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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.[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).[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, nonfatal 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 analyzed 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, 0.90; 95% confidence interval [CI], 0.78 to 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 to 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 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.[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 m2 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 m^2, 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 [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).[12] 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.[7] 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).[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 favoring sacubitril/valsartan (95% CI, 1.16 to1.39; 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 favoring eplerenone (95% CI, 1.05 to 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 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.[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 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

REFERENCES

1. Freemantle N, Calvert M, Wood J, Eastaugh J, Griffin C. Composite outcomes in randomized trials: greater precision but with greater uncertainty? JAMA. 2003; 289:2554–2559.

2. Lubsen J, Kirwan BA. Combined endpoints: can we use them? Stat Med. 2002; 21:2959–2970.

3. Montori VM, Permanyer-Miralda G, Ferreira-Gonzalez I, Busse JW, Pacheco-Huergo V, Bryant D, Alonso J, Akl EA, Domingo-Salvany A, Mills E, Wu P,Schunemann HJ, Jaeschke R, Guyatt GH. Validity of composite end points in clinical trials. BMJ. 2005; 330:594–596.

4. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133: 601–9.

5. Ferreira-Gonzalez I, Busse JW, Heels-Ansdell D, Montori VM, Akl EA, Bryant DM, Alonso-Coello P, Alonso J, Worster A, Upadhye S, Jaeschke R, Schunemann HJ, Permanyer-Miralda G, Pacheco-Huergo V, Domingo-Salvany A, Wu P, Mills EJ, Guyatt GH. Problems with use of composite end points in cardiovascular trials: systematic review of randomised controlled trials. BMJ. 2007; 334:786.

6. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J. 2012; 33:176–182.

7. Redfors B, Gregson J, Crowley A, McAndrew T, Ben-Yehuda O, Stone GW, Pocock SJ. The win ratio approach for composite endpoints: practical guidance based on previous experience. Eur Heart J. 2020; 41:4391-4399

8. Jering KS, Claggett B, Pfeffer MA, Granger C, Køber L, Lewis EF, Maggioni AP, Mann D, McMurray JJV, Rouleau JL, Solomon SD, Steg PG, van der Meer P, Wernsing M, Carter K, Guo W, Zhou Y, Lefkowitz M, Gong J, Wang Y, Merkely B, Macin SM, Shah U, Nicolau JC and Braunwald E. Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics. Eur J Heart Fail. 2021; 23:1040-1048.

9. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, Maggioni AP, Mann DL, McMurray JJV, Rouleau JL, Solomon SD, Steg PG, Berwanger O, Cikes M, De Pasquale CG, East C, Fernandez A, Jering K, Landmesser U, Mehran R, Merkely B, Vaghaiwalla Mody F, Petrie MC, Petrov I, Schou M, Senni M, Sim D, van der Meer P, Lefkowitz M, Zhou Y, Gong J and Braunwald E. Angiotensin receptor-neprilysin inhibition in acute myocardial infarction. N Engl J Med. 2021; 385:1845-1855.

10. Pfeffer MA, Claggett B, Lewis EF, Granger CB, Køber L, Maggioni AP, Mann DL, McMurray JJV, Rouleau JL, Solomon SD, Steg PG, Berwanger O, Cikes M, De Pasquale CG, Fernandez A, Filippatos G, Jering K, Landmesser U, Menon V, Merkely B, Petrie MC, Petrov I, Schou M, Senni M, Sim D, van der Meer P, Lefkowitz M, Zhou Y, Wang Y and Braunwald E. Impact of sacubitril/valsartan versus ramipril on total heart failure events in the PARADISE-MI Trial. Circulation. 2022; 145:87-89.

11. Pocock SJ, Stone GW. The primary outcome fails — what next? N Engl J Med. 2016; 375:861-870

12. Oakes D. On the win-ratio statistic in clinical trials with multiple types of event. Biometrika. 2016; 103:742–745.

13. Ferreira JP, Jhund PS, Duarte K, Claggett BL, Solomon SD, Pocock S, Petrie MC, Zannad F, McMurray JJV. Use of the win ratio in cardiovascular trials. JACC Heart Fail. 2020; 8:441–450.

14. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; 336:525-533

15. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K and Zile MR. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371:993-1004.

16. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J and Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med. 2003; 348:1309-1321

17. Dong G, Qiu J, Wang D, Vandemeulebroecke M. The stratified win ratio. J Biopharm Stat. 2018; 28:778–796.

Table 1. Selected Baseline Characteristics of Randomized Patients

Characteristic	Sacubitril-valsartan N=2830	Ramipril N=2831
Age – yrs	64.0 ± 11.6	63.5 ± 11.4
Female sex – no. (%)	663 (23.4%)	700 (24.7%)
Race – no. (%)		
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 – no. (%)	1508 (53.3%)	1548 (54.7%)
>1 risk enrichment factors – no. (%)	1490 (52.7%)	1464 (51.7%)
Medical history – no. (%)		
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/1.73m^2	71.7 ± 21.7	71.9 ± 23.1
Qualifying MI – no. (%)		
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 – no. (%)	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*	2216 (78.3%)	2220 (78.4%)

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

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*	2216 (78.3%)	2220 (78.4%)

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.

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.

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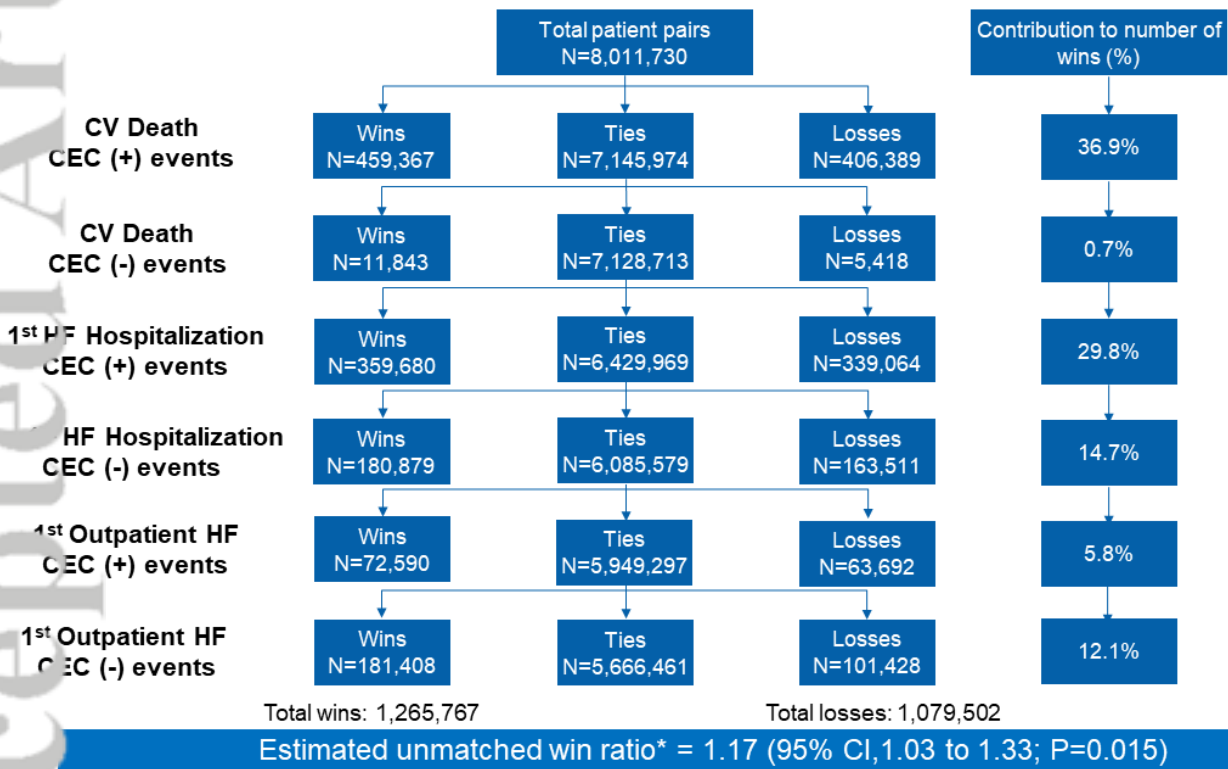
* The win ratio is given as the total number of winner pairs divided by the total number of loser pairs. In the present study, a win ratio > 1 indicates benefit of sacubitril/valsartan.

