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RESEARCH ARTICLE

Sacubitril/valsartan compared to ramipril in high-risk post-myocardial infarction patients stratified according to use of mineralocorticoid receptor antagonists: Insight from the PARADISE MI trial

Morten Schou[1]*, Brian Claggett[2], Zi Michael Miao[2], Alberto Fernandez[3], Gerasimos Filippatos[4], Christopher Granger[5], Karola Jering[2], Aldo P. Maggioni[6], Finnian McCausland[7], Julio Nuñez Villota[8], Jean-Lucien Rouleau[9], Freny Vaghaiwalla Mody[10,11,12], Peter van der Meer[13], Dragos Vinereanu[14], Martina McGrath[7], Yinong Zhou[15], Douglas L. Mann[16], Scott D. Solomon[2], Philippe Gabriel Steg[17], Eugene Braunwald[18], John J.V. McMurray[19], Marc A. Pfeffer[2], and Lars Køber[20]

[1]Department of Cardiology, Herlev-Gentofte University Hospital, Copenhagen, Denmark; [2]Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School Boston, Boston, MA, USA; [3]Cardiology Service, Sanatorio Modelo Quilmes, Quilmes, Argentina; [4]National and Kapodistrian University of Athens, School of Medicine, Department of Cardiology, Attikon University Hospital, Athens, Greece; [5]Duke University Medical Center, Durham, NC, USA; [6]ANMCO Research Center, Florence, Italy; [7]Renal Division, Department of Medicine (F.R.M.), Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA; [8]Servicio de Cardiología, Hospital Clínico Universitario, Valencia, Spain; [9]Montréal Heart Institute, University of Montréal, Montréal, QC, Canada; [10]Veterans Affairs Greater Los Angeles Healthcare System, Los Angeles, CA, USA; [11]Division of Cardiology, University of California, Los Angeles, CA, USA; [12]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [13]Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; [14]University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital, Bucharest, Romania; [15]Novartis Pharmaceutical Corporation, East Hanover, NJ, USA; [16]Washington University School of Medicine, St Louis, MO, USA; [17]Université de Paris, AP-HP (Assistance Publique-Hôpitaux de Paris), FACT (French Alliance for Cardiovascular Trials) and INSERM U-1148, Paris, France; [18]TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, and Harvard Medical School Boston, Boston, MA, USA; [19]British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, Scotland; and [20]Rigshospitalet, Blegdamsvej, University of Copenhagen, Copenhagen, Denmark

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Aim

It is unknown whether safety and clinical endpoints by use of sacubitril/valsartan (an angiotensin receptor–neprilysin inhibitor [ARNI]) are affected by mineralocorticoid receptor antagonists (MRA) in high-risk myocardial infarction (MI) patients. The aim of this study was to examine whether MRA modifies safety and clinical endpoints by use of sacubitril/valsartan in patients with a MI and left ventricular systolic dysfunction (LVSD) and/or pulmonary congestion.

Methods and results

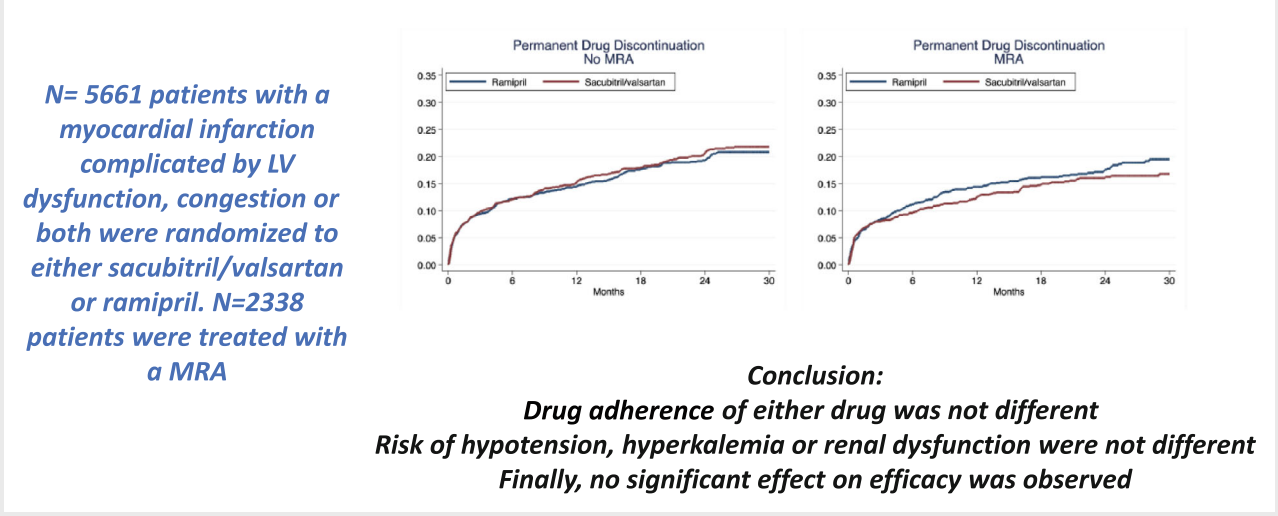
Patients ($n = 5661$) included in the PARADISE MI trial (Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After MI) were stratified according to MRA. Primary outcomes in this substudy were worsening heart failure or cardiovascular death. Safety was defined as symptomatic hypotension, hyperkalaemia >5.5 mmol/L, or permanent drug discontinuation. A total of 2338 patients (41%) were treated with MRA. Safety of ARNI compared to ramipril was not altered significantly by ± MRA, and both groups had similar increase in symptomatic hypotension with ARNI. In patients taking MRA, the risk of hyperkalaemia or permanent drug discontinuation was not significantly altered by ARNI ($p > 0.05$ for all comparisons). The effect of

