

SAC 27 y 28
mayo 2022



Congreso de la
Sociedad Asturiana
de **Cardiología**
Sede: Parador de Corias



Cangas de Narcea

Manejo contemporáneo de la Insuficiencia Cardíaca

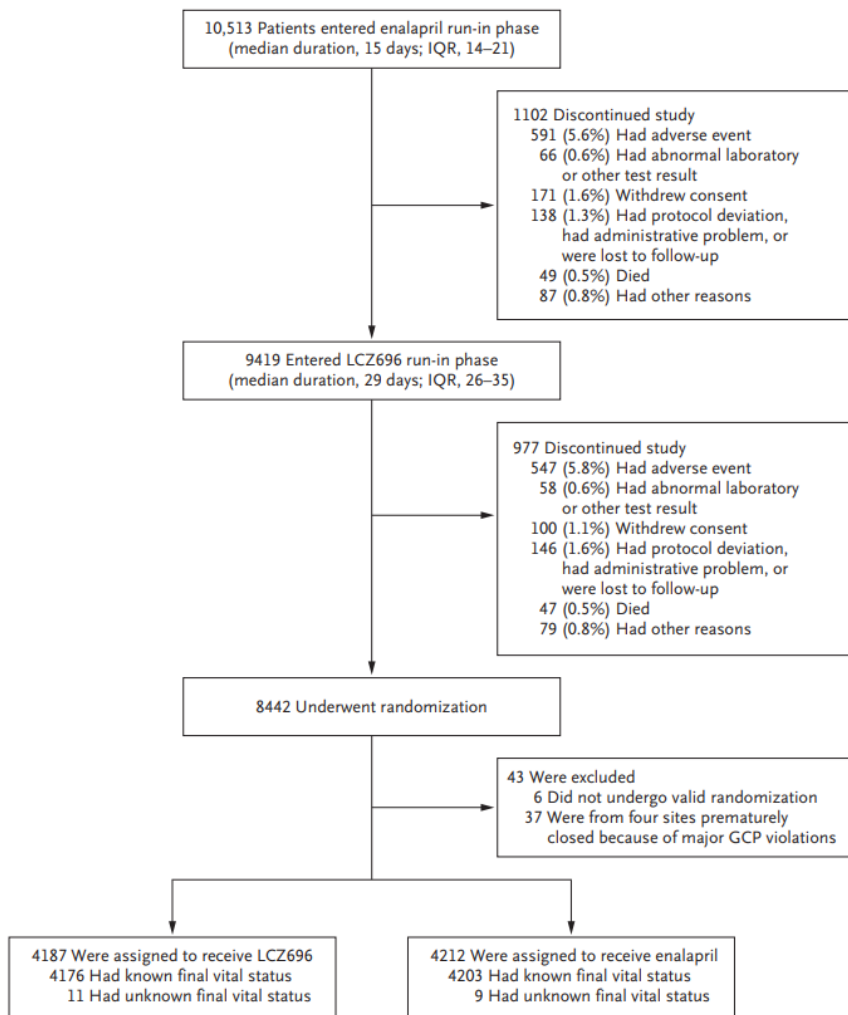
*En FEVI reducida mi prioridad es
introducir Sacubitril-Valsartán*

Julio Casares Medrano
Cardiólogo
Oviedo-Avilés

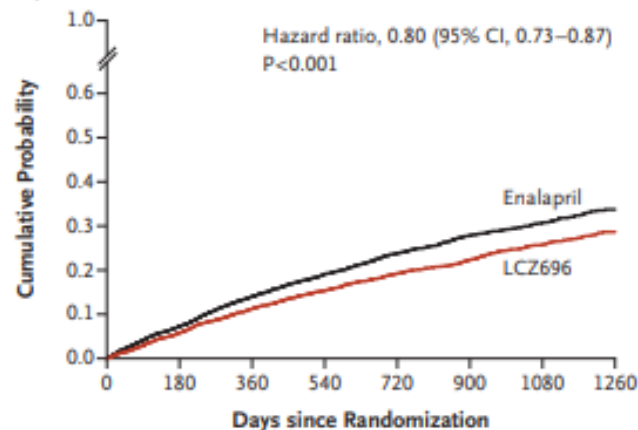


Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

PARADIGM-HF

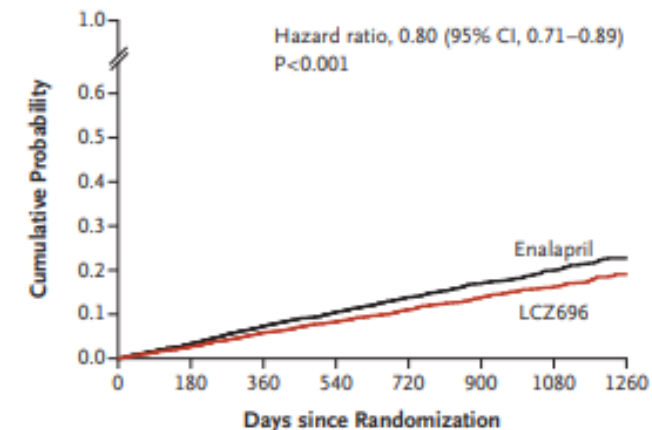


A Primary End Point



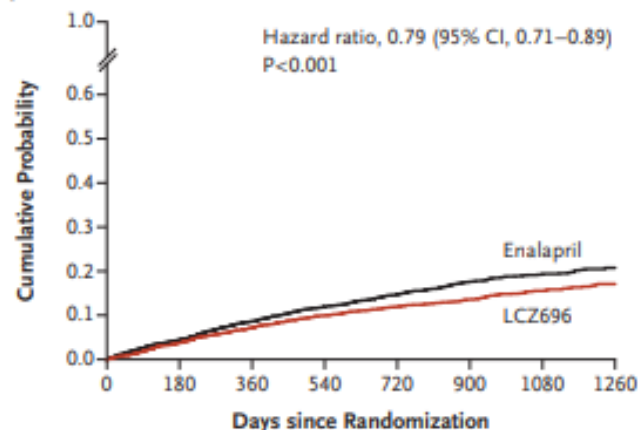
No. at Risk									
LCZ696	4187	3922	3663	3018	2257	1544	896	249	
Enalapril	4212	3883	3579	2922	2123	1488	853	236	

B Death from Cardiovascular Causes



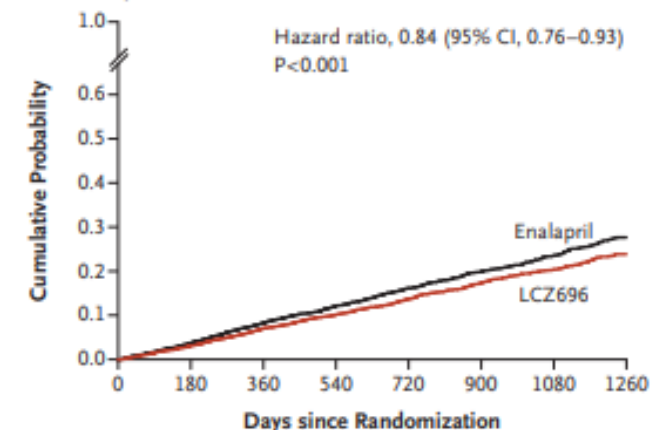
No. at Risk									
LCZ696	4187	4056	3891	3282	2478	1716	1005	280	
Enalapril	4212	4051	3860	3231	2410	1726	994	279	

C Hospitalization for Heart Failure



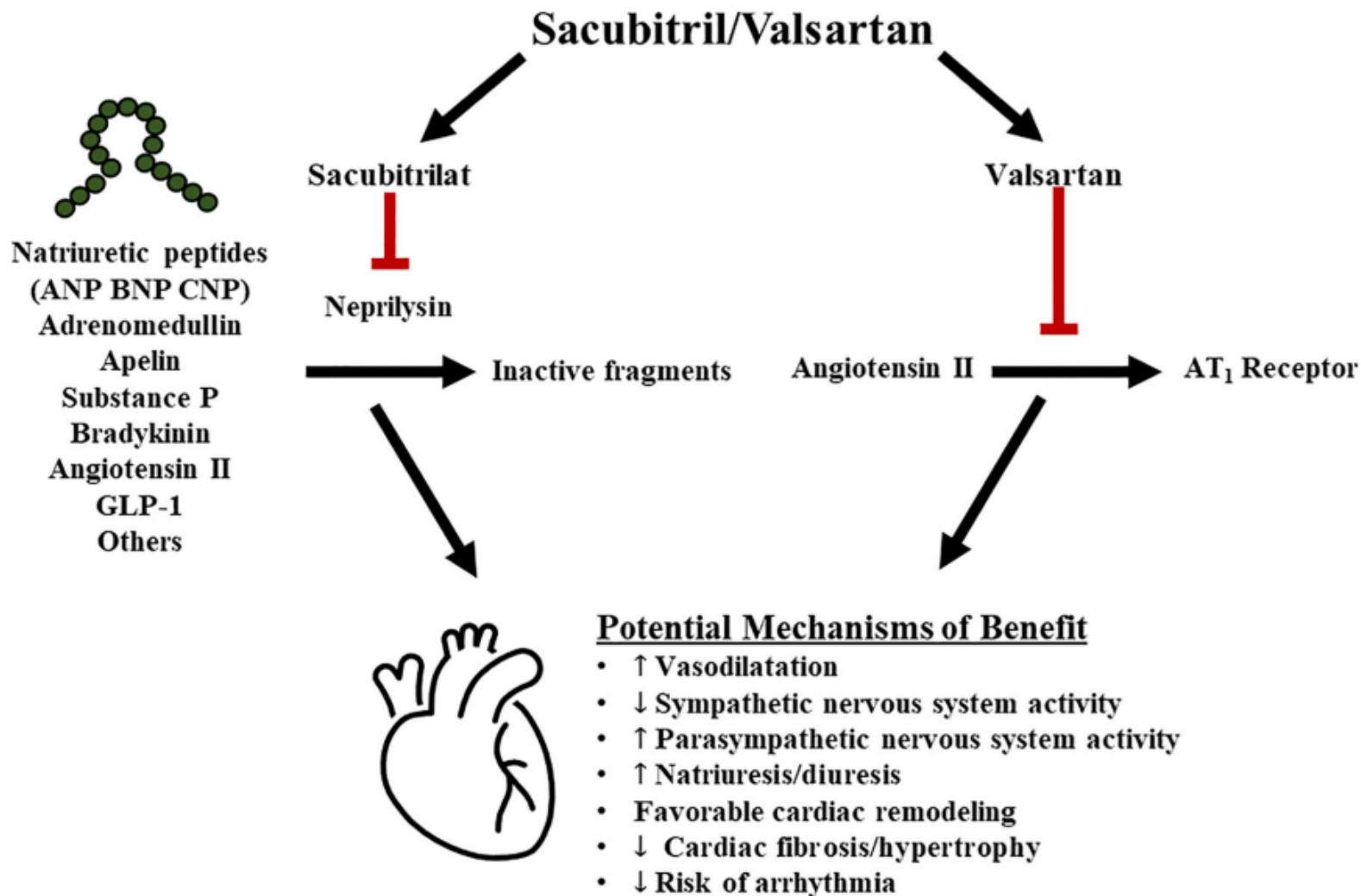
No. at Risk									
LCZ696	4187	3922	3663	3018	2257	1544	896	249	
Enalapril	4212	3883	3579	2922	2123	1488	853	236	

D Death from Any Cause



No. at Risk									
LCZ696	4187	4056	3891	3282	2478	1716	1005	280	
Enalapril	4212	4051	3860	3231	2410	1726	994	279	

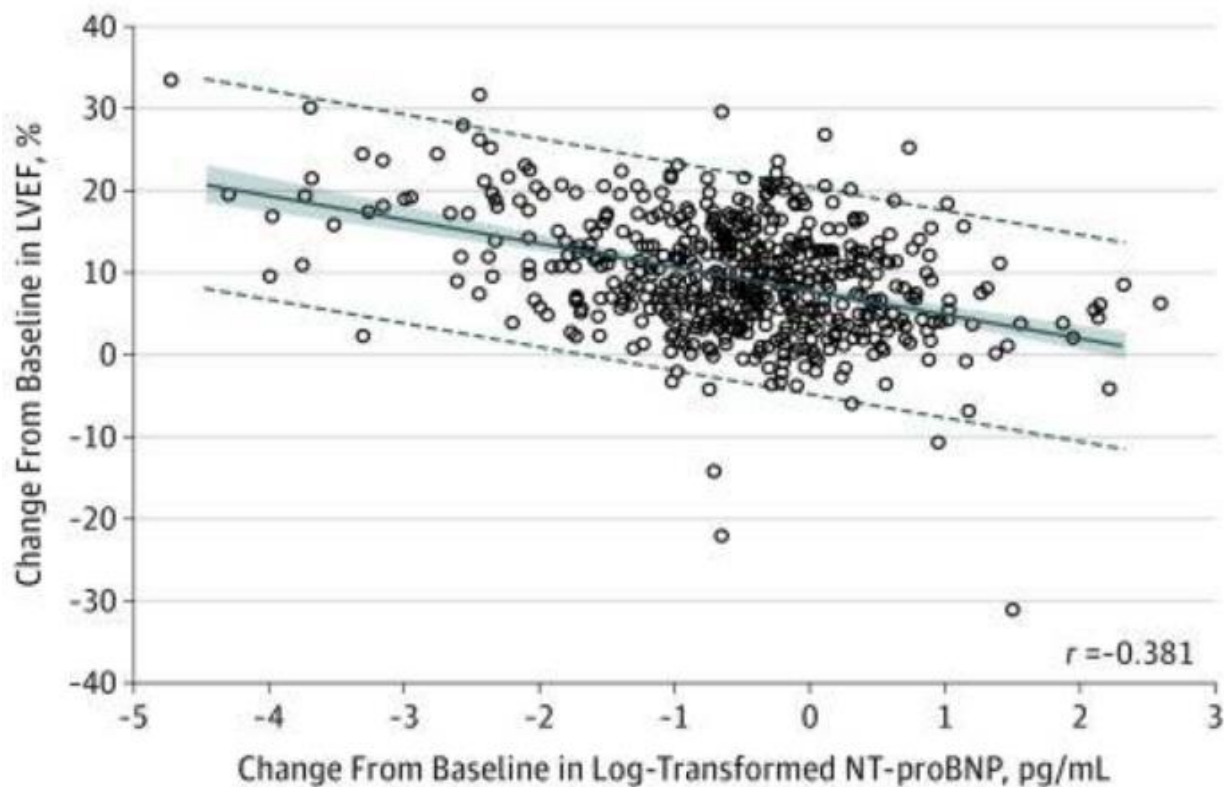
Potential mechanisms of therapeutic benefit of sacubitril/valsartan



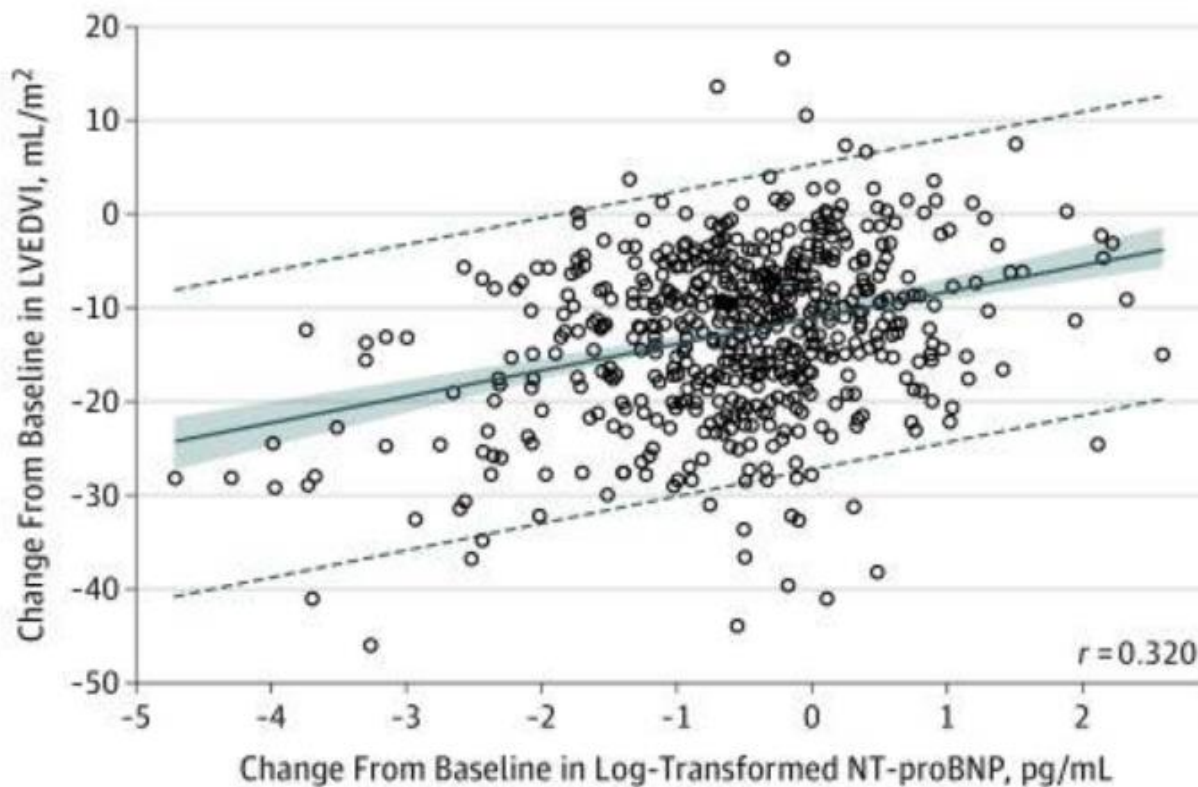
Association of Change in N-Terminal Pro-B-Type Natriuretic Peptide Following Initiation of Sacubitril-Valsartan Treatment With Cardiac Structure and Function in Patients With Heart Failure With Reduced Ejection Fraction

