Heart Failure

Federica Moscucci, MD

SAPIENZA
UNIVERSITÀ DI ROMA

Definition

Clinical syndrome caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.

EUROPEAN SOCIETY OF CARDIOLOGY

ESC
European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

ESC GUIDELINES

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

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

With the special contribution of the Heart Failure Association (HFA) of the ESC

Terminology

Table 3 **Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

HF = heart failure; HFmrEF = heart failure with mildly reduced ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LV = left ventricle; LVEF = left ventricular ejection fraction.

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

[b]For the diagnosis of HFmrEF, the presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis more likely.

[c]For the diagnosis of HFpEF, the greater the number of abnormalities present, the higher the likelihood of HFpEF.

(European Heart Journal 2016; 37- ESC GUIDELINES)

Terminology

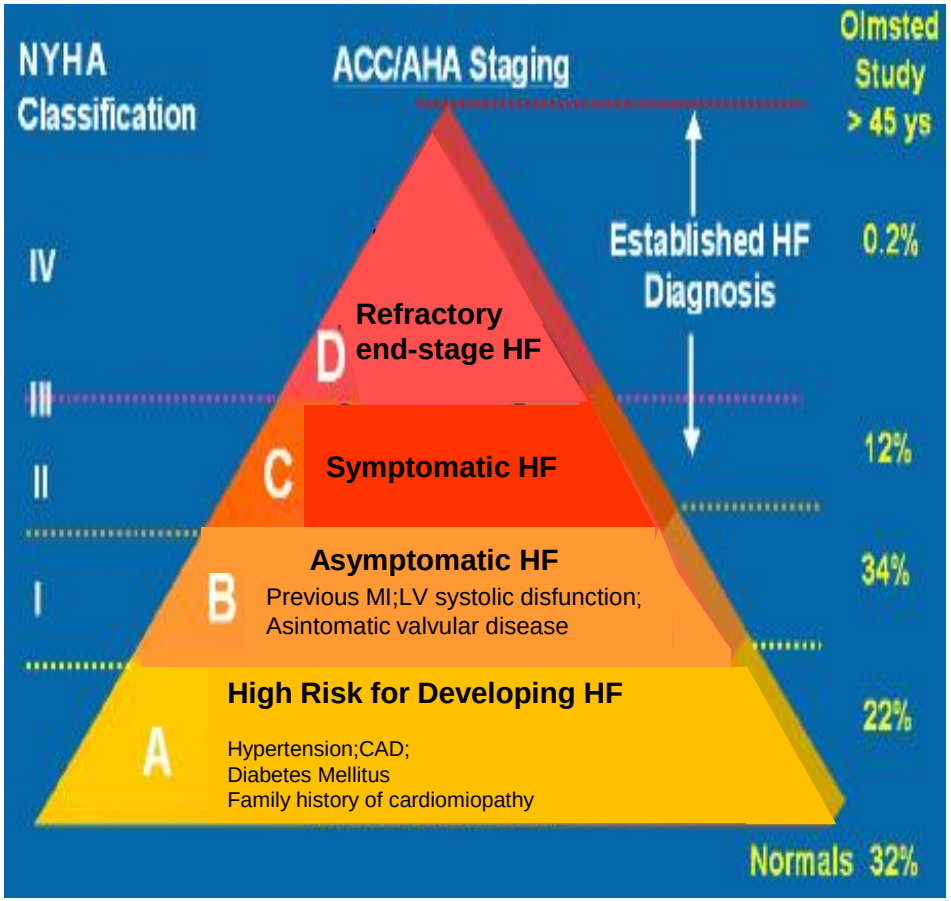
Web Table 3.2 New York Heart Association functional classification based on severity of symptoms and physical activity

Class I	No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue, or palpitations.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue, or palpitations.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased.

Web Table 3.3 ACCF/AHA stages of heart failure

A	At high risk for HF but without structural heart disease or symptoms of HF.
B	Structural heart disease but without signs or symptoms of HF.
C	Structural heart disease with prior or current symptoms of HF.
D	Refractory HF requiring specialized interventions.

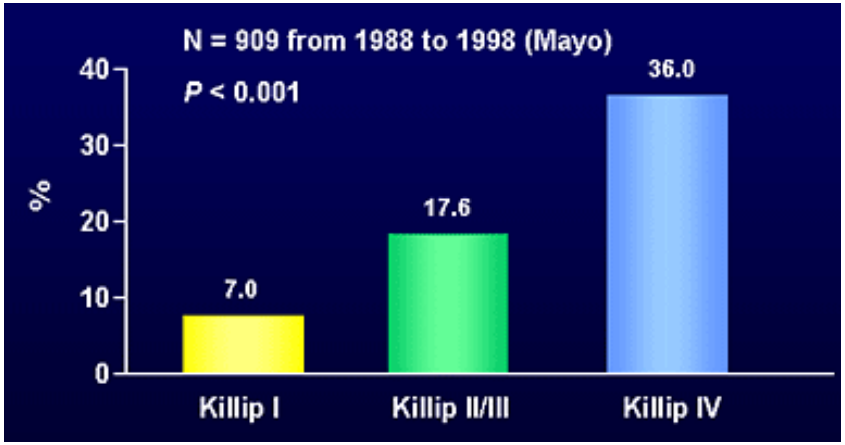
ACCF/AHA = American College of Cardiology Foundation/American Heart Association; HF = heart failure.



Terminology

Killip Classification of CHF

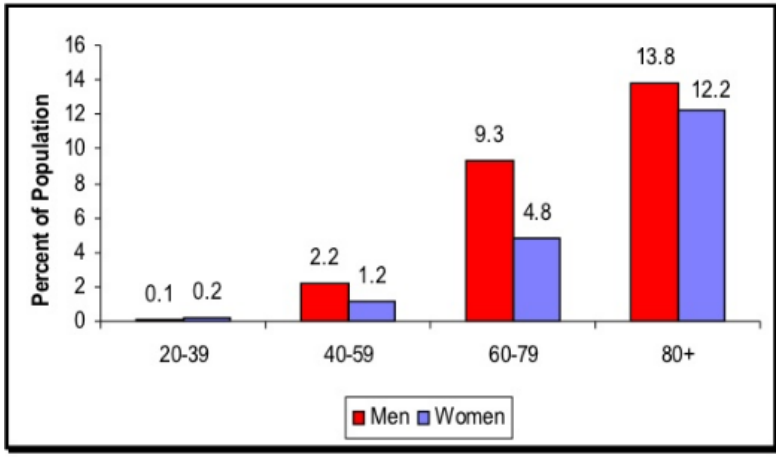
- Class I: no clinical signs of heart failure
- Class II: crackles, s3 gallop and elevated jugular venous pressure
- Class III: frank pulmonary edema
- Class IV: cardiogenic shock



In-Hospital Mortality by Killip Class

International Journal of Clinical Cardiology
ISSN: 2378-2951

Prevalence, Incidence and Mortality rates



6 million people in the US (NHLBI 2009)

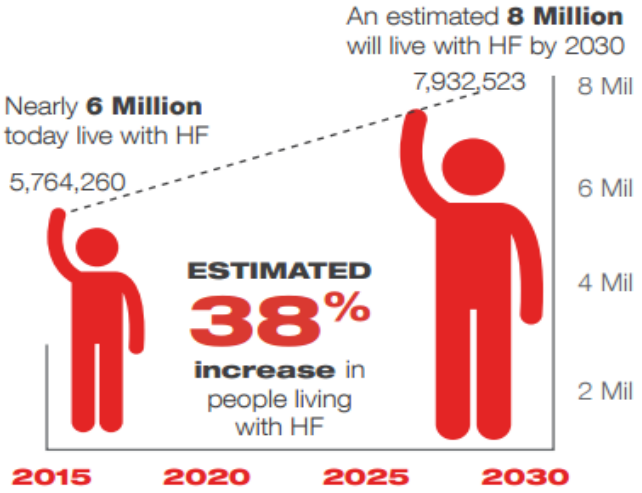
Prevalence
- ✓ Worldwide: 23 million
- ✓ USA: 5.8 million
- ✓ Europe: 15 million

Incidence
- ✓ Worldwide: 2 million new cases/year
- ✓ USA: 550.000 new cases/year

(Circulation Research 2013)

Mortality at 5 years of follow-up:
- ✓24.4% for age 60 year
- ✓ 54.4% for age 80 year

(JAMA Internal Medicine 2015; 175)



American Heart Association.

Etiology

Common causes of chronic heart failure

-Coronary artery disease
-Hypertensive cardiovascular disease
-Diabetes mellitus
-Valvular heart disease
-Dilated cardiomyopathy (20-30% are familial)
-Infiltrative cardiomyopathy
-Hypertrofic cardiomyopathy

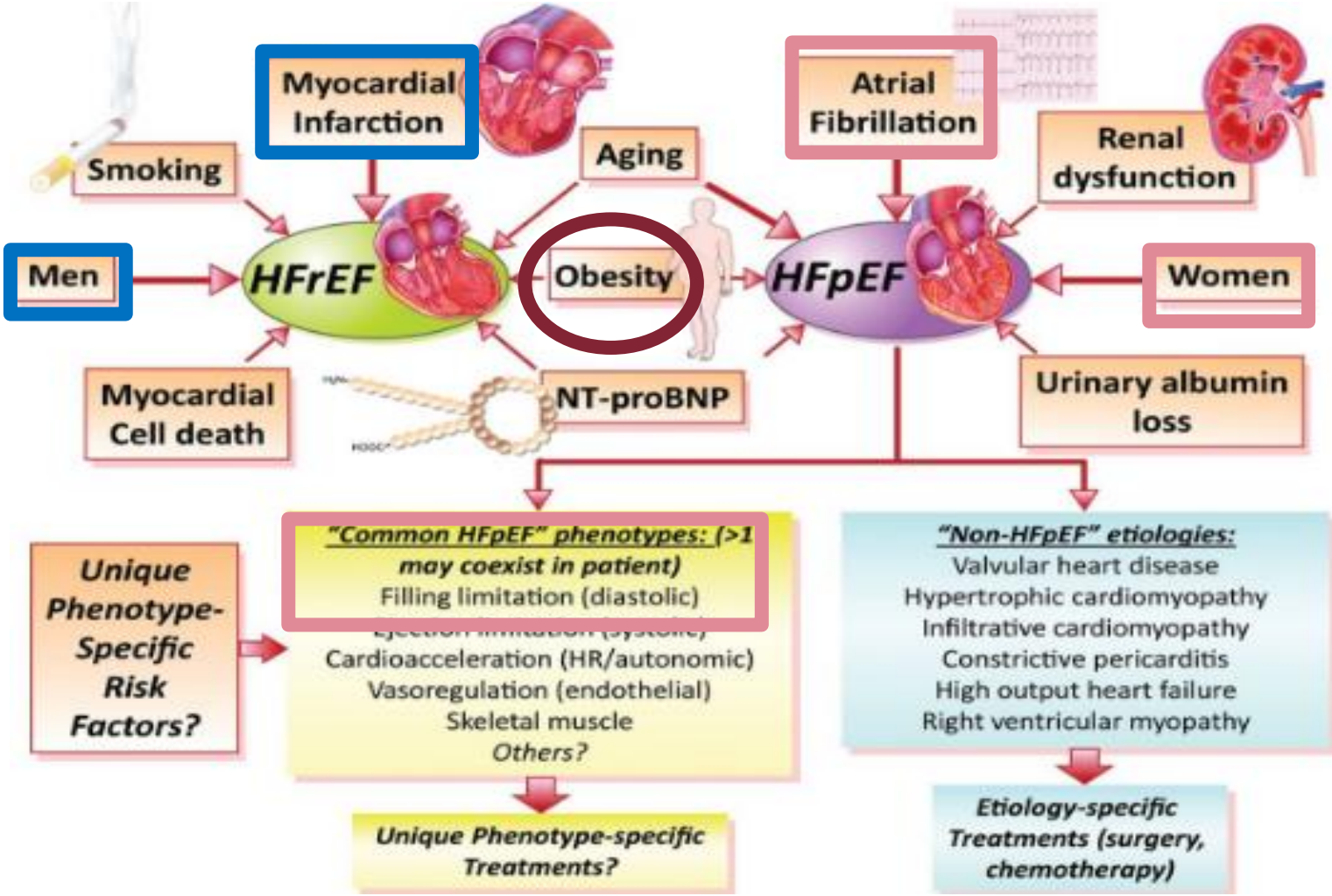
Elderly

Etiology

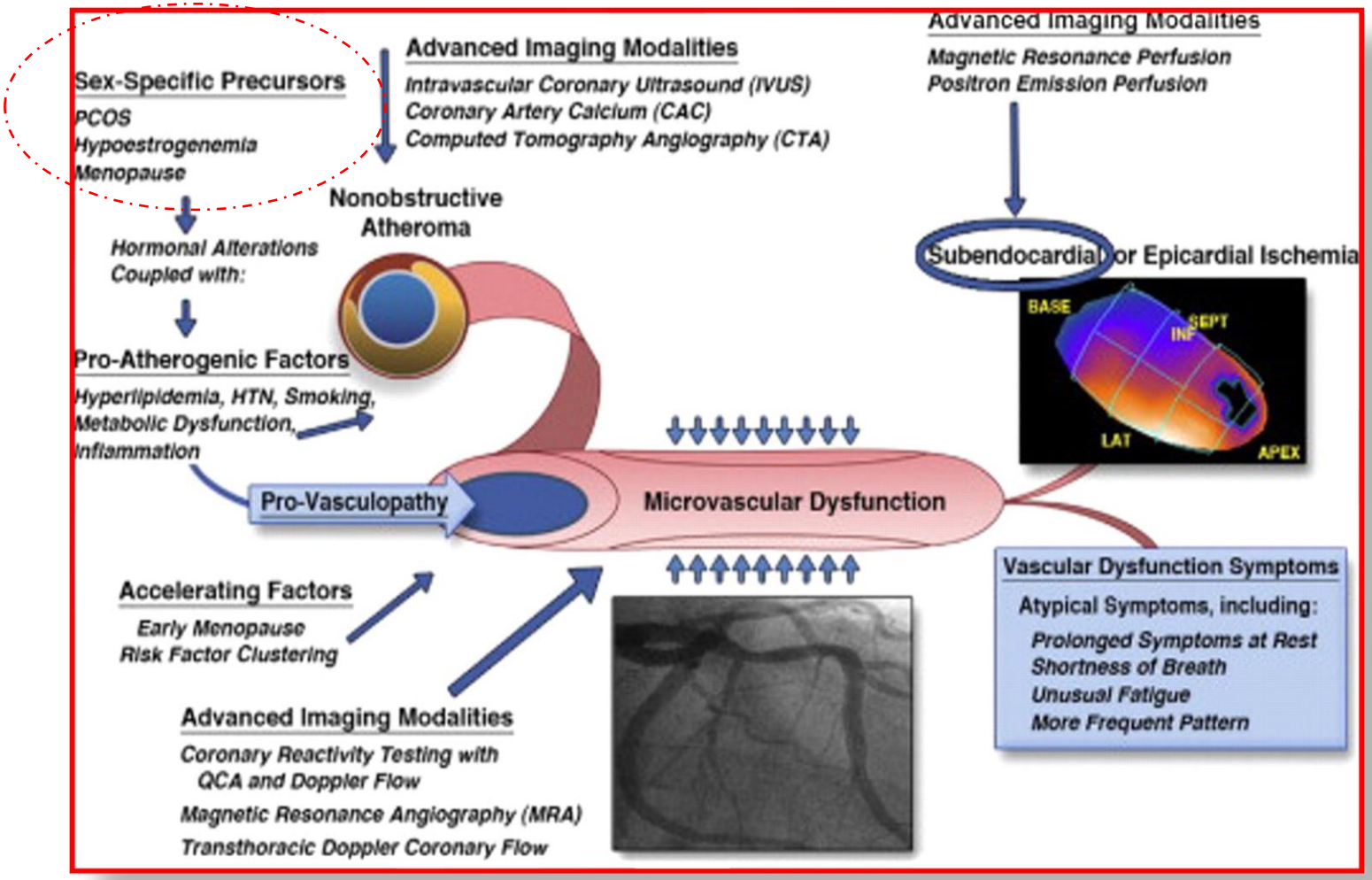
Exacerbating factors for acute heart failure

-Acute myocardial infarction
-Uncorrected high blood pressure
-Atrial fibrillation and other arrhythmias
-Negative inotropic drugs (e.g. verapamil, nifedipine)
-**Other drugs** (e.g. nonsteroidal anti-inflammatory drugs)
-Endocrine abnormalities (e.g. diabetes mellitus)
-**Drug noncompliance**
-**Concurrent infection**

Etiology

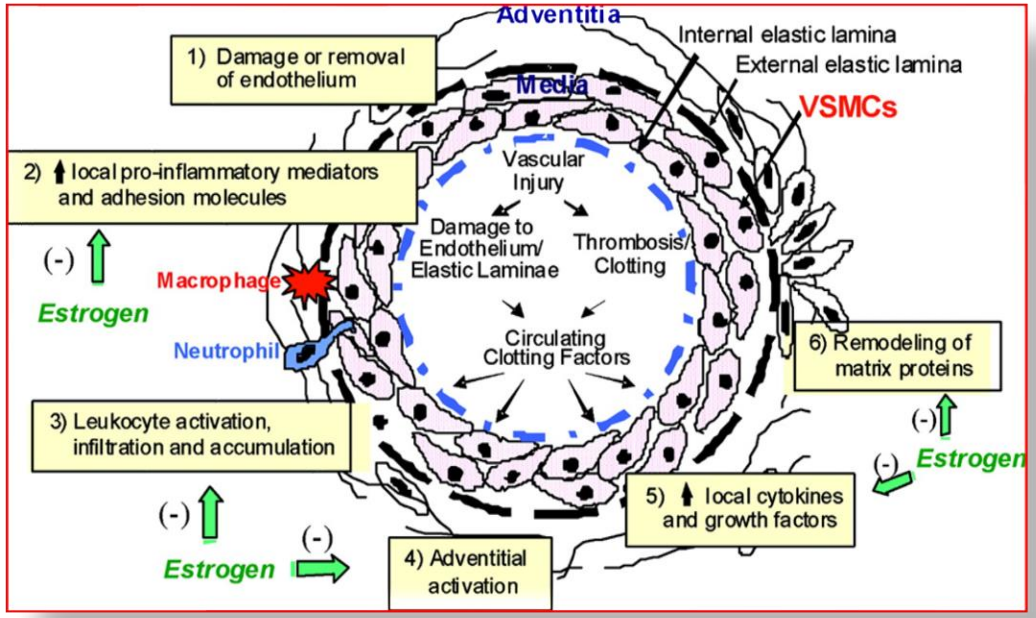

Myocardial Infarction
Smoking
Aging
Atrial Fibrillation
Renal dysfunction
Men
HFrEF
Obesity
HFpEF
Women
Myocardial Cell death
NT-proBNP
Urinary albumin loss
"Common HFpEF" phenotypes: (>1 may coexist in patient)
Filling limitation (diastolic)
Cardioacceleration (HR/autonomic)
Vasoregulation (endothelial)
Skeletal muscle
Others?
"Non-HFpEF" etiologies:
Valvular heart disease
Hypertrophic cardiomyopathy
Infiltrative cardiomyopathy
Constrictive pericarditis
High output heart failure
Right ventricular myopathy
Unique Phenotype-Specific Risk Factors?
Unique Phenotype-specific Treatments?
Etiology-specific Treatments (surgery, chemotherapy)