*Corresponding author. Department of Cardiology, Herlev-Gentofte University Hospital, Herlev Ringvej 75, Copenhagen 2730, Denmark. Email: morten.schou.04@regionh.dk

ARNI compared with ramipril was similar in those who were and were not taking MRA (hazard ratio [HR]$_{MRA}$ 0.96, 95% confidence interval [CI] 0.77–1.19 and HR$_{MRA-}$ 0.87, 95% CI 0.71–1.05, for the primary endpoint; $p = 0.51$ for interaction [Clinical Endpoint Committee adjudicated]); similar findings were observed if investigator-reported endpoints were evaluated ($p = 0.61$ for interaction).

Conclusions Use of a MRA did not modify safety or clinical endpoints related to initiation of ARNI compared to ramipril in the post-MI setting in patients with LVSD and/or congestion.

Graphical Abstract



Sacubitril/valsartan and a mineralocorticoid receptor anatogonist (MRA) can be initiated safely and used simultaneously in post-myocardial infarction complicated by left ventricular (LV) dysfunction, congestion or both – Insight from the PARADISE MI trial.

Keywords ACE inhibitors • Drug adherence • Heart failure • Left ventricular dysfunction • Mineralocorticoid receptor antagonists • Myorcardial infarction • Sacubitril/valsartan

Introduction

In the EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) trial eplerenone (a mineralocorticoid receptor antagonist [MRA]) was superior to placebo in patients with a myocardial infarction (MI) complicated by left ventricular systolic dysfunction (LVSD) and either pulmonary congestion or type 2 diabetes, or both.[1] The PARADISE MI (Prospective ARNI vs. ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events after MI) trial examined sacubitril/valsartan versus ramipril and included MI patients with either LVSD, pulmonary congestion, or both.[2] A significant overlap in patient selection between the two trials does, therefore, exist and following this ≈40% of the patients in the PARADISE MI trial were treated with a MRA at baseline.[2,3] More knowledge on the safety and drug adherence after initiation of sacubitril/valsartan in combination with MRA use during an acute hospitalization is warranted in patients within all stages of heart failure (HF), since new HF guidelines recommend early initiation of up to four drugs when considered indicated.[4,5]

The PARADSE MI trial did not meet its primary endpoint,[2] but explorative *post hoc* analyses suggested that sacubitril/valsartan improved clinical outcomes compared to ramipril when investigator-reported endpoints reflecting daily clinical practice, as well as the total events were evaluated.[6] In the PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) and PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trials, treatment with MRA did not modify the treatment effect of sacubitril/valsartan.[7,8] Though, in the PARADIGM-HF trial patients randomized to enalapril had a 40% increased risk of hyperkalaemia and more knowledge is needed about early initiation of sacubitril/valsartan, use of a MRA and effect on outcomes in patients hospitalized for a MI,[9] since the post discharge time may reflect a vulnerable period for the patients with

a high risk of clinical deterioration, adverse events and drug discontinuation.[10]

Therefore, we examined whether the use of MRA and initiation of sacubitril/valsartan interacted and altered important safety and clinical endpoints in high-risk MI patients with LVSD or pulmonary congestion, or both.

Methods

Trial design

The design and main results of the PARADISE-MI trial (ClinicalTrials.gov, NCT02924727) have been published.[2,3,6] Briefly, PARADISE-MI was an international, multicentre, randomized, double-blind, parallel-group trial to compare the efficacy and safety of sacubitril/valsartan versus ramipril on morbidity and mortality in high-risk patients following an acute MI.

Eligibility

Patients aged ≥18 years without a history of HF were eligible if they experienced an acute and spontaneous MI 0.5–7 days prior to randomization that was associated with a left ventricular ejection fraction ≤40%, pulmonary congestion requiring intravenous treatment, or both conditions and had at least one of the following pre-specified risk-enrichment factors: age ≥70 years, diabetes mellitus, previous MI, 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 MI, Killip class III or IV, or ST-elevation MI 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 1:1 after the index event to receive either sacubitril/valsartan (uptitration to 97–103 mg twice daily) or ramipril (uptitration to 5 mg twice daily) without a run-in phase. Randomization was performed with the use of interactive-response technology, with stratification according to geographic region and type of MI (ST-segment or non-ST-segment elevation). Ongoing treatment with ACE inhibitors or ARBs was discontinued at randomization. Background therapy was at the discretion of the treating physician.

