REVERSE REMODELING◆ REMISSION◆RECOVERY?

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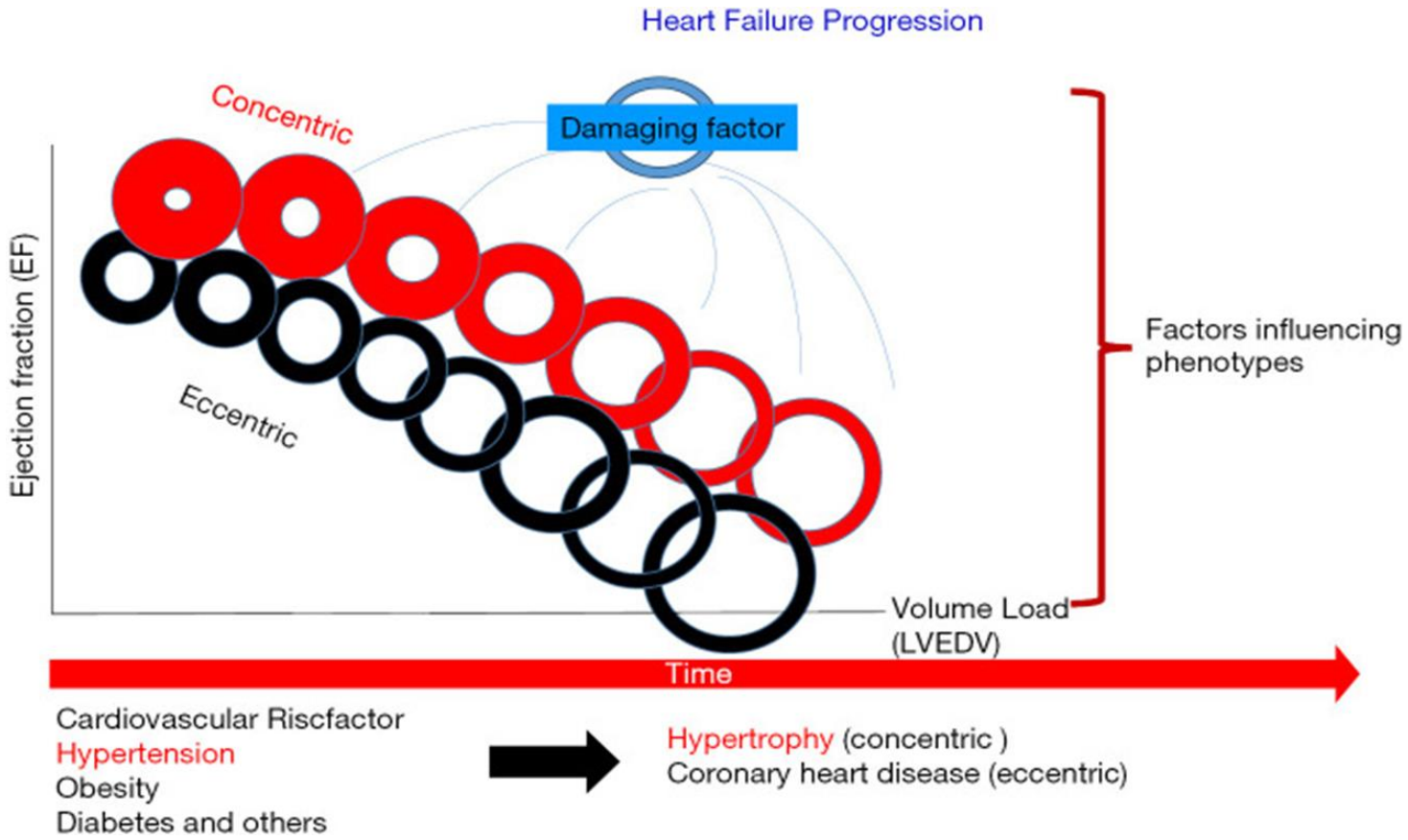
Miami Valves, February 2023

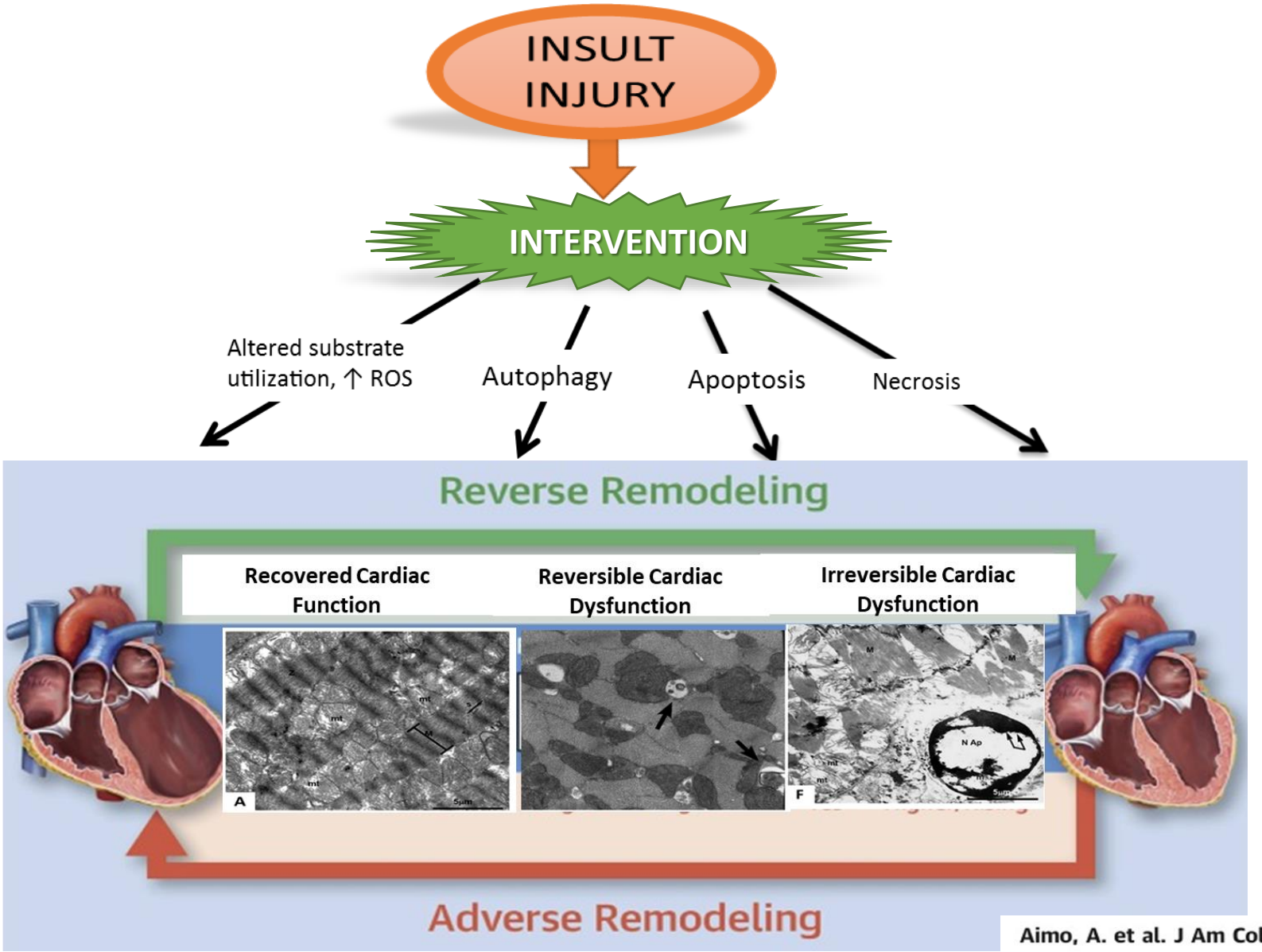
UHealth UNIVERSITY OF MIAMI HEALTH SYSTEM | UNIVERSITY OF MIAMI MILLER SCHOOL of MEDICINE

“Heart Failure is Characterized by Progressive Decline”

INSULT
INJURY



Our Understanding of the Trajectory of HF has Changed



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

Remodeling, Reverse Remodeling, Remission and Recovery

Remodeling: first use in medical literature 1982

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Reverse Remodeling: first use in medical literature Barry and Arlene Levine 1997

- Understood to occur as a result of removal of the triggering injury/ insult that contributes to remodeling and/or institution of interventions that mitigate exacerbating factors, hemodynamic load, maladaptive neurohormonal activation etc that drive remodeling. Genome expression changes leading resulting in molecular and cellular modifications that modify tissue and organs

Remission and Recovery: First descriptions related to device-based interventions (LVAD and CRT) changes manifested clinically as normalization or near normalization of the size, shape and function of the heart following a period of clinical decompensation and objectively measured dysfunction

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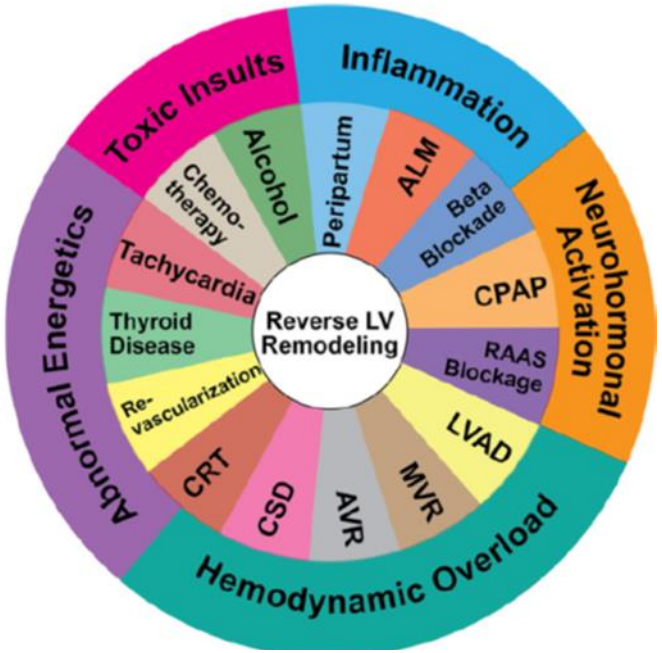
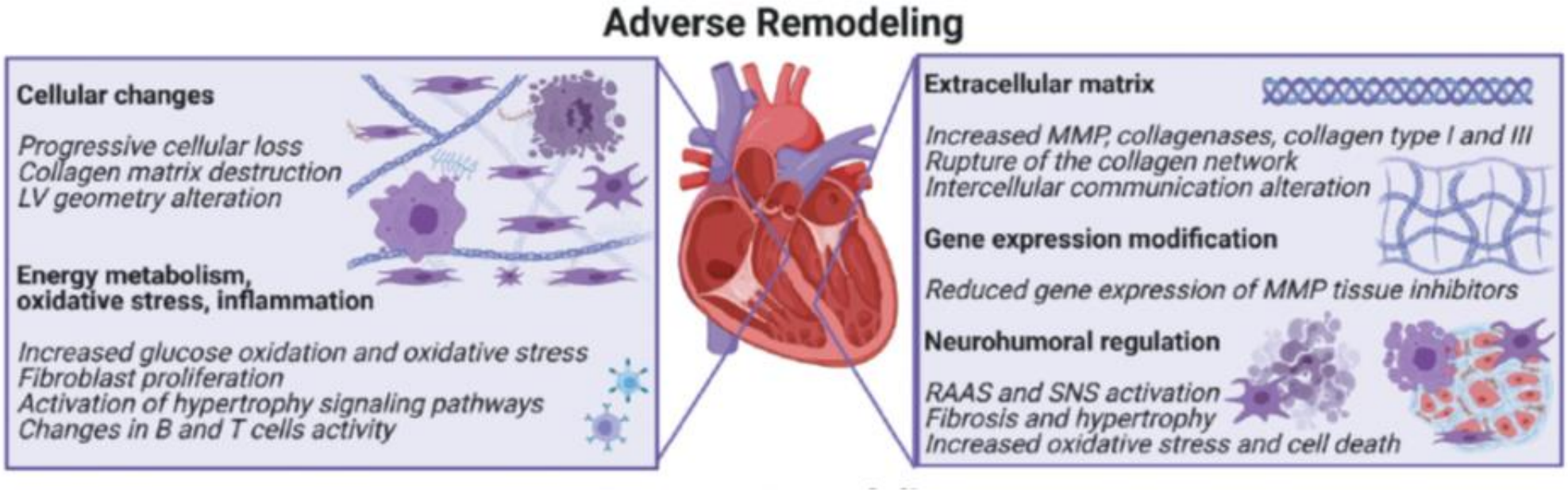
Kawai K, Takaoka H, Hata K, et al. Am J Cardiol. 1999;84:671-6.

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 and function of the heart after injury/insult.





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Reverse Remodeling in Heart Failure with Intensification of Vasodilator Therapy

T. BARRY LEVINE, M.D., ARLENE B. LEVINE, M.D., STEVEN J. KETEYIAN, PH.D., BARBARA NARINS R.N., MICHAEL LESCH, M.D.

Henry Ford Heart and Vascular Institute, Detroit, Michigan, USA

Echo parameter	Initial (n = 99)	6 Month (n = 99)	p Value
LV ejection fraction (%)	21 ± 9	30 ± 13	< 0.0001
LV end-diastolic diameter (cm)	6.6 ± 0.9	6.3 ± 1.0	0.002
Mitral regurgitation (1 = mild, 2 = mild–mod, 3 = moderate	2.1 ± 1.3	1.4 ± 1.3	0.0002
Wall thickness (cm)	1.0 ± 0.2	1.1 ± 0.2	NS

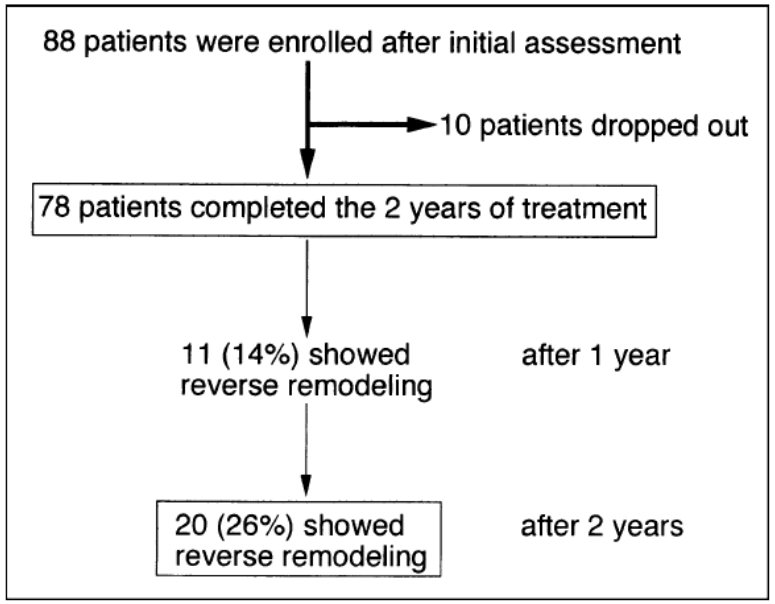
Data are presented as mean value ± standard deviation. All 99 patients underwent initial and 6-month follow-up echocardiography.
Abbreviations: Echo = echocardiographic, LV = left ventricular, NS = not significant.

Levine TB, Levine AB, Keteyian SJ, Narins B and Lesch M. Reverse remodeling in heart failure with intensification of vasodilator therapy. Clin Cardiol. 1997;20:697-702.

Prevalence, Predictors, and Prognosis of Reversal of Maladaptive Remodeling With Intensive Medical Therapy in Idiopathic Dilated Cardiomyopathy

Keisuke Kawai, MD, Hideyuki Takaoka, MD, Katsuya Hata, MD, Yoshiyuki Yokota, MD, and Mitsuhiro Yokoyama, MD

Reverse Remodeling



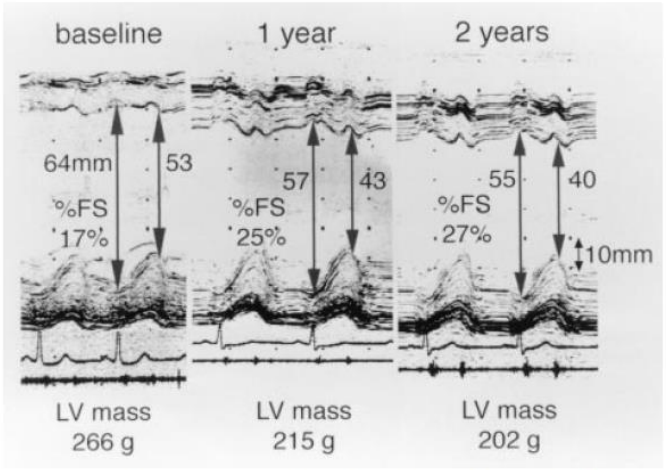


FIGURE 2. Subsequent M-mode echocardiography in the left ventricle at the level of the chordae tendineae in a representative case that showed reverse remodeling with intensive medical therapy. *Left*, echocardiograms obtained at the first examination. *Middle and right*, echocardiograms taken 1 year and 2 years after the initiation of treatment, respectively.

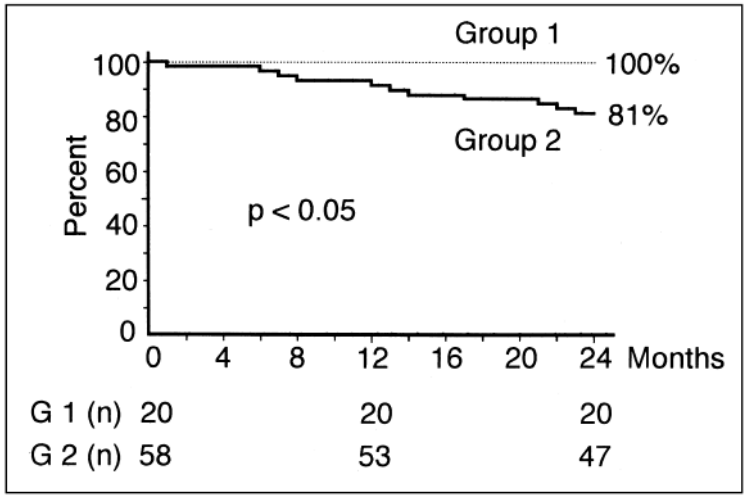


FIGURE 3. Cumulative 24-month survival rates for all cardiac events (death and hospital admission) in the 2 groups. The numbers below the graph represent the patients at risk for the 2 groups. G 1 = group 1; G 2 = group 2.

FIGURE 1. Outcome after 1 and 2 years of treatment of 88 patients with IDC. 78 patients completed 2 years of treatment.

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At the time of the baseline evaluation, 7% of patients were treated with ACE I and none with b blockers.