Microvascular Coronary Disease

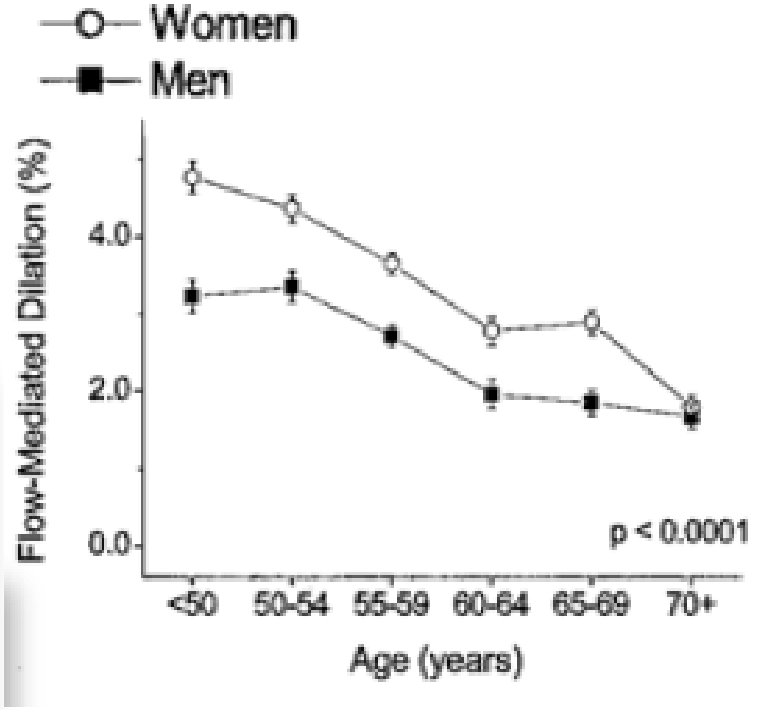


Endothelial Dysfunction

- Women have better endothelial function than men
- Advantage declines with age

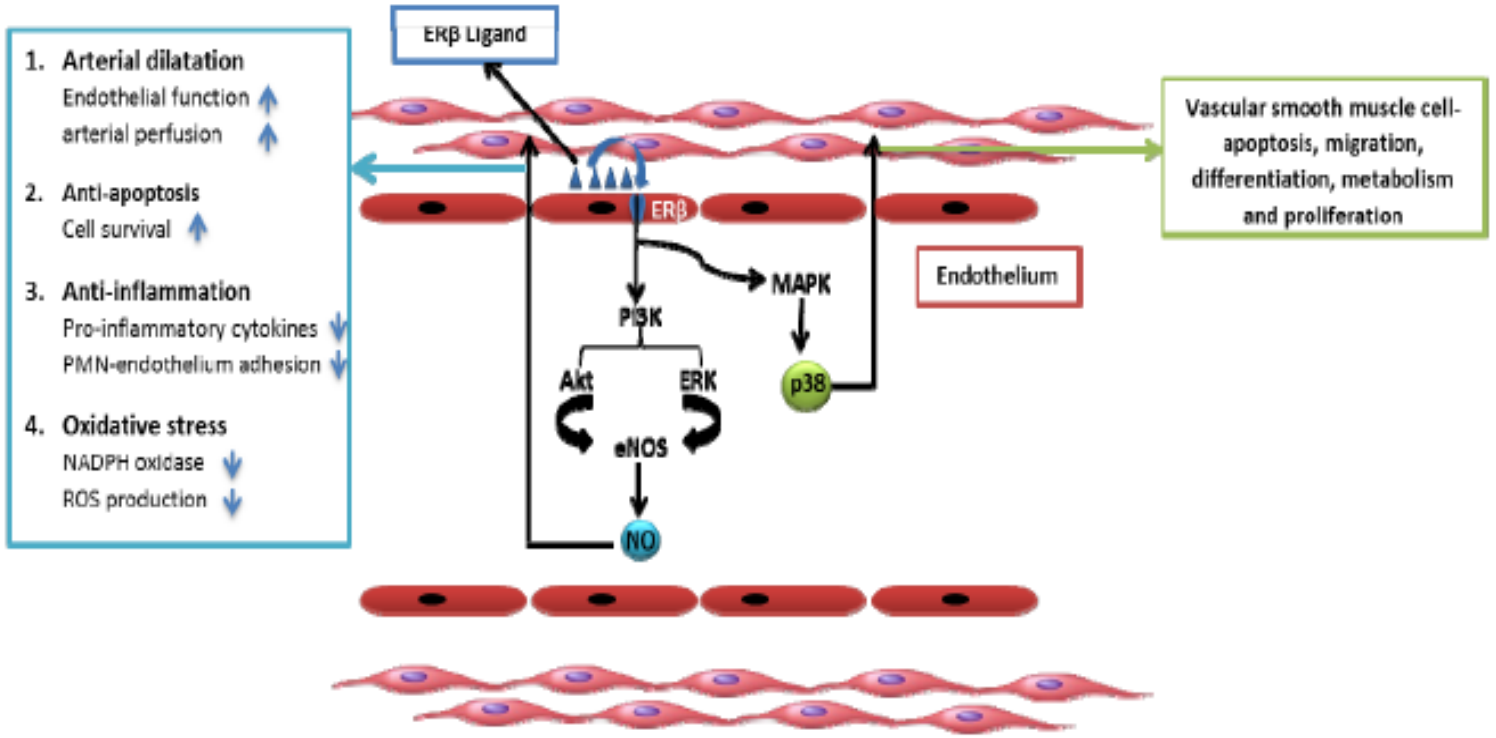


Xing, D. et al. Arterioscler Thromb Vasc Biol 2009;29:289-295



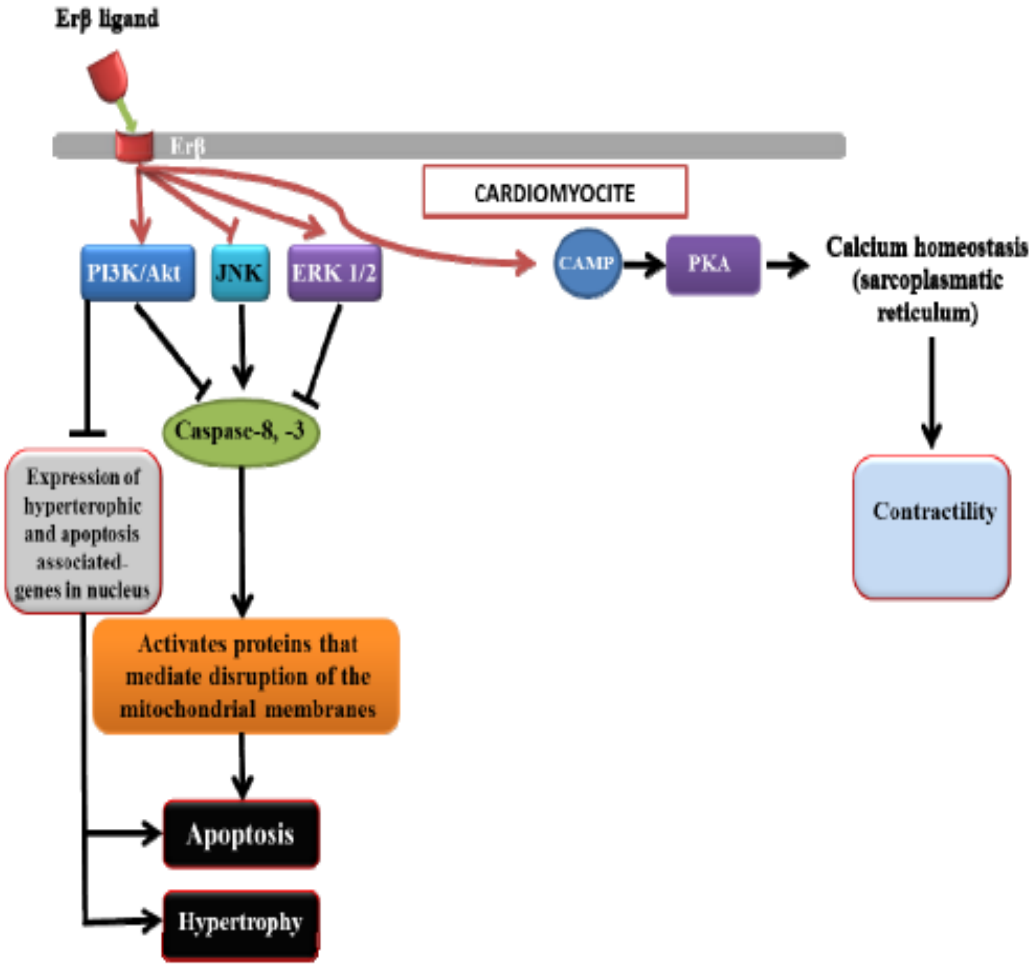
Framingham Heart Study, N=2,883
Benjamin EJ et al., Circulation 2004

Erβ receptor on endothelium



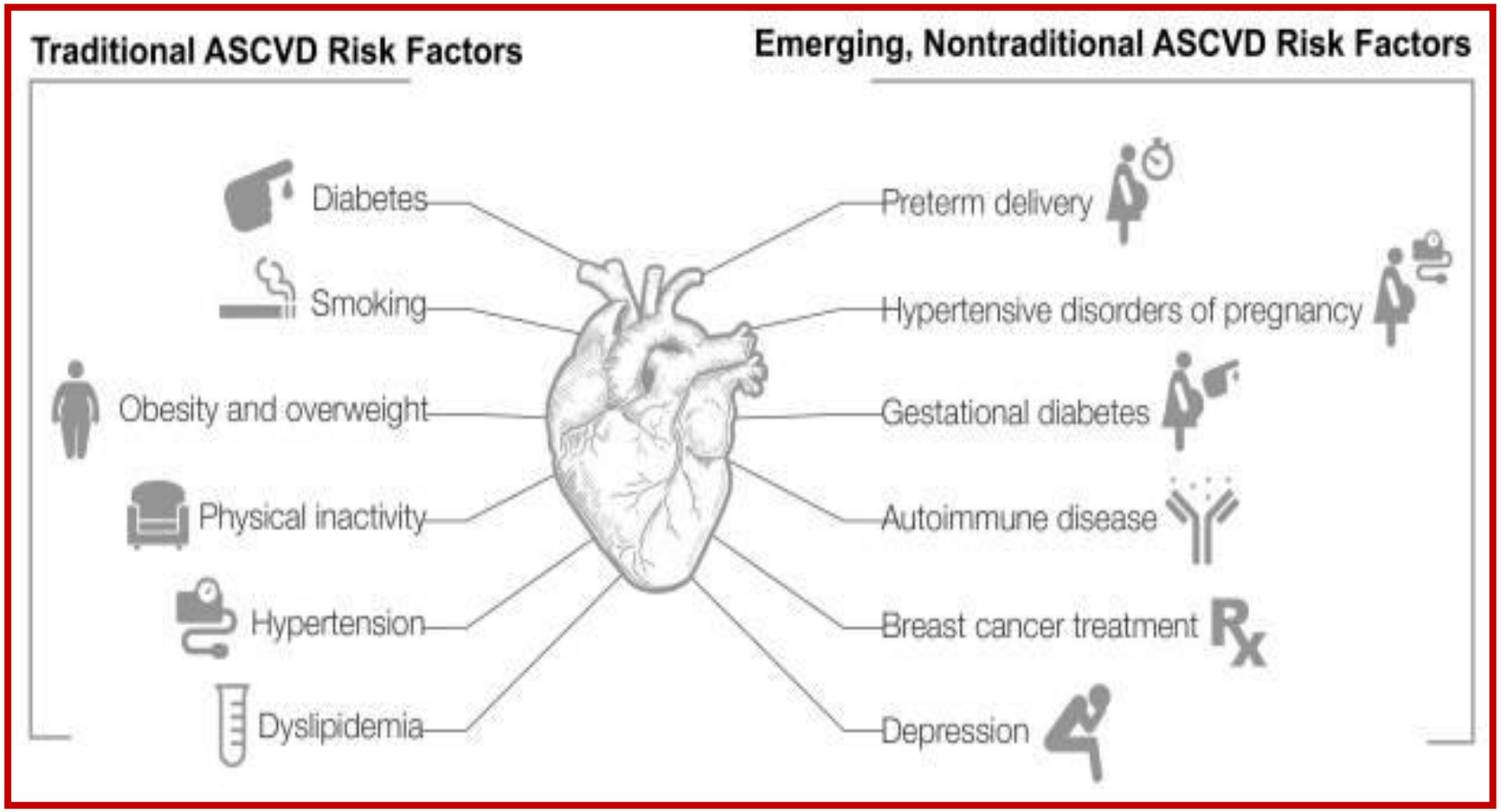
Muka T et al,
Maturitas. 2016 Apr

Possible Erβ receptor actions in cardiomyocytes



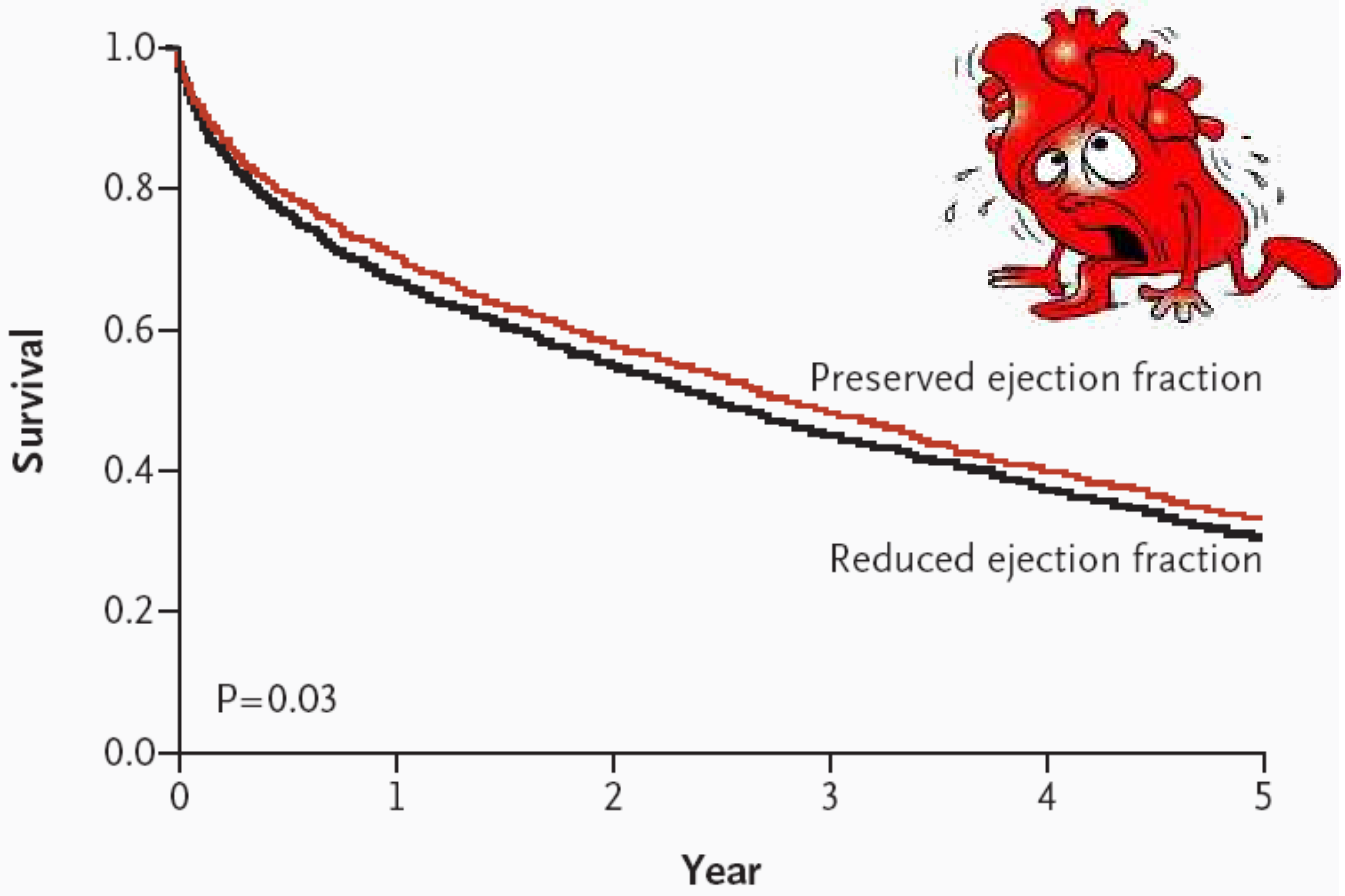
Muka T et al, Maturitas. 2016 Apr

Traditional vs Emerg(ED) CV risk factors in women



Garcia M Circ Res 2016

HEART FAILURE "PROGNOSIS"



No. at Risk						
Reduced ejection fraction	2424	1637	1350	1049	813	604
Preserved ejection fraction	2166	1539	1270	1001	758	574

N Engl J Med 2006;355:251-9.

Pathophysiology

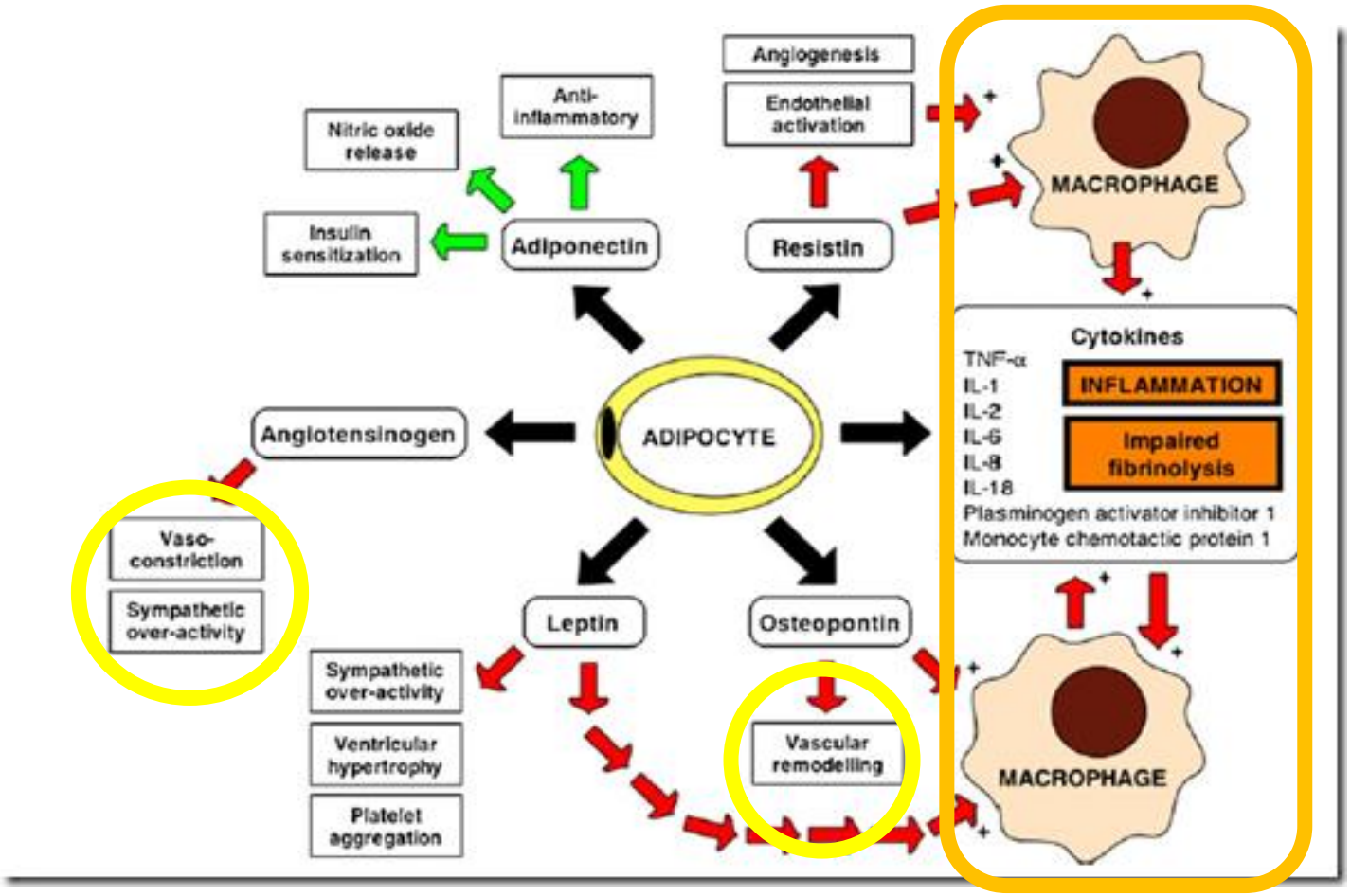
Pathophysiology

Metabolic Syndrome Criteria

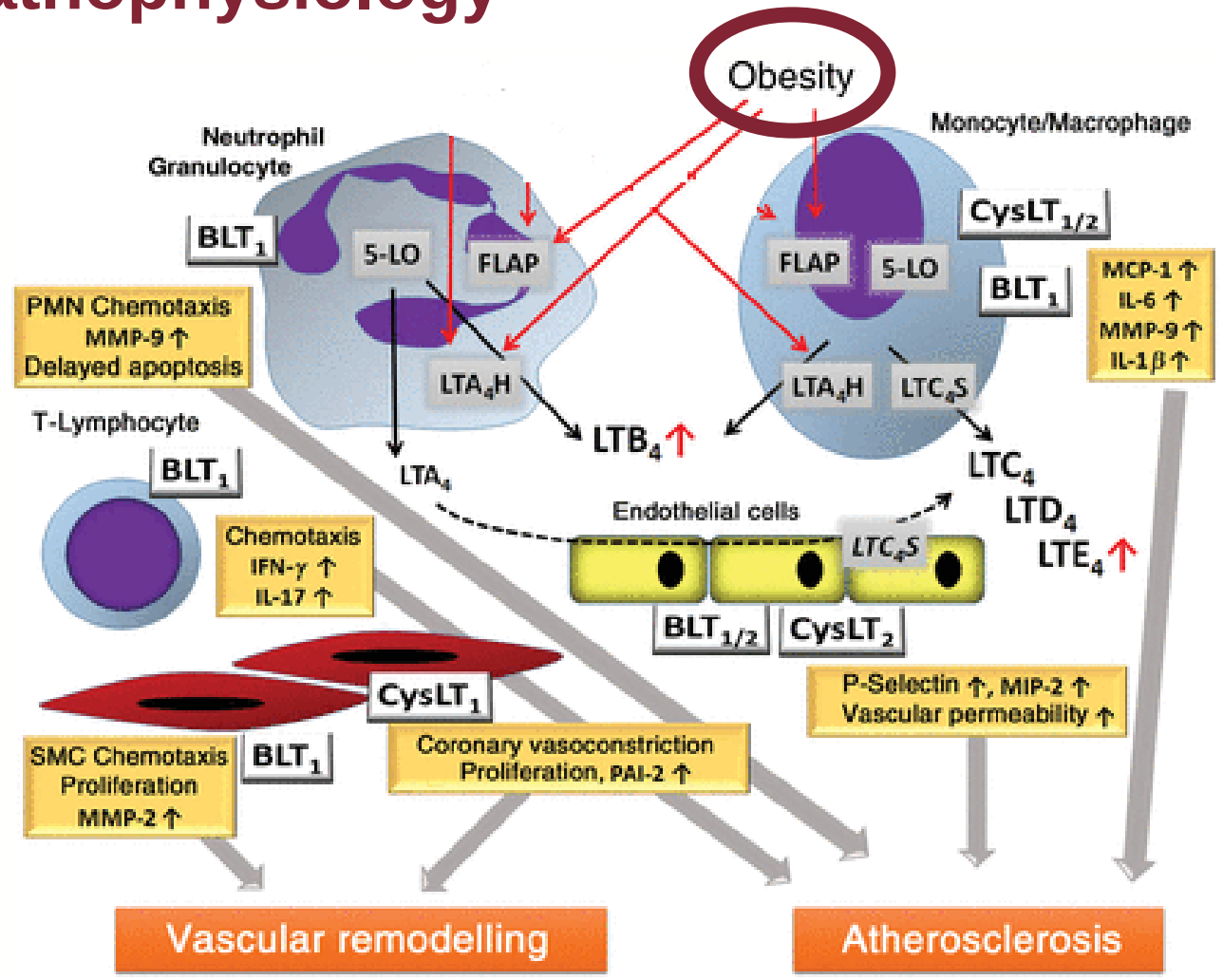
	NCEP-ATPIII, 2001	AHA/NHLBI, 2005	IDF, 2005	JIS, 2009
Criteria required	Any ≥3 of	Any ≥3 of	Mandatory: Waist circumference ≥94 cm (Europid men) or ≥80 cm (Europid women) Plus ≥2 of:	Any ≥3 of
Fasting blood glucose	fasting glucose ≥110 mg/dl (≥6.1 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)	fasting glucose ≥100 mg/dl (≥5.6 mmol/l)
High-density lipoprotein cholesterol	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women	<40 mg/dl (<1.04 mmol/l) in men <50 mg/dl (< 1.29 mmol/l) in women
Triglycerides	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)	≥150 mg/dl (≥1.7 mmol/l)
Waist circumference	≥102 cm (men) ≥88 cm (women)	≥102 cm (men) ≥88 cm (women)		≥94 cm (men) or ≥80 cm (women) for Mediterranean population
Hypertension	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder	≥130/85 mmHg or specific treatment for this disorder