† 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.
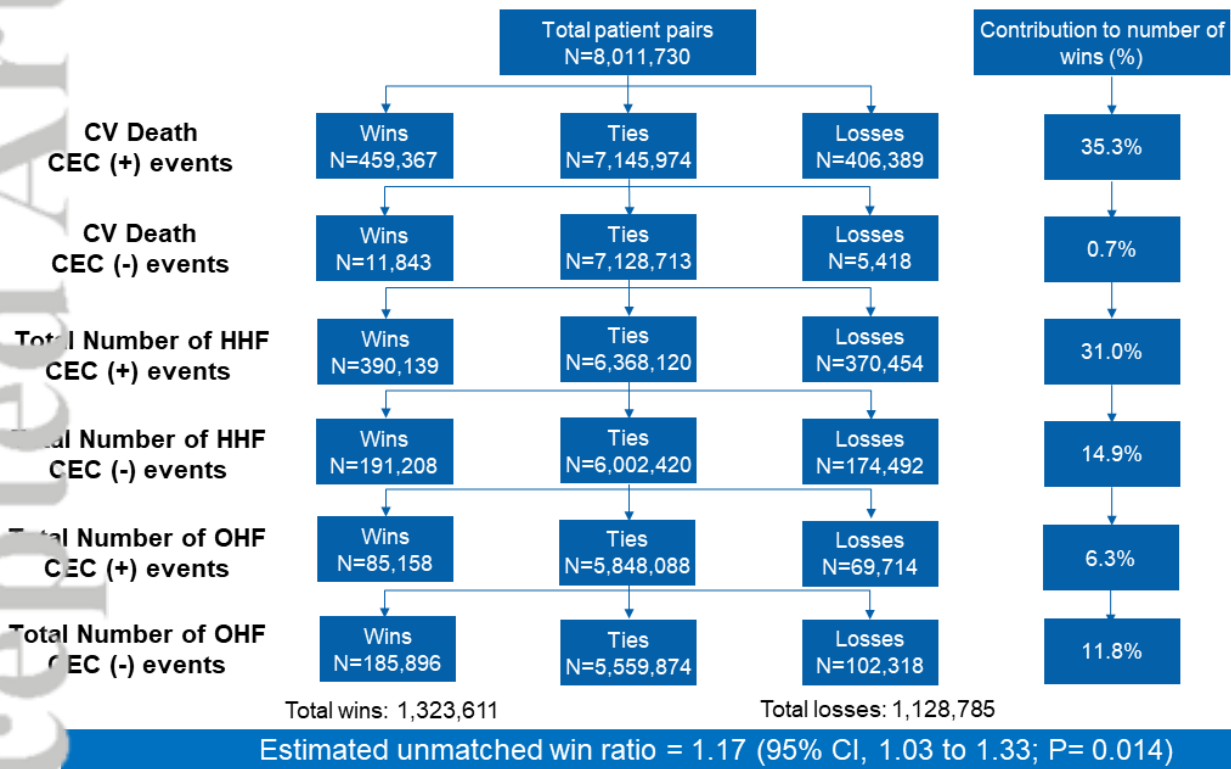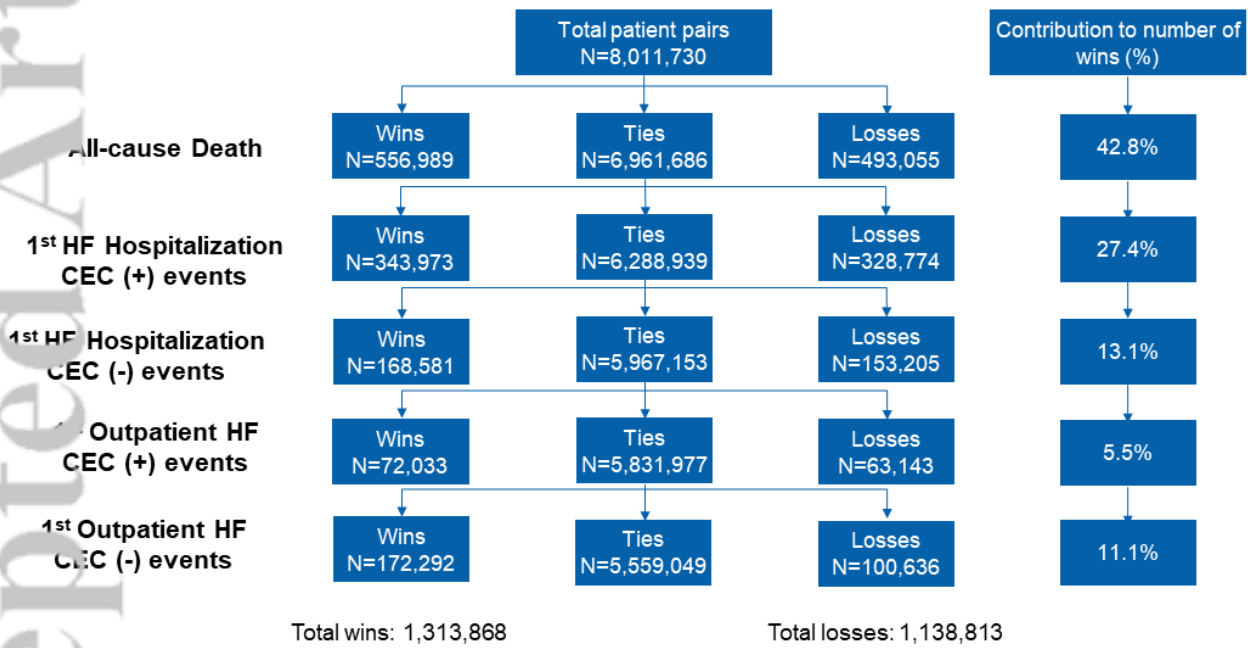
Principal Composite Outcome

