

만성 심부전 약물치료의 최신지견



2019. 03. 20
고신의대 순환기내과
김봉준

Guideline of HF



European Heart Journal (2016) **37**, 2129–2200
doi:10.1093/eurheartj/ehw128

ESC GUIDELINES

2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)

Developed with the special contribution of the Heart Failure Association (HFA) of the ESC

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Guideline of HF

KSHF guideline for the management of
CHRONIC HEART FAILURE 2016

만성 심부전 진료지침

대한심장학회 심부전연구회



KSHF guideline for the management of
ACUTE HEART FAILURE 2017

급성 심부전 진료지침

대한심장학회 심부전연구회



What is Heart Failure ?

KSHF 2016

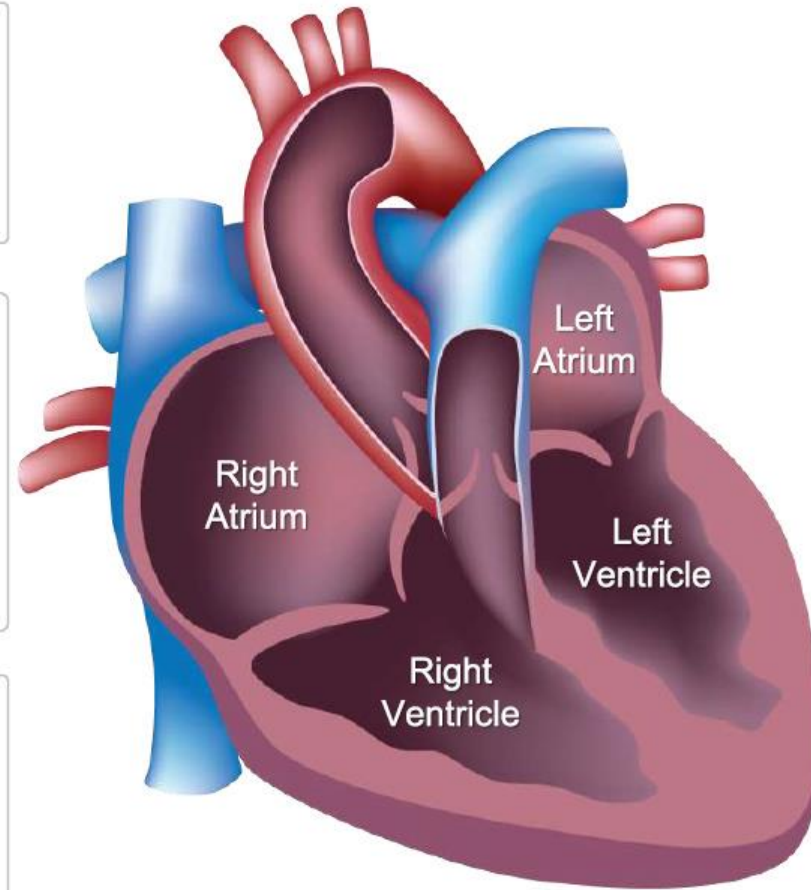
- 심장의 구조적 혹은 기능적 이상으로 말초 기관에 필요한 만큼의 산소를 전달하지 못하는 상태¹

ESC 2016

- Clinical syndrome characterized by typical symptoms that may be accompanied by signs caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress²

ACCF/AHA 2013

- Complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood³



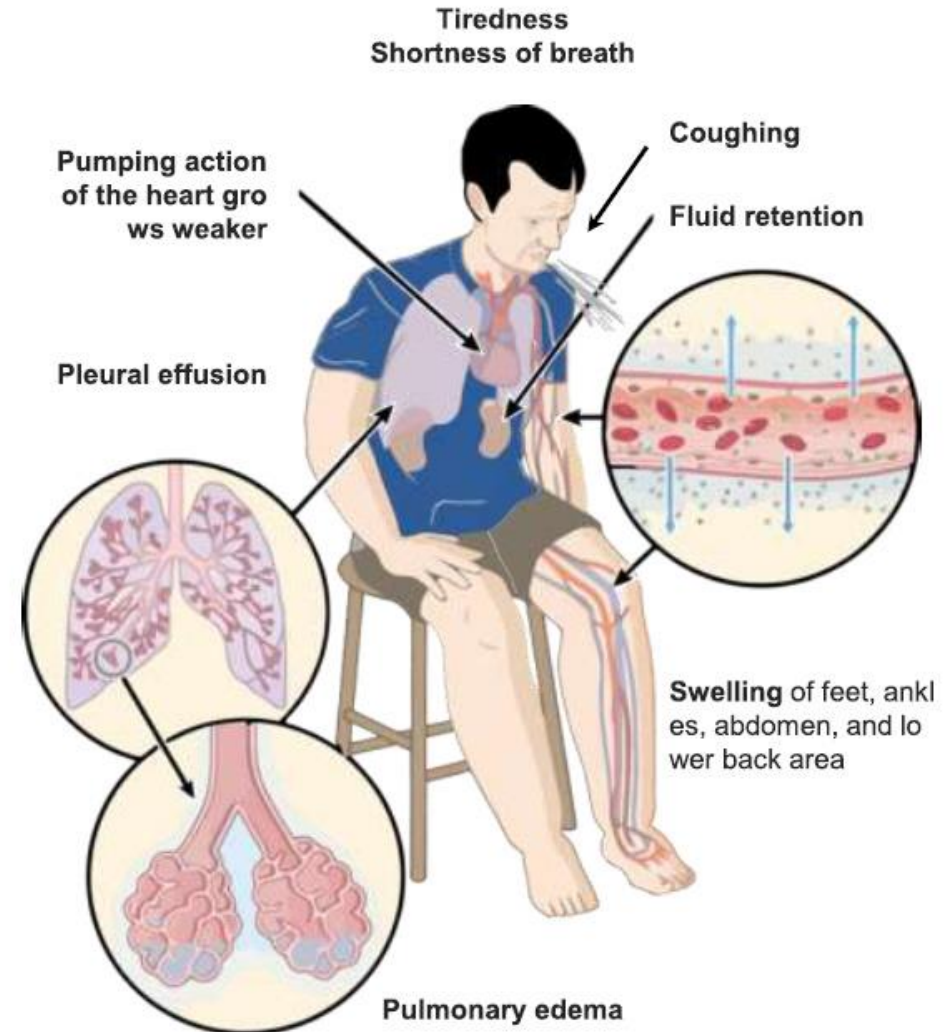
Clinical manifestation of HF

Symptoms

- Breathlessness
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Reduced exercise tolerance
- Fatigue
- Ankle swelling

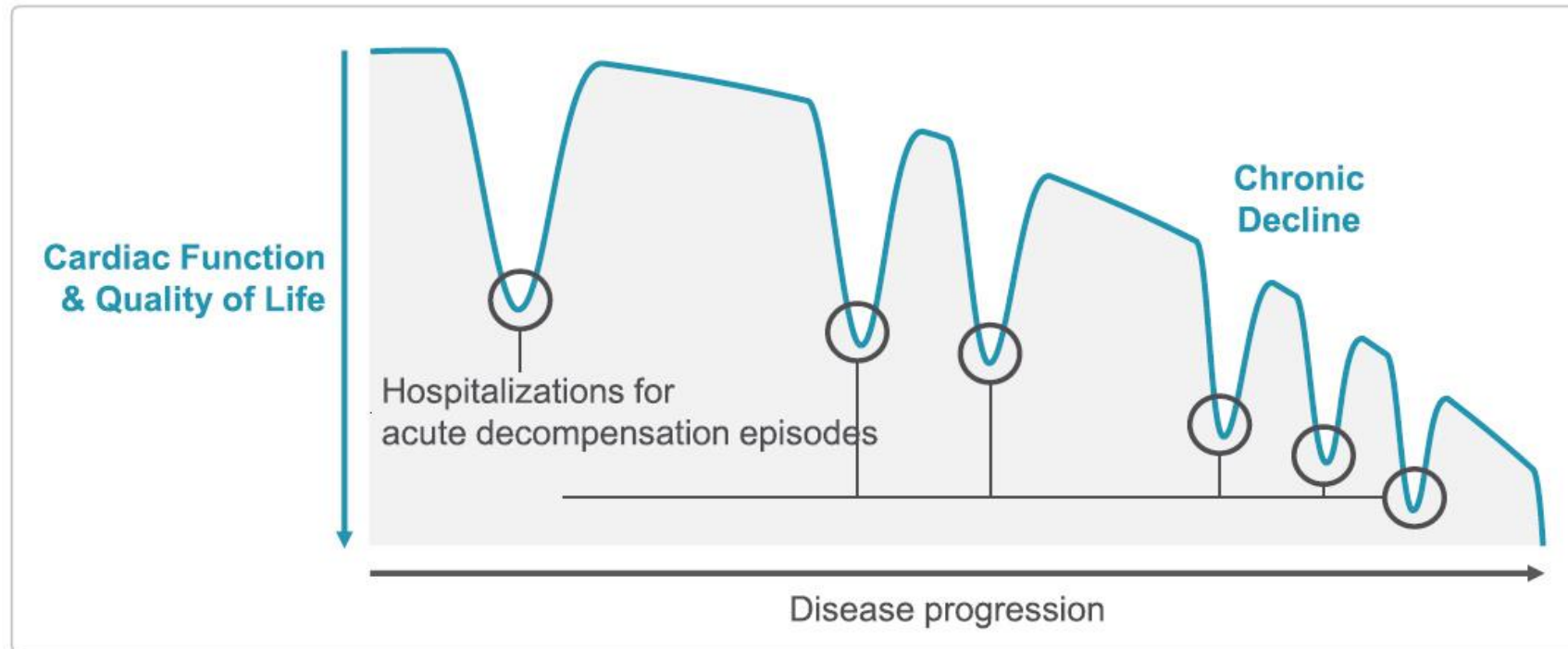
Signs

- Elevated jugular venous pressure
- Third heart sound
- Laterally displaced apical impulse
- Pulmonary crackles
- Peripheral edema



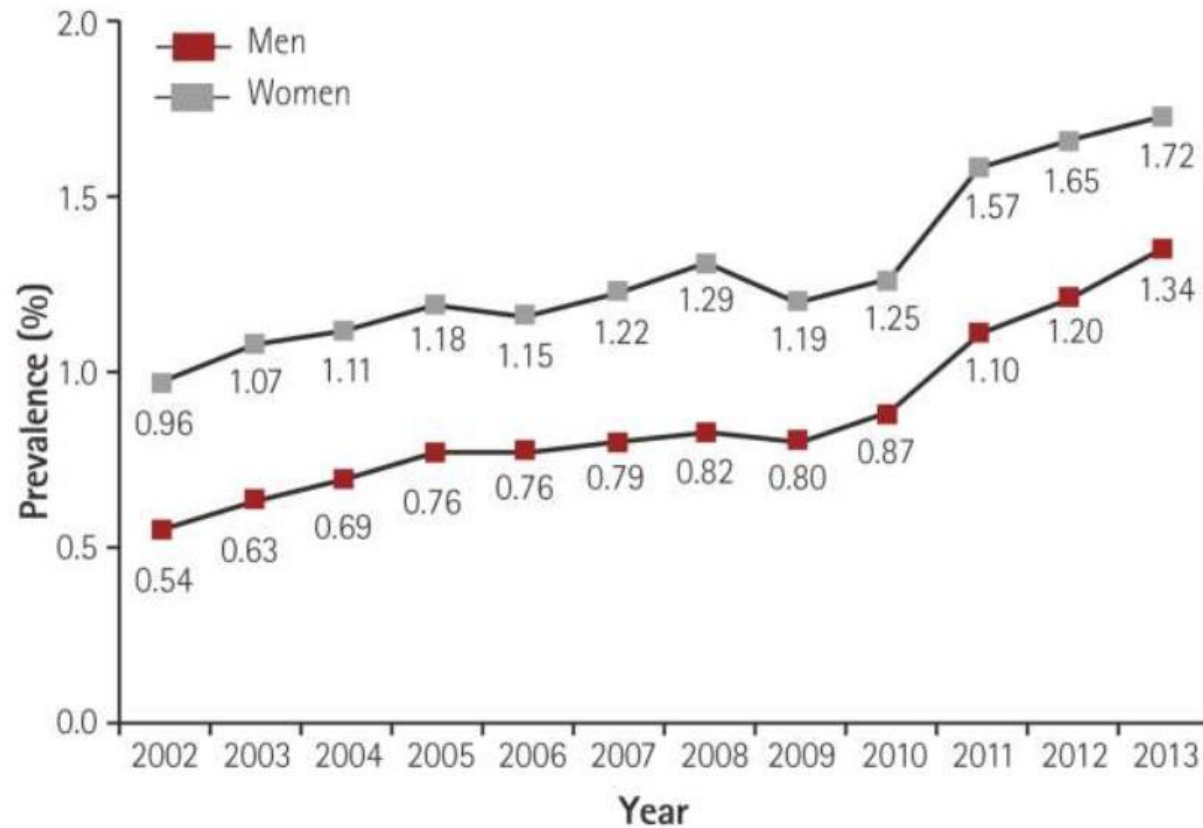
HF is a progressive disease

- Heart failure is a **chronic condition**, punctuated by **acute episodes**
- Each **acute event** results in further **organ damage**: myocardial and renal damage occurring during such episodes may contribute to progressive left ventricular and/or renal dysfunction
- Increasing **frequency of acute events** with **disease progression** leads to **higher rates of hospitalization** and **increased risk of mortality**



