HEART FAILURE MANAGEMENT

For General Practitioners

Win Myint Aung, MD, DM, MBA, FRCP, FACP

DISCLOSURE

- None

MMPGA

Knowledge without borders

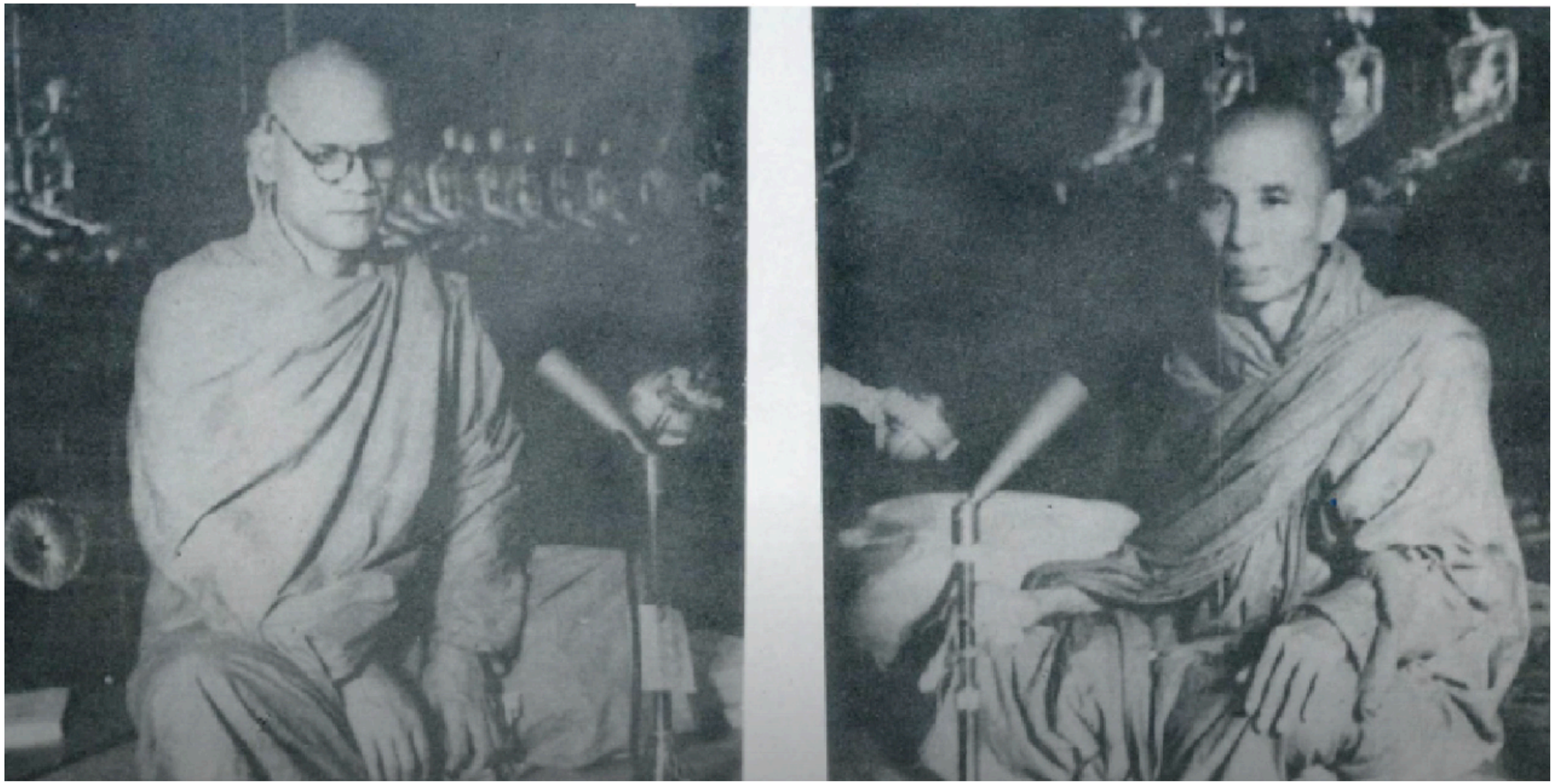
MEDGROW

winaung960

PURPOSE

- Define and classify heart failure
- Pathophysiology
- Medical management strategy
- Device therapy
- New in horizon

Evidence Based Medicine



HEART FAILURE DEFINITION

- An abnormality of cardiac structure or function is responsible for the inability of heart to fill with or eject blood at a rate commensurate with the requirements of the metabolizing tissues. (Harrison's Principle of Internal Medicine)

CLASSIFICATION (NYHA)

- Class I - No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs etc.
- Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.
- Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20—100 m).Comfortable only at rest.
- Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

CLASSIFICATION (ACC/AHA)

- **Stage A:** Patients at risk for heart failure who have not yet developed structural heart changes (i.e. those with HTN, diabetes, those with coronary disease without prior infarct)
- **Stage B:** Patients with structural heart disease (i.e. reduced ejection fraction, left ventricular hypertrophy, chamber enlargement) who have not yet developed symptoms of heart failure
- **Stage C:** Patients who have developed clinical heart failure
- **Stage D:** Patients with refractory heart failure requiring advanced intervention (i.e. biventricular pacemakers, left ventricular assist device, transplantation)

At Risk for Heart Failure

Heart Failure

STAGE A
At high risk for HF but without structural heart disease or symptoms of HF

e.g., Patients with:
- HTN
- Atherosclerotic disease
- DM
- Obesity
- Metabolic syndrome

or

Patients
- Using cardiotoxins
- With family history of cardiomyopathy

THERAPY

Goals
- Heart healthy lifestyle
- Prevent vascular, coronary disease
- Prevent LV structural abnormalities

Drugs
- ACEI or ARB in appropriate patients for vascular disease or DM
- Statins as appropriate

Structural heart disease

STAGE B
Structural heart disease but without signs or symptoms of HF

e.g., Patients with:
- Previous MI
- LV remodeling including LVH and low EF
- Asymptomatic valvular disease

THERAPY

Goals
- Prevent HF symptoms
- Prevent further cardiac remodeling

Drugs
- ACEI or ARB as appropriate
- Beta blockers as appropriate

In selected patients
- ICD
- Revascularization or valvular surgery as appropriate

Development of symptoms of HF

STAGE C
Structural heart disease with prior or current symptoms of HF

e.g., Patients with:
- Known structural heart disease and
- HF signs and symptoms

HF*p*EF

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Prevent hospitalization
- Prevent mortality

Strategies
- Identification of comorbidities

Treatment
- Diuresis to relieve symptoms of congestion
- Follow guideline driven indications for comorbidities, e.g., HTN, AF, CAD, DM

HF*r*EF

THERAPY

Goals
- Control symptoms
- Patient education
- Prevent hospitalization
- Prevent mortality

Drugs for routine use
- Diuretics for fluid retention
- ACEI or ARB
- Beta blockers
- Aldosterone antagonists

Drugs for use in selected patients
- Hydralazine /isosorbide dinitrate
- ACEI and ARB
- Digitalis

In selected patients
- CRT
- ICD
- Revascularization or valvular surgery as appropriate

Refractory symptoms of HF at rest, despite GDMT

STAGE D
Refractory HF

e.g., Patients with:
- Marked HF symptoms at rest
- Recurrent hospitalizations despile GDMT

THERAPY

Goals
- Control symptoms
- Improve HRQOL
- Reduce hospital readmissions
- Establish patient's end - of-life goals

Options
- Advanced care measures
- Heart transplant
- Chronic inotropes
- Temporary or permanent MCS
- Experimental surgery or drugs
- Palliative care and hospice
- ICD deactivation

FORMS OF HEART FAILURE

- Systolic vs Diastolic
- Low output vs High output
- Acute vs Chronic
- Right Sided vs Left Sided
- Backward vs Forward

What is common cause of congestive heart failure?

