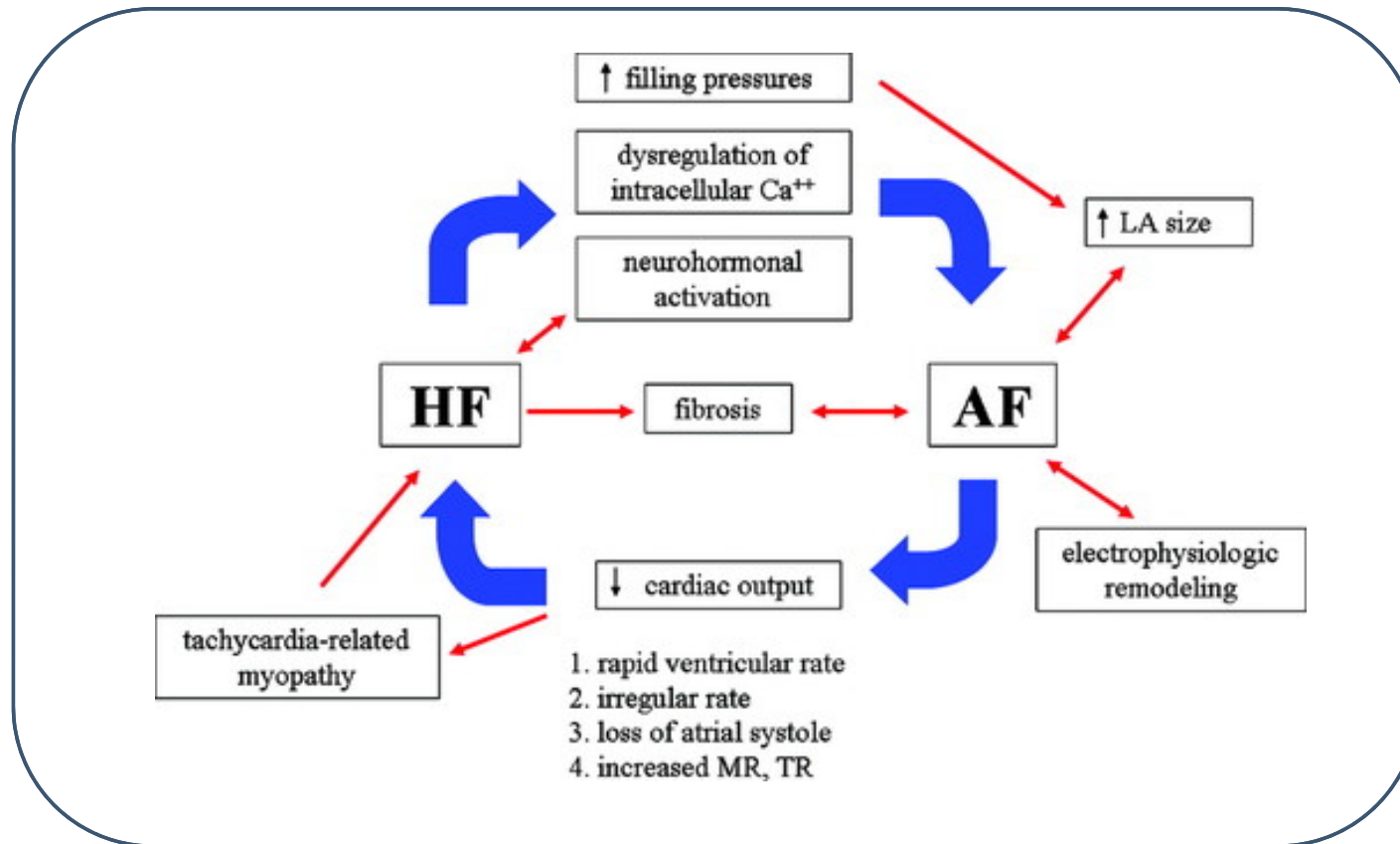


ARNI : Contemporary Management of Sudden Cardiac Death in Heart Failure Patients

In-Soo Kim
Gangnam Severance Hospital, Seoul, Korea

Vicious pathophysiological cycle of AF and HF

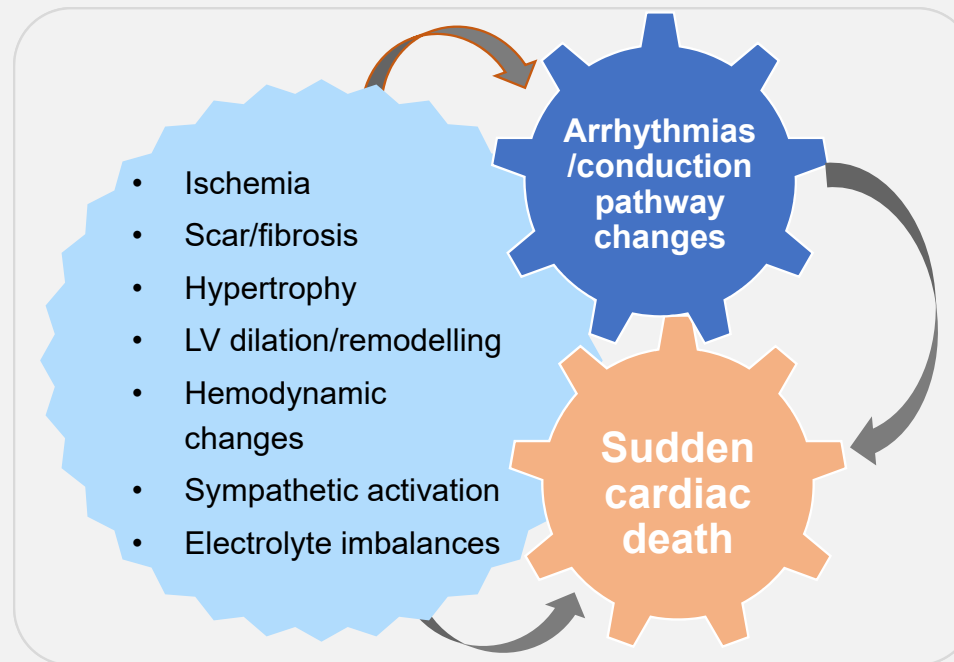
- AF may facilitate the development or progression of **heart failure** in several ways



Sudden cardiac deaths: Driven largely by arrhythmias

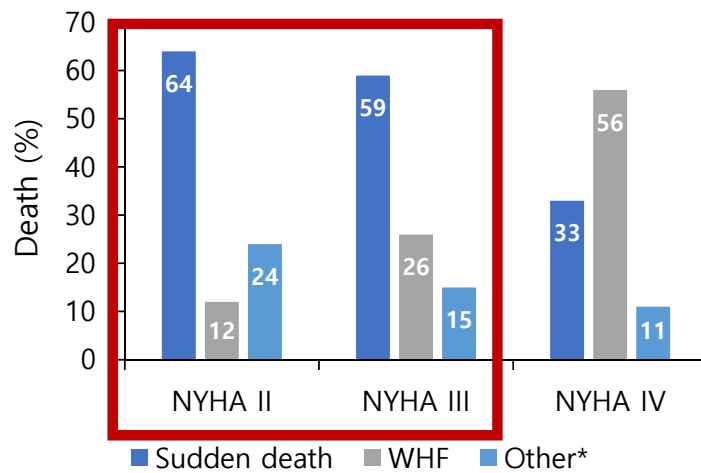
- Arrhythmias, particularly ventricular arrhythmias, contribute to the majority of SCDs (~50%) in patients with HF^{1,2}

Complex pathophysiology of SCD



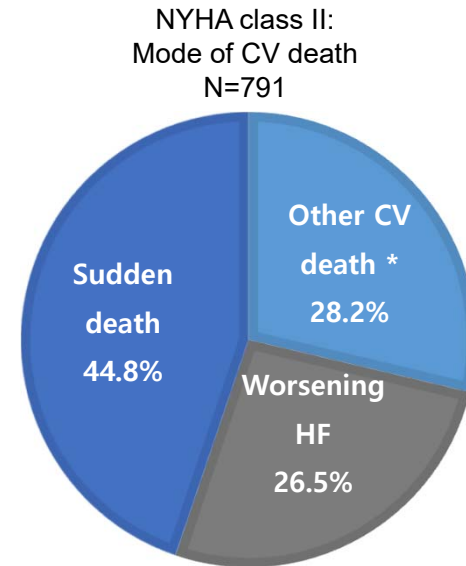
1. Harris and Lysitsas, BJA education, 2016, 16:221-229; 2. Weeks et al., Heart Fail Rev (2016) 21:415-431

HFrEF and HFpEF patients are at high risk of sudden death



*Other death includes all CV deaths not ascribed to WHF or sudden death

A post-hoc analysis from MERIT-HF (n=3,991)¹
Mean follow up, 1 year



*Other CV death includes all CV deaths not ascribed to pump failure or sudden death

An analysis from PARADIGM-HF (n=8,399)²
Median follow up, 2.3 years

1. MERIT-HF Study Group. *Lancet*. 1999;353(9169):2001-7; 2. Desai et al. *Eur Heart J*. 2015;36:1990-7

Heart failure is in progress in patients with stable symptoms, Sudden cardiac death can occur without worsening symptoms.

