Ventricular Remodeling in Heart Failure

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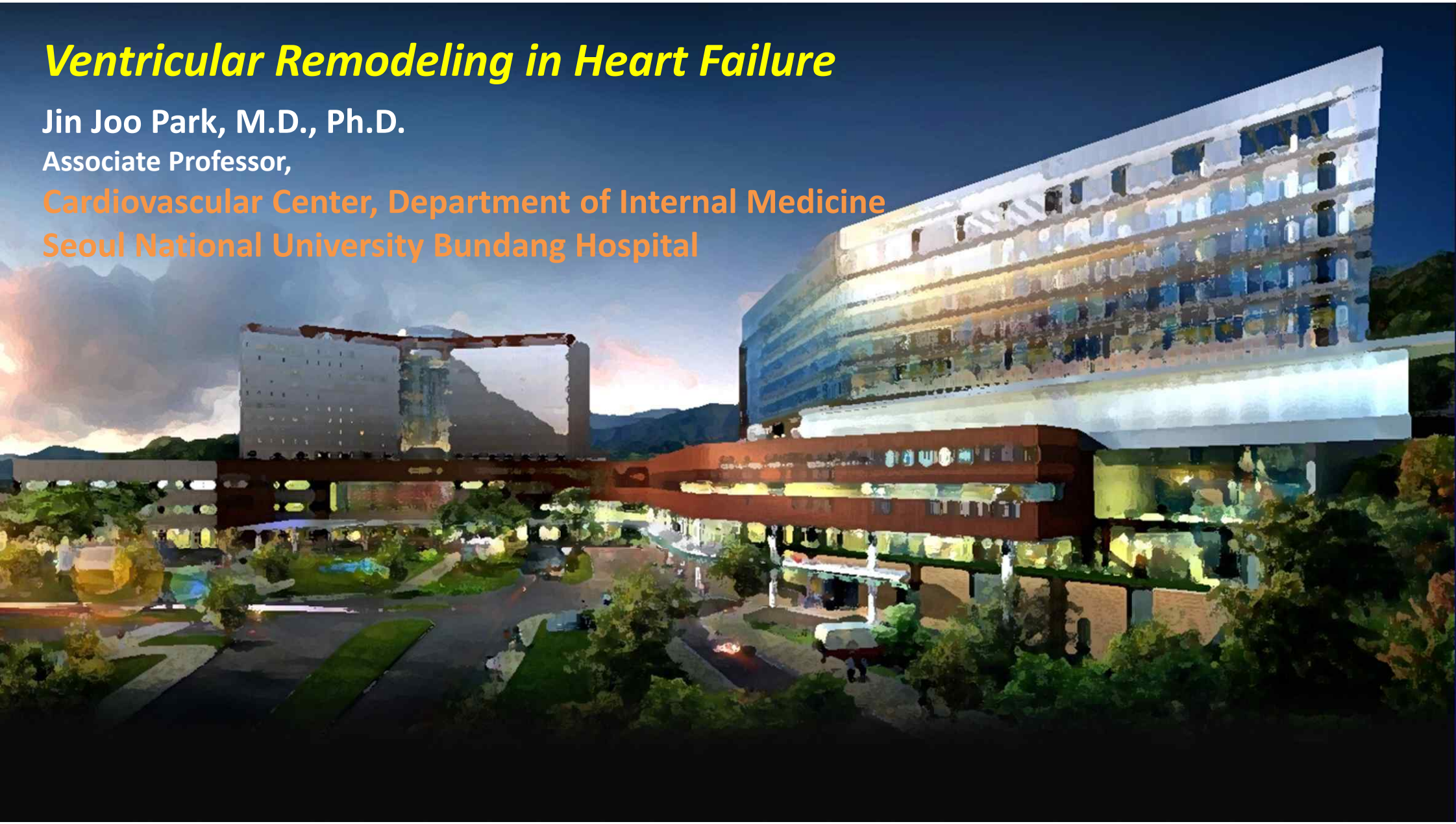
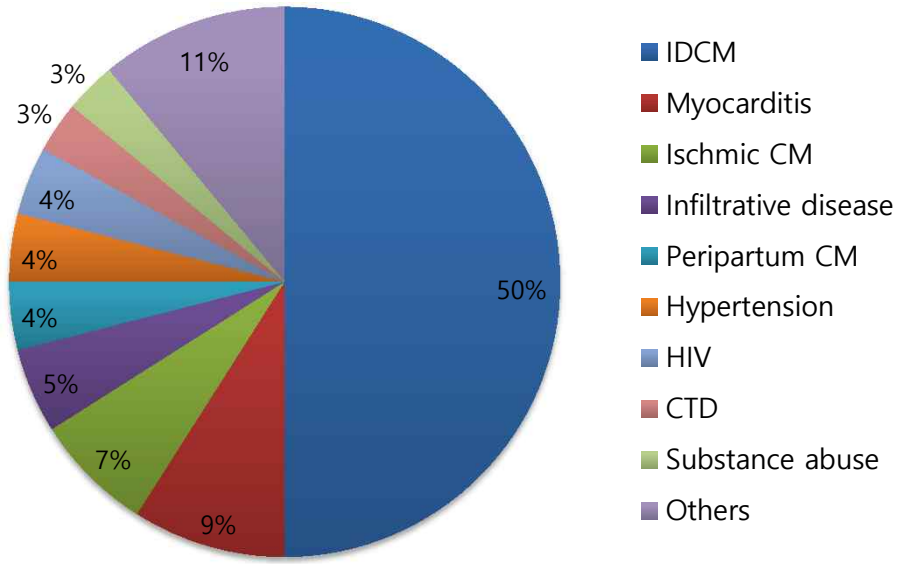


Definition of Dilated cardiomyopathy

Definition of DCM

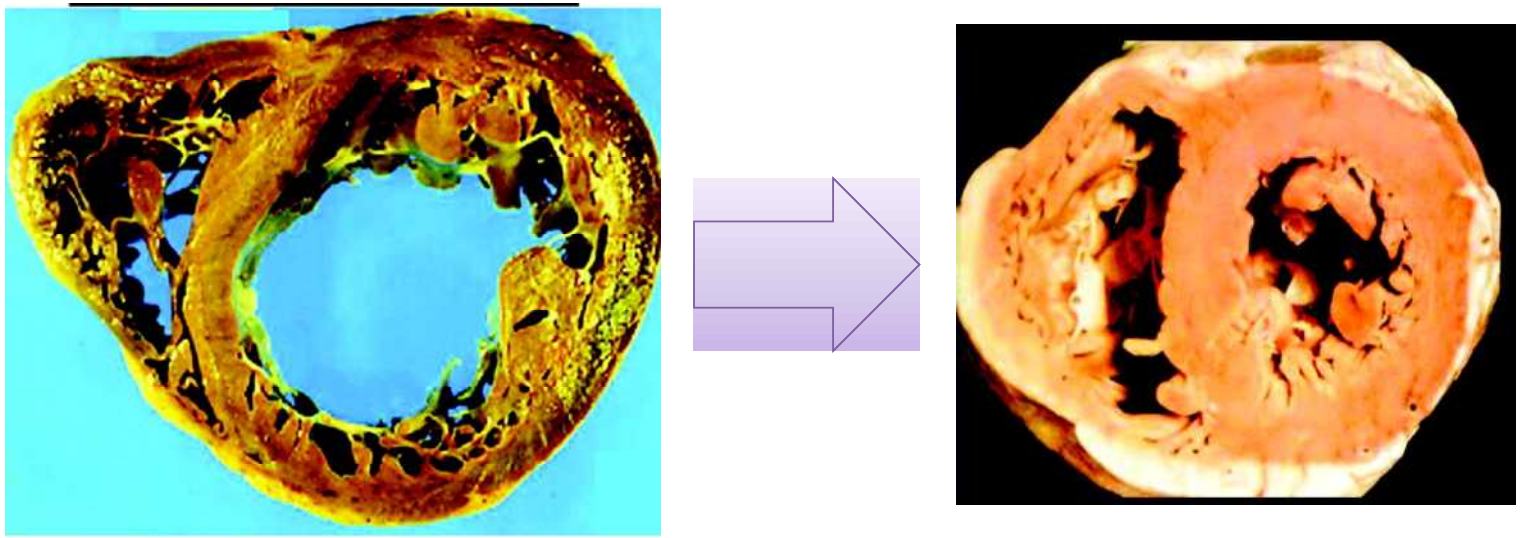
- Evidence of dilatation of LV ± RV
- Impaired contraction of LV ± RV (e.g., LVEF < 40%)
- ***idiopathic DCM***: after exclusion of primary and secondary causes of heart disease (e.g., myocarditis and coronary artery disease)

Etiologies of DCM



Felker et al, NJEM 2000

Is DCM Reversible?