- Dilated cardiomyopathy
- valvular heart disease
- Ischemic Heart Disease
- Hypertensive Heart Disease
- None of the above

Total Results: 0

What is common cause of congestive heart failure?

Dilated cardiomyopathy

valvular heart disease

Ischemic Heart Disease

Hypertensive Heart Disease

None of the above

What is common cause of congestive heart failure?

Dilated cardiomyopathy

valvular heart disease

Ischemic Heart Disease

Hypertensive Heart Disease

None of the above

CAUSES OF HEART FAILURE

- Ischemic heart disease – 40 percent
- Dilated cardiomyopathy – 32 percent
- Primary valvular heart disease – 12 percent
- Hypertensive heart disease – 11 percent
- Other – 5 percent (Toxins, infiltrative, inflammatory, pericardium, congenital, arrythmia induced)

Am Heart J. 2002;143(3):398

FACTORS PRECIPITATING CHF

- Non-adherence with medication regimen, sodium and/or fluid restriction
- Acute myocardial ischemia
- Uncorrected high blood pressure
- AF and other arrhythmias
- Recent addition of negative inotropic drugs (e.g., verapamil, nifedipine, diltiazem, beta blockers)
- Pulmonary embolus
- Initiation of drugs that increase salt retention (e.g., steroids, thiazolidinediones, NSAIDs)
- Excessive alcohol or illicit drug use
- Endocrine abnormalities (e.g., diabetes mellitus, hyperthyroidism, hypothyroidism)
- Concurrent infections (e.g., pneumonia, viral illnesses)
- Additional acute cardiovascular disorders (e.g., valve disease endocarditis, myopericarditis, aortic dissection)

The following laboratory test is useful in doagnosis of CHF.

- Basic metabolic panel
- Complete blood count
- urine analysis
- N-terminal pro-BNP (NT-porBNP)
- None of the above

Total Results: 0

The following laboratory test is useful in doagnosis of CHF.

Basic metabolic panel

Complete blood count

urine analysis

N-terminal pro-BNP (NT-porBNP)

None of the above

The following laboratory test is useful in doagnosis of CHF.

Basic metabolic panel

Complete blood count

urine analysis

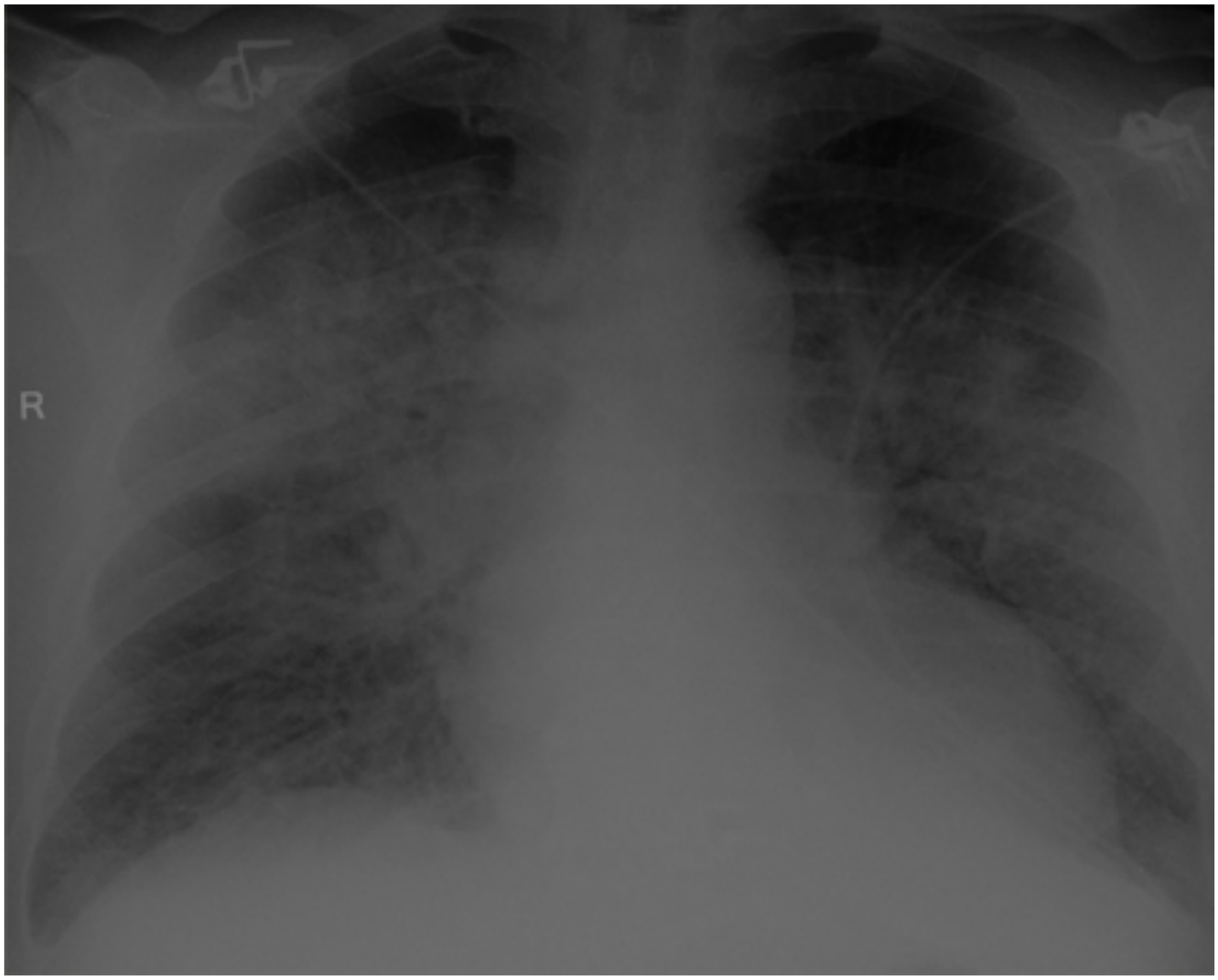
N-terminal pro-BNP (NT-porBNP)

