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대한심장학회
심부전연구회
The Korean Society of Heart Failure

How to Manage Stable HF with Recovered or Improved EF

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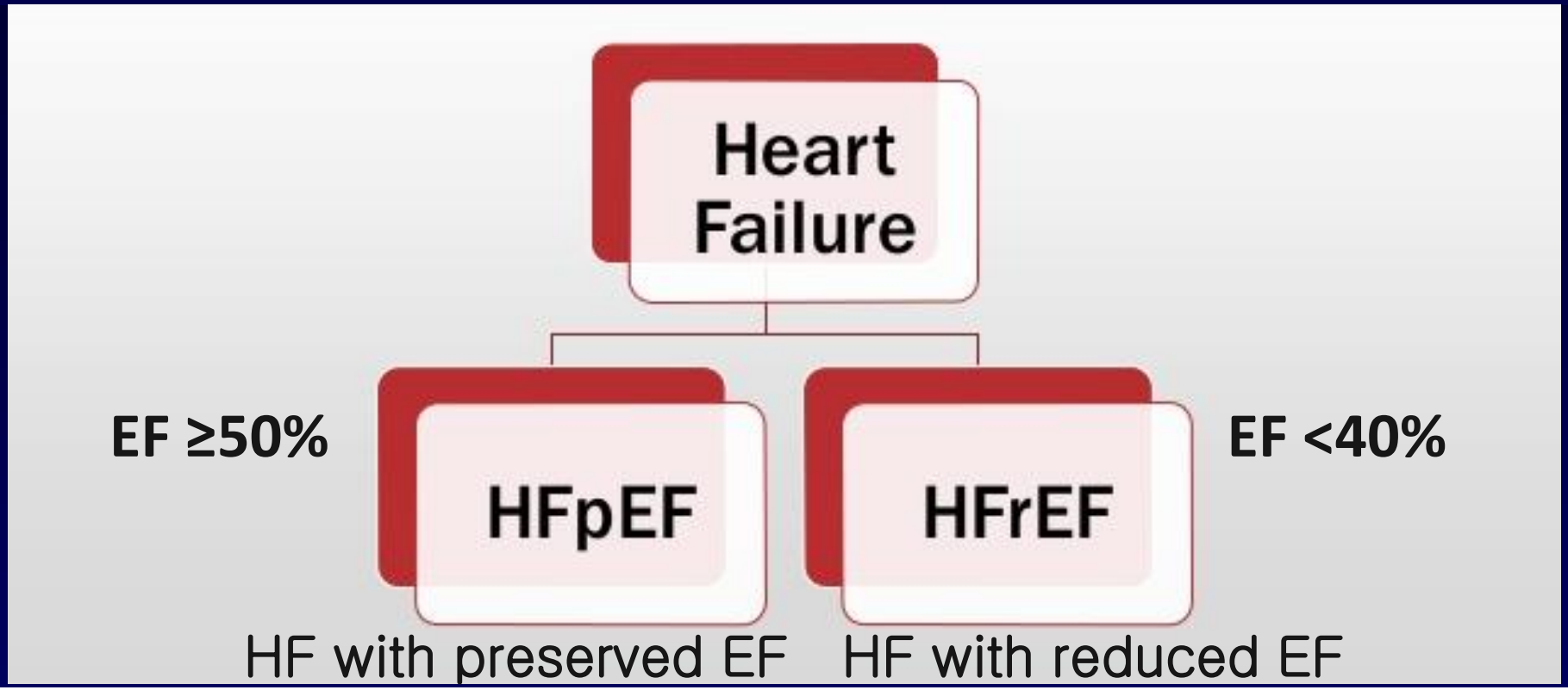
The Korean Society of Cardiology
COI Disclosure

Name of First Author: Jae Yeong Cho

The authors have no financial conflicts of interest to disclose concerning the presentation

Introduction

Classic Classification



Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

2016 ESC guidelines for HF: Eur Heart J 2016;37(27):2129-200

What is HF with recovered EF?

- Heart failure
- Current LVEF ≥ 40 or 50%
- Any previously documented LVEF < 40 or 50%

- Should not be classified with HFpEF (HF with preserved EF)

Punnoose et al. JCF 2011;17:527-532
Basuray et al. Circulation 2014;129:2380-2387
Kalogeropoulos et al. JAMA cardiology 2016;1:510-518

Nomenclature: What is the right word?

- HF with recovered EF = HFrecEF
- HF with improved EF
- HF with better EF

Punnoose et al. JCF 2011;17:527-532
Basuray et al. Circulation 2014;129:2380-2387
Kalogeropoulos et al. JAMA cardiology 2016;1:510-518

U–Penn Heart Failure Cleveland

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

Background—We hypothesized that patients with heart failure (HF) who recover left ventricular function (HF-Recovered) have a distinct clinical phenotype, biology, and prognosis compared with patients with HF with reduced ejection fraction (HF-REF) and those with HF with preserved ejection fraction (HF-PEF).

Methods and Results—The Penn Heart Failure Study (PHFS) is a prospective cohort of 1821 chronic HF patients recruited from tertiary HF clinics. Participants were divided into 3 categories based on echocardiograms: HF-REF if EF was <50%, HF-PEF if EF was consistently ≥50%, and HF-Recovered if EF on enrollment in PHFS was ≥50% but prior EF was <50%. A significant portion of HF-Recovered patients had an abnormal biomarker profile at baseline, including 44% with detectable troponin I, although in comparison, median levels of brain natriuretic factor, soluble fms-like tyrosine kinase receptor-1, troponin I, and creatinine were greater in HF-REF and HF-PEF patients. In unadjusted Cox models over a maximum follow-up of 8.9 years, the hazard ratio for death, transplantation, or ventricular assist device placement in HF-REF patients was 4.1 (95% confidence interval, 2.4–6.8; $P<0.001$) and in HF-PEF patients was 2.3 (95% confidence interval, 1.2–4.5; $P=0.013$) compared with HF-Recovered patients. The unadjusted hazard ratio for cardiac hospitalization in HF-REF patients was 2.0 (95% confidence interval, 1.5–2.7; $P<0.001$) and in HF-PEF patients was 1.3 (95% confidence interval, 0.90–2.0; $P=0.15$) compared with HF-Recovered patients. Results were similar in adjusted models.

Conclusions—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. (*Circulation*. 2014;129:2380-2387.)

Key Words: heart failure ■ myocardium ■ ventricular remodeling

Basuray et al. Circulation 2014;129:2380-2387

Research Emory

JAMA Cardiology | Original Investigation

Characteristics and Outcomes of Adult Outpatients With Heart Failure and Improved or Recovered Ejection Fraction

Andreas P. Kalogeropoulos, MD, MPH, PhD; Gregg C. Fonarow, MD; Vasiliki Georgiopoulou, MD, MPH, PhD; Gregory Burkman, MD; Sarawut Siwamogsatham, MD; Akash Patel, MD; Song Li, MD; Lampros Papadimitriou, MD, PhD; Javed Butler, MD, MPH, MBA

RESULTS The study cohort comprised 2166 participants. Their median age was 65 years, 41.4% (896 of 2166) were female, 48.7% (1055 of 2166) were white and 45.2% (1368 of 2166) black, and 63.2% (1368 of 2166) had coronary artery disease. Preserved (>40%) LVEF at inception was present in 816 of 2166 (37.7%) patients. Of these patients, 350 of 2166 (16.2%) had previously reduced (≤40%) LVEF and were classified as having HFrecEF, whereas 466 of 2166 (21.5%) had no previous reduced LVEF and were classified as having HFpEF. The remaining 1350 (62.3%) patients were classified as having HFrEF. After 3 years, age and sex–adjusted mortality was 16.3% in patients with HFrEF, 13.2% in patients with HFpEF, and 4.8% in patients with HFrecEF ($P < .001$ vs HFrEF or HFpEF). Compared with patients with HFpEF and patients with HFrEF, patients with HFrecEF had fewer all-cause (adjusted rate ratio [RR] vs HFpEF, 0.71; 95% CI, 0.55-0.91; $P = .007$), cardiovascular (RR, 0.50; 95% CI, 0.35-0.71; $P < .001$), and HF-related (RR, 0.48; 95% CI, 0.30-0.76; $P = .002$) hospitalizations and were less likely to experience composite end points commonly used in clinical trials (death or cardiovascular hospitalization and death or HF hospitalization).

CONCLUSIONS AND RELEVANCE Outpatients with HFrecEF have a different clinical course than patients with HFpEF and HFrEF, with lower mortality, less frequent hospitalizations, and fewer composite end points. These patients may need to be investigated separately in outcomes studies and clinical trials.

EXPOSURES Type of HF at baseline, classified as HF with reduced ejection fraction (HFrEF) (defined as current LVEF ≤40%), HF with preserved ejection fraction (HFpEF) (defined as current and all previous LVEF reports >40%), and HF with recovered ejection fraction (HFrecEF) (defined as current LVEF >40% but any previously documented LVEF ≤40%).

Kalogeropoulos et al. JAMA cardiology 2016;1:510-518

HLC 2326 1–9

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http://dx.doi.org/10.1016/j.hlc.2017.02.013

ORIGINAL ARTICLE

Predictors of Left Ventricular Functional Recovery and Their Impact on Clinical Outcomes in Patients With Newly Diagnosed Dilated Cardiomyopathy and Heart Failure

Jae Yeong Cho [a], Kye Hun Kim [a*], Ji Eun Song [b], Ji Eun Kim [a], Hyukjin Park [a], Hyun Ju Yoon [a], Nam Sik Yoon [a], Young Joon Hong [a], Hyung Wook Park [a], Ju Han Kim [a], Youngkeun Ahn [a], My Jeong Gwan Cho [a], Jong Chun Park [a]

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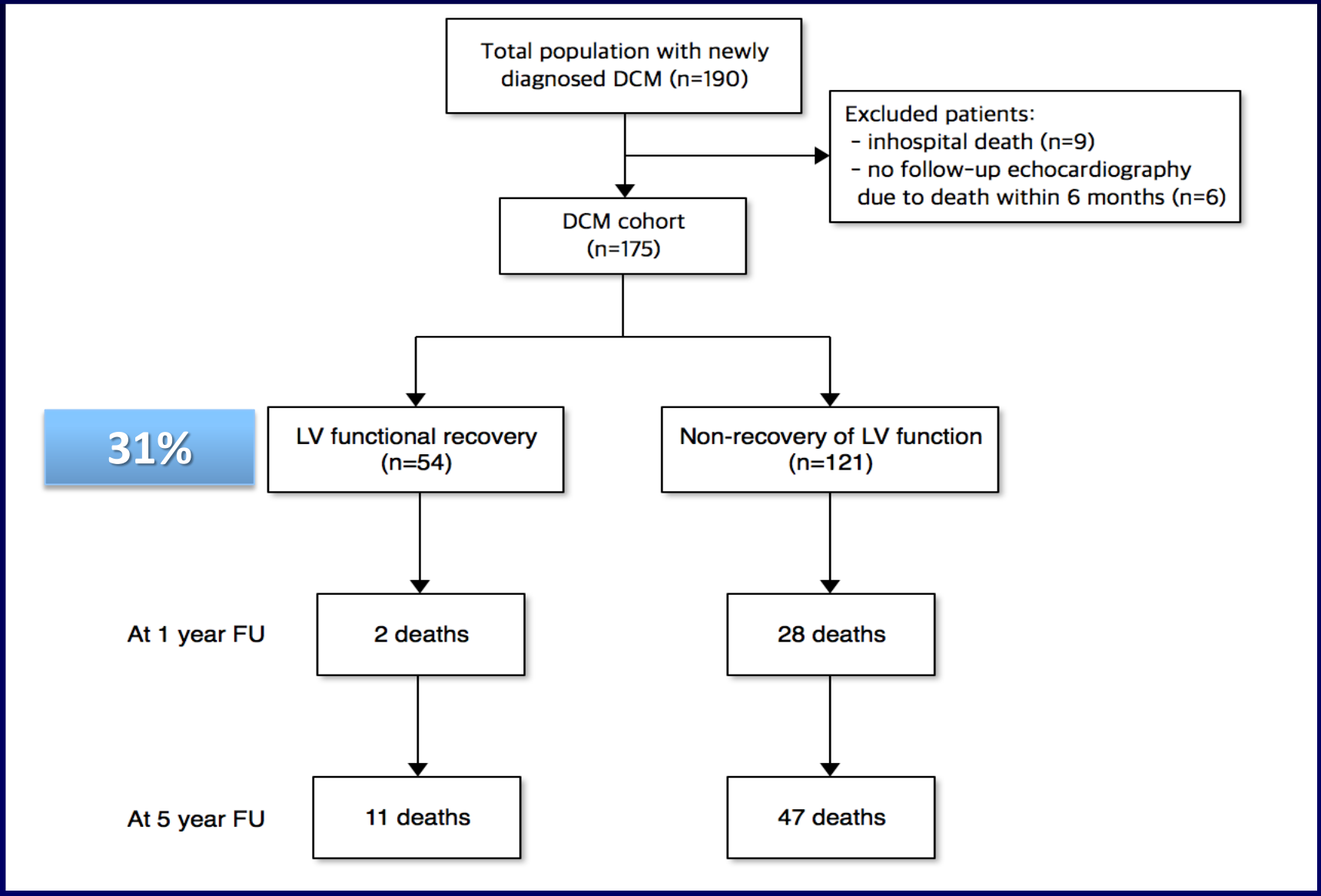
Received 20 October 2016; received in revised form 31 January 2017; accepted 9 February 2017; online published-ahead

Background To identify the predictors of left ventricular functional recovery (LV in acute heart failure (AHF) patients with newly diagnosed dilate

Methods A total of 175 consecutive patients with newly diagnosed DCM according to LVFR on follow-up echocardiography; the recover males) vs. the non-recovered group (n = 121, 60.5 ± 15.1 years, 7 cardiographic findings were compared, and major adverse cardia including death, rehospitalisation, and stroke were analysed.

The primary end-point was LVFR on follow-up echocardiography at six months after discharge from the index AHF. Left ventricular functional recovery was defined as LVEF ≥50% on follow-up echocardiography at six months in the present study [12]. The secondary end-point was the development of major adverse cardiac and cerebrovascular events (MACCE) during five years of clinical follow-up. Death, HF rehospitalisation, or stroke during clinical follow-up was defined as MACCE in the present study, and clinical follow-up ended in the case of death.

Incidence of HFrecEF in newly diagnosed DCM



Cho JY, Kim KH et al. Heart Lung Circ 2017

Recovery in Patients With Dilated Cardiomyopathy With Loss-of-Function Mutations in the Titin Gene

Kevin Luk, BSc[1,2]; Abeer Bakhsh, MD[3,4]; Nadia Giannetti, MD[3,4]; Eleanor Elstein, MD[3]; Mark Lathrop, PhD[5,6]; George Thanassoulis, MD[2,3,7]; James C. Engert, PhD[2,3,6,7]

31 recovery out of 141 = 22%

Table. Characteristics of Patients With Dilated Cardiomyo

Clinical Characteristics	No. (%) Recovered EF (n = 31)	Nonrecovered EF (n = 82)	Transplant (n = 28)	*P* Value[a]
Male	21 (67.7)	52 (63.4)	22 (78.6)	>.99
Age at diagnosis, mean (SD), y	53.6 (11.9)	54.8 (12.1)	49.7 (9.4)	>.99
Worst LVEF, median (IQR)[b]	20 (17.5-30.0)	15 (15.0-20.0)	15 (12.5-15.0)[c]	<.001
Best LVEF, median (IQR)[d]	60 (50.0-65.0)	40 (30.0-45.0)	30 (30.0-33.7)[e]	<.001
Family history	8 (25.8)	13 (15.9)	11 (39.3)	.63
Diabetes	8 (25.8)	23 (28.0)	9 (32.1)	.82
Hypertension	10 (32.3)	36 (43.9)	13 (46.4)	.30
Chemotherapy	0	1 (1.2)	1 (3.6)	>.99
Peripartum	1 (3.2)	2 (2.4)	1 (3.6)	>.99
Stimulant use	2 (6.5)	3 (3.7)	0	.30
High alcohol intake	6 (19.4)	8 (9.8)	2 (7.1)	.12
Arrhythmia	12 (38.7)	35 (42.7)	12 (42.9)	.84
TTNtv present, No./total No. (%)[f]	4/28 (14.3)	15/76 (19.7)	7/24 (29.2)	.44

Abbreviations: EF, ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; TTNtv, titin truncating variant.

[a] Tests were performed using *t* test for age at diagnosis, Mann-Whitney test for worst LVEF and best LVEF, and Fisher exact test for all other clinical characteristics. All *P* values are for recovered EF vs the other 2 groups combined.

[b] For patients with nonrecovered EF or transplant, n = 88. Worst LVEF measures are always recorded pretransplant.

[c] n = 6.

[d] For patients with nonrecovered EF or transplant, n = 87. Best LVEF measures are always recorded pretransplant.

[e] n = 5.

[f] For TTNtv present, n = 128.

