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Comparative efficacy and safety of cardio-renoprotective pharmacological interventions in chronic kidney disease: an umbrella review of network meta-analyses and a multicriteria decision analysis

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Abstract

This umbrella review aims to evaluate the available network meta-analyses in order to provide pooled estimates comparing the effects of sodium-glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1a) and non-steroidal mineralocorticoid receptor antagonists (ns-MRA) in chronic kidney disease. A multicriteria decision analysis will be implemented to generate rankings of the above interventions evaluating multiple potentially conflicting endpoints at the same time.

- 1 Objective: This umbrella review aims to evaluate the available network meta-analyses in order to provide pooled estimates comparing the effects of sodium-glucose co-transporter 2 inhibitors (SGLT2i), glucagon-like peptide-1 receptor agonists (GLP1a) and non-steroidal mineralocorticoid receptor antagonists (ns-MRA) in chronic kidney disease. A multicriteria decision analysis will be implemented to generate rankings of the above interventions evaluating multiple potentially conflicting endpoints at the same time.
- 2 Study design: The network meta-analysis will be reported following the PRISMA-NMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for systematic reviews incorporating network meta-analysis) guidelines.
- 3 Inclusion criteria: The study population consists of patients with chronic kidney disease as defined by the KDIGO (Kidney Disease: Improving Global Outcomes) guidelines. The diagnosis of chronic kidney disease will be based on the presence of an estimated glomerular filtration rate (eGFR) below 60 ml/min/1.73 m² and/or a urinary albumin-to-creatinine ratio (UACR) greater than 30 mg/g. The evaluated interventions will include SGLT2i, GLP1a and nsMRA, while placebo will serve as the comparator. The efficacy outcomes of interest will consist of major cardiovascular events and kidney disease progression, as defined by the cardiovascular and kidney-specific composite endpoints of each randomized controlled trial (RCT). The safety endpoints will include the risk of acute kidney injury, any serious adverse event and any adverse event leading to permanent drug discontinuation. Pairwise meta-analyses or meta-analyses of observational studies will not be evaluated.
- 4 Literature search: The following databases will be systematically searched from inception: Medline, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL). An additional search through Google Scholar will be performed to identify possible missing network meta-analyses. No date or language restrictions will be applied.
- 5 Data collection: The following parameters will be extracted from the included network meta-analyses: year of publication, country, type of population (presence of diabetes mellitus), network nodes, statistical model (frequentist or Bayesian), evaluation of transitivity, assessment of heterogeneity, treatment ranking, certainty of evidence evaluation, funding and presence of a pre-registered protocol. The information regarding the methodology of the original RCTs include the following: trial name or registration number, year of publication, type of population (presence of chronic kidney disease), examined intervention, sample size, mean age, percentage of females, mean body mass index, percentage of diabetes mellitus and cardiovascular disease history, mean eGFR and UACR. 2.6. 6. Quality assessment: The risk of bias in the included network meta-analyses will be assessed by combining the ROBIS with the ROB-NMA tool. In particular, the ROBIS tool will be used to assess the risk of bias in systematic reviews by covering the domains of study eligibility criteria, identification and selection of studies, data

collection and study appraisal. The ROB-NMA tool will be applied as a more specific tool for the quality assessment of network meta-analyses, as it takes into account the domains of interventions and network geometry, effect modification and synthesis. The risk of bias in the original RCTs will be assessed using the RoB-2 tool, evaluating the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.

- 6 Data analysis: Network meta-analysis will be performed by pooling the data derived from the original RCTs. A frequentist methodology will be applied and random-effects statistical models will be fitted by assuming a common heterogeneity parameter across comparisons. The plausibility of the transitivity assumption will be tested by examining the distribution of important covariates (age, female sex, body mass index, eGFR and UACR) across interventions. Statistical significance will be defined at the level of 5%. The ranking of interventions will be performed through their estimated P-scores for each endpoint, with higher P-score values indicating better treatments. Sensitivity analyses will be conducted by separately examining studies at low risk of bias, patients with diabetes mellitus, patients with cardiovascular disease, those with an eGFR ≥ 30 mg/g. A multicriteria decision analysis will be conducted to define the optimal compromise intervention, taking into account the calculated P-scores for the efficacy and safety endpoints. the distance-based TOPSIS (Technique for Order of Preference by Similarity to Ideal Solution) method will be implemented to select the best treatment as the one with the maximum distance from the positive ideal point and the minimum distance from the negative ideal one. Weights will be assigned to endpoints both objectively (entropy method) and subjectively (analytical hierarchical process). Three scenarios will be examined to reflect different clinical priorities by assigning more importance to the cardiovascular composite endpoint, the renal endpoints (kidney-specific composite endpoint and acute kidney injury risk), and the safety outcomes (risk of serious adverse events and drug discontinuation).