None of the above

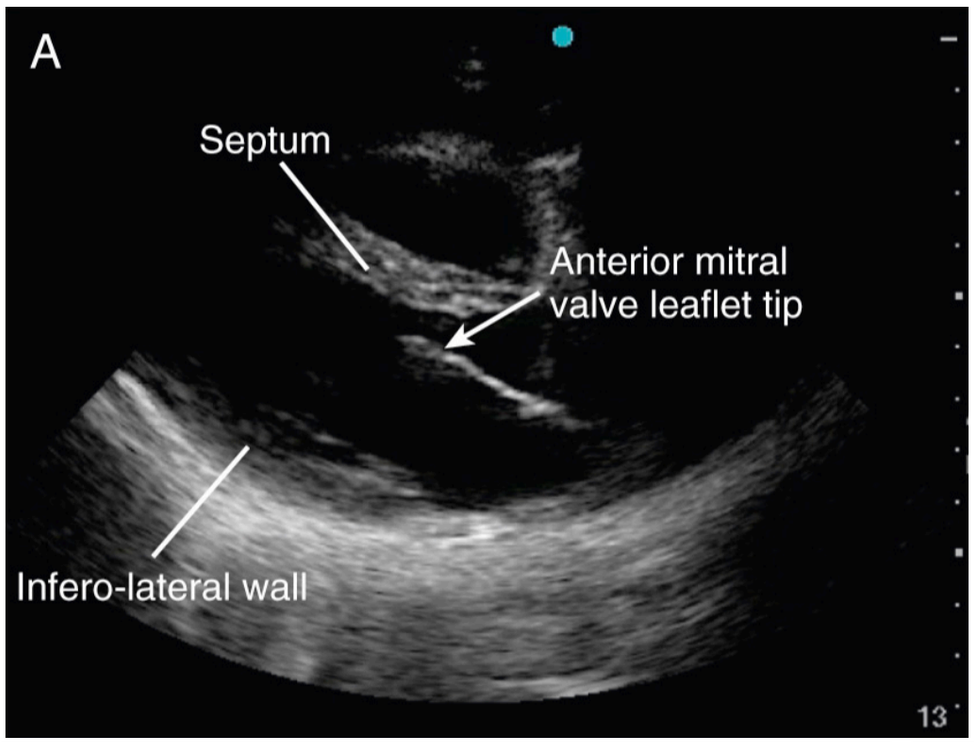
DIAGNOSIS

- Symptoms: SOB on exertion and rest, orthopnoea, PND, leg swelling.
- Signs: JVP, S3, basal crepitations, dependent edema
- Lab: B-type natriuretic peptide (BNP) >35 pg/ml or N-terminal pro-BNP (NT-porBNP) >125 pg/ml
- CXR
- TTE is most useful and widely available.

