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SACUBITRIL/VALSARTAN VERSUS RAMIPRIL FOR PATIENTS WITH ACUTE MYOCARDIAL INFARCTION: WIN-RATIO ANALYSIS OF THE PARADISE-MI TRIAL

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ABSTRACT

Background

The win ratio can incorporate different types of outcomes and enhance statistical power, making it a useful method for analyzing composite outcomes in cardiovascular trials. The application of this approach to the PARADISE-MI trial provides an additional perspective into understanding the effects of sacubitril/valsartan in patients with acute myocardial infarction.

Methods

We conducted a post-hoc analysis of the PARADISE-MI trial, which randomly assigned patients with acute myocardial infarction complicated by a reduced left ventricular ejection fraction, pulmonary congestion, or both to receive either sacubitril/valsartan (97 mg of sacubitril and 103 mg of valsartan twice daily) or ramipril (5 mg twice daily) in addition to guideline-recommended therapy. The principal composite outcome was analyzed in the hierarchical order of death due to cardiovascular causes, first hospitalization for heart failure, and first outpatient episode of symptomatic heart failure. We included events confirmed by the clinical event classification (CEC) committee as well as events identified by investigators that did not meet study definitions. Results were analyzed by the unmatched win ratio method. A win ratio that exceeds 1.00 reflects a better outcome.
Results

A total of 5661 patients underwent randomization; 2830 were assigned to receive sacubitril-valsartan and 2831 to receive ramipril. The hierarchical analysis of the principal composite outcome demonstrated a larger number of wins [1,265,767 (15.7%)] than losses [1,079,502 (13.4%)] in the sacubitril/valsartan group (win ratio of 1.17, 95% confidence interval [CI], 1.03 to 1.33; P=0.015). Sensitivity analyses using alternative definitions of the composite outcome showed results similar to those of the principal analysis, except for analysis restricted to events that met CEC definitions (win ratio of 1.11, 95% CI, 0.96 to 1.30; P=0.16).

Conclusion

In this post-hoc analysis of the PARADISE-MI trial using the win ratio and including investigator-identified events not having CEC confirmation, sacubitril/valsartan was superior to ramipril among high-risk survivors of acute myocardial infarction.
INTRODUCTION

Analyses of composite endpoints are frequently used in the primary analysis of cardiovascular clinical trials.\textsuperscript{1,2} Composite endpoints such as cardiovascular death or heart failure hospitalization usually incorporate nonfatal and fatal events and offer the advantages of greater statistical power and a more comprehensive evaluation of treatment effects than single endpoints (such as cardiovascular death alone).\textsuperscript{3} Conventional statistical methods such as the Cox proportional hazards regression are based on time-to-first occurrence of any event in the composite, which is often the outcome of lesser clinical relevance.\textsuperscript{4} Consequently, nonfatal events typically dominate the results of current cardiovascular trials.\textsuperscript{5} For example, a patient who is hospitalized for heart failure early in the trial and experiences a cardiovascular death later is counted as a hospitalization for heart failure in the primary endpoint.

To overcome the limitations of conventional methods, the win ratio was introduced as a new approach for examining composite endpoints.\textsuperscript{6} The win ratio accounts for both the clinical relevance and timing of the individual endpoint components. The more serious events are given a higher priority and are analyzed first.\textsuperscript{7}

The PARADISE-MI (Prospective ARNI versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after Myocardial Infarction) trial was designed to test the hypothesis that sacubitril/valsartan was superior to ramipril among high-risk survivors of acute myocardial infarction.\textsuperscript{8} The pre-specified primary
composite adjudicated outcome of death due to cardiovascular causes, hospitalization for heart failure, or outpatient heart failure, whichever occurred first, was not reduced by sacubitril/valsartan compared to ramipril (hazard ratio, 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.17). A pre-specified analysis suggested a statistically significant benefit when investigator-reported first events (irrespective of whether or not adjudicated) were considered (HR, 0.85; 95% CI, 0.75 to 0.96, P=0.01).

