Re-examining the Role of Sulfonylureas in the Management of Type 2 Diabetes
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Background
Sulfonylureas have been used for over 50 years despite ongoing controversy of possible cardiovascular safety. In recent years, sulfonylurea use has waned since the introduction of new antihyperglycemic drug classes.

However, publication of the CAROLINA trial could reignite interest in using sulfonylureas because this trial showed the risk of cardiovascular events was no worse for glimepiride (a sulfonylurea) compared to linagliptin (a DPP4i).

Application of the CAROLINA results to Canadian clinical practice is questionable because these particular agents are not commonly used. Linagliptin was the third DPP4i agent approved for use in Canada and we have found that glimepiride is used in <1% of Albertans with diabetes.

Objectives
- Evaluate trends in antihyperglycemic drug choice secondary to metformin when treatment intensification is required for the management of type 2 diabetes.
- Specifically focusing on how sulfonylureas are used.
- Describe possible predictors of drug therapy choice.

Hypothesis
Sulfonylureas are the most common class of antihyperglycemic drugs started at initial treatment intensification.

Methods
A retrospective, cohort study was conducted using pharmacy dispensation, claims, and hospitalization records between April 2003 and March 2018 provided by Alberta Health.

The population of interest included adult new metformin users with type 2 diabetes who were not pregnant, had at least 1 treatment intensification instance during the observation window, and had at least 1 year of follow up after treatment intensification.

At treatment intensification, people were categorized as starting either sulfonylurea-based or non-sulfonylurea-based therapy. Those prestated sulfonylurea-based therapy were further classified as a persistent or non-persistent user if 1 year based on gaps in dispensations.

Logistic regression will be used to determine predictors of drug therapy choice and persistence with sulfonylureas.

This study was approved by the University of Alberta Health Research Ethics Board (Pro0000317).

Results

Preliminary Observations
- Of 165,056 new metformin users followed for a mean of 6.0 (SD 2.2) years, 55,909 (34%) had at least one treatment intensification (see figure 2).
  - The mean time to first treatment intensification was 1.3 (SD 1.7) years; mean age of those individuals was 55 years and 62% were male (see table 1).
  - The most common antihyperglycemic class started at the first treatment intensification was sulfonylureas (47%), followed by DPP4i (21%), insulin (9%), SGLT2i (5%), and GLP-1ra (4%) (see figure 3).
- Of those starting a sulfonylurea at the first treatment intensification, 61% were persistent at 1 year follow up (see figure 2 and table 2).
- Univariate analyses found several statistically significant predictors of drug therapy choice and predictors of persistence (see tables 1 and 2).
- Analysis is ongoing.

Discussion and Future Direction
- Preliminary results show that sulfonylureas are the most commonly prescribed antihyperglycemic drug at initial treatment intensification and the majority of people starting a sulfonylurea continue using it for at least 1 year.
  - Although many variables are statistically significant predictors of drug therapy choice and persistence in univariate analyses, the magnitude of difference between groups does not appear to be clinically important. The exception is age, whereby sulfonylurea users were 2 years older than non-users.
  - Next steps include multivariate logistic regression analysis, extending the observation window to second treatment intensification instance for those not already prescribed a sulfonylurea, subgroup analyses, and sensitivity analyses.
  - These observations confirm that sulfonylureas remain an important treatment option in type 2 diabetes and that further research into the cardiovascular safety of these drugs is warranted.

This research is not without limitations. It is possible that the administrative data may have coding errors, however, internal auditing reduces this risk. We were unable to determine whether an individual consulted the medication on their prescription record. Lastly, our observation study design limits our ability to make causal inferences.

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References
- References are available upon request.