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RESEARCH ARTICLE

Sacubitril/valsartan versus ramipril for patients with acute myocardial infarction: win-ratio analysis of the PARADISE-MI trial

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Aim

The win ratio can incorporate different types of outcomes and enhance statistical power, making it a useful method for analysing 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 and results

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 analysed 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 events classification (CEC) committee as well as events identified by investigators that did not meet study definitions. Results were analysed by the unmatched win-ratio method. A win ratio that exceeds 1.00 reflects a better outcome. 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] 1.03–1.33; $p = 0.015$). 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 0.96–1.30; $p = 0.16$).

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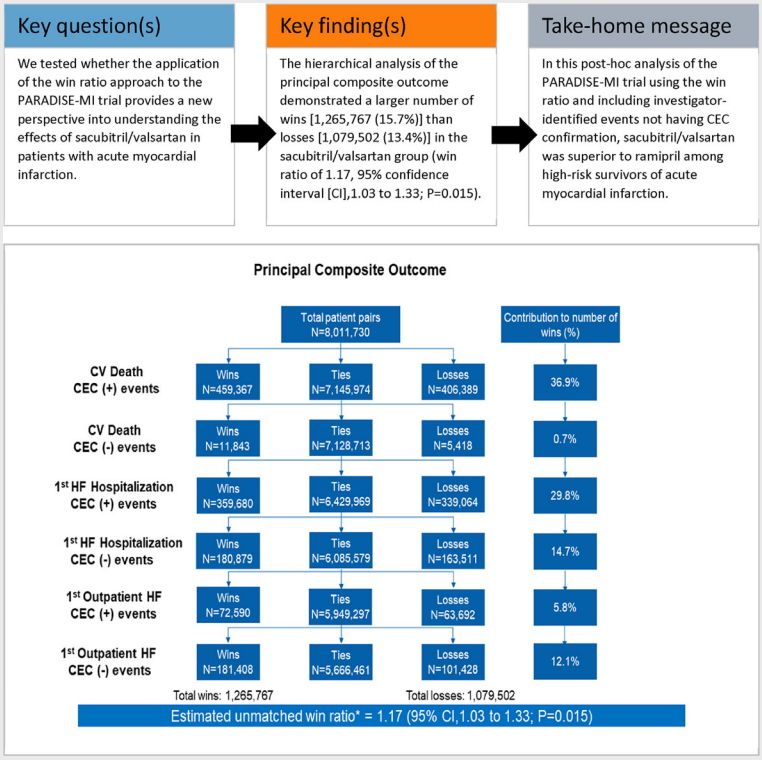
Conclusion In this post-hoc analysis of the PARADISE-MI trial using the win ratio and including investigator-identified events not having CEC confirmation, sacubitril/valsartan was superior to ramipril among high-risk survivors of acute myocardial infarction.

Graphical Abstract



PARADISE-MI win ratio analysis summary. CEC, clinical event classification; CI, confidence interval; CV, cardiovascular; HF, heart failure.

Keywords Acute myocardial infarction • Angiotensin receptor–neprilysin inhibition • Sacubitril/valsartan • Win ratio

Introduction

Analyses of composite endpoints are frequently used in the primary analysis of cardiovascular clinical trials.[1,2] Composite endpoints such as cardiovascular death or heart failure hospitalization usually incorporate non-fatal 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).[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.[4] Consequently, non-fatal events typically dominate the results of current cardiovascular trials.[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.[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 analysed first.[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.[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 [HR] 0.90; 95% confidence interval [CI] 0.78–1.04; $p = 0.17$).[9] 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 0.75–0.96; $p = 0.01$).[10]

When the primary outcome is not met, secondary analyses will not change the neutral results.[11] 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 totality of evidence across fatal and non-fatal outcomes into a hierarchical composite endpoint analysed 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.[8,9] Briefly, PARADISE-MI was an international, multicentre, 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 ≥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 ≤40%, pulmonary congestion that required intravenous treatment, or both conditions and had at least one of the following pre-specified risk-enrichment factors: age ≥70 years, diabetes mellitus, previous myocardial infarction, an estimated glomerular filtration rate (eGFR) of <60 ml/min/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-elevation myocardial infarction without reperfusion within 24 h after presentation.