When the primary outcome is not met, secondary analyses will not change the neutral results. However, secondary analyses may help to better understand the results by comprehensively capturing all available information contained in both adjudicated and investigator-reported outcomes. The hierarchical structure and ability to incorporate different types of outcomes of the win ratio approach make it an attractive method in pursuit of this goal. Thus, the aim of the present post-hoc analysis was to provide additional analyses of the PARADISE-MI trial integrating the totally of evidence across fatal and nonfatal outcomes into a hierarchical composite endpoint analyzed according to the win ratio method.
METHODS

Trial Design

The design and main results of the PARADISE-MI trial (ClinicalTrials.gov, NCT02924727) have been published.\textsuperscript{8,9} Briefly, PARADISE-MI was an international, multicenter, randomized, double-blind, parallel group trial to compare the efficacy and safety of sacubitril/valsartan compared with ramipril on morbidity and mortality in high risk patients following an acute myocardial infarction.

Eligibility

Patients aged \( \geq 18 \) years without a history of heart failure were eligible if they experienced an acute myocardial infarction within 7 days of randomization that was associated with a left ventricular ejection fraction \( \leq 40\% \), pulmonary congestion that required intravenous treatment, or both conditions and had at least one of the following prespecified risk-enrichment factors: age \( \geq 70 \) years, diabetes mellitus, previous myocardial infarction, an estimated glomerular filtration rate [eGFR] of \(< 60 \) ml per minute per 1.73 m\(^2\) of body-surface area at screening, atrial fibrillation, a left ventricular ejection fraction \(< 30\% \) associated with the index myocardial infarction, Killip class III or IV, or ST-segment elevation myocardial infarction without reperfusion within 24 hours after presentation.
Patients were excluded for hemodynamic instability during the 24 hours preceding randomization, an eGFR < 30 ml/min/1.73 m², a serum potassium level > 5.2 mmol/L, a history of angioedema, or an inability to take an ACE inhibitor or angiotensin receptor blocker.

**Trial Procedures**

Patients were randomized in a 1:1 ratio, between 12 hours and 7 days after the index infarction to receive either sacubitril/valsartan (97-103 mg twice daily) or ramipril (5 mg twice daily. Concealed randomization was performed with the use of interactive-response technology, with stratification according to geographic region and type of myocardial infarction (ST-segment or non–ST segment elevation). Treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) was discontinued at randomization. Patients, investigators, caregivers, and outcome assessors were unaware of treatment assignments.

**Outcomes**

All potential outcomes underwent review and adjudication by an independent clinical events classification (CEC) committee. For the purpose of the present analysis, we considered information from events that met CEC definitions, which we defined as CEC (+) events, and also from events that did not meet CEC definitions, which we defined as CEC (-) events. In this sense, CEC (+) events included both site-reported events with
adequate and complete source documentation to meet standardized study definitions, as well as events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data. Conversely, CEC (-) events comprised investigator-reported events that were not confirmed by the CEC committee for different reasons, including missing or incomplete source documentation, insufficient signs, and symptoms and/or no qualifying intravenous treatment to characterize episodes of heart failure, or other reasons that prevented events from meeting pre-specified study definitions.

The principal analysis was a hierarchical composite outcome analyzed in the order of: (1) death due to cardiovascular causes based on CEC (+) events; (2) death due to cardiovascular causes based on CEC (-) events; (3) first hospitalization for heart failure based on CEC (+) events; (4) first hospitalization for heart failure based on CEC (-) events; (5) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (+) events; and (6) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (-) events.

We hypothesized that the inclusion of both CEC (+) and CEC (-) events in the principal hierarchical composite outcome could be informative for several reasons. First, some CEC disagreements with investigator-reported hospitalizations for heart failure or outpatient heart failure were due to the lack of detailed source documentation.
needed to confirm CEC definitions. Moreover, some fatal events were short of complete data to allow a reasonable differentiation of cardiovascular or non-cardiovascular cause of death. Thus, it is likely that a proportion of CEC (-) events did represent true outcomes.

Second, some events that would be considered as being worsening heart failure in routine practice did not meet strict CEC definitions because of insufficient signs and symptoms and/or lack of qualifying treatment. Therefore, additional information provided by CEC (-) events may improve the generalizability of the results by more closely resembling the clinical judgment applied by clinicians in routine practice. Third, by using all available trial information, this approach, closer to clinical practice, allows a more complete and comprehensive assessment of the comparison between the two treatment arms on different outcomes. Fourth, considering both types of events in the same hierarchical composite outcome may increase the statistical power to reliably detect potential treatment effects. Finally, fatal events and CEC (+) events were given a higher priority and were analyzed before CEC (-) events.

