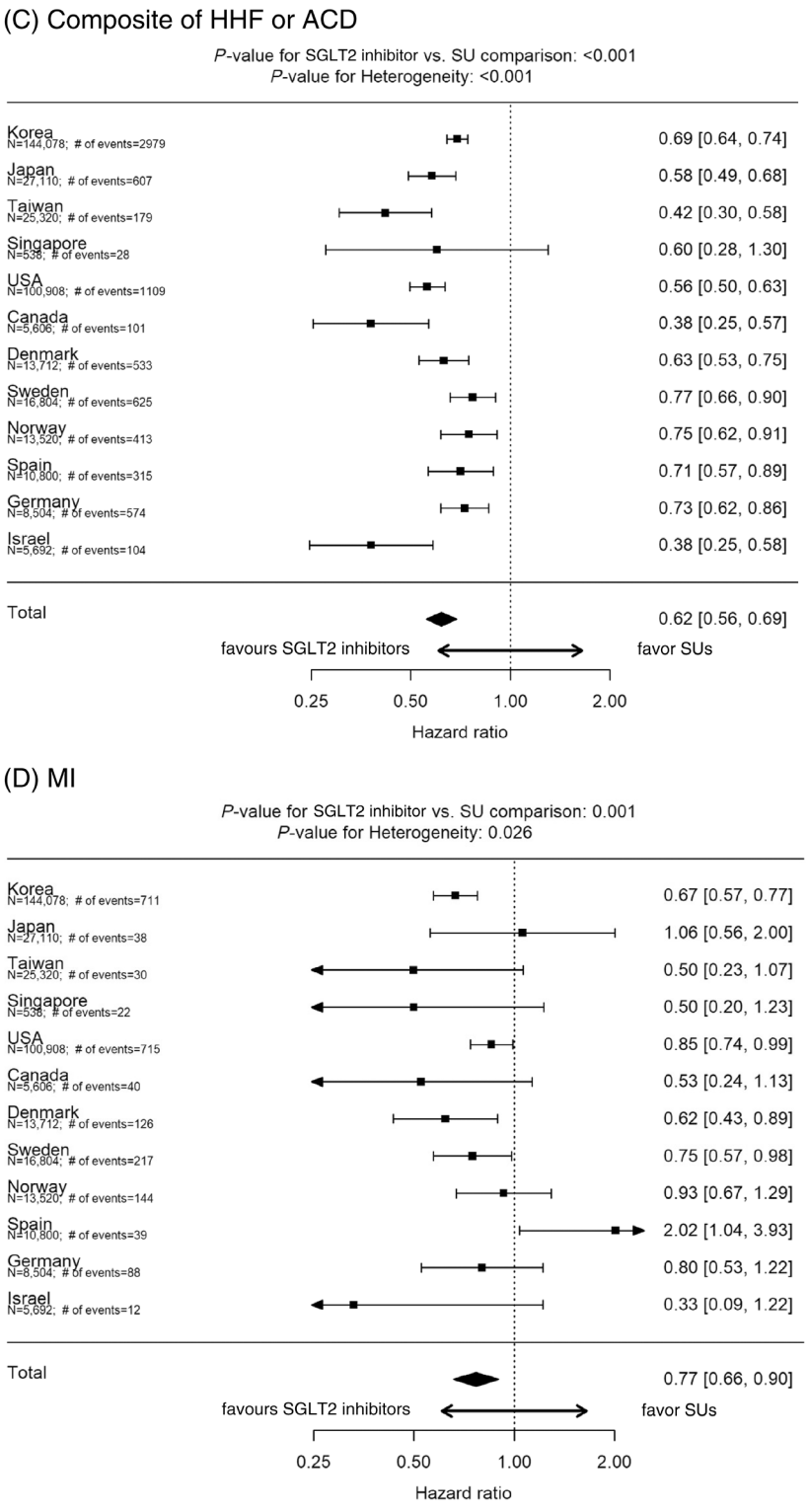

FIGURE 1 (Continued)

cardiorenal disease) in patients with T2D. The significantly larger proportion of patients receiving SUs versus SGLT2 inhibitors observed in our analysis suggests a substantial degree of clinical inertia in terms of screening and diagnosis of cardiorenal disease and/or a lack of awareness in terms of guideline-directed medical therapy selection.