Misperceptions

Stable symptoms

Low risk

- Annual mortality 6-20%
- Post-discharge 25-30% mortality risk within 1 year
- Over a million hospitalizations each year in US and Europe
- >40% of deaths in this cohort are due to sudden death



Reality

안정적인 질환이 아닙니다
(Not stable disease)

실제 위험보다 낮게 평가되고 있습니다
(Under-appreciation of the risk of adverse outcomes)

약물요법을 받더라도 적절한 용량을 복용하고 있지 않으며, Device 등의 치료가 최적화되어 있지 않습니다
(Not on optimal drug and device-based therapy)

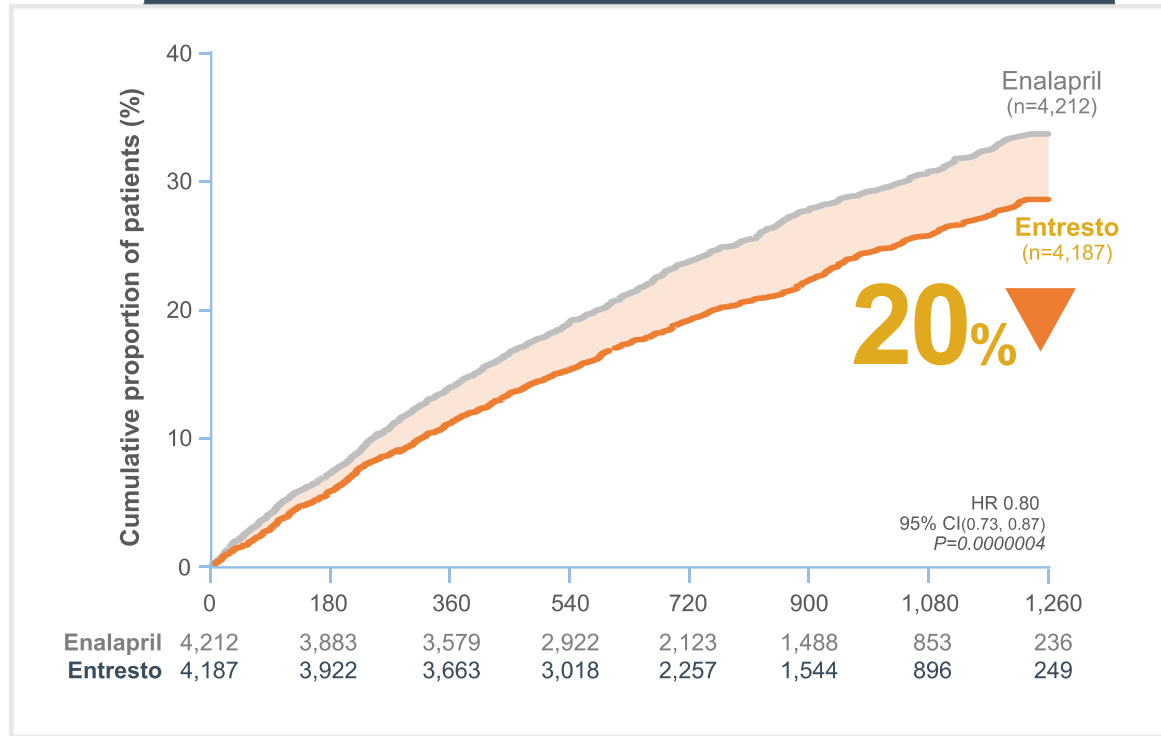
증상 악화없이 돌연사가 발생할 위험이 있습니다
(Risk of sudden death without worsening symptoms)

NYHA, New York Heart Association

1. Butler J et al. Eur J Heart Fail 2016;18,:350-52

엔트레스토는 Enalapril 대비 심부전 환자의 사망 및 입원 위험을 유의하게 감소시켰습니다 (PARADIGM-HF study)

PARADIGM-HF: Reduction of CV Death or First HF Hospitalization²



Sudden Cardiac Death¹

20%↓

(HR=0.80, 95% CI 0.68-0.94 P=0.008)

ED Visit for HF³

30%↓

(HR=0.70, 95% CI 0.52-0.94 P=0.017)

Stays in Intensive Care³

18%↓

(HR=0.82, 95% CI 0.72-0.94 P=0.005)

(vs. Enalapril)

PARADIGM-HF study design: A multinational, randomized, double-blind, active-controlled, 2-arm, event-driven trial. 8,442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less were randomly assigned to receive either LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy.

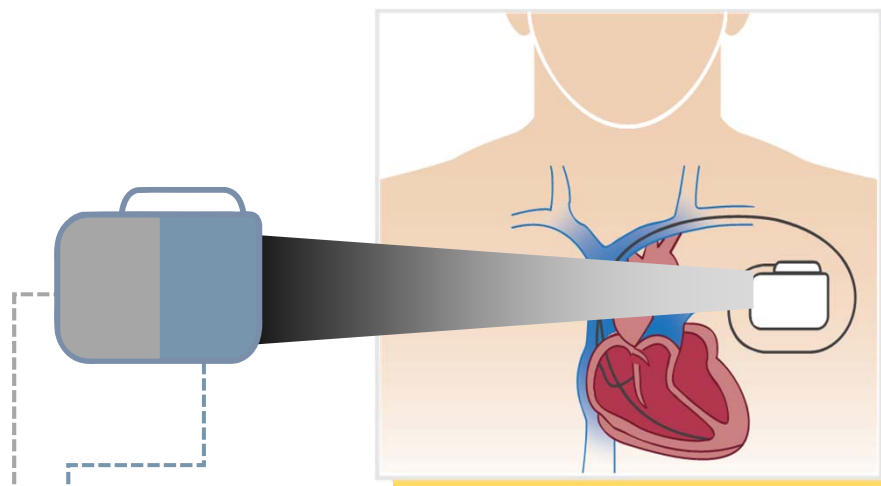
1. Desai et al. *Eur Heart J* 2015;36:1990-7. 2. McMurray et al. *N Engl J Med* 2014;371:993-1004. 3. Packer et al. *Circulation*. 2015;131:54-61.



* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF

The benefit of sacubitril/valsartan on sudden death was independent of ICD use. ¹

Post-hoc Analysis of PARADIGM-HF



	Sudden cardiac death n (%)	Hazard ratio (95% CI)	p-value for interaction
-ICD	525 (93.6%)	0.82 (0.69–0.98)	0.17
+ICD	36 (6.4%)	0.49 (0.25–0.98)	

ICD, Implantable cardioverter-defibrillator

Post-hoc Analysis of PARADIGM-HF



1. Desai et al. Eur Heart J 2015;36:1990–7

* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF

2016 ESC / 2017 AHA/ACC/HRS guidelines for the diagnosis and treatment of acute and chronic heart failure

2016 ESC guideline

Recommendations for the management of ventricular tachyarrhythmias in heart failure ¹		
Recommendations	Class	Level
Treatment with beta-blocker, MRA and sacubitril/valsartan reduces the risk of sudden death and is recommended for patients with HFrEF and ventricular arrhythmias	I	A

Sacubitril/valsartan demonstrated a reduction in sudden death and cardiac mortality compared with ACEi²

2017 AHA/ACC/HRS guideline

Recommendations for pharmacological prevention of SCD ¹		
Recommendations	Class	Level
In patients with HFrEF (LVEF ≤40%), treatment with a beta blocker, MRA and either an ACEI, ARB, or an angiotensin receptor neprilysin inhibitor is recommended to reduce SCD and all-cause mortality	I	A

Sacubitril/valsartan demonstrated a reduction in sudden death and cardiac mortality compared with ACEi²



1. Ponikowski et al. Eur Heart J. 2016;37:2129–2200; 2. Desai et al. Eur Heart J. 2015;36:1990-7
 2. Al-Khatib et al. Circulation. 2017;000:e000–e000. DOI: 10.1161/CIR.0000000000000549; 2. Desai et al. Eur Heart J 2015;36:1990-7

* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF



Sacubitril/Valsartan and Sudden Cardiac Death According to Implantable Cardioverter- Defibrillator Use and Heart Failure Cause : A PARADIGM-HF Analysis



Rohde LE, et al. *JACC Heart Fail.* 2020;8:844-855.

Background

Aim

- To investigate **the effect of sacubitril/valsartan therapy on sudden cardiac death (SCD) according to the use of and eligibility for an ICD**, stratified by heart failure cause.

Methods

- **Patients enrolled in the PARADIGM-HF trial (n = 8,399) were evaluated to assess patterns of ICD implantation and eligibility according to clinical guidelines.***
- PARADIGM-HF trial was a randomized, double-blind, prospective comparison between ARNI sacubitril/valsartan and enalapril therapy in subjects with chronic HF, NYHA functional class II to IV functional status, and LVEF $\leq 35\%$ evaluated within the previous 6 months who were treated with guideline-recommended medical therapies.
- **The impact of ICD and sacubitril/valsartan therapy on SCD was evaluated by using cause-specific Cox models and competing risk analysis.**

Endpoint

- Clinical endpoints of interest were **sudden deaths and all-cause mortality.**

*ICD eligibility was defined according to the 2013 ACC/AHA Guideline for the Management of Heart Failure recommendations for SCD primary prevention

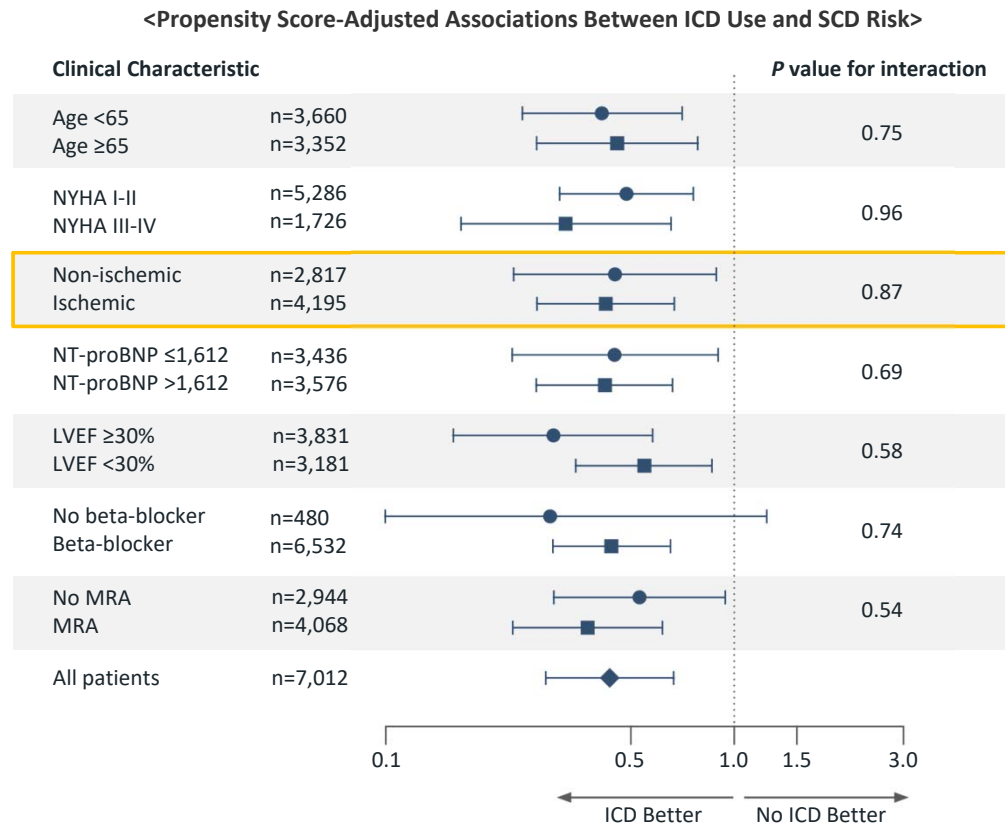
*ICD, implantable cardioverter-defibrillator; ARNI, angiotensin receptor neprilysin inhibition; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction.

1. Rohde LE, et al. JACC Heart Fail. 2020;8:844-855.



Results: SCD rates and ICD use and eligibility

- In a propensity score adjusted analysis, **use of ICD was associated with a 56% lower risk of SCD in ICD-eligible patients** (HR: 0.44; 95% CI: 0.30 to 0.64; $P < 0.001$), in both patients with **ischemic** (HR: 0.43; 95% CI: 0.27 to 0.67; $P < 0.001$) and **nonischemic** causes of HF (HR: 0.45; 95% CI: 0.23 to 0.88; $P = 0.02$).



ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MRA, mineralocorticoid receptor antagonist.



1. Rohde LE, et al. JACC Heart Fail. 2020;8:844-855.

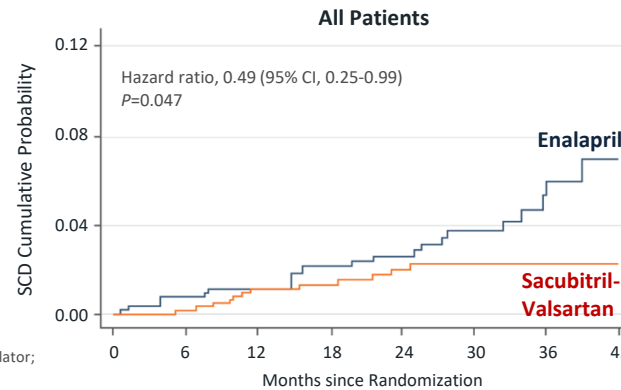
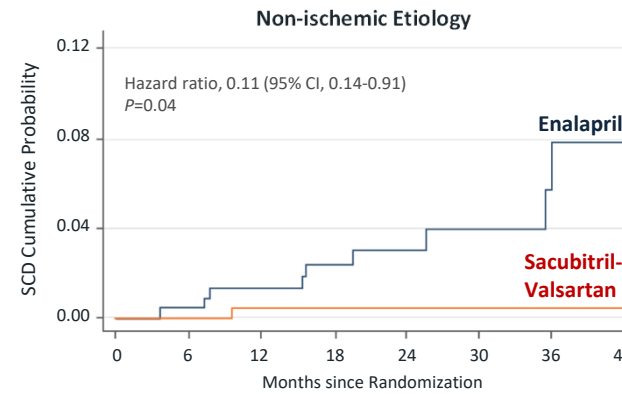
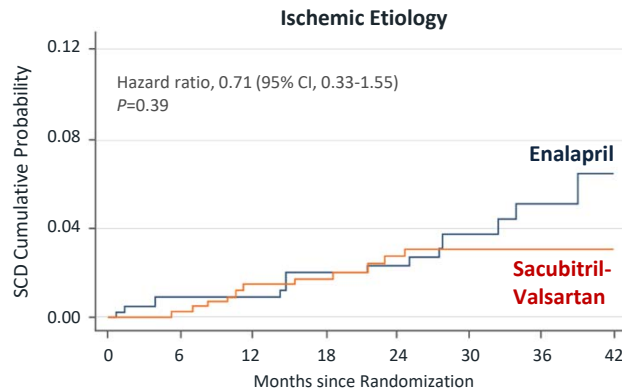
* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF

Results: ARNI effect and ICD use and eligibility (s/p ICD pts)

- **Sacubitril/valsartan** reduced SCD risk in patients with an ICD (HR: 0.49; 95% CI: 0.25 to 0.99; $P < 0.047$).



<Sacubitril/Valsartan Effect on SCD in ICD users>



SV, sacubitril/valsartan; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.

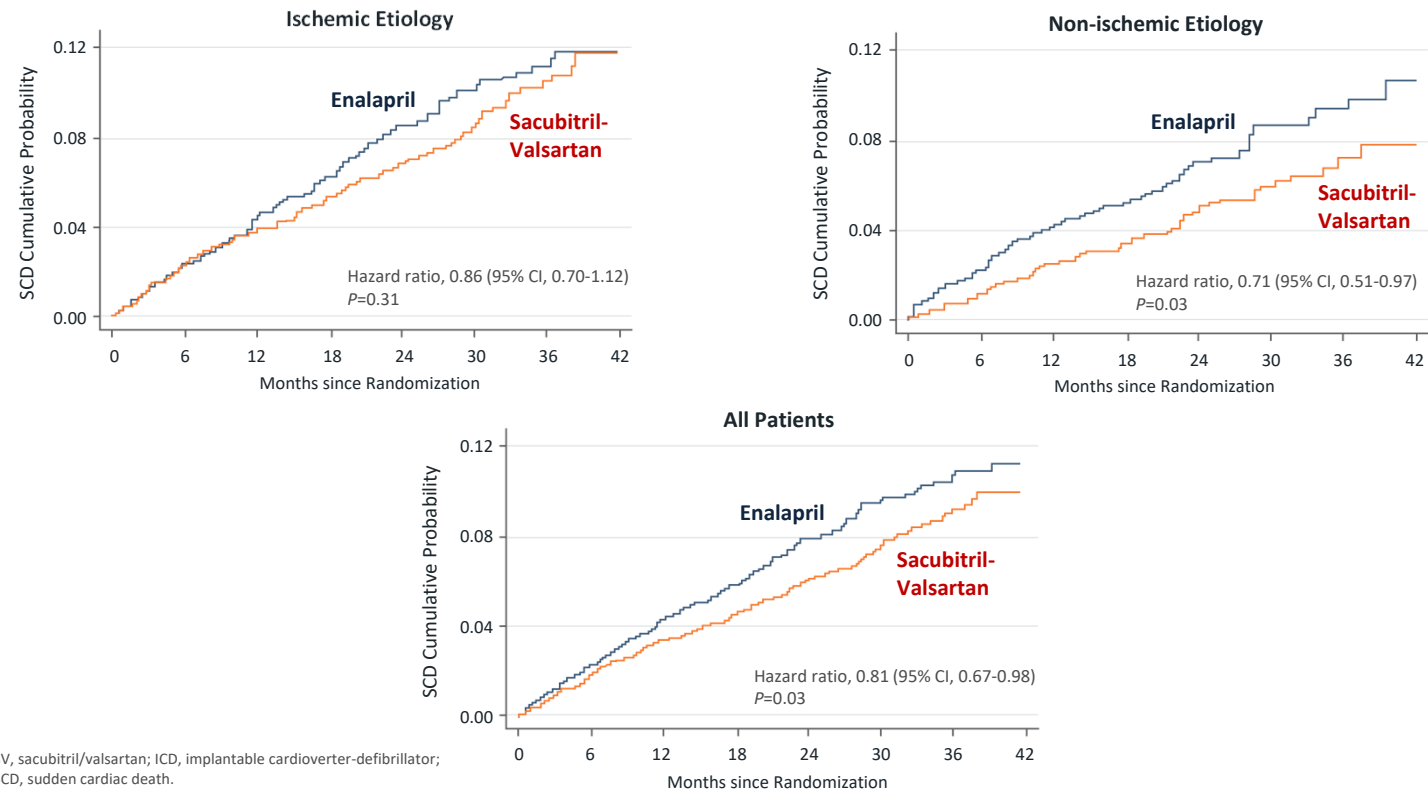




Results: ARNI effect and ICD use and eligibility (without ICD pts)

- In the subgroup of patients who were potentially eligible according to the ACC/AHA guideline **without an ICD**, **sacubitril/valsartan also significantly reduced SCD** (HR: 0.81; 95% CI: 0.67 to 0.98; $P=0.03$).

<Sacubitril/Valsartan Effect on SCD in ICD-Eligible Patients **Without an ICD**>



SV, sacubitril/valsartan; ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death.



1. Rohde LE, et al. JACC Heart Fail. 2020;8:844-855.

* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF

Conclusion of this sub-study



Sacubitril/valsartan reduced SCD risk regardless of use of an ICD or eligibility, particularly in ICD users and **nonischemic cardiomyopathy**.



These findings strengthen the intriguing hypothesis that **ICDs and sacubitril/valsartan may be preventing different forms of SCD**, related in part to the cause of HF.

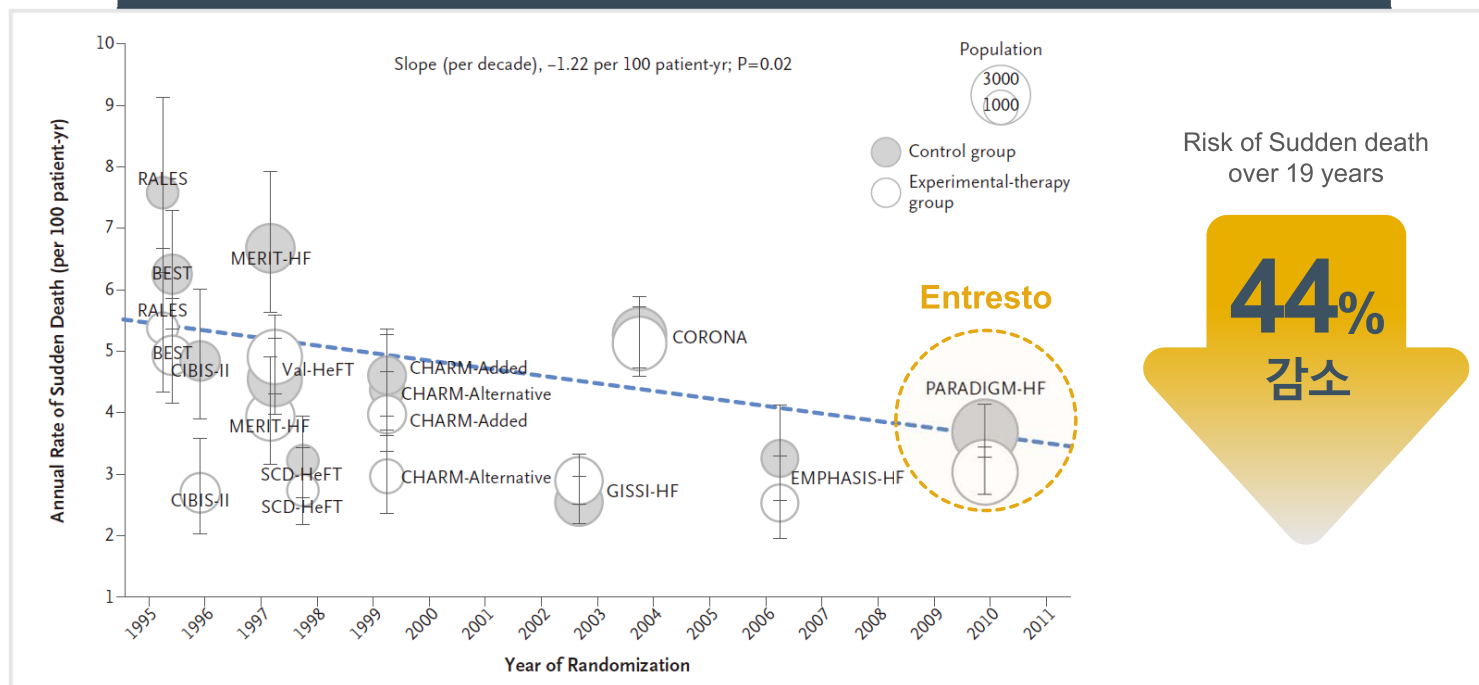
ICD, implantable cardioverter-defibrillator; SCD, sudden cardiac death; HF, heart failure.



The Sudden death risk has been decreased as drug therapy developed ¹

- ⊕ Propensity to reduce yearly sudden death with optimal drug therapy, **Decreased 44% of sudden death** for about 20 years (HR 0.56; 95% CI 0.33 – 0.93; $p=0.03$)*.

Trends in the rate of sudden death over time¹



*With adjustment for randomized group, with the trial as a random effect

Study design: Data from 40,195 patients who had heart failure with reduced ejection fraction and were enrolled in any of 12 clinical trials spanning the period from 1995 through 2014. Patients with implantable cardioverter-defibrillator at enrollment were excluded.

1. Shen L, et al. N Engl J Med 2017 Jul 6;377:41-51.



Effects of angiotensin-neprilysin inhibition compared to angiotensin inhibition on ventricular arrhythmias in reduced ejection fraction patients under continuous remote monitoring of implantable defibrillator devices

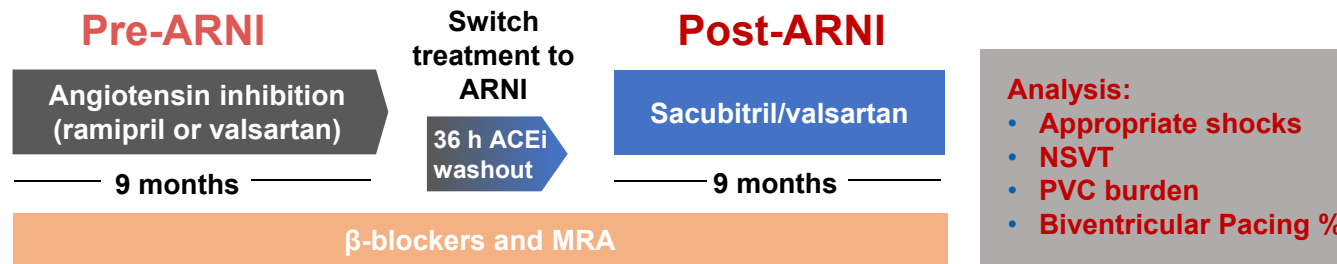
Carlos de Diego, MD, PhD,^{*†} Luis González-Torres, MD,^{*†} José María Núñez, MD,[†]
Raúl Centurión Inda, MD,^{*} David A. Martin-Langerwerf, MD,[†] Antonio D. Sangio, MD,[†]
Piotr Chochowski, MD,^{*} Pilar Casasnovas, MD,^{*} Julio C. Blazqu ez, MD,^{*}
Jes s Almendral, MD, PhD[†]

From the ^{}Hospital Universitario de Torrevieja, Alicante, Spain, [†]Hospital Universitario de Elche Vinalop , Universidad Cat lica de Murcia, Alicante, Spain, and [‡]Grupo HM Hospitales, Universidad CEU San Pablo, Madrid, Spain.*

de Diego et al. Heart Rhythm. 2018;15(3):395-402

This slide is intended to provide information regarding underlying mechanisms of sacubitril/valsartan for reducing the risk of CV death and hHF in patients with HFrEF; not to propose additional benefit of sacubitril/valsartan.

Study design and patient population



Patient population:

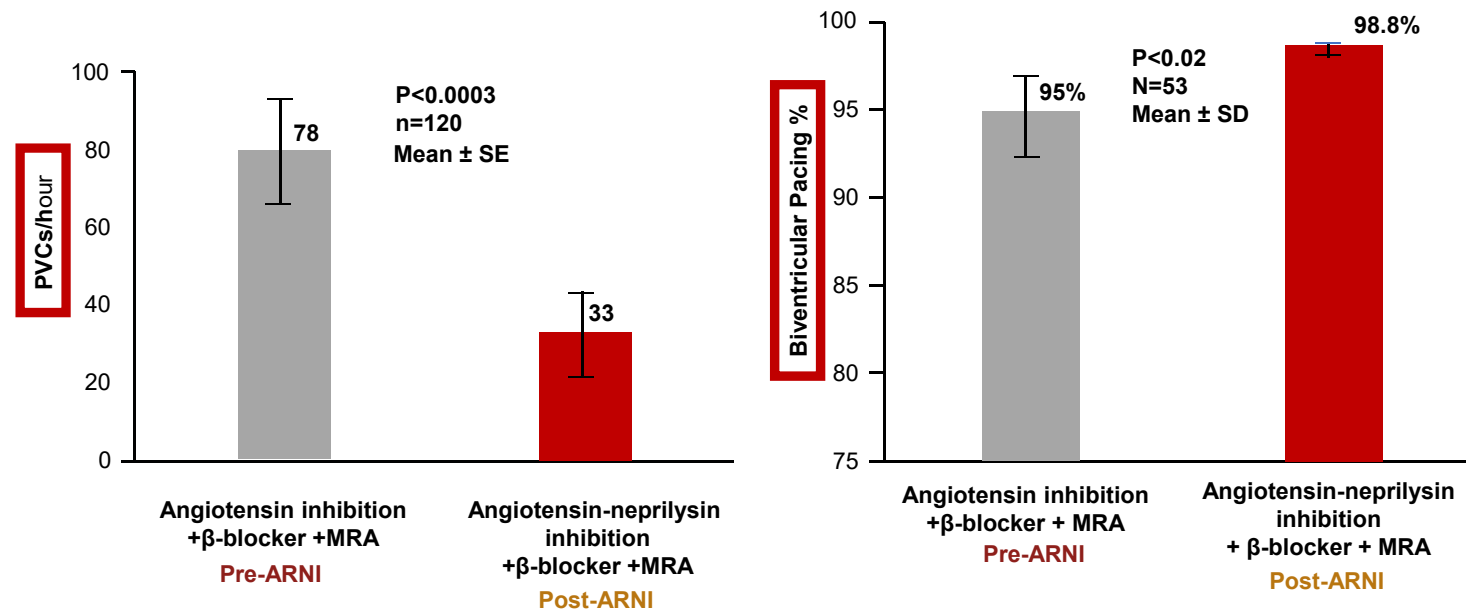
120 HFrEF patients with ICD or ICD-CRT referred to cardiology HF/arrhythmia outpatient clinic:

- HF symptoms with NYHA class \geq II despite optimal medical therapy, including initiation and titration of ACEi (ramipril) or ARB (valsartan), β -blockers, and MRA if tolerated
- LVEF \leq 40%
- Under home monitoring of an ICD
- Patients serve as their own control by design

de Diego et al. Heart Rhythm. 2018;15(3):395-402

This slide is intended to provide information regarding underlying mechanisms of sacubitril/valsartan for reducing the risk of CV death and hHF in patients with HFrEF; not to propose additional benefit of sacubitril/valsartan.

A decrease in PVC burden after sacubitril/valsartan was associated with an increase in biventricular pacing %



The increments seen in biventricular pacing with sacubitril/valsartan (3.8%) could have significant impact on symptomatic improvement and on mortality

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

This slide is intended to provide information regarding underlying mechanisms of sacubitril/valsartan for reducing the risk of CV death and hHF in patients with HFrEF; not to propose additional benefit of sacubitril/valsartan.

Sacubitril/valsartan significantly increased time of survival free from appropriate ICD shocks, compared with ACEi/ARB¹

- The most common mechanism of sudden death in patients with an ICD was VT/VF treated with an appropriate shock followed by EMD²
- ICD patients suffer from poorer psychological well-being following shocks, which impacts QoL³⁻⁵

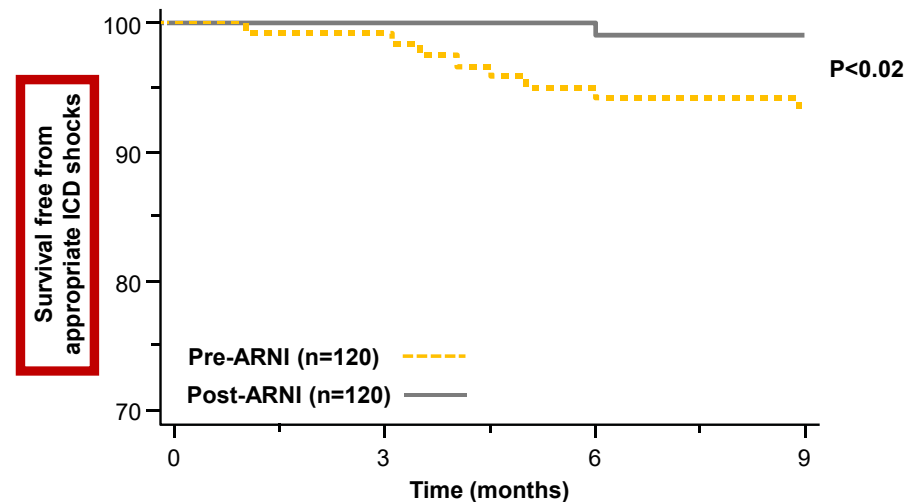
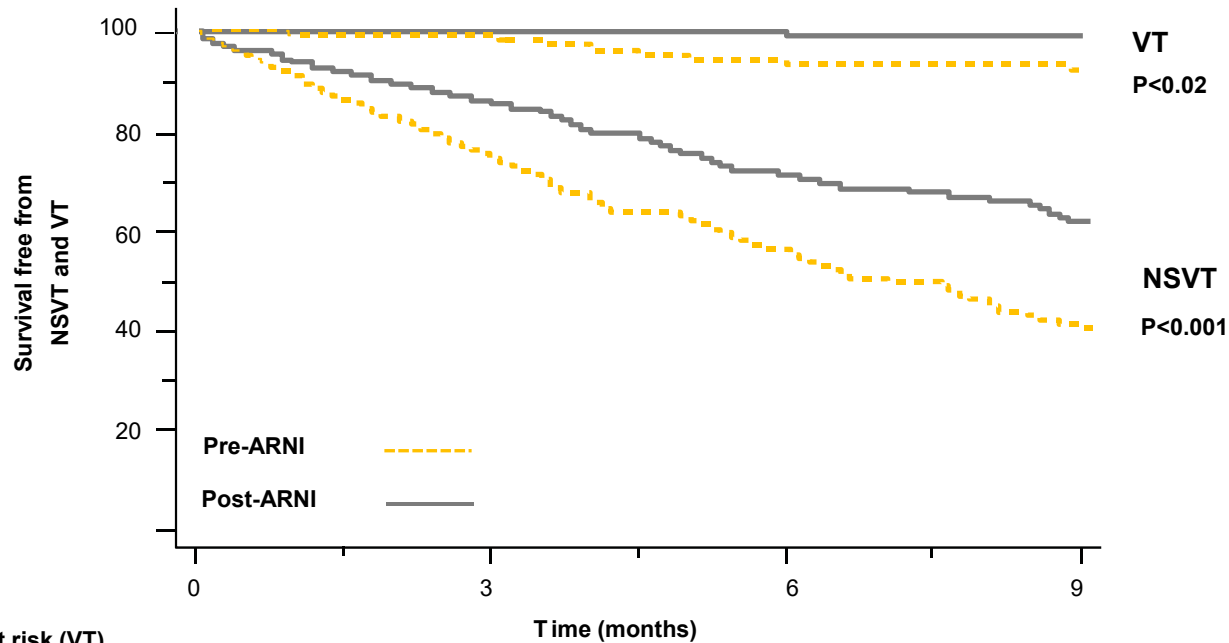


Figure from de Diego et al

1, de Diego et al. Heart Rhythm. 2018;15(3):395-402; 2. Mitchell et al. J Am Coll Cardiol. 2002;39:1323– 8; 3. Tomzik et al. Front Cardiovasc Med. 2015;234. doi : 10.3389/fcvm.2015.00034; 4. Passman, et al. Arch Intern Med 2007;167(20):2226-32. 5. Mark et al. New Engl J Med. 2008;359(10):999-1008; Figure from de Diego et al

This slide is intended to provide information regarding underlying mechanisms of sacubitril/valsartan for reducing the risk of CV death and hHF in patients with HFrEF; not to propose additional benefit of sacubitril/valsartan.

Sacubitril/valsartan significantly increased time of survival free from VT and NSVT, compared with ACEi/ARB



Number at risk (VT)

	0	3	6	9	
ARNI	120	120	120	119	119
ACEi/ARB	120	119	119	115	113

Number at risk (NSVT)

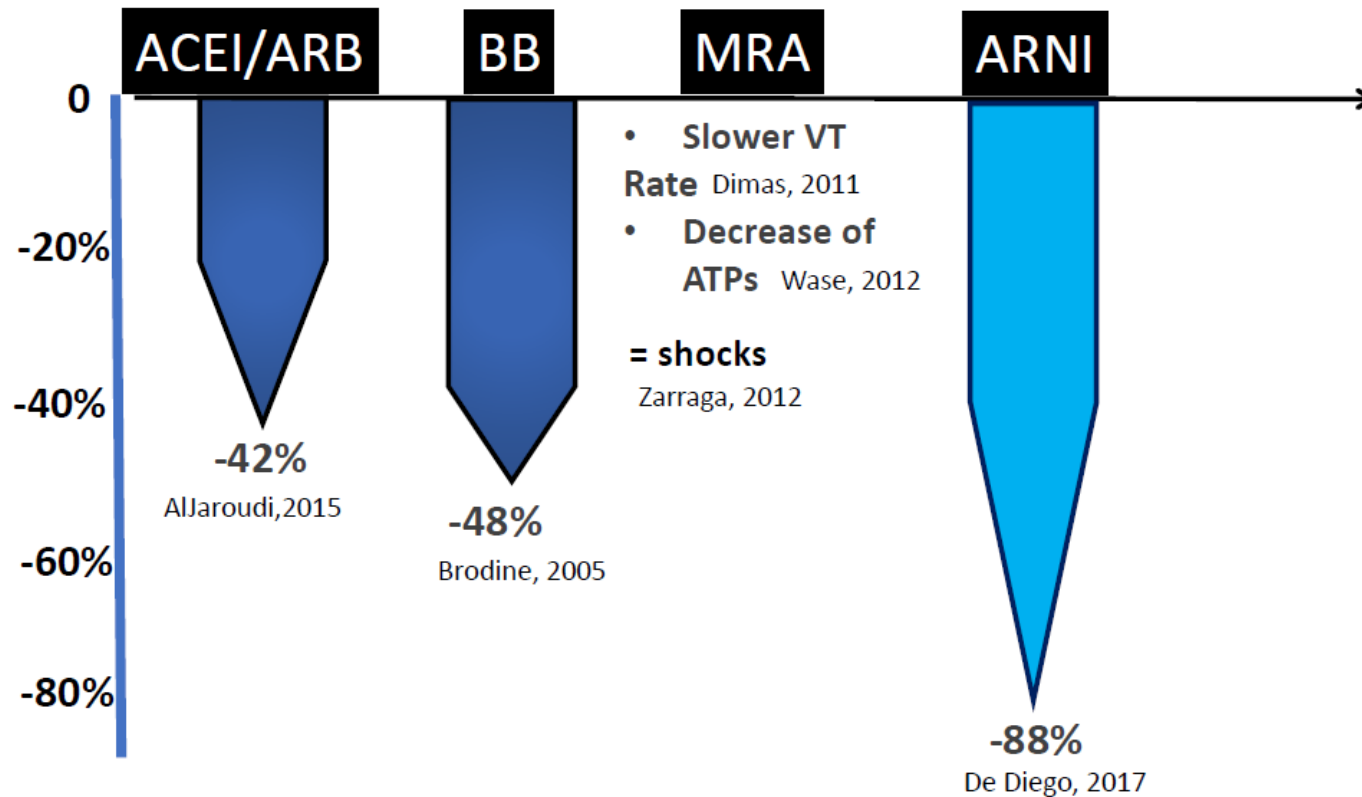
	0	3	6	9		
ARNI	120	111	103	95	86	82
ACEi/ARB	120	104	90	77	67	59

1. de Diego et al. Heart Rhythm. 2018;15(3):395-402

This slide is intended to provide information regarding underlying mechanisms of sacubitril/valsartan for reducing the risk of CV death and hHF in patients with HFrEF; not to propose additional benefit of sacubitril/valsartan.

After implanting an ICD, drug optimization also decrease ICD shocks and mortality

Reduction of appropriate ICD shocks



엔트레스토 제품정보 및 급여 기준 1,2



50mg



100mg



200mg

• 적응증

만성 심부전 : 좌심실 수축기능이 정상보다 낮은 만성 심부전 환자 (NYHA class II-IV)에서 심혈관 질환으로 인한 사망 및 심부전으로 인한 입원 위험성 감소

이 약은 다른 심부전 치료제와 병용하여 투여한다.

• 가격

전 제형 1,792원/정 [환자 부담금 32,256원/월(30일), 급여 적용 시 30%],
2023년 1월 1일부
입원 진료 시 환자 부담금은 요양 급여 비용 총액의 20%

• 급여 기준

좌심실 수축기능이 저하된 만성 심부전 환자(NYHA class II~IV)중, 좌심실 박출률(LVEF: Left Ventricular Ejection Fraction)이 40% 이하인 환자로서 -ACE 억제제 또는 Angiotensin II 수용체 차단제를 표준치료 (베타차단제, aldosterone antagonist 등)와 병용하여 4주 이상 안정적인 용량(stable dose)으로 투여 중인 경우

단, 급성 비보상성 심부전*으로 입원 후 혈액학적으로 안정화된 환자**의 경우에는 ACE 억제제 또는 Angiotensin II 수용체 차단제 미 투여시에도 인정함

*급성 비보상성 심부전: Fluid overload(체액 과부하)의 증상과 징후가 있는 환자로 입원 중
-흉부 X-ray 상 폐울혈 소견이 있고,
-NT-proBNP ≥ 1600pg/ml, 또는 BNP ≥ 400pg/ml 인 경우

**혈액학적으로 안정화된 환자(다음은 모두 만족)
-최근 6시간 이상 저혈압 증상이 없고 수축기 혈압이 100 mmHg 이상
-최근 6시간 이상 주사용 이뇨제의 증량이 없음
-최근 6시간 이상 주사용 혈관 확장제 (nitrate 계 포함)의 사용이 없음
-최근 24시간 이상 주사용 승압제 (inotropic drugs)의 사용이 없음
-eGFR ≥ 30 mL/min/1.73m²
-Serum potassium ≤ 5.2 mmol/L

Summary.

How did Entresto reduce the risk of sudden death?

Potential Mechanism of Entresto in Reducing Risk of Sudden Death

1 Reduction of ventricular arrhythmia¹⁶

- ⊙ ICD를 삽입한 심부전 환자에서 심실 부정맥 발생률을 유의하게 감소 (vs. ACEi/ARB)

2 Suppression of cardiac fibrosis and remodeling^{16,21}

- ⊙ 치명적인 부정맥을 일으킬 수 있는 심장의 섬유화 및 재형성을 억제 (vs. ACEi/ARB)

3 Reduction of myocyte injury and myocardial wall stress^{15,22,23}

- ⊙ 심근세포 손상 지표인 hsTnT 수치를 유의하게 감소
- ⊙ Cardiac wall stress를 나타내는 지표인 NT-proBNP 수치를 감소

4 Decrease of sympathetic tone^{16,24}

- ⊙ Natriuretic peptide가 교감신경의 과활성화를 저해

ICD, Implantable cardioverter-defibrillator; ACEi, Angiotensin converting enzyme inhibitor; ARB, Angiotensin receptor blocker; hsTnT, High sensitivity troponin T; NT-proBNP;

Amino-terminal pro-brain natriuretic peptide

15. Packer M, et al. Circulation 2015 Jan 6;131:54-61. 16. de Diego C, et al. Heart Rhythm. 2017 Nov 14;pii:S1547-5271(17)31331-0. 21. L Gonzalez-Torres, et al. Clin Cardiol

J 2018 Jan;2:6-9. 22. Jhund et al. Eur Heart J 2015; 36(Suppl 1):22 (P214). 23. Wachter R, et al. Postgrad Med 2018 Apr;130:308-16. 2. Langenickel TH & Dole WP. Drug

Discovery Today: Ther Strateg 2012;9:e131-9.

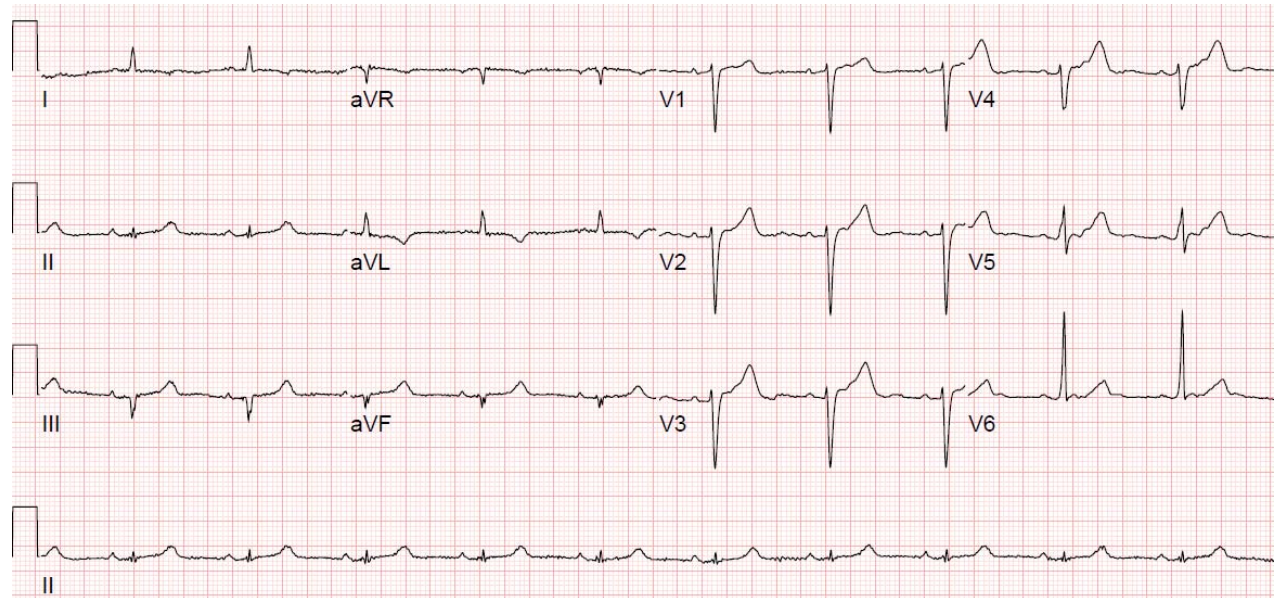
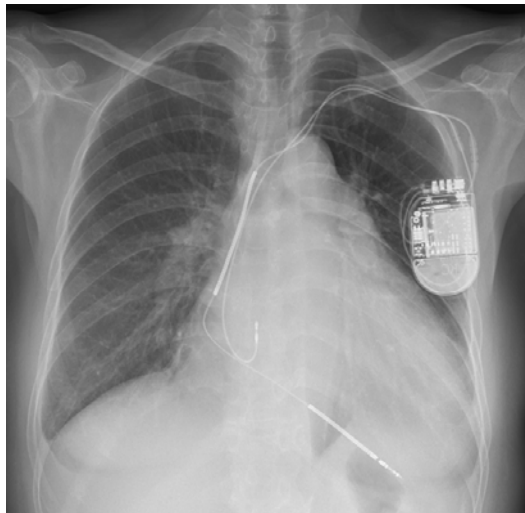
Case1. F/62, Dyspnea aggravation (despite medical Tx) - DCMP (EF 34%, LVEDD 59), NSVT, s/p '13 ICD implant

1*

BUN/Cr 28/1.3 (\leftarrow 0.9)
NT-proBNP 2400 \rightarrow **>35000**

94/57 mmHg, HR 67 bpm

Valsartan 40mg qd
Carvedilol 3.125mg qd
Aldactone 12.5mg qd
Lasix 20mg qd
Amiodarone 100mg qd

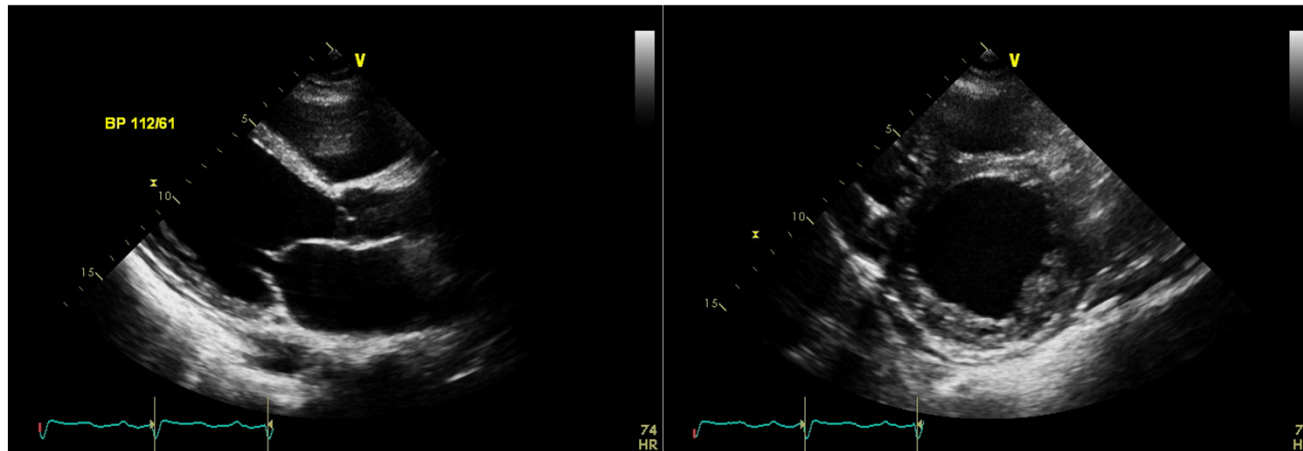


 Entresto[®]
(sacubitril/valsartan) tablets

* Ref. 대한심부전학회 2022 심부전 진료지침 중 for patients with chronic HFrEF

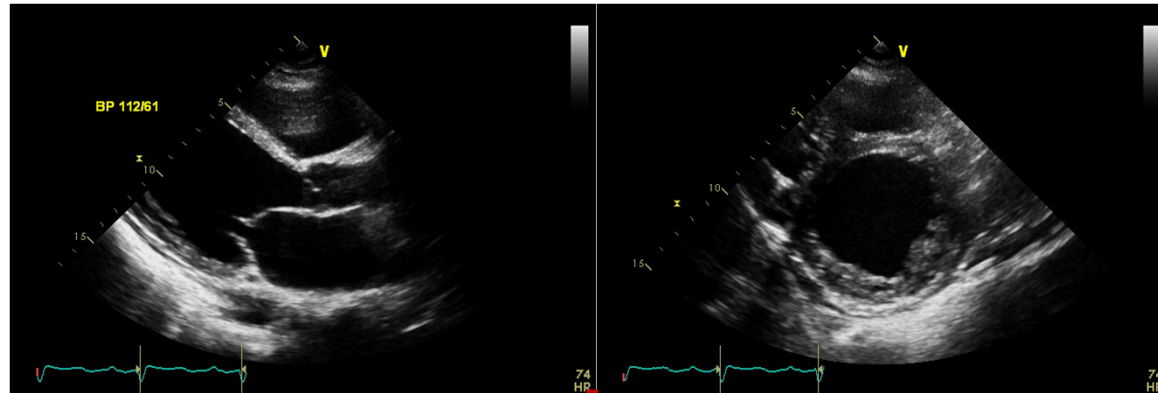
Case1. F/62, Dyspnea aggravation (despite medical Tx) - DCMP (EF 34%, LVEDD 59), NSVT, s/p '13 ICD implant

EF 34% → 16%
LVEDD 59 → 64 mm

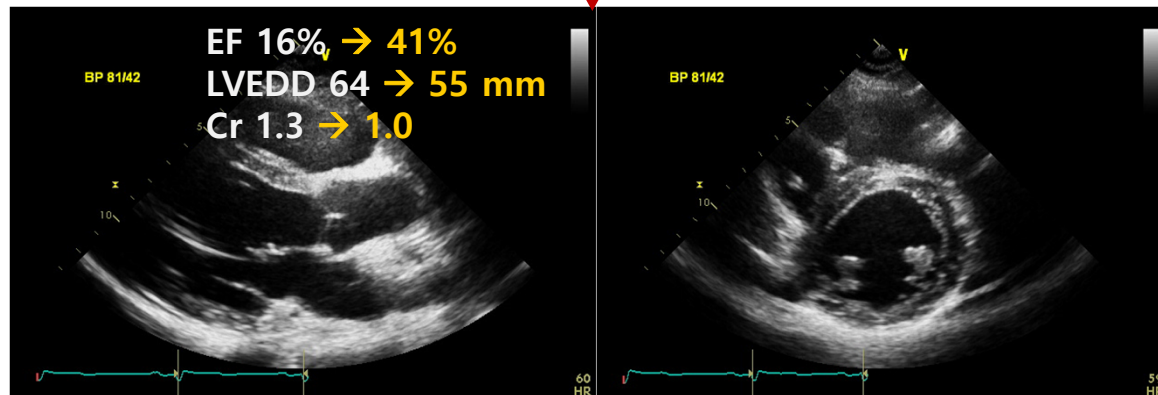


: Valsartan 40mg qd → Entresto 25mg bid
Aldactone 12.5mg qd
Lasix 20mg qd
Amiodarone 100mg qd
Carvedilol 3.125mg qd (HF stabilization 이후 add)
(Empagliflozin 10mg qd - patient refuse)

Case1. F/62, Dyspnea aggravation (despite medical Tx) - DCMP (EF 34%, LVEDD 59), NSVT, s/p '13 ICD implant



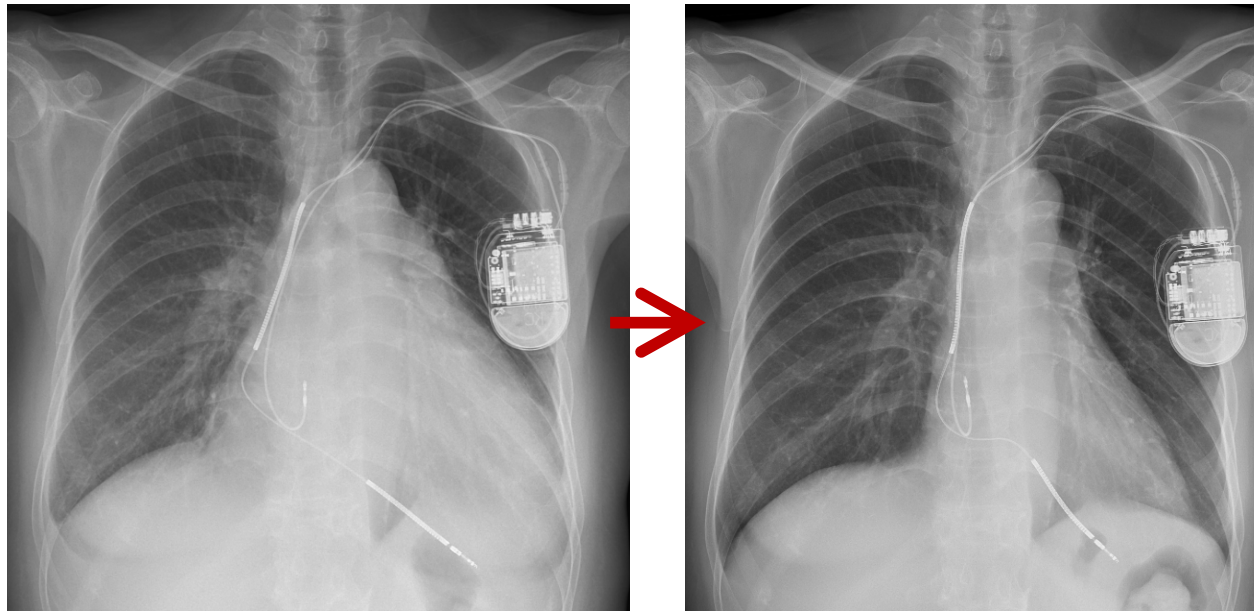
After 12 months ↓



Case1. F/62, Dyspnea aggravation (despite medical Tx)
- DCMP (EF 34%, LVEDD 59), NSVT, s/p '13 ICD implant

