Angiotensin Receptor Neprilysin Inhibition (ARNI) Following Acute Myocardial Infarction: Primary Results of the PARADISE-MI Trial

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for the PARADISE-MI Committees, National Leaders and Investigators

Disclosures

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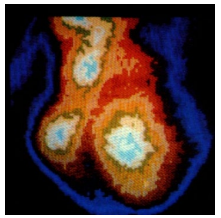
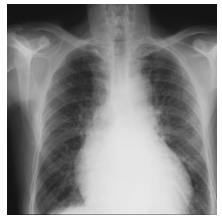
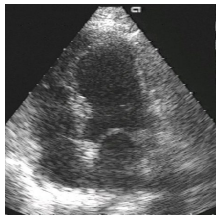
Consulting fees from AstraZeneca, Boehringer Ingelheim and Eli Lilly Alliance, Corvidia, DalCor, GlaxoSmithKline, NHLBI CONNECTs (Master Protocol Committee), Novartis, Novo Nordisk, Peerbridge and Sanofi; and has equity in DalCor and Peerbridge.



SAVE
Radionuclide
EF ≤ 40%
(1992)

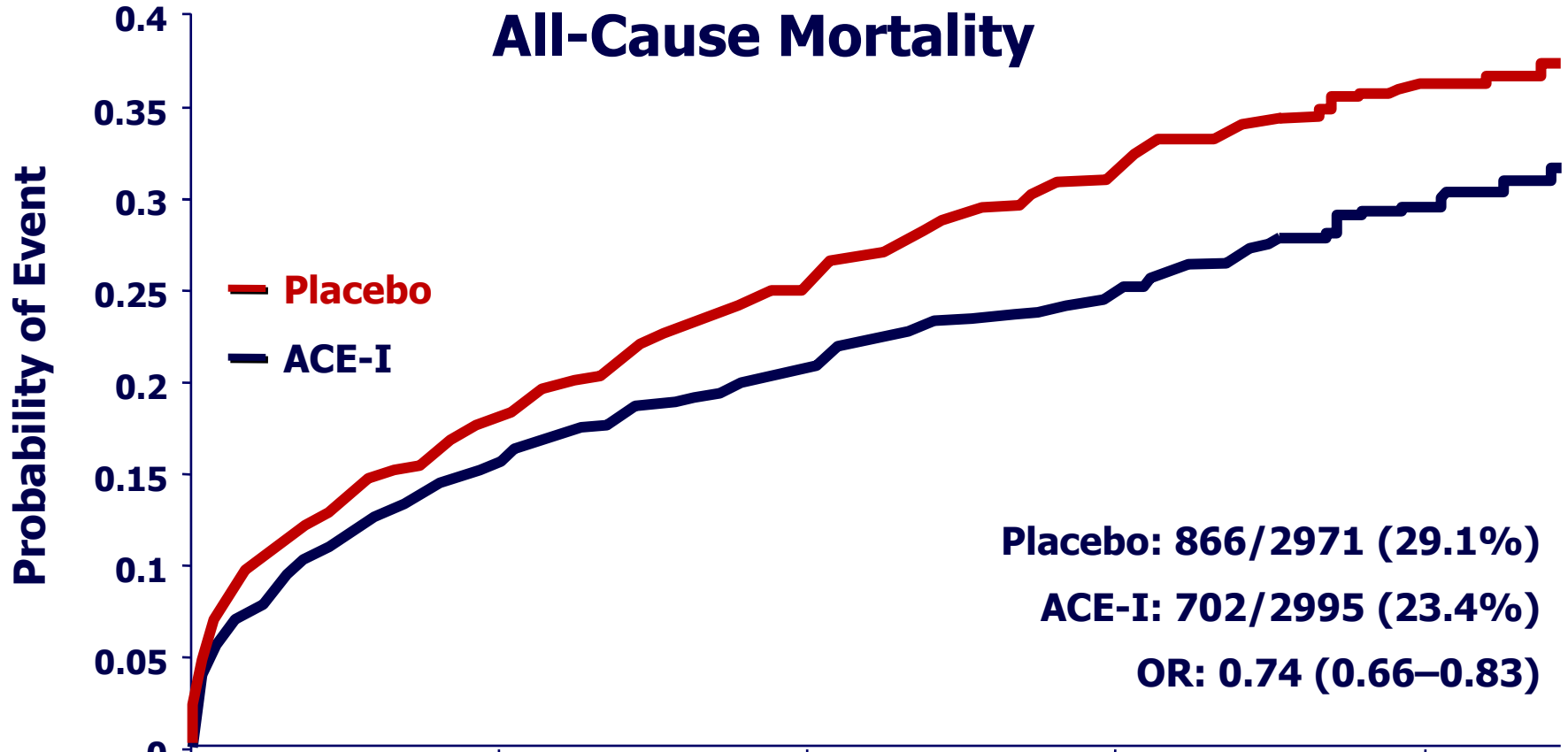


AIRE
Clinical and/or
radiographic signs
of HF (1993)



TRACE
Echocardiographic
EF ≤ 35%
(1995)