**Statistical Analysis**

The analyses included all of the participants who underwent randomization (intention-to-treat principle). Baseline characteristics are summarized by randomized group using means (± standard deviation) and frequencies for continuous and categorical variables, respectively.
The results for the principal hierarchical composite outcome were analyzed with the unmatched win ratio method\textsuperscript{6,7}, in which, every patient in the sacubitril/valsartan group was compared with every patient in the ramipril group during a shared follow-up time defined as the minimum of their follow-up times. Pairs were classified as winners for sacubitril/valsartan if participants randomized to ramipril died due to a cardiovascular cause first during follow-up and losers if those randomized to sacubitril-valsartan died due to a cardiovascular cause first. If both participants in a pair completed or exited the study before a fatal cardiovascular event, they were classified according to who experienced any of the nonfatal events first in a hierarchical order. A pair was tied if a decision could not be made on whether it was a winner or a loser. The win ratio was defined as the total number of winner pairs divided by the total number of loser pairs (Table S1). Therefore, a win ratio > 1 indicates benefit of sacubitril/valsartan. The ratio of wins and losses as well as the cumulative win ratios at each tier of the principal hierarchical composite outcome were also calculated.

Four sensitivity analyses were performed:

1) The hierarchical composite outcome included total (first and recurrent events), analyzed in the order of: (1) death due to cardiovascular causes based on CEC (+) events; (2) death due to cardiovascular causes based on CEC (-) events; (3) total hospitalizations for heart failure based on CEC (+) events; (4) total hospitalizations for heart failure based on CEC (-) events; (5) total outpatient symptomatic heart failure
based on CEC (+) events; and (6) total outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (-) events (Table S2).

2) The hierarchical outcome included all-cause mortality, analyzed in the order of: (1) all-cause death; (2) first hospitalization for heart failure based on CEC (+) events; (3) first hospitalization for heart failure based on CEC (-) events; (4) first outpatient symptomatic heart failure based on CEC (+) events; and (5) first outpatient symptomatic heart failure based on CEC (-) events (Table S3).

3) The principal analysis restricted to events that occurred during the first year of follow-up (Table S4).

4) The principal analysis restricted to CEC (+) events (Table S5).

5) The hierarchical composite outcome analyzed in the order of: (1) death due to cardiovascular causes based on CEC (+) events; (2) first hospitalization for heart failure based on CEC (+) events; (3) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (+); (4) death due to cardiovascular causes based on CEC (-) events; (5) first hospitalization for heart failure based on CEC (-) events; and (6) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (-) events.

All sensitivity analyses were also conducted using the unmatched win ratio method.
A two-sided P value of less than 0.05 was considered to indicate statistical significance. The 95% CIs were estimated for the win ratio effect measures.
RESULTS

Baseline Characteristics

A total of 5,661 patients from 495 sites in 41 countries were randomized to either sacubitril/valsartan (n=2,830) or ramipril (n=2,831) at a median of 4.3 days after the index myocardial infarction. The median follow-up duration was 22 months in each group. The baseline characteristics of the patients were well balanced between the groups (Table 1). Left ventricular ejection fraction was ≤40% in 81.4% of the patients, 54.0% had pulmonary congestion, and 35.5% had both features; also, 52.2 % of patients had ≥1 prespecified risk enrichment factors. Patients received high rates of guideline-recommended therapies, including dual antiplatelet therapy (92%), statins (95%), and beta-blockers (85%).

Principal Composite Outcome

The hierarchical analysis of the principal composite outcome is shown in Figure 1. The total number of wins was 1,265,767 (15.7%) and the total number of losses was 1,079,502 (13.4%) in the sacubitril/valsartan group. The total number of ties was 5,666,461 (70.9%). The win ratio was 1.17 (95% confidence interval [CI], 1.03 to 1.33; P=0.015). The two principal contributors to the number of wins were CEC (+) death due to cardiovascular causes (36.9% of wins) and CEC (+) hospitalization for heart failure (29.8% of wins).
The ratios of win and losses in each of the six tiers indicate that, in every case, the wins exceed the losses (Figure S1). Correspondingly, the cumulative win ratios in each tier suggest a consistent benefit of sacubitril/valsartan over ramipril (Figure S2).

**Sensitivity Analyses**

The win ratio for the hierarchical composite endpoint tested in the order of death due to cardiovascular causes, total hospitalization for heart failure, and total outpatient symptomatic heart failure including both CEC (+) and CEC (-) events was 1.17 (95% CI, 1.03 to 1.33; P=0.014), Figure 2.