1*

After 24 months



Case2. M/33, Dyspnea, DOE (despite medical Tx) - DCMP (EF 20%, LVEDD 68), **SR with QRS 182ms**

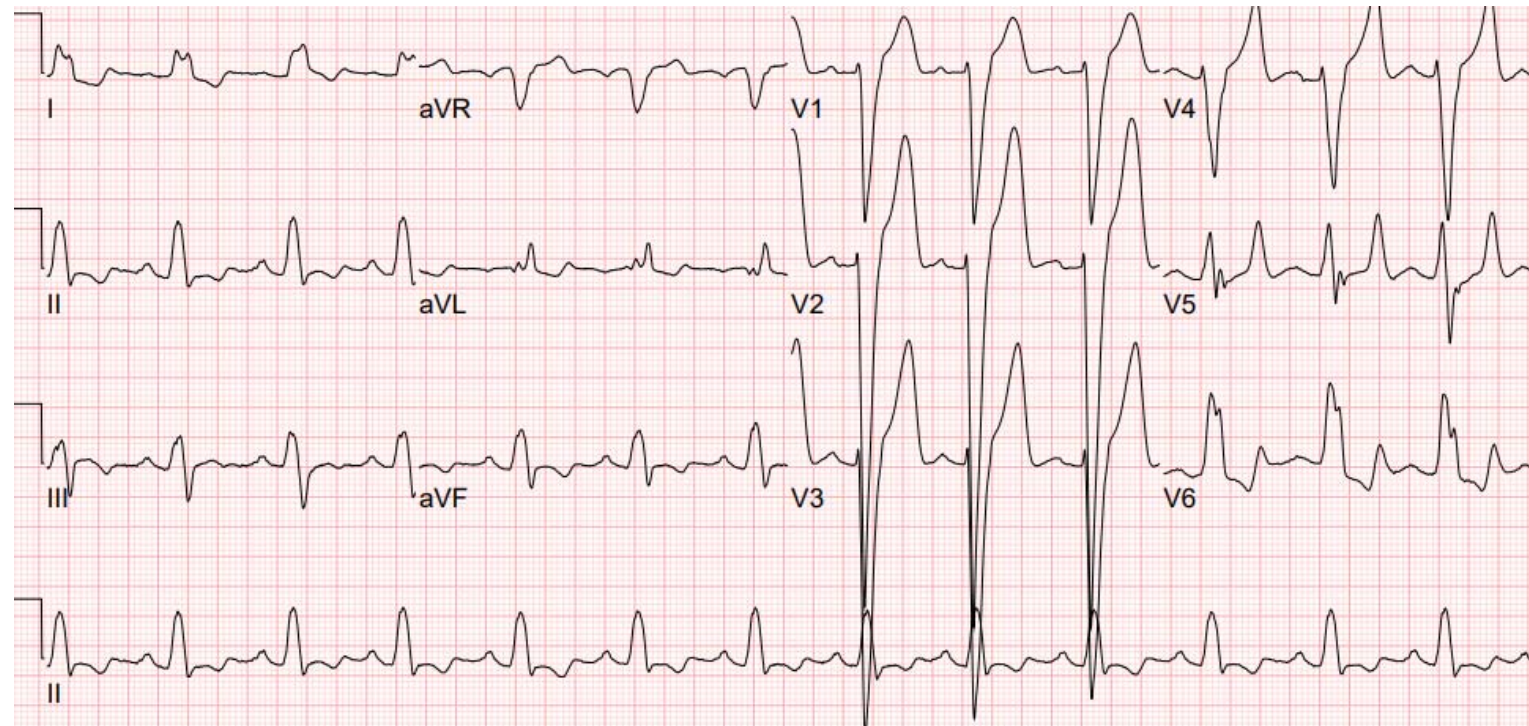
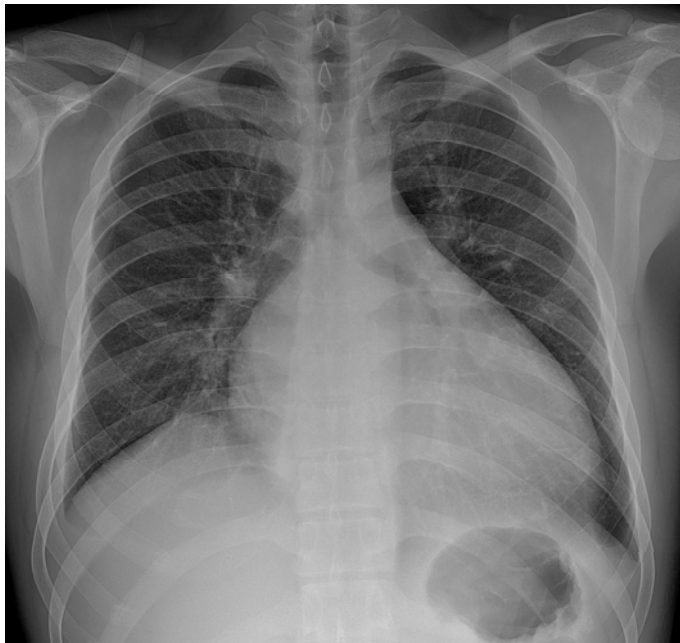
104/77 mmHg, HR 87 bpm

Entresto 100mg bid → 200mg bid

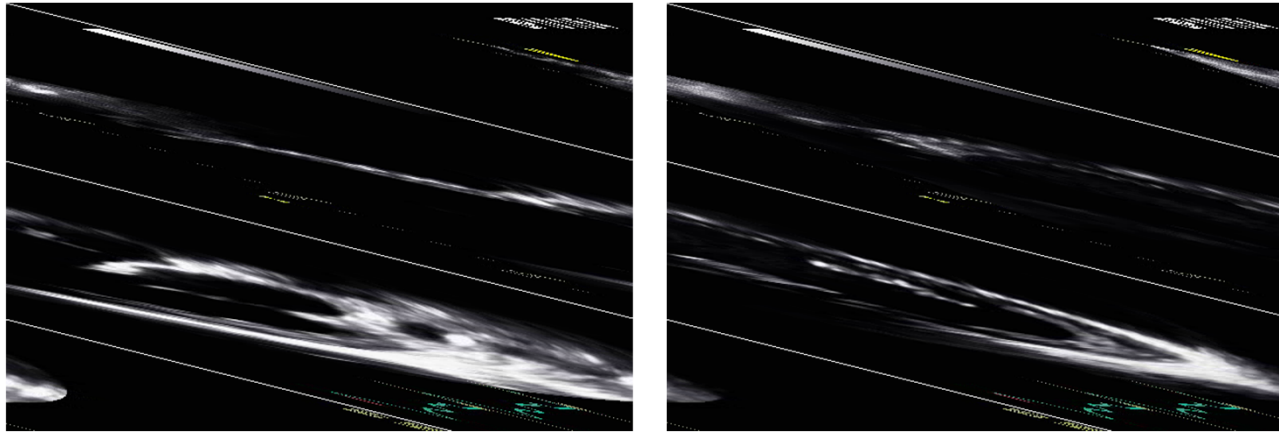
Aldactone 12.5mg qd

Lasix 20mg qd

Bisoprolol 1.25mg qd (HF stabilization 이후 add)