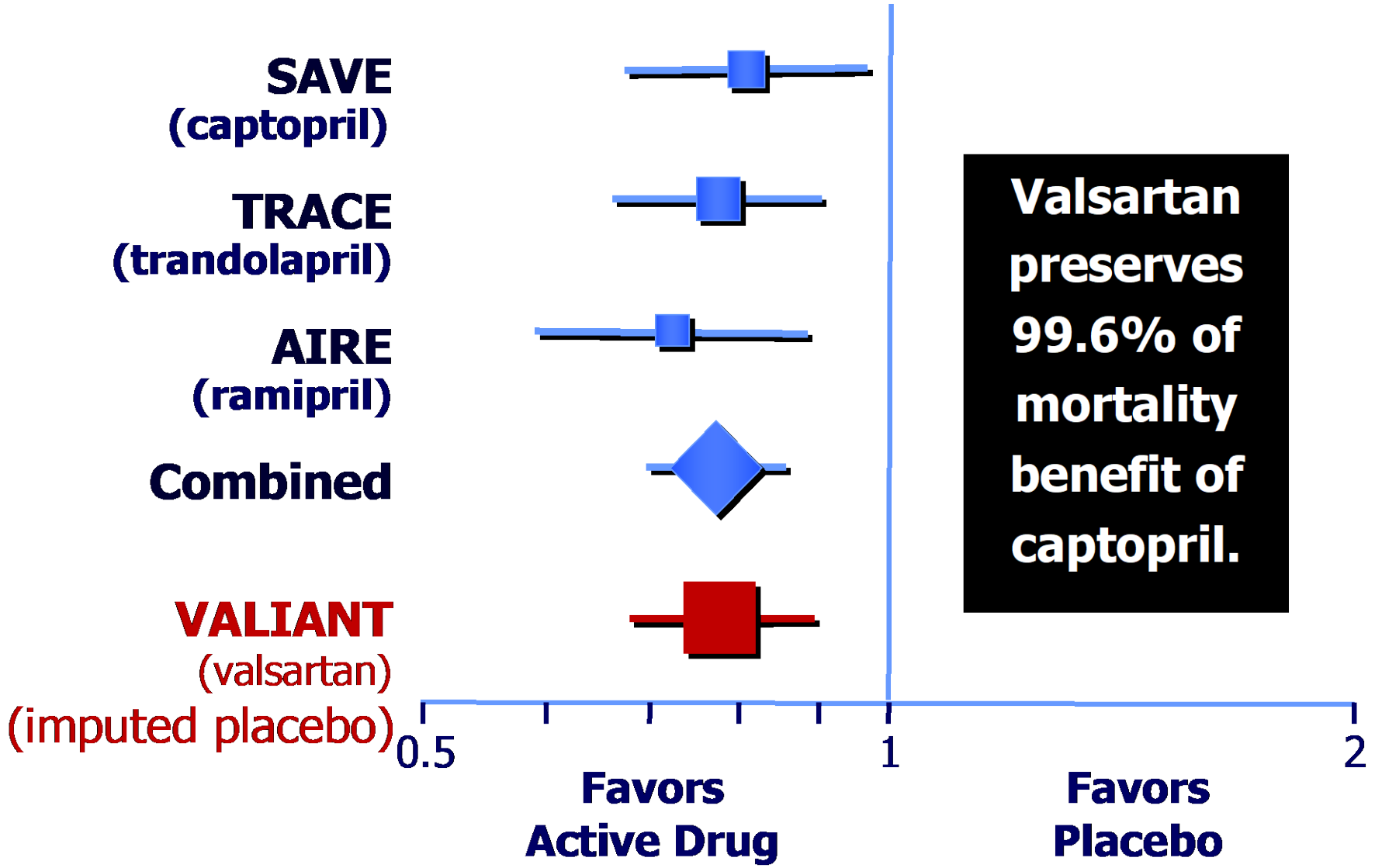
All-Cause Mortality



Years	0	1	2	3	4
ACE-I	2995	2250	1617	892	223
Placebo	2971	2184	1521	853	138

Flather MD, et al. *Lancet*. 2000;355:1575–1581

Mortality in SAVE, TRACE, AIRE, and VALIANT



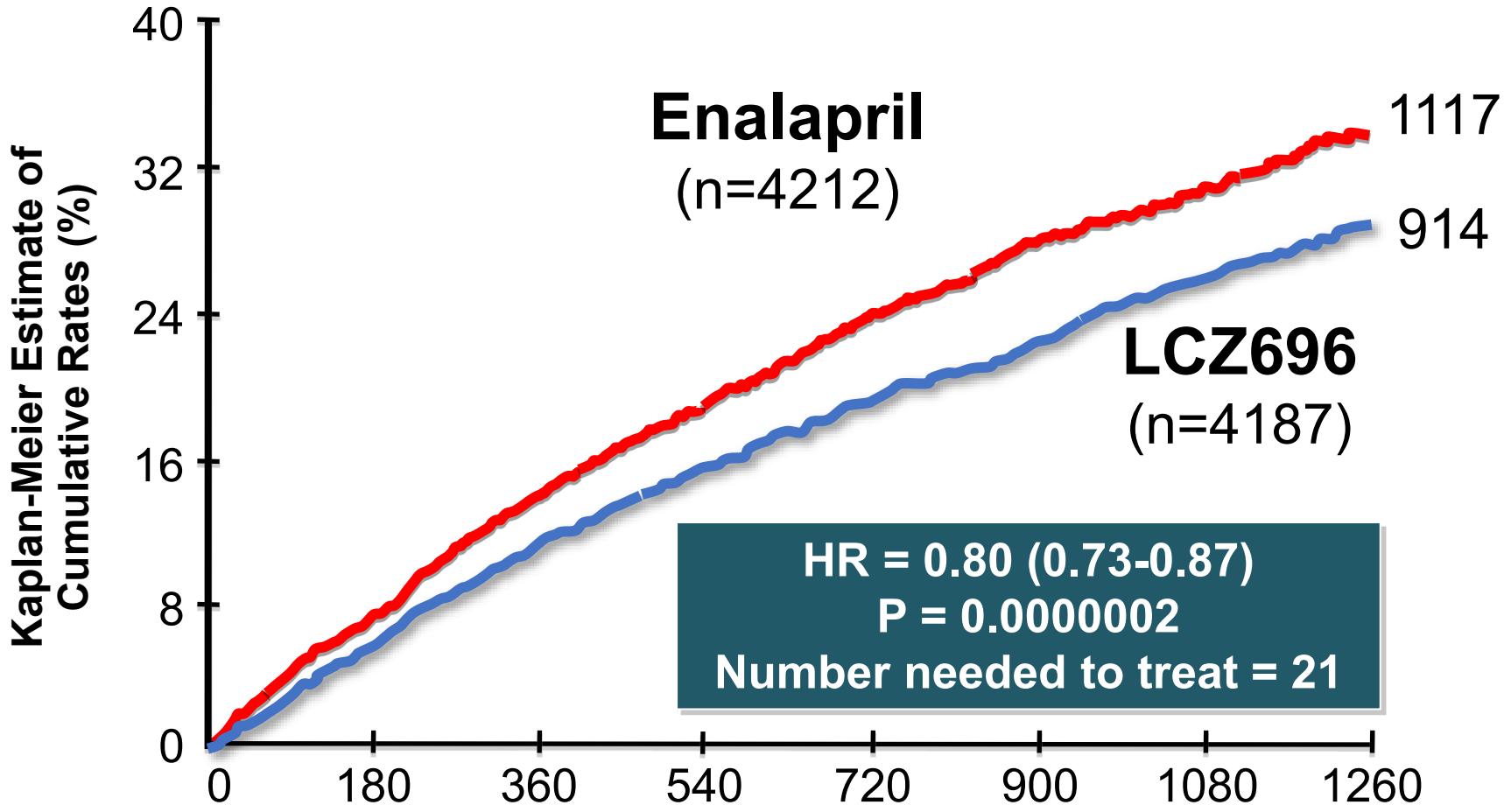
Pfeffer, McMurray, Velazquez, *et al. N Engl J Med* 2003;349

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

2014

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

The NEW ENGLAND JOURNAL of MEDICINE



Patients at Risk

LCZ696	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

McMurray, *N Engl J Med.* 2014

AMI (0.5-7 days with LVEF ≤40% and/or pulmonary congestion)

PLUS any risk enhancer

Age ≥70 years	Atrial fibrillation
eGFR <60	LVEF < 30%
Diabetes	Killip class ≥III
Prior MI	STEMI without reperfusion

Major Exclusions:

Prior HF **Clinical instability** **eGFR <30**

Sacubitril/Valsartan

Target 97/103 mg BID

N=2830

No run-in

double-blind active-controlled

Ramipril

Target 5 mg BID

N=2831

Event driven: 711 primary endpoints

Median follow-up: 23 months

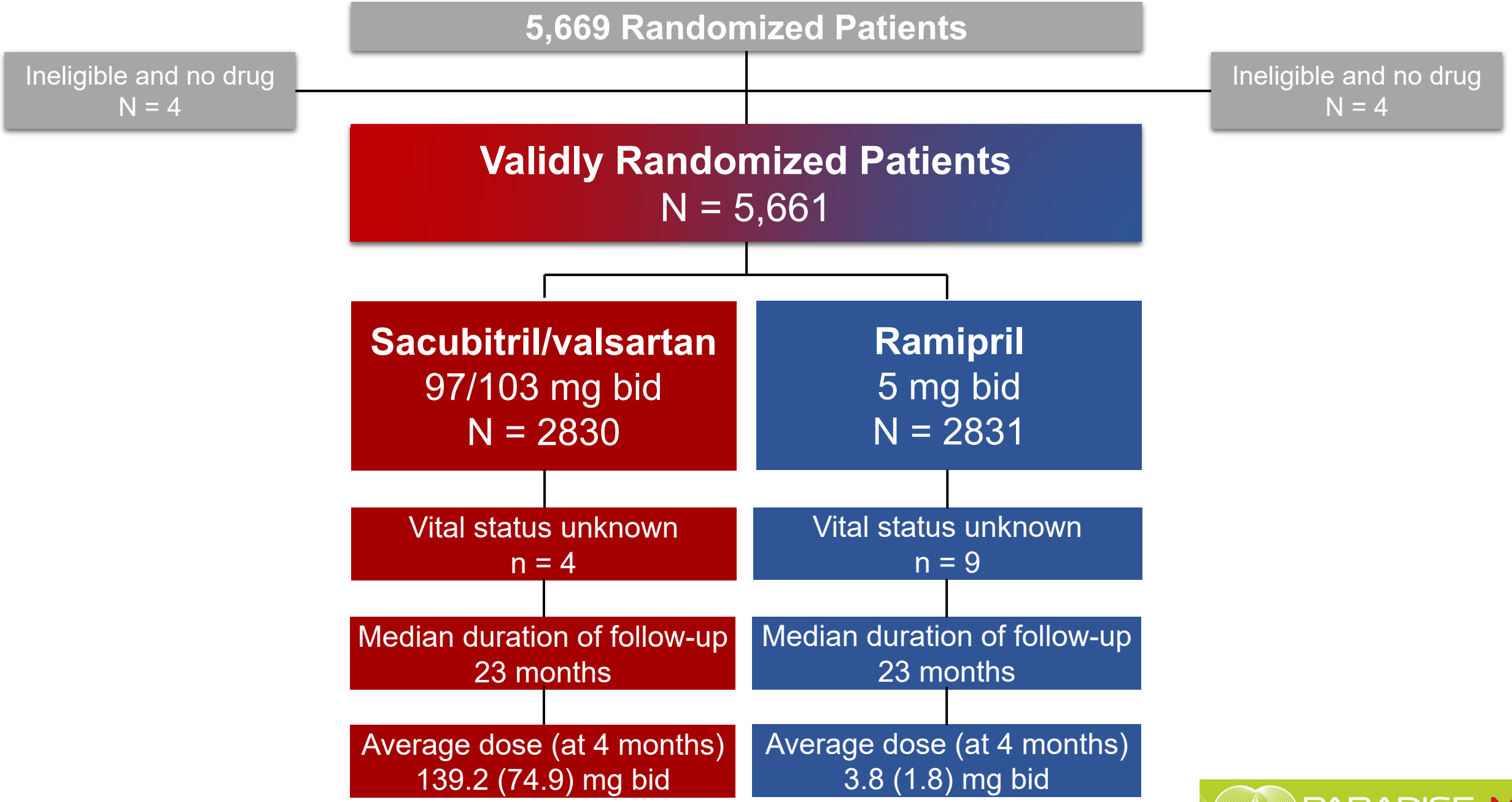
Primary Endpoint: CV death, HF hospitalization, outpatient development of HF
Secondary Endpoint: CV death or first HF hospitalization

Jering, *Eur J Heart Fail.* 2021

5,669 patients from 495 Sites in 41 Countries

(December 9, 2016 – March 16, 2020; last follow-up on December 31, 2020)

NORTH AMERICA 528 Patients		WESTERN EUROPE 1858 Patients		CENTRAL EUROPE 1499 Patients		ASIA-PACIFIC/OTHER 1105 Patients	
Canada	73	Austria	110	Bulgaria	211	Australia	59
United States	455	Belgium	80	Croatia	53	China	212
LATIN AMERICA 680 Patients		Denmark	133	Czech Republic	152	India	330
Argentina	251	Finland	25	Greece	66	Israel	101
Brazil	178	France	144	Hungary	228	Philippines	51
Colombia	135	Germany	271	Poland	45	Republic of Korea	49
Mexico	88	Italy	161	Romania	192	Singapore	87
Peru	28	Netherlands	342	Russian Federation	323	South Africa	45
		Norway	35	Slovakia	153	Taiwan	91
		Portugal	67	Turkey	76	Thailand	80
		Spain	167				
		Sweden	76				
		Switzerland	43				
		United Kingdom	204				


5,669 Randomized Patients
Ineligible and no drug
N = 4
Ineligible and no drug
N = 4
Validly Randomized Patients
N = 5,661
Sacubitril/valsartan
97/103 mg bid
N = 2830
Ramipril
5 mg bid
N = 2831
Vital status unknown
n = 4
Vital status unknown
n = 9
Median duration of follow-up
23 months
Median duration of follow-up
23 months
Average dose (at 4 months)
139.2 (74.9) mg bid
Average dose (at 4 months)
3.8 (1.8) mg bid

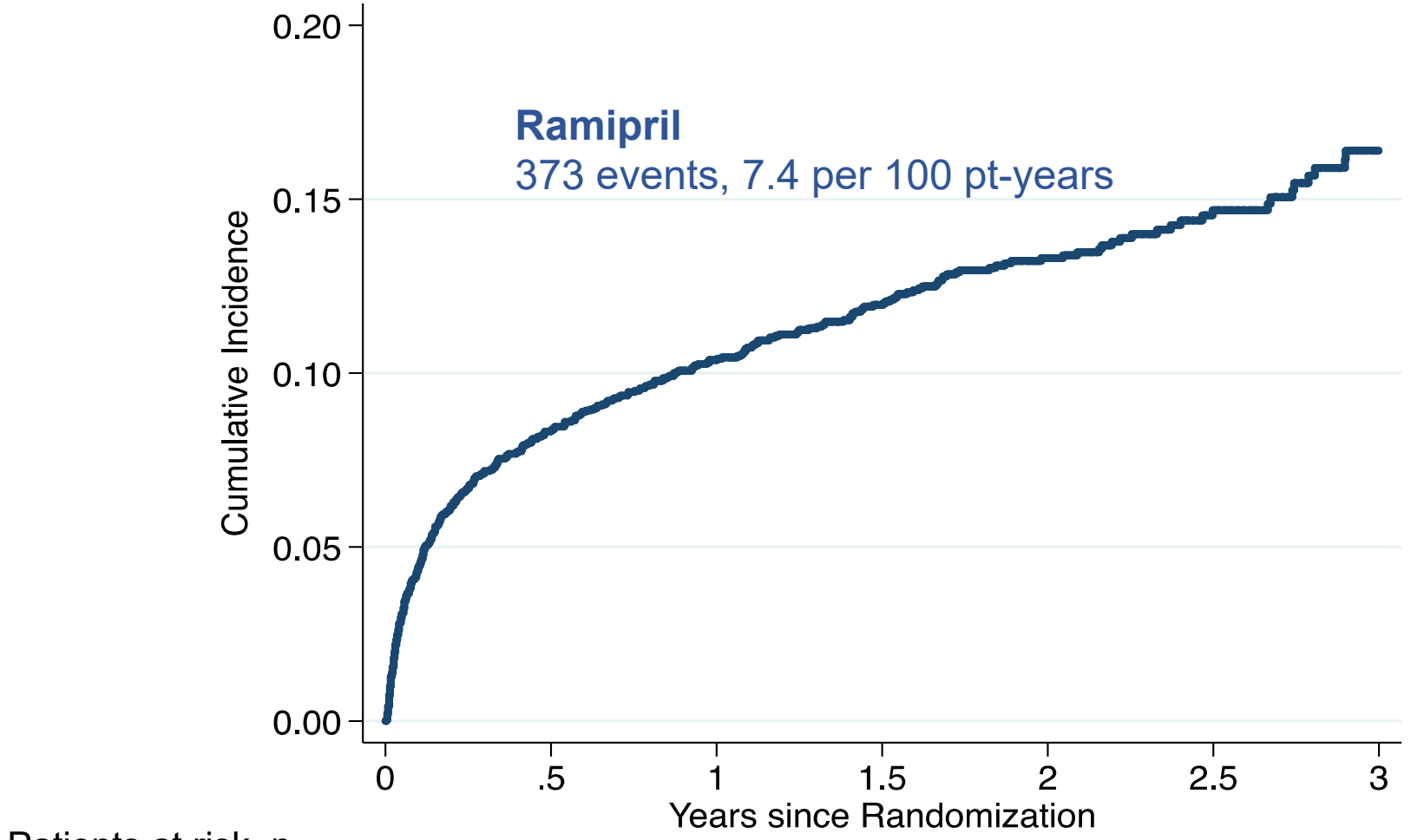
Baseline Characteristics

Characteristic	Sacubitril/Valsartan N = 2830	Ramipril N = 2831
Age (years), mean (SD)	64 (12)	64 (11)
Female sex (%)	23	25
Race – Asian/Black/Caucasian (%)	17 / 1 / 75	17 / 1 / 76
Prior heart failure	excluded	excluded
Prior MI (%)	16	16
Prior stroke (%)	4	5
Hypertension (%)	65	65
Diabetes (%)	43	42
Smoking (%)	22	21
Atrial fibrillation / flutter (%)	14	13
eGFR (ml/min/1.73m^2), mean (SD)	72 (22)	72 (23)