Case 1

51/M

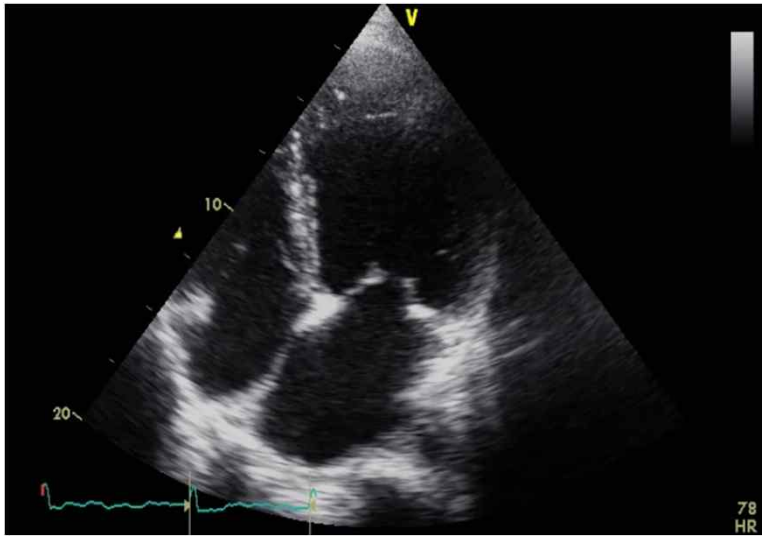
Multiple admissions for ADHF

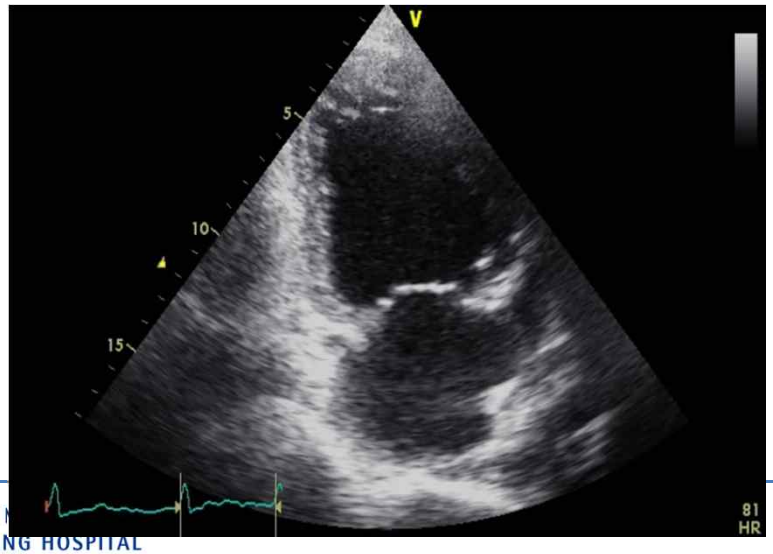
2012-04-11: ADHF (EF 14%)

2013-04-11: ADHF (EF 15%)

2013-04-13: ADHF with cardiogenic shock

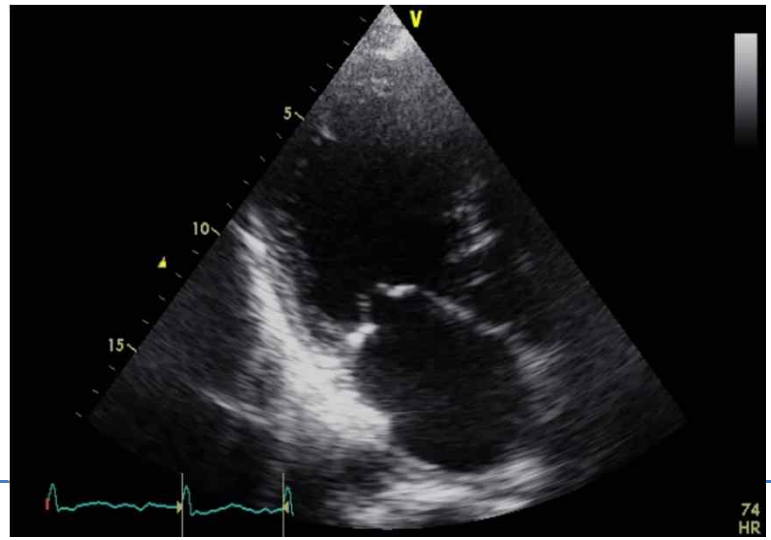
Echo



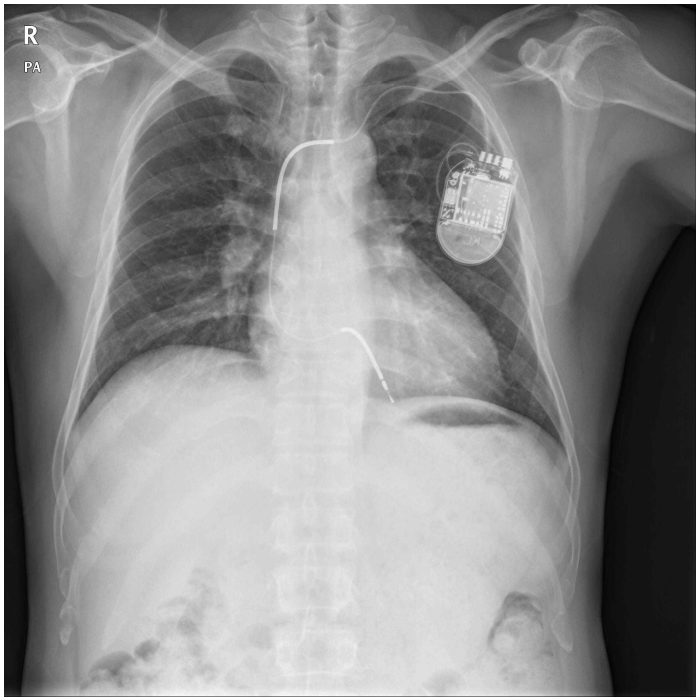


Echo:

- idiopathic DCMP with severe LV dysfunction (**EF = 21%**) combined with RV dysfunction
- non-valvular A.fib
- concentric LVH
- mild MR, TR



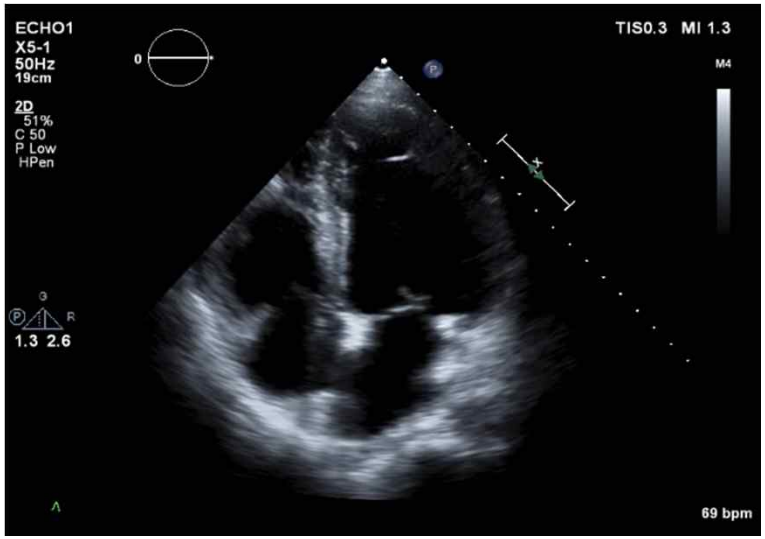
ICD implantation, GDMT until Heart-TPL



Medical treatment

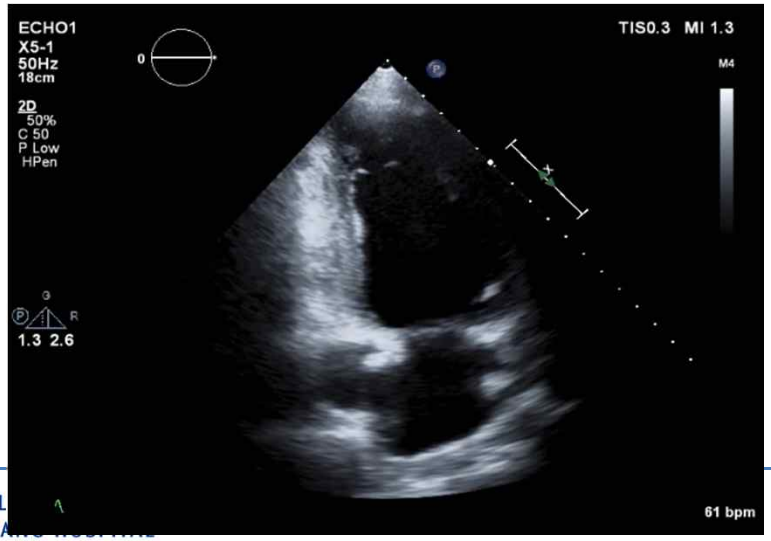
- Bisoprolol 10mg qd
- Ramipril 10mg qd
- Spironolactone 25mg qd
- Furosemide 40mg qd
- Warfarin