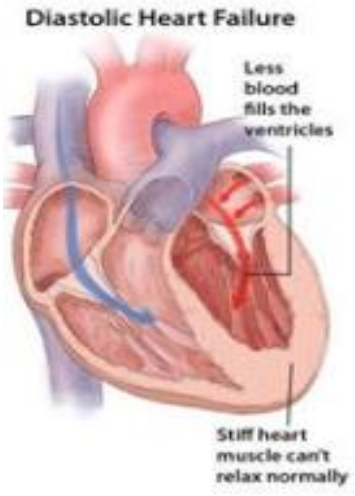
NCEP ATP III: National Cholesterol Education Program Adult Treatment Panel III, IDF: International Diabetes Federation, AHA: American Heart Association, NHLBI: National Heart Lung and Blood Institute, JIS: Joint Interim Society statement

Pathophysiology



Pathophysiology





HFpEF
(diastolic Heart Failure)

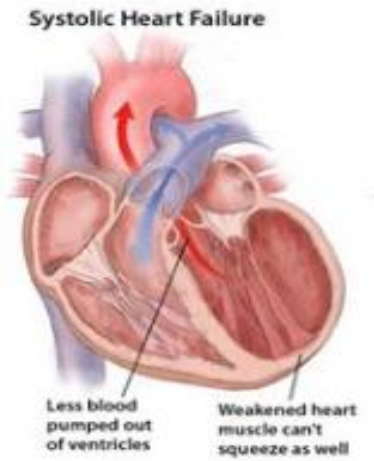
Acute pulmonary edema

Cerebral Infarction/hemorrhage

Atrial Fibrillation

Vasculopaties
Disseminated
Cerebral
Coronary

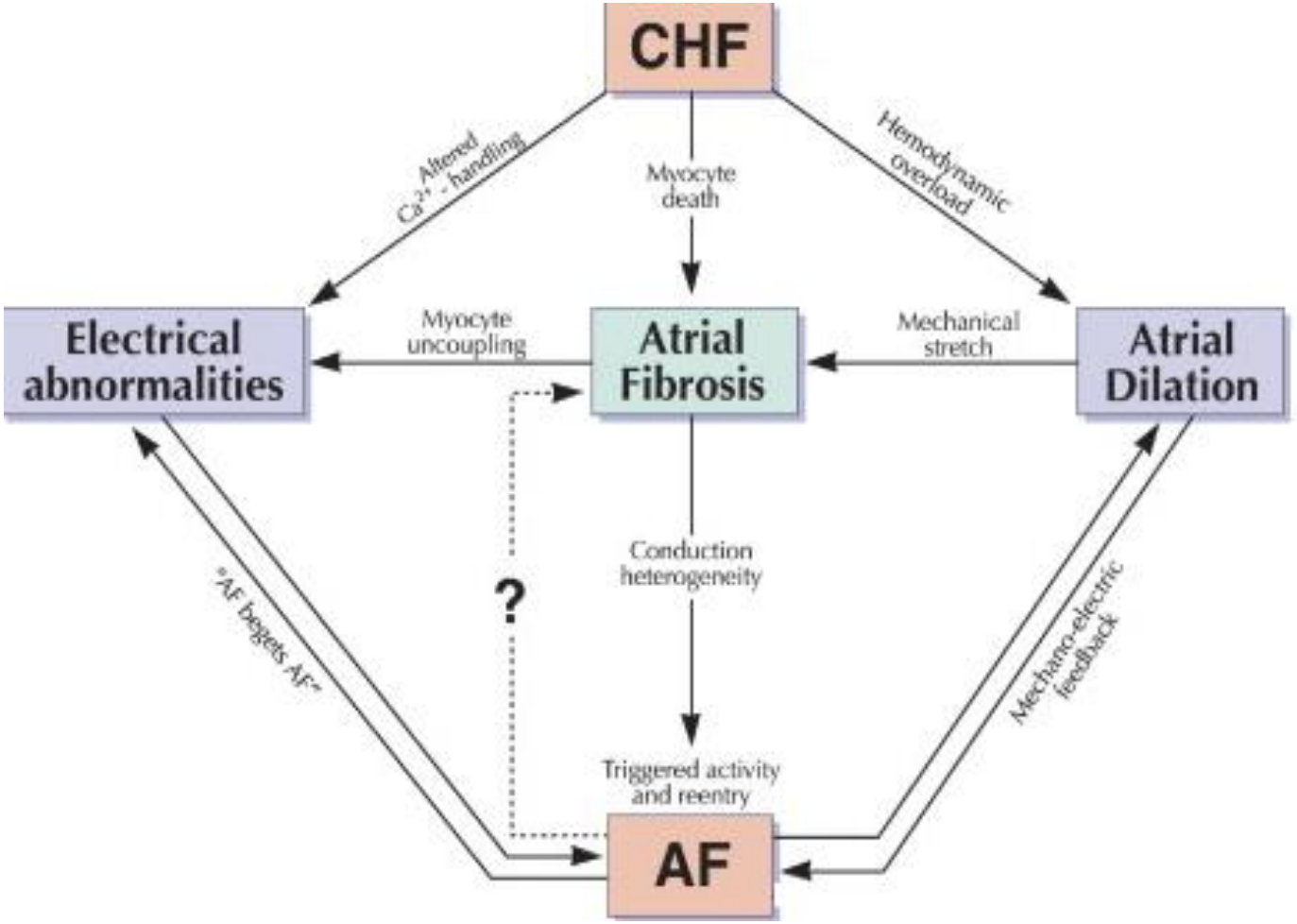
Sudden Arrhithmic Death



Coronary Artery Disease

Myocardial Infarction

HFrEF
(sistolic Heart Failure)


CHF
Altered Ca2+ - handling
Myocyte death
Hemodynamic overload
Electrical abnormalities
Myocyte uncoupling
Atrial Fibrosis
Mechanical stretch
Atrial Dilation
"AF begets AF"
?
Conduction heterogeneity
Mechano-electric feedback
Triggered activity and reentry
AF

(1) Symptoms & Signs Of Heart Failure

- Typical symptoms: breathlessness, orthopnoea, paroxysmal nocturnal dyspnoea, exercise intolerance, fatigue, swelling
- Typical signs: raised jugular venous pressure, hepatojugular reflux, third heart sound, oedema, pulmonary crepitations

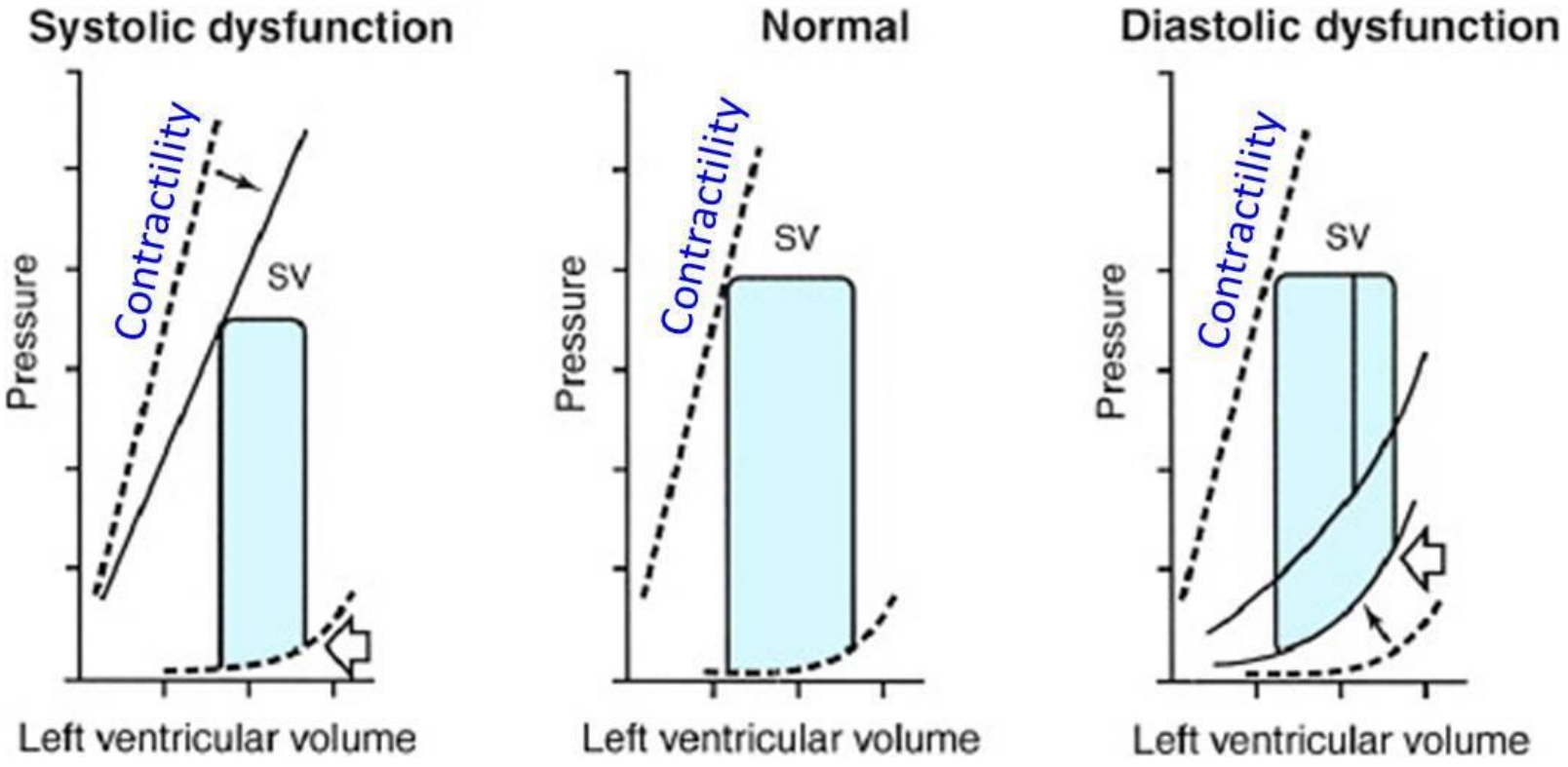
(2) Preserved LV Ejection Fraction

- Currently taken as LV ejection fraction ≥50%
- Without LV dilatation

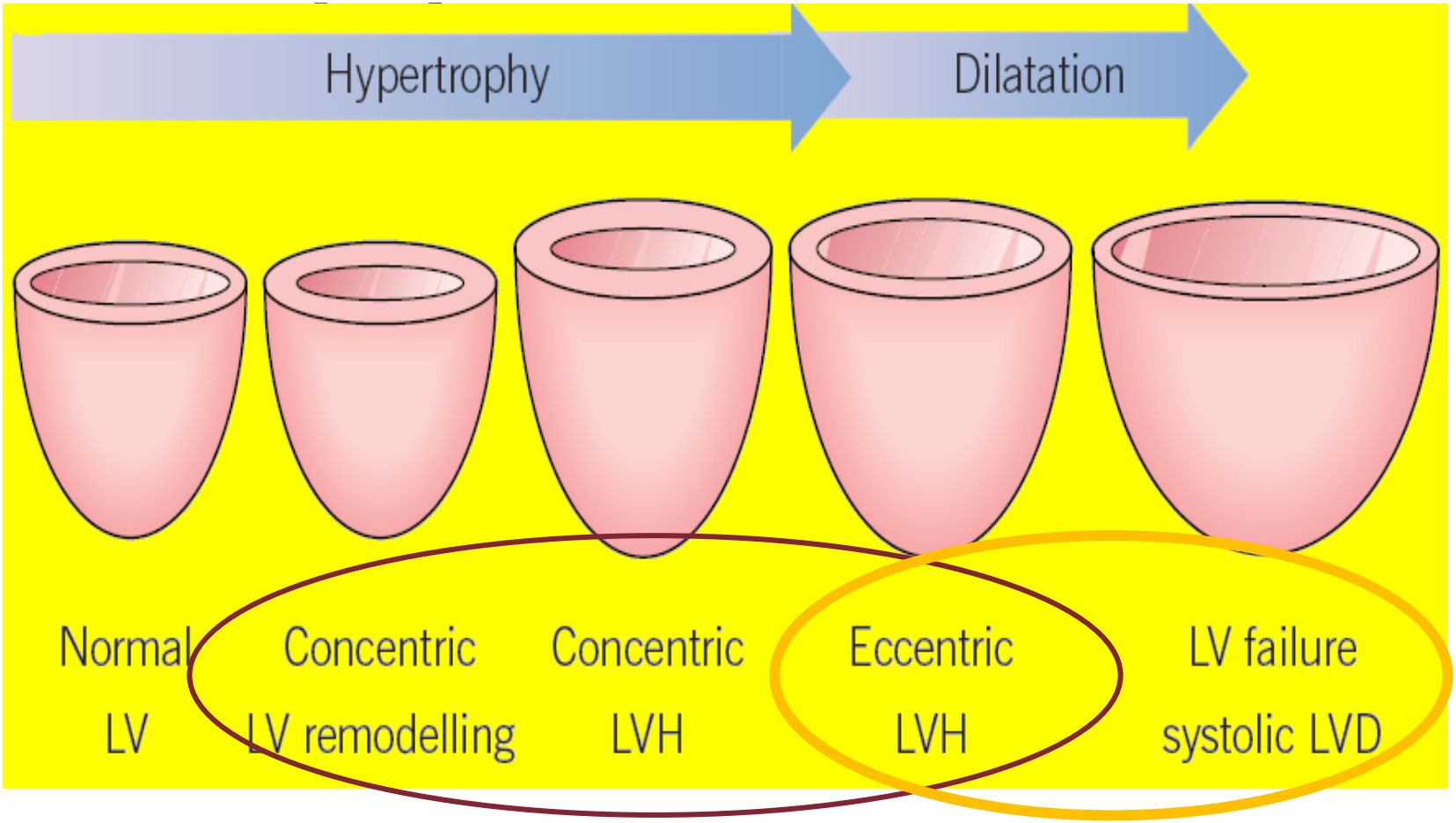
(3) LV Diastolic Dysfunction

- Structural: LV hypertrophy, left atrial dilatation
- Doppler: raised E/e' ratio, abnormal mitral inflow, prolonged pulmonary venous A reversal duration
- Biomarkers: raised NT-proBNP, BNP
- Rhythm: atrial fibrillation
- Invasive hemodynamics: increased LV end-diastolic pressure, prolonged tau, increased LV stiffness

Pressure-volume loops



Progression of left ventricle



Symptoms and signs

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

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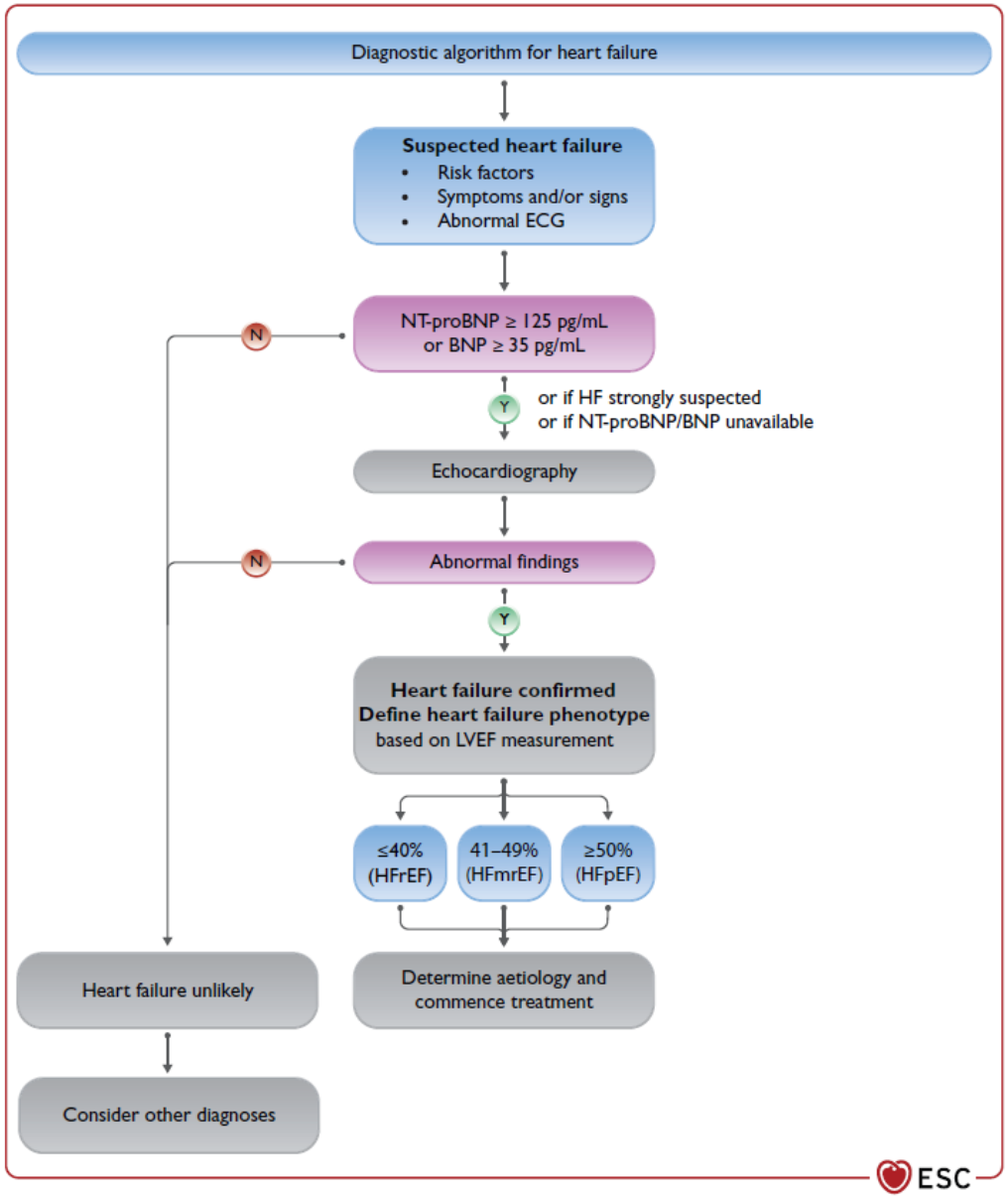
Symptoms and signs

Diagnosis



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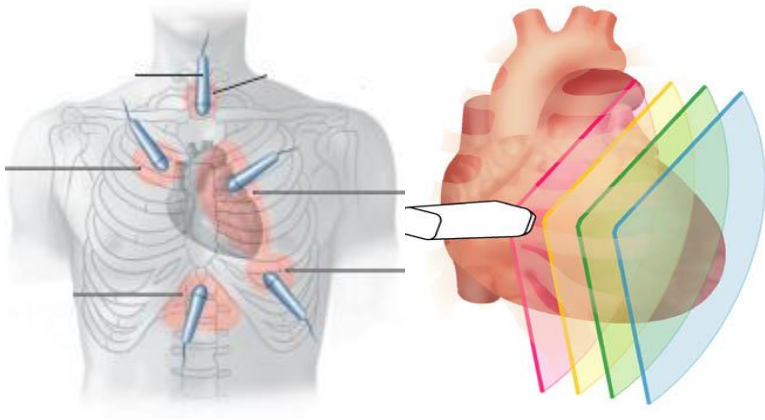
Echocardiography

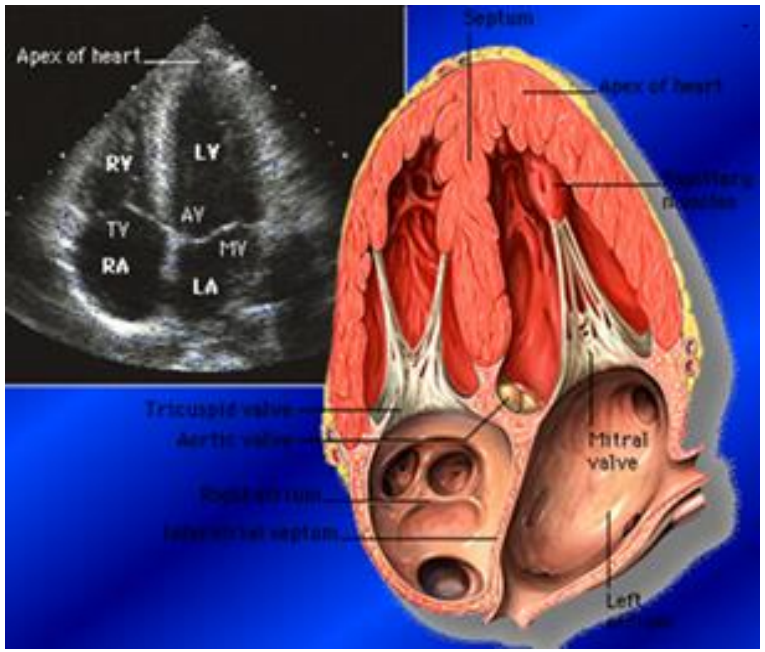


Transthoracic echocardiography (TTE) is the method of choice for assessment of myocardial systolic and diastolic function of both left and right ventricles.