PROVE-HF

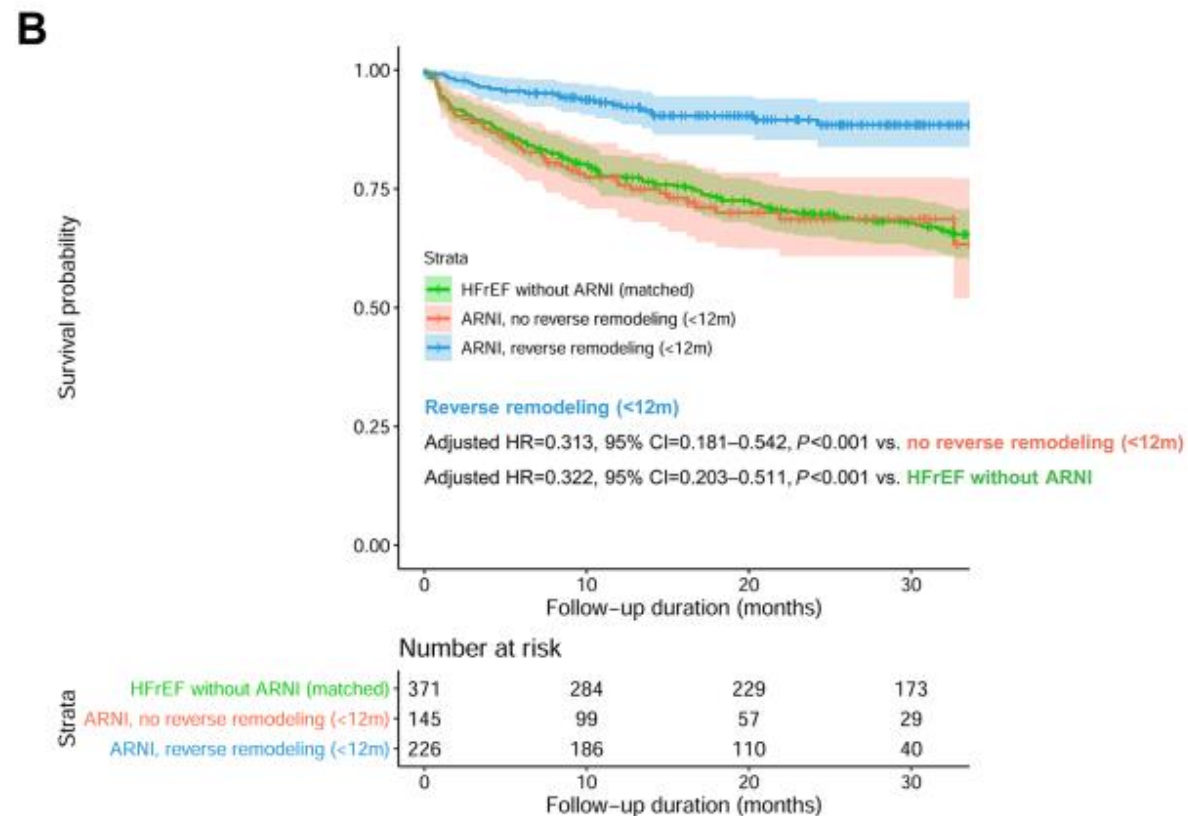
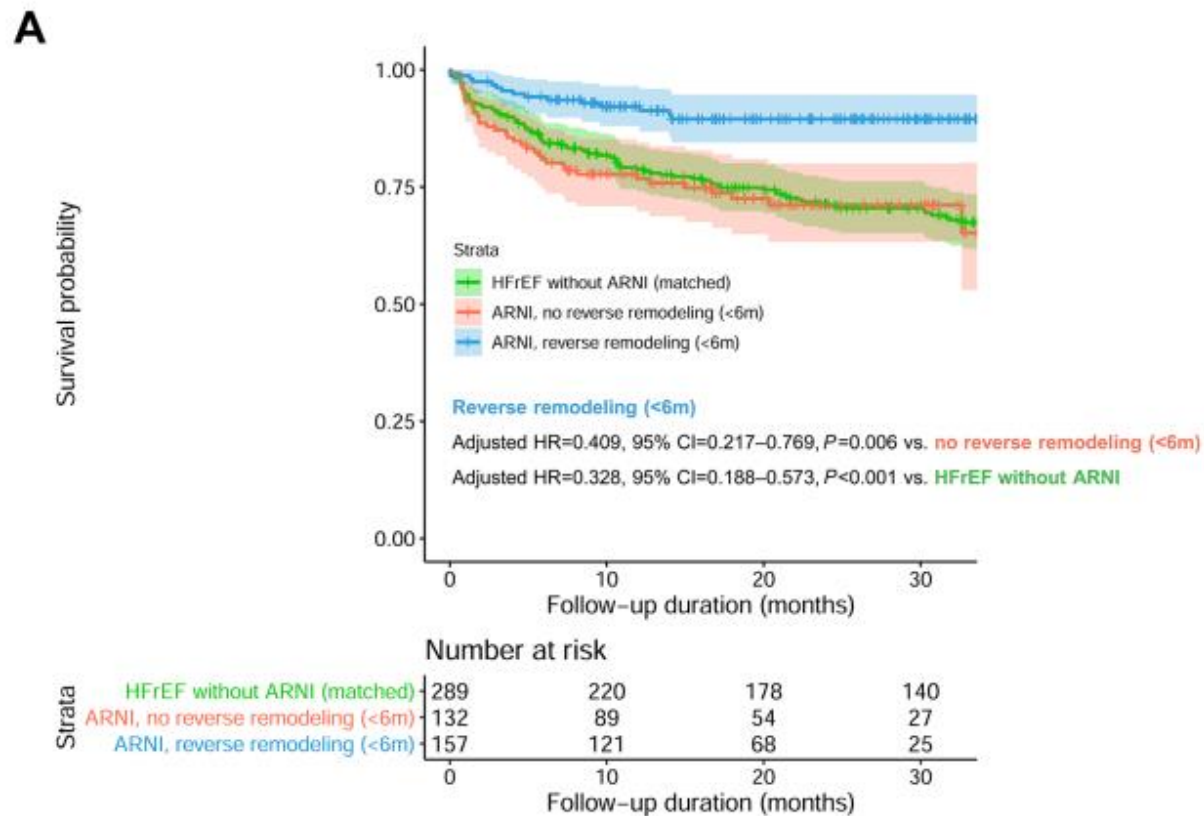
A Left ventricular ejection fraction (LVEF)



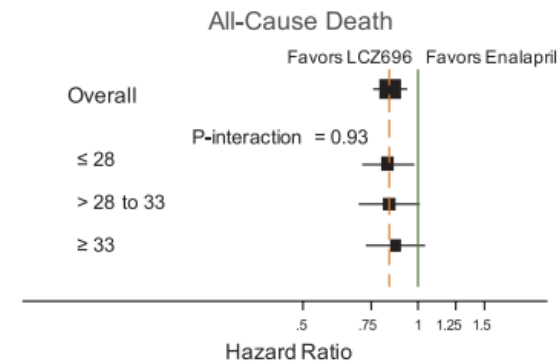
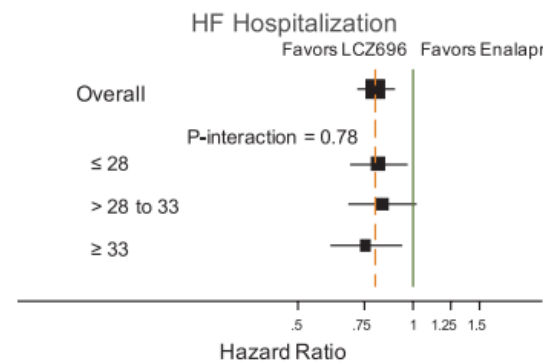
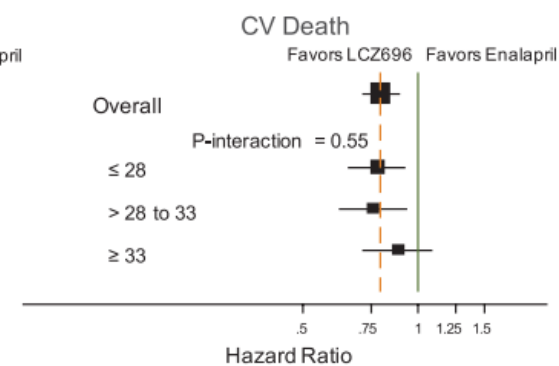
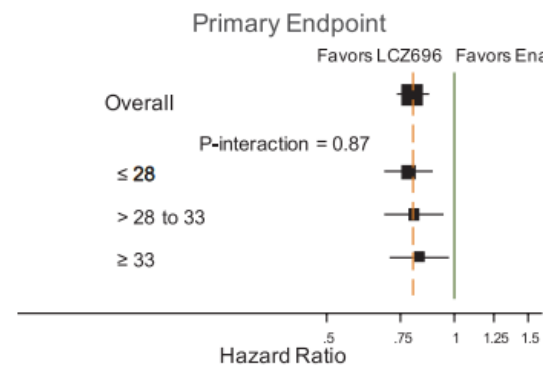
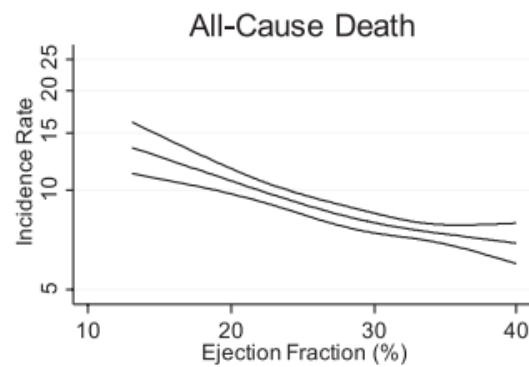
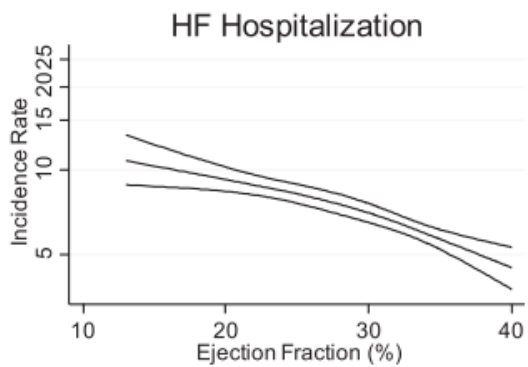
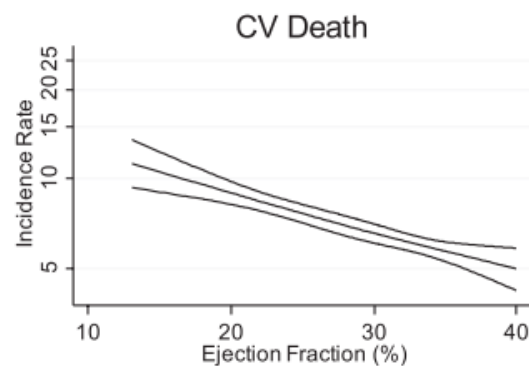
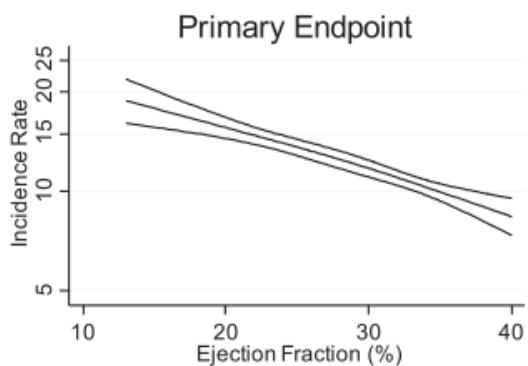
B Left ventricular end-diastolic volume index (LVEDVI)



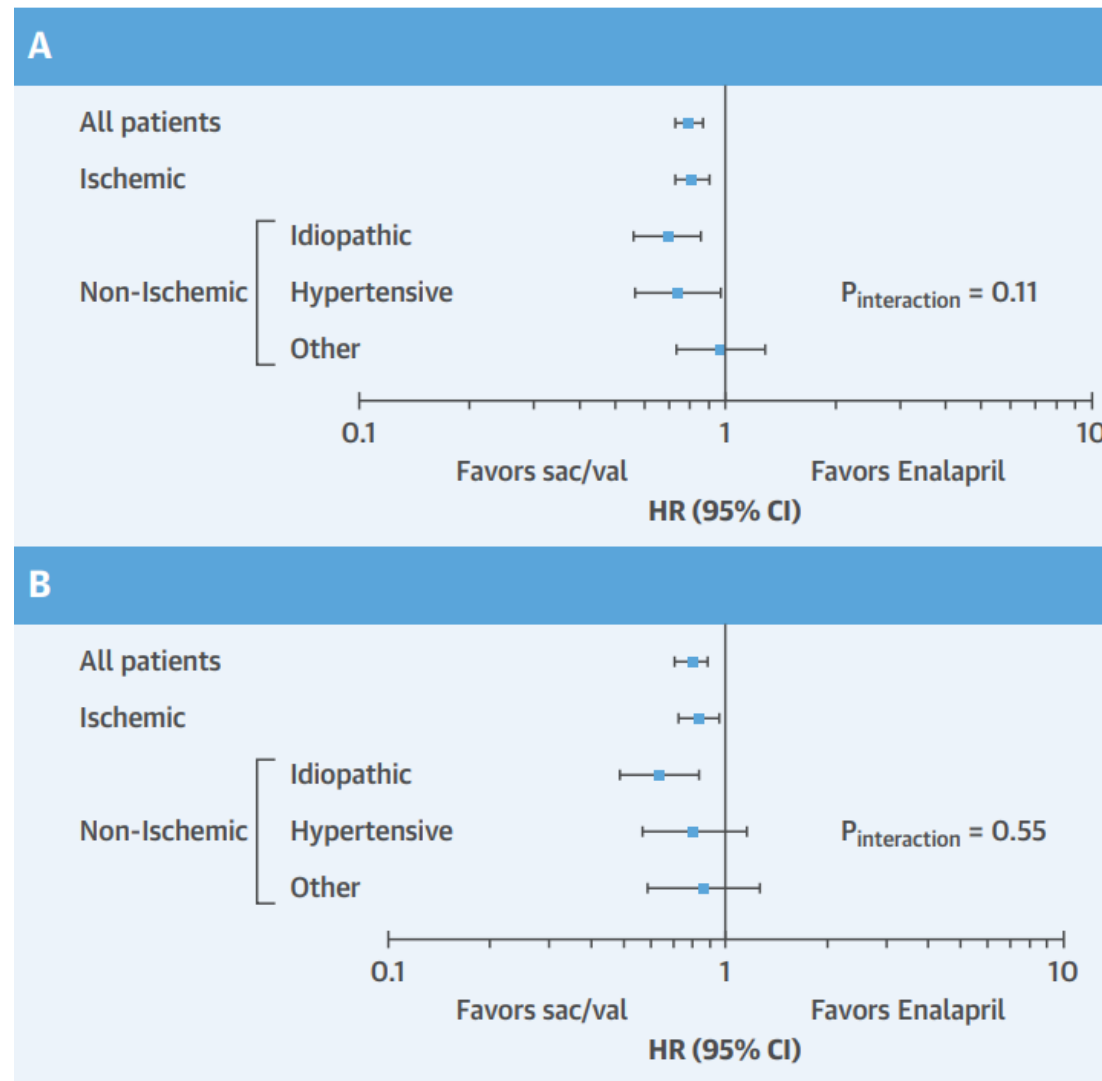
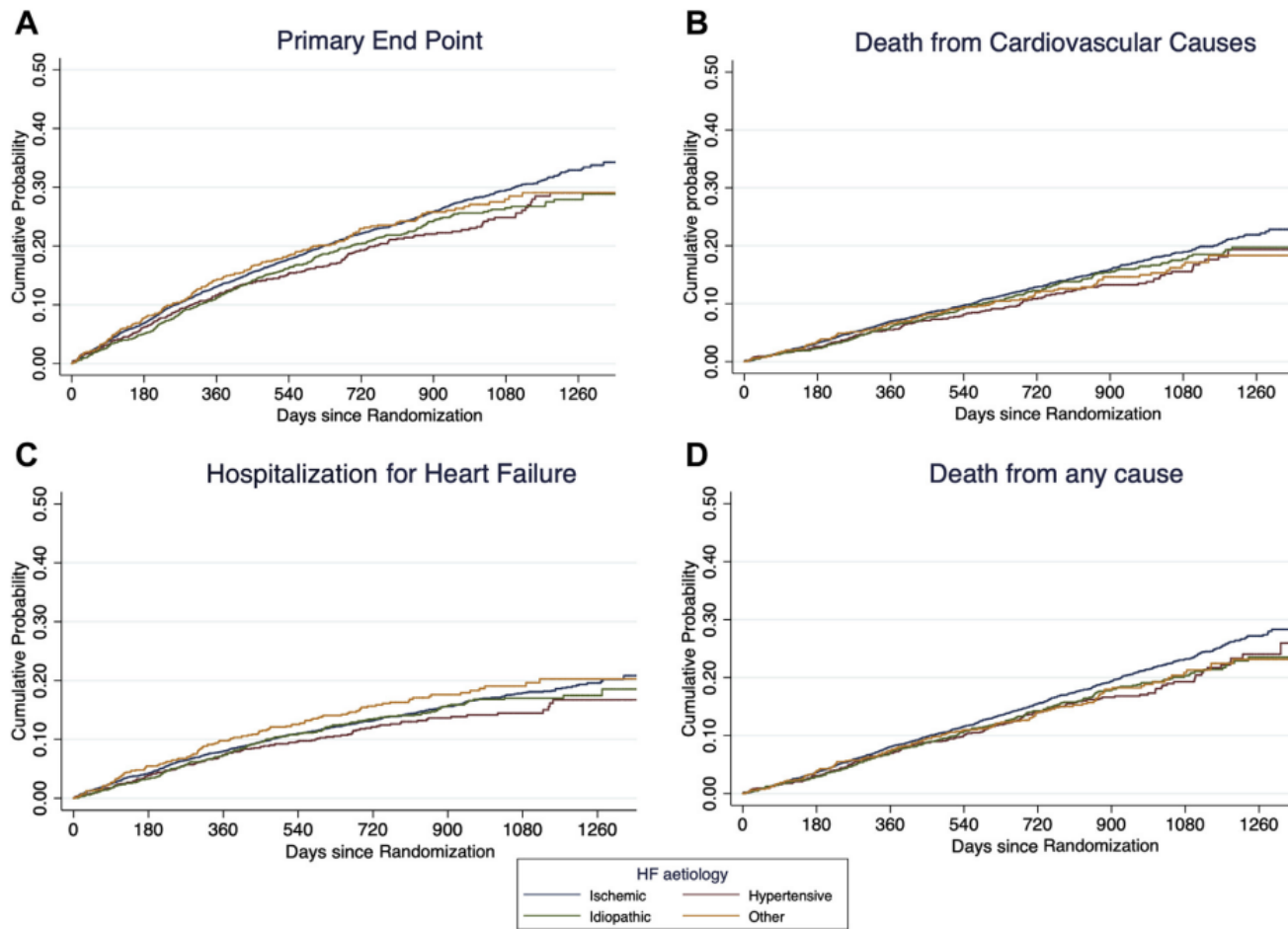
Reverse remodelling by sacubitril/valsartan predicts the prognosis in heart failure with reduced ejection fraction