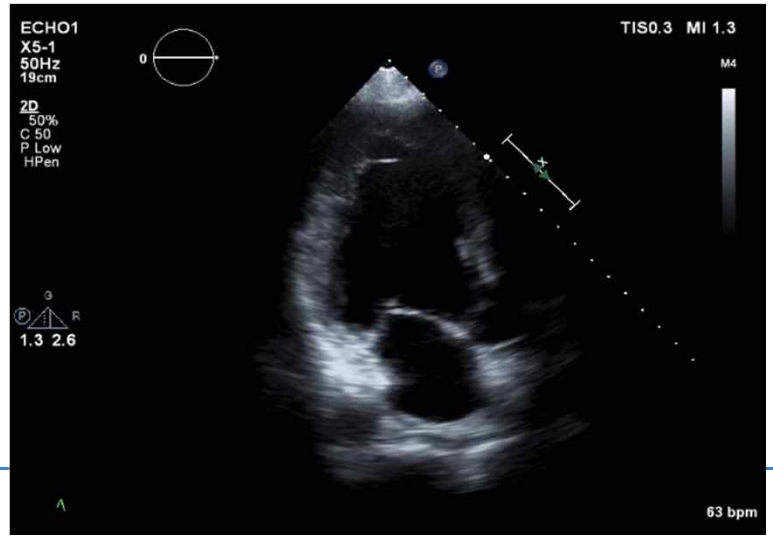
Improved DCM



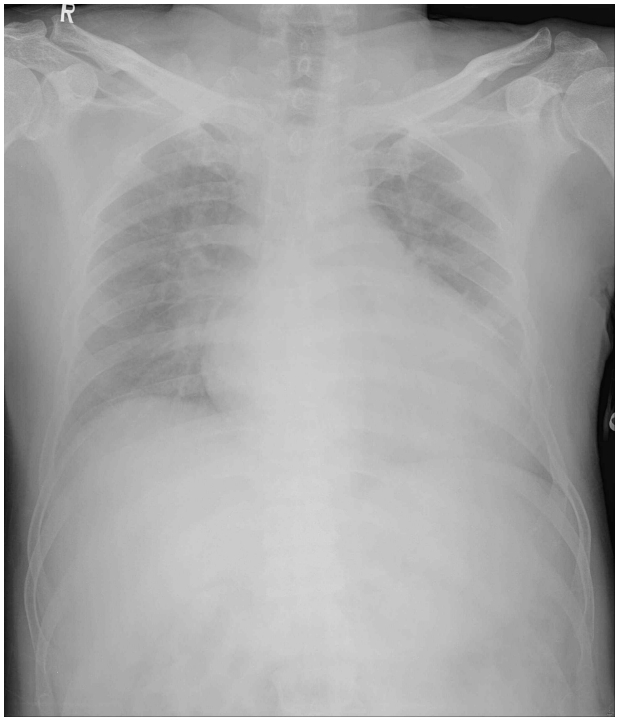
Echo

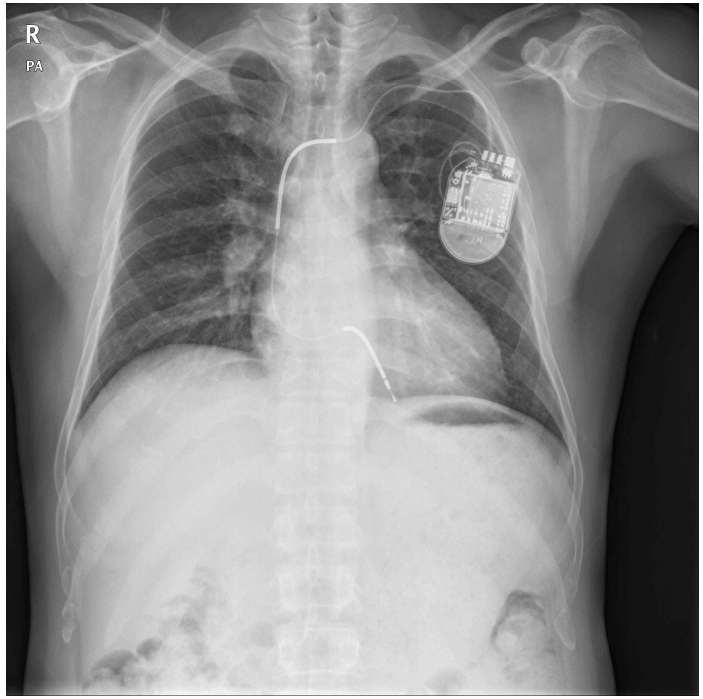
- idiopathic DCMP mild LV dysfunction with improved RV dysfunction
- LVEDD=58mm← 61mm, **LVEF=50%←21%**
- grade I diastolic dysfunction
- LA enlargement