Prevalence of HFrecEF (Cross-sectional)

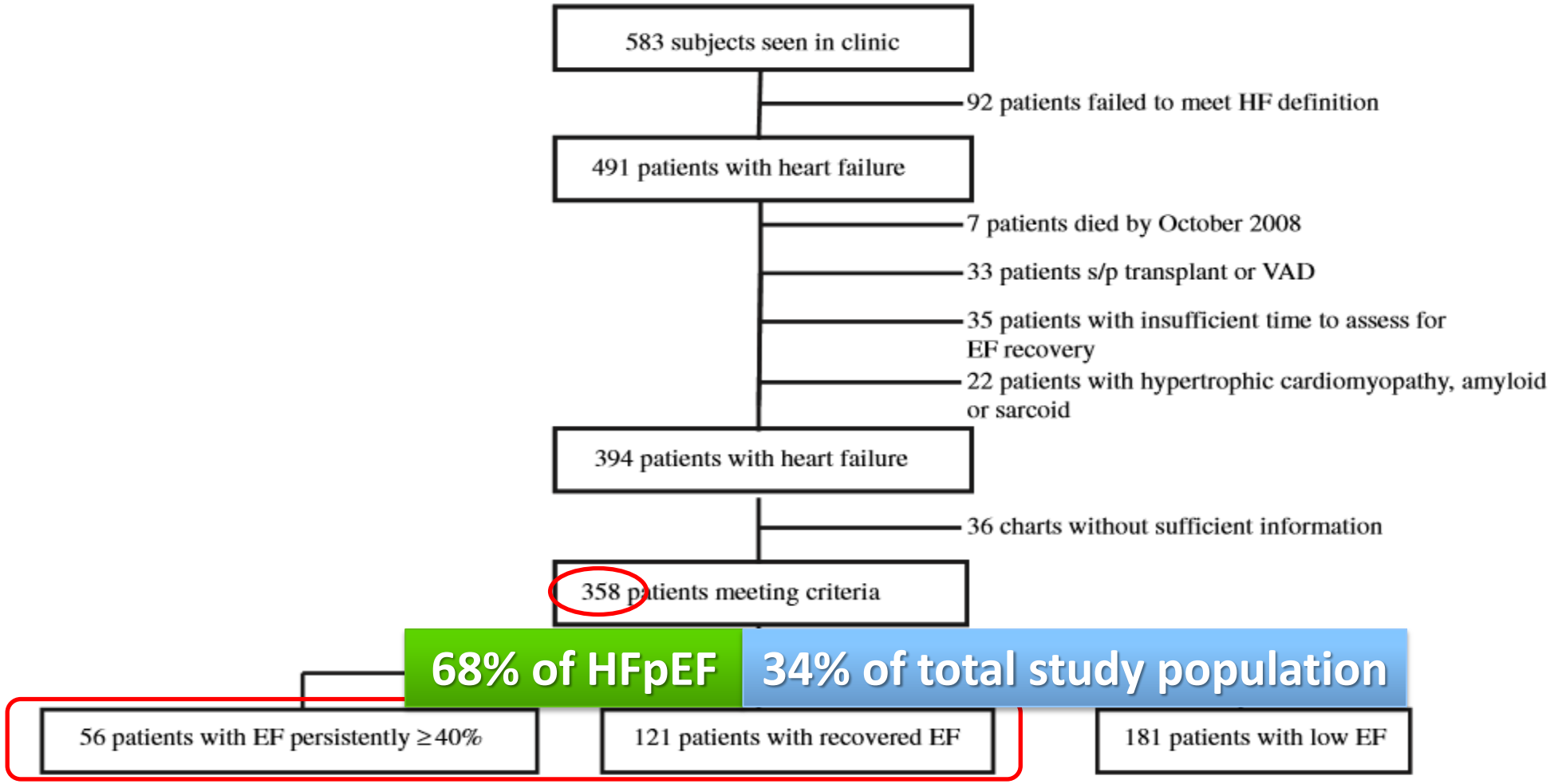
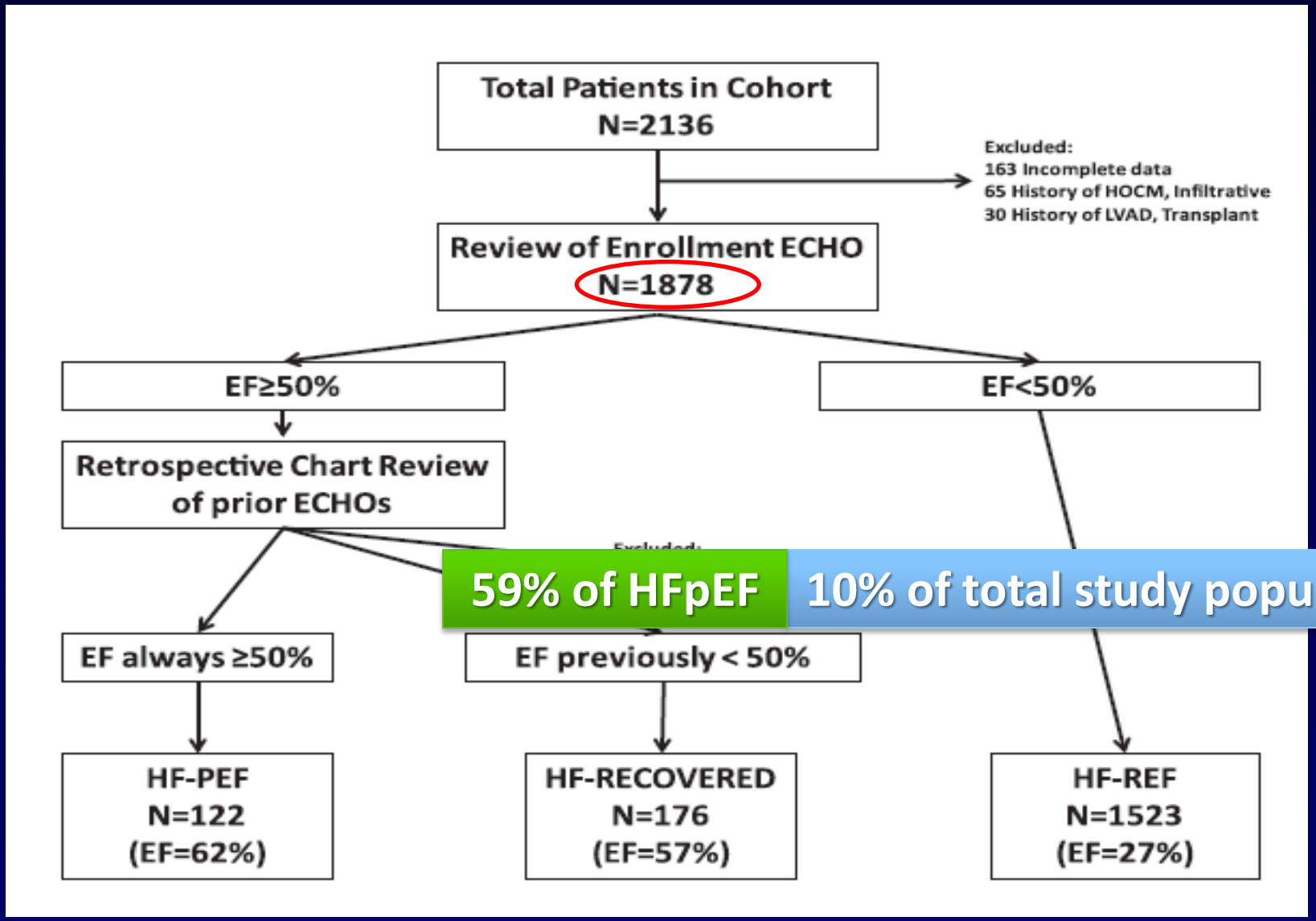


Fig. 1. Flow diagram of patient selection and classification. Of 583 consecutive patients initially screened, 358 patients met inclusion criteria and were sorted into 3 categories based on most recent and lowest measured ejection fraction (EF). HF, heart failure; VAD, ventricular assist device.

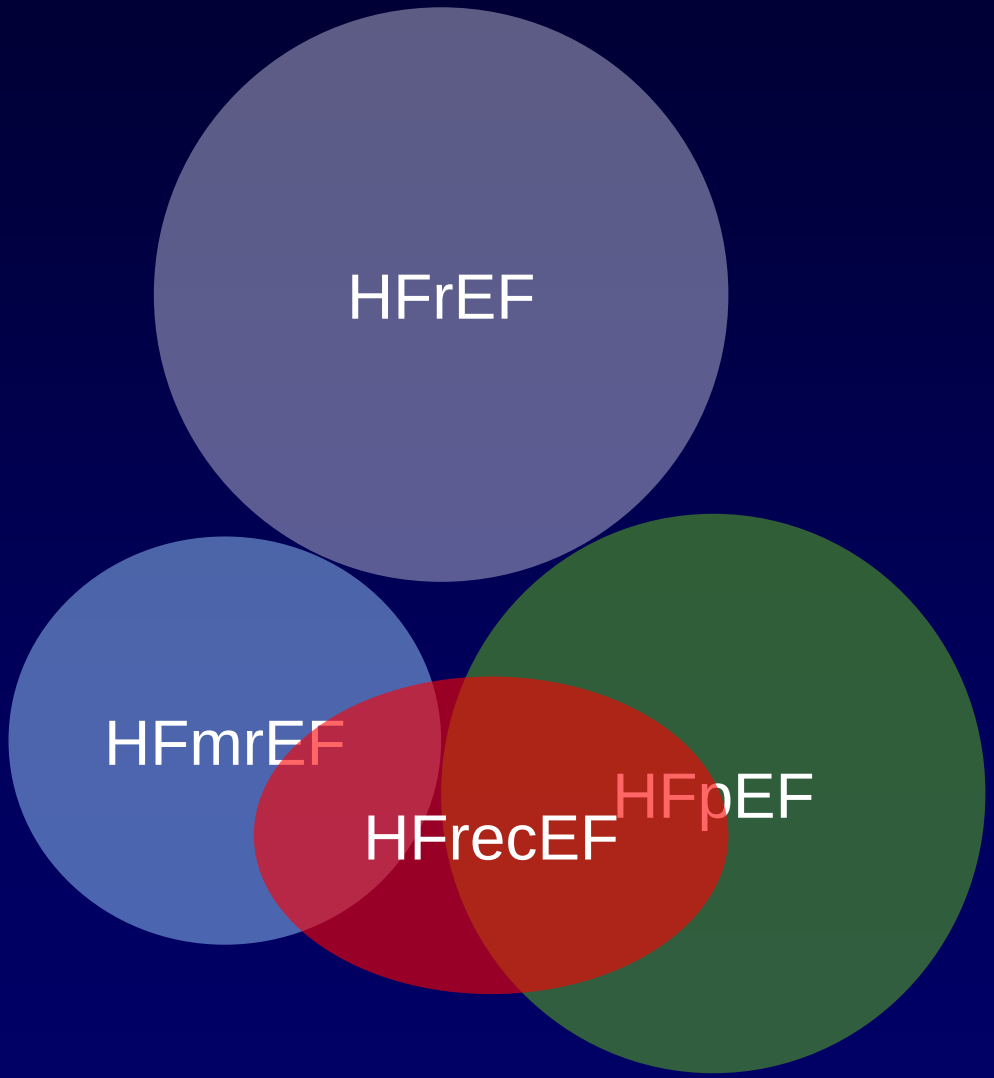
Punnoose et al. JCF 2011;17:527-532

Prevalence of HFrecEF (Cross-sectional)



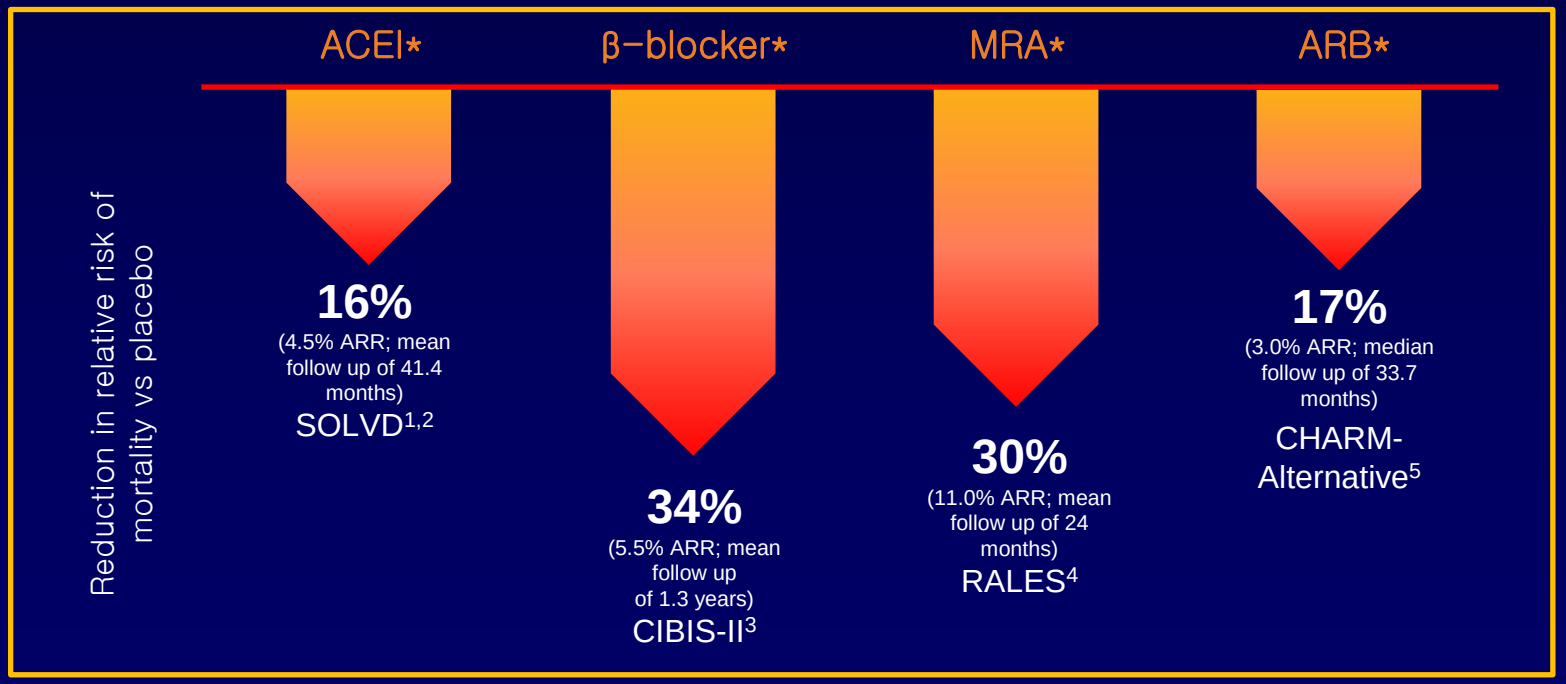
Basuray et al. Circulation 2014;129:2380-2387

Prevalence of HFrecEF (Cross-sectional)



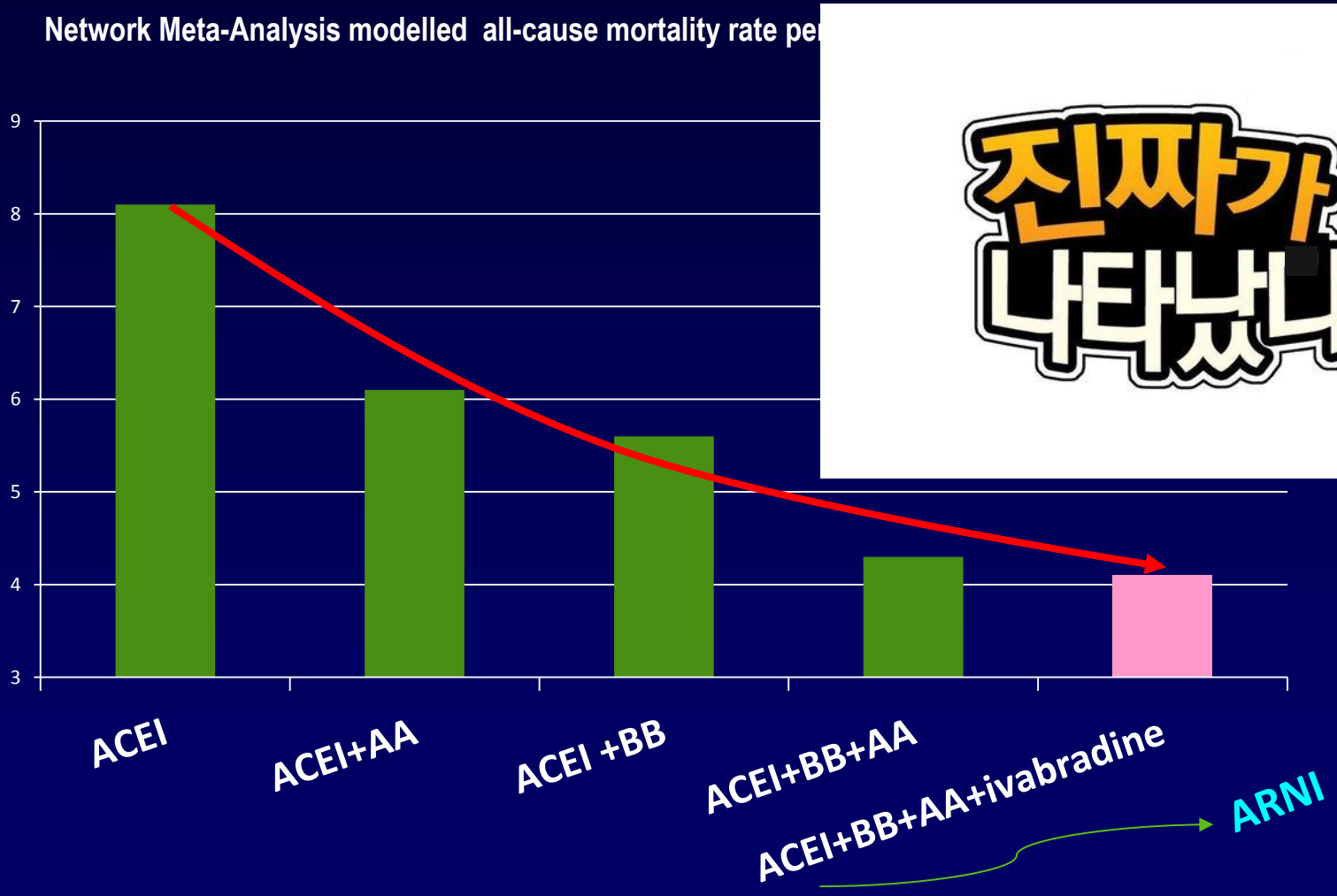
Emerging distinct HF spectrum

- **Disease-modifying agents**
  - **ACEi/ARB, BB, MRA**



Reduced Mortality

As HF recovery increases, HFrecEF emerges



Characteristics of HFrecEF

HF with recovered EF vs. HFpEF

Clinical Investigations

Heart Failure With Recovered Ejection Fraction: A Distinct Clinical Entity

LYNN R. PUNNOOSE, MD,[1] MICHAEL M. GIVERTZ, MD,[2] ELDRIN F. LEWIS, MD, MPH,[2] PARAKASH PRATIBHU, MBA, MPH,[2] LYNNE W. STEVENSON, MD,[2] AND AKSHAY S. DESAI, MD, MPH[2]

New York, New York; and Boston, Massachusetts

- 60-70% of HFpEF had recovered from a previously low EF
- Younger age
- Lower prevalence of HTN, DM, AF
- Larger LV chamber size
- Less likely to have ischemic heart disease

Punnoose et al. JCF 2011;17:527-532

HF with recovered EF vs. HFpEF

Heart Failure

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

- Less severe symptoms - NYHA class I or II
- More BB, ACEi/ARB
- BP higher than HFrEF, but lower than HFpEF

Basuray et al. Circulation 2014;129:2380-2387

Biochemically distinct HFrecEF

Table 2. Serum Biomarkers Collected at Enrollment

	Reduced (n=1187)	Preserved (n=94)	Recovered (n=142)	*P* Value*
BNP, pg/mL	214 (65, 681)	77 (39, 234)	66 (25, 159)	<0.001
PlGF, pg/mL	18.8 (15.2, 23.1)	18.5 (15.6, 22.5)	18.4 (15.2, 22.3)	0.86
sFlt-1, pg/mL	311 (261, 384)	310 (267, 363)	281 (247, 326)	<0.001
hsCRP, mg/L	0.37 (0.15, 0.92)	0.34 (0.15, 0.98)	0.26 (0.11, 0.70)	0.11
MPO, pmol/L	136 (94, 224)	165 (106, 262)	130 (94, 207)	0.20
ST2, ng/mL	24.7 (19.8, 41.3)	27.9 (21.5, 40.0)	25.1 (18.2, 34.7)	0.037
TnI				<0.001
Detectable, n (%)	810 (68)	45 (48)	63 (44)	
TnI, median (IQR) , ng/mL	0.020 (0.010–0.040)	0.010 (0.010–0.030)	0.010 (0.010–0.020)	
Creatinine, mg/dL	0.93 (0.77, 1.27)	0.90 (0.77, 1.39)	0.82 (0.72, 1.12)	0.003
Uric acid, mg/dL	7.0 (5.7, 8.9)	7.2 (5.5, 8.6)	6.5 (5.1, 8.6)	0.035

Values are median (25th, 75th percentiles) unless noted otherwise. BNP indicates B-type natriuretic peptide; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; MPO, myeloperoxidase; PlGF, placental growth factor; sFlt-1, soluble fms-like tyrosine kinase receptor-1; ST2, soluble Toll-like receptor-2; and TnI, troponin I.

