COMMENT ON SUISSA

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

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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).

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

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.

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