Patients were excluded for haemodynamic instability during the 24 h preceding randomization, an eGFR <30 ml/min/1.73 m^2, a serum potassium level >5.2 mmol/L, a history of angioedema, or an inability to take an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Trial procedures

Patients were randomized in a 1:1 ratio, between 12 h 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 ACE-inhibitors and 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 analysed in the order of: (i) death due to cardiovascular causes based on CEC (+) events; (ii) death due to cardiovascular causes based on CEC (−) events; (iii) first hospitalization for heart failure based on CEC (+) events; (iv) first hospitalization for heart failure based on CEC (−) events; (v) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (+) events; and (vi) 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 analysed 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 analysed with the unmatched win-ratio method,[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 non-fatal 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 (online supplementary *Table Appendix 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.

Five sensitivity analyses were performed:

1. The hierarchical composite outcome included total (first and recurrent events), analysed in the order of: (i) death due to cardiovascular causes based on CEC (+) events; (ii) death due to cardiovascular causes based on CEC (−) events; (iii) total hospitalizations for heart failure based on CEC (+) events; (iv) total hospitalizations for heart failure based on CEC (−) events; (v) total outpatient symptomatic heart failure based on CEC (+) events; and (vi) total outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (−) events (online supplementary *Table S2*).
2. The hierarchical outcome included all-cause mortality, analysed in the order of: (i) all-cause death; (ii) first hospitalization for heart failure based on CEC (+) events; (iii) first hospitalization for heart failure based on CEC (−) events; (iv) first outpatient symptomatic heart failure based on CEC (+) events; and (v) first outpatient symptomatic heart failure based on CEC (−) events (online supplementary *Table S3*).
3. The principal analysis restricted to events that occurred during the first year of follow-up (online supplementary *Table S4*).
4. The principal analysis restricted to CEC (+) events (online supplementary *Table S5*).
5. The hierarchical composite outcome analysed in the order of: (i) death due to cardiovascular causes based on CEC (+) events; (ii) first hospitalization for heart failure based on CEC (+) events; (iii) first outpatient symptomatic heart failure treated with intravenous or sustained oral diuretic therapy based on CEC (+) events; (iv) death due to cardiovascular causes based on CEC (−) events; (v) first hospitalization for heart failure based on CEC (−) events; and (vi) 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 <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 5661 patients from 495 sites in 41 countries were randomized to either sacubitril/valsartan (n = 2830) or ramipril (n = 2831) 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 groups (*Table 1*). Left ventricular ejection fraction was ≤40% in 81.4% of patients, 54.0% had pulmonary congestion, and 35.5% had both features; also, 52.2% of patients had ≥1 pre-specified 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% CI 1.03–1.33; 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 (online supplementary *Figure Appendix S1*). Correspondingly, the cumulative win ratios in each tier suggest a consistent benefit of sacubitril/valsartan over ramipril (online supplementary *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 1.03–1.33; p = 0.014) (*Figure 2*).

Similarly, a hierarchical analysis of a composite outcome analysed 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 1.02–1.31; 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 1.02–1.35; p = 0.025) (*Figure 4*).

The win ratio for a hierarchical composite outcome that included only CEC (+) events was 1.11 (95% CI 0.96–1.30; 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*).