Results of this study should be considered in the context of potential limitations related to CVD-REAL, which have been detailed previously.[6] Specifically, these relate to the possibility of residual confounders, the relatively short follow-up (~1 year), differences in socioeconomic standards and the fact that data analysis was performed up

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universitetsbiblioteket, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

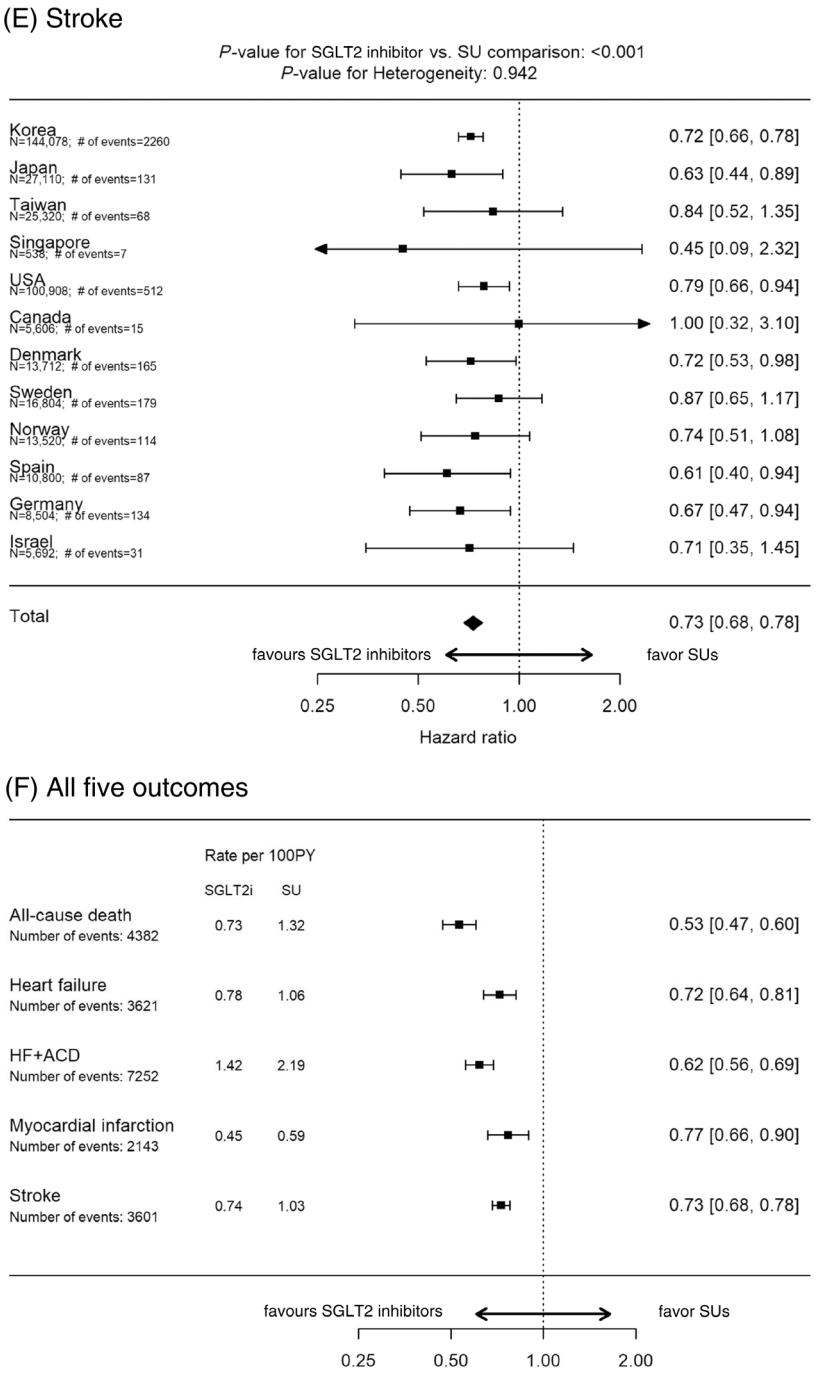

FIGURE 1 (Continued)

to 2017 only. Strengths of this study are the population-based, nationwide and unselected real-world design, which provides high external validity and a large sample size, allowing for country-wise propensity score-matched analyses. Results were consistent across geographical regions.

In conclusion, in this large analysis of real-world clinical data across 13 countries and >385 000 patients, initiation of SGLT2 inhibitors was associated with a significantly lower risk of HHF, ACD, HHF or ACD, MI and stroke versus initiation of SUs. These findings are complementary to previous RCTs,[7,9,10] which did not include head-to-head comparisons of SGLT2 inhibitors with other agents, and are consistent with meta-analyses and real-world evidence of SGLT2 inhibitors versus SUs.[13,14] Taken together, these data provide compelling evidence on the role of SGLT2 inhibitors for people with diabetes across a wide spectrum of CV risk.