CXR

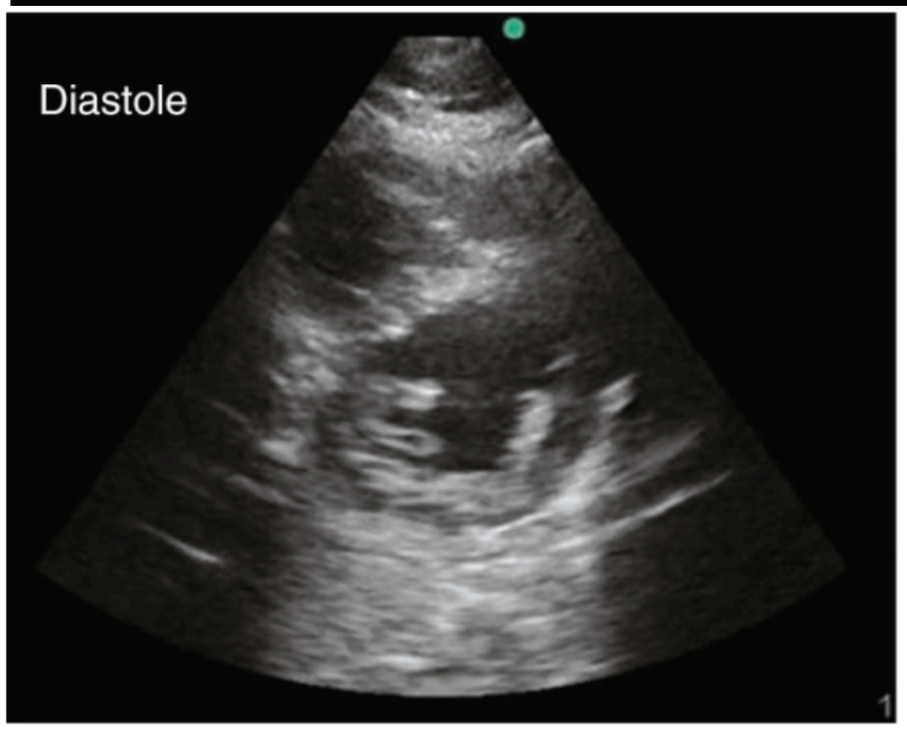


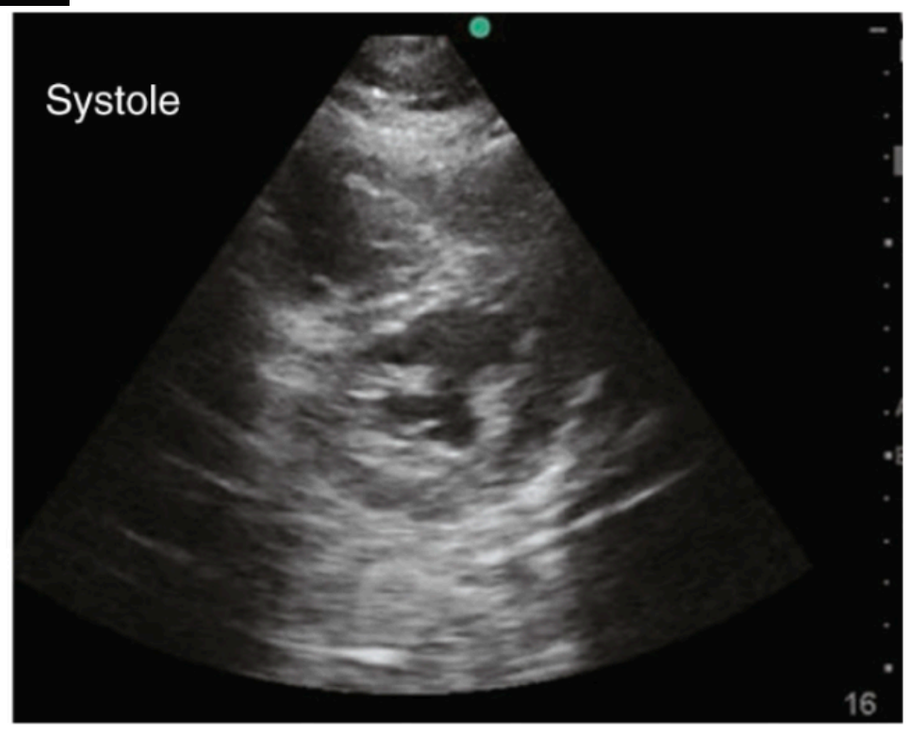
TTE



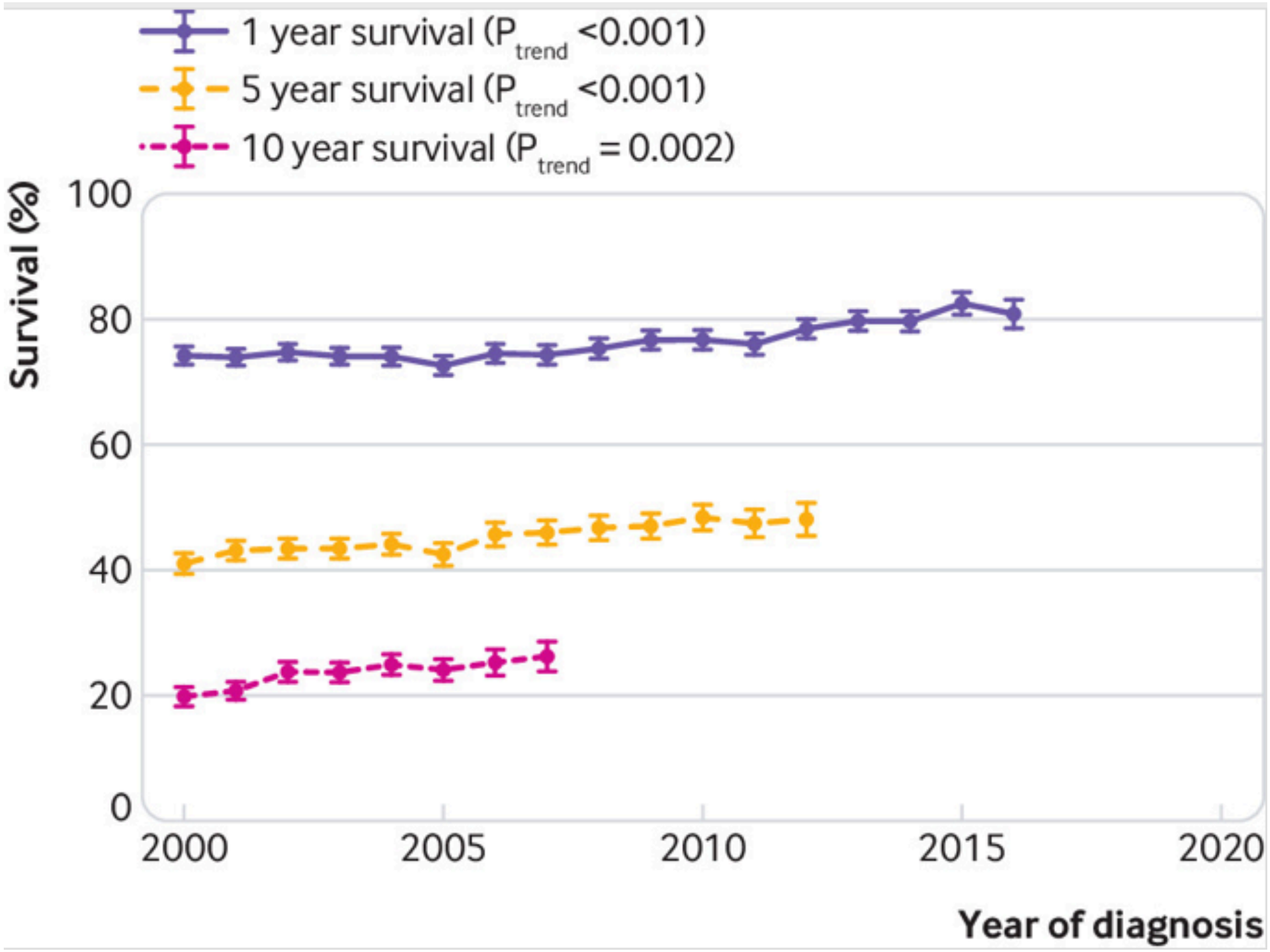
Parasternal long Axis View to assess movement of anterior leaflet of mitral valve during early diastole.

Parasternal shot axis view to access global and regional wall motion abnormality.





HEART FAILURE SURVIVAL TRENDS



BMJ 2019; 364 :l223

Which drug showed no improvement in overall mortality in management of CHF?

- Lisinopril
- Carvidelol
- Furosemide
- Spironolactone
- Sacubitril/Valsartan

Total Results: 0

Which drug showed no improvement in overall mortality in management of CHF?

Lisinopril

Carvidelol

Furosemide

Spironolactone

Sacubitril/Valsartan

Which drug showed no improvement in overall mortality in management of CHF?

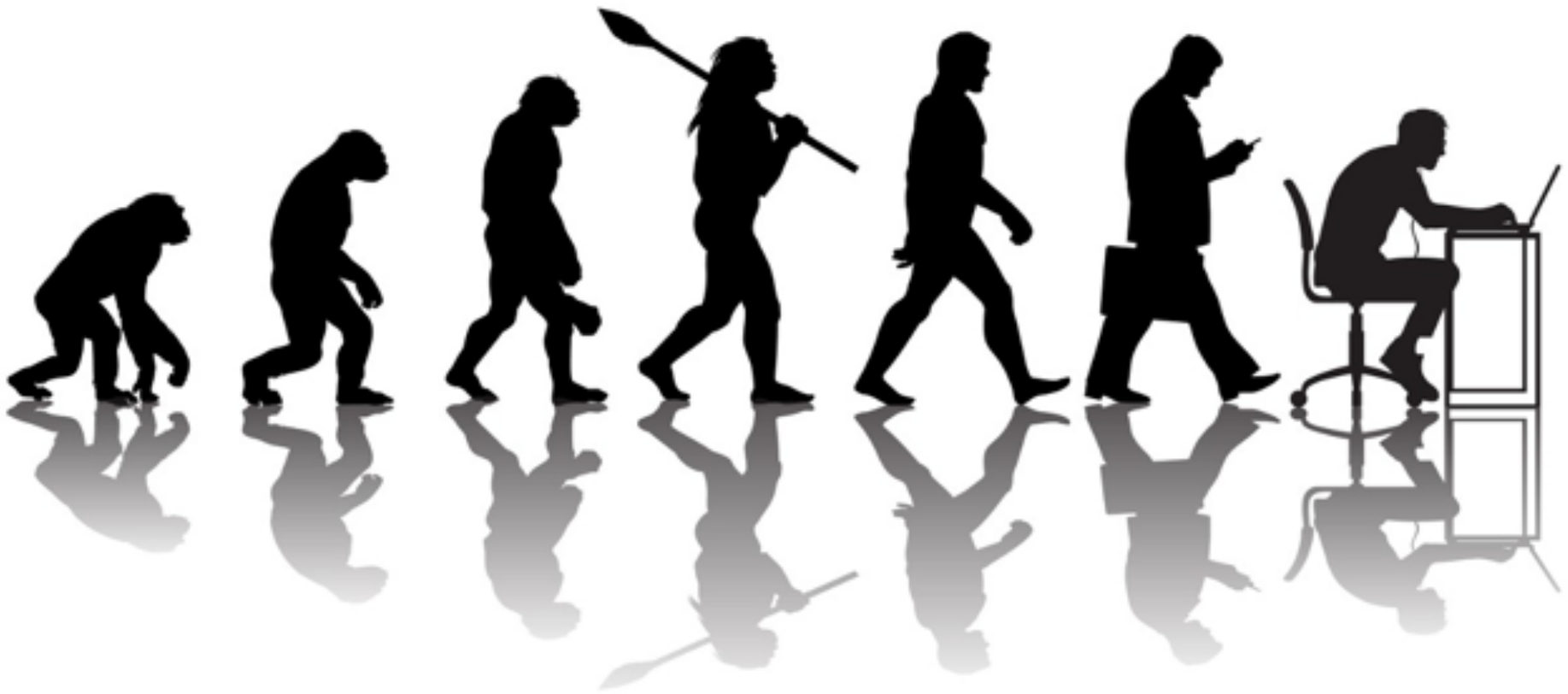
Lisinopril

Carvidelol

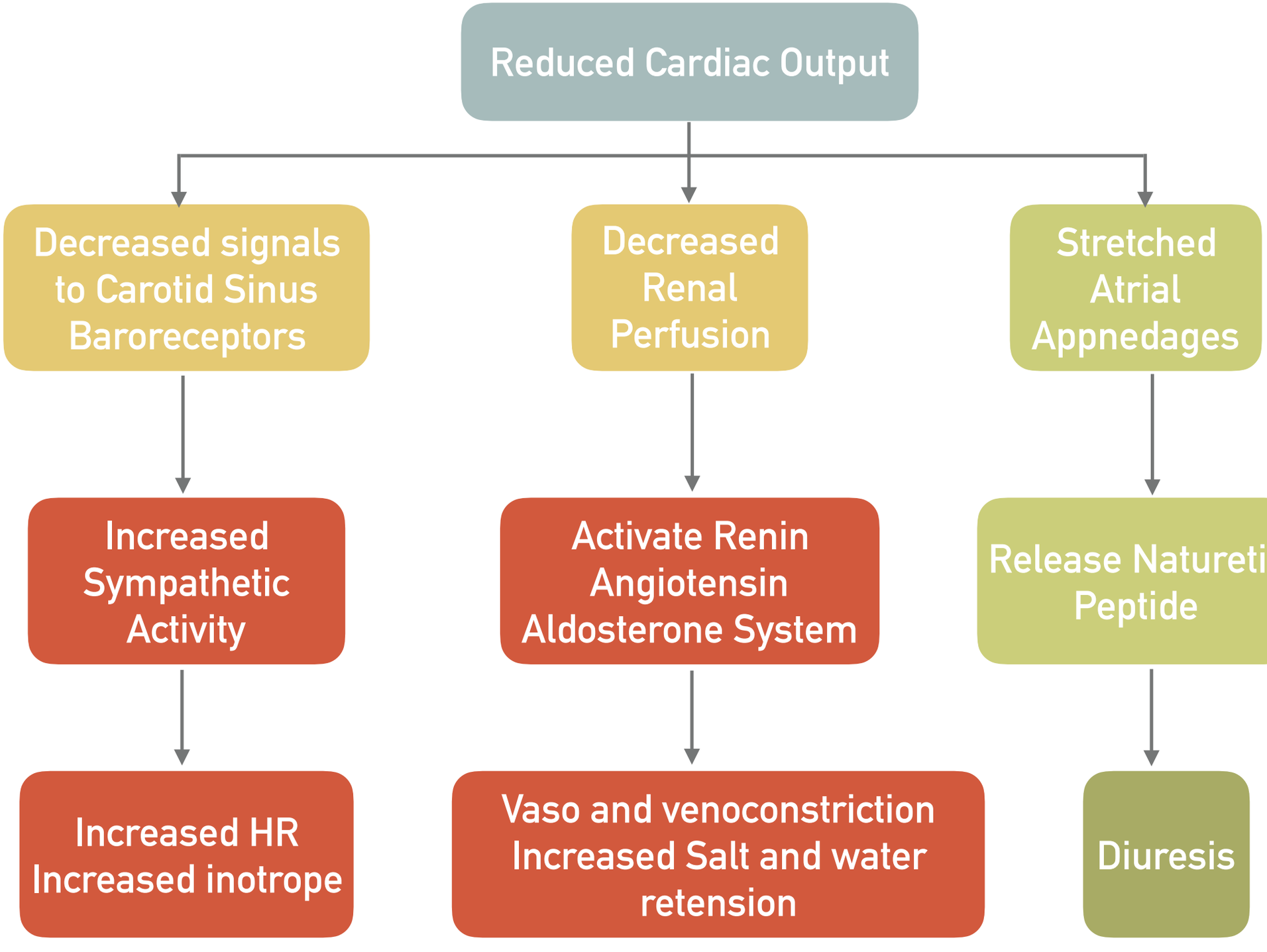
Furosemide

Spironolactone

Sacubitril/Valsartan



PATHOPHYSIOLOGY



DIG STUDY

- In the main trial, patients with left ventricular ejection fractions of 0.45 or less were randomly assigned to digoxin (3397 patients) or placebo (3403 patients) in addition to diuretics and angiotensin-converting–enzyme inhibitors (median dose of digoxin, 0.25 mg per day; average follow-up, 37 months).
- There were 1181 deaths (34.8 percent) with digoxin and 1194 deaths (35.1 percent) with placebo (risk ratio when digoxin was compared with placebo, 0.99; 95 percent confidence interval, 0.91 to 1.07; P = 0.80)
- There were 6 percent fewer hospitalizations overall in that group than in the placebo group, and fewer patients were hospitalized for worsening heart failure (26.8 percent vs. 34.7 percent; risk ratio, 0.72; 95 percent confidence interval, 0.66 to 0.79; P<0.001).

N Engl J Med 1997; 336:525-533

DIG STUDY LESSON LEARNED

- Digoxin did not reduce overall mortality, but it reduced the rate of hospitalization both overall and for worsening heart failure.
- May consider for heart failure associated with tachyarrythmia
- Narrow Therapeutic range, crucial to monitor the drug level especially for elder population and patient with impaired renal function

N Engl J Med 1997; 336:525-533

V-HEFT

- randomized 642 patients with symptomatic chronic compensated systolic heart failure to combination isosorbide dinitrate (ISDN)/hydralazine, prazosin, or placebo. At a mean follow-up of 2.3 years
- The cumulative mortality rates at two years were 25.6 percent in the hydralazine–isosorbide dinitrate group and 34.3 percent in the placebo group; at three years, the mortality rate was 36.2 percent versus 46.9 percent.
- Left ventricular ejection fraction (measured sequentially) rose significantly at eight weeks and at one year in the group treated with hydralazine and isosorbide dinitrate

N Engl J Med 1986; 314:1547–52.

V-HEFT LESSON LEARNED

- Dose: combination of hydralazine (300 mg per day) and isosorbide dinitrate (160 mg per day)
- Recommend all patients with current or previous symptomatic HFrEF who can't tolerate ACE-inhibitor or ARB therapy (AHA/ACCF Heart Failure Guidelines, 2013)
- Recommended for African-American subgroup with NYHA III-IV

ACEI

- Enalapril (2.5 to 40 mg per day) on the prognosis of severe congestive heart failure (New York Heart Association [NYHA] functional class IV), we randomly assigned 253 patients in a double-blind study to receive either placebo (n = 126) or enalapril (n = 127)
- The crude mortality at the end of six months (primary end point) was 26 percent in the enalapril group and 44 percent in the placebo group — a reduction of 40 percent (P = 0.002). Mortality was reduced by 31 percent at one year (P = 0.001).

N Engl J Med 1987; 316:1429–35

ACEI LESSONS LEARNED

- Several other studies; SOLVED, SAVE, AIRE; using different ACEI (Captopril, Ramipril, Lisinopril) produced same out come—> class effect
- Improved mortality correlate well with the doses used; increase the dose in 1-2 weeks intervals
- Abrupt withdrawal of treatment with an ACE inhibitor can lead to clinical deterioration and should be avoided.

ARB STUDIES

Study	Drug	Outcome	Recommendation
ELITE II	Losartan (50) vs Captopril	No significant difference	Good alternative, benefit higher with 150 mg
Val-HeFT	ACEi + Valsartan (320)	Add Valsartan on preexisting CHF Rx has added benefit	Added benefit
CHARM (added/ Alternative)	Candersartan	significantly reduces all-cause mortality, cardiovascular death, and heart failure hospitalizations	Alternative/ Added benefit
RESOLVED	Candesartan and/or Enalpril	Candesartan is well tolerated and equally effective	Combination is safe/Good alternative

ARB LESSON LEARNED

- ARB is first line “reasonable alternative”in patient not tolerated to ACEI
- ACEI+ARB may have potential benefits for patient who are not tolerated to aldosterone antagonist
- Routine combined use of an ACE inhibitor, ARB, and aldosterone antagonist is potentially harmful

BETA BLOCKERS

Study	Drug	Result	Recommendation
CIBIS	Bisoprolol 1.25 -10 mg	Hazard ratio 0.66	First line therapy
CAPRICON	Carvedilol 37 mg	35% Decrease in death	First line therapy
MERIT-HF	Metoprolol Succinate (12.5 - 200 mg)	34% reduction in death	First line therapy

LESSON LEARNED

- Addition of BB on patient with ACEI showed greater reduction in mortality
- Started low dose and titrated up to adequate beta-blockage
- Should be use in caution in patient with reactive airway disease or asymptomatic bradycardia
- Abrupt withdrawal will do harm

ALDOSTERONE RECEPTOR ANTAGONIST

Study	Drugs	Outcome	Recommendation
RALES	Spironolactone 12.5-25 mg	35% RR reduction of death and hospitalization	Patient with EF<35%, DM, <40% CAD
EMPHASIS-HF	Eplerenone 25-50 mg		Patient with EF<35%, DM, <40% CAD

ALDOSTERONE RECEPTOR ANTAGONIST LESSONS LEARNED

- Start low dose and titrated up; alternate day dose for poor renal function (eGFR 30-49)
- K supplement should be DC; K should be monitored
- Avoid in patient with hyperkalemia

MAGNITUDE OF BENEFIT

Guideline Directed Medical Therapy	RR Reduction in mortality (%)	NNT for mortality Reduction	RR Reduction in HF Hospitalization
ACEI/ARB	17	26	31
BB	34	9	41
Aldosterone Antagonist	30	6	35
Hydralazine +Nitrate	43	7	33

OTHER DRUGS

- Diuresis (recommended in patients with HFrEF with fluid retention)
- Anticoagulation (not beneficial unless patient has Afib)
- Statin (not beneficial unless CAD)
- n-3 polyunsaturated fatty acids AKA Omega-3 FA(may be beneficial)

HARMFUL THERAPY

- NSAIDs
- Hormonal Therapy
- Thiazolidinedione
- Long-term use of an infusion of a positive inotropic drug is not recommended and may be harmful except as palliation

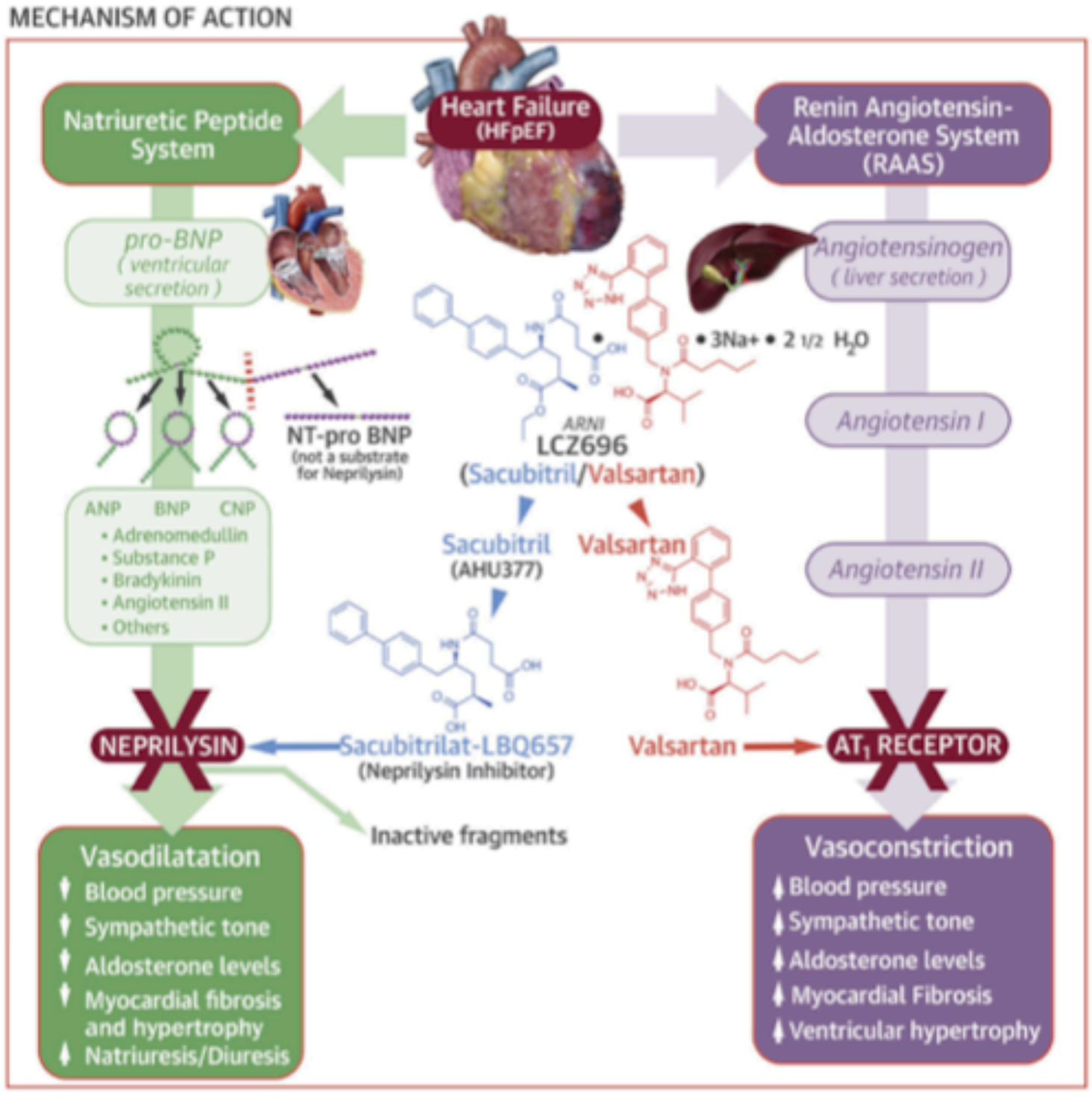
NEWER THERAPY

- PARADIGM-HF Trial: In this double-blind trial, we randomly assigned 8442 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive either **sacubitril**(neprilysin inhibitor) + **valsartan**(at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily)

- A total of 711 patients (17.0%) receiving **sacubitril**+ **valsartan** and 835 patients (19.8%) receiving enalapril died (hazard ratio for death from any cause, 0.84; 95% CI, 0.76 to 0.93; P<0.001); of these patients, 558 (13.3%) and 693 (16.5%), respectively, died from cardiovascular causes (hazard ratio, 0.80; 95% CI, 0.71 to 0.89; P<0.001). As compared with enalapril, **sacubitril**+ **valsartan** also reduced the risk of hospitalization for heart failure by 21% (P<0.001) and decreased the symptoms and physical limitations of heart failure (P=0.001).

N Engl J Med 2014; 371:993-1004

MECHANISM


MECHANISM OF ACTION
Natriuretic Peptide System
Heart Failure (HFpEF)
Renin Angiotensin-Aldosterone System (RAAS)
pro-BNP (ventricular secretion)
Angiotensinogen (liver secretion)
• 3Na+ • 2 1/2 H2O
NT-pro BNP (not a substrate for Neprilysin)
ARNI
LCZ696
(Sacubitril/Valsartan)
Angiotensin I
ANP BNP CNP
• Adrenomedullin
• Substance P
• Bradykinin
• Angiotensin II
• Others
Sacubitril (AHU377)
Valsartan
Angiotensin II
NEPRILYSIN
Sacubitrilat-LBQ657
(Neprilysin Inhibitor)
Valsartan
AT1 RECEPTOR
Inactive fragments
Vasodilatation
Blood pressure
Sympathetic tone
Aldosterone levels
Myocardial fibrosis and hypertrophy
Natriuresis/Diuresis
Vasoconstriction
Blood pressure
Sympathetic tone
Aldosterone levels
Myocardial Fibrosis
Ventricular hypertrophy

NEWER THERAPY

- BEAUTIFUL trial: a multi-center, randomized, double-blinded, placebo-controlled study of 10,917 patients to assess the mortality–morbidity benefits of **ivabradine** use in patients with coronary artery disease (CAD) and left ventricular systolic dysfunction. A total of 5479 patients were randomized into a group receiving 5 mg **ivabradine** (uptitrating to 7.5 mg twice per day), and 5438 to the placebo group and followed up for 12–35 months (median 19 months). HR at least 70 bpm (5392 patients),
- **ivabradine** appeared to reduce admission for acute MI by 36% (fatal and nonfatal; $p = 0.001$); reduce composite admission for acute MI or unstable angina by 22% ($p = 0.023$); and additionally to reduce coronary revascularization by 30% ($p = 0.016$).
- SHIFT: improved overall Quality of life

IVABRADINE RECOMMENDATION

- ESC: in symptomatic patients (NYHA category II–IV) with severe left ventricular systolic impairment (EF ≤ 35%), in sinus rhythm with resting heart rate at least 70 bpm, in spite of treatment with an evidence-based dose of a β blocker (or maximally tolerated dose below that), ACEi (or ARB) and an MRA.
- unable to tolerate, or have contraindications, to β blockers, again in conjunction with an ACEi (or ARB) and an MRA
- as an antianginal drug in suitable patients with HFrEF (sinus rhythm with HR at least 70 bpm) with symptomatic stable angina pectoris.