Table 1 Selected baseline characteristics of randomized patients

Characteristic	Sacubitril/valsartan (*n* = 2830)	Ramipril (*n* = 2831)
Age, years	64.0 ± 11.6	63.5 ± 11.4
Female sex	663 (23.4)	700 (24.7)
Race		
Asian	475 (16.8)	478 (16.9)
Black	35 (1.2)	40 (1.4)
Caucasian	2125 (75.1)	2138 (75.5)
Other	195 (6.9)	175 (6.2)
Heart rate, bpm	75.6 ± 11.8	75.7 ± 11.7
Systolic blood pressure, mmHg	120.8 ± 13.4	121.0 ± 13.2
Diastolic blood pressure, mmHg	73.8 ± 9.9	73.7 ± 9.7
Body mass index, kg/m^2	28.2 ± 5.0	28.1 ± 5.1
Left ventricular ejection fraction, %	36.4 ± 9.3	36.6 ± 9.6
Pulmonary congestion	1508 (53.3)	1548 (54.7)
>1 risk enrichment factors	1490 (52.7)	1464 (51.7)
Medical history		
Prior MI	463 (16.4)	457 (16.1)
Prior revascularization	471 (16.6)	463 (16.4)
Prior stroke	121 (4.3)	142 (5.0)
Hypertension	1845 (65.2)	1831 (64.7)
Diabetes	1221 (43.1)	1180 (41.7)
Current smoking	613 (21.7)	583 (20.6)
Atrial fibrillation/flutter	402 (14.2)	382 (13.5)
Serum creatinine, mg/dl	1.1 ± 0.3	1.1 ± 0.3
Estimated GFR, ml/min/1.73 m^2	71.7 ± 21.7	71.9 ± 23.1
Qualifying MI		
Type of MI		
STEMI	2153 (76.1)	2138 (75.5)
NSTEMI/other	677 (23.9)	693 (24.5)
Killip class ≥II	1595 (56.4)	1606 (56.7)
Time to randomization, days	4.3 ± 1.8	4.3 ± 1.7
Medical treatment at randomization	361 (12.8)	344 (12.2)
Dual antiplatelet therapy	2608 (92.2)	2614 (92.3)
Beta-blocker	2414 (85.3)	2413 (85.2)
Mineralocorticoid receptor antagonist	1155 (40.8)	1183 (41.8)
Diuretics	1271 (44.9)	1250 (44.2)
Statin	2674 (94.5)	2696 (95.2)
ACE-inhibitor/ARB[a]	2216 (78.3)	2220 (78.4)

Values are given as mean ± standard deviation, or *n* (%). Percentages may not total 100 because of rounding.
ACE, angiotensin-converting enzyme; ARB angiotensin receptor blocker; CV, cardiovascular; GFR glomerular filtration rate; HHF, hospitalization for heart failure; MI myocardial infarction; NSTEMI non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a]ACE-inhibitor or ARB use within 7 days before randomization.

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 and investigator-identified events not having CEC confirmation) (*Graphical Abstract*). 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 0.75–0.96, $p = 0.01$).[10] 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 favouring 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 non-fatal events was related to difficulties in obtaining detailed source documentation needed to