At 2 years 81% of patients were on ACE inhibitors and 59% b blockers

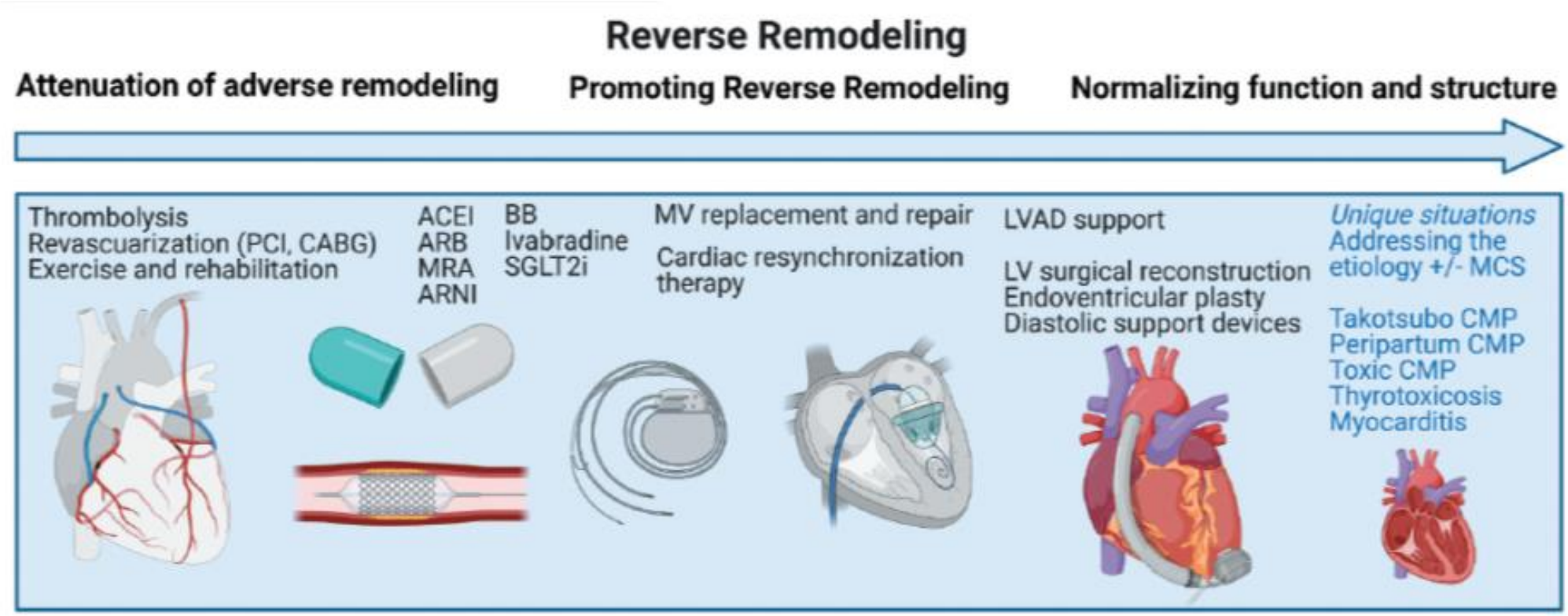
11 patients had reverse remodeling after 1 year, 9 had later reversal of remodeling

20 patients (26%) showed reverse remodeling after 2 years of treatment.

Am J Cardiol. 1999;84:671-6

Reverse Remodeling

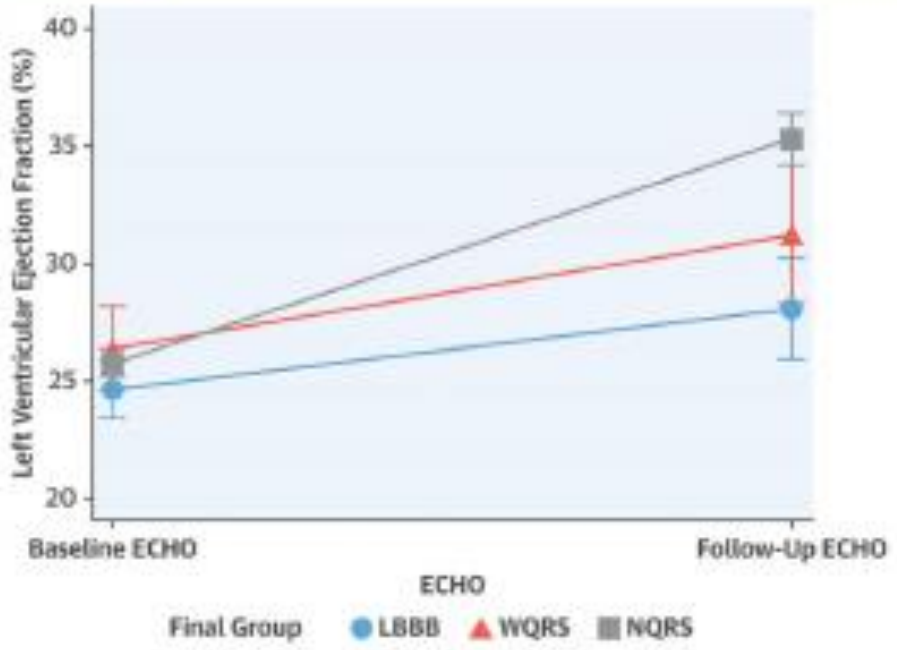
- Understood to occur as a result of LVRR is the result of removal of the triggering injury/ insult) and/or institution of interventions that mitigate and interfere with the process of LV remodeling. Genome expression resulting in molecular, cellular and interstitial changes occur in response



CRT and Reverse Remodeling

Fig. 5 Mean change in left ventricular EF with 95% confidence interval for patients with a new diagnosis of EF ≤ 35% and a follow-up echocardiogram 3–6 months later. Graph is stratified by three QRS morphologies (LBBB, wide QRS non-LBBB, and a narrow QRS duration ≤ 120 ms). From: Sze et al. [44]

CENTRAL ILLUSTRATION: Mean Left Ventricular Ejection Fraction With 95% Confidence Interval: Baseline and Follow-Up Echocardiogram, Graphed for the 3 QRS Groups



Sze, E. et al. J Am Coll Cardiol. 2018;71(3):306-17.

Most Pharmacologic Therapies with Beneficial Effect on Morbidity and Mortality Demonstrate Capacity for Reverse Remodeling

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]

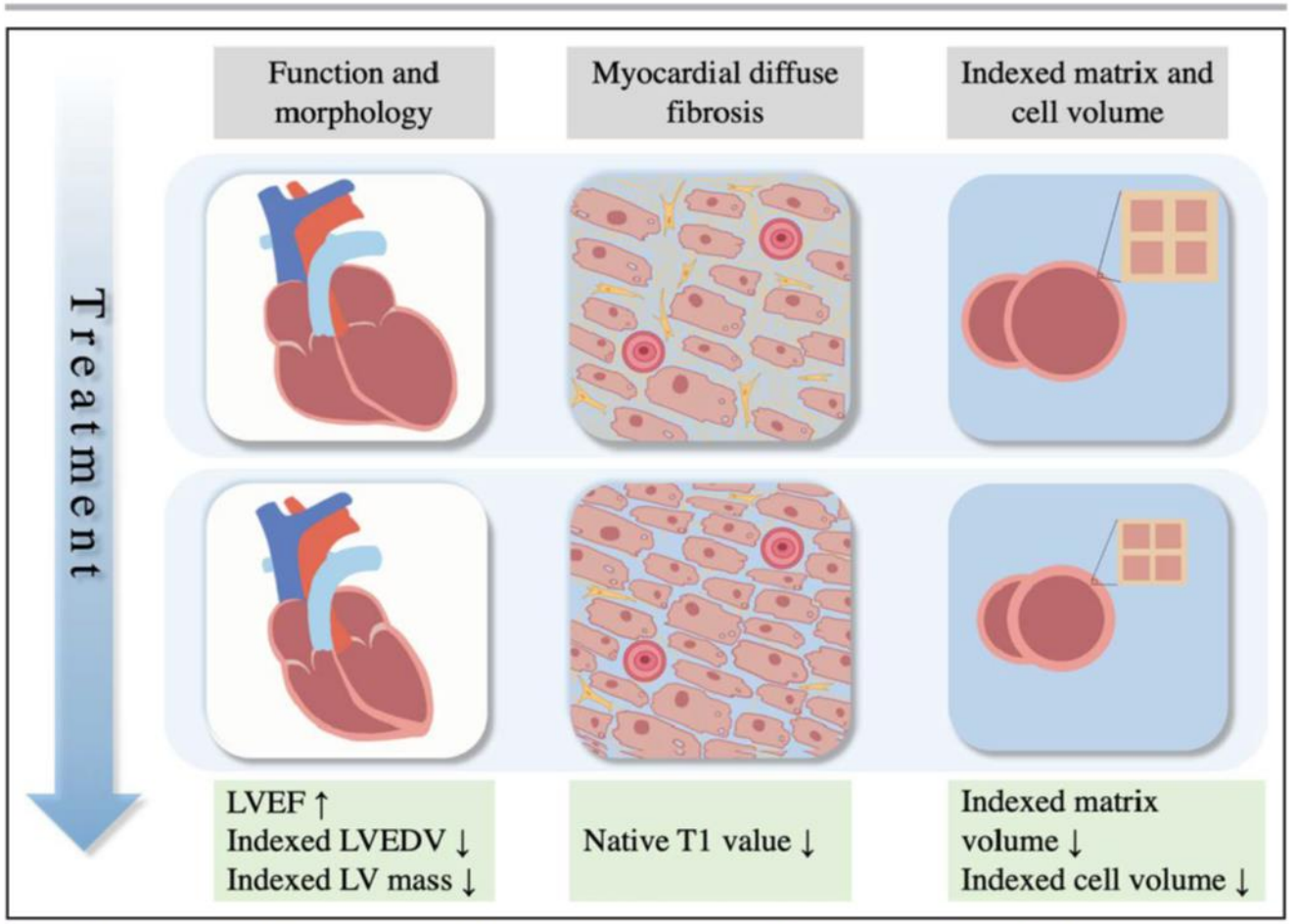


Figure 4. Left ventricular (LV) function, morphology, and tissue reverse remodeling in patients with dilated cardiomyopathy after guideline-directed medical therapy (GDMT).

The schematic illustrates patients with dilated cardiomyopathy (DCM) with LV reverse remodeling in DCM after GDMT (**A**). The study demonstrated the change of myocardial diffuse fibrosis (**B**), indexed matrix, and cell volume (**C**) after GDMT alongside with the left ventricular reverse remodeling. LVEDV indicates left ventricular end diastolic volume; and LVEF, left ventricular ejection fraction.

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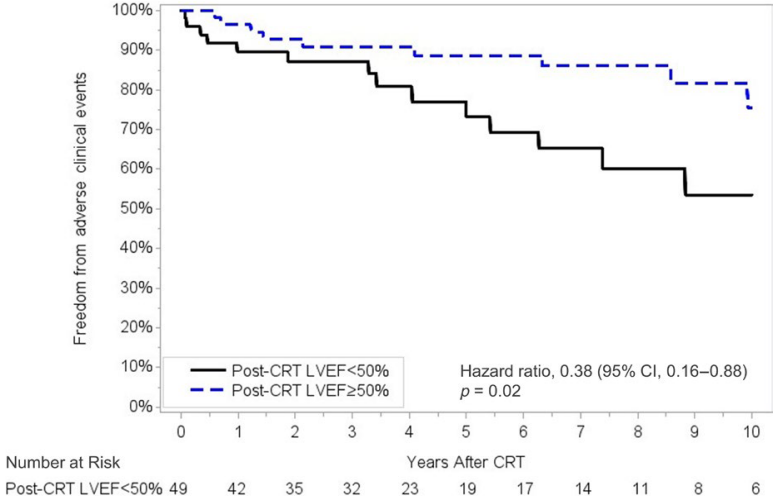
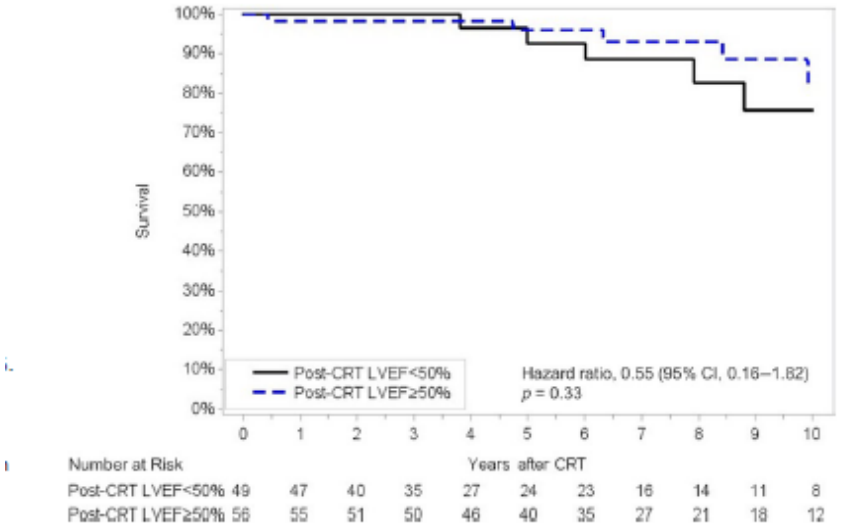
Myocardial recovery after cardiac resynchronization therapy in left bundle branch block-associated idiopathic nonischemic cardiomyopathy: A NEOLITH II substudy

- 105 subjects (mean age 61 years, 44% male, mean initial LVEF 22.6% ± 6.6%, 81% NYHA class III, and 98% CRT-D),
- Myocardial recovery (post-CRT LVEF ≥50%) after CRT was observed in 56 (54%) subjects.
- Subjects with, when compared to <50%, had lower risk for adverse clinical events

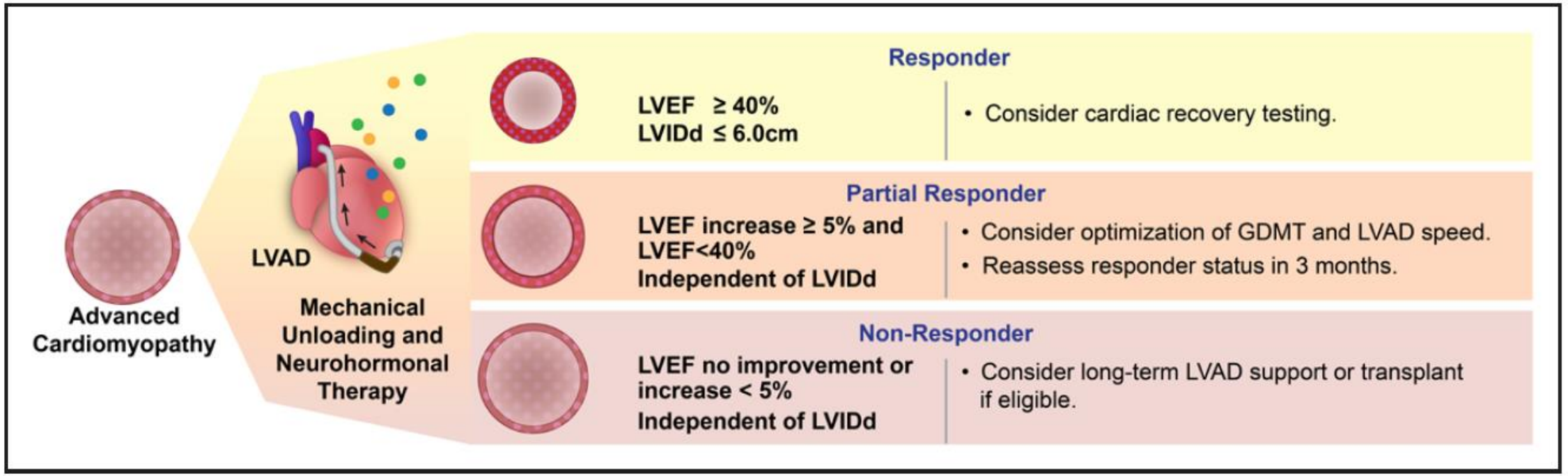




Wang et al. *Ann Noninvasive Electrocardiol.* 2019;24:e12603.

Framework to Classify Reverse Cardiac Remodeling With Mechanical Circulatory Support The Utah-Inova Stages

All patients implanted with a continuous-flow LVAD from 2009 to 2017 and followed through 2018 at 3 study sites



Shah P, Psotka M, Circ Heart Fail. 2021;14:e007991.

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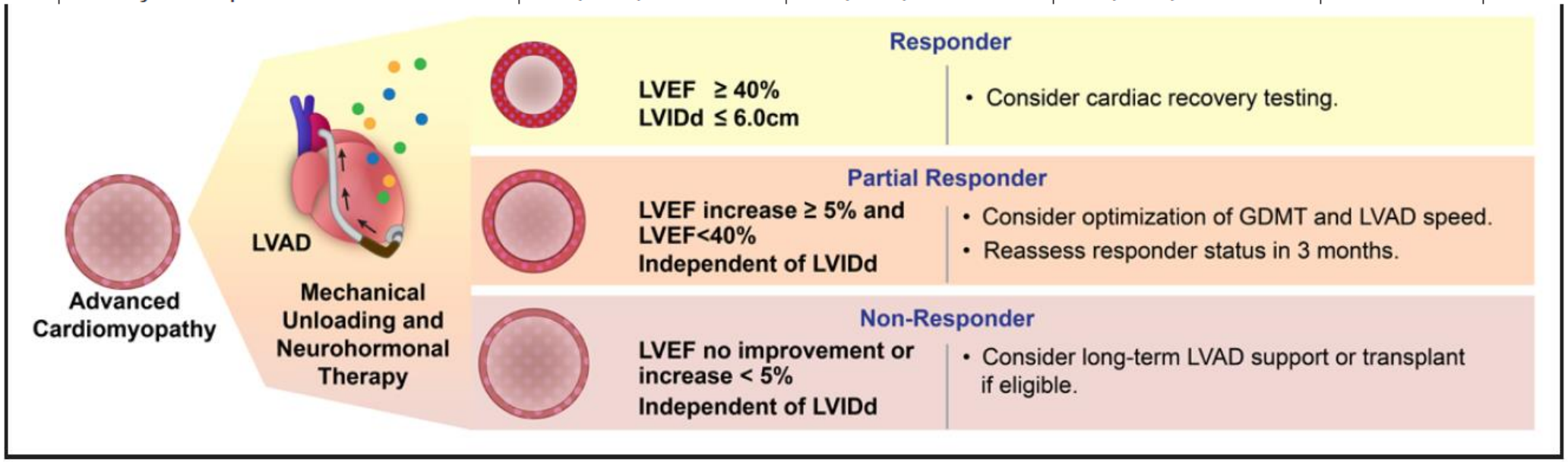
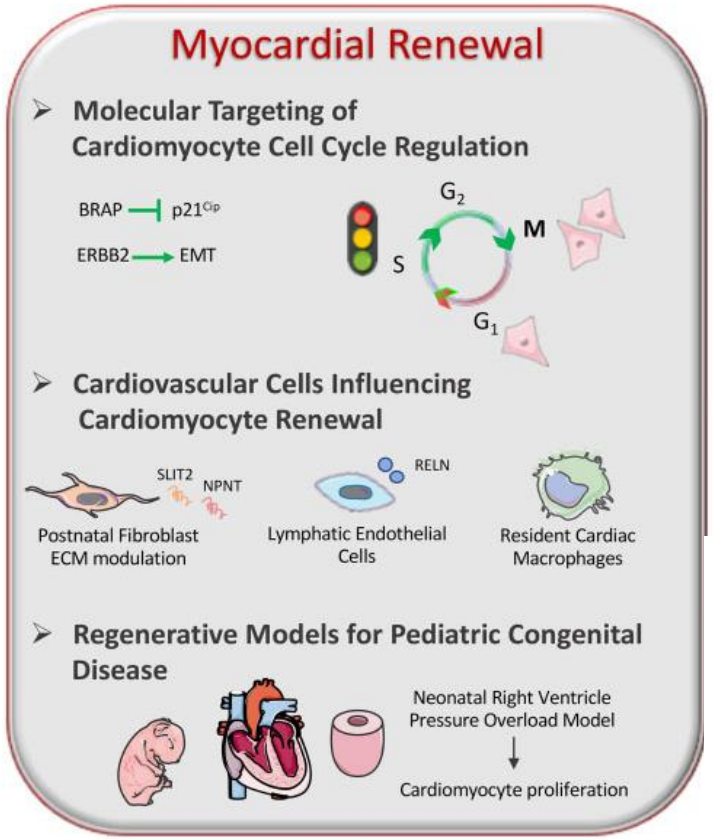
Factors associated with LVAD & Reverse Remodeling

Characteristic	Nonresponder (n=212), 59%	Partial responder (n=112), 31%	Responder (n=34), 10%	*P* value
Age, y; median (IQR)	59 (51–66)	59 (50–67)	56 (44–65)	0.23
Male	186 (89%)	91 (80%)	24 (71%)	0.01
HF duration, mo	72 (25–132)	60 (23–108)	16 (6–44)	<0.001
Ischemic cardiomyopathy	90 (43%)	38 (33%)	9 (27%)	0.08
Hypertension	104 (50%)	62 (54%)	16 (47%)	0.63
Diabetes	84 (40%)	36 (32%)	9 (27%)	0.15
Smoking history	100 (48%)	54 (47%)	15 (44%)	0.93
Atrial fibrillation	85 (41%)	53 (47%)	12 (35%)	0.41
Axial-flow device	117 (56%)	78 (68%)	26 (77%)	0.01
Study site 4 patient	71 (34%)	42 (37%)	14 (41%)	0.66



Cell Based Therapy and Reverse Remodeling



Study	No. of patients	Baseline LVEF (%)	Follow-up (months)	Cell type	Cell dose	Delivery route	Outcome
ASTAMI[19] (2006)	100	46	6	BMC	8, $7x10^6$	IC	No effect
REPAIR-AMI[18] (2006)	204	48	12	BMC	2, $4x10^8$	IC	LVEF increased 2.5%
TOPCARE-CHD[20] (2006)	121	40	12	BMC	$214x10^6$	IC	LVEF increased 1.8%
BOOST[22] (2009)	60	51	6	BMC	2, $5x10^9$	IC	LVEF increased 6.7%
STAR-heart[21] (2010)	391	33	60	BMC	6, $6x10^7$	IC	LVEF increased 6.2%
FocusHF[26] (2011)	30	37	6	BM-MNC	$484x10^6$	IM	No effect on LVEF, scar reduction
SICIPIO[25] (2011)	14	30	4	CSC	$1x10^6$	IC	LVEF increased 8.2%
CADUCEUS[24] (2012)	25	39	6	CDC	12, $5x10^6$ $25x10^6$	IC	No effect on LVEF, scar reduction

Table 1. Prospective randomized trials of stem cell therapy in ischemic heart failure. BMC: bone marrow stem cells; BM-MNC: bone marrow mononuclear cells; CSC: cardiac stem cells; CDC: cardiosphere derived cells; LVEF: left ventricular ejection fraction.