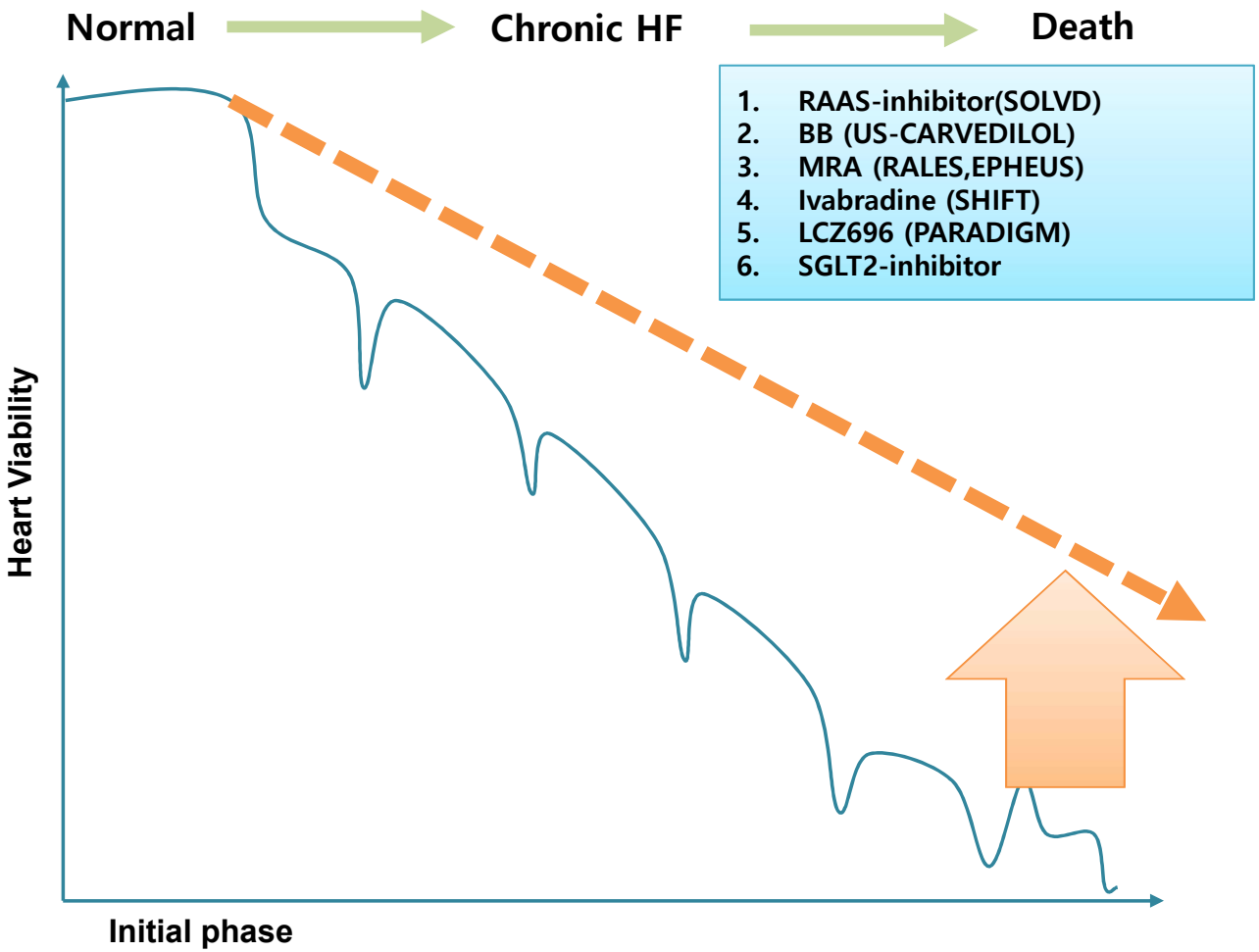


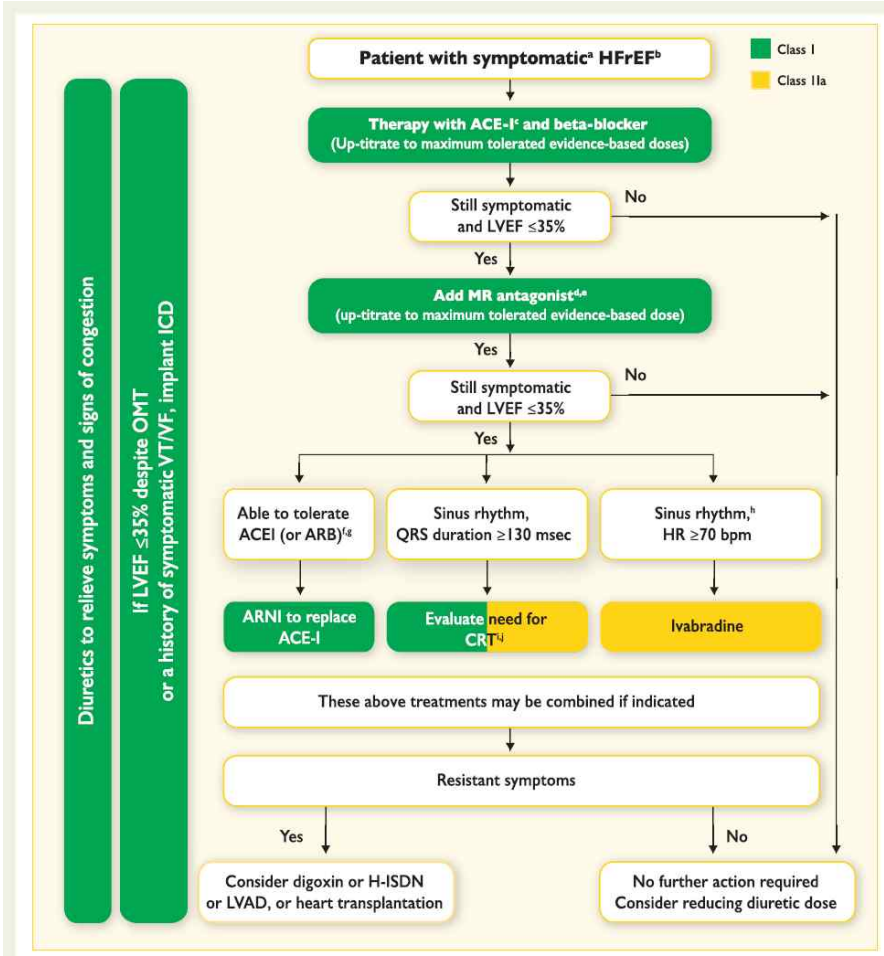
Before and After GDMT





OMT





Gheorghiade M. Am J Cardiol. 2005;96(suppl 6A):1-4G.

Definition of Cardiac Remodeling

Genomic expression, molecular, cellular and interstitial changes that are manifested clinically as **changes in size, shape and function** of the heart after cardiac injury.

"International Forum on Cardiac Remodeling" (1998)

Mechanism of Cardiac Remodeling

Abnormal hemodynamic workload
Ischemia
Inflammation

Injured Heart

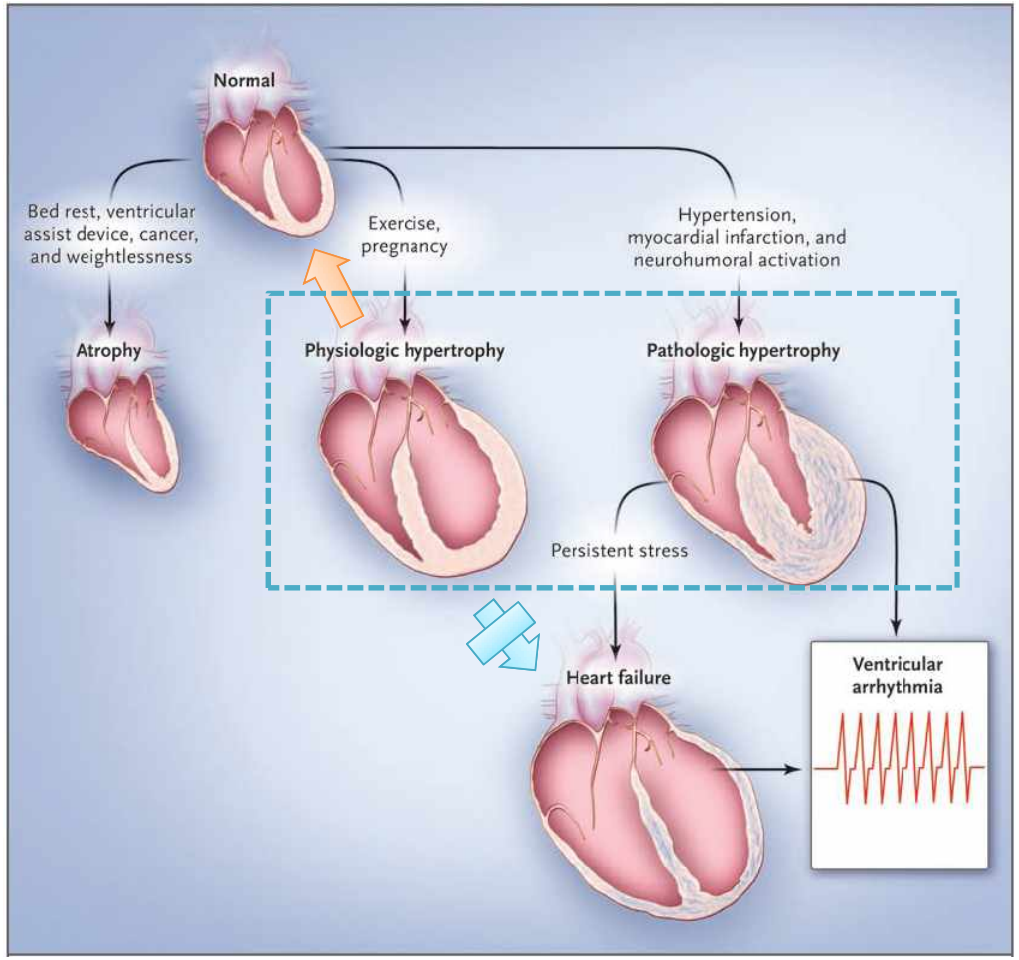
Biomechanical stress (hemodynamics)

Neurohumoral Inflammatory

Adaptive & maladaptive process

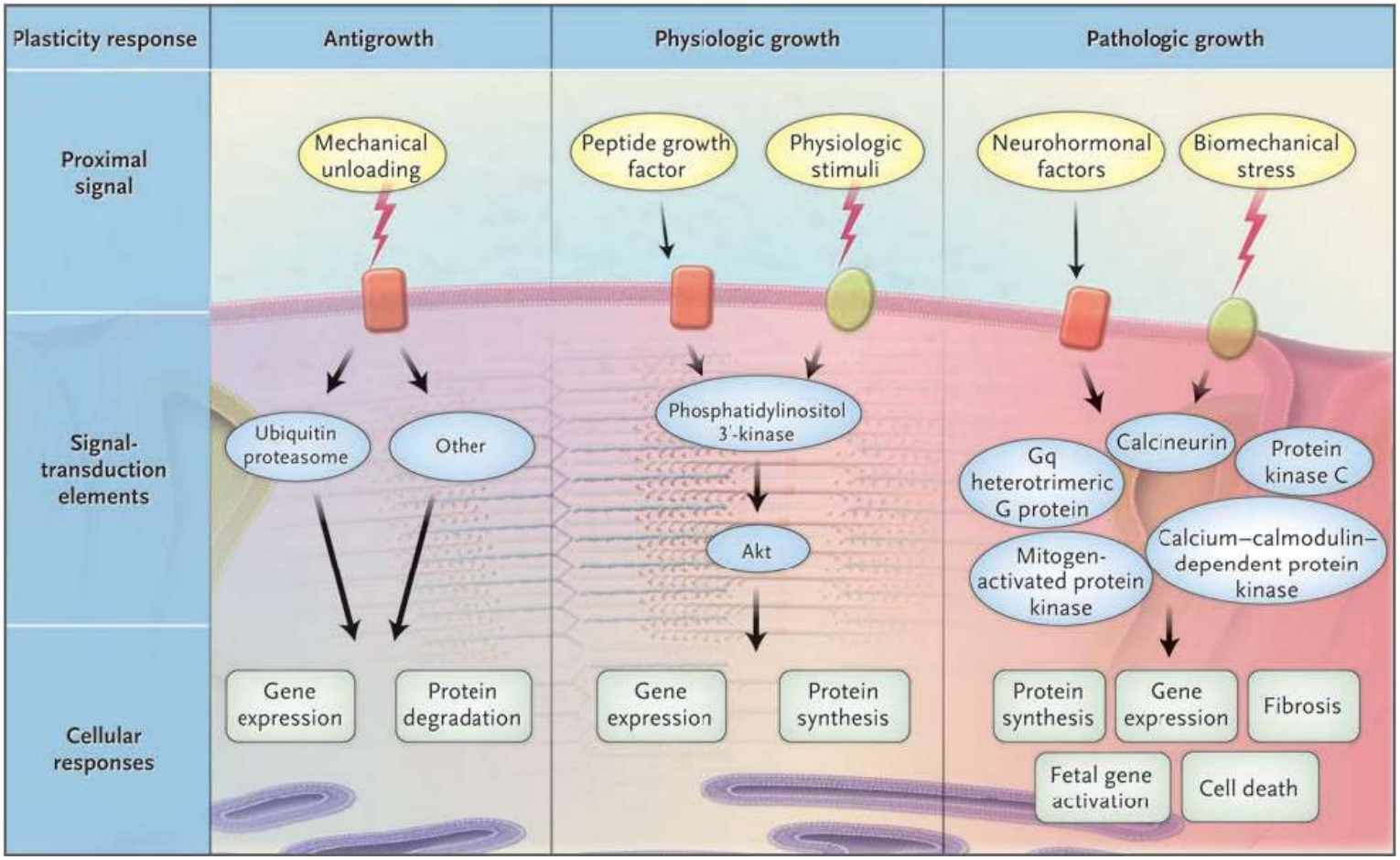
LV dilation

Cardiac Plasticity



Hill, Olson, NJEM 2007

Extracellular signals trigger intracellular events



Hill, Olson, NJEM 2007

Mechanism of progressive remodeling and HF

Cell Growth	Fibrosis	Apoptosis	Counter-regulatory Factors
Angiotensin II	Angiotensin II	TNF-a	ANP
Catecholamines	Endothelin	Fas ligand	BNP
Endothelin	Aldosterone		Bradykinin
TNF-a	TGF-b		Nitric Oxide
Growth hormone			
IGF			
Cardiotropn-1			
Mechanical stretch			

Strategy to Prevent HF progression, or LV reverse remodeling?

1. Treatment of **Etiologies**
2. Blocking neurohumoral activation
   - ACEi/ARB
   - Beta-blocker
   - Sacubitril-Valsartan
   - Aldosterone antagonist
   - Ivabradine
   - SGLT2-inhibitors (?)
3. Cardiac resynchronization therapy (CRT)
4. Mechanical or surgical Therapy (LVAD, Dor)

Reversible causes of DCM

Infectious
Viral
Adenovirus
Coxsackie virus
Cytomegalovirus
HIV
Influenza virus
Varicella
Hepatitis
Epstein-Barr
Echovirus
Parvovirus
Other

Bacterial
Streptococci-rheumatic fever
Typhoid fever
Diphtheria
Brucellosis
Psitticosis
Rickettsial
  Leptospirosis
  Syphillis
Lyme disease

Mycobacterial-fungal
Histoplasmosis
Cryptococcosis

Parasitic
Toxoplasmosis
Trypanosomiasis (Chagas disease)
Shistosomiasis
Trichinosis

Deposition ds.
Hemochromatosis
Amyloidosis

Nutritional deficiencies
Thiamine
Selenium
Carnitine
Niacin (pellagra)

Electrolyte and renal abnormalities

Hypophosphatemia
Uremia

Medications
Chemotherapeutic agents
Anthracyclines
Cyclophosphamide
Trastuzumab
Antiretroviral drugs
Zidovudine
Didanosine
Zalcitabine
Phenothiazines
Chloroquine
Clozapine

Toxins
Ethanol
Cocaine
Adriamycin
Cyclophosphamide
Amphetamines
Cobalt
Lead
Lithium
Mercury
Carbon monoxide
Beryllium
Methysergide

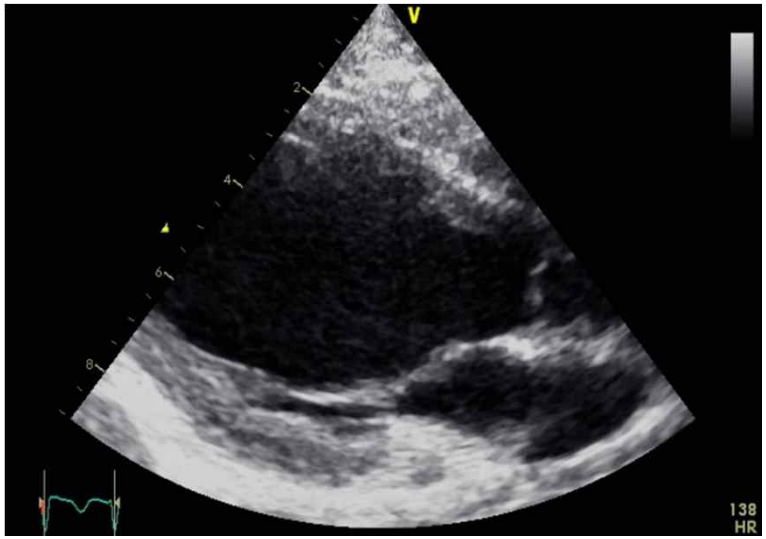
Inflammatory/AID
Systemic lupus erythematosis
Dermatomyositis
Scleroderma
Rheumatoid arthritis
Sarcoidosis
Hypersensitivity myocarditis
Other autoimmune myocarditis
Giant cell arteritis
Kawasaki disease

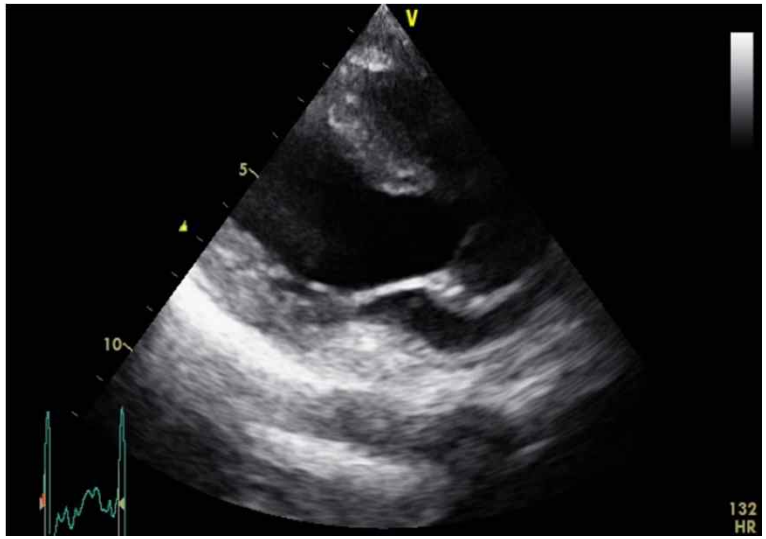
Endocrinologic disorder
Thyroid hormone excess or deficiency
Growth hormone excess or deficiency
Pheochromocytoma
Diabetes mellitus
Cushing's syndrome
Pheochromocytoma or other catecholamine excess

Familial, genetic CMP
Duchenne's muscular dystrophy
Myotonic dystrophy
Friedreich's ataxia
Arrhythmogenic right ventricular cardiomyopathy

Miscellaneous
Peripartum cardiomyopathy
Tachycardia
Heat stroke
Hypothermia
Sleep apnea
Radiation
(Calcium overload)
(Oxygen free radical damage)

Stress induced CMP





Mid apical akinesia with basal
Hypercontrcation EF=15%

Tachycardia-mediated CMP

- ***If chronic tachycardia*** *continued more than 10-15% of the day, with an atrial rate of more than 150% of that predicted for age, tachycardiomyopathy occurs.*

- **Possible mechanisms**:
  - Myocardial energy depletion
  - Impaired energy utilization
  - Myocardial ischemia

- **Treatment**: controlling the heart rate
- **Prognosis**: partially or completely reversible after normalization of heart rate

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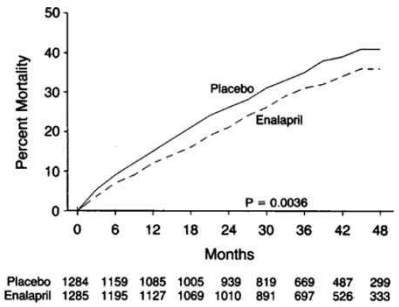
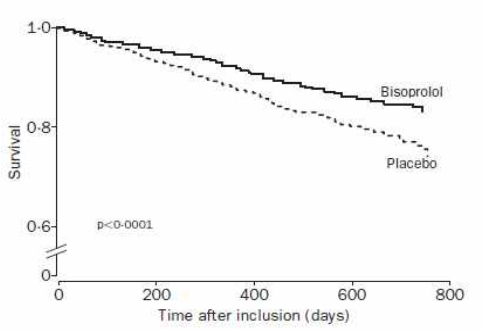
   - Aldosterone antagonist
   - Ivabradine
   - SGLT2-inhibitors (?)
3. Cardiac resynchronization therapy (CRT)
4. Mechanical or surgical Therapy (LVAD, Dor)

