



COMMENT ON SUISSA

Lower Risk of Death With SGLT2 Inhibitors in Observational Studies: Real or Bias? *Diabetes Care* 2018;41:6–10

Diabetes Care 2018;41:e106–e108 | <https://doi.org/10.2337/dc18-0338>

Marcus Thuresson,¹
 Matthew A. Cavender,^{2,3} Alex Z. Fu,⁴
 John P. Wilding,⁵ Kamlesh Khunti,⁶
 Reinhard W. Holl,⁷ Anna Norhammar,⁸
 Kåre I. Birkeland,⁹
 Marit Eika Jørgensen,^{10,11}
 Eric Wittbrodt,¹² Niklas Hammar,^{8,13}
 Peter Fenici,¹⁴ and
 Mikhail Kosiborod,¹⁵ on behalf of the
 CVD-REAL Investigators and Study
 Group*

In his Perspectives, Suissa (1) offers a critique of the methodological approach used in the Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT-2 Inhibitors (CVD-REAL) study (2). We welcome thoughtful analysis and critical reexamination of large pharmacoepidemiological studies, such as ours, as a part of important scientific discourse, and we agree that these investigations offer important insights into the comparative effectiveness of therapeutic approaches.

According to Suissa, the main potential issue is the possibility of “immortal time bias,” which occurs when two patient groups are formed within a time interval in a hierarchical manner: the first group is selected and followed from first prescription of a sodium–glucose cotransporter 2 inhibitor (SGLT2i), and the comparator group from the first prescription of an

“other glucose-lowering drug” (oGLD). Based on the baseline characteristics of patients initiated on SGLT2i and those on oGLD in CVD-REAL, Suissa (1) states, “we can presume that most, if not all, of the initiators of SGLT2i had been prior initiators of oGLD (the comparator drug) sometime between the study entry date (November 2012) and the day they initiated SGLT2i.” The time between the first use of oGLD and first use of SGLT2i in SGLT2i-treated patients would then represent “immortal time,” potentially introducing bias.

We agree that such an approach could introduce an immortal time bias; however, the assumption that nearly all patients in the SGLT2i group were prior initiators of oGLD during the study period is based on comparing the baseline patient characteristics prior to propensity matching. We

included the index year, baseline glucose-lowering (and many other) medications, and time since initiation of the first glucose-lowering medication in the propensity score to ensure that an SGLT2i patient was matched with a similar oGLD patient. This is illustrated by the well-balanced baseline medication use after propensity matching. In fact, less than 50% of propensity-matched patients treated with SGLT2i had prior oGLD initiation during the study period (e.g., 46% in Sweden and 40% in Norway). Furthermore, because we did not simply select the first oGLD prescription as the index date in the comparator group but instead selected a random initiation date, a smaller but comparable proportion of oGLD-treated patients also had prior initiation of a different oGLD during the study period (e.g., 32% in Sweden and 30% in Norway).

¹Statisticon AB, Uppsala, Sweden

²University of North Carolina at Chapel Hill, Chapel Hill, NC

³Baim Institute for Clinical Research, Boston, MA

⁴Georgetown University Medical Center, Washington, DC

⁵University of Liverpool, Liverpool, U.K.

⁶University of Leicester, Leicester, U.K.

⁷Ulm University, Ulm, Germany

⁸Karolinska Institutet, Stockholm, Sweden

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

¹⁰Steno Diabetes Center Copenhagen, Gentofte, Denmark

¹¹National Institute of Public Health, University of Southern Denmark, Copenhagen, Denmark

¹²AstraZeneca, Wilmington, DE

¹³AstraZeneca, Gothenburg, Sweden

¹⁴AstraZeneca, Cambridge, U.K.

¹⁵Saint Luke's Mid America Heart Institute and University of Missouri-Kansas City, Kansas City, MO

Corresponding author: Mikhail Kosiborod, mkosiborod@saint-lukes.org.

This article contains Supplementary Data online at <http://care.diabetesjournals.org/lookup/suppl/10.2337/dc18-0338/-/DC1>.

*A complete list of the CVD-REAL Investigators and Study Group can be found in the Supplementary Data online.

© 2018 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. More information is available at <http://www.diabetesjournals.org/content/license>.