NEWER THERAPY

- 3730 patients with class II, III, or IV heart failure and an ejection fraction of 40% or less to receive empagliflozin (10 mg once daily) or placebo, in addition to recommended therapy. The primary outcome was a composite of cardiovascular death or hospitalization for worsening heart failure.

- During a median of 16 months, a primary outcome event occurred in 361 of 1863 patients (19.4%) in the empagliflozin group and in 462 of 1867 patients (24.7%) in the placebo group (hazard ratio for cardiovascular death or hospitalization for heart failure, 0.75; 95% confidence interval [CI], 0.65 to 0.86; P<0.001).

- The effect of empagliflozin on the primary outcome was consistent in patients regardless of the presence or absence of diabetes.

N Engl J Med 2020; 383:1413-1424

EMPAGLIFLOZIN RECOMMENDATION

- Empagliflozin has a lower risk of cardiovascular death or hospitalization for heart failure than those in the placebo group, regardless of the presence or absence of diabetes.
- Mechanism of action is yet to be defined. Antihypertensive, glycosuric, antioxidant, sub-receptor regulation and anti insulin were hypothesized.

The followinf treatment has been proven to be beneficial in treating patient with HFpEF.

- ACEI
- ARB
- Betablocker
- Dobutamine
- None of the above

Total Results: 0

The followinf treatment has been proven to be beneficial in treating patient with HFpEF.

ACEI

ARB

Betablocker

Dobutamine

None of the above

The followinf treatment has been proven to be beneficial in treating patient with HFpEF.

ACEI

ARB

Betablocker

Dobutamine

None of the above

HEART FAILURE WITH PRESERVED EF (HFPEF)

- EF>50%
- Common in patient with HTN, DM, Obesity, AFib, CKD, OSA
- Treat underlying condition
- Diuresis
- Aldosterone receptor antagonist
- **sacubitril**+ **valsartan** (PARAGON-HF)

The following non-phermacological therapy is proven to be beneficial in management of refractory CHF.

Implantable Cardiac Defibrillator	A
Cardiac Resynchronization Therapy	B
Left ventricular Assist Device	C
All of the above	D
None of the above	E

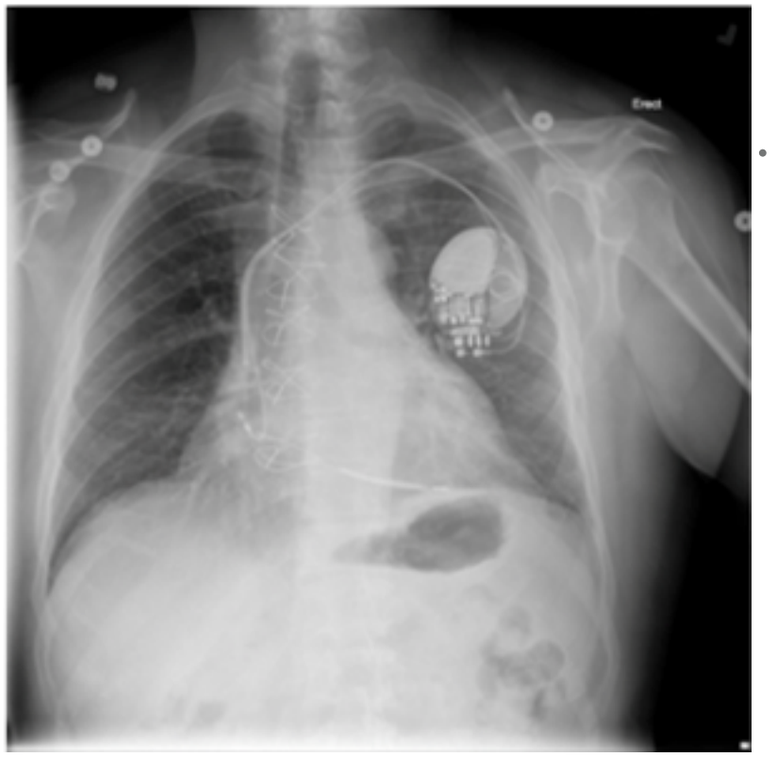
The following non-phermacological therapy is proven to be beneficial in management of refractory CHF.

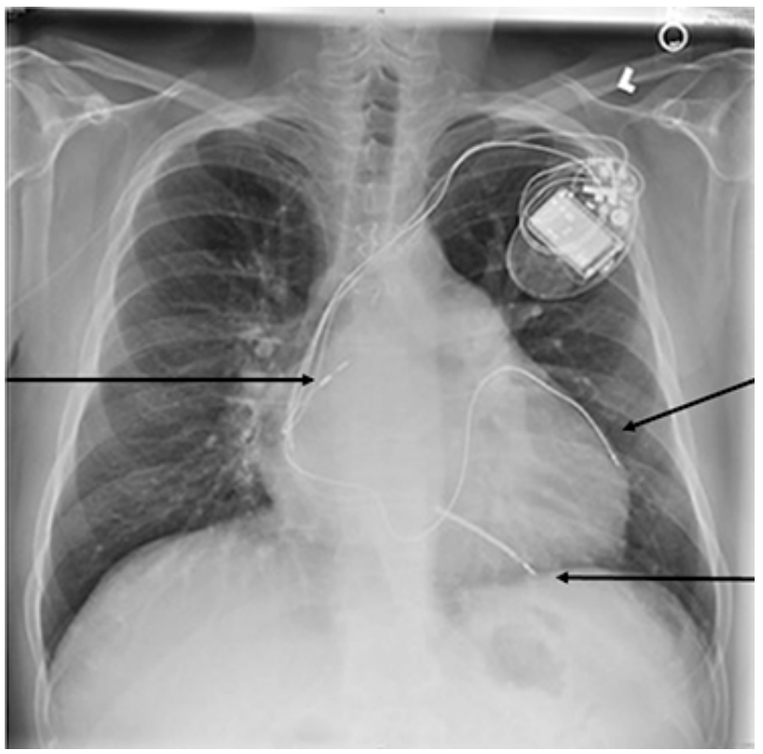
Inplantable Cardiac Defibrillator	A
Cardiac Resyncronization Therapy	B
Left ventricular Assist Device	C
All of the above	D
None of the above	E

The following non-phermacological therapy is proven to be beneficial in management of refractory CHF.

