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Title: SGLT2i use in adults with chronic kidney disease: a cross-sectional study identifying care gaps to inform knowledge translation
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Reviewer 1: Dr. Claudio Rigatto
Institution: University of Manitoba
General comments (author response in bold)

Multiple large randomized clinical trials have established SGLT2i as powerful disease-modifying therapies for prevention of mortality, hospitalization, HF events, and kidney failure outcomes in patients with CKD, CVD, and HF, irrespective of diabetic status. Given the robust evidence of benefit in multiple clinical conditions, and the multiple indications for use beyond simple glycemic control, it is important to evaluate gaps and challenges in improving SGLT2i utilization, and the authors should be commended for doing so. The current manuscript examines the prevalence of clinical indications for SGLT2i use as of March 31, 2019.

The manuscript has many strengths. The topic is important, the data sources and methodology well validated and mostly well explained (vide infra), and the paper is beautifully written. There is very little to criticize in terms of execution here, and I very much enjoyed reading the manuscript.
Positive feedback always appreciated in this line of work!!!

The main weakness in my view relates to the modest impact of the findings.

1. The current prevalence and overlap of the different indications for SGLT2i use is indeed of moderate interest, and I agree with the authors that it will provide a useful "baseline" for future assessment of population level knowledge translation. However, little can be concluded about the reported low proportion of patients with an indication for SGLT2i who are on the drug, given that the study period mostly preceded the publication of landmark trials in CVD and CKD.
This is an understandable and well-taken point.
Our reasoning was that understanding the current predictors would still be important. Among other things, we highlight the need to ensure those with good glycemic control, women, older adults, and those living in lower income neighbourhoods are not missed as we adjust to the new kidney and heart-oriented paradigm of SGLT2i prescribing.
This information has been useful to the Alberta Kidney Strategic Clinical Network despite this limitation.

2. While the authors clearly acknowledge this, I cannot help thinking that the impact of this data would be significantly higher if the authors were able to include more recent data covering a longer period after the publication of the landmark studies. If it were at all feasible, adding another few years of follow-up data (at least through to Dec 2021) to examine rates of prescription over time and as a function of provincial insurance coverage, among other key factors. In my view this would take the manuscript from modest to much higher impact state.

We do not have data up to March 31, 2020 available for analysis at this time. The most recent I have seen published / presented in similar Canadian studies appears to be 2020. This would only be a years' difference from our data.
It is true that SGLT2i use rates have been higher in other work, which may have to do with timing and selection (e.g.: non-CKD populations), as well as the definition of current SGLT2i use (we use day's dispense + 30 days covering March 31, 2020; other analyses may use ">= 1 medication record in a single year"). Additionally, in other work we are doing, we have discovered inter provincial variability, with higher SGLT2i-use in ON for a similar patient population, perhaps due to ON full benefit listing status of SGLT2i compared to AB's special authorization requirement. These are all reasons for why, for example, the recent abstract by Ozaki et al. (https://www.ahajournals.org/doi/abs/10.1161/circ.144.suppl_1.10401) using ON data up to 2020, examining SGLT2i use in adults with DM and CVD, are much higher than what we see in our study; additionally, we did not look at the CVD population specifically.
The associations we have identified in adults with DM and SGLT2i-eligible CKD (which were similar in all adults with DM on sensitivity analysis) are likely to apply regardless of what the current SGLT2i uptake is. Some of them have been documented in similar previous studies, and all are very similar to what was reported on ON adults with CVD in the Ozaki abstract. The HbA1c relationship (lower HbA1c associated with less SGLT2i use) is a very novel finding of significant importance, as it speaks to the uneasy transition we find ourselves in, between glucocentric and end-organ modes of diabetes care. All this is to say, we believe the results stand well enough to be reported even if the index date of this cross-section is March 31, 2021.

3. Finally, one small technical critique: the authors should clarify the end date of their cross-sectional study. Mar 31, 2019, precedes the publication of the landmark CKD (Credence, DAPA-CKD) and HF (DAPA-HF, Emperor trials: reduced and preserved), yet they state in the manuscript that the study period included 8 months of time after CREDENCE was published (April 2019).
Our mistake. This has been corrected:

The CREDENCE trial had not yet been published. This study was therefore not meant to be evaluative, but, rather, to identify and explore this gap between current prescribing and the emerging evidence of cardiorenal benefit in CKD.

