Heart Failure with recovered/improved EF : a distinct patient population?

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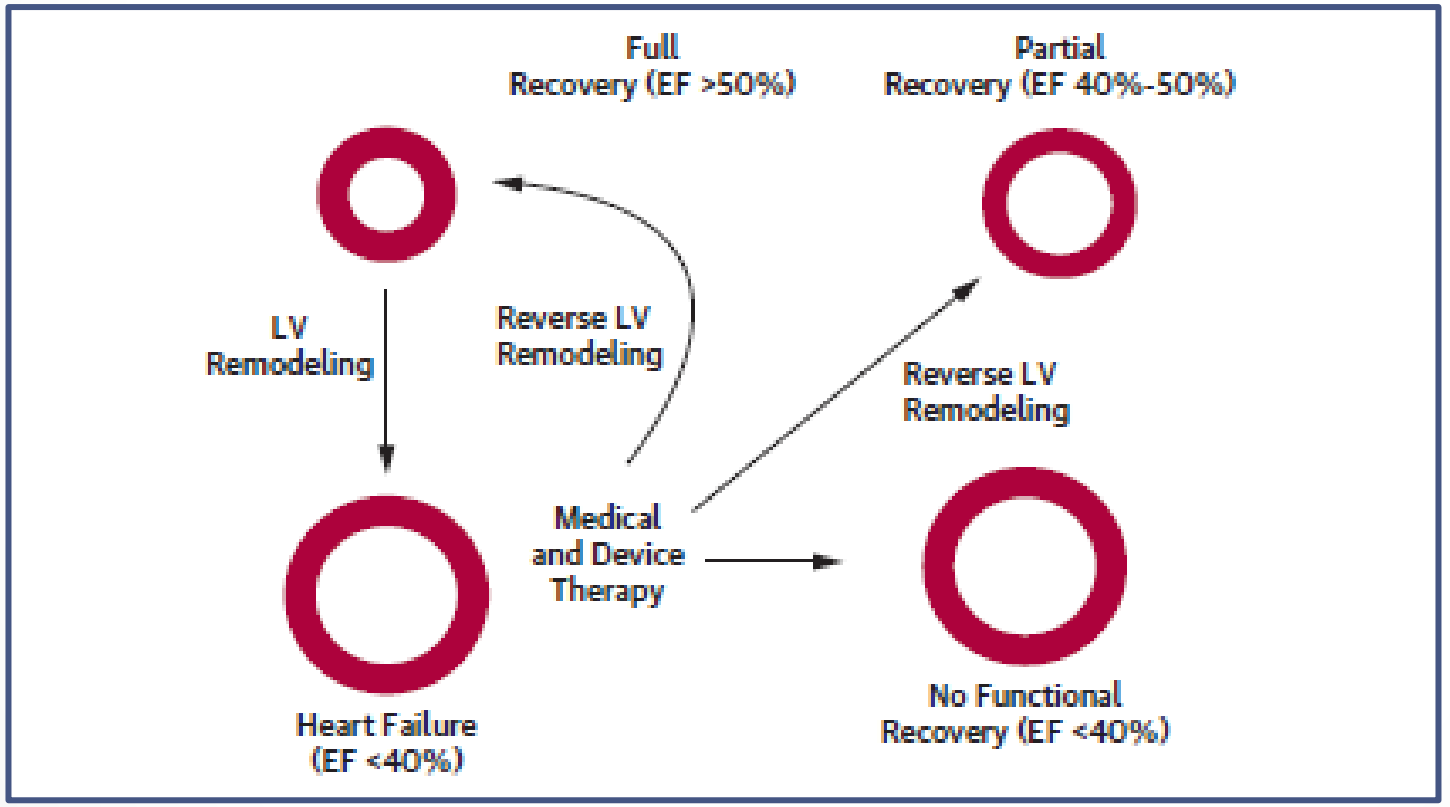
Trajectory of LVEF in pts with HF



- Jane E. Wilcox et al JACC Heart Failure With Recovered Left Ventricular Ejection Fraction

The first introduction of HF with recovered LVEF : a distinct clinical entity

358 HF patients

- LV-PEF= 56 with EF persistently ≥40%
- LV-LEF=181 with HF- low EF<40%.
- LV-REF= 121 with EF recovered to ≥40%

	HF-PEF (n = 56)	HF-REF (n = 121)	HF-LEF (n = 181)	HF-REF vs HF-PEF *P* Value	HF-REF vs HF-LEF *P* Value
Ischemia	4 (7)	21 (17)	57 (31)	.07	.006
Nonischemic causes	25 (45)	72 (60)	81 (45)		
Valvular disease*	6 (11)	10 (8)	16 (9)	.60	.86
Hypertensive disease†	5 (9)	8 (7)	6 (3)	.58	.18
Pulmonary hypertension	5 (9)	1 (1)	1 (1)	.006	.77
Restrictive process	3 (5)	2 (2)	3 (2)	.17	1.0
Alcohol/drug induced†	1 (2)	23 (19)	29 (16)	.002	.50
Tachycardia mediated†	2 (4)	9 (7)	4 (2)	.32	.03
Familial	0	4 (3)	12 (7)	.17	.21
Viral myocarditis†	0	5 (4)	7 (4)	.12	.91
Cause not specified	27 (48)	44 (36)	69 (38)	.13	.75

EF recovered to ≥40% patients (33%) vs. LV-PEF

- Younger, less AF, HTN, and DM

EF recovered to ≥40% vs. LV-LEF

- Younger and had lower rates of CAD
- Had the mildest reported HF symptoms and fewest previous HF hospitalizations.

L.R. Punnoose, M.M. Givertz, E.F. Lewis, et al., Heart failure with recovered ejection fraction: a distinct clinical entity, J. Card. Fail. 17 (2011) 527–532.

Author Year	Number of patients	Follow up	Rate of recover
1.Punnosse LR 2011	358	6 years	34%
2.Wilcox JE 2012	3994	2 years	29%
3.Basuray A 2014	1821	9 years	10%
4.Klogeropouls AP 2016	2166	3 years	37%
5.Ghimire A 2019	3124	6 months	16%

Adapted from U. Elkayam 2020

Recently defined unique patient population

HF with Recovered EF (HFrecEF)

Scientific Expert Panel , JACC 2020:

- A decreased LVEF **<40%** at baseline
- A ≥10% absolute improvement in LVEF
- A second measurement of LVEF >40%.

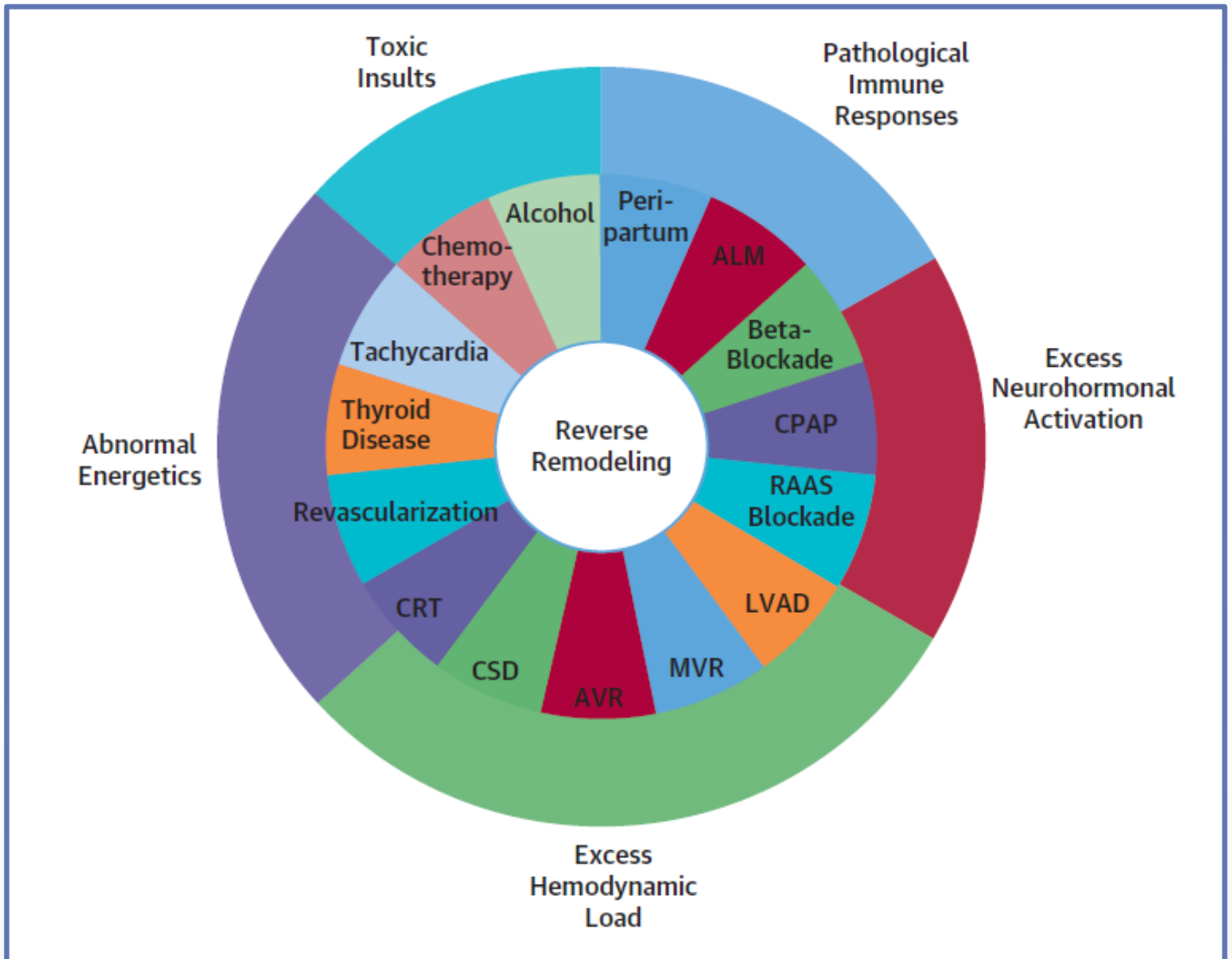
HF with improved EF (HFimpEF)