EJHF_2663_Figure 1_final.tif

Sensitivity Analysis 1

	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	35.3%
CV Death **CEC (-) events**	Wins N=11,843	Ties N=7,128,713	Losses N=5,418	0.7%
Total Number of HHF **CEC (+) events**	Wins N=390,139	Ties N=6,368,120	Losses N=370,454	31.0%
Total Number of HHF **CEC (-) events**	Wins N=191,208	Ties N=6,002,420	Losses N=174,492	14.9%
Total Number of OHF **CEC (+) events**	Wins N=85,158	Ties N=5,848,088	Losses N=69,714	6.3%
Total Number of OHF **CEC (-) events**	Wins N=185,896	Ties N=5,559,874	Losses N=102,318	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)

EJHF_2663_Figure 2_final.tif

Sensitivity Analysis 2
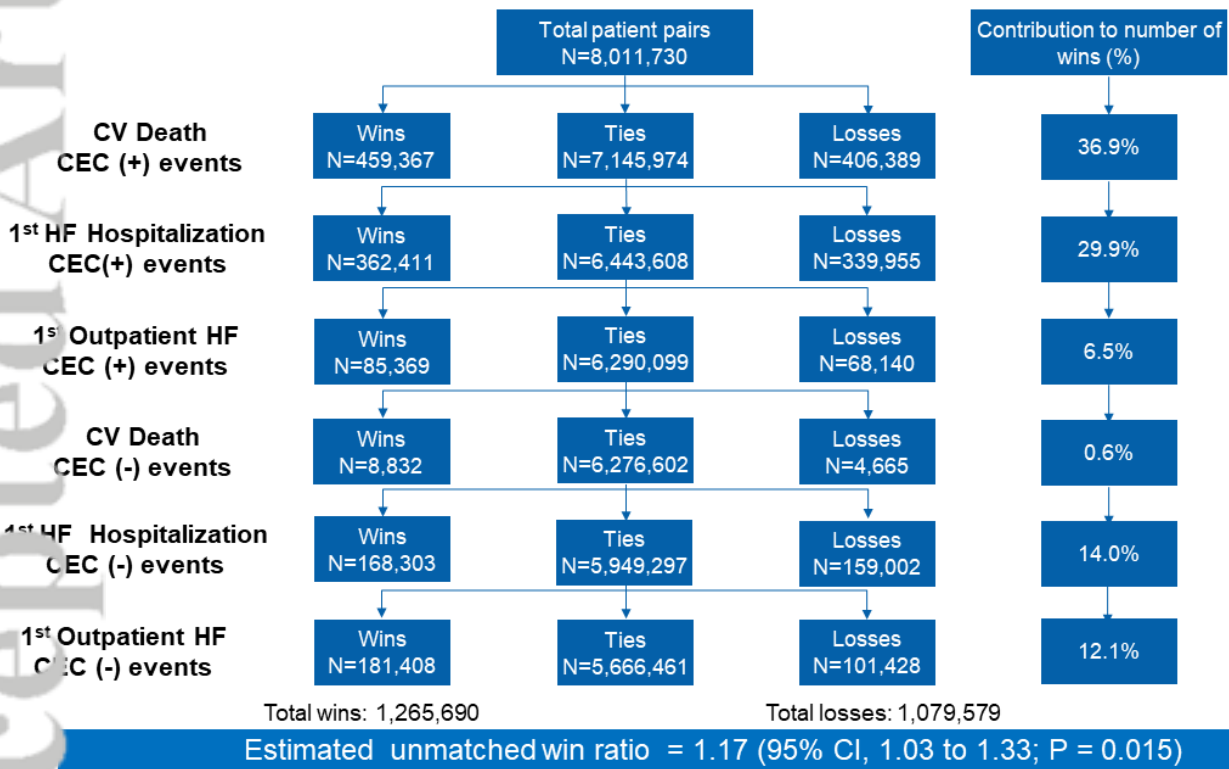
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Sensitivity Analysis 3
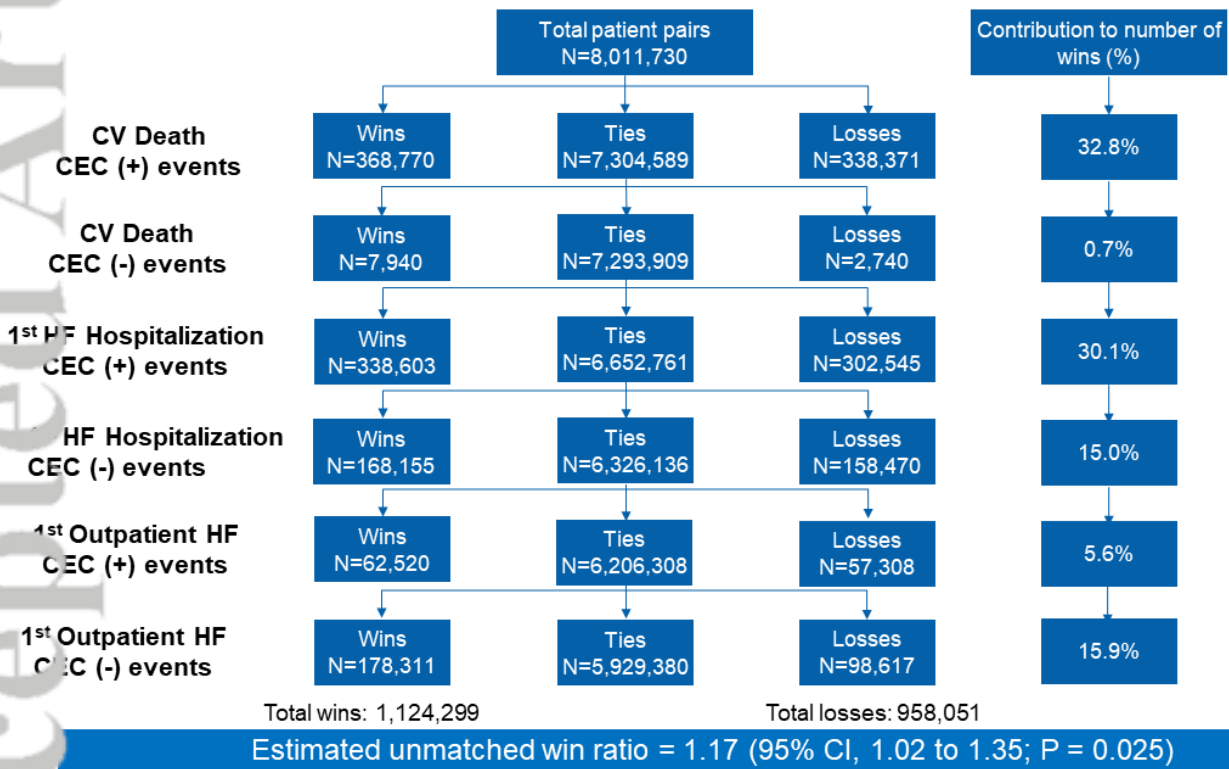
EJHF_2663_Figure 4_final.tif

Sensitivity Analysis 4

EJHF_2663_Figure 5_final.tif

Sensitivity Analysis 5

EJHF_2663_Figure 6_final.tif