To scrutinize whether this modest difference in the proportions of patients with prior oGLD initiation during the study period (but before index treatment) could have introduced bias, sensitivity analyses were performed in Sweden and Norway (countries where data were immediately available for reanalyses). In these analyses, only the first initiation of therapy (SGLT2i or oGLD) was selected. As expected, this resulted in substantial decrease (46% in both Sweden and Norway) in patients initiating SGLT2i. The results for Sweden (hazard ratio [HR] 0.625 [95% CI 0.498–0.784]) and for Norway (0.541 [0.422–0.693]) show very similar point estimates to the original analyses for SGLT2i versus oGLD for all-cause death (Sweden: 0.612 [0.514–0.728]; Norway: 0.495 [0.414–0.592]), with no substantive impact on the clinical interpretation of our original findings.

Furthermore, we reexamined our methodology to evaluate the potential bias based on the prioritization of SGLT2i use in the patient selection. Because of the infrequent SGLT2i use and our intent to use the largest pool of SGLT2i users, the group initiated on SGLT2i was prioritized in the patient selection. Thus, if a patient had initiated both an oGLD and an SGLT2i during the study period, that patient would be preferentially selected as an SGLT2i user. This design implies that selection of patients in the oGLD group was conditional on not subsequently receiving an SGLT2i during the study. In a scenario where a patient dies soon after initiation of oGLD, that patient would have a lower likelihood of being eligible for later initiation of SGLT2i and theoretically would be more likely to be in the oGLD group; this could potentially introduce bias in the mortality analysis. As previously stated by Suissa et al. (3), such bias “will be trivial if the number of users of the newer drug [in this case SGLT2i] is small compared with the users of the comparator [in this case oGLD].” A short follow-up time would also tend to reduce such potential bias. These are exactly the conditions in the CVD-REAL study, and therefore the extent of such bias should be minimal.

To examine whether such bias exists, we pursued two additional sensitivity analyses in Sweden and Norway. First, we randomly selected the index date for both treatment groups. As expected, this resulted in a substantial decrease (32–35%) in patients initiating SGLT2i; however, the

HRs for the outcome of all-cause death (Sweden: HR 0.649 [95% CI 0.520–0.809]; Norway: 0.558 [0.441–0.707]) were very similar to the original analyses. Second, we used an alternative design, conceptually similar to that advocated by Suissa et al. (3), in which every patient might contribute to the analysis with more than one episode of new treatment initiation, with 1:1 propensity matching for episodes of glucose-lowering agent initiation (oGLD or SGLT2i) rather than for individual patients and with dependence within patients taken into account. This method allows for all oGLD exposure episodes to contribute to oGLD estimates and all SGLT2i exposure episodes to contribute to SGLT2i estimates. This provides unbiased (from the standpoint of “immortal time bias”) estimation of treatment effects, while maximizing patient numbers. Again, the HRs (SGLT2i vs. oGLD) were similar to the original analyses (Sweden: HR 0.602 [95% CI 0.507–0.715]; Norway: 0.616 [0.514–0.739]). Regarding the other critiques, we acknowledge that the mortality rates in the U.S. were lower than in Europe. There are several likely explanations—including younger age and lower comorbidity burden in the commercially insured U.S. population as compared with national complete population registers in Scandinavia. As acknowledged in the article (2), mortality data were also not available for a large proportion of patients in the U.S. Truven Health MarketScan database. This underreporting of death events was likely attributable to administrative reasons, representing “data missing completely at random”; there is no evident reason this could have biased the point estimates in favor of SGLT2i (in fact, it would likely bias our findings toward the null hypothesis).

With respect to the large proportion of patients without established cardiovascular disease (CVD) in our study, this does not necessarily imply that the magnitude of relative risk reduction associated with SGLT2i should be less pronounced. In recent analyses (4), we observed that although the absolute risks of heart failure and death—and the absolute risk reductions associated with SGLT2i versus oGLD—were markedly different in patients with and without established CVD, the relative risks were nearly identical. This notion of different absolute but similar relative risk reductions with SGLT2i for the outcomes of death and heart failure across the subgroups of prevalent CVD is further supported by recent

analyses from the CANagliflozin cardiovascular Assessment Study (CANVAS) (5).

