AMERICAN COLLEGE of CARDIOLOGY

Reverse Remodeling in Heart Failure with Reduced EF:

How can we achieve it?

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Disclosures

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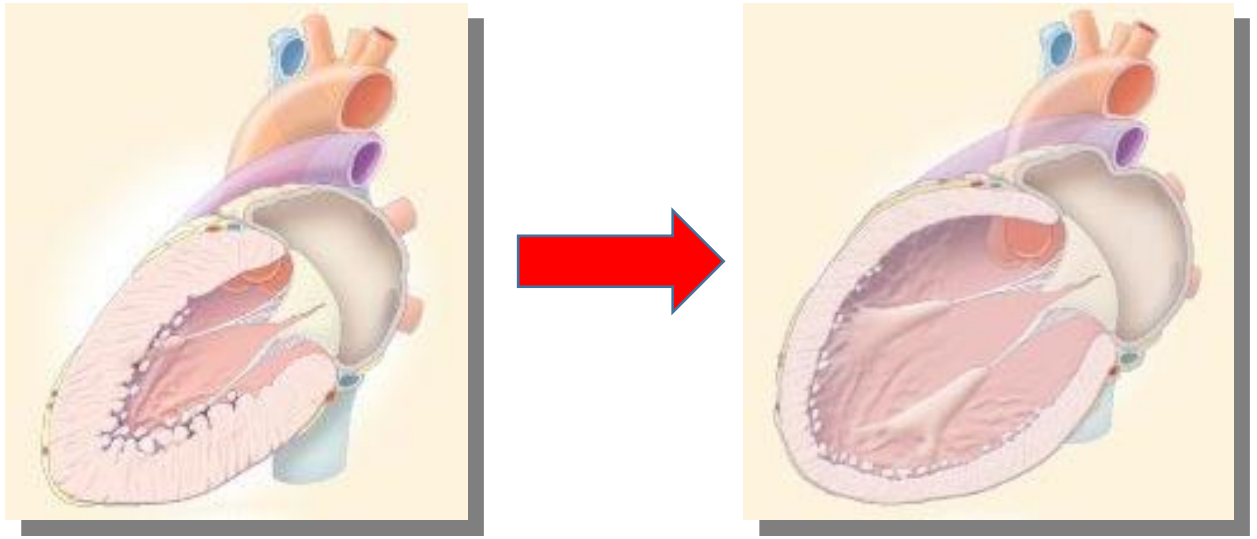
- Clinical endpoint committees/data safety monitoring boards for Abbott, AbbVie, Amgen, CVRx, Janssen, MyoKardia, and Takeda
- Trustee, American College of Cardiology

Cardiac remodeling and HF progression

- Cardiac remodeling is defined as change in size, shape, and performance of the myocardium
- Dilation may affect all 4 chambers of the heart
- Reduction in performance includes reduced LV systolic and diastolic function

Through numerous acute and/or ongoing insults (including activation of the RAAS and SNS) normal myocardium becomes progressively remodeled



Normal heart

Remodeled heart

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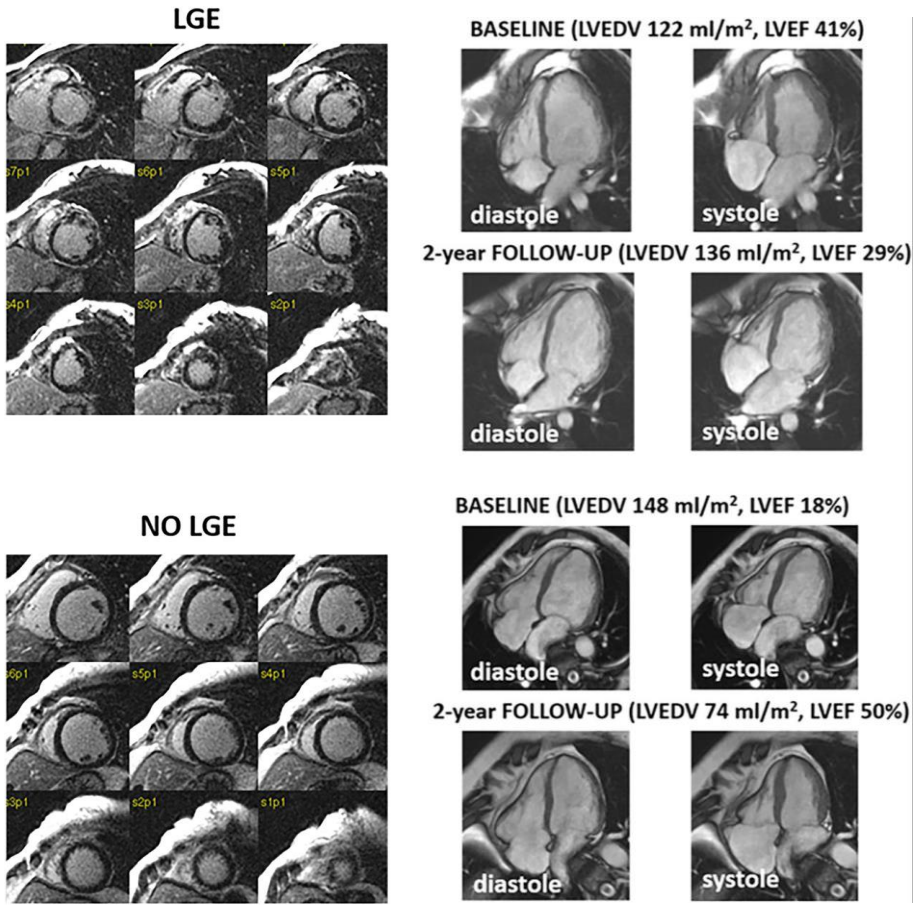
Variables predictive of reverse cardiac remodeling

Parameters	Variables
Clinical parameters	Non-ischemic HFrEF Shorter HF duration Female sex Absence of LBBB
Therapies	Guideline-directed medical therapy CRT
Echo/CMR	Lower LVEF, larger volumes Greater contractility on GLS Absence of LGE
Biomarkers	Lower NT-proBNP Lower hs-cTn Lower sST2 Other markers



Aimo, et al, J Am Coll Cardiol, 2019

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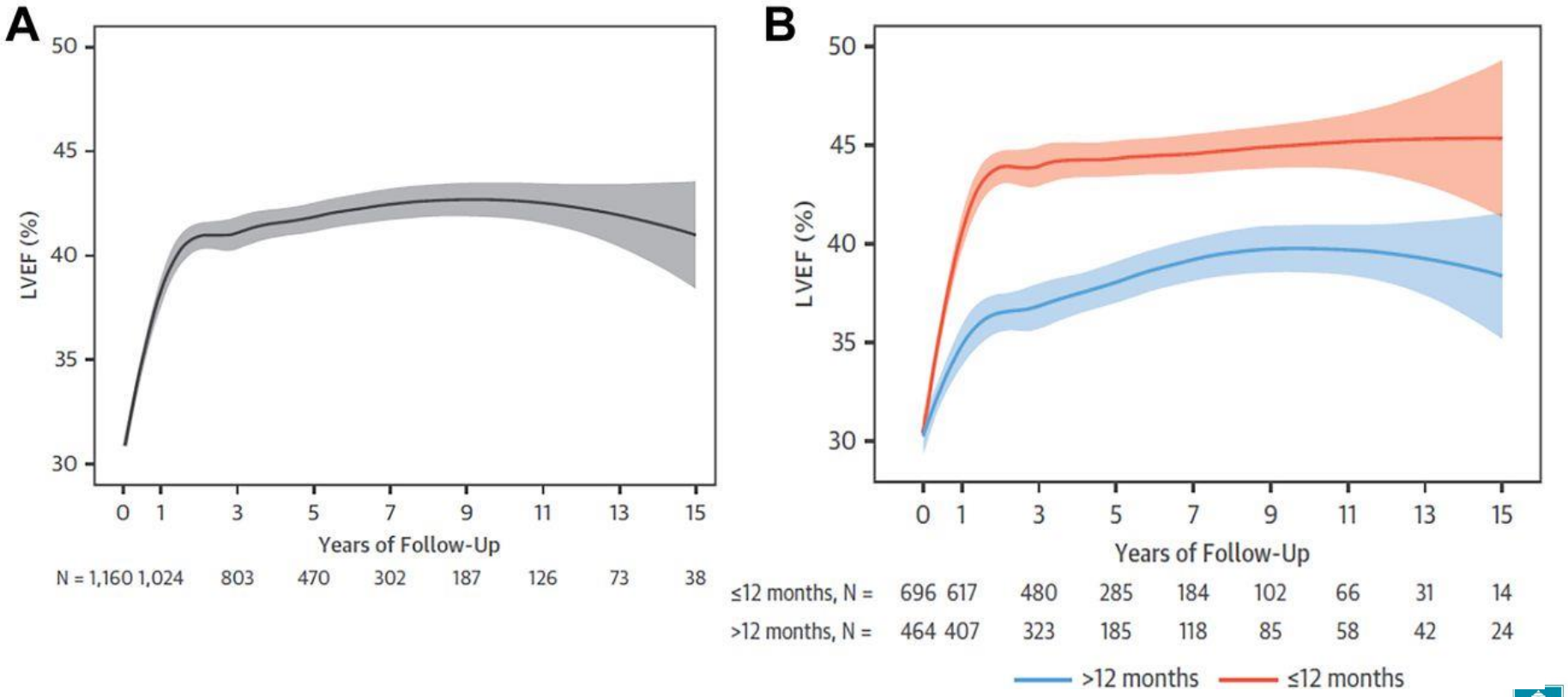
LVEF trajectory after GDMT

An "inverted U shape" trajectory of LVEF is seen with early reverse remodeling followed by a plateau phase and, in some cases, a decline, typically associated with worse prognosis.