Influence of Ejection Fraction on Outcomes and Efficacy of Sacubitril/Valsartan (LCZ696) in Heart Failure with Reduced Ejection Fraction



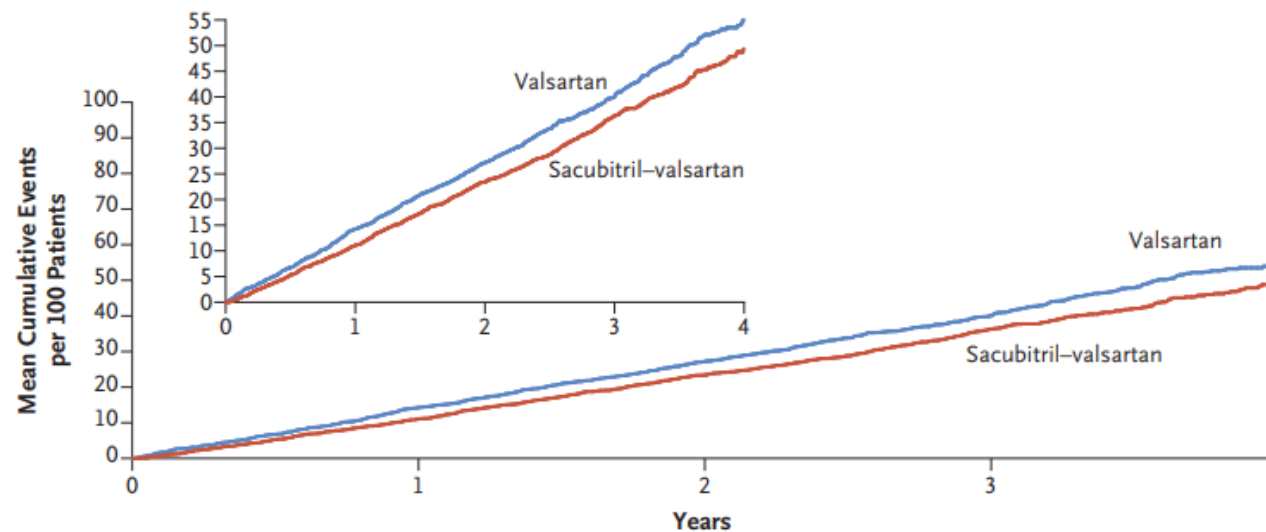
Outcomes and Effect of Treatment According to Etiology in HFrEF An Analysis of PARADIGM-HF



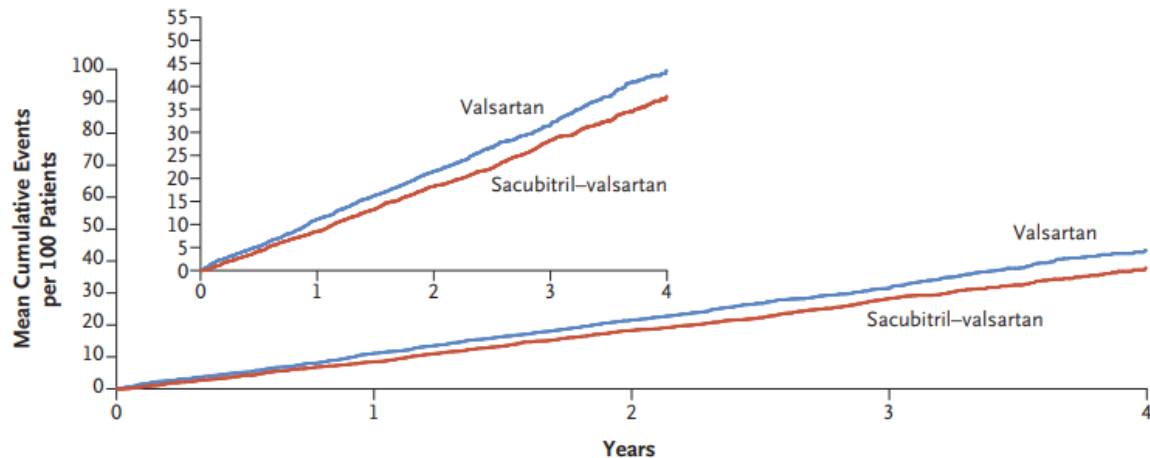
Angiotensin–Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction

PARAGON-HF

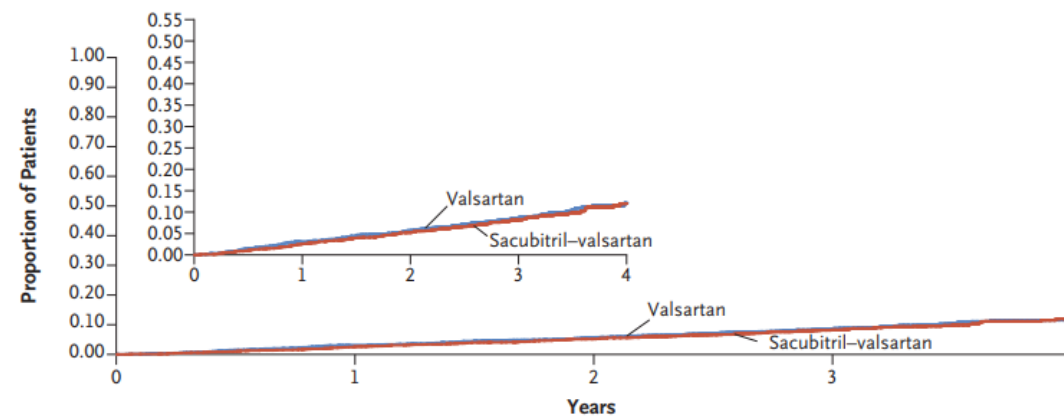
A Total Hospitalizations for Heart Failure and Death from Cardiovascular Causes



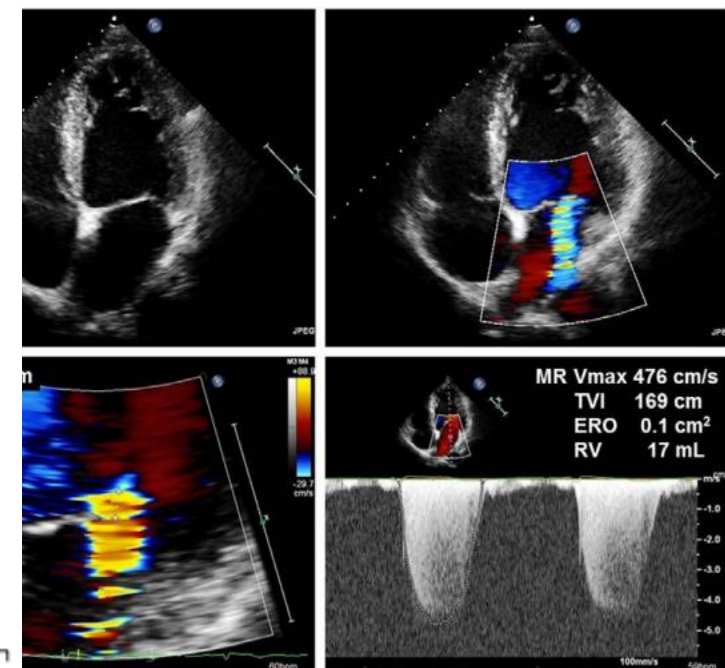
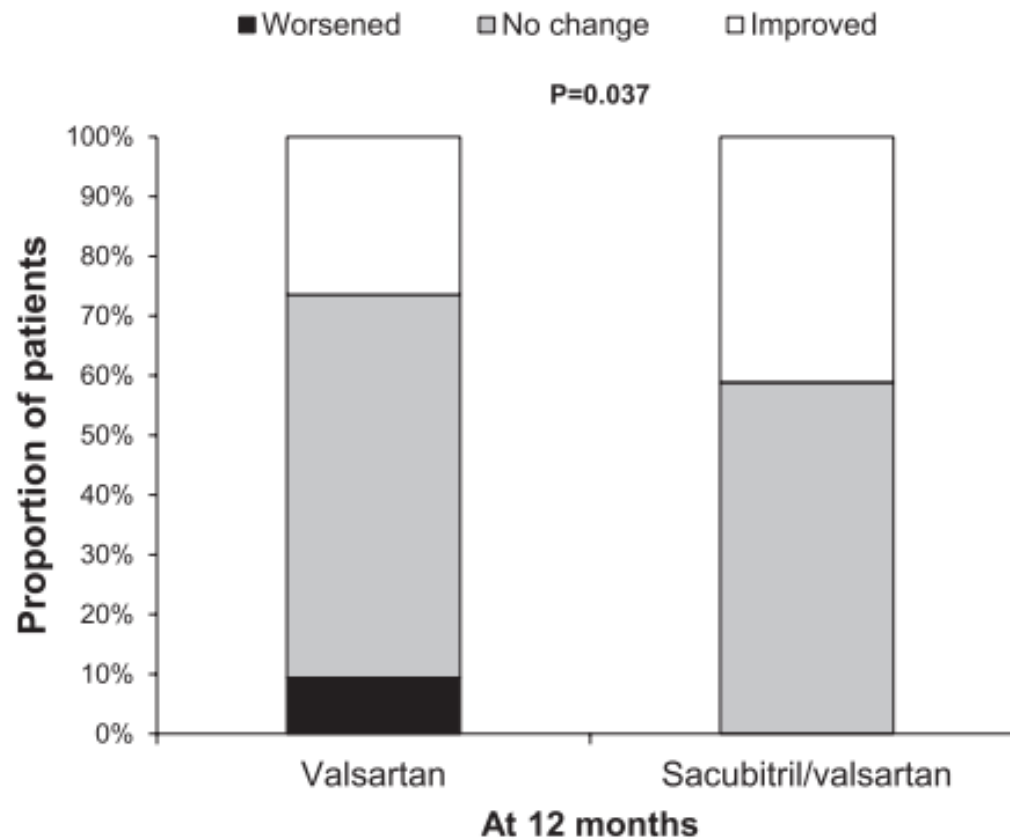
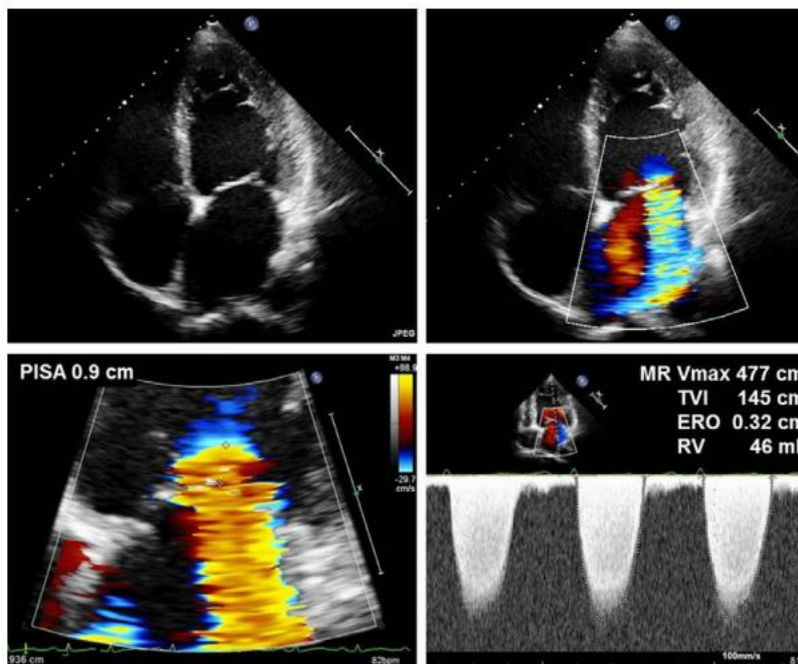
B Total Hospitalizations for Heart Failure



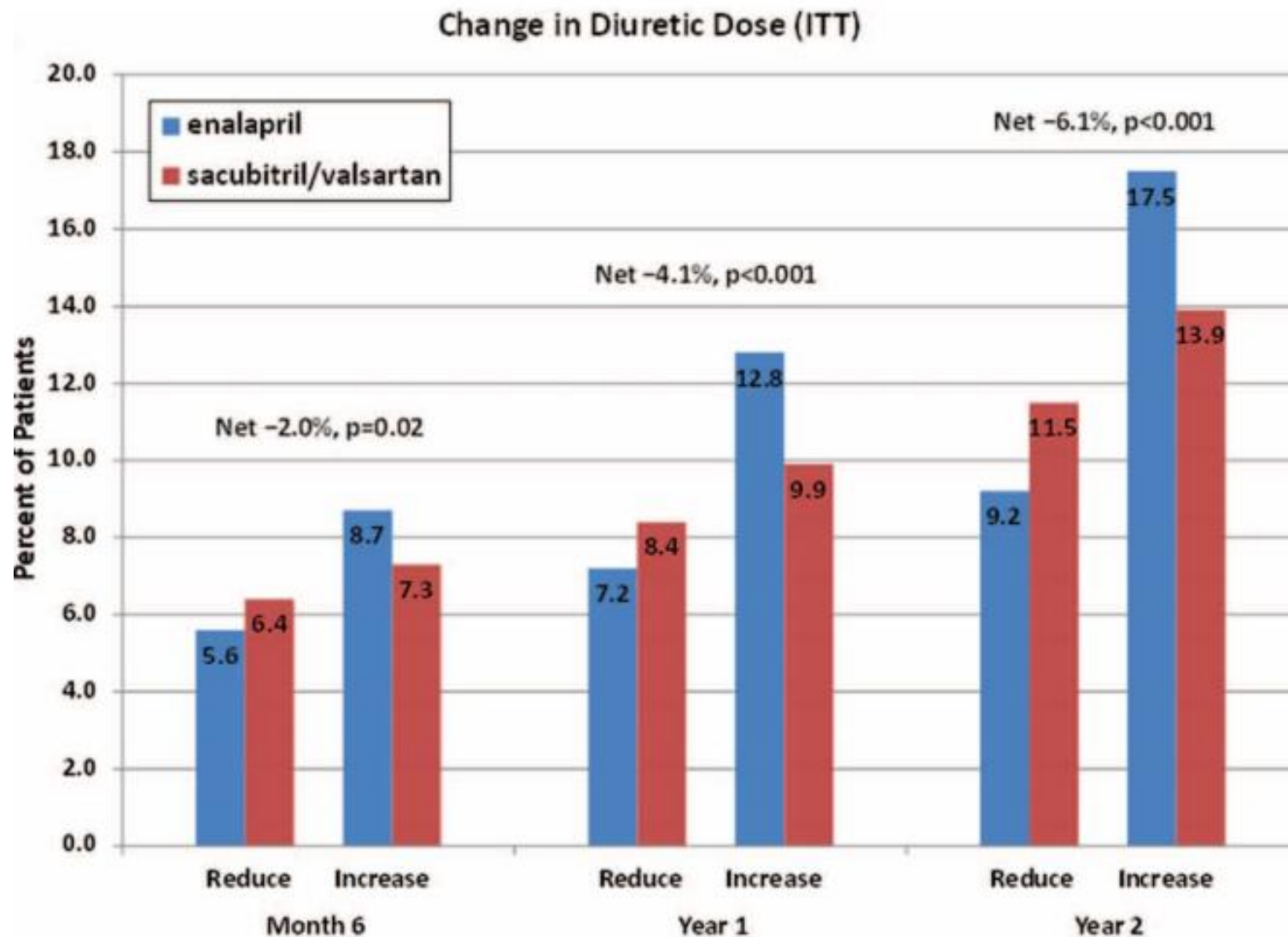
C Death from Cardiovascular Causes



Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation PRIME Study

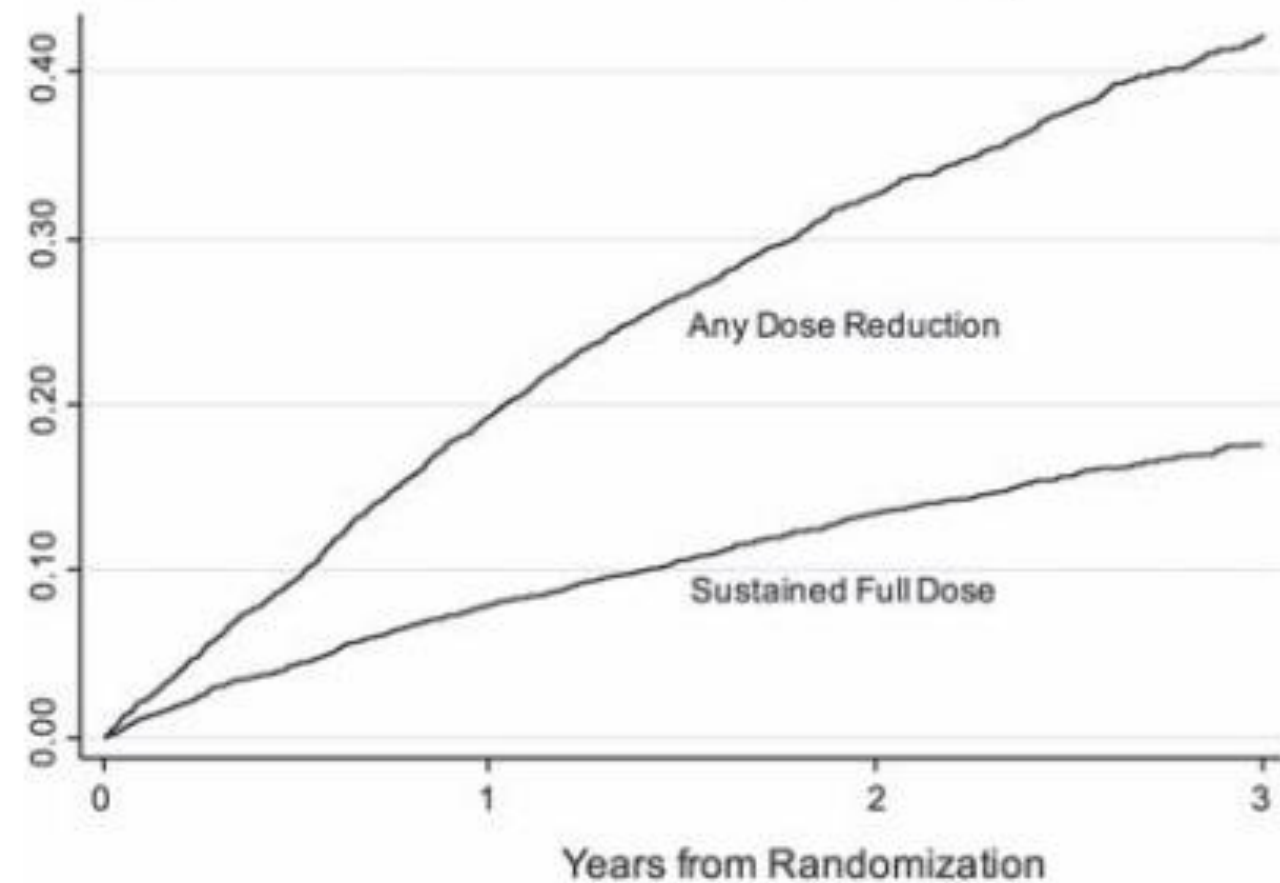


Reduced loop diuretic use in patients taking sacubitril/valsartan compared with enalapril: the PARADIGM-HF trial

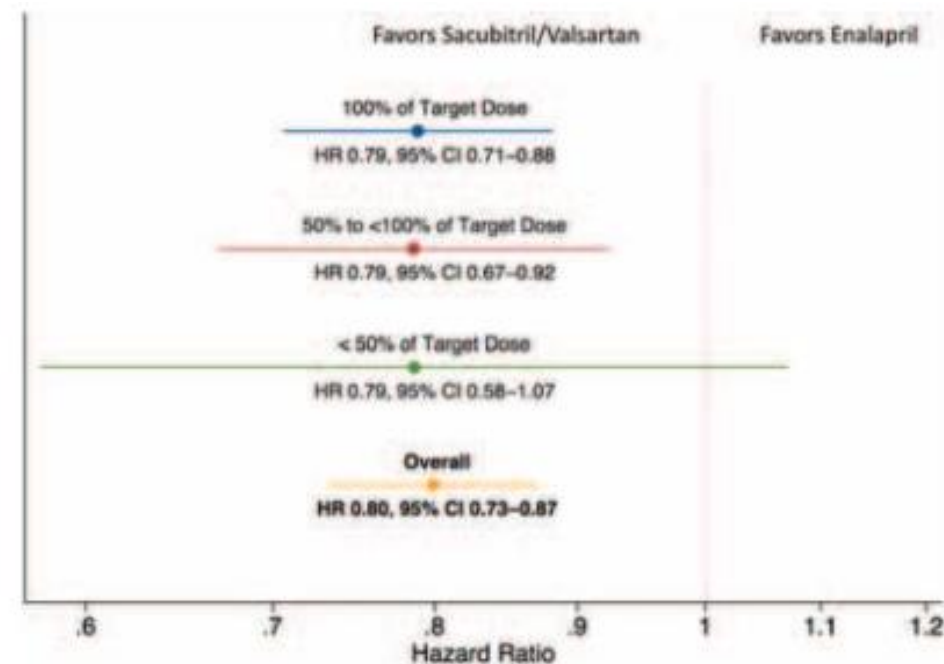
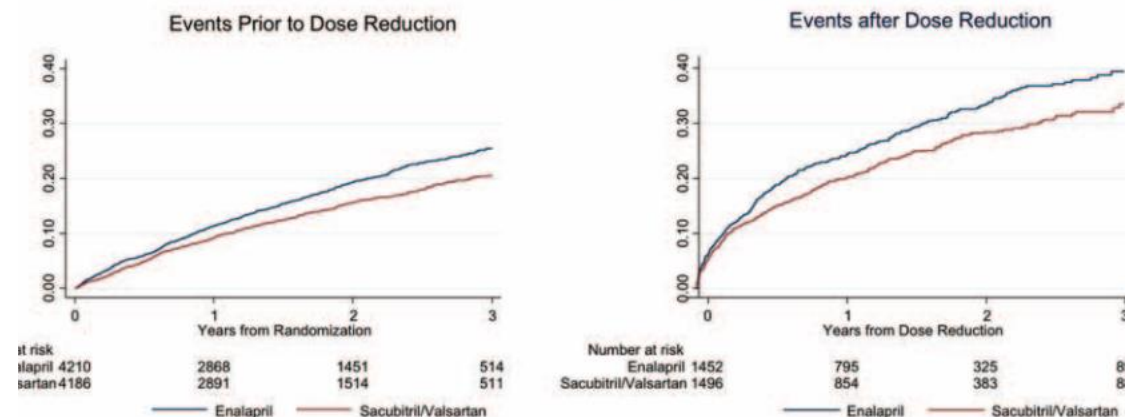


Efficacy of sacubitril/valsartan vs. enalapril at lower than target doses in heart failure with reduced ejection fraction: the PARADIGM-HF trial

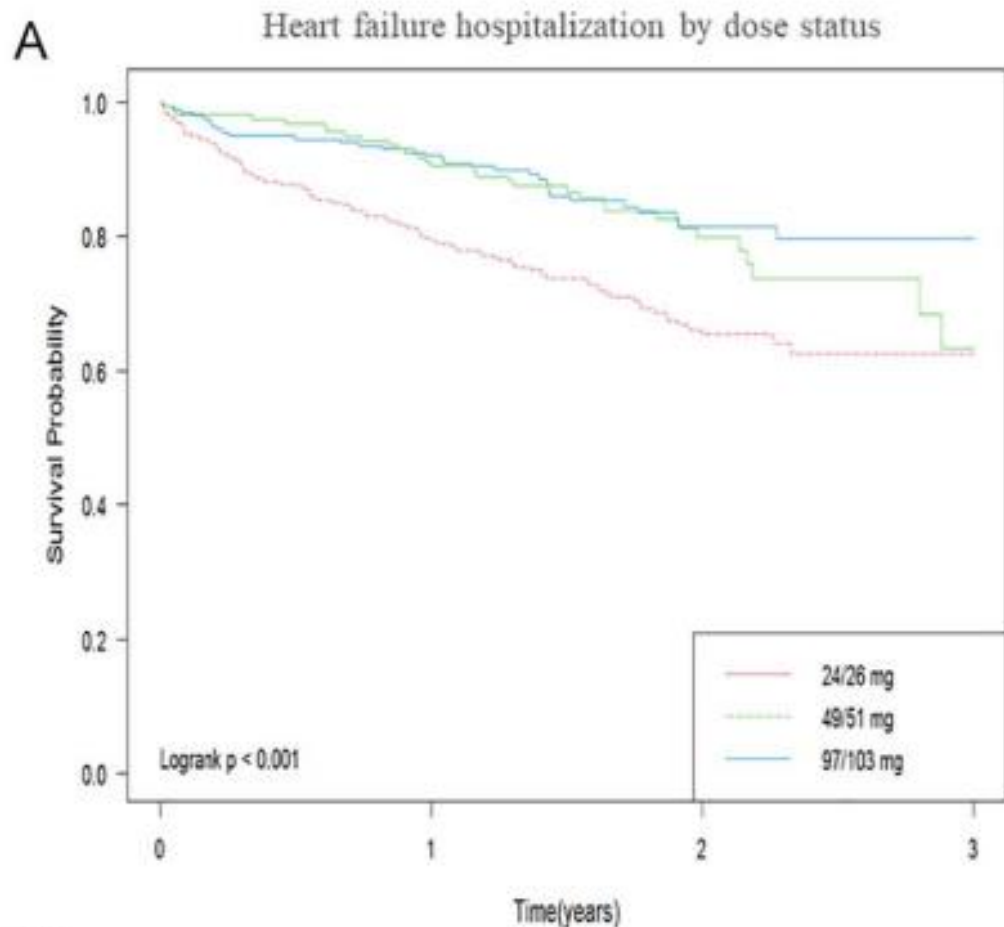
Cardiovascular Death or Heart Failure Hospitalization



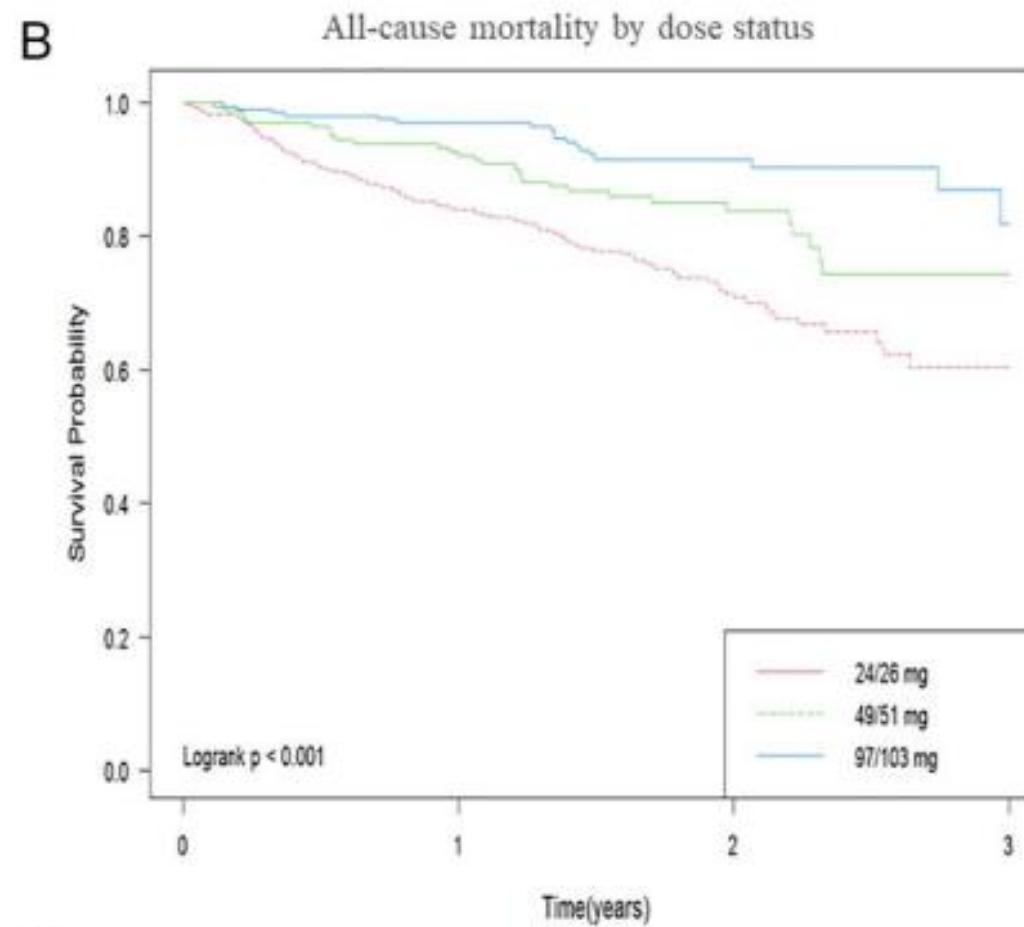
Cardiovascular Death or Heart Failure Hospitalization by Dose Reduction Status



Evaluating Sacubitril/Valsartan Dose Dependence on Clinical Outcomes in Patients With Heart Failure With Reduced Ejection Fraction



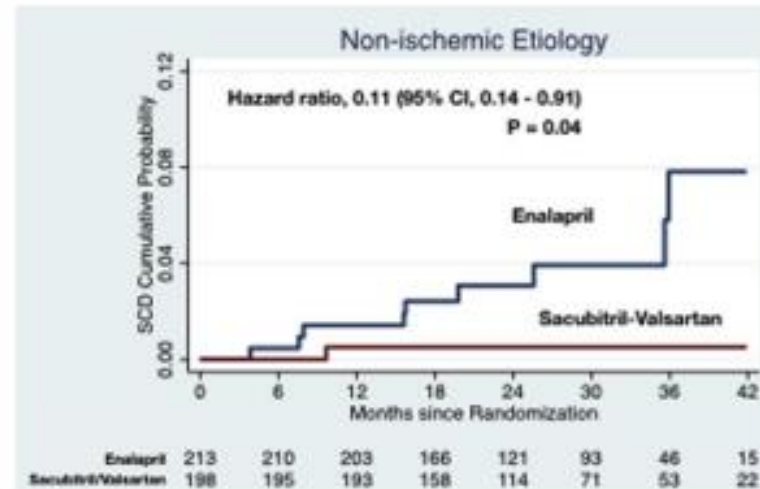
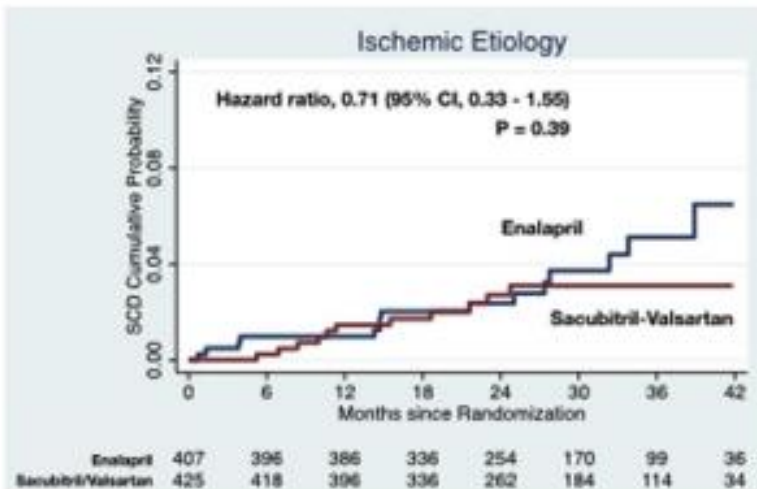
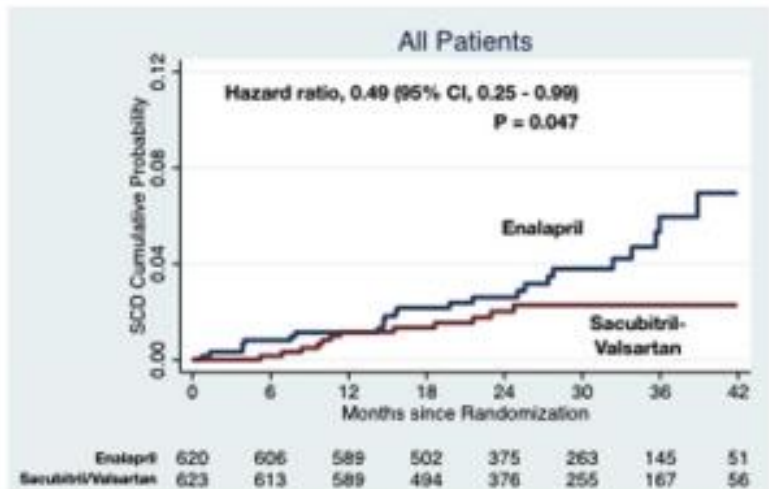
No. at risk	0	1	2	3
24/26 mg	349	244	85	14
49/51 mg	164	136	53	9
97/103 mg	205	182	66	11