In summary, we do not believe that immortal time bias affected the results of the CVD-REAL study in a substantive way. Although the design of the study allowed for a potential bias in survival analyses, the extent of this bias appears minimal in multiple sensitivity analyses, with no meaningful impact on the clinical interpretation. Given the expectation of greater use of SGLT2i over time and longer inclusion times in future CVD-REAL analyses, we plan to incorporate additional analytic approaches to further minimize the risk of any bias.

Acknowledgments and Funding. Editorial support was provided by Nicola Truss of inScience Communications, Springer Healthcare, and was funded by AstraZeneca. K.K. is supported by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care East Midlands.

Duality of Interest. M.T. is an employee of Statistician who was under contract to AstraZeneca for this study. M.A.C. has received personal fees from AstraZeneca, Merck, Sanofi, and Chiesi and research support (nonsalary) from Abbott Laboratories, AstraZeneca, GlaxoSmithKline, The Medicines Company, Merck, and Takeda. A.Z.F. has received grants from AstraZeneca and Merck and personal fees from Asclepius Analytics and Complete HEOR Solutions. J.P.W. has received lecture fees from Astellas, AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Novo Nordisk, Orexigen, and Sanofi; consultancy (institutional) from AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, and Orexigen; and grants to his institution from Takeda, Novo Nordisk, and AstraZeneca. K.K. has been a consultant and speaker for AstraZeneca, Novartis, Novo Nordisk, Sanofi, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim; received grants in support of the investigator and investigator-initiated trials from AstraZeneca, Novartis, Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, Merck Sharp & Dohme, and Roche; and has served on advisory boards for AstraZeneca, Novartis, Novo Nordisk, Sanofi, Lilly, Merck Sharp & Dohme, Janssen, and Boehringer Ingelheim. R.W.H. has received grants from AstraZeneca. A.N. has received personal fees from AstraZeneca for this study and honoraria for lectures and advisory board meetings from Novo Nordisk, Boehringer Ingelheim, and Lilly. K.I.B. has received grants to his institution from AstraZeneca for this study and fees for lectures and consulting from Novo Nordisk, Sanofi, Lilly, Boehringer Ingelheim, and Merck Sharp & Dohme. M.E.J. is a shareholder of Novo Nordisk, was employed by Steno Diabetes Center A/S (a research hospital in the Danish National Health Service owned by Novo Nordisk A/S) until 31 December 2016, and has received grants from AstraZeneca. E.W., N.H., and P.F. are employees of AstraZeneca. M.K. has received research grants from AstraZeneca and Boehringer Ingelheim; has served on advisory boards for AstraZeneca, Boehringer Ingelheim, Sanofi, Glytec, Novo Nordisk, Janssen, ZS Pharma,

Eisai, and Merck (Diabetes); and has been a consultant for AstraZeneca, Sanofi, GlaxoSmithKline, Amgen, Janssen, Intarcia, Novo Nordisk, and ZS Pharma. No other potential conflicts of interest relevant to this article were reported.

References

1. Suissa S. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? *Diabetes Care* 2018;41:6–10
2. Kosiborod M, Cavender MA, Fu AZ, et al.; CVD-REAL Investigators and Study Group. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (Comparative Effectiveness of Cardiovascular Outcomes in New Users of Sodium-Glucose Cotransporter-2 Inhibitors). *Circulation* 2017;136:249–259
3. Suissa S, Moodie EE, Dell’Aniello S. Prevalent new-user cohort designs for comparative drug effect studies by time-conditional propensity scores. *Pharmacoepidemiol Drug Saf* 2017;26:459–468
4. Cavender MA, Norhammar A, Birkeland KI, et al.; CVD-REAL Investigators and Study Group. Hospitalization for heart failure and death in new users of SGLT2 inhibitors in patients with and without cardiovascular disease: CVD-REAL Study. *Diabetes* 2017;66(Suppl. 1):A99–A100
5. Mahaffey KW, Neal B, Perkovic V, et al.; CANVAS Program Collaborative Group. Canagliflozin for primary and secondary prevention of cardiovascular events: results from the CANVAS program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018;137:323–334