Benefits and Harms of Sacubitril in Adults With Heart Failure and Reduced Left Ventricular Ejection Fraction

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The quality of evidence regarding patient-centered outcomes in adults with heart failure (HF) after sacubitril combined with valsartan has not been systematically appraised. We searched 4 databases in February 2017 and graded the quality of evidence according to the Grading of Recommendations Assessment, Development and Evaluation working group approach. We reviewed 1 meta-analysis and multiple publications of 2 randomized controlled trials (RCT) and 1 unpublished RCT. In adults with HF and reduced ejection fraction, low-quality evidence from 1 RCT of 8,432 patients suggests that sacubitril combined with valsartan reduces all-cause (number needed to treat [NNT] to prevent 1 event [NNTp] = 35) and cardiovascular mortality (NNTp = 32), hospitalization (NNTp = 11), emergency visits (NNTp = 69), and serious adverse effects, leading to treatment discontinuation (NNTp = 63) and improves quality of life when compared with enalapril. In adults with HF and preserved ejection fraction, very low-quality evidence from 1 RCT of 301 patients suggests that there are no differences in mortality, morbidity, or adverse effects between sacubitril combined with valsartan and valsartan alone. In conclusion, in adults with HF and reduced ejection fraction, to reduce cardiovascular mortality and hospitalizations and improve quality of life, clinicians may recommend sacubitril combined with valsartan over angiotensin-converting enzyme inhibitors. **(Am J Cardiol 2017;120:1166–1170)**

"Scientific knowledge is a body of statements of varying degrees of uncertainty—some most unsure, some nearly sure, but none absolutely certain." Richard P. Feynman

Despite various available treatment options, heart failure (HF) is among the most common cause for mortality, poor quality of life, and high health-care utilization.[1,2] Inhibition of neprilysin, neutral endopeptidase, results in natriuretic effects, vasodilatation, hypotension, and lower cardiac upload.[3] Neprilysin inhibitor omapatrilat reduced blood pressure and cardiovascular mortality in adults with HF but caused angioedema, leading to withdrawal of this drug.[3] Angiotensin receptor neprilysin inhibitor (ARNI) sacubitril combined with angiotensin receptor blocker valsartan in adults with HF demonstrated a favorable benefits-to-harms balance in randomized controlled trials (RCTs).[4–7] Previous reviews and the latest guidelines did not appraise the quality of evidence according to the risk of bias in the body of evidence, publication status, consistency, and magnitude of the treatment effects in patient subpopulations.[3,8–10] We aimed at critical appraisal of all available evidence regarding the benefits and harms of ARNI in adults with HF.

Methods

We developed a protocol for a systematic literature review following recommendations from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (Appendix A).

We refined the clinical questions and defined the target population as patients with HF treated with either ARNI or any control treatments. Eligible outcomes included all-cause mortality, mortality caused by HF, treatment utilization (hospitalization, office visits, emergency department visits), quality of life measured with validated scales, and all adverse effects.

We conducted a comprehensive search in PubMed, EMBASE, the Cochrane Library, www.clinicaltrials.gov, and PharmaPendium (www.pharmapendium.com) up to February 2017 to find systematic reviews, published and unpublished RCTs, and nationally representative controlled observational studies that reported adjusted effect estimates. An external contractor, DOC Data Software Platform v2.0 (Doctor Evidence LLC, Santa Monica, CA) performed dual abstraction and quality control of the data. We evaluated the quality of the primary studies using the Cochrane risk of bias tool on a 3-point scale: high bias, low bias, and unclear. The authors assigned the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using the Grading of Recommendations Assessment, Development and Evaluation methodology (Appendix A).[11]

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See page 1168 for disclosure information.

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Table 1
GRADE summary of findings. Valsartan and sacubitril versus enalapril in adults with heart failure and reduced ejection fraction