Study	No. of patients	Baseline LVEF (%)	Follow-up (months)	Cell type	Cell dose	Delivery route	Outcome
Bocchi et al.[43] (2008)	22	21%	15	BMC	not specified	IC	LVEF increase 8.8%
Seth et al.[42] (2010)	85	23%	36	BMC	168x106	IC	LVEF increased 5.9%
Vrtovec et al. [4] (2011)	55	26%	12	Autologous CD34+	123x106	IC	LVEF increased 4.6%

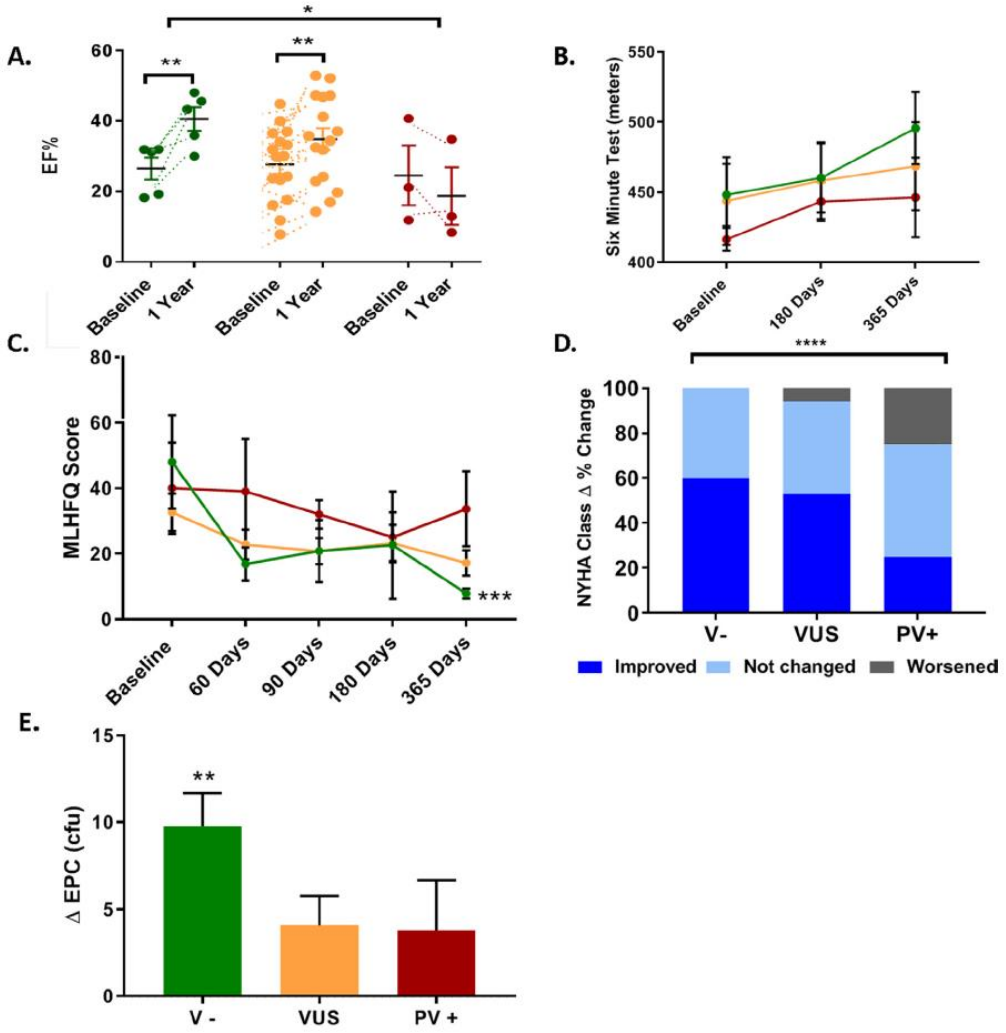
Table 2. Prospective randomized trials of stem cell therapy in nonischemic heart failure. LVEF: left ventricular ejection fraction; IC: intracoronary; BMC: bone-marrow cells; NS: not significant.

Genetic determinants of responsiveness to mesenchymal stem cell injections in non-ischemic dilated cardiomyopathy

Angela C. Rieger , Robert J. Myerburg , Victoria Florea , Bryon A. Tompkins ,Makoto Natsumed, Courtney Premer , Aisha Khana , Ivonne H. Schulmana, Mayra Vidro-Casianoa, Darcy L. DiFedea, Alan W. Heldman, Raul Mitrani
Joshua M. Hare

POSEIDON-DCM 37 patients randomized to autologous vs allogenic mesenchymal stem cell treatment

- (n = 34) underwent genetic sequence analysis
- The results were classified as positive for pathological variants (PV+; n = 8), negative for any variants (V−; n = 6), or as variants of uncertain significance (VUS; n = 20).
- EF improved in males by 6.2 units (P = 0.04) and in females by 8.6 units (P = 0.04; males vs. females, P = 0.57)
- MACE rates were lower in V− (0%) than PV+ (61.9%) or VUS (42.2%; p = 0.021 log-rank).
- 55% patients negative for pathogenic variants transitioning to Hfrec

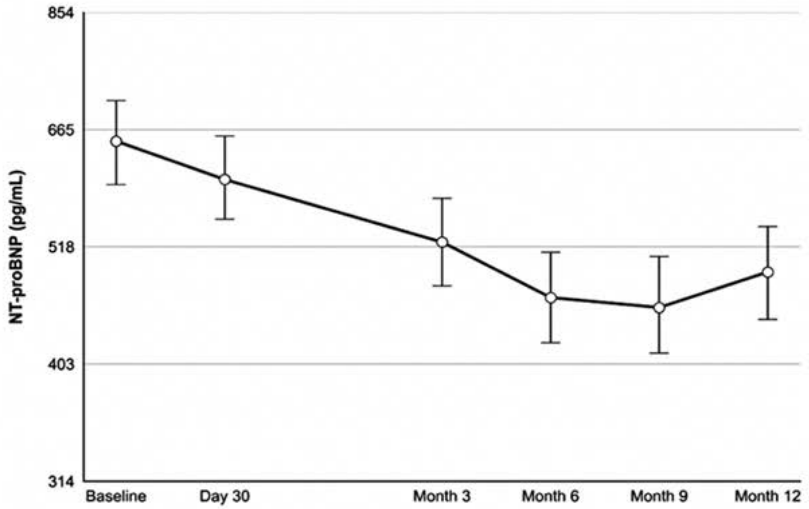


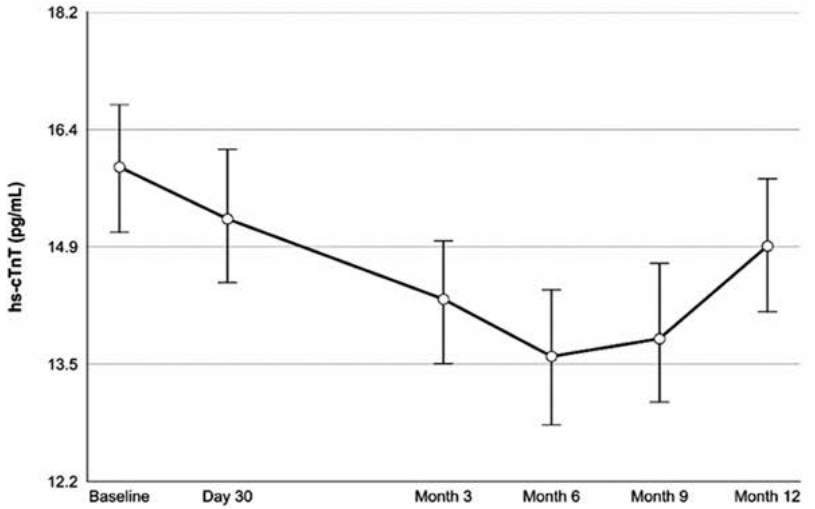
Rieger AC, Myerburg RJ, EBioMedicine. 2019;48:377-385.

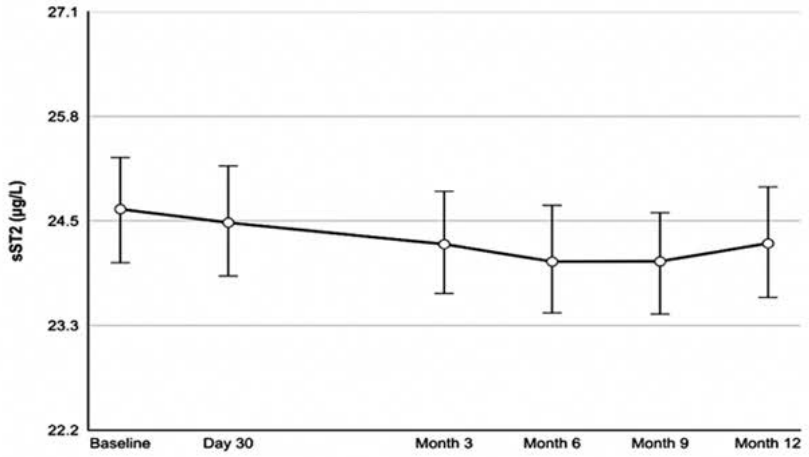
How do we predict Recovery/Remission

Association Between Angiotensin Receptor–Neprilysin Inhibition, Cardiovascular Biomarkers, and Cardiac Remodeling in Heart Failure With Reduced Ejection Fraction

Sean P. Murphy , MB, BCh, BAO; Margaret F. Prescott, PhD; Alan S. Maisel, MD; Javed Butler, MD, MPH;
Ileana L. Piña , MD, MPH; G. Michael Felker , MD, MHS; Jonathan H. Ward, PharmD; Kristin M. Williamson, PharmD;
Alexander Camacho , PhD; Ritvik R. Kandanelly, MS; Scott D. Solomon , MD; James L. Januzzi , MD





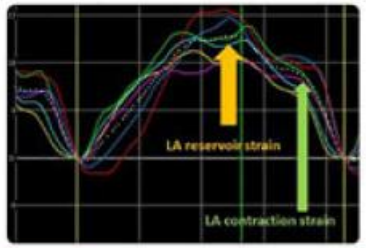


Left Atrial Strain and Remodeling

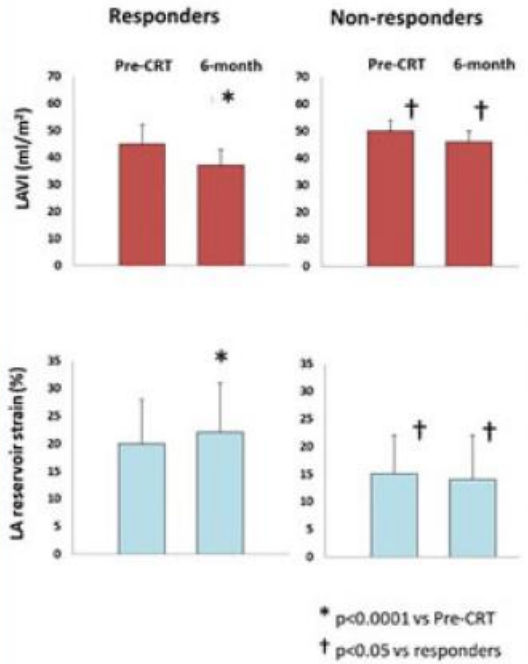
Left atrial strain is a predictor of left ventricular systolic and diastolic reverse remodeling in CRT candidates

METHODS

- ✓ 221 heart failure patients undergoing CRT implantation according to current recommandations in 5 Tertiary Care Hospitals
- ✓ Echocardiography performed at baseline and 6-month follow-up to assess LV systolic and diastolic remodelling
- ✓ Evaluation of leaft atrial size and function throught the measure of left atrial strain



RESULTS



Multivariable predictors of LV systolic remodeling	β	*p-value*
MR moderate-to-severe	0.215	0.001
E/e'	0.139	0.039
Left atrial reservoir strain	-0.138	0.049
LV mechanical dyssynchrony	-0.288	<0.0001

Multivariable predictors of LV diastolic remodeling	β	
MR moderate-to-severe	0.203	0.003
Left atrial reservoir strain	-0.174	0.011

CONCLUSIONS

CRT induces a significant improvement in LAVI and LARS in responders. In CRT candidates. The evaluation of LARS before CRT delivery is an independent predictor of LV systolic and diastolic remodelling at FU

2D/3D Echocardiographic features of patients with reverse remodeling after cardiac resynchronization therapy

Sara Cimino MD, PhD | Viviana Maestrini MD, PhD | Donatella Cantisani MD | Valentina Petronilli MD | Domenico Filomena MD | Maria C. Gatto MD, PhD | Lucia I. Birtolo MD | Agostino Piro MD, PhD | Carlo Lavalle MD | Luciano Agati MD

	CRTR− n = 12 (50%)			CRTR+ n = 12 (50%)		
Parameters	Before	After	*P*	Before	After	*P*
LVEF, 3D (%)	21 ± 4.3	22 ± 5	NS	29 ± 4	35 ± 10	0.002
LVEDV, 3D (mL)	192 ± 63	194 ± 59	NS	168 ± 9	155 ± 9	0.048
LVESV, 3D (mL)	150 ± 50	151 ± 60	NS	118 ± 31	89 ± 33	0.015
GLS (%)	−8 ± 2	−8 ± 5	NS	−10 ± 2	−12 ± 4	0.003

Abbreviations: GLS = global longitudinal strain; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume.

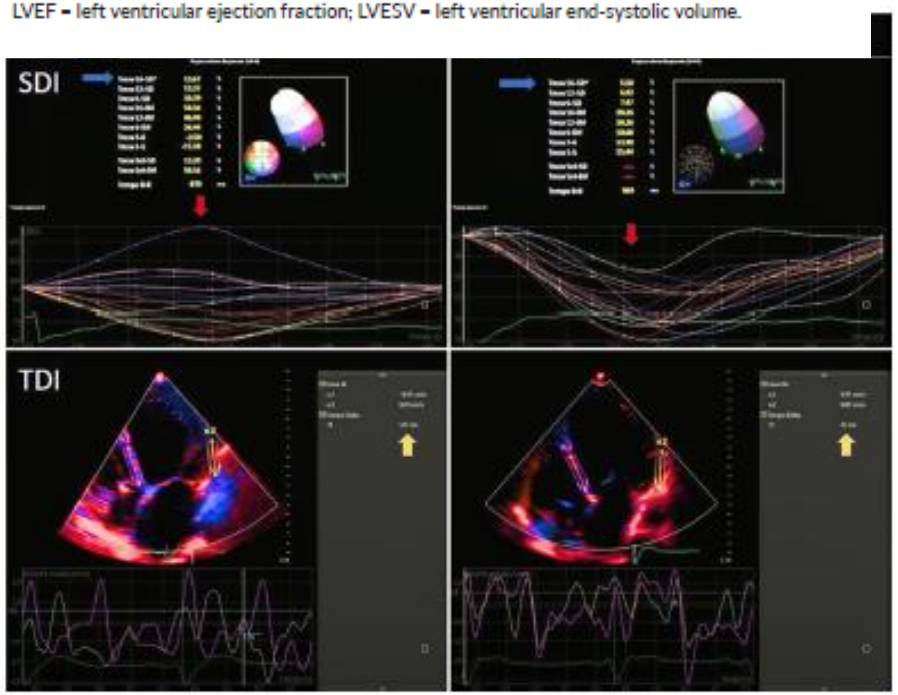


TABLE 3 Comparison of echocardiography findings at baseline evaluation in CRT responder (CRTR+) vs nonresponder (CRTR−) group

Parameters	CRTR− n = 12 (50%)	CRTR+ n = 12 (50%)	*P* value
LVEF, 3D (%)	21 ± 4.3	29 ± 4	0.002
LVEDV, 3D (mL)	192 ± 63	168 ± 9	0.031
LVESV, 3D (mL)	150 ± 50	118 ± 31	0.024
Septal flash, n (%)	12 (100%)	12 (100%)	NS
E/A ratio	1.12 ± 0.8	0.8 ± 02	0.002
E/e' average	14 ± 3	6 ± 0.8	<0.001
GLS (%)	−8 ± 2	−10 ± 2	0.03
Max delay TDI (msec)	90 ± 44	89 ± 17	NS
RPEI-LPEI (msec)	42 ± 13	37 ± 16	NS
SDI (%)	15 ± 4	13 ± 3	NS
TAPSE (mm)	15 ± 7	24 ± 1	<0.001
PASP (mm Hg)	42 ± 13	29 ± 14	0.002

Bold values are significant *P* values.
Abbreviations: GLS = global longitudinal strain; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; PASP = pulmonary artery systolic pressure; RPEI-LPEI = right pre-ejection time–left pre-ejection time; SDI = systolic dyssynergy index; TAPSE = tricuspid annular plane systolic excursion; TDI = tissue Doppler imaging.

What does Recovery Mean?

