Điều trị suy tim phân xuất tống máu bảo tồn

(Treatment of Heart Failure with a Preserved Ejection Fraction)

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Các vấn đề của Suy tim PXTM bảo tồn

- Hội chứng lâm sàng giống nhau giữa ST/PXTM giảm và ST/PXTM bảo tồn
- Suy tim PXTM bảo tồn:
  - Tử vong 5 năm # 60%
  - Nhập viện 50%/6 tháng
  - Thường ở người cao tuổi; nữ > nam
  - 85% có tiền sử THA
  - Suy tim do thiếu máu cục bộ: PXTM giảm > PXTM bảo tồn
  - Điều trị bằng thuốc kém hiệu quả

Mode of Death Distribution in Randomized Controlled Trials

- HFpEF: 50-70% tử vong do tim mạch
- HFpEF: 30-40% tử vong không do tim mạch
  (ǂ HFrEF: 15%)

CATEGORY	HFpEF *n* (%)				HFrEF Mean % (range)	
	I-Preserve	CHARM-P	PEP-CHF	DIG-P	Drugs	Devices
Total	881	481	109	231		
Sudden death	231 (26)	134 (28)	NR	NR	42 (23-58)	28 (21-34)
Heart failure	125 (14)	102 (21)	NR	64 (28)	36 (27-56)	45 (34-63)
Myocardial infarction	44 (5)	13 (3)	NR	NR	7 (2-15)	6 (3-15)
Stroke	76 (9)	33 (7)	NR	NR	5 (3-6)	5 (3-6)
Cardiovascular procedure	13 (1)	13 (3)	NR	NR	2 (1-3)	2 (1-3)
Other cardiac	10 (1)	35 (7)	NR	NR	7 (2-11)	6 (3-10)
Other vascular	32 (4)	NR	NR	NR	NR	NR
Noncardiovascular	268 (30)	141 (29)	31 (28)	69 (30)	14 (4-20)	15 (5-17)
Unknown	81 (9)	NR	NR	NR	NR	NR

CV, Cardiovascular; *NR*, not reported.

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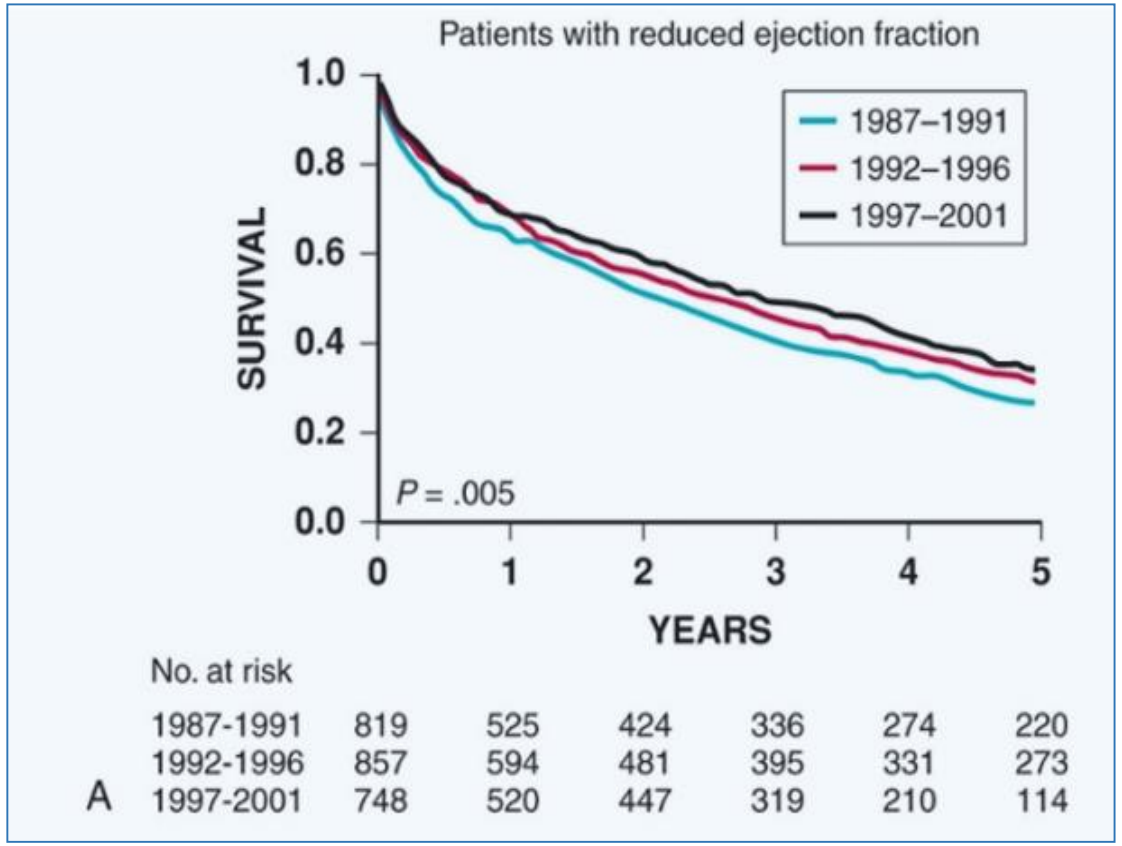
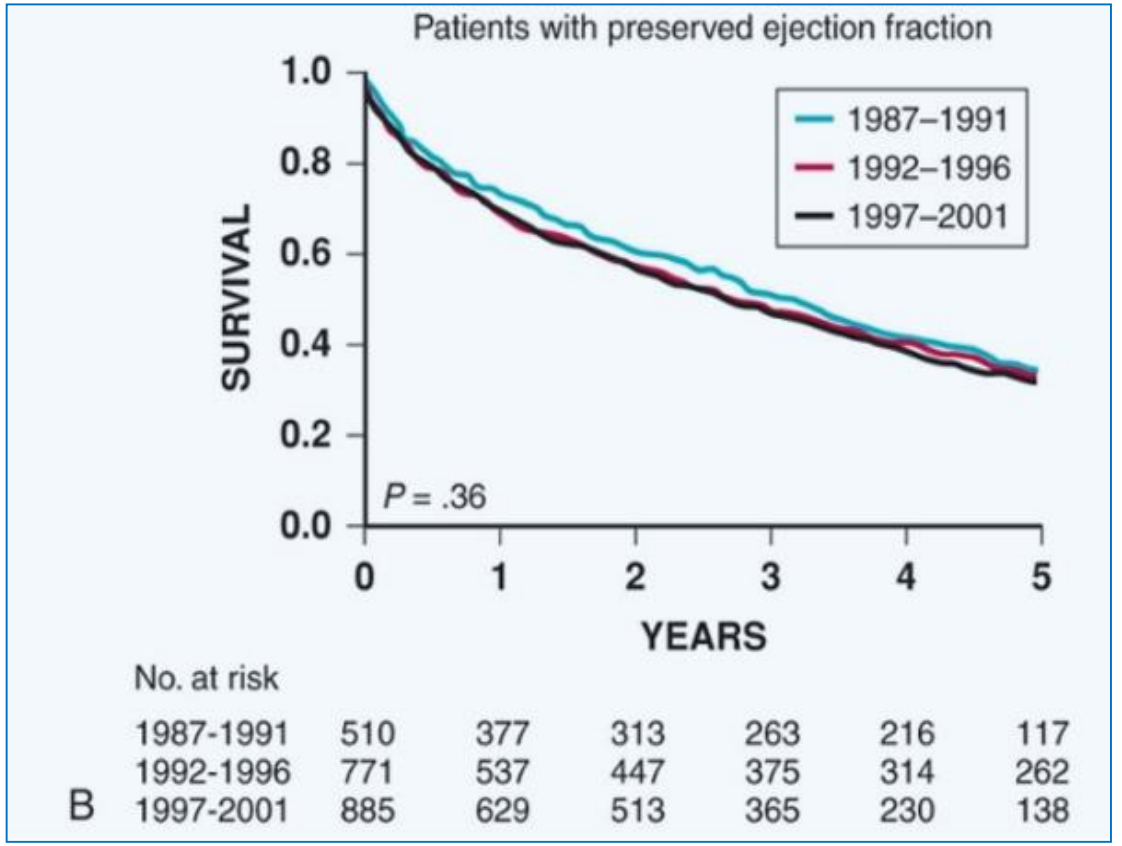
TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Mortality and morbidity in patients with HFrEF or HFpEF in epidemiologic studies





