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STUDY DESIGN

Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI): design and baseline characteristics

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Aims

Patients surviving an acute myocardial infarction (AMI) are at risk of developing symptomatic heart failure (HF) or premature death. We hypothesized that sacubitril/valsartan, effective in the treatment of chronic HF, prevents development of HF and reduces cardiovascular death following high-risk AMI compared to a proven angiotensin-converting enzyme (ACE) inhibitor. This paper describes the study design and baseline characteristics of patients enrolled in the Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI) trial.

Methods and results

PARADISE-MI, a multinational (41 countries), double-blind, active-controlled trial, randomized patients within 0.5–7 days of presentation with index AMI to sacubitril/valsartan or ramipril. Transient pulmonary congestion and/or left ventricular ejection fraction (LVEF) ≤40% and at least one additional factor augmenting risk of HF or death (age ≥70 years, estimated glomerular filtration rate <60 mL/min/1.73 m^2, diabetes, prior myocardial infarction, atrial fibrillation, LVEF <30%, Killip class ≥III, ST-elevation myocardial infarction without reperfusion) were required for inclusion. PARADISE-MI was event-driven targeting 708 primary endpoints (cardiovascular death, HF hospitalization or outpatient development of HF). Randomization of 5669 patients occurred 4.3 ± 1.8 days from presentation with index AMI. The mean age was 64 ± 12 years, 24% were women. The majority (76%) qualified with ST-segment elevation myocardial infarction; acute percutaneous coronary intervention was performed in 88% and thrombolysis in 6%. LVEF was 37 ± 9% and 58% were in Killip class ≥II.

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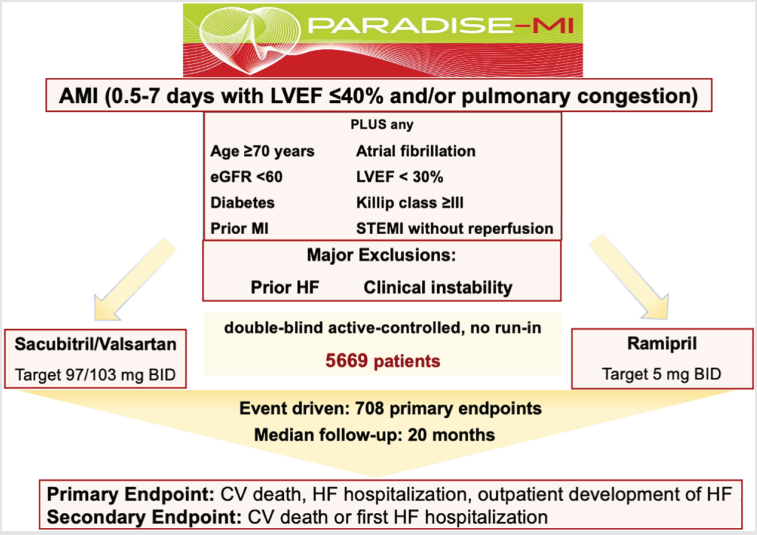
Conclusions Baseline therapies in PARADISE-MI reflect advances in contemporary evidence-based care. With enrollment complete PARADISE-MI is poised to determine whether sacubitril/valsartan is more effective than a proven ACE inhibitor in preventing development of HF and cardiovascular death following AMI.

Graphical Abstract



PARADISE-MI study design. AMI, acute myocardial infarction; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.

Keywords Acute myocardial infarction • Heart failure • Angiotensin-converting enzyme inhibitor • Angiotensin receptor–neprilysin inhibitor • Sacubitril/valsartan

Introduction

Across the broad spectrum of acute myocardial infarction (AMI), prompt initiation of guideline-proven therapies has resulted in reduced in-hospital mortality.[1–4] However, patients with transient pulmonary congestion and/or reduced left ventricular ejection fraction (LVEF) remain at augmented risk for developing chronic heart failure and/or death following discharge.[5] This higher risk segment of the AMI population has been the focus of several international randomized placebo-controlled clinical trials of angiotensin-converting enzyme inhibitors (ACEi), demonstrating effectiveness in reducing rates of cardiovascular death as well as the development of heart failure following AMI.[6–9]

With the subsequent development of angiotensin receptor blockers (ARBs), it was hypothesized that this more selective mode of inhibiting the renin–angiotensin system (RAS) may provide greater efficacy and tolerability than ACEi.[10] This hypothesis was tested in two large randomized trials comparing an ARB to a proven ACEi in patients with a recent AMI with additional risk augmenting characteristics.[11,12] Although neither trial demonstrated superiority, one specifically designed to test for non-inferiority showed that valsartan preserved the clinical benefits achieved by treatment with an ACEi.[12] Additionally, the combination of both ACEi and ARB resulted in more adverse drug-related events without further improvement in clinical outcomes, indicating that higher doses of these RAS inhibitors (RASi) would not be expected to produce additional benefits.[12] International guidelines and quality monitoring metrics of major societies reflect these findings with recommendations to use either an ACEi or an ARB but not both as a component of comprehensive medical therapy for AMI.[1–4]