HF epidemiology in Korea

Increased by 104%, from 0.75% in 2002 to 1.53% in 2013



Mortality of HF in Korea

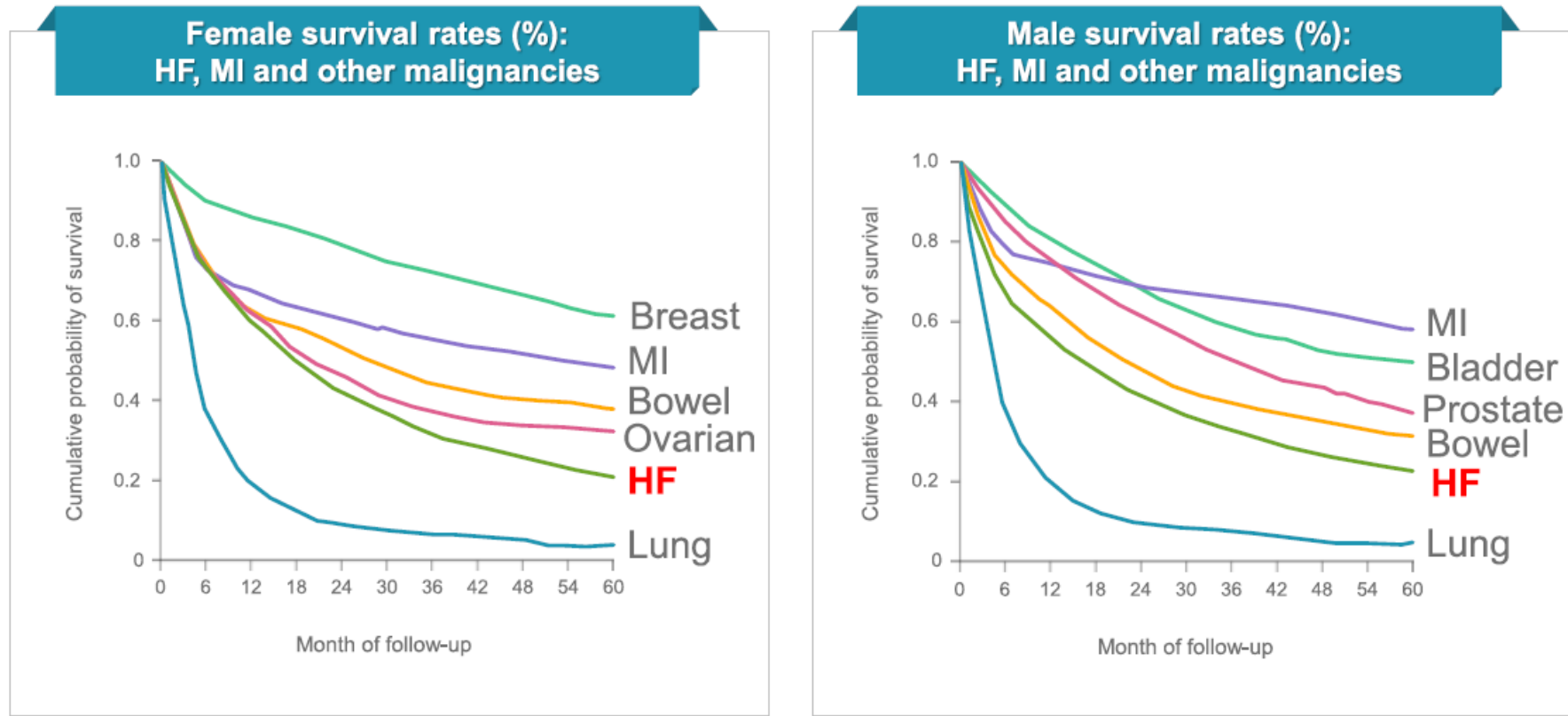


HF=heart failure

1. Lee et al. A multicentre cohort study of acute heart failure syndromes in Korea: rationale, design, and interim observations of the Korean Acute Heart Failure (KorAHF) registry. Eur J. HF (2014) 16, 700–708

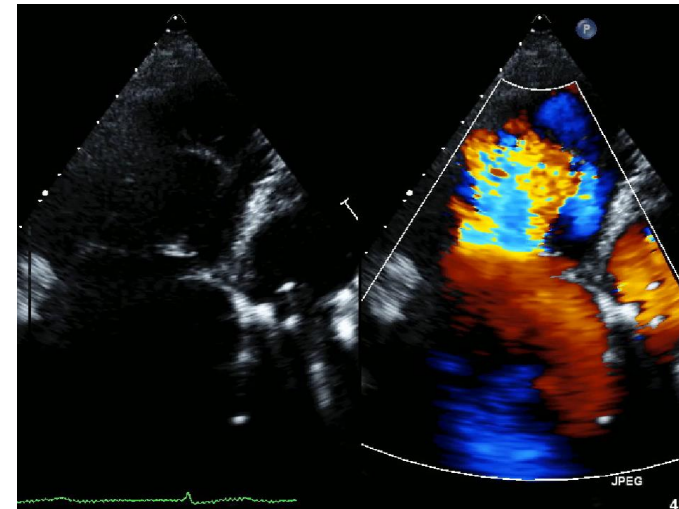
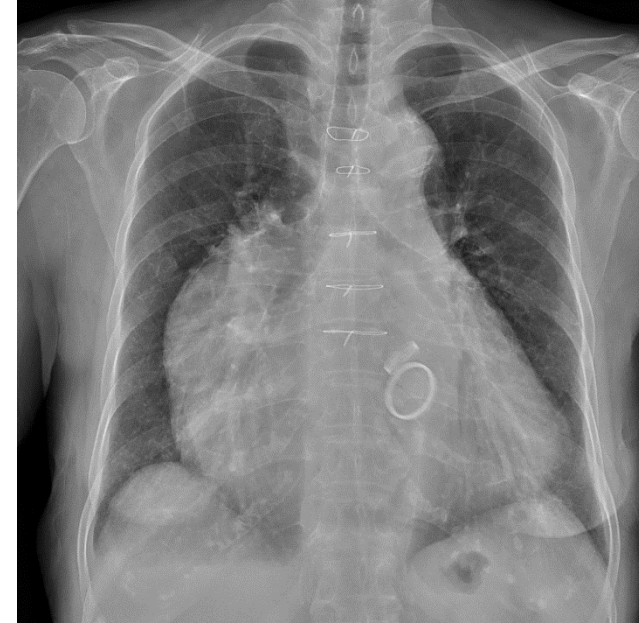
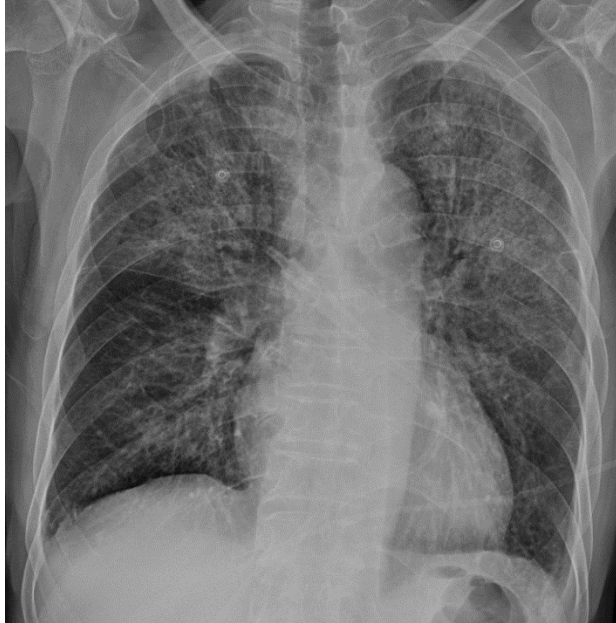
2. Choi et al. Characteristics, Outcomes and Predictors of Long-Term Mortality for Patients Hospitalized for Acute Heart Failure: A Report From the Korean Heart Failure Registry. Korean Circ J. 2011 Jul; 41(7): 363–371.

Mortality of HF in Korea



All patients with a first admission to any Scottish hospital in 1991 for HF, MI or the four most common types of cancer specific to men and women were identified, and 5-year survival rates compared.

Acute HF vs Chronic HF



Chronic HF : HFrEF vs HFpEF

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).

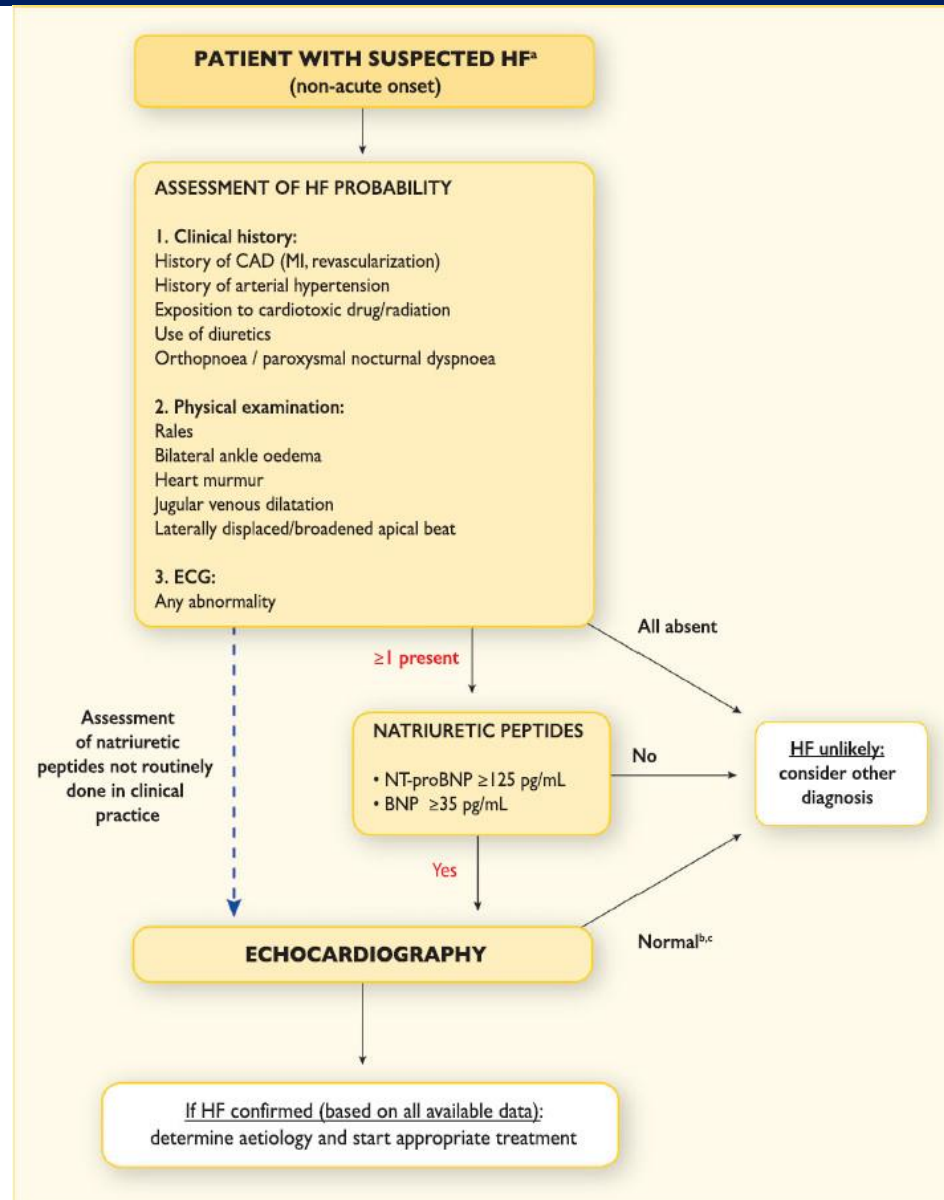


- Normal end-diastolic volume
- ↑ wall thickness and mass
- High ratio of mass:volume

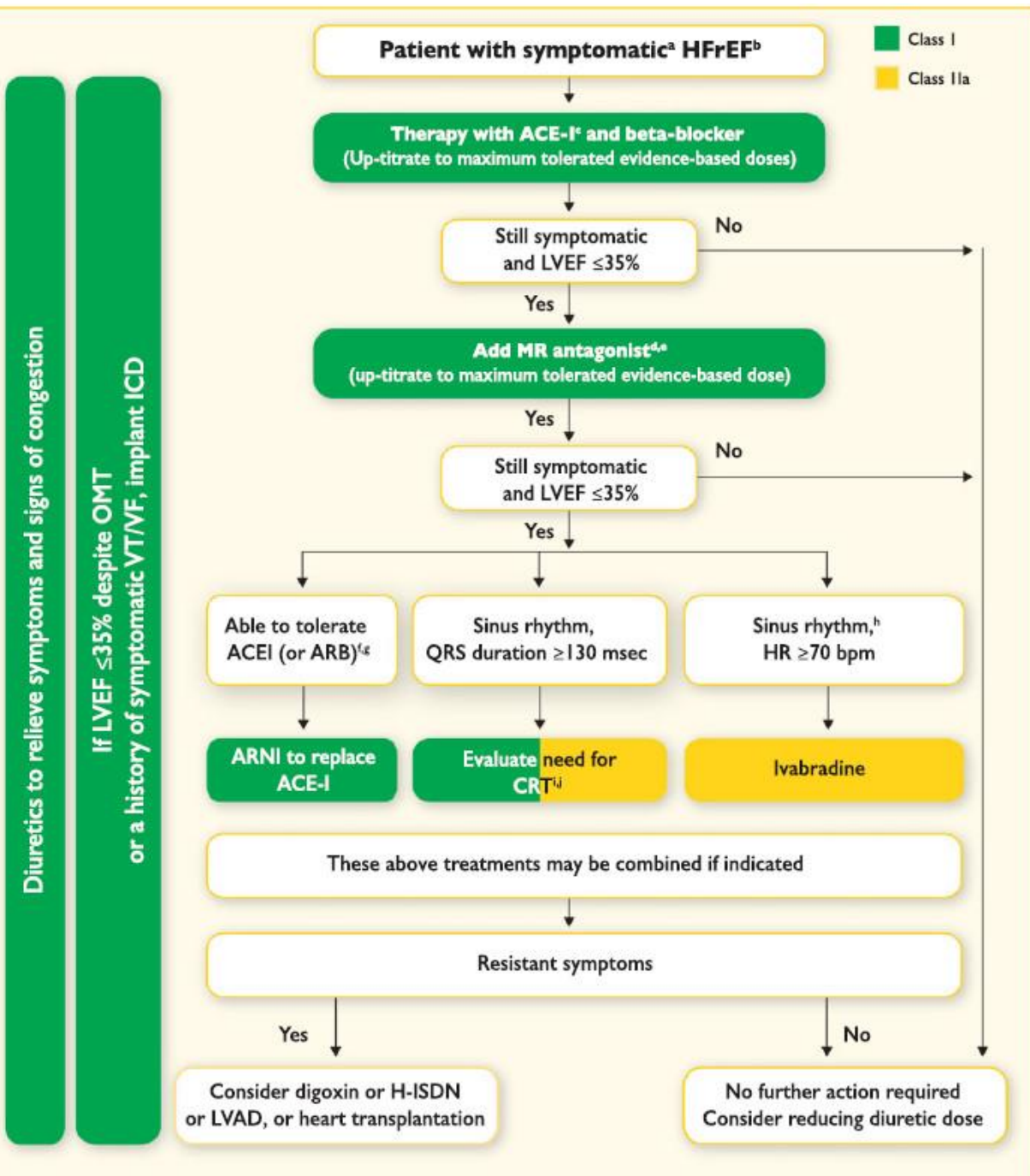


- ↑ end-diastolic volume
- ↓ wall thickness
- Low ratio of mass:volume

Approach of Chronic HF



Management of HF reduced EF



Medical Tx of HFrEF

Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction

Recommendations	Class ^a	Level ^b	Ref ^c
An ACE-I ^d is recommended, in addition to a beta-blocker, for symptomatic patients with HFrEF to reduce the risk of HF hospitalization and death.	I	A	2, 163–165
A beta-blocker is recommended, in addition an ACE-I ^d , for patients with stable, symptomatic HFrEF to reduce the risk of HF hospitalization and death.	I	A	167–173
An MRA is recommended for patients with HFrEF, who remain symptomatic despite treatment with an ACE-I ^d and a beta-blocker, to reduce the risk of HF hospitalization and death.	I	A	174, 175

ACE-I

Captopril ^a	6.25 <i>t.i.d.</i>	50 <i>t.i.d.</i>
Enalapril	2.5 <i>b.i.d.</i>	10–20 <i>b.i.d.</i>
Lisinopril ^b	2.5–5.0 <i>o.d.</i>	20–35 <i>o.d.</i>
Ramipril	2.5 <i>o.d.</i>	10 <i>o.d.</i>
Trandolapril ^a	0.5 <i>o.d.</i>	4 <i>o.d.</i>