Writing Committee of the Universal Definition of Heart Failure 2021:

- A decreased LVEF **≤40%** at baseline
- A ≥10% absolute improvement in LVEF
- A second measurement of LVEF >40%.

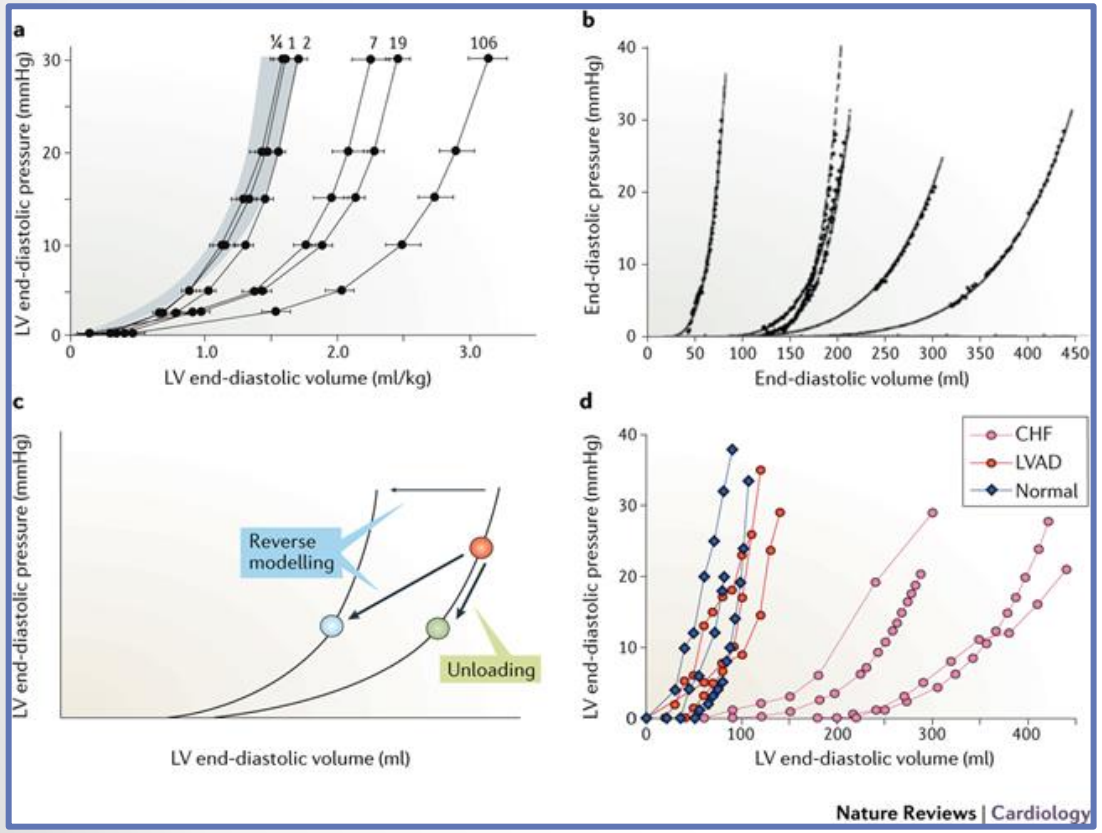
- Jane E. Wilcox et al .Heart Failure With Recovered Left Ventricular Ejection Fraction. JACC Scientific Expert Panel. 2020
- Biykem Bozkurt* at al report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. European Journal of Heart Failure (2021) 23, 352–380

Etiology of cardiomyopathy with LV recovery with reverse remodeling

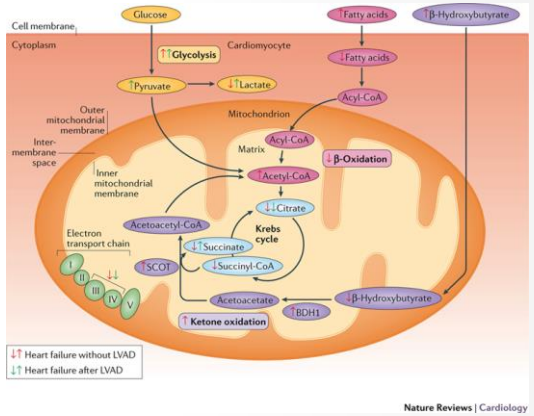


Physiology & biology of reverse remodeling

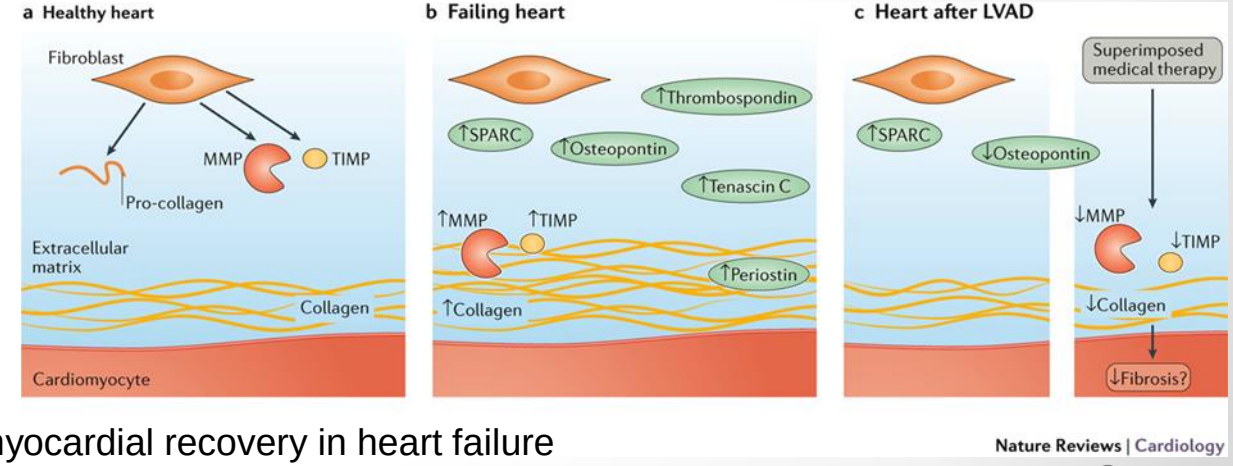
- Restoration of more normal cardiac myocyte size and LV chamber geometry
- A leftward shift of the end-diastolic pressure volume relationship
- Improved myocyte contractility and improved LV chamber contractility



Metabolic shift in heart failure



Altered extracellular matrix



Kim, G. H. *et al.* (2017) Reverse remodelling and myocardial recovery in heart failure *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2017.139

Prospective Multicenter Study of Myocardial Recovery Using Left Ventricular Assist Devices (RESTAGE-HF [Remission from Stage D Heart Failure])

Medium-Term and Primary End Point Results

Circulation. 2020;142:2016–2028.

Clinical Perspective

What Is New?