Reviewer 2: Dr. A. Ishani
Institution: Minneapolis VAMC
General comments (author response in bold)

This is a very topical manuscript.
The authors attempt to achieve too much with this manuscript. As a result, it is very confusing to read. There are too many objectives. The authors attempt to define the population who would benefit, those who are on the drug and then predictors of being on the drug. Then also do this for those with diabetes. I would simplify this and remove the predictors of being on the drugs and make hat a separate manuscript.
The first objective regarding other indications for SGLT2i has been removed. The objectives are now:

As a first step in these efforts, we examined a cross-section of adults with diabetes, to answer the following questions: (1) What is the prevalence of SGLT2i-eligible adults with CKD? (2) Among adults with CKD, are sociodemographic factors, health status, diabetes status, and health care utilization associated with SGLT2i use? We examined predictors of SGLT2i use to identify potential directions and opportunities to accelerate SGLT2i use in adults with CKD. (3) What is the prevalence SGLT2i-eligible adults with CKD in the general Alberta population, both with and without diabetes? The prevalence of the CKD indication in all Albertan adults, regardless of diabetes status, will foreshadow the magnitude of the knowledge translation challenge to come.

Specific recommendations include:

1. page 3 lines 32: Don't review all the indications and then what you are interested in - just give us what you are interested in. Would just focus on 3a and 3b
Done.

2. Reduce the number of indications (ie number 4 - also why pick the cut off of 7% a1c?)
Done. Only two enumerated indications now – (A) and (B), referring to the two definitions of SGLT2i eligible adults with CKD.

3. Inclusion - those with just one serum creatinine - but later need multiple to define CKD - makes it very confusing.
To clarify, those with only a single creatinine measurement regardless of its value were not considered to have CKD, even though they were included in the cohort. This is because a single measurement with eGFR < 60 could reflect an acute kidney injury, as opposed to CKD.
This is distinct from the inclusion criteria, which were cast broadly to capture adults with diabetes comprehensively. The >=1 creatinine value is also a condition of the ethics application for data access / sharing, since the research organization's mandate relates to kidney disease (AKDN), and is standard for most research projects using these data. The confusion is understandable, though.

4. Table 2 - maybe better if DM+CKD on SGLT2 vs not on SGLT. In its current state - leads to more confusion as this paper is focused on the CKD subgroup - so no need to compare to those without ckd
Revised as suggested.

5. Table 3 - I like the layout. Again, would focus on the CKD population. Others are interesting but very distracting from the main message
Revised as suggested

6. Figure 1 is also very confusing. I would just focus on those with DM and CKD. There are also 2 sets of N in this figure. the capital N seems obvious, the little n= unclear what that number refers to in the context of the Capital N.
Revised as suggested. There is no longer a need for capital N vs little n.

7. The authors discuss individuals who potentially shouldn't be on the drug in the discussion - these patients should be excluded from their denominator also (ie urinary

tract infections, recurrent AKI, etc) - otherwise they are overstating the eligible population
Tracking of UTI / genital mycotic infections may be limited in administrative data and are not necessarily contraindications to future SGLT2i use – mentioned in discussion as an exploration of perceived risks that might be affecting low SGLT2i use in older adults.
As for DKA – codes specifying type 1 diabetes including 250.11 (DKA with fifth digit "1" specifying type 1 diabetes) and ICD-10 code E10 (T1DM) were used as exclusion criteria to winnow down the population of adults for whom SGLT2i may be (controversially) contraindicated. DKA events in the remaining adults are rare – affecting, at most, +/- 0.2% of eligibility in adults who are already on SGLT2i or who have been on SGLT2i previously (and would have a much lower prevalence in adults who are not yet on SGLT2i) – we have not excluded them from the analysis.

Reviewer 3: Dr. Muhammad Siddiqui
Institution: Saskatchewan Health Authority
General comments (author response in bold)

Abstract

Methods: Please revise 2019 to over the period of 2002-2019
To clarify, the cross-section was composed of those alive on March 31, 2019, and their CKD and SGLT2i use status was determined as of March 31, 2019. Data as far back as 2002 was used to identify these patients and their variables. If it is more desireable that the abstract reflect data availability as opposed to the time of the "snapshot" – done!
"Cross-sectional study using Alberta linked administrative data in adults with diabetes from 2002-2019"

Results: Please add OR with CI for significant demographics, co-morbidities, and health care utilization on SGLT2i
A range of adjusted odds ratios is now provided with some indication of statistical significance.

Main Text
1. The introduction provides a good, generalized background of the topic. The authors have included explanation of the topic, context, and explained what are being challenged or extended to make the introduction substantial. The authors have introduced the related work clearly.
Thank you!

2. Methods section written very well.

3. The data analysis is quite standard and looks appropriate for the study.

4. In table 2 please revise freq/SD -> Percentage/SD
Done as suggested.