ARBs

Candesartan	4–8 <i>o.d.</i>	32 <i>o.d.</i>
Valsartan	40 <i>b.i.d.</i>	160 <i>b.i.d.</i>
Losartan ^{b,c}	50 <i>o.d.</i>	150 <i>o.d.</i>

Beta-blockers

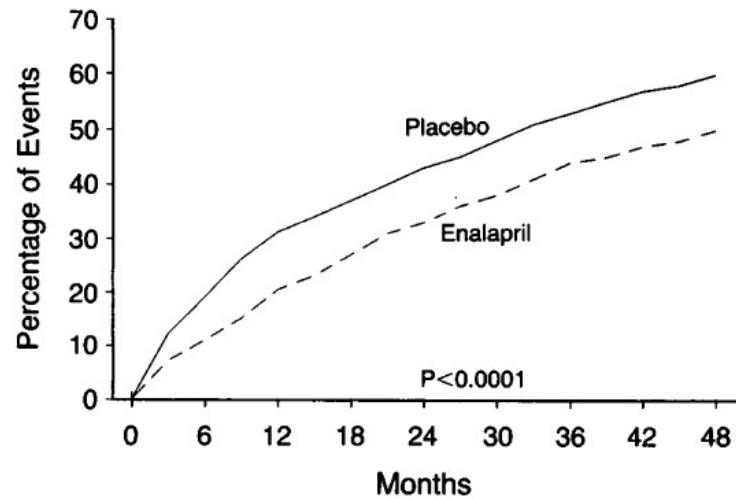
Bisoprolol	1.25 <i>o.d.</i>	10 <i>o.d.</i>
Carvedilol	3.125 <i>b.i.d.</i>	25 <i>b.i.d.</i> ^d
Metoprolol succinate (CR/XL)	12.5–25 <i>o.d.</i>	200 <i>o.d.</i>
Nebivolol ^c	1.25 <i>o.d.</i>	10 <i>o.d.</i>

RAS inhibitor

SOLVE trial

Enalapril (n=1285) vs Placebo (n=1284)

총 사망률 16%감소



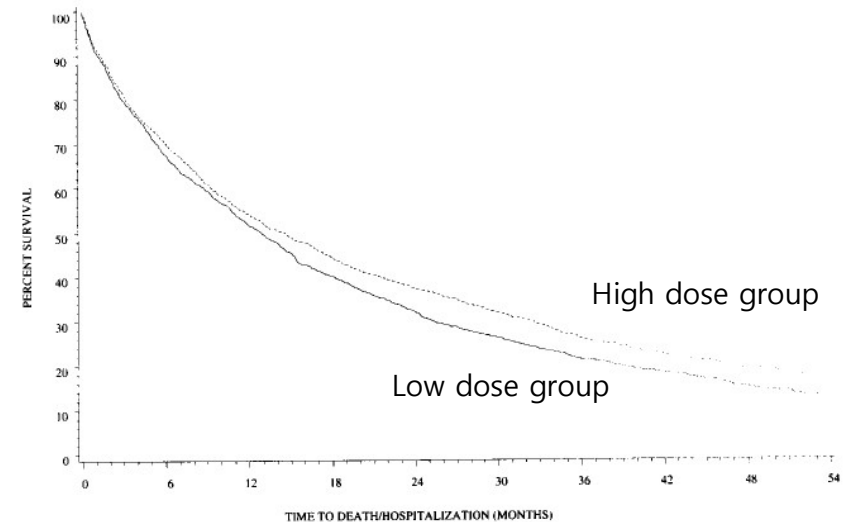
NEJM 1991;325(5):293-302

ATLAS study

Lisinopril

Low dose (n=1596) vs High dose (n=1568)

사망률과 재입원율 15% 감소

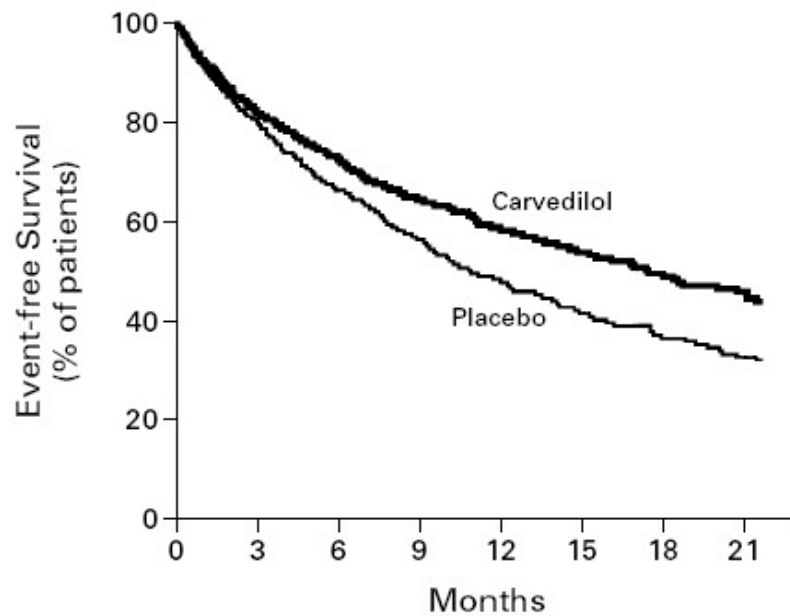


Circulation 1999 Dec 7;100(23):2312-8

B-blocker / Spironolactone

EF < 25%

Carvedilol (n=1156) vs Placebo (n=1133)



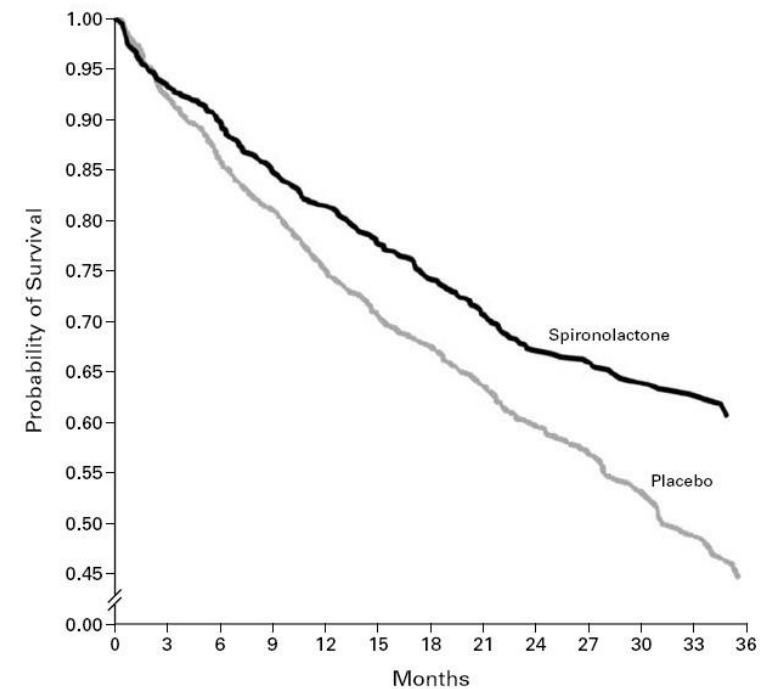
NO. OF PATIENTS AT RISK

Placebo	1133	767	513	377	262	154	88	55
Carvedilol	1156	789	559	431	318	208	122	81

NEJM 1991;325(5):293-302

EF < 35%

Spironolactone (n=822) vs Placebo (n=841)

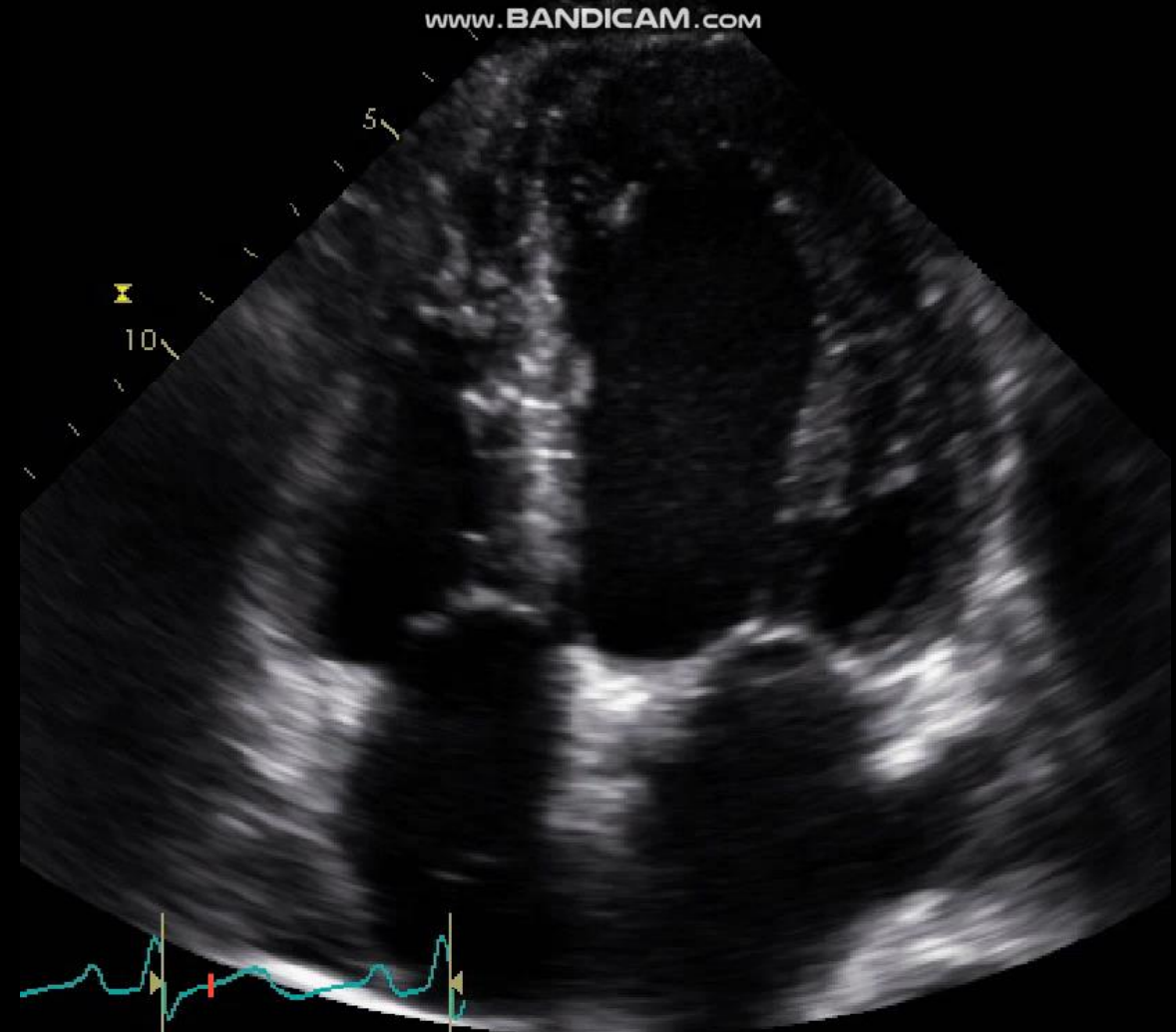


NO. AT RISK

Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

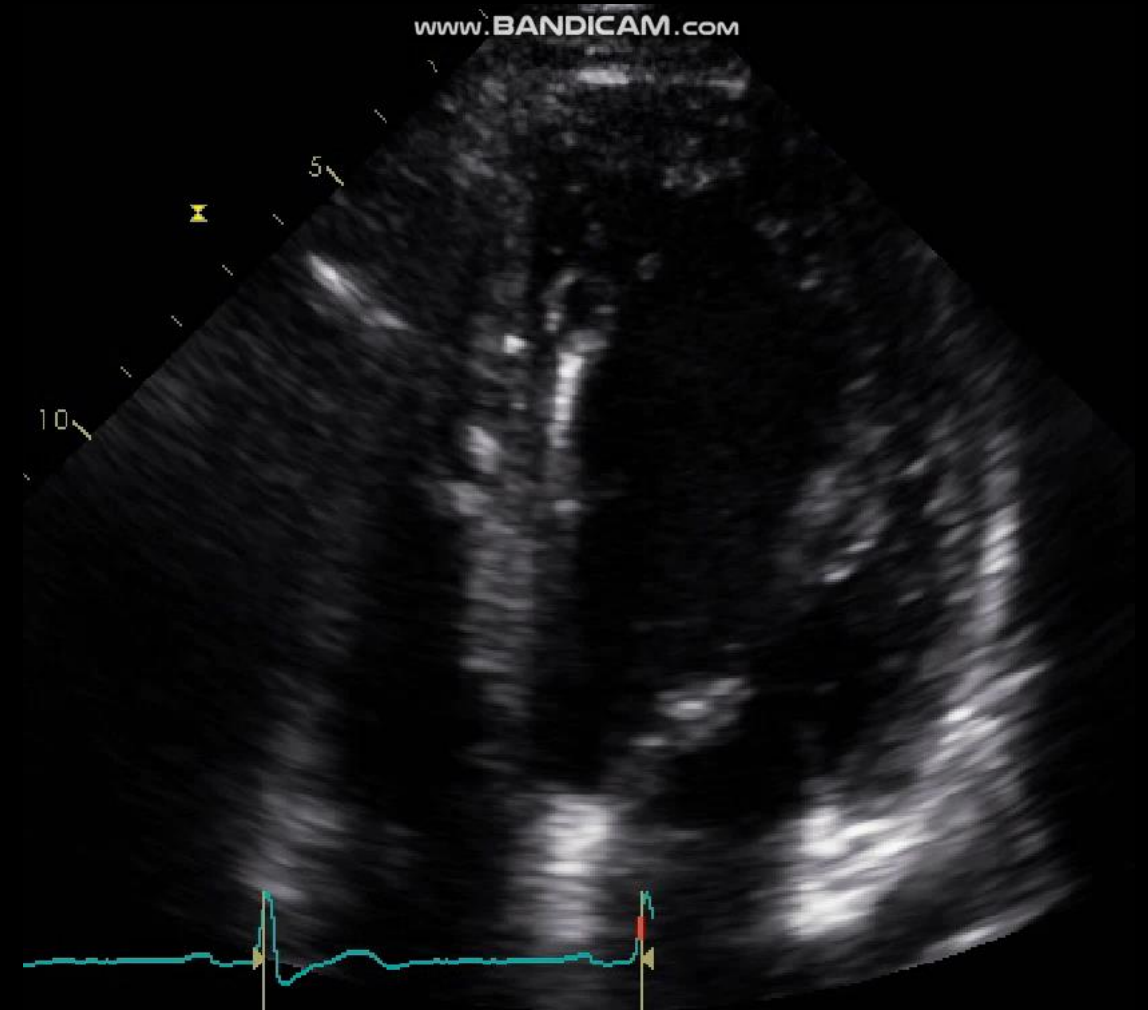
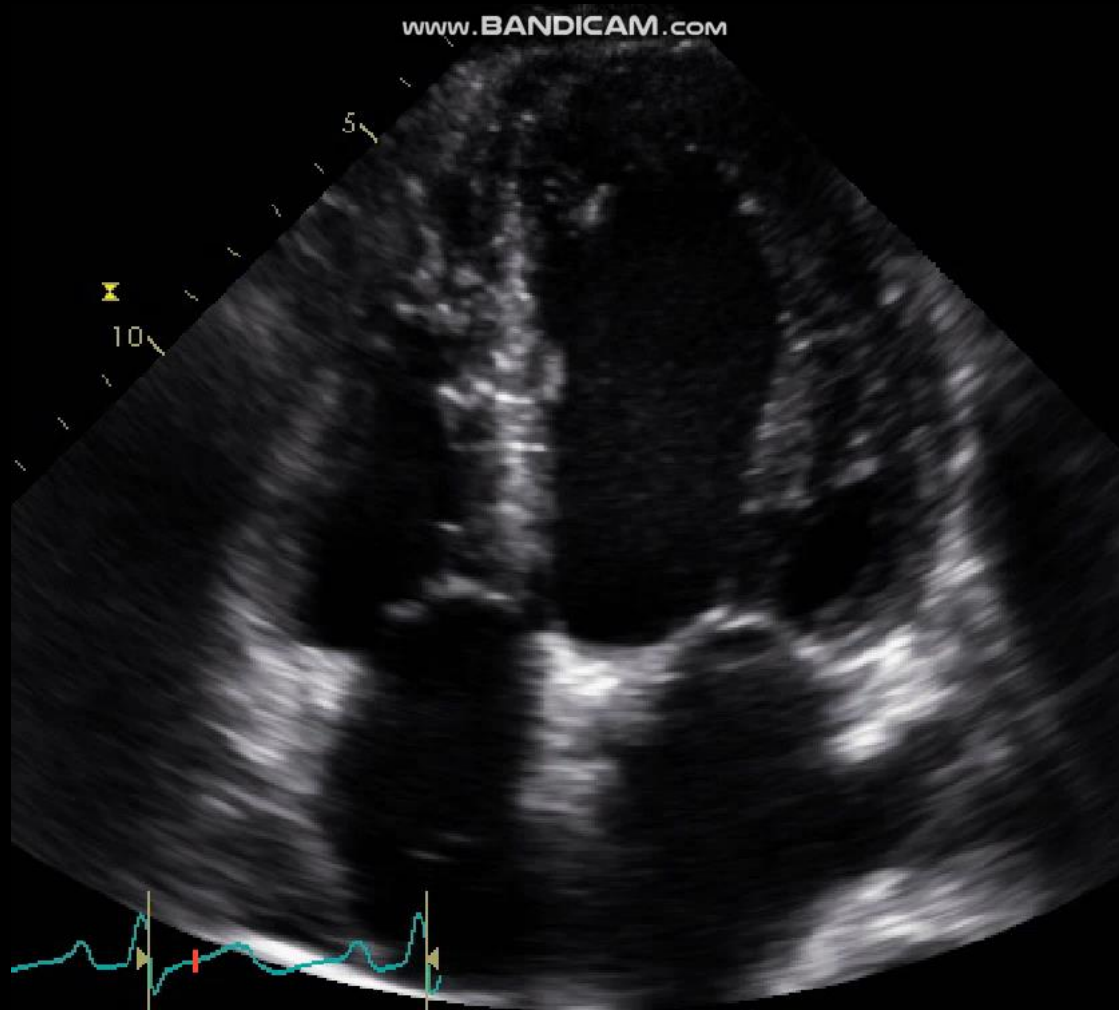
NEJM 1999;341(10):709-17