Exposure and endpoints

Exposure: baseline use of mineralocorticoid receptor antagonists

Use of MRA was exposure of interest. Therefore, patients randomized to ramipril or sacubitril/valsartan were subsequent stratified according to use of MRA at baseline.

Safety endpoints: permanent drug discontinuation, symptomatic hypotension, hyperkalaemia, increase in serum creatinine

In the present substudy permanent drug discontinuation of either sacubitril/valsartan or ramipril, symptomatic hypotension, hyperkalaemia (potassium >5.5 or >6.0 mmol/L) or elevated creatinine (≥2.0, 2.5 or 3.0 mg/dl) were evaluated. Drug discontinuation for MRA was defined as >90-day interruption in treatment.[11] Safety analyses were restricted to patients who had received at least one dose of study drug.

Clinical endpoints: time to cardiovascular death or development of clinical heart failure

The composite primary outcome of the present substudy was the first occurrence of death from cardiovascular causes or incident HF adjudicated by the Clinical Endpoint Committee (CEC) or documented by investigator reports.[2,3,6] Incident HF included hospitalization for HF and outpatient episodes of symptomatic HF treated with intravenous or sustained oral diuretic therapy. Secondary endpoints included the components of the primary endpoint and all-cause death. Total event analysis (CEC adjudicated) (cardiovascular death and first and recurrent HF hospitalizations) was performed as a supplementary analysis.[2,12–14]

Statistics

Data are presented as mean standard deviation when distributed normally, median (interquartile range) for non-normal distributions, and frequency (percentage) for categorical variables. Baseline characteristics and safety data of MRA users and non-users were compared with the Student's *t*-test, Mann–Whitney U test, and Pearson chi-square test where appropriate. The primary clinical and safety outcomes were analysed using Cox regression in a time-to-first-event analysis. For clinical endpoints, models were stratified by type of MI and adjusted for geographic region and percutaneous coronary intervention (PCI) use at baseline. Heterogeneity of treatment effect was tested for with the use of formal interaction between allocation to sacubitril/valsartan or ramipril, use of MRA and the relevant outcomes. Timing and occurrence of recurrent events (hospitalizations for HF, outpatient HF, or cardiovascular death) were analysed using a negative binominal regression model with a Weibull baseline intensity function with treatment assignment, type of MI, geographic region and PCI use at baseline included as factors in the model. A *p*-value <0.05 was considered statistically significant.[15,16] Due to the retrospective nature of the study, no adjustment was made for multiple comparisons.[17] Mean values of serum potassium at each study visit were estimated by randomized treatment assignment and baseline MRA status, with overall differences between ramipril and sacubitril/valsartan patients tested using mixed-effects linear regression models that used study visit as a fixed effect and patient-level random intercept terms. All analyses were conducted using STATA (Version 16, Stata Corp., College Station, TX, USA).

Results

Study population

In *Table 1* the PARADISE-MI patients are presented according to the use of MRA at randomization and allocation to either ramipril or sacubitril/valsartan. The 2238 patients (41%) who were treated with a MRA at baseline had a lower left ventricular ejection fraction, more often presented with pulmonary congestion, and more frequently used diuretics (online supplementary *Table S1*). The randomization to either ramipril or sacubitril/valsartan produced balanced groups after stratification for use of MRA or not (*Table 1*).

Table 1 Baseline characteristics stratified according to treatment allocation (ramipril vs. sacubitril/valsartan) and treatment with and without a mineralocorticoid receptor antagonist