Sacubitril/valsartan is a first-in class angiotensin receptor–neprilysin inhibitor (ARNI) combining the ARB valsartan with sacubitril, a neprilysin inhibitor. Sacubitril/valsartan simultaneously blocks the effects of the angiotensin II type 1 receptor through valsartan and inhibits the breakdown of several vasoactive peptides that are degraded by neprilysin, including the biologically active natriuretic peptides.[13] In patients with heart

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failure with reduced ejection fraction, sacubitril/valsartan reduced cardiovascular death and heart failure hospitalization, and all-cause mortality, in comparison with a proven ACEi.[14,15] In a more recent large clinical outcome trial in patients with heart failure with preserved ejection fraction, this ARNI also reduced rates of heart failure hospitalization relative to valsartan.[16]

Patients surviving an AMI, particularly those with features of higher risk of subsequent heart failure development, constitute an expanding population of individuals in jeopardy of developing symptomatic heart failure or premature death.

Prospective ARNI vs. ACE inhibitor trial to DetermIne Superiority in reducing heart failure Events after Myocardial Infarction (PARADISE-MI) was designed to determine whether sacubitril/valsartan would be superior to ramipril in reducing the composite endpoint of cardiovascular death, heart failure hospitalization or outpatient development of heart failure.[17] This paper provides the design features and baseline characteristics of the patients enrolled in PARADISE-MI. This article is submitted prior to final database lock, and no information regarding treatment assignment is available. Also, minor changes may occur when the results are presented.

Methods

PARADISE-MI was a multinational (41 countries, 495 sites) (online supplementary *Appendix A*) double-blind, double dummy, randomized, active-controlled trial of AMI patients. Consenting women and men ≥18 years of age without known prior heart failure were randomized 0.5 to 7 days after presentation with a spontaneous AMI (online supplementary *Appendix B*). Patients were required to have either evidence of left ventricular systolic dysfunction (LVEF ≤40%) and/or transient pulmonary congestion requiring intravenous treatment during the index event and at least one of the following eight pre-defined risk augmenting factors (online supplementary *Appendix B*): (i) age ≥70 years; (ii) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 at screening; (iii) diabetes mellitus; (iv) prior myocardial infarction; (v) atrial fibrillation associated with the index AMI; (vi) LVEF <30% associated with the index myocardial infarction; (vii) Killip class III or IV (defined in online supplementary *Appendix B*) associated with the index AMI requiring temporary intravenous treatment; or (viii) ST-segment elevation myocardial infarction (STEMI) without reperfusion therapy within the first 24 h after presentation.

Key exclusion criteria, in addition to prior heart failure, were clinical instability at the time of randomization (requiring intravenous diuretics, vasopressors or inotropic agents in the 24 h preceding randomization), eGFR <30 mL/min/1.73 m^2, serum potassium >5.2 mmol/L, history of angioedema, and intolerance to ACEi or ARB (full list of exclusion criteria in online supplementary *Appendix C*). The study complies with the Declaration of Helsinki. Locally appointed ethics committees approved the study protocol and all participants provided written informed consent.

Eligible, consenting patients were randomized in a 1:1 ratio via an interactive response technology to double-blind treatment with either sacubitril/valsartan or ramipril. Randomization was stratified by type of myocardial infarction (STEMI vs. non-STEMI) and geographic region (with a full list of countries included in each region provided in online supplementary *Appendix D*). Three matching blinded dose levels were supplied for each treatment arm. For ramipril, dose levels 1, 2 and 3 were 1.25 mg, 2.5 mg and 5 mg, respectively. The matching doses for sacubitril/valsartan were 50 mg (sacubitril/valsartan 24/26 mg), 100 mg (sacubitril/valsartan 49/51 mg) and 200 mg (sacubitril/valsartan 97/103 mg), corresponding to dose levels 1, 2 and 3, respectively. The aim was to achieve dose level 3, with both up- and down-titrations permitted to manage patient safety and tolerability. PARADISE-MI did not include a run-in period that would have assessed drug tolerability prior to randomization. The target dose of sacubitril/valsartan in PARADISE-MI was selected to provide equivalent exposure as valsartan 160 mg bid, the target dose of valsartan in the Valsartan in Acute Myocardial Infarction (VALIANT) trial.[12] Study medication in PARADISE-MI was to be administered twice daily. Initiation of either dose level 1 or 2 was at the investigator's discretion depending on clinical status and history of prior RASi use. Background therapy in PARADISE-MI was individualized by the treating physician without prohibition of guideline-recommended therapy except for the use of ACEi or ARB. Follow-up visits were scheduled for weeks 1, 2 and 4, then at months 2 and 4, and thereafter at 4-month intervals.

