New Updates on Treatment of Heart Failure-Get With the Guidelines

Harry Balian, MD F.A.C.C, FSCAI
Cardiovacular Disease, Interventional Cardiology and Endovascular and Structural Heart Specialist
Director of Cardiac Cath Lab
Chairman of Cardiology
Glendale Adventist Heart & Vascular Institute

AAMS-Spring Symposium 5.21.22

Objectives

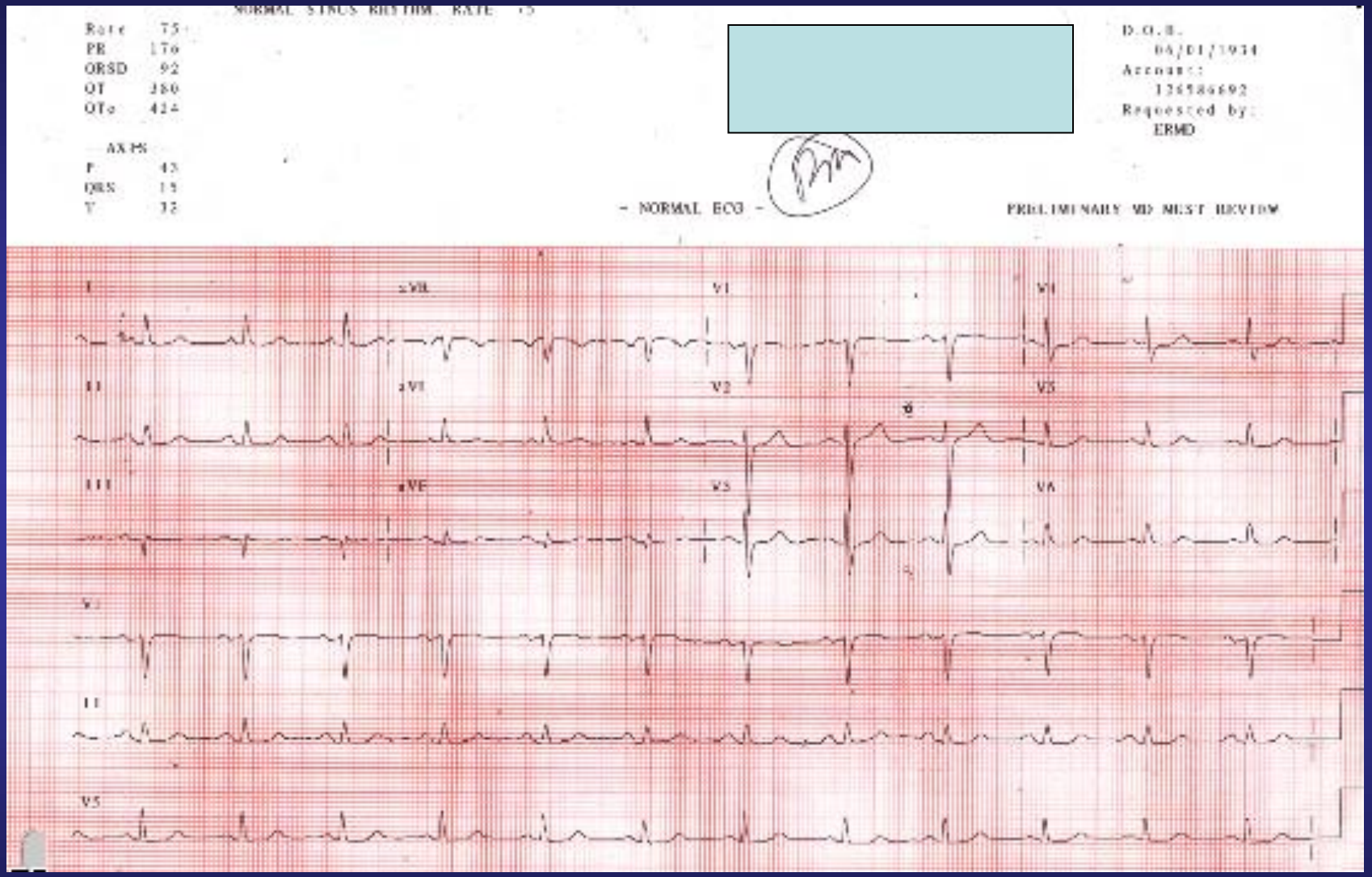
- Define Heart Failure-Systolic and Diastolic
- Outline anatomy of the cardiac myocyte
- Classification of Heart Failure
- Treatment of Heart Failure
- Major landmark Trials
- Discuss ICDs-Transvenous/Subcutaneous
- Lifestyle modification
- Closing remarks

Mr A

- 78 y/o male w/ prior stent placed two years ago, active smoker, dyslipidemic, diabetic, was gardening and developed chest pain
- He was admitted to GAMC for ACS workup
- PE-123/66, P 120s, regularly, regular
- Lungs: CTA
- Heart: regularly, regular
- Abd: minimally protuberant
- Ext: 1+ nonpitting edema

Workup

- ECG-obtained-Sinus rhythm with no overt ST changes
- Echo-EF of 60% with no wall motion abnormalities
- Stress test-moderate anterior wall reversible defect
- (on the ECG portion of the tmst-pt walked for 4 minutes with anterolateral ST depressions-2 mm horizontal, with bigeminy


NORMAL SINUS RHYTHM. RATE 75
Rate 75
PR 176
QRSD 92
QT 380
QTc 424
AXES
P 43
QRS 19
T 32
[redacted]
D.O.B.
04/01/1934
Account:
126586692
Requested by:
ERMD
- NORMAL ECG -
PRELIMINARY MD MUST REVIEW
I
aVR
V1
V4
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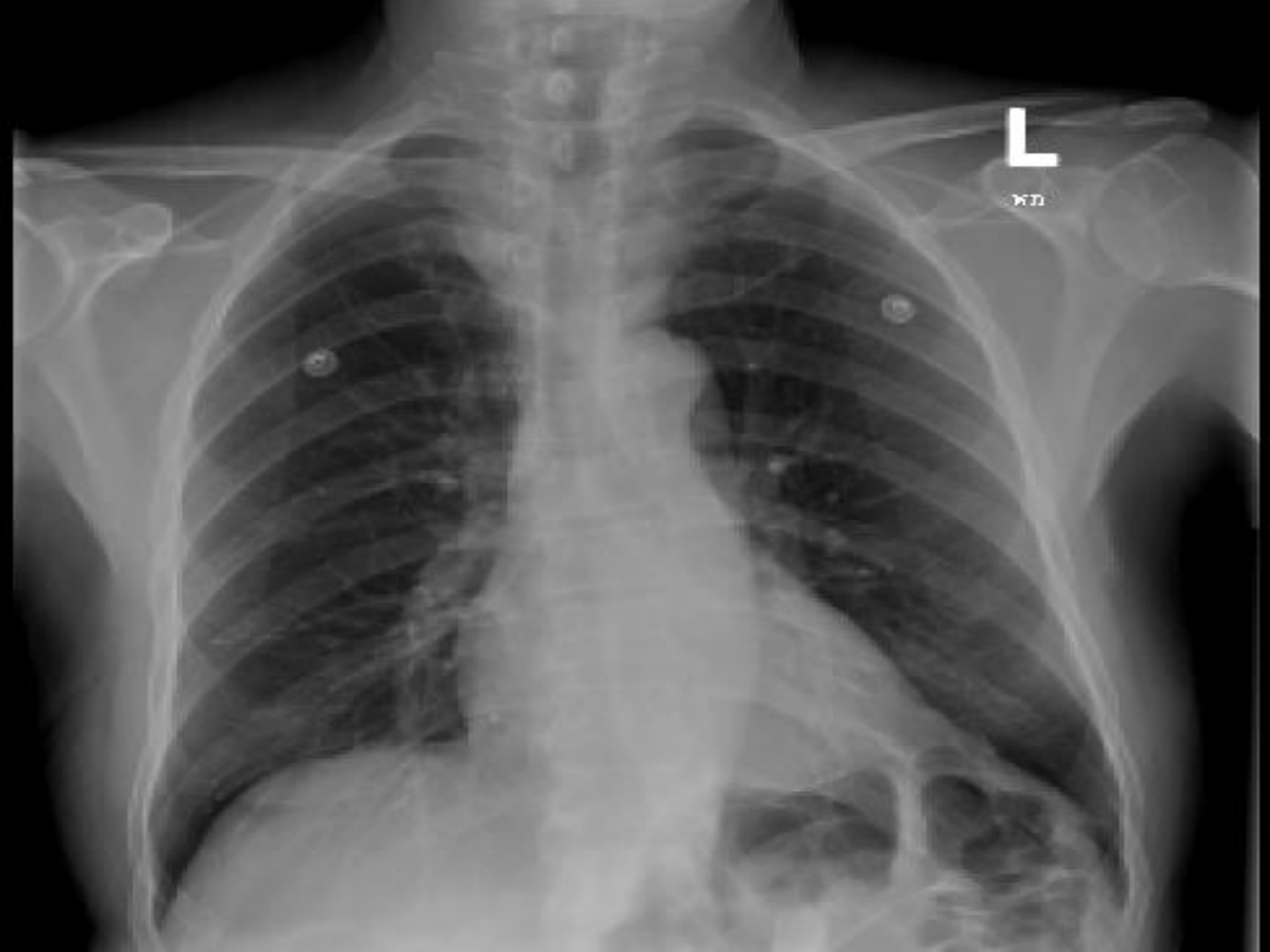
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5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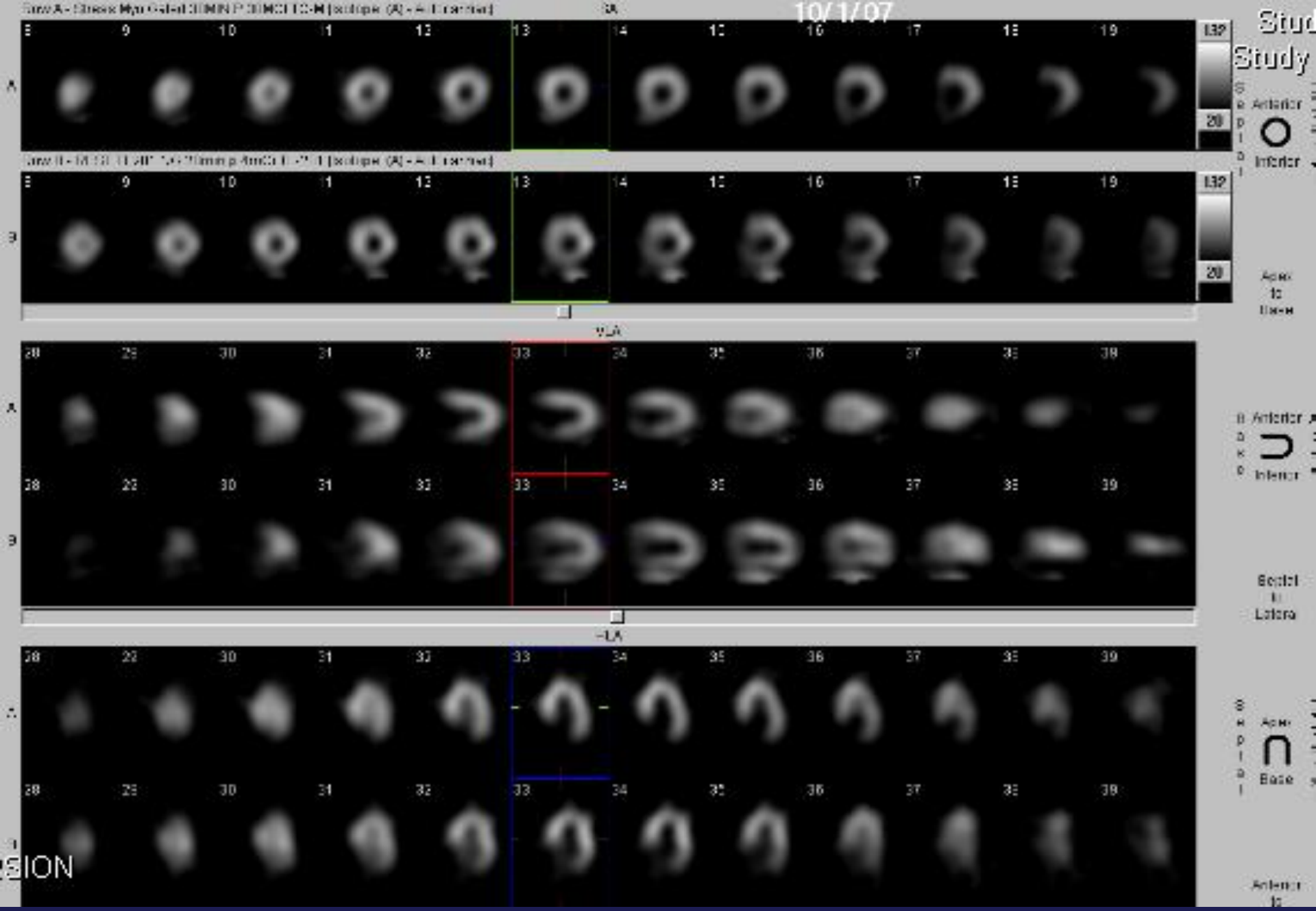
10/1/07
Study
Anterior
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Apex
to
Base
Septal
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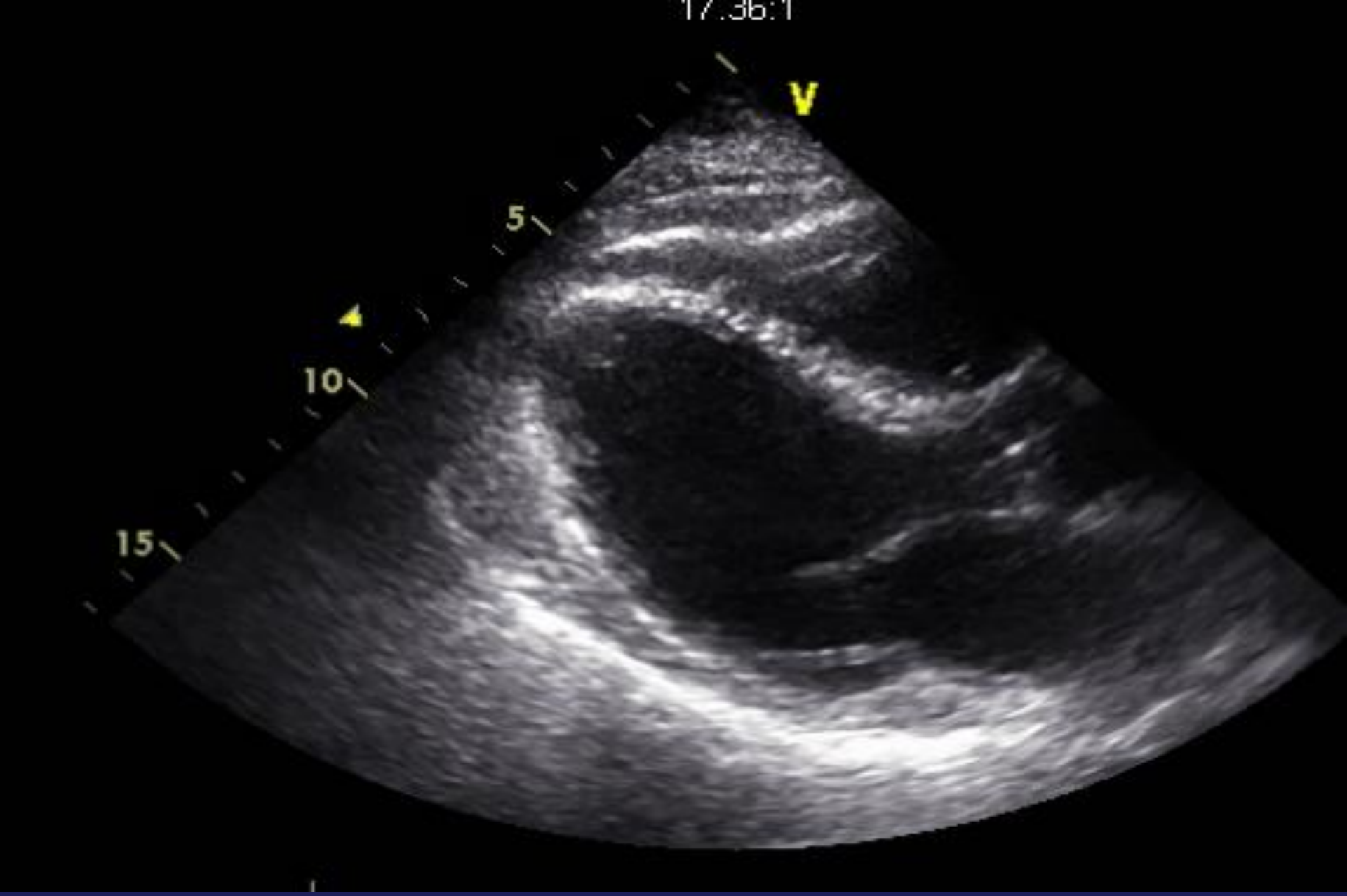
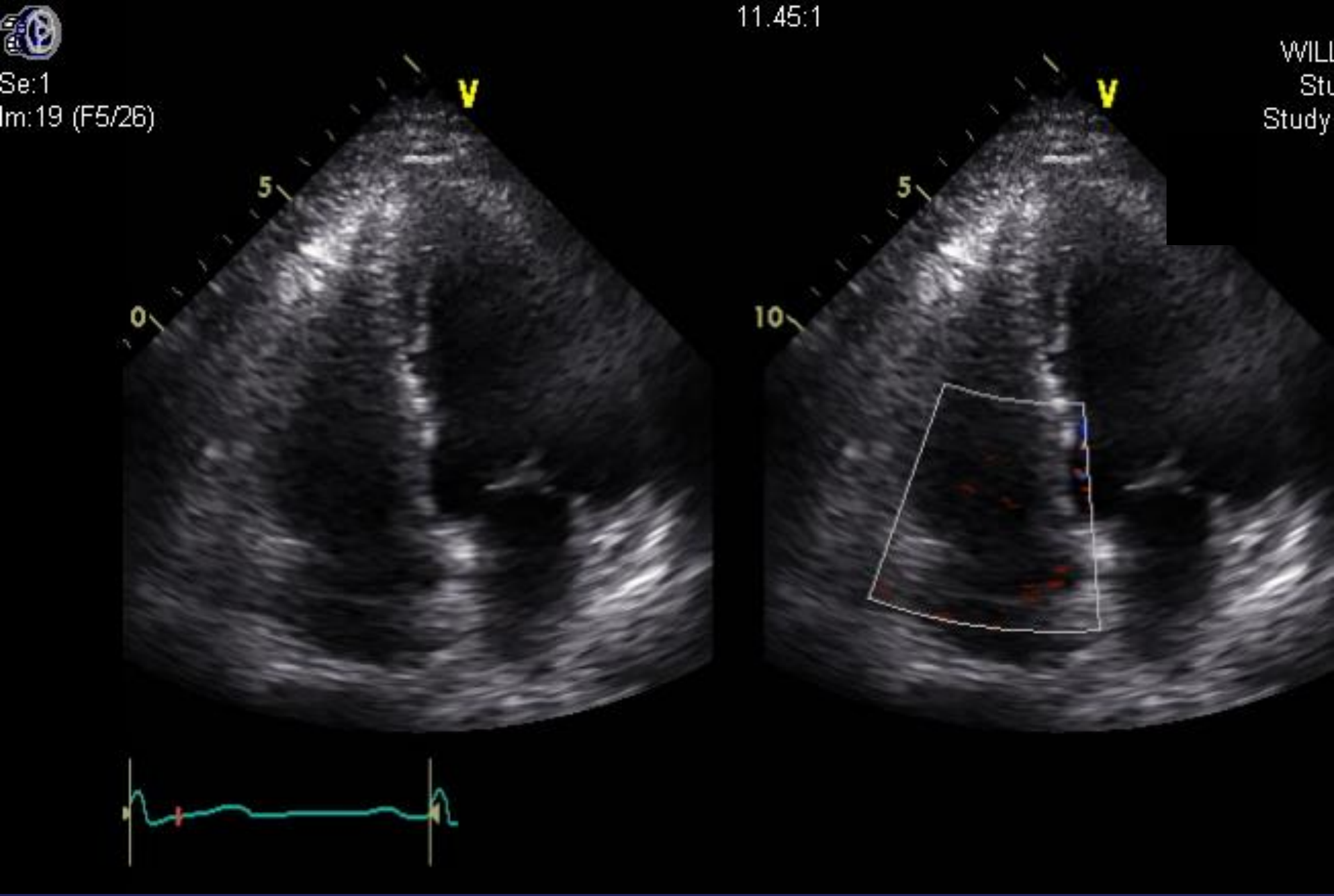
Lateral
Base
to
Apex
SION


17.36:1
V
5
10
15


11.45:1
Se:1
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WILL
Stu
Study
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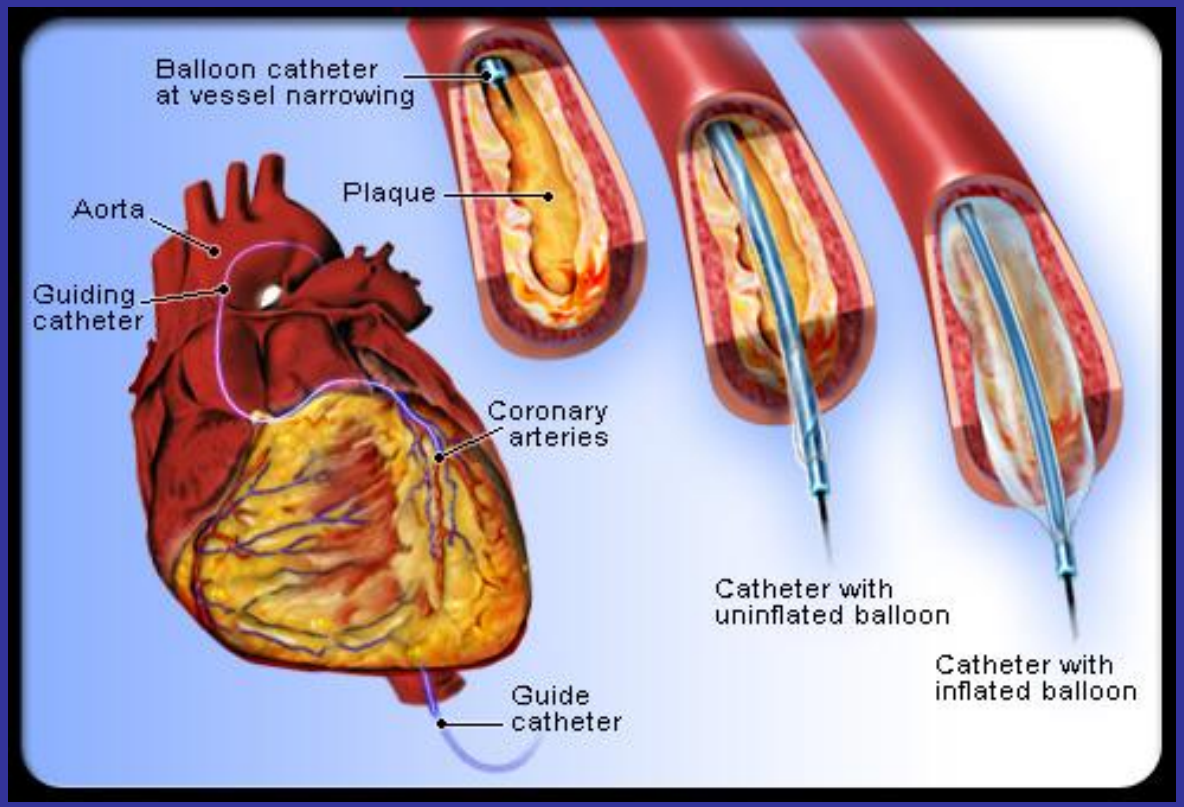
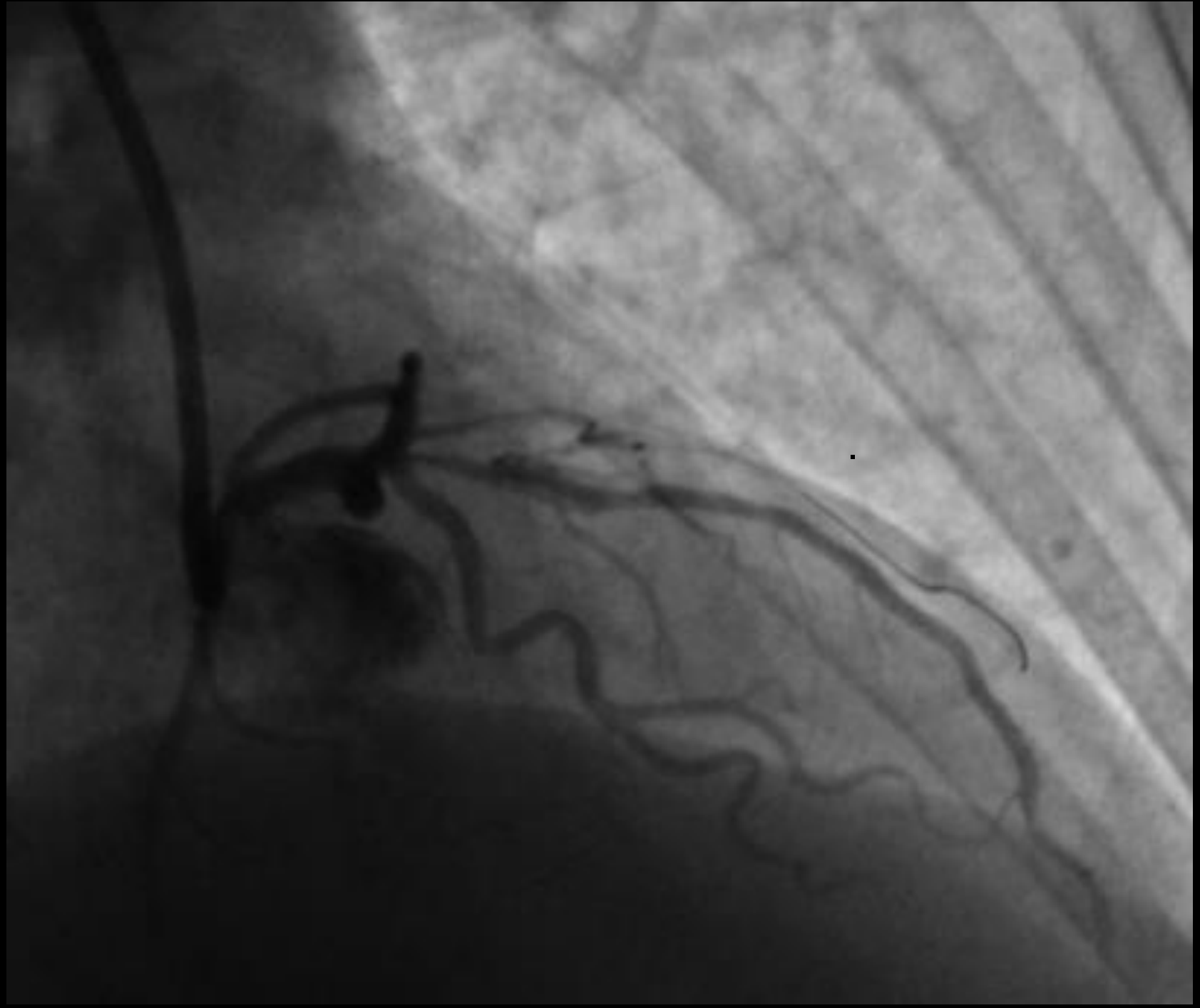
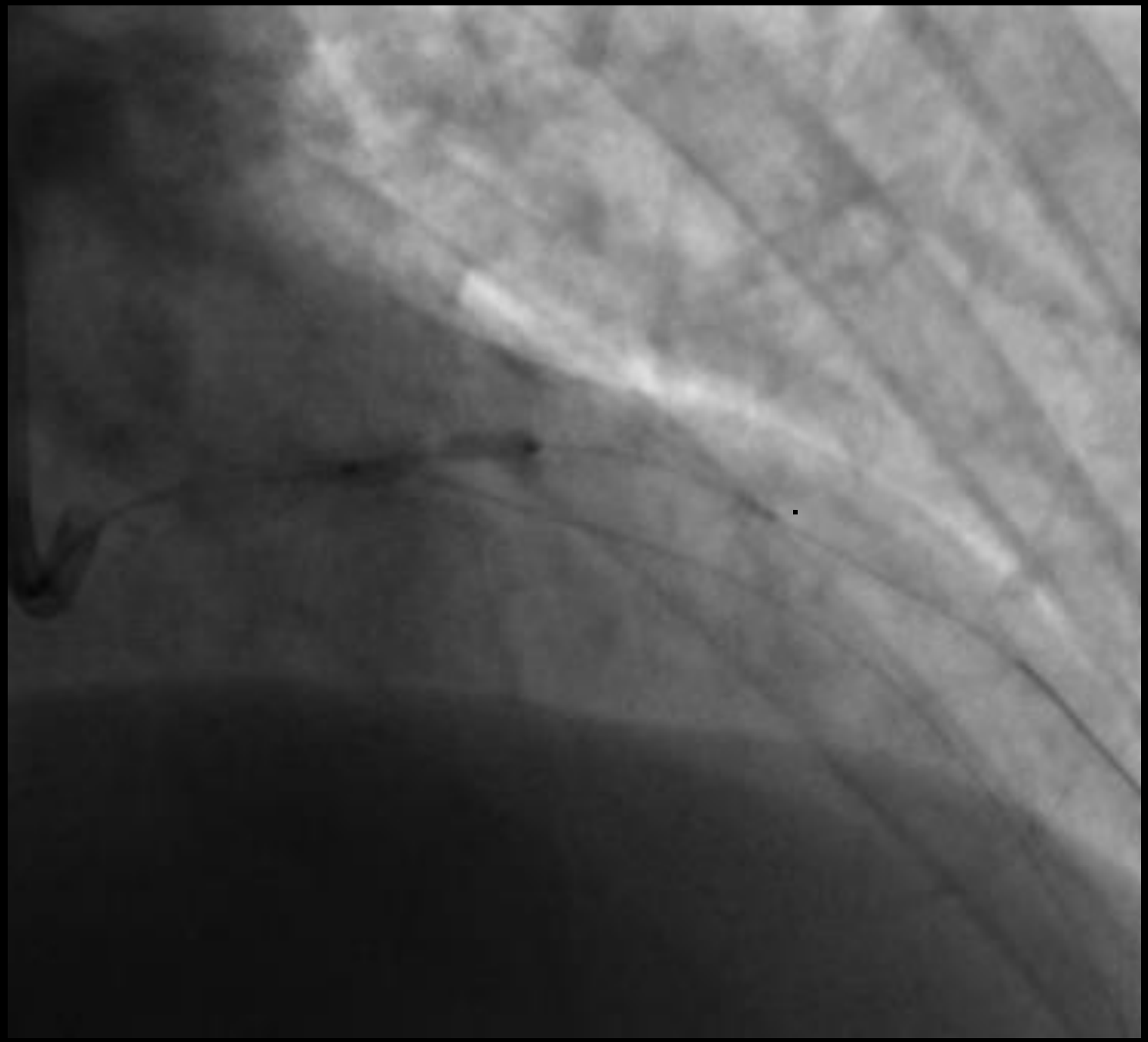
10

