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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We read with interest the Perspective by Suissa (1), in which concerns were raised about our recently published article (2). We thank the author for important points raised and appreciate the concern about the lower rate of all-cause death associated with sodium–glucose cotransporter 2 inhibitors (SGLT2i) compared with insulin treatment in a broad population with type 2 diabetes. Suissa (1) adequately describes two well-known epidemiological phenomena as likely explanations for the possible discrepancy between our results and those of randomized controlled studies, namely, time-lag and immortal time biases. As in any observational study, we cannot rule out that residual confounding factors have affected our results. However, in our study we were also aware of the risk of biases raised by Suissa and we believe they are accounted for according to the following.

First, Suissa's statement regarding second- and third-line treatment cannot easily be translated to Swedish clinical practice. Insulin (predominantly isophane, about 70%) was strongly recommended as second-line treatment for type 2 diabetes in Sweden between 1999 and 2017 and is still used frequently. In Sweden, patients with type 2 diabetes generally start insulin therapy much earlier than in other regions, making time-lag bias a less likely explanation for the results.

Second, our study was already designed as proposed in Fig. 2*B* of Suissa (1), i.e., including both treatment duration and prior medications in the propensity score. This is also described in our article (2). To further clarify the situation of time-lag bias, described in Fig. 2*A* and Fig. 3 of Suissa (1), we argue that this cannot occur in our study because these patients would not have been included in any of the two propensity-matched groups.

Third, the issue regarding incident versus prevalent users is not entirely correct as described by Suissa. Although both patients treated with dipeptidyl peptidase 4 inhibitors (DPP-4i) and those treated with insulin might have used the drugs previously, the definition of new users in our article includes a period of at least 1 year without the drugs of interest prior to the index date and ensures that the studied groups are treated similarly at baseline. Importantly, we also performed analyses where we included the first-ever dispense of SGLT2i, DPP-4i, and insulin, with similar results (2).

Last, different outcomes between SGLT2i and DPP-4i treatments could potentially be an issue. However, because we only compared patients treated with SGLT2i versus insulin and DPP-4i versus insulin, respectively, we believe that this will not influence the direct comparisons to insulin. Of note, we have recently published direct comparisons between SGLT-2i and DPP-4i elsewhere (3).

We argue that observational studies can provide important new knowledge about the effectiveness of different treatments in a real clinical setting. Furthermore, when the findings of a randomized controlled trial (4) and a comparative effectiveness study (3,5) are aligned, it provides further evidence on treatment effects, extending the randomized controlled trial findings to broader populations in a real clinical setting. Nonetheless, observational studies can never completely control for residual confounding factors, and every attempt to mitigate this issue should be made.

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References

1. Suissa S. Lower risk of death with SGLT2 inhibitors in observational studies: real or bias? Diabetes Care 2018;41:6–10
2. Nyström T, Bodegard J, Nathanson D, Thuresson M, Norhammar A, Eriksson JW. Novel oral glucose-lowering drugs are associated with lower risk of all-cause mortality, cardiovascular events and severe hypoglycaemia compared with insulin in patients with type 2 diabetes. Diabetes Obes Metab 2017;19:831–841
3. Persson F, Nyström T, Jørgensen ME, et al. Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: a multinational observational study. Diabetes Obes Metab 2018;20:344–351
4. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–2128
5. Birkeland KI, Jørgensen ME, Carstensen B, et al. Cardiovascular mortality and morbidity in patients with type 2 diabetes following initiation of sodium-glucose co-transporter-2 inhibitors versus other glucose-lowering drugs (CVD-REAL Nordic): a multinational observational analysis. Lancet Diabetes Endocrinol 2017;5:709–717