To minimize the potential risk of angioedema, patients who were randomized to sacubitril/valsartan, but who were previously treated with an ACEi during the 36 h prior to randomization, received two doses of valsartan as a bridge for their first study day before beginning their long-term double-blind sacubitril/valsartan treatment in a manner that maintained blinding to treatment assignment.

The primary objective of PARADISE-MI was to determine whether sacubitril/valsartan would be superior to ramipril in reducing the incidence of cardiovascular death, heart failure hospitalization or outpatient development of heart failure, in a time-to-first event analysis. The first of the secondary outcomes was a double composite of cardiovascular death or heart failure hospitalization. Additional secondary objectives were to assess the effects of sacubitril/valsartan compared to ramipril for the time to first occurrence of: heart failure hospitalization or outpatient heart failure (delaying new onset of symptomatic heart failure); the composite of cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke; and the cumulative number of composite events, including hospitalizations (first and recurrent) due to heart failure, non-fatal myocardial infarction, stroke plus cardiovascular deaths (online supplementary *Appendix E*) (*Graphical Abstract*).

Statistics

PARADISE-MI was designed as an event-driven trial. Enrolled patients were to be followed until at least 708 patients had experienced a primary event of cardiovascular death, heart failure hospitalization or outpatient development of heart failure, and at least 592 patients had experienced the double composite endpoint of cardiovascular death or heart failure hospitalization (online supplementary *Appendix E*). This number of primary composite events provided 80% power to detect a relative risk reduction (RRR) of 19% (i.e. a hazard ratio of 0.81) with a 5% two-sided type I error rate. It was anticipated that the required number of double composite events of cardiovascular death or heart failure hospitalization would provide 78% nominal power assuming a true RRR of 20% for this secondary endpoint. We estimated that 5650 patients, followed for a mean duration of about 19 months, would be needed to provide the necessary number of confirmed endpoints to test the study hypothesis.

Upon study completion, the primary composite endpoint of cardiovascular death, heart failure hospitalization or outpatient development of heart failure, will be analyzed using a Cox proportional hazards regression model, stratified by type of myocardial infarction with treatment, percutaneous coronary intervention (PCI) use at baseline and

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region included as factors in the model. Together with the primary endpoint, the secondary endpoints will be assessed according to a hierarchical testing procedure in the order specified above and in online supplementary *Appendix E* to control the type I error.

Of 23 pre-specified subgroups of interest (online supplementary *Appendix D*), the classification of patients according to the number of qualifying risk augmenting factors will be considered to be of greatest importance with particular attention given to the patients qualifying with two or more of the eight factors.

Safety will be assessed by tracking adverse events and serious adverse events. Hypotension, hyperkalaemia, renal dysfunction, cough and angioedema will be specifically queried. An analysis on death from all causes is pre-specified.

In addition to clinical events, PARADISE-MI will also assess potential differences in health status between the two therapies using the EuroQol five dimensions (EQ-5D) administered at week 1, month 4, month 12, month 24 and at the end of the trial, with the change from first measurement to 1 year considered the principal analysis.

Mechanistic insights will be explored from an echocardiographic substudy of approximately 475 patients in sinus rhythm with the objective of determining whether sacubitril/valsartan has greater measurable impact on attenuating the adverse cardiac structural changes (remodeling) associated with a myocardial infarction. Eligible participants underwent echocardiography using a study-specific protocol at randomization and repeated after 8 months. Echocardiograms were analysed in a blinded fashion at a core laboratory (Brigham and Women's Hospital, Boston, MA). The change in LVEF and in left atrial volume are the coprimary outcomes for this substudy. In approximately one-third of the echocardiographic substudies, lung ultrasound was also performed with the objective of evaluating changes in pulmonary congestion over the first 8 months based on the presence of B-lines across the lung fields. A biorepository collecting and storing plasma samples at baseline, day 14 and month 8 was also established for assessing the associations between biomarkers and risk of adverse outcomes as well as comparing the effects of the two study drugs.

The unforeseen coronavirus disease 2019 (COVID-19) pandemic erupted during the active blinded follow-up phase of PARADISE-MI, having the potential to negatively impact several aspects of trial conduct. When evaluating the chronologic and geographic activity of SARS-CoV-2 infections, study activity prior to 1 March 2020 was considered minimally affected. As such, a second interim analysis (besides the one originally planned at approximately two-thirds of the target number of primary endpoints) with appropriate alpha spending was conducted considering only data occurring prior to that date. In the absence of a Data and Safety Monitoring Committee recommendation for early termination, that date will also be used after final database lock for a pre-specified sensitivity analysis to understand the potential impact of COVID-19 on the results of PARADISE-MI (online supplementary *Appendix F*).