Similarly, a hierarchical analysis of a composite outcome analyzed in the order of all-cause death, first hospitalization for heart failure, and first outpatient symptomatic heart failure including both CEC (+) and CEC (-) events yielded a win ratio of 1.15 (95% CI, 1.02 to 1.31; P=0.024), Figure 3.

Analysis of our principal composite outcome considering only events that occurred during the first year of follow-up yielded a win ratio of 1.17 (95% CI, 1.02 to 1.35; P=0.025), Figure 4.

The win ratio for a hierarchical composite outcome that included only CEC (+) events was 1.11 (95% CI, 0.96 to 1.30; P=0.16), Figure 5.

Finally, analysis that prioritized CEC (+) events over CEC (-) events resulted in a win ratio of 1.17 (95% CI; 1.03, 1.33; P = 0.015), Figure 6.
DISCUSSION

In this post-hoc win ratio re-analysis of the PARADISE-MI trial, sacubitril/valsartan was superior to ramipril among patients with acute myocardial infarction complicated by reduced left ventricular ejection fraction, pulmonary congestion, or both with respect to a hierarchical composite outcome of cardiovascular death, hospitalization for heart failure, and outpatient heart failure (considering information from both CEC-confirmed events confirmed and investigator-identified events not having CEC confirmation). In this sense, by simultaneously considering the hierarchy of outcomes and the totality of trial evidence across multiple domains of endpoints, these findings provide an additional perspective into understanding the effects of sacubitril/valsartan in patients with acute myocardial infarction.

The present re-analysis of the PARADISE-MI trial based on the win ratio method expands the results from primary time-to-first event analysis by comparing every patient in the sacubitril/valsartan group with every patient in the ramipril group. In addition, the win ratio method made greater use of fatal cardiovascular events than the conventional time-to-first event analysis. The latter disregards all fatal events that occurred after the first event. Because we used death due to cardiovascular causes as the top of the hierarchy, non-cardiovascular deaths could have constituted a competing risk for the other outcomes. Nevertheless, a sensitivity analysis that replaced cardiovascular
deaths for all-cause deaths in the composite hierarchical outcome reached similar results. (Figure 3)

Despite the fact that sacubitril/valsartan did not meet the primary endpoint with central adjudication, previous pre-specified secondary analyses of the PARADISE-MI trial found that statistical significance was met when all investigator-reported events (which consist of positively and negatively adjudicated outcomes) were considered (HR 0.85; 95% CI, 0.75 to 0.96, P=0.01). The present win ratio analysis complements these findings by considering not only investigator reported events, but also outcomes identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data. Another key difference between the previous time-to-first event analysis of investigator-reported outcomes and the present win ratio analysis, is that the latter prioritized fatal and more serious events. Events that met CEC definitions were also prioritized and contributed about 70% of the wins favoring sacubitril/valsartan. Thus, the win ratio analysis of PARADISE-MI offers new insights concerning the relative impact of each component of the principal composite outcome.

The sensitivity analyses using alternative definitions of the hierarchical composite outcome showed results similar to those of the principal analysis, except for analysis restricted to events that met CEC definitions. On the other hand, despite the lack of statistical significance, the magnitude and directionality of the win ratio analysis
of sacubitril/valsartan versus ramipril based on events that met CEC definitions were consistent with the principal analysis. It is possible that analysis restricted to CEC-confirmed events excluded true events, since one of the reasons for CEC disagreements with investigator-reported nonfatal events was related to difficulties in obtaining detailed source documentation needed to meet the strict endpoint definitions in a trial that had substantial follow up occurring during the COVID pandemic. Additionally, events that would be considered as heart failure episodes in clinical practice were not confirmed as trial outcomes because of insufficient signs and symptoms and/or lack of qualifying intravenous treatment. For these reasons, we believe that considering information from both CEC-confirmed events and events that did not meet CEC definitions in the same hierarchical composite outcome allowed a more comprehensive assessment of the effects of sacubitril/valsartan in the context of an acute myocardial infarction.

Since the win ratio method was introduced in 2012, there has been a growth in its use, including several cardiovascular therapies that have achieved FDA approval. In addition, the win ratio methodology was used as exploratory re-analyses of previous heart failure and acute coronary syndrome trials. In a post-hoc analysis of the DIG (Digitalis Investigation Group) trial comparing digoxin with placebo, the win ratio tested as death due to cardiovascular cause, followed by hospitalizations for heart failure, was 1.14 (95% CI, 1.05 to 1.20; P < 0.001). In the PARADIGM-HF
(Prospective comparison of angiotensin receptor neprilysin inhibitor with angiotensin converting enzyme inhibitor to Determine Impact on Global Mortality and Morbidity in Heart Failure) trial, the win ratio for a hierarchical composite outcome tested in the order of death due to cardiovascular causes, hospitalization for heart failure, and emergency department visit for worsening heart failure was 1.27 favoring sacubitril/valsartan (95% CI, 1.16 to 1.39; P < 0.001). In the EPHESUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study) trial, the win ratio for a hierarchical composite outcome of death due to cardiovascular causes, stroke, myocardial infarction, and hospitalizations for heart failure was 1.15 favoring eplerenone (95% CI, 1.05 to 1.27; P=0.0026). Our finding of a win ratio of 1.17 is consistent with the previous cardiovascular trials (win ratios ranging between 1.14 and 1.27).

Despite the increased usage and the fact that it recognizes all events, while taking into account the relative clinical importance of the component outcomes, the win ratio has some disadvantages. These are related to the fact that it represents a novel statistical approach, and, as such, some clinical trialists, physicians, and patients may lack familiarity in interpreting the results of trials analyzed by the win ratio method. Additionally, the win ratio method does not consider the exact times from randomization to event occurrence. Finally, power calculations for the win ratio involve simulations and, at present, there is little guidance available in this regard.
The present analysis has limitations that merit consideration. First, the main reason for the statistically significant results using the win ratio appears to be the addition of the CEC (-) investigator reported events, since the analysis restricted to the CEC (+) results is similar to the primary analysis approach. Second, given the post-hoc nature of the analysis, our findings should be considered exploratory or hypothesis generating. Third, other relevant outcomes were not examined, including the evaluation of continuous outcomes, kidney events, patient-reported outcomes, biomarkers, and safety events. Fourth, we calculated the win ratio using the unmatched or all-pairs approach instead of the matched-pairs approach. This may have led to a greater comparison of patients with high-risk baseline variables than patients with low risk at baseline and to a conservative estimate of treatment effect. Nevertheless, it has been shown that is difficult to objectively define the matching process in advance and is often not possible to match all patients. Moreover, for the matched win ratio approach to have credibility, the method of matching (and development of any risk score, and time stratification if required) needs to be rigorously pre-defined in a Statistical Analysis Plan, which is not the case of the present study since our analysis was defined post-hoc. Therefore, we opted for the unmatched approach. Fifth, we did not perform a weighted win-loss approach, which are considered by some authors as being more efficient than unweighted win ratio methods. On the other hand, artificial the win ratio method already gives priority to more serious and fatal events. Finally, a sub-ranking of CEC
(+/-) over CEC(-) events could carry the ranking outside the investigator domain.

However, a sensitivity analysis prioritizing CEC(+) events over CEC(-) yielded results similar to those of the principal analysis.

In summary, in this post-hoc win ratio analysis of the PARADISE-MI trial, sacubitril/valsartan was superior to ramipril among high-risk survivors of myocardial infarction. This study provides an example of how the win ratio approach may be as a useful adjunct to the conventional time-to-first event analysis for trials with composite outcomes, especially where ranking of the clinical importance of the different types of events is considered relevant.

**SOURCES OF FUNDING**

Funded by Novartis.
REFERENCES


Table 1. Selected Baseline Characteristics of Randomized Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Sacubitril-valsartan</th>
<th>Ramipril</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=2830</td>
<td>N=2831</td>
</tr>
<tr>
<td>Age – yrs</td>
<td>64.0 ± 11.6</td>
<td>63.5 ± 11.4</td>
</tr>
<tr>
<td>Female sex – no. (%)</td>
<td>663 (23.4%)</td>
<td>700 (24.7%)</td>
</tr>
<tr>
<td>Race – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>475 (16.8%)</td>
<td>478 (16.9%)</td>
</tr>
<tr>
<td>Black</td>
<td>35 (1.2%)</td>
<td>40 (1.4%)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>2125 (75.1%)</td>
<td>2138 (75.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>195 (6.9%)</td>
<td>175 (6.2%)</td>
</tr>
<tr>
<td>Heart rate – bpm</td>
<td>75.6 ± 11.8</td>
<td>75.7 ± 11.7</td>
</tr>
<tr>
<td>Systolic blood pressure – mmHg</td>
<td>120.8 ± 13.4</td>
<td>121.0 ± 13.2</td>
</tr>
<tr>
<td>Diastolic blood pressure – mmHg</td>
<td>73.8 ± 9.9</td>
<td>73.7 ± 9.7</td>
</tr>
<tr>
<td>Body mass index – kg/m²</td>
<td>28.2 ± 5.0</td>
<td>28.1 ± 5.1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction - %</td>
<td>36.4 ± 9.3</td>
<td>36.6 ± 9.6</td>
</tr>
<tr>
<td>Pulmonary congestion – no. (%)</td>
<td>1508 (53.3%)</td>
<td>1548 (54.7%)</td>
</tr>
<tr>
<td>&gt;1 risk enrichment factors – no. (%)</td>
<td>1490 (52.7%)</td>
<td>1464 (51.7%)</td>
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<tr>
<td>Medical history – no. (%)</td>
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<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>463 (16.4%)</td>
<td>457 (16.1%)</td>
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<tr>
<td>Prior revascularization</td>
<td>471 (16.6%)</td>
<td>463 (16.4%)</td>
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<tr>
<td>Prior stroke</td>
<td>121 (4.3%)</td>
<td>142 (5.0%)</td>
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<tr>
<td>Hypertension</td>
<td>1845 (65.2%)</td>
<td>1831 (64.7%)</td>
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<tr>
<td>Diabetes</td>
<td>1221 (43.1%)</td>
<td>1180 (41.7%)</td>
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<tr>
<td>Current smoking</td>
<td>613 (21.7%)</td>
<td>583 (20.6%)</td>
</tr>
<tr>
<td>Atrial fibrillation/flutter</td>
<td>402 (14.2%)</td>
<td>382 (13.5%)</td>
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<tr>
<td>Serum creatinine – mg/dl</td>
<td>1.1 ± 0.3</td>
<td>1.1 ± 0.3</td>
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<tr>
<td>Estimated GFR - ml/min/1.73m²</td>
<td>71.7 ± 21.7</td>
<td>71.9 ± 23.1</td>
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<tr>
<td>Qualifying MI – no. (%)</td>
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<tr>
<td>Type of MI</td>
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<tr>
<td>STEMI</td>
<td>2153 (76.1%)</td>
<td>2138 (75.5%)</td>
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<tr>
<td>NSTEMI/other</td>
<td>677 (23.9%)</td>
<td>693 (24.5%)</td>
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<tr>
<td>Killip class ≥II</td>
<td>1595 (56.4%)</td>
<td>1606 (56.7%)</td>
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<tr>
<td>Time to randomization – days</td>
<td>4.3 ± 1.8</td>
<td>4.3 ± 1.7</td>
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<tr>
<td>Medical treatment at randomization – no. (%)</td>
<td>361 (12.8%)</td>
<td>344 (12.2%)</td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>2608 (92.2%)</td>
<td>2614 (92.3%)</td>
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<tr>
<td>Medication</td>
<td>Group A</td>
<td>Group B</td>
</tr>
<tr>
<td>----------------------------------</td>
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<tr>
<td>Beta blocker</td>
<td>2414 (85.3%)</td>
<td>2413 (85.2%)</td>
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<tr>
<td>Mineralocorticoid receptor antagonist</td>
<td>1155 (40.8%)</td>
<td>1183 (41.8%)</td>
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<td>Diuretics</td>
<td>1271 (44.9%)</td>
<td>1250 (44.2%)</td>
</tr>
<tr>
<td>Statin</td>
<td>2674 (94.5%)</td>
<td>2696 (95.2%)</td>
</tr>
<tr>
<td>ACE inhibitor/ARB*</td>
<td>2216 (78.3%)</td>
<td>2220 (78.4%)</td>
</tr>
</tbody>
</table>

Plus-minus values are means ± SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-converting-enzyme, ARB angiotensin-receptor blocker, GFR glomerular filtration rate, MI myocardial infarction, NSTEMI non-ST-elevation myocardial infarction and STEMI ST-elevation myocardial infarction.

*ACE inhibitor or ARB use within seven days before randomization.

CV denotes cardiovascular, HHF denotes hospitalization for heart failure
FIGURE LEGENDS

Figure 1. Use of win ratio in the PARADISE-MI trial for the hierarchical principal composite outcome of death due to cardiovascular causes, first hospitalization for heart failure, and first outpatient symptomatic heart failure (considering information from both CEC-confirmed events and events that did not meet CEC definitions).

CV denotes cardiovascular, HF denotes heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

‡ CEC (-) events included site-reported events that were not confirmed in the adjudication process.
Figure 2. Use of win ratio in the PARADISE-MI trial for the hierarchical composite outcome of death due to cardiovascular causes, total hospitalization for heart failure, and total outpatient symptomatic heart failure (considering information from both CEC-confirmed events and events that did not meet CEC definitions).

CV denotes cardiovascular, HF denotes heart failure, OHF denotes outpatient heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

‡ CEC (-) events included site-reported events that were not confirmed in the adjudication process.
Figure 3. Use of win ratio in the PARADISE-MI trial for the hierarchical composite of all-cause death, first hospitalization for heart failure, and first outpatient symptomatic heart failure (considering information from both CEC-confirmed events and events that did not meet CEC definitions).

HF denotes heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

‡ CEC (-) events included site-reported events that were not confirmed in the adjudication process.
CV denotes cardiovascular, MI denotes myocardial infarction, HF denotes heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

‡ CEC (-) events included site-reported events that were not confirmed in the adjudication process.
Figure 5. Use of win ratio in the PARADISE-MI trial for the hierarchical composite outcome of death due to cardiovascular causes, first hospitalization for heart failure, and first outpatient symptomatic heart failure (based on CEC-confirmed events).

CV denotes cardiovascular, HF denotes heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

CEC (-) events included site-reported events that were not confirmed in the adjudication process.
Figure 6. Use of win ratio in the PARADISE-MI trial for the hierarchical principal composite outcome of death due to cardiovascular causes, first hospitalization for heart failure, and first outpatient symptomatic heart failure (considering information from both CEC-confirmed events and events that did not meet CEC definitions).

CV denotes cardiovascular, HF denotes heart failure, CI denotes confidence interval, CEC denotes clinical events committee

* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† CEC (+) events included both site-reported events with adequate and complete source documentation to meet standardized study definitions and events not reported by the sites, but which were identified and confirmed through triggered events, review of adverse events and hospital admissions, or screening of laboratory data.

‡ CEC (-) events included site-reported events that were not confirmed in the adjudication process.
Principal Composite Outcome

Total patient pairs N=8,011,730

Contribution to number of wins (%)

CV Death
CEC (+) events
Wins N=459,367
Ties N=7,145,974
Losses N=406,389
36.9%

CV Death
CEC (-) events
Wins N=11,843
Ties N=7,128,713
Losses N=5,418
0.7%

1st HF Hospitalization
CEC (+) events
Wins N=399,680
Ties N=6,429,969
Losses N=339,064
29.8%

HF Hospitalization
CEC (-) events
Wins N=180,979
Ties N=6,086,579
Losses N=183,511
14.7%

1st Outpatient HF
CEC (+) events
Wins N=72,590
Ties N=6,949,297
Losses N=63,692
5.8%

1st Outpatient HF
CEC (-) events
Wins N=181,408
Ties N=5,666,461
Losses N=101,428
12.1%

Total wins: 1,265,767
Total losses: 1,079,502

Estimated unmatched win ratio* = 1.17 (95% CI, 1.03 to 1.33; P=0.015)

EJHF_2663_Figure 1_final.tif
Sensitivity Analysis 1

Total patient pairs: N=8,011,730

CV Death
CEC (+) events
- Wins: 459,367
- Ties: 7,146,974
- Losses: 406,389
- Contribution to number of wins (%): 35.3%

CV Death
CEC (-) events
- Wins: 11,843
- Ties: 7,128,713
- Losses: 5,418
- Contribution to number of wins (%): 0.7%

Total Number of H HF
CEC (+) events
- Wins: 390,139
- Ties: 6,368,120
- Losses: 370,454
- Contribution to number of wins (%): 31.0%

Total Number of H HF
CEC (-) events
- Wins: 191,208
- Ties: 6,002,420
- Losses: 174,492
- Contribution to number of wins (%): 14.9%

Total Number of O HF
CEC (+) events
- Wins: 86,158
- Ties: 6,848,088
- Losses: 68,714
- Contribution to number of wins (%): 6.3%

Total Number of O HF
CEC (-) events
- Wins: 185,896
- Ties: 5,559,874
- Losses: 102,318
- Contribution to number of wins (%): 11.8%