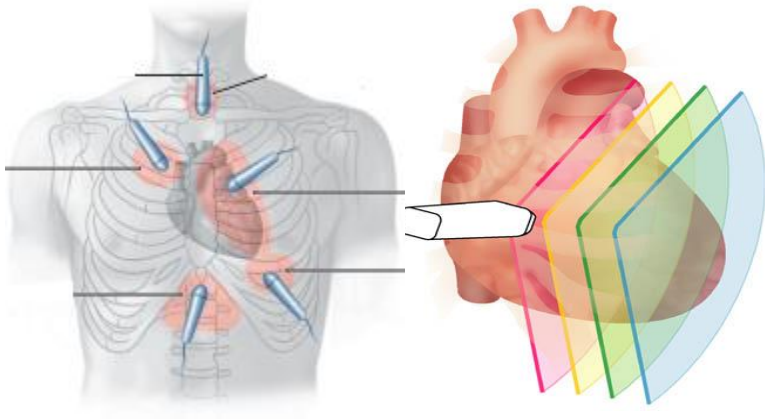
- Assessment of LV measuring ***LVEF***

- Assessment of RV and pulmonary

Arterial pressure measuring
TAPSE (tricuspid annular plane systolic excursion) and tissue Doppler-derived tricuspidal lateral annular systolic dysfunction

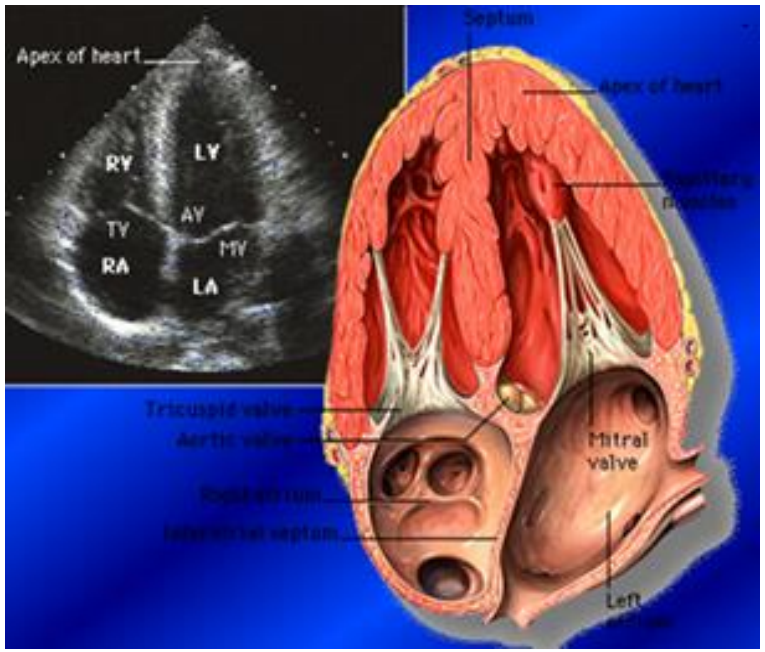


Echocardiography

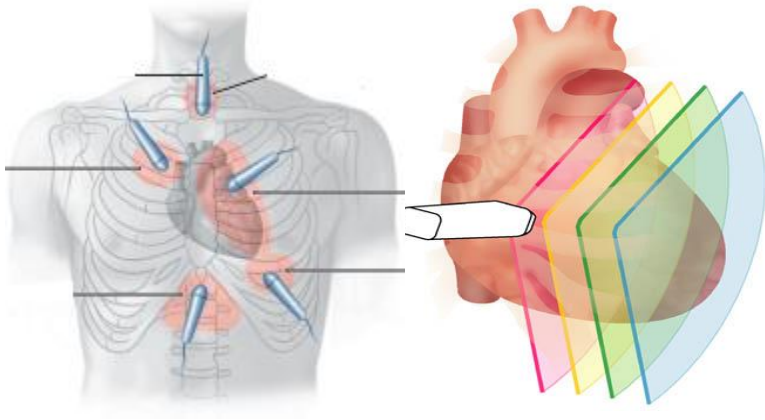


- DIASTOLIC FUNCTION EVALUATION

By Doppler echocardiography the left ventricular filling is analyzed both by transvalvular mitral flow (related to changes in the gradient A-V) and through the flow profile of the pulmonary veins (faithful mirror of the left atrial filling)



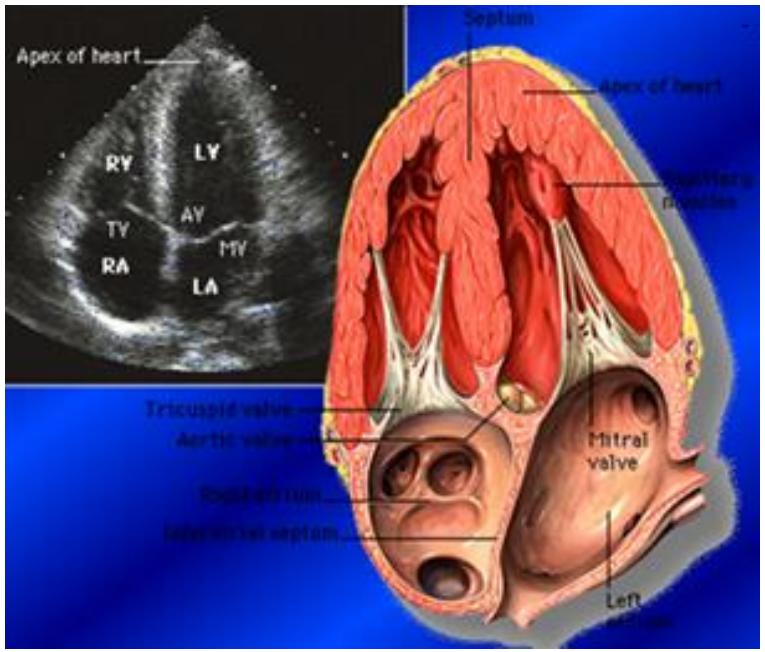
Echocardiography

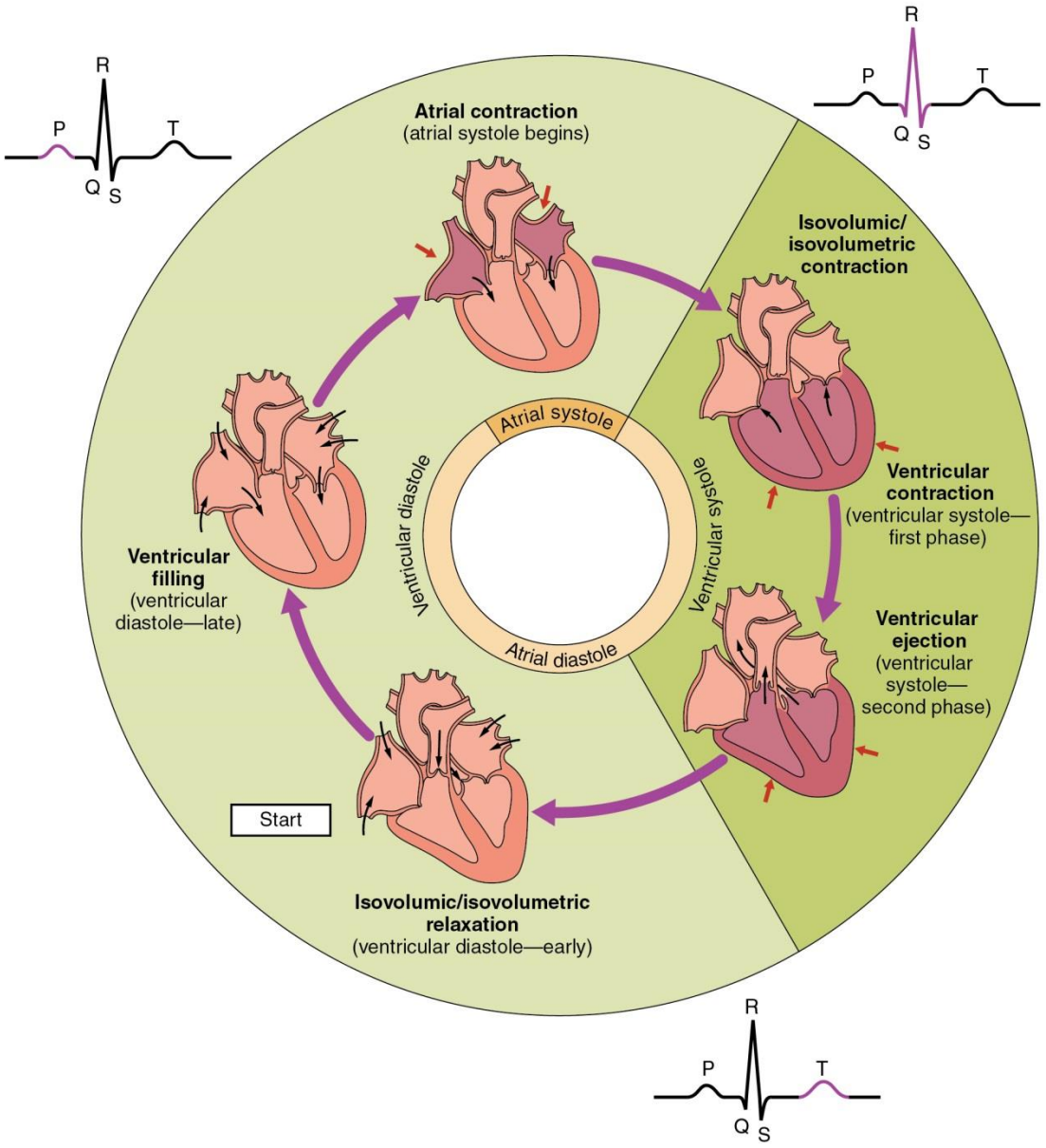


The components of the transvalvular mitral flow velocity are formed by the wave E (early diastolic rapid filling) and A wave (atrial diastolic contraction).

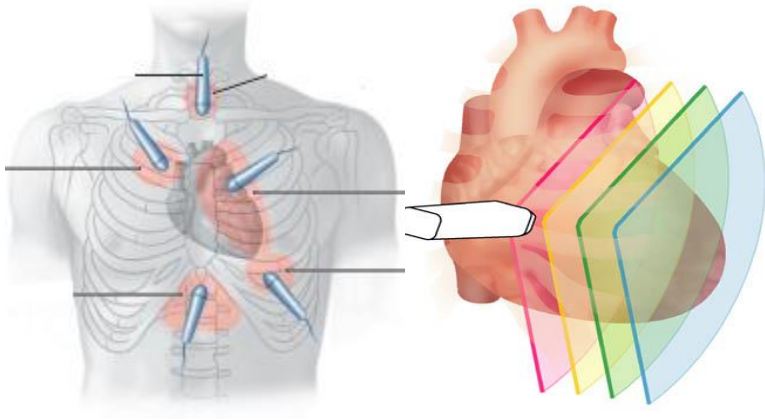
Useful indication of diastolic function can be deduced from:

- ✓ E/A ratio
- ✓ the deceleration time (DT)
- ✓ isovolumic relaxation time (IVRT)




R
P
T
Q
S
Atrial contraction
(atrial systole begins)
Isovolumic/
isovolumetric
contraction
Ventricular
contraction
(ventricular systole—
first phase)
Ventricular
ejection
(ventricular
systole—
second phase)
Isovolumic/isovolumetric
relaxation
(ventricular diastole—early)
Ventricular
filling
(ventricular
diastole—late)
Start
Atrial systole
Atrial diastole
Ventricular diastole
Ventricular systole

Echocardiography



- Pulmonary Vein Flow:

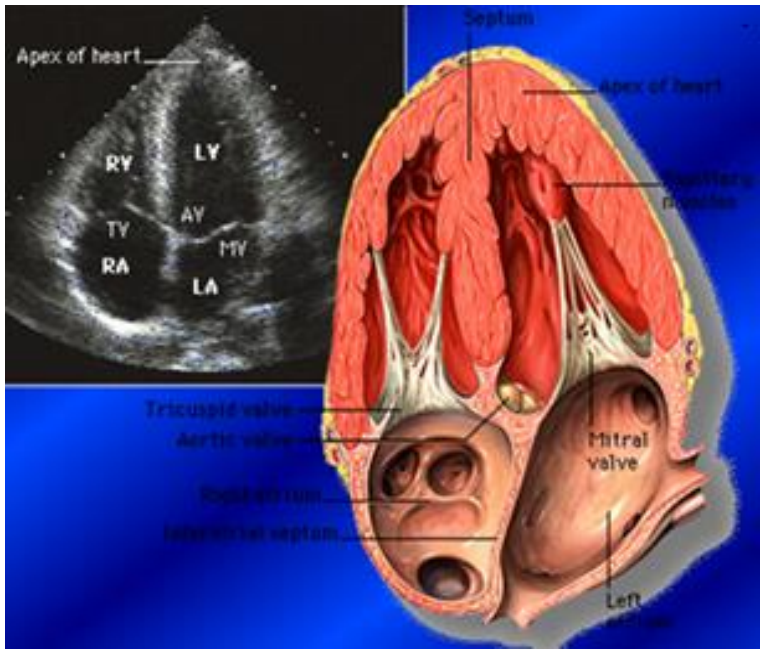
There are usually four distinct components in the PVF:

✓ S1 corresponds to protosystole and is determined by atrial relaxation

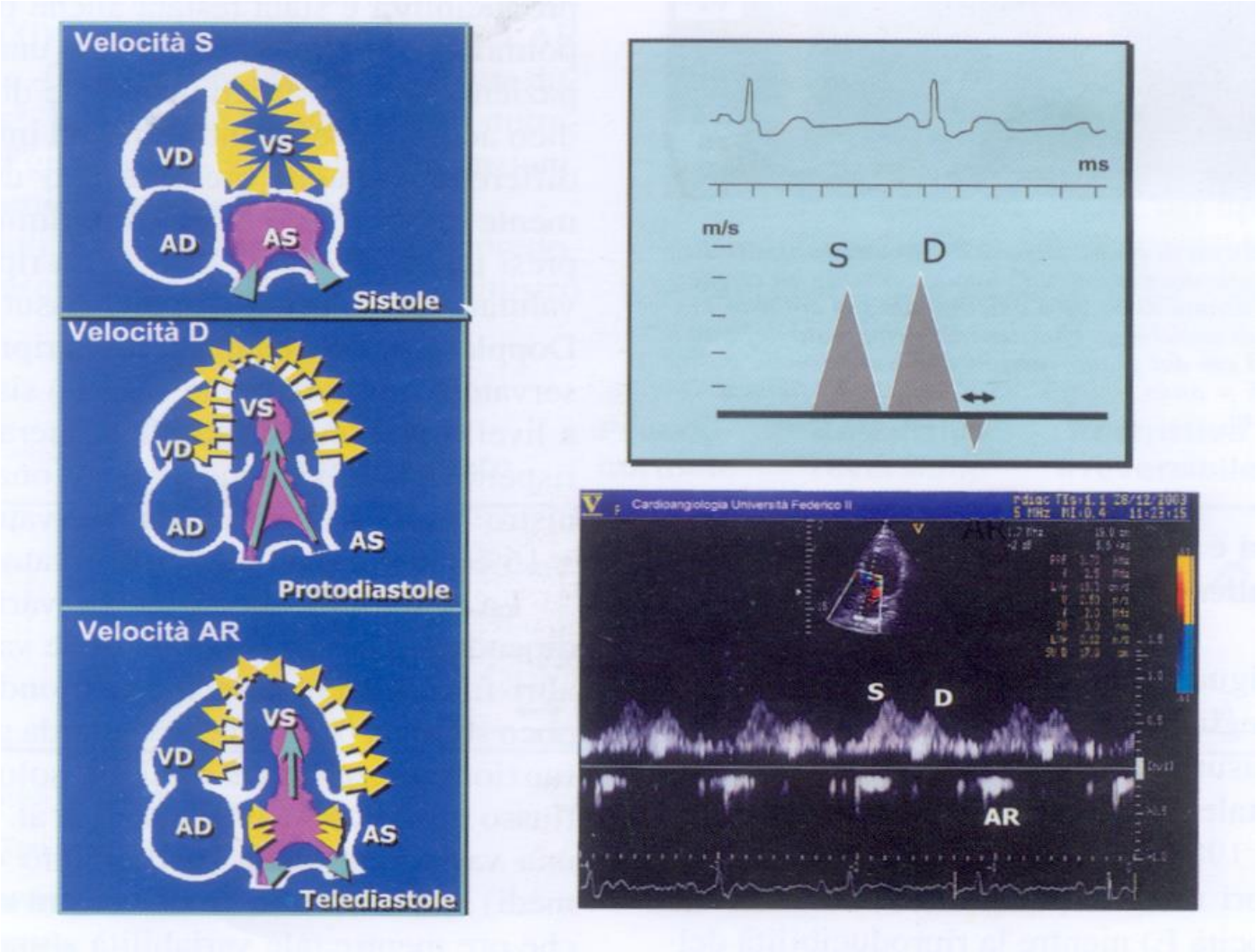
✓ S2 corresponds to the meso and end-systole and is determined by the increase in pressure in VP

✓ D corresponds to the proto and mesodiastole and is determined by the decrease of left atrial pressure related to the opening of the mitral

