IMPACT OF SODIUM-GLUCOSE CO-TRANSPORTER 2 INHIBITORS ON CARDIOVASCULAR OUTCOMES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A SYSTEMATIC REVIEW (CP-013)

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Background
- Type 2 Diabetes mellitus (T2DM) and its complications cause a substantial burden of disease on societies worldwide and its prevalence is increasing significantly in every country, which is mainly due to lifestyle changes
- It is estimated that around 65% of people with T2DM will die as a result of cardiovascular (CV) complications
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a novel class of anti-diabetics proven to reduce blood pressure, blood glucose and body weight
- Lately, the food and drug administration (FDA) has mandated all new anti-diabetic medications to provide evidence that they do not increase risk of CV outcomes (e.g. myocardial infarction (MI), stroke, cardiac death etc.)
- However, the long-term CV safety implication of these agents remain unclear

Study Objective
- To provide a comprehensive summary and critical analysis of available literature pertaining to CV safety (MI, stroke, angina and CV related death) of SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin) in patients with T2DM

Methods
- Design
  - Systematic review
- Databases searched
  - EMBASE and MEDLINE
- Search terms
- Study inclusion criteria
  - Randomized controlled trials (RCTs) assessing CV safety of SGLT2 inhibitors compared with placebo or anti-diabetic medications
- Risk of Bias Assessment tool (Cochrane Collaboration)
- Any study that had ≥ 1 high risk of bias or ≥ 2 unclear risks of bias was deemed to be of unclear quality

Results
- The results of literature search are shown in Figure 1.
- Total of 16 RCTs were included after full-text review
- All studies reported at least one of the pre-defined outcomes (CV death, MI, or stroke)
- A summary of study characteristics and results are given in Table 1.
- Nineteen CV deaths were reported in SGLT2 inhibitors groups versus 10 CV deaths in placebo or other comparator arms; numerically higher in the dapagliflozin arms
- The number of CV events was numerically higher in SGLT2 inhibitors groups than in other arms (4 cases of non-fatal MI, 1 case of stroke and 3 other CV events)
- Risk of bias assessment showed mixed results, with overall quality assessments deemed unclear for 4 of the 16 eligible studies (25.0%)

Findings in this study are only hypothesis generating given that none of these outcomes were part of the primary or secondary endpoints of almost all the included studies (15/16) and statistical evaluations were lacking
- Only 1 study (Zimmam et al. 2015) assessed CV safety of empagliflozin as a primary endpoint when compared to placebo and showed lower CV-related deaths in the empagliflozin group with no significant between-group differences in the rates of other CV events such as stroke or MI
- We could not pool results and meta-analyze them as they would be weighted almost entirely for Zimmam et al.
- Most studies were found to be well designed and at low risk of bias
- Majority of studies did not have power to detect differences between groups in terms of CV outcomes
- Relatively short follow-up period may have not allowed for detection of CV outcomes

Conclusions and Impact on clinical practice
- CV outcomes do occur in patients taking SGLT2 inhibitors yet the clinical significance remains unclear
- Pharmacists should proactively monitor and report CV outcomes occurring in patients on SGLT2 inhibitors
- Future research is warranted to determine if safety profiles are drug and/or dose related or could be considered a class effect as a whole before they become widely adopted in clinical practice

Table 1. Study characteristics and results

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Design</th>
<th>Comparator</th>
<th>Sample size</th>
<th>Intervention (mg/day)</th>
<th>CV Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lewin et al. (2015)</td>
<td>R, DB, AC</td>
<td>CANA 100 mg OD; or PC as add-on</td>
<td>(N=478)</td>
<td>CANA 100 mg OD; or PC CV death: CANA arm; (N=1) Other* Overall Good</td>
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<tr>
<td>DeFronzo et al. (2014)</td>
<td>R, DB, PC</td>
<td>EMPA 10 or 25 mg OD; or PC as add-on</td>
<td>(N=358)</td>
<td>EMPA 10 or 25 mg combined with linagliptin 5 mg; linagliptin 5 mg alone; EMPA-25 mg alone CV death: EMPA arm; (N=1) Other* Overall Good</td>
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<tr>
<td>Bode et al. (2015)</td>
<td>R, DB, MC</td>
<td>DAPA 2.5, 5, or 20 mg OD; or PC as add-on</td>
<td>(N=519)</td>
<td>DAPA 2.5, 5, or 20 mg OD; or PC CV death: DAPA arm; (N=1) Other* Overall Good</td>
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<tr>
<td>Del Prato et al. (2014)</td>
<td>R, DB, AC</td>
<td>CANA 300 mg or sitagliptin 100 mg OD</td>
<td>(N=714)</td>
<td>CANA100 or 300 mg; or PC OD CV death: CANA arm; (N=1)* Other* Overall Good</td>
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Discussion and Limitations
- No funding was provided to assist in performing the review and all authors have no potential conflicts of interest to declare