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ORIGINAL RESEARCH

# Sex Differences in Clinical Characteristics and Outcomes After Myocardial Infarction With Low Ejection Fraction: Insights From PARADISE-MI

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**BACKGROUND:** Studies demonstrated sex differences in outcomes following acute myocardial infarction, with women more likely to develop heart failure (HF). Sacubitril/valsartan has been shown to reduce cardiovascular death and HF hospitalizations in patients with HF with reduced ejection fraction.

**METHODS AND RESULTS:** A total of 5661 patients (1363 women [24%]) with acute myocardial infarction complicated by reduced left ventricular ejection fraction ( $\leq 40\%$ ), pulmonary congestion, or both and  $\geq 1$  of 8 risk-augmenting factors were randomized to receive sacubitril/valsartan or ramipril. The primary outcome was cardiovascular death or incident HF. Baseline characteristics, clinical outcomes, and safety events were compared according to sex, a prespecified subgroup. Female participants were older and had more comorbidities. After multivariable adjustment, women and men were at similar risks for cardiovascular death or all-cause death. Women were more likely to have first HF hospitalization (hazard ratio [HR], 1.34 [95% CI, 1.05–1.70];  $P=0.02$ ) and total HF hospitalizations (HR, 1.39 [95% CI, 1.05–1.84];  $P=0.02$ ). Sex did not significantly modify the treatment effect of sacubitril/valsartan compared with ramipril on the primary outcome ( $P$  for interaction=0.11).

**CONCLUSIONS:** In contemporary patients who presented with reduced left ventricular ejection fraction, pulmonary congestion, or both, following acute myocardial infarction, women had a higher incidence of HF during follow-up. Sex did not modify the treatment effect of sacubitril/valsartan relative to ramipril.

**REGISTRATION:** URL: <https://www.clinicaltrials.gov>; Unique identifier: NCT02924727.

**Key Words:** heart failure ■ myocardial infarction ■ sacubitril/valsartan ■ sex differences

**H**eat disease is a leading cause of mortality in women.<sup>1</sup> Once thought to be primarily a problem in men, ischemic heart disease is also known to afflict women with similar incidence, albeit at an older age.<sup>2</sup> Until recently, at a population level, women had higher

mortality from cardiovascular disease than men, with ischemic heart disease as a major contributor.<sup>1</sup>

Prior studies have shown sex differences in outcomes following myocardial infarction (MI), although the results have been inconsistent. Some studies

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## CLINICAL PERSPECTIVE

### What Is New?

- In a contemporary clinical trial cohort of patients with high-risk myocardial infarction, women were older with more comorbidities. Women and men had similar rates of all-cause mortality and cardiovascular death.
- Women were more likely to have heart failure hospitalization after high-risk myocardial infarction, over a median follow-up duration of 22 months.
- Sacubitril/valsartan was well tolerated in both men and women.

### What Are the Clinical Implications?

- Clinicians should pay close attention to the increased risk of heart failure hospitalization after high-risk myocardial infarction to mitigate adverse clinical outcomes.
- Historically, women were less likely to receive guideline-directed medical therapy after myocardial infarction. Sacubitril/valsartan was safe and well tolerated in both sexes and should not be withheld in women when clinically indicated.

## Nonstandard Abbreviations and Acronyms

<b>CEC</b>	clinical events committee
<b>PARADISE-MI</b>	Prospective ARNI (Angiotensin Receptor–Nepriylsin Inhibitor) Versus ACE (Angiotensin-Converting Enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction
<b>VALIANT</b>	Valsartan in Acute Myocardial Infarction

showed higher mortality in women after MI, whereas others found such differences only existed in certain types of MI or were attenuated after adjusting for differences in patient characteristics.<sup>3–5</sup> In the VALIANT (Valsartan in Acute Myocardial Infarction) trial, women experienced a higher risk of heart failure (HF) following MI; mortality and risk of recurrent MI or stroke did not differ significantly between men and women after adjusting for baseline differences.<sup>6</sup> However, since the VALIANT trial, there have been significant changes in the management of MI with or without HF. With the adoption of timely primary percutaneous coronary intervention (PCI), increased use of medical therapies,

such as statins,  $\beta$ -blockers, angiotensin-converting enzyme inhibitors (ACEis), and angiotensin receptor blockers, mortality and other cardiovascular outcomes following MI have improved.<sup>7</sup>

The angiotensin receptor–neprilysin inhibitor (ARNI) sacubitril/valsartan reduced cardiovascular death and HF hospitalization compared with an ACEi in patients with HF with reduced ejection fraction.<sup>8</sup> In patients with HF with preserved ejection fraction, sacubitril/valsartan reduced HF hospitalizations compared with an angiotensin receptor blocker, valsartan, in patients with an ejection fraction below normal.<sup>9</sup> This benefit was particularly pronounced in women versus men.<sup>10</sup> PARADISE-MI (Prospective ARNI Versus ACE Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction) provides a contemporary population to evaluate potential sex differences in patient characteristics and outcomes following MI, and it determines whether women derive a greater benefit from an ARNI following MI.

## METHODS

### Data Sharing

The sponsor of PARADISE-MI is committed to sharing access to patient-level data and supporting clinical documents from eligible studies with qualified external researchers. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. The trial data availability is according to the criteria and process described.<sup>11</sup>

### Study Design and Patient Characteristics

The design and results of PARADISE-MI have been previously published.<sup>7,12</sup> Briefly, PARADISE-MI was a multicenter, double-blind, active-comparator, randomized trial evaluating the efficacy and safety of sacubitril/valsartan compared with ramipril. A total of 5661 patients (1363 women [24.0%]) were randomized in a 1:1 manner to receive sacubitril/valsartan or ramipril, with a median follow-up of 22 months. The key eligibility criteria included adults without a history of HF, who had a spontaneous MI within 0.5 to 7 days before randomization associated with a reduced left ventricular ejection fraction (LVEF;  $\leq 40\%$ ), pulmonary congestion, or both, and with at least 1 of 8 risk-augmenting factors (age  $\geq 70$  years, diabetes, previous MI, estimated glomerular filtration rate [eGFR]  $< 60$  mL/min per  $1.73\text{ m}^2$ , atrial fibrillation, LVEF  $< 30\%$  associated with index MI, Killip class III or IV, or ST-segment-elevation MI without reperfusion within 24 hours after presentation).<sup>12</sup> Key exclusion criteria included clinical

instability within 24 hours before randomization, an eGFR <30 mL/min per 1.73 m<sup>2</sup>, serum potassium level >5.2 mmol/L, and inability to take an ACEi or an angiotensin receptor blocker. Medications were titrated to a target dose of ramipril, 5 mg twice daily, and sacubitril/valsartan, 97/103 mg twice daily, over 3 to 4 weeks.<sup>7</sup> The PARADISE-MI Women subtrial is a prespecified subgroup analysis of PARADISE-MI evaluating potential sex differences in clinical characteristics and outcomes following acute MI. The trial protocol for PARADISE-MI was approved by the institutional review board at each trial center, and trial participants gave informed consent.