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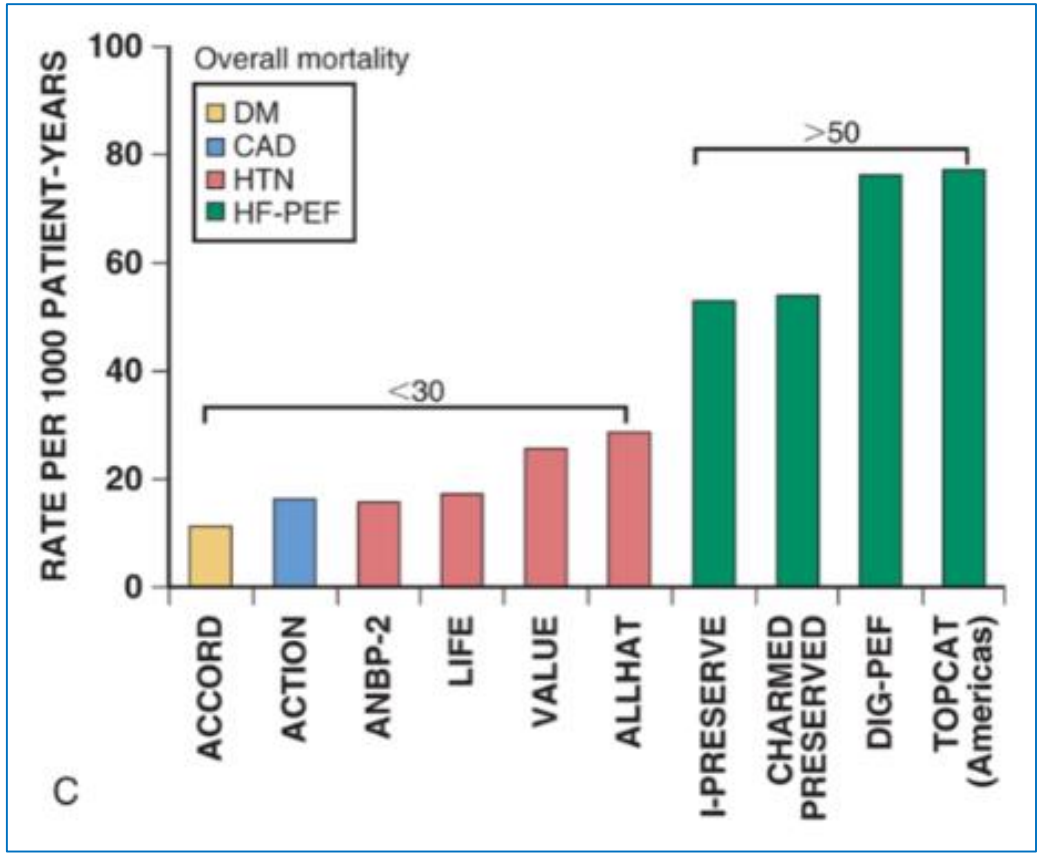
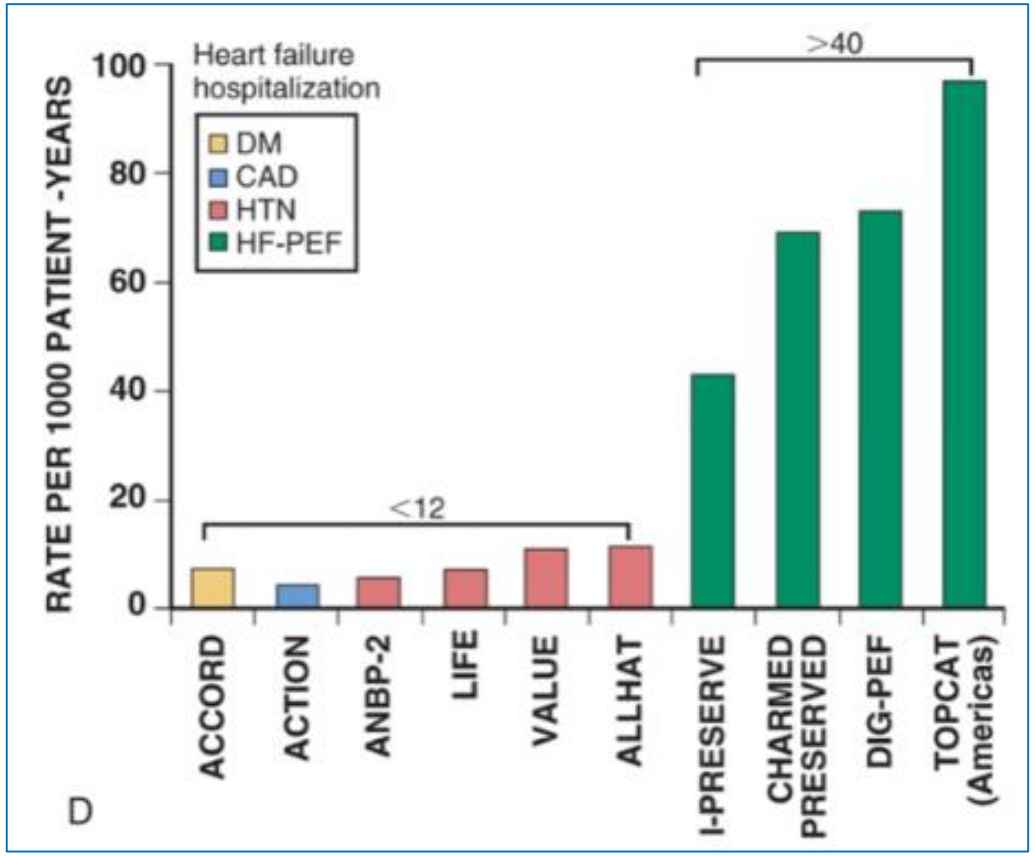
Mortality and morbidity in patients with HFrEF or HFpEF in RCTs





HFpEF có bệnh kèm theo (THA, ĐTĐ, BĐMV): tử vong ≥ 2 HFpEF không bệnh kèm theo

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Định nghĩa suy tim

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).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.

[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with diuretics.

[b]BNP>35 pg/ml and/or NT-proBNP>125 pg/mL.

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Nguyên nhân suy tim (1)

DISEASED MYOCARDIUM		
Ischaemic heart disease	Myocardial scar	
	Myocardial stunning/hibernation	
	Epicardial coronary artery disease	
	Abnormal coronary microcirculation	
	Endothelial dysfunction	
Toxic damage	Recreational substance abuse	Alcohol, cocaine, amphetamine, anabolic steroids.
	Heavy metals	Copper, iron, lead, cobalt.
	Medications	Cytostatic drugs (e.g. anthracyclines), immunomodulating drugs (e.g. interferons monoclonal antibodies such as trastuzumab, cetuximab), antidepressant drugs, antiarrhythmics, non-steroidal anti-Inflammatory drugs, anaesthetics.
	Radiation	
Immune-mediated and inflammatory damage	Related to infection	Bacteria, spirochaetes, fungi, protozoa, parasites (Chagas disease), rickettsiae, viruses (HIV/AIDS).
	Not related to infection	Lymphocytic/giant cell myocarditis, autoimmune diseases (e.g. Graves' disease, rheumatoid arthritis, connective tissue disorders, mainly systemic lupus erythematosus), hypersensitivity and eosinophilic myocarditis (Churg–Strauss).
Infiltration	Related to malignancy	Direct infiltrations and metastases.
	Not related to malignancy	Amyloidosis, sarcoidosis, haemochromatosis (iron), glycogen storage diseases (e.g. Pompe disease), lysosomal storage diseases (e.g. Fabry disease).
Metabolic derangements	Hormonal	Thyroid diseases, parathyroid diseases, acromegaly, GH deficiency, hypercortisolaemia, Conn's disease, Addison disease, diabetes, metabolic syndrome, phaeochromocytoma, pathologies related to pregnancy and peripartum.
	Nutritional	Deficiencies in thiamine, L-carnitine, selenium, iron, phosphates, calcium, complex malnutrition (e.g. malignancy, AIDS, anorexia nervosa), obesity.
Genetic abnormalities	Diverse forms	HCM, DCM, LV non-compaction, ARVC, restrictive cardiomyopathy (for details see respective expert documents), muscular dystrophies and laminopathies.

TL: Ponikowski P. 2016 ESC Guideline for the diagnosis and treatment of acute and chronic heart failure. Eur. H. J, May 20, 2016

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Nguyên nhân suy tim (2)

ABNORMAL LOADING CONDITIONS		
Hypertension		
Valve and myocardium structural defects	Acquired	Mitral, aortic, tricuspid and pulmonary valve diseases.
	Congenital	Atrial and ventricular septum defects and others (for details see a respective expert document).
Pericardial and endomyocardial pathologies	Pericardial	Constrictive pericarditis Pericardial effusion
	Endomyocardial	HES, EMF, endocardial fibroelastosis.
High output states		Severe anaemia, sepsis, thyrotoxicosis, Paget's disease, arteriovenous fistula, pregnancy.
Volume overload		Renal failure, iatrogenic fluid overload.
ARRHYTHMIAS		
Tachyarrhythmias		Atrial, ventricular arrhythmias.
Bradyarrhythmias		Sinus node dysfunctions, conduction disorders.

ARVC = arrhythmogenic right ventricular cardiomyopathy; DCM = dilated cardiomyopathy; EMF = endomyocardial fibrosis; GH = growth hormone; HCM = hypertrophic cardiomyopathy; HES = hypereosinophilic syndrome; HIV/AIDS = human immunodeficiency virus/acquired immune deficiency syndrome; LV = left ventricular.

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Nguyên nhân suy tim tâm trương

- Bệnh động mạch vành
- Tăng huyết áp
- Hẹp van động mạch chủ
- Bệnh cơ tim phì đại
- Bệnh cơ tim hạn chế

Triệu chứng cơ năng và thực thể của suy tim (1)

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse

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Triệu chứng cơ năng và thực thể của suy tim (2)

Less typical	Less specific
Nocturnal cough	Weight gain (>2 kg/week)
Wheezing	Weight loss (in advanced HF)
Bloated feeling	Tissue wasting (cachexia)
Loss of appetite	Cardiac murmur
Confusion (especially in the elderly)	Peripheral oedema (ankle, sacral, scrotal)
Depression	Pulmonary crepitations
Palpitations	Reduced air entry and dullness to percussion at lung bases (pleural effusion)
Dizziness	Tachycardia
Syncope	Irregular pulse
Bendopnea[53]	Tachypnoea
	Cheyne Stokes respiration
	Hepatomegaly
	Ascites
	Cold extremities
	Oliguria
	Narrow pulse pressure