Characteristics	No MRA ($n = 3323$)		*p*-value	MRA ($n = 2338$)		*p*-value
	Ramipril ($n = 1648$)	Sacubitril/valsartan ($n = 1675$)		Ramipril ($n = 1183$)	Sacubitril/valsartan ($n = 1155$)	
Age, years	64 (12)	64 (12)	0.35	63 (11)	64 (11)	0.23
Female sex, %	25	23	0.17	24	24	0.87
Race, *n* (%)			0.20			0.58
Asian	315 (19.1)	320 (19.1)		163 (13.8)	155 (13.4)	
Black	35 (2.1)	25 (1.5)		5 (0.4)	10 (0.9)	
White	1202 (72.9)	1208 (72.1)		936 (79.1)	917 (79.4)	
Other	96 (5.8)	122 (7.3)		79 (6.7)	73 (6.3)	
Region, *n* (%)			0.97			0.98
Asia-Pacific	353 (21.4)	360 (21.5)		198 (16.7)	191 (16.5)	
Central Europe	353 (21.4)	371 (22.1)		396 (33.5)	379 (32.8)	
Latin America	181 (11.0)	189 (11.3)		159 (13.4)	150 (13.0)	
North America	207 (12.6)	206 (12.3)		57 (4.8)	58 (5.0)	
Western Europe	554 (33.6)	549 (32.8)		373 (31.5)	377 (32.6)	
Clinical data						
BMI, kg/m^2	28 (5)	28 (5)	0.94	28 (5)	28 (5)	0.36
SBP, mmHg	122 (14)	122 (14)	0.50	120 (13)	120 (13)	0.98
DBP, mmHg	74 (10)	74 (10)	0.97	73 (9)	74 (10)	0.72
HR, bpm	75 (12)	75 (12)	0.73	76 (11)	76 (12)	0.89
LVEF, %	38 (10)	38 (10)	0.36	34 (8)	34 (8)	0.50
Pulmonary congestion, *n* (%)	870 (52.8)	835 (49.9)	0.09	678 (57.3)	673 (58.3)	0.64
Killip class ≥2, *n* (%)	897 (56.1)	885 (54.6)	0.39	709 (61.8)	710 (63.6)	0.36
Serum creatinine, mg/dl	1.1 (0.3)	1.1 (0.3)	0.63	1.1 (0.3)	1.1 (0.3)	0.63
eGFR, ml/min/1.73 m^2	73 (23)	72 (22)	0.53	71 (22)	71 (21)	0.81
Serum potassium, mmol/L	4.3 (0.5)	4.3 (0.6)	0.59	4.3 (0.6)	4.3 (0.6)	0.48
Type of myocardial infarction, *n* (%)			0.70			0.74
STEMI	1227 (74.5%)	1257 (75.0)		911 (77.0)	896 (77.6)	
NSTEMI or other				272 (23)	259 (22.4)	
Comorbidities, *n* (%)						
Diabetes	670 (40.7)	726 (43.3)	0.12	510 (43.1)	495 (42.9)	0.90
Hypertension	1056 (64.1)	1082 (64.6)	0.75	775 (65.5)	763 (66.1)	0.78
Atrial fibrillation	215 (13.0)	216 (12.9)	0.83	167 (14.1)	186 (16.1)	0.16
Dual antiplatelet therapy, *n* (%)	1506 (91.4)	1540 (91.9)	0.56	1108 (93.7)	1068 (92.5)	0.26
Statin, *n* (%)	1557 (94.5)	1580 (94.3)	0.85	1139 (96.3)	1094 (94.7)	0.07
Beta-blocker, *n* (%)	1363 (82.7)	1395 (83.3)	0.66	1050 (88.8)	1019 (88.2)	0.69
Diuretics, *n* (%)	567 (34.4)	576 (34.4)	0.99	683 (57.7)	(695 (60.2)	0.23

BMI, body mass-index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HR, heart rate; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonists; NSTEMI, non-ST-elevation myocardial infarction; SBP, systolic blood pressure; STEMI, ST-elevation myocardial infarction.

Safety endpoints: permanent drug (ramipril or sacubitril/valsartan) discontinuation, symptomatic hypotension, hyperkalaemia, increase in serum creatinine

In the whole population, MRA use was associated with a lower risk of permanent drug discontinuation in both unadjusted (hazard ratio [HR]$_{MRA}$ 0.83 [0.73–0.94], $p = 0.001$) and adjusted analyses (HR$_{MRA}$ 0.78 [0.69–0.89], $p < 0.001$). No significant associations for risk of hyperkalaemia or hypotension were observed ($p > 0.05$ for all comparisons). In the patients randomized to either sacubitril/valsartan or ramipril, none of the safety endpoints of the present substudy were affected by use of MRA (*Table 2*, *Figure 2* and online supplementary *Figure S2*). Permanent drug discontinuation, risk of hyperkalaemia, and symptomatic hypotension were not increased by initiation of sacubitril/valsartan on MRA background therapy compared to initiation of sacubitril/valsartan and no MRA. Time to permanent drug discontinuation of sacubitril/valsartan and ramipril was similar regardless of baseline use of MRA (HR$_{MRA+}$ 0.86 [0.71–1.06], $p = 0.16$ [377 events] and HR$_{MRA-}$ 1.04 [0.89–1.22], $p = 0.61$ [641 events]; $p = 0.15$ for interaction) (*Figure 2A,B*). Importantly, drug discontinuation of MRA did not differ significantly between the sacubitril/valsartan arm compared