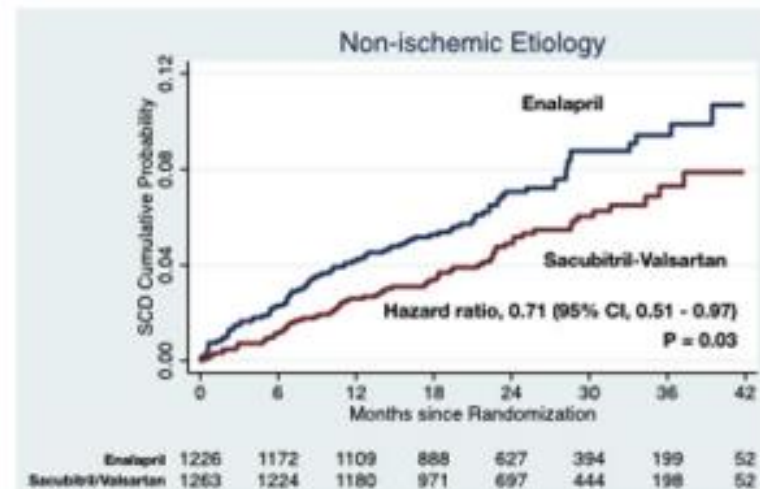
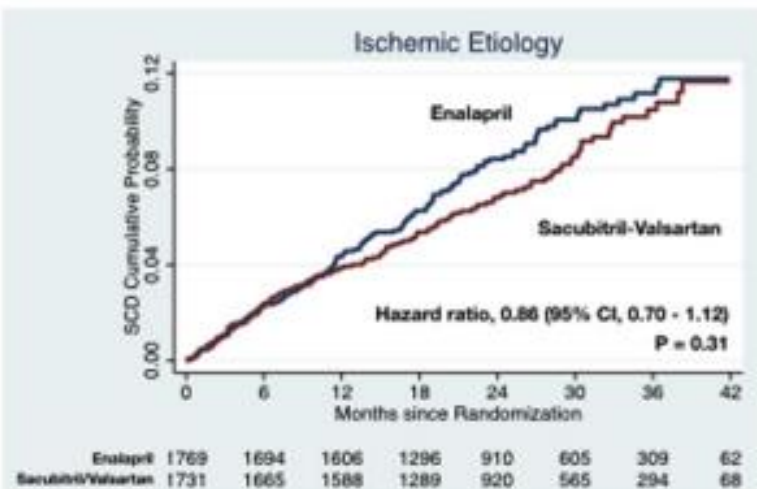
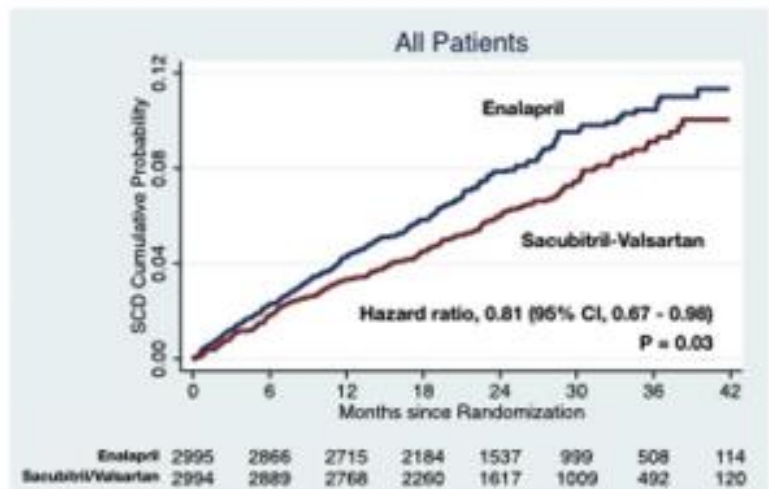
No. at risk	0	1	2	3
24/26 mg	350	293	115	17
49/51 mg	165	151	63	15
97/103 mg	205	199	88	14

Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter-Defibrillator Use and Heart Failure Cause A PARADIGM-HF Analysis

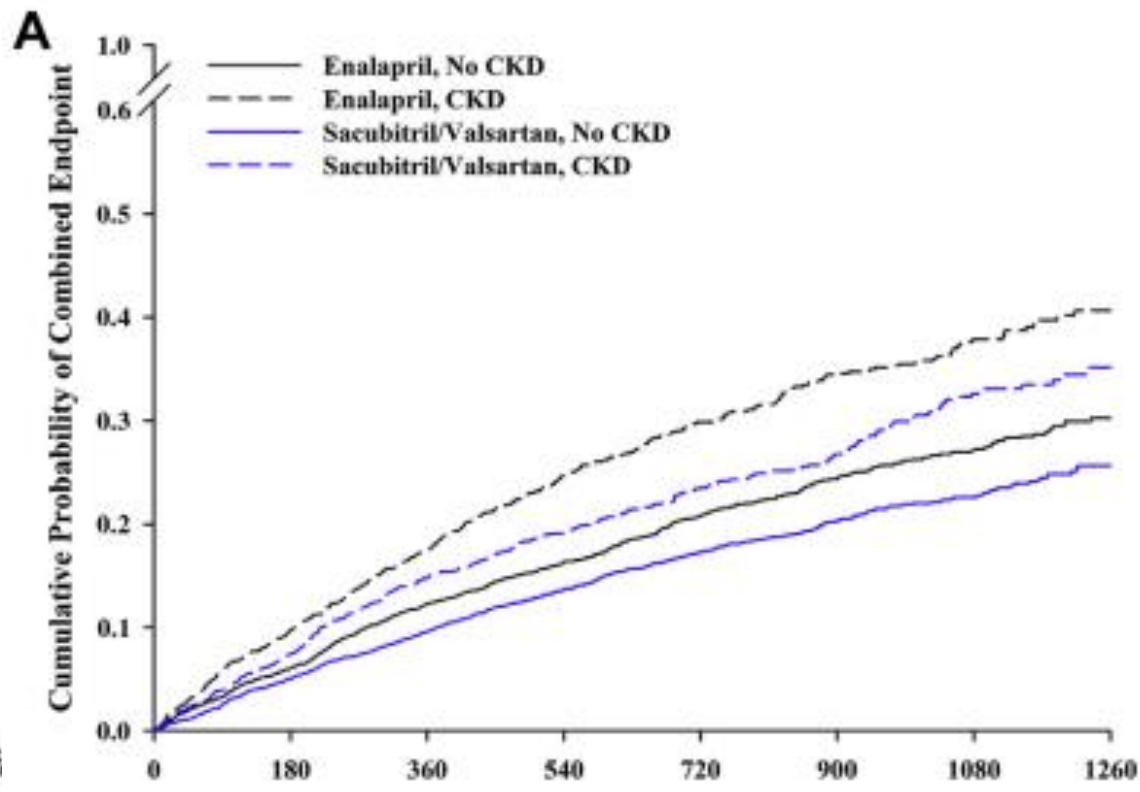
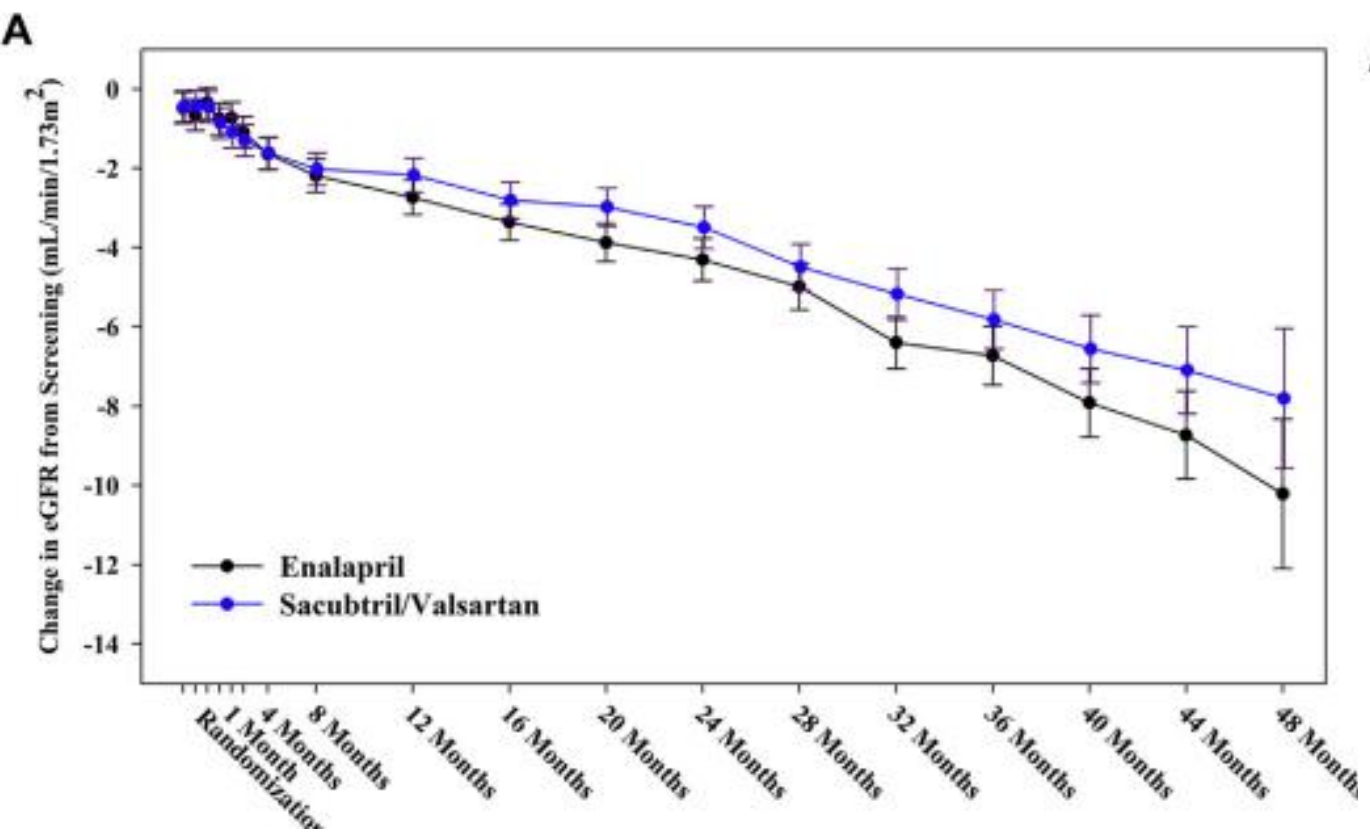
ICD at baseline
N = 1,243



ICD Eligible & no ICD
N = 5,989

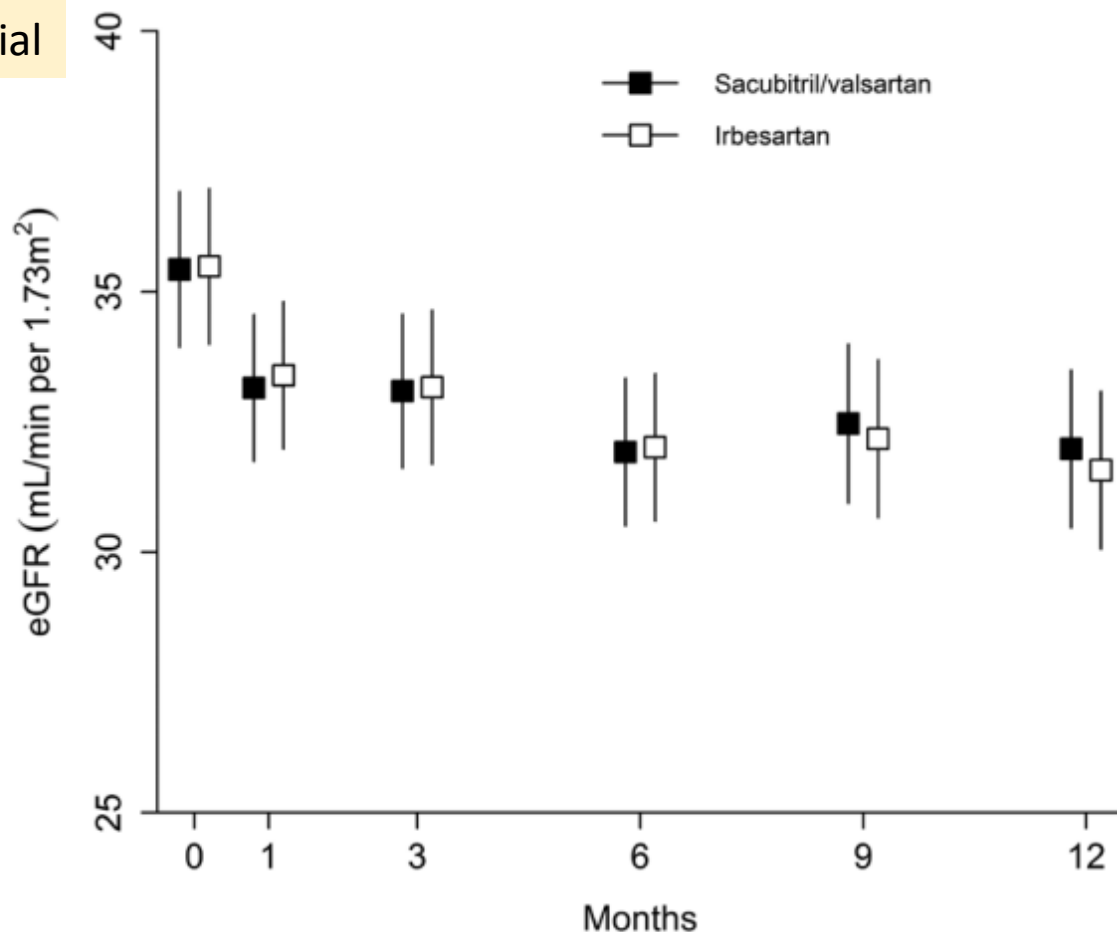


Renal Effects and Associated Outcomes During Angiotensin-Neprilysin Inhibition in Heart Failure



Effects of Sacubitril/Valsartan Versus Irbesartan in Patients With Chronic Kidney Disease A Randomized Double-Blind Trial

UK HARP-III trial



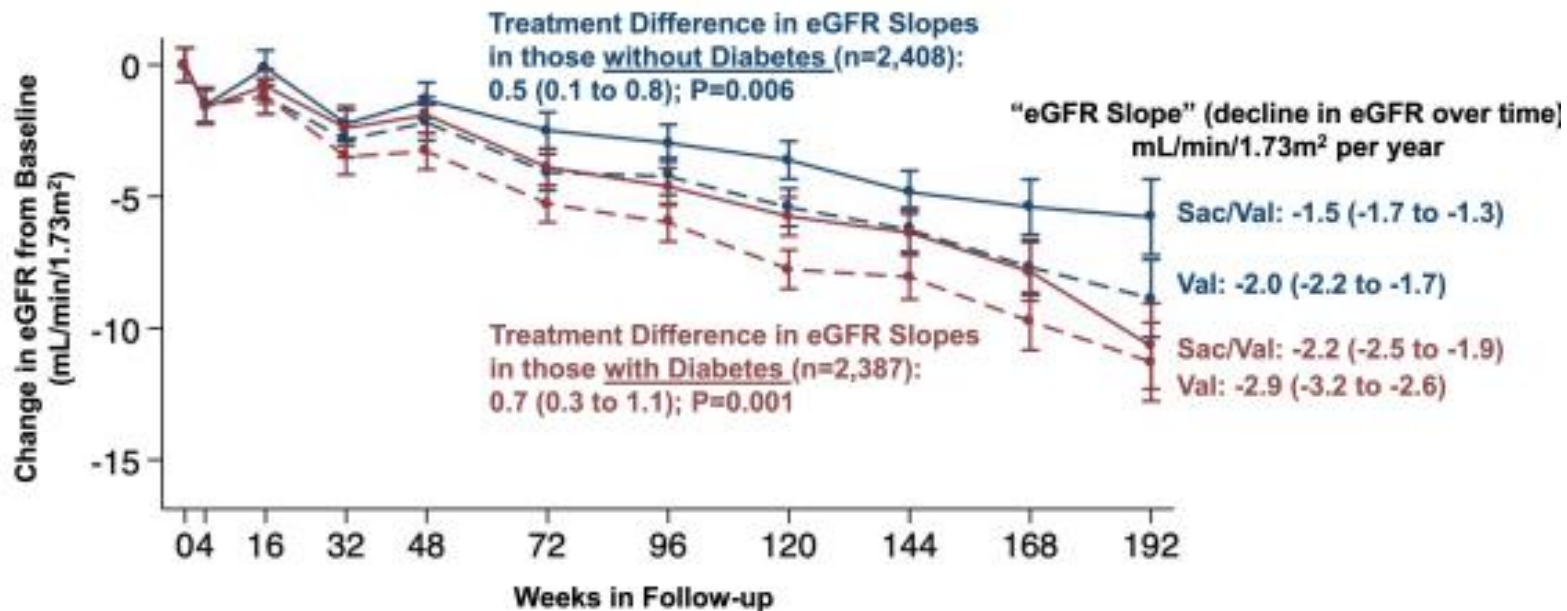
eGFR (mL/min per 1.73m²)