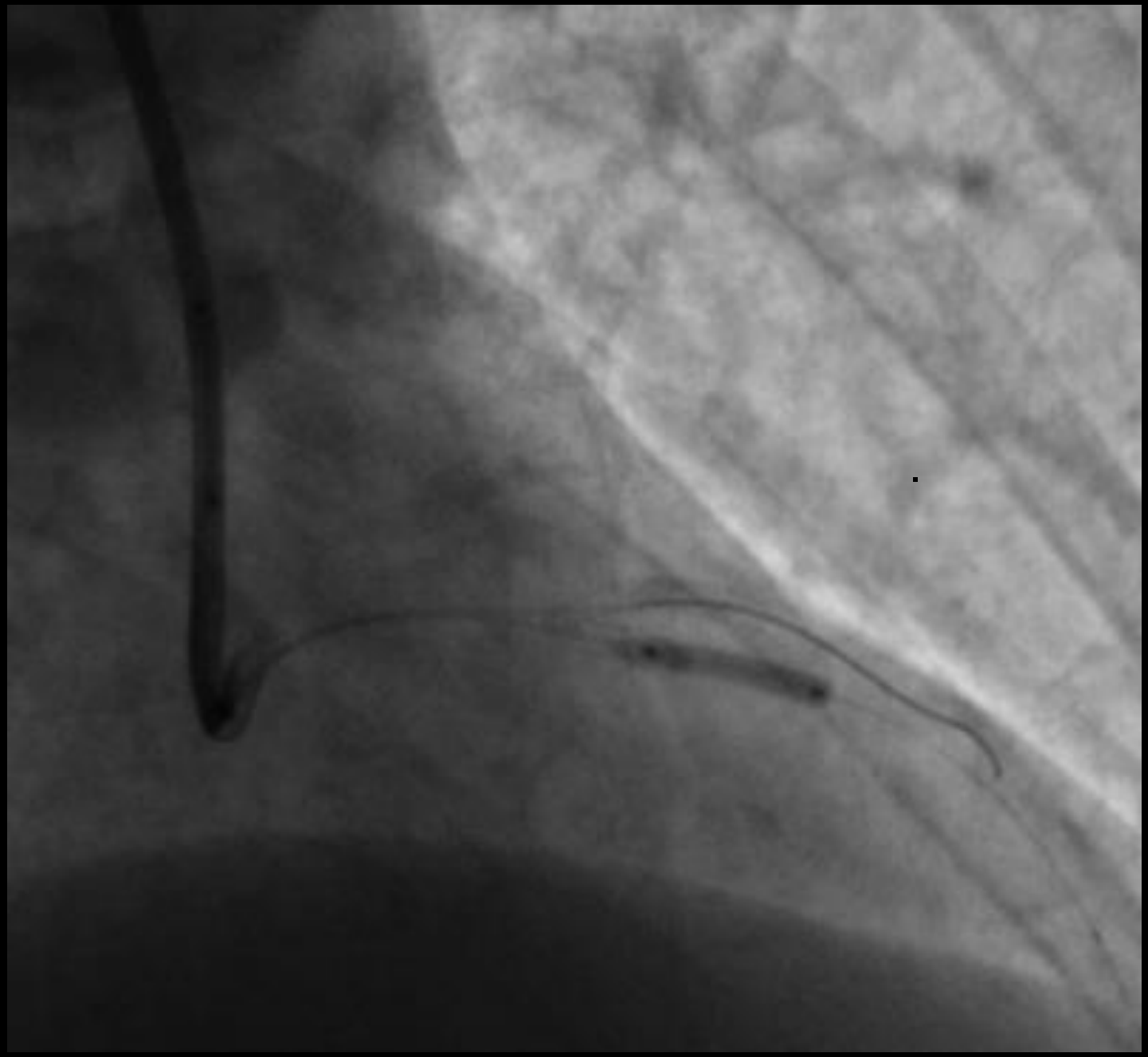
Cath was proposed and performed

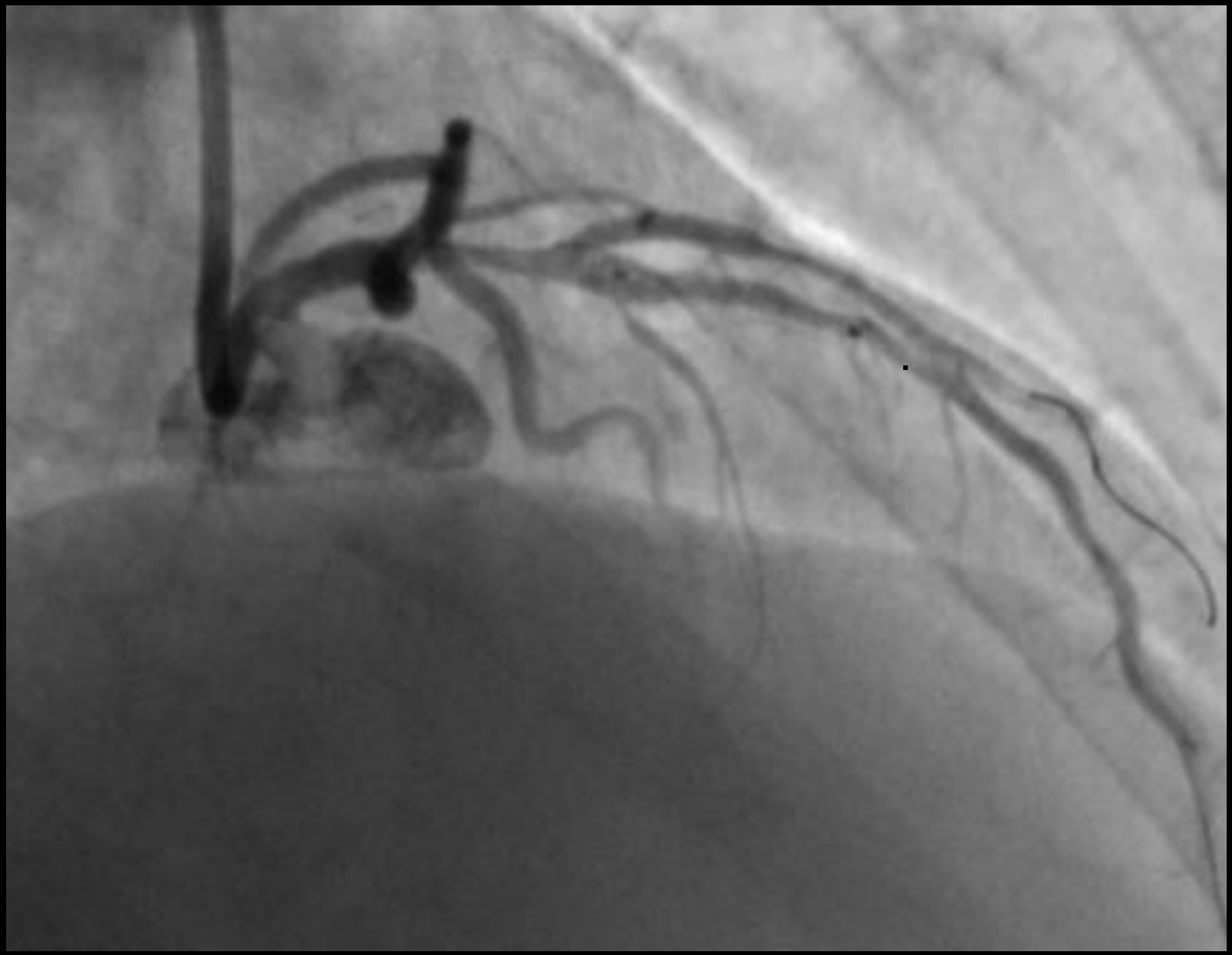
opening a blocked coronary artery

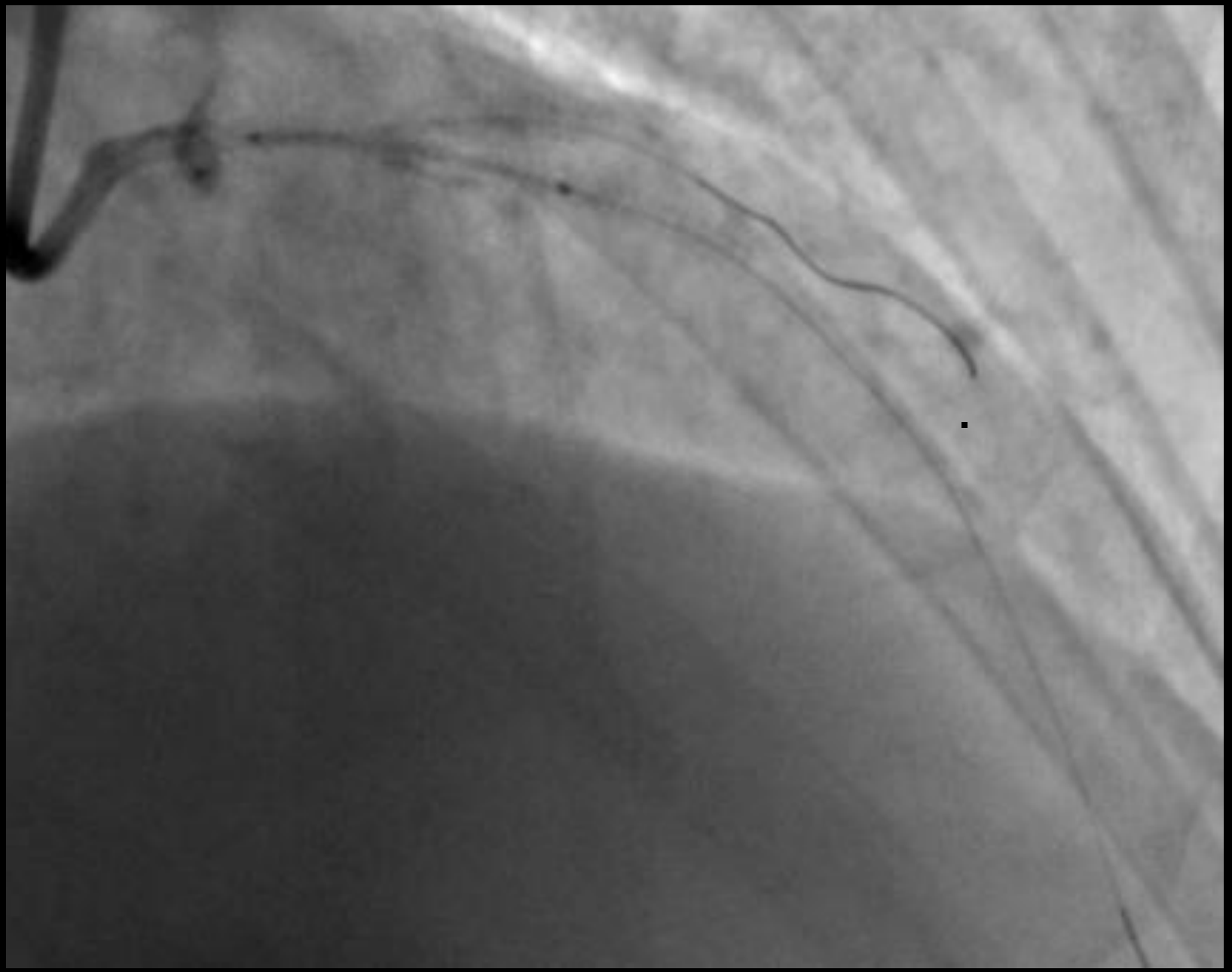




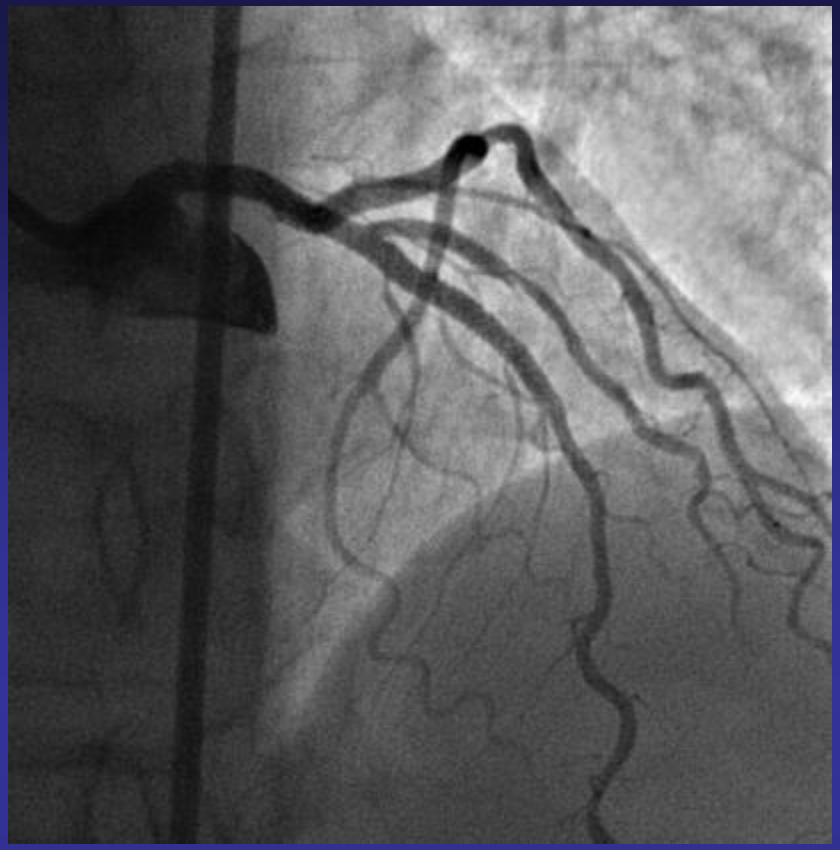


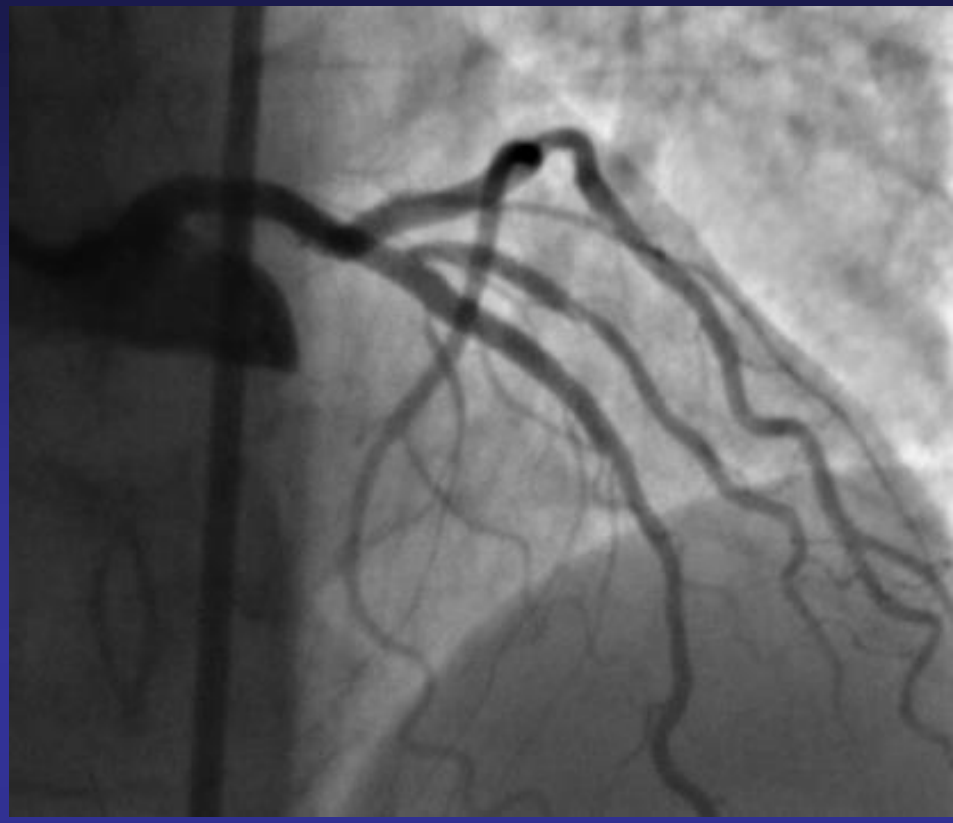






coronary stent

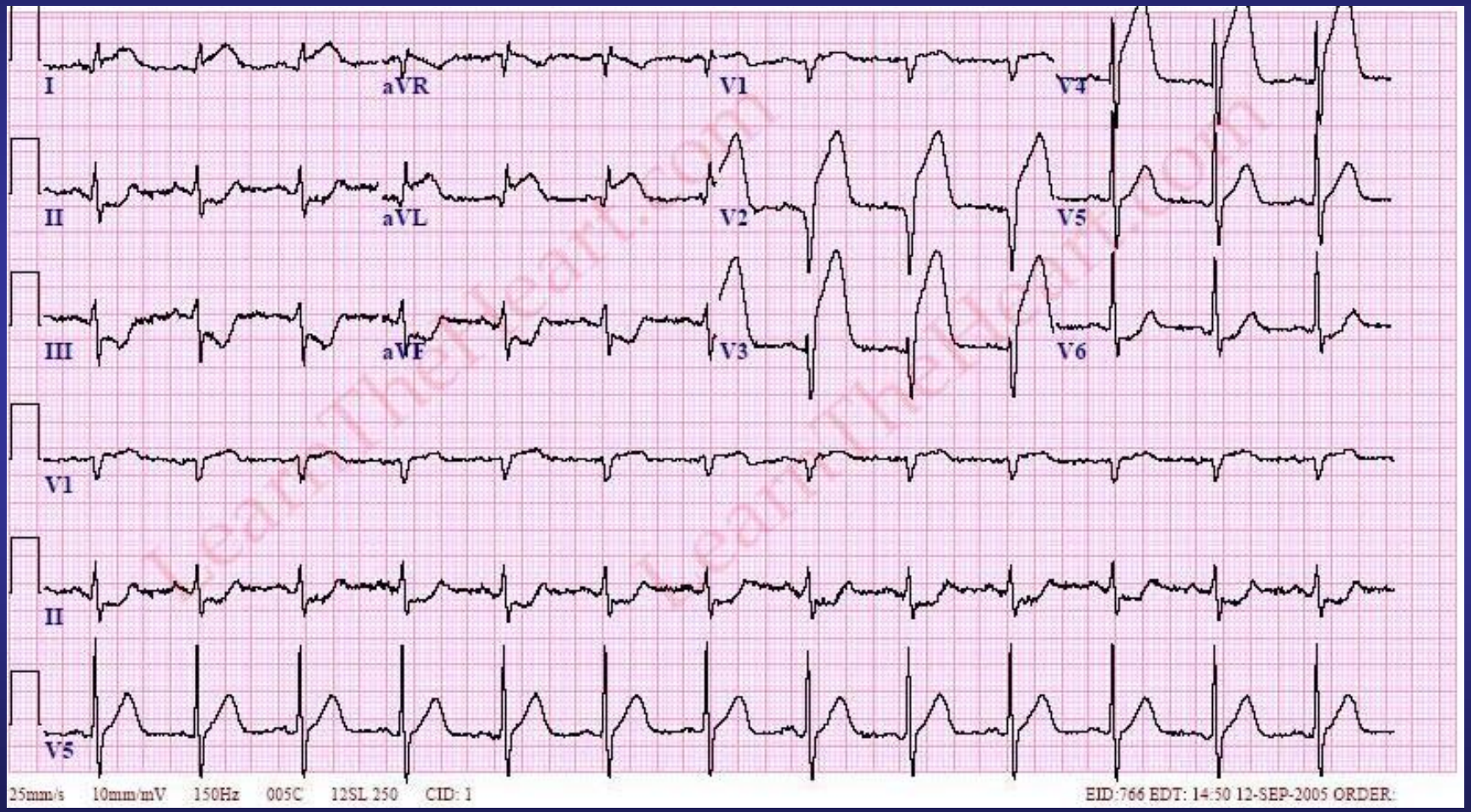




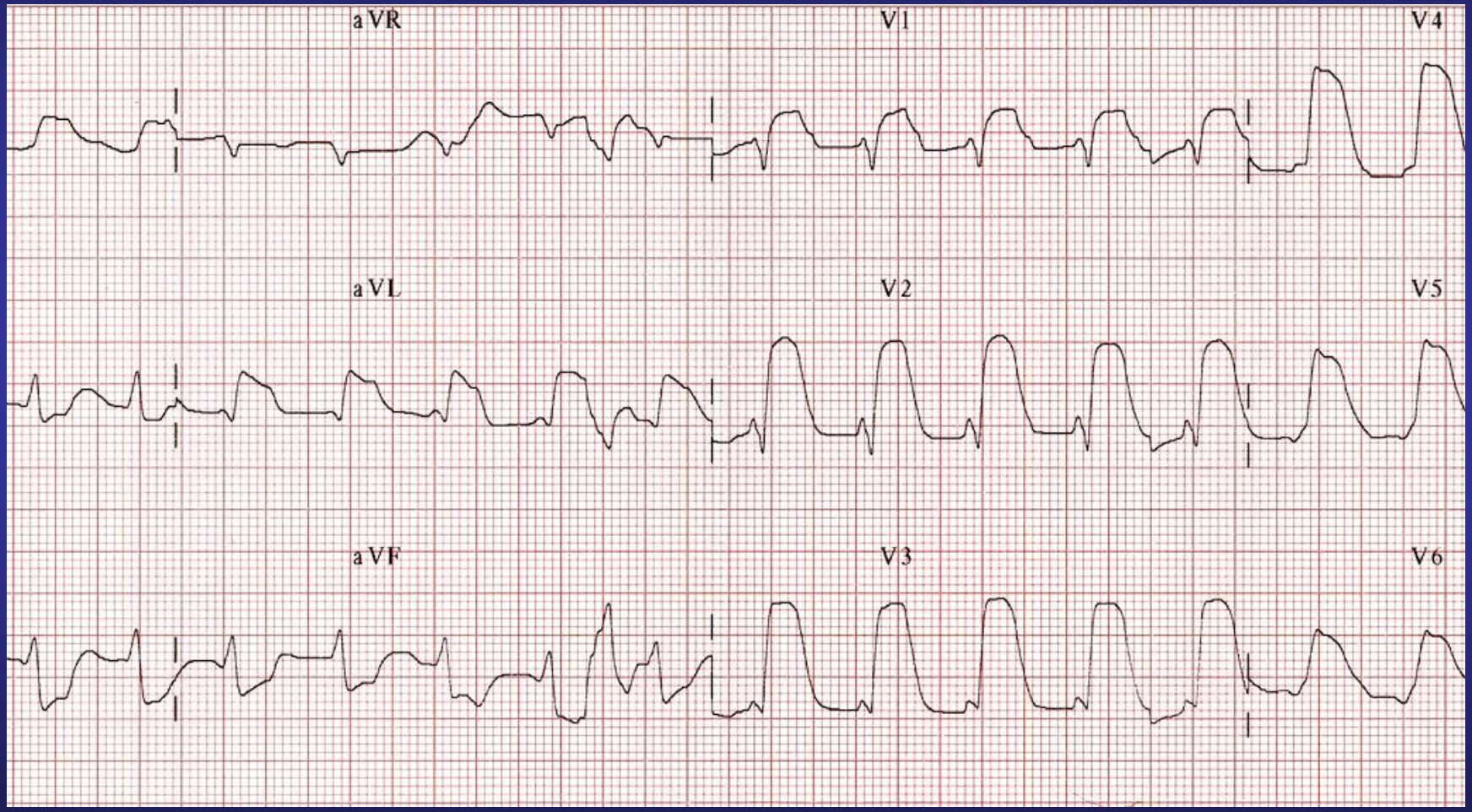
Follow-up

- Pt was discharged home on aspirin and Plavix because of his newly placed stents and told that he must take them daily.
- Unfortunately, he decided to take aspirin only and two weeks later, I received the dreaded ER phone call.
- Pt came to ER in full arrest and was resuscitated in ER