Results

Between 9 December 2016 and 16 March 2020, 5669 patients were randomized. Randomization occurred 4.3 ± 1.8 days from index AMI presentation. The mean age was 63.7 ± 11.5 years, with 1055 (18.6%) aged 75 years or older. Overall, 1367 (24.1%) of those enrolled were women (*Table 1*).

In 3061 (54.0%) patients, eligibility was by pulmonary congestion (irrespective of LVEF); 4615 (82.6%) had LVEF ≤40% and 972 (17.4%) had an LVEF >40% and were eligible due to pulmonary congestion alone (*Figure 1*).

Table 1 Baseline demographic characteristics and medical history

Characteristic	
Patients, *n*	5669
Demographics	
Mean age, years	63.7 ± 11.5
Age ≥65 years	2830 (49.9%)
Age ≥75 years	1055 (18.6%)
Female sex	1367 (24.1%)
Race	
Asian	956 (16.9%)
Black	75 (1.3%)
Caucasian	4267 (75.3%)
Other	371 (6.5%)
Geographic region	
Asia/Pacific	1105 (19.5%)
Central Europe	1499 (26.4%)
Latin America	680 (12.0%)
North America	528 (9.3%)
Western Europe	1857 (32.8%)
Medical history (%)	
Prior heart failure – excluded	
Prior stroke	263 (4.6%)
Previous myocardial infarction	948 (16.7%)
Prior percutaneous coronary intervention	825 (14.6%)
Prior coronary artery bypass	204 (3.6%)
Hypertension	3672 (64.8%)
Hyperlipidemia	2959 (52.3%)
Diabetes	2400 (42.3%)
Current tobacco use	1199 (21.2%)
Atrial fibrillation	723 (12.8%)
Peripheral artery disease	342 (6.0%)
Implantable cardioverter-defibrillator	21 (0.4%)
Chronic obstructive pulmonary disease	338 (6.0%)
Cancer	330 (5.8%)
Depression	328 (5.8%)

Of the eight inclusion factors designed to augment risk, 2697 patients (47.6%) had one risk augmenting factor, 1744 (30.8%) had two and 1228 (21.7%) three or more of the eight designated risks. Diabetes, present in 2400 patients (42.3%), and age over 70 years, present in 1973 patients (34.8%), were the most common of these eight inclusion factors (*Table 2*).

For 4294 (75.7%) patients, the qualifying myocardial infarction was ST-segment elevation and for 1375 (24.3%) non-ST-segment elevation. ECG infarct location was categorized as anterior in 3853 (68.0%), inferior in 1059 (18.7%), and classified as other in 757 (13.3%). A PCI was performed in 5007 (88.3%) patients, with a drug-eluting stent placed in 4374 (90.5%) of the patients who underwent PCI (*Table 3*). ACEi or ARBs were used in 86.5% during the AMI prior to randomization (*Table 4*).

As anticipated, during the 30 years since the introduction of ACEi for the treatment of high-risk AMI patients, major changes in the baseline characteristics and management have occurred.

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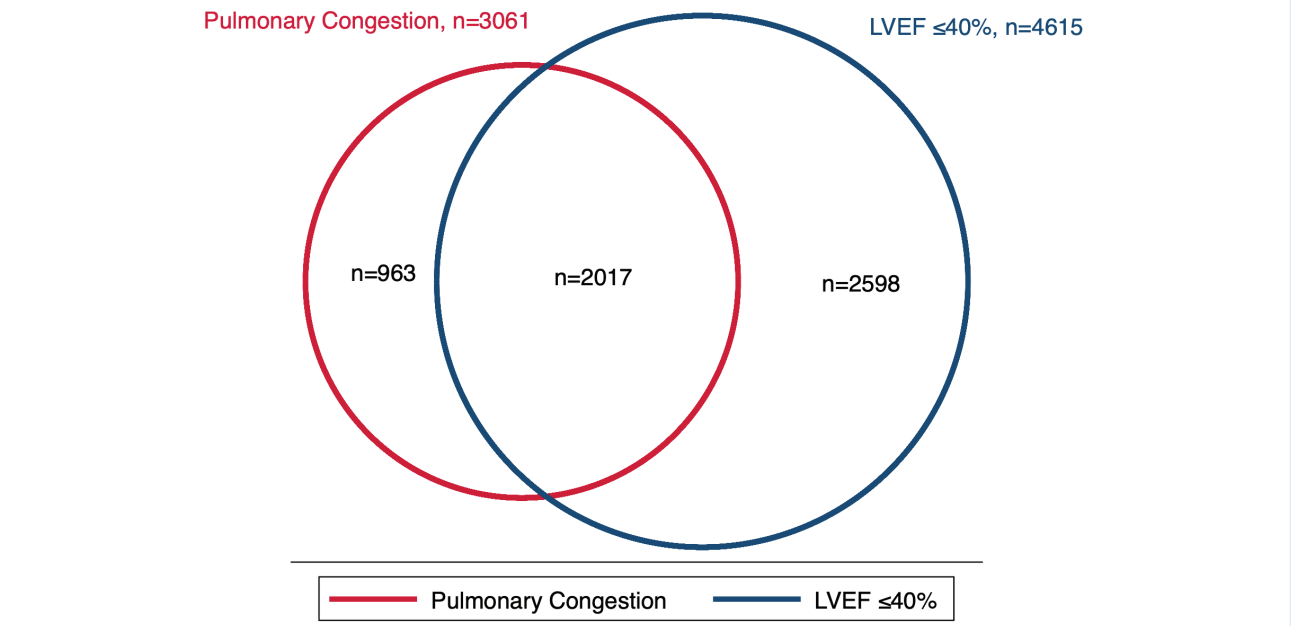

