Meta-analysis protocol

Aim

To evaluate the efficacy of SGLT-2 inhibitors, GLP-1 agonists and DPP-4 inhibitors for type 2 diabetes across a broad range of cardiovascular outcomes using a network meta-analysis approach.

Population

Type 2 diabetes mellitus
NOT type 1 diabetes mellitus or pre-diabetes
No limit set on background medication therapy
No limit set on background cardiovascular risk or disease.

Intervention

SGLT-2 inhibitors
GLP-1 agonists
DPP-4 inhibitors
Only data for participants taking phase 3 trial doses will be used.

Comparison

Control: Placebo or no active treatment
Interclass comparisons: SGLT-2 inhibitor, GLP-1 agonist and DPP-4 inhibitor, where the comparator is of a different class from the intervention. For example, SGLT-2 inhibitor vs. GLP-1 agonist. Intraclass comparisons will not be used, for example, empagliflozin vs. canagliflozin, liraglutide vs. exenatide, sitagliptin vs. linagliptin. Comparison treatment was never active treatment of a class not included in the intervention (e.g. biguanide, sulphonylurea, insulin, thiazolidinedione), though these drugs could be used as background therapy.

Outcome

Primary
- all-cause mortality

Secondary
- cardiovascular mortality
- non-fatal and all myocardial infarction
- non-fatal and all stroke
- heart failure events
- unstable angina

Safety outcome
- any hypoglycaemia
- major hypoglycaemia
- any adverse event
- serious adverse event

- adverse event leading to study withdrawal

Additional outcomes investigated in cardiovascular outcome trials (definition below)

- pooled CV mortality, non-fatal MI and non-fatal stroke. This outcome is the primary outcome used for CV outcome trials.

Search strategy

Databases searched:

- MEDLINE (via ncbi.nlm.nih.gov), Embase (via ovidsp.ovid.com) and CENTRAL (via www.cochranelibrary.com)
- From database inception through October 11, 2017

The initial search will be carried out by SLZ. All references will be collated on Endnote X7.

After removal of duplicates using the function on Endnote X7, the remaining articles will be subject to a screening and review steps:

1. Screening: Title and abstract will be screened with removal of obviously non-relevant studies. This step will be done by two authors (SLZ and AJR) without overlap i.e. the list of studies will be split evenly between SLZ and AJR and screened individually. Non-relevant studies will be decided at the reviewers' discretion and should be studies that are obviously not relevant to the study question. Specific reason for exclusion will not be recorded, and the reason will be given as "Non-relevant". Reviewers will be overly inclusive at this stage to reduce chance of omitting relevant articles.
2. Review: Remaining articles will be reviewed by SLZ and AJR in parallel and independently. The purpose at this stage is to more closely assess studies based on inclusion and exclusion criteria. Where necessary, full text will be reviewed. Reasons for exclusion will be recorded.

Additional systematic reviews and meta-analyses will be identified on MEDLINE by searching the drug class names and using pre-set systematic review and meta-analysis filters. These will then be hand screened for additional trials.

The search terms for each database are provided in the eMethods 1 (Detailed Statistical Methods).

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Study inclusion criteria

1. Randomised clinical trial
2. Tests SGLT-2 inhibitors, GLP-1 agonists and DPP-4 inhibitors at phase-3 trial doses.

   SGLT-2 inhibitors
   - Empagliflozin total daily dose 10 to 25mg
   - Canagliflozin total daily dose 100 to 300mg
     Dapagliflozin total daily dose 5 to 10mg
   - Ipragliflozin total daily dose 50 to 100mg
   - Luseogliflozin total daily dose 2.5 to 5mg
   - Ertugliflozin total daily dose 5 to 10mg

   - GLP-1 analogues
     - Dulaglutide 0.75-1.5mg once weekly
     - Semaglutide 0.5-1mg once weekly
     - Liraglutide 1.2-1.8mg daily
     - Lixisenatide 10-20mcg daily
     - Taspoglutide 10-20mg once weekly
     - Exenatide 5-10mcg BD
     - Albiglutide 30-50mg once weekly
   - DPP-4 inhibitors
     - Alogliptin total daily dose 12.5 to 25mg
     - Saxagliptin total daily dose 2.5 to 5mg
     - Sitagliptin total daily dose 25 to 100mg
     - Linagliptin total daily dose 5mg
     - Vildagliptin total daily dose 50 to 100mg
3. Compared with placebo, no treatment, or interclass comparisons using a drug of a different class (SGLT-2 inhibitor, DPP-4 inhibitor, GLP-1 agonist)
4. Follow-up of 12 weeks or longer
5. English language

Note:
Can use data from secondary analyses of a trial if present data relevant to outcomes and the original trial meets entry inclusion criteria.
For trials with open label extension periods after the fixed randomised period, only data from the randomised period was used.

