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ORIGINAL ARTICLE

Benefits and adverse effects of sacubitril/valsartan in patients with chronic heart failure: A systematic review and meta-analysis

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Abstract

This review aims to assess the benefits and adverse effects of sacubitril/valsartan in heart failure, with a focus on important patient outcomes. A systematic review was conducted of double-blind randomized controlled trials (RCTs) comparing sacubitril/valsartan versus a reference drug, in heart failure patients with reduced (HFrEF) and preserved (HFpEF) ejection fraction, published in French or English. Searches were undertaken of Medline, Cochrane Central, and Embase. The primary outcomes were all-cause mortality and adverse events. From 2 082 articles analyzed, 5 were included. For all-cause mortality, the absolute numbers for HFrEF (2 RCTs, 4627 patients) were 16% on sacubitril/valsartan and 18% on enalapril, with a risk ratio (RR) of 0.85 [CI = 0.78, 0.93], and 13% vs 14% in with HFpEF (2 RCTs, 5097 patients), with no statistical difference. Under the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the evidence for HFrEF patients was of moderate quality. For HFrEF patients, an increased risk of symptomatic hypotension and angioedema (low quality of evidence) was shown. There was no statistical difference for the risk of hyperkalemia or worsening renal function. There was a protective RR (0.50 [0.34, 0.75]) for worsening renal function for patients with HFpEF, with a high quality of evidence despite similar absolute numbers (1.4% vs. 2.8%). To keep in mind for shared decision-making, sacubitril/valsartan reduces all-cause mortality in HFrEF patients but for HFpEF further data are needed. Take into consideration the small number of studies to date to assess the risks.

KEYWORDS
decision making shared, general practice, heart failure, sacubitril-valsartan, systematic review

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; CHF, chronic heart failure; CI, confidence interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HFpEF, heart failure patients with preserved ejection fraction; HFrEF, heart failure patients with reduced ejection fraction; LVEF, left ventricular ejection fraction; NNH, number needed to harm; NNT, number needed to treat; NYHA, New York Health Association; RCT, randomized controlled trial; RoB2, version 2 of the Cochrane tool for assessing risk of bias in randomized trials; RR, risk ratio.

1 | INTRODUCTION

The prevalence of chronic heart failure (CHF) is up to 1%–2% of the adult population in developed countries, rising to >10% after the age of 70.[1]

The European Society of Cardiology updated its guidelines for the management of heart failure in 2016,[1] introducing a new drug class in the therapeutic algorithm, LCZ696, represented by Entresto®. It is a combination of a neprilysin inhibitor, sacubitril, with valsartan, an angiotensin receptor blocker. Inhibition of neprilysin increases the levels of vasoactive peptides and decreases vasoconstriction, sodium retention, and maladaptive remodeling. Valsartan was chosen to be combined with to inhibit the renin–angiotensin system and minimized the risk of serious angioedema in comparison with ACE inhibitors.[2]

This new drug is proposed as a replacement for an angiotensin converting enzyme inhibitor (ACEI) when patients with heart failure with reduced ejection fraction (HFrEF) remain symptomatic (class II–III of the New York Health Association (NYHA) classification) despite optimal treatment including a beta-blocker, ACEI and mineralocorticoid antagonist.

This drug is still relatively new and is being tested in several populations. We are interested in patients with HFrEF and those with preserved ejection fraction (HFpEF). These patient populations differ with regard to underlying aetiologies, demographics, co-morbidities, and response to therapies.[1] In a shared decision-making process, data are required on what can be expected from treatment in terms of size of effect, especially on important patient outcomes.[3,4]

We conducted a systematic review of the literature in which the benefit–risk balance of sacubitril/valsartan is evaluated in CHF, based on double-blind randomized controlled trials with a focus on important patient outcomes.

2 | MATERIALS AND METHODS

2.1 | Databases and inclusion criteria

A systematic review was conducted using Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and Embase. The search strategy was developed with an experienced medical university librarian (NPD). The strategy consisted of the following MeSH terms: “heart failure,” “heart failure, systolic,” “heart failure, diastolic,” “dyspnea, paroxysmal,” “edema, cardiac,” “cardio-renal syndrome,, “LCZ696,” “LBQ657” (an active metabolite of sacubitril), “neprilysin inhibitor” or “Entresto” or “valsartan and sacubitril.” The search equations are available in the appendices (Appendix S1, Search Equation). The strategies for Medline, CENTRAL, and Embase were first requested on April 24, 2018. An update was carried out on October 17, 2019, owing to the publication of new relevant data including a large-scale trial involving patients with HFpEF.[5] The articles were analyzed in parallel independently by two investigators (EC and SB). In cases of disagreement, a consensus was sought, with additional analysis by the third and fourth investigators (HVR and SBG).