✓ A corresponds to the end-diastole and is determined by atrial systole



Echocardiography



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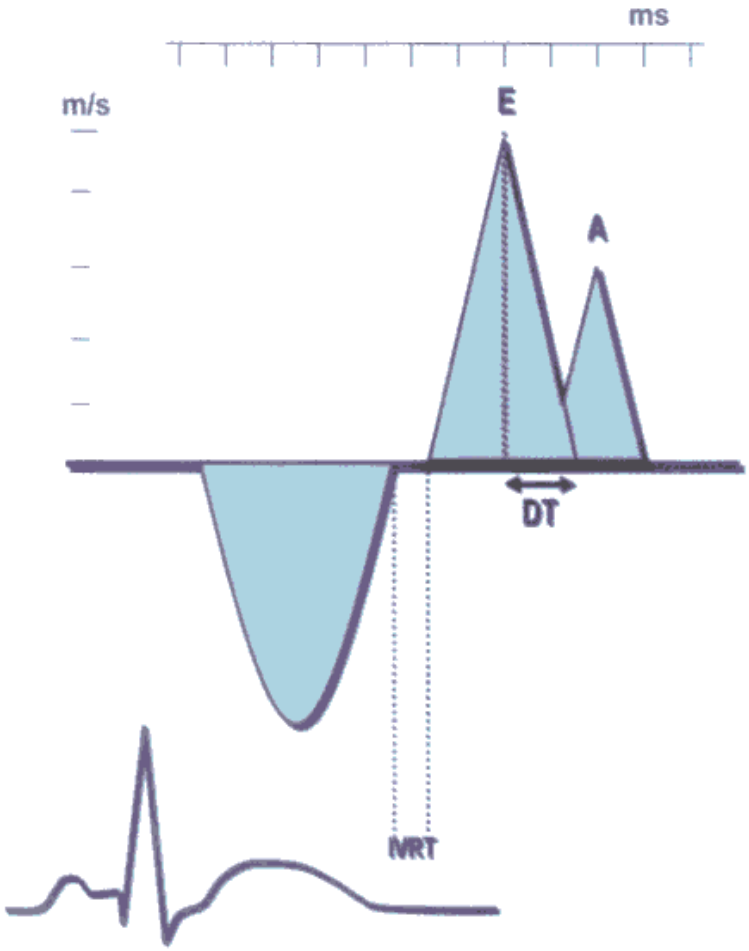
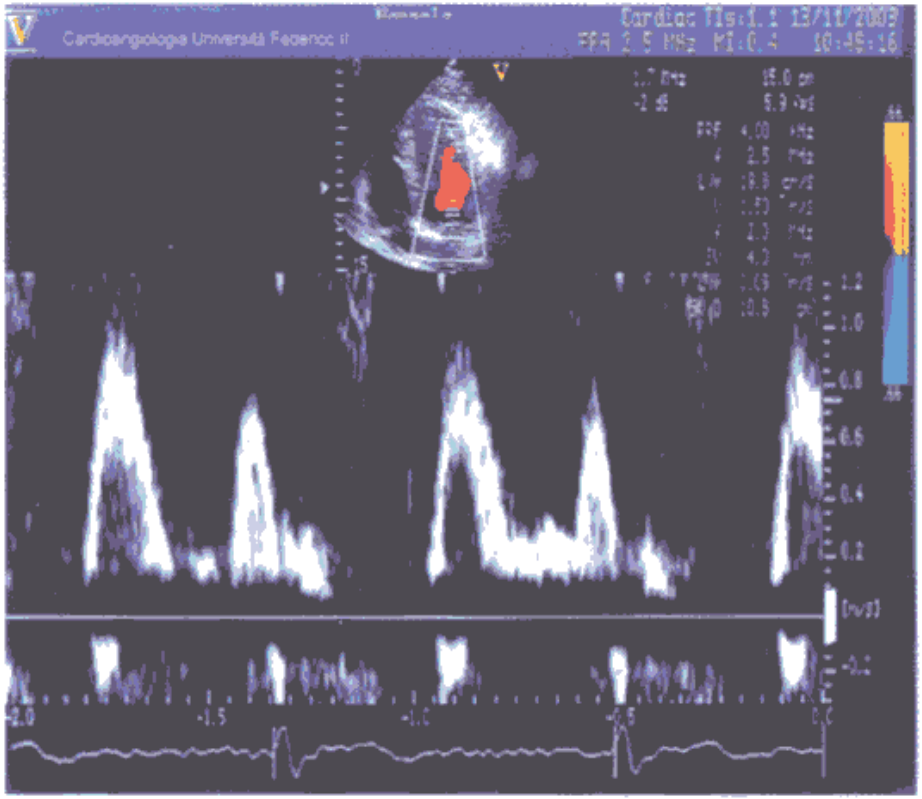
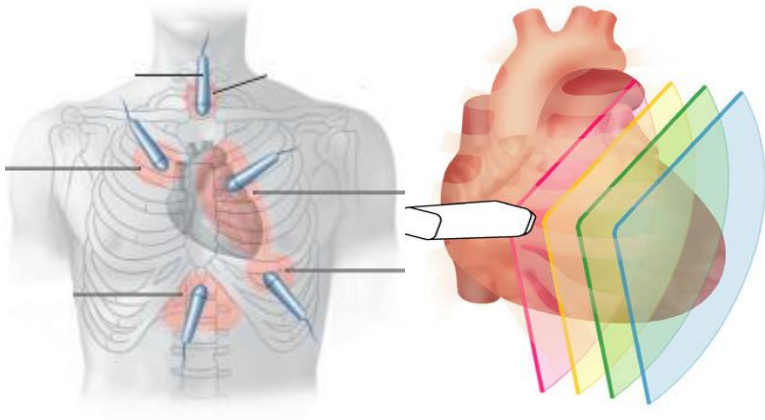




Echocardiography



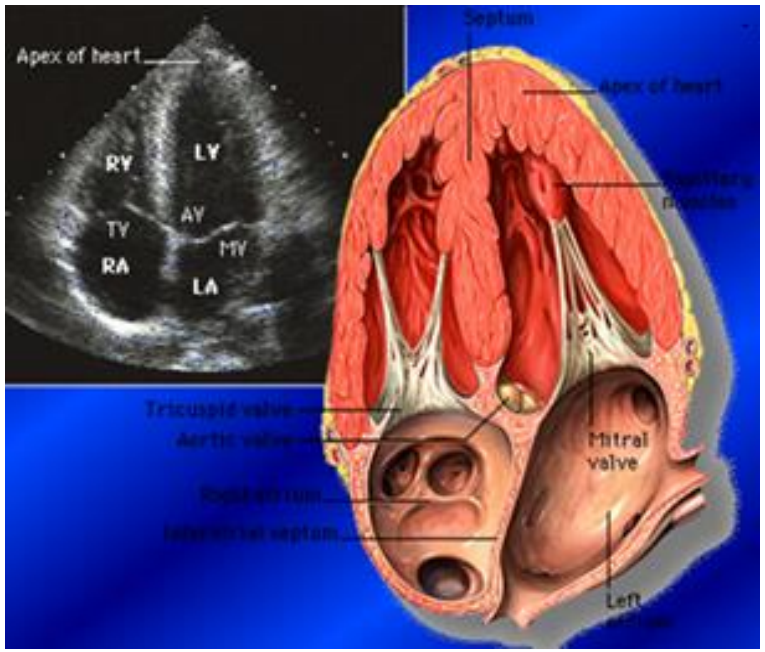
Normal Pattern:

IVRT 70-90 msec

DT about 200 msec

1< E/A <2

S/D about 1



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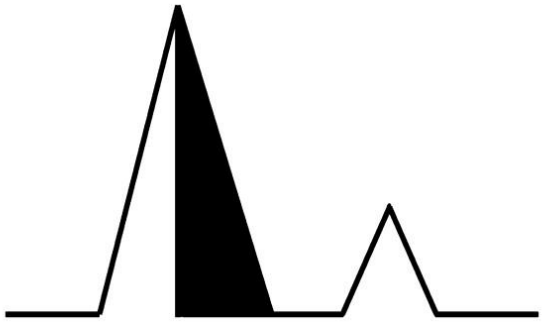
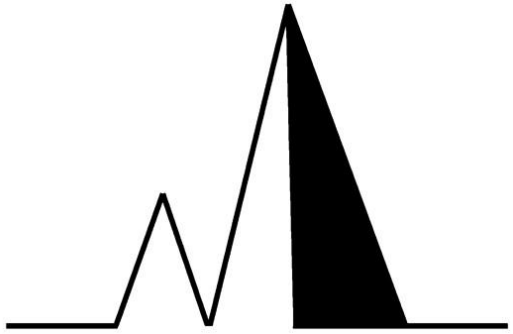
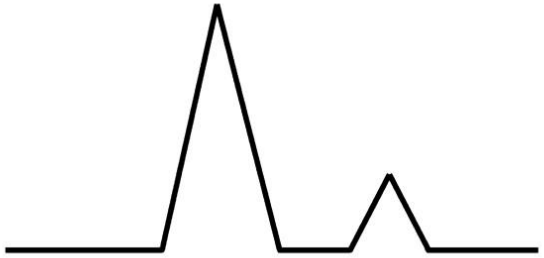


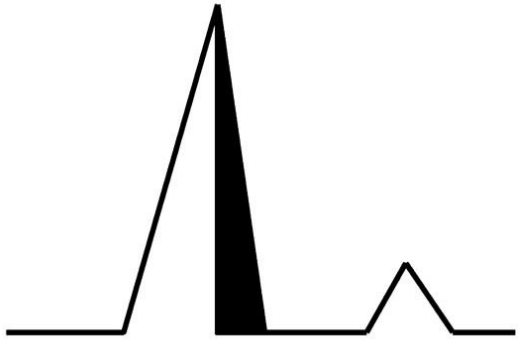
Normal diastolic function
E:*A* 0.75 –1.5
DT 180–240 ms



Mild diastolic dysfunction
E:*A*<0.75
DT>240 ms

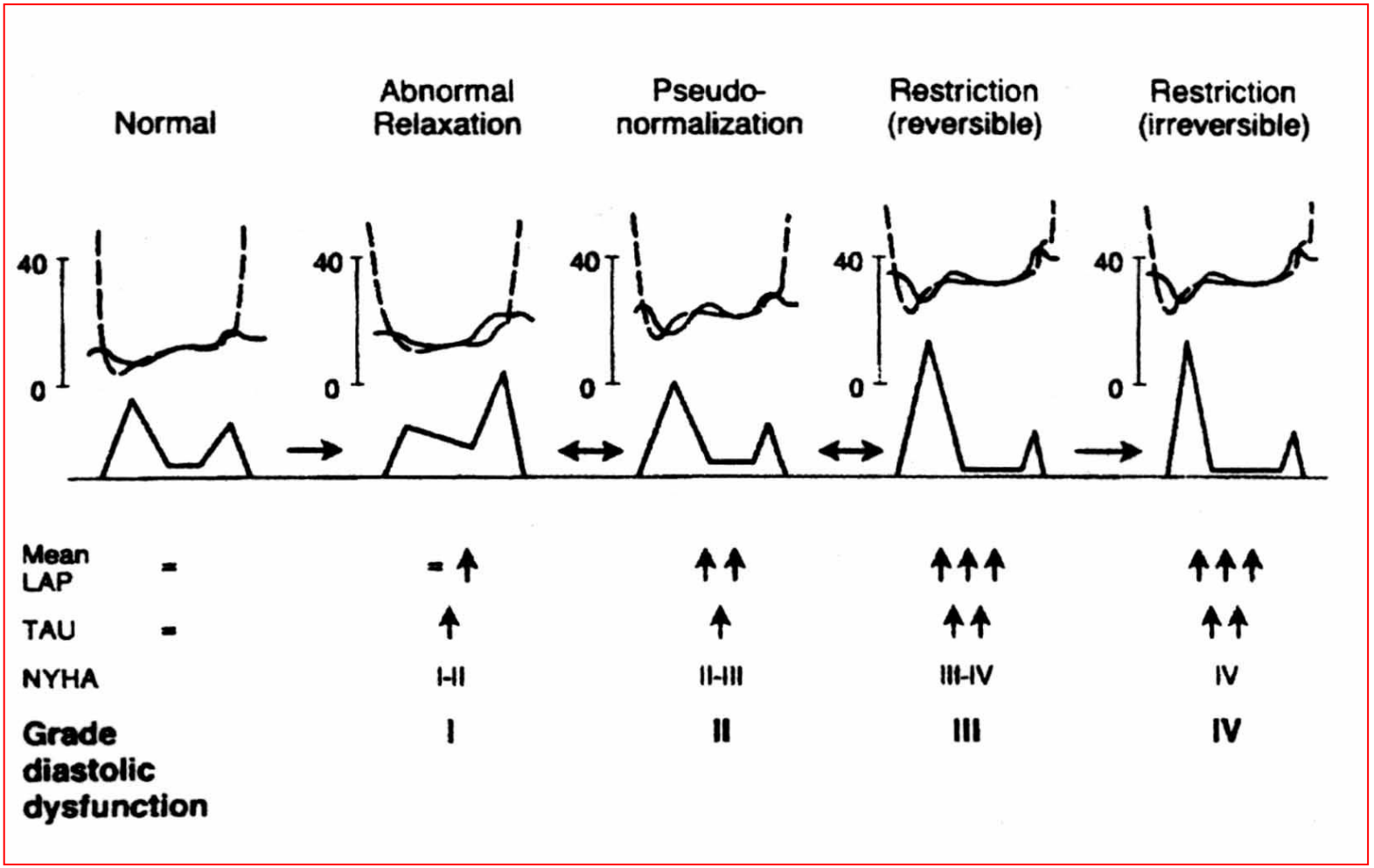


Moderate diatolic dysfunction
E:*A* 0.75–1.5-pseudonormalization
DT 180–240 ms

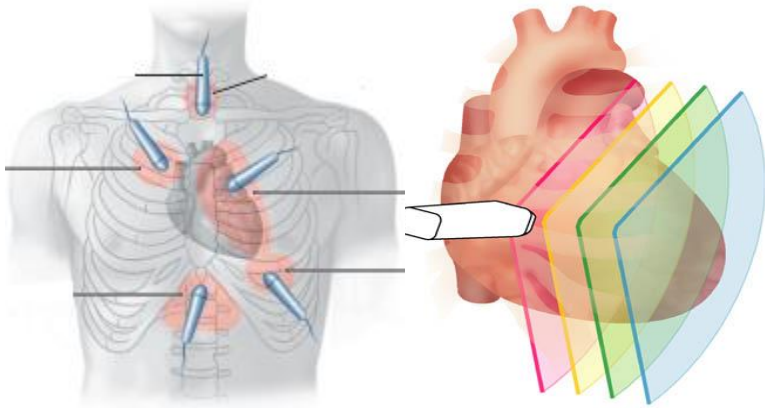


Severe diastolic dysfunction
E:*A*>1.5
DT<180 ms

Echocardiography



Echocardiography



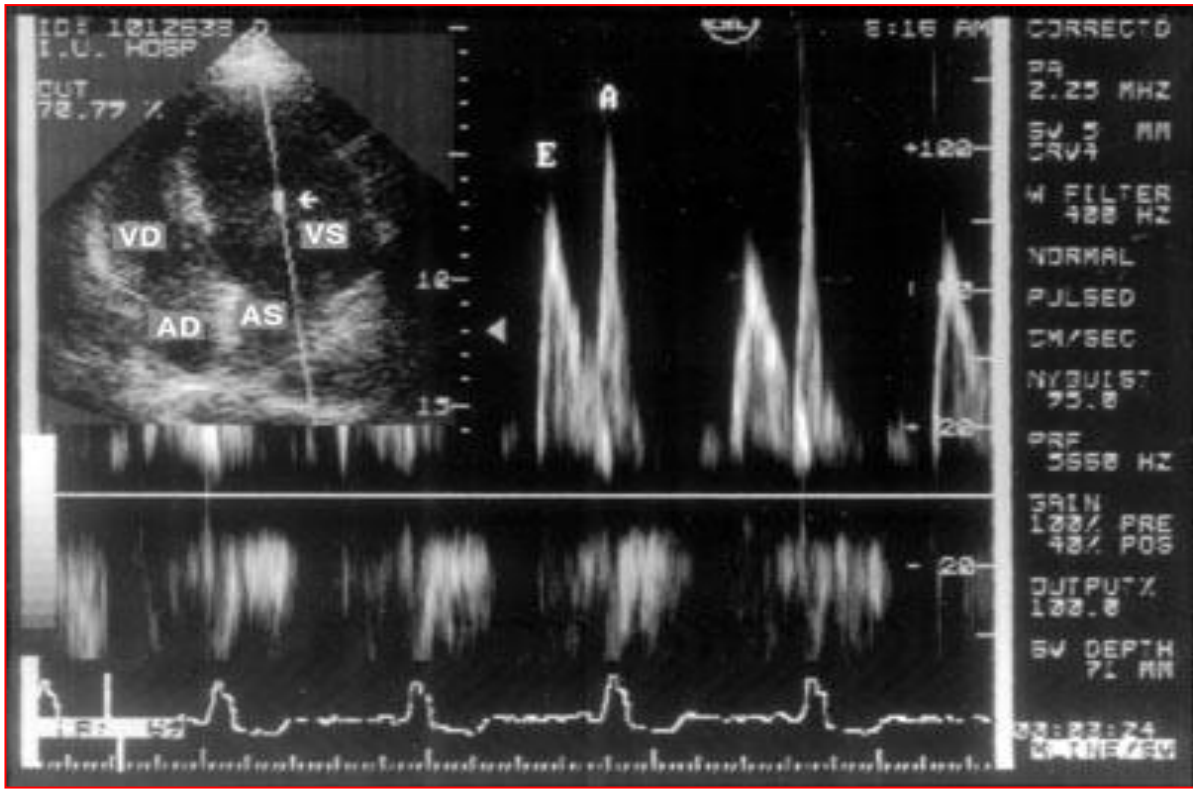
Mild diastolic disfunction (grade 1, impaired relax):

IVRT >100 msec

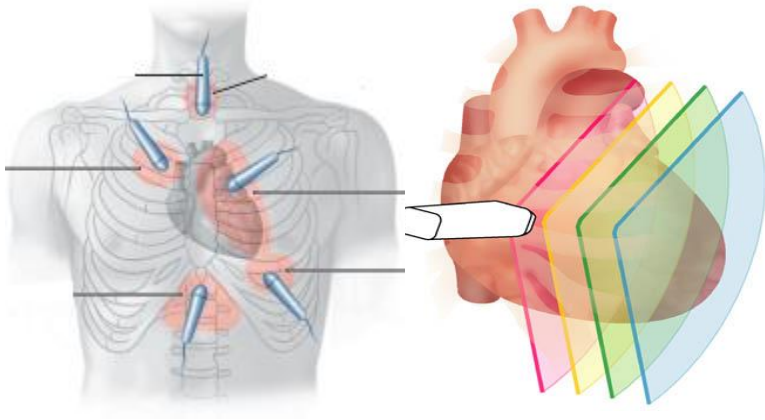
DT > 220 msec

E/A <1

S/D >1.5



Echocardiography



Modearate diastolic disfunction (grade 2, pseudonormal) :

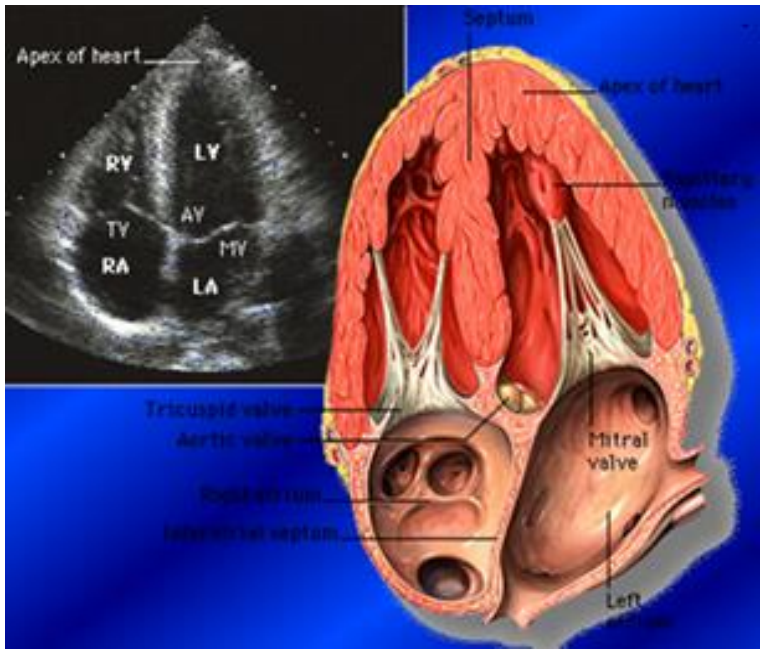
IVRT 60-100 msec

DT 150-200 msec

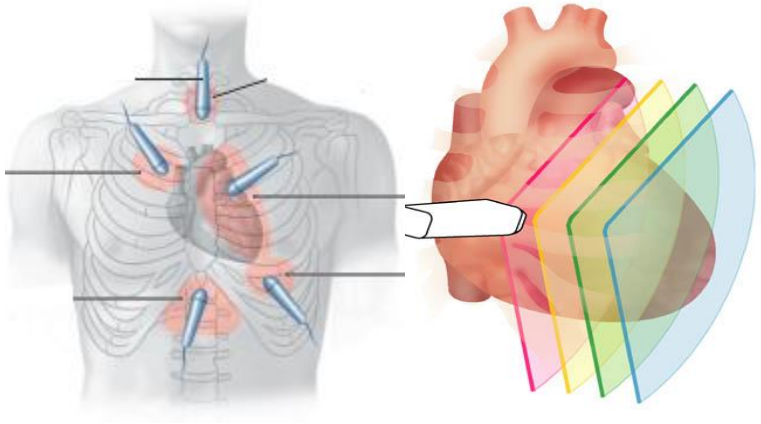
1<E/A <2

S/D about 1

A_r wave>0.3 m/s



Echocardiography



Severe diastolic disfunction (grade 3, restrictive) :