Figure 1 Number of patients qualifying with transient pulmonary congestion requiring intravenous therapy and/or with left ventricular systolic dysfunction [left ventricular ejection fraction (LVEF) ≤40%]. Of the 5669 randomized patients, 91 could not be classified according to this scheme.

Table 2 Risk augmenting factors present at the time of the qualifying myocardial infarction

Characteristic[a]	
Number of risk augmenting factors	
≤1	2697 (47.6%)
2	1744 (30.8%)
≥3	1228 (21.7%)
Risk augmenting factors	
Age ≥70 years	1973 (34.8%)
eGFR <60 mL/min/1.73 m^2 at screening	1364 (24.1%)
Diabetes	2400 (42.3%)
Prior MI	919 (16.2%)
Atrial fibrillation (with index MI)	518 (9.1%)
LVEF <30% (with index MI)	1206 (21.3%)
Killip class ≥III (with index MI)	1435 (25.3%)
STEMI without reperfusion within 24 h of presentation	524 (9.2%)

eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; MI, myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a]Investigator-reported and may differ from *Table 1* based on definitions used.

The baseline characteristics of patients enrolled in the major randomized trials of ACEi and of ARB and PARADISE-MI are summarized in *Table 5*. This information is shown without statistical comparisons to offer an appreciation of the alterations in evidence-based practice changing treatment. Despite the higher proportion of patients with diabetes in PARADISE-MI, the greater use of PCI, beta-blockers, statins and dual antiplatelet therapy would be anticipated to result in lower event rates in the current study. As such, PARADISE-MI is poised to determine whether replacing an ACEi with sacubitril/valsartan provides a meaningful advance in preventing heart failure and reducing cardiovascular death in a population of AMI patients with features of augmented risk receiving contemporary treatment.

Discussion

The aging of populations and the rising incidence of diabetes are anticipated to contribute to a further increase of the public health burden of AMI.[18] Fortunately, there have been concomitant improvements in the utilization of recent therapeutic and procedural advances of AMI care that have collectively reduced in-hospital mortality.[1–4] National registries of AMI patients show clear reductions in 30-day mortality, which coincide with greater use of reperfusion, statins, beta-blockers, ACEi or ARBs, as well as antiplatelet agents.[19,20] Of these additive advances, prompt uptake of effective reperfusion strategies, particularly primary PCI with stenting, has been shown to be a major contributor to these improvements in 30-day survival rates.[19,21]

These temporal improvements in AMI management have expanded the pool of myocardial infarction survivors at heightened risk for the development of symptomatic heart failure during the chronic phase.[22,23] Whether the diagnosis of heart failure is made accompanying a hospitalization or in the outpatient setting, the transition from asymptomatic at risk to clinically recognized heart failure is associated with a multifold higher rate of death.[6,24–26] Therapies shown to be effective in treating

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Table 3 Characteristics of the qualifying myocardial infarction