AUTHOR CONTRIBUTIONS

Mikhail N. Kosiborod, Peter Fenici and Marcus Thuresson contributed to the development of the study concept and design, data collection and/or analysis, interpretation of the data, and provided critical

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universiteitsbibliotheek, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

review and revision the manuscript. Su-Yen Goh contributed to the data collection, interpretation of the data, wrote the first draft of the manuscript and provided critical review and revision of subsequent drafts. Carolyn S. P. Lam, Matthew A. Cavender, Shun Kohsaka, Anna Norhammar, Kåre I. Birkeland, Reinhard W. Holl, Dídac Mauricio, Navdeep Tangri, Jonathan E. Shaw and Dae Jung Kim contributed to the data collection, interpretation of the data, and critical review and revision of the manuscript. All authors provided their final approval and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriate investigated and resolved.

ACKNOWLEDGEMENTS

This study was funded by AstraZeneca. The authors acknowledge Kevin Kennedy (Saint Luke's Mid America Heart Institute) for his independent validation of the data. The authors would also like to acknowledge Marit E. Jørgensen (Steno Diabetes Center, Copenhagen, Gentofte, Denmark and University of Southern Denmark, Copenhagen, Denmark), Avraham Karasik (Maccabi Health Service, Research and Innovation Institute, Tel Aviv, Israel) and Chern-En Chiang (Taipei Veterans General Hospital, Taipei, Taiwan) for data collection from their respective countries. Editorial support in styling, formatting and submission of the manuscript was provided by Róisín O'Connor, inScience Communications, Springer Healthcare, and funded by AstraZeneca.

CONFLICT OF INTEREST STATEMENT

Su-Yen Goh has received institutional grants from AstraZeneca, Medtronic and Sanofi. She has participated in advisory boards for Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, Medtronic, MSD and Sanofi, and has received honoraria/speaker fees. Mikhail N. Kosiborod has received research grants from AstraZeneca and Boehringer Ingelheim, other research support from AstraZeneca, and has received honoraria from AstraZeneca, Boehringer Ingelheim and Novo Nordisk. He has acted as a consultant or participated on advisory boards for 35Pharma, Alnylam, Amgen, Applied Therapeutics, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Dexcom, Eli Lilly, Esperion Therapeutics, Janssen, Lexicon, Merck (Diabetes and Cardiovascular), Novo Nordisk, Pharmacosmos, Pfizer, Sanofi, Structure Therapeutics, Vifor Pharma and Youngene Therapeutics. Carolyn S. P. Lam has received research support from Boston Scientific, Bayer, Roche Diagnositics, AstraZeneca, Medtronic and Vifor Pharma, and has served as a consultant or on an Advisory Board/Steering Committee/Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus. Matthew A. Cavender has received personal fees from AstraZeneca, Merck, Sanofi-Aventis, Chiesi and research support (non-salary) from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, The Medicines Company, Merck and Takeda. Shun Kohsaka has received grants from Bayer Yakuhin and Daiichi Sankyo and consulting fees from Bayer Yakuhin, Bristol-Myers Squibb, and Pfizer. Anna Norhammar has received honoraria for lectures and advisory board meetings for AstraZeneca, Novo Nordisk, Boehringer Ingelheim and Lilly. Kåre I. Birkeland has received grants to his institution from AstraZeneca for this study and has given lectures and consulted for Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim and Merck Sharp & Dohme. Reinhard W. Holl reports grants to the University Hospital, Ulm, from AstraZeneca. Dídac Mauricio has received honoraria for lectures or consulting from AB-Biotics, Almirall, Amgen, Eli Lilly, Esteve, Ferrer, Janssen, Menarini, Merck Sharp & Dohme, Novo Nordisk and Sanofi. Navdeep Tangri has received consulting fees from Otsuka, Tricida and AstraZeneca. He has received research support from AstraZeneca, including for this work. His research programme is supported by the Canadian Institute for Health Research and Research Manitoba. Jonathan E. Shaw has received honoraria for advisory boards and lectures from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck Sharp & Dohme, Mylan, Novartis, Novo Nordisk and Sanofi. Marcus Thuresson is an employee at Statisticon AB, for which AstraZeneca is a client. Peter Fenici is an AstraZeneca employee and holds stock options. Dae Jung Kim has received grant support from Boehringer Ingelheim, LG Chem, Sanofi and AstraZeneca, has been a consultant for AstraZeneca, Novo Nordisk and Sanofi, has received speaker fees from Novo Nordisk, Boehringer Ingelheim, Handok, LG Chem, Novartis Korea, Hanmi, DongWha Pharm, Lilly Korea and AstraZeneca.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15092.