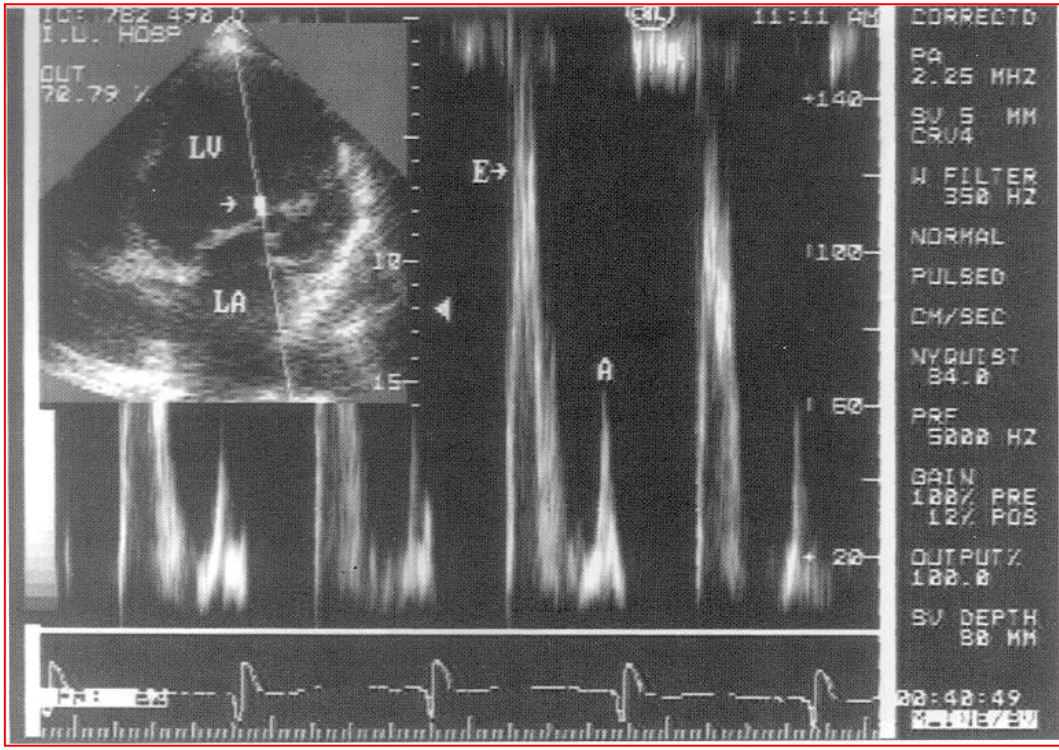
IVRT <60 msec

DT <150 msec

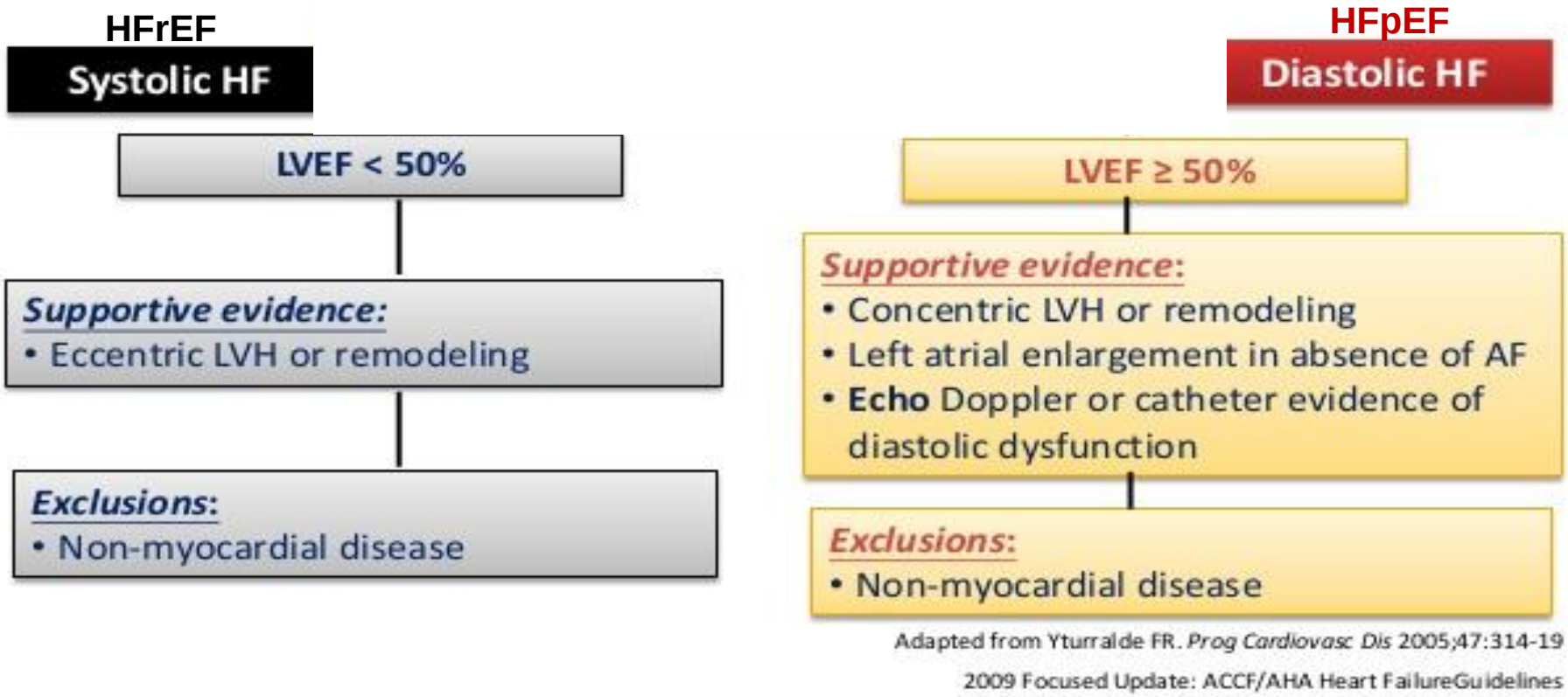
E/A >2

S/D < 1

A_r wave >>0.3 m/s



Diagnostic Criteria



Adapted from Yturralde FR. *Prog Cardiovasc Dis* 2005;47:314-19

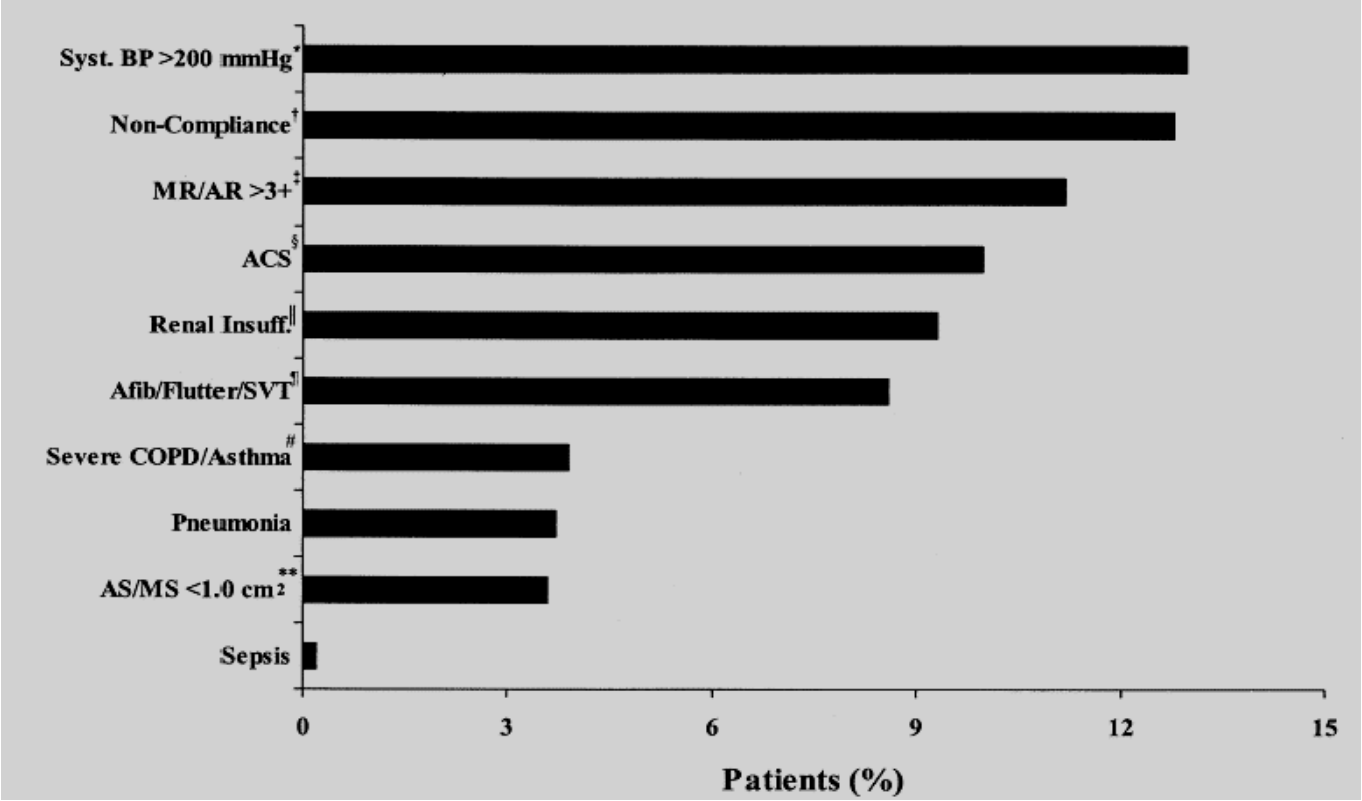
2009 Focused Update: ACCF/AHA Heart FailureGuidelines

SHF vs. DHF

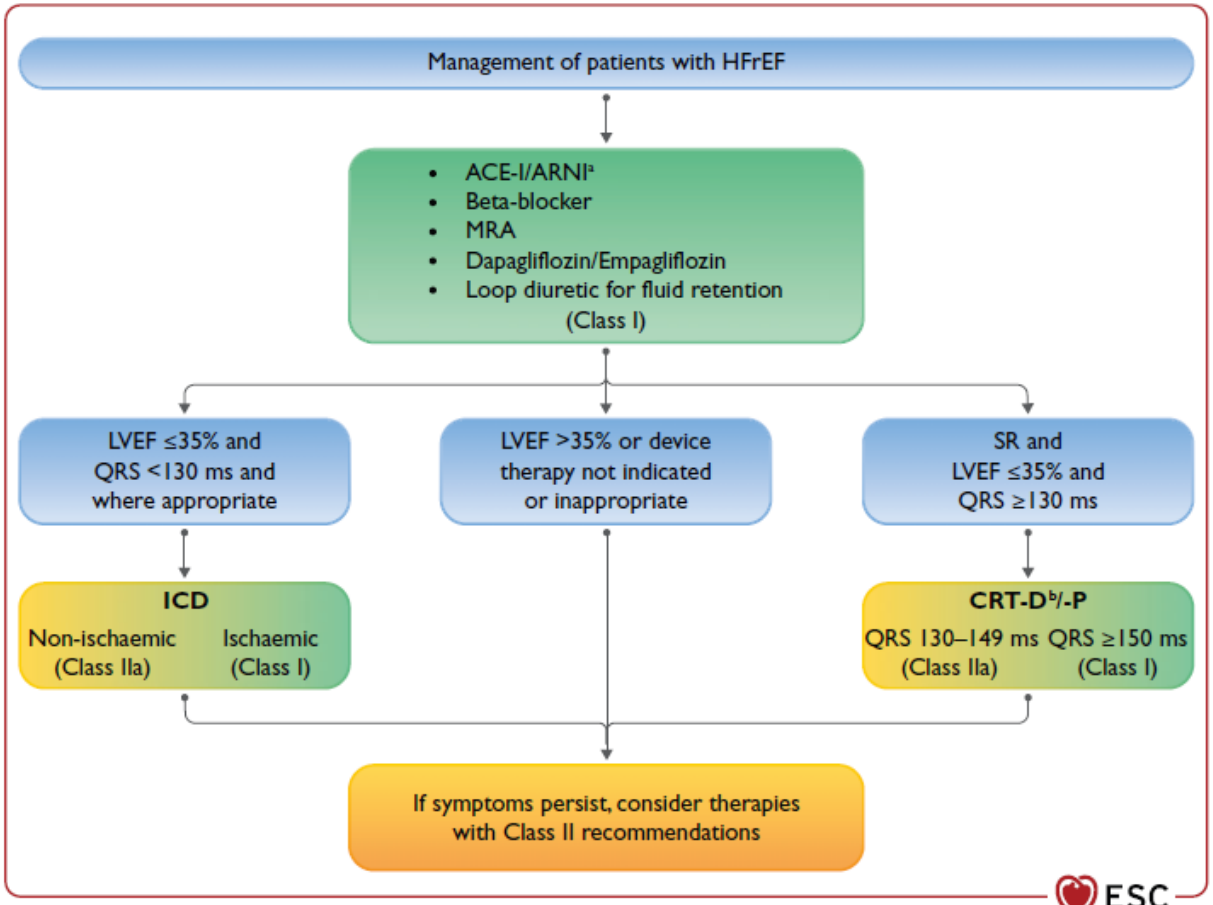
	Systolic heart failure	*Diastolic heart failure*
Pathophysiology	Impaired myocardial contractility Dilated heart	Impaired relaxation and filling Hypertrophied heart
Ejection Fraction	Reduced	Normal
Signs and Symptoms	Similar	
Mortality and Morbidity	No significant difference	
BNP/NT-proBNP Levels	More elevated	Less elevated
Patient Characteristics	Prior myocardial infarction	Older Woman Obesity Hypertensive Atrial fibrillation
Evidence Supported Treatment	Well	Poor

Diastolic Heart Failure (HFpEF)

in heart failure with preserved ejection fraction (which is the most frequent type of failure ever) hypertensive crisis are the most frequent precipitating factor, followed by poor compliance of patients to therapy (often elderly patients with co-morbidities)



Recommendations to prevent or delay the development of overt heart failure or prevent death before the onset of symptoms



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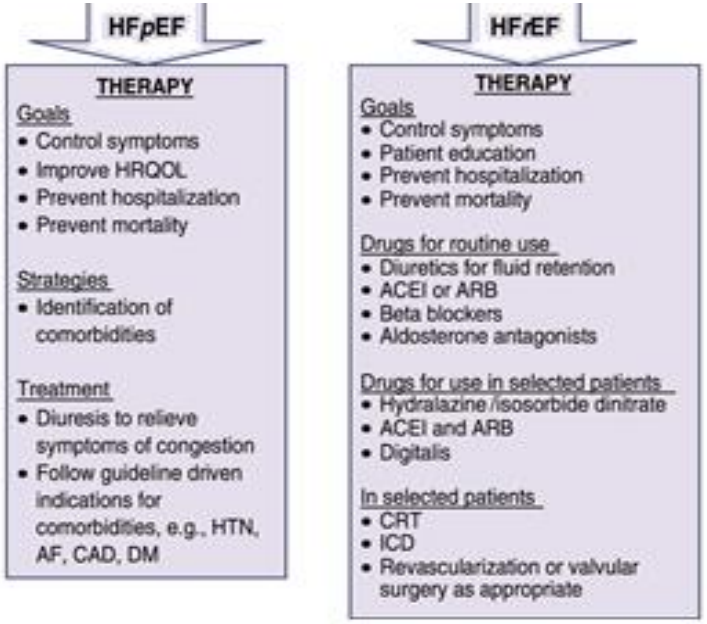
Pharmacological treatments indicated in patients with symptomatic (NYHA Class II-IV) heart failure with reduced ejection fraction (HFrEF)

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.

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.

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.



ACEi= angiotensin-converting enzyme inhibitor
MRA=mineralcorticoid receptor antagonist
d)Or Angiotensin Receptor Blocker if ACEi is not tollerated/controindicated
HRQOL=heart-related quality of life
HTN= hypertension

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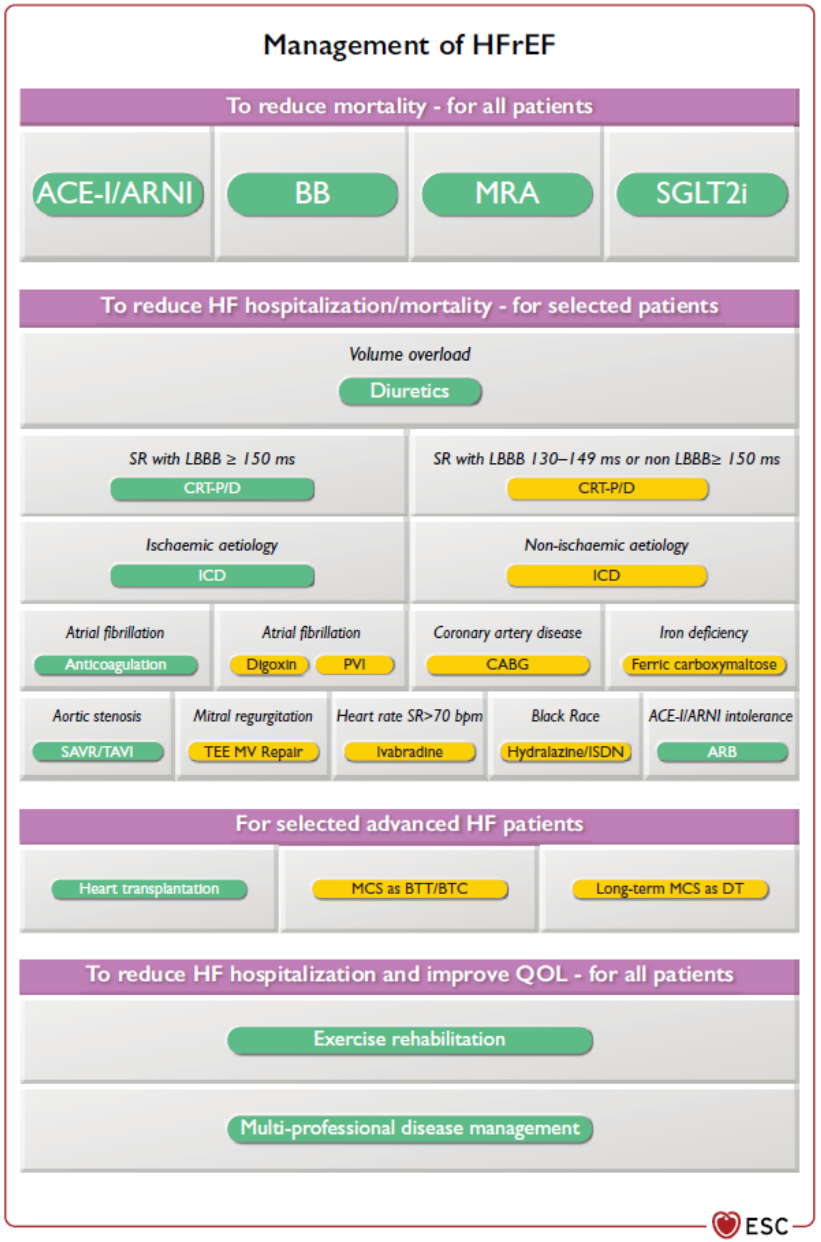

ARNI= angiotensin receptor neprilysin inhibitor (new therapeutic class of agents acting on the renin-angiotensin-aldosterone system)

CRT= cardiac resynchronization therapy
H-ISDN=hydralazine and isosorbide dinitrate
LVAD= left ventricular assist device
OMT= optimal medical therapy
VT/VF= ventricular tachycardia/fibrillation
ICD= implntable cardioverter defibrillator

Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) HFrEF

Diuretics
Diuretics are recommended in order to improve symptoms and exercise capacity in patients with signs and/or symptoms of congestion.
Diuretics should be considered to reduce the risk of HF hospitalization in patients with signs and/or symptoms of congestion.
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]
If-channel inhibitor
Ivabradine should be considered to reduce the risk of HF hospitalization or cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm despite treatment with an evidence-based dose of beta-blocker (or maximum tolerated dose below that), ACE-I (or ARB), and an MRA (or ARB).
Ivabradine should be considered to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients with LVEF ≤35%, in sinus rhythm and a resting heart rate ≥70 bpm who are unable to tolerate or have contra-indications for a beta-blocker. Patients should also receive an ACE-I (or ARB) and an MRA (or ARB).
ARB
An ARB is recommended to reduce the risk of HF hospitalization and cardiovascular death in symptomatic patients unable to tolerate an ACE-I (patients should also receive a beta-blocker and an MRA).
An ARB may be considered to reduce the risk of HF hospitalization and death in patients who are symptomatic despite treatment with a beta-blocker who are unable to tolerate an MRA.

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Other pharmacological treatments recommended in selected patients with symptomatic (NYHA Class II-IV) HFrEF

Hydralazine and isosorbide dinitrate
Hydralazine and isosorbide dinitrate should be considered in self-identified black patients with LVEF ≤35% or with an LVEF <45% combined with a dilated LV in NYHA Class III–IV despite treatment with an ACE-I a beta-blocker and an MRA to reduce the risk of HF hospitalization and death.
Hydralazine and isosorbide dinitrate may be considered in symptomatic patients with HFrEF who can tolerate neither an ACE-I nor an ARB (or they are contra-indicated) to reduce the risk of death.
Other treatments with less-certain benefits
Digoxin
Digoxin may be considered in symptomatic patients in sinus rhythm despite treatment with an ACE-I (or ARB), a beta-blocker and an MRA, to reduce the risk of hospitalization (both all-cause and HF-hospitalizations).
N-3 PUFA
An n-3 PUFA[a] preparation may be considered in symptomatic HF patients to reduce the risk of cardiovascular hospitalization and cardiovascular death.

