Εξελίξεις στη θεραπεία της Καρδιακής Ανεπάρκειας: Θεραπευτική μετάβαση του ασθενούς από το νοσοκομείο στο σπίτι

Στράτος Θεοφιλογιαννάκος, MD, PhD

Ιατρείο Καρδιακής Ανεπάρκειας, 3η Καρδιολογική Κλινική ΑΠΘ, Ιπποκράτειο Νοσοκομείο

&

Κλινική Άγιος Λουκάς

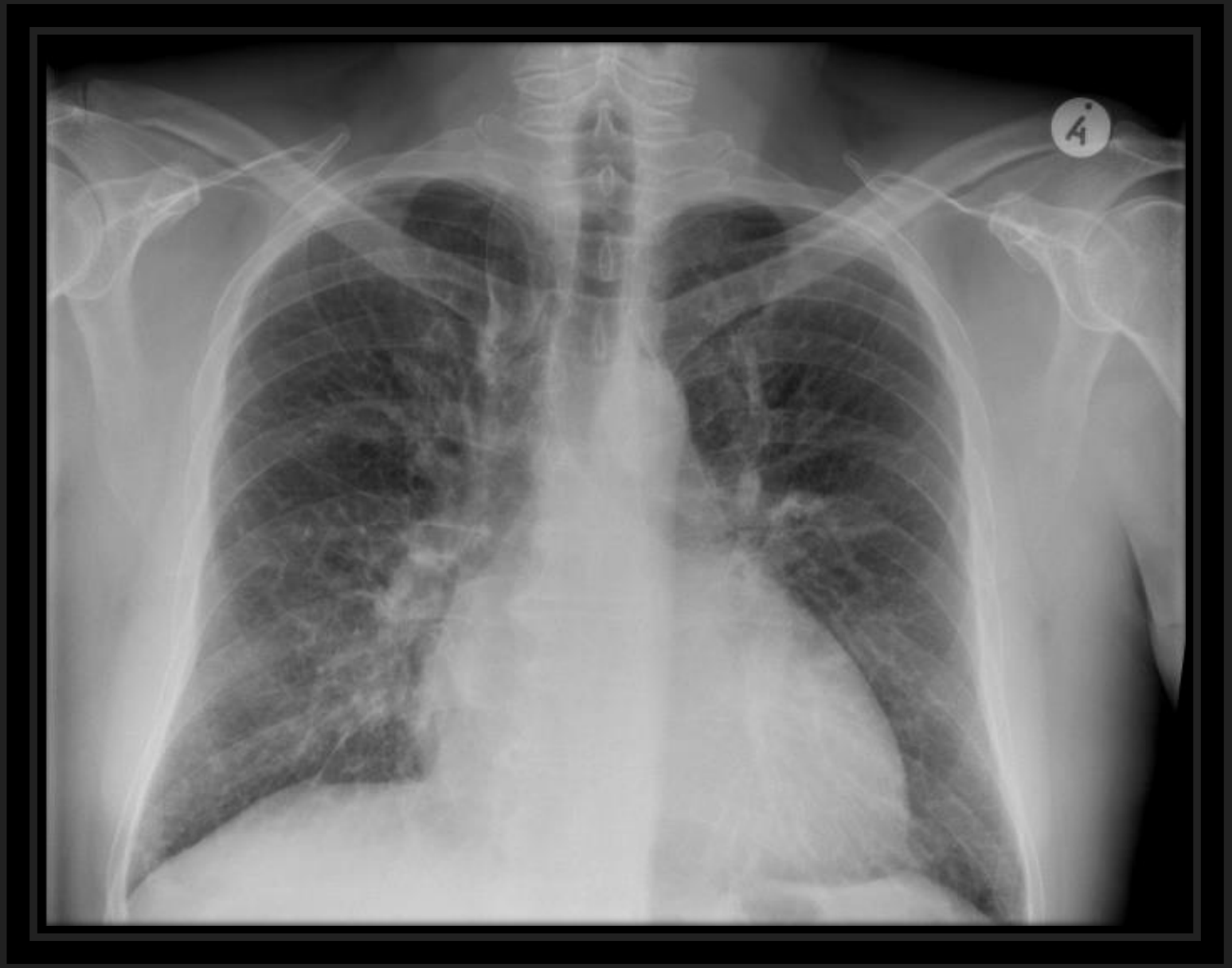
Διευκρινίσεις (Δήλωση Σύγκρουση Συμφερόντων)

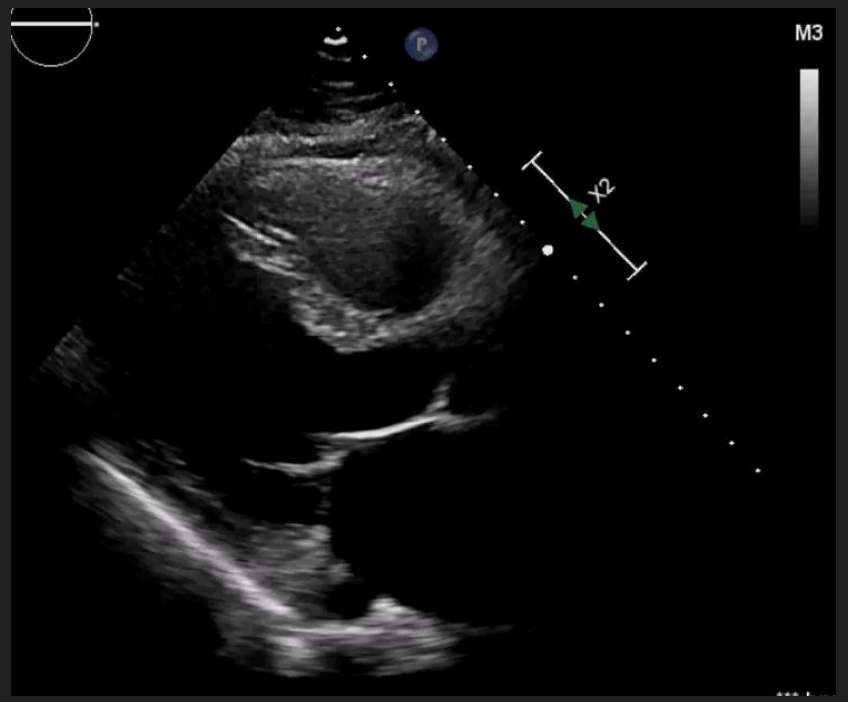
- Η παρουσίαση αυτή προορίζεται μόνο για μη-προωθητικό επιστημονικό σκοπό και μπορεί να περιέχει πληροφορίες σχετικά με τα προϊόντα ή τις ενδείξεις τους, που επί του παρόντος μπορεί να είναι υπό διερεύνηση ή/και που δεν έχουν εγκριθεί από τις ρυθμιστικές αρχές.
- Η παρουσίαση αυτή εκφράζει αποκλειστικά τις απόψεις του ομιλητή.
- Οι πληροφορίες που περιέχονται είναι ακριβείς κατά τη δημιουργία της παρουσίασης.
- Τυχόν δεδομένα σχετικά με προϊόντα τα οποία δεν ανήκουν στη Novartis βασίζονται σε δημόσια διαθέσιμες πληροφορίες κατά τη δημιουργία της παρουσίασης.

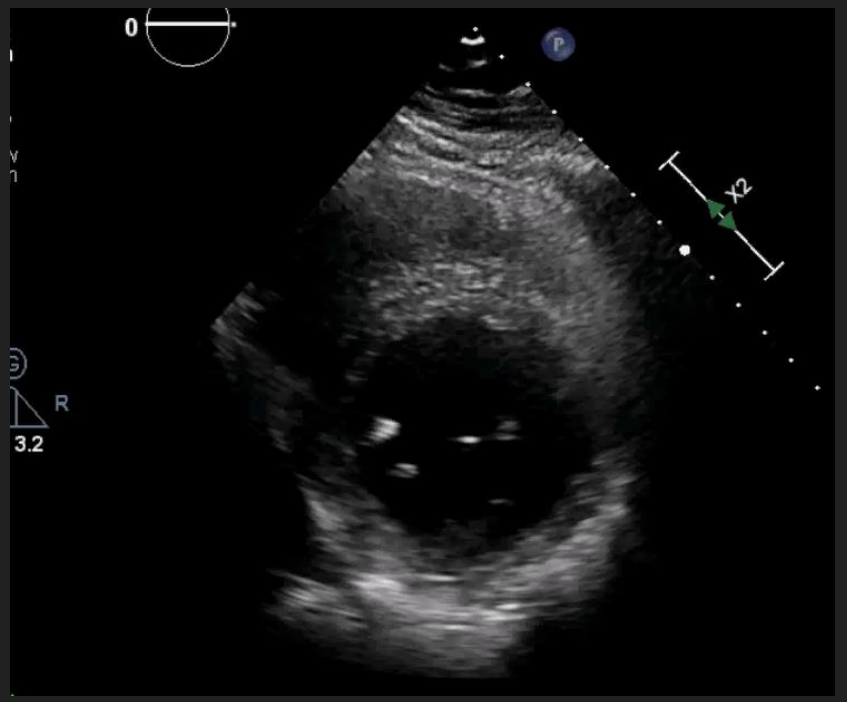
Περιστατικό

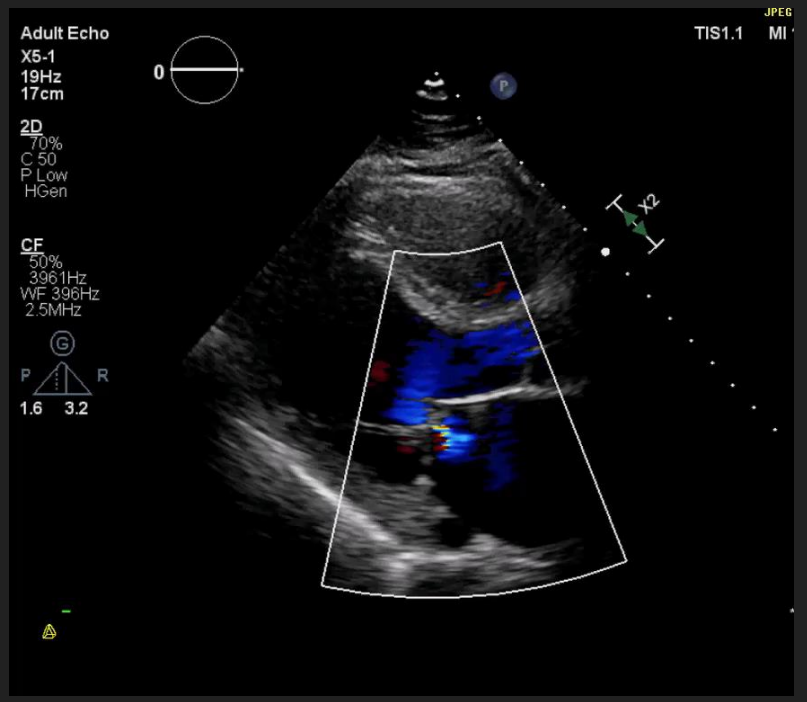
- Άνδρας 57 ετών
- Εισαγωγή για **δύσπνοια** και **αίσθημα παλμών**
- Χωρίς ιστορικό Δομικής Καρδιοπάθειας
- Φάρμακα: -
- Οικογενειακό Ιστορικό: -
- ΑΠ=140/90
- ΗΚΓ: **Ταχεία AF** (αγνώστου ενάρξεως)
- Εργαστηριακά:
  - Ht=48.2%, WBC=10000, PLT=234000
  - Ουρία= 33 mg/dl, Κρεατινίνη=1,12 mg/dl, Κάλιο=5,3 mmol/l, Νάτριο=143 mmol/l
  - **NT-proBNP= 3229 pg/ml**

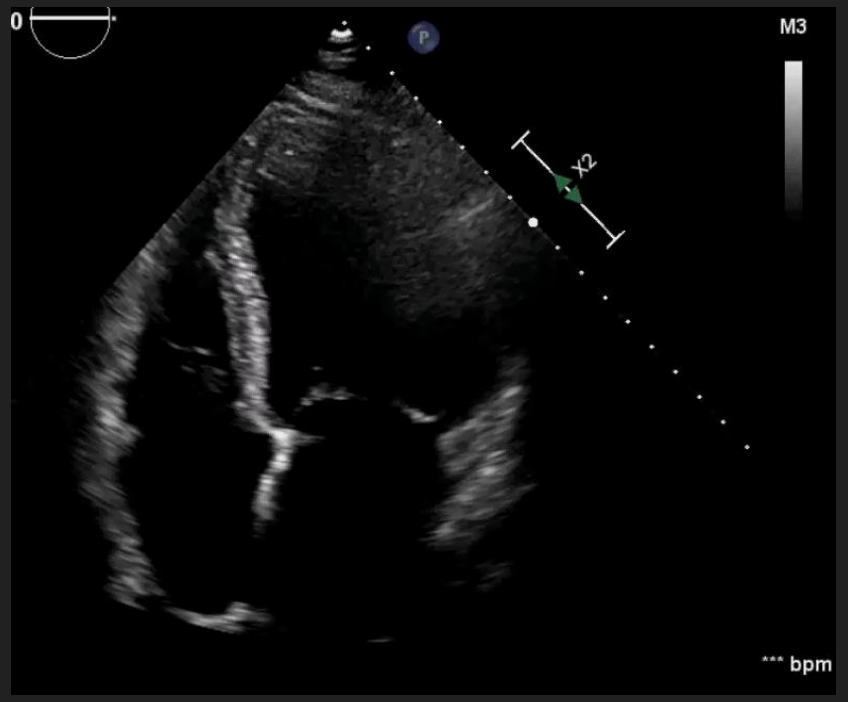
Α/Α ΘΩΡΑΚΑ

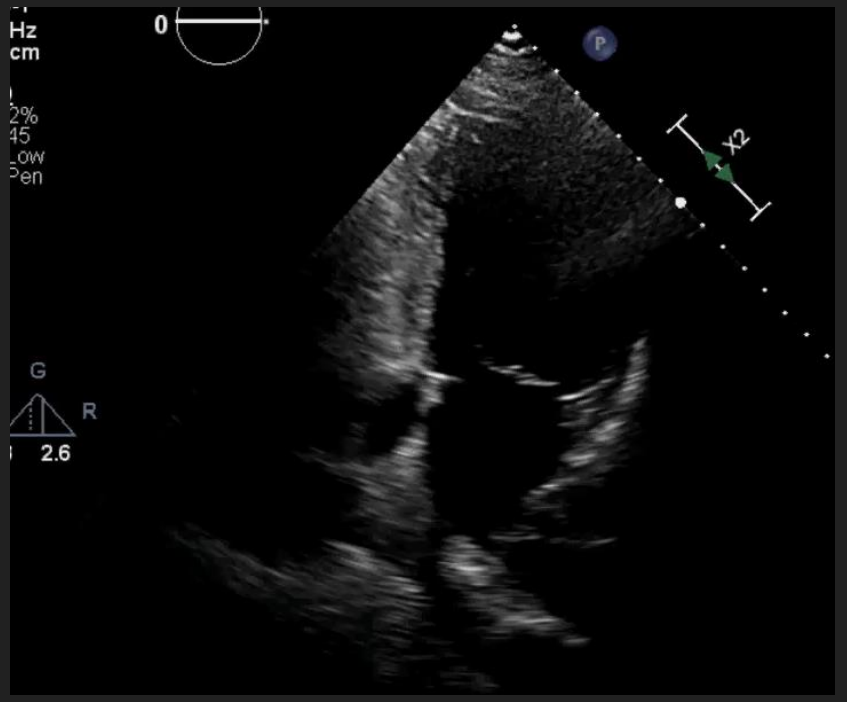


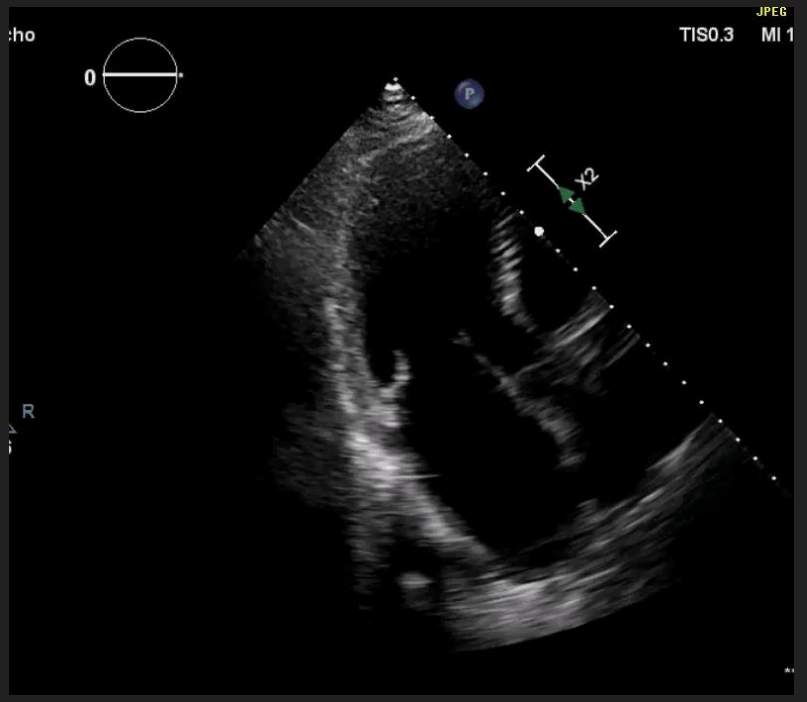

M3
X2


0
X2
R
3.2


Adult Echo
X5-1
19Hz
17cm
2D
70%
C 50
P Low
HGen
CF
50%
3961Hz
WF 396Hz
2.5MHz
P
R
1.6
3.2
TIS1.1
MI
0
X2


0
M3
X2
*** bpm

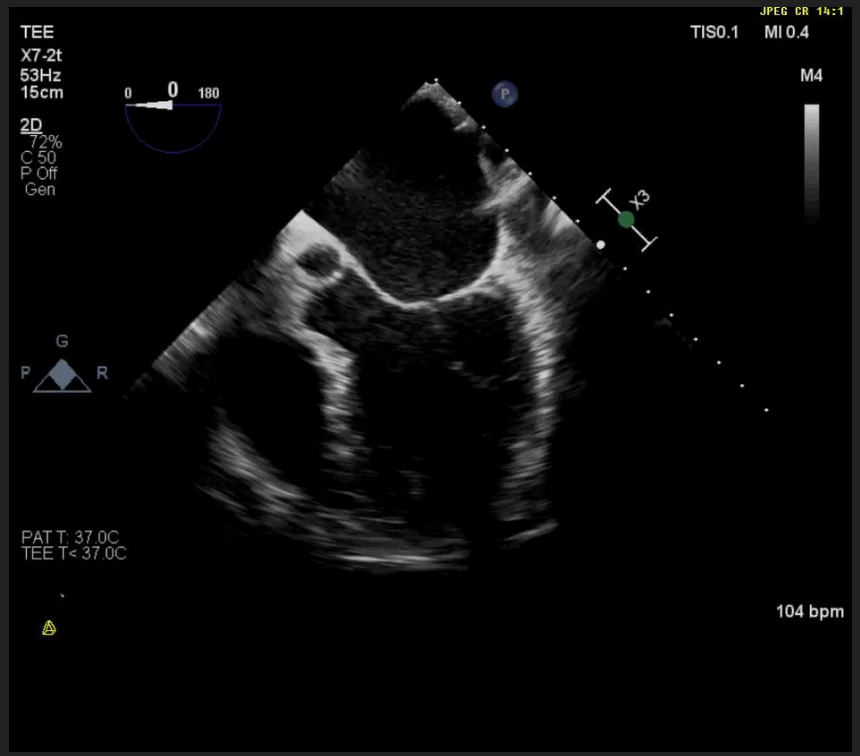

0
X2
G
R
2.6

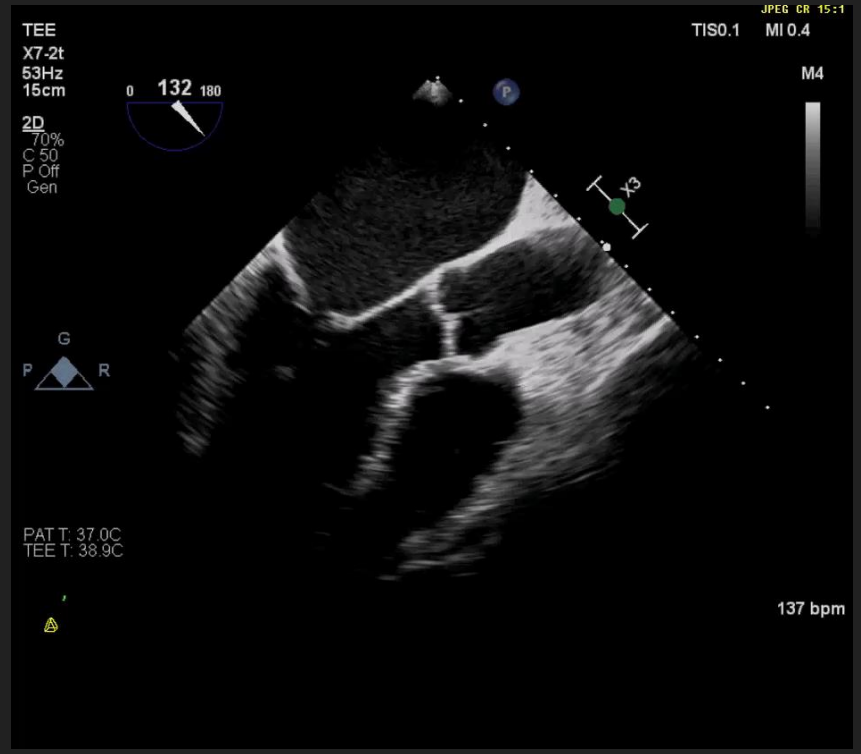

0
X2
R
TIS0.3
MI

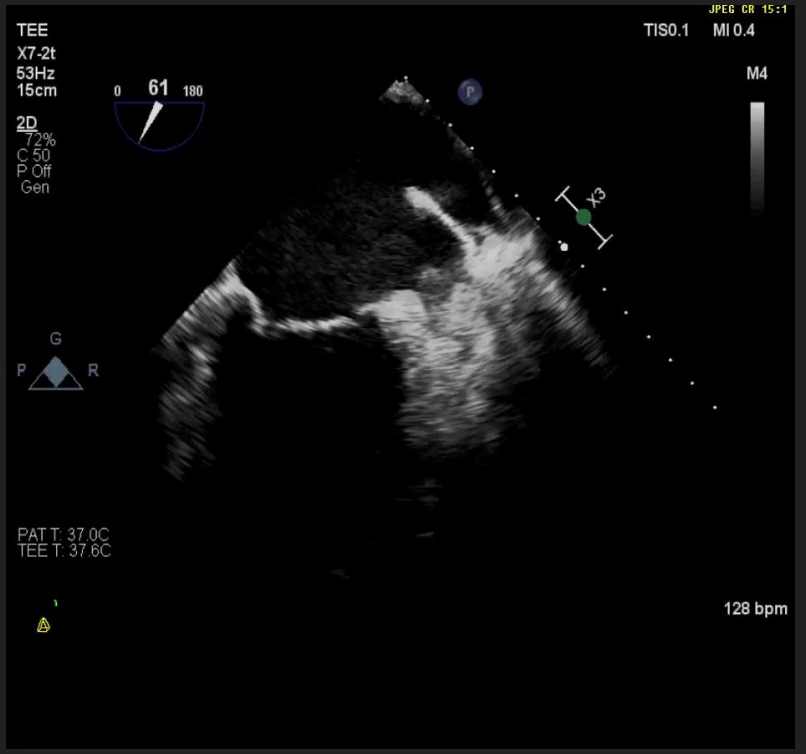
Αγωγή Εισόδου

- Ενδοφλέβια διουρητικά (Φουροσεμίδη)
- Βισοπρολόλη (2.5 mg X 2)
- Διγοξίνη (0.125 mg X1)
- Επλερενόνη (25 mg X1)
- Ριβαροξαμπάνη (20 mg x 1)

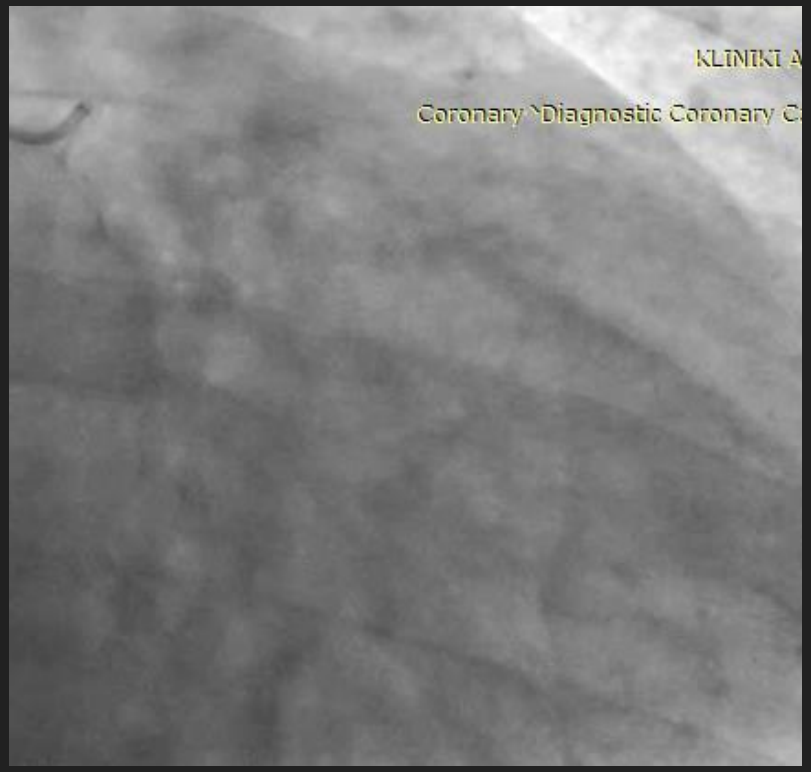
2η ημέρα νοσηλείας: Παροδικό Ισχαιμικό ΑΕΕ

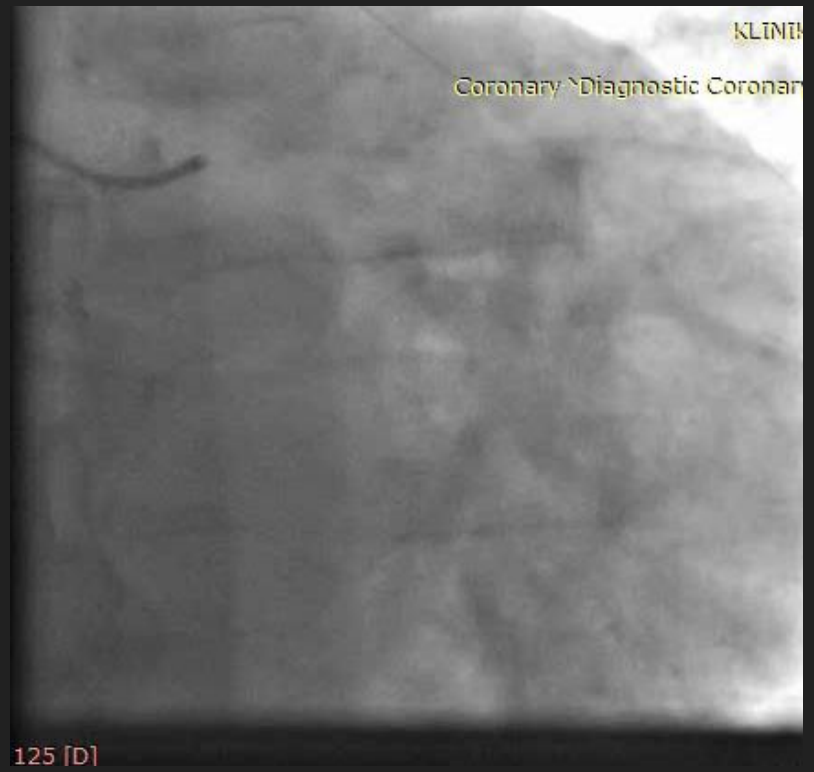


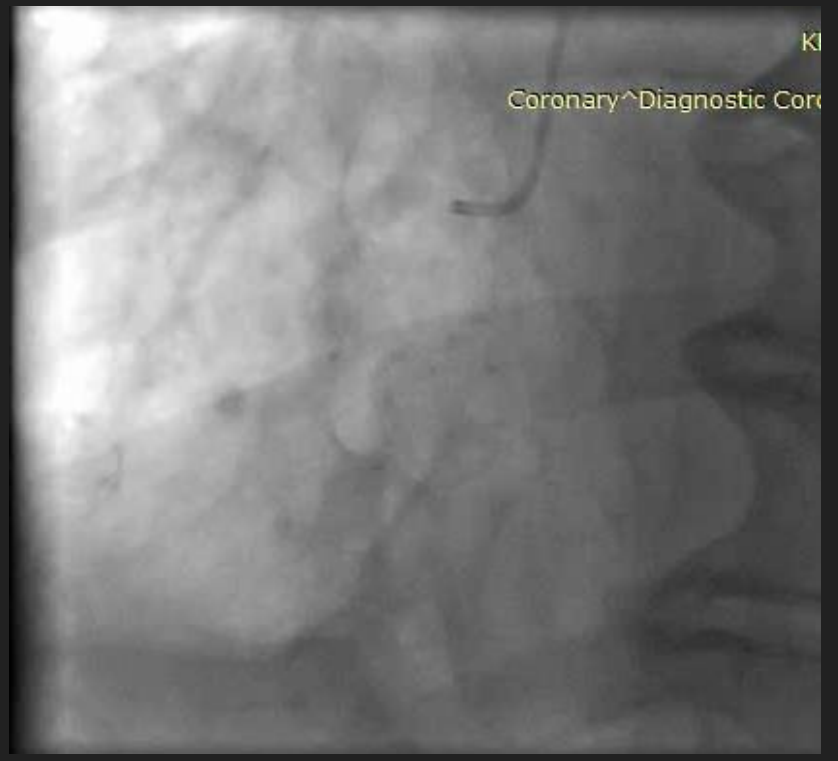




Στεφανιογραφικός έλεγχος







ΑΝΤΙΜΕΤΩΠΙΣΗ

Αγωγή Εισόδου:

- Ενδοφλέβια διουρητικά (Φουροσεμίδη)
- Βισοπρολόλη (2.5 mg X 2)
- Διγοξίνη (0.125 mg X1)
- Επλερενόνη 25 mg X1
- Ριβαροξαμπάνη 20 mg x 1

5η ημέρα

Ουρία= 38 mg/dl, Κρεατινίνη=1,26 mg/dl,
Κάλιο=5,06 mmol/l, Νάτριο=144 mmol/l
ΑΠ=125/75 mmHg

❖ **Σακουμπιτρίλη/Βαλσαρτάνη 24/26 mg**

7η ημέρα (εξιτήριο) - Αγωγή εξόδου:

1. Βισοπρολόλη 2.5 mg X 2
2. Φουροσεμίδη 40 mg X1
3. Επλερενόνη 25 mg X1
4. Σακουμπιτρίλη/Βαλσαρτάνη 24/26 mg X2
5. Ριβαροξαμπάνη 20 mg x 1

4 εβδομάδες αργότερα

NYHA II

ΑΠ=115/75, Συχνότητα=63/λεπτό

Εργαστηριακά:

- Ουρία= 46.9 mg/dl, Κρεατινίνη=1,37 mg/dl,
- Κάλιο=5,2 mmol/l, Νάτριο=141 mmol/l,

Μείωση δόσης Φουροσεμίδης 20 mg X1

Αύξηση δόσης **Επλερενόνης** 50 mg X1

Αύξηση δόσης **Σακουμπιτρίλη/Βαλσαρτάνη** 49/51 mg X2

2 μήνες αργότερα

NYHA I-II

ΑΠ=115/80, Συχνότητα=60/λεπτό

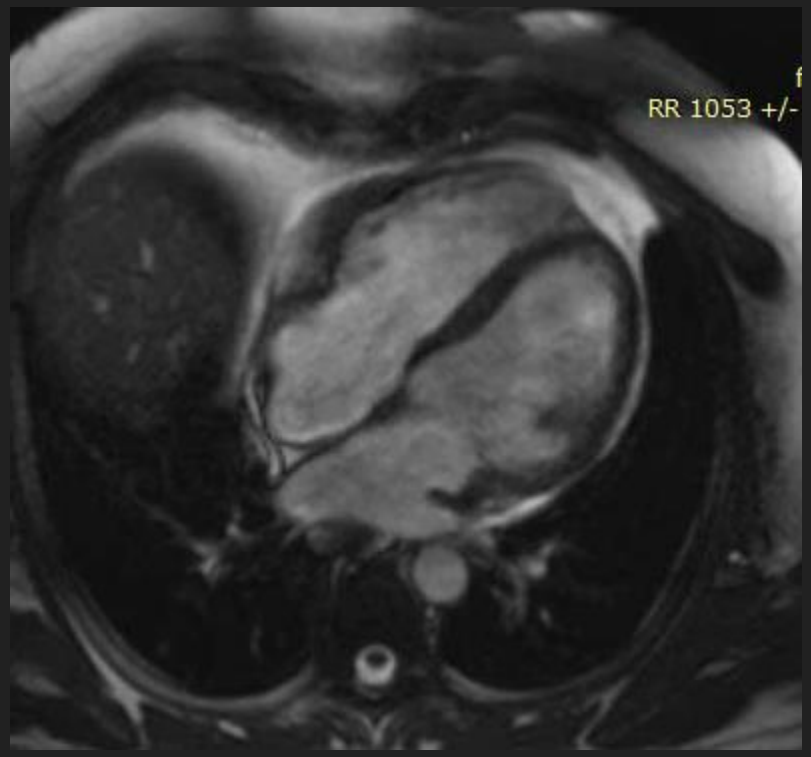
Εργαστηριακά:

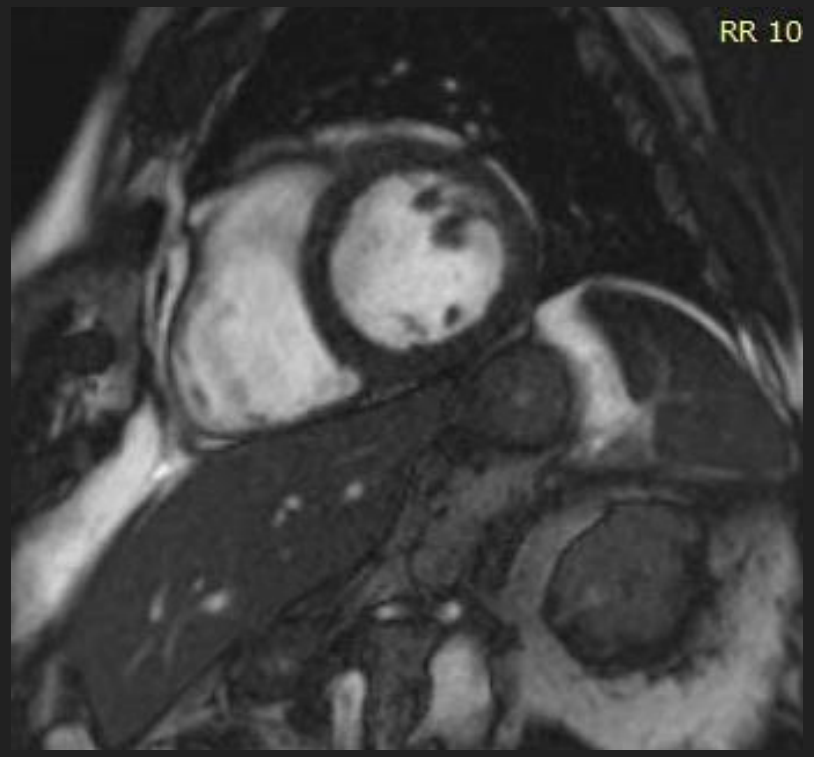
- Ουρία= 40.3 mg/dl, Κρεατινίνη=1,26 mg/dl,
- Κάλιο=4,64 mmol/l, Νάτριο=145 mmol/l,

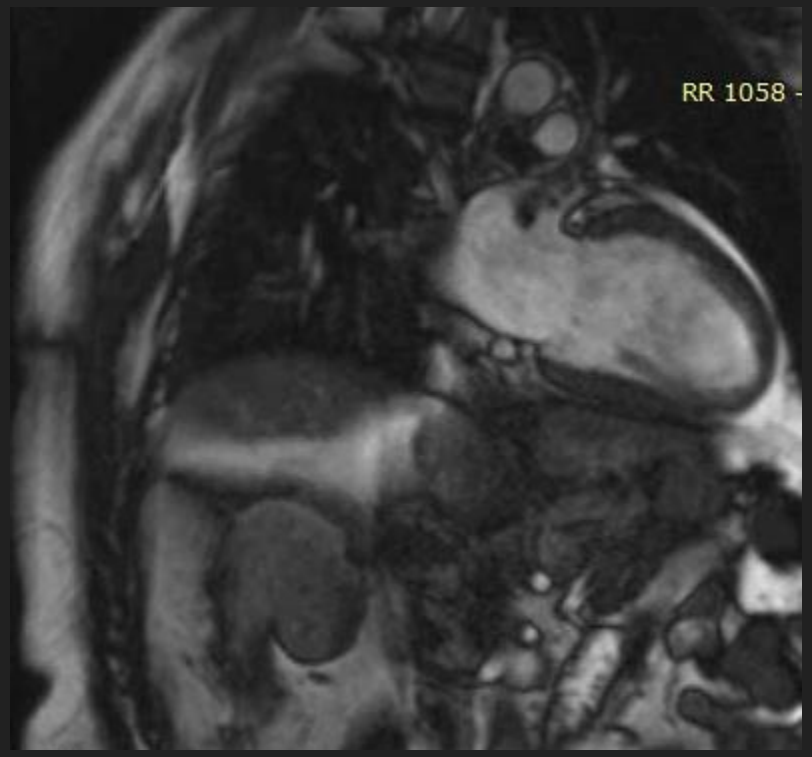
Αύξηση δόσης **Σακουμπιτρίλη/Βαλσαρτάνη** 97/103 mg X2

6 μήνες αργότερα

NYHA I,
NT-proBNP=180 pg/ml







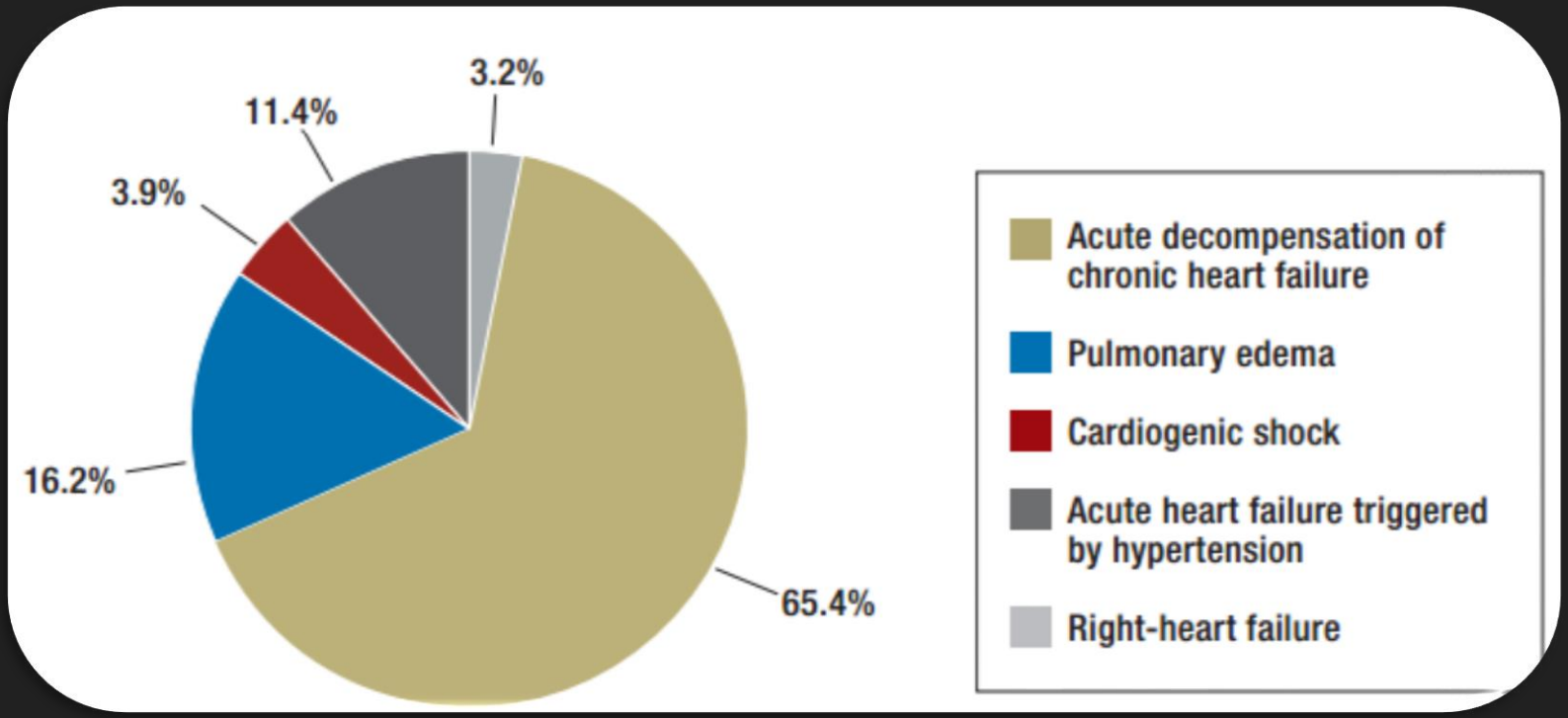
Acute Heart Failure Subtypes

- **Decompensated HF**: dyspnoea or tachycardia and pulmonary congestion or interstitial oedema verified by chest X-ray
- **Pulmonary oedema**: HF accompanied by alveolar oedema in the chest X-ray or with O_2 saturation <90% (without supplemental oxygen)
- **Cardiogenic shock**: AHF accompanied by low blood pressure (SBP<90 mmHg) and oliguria (<0.5 mL/kg/h for at least 6 h) or low cardiac index (<2.2 L/min/m^2).
- **HF and hypertension**: high blood pressure (>180/100 mmHg) accompanied by symptoms of HF (dyspnoea and tachycardia) and radiological findings of pulmonary congestion or oedema and with preserved left ventricular (LV) function at index hospitalization or before.
- **Right HF**: HF due to right-sided pathophysiology with increased jugular venous pressure and liver size and usually accompanied by peripheral oedema as unique or concomitant to left HF.

MS. Nieminen et al, Eur Heart J (2006) 27 (22): 2725-2736

EuroHeart Failure Survey II

The frequency of clinical subtypes of acute heart failure



MS. Nieminen et al, Eur Heart J (2006) 27 (22): 2725-2736

Acute Heart Failure Outcome in Different Registries

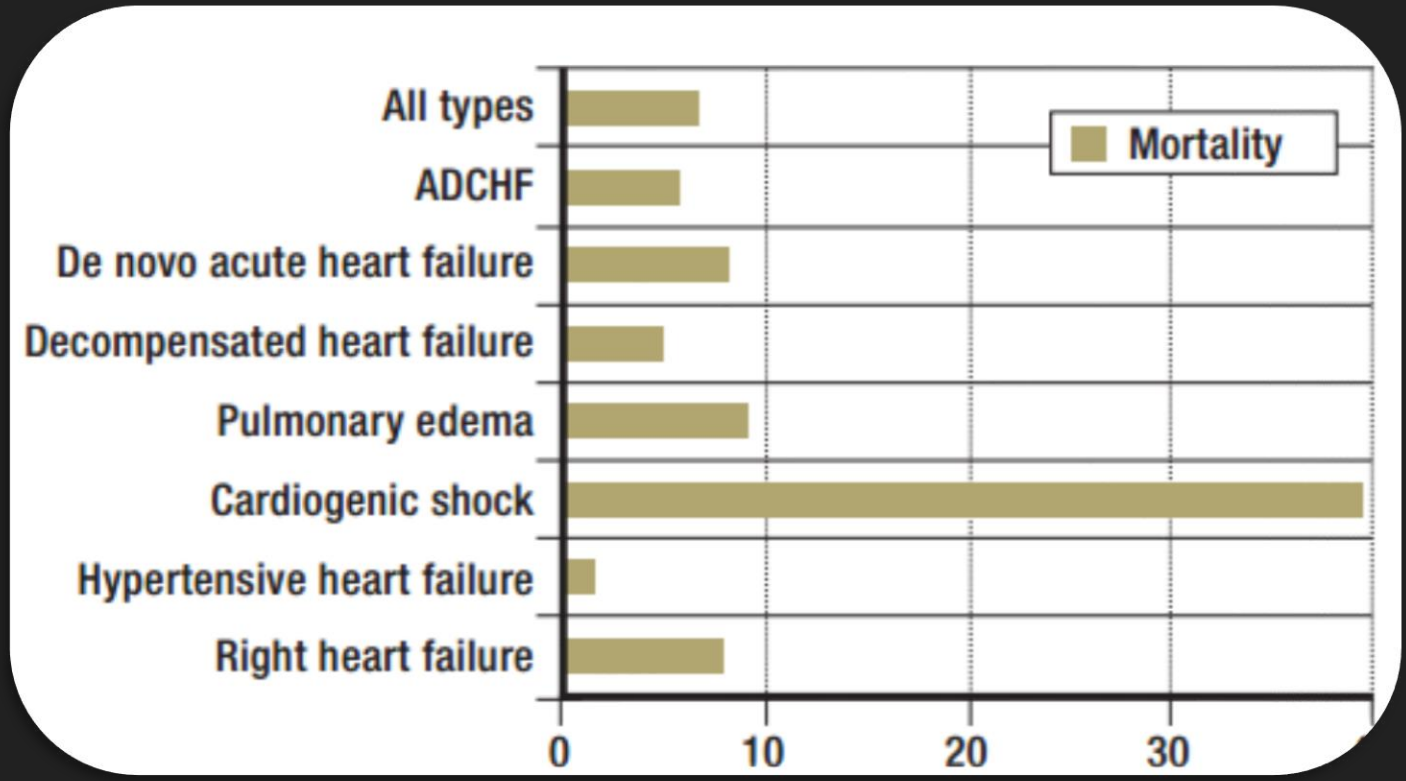
	ADHERE	OPTIMIZE-HF	EHFS I	EHFS II	ESC-HF Pilot (AHF arm)	ALARM-HF
Patients, No.	105 388	48 612	11 327	3580	1892	4953
In-hospital mortality, %	4.0	4.0	6.9	6.7	3.8	11.0
Hospital stay, median, days	4	4	11	9	8	6
30-90-days mortality, %	11.2 (30 days)	9.0 (60-90 days)	6.6 (90 days)			
1-year mortality, %	36					
Readmission (time period),	22.1 (30 days) 65.8 (1 year)	30.0 (60-90 days)	24.0 (90 days)			

Farmakis et al, Rev Esp Cardiol. 2015;68(3):245–248

AHF Mortality

EuroHeart Failure Survey II

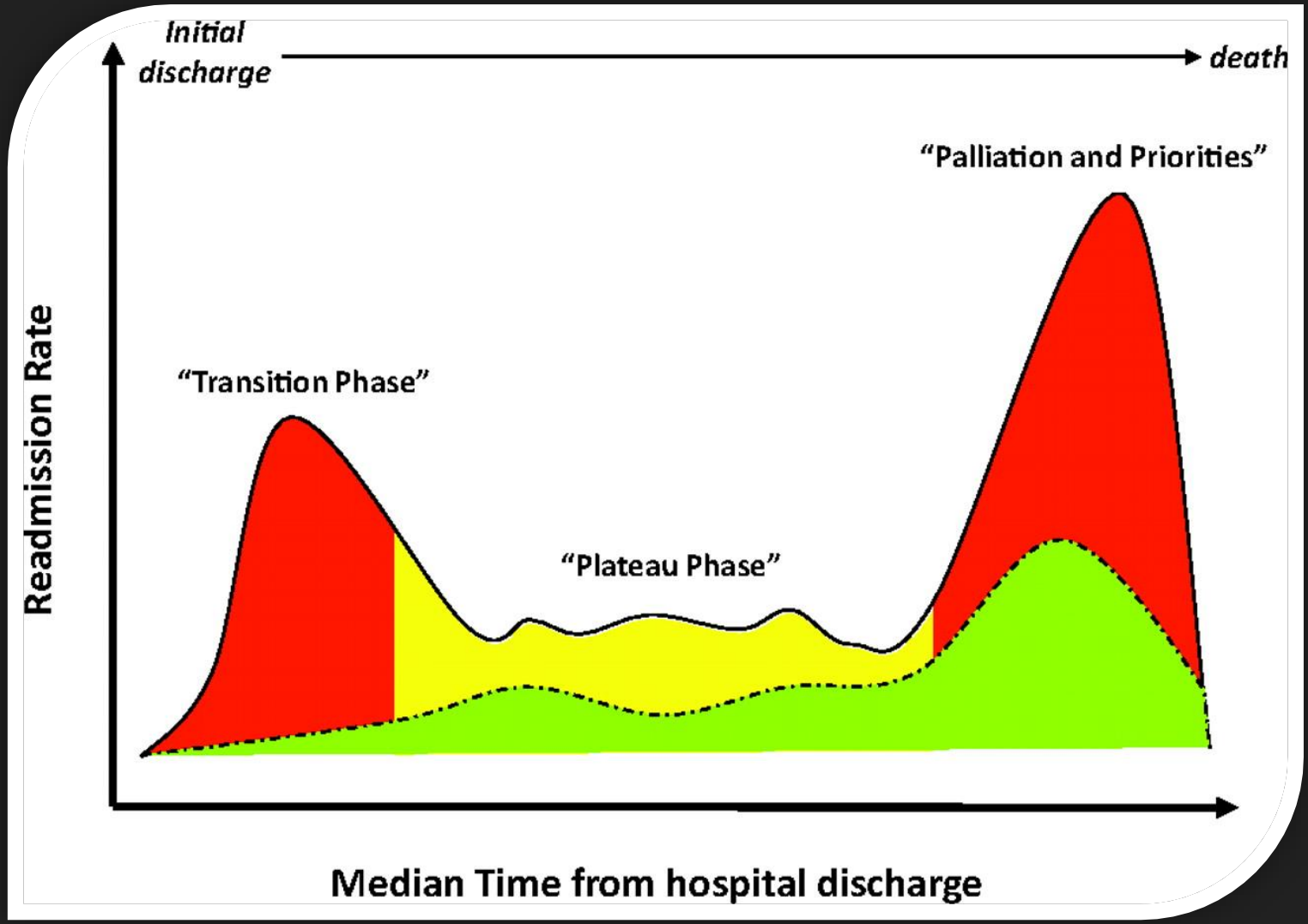
In-hospital mortality as a function of the past history and clinical presentation of acute heart failure



MS. Nieminen et al, Eur Heart J (2006) 27 (22): 2725-2736

Phases of Readmission after an initial Discharge

- The early post-discharge phase after hospitalization for heart failure carries particularly high risk of poor outcomes and has been termed the vulnerable phase.
- No treatment has definitively reduced rates of early death and rehospitalization other than optimizing guideline-directed chronic HF therapies.



AS. Desai, Circulation, 2012

Vulnerable phase after hospitalization for ADHF



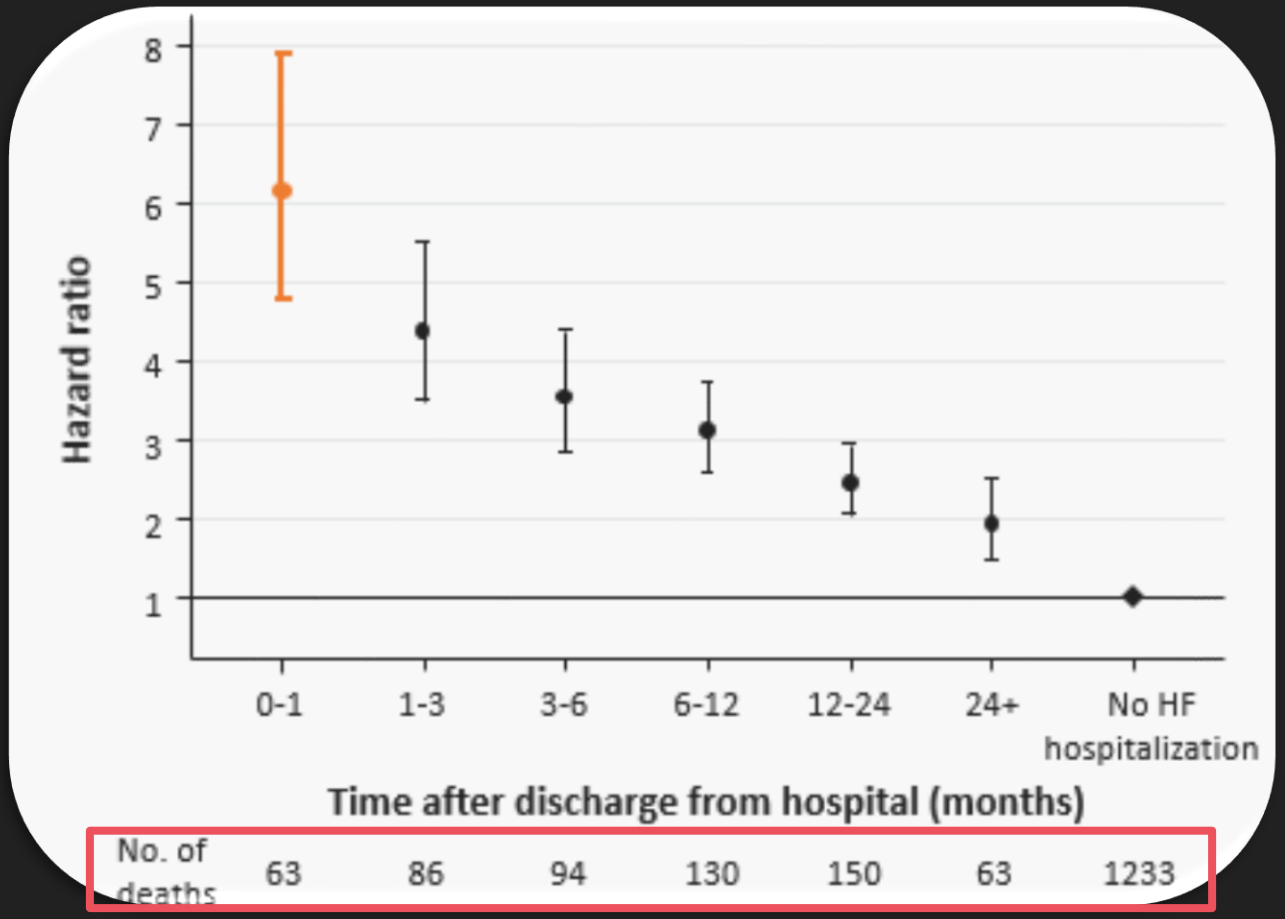

Heart failure hospitalization → **Stabilization and post-discharge period** → **Chronic heart failure**

Approximately **25%** of patients will be readmitted to hospital within **30 days** after discharge

Mortality during this **30-day** period can reach up to **10%**

Greene et al. Nat Rev Cardiol 2015;12:220–29

Mortality risk is twice as high during first 30 days compared to 6 months after discharge



Solomon et al. Circulation 2007;116:1482-87

ESC Guidelines Recommendations

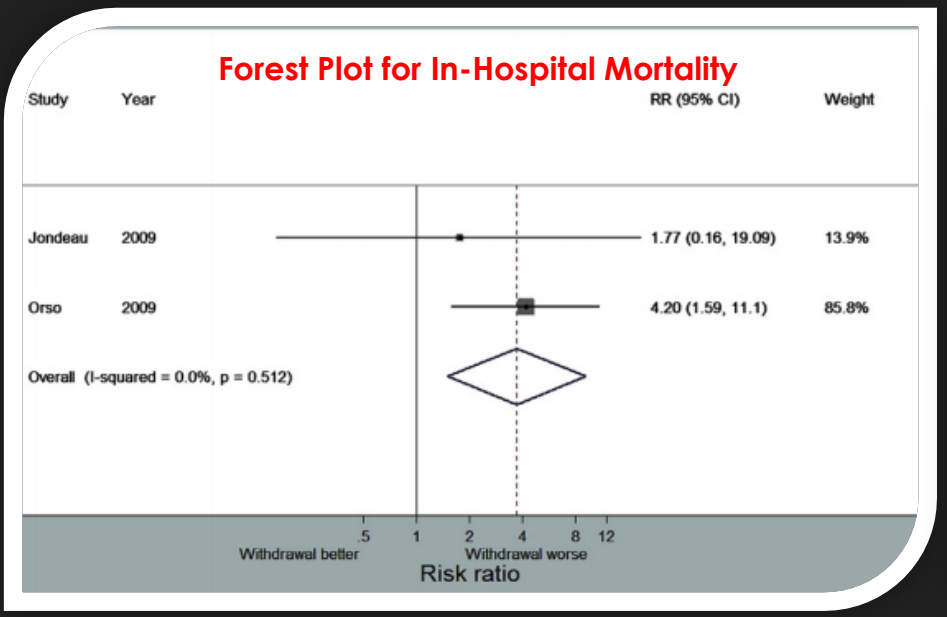
Recommendations regarding oral evidence-based disease-modifying therapies in patients with acute heart failure	Class [a]	Level [b]
In case of worsening of chronic HFrEF, every attempt should be made to continue evidence-based, disease-modifying therapies, in the absence of haemodynamic instability or contra-indications.	I	C

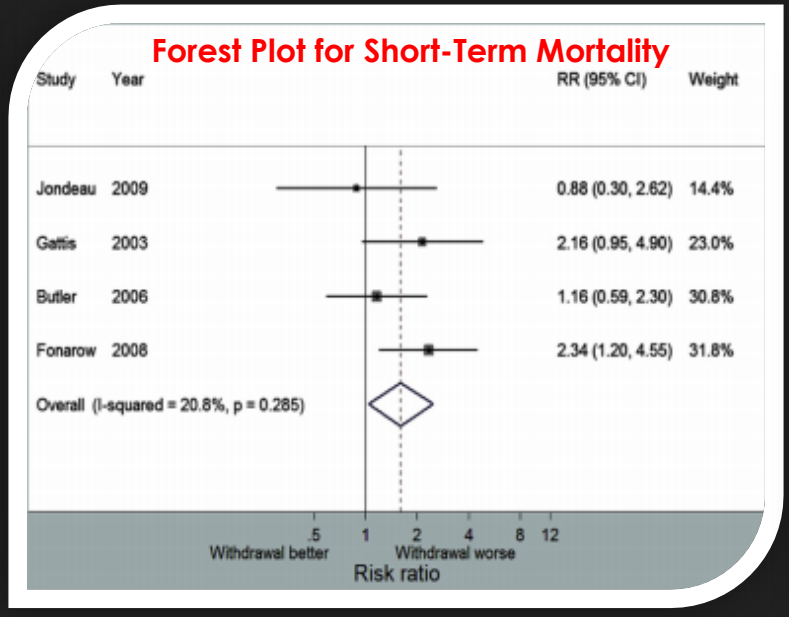
To address this vulnerable phase, the ESC guidelines recommend the optimization of chronic HF treatment while the patient is hospitalized, and a timely follow-up after discharge.

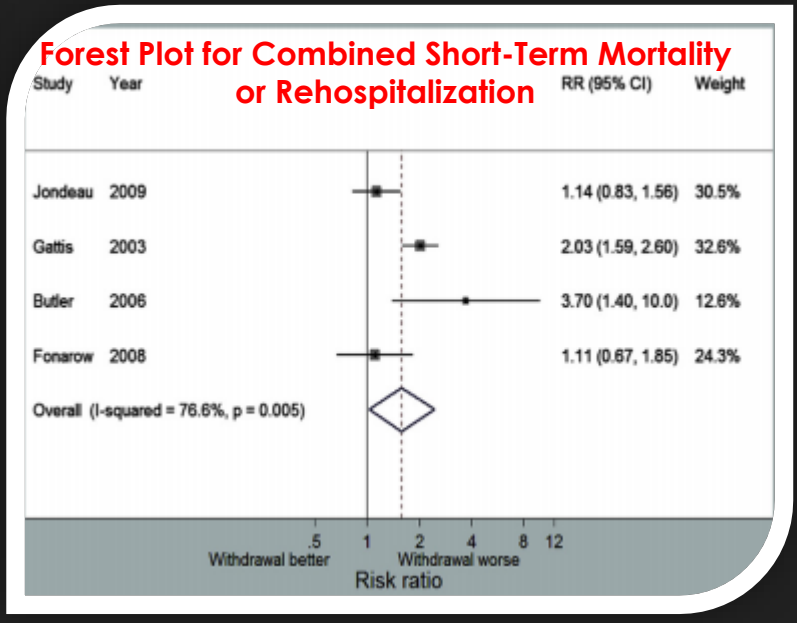
ESC Guidelines Heart Failure 2016

Beta-Blockers Withdrawal in AHF: a Meta-analysis

- Concern about the negative inotropic effects of beta-blockers and thus the potential worsening of hemodynamics leads many physicians to stop beta-blockers in ADHF.







Continuation of beta-blockers in ADHF was associated with significant reductions in risk of in-hospital mortality, short-term mortality, and short-term combined rehospitalization or death.

Prins et al JACC: Heart Failure 2015

OPTIMIZE-HF Registry: ACC/AHA performance measures influences on early clinical outcomes (2005)

- Sixty- to ninety-day post-discharge follow-up data were prospectively collected from 5791 patients at 91 US hospitals.

Table 4. Unadjusted and Risk-Adjusted Process-Outcome Links for ACC/AHA Hospital Performance Measures for Heart Failure

Performance Measures	Predictive of Mortality at 60- to 90-d Follow-up		Predictive of Mortality or Rehospitalization at 60- to 90-d Follow-up	
	Hazard Ratio (95% CI)	*P* Value	Odds Ratio (95% CI)	*P* Value
Unadjusted				
Discharge instructions	0.86 (0.66-1.13)	.29	0.97 (0.85-1.12)	.69
Evaluation of LV systolic function	0.75 (0.55-1.03)	.08	0.86 (0.71-1.04)	.11
ACE inhibitor/ARB for LV systolic dysfunction	0.48 (0.31-0.73)	<.001	0.55 (0.43-0.70)	<.001
Smoking cessation counseling	0.54 (0.30-0.96)	.04	0.67 (0.49-0.92)	.01
Warfarin for atrial fibrillation	0.81 (0.58-1.13)	.22	0.87 (0.71-1.07)	.18
β-Blocker at discharge	0.42 (0.27-0.63)	<.001	0.69 (0.52-0.91)	.008
Risk-adjusted				
Discharge instructions	0.90 (0.66-1.23)	.51	1.07 (0.89-1.28)	.46
Evaluation of LV systolic function	0.91 (0.65-1.28)	.59	1.06 (0.81-1.38)	.67
ACE inhibitor/ARB for LV systolic dysfunction	0.61 (0.35-1.06)	.08	0.51 (0.34-0.78)	.002
Smoking cessation counseling	0.75 (0.41-1.37)	.35	0.74 (0.50-1.09)	.12
Warfarin for atrial fibrillation	0.74 (0.50-1.09)	.13	0.83 (0.64-1.09)	.19
β-Blocker at discharge	0.48 (0.30-0.79)	.004	0.73 (0.55-0.96)	.02

- None of the current recommended ACC/AHA heart failure performance measures was strongly associated with **60- to 90-day post-discharge mortality**, and **only the ACE inhibitor/ARB** performance measure strongly influenced post-discharge mortality or rehospitalization.
- the association between process and 60- to 90-day outcome was stronger for **b-blocker prescription at discharge** than for any of the current ACC/AHA performance measures

G Fonarow et al JAMA 2007

Studies of In-Hospital Use of b-Blocker, ACEI/ARB in Patients Hospitalized for HFRF

Therapy First Author (Ref. #)	Study Design	N	Key Results
Beta-blocker			
Initiation			
Gattis et al. (3) (IMPACT-HF)	Randomized (open-label) clinical trial: Carvedilol initiation pre-hospital discharge vs. initiation >2 weeks post-discharge at physician discretion	363	At 60 days post-randomization, 91% randomized to pre-discharge carvedilol initiation were treated with a beta-blocker, compared with 73% randomized to post-discharge initiation ($p < 0.001$). No difference in rates of serious adverse events or index hospitalization length of stay between groups.
Hernandez et al. (5) (OPTIMIZE-HF registry linked to Medicare claims)	Observational: Among patients eligible for beta-blockers, in-hospital beta-blocker initiation vs. no initiation	3,001 (subset with reduced ejection fraction)	At 1 yr post-discharge, beta-blocker initiation associated with lower adjusted risk for all-cause mortality (HR: 0.77; 95% CI: 0.68-0.87), all-cause rehospitalization (HR: 0.89; 95% CI: 0.80-0.99), and mortality or rehospitalization (HR: 0.87; 95% CI: 0.79-0.96).
Continuation or withdrawal			
Fonarow et al. (7) (OPTIMIZE-HF Registry)	Observational: Among patients eligible for beta-blockers, in-hospital beta-blocker continuation vs. no beta-blocker; beta-blocker withdrawal vs. continuation	2,373	At 60-90 days post-discharge, beta-blocker continuation associated with a lower propensity adjusted risk for mortality (HR: 0.60; 95% CI: 0.37-0.99; $p = 0.044$) and mortality or rehospitalization (odds ratio: 0.69; 95% CI: 0.52-0.92; $p = 0.012$), compared with no beta-blocker. 92% of patients newly initiated on beta-blocker therapy remained on therapy. Beta-blocker withdrawal associated with higher adjusted mortality risk compared with continuation (HR: 2.3; 95% CI: 1.2-4.6; $p = 0.013$). 57% of patients with in-hospital beta-blocker discontinuation were restarted on therapy within 60-90 days.
Angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker			
Initiation			
Sanam et al. (11) (Medicare beneficiaries)	Observational: Among patients without prior ACEI/ARB use and without known contraindications, discharge ACEI/ARB prescription vs. no prescription	954 (propensity matched cohort)	At 30 days post-discharge, ACEI/ARB prescription associated with significantly lower propensity adjusted all-cause readmission (HR: 0.74; 95% CI: 0.56-0.97; $p = 0.030$) and 30-day all-cause mortality (HR: 0.56; 95% CI: 0.33-0.98; $p = 0.041$). All associations remained significant at 1 yr post-discharge.
Continuation or withdrawal			
Gilstrap et al. (10) (GWTG-HF linked to Medicare claims)	Observational: Among eligible patients, ACEI/ARB withdrawal vs. continuation	16,052	At 1-year post-discharge, in-hospital ACEI/ARB withdrawal was associated higher adjusted mortality risk compared with continuation (HR: 1.35; 95% CI: 1.13-1.61; $p < 0.001$).

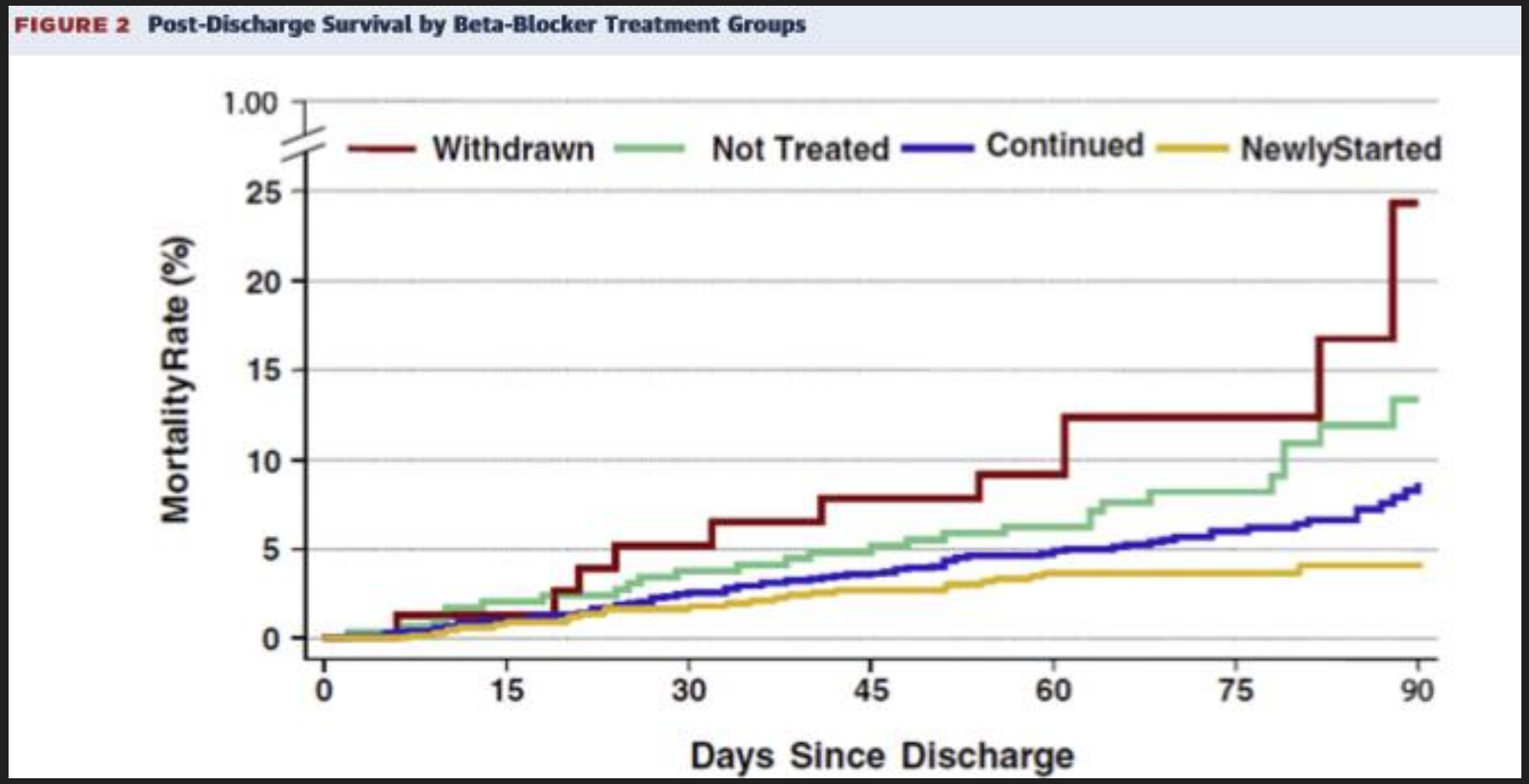
AA. Bhagat JACC Heart Failure 2018

Studies of In-Hospital Use of MRA in Patients Hospitalized for HFRF

Mineralocorticoid receptor antagonist			
Initiation			
Pereira et al. (15)	Nonrandomized clinical trial, single-blind (patients): Patients not receiving background MRA therapy and meeting other study criteria assigned short in-hospital course of spironolactone 50-100 mg/d plus standard care vs. standard care alone.	100	Spironolactone not associated with excess in-hospital worsening renal function or hyperkalemia. Greater proportions of patients receiving spironolactone were free of congestion at day 3: less edema, rales, jugular venous pressure and orthopnea (all $p < 0.05$).
Butler J et al. (17) (ATHENA-HF)	Randomized clinical trial: High-dose spironolactone 100 mg/d for 4 days plus standard care vs. standard care alone. Overall, 11% of patients on spironolactone at baseline.	360	Spironolactone not associated with excess in-hospital worsening renal function or hyperkalemia. Spironolactone therapy did decrease NT-proBNP level or improve clinical markers of congestion compared with standard care.
Lam et al. (20) (Medicare beneficiaries)	Observational: Among patients without MRA use at admission and without known contraindications, discharge MRA prescription vs. no prescription	648 (propensity matched cohort)	At 30 days post-discharge, MRA therapy not associated with propensity adjusted risk of all-cause readmission (HR: 0.92; 95% CI: 0.64-1.32; $p = 0.650$), all-cause mortality (HR: 0.84; 95% CI: 0.38-1.88; $p = 0.678$), or HF readmission (HR: 0.74; 95% CI: 0.41-1.31; $p = 0.301$). Associations remained consistent at 1-yr follow-up.
Prescription at discharge			
Hamaguchi et al. (19) (JCARE-CARD registry)	Observational: Use of spironolactone at discharge vs. no use at discharge	946	Over mean post-discharge follow-up of 2.2 yrs, discharge use of spironolactone associated with lower adjusted risk of all-cause (HR: 0.62; 95% CI: 0.41-0.93; $p = 0.020$) and cardiovascular death (HR: 0.52; 95% CI: 0.32-0.87; $p = 0.013$). Spironolactone not associated with adjusted risk of all-cause hospitalization (HR: 0.79; 95% CI: 0.59-1.05; $p = 0.101$).
Hernandez et al. (21) (GWTG-HF linked to Medicare claims)	Observational: Among patients eligible for therapy, discharge MRA prescription vs. no prescription	5,887	At 3 years post-discharge, MRA therapy not associated with adjusted risk of mortality (HR: 1.04; 95% CI: 0.96-1.14; $p = 0.32$) or cardiovascular rehospitalization (HR: 1.00; 95% CI: 0.91-1.09; $p = 0.94$). At 3 years, MRA therapy associated with lower adjusted risk of HF rehospitalization (HR: 0.87; 95% CI: 0.77-0.98; $p = 0.02$). MRA therapy associated with higher adjusted risk of hospitalization for hyperkalemia at 30 days (HR: 2.54; 95% CI: 1.51-4.29; $p < 0.001$) and 1 yr (HR: 1.50; 95% CI: 1.23-1.84; $p < 0.001$).
Curtis et al. (22) (GWTG-HF linked to Medicare claims)	Observational: Among patients eligible for therapy, discharge MRA prescription vs. no prescription	2,086	Within 90 days post-discharge, 79% of patients with a discharge prescription filled a prescription for therapy, compared with 13% without a discharge prescription ($p < 0.001$). 8% of patients with a discharge prescription discontinued therapy within 1 yr.

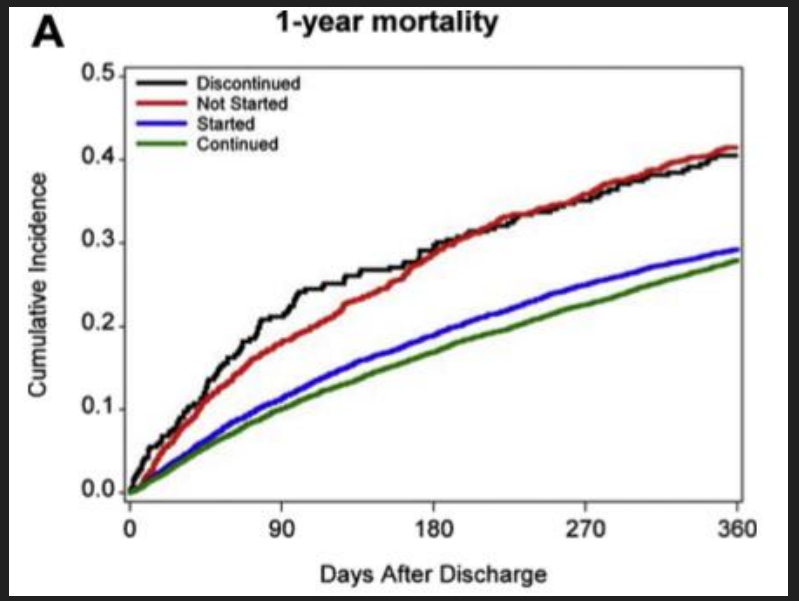
AA. Bhagat JACC Heart Failure 2018

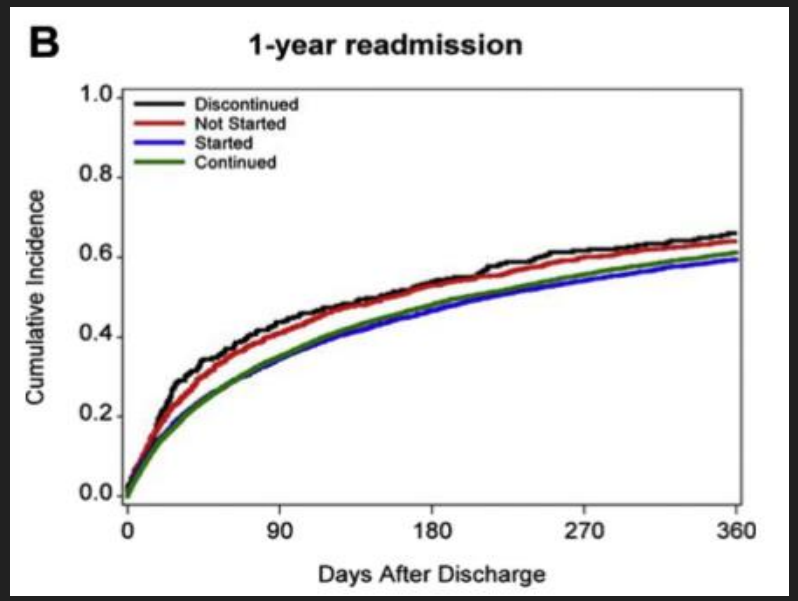
Post-Discharge Survival by Beta-Blocker Treatment Groups

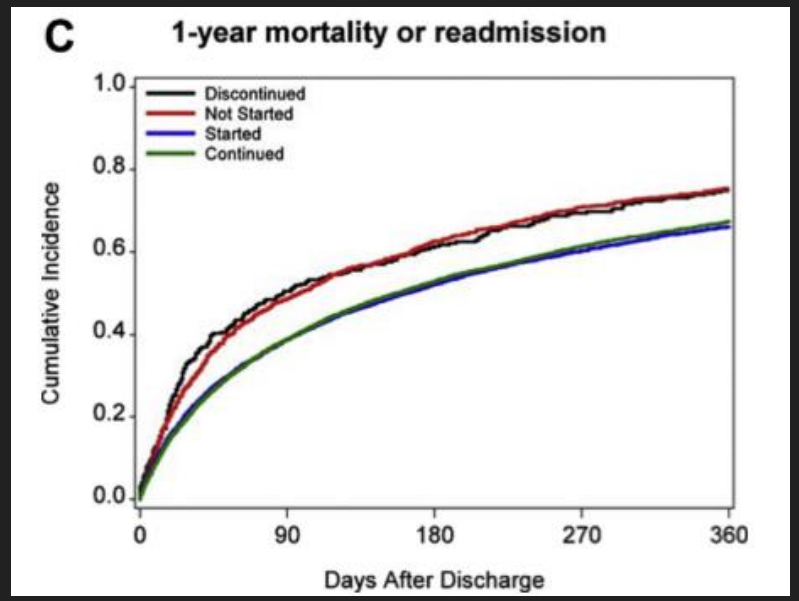


CG Fonarow et al JACC 2008

Post-Discharge Survival by ACE inhibitors Treatment Groups



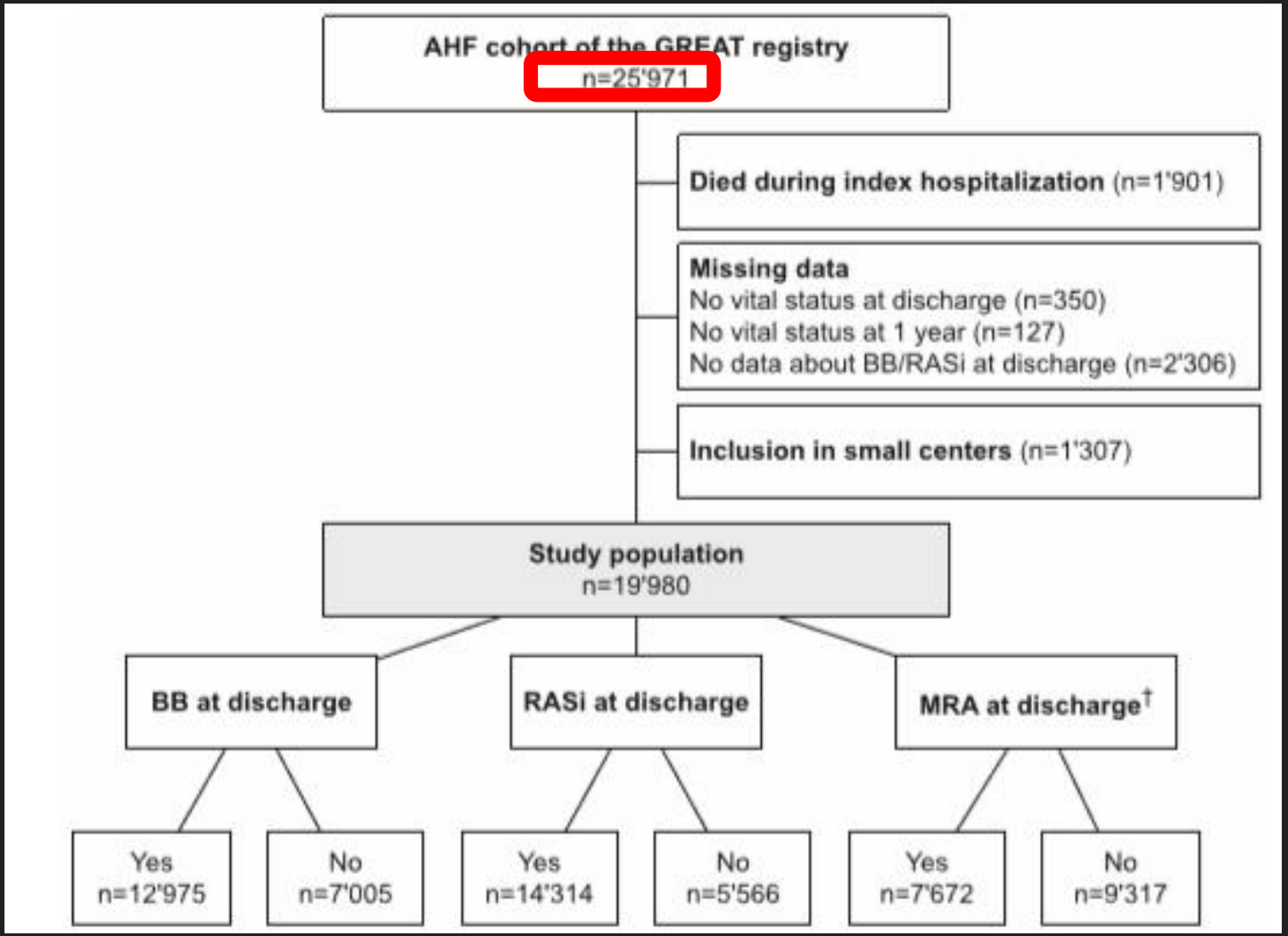




Gilstrap et al J Am Heart Assoc 2017

Heart Failure Therapies before Discharge in AHF

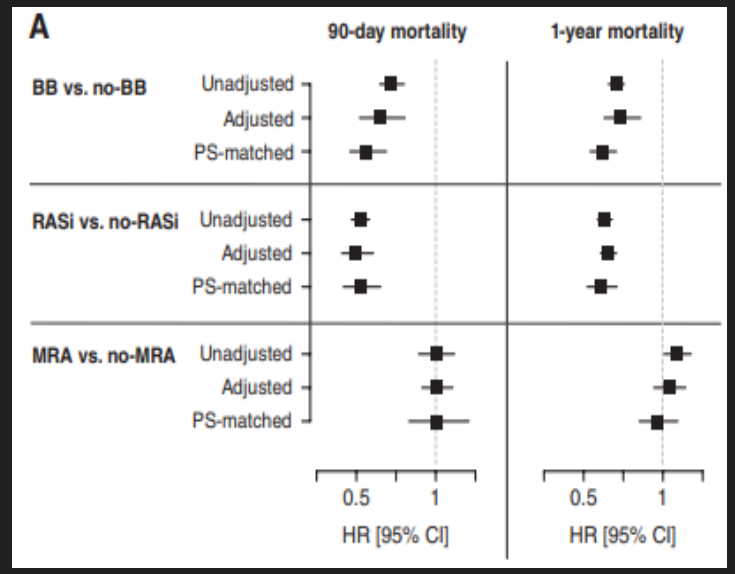
Heart failure oral therapies including beta-blockers , renin–angiotensin system inhibitors and mineralocorticoid receptor antagonists, administered before hospital discharge after acute heart failure **might improve outcome**. However, concerns have been raised because early administration of HFOTs **may worsen patient's condition**.

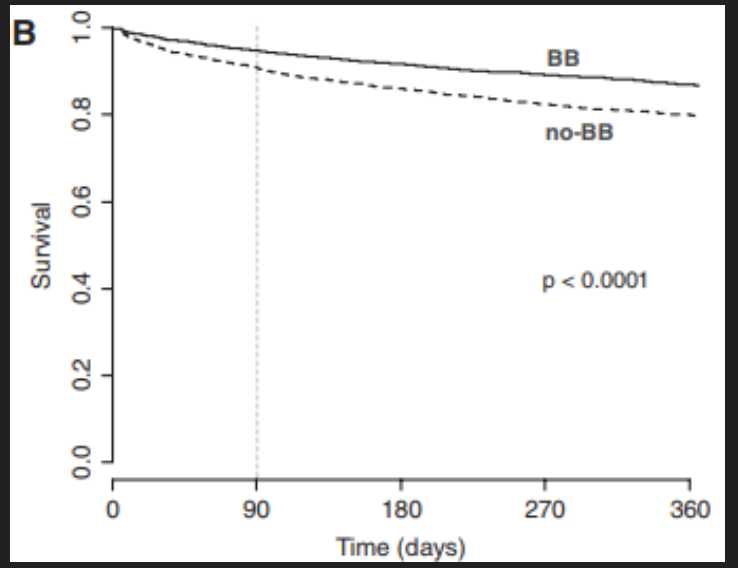


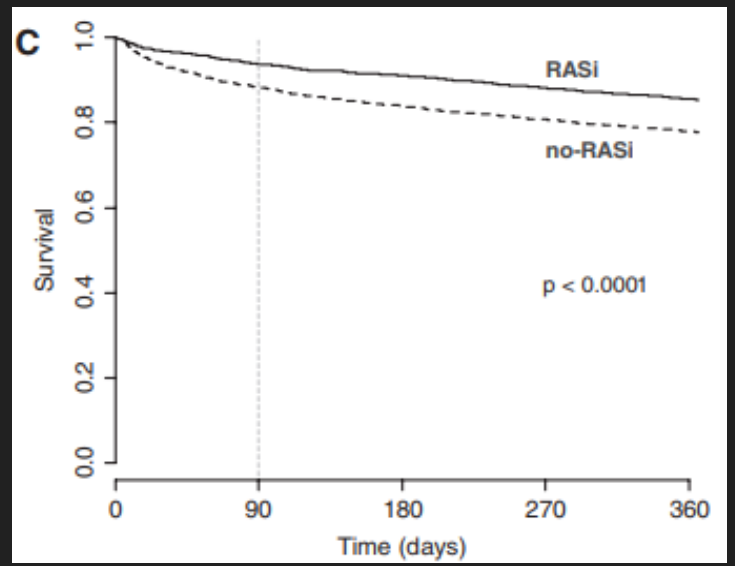
E Gayat et al Eur Heart Failure J 2018

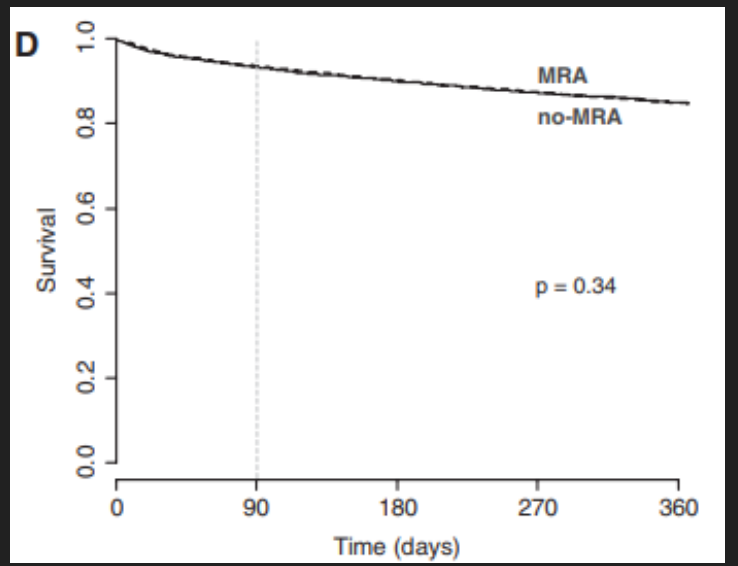
Heart failure oral therapies at discharge are associated with better outcome in acute heart failure

- BB and RASi at discharge were associated with lower 90-day mortality risks compared to the respective untreated groups.
- The favourable associations of BB and RASi at discharge with 90-day mortality were present in many subgroups including patients with reduced or preserved left ventricular ejection fraction and persisted up to 1 year after discharge.





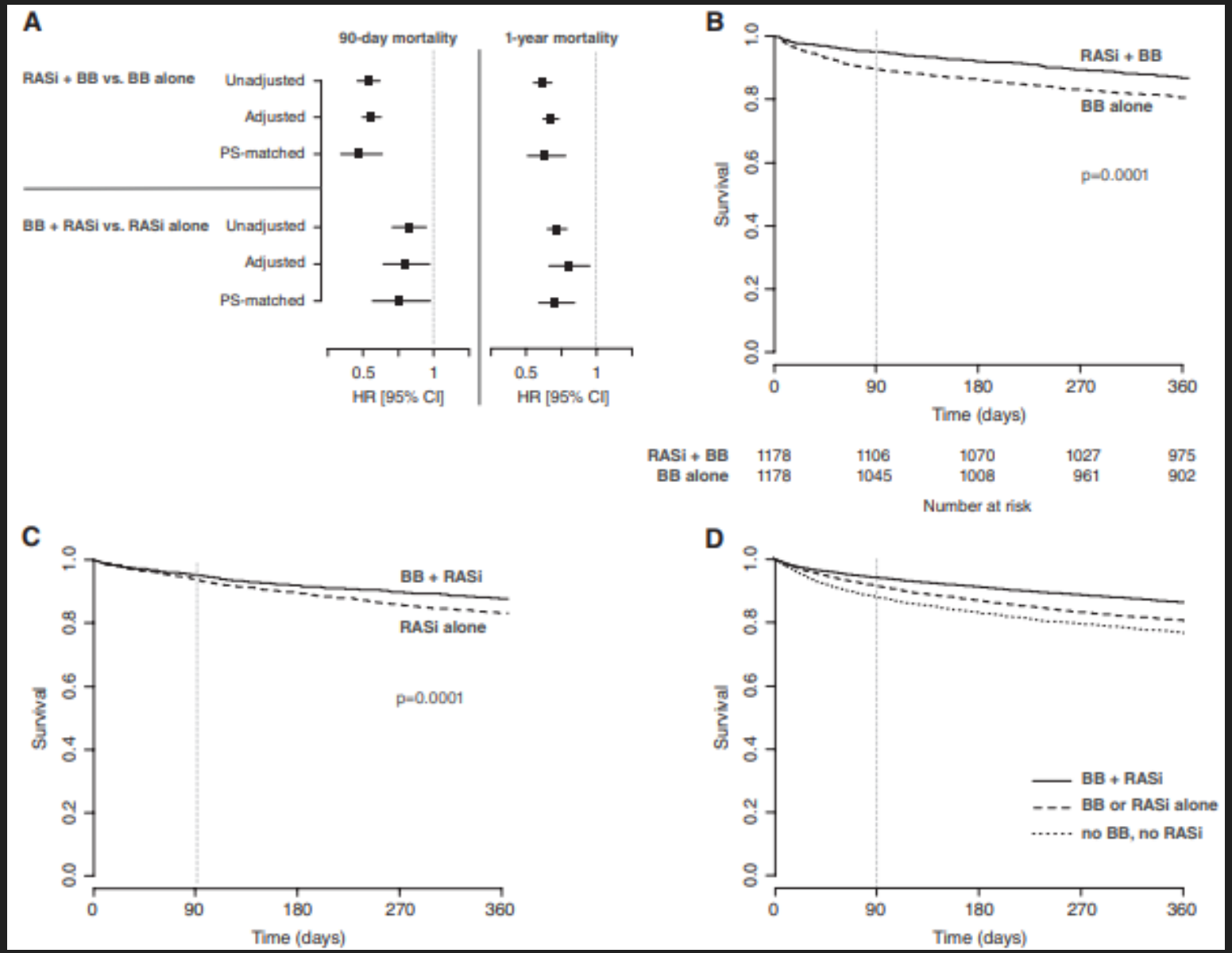




E Gayat et al Eur Heart Failure J 2018

Heart failure therapies at discharge are associated with better outcome in AHF

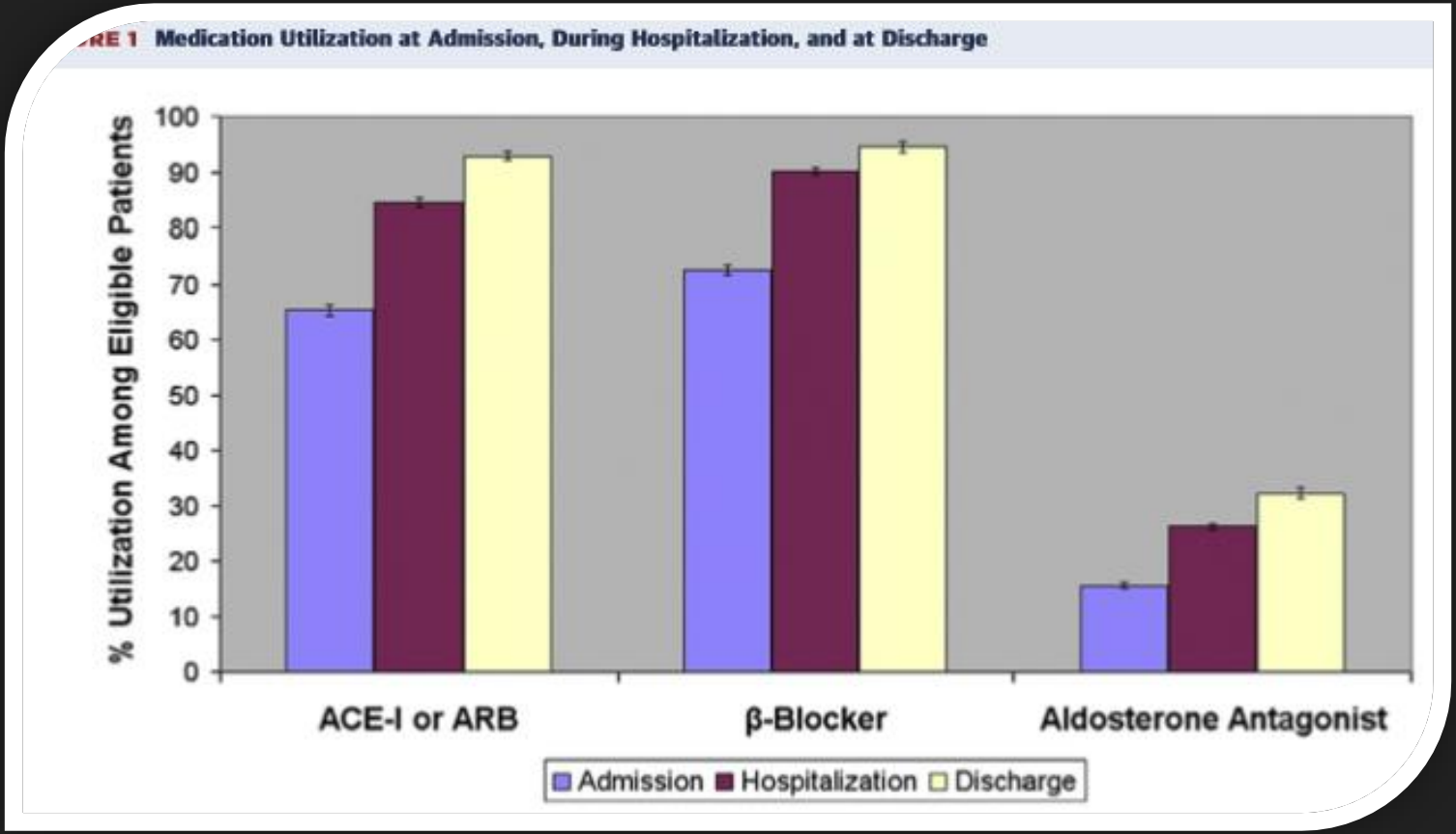
- **The combination of RASi and BB** was associated with an even lower risk of death than RASi or BB alone.



E Gayat et al Eur Heart Failure J 2018

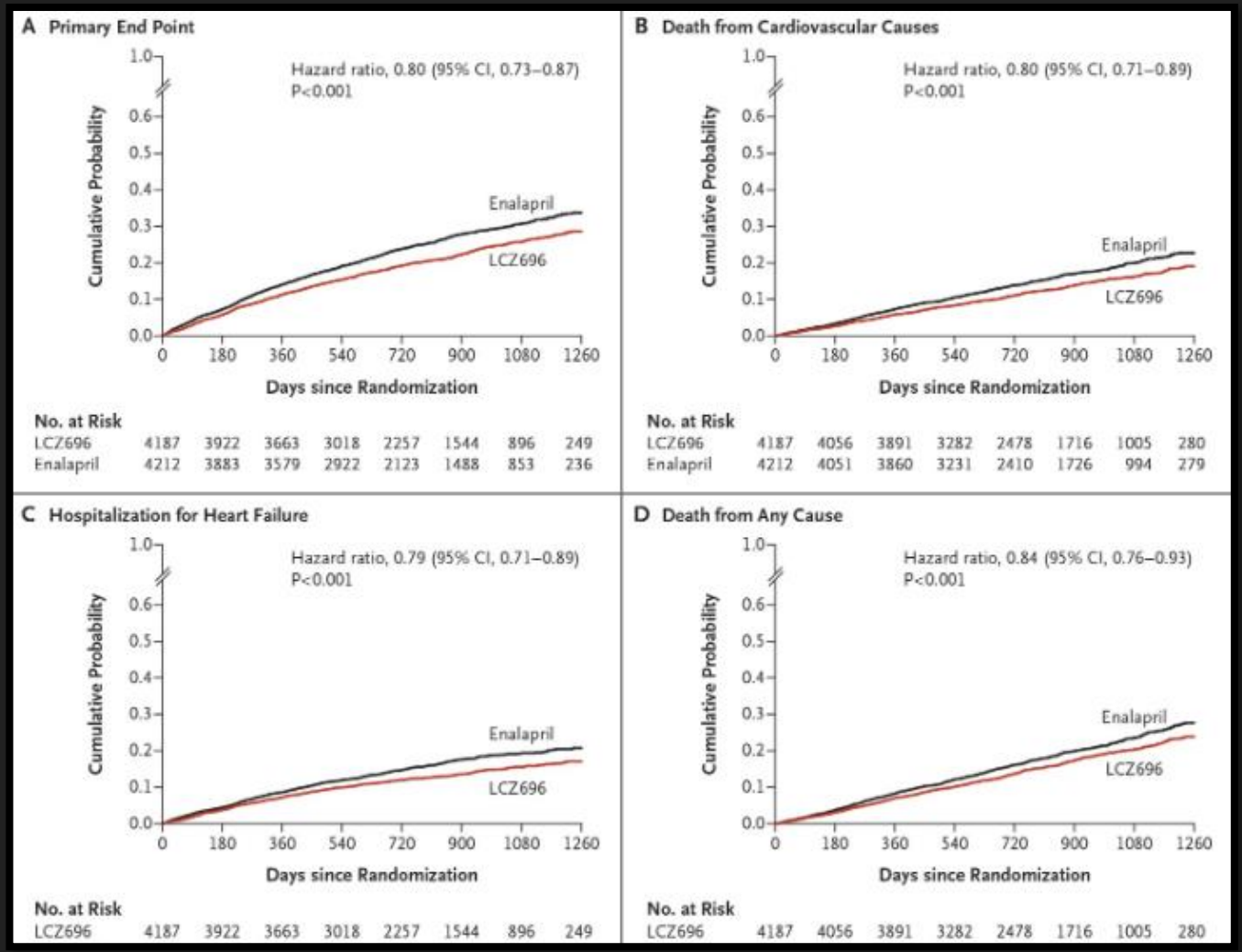
Medication Utilization at Admission, During Hospitalization, and at Discharge:

Analysis from the Get With the Guidelines Heart Failure Registry



Krantz et al Am J Cardiol 2011

Sacubitril/Valsartan: a new era in HFrEF Therapy

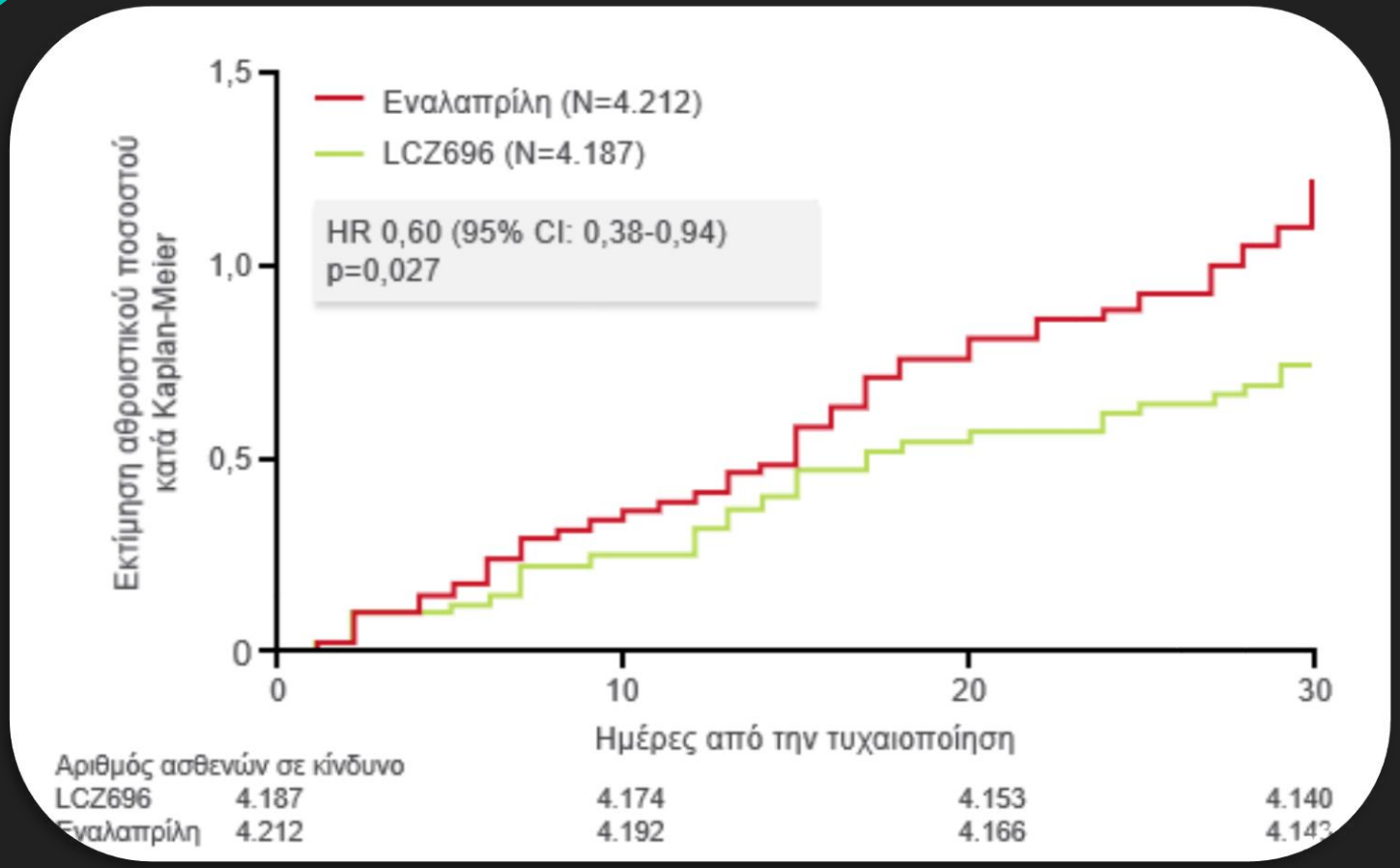


But:

1. Patients who were eligible for inclusion in the PARADIGM-HF trial were ambulatory outpatients who had received an ACE inhibitor or ARB for a minimum of 4 weeks.
2. The trial had sequential run-in periods during which all patients received high-dose enalapril and sacubitril–valsartan before they underwent randomization.
3. Patients with acute decompensated heart failure, which was defined by the presence of signs and symptoms that may lead to the use of intravenous therapy, were excluded from the trial.

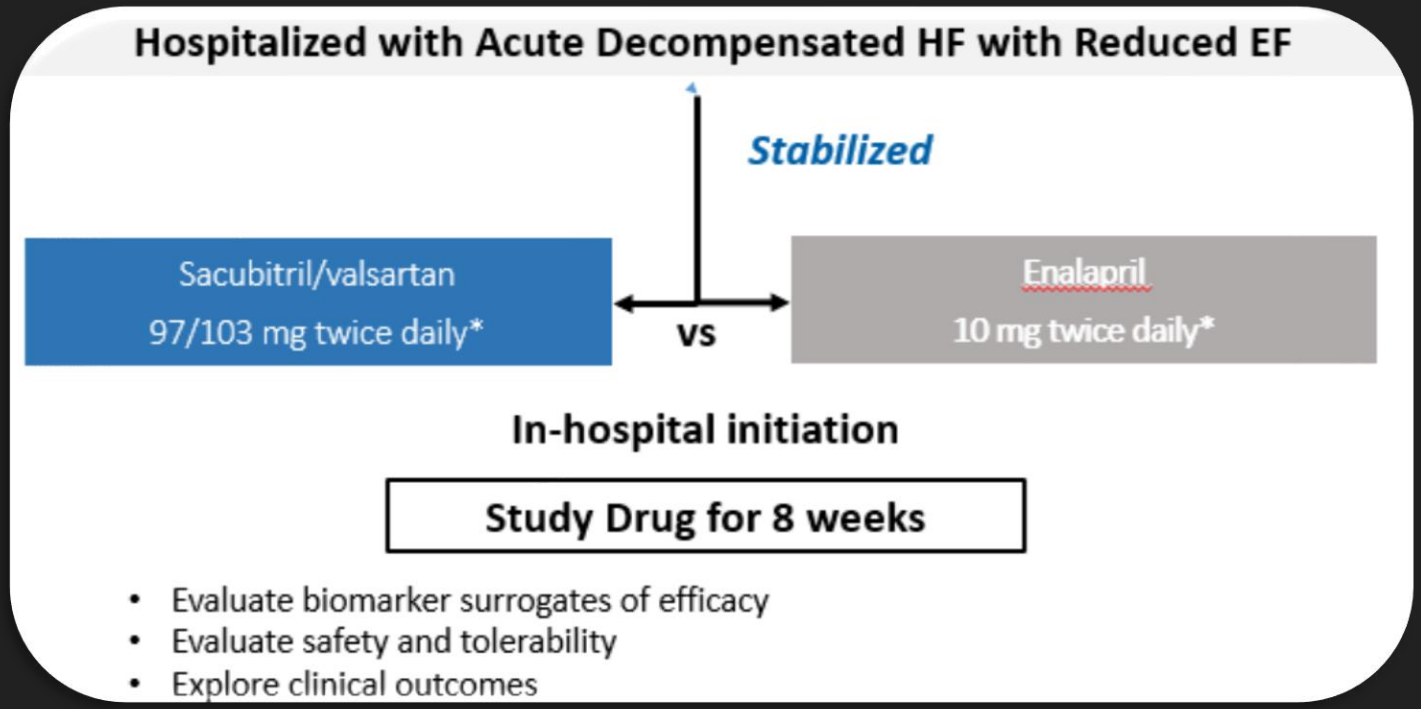
JV. McMurray NEJM 2014

Reduction of Hospitalization with LCZ696 the first 30 days after Randomization



JV. McMurray NEJM 2014

Pioneer HF: Sacubitril/Valsartan in AHF



Velazquez EJ et al. Late Breaker AHA 2018. Chicago, IL, USA November 10-12, 2018.

881 HF patients with:

- reduced ejection fraction (<40%)
- elevated NT-proBNP concentrations
- with a primary diagnosis of acute decompensated HF.

Inclusion criteria:

- all patients to be stabilized before randomization (a maintained systolic blood pressure >100 mm Hg and no increase in the use of intravenous diuretics/no use of intravenous vasodilators in the preceding 6 hours, no use of intravenous inotropes during the preceding 24 hours).
- No less than 24 hours and up to 10 days after initial presentation for AHF

EJ. Velazquez et al, N Engl J Med 2018

Patients Characteristics

Table 1. Characteristics of the Patients at Baseline.*

Variable	Sacubitril–Valsartan (N=440)	Enalapril (N=441)
Age — yr		
Median	61	63
Interquartile range	51–71	54–72
Female sex — no. (%)	113 (25.7)	133 (30.2)
Race — no. (%)†		
Black	158 (35.9)	158 (35.8)
White	261 (59.3)	254 (57.6)
Body-mass index‡		
Median	30.5	30.0
Interquartile range	25.9–37.1	25.8–36.3
Previous heart failure — no. (%)	298 (67.7)	278 (63.0)
Previous use of medication — no. (%)		
ACE inhibitor or ARB	208 (47.3)	214 (48.5)
Beta-blocker	262 (59.5)	263 (59.6)
MRA	48 (10.9)	40 (9.1)
Loop diuretic	262 (59.5)	240 (54.4)
Hydralazine	30 (6.8)	33 (7.5)
Nitrate	43 (9.8)	40 (9.1)
Digoxin	41 (9.3)	35 (7.9)
NYHA class — no. (%)		
I	4 (0.9)	5 (1.1)
II	100 (22.7)	122 (27.7)
III	283 (64.3)	269 (61.0)
IV	39 (8.9)	36 (8.2)
Not assessed	14 (3.2)	9 (2.0)
Systolic blood pressure — mm Hg§		
Median	118	118
Interquartile range	110–133	109–132
Pulse — beats per min§		
Median	81	80
Interquartile range	72–92	72–91
Left ventricular ejection fraction — %¶		
Median	24	25
Interquartile range	18–30	20–30
NT-proBNP at screening — pg/ml¶		
Median	4821	4710
Interquartile range	3109–8767	2966–8280
NT-proBNP at randomization — pg/ml§		
Median	2883	2536
Interquartile range	1610–5403	1363–4917
Serum creatinine — mg/dl§		
Median	1.28	1.27
Interquartile range	1.07–1.51	1.05–1.50
Estimated GFR — ml/min/1.73 m^2§		
Median	58.4	58.9
Interquartile range	47.5–71.5	47.4–70.9
Serum potassium — mmol per liter§		
Median	4.20	4.25
Interquartile range	4.00–4.50	3.90–4.60

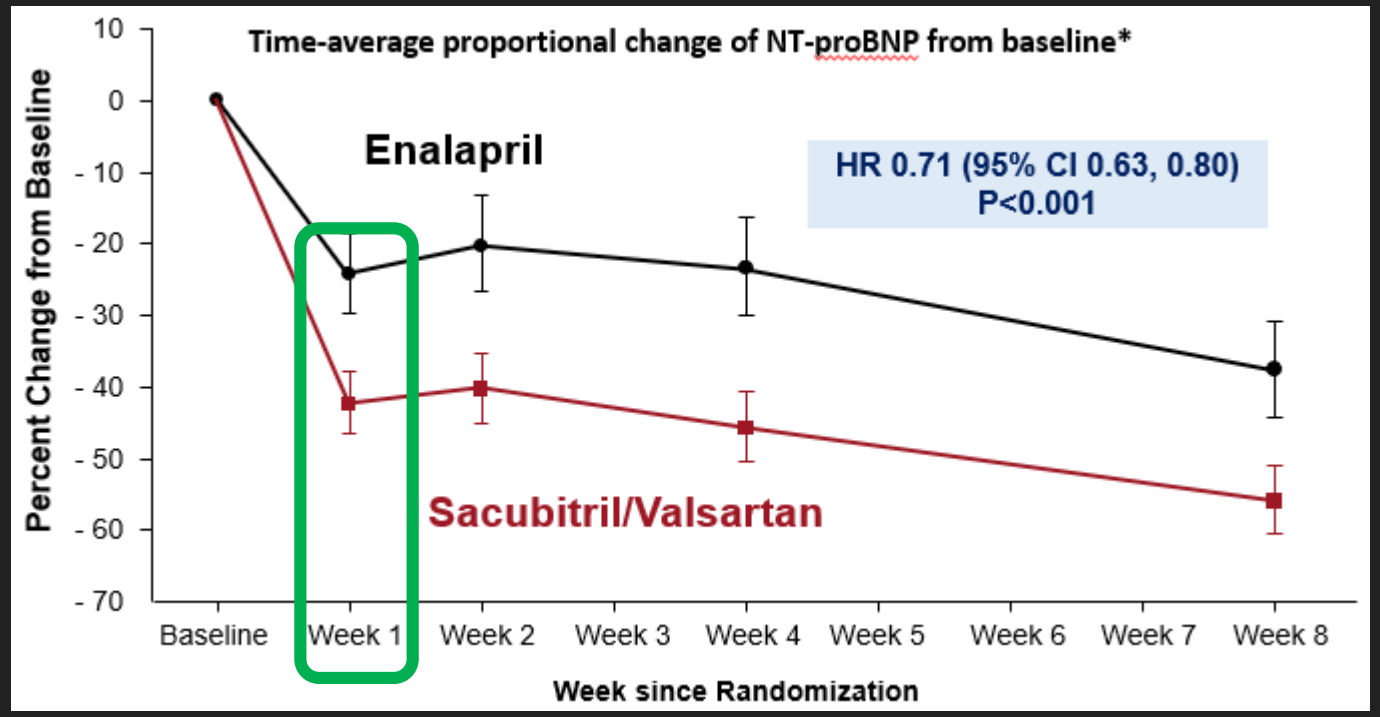
33% Denovo HF

>50% Naïve patient

EJ. Velazquez et al, N Engl J Med 2018

Pioneer HF: Primary Endpoint

NT- proBNP : Enalapril Vs Sacubitril/Valsartan

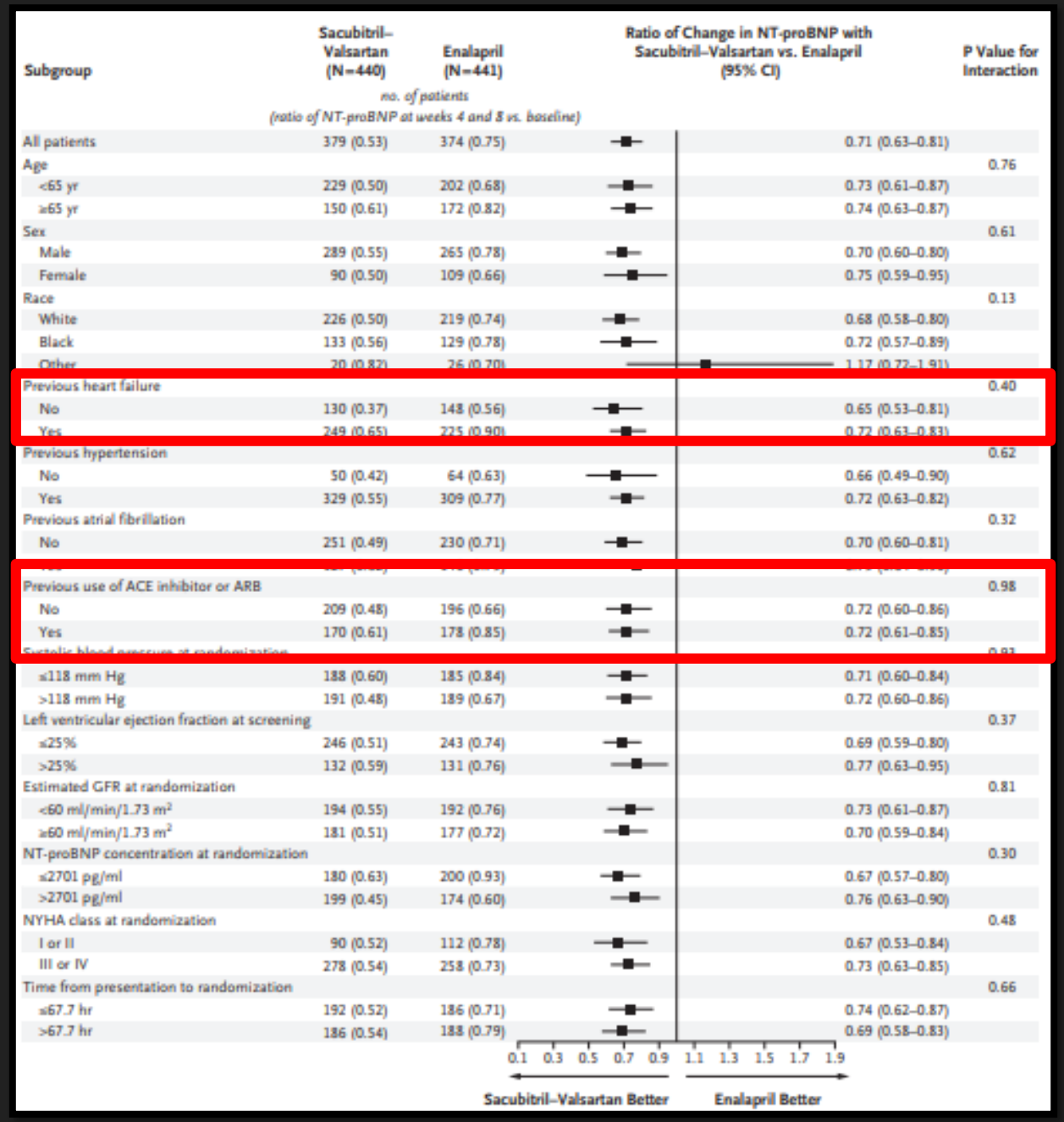


There was a 29% reduction in the primary endpoint—defined as the proportional change in NT-proBNP from baseline to the mean of concentrations at weeks 4 and 8—among patients treated with sacubitril/valsartan (n = 440) compared with enalapril (n = 441).

EJ. Velazquez et al, N Engl J Med 2018

Subgroup Analysis

- Results of analyses of subgroups that were defined according to demographic and clinical characteristics of interest reflected a consistently beneficial effect of sacubitril–valsartan, as compared with enalapril, with regard to the primary efficacy outcome.
- Subgroup analyses showed no significant differences between the two treatments with regard to the key safety outcomes.

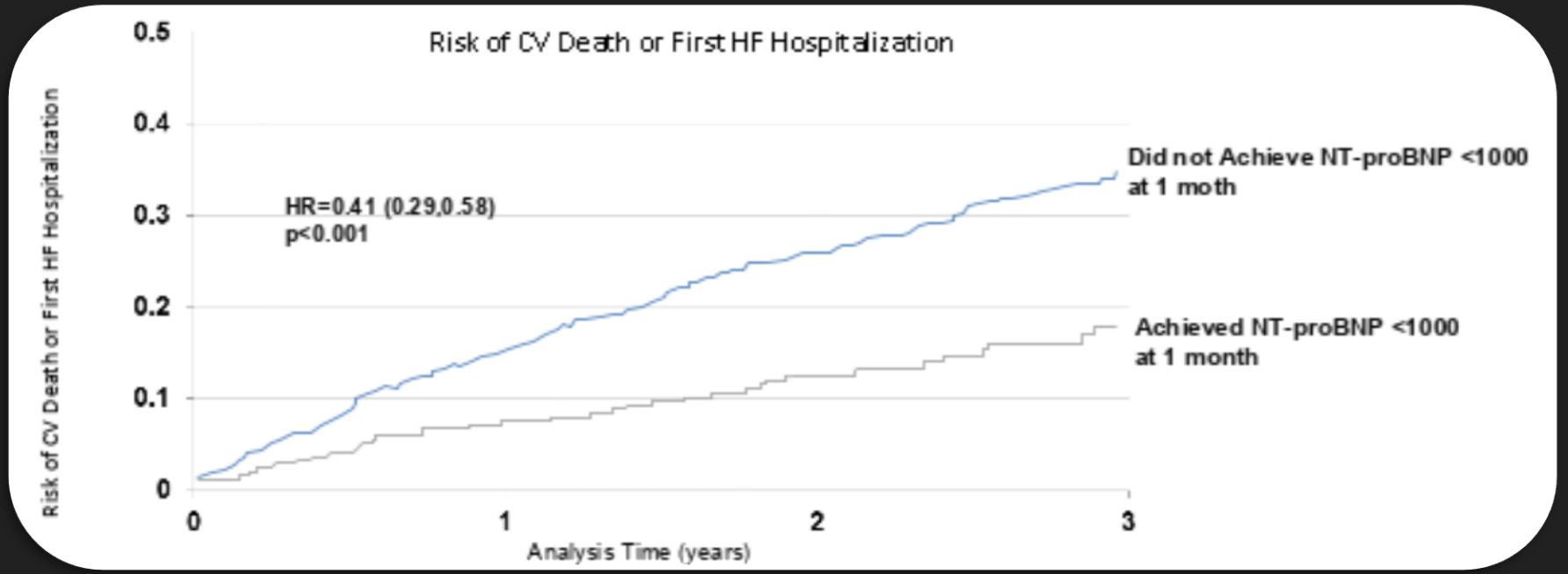


Subgroup	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Ratio of Change in NT-proBNP with Sacubitril–Valsartan vs. Enalapril (95% CI)	P Value for Interaction
	no. of patients (ratio of NT-proBNP at weeks 4 and 8 vs. baseline)			
All patients	379 (0.53)	374 (0.75)	0.71 (0.63–0.81)	
Age				0.76
<65 yr	229 (0.50)	202 (0.68)	0.73 (0.61–0.87)	
≥65 yr	150 (0.61)	172 (0.82)	0.74 (0.63–0.87)	
Sex				0.61
Male	289 (0.55)	265 (0.78)	0.70 (0.60–0.80)	
Female	90 (0.50)	109 (0.66)	0.75 (0.59–0.95)	
Race				0.13
White	226 (0.50)	219 (0.74)	0.68 (0.58–0.80)	
Black	133 (0.56)	129 (0.78)	0.72 (0.57–0.89)	
Other	20 (0.82)	26 (0.70)	1.17 (0.72–1.91)	
Previous heart failure				0.40
No	130 (0.37)	148 (0.56)	0.65 (0.53–0.81)	
Yes	249 (0.65)	225 (0.90)	0.72 (0.63–0.83)	
Previous hypertension				0.62
No	50 (0.42)	64 (0.63)	0.66 (0.49–0.90)	
Yes	329 (0.55)	309 (0.77)	0.72 (0.63–0.82)	
Previous atrial fibrillation				0.32
No	251 (0.49)	230 (0.71)	0.70 (0.60–0.81)	
Previous use of ACE inhibitor or ARB				0.98
No	209 (0.48)	196 (0.66)	0.72 (0.60–0.86)	
Yes	170 (0.61)	178 (0.85)	0.72 (0.61–0.85)	
Systolic blood pressure at randomization				0.93
≤118 mm Hg	188 (0.60)	185 (0.84)	0.71 (0.60–0.84)	
>118 mm Hg	191 (0.48)	189 (0.67)	0.72 (0.60–0.86)	
Left ventricular ejection fraction at screening				0.37
≤25%	246 (0.51)	243 (0.74)	0.69 (0.59–0.80)	
>25%	132 (0.59)	131 (0.76)	0.77 (0.63–0.95)	
Estimated GFR at randomization				0.81
<60 ml/min/1.73 m^2	194 (0.55)	192 (0.76)	0.73 (0.61–0.87)	
≥60 ml/min/1.73 m^2	181 (0.51)	177 (0.72)	0.70 (0.59–0.84)	
NT-proBNP concentration at randomization				0.30
≤2701 pg/ml	180 (0.63)	200 (0.93)	0.67 (0.57–0.80)	
>2701 pg/ml	199 (0.45)	174 (0.60)	0.76 (0.63–0.90)	
NYHA class at randomization				0.48
I or II	90 (0.52)	112 (0.78)	0.67 (0.53–0.84)	
III or IV	278 (0.54)	258 (0.73)	0.73 (0.63–0.85)	
Time from presentation to randomization				0.66
≤67.7 hr	192 (0.52)	186 (0.71)	0.74 (0.62–0.87)	
>67.7 hr	186 (0.54)	188 (0.79)	0.69 (0.58–0.83)	

EJ. Velazquez et al, N Engl J Med 2018

Relationship of NT-proBNP and Cardiovascular Events

Reduction in NT-proBNP Following HF Treatment is Associated with Reduction in CV Death and HF Hospitalization



Achieving levels of NT-proBNP <1000 as early as 1 month after randomization to HF therapy was associated with a significant reduction in risk of CV death or first HF hospitalization

Zile MR, et al. J Am Coll Cardiol. 2016

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)

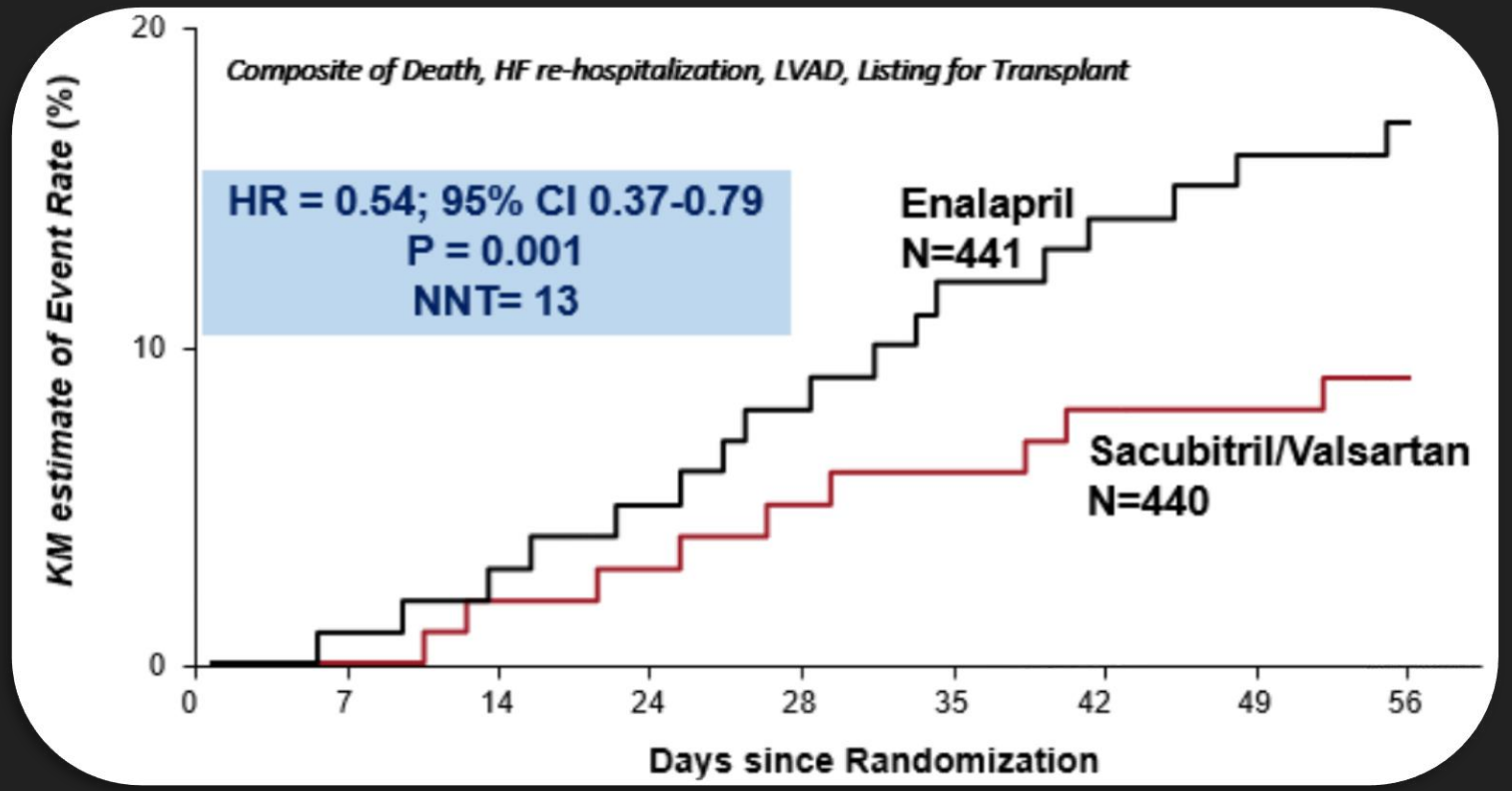
- The sacubitril/valsartan was well tolerated,
- with comparable rates of worsening renal function, hyperkalemia, symptomatic hypotension, and angioedema when compared with enalapril alone.

EJ. Velazquez et al, N Engl J Med 2018

Clinical Endpoints

Regarding the clinical endpoint, there was a:

- **46% reduction in death, HF rehospitalization, need for a left ventricular assist device, or transplant,**
- **a benefit that was driven by reductions in HF hospitalizations.**



EJ. Velazquez et al, N Engl J Med 2018

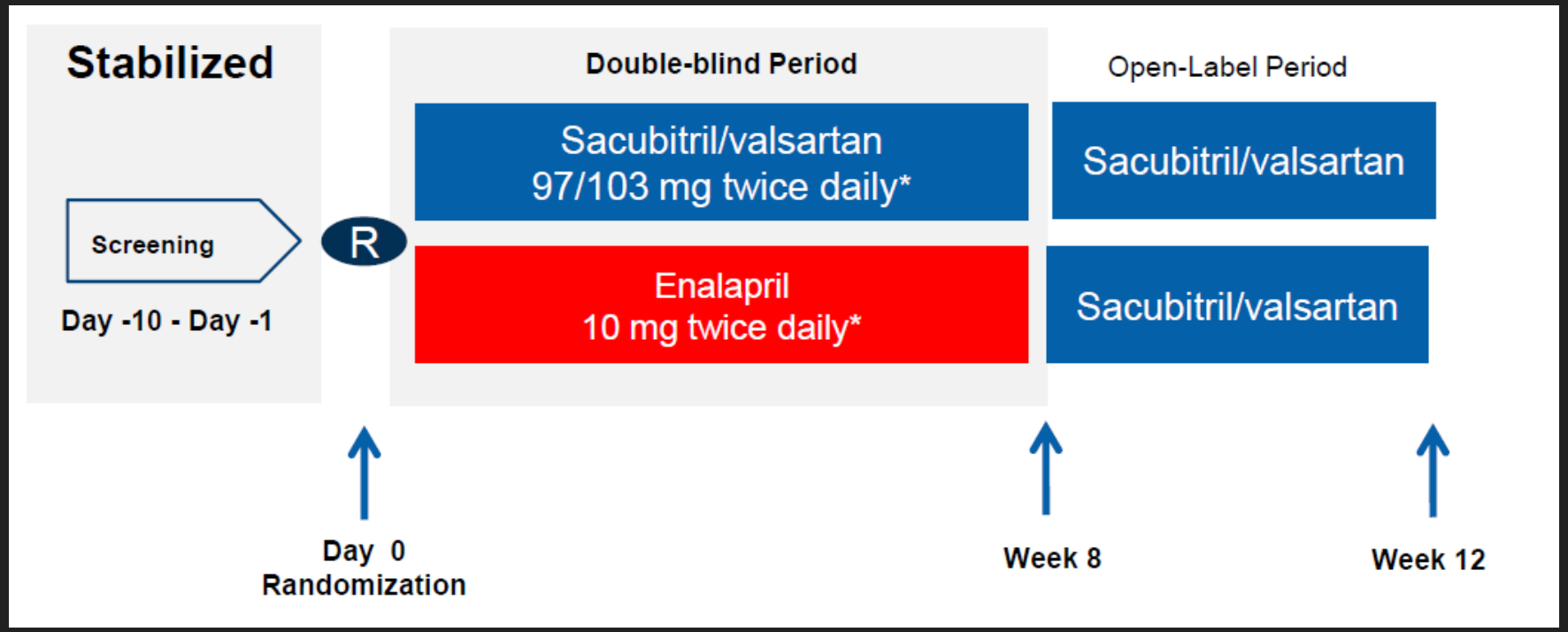
Secondary Biomarkers

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
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)

Sac/Val led to a reduction in the concentration of high-sensitivity cardiac troponin T, which is a biomarker of myocardial injury associated with abnormalities of cardiac structure and function and with a worse prognosis among patients with heart failure.

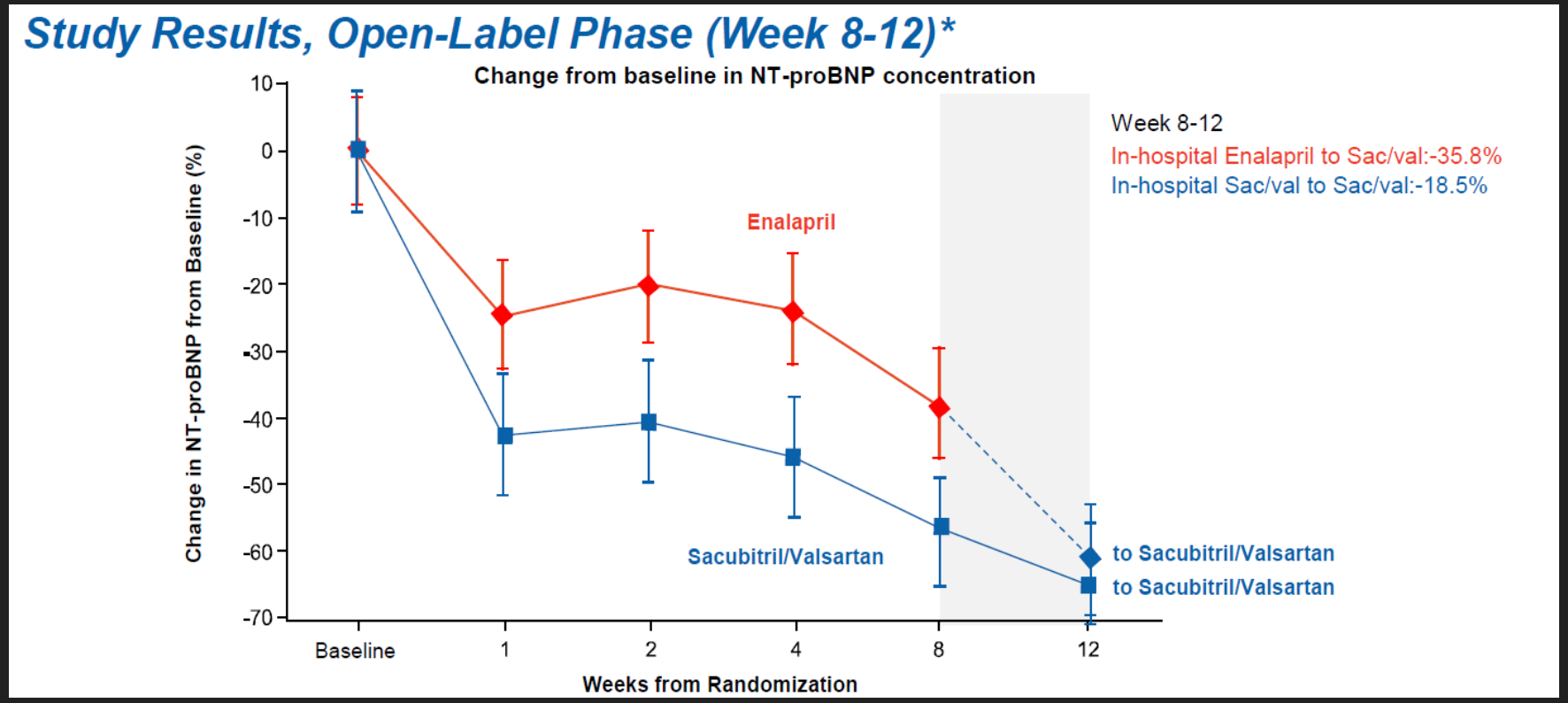
EJ. Velazquez et al, N Engl J Med 2018

PIONEER HF – Open label extension results (week 8 to week12)



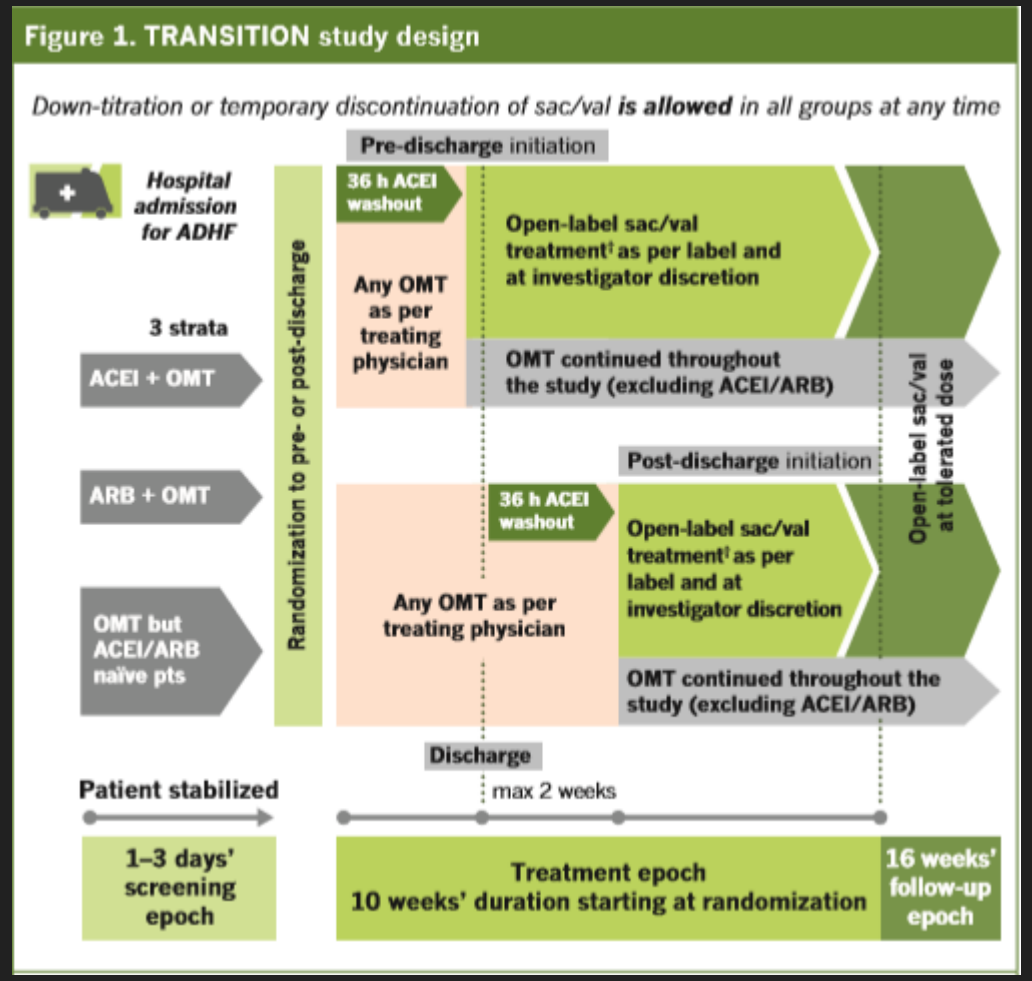
DeVore AD et al ACC 2019. March 2019

PIONEER – HF / Open label extension results / week 12



DeVore AD et al ACC 2019. March 2019

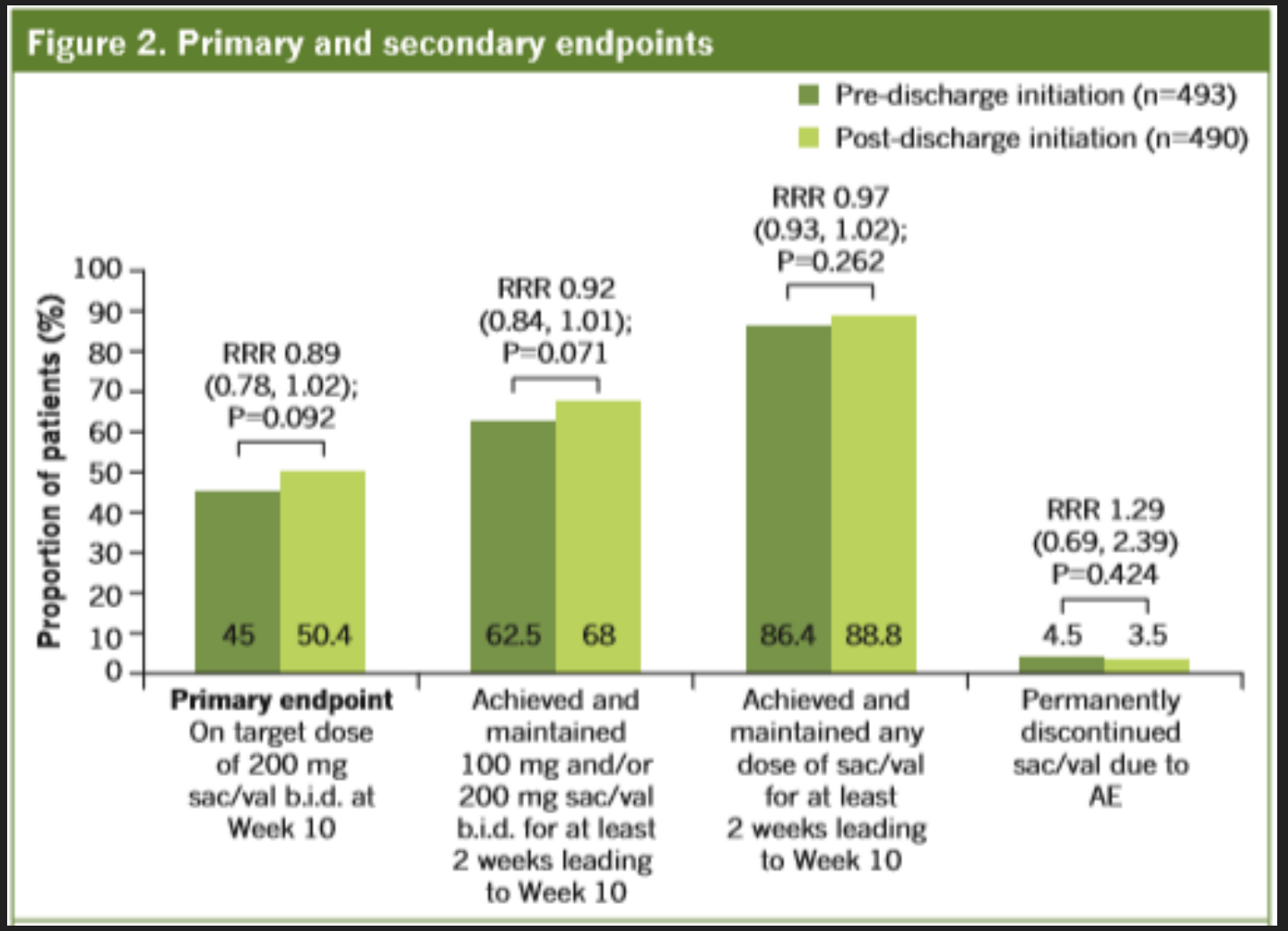
TRANSITION trial: a randomized trial of pre-discharge vs. post-discharge initiation of sacubitril/valsartan



The TRANSITION study aims to provide evidence that it **is feasible and safe to initiate sacubitril/valsartan early *after hemodynamic stabilization* following an acute decompensation event**, and in combination with guideline-recommended optimization of other HFrEF treatments **before the patient is discharged**.

M Senni et al ESC Congress 2018

TRANSITION: Primary and Secondary Endpoints



Wachter R. et al. ESC 2018, Aug 25-29; Munich

TITRATIOSN- RESULTS

Table 2. Most common adverse events (≥4% of patients in any group), during the 10-week treatment epoch regardless of study drug relationship

Preferred term	Pre-discharge N=497 n (%)	Post-discharge N=496 n (%)	P-value*
Hyperkalemia	55 (11.1)	56 (11.3)	0.9201
Hypotension	61 (12.3)	45 (9.1)	0.1229
Cardiac failure	34 (6.8)	42 (8.5)	0.3426
Dizziness	28 (5.6)	21 (4.2)	0.3795
Peripheral edema	17 (3.4)	24 (4.8)	0.2696
Renal impairment	25 (5.0)	15 (3.0)	0.1455
Diarrhea	12 (2.4)	23 (4.6)	0.0604
Urinary tract infection	20 (4.0)	15 (3.0)	0.4918

Figure 3. Most common AEs (≥2 events in any treatment group) leading to permanent discontinuations* during the 10-week treatment period

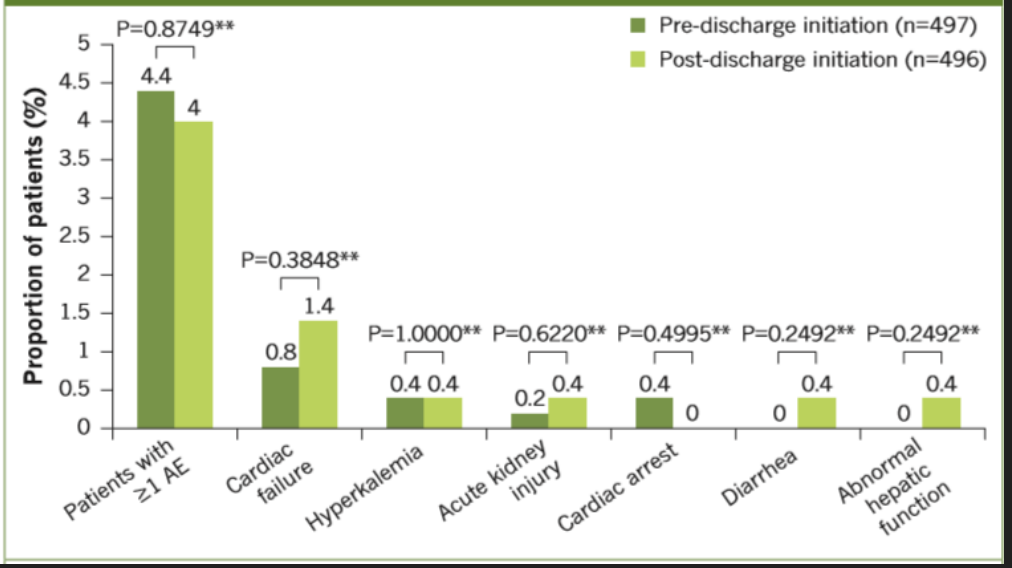
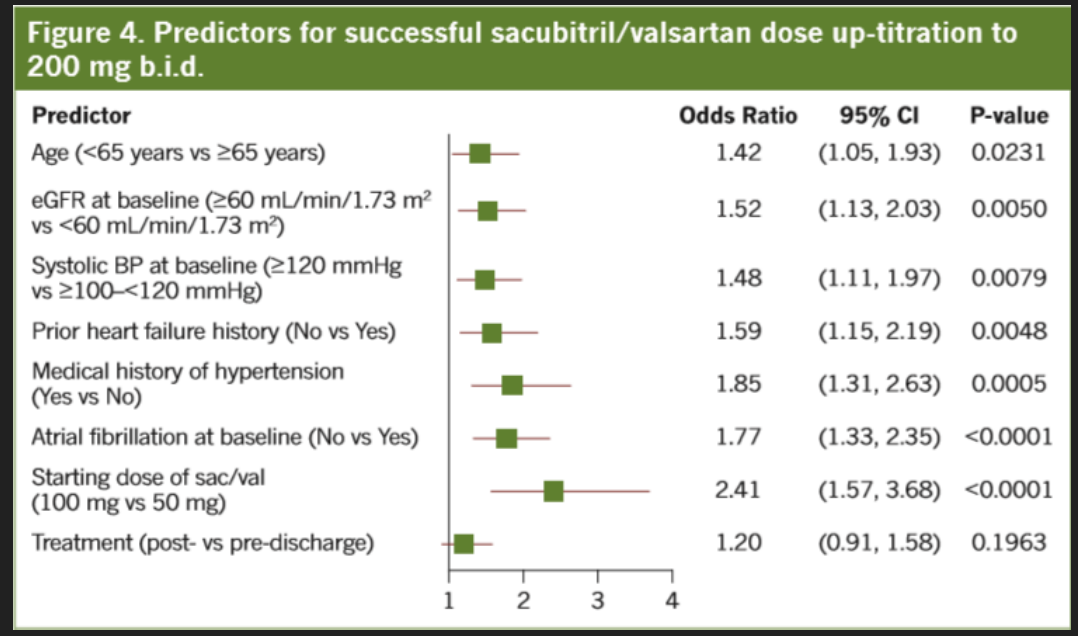


Figure 4. Predictors for successful sacubitril/valsartan dose up-titration to 200 mg b.i.d.

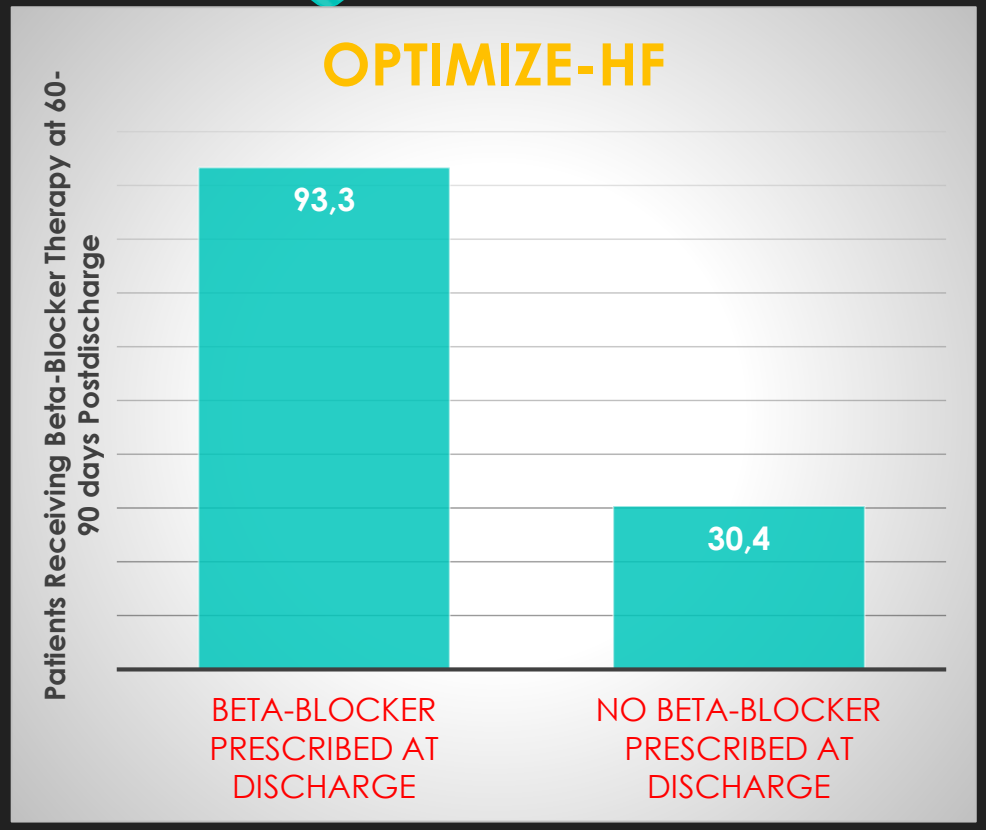


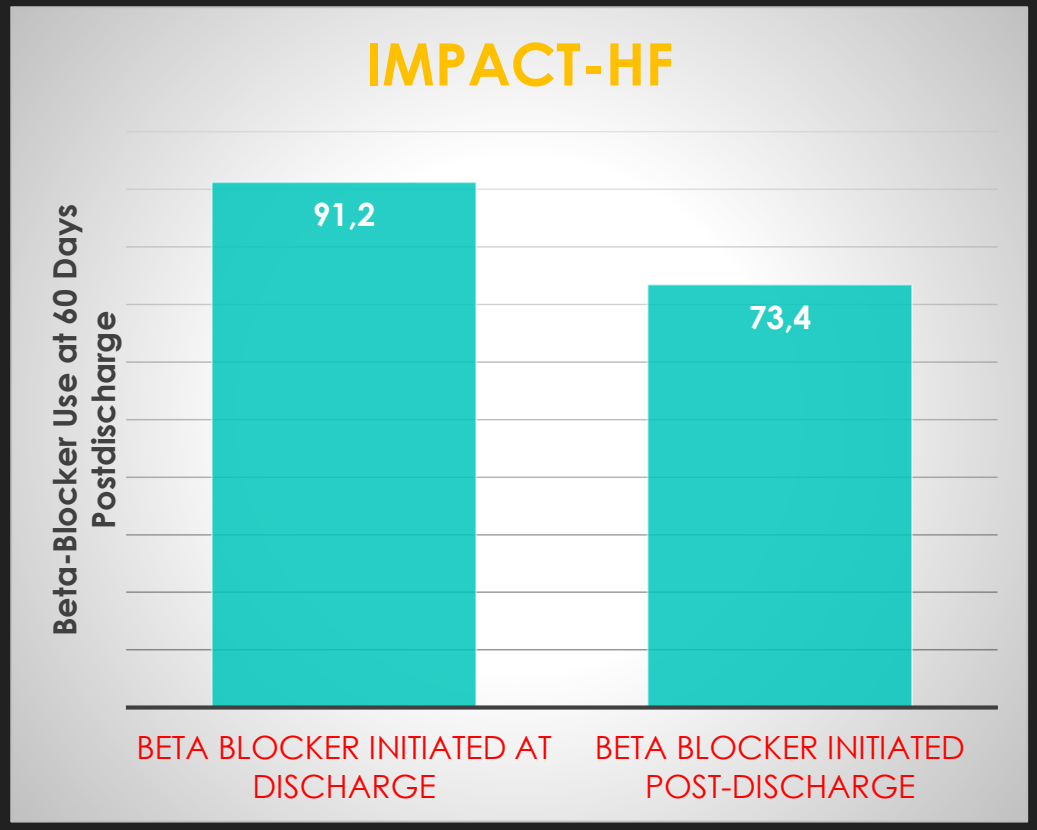
Conclusion

- About half of the HFrEF patients stabilized after an acute HF decompensation event achieved the recommended target dose of 200 mg sacubitril/valsartan b.i.d. within 10 weeks
- The incidence of adverse events and discontinuations of sacubitril/valsartan due to adverse events was similar in pre- versus post-discharge groups
- Patients with fewer comorbidities, higher systolic blood pressure or newly diagnosed HF were more likely to tolerate the up-titration of sacubitril/valsartan to target dose within 10 weeks
- Initiation of sacubitril/valsartan in a wide range of HFrEF patients, in-hospital or shortly after discharge, was feasible and overall well tolerated

Wachter R. et al. ESC 2018, Aug 25-29; Munich

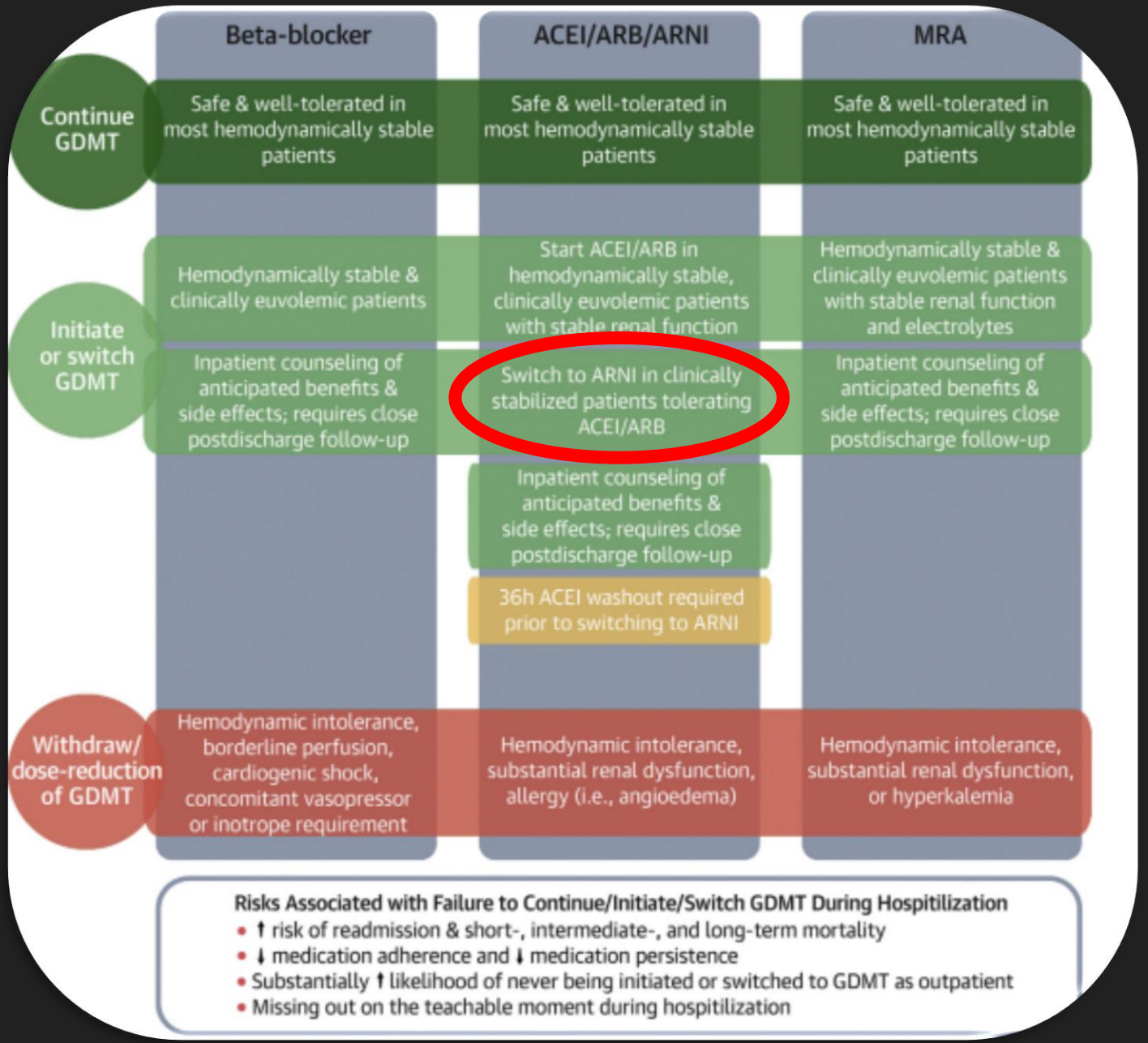
Post-discharge Treatment Compliance





Patients Leaving the Hospital on GDMT May Have Improved Treatment Adherence at 60 and 90 days

Fonarow GC et al. Am Heart J. 2007 & Gatis WA et al. JACC 2004



AA. Bhagat JACC Heart Failure 2018

CONCLUSIONS

- There is no better time to initiate and intensify lifesaving chronic therapy for patients than when they are in the hospital.
- The problem was that sacubitril/valsartan had been studied in PARADIGM-HF, where initiation was done in a very table population.
- In PIONEER-HF trial the sacubitril/valsartan was well tolerated before discharge with 29% reduction in NT-proBNP and 46% reduction in death, HF rehospitalization need for a left ventricular assist device, or transplant in pts receiving Sac/Val Vs Enalapril.
- Caution should be used when initiating ACEI/ARB/ARNI in hypovolemic patients (such as patients who are "overdiuresed") because renin-angiotensin-aldosterone system activation is high and ACEI/ARB/ARNI may cause excessive blood pressure lowering.
- Early post-discharge follow-up with close monitoring of hemodynamics, renal function, electrolytes, and symptoms in the weeks after initiation of these therapies is required, especially in treatment-naïve patients