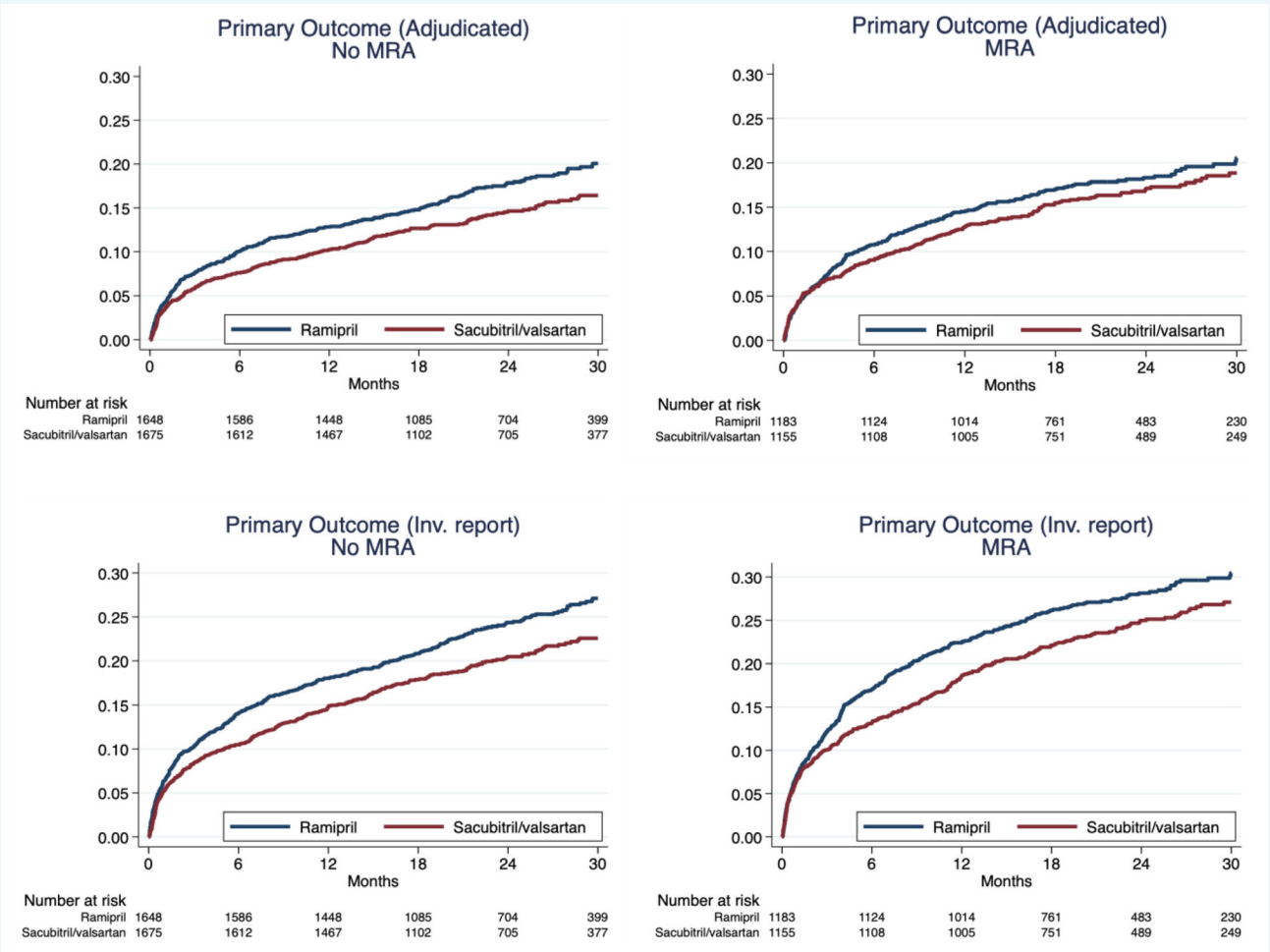


Figure 1 Time to cardiovascular death or development of clinical heart failure (main clinical outcomes). (*A*) Kaplan–Meier curves for primary outcome (adjudicated) by no mineralocorticoid receptor antagonist (MRA) and MRA ($p = 0.51$ for interaction). (*B*) Kaplan–Meier curves for primary outcome (investigator-reported) by no MRA and MRA ($p = 0.61$ for interaction).

to the ramipril arm (HR 1.04 [0.89–1.21], $p = 0.63$) (*Figure 2A,C*). To avoid overlooking an effect on serum potassium, the treatment effects on serum potassium considered as a continuous variable were also analysed. No significant differences were observed (online supplementary *Figure S3*).

However, a significant increase in symptomatic hypotension was observed when sacubitril/valsartan was initiated (HR_{MRA+} 1.37 [1.17–162], $p < 0.001$and HR_{MRA-}1.39 [1.21–1.59], $p < 0.001$), but no treatment modification by use of MRA was observed ($p = 0.97$ for interaction).

Clinical endpoints: time to cardiovascular death or development of clinical heart failure

In the whole population, use of MRA at baseline was associated with an increased risk of the primary composite endpoint (HR_{MRA} 1.31 [1.07–1.61], $p = 0.01$) (event rates: 9.9 per 100 person-years vs. 8.8 events per 100 person-years). After adjustment for confounding (number of cardiovascular risk factors; age, pulmonary congestion; PCI, LVSD; history of hypertension, region of randomization; PCI use, type of MI), the association was no longer significant (HR_{MRA} 1.05 [0.86–1.29], $p = 0.62$). Use of MRA did not significantly modify the treatment effect of sacubitril/valsartan compared to ramipril on the primary composite endpoint (HR_{MRA+} 0.96 [0.77–1.19], $p = 0.70$ and HR_{MRA-} 0.87 [0.71–1.05], $p = 0.15$) and no significant treatment modification was observed of either the primary endpoint ($p = 0.51$ for interaction) (*Figure 1A*), its components or all-cause death (HR_{MRA+} 0.91 [0.69–1.20], $p = 0.50$ and HR_{MRA-} 0.86 [0.67–1.10], $p = 0.23$) ($p = 0.78$ for interaction) (*Table 3*). Using the investigator-reported endpoints yielded similar results and baseline use of MRA did not significantly modify the treatment effect of sacubitril/valsartan compared to ramipril (HR_{MRA+} 0.88 [0.73–1.07], $p = 0.19$ and HR_{MRA-} 0.83 [0.70–0.98], $p = 0.03$) ($p = 0.61$ for interaction) (primary composite endpoint) (*Figure 1B*). In the supplementary analysis evaluating total disease burden (= total (first and recurrent) event analysis), use of MRA did not modify the treatment effect