Bendopnea: khó thở khi gặp người tới trước

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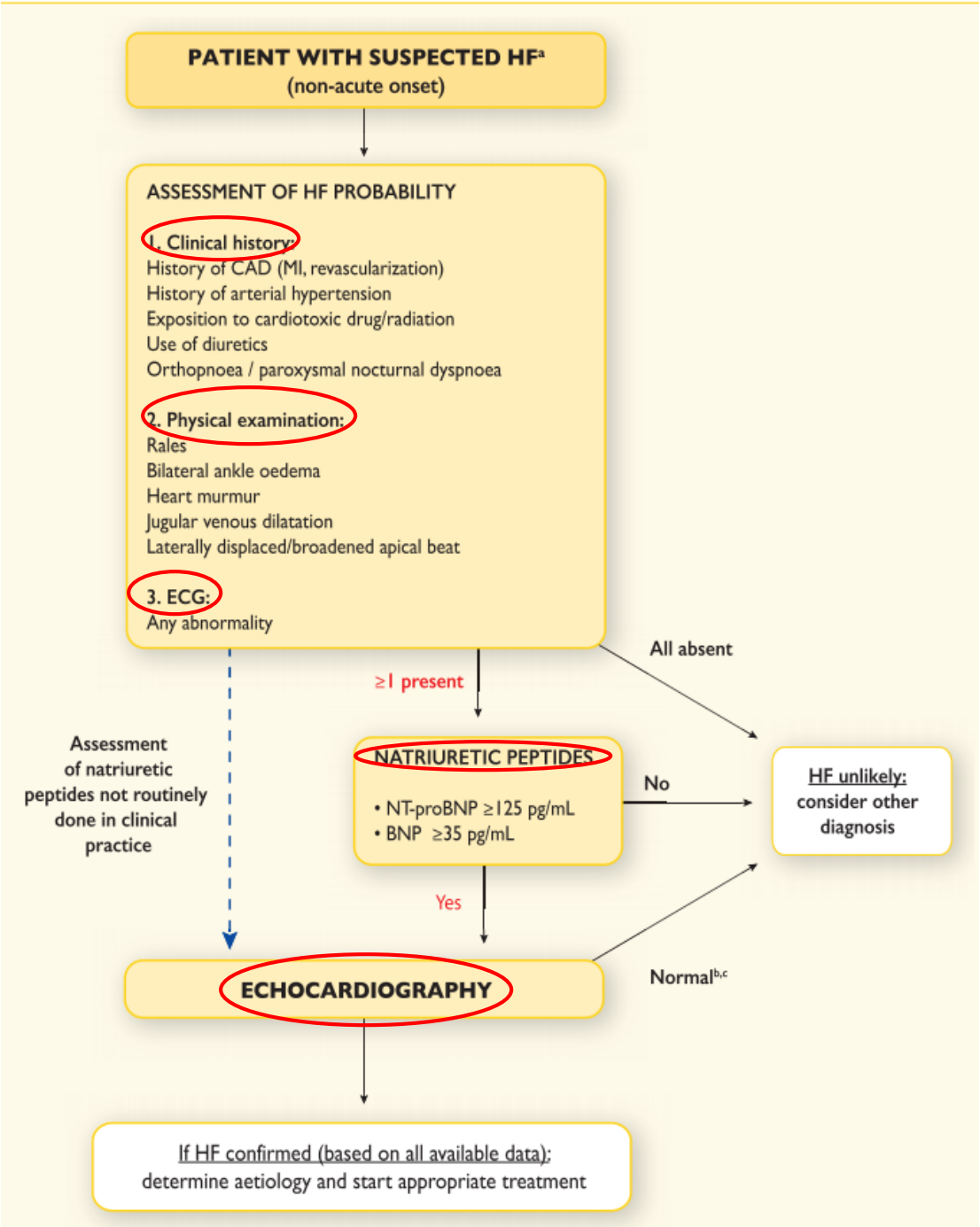
Quy trình chẩn đoán suy tim



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Tiêu chuẩn chẩn đoán suy tim PXTM bảo tồn

1. Có triệu chứng cơ năng và/hoặc thực thể của suy tim
2. PXTM bảo tồn (LVEF ≥ 50%)
3. Tăng Natriuretic Peptide (BNP > 35 pg/ml và/hoặc NT-ProBNP > 125 pg/ml)
4. Chứng cứ biến đổi cấu trúc và chức năng của tim

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Mechanism and factors contributing to pathophysiology of HFpEF (1)

Cardiovascular
Left Ventricular Structure
Concentric remodeling Left ventricular hypertrophy
Left Ventricular Function
Diastolic dysfunction: abnormal relaxation, decreased recoil, abnormal filling, decreased distensibility, increased diastolic pressure Systolic dysfunction: abnormal midwall and long-axis shortening, decreased twist Hemodynamic load Increased afterload and filling load Heterogeneity Dyssynergy, dyssynchrony

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TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Mechanism and factors contributing to pathophysiology of HFpEF (2)

Left atrial structure and function

Increased LA volume and stiffness, decreased LA reservoir function, passive conduit function, and active booster pump function

Ischemia

Subendocardial and microvascular disease, impaired coronary, pulmonary, and peripheral flow reserve

Rate and rhythm abnormalities

Chronotropic incompetence, atrial fibrillation, supraventricular tachycardia

Vascular dysfunction

Arterial stiffening, endothelial dysfunction

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Mechanism and factors contributing to pathophysiology of HFpEF (3)

Cardiomyocyte

Abnormal calcium homeostasis (↑ diastolic calcium or ↓ rate of calcium reuptake → incomplete or impaired relaxation)

- Sarcolemmal calcium channels (Na^+/Ca^{2+} exchanger and calcium pump)
- Sarcoendoplasmic reticulum Ca^{2+}-ATPase (SERCA) abundance and function
- Proteins modifying SERCA activity: phospholamban, calmodulin, calsequestrin abundance, and phosphorylation state
- Sarcoplasmic reticulum calcium release channels

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Mechanism and factors contributing to pathophysiology of HFpEF (4)

Energetics (↓ ATP or ↑ ADP slows actin-myosin cross-bridge release)

ADP/ATP ratio, ADP and P_i concentration, phosphocreatine shuttle function

Proteins regulating cross-bridge formation and calcium sensitivity

Troponin C: calcium binding

Troponin I: phosphorylation state

Cytoskeletal proteins

Microtubules (increased density) → ↑ diastolic stiffness

Titin isoforms (↑ noncompliant isoform and phosphorylation state) → ↑ diastolic stiffness

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Mechanism and factors contributing to pathophysiology of HFpEF(5)

Extracellular Matrix
Collagen structure, geometry, content, collagen I/III ratio
Collagen homeostasis, synthesis, postsynthetic processing, post-translational cross-linking, degradation
Basement membrane proteins
Bioactive proteins and peptides: MMP/TIMP, SPARC, TGF-β
Fibroblast structure, function, phenotype
Myofibroblast transdifferentiation

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Mechanism and factors contributing to pathophysiology of HFpEF(6)

Extracardiac
Extrinsic forces (RV-LV interaction and pericardial constraint)
Peripheral muscle and ergoreflex dysfunction
Pulmonary hypertension (secondary to chronic pulmonary venous hypertension)
Neurohormonal activation
Comorbid conditions (renal dysfunction, anemia, chronic lung disease)

ADP, Adenosine diphosphate; *ATP*, adenosine triphosphate; *MMP*, matrix metalloproteinase; *RV-LV*, right ventricle–left ventricle; *SPARC*, secreted protein, acidic and rich in cysteine [osteonectin]; *TGF*, transforming growth factor; *TIMP*, tissue inhibitor of metalloproteinase.

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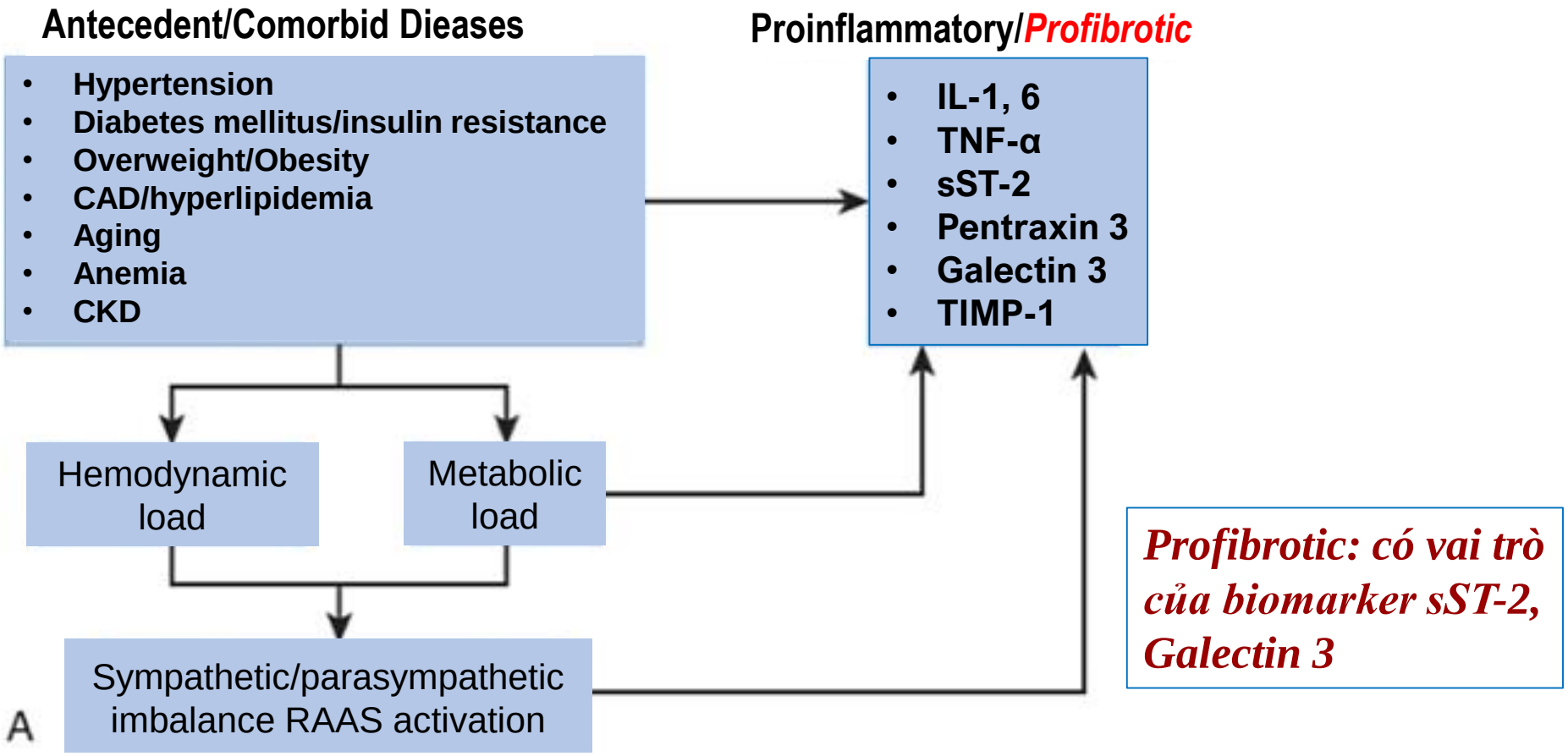
TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Pathophysiologic mechanisms underlying the development of HFpEF(1)