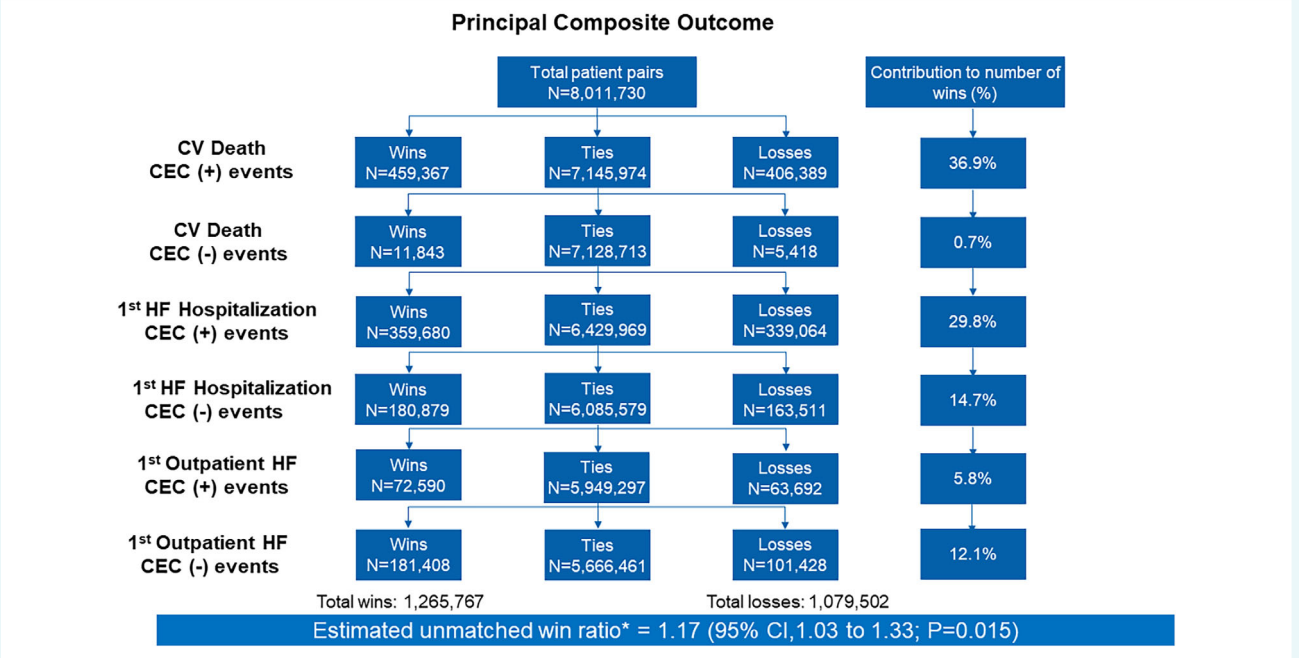


Figure 1 Use of win ratio in the PARADISE-MI trial for the hierarchical principal composite outcome of death due to cardiovascular (CV) causes, first hospitalization for heart failure (HF), and first outpatient symptomatic HF (considering information from both clinical events classification [CEC]-confirmed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

meet the strict endpoint definitions in a trial that had substantial follow-up occurring during the COVID-19 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 Food and Drug Administration approval.[7,12] 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 1.05–1.20; $p < 0.001$).[13,14] 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 favouring sacubitril/valsartan (95% CI 1.16–1.39; $p < 0.001$).[13,15] 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 favouring eplerenone (95% CI 1.05–1.27; $p = 0.0026$).[13,16] 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 analysed 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