49/M Dsypnea



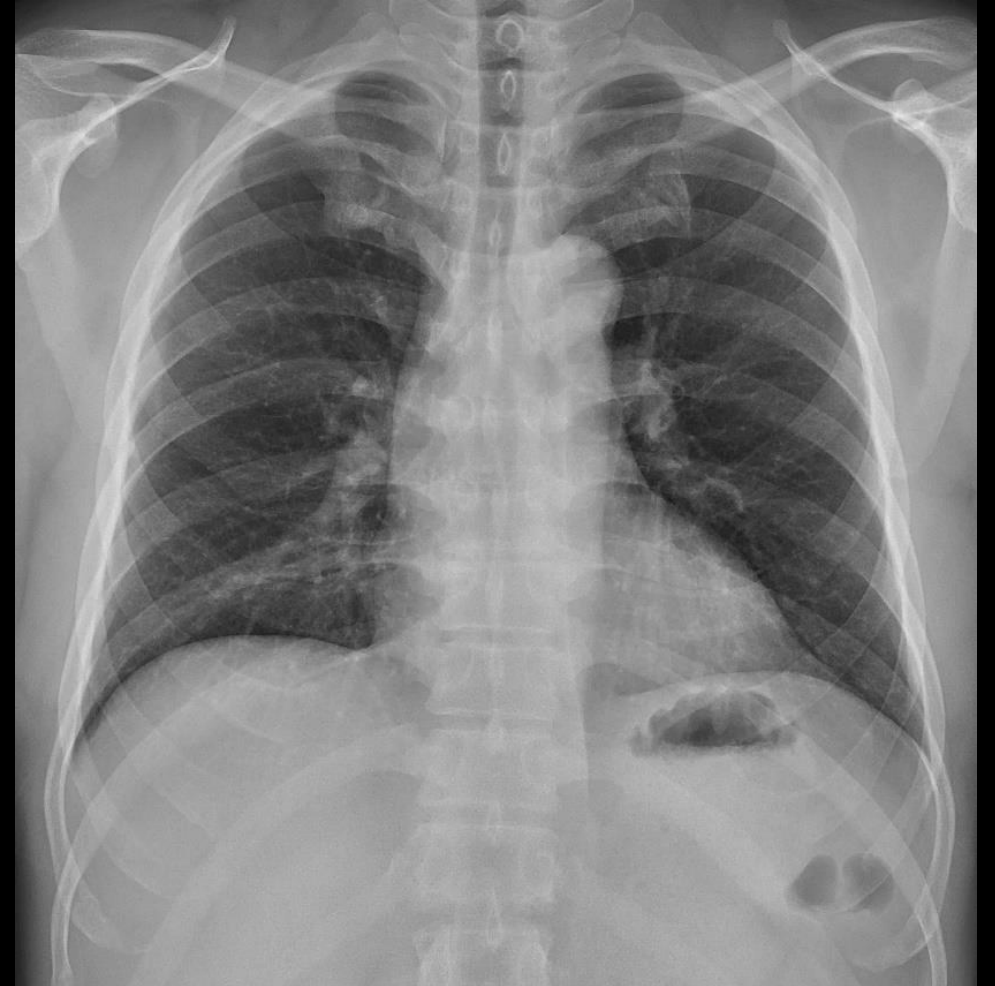
	SLP	항목	수량	회	일	D	P	자	투여방법
1		퇴원 Discharge order							
2	C10	Capril 50mg tab << 50.000 MG >>	1.0000	3	7				P0.내복
3	C10	*** TID(매 식후 30분) ***							
4	C10	Lasix 40mg tab << 40.000 MG >>	1.0000	2	7				P0.내복
5	C10	*** BID(아침,저녁식후30분) ***							
6	C10	Lipitor 20mg tab << 20.000 MG >>	1.0000	1	7				P0.내복
7	C10	Concor 5mg tab << 5.000 MG >>	1.0000	1	7				P0.내복
8	C10	Aldactone 25mg tab << 12.500 MG >>	0.5000	1	7				P0.내복
9	C10	*** QD(아침식후30분) ***							

49/M Dsypnea



6 month f/u

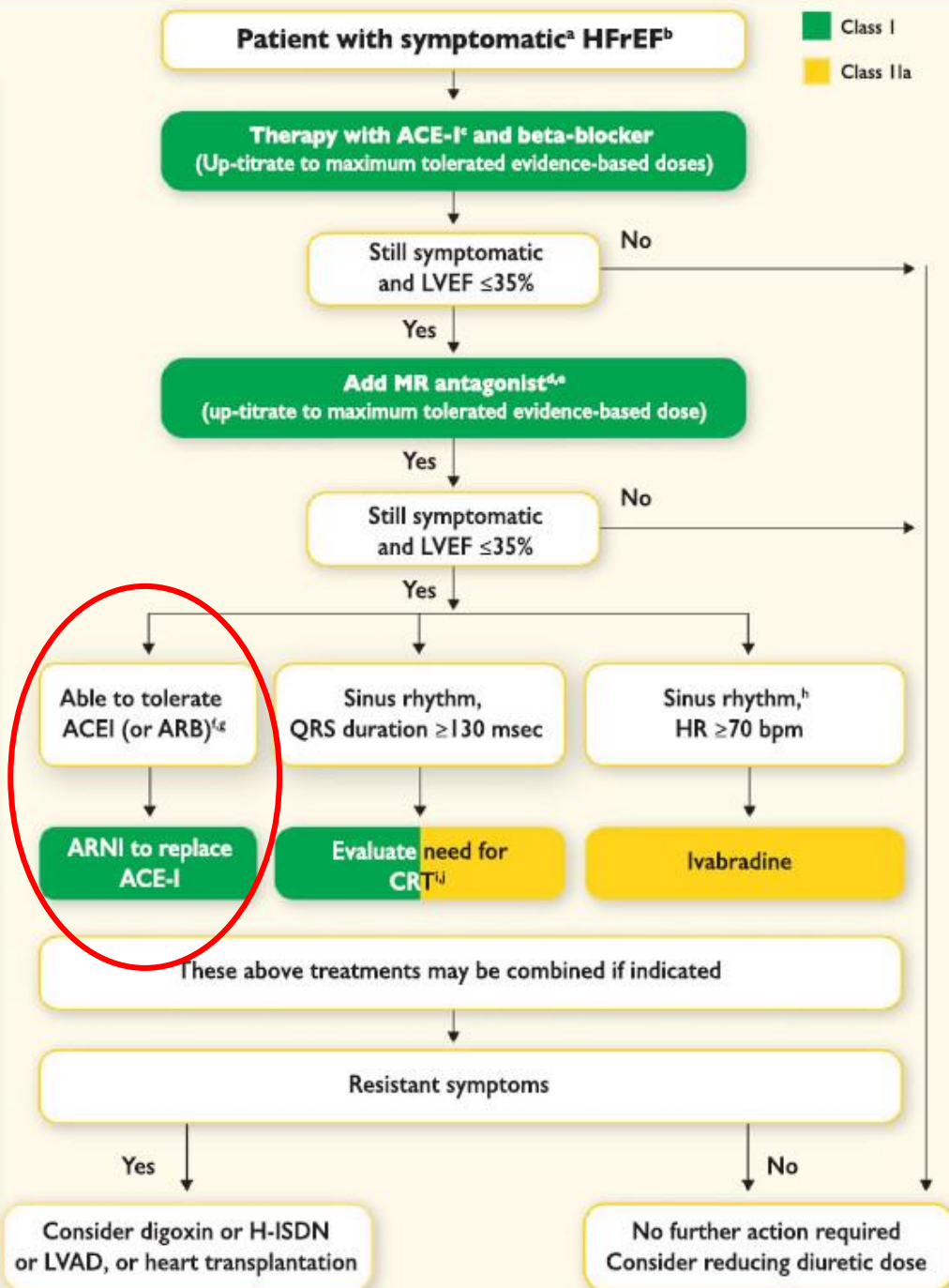
49/M Dsypnea



12 month f/u

Diuretics to relieve symptoms and signs of congestion

If LVEF $\leq 35\%$ despite OMT
or a history of symptomatic VT/VF, implant ICD



엔트레스토 필름코팅정 100mg [원내, ENTRES1] [전문]

ENTRESTO FILM COATED TAB 100mg

- ▶ **제조사** | Novartis AG [HOME PAGE](#)
- ▶ **판매사** | 한국노바티스 (Novartis Korea) [HOME PAGE](#)
- ▶ **조성** | Sacubitril-Valsartan sodium salt hydrate 113,103mg
(100mg as Sacubitril-Valsartan)



Angiotensin receptor–Neprilysin Inhibition

The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

SEPTEMBER 11, 2014

VOL. 371 NO. 11

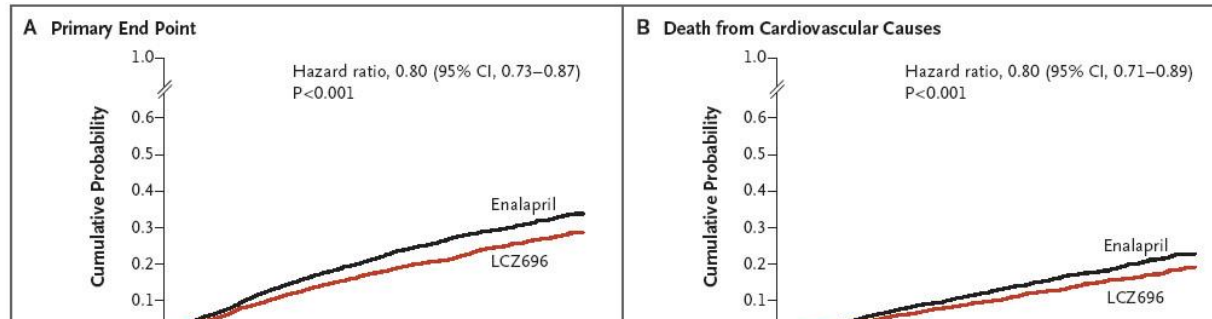
Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D.,
Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D.,
Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D.,
for the PARADIGM-HF Investigators and Committees*

