5th IHEF CARD
The 5th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

in conjunction with :
WHFS25
World Heart Failure Society Congress 2025

The Road to myocardial revival in Heart Failure reduce Ejection Fraction (HFrEF)

Andika Rizki Lubis, M.D

Tarakan General Hospital Jakarta

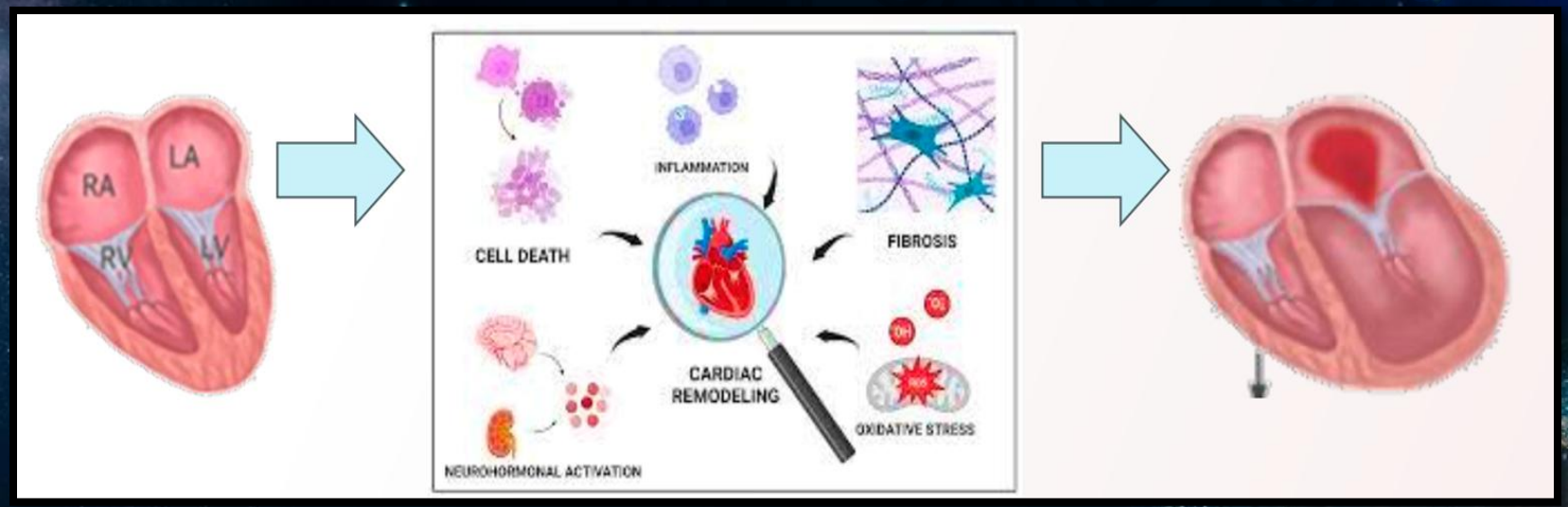
Indonesian Heart Failure and Cardiometabolic disease working group

Disclosure

- Supported by Novartis

Definition

- Cardiac remodeling a group of molecular, cellular and interstitial changes that manifest clinically as changes in size, mass, geometry and function of the heart after injury.
- The clinical diagnosis of remodeling detection of morphological changes in the cavity diameter, mass (hypertrophy and atrophy),geometry (heart wall thickness and shape), areas of scar after MI, fibrosis and inflammatory infiltrate (e.g in myocarditis)



Azevedo PS, et al. Arq Bras Cardiol. 2016; 106(1):62-69

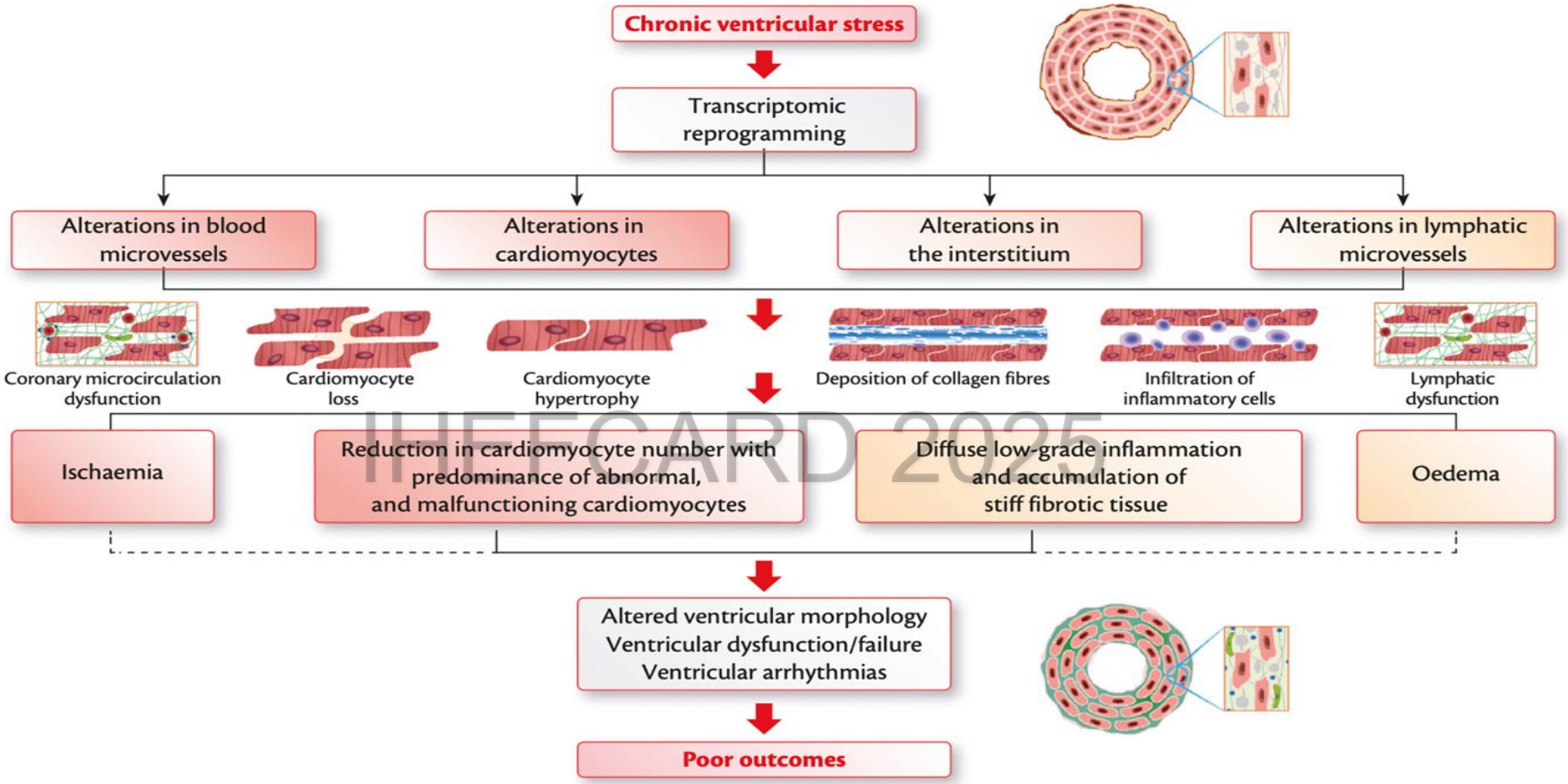


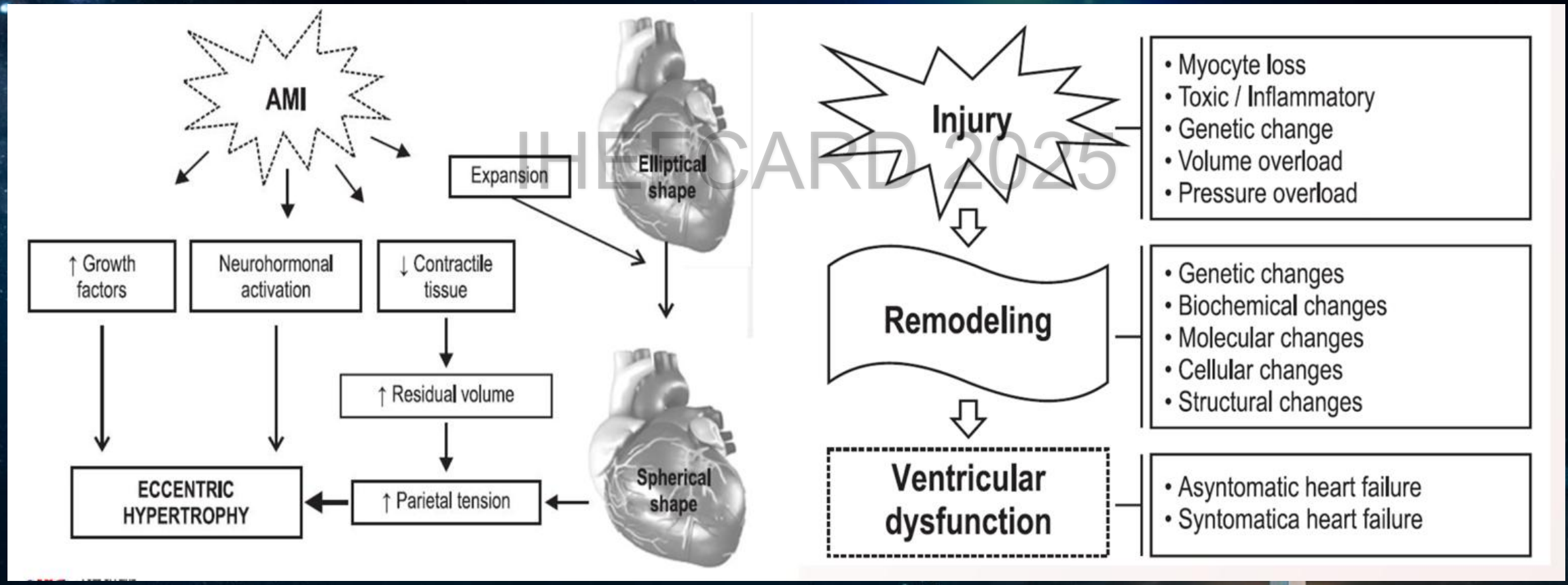
Figure 5.3.1 Sequence of alterations that develop in the microstructural components of the myocardium in the chronically stressed ventricle and that, in turn, contribute to the development of alterations in ventricular morphology and function associated with poor outcomes of ventricular remodelling.

The ESC Textbook of Heart Failure. HFA (Heart Failure Association) 2024

Review Article

Cardiac Remodeling: Concepts, Clinical Impact, Pathophysiological Mechanisms and Pharmacologic Treatment

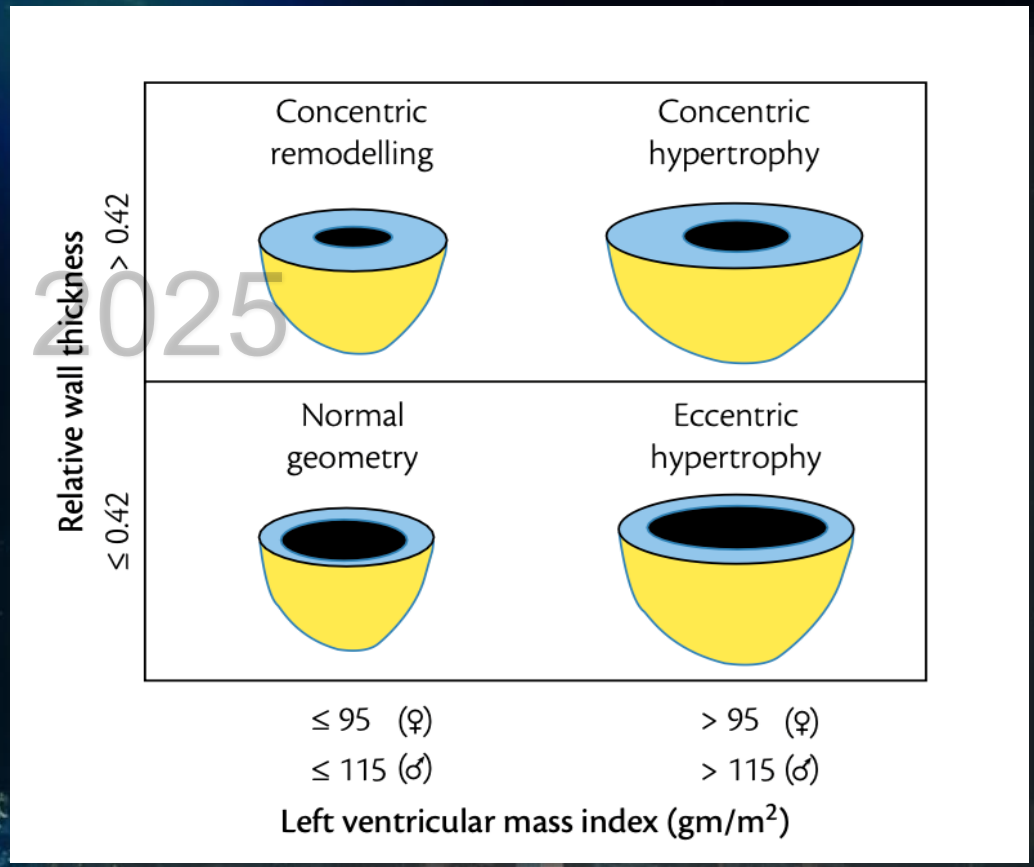
Paula S. Azevedo, Bertha F. Polegato, Marcos F. Minicucci, Sergio A. R. Paiva, Leonardo A. M. Zornoff
Faculdade de Medicina de Botucatu, São Paulo, SP – Brazil



Arq Bras Cardiol. 2016; 106(1):62-69DOI: 10.5935/abc.20160005

Ventricular remodelling

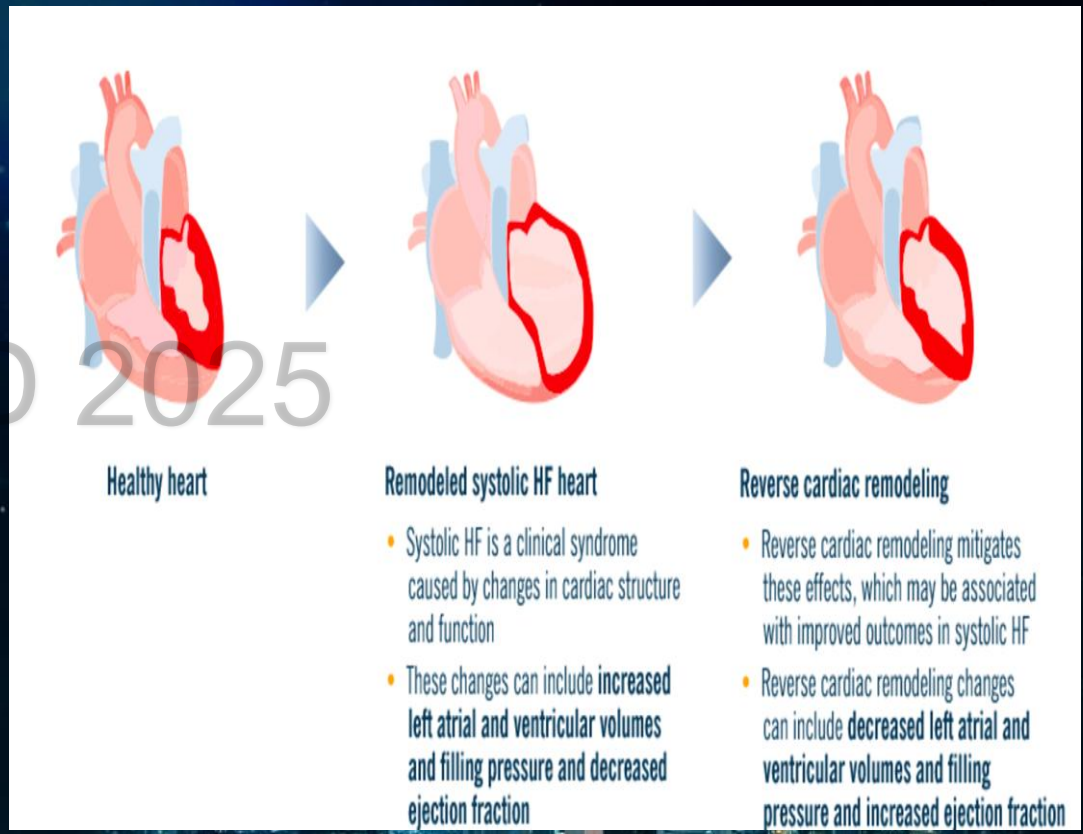
- Early phases of myocardial injury → reduction of cardiac function without changes in size or structure, whereas eccentric remodelling occurs within weeks, months, or even years.
- Ventricular remodelling → divided into 2 groups concentric and eccentric. Concentric remodelling is defined as ventricular hypertrophy with increased wall thickness, but without dilatation and usually with normal systolic function.
- Neurohumoral inhibition not only may improve outcome, but also may even prevent or reverse, at least in part, eccentric remodelling.



The ESC Textbook of Heart Failure. HFA (Heart Failure Association) 2024

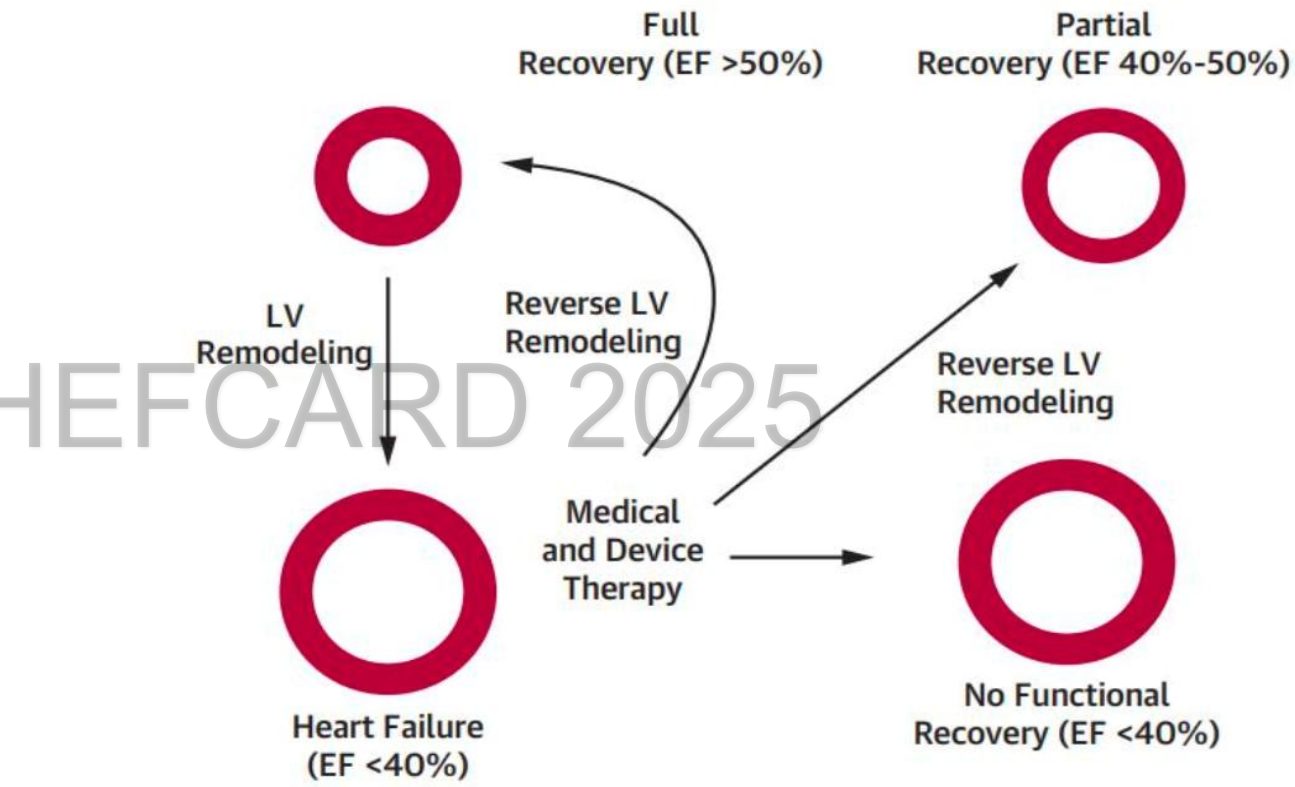
Reverse Remodelling

- Reverse remodelling (RR) □ a process the heart undergoes structural and functional changes that □improvement to a more normal state.
- RR can result from □ pharmacological treatment, interventional/ surgical procedures) or after certain physiologic events or lifestyle modification, such as partum, significant weight loss, or alcohol abstinence.
- Insofar as the calculation of LVEF incorporates LV end-diastolic volume in the denominator of the equation, improvements in LVEF are associated with a reciprocal decrease in LV end-diastolic volume □reverse LV remodeling



Inês Falcão-Pires et all.Mechanisms of myocardial reverse remodelling and its clinical significance: A scientific statement of the ESC Working Group on Myocardial Function. uropean Journal of Heart Failure (2024)

FIGURE 1 Changes in LVEF With GDMT in Patients With Heart Failure With a Reduced EF



Patients with heart failure with recovered ejection fraction (HFrecEF) treated with guideline-directed medical and device therapies (GDMT) may have a complete recovery of left ventricular ejection fraction (LVEF) >50%, partial recovery of LVEF (EF 40% to 50%), or no functional recovery of LVEF (EF <40%).

Predictors Reverse Remodeling

THE PRESENT AND FUTURE

JACC SCIENTIFIC EXPERT PANEL

Heart Failure With Recovered Left Ventricular Ejection Fraction

JACC Scientific Expert Panel

Jane E. Wilcox, MD,[a] James C. Fang, MD,[b] Kenneth B. Margulies, MD,[c] Douglas L. Mann, MD[d]

VOL. 76, NO. 6, 2020

TABLE 2 Predicting Reverse LV Remodeling Among Patients With HFrEF

	Predictors of Reverse LV Remodeling
Clinical parameters	Nonischemic etiology Lower duration of HF Female No LBBB LBBB in CRT
Genetic factors	Pathogenic gene variants not involving structural cytoskeletal proteins or Z-disk proteins
Echocardiography/CMR imaging	Lower LVEF, greater contractility on strain imaging Greater LV diameters LGE absence
Biomarkers	Lower NT-proBNP Lower troponin Lower sST2 Galectin-3, emerging biomarkers (mimecan, microRNAs, orexin)

Modified with permission from Aimo et al. (58).

CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with a reduced ejection fraction; LBBB = left bundle branch block; LGE = late gadolinium enhancement; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sST2 = soluble ST (suppression of tumorigenicity) 2.

ESC HEART FAILURE
ORIGINAL ARTICLE
ESC Heart Failure 2024; 11: 783–794
Published online 20 December 2023 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/ehf2.14619

Incidence and predictors of heart failure with improved ejection fraction category in a HFrEF patient population

Balázs Solymossi[1], Balázs Muk[1], Róbert Sepp[2], Tamás Habon[3], Attila Borbély[4], Krisztina Heltai[5], Zsuzsanna Majoros[6], Zoltán Járai[7], Dénes Vágány[6], Ákos Szatmári[8], Erzsébet Sziliczei[9], Fanni Bánfi-Bacsárdi[1] and Noémi Nyolczas[1]*

Table 3 Factors predicting the development of the HFimpEF category in the whole study population (833 patients)—univariate and multivariate logistic regression analysis

	OR	95% CI	*P* value
Parameters of univariate logistic regression analysis			
Female sex	2.08	1.42–3.04	<0.001
<65 years of age	1.50	1.05–2.14	0.026
Non-ischaemic aetiology	2.05	1.41–3.00	<0.001
HR < 90 min^{-1}	1.68	1.11–2.54	0.015
eGFR (increase of 5 mL/min/1.73 m^2)	1.08	1.01–1.15	0.016
QRS (increase of 10 ms)	0.93	0.87–0.99	0.023
LVESD (increase of 5 mm)	0.85	0.76–0.96	<0.01
LVEDD (increase of 5 mm)	0.82	0.73–0.93	<0.01
LA diameter (increase of 5 mm)	0.80	0.69–0.93	<0.01
Parameters of multivariate logistic regression analysis			
Female sex	1.73	1.01–2.96	0.045
Non-ischaemic aetiology	1.95	1.15–3.30	0.013
LVEDD ≤ 60 mm	2.04	1.18–3.51	0.011

ESC European Society of Cardiology
European Journal of Heart Failure (2024) 26, 1454–1479
doi:10.1002/ejhf.3264
REVIEW ARTICLE

Mechanisms of myocardial reverse remodelling and its clinical significance: A scientific statement of the ESC Working Group on Myocardial Function

Inês Falcão-Pires[1*†], Ana Filipa Ferreira[1†], Fábio Trindade[1†], Luc Bertrand[2,3], Michele Ciccarelli[4], Valeria Visco[4], Dana Dawson[5], Nazha Hamdani[6,7,8,9], Linda W. Van Laake[10], Frank Lezoualc'h[11], Wolfgang A. Linke[12], Ida G Lunde[13,14], Peter P. Rainer[15,16,17], Mahmoud Abdellatif[15,16], Jolanda Van der Velden[18], Nicola Cosentino[19,20], Alessia Paldino[21,22], Giulio Pompilio[19,23], Serena Zacchigna[21,22], Stephane Heymans[24,25], Thomas Thum[26], and Carlo Gabriele Tocchetti[27]

Table 1 Class I drugs that induce reverse remodelling

Guideline-recommended drugs	Mechanism of action	Pathologic condition/ cardiac insult	Effect on reverse remodelling
AT_1 blocker	RAAS inhibition (angiotensin II receptor antagonism; blood pressure reduction)	HFrEF Hypertension STEMI	↓ Hypertrophy ↓ Fibrosis ↑ Coronary flow reserve
Angiotensin receptor–neprilysin inhibitor[a]	RAAS inhibition (angiotensin II receptor antagonism; blood pressure reduction) + natriuretic peptide degradation inhibition (neprilysin inhibition) + improving cGMP signalling (neprilysin inhibition)	HFrEF	↓ NT-proBNP ↑ LVEF ↓ Hypertrophy ↓ LVEDVI, LVESVI ↑ Diastolic function (↓ LAVI, ↓ E/e') ↓ NYHA class ↓ Hospitalization ↓ Mortality risk
Angiotensin-converting enzyme inhibitor	RAAS inhibition (conversion of angiotensin I to angiotensin II is prevented; blood pressure reduction) Bradykinin degradation inhibition (bradykinin preservation enhances vasodilatation)	HFrEF Hypertension STEMI	↓ Hypertrophy ↓ LVESV and LVEDV ↑ Ejection fraction ↓ Hospitalization ↓ Mortality risk

Left Ventricular Reverse Remodeling in Heart Failure: Remission to Recovery

Jacinthe Boulet, MD, CM[a] and Mandeep R. Mehra, MD, MSc, FRCP[b]

[a]Department of Medicine, Division of Cardiology, Montreal Heart Institute, Montreal, Canada; [b]Department of Medicine, Division of Cardiology, Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston, Massachusetts, USA

LVEF Improvements with Reverse Remodeling

ACEI or ARB
1-4%[78-80]

BB
4-12%[81-84]

MRA
4%[85,86]

ARNI
9-15%[87,88]

SGLT2i
1-6%[89-90]

CRT
2-24%[91-93]

MitraClip
3%[94,95]

LV Size Reductions with Reverse Remodeling

ACEI or ARB
LVEDV 12-13 ml/m^2 [96-97]
LVESV 13 ml/m^2 [96-97]
LVEDD 2.4 mm[98]
LVESD 6.2 mm[98]

BB
LVESV 4.8 ml[99]

MRA
LVEDV 17.3 ml[100]
LVESV 18.5 ml[100]

ARNI
LVEDV$_i$ 12.25 ml/m^2 [87]
LVESV$_i$ 15.29 ml/m^2 [87]

SGLT2i
LV mass$_i$ 2.6-13.7 g/m^2 [101-103]

CRT
LVEDV$_i$ 21 ml/m^2 [104]
LVESV$_i$ 18.4 ml/m^2 [104]

MV repair
LVEDV$_i$ 15 ml/m^2 [105-106]
LVESV$_i$ 6.6-13 ml/m^2 [105-107]

MV replacement
LVESV$_i$ 6.5-6.8 ml/m^2 [106-107]

MitraClip
LVEDV 26 ml[108]
LVESV 16 ml[108]

Cellular and molecular determinants of LV function recovery

TABLE 1 Cellular and Molecular Determinants of Recovery of LV Function

	Beta-Blocker	ACE Inhibitor	ARB	Aldosterone Antagonists	LVAD	CRT	CSD
Myocyte defects							
Hypertrophy	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Fetal gene expression	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
Myocytolysis	Decreased	ND	ND	ND	Decreased	ND	ND
Beta-adrenergic desensitization	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
EC coupling	Increased	Increased	Increased	ND	Increased	Increased	Increased
Cytoskeletal proteins	ND	ND	ND	Increased	Increased	ND	Increased
Myocardial defects							
Myocyte apoptosis	Decreased	Decreased	Decreased	ND	Decreased	Decreased	Decreased
MMP activation	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased	Decreased
Fibrosis	Decreased	Decreased	Decreased	Decreased	Increased*	Decreased	Decreased
Angiogenesis	Increased	Increased	Increased	Increased	Decreased	Increased	Increased
LV dilation	Decreased	Stabilized	Stabilized	Stabilized	Decreased	Decreased	Decreased

Reproduced with permission from Mann et al. (17)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CRT = cardiac resynchronization therapy; CSD = cardiac support device; EC = excitation-contraction; LV = left ventricular; LVAD = left ventricular assist device; MMP = matrix metalloproteinase; ND = not done.

ESC Heart Failure 2024; 11: 783–794
DOI: 10.1002/ehf2.14619

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ARNi in Cardiac Reverse Remodelling

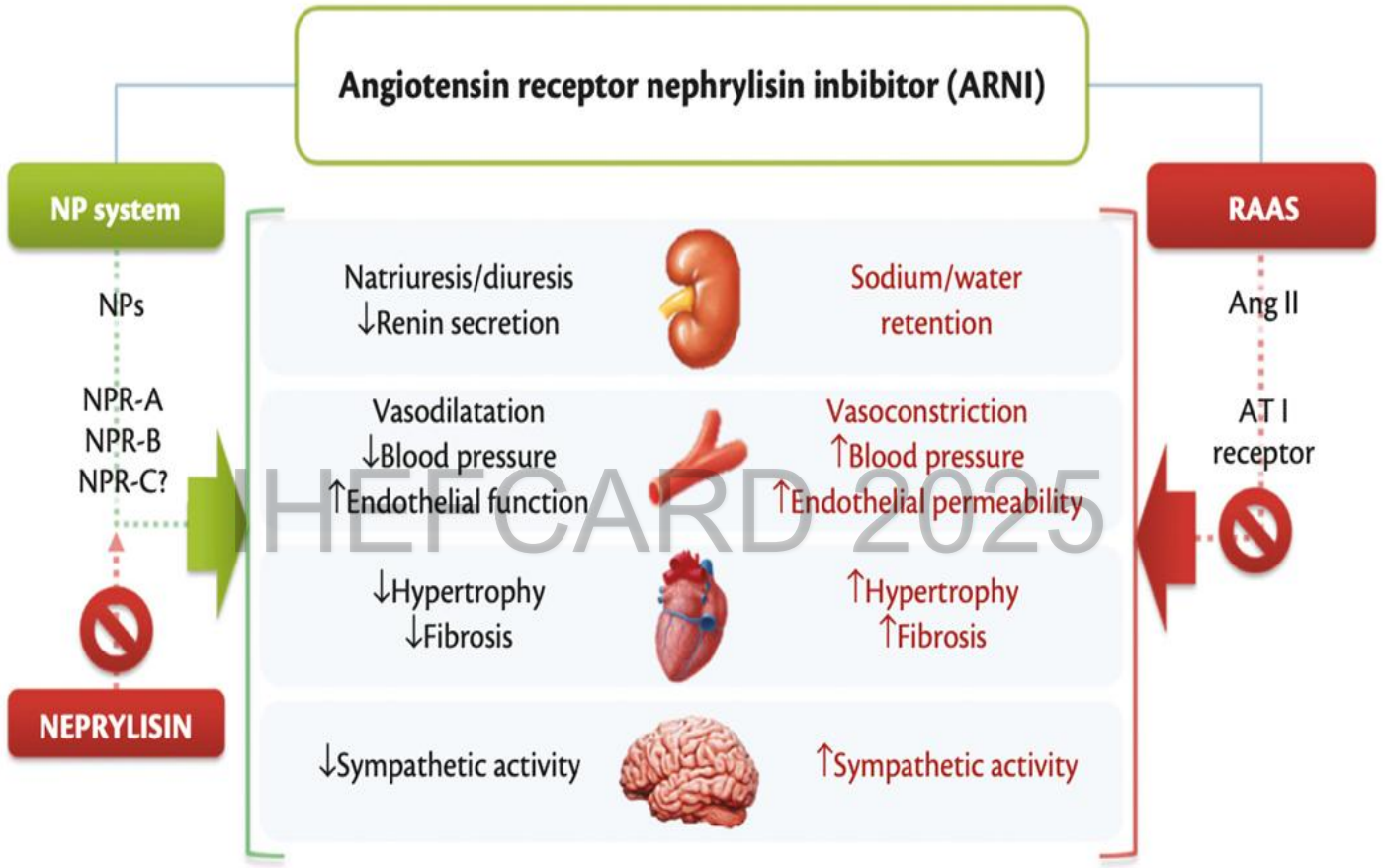
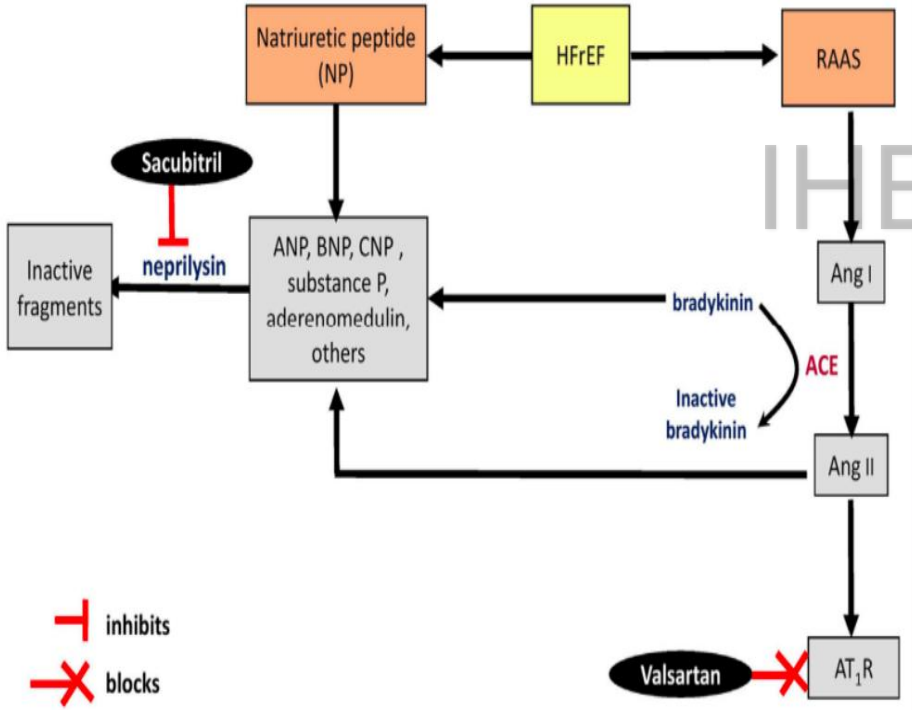


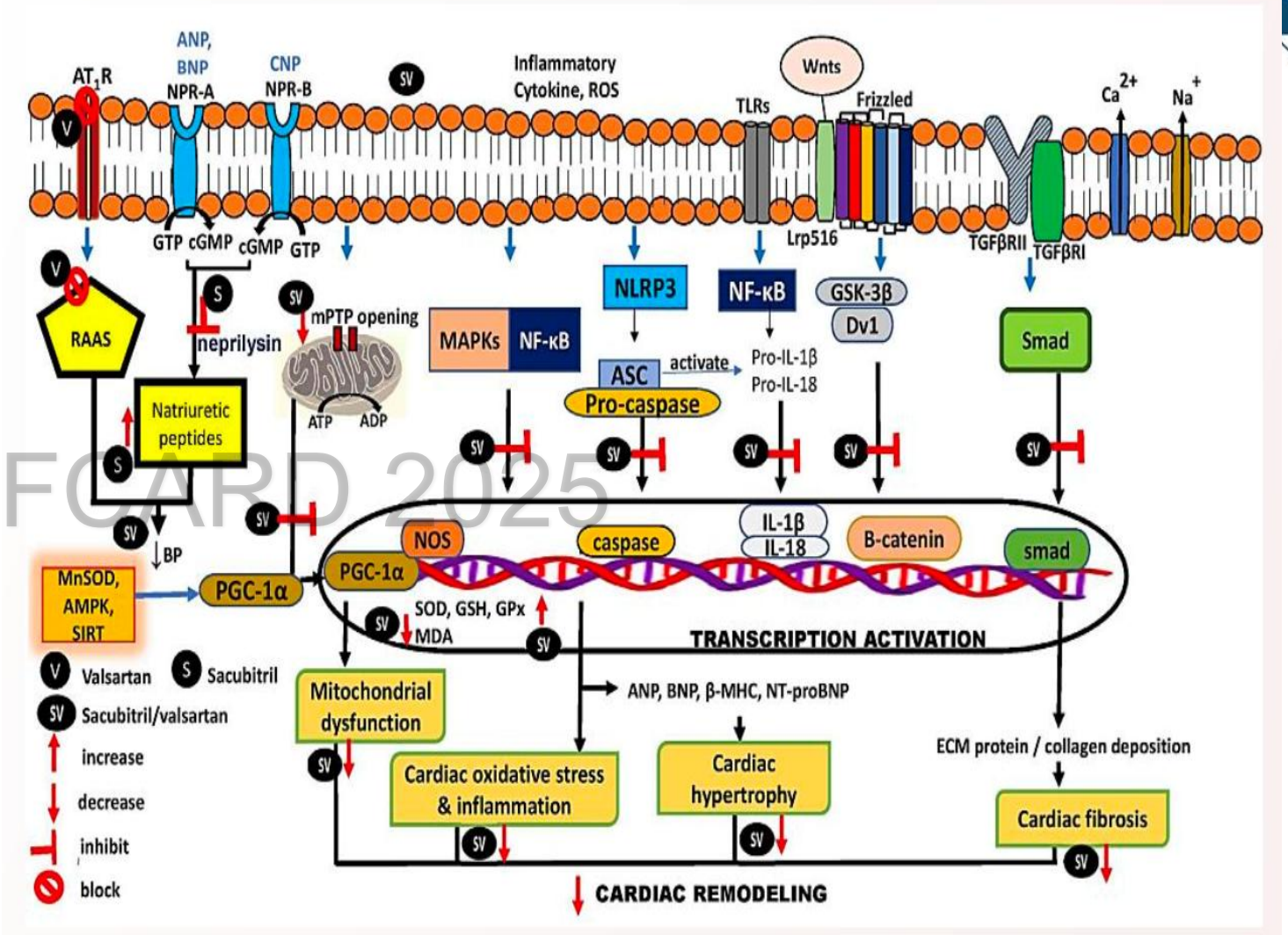
Figure 8.3.2 Beneficial effects of angiotensin receptor–neprilysin inhibitor in heart failure.

Reproduced from Volpe M. Natriuretic peptides and cardio-renal disease. *Int J Cardiol*. 2014 Oct 20;176(3):630–9. doi: 10.1016/j.ijcard.2014.08.032 with permission from Elsevier.

The ESC Textbook of Heart Failure. HFA (Heart Failure Association) 2024

Molecular mechanisms of sacubitril/valsartan in cardiac remodeling





Mustafa NH, Jalil J, Zainalabidin S,Saleh MSM, Asmadi AY and Kamisah Y, 2022
Molecular mechanisms of sacubitril/valsartan incardiac remodeling.
Front. Pharmacol. 13:892460. doi: 10.3389/fphar.2022.892460

ARNi and Reverse Remodelling

- Several mechanistic studies the beneficial effects of sacubitril/ valsartan in HFrEF include LV reverse remodelling, improvement in systolic and diastolic function, and reduction in functional mitral regurgitation and arterial stiffness.
- In the Prospective Study of Biomarkers, Symptom Improvement, and Ventricular Remodeling During Sacubitril/ Valsartan Therapy for HF (PROVE- HF), the median LV ejection fraction (LVEF) increased from approximately 28% 38% during 12 months, whereas both end-diastolic and end- systolic volume indices decreased significantly
- the Effects of Sacubitril/ Valsartan vs. Enalapril on Aortic Stiffness in Patients With Mild to Moderate HF With Reduced Ejection Fraction (EVALUATE- HF) trial, in which signs of LV reverse remodelling became apparent as early as 12 weeks of sacubitril/ valsartan treatment, compared to treatment with enalapril.

The ESC Textbook of Heart Failure. HFA (Heart Failure Association) 2024

ARNi in ACS with HF

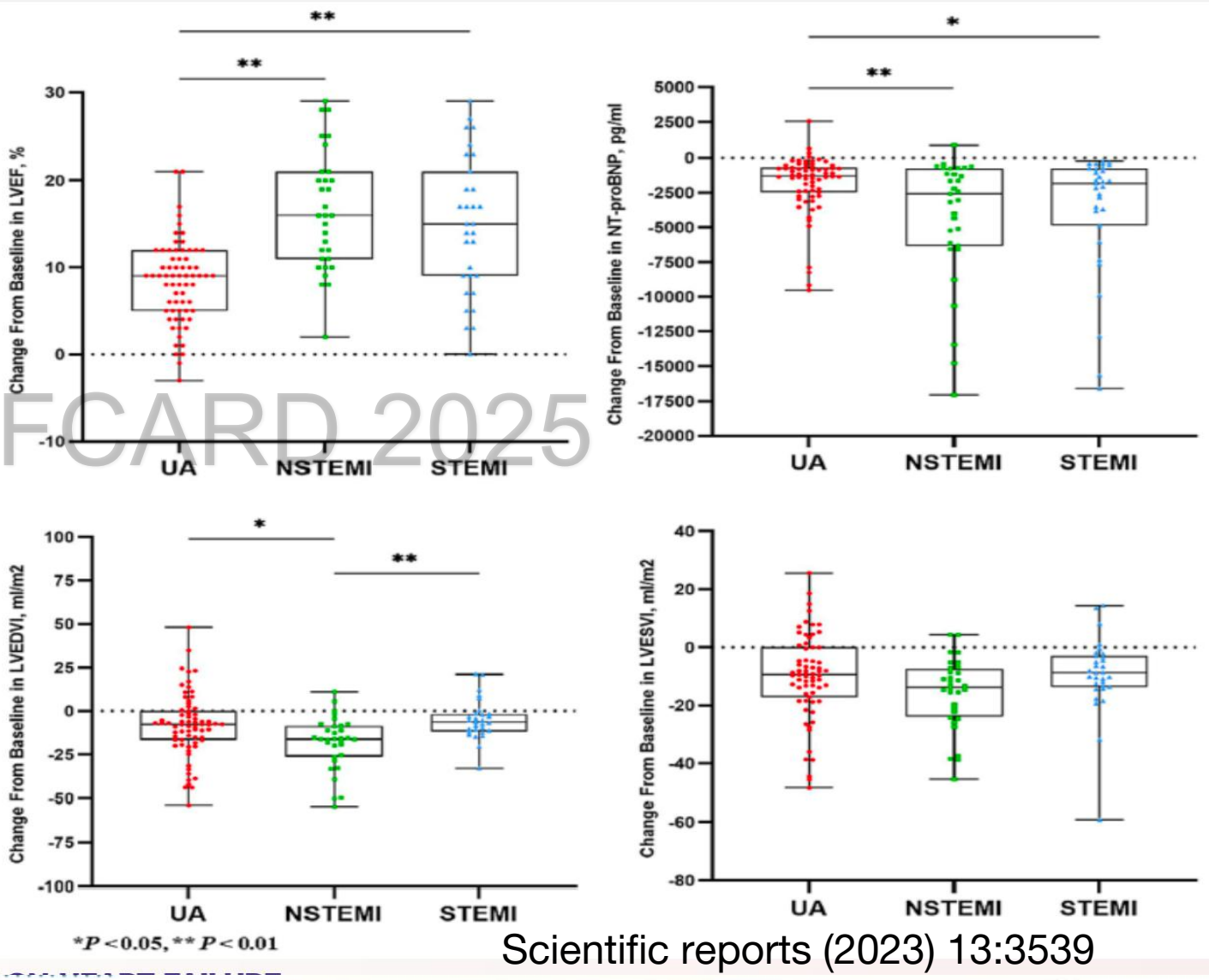
ESC HEART FAILURE
ESC Heart Failure 2024; **11**: 937–949
Published online 15 January 2024 in Wiley Online Library (wileyonlinelibrary.com) **DOI:** 10.1002/ehf2.14646

ORIGINAL ARTICLE

Improved heart function and cardiac remodelling following sacubitril/valsartan in acute coronary syndrome with HF

Henan Liu[1,2†], Yongkang Su[1,3†], Jian Shen[1,3], Yang Jiao[1,3], Ying Li[1,3], Bing Liu[4], Xiaoling Hou[1], Qinhua Yundai Chen[1], Zhijun Sun[1], Qing Xi[5], Bin Feng[1*] and Zhenhong Fu[1*]

- 275 ACS patients with reduced left ventricular ejection fraction after PCI
- Patients with myocardial infarction and reduced left ventricular ejection fraction might benefit more from the initiation of S/V as first-line heart failure treatment after PCI.

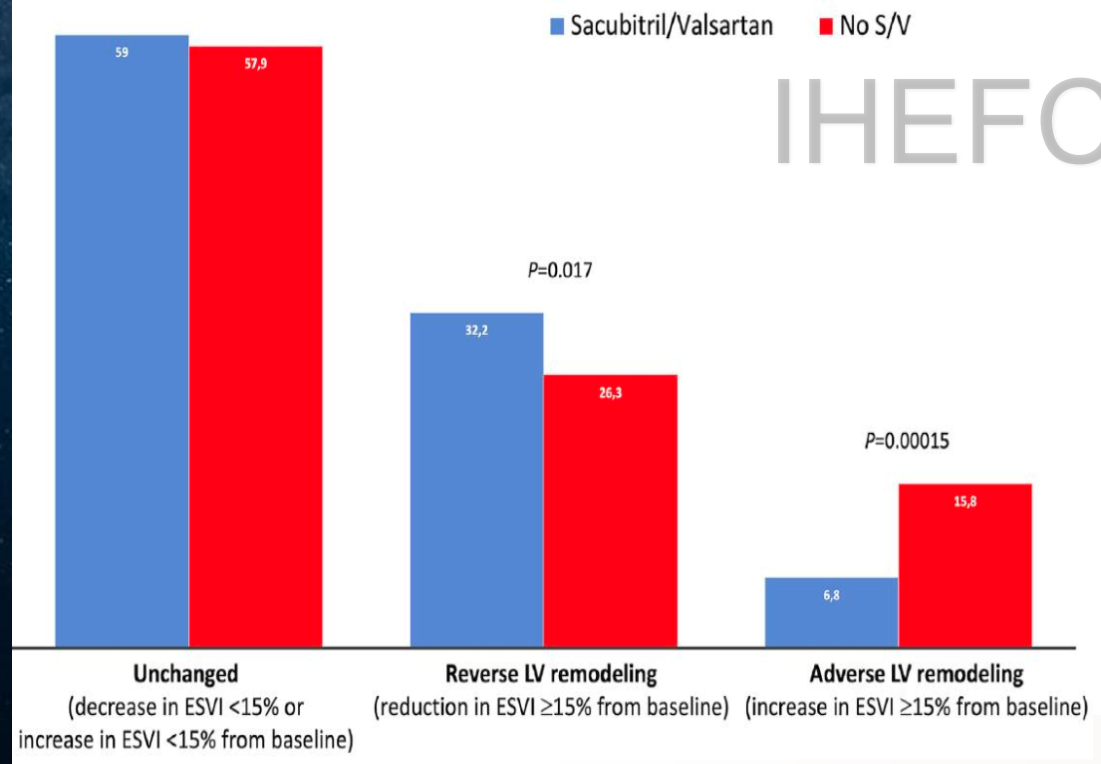


Scientific reports (2023) 13:3539

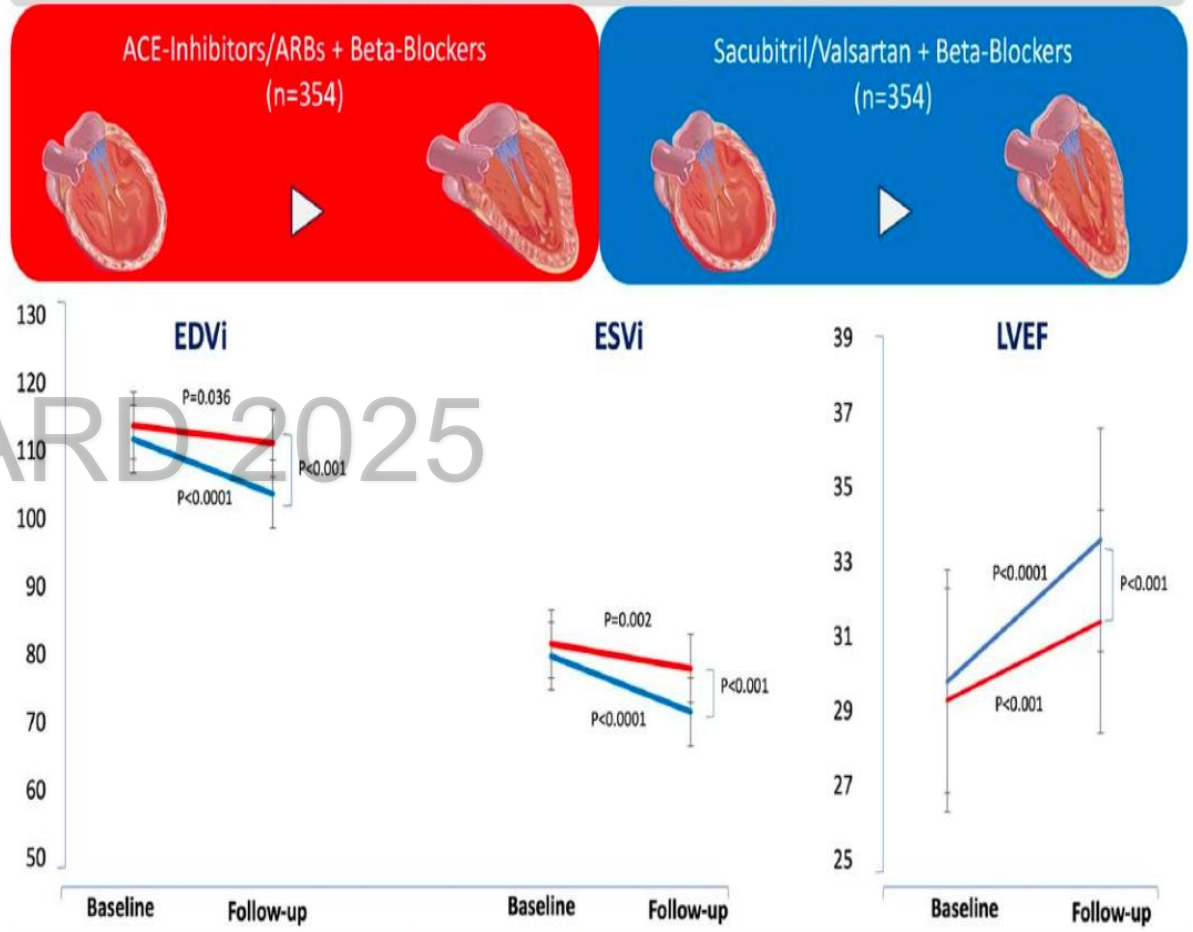
Clinical Research in Cardiology (2024) 113:856–865
https://doi.org/10.1007/s00392-023-02306-0

ORIGINAL PAPER

Effect of sacubitril/valsartan on cardiac remodeling compared with other renin–angiotensin system inhibitors: a difference-in-difference analysis of propensity-score matched samples



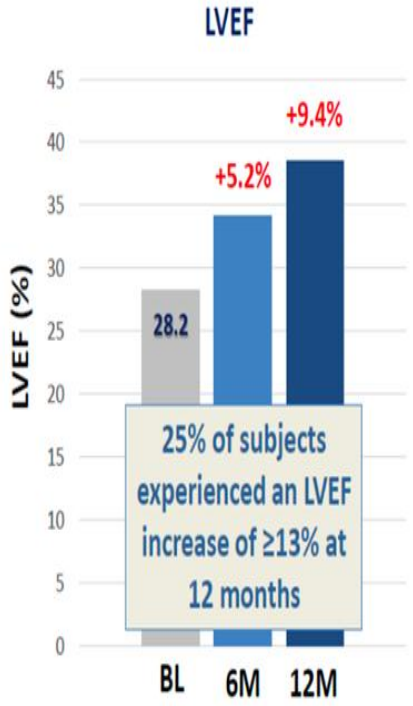
Effect of Sacubitril/Valsartan on Cardiac Remodeling Compared with Other Renin-Angiotensin System Inhibitors:
A Difference-in-Difference Analysis of Propensity Score Matched Samples

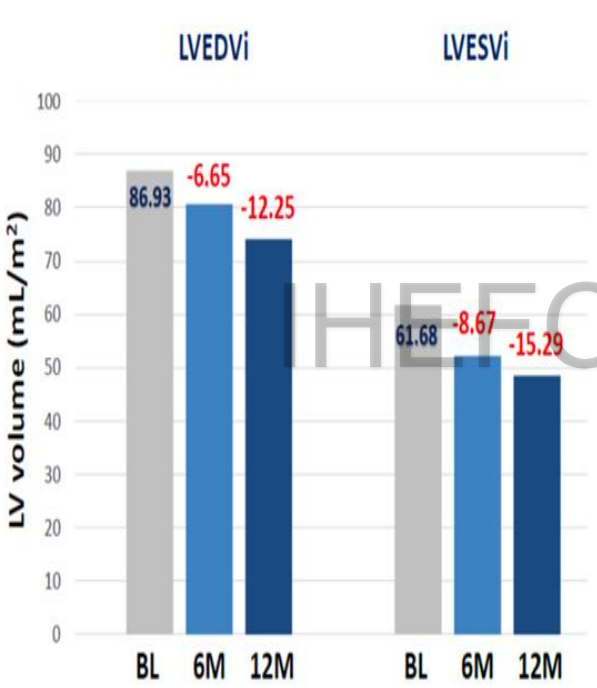


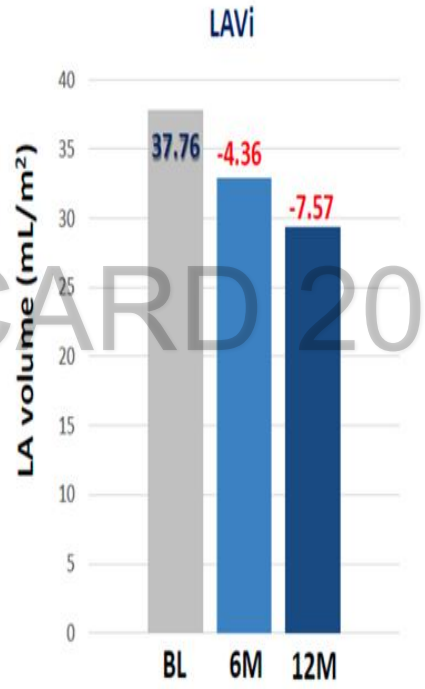
Changes on cardiac remodeling parameters:
Echocardiography at baseline and after 8-12 months

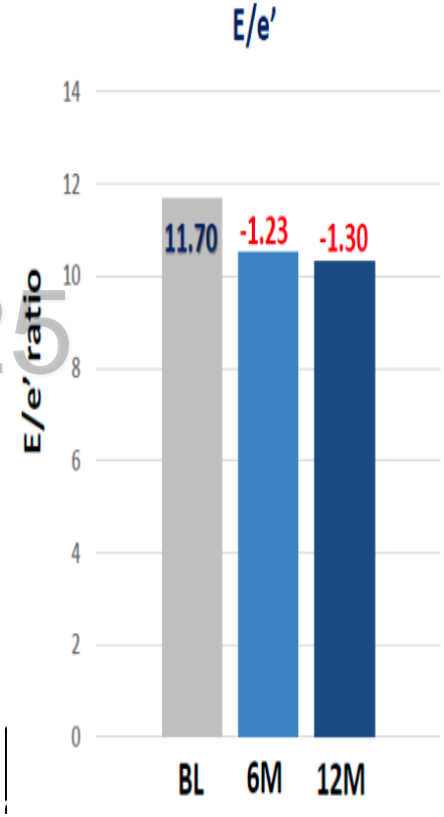
Results

PROVE-HF
Echocardiographic results at 6 & 12 months





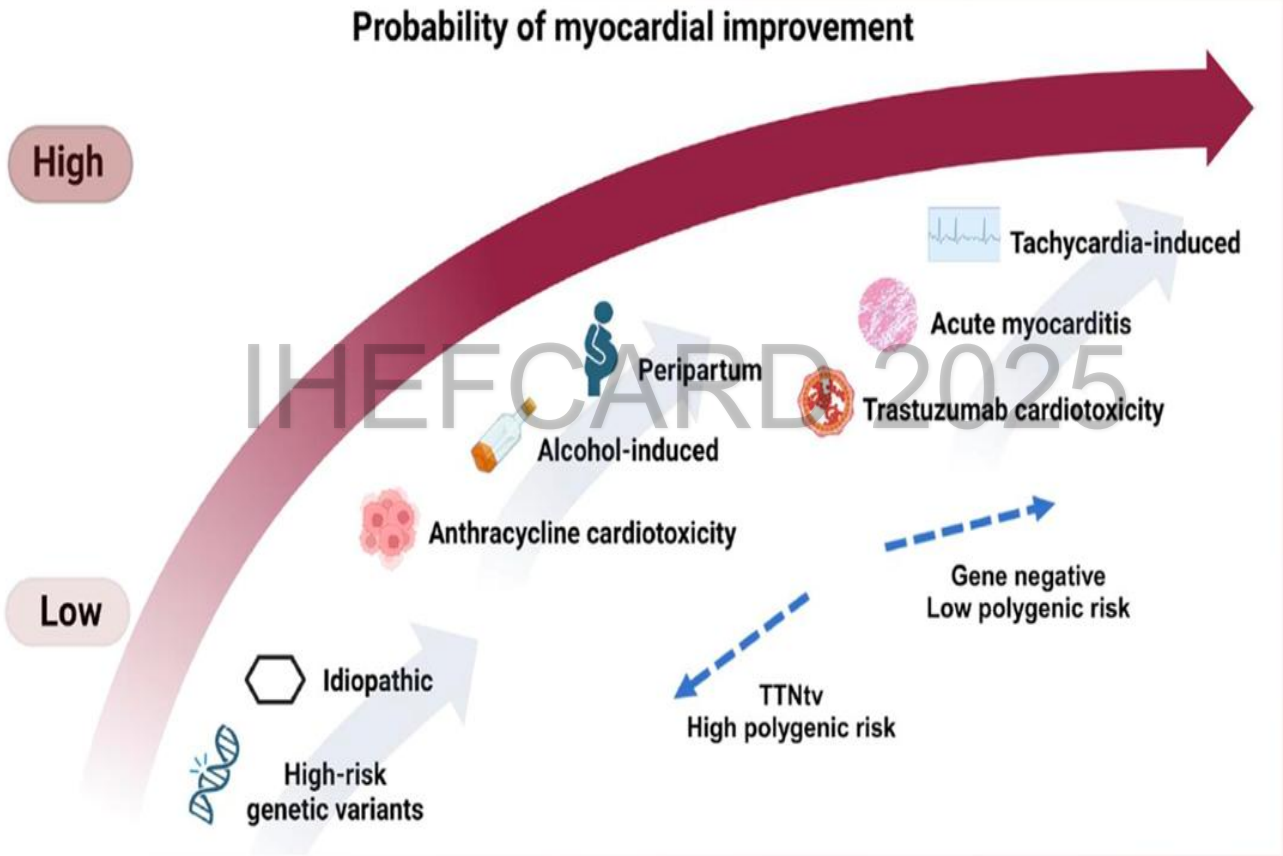




LVMi fell from 124.77 to 107.82 g/m² (mean -16.00 g/m²; P <.001)

Baseline to 12 months: all P <.001

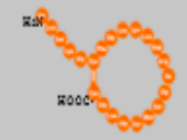
Suggested probability of LVEF improvement and normalization among different common aetiologies of dilated cardiomyopathy



Current Heart Failure Reports (2023) 20:542–554
https://doi.org/10.1007/s11897-023-00636-8

NP system

- The NP system acts in opposition to the effects of RAAS and SNS activation protective effects on the cardiovascular system by increasing renal natriuresis and diuresis, promoting vasodilatation, and decreasing the activity of the RAAS and SNS.
- There are three types on NPs, namely, atrial natriuretic peptide (ANP), B- type natriuretic peptide (BNP), and C- type natriuretic peptide (CNP).

Atrial natriuretic peptide (ANP)	B-type natriuretic peptide (BNP)	C-type natriuretic peptide (CNP)
		
▪ Expressed in the atria ▪ Measurable in plasma	▪ Expressed in atrial and ventricular tissue ▪ Measurable in plasma	▪ Expressed in vascular endothelial cells and central nervous system
$t_{1/2}$ in circulation = ~2 mins	**$t_{1/2}$ in circulation = ~20 mins**	**$t_{1/2}$ in circulation = ~3 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	Effects: ▪ Vasorelaxation ▪ ↑ Diuresis/natriuresis ▪ ↓ RAAS activation (including aldosterone) ▪ ↓ Sympathetic tone ▪ ↑ RBF and GFR ▪ Myocardial relaxation ▪ Lipid mobilization, metabolic effects	Effects: ▪ Vasorelaxation ▪ More potent dilation of veins than ANP and BNP ▪ Bone growth regulation ▪ ↓ Proliferation ▪ ↓ Hypertrophy ▪ ↓ Fibrosis ▪ ↓ Inflammation ▪ ↓ Thrombosis

vin 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;

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

JAMA. 2019;322(10):1085-1095. doi:10.1001/jama.2019.12821
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Editorial page 1061
Related article page 1077
Supplemental content

Author Affiliations: Massachusetts General Hospital, Boston (Januzzi, Camacho); Baim Institute for Clinical Research, Boston, Massachusetts (Januzzi); Novartis Pharmaceuticals, East Hanover, New Jersey (Prescott, McCague, Rocha, Williamson); University of Mississippi Medical Center, Jackson (Butler); Duke University Medical Center and Duke Clinical Research Institute, Durham, North Carolina (Felker); University of California, San Diego School of Medicine, San Diego (Maisel); Detroit Medical Center, Detroit, Michigan (Piña); Brigham and Women's Hospital, Boston, Massachusetts (Shah, Solomon).

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

Corresponding Author: James L. Januzzi Jr, MD, Massachusetts General Hospital, Yawkey 10B, 55 Fruit St, Boston, MA 02114 (JLJanuzzi@partners.org).

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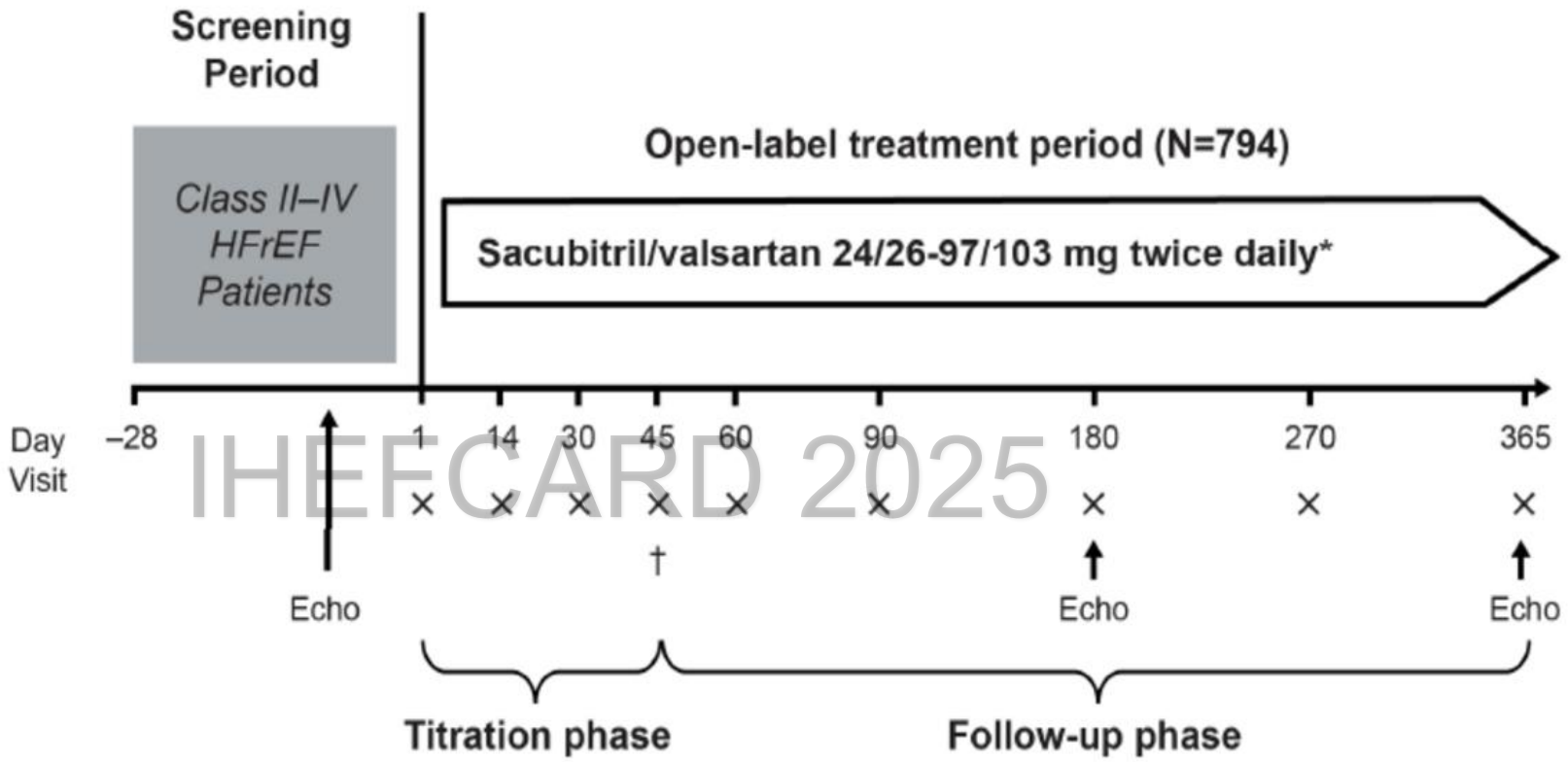
James L. Januzzi Jr, MD; Margaret F. Prescott, PhD; Javed Butler, MD, MPH, MBA; G. Michael Felker, MD, MHS; Alan S. Maisel, MD; Kevin McCague, MA; Alexander Camacho, PhD; Ileana L. Piña, MD, MPH; Ricardo A. Rocha, MD; Amil M. Shah, MD, MPH; Kristin M. Williamson, PharmD; Scott D. Solomon, MD; PROVE-HF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

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

Available at jama.com

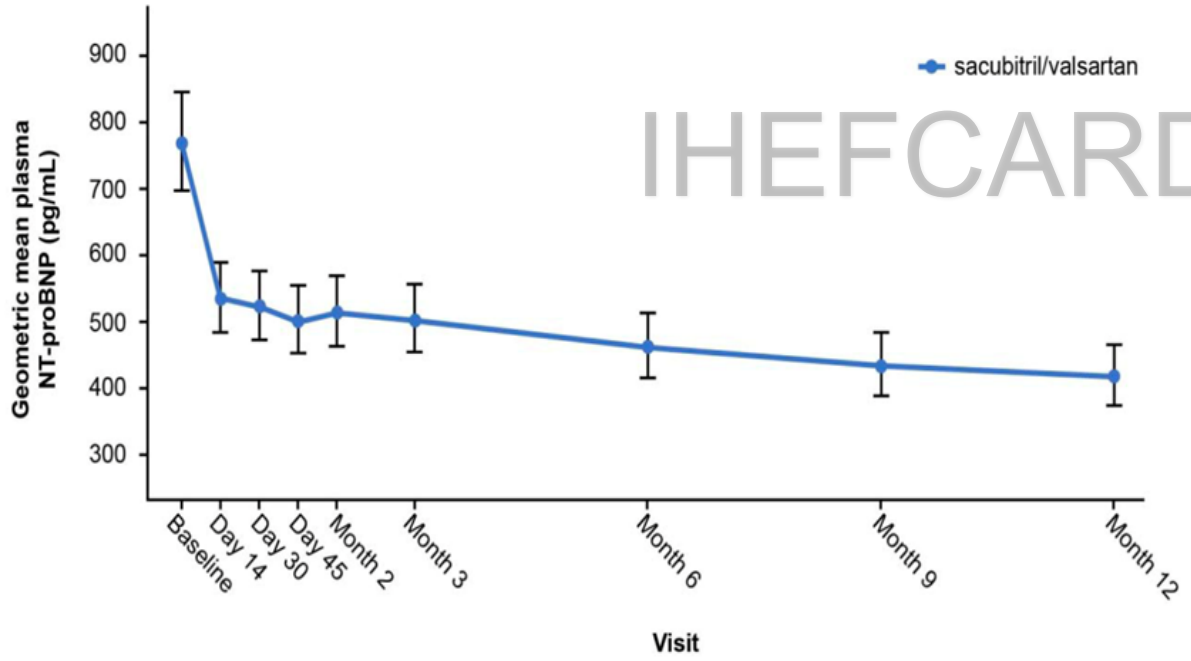
Methods



- **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

NT-proBNP concentrations

Rapid and significant decrease in NT-proBNP, with the majority occurring in the first 2 weeks after Sac/Val . 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)

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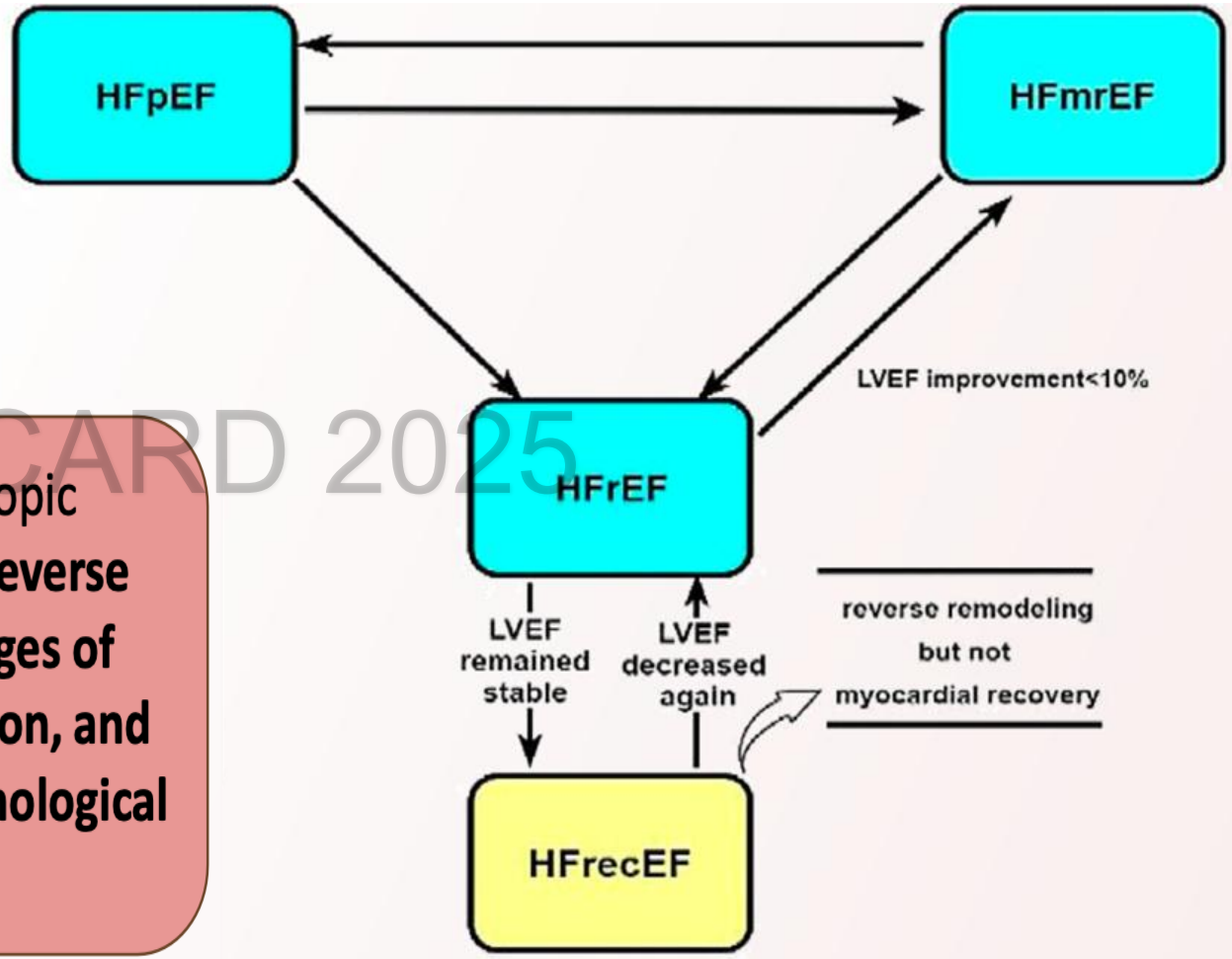
Withdrawal therapy
what's the effect

Heart failure with recovered ejection fraction: Current understanding and future prospects

Xi Chen, MD and Meifang Wu, MD

Department of Cardiology, Affiliated Hospital of Putian University, Fujian, China

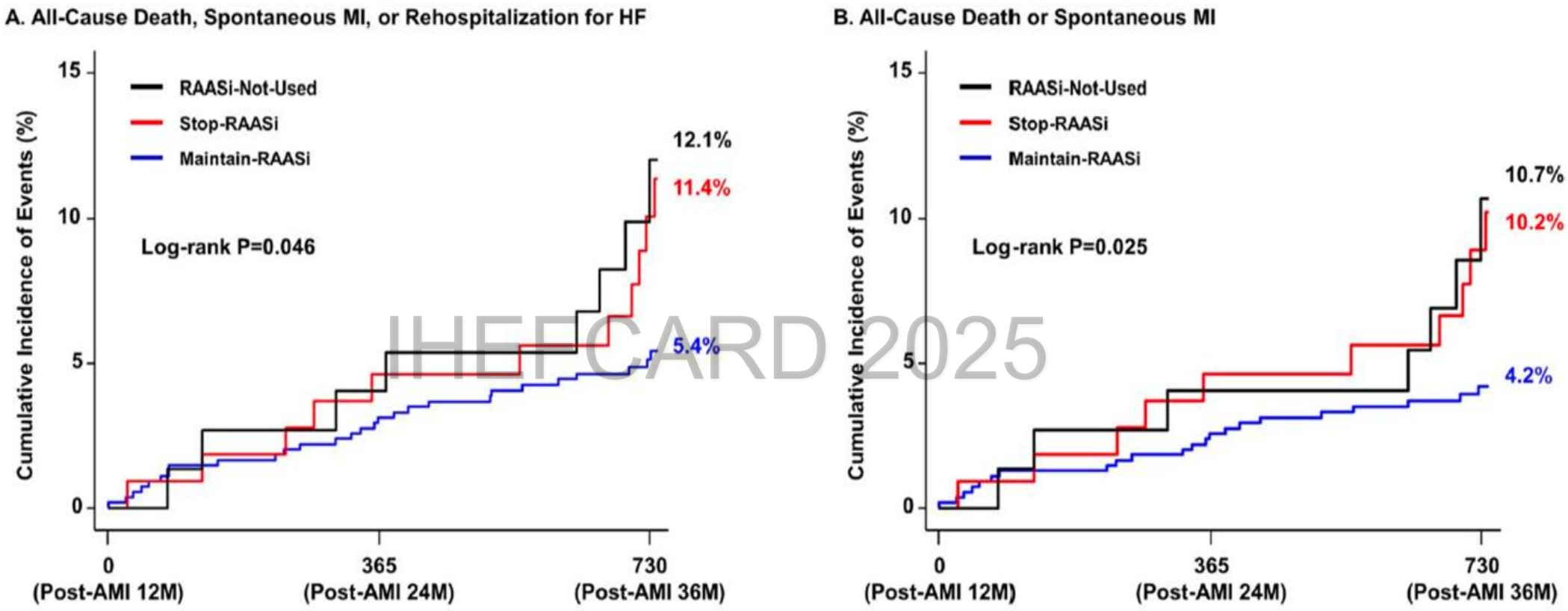
Furthermore, it is revealed from a microscopic perspective that even if partial or **complete reverse remodeling** occurs, the **morphological changes of cardiomyocytes, extracellular matrix deposition, and abnormal transcription and expression of pathological genes still exist.**



Discontinuation RAASi

A. LV Ejection Fraction, %

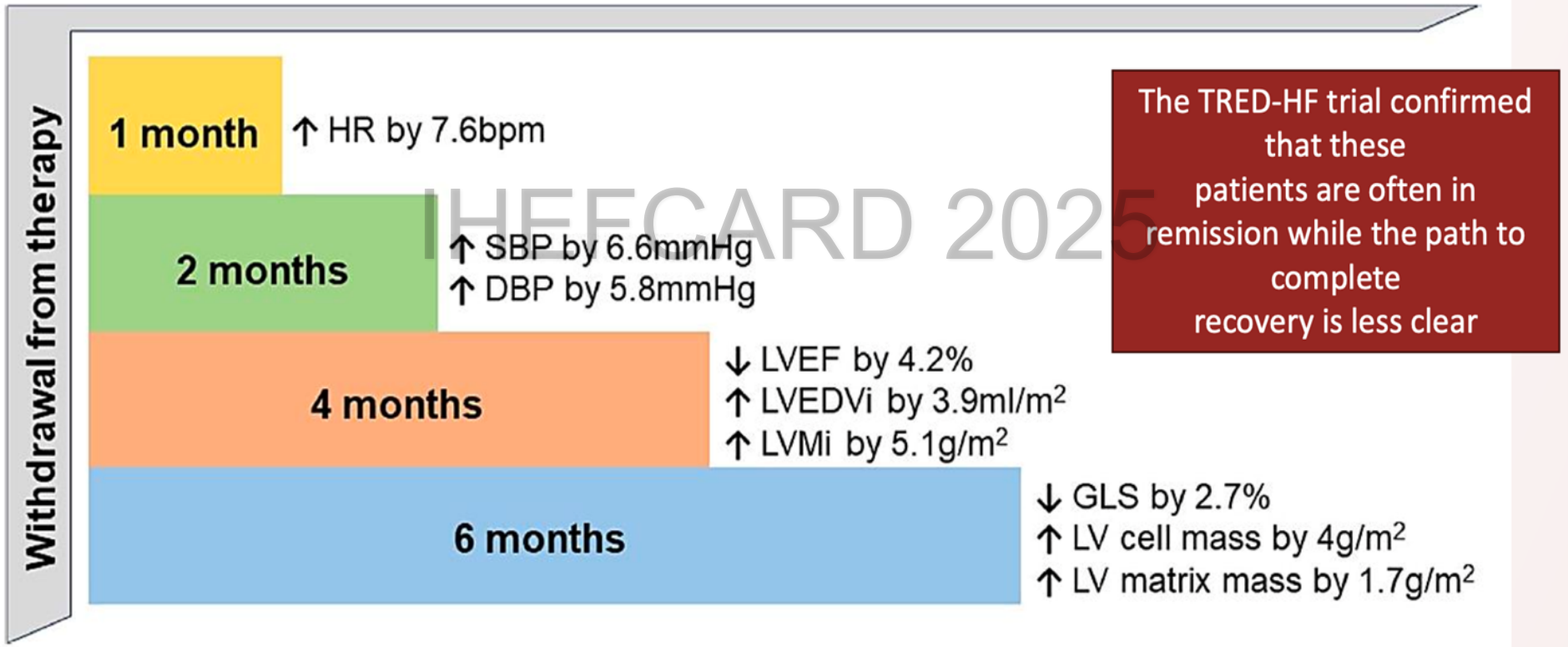
B. NT-proBNP, pg/mL



In post-AMI HF patients with restored LV systolic function, **discontinuation of RAASi** was associated with a significantly **increased risk of all-cause death, MI, or rehospitalization for HF**. This result strongly suggests the **importance of continuation of RAASi** in post-AMI patients with HFrEF, **even after recovery of LVEF**.

Scientific reports (2023) 13:3539

Main changes in clinical and imaging parameters observed in patients who withdrew from therapy in TRED-HF



Current Heart Failure Reports (2023) 20:542–554
https://doi.org/10.1007/s11897-023-00636-8

Chronic drug treatment in PPCM after delivery

Drug	Persisting heart failure and absence of complete LV recovery	Complete and sustained recovery (LVEF > 55% and NYHA functional class I)
Beta-blocker	Essential for all patients in standard or maximally tolerated dosages	Continue all drugs (beta-blocker, ACEI/ARB/ARNI, MRA) for at least 12–24 months after full recovery, individual approach/discuss with patient. Discontinue stepwise and monitor symptoms and LV function: 1. MRA 2. ACEI/ARB/ARNI 3. Beta-blocker
ACEI	Essential for all patients in standard or maximally tolerated dosages	
ARB	Recommended in patients who do not tolerate ACEI	
ARNI	Recommended in patients with LVEF < 40% who are symptomatic despite maximal dosages of beta-blocker, ACEI/ARB and MRA	
MRA	Recommended in patients with LVEF < 40%, preferably eplerenone due to less hormonal side effects and less blood pressure reduction compared to spironolactone	
Ivabradine	Recommended in patients in sinus rhythm with a persisting heart rate > 70 b.p.m. at rest despite maximal tolerated beta-blocker up-titration	Discontinue if heart rate < 50 b.p.m. and/or in case of complete recovery
Diuretics	Recommended in patients with fluid overload	Taper dose/discontinue if no signs of fluid overload, maintain only if part of antihypertensive therapy

K Sliwa, et al. ESC Position paper on PPCM, European Journal of Heart Failure (2019) 21, 827–843

Heart failure with improved ejection fraction: HFimpEF

Definition: initial LVEF <40% and ↑LVEF >40% by ≥10%

Rate: 10–40%

Ischaemic aetiology	Dilated CMP / Myocarditis	Valvular heart disease	Arrhythmia-induced CMP	Chemotherapy cardiotoxicity	Stress-induced CMP	Hyperthyroidism-induced CMP

Myocardial revascularisation:
• CABG > PCI
	• Spontaneous recovery following myocarditis
	• Anti-inflammatory treatment
	• Specific treatment, e.g. enzyme substitution
		• Surgical valve replacement or repair
		• TAVI/mitraClip
			• Rate control
			• Rhythm control:
			  • AAD
			  • Cardioversion
			  • Ablation
				• Drug cessation
				• Cardioprotective treatment
					• Spontaneous recovery of systolic function
					• Beta-blockers
						• Thyreostatic drugs
						• Propranolol
						• Radioiodine ablation

Maintenance of optimal medical therapy: ACEI/ARB or ARNI + beta-blocker + MRA + SGLT2i ± ivabradine

Continuation of maintenance dose of oral diuretic

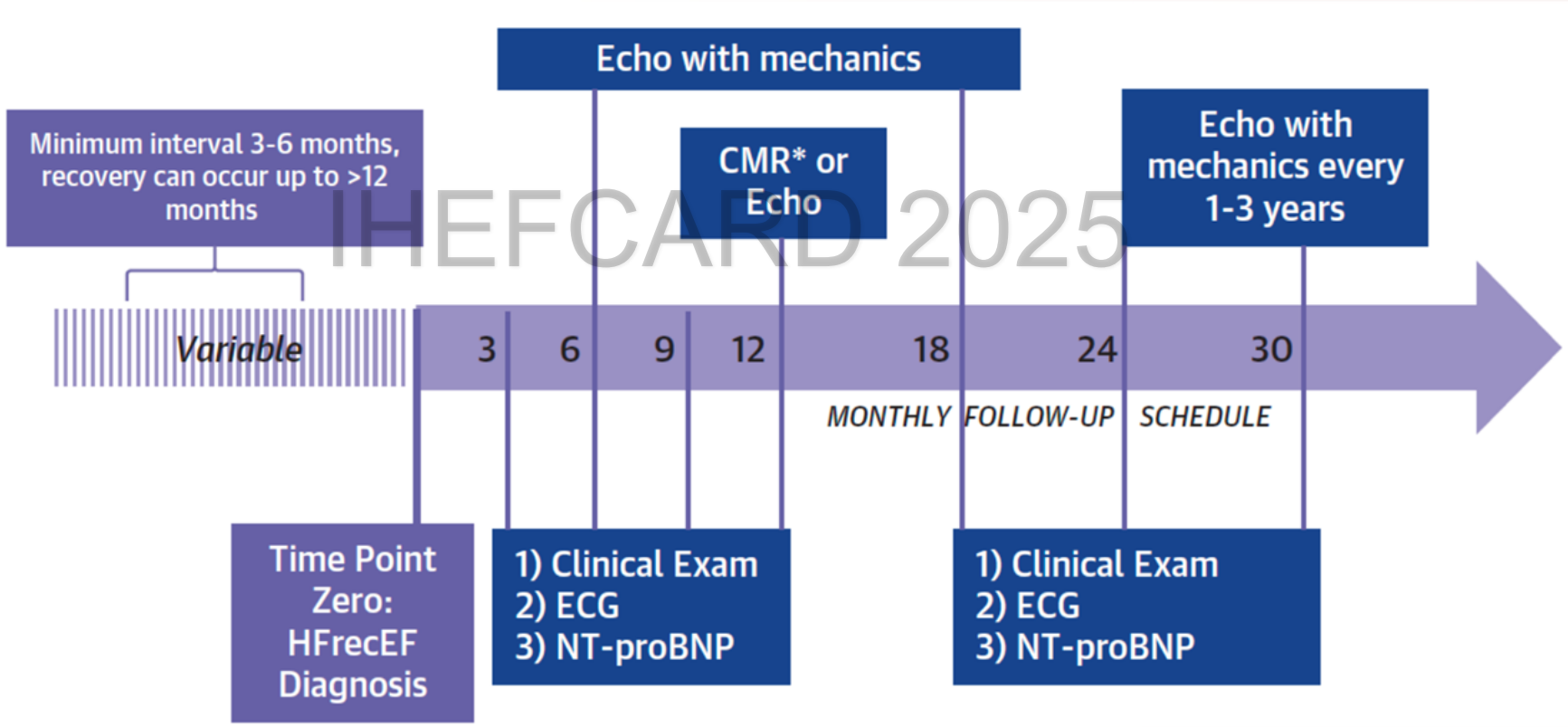
ICD/CRT replacement despite LVEF improvement / delay of ICD implantation for 3–6 months in primary prevention, particularly in non-ischaemic HF

Medical consult, physical examination ECG, TTE, natriuretic peptides every 6 months during first 12–18 months of improvement

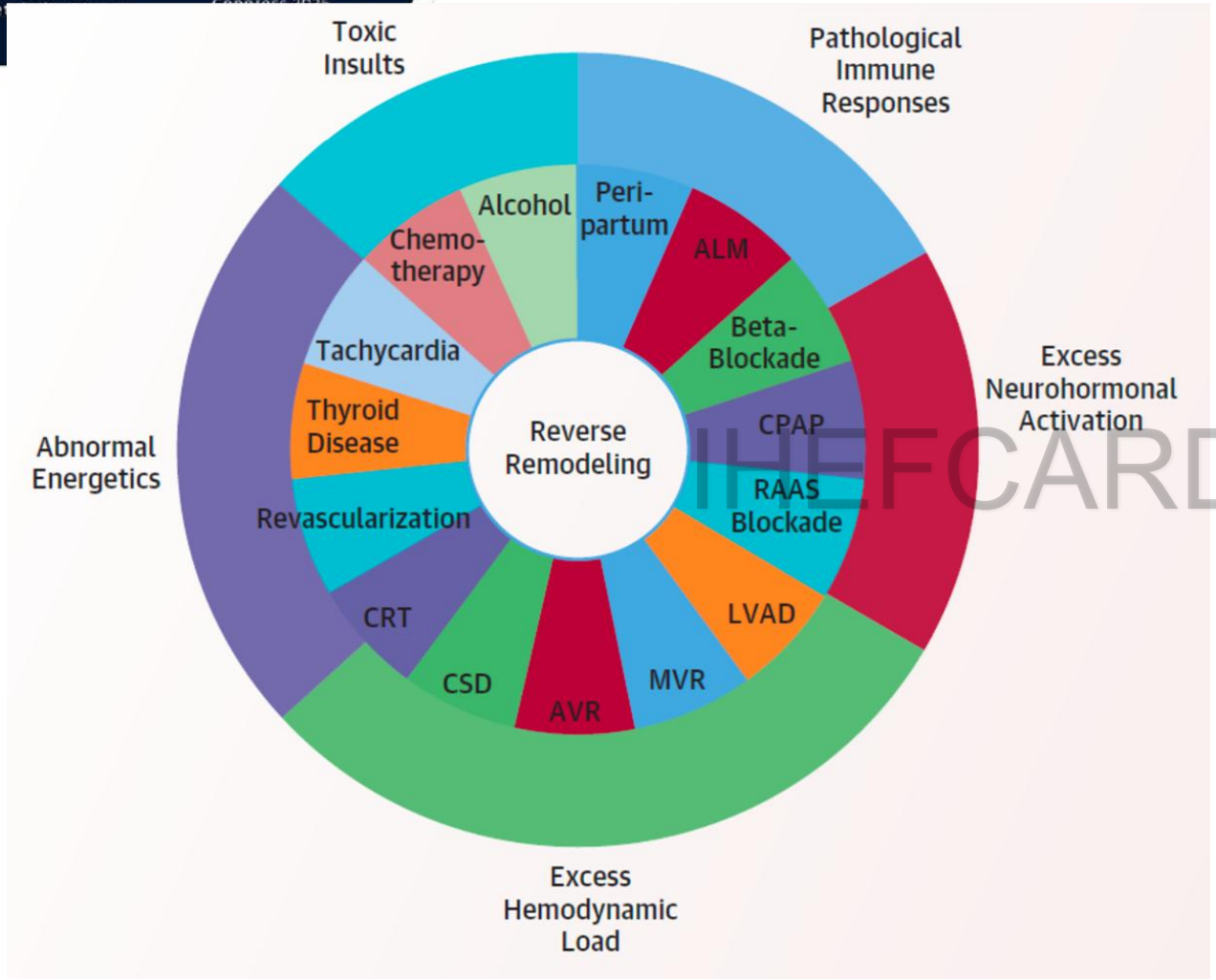
Genetic profiling: tTTN mutations–good response to GDMT; LMNA, SCN5A, FLNC, DSP– high risk of SCD

Wybraniec, MT et al. Int. J. Environ. Res. Public Health 2022, 19, 14400.
https://doi.org/10.3390/ijerph192114400

Sample Follow-Up and Clinical Testing Schedule for an HFrecEF Patient Deemed High-Risk for Recurrence of HF



JACC Scientific Expert Panel, 2020
https://doi.org/10.1016/j.jacc.2020.05.075



HIGHLIGHTS

- This consensus document was created because there are no guidelines for the management of patients with HFrecEF.
- A working definition of HFrecEF that is consistent with the majority of studies in the literature includes the following: 1) documentation of a decreased LVEF <40% at baseline; 2) ≥10% absolute improvement in LVEF; and 3) a second measurement of LVEF >40%.
- Guideline-directed medical and device therapy for patients with HFrecEF should be continued indefinitely until the biology and clinical epidemiology of HFrecEF is better understood.
- HFrecEF patients should have close clinical follow-up due to the high risk of heart failure relapse.

JACC Scientific Expert Panel, 2020 https://doi.org/10.1016/j.jacc.2020.05.075

Conclusion

- Cardiac adverse remodeling is associated with the development and progression of ventricular dysfunction, arrhythmias and poor prognosis
- The most important predictors of cardiac reverse remodeling were female sex, non-ischemic etiology, narrower QRS width, better kidney function and smaller diameter of the left ventricle and left atrium
- Reverse remodeling may lead to improve myocardial function and, in some patients, to myocardial remission and myocardial recovery, but major abnormalities persist at the molecular level contributing to an elevated risk ofcardiovascular events
- The earlier the remodeling changes are altered with the use of guideline-directed medical therapy, devices, and with available surgical options, thegreater is the chance of reverse remodeling of LV morphology and architectural changes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LV ejection fraction (LVEF)

- 2D (biplane method of discs = modified Simpson's rules) or 3D (to be used if good image quality)
- LVEF = ((LVEDV − LVESV)/LEDV) × 100%
- LVEF is not significantly related to gender, age, and BSA
- Reference upper 2DE limits
  - Men: LVEDV = 74 ml/m², LVESV = 31 ml/m²
  - Women: LVEDV = 61 ml/m², LVESV = 24 ml/m²
  - LVEF = 63 ± 5%; range 53–73% above 20 years
- A value of LVEF < 53% is suggestive of abnormal LV systolic function

Global longitudinal strain (GLS) (Fig. 4.1.7)

- The most commonly used strain-based measure of LV global systolic function
- Obtained often with speckle tracking, less frequently with Doppler tissue imaging (DTI)

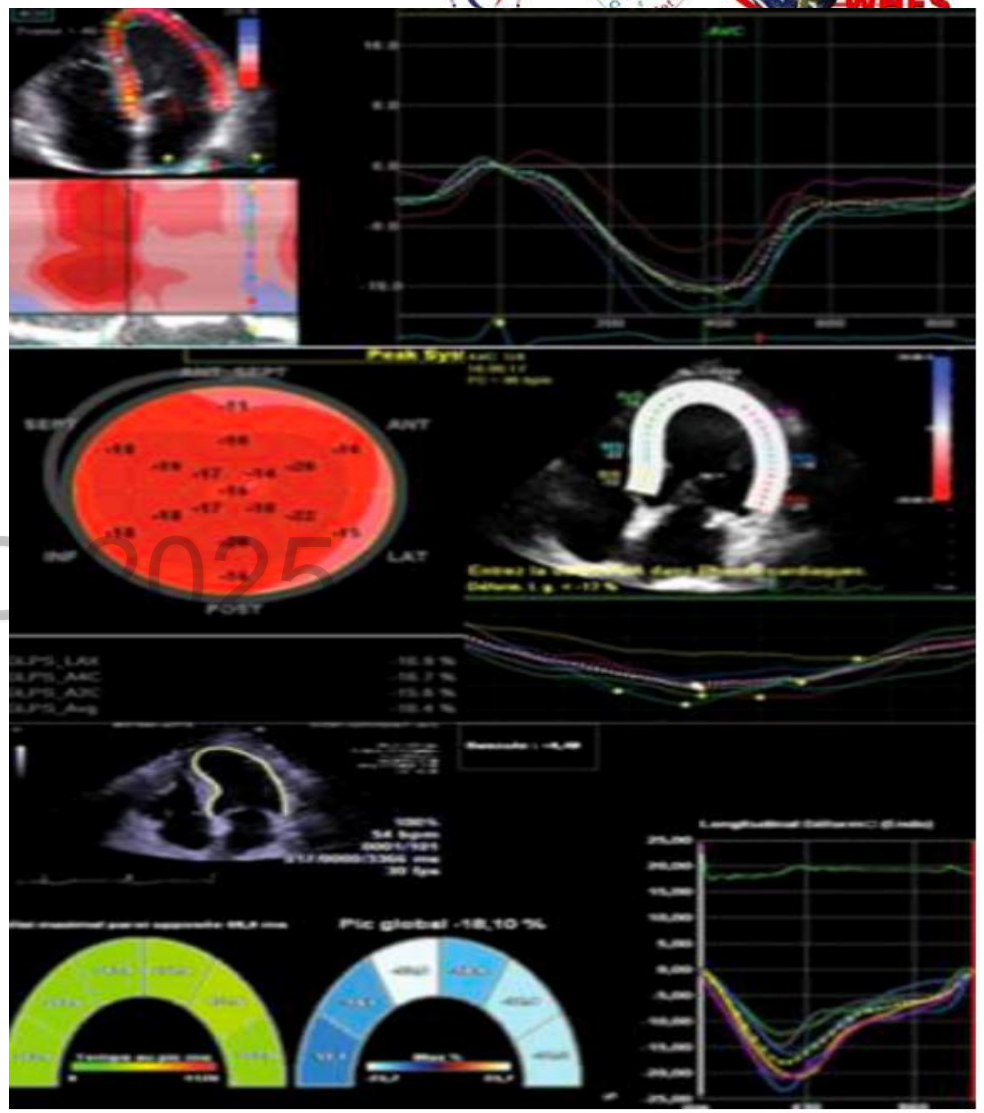

Fig. 4.1.7 Examples of measurement of GLS using different software

ESC European Society of Cardiology
European Journal of Heart Failure (2024) 26, 1454–1479
doi:10.1002/ejhf.3264
REVIEW ARTICLE

Mechanisms of myocardial reverse remodelling and its clinical significance: A scientific statement of the ESC Working Group on Myocardial Function

Inês Falcão-Pires[1*†], Ana Filipa Ferreira[1†], Fábio Trindade[1†], Luc Bertrand[2,3], Michele Ciccarelli[4], Valeria Visco[4], Dana Dawson[5], Nazha Hamdani[6,7,8,9], Linda W. Van Laake[10], Frank Lezoualc'h[11], Wolfgang A. Linke[12], Ida G Lunde[13,14], Peter P. Rainer[15,16,17], Mahmoud Abdellatif[15,16], Jolanda Van der Velden[18], Nicola Cosentino[19,20], Alessia Paldino[21,22], Giulio Pompilio[19,23], Serena Zacchigna[21,22], Stephane Heymans[24,25], Thomas Thum[26], and Carlo Gabriele Tocchetti[27]

Beta-blockers	β-adrenergic receptor inhibition (inotropic/chronotropic effects, blood pressure reduction, depending on selectivity)	HFrEF Hypertension STEMI Ischaemic and non-ischaemic cardiomyopathy Atrial fibrillation (ventricular rate control)	↓ LVM ↓ Hypertrophy ↓ LVEDV and LVESV ↑ Diastolic function ↑ Ejection fraction ↑ Exercise capacity ↑ Diastolic coronary blood flow time ↑ Myocardial oxygen supply/demand ↓ Adverse events ↓ Mortality risk
Mineralocorticoid receptor antagonists	Aldosterone antagonism at its receptors	HFrEF HFpEF STEMI Hypertension (resistant)	↓ LVMI
Sodium–glucose cotransporter 2 inhibitors	Reduction of the reabsorption of filtered glucose (glycaemia control) and sodium + anti-inflammatory, antioxidative effects, endothelial function improvement, modulation of neurohormonal pathways	HFrEF HFpEF	↓ NT-proBNP ↑ LVEF ↑ Diastolic function (↓ E/e') ↓ LVESV, LVEDV ↓ LVM ↓ LAVI ↓ E-wave deceleration time