The following drugs will be excluded as there are no phase 3 doses:
SGLT-2 inhibitors
- Remogliflozin
- Tofogliflozin

DPP-4 inhibitors
- Omarigliptin

- Teneleglíptin
- Gemigliptin
- Evogliptin

Data extraction

2 study authors (SLZ and AJR) will extract data in parallel and independently onto a dedicated spreadsheet. The spreadsheet will be prepared on Microsoft Excel and contain columns for all required extracted data. The spreadsheet will then be compared between two reviewers to ensure validity and accuracy of data extraction.

The following information will be extracted:

- Basic trial information:
    - First author, study acronym, year, journal of publication, trial NCT number
    - Cardiovascular outcome trial – yes or no
        - Definition of cardiovascular outcome trial (adapted from Food and Drug Administration): “Large, phase 3 safety trial with cardiovascular outcomes as the primary endpoints, enrolling participants with increased cardiovascular risk.”
    - Study inclusion and exclusion criteria, specifically regarding whether participants were recruited or excluded based on cardiovascular risk factors or cardiovascular disease.
- For all primary, secondary and safety outcomes:
    - Event count in treatment and control (raw numbers)
    - Relative risk or hazard ratio where reported
    - Upper and lower 95% confidence intervals where reported
    - P value where reported

NCT database search for additional events

Where not reported on paper (and NCT number available), outcomes (MI, stroke, heart failure, unstable angina) will be extracted from the Clinical Trials database using the following definitions:

Myocardial infarction:

- acute myocardial infarction
- myocardial infarction
- acute coronary syndrome
- coronary artery occlusion

Stroke:

- Ischaemic stroke
- Cerebrovascular accident
- Transient ischaemic attack
- Lacunar infarction
- Brainstem infarction
- Brainstem stroke
- Cerebral infarction

Heart failure:

- Cardiac failure congestive
- Cardiac failure
- Cardiac failure acute
- Left ventricular failure
- Acute left ventricular failure
- Cardiogenic shock
- Congestive cardiomyopathy

Unstable angina:

- Unstable angina

Statistical analysis

Statistical techniques

Frequentist random-effects network and pair-wise meta-analysis using meta and netmeta package on R. Event counts and total number will be used to generate risk ratios which will be pooled. Meta-analysis will be presented as RR with 95% CI. Studies that have no events in either arm will be excluded from pooled analysis as they do not contribute to the overall effect. Studies with events in one arm but none in the other will have a continuity correction of 0.5 applied to the zero arm. Results will be presented graphically in forest plots comparing SGLT-2 inhibitors, GLP-1 agonists, DPP-4 inhibitors and control.

The P-score will be generated and used to provide a measure for a given outcome, the probability that a particular drug class ranks superior to the other drug classes/control. P-scores will be presented for all primary, secondary and safety outcomes.

Sensitivity analysis

Analysis will be repeated for all primary and secondary outcomes excluding the following study types:

- Studies at high risk of bias
- Studies with follow up duration shorter than 52 weeks
- Studies enrolling participants with low cardiovascular risk
- Studies enrolling participants with recent acute coronary syndrome

Additional analyses

Results (primary, secondary and safety outcomes) for fixed-effects model will also be provided.

Network meta-analysis of individual drug types for the primary outcome will be undertaken.

P-value cut-off of 0.05, two-sided

Inconsistency

Inconsistency will be assessed by breaking down each comparison between two treatments into direct evidence (derived from pairwise comparison data) and indirect evidence (calculated by network meta-analysis). The ratio of these (ratio of ratios) will be used to give an estimate of inconsistency within the network. A RoR where the 95% CI does not cross one will be used to provide evidence of statistically significant inconsistency within that design.

Risk of bias assessment

Cochrane risk of bias assessment undertaken by two investigators (SLZ and AJR) independently (Chapter 8, Cochrane Handbook). Any discrepancy will be resolved through discussion, and if necessary a third reviewer. Risk of bias for individual trials will be presented in table format with an overall summary presented as Risk of bias graph.

For summarising risk of bias for a study across outcomes, Cochrane provides a framework that leaves the overall assessment at the discretion of the reviewers based on their own judgement on the relative importance of different domains (Table 8.7a, Cochrane Handbook).

As such, studies will be deemed to have overall high risk of bias if:

- High risk of bias in 1 or more of the following domains:
    - Allocation concealment
    - Blinding
- Unclear in 3 or more domains