- Increased oxidative stress
- Cardiomyocyte injury and stress

Basuray et al. Circulation 2014;129:2380-2387

Functional capacity: 40/M with DCM

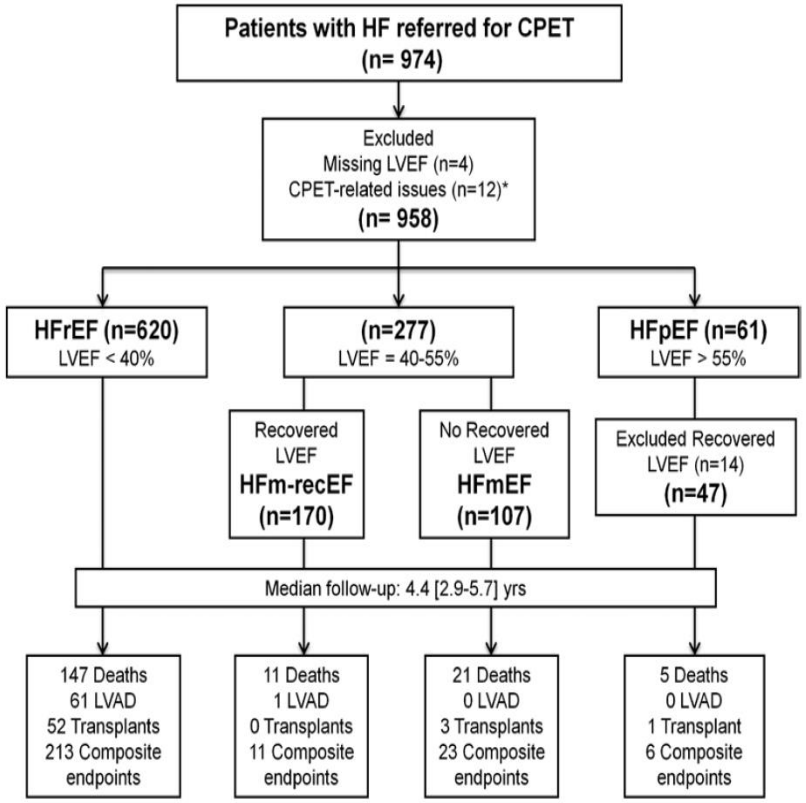
- 2015/05/20 HFrEF
  - LVEDD 62mm
  - EF 28%
  - $VO2_{max}$ 18.55 ml/kg/min (5.3 METs)

- 2015/11/27 HFrecEF
  - LVEDD 49mm
  - EF 57%
  - $VO2_{max}$ 16.8 ml/kg/min (4.8 METs)

Heart Failure and Midrange Ejection Fraction

Implications of Recovered Ejection Fraction for Exercise Tolerance and Outcomes

Wilson Nadruz, Jr, MD, PhD; Erin West, MSc; Mário Santos, MD; Hicham Skali, MD, MSc; John D. Groarke, MBBCh, MPH; Daniel E. Forman, MD; Amil M. Shah, MD, MPH



Variables	HFrEF, n=620 (66%)	HFm-recEF, n=170 (18%)	HFmEF, n=107 (11%)	HFpEF, n=47 (5%)
Ventilatory				
Peak Vo_2, mL/min/Kg	14.4±5.2	18.0±6.3*	17.2±8.8*	14.6±7.9†
% Predicted peak Vo_2	56.7±18.3	70.6±18.4*	70.0±23.6*	69.0±20.8*
VE/Vco_2 slope	34.5±9.2	28.8±5.8*	30.6±6.4*	32.1±7.9
Hemodynamic				
Resting HR, beats per minute	74.2±14.5	69.1±12.7*	69.5±13.7*	69.9±12.1
Peak HR, beats per minute	121.3±28.1	131.8±24.8*	124.4±31.1	114.5±27.3†
Chronotropic index	0.52±0.28	0.64±0.24*	0.57±0.28	0.51±0.26†
Resting SBP, mm Hg	114.1±18.9	120.7±19.8*	120.1±19.2*	129.2±20.9*,†,‡
Peak SBP, mm Hg	134.9±26.9	151.8±28.0*	151.6±30.4*	156.1±33.5*
Resting DBP, mm Hg	73.5±11.1	75.3±11.9	73.8±11.3	74.6±9.8
Peak DBP, mm Hg	74.4±12.5	77.4±11.8*	76.0±12.7	75.6±12.0
Peak RER	1.19±0.13	1.20±0.12	1.20±0.13	1.15±0.12†

Nadruz et al. Circ Heart Fail. 2016;9:e002826

Limitation in restoration of global longitudinal strain

KSE 2016
The 41st Annual Scientific Meeting
November 19 Sat. ~ 20 Sun, 2016
Sheraton Grand Wakerhill Hotel, Seoul

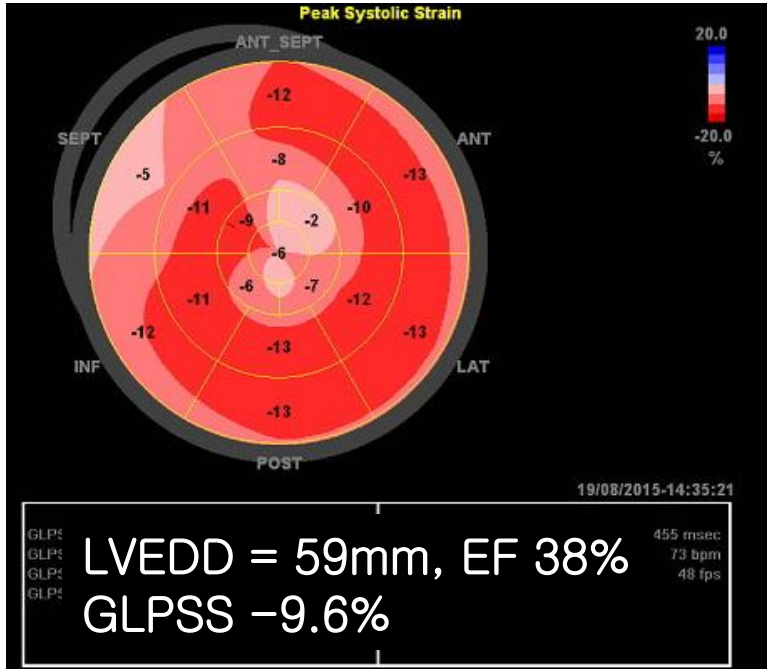
Global Longitudinal Strain is not Completely Recovered in Dilated Cardiomyopathy with Recovered Left Ventricular Ejection Fraction

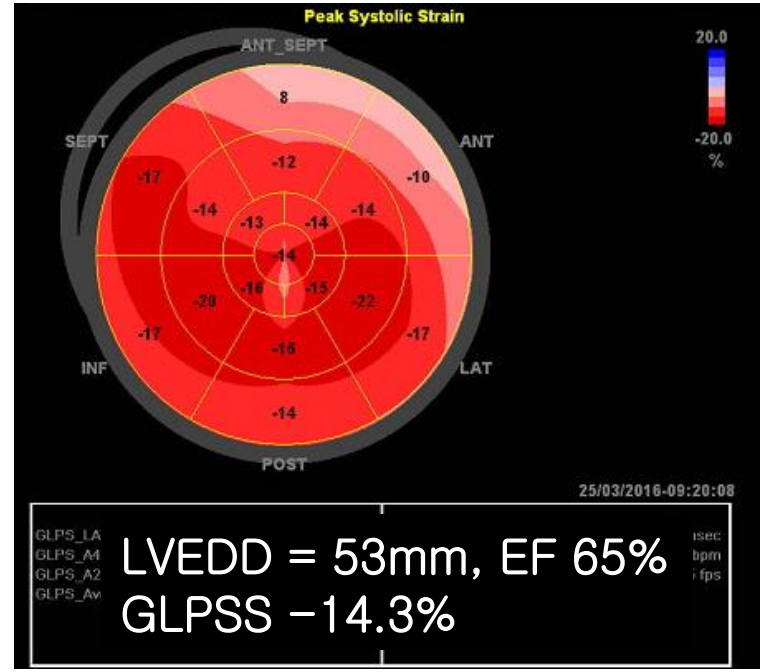
Jae Yeong Cho, Kye Hun Kim, Ji Eun Kim, Hyukjin Park, Hyun Ju Yoon, Jong Chun Park

Department of Cardiovascular Medicine, Chonnam National University Hospital, Gwangju, Republic of Korea

Results

- **Similarly, initial GLPSS was not different between groups (-8.6±3.7% vs. -7.9±3.3%, p=0.368), but FU GLPSS was better in the recovered group (-15.1±2.8 vs. -9.6±3.9, p <0.001).**

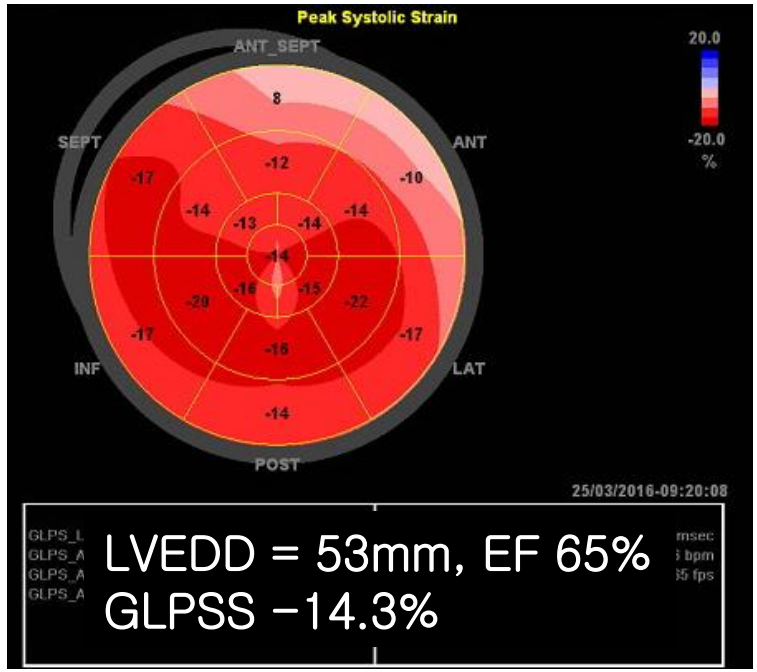


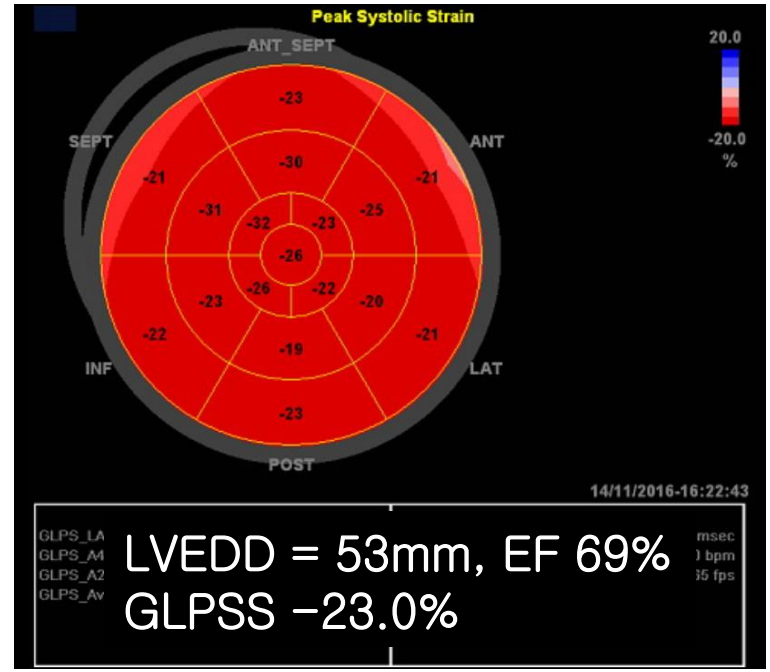


Cho, Kim et al. KSE 2016

Results

- **However, GLPSS in the recovered group was always worse than GLPSS in age- and sex-matched normal populations (-15.1±2.8 vs. -20.8±2.0, p<0.001).**





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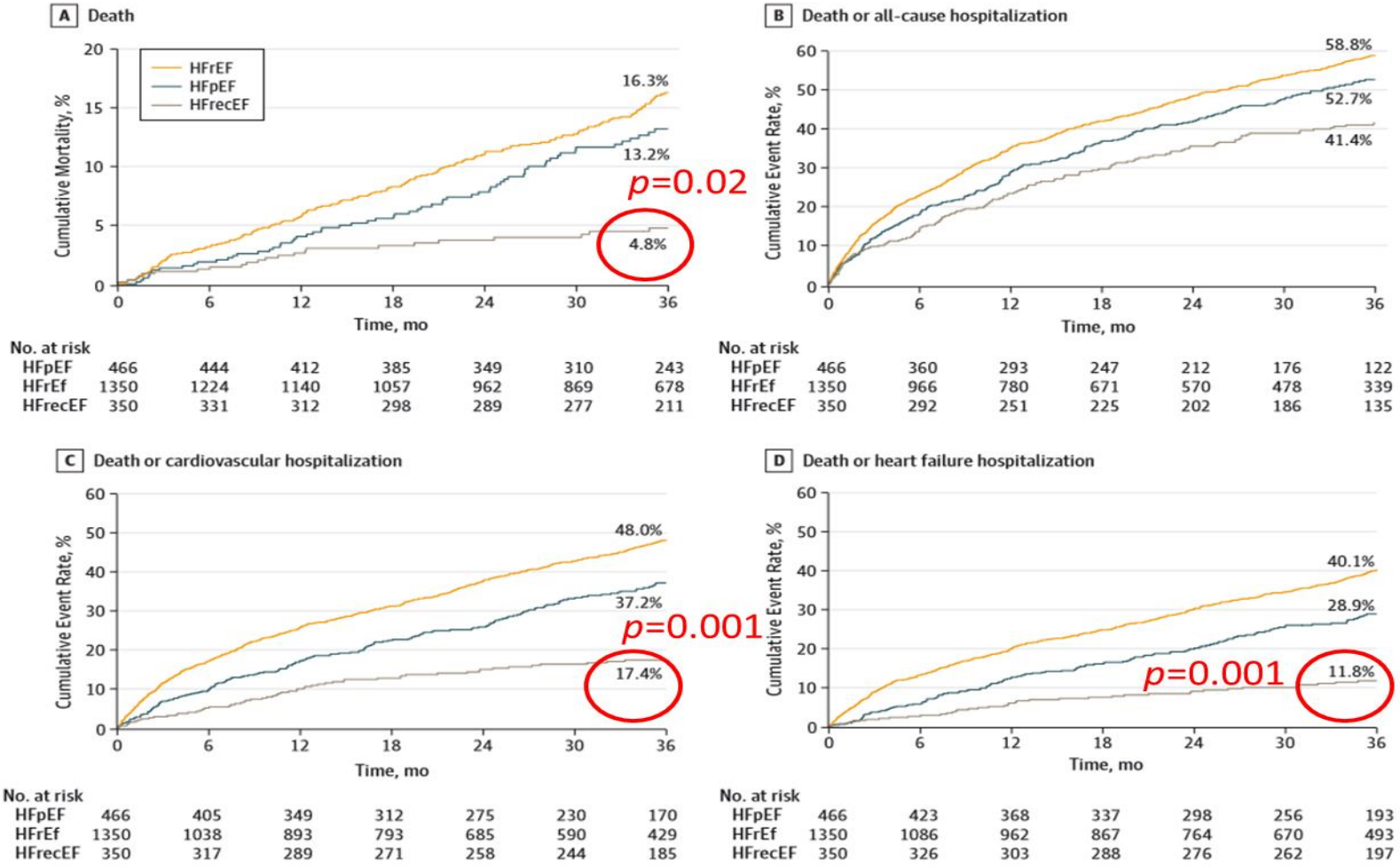
Prognosis of HFrecEF

Clinical Outcomes of HFrecEF

Figure. Kaplan-Meier Curves, Adjusted for Age and Sex, Across the 3 Heart Failure Groups

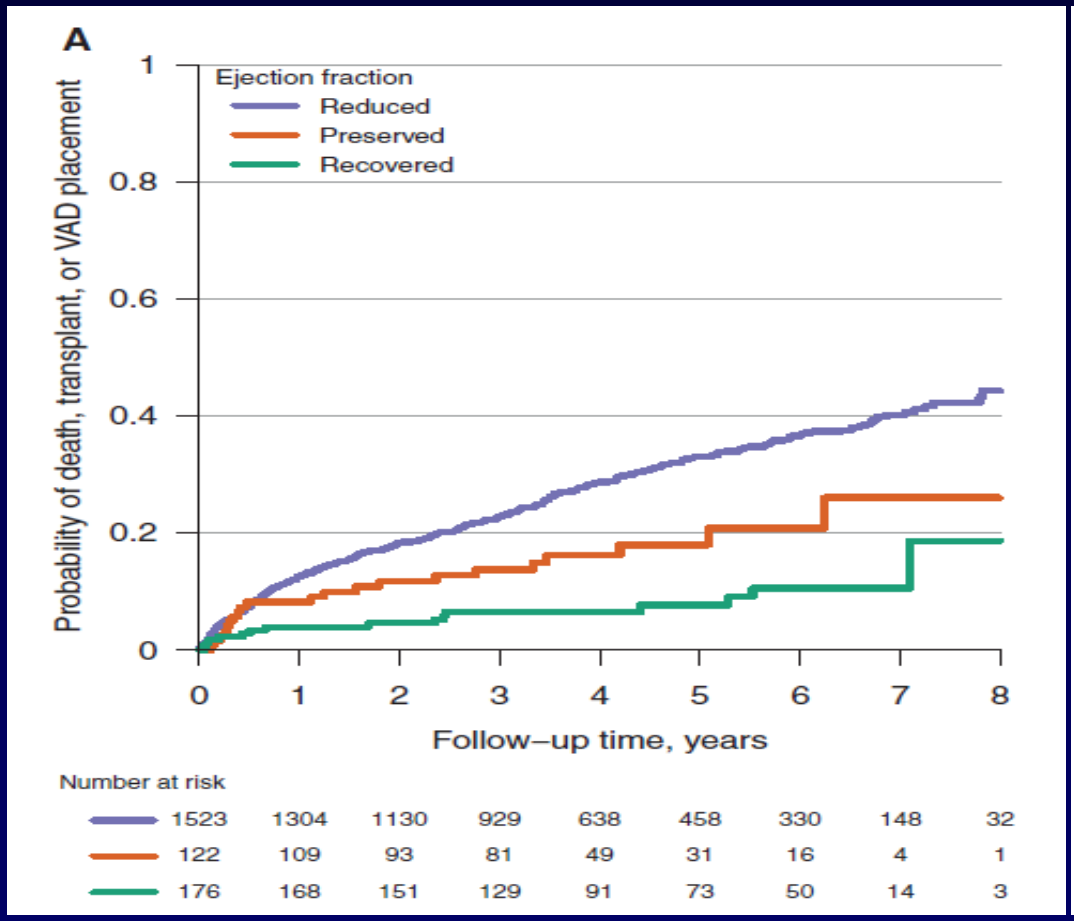


The stratified log-rank χ^2_2 was 15.0 ($P < .001$) for difference in mortality between groups. HFpEF indicates heart failure with preserved ejection fraction; HFrecEF, heart failure with recovered ejection fraction; and HFrEF, heart failure with reduced ejection fraction.

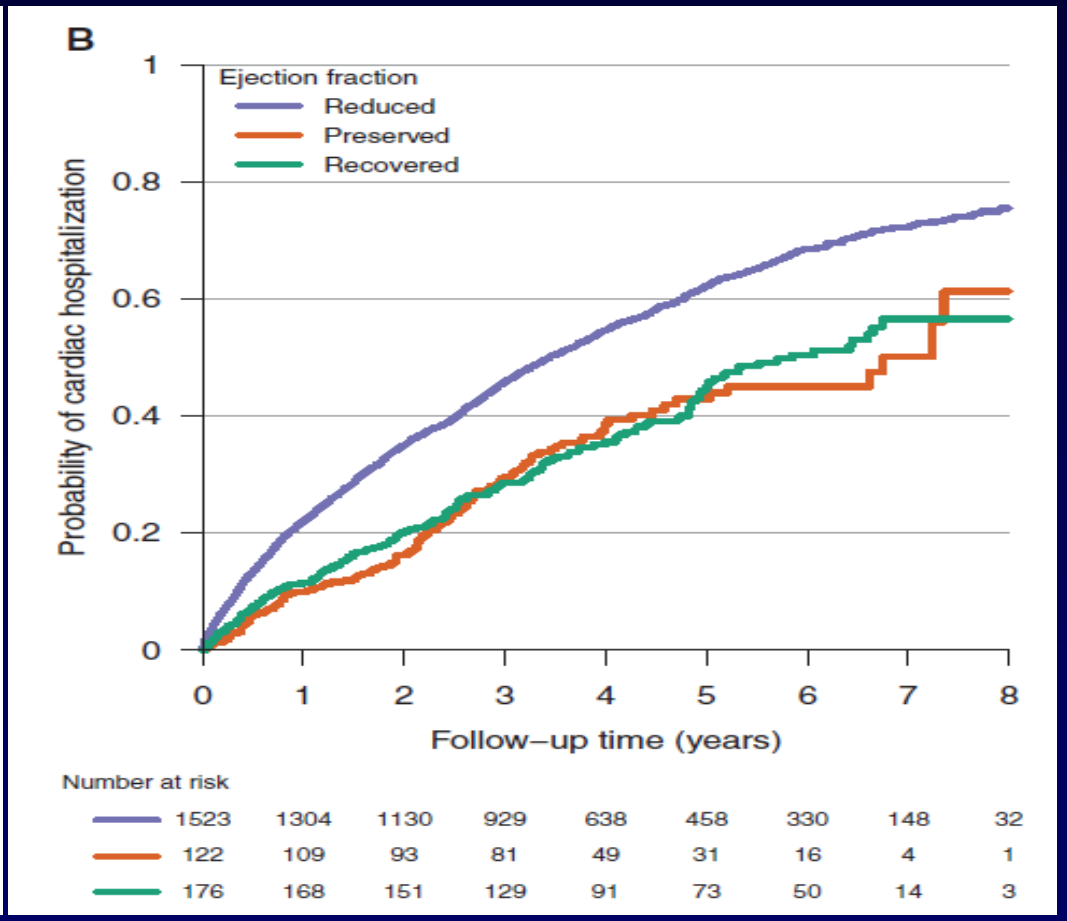
JAMA cardiology 2016;1:510-518

Clinical Outcomes of HFrecEF

Death+TPL+VAD



Rehospitalization



- Nearly 20% of the HFrecEF suffered from death, TPL, or VAD by 8 years of follow-up

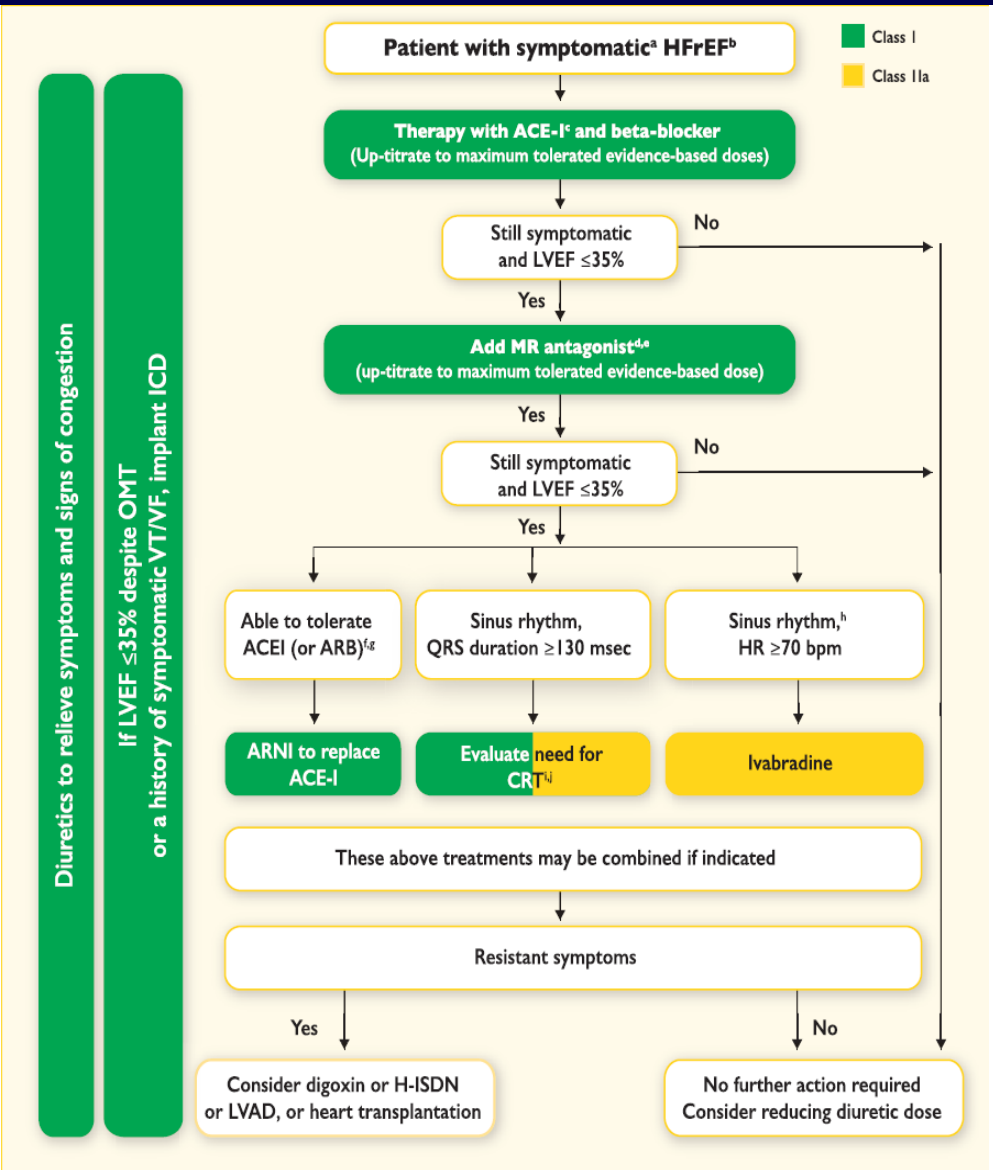
Basuray et al. Circulation 2014;129:2380-2387

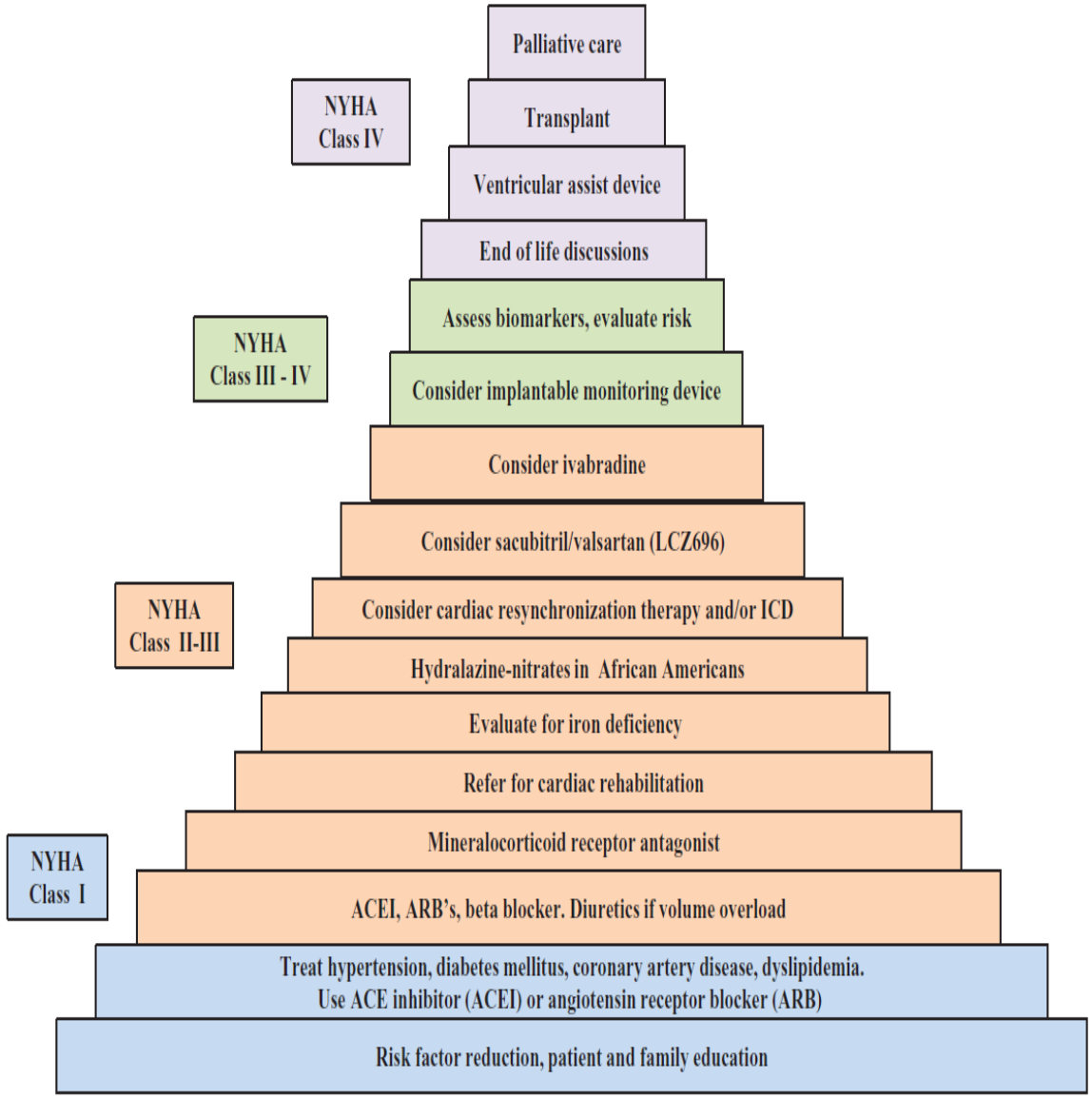
Management of HFrecEF

Title	Treating patients with ENTRESTO in daily clinical practice
Presenter(s)	Prof Faiez Zannad, France
Date	April 19, 2017, 13:00 hrs CEST
Description	Prof Zannad will discuss about a couple of patients with HF and the rationale for starting ENTRESTO, and the consequent outcomes.

"Statins, we don't know maybe lifelong. ACEi? We don't know. Trials just cover 1 or 2 years. You need to keep going for life."

Approach to the patients with HFrEF: Guidelines





2016 ESC guidelines for HF: Eur Heart J 2016;37(27):2129-200

No current guidelines about HFrecEF

are all used to achieve this objective.[1–6] However, little is known about the natural history, prognosis, and need for continued long-term therapies in patients when there is recovery of LV function (eg, HF and recovered ejection fraction [HF-Recovered]).[7–10] In fact, many of these patients continue HF-REF treatment, whereas others may discontinue therapy or become misclassified as having HF with preserved ejection fraction (HF-PEF).[11]

Basuray et al. Circulation. 2014;129:2380-2387

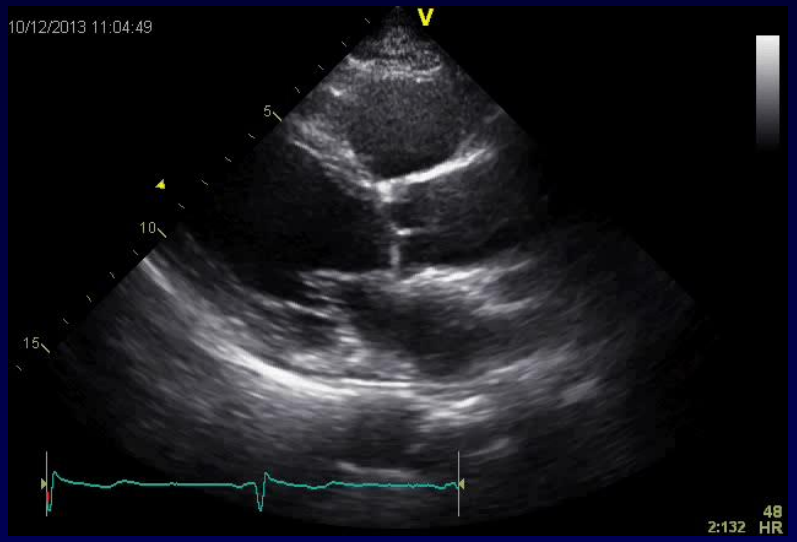
Guideline-based therapy 는 언제까지 필요한가?

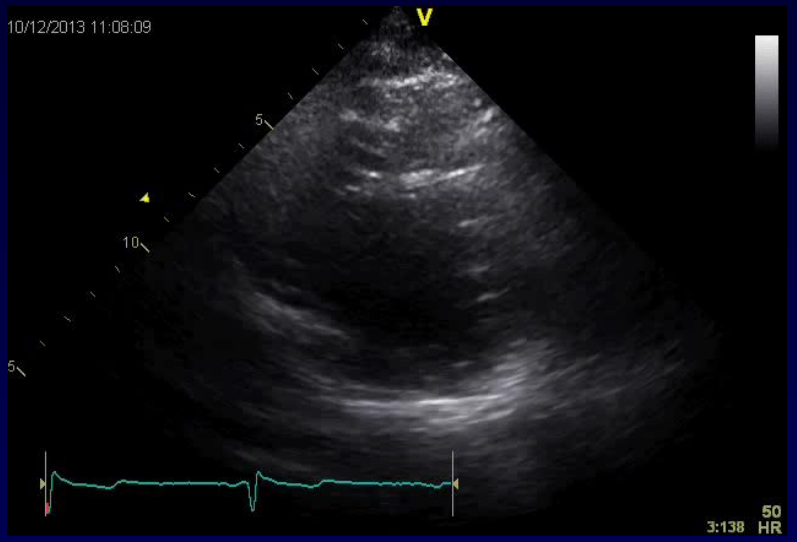
- EF 호전 후 ACEi/ARB 나 BB 를 중단할 수 있을까?
- 약을 중단하면 반드시 재발하는가?
- 약을 중단하지 않아도 재발하는 비율은?
- BB를 중단하면 재발하는가?
- ACEi/ARB 를 중단하면 재발하는가?

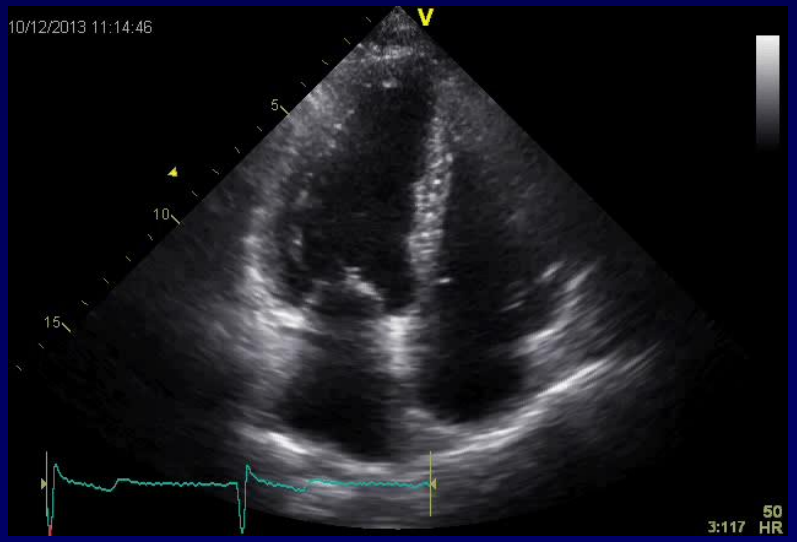
CASE I : 62 / F, HFrecEF

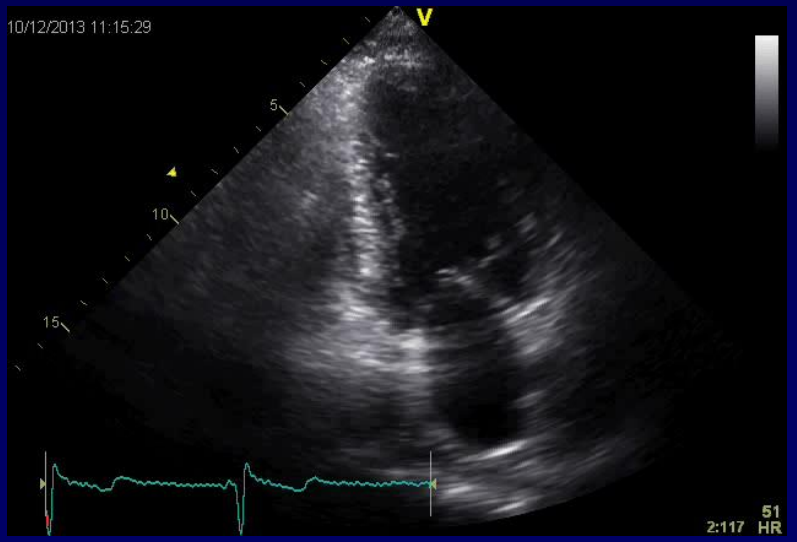
#99'-12-13 DCMP, EF=20%
#01'-02-18 EF=58%
#04'-05-21 EF=67%
#06'-08-22 EF=63.8%
#07'-08-14 EF=66.7%
#08'-11-04 EF=60.8%
#11'-05-03 EF=63% Frequent PVCs
#13'-12-10 EF=62.8% MR, TR
#15'-02-24 EF=63.7% AR

CASE : 62 / F, HFrecEF

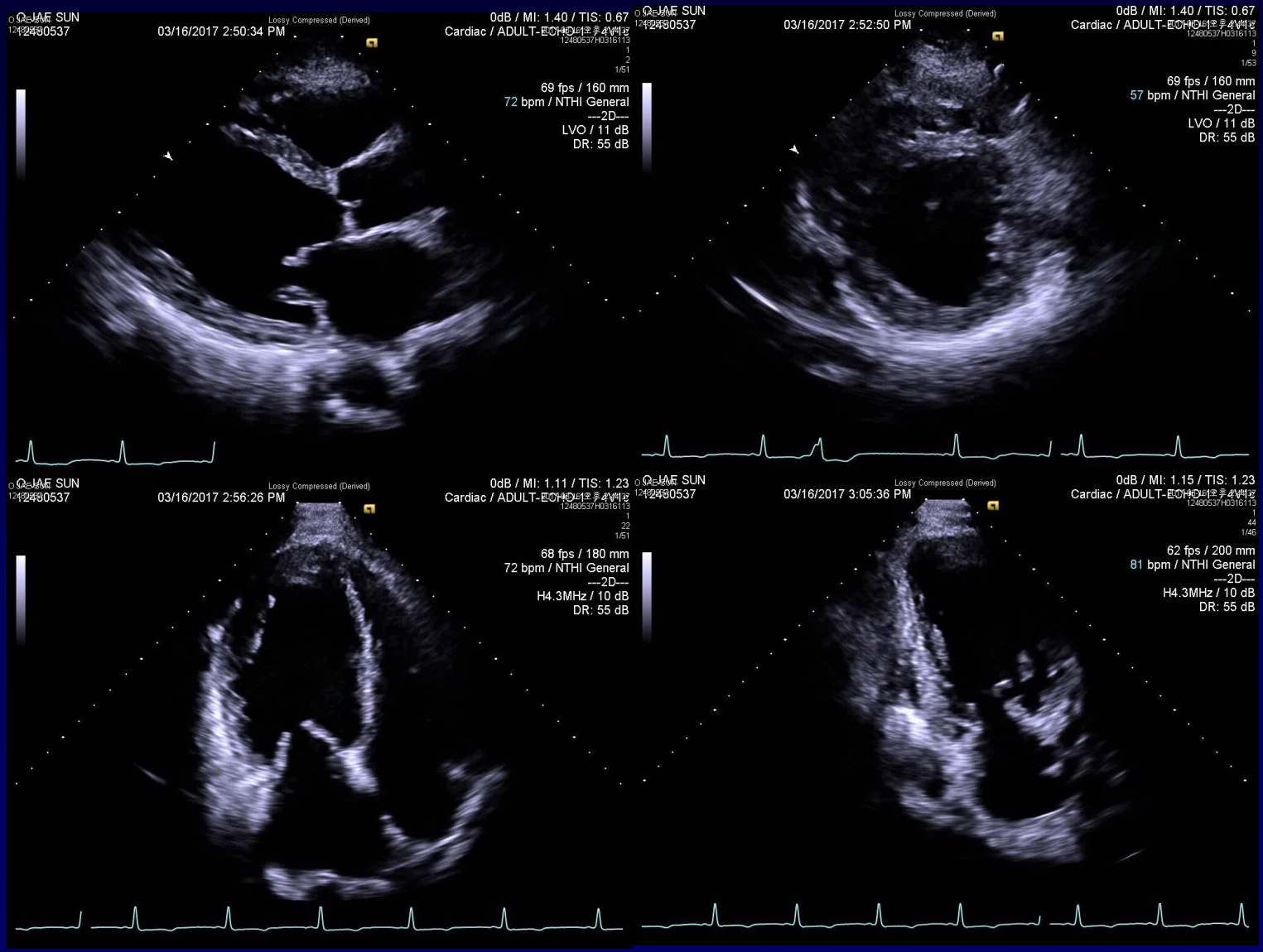




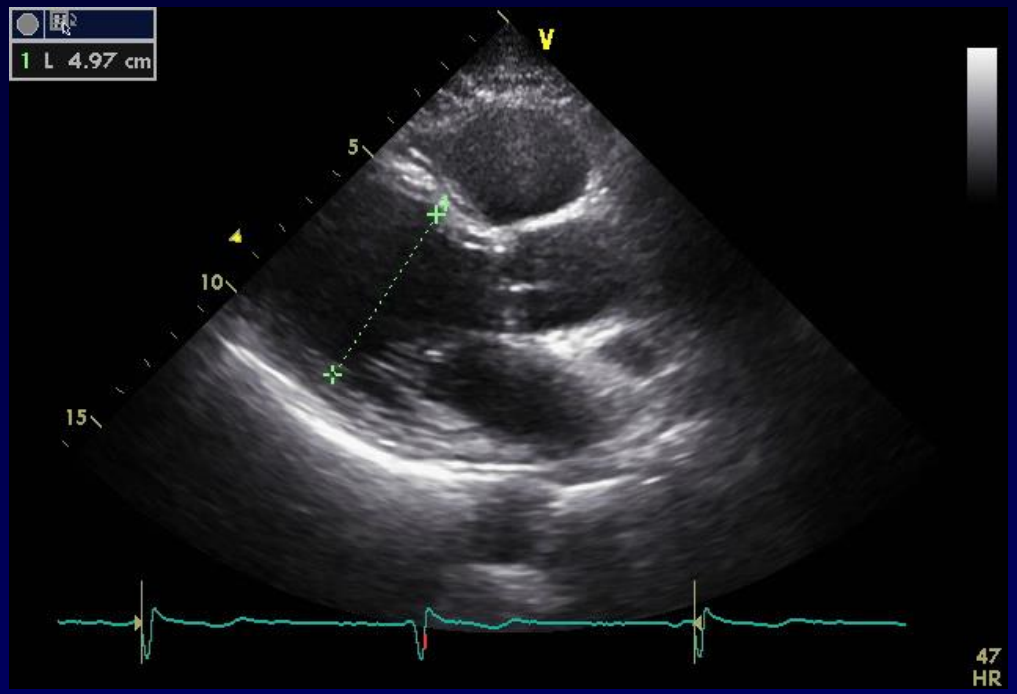


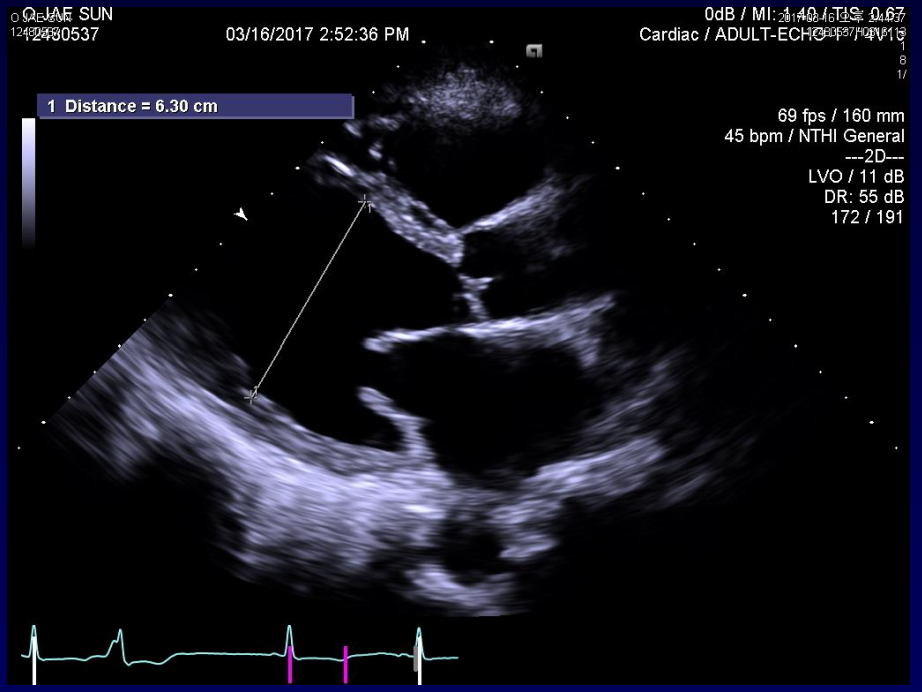


CASE : 62 / F - med (-) for 2 mo, DOE NYHA III



CASE : 62 / F – HFrecEF → HFrEF

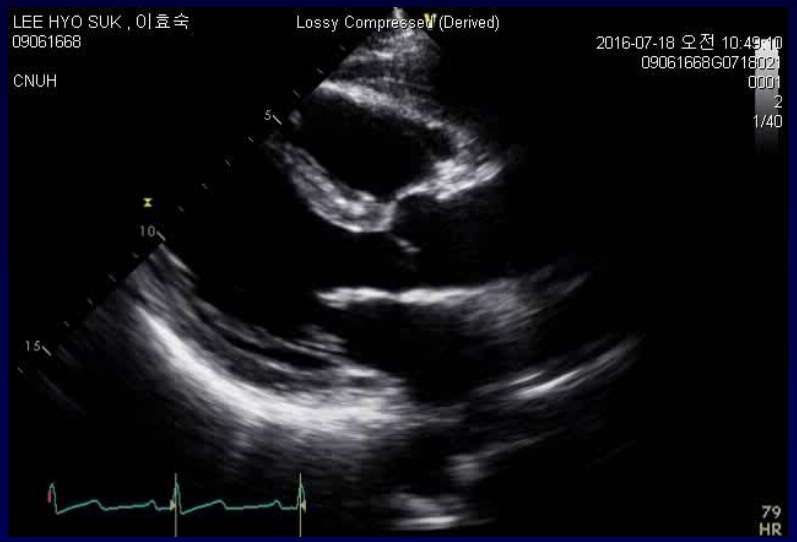


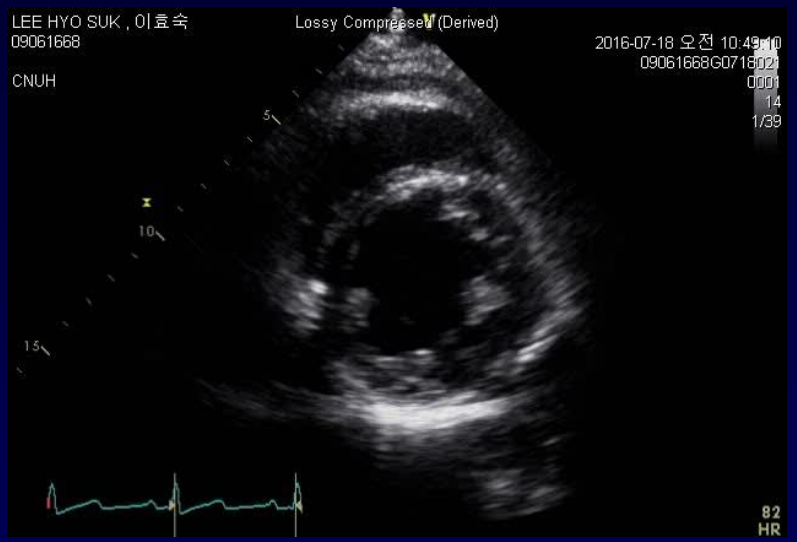


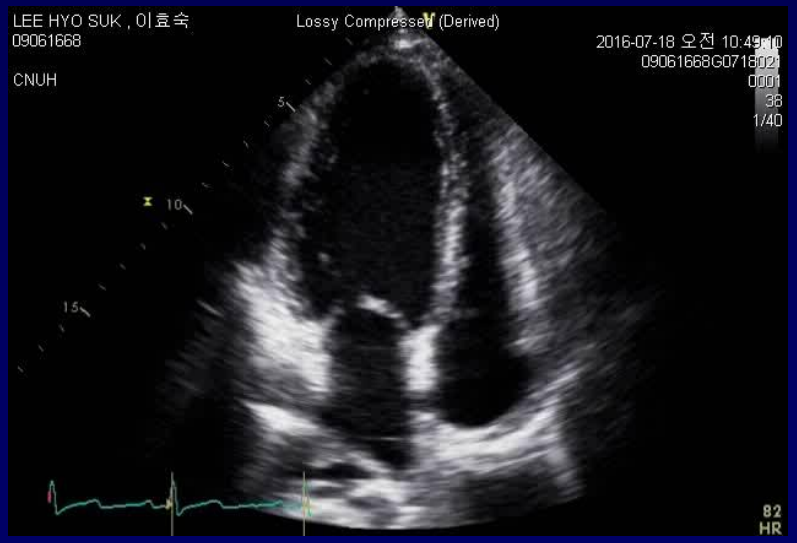
LVEDD 49.7 mm → 63.0 mm

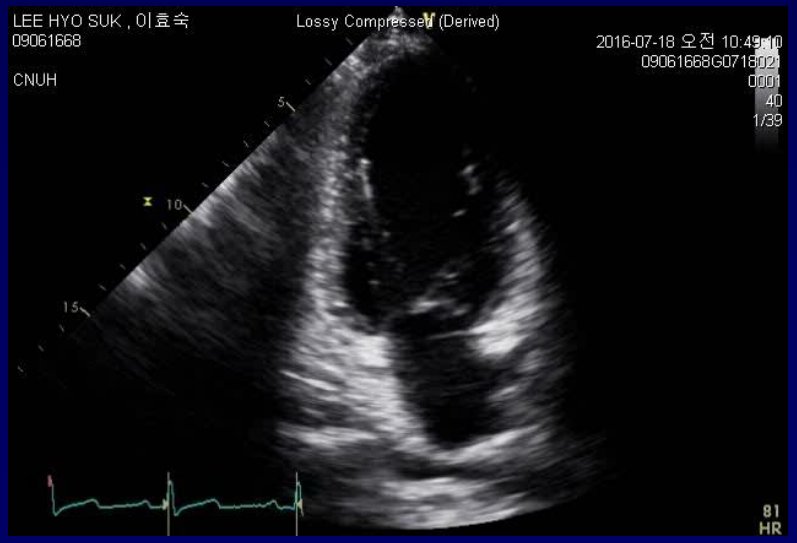
LVEF 63.7% → 25.1%

CASE II – 44/F, HFrecEF

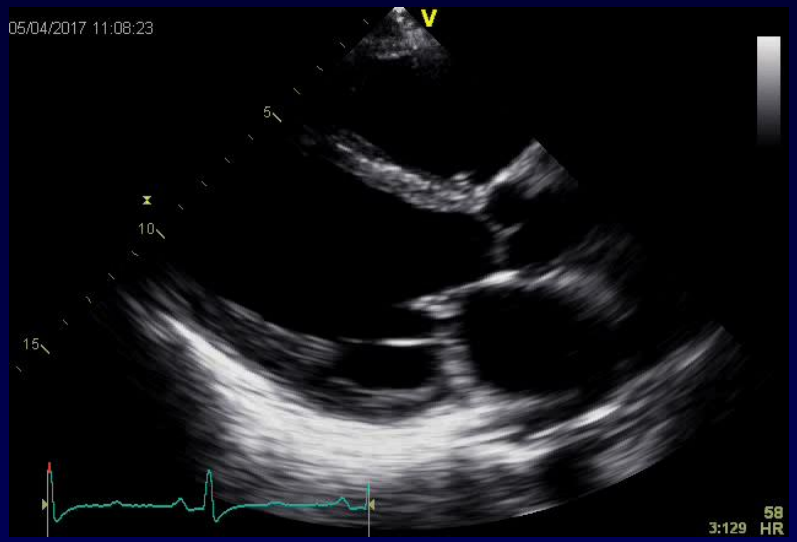


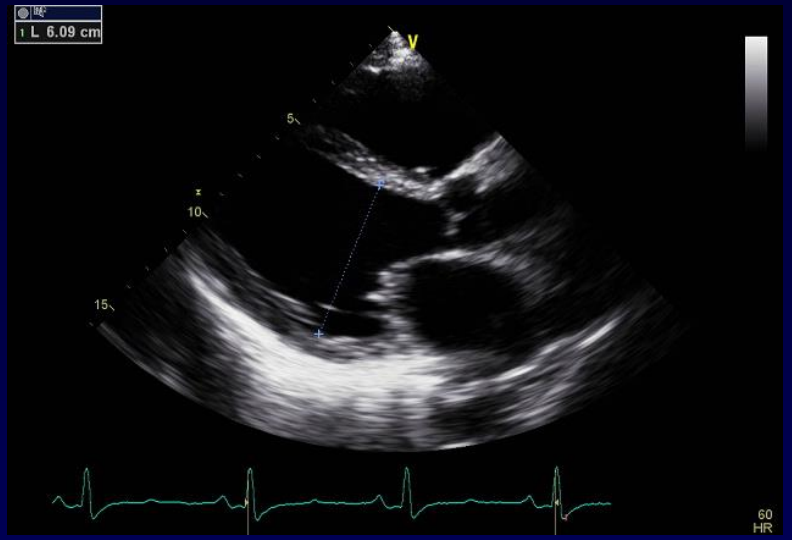


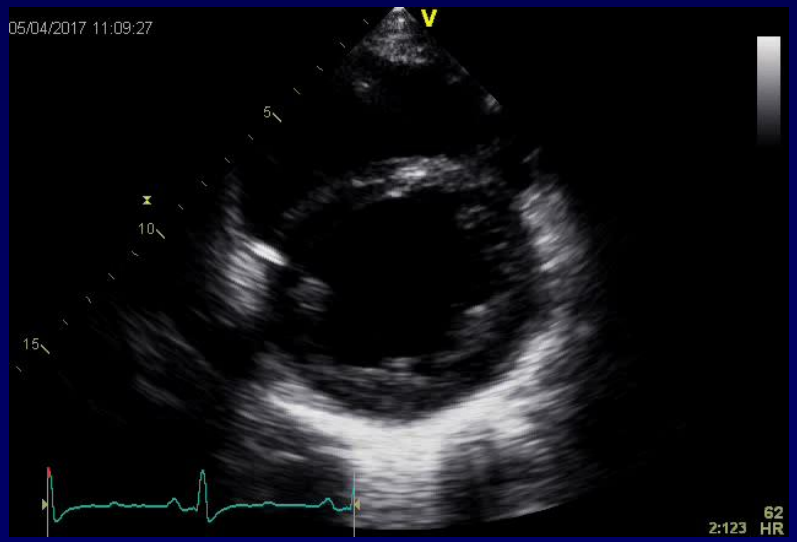


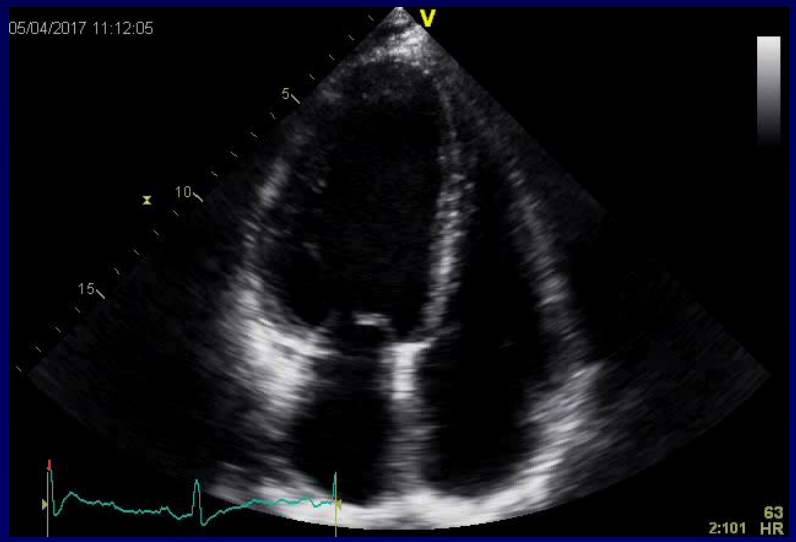


CASE II – 44/F, HFrEF, med (-)

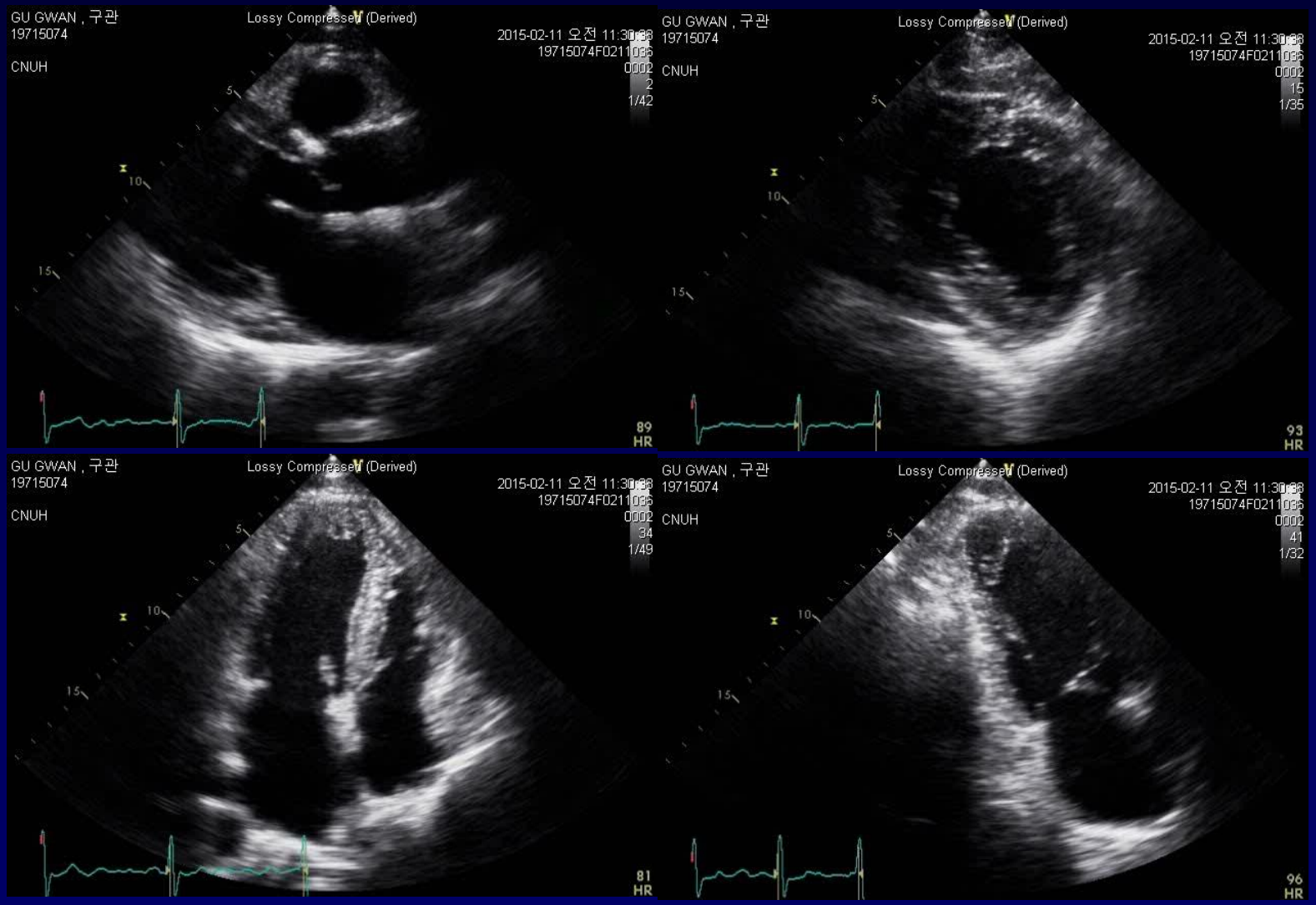




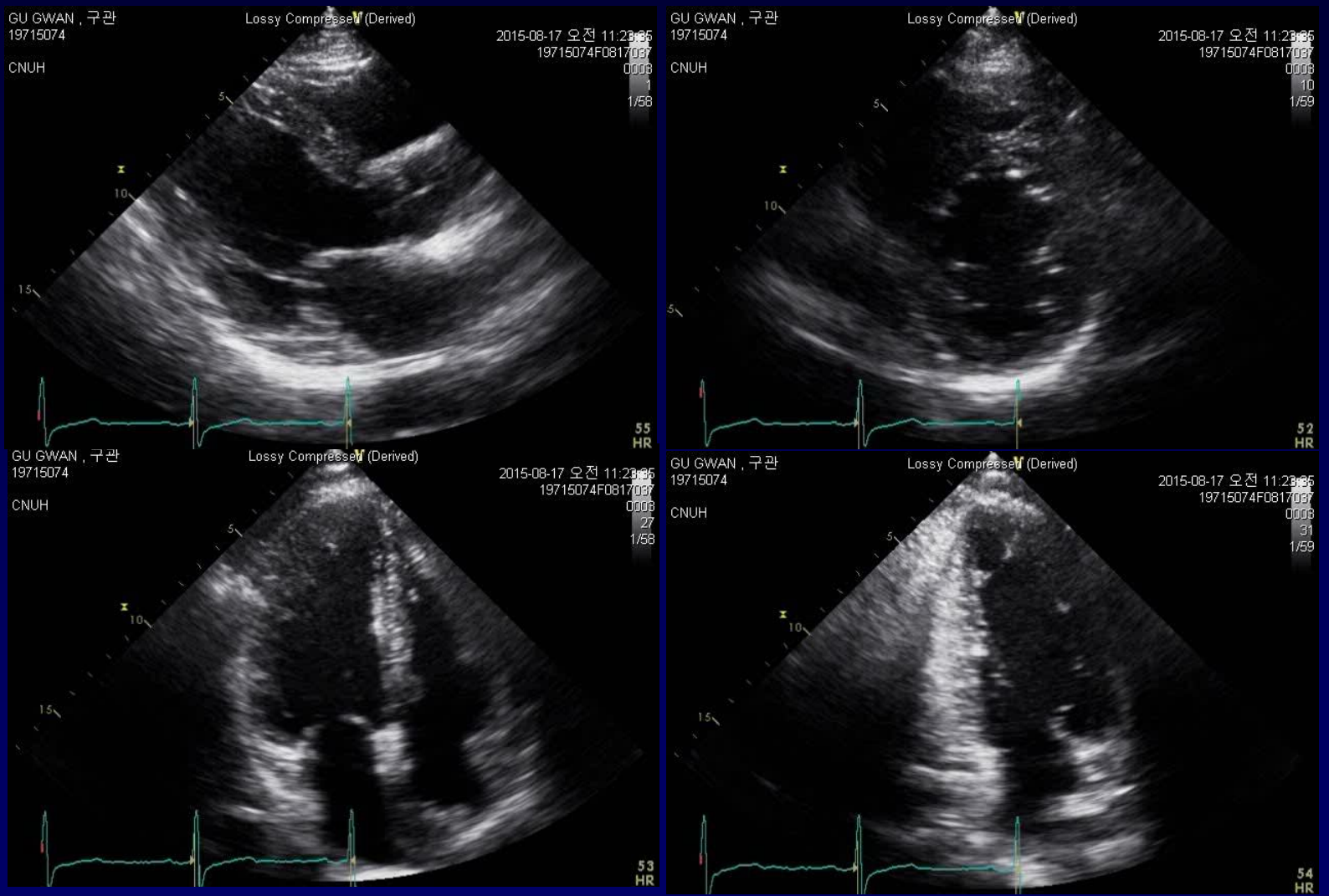




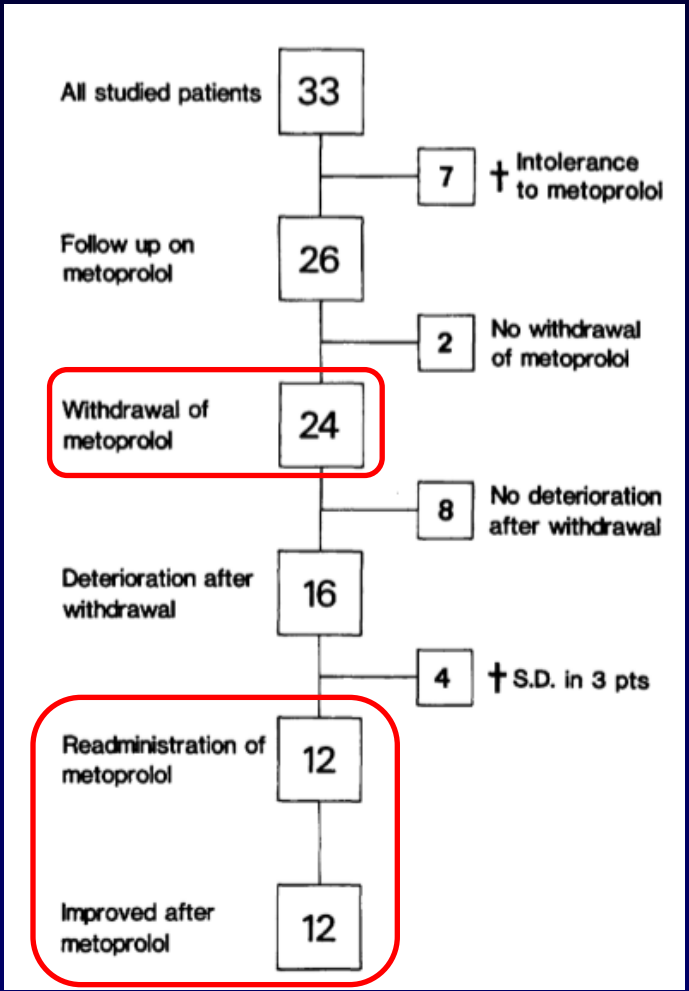
CASE III – 54/M, HFrecEF, alcohol (+), med (-)

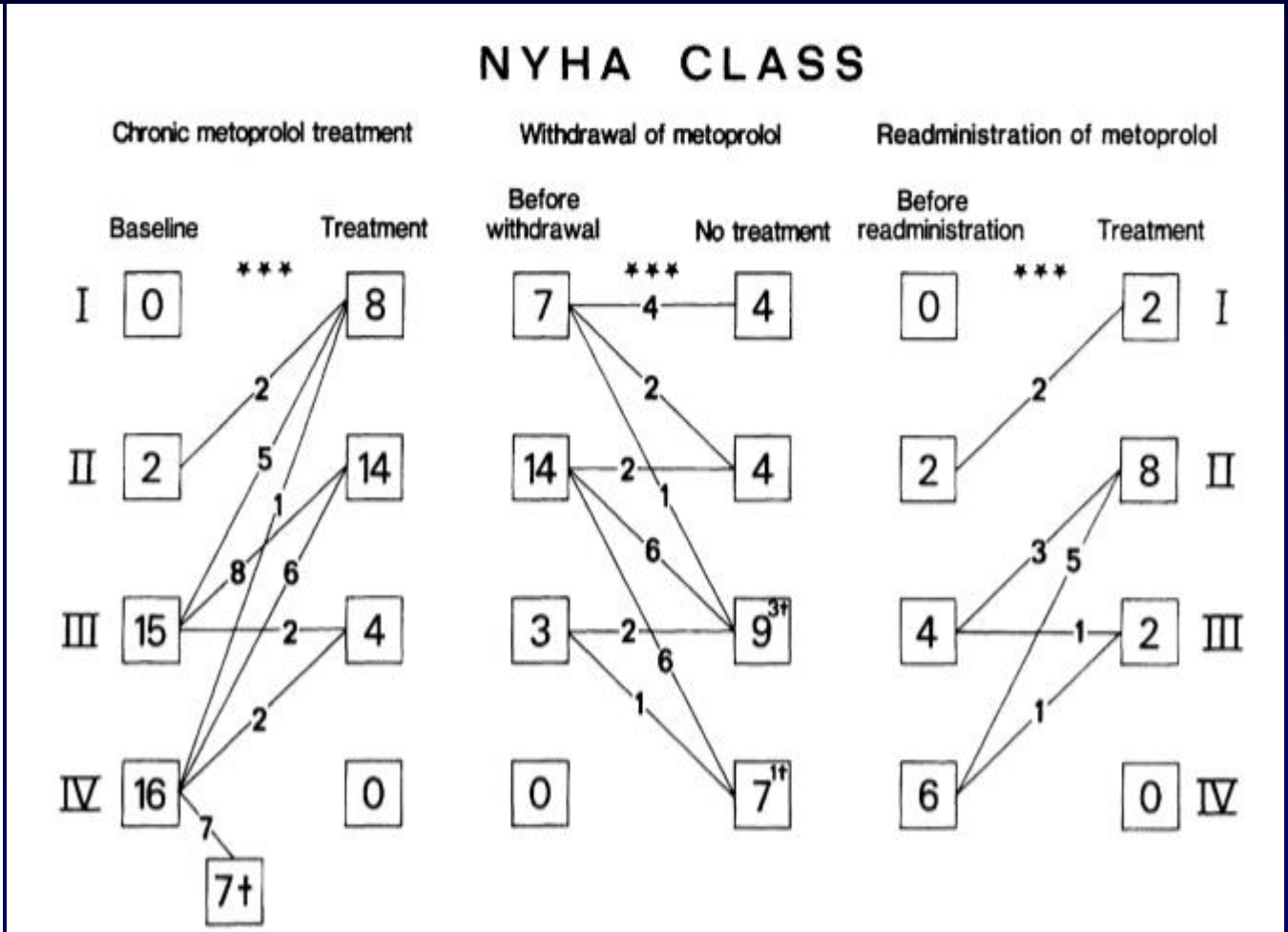


CASE III – 54/M, HFrecEF, alcohol(-), med (+)



Neurohormonal antagonist – Beta-blockers





Waagstein et al. Circulation 1989;80:551-563

Beta-blocker withdrawal and readministration in DCM

TABLE 3. Comparison of Noninvasive Variables During Treatment, Withdrawal and Readministration of Metoprolol

Variable	Long-term treatment			Withdrawal			Readministration		
	Baseline (n=26)	p	Treatment (n=26)	Before withdrawal (n=24)	p	No treatment (n=24)	Before readministration (n=12)	p	Treatment (n=12)
Follow-up (mo)			15.9±9.5			7.7±4.9			6.3±3.3
NYHA Class	3.3±0.6	0.0001	1.8±0.7	1.8±0.6	0.0001	2.8±1.1	3.3±0.8	0.0001	2.0±0.6
HR (beats/min)	80±16	0.0001	57±10	56±10	0.0001	77±14	84±21	0.0001	54±8
Systolic BP (mm Hg)	122±17	NS	128±16	129±16	NS	125±15	119±20	0.080	129±15
Diastolic BP (mm Hg)	79±13	NS	81±10	81±10	NS	84±12	84±14	NS	83±13
LVEDD (mm)	7.26±0.86	0.0001	6.44±1.11	6.49±1.14	0.003	6.81±1.19	7.28±0.79	0.071	6.91±0.77
LVESD (mm)	6.40±0.83	0.0001	5.14±1.23	5.20±1.26	0.0001	5.77±1.35	6.48±0.81	0.004	5.81±0.80
FS (%)	12.0±3.2	0.0001	21.0±7.5	20.8±6.9	0.0001	16.1±7.4	11.0±3.4	0.0019	16.1±3.5
EF	0.25±0.06	0.0001	0.41±0.13	0.41±0.12	0.0001	0.32±0.13	0.23±0.06	0.002	0.33±0.07
Mean Vcf (circumference/sec)	0.51±0.13	0.0001	0.73±0.22	0.73±0.21	0.016	0.61±0.25	0.45±0.12	0.023	0.58±0.10
LAD (mm)	5.16±0.93	0.0001	4.52±0.76	4.54±0.75	0.0001	4.80±0.83	5.24±0.40	0.040	4.94±0.49
MR (grade)	1.7±0.9	0.0001	0.4±0.6	0.4±0.6	0.0001	1.4±1.2	2.2±1.0	0.0001	0.6±0.9
TR (grade)	0.6±0.9	0.017	0.1±0.3	0.1±0.3	NS	0.4±0.8	0.5±0.9	NS	0.2±0.4
RFW (%)	12.0±4.5	0.0001	6.1±3.5	6.2±3.6	0.067	11.3±13.4	17.7±17.7	0.028	5.5±4.2
LVET (%)	87±6	0.0011	92±8	92±7	NS	91±8	89±9	NS	89±9

All values are mean±SD.

NYHA, New York Heart Association; HR, heart rate; BP, blood pressure; LVEDD, left ventricular end-diastolic dimension; LVESD, left ventricular end-systolic dimension; FS, fractional shortening; EF, ejection fraction; Vcf, velocity of circumferential shortening; LAD, left atrial diameter; MR, mitral regurgitation; TR, tricuspid regurgitation; RFW, rapid filling wave; LVET, left ventricular ejection time.

Waagstein et al. Circulation 1989;80:551-563

Cessation of HF medication – ACEi/ARB + BB

CLINICAL STUDIES

Recovery and recurrence of left ventricular systolic dysfunction in patients with idiopathic dilated cardiomyopathy

Jeonggeun Moon MD, Young-Guk Ko MD, Namsik Chung MD, Jong-Won Ha MD, Seok-Min Kang MD, Eui-Young Choi MD, Se-Joong Rim MD

J Moon, Y-G Ko, N Chung, et al. Recovery and recurrence of left ventricular systolic dysfunction in patients with idiopathic dilated cardiomyopathy. Can J Cardiol 2009;25(5):e147-e150.

BACKGROUND: Some patients with nonischemic left ventricular (LV) systolic failure recover to have normal LV systolic function. However, few studies on the rates of recovery and recurrence have been reported, and no definitive indicators that can predict the recurrence of LV dysfunction in recovered idiopathic dilated cardiomyopathy (IDCMP) patients have been determined. It was hypothesized that patients who recovered from nonischemic LV dysfunction have a substantial risk for recurrent heart failure.
METHODS: Forty-two patients (32 men) with IDCMP (mean [± SD] age 56.9±8.7 years) who recovered from systolic heart failure (LV ejection fraction [LVEF] of 26.5±6.9% at initial presentation) to a near-normal state (LVEF of 40% or greater, and a 10% increase or greater in absolute value) were monitored for recurrence of LV systolic dysfunction. Patients with significant coronary artery disease were excluded. Patients were monitored for 41.0±26.3 months after recovery (LVEF 53.4±7.6%) from LV dysfunction.
RESULTS: LV systolic dysfunction reappeared (LVEF 27.5±8.1%) during the follow-up period in eight of 42 patients (19.0%). No significant difference between the groups with or without recurrent heart failure was observed in the baseline clinical and echocardiographic characteristics. However, more patients in the recurred IDCMP group than those in the group that maintained the recovery state had discontinued antiheart failure medication (62.5% versus 5.9%, P<0.05).
CONCLUSIONS: LV dysfunction recurs in some patients with reversible IDCMP. The recurrence was significantly correlated with the discontinuation of antiheart failure drugs. The results suggest that continuous medical therapy may be mandatory in patients who recover from LV systolic dysfunction.

Key Words: *Congestive heart failure; DCMP; Prognosis*

Clinical characteristics of patients

Number of patients	42
Age, years, mean ± SD	56.9±8.7
Sex, n (%)	
Male	32 (76)
Female	10 (24)
Initial New York Heart Association class, n (%)	
III	33 (79)
IV	9 (21)
Initial EF, %, mean ± SD	26.5±6.9
Prescribed antiheart failure medication, n (%)	
ACE inhibitors or ARBs, no beta-blockers	22 (52)
ACE inhibitors or ARBs, plus beta-blockers	20 (48)
Time to recovery of EF, months, mean ± SD	15.4±11.8
EF at the time of recovery, %, mean ± SD	53.4±7.6

ACE Angiotensin-converting enzyme; ARB Angiotensin II receptor blocker; EF Ejection fraction

Moon et al. Can J Cardiol 2009;25:e147-e150

Cessation of HF medication – ACEi/ARB + BB

TABLE 4
Factors that influence recurrent left ventricular systolic dysfunction

Influencing factors	OR	P
Sex	0.881	0.34
Before recovery		
Age	0.997	0.995
Causative disease	4.461	0.344
New York Heart Association class	0.917	0.364
Framingham score	0.749	0.309
Ejection fraction	0.861	0.212
LVEDD	1.113	0.168
LVESD	1.009	0.126
Mitral regurgitation (≥ grade 2)	0.063	0.126
Concomitant beta-blocker usage	0.361	0.407
Time to recovery	0.861	0.434
After recovery		
Ejection fraction	0.749	0.401
LVEDD	1.313	0.826
LVESD	0.695	0.146
Cessation of antiheart failure medications	26.667 (95% CI 3.529–201.478)	0.007*

**P<0.05 indicates significance. LVEDD Left ventricular end-diastolic dimension; LVESD Left ventricular end-systolic dimension*

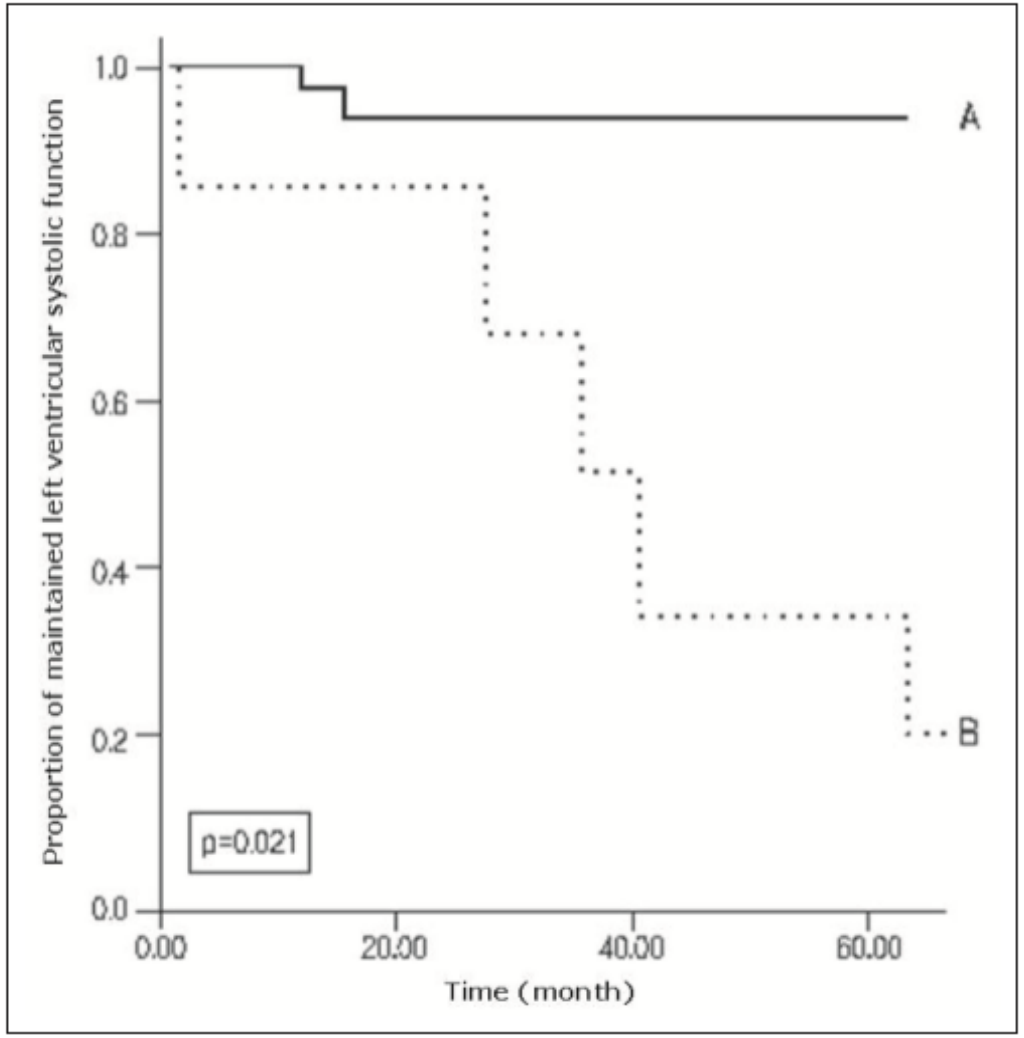


Figure 1) *Recurrence of heart failure (Kaplan-Meier curve).* **A** *Patients who maintained their antiheart failure medication.* **B** *Patients who discontinued their antiheart failure medication*

Moon et al. Can J Cardiol 2009;25:e147-e150

Quality Metrics/Performance Measures

ACCF/AHA/AMA-PCPI 2011 HF Performance Measurement Set (cont.)

Measure	Description*	Care Setting	Level of Measurement
4. Symptom management†	Percentage of patient visits for those patients aged ≥18 y with a diagnosis of HF and with quantitative results of an evaluation of both level of activity AND clinical symptoms documented in which patient symptoms have improved or remained consistent with treatment goals since last assessment OR patient symptoms have demonstrated clinically important deterioration since last assessment with a documented plan of care	Outpatient	Individual practitioner
5. Patient self-care education†‡	Percentage of patients aged ≥18 y with a diagnosis of HF who were provided with self-care education on ≥3 elements of education during ≥1 visits within a 12 mo period	Outpatient	Individual practitioner
6 Beta-blocker therapy for LVSD (outpatient and inpatient setting)	Percentage of patients aged ≥18 y with a diagnosis of HF with a current or prior LVEF <40% who were prescribed beta-blocker therapy with bisoprolol, carvedilol, or sustained release metoprolol succinate either within a 12 mo period when seen in the outpatient setting or at hospital discharge	Inpatient and Outpatient	Individual practitioner Facility

NEW

*Please refer to the complete measures for comprehensive information, including measure exception.
†Test measure designated for use in internal quality improvement programs only. These measures are not appropriate for any other purpose, e.g., pay for performance, physician ranking or public reporting programs.
‡New measure.

Adapted from Bonow et al. J Am Coll Cardiol. 2012;59:1812-32.

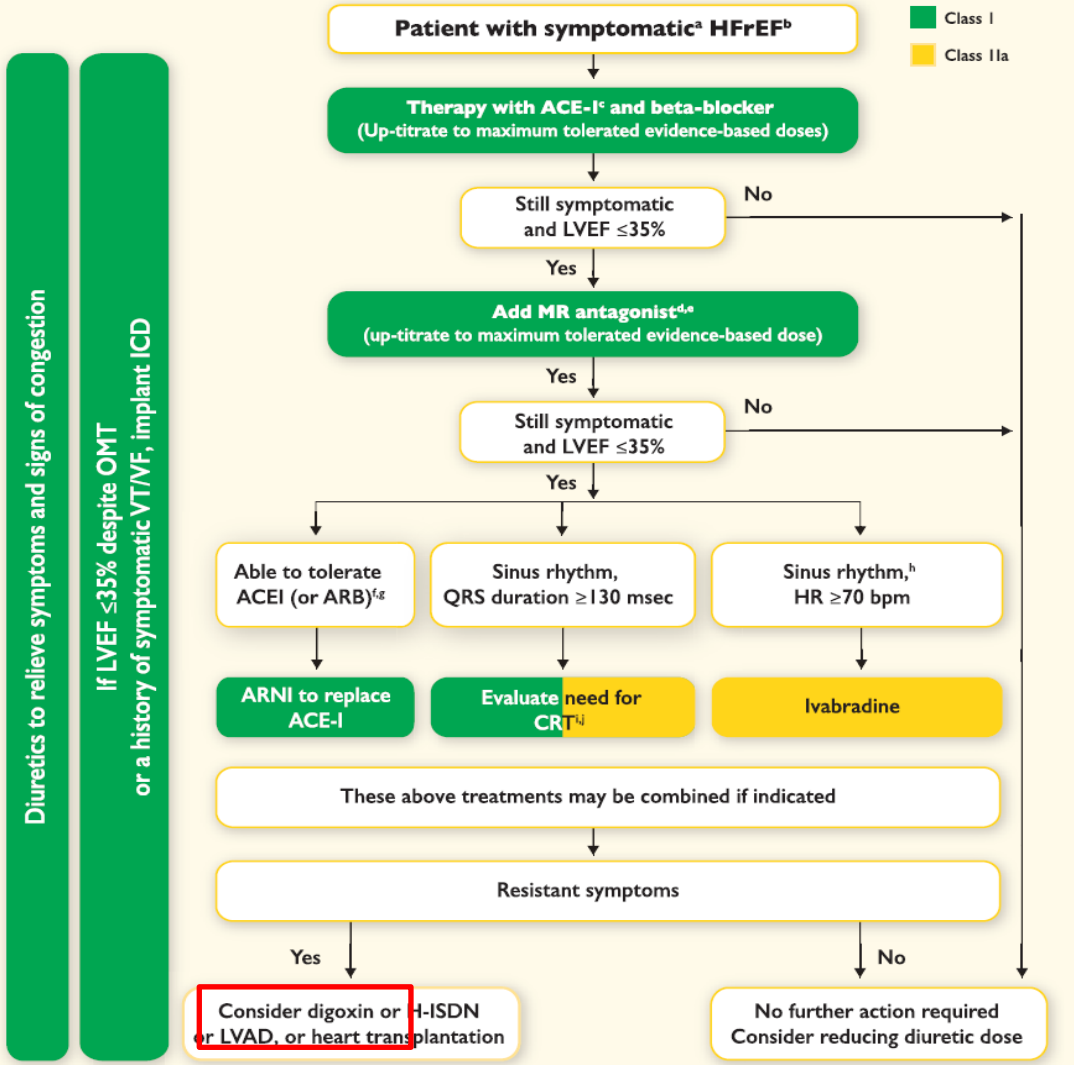
ACCF/AHA/AMA-PCPI 2011 HF Performance Measurement Set (cont.)

Measure	Description*	Care Setting	Level of Measurement
7. ACE Inhibitor or ARB Therapy for LVSD (outpatient and inpatient setting)	Percentage of patients aged ≥18 y with a diagnosis of HF with a current or prior LVEF <40% who were prescribed ACE inhibitor or ARB therapy either within a 12 mo period when seen in the outpatient setting or at hospital discharge	Inpatient and Outpatient	Individual practitioner Facility
8. Counseling regarding ICD implantation for patients with LVSD on combination medical therapy†‡ NEW	Percentage of patients aged ≥18 y with a diagnosis of HF with current LVEF ≤35% despite ACE inhibitor/ARB and beta-blocker therapy for at least 3 mo who were counseled regarding ICD implantation as a treatment option for the prophylaxis of sudden death	Outpatient	Individual practitioner
9. Post-discharge appointment for heart failure patients	Percentage of patients, regardless of age, discharged from an inpatient facility to ambulatory care or home health care with a principal discharge diagnosis of HF for whom a follow-up appointment was scheduled and documented including location, date and time for a follow-up office visit, or home health visit (as specified)	Inpatient	Facility

*Please refer to the complete measures for comprehensive information, including measure exception.
†Test measure designated for use in internal quality improvement programs only. These measures are not appropriate for any other purpose, e.g., pay for performance, physician ranking or public reporting programs.
‡New measure.

Adapted from Bonow et al. J Am Coll Cardiol. 2012;59:1812-32.

Guidelines for Digitalis



NYHA II-IV despite drug/device therapy recommended by HF-guidelines

Ventricular rate control

Especially if
- BB/ACEI/ARB/MRA/ARNI therapy is limited:
  - low RR
  - GFR < 30 ml/min, K^+↑
  - side effects
- CRT no option
- atrial fibrillation with rapid ventricular rate

Especially if
- acute setting with HF and/or hypotension
- BB/CCB therapy limited (e.g. low RR, side effects)
- inefficient rate control with BB/CCB alone

	Digoxin	Digitoxin
Target serum concentration	0.5 – 0.9 ng/ml	8 – 18 ng/ml
Daily dose	0.0625 – 0.25 mg	0.05 – 0.1 mg*

(GFR < 60 ml/min: prefer Digitoxin)

2016 ESC guidelines for HF: Eur Heart J 2016;37(27):2129-200 Bavendiek, et al. Eur Heart J. 2017;[Epub ahead of print]

Digitalis Use

KorAHF registry

Lee SE et al. Eur J Heart Fail 2014;16:700-708

recovered

Punnoose et al. JCF 2011;17:527-532

	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
Loop diuretic	44 (79)	58 (48)	137 (76)	.004	<.001
Daily furosemide dose (mg)	167 ± 203	110 ± 154	132 ± 162	.11	.38
Aldosterone receptor antagonist	11 (20)	23 (19)	68 (38)	.96	.001
ACE inhibitor or ARB	32 (59)	98 (81)	146 (81)	.001	.68
Calcium channel blocker	12 (21)	9 (7)	4 (2)	.01	.03
Beta-blocker	41 (73)	99 (82)	157 (87)	.03	.35
Digoxin	8 (14)	22 (18)	71 (39)	.43	.001
Antiarrhythmic	4 (7)	14 (12)	48 (27)	.31	.002
Anticoagulant	26 (46)	28 (23)	84 (46)	.004	<.001
Antiplatelet agent	45 (80)	58 (48)	98 (54)	.002	.35
Lipid-modifying agent	39 (70)	55 (45)	98 (54)	.007	.17

Basuray et al. Circulation. 2014;129:2380-2387

	Reduced (n=1523)	Preserved (n=122)	Recovered (n=176)	*P* Value*
Medication use, n (%)				
ACE inhibitors or ARBs	1371 (90)	85 (70)	149 (85)	<0.001
Aldosterone antagonists	580 (38)	20 (16)	35 (20)	<0.001
Aspirin	879 (58)	64 (52)	86 (49)	0.053
β-Blockers	1399 (92)	84 (69)	154 (88)	<0.001
Digoxin	659 (43)	9 (7)	41 (23)	<0.001
Diuretics	1252 (82)	87 (71)	121 (69)	<0.001
Statins	811 (53)	58 (48)	94 (53)	0.48

Table 3 Pharmacological treatments during hospitalization

Medications	Sustained use *n* (%)	Transient use *n* (%)
Nitrates	514 (24.9)	399 (19.3)
Hydralazine	12 (0.6)	10 (0.5)
Loop diuretics	1371 (66.4)	340 (16.5)
Thiazide diuretics	175 (8.5)	119 (5.8)
Amiodarone	121 (5.9)	138 (6.7)
Digoxin	499 (24.2)	152 (7.4)
Heparin/LMWH	19 (0.9)	833 (40.3)
Warfarin	556 (26.9)	78 (3.8)
Aspirin	1093 (52.9)	262 (12.7)
Statins	805 (39)	117 (5.7)
Ivabradine	1 (0)	0 (0)
Dronedarone	2 (0.1)	2 (0.1)
Diabetes medications	723 (35)	
Parenteral medications	*n* (%)	
Diuretics	1478 (71.5)	
Dobutamine	494 (23.9)	
Dopamine	373 (18.1)	
Milrinone	31 (1.5)	
Norepinephrine	144 (7)	
Nitroprusside	16 (0.8)	
Nitroglycerine	817 (39.5)	

LMWH, low molecular weight heparin.

Digoxin-associated mortality in AF or CHF

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CLINICAL RESEARCH

Atrial fibrillation

Digoxin-associated mortality: a systematic review and meta-analysis of the literature

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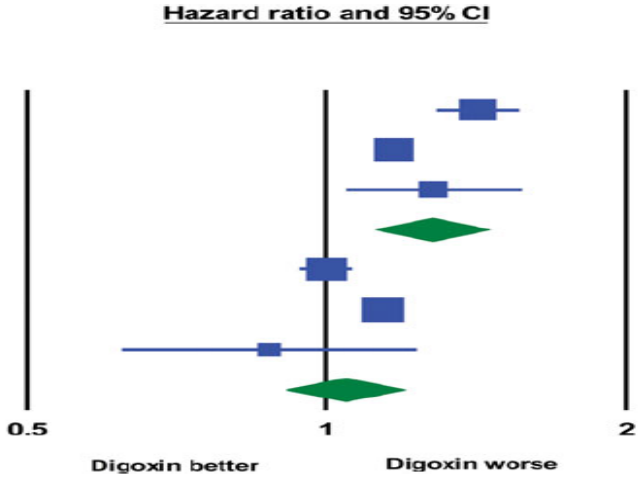
Conclusions

This meta-analysis of the contemporary literature indicates that digoxin therapy particularly without proper serum level control is associated with an increased mortality risk in patients with AF and with CHF. Our sensitivity analysis, however, suggests negative effects of digoxin particularly in the AF population but somewhat less unfavourable effects in the CHF population. Coupled with the notion emphasized by Rathore *et al.*,[33] this calls for randomized trials of dose-adjusted digoxin therapy at least in CHF patients. Until such proper randomized controlled trials are being completed, digoxin should be used with great caution (including monitoring plasma levels), particularly when administered for rate control in AF.

Study	Patient cohort	Patients	Statistics			
			Hazard ratio	95%	CI	p-Value
Hallberg (RIKS-HIA), 2007 - AF	AF	21459	1,42	1,29	1,56	0,00
Shah, 2014 - AF	AF	46262	1,17	1,15	1,20	0,00
Chao, 2014 - AF	AF	4260	1,28	1,05	1,57	0,02
Total	**AF**		**1,28**	**1,12**	**1,46**	**<0,01**
Hallberg (RIKS-HIA), 2007 - CHF (AF)	CHF	16960	1,00	0,94	1,06	1,00
Shah, 2014 - CHF	CHF	27972	1,14	1,11	1,17	0,00
Chao, 2014 - CHF	CHF	521	0,88	0,62	1,23	0,45
Total	**CHF**		**1,05**	**0,91**	**1,20**	**0,52**



Vamos et al. Eur Heart J. 2015;36:1831-8

When should we discontinue diuretics in HFrecEF?

- No standardized approach to weaning diuretic therapy after improvement
- BNP and ST2 elevation → abnormal ventricular wall stress

Punnoose et al. JCF 2011;17:527-532

	HF-PEF (n = 56)	HFrecEF (n = 121)	HF-LEF (n = 181)	HF-REF vs HF-PEF *P* Value	HF-REF vs HF-LEF *P* Value
Loop diuretic	44 (79)	58 (48)	137 (76)	.004	<.001
Daily furosemide dose (mg)	167 ± 203	110 ± 154	132 ± 162	.11	.38
Aldosterone receptor antagonist	11 (20)	23 (19)	68 (38)	.96	.001
ACE inhibitor or ARB	32 (59)	98 (81)	146 (81)	.001	.68
Calcium channel blocker	12 (21)	9 (7)	4 (2)	.01	.03
Beta-blocker	41 (73)	99 (82)	157 (87)	.03	.35
Digoxin	8 (14)	22 (18)	71 (39)	.43	.001
Antiarrhythmic	4 (7)	14 (12)	48 (27)	.31	.002
Anticoagulant	26 (46)	28 (23)	84 (46)	.004	<.001
Antiplatelet agent	45 (80)	58 (48)	98 (54)	.002	.35
Lipid-modifying agent	39 (70)	55 (45)	98 (54)	.007	.17

Stevenson et al. Circulation. 2014;129:2364-7

When should we discontinue diuretics in HFrecEF?

- Complaint of frequency
- Renal dysfunction
- BW loss - dehydration

또 과연 **Echo** 는 얼마나 자주 해야할까?
Routine FU of Echo in HF

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Association of survival time with transthoracic echocardiography in stable patients with heart failure: Is routine follow-up ever appropriate?

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ABSTRACT

Background: The appropriateness of repeat transthoracic echocardiography (TTE) for stable heart failure (HF) is based on timing of the follow-up examination, but this lacks scientific support. We sought the association of routine follow-up TTE on survival and readmission in stable HF.

Methods: Patients with HF were selected from consecutive HF admissions from 2008 to 2012. Groups were divided into: no follow-up TTE; routine <1 year with no change in status ("rarely appropriate"), ≥1 year follow-up with no change in status ("maybe appropriate") and TTE due to change in clinical status ("appropriate"). Survival analysis was performed for the combined endpoint of HF readmission and death, and a separate analysis was performed for HF readmission, with death as a competing risk.

Results: Of 550 HF patients, 141 had a follow-up TTE, including 41 (29%) within 1 year. The event-free time in years was similar between no TTE (1.10 years [95%CI: 0.69, 1.49], routine TTE <1 year (2.61 years [95% CI: 1.08, 3.04], routine >1 year (2.45 years [95% CI: 1.37, 5.78]); all were greater than symptomatic patients (0.09 years [95% CI: 0.02, 1.80]). HF readmission was independently associated with statins, renal disease, coronary angiography and NYHA class, but not follow-up TTE timing. There were no differences in the cumulative incidence for death between groups. There were no differences in change in management in routine TTE <1 year and ≥1 year.

Conclusion: The distinction of appropriateness of routine repeat TTE in stable HF patients, based on testing <1 or ≥1 year after index admission appears unjustified.

Fonseca, et al. Int J Cardiol 2017;230:619-624

Adverse events according to TTE FU type

- **Appropriate** – patients with FU TTE d/t a change in clinical status or cardiac exam.
- **Inappropriate** – routine F/U <1 year
- **Uncertain** – routine F/U ≥ 1 year
- **No-TTE** – patients with no follow-up TTE

Table 1
Outcomes in follow-up TTE and follow-up TTE groups (Inappropriate, Uncertain and Appropriate groups).

	HF readmission, n (%)	Death, n (%)	HF/death, n (%)
TTE	28 (19.9)	63 (44.7)	91 (64.5)
No TTE	166 (40.6)	170 (41.6)	336 (82.2)
p (TTE vs none)	<0.01	0.58	<0.01
Inappropriate	10 (24.4)	17 (41.5)	27 (65.9)
Uncertain	1 (5.3)	8 (42.1)	9 (47.4)
Appropriate	17 (21.0)	38 (46.9)	55 (67.9)
p (all groups)	<0.01	0.85	<0.01
p (Inappropriate, Uncertain and Appropriate groups)	0.21	0.82	0.24
p (Inappropriate and Uncertain groups)	0.15	1	0.28
p (Inappropriate and Appropriate groups)	0.84	0.71	0.98
p (Uncertain and Appropriate groups)	0.18	0.9	0.16

Abbreviations: HF = heart failure, TTE = transthoracic echocardiography.

ACCF/AHA/AMA-PCPI 2011 HF Performance Measurement Set (9 measures)

Measure	Description*	Care Setting	Level of Measurement
1. LVEF assessment	Percentage of patients aged ≥18 y with a diagnosis of HF for whom the quantitative or qualitative results of a recent or prior (any time in the past) LVEF assessment is documented within a 12 mo period	Outpatient	Individual practitioner
2. LVEF assessment	Percentage of patients aged ≥18 y with a principal discharge diagnosis of HF with documentation in the hospital record of the results of an LVEF assessment that was performed either before arrival or during hospitalization, OR documentation in the hospital record that LVEF assessment is planned for after discharge	Inpatient	• Individual practitioner • Facility
3. Symptom and activity assessment	Percentage of patient visits for those patients aged ≥18 y with a diagnosis of HF with quantitative results of an evaluation of both current level of activity and clinical symptoms documented	Outpatient	Individual practitioner

*Please refer to the complete measures for comprehensive information, including measure exception.

Adapted from Bonow et al. J Am Coll Cardiol. 2012;59:1812-32.

Genetics of milder form of DCM

EUROPEAN SOCIETY OF CARDIOLOGY®

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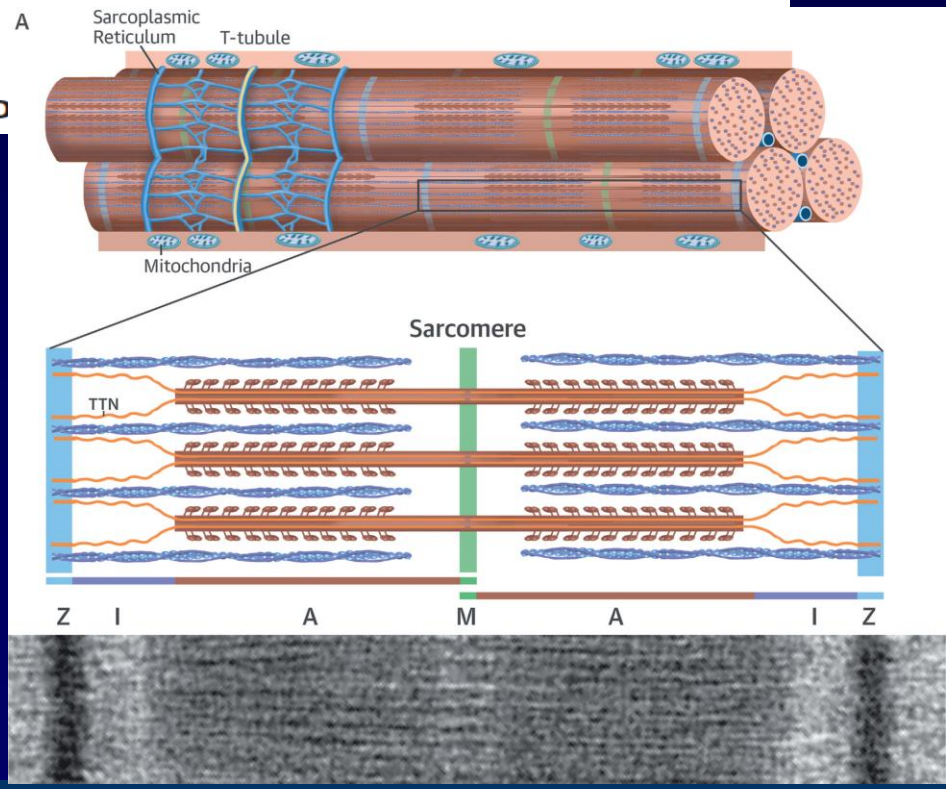
doi:10.1002/ejhf.673

RESEARCH ARTICLE

Truncating titin mutations are associated with a mild and treatable form of dilated cardiomyopathy

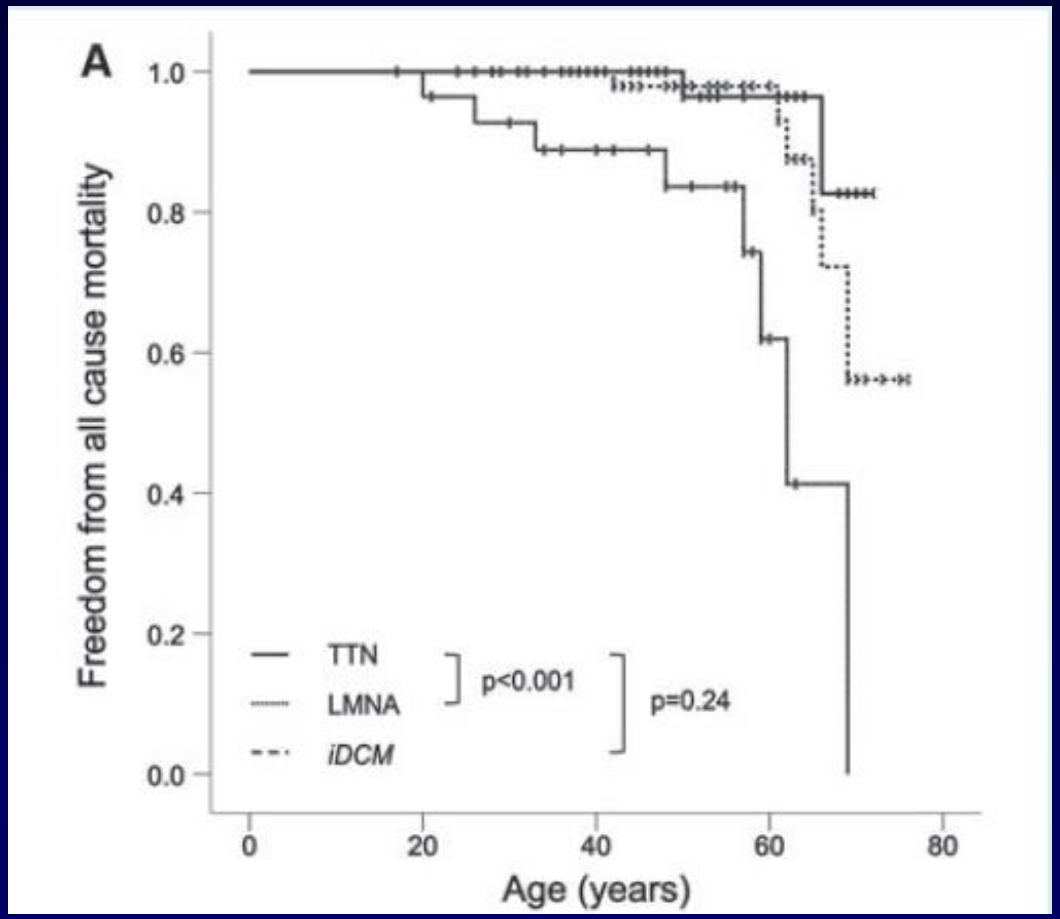
Joeri A. Jansweijer[1†], Karin Nieuwhof[2†], Francesco

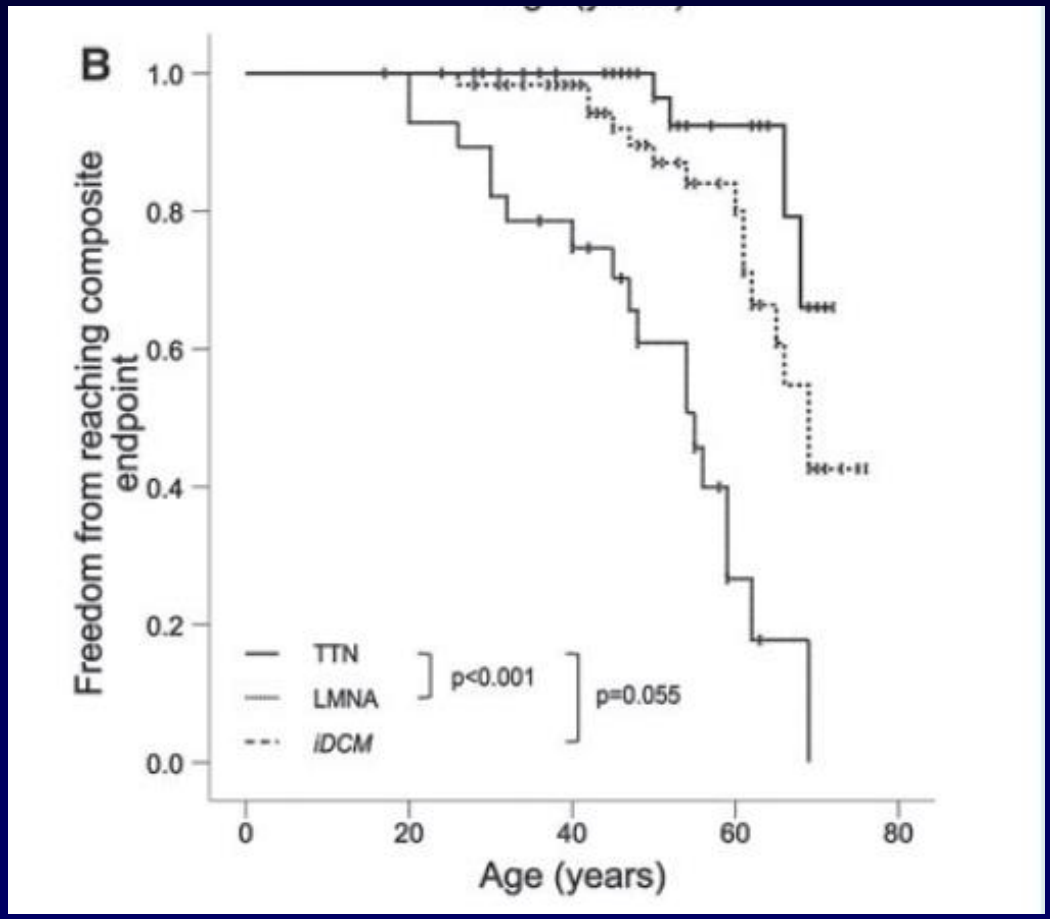
Jansweijer et al. Eur J Heart Fail. 2017;19:512-521



Burke, M.A. et al. J Am Coll Cardiol. 2016;68(25):2871-86.

Survival: tTTN mutation vs. LMNA mutation





Jansweijer et al. Eur J Heart Fail. 2017;19:512-521

Recovery in Patients With Dilated Cardiomyopathy With Loss-of-Function Mutations in the Titin Gene

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Table. Characteristics of Patients With Dilated Cardiomyopathy

Clinical Characteristics	No. (%)			*P* Value[a]
	Recovered EF (n = 31)	Nonrecovered EF (n = 82)	Transplant (n = 28)	
Male	21 (67.7)	52 (63.4)	22 (78.6)	>.99
Age at diagnosis, mean (SD), y	53.6 (11.9)	54.8 (12.1)	49.7 (9.4)	>.99
Worst LVEF, median (IQR)[b]	20 (17.5-30.0)	15 (15.0-20.0)	15 (12.5-15.0)[c]	<.001
Best LVEF, median (IQR)[d]	60 (50.0-65.0)	40 (30.0-45.0)	30 (30.0-33.7)[e]	<.001
Family history	8 (25.8)	13 (15.9)	11 (39.3)	.63
Diabetes	8 (25.8)	23 (28.0)	9 (32.1)	.82
Hypertension	10 (32.3)	36 (43.9)	13 (46.4)	.30
Chemotherapy	0	1 (1.2)	1 (3.6)	>.99
Peripartum	1 (3.2)	2 (2.4)	1 (3.6)	>.99
Stimulant use	2 (6.5)	3 (3.7)	0	.30
High alcohol intake	6 (19.4)	8 (9.8)	2 (7.1)	.12
Arrhythmia	12 (38.7)	35 (42.7)	12 (42.9)	.84
TTNtv present, No./total No. (%)[f]	4/28 (14.3)	15/76 (19.7)	7/24 (29.2)	.44

Abbreviations: EF, ejection fraction; IQR, interquartile range; LVEF, left ventricular ejection fraction; TTNtv, titin truncating variant.

[a] Tests were performed using *t* test for age at diagnosis, Mann-Whitney test for worst LVEF and best LVEF, and Fisher exact test for all other clinical characteristics. All *P* values are for recovered EF vs the other 2 groups combined.

[b] For patients with nonrecovered EF or transplant, n = 88. Worst LVEF measures are always recorded pretransplant.

[c] n = 6.

[d] For patients with nonrecovered EF or transplant, n = 87. Best LVEF measures are always recorded pretransplant.

[e] n = 5.

[f] For TTNtv present, n = 128.

Discussion

We demonstrate that truncating *TTN* mutations are frequently observed in patients with DCM who recover systolic function with standard medical therapy alone. Our results suggest that despite the key role played by *TTN* in cardiac function, individuals with these mutations can recover systolic function and are equally likely to experience recovery as those with other causes of DCM. While it was recently shown that recovery is possible in patients with DCM who have a truncating mutation in *TTN* with mechanical unloading therapy support, [2] [3] our findings that recovery is possible in those receiving medical therapy alone is consistent with another recently published study. [4] However, not all patients with *TTN* mutations receiving medical therapy recovered. While the specific mutations that cause DCM and their penetrance are known to play a role in age at onset and prognosis, [5] [6] to our knowledge, it remains unknown whether recovery from DCM also depends on the specific *TTN* mutation or penetrance. Because the recovery of left ventricular function in response to pharmacological therapy is variable, future studies should assess whether *TTN* mutations could affect the decision to continue medical therapy in patients with DCM who demonstrate sustained recovery.

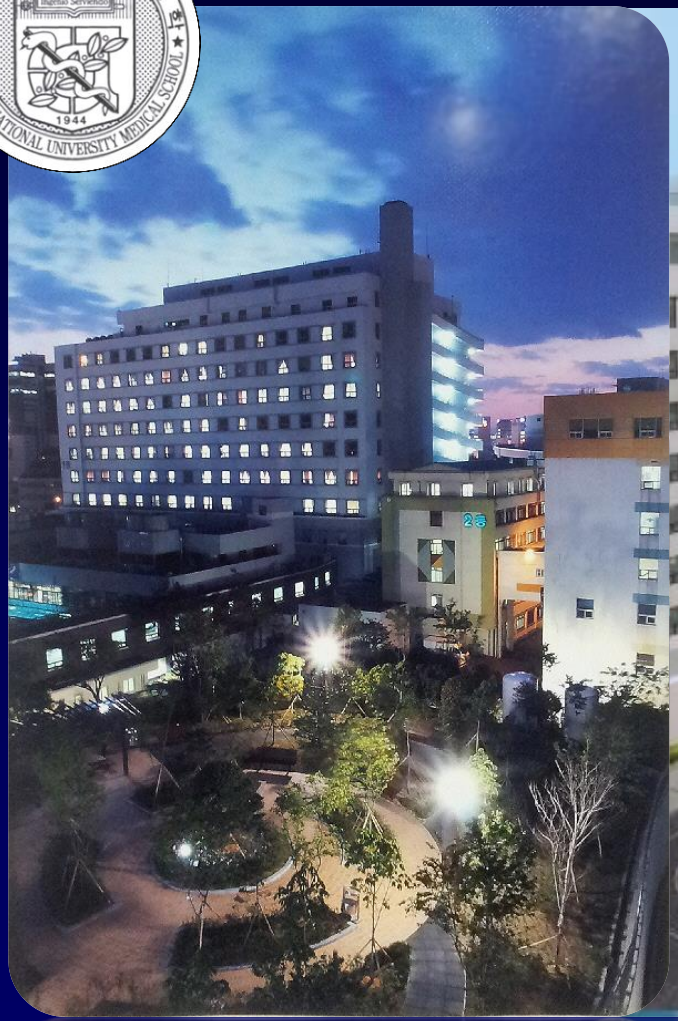
Conclusions

Similar to other recent work, [4] our results suggest that further understanding of the variables that affect recovery from DCM, including the effect of genetics and their possible interactions with medical therapy, may be important in identifying each patient's long-term management.

Take Home Messages

- HFrecEF is suggested to be a distinct HF phenotype
- HFrecEF is not recovered HF, just having better EF
  - Prognosis, Biomarkers, GLPSS, functional capacity
- It is important to continue disease-modifying agents
- Clinical Guideline for HFrecEF to better tailor therapy is warranted
- Also genetics may play a role in the future treatment

Thank you for your attention



Heart Failure with Recovered EF

Chemical Conversion of ~~Atrial Fibrillation~~ Heart Failure?