1.Lupon J., et al (2018) Dynamic trajectories of left ventricular ejection fraction in heart failure. J Am Coll Cardiol **72**:591–601

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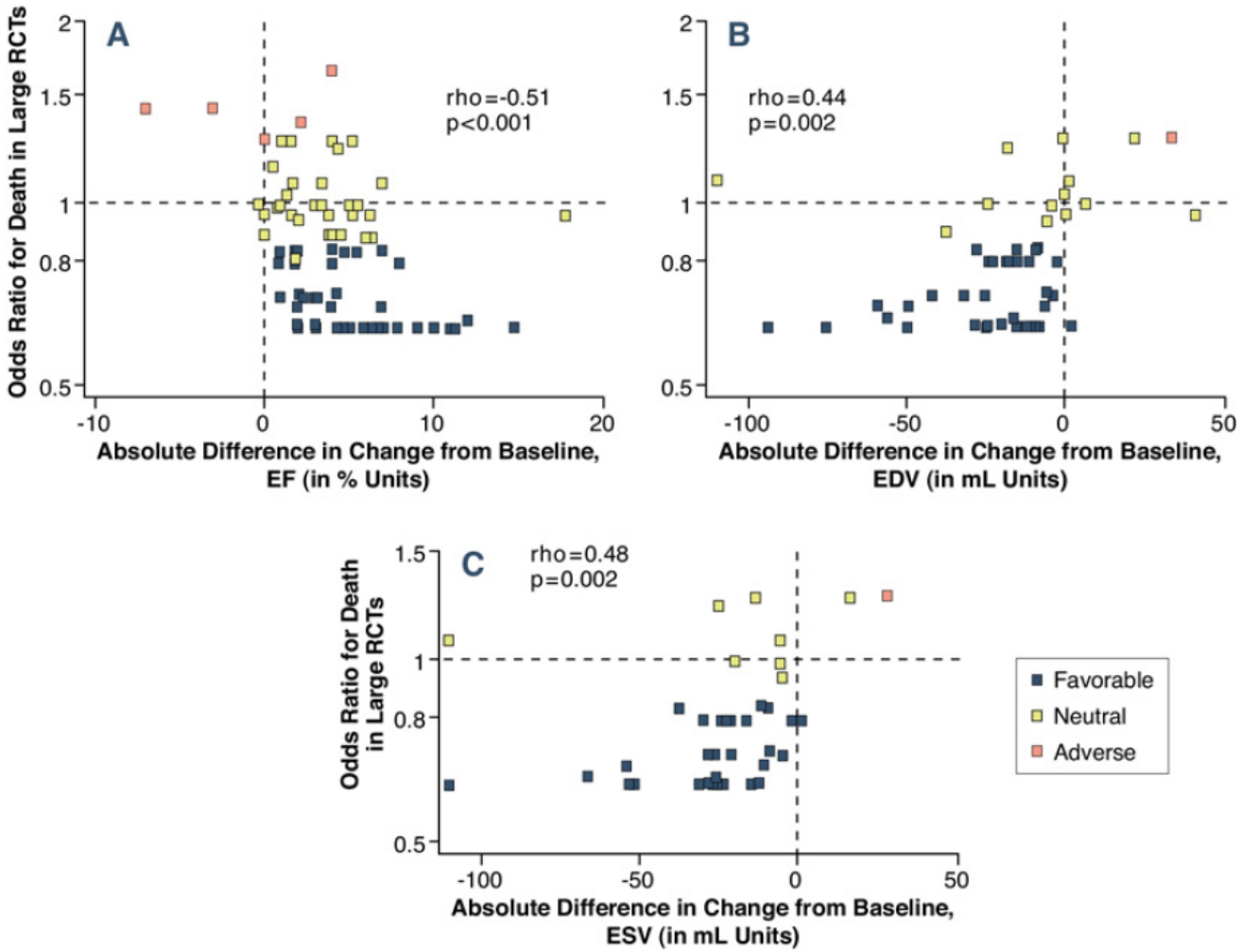
Reverse remodeling and outcomes



Heart failure therapies that lead to “reverse” remodeling also foster significant improvement in prognosis

Kramer et al, et al J Am Coll Cardiol, 2010

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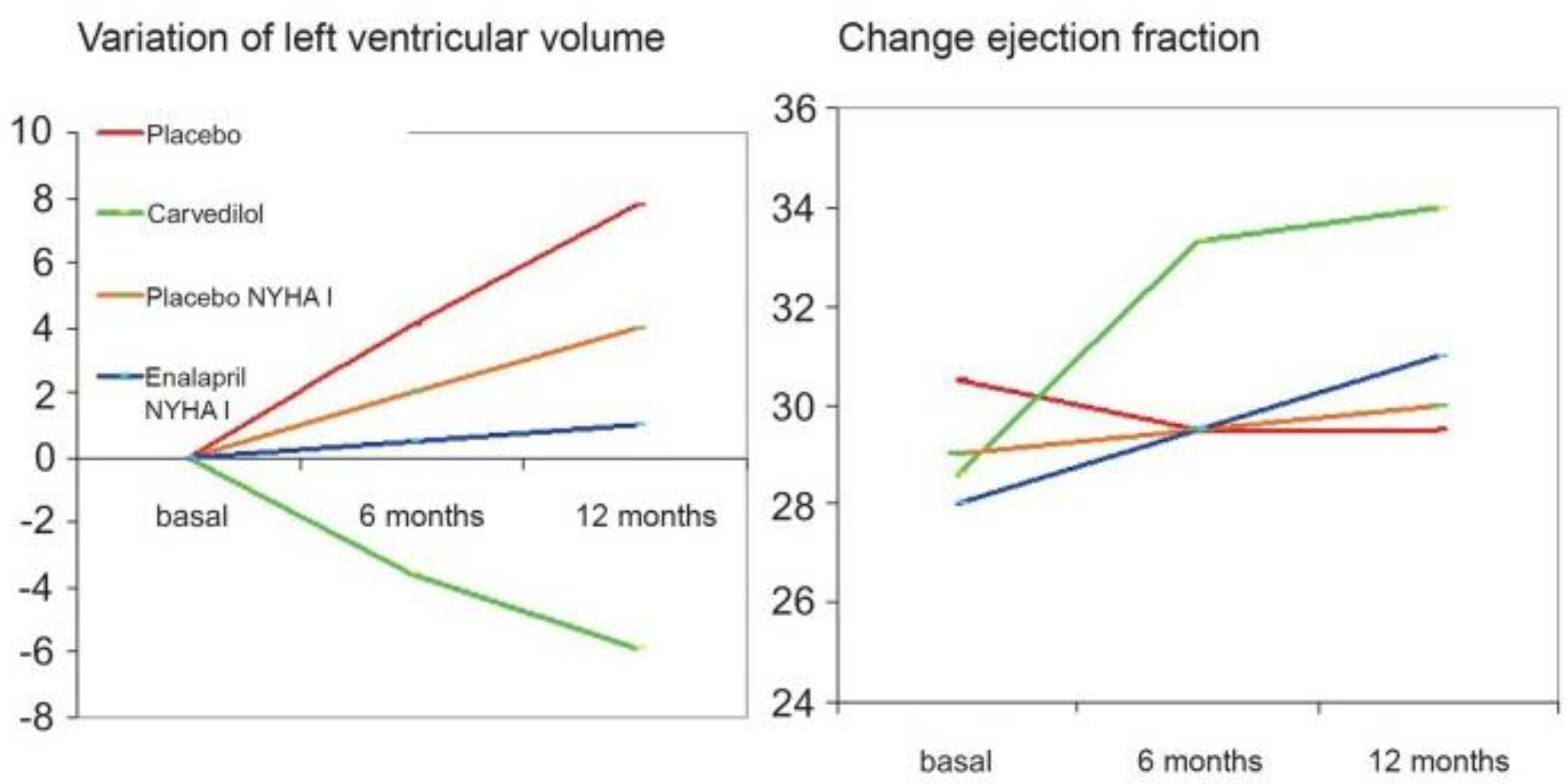
Guideline-directed medical therapy may improve remodeling indices in HFrEF