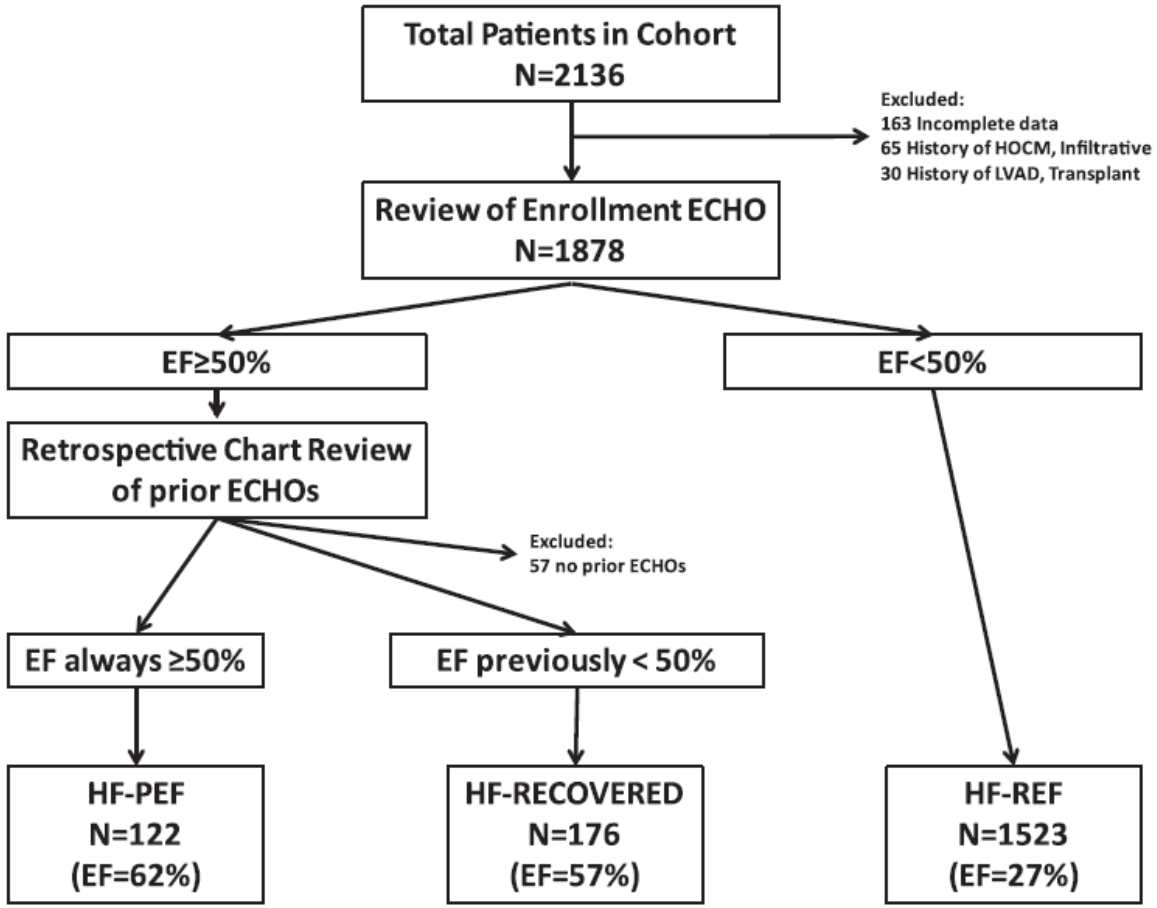
Heart Failure With Recovered Ejection Fraction

Clinical Description, Biomarkers, and Outcomes

Anupam Basuray, MD, MPH; Benjamin French, PhD; Bonnie Ky, MD, MSCE; Esther Vorovich, MD; Caroline Olt, BA; Nancy K. Sweitzer, MD, PhD; Thomas P. Cappola, MD, ScM; James C. Fang, MD

The Penn Heart Failure Study (PHFS)

- Prospective cohort of 1821 chronic HF patients from 3 tertiary HF clinics. Participants were divided into 3 categories by echo parameters
- HF-REF if EF was <50%,
- HF-PEF if EF was consistently ≥50%
- HF-Recovered if EF on enrollment in PHFS was ≥50% but prior EF was <50%.



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- Median levels of BNP troponin I, and creatinine were greater in HF-REF and HF-PEF patients compared with HF-REC.
- 30% of HF-REC had a BNP above the 95th percentile. Nearly half had evidence of oxidative stress (uric acid) and detectable troponin I levels
- The hazard ratio for death, transplantation, or ventricular assist device placement in HF-REF was 4.1 and in HF-PEF was 2.3 compared with HF-REC
- The unadjusted HR for cardiac hospitalization was 2.0 for HF-REF patients c/w HF-REC there was no difference HF-PEF patients and HF-REC [1.3 (0.90–2.0; P=0.15)]

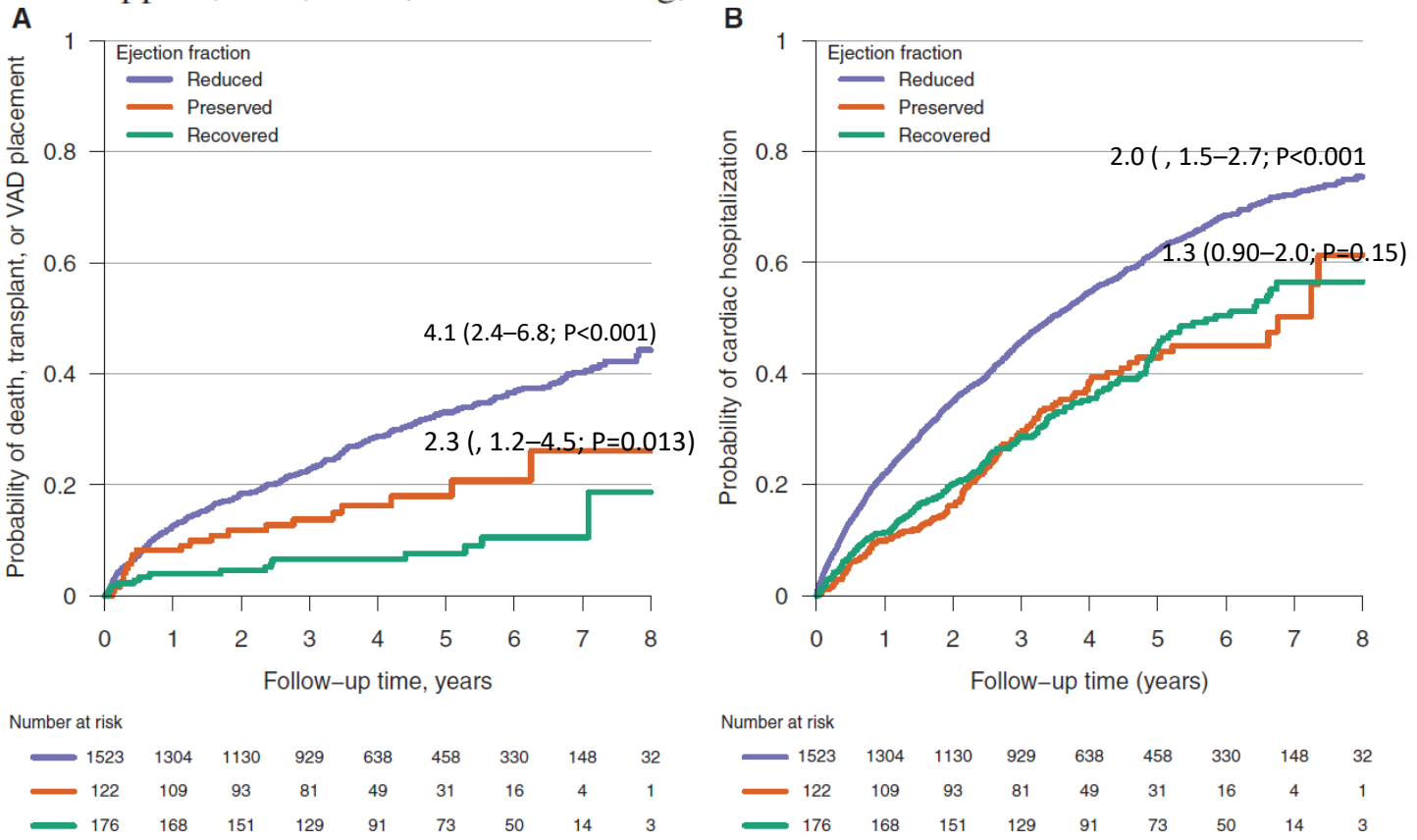
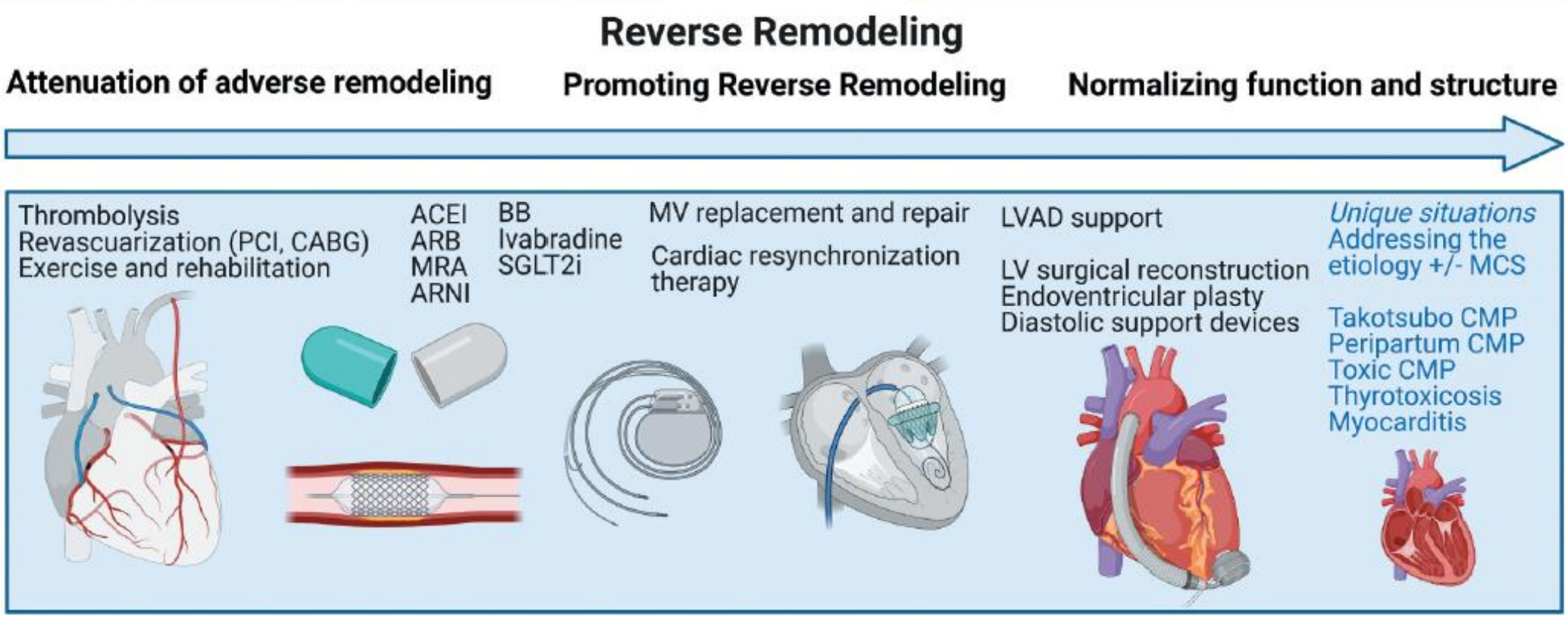


Figure 2. Probability of all-cause death, cardiac transplantation, or ventricular assist device (VAD) placement for all participants (**A**) and probability of cardiac hospitalization for all participants (**B**) from time of referral to an outpatient heart failure specialty care center.

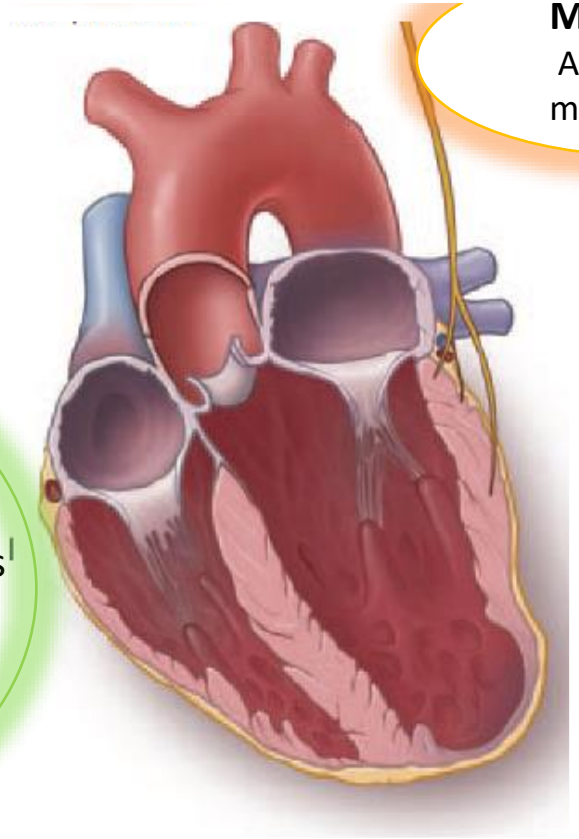
Remodeling


Reverse Remodeling
Attenuation of adverse remodeling
Promoting Reverse Remodeling
Normalizing function and structure
Thrombolysis
Revascuarization (PCI, CABG)
Exercise and rehabilitation
ACEI
ARB
MRA
ARNI
BB
Ivabradine
SGLT2i
MV replacement and repair
Cardiac resynchronization therapy
LVAD support
LV surgical reconstruction
Endoventricular plasty
Diastolic support devices
Unique situations
Addressing the etiology +/- MCS
Takotsubo CMP
Peripartum CMP
Toxic CMP
Thyrotoxicosis
Myocarditis

Thank you

Neurohormonal
RAASi ,BB,ARNi

MODULATE
ANS neuro modulation



REPURPOSE
Myocytes
Collagen matrix modulators
Mitochondrial optimizers
Calcium synthesizers
Matrix modifiers

REPROGRAM
Genetic/Post Translational Modulation

REPAIR
Stem cell therapy
Bioengineered patches

Reverse Remodeling/Remission

Supplemental

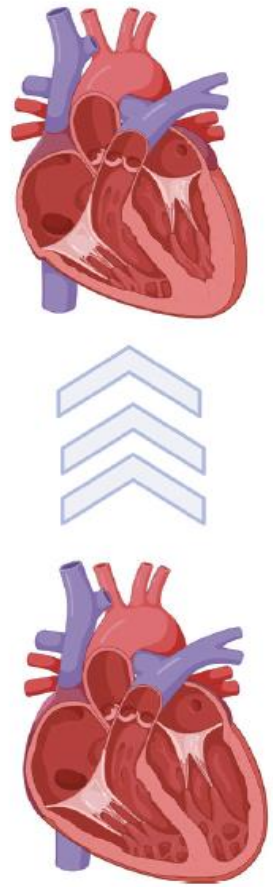
LVEF Improvements with Reverse Remodeling

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

BB
4-12%[81-84]

MRA
4%[85,86]

ARNI
9-15%[87,88]

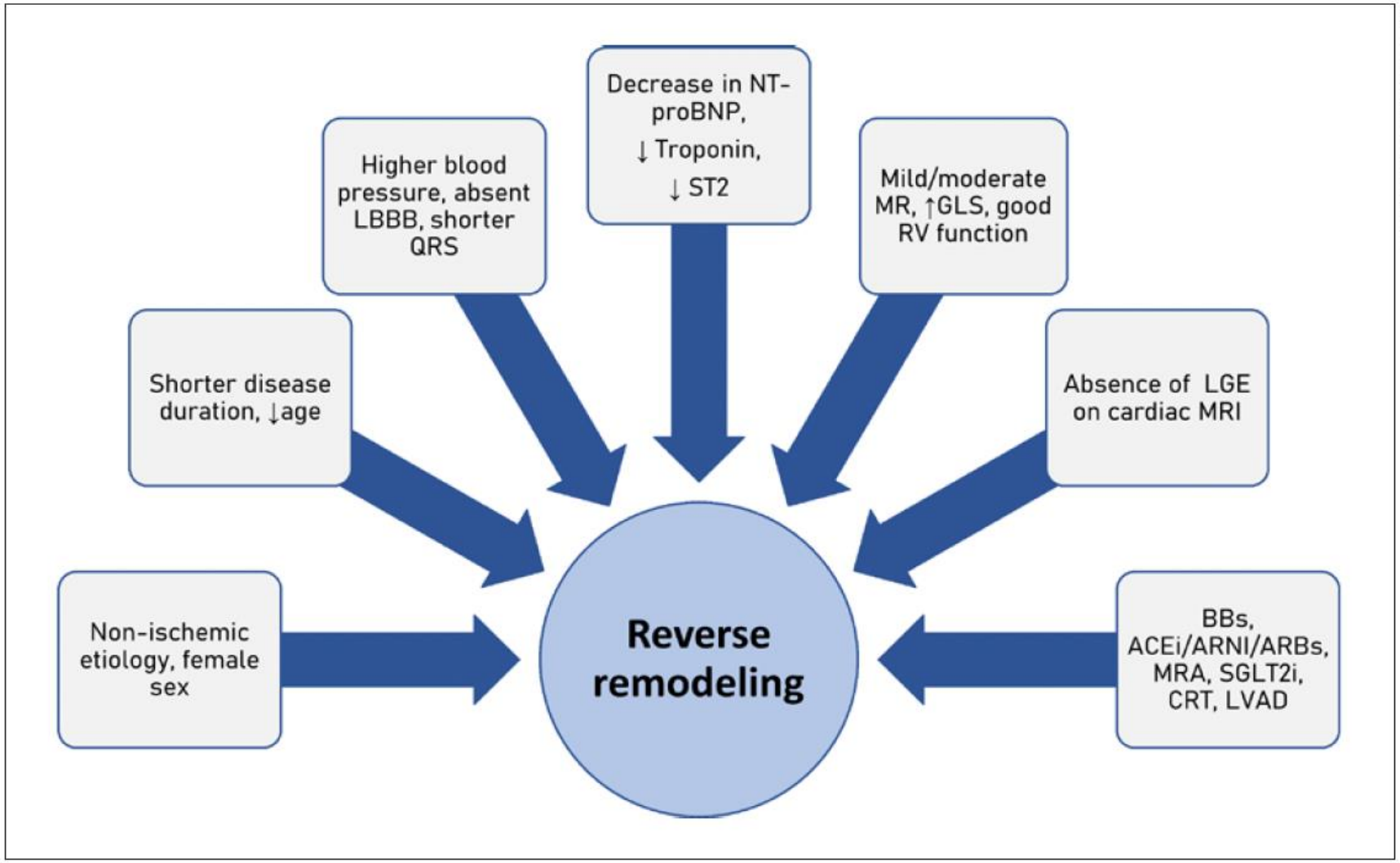


SGLT2i
1-6%[89-90]

CRT
2-24%[91-93]

MitraClip
3%[94,95]

Factors Associated with Reverse Remodeling



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Cell Based Therapy and Reverse Remodeling

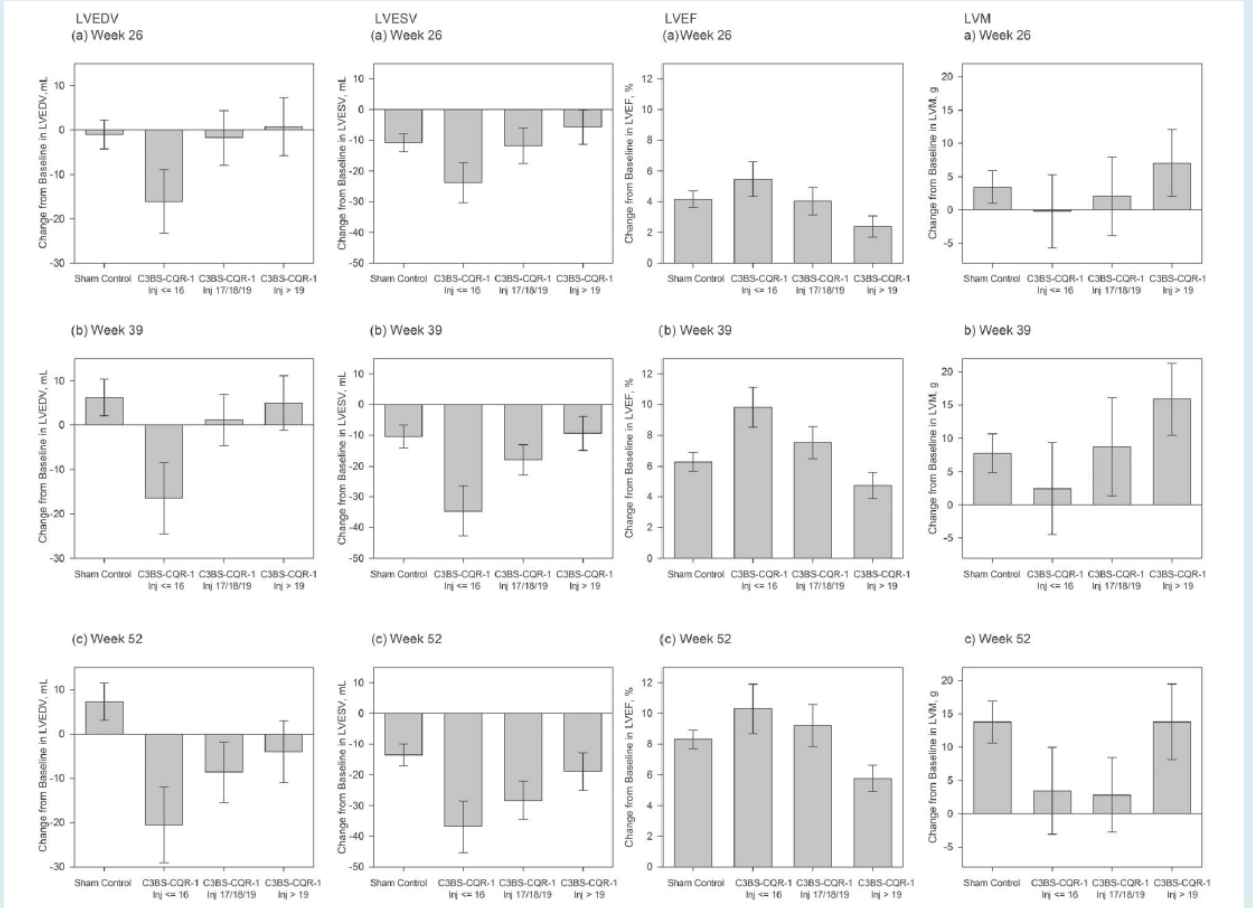


Figure 2 Changes in left ventricular end-diastolic volume (LVEDV), left ventricular end-systolic volume (LVESV), left ventricular ejection fraction (LVEF) and left ventricular mass (LVM) by number of cardiopoietic cell (C3BS-CQR-1) injections administered as compared to control. Plotted are the mean changes from baseline ± standard error.

Teerlink JR, Metra M, *Eur J Heart Fail*. 2017;19:1520-1529.

Predictors of Recovery

TABLE 2 Baseline Echocardiography and Change at 12 Months by Treatment Group

	Baseline			Change at 12 Months		
	NT-proBNP Guided (n = 67)	Usual Care (n = 57)	p Value	NT-proBNP Guided (n = 67)	Usual Care (n = 57)	p Value
ESVi, ml/m^2	87.5 ± 38.5	90.7 ± 34.9	0.39	−15.2 ± 20.4	−17.4 ± 28.4	0.82
EDVi, ml/m^2	119.6 ± 38.6	122.7 ± 36.8	0.46	−13.3 ± 20.6	−15.9 ± 29.8	0.95
Ejection fraction, %	29.0 ± 9.7	27.7 ± 10.7	0.37	+6.0 ± 8.0	+6.6 ± 10.5	0.75
Cardiac index, l/min/m^2	2.0 ± 0.7	1.9 ± 0.6	0.97	+0.1 ± 0.6	0.0 ± 0.6	0.56
E/e′	21.0 ± 10.2	21.0 ± 9.6	0.74	−0.4 ± 10.9	−1.4 ± 8.1	0.88
LA volume index, ml/m^2	46.7 ± 15.2	48.8 ± 16.4	0.46	−4.9 ± 12.1	−3.1 ± 13.1	0.73
RA area, ml	21.5 ± 7.8	21.2 ± 6.8	0.79	−1.6 ± 4.2	−1.4 ± 6.2	0.95
TAPSE, cm	1.7 ± 0.5	1.7 ± 0.6	0.70	0.0 ± 0.6	+0.1 ± 0.6	0.39
RV systolic pressure, mm Hg	37.4 ± 14.3	36.4 ± 10.8	0.97	−1.7 ± 13.0	−3.2 ± 11.3	0.30
Global LV strain, %	−8.7 ± 3.4	−9.7 ± 3.8	0.20	−2.4 ± 3.6	−1.1 ± 3.6	0.19

Values are mean ± SD.

EDVi = end-diastolic volume index; E/e′ = ratio of early transmitral peak velocity to early diastolic peak annular velocity; ESVi = end-systolic volume index; LA =left atrial; LV = left ventricular; RA = right atrial; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; other abbreviations as in Table 1.

Table 2. The effect of therapy on cellular and molecular changes in LV RR

	β-Blockers	ACEi	ARB	MRA	LVAD	CRT	ARNI	SGLT2
Cardiomyocyte changes								
Hypertrophy	↓	↓	↓	↓	↓	↓	↓	↓
Foetal gene expression	↓	↓	↓	ND	↓	↓	↓	
Myocytolysis	↓	ND	ND	ND	↓	ND	ND	ND
Beta-adrenergic desensitization	↓	↓	↓	ND	↓	↓	ND	ND
EC coupling	↑	↑	↑	ND	↑	↑	ND	–
Cytoskeletal changes	ND	ND	ND	↑	↑	↓	↓	ND
Myocardial changes								
Myocyte apoptosis	↓	↓	↓	ND	↓	↓	↓	↓
MMP activation	↓	↓	↓	↓	↓	↓	↓	↓
Fibrosis	↓	↓	↓	↓	↑	↓	↓	↓
Angiogenesis	↑	↑	↑	↑	↓	↑	↑	↑
LV geometry changes								
LV dilatation	↓	Stabilization	Stabilization	Stabilization	↓	↓	↓	↓

ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CRT, cardio resynchronization therapy; EC, excitation-contraction; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonists; ND, no data.

Most Therapies with Beneficial Effect on Morbidity and Mortality Demonstrate Capacity for Reverse Remodeling

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]

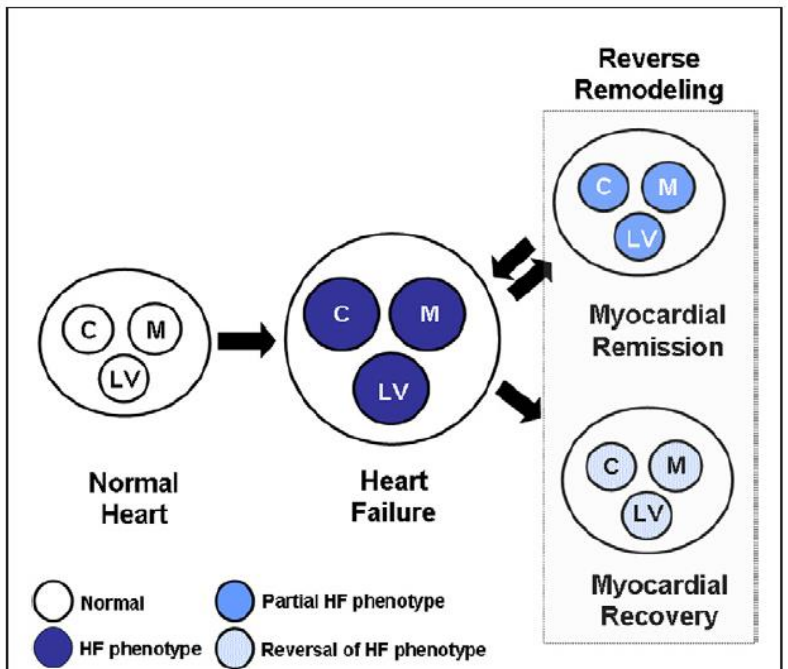
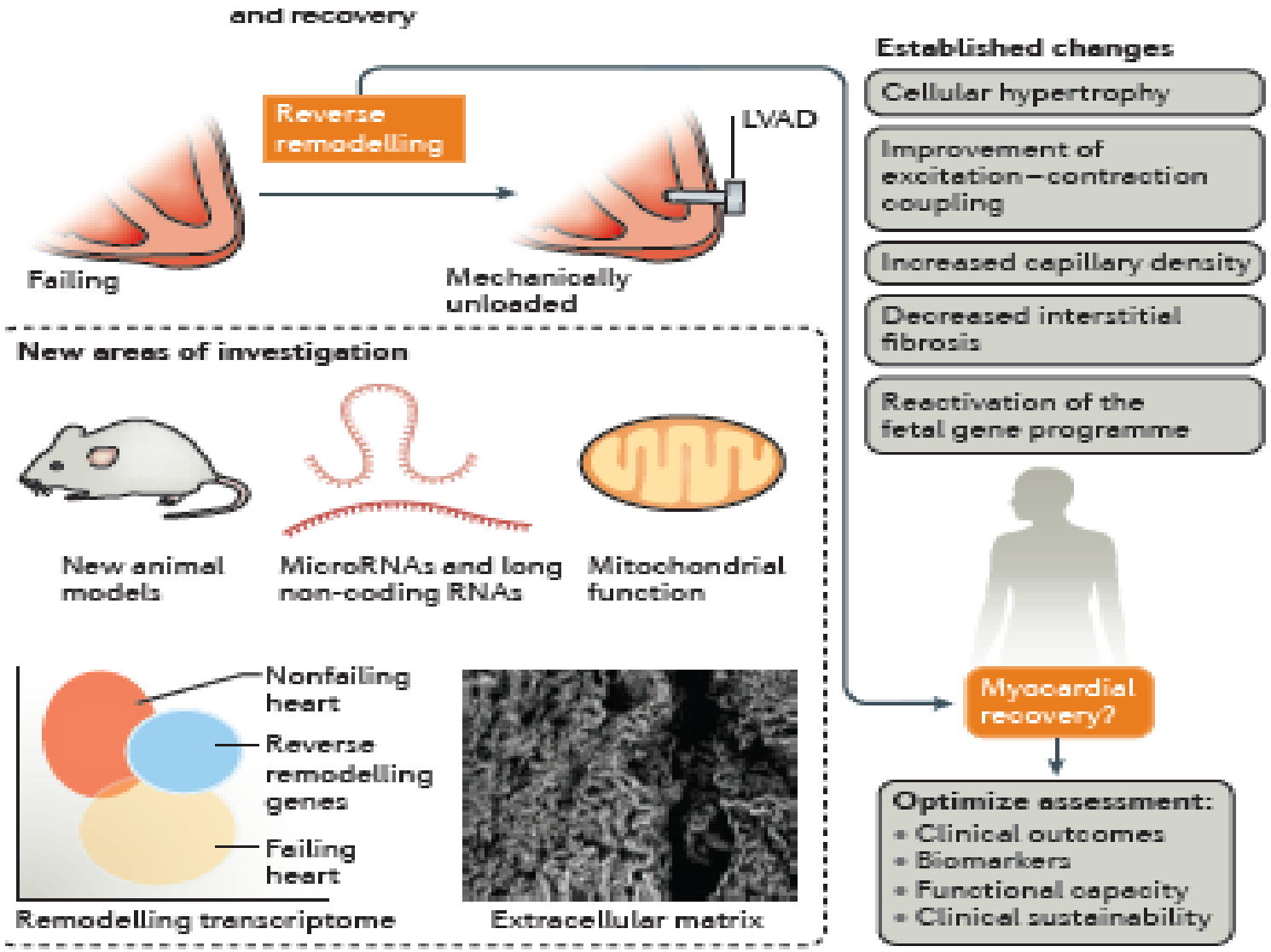


Figure 3 **Reverse Remodeling and Myocardial Recovery**

Cardiac remodeling arises secondary to abnormalities that arise in the biology of the cardiac myocyte (C), the myocardium (cardiocytes and extracellular matrix [M]), as well as LV geometry, which have collectively been referred to as the heart failure (HF) phenotype. During reverse remodeling, there is a reversal of the abnormalities in the cardiac myocyte as well as the extracellular matrix, leading to a reversal of the abnormalities in left ventricular (LV) geometry. Reverse remodeling can lead to 2 clinical outcomes: 1) myocardial recovery, characterized by freedom from future cardiac events; or 2) myocardial remission, which is characterized by recurrence of heart failure events.


and recovery
Established changes
Reverse remodelling
LVAD
Failing
Mechanically unloaded
Cellular hypertrophy
Improvement of excitation–contraction coupling
Increased capillary density
Decreased interstitial fibrosis
Reactivation of the fetal gene programme
New areas of investigation
New animal models
MicroRNAs and long non-coding RNAs
Mitochondrial function
Myocardial recovery?
Nonfailing heart
Reverse remodelling genes
Failing heart
Remodelling transcriptome
Extracellular matrix
Optimize assessment:
• Clinical outcomes
• Biomarkers
• Functional capacity
• Clinical sustainability

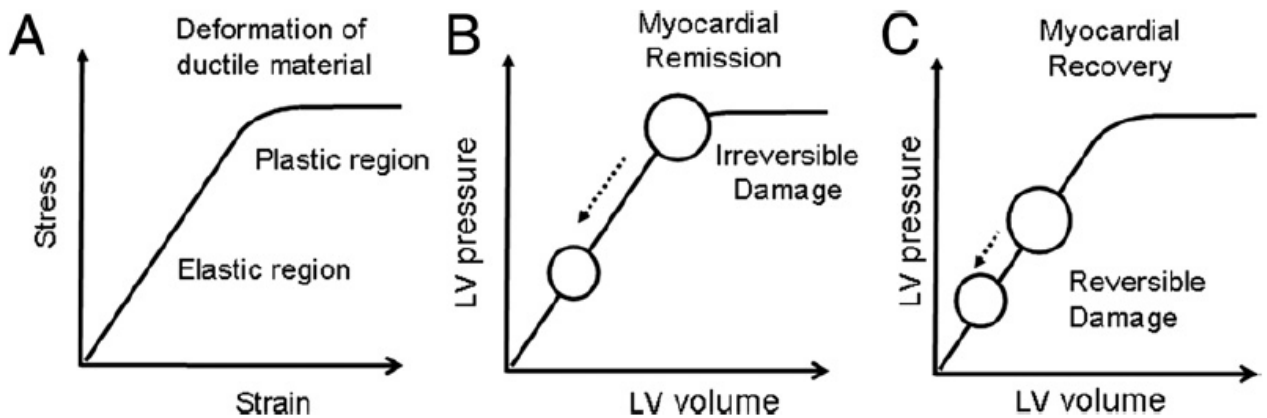
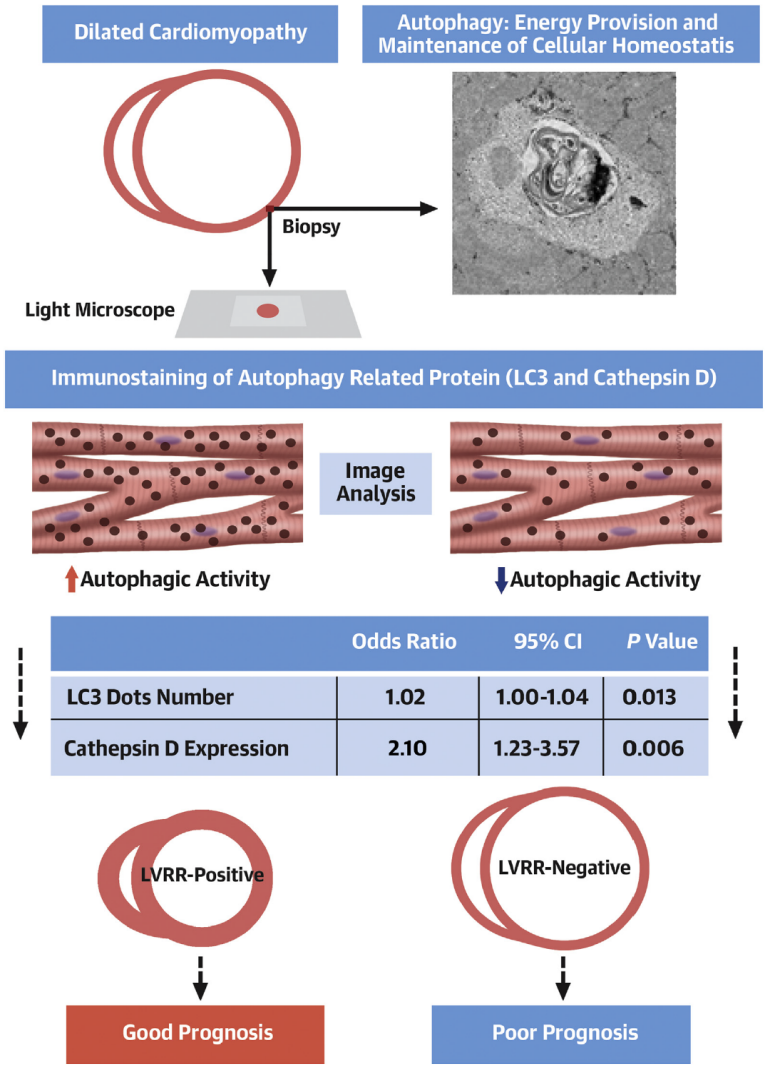


Figure 2 **Mechanical Engineering Science and Cardiac Remodeling**

(A) Diagram of a stress-strain curve of a ductile material, illustrating the relationship between an applied force (stress) and deformation (strain). Deformation can lead to reversible changes in a material (elastic deformation) if the properties of the material are not changed and irreversible changes in a material (plastic deformation). **(B)** Hypothetical model of reverse remodeling in a heart that has undergone irreversible damage (plastic deformation). **(C)** Hypothetical model of reverse remodeling with recovery in a heart that has undergone reversible damage (elastic deformation). LV = left ventricular.

CENTRAL ILLUSTRATION Probability of Left Ventricular Reverse Remodeling According to Autophagy Findings



Kanamori, H. et al. J Am Coll Cardiol. 2022;79(8):789–801.

Autophagy findings (autophagic vacuole number and cathepsin D expression) from left endomyocardial biopsies from 42 patients with dilated cardiomyopathy predict left ventricular reverse remodeling in dilated cardiomyopathy. Enhancing autophagy would promote good prognosis.
LC3 = microtubule-associated protein 1 light chain 3; LVRR = left ventricular reverse remodeling.

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May 1995:1225–31

Carvedilol Improves Left Ventricular Function and Symptoms in Chronic Heart Failure: A Double-Blind Randomized Study

STEPHANIE L. OLSEN, MD, EDWARD M. GILBERT, MD, FACC, DALE G. RENLUND, MD, FACC, DAVID O. TAYLOR, MD, FACC, FRANK D. YANOWITZ, MD, FACC, MICHAEL R. BRISTOW, MD, PHD, FACC

Table 2. Response to Carvedilol Therapy: Noninvasive Variables

	Carvedilol Group (n = 34)		Placebo Group (n = 23)		
	Baseline	4 mo	Baseline	4 mo	p Value
Symptom score	4.9 ± 0.6	2.6 ± 0.4	4.2 ± 0.1	4.0 ± 0.7	0.0277
NYHA functional class					
I	0	4	0	0	
II	16	27	14	16	
III	18	3	10	6	0.0170
IV	0	0	0	1	
LVIDD (mm)	73 ± 9	70 ± 9	79 ± 14	76 ± 15	0.7200
FS (%)	15 ± 0.6	20 ± 1	17 ± 3	20 ± 3	0.0037
Rest LVEF (%)	20 ± 1	31 ± 2	19 ± 1	20 ± 2	0.0001
Exercise LVEF (%)	21 ± 1	29 ± 2	20 ± 2	21 ± 2	0.0001

Data presented are mean value ± SEM or number of patients. FS = fractional shortening; LVIDD = left ventricular internal diastolic dimension; other abbreviations as in Table 1.

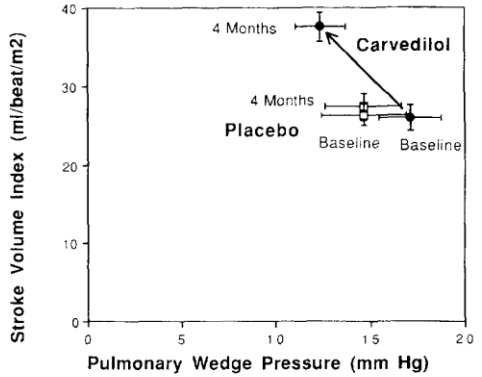


Figure 1. Relation between pulmonary wedge pressure and stroke volume index at baseline and at the end of study for the carvedilol **(circles)** and placebo **(squares)** groups. Results are mean value ± SEM.

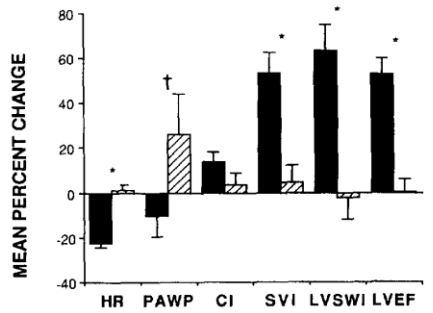


Figure 2. Percent changes in heart rate (HR), pulmonary artery wedge pressure (PAWP), cardiac index (CI), stroke volume index (SVI), left ventricular stroke work index (LVSWI) and left ventricular ejection fraction (LVEF) in the carvedilol **(solid bars)** and placebo **(hatched bars)** group. Results are mean value ± SEM. *$p < 0.001$, †$p < 0.02$, change in carvedilol vs. placebo group.

Remodeling, Reverse Remodeling, Remission and Recovery

- Remodeling: first use in medical literature 1982 by Hochman and Bulkley, describing histopatholgy of experimental myocardial infarction in rat. Later in 1982 Erlebacher et al used the term to describe LV structural/geometric changes ,by echo, in humans post MI. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling.
- Reverse Remodeling first use in medical literature 1999 Kawai et al. Understood to occur as a result of LVRR is the result of removal of the triggering injury/ insult) and/or institution of interventions that mitigate and interfere with the process of LV remodeling. Genome expression resulting in molecular, cellular and interstitial changes occur in response
- Remission and Recovery
- to interventions that mitigate the source of myocardial injury, or reduce
- or eliminate the neurohormonal and/or hemodynamic factors that contribute
- to the progression of the LV remodeling process.
- changes and manifested clinically as changes in size, shape and function of the heart resulting
- from cardiac load or injury, cardiac remodeling is influenced by hemodynamic load,
- neurohormonal activation and other factors still under investigation

Boulet J and Mehra MR. Structural Heart. 2021;5:466-481.
Merlo M, Caiffa T, Gobbo M, et al. Int J Cardiol Heart Vasc.2018;18:52-57
Cohn JN, Ferrari R and Sharpe N. J Am Coll Cardiol. 2000;35:569-82.
Kawai K, Takaoka H, Hata K, et al. Am J Cardiol. 1999;84:671-6.

References

- 1. Boulet J and Mehra MR. Left Ventricular Reverse Remodeling in Heart Failure: Remission to Recovery. Structural Heart. 2021;5:466-481.
- 2. Merlo M, Caiffa T, Gobbo M, Adamo L and Sinagra G. Reverse remodeling in Dilated Cardiomyopathy: I1. Boulet J and Mehra MR. Left Ventricular Reverse Remodeling in Heart Failure: Remission to Recovery. Structural Heart. 2021;5:466-481.
- 3. Cohn JN, Ferrari R and Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35:569-82.nsights and future perspectives. Int J Cardiol Heart Vasc. 2018;18:52-57.
- Kawai K, Takaoka H, Hata K, Yokota Y and Yokoyama M. Prevalence, predictors, and prognosis of reversal of maladaptive remodeling with intensive medical therapy in idiopathic dilated cardiomyopathy. Am J Cardiol. 1999;84:671-6.
- Sze E and Daubert JP. Left bundle branch block-induced left ventricular remodeling and its potential for reverse remodeling. J Interv Card Electrophysiol. 2018;52:343-352.
- Rieger AC, Myerburg RJ, Florea V, Tompkins BA, Natsumeda M, Premer C, Khan A, Schulman IH, Vidro-Casiano M, DiFede DL, Heldman AW, Mitrani R and Hare JM. Genetic determinants of responsiveness to mesenchymal stem cell injections in non-ischemic dilated cardiomyopathy. EBioMedicine. 2019;48:377-385.

ORIGINAL ARTICLE

Association Between Angiotensin Receptor–Neprilysin Inhibition, Cardiovascular Biomarkers, and Cardiac Remodeling in Heart Failure With Reduced Ejection Fraction

Sean P. Murphy, MB, BCh, BAO; Margaret F. Prescott, PhD; Alan S. Maisel, MD; Javed Butler, MD, MPH; Ileana L. Piña, MD, MPH; G. Michael Felker, MD, MHS; Jonathan H. Ward, PharmD; Kristin M. Williamson, PharmD; Alexander Camacho, PhD; Ritvik R. Kandanelly, MS; Scott D. Solomon, MD; James L. Januzzi, MD

12 months of treatment. A multivariate latent growth curve model assessed associations between simultaneous changes in biomarkers and left ventricular ejection fraction and left atrial volume index.

RESULTS: Seven hundred fifteen out of 794 total study participants were included (mean age 65 years, 73% male). Mean baseline left ventricular ejection fraction and left atrial volume index were 29% and 40 mL/m2, respectively. Adjusted geometric mean baseline concentrations for biomarkers included NT-proBNP of 649 pg/mL, hs-cTnT of 15.9 ng/L, and sST2 of 24.7 ng/mL. Following initiation of S/V, circulating concentrations of NT-proBNP, hs-cTnT, and sST2 significantly decreased within 30 days and remained significantly different than baseline at all subsequent timepoints. From baseline to month 12, decreases in adjusted biomarker concentrations averaged −27.9% (95% CI, −35.1% to −20.7%; P<0.001) for NT-proBNP; −6.7% (95% CI, −8.8% to −4.7%; P<0.001) for hs-cTnT; and −1.6% (95% CI, −2.9% to −0.4%; P<0.001) for sST2. NT-proBNP concentrations were predictive of later changes in hs-cTnT. The magnitude of reductions in NT-proBNP and hs-cTnT concentrations associated with improvements in left ventricular ejection fraction and left atrial volume index. There was no association between changes in sST2 and changes in other measures.

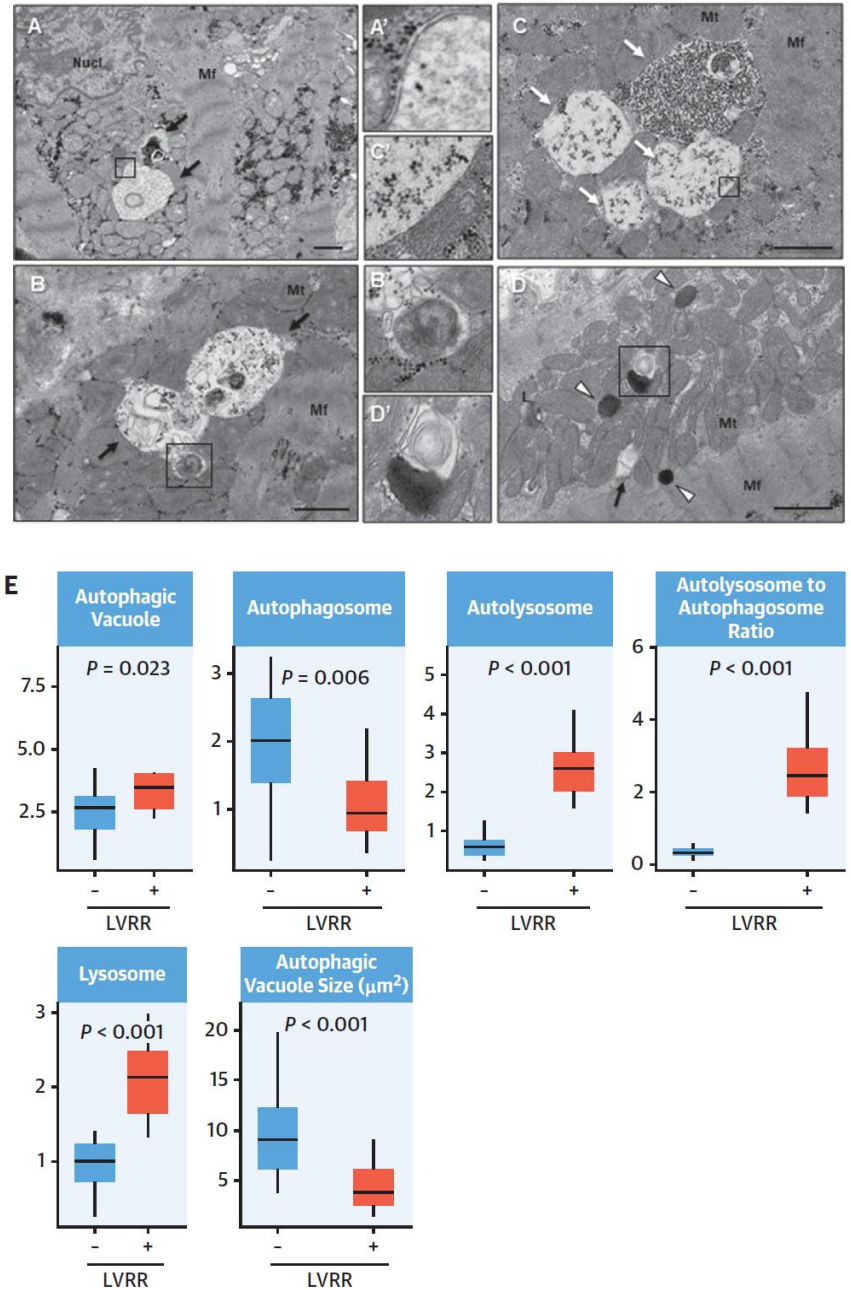
TABLE 1 Demographic and Clinical Characteristics of Followed Patients

	Total (N = 42)	LVRR-positive (n = 21)	LVRR-Negative (n = 21)	*P* Value*
Age, y	55.5 (45.2-67.0)	54.0 (46.0-66.6)	56.0 (44.0-67.0)	0.980
Male	27 (64. 3)	13 (61.9)	14 (66.7)	>0.999
BMI, kg/m^2	23.1 (21.3-27.5)	22.8 (19.2-27.6)	23.5 (21.5-27.1)	0.325
Family history	2 (4.8)	1 (4.8)	1 (4.8)	>0.999
Hypertension	8 (19.0)	5 (23.8)	3 (14.3)	0.697
Diabetes mellitus	14 (33.3)	4 (19.0)	10 (47.6)	0.100
Dyslipidemia	12 (28.6)	5 (23.8)	7 (33.3)	0.734
Duration of HF >90 days	12 (28.6)	5 (23.8)	7 (33.3)	0.734
NYHA functional class I/II/III/IV	10/16/16/0	4/7/10/0	6/9/6/0	0.570
SBP, mm Hg	125.5 (101.0-146.2)	128.0 (118.0-149.0)	120.0 (90.0-140.0)	0.227
DBP, mm Hg	69.5 (60.8-77.8)	69.0 (64.0-80.0)	70.0 (60.0-75.0)	0.357
HR, beats/min	76.0 (67.2-87.8)	78.0 (70.0-92.0)	75.0 (67.0-83.0)	0.159
Clinical chemistry				
Hb, g/dL	13.7 (12.0-14.9)	13.5 (11.7-14.9)	13.7 (12.2-14.2)	0.940
HbA_{1c}, %	6.2 (5.7-7.0)	5.8 (5.6-6.5)	6.3 (6.0-7.2)	0.104
BNP, pg/mL	355.0 (108.6-697.2)	365.5 (79.3-653.0)	352.3 (178.0-923.7)	0.382
eGFR, mL/min/1.73 m^2	64.4 (52.8-78.3)	61.8 (50.7-70.5)	72.3 (55.5-87.8)	0.166
Electrocardiographic and echocardiographic data				
Atrial fibrillation	7 (16.7)	3 (14.3)	4 (19.0)	>0.999
CLBBB	2 (4.8)	0 (0.0)	2 (9.5)	0.448
QRS duration, ms	100.0 (95.0-109.5)	99.0 (95.0-110.0)	100.0(95.0-108.0)	0.762
LAD, mm	45.5 (41.0-49.8)	44.0 (39.0-47.0)	47.0 (42.0-55.0)	0.038
IVSth, mm	9.0 (8.0-10.0)	9.0 (8.0-11.0)	9.0 (7.0-11.0)	0.295
LVPWth, mm	9.0 (8.0-11.0)	10.0 (8.0-11.0)	9.0 (8.0-11.0)	0.295
LVEDD, mm	60.5 (56.0-66.0)	60.0 (54.0-64.0)	61.0 (56.0-72.0)	0.377
LVEF, %	32.5 (25.0-40.5)	37.0 (25.0-41.0)	30.0 (24.0-39.0)	0.268
MR severity grade				0.410
0 (no MR), I, II	35 (83.3)	19 (90.5)	16 (76.2)	
III, IV	7 (16.7)	2 (9.5)	5 (23.8)	
Catheterization data				
LVEDVI, mL/m^2	132.0 (123.0-164.0)	131.5 (122.2, 148.2)	144.0 (125.0-183.0)	0.272
LVESVI, mL/m^2	89.0 (71.9-112.0)	85.9 (75.7-102.3)	103.0 (71.9-135.5)	0.270
PCWP, mm Hg	12.5 (8.0-22.8)	9.0 (6.0-15.0)	18.0 (12.0-27.0)	0.026
Cardiac index, L/min/m^2	2.7 (2.2-3.4)	3.1 (2.4-4.3)	2.5 (2.1-3.0)	0.058
Medication at EMB				
ACE inhibitor or ARB	36 (85.7)	20 (95.2)	16 (76.2)	0.184
β-blocker	26 (61.9)	9 (42.9)	17 (81.0)	0.025
Aldosterone receptor antagonists	26 (61.9)	12 (57.1)	14 (66.7)	0.751
Medication during follow-up				
ACE inhibitor or ARB	38 (90.5)	19 (90.5)	19 (90.5)	>0.999
β-blocker	38 (90.5)	18 (85.7)	20 (95.2)	0.606
Carvedilol, mg	10.0 (5.0-17.5)	5.0 (5.0-15.0)	12.5 (8.8-16.2)	0.515
Bisoprolol, mg	2.5 (1.9-5.0)	2.5 (2.5-5.0)	2.5 (1.2-5.0)	0.298
Aldosterone receptor antagonist	30 (71.4)	14 (66.7)	16 (76.2)	0.73430
Diuretic	33 (78.6)	16 (76.2)	17 (81.0)	>0.999
Anticoagulant agent	14 (33.3)	4 (19.0)	10 (47.6)	0.100
Cardiac rehabilitation	21 (50.0)	10.0 (47.6)	11 (52.4)	>0.999

Values are median (IQR), n (%), or n. *Differences between LVRR-positive and LVRR-negative patients were evaluated by means of Mann-Whitney *U* test for continuous variables and Fisher exact test for categoric variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BMI = body mass index; BNP = B-type natriuretic peptide; CLBBB = complete left bundle branch block; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; EMB = endomyocardial biopsy; Hb = hemoglobin; HR = heart rate; IVSth = intraventricular septum thickness; LVEDD = left ventricular end-diastolic diameter; LVEF = left ventricular ejection fraction; LVPWth = left ventricular posterior wall thickness; LVRR = left ventricular reverse remodeling; MR = mitral regurgitation; NYHA = New York Heart Association functional class; PCWP = pulmonary capillary wedge pressure; SBP = systolic blood pressure.

FIGURE 1 Electron Micrographs of Autophagic Vacuoles in Cardiomyocytes



Impact of Autophagy on Prognosis of Patients With Dilated Cardiomyopathy

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Framework to Classify Reverse Cardiac Remodeling With Mechanical Circulatory Support

The Utah-Inova Stages

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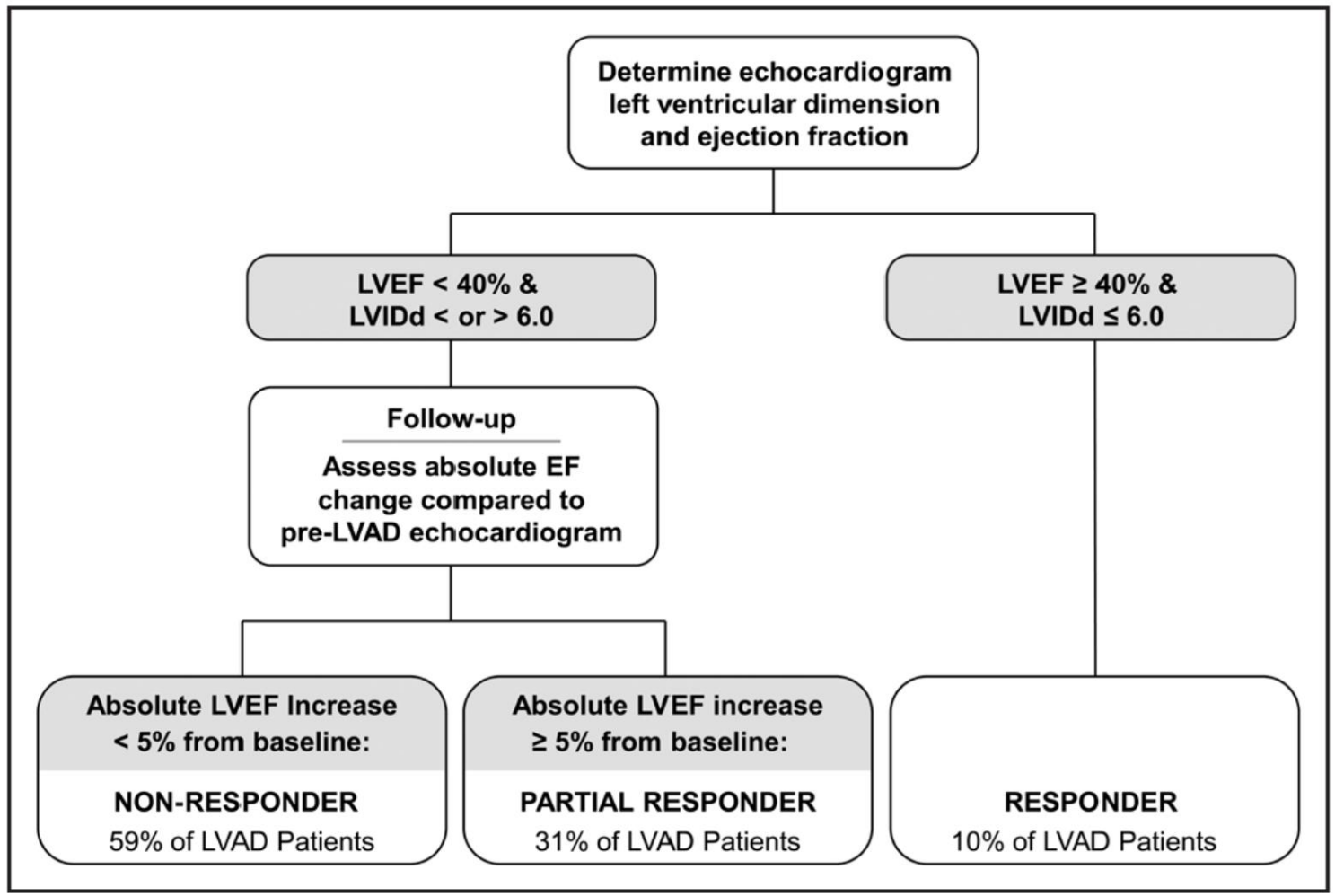
Circ Heart Fail. 2021;14:e007991. DOI: 10.1161/CIRCHEARTFAILURE.120.007991


Determine echocardiogram left ventricular dimension and ejection fraction
LVEF < 40% & LVIDd < or > 6.0
LVEF ≥ 40% & LVIDd ≤ 6.0
Follow-up
Assess absolute EF change compared to pre-LVAD echocardiogram
Absolute LVEF Increase < 5% from baseline:
NON-RESPONDER
59% of LVAD Patients
Absolute LVEF increase ≥ 5% from baseline:
PARTIAL RESPONDER
31% of LVAD Patients
RESPONDER
10% of LVAD Patients

Box 1 | **Future research directions**

Changes during reverse remodelling

Available evidence shows that reverse remodelling is associated with cellular and molecular changes (see figure):

- Decrease in cardiac myocyte size
- Restoration of expression levels of genes related to excitation–contraction coupling towards levels of a nonfailing heart
- Reduction in total collagen content with haemodynamic unloading and angiotensin-converting enzyme inhibitor therapy
- Increased myocardial microvascular density with haemodynamic unloading
- Reversal of the abnormal fetal gene programme towards a gene programme of a nonfailing heart