Angiotensin receptor–Neprilysin Inhibition

NYHA class II,III,IV with LV EF <40%

ARNI vs Enalapril

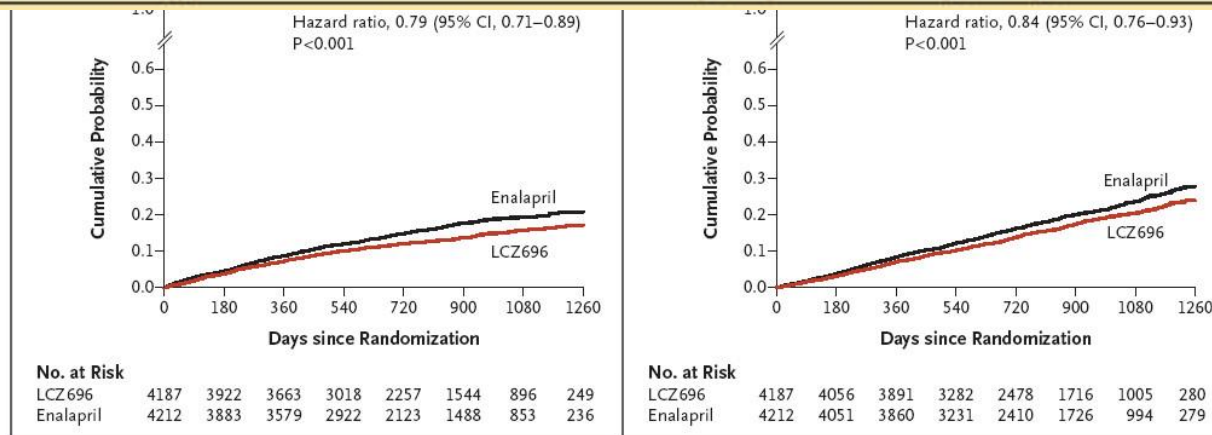


Angiotensin receptor neprilysin inhibitor

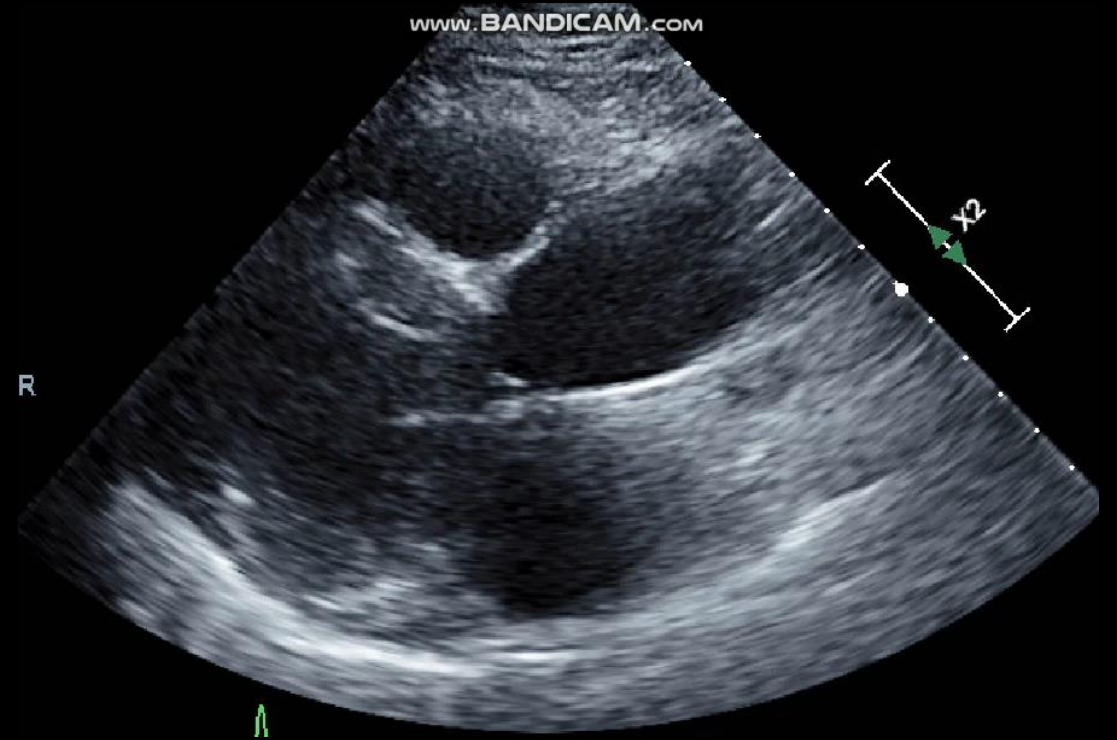
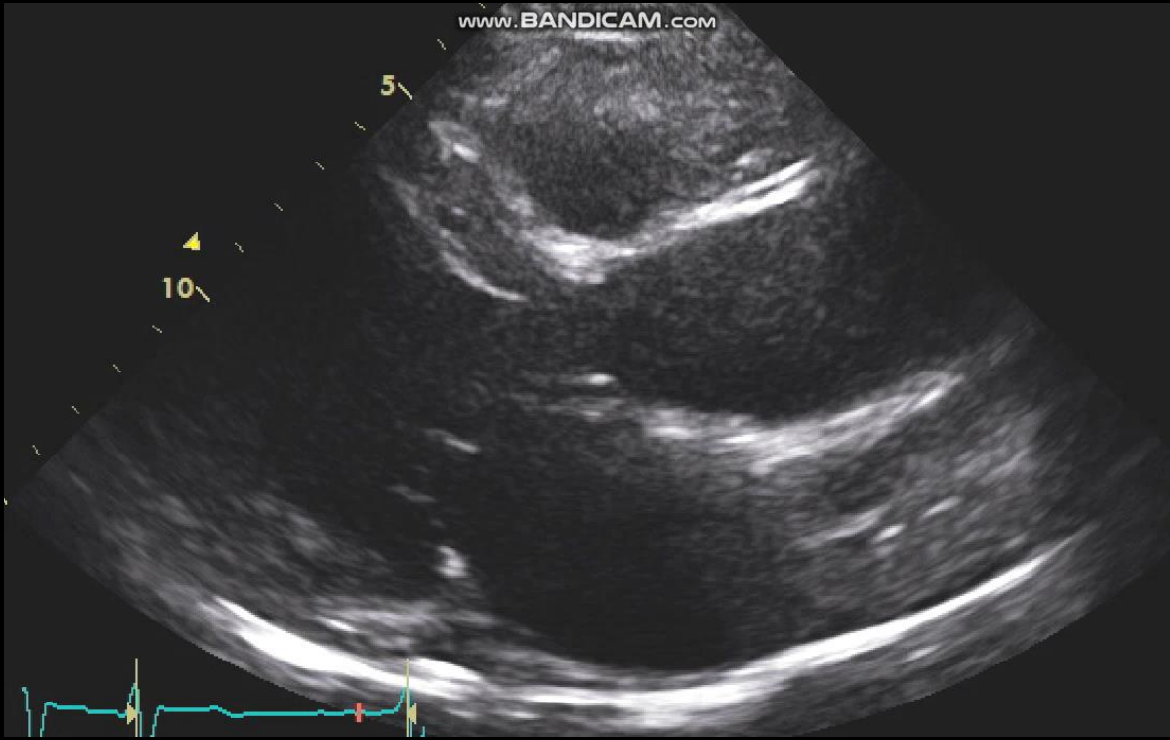
Sacubitril/valsartan is recommended as a replacement for an ACE-I to further reduce the risk of HF hospitalization and death in ambulatory patients with HFrEF who remain symptomatic despite optimal treatment with an ACE-I, a beta-blocker and an MRA^d

I

B



74/F HFrEF, CAOD 3VD



PIONEER-HF : ARNI in ADHF

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure

Eric J. Velazquez, M.D., David A. Morrow, M.D., M.P.H.,
Adam D. DeVore, M.D., M.H.S., Carol I. Duffy, D.O., Andrew P. Ambrosy, M.D.,
Kevin McCague, M.A., Ricardo Rocha, M.D., and Eugene Braunwald, M.D.,
for the PIONEER-HF Investigators*

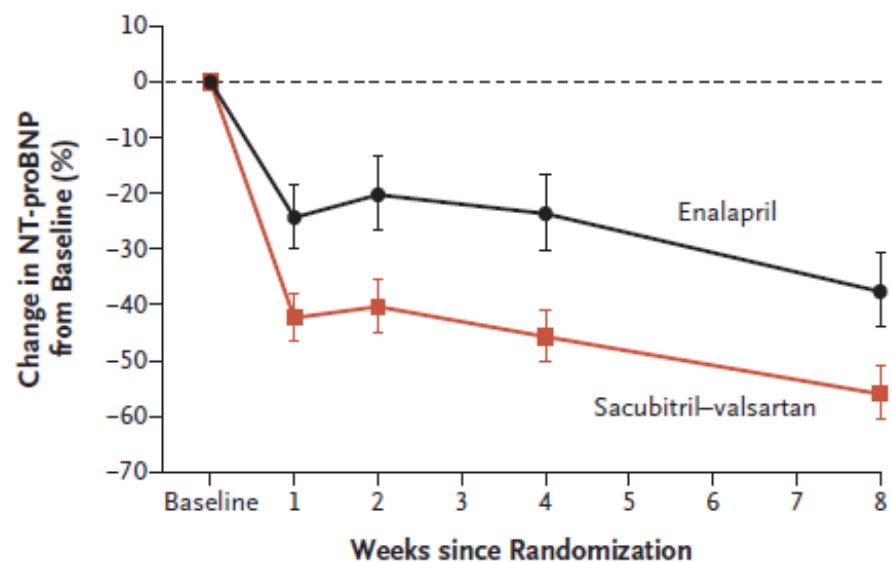
Study design

- Multicenter (126 sites in USA), randomized, double-blind, active-controlled trial of the in-hospital initiation of sacubitril–valsartan therapy, as compared with enalapril therapy, among patients who had been admitted for acute decompensated heart failure with reduced ejection fraction.
- Inclusion Criteria
 - LVEF < 40%
 - NT-proBNP > 1600pg/mL or BNP > 400pg/mL
 - Primary diagnosis of ADHF
 - Hemodynamically stable state

Hemodynamically stable

- Before randomization, patients were required to be hemodynamically stable, which was defined
- maintenance of a systolic blood pressure of at least 100 mm Hg for the preceding 6 hours
- no increase in the dose of intravenous diuretics
- no use of intravenous vasodilators during the preceding 6 hours
- no use of intravenous inotropes during the preceding 24 hours.

Efficacy and Safety



No. at Risk

Enalapril	394	359	351	350	348
Sacubitril-valsartan	397	355	363	365	349

Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril-Valsartan (N=440)	Enalapril (N=441)	Sacubitril-Valsartan vs. Enalapril
Key safety outcomes — no. (%)			Relative risk (95% CI)
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			Ratio of change (95% CI)
Change in high-sensitivity troponin T concentration	-36.6 (-40.8 to -32.0)	-25.2 (-30.2 to -19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	-28.7 (-35.5 to -21.3)	-33.1 (-39.5 to -25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	-8.3 (-3.6 to -12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			Hazard ratio (95% CI)§
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

ARNI in functional MR

Circulation

ORIGINAL RESEARCH ARTICLE



Angiotensin Receptor Neprilysin Inhibitor for Functional Mitral Regurgitation

PRIME Study

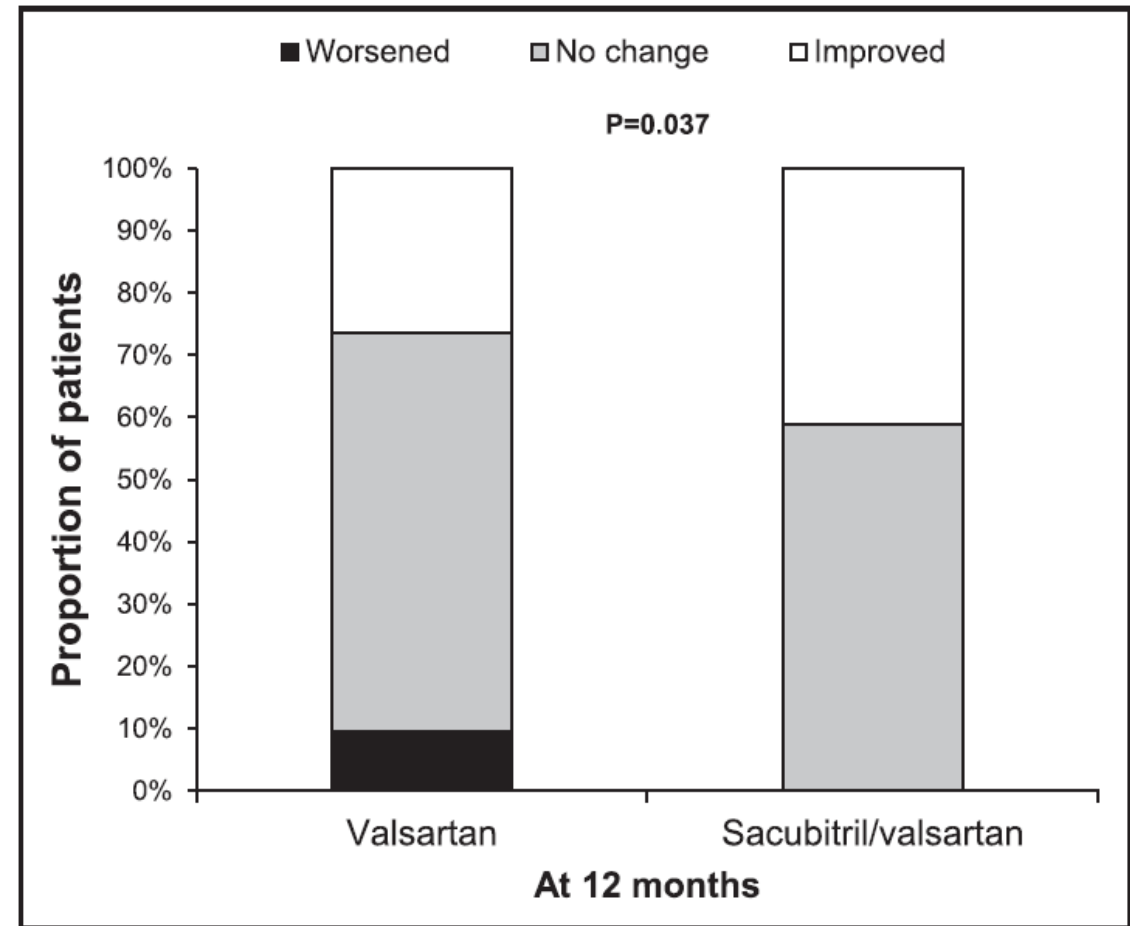
Prime Study : ARNI in functional MR

BACKGROUND: The morbidity and mortality of patients with functional mitral regurgitation (MR) remain high, but no pharmacological therapy has been proven effective. The hypothesis of this study was that sacubitril/valsartan would be superior to valsartan alone in improving functional MR via dual inhibition of the renin-angiotensin system and neprilysin.

METHODS: In this double-blind trial, we randomly assigned 118 patients with heart failure with chronic functional MR secondary to left ventricular (LV) dysfunction to receive either sacubitril/valsartan or valsartan, in addition to standard medical therapy for heart failure. The primary end point was the change in effective regurgitant orifice area of functional MR from baseline to the 12-month follow-up. Secondary end points included changes in regurgitant volume, LV end-systolic volume, LV end-diastolic volume, and incomplete mitral leaflet closure area.

RESULTS: The decrease in effective regurgitant orifice area was significantly greater in the sacubitril/valsartan group than in the valsartan group (-0.058 ± 0.095 versus -0.018 ± 0.105 cm²; $P=0.032$) in an intention-to-treat analysis including 117 (99%) patients. Regurgitant volume was also significantly decreased in the sacubitril/valsartan group in comparison with the valsartan group (mean difference, -7.3 mL; 95% CI, -12.6 to -1.9 ; $P=0.009$). There were no significant between-group differences regarding the changes in incomplete mitral leaflet closure area and LV volumes, with the exception of LV end-diastolic volume index ($P=0.044$). We noted no significant difference in the change of blood pressure between the treatment groups, and 7 patients (12%) in the sacubitril/valsartan group and 9 (16%) in the valsartan group had ≥ 1 serious adverse events ($P=0.54$).

CONCLUSIONS: Among patients with secondary functional MR, sacubitril/valsartan reduced MR to a greater extent than did valsartan. Our findings suggest that an angiotensin receptor-neprilysin inhibitor might be considered for optimal medical therapy of patients with heart failure and functional MR.



Diuretics to relieve symptoms and signs of congestion

If LVEF $\leq 35\%$ despite OMT
or a history of symptomatic VT/VF, implant ICD

Patient with symptomatic^a HFrEF^b

Class I

Class IIa

Therapy with ACE-I^c and beta-blocker
(Up-titrate to maximum tolerated evidence-based doses)

Still symptomatic
and LVEF $\leq 35\%$

No

Yes

Add MR antagonist^{d,e}
(up-titrate to maximum tolerated evidence-based dose)

Yes

Still symptomatic
and LVEF $\leq 35\%$

No

Yes

Able to tolerate
ACEI (or ARB)^{f,g}

Sinus rhythm,
QRS duration ≥ 130 msec

Sinus rhythm,^h
HR ≥ 70 bpm

ARNI to replace
ACE-I

Evaluate need for
CRT^{i,j}

Ivabradine

These above treatments may be combined if indicated

Resistant symptoms

Yes

Consider digoxin or H-ISDN
or LVAD, or heart transplantation

No

No further action required
Consider reducing diuretic dose

Ivabradine



❑ 프로코라란 정 5mg [원내, PROC05] [전문]

PROCORALAN TAB 5mg

▶ 제 조 사 | Les Laboratoires Servier [HOME PAGE](#)

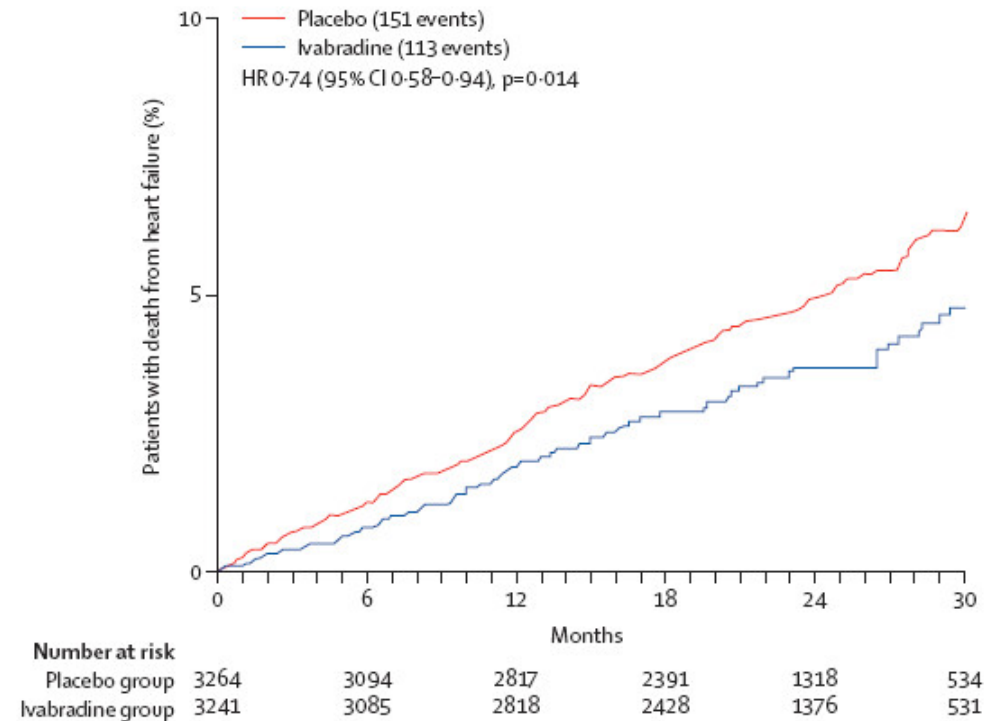
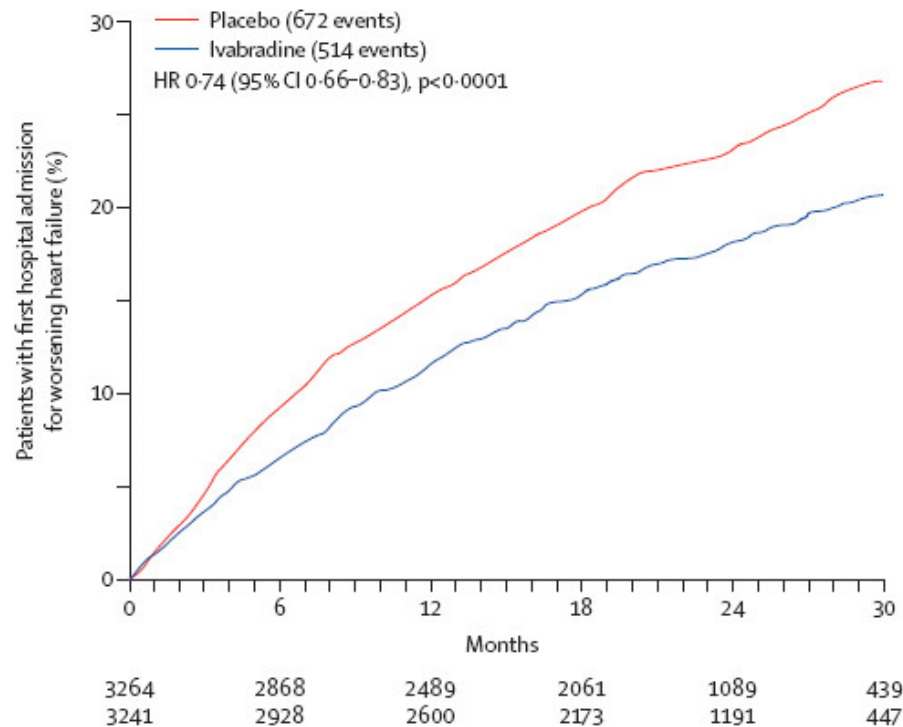
▶ 판 매 사 | 한국세르비에(주) (Servier Korea Ltd.) [HOME PAGE](#)

▶ 조 성 | ivabradine hydrochloride 5.39mg (5mg as ivabradine)

- HFrEF 에서 tachycardia가 지속되면 좌심실 충만장애가 생기고 심근 산소소모량이 증가하여 장기적으로 심부전을 악화시킬 수 있다.
- Ivabradine은 심박조율기에 있는 funny channel (I_f)을 선택적으로 억제하여 순수하게 심장 박동수만 감소시키고 혈압 또는 심근수축력에는 영향을 미치지 않는다

Ivabradine

Symptomatic HF, LV EF<35%, sinus rhythm with HR>70,
Ivabradine group (N=3241) vs Placebo group (N=3264)
median f/u 22.9 month



Management of HF preserved EF

Diagnosis of HFpEF

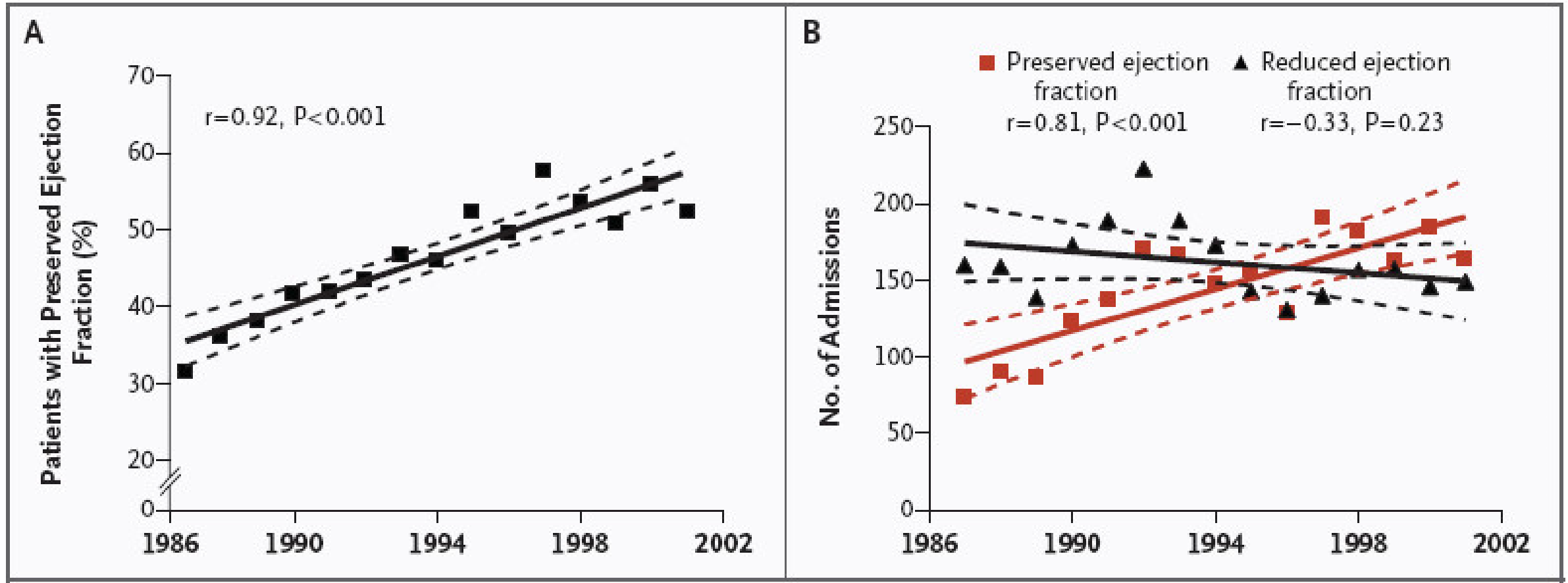
All of following

- **Presence of symptoms and signs of HF**
- **EF $\geq$ 50%**
- **Elevated levels of BNP (> 35 pg/mL) or NT proBNP (> 125 pg/ml)**
- **Objective echocardiographic evidence of other cardiac functional or structural alterations**

Functional : diastolic dysfunction, E/e' ratio

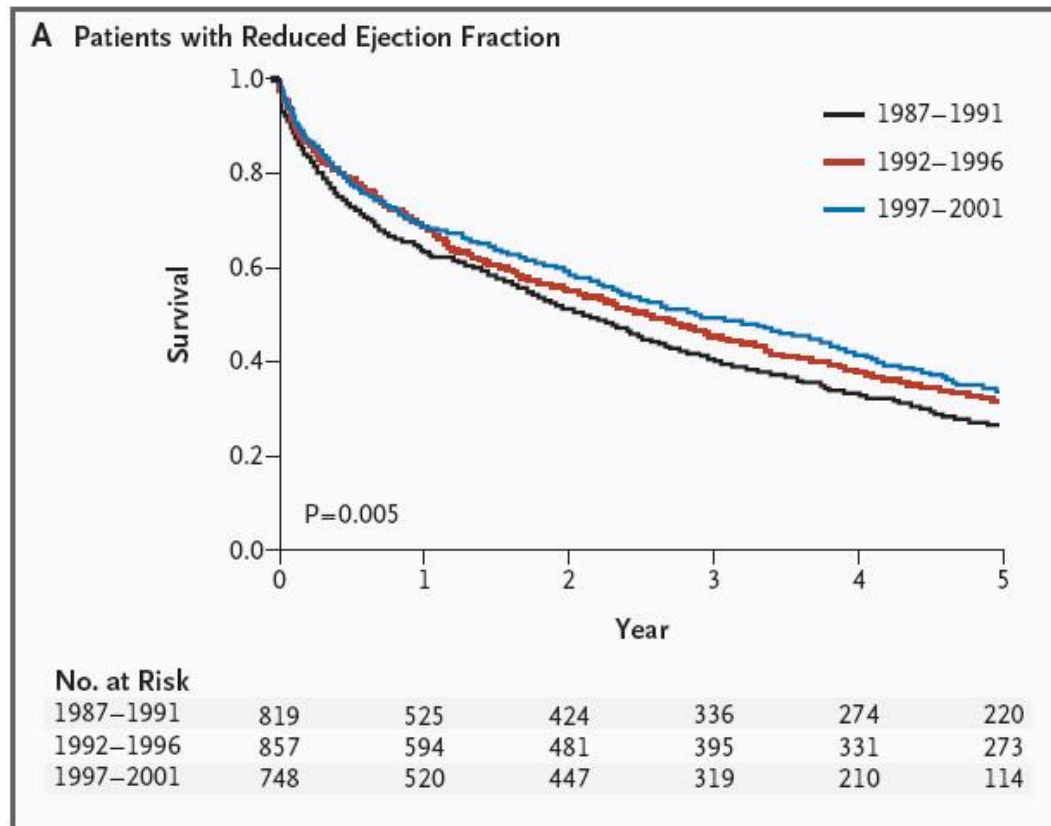
Structural : left ventricular hypertrophy, left atrial volume

Epidemiology of HFpEF

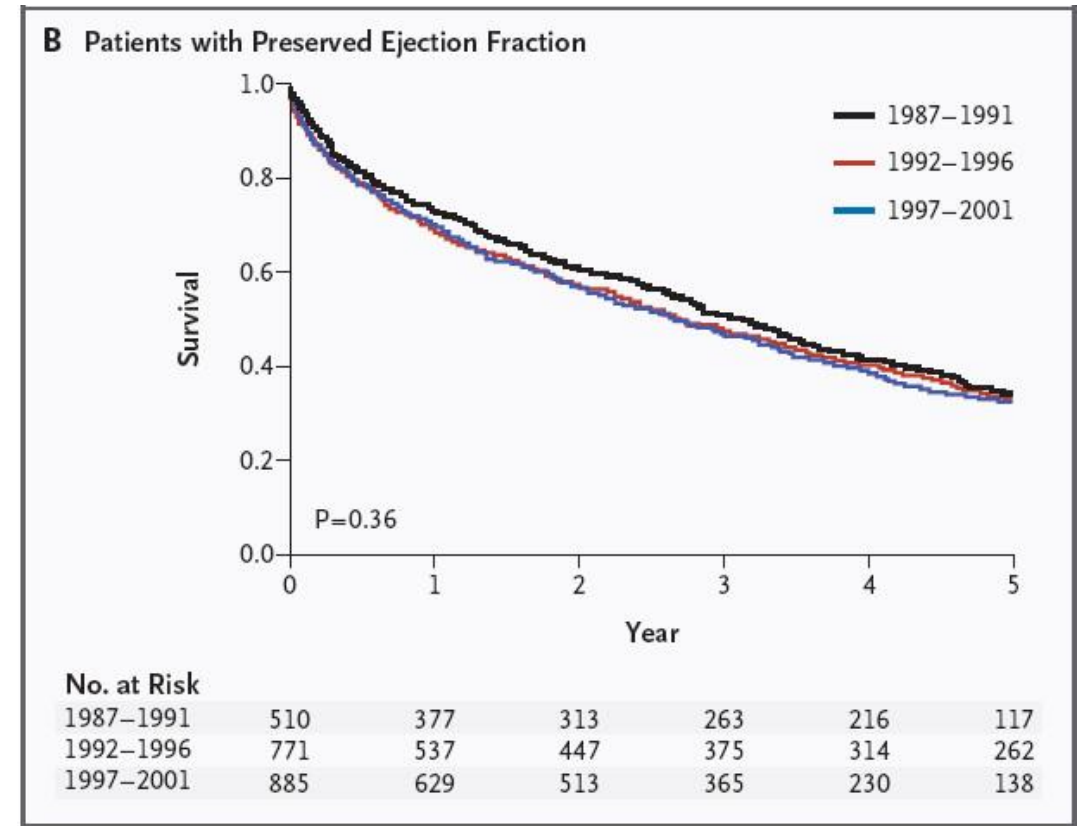


Trends in HFpEF outcome

Improving outcome in HFrEF



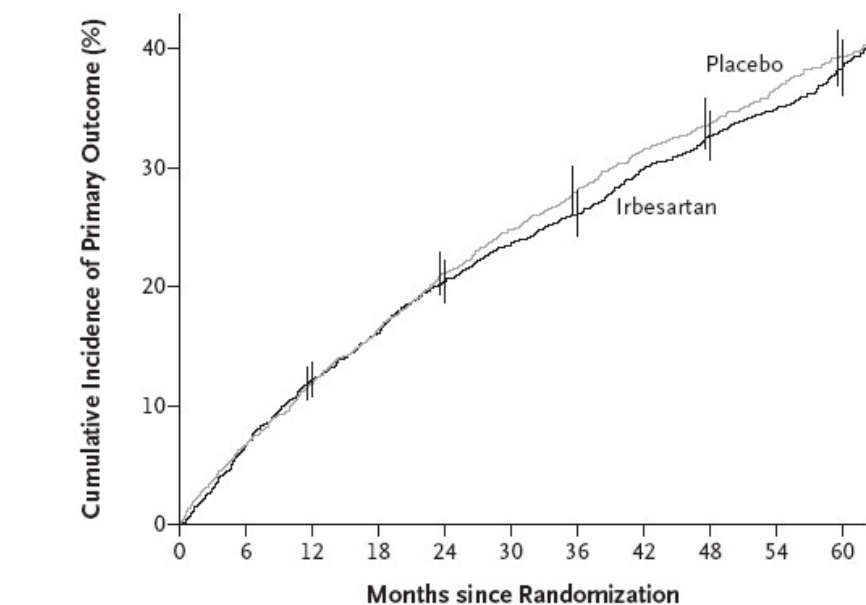
Unchanging outcome in HFpEF



ARB / MRA in HFpEF

Age > 60, NYHA II-IV, LVEF > 45%

Irbesartan (N=2067) vs Placebo (N=2061)

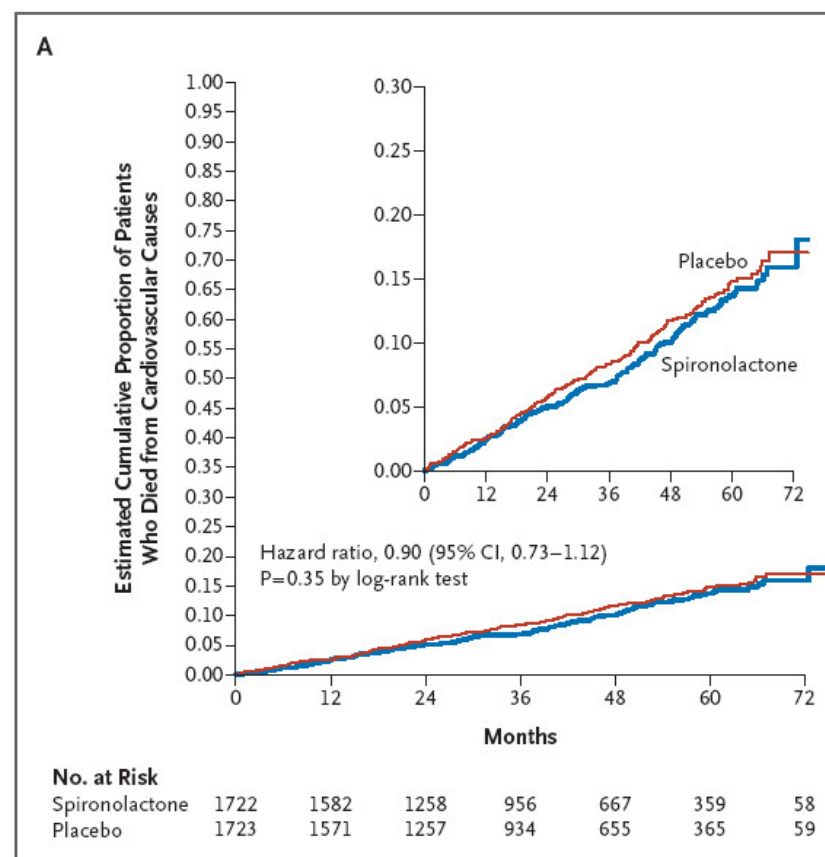


No. at Risk											
Irbesartan	2067	1929	1812	1730	1640	1569	1513	1291	1088	816	497
Placebo	2061	1921	1808	1715	1618	1539	1466	1246	1051	776	446

NEJM 2008;359:2456-2467

TOPCAT study LV EF > 45%

Spironolactone (N=1722) vs Placebo (N=1723)



No. at Risk							
Spironolactone	1722	1582	1258	956	667	359	58
Placebo	1723	1571	1257	934	655	365	59

NEJM 2014;370(15):1383-92

Management of HFpEF

→ 증상에 대한 치료와 심부전을 진행시킬 수 있는 동반질환 혹은 위험인자를 교정하는 것이 주된 치료

1. 동반된 고혈압은 합병증의 발생을 줄이기 위해 고혈압 진료지침에 따라 치료해야 한다.
(Class I, Level of Evidence B)
2. 수분 저류에 의한 증상은 이뇨제를 사용해 치료해야 한다. (Class I, Level of Evidence C)
3. 표준 약물치료에도 불구하고 심부전 증상이 지속되고 협심증 혹은 심근 허혈이 이를 악화시킬 것으로 판단되는 경우 관상동맥중재술을 시행하는 것은 타당하다. (Class IIa, Level of Evidence C)
4. 박출률 보존 심부전 환자에서 심부전 증상의 호전을 위하여 심방세동을 진료지침(참고: 4.5.1. 심방세동)에 따라 치료하는 것은 타당하다. (Class IIa, Level of Evidence C)
5. 고혈압의 조절을 위해 앤지오텐신전환효소억제제, 앤지오텐신 수용체 길항제 및 베타차단제 등을 사용하는 것은 타당하다. (Class IIa, Level of Evidence C)
6. 심부전 증상의 호전을 위해 앤지오텐신 수용체 길항제나 알도스테론 길항제를 사용하는 것을 고려할 수 있다. (Class IIb, Level of Evidence B)

34/F High BP, DOE

2018-01-12 심장내과 김봉준

>> 주호소

두통 15일
코에 출혈이 잘 생긴다

>> 통증

>> Numerical Rating Scale

☒ 0(없음) ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7 ☐ 8 ☐ 9 ☐ 10

>> 현병력

평소 혈압 정상

어제 오후부터 눈이 침침하고 아파서 해동병원 내원
혈압이 높아 (SBP 220) 상급병원 의뢰됨

ECG - T inv on lat.lead
LVH

chest PA - cardiomegaly

3년전 담낭염으로 치료받은 병력 (+)

>> 신체검사

혈압 240 / 170mmHg	맥박 90 회/min	
전신	외관 급성병색	의식상태 정상
피부	피부촉진 온	건조입술 -
두경부	결막 정상 목 정상	공막 정상
심장	부정맥 -	
가슴 (폐)	호흡음 정상	천명 - 청진음 -
복부	촉진및시진 유연	청진 정상
사지	정상	

>> 추정진단

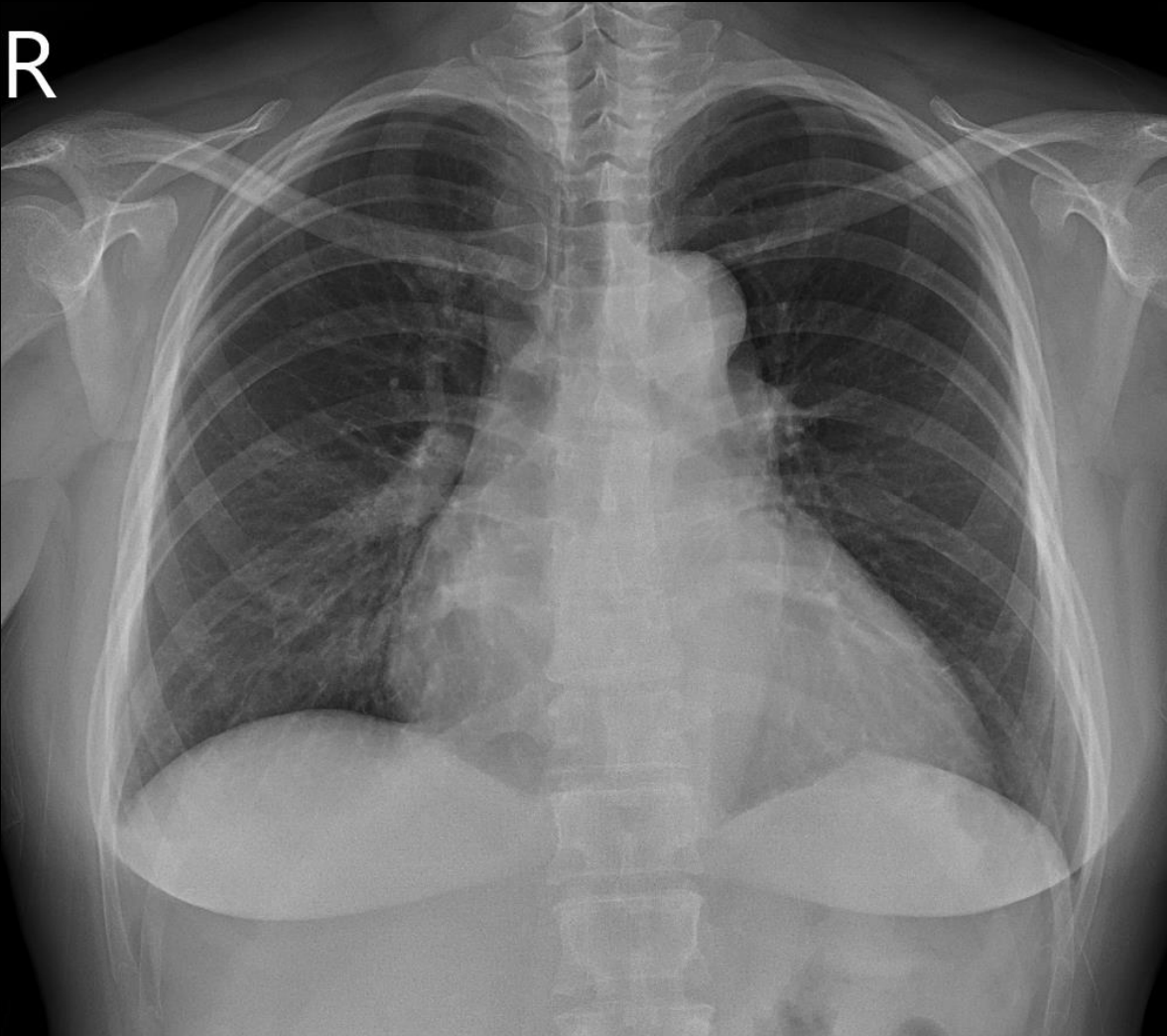
R/O secondary hypertension

>> 치료계획

입원
- 혈압조절
- HTN evaluation

34/F High BP, DOE

R



- Hb 9.4
- WBC 1194
- Plt 129k
- BUN 34.8
- Cr 3.06
- eGFR 17
- Na 136.
- K 3.3
- Bil total 2.25
- Direct bil 0.49
- Hs-CRP 0.658
- Pro BNP >35000 pg/mL (0-125)
- CK-MB 1.7 ng/mL
- Troponin-I 72 ng/L(0-40)
- Cholesterol total 193.5
- HDLcholesterol 34.1
- Triglyceride 165
- LDLcholesterol 135.4
- Spot urine
Pro/Cr ratio 3728.8 (<160)
Total protein 176 mg/dL (<10)

34/F HBP, DOE

ECHO
X5-1
50Hz
16cm

2D
60%
C 50
P Low
HGen



92 (Derived)

TIS0.4 MI 1.2

M3

ECHO
X5-1
47Hz
22cm

2D
63%
C 50
P Low
HGen



92 (Derived)

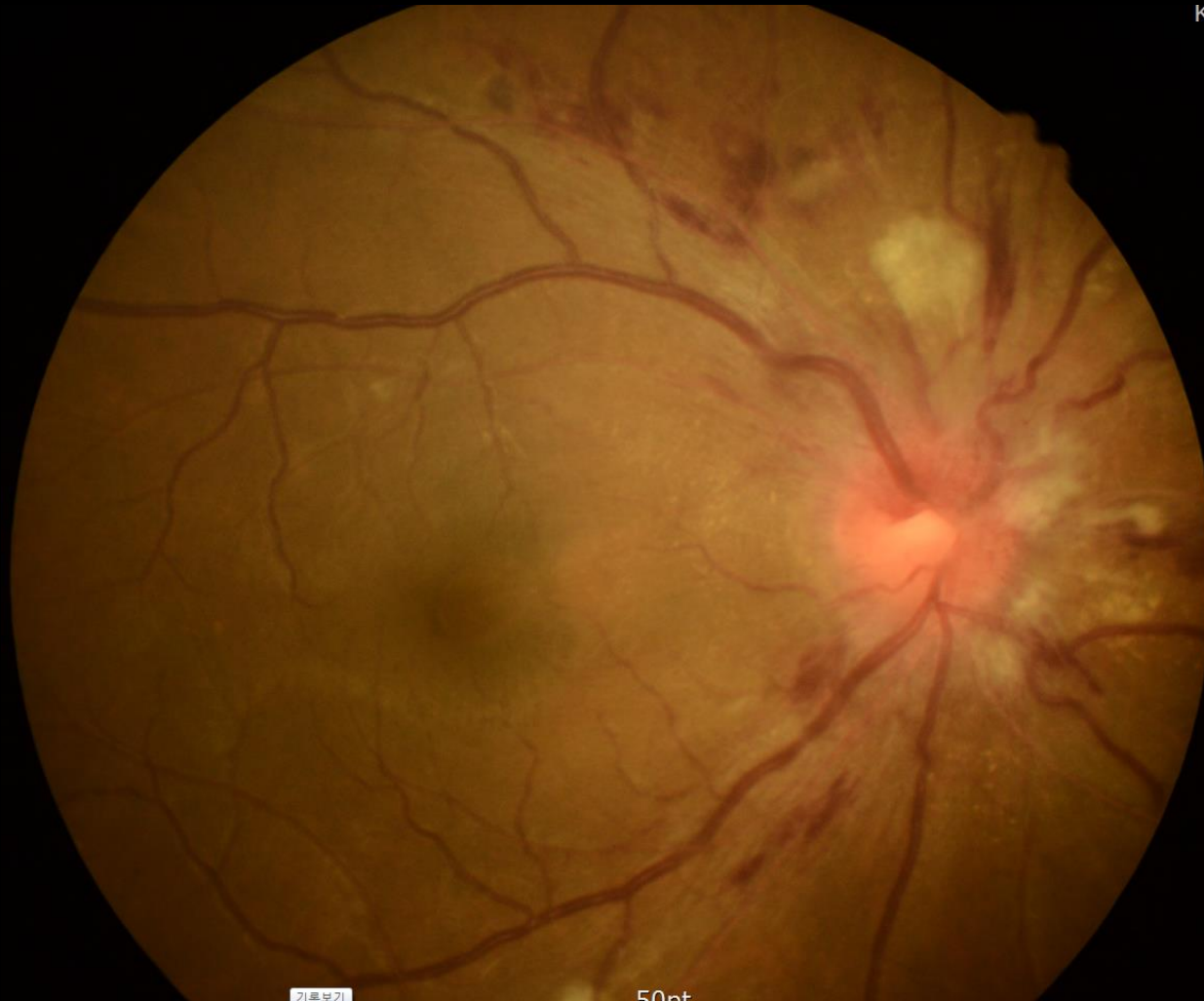
TIS0.4 MI 1.3

M3

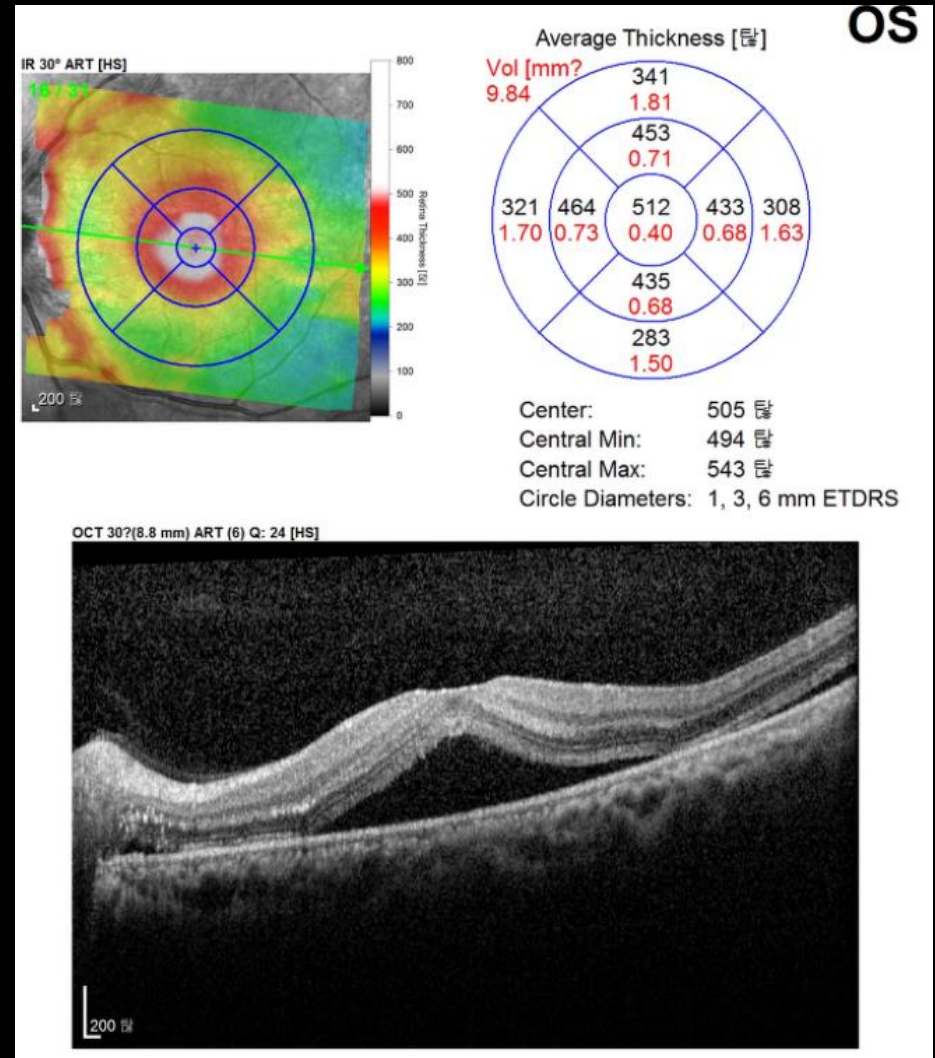
85 bpm

93 bpm

OT consult

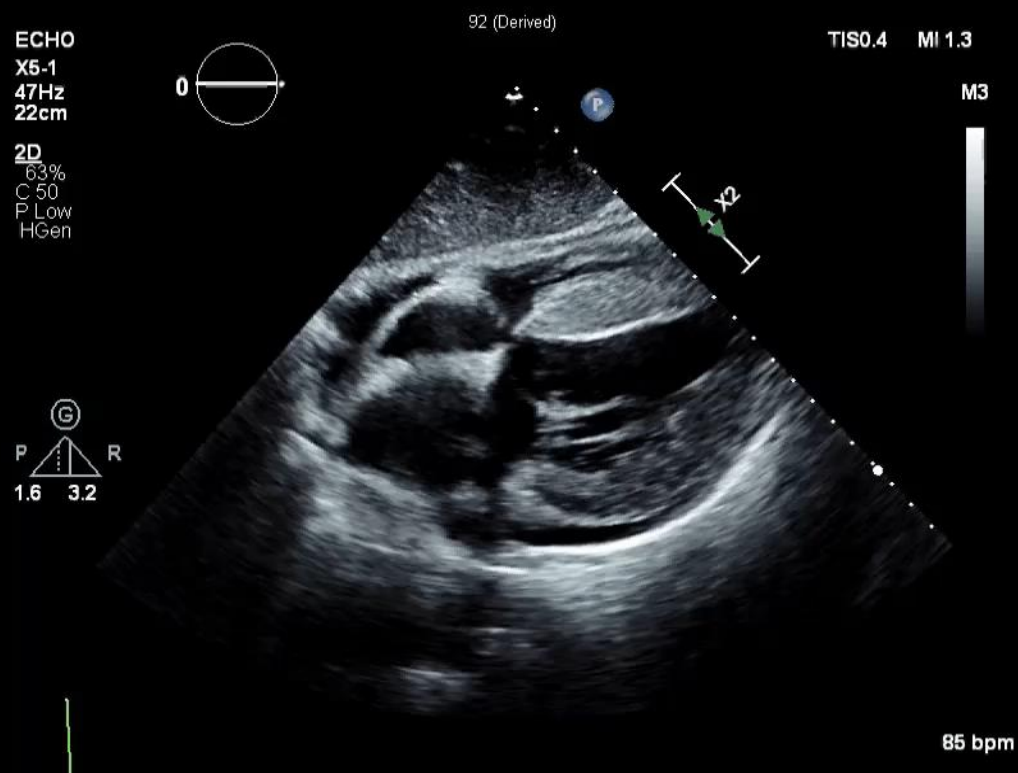


KC



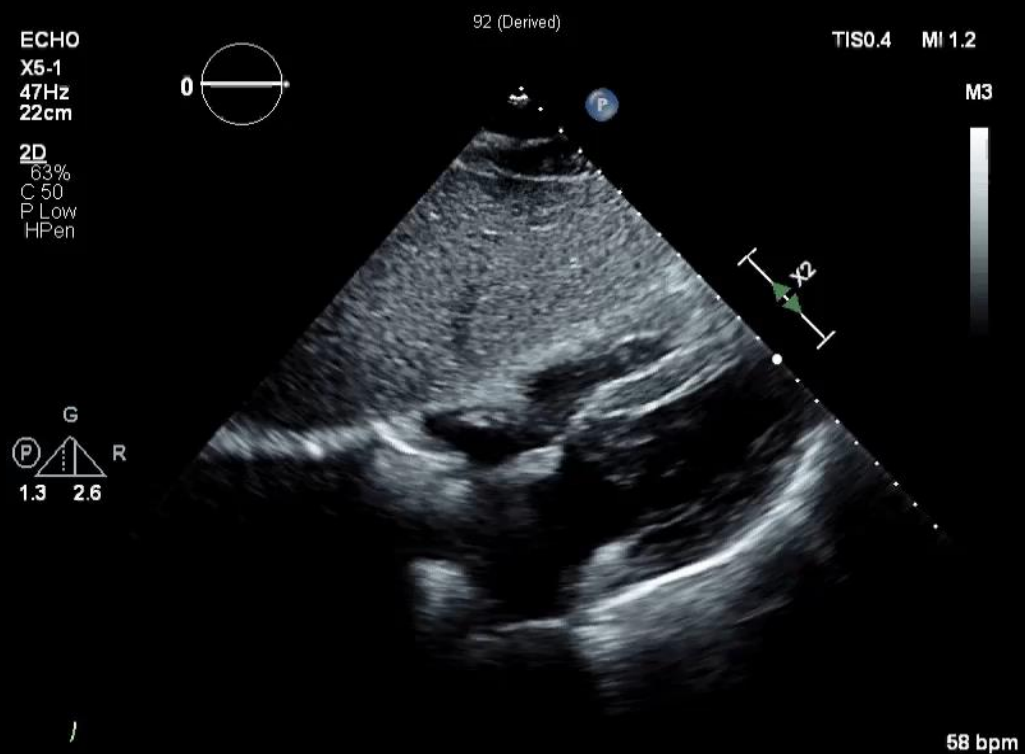
- Amlodipine 10mg QD
- Valsartan 160mg QD
- Carvedilol 25mg BID
- Nifedipine 60mg QD
- atorvastatin 10mg QD

2018. 1. 12



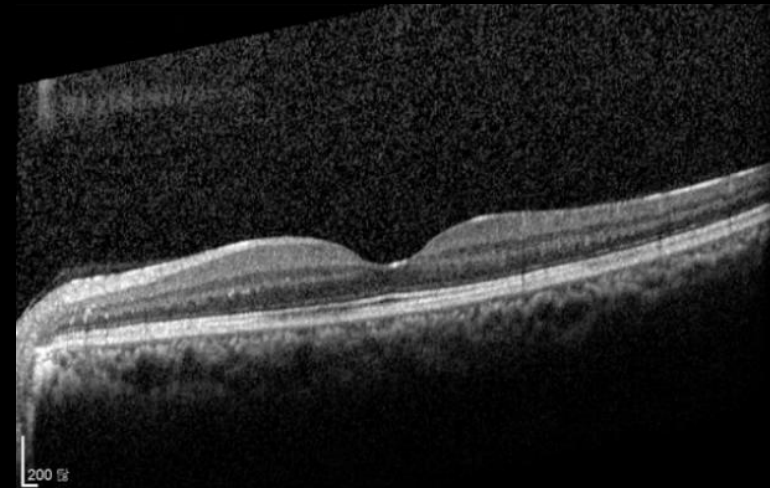
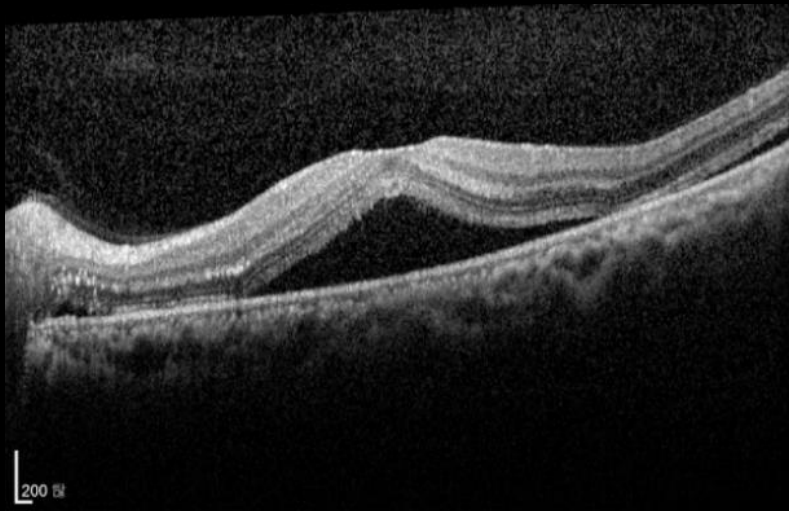
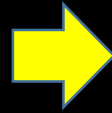
LVEF 59.5%
LAD 44.3 mm
IVSd 15.5 mm
LVMI 197.7 g/m²
E/E' 19.3

2018. 7. 13

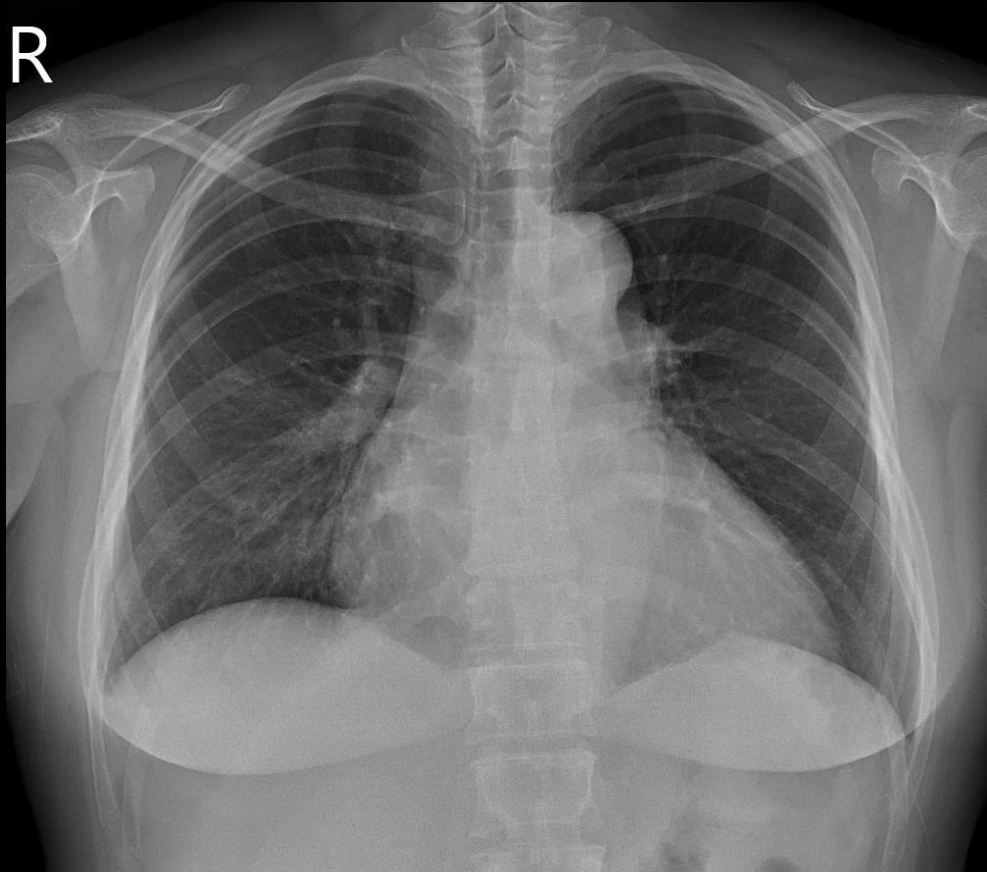


LVEF 67.4%
LAD 41.6 mm
IVSd 12.04 mm
LVMI 111.00 g/m²
E/E' 10.9

눈이 좋아졌어요

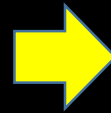


2018. 1. 12



Pro BNP > 35000

2018. 11. 30



Pro BNP normal

Summary – 만성심부전의 약물치료

- Chronic HF – HFrEF, HFpEF (HFmrEF)
- 초기 진단 및 평가에 심초음파가 중요
- HFrEF
 - : Optimal medical Tx – ACEI (ARB), B-blocker, MRA
 - : 반응 없으면 → ARNI, Ivabradine 고려
- HFpEF
 - 증상 치료, 위험인자 및 동반질환 교정이 중요

경청해 주셔서 감사합니다.