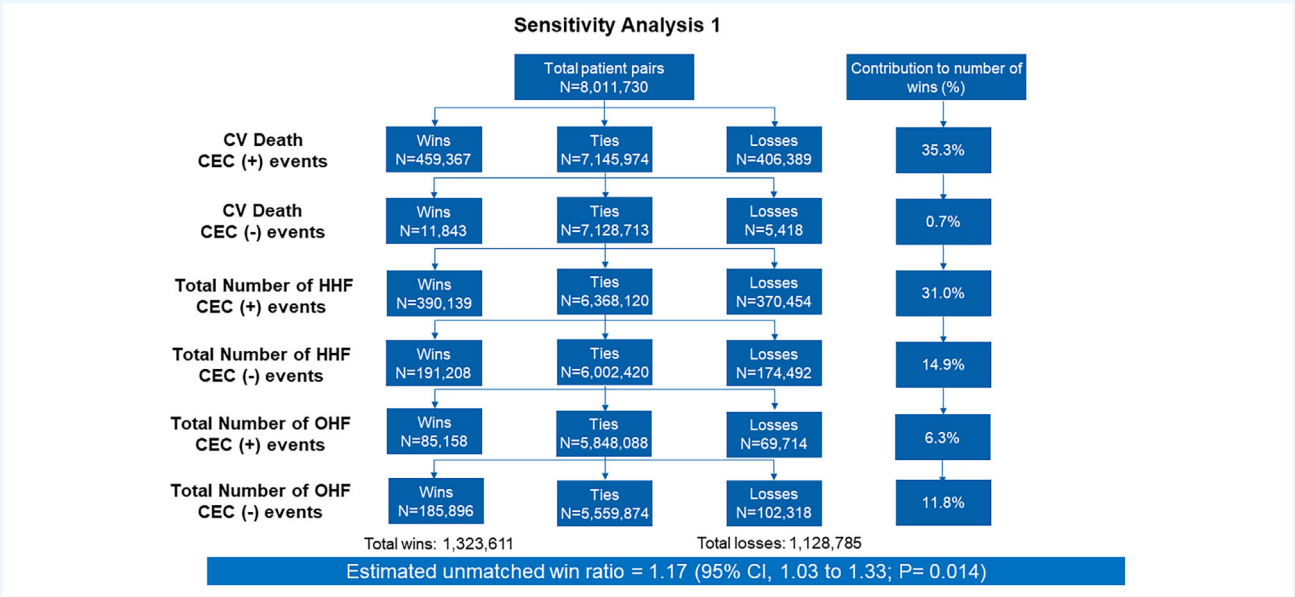


Figure 2 Use of win ratio in the PARADISE-MI trial for the hierarchical composite outcome of death due to cardiovascular (CV) causes, total hospitalization for heart failure (HHF), and total outpatient symptomatic HF (considering information from both clinical events classification [CEC]-confirmed events and events that did not meet CEC definitions). 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. CI, confidence interval; OHF, outpatient heart failure. 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.

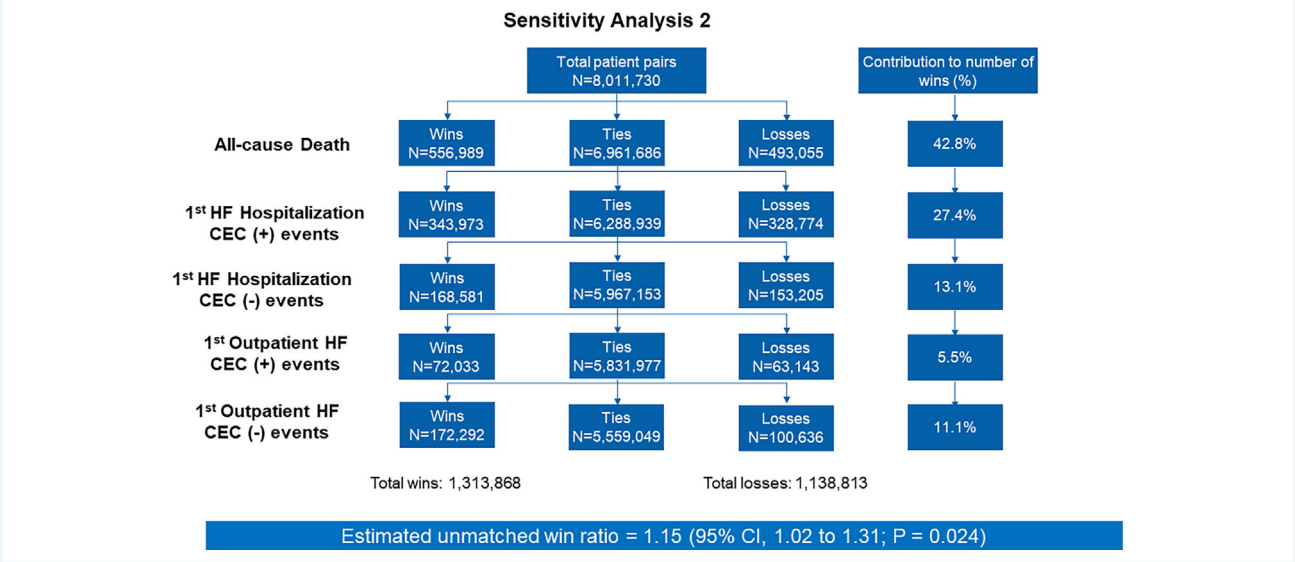


Figure 3 Use of win ratio in the PARADISE-MI trial for the hierarchical composite of all-cause death, first hospitalization for heart failure (HF), and first outpatient symptomatic HF (considering information from both clinical events classification [CEC]-confirmed events and events that did not meet CEC definitions). 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. CI, confidence interval. 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.