Myocardial recovery

The progression from reverse remodelling to true myocardial recovery needs to demonstrate recovery at the clinical level, including:

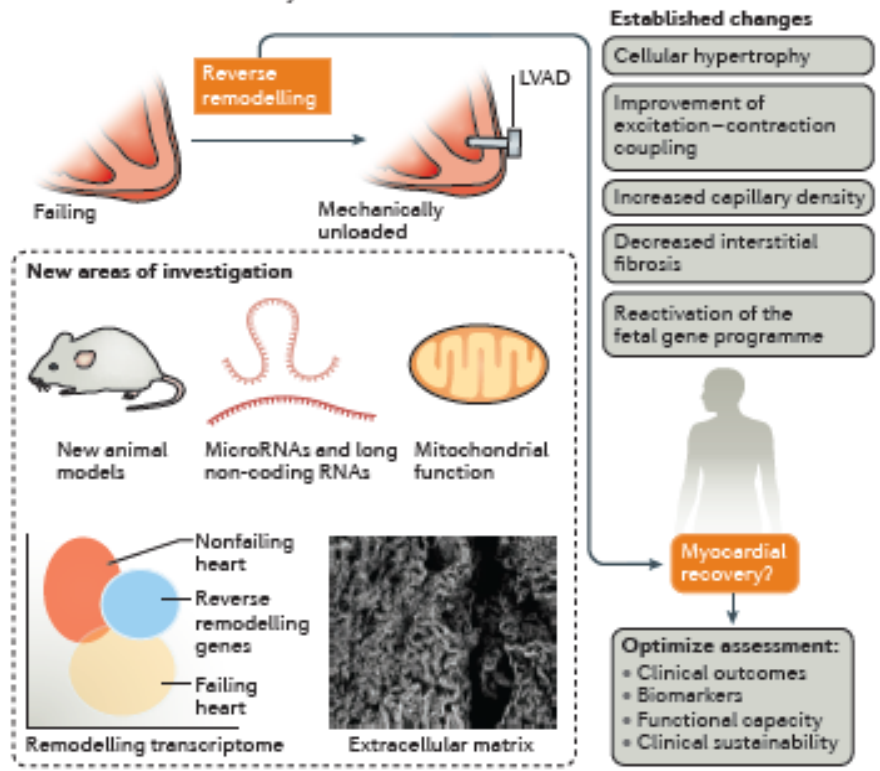
- A sustained clinical response with a decrease in long-term morbidity and mortality to match rates in individuals with nonfailing hearts
- Restoration in cardiac biomarkers indicative of myocardial recovery
- Restoration of exercise capacity

New areas of investigation

- Continue to develop animal models of myocardial recovery to define more precisely the molecular and cellular changes observed in human myocardial tissue, in particular, to explore the transcriptional changes in the setting of reverse remodelling (see figure)
- Investigate the changes in mitochondrial structure and function in individuals who have myocardial reverse remodelling and possible recovery
- Understand the changes in the extracellular matrix, incorporating the 3D structure and non-collagen protein changes in addition to the fibrillar component, as a means to study myocardial stiffness and changes in myocardial recovery

Optimize assessment of myocardial reverse remodelling and recovery

- Define the metrics to assess the varying degrees of myocardial recovery, in particular in the setting of left ventricular assist device support, to quantify myocardial recovery
- Develop noninvasive imaging modalities to aid in the quantification of myocardial recovery in the setting of medical or device therapy
- Establish collaborative research networks to provide paired human tissue samples with standardized metrics for assessment of myocardial reverse remodelling and recovery
- Explore the relative contribution of genetic factors, extracellular matrix, and mitochondria in the determination of reverse remodelling and recovery



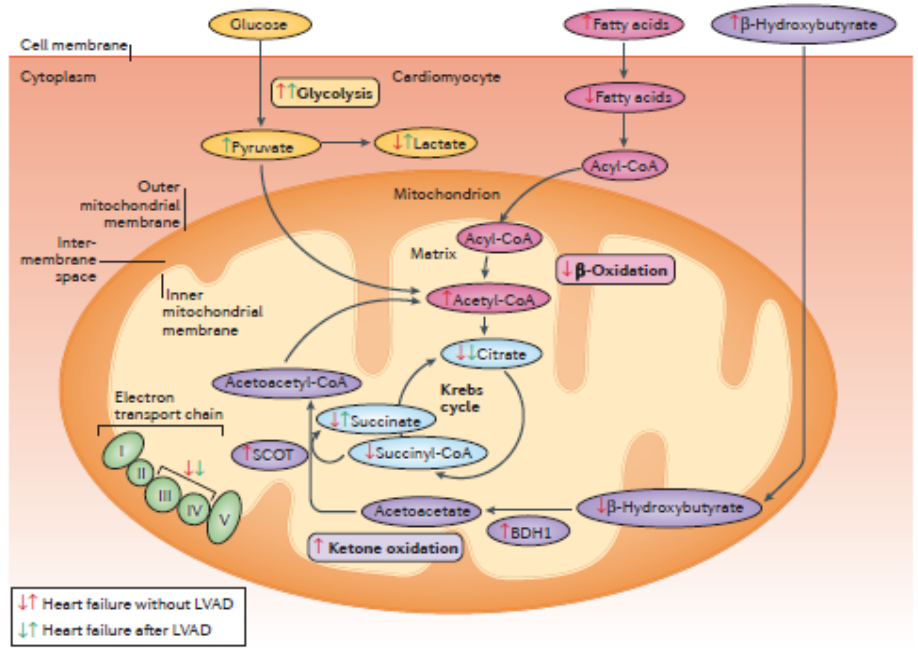


Figure 2 | **Metabolic shift in heart failure.** In advanced heart failure, cardiomyocyte fatty acid uptake and β-oxidation, which in the healthy adult heart generates most of the cardiac ATP, and the oxidative function of mitochondria decrease. In failing myocardium, the electron transport chain has significantly lower respiration capacity compared with normal hearts, and the mitochondrial oxidative capacity remains reduced after left ventricular assist device (LVAD) unloading[37]. In the failing heart, the predominant fuel source shifts from mitochondrial fatty acid oxidation towards glycolytic pathways. The increased glycolysis remains elevated after LVAD support, which together with the defect in mitochondrial oxidation leads to increased cytosolic lactate rather than the increased pyruvate that enters the Krebs cycle. In patients with advanced heart failure, elevations in the serum concentration of ketone bodies (such as β-hydroxybutyrate) are accompanied by alterations in metabolites, such as increased levels of acetoacetate and acetoacetyl-CoA, and enzymes, such as increased expression levels of genes coding for the enzymes implicated in ketone oxidation D-β-hydroxybutyrate dehydrogenase (BDH1) and succinyl-CoA:3-oxoacid-CoA transferase (SCOT), consistent with the upregulation of the ketone oxidation pathway in the heart[35,36].

Table 1 | Proposed molecular mechanisms of reverse remodeling in humans

Type of change	RAAS inhibition	β-AR blockade	Mechanical unloading*
Histological changes			
Reduced myocyte size	–	–	+
Decreased interstitial fibrosis	+	–	+
Increased capillary density	–	–	+
Molecular changes			
Inhibition of fetal gene expression	–	+	+
Improved β-adrenergic response	–	+	+
SERCA2 gene upregulation	–	+	+
Improved calcium handling	–	+	+

*By left ventricular assist devices or cardiac support devices. Abbreviations: β-AR, β-adrenergic receptor; RAAS, renin–angiotensin–aldosterone system; SERCA2a, sarcoplasmic/endoplasmic reticulum calcium ATPase 2 isoform 2.

NT-proBNP Goal Achievement Is Associated With Significant Reverse Remodeling and Improved Clinical Outcomes in HFrEF

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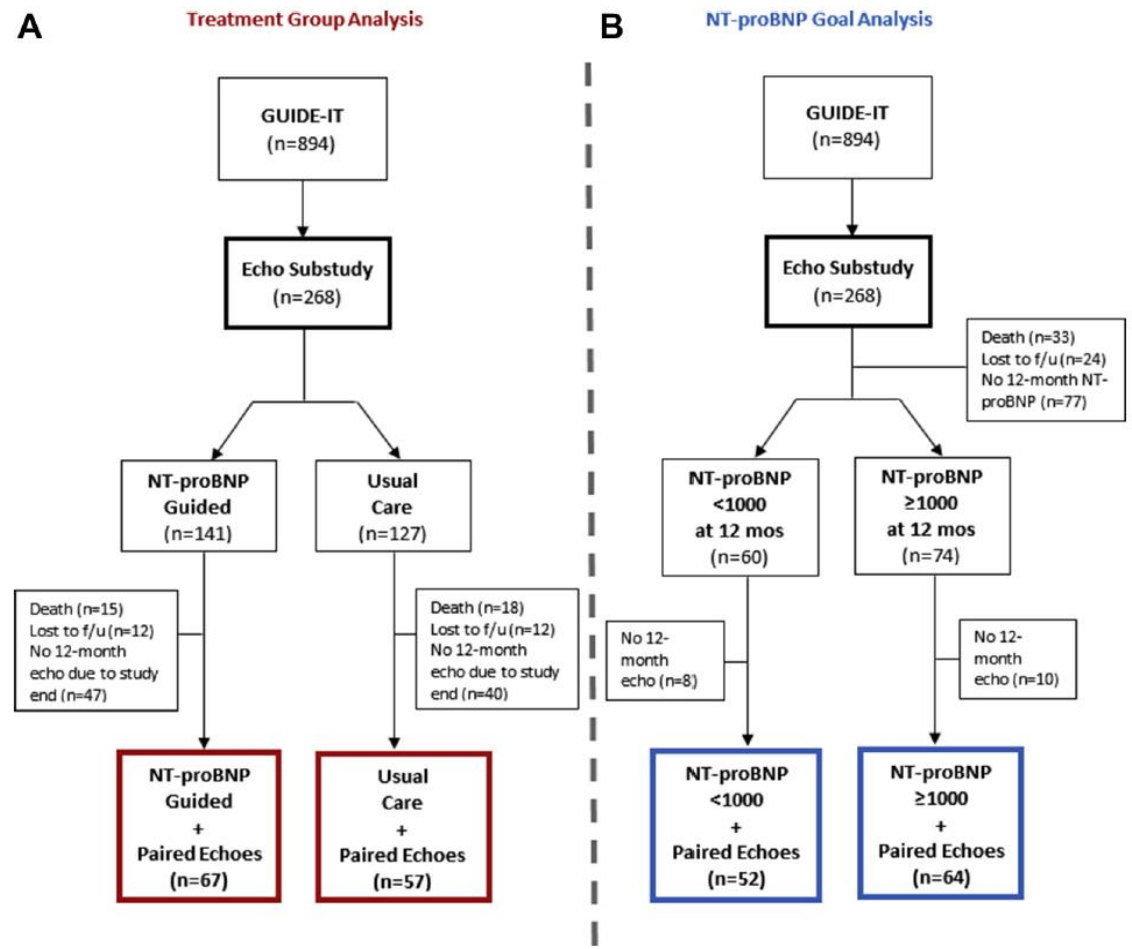
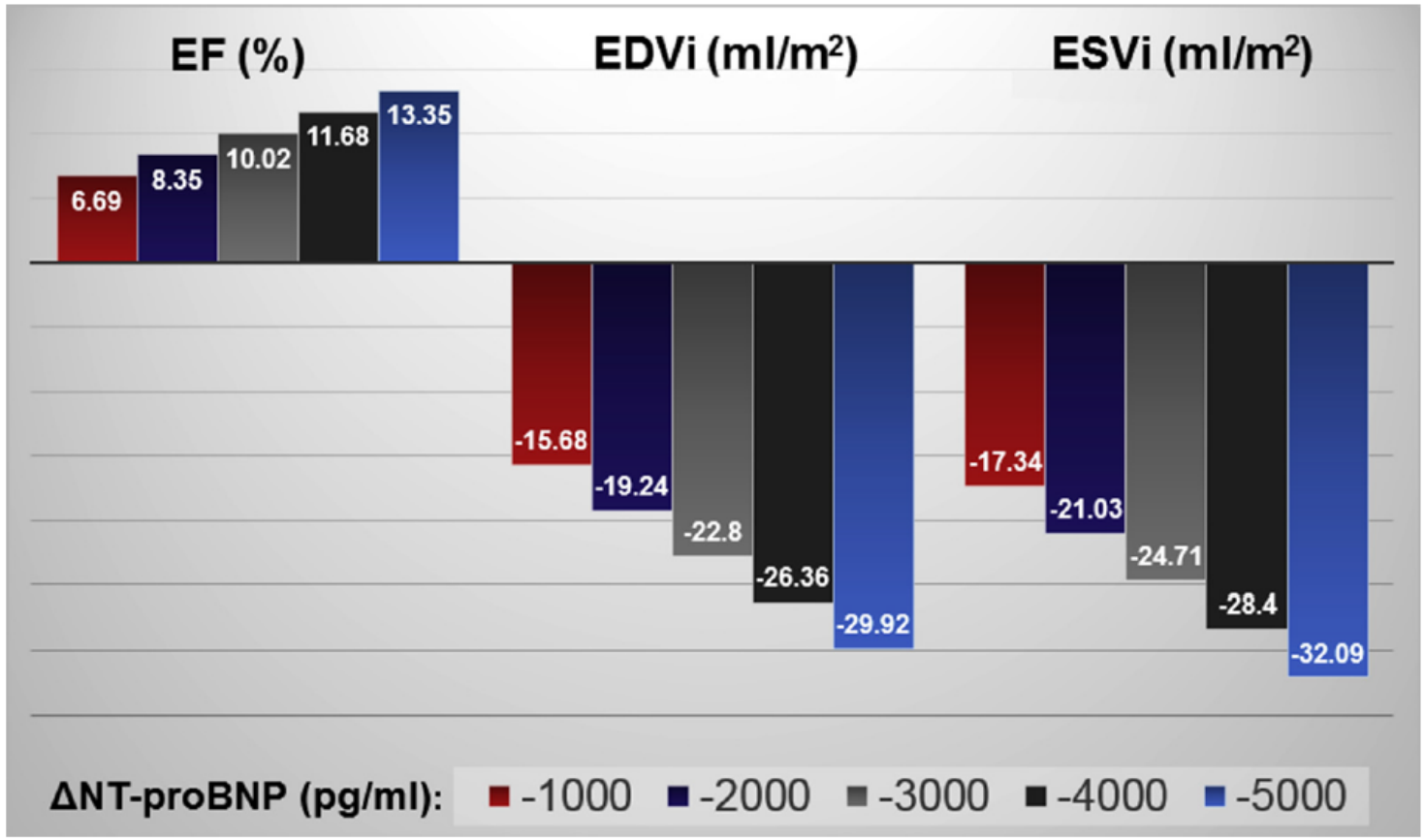
FIGURE 1 Consolidated Standards of Reporting Trials Diagrams



(A) Randomized treatment group analysis. **(B)** NT-proBNP goal analysis. Echo = echocardiogram; f/u = follow-up; GUIDE-IT = Guiding Evidence Based Therapy Using Biomarker Intensified Treatment; NT-proBNP = pro-B-type natriuretic peptide.

FIGURE 4 NT-proBNP Change and Absolute Change in Ejection Fraction and Left Ventricular Volumes at 12 Months



Regression modeling demonstrates that greater decreases in NT-proBNP correspond to greater increases in ejection fraction (EF) and greater decreases in left ventricular volumes. EDVi = indexed end-diastolic volume; ESVi = indexed end-systolic volume.

TABLE 5 Clinical Outcomes After 12 Months

	NT-proBNP <1,000 pg/ml at 12 Months (n = 52)		NT-proBNP ≥1,000 pg/ml at 12 Months (n = 64)		
	Number of Events	KM Rate (95% CI)	Number of Events	KM Rate (95% CI)	p Value*
Death/HF hospitalization	0	0.0	15	0.30 (0.19-0.46)	<0.001
Death	0	0.0	7	0.16 (0.08-0.31)	0.04
HF hospitalization	0	0.0	13	0.27 (0.17-0.43)	0.002

*Log-rank test.

CI = confidence interval; HF = heart failure; KM = Kaplan-Meier.

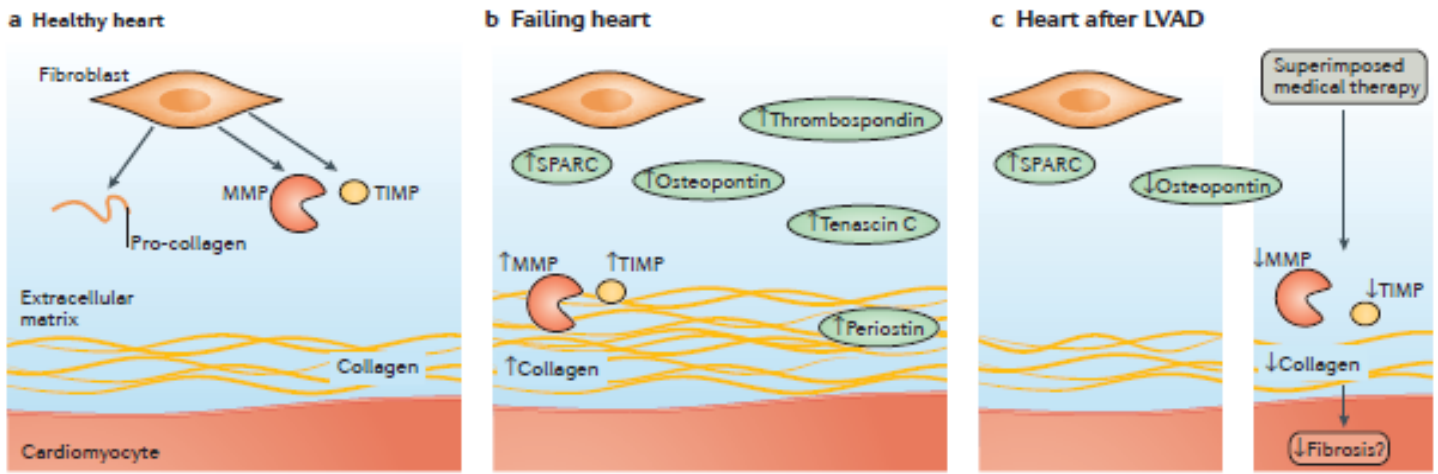
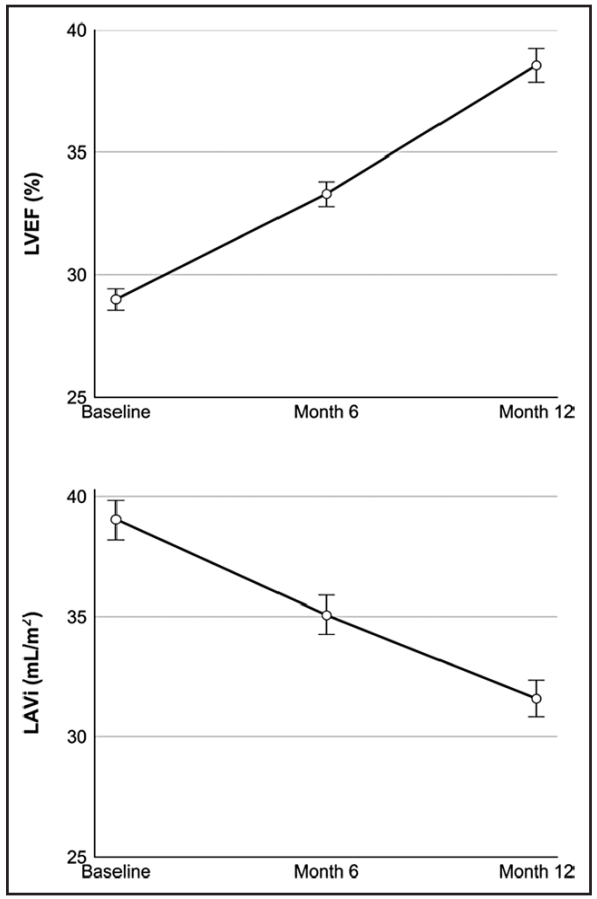


Figure 3 | **Altered extracellular matrix. a** | Schematic diagram of the myocardial extracellular matrix and associated proteins. **b** | In the failing myocardium, the levels of matrix metalloproteinases (MMP) are increased, whereas the levels of their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), decrease, and the levels of matricellular proteins including osteopontin and SPARC (also known as osteonectin), are also elevated. Collagen content increases as a result of changes in the expression of genes encoding proteins associated with a profibrotic phenotype, such as collagen, fibronectin, and tumour necrosis factor, in cardiac fibroblasts. **c** | In failing myocardium with left ventricular assist device (LVAD) support, medical therapy with angiotensin-converting enzyme inhibitors might improve the MMP/TIMP ratio and reduce myocardial collagen content. Matricellular proteins such as osteopontin return to normal levels, but SPARC levels remain elevated[44], with partially preserved collagen organization and extracellular matrix–myocyte interaction.