Clinical trials in HFrEF

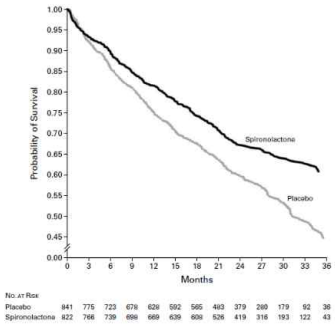
SOLVED



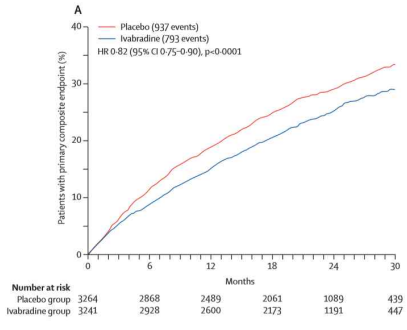
CIBIS II Investigators



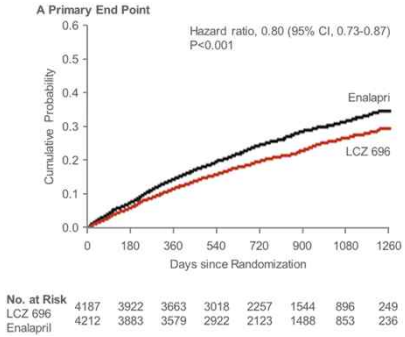
RALES

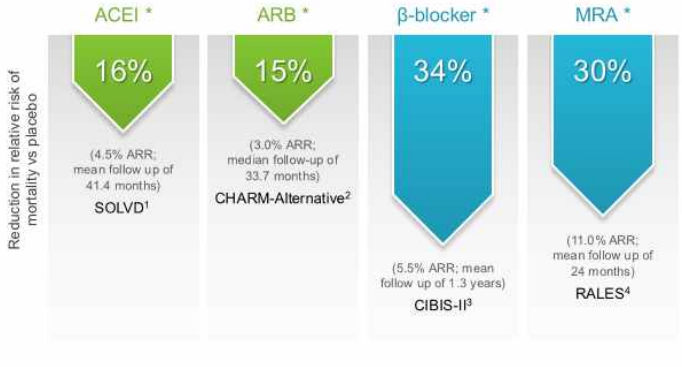


SHIFT

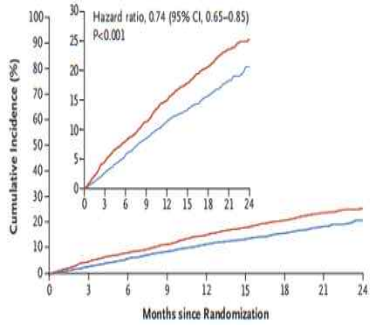


PARADIGM

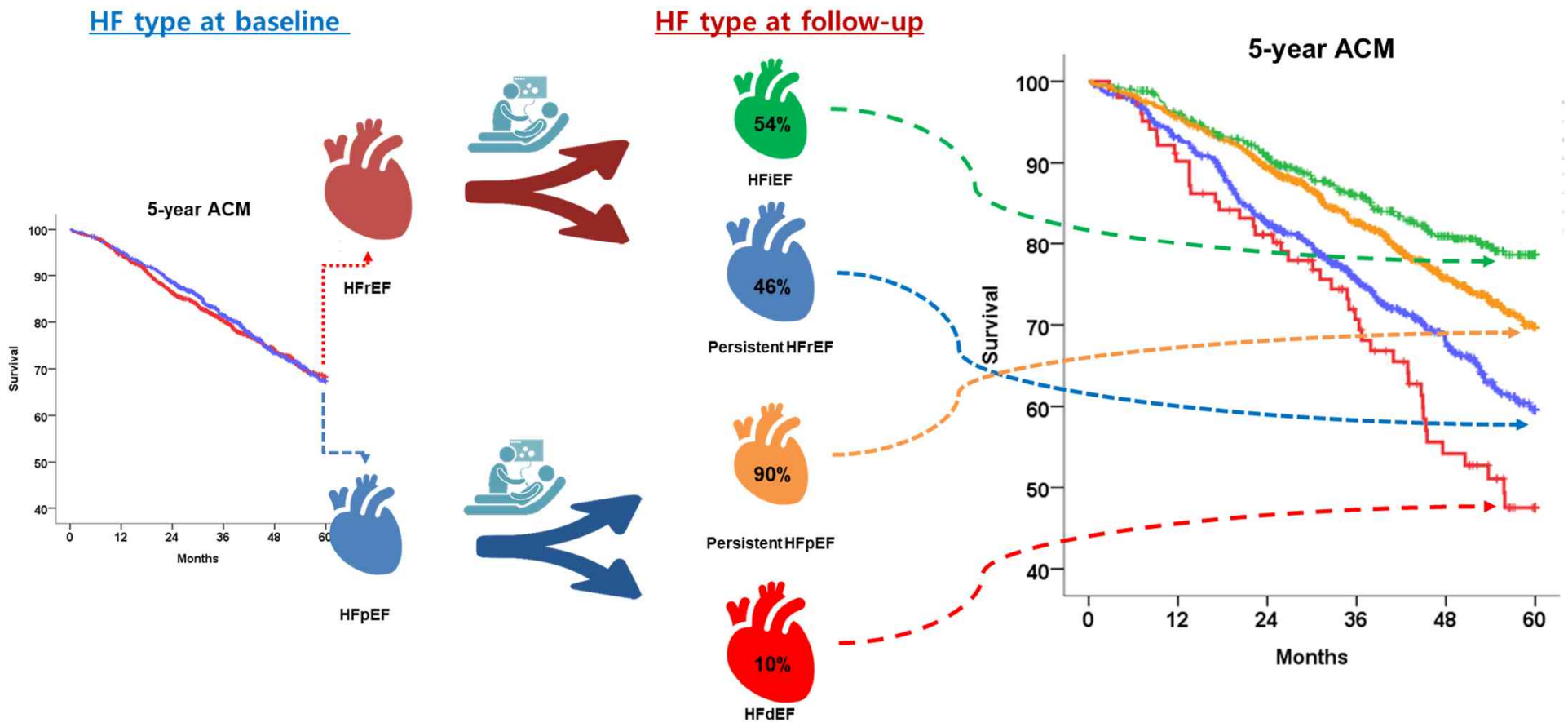




DAPA-HF

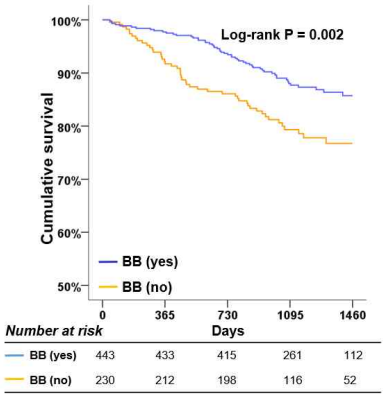


Change of HF phenotype during follow-up

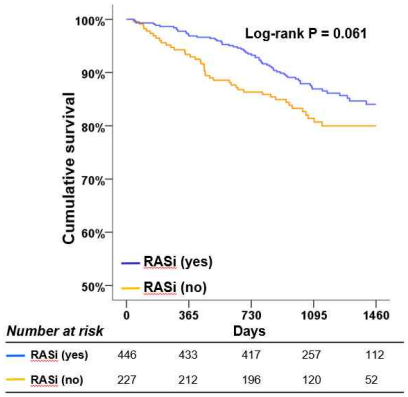


GDMT in HFiEF

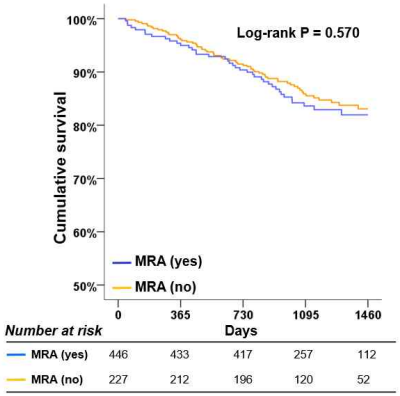
Beta blockers



RAS inhibitors



MRA



	Unadjusted			Adjusted		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.06	1.04-1.07	<0.001	1.05	1.03-1.06	<0.001
Male	1.28	0.88-1.87	0.198			
De-novo onset	2.46	1.71-3.54	<0.001	0.56	0.37-0.84	0.005
Hypertension	1.99	1.36-2.90	<0.001			
Diabetes mellitus	2.41	1.67-3.48	<0.001			
Ischemic heart disease	2.93	1.98-4.33	<0.001	1.63	1.05-2.52	0.029
COPD	1.01	0.51-2.00	0.971			
Chronic kidney disease	3.22	2.12-4.91	<0.001	1.73	1.06-2.80	0.024
Cerebrovascular accident	3.21	2.07-4.96	<0.001	2.00	1.23-3.24	0.005
Malignancy	1.52	0.88-2.62	0.130			
NYHA functional class			0.079			
II	1	Reference				
III	1.22	0.67-2.24				
IV	1.74	0.97-3.10				
Beta-blocker at HFiEF diagnosis	0.54	0.37-0.80	0.002	0.61	0.41-0.91	0.015
RASi at HFiEF diagnosis	0.69	0.46-1.02	0.063			
MRA at HFiEF diagnosis	1.12	0.75-1.67	0.570			

Park JJ, Park CS, Choi DJ et al, JAHA 2019

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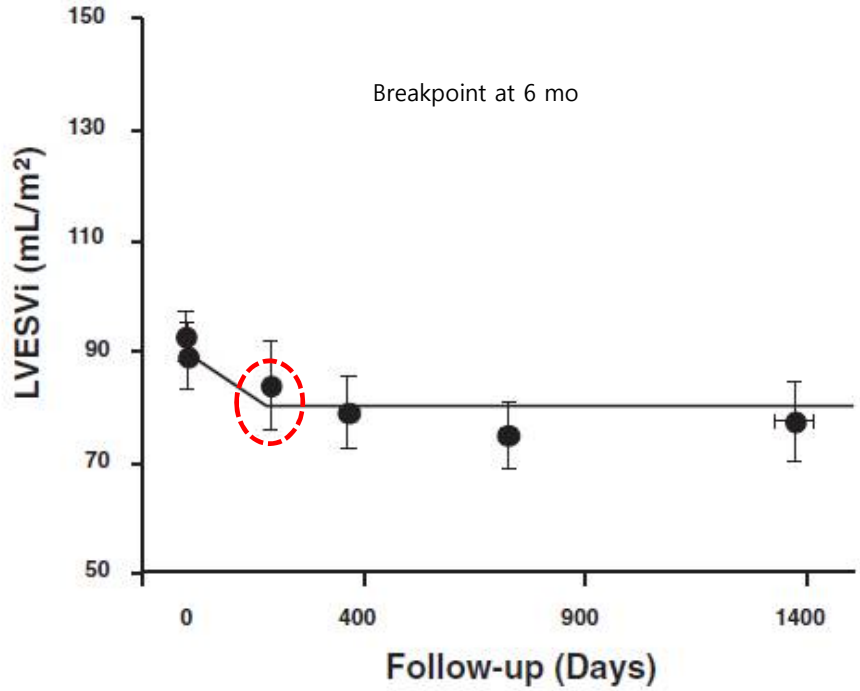
3. **Cardiac resynchronization therapy (CRT)**
4. Mechanical or surgical Therapy (LVAD, Dor)

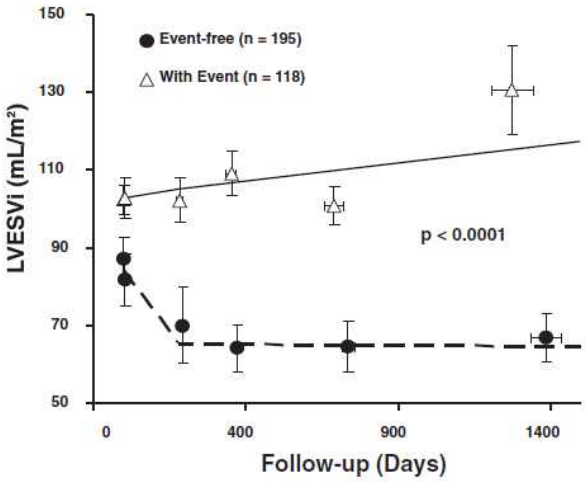
Cardiac resynchronizing therapy (CRT)

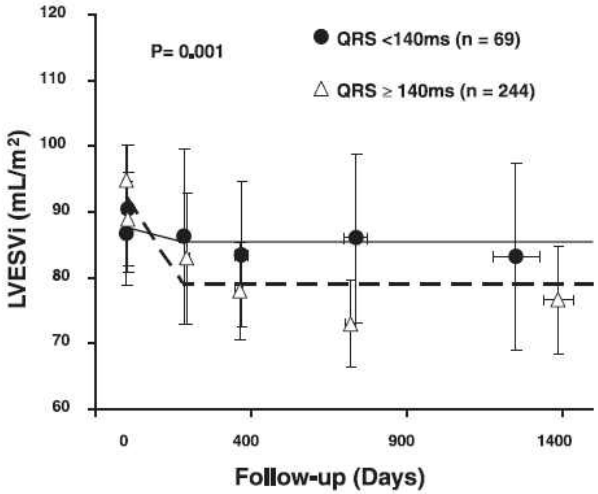
Patient: Patients with CRT implantation (n=313)
Outcomes: Clinical endpoints (death, HT, LVAD) (n=118, 37.6%); remodeling, clinical outcomes

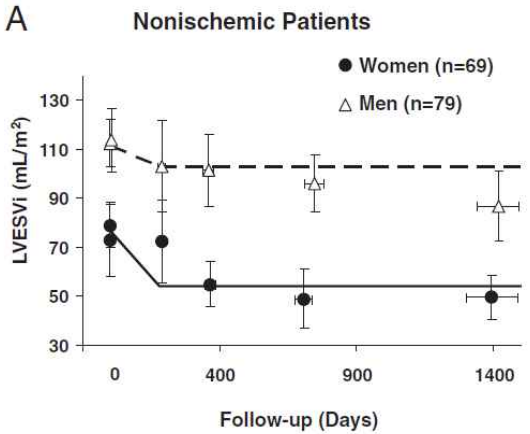


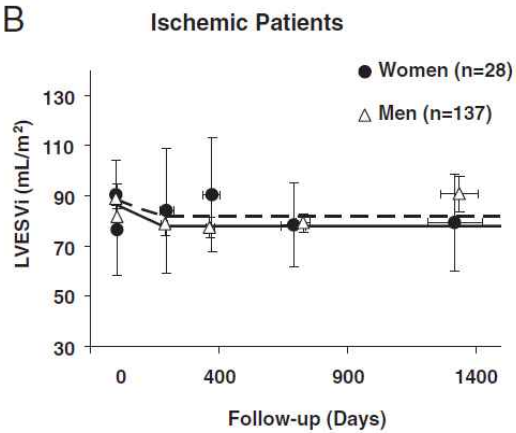
Verhaert et al. JACC 2010

CRT & LVRR









Verhaert et al. JACC 2010

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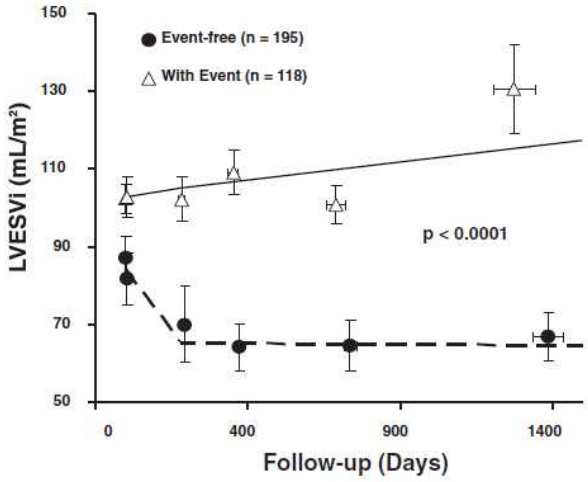
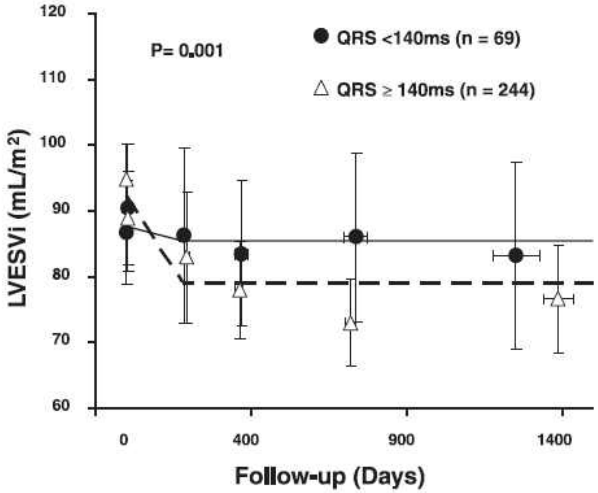
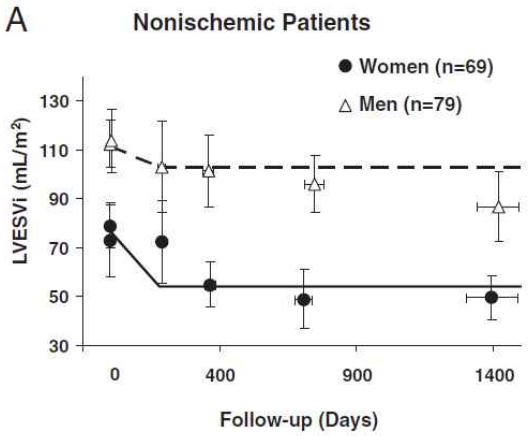
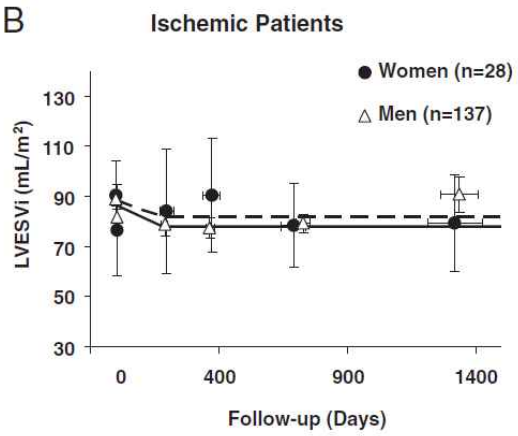