- RESTAGE-HF (Remission from Stage D Heart Failure) demonstrates that optimized left ventricular assist device (LVAD) mechanical hemodynamic unloading, combined with a standardized specific aggressive pharmacological regimen designed to induce reverse remodeling and regular testing of underlying myocardial function, enhances the incidence of LVAD explantation in a prospective multicenter study in patients with chronic advanced heart failure.
- Forty percent of all enrolled (16/40) patients achieved the primary end point (alive free from mechanical support/heart transplantation 1 year after LVAD explant), $P<0.0001$, and 52.3% (19/36) receiving the protocol were explanted overall.
- The RESTAGE-HF protocol was reproducible, with explants occurring in all 6 participating sites, a key component for broader application of this strategy.

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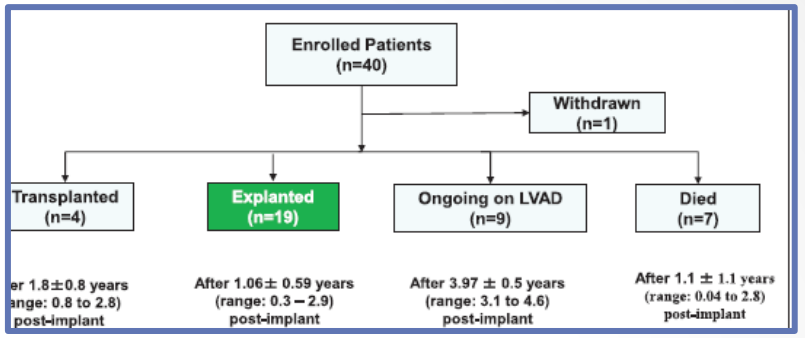
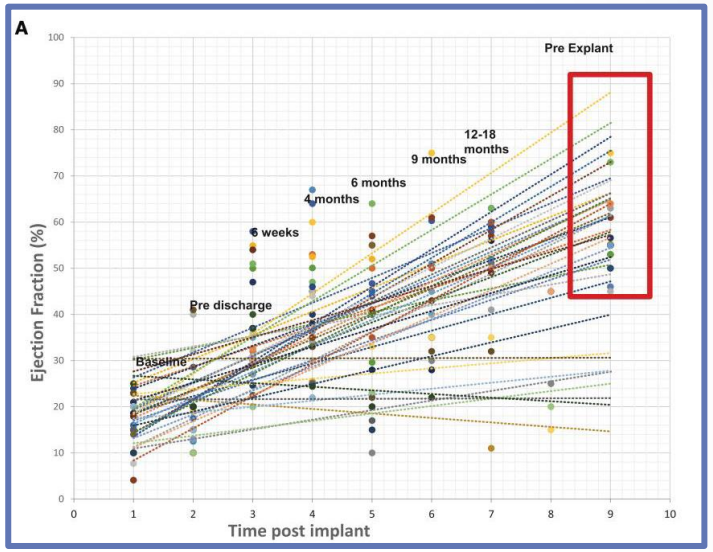
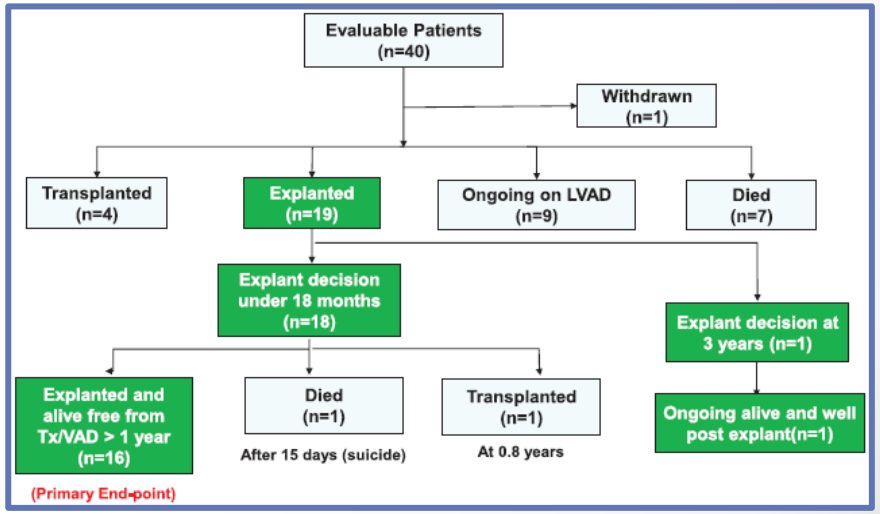
Key Words: cardiomyopathy ■ heart failure ■ recovery ■ remodelling ■ transplantation ■ ventricular assist device

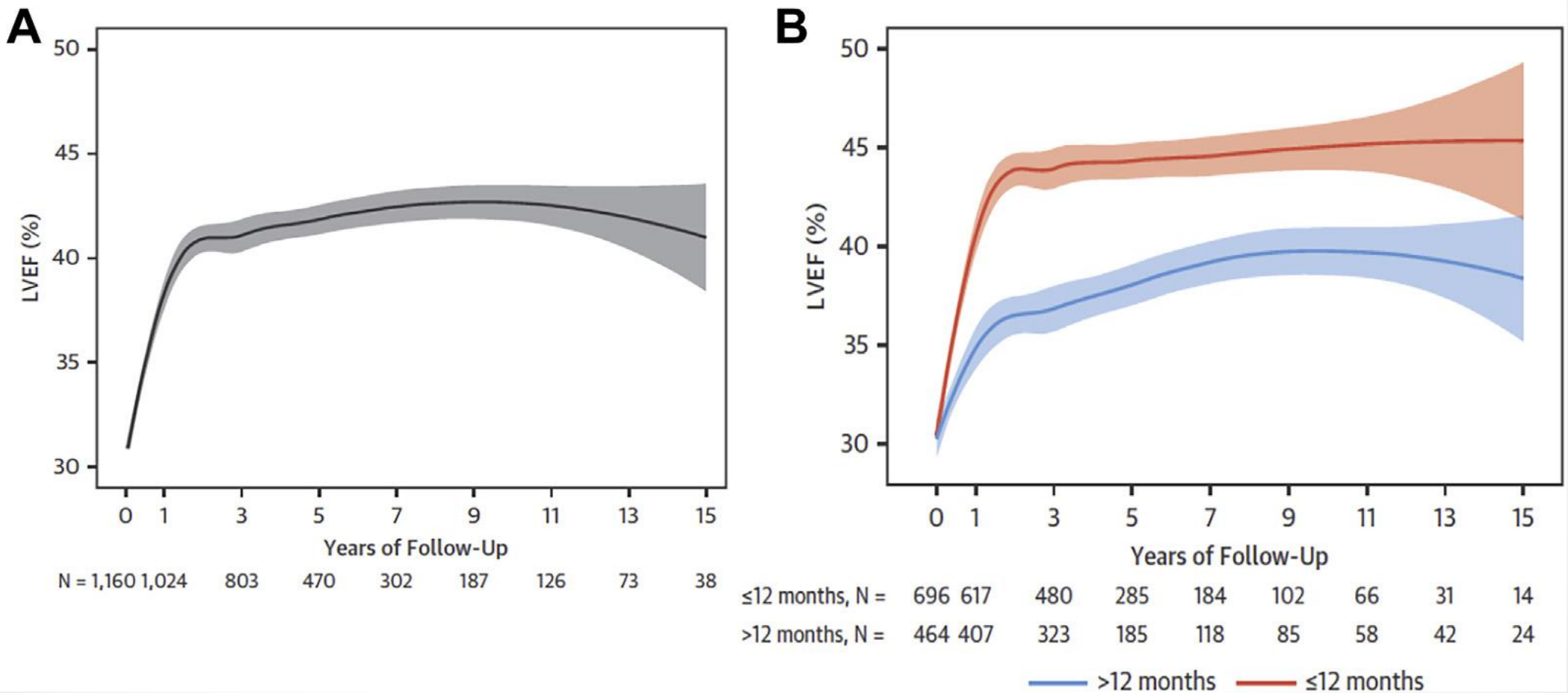
Sources of Funding, see page 2026







LVEF Trajectories After Initiation of Guideline-Recommended Therapy for HF

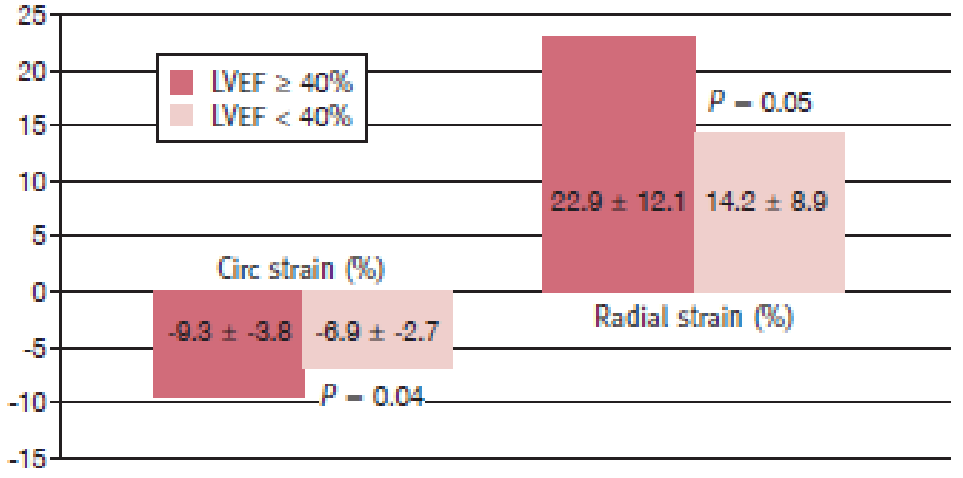


Lupon J, Gavidia-Bovadilla G, Ferrer E, et al. J Am Coll Cardiol 2018;72: 591–601.