DEVICE THERAPY

- ICD therapy is recommended for primary prevention of SCD to reduce total mortality in selected patients with non- ischemic DCM or ischemic heart disease at least 40 days post-MI with LVEF of <35%
- CRT is indicated for patients who have LVEF of 35% or less, sinus rhythm, left bundle-branch block (LBBB) with a QRS duration of 150 ms or greater, and NYHA class II, III, or ambulatory IV symptoms on GDMT



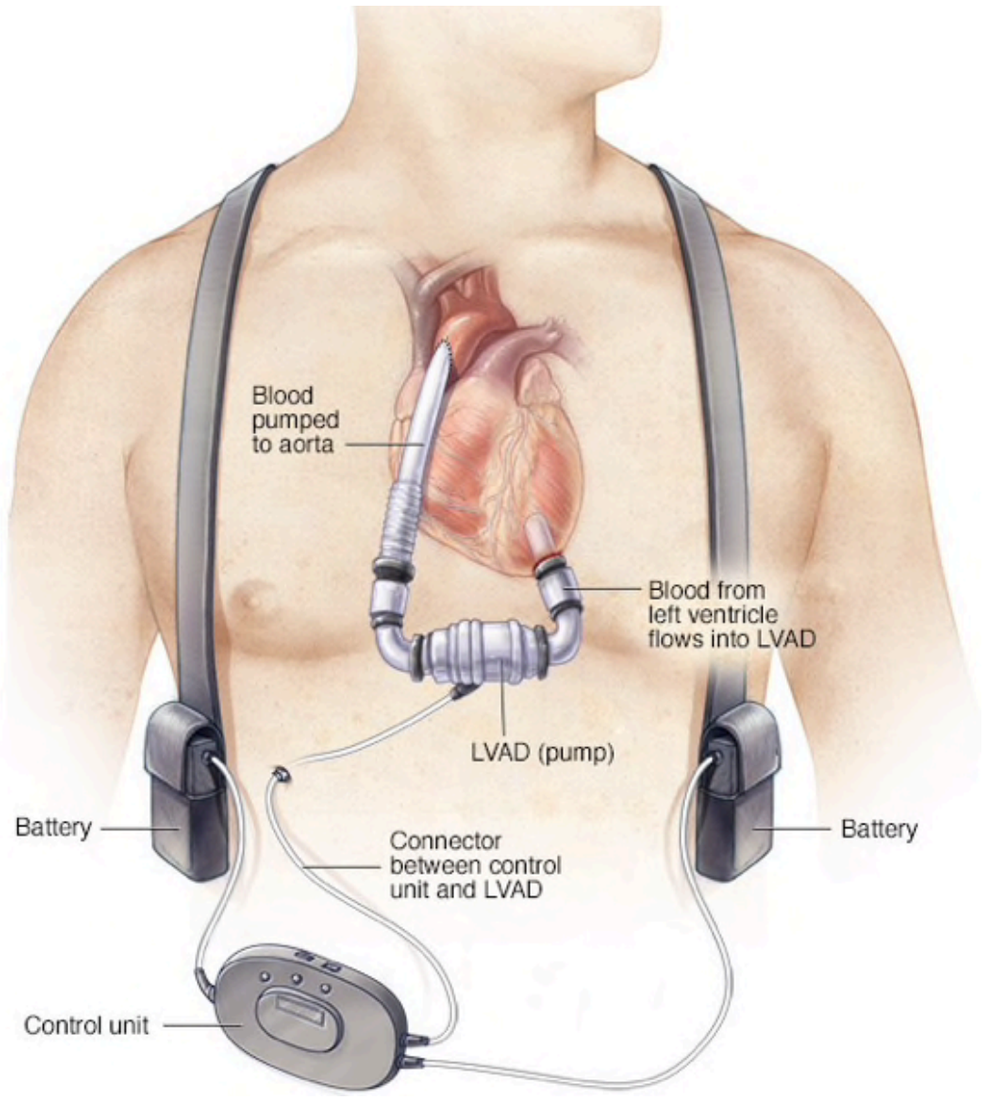


DEVICE THERAPY LESSON LEARNED

- ICD implantation is recommended only after a sufficient trial (minimum 3 months) of optimal medical therapy (OMT) has failed to increase the LVEF to .35%
- Patients with a QRS duration ≥130 ms should be considered for a defibrillator with CRT (CRT-D) rather than ICD
- Patients with serious co-morbidities who are unlikely to survive substantially more than 1 year are unlikely to obtain substantial benefit from an ICD

LEFT VENTRICULAR ASSIST DEVICE

- Indicated for patient to improve quality of life before heart transplant
- clinically meaningful survival benefit and an improved quality of life.
- acceptable alternative therapy in selected patients who are not candidates for cardiac transplantation.



N Engl J Med 2001; 345:1435-1443

CARE IN TRANSITION

- Initiation of GDMT if not previously established and not contraindicated
- precipitant causes of HF, barriers to optimal care transitions, and limitations in post-discharge support
- assessment of volume status and supine/upright hypotension with adjustment of HF therapy as appropriate
- titration and optimization of chronic oral HF therapy
- assessment of renal function and electrolytes where appropriate
- assessment and management of comorbid conditions
- reinforcement of HF education, self-care, emergency plans, and need for adherence
- consideration for palliative care or hospice care in selected patients
- Multidisciplinary HF disease-management programs

TAKE HOME MESSAGES

- Success of heart failure therapy is understanding of pathophysiology and application of Goal Directed Medical Therapy (GDMT)
- Making the correct diagnosis and early intervention improves overall outcome
- Transitional care and collaboration is key in success of CHF management

REFERENCES

- Taylor Clare J, et al. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population based cohort study *BMJ 2019;*364 :l223
- The Digitalis Investigation Group; The Effect of Digoxin on Mortality and Morbidity in Patients with Heart Failure; N Engl J Med 1997; 336:525-533
- Cohn JN, et al. "Effect of vasodilator therapy on mortality in chronic congestive heart failure". *N Engl J Med*. 1986. 314(24):1547-52.
- The Consensus Trial Study Group; Effects of Enalapril on Mortality in Severe Congestive Heart Failure; N Engl J Med 1987; 316:1429-1435
- 2013 ACCF/AHA Guideline for the Management of Heart Failure; JACC Vol. 62, No. 16, 2013
- Pitt B, et al; Effect of losartan compared with captopril on mortality in patients with symptomatic heart failure: randomised trial--the Losartan Heart Failure Survival Study ELITE II. Lancet. 2000 May 6;355(9215):1582-7. doi: 10.1016/s0140-6736(00)02213-3. PMID: 10821361.

REFERENCES

- Jay N. Cohn, J.N. et al; A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure; N Engl J Med 2001; 345:1667-1675;
- CBIS II Authors. The Cardiac Insufficiency Bisoprolol Study II (CIBIS- II): a randomised trial. Lancet 1999;353:9–13.
- Packer M, Coats AJ, Fowler MB, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med 2001;344:1651–8.
- Pitt, B. Et al; The Effect of Spironolactone on Morbidity and Mortality in Patients with Severe Heart Failure; N Engl J Med 1999; 341:709-717
- Zannad, F. Et al; Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms; N Engl J Med 2011; 364:11-21
- McMurray, J.J. et al; Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure; N Engl J Med 2014; 371:993-1004

REFERENCES

- Fox K, et al; BEAUTIFUL Investigators. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL). Lancet. 2008 Sep 6; 372(9641):807-16.
- Swedberg K, et al; Effects on outcomes of heart rate reduction by ivabradine in patients with congestive heart failure: is there an influence of beta-blocker dose?: findings from the SHIFT (Systolic Heart failure treatment with the I(f) inhibitor ivabradine Trial) study; J Am Coll Cardiol. 2012 May 29; 59(22):1938-45.
- Rose, E.A. et al; Long-Term Use of a Left Ventricular Assist Device for End-Stage Heart Failure; N Engl J Med 2001; 345:1435-1443
- Zinman B, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117 – 2128.
- Packer, M. Et al; EMPEROR-Reduced Trial Investigators; Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure; N Engl J Med 2020; 383:1413-1424