Index MI	Sacubitril/Valsartan N = 2830	Ramipril N = 2831
STEMI / NSTEMI (%)	76 / 24	76 / 24
Reperfusion (PCI / lytics) (%)	89 (88 / 4)	89 (88 / 5)
Location – Anterior / inferior (%)	68 / 19	68 /18
Time to randomization (days), mean (SD)	4.3 (1.8)	4.3 (1.7)
LVEF (%), mean (SD)	36 (9)	37 (10)
Killip class ≥II (%)	56	57
Medications at baseline:		
Dual antiplatelet therapy (%)	92	92
Beta blocker (%)	85	85
Aldosterone antagonist (%)	41	42
Statin (%)	94	95
ACEi/ARB (%)	78	78

PARADISE-MI Primary Outcome

CV death, first HF hospitalization or outpatient HF

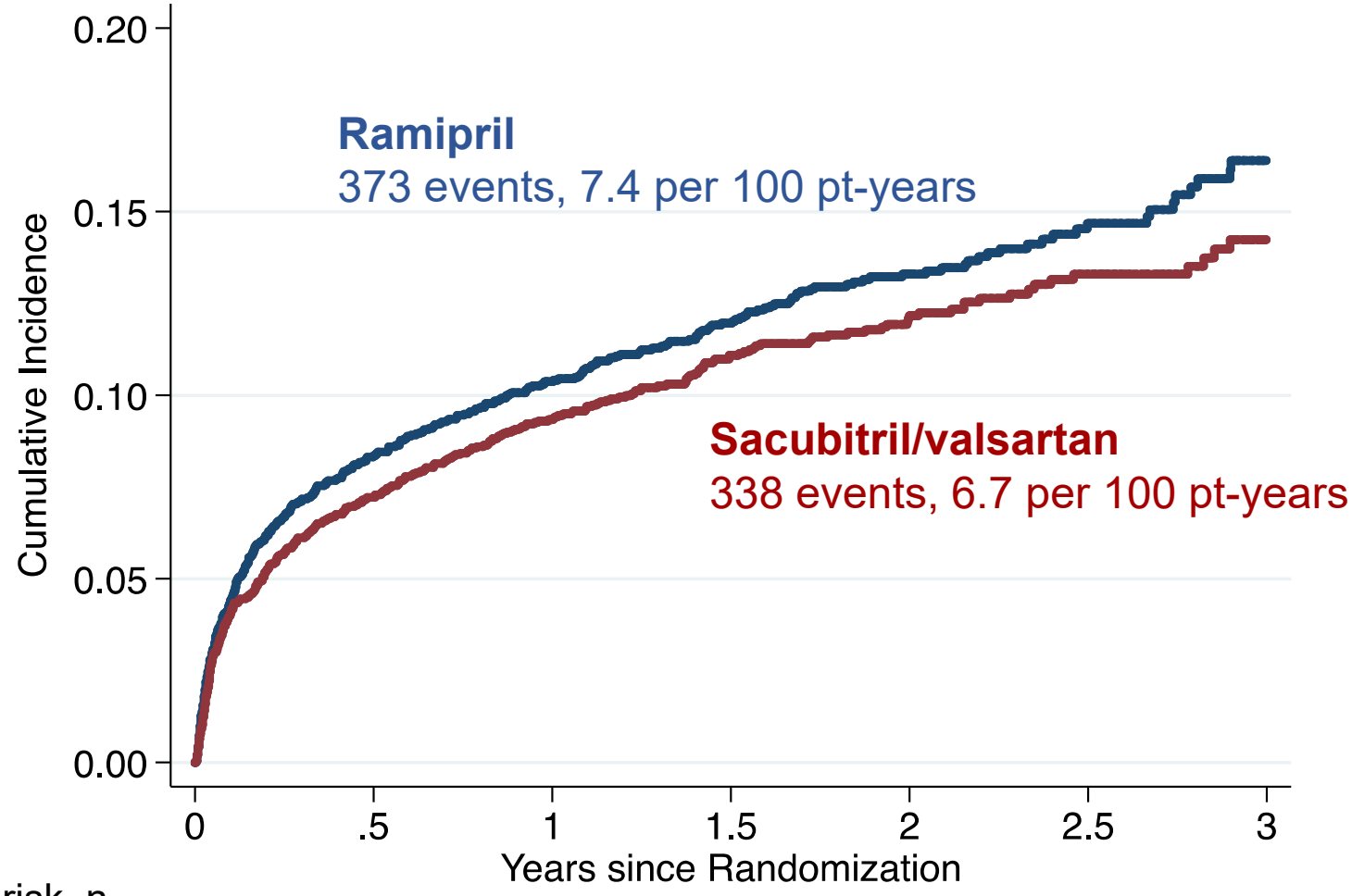


Patients at risk, n

Ramipril	2831	2577	2318	1725	1091	570	278

PARADISE-MI Primary Outcome

CV death, first HF hospitalization or outpatient HF

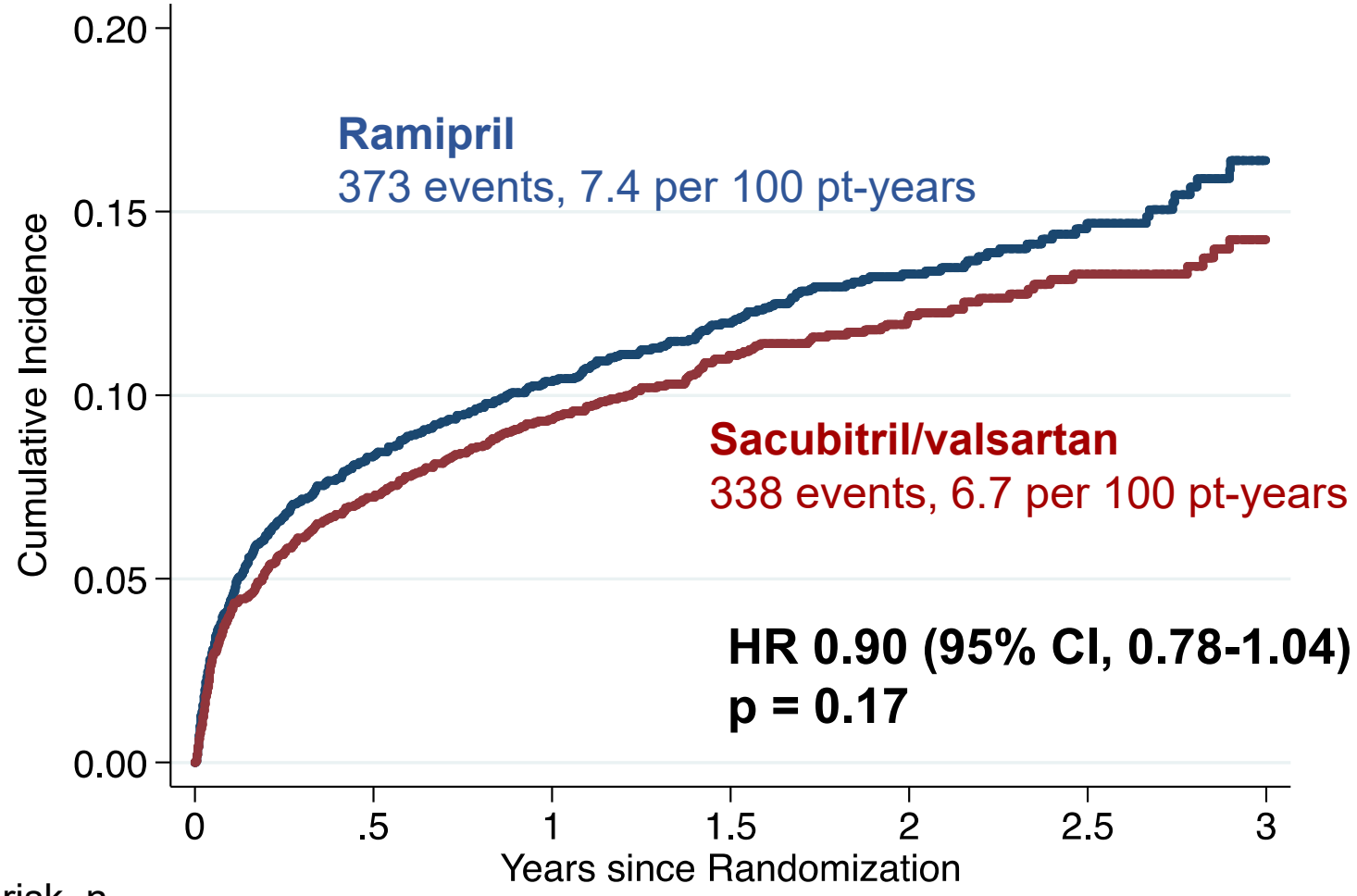


Patients at risk, n

Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril/valsartan	2830	2614	2342	1732	1101	567	280

PARADISE-MI Primary Outcome

CV death, first HF hospitalization or outpatient HF



Patients at risk, n

Ramipril	2831	2577	2318	1725	1091	570	278
Sacubitril/valsartan	2830	2614	2342	1732	1101	567	280

ACC.21

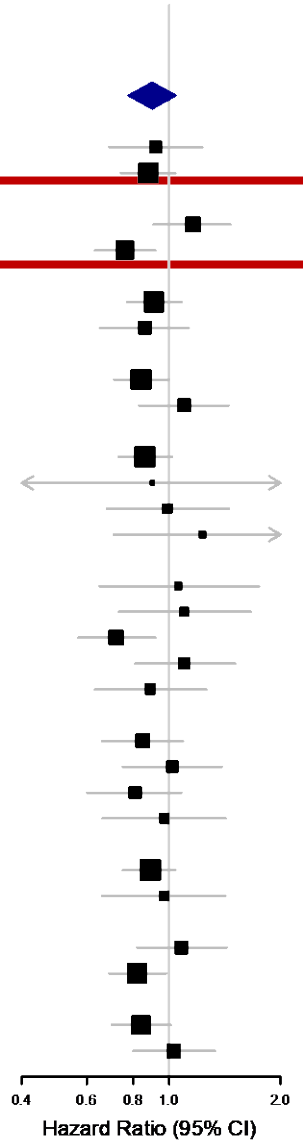
PARADISE-MI

CEC Adjudicated Primary Outcome	Events (%) and Event Rate [per 100 pt-yrs]		Hazard Ratio (95% CI) p-value
	Sacubitril/valsartan (N = 2830)	Ramipril (N = 2831)	
Primary Outcome Event rate	**338 (11.9%)** [6.7]	**373 (13.2%)** [7.4]	**0.90** (0.78-1.04) P=0.17
Patients with:			
CV Death	**168 (5.9%)** [3.1]	**191 (6.7%)** [3.6]	**0.87** (0.71-1.08) P=0.20
HF Hospitalization	**170 (6.0%)** [3.3]	**195 (6.9%)** [3.8]	**0.87** (0.70-1.06) P=0.17