The inclusion criteria were: double-blind randomized controlled trials (RCTs), sacubitril/valsartan versus placebo or reference molecule, patients ≥18 years, patients treated for CHF, and English or French language. The articles were screened by title and then by abstract. We used an eligibility form based on the selection criteria and read the full text of potentially relevant articles to assess their eligibility independently. The data were then extracted from the included studies and integrated into an Excel data table. For each parameter, the total number of events was collected for each arm. This article presents results separately for patients with HFrEF and those with HFpEF. This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 checklist) statement (Appendix S2, PRISMA checklist).[6]

2.2 | Outcomes and evaluation of studies

In terms of benefits, the primary outcome was all-cause mortality. For adverse effects, the primary outcome was the occurrence of: hypotension, angioedema, hyperkalemia, or renal insufficiency. Secondary endpoints were cardiovascular mortality, hospitalization for heart failure, hospitalization for any cause, or hospitalization for cardiovascular causes. The occurrence of outcomes over time was specified according to the available data. Where necessary, the authors of the included articles were contacted by e-mail to obtain additional data.

The quality of the included articles was assessed using items from version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2),[7] by two independent authors (EC and HVR). Protocols and supplementary files were used to assess the risk of bias if they were available. An assessment was conducted for each trial for each outcome concerning the following five domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. For each domain, the risk of bias was rated as “high,” “some concerns,” or “low” according to the algorithms that map responses to signaling questions onto a proposed risk-of-bias judgment, in order to obtain an overall risk of bias for each specific outcome: low risk of bias, some concerns, high risk of bias.

2.3 | Statistical analysis

Statistical analyses were performed using RevMan 5.4. All outcomes described in the studies were dichotomous variables (death, side effects, etc.) or censored events. The characteristics of the studies were summarized and presented as means ± standard deviation and number (%). Relative risks (RRs) were calculated with 95% confidence intervals (CIs). The analysis was performed using a fixed-effects model. Statistical heterogeneity among trials was assessed by examining forest plots, confidence intervals, and heterogeneity tests based on the most commonly used criterion for measuring the significance of heterogeneity between studies, namely the I^2

statistic. Values of I^2 range from 0% to 100%, being considered low at 25%, modest at 25%–50%, and high at 50%. Statistical analysis for the mortality outcome was performed according to the duration of follow-up. When mortality was expressed in studies as survival (i.e., censored data), it was verified that the hazard ratio could replace the RR, especially when considering numbers lost to follow-up. The type I error was set at 5% for all statistical analyses. The number needed to treat (NNT) was expected to be calculated if the follow-up durations were comparable.

The level of evidence of the meta-analysis results was assessed using the GRADE[8] approach and was rated as high, moderate, low, or very low. For assessments of the overall quality of evidence for each outcome that included pooled data from RCTs only, we downgraded the evidence from 'high quality' by one level for serious (or by two for very serious) study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates, or potential publication bias. Publication bias was expected to be represented as a funnel plot if the number of studies was sufficient.[9] This study was registered in the PROSPERO registry under the reference number CRD42018100474.

3 | RESULTS

The PRISMA diagram (Figure 1) gives the details of study inclusion. Out of 2082 articles analyzed, 5 were finally included.[5,10–13] Characteristics of the included studies are shown in Table 1.

3.1 | HFrEF patients

3.1.1 | Benefits

For the primary outcome, all-cause mortality data are shown in Figure 2. For all-cause mortality (two RCTs, 9280 patients), the RR was 0.85 [0.78, 0.93] and the absolute numbers were roughly 16% on sacubitril/valsartan and 18% on placebo. The number needed to treat to avoid one death was 89 for a 27 months treatment duration in the PARADIGM-HF study and the NNT was 35 for 2 months in the PIONEER-HF study. Based on assessment of the risk of bias, the two studies were of good quality for this outcome. Under the GRADE approach the evidence was of moderate quality owing to potential publication bias (Table 2). Two RCTs were excluded from our analysis because they were not published in a peer reviewed journal at the time of our review, and these presented all-cause mortality data in the trial registry ClinicalTrial.gov.[14,15] The small number of RCTs prevented us from presenting an informative funnel plot.