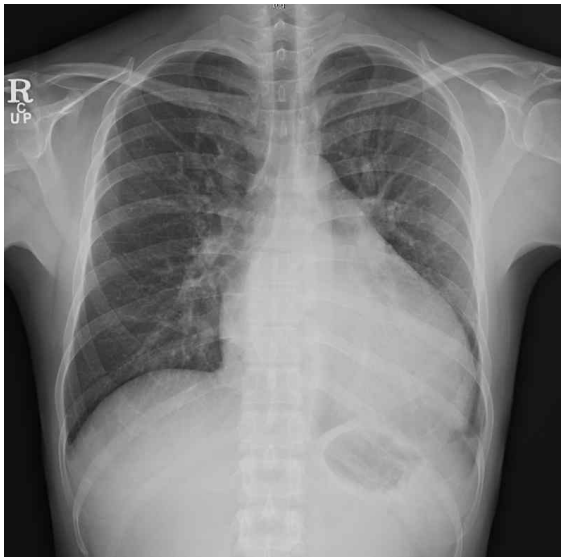


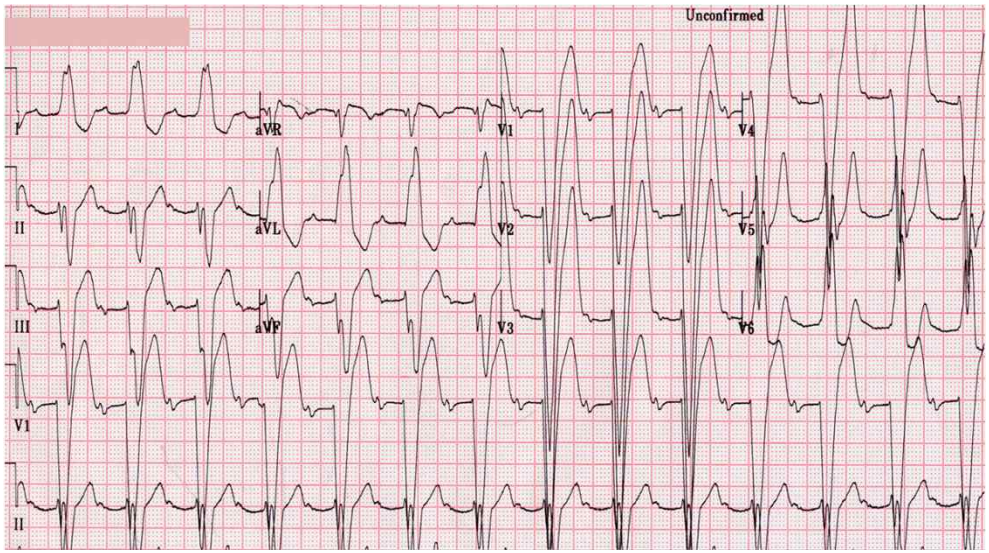




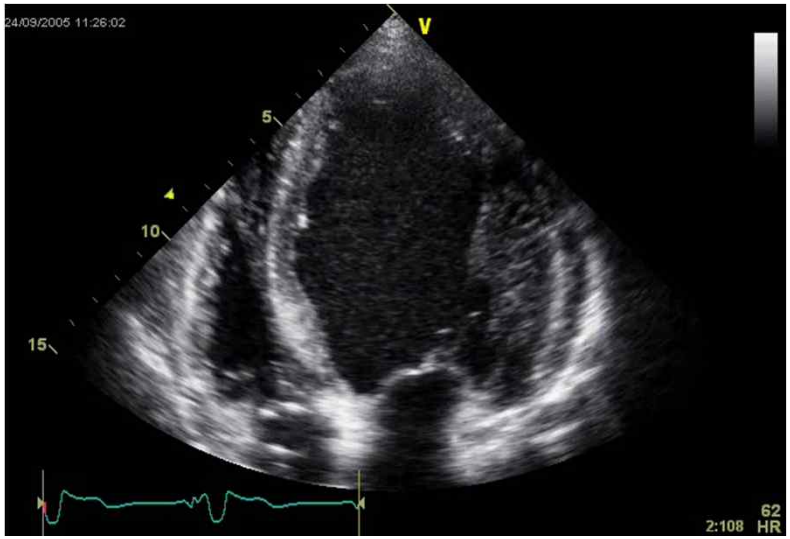
Verhaert et al. JACC 2010

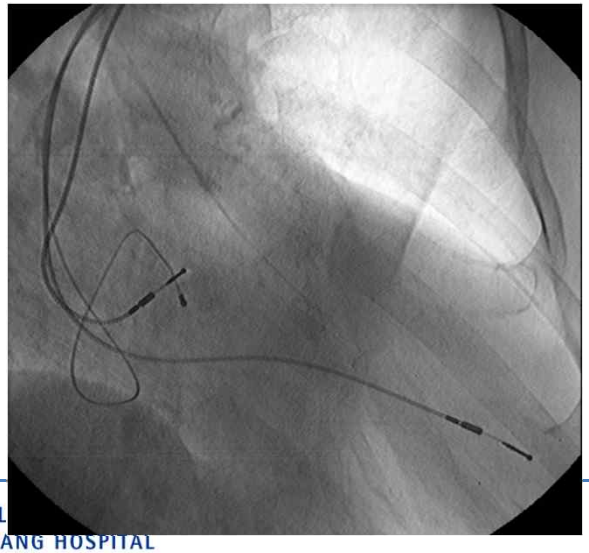
Case 3

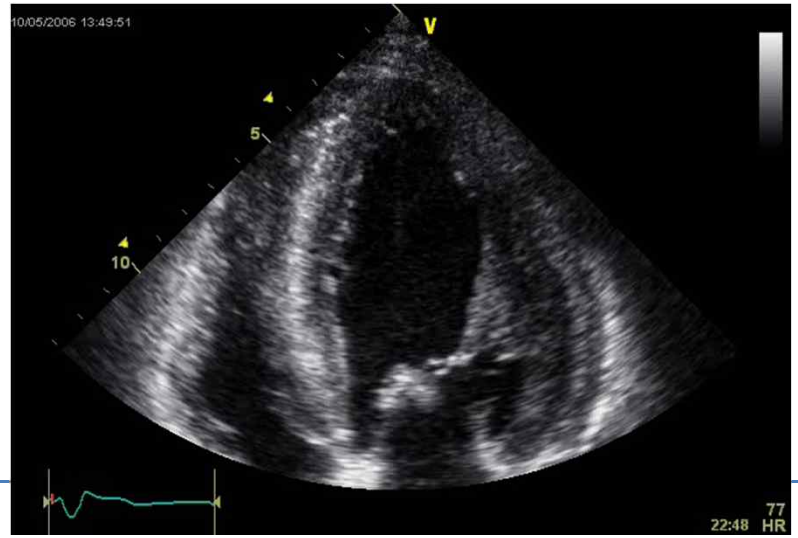




LVRR 6mo after CRT-implantation







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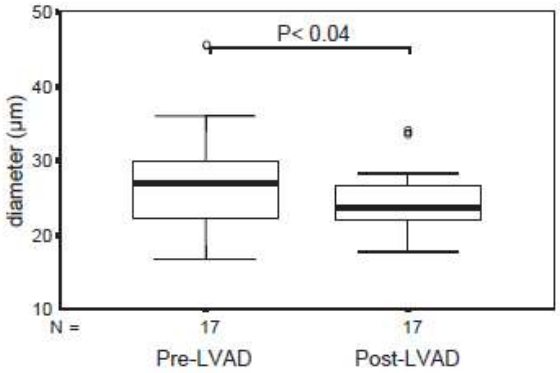
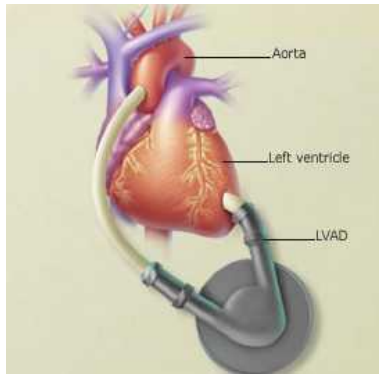
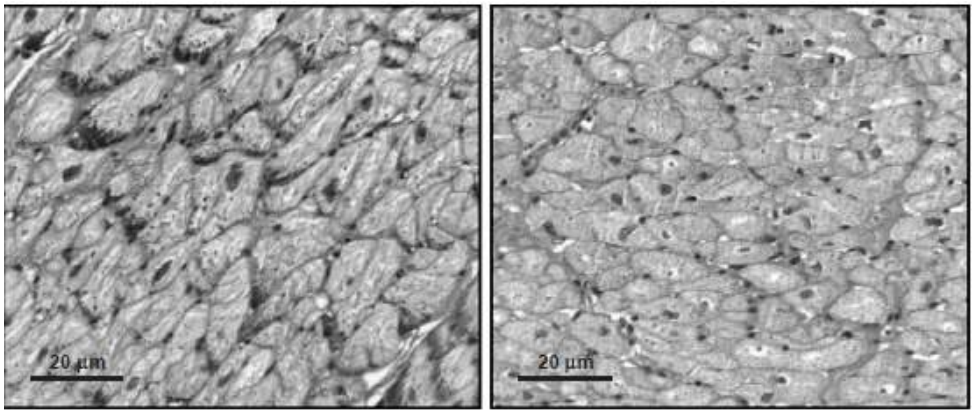
    - ACEi/ARB
    - Beta-blocker
    - Sacubitril-Valsartan
    - Aldosterone antagonist
    - Ivabradine
    - SGLT2-inhibitors (?)
3. Cardiac resynchronization therapy (CRT)
4. **Mechanical or surgical Therapy (LVAD, Dor)**

LVAD and LVRR (mechanical unloading)

Cardiomyocyte diameter







Wohlschlaeger et al. Cardiovasc Res 2005

Conclusions

- ✓ *For LVRR of DCM, it is essential..*
  - *To identify and correct the underlying causes*
  - *To modulate the neurohumoral activation*
  - *To improvement of biomechanical stress (hemodynamics)*


Thank You For Your Attention!
Seoul National University Bundang Hospital