Characteristic	
STEMI	4294 (75.7%)
NSTEMI/other	1375 (24.3%)
Infarct location	
Anterior	3853 (68.0%)
Inferior	1059 (18.7%)
Other	757 (13.3%)
LVEF ≤40%	4615 (82.6%)
Pulmonary congestion requiring intravenous treatment	3061 (54.0%)
Time from presentation to randomization, days	4.3 ± 1.8
Killip class	
I	2282 (40.2%)
II	1773 (31.3%)
III	1138 (20.1%)
IV	297 (5.2%)
Missing	179 (3.2%)
Acute reperfusion	5067 (89.4%)
Thrombolytic therapy	307 (6.2%)
Percutaneous coronary intervention	5007 (88.3%)
Stent placement	4776 (84.3%)
Bare metal stent	440 (7.8%)
Drug-eluting stent	4374 (77.2%)
Medication use for the qualifying AMI	
Aspirin	5582 (98.5%)
P2Y12 inhibitor	5562 (98.1%)
Glycoprotein IIb/IIIa inhibitor	1100 (19.4%)
Antithrombin agents[a]	4556 (80.4%)
Intravenous diuretic	2646 (46.7%)
Intravenous vasodilator	1063 (18.8%)
Intravenous inotrope	299 (5.3%)
Intravenous vasopressor	276 (4.9%)

AMI, acute myocardial infarction; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-elevation myocardial infarction; STEMI, ST-elevation myocardial infarction.
[a]Examples of antithrombin agents include unfractionated heparin, low molecular weight heparin, and direct thrombin inhibitors.

Table 4 Clinical characteristics and concomitant medication use at randomization

Characteristic	
Heart rate, bpm	75.7 ± 11.8
Systolic blood pressure, mmHg	120.9 ± 13.3
Diastolic blood pressure, mmHg	73.8 ± 9.8
Body mass index, kg/m^2	28.1 ± 5.0
eGFR, mL/min/1.73 m^2	71.8 ± 22.4
Medication use at randomization	
Beta-blocker	4826 (85.1%)
Aldosterone antagonist	2341 (41.3%)
Oral diuretic	2524 (44.5%)
Statin	5373 (94.8%)
Other lipid-lowering therapy	200 (3.5%)
Nitrate	1154 (20.4%)
Cardiac glycoside	94 (1.7%)
Calcium channel blocker	513 (9.0%)
Anticoagulation	2147 (37.9%)
Antiarrhythmic drug	312 (5.5%)
Diabetes therapy	1896 (33.4%)
Insulin	921 (16.2%)
Oral antidiabetic agent	1411 (24.9%)
ACEi, during treatment of the index MI	3481 (61.4%)
ARB, during treatment of the index MI	1425 (25.1%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; MI, myocardial infarction.

symptomatic heart failure such as ACEi, beta-blockers and mineralocorticoid receptor antagonists when formally tested in AMI populations have also been shown to prevent heart failure and reduce subsequent cardiovascular mortality.[6–9,27,28]

Sacubitril/valsartan has been shown to be superior to the ACEi enalapril in reducing rates of death and heart failure hospitalizations in patients with symptomatic heart failure and reduced ejection fraction.[14] In patients with symptomatic heart failure with preserved ejection fraction, rates of hospitalization for heart failure were reduced with sacubitril/valsartan compared to the ARB valsartan.[16] The totality of evidence from these two trials recently led to an expanded indication by the Food and Drug Administration for the use of sacubitril/valsartan 'to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with LVEF below normal'.[29] However, a prospective randomized clinical trial in an AMI population is needed to ascertain whether sacubitril/valsartan prevents the development of heart failure and reduces cardiovascular deaths when compared to a previously proven RASi.

To address this question, PARADISE-MI was designed to compare sacubitril/valsartan to an active comparator with proven effectiveness in this target population. Three ACEi (captopril, trandolapril and ramipril) have been shown to improve survival and prevent heart failure in prior placebo-controlled AMI trials and have received approval for this indication by international regulatory agencies.[6–8] Valsartan is the only ARB that has achieved similar regulatory approval for this indication and as such could have also served as an appropriate active comparator.[12] Of the effective agents, ramipril was chosen at the approved target dose of 5 mg bid, because it is the most commonly used ACEi in post-AMI patients worldwide.[30] In addition, ramipril is also the best studied ACEi in randomized clinical trials demonstrating clinical benefits across a broad range of patient populations including high-risk vascular disease, diabetes, and kidney disease.[31,32]

PARADISE-MI was designed as an active comparator-controlled, event-driven trial to ascertain whether sacubitril/valsartan offers incremental clinical value and has a satisfactory safety profile compared to a proven ACEi in a contemporarily treated AMI population with features of augmented risk. The exclusion of patients with previous heart failure and the initiation of therapy during AMI, without a run-in period, make PARADISE-MI a unique

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Table 5 Comparison of baseline patient characteristics in PARADISE-MI vs. angiotensin-converting enzyme inhibitor/angiotensin receptor blocker reference trials