Table 2 Safety outcomes (symptomatic hypotension, serum potassium and creatinine level)

Safety endpoint of interest	No MRA ($n = 3323$)		*p*-value	MRA ($n = 2338$)		*p*-value	*p*-value for interaction
	Ramipril ($n = 1648$)	Sacubitril/valsartan ($n = 1675$)		Ramipril ($n = 1183$)	Sacubitril/valsartan ($n = 1155$)		
Symptomatic hypotension, *n* (%)	363 (22)	474 (29)	< 0.001	257 (22)	327 (28)	< 0.001	0.88
Drug discontinued due to adverse event, *n* (%)	209 (13)	215 (13)	0.89	170 (14)	142 (12)	0.14	0.23
Any serious adverse event, *n* (%)	643 (39)	684 (41)	0.28	483 (41)	462 (40)	0.68	0.32
Adverse event: hyperkalaemia, *n* (%)	155 (10)	170 (10)	0.49	130 (11)	131 (11)	0.70	0.80
Laboratory tests							
Elevated serum creatinine level							
≥2.0 mg/dl	101 (6.4)	101 (6.2)	0.87	70 (6.1)	61 (5.5)	0.51	0.68
≥2.5 mg/dl	39 (2.5)	43 (2.6)	0.73	26 (2.3)	24 (2.1)	0.85	0.71
≥3.0 mg/dl	21 (1.3)	17 (1.0)	0.47	13 (1.1)	6 (0.5)	0.12	0.38
Elevated serum potassium level							
>5.5 mmol/L	190 (12)	212 (13)	0.34	171 (15)	191 (17)	0.16	0.70
>6.0 mmol/L	48 (3.0)	44 (2.7)	0.60	47 (4.1)	48 (4.3)	0.82	0.59

MRA, mineralocorticoid receptor antagonist.

of sacubitril/valsartan (relative risk $[RR]_{MRA+}$ 0.86 [0.64–1.16], $p = 0.32$ and RR_{MRA-} 0.76 [0.59–0.99], $p = 0.05$) ($p = 0.57$ for interaction) (online supplementary *Figure S1*).

Supplementary analyses on patients receiving and not receiving mineralocorticoid receptor antagonists at randomization

As mentioned previously, 2338 patients (41%) received MRA at baseline. A total of 3131 patients (55%) suffered from LVSD combined with either congestion or type 2 diabetes. Of those, 1513 (48%) were treated with a MRA. In the rest of the population ($n = 2530$), 825 (31%) received MRA. During follow-up, 763 (23%) patients out of 3323 had MRA initiated.

Discussion

Main findings

In analyses based on data from 5661 high-risk MI patients included in the PARADISE MI trial, patients that had prescribed MRAs in the post-MI setting were at higher risk than those not receiving MRAs, but use of MRA did not modify important safety and clinical endpoints between patients treated with sacubitril/valsartan compared to ramipril (*Figures 1 and 2*).

Safety endpoints

The combination, initiation of sacubitril/valsartan without a run-in phase and use of MRA during a hospitalization did not affect adherence to neither sacubitril/valsartan nor MRA and is an important clinical finding. Many clinicians are concerned to initiate these two drugs out of fear of precipitating adverse events including hypotension, hyperkalaemia or worsening renal function. An increase in the risk of those clinical important safety endpoints were not observed when MRA and sacubitril/valsartan were used in combination. Our analyses support that the present two HF drugs can be initiated safely and used simultaneously in post-MI patients with high risk of HF.

Efficacy endpoints

In accordance with analyses from the PARADIGM-HF and the PARAGON-HF trials, we did not observe that the treatment effects of sacubitril/valsartan compared to an active comparator were significantly modified by background MRA therapy.[7,8] Further, the lack of interaction between use of MRA, allocation to either ramipril or sacubitril/valsartan and the primary endpoint (investigator-reported) suggest that use of MRA should not deter treating physicians from initiation of sacubitril/valsartan directly or replacing an ACE inhibitor or ARB with sacubitril/valsartan if it is considered indicated and time saving, e.g. in patients that are planned to be referred to a nurse-driven outpatient rehabilitation and HF clinic for further optimization and secondary prevention. Patients receiving MRAs had a worse outcome than patients not receiving this drug class. It may be due to confounding by indication, and it should be kept in mind that the patients in PARADISE MI were not allocated to MRA or placebo but initiated if the treating clinician found it indicated.