First hospitalization for worsening heart failure was analyzed as a secondary outcome, for the same two RCTs (Figure 2). The NNT to avoid one hospitalization for heart failure was 36 in PARADIGM-HF study with a treatment during 27 months and 17 in the PIONEER-HF study for a 2 months treatment duration. The RR was 0.80 [0.72, 0.89] and the absolute numbers were about 12% on sacubitril/valsartan and 15% on enalapril. The risk bias assessment found a low overall risk of bias for the two studies. The GRADE approach found a moderate quality because of serious inconsistency (I^2 was 66%).

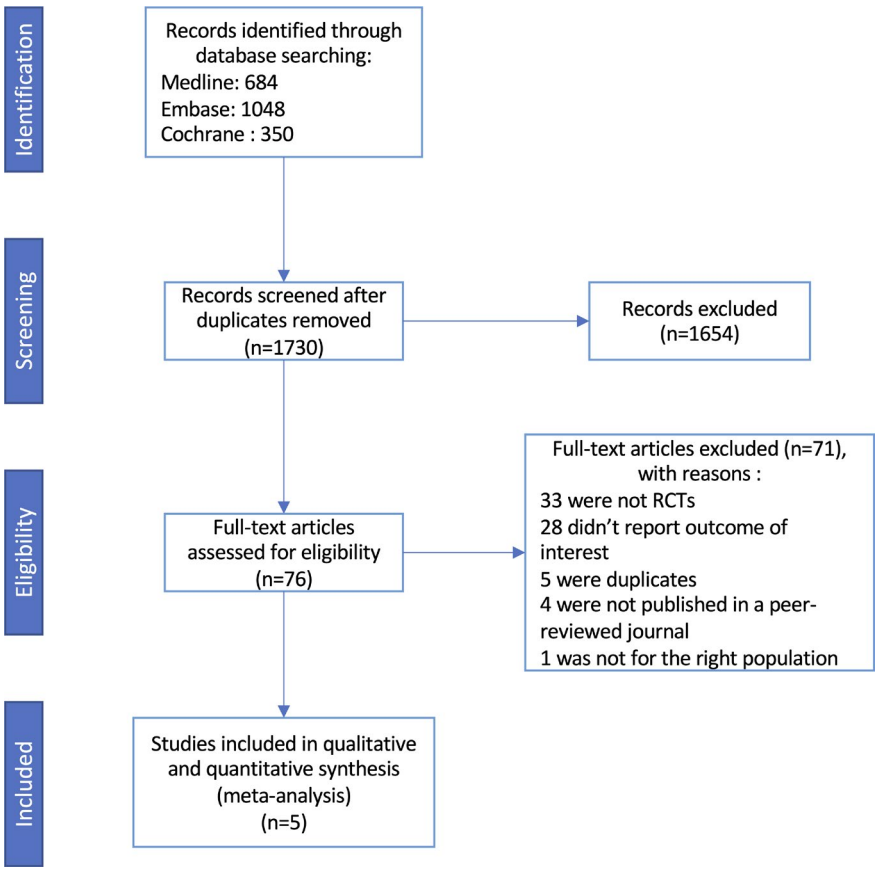

FIGURE 1 PRISMA diagram

TABLE 1 Characteristics of the included studies

Included studies	Drug	Control	Patients	Population	Mean duration follow-up (months)	Primary outcomes of the ECR	RR All-cause mortality
PARADIGM-HF, 2014	Sacubitril/ Valsartan	Enalapril	8442	HFrEF	27	Death from cardiovascular causes or hospitalization for heart failure	0.86 [0.78, 0,94]
PIONEER-HF, 2019	Sacubitril/ Valsartan	Enalapril	882	HFrEF	2	Time-averaged proportional change in NT-proBNP	0.67 [0.30, 1.47]
EVALUATE-HF, 2019	Sacubitril/ Valsartan	Enalapril	464	HFrEF	3	Central aortic stiffness	N.A.
PARAGON-HF, 2019	Sacubitril/ Valsartan	Valsartan	4822	HFpEF	35	Hospitalizations for heart failure and death from cardiovascular causes	0.97 [0.85, 1.12]
PARAMOUNT-HF, 2012	Sacubitril/ Valsartan	Valsartan	149	HFpEF	8	Change in NT-proBNP	0.51 [0.05, 5.57]

Studies are classified by HF population type and number of patients included. N.A., Non-available; NT-proBNP, N-terminal pro–B-type natriuretic peptide.

