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Title: The impact of the Choosing Wisely Canada campaign on the simultaneous use of angiotensin converting enzyme inhibitors (ACE-I) and angiotensin renin blockers (ARB): interrupted time series analysis
Authors: Tracey-Lea Laba PhD, Heather C. Worthington MSc, Lucy Cheng MSc, Fiona K.I. Chan MSc, Nick Bansback PhD, Michael R. Law PhD

Reviewer 1
General comments (author response in bold)

Methods: The manuscript is lacking a precise description of the CW intervention.
Thank you for this comment. We have amended the Methods Section to include a Study Design section which states:
We used a quasi-experimental interrupted time series (ITS) analysis11 to determine the impact of the CW recommendation of "Don't prescribe angiotensin converting enzyme (ACE) inhibitors in combination with angiotensin II receptor blockers (ARBs) for the treatment of hypertension, diabetic nephropathy and heart failure" which was publicly released in Canada on October 29, 2014. (p. 4)

Statistics: Please provide more details on how you weighted the data by population size to account for deaths in the cohort and on the time elapsed. Consider presenting the code in an appendix.
We used the weighted least squares through the "gls()" function in R. In specifying weights=(1/population) to assume that the variance of the error term is proportional to the population of the cohort, which is a common assumption in this setting. This weighting is to take account for the dynamic change of cohort size and time proximity change over time.
We have provided the code in the Supplementary appendix. (p. 5)

Discussion: As discussed in the limitations section, a control group would have helped. Consider using data from other countries where CW has not been implemented (data can be standardized for different absolute levels of the combination prescription).
Many thanks for this suggestion. We agree that a control group would have been useful, but the approach suggested would require individual level population level data from another country which is not permissible under the current ethics approval.

Reviewer 2
General comments (author response in bold)

1. The increase in dual RAS inhibitor therapy initiation is surprising. I wonder if the authors could elaborate on how combination therapy was defined (in terms of duration of prescription overlap) to exclude patients who were merely switching from one class to another (for example, due to ACE-inhibitor associated cough).
Many thanks for this very useful comment. We have defined combination treatment when an individual was exposed to both an ACEI- and ARB at the same time as indicated by dispensing data. We have used a definition of a gap in treatment of 90 days to indicate treatment cessation. With this method, because we are recording dispensing claims, there is some chance that people who are switching between monotherapy due to adverse effects may have been incorrectly

identified as on combination treatment until medicine supply had ceased. This is a limitation of our study and we have added that to our limitations section:
It is also possible that the number of people on combination treatment may have been overestimated given our 90-day definition of cessation could not exclude people who may have reasonably switched from one class to another for example due to adverse effects.
We have expanded our description of how combination therapy was defined in the methods, Outcomes section:
"We defined combination treatment as when an individual is exposed to both an ACEI and an ARB at the same time, as indicated by dispensing data. To determine combination treatment, we identified all prescriptions containing an ACEI or ARB using the Anatomical Therapeutic Classification codes C09A-D. For each individual, we created a matrix which indicated if an ACEI or ARB-containing medication was dispensed. We used a gap in treatment of more than 90-days to indicate treatment cessation. A variable was created to indicate in each month when both an ACEI and an ARB-containing medication (i.e. combination therapy) was initiated and/or stopped." (pp. 4, 5, 8)

2. Similar to #1, I note that 19% of patients in the combination group had heart failure. In systolic heart failure patients, sacubutril-valsartan (ATC C09DX04) has been shown to be more efficacious than enalapril, and a substantial number of patients may have been switched from ACE inhibitors to ARB/ARNI combination therapy. There would be overlap in PDC depending on when the patient fills the prescription relative to when a therapeutic switch is made. How were these cases identified and excluded? Would it be possible to provide sensitivity analysis excluding sacubutril-valsartan?
Many thanks for this useful comment. Upon inspection of our dataset, sacubutril-valsartan (ATC C09DX04) does not appear in the Pharmanet claims for the overall cohort.

3. I wonder if the authors could provide a flow diagram to indicate how dual therapy cohort of 51,327 were identified from 1,104,593 individuals with qualifying diagnoses, and exclusion of patients based on each criterion (MSP enrolment, switch from one drug class to another).
We have provided a flow diagram in the Supplementary appendix, Figure S1. (Supplementary appendix)