DATA AVAILABILITY STATEMENT

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure. Data for studies directly listed on Vivli can be requested through Vivli at www.vivli.org. Data for studies not listed on Vivli could be requested through Vivli at https://vivli.org/members/enquiries-about-studies-not-listed-on-the-vivli-platform/. AstraZeneca Vivli member page is also available outlining further details: https://vivli.org/ourmember/astrazeneca/.

ORCID

Su-Yen Goh https://orcid.org/0000-0003-3758-9982
Carolyn S. P. Lam https://orcid.org/0000-0003-1903-0018
Matthew A. Cavender https://orcid.org/0000-0002-4466-4760
Kåre I. Birkeland https://orcid.org/0000-0003-3002-6933
Dae Jung Kim https://orcid.org/0000-0003-1025-2044

REFERENCES

1. Azoulay L, Suissa S. Sulfonylureas and the risks of cardiovascular events and death: a methodological meta-regression analysis of the observational studies. *Diabetes Care*. 2017;40(5):706-714.
2. Rosenstock J, Kahn SE, Johansen OE, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. *JAMA*. 2019;322(12):1155-1166.

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universitetsbiblioteket, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

3. Kanie T, Mizuno A, Takaoka Y, et al. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1 receptor agonists and sodium-glucose co-transporter-2 inhibitors for people with cardiovascular disease: a network meta-analysis. *Cochrane Database Syst Rev*. 2021;10:CD013650.
4. Dave CV, Kim SC, Goldfine AB, Glynn RJ, Tong A, Patorno E. Risk of cardiovascular outcomes in patients with type 2 diabetes after addition of SGLT2 inhibitors versus sulfonylureas to baseline GLP-1RA therapy. *Circulation*. 2021;143(8):770-779.
5. Franklin JM, Patorno E, Desai RJ, et al. Emulating randomized clinical trials with nonrandomized real-world evidence studies: first results from the RCT DUPLICATE initiative. *Circulation*. 2021;143(10):1002-1013.
6. Khunti K, Kosiborod M, Kim DJ, et al. Cardiovascular outcomes with sodium-glucose cotransporter-2 inhibitors vs other glucose-lowering drugs in 13 countries across three continents: analysis of CVD-REAL data. *Cardiovasc Diabetol*. 2021;20(1):159.
7. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N Engl J Med*. 2017;377(7):644-657.
8. Kosiborod M, Lam CSP, Kohsaka S, et al. Cardiovascular events associated with SGLT-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL 2 study. *J Am Coll Cardiol*. 2018;71(23):2628-2639.
9. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N Engl J Med*. 2015;373(22):2117-2128.
10. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2019;380(4):347-357.
11. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK prospective diabetes study (UKPDS) group. *Lancet*. 1998;352(9131):837-853.
12. Simpson SH, Lee J, Choi S, Vandermeer B, Abdelmoneim AS, Featherstone TR. Mortality risk among sulfonylureas: a systematic review and network meta-analysis. *Lancet Diabetes Endocrinol*. 2015;3(1):43-51.
13. Lee G, Oh SW, Hwang SS, et al. Comparative effectiveness of oral antidiabetic drugs in preventing cardiovascular mortality and morbidity: a network meta-analysis. *PLoS ONE*. 2017;12(5):e0177646.
14. Dawwas GK, Smith SM, Park H. Cardiovascular outcomes of sodium glucose cotransporter-2 inhibitors in patients with type 2 diabetes. *Diabetes Obes Metab*. 2019;21(1):28-36.
15. American Diabetes A. Standards of care in diabetes-2023 abridged for primary care providers. *Clin Diabetes*. 2022;41(1):4-31.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Goh S-Y, Kosiborod MN, Lam CSP, et al. Lower risk of cardiovascular events and death associated with initiation of sodium-glucose cotransporter-2 inhibitors versus sulphonylureas: Analysis from the CVD-REAL 2 study. *Diabetes Obes Metab*. 2023;25(8):2402-2409. doi:10.1111/dom.15092

14631326, 2023, 8, Downloaded from https://dom-pubs.pericles-prod.literatumonline.com/doi/10.1111/dom.15092 by Universitetsbiblioteket, Wiley Online Library on [22/10/2023]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License