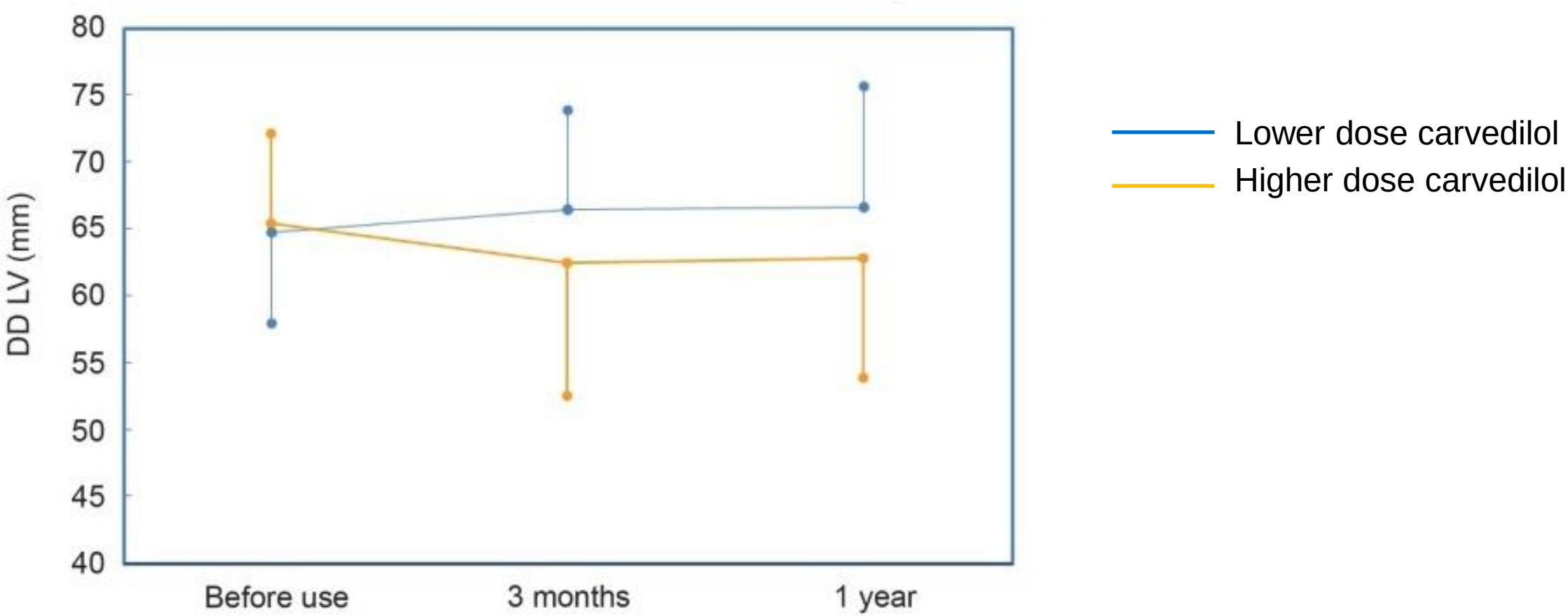
Therapy	Impact on remodeling in HFrEF
Cardiac resynchronization therapy	Strong
Beta blockers	Strong
Renin-angiotensin inhibitors	Moderate to strong
Mineralocorticoid receptor antagonists	Moderate
SGLT2 inhibitors	No clinical data
ARNI	Strong

Effects of Beta Blockers and ACE inhibitors on remodeling



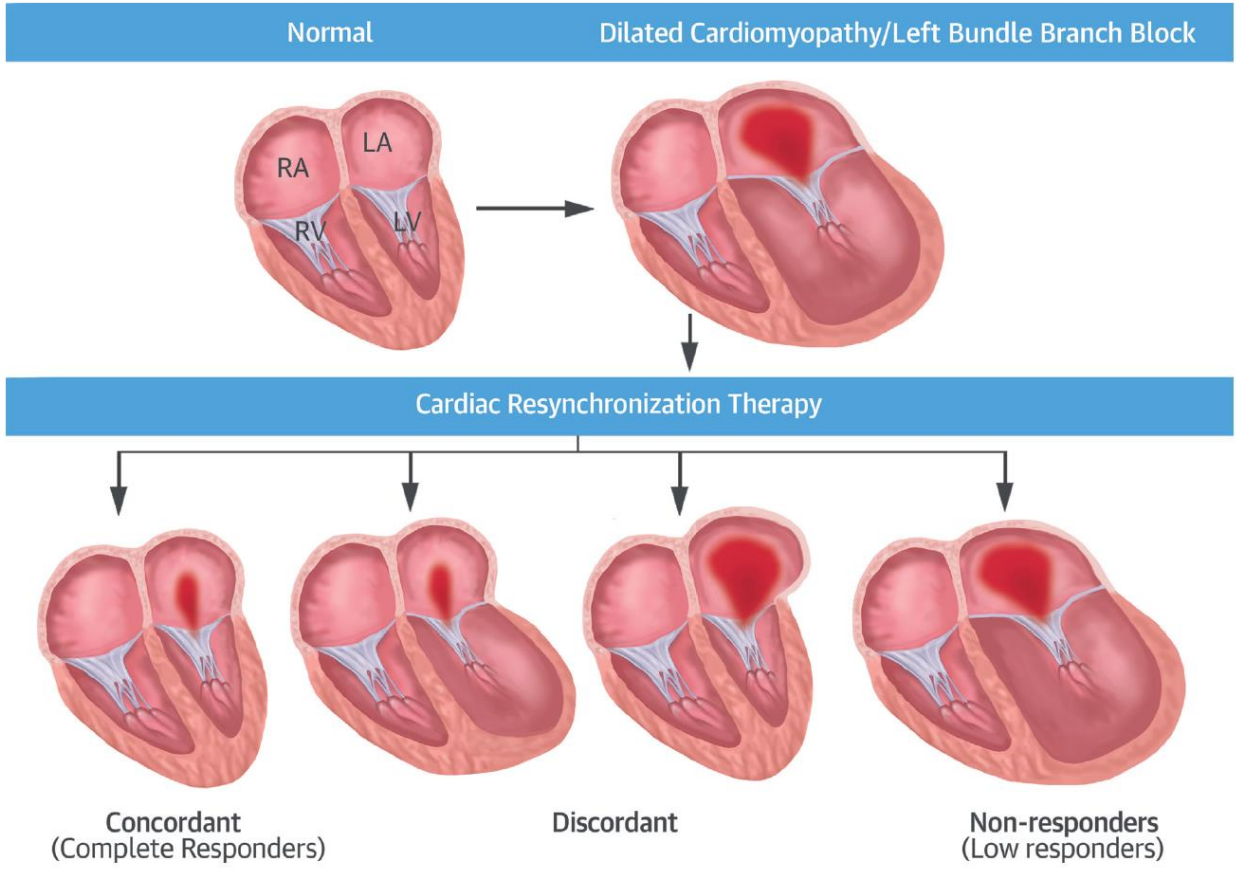
Cohn JN et al JACC 2000; 35: 569-82.

Impact of beta blockers is dose-dependent



Melo D et al. JACC 2011; 57 (supl A): 17.