Outpatient HF*	**39 (1.4%)** [0.7]	**57 (2.0%)** [1.1]	**0.68** (0.45-1.03) P=0.07

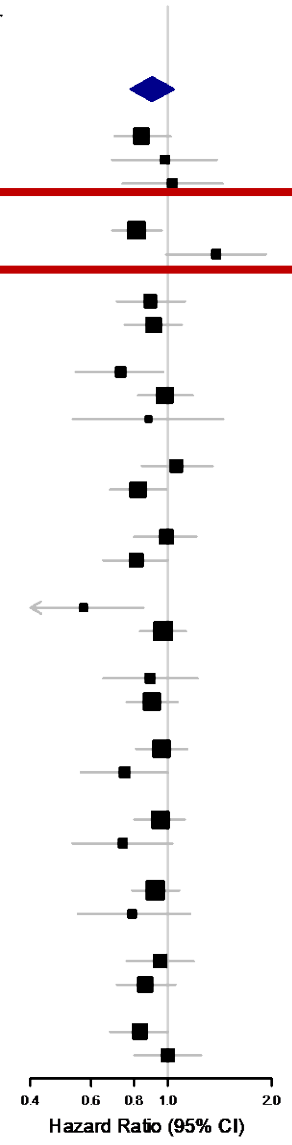
*outpatient development of HF with documented signs and symptoms requiring initiation/intensification of diuretic therapy maintained over ≥28 days

Pre-Specified Subgroups for Primary Endpoint

Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
Overall	**711/5661**	**0.90 (0.78–1.04)**	
Number of risk factors			0.78
<=1	183/2707	0.92 (0.69–1.23)	
>1	528/2954	0.88 (0.74–1.04)	
Age (years)			0.007
< 65 years	269/2837	1.16 (0.91–1.47)	
>= 65 years	442/2824	0.76 (0.63–0.92)	
Age (years)			0.7
< 75 years	512/4610	0.91 (0.77–1.08)	
>= 75 years	199/1051	0.86 (0.65–1.13)	
Gender			0.11
Male	514/4298	0.84 (0.71–1.00)	
Female	197/1363	1.10 (0.83–1.45)	
Race			0.63
Caucasian	536/4263	0.86 (0.73–1.02)	
Black	18/75	0.90 (0.35–2.34)	
Asian	105/953	0.99 (0.68–1.45)	
Other	52/370	1.23 (0.71–2.14)	
Region			0.19
North America	62/529	1.06 (0.65–1.75)	
Latin America	92/679	1.10 (0.73–1.66)	
Western Europe	272/1853	0.72 (0.57–0.92)	
Central Europe	155/1499	1.10 (0.81–1.51)	
Asia/Pacific	130/1101	0.89 (0.63–1.26)	
LVEF			0.68
<=30%	248/1639	0.85 (0.66–1.09)	
30 < LVEF <=35%	161/1160	1.02 (0.75–1.39)	
35< LVEF <=40%	180/1809	0.81 (0.60–1.08)	
>40%	104/971	0.97 (0.66–1.42)	
LVEF			0.69
<=40%	589/4608	0.89 (0.75–1.04)	
>40%	104/971	0.97 (0.66–1.42)	
Killip class			0.1
Class I	201/2281	1.08 (0.82–1.43)	
Class >=II	491/3201	0.82 (0.69–0.98)	
Type of MI			0.2
STEMI	471/4277	0.84 (0.70–1.01)	
NSTEMI/other	240/1384	1.03 (0.80–1.33)	



Subgroup	No. of Events/Patients	Hazard Ratio (95% CI)	P Value for Interaction
Overall	**711/5661**	**0.90 (0.78–1.04)**	
Infarct location			0.5
Anterior	443/3853	0.84 (0.70–1.02)	
Inferior	128/1053	0.98 (0.69–1.39)	
Other	140/755	1.03 (0.74–1.44)	
PCI use at baseline			0.005
Yes	571/4980	0.81 (0.69–0.96)	
No	140/681	1.38 (0.99–1.93)	
Time from index MI to randomization			0.93
< 4.357 days	295/2830	0.89 (0.71–1.12)	
>= 4.357 days	416/2831	0.91 (0.75–1.10)	
SBP at baseline			0.21
<=110mmHg	191/1369	0.73 (0.54–0.97)	
>110–140mmHg	458/3849	0.98 (0.82–1.18)	
>140mmHg	62/440	0.88 (0.53–1.45)	
eGFR at screening (mL/min/1.73m2)			0.1
<60	270/1369	1.06 (0.84–1.35)	
>=60	441/4292	0.82 (0.68–0.99)	
Diabetic			0.18
Yes	368/2398	0.99 (0.80–1.21)	
No	343/3263	0.81 (0.65–1.00)	
AF with index MI			0.017
Yes	98/525	0.57 (0.38–0.85)	
No	613/5136	0.97 (0.83–1.13)	
Prior MI			0.96
Yes	157/920	0.89 (0.65–1.22)	
No	554/4741	0.90 (0.76–1.07)	
Hypertension			0.14
Yes	522/3676	0.96 (0.81–1.14)	
No	189/1985	0.75 (0.56–1.00)	
Prior ACEi or ARB use			0.19
Yes	568/4436	0.95 (0.80–1.12)	
No	143/1225	0.74 (0.53–1.03)	
Beta blocker use			0.47
Yes	600/4827	0.92 (0.79–1.08)	
No	111/834	0.79 (0.55–1.16)	
MRA use			0.51
Yes	317/2338	0.95 (0.76–1.19)	
No	394/3323	0.86 (0.71–1.05)	
Loop diuretic use			0.21
Yes	409/2295	0.83 (0.68–1.00)	
No	302/3366	1.00 (0.80–1.25)	



Secondary Endpoints	Events (%) and Event Rate [per 100 pt-yrs]		Hazard Ratio (95% CI) p-value
	Sacubitril/valsartan (N = 2830)	Ramipril (N = 2831)	
CV Death or HF hospitalization Event rate	**308 (10.9%)** [6.0]	**335 (11.8%)** [6.6]	**0.91** (0.78-1.07) P=0.25
HF hospitalization or outpatient heart failure	**201 (7.1%)** [4.0]	**237 (8.4%)** [4.7]	**0.84** (0.70-1.02) P=0.07
CV death, non-fatal MI or non-fatal stroke	**315 (11.1%)** [6.1]	**349 (12.3%)** [6.8]	**0.90** (0.77-1.05) P=0.18
CV death and *total* hospitalizations for heart failure, MI or stroke	**591** [11.0]	**682** [12.8]	**0.84*** (0.70-1.00) P=0.045
All-cause death	**213 (7.5%)** [4.0]	**242 (8.5%)** [4.5]	**0.88** (0.73-1.05) P=0.16

*Rate ratio derived from negative binomial regression with Weibull baseline intensity function

Total (first and recurrent) CEC Adjudicated Events

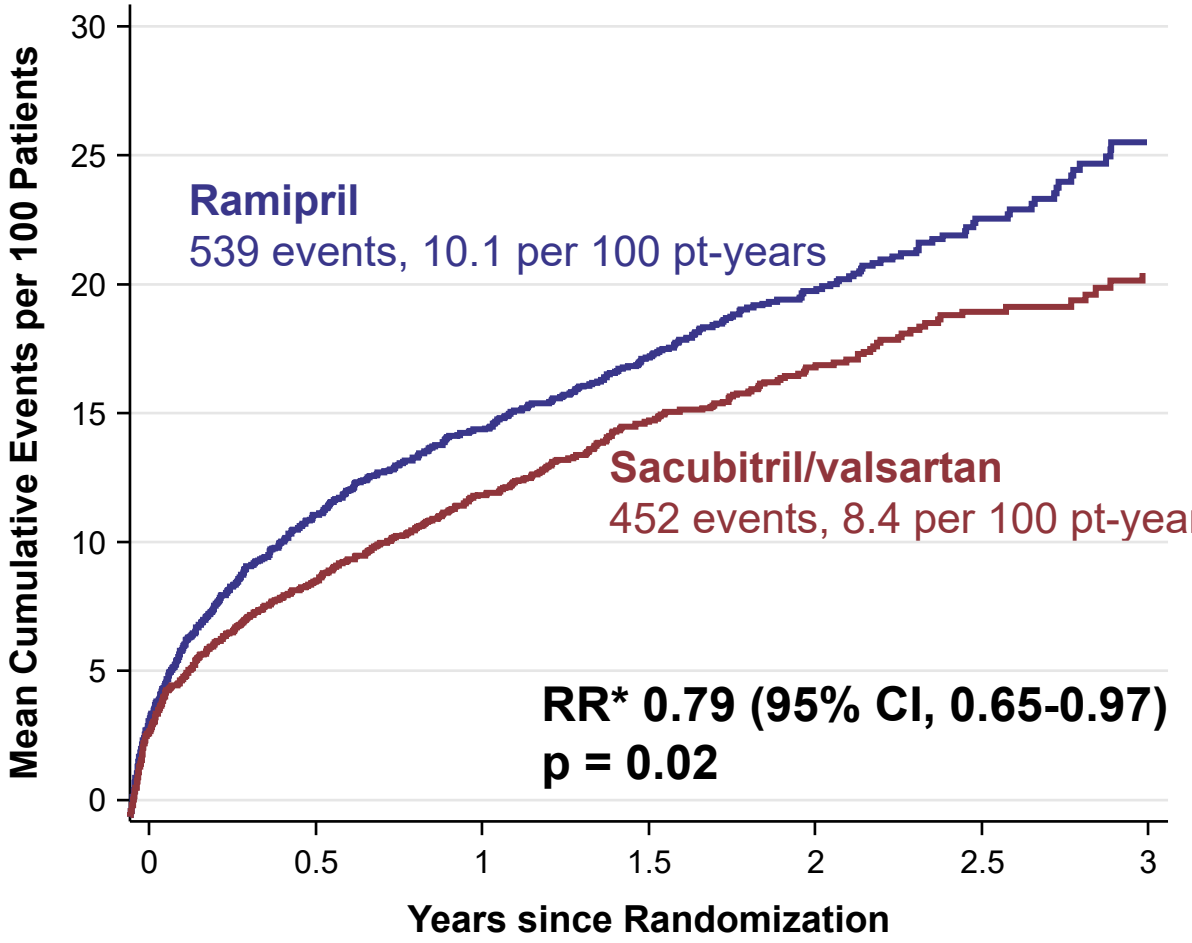
Total (first and recurrent) CEC Adjudicated Events	Events and Event Rate [per 100 pt-yrs]		Ratio (95% CI) p-value
	Sacubitril/valsartan (N = 2830)	Ramipril (N = 2831)	
Total HF hospitalizations, outpatient HF events and CV death	**452** [8.4]	**539** [10.1]	**RR*** **0.79** (0.65-0.97) P=0.02
Components			
CV Death	**168** [3.1]	**191** [3.6]	**HR 0.87** (0.71-1.08) P=0.20
Total HF Hospitalizations	**240** [4.5]	**286** [5.4]	**RR*** **0.81** (0.64-1.04) P=0.10
Total Outpatient HF Events	**44** [0.8]	**62** [1.2]	**RR*** **0.70** (0.46-1.06) P=0.10

*Rate ratio derived from negative binomial regression with Weibull baseline intensity function

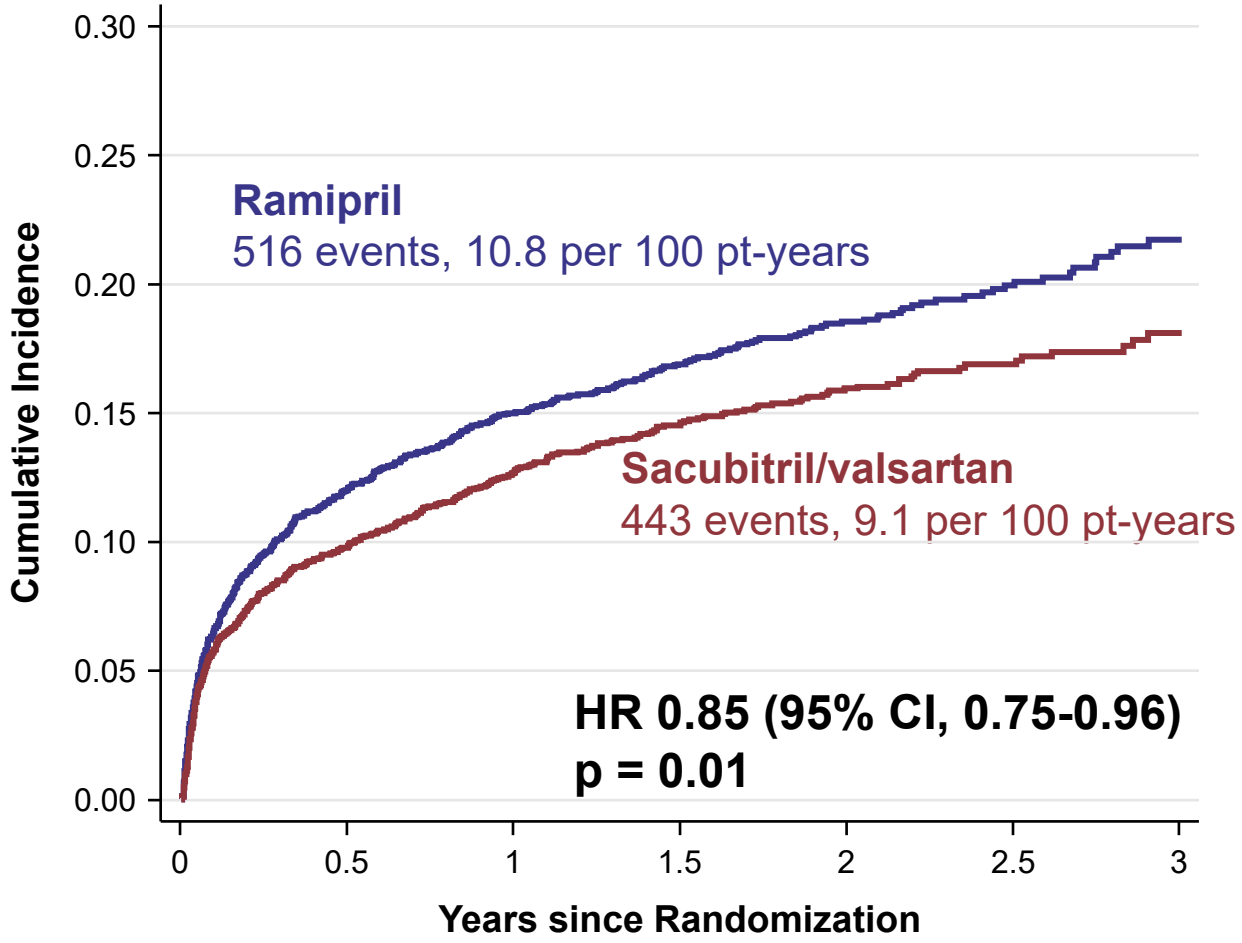
Investigator Reported Outcomes

Investigator Reported Primary Outcome	Events (%) and Event Rate [per 100 pt-yrs]		Hazard Ratio (95% CI) p-value
	Sacubitril/valsartan (N = 2830)	Ramipril (N = 2831)	
Primary Outcome Event rate	**443 (15.7%)** [9.1]	**516 (18.2%)** [10.8]	**0.85** (0.75-0.96) P=0.01
Patients with:			
CV Death	**155 (5.5%)** [2.9]	**179 (6.3%)** [3.4]	**0.86** (0.69-1.07) P=0.17
HF Hospitalization	**252 (8.9%)** [5.0]	**285 (10.1%)** [5.8]	**0.88** (0.74-1.04) P=0.12
Outpatient HF	**111 (3.9%)** [2.1]	**160 (5.7%)** [3.1]	**0.69** (0.54-0.88) P=0.003

Total (first and recurrent) CEC Adjudicated Primary Events



Investigator Reported Primary Endpoint



*Rate ratio derived from negative binomial regression with Weibull baseline intensity function

Adverse Events

Reports (%)	Sacubitril/Valsartan N = 2830	Ramipril N = 2831
Angioedema (adjudicated)	14 (0.5%)	17 (0.6%)
SAE	1146 (40.5%)	1126 (39.8%)
AE	2352 (83.1%)	2325 (82.1%)
Hypotension	802 (28.4%)*	620 (22.0%)
Cough	255 (9.0%)*	371 (13.1%)
Renal impairment	329 (11.7%)	326 (11.6%)
Hyperkalemia	301 (10.7%)	285 (10.1%)
Liver abnormalities	132 (4.7%)*	167 (5.9%)

*p<0.05

Laboratory Abnormalities

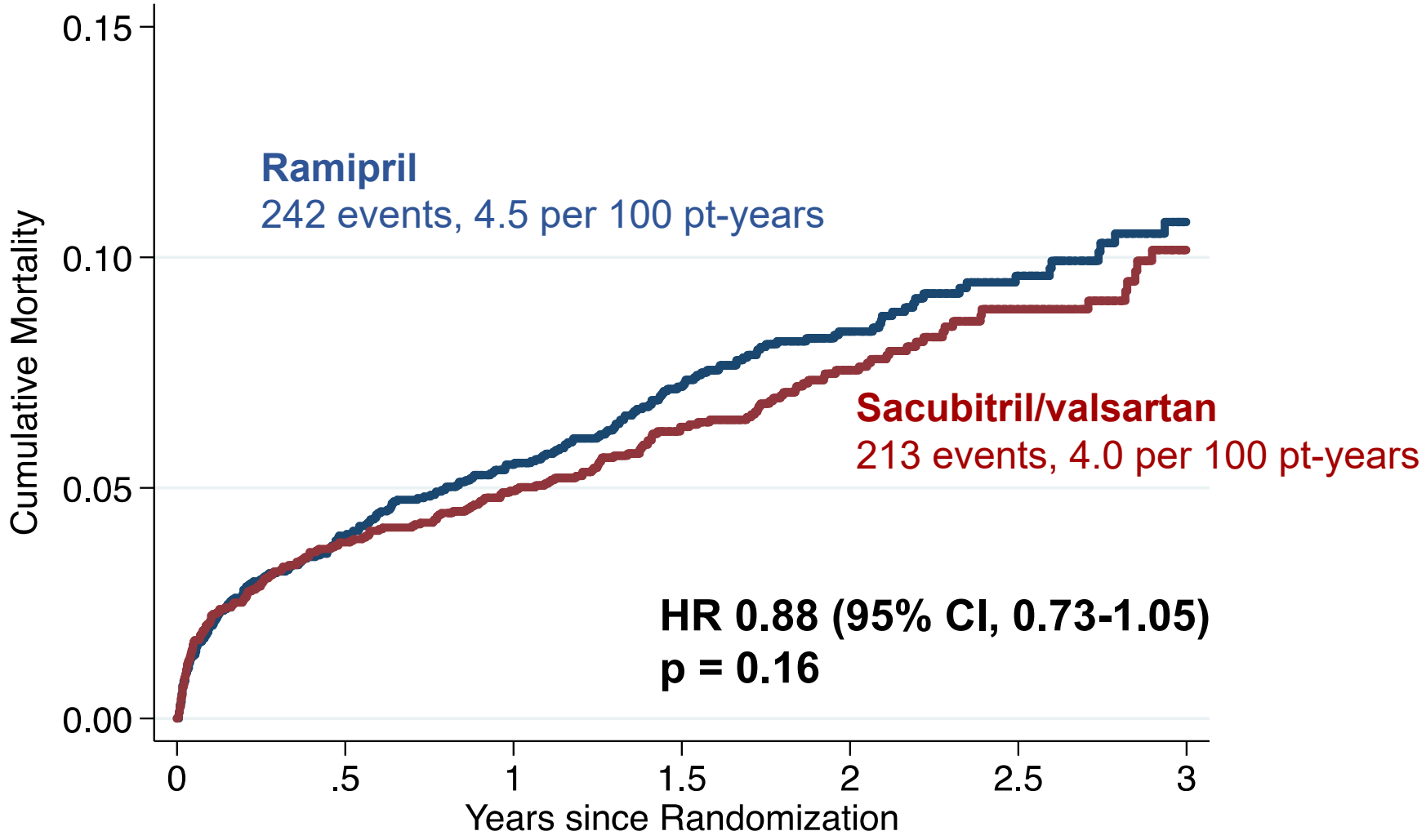
Patients having (%)	Sacubitril/Valsartan N = 2830	Ramipril N = 2831
Serum creatinine ≥2.0mg/dl	162 (5.9%)	171 (6.3%)
≥2.5 mg/dl	67 (2.4%)	65 (2.4%)
≥3.0 mg/dl	23 (0.8%)	34 (1.2%)
Potassium >5.5 mmol/l	403 (14.7%)	361 (13.2%)
>6.0 mmol/l	92 (3.4%)	95 (3.5%)
AST >3x ULN	23 (0.9%)	27 (1.0%)
>5x ULN	8 (0.3%)	13 (0.5%)
ALT >3x ULN	32 (1.2%)	38 (1.4%)
>5x ULN	11 (0.4%)	12 (0.5%)

Permanent Study Drug Discontinuation (excluding deaths)

Discontinuation (%)	Sacubitril/Valsartan N = 2830	Ramipril N = 2831
Discontinuation (excluding death)	501 (17.8%)	517 (18.4%)
Discontinuation due to AE	356 (12.6%)	379 (13.4%)
Cough	35 (1.2%)*	65 (2.3%)
Hypotension	37 (1.3%)*	16 (0.6%)
Renal impairment	19 (0.7%)	18 (0.6%)
Hyperkalemia	12 (0.4%)	14 (0.5%)

*p<0.005

PARADISE-MI All Deaths



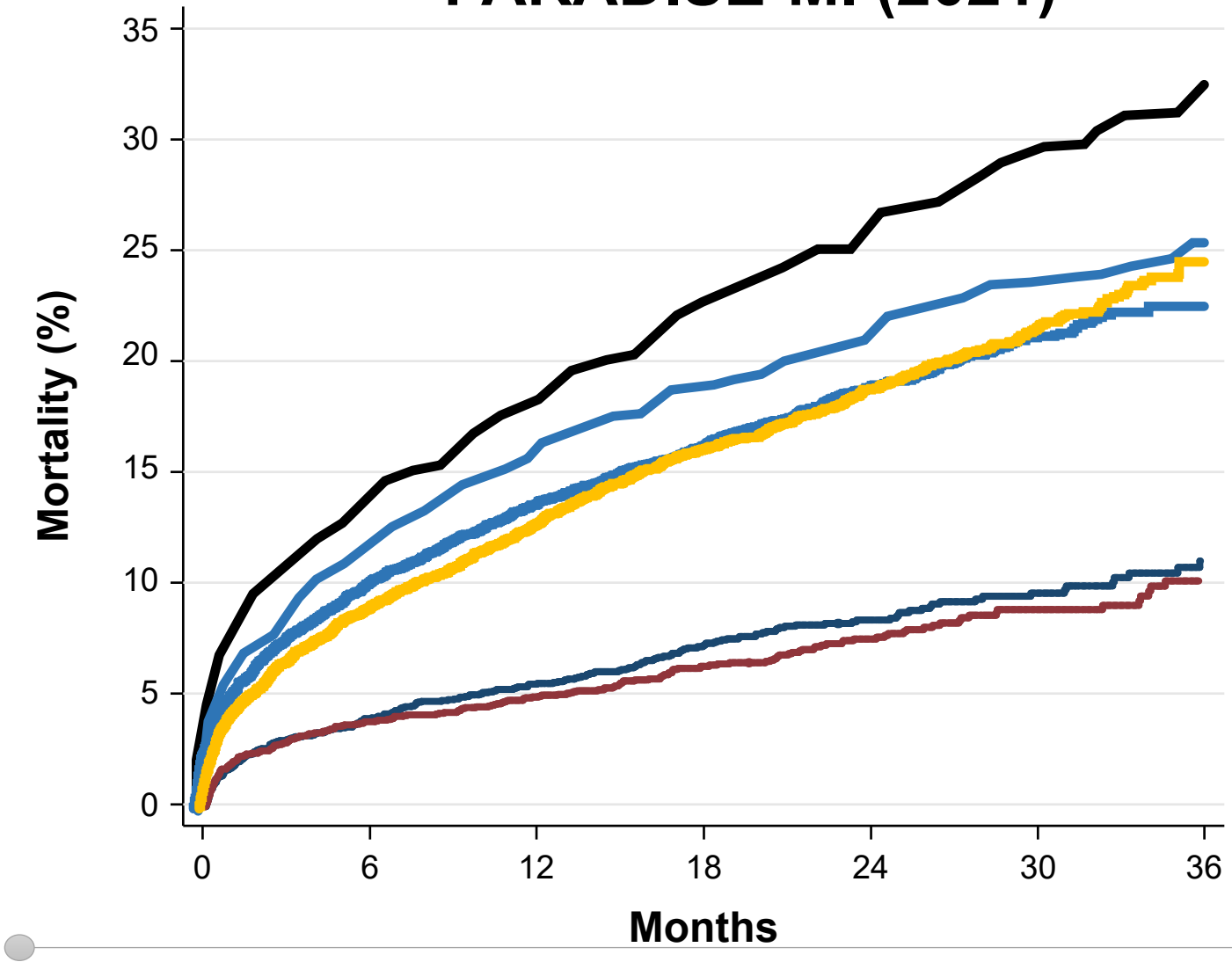
Patients at risk, n							
Ramipril	2831	2715	2467	1852	1190	631	311
Sacubitril/valsartan	2830	2721	2473	1856	1198	629	319

Summary

In a vigorously managed enhanced risk AMI population compared to active therapy with ramipril:

- Sacubitril/valsartan did not result in a significantly lower rate of CV death, heart failure hospitalization or outpatient heart failure requiring treatment.
- Pre-specified observations of reductions in both the investigator reports of the primary composite as well as in the total (recurrent) adjudicated events support incremental clinical benefits of sacubitril/valsartan.
- The safety and tolerability of sacubitril/valsartan in this AMI population was comparable to that of the ACEi.

Deaths in SAVE, AIRE, TRACE (1990s), VALIANT (2003) and PARADISE-MI (2021)



Placebo

ACE Inhibitor

Valsartan

Ramipril

Sacubitril/valsartan

HR 0.88 (95% CI, 0.73-1.05)
p = 0.16

PARADISE-MI

Steering Committee

Marc Pfeffer (Chair), Eugene Braunwald, Christopher B. Granger, Lars Kober, Douglas Mann, Aldo P. Maggioni, John J.V. McMurray, Jean L. Rouleau, Scott D. Solomon, Philippe Gabriel Steg

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