Sacubitril/valsartan	35.4	33.1	33.1	31.9	32.5	32.0
Irbesartan	35.5	33.4	33.2	32.0	32.2	31.6

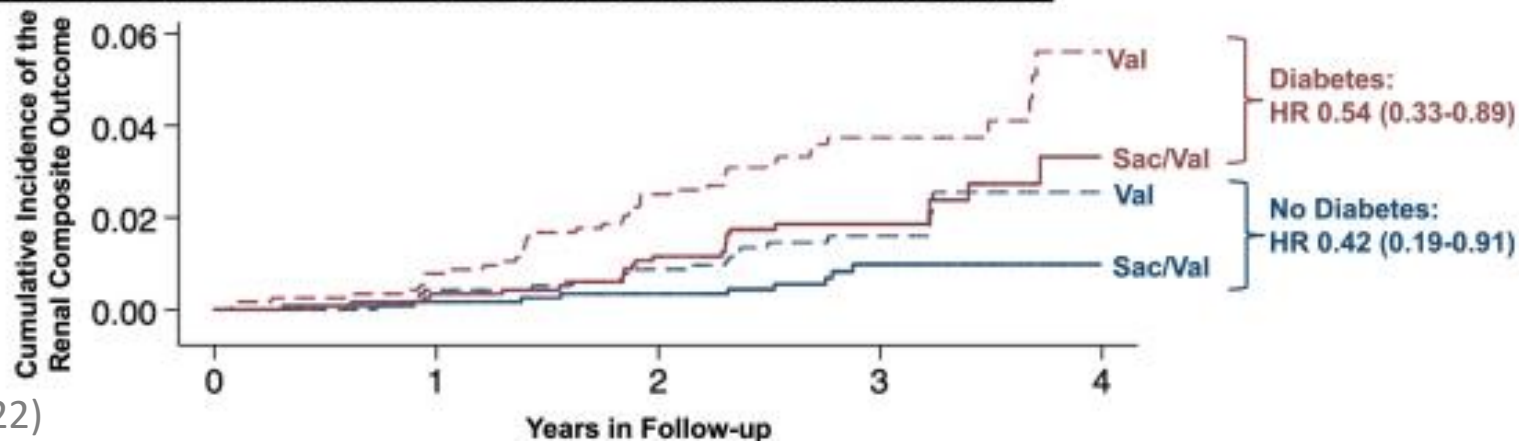
Outcome	Sacubitril/ Valsartan (n=207)	Irbesartan (n=207)	P Value
Potassium, mmol/L			
≥5.5 to <6.0	44 (21%)	38 (18%)	
≥6.0 to <6.5	20 (10%)	7 (3%)	
≥6.5	2 (1%)	5 (2%)	
Total: Any potassium ≥5.5 mmol/L	66 (32%)	50 (24%)	0.10
Estimated glomerular filtration rate			
≥25% reduction in CKD-EPI eGFR*	71 (34%)	67 (32%)	0.75

Effects of sacubitril/valsartan versus valsartan on renal function in patients with and without diabetes and heart failure with preserved ejection fraction: insights from PARAGON-HF

Effect of Sacubitril/Valsartan vs. Valsartan on eGFR Slope

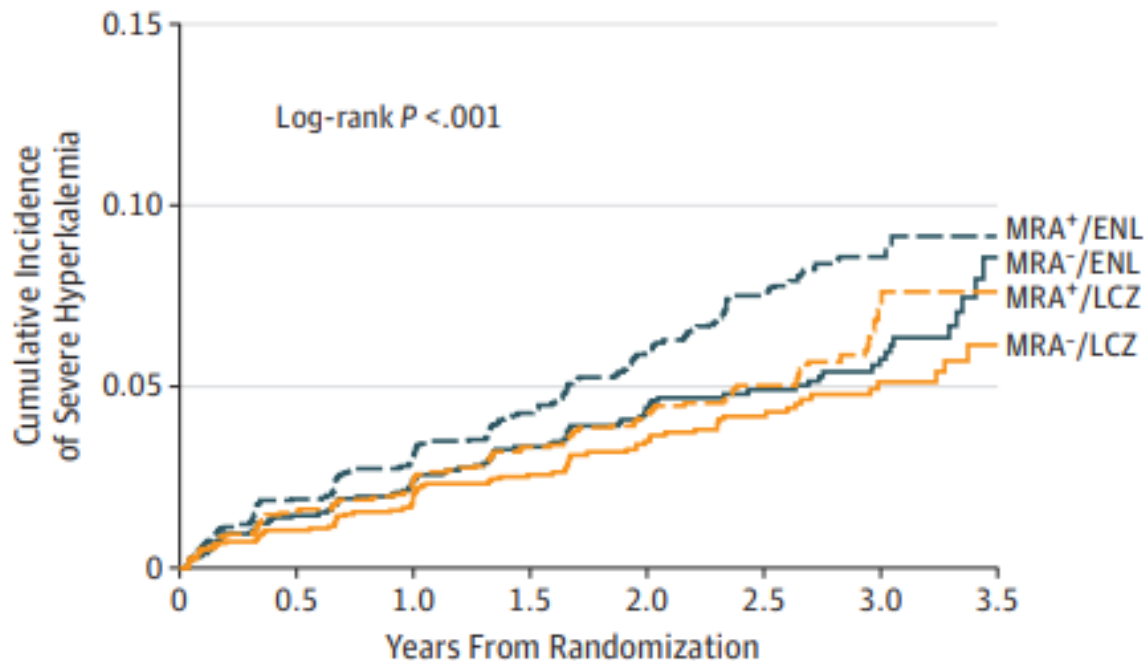


Effect of Sacubitril/Valsartan vs. Valsartan on Renal Composite Outcome

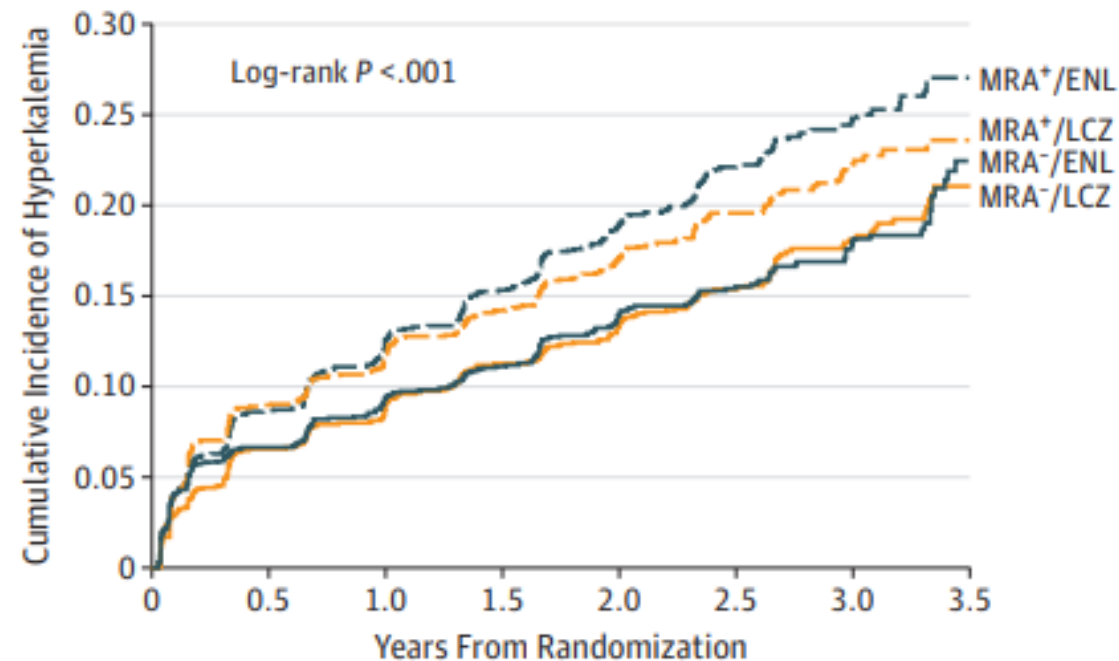


Reduced Risk of Hyperkalemia During Treatment of Heart Failure With Mineralocorticoid Receptor Antagonists by Use of Sacubitril/Valsartan Compared With Enalapril A Secondary Analysis of the PARADIGM-HF Trial

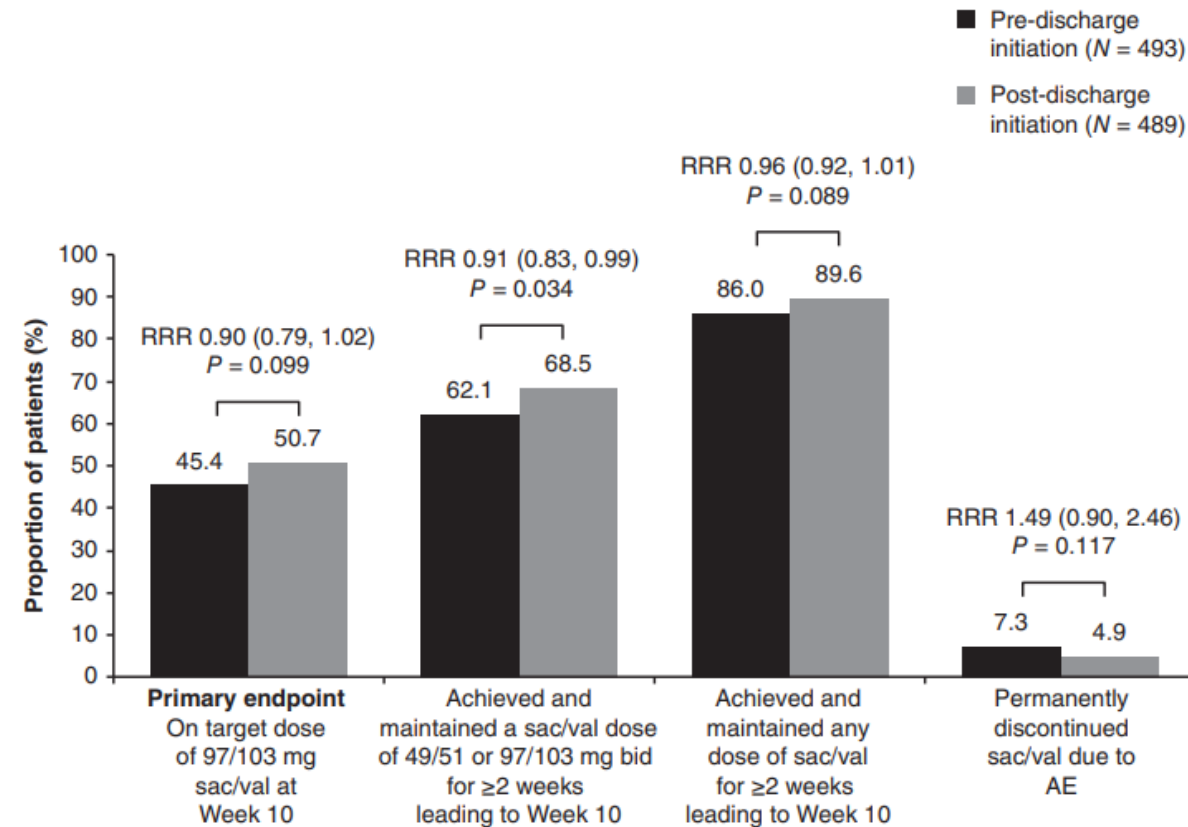
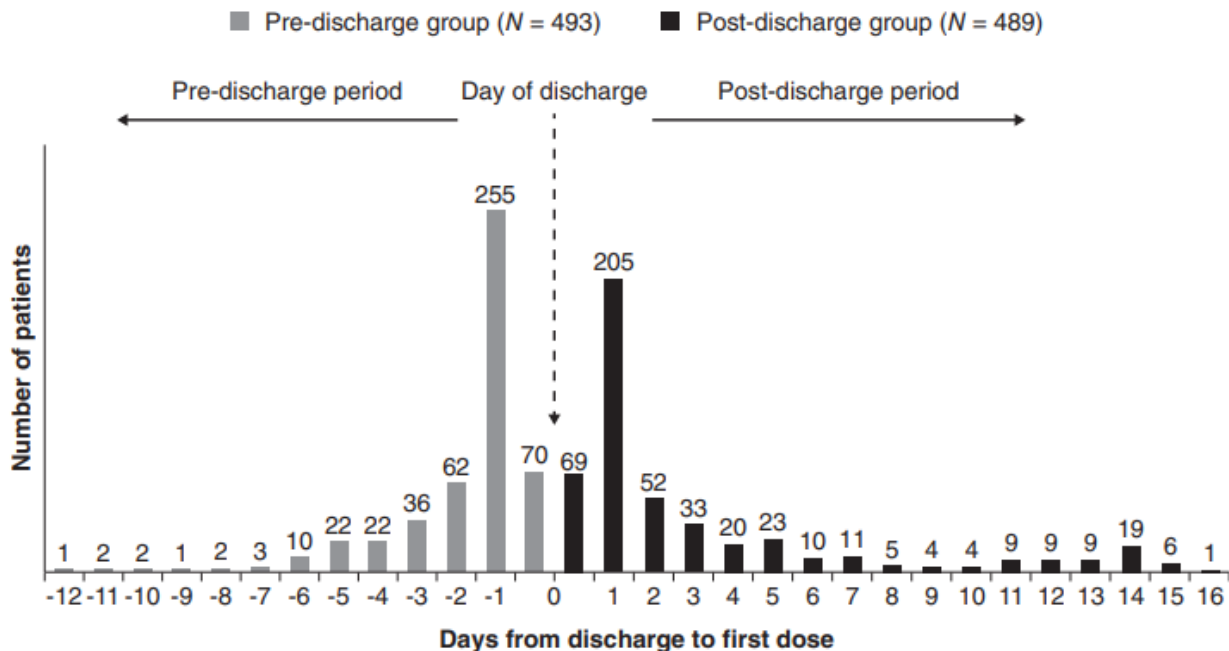
A Severe hyperkalemia (potassium level >6.0 mEq/L)



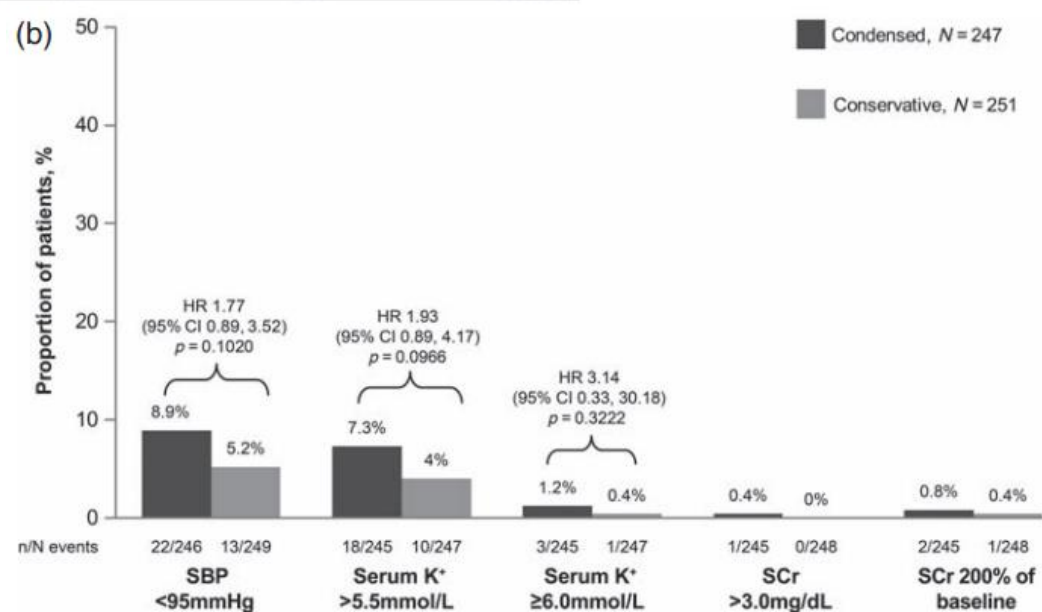
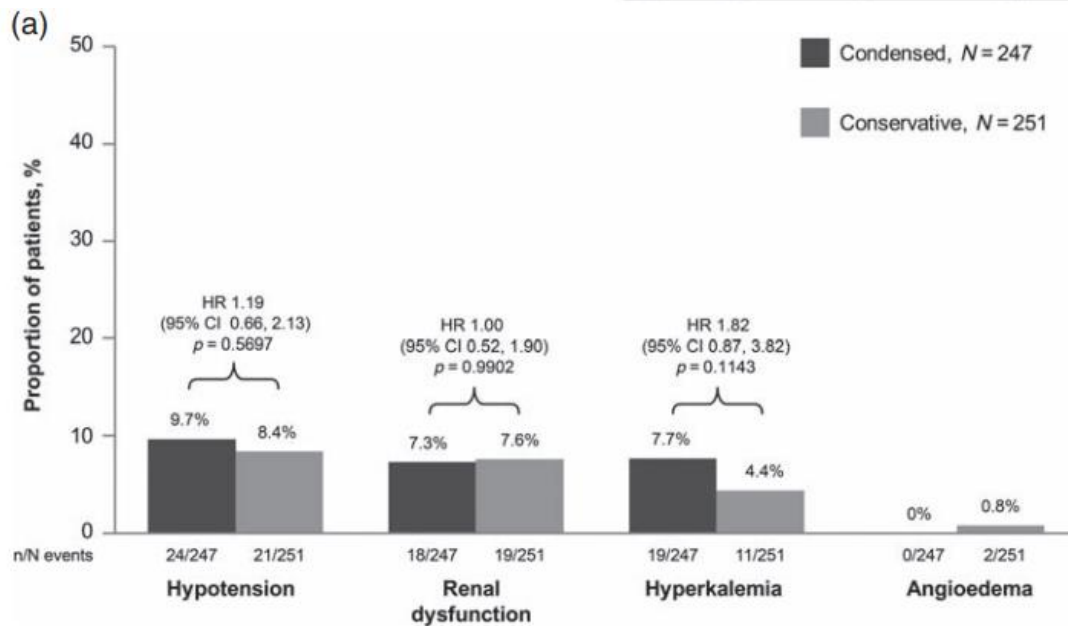
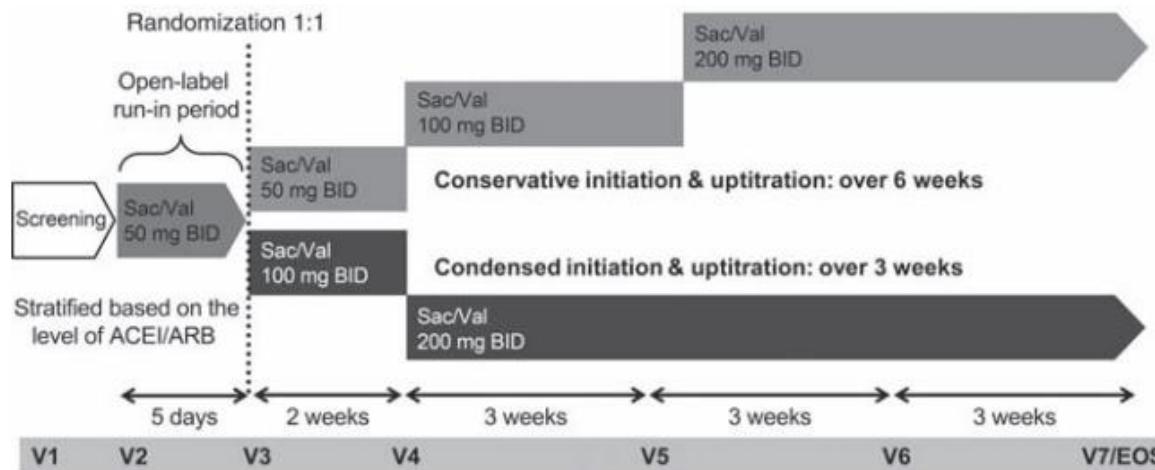
B Hyperkalemia (potassium level >5.5 mEq/L)



Initiation of sacubitril/valsartan in haemodynamically stabilised heart failure patients in hospital or early after discharge: primary results of the randomised TRANSITION study



Initiating sacubitril/valsartan (LCZ696) in heart failure: results of TITRATION, a double-blind, randomized comparison of two uptitration regimens



Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

PIONEER-HF

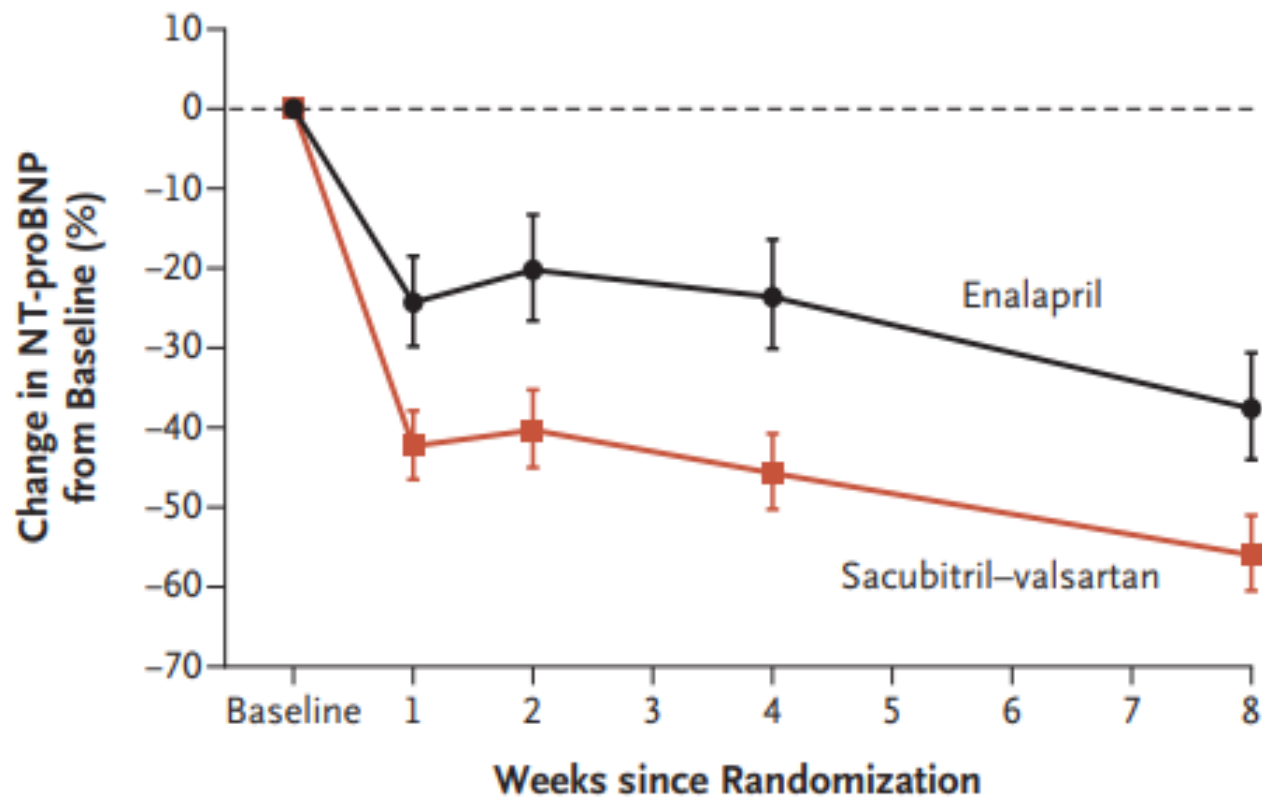


Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			Relative risk (95% CI)
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			Ratio of change (95% CI)
Change in high-sensitivity troponin T concentration	-36.6 (-40.8 to -32.0)	-25.2 (-30.2 to -19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	-28.7 (-35.5 to -21.3)	-33.1 (-39.5 to -25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	-8.3 (-3.6 to -12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

Sacubitril/valsartan versus ramipril in patients with ST-segment Elevation Myocardial Infarction and cardiogenic SHOCK (SAVE-SHOCK): a pilot randomized controlled trial

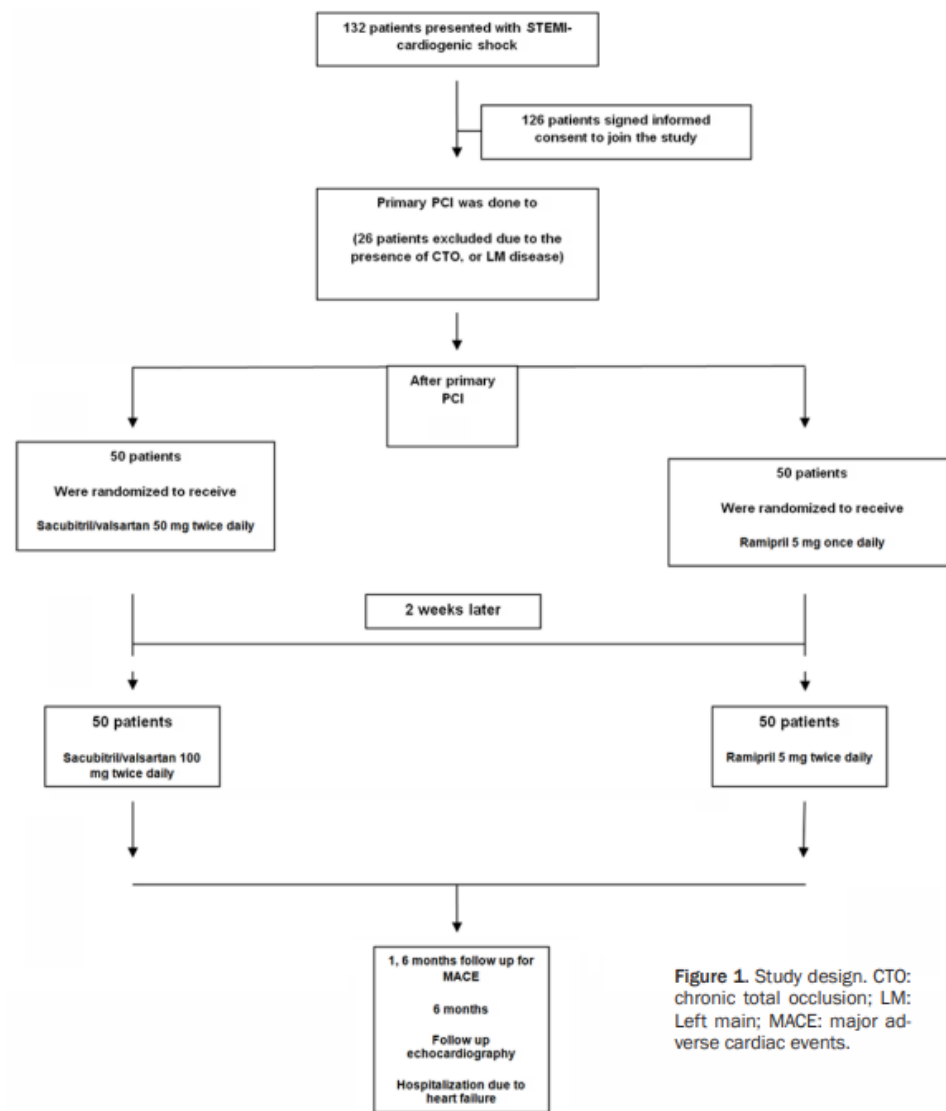


Figure 1. Study design. CTO: chronic total occlusion; LM: Left main; MACE: major adverse cardiac events.

Table 4. Clinical efficacy outcomes

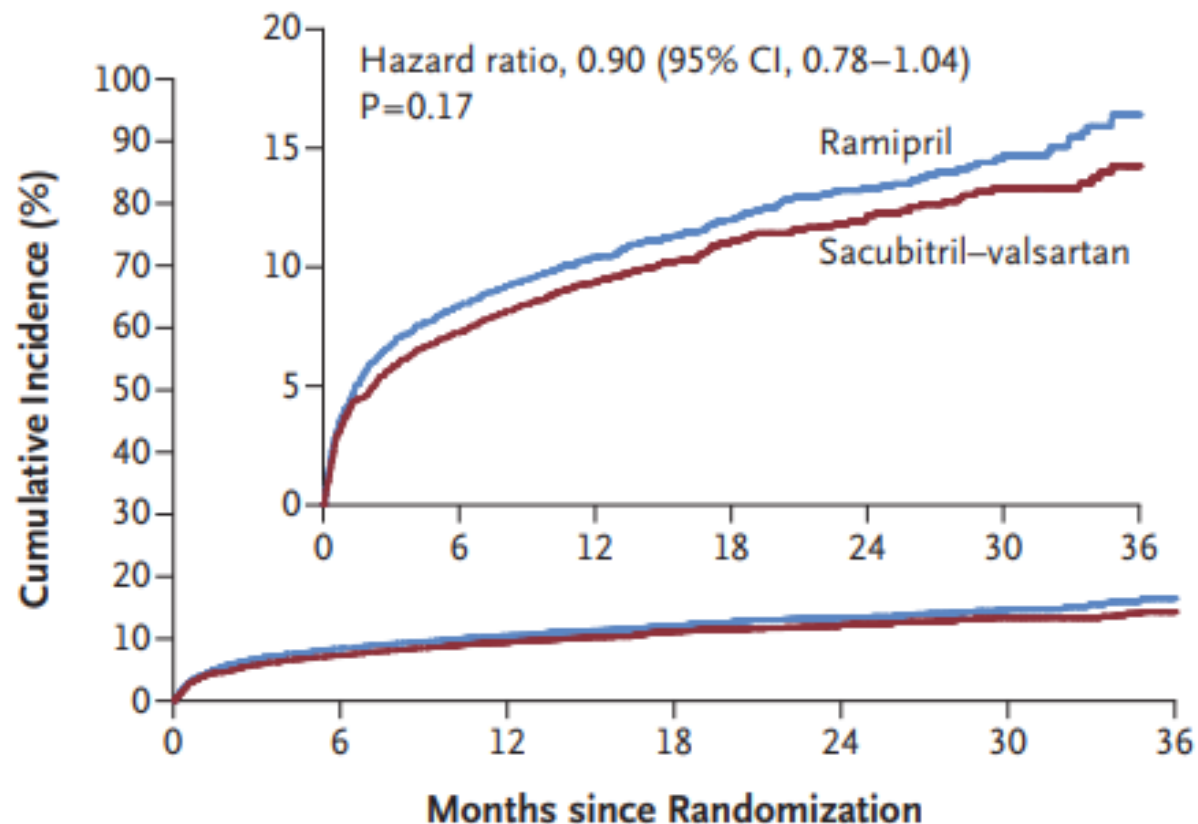
	Sacubitril/ valsartan (N=50 patients)	Ramipril (N=50 patients)	P-Value
In-hospital			
MACE, %	6 (12%)	5 (10%)	1.000
All-cause death, %	0 (0%)	0 (0%)	
Cardiac death, %	3 (6%)	2 (4%)	1.000
Recurrent myocardial infarction, %	0 (0%)	0 (0%)	
Stroke, %	2 (4%)	1 (2%)	1.000
Bleeding, %	1 (2%)	2 (4%)	1.000
CIN	2 (4%)	3 (6%)	1.000
Renal replacement therapy	0 (0%)	1 (2%)	1.000
30 days follow up			
MACE, %	1 (2%)	4 (8%)	0.362
HF hospitalization, %	0 (0%)	2 (4%)	0.495
All-cause death, %	0 (0%)	0 (0%)	
Cardiac death, %	0 (0%)	0 (0%)	
Myocardial infarction, %	1 (2%)	2 (4%)	1.000
Stroke, %	0 (0%)	0 (0%)	
6 months follow up			
MACE, %	12 (24%)	21 (42%)	0.088
HF hospitalization, %	9 (18%)	19 (38%)	0.044
All-cause death, %	1 (2%)	0 (0%)	0.317
Cardiac death, %	1 (2%)	0 (0%)	1.000
Myocardial infarction, %	1 (2%)	2 (4%)	1.000
Stroke, %	0.0	1 (2%)	1.000

Angiotensin Receptor–Neprilysin Inhibition in Acute Myocardial Infarction

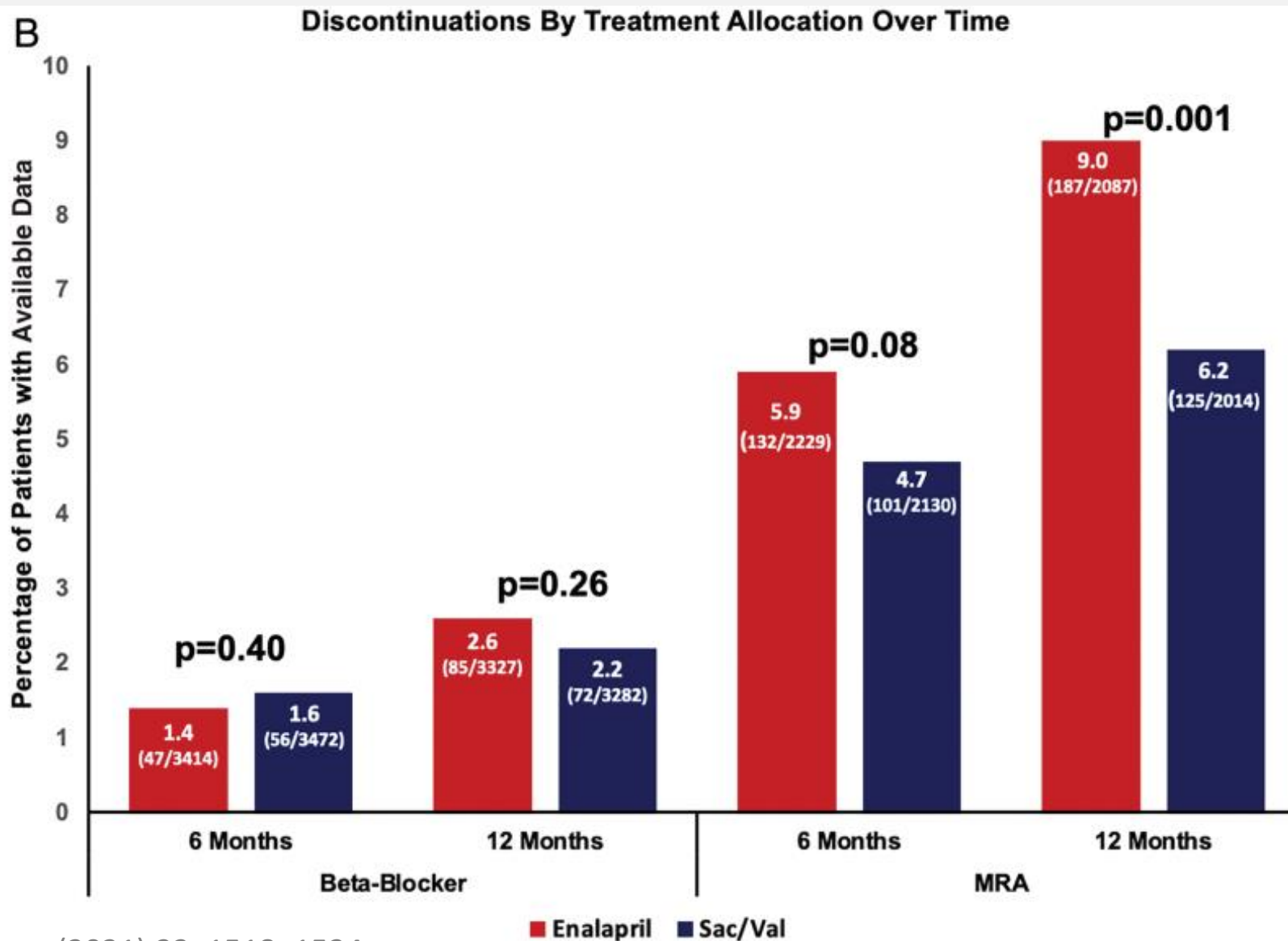
PARADISE-MI

Table 1. (Continued.)

Characteristic	Sacubitril–Valsartan (N = 2830)	Ramipril (N = 2831)
Location of myocardial infarction — no. (%)		
Anterior	1919 (67.8)	1934 (68.3)
Inferior	535 (18.9)	518 (18.3)
Other	376 (13.3)	379 (13.4)
Killip class ≥II — no. (%)	1595 (56.4)	1606 (56.7)
Time to randomization — days	4.3±1.8	4.3±1.7
Medical treatment at randomization — no. (%)		
Dual antiplatelet therapy	2608 (92.2)	2614 (92.3)
Beta-blocker	2414 (85.3)	2413 (85.2)
Mineralocorticoid-receptor antagonist	1155 (40.8)	1183 (41.8)
Diuretic	1271 (44.9)	1250 (44.2)
Statin	2674 (94.5)	2696 (95.2)
ACE inhibitor or ARB	2216 (78.3)	2220 (78.4)

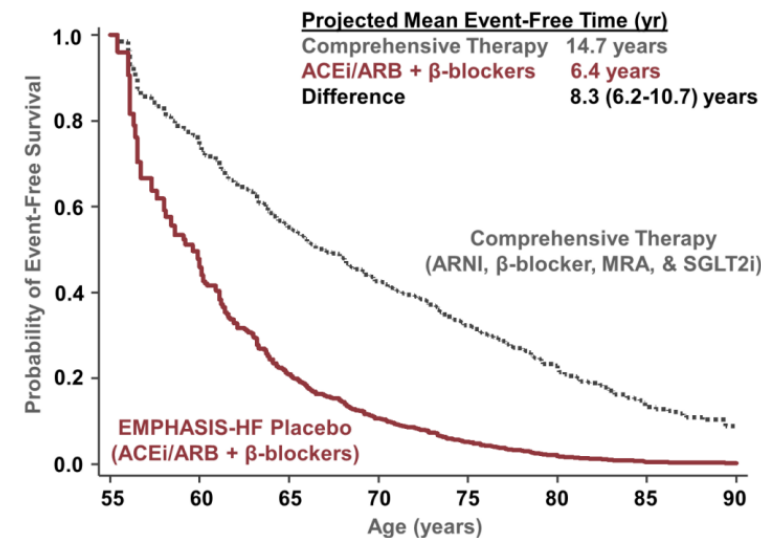


Effect of sacubitril/valsartan vs. enalapril on changes in HF therapies over time: the PARADIGM-HF trial

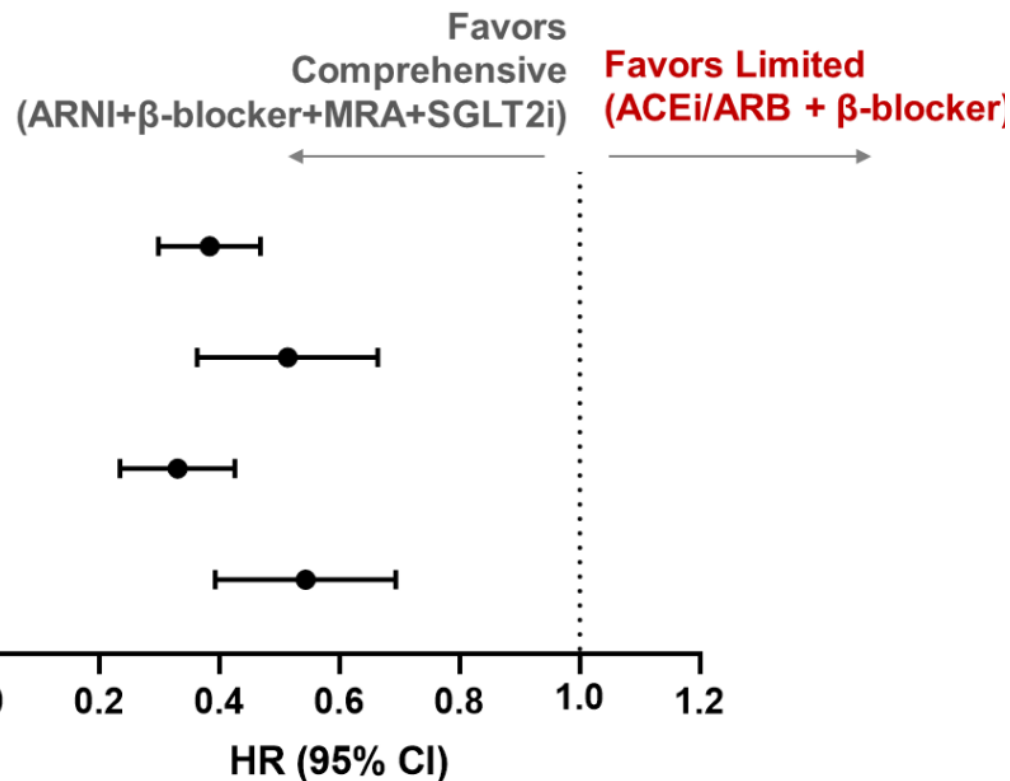
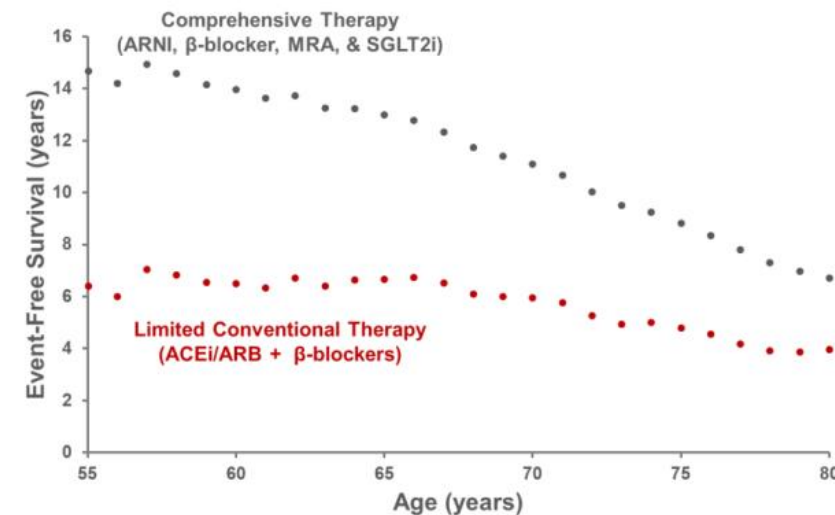


Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

A. Projected Event-Free Survival after 55 Years



A. Estimated Survival Free from Primary Endpoint



What the near Future Holds for Sacubitril/Valsartan: A Summary of Major Ongoing Studies



Acute Coronary Syndrome:

1. The Effects of Sacubitril-Valsartan vs. Enalapril on Left Ventricular Remodeling in ST-elevation Myocardial Infarction.
2. The Role of Sacubitril/Valsartan in Post-acute Myocardial Infarction.
3. Sacubitril/Valsartan vs. Valsartan for Hypertensive Patients With Acute Myocardial Infarction.
4. Angiotensin-Nephrilysin Inhibition in Diastolic Dysfunction.
5. Early Treatment of ARNI on Myocardial Remodeling and Progress.



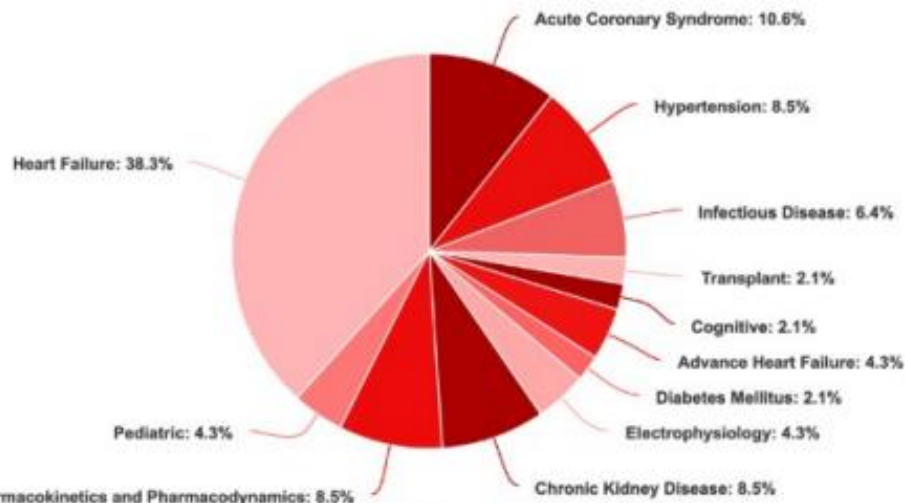
Hypertension:

1. Natriuretic Peptide-Renin-Angiotensin-Aldosterone System Rhythm Axis and Nocturnal Blood Pressure.
2. Sacubitril/Valsartan in Resistant HTN.
3. Effect of LCZ696 on Urinary Microalbumin and Pulse Wave Velocity in Perimenopausal Patients With HTN.
4. Sacubitril/Valsartan vs. Amlodipine in Hypertension and Left Ventricular Hypertrophy.



Infectious Disease:

1. Effects of Sacubitril/Valsartan on Subclinical Heart Failure in HIV (The ENCHANTMENT HIV Study).
2. Angiotensin Receptor-Nephrilysin Inhibition in Chagas Cardiomyopathy With Reduced Ejection Fraction.
3. Efficacy and Safety of Sacubitril/Valsartan Compared With Enalapril on Morbidity, Mortality, and NT-proBNP Change in Patients With CCC.



Pharmacokinetics and Pharmacodynamics: 8.5%



Transplant:

1. Effect of Angiotensin Converting Enzyme and Sacubitril Valsartan in Patients After Bone Marrow Transplantation.



Cognitive:

1. Efficacy and Safety of LCZ696 Compared to Valsartan on Cognitive Function in Patients With Chronic Heart Failure and Preserved Ejection Fraction (PERSPECTIVE).



Advance Heart Failure:

1. Sacubitril/Valsartan in Left Ventricular Assist Device Recipients.
2. Safety and Efficacy of ARNI After LVAD Implant (SEAL-IT) Study.



Diabetes Mellitus:

1. NAUTICAL: Effect of Natriuretic Peptide Augmentation on Cardiometabolic Health in Black Individuals.



Electrophysiology:

1. Effective Study of ARNI on Ventricular Arrhythmia in HFpEF
2. Effect of ARNI in Patients With Persistent AF and Enlarged Left Atrium After Catheter Ablation.



Pharmacokinetics and Pharmacodynamics:

1. Pharmacodynamic Effects of Sacubitril/Valsartan on Natriuretic Peptides, Angiotensin and Nephrilysin.
2. Mechanisms Underlying Hypotensive Response to ARB/NEP Inhibition - Aim 1.
3. Mechanisms Underlying Hypotensive Response to ARB/NEP Inhibition - Aim 2.
4. Mechanisms Underlying Hypotensive Response to ARB/NEP Inhibition - Aim 3.



Pediatric:

1. CLCZ696B2319 E1 OL Extension Study to Evaluate Long-term Safety of Sacubitril/Valsartan in Pediatric Patients With HF.
2. Study to Evaluate Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of LCZ696 Followed by a 52-week Study of LCZ696 Compared With Enalapril in Pediatric Patients With HF.



Chronic Kidney Disease:

1. The Effect of Sacubitril/Valsartan on Cardiovascular Events in Dialysis Patients and Efficacy Prediction of Baseline LVEF Value.
2. Observation on the Effect of Sacubitril/Valsartan in Advanced CKD Patients With HF.
3. Efficacy and Safety of Sacubitril/Valsartan in Maintenance Hemodialysis Patients With HF.
4. Roxadustat Combined With Sacubitril Valsartan Sodium Tablets in the Treatment of Cardiorenal Anemia Syndrome.

Heart Failure:

1. The Bio-Clinical Effects of the (Sacubitril-Valsartan) Combination on Patients With Chronic Heart Failure.
2. Changes in NT-proBNP and Outcomes, Safety, and Tolerability in HFpEF Patients With Acute Decompensated Heart Failure (ADHF) Who Have Been Stabilized During Hospitalization and Initiated In-hospital or Within 30 Days Post-discharge (PARAGLIDE-HF).
3. Influence of Sacubitril/Valsartan on Autonomic Cardiac Nervous System in Heart Failure Patients: an Exploratory Study.
4. The Effects of Sacubitril/Valsartan on Cardiac Oxygen Consumption and Efficiency of Cardiac Work in Heart Failure Patients (TurkuPET).
5. ARNI vs. Placebo in Patients With Congenital systemic Right Ventricle Heart Failure (PARACYS-RV).
6. Comparison of BNP and NT-proBNP in the Management of Patients With Chronic and Acute Heart Failure.
7. Role of ARNI in Ventricular Remodeling in Hypertensive LVH (REVERSE-LVH).
8. OptiVal for Precision Medical Management of Heart Failure (OPTIMED-HF).
9. Efficacy of a Streamlined Heart Failure Optimization Protocol (SHORT).
10. TRANSFORM Heart Failure With Reduced Ejection Fraction (TRANSFORM HFpEF).
11. Community Pharmacy Medication Therapy Management for Heart Failure.
12. Effect of Angiotensin-Nephrilysin Inhibition (ARNI) on Prognosis of Chronic Heart Failure.
13. Natriuretic Response to Expansion and diuretics in Humans With Heart Failure (NATRUM-HF).
14. The Effect of Angiotensin Receptor-Nephrilysin Inhibition on Cardiac Fibrosis in Patients With HFpEF (ARNICFH).
15. LCZ696 in Advanced LV Hypertrophy and HFpEF.
16. Study of Efficacy of Oral Sacubitril/Valsartan in Adult Patients With Non-obstructive Hypertrophic Cardiomyopathy.
17. Personalised Prospective Comparison of ARNI With ARB in Patients With Natriuretic Peptide elevation (PARABLE).
18. Sacubitril/Valsartan vs. Lifestyle in Hypertrophic Cardiomyopathy (SILCOFCM).

En el manejo de la IC con FE reducida, mi prioridad es introducir sacubitril-valsartan porque

- Aporta mayores beneficios que IECA (Enalapril), en “escenario Paradigm”
 - Pronóstico (global)
 - Parámetros funcionales de VI
 - Consistentes en subgrupos
- Es seguro (evaluando eventos renales e hiperK como principales riesgos)
- Se puede introducir en fases precoces – paciente hospitalizado
- Demuestra eficacia asociado a otras líneas terapéuticas de beneficio pronóstico

Gracias por vuestra atención