	SAVE/AIRE/TRACE (n = 5966)	OPTIMAAL/VALIANT (n = 20 180)	PARADISE-MI (n = 5669)
Year of publication	1992, 1993, 1995	2002, 2003	2021
Mean age, years	63.0	65.6	63.7
Female sex, %	23.7	30.5	24.1
Q wave or STEMI, %	70.8	65.7	75.7
Mean heart rate, bpm	79	76	76
Mean systolic blood pressure, mmHg	116	123	121
Mean diastolic blood pressure, mmHg	72	72	74
Mean body mass index, kg/m^2	26 (SAVE, TRACE)	28	28
Mean eGFR, mL/min/1.73 m^2	70.0 (SAVE)	69.3	71.8
Killip class >I, %	73.0	71.0	58.4
Prior myocardial infarction, %	31.2	25.3	16.7
Diabetes mellitus, %	16.2	23.9	42.3
Aspirin use, %	74.5	87.6	98.1
P2Y12 inhibitor use, %	NR	NR	97.9
Acute reperfusion, %	43.0	48.3	89.4
Thrombolytic therapy, %	44.5	40.4	6.2
Percutaneous coronary intervention, %	17 (SAVE)	14.8 (VALIANT)	88.3[a]
Beta-blocker use, %	25.3	65.5	85.1
Statin use, %	NR	32.9	94.8
Calcium channel blocker use, %	29.2	9.0	9.0
Digoxin, %	21.8	10.5	1.7
Diuretic use, %	52.3	42.9	44.5
Current tobacco use, %	53 (SAVE)	31.7 (VALIANT)	21.2

eGFR, estimated glomerular filtration rate; NR, not reported; STEMI, ST-elevation myocardial infarction.
[a]Drug-eluting stents used in 90.4% of patients who underwent PCI in PARADISE-MI.

test of the safety and effectiveness of sacubitril/valsartan for the prevention rather than the treatment of symptomatic heart failure.

Supplementary Information

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

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References

1. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, Ettinger SM, Fang JC, Fesmire FM, Franklin BA, Granger CB, Krumholz HM, Linderbaum JA, Morrow DA, Newby LK, Ornato JP, Ou N, Radford MJ, Tamis-Holland JE, Tommaso CL, Tracy CM, Woo YJ, Zhao DX. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;**61**:485–510.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, Jaffe AS, Jneid H, Kelly RF, Kontos MC, Levine GN, Liebson PR, Mukherjee D, Peterson ED, Sabatine MS, Smalling RW, Zieman SJ. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;**64**:e139–e228.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, Caforio AL, Crea F, Goudevenos JA, Halvorsen S, Hindricks G, Kastrati A, Lenzen MJ, Prescott E, Roffi M, Valgimigli M, Varenhorst C, Vranckx P, Widimský P; ESC Scientific Document Group. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J* 2018;**39**:119–177.
4. Collet JP, Thiele H, Barbato E, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GC; ESC Scientific Document Group. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. *Eur Heart J* 2021;**42**:1289–1367.
5. Van Diepen S, Chen AY, Wang TY, Alexander KP, Ezekowitz JA, Peterson ED, Roe MT. Influence of heart failure symptoms and ejection fraction on short- and long-term outcomes for older patients with non-ST-segment elevation myocardial infarction. *Am Heart J* 2014;**167**:267–273.e1.
6. Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown EJ, Cuddy TE, Davis BR, Geltman EM, Goldman S, Flaker GC, Klein M, Lamas GA, Packer M, Rouleau J, Rouleau JL, Rutherford J, Wertheimer JH, Hawkins CM. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. The SAVE Investigators. *N Engl J Med* 1992;**327**:669–677.
7. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effect of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. *Lancet* 1993;**342**:821–828.
8. Kober L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K, Videbaek J, Cole DS, Auclert L, Pauly NC. A clinical trial of the ACE inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. TRACE Study Group. *N Engl J Med* 1995;**333**:1670–1676.
9. Flather MD, Yusuf S, Køber L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moyé L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. *Lancet* 2000;**355**:1575–1581.
10. Goodfriend TL, Elliott ME, Catt KJ. Angiotensin receptors and their antagonists. *N Engl J Med* 1996;**334**:1649–1655.
11. Dickstein K, Kjekshus J. Effects of losartan and captopril on mortality and morbidity in high-risk patients after acute myocardial infarction: the OPTIMAAL randomised trial. *Lancet* 2002;**360**:752–760.
12. Pfeffer MA, McMurray JJ, Velazquez EJ, Rouleau J-L, Køber L, Maggioni AP, Solomon SD, Swedberg K, Van de Werf F, White H, Leimberger JD, Henis M, Edwards S, Zelenkofske S, Sellers MA, Califf RM; Valsartan in Acute Myocardial Infarction Trial Investigators. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med* 2003;**349**:1893–1906.
13. McMurray JJ. Neprilysin inhibition to treat heart failure: a tale of science, serendipity, and second chances. *Eur J Heart Fail* 2015;**17**:242–247.
14. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. Angiotensin–neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;**371**:993–1004.
15. Velazquez EJ, Morrow DA, DeVore AD, Duffy CI, Ambrosy AP, McCague K, Rocha R, Braunwald E; PIONEER-HF Investigators. Angiotensin–neprilysin inhibition in acute decompensated heart failure. *N Engl J Med* 2019;**380**:539–548.
16. Solomon SD, McMurray JJ, Anand IS, Ge J, Lam CS, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Düngen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP; PARAGON-HF Investigators and Committees. Angiotensin–neprilysin inhibition in heart failure with preserved ejection fraction. *N Engl J Med* 2019;**381**:1609–1620.
17. Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI). https://clinicaltrials.gov/ct2/show/NCT02924727 (25 February 2021).
18. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, De Ferranti S, Després JP, Fullerton HJ, Howard VJ, Huffman MD, Judd SE, Kissela BM, Lackland DT, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Matchar DB, McGuire DK, Mohler ER, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Willey JZ, Woo D, Yeh RW, Turner MB; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics – 2015 update: a report from the American Heart Association. *Circulation* 2015;**131**:e29–e322.
19. Chung SC, Gedeborg R, Nicholas O, James S, Jeppsson A, Wolfe C, Heuschmann P, Wallentin L, Deanfield J, Timmis A, Jernberg T, Hemingway H. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014;**383**:1305–1312.
20. Aissaoui N, Puymirat E, Delmas C, Ortuno S, Durand E, Bataille V, Drouet E, Bonello L, Bonnefoy-Cudraz E, Lesmeles G, Guerot E, Schiele F, Simon T, Danchin N. Trends in cardiogenic shock complicating acute myocardial infarction. *Eur J Heart Fail* 2020;**22**:664–672.
21. Curry LA, Spatz E, Cherlin E, Thompson JW, Berg D, Ting HH, Decker C, Krumholz HM, Bradley EH. What distinguishes top-performing hospitals in acute myocardial infarction mortality rates? *Ann Intern Med* 2011;**154**:384–390.
22. Jhund PS, McMurray JJ. Heart failure after acute myocardial infarction: a lost battle in the war on heart failure? *Circulation* 2008;**118**:2019–2021.
23. Sulo G, Igland J, Vollset SE, Nygård O, Ebbing M, Sulo E, Egeland GM, Tell GS. Heart failure complicating acute myocardial infarction; burden and timing of occurrence: a nation-wide analysis including 86 771 patients from the Cardiovascular Disease in Norway (CVDNOR) project. *J Am Heart Assoc* 2016;**5**:e002667.
24. Lewis EF, Moye LA, Rouleau JL, Sacks FM, Arnold JM, Warnica JW, Flaker GC, Braunwald E, Pfeffer MA. Predictors of late development of heart failure

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in stable survivors of myocardial infarction: the CARE study. *J Am Coll Cardiol* 2003;**42**:1446–1453.
25. Arnold JM, Yusuf S, Young J, Mathew J, Johnstone D, Avezum A, Lonn E, Pogue J, Bosch J. Prevention of heart failure in patients in the Heart Outcomes Prevention Evaluation (HOPE) study. *Circulation* 2003;**107**:1284–1290.
26. Lewis EF, Velazquez EJ, Solomon SD, Hellkamp AS, McMurray JJ, Mathias J, Rouleau JL, Maggioni AP, Swedberg K, Kober L, White H, Dalby AJ, Francis GS, Zannad F, Califf RM, Pfeffer MA. Predictors of the first heart failure hospitalization in patients who are stable survivors of myocardial infarction complicated by pulmonary congestion and/or left ventricular dysfunction: a VALIANT study. *Eur Heart J* 2008;**29**:748–756.
27. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet* 2001;**357**:1385–1390.
28. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M; Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. *N Engl J Med* 2003;**348**:1309–1321.
29. Entresto. US Prescribing Information. Novartis Pharmaceuticals, East Hanover, NJ, USA. https://www.novartis.us/sites/www.novartis.us/files/entresto.pdf?source=news_body_link (9 March 2021).
30. Hansen ML, Gislason GH, Køber L, Schramm TK, Folke F, Buch P, Abildstrom SZ, Madsen M, Rasmussen S, Torp-Pedersen C. Different angiotensin-converting enzyme inhibitors have similar clinical efficacy after myocardial infarction. *Br J Clin Pharmacol* 2008;**65**:217–223.
31. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G; Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;**342**:145–153.
32. Yusuf S, Teo KK, Pogue J, Dyal L, Copland I, Schumacher H, Dagenais G, Sleight P, Anderson C; ONTARGET Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med* 2008;**358**:1547–1559.

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