The 3rd Indonesian Symposium on Heart Failure and Cardiometabolic Disease 2023

When Ejection Fraction Recovers, What's Next?

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Sebelas Maret University Hospital

Case Illustration

Klinik Gagal Jantung Sebelas Maret
(Sebelas Maret Heart Failure Clinic)

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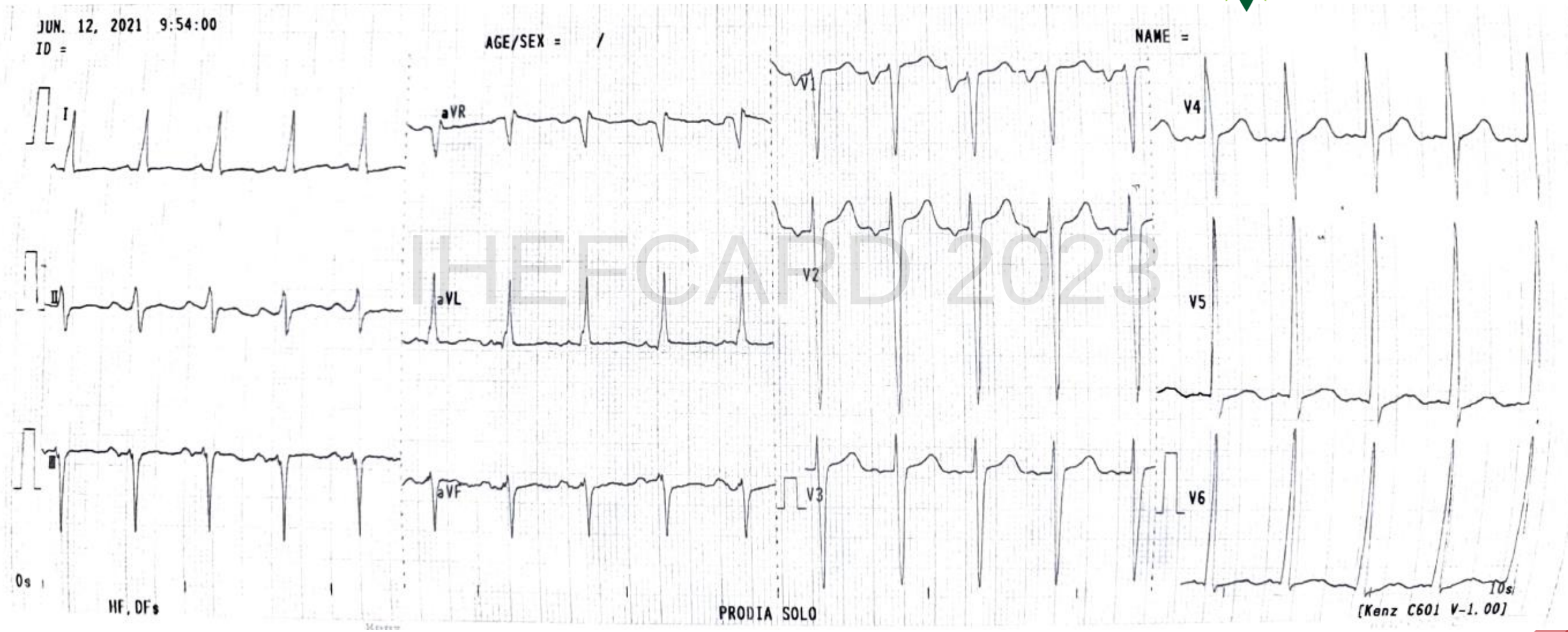
Care, Commitment, Conscience
SNARS 1

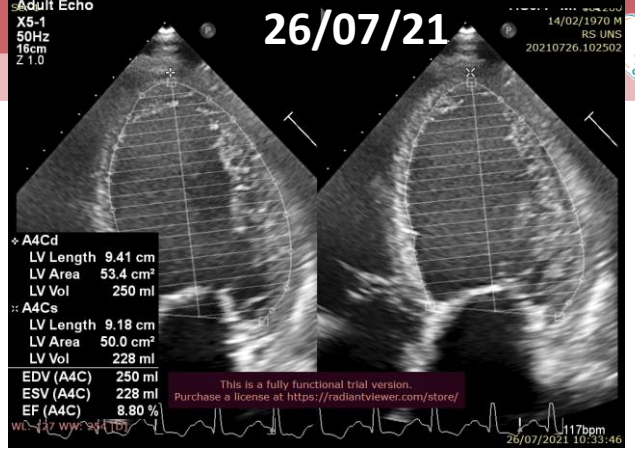
- Male, 46th y.o
- DoE (+), PND (+), Op (+)
- Hx dislipidemia, cigarette smoker, alcohol consumption in moderation
- family history of DCM
- Coronary CT
  - Moderate stenosis mid LAD (50%)
  - CAD RADS 3/HRP

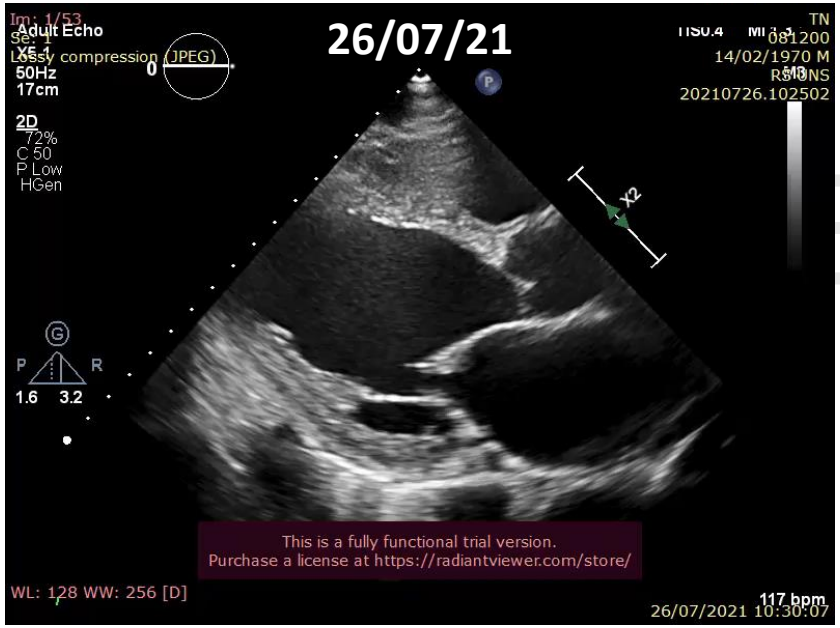
Lab	Value
FBG	108 mg/dL
Total cholesterol	169 mg/dL
LDL cholesterol	128 mg/dL
Triglyceride	99 gmdL
Creatinin	1.14 mg/dL
eLFG	77 mL/min/1.73 m2

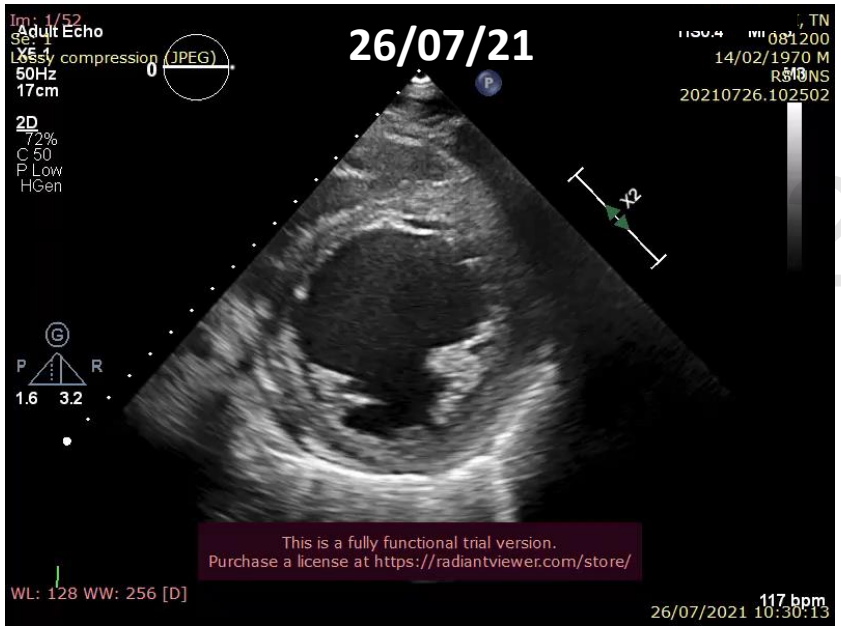


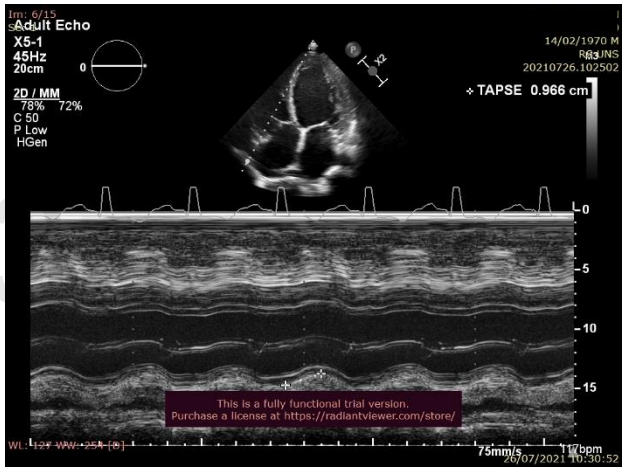
Klinik Gagal Jantung Sebelas Maret
(Sebelas Maret Heart Failure Clinic)

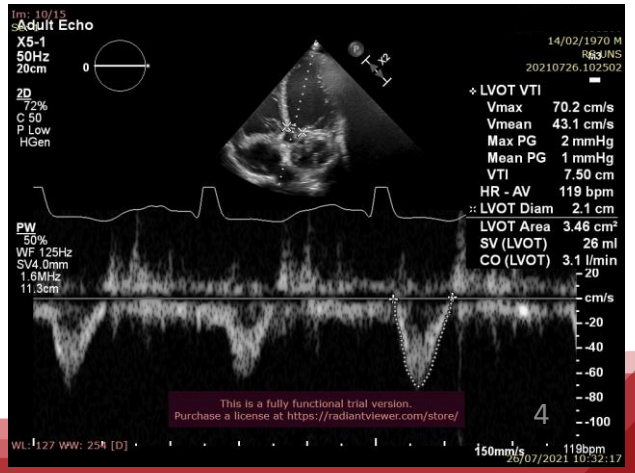
Echocardiography











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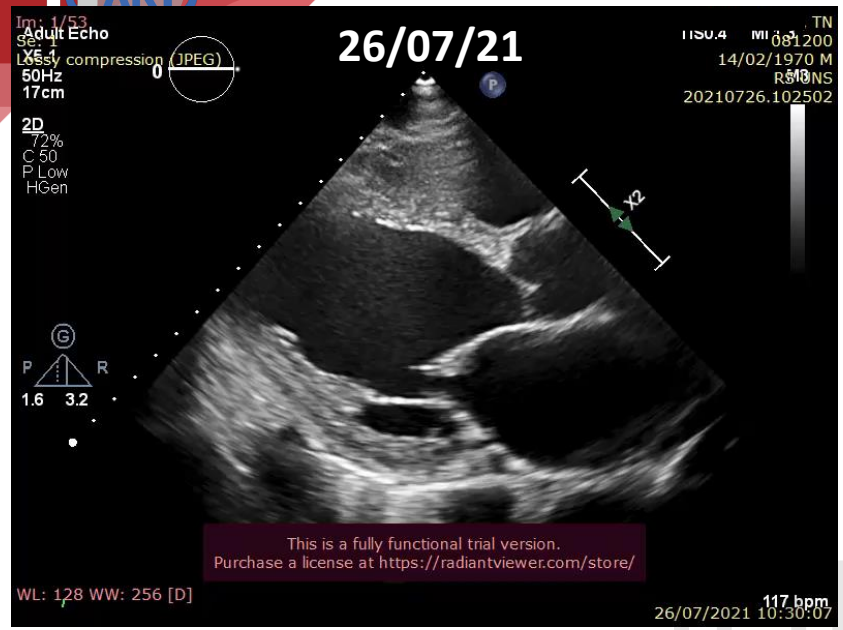
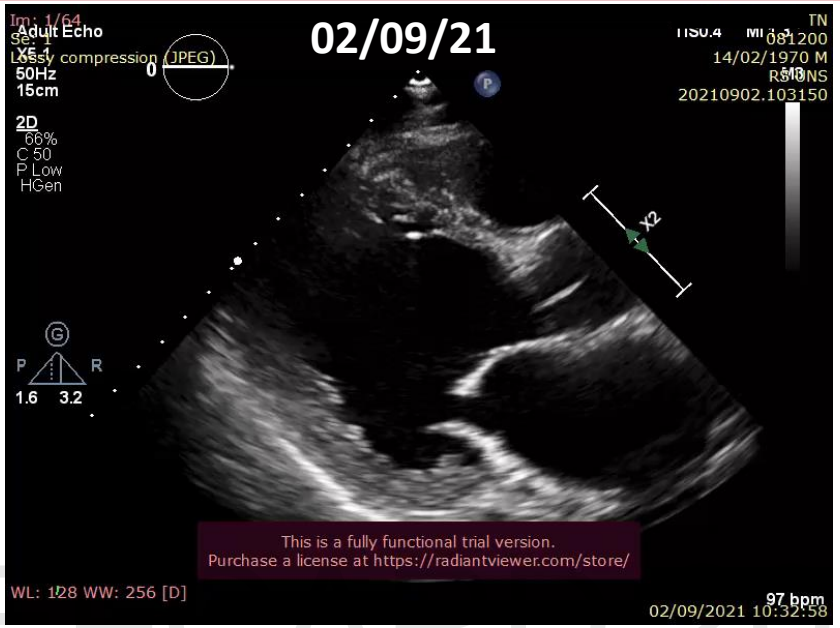
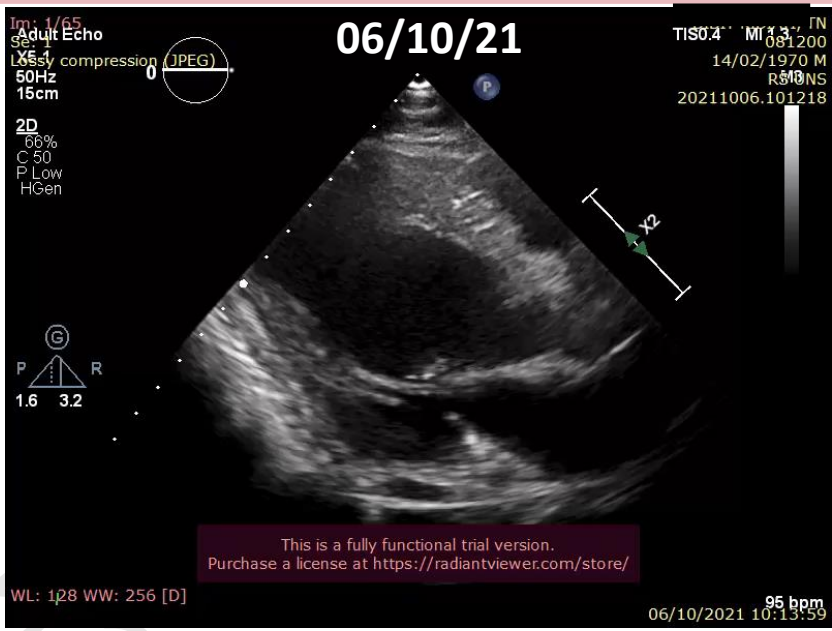
Therapy

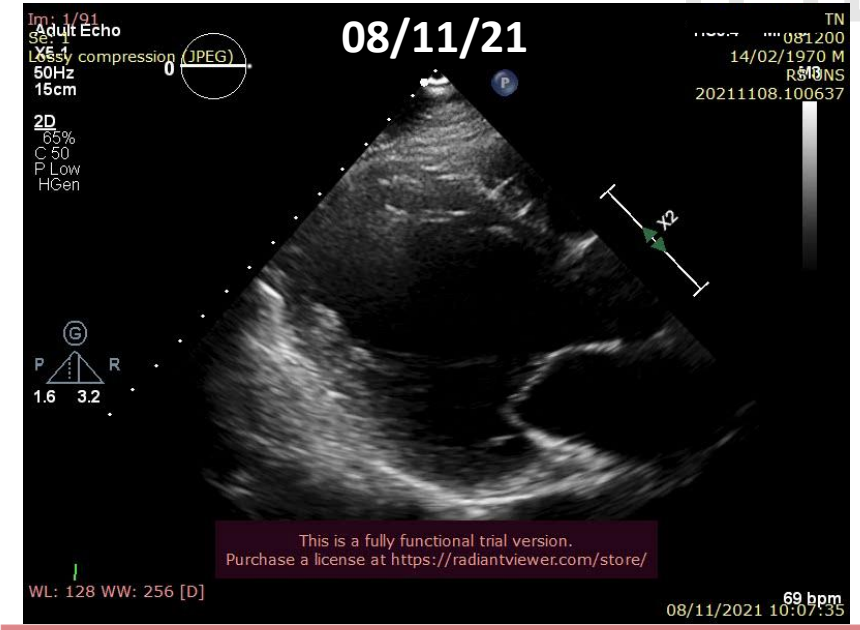
- ARNI 50mg b.i.d titrated
- Carvedilol 6.25mg b.i.d titrated
- Spironolacton 25mg o.d
- Furosemide 40 iv titrated
- SGLT2i 10mg o.d
- Atorvastatin 20mg o.d
- Acetyl salicylic acid o.d

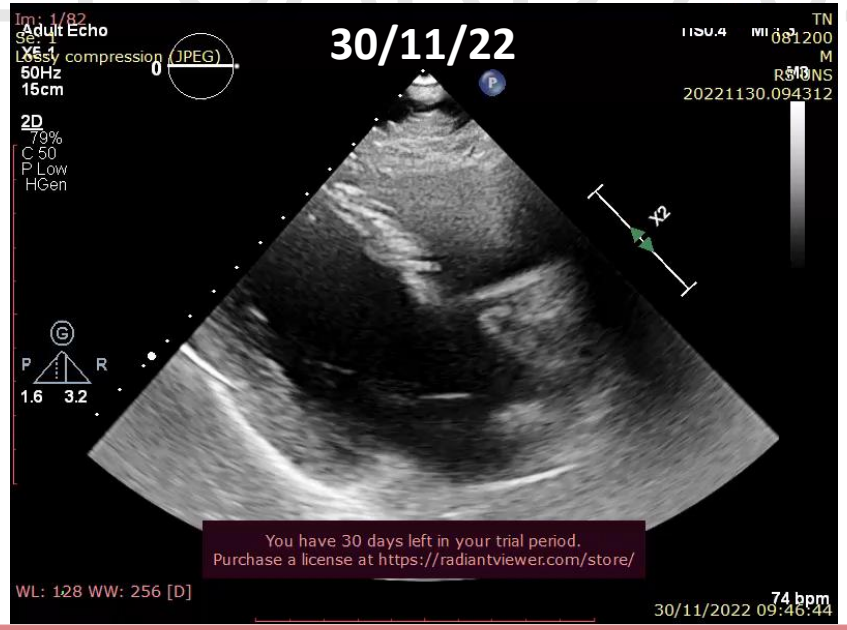
@ina.hf | +62811-1900-8855 | pokjahf@gmail.com











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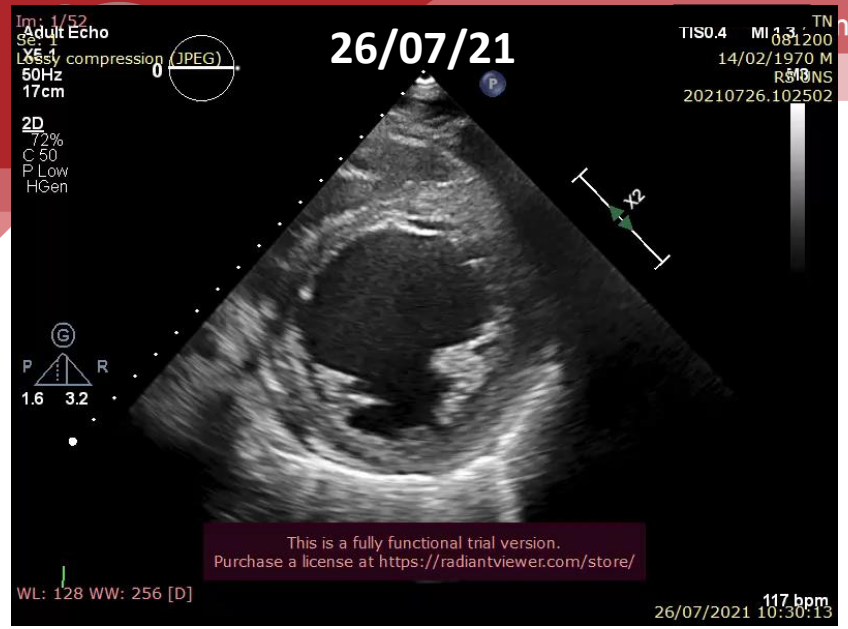
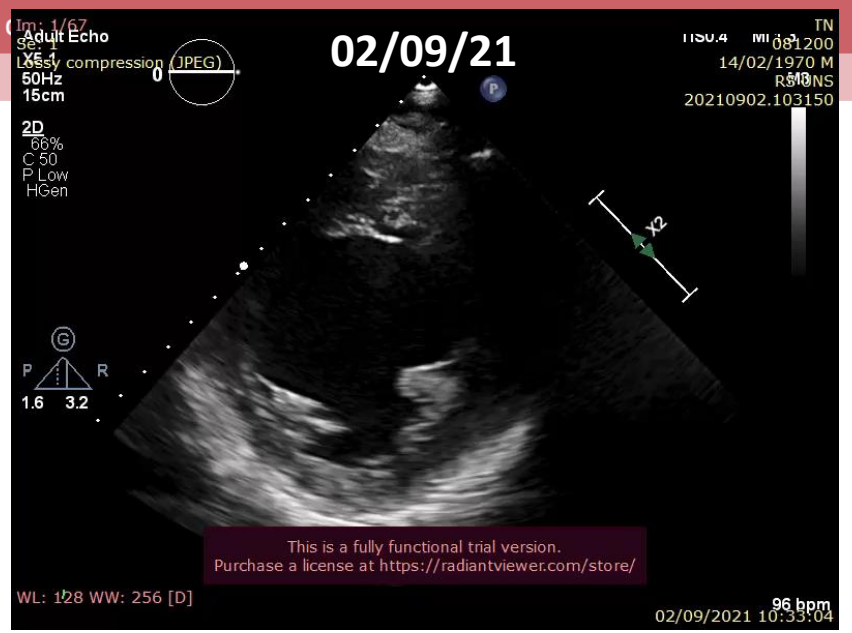
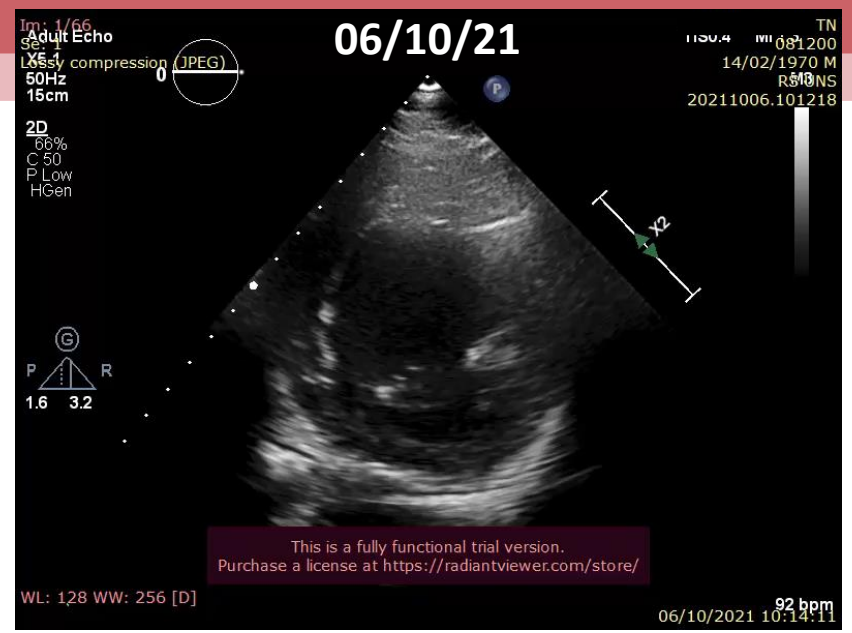
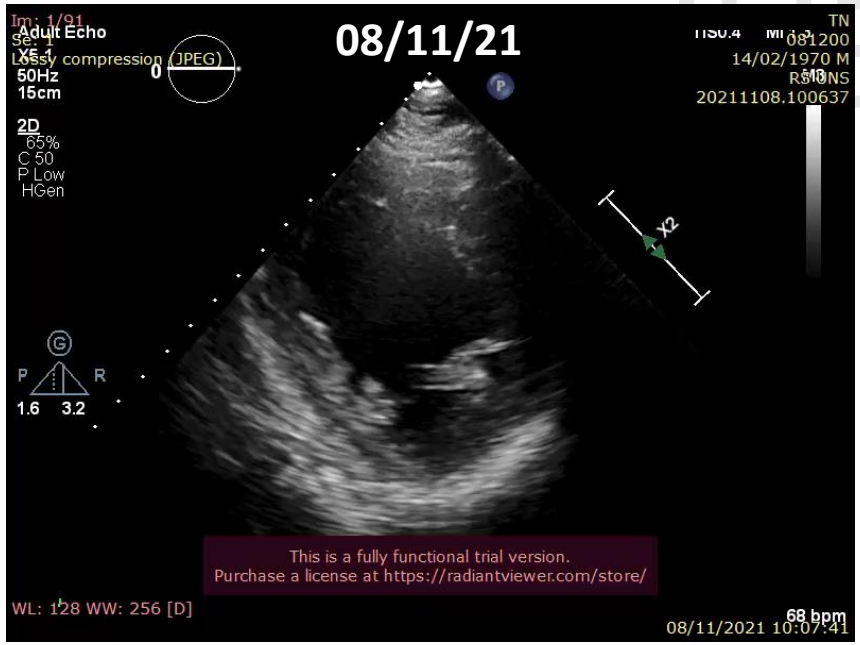
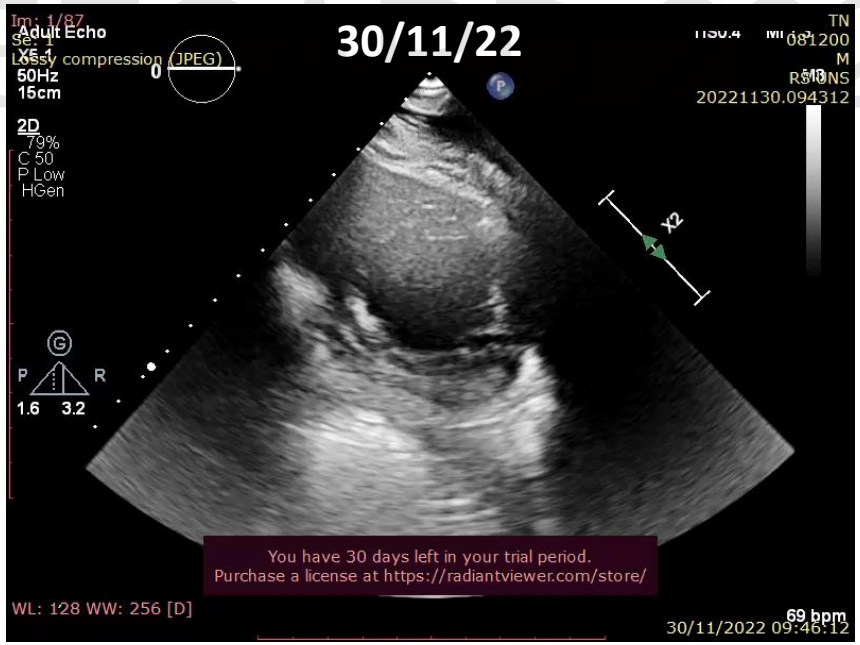
SNARS 1











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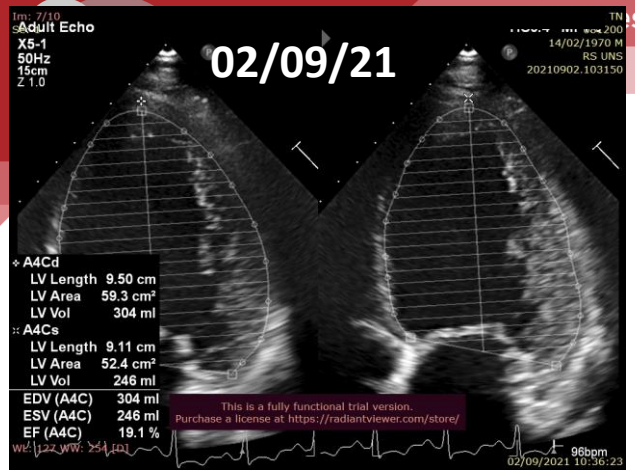
02/09/21
A4Cd
LV Length 9.50 cm
LV Area 59.3 cm²
LV Vol 304 ml
A4Cs
LV Length 9.11 cm
LV Area 52.4 cm²
LV Vol 246 ml
EDV (A4C) 304 ml
ESV (A4C) 246 ml
EF (A4C) 19.1 %
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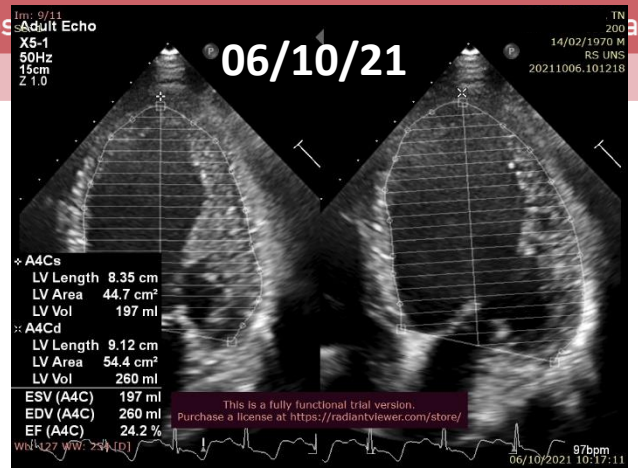
06/10/21
A4Cs
LV Length 8.35 cm
LV Area 44.7 cm²
LV Vol 197 ml
A4Cd
LV Length 9.12 cm
LV Area 54.4 cm²
LV Vol 260 ml
ESV (A4C) 197 ml
EDV (A4C) 260 ml
EF (A4C) 24.2 %
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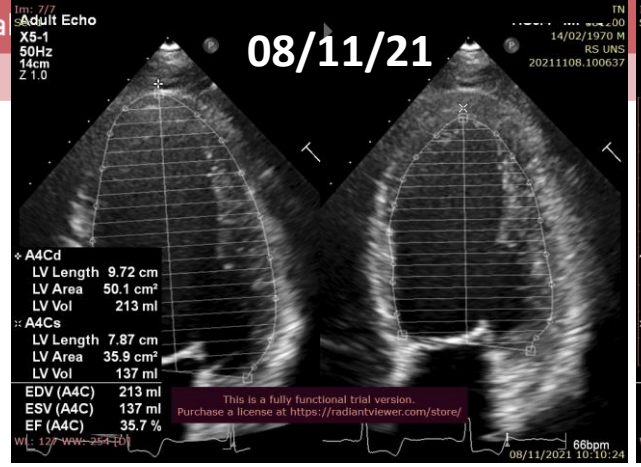
08/11/21
A4Cd
LV Length 9.72 cm
LV Area 50.1 cm²
LV Vol 213 ml
A4Cs
LV Length 7.87 cm
LV Area 35.9 cm²
LV Vol 137 ml
EDV (A4C) 213 ml
ESV (A4C) 137 ml
EF (A4C) 35.7 %
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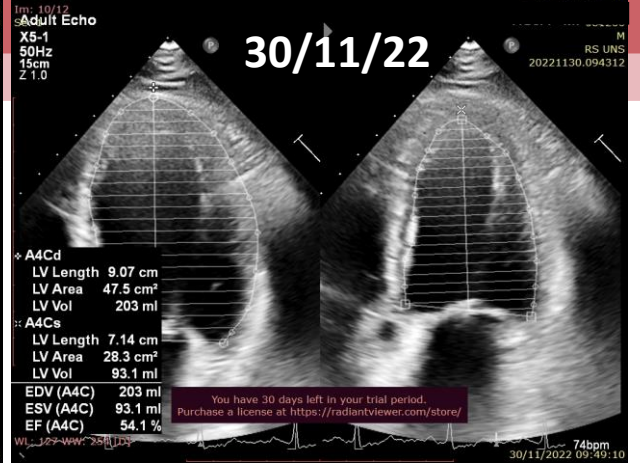
30/11/22
A4Cd
LV Length 9.07 cm
LV Area 47.5 cm²
LV Vol 203 ml
A4Cs
LV Length 7.14 cm
LV Area 28.3 cm²
LV Vol 93.1 ml
EDV (A4C) 203 ml
ESV (A4C) 93.1 ml
EF (A4C) 54.1 %
You have 30 days left in your trial period.
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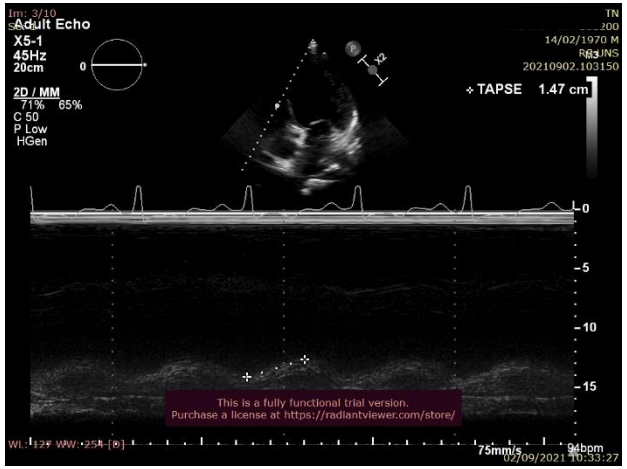
TAPSE 1.47 cm
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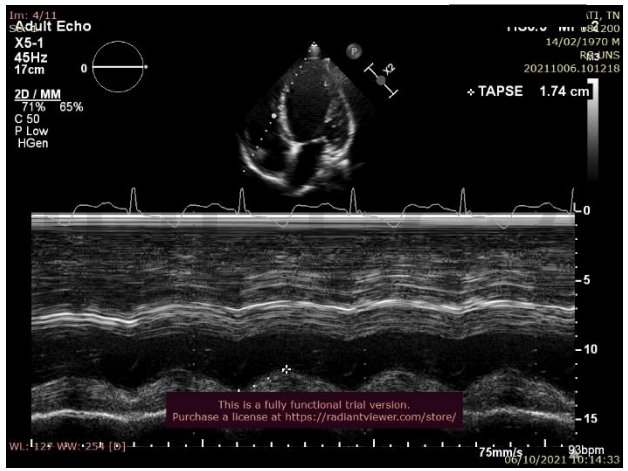
TAPSE 1.74 cm
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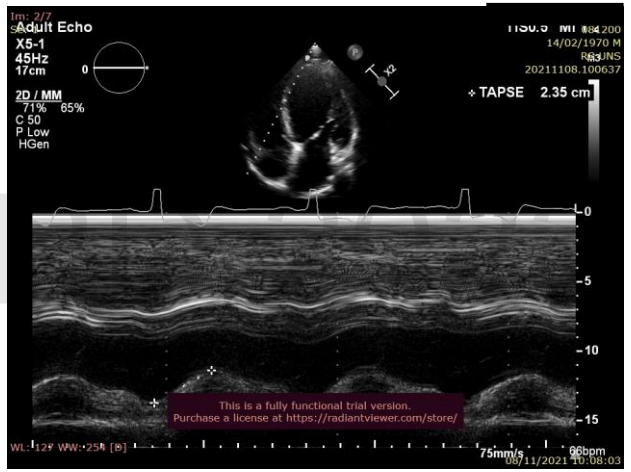
TAPSE 2.35 cm
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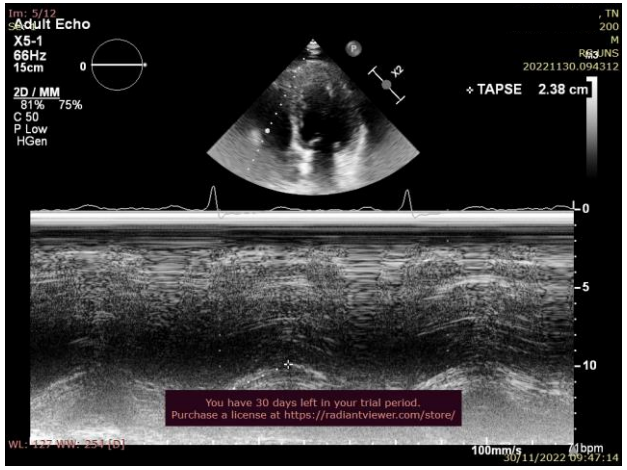
TAPSE 2.38 cm
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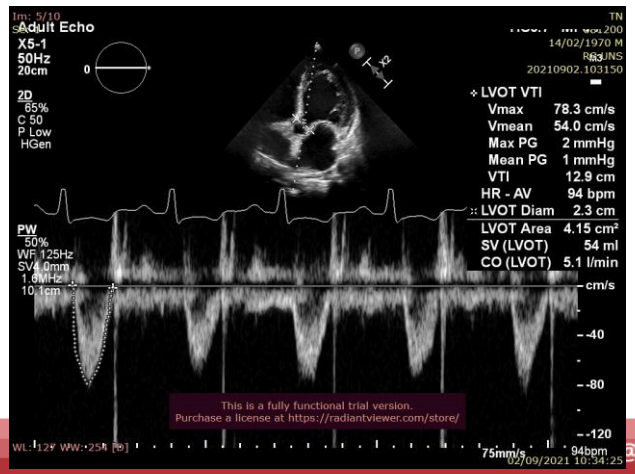
LVOT VTI
Vmax 78.3 cm/s
Vmean 54.0 cm/s
Max PG 2 mmHg
Mean PG 1 mmHg
VTI 12.9 cm
HR - AV 94 bpm
LVOT Diam 2.3 cm
LVOT Area 4.15 cm²
SV (LVOT) 54 ml
CO (LVOT) 5.1 l/min
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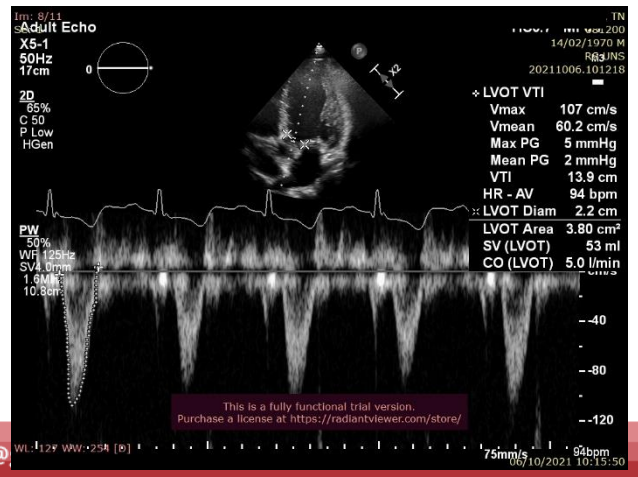
LVOT VTI
Vmax 107 cm/s
Vmean 60.2 cm/s
Max PG 5 mmHg
Mean PG 2 mmHg
VTI 13.9 cm
HR - AV 94 bpm
LVOT Diam 2.2 cm
LVOT Area 3.80 cm²
SV (LVOT) 53 ml
CO (LVOT) 5.0 l/min
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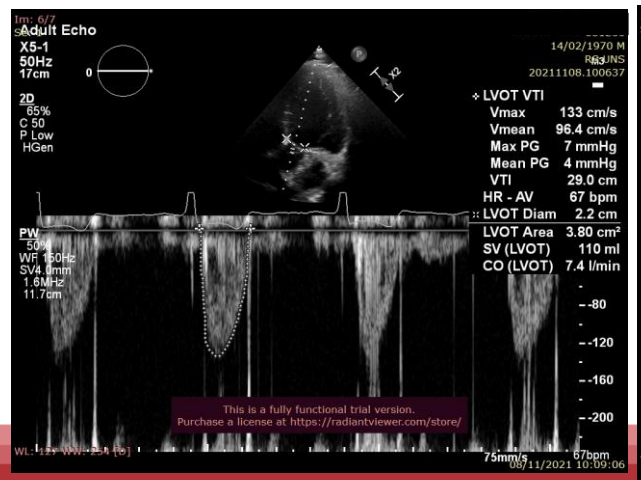
LVOT VTI
Vmax 133 cm/s
Vmean 96.4 cm/s
Max PG 7 mmHg
Mean PG 4 mmHg
VTI 29.0 cm
HR - AV 67 bpm
LVOT Diam 2.2 cm
LVOT Area 3.80 cm²
SV (LVOT) 110 ml
CO (LVOT) 7.4 l/min
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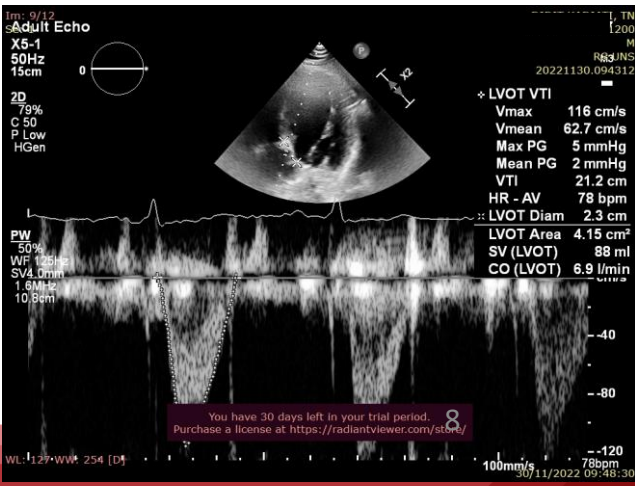
LVOT VTI
Vmax 116 cm/s
Vmean 62.7 cm/s
Max PG 5 mmHg
Mean PG 2 mmHg
VTI 21.2 cm
HR - AV 78 bpm
LVOT Diam 2.3 cm
LVOT Area 4.15 cm²
SV (LVOT) 88 ml
CO (LVOT) 6.9 l/min
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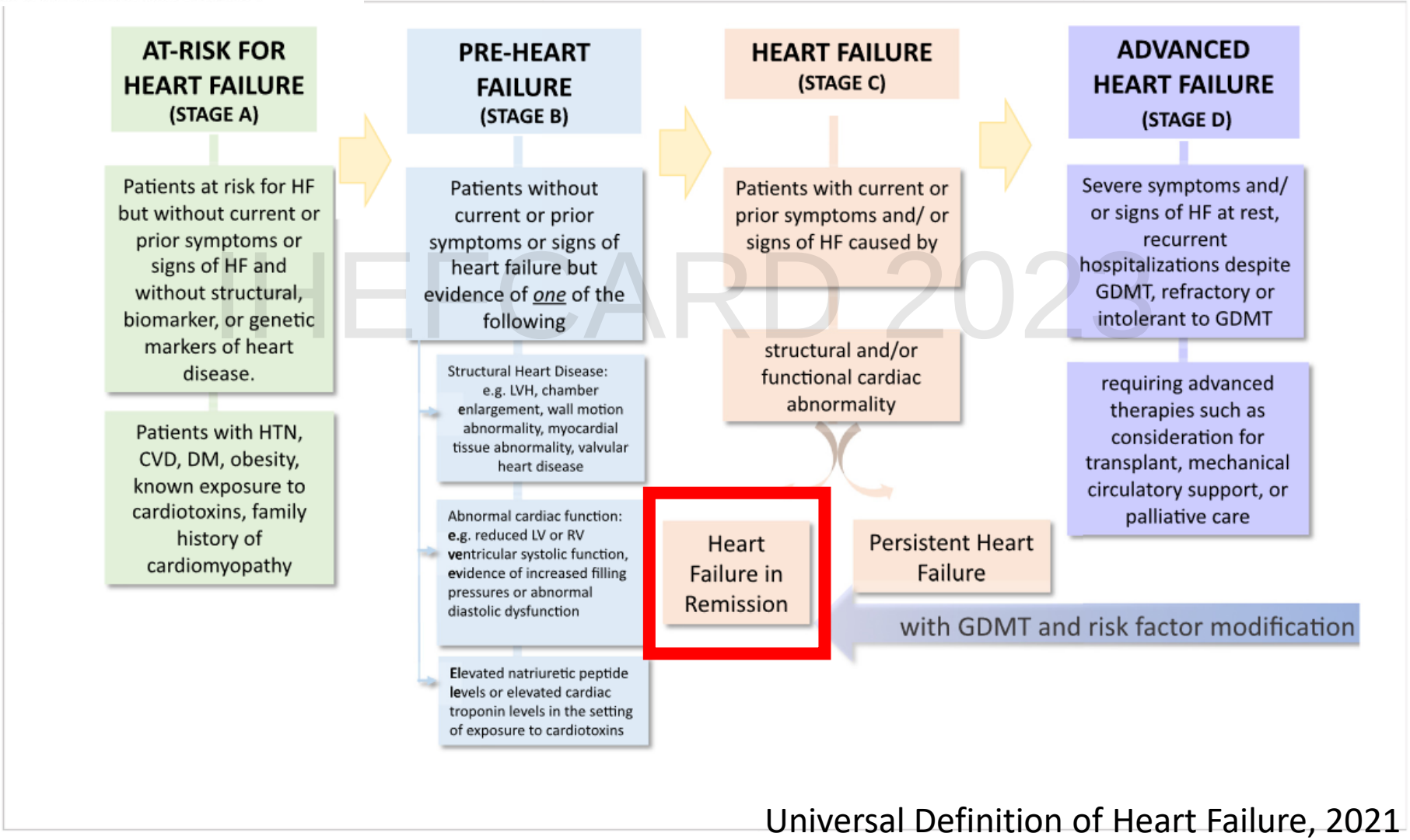
What is Recovered EF?

Consensus Statement

Universal Definition and Classification of Heart Failure

A Report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure

Endorsed by Canadian Heart Failure Society, Heart Failure Association of India, the Cardiac Society of Australia and New Zealand, and the Chinese Heart Failure Association



Universal Definition of Heart Failure, 2021

Definiton of HF Improved EF

HF with reduced EF (HFrEF):

- HF with LVEF ≤ 40%

HF with mildly reduced EF (HFmrEF):

- HF with LVEF 41-49%

HF with preserved EF (HFpEF):

- HF with LVEF ≥ 50%

HF with improved EF (HFimpEF):

- HF with a baseline LVEF ≤ 40%, a ≥ 10 point increase from baseline LVEF, and a second measurement of LVEF > 40%

Figure 3. New classification of HF according to LVEF.

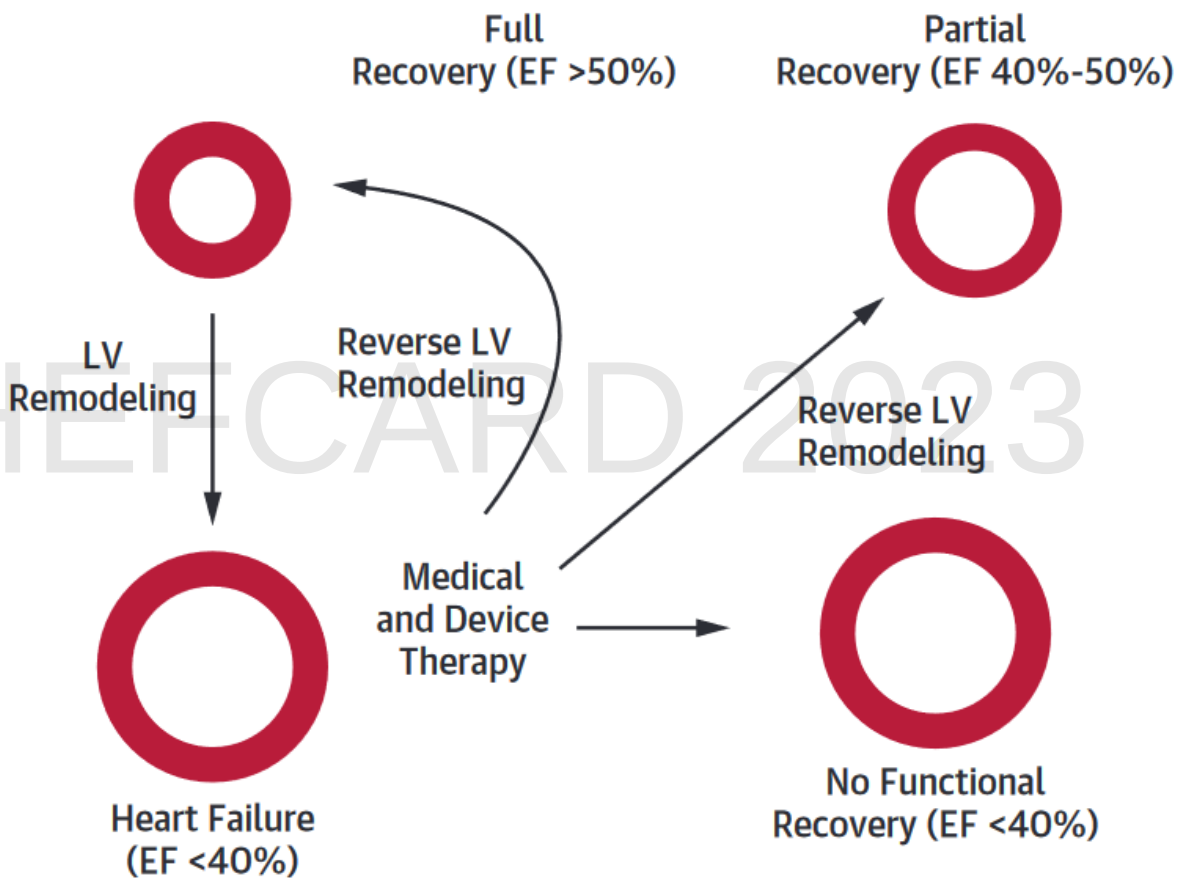
Universal Definition of Heart Failure, 2021

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] Dougl

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%).

Wilcox et al., https://doi.org/10.1016/j.jacc.2020.05.075

TABLE 1 LVEF Improvement in HFrEF Patients

First Author (Ref. #)	Publication Year	Study Size (n)	Population	Baseline Medical Therapy (>70% Use)	Definition of LVEF Improvement	Frequency of LVEF Improvement (%)	Baseline Characteristics Associated With LVEF Improvement
Cioffi (Online Ref. 9)	2004	110	Chronic HFrEF	Digoxin, diuretics	LVEF >51%	18	Absence of diabetes, higher SBP, shorter duration of HF, nonischemic origin
McNamara (Online Ref. 10)	2011	373	ROCM	ACE, BB	LVEF ≥50%	25	Smaller LVIDs, higher SBP, race other than black, higher NYHA class
Merlo (14)	2011	242	Chronic HFrEF	ACE, BB, digoxin	Increase in LVEF >10%	37	Higher SBP, absence of LBBB
Biteker (Online Ref. 11)	2011	24	PPCM	ACE, diuretics	LVEF >50%	46	Smaller LVIDd, smaller LVIDs, higher LVEF, smaller LA diameter
Wilcox (Online Ref. 12)	2012	3,994	Chronic HFrEF	ACE, BB	Increase in LVEF >10%	Not given	Female, nonischemic origin, higher LVEF, higher SBP, no digoxin use
Dunlay (Online Ref. 13)	2012	674	Chronic HFrEF	ACE, BB	LVEF ≥50%	39	Not given
Basuray (5)	2014	1,821	Chronic HFrEF	ACE, BB, diuretics	LVEF ≥50%	Not given	Female, nonischemic origin
McNamara (Online Ref. 14)	2015	100	PPCM	ACE, BB	LVEF ≥50%	72	Smaller LVIDs, nonblack race
Florea (7)	2016	4,410	Chronic HFrEF	ACE, diuretics	LVEF ≥40%	9	Female, nonischemic origin, higher DBP, smaller LVIDd, BB therapy, valsartan therapy
Bermejo (Online Ref. 15)	2017	242	Chronic HFrEF	ACE, BB, diuretics	LVEF >40%	52	Younger age, higher NYHA class, ACE/BB use, nonischemic origin, lack of ICD placement
Chang (Online Ref. 16)	2017	318	African-American chronic HFrEF	ACE, BB, diuretics	LVEF ≥40%	19	Higher LVEF, shorter duration of HF, no digoxin use, use of I/H
Lupón (22)	2017	940	Chronic HFrEF	ACE, BB, diuretics	LVEF ≥45%	25	Younger age, female, nonischemic origin, nondiabetic, shorter duration of HF, higher NYHA class
Kim (Online Ref. 17)	2017	90	Takotsubo CM	None	LVEF ≥50%	70	Younger age, absence of hypothyroidism, shorter QT interval, ACE or ARB use

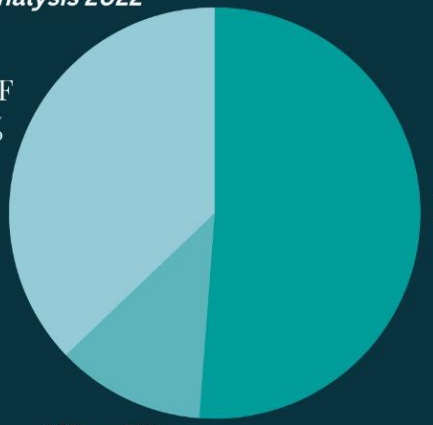
ACE = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BB = beta blocker; CM = cardiomyopathy; DBP = diastolic blood pressure; HFrEF = heart failure with reduced ejection fraction; I/H = isosorbide dinitrate and hydralazine; ICD = implantable cardioverter-defibrillator; LA = left atrium; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; LVIDd = left ventricular internal dimension in diastole; LVIDs = left ventricular internal dimension in systole; NYHA = New York Heart Association; PPCM = peripartum cardiomyopathy; Ref. = reference; ROCM = recent onset cardiomyopathy; SBP = systolic blood pressure.

Gulati G & Udelson JE, JACC heart fail. 2018 Sep;6(9):725-733. doi: 10.1016/j.jchf.2018.05.004.

BASIC DEMOGRAPHIC

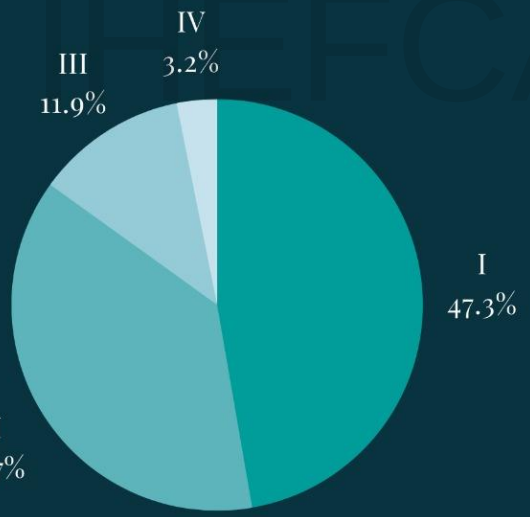
Interim Analysis 2022

Total Patient : 916



Heart Failure Classification

New York Heart Association Fuctional Class

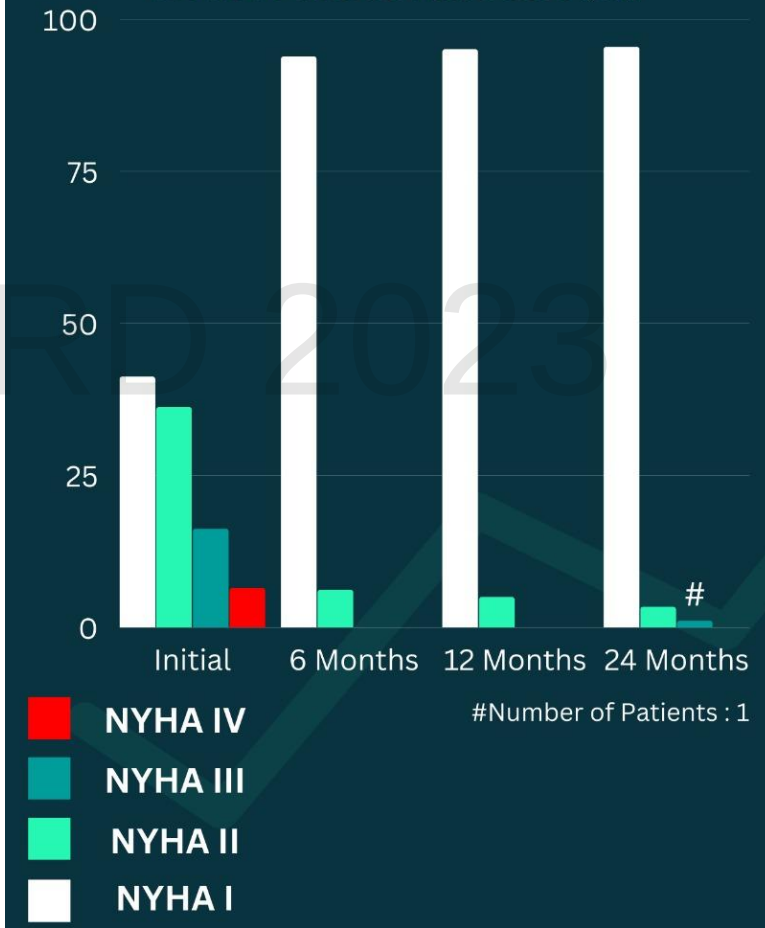


corehfrsuns@gmail.com

HFrEF : IMPROVEMENT

Interim Analysis 2022

NYHA Functional Class (%)