Left Ventricular Reverse Remodeling in ROCM

- 47% of the patients with ROCM demonstrated cardiac function improvement beyond the device threshold by 6 months
- LV size and volume were predictors of LV improvement
- Apical rotation was introduced in our study as 2D strain prognostic parameter and found to be an independent predictor of LV remodeling.

Figure 1. Differences in baseline circumferential and radial strain between patients with LVEF improvement beyond 40% and those who did not improve to this magnitude



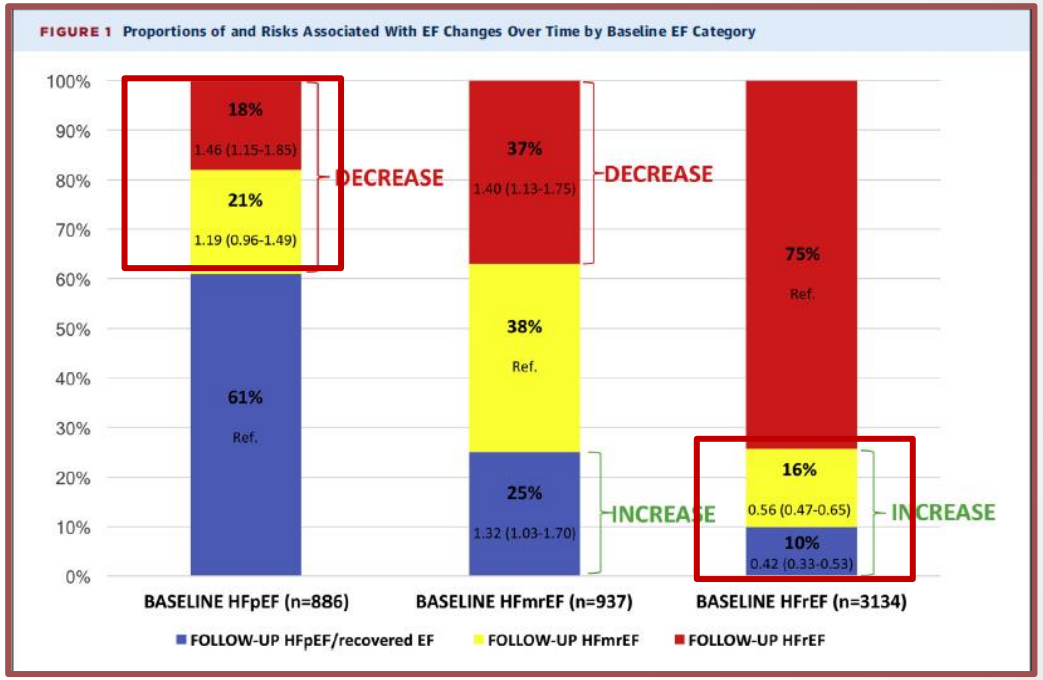
Circ Strain = circumferential strain, LVEF= left ventricular ejection fraction

Isr Med Assoc J 2018 Dec;20(12):749-753.

Prevalence and Prognostic Implications of Longitudinal Ejection Fraction Change in Heart Failure (SwedeHF)

4942 pts at least 2 LVEF measurements registered in the Swedish Heart Failure Registry

- Predictors of increased EF included female sex, cases of less severe HF, and comorbidities.
- Predictors of decreased EF included DM, IHD.
- Increased EF was associated with a more favorable outcome, whereas decreased EF with poor prognosis.
- The prognostic differences were most evident for transitions to and from HFrEF.
- Use of ACE inhibitors/ARBs was associated with stable EF.



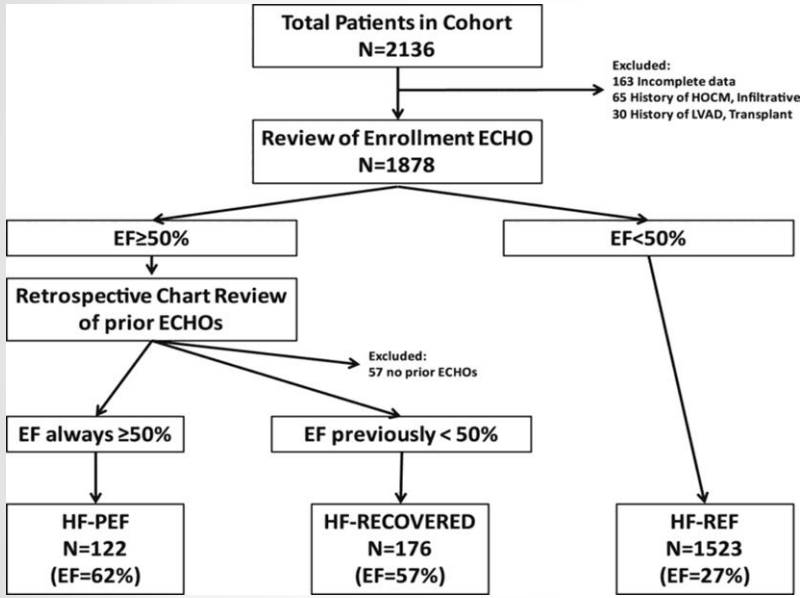
Gianluigi Savarese et al. JACC Heart failure . 2019 Apr;7(4):306-317

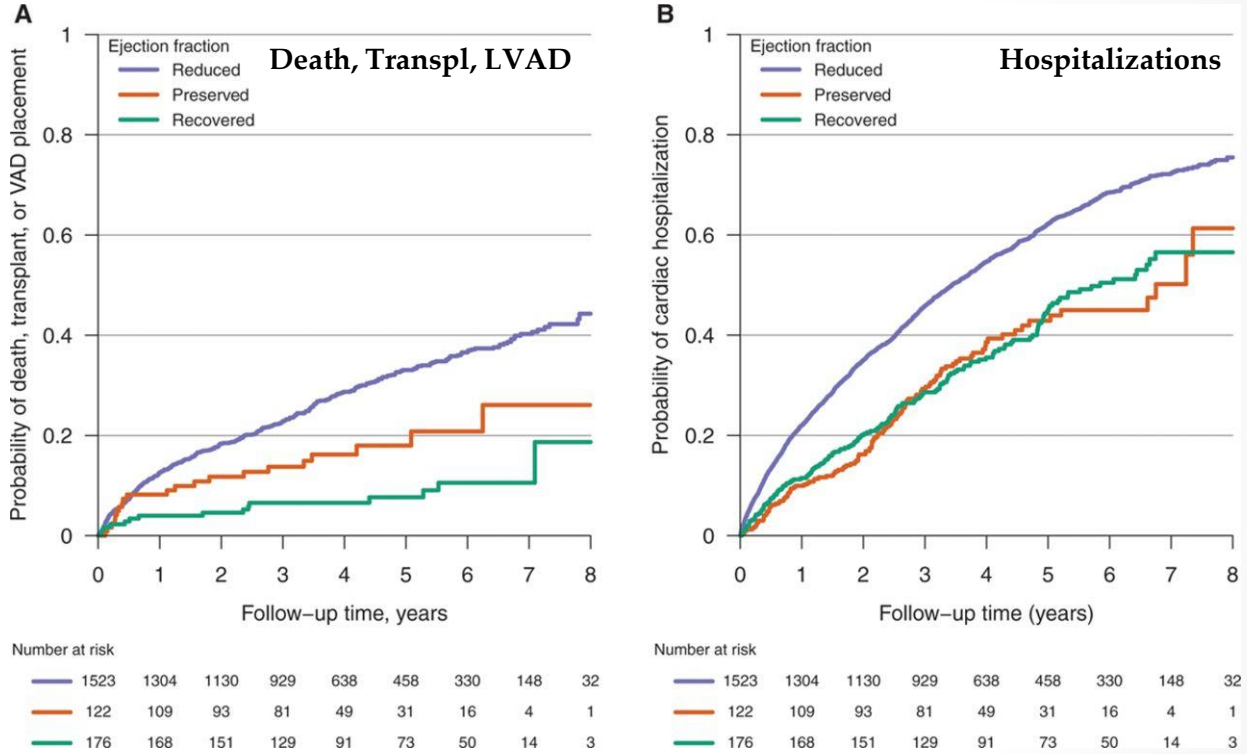
What are the prognostic implications of LV recovery?