Profibrotic: có vai trò của biomarker sST-2, Galectin 3

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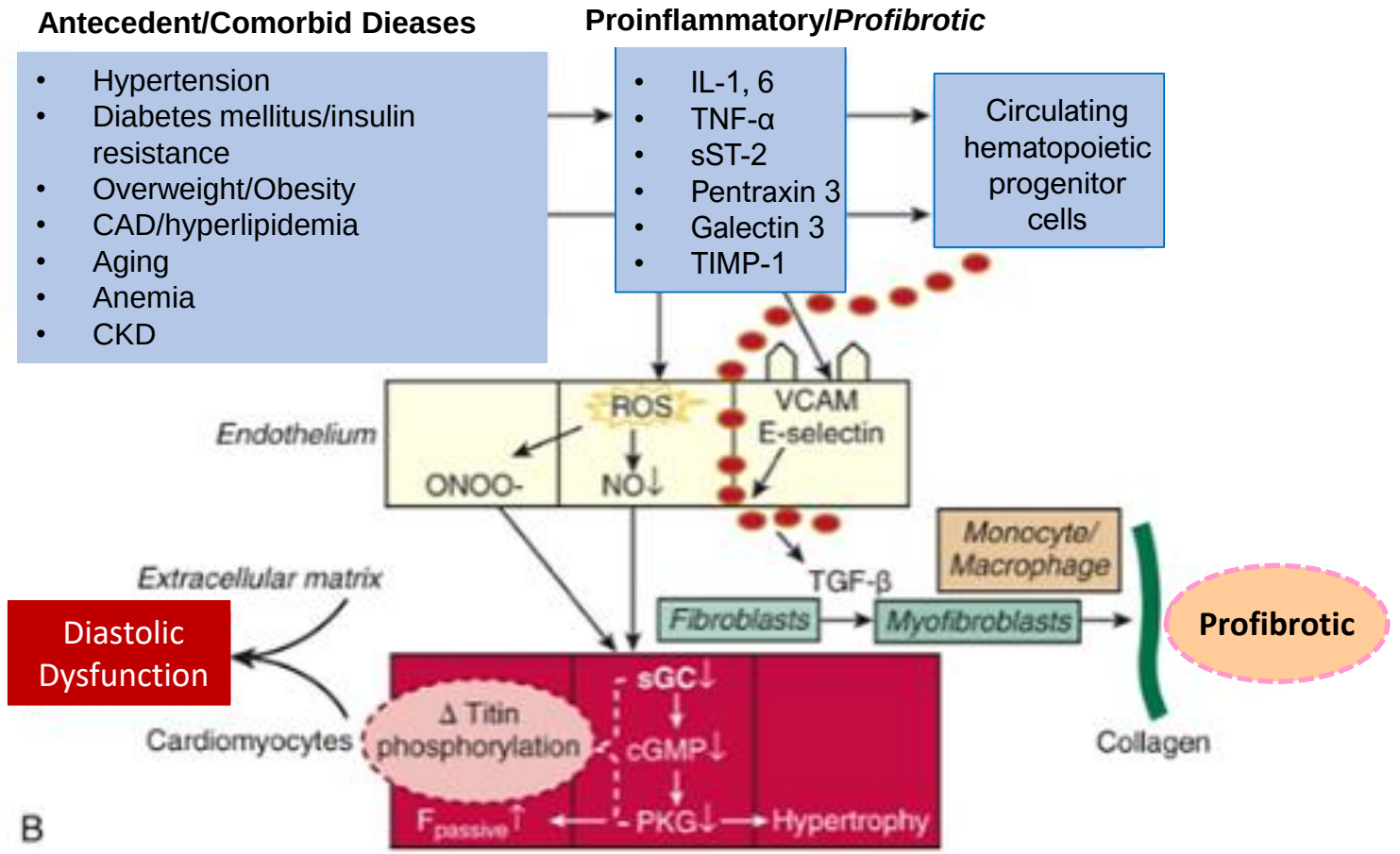
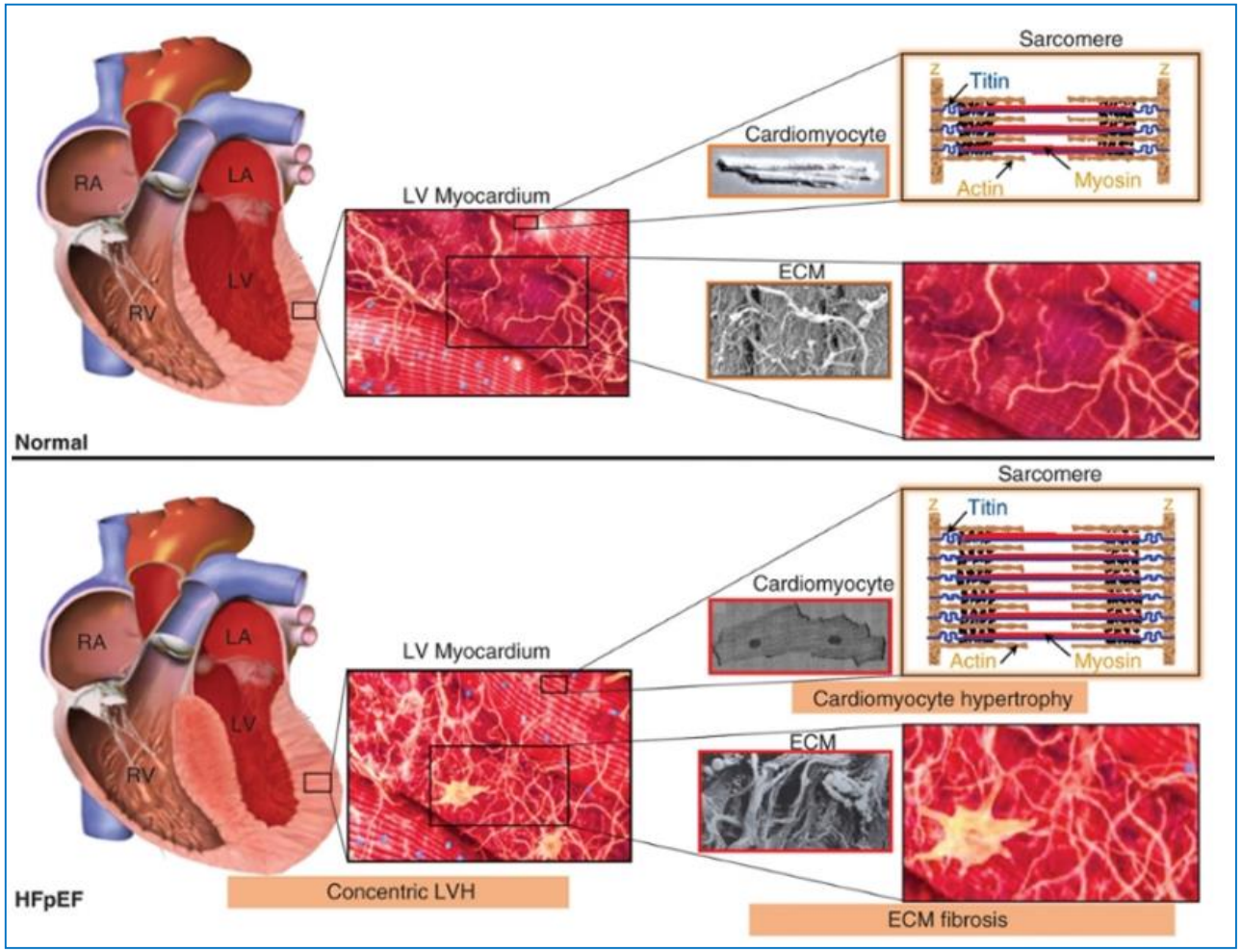
Pathophysiologic mechanisms underlying the development of HFpEF(2)



TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Ventricular, cellular, extracellular matrix and molecular structural changes in patients with HFpEF



- ECM: extracellular matrix
- Interstitial Fibrosis/HFpEF

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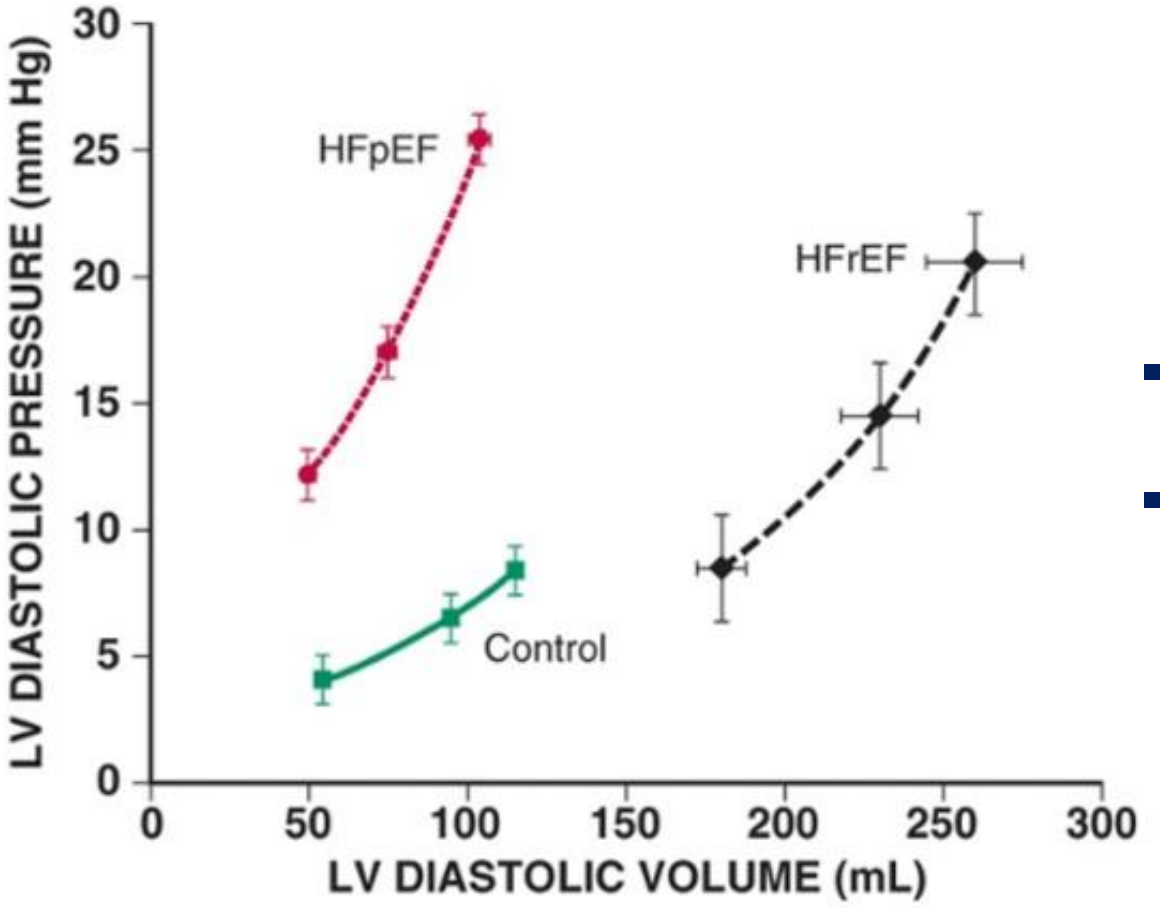
TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Difference in diastolic chamber distensibility in patients with HFrEF vs HFpEF



- Increased stiffness in HFpEF
- Increased distensibility in HFrEF

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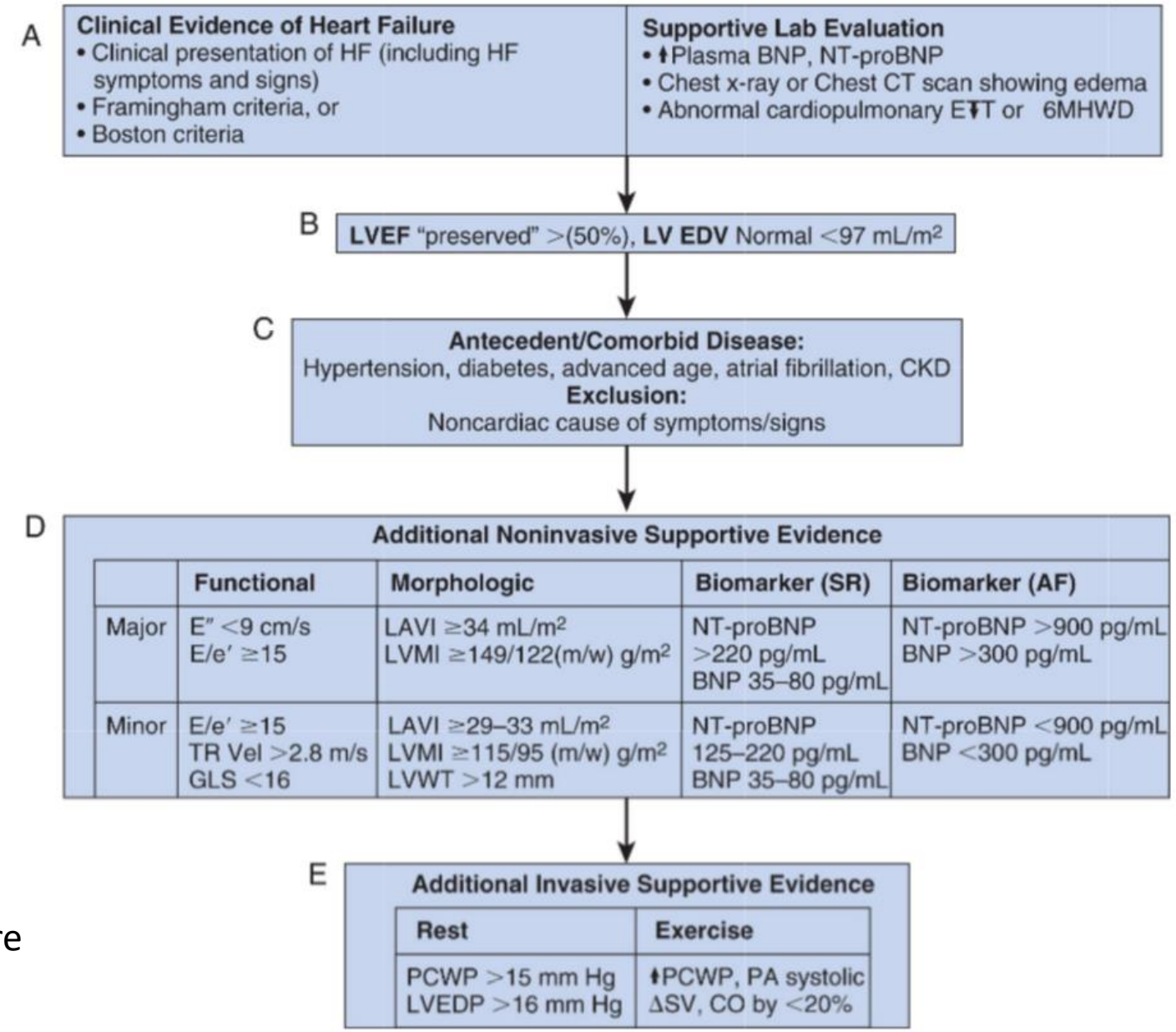
Diagnostic criteria for HFpEF



6 MHW: 6 minutes hall walk
LAVI: left atrial volume index
LVMI: left ventricular mass index
PCWP: pulmonary capillary wedge pressure

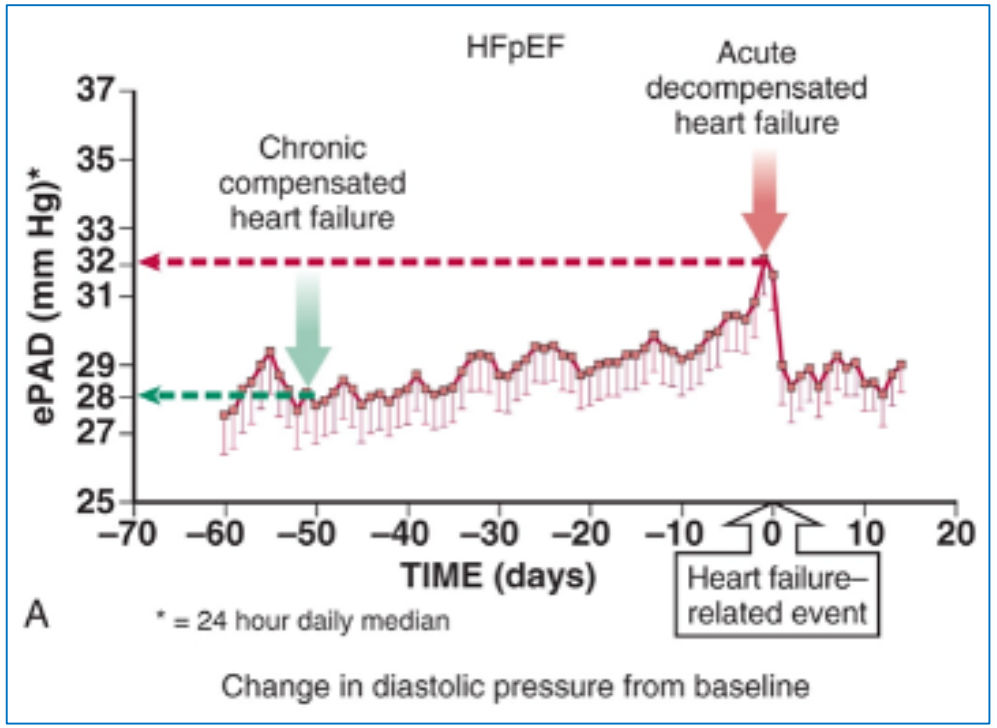
Pham Nguyen Vinh

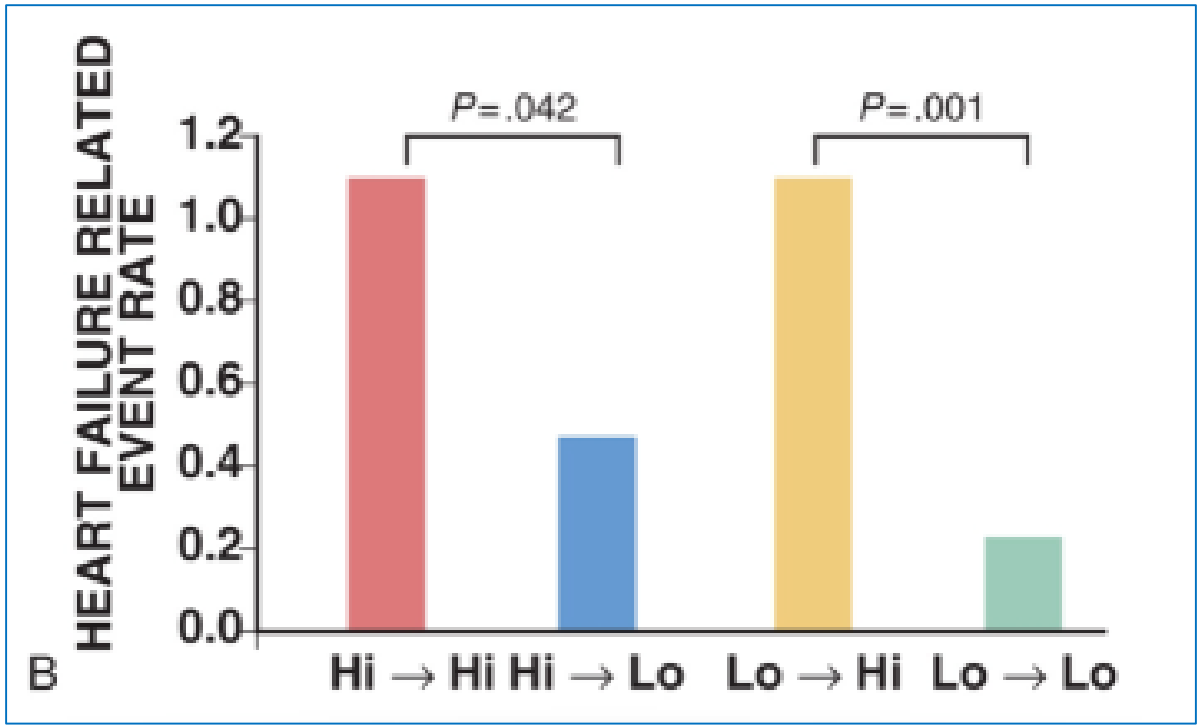
TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Các nguyên nhân ít gặp của Suy tim PXTM bảo tồn

- Bệnh cơ tim phì đại
- Bệnh cơ tim thâm nhiễm (TD: Amyloidosis)
- Bệnh van tim
- Viêm màng ngoài tim co thắt

LV diastolic pressure in HFpEF patients predict mortal and morbid events





- ePAD: increased LV diastolic pressure
- ↑ePAD ➡ ↑ acute decompensated heart failure

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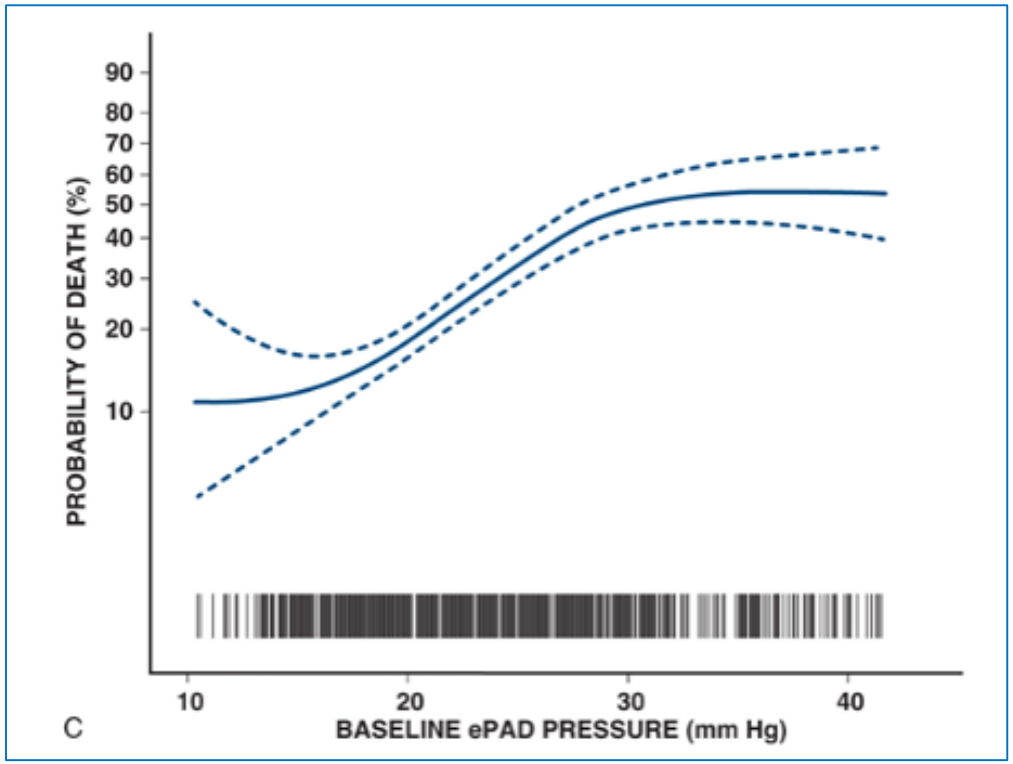
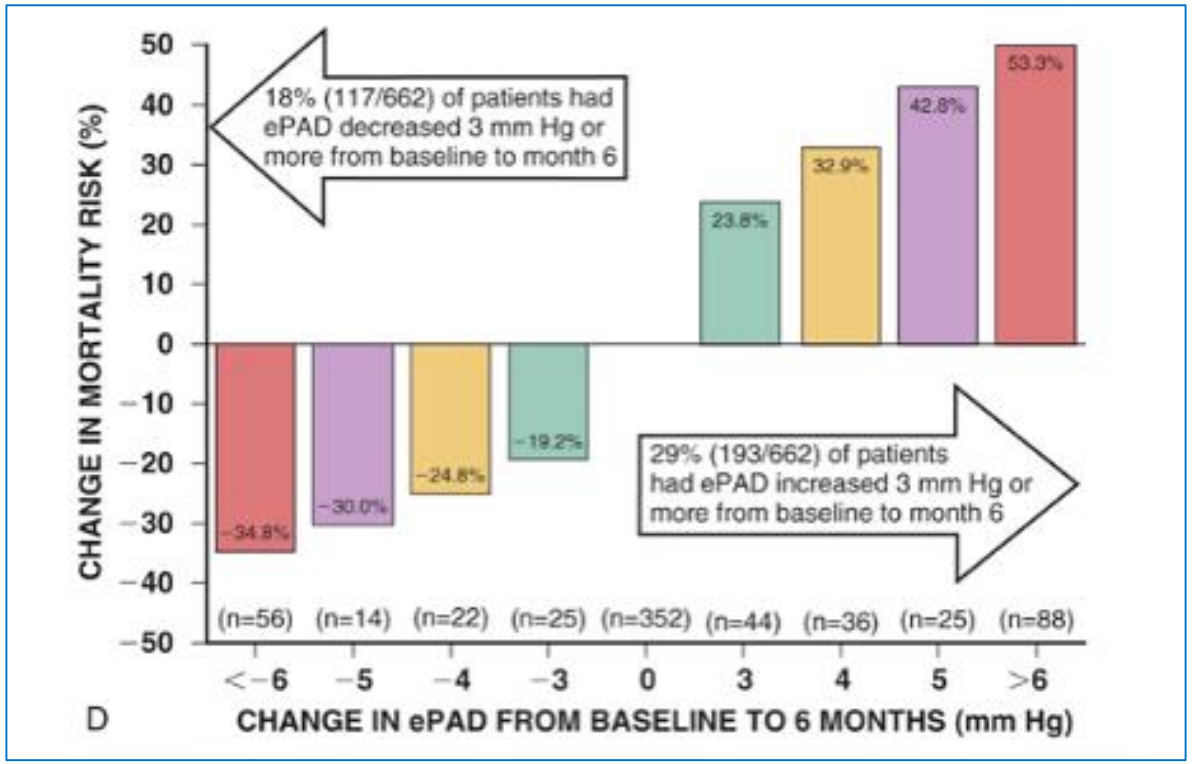
LV diastolic pressure in HFpEF patients predict mortal and morbid events





* Baseline LV diastolic filling pressure and changes: predictors of all cause mortality

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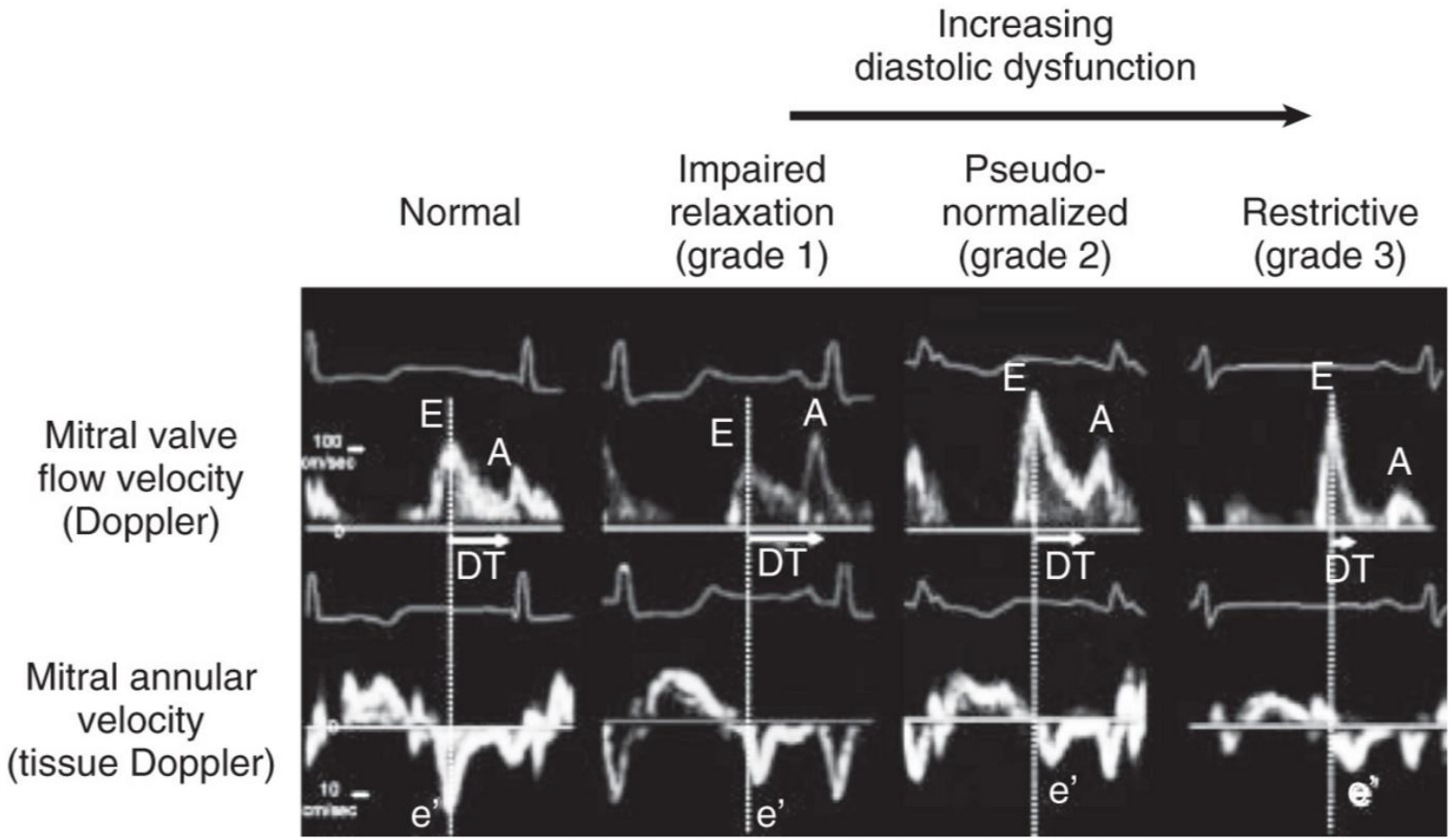
Evaluation of diastolic function based on LV filling dynamics by Echo



Pham Nguyen Vinh

TL: Little WC, Oh JK. Circulation 2009, 120:802

Khảo sát lâm sàng cấu trúc và chức năng tim mạch

- **Cấu trúc thất trái:**
  - Thể tích thất trái
    - LV vol < 75 mL/m^2: tiêu chuẩn chẩn đoán ST/PXTM bảo tồn
  - Khối lượng thất trái
  - Hình thể thất trái (LV geometry)
    - Tái cấu trúc đồng tâm
- **Chức năng thất trái:**
  - Chức năng tâm trương

Điều trị suy tim PXTM bảo tồn (HFpEF)

- Không biện pháp điều trị giúp giảm tử vong HFpEF
- Điều trị chính: nguyên nhân HFpEF
- Điều trị các bệnh kèm theo
- Điều trị T/C cơ năng, thực thể

Management Success (RCTs) in Heart Failure

TREATMENT	HFrEF	HFpEF	HFpEF STUDY
Beta blockers	Yes	No	SENIORS
ACEIs/ARBs	Yes	No	CHARM, I-Preserve PEP-CHF
Digitalis	Yes	No	DIG-PEF
PDE5-I	ND	No	RELAX
Aldo Antag (MRA)	Yes	"Yes"	TOPCAT
Hydralazine/N_2	Yes	No	NEAT-HFpEF
Endothelin Antag	No	Yes p II	Sitaxsentan
Sacubitril/valsartan	Yes	Yes p II	PARAMOUNT; PARAGON
CRT/ICD	Yes	ND	
Vagal/spinal cord stimulators	No	ND	
Baroreceptors	Yes p II	ND	HOPE4HF; BEAT-HF
Exercise	Yes	"Yes"	Meta-analysis
IHM	Yes	Yes	CHAMPION

CRT: chronic resynchronization therapy; ICD: implantable cardioverter-defibrillator; IHM: implantable hemodynamic monitor; MRA: mineralocorticoid receptor antagonist; PDE5: phosphodiesterase-5; RCTs: randomized controlled trials.

TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Khuyến cáo ĐT suy tim PXTM bảo tồn (HFpEF) và suy tim PXTM trung gian (HFmrEF)

Recommendations	Class [a]	Level [b]	Ref [c]
it is recommended to screen patients with HFpEF or HFmrEF for both cardiovascular and non-cardiovascular comorbidities, which, if present, should be treated provided safe and effective interventions exist to improve symptoms, well-being and/or prognosis.	I	C	
Diuretics are recommended in congested patients with HFpEF or HFmrEF in order to alleviate symptoms and signs.	I	B	178, 179

HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

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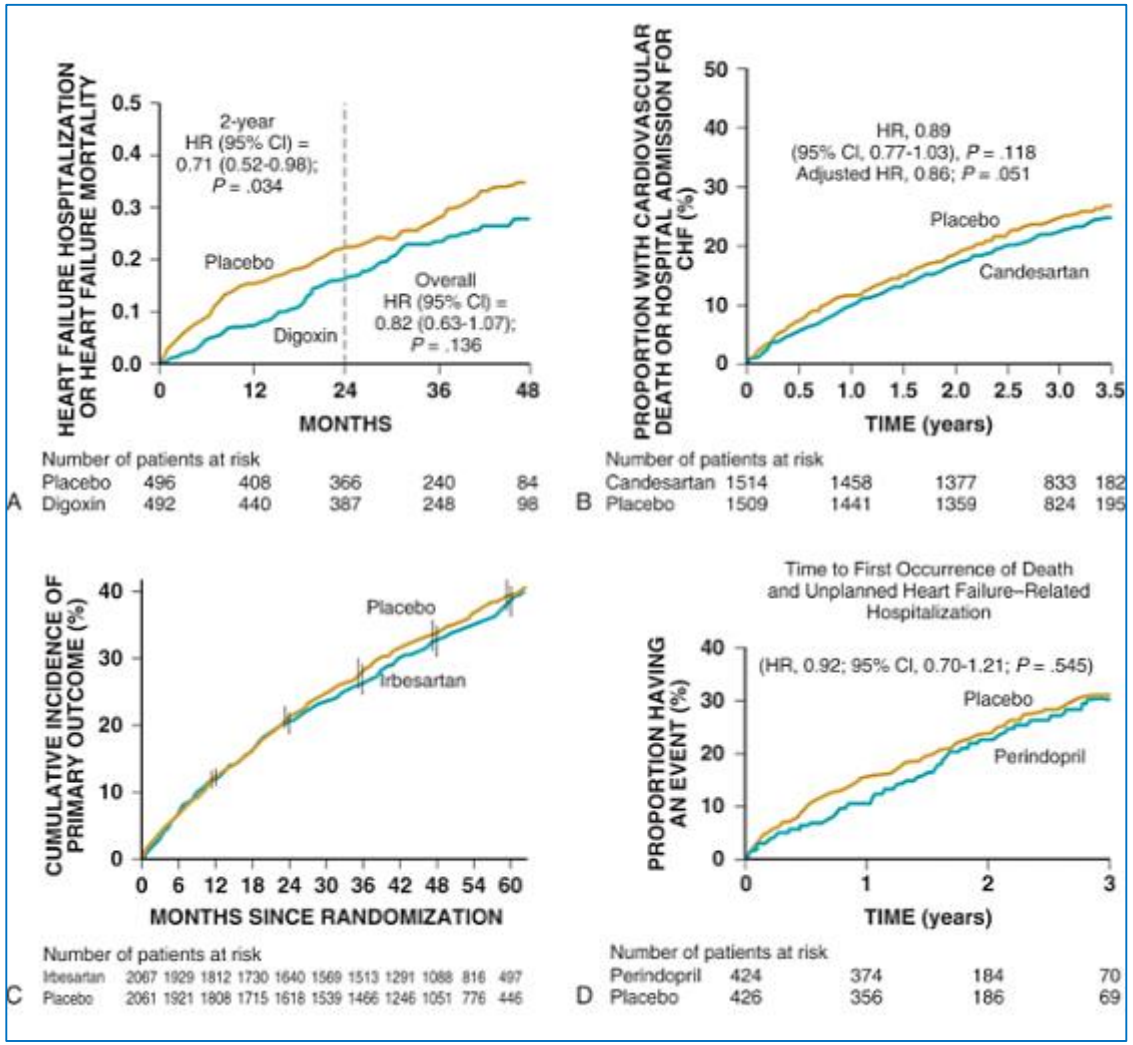
Hiệu quả trên tử vong của điều trị suy tim PXTM bảo tồn

- UCMC, chẹn thụ thể AG II, chẹn beta, đối kháng aldosterone: không nghiên cứu chứng minh giảm tử vong
- Người cao tuổi: Nebivolol giảm tử vong và nhập viện HFrEF, HFpEF hoặc HFmrEF*

TL: * Van Veldhuisen DJ et al. J Am Coll Cardiol 2009, 53: 2150-2158
* Flather MD et al. Eur Heart J 2005: 26: 215-225

Kaplan-Meier survival curves/RCTs of HFpEF (1)



A: DIG trial
B: CHARM-Preserved trial
C: I-Preserve trial
D: PEP-CHF trial

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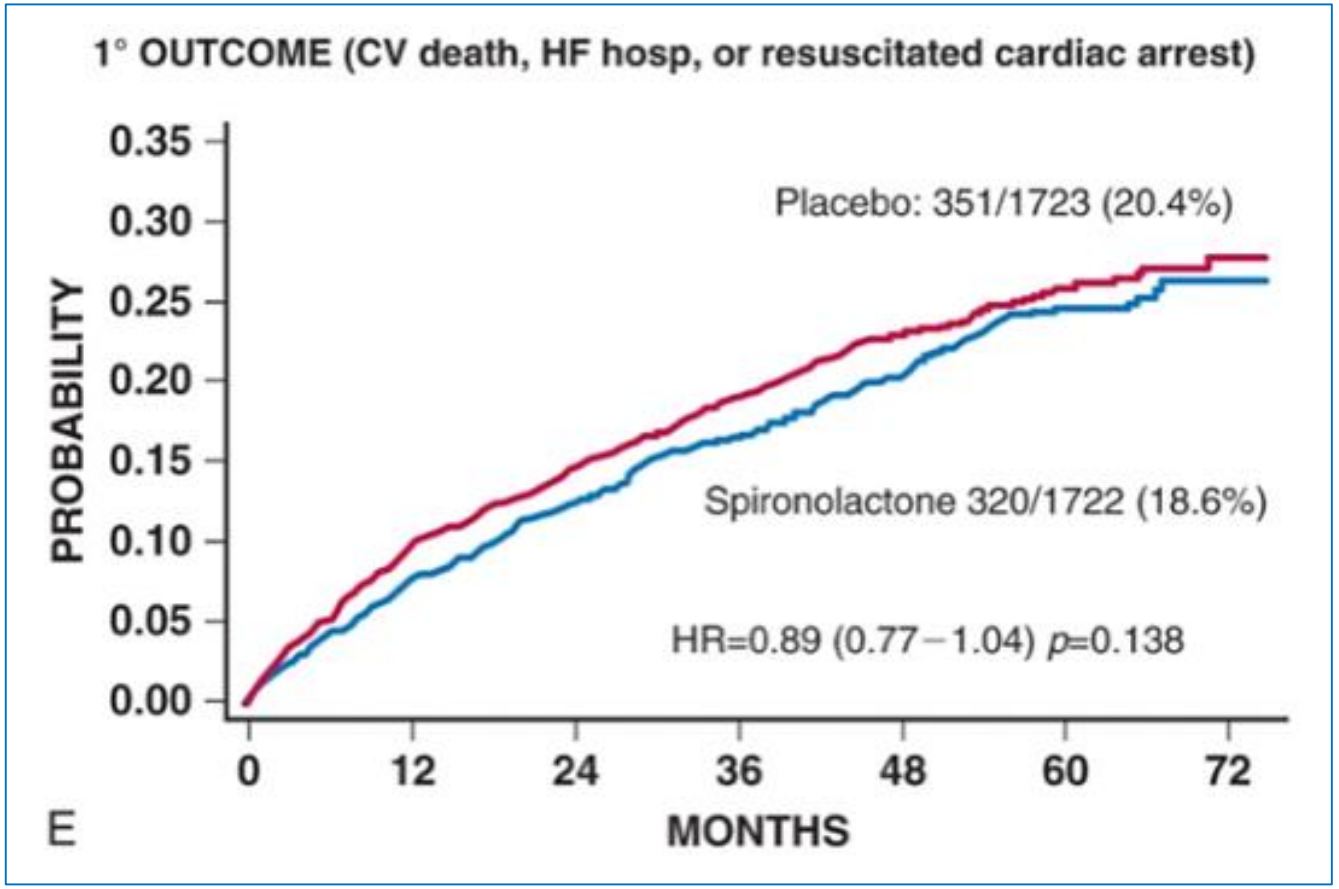
TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

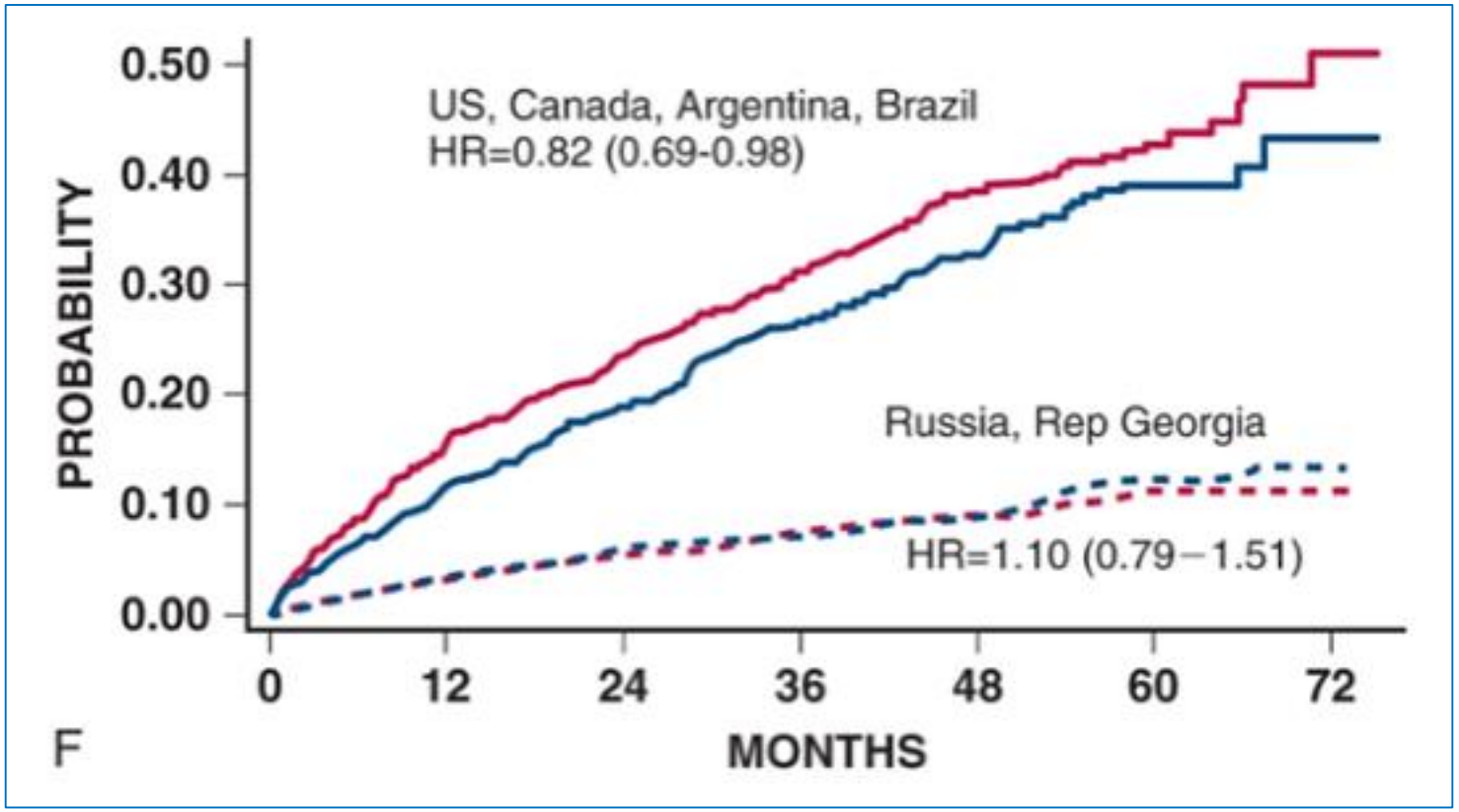
Kaplan-Meier survival curves/ RCTs of HFpEF (2)



E: TOPCAT trial

TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Kaplan-Meier survival curves/ RCTs of HFpEF (3)

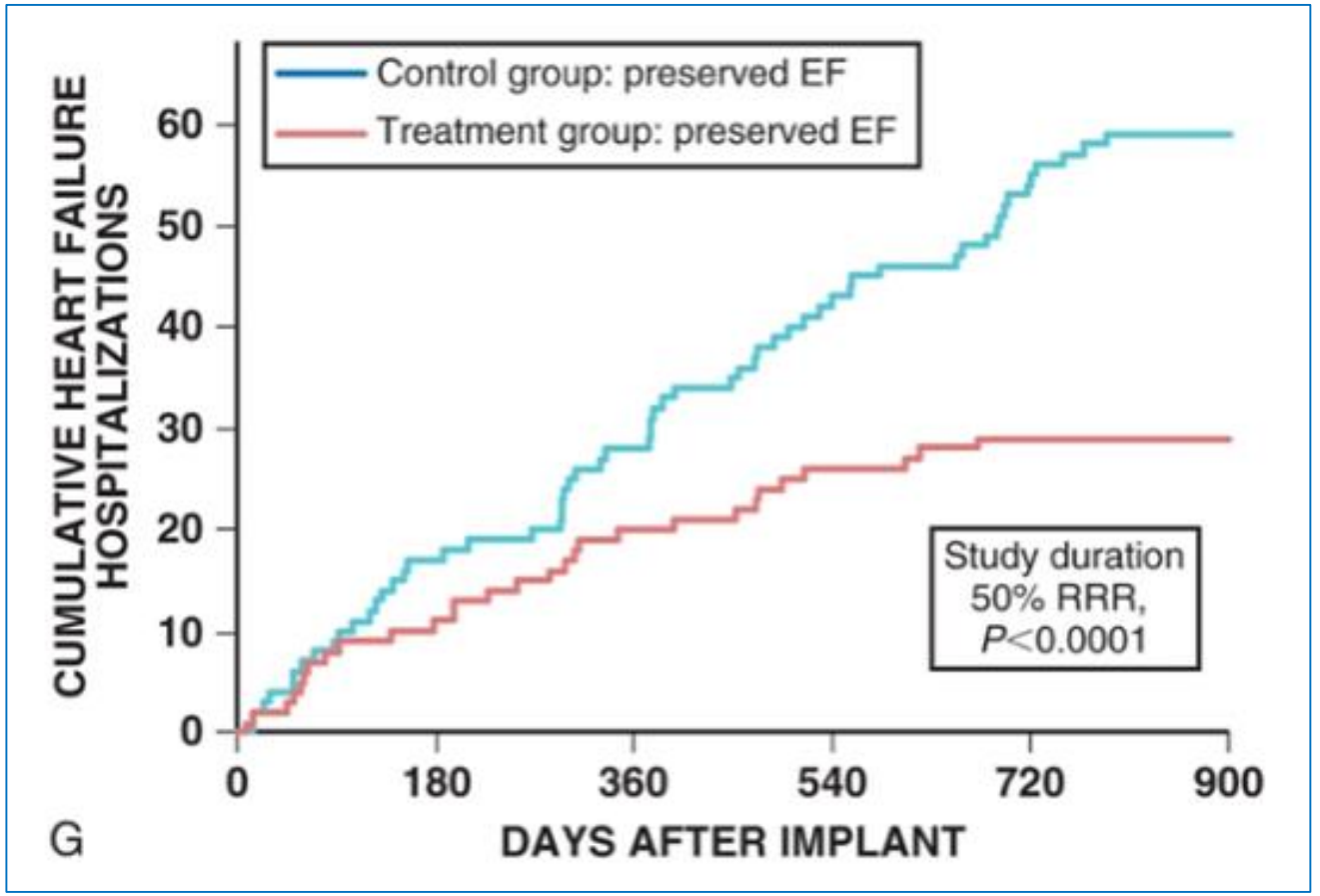


F: TOPCAT trial

Pham Nguyen Vinh

TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Kaplan-Meier survival curves/ RCTs of HFpEF (4)



G: CHAMPION trial

CHAMPION: using CardioMEMS Heart Sensor → PA diastolic pressure

TL: Zile MR, Litwin SE. In Braunwald's Heart Disease, 2018, 11th ed. Elsevier, p.523-542.

Các biện pháp xử trí suy tim PXTM bảo tồn

- Non pharmacologic therapy
- Treatment of comorbid conditions
- Sensor-Based strategies:
  - N/c COMPASS-HF: using IHMs (implantable hemodynamic monitors)
  - N/c CHAMPION
  - N/c REDUCE LAP-HF I

* IASD: Intraatrial Shunt Device to reduce LA pressure

Pham Nguyen Vinh

Điều trị nguyên nhân suy tim PXTM bảo tồn:

rất quan trọng: THA, TMCB, van tim,…

Điều trị loạn nhịp và các bệnh kèm theo/ST/PXTM BT

- Chuyển nhịp hoặc hủy ổ loạn nhịp/ Rung nhĩ
- Điều trị THA, ĐTĐ, COPD theo khuyến cáo
- Điều trị thiếu máu

Kết luận

- Cơ chế HFpEF: phức tạp
- Chẩn đoán: LS, ECG, XQ, siêu âm tim, biomarkers
- Điều trị: một thách thức
  - Thuốc: ít hiệu quả
  - Điều trị nguyên nhân; bệnh đi kèm
  - Biện pháp mới: sensor – based strategies, IASD.

Cám ơn Quý đồng nghiệp!