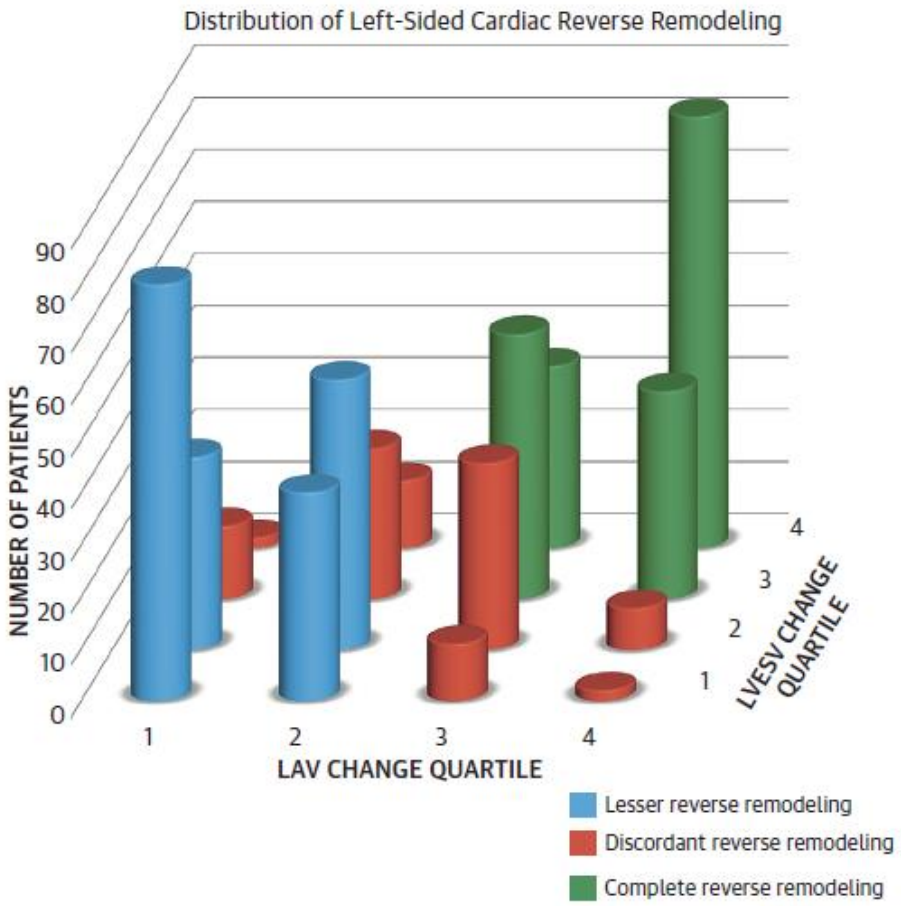
Various responses to CRT

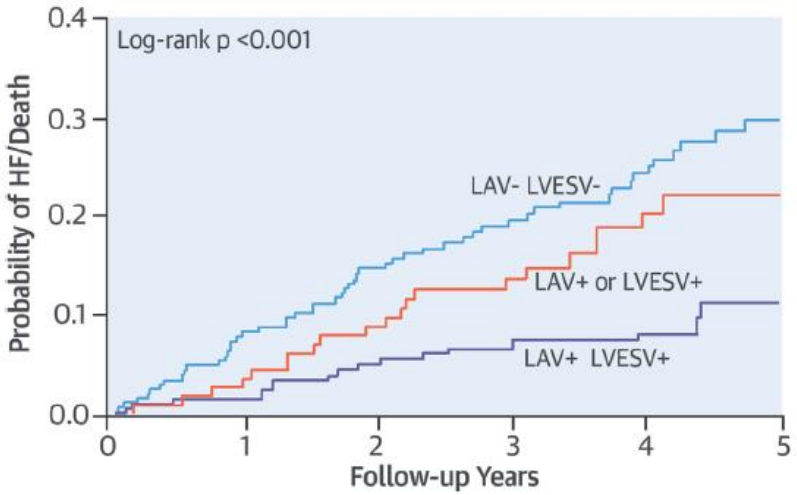


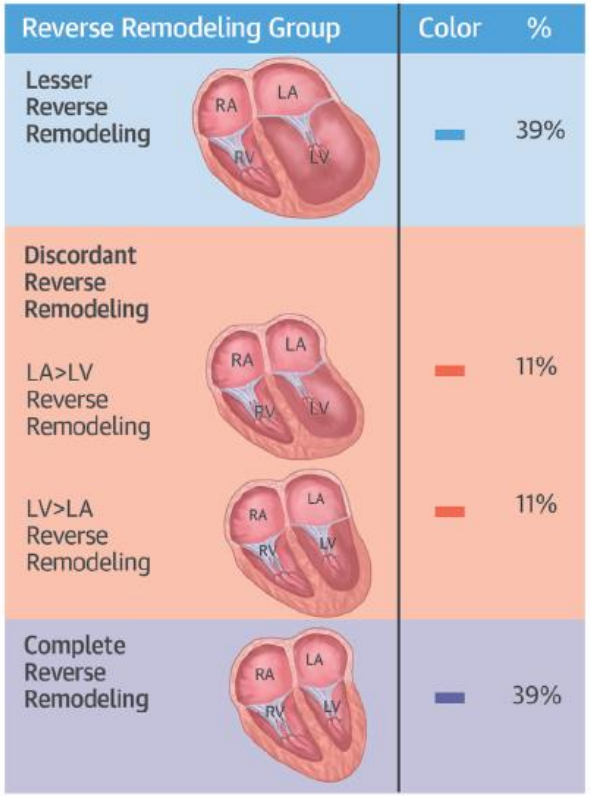
- CRT exerts variable—and often significant reverse remodeling effects
- Changes following CRT include reduced LV size, improved LV function, reduction in LA volumes, and improvement in MR

Waring and Litwin, JACC 2016;68:1277-80.

Importance of complete left sided RR







Mathias, A. et al. J Am Coll Cardiol. 2016;68(12):1268-76.

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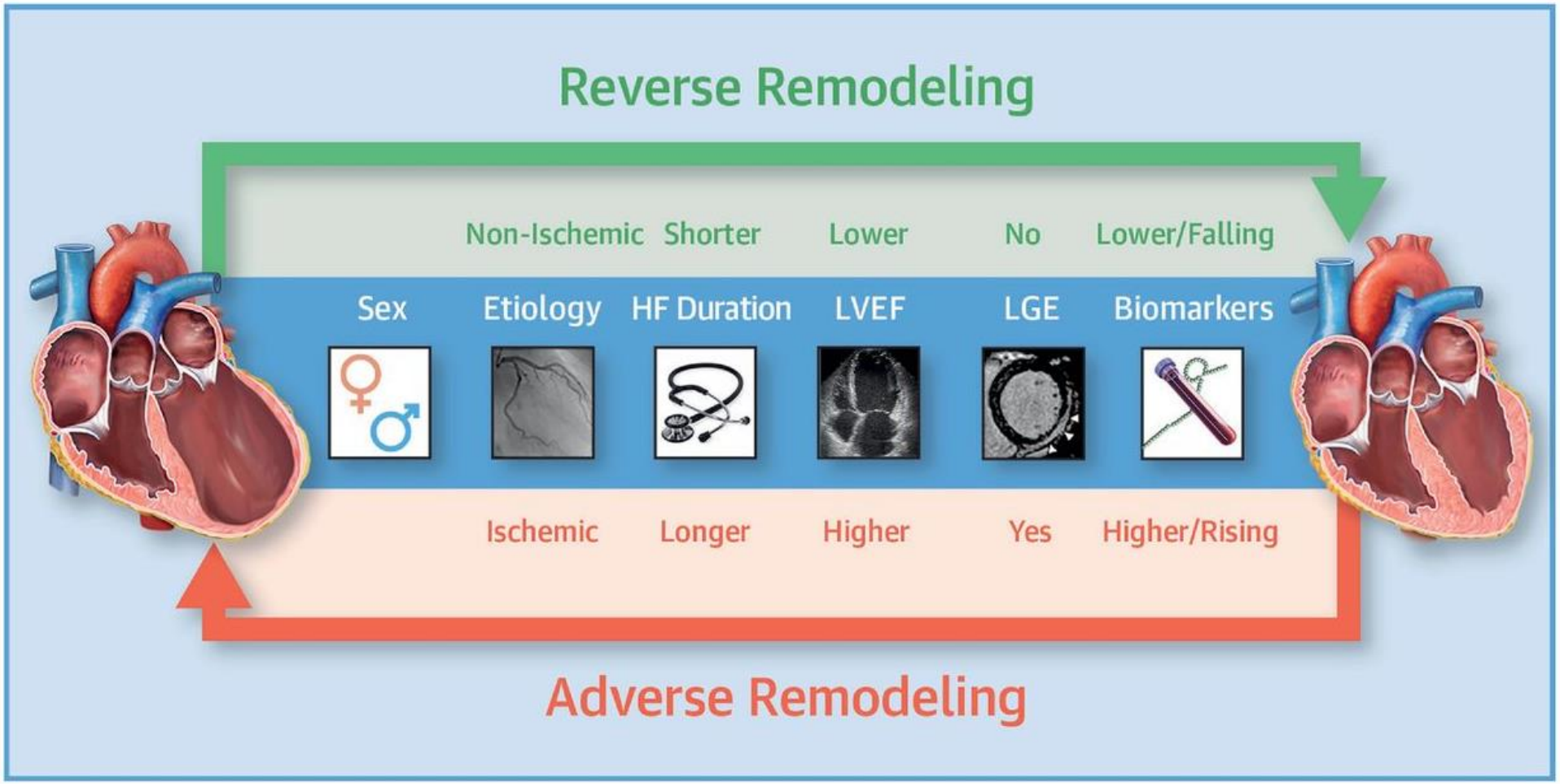
Predicting remodeling



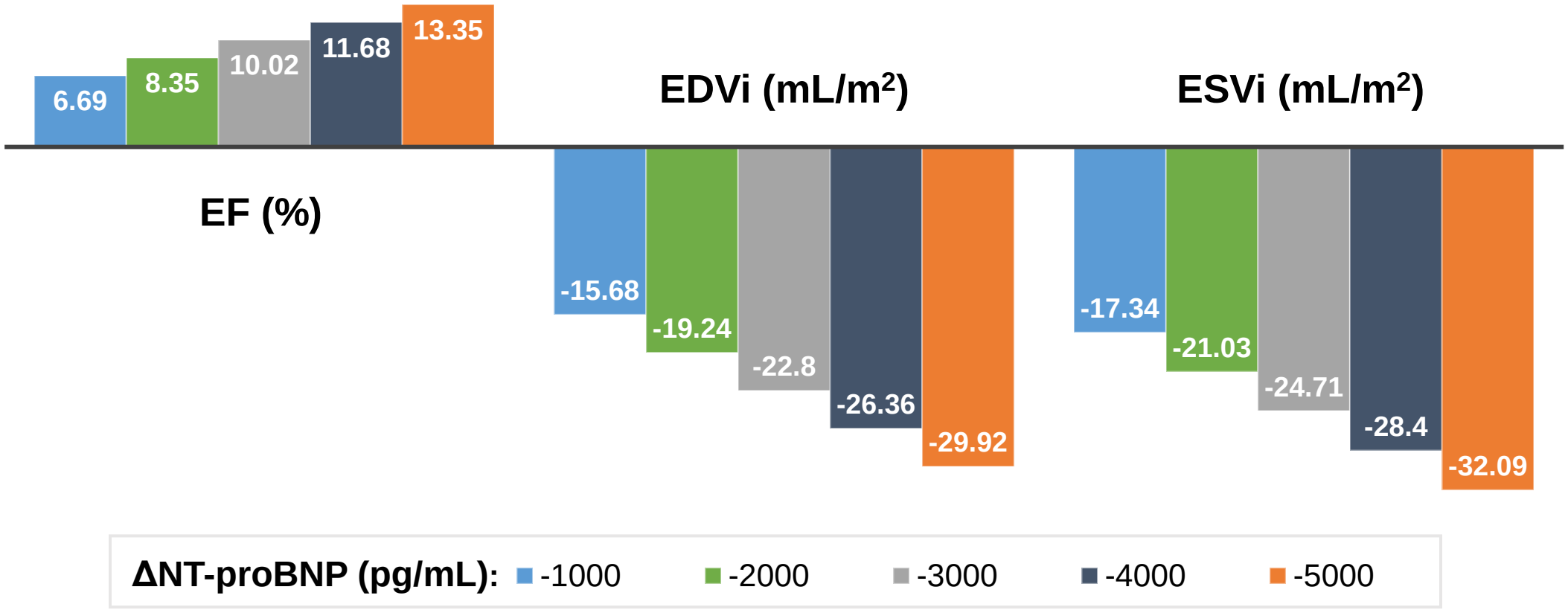
Aimo, A. et al. J Am Coll Cardiol HF. 2019;7(9):782-94.