PUFA= polyunsaturated fatty acid

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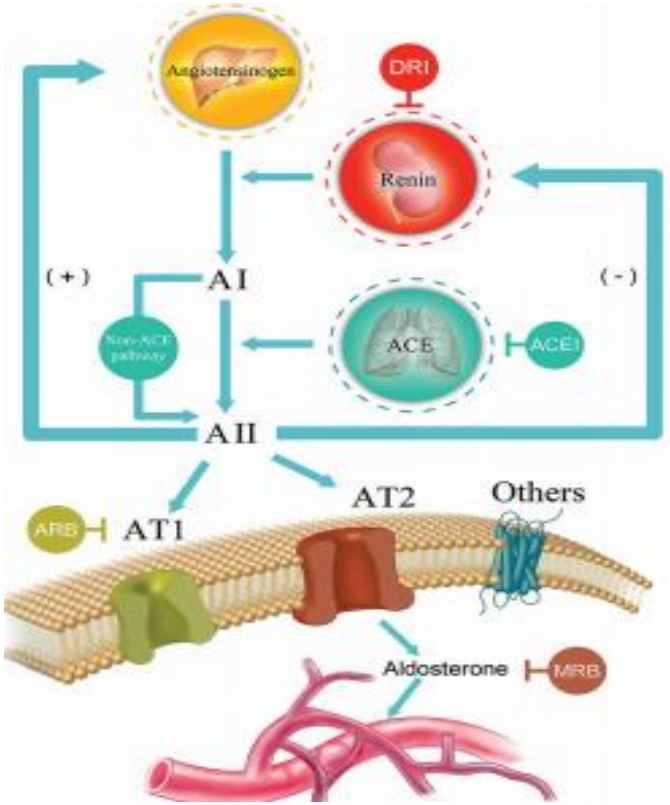
Pharmacological targets in Renin-Angiotensin-Aldosterone System



Evidence-based doses of disease-modifying drugs in key randomized trials in heart failure with reduced ejection fraction (or after myocardial infarction)

	Starting dose (mg)	Target dose (mg)
ACE-I		
Captopril[a]	6.25 *t.i.d.*	50 *t.i.d.*
Enalapril	2.5 *b.i.d.*	10–20 *b.i.d.*
Lisinopril[a]	2.5–5.0 *o.d.*	20–35 *o.d.*
Ramipril	2.5 *o.d.*	10 *o.d.*
Trandolapril[a]	0.5 *o.d.*	4 *o.d.*
Beta-blockers		
Bisoprolol	1.25 *o.d.*	10 *o.d.*
Carvedilol	3.125 *b.i.d.*	25 *b.i.d.*[d]
Metoprolol succinate (CR/XL)	12.5–25 *o.d.*	200 *o.d.*
Nebivolol[c]	1.25 *o.d.*	10 *o.d.*
ARBs		
Candesartan	4–8 *o.d.*	32 *o.d.*
Valsartan	40 *b.i.d.*	160 *b.i.d.*
Losartan[b,c]	50 *o.d.*	150 *o.d.*
MRAs		
Eplerenone	25 *o.d.*	50 *o.d.*
Spironolactone	25 *o.d.*	50 *o.d.*
ARNI		
Sacubitril/valsartan	49/51 *b.i.d.*	97/103 *b.i.d.*

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Recommendations for implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class [a]	Level [b]	Ref [c]
Secondary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status.	I	A	223–226
Primary prevention An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA Class II–III), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than one year with good functional status, and they have:			
• IHD (unless they have had an MI in the prior 40 days – see below).	I	A	149, 156, 227
• DCM.	I	B	156, 157, 227
ICD implantation is not recommended within 40 days of an MI as implantation at this time does not improve prognosis.	III	A	158, 228
ICD therapy is not recommended in patients in NYHA Class IV with severe symptoms refractory to pharmacological therapy unless they are candidates for CRT, a ventricular assist device, or cardiac transplantation.	III	C	229–233
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals and the patient's needs and clinical status may have changed.	IIa	B	234–238
A wearable ICD may be considered for patients with HF who are at risk of sudden cardiac death for a limited period or as a bridge to an implanted device.	IIb	C	239–241

CAD = coronary artery disease; CRT = cardiac resynchronization therapy; DCM = dilated cardiomyopathy; HF = heart failure; ICD = implantable cardioverter-defibrillator; IHD = ischaemic heart disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NYHA = New York Heart Association, OMT = optimal medical therapy.
[a]Class of recommendation.

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Cardiac resynchronization therapy

Recommendations	Class [a]	Level [b]	Ref [c]
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	A	261–272
CRT should be considered for symptomatic patients with HF in sinus rhythm with a QRS duration ≥150 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIa	B	261–272
CRT is recommended for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	I	B	266, 273
CRT may be considered for symptomatic patients with HF in sinus rhythm with a QRS duration of 130–149 msec and non-LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.	IIb	B	266, 273
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class who have an indication for ventricular pacing and high degree AV block in order to reduce morbidity. This includes patients with AF (see Section 10.1).	I	A	274–277
CRT should be considered for patients with LVEF ≤35% in NYHA Class III–IV[d] despite OMT in order to improve symptoms and reduce morbidity and mortality, if they are in AF and have a QRS duration ≥130 msec provided a strategy to ensure bi-ventricular capture is in place or the patient is expected to return to sinus rhythm.	IIa	B	275, 278–281
Patients with HFrEF who have received a conventional pacemaker or an ICD and subsequently develop worsening HF despite OMT and who have a high proportion of RV pacing may be considered for upgrade to CRT. This does not apply to patients with stable HF.	IIb	B	282
CRT is contra-indicated in patients with a QRS duration < 130 msec.	III	A	266, 283–285

AF = atrial fibrillation; AV = atrio-ventricular; CRT = cardiac resynchronization therapy; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; ICD = implantable cardioverter-defibrillator; LBBB = left bundle branch block; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; OMT = optimal medical therapy; QRS = Q, R and S waves (combination of three of the graphical deflections); RV = right ventricular.

[a] commendation.

[b] idence.

[c] (s) supporting recommendations.

[d] nent for patients with end-stage HF who might be managed conservatively rather than with treatments to improve symptoms or prognosis.

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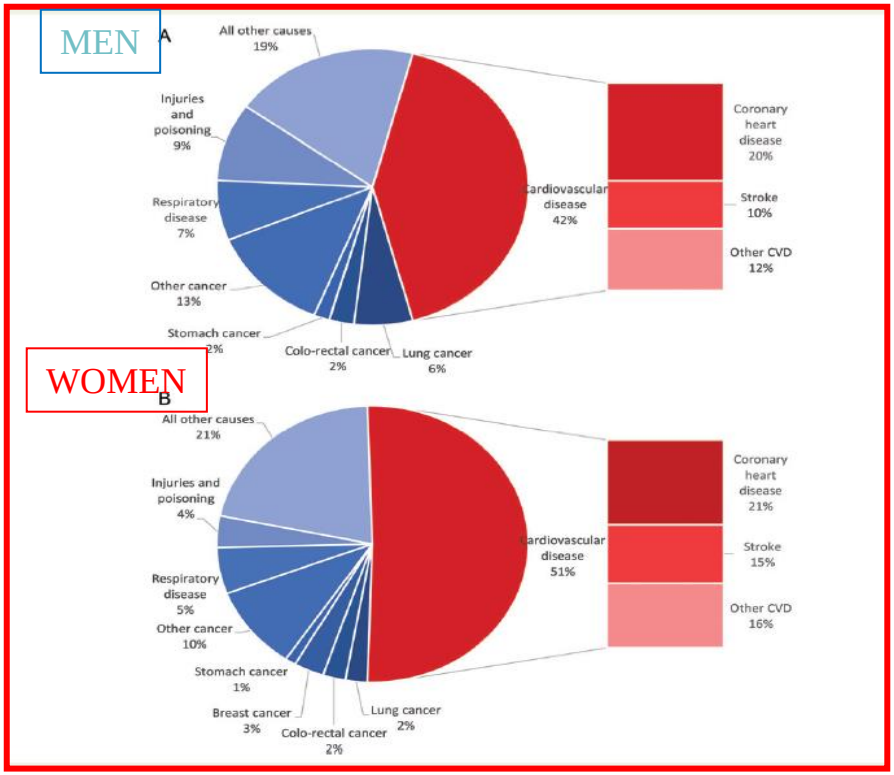
Recommendations for telemonitoring

Recommendations	Class[a]	Level[b]
Non-invasive HTM may be considered for patients with HF in order to reduce the risk of recurrent CV and HF hospitalizations and CV death.[374]	IIb	B
Monitoring of pulmonary artery pressure using a wireless haemodynamic monitoring system may be considered in symptomatic patients with HF in order to improve clinical outcomes.[372]	IIb	B

CV = cardiovascular; HF = heart failure; HTM = home telemonitoring; LVEF = left ventricular ejection fraction.
[a]Class of recommendation.
[b]Level of evidence.

Epidemiology

Heart failure represents a serious public health problem that affects **15 million people in Europe** and **over 1 million in Italy**, with *a fatal outcome in 50% of patients within 5 years* of diagnosis, if not adequately treated. In our country, 10% of patients are over the age of 70 and heart failure is the **main cause of hospitalization in those over 65**.

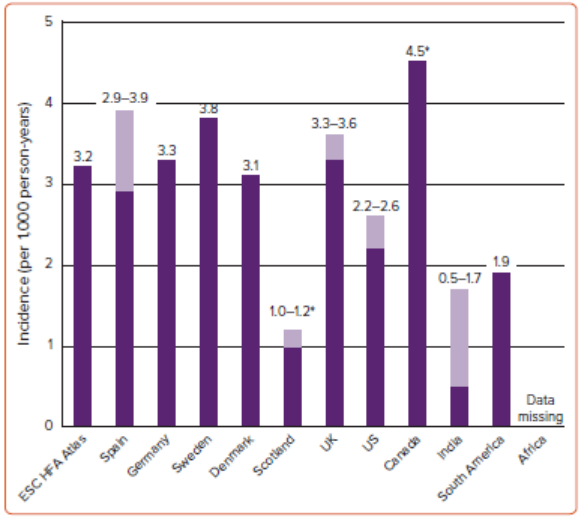


TS Luscher: Epidemiology of cardiovascular disease: the new ESC Atlas and beyond. EHJ 2018

Prevalence/Incidence

In general, however, it is known that the **prevalence increases with increasing age**, ranging from approximately 1% in subjects aged under 55 to **over 10% in those aged over 70.**

Figure 2: Incidence of Heart Failure Worldwide



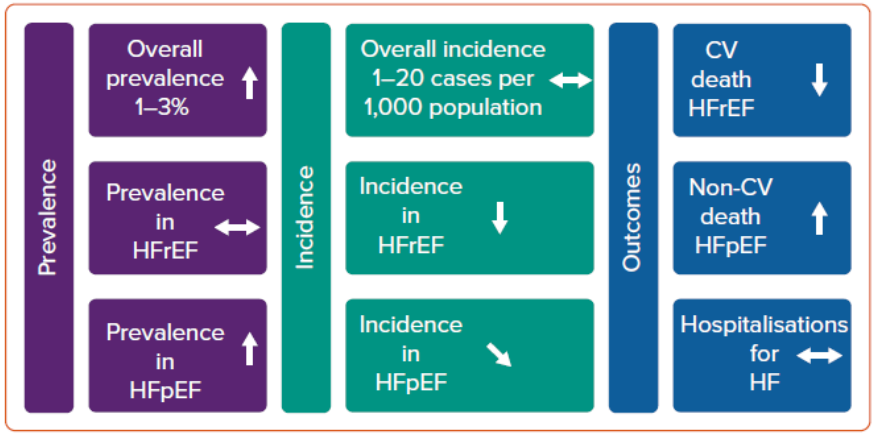
*Per 1,000 population. ESC = European Society of Cardiology; HFA = Heart Failure Association.

HFrEF/HFmrEF/HFpEF

Finally, of all patients with established heart failure, approximately **half** have a reduced ejection fraction (**HFrEF**) while the other **half** is divided between mildly reduced ejection fraction (**HFmrEF**) and preserved ejection fraction (**HFpEF**).

Koh AS, et al. Eur J Heart Fail. 2017; 19(12): 1624-1634

Figure 3: Summary of Trends in Global Burden of Heart Failure



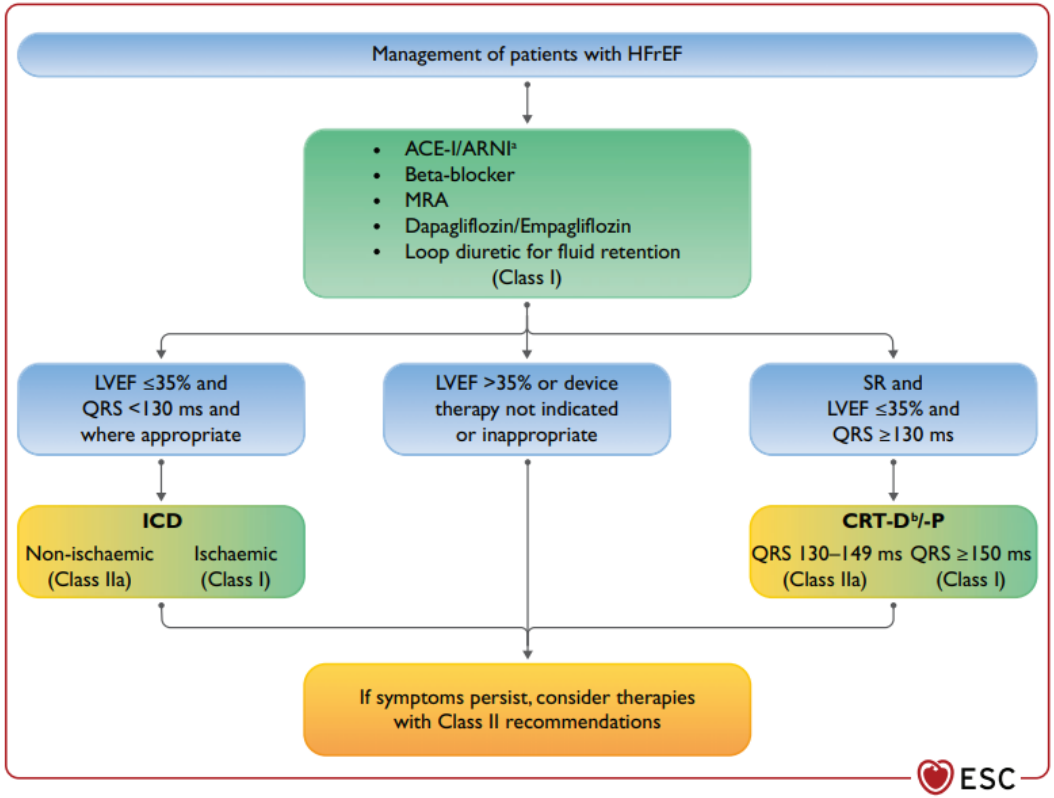
CV = cardiovascular; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction.

Shahim B et al (2023). Global Public Health Burden of Heart Failure: An Updated Review. *Cardiac failure review*, *9*, e11.

ESC 2021 guidelines

DISEASE-MODIFYING THERAPIES

The most relevant innovations in the field of heart failure treatment concern patients with reduced ejection fraction (≤40%), for which a new therapeutic algorithm is proposed



McDonagh TA, et al Eur Heart J 2021; 00: 1-128

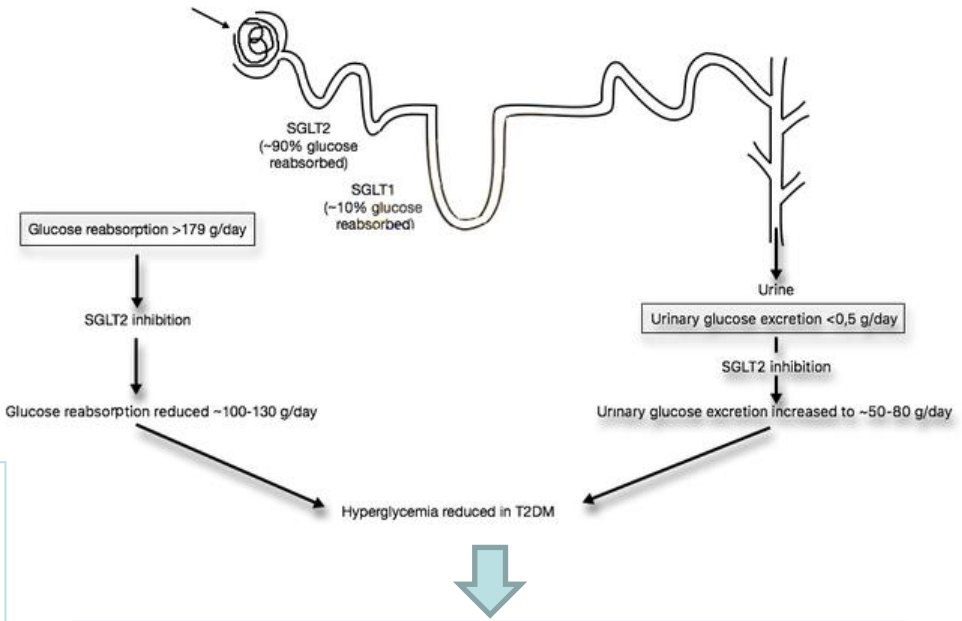
Heart failure: glifozine, the therapeutic revolution that will save the lives of 40 thousand/year chronically ill patients

XVI Congresso Nazionale FIMeG 2023

EMPA-REG OUTCOME NEJM 2015

What was surprising was the large and immediate reduction (6 weeks) in hospitalizations for heart failure in the treated group equal to 35% and, for the first time, a reduction in cardiovascular death (-38%) and from all causes (-32 %) in a diabetic population at high cardiovascular risk.

The early advantage obtained suggested an effect that **went beyond glycemic compensation** but was probably linked to the volume reduction secondary to osmotic diuresis.



significant and large reduction in deterioration of renal function or in the risk of starting dialysis treatment in patients with moderate-severe chronic kidney disease and glomerular filtration rate equal to or greater than 30 ml/min/1.73m2

ESC European Society of Cardiology
European Heart Journal (2021) **42**, 3599–3726
doi:10.1093/eurheartj/ehab368

"Today we have a "game of aces" of drugs,
beta blockers, sacubritil/valsartan,
aldosterone antagonists and glyphozines,
the full implementation of which could
reduce mortality and hospitalizations
by up to 65% compared to 15% with conventional therapies"

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.
[a]Class of recommendation.
[b]Level of evidence.

L'algoritmo per il trattamento dello scompenso cardiaco HFrEF prevede poi, nei casi in cui la terapia farmacologica non risulti sufficiente, l'impiego di **un defibrillatore impiantabile (ICD) o della terapia di resincronizzazione cardiaca (CRT)**.

Recommendations for cardiac resynchronization therapy implantation in patients with heart failure

Recommendations	Class[a]	Level[b]
CRT is recommended for symptomatic patients with HF in SR with a QRS duration ≥150 ms and LBBB QRS morphology and with LVEF ≤35% despite OMT in order to improve symptoms and reduce morbidity and mortality.[205–215]	I	A
CRT rather than RV pacing is recommended for patients with HFrEF regardless of NYHA class or QRS width who have an indication for ventricular pacing for high degree AV block in order to reduce morbidity. This includes patients with AF.[216–219]	I	A

Recommendations for an implantable cardioverter-defibrillator in patients with heart failure

Recommendations	Class[a]	Level[b]
Secondary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia causing haemodynamic instability, and who are expected to survive for >1 year with good functional status, in the absence of reversible causes or unless the ventricular arrhythmia has occurred <48 h after a MI.[162–164]	I	A
Primary prevention		
An ICD is recommended to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of an ischaemic aetiology (unless they have had a MI in the prior 40 days—see below), and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,165]	I	A
An ICD should be considered to reduce the risk of sudden death and all-cause mortality in patients with symptomatic HF (NYHA class II–III) of a non-ischaemic aetiology, and an LVEF ≤35% despite ≥3 months of OMT, provided they are expected to survive substantially longer than 1 year with good functional status.[161,166,167]	IIa	A
Patients should be carefully evaluated by an experienced cardiologist before generator replacement, because management goals, the patient's needs and clinical status may have changed.[168–172]	IIa	B

The 2021 ESC guidelines for the management of heart failure then provide specific recommendations for the treatment of patients with **mildly reduced ejection fraction** (between 41% and 49%). In this case the indications regarding pharmacological treatment include a Class I recommendation for the use of **diuretics** and Class IIa recommendations for the use of ACE inhibitors, ARBs, beta-blockers, MRAs and valsartan/sacubitril to reduce the risk of hospitalization and death.

Finally, **no particular innovations have been introduced with regard to patients with heart failure with preserved ejection fraction**, for which a Class I indication is foreseen for screening and treatment of comorbidities and use of diuretics in case of symptoms.

ESC European Society of Cardiology
European Heart Journal (2023) 00, 1–13
https://doi.org/10.1093/eurheartj/ehad195

2023 Update

Since then, two trials have become available with the **SGLT2 inhibitors**, empagliflozin and dapagliflozin, in patients with **HF and LVEF >40%,** that justify an update in the recommendations for both **HFmrEF** and **HFpEF**.

EMPEROR-Preserved trial	DELIVER trial reported
Anker SD,. *N Engl J Med* 2021;**385**:1451–61	Solomon SD, *Engl J Med* 2022;**387**:1089–98.
• 5988 patients with HF (NYHA class II–IV) • LVEF was >40% • raised plasma concentrations of NT-proBNP	• 6263 patients with HF (NYHA class II–IV) • LVEF was >40% (even if previously<40%) • raised plasma concentrations of NT-proBNP
Empagliflozin 10 mg once daily vs placebo	Dapagliflozin 10 mg once daily vs placebo

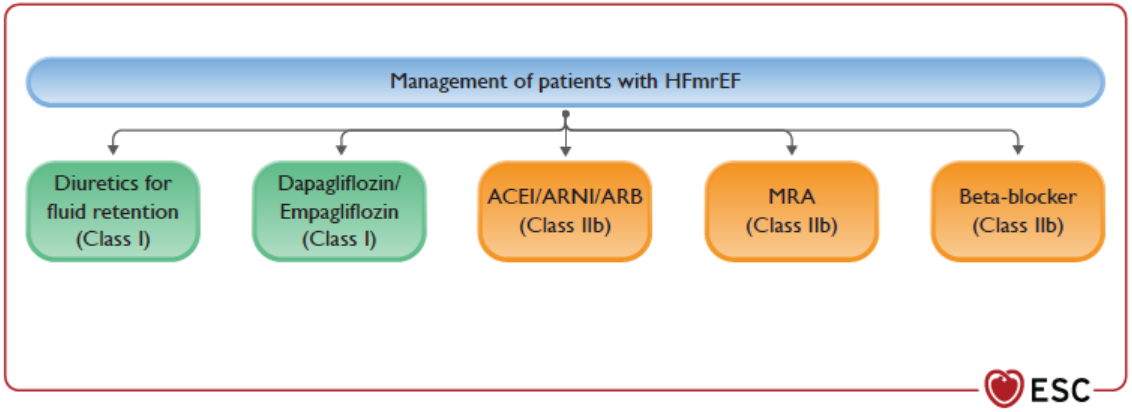
composite of CV death or hospitalization for HF

Empagliflozin reduced the primary endpoint	Dapagliflozin reduced the primary endpoint
The effects were seen in patients with and without type 2 diabetes mellitus (T2DM).8 The majority of patients were on an ACE-I/ARB/ARNI (80%) and beta-blocker (86%) and 37% were on an MRA.	The background use of therapies for concomitant CV disease was high: 77% were on a loop diuretic, 77% were on an ACE-I/ARB/ARNI, 83% were on a beta-blocker, and 43% were on an MRA.