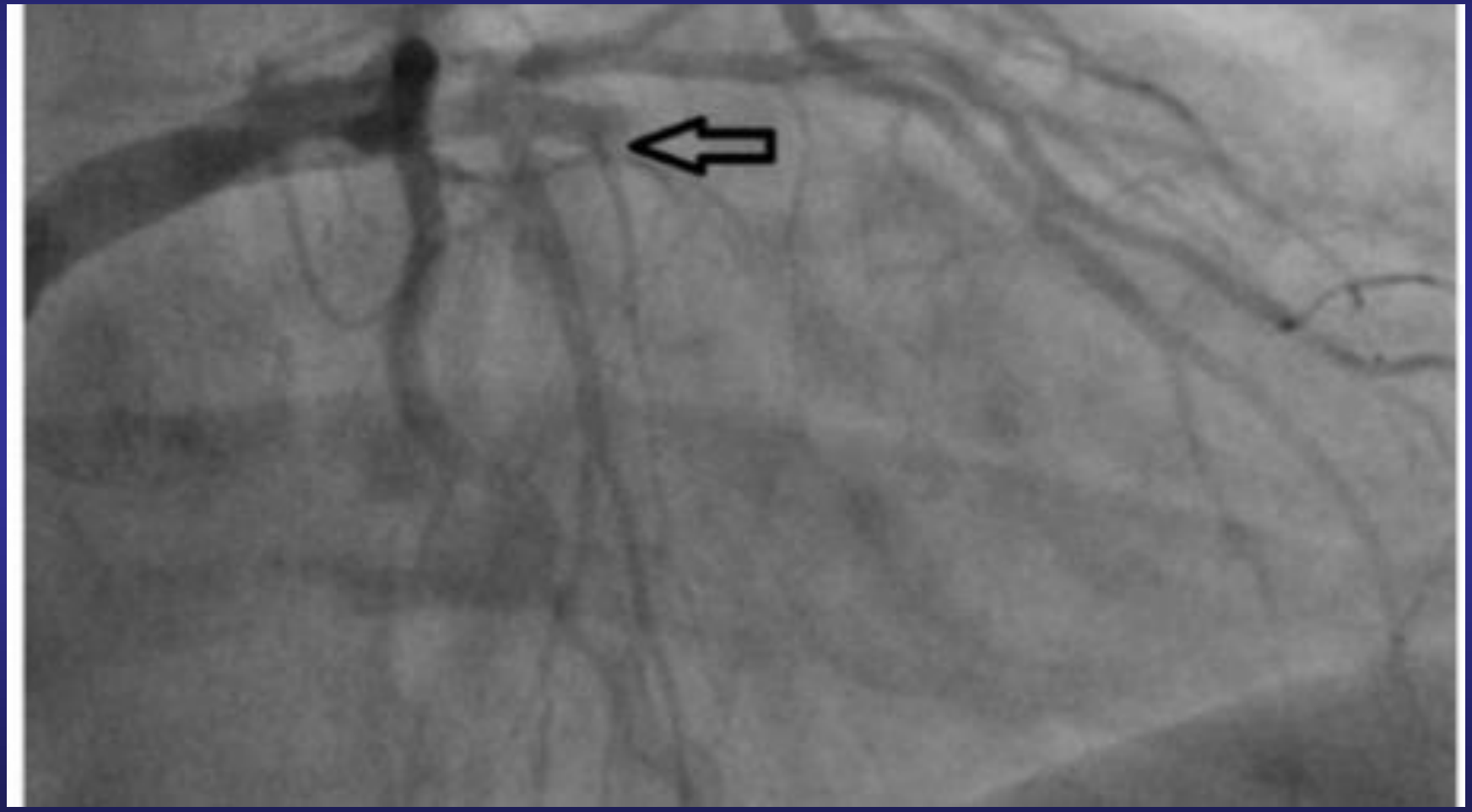
Stat ECG


I
aVR
V1
V4
II
aVL
V2
V5
III
aVF
V3
V6
V1
II
V5
25mm/s 10mm/mV 150Hz 005C 12SL 250 CID: 1
EID:766 EDT: 14:50 12-SEP-2005 ORDER:

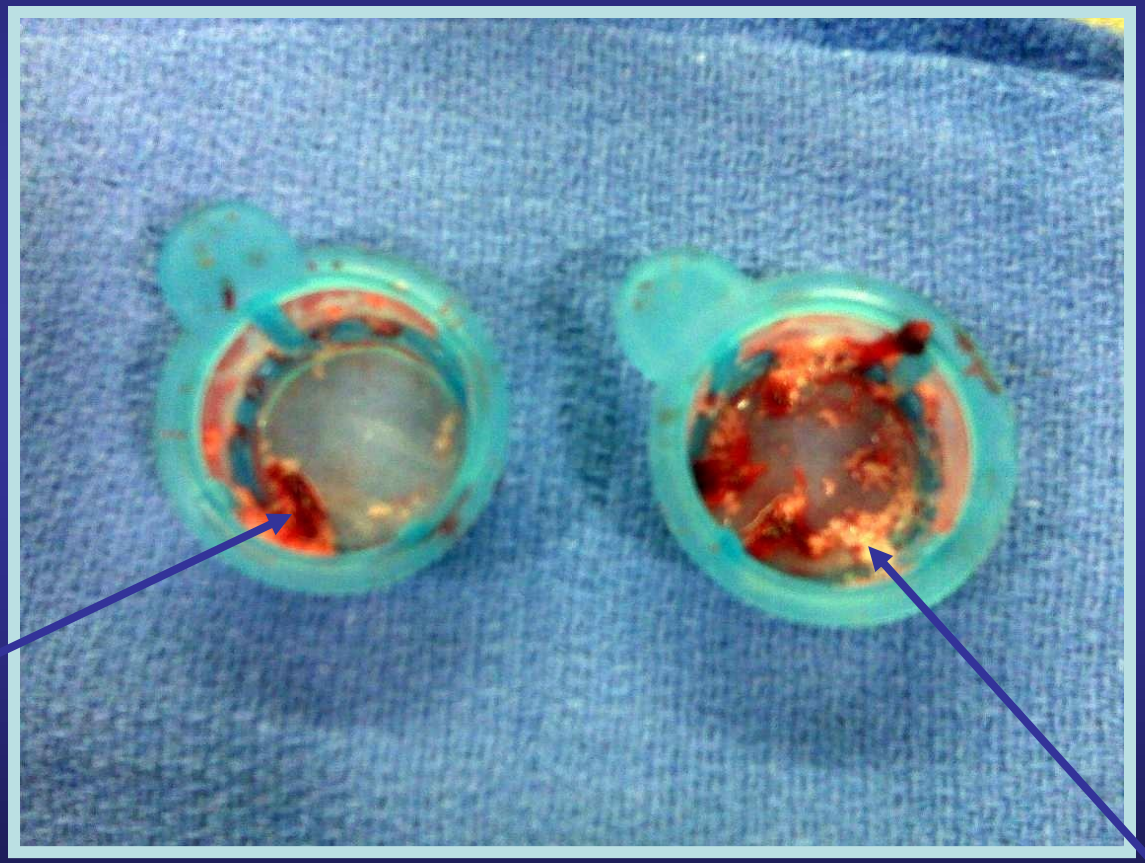
Repeat ECG



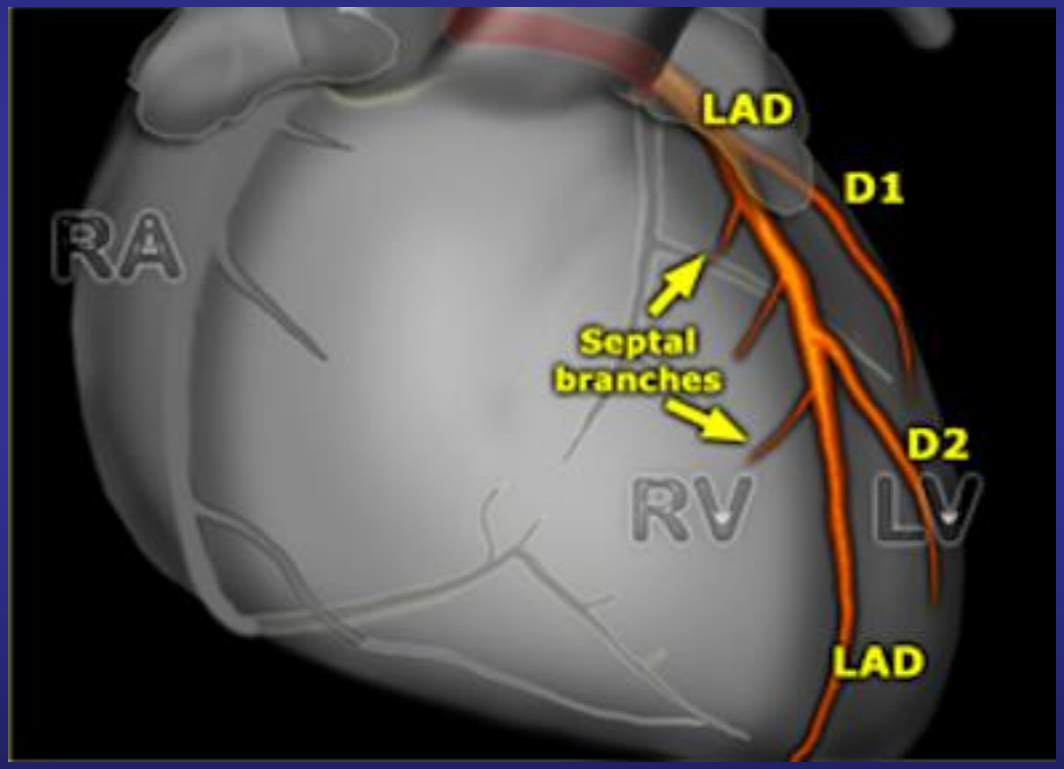
Emergent Cath

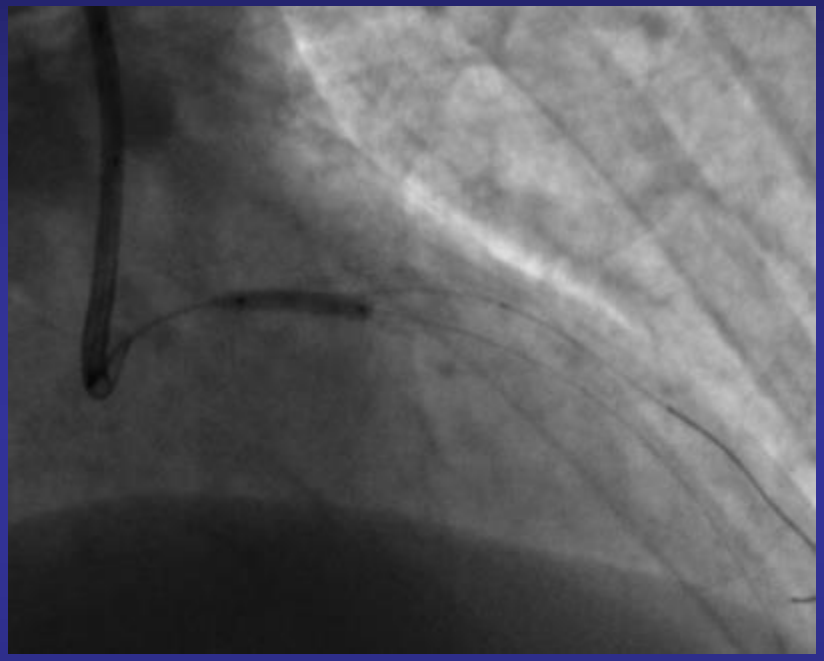


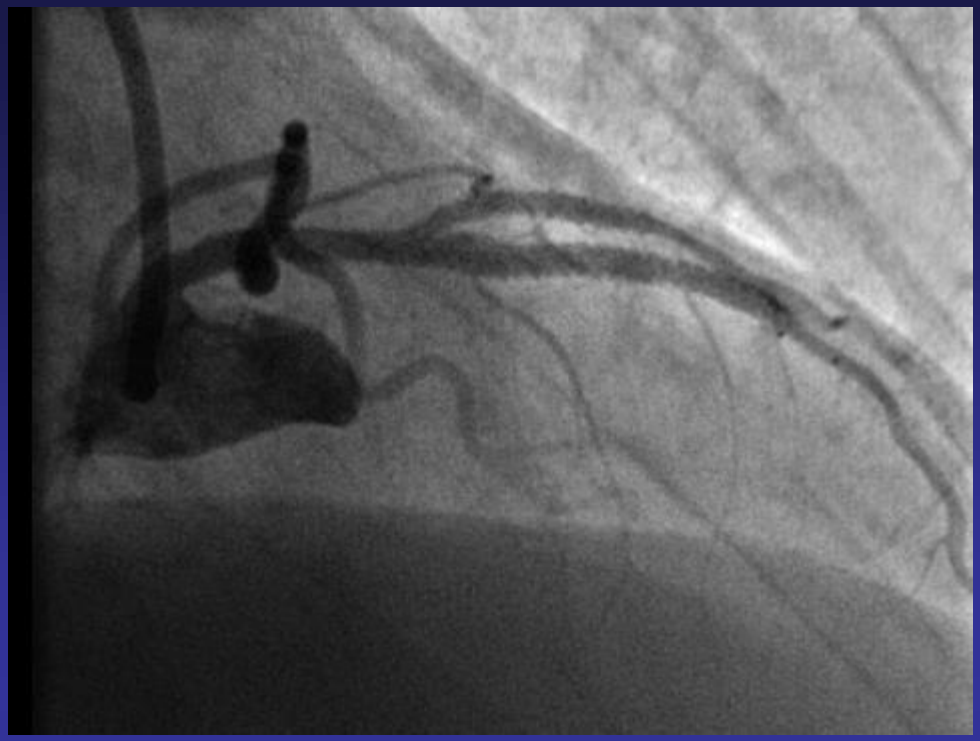
fatty deposits and clots removed from coronary arteries during the myocardial infarction

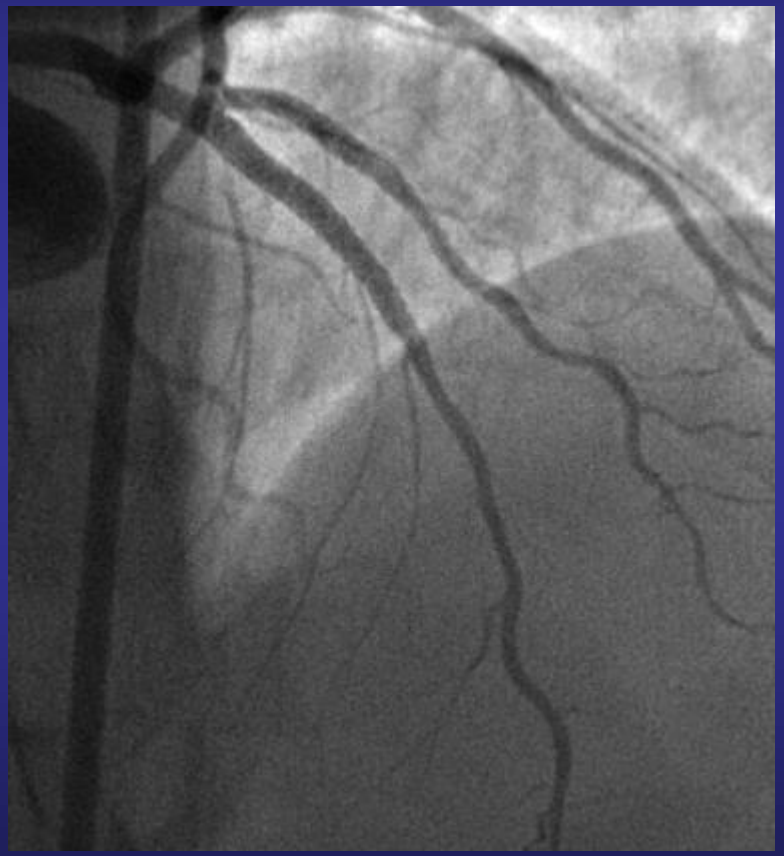


LAD stent thrombosis

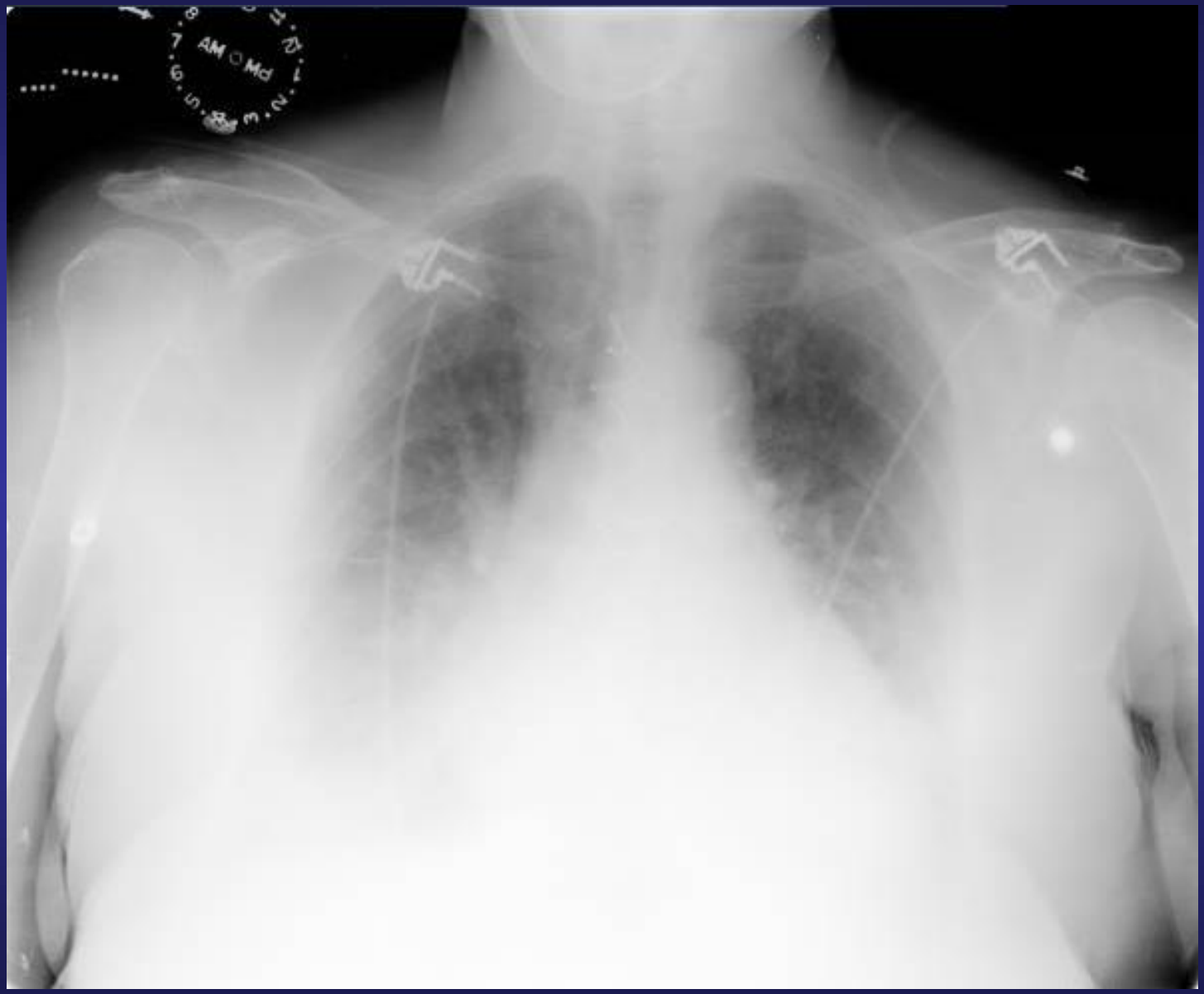








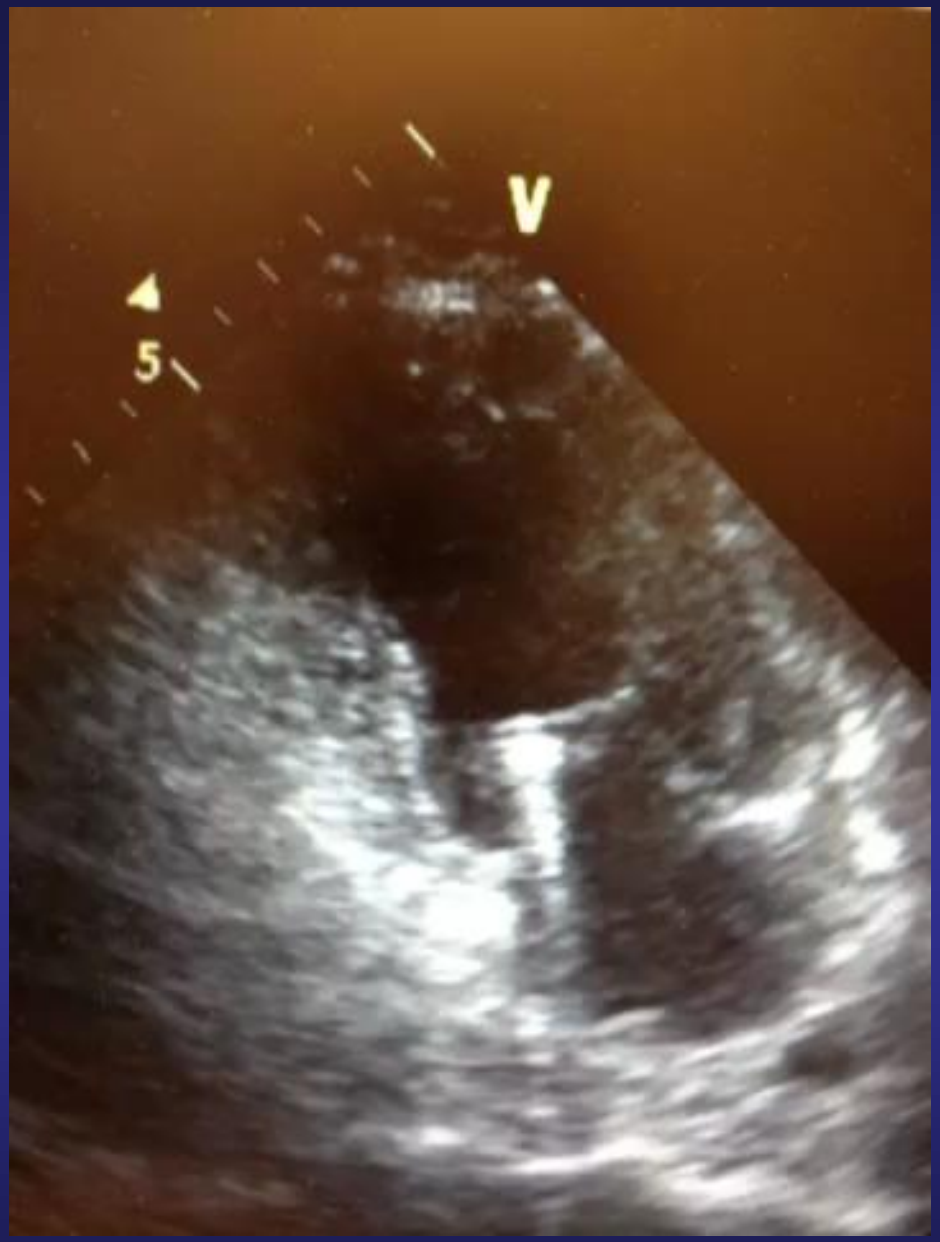
Patient's CXR post procedure



Follow-up

- Stent thrombosis due to med noncompliance
- Repeat echocardiogram shows EF of 25% with anterior wall severe hypokinesis
- Pt is heart failure with pulmonary edema