Biomarkers predictive of remodeling

- BNP, NT-proBNP
- Soluble ST2: a biomarker of myocardial fibrosis and remodeling
- High sensitivity cardiac troponin
- Collagen markers, mimecan, IGFBP7

Change in LV structure and function at 1 year by NT-proBNP reduction

GUIDE-IT
GUIDing Evidence Based Therapy Using Biomarker Intensified Treatment



EF, ejection fraction; EDVi, end-diastolic volume index; ESVi, end-systolic volume index; LV, left ventricular; NTproBNP, N-terminal-pro-B type natriuretic peptide.

Daubert MA, et al. *JACC Heart Fail.* 2019;7:158–168.

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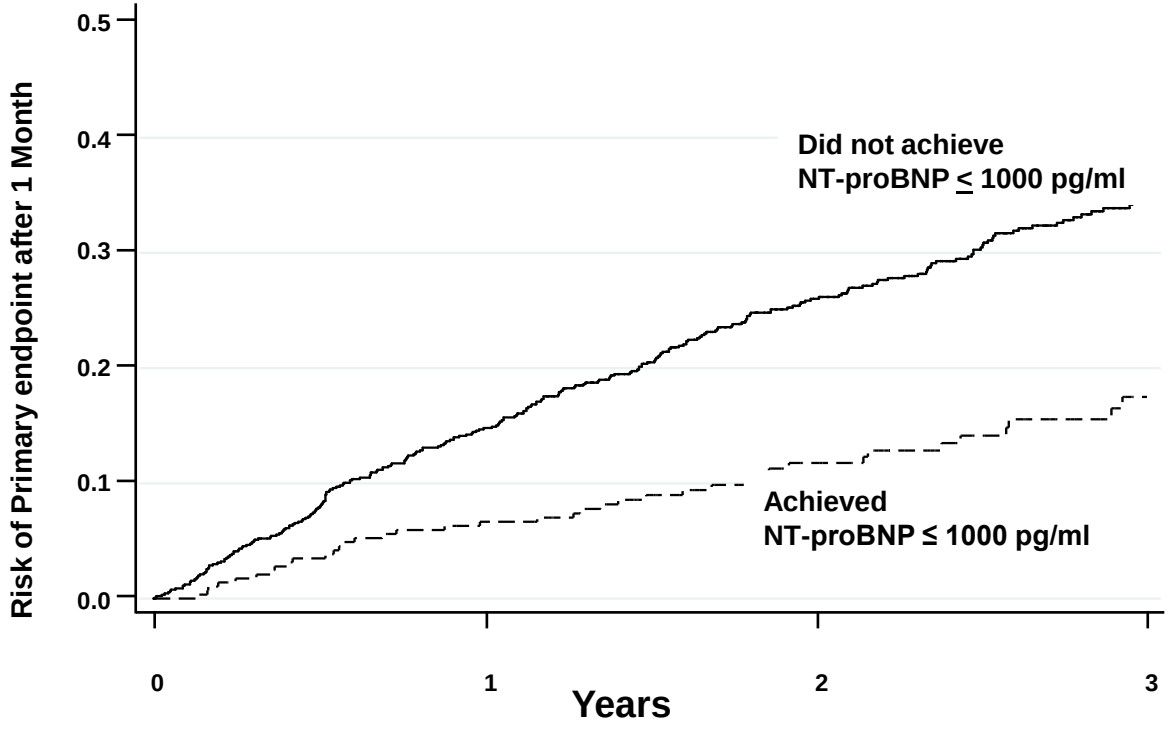
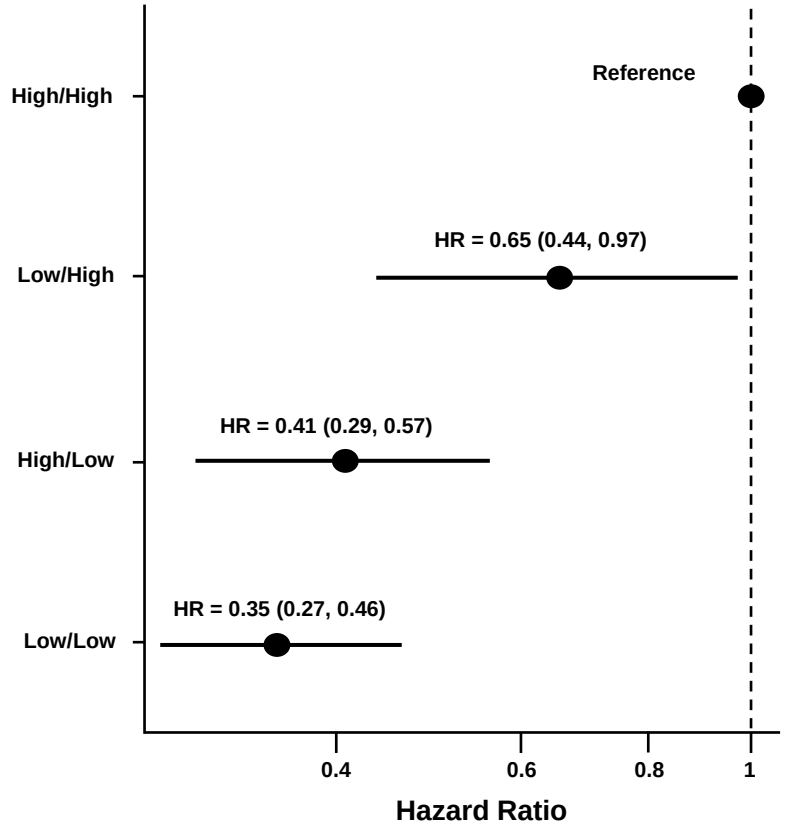
30 day NT-proBNP in PARADIGM





Zile et al. J Am Coll Cardiol. 2016 Dec 6;68(22):2425-2436.

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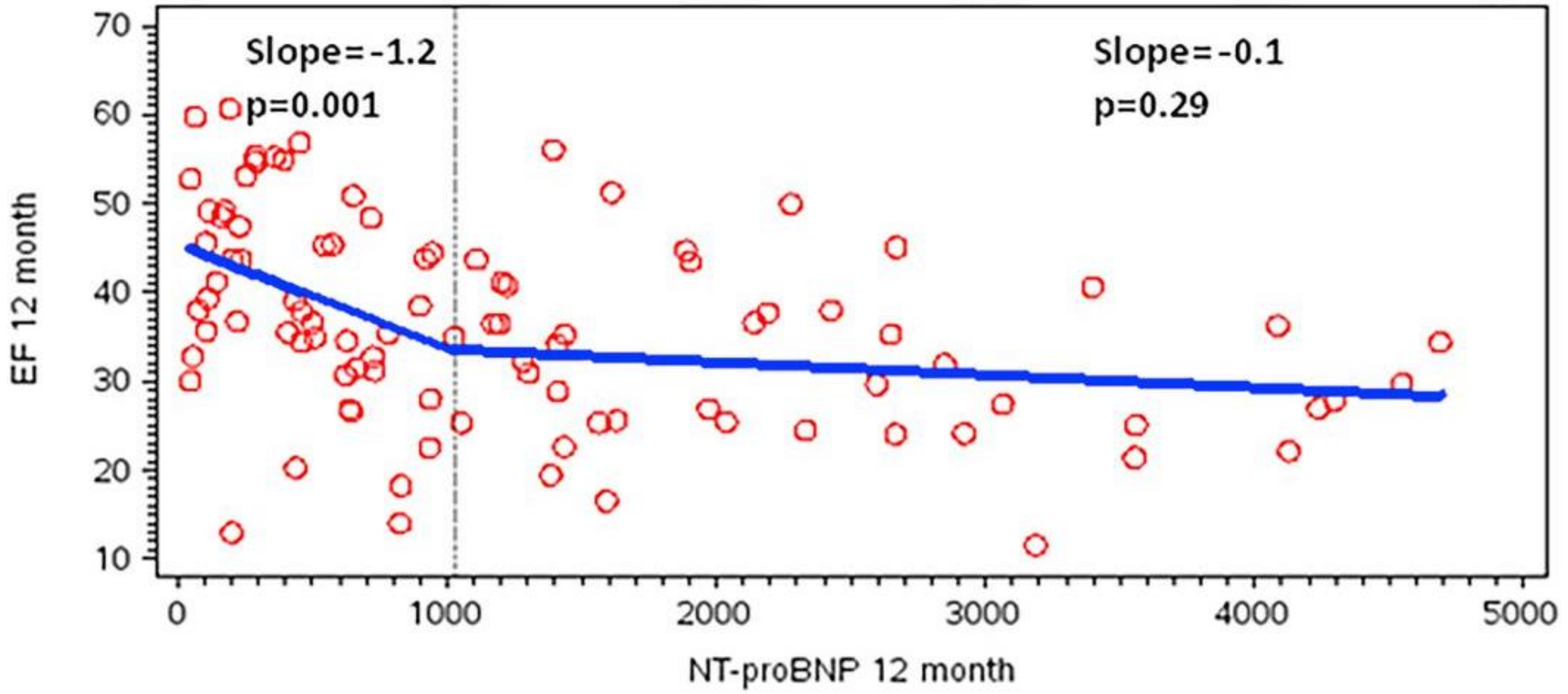
Reverse cardiac remodeling begins to accelerate at an NT-proBNP of 1000 pg/mL



EF, ejection fraction NT-proBNP, N-terminal-pro-B type natriuretic peptide. Daubert MA, et al. *JACC Heart Fail.* 2019;7:158–168.

Guideline-directed medical therapy may improve remodeling indices in HFrEF

Therapy	Impact on remodeling in HFrEF
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SGLT2 inhibitors	No clinical data
ARNI	Strong

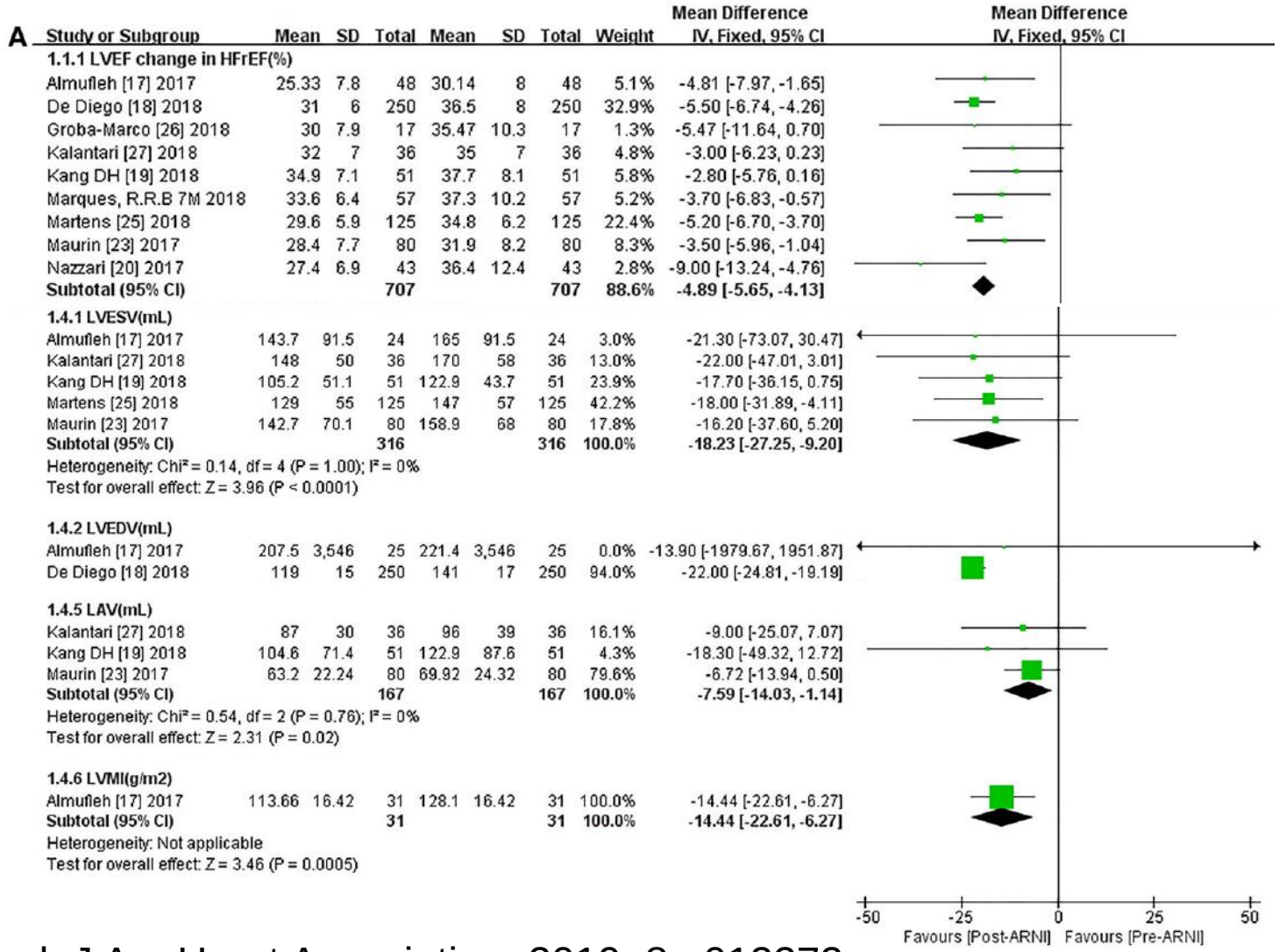
What is known about ARNI and remodeling?

- Martens et al, Cardiovasc Ther, 2018
  - 125 patients with HFrEF treated for median of 118 days
  - LVEF improved (29.6 ± 6% vs 34.8 ± 6%; *P* < .001) and left ventricular end-systolic (LVESV) and end-diastolic volume (LVEDV) decreased (LVESV; 147 ± 57 mL vs 129 ± 55 mL; *P* < .001 and LVEDV; 206 ± 71 mL vs 197 ± 72 mL; *P* = .027)
  - Diastolic function improved
  - Dose-dependent effect was noted for changes in LVEF (*P* < .001) and LVESV (*P* = .031), with higher doses of sacubitril/valsartan leading to more reverse remodeling

What is known about ARNI and remodeling?

- Kang, et al, Circulation 2019
  - 118 patients with heart failure with chronic functional MR secondary to LV dysfunction (mean LVEF at baseline of 34%) randomized to either sacubitril/valsartan or valsartan
  - MR improved with sacubitril/valsartan versus valsartan
  - LV end-diastolic volume index was significantly different in those treated with sacubitril/valsartan (*P*=0.044) but LVEF was no different between groups (+2.5 vs +2.6%; *P*=0.84)

Meta analysis



Pooled studies of sacubitril/valsartan in HFrEF suggested an effect on LVEF, LV volumes, LA volumes, and LV mass.

Wang, et al, J Am Heart Association, 2019; 8:e012272

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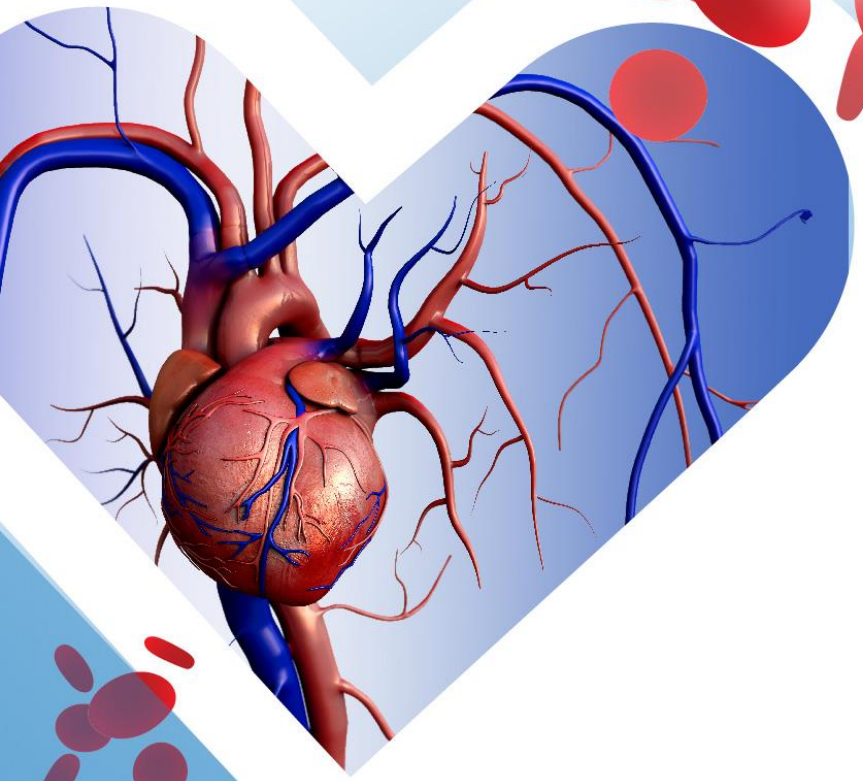


PROVE-HF

Prospective Study of Biomarkers, Symptom Improvement and Ventricular Remodeling During Entresto Therapy for Heart Failure *(PROVE-HF; NCT02887183)*

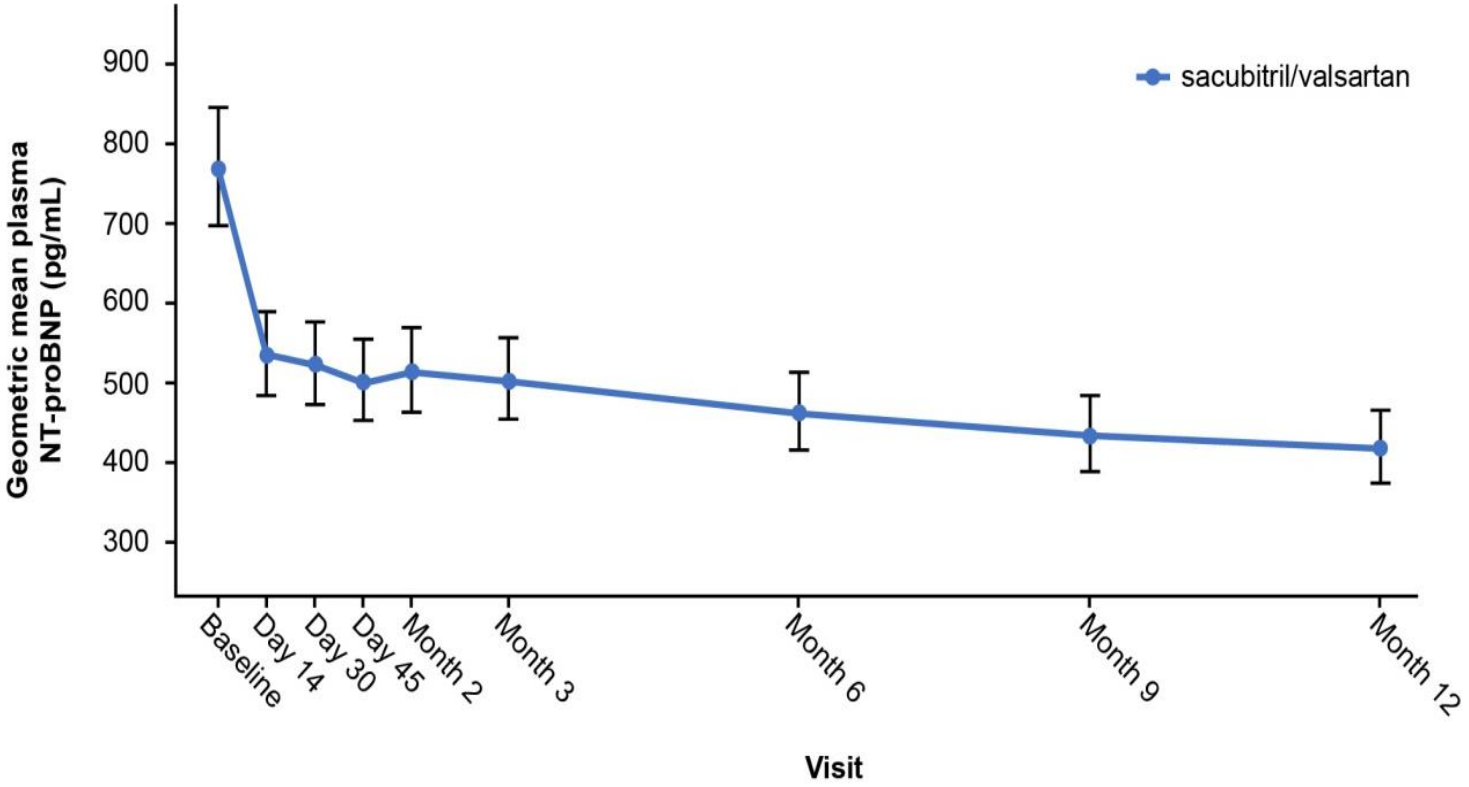
James L. Januzzi MD[1,2], Margaret F. Prescott PhD[3], Javed Butler MD MPH MBA[4], G. Michael Felker MD MHS[5], Alan S. Maisel MD[6], Kevin McCague MA[3], Alexander Camacho PhD[1], Ileana L. Piña MD MPH[7], Ricardo A. Rocha MD[3], Amil M. Shah MD MPH[8], Kristin M. Williamson PharmD[3], and Scott D. Solomon MD[8] on behalf of the PROVE-HF Investigators

[1]Massachusetts General Hospital, [2]Baim Institute for Clinical Research, Boston, MA, USA; [3]Novartis Pharmaceuticals, East Hanover, NJ, USA; [4]University of Mississippi Medical Center, Jackson, MS, USA; [5]Duke University Medical Center and Duke Clinical Research Institute, Durham, NC, USA; [6]University of California, San Diego School of Medicine, San Diego, CA, USA; [7]Detroit Medical Center, Detroit, MI, USA; [8]Brigham and Women's Hospital, Boston, MA, USA

NT-proBNP concentrations

PROVE-HF

Rapid and significant reduction of NT-proBNP was observed, with majority of reduction within the first 2 weeks



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

Januzzi, et al, JAMA 2019

Primary endpoint

PROVE-HF

- **From baseline to 12 months, significant correlations were observed between the change in NT-proBNP concentration and cardiac remodeling parameters.**
- **Parallel latent growth curve analyses demonstrated strong association between early NT-proBNP change and subsequent reverse cardiac remodeling.**

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

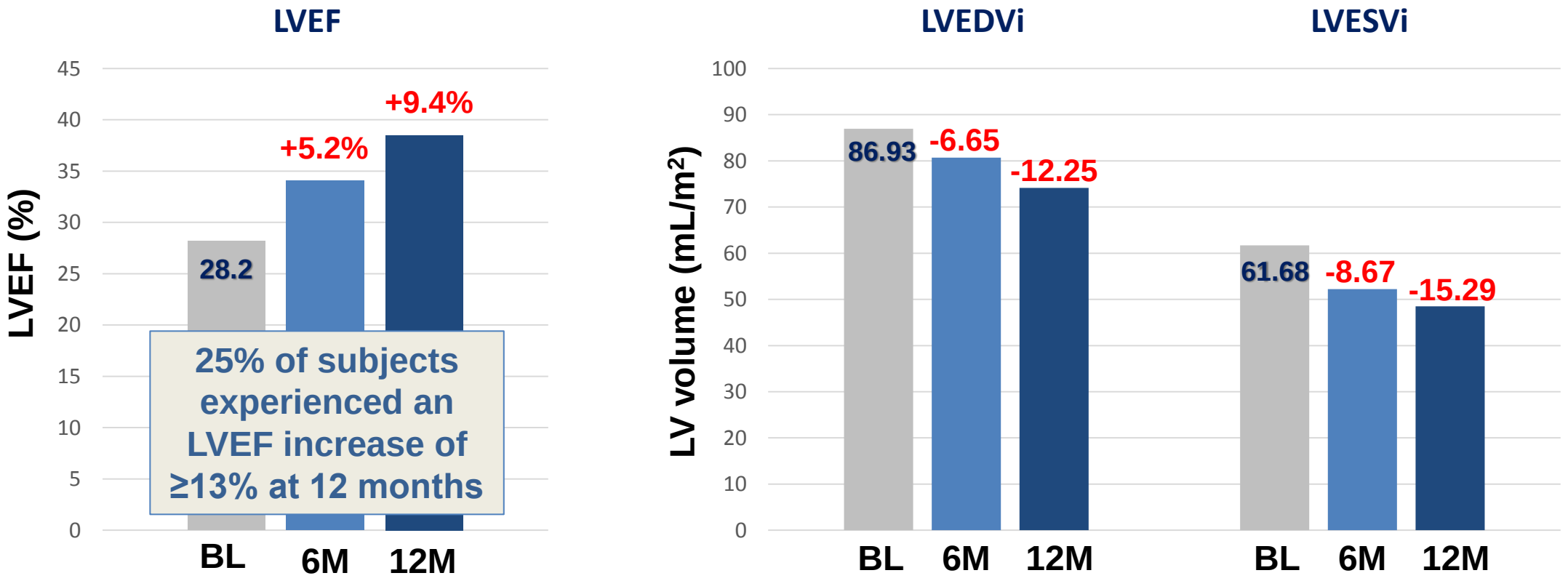
IQR, interquartile range; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; mL, milliliter; LAVi, left atrial volume index; E/E’, ratio of early diastolic filling velocity and early diastolic mitral annular velocity

Januzzi, et al, JAMA 2019

Reverse cardiac remodeling (1)

PROVE-HF

Baseline to 12 months: all P <.001



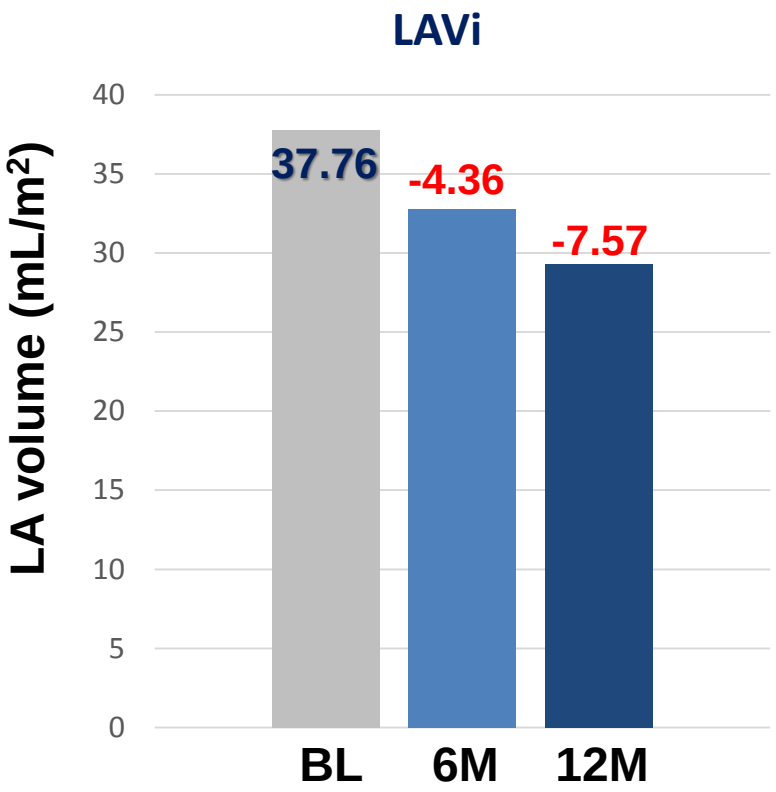
BL, baseline; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; LVESVi, left ventricular end-systolic volume index