Outcomes	Risk with intervention/ control per 1000	Attributable avoided events per 1000 treated (95% CI)	Relative effect (95% confidence interval)	Number of participants (studies)	NNT (95%CI)	Favors valsartan and sacubitril
Mortality, all-cause	**170/198**	**35 (22;84)**	**RR 0.86 (0.78;0.94)**	**8399 (1 RCT)**[12,14–20]	**28 (12;45)**	**X**†
Mortality, cardiovascular causes	**133/165**	**32 (22;62)**	**RR 0.81 (0.73;0.90)**	**8399 (1 RCT)**[12,14–20]	**31 (16;466)**	**X**†
Composite endpoint: cardiovascular death or HF hospitalization	**218/265**	**47 (29;65)**	**RR 0.82 (0.76;0.89)**	**8399 (1 RCT)**[12,14–20]	**21 (15;35)**	**X**†
Quality of life*	**NR**	**NR**	**MD 1.6 (0.6;2.7)**	**7706 (1 RCT)**[12,14–20]	**SMD 0.1 (0.03; 0.12)**	**X**†
Hospitalization, HF	**128/156**	**36 (23;77)**	**RR 0.82 (0.74;0.91)**	**8399 (1 RCT)**[12,14–20]	**28 (13;43)**	**X**†
Hospitalization, all-cause	**434/345**	**11 (9;14)**	**RR 0.79 (0.75;0.84)**	**8399 (1 RCT)**[12,14–20]	**89 (69;109)**	**X**†
Hospitalization due to HF	**156/111**	**22 (33;17)**	**RR 0.71 (0.64;0.79)**	**8399 (1 RCT)**[12,14–20]	**45 (31;59)**	**X**†
Emergency department visit for HF	**36/21**	**69 (47;133)**	**RR 0.59 (0.46;0.76)**	**8399 (1 RCT)**[12,14–20]	**14 (8;21)**	**X**‡
Discontinuation, adverse events	**107/123**	**63 (34;426)**	**RR 0.87 (0.77;0.98)**	**8399 (1 RCT)**[12,14–20]	**16 (2;30)**	**X**†
Total, other adverse events	**589/613**	**24 (3;44)**	**RR 0.96 (0.93;0.996)**	**8432 (1 RCT)**[12,14–20]	**42 (22;373)**	**X**†
Total, serious adverse events	**460/506**	**46 (24;67)**	**RR 0.91 (0.87;0.95)**	**8432 (1 RCT)**[12,14–20]	**22 (15;41)**	**X**†
Number of patients with first confirmed renal dysfunction	22/25	NA	RR 0.88 (0.67;1.15)	8399 (1 RCT)[12,14–20]	NS	No‡

Population: Adults with heart failure and reduced ejection fraction.
Settings: Outpatient.
Intervention: Valsartan + sacubitril (200 mg twice daily orally).
Comparator: Enalapril (10 mg twice daily orally).
CI = confidence interval; NNT = number needed to treat to achieve (prevent) an outcome in 1 patient; NR = not reported; NS = not statistically significant; RCT = randomized controlled trial; RR = risk ratio.
* Change from baseline to month 8 for the Kansas City Cardiomyopathy Questionnaire (KCCQ) Clinical Summary Score.
† Low quality of evidence.
‡ Very low quality of evidence.
Values in bold are statistically significant differences at 95% confidence limits.
Between-studies differences in continuous outcomes: MD, mean difference in absolute values of continuous outcomes between intervention and comparator; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0 to 0.5 standard deviations), moderate (SMD, 0.5 to 0.8 standard deviations), and large (SMD >0.8 standard deviations).
NNT is calculated as 1 per absolute risk difference. Attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000.

Results

Our comprehensive search in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov identified 1 meta-analysis and multiple publications of 2 RCTs and 1 unpublished RCT that examined the benefits and harms of ARNI in adults with HF.[4–7,12–21]

Low-quality evidence suggests that sacubitril combined with valsartan reduces all-cause and cardiovascular mortality, hospitalization, emergency visits, and serious adverse effects, and improves quality of life when compared with enalapril in adults with HF and reduced ejection fraction (Table 1). The magnitude of the effect is small, with less than 100 attributable events per 1,000 treated (Table 1 and Figure 1). Planned subgroup analysis suggests that sacubitril combined with valsartan reduces a composite outcome of mortality, cardiovascular causes of hospitalization, or worsening HF in all subgroups except adults with severe HF (New York Heart Association class III or IV, significant interaction effect; Appendix B, Table S1). Sacubitril combined with valsartan reduces cardiovascular mortality in all subgroups except in patients with diabetes (significant interaction effect; Appendix B, Table S1). Women, older adults, and nonwhite patients may have similar rates of cardiovascular death after sacubitril combined with valsartan when compared with enalapril, but this should be confirmed in future studies (interaction effects are not significant; Appendix B, Table S1).

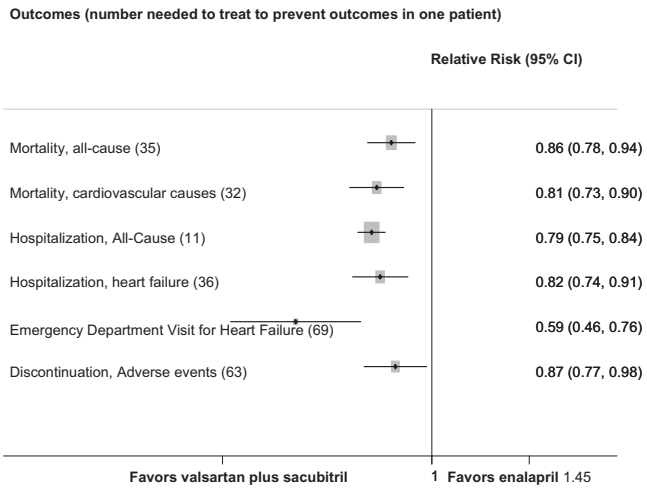

Figure 1. Relative risk and number needed to treat to prevent outcomes in 1 patient after valsartan and sacubitril versus enalapril in adults with heart failure and reduced ejection fraction (based on 1 RCT NCT01035255).

Very low-quality evidence suggests that there are no differences in mortality, morbidity, or adverse effects between