Heart Failure With Recovered Ejection Fraction

Clinical Description, Biomarkers, and Outcomes

Recovered if EF on enrollment in PHFS was ≥50% but prior EF was <50%.



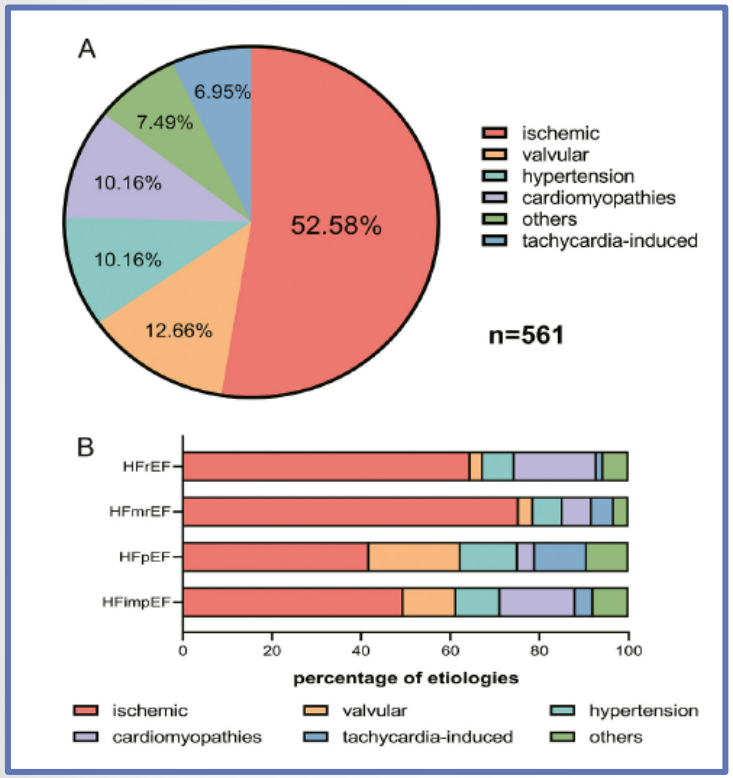


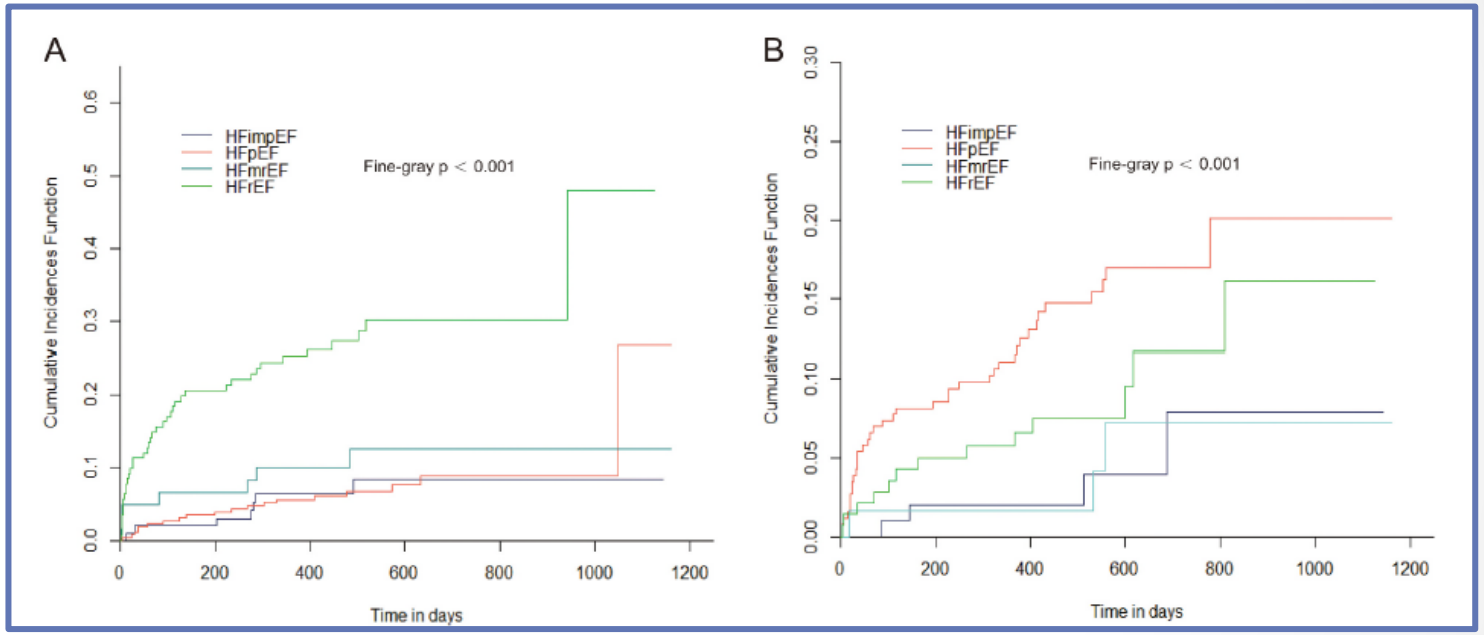
HF-Recovered is associated with a better biomarker profile and event-free survival than HF-REF and HF-PEF. However, these patients still have abnormalities in biomarkers and experience a significant number of HF hospitalizations, suggesting persistent HF risk.

Basury A et al Circulation. The Penn HF Study 2014;129:2380–2387

Clinical characteristics, predictors, and outcomes of heart failure with improved ejection fraction

Kangkang Su [a], Mingquan Li [b], Lili Wang [c], Shipeng Tian [c], Jingjing Su [d], Jian Gu [c], Shuxia Chen [c,*]

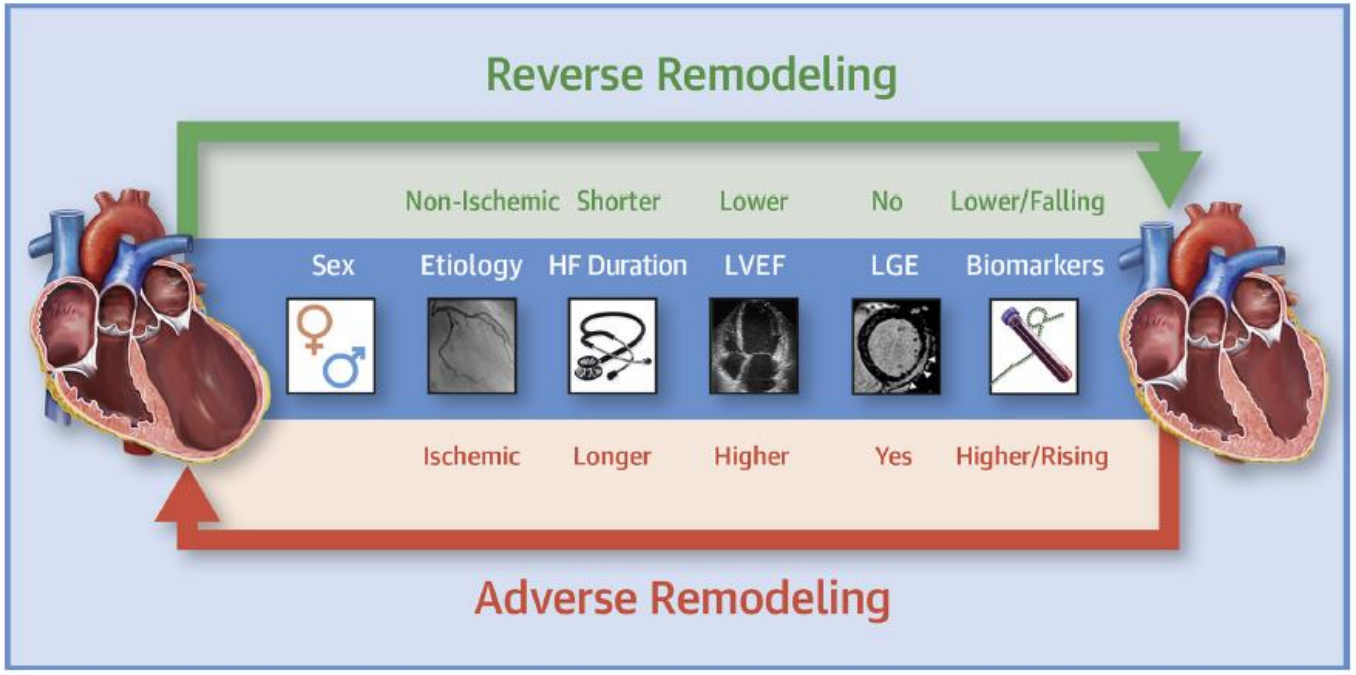




HFimpEF is an independent HF phenotype with prognosis similar to HFmrEF and superior to HFpEF and HFrEF