- He was diuresed, extubated and was in the hospital for 1 month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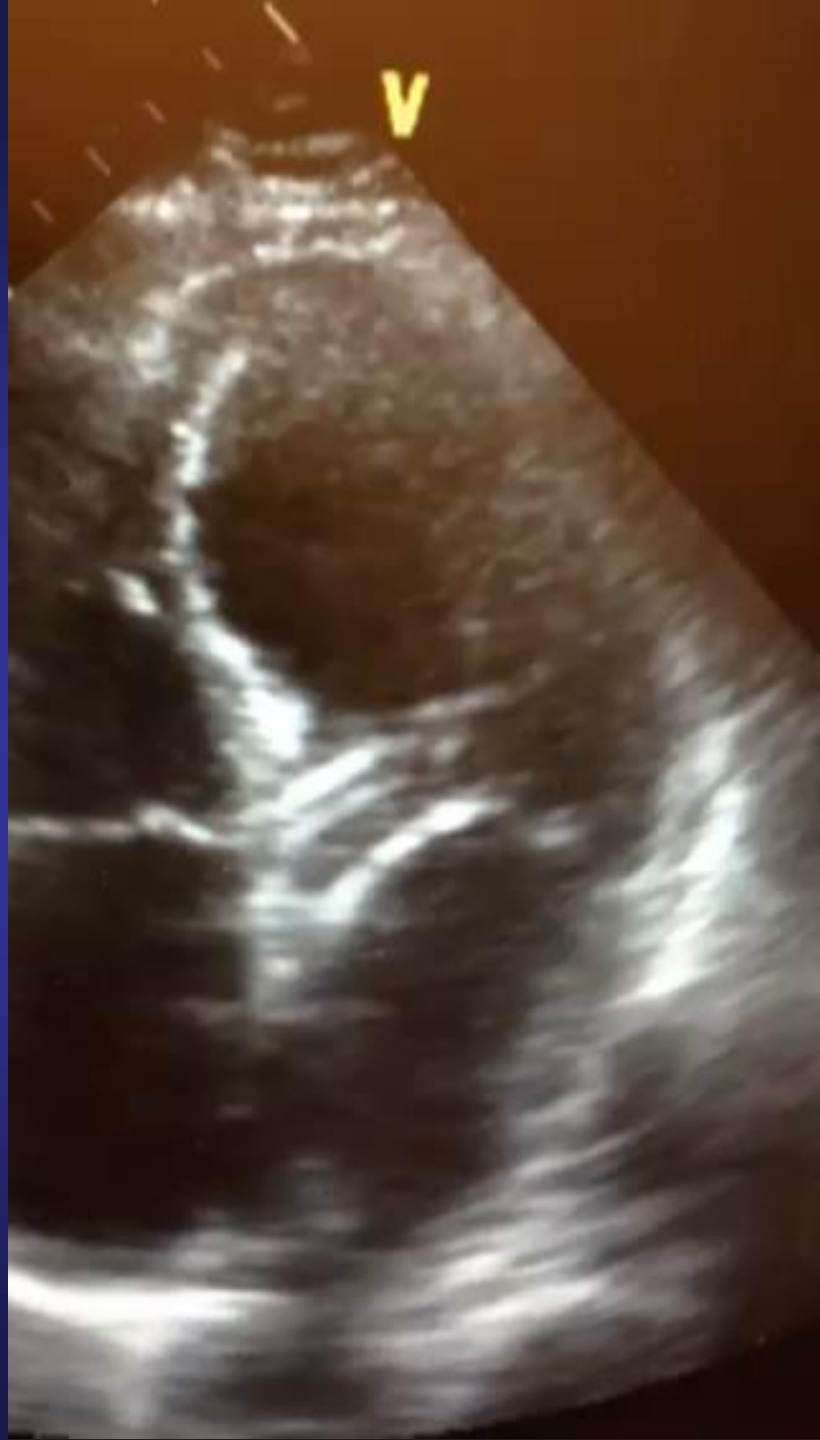
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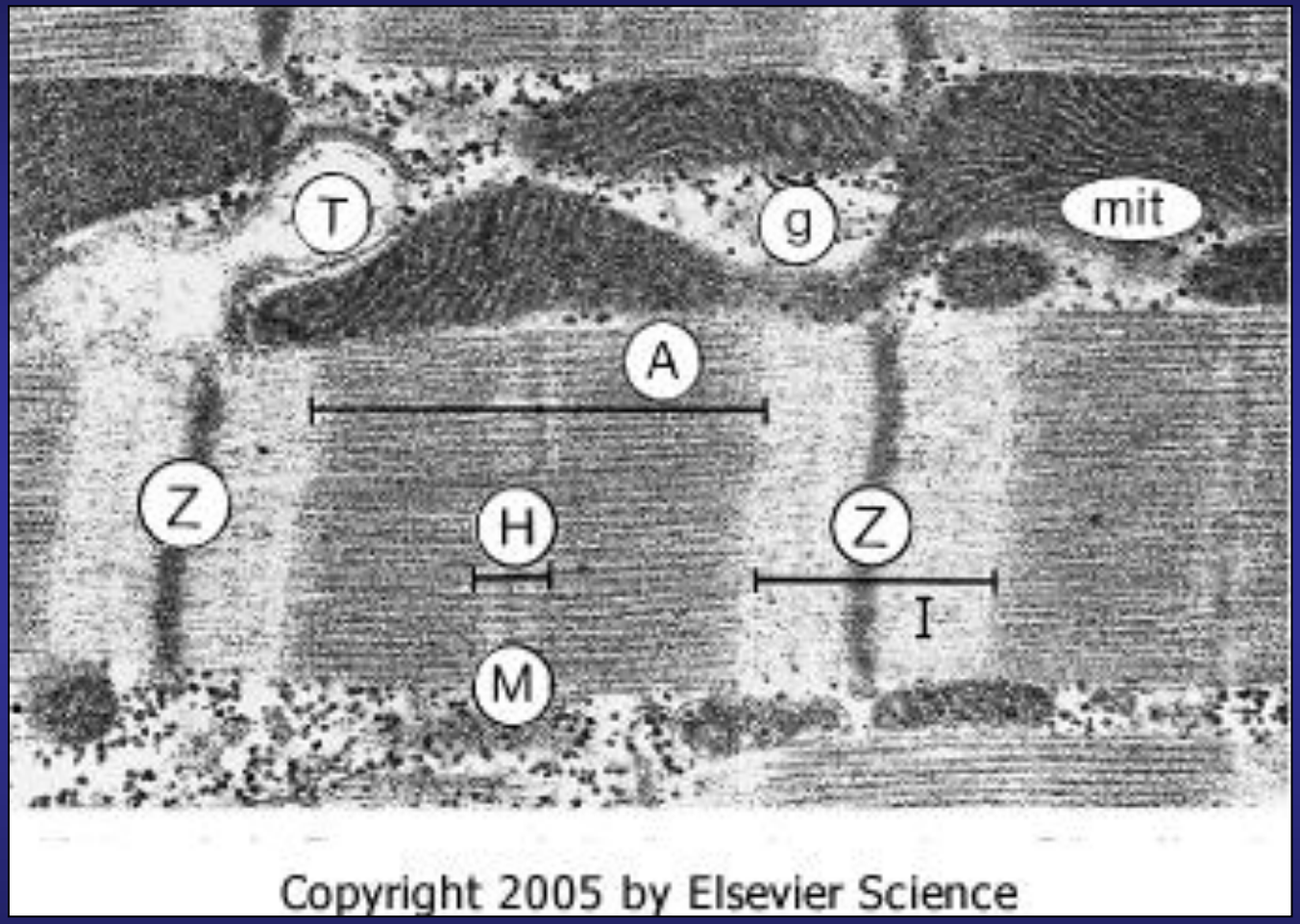
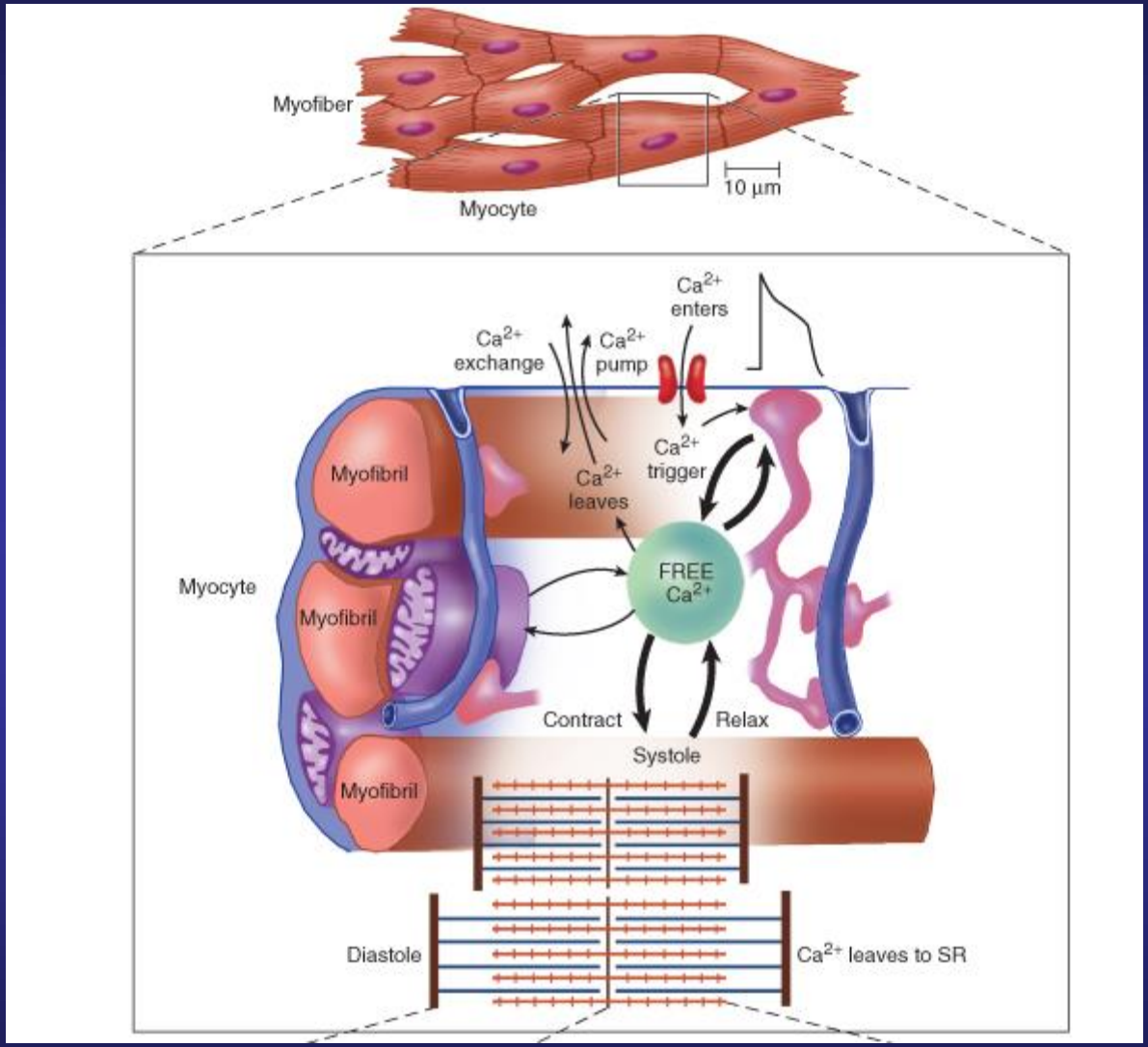
What is Heart Failure

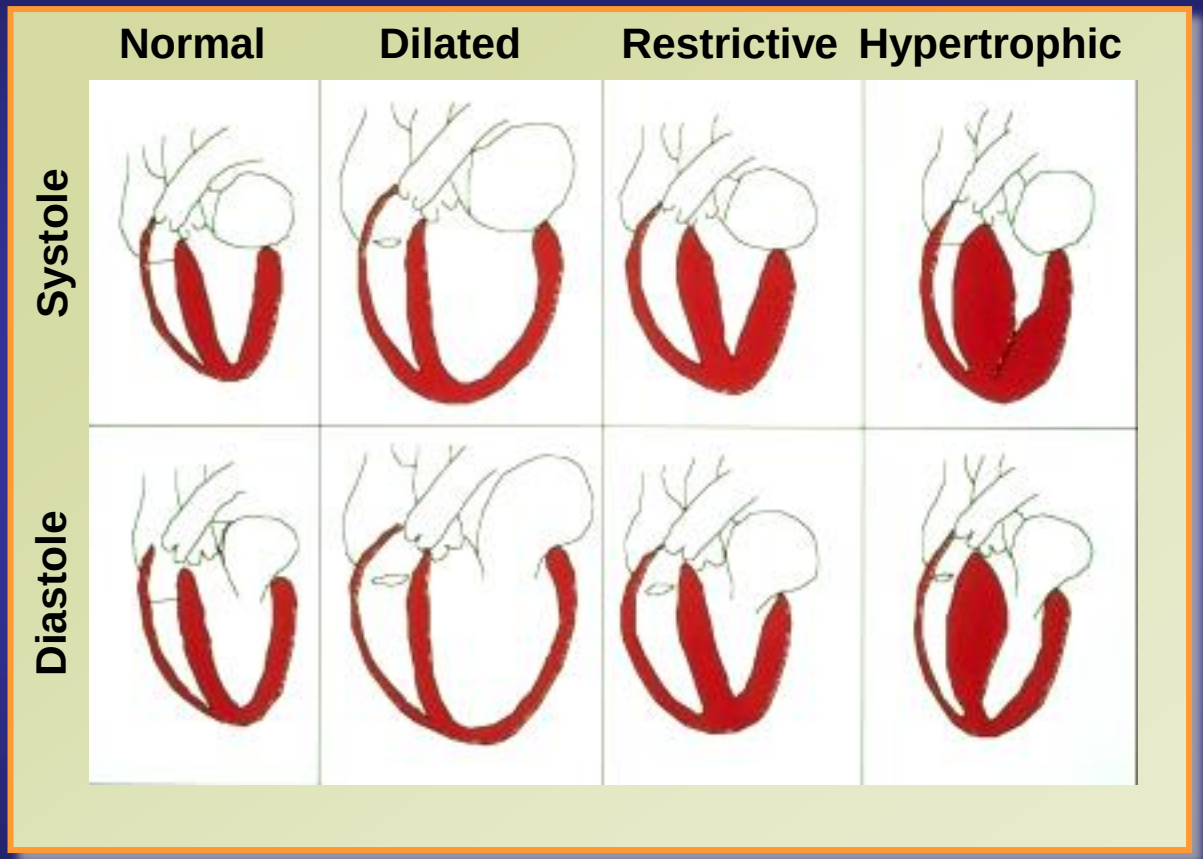
- Myocardial dysfunction that is either due to weakening of the contractile properties of the heart or relaxation properties (ie. Systolic or diastolic dysfunction, respectively)
- Clinical syndrome characterized by symptoms and signs of volume overload with reduced exercise tolerance




Myofiber
10 µm
Myocyte
Ca2+ enters
Ca2+ exchange
Ca2+ pump
Ca2+ trigger
Ca2+ leaves
Myofibril
Myocyte
Myofibril
FREE Ca2+
Contract
Relax
Systole
Myofibril
Diastole
Ca2+ leaves to SR

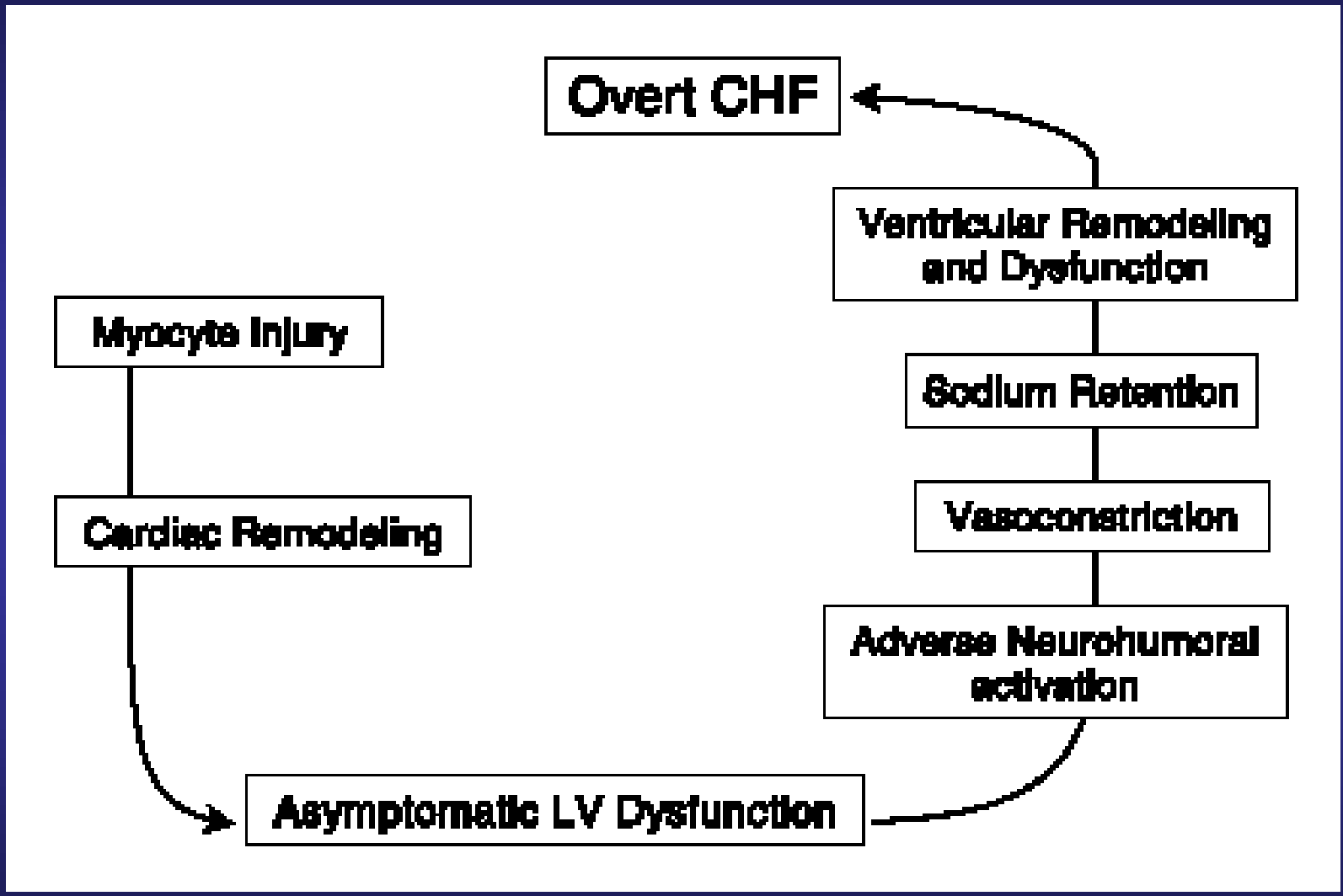
Defining Heart Failure

- HF exists when the heart is unable to pump sufficient blood to meet the metabolic needs of the body at normal filling pressures, provided the venous return to the heart is normal.[1]



[1] Schlant RC, Sonnenblick EH. *Hurst's The Heart*. 8th ed. New York: McGraw-Hill; 1994:515-55.

How Does Heart Failure Begin?



CV Neurohormonal Imbalance in Heart Failure

SNS and RAAS are overactivated in heart failure while beneficial effects of ECPs are diminished

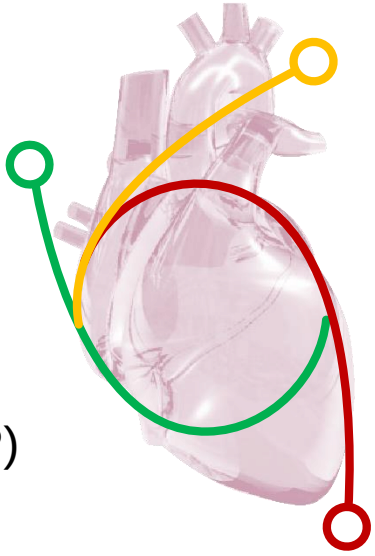
Endogenous Compensatory Peptides Effects [2-4]

Salt & Fluid retention
Vasoconstriction
Blood pressure
Sympathetic tone
Fibrosis
Hypertrophy

Natriuretic Peptides (ANP, BNP)
Vasoactive peptides

Neprilysin

Inactive Fragments



RAAS Effects [1,2,4]

Salt & Fluid retention
Vasoconstriction
Blood Pressure
Fibrosis
Hypertrophy

NPs, natriuretic peptides; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system.

1. Kemp CD, Conte JV. *Cardiovasc Pathol.* 2012;21(5):365-371. 2. Mangiafico S et al. *Eur Heart J.* 2013;34:886-893. 3. Nathisuwan S, Talbert RL. *Pharmacotherapy.* 2002;22:27-42. 4. Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015.

CV Neurohormonal Imbalance in Heart Failure

Traditional Therapies have not enhanced ECPs

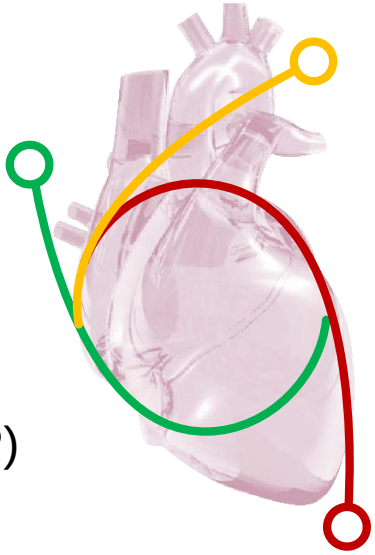
Endogenous Compensatory Peptides Effects [2-4]

Salt & Fluid retention
Vasoconstriction
Blood pressure
Sympathetic tone
Fibrosis
Hypertrophy

Natriuretic Peptides (ANP, BNP)
Vasoactive peptides

Neprilysin

Inactive Fragments



Beta-Blockers

Suppress the deleterious effects of SNS[1,4,5]

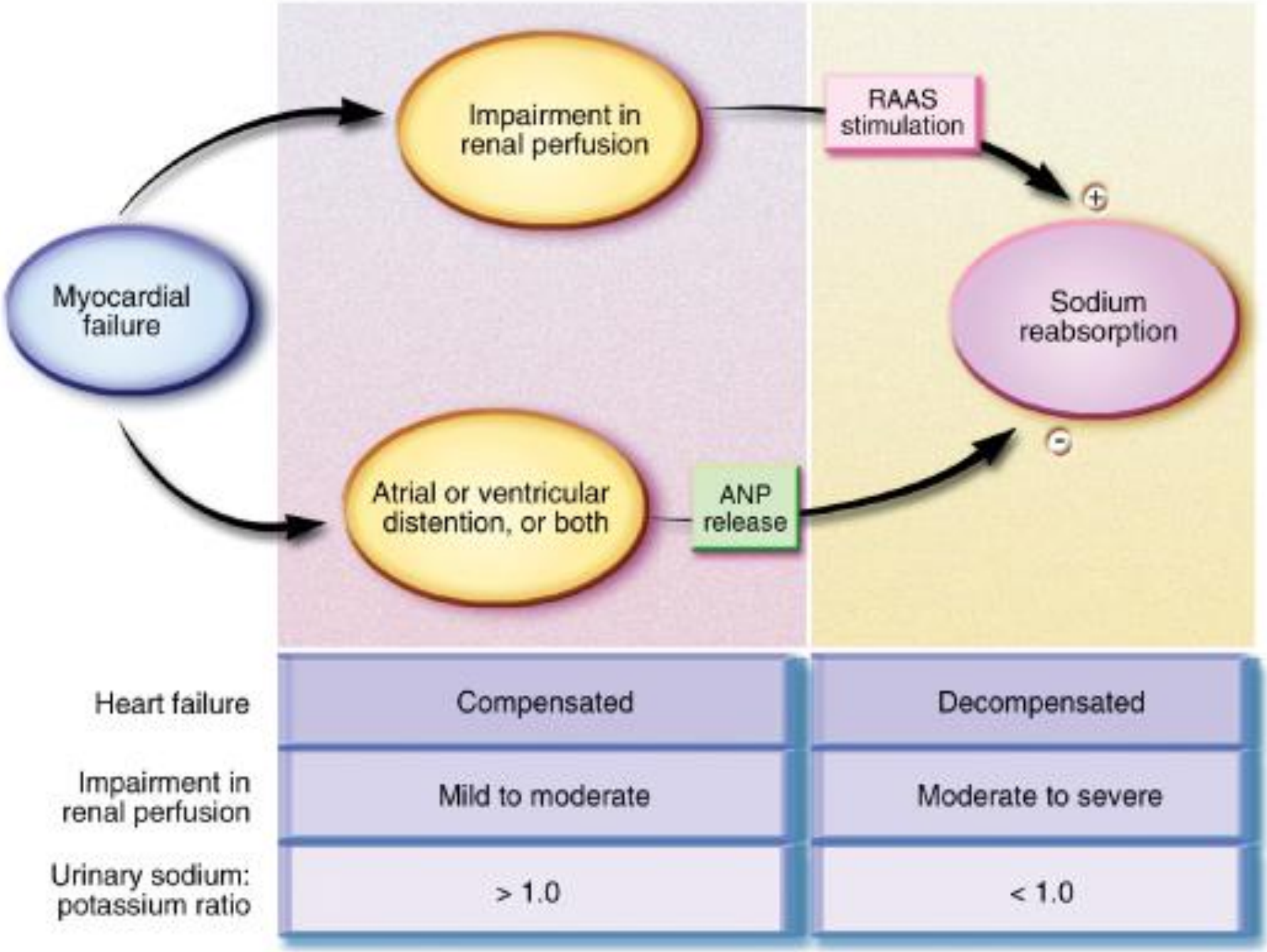
ACEi /ARB

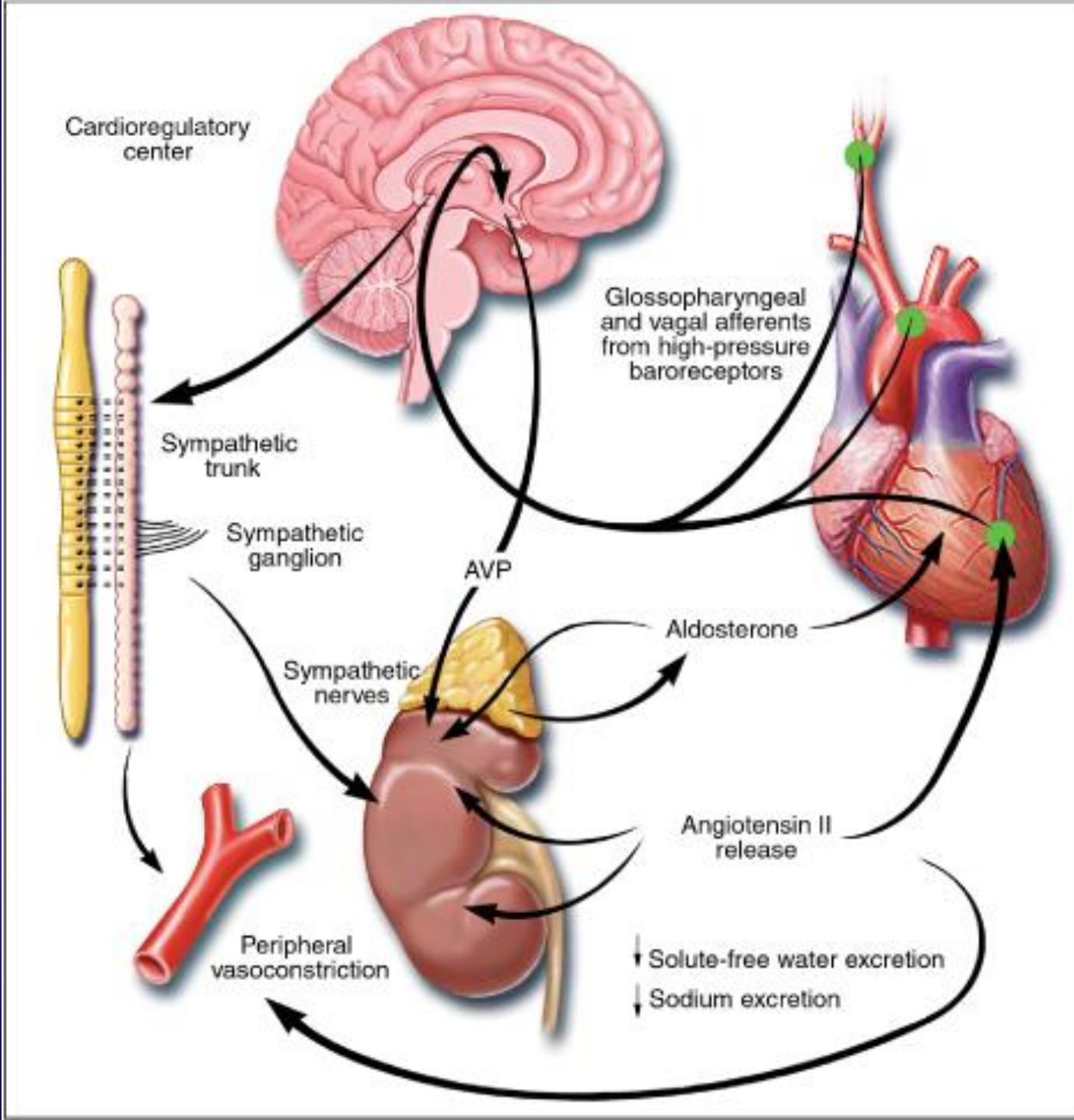
Suppress the deleterious effects of RAAS[1,2,4,5]

Link to Effects of Neprilysin Inhibition

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ECPs, endogenous compensatory peptides; HF, heart failure; NPs, natriuretic peptides; SNS, sympathetic nervous system; RAAS, renin-angiotensin-aldosterone system.