3.1.2 | Adverse events

The measured adverse events are shown in Figure 2. Three RCTs (9777 patients) had available data for worsening renal function and hyperkalemia and showed no significant difference, with RR of 0.89 [0.73, 1.09] and 0.96 [0.88, 1.05] between sacubitril/valsartan and enalapril groups, respectively. The absolute numbers were about 3%–4% for worsening renal function and 16% for hyperkalemia. For the risk of symptomatic hypotension and angioedema, the same three RCTs had data for 9744 patients. In the only study showing a significant risk of hypotension, PARADIGM-HF study, the number needed to harm was 21, with a follow-up duration of 27 months. The absolute numbers for symptomatic hypotension were roughly 13% on sacubitril/valsartan and 9% on enalapril, with 0.5% on sacubitril/valsartan and 0.2% on enalapril for angioedema. The risk of bias for these four outcomes was low. The quality of evidence was low for hypotension and angioedema (Table 2). Regarding the risk of congestive heart failure events, two RCTs (9313 patients) contained available data. The meta-analysis found a RR of 0.89 [0.72, 1.11], and I^2 was 75%. The risk of bias was uncertain for one RCT (PARADIGM-HF 2014) for this outcome because of the lack of information in the analysis of these data, which were not presented in the main article but in an appendix. The quality of evidence for this outcome was very low (Table 2).

3.2 | HFpEF patients

3.2.1 | Benefits

For patients with HFpEF, the primary outcome, all-cause mortality, was reported in two RCTs (Figure 3): PARAMOUT-HF and PARAGON-HF, representing 5097 patients. The meta-analysis showed no statistical difference (RR 0.97 [0.85, 1.11]). The absolute numbers were roughly 13% on sacubitril/valsartan and 14% on valsartan. The overall risk of bias was low for these two RCTs for this specific outcome.

3.2.2 | Adverse events

All adverse events in the HFpEF patient population are presented in Figure 3. With regard to worsening renal function, the meta-analysis reported a protective RR: 0.50 [0.34, 0.75] for data from 5097 patients. The absolute numbers were 1.4% on sacubitril/valsartan and 2.8% on valsartan. The PARAGON-HF study found a significant difference with a RR: 0.51 [0.34, 0.78], the NNT is 77 with 35 months of follow-up. We found a low overall risk of bias for the two RCTs for this specific outcome. The GRADE assessment found a high quality of evidence. The difference was not statistically significant for the risk of hyperkalemia (RR 0.88 [0.77, 1.01]). The risk of bias was uncertain for PARAGON-HF for hyperkalemia because of missing outcome data. The assessment of the quality of evidence found this to be low. Regarding the risk of angioedema and symptomatic hypotension, for the same two RCTs (5097 patients), the meta-analysis reported an excess risk (respectively RR 3.43 [1.20, 9.78] and RR 1.43 [1.24, 1.65]) with the following absolute numbers: about 0.6% on sacubitril/valsartan and 0.2% on valsartan for angioedema events, and about 16% on sacubitril/valsartan versus 11% for symptomatic hypotension events. Distinctively, the PARAGON-HF study found a significative difference for these two outcomes and the number needed to harm (NNH) was 20 for symptomatic hypotension and 242 for angioedema. The risk of bias for this outcome was low in the two RCTs. The quality of evidence for these results is moderate for angioedema and high for symptomatic hypotension. For congestive heart failure events during the follow-up of the same two RCTs, there was no statistical difference, with absolute numbers about 3.5% in the two groups.