Clinical perspectives

Based on the main results from PARADISE MI, sacubitril/valsartan is not indicated in high-risk patients in the post-MI setting. Clinicians should focus on initiation of a MRA based on the results from the

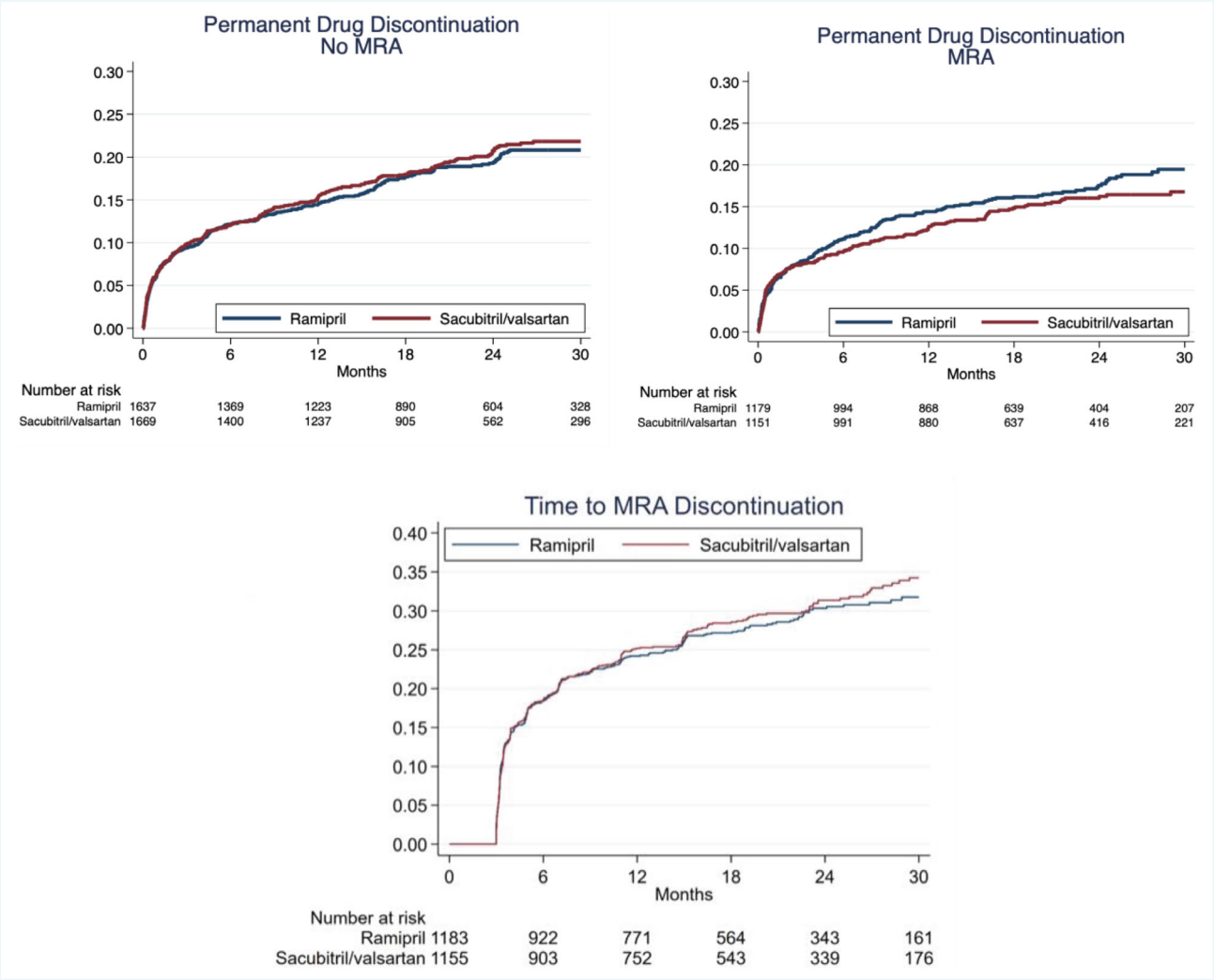


Figure 2 Time to permanent drug discontinuation (main safety outcome) of either sacubitril/valsartan compared to ramipril (*A*, *B*) and >90-day drug discontinuation of mineralocorticoid receptor antagonist (MRA) in the sacubitril/valsartan and ramipril groups (*C*). No difference in permanent drug discontinuation between ramipril and sacubitril/valsartan was observed and the use of MRA did not modify this ($p = 0.150$ for interaction).

EPHESUS trial[1] and on adherence of MRA afterwards based on our results. Though, some of the patients may suffer from early stages of chronic HF, for example patients receiving loop diuretics and mild HF symptoms at discharge. In recently published HF guidelines,[4,5] it is recommended that patients with HF and LVSD (HF stage C) should receive up to four disease-modifying drugs including sacubitril/valsartan. Our analyses suggest that it is safe to use MRA and sacubitril/valsartan in patients with high-risk HF stage B even during a hospitalization for MI, but our results should be extrapolated to patients with HF stage C with caution due to the post-discharge vulnerable phase after a MI. Further, the use of MRA in the post-MI setting did not explain the observed attenuated treatment effect of sacubitril/valsartan in the PARADISE MI trial and there is still room to improve secondary prevention and additional efforts, for example evaluation of a sodium–glucose cotransporter 2 inhibitor to reduce morbidity and mortality in this high-risk patient group is needed.[18,19] Finally, whether MRA initiation in daily clinical practice can be further improved in high-risk MI patients needs to be further addressed and only 48% of the patients with a MRA indication at randomization received this important drug.[20] Though, a large fraction of patients included in the PARADISE MI trial (45%) did not have a MRA indication (patients without the combination of LVSD and either type 2 diabetes or clinical HF) and a total of 41% of the patients were treated with a MRA, which may indicate a high level of care in our setting.