1. Kemp CD, Conte JV. *Cardiovasc Pathol.* 2012;21(5):365-371. 2. Mangiafico S et al. *Eur Heart J.* 2013;34:886-893. 3. Nathisuwan S, Talbert RL. *Pharmacotherapy.* 2002;22:27-42. 4. Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015. 5. Mann DL. Management of Patients with Heart Failure with Reduced Ejection Fraction. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015


Myocardial failure
Impairment in renal perfusion
RAAS stimulation
Sodium reabsorption
Atrial or ventricular distention, or both
ANP release
Heart failure
Compensated
Decompensated
Impairment in renal perfusion
Mild to moderate
Moderate to severe
Urinary sodium: potassium ratio
> 1.0
< 1.0


Cardioregulatory center
Glossopharyngeal and vagal afferents from high-pressure baroreceptors
Sympathetic trunk
Sympathetic ganglion
AVP
Aldosterone
Sympathetic nerves
Angiotensin II release
Peripheral vasoconstriction
Solute-free water excretion
Sodium excretion

Definitions of Chronic HF and LVEF

HF results from any **structural or functional impairment** of ventricular filling or ejection of blood[1]

- Current clinical practice guidelines classify types of HF by LVEF[1,2]
- However, there are several limitations to the use of LVEF in HF[3-5]
  - LVEF varies by age, sex, and ethnicity and can change over time in the same patient
  - Methods used to measure LVEF can also be imprecise

Normal LVEF Ranges (%)[a]

	Mean ± SD	Normal range
Female	64 ± 5	54-74
Male	62 ± 5	52-72

Data were derived from Lang et al.[3]

Chronic HF Is a Complex Clinical Syndrome[1]

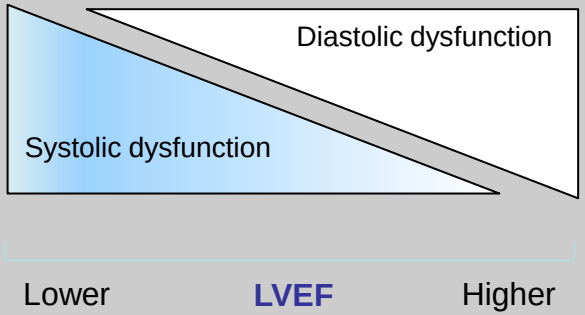
Types of HF emerge from **distinct pathophysiological mechanisms**[2,3]

Historically, LVEF has been used to select and dichotomize HF patients into types for clinical trials[1]

Patients present with **variable degrees of systolic and diastolic dysfunction**[4]

HFrEF and HFpEF are considered to be two extremes in a continuous spectrum of overlapping types of HF[4]

HF spectrum[4]



Burden of Chronic HF

An estimated 6.2 million Americans had HF based on data from NHANES 2013-2016[1]

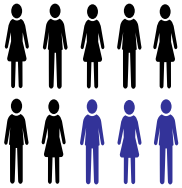
Approximately 5 million people with chronic HF have below-normal LVEF[1-3]

The prevalence of HF is projected to increase by 46% from 2012-2030, resulting in >8 million people with HF[1]

Hospitalization and Mortality Trends in Patients With Chronic HF

High hospitalization rates are associated with HF

- Among patients with HF in Olmsted County, 83% were hospitalized at least once and 43% were hospitalized at least 4 times. More than half of all hospitalizations were related to non-CV causes[1]
- 80% of HF hospitalizations are admitted from the emergency department[2]



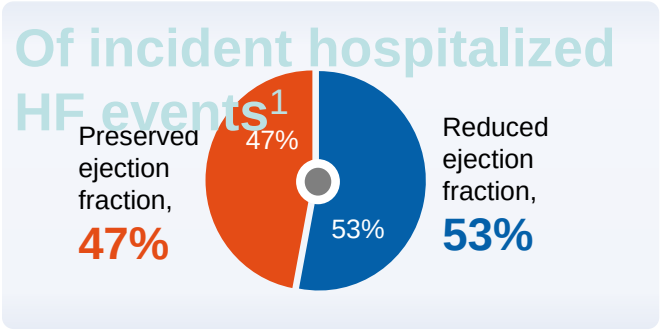
At 1 year, mortality in HF was 29.6% among Medicare beneficiaries[1]

- In NHLBI's ARIC study, the 30-day, 1-year, and 5-year case fatality rates after HF hospitalization were 10.4%, 22%, and 42.3%, respectively[1]

Epidemiology

Prevalence of Heart Failure With Reduced Ejection Fraction (HFrEF)

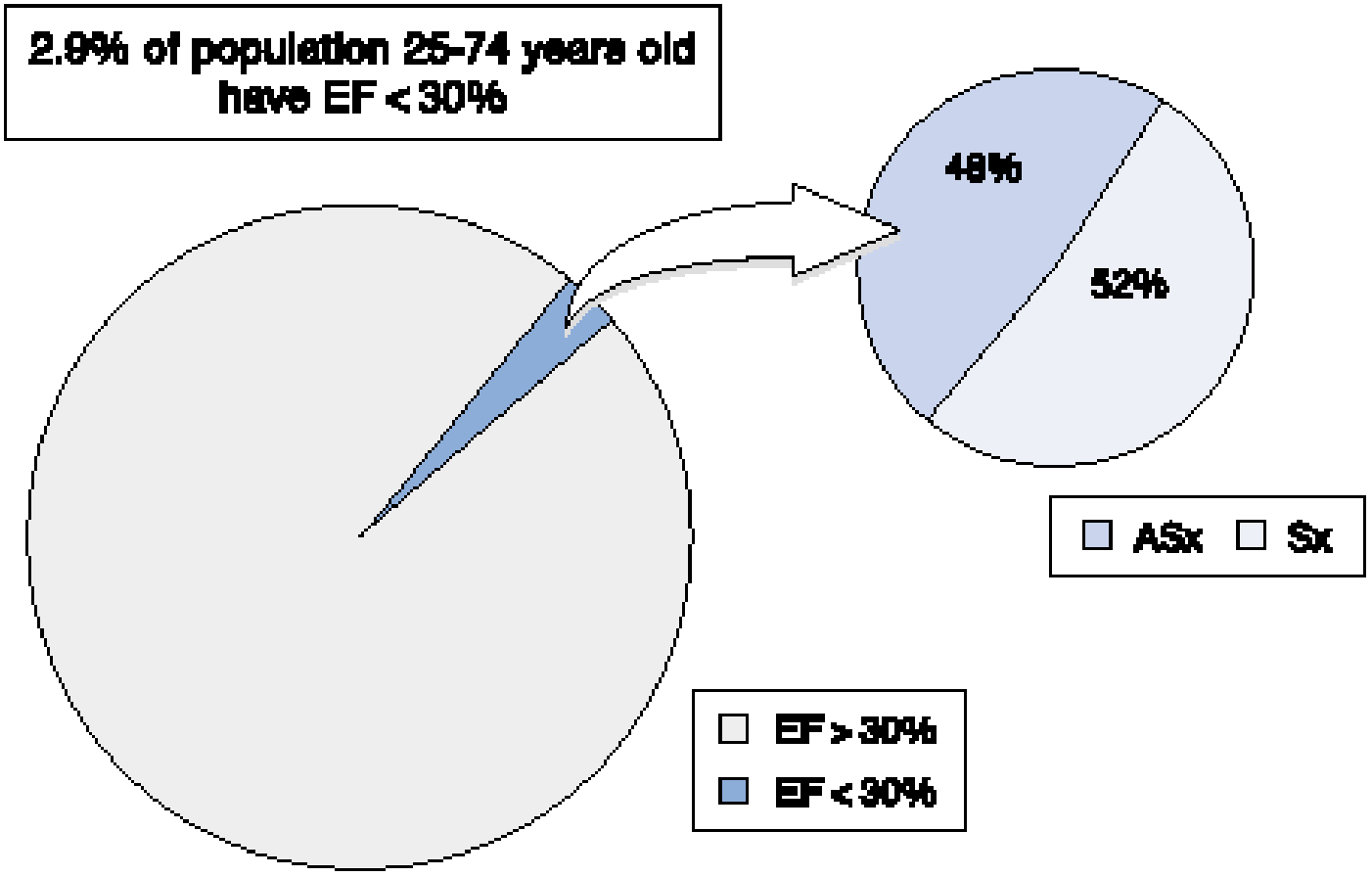
- An estimated 6.5 million Americans aged ≥20 years have heart failure and 960,000 new cases occur annually[1]
- The total number of Americans living with HF is projected to increase 46% from 2012 to 2030, resulting in >8 million people ≥18 years of age with HF[2]
- Approximately half of patients presenting with symptoms of HF have reduced LVEF (≤40%)[3]



HF, heart failure; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction

1. Benjamin EJ et al. *Circulation*. 2017;135(10):e146-e603.
2. Heidenreich PA, et al. *Circ Heart Fail.* 2013;6:606-619.
3. Yancy CW. et al. *Circulation.* 2013;128:e240-e327.

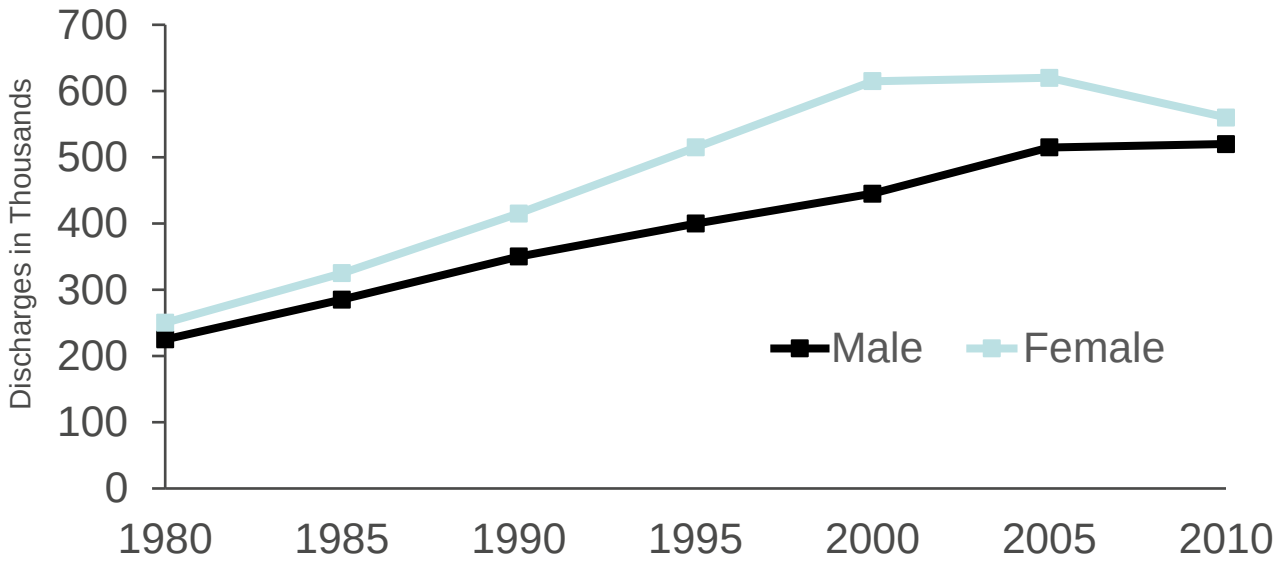
Epidemiology of Heart Failure



Heart Failure Hospitalization

- Heart failure hospitalization has steadily increased since 1980
- More than 1 million hospitalizations have a primary diagnosis of HF each year in the US

Discharges From Hospitalization Due to HF (US, 1980–2010)[1*]



*Approximately half of patients presenting with symptoms of HF have reduced LVEF (≤40%)[2]

1.Benjamin EJ et al. *Circulation*. 2017;135(10):e146-e603.
2.Yancy CW. et al. *Circulation.* 2013;128:e240-e327.

Hospital Readmission and Mortality Rates*

Hospital Readmission and Mortality Rates Are High for HF Patients

Approximately 25% of patients are readmitted within 30 days of discharge[a1]

The average 30-day CV readmission rate in the US for Medicare beneficiaries is 12.8% (*nonADHERE: 12.9%; ADHERE: 12.3%*)[2]

Among Medicare beneficiaries, the overall 1-year HF mortality rate is 29.6%[3]

The 5-year HF mortality rate remains at ~50%[3]

*Approximately half of patients presenting with symptoms of HF have reduced LVEF (≤40%)

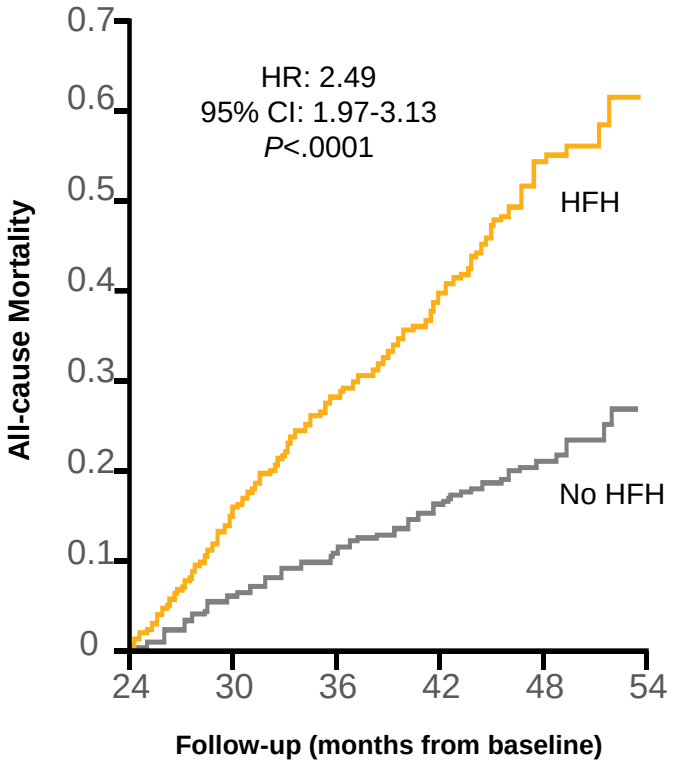
[a]Based on survey data on hospitals that enrolled in either of 2 national quality initiatives to reduce readmission (ie, the Hospital to Home [H2H] National Quality Improvement Initiative or the State Action on Avoidable Rehospitalizations Initiative [STAAR]) by July 1, 2010.

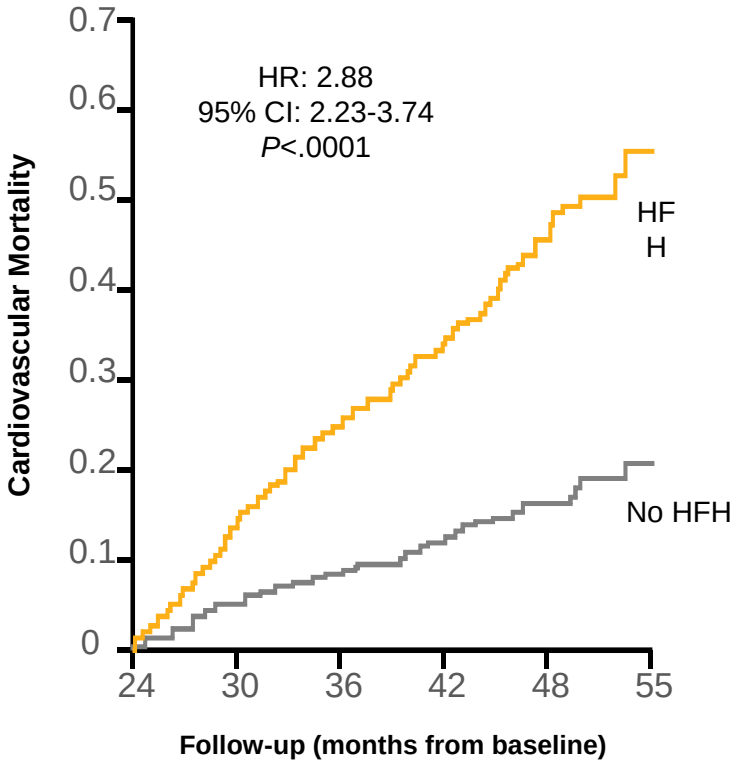
ADHERE, Acute Decompensated Heart Failure National Registry; CV, cardiovascular; HF, heart failure

1.Bradley EH et al. *Circ Cardiovasc Qual Outcomes*. 2013;6:444-450; 2. Kociol RD et al. *Am Heart J*. 2010;160:885-92;
3. Benjamin EJ et al. *Circulation*. 2017;135(10):e146-e603.

Mortality Following HF Hospitalization

Patients with CHF hospitalized during the first 2 years of follow-up



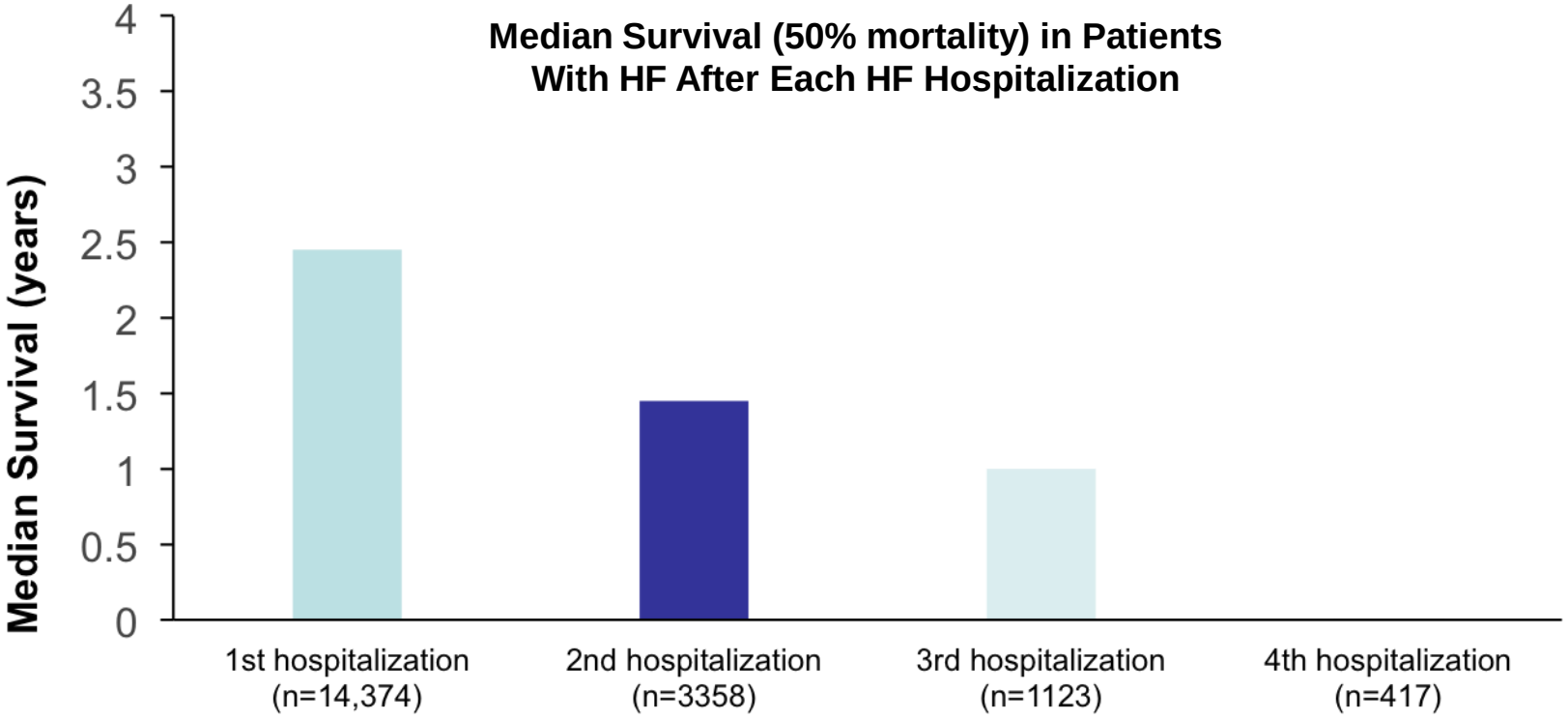


In this post-hoc propensity matched study of the Digitalis Intervention Group trial, 1057 patients in the US and Canada with chronic HF who had HFHs during the first 2 years of follow-up were matched with 1057 patients with chronic HF who had no HFH. Cox regression analysis was used to estimate the effect of incident HFH during the first 2 years after randomization on post–2-year mortality.

CHF, coronary heart failure; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio

Ahmed A et al. *J Card Fail*. 2008;14:211-218

Outcomes Worsen With Each Hospitalization

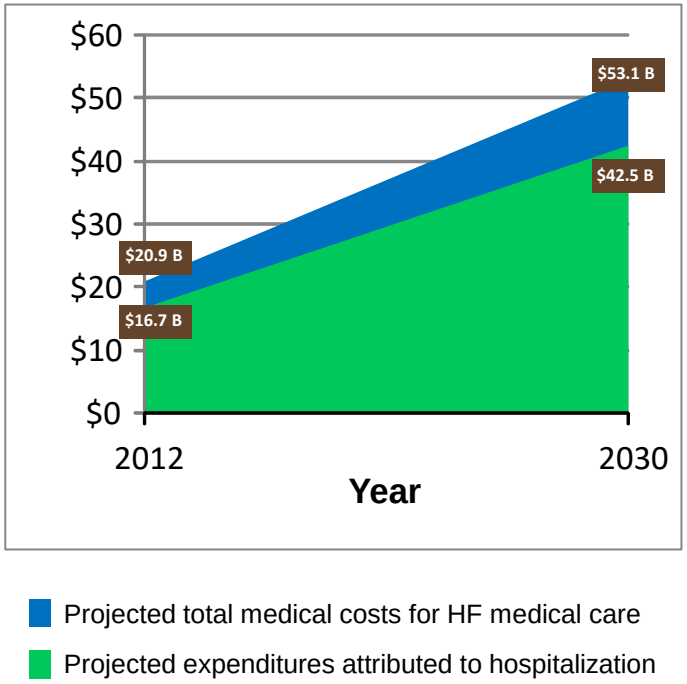


Based on a cohort of 14,374 patients, identified using the health care utilization databases, with a first hospitalization for HF among all residents of British Columbia between 2000 and 2004.
CI, confidence interval; HF, Heart Failure
Setoguchi S et al. *Am Heart J.* 2007;154:260-266.

The Economic and Health Burden

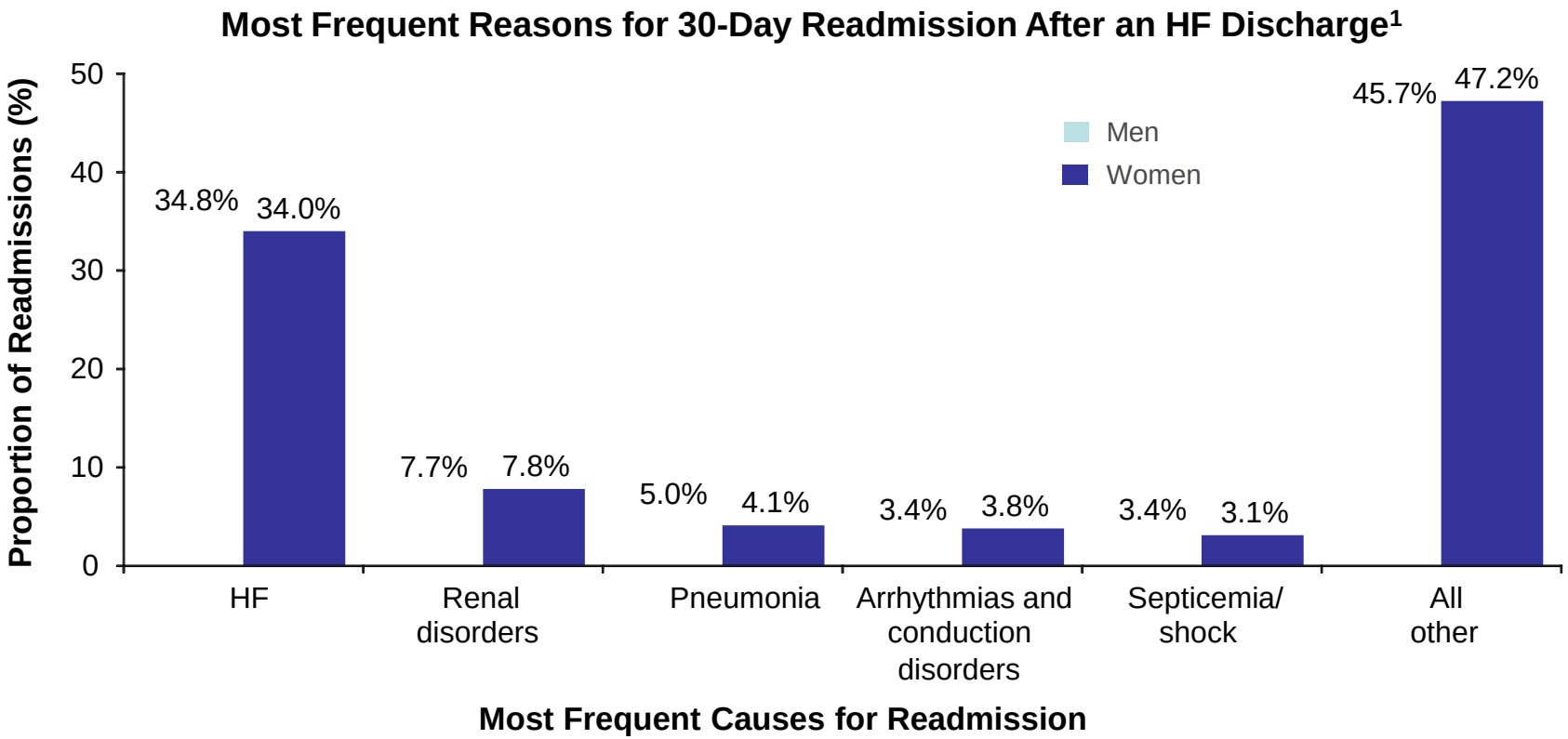
- There are approximately 1 million HF discharges in the US per year[1]
- American Heart Association (AHA) statistics reported nearly 509,000 ED encounters for HF in 2012[1]
- Total medical costs of HF are projected to increase from $20.9 billion in 2012 to $53.1 billion in 2030, a 2.5-fold increase. Of this, 80% of the costs will be attributable to hospitalization, assuming continuation of current hospitalization practices[2]

By 2030, >8 million people in the US will have HF[2]



1. Benjamin EJ et al. *Circulation*. 2017;135(10):e146-e603.
2. Heidenreich PA et al. *Circ Heart Fail*. 2013;6:606-619.

Reasons for 30-Day Readmission After HF Discharge



HF is the most common cause of readmission after a HF hospitalization[2]

HF, heart failure; LVEF, left ventricular ejection fraction

1. Dharmarajan et al. *JAMA*. 2013;309:355-363; 2. Yancy C et al. *Circulation*. 2013;128(16):e240-327.

New York Heart Failure Classification

Class I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain
Class II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain
Class III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea, or anginal pain
Class IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Approximate 2 year mortality in pts with LV dysfunction treated with ACE inhibitors