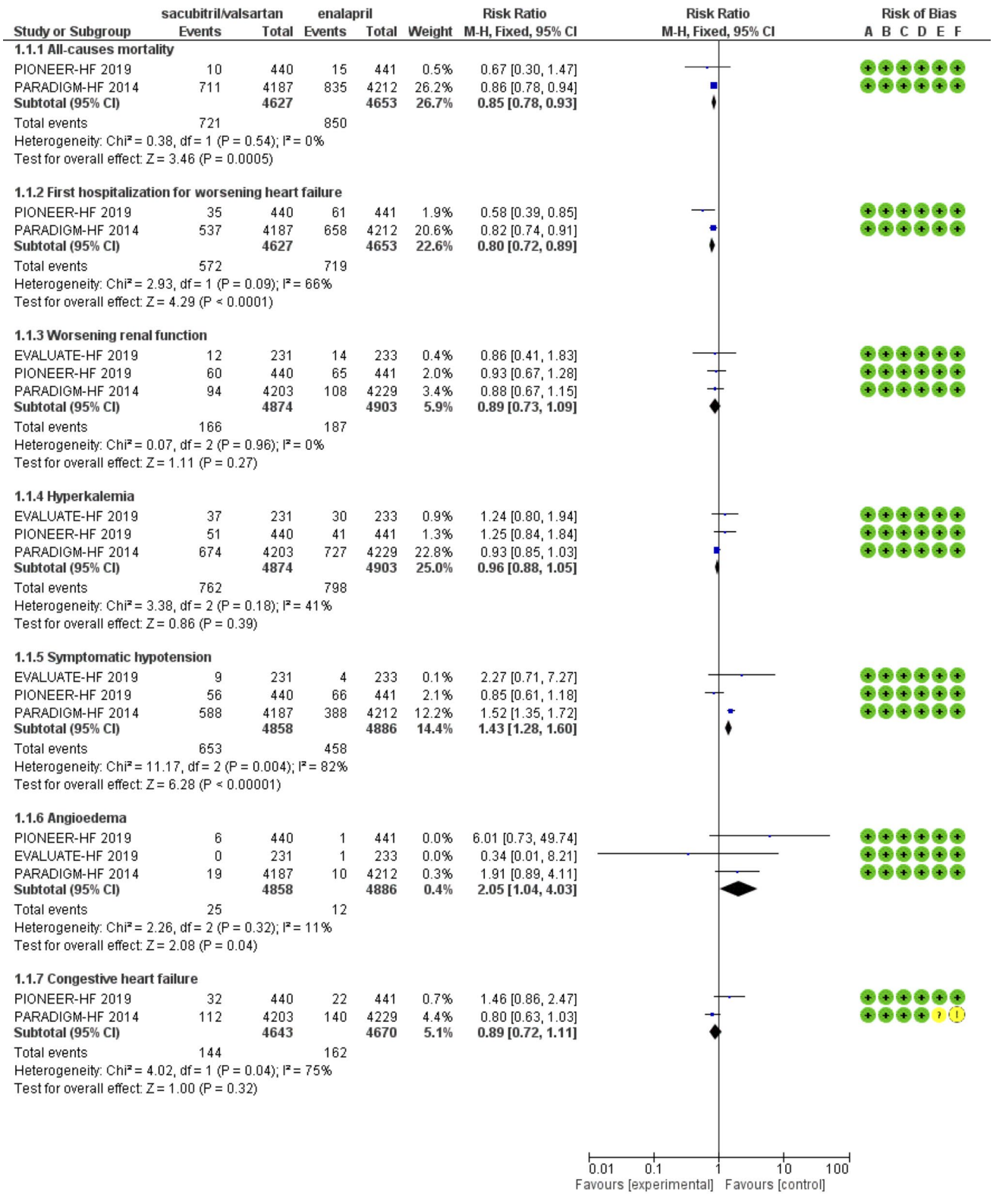

FIGURE 2 Forest plot for benefits and adverse effects in heart failure patients with reduced ejection fraction, and bias assessment. Risk of bias was assessed using the RoB 2 tool

TABLE 2 GRADE evidence profile

Quality assessment							Summary of findings			
							No. of events/No. of patients			
Population	No. of studies	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Sacubitril/ Valsartan	Control	RR (95% CI)	Quality
HFrEF	All-cause mortality Two (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Likely publication bias[f]	721/4627	850/4653	0.85 [0.78, 0.93]	⊕⊕⊕O Moderate
	First hospitalization for worsening heart failure Two (RCTs)	No serious risk of bias	Serious inconsistency[d]	No serious indirectness	No serious imprecision	Undetected	572/4627	719/4653	0.80 [0.72, 0.89]	⊕⊕⊕O Moderate
	Worsening renal function Three (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Likely publication bias[f]	166/4874	187/4903	0.89 [0.73, 1.09]	⊕⊕⊕O Moderate
	Hyperkalemia Three (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Likely publication bias[f]	762/4874	798/4903	0.96 [0.88, 1.05]	⊕⊕OO Low
	Symptomatic hypotension Three (RCTs)	No serious risk of bias	Serious inconsistency[d]	No serious indirectness	No serious imprecision	Likely publication bias[f]	653/4858	458/4886	1.43 [1.28, 1.60]	⊕⊕OO Low
	Angioedema Three (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Likely publication bias[f]	25/4858	12/4886	2.05 [1.04, 4.03]	⊕⊕OO Low
	Congestive heart failure Three (RCTs)	Serious risk of bias[a]	Serious inconsistency[d]	No serious indirectness	Serious imprecision[e]	Likely publication bias[f]	144/4643	162/4670	0.89 [0.72, 1.11]	⊕OOO Very Low
HFpEF	All-cause mortality Two (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	343/2556	351/2541	0.97 [0.85, 1.11]	⊕⊕⊕O Moderate
	Worsening renal function Two (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	36/2556	71/2541	0.50 [0.34, 0.75]	⊕⊕⊕⊕ High
	Hyperkalemia Two (RCTs)	Serious risk of bias[b]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	328/2535	370/2519	0.88 [0.77, 1.01]	⊕⊕OO Low
	Symptomatic hypotension Two (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	Undetected	408/2556	284/2541	1.43 [1.24, 1.65]	⊕⊕⊕⊕ High
	Angioedema Two (RCTs)	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	15/2556	4/2541	3.43 [1.20, 9.78]	⊕⊕⊕O Moderate
	Congestive heart failure Two (RCTs)	Serious risk of bias[c]	No serious inconsistency	No serious indirectness	Serious imprecision[e]	Undetected	90/2568	89/2554	1.01 [0.75, 1.34]	⊕⊕OO Low

[a]We noted some concerns about the risk of bias in a selection of the reported results because there is no information about the analysis of these data in PARADIGM-HF.

[b]We noted some concerns about the risk of bias due to missing outcome for this outcome in PARAGON-HF.

[c]We noted some concerns about the risk of bias in selection of the reported result because there is no information about the analysis of these data in PARAGON-HF.

[d]Unexplained heterogeneity; $I^2 \geq 50\%$.

[e]CI includes possible benefit from both treatments.

[f]Other data for these outcomes were available from at least one record excluded from the review because they were not published in peer-reviewed journals (results were available in trial registries at clinicaltrial.gov).

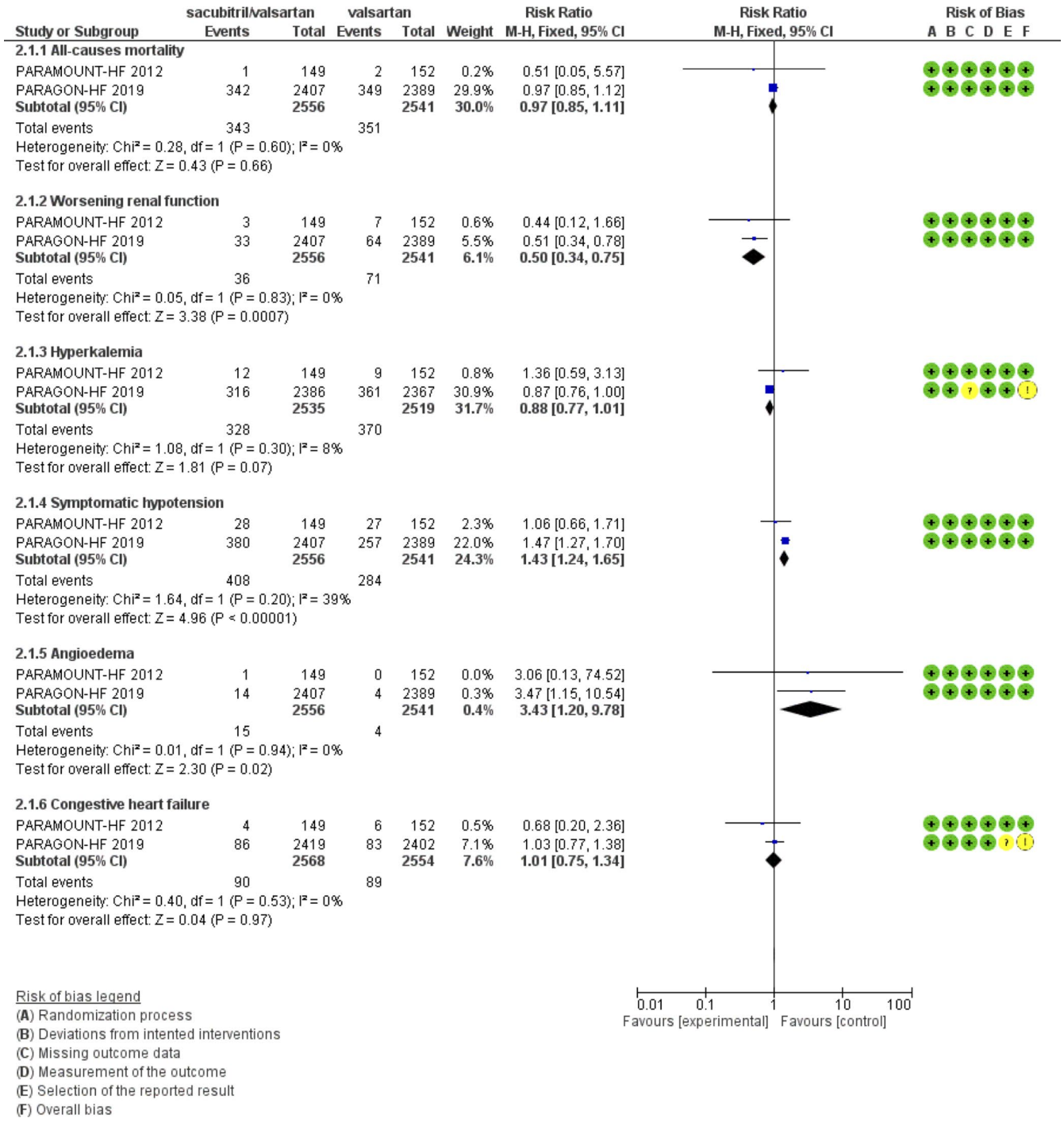

FIGURE 3 Forest plot for benefits and adverse effects in heart failure patients with preserved ejection fraction, and bias assessment. Risk of bias was assessed using the RoB 2 tool

4 | DISCUSSION

4.1 | Summary

The absolute numbers for all-cause mortality in patients with HFrEF were 16% on sacubitril/valsartan and 18% on placebo, with a RR of 0.85 [0.78, 0.93]. The two studies were of good quality for this outcome and this result had a moderate quality of evidence, following the GRADE approach. For the 5097 patients with HFpEF included in the two studies, the meta-analysis showed no statistical difference, with a RR 0.97 [0.85, 1.11] for this primary outcome.

Regarding adverse events, for patients with HFrEF the statistical analysis showed an increased risk of symptomatic hypotension and angioedema, but the absolute numbers were similar for angioedema and the quality of evidence for these outcomes was low. There was no statistical difference for the risk of hyperkalemia or worsening renal function in this population. For patients with HFpEF, the meta-analysis reported a protective RR (0.50 [0.34, 0.75]) for worsening

renal function and, despite similar absolute numbers (1.4% on sacubitril/valsartan and 2.8% on valsartan), we noted a high quality of evidence. There was a statistical excess risk of angioedema and symptomatic hypotension, with absolute numbers approaching 0.6% on sacubitril/valsartan versus 0.2% on valsartan for angioedema events, and 16% versus 11% for symptomatic hypotension events, with a moderate and high quality of evidence, respectively.

4.2 | Strengths and limitations

This review focuses on clinically important patient outcomes and the need to provide information on beneficial and adverse effects in a patient-centered approach for shared medical decision-making.[16,17] However, absolute numbers are of interest to general practitioners (GPs) when presenting an evidence-based evaluation of the benefits and risks of treatment to their patients. One key feature of our work was the consideration of adverse events, and again absolute numbers seem to be informative, as opposed to NNT.

A health sciences librarian with expertise in literature search (NPD) established the search parameters, bringing a quality criterion to this review.[18] The data were obtained from three main databases. It is therefore possible that some RCTs published in other databases or unpublished RCTs may not have been included. However, it has been shown that the use of databases other than Medline has little influence on the results of systematic reviews because >80% of RCTs are indexed in Medline.[19,20]

This study also had some limitations. We choose to include all types of heart failure and to separate populations according to inclusion criteria of the studies selected. Two studies which defined an HFpEF population included a larger population (left ventricular ejection fraction (LVEF) ≥45%) than the HFpEF is defined in the 2016 ESC guidelines (LVEF≥50%). No included studies looked at the specific mid-range heart failure population (left ventricular ejection fraction between 40% and 50%). The recent inclusion of sacubitril/valsartan in the pharmacopoeia explains the low number of studies and suggests that the evaluation of this drug requires more data to be published. The few studies included did not permit us to produce funnel plots. We found RCTs that had not been published in peer-reviewed journals with data for our outcomes of interest, which were available in registries such as clinicaltrial.gov. The existence of such unpublished data gives rise to fears of possible publication bias. One of the main limitations of the study stems from its meta-analytic nature: a meta-analysis is subject to the biases of each of the studies it includes. For example, a run-in period, as used in the PARADIGM-HF, limits the evaluation of adverse events because patients who experience adverse events early on are excluded during this period prior to randomization.

4.3 | Comparison with existing literature

To the best of our knowledge, no other systematic review concerning sacubitril/valsartan in HF existed before we began our work, and at the time of the declaration of our protocol on the Prospero registry, no other similar work was reported. However, Zhang et al. published similar research in August 2020.[21] They surveyed the three main databases as well as clinical trial.gov with similar keywords and included six RCTs: the five included in our work and the PRIME study by Kang et al. (2019).[22] This last record was excluded from our systematic review because the population, patients with mitral regurgitation, was too specific and the RCT was designed to assess echocardiographic criteria for primary and secondary outcomes (change in effective regurgitant area of functional mitral regurgitation). However, the results are similar in terms of effectiveness on mortality, with an odds ratio (OR) reaching 0.83 [0.74, 0.92] for patients with HFrEF and no significant difference in patients with HFpEF, although an OR cannot provide a representative effect size. The findings for adverse effects pooled the patients with HFrEF and HFpEF. This combination supposes that these two populations react in the same way to sacubitril/valsartan. However, HFrEF and HFpEF represent diverse phenotypes of demography, clinical presentation, etiology, and outcomes.[23] Patients with HFpEF are older, more often women, and more commonly have a history of hypertension and atrial fibrillation.[1] In addition, we provide an accurate analysis of the risk of bias by criterion, as recommended by the latest version of the Cochrane bias risk assessment tool: the ROB 2. Our meta-analysis also differs by providing an assessment of the quality of evidence of each of the results, following the GRADE approach. It seems crucial to take these parameters into account when determining the extent to which it is possible to rely on a given result. While we were finalizing our article, the review of Nielsen et al. was published in November, 2020.[24] Our study differs by a more rigorous selection of studies and direct clinical patient outcomes and an evaluation of the risk of bias based on the most recent version of the Cochrane tool (RoB2) and a criterion-by-criterion assessment as recommended (and not in a global way, per study).

With regard to our results for renal function, the meta-analysis of Spannella et al.[25] supports the role of sacubitril/valsartan in preservation of renal function, especially in older patients and patients with HF with preserved ejection fraction, a result that needs further investigation.

5 | CONCLUSION

This study provides clinical evidence that enables GPs to discuss the risk/benefit balance of prescribing sacubitril/valsartan to their patients with HFrEF, thus promoting a patient-centered approach in a shared medical decision-making process. To keep in mind for shared decision-making, sacubitril/valsartan reduces all-cause mortality in HFrEF patients but for HFpEF further data are needed. Take into consideration the small number of studies to date to assess the risks. The quality of evidence under the GRADE approach for the evaluation criteria relevant to this work was high to very low. In other words, further research is likely to have a significant impact on the results and could alter the assessment of the effects (benefits or

risks). As a consequence, the results of our review should be treated with caution and may be modified as a result of new data obtained from RCTs.

NOMENCLATURE OF TARGETS AND LIGANDS

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding et al., 2018),[26] and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).[26]

DISCLOSURE

The authors have no conflict of interest to declare for the work presented here. This study does not have the support of any pharmaceutical company.

ETHICAL APPROVAL

Ethical approval was not necessary for this study because only de-identified pooled data from individual studies were analyzed.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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