Su K et al International Journal of Cardiology 357 (2022) 72–80

Predictors of LV reverse remodeling



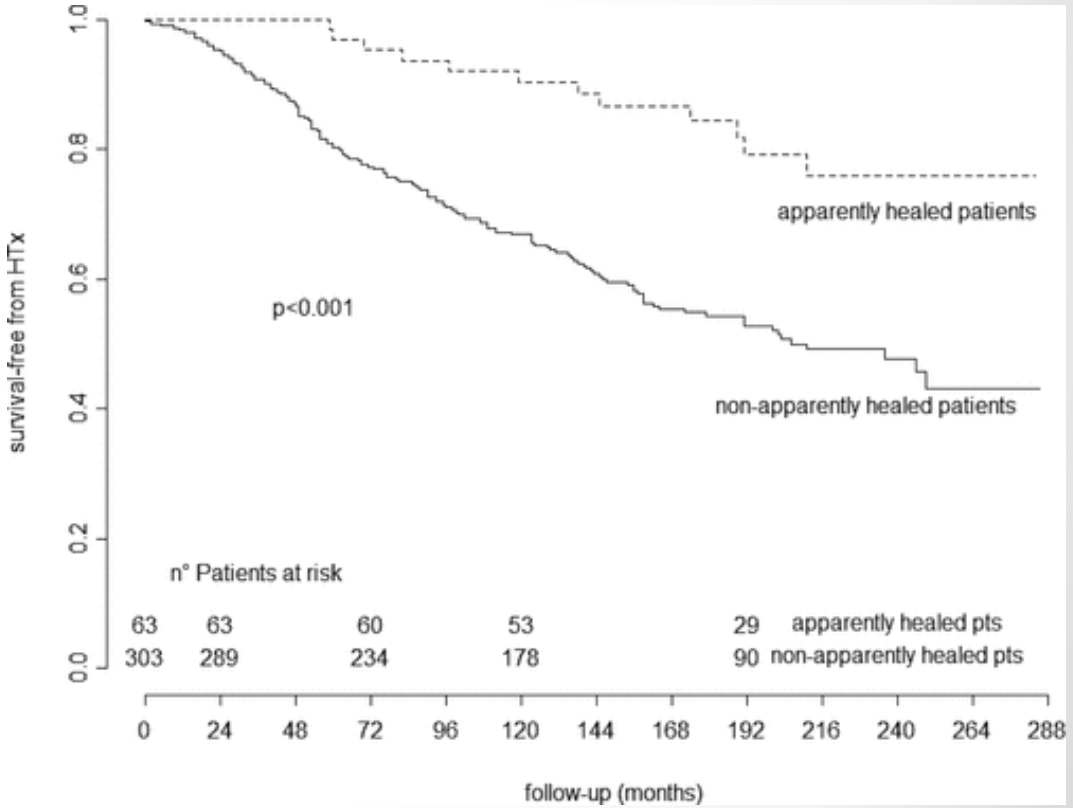
Aimo, A. et al. J Am Coll Cardiol HF. 2019;7(9):782-94.

Predictor Category	Predictors	(Ref. #)
Clinical parameters	Nonischemic cause	(7,14,15)
	Lower HF duration	(7)
	Female	(15)
	No LBBB	(7)
	LBBB in CRT	(19)
Therapies	BB therapy	(7)
	ACE inhibitor/ARB therapy	(11)
	MRA (spironolactone)	(11)
	CRT	(19)
Echo/CMR imaging	Lower LVEF, greater LV diameters	(7,14,49)
	Greater contractility on strain imaging	(21)
	LV dyssynchrony, lower LV volumes, preserved LV contractile reserve, lower degree of mitral regurgitation, lower LA dimensions, preserved right heart geometry and function (CRT)	(22-24,46,47,50,51)
	LGE absence	(6,29,30)
Biomarkers	Lower NT-proBNP	(31-34)
	Lower troponin	(35,36)
	Lower sST2	(7,13)
	Gal-3, emerging biomarkers (mimecan, miRNAs, orexin)	(40,42-44)

Does Real Healing Exist?

Persistent Recovery of Normal Left Ventricular Function and Dimension in Idiopathic Dilated Cardiomyopathy During Long-Term Follow-up: Does Real Healing Exist?

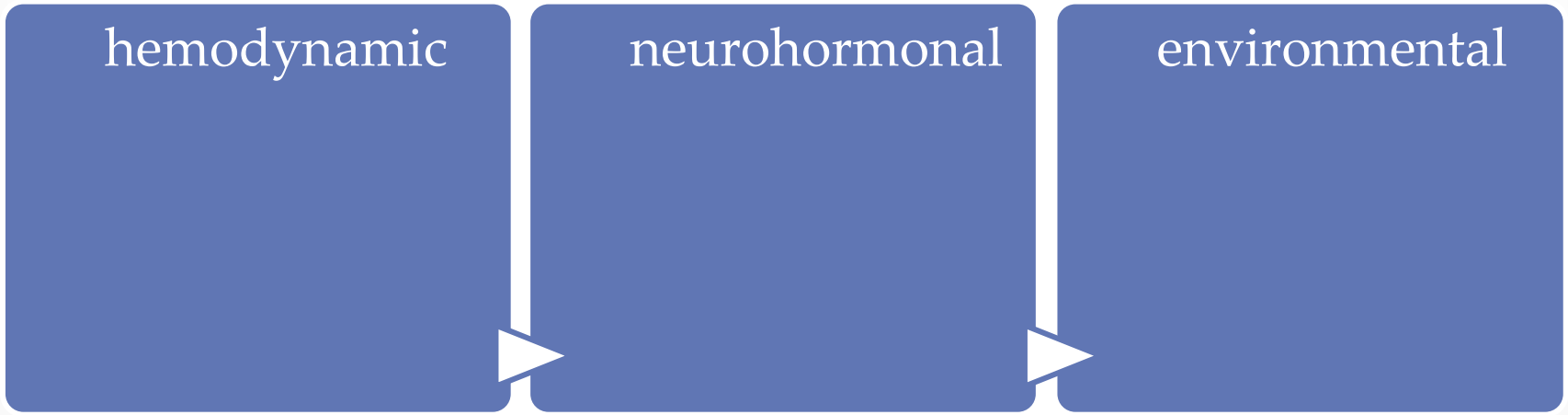
- Persistent apparent healing was evaluated among 408 patients with DCM receiving tailored medical treatment
- Persistent apparent healing was defined as LVEF ≥50% and LVDDi≤33 mm/m^2 at both mid-term (19±4 months) and long-term (103±9 months) f/u
- At mid-term 15% were apparently healed
- **9% showed persistent apparent healing at long-term evaluation.**
- No predictors of persistent apparent healing were found.



Merlo M et al J Am Heart Assoc. 2015;4:e001504

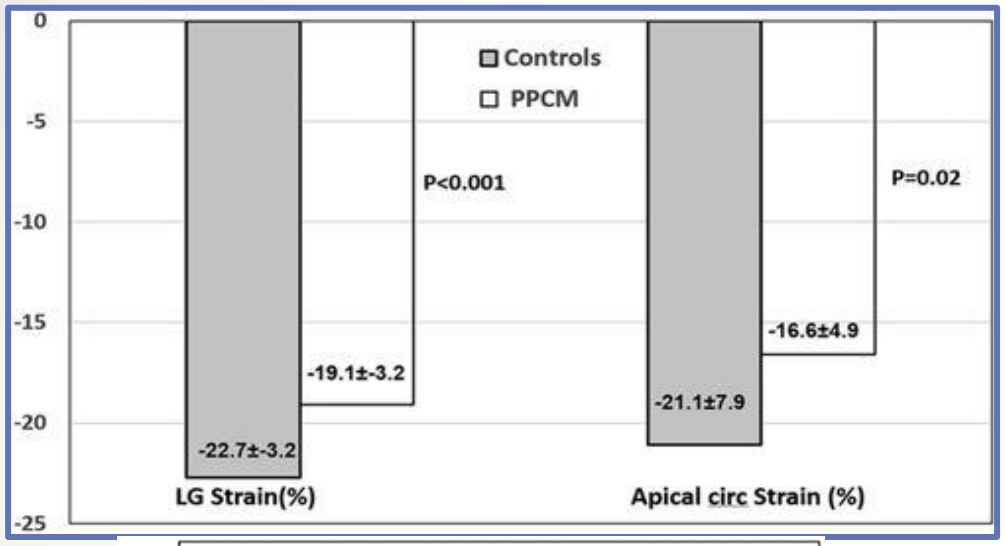
Does reverse remodeling and LV function recovery means normal heart?