New York Heart Association class	Mortality, %
I	10
II	20
III	30-40
IV	40-50

Symptoms of Congestive Heart Failure

None

- Truly asymptomatic
- Asymptomatic because of sedentary lifestyle

Dyspnea on exertion

Decreased exercise tolerance

Orthopnea

Paroxysmal nocturnal dyspnea

Fatigue

Edema

Abdominal pain and distention

Palpitations

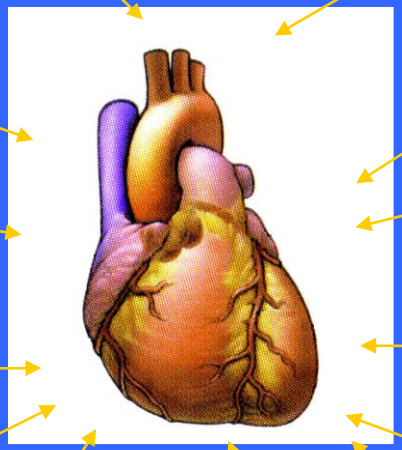
Syncope or presyncope

Embolic events (central nervous system, peripheral)

Physical Findings of Pts with CHF

Carotid	Normal or ↓ volume
Jugular venous pressure	Normal or ↑
Hepatojugular reflux	+ or -
Parasternal lift	+ or -
Apical impulse	Normal or diffuse in character, normal in position or laterally displaced
Palpable S_3, S_4, or P_2	+ or -
S_1	Normal or ↓ intensity
S_3, S_4	+ or -
MR or TR murmur	+ or -
Rales	+ or -
Pulsus alternans	+ or -
Edema	+ or -
Ascites	+ or -
Hepatomegaly	+ or -
Muscle wasting	+ or -
Blood pressure	Normal, ↑, orthostatic, or ↓

Causes of Left Ventricular Dysfunction



- Coronary artery disease
- Volume overload
- Metabolic
- Pressure overload
- Neurologic diseases
- Connective tissue diseases
- Heavy metals
- Primary cardiomyopathy
- Inherited diseases
- Other diseases
- Restrictive disease
- Infections
- Drugs

Courtesy of A. Agocha, MD

Causes of Heart Failure

Idiopathic
Familial
Infectious agents: bacterial, viral (including **human immunodeficiency virus**), fungal, ***Borrelia burgdorferi*** **(Lyme disease)**
Acute rheumatic fever
Infiltrative disorders: **amyloid**, hemochromatosis, sarcoid
Toxic: heroin, **cocaine**, alcohol, amphetamines, doxorubicin (Adriamycin), cyclophosphamide, sulfonamides, lead, arsenic, cobalt, phosphorus, ethylene glycol, some antiviral agents
Nutritional deficiencies: protein, thiamine, selenium
Electrolyte disorders: hypocalcemia, hypophosphatemia, hyponatremia, hypokalemia
Collagen vascular disorders: lupus, rheumatoid arthritis, systemic sclerosis, polyarteritis nodosa, hypersensitivity vasculitis, Takayasu's syndrome, polymyositis, Reiter's syndrome
Endocrine and metabolic diseases: diabetes mellitus, thyroid disease, hypoparathyroidism with hypocalcemia, pheochromocytoma, acromegaly
Tachycardia-induced cardiomyopathy
Miscellaneous: peripartum cardiomyopathy, sleep apnea syndrome, Whipple's disease, L-carnitine deficiency

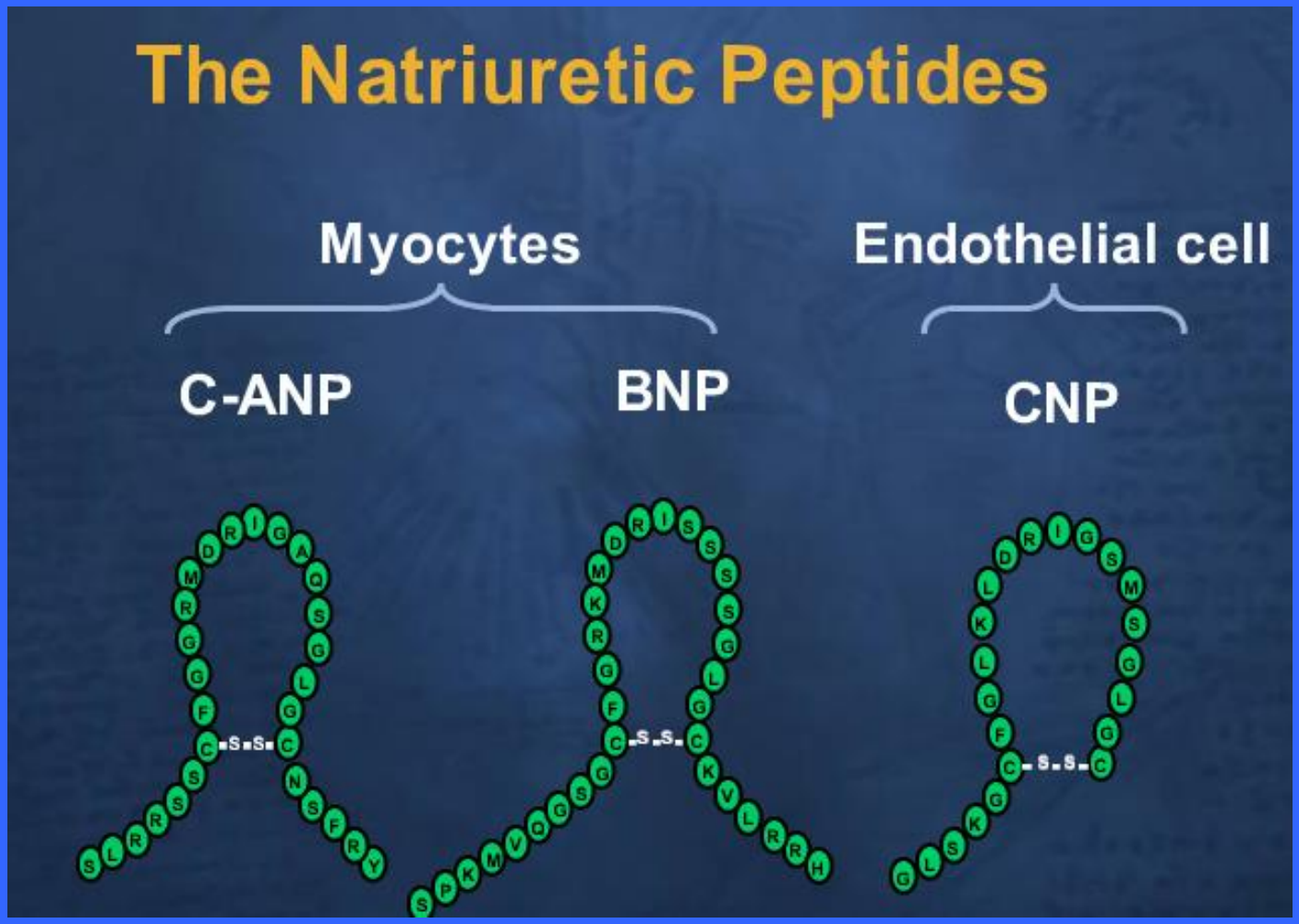
Diagnosis of CHF

- History and Physical Exam
- Pt’s weight-i.e weight gain of many pounds within a short period of time is a red flag
- Decreased urine output/pedal edema
- Labs-CXR/BNP/EKG/Echo

Other Labs

- EKG in dilated CM-
- Biatrial enlargement
- Widened QRS
- Voltage gain with LVH/RVH
- Voltage loss with pericardial effusion

Labs to Order to assess degree of Heart Failure



Reference Ranges BNP (pg/ml)

767 Subjects w/o CV Disease or LV Systolic or Diastolic Dysfunction

(5th-95th percentile)

Gender	45-54	55-64	65-74	74-83
Female	8 - 73	10 - 93	13 - 120	16 - 155
Male	4 - 40	5 - 52	7 - 67	9 - 86

BNP in Dyspnea - Caveats

- High BNP – No HF (False +)
  - Elderly women
  - Pulmonary embolus
  - Myocardial infarction
  - Compensated HF + pulm disease

HF (causing) drugs

- Ephedra (herbal ectasy)
- trastuzumab (Herceptin)
- anthracyclines
- cyclophosphamide
- EtOH - cocaine
- NSAIDS – Cox II inhibitors
- Radiation
  - Premature CAD
  - Valve disease
  - Constriction
  - Restriction

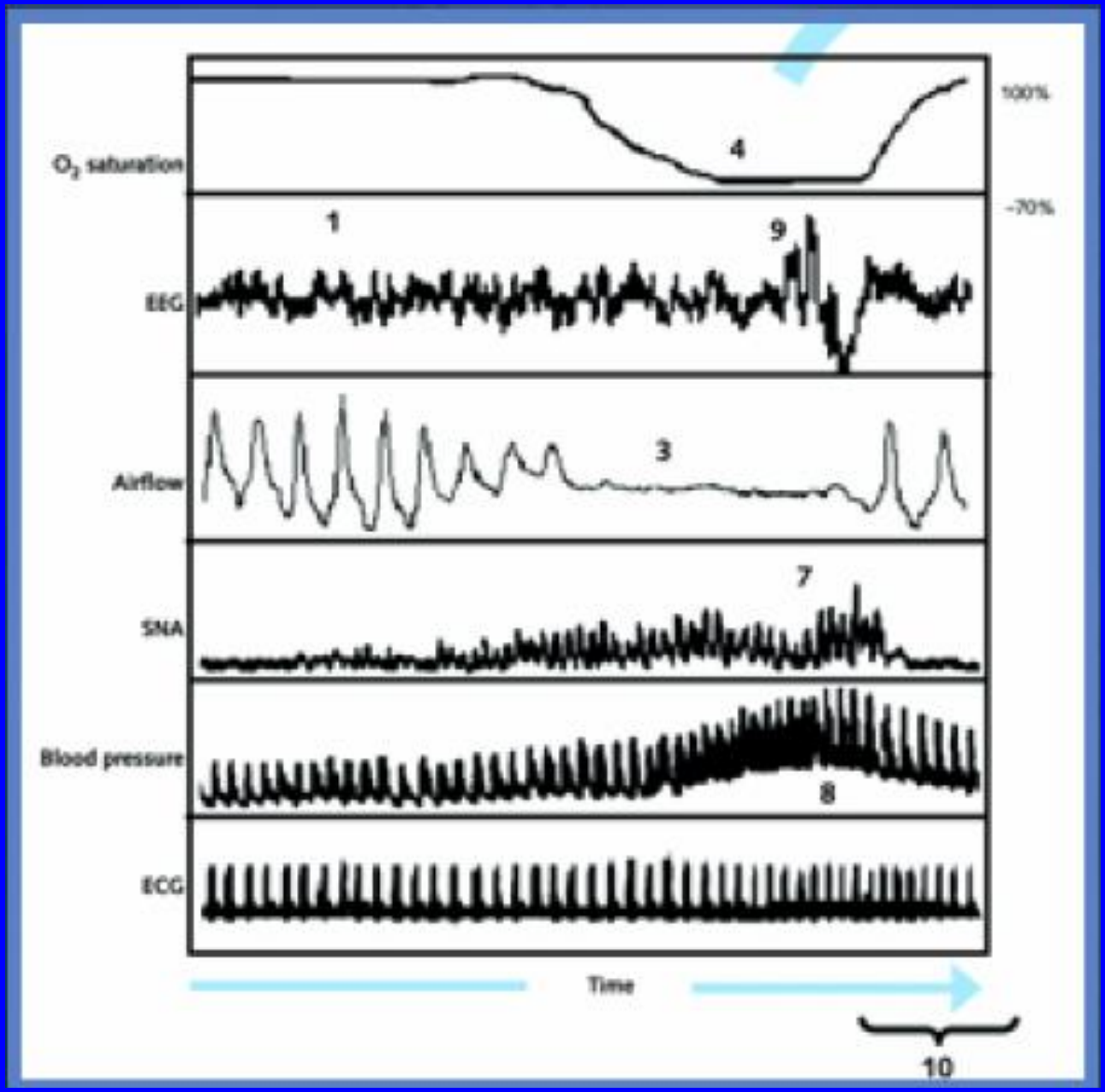
Hot Topic

Sleep and HF

- Obstructive Sleep Apnea
- Cheyne Stokes Respiration - Central Sleep Apnea

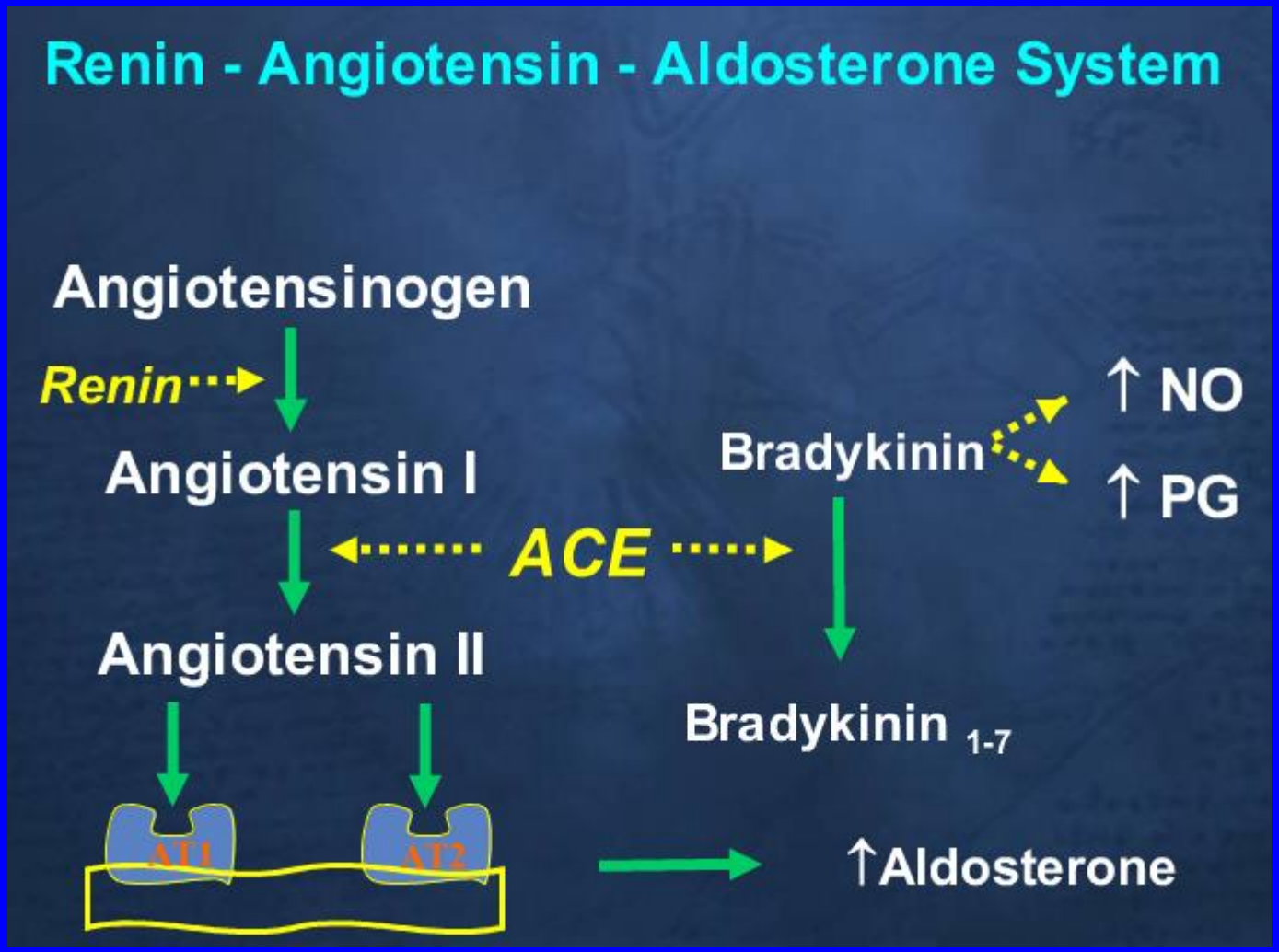
Sleep disordered breathing and it's treatment in CHF

LJ Cormican et al, Heart, 2005


O_2 saturation
100%
~70%
4
1
9
EEG
Airflow
3
7
SNA
Blood pressure
8
ECG
Time
10

Management of CHF
Neurohormonal Hypothesis

- LV dysfunction characterized by neurohormonal activation
- Neurohormonal activation drives adverse ventricular remodeling
- Intervention by neurohormonal antagonism favorably alters the natural history of CHF


Renin - Angiotensin - Aldosterone System
Angiotensinogen
Renin
Angiotensin I
ACE
Angiotensin II
Bradykinin
↑ NO
↑ PG
Bradykinin 1-7
AT1
AT2
↑Aldosterone

Acute decompensated CHF

- Diuretics-IV lasix
- Stabilize the BP-may need vasopressors (i.e. dopamine-renal dose and dobutamine)
- If BP is low-pt has low perfusion pressure, diuretics won't be effective
- Avoid beta blockers in the setting of acute decompensated CHF as it will worsen the pt's condition

Chronic CHF

- Beta blockers
- Diuretics-if pt has residual pulm edema
- ACEI or ARB
- Digoxin (if pt is symptomatic and has EF of < 30%)
- Aldactone
- Consider resynchronization therapy (i.e, BIV-ICD

Pharmacotherapy of Chronic CHF

First-Line Treatment

- Diuretic
- Digitalis
- ACE inhibitor
- Anticoagulation
- Beta-blockers

Pharmacotherapy of Chronic CHF

Diuretics–Deleterious Effects

- Decrease cardiac output
- Activate neurohormonal systems
- Azotemia
- Electrolyte disturbances
- Proarrhythmia
- Hyperlipidemia, hyperglycemia

Beta-Blockers for Heart Failure

- Beta blockers have been evaluated in more than 20,000 patients with heart failure who participated in over 20 placebo-controlled clinical trials
- Trials enrolled patients with LV systolic dysfunction, already on diuretic, ACE-I with or without digitalis
- Long-term treatment decreases symptoms, risk of death and hospitalization