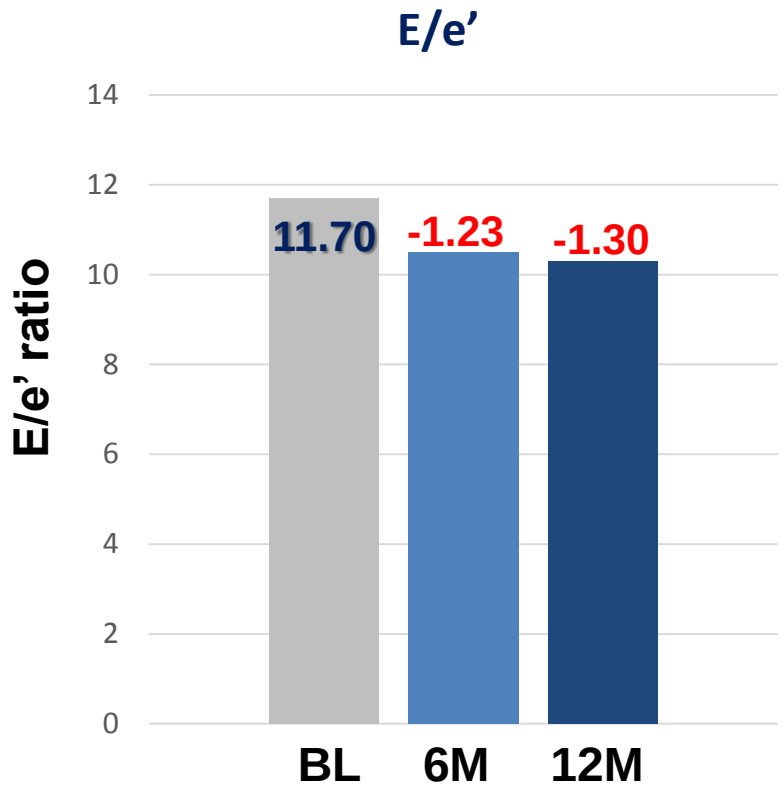
Januzzi, et al, JAMA 2019

Reverse cardiac remodeling (2)

PROVE-HF

Baseline to 12 months: all P <.001





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

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

Januzzi, et al, JAMA 2019

Subgroups of interest

PROVE-HF

- Reverse cardiac remodeling was comparable in each subgroup of interest

All P <0.001 except where noted

New-onset HF/ACEI-ARB naïve (N=118)	
Parameter	**LS Mean change, BL to 12 months (95% CI)**
LVEF (%)	+12.8 (+11.05, +14.5)
LVEDVi (mL/m²)	-13.81 (-15.78, -11.83)
LVESVi (mL/m²)	-17.88 (-20.07, -15.68)
LAVi (mL/m²)	-8.44 (-9.73, -7.15)
E/e'	-2.60 (-3.83, -1.37)

NP < PARADIGM incl criteria* (N=292)	
Parameter	**LS Mean change, BL to 12 months (95% CI)**
LVEF (%)	+9.4 (+8.6, +10.3)
LVEDVi (mL/m²)	-11.32 (-12.24, -10.40)
LVESVi (mL/m²)	-14.15 (-15.15, -13.15)
LAVi (mL/m²)	-7.06 (-7.54, -6.58)
E/e'	-0.93 (-1.43, -0.43)

Not reaching target dose (N=278)	
Parameter	**LS Mean change, BL to 12 months (95% CI)**
LVEF (%)	+9.4 (+8.4, +10.3)
LVEDVi (mL/m²)	-10.99 (-12.21, -9.77)
LVESVi (mL/m²)	-14.32 (-15.67, -12.97)
LAVi (mL/m²)	-7.23 (-7.97, -6.50)
E/e'	-0.46 (-1.32, +0.40); P =NS

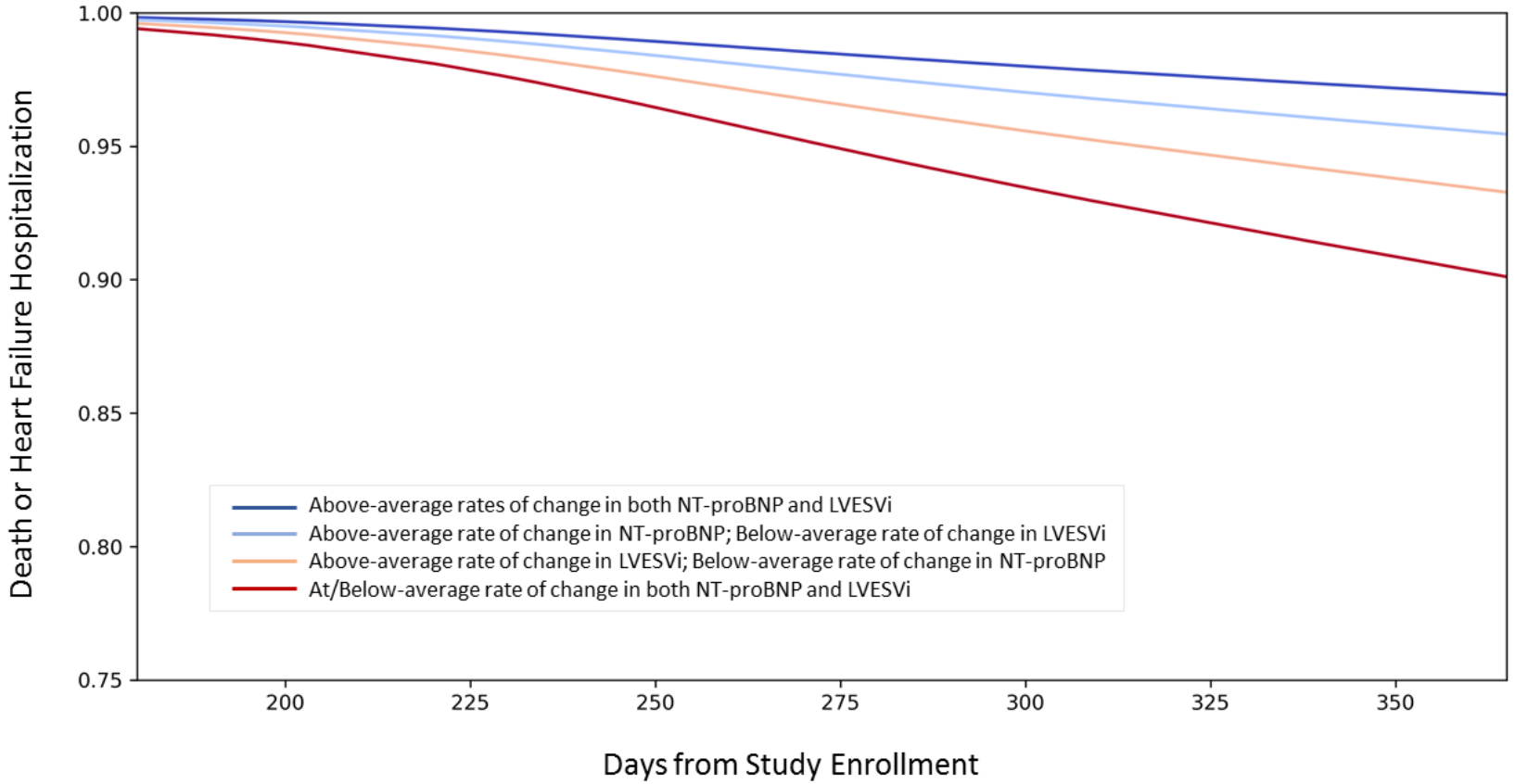
*NT-proBNP < 600 pg/mL if not hospitalized or < 400 pg/mL if hospitalized within the past 12 months; BNP < 150 pg/mL if not hospitalized or < 100 pg/mL if hospitalized for HF within the past 12 months; BL, baseline; LS, least-square; LVEF, left ventricular ejection fraction; LVEDVi, left ventricular end-diastolic volume index; mL, milliliter; LAVi, left atrial volume index; E/E', ratio of early diastolic filling velocity and early diastolic mitral annular velocity; NP, natriuretic peptide.

Januzzi, et al, JAMA 2019

Death or HF hospitalization by 12 months

PROVE-HF

Patients with larger and faster reduction in NT-proBNP and LVESVi by 6 months had lowest rates of subsequent death or HF hospitalization by 12 months



Januzzi et al, Circ Heart Fail. 2020 Jun 2:CIRCHEARTFAILURE119006946

Conclusions

- Progressive, “forward” remodeling of the heart is a pivotal aspect of HFrEF progression and linked to risk for events
- “Reverse” remodeling is associated with lower event rates
- Therapies with favorable effects in HFrEF also tend to variably foster reverse remodeling
- Among available therapies that have the most substantial reverse remodeling effects are CRT, beta blockers, and sacubitril/valsartan