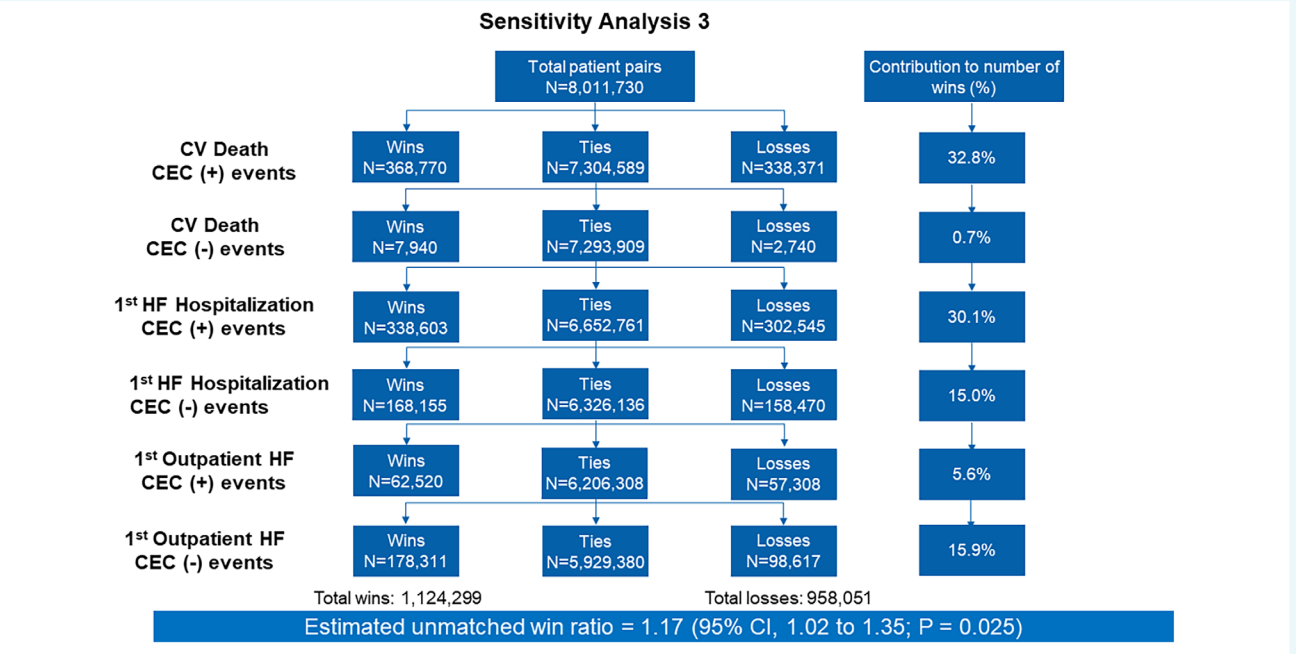


Figure 4 Use of win ratio in the PARADISE-MI trial for the principal composite outcome restricted to events that occurred during the first year of follow-up. CEC, clinical events classification; CI, confidence interval; CV, cardiovascular; HF, heart failure. CEC (+) events included both site-reported 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. 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.