Patients with Heart Failure Who Should Not be Beta-Blocked

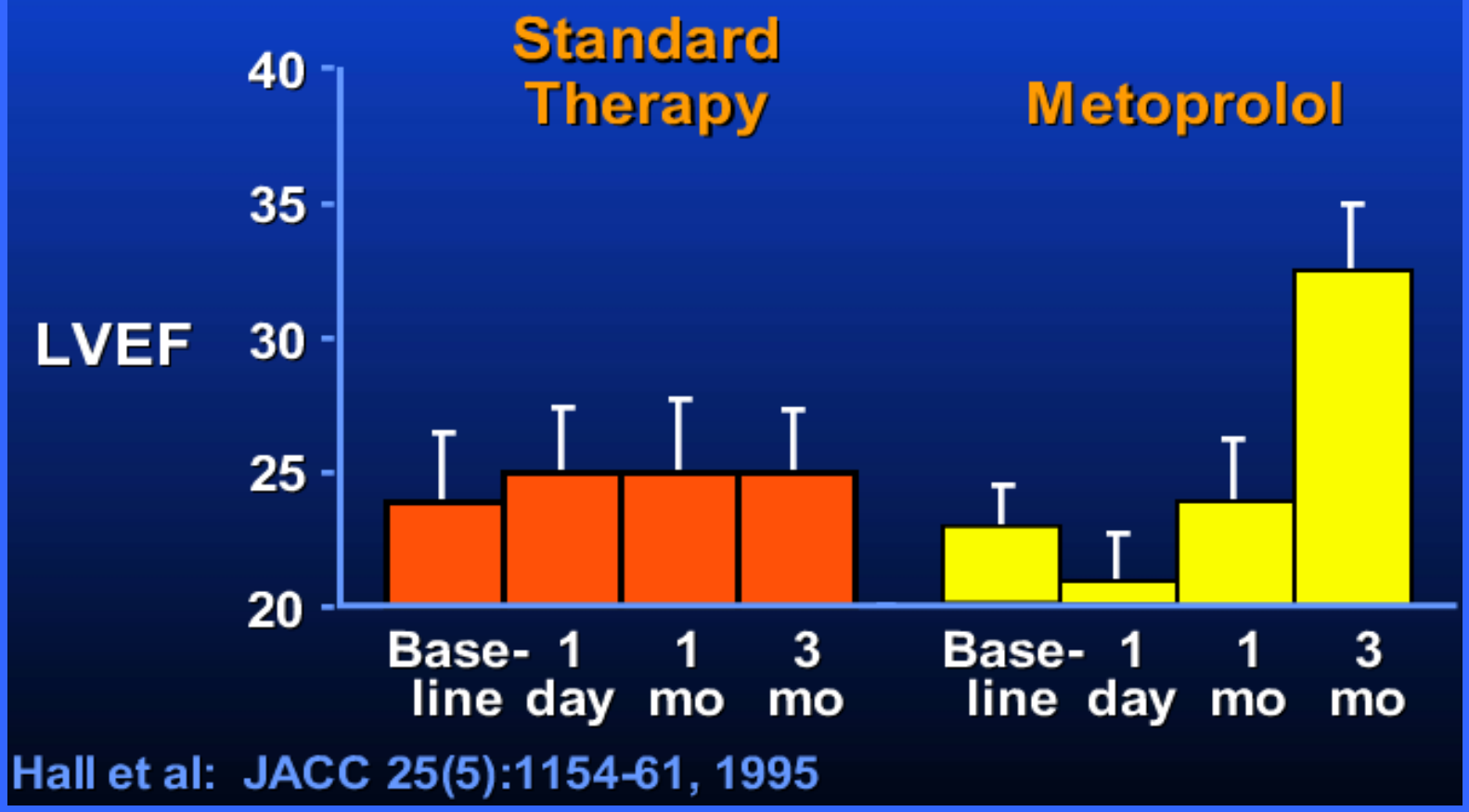
General considerations

- Bronchospasm
- Bradycardia
- Major depression

Heart failure considerations

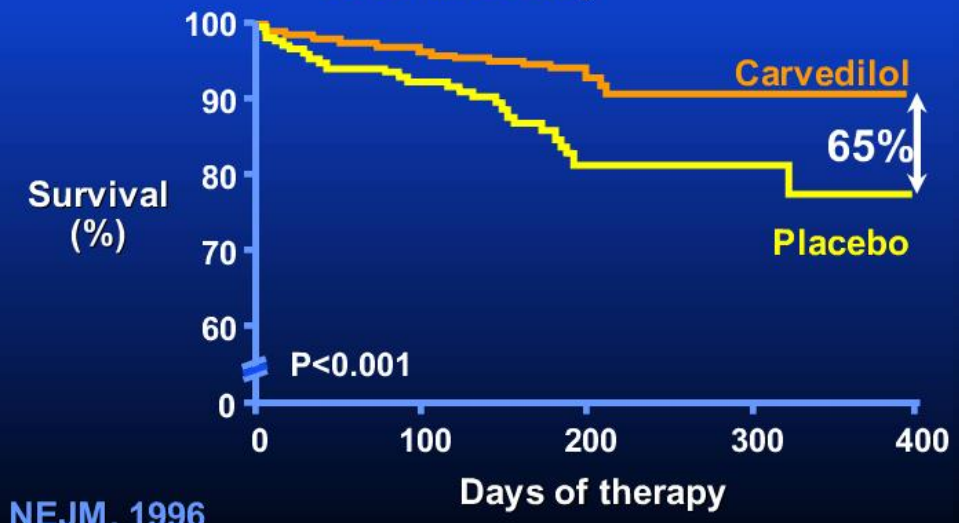
- Unstable
- Intravenous inotropes

Deterioration of LV Function with Initiation of Metoprolol Therapy



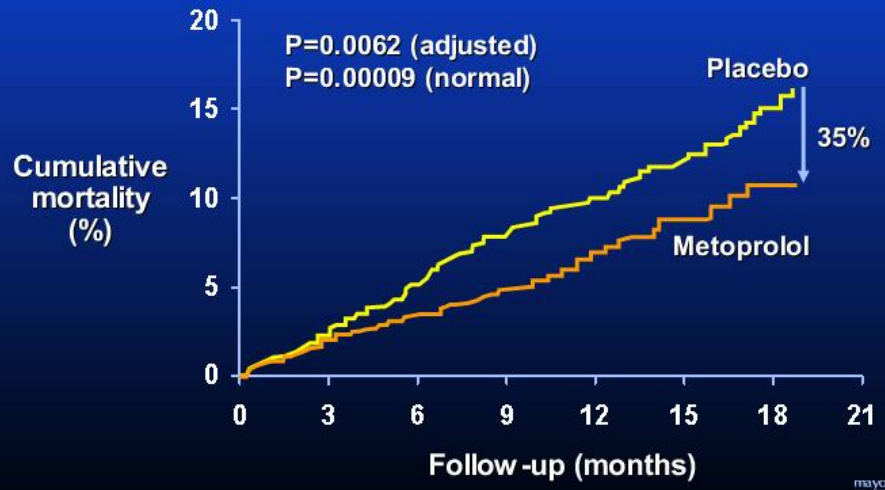
Hall et al: JACC 25(5):1154-61, 1995

U.S. Carvedilol Trial
Total Mortality



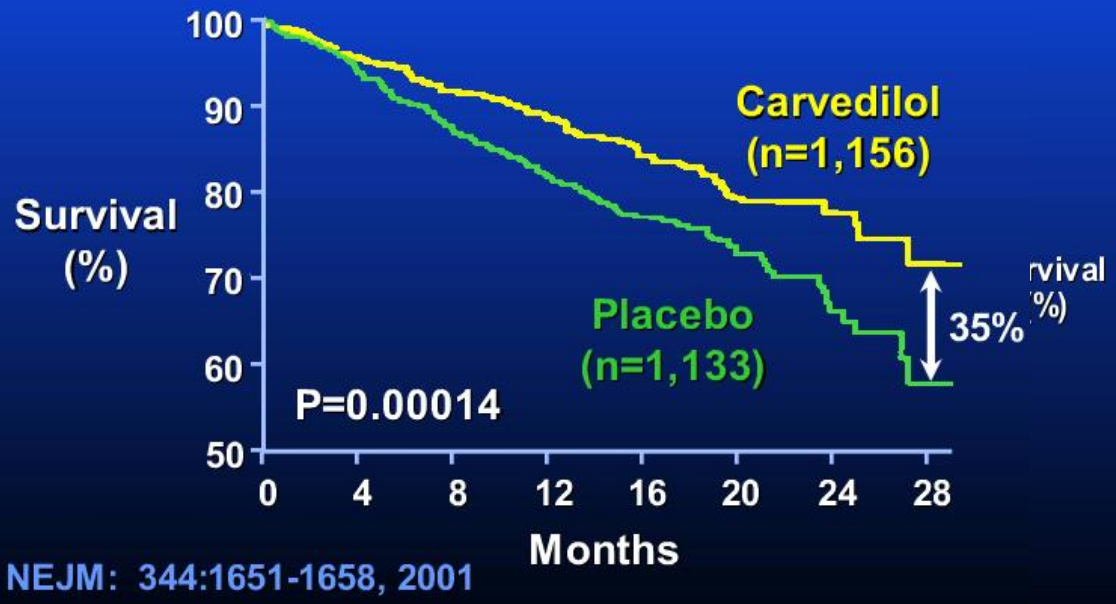
NEJM, 1996

MERIT-HF
Total Mortality



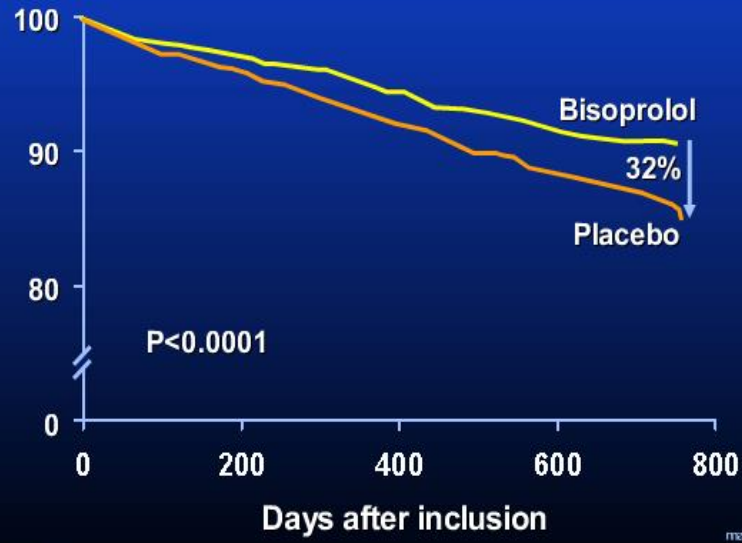
Lancet 353:2003, 1999

COPERNICUS



NEJM: 344:1651-1658, 2001

CIBIS II
All-Cause Mortality

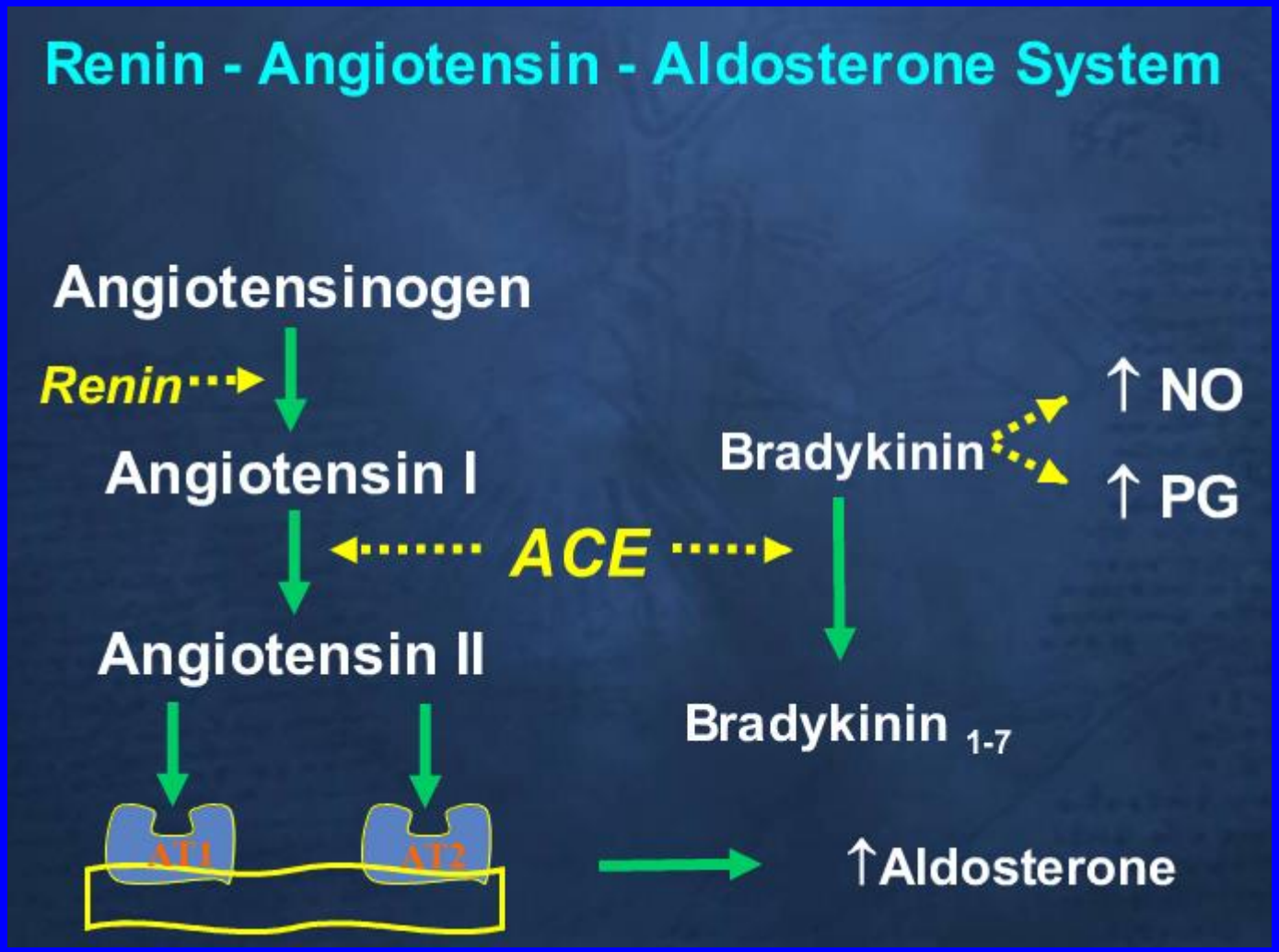


Lancet 353:9-13, 1999

Adjunctive treatments to Heart Failure

ACE Inhibitors
Anti-Ischemic Benefit

- Reduce risk of initial myocardial infarction
- Reduce risk of recurrent myocardial infarction


Renin - Angiotensin - Aldosterone System
Angiotensinogen
Renin
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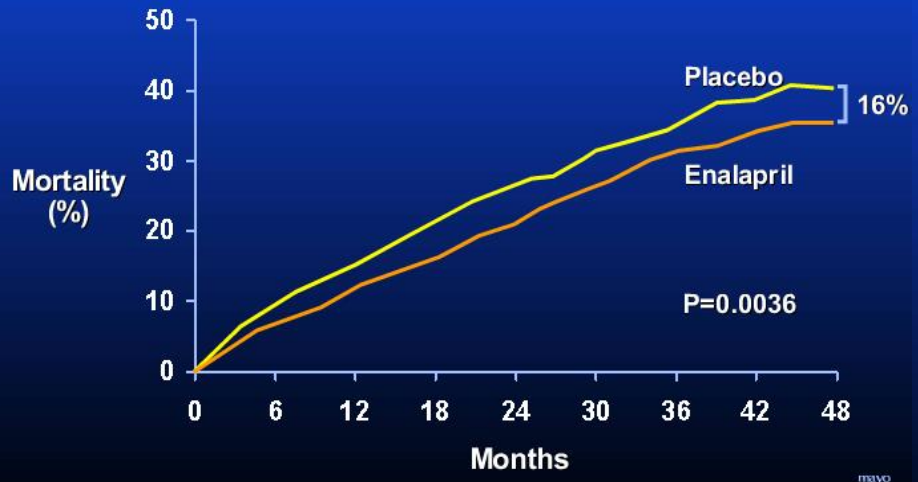
ACE
Angiotensin II
Bradykinin
↑ NO
↑ PG
Bradykinin 1-7
AT1
AT2
↑Aldosterone

Major Trials involving ACEI benefits in CHF

- ELITE
- CHARM
- SOLVD
- CONSENSUS I

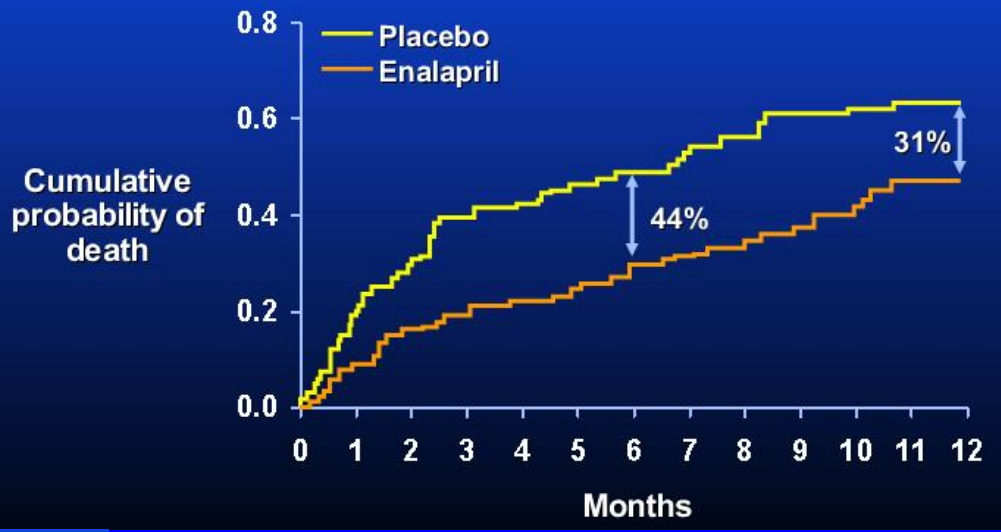
SOLVD-Treatment Results

Effects of Placebo or Enalapril on Mortality



The SOLVD Investigators: NEJM 325:293, 1991

CONSENSUS I Results: Effects of Enalapril on Cumulative Mortality



CHARM

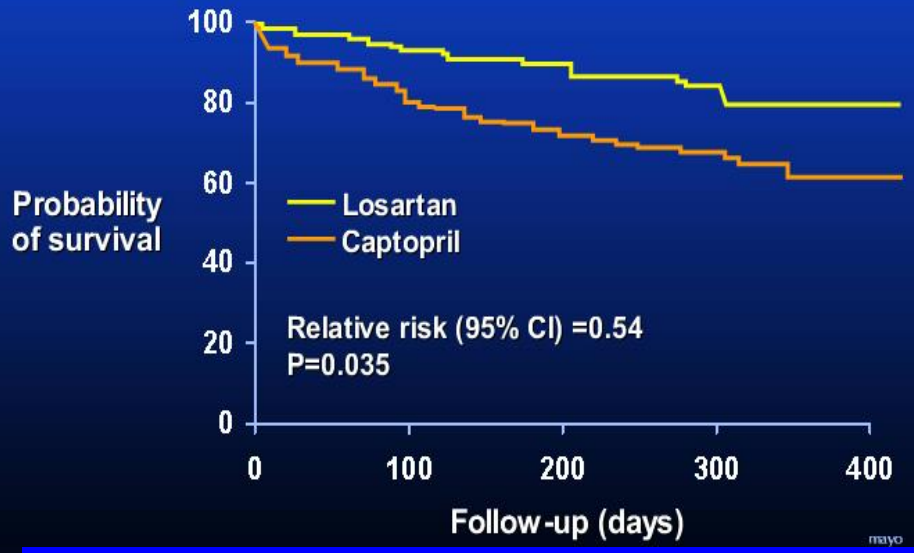
Candesartan for CHF; Class II-IV

Substudies	N	Combined Mortality & Hospitalization	CV Mortality
Added	2548	↓ 4.4%*	↓ 3.6%*
Alternative	2028	↓ 7.0%*	↓ 3.2%*
Preserved	3025	↓ 2.3%	↓ 0.1%
Overall	7601	↓ 4.3%*	↓ 2.1%*

*p≤0.05

ELITE

Cumulative Kaplan-Meier Estimates for Survival



Worsening Renal Function During Initiation of HF Therapy

ACE I and ARB increase Crt

- With initiation of ACEi / ARB
- ↑ Crt ≤ 30% is expected

  (Isles, Clinical Medicine, June, 2002)
- > 30%, consider

  hypovolemia

  hypotension

  bilateral RVD

  NSAID

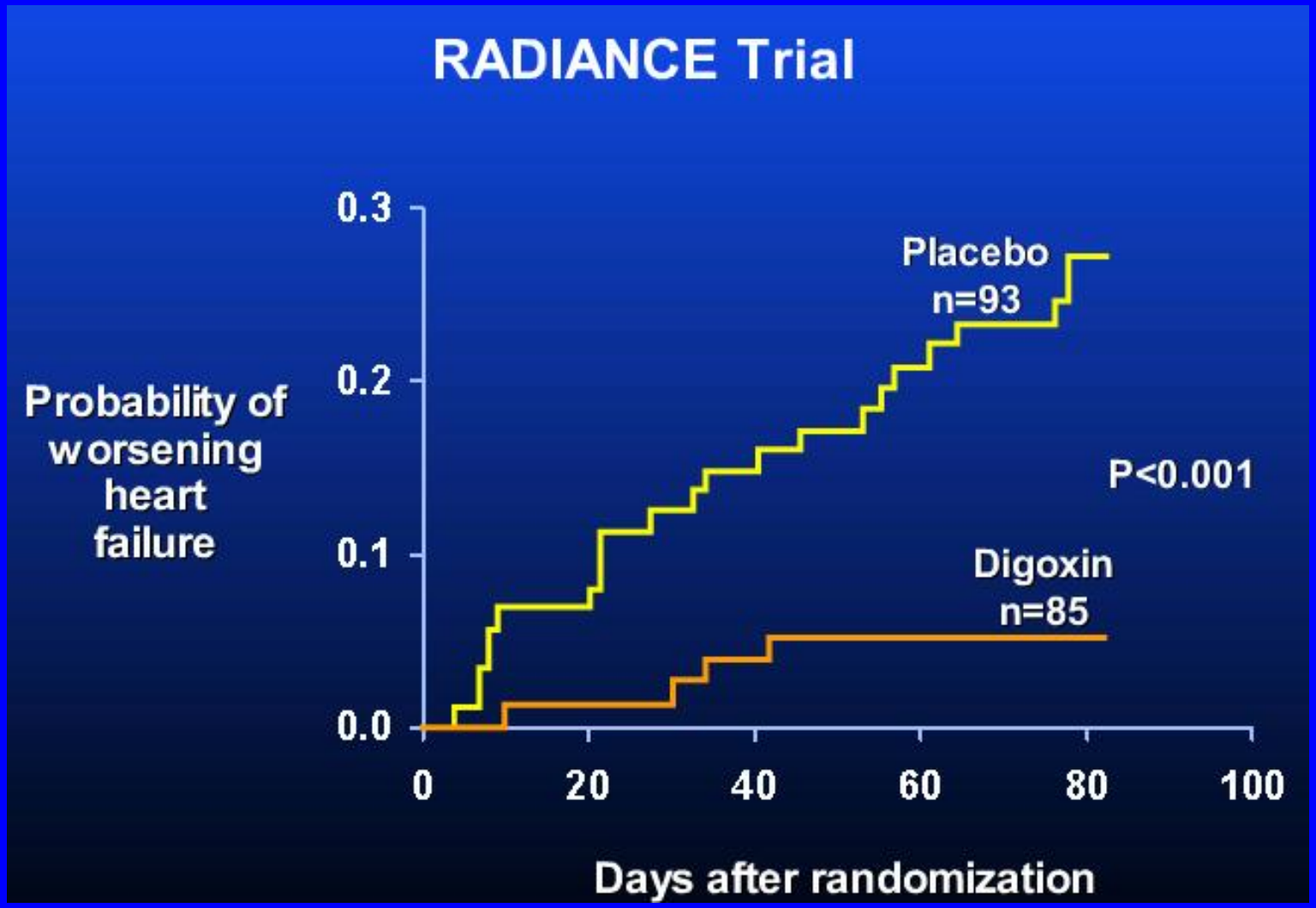
  chronic renal insuff

Pharmacotherapy of Congestive Heart Failure

Digitalis

- Placebo-controlled NIH multicenter mortality trial
- Safe
- Decreases rate of hospitalization
- Improves functional capacity
- No mortality benefit

NEJM 336:525-33, 1997


RADIANCE Trial
Probability of worsening heart failure
0.3
0.2
0.1
0.0
Placebo
n=93
Digoxin
n=85
P<0.001
0
20
40
60
80
100
Days after randomization

Effect of Aldosterone Antagonism on Mortality in CHF
Potential Mechanisms

- Reduced myocardial fibrosis
- Reduced renal damage
- Reduced vascular damage
- Improved endothelial function
- Improved Aortic Compliance
- Reduced free radical formation
- Potassium conservation

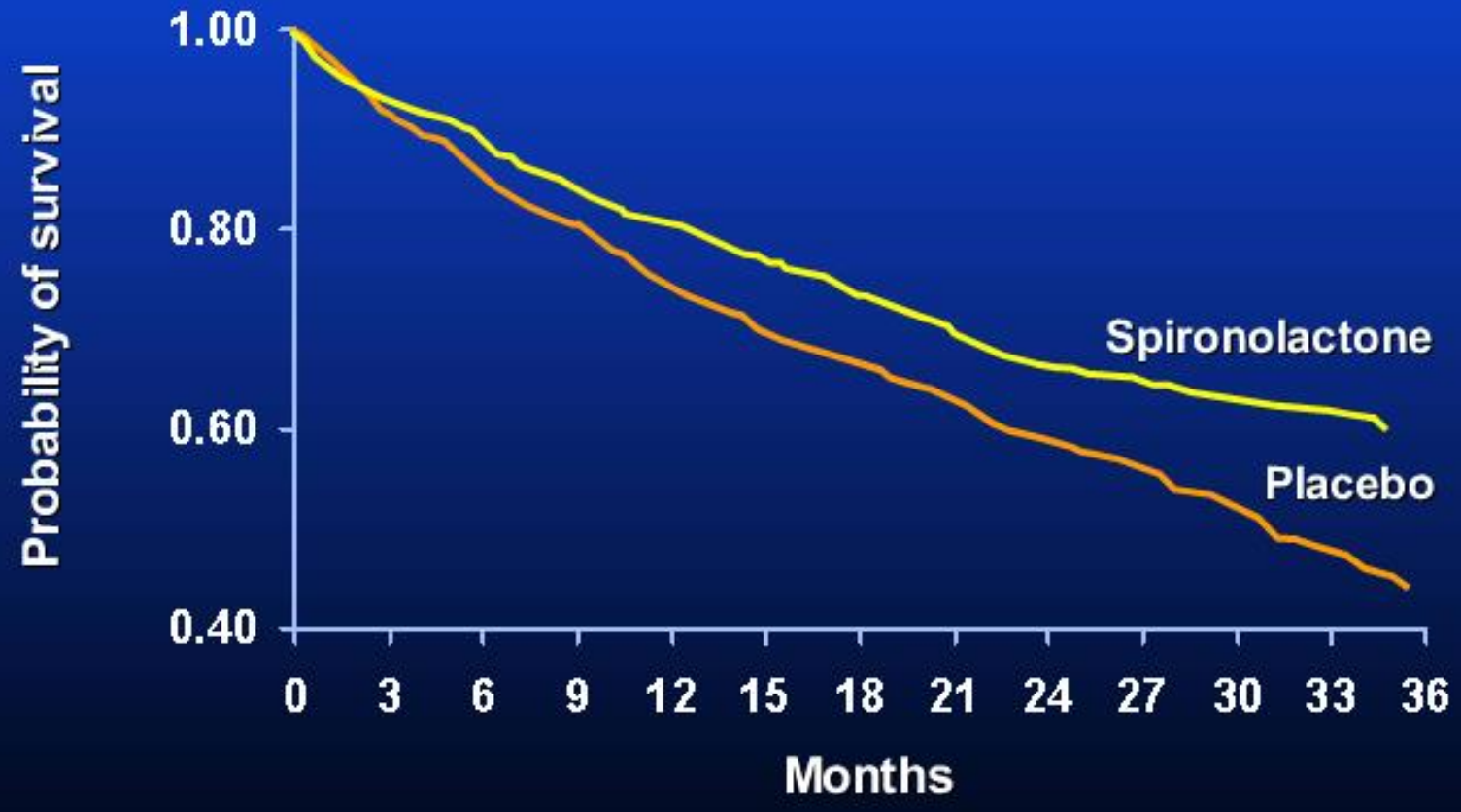
Aldosterone

RALES

EPHEYSES

TOPCAT

Effect of Spironolactone on Survival in Patients with Severe CHF



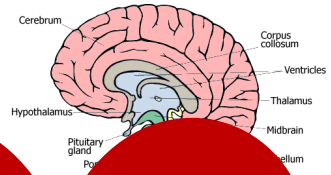
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

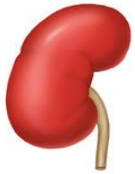
Where Do the Medications Work?

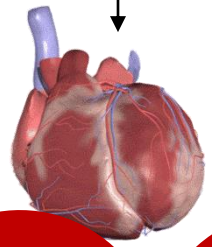
Baroreceptor response

R-A-A-S activation
Decreased GFR

Ventricular wall tension
Goal: increase SV







Beta Blockers

•ACE/ARB
•Aldosterone Antagonist
•Sacubitril/ARB

Funny Channel Blocker

ocyte growth

Heart Rate
Contractility

Hypertrophy

Adapted from https://quizlet.com/101258231/pathophysiology-chapter-19-heart-failure-dysrhythmias-common-sequelae-of-cardiac-diseases-flash-cards/

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 11, 2014 VOL. 371 NO. 11

Angiotensin–Neprilysin Inhibition versus Enalapril in Heart Failure

John J.V. McMurray, M.D., Milton Packer, M.D., Akshay S. Desai, M.D., M.P.H., Jianjian Gong, Ph.D., Martin P. Lefkowitz, M.D., Adel R. Rizkala, Pharm.D., Jean L. Rouleau, M.D., Victor C. Shi, M.D., Scott D. Solomon, M.D., Karl Swedberg, M.D., Ph.D., and Michael R. Zile, M.D., for the PARADIGM-HF Investigators and Committees*

METHODS

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 LCZ696 (at a dose of 200 mg twice daily) or enalapril (at a dose of 10 mg twice daily), in addition to recommended therapy. The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure, but the trial was designed to detect a difference in the rates of death from cardiovascular causes.

RESULTS

The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with LCZ696 had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the LCZ696 group and 1117 patients (26.5%) in the enalapril group (hazard ratio in the LCZ696 group, 0.80; 95% confidence interval [CI], 0.73 to 0.87; P<0.001). A total of 711 patients (17.0%) receiving LCZ696 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, LCZ696 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). The LCZ696 group had higher proportions of patients with hypotension and nonserious angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

CONCLUSIONS

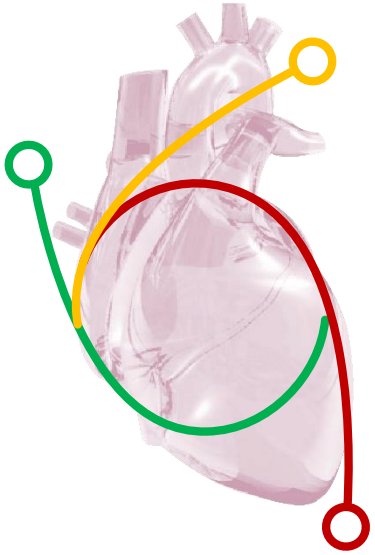
LCZ696 was superior to enalapril in reducing the risks of death and of hospitalization for heart failure. (Funded by Novartis; PARADIGM-HF ClinicalTrials.gov number, NCT01035255.)

Sacubitril/Valsartan

Restoring Neurohormonal Balance

Endogenous Compensatory Peptides Effects [2-4]

Salt & Fluid retention
Vasoconstriction
Blood pressure
Sympathetic tone
Fibrosis
Hypertrophy



Neprilysin Inhibition

Enhances the beneficial effects of endogenous compensatory peptides

Sacubitril/ Valsartan[6]

Beta-Blockers

Suppress the deleterious effects of SNS[1,4,5]

ACEi /ARB

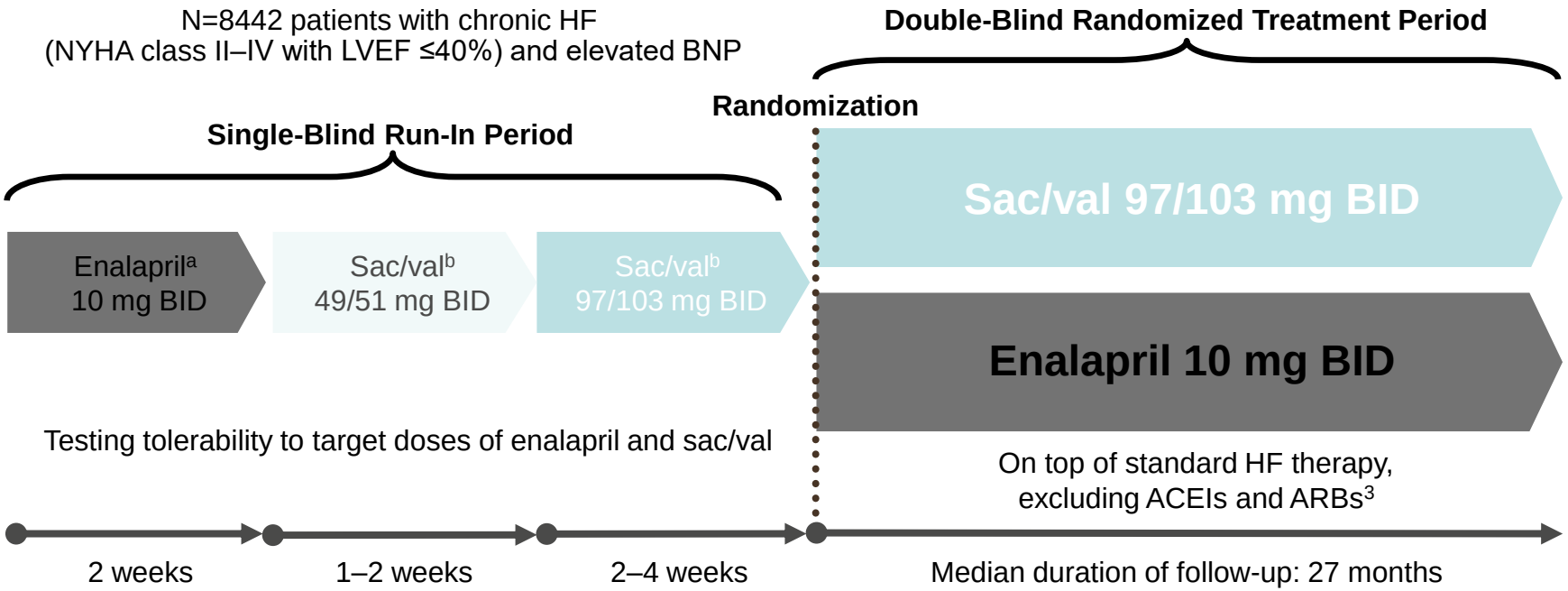
Suppress the deleterious effects of RAAS[1,2,4,5]

1. Kemp CD, Conte JV. *Cardiovasc Pathol.* 2012;21(5):365-371. 2. Mangiafico S et al. *Eur Heart J.* 2013;34:886-893. 3. Nathisuwan S, Talbert RL. *Pharmacotherapy.* 2002;22:27-42. 4. Hasenfuss G, Mann DL. Pathophysiology of heart failure. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015. 5. Mann DL. Management of Patients with Heart Failure with Reduced Ejection Fraction. In: Mann DL et al, eds. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine. 10th ed. Philadelphia, PA: Elsevier; 2015 6. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.