Multivariable-adjusted left ventricular ejection fraction (LVEF) and left atrial volume index (LAVi) from baseline to month 12.
Initiation of sacubitril/valsartan was associated with improvements in
LVEF and LAVi; LVEF increased by 8.9 percentage points (95% CI,
8.7–9.2 points), while LAVi decreased by 22.0% (95% CI, −21.0% to −23.0%; P<0.001).

Prediction of Left Ventricular Reverse Remodelling: A Mini Review on Clinical Aspects

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Table 2. The effect of therapy on cellular and molecular changes in LV RR

	β-Blockers	ACEi	ARB	MRA	LVAD	CRT	ARNI	SGLT2
Cardiomyocyte changes								
Hypertrophy	↓	↓	↓	↓	↓	↓	↓	↓
Foetal gene expression	↓	↓	↓	ND	↓	↓	↓	
Myocytolysis	↓	ND	ND	ND	↓	ND	ND	ND
Beta-adrenergic desensitization	↓	↓	↓	ND	↓	↓	ND	ND
EC coupling	↑	↑	↑	ND	↑	↑	ND	–
Cytoskeletal changes	ND	ND	ND	↑	↑	↓	↓	ND
Myocardial changes								
Myocyte apoptosis	↓	↓	↓	ND	↓	↓	↓	↓
MMP activation	↓	↓	↓	↓	↓	↓	↓	↓
Fibrosis	↓	↓	↓	↓	↑	↓	↓	↓
Angiogenesis	↑	↑	↑	↑	↓	↑	↑	↑
LV geometry changes								
LV dilatation	↓	Stabilization	Stabilization	Stabilization	↓	↓	↓	↓

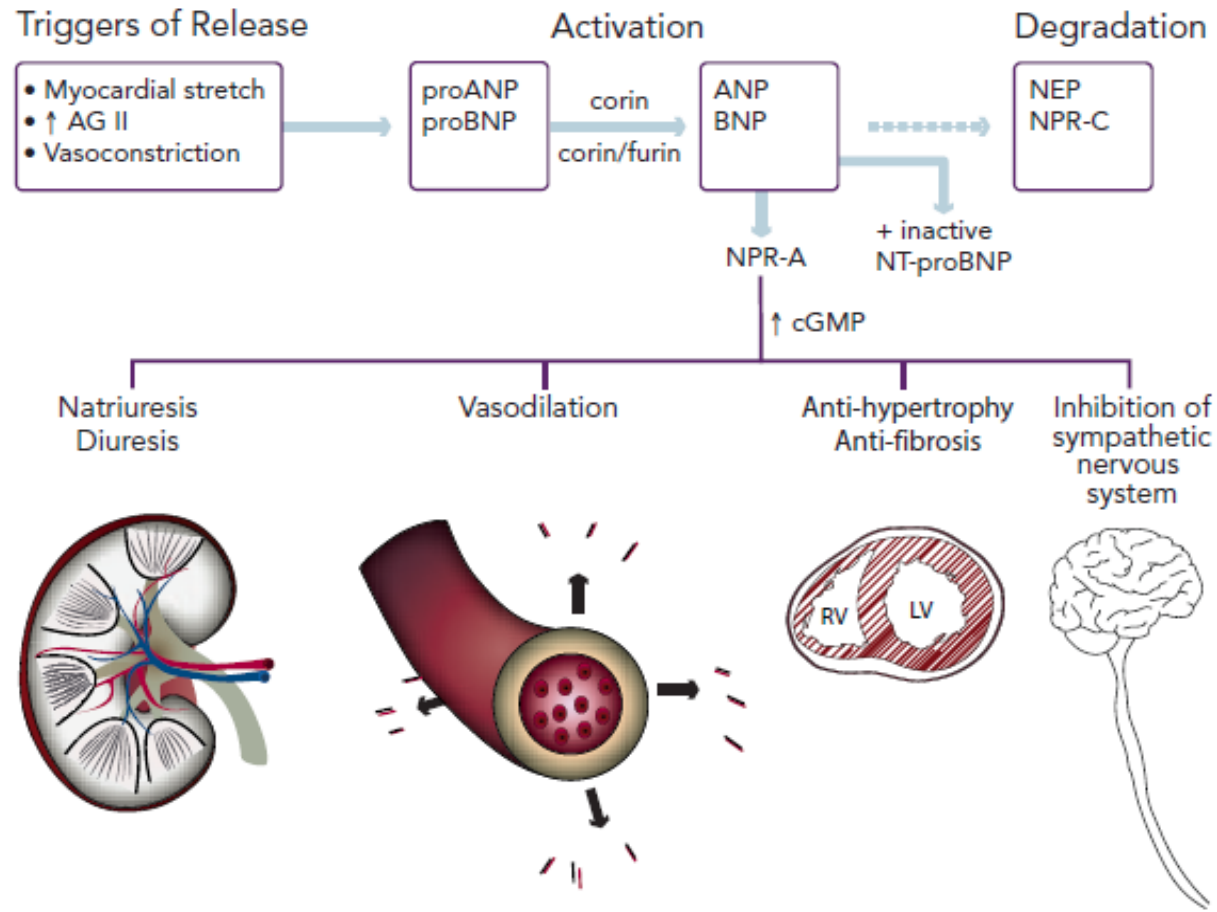
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CRT, cardio resynchronization therapy; EC, excitation-contraction; LVAD, left ventricular assist device; MRA, mineralocorticoid receptor antagonists; ND, no data.

Table 1. Overview of clinical studies aimed at identifying predictors of RR

Study	Studied population	RR criteria	RR observed	RR predictors
Merlo et al. [2], J Am Coll Cardiol 2011	*n* = 242, iDCMP	↑LVEF of ≥10% or ↑LVEF over 50%, ↓LVEDD ≥10% or at ≤33 mm/m^2	37%	Higher systolic blood pressure, LBBB absence
Amorim et al. [3], Int J Cardiovasc Imaging 2016	*n* = 113, iDCMP	↑LVEF of >10%, ↓LVEDD (not specified), without MR deterioration	34.5%	Mild hypertension, ventricular hypertrophy on ECG, LBBB absence, shorter QRS duration, higher haematocrit, lower LVDDi, higherVO_2/log 10[VE] and lower dVE/VCO_2/VO_2, ACEi/ARB treatment, maximum doses of ACEi/ARB and BB
Matsumura et al. [4], Am J Cardiol 2013	*n* = 19, iDCMP	↓LVEDD to ≤55 mm, fractional shortening improvement to ≥25%	37%	LVRR predictors not evaluated
Kubanek et al. [5], J Am Coll Cardiol 2013	*n* = 44, DCMP (symptoms for less than 6 months)	↑LVEF of ≥10% and to more than 35%, ↓LVEDD of ≥10%	45%	Input predictors: LGE range on CMR and greater myocardial oedema on CMR; after 3 months: BNP value; after 6 months: LVEDDi, E/E' ratio
Hoshikawa et al. [6], Am J Cardiol 2011	*n* = 33, iDCMP	↓LVEDD to ≤55 mm, fractional shortening improvement to ≥25%	42%	No statistically significant differences in the observed predictors
Ikeda et al. [7], Heart Vessels 2015	*n* = 207, iDCMP	↑LVEF of ≥10% and to ≥35%, ↓LVEDDi of ≥10%	52%	LVEDDi decrease during the first 6 months was predictive for LVRR in the later phase
Masci et al. [8], Circ Cardiovasc Imaging 2013	*n* = 58, iDCMP	↑LVEF of ≥10%, ↓LVEDV of ≥10% (according to CMR)	38%	The LGE absence at baseline examination, regardless of the clinical condition and severity of LV dysfunction and dilatation
Luo et al. [9], Chinese J Cardiovac Dis 2021	*n* = 129, HFrEF	↑LVEF of ≥10% and to more than 40%	29.5%	LVEDD ≤55 mm, higher DBP, higher heart rate, the absence of MI
Wilcox et al. [10], Am Heart J 2012	*n* = 3,994, HFrEF or post-IM HFrEF	↑LVEF of ≥10%	28.6%	Female sex, the absence of previous MI, nonischaemic aetiology of HF, no digoxin treatment
Lupón et al. [11], Int J Cardiol 2015	*n* = 304, HFrEF	↑LVEF of ≥15% or ↑LVEF of ≥10% and ↓LVESDi of ≥20% or LVESV of ≥40%	34.2%	ST2-R2 score: ST2 <48 ng/mL, nonischaemic aetiology, the absence of LBBB, HF duration <12 months, baseline LVEF <24%, BB treatment
Choi JO et al. [12], Circ J 2013	*n* = 253, nonischaemic DCMP	(1) ↑LVEF of ≥20% or ≥10% if LVEV reaches ≥50% and (2) ↓LVEDDi of ≥10% or LVEDDi ≤33 mm/m^2	38%	Higher systolic BP, QRS <120 ms, BB treatment, baseline LVEF, lower LVESDi
Viorel et al. [13], Circ Heart Fail 2016	*n* = 3,519, HFrEF	LVEF >40%	9.1%	Female sex, nonischaemic aetiology, lower BMI, higher DBP, LVEDDi, BB and valsartan treatment
Agra Bermejo et al. [14], Cardiol J 2018	*n* = 449, HFrEF	LVEF >40%	52%	NYHA, ACEi, and BB treatment; nonischaemic aetiology; no ICD implantation
Jung et al. [15], J Cardiovasc Imaging	*n* = 160, DCMP without AF	↑LVEF of >10% or LVEF >50%, ↓LVEDDi of ≥10% or LVEDDi ≤33 mm/m^2	28%	GLS

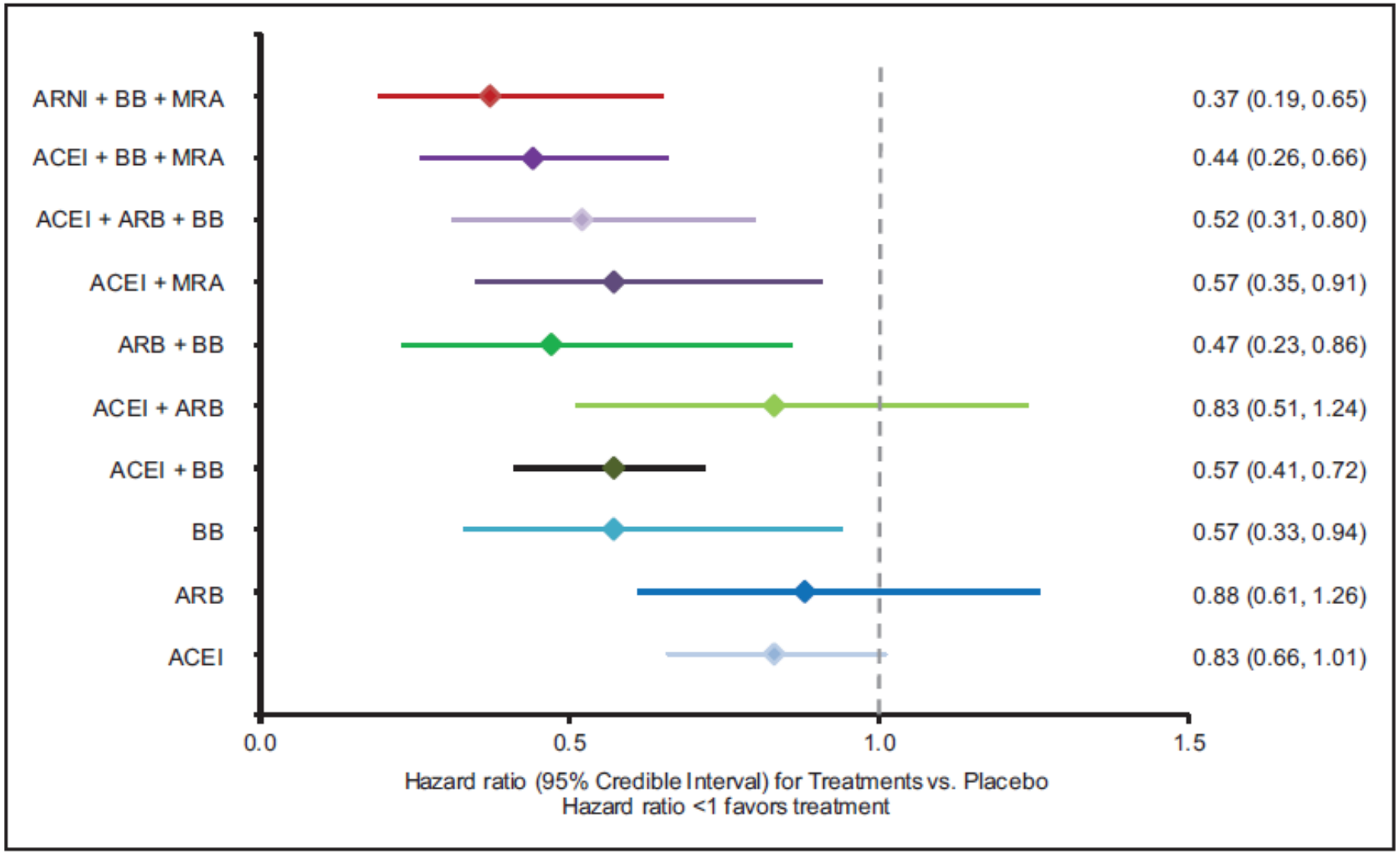
ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BB, beta blockers; BMI, body mass index; CMR, cardiac magnetic resonance; DCMP, dilated cardiomyopathy; DBP, diastolic blood pressure; LVEF, left ventricular ejection fraction; GLS, global longitudinal strain; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter defibrillator; MI, myocardial infarction; LBBB, left bundle branch block; LGE, late gadolinium enhancement; LVEDD, left ventricular end-diastolic dimension; LVEDDi, left ventricular end-diastolic dimension index; LVESDi, left ventricular end-systolic dimension index; LVRR, left ventricular reverse remodelling; MR, mitral regurgitation.

Counter-Regulatory Neurohormonal Systems are also activated in Chronic HF



AG II = angiotensin II; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; LV = left ventricle; NEP = neutral endopeptidase 24.11; NPR-A = natriuretic peptide receptor A; NPR-C = natriuretic peptide receptor C; RV = right ventricle.

Comparative Risk Reduction of Approved Therapies



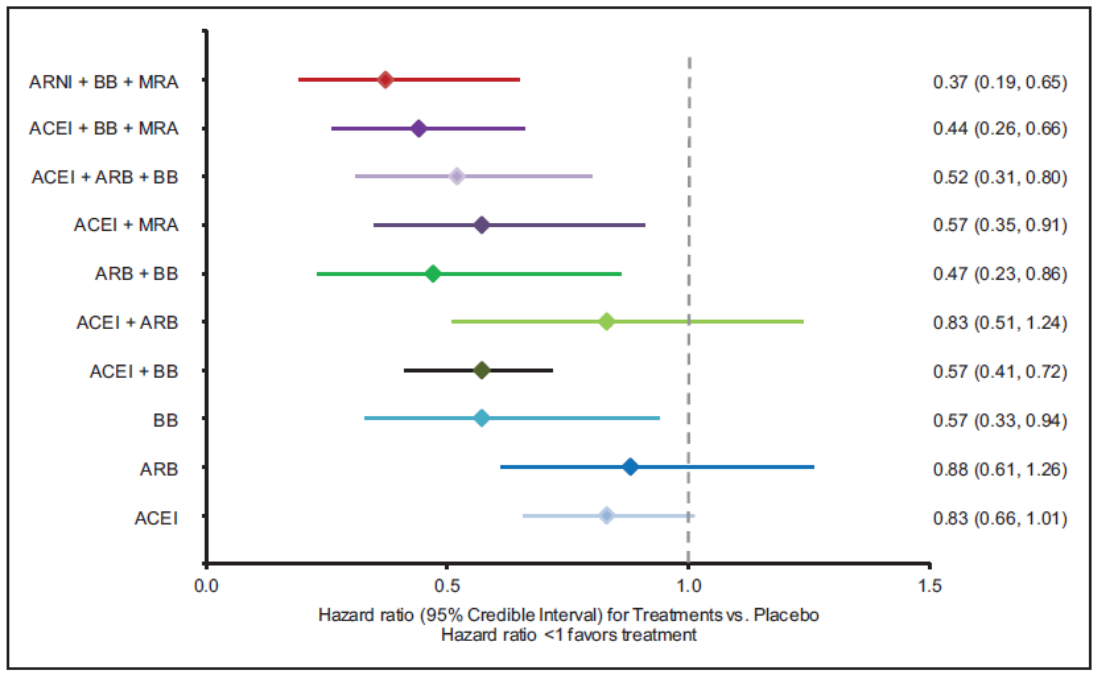
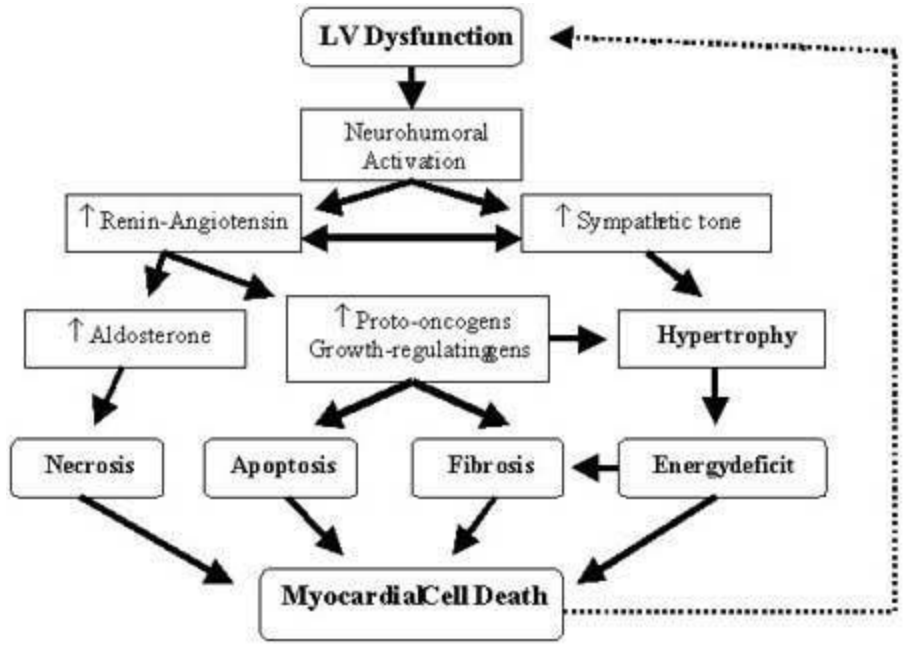


Figure 5. Results of random effect network meta-analysis for all-cause mortality: hazard ratios for intervention versus placebo for all-cause mortality and 95% credible intervals. ACEI indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin-II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; BB, beta blocker; and MRA, mineralocorticoid receptor antagonist.


LV Dysfunction
Neurohumoral Activation
↑ Renin-Angiotensin
↑ Sympathetic tone
↑ Aldosterone
↑ Proto-oncogens Growth-regulatinggens
Hypertrophy
Necrosis
Apoptosis
Fibrosis
Energydeficit
MyocardialCell Death