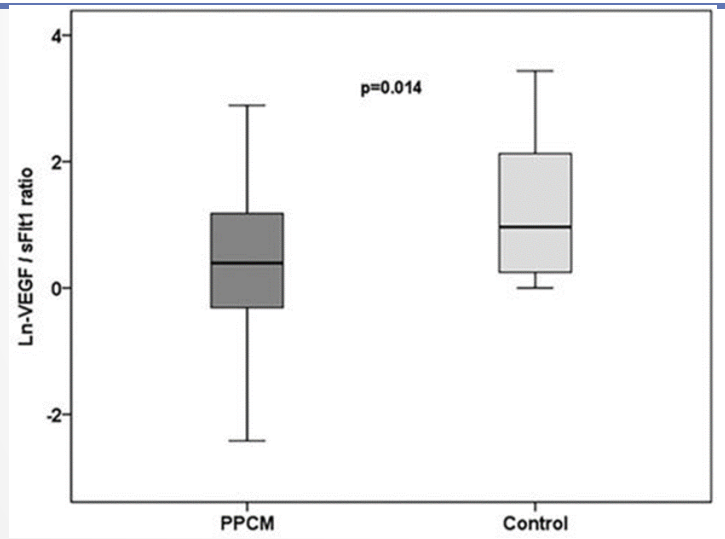
- Recovery represents a new "steady state" that is prone to relapse in response stress



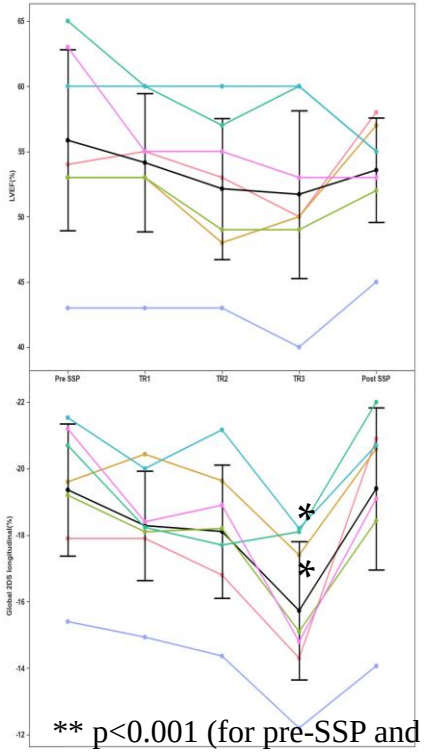
Does a recovered EF mean normal heart?

Residual Myocardial Injury in Recovered PPCM





- 29% of patients with PPCM with normal LVEF ≥55% at subsequent pregnancy had impaired 2DS



** p<0.001 (for pre-SSP and TR3)

S.Goland ,…. R.Kuperstein ESC Heart Fail. 2022 .

Sorel Goland. Circulation: Heart Failure. Angiogenic Imbalance and Residual Myocardial Injury in Recovered Peripartum Cardiomyopathy Patients, Volume: 9, Issue: 11, DOI: (10.1161/CIRCHEARTFAILURE.116.003349)

Residual alterations of cardiac and endothelial function in patients who recovered from Takotsubo cardiomyopathy

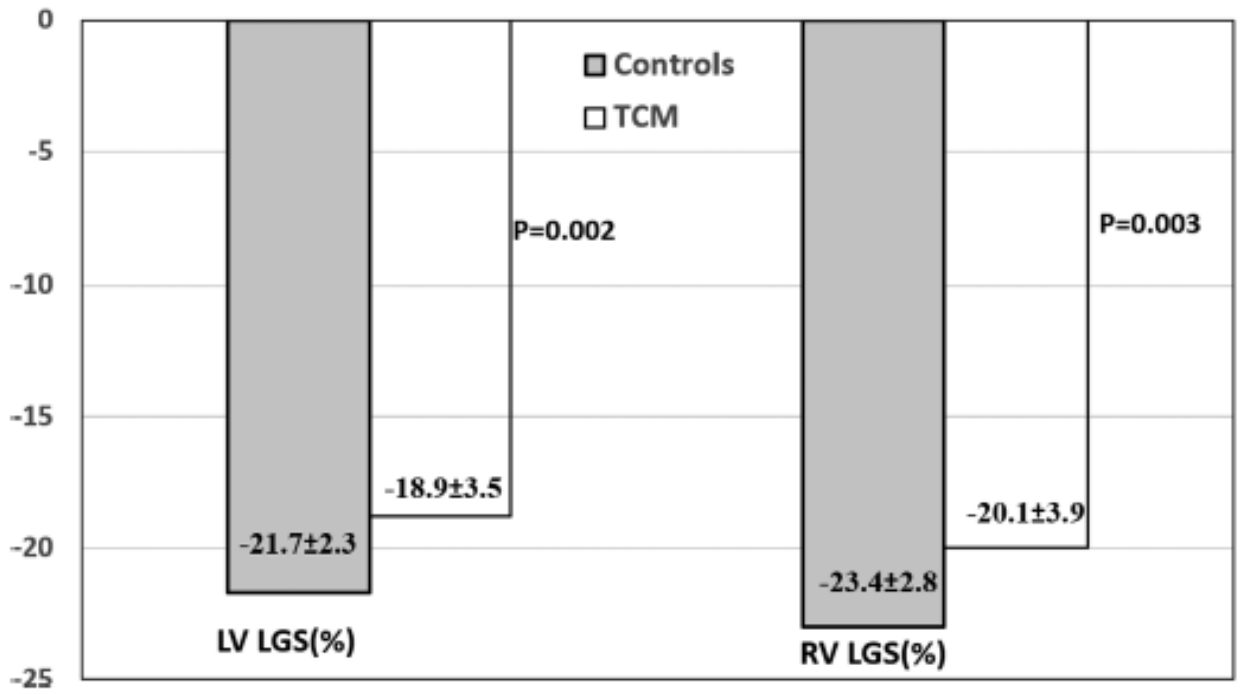


FIGURE 1 Comparison 2-dimentional strain values between patients with prior Takotusubo cardiomyopathy (TCM) and controls. LGS, longitudinal global strain; LV, left ventricle; RV, right ventricle

Zilberman L,…. Goland S Clin Cardiol. 2021; 44(6): 797–804.

Genetic testing in cardiomyopathies with LV recovery

- Because fatal arrhythmias may occur despite normalization of LVEF, considerations for prophylactic placement of an ICD have been recommended independent of EF for specific mutations in genes such as LMNA, SCN5A, and FLNC
- Genetic testing may be considered for patients with DCM related to an acquired or environmental cause that may overlap with a genetic cause (such as peripartum or alcoholic cardiomyopathy).

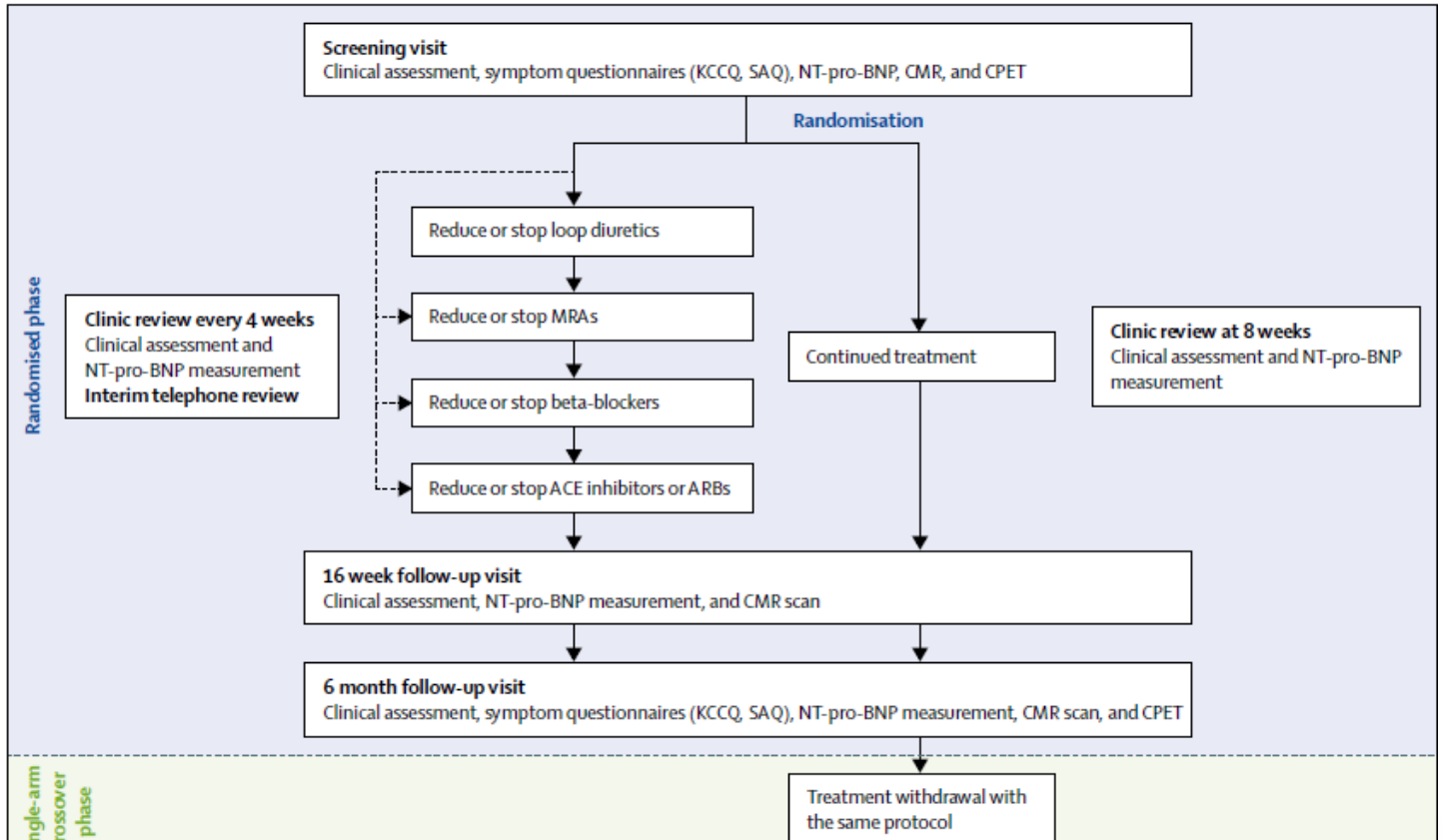
- Arthur Wilde et al 2022 ;24(8):1307-1367 Expert Consensus Statement on the state of genetic testing for cardiac diseases
- Ware JS, Amor-Salamanca A, Tayal U, Govind R, Serrano I, Salazar-Mendiguchıa J et al. Genetic etiology for alcohol-induced cardiac toxicity. J Am Coll Cardiol 2018;71:2293–302.
- Ware JS, Li J, Mazaika E, Yasso CM, Desouza T, Cappola TP et al.; IMAC-2 and IPAC Investigators. Shared genetic predisposition in peripartum and dilated cardiomyopathies. N Engl J Med 2016;374:233–41.
- Rahul Goli et al. Genetic landscape of PPCM *Circulation*. 2021 May 11; 143(19): 1852–1862.

- Recovery of EF in patients with HFimpEF is associated with improved prognosis
- Rate of hospitalization is still high and similar to HFpEF
- A significant proportion can develop recurrent LV systolic dysfunction and recurrent HF events

Should we continue GDMT after recovery?

Withdrawal of pharmacological treatment for heart failure in patients with recovered DCM (TRED-HF)

- 51 patients with previous DCM , asymptomatic, LVEF fraction <40% improved to ≥50% , normalized LVEDV had normalized , NT-pro-BNP <250 ng/L.
- 25 were randomly assigned to the treatment withdrawal and 26 to continue



Halliday B et al 2019 Jan 5;393(10166):61-

Relapse at 6 months :

The primary outcome, relapse of HF, for drug discontinuation vs. continuation, was 44% vs. 0%, p = 0.0001.

In the control (continuation) arm, following 6-month cross-over, relapse occurred in 36% of patients.

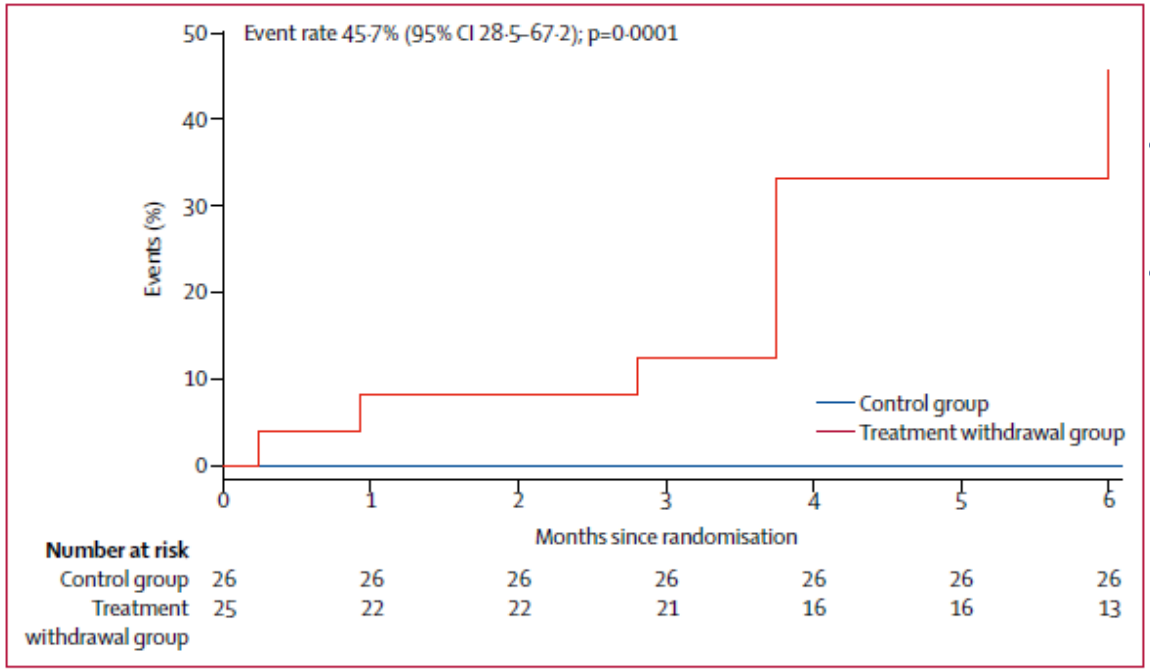


Figure 3: **Kaplan-Meier curve of time to primary endpoint in randomised phase, according to treatment group**
One patient dropped out at 7 days.

- Many patients deemed to have recovered from DCM will relapse following treatment withdrawal.
- Until robust predictors of relapse are defined, treatment should continue indefinitely.

Device therapy

ICD generator change

- Patients with genetic mutations associated with arrhythmic risk, history of ventricular arrhythmia, persistently abnormal ECG.

Maintenance of CRT pacing

- Small prospective randomized experience showed that 78% of super-responders experienced a deterioration in clinical and echocardiographic parameters within 12 months after CRT deactivation .

Proclemer A, Muser D, Facchin D. Heart Fail Clin 2017;13:225–32.
Cay S, Ozeke O, Ozcan F, Aras D, Topaloglu S. Europace 2016;18: 842–50
Jane E. Wilcox et al . JACC Scientific Expert Panel. 2020

Follow-up and management recommendations

- Close clinical follow-up due to the high risk of HF relapse
- After stabilization of EF for > 1 year F/U q 6 months for > 3 years, then at least once every year for life
- In addition to review of signs and symptoms during the F/U it is recommended to repeat BNP level
- Annual echocardiography for > 2 years (for life) and any time that signs and /or symptoms of HF develop
- MRI at time of diagnosis
- GDMT and device therapy for patients with HFimpEF should be continued indefinitely until the biology and clinical epidemiology of HFimpEF is better understood.

Jane E. Wilcox et al .Heart Failure With Recovered Left Ventricular Ejection Fraction. JACC Scientific Expert Panel. 2020

Thank you!