Total wins: 1,323,611
Total losses: 1,128,785

Estimated unmatched win ratio = 1.17 (95% CI, 1.03 to 1.33; P=0.014)
Sensitivity Analysis 2

All-cause Death

1st HF Hospitalization
CEC (+) events

1st HF Hospitalization
CEC (-) events

- Outpatient HF
CEC (+) events

1st Outpatient HF
CEC (-) events

Total patient pairs N=8,011,730

Wins N=556,989
Ties N=6,961,666
Losses N=493,055
Contribution to number of wins (%)
42.8%

Wins N=343,973
Ties N=6,288,939
Losses N=328,774
27.4%

Wins N=168,881
Ties N=5,967,153
Losses N=153,205
13.1%

Wins N=72,033
Ties N=5,831,977
Losses N=53,143
5.5%

Wins N=172,292
Ties N=6,559,049
Losses N=100,636
11.1%

Total wins: 1,313,868
Total losses: 1,138,813

Estimated unmatched win ratio = 1.15 (95% CI, 1.02 to 1.31; P = 0.024)

EJHF_2663_Figure 3_final.tif
Sensitivity Analysis 3

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Total Patient Pairs</th>
<th>Wins</th>
<th>Ties</th>
<th>Losses</th>
<th>Contribution to Number of Wins (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death CEC (+) events</td>
<td>N=8,011,730</td>
<td>368,770</td>
<td>7,304,589</td>
<td>338,371</td>
<td>32.8%</td>
</tr>
<tr>
<td>CV Death CEC (-) events</td>
<td>N=7,940</td>
<td>7,293,909</td>
<td>2,740</td>
<td>0.7%</td>
<td></td>
</tr>
<tr>
<td>1st HF Hospitalization CEC (+) events</td>
<td>N=338,603</td>
<td>6,652,761</td>
<td>302,545</td>
<td>30.1%</td>
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</tr>
<tr>
<td>1st HF Hospitalization CEC (-) events</td>
<td>N=168,155</td>
<td>6,326,136</td>
<td>158,470</td>
<td>15.0%</td>
<td></td>
</tr>
<tr>
<td>1st Outpatient HF CEC (+) events</td>
<td>N=62,520</td>
<td>6,206,308</td>
<td>57,308</td>
<td>5.6%</td>
<td></td>
</tr>
<tr>
<td>1st Outpatient HF CEC (-) events</td>
<td>N=178,311</td>
<td>5,929,380</td>
<td>58,617</td>
<td>15.9%</td>
<td></td>
</tr>
</tbody>
</table>

Total wins: 1,124,299
Total losses: 958,051

Estimated unmatched win ratio = 1.17 (95% CI, 1.02 to 1.35; P = 0.025)
Sensitivity Analysis 4

Total patient pairs N=8,011,730

CV Death
CEC (+) events

Wins N=453,367
Ties N=7,145,974
Losses N=406,389

Contribution to number of wins (%)

50.6%

1st HF Hospitalization
CEC (+) events

Wins N=352,411
Ties N=6,443,608
Losses N=339,955

40.0%

1st Outpatient HF
CEC (+) events

Wins N=85,369
Ties N=6,280,099
Losses N=68,140

9.4%

Total wins: 907,147
Total losses: 814,484

Estimated unmatched win ratio* = 1.11 (95% CI, 0.96 to 1.30; P=0.16)

EJHF_2663_Figure 5_final.tif
Sensitivity Analysis 5

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Total Patient Pairs</th>
<th>Contribution to Number of Wins (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Death CEC (+) events</td>
<td>N=8,011,730</td>
<td>36.9%</td>
</tr>
<tr>
<td>1st HF Hospitalization CEC (+) events</td>
<td></td>
<td>29.9%</td>
</tr>
<tr>
<td>1st Outpatient HF CEC (+) events</td>
<td></td>
<td>6.5%</td>
</tr>
<tr>
<td>CV Death CEC (-) events</td>
<td></td>
<td>0.6%</td>
</tr>
<tr>
<td>1st HF Hospitalization CEC (-) events</td>
<td></td>
<td>14.0%</td>
</tr>
<tr>
<td>1st Outpatient HF CEC (-) events</td>
<td></td>
<td>12.1%</td>
</tr>
</tbody>
</table>

Total wins: 1,265,690
Total losses: 1,079,579

Estimated unmatched win ratio = 1.17 (95% CI, 1.03 to 1.33; P = 0.015)