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, dapagliglozin and empagliflozin) in patients with T2DM

Methods

- Design
  - Systematic review
- Databases searched
  - EMBASE and MEDLINE
- Search terms
  - Included: “SGLT2 inhibitors”, “Canagliflozin”, “Dapagliflozin”, “Empagliflozin”, “cardiovascular”, “safety”, “myocardial infarction”, “stroke”, “cardiovascular death”
- 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%)

Discussion and Limitations

- 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 (Zimman 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 Zimman 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

Figure 1. Flow diagram for study selection and inclusion

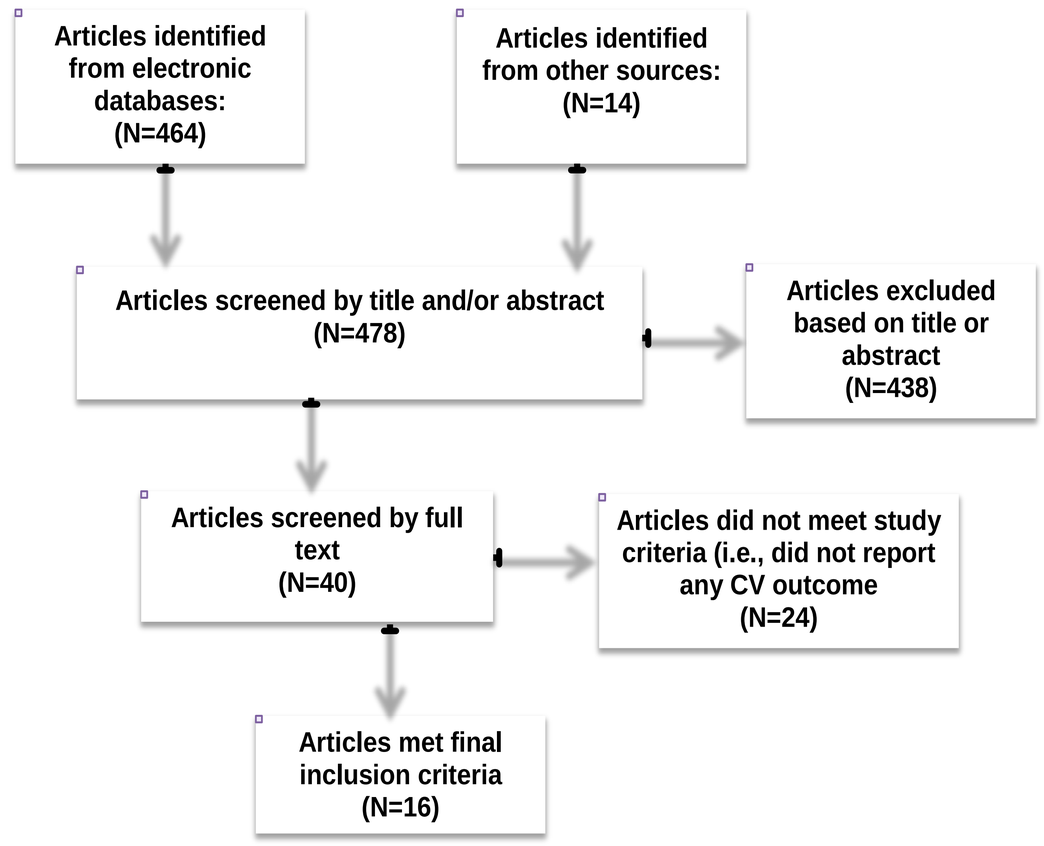

Table 1. Study characteristics and results

Study Reference	Design/ Duration	Sample Size	Intervention (mg per day)	CV Outcomes
Lewin et al. (2015)	R, DB, MC, AC/52 wk.	N=677	EMPA 10 or 25 mg combined with linagliptin 5 mg; linagliptin 5 mg alone; EMPA 10 mg alone; or EMPA 25 mg alone	CV death: EMPA arm; (N=1)
DeFronzo et al. (2015)	R, DB, MC, AC/52 wk.	N=686	EMPA 10 or 25 mg combined with linagliptin 5 mg; linagliptin 5 mg alone; EMPA 10 mg alone; or EMPA 25 mg alone as add-on to MTF	CV death: EMPA arm; (N=1)
Ferrannini et al. (2013)	R, PC/12 wk.	N=408	EMPA 5, 10 or 25 mg OD; or PC; or open-label MTF	CV events: EMPA arm; (N=2 MI); MTF arm; (N=1 angina)*
Kovacs et al. (2014)	R, PC/24 wk.	N=498	EMPA 10 or 25 mg OD; or PC as add-on to pioglitazone ± MTF	CV death: EMPA arm; (N=1); PC arm; (N=1)*
Haring et al. (2013)	R, DB, PC/24 wk.	N=669	EMPA 10 or 25 mg OD; or PC as add-on treatment to MTF + sulfonylurea	CV death: EMPA arm; (N=1)*
Strojek et al. (2011)	R, DB, PC, MC/24 wk.	N=597	DAPA 2.5, 5, or 20 mg OD; or PC as add-on to open-label Glimepiride 4 mg/day	CV events: DAPA arm; (N=1 stroke) CV death: DAPA arm; (N=1)
Strojek et al. (2014)	R, PC/48 wk.	N=519		CV death: DAPA arm; (N=1)
Nauck et al. (2014)	R, DB, AC/104 wk.	N=814	DAPA 10 mg or GLP 20 mg OD	CV death: GLP arm; (N=1)
Wilding et al. (2012)	R, PC, MC/48 wk.	N=808	DAPA 2.5, 5, or 10 mg OD; or PC	CV death: DAPA arm; (N=3)
Bailey et al. (2010)	R, DB, PC, MC/102 wk.	N=546	DAPA 2.5, 5, or 10 mg OD; or PC	CV events: DAPA arm; (N=2 MI, N=3 others)*