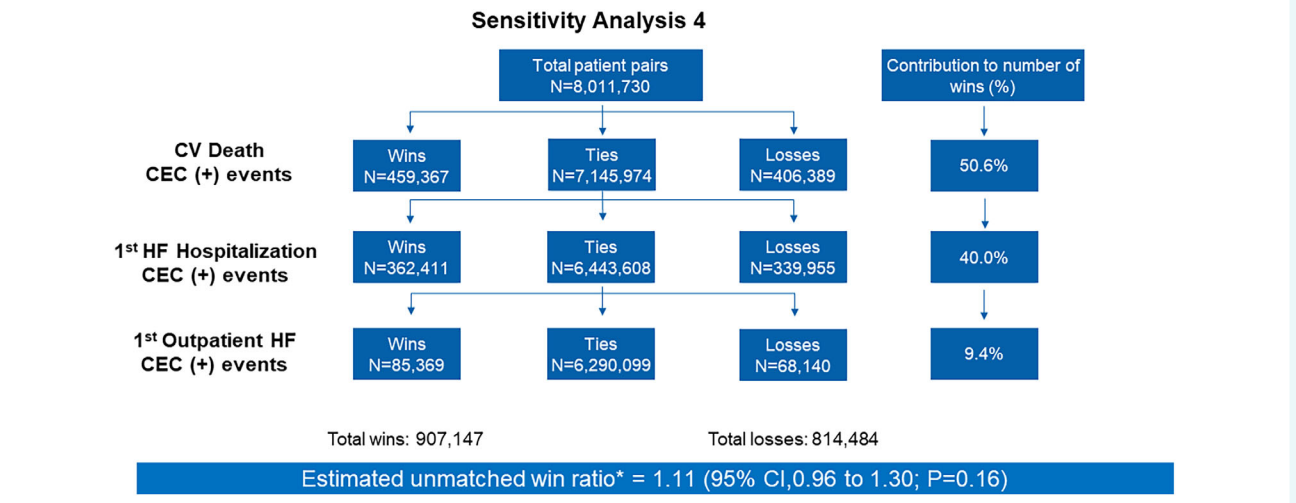


Figure 5 Use of win ratio in the PARADISE-MI trial for the hierarchical composite outcome of death due to cardiovascular (CV) causes, first hospitalization for heart failure (HF), and first outpatient symptomatic HF (based on clinical events classification [CEC]-confirmed events). CEC (+) events included 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. CI, confidence interval. 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.

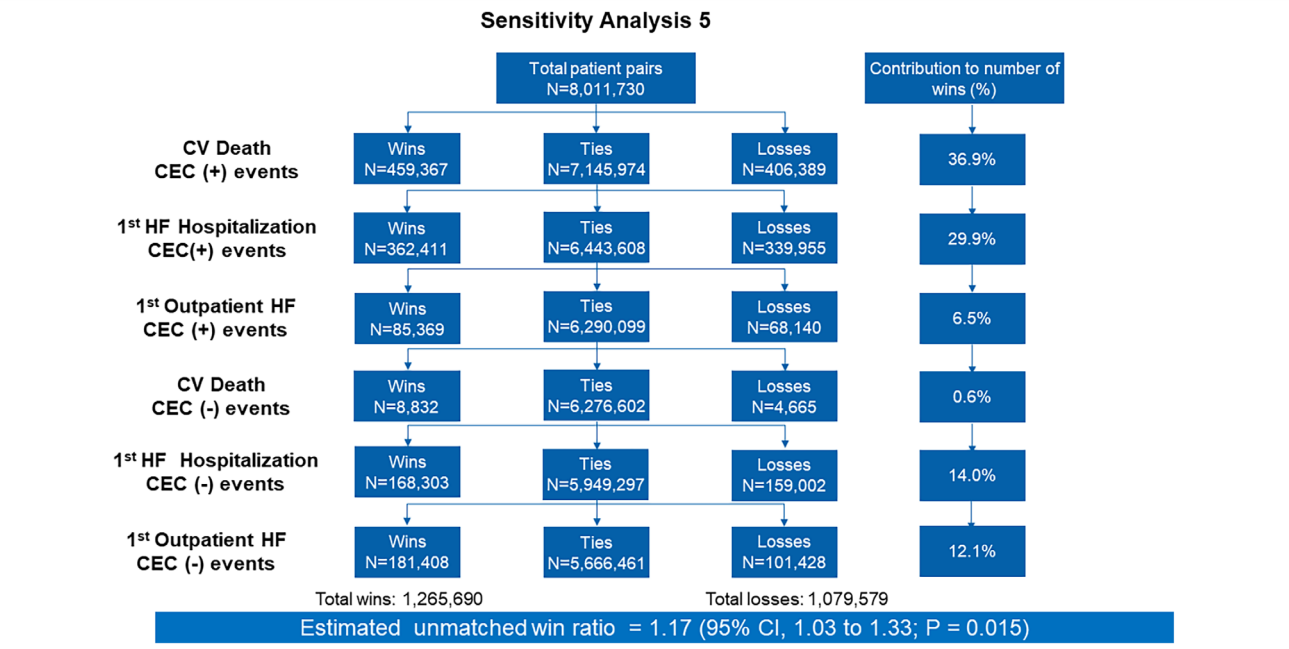


Figure 6 Use of win ratio in the PARADISE-MI trial for the hierarchical principal composite outcome of death due to cardiovascular (CV) causes, first hospitalization for heart failure (HF), and first outpatient symptomatic HF (considering information from both clinical events classification [CEC]-confirmed events and events that did not meet CEC definitions). 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. CI, confidence interval. 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.

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.[19] 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 is considered by some authors as being more efficient than unweighted win-ratio methods. On the other hand, 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.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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