Methodological considerations

The PARADISE MI enrolled patients from several countries and the results of the study can, therefore, be extrapolated to most of the world. Data are collected in the clinical trial environment and

Table 3 Primary and secondary endpoints stratified according to treatment allocation (ramipril vs. sacubitril/valsartan) and treatment with and without a mineralocorticoid receptor antagonist

Endpoint of interest	No MRA ($n = 3323$)		MRA ($n = 2338$)		*p*-value for interaction
	Ramipril ($n = 1648$)	Sacubitril/valsartan ($n = 1675$)	Ramipril ($n = 1183$)	Sacubitril/valsartan ($n = 1155$)	
CEC adjudicated					
Primary composite endpoint					
Events (%)	210 (13)	184 (11)	163 (14)	154 (13)	
Rate (100 py) hazard ratio	7.1	6.1 0.87 (0.71–1.05)	7.9	7.5 0.96 (0.77–1.19)	0.51
Cardiovascular death					
Events (%)	106 (6)	87 (5)	85 (7)	81 (7)	
Rate (100 py) hazard ratio	3.4	2.7 0.82 (0.62–1.09)	3.9	3.7 0.96 (0.71–1.30)	0.48
Development of HF[a]					
Events (%)	136 (8)	114 (7)	101 (9)	87 (8)	
Rate (100 py) hazard ratio	4.6	0.83 (0.64–1.06)	4.9	0.87 (0.65–1.16)	0.79
All-cause death					
Events (%)	134 (8)	115 (7)	108 (9)	98 (8)	
Rate (100 py) hazard ratio	4.2	3.6 0.86 (0.67–1.10)	4.9	4.5 0.91 (0.69–1.20)	0.78
Investigator-reported					
Primary composite endpoint					
Events (%)	284 (17)	239 (14)	232 (20)	204 (18)	
Rate (100 py) hazard ratio	10.0	8.2 0.83 (0.70–0.98)	12	10.4 0.88 (0.73–1.07)	0.61
Cardiovascular death					
Events (%)	98 (6)	80 (5)	81 (7)	75 (6)	
Rate (100 py) hazard ratio	3.1	2.5 0.82 (0.61–1.10)	3.7	3.4 0.93 (0.68–1.27)	0.58
Development of HF[a]					
Events (%)	223 (14)	180 (11)	182 (15)	149 (13)	
Rate (100 py) hazard ratio	7.9	6.2 0.79 (0.65, 0.96)	9.4	7.6 0.82 (0.66, 1.02)	0.81

CEC, Clinical Endpoint Committee; HF, heart failure; MRA, mineralocorticoid receptor antagonist; py, person-years.
[a]Development of HF: HF hospitalization or outpatient diagnosis of HF.

careful extrapolation to daily clinical practice should be performed since risks of worsening renal function and hyperkalaemia may be higher here. Further, most included patients were revascularized and were well treated with anti-thrombotic treatment, statins, and beta-blockers. We cannot differentiate between spironolactone and eplerenone and do neither have precise data on doses nor exact date of initiation of MRA. Though at present, a class effect of this drug class is proposed.[4,5] Our analyses do, therefore, illustrate that it is safe to add sacubitril/valsartan to a background therapy of a beta-blocker and a MRA. More research is needed on simultaneously initiation of sacubitril/valsartan and a MRA Due to the randomization of the patients to either ramipril or sacubitril/valsartan, our data are unique for drug adherence analyses of ramipril and sacubitril/valsartan in relation to use of MRA. Patients were clinically selected for MRAs, and it should be noted that these patients were as expected at higher risk than patients not receiving MRAs (online supplementary *Table S1*). As a trial, safety data were prospectively recorded. Since the use of CEC adjudicated and investigator-reported endpoints produced different results in the overall study population, we chose to evaluate the interplay between sacubitril/valsartan and MRA in both analyses. We reached the same result, which makes our conclusions more robust. Finally, the present analyses represent *post hoc* analyses of a trial that did not meet its primary outcome and should, therefore, be considered exploratory. Due to the sample size and large number of events, we do not think our results reflect type II errors; opposite, lack of power in the present subgroup analyses cannot be fully excluded. Further, we do not report any significant interactions and our results do, therefore, not reflect type I errors or spurious subgroup findings,[21] but plausible associations of clinical significance. Only 24% of the included patients were women and only 31% were enrolled outside Europe and North America, which challenge the generalizability of our results. Continued efforts to improve diversity in patient selection in global randomized clinical trials should be pursued.[22]

Conclusions

In high-risk MI patients with LVSD or pulmonary congestion or both, use of MRA and initiation of sacubitril/valsartan do not interact with respect to important safety and clinical endpoints like permanent drug discontinuation of either drug and time to cardiovascular death or development of clinical HF.

Supplementary Information

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

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[Correction added on 12 February 2024, after first online publication: The Glossary section has been removed in this version.]

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