Leiter et al. (2014)	R, DB, PC/24 wk.	N=964	DAPA 10 mg OD; or PC	CV death: DAPA arm; (N=2); placebo arm; (N=1)
Kohan et al. (2014)	R, DB, PC, MC/104 wk.	N=252	DAPA 5 or 10 mg OD; or PC	CV death: DAPA arm; (N=2); placebo arm; (N=3)
Del Prato et al. (2015)	R, DB/208 wk.	N=814	DAPA 2.5, 5 or 10 mg Od; or GLP 5, 10 or 20 mg OD, combined with open-label MTF	CV death: DAPA/MTF arm; (N=2); GLP/MTF arm; (N=5)
Bode et al. (2015)	R, DB, PC/104 wk.	N=714	CANA100 or 300 mg; or PC OD	CV death: CANA arm; (N=1)*
Schernthaner et al. (2013)	R, DB, AC/52 wk.	N=755	CANA 300 mg or sitagliptin 100 mg OD	CV death: CANA arm; (N=2)*

R: randomized, DB: double-blinded, PC: placebo-controlled, AC: active-controlled, MC: multicenter, wk.: weeks., OD: once daily, EMPA: empagliflozin, DAPA: dapagliflozin, CANA: canagliflozin, CV: cardiovascular, GLP: glipizide, MTF: metformin

*Not related to study drug as reported by authors

Table 2. Risk of bias assessment

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other*	Overall Quality
Schernthaner et al. (2013)	Low risk	Low risk	Low risk	Low risk	Low risk	Unclear	Good
Bode et al. (2015)	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear
Bailey et al (2010)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
Strojek et al. (2011)	Low risk	Unclear	Low risk	Unclear	Low risk	Unclear	Good
Leiter et al. (2014)	Low risk	Low risk	Unclear	Low risk	Low risk	Unclear	Good
Kohan et al. (2014)	Unclear	Unclear	Low risk	Low risk	Unclear	Low risk	Unclear
Strojek et al. (2014)	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Good
Wilding et al. (2012)	Low risk	Unclear	Low risk	Low risk	Low risk	Unclear	Good
Del Prato et al. (2015)	Low risk	Low risk	Low risk	Unclear	Low risk	High risk	Unclear
Nauck et al. (2014)	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk	Good
Ferrannini et al. (2013)	Low risk	Unclear	High risk	Low risk	Low risk	Low risk	Unclear
Kovacs et al. (2014)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
Lewin et al. (2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
DeFronzo et al. (2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good
Zimman et al. (2015)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Good

*Other sources of bias: Based on study design or confounding factors (e.g. variation in baseline characteristics)

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