PARADIGM-HF

PARADIGM-HF

Study Design



36 hour washout was required between enalapril and sac/val run-in and prior to randomization

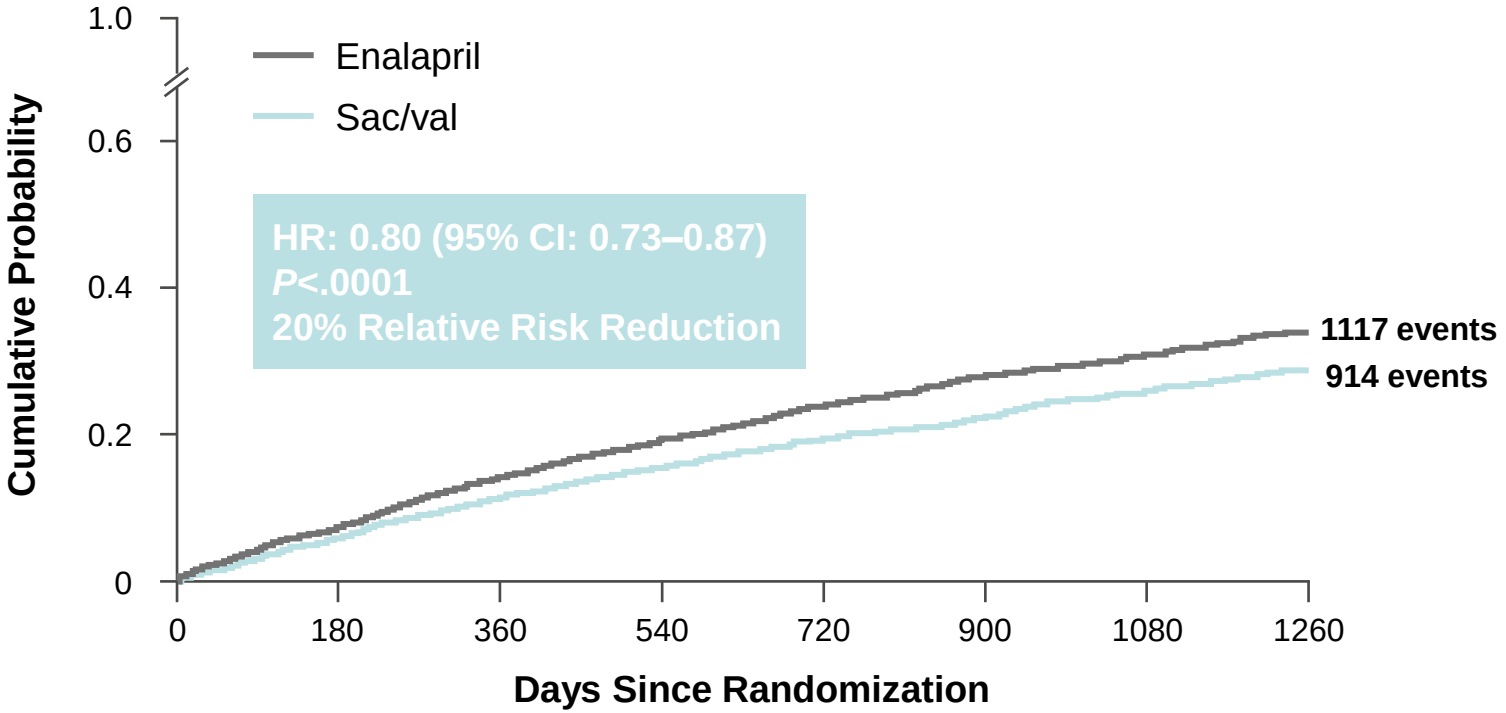
Primary outcome: To demonstrate superiority of sacubitril/valsartan over enalapril in reducing composite of death from CV causes or a first hospitalization for HF

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BID, twice daily; BNP, brain natriuretic peptide; NYHA, New York Heart Association; Sac/val, Sacubitril/valsartan.
aEnalapril 5 mg BID for 1–2 weeks followed by enalapril 10 mg BID was an optional starting run-in dose for patients treated with ARBs or with a low dose of ACEI.
bDosing in clinical trials was based on the total amount of both components of sac/val; 24/26 mg, 49/51 mg, and 97/103 mg were referred to as 50 mg, 100 mg, and 200 mg, respectively. Sac/val was formerly known as LCZ696 in clinical trials.
1. Entresto (sacubitril/valsartan) [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; August 2015.
2. McMurray JJ et al. *Eur J Heart Fail*. 2013;15(9):1062-1073. 3. McMurray JJ et al. *N Engl J Med*. 2014;371(11):993-1004.

PARADIGM-HF

Primary Endpoint: Time to First Occurrence of CV Death or HF Hospitalization

- The difference in favor of sacubitril/valsartan was seen early in the PARADIGM-HF trial and at each interim analysis



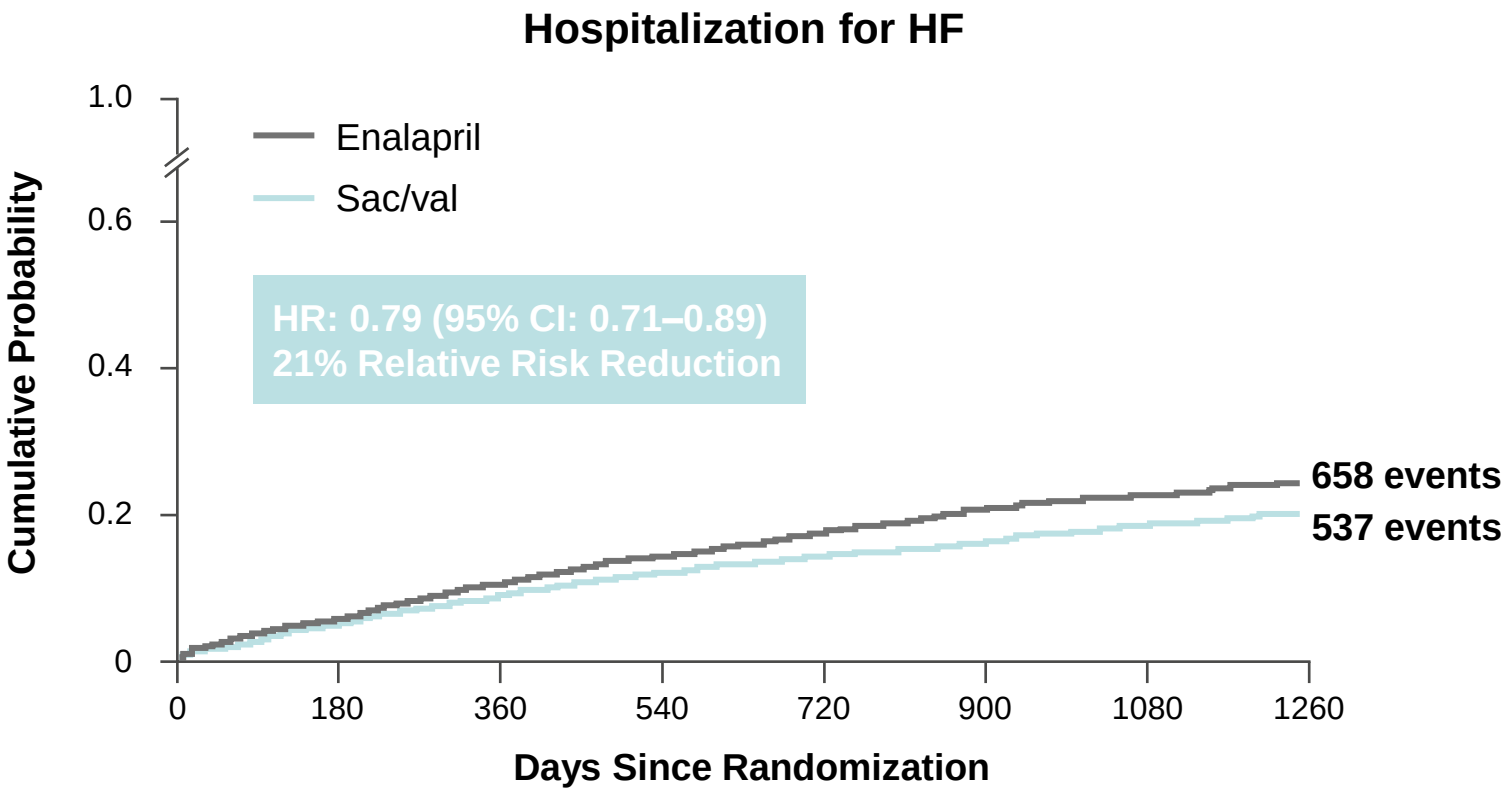
No. at risk								
Sac/val	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

CI, confidence interval; HR, hazard ratio; HF, heart failure; CV, cardiovascular

McMurray JJ et al. *N Engl J Med.* 2014;371(11):993-1004.

PARADIGM-HF

*Components of Primary Endpoint: Time to First Occurrence of Hospitalization for HF**



No. at risk								
Sac/val	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

*Analyses of the components of the primary composite endpoint were not prospectively planned to be adjusted for multiplicity

CI, confidence interval; HR, hazard ratio; HF, heart failure

McMurray JJ et al. *N Engl J Med.* 2014;371(11):993-1004.

PARADIGM-HF: Clinical Progression Analysis

Heart Failure Hospitalizations

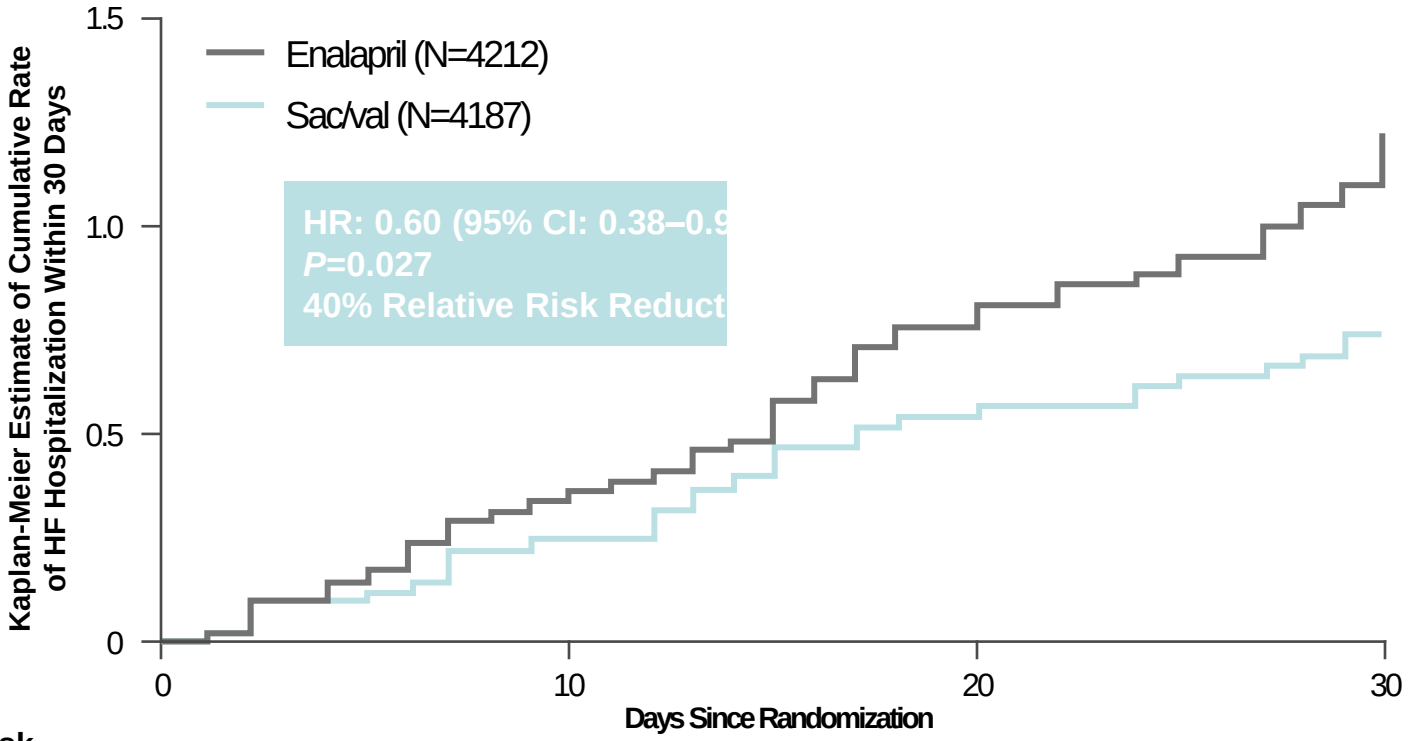
When all (including repeat) hospitalizations were considered, compared with patients in the enalapril group, patients in the sacubitril/valsartan group had 23.0%

Type of Hospitalization[a]	Sac/Val N=4187	Enalapril N=4212	HR (95% CI)	P Value
HF, n	851	1079	0.77 (0.67–0.89)[b]	<0.001

This was an exploratory objective.
[a]All (including repeat) hospitalizations.
[b]Rate ratio estimated from a negative binomial model.
Packer M et al. *Circulation.* 2015;131:54-61.

PARADIGM-HF: Clinical Progression Analysis

Time to First Occurrence of Hospitalization within 30 Days



No. at risk				
Sac/val	4187	4174	4153	4140
Enalapril	4212	4192	4166	4143

- Shown is the Kaplan-Meier estimate of the cumulative probability of a first hospitalization for HF during the first 30 days after randomization. The analysis at 30 days was prespecified and also represented the earliest time point at which the difference between the sac/val and enalapril groups was statistically significant

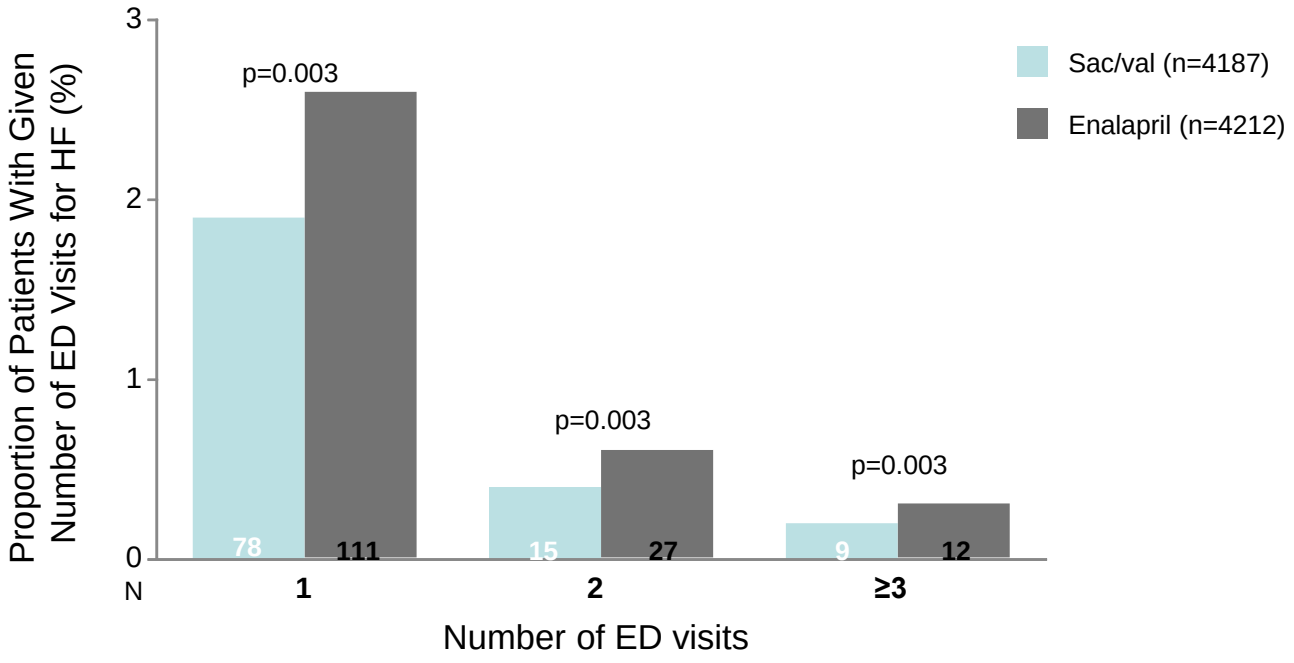
This was a prespecified analysis.

Packer M et al. *Circulation.* 2015;131:54-61.

PARADIGM-HF: Clinical Progression Analysis

Number of ED Visits

The total number of ED visits for HF was lower in the sacubitril/valsartan group than in the enalapril group



This was a prespecified analysis.
*The rate ratio was estimated from a negative binomial model.
ED, emergency department; HF, heart failure; CI, confidence interval; HR, hazard ratio
Packer M et al. *Circulation*. 2015;131:54-61.

Sacubitril/Valsartan

Adverse Reactions Occurring at an Incidence of ≥5% in the Double-Blind Period

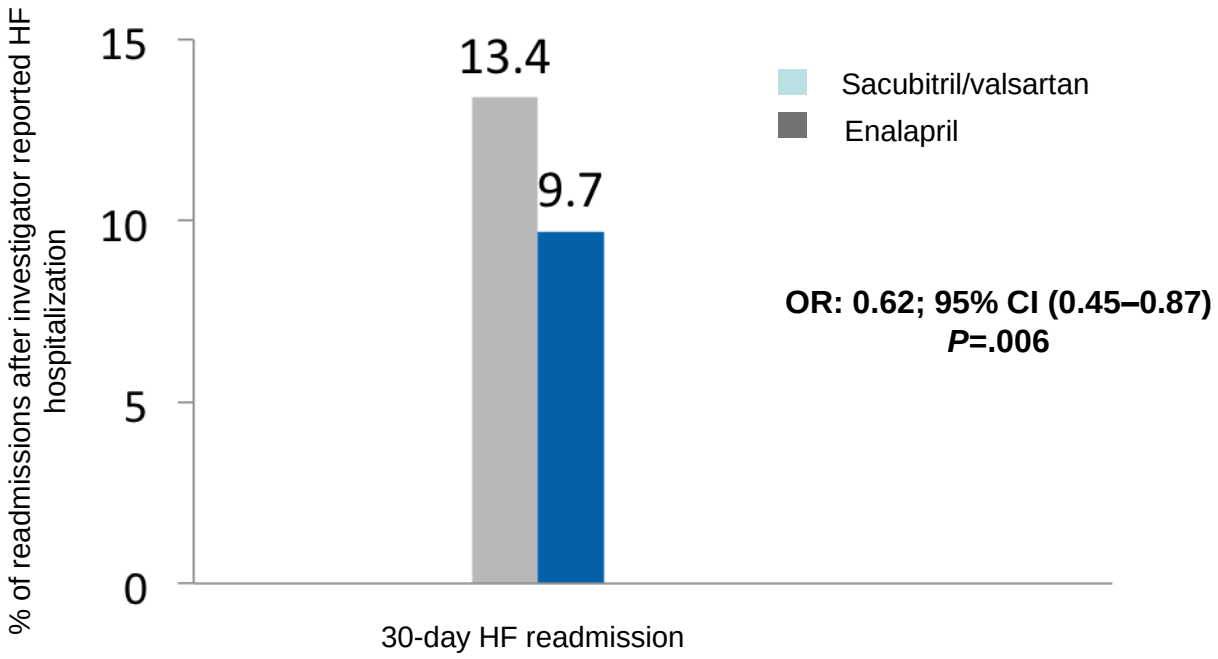
Adverse Reactions Occurring ≥5%	Sac/Val N=4203 (%)	Enalapril N=4229 (%)
Hypotension	18	12
Hyperkalemia	12	14
Cough	9	13
Dizziness	6	5
Renal failure/acute renal failure	5	5

- In the PARADIGM-HF trial, the incidence of angioedema was 0.1% in both the enalapril and sacubitril/valsartan run-in periods. In the double-blind period, the incidence of angioedema was higher in patients treated with sacubitril/valsartan than enalapril (0.5% and 0.2%, respectively). The incidence of angioedema in Black patients was 2.4% with sacubitril/valsartan and 0.5% with enalapril
- Orthostasis was reported in 2.1% of patients treated with sacubitril/valsartan compared to 1.1% of patients treated with enalapril during the double-blind period of PARADIGM-HF. Falls were reported in 1.9% of patients treated with sacubitril/valsartan compared to 1.3% of patients treated with enalapril

PARADIGM-HF: 30 Day Readmission

30-Day HF Hospital Readmission Following a HF Hospitalization

30-Day HF Readmissions After All Investigator-Reported HF Discharges During a Median Follow-up of 27 Months After Randomization



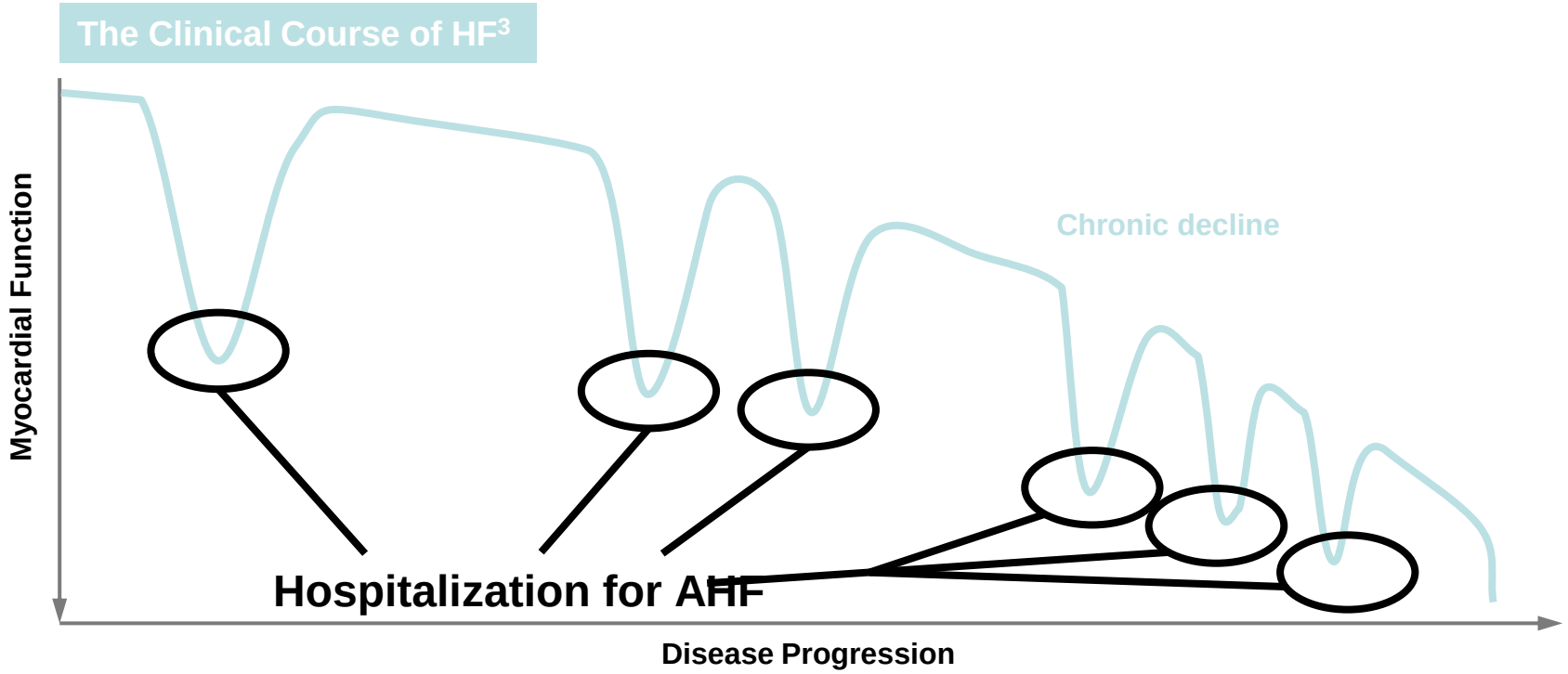
In the sacubitril/valsartan population, following investigator-reported HF hospitalizations, there was a reduction of 30-day readmission for HF of 38% vs. enalapril (*P*=.006)

Patient flow for analysis and baseline characteristics

This was a post hoc analysis.
HF, heart failure; OR, odds ratio; CI, confidence interval
Desai AS et al. *J Am Coll Cardiol*. 2016;68(3):241-8.

Transitions of Care and Outcomes After Hospital Discharge

- Rehospitalization and mortality are common after hospital discharge[1]
- Improved communication and transition-of-care processes within multidisciplinary teams could lead to an improvement in patient outcomes[2]



HF, heart failure

1. Fonarow GC et al. *J Am Coll Cardiol.* 2007;50:768-777; 2. Albert NM et al. *Circ Heart Fail.* 2015;8:384-409; 3. Allen LA et al. *Circulation*. 2012;125:1928-1952.

Summary

- Sacubitril/valsartan is a combination of a neprilysin inhibitor and an ARB
- Sacubitril/valsartan is indicated to reduce the risk of CV death and hospitalization for HF in patients with chronic HFrEF (NYHA class II–IV)
- Sacubitril/valsartan was superior to enalapril in reducing the risk of the combined endpoint of CV death or hospitalization for HF, based on a time-to-event analysis
- Sacubitril/valsartan has an acceptable safety and tolerability profile
- The most commonly reported adverse reactions were hypotension, hyperkalemia, cough, dizziness, and renal failure

Ivabradine (Corlanor)

- Reduces heart rate via *If "funny* channel"
  - Acts at the SA node, doesn't reduce BP
- EF < 35%, Heart Rate > 70 bpm
  - On maximally tolerated beta blockers
- 5 or 7.5 mg twice a day
- SHIFT study (in Europe)
  - Reduced hospitalization for worsening HF or CV death by 18% after 3 months of treatment
  - Reduced risk of death from HF by 26%
  - Reduced risk of hospitalization from HF by 26%
  - Approved in 2015 in USA (2005 in Europe)

Gaziano et al. June 22, 2016. JAMA Cardiology.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CLINICAL PRACTICE GUIDELINE: EXECUTIVE SUMMARY

2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: Executive Summary

A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines

Writing Committee Members*

Paul A. Heidenreich, MD, MS, FACC, FAHA, FHFSA, *Chair*†
Biykem Bozkurt, MD, PhD, FACC, FAHA, FHFSA, *Vice Chair*†

David Aguilar, MD, MSc, FAHA†
Larry A. Allen, MD, MHS, FACC, FAHA, FHFSA†
Joni J. Byun†
Monica M. Colvin, MD, MS, FAHA†
Anita Deswal, MD, MPH, FACC, FAHA, FHFSA‡
Mark H. Drazner, MD, MSc, FACC, FAHA, FHFSA†
Shannon M. Dunlay, MD, MS, FAHA, FHFSA†
Linda R. Evers, JD†
James C. Fang, MD, FACC, FAHA, FHFSA†
Savitri E. Fedson, MD, MA†
Gregg C. Fonarow, MD, FACC, FAHA, FHFSA§
Salim S. Hayek, MD, FACC†
Adrian F. Hernandez, MD, MHS‡
Prateeti Khazanie, MD, MPH, FHFSA†
Michelle M. Kittleson, MD, PhD†
Christopher S. Lee, PhD, RN, FAHA, FHFSA†
Mark S. Link, MD†
Carmelo A. Milano, MD†
Lorraine C. Nnacheta, DrPH, MPH†
Alexander T. Sandhu, MD, MS†
Lynne Warner Stevenson, MD, FACC, FAHA, FHFSA†
Orly Vardeny, PharmD, MS, FAHA, FHFSA‖
Amanda R. Vest, MBBS, MPH, FHFSA‖
Clyde W. Yancy, MD, MSc, MACC, FAHA, FHFSA†

*Writing committee members are required to recuse themