**Research methods**

PUBMED:

1. (Sacubitril valsartan) AND (preserved).
2. (LCZ696) AND (preserved).
3. (Sacubitril valsartan) AND (HFpEF).
4. (LCZ696) AND (HFpEF).

WEB OF SCIENCE:

1. Sacubitril valsartan (all Fields) AND preserved (All Fields).
2. LCZ696 (all Fields) AND preserved (All Fields).
3. Sacubitril valsartan (all Fields) AND HFpEF (All Fields).
4. LCZ696 (all Fields) AND HFpEF (All Fields).

**Supplementary table I**

|  |  |
| --- | --- |
| **TITLE** | **Reported on page** |
| Title | 1 | Identify the report as a systematic review, meta-analysis, or both. | 1 |
| **ABSTRACT** |
| Structured summary | 2 | Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. | 3 |
| **INTRODUCTION** |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known.  | performed, page 4 |
| Objectives | 4 | Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).  | performed, page 4 |
| **METHODS** |
| Protocol and registration | 5 | Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.  | Performed, page 4 |
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. | performed, page 4, 5 |
| Information sources  | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.  | performed, page 4, 5, 6 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | performed, page 4, 5, 6 and appendix |
| Study selection  | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).  | performed, page 5, 6, Figure 1 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | performed, page 5, 6 |
| Data items  | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | performed, page 5, Table 1 and 2 |
| Risk of bias in individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | performed, page 5, 5 appendix |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means).  | performed, page 5, 6 |
| Synthesis of results | 14 | Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis. | performed, page 5, 6 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).  | performed, page 5, 6 |
| Additional analyses | 16 | Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. | performed, page 5, 6 |
| **RESULTS** |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | performed, page 6 and Figure 1 |
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | performed, Table 1 and 2  |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12). | performed, appendix |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot. | performed, figure 2 and 3 |
| Synthesis of results  | 21 | Present results of each meta-analysis done, including confidence intervals and measures of consistency. | performed, page 6, 7 |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies (see Item 15). | Performed, appendix |
| Additional analysis | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). | performed, page 6, 7 |
| **DISCUSSION** |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). | Full discussion page 7, 8, 9 |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | Full discussion page 9 |
| **FUNDING** |
| Funding  | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. | Performed |

Supplementary table I: PRISMA checklist

**Supplementary table II**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | PARAMOUNT | PARAGON | Shi et al. | PARALLAX |
| Random sequence generation – **selection bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |
| Allocation concealment – **selection bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |
| Blinding of participants and personnel – **performance bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |  | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |
| Blinding of outcome assessment – **detection bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |  | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |
| Incomplete outcome data – **attrition bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |
| Selective reporting – **reporting bias** | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente | Immagine che contiene testo, segnale, clipart  Descrizione generata automaticamente |

Supplementary table II: Potential bias of all in the present meta-analysis included trials as judged by the authors and in accordance with the Cochrane’s Collaboration risk of bias assessment tool.

**Supplementary table III**

|  |  |
| --- | --- |
| Outcome | Egger test p-value |
| All-cause mortality | 0.5617 |
| Heart failure decompensation | 0.2290 |
| All-cause mortality and heart failure decompensation | 0.1360 |
| **Hyperkalaemia** | **0.0327** |
| Hypotension | 0.6095 |
| NYHA class improvement | 0.1584 |

Supplementary table III: Egger test p-value for different outcomes

**Supplementary figures:**



**Supplementary figure I:** Funnel plots for efficacy and safety outcomes. CI, confidence interval; HF, heart failure; NYHA, New-York heart association.



**Supplementary figure II:** Sensitivity analysis through the leave-one-out meta-analysis method for the evaluated outcomes. CI, confidence interval; HF, heart failure; NYHA, New-York heart association.