The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Rewriting the Heart's Story: Novel Neurohormonal Modulation and Cardiac Remodelling

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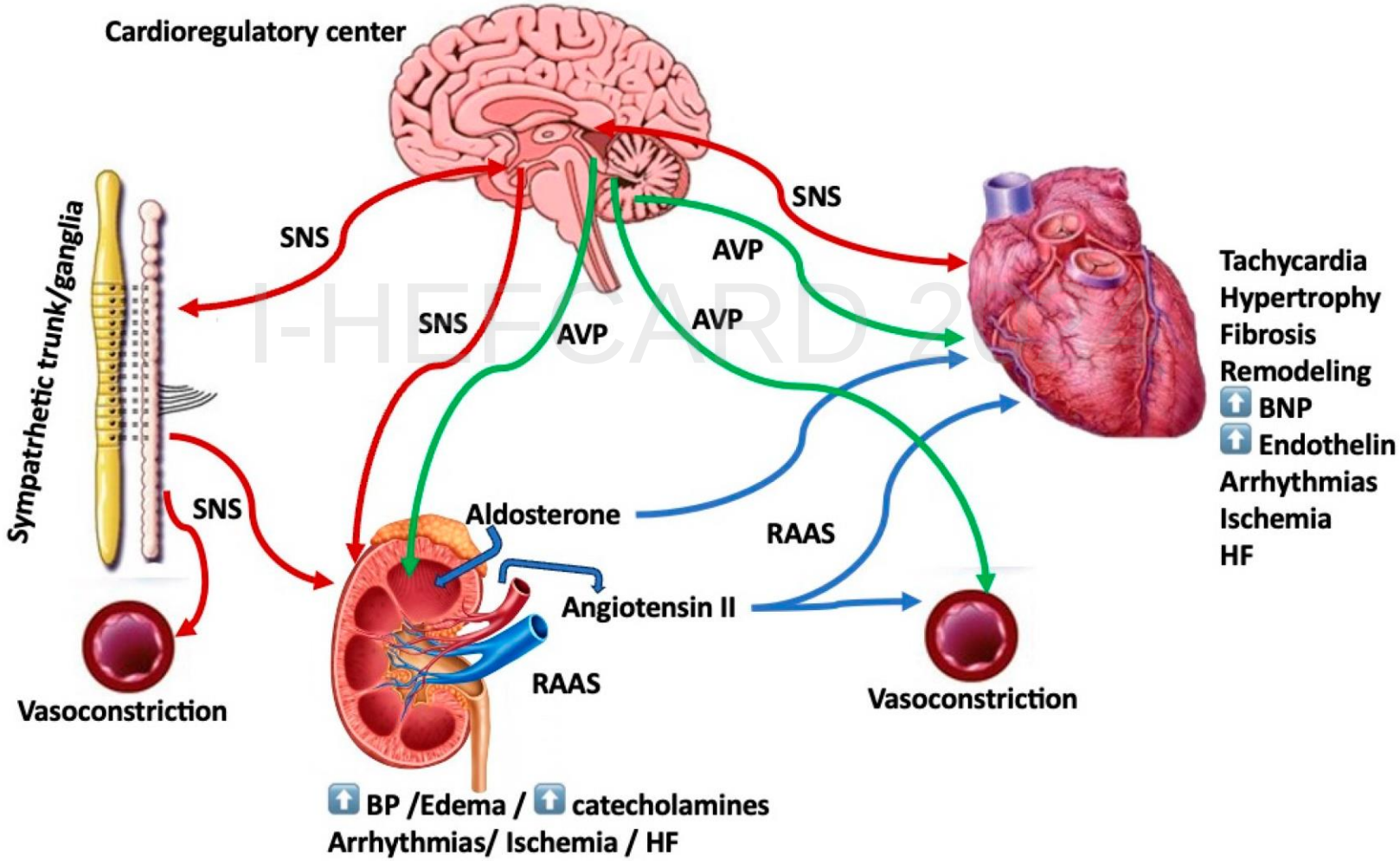
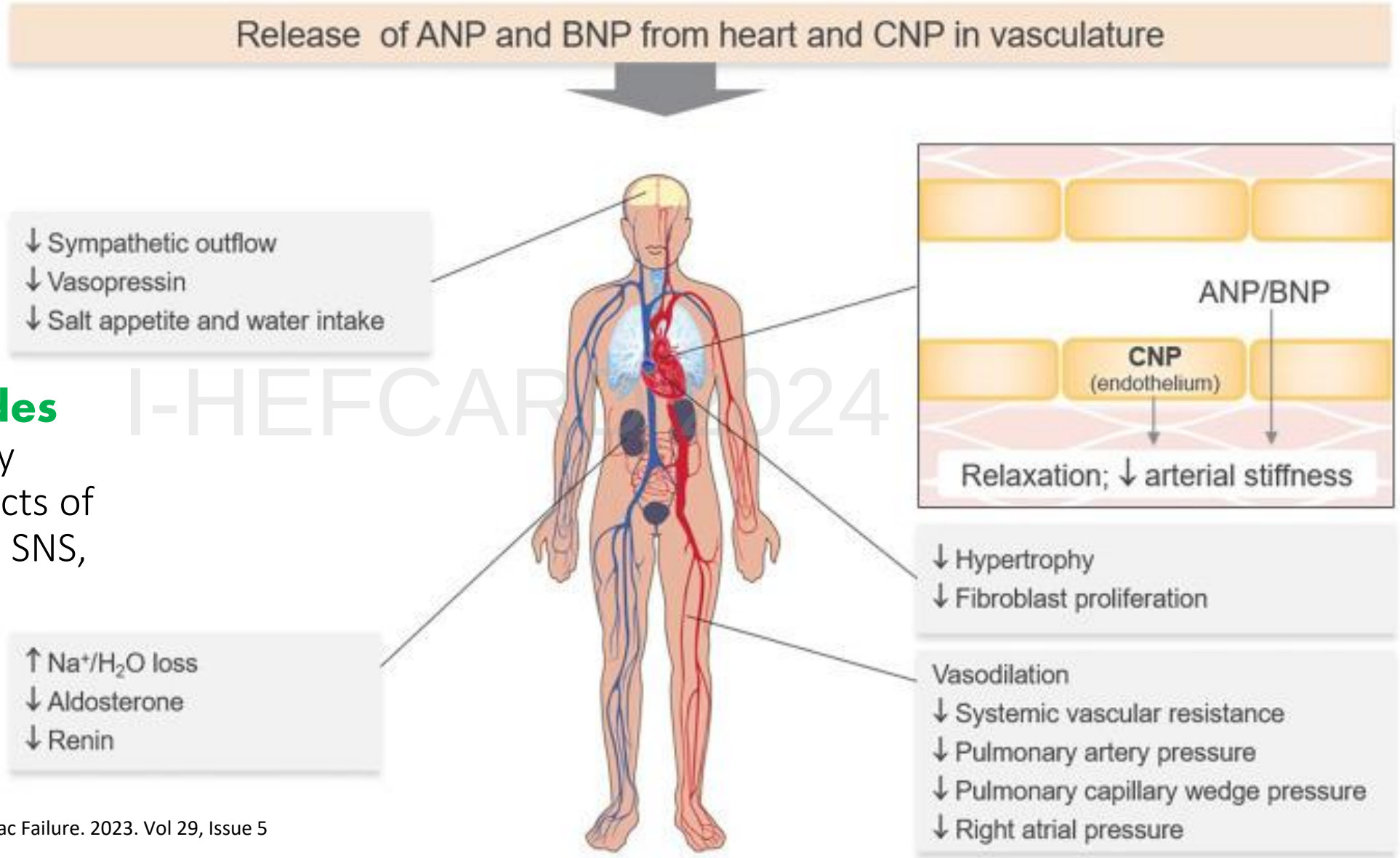
Neurohormonal activation in Heart Failure



Manolis AA, et al. Neurohormonal Activation in Heart Failure. *Int J Mol Sci.* 2023, 24(20), 15472

Natriuretic Peptides

plays key roles in HF by counteracting the effects of overstimulation of the SNS, RAA and AVP



Tsutsui H, et al. Journal of Cardiac Failure. 2023. Vol 29, Issue 5

NP produced in response to stress to fight tissue damage

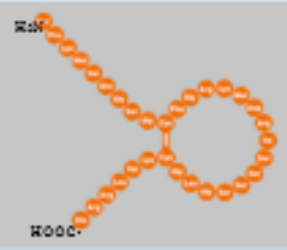
Atrial natriuretic peptide (ANP)

- Expressed in the atria
- Measurable in plasma

$t_{½}$ in circulation = ~2 mins

Effects:
- Vasorelaxation
- ↑ Diuresis/natriuresis
- ↓ Proliferation
- ↓ Hypertrophy
- ↓ Fibrosis
- ↓ RAAS activation (including aldosterone)
- ↓ Sympathetic tone
- ↓ Cardiac preload
- ↑ Venous capacitance
- ↑ RBF and GFR
- Myocardial relaxation
- Lipid mobilization, metabolic effects

B-type natriuretic peptide (BNP)



- Expressed in atrial and ventricular tissue
- Measurable in plasma

$t_{½}$ in circulation = ~20 mins

Effects:
- Vasorelaxation
- ↑ Diuresis/natriuresis
- ↓ RAAS activation (including aldosterone)
- ↓ Sympathetic tone
- ↑ RBF and GFR
- Myocardial relaxation
- Lipid mobilization, metabolic effects

C-type natriuretic peptide (CNP)

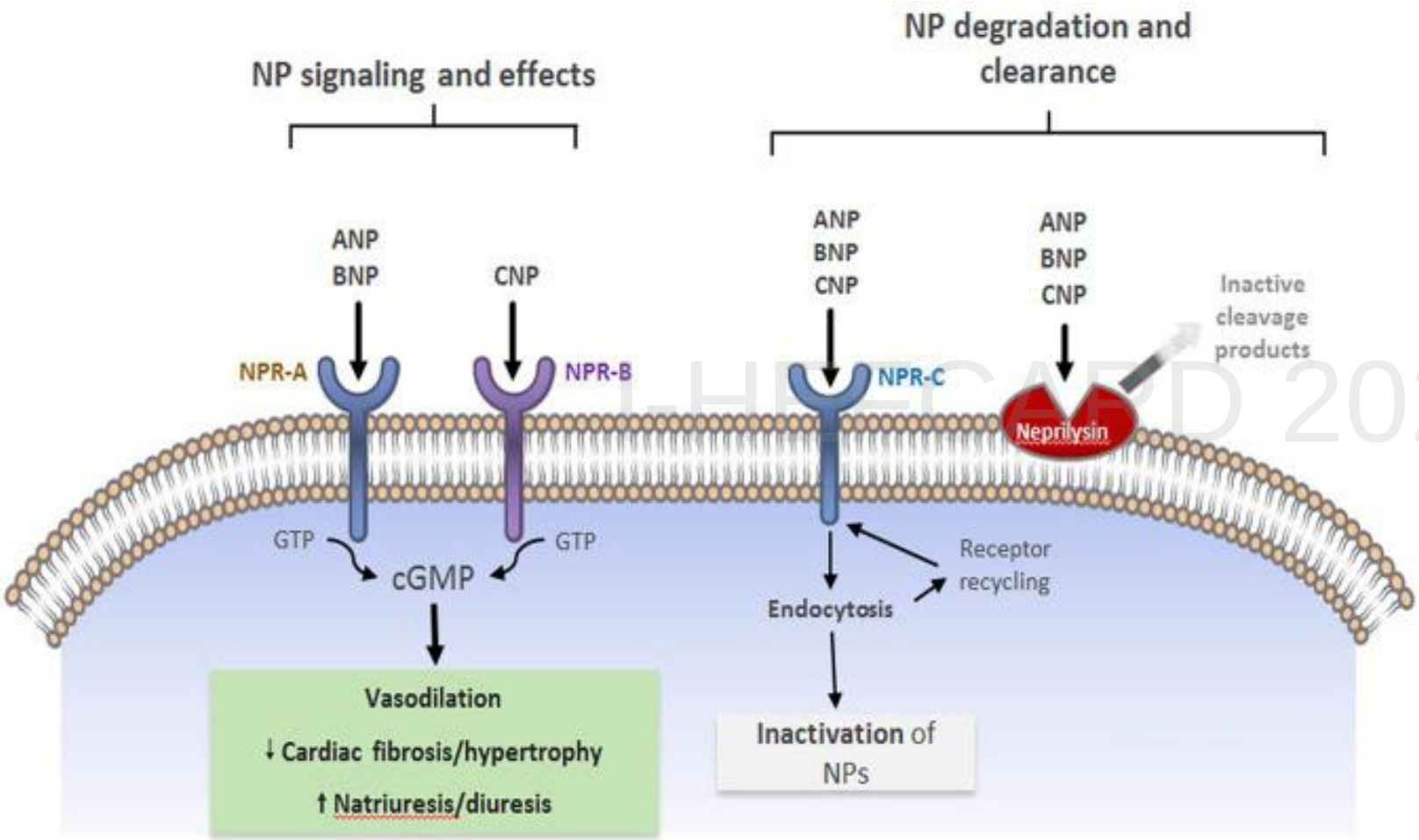
- Expressed in vascular endothelial cells and central nervous system

$t_{½}$ in circulation = ~3 mins

Effects:
- Vasorelaxation
- More potent dilation of veins than ANP and BNP
- Bone growth regulation
- ↓ Proliferation
- ↓ Hypertrophy
- ↓ Fibrosis
- ↓ Inflammation
- ↓ Thrombosis

ANP = atrial natriuretic peptide;
BNP = B-type natriuretic peptide;
CNP = C-type natriuretic peptide;
GFR = glomerular filtration rate;
RAAS=renin-angiotensin-aldosterone system;
RBF=renal blood flow; t1/2=half-life

Levin et al. N Engl J Med 1998;339;321–8; Gardner et al. Hypertension 2007;49:419–26; Pandey. J Am Soc Hypertens 2008;2:210–16; Von Lueder et al. Pharmacol Ther 2014;144:41–9; Potter. FEBS J 2011;278:1808–17; Lumsden et al. Curr Pharm Des 2010;16:4080–8; Mangiafico et al. Eur Heart J 2013;34:886–93; Kousholt. Dan Med J 2012;59:B4469 Potter et al. Handb Exp Pharmacol 2009;191:341–66



With progressive deterioration of cardiac function, NP lose efficiency by:
- decrease NP availability due to reduced production
- increased removal
- enzymatic degradation through neprilysin

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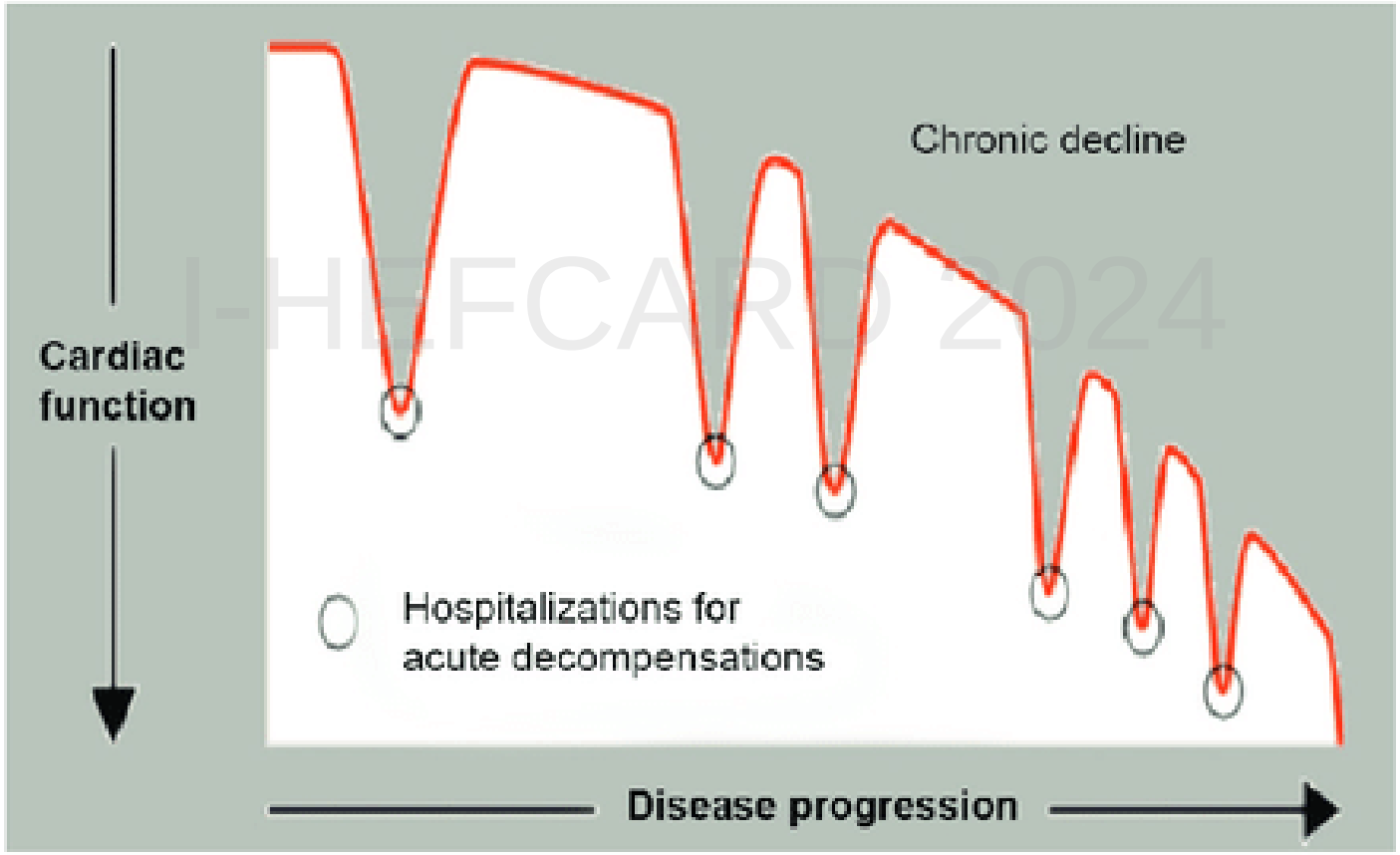
Underlying neurohormonal imbalance results in continued disease progress



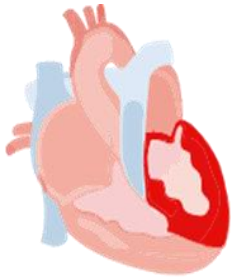
Cardiac Remodeling

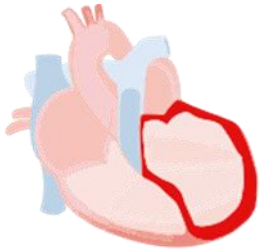
Defined as a cluster of genetic, molecular, cellular and interstitial alterations that are set in place after cardiac load or injury

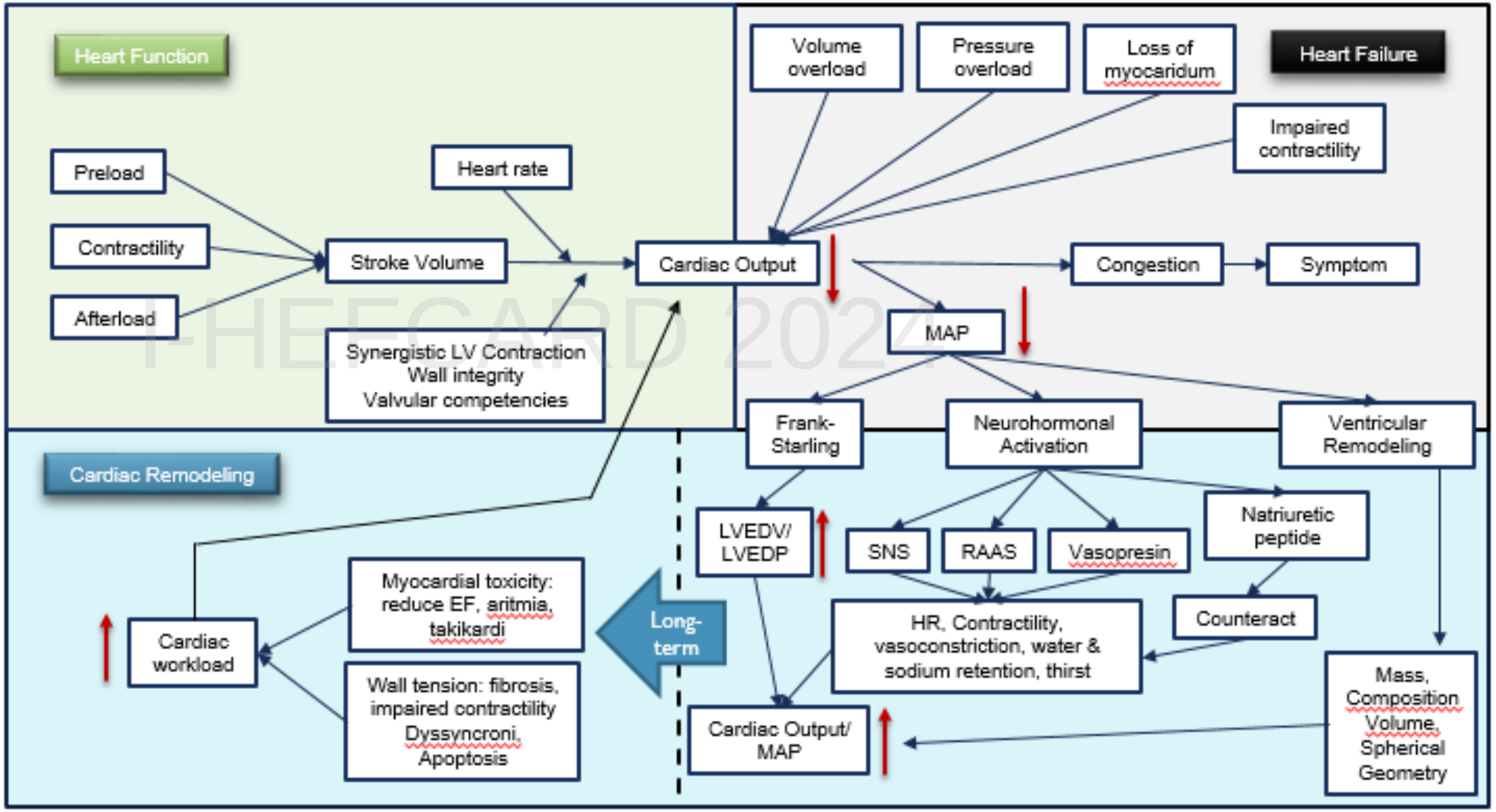
Results in increased heart volume and changes form elliptical to a spherical shape, leading to LV systolic and diastolic dysfunction.

Myocardial remodeling in HF patients is a determinant of the clinical course of HF and confers a poor prognosis; conversely, when reversed it ameliorates CV outcomes

Frank-Sterlink Law on Reverse Cardiac Remodeling

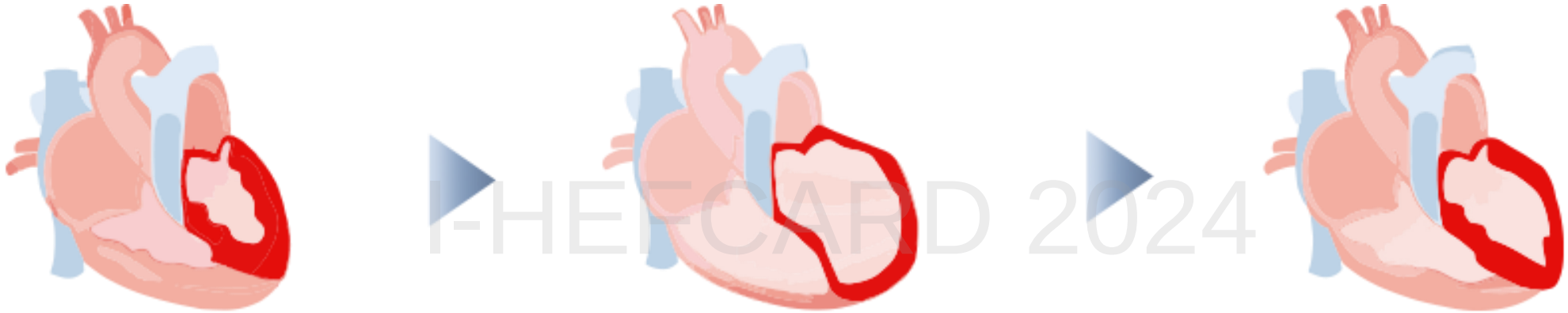






Modified from: Kemp CD, Conte JV. the pathophysiology of heart failure; *Car Path J*, 2012;21:365-371.

Remodeling can involve changes in heart geometry, function, or both, as reflected by a decrease in LVEF and an increase in left ventricular filling volume and pressure



Healthy heart

Remodeled systolic HF heart

- Systolic HF is a clinical syndrome caused by changes in cardiac structure and function
- These changes can include **increased left atrial and ventricular volumes and filling pressure and decreased ejection fraction**

Reverse cardiac remodeling

- Reverse cardiac remodeling mitigates these effects, which may be associated with improved outcomes in systolic HF
- Reverse cardiac remodeling changes can include **decreased left atrial and ventricular volumes and filling pressure and increased ejection fraction**

Cardiac Remodeling Predictor Outcome

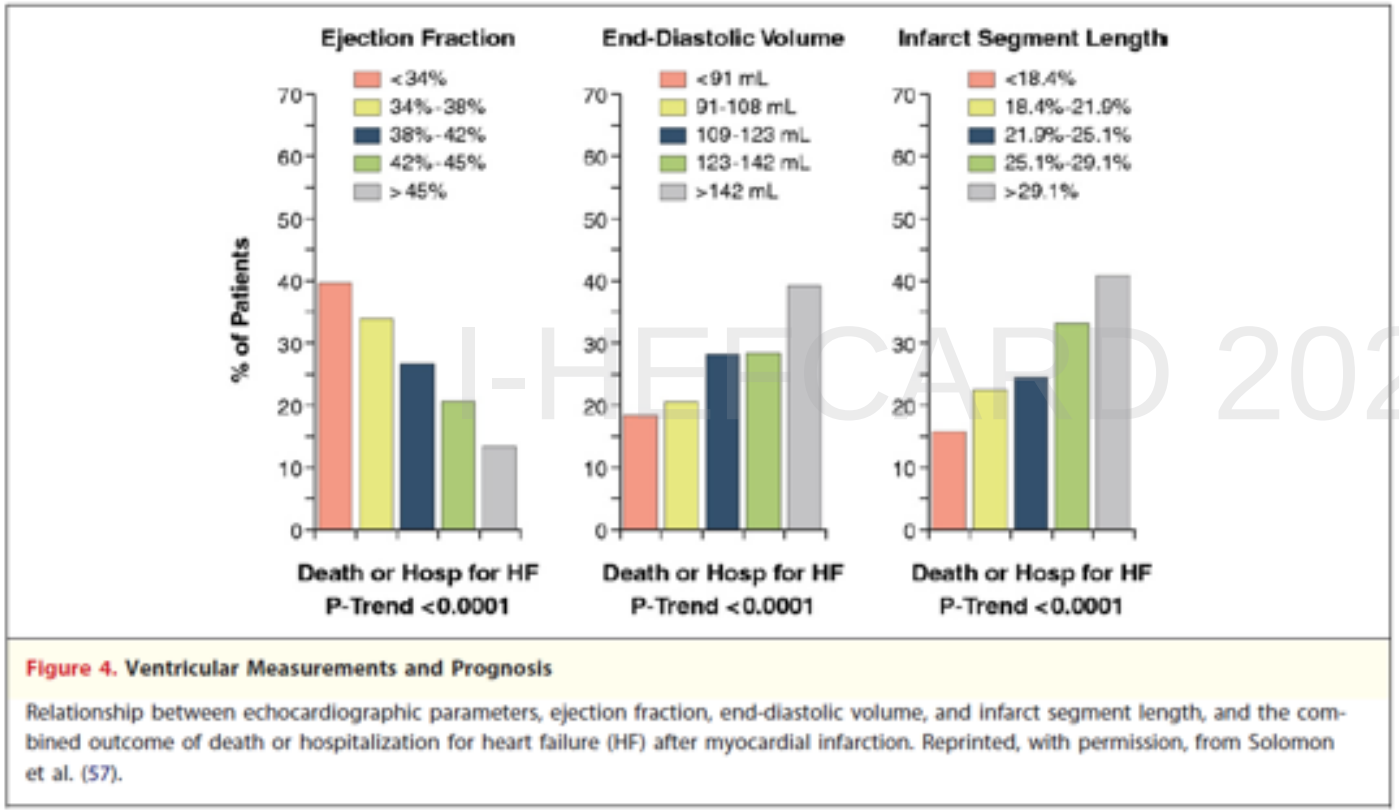


Figure 4. Ventricular Measurements and Prognosis

Relationship between echocardiographic parameters, ejection fraction, end-diastolic volume, and infarct segment length, and the combined outcome of death or hospitalization for heart failure (HF) after myocardial infarction. Reprinted, with permission, from Solomon et al. (57).

- LVEF and EDV were each independent predictors of the primary combined end point of death of heart failure hospitalization
- Lower EF & higher EDV → higher % of patient that end up with the combined primary outcome

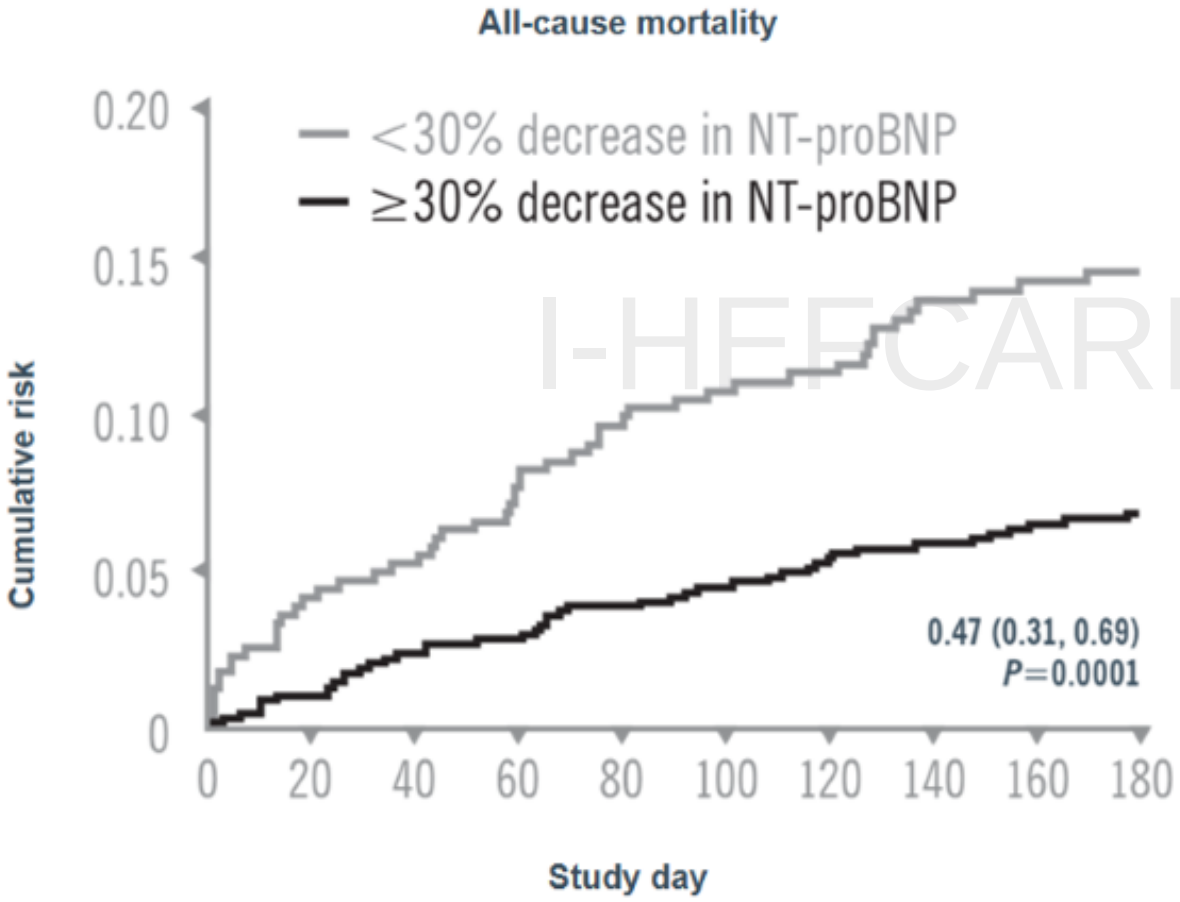
Undelson JE, Konstam MA. Ventricular Remodeling: Fundamental to the progression (and Regresion) of Heart Failure; *JACC*, 2011;57:1477-1479.
McMurray J, et al. Left Ventricular Remodeling in Heart Failure: Current concepts in clinical significance and assessment. *JACC* , 2011;4:102-104.

BNP and NT-proBNP

Biomarkers of heart failure

- Gold standard biomarkers for the diagnosis and prognosis of patients with HF.
- These biomarkers:
  - Increases in response to myocardial wall stress and cardiac congestion
  - Can be changed by heart failure therapy
  - Supported by heart failure clinical guidelines
  - Can be used to predict future outcomes and heart failure therapy
- High BNP and NT-proBNP levels are a sign of heart congestion and cardiovascular risk (death and worsening of HF)

What is the importance of reducing NT-proBNP?



A reduction in NT-proBNP of more than 30 percent has been shown to be associated with a reduced risk of heart failure hospitalization and cardiovascular death.

Sacubitril/Valsartan

- In the PARADIGM HF Study, sacubitril/valsartan (SV) was shown to increase the efficacy of HFrEF therapy (reduce cardiovascular mortality & rehospitalization).[1]

- Cardiac muscle remodeling plays an important role in the aggravation of low ejection fraction (HFrEF) heart failure and is associated with an increased risk of cardiovascular events.[2]
  - Previously, there were no studies that specifically studied the effect of S/V on cardiac remodeling

- **PROVE-HF** examines the association between decreased NT-proBNP after S/V initiation and long-term changes in cardiac remodeling parameters.[4]

1.McMurray JJ, Packer M, Desai AS, *et al*, *N Engl J Med.* 2014 Sep 11;371(11):993-1004; 2.Kramer DG, Trikalinos TA, Kent DM *et al*, *J Am Coll Cardiol.* 2010 Jul 27;56(5):392-406; 3.Zile MR, Claggett BL, Prescott MF, *et al, J Am Coll Cardiol.* 2016 Dec 6;68(22):2425-2436; 4. Januzzi JL, Butler J, Fombu E, et al; Am Heart J, 2018;199:130-136

JAMA | Original Investigation

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

James L. Januzzi Jr, MD; Margaret F. Prescott, PhD; Javed Butler, MD, MPH, MBA; G. Michael Felker, MD, MHS; Alan S. Maisel, MD; Kevin McCague, MA; Alexander Camacho, PhD; Ileana L. Piña, MD, MPH; Ricardo A. Rocha, MD; Amil M. Shah, MD, MPH; Kristin M. Williamson, PharmD; Scott D. Solomon, MD; for the PROVE-HF Investigators

IMPORTANCE In patients with heart failure and reduced ejection fraction (HFrEF), treatment with sacubitril-valsartan reduces N-terminal pro-b-type natriuretic peptide (NT-proBNP) concentrations. The effect of sacubitril-valsartan on cardiac remodeling is uncertain.

OBJECTIVE To determine whether NT-proBNP changes in patients with HFrEF treated with sacubitril-valsartan correlate with changes in measures of cardiac volume and function.

DESIGN, SETTING, AND PARTICIPANTS Prospective, 12-month, single-group, open-label study of patients with HFrEF enrolled in 78 outpatient sites in the United States. Sacubitril-valsartan was initiated and the dose adjusted. Enrollment commenced on October 25, 2016, and follow-up was completed on October 22, 2018.

EXPOSURES NT-proBNP concentrations among patients treated with sacubitril-valsartan.

MAIN OUTCOMES AND MEASURES The primary outcome was the correlation between changes in $\log_e$-NT-proBNP concentrations and left ventricular (LV) EF, LV end-diastolic volume index (LVEDVI), LV end-systolic volume index (LVESVI), left atrial volume index (LAVI), and ratio of early transmitral Doppler velocity/early diastolic annular velocity (E/e') at 12 months.

RESULTS Among 794 patients (mean age, 65.1 years; 226 women [28.5%]; mean LVEF = 28.2%), 654 (82.4%) completed the study. The median NT-proBNP concentration at baseline was 816 pg/mL (interquartile range [IQR], 332-1822) and 455 pg/mL (IQR, 153-1090) at 12 months (difference, $P < .001$). At 12 months, the change in $\log_e$-NT-proBNP concentration was correlated with changes in LVEF ($r = -0.381$ [IQR, −0.448 to −0.310]; $P < .001$), LVEDVI ($r = 0.320$ [IQR, 0.246 to 0.391]; $P < .001$), LVESVI ($r = 0.405$ [IQR, 0.335 to 0.470]; $P < .001$), LAVI ($r = 0.263$ [IQR, 0.186 to 0.338]; $P < .001$), and E/e' ($r = 0.269$ [IQR, 0.182 to 0.353]; $P < .001$). At 12 months, LVEF increased from 28.2% to 37.8% (difference, 9.4% [95% CI, 8.8% to 9.9%]; $P < .001$), while LVEDVI decreased from 86.93 to 74.15 mL/m^2 (difference, −12.25 mL/m^2 [IQR, −12.92 to −11.58]; $P < .001$) and LVESVI decreased from 61.68 to 45.46 mL/m^2 (difference, −15.29 mL/m^2 [95% CI, −16.03 to −14.55]; $P < .001$). LAVI and E/e' ratio also decreased significantly. The most frequent adverse events were hypotension (17.6%), dizziness (16.8%), hyperkalemia (13.2%), and worsening kidney function (12.3%).

CONCLUSIONS AND RELEVANCE In this exploratory study of patients with HFrEF treated with sacubitril-valsartan, reduction in NT-proBNP concentration was weakly yet significantly correlated with improvements in markers of cardiac volume and function at 12 months. The observed reverse cardiac remodeling may provide a mechanistic explanation for the effects of sacubitril-valsartan in patients with HFrEF.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02887183

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Related article page 1077
Supplemental content

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Group Information: The PROVE-HF Investigators are listed at the end of the article.

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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

Published September 2, 2019

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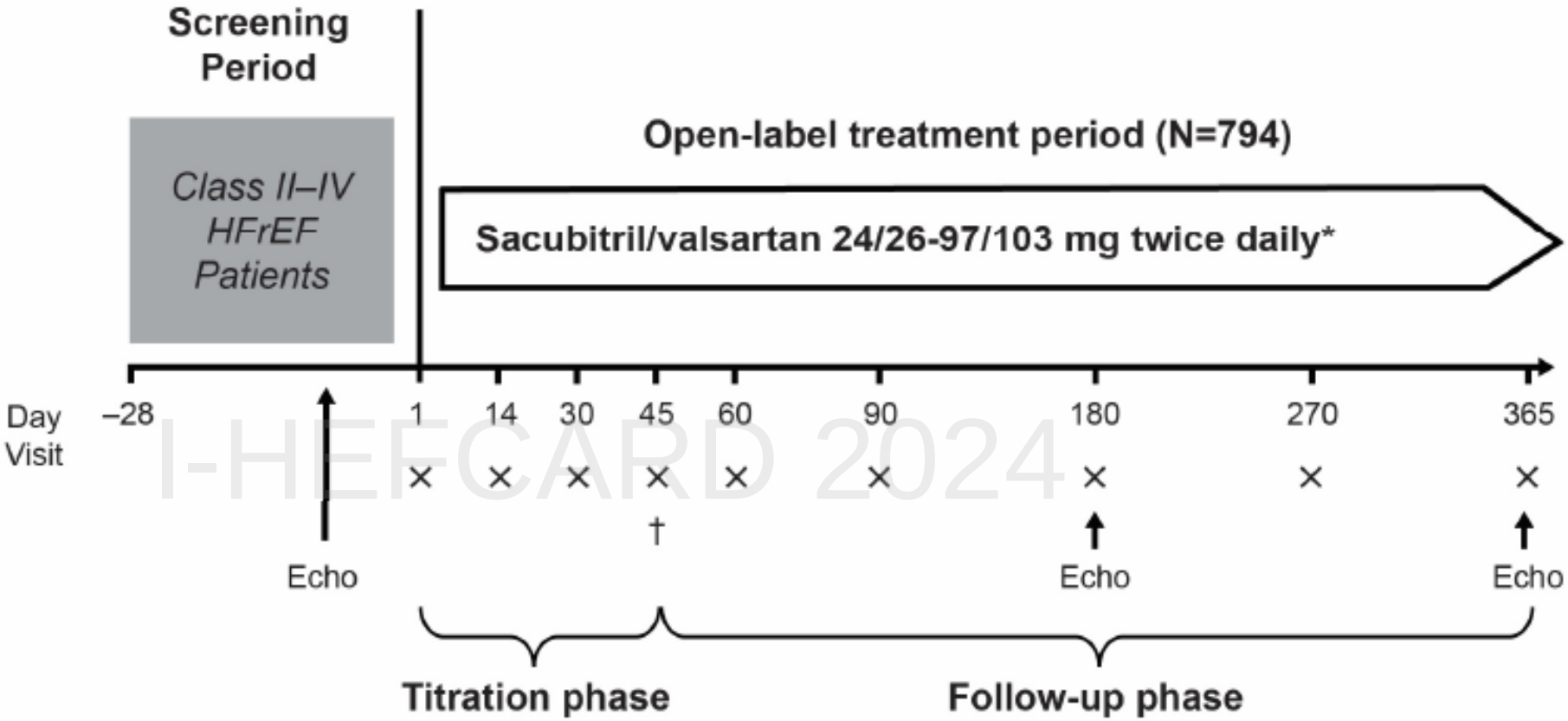
Methods

- A prospective, 12-month, single-group, open-label study in 794 patients with HFrEF enrolled at 78 outpatient establishments in the United States.
- Adult patients with symptomatic HFrEF (LVEF 40%) who can be treated with S/V as indicated
- S/V is initiated and titrated after ACEI/ARB is discontinued
- Blood samples (x) were obtained at each study visit for measurement of NT-proBNP
- Echocardiography was performed at baseline, 6th and 12th months, and then interpreted in the clinical core laboratory

Key Inclusion Criteria	Key Exclusion Criteria
• Aged ≥18 years • Patients with HFrEF who are candidates for on-label sacubitril/valsartan treatment per the standard of care • NYHA functional class II, III, or IV • LVEF ≤40% within the preceding 6 months according to any local measurement, and no subsequent documentation of EF >40% • Stable dose of loop diuretic for the 2 weeks preceding study start	• History of hypersensitivity/allergy or suspected contraindication to ACEI, ARB, or ARNI • Any angioedema history • Concomitant use of ACEI therapy, nesiritide, aliskiren, or drugs that may affect absorption of the study medication • Current or previous treatment with sacubitril/valsartan • Inadequate washout of other investigational drugs before study initiation • Enrollment in another clinical trial within 30 days of screening • Potassium >5.2 mEq/L at screening • History of malignancy within 1 year • Pregnancy, lactation, or use of any method of contraception that is not highly effective • Implantation of CRT/D within 6 months • Prior or planned heart transplant or LVAD

Januzzi JL, Butler J, Fombu E, et al; Am Heart J, 2018;199:130-136.

Methods

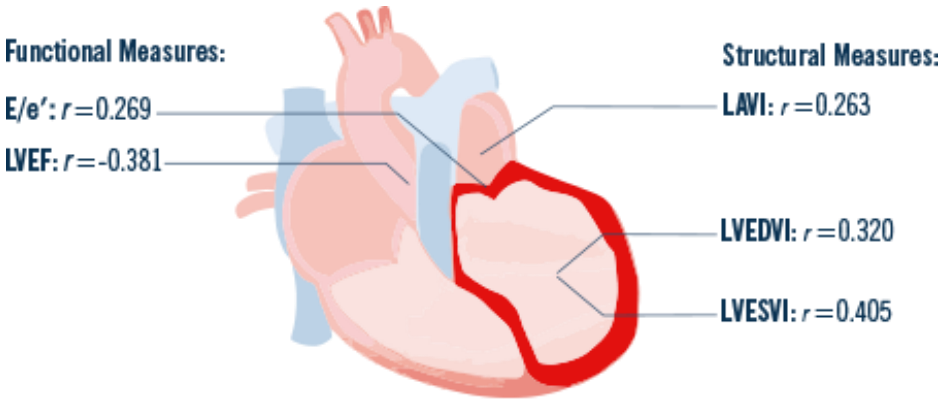


- **Blood samples** (x) were obtained at **each study visit** for NT-proBNP measurement
- An **echocardiogram** was performed at **baseline, 6- and 12-months**, and interpreted by a core lab in a clinically and temporally blinded fashion

Januzzi JL, et al. Suplementary online content of 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; *Am Heart J,* 2018;199:130-136.

Objective

- **Primary Objective**:
  - Correlation between NT-proBNP changes and remodeling at 12 months:
    - Left ventricular ejection fraction (LVEF)
    - Left ventricular end-diastolic volume index (LVEDVi)
    - Left ventricular end systolic volume index (LVESVi)
    - Left atrial volume index (LAVi)
    - Ratio of the initial mitral diastolic filling rate/mitral annular initial diastolic filling rate (E/e')



- **Secondary Objective**
  - Relationship between NT-proBNP changes and remodeling at 6 . month
  - Effects of S/V on cardiac remodeling in a specific subgroup of patients not seen in the PARADIGM-HF study:

1) New diagnosed heart failure (Naive) and/or ACEI/ARB naive

2) Patients with BNP or NT-proBNP concentrations below the PARADIGM-HF . inclusion criteria

3) Patients who do not reach the target S/V dose (200 mg 2x1)

Januzzi JL, Butler J, Fombu E, *et al*; *Am Heart J,* 2018;199:130-136.

Baseline characteristics (N=794)

Parameter	N=794
Age, years; mean (SD)	65.1 (12.4)
Male sex; n (%)	568 (71.5)
NYHA Class II or III; n (%)	780 (98.2)
Race; n (%)	
White	581 (73.4)
Black	180 (22.7)
Body-mass index, kg/m^2, mean (SD)	31.3 (6.9)
Past Medical History; n (%)	
Hypertension	699 (88.0)
Diabetes mellitus	361 (45.5)
Myocardial infarction	329 (41.4)
Atrial fibrillation/flutter	280 (35.3)
Guideline-directed HFrEF therapy; n (%)	
Beta blocker	757 (95.3)
ACEI/ARB	602 (75.8)
MRA	281 (35.4)
CRT/CRT-ICD	122 (15.4)
ICD-alone	226 (28.5)

Measurement of cardiac parameters, median (interquartile range):

- LVEF = 28.2 (24.5, 32.7) %
- LVEDVi = 86.93 (76.17, 100.43) mL/m^2
- LVESVi = 61.68 (51.95, 75.00) mL/m^2
- LAVi = 37.76 (31.63, 46.09) mL/m^2
- E/e' =11.70 (8.80, 16.00)

Subgroup:

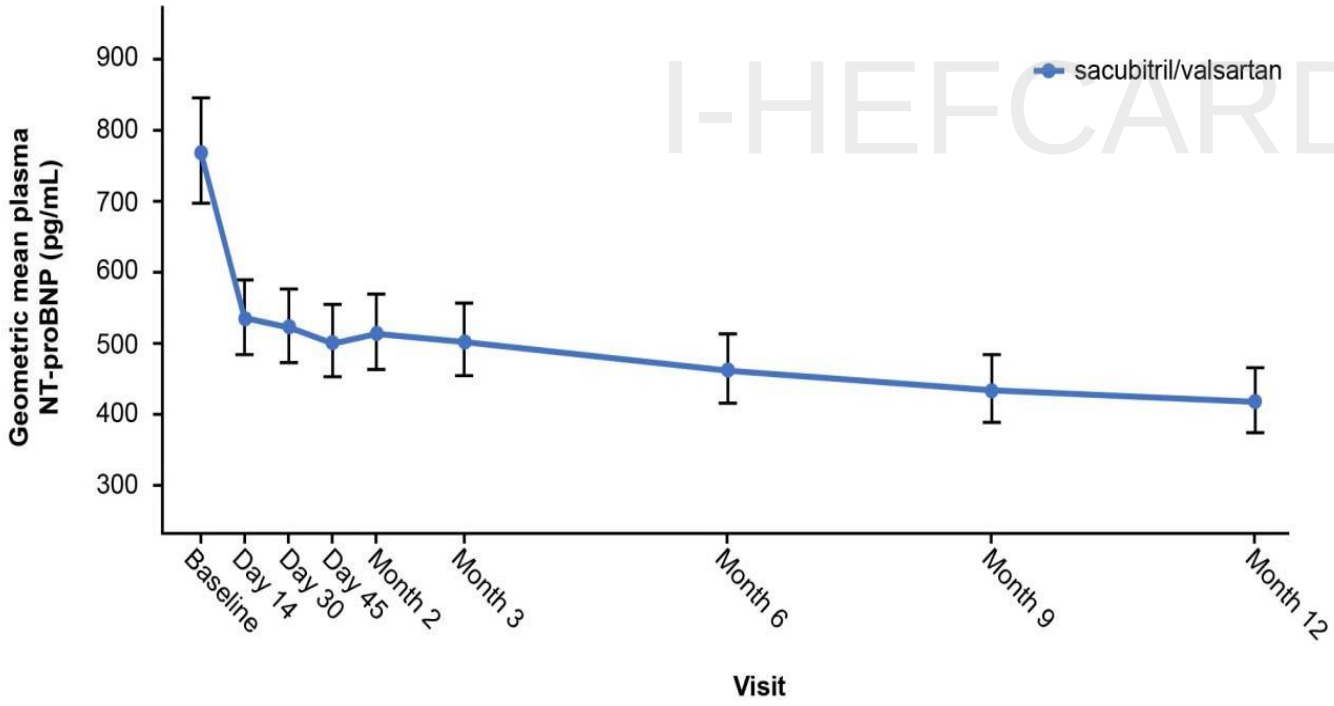
- New onset heart failure and/or ACEI/ARB naive : N = 118 (14.9%)
- BNP or NT-proBNP concentrations below the PARADIGM-HF inclusion criteria: N = 292 (36.8%)
- In the titrated dose, 278 (35.0%) did not reach the target dose

N (%) unless otherwise noted; SD, standard deviation; NYHA, New York Heart Association; ACEI, ACE inhibitor; ARB, angiotensin II receptor blocker; MRA, mineralocorticoid receptor antagonist; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator

Januzzi et al. JAMA. 2019;322(11):1085–1095

NT-proBNP concentrations

Rapid and significant decrease in NT-proBNP, with the majority occurring in the first 2 weeks after S/V . administration



Time point	N	Median NT-proBNP (25th, 75th percentile), pg/mL
Baseline	760	816 (332, 1822)
Day 14	754	528 (226, 1378)
Day 30	740	546 (211, 1321)
Day 45	734	514 (192, 1297)
Month 2	721	535 (210, 1299)
Month 3	719	488 (211, 1315)
Month 6	699	473 (179, 1163)
Month 9	659	444 (170, 1153)
Month 12	638	455 (153, 1090)

Januzzi et al. JAMA. 2019;322(11):1085–1095

Primary end point

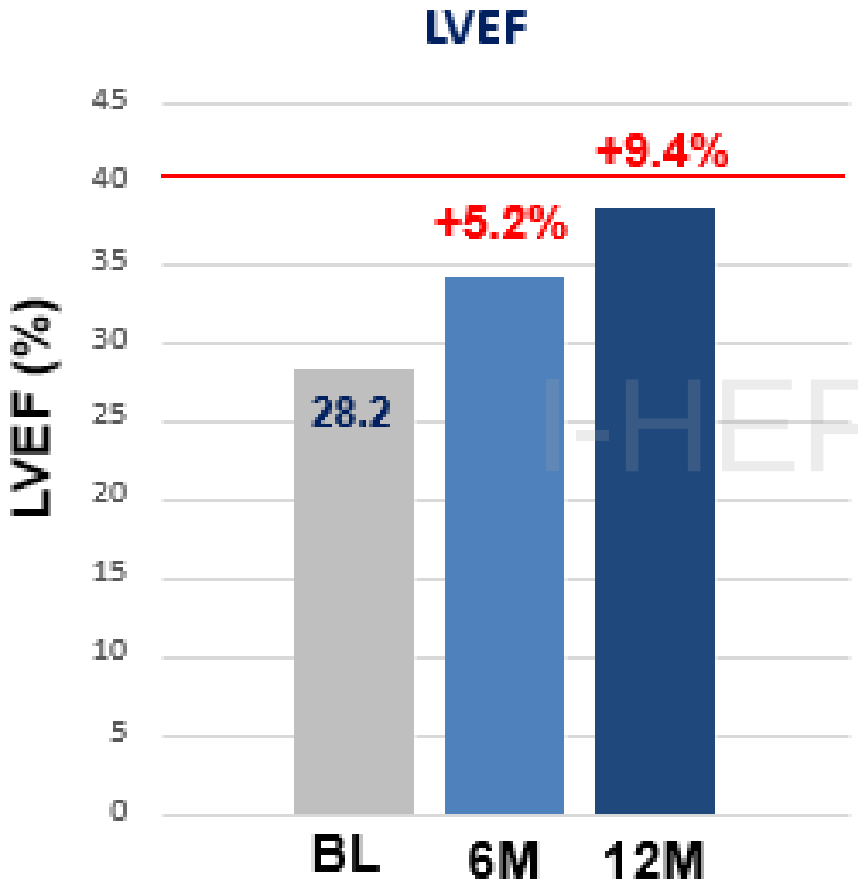
- From baseline to 12 months, there was a significant correlation between changes in NT-proBNP concentrations and cardiac remodeling parameters.
- Parallel latent growth curve analysis showed a strong association between early NT-proBNP changes and reverse cardiac remodeling.

Parameter	Pearson r (IQR)	P value
NT-proBNP (pg/mL) / LVEF (%)	-0.381 (-0.448, -0.310)	<.0001
NT-proBNP (pg/mL) / LVEDVi (mL/m^2)	0.320 (0.246, 0.391)	<.0001
NT-proBNP (pg/mL) / LVESVi (mL/m^2)	0.405 (0.335, 0.470)	<.0001
NT-proBNP (pg/mL) / LAVi (mL/m^2)	0.263 (0.186, 0.338)	<.0001
NT-proBNP (pg/mL) / E/E’	0.269 (0.182, 0.353)	<.0001

IQR, interquartile range; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; mL, milliliter; LAVi, left atrial volume index; E/E’, ratio of early diastolic filling velocity and early diastolic mitral annular velocity

Januzzi et al. JAMA. 2019;322(11):1085–1095

Results



25% of subjects experienced an increase in LVEF of about 13% at 12 months

BL, baseline; LVEF, left ventricular ejection fraction

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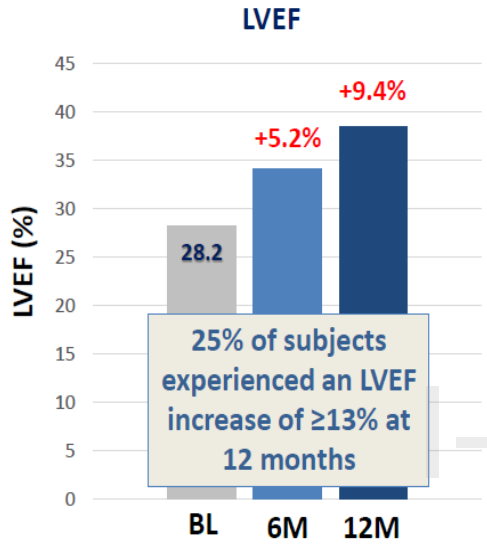
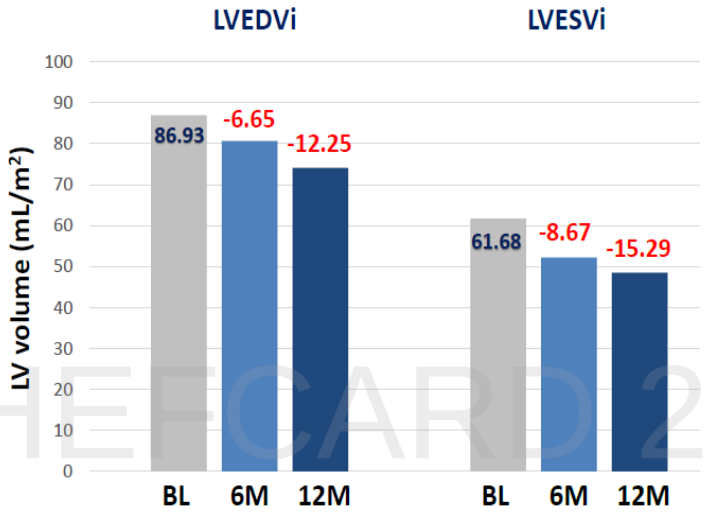
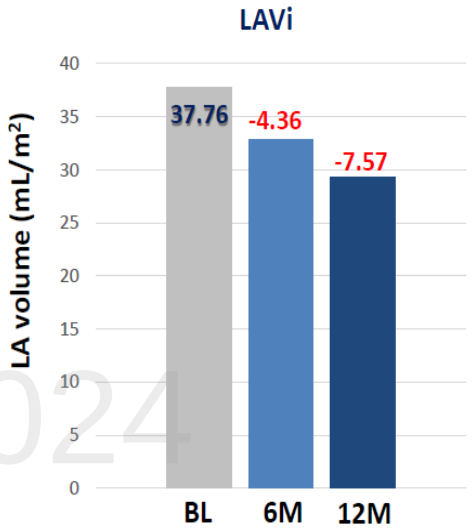
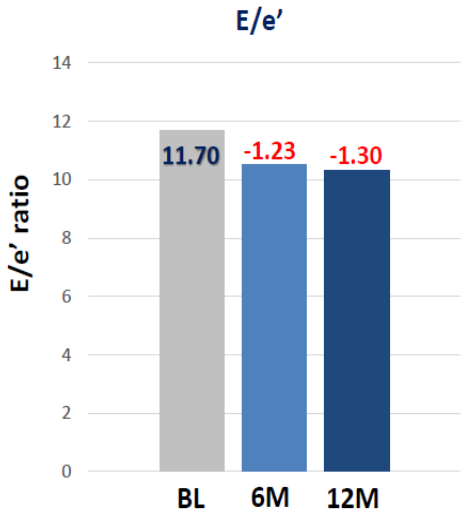
Echocardiographic results at 6 & 12 months









LVMi fell from 124.77 to 107.82 g/m² (mean -16.00 g/m²; P <.001)

Baseline up to 12 months: all P < .001

BL, baseline; mL, milliliter; LA, left atrial; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index; LAVi, left atrial volume index; E/e', ratio of early diastolic filling velocity and early diastolic mitral annular velocity; LVMi, left ventricular mass index.

Januzzi et al. JAMA. 2019;322(11):1085–1095

Then, what's next?

- Can we predict reverse remodeling?
- Should we stop or continue GDMT?

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CLINICAL RESEARCH

Prediction of Left Ventricular Ejection Fraction Change Following Treatment With Sacubitril/Valsartan

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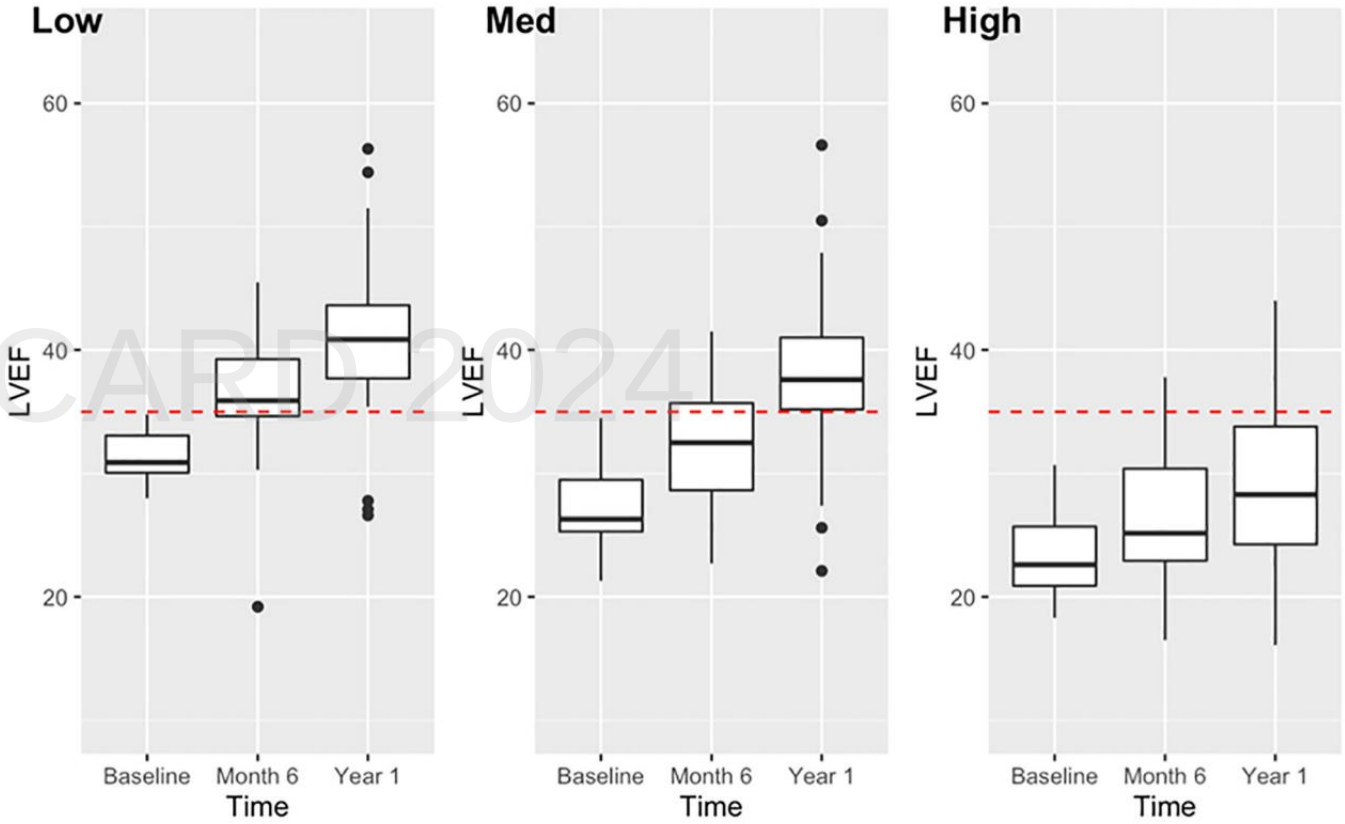
Many person with HFrEF eligible for ICD insertion experience an increase in LVEF ≥ 35% after treatment with Sac/Val. Early indentification of those less likely to improve their LVEF might allow for more refined selection of primary ICD candidates

FIGURE 3 LVEF at Baseline and 6 and 12 Months Across Categories Predicting LVEF Likelihood of LVEF of <35% in the Validation Cohort



An ejection fraction of 35% is depicted by the red dotted line. Although a substantial percentage of change in LVEF occurred by 6 months, extending follow-up to 12 months identifies further reverse cardiac remodeling. LVEF = left ventricular ejection fraction; Med = medium.

TABLE 3 Baseline Characteristics of the Study Population Across Categories Predicting Change of LVEF by 12 Months in the Validation Cohort

	Likelihood of LVEF of <35%/ICD Eligibility			
	Low (n = 36)	Medium (n = 33)	High (n = 35)	*P* Value
Age, y	68.14 ± 13.78	63.85 ± 12.96	62.43 ± 12.32	0.16
Male	31 (86.1)	22 (66.7)	25 (71.4)	0.15
Black	4 (11.1)	10 (30.3)	10 (28.6)	0.11
NYHA functional class				0.49
II	31 (86.1)	26 (78.8)	27 (77.1)	
III	5 (13.9)	5 (15.2)	8 (22.9)	
IV	0 (0.0)	1 (3.0)	0 (0.0)	
New-onset HF	4 (11.1)	7 (21.2)	3 (8.6)	0.27
HF duration, mo	49.5 ± 43.0	69.2 ± 86.1	94.2 ± 84.3	0.04
Nonischemic HF etiology	15 (41.7)	17 (51.5)	21 (60.0)	0.30
Prior HF hospitalization	14 (38.9)	17 (51.5)	15 (42.9)	0.56
BMI, kg/m^2	30.53 ± 5.78	30.55 ± 7.63	32.53 ± 6.54	0.36
Medical history				
Hypertension	30 (83.3)	25 (75.8)	29 (82.9)	0.68
CKD	13 (36.1)	11 (33.3)	10 (28.6)	0.79
TIA	0 (0.0)	1 (3.0)	1 (2.9)	0.57
Stroke	4 (11.1)	4 (12.1)	3 (8.6)	0.89
Myocardial infarction	14 (38.9)	13 (39.4)	14 (40.0)	0.99
Coronary revascularization	17 (47.2)	13 (39.4)	7 (20.0)	0.05
Prior PCI	9 (25.0)	6 (18.2)	4 (11.4)	0.34
Prior CABG	10 (27.8)	9 (27.3)	3 (8.6)	0.08
Diabetes mellitus	16 (44.4)	16 (48.5)	16 (45.7)	0.94
Atrial fibrillation	20 (55.6)	10 (30.3)	12 (34.3)	0.07
Atrial flutter	2 (5.6)	2 (6.1)	3 (8.6)	0.86

Baseline GDMT use				
ACE inhibitor/ARB	27 (75.0)	25 (75.8)	28 (80.0)	0.87
Beta-blocker	36 (100.0)	33 (100.0)	30 (85.7)	0.006
MRA	13 (36.1)	15 (45.5)	18 (51.4)	0.42
CRT-D	4 (11.1)	1 (3.0)	10 (28.6)	0.009
ICD alone	9 (25.0)	12 (36.4)	11 (31.4)	0.59
Baseline vital signs				
Systolic blood pressure, mm Hg	126.25 ± 15.42	124.93 ± 17.27	124.04 ± 15.71	0.88
Diastolic blood pressure, mm Hg	75.79 ± 9.69	73.81 ± 8.38	78.21 ± 10.10	0.26
Pulse rate, beats/min	72.89 ± 13.62	72.26 ± 9.42	73.25 ± 11.45	0.95
Baseline laboratory results				
eGFR	58.19 ± 20.62	64.96 ± 22.78	66.05 ± 14.08	0.30
NT-proBNP, pg/mL	2,434 ± 4,767.40	1,804.53 ± 2,490.98	1,574.84 ± 1,529.14	0.54
hs-cTnT, ng/L	21.5 (11.0-30.5)	13.0 (9.5-30.0)	22.0 (11.0-32.0)	0.53
Baseline echocardiographic parameters				
LVEF, %	30.9 (30.1-33.1)	26.3 (25.3-29.5)	22.6 (20.9-25.7)	<0.001
LVEDVi, mL	80.8 (72.8-87.6)	89.9 (77.0-97.0)	100 (85.5-122.8)	<0.001
LVESVi, mL	54.7 (49.7-60.2)	62.8 (54.2-72.5)	78.5 (62.4-97.0)	<0.001
LAEDVi, mL	35.6 (28.6-44.4)	36.1 (30.8-41.8)	42.3 (37.9-48.4)	0.02
E/e′, ratio	10.0 (7.9-15.0)	11.8 (8.5-16.1)	12.1 (9.5-16.3)	0.27
LV mass index, g/m^2	125.6 (101.5-145.2)	122.4 (102.5-144.2)	134.5 (120.4-181.6)	0.05

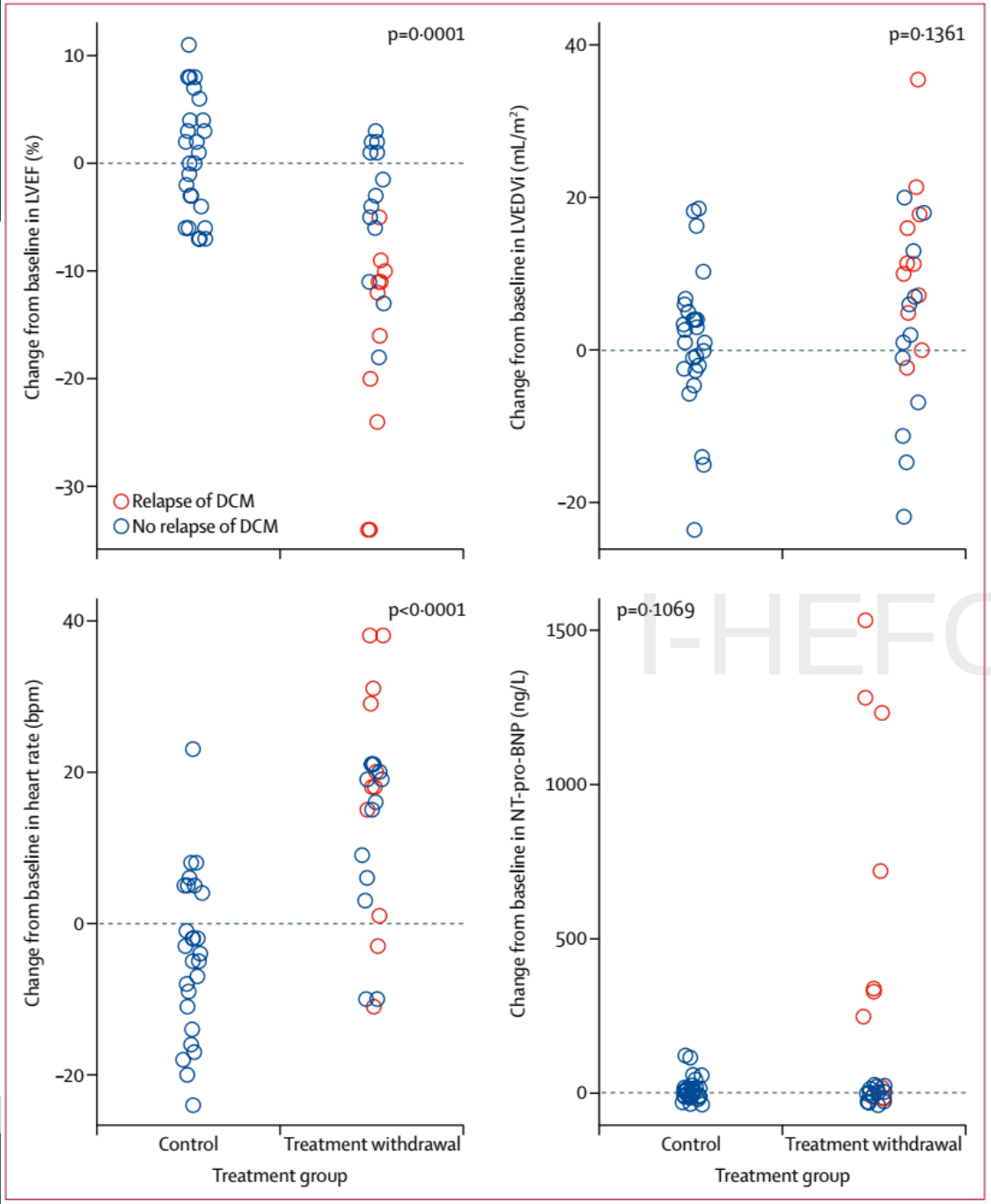


Figure 5: **Change in secondary endpoint variables between baseline and follow-up in the randomised phase of the study, based on treatment group**

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): an open-label, pilot, randomised trial

Brian P Halliday, Rebecca Wassall, Amrit S Lota, Zohya Khalique, John Gregson, Simon Newsome, Robert Jackson, Tsveta Rahneva, Rick Wage, Gillian Smith, Lucia Venneri, Upasana Tayal, Dominique Auger, William Midwinter, Nicola Whiffin, Ronak Rajani, Jason N Dungu, Antonis Pantazis, Stuart A Cook, James S Ware, A John Baksi, Dudley J Pennell, Stuart D Rosen, Martin R Cowie, John G F Cleland, Sanjay K Prasad

Withdrawal of pharmacological heart failure treatment in patients with recovered dilated cardiomyopathy was associated with relapse in 40% of cases. This finding suggests that complete withdrawal of treatment should not usually be attempted in such patients

What does the guideline say?

Pasien dengan FEVKi ≤40%

Obat utama, lakukan inisiasi dan titrasi hingga dosis optimal/toleransi

- Penghambat SRAA (urutan sesuai prioritas)*
  1. ACE-I
  2. ARNI
  3. ARB
- Penyekat reseptor beta
- Antagonis aldosteron
- Penghambat SGLT2**
- Diuretik loop (bila ada tanda dan gejala kongesti)

Obat/alat tambahan digunakan sesuai indikasi komorbiditas

- Irama sinus & laju jantung > 70 per menit: ivabradine
- Fibrilasi atrium: antikoagulan
- Defisiensi besi: *ferric carboxymaltose*
- Etiologi iskemik: revaskularisasi
- Penyakit jantung katup: perbaikan/penggantian katup
- Lebar kompleks QRS > 120ms: terapi resinkronisasi jantung
- Menurunkan kejadian henti jantung mendadak: defibrillator intrakardiak

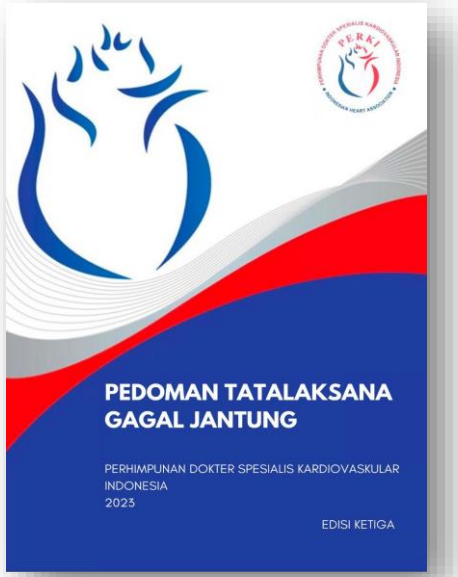
- Rehabillitasi Jantung
- Penanganan tim multidisiplin untuk kontrol faktor risiko dan komorbiditas

Evaluasi klinis (tanda dan gejala kongestif) & ekokardiografi (dalam 6 bulan)[a]

Tidak terdapat perbaikan klinis/perburukan gagal jantung:
- Optimalisasi diuretik (penambahan dosis atau penggantian menjadi sediaan injeksi)
- Optimalisasi dosis obat gagal jantung
- Evaluasi dan kontrol faktor risiko serta komorbiditas
- Vericiguat**

Perbaikan klinis & fraksi ejeksi:
- Terapi dilanjutkan

*Pilih salah satu, sesuai prioritas ketersediaan
**Apabila tersedia
[a]Ekokardiografi evaluasi dilakukan dalam 6 bulan paska inisiasi pada pasien yang stabil secara klinis untuk mengevaluasi perbaikan klinis, evaluasi ekokardiografi selanjutnya dilakukan sesuai dengan kondisi klinis pasien



Take Home Messages

- In HFrEF patients treated with sacubitril/valsartan, a significant decrease in NT-proBNP was associated with reverse cardiac remodeling and better outcome.

- The degree of reverse remodeling demonstrated may help to elucidate the mechanism by which sacubitril/valsartan reduces morbidity and mortality in HFrEF patients.

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