## End Points and Follow-Up

The primary composite outcome in PARADISE-MI was cardiovascular death or incident HF, defined as hospitalization for HF or outpatient symptomatic HF requiring intravenous or sustained oral diuretic therapy. Secondary outcomes included the composite of cardiovascular death or HF hospitalization; the composite of HF hospitalization or outpatient HF; the composite of cardiovascular death, nonfatal MI, or nonfatal stroke; cardiovascular death; and all-cause death. Clinical outcomes were reported by the primary site investigator and were adjudicated (using clearly defined end points) by an independent clinical events committee (CEC) blinded to treatment allocation.<sup>7</sup> For the primary composite end point, cardiovascular death or incident HF, both CEC-adjudicated and investigator-reported events were analyzed. The coronary composite end point of death from coronary heart disease, nonfatal MI, hospitalization for angina, or coronary revascularization was included as an exploratory outcome.

For the total (first and recurrent) event analysis, CEC-adjudicated end points included cardiovascular death and total cardiovascular events (HF hospitalization, MI, or stroke), cardiovascular death and total HF events (HF hospitalization or outpatient HF), total HF hospitalizations, total outpatient HF events, and total HF events. Investigator-reported cardiovascular death and total HF events, total HF hospitalizations, total outpatient HF events, and total HF events were also examined.

For safety end points, rates of adverse events, serious adverse events, and drug discontinuation attributable to adverse events were compared between men and women. Key adverse events of interest include hypotension, cough, angioedema, hyperkalemia, hepatotoxicity, hypersensitivity, renal impairment, cognitive impairment, risk of malignancy, and statin drug-drug interaction. Laboratory abnormalities of elevated serum creatinine, serum potassium, aspartate aminotransferase, and alanine aminotransferase above

predefined thresholds were also compared between men and women.

## Statistical Analysis

Demographics, baseline characteristics, and baseline medications were compared between men and women using the  $\chi^2$  test for comparison of categorical variables and *t*-test for comparison of normally distributed continuous variables. Efficacy analyses were performed according to the intention-to-treat principle. The association between sex and the primary composite outcome, its components, and the secondary outcomes was evaluated using Cox proportional hazards regression models in a time-to-first event analysis. To assess whether sex modified the treatment effect of sacubitril/valsartan relative to ramipril, a sex-by-treatment interaction term was included in models adjusted for PCI use at baseline and geographic region, and it was stratified by type of MI. Total (first and recurrent) events were analyzed using a negative binomial model with a Weibull baseline intensity function. Models were adjusted for age, self-reported race, geographic region, number of risk-augmenting factors, baseline LVEF, intravenous treatment for pulmonary congestion, history of prior MI, hypertension, diabetes, current tobacco use, eGFR, type of index MI, ST-segment-elevation MI (STEMI) without reperfusion within 24 hours of presentation, PCI at baseline, Killip class, and treatment assignment. Proportional hazards assumptions were assessed via Schoenfeld residuals.

Adverse events were compared between men and women using the  $\chi^2$  test for comparison of categorical variables. Statistical significance was assessed using a 2-sided  $\alpha$  level of 0.05 without adjustment for multiplicity. All statistical analyses were conducted using Stata software, version 16 (StataCorp, College Station, TX).

## RESULTS

### Patient Characteristics

There were significant differences in baseline characteristics between men (*n*=4298) and women (*n*=1363) in PARADISE-MI. Women were older, had higher LVEF, were more likely to present with pulmonary congestion, and had >1 risk-augmenting factor (Table 1).

Women were less likely to have had a prior stroke, MI, or coronary revascularization but more likely to have hypertension and diabetes (Table 1). Fewer women in PARADISE-MI were active smokers. Women had a slightly higher systolic blood pressure and lower eGFR than men. Fewer women presented with STEMI, and of those with STEMI, women were less likely to receive reperfusion therapy. Moreover, for those with a STEMI, fewer women than men received reperfusion therapy within 24 hours of presentation

**Table 1. Baseline Characteristics in Women Versus Men**

Characteristic	Men (n=4298)	Women (n=1363)	P value
Age, y	62.5±11.4	67.8±10.9	<0.001
Race, n (%)			0.01
Asian	755 (17.6)	198 (14.5)	
Black	51 (1.2)	24 (1.8)	
White	3200 (74.5)	1063 (78.0)	
Other*	292 (6.8%)	78 (5.7%)	
Region, n (%)			<0.001
Asia/Pacific and others	880 (20.5)	222 (16.3)	
Central Europe	1104 (25.7)	395 (29.0)	
Latin America	501 (11.7)	178 (13.1)	
North America	383 (8.9)	145 (10.6)	
Western Europe	1430 (33.3)	423 (31.0)	
Heart rate, bpm	75.3±11.7	76.8±11.9	<0.001
Pulse pressure, mmHg	46.5±11.5	49.3±12.3	<0.001
Systolic blood pressure, mmHg	120.5±13.2	122.0±13.5	<0.001
Diastolic blood pressure, mmHg	74.1±9.7	72.7±9.8	<0.001
Body mass index, kg/m <sup>2</sup>	28.0±4.7	28.4±5.8	0.01
Left ventricular ejection fraction, %	36.1±9.2	38.0±9.9	<0.001
Pulmonary congestion, n (%)	2258 (52.5)	798 (58.5)	<0.001
>1 Risk-augmenting factor, n (%)	2130 (49.6)	824 (60.5)	<0.001
Medical history, n (%)			
Prior MI	764 (17.8)	156 (11.4)	<0.001
Prior CABG or PCI	780 (18.1)	154 (11.3)	<0.001
Prior stroke	180 (4.2)	83 (6.1)	0.01
Hypertension	2667 (62.1)	1009 (74.0)	<0.001
Diabetes	1776 (41.3)	625 (45.9)	0.003
Current smoking	985 (22.9)	211 (15.5)	<0.001
Atrial fibrillation/flutter	607 (14.1)	177 (13.0)	0.41
Estimated GFR, mL/min per 1.73m <sup>2</sup>	73.2±21.8	67.6±23.7	<0.001
Qualifying MI: STEMI	3328 (77.4)	963 (70.7)	<0.001
Coronary reperfusion	3879 (90.3)	1158 (85.0)	<0.001
STEMI without reperfusion within 24 h	352 (8.2)	144 (10.6)	0.01
Thrombolytic therapy	207 (4.8)	46 (3.4)	<0.001
Percutaneous coronary intervention	3835 (89.2)	1145 (84.0)	<0.001
Drug-eluting stent	3452 (80.3)	1006 (73.8)	<0.001
Location of MI, n (%)			0.03
Anterior	2944 (68.5)	909 (66.7)	
Inferior	810 (18.8)	243 (17.8)	
Other	544 (12.7)	211 (15.5)	
Killip class ≥II, n (%)	2383 (57.4)	818 (61.4)	0.01
Time to randomization, d	4.3±1.8	4.4±1.7	0.03
Dual-antiplatelet therapy, n (%)	3984 (92.7)	1238 (90.8)	0.03

(Continued)

**Table 1. Continued**

Characteristic	Men (n=4298)	Women (n=1363)	P value
β-Blocker, n (%)	3688 (85.8)	1139 (83.6)	0.04
MRA, n (%)	1780 (41.4)	558 (40.9)	0.76
Diuretics, n (%)	1869 (43.5)	652 (47.8)	0.01
Statin, n (%)	4080 (94.9)	1290 (94.6)	0.68
ACE inhibitor/ARB, n (%)	3360 (78.2)	1076 (78.9)	0.55

Data are given as mean±SD unless otherwise indicated. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; bpm, beats per minute; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; MI, myocardial infarction; MRA, mineralocorticoid receptor agonist; PCI, percutaneous coronary intervention; and STEMI, ST-segment-elevation MI.

\*Other includes Native American, Pacific Islander, Unknown Race, and Other Race.

(Table 1). Women were more likely to be in Killip class ≥II (61.4% versus 57.4%;  $P=0.01$ ) at presentation. At randomization, women and men had similar use of mineralocorticoid receptor antagonists, statins, and ACEis/angiotensin receptor blockers. Women were less likely to be on β-blockers and dual-antiplatelet therapy but were more likely to receive diuretic therapy at randomization (Table 1).

## Primary Outcomes

The primary outcome (cardiovascular death or incident HF) occurred as 197 CEC-adjudicated events in women (8.5 per 100 person-years) and 514 CEC-adjudicated events in men (6.6 per 100 person-years), with an unadjusted hazard ratio (HR) of 1.25 (95% CI, 1.06–1.47;  $P=0.01$ ; Table 2). After adjusting for baseline demographics and risk factors, the association of sex with the primary composite outcome was attenuated (HR, 1.10 [95% CI, 0.92–1.33];  $P=0.28$ ). Sex did not significantly modify the treatment effect of sacubitril/valsartan relative to ramipril on the CEC-adjudicated primary outcome ( $P$  for interaction=0.11; Figure 1). Similar results were observed for investigator-reported outcomes. Women remained at a greater risk of having investigator-reported primary outcomes (HR, 1.18 [95% CI, 1.01–1.38];  $P=0.03$ ) after adjusting for baseline demographics and risk factors (Table 2).

## Secondary Outcomes and Components of the Primary Composite Outcome

Women and men had a similar incidence of cardiovascular death, outpatient HF, all-cause death, composite coronary events, and the composite of cardiovascular death, nonfatal MI, or nonfatal stroke (Table 2). Women had a higher rate of HF-related outcomes than men. Women had a higher incidence of CEC-adjudicated HF hospitalization (5.0 per 100 person-years in women

**Table 2. Unadjusted and Adjusted Outcomes in Men and Women**

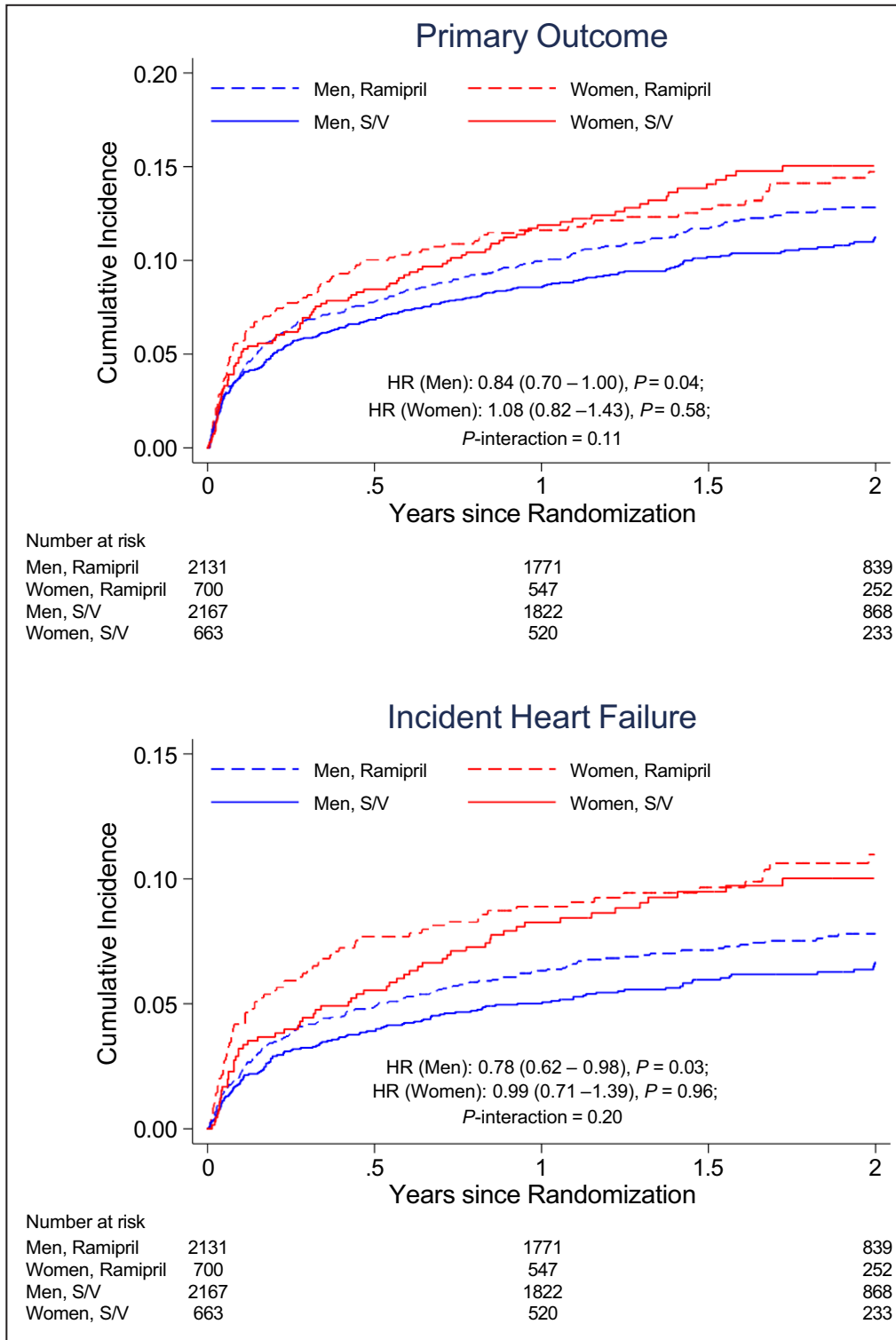
Outcomes	Men (N=4298)		Women (N=1363)		Unadjusted outcomes		Adjusted outcomes*		P for interaction value†
	No. of events	Incidence rate (per 100 person-years)	No. of events	Incidence rate (per 100 person-years)	HR (95% CI) (reference=men)	P value	HR (95% CI) (reference=men)	P value	
Clinical events committee–adjudicated outcomes									
Primary composite outcome	514	6.6	197	8.5	1.25 (1.06–1.47)	0.01	1.10 (0.92–1.32)	0.28	0.11
Cardiovascular death	272	3.3	87	3.5	1.03 (0.81–1.31)	0.81	0.87 (0.67–1.14)	0.33	0.32
HF hospitalization	247	3.1	118	5.0	1.55 (1.25–1.93)	<0.001	1.34 (1.05–1.70)	0.02	0.28
Outpatient HF	70	0.9	26	1.1	1.20 (0.76–1.88)	0.43	1.08 (0.67–1.76)	0.75	0.16
Cardiovascular death or HF hospitalization	463	5.9	180	7.7	1.26 (1.06–1.50)	0.01	1.10 (0.91–1.33)	0.33	0.12
HF hospitalization or outpatient HF	301	3.9	137	5.9	1.48 (1.21–1.81)	<0.001	1.29 (1.04–1.61)	0.02	0.20
Cardiovascular death, nonfatal MI, or nonfatal stroke	507	6.5	157	6.5	1.00 (0.83–1.19)	0.98	0.92 (0.75–1.12)	0.39	0.79
All-cause death	344	4.2	111	4.4	1.05 (0.84–1.29)	0.69	0.83 (0.66–1.06)	0.14	0.26
Composite coronary end point‡	578	7.8	155	6.7	0.85 (0.71–1.01)	0.07	0.83 (0.68–1.00)	0.05	0.66
Investigator-reported outcomes									
Primary composite outcome	688	9.2	271	12.4	1.30 (1.13–1.49)	<0.001	1.18 (1.01–1.38)	0.03	0.31
Cardiovascular death	252	3.1	82	3.3	1.05 (0.82–1.34)	0.71	0.90 (0.68–1.19)	0.45	0.86
HF hospitalization	365	4.7	172	7.6	1.54 (1.29–1.85)	<0.001	1.34 (1.10–1.64)	0.004	0.24
Outpatient HF	195	2.5	76	3.2	1.26 (0.96–1.64)	0.09	1.19 (0.89–1.58)	0.23	0.39

HF indicates heart failure; HR, hazard ratio; and MI, myocardial infarction.

\*Models adjusted for age, race, geographic region, number of risk-augmenting factors, baseline left ventricular ejection fraction, intravenous treatment for pulmonary congestion, history of MI, hypertension, diabetes, current tobacco use, estimated glomerular filtration rate, type of index MI, ST-segment–elevation MI without reperfusion, percutaneous coronary intervention, Killip class, and treatment assignment.

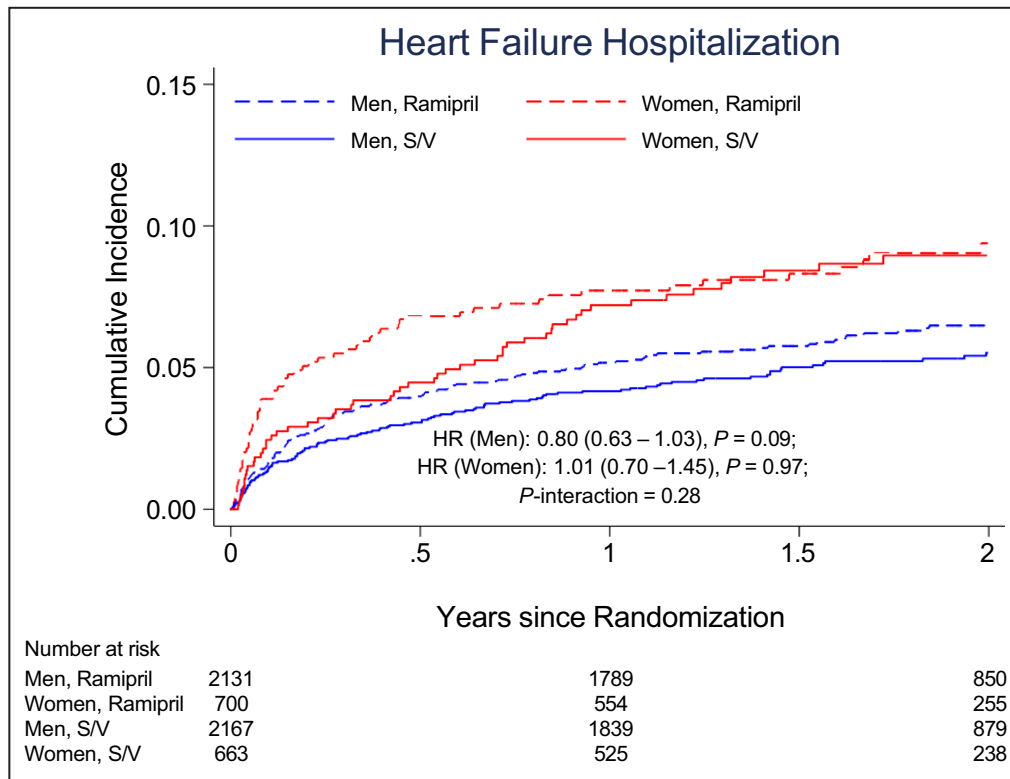
†P for interaction: interaction between sex and treatment, adjusted for percutaneous coronary intervention and geographic region, stratified by type of MI.

‡Coronary composite end point: death from coronary heart disease, nonfatal MI, hospitalization for angina, or coronary revascularization.



**Figure 1.** The cumulative incidence for the primary composite outcome according to sex and treatment assignment in PARADISE-MI.

The HR (reference=ramipril) is adjusted for percutaneous coronary intervention and geographic region, stratified by type of myocardial infarction. HR indicates hazard ratio; PARADISE-MI, Prospective ARNI (Angiotensin Receptor–Neprilysin Inhibitor) Versus ACE (Angiotensin-Converting Enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; and S/V, sacubitril/valsartan.



**Figure 2.** The cumulative incidence for incident heart failure (heart failure hospitalization or outpatient heart failure) and heart failure hospitalization according to sex and treatment assignment in PARADISE-MI.

The HR (reference=ramipril) is adjusted for percutaneous coronary intervention and geographic region, stratified by type of myocardial infarction. HR indicates hazard ratio; PARADISE-MI, Prospective ARNI (Angiotensin Receptor–Neprilysin Inhibitor) Versus ACE (Angiotensin-Converting Enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; and S/V, sacubitril/valsartan.

versus 3.1 per 100 person-years in men; unadjusted HR, 1.55 [95% CI, 1.25–1.93];  $P < 0.001$ ; Figure 2), as well as a higher incidence of investigator-reported HF hospitalization (7.6 per 100 person-years in women versus 4.7 per 100 person-years in men; unadjusted HR, 1.54 [95% CI, 1.29–1.85];  $P < 0.001$ ). Similarly, in crude analyses, women were more likely to experience cardiovascular death or HF hospitalization (HR, 1.26 [95% CI, 1.06–1.50];  $P = 0.01$ ) and HF hospitalization or outpatient HF (HR, 1.48 [95% CI, 1.21–1.81];  $P < 0.001$ ). Women and men had similar incidence rates of all-cause death and cardiovascular death (Figure 3). After adjusting for baseline characteristics, women were still 34% more likely to have a CEC-adjudicated HF hospitalization and 29% more likely to have a CEC-adjudicated HF hospitalization or outpatient HF (Table 2). Similar differences were seen in investigator-reported HF hospitalizations (HR, 1.34 [95% CI, 1.10–1.64];  $P = 0.004$ ). The proportional hazards assumption was found to be significantly violated for some adjusted models. Sensitivity analyses were conducted using an

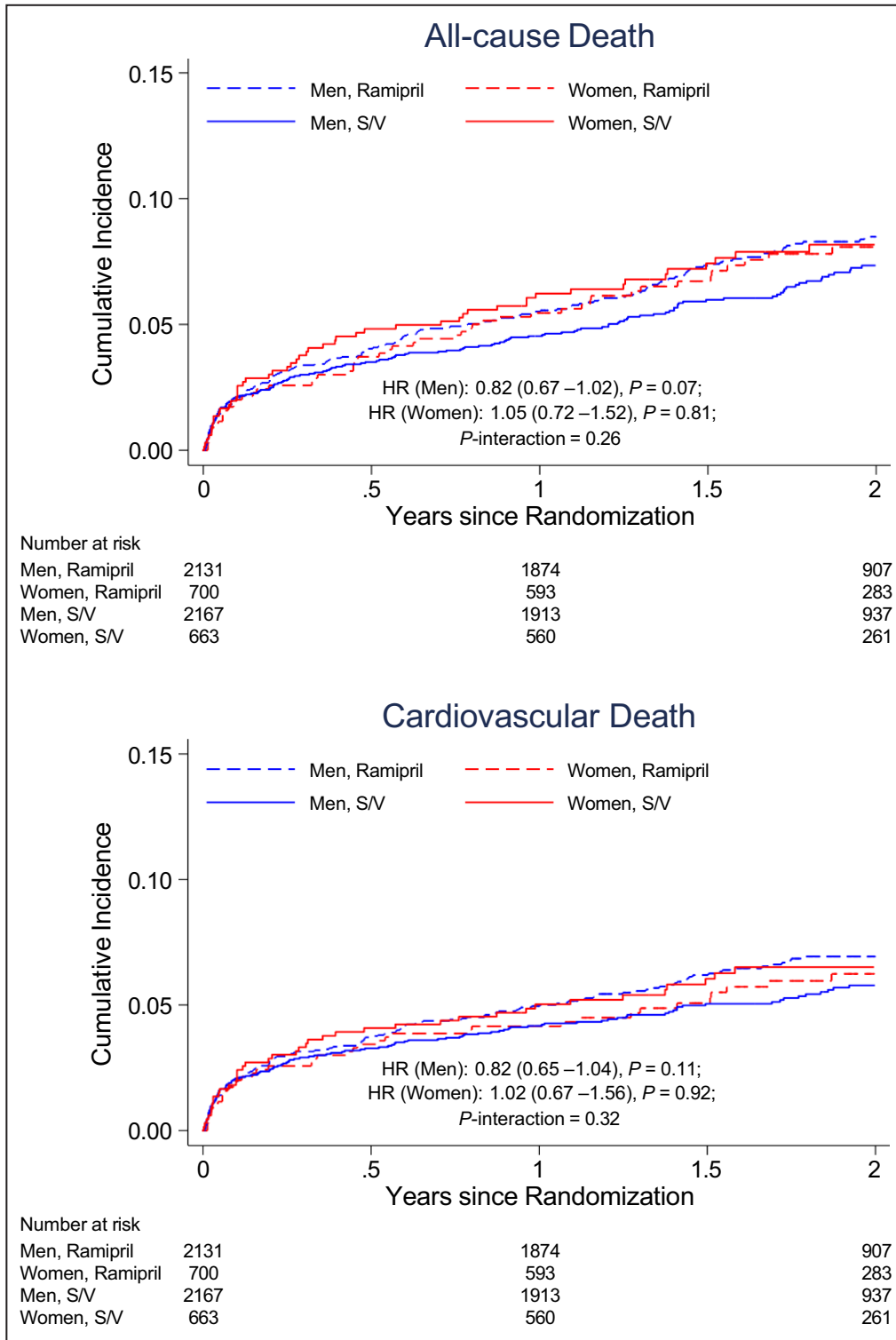
alternative model constructed to address these violations and produced consistent results (Table S1).

### Total (First and Recurrent) Events

For the CEC-adjudicated composite of cardiovascular death and total cardiovascular events, there was a trend toward a higher event rate in women, compared with men (13.7 per 100 person-years in women versus 11.4 per 100 person-years in men; rate ratio [RR], 1.22 [95% CI, 0.99–1.50];  $P = 0.06$ ). The difference was attenuated after adjusting for baseline characteristics (RR, 1.05 [95% CI, 0.86–1.29];  $P = 0.64$ ). When considering investigator-reported outcomes, women were more likely to experience cardiovascular death or total HF events (unadjusted RR, 1.46 [95% CI, 1.21–1.76];  $P < 0.001$ ; adjusted RR, 1.21 [95% CI, 1.00–1.47];  $P = 0.04$ ).

Women were more likely to have total HF hospitalizations and total HF events, both CEC adjudicated and investigator reported (Table 3). After adjusting for baseline characteristics, women were still 39% more





**Figure 3.** The cumulative incidence for all-cause and cardiovascular death, according to sex and treatment assignment in PARADISE-MI.

The HR (reference=ramipril) is adjusted for percutaneous coronary intervention and geographic region, stratified by type of myocardial infarction. HR indicates hazard ratio; PARADISE-MI, Prospective ARNI (Angiotensin Receptor–Neprilysin Inhibitor) Versus ACE (Angiotensin-Converting Enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; and S/V, sacubitril/valsartan.

**Table 3. Total (First and Recurrent) Events in Women Versus Men**

Outcomes	Men (N=4298)		Women (N=1363)		Unadjusted outcomes		Adjusted outcomes*		P for interaction value†
	No. of events	Event rate (per 100 person-years)	No. of events	Event rate (per 100 person-years)	Rate ratio (95% CI) (reference=men)	P value	Rate ratio (95% CI) (reference=men)	P value	
Clinical events committee–adjudicated outcomes									
Cardiovascular death and total cardiovascular events (HHF, MI, and CVA)	930	11.4	343	13.7	1.22 (0.99–1.50)	0.06	1.05 (0.86–1.29)	0.64	0.40
Cardiovascular death and total HF events‡	710	8.7	281	11.2	1.30 (1.03–1.64)	0.03	1.08 (0.86–1.36)	0.50	0.22
Total HF hospitalizations	360	4.4	166	6.6	1.54 (1.17–2.02)	0.002	1.39 (1.05–1.84)	0.02	0.37
Total outpatient HF events	78	1.0	28	1.1	1.17 (0.72–1.88)	0.53	1.03 (0.61–1.72)	0.92	0.23
Total HF events‡	438	5.3	194	7.8	1.48 (1.51–1.89)	0.002	1.31 (1.01–1.69)	0.04	0.22
Investigator-reported outcomes									
Cardiovascular death and total HF events‡	1023	12.5	451	18.0	1.46 (1.21–1.76)	<0.001	1.21 (1.00–1.47)	0.04	0.22
Total HF hospitalizations	557	6.8	285	11.4	1.72 (1.37–2.17)	<0.001	1.47 (1.16–1.86)	0.001	0.23
Total HF events‡	770	9.4	368	14.7	1.59 (1.31–1.93)	<0.001	1.37 (1.13–1.67)	0.002	0.13

CVA indicates cerebrovascular accident; HF, heart failure; HHF, hospitalization for HF; and MI, myocardial infarction.

\*Models adjusted for age, race, geographic region, number of risk-augmenting factors, baseline left ventricular ejection fraction, intravenous treatment for pulmonary congestion, history of MI, hypertension, diabetes, current tobacco use, estimated glomerular filtration rate, type of index MI, ST-segment–elevation MI without reperfusion, percutaneous coronary intervention, Killip class, and treatment assignment.

†P for interaction: interaction between sex and treatment, adjusted for percutaneous coronary intervention and geographic region, stratified by type of MI.

‡Total HF events; HF hospitalizations and outpatient episodes of HF.

likely to experience CEC-adjudicated total HF hospitalizations, and they were 31% more likely to experience CEC-adjudicated total HF hospitalizations and outpatient episodes of HF (Table 3). There were similar differences in investigator-reported outcomes: women were 47% more likely to have HF hospitalizations and 37% more likely to have HF hospitalizations and outpatient HF compared with men (Table 3).

## Safety Events

Irrespective of treatment assignment, women were more likely to have serious adverse events (44.6% versus 38.7%;  $P < 0.001$ ) and adverse events (86.1% versus 81.5%;  $P < 0.001$ ). Women had similar rates of drug discontinuation attributable to adverse events compared with men (14.5% versus 12.5%;  $P = 0.07$ ), with no significant sex-by-treatment interaction (Table 4 and Figure 4). Women were more likely to have cough (14.7% versus 9.9%;  $P < 0.001$ ), hepatotoxicity (6.7% versus 4.8%;  $P = 0.008$ ), and renal impairment (15.8% versus 10.2%;  $P < 0.001$ ; Table 4) than men. After adjusting for baseline eGFR, women were still more likely to have serious adverse events (odds ratio [OR], 1.21 [95% CI, 1.07–1.38];  $P = 0.003$ ), adverse events (OR, 1.37 [95% CI, 1.14–1.64];  $P = 0.001$ ), and renal impairment (OR, 1.34 [95% CI, 1.11–1.61];  $P = 0.002$ ). Women were more likely to have elevated liver enzymes; however, the event rate was low for both men and women. Both women and men were more likely to have hypotension when randomized to sacubitril/valsartan and less likely to have cough when compared with those randomized to ramipril (Table 4). Differences in treatment-related adverse events, serious adverse events, or drug discontinuation attributable to adverse events between sacubitril/valsartan and ramipril did not differ by sex ( $P$  for interaction  $> 0.05$  for all adverse events of interest; Table 4).

## DISCUSSION

Our analyses identified significant differences in baseline clinical characteristics in men and women following high-risk MI. There were no significant differences in all-cause death or cardiovascular death between men and women. However, women were more likely to have HF-related events, in particular HF hospitalizations. Women were also more likely to experience drug-related serious adverse events.

Consistent with prior studies, women in PARADISE-MI were older than men, and they had a higher prevalence of comorbidities, such as hypertension and diabetes, but a lower prevalence of prior MI.<sup>13–15</sup> Estrogen has been shown to have a cardioprotective effect, and as a result, women tend to be older when they develop cardiovascular disease.<sup>14,15</sup>

After menopause, women have similar risks of developing cardiovascular disease compared with their male counterparts. Because women tend to be older, they likely have a higher burden of comorbidities and cardiovascular risk factors.

Analysis of the INTERHEART study shows that the same risk factors appear to contribute to higher population-attributable risk in women compared with men.<sup>16</sup> For example, diabetes is associated with 19.1% population-attributable risk in women, compared with 10.1% in men, and hypertension is associated with 35.8% and 19.5% population-attributable risk in women and men, respectively. Consistent with other studies, women in PARADISE-MI also had higher Killip class when they presented with their qualifying MI.<sup>17</sup> These epidemiologic differences may contribute to different outcomes in men and women with acute coronary syndromes (ACSs).

Significant advances in the treatment of acute MI have been made for both men and women. Indeed, the mortality rate following ACS has steadily decreased in the past several decades.<sup>1</sup> Some studies suggest that women have similar or lower mortality following ACS after adjusting for comorbidities and severity of angiographically documented disease.<sup>3,18,19</sup> Others show that women are treated less aggressively when presenting with ACS, and they have higher in-hospital, 1-year, and 5-year mortality, with some differences persisting even after adjusting for baseline differences.<sup>1,13,20–22</sup> However, in PARADISE-MI, no significant differences were detected in all-cause death or cardiovascular death between men and women, both in crude and adjusted analyses over 2.5 to 3 years.

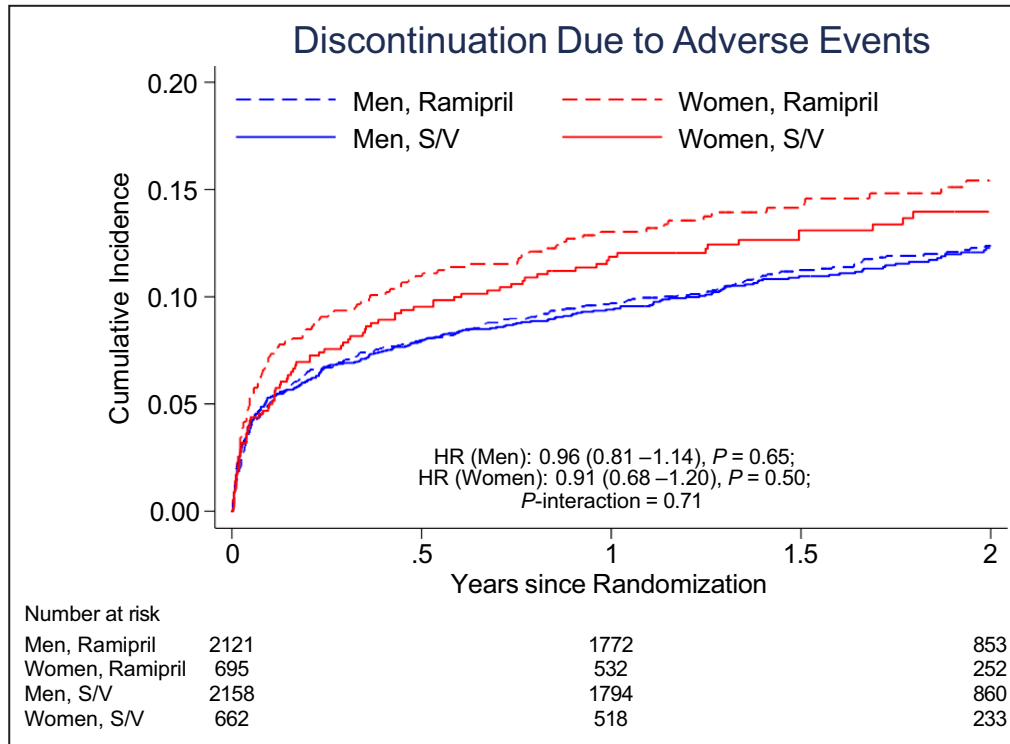
In addition to mortality, nonfatal events, such as recurrent coronary events and HF events, are also important outcomes following acute MI. In PARADISE-MI, men were more likely to have prior MI and coronary interventions. However, we did not find any significant differences in adjusted and unadjusted composite coronary end points following the index MI. In comparison, in prior studies, women were more likely to have other nonfatal complications after MI, such as stroke, HF, serious bleeding after PCI, and reinfarction.<sup>5,23</sup> In a recent analysis of patients from the ISACS-TC (The International Survey of Acute Coronary Syndromes in Transitional Countries) registry, women were 34% more likely to develop de novo HF following STEMI, and those who developed HF were 29% more likely to die within 30 days.<sup>24</sup> Our analyses showed that women were 29% more likely to have first HF hospitalization or outpatient HF and 34% more likely to have first HF hospitalization alone, even after adjusting for baseline differences. For total HF events, women were 39% more likely to have HF hospitalizations and 31% more likely to have total HF events (HF hospitalization and outpatient HF). This was comparable to the VALIANT trial,

**Table 4. Adherence, Tolerability, and Safety in Men and Women**

Variable	Men		Women			Interaction P value* (sex x treatment)	P value (women vs men)
	All	Sacubitril- valsartan (n=2167)	Ramipril (n=2131)	All	Sacubitril- valsartan (n=663)		
Drug discontinuation because of adverse events	539 (12.5)	266 (12.3)	273 (12.8)	197 (14.5)	91 (13.7)	106 (15.1)	0.71
Serious adverse event	1664 (38.7)	856 (39.5)	808 (37.9)	608 (44.6)	290 (43.7)	318 (45.4)	0.28
Adverse event	3503 (81.5)	1778 (82.0)	1725 (80.9)	1174 (86.1)	574 (86.6)	600 (85.7)	0.10
Adverse events of interest							
Hypotension	1067 (24.8)	607 (28.0)	460 (21.6)	355 (26.0)	195 (29.4)	160 (22.9)	0.97
Cough	426 (9.9)	184 (8.5)	242 (11.4)	200 (14.7)	71 (10.7)	129 (18.4)	0.10
Angioedema	21 (0.5)	9 (0.4)	12 (0.6)	10 (0.7)	5 (0.8)	5 (0.7)	0.64
Hepatotoxicity	208 (4.8)	92 (4.2)	116 (5.4)	91 (6.7)	40 (6.0)	51 (7.3)	0.82
Hyperkalemia	456 (10.6)	231 (10.7)	225 (10.6)	130 (9.5)	70 (10.6)	60 (8.6)	0.30
Cognitive impairment	82 (1.9)	40 (1.8)	42 (2.0)	32 (2.3)	14 (2.1)	18 (2.6)	0.75
Hypersensitivity	451 (10.5)	240 (11.1)	211 (9.9)	167 (12.3)	82 (12.4)	85 (12.1)	0.59
Risk of malignancy	118 (2.7)	61 (2.8)	57 (2.7)	38 (2.8)	24 (3.6)	14 (2.0)	0.15
Renal impairment	440 (10.2)	221 (10.2)	219 (10.3)	215 (15.8)	108 (16.3)	107 (15.3)	0.64
Statin drug-drug interaction	169 (3.9)	75 (3.5)	94 (4.4)	66 (4.8)	31 (4.7)	35 (5.0)	0.54
Laboratory abnormalities							
Elevated serum creatinine level							
>2.0mg/dL	263 (6.1)	129 (6.0)	134 (6.3)	70 (5.1)	33 (5.0)	37 (5.3)	0.99
>2.5mg/dL	112 (2.6)	53 (2.4)	59 (2.8)	20 (1.5)	14 (2.1)	6 (0.9)	0.048
>3.0mg/dL	46 (1.1)	16 (0.7)	30 (1.4)	11 (0.8)	7 (1.1)	4 (0.6)	0.07
Elevated serum potassium level							
>5.5mmol/L	570 (13.3)	301 (13.9)	269 (12.6)	194 (14.2)	102 (15.4)	92 (13.1)	0.68
>6.0mmol/L	146 (3.4)	69 (3.2)	77 (3.6)	41 (3.0)	23 (3.5)	18 (2.6)	0.22
Elevated aspartate aminotransferase level							
>3x Upper limit of reference range	29 (0.7)	13 (0.6)	16 (0.8)	21 (1.5)	10 (1.5)	11 (1.6)	0.75
>5x Upper limit of reference range	11 (0.3)	5 (0.2)	6 (0.3)	10 (0.7)	3 (0.5)	7 (1.0)	0.52
Elevated alanine aminotransferase level							
>3x Upper limit of reference range	50 (1.2)	23 (1.1)	27 (1.3)	20 (1.5)	9 (1.4)	11 (1.6)	0.95
>5x Upper limit of reference range	12 (0.3)	7 (0.3)	5 (0.2)	11 (0.8)	4 (0.6)	7 (1.0)	0.34

Data are given as number (percentage) unless otherwise indicated.

\* P for interaction: adjusted for percutaneous coronary intervention and region, stratified by type of myocardial infarction.



**Figure 4.** The cumulative incidence of study drug discontinuation because of adverse events, according to sex and treatment assignment in PARADISE-MI.

The HR (reference=ramipril) is adjusted for baseline estimated glomerular filtration rate. HR indicates hazard ratio; PARADISE-MI, Prospective ARNI (Angiotensin Receptor–Neprilysin Inhibitor) Versus ACE (Angiotensin-Converting Enzyme) Inhibitor Trial to Determine Superiority in Reducing Heart Failure Events After Myocardial Infarction; and S/V, sacubitril/valsartan.

where women were 36% more likely to be hospitalized for HF after adjusting for baseline differences.<sup>6</sup> When considering total events (first and recurrent), women were 48% more likely to have total HF events; however, this difference dissipates after adjusting for baseline differences.

These differences in outcomes are likely multifactorial, attributable to both underlying sex-based differences in the pathophysiological features and sex-related differences in the treatment of ACS. Women have smaller epicardial coronary arteries and are less likely to have obstructive coronary artery disease; the role of microvasculature seems to be more prominent in coronary perfusion.<sup>25</sup> Furthermore, after MI, women and men undergo left ventricular remodeling differently. Postmortem studies suggest that men have a higher apoptotic rate after acute MI and are more likely to undergo ventricular dilation.<sup>26</sup> Although it may be detrimental in the long-term, initial dilation in the immediate phase may be beneficial in maintaining stroke volume and cardiac output.<sup>26</sup> In response to volume overload, women are more prone to develop concentric remodeling, whereas men undergo eccentric remodeling.<sup>26</sup> Men tend to develop HF with reduced ejection fraction, whereas women tend to develop HF

with preserved ejection fraction. These differences in pathophysiological features may account for some difference in outcomes.

In addition to sex-based differences in pathophysiological features, studies have shown that women are treated differently when they present with acute MI. In the ISACS-TC registry, women had a longer delay before arrival at the hospital (median, 270 minutes for women versus 240 minutes for men) because of the lag between first medical contact and hospital presentation.<sup>27</sup> Women are less likely to receive reperfusion therapy when they present with MI,<sup>5,28,29</sup> and they have a longer door-to-balloon time when presenting with STEMI.<sup>28,30</sup> Women are also less likely to receive aggressive medical management<sup>5</sup> attributable to less treatment initiation (not treatment adherence).<sup>31</sup> Consistent with prior studies, in PARADISE-MI, fewer women than men received reperfusion therapy (including PCI) within 24 hours after presenting with STEMI.

Our analysis also showed a higher incidence of drug-related adverse events in women. In the primary analysis, participants randomized to receive sacubitril/valsartan had a higher incidence of hypotension and a lower incidence of cough than those assigned to ramipril.<sup>12</sup> In our analysis, women had more serious adverse

events and adverse events, mostly driven by more cough, hepatotoxicity, and renal impairment regardless of study drug assigned. Given women's and men's differences in physiological features, body composition, and hormonal changes, it is possible that sacubitril/valsartan and ramipril have different pharmacokinetics in women and men.<sup>32</sup> It has been well established that women and men have different ACEi-related adverse events, women are 2 to 3 times more likely to report cough when taking an ACEi,<sup>32–34</sup> and women are more likely to have spontaneously reported adverse drug events.<sup>35</sup> On the other hand, it has not been well established whether women have more adverse events with sacubitril/valsartan.<sup>36</sup> Indeed, we did not find sex to be a modifier for study drug–related adverse events. Further studies are needed to assess the different adverse event profile in men versus women.

Our study findings should be interpreted with the following limitations. First, our subgroup analysis of PARADISE-MI included a population who was highly selected for left ventricular dysfunction, therefore limiting the generalizability of our findings. In particular, although the observed differences in demographics between men and women and disparities in receiving invasive management for acute MI were consistent with prior studies, additional large and current epidemiologic studies are needed. Second, among the 5661 participants, only 24% (1363) were women, likely underpowered to detect differences in women receiving ramipril versus sacubitril/valsartan.

In conclusion, in contemporary patients with acute MI and with reduced LVEF, pulmonary congestion, or both, women were older and had more comorbidities compared with men. Women received less aggressive treatment, were more likely to experience adverse events, and had a higher rate of HF during follow-up. Sex did not modify the treatment effects of sacubitril/valsartan.

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### Supplemental Material

Table S1

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