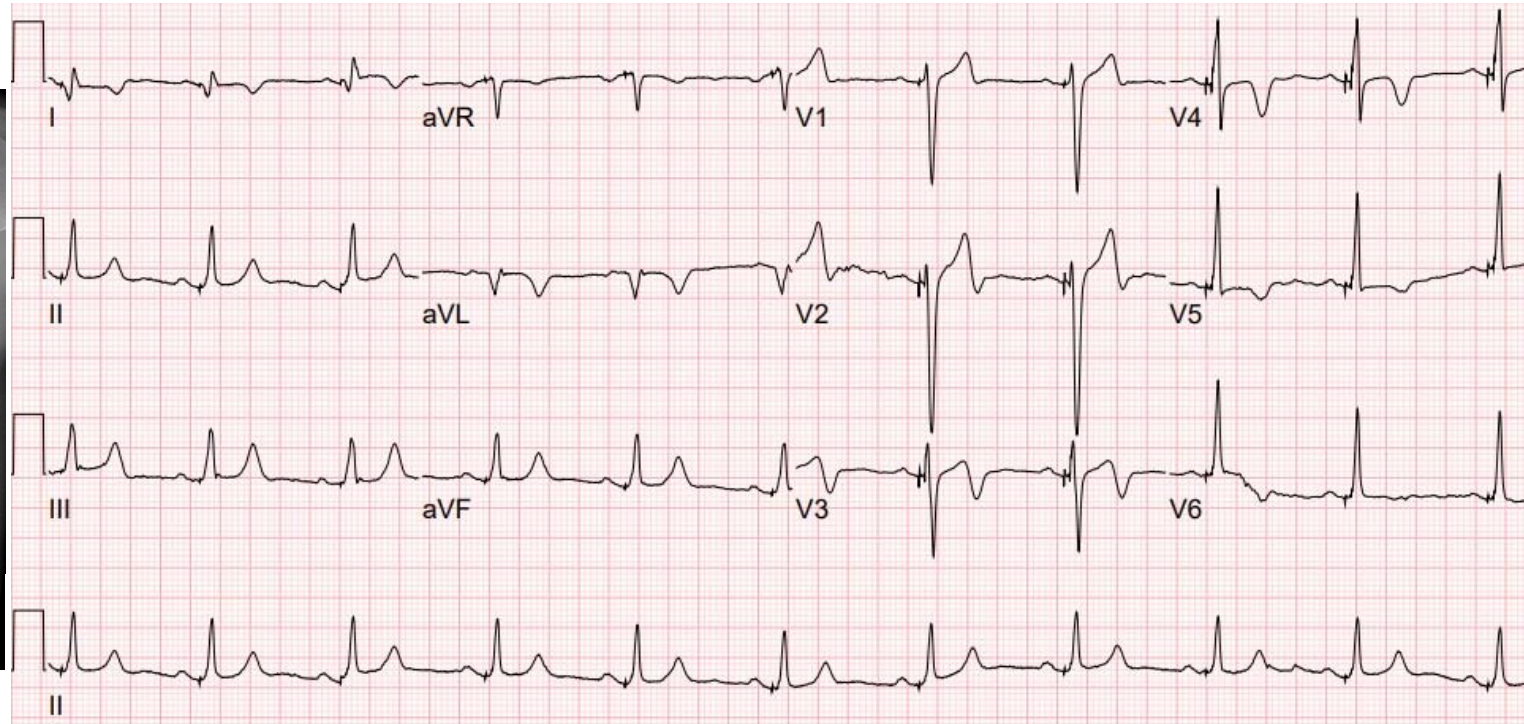
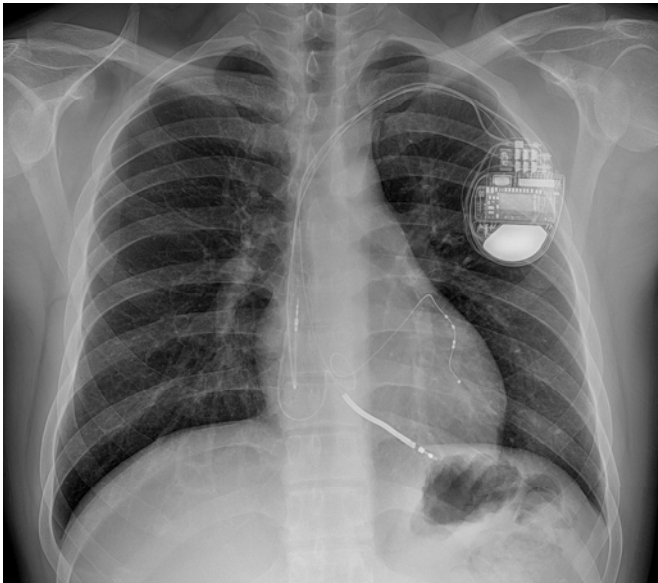
Case2. M/33, Dyspnea, DOE (despite medical Tx)
- DCMP (EF 20%, LVEDD 68), SR with QRS 182ms



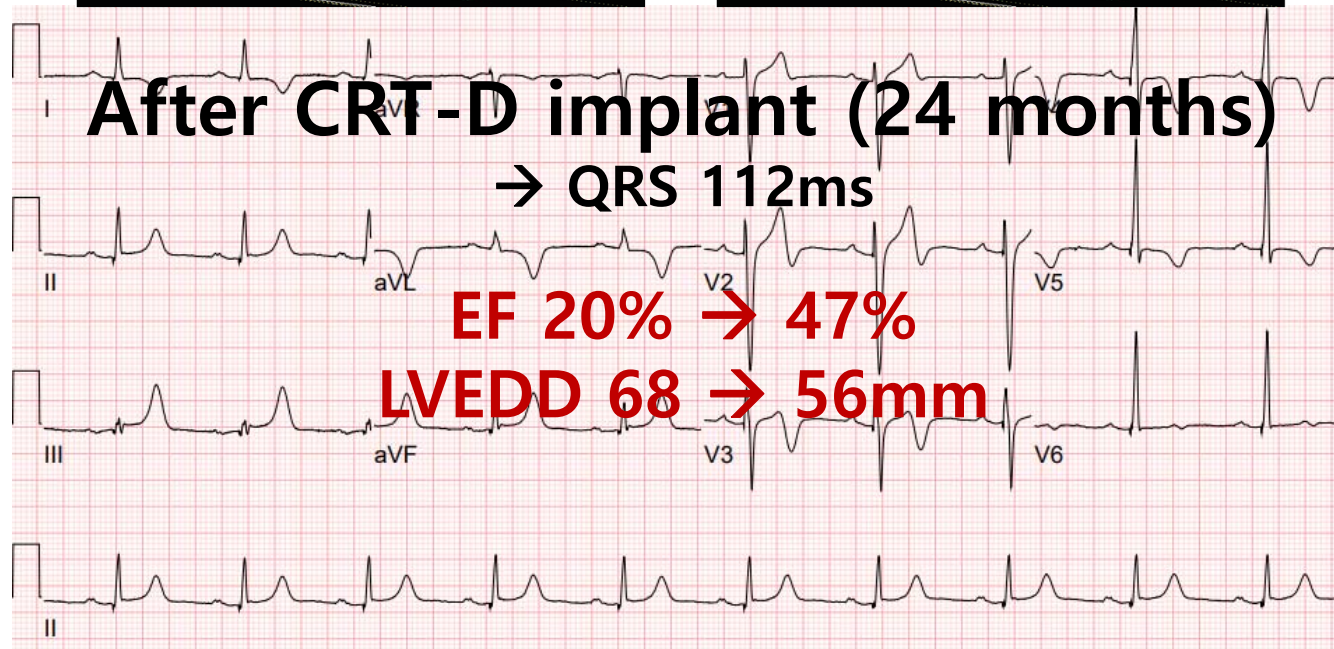
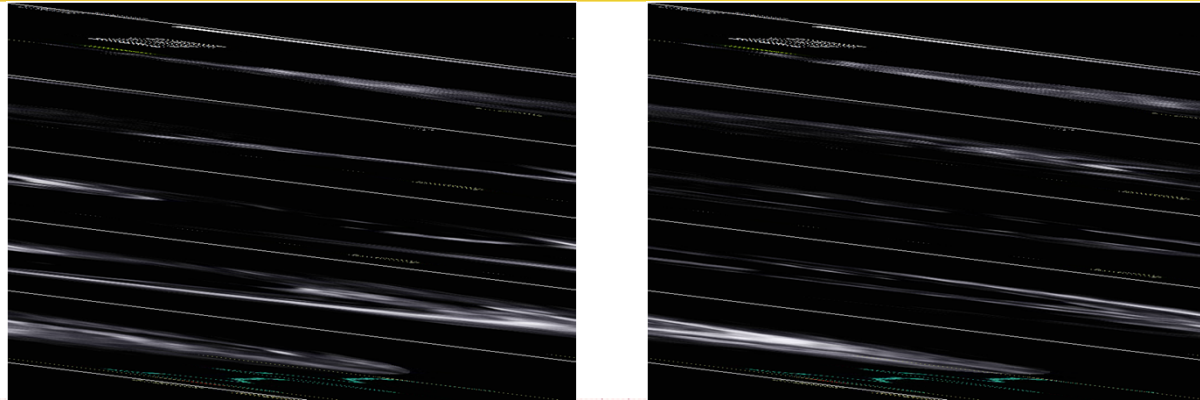
→ CRT-D implant

Case2. M/33, Dyspnea, DOE (despite medical Tx)
- DCMP (EF 20%, LVEDD 68), SR with QRS 182ms

After CRT-D implant (12 months)
→ QRS 148ms



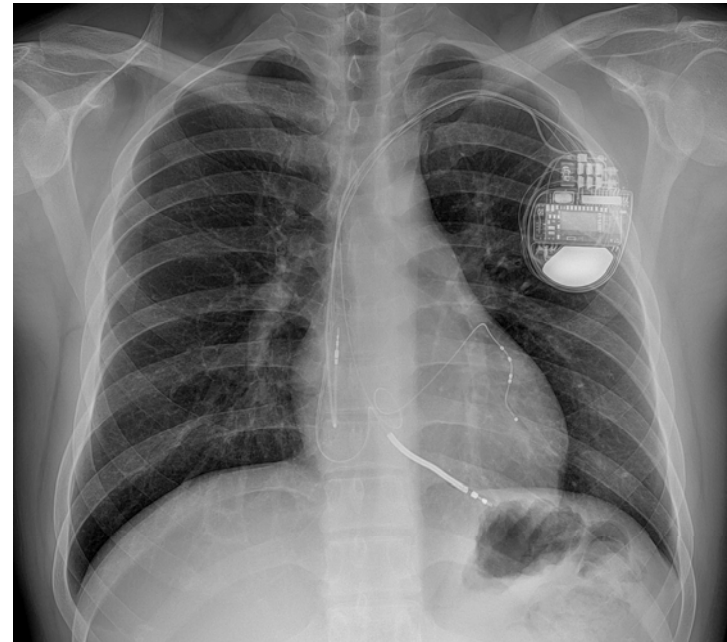
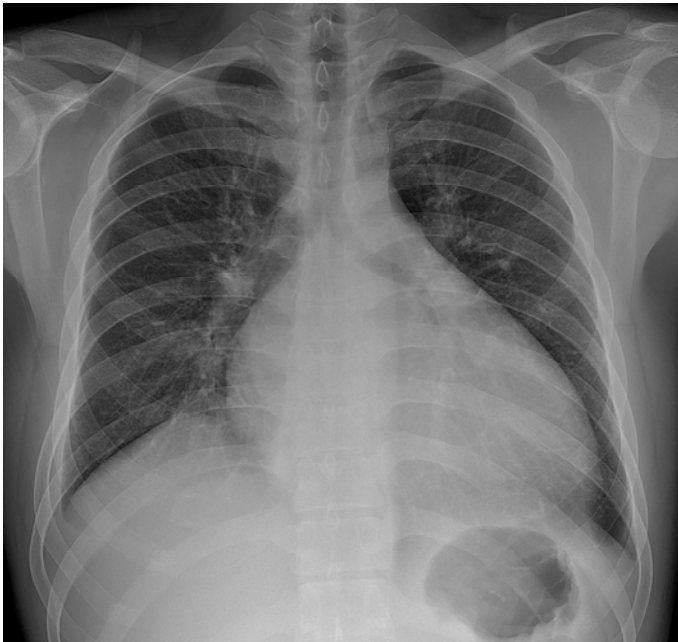
Case2. M/33, Dyspnea, DOE (despite medical Tx) - DCMP (EF 20%, LVEDD 68), SR with QRS 182ms



Case2. M/33, Dyspnea, DOE (despite medical Tx)
- DCMP (EF 20%, LVEDD 68), SR with QRS 182ms

1*

After 24 months



**Thank you
for your attention!**