2023 Update: New therapeutic strategies

HFmrEF

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFmrEF to reduce the risk of HF hospitalization or CV death.[c 6,8]	I	A

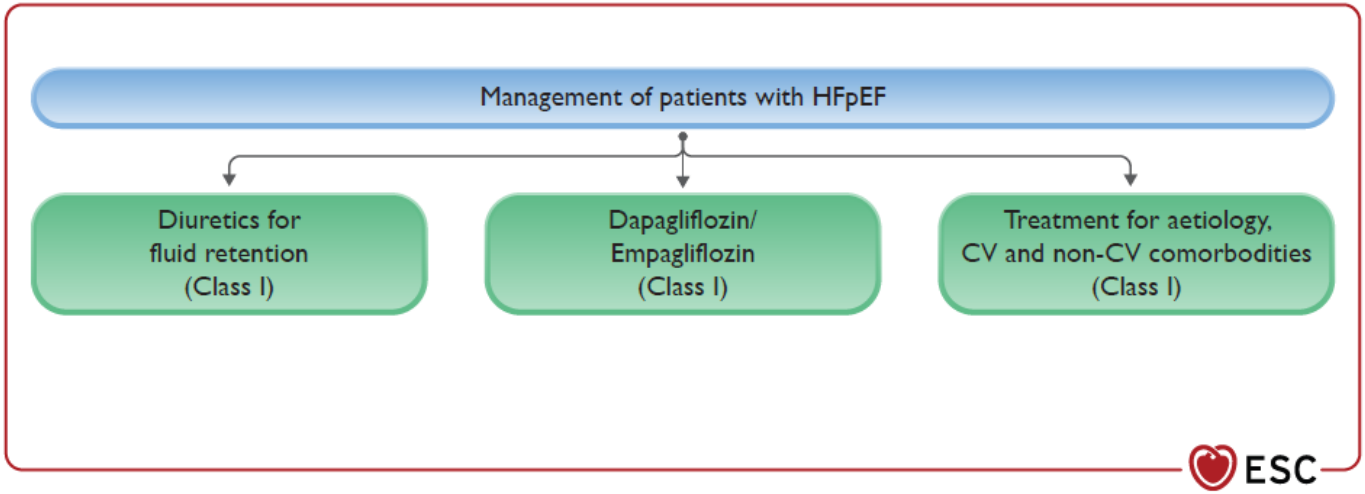


ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

2023 Update: New therapeutic strategies

HFpEF

Recommendation	Class[a]	Level[b]
An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HFpEF to reduce the risk of HF hospitalization or CV death.[c 6,8]	I	A



ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–13
https://doi.org/10.1093/eurheartj/ehad195

ARTICLES
https://doi.org/10.1038/s41591-021-01659-1
nature medicine
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OPEN

The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial

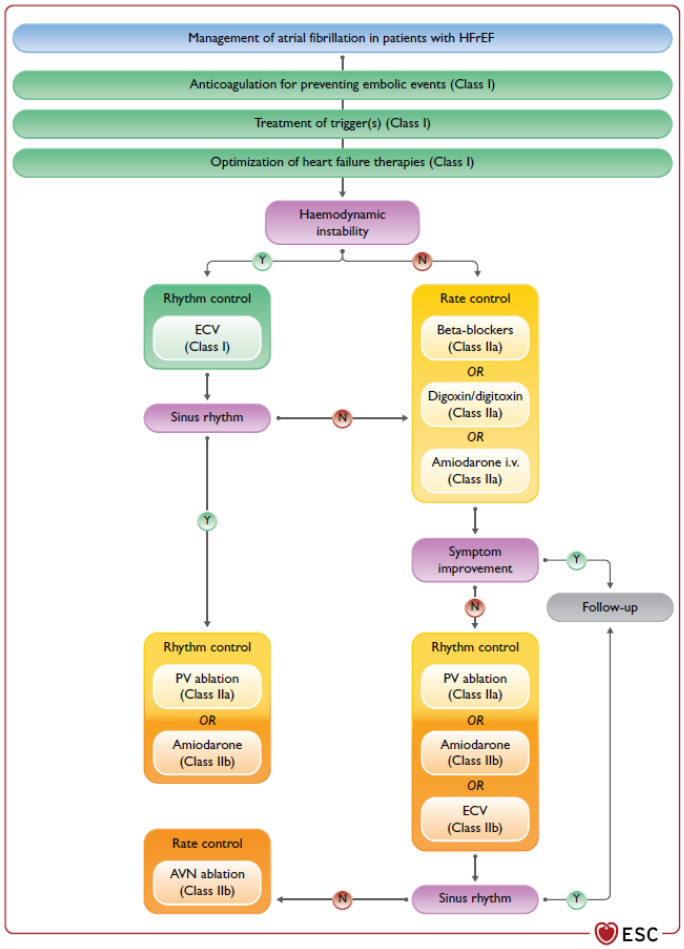
- **Clinical benefit** was observed for both acute de novo and decompensated chronic heart failure and was observed **regardless of ejection fraction or the presence or absence of diabetes**.

- Empagliflozin was well tolerated; serious adverse events were reported in 32.3% and 43.6% of the empagliflozin- and placebo-treated patients, respectively.

- **These findings indicate that initiation of empagliflozin in patients hospitalized for acute heart failure is well tolerated and results in significant clinical benefit in the 90 days after starting treatment.**

Scompenso cardiaco e comorbilità: fibrillazione atriale

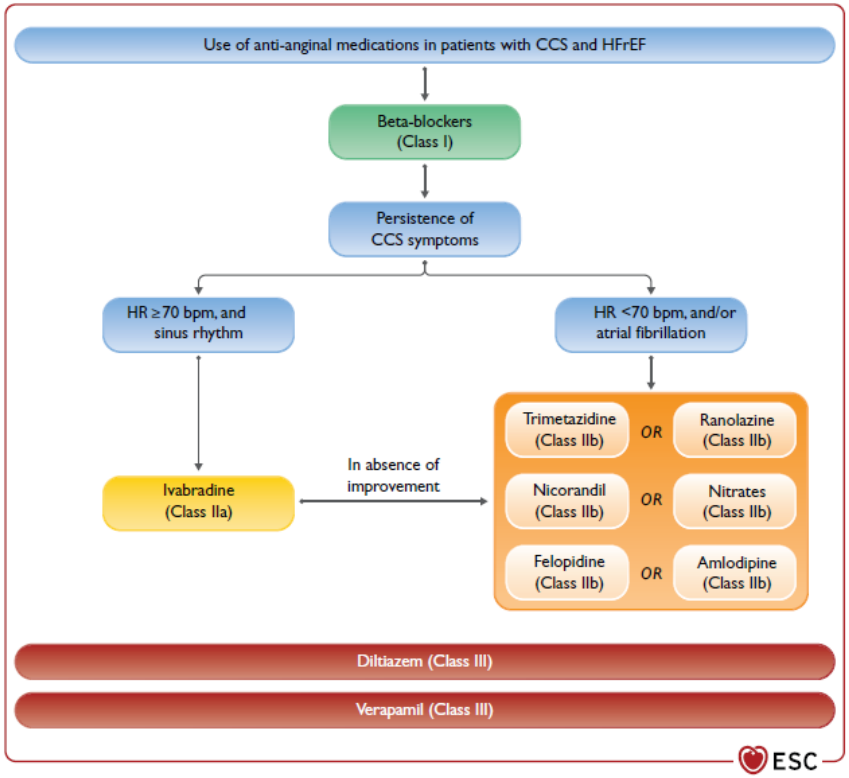
Per quanto riguarda quelli con fibrillazione atriale, ad esempio, diventa di classe I la raccomandazione a **preferire un DOAC rispetto agli antagonisti della vitamina K** nei casi in cui non è presente una moderata o grave stenosi mitralica o una protesi valvolare, mentre passa in classe IIa l'indicazione relativa all'uso dei beta-bloccanti.



McDonagh TA, et al Eur Heart J 2021; 00: 1-128

Scompenso cardiaco e comorbilità: cardiopatia ischemica cronica

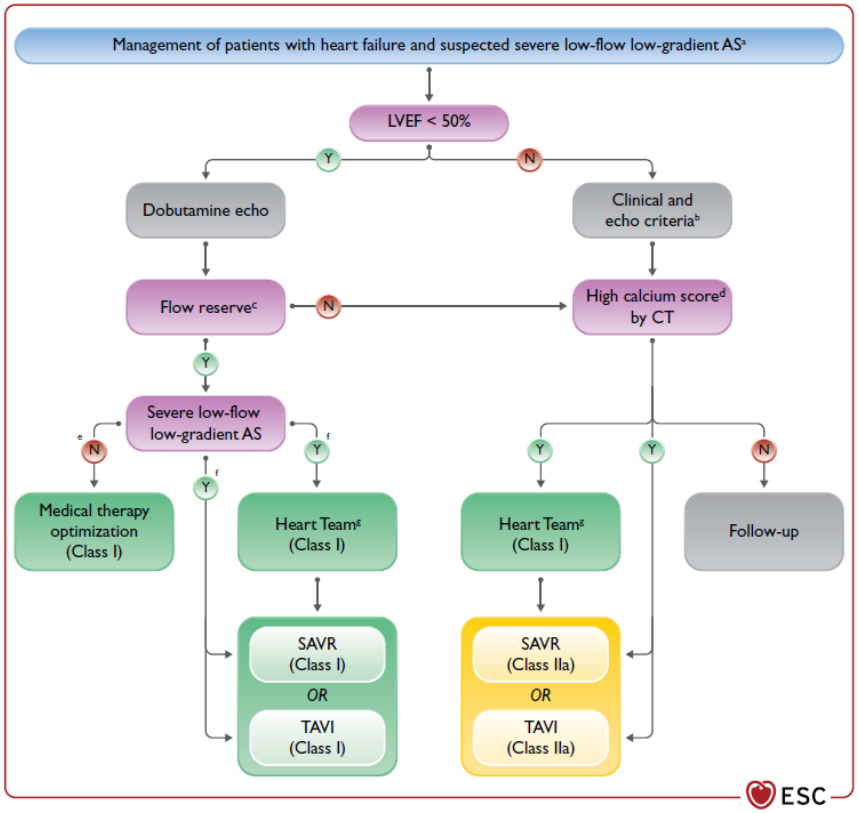
Recommendations	Class[a]	Level[b]
CABG should be considered as the first-choice revascularization strategy, in patients suitable for surgery, especially if they have diabetes and for those with multivessel disease.[581,587,588,590]	IIa	B
Coronary revascularization should be considered to relieve persistent symptoms of angina (or an angina-equivalent) in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, despite OMT including anti-anginal drugs.	IIa	C
In LVAD candidates needing coronary revascularization, CABG should be avoided, if possible.	IIa	C
Coronary revascularization may be considered to improve outcomes in patients with HFrEF, CCS, and coronary anatomy suitable for revascularization, after careful evaluation of the individual risk to benefit ratio, including coronary anatomy (i.e. proximal stenosis >90% of large vessels, stenosis of left main or proximal LAD), comorbidities, life expectancy, and patient's perspectives.	IIb	C
PCI may be considered as an alternative to CABG, based on Heart Team evaluation, considering coronary anatomy, comorbidities, and surgical risk.	IIb	C



In riferimento ai soggetti con scompenso cardiaco e sindromi coronariche croniche, invece, passa dalla classe I alla classe IIa la raccomandazione all'impiego della rivascolarizzazione nei soggetti con angina farmaco-resistente.

McDonagh TA, et al Eur Heart J 2021; 00: 1-128

Scompenso cardiaco e comorbilità: valvulopatia aortica



Per quanto riguarda i pazienti con scompenso cardiaco e valvulopatie, invece, le linee guida 2021 introducono un'**indicazione di Classe I per una procedura TAVI o SAVR nei soggetti con stenosi aortica grave** per ridurre la mortalità e migliorare la sintomatologia. Si raccomanda (Classe I) che la scelta fra TAVI e SAVR venga effettuata **dall'Heart Team** in accordo con le preferenze del paziente e valutazioni relative a età, rischio chirurgico e altri aspetti clinici, anatomici e procedurali.

McDonagh TA, et al Eur Heart J 2021; 00: 1-128

Scompenso cardiaco e comorbilità: anemia ferropriva

Una sezione delle linee guida è poi dedicata alla gestione dei pazienti con scompenso cardiaco e carenza di ferro o anemia. In generale il documento raccomanda (Classe I) di **effettuare uno screening con emocromo completo, concentrazione della ferritina sierica e TSAT per valutare la presenza di queste condizioni in tutti i pazienti con scompenso cardiaco**. L'integrazione con carbossimaltosio ferrico dovrebbe essere invece presa in considerazione (Classe IIa) nei pazienti con scompenso cardiaco sintomatico, recente ospedalizzazione e frazione di eiezione inferiore o uguale al 50% per ridurre il rischio di ospedalizzazioni per scompenso cardiaco.

McDonagh TA, et al Eur Heart J 2021; 00: 1-128

Heart Fail Clin. 2019 Jul;15(3):359-369.

Anemia and Iron Deficiency in Heart Failure
Clinical and Prognostic Role

Damiano Magrì, MD, PhD[a], Fabiana De Martino, MD[b],
Federica Moscucci, MD[c],
Piergiuseppe Agostoni, MD, PhD[b,d,*],
Susanna Sciomer, MD[c]

Scompenso cardiaco e comorbilità: cardiotossicità e amiloidosi cardiaca

Nell'ambito dei pazienti con scompenso cardiaco e cancro le linee guida invece raccomandano (Classe I), in caso di elevato rischio di cardiotossicità, di effettuare una valutazione cardiovascolare prima di programmare un trattamento oncologico, preferibilmente a opera di un cardiologo con esperienza nel settore della cardio-oncologia. Novità, infine, anche per quanto riguarda i pazienti con scompenso cardiaco e amiloidosi, per i quali è stata introdotta una raccomandazione di Classe I all'utilizzo di tafamidis nei soggetti con amiloidosi cardiaca da transtiretina ereditaria (hATTR) e classe NYHA I o II e in quelli con amiloidosi cardiaca da transtiretina wild type (wtATTR) e classe NYHA I o II.

McDonagh TA, et al Eur Heart J 2021; 00: 1-128

Follow up, telemedicina e intelligenza artificiale

CLINICAL INVESTIGATIONS

CLINICAL CARDIOLOGY WILEY

QT and Tpeak-Tend interval variability: Predictive electrical markers of hospital stay length and mortality in acute decompensated heart failure. Preliminary data

Variables	χ^2	Univariable analysis hazard ratio (95% CI)	*p* Values	χ^2	Multivariable analysis hazard ratio (95% CI)	*p* Values
QT mean	-	-	.644	-	-	ns
QT SD	6.97	1.10 (1.03–1.18)	.008	-	-	ns
Te mean	8.56	1.02 (1.01–1.03)	.003	8.56	1.02 (1.01–1.03)	.003
Te SD	5.51	1.12 (1.02–1.23)	.019	-	-	ns
QTVN	-	-	.124	-	-	ns
TeVN	-	-	.508	-	-	ns

Clin Cardiol. 2022;45:1192–1198.

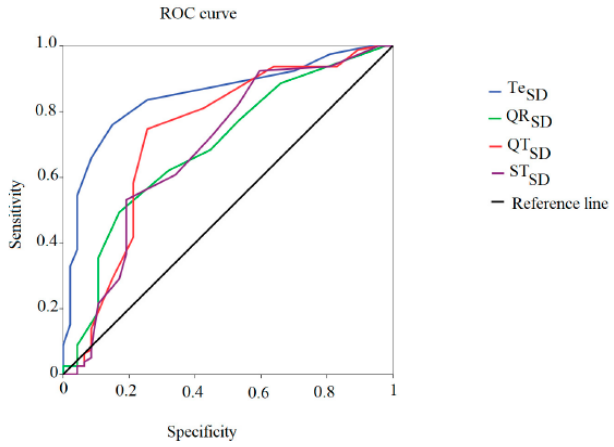
Journal of *Cardiovascular Development and Disease*

MDPI

Article

Electrocardiographic and other Noninvasive Hemodynamic Markers in Decompensated CHF Patients

Gianfranco Piccirillo [1], Federica Moscucci [2,*], Martina Mezzadri [1], Cristina Caltabiano [1], Ilaria Di Diego [1], Myriam Carnovale [1], Andrea Corrao [1], Sara Stefano [1], Claudia Scinicariello [1], Marco Giuffrè [1], Valerio De Santis [1], Susanna Sciomer [1], Pietro Rossi [3] and Damiano Magrì [4]



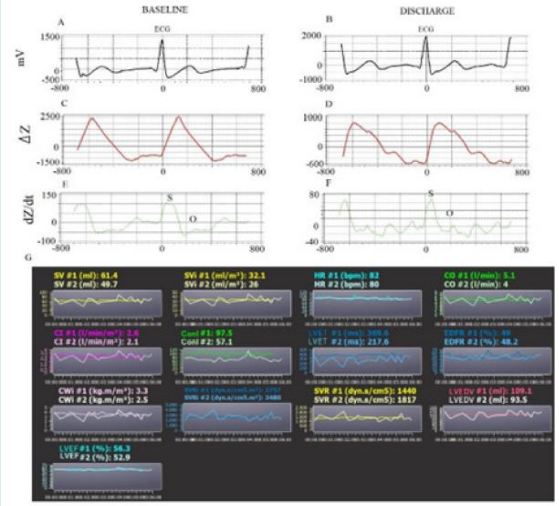
biomedicines

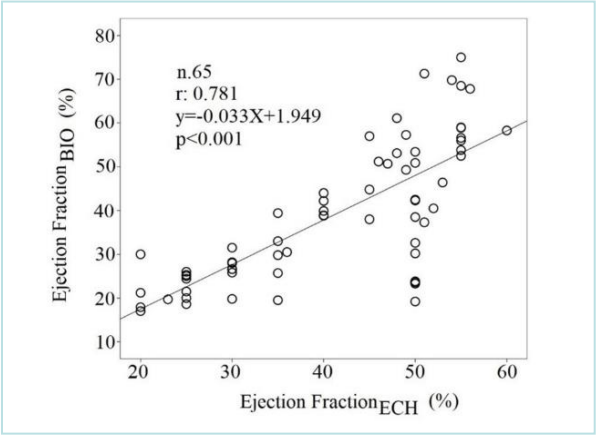
MDPI

Article

Noninvasive Hemodynamic Monitoring in Advanced Heart Failure Patients: New Approach for Target Treatments

Gianfranco Piccirillo [1], Federica Moscucci [1,*], Andrea Corrao [1], Myriam Carnovale [1], Ilaria Di Diego [1], Ilaria Lospinuso [1], Cristina Caltabiano [1], Martina Mezzadri [1], Pietro Rossi [2] and Damiano Magrì [3]





Research article

Clin Ter 2022; 173 (4):356-361 doi: 10.7417/CT.2022.2446

Short-Period Temporal Dispersion Repolarization Markers in Elderly Patients with Decompensated Heart Failure

G. Piccirillo[1], F. Moscucci[2], M. Carnovale[1], A. Corrao[1], I. Di Diego[1], I. Lospinuso[1], C. Caltabiano[1], M. Mezzadri[1], P. Rossi[3], D. Magrì[4]

Table 3. Prediction of Mortality in All Study Patients by Logistic Regression

Variables	Univariable Analysis Odd Ratio (95% CI)	P values	Multivariable Analysis Odd Ratio (95% CI)	P values
QTe SD, ms	1.15 (1.03-1.30)	0.015		ns
Te mean, ms	1.04 (1.01-1.06)	0.002	1.04 (1.02-1.09)	0.004
Te SD, ms	1.15 (1.01-1.31)	0.033		ns
NT-pro BNP	1.00 (1.00-1.00)	0.009	1.00(1.00-1.00)	0.003
LVMI	0.99 (0.98-1.0)	0.030	0.98 (0.96-1.0)	0.037
TRPG	1.04 (1.00-1.08)	0.033		ns

QTeSD: QTend standard deviation; ; Te mean: Tend mean; TeSD: Tend standard deviation; NT-pro-BNP: N-terminal-pro Brain Natriuretic Peptide¸ LVMI: Left Ventricular Mass Index; TRPG: Tricuspid Regurgitation Peak Gradient;

In conclusion, repolarization temporal dispersion markers could be used as clinical tools in decompensated CHF subjects, in particular Te mean could be considered risk factor for mortality, meanwhile TeSD could be used as worsening CHF predictor.

The applicability of this evidence is extremely promising, in particular for telemonitoring in clinical and research fields.

Journal of
Clinical Medicine

MDPI

Article

Sex Differences in Repolarization Markers: Telemonitoring for Chronic Heart Failure Patients

Federica Moscucci [1,*], Susanna Sciomer [2], Silvia Maffei [3], Antonella Meloni [4], Ilaria Lospinuso [2], Myriam Carnovale [2], Andrea Corrao [2], Ilaria Di Diego [2], Cristina Caltabiano [2], Martina Mezzadri [2], Anna Vittoria Mattioli [5], Sabina Gallina [6], Pietro Rossi [7], Damiano Magrì [8] and Gianfranco Piccirillo [2]