Effects of Sacubitril/Valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) According to Background Therapy

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Background—In the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), the angiotensin receptor neprilysin inhibitor sacubitril/valsartan was more effective than the angiotensin-converting enzyme inhibitor enalapril in patients with heart failure and reduced ejection fraction. We examined whether this benefit was consistent irrespective of background therapy.

Methods and Results—We examined the effect of study treatment in the following subgroups: diuretics (yes/no), digitalis glycoside (yes/no), mineralocorticoid receptor antagonist (yes/no), and defibrillating device (implanted defibrillating device, yes/no). We also examined the effect of study drug according to β-blocker dose (≥50% and <50% of target dose) and according to whether patients had undergone previous coronary revascularization. We analyzed the primary composite end point of cardiovascular death or heart failure hospitalization, as well as cardiovascular death. Most randomized patients (n=8399) were treated with a diuretic (80%) and β-blocker (93%); 47% of those taking a β-blocker were treated with ≥50% of the recommended dose. In addition, 4671 (56%) were treated with a mineralocorticoid receptor antagonist, 2539 (30%) with digoxin, and 1243 (15%) had a defibrillating device; 2640 (31%) had undergone coronary revascularization. Overall, the sacubitril/valsartan versus enalapril hazard ratio for the primary composite end point was 0.80 (95% confidence interval, 0.73–0.87; $P<0.001$) and for cardiovascular death was 0.80 (0.71–0.89; $P<0.001$). The effect of sacubitril/valsartan was consistent across all subgroups examined. The hazard ratio for primary end point ranged from 0.74 to 0.85 and for cardiovascular death ranged from 0.75 to 0.89, with no treatment-by-subgroup interaction.

Conclusions—The benefit of sacubitril/valsartan, over an angiotensin-converting enzyme inhibitor, was consistent regardless of background therapy and irrespective of previous coronary revascularization or β-blocker dose.

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Key Words: heart failure ■ neprilysin ■ sacubitril/valsartan

Sacubitril/valsartan (formerly known as LCZ 696) is a first-in-class angiotensin receptor neprilysin inhibitor shown to be superior to enalapril in patients with heart failure with reduced ejection fraction (EF).[1,2] As such, sacubitril/valsartan has been recommended as a more effective alternative to an angiotensin-converting enzyme (ACE) inhibitor to be used in conjunction with other evidence-based treatments for this type of heart failure.[3,4] Of course, it is of interest to know how the effect of sacubitril/valsartan compares with that of enalapril when combined with these other proven therapies. Here, we

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examine outcomes in patients randomly assigned to sacubitril/valsartan, versus enalapril, according to background use of

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*A list of all PARADIGM-HF study participants is given in the Data Supplement.

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β-blockers, mineralocorticoid receptor antagonists (MRAs), diuretics, digitalis glycosides implanted cardioverter/defibrillator devices, and previous coronary revascularization.[5–14]

Methods

Patients

The background and results of PARADIGM-HF have been published.[1–3] Briefly, PARADIGM-HF was a randomized, double-blind, and prospective comparison of sacubitril/valsartan with enalapril in patients with chronic heart failure with reduced EF. Eligibility requirements at screening included an age of at least 18 years, New York Heart Association functional class II–IV symptoms, and a left ventricular EF of ≤40%. Patients were required to be taking an ACE inhibitor or angiotensin receptor blocker in a dose equivalent to enalapril 10 mg daily for at least 4 weeks before screening, along with a stable dose of a β-blocker (unless contraindicated or not tolerated) and a MRA if indicated. Exclusion criteria included symptomatic hypotension or systolic blood pressure <100 mm Hg at screening or <95 mm Hg at randomization, estimated glomerular filtration rate <30 mL/min per 1.73 m^2, serum potassium >5.2 mmol/L at screening or >5.4 mmol/l at randomization, and unacceptable side effects to ACE inhibitors or angiotensin receptor blockers. The trial was approved by the ethics committees at each institution participating in the trial, and all patients gave written, informed consent.

Trial Outcomes

The primary outcome of PARADIGM-HF was the composite of cardiovascular death or heart failure hospitalization, and examination of each component of this composite was prespecified. In this report, we examine the effect of sacubitril/valsartan compared with that of enalapril on the primary outcome and cardiovascular death

Background Treatment Subgroups

We examined the effect of sacubitril/valsartan, compared with that of enalapril according to background pharmacological and device therapy. Subgroups were limited to those >1000 and only split into 2 groups to minimize the likelihood of a type 1 error.[15,16] Therefore, the groups analyzed included diuretics (yes/no), digitalis glycoside (yes/no), MRA (yes/no) and defibrillating device (implantable cardioverter-defibrillator or cardiac resynchronization therapy plus defibrillator, yes/no). The subgroups of patients not taking a β-blocker and without cardiac resynchronization therapy were too small to analyze. We did, however, examine the effect of study drug according to β-blocker dose, defined as ≥50% target dose and <50% of target dose. Target daily doses were taken from contemporary guidelines and included carvedilol 50 mg, bisoprolol 10 mg, metoprolol succinate 200 mg, metoprolol tartrate 200 mg, and nebivolol 10 mg; patients (n=254) taking other β-blockers were classified as taking <50% target dose. We also examined the effect of study drug according to whether patients had undergone previous coronary revascularization, given the evidence that surgical revascularization has beneficial effects on clinical outcomes.

Statistical Analysis

The efficacy analyses were performed using a Cox proportional hazards model, including treatment and region. An analysis was performed in each subgroup, and a treatment-by-subgroup interaction

Table. Primary End Point (Composite of Death From Cardiovascular Causes or Hospitalization for Heart Failure) and Death From Cardiovascular Causes According to Baseline Treatment, History of Coronary Revascularization, and Baseline β-blocker Dose

	Primary End Point				Cardiovascular Death			
	Enalapril n/N (%)	Sacubitril/ Valsartan n/N (%)	HR (95% CI)	Interaction *P* Value	Enalapril n/N (%)	Sacubitril/ Valsartan n/N (%)	HR (95% CI)	Interaction *P* Value
All patients	1117/4212 (26.5)	914/4187 (21.8)	0.80 (0.73–0.87)		693/4212 (16.5)	558/4187 (13.3)	0.80 (0.71–0.89)	
Diuretic								
No (n=1661)	157/837 (18.8)	129/824 (15.7)	0.83 (0.65–1.04)	0.915	107/837 (12.8)	92/824 (11.2)	0.89 (0.67–1.17)	0.513
Yes (n=6738)	960/3375 (28.4)	785/3363 (23.3)	0.80 (0.72–0.87)		586/3375 (17.4)	466/3363 (13.9)	0.79 (0.70–0.89)	
MRA								
No (n=3728)	494/1812 (27.2)	399/1916 (20.8)	0.74 (0.65–0.84)	0.104	304/1812 (16.8)	243/1916 (12.7)	0.75 (0.63–0.89)	0.319
Yes (n=4671)	623/2400 (26.0)	515/2271 (22.7)	0.85 (0.76–0.96)		389/2400 (16.2)	315/2271 (13.9)	0.84 (0.73–0.98)	
Digoxin								
No (n=5860)	717/2896 (24.8)	617/2964 (20.8)	0.81 (0.73–0.91)	0.623	431/2896 (14.9)	370/2964 (12.5)	0.82 (0.72–0.95)	0.537
Yes (n=2539)	400/1316 (30.4)	297/1223 (24.3)	0.78 (0.67–0.90)		262/1316 (19.9)	188/1223 (15.4)	0.76 (0.63–0.92)	
ICD/CRT								
No (n=7156)	942/3592 (26.2)	761/3564 (21.4)	0.79 (0.72–0.87)	0.561	609/3592 (17.0)	491/3564 (13.8)	0.80 (0.71–0.90)	0.912
Yes (n=1243)	175/620 (28.2)	153/623 (24.6)	0.84 (0.67–1.04)		84/620 (13.6)	67/623 (10.8)	0.76 (0.55–1.05)	
Previous coronary revascularization								
No (n=5759)	761/2921 (26.1)	626/2838 (22.1)	0.83 (0.74–0.92)	0.256	504/2921 (17.3)	397/2838 (14.0)	0.80 (0.70–0.91)	0.925
Yes (n=2640)	356/1291 (27.6)	288/1349 (21.4)	0.74 (0.63–0.86)		189/1291 (14.6)	161/1349 (11.9)	0.81 (0.65–1.00)	
β-blocker target dose								
<50% (n=4167)	566/2123 (26.7)	455/2044 (22.3)	0.82 (0.72–0.93)	0.973	353/2123 (16.6)	289/2044 (14.1)	0.85 (0.73–0.99)	0.923
≥50% (n=3644)	440/1789 (24.6)	390/1855 (21.0)	0.82 (0.72–0.94)		258/1789 (14.4)	229/1855 (12.4)	0.84 (0.70–1.00)	

CI indicates confidence interval; CRT, cardiac resynchronization therapy; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; and MRA, mineralocorticoid receptor antagonist.

was tested. All analyses were performed using Stata version 14 (College Station, TX). $P<0.05$ was considered statistically significant.

Results

The large majority of patients in PARADIGM-HF were treated with a diuretic (80%) and β-blocker (93%); 3645 patients (47% of those taking a β-blocker) were treated with ≥50% of a guideline-recommended dose of β-blocker. Of the 8399 patients randomized, 4671 (56%) were treated with an MRA, 2539 (30%) with a digitalis glycoside, and 1243 (15%) had a defibrillating device in situ. Overall, 2640 (31%) had a history of coronary revascularization.

Figures 1 and 2 show the cumulative incidence of the primary end point and of death from cardiovascular causes in

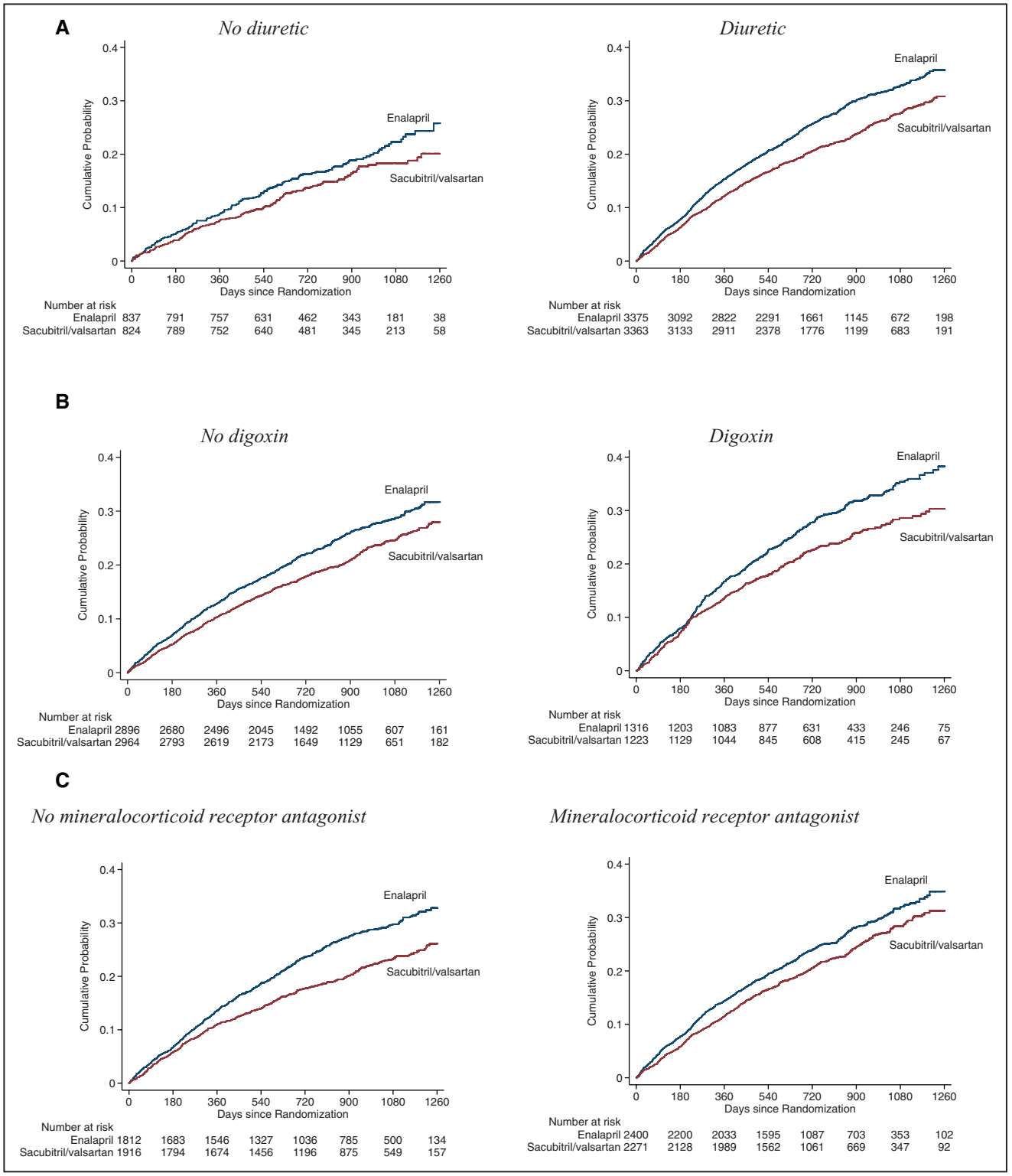

Figure 1. *Continued*

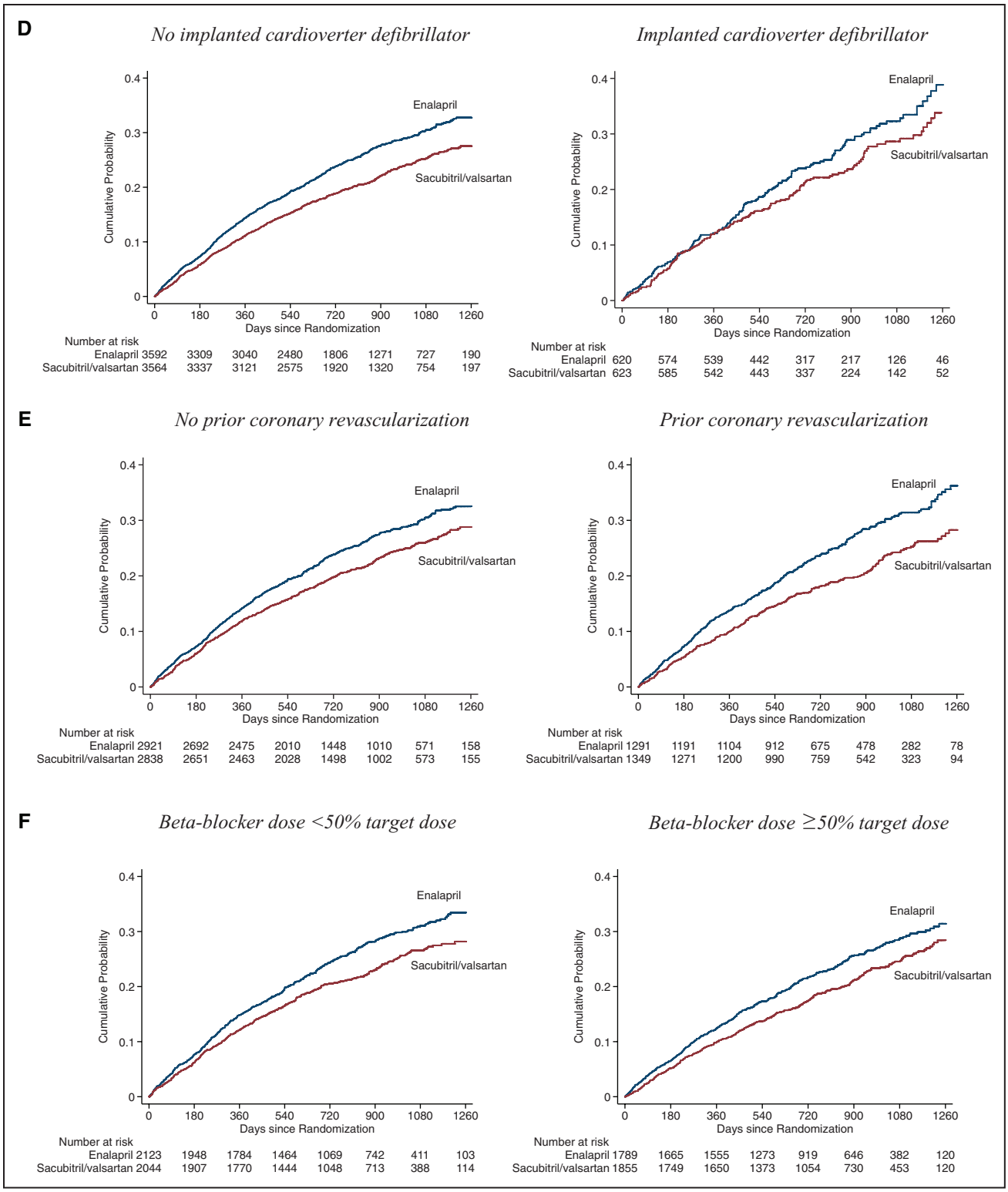

Figure 1 Continued. Cumulative incidence of the primary end point (composite of death from cardiovascular causes or hospitalization for heart failure) in the enalapril and sacubitril/valsartan groups, according to background treatment (**A**, by diuretic therapy; **B**, by digoxin therapy; **C**, by mineralocorticoid receptor antagonist therapy; **D**, by implanted cardioverter-defibrillator; **E**, by coronary revascularization; and **F**, by β-blocker dose <50% and ≥50% of target).

each treatment subgroups examined. In each subgroup, the incidence of the primary end point in the enalapril group was higher in patients who received the background treatment of interest than in those who did not. This finding was also observed in patients with previous coronary revascularization, compared with those who did not. The same pattern was observed for cardiovascular death with the exception of previous coronary revascularization. In patients with previous

coronary revascularization, the pattern was reversed, with a lower risk of death from cardiovascular causes compared with those who had not undergone coronary revascularization. In the case of β-blockers, those receiving a lower dose had worse outcomes than those taking a higher dose.

The Table summarizes the sacubitril/valsartan versus enalapril hazard ratio for the primary composite outcome of cardiovascular death or heart failure hospitalization, and cardiovascular death alone, according to background therapy. As can be seen, the benefit of sacubitril/valsartan over enalapril was consistent across all treatment subgroups, with no suggestion of a statistically significant interaction between background therapy and treatment effect for either end point.

As described in the Methods section of this article, we did not examine subgroups with <1000 patients because the increased play of chance with small numbers. We did, however, examine the effect of sacubitril/valsartan compared with that of enalapril according to background β-blocker dose. The effect of sacubitril/valsartan, versus enalapril, was identical in patients treated with ≥50% of target doses of β-blockers, compared with those treated with a lower dose (Table).

Among patients with a defibrillating device, the effect of sacubitril/valsartan, versus enalapril, on both outcomes analyzed was similar to that in patients without such a device (Table).

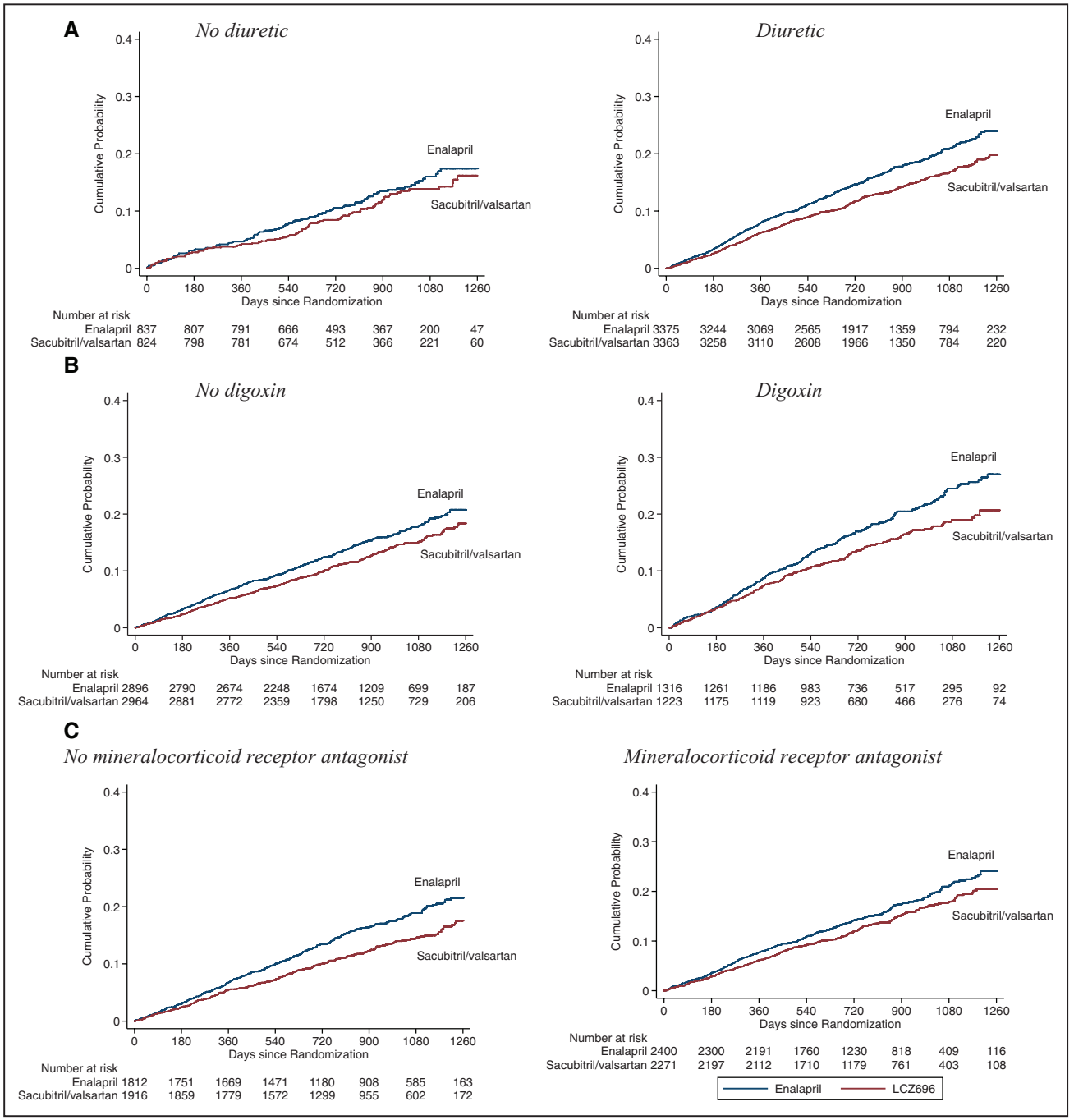

Figure 2. *Continued*

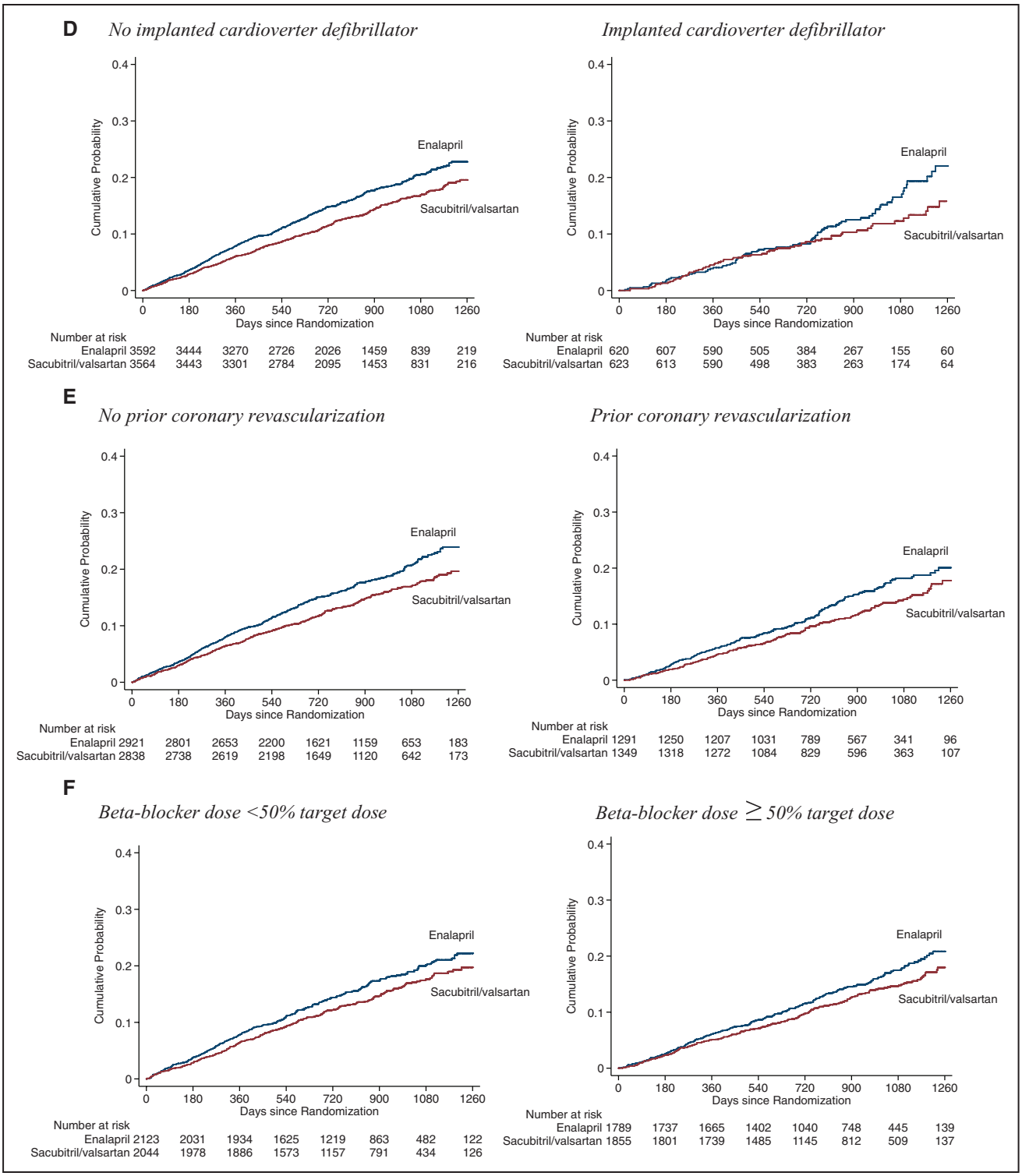

Figure 2 Continued. Cumulative incidence of death from cardiovascular causes in the enalapril and sacubitril/valsartan groups, according to background treatment (**A**, by diuretic therapy; **B**, by digoxin therapy; **C**, by mineralocorticoid receptor antagonist therapy; **D**, by implanted cardioverter-defibrillator; **E**, by coronary revascularization; and **F**, by β-blocker dose <50% and ≥50% of target).

Finally, patients with and without previous coronary revascularization also had a similar benefit of sacubitril/valsartan over enalapril (Table).

There were a few minor differences in the baseline characteristics between treatment groups within each subgroup; however, if corrected for multiple comparisons, none were statistically significant (Data Supplement). The estimate of effect of sacubitril/valsartan on the primary end point and cardiovascular death was not changed by adjusting for these variables in a multivariable model (Data Supplement).

Discussion

PARADIGM-HF was designed to compare sacubitril/valsartan to an ACE inhibitor in a broad spectrum of patients with heart failure with reduced EF using the target dose of enalapril shown to reduce mortality, when compared with placebo, in the SOLVD-T treatment trial (Studies of Left Ventricular Dysfunction).[6] When SOLVD-T was conducted, background therapy consisted mainly of diuretics (85%) and a digitalis glycoside (67%); only 7.7% of patients were treated with a β-blocker at baseline.

Since the completion of SOLVD-T, digoxin has been shown to reduce the risk of hospital admission for worsening heart failure when added to an ACE inhibitor and, more importantly, other treatments, notably β-blockers, and MRAs have been shown to reduce both mortality and hospitalization when used incrementally.[7–12] Implantable cardioverter/defibrillators, which also reduce mortality, are another innovative treatment introduced since the time of SOLVD-T.[13] Finally, the use of coronary revascularization has also become more prevalent since the time of SOLVD-T (31% of patients in PARADIGM-HF had undergone this when compared with 21% patients in SOLVD-T) and has recently been shown to improve long-term survival in patients with heart failure with reduced EF and obstructive epicardial coronary artery disease.[14] Consequently, it is important to examine whether sacubitril/valsartan, proposed as a more effective alternative to an ACE inhibitor, had a consistent benefit over enalapril irrespective of contemporary background therapy. We have clearly shown that this is the case with respect to digitalis glycosides and MRAs. Because β-blockers were used in the vast majority of patients, we could not carry out a meaningful analysis of the effects of sacubitril/valsartan in individuals not receiving this treatment. We did, however, examine the effect of sacubitril/valsartan according to β-blocker dose and found that the benefit over enalapril was consistent irrespective of dose category. The findings were similar for patients with and without an implanted defibrillating device and also for patients who had previously undergone coronary revascularization.

In each treatment subgroup, the incidence of the primary end point was higher in patients who received the treatment of interest than in those who did not, likely reflecting confounding by indication, that is, that these additional therapies were used in patients with more advanced heart failure (eg, a severely and persistently reduced left ventricular EF) or with comorbidities associated with worse outcomes (eg, atrial fibrillation). The same was largely true for cardiovascular death with 2 exceptions. The rates of cardiovascular death were similar irrespective of defibrillating device status although there were relatively few events in those with such devices and limited power to show a difference between patients with and without a device. In patients with previous coronary revascularization, the rate of cardiovascular death was lower than in those without previous revascularization (ie, the converse of what was seen for the primary end point). This may be a chance finding, reflect confounding by indication (surgery is more likely to be undertaken in healthier patients), or a powerful effect of revascularization on survival but not hospital admission. In the case of β-blockers, the worse outcomes in those taking a lower dose may reflect confounding (sicker patients unable to tolerate higher doses) or a greater benefit from higher doses.[17]

As with all analyses like these, there are limitations. Most of these subgroups were not prespecified. Despite requiring each subgroup to include at least 1000 patients, such analyses are inherently underpowered. We could not examine the effect of sacubitril/valsartan compared with that of enalapril in patients receiving other evidence-based therapies.[18,19] The use of evidence-based, guideline-directed therapies may have led to confounding by indication and geographic variations in their use may have led to further confounding. However, analyses of the geographic variation in efficacy of sacubitril/valsartan confirmed that the efficacy of the drug did not vary by geographic region.[3] Furthermore, our results were adjusted for geographic region as randomization was stratified by region and further adjustment made no difference to the findings.[20] Only 574 patients had a cardiac resynchronization therapy device implanted, and both ivabradine and hydralazine combined with isosorbide dinitrate were used infrequently.

In summary, we found a consistent benefit of sacubitril/valsartan, over an ACE inhibitor, regardless of background therapy, including the use of a diuretic, MRA, digoxin, and implanted cardiac defibrillator. A similar benefit was also observed in patients with and without previous coronary revascularization and irrespective of β-blocker dose.

Disclosures

Drs Gong, Lefkowitz, Rizkala, and Shi are employees of Novartis. The PARADIGM-HF trial was sponsored by Novartis. Dr McMurray's employer, University of Glasgow, was paid by Novartis for Dr McMurray's time spent as co-chairman of the PARADIGM-HF trial. All other authors have consulted for or received research support from Novartis. Dr Okumura has no conflicts to report.

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CLINICAL PERSPECTIVE

In the PARADIGM-HF trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), the angiotensin receptor neprilysin inhibitor sacubitril/valsartan was superior to the angiotensin-converting enzyme inhibitor enalapril in patients with heart failure and reduced ejection fraction. We examined whether the benefit of sacubitril/valsartan was consistent irrespective of background therapy defined as diuretics (yes/no), digitalis glycoside (yes/no), mineralocorticoid receptor antagonist (yes/no), and an implanted defibrillating device (yes/no). We also examined the effect of study drug according to β-blocker dose (≥50% and <50% of target dose) and according to whether patients had undergone previous coronary revascularization. We tested treatment consistency for the primary composite end point of cardiovascular death or heart failure hospitalization, as well as cardiovascular death. Most randomized patients (n=8399) were treated with a diuretic (80%) and β-blocker (93%); 47% of those taking a β-blocker were treated with ≥50% of the recommended dose. In addition, 4671 (56%) were treated with a mineralocorticoid receptor antagonist, 2539 (30%) with a digoxin, and 1243 (15%) had a defibrillating device; 2640 (31%) had undergone coronary revascularization. Overall, the sacubitril/valsartan versus enalapril hazard ratio for the primary composite end point was 0.80 (95% confidence interval, 0.73–0.87; $P<0.001$) and for cardiovascular death 0.80 (95% confidence interval, 0.71–0.89; $P<0.001$). The effect of sacubitril/valsartan was consistent across all treatment subgroups examined. The hazard ratio for primary end point ranged from 0.74 to 0.85 and for cardiovascular death from 0.75 to 0.89, with no significant treatment-by-subgroup interaction. The benefit of the angiotensin receptor neprilysin inhibitor sacubitril/valsartan over the angiotensin-converting enzyme inhibitor enalapril was consistent regardless of background pharmacological and device therapy and irrespective of previous coronary revascularization or β-blocker dose.

Circulation
Heart Failure

Effects of Sacubitril/Valsartan in the PARADIGM-HF Trial (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure) According to Background Therapy

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SUPPLEMENTAL MATERIAL

Table 1: Baseline characteristics according to baseline diuretic

	Diuretic (Yes)				P value	Diuretic (No)				P value
	Enalapril		Sacubitril/valsartan			Enalapril		Sacubitril/valsartan		
n (%)	n=3375 (40)		n=3363 (40)			n=837 (10)		n=824 (10)		
Age, year	64 ± 11		64 ± 12		0.42	63 ± 11		64 ± 11		0.15
Sex (female), n (%)	762	(22.6%)	715	(21.3%)	0.19	191	(22.8%)	164	(19.9%)	0.15
Race, n (%)										
White	2268	(67.2%)	2262	(67.3%)	0.99	513	(61.3%)	501	(60.8%)	0.91
Black	186	(5.5%)	188	(5.6%)		29	(3.5%)	25	(3.0%)	
Asian	557	(16.5%)	559	(16.6%)		193	(23.1%)	200	(24.3%)	
Other	364	(10.8%)	354	(10.5%)		102	(12.2%)	98	(11.9%)	
Region, n (%)										
North America	249	(7.4%)	239	(7.1%)	0.96	43	(5.1%)	71	(8.6%)	0.016
Latin America	549	(16.3%)	567	(16.9%)		171	(20.4%)	146	(17.7%)	
Western Europe and other	857	(25.4%)	842	(25.0%)		168	(20.1%)	184	(22.3%)	
Central Europe	1174	(34.8%)	1170	(34.8%)		259	(30.9%)	223	(27.1%)	
Asia	546	(16.2%)	545	(16.2%)		196	(23.4%)	200	(24.3%)	
Systolic blood pressure, mm Hg	121 ± 15		121 ± 15		0.90	121 ± 15		122 ± 15		0.04

Heart rate, beats/min	73 ± 12		73 ± 12		0.35	71 ± 12		71 ± 12		0.50
Body mass index, kg/m^2	28 ± 6		28 ± 6		0.81	27 ± 5		27 ± 5		0.51
Serum creatinine, mg/dL	1.13 ± 0.31		1.14 ± 0.31		0.32	1.08 ± 0.26		1.08 ± 0.26		0.86
Clinical features of heart failure										
Left ventricular ejection fraction, %	29 ± 6		29 ± 6		0.22	30 ± 6		30 ± 6		0.23
Median BNP, pg/mL (IQR)	256.3 [155.8, 479.3]		263.5 [156.4, 494.4]		0.34	235.7 [145.1, 410.3]		224.9 [144.5, 391.4]		0.50
Median NT-proBNP, pg/mL (IQR)	1658.0 [935.0, 3479.5]		1741.0 [925.5, 3423.5]		0.72	1348.0 [776.0, 2662.0]		1287.5 [774.0, 2459.0]		0.43
NYHA functional class, n (%)										
I	134	(4.0%)	128	(3.8%)	0.22	75	(9.0%)	52	(6.3%)	0.11
II	2308	(68.5%)	2361	(70.3%)		613	(73.4%)	637	(77.6%)	
III	905	(26.8%)	838	(24.9%)		144	(17.2%)	131	(16.0%)	
IV	24	(0.7%)	32	(1.0%)		3	(0.4%)	1	(0.1%)	
Ischemic etiology, n (%)	1979	(58.6%)	1953	(58.1%)	0.64	551	(65.8%)	553	(67.1%)	0.58
Medical history, n (%)										
Hypertension	2417	(71.6%)	2405	(71.5%)	0.93	554	(66.2%)	564	(68.4%)	0.33

Diabetes mellitus	1223	(36.2%)	1211	(36.0%)	0.85	233	(27.8%)	240	(29.1%)	0.56
Atrial fibrillation	1321	(39.1%)	1283	(38.2%)	0.40	253	(30.2%)	234	(28.4%)	0.41
Previous heart failure hospitalization	2196	(65.1%)	2183	(64.9%)	0.89	471	(56.3%)	424	(51.5%)	0.05
Myocardial infarction	1416	(42.0%)	1395	(41.5%)	0.69	400	(47.8%)	423	(51.3%)	0.15
Stroke	293	(8.7%)	273	(8.1%)	0.40	77	(9.2%)	82	(10.0%)	0.60
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	2638	(78.2%)	2649	(78.8%)	0.55	628	(75.0%)	617	(74.9%)	0.94
Previous use of ARB	754	(22.3%)	720	(21.4%)	0.36	209	(25.0%)	209	(25.4%)	0.85
Digitalis	1139	(33.7%)	1068	(31.8%)	0.08	177	(21.1%)	155	(18.8%)	0.23
β-Blocker	3139	(93.0%)	3140	(93.4%)	0.56	773	(92.4%)	759	(92.1%)	0.85
Mineralocorticoid antagonist	1980	(58.7%)	1898	(56.4%)	0.06	420	(50.2%)	373	(45.3%)	0.05
Implantable cardioverter-defibrillator	522	(15.5%)	507	(15.1%)	0.66	98	(11.7%)	116	(14.1%)	0.15
Cardiac resynchronization therapy	244	(7.2%)	244	(7.3%)	0.97	38	(4.5%)	48	(5.8%)	0.24

Table 2: Baseline characteristics according to baseline MRA

	Mineralocorticoid antagonist (Yes)		P value	Mineralocorticoid antagonist (No)		P value
	Enalapril	Sacubitril/valsartan		Enalapril	Sacubitril/valsartan	
n (%)	n=2400 (29)	n=2271 (27)		n=1812 (22)	n=1916 (23)	
Age, year	62 ± 11	62 ± 11	0.18	66 ± 11	66 ± 11	0.43
Sex (female), n (%)	544 (22.7%)	482 (21.2%)	0.23	409 (22.6%)	397 (20.7%)	0.17
Race, n (%)						
White	1562 (65.1%)	1480 (65.2%)	0.87	1219 (67.3%)	1283 (67.0%)	0.97
Black	151 (6.3%)	140 (6.2%)		64 (3.5%)	73 (3.8%)	
Asian	426 (17.8%)	418 (18.4%)		324 (17.9%)	341 (17.8%)	
Other	261 (10.9%)	233 (10.3%)		205 (11.3%)	219 (11.4%)	
Region, n (%)						
North America	115 (4.8%)	102 (4.5%)	0.94	177 (9.8%)	208 (10.9%)	0.76
Latin America	470 (19.6%)	454 (20.0%)		250 (13.8%)	259 (13.5%)	
Western Europe and other	505 (21.0%)	462 (20.3%)		520 (28.7%)	564 (29.4%)	
Central Europe	890 (37.1%)	843 (37.1%)		543 (30.0%)	550 (28.7%)	
Asia	420 (17.5%)	410 (18.1%)		322 (17.8%)	335 (17.5%)	
Systolic blood pressure, mm Hg	119 ± 15	120 ± 15	0.17	124 ± 16	123 ± 16	0.70
Heart rate, beats/min	73 ± 12	72 ± 12	0.35	72 ± 12	72 ± 12	0.51
Body mass index, kg/m^2	28 ± 6	28 ± 6	0.29	28 ± 6	28 ± 5	0.06

Serum creatinine, mg/dL	1.11 ± 0.29		1.12 ± 0.30		0.52	1.13 ± 0.31		1.13 ± 0.30		0.62
Clinical features of heart failure										
Left ventricular ejection fraction, %	29 ± 6		29 ± 6		0.72	30 ± 6		30 ± 6		0.91
Median BNP, pg/mL (IQR)	255.1 [152.4, 478.4]		257.6 [149.8, 496.6]		0.74	244.2 [154.2, 447.5]		252.5 [159.5, 449.6]		0.56
Median NT-proBNP, pg/mL (IQR)	1630.0 [898.0, 3398.0]		1640.0 [881.0, 3270.0]		0.60	1563.0 [876.0, 3105.0]		1618.0 [909.0, 3080.0]		0.59
NYHA functional class, n (%)										
I	118	(4.9%)	98	(4.3%)	0.72	91	(5.0%)	82	(4.3%)	0.008
II	1623	(67.7%)	1551	(68.4%)		1298	(71.8%)	1447	(75.6%)	
III	639	(26.7%)	605	(26.7%)		410	(22.7%)	364	(19.0%)	
IV	17	(0.7%)	13	(0.6%)		10	(0.6%)	20	(1.0%)	
Ischemic etiology, n (%)	1369	(57.0%)	1274	(56.1%)	0.52	1161	(64.1%)	1232	(64.3%)	0.88
Medical history, n (%)										
Hypertension	1645	(68.5%)	1605	(70.7%)	0.11	1326	(73.2%)	1364	(71.2%)	0.18
Diabetes mellitus	811	(33.8%)	751	(33.1%)	0.60	645	(35.6%)	700	(36.5%)	0.55
Atrial fibrillation	884	(36.8%)	820	(36.1%)	0.61	690	(38.1%)	697	(36.4%)	0.28
Previous heart failure hospitalization	1633	(68.0%)	1559	(68.6%)	0.66	1034	(57.1%)	1048	(54.7%)	0.15
Myocardial infarction	1013	(42.2%)	942	(41.5%)	0.61	803	(44.3%)	876	(45.7%)	0.39

Stroke	211	(8.8%)	193	(8.5%)	0.72	159	(8.8%)	162	(8.5%)	0.73
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	1862	(77.6%)	1797	(79.1%)	0.20	1404	(77.5%)	1469	(76.7%)	0.55
Previous use of ARB	542	(22.6%)	476	(21.0%)	0.18	421	(23.2%)	453	(23.6%)	0.77
Diuretics	1980	(82.5%)	1898	(83.6%)	0.33	1395	(77.0%)	1465	(76.5%)	0.70
Digitalis	839	(35.0%)	744	(32.8%)	0.11	477	(26.3%)	479	(25.0%)	0.35
β-Blocker	2259	(94.1%)	2127	(93.7%)	0.51	1653	(91.2%)	1772	(92.5%)	0.16
Implantable cardioverter-defibrillator	361	(15.0%)	341	(15.0%)	0.98	259	(14.3%)	282	(14.7%)	0.71
Cardiac resynchronization therapy	156	(6.5%)	169	(7.4%)	0.21	126	(7.0%)	123	(6.4%)	0.51

Table 3: Baseline characteristics according to baseline Digitalis

	Digitalis (Yes)				P value	Digitalis (No)				P value
	Enalapril		Sacubitril/valsartan			Enalapril		Sacubitril/valsartan		
n (%)	n=1316 (16)		n=1223 (15)			n=2896 (34)		n=2964 (35)		
Age, year	63 ± 12		62 ± 13		0.04	64 ± 11		65 ± 11		0.24
Sex (female), n (%)	306	(23.3%)	267	(21.8%)	0.39	647	(22.3%)	612	(20.6%)	0.11
Race, n (%)					0.80					0.98
White	722	(54.9%)	666	(54.5%)		2059	(71.1%)	2097	(70.7%)	
Black	83	(6.3%)	71	(5.8%)		132	(4.6%)	142	(4.8%)	
Asian	331	(25.2%)	326	(26.7%)		419	(14.5%)	433	(14.6%)	
Other	180	(13.7%)	160	(13.1%)		286	(9.9%)	292	(9.9%)	
Region, n (%)					0.69					0.99
North America	80	(6.1%)	83	(6.8%)		212	(7.3%)	227	(7.7%)	
Latin America	256	(19.5%)	243	(19.9%)		464	(16.0%)	470	(15.9%)	
Western Europe and other	208	(15.8%)	187	(15.3%)		817	(28.2%)	839	(28.3%)	
Central Europe	440	(33.4%)	382	(31.2%)		993	(34.3%)	1011	(34.1%)	
Asia	332	(25.2%)	328	(26.8%)		410	(14.2%)	417	(14.1%)	
Systolic blood pressure, mm Hg	120 ± 15		120 ± 14		0.96	122 ± 15		122 ± 15		0.28
Heart rate, beats/min	75 ± 13		75 ± 12		0.84	72 ± 12		71 ± 12		0.35

Body mass index, kg/m^2	28 ± 6		27 ± 6		0.14	28 ± 5		28 ± 5		0.77
Serum creatinine, mg/dL	1.12 ± 0.30		1.10 ± 0.29		0.09	1.12 ± 0.30		1.14 ± 0.30		0.04
Clinical features of heart failure										
Left ventricular ejection fraction, %	29 ± 6		29 ± 6		0.87	30 ± 6		30 ± 6		0.36
Median BNP, pg/mL (IQR)	259.1 [149.8, 519.6]		269.1 [156.7, 548.1]		0.17	245.1 [154.3, 447.9]		249.1 [153.8, 447.9]		0.90
Median NT-proBNP, pg/mL (IQR)	1882.0 [1014.5, 3909.5]		1939.0 [1024.0, 3934.0]		0.45	1502.0 [839.0, 3032.0]		1513.0 [847.0, 2912.0]		0.81
NYHA functional class, n (%)					0.08					
I	56	(4.3%)	42	(3.4%)		153	(5.3%)	138	(4.7%)	0.57
II	865	(65.8%)	855	(69.9%)		2056	(71.1%)	2143	(72.5%)	
III	384	(29.2%)	312	(25.5%)		665	(23.0%)	657	(22.2%)	
IV	10	(0.8%)	14	(1.1%)		17	(0.6%)	19	(0.6%)	
Ischemic etiology, n (%)	656	(49.8%)	596	(48.7%)	0.57	1874	(64.7%)	1910	(64.4%)	0.83
Medical history, n (%)										
Hypertension	850	(64.6%)	783	(64.0%)	0.77	2121	(73.2%)	2186	(73.8%)	0.66
Diabetes mellitus	472	(35.9%)	410	(33.5%)	0.22	984	(34.0%)	1041	(35.1%)	0.36
Atrial fibrillation	707	(53.7%)	637	(52.1%)	0.41	867	(29.9%)	880	(29.7%)	0.84
Previous heart failure hospitalization	859	(65.3%)	786	(64.3%)	0.60	1808	(62.4%)	1821	(61.4%)	0.84
Myocardial infarction	400	(30.4%)	366	(29.9%)	0.81	1416	(48.9%)	1452	(49.0%)	0.43

Stroke	109	(8.3%)	102	(8.3%)	0.96	261	(9.0%)	253	(8.5%)	0.94
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	990	(75.2%)	928	(75.9%)	0.70	2276	(78.6%)	2338	(78.9%)	0.79
Previous use of ARB	331	(25.2%)	298	(24.4%)	0.65	632	(21.8%)	631	(21.3%)	0.62
Diuretics	1139	(86.6%)	1068	(87.3%)	0.56	2236	(77.2%)	2295	(77.4%)	0.84
β-Blocker	1210	(91.9%)	1107	(90.5%)	0.20	2702	(93.3%)	2792	(94.2%)	0.16
Mineralocorticoid antagonist	839	(63.8%)	744	(60.8%)	0.13	1561	(53.9%)	1527	(51.5%)	0.07
Implantable cardioverter-defibrillator	162	(12.3%)	145	(11.9%)	0.73	458	(15.8%)	478	(16.1%)	0.74
Cardiac resynchronization therapy	83	(6.3%)	89	(7.3%)	0.33	199	(6.9%)	203	(6.8%)	0.97

Table 4: Baseline characteristics according to baseline ICD/CRT

	ICD/CRT (Yes)				P value	ICD/CRT (No)				P value
	Enalapril		Sacubitril/valsartan			Enalapril		Sacubitril/valsartan		
n (%)	n=620 (7)		n=623 (7)			n=3592 (43)		n=3564 (42)		
Age, year	65 ± 10		65 ± 10		0.84	64 ± 12		64 ± 12		0.78
Sex (female), n (%)	93	(15.0%)	75	(12.0%)	0.17	860	(23.9%)	804	(22.6%)	0.13
Race, n (%)										
White	536	(86.5%)	528	(84.8%)	0.86	2245	(62.5%)	2235	(62.7%)	0.62
Black	39	(6.3%)	45	(7.2%)		176	(4.9%)	168	(4.7%)	
Asian	16	(2.6%)	13	(2.1%)		734	(20.4%)	746	(20.9%)	
Other	29	(4.7%)	37	(5.9%)		437	(12.2%)	415	(11.6%)	
Region, n (%)										
North America	158	(25.5%)	169	(27.1%)	0.87	134	(3.7%)	141	(4.0%)	0.67
Latin America	26	(4.2%)	35	(5.6%)		694	(19.3%)	678	(19.0%)	
Western Europe and other	324	(52.3%)	304	(48.8%)		701	(19.5%)	722	(20.3%)	
Central Europe	99	(16.0%)	102	(16.4%)		1334	(37.1%)	1291	(36.2%)	
Asia	13	(2.1%)	13	(2.1%)		729	(20.3%)	732	(20.5%)	
Systolic blood pressure, mm Hg	118 ± 15		118 ± 14		0.40	122 ± 15		122 ± 15		0.48

Heart rate, beats/min	69 ± 11		68 ± 10		0.59	73 ± 12		73 ± 12		0.08
Body mass index, kg/m^2	29 ± 5		29 ± 5		0.83	28 ± 6		28 ± 5		0.46
Serum creatinine, mg/dL	1.24 ± 0.32		1.24 ± 0.31		0.30	1.10 ± 0.29		1.11 ± 0.29		0.81
Clinical features of heart failure										
Left ventricular ejection fraction, %	27 ± 7		27 ± 6		0.48	30 ± 6		30 ± 6		0.27
Median BNP, pg/mL (IQR)	245.0 [162.9, 434.9]		244.8 [158.4, 458.4]		0.69	251.5 [151.6, 475.0]		257.2 [153.1, 476.4]		0.61
Median NT-proBNP, pg/mL (IQR)	1526.0 [842.0, 2954.0]		1569.0 [903.0, 2851.0]		0.76	1620.0 [891.0, 3390.0]		1647.0 [881.0, 3281.0]		0.52
NYHA functional class, n (%)										
I	18	(2.9%)	24	(3.9%)	0.02	191	(5.3%)	156	(4.4%)	0.80
II	470	(75.8%)	461	(74.2%)		2451	(68.3%)	2537	(71.3%)	
III	129	(20.8%)	133	(21.4%)		920	(25.7%)	836	(23.5%)	
IV	3	(0.5%)	3	(0.5%)		24	(0.7%)	30	(0.8%)	
Ischemic etiology, n (%)	407	(65.6%)	425	(68.2%)	0.54	2123	(59.1%)	2081	(58.4%)	0.33
Medical history, n (%)										
Hypertension	409	(66.0%)	430	(69.0%)	0.94	2562	(71.3%)	2539	(71.2%)	0.25
Diabetes mellitus	252	(40.6%)	249	(40.0%)	0.85	1204	(33.5%)	1202	(33.7%)	0.81

Atrial fibrillation	236	(38.1%)	234	(37.6%)	0.27	1338	(37.2%)	1283	(36.0%)	0.85
Previous heart failure hospitalization	399	(64.4%)	416	(66.8%)	0.15	2268	(63.1%)	2191	(61.5%)	0.37
Myocardial infarction	351	(56.6%)	364	(58.4%)	0.99	1465	(40.8%)	1454	(40.8%)	0.52
Stroke	67	(10.8%)	62	(10.0%)	0.74	303	(8.4%)	293	(8.2%)	0.62
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	488	(78.7%)	517	(83.0%)	0.84	2778	(77.3%)	2749	(77.1%)	0.06
Previous use of ARB	139	(22.4%)	107	(17.2%)	0.90	824	(22.9%)	822	(23.1%)	0.19
Diuretics	522	(84.2%)	507	(81.4%)	0.46	2853	(79.4%)	2856	(80.1%)	0.19
Digitalis	162	(26.1%)	145	(23.3%)	0.09	1154	(32.1%)	1078	(30.2%)	0.24
β-Blocker	600	(96.8%)	601	(96.5%)	0.6	3312	(92.2%)	3298	(92.5%)	0.77
Mineralocorticoid antagonist	361	(58.2%)	341	(54.7%)	0.03	2039	(56.8%)	1930	(54.2%)	0.21
Cardiac resynchronization therapy	215	(34.7%)	223	(35.8%)	0.83	67	(1.9%)	69	(1.9%)	0.68

Table 5: Baseline characteristics according to Prior coronary revascularization

	Prior coronary revascularization (Yes)				P value	Prior coronary revascularization (No)				P value
	Enalapril		Sacubitril/valsartan			Enalapril		Sacubitril/valsartan		
n (%)	n=1291 (15)		n=1349 (16)			n=2921(35)		n=2838 (34)		
Age, year	65 ± 10		66 ± 10		0.26	63 ± 12		63 ± 12		0.36
Sex (female), n (%)	176	(13.6%)	174	(12.9%)	0.58	777	(26.6%)	705	(24.8%)	0.13
Race, n (%)										
White	996	(77.1%)	1061	(78.7%)	0.52	1785	(61.1%)	1702	(60.0%)	0.54
Black	27	(2.1%)	29	(2.1%)		188	(6.4%)	184	(6.5%)	
Asian	183	(14.2%)	165	(12.2%)		567	(19.4%)	594	(20.9%)	
Other	85	(6.6%)	94	(7.0%)		381	(13.0%)	358	(12.6%)	
Region, n (%)										
North America	146	(11.3%)	171	(12.7%)	0.42	146	(5.0%)	139	(4.9%)	0.63
Latin America	126	(9.8%)	143	(10.6%)		594	(20.3%)	570	(20.1%)	
Western Europe and other	430	(33.3%)	428	(31.7%)		595	(20.4%)	598	(21.1%)	
Central Europe	417	(32.3%)	451	(33.4%)		1016	(34.8%)	942	(33.2%)	
Asia	172	(13.3%)	156	(11.6%)		570	(19.5%)	589	(20.8%)	
Systolic blood pressure, mm Hg	120 ± 15		121 ± 15		0.15	122 ± 16		122 ± 15		0.74
Heart rate, beats/min	70 ± 11		70 ± 12		0.99	73 ± 12		73 ± 12		0.25

Body mass index, kg/m^2	29 ± 5		28 ± 5		0.44	28 ± 6		28 ± 6		0.88
Serum creatinine, mg/dL	1.18 ± 0.29		1.19 ± 0.31		0.25	1.09 ± 0.30		1.09 ± 0.29		0.99
Clinical features of heart failure										
Left ventricular ejection fraction, %	29 ± 6		30 ± 6		0.03	29 ± 6		29 ± 6		0.82
Median BNP, pg/mL (IQR)	246.5 [152.7, 421.3]		249.9 [162.3, 416.7]		0.33	252.4 [153.9, 491.0]		257.9 [149.7, 506.0]		0.92
Median NT-proBNP, pg/mL (IQR)	1431.0 [812.0, 2530.0]		1455.0 [843.0, 2718.0]		0.33	1730.0 [928.0, 3690.0]		1747.0 [922.0, 3486.0]		0.62
NYHA functional class, n (%)										
I	57	(4.4%)	48	(3.6%)	0.63	152	(5.2%)	132	(4.7%)	0.07
II	943	(73.0%)	1000	(74.3%)		1978	(67.9%)	1998	(70.5%)	
III	283	(21.9%)	291	(21.6%)		766	(26.3%)	678	(23.9%)	
IV	8	(0.6%)	6	(0.4%)		19	(0.7%)	27	(1.0%)	
Ischemic etiology, n (%)	1210	(93.7%)	1276	(94.6%)	0.34	1320	(45.2%)	1230	(43.3%)	0.16
Medical history, n (%)										
Hypertension	961	(74.4%)	1022	(75.8%)	0.43	2010	(68.8%)	1947	(68.6%)	0.87
Diabetes mellitus	593	(45.9%)	578	(42.8%)	0.11	863	(29.5%)	873	(30.8%)	0.31
Atrial fibrillation	435	(33.7%)	424	(31.4%)	0.21	1139	(39.0%)	1093	(38.5%)	0.71

Previous heart failure hospitalization	819	(63.4%)	831	(61.6%)	0.33	1848	(63.3%)	1776	(62.6%)	0.59
Myocardial infarction	1035	(80.2%)	1092	(80.9%)	0.61	781	(26.7%)	726	(25.6%)	0.32
Stroke	131	(10.1%)	123	(9.1%)	0.37	239	(8.2%)	232	(8.2%)	0.99
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	1029	(79.7%)	1094	(81.1%)	0.37	2237	(76.6%)	2172	(76.5%)	0.96
Previous use of ARB	270	(20.9%)	260	(19.3%)	0.29	693	(23.7%)	669	(23.6%)	0.89
Diuretics	1018	(78.9%)	1066	(79.0%)	0.92	2357	(80.7%)	2297	(80.9%)	0.81
Digitalis	242	(18.7%)	249	(18.5%)	0.85	1074	(36.8%)	974	(34.3%)	0.05
β-Blocker	1211	(93.8%)	1271	(94.2%)	0.65	2701	(92.5%)	2628	(92.6%)	0.85
Mineralocorticoid antagonist	681	(52.7%)	663	(49.1%)	0.06	1719	(58.8%)	1608	(56.7%)	0.09
Implantable cardioverter-defibrillator	337	(26.1%)	352	(26.1%)	0.99	283	(9.7%)	271	(9.5%)	0.86
Cardiac resynchronization therapy	141	(10.9%)	133	(9.9%)	0.37	141	(4.8%)	159	(5.6%)	0.19

Table 6: Baseline characteristics according to baseline beta-blocker dose (target dose ≥50% vs. <50%)

	Beta-blocker target dose (≥50%)				P value	Beta-blocker target dose (<50%)				P value
	Enalapril		Sacubitril/valsartan			Enalapril		Sacubitril/valsartan		
n (%)	n=1789 (21)		n=1855 (22)			n=2123 (25)		n=2044 (24)		
Age, year	64 ± 11		64 ± 11		0.75	64 ± 12		64 ± 12		0.94
Sex (female), n (%)	387	(21.6%)	366	(19.7%)	0.16	496	(23.4%)	442	(21.6%)	0.18
Race, n (%)										
White	1456	(81.4%)	1496	(80.6%)	0.89	1164	(54.8%)	1113	(54.5%)	0.96
Black	96	(5.4%)	100	(5.4%)		103	(4.9%)	101	(4.9%)	
Asian	96	(5.4%)	110	(5.9%)		570	(26.8%)	563	(27.5%)	
Other	141	(7.9%)	149	(8.0%)		286	(13.5%)	267	(13.1%)	
Region, n (%)										
North America	179	(10.0%)	205	(11.1%)	0.84	104	(4.9%)	98	(4.8%)	0.97
Latin America	240	(13.4%)	244	(13.2%)		423	(19.9%)	415	(20.3%)	
Western Europe and other	539	(30.1%)	556	(30.0%)		424	(20.0%)	393	(19.2%)	
Central Europe	742	(41.5%)	751	(40.5%)		602	(28.4%)	576	(28.2%)	
Asia	89	(5.0%)	99	(5.3%)		570	(26.8%)	562	(27.5%)	
Systolic blood pressure, mm Hg	123 ± 16		123 ± 15		0.88	120 ± 15		121 ± 15		0.06

Heart rate, beats/min	72 ± 12		72 ± 12		0.15	73 ± 12		73 ± 12		0.60
Body mass index, kg/m^2	30 ± 6		30 ± 6		0.65	27 ± 5		27 ± 5		0.06
Serum creatinine, mg/dL	1.13 ± 0.29		1.15 ± 0.29		0.14	1.11 ± 0.30		1.11 ± 0.30		0.95
Clinical features of heart failure										
Left ventricular ejection fraction, %	30 ± 6		30 ± 6		0.92	29 ± 6		29 ± 6		0.07
Median BNP, pg/mL (IQR)	241.4 [152.0, 424.7]		243.6 [151.7, 434.5]		0.73	256.7 [154.7, 491.4]		267.1 [155.9, 503.1]		0.39
Median NT-proBNP, pg/mL (IQR)	1549.0 [859.0, 3062.0]		1546.5 [869.0, 2941.5]		0.93	1654.0 [913.0, 3387.0]		1685.5 [914.0, 3438.0]		0.73
NYHA functional class, n (%)										
I	67	(3.7%)	76	(4.1%)	0.35	126	(5.9%)	94	(4.6%)	0.05
II	1230	(68.8%)	1309	(70.8%)		1489	(70.2%)	1480	(72.4%)	
III	472	(26.4%)	452	(24.4%)		497	(23.4%)	453	(22.2%)	
IV	18	(1.0%)	13	(0.7%)		8	(0.4%)	16	(0.8%)	
Ischemic etiology, n (%)	1070	(59.8%)	1131	(61.0%)	0.45	1277	(60.2%)	1217	(59.5%)	0.66
Medical history, n (%)										
Hypertension	1365	(76.3%)	1400	(75.5%)	0.58	1406	(66.2%)	1375	(67.3%)	0.48
Diabetes mellitus	666	(37.2%)	687	(37.0%)	0.93	690	(32.5%)	661	(32.3%)	0.89

Atrial fibrillation	745	(41.6%)	770	(41.5%)	0.91	726	(34.2%)	625	(30.6%)	0.014
Previous heart failure hospitalization	1154	(64.5%)	1170	(63.1%)	0.39	1341	(63.2%)	1268	(62.0%)	0.43
Myocardial infarction	806	(45.1%)	852	(45.9%)	0.59	887	(41.8%)	860	(42.1%)	0.85
Stroke	176	(9.8%)	160	(8.6%)	0.22	160	(7.5%)	170	(8.3%)	0.36
Treatment at randomization, n (%)										
Previous use of ACE inhibitor	1419	(79.3%)	1503	(81.0%)	0.18	1625	(76.5%)	1551	(75.9%)	0.59
Previous use of ARB	383	(21.4%)	355	(19.1%)	0.08	502	(23.6%)	499	(24.4%)	0.54
Diuretics	1422	(79.5%)	1501	(80.9%)	0.24	1717	(80.9%)	1639	(80.2%)	0.52
Digitalis	491	(27.4%)	478	(25.8%)	0.24	719	(33.9%)	629	(30.8%)	0.03
Mineralocorticoid antagonist	1017	(56.8%)	1007	(54.3%)	0.13	1242	(58.5%)	1120	(54.8%)	0.01
Implantable cardioverter-defibrillator	377	(21.1%)	395	(21.3%)	0.81	223	(10.5%)	206	(10.1%)	0.59
Cardiac resynchronization therapy	170	(9.5%)	177	(9.5%)	0.86	105	(4.9%)	104	(5.1%)	0.96

Table 7 Primary endpoint (composite of death from cardiovascular causes or hospitalization for heart failure) and death from cardiovascular causes according to baseline treatment, history of coronary revascularization and baseline beta-blocker dose adjusted for baseline factors (region, age, sex, systolic blood pressure, heart rate, body mass index, serum creatinine, ejection fraction, NYHA class, ischemic etiology, NT-proBNP, history of hypertension, myocardial infarction, stroke, diabetes mellitus, previous hospitalization for heart failure, previous use of ACE inhibitor, ARB and when part of the subgroup, diuretic, digitalis, mineralocorticoid receptor antagonist and ICD use).

	Primary end-point		Cardiovascular death	
	HR (95% CI)	Interaction p-value	HR(95% CI)	Interactionp-value
Diuretic				
No (n=1661)	0.84 (0.66-1.06)	0.671	0.90 (0.68-1.20)	0.407
Yes (n=6738)	0.80 (0.72-0.878		0.79 (0.70-0.90)	
MRA				
No (n=3728)	0.74 (0.65-0.85)	0.104	0.76 (0.64-0.91)	0.317
Yes (n=4671)	0.86 (0.76-0.97)		0.86 (0.74-1.00)	
Digoxin				
No (n=5860)	0.82 (0.74-0.92)	0.766	0.84 (0.73-0.96)	0.622
Yes (n=2539)	0.78 (0.68-0.92)		0.77 (0.64-0.94)	
ICD/CRT				
No (n=7156)	0.80 (0.73-0.88)	0.524	0.81 (0.72-0.92)	0.988
Yes (n=1243)	0.86 (0.69-1.07)		0.79 (0.57-1.10)	
Prior coronary revascularization				
No (n=5759)	0.84 (0.75-0.93)	0.311	0.82 (0.71-0.93)	0.949
Yes (n=2640)	0.75 (0.64-0.88)		0.82 (0.63-1.01)	
Beta-blocker target dose				
<50% (n=4167)	0.83 (0.73-0.96)	0.964	0.87 (0.73-1.04)	0.978
≥50% (n=3644)	0.85 (0.75-0.96)		0.87 (0.75-1.02)	

PARADIGM-HF Investigators

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