#Number of Patients : 1

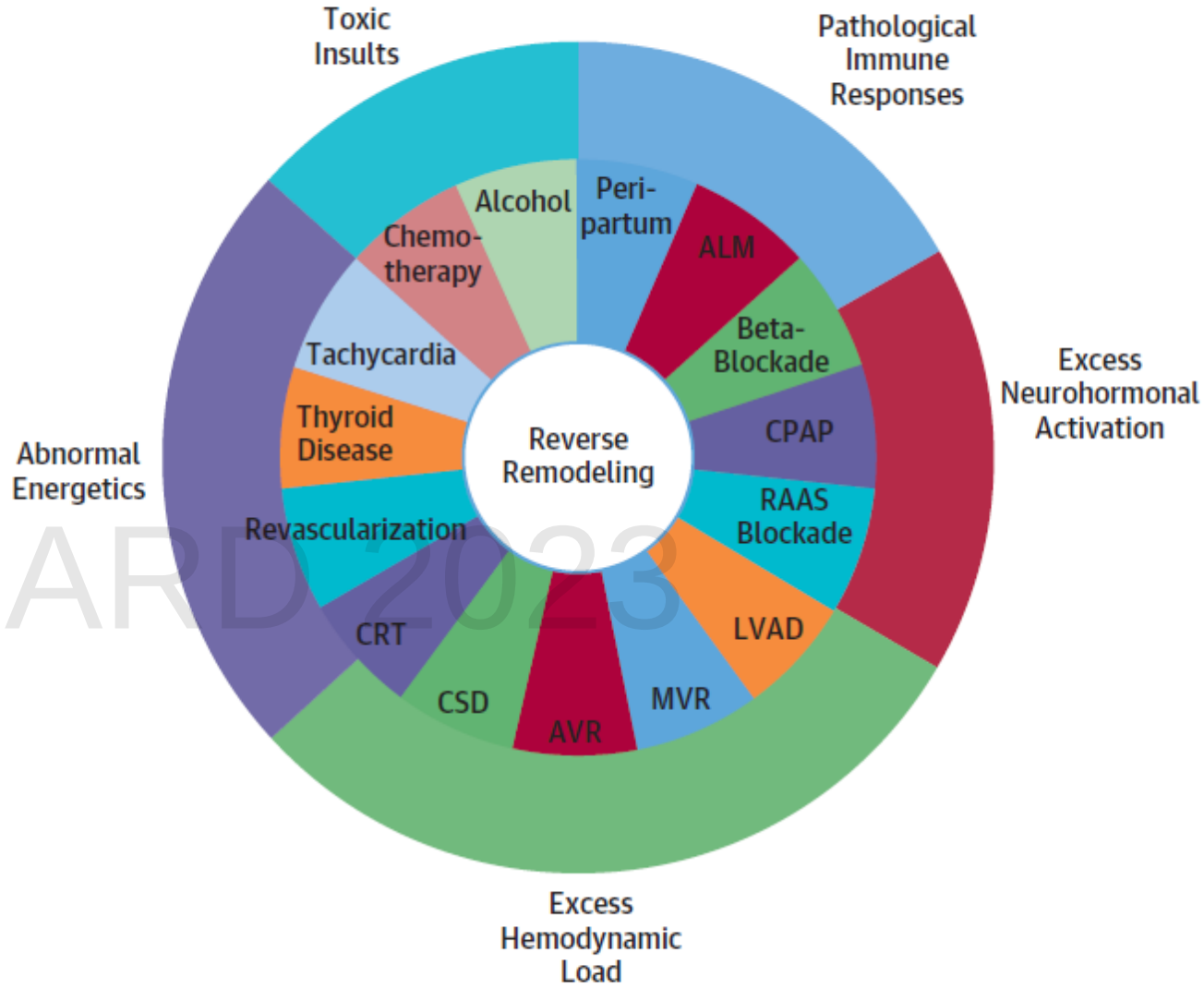
EF Improvement to at least 40%*

*During 2-Years of Follow-Up

corehfrsuns@gmail.com

Recovered EF Spectrum

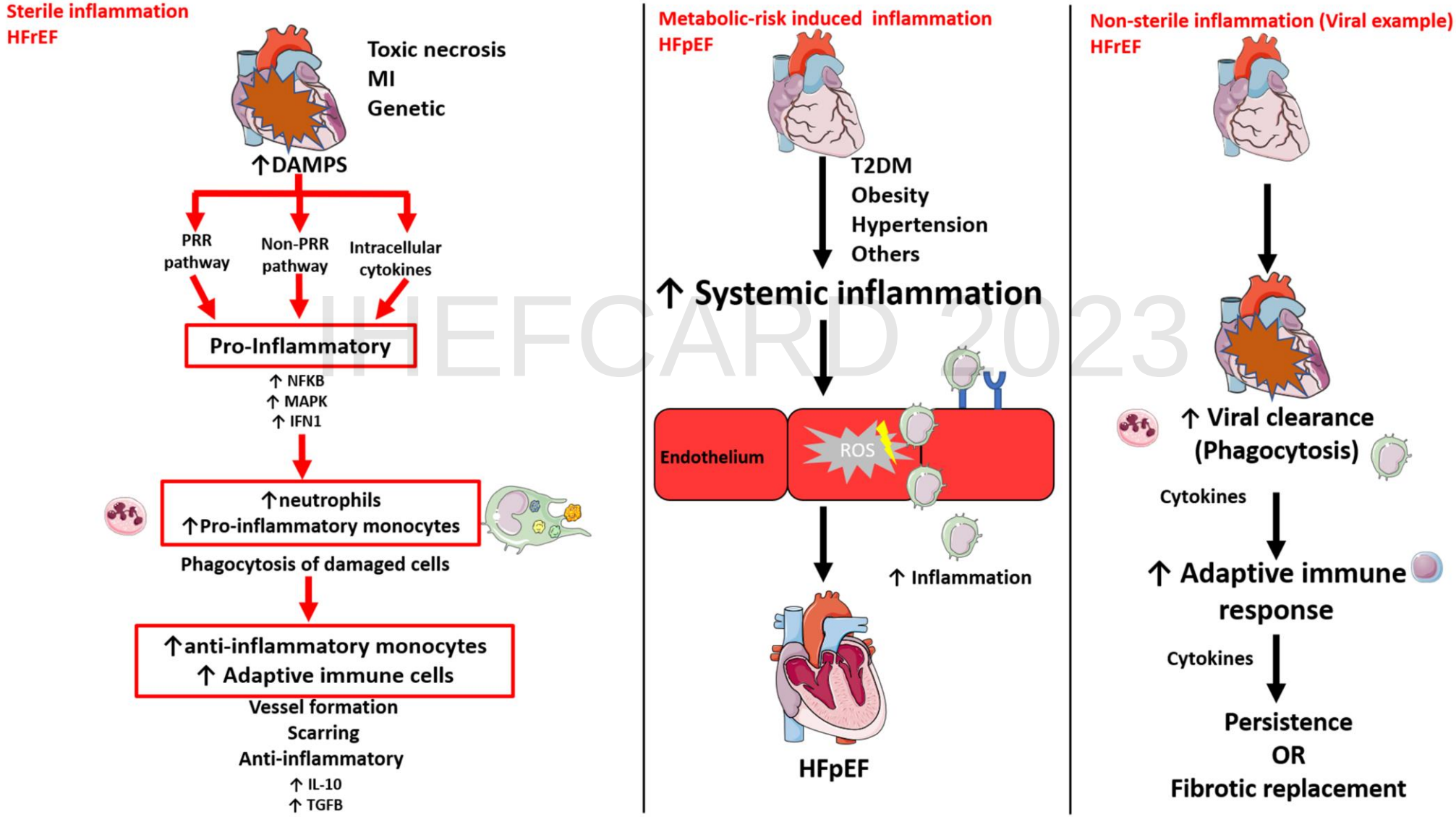
FIGURE 2 Recovery of LVEF in Clinical Settings



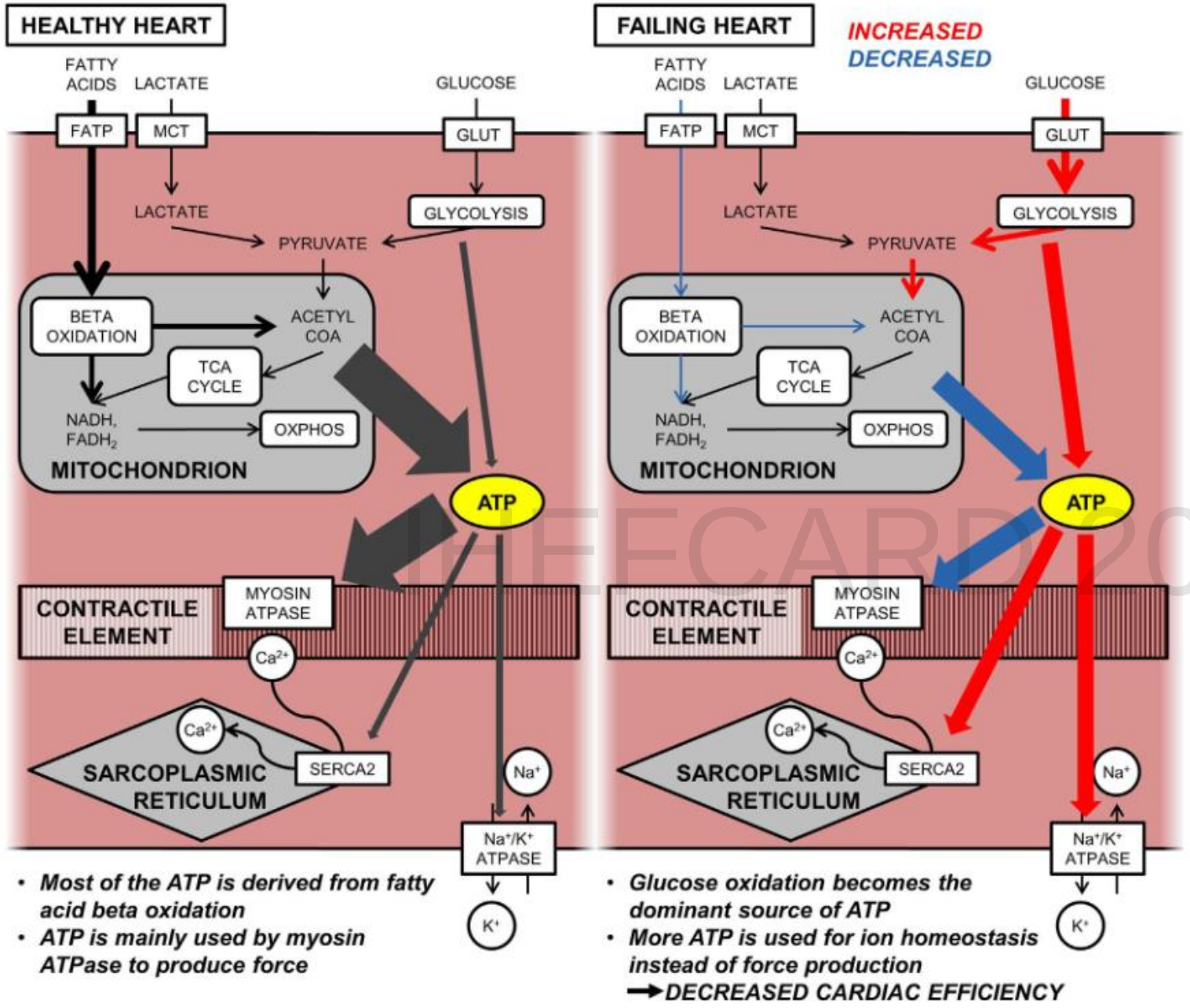
The segments of the outmost ring highlight pathophysiological processes implicated by reverse left ventricular remodeling, in particular clinical settings that comprise the middle ring. Reproduced with permission from Hellawell et al. (16). ALM = acute lymphocytic myocarditis; AVR = aortic valve replacement; CPAP = continuous positive airway pressure; CRT = cardiac resynchronization therapy; CSD = cardiac support device; LVAD = left ventricular assist device; LVEF = left ventricular ejection fraction; MVR = mitral valve repair/replacement; RAAS = renin-angiotensin-aldosterone system.

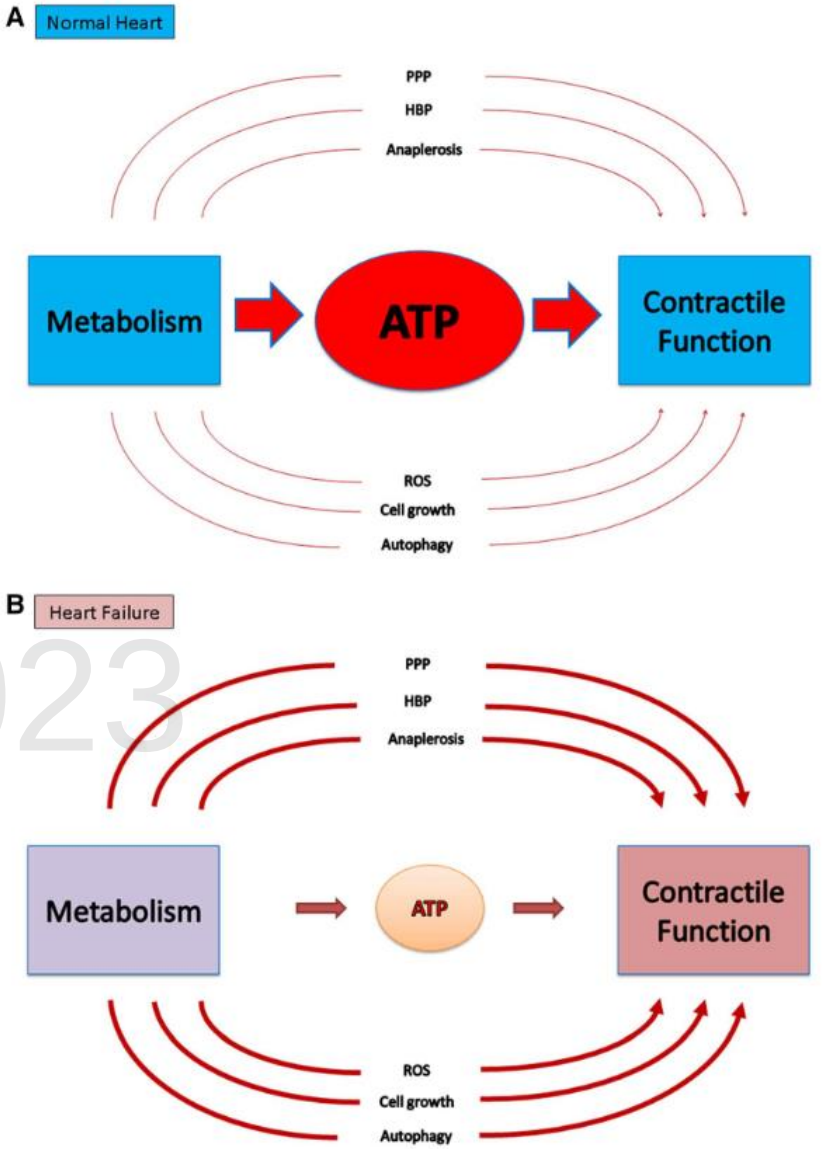
Wilcox et al. HFrecEF Consensus Recommendations. doi: 10.1016/j.jacc.2020.05.075.

Pathophysiology of Worsening EF



Simmonds, S.J.et al. *Cells* **2020**, *9*, 242. https://doi.org/10.3390/cells9010242





Tuomaninen T, Experimental Cell Research 360 (2017) 12–18

Fig. 1. Energy production and expenditure in cardiomyocytes of healthy and failing heart. Normally, most of the cardiomyocyte ATP is produced via oxidation of fatty acids and consumed mainly by myosin ATPase in the contractile machinery to produce the force of heart contraction. In failing heart, metabolic phenotype shifts towards the use of glucose oxidation. At the same time changes in ion homeostasis reduce the cardiac efficiency, which together with the impairments in energy production leads to insufficient force production. *FATP, fatty acid transporter; MCT, monocarboxylate transporter; GLUT, glucose transporter; OXPHOS, oxidative phosphorylation.*

GDMT Associated Cardiac Reverse Remodeling

GDMT on Cardiac Reverse Remodelling

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.

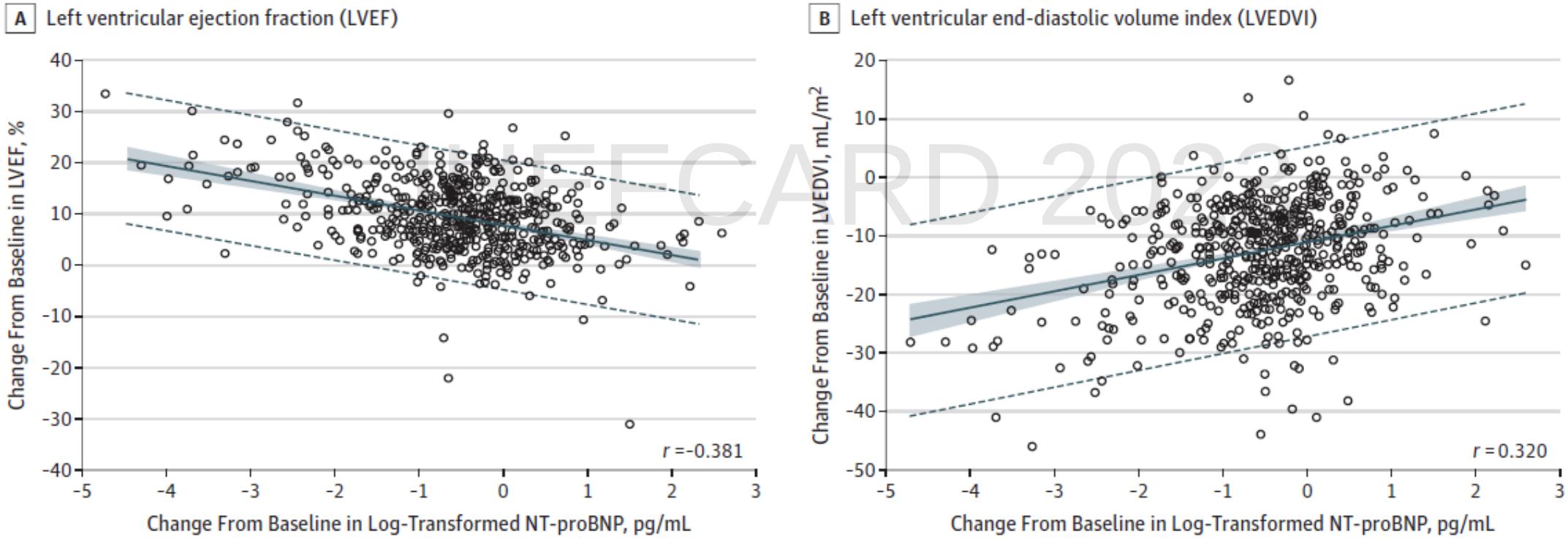
Wilcox et al., https://doi.org/10.1016/j.jacc.2020.05.075

Research

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



Januzzi et al. *JAMA*. 2019;322(11):1085-1095. doi:10.1001/jama.2019.12821

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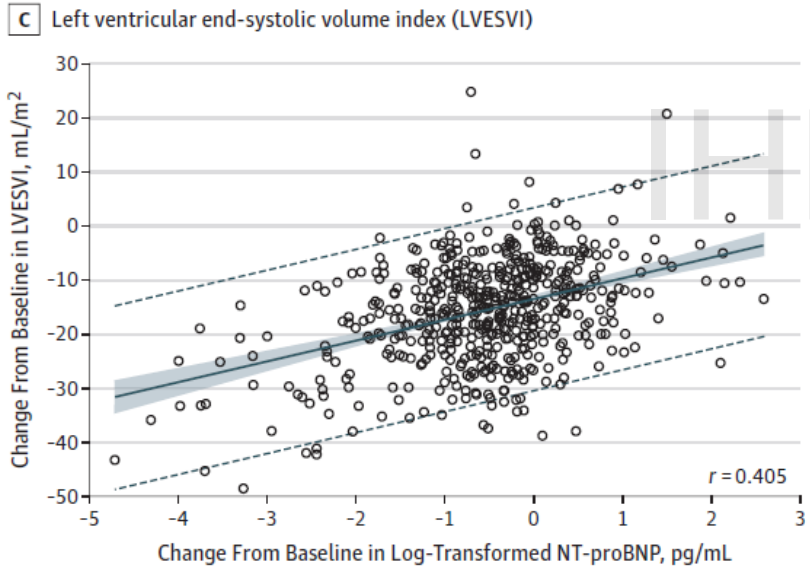
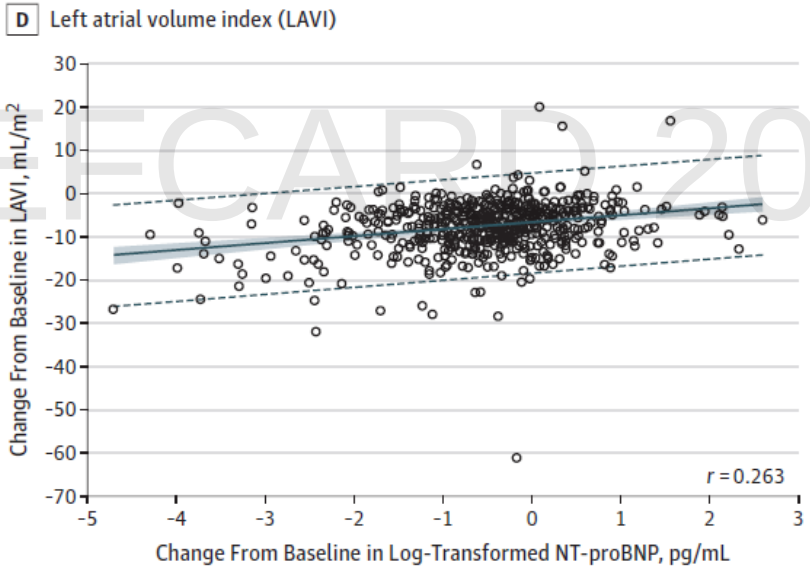
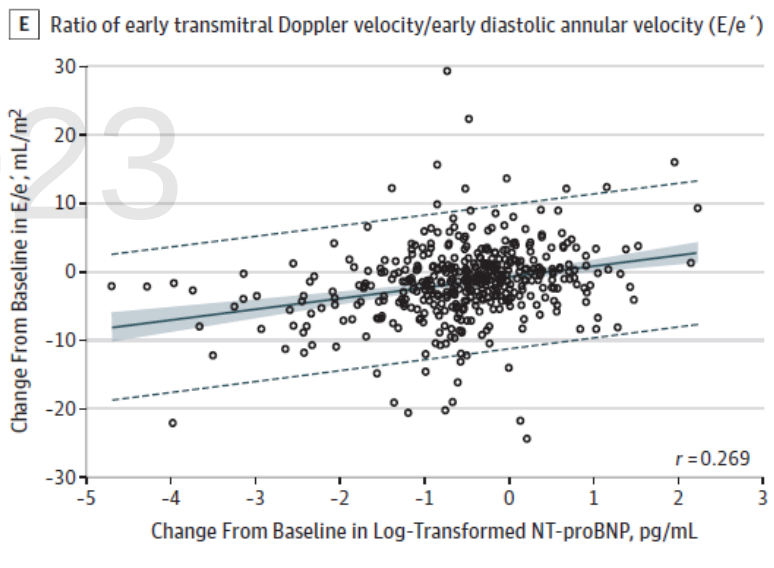






Januzzi et al. *JAMA*. 2019;322(11):1085-1095. doi:10.1001/jama.2019.12821

Table 2. Change in Cardiac Remodeling Measurements From Baseline to 6 and 12 Months After Initiation of Sacubitril-Valsartan in All Study Participants[a]

	All Patients				
	Baseline Value, Median (25th to 75th Percentile)	6-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 6 mo (95% CI)	12-mo Value, Median (25th to 75th Percentile)	LS Mean Change From Baseline at 12 mo (95% CI)
LVEF, %	n = 757	n = 716		n = 648	
	28.2 (24.5 to 32.7)	34.1 (29.0 to 39.65)	5.2 (4.8 to 5.6)	37.8 (32.3 to 45.2)	9.4 (8.8 to 9.9)
LVEDVI, mL/m^2	n = 756	n = 716		n = 648	
	86.93 (76.17 to 100.43)	79.50 (69.34 to 93.52)	−6.65 (−7.11 to −6.19)	74.15 (63.46 to 86.30)	−12.25 (−12.92 to −11.58)
LVESVI, mL/m^2	n = 756	n = 716		n = 648	
	61.68 (51.95 to 75.00)	52.25 (42.34 to 65.25)	−8.67 (−9.18 to −8.15)	45.46 (34.84 to 57.56)	−15.29 (−16.03 to −14.55)
LAVI, mL/m^2	n = 747	n = 696		n = 639	
	37.76 (31.63 to 46.09)	32.80 (27.62 to 40.13)	−4.36 (−4.73 to −3.99)	29.31 (24.40 to 35.85)	−7.57 (−7.98 to −7.15)
E/e'	n = 642	n = 604		n = 552	
	11.70 (8.80 to 16.00)	10.50 (7.70 to 14.70)	−1.23 (−1.63 to −0.83)	10.20 (7.70 to 14.30)	−1.30 (−1.74 to −0.86)

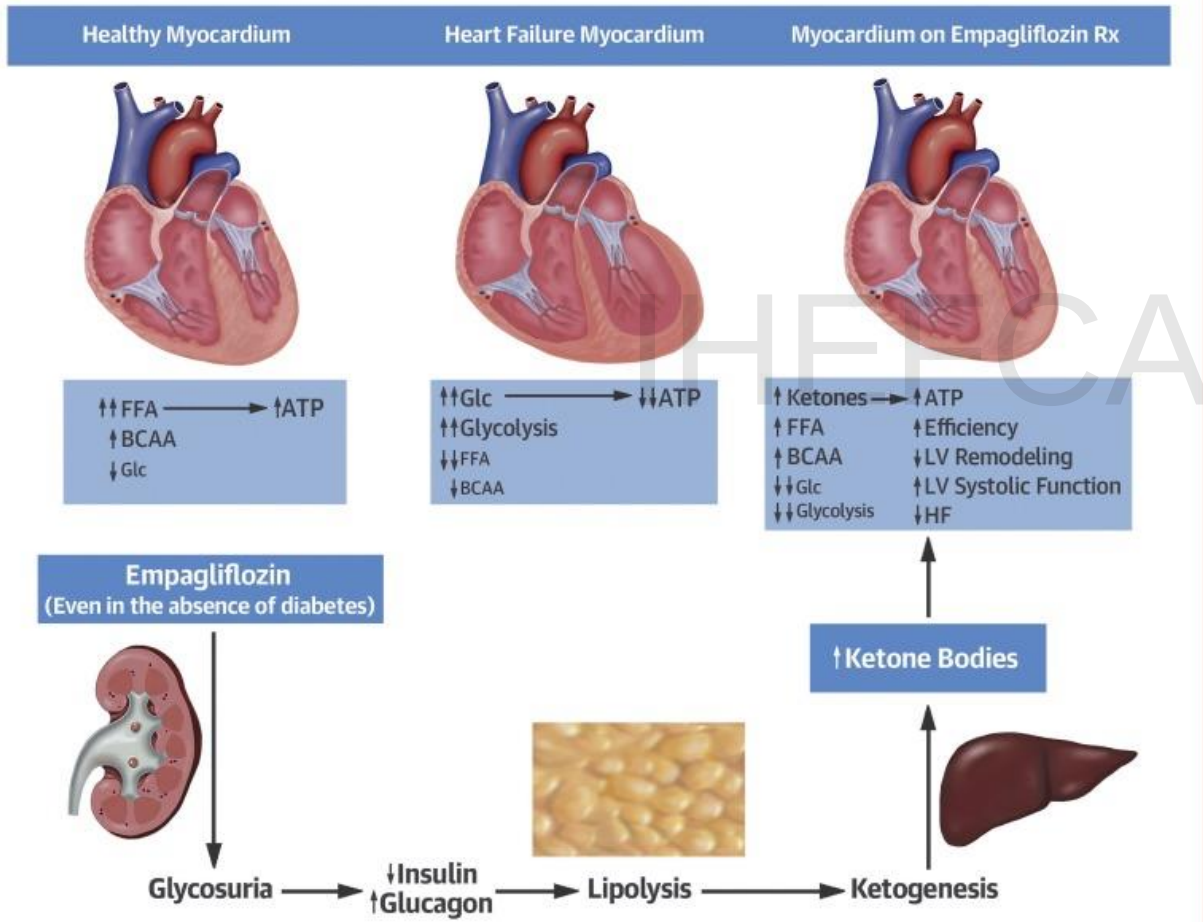
Abbreviations: E/e', ratio of early transmitral Doppler velocity/early diastolic annular velocity; LAVI, left atrial volume index; LS, least-square; LVEF, left ventricular ejection fraction; LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index.

[a] All comparisons were significant at $P < .001$.

Januzzi et al. *JAMA*. 2019;322(11):1085-1095. doi:10.1001/jama.2019.12821

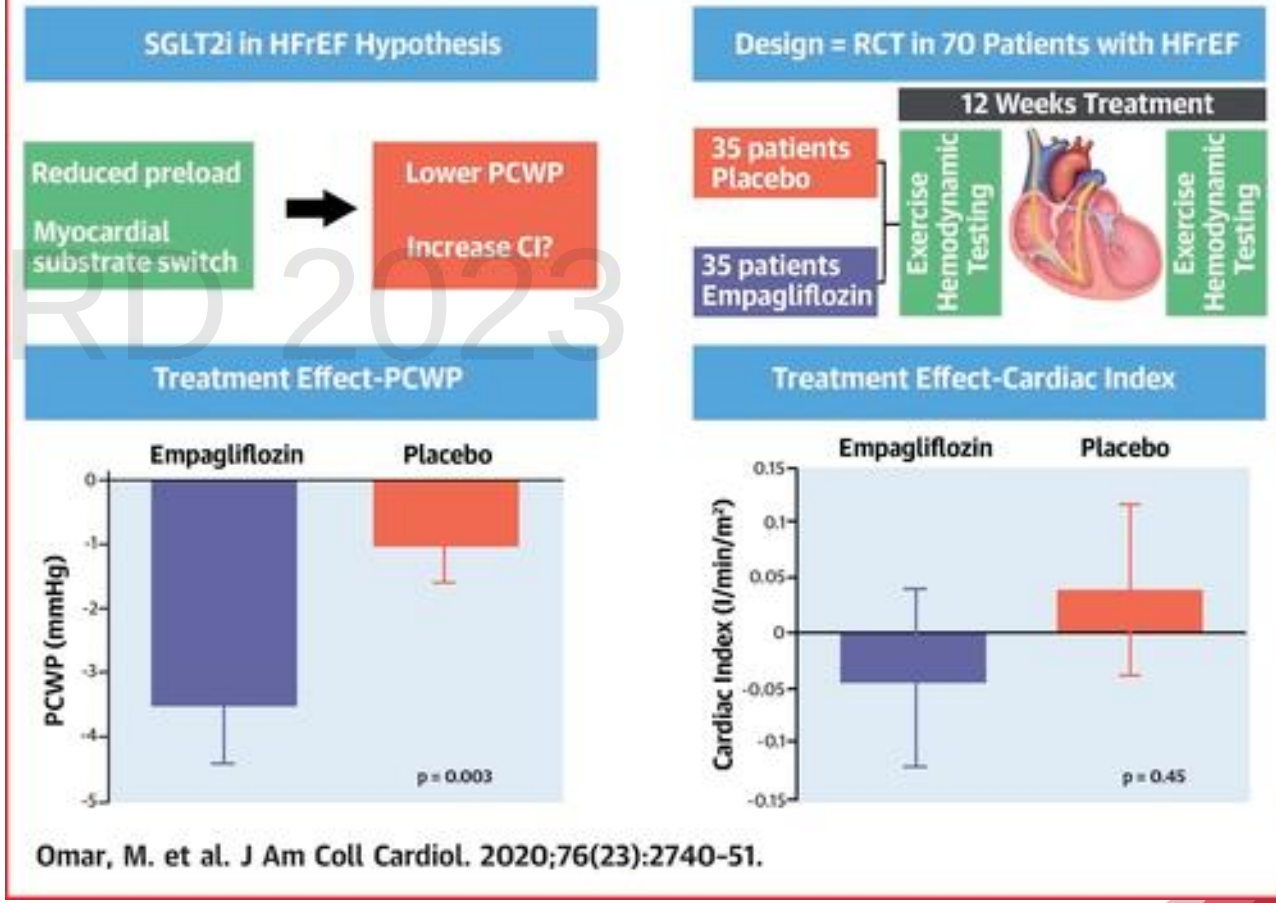
SGLT2i in Reverse Cardiac Remodeling

CENTRAL ILLUSTRATION: Postulated Effect of Empagliflozin on Heart Failure



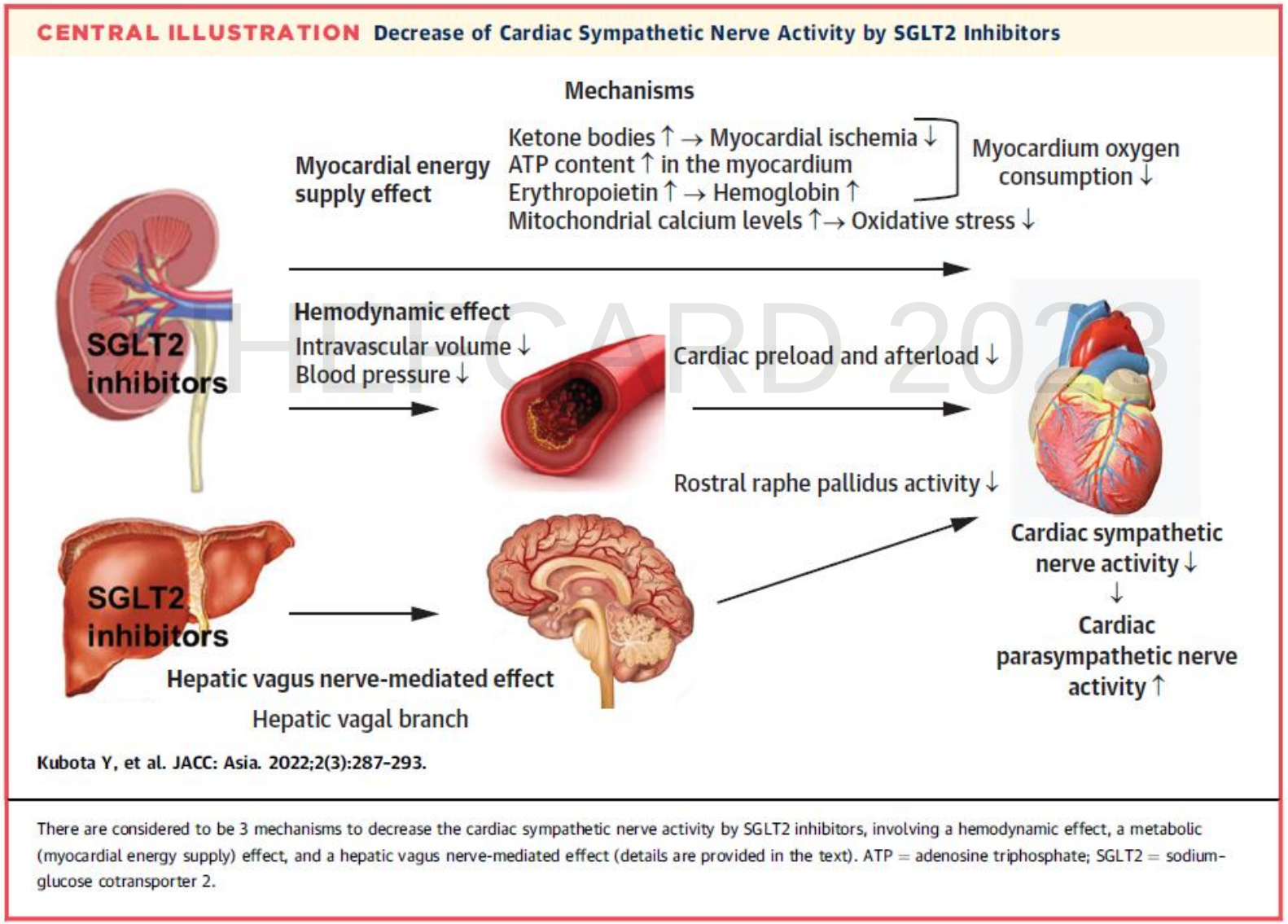
Santos-Gallego, C.G. et al. J Am Coll Cardiol. 2019;73(15):1931-44.

CENTRAL ILLUSTRATION: Impact of Empagliflozin on Central Cardiac Hemodynamics in Heart Failure With Reduced Ejection Fraction



Omar, M. et al. J Am Coll Cardiol. 2020;76(23):2740-51.

SGLT2i in Reverse Cardiac Remodeling



There are considered to be 3 mechanisms to decrease the cardiac sympathetic nerve activity by SGLT2 inhibitors, involving a hemodynamic effect, a metabolic (myocardial energy supply) effect, and a hepatic vagus nerve-mediated effect (details are provided in the text). ATP = adenosine triphosphate; SGLT2 = sodium-glucose cotransporter 2.

Can We Predict Reverse Remodelling in HF?

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)

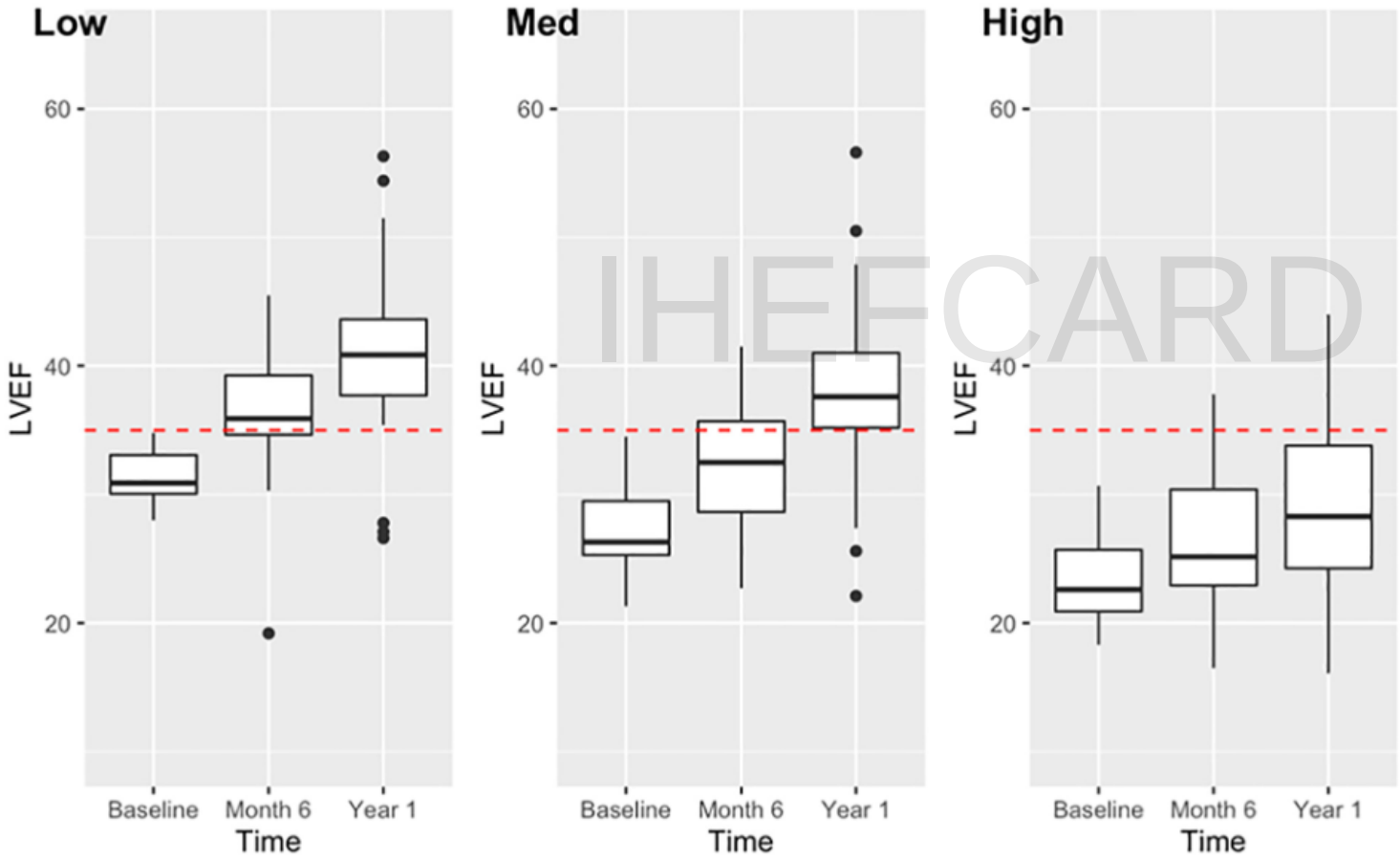
Modified with permission from Aimo et al. (58).

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.

Wilcox et al. HFrecEF Consensus Recommendations. doi: 10.1016/j.jacc.2020.05.075.

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

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 4 Odds Ratios of Early ICD Eligibility Across Likelihood Categories

	Rate of LVEF of <35%	Odds Ratio (95% CI)	*P* Value
Low likelihood	4 (3.8)	1.00	—
Medium likelihood	31 (30.1)	10.9 (4.1-37.8)	<0.001
High likelihood	87 (83.7)	129.2 (46.7-465.6)	<0.001

Values are n (%).
Abbreviations as in Tables 1 and 2.

Mohebi R, et al. 2023. https://doi.org/10.1016/j.jchf.2022.09.009

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

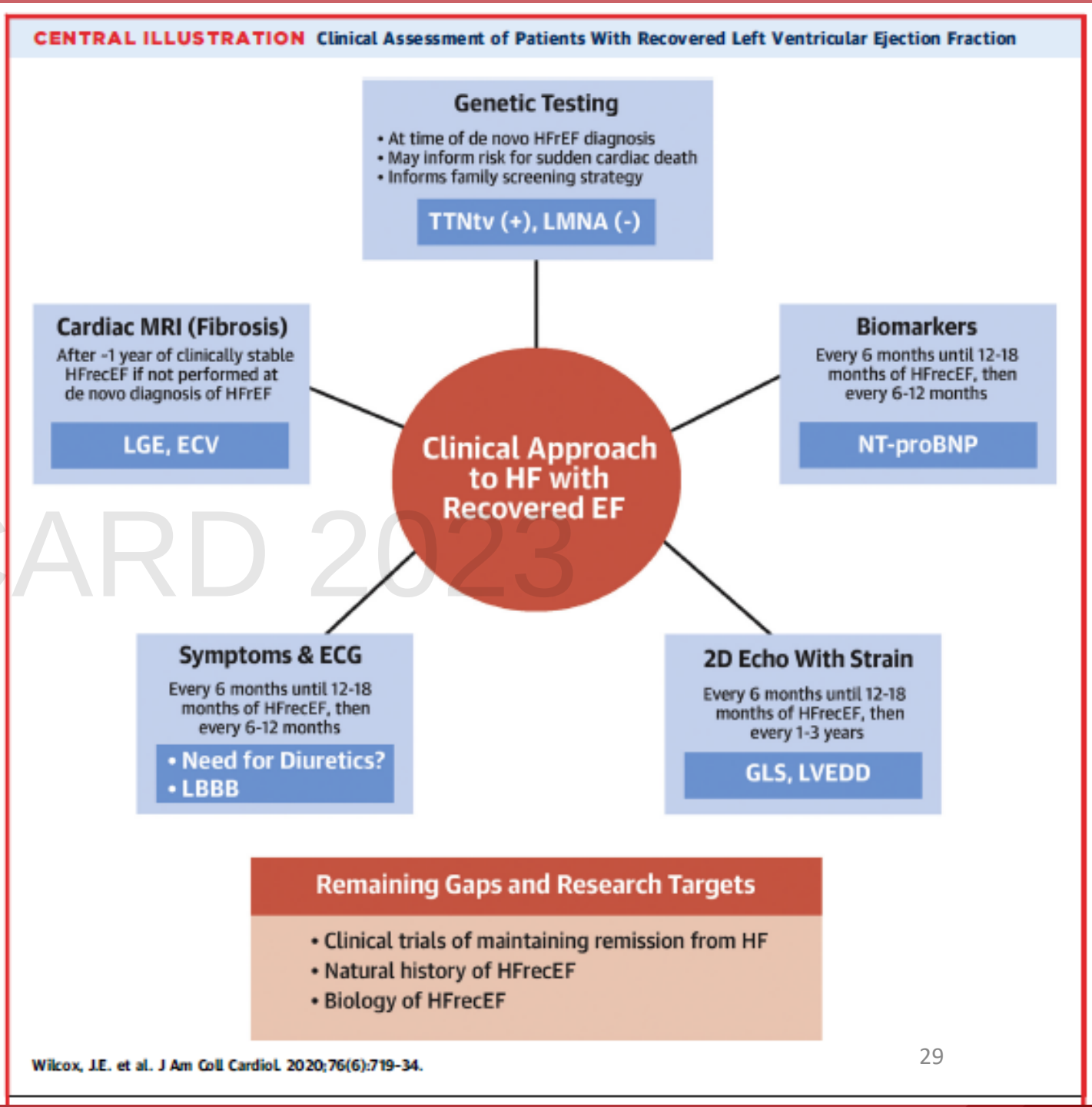
Mohebi R, et al. 2023. https://doi.org/10.1016/j.jchf.2022.09.009

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
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

Mohebi R, et al. 2023. https://doi.org/10.1016/j.jchf.2022.09.009

Clinical Approach in Recovered EF



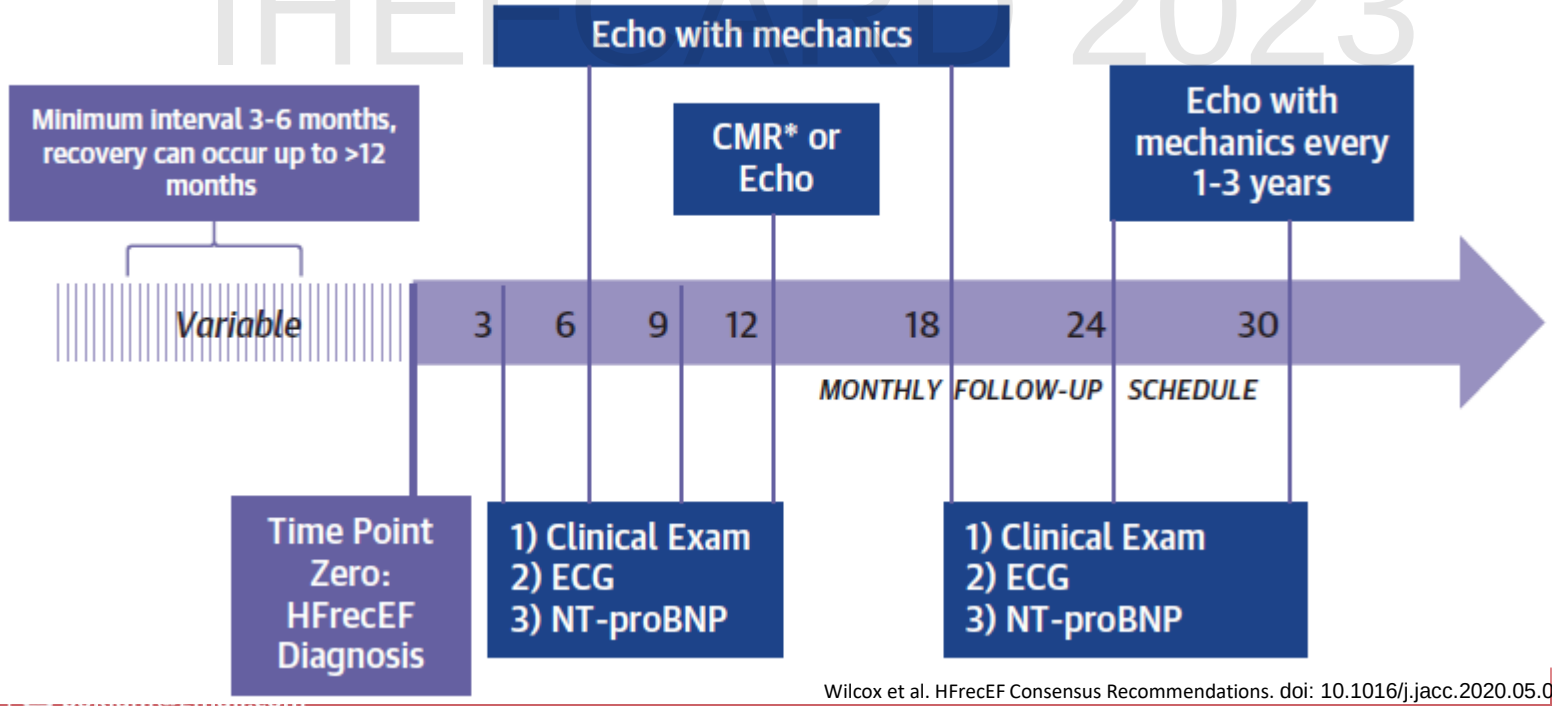
Wilcox et al. HFrecEF Consensus Recommendations. doi: 10.1016/j.jacc.2020.05.075.

TABLE 3 Recommended Interval Follow-Up for HFrecEF

Interval Follow-Up Time Period (After Meeting the HFrecEF Definition)	Clinical Examination and ECG	Holter Monitoring (24 h)	NT-pro BNP	Echocardiography With Mechanics (Strain)	CMR
Every 6 months (until 12–18 months of HFrecEF).	X		X	X	
After ~1 yr of "clinically stable" HFrecEF					X*
Every 6–12 months (at minimum).	X		X		
Optimal interval of echocardiography/imaging is unknown. It is reasonable clinical practice to assess durability every 1–3 yrs after stable recovery depending on etiology.				X	
Every 1–2 yrs for certain genetic cardiomyopathies at risk of atrial dysrhythmias (e.g., *TTN*).		X			

*Consider CMR if one was not performed at de novo diagnosis of HFrEF.

CMR = cardiac magnetic resonance; ECG = electrocardiogram; HFrecEF = heart failure with recovered ejection fraction; other abbreviations as in Table 2.



Wilcox et al. HFrecEF Consensus Recommendations. doi: 10.1016/j.jacc.2020.05.075.

Worsening EF Recurrency

TABLE 2 HFrEF Recurrence in HFiEF Patients

First Author (Ref. #)	Publication Year	Study Size (n)	Median Follow-Up (Months)	Frequency of HFrEF Recurrence (%)	Factors Associated With HFrEF Recurrence
Cioffi (Online Ref. 9)	2004	20	17	40	Not available
Moon (44)	2009	42	48	19	Discontinuation of HF therapy
Park (25)	2014	85	50	39	Older age, longer duration of HF before improvement, diabetes, larger LVIDd
de Groote (21)	2014	174	96	22	Lower LVEF, LBBB, larger LVIDd, slower heart rate
Nadruz (19)	2016	123	32	29	Older age, HTN, lower GFR

GFR = glomerular filtration rate; HRiEF = heart failure with improved ejection fraction; HTN = hypertension; other abbreviations as in Table 1.

Gulati G & Udelson JE, JACC heart fail. 2018 Sep;6(9):725-733. doi: 10.1016/j.jchf.2018.05.004.

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 K
Gillian Smith, Lucia Venneri, Upasana Tayal, Dominique
Antonis Pantazis, Stuart A Cook, James S Ware, A John E

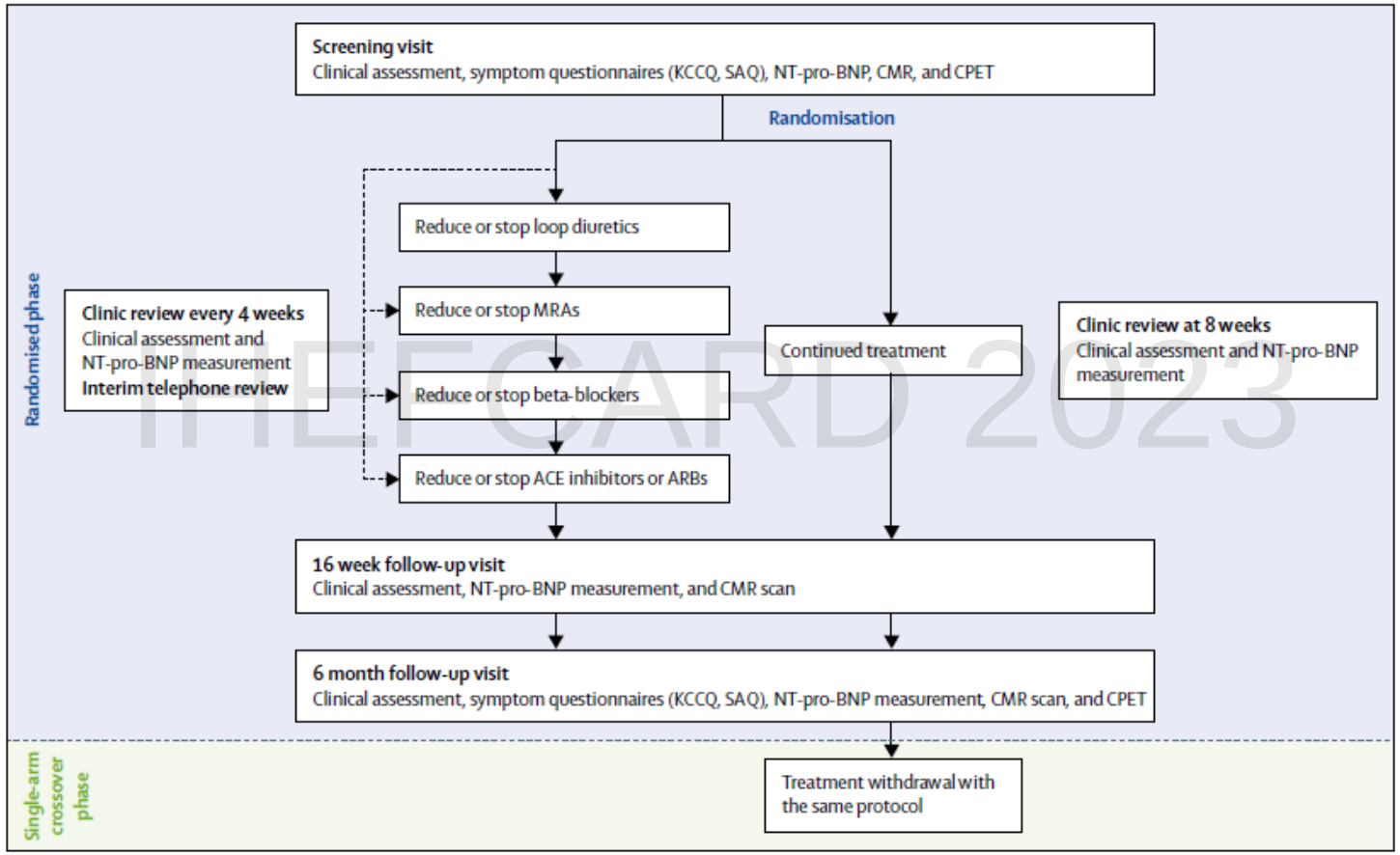


Figure 1: **Flowchart of TRED-HF study design**
ACE–angiotensin converting enzyme. ARB–angiotensin receptor blocker. CMR–cardiovascular magnetic resonance. CPET–cardiopulmonary exercise test. KCCQ–Kansas City Cardiomyopathy Questionnaire. MRA–mineralocorticoid receptor antagonist. NT-pro-BNP–N-terminal pro-B-type natriuretic peptide. SAQ–symptom assessment questionnaire.

Halliday BP, et al. *Lancet* 2019; 393: 61–73

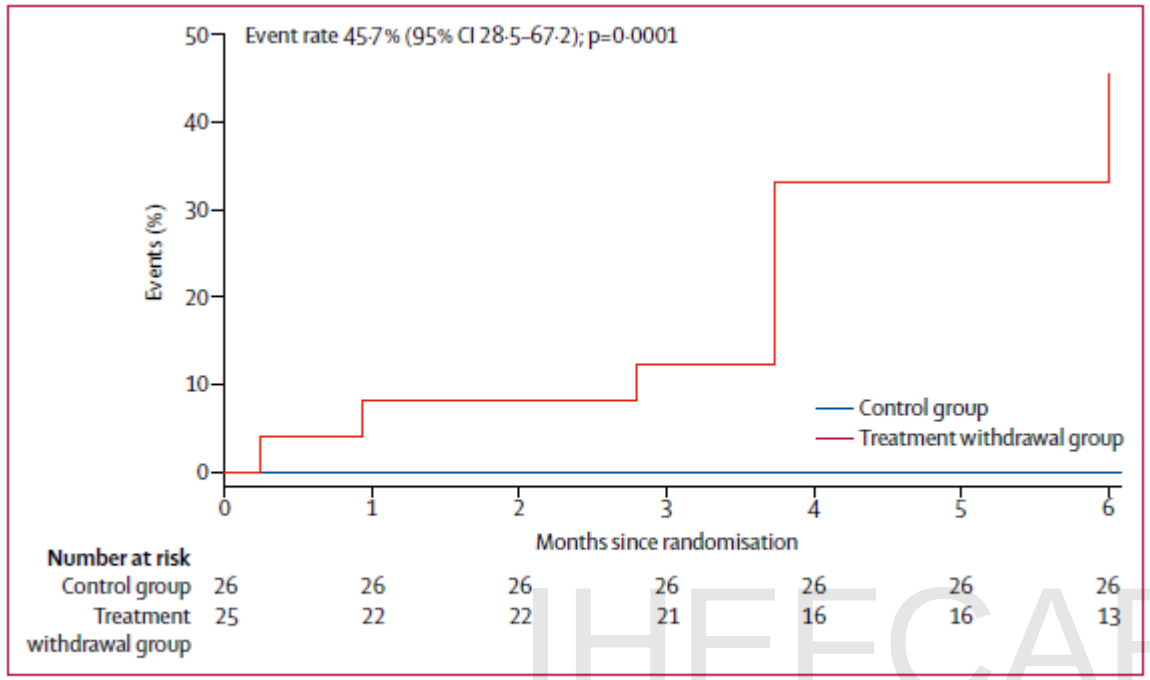


***Figure 3*: Kaplan-Meier curve of time to primary endpoint in randomised phase, according to treatment group**
One patient dropped out at 7 days.

In conclusion, in this pilot study, 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. Future work could identify patient subgroups who have permanent recovery of myocardial function for whom withdrawal is safe or for whom only some medications need to be continued in the long term.

Halliday BP, et al. *Lancet* 2019; 393: 61–73

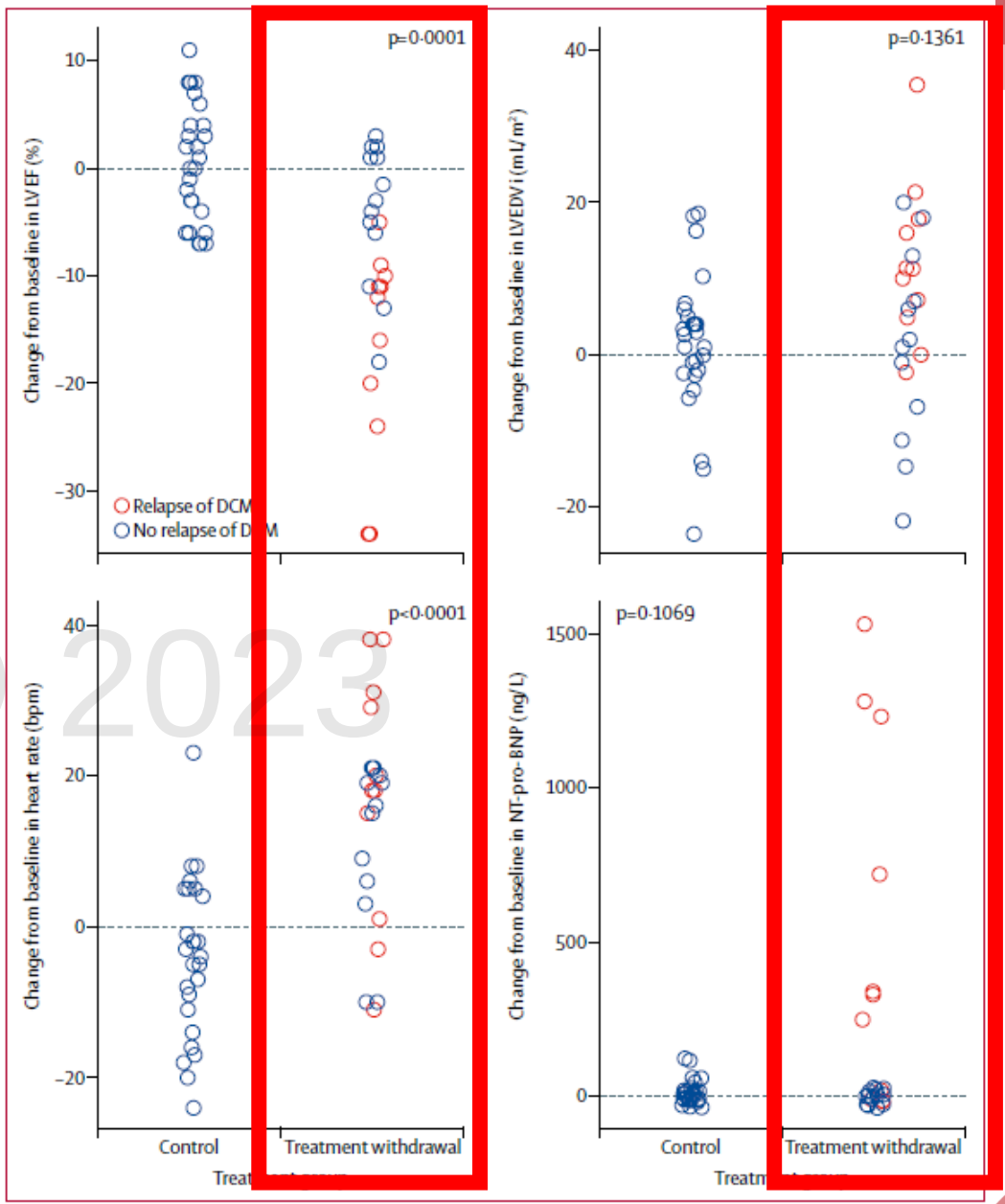


***Figure 5*: Change in secondary endpoint variables between baseline and follow-up in the randomised phase of the study, based on treatment group**
Each circle represents one patient. bpm=beats per min. DCM=dilated cardiomyopathy. LVEDVi=left ventricular end-diastolic volume indexed to body surface area. LVEF=left ventricular ejection fraction. NT-pro-BNP=N-terminal pro-B-type natriuretic peptide.

Take Home Messages

- Remission of heart failure often associated with heart failure reverse remodeling
- Search and treat for heart failure etiology are the most valuable step for the patient to achieve a remission
- Optimalization of GDMTs is one of the most proper way to succeed cardiac reverse remodeling
- Withdrawal of GDMTs may induced relapse of heart failure in recovery EF population
- Monitoring of clinical sign & symptom , re-evaluation of echocardiography and NT-pro BNP can keep the patients “clinicaly stable” in recovery condition

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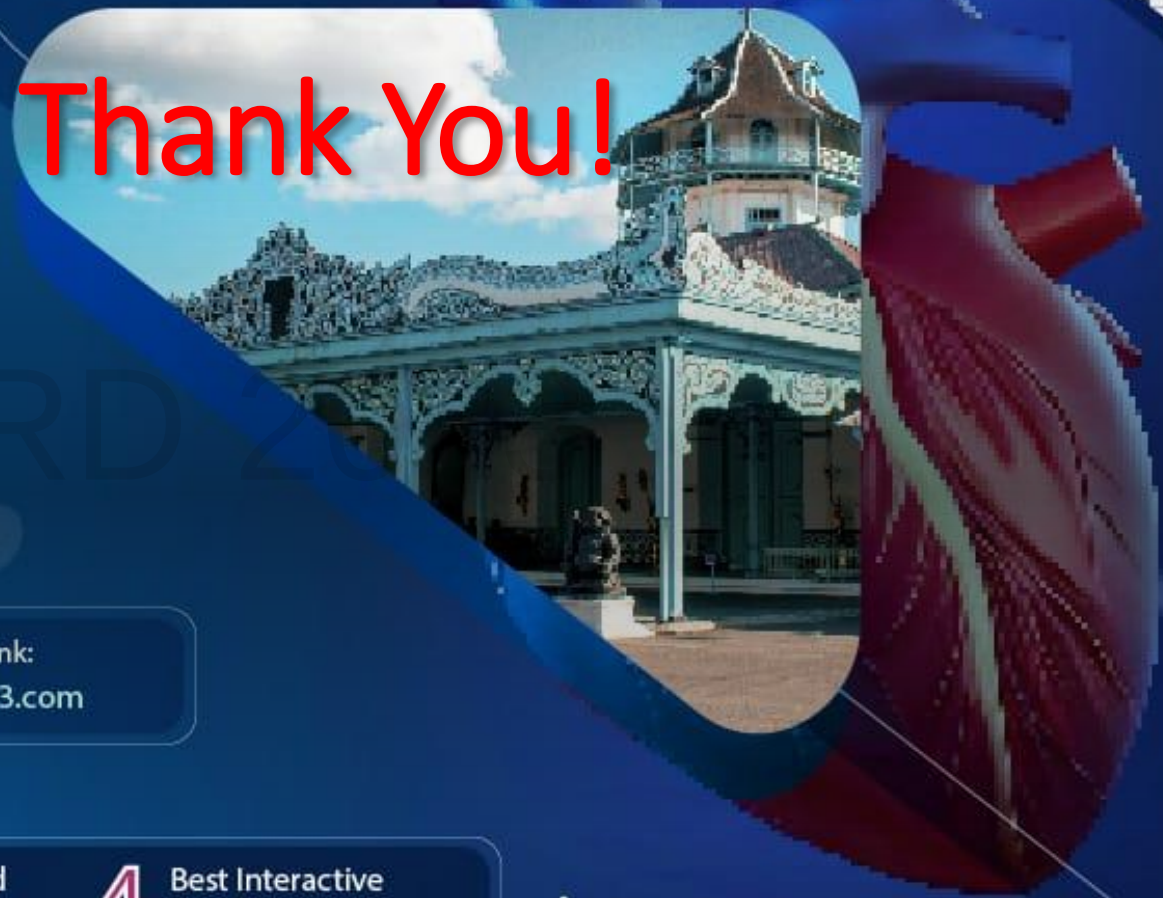
Tailoring Strategies Toward Challenges in Cardiovascular: From Whiners to Winners



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