Therapeutic strategies in cardio-renal-metabolic syndrome: a systematic review

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Introduction

Cardio-Renal-Metabolic syndrome results from interactions between cardiovascular, metabolic, and renal risk factors, causing multi-organ dysfunction, increased morbidity, and premature mortality. Sodium–glucose cotransporter-2 inhibitors (SGLT2i), Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA), and Mineralocorticoid Receptor Antagonists (MRA) exert pleiotropic effects and improve cardiovascular and renal outcomes beyond glycemic control

Aim and objectives

to compare the risk–benefit profile of currently available pharmacological therapies, with a specific focus on their clinical efficacy and safety

Material and methods

A systematic review (SR) was conducted by searching PubMed, according to the Prisma guidelines, for studies published between August 8, 2015, and August 8, 2025. Search terms combined "SGLT2 inhibitors", diabetes, "chronic kidney disease", cardiovascular disease", and "CRM syndrome". Eligible outcomes included major adverse cardiovascular events (MACE), renal outcomes, and safety

Results

Dapagliflozin reduced the risk of cardiovascular (CV) death or hospitalization for heart failure (HF) by 29% [HR 0.71; 95% CI 0.55–0.92] and slowed kidney disease progression by 24% [HR 0.76; 95% CI 0.67–0.87].

Canagliflozin reduced the composite renal outcome [HR 0.66; 95% CI 0.53–0.81], HF hospitalizations [HR 0.61; 95% CI 0.47–0.80], and major adverse cardiovascular events (MACE) [HR 0.80; 95% CI 0.67–0.95].

Empagliflozin lowered MACE [HR 0.86; 95% CI 0.74–0.99], all-cause mortality (−32%), and CKD progression [HR 0.72; 95% CI 0.64–0.82], while ertugliflozin demonstrated non-inferiority for MACE and reduced HF hospitalizations by 30%.

Consistently, *Semaglutide* (GLP-1RA) and *Finerenone* (MRA) also showed favorable effects: semaglutide reduced MACE by up to 26% [HR 0.74; 95% CI 0.51–1.08], whereas *Finerenone* decreased HF hospitalizations by 17% [HR 0.83; 95% CI 0.75–0.92] and the composite renal outcome by 20% [HR 0.80; 95% CI 0.72–0.90]

Identification of studies via databases and registers

Identification

Records identified from databases searching (n =1335)

Records removed by applying filter and select only Systematic Reviews, meta-analyses, and RCT published in the last 10 years (n =778)

Screening

Records screened based on Title, abstract and inclusion criteria (n =36)

Reports excluded:
Secondary outcome not relevant (n=20)
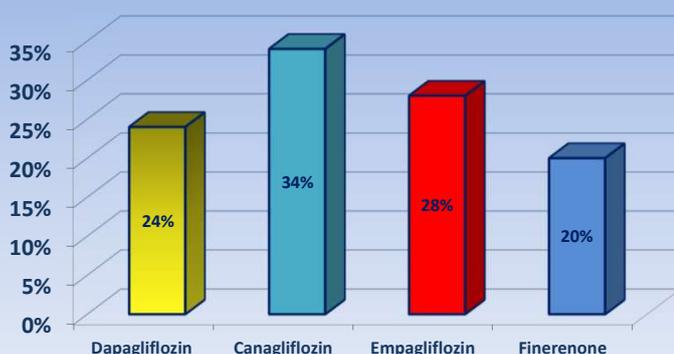Superseded by more recent evidence (n=1)
No relevant data (n =3)

Full text analyzed (n =12 RCT + 8 Study identified through reference mining)

Included

Studies included in the review (n =20)

Cardiovascular Outcomes Risk Reduction (%)

- Dapaglifozin: 29%
- Canagliflozin: 39%
- Ertugliflozin: 30%
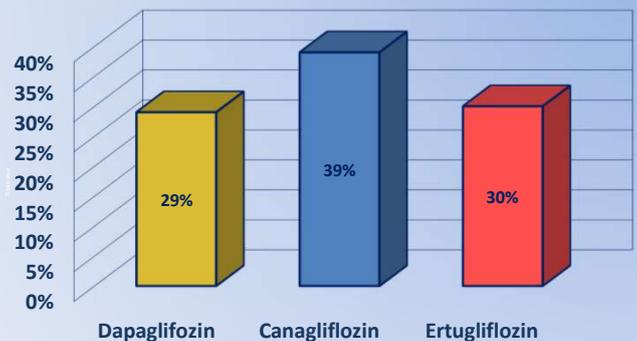
Kidney outcome Risk Reduction %

- Dapagliflozin: 24%
- Canagliflozin: 34%
- Empagliflozin: 28%
- Finerenone: 20%

Conclusion and relevance

Our analysis confirms the role of SGLT2 inhibitors and GLP-1 receptor agonists in the management of CRM syndrome, demonstrating cardiovascular and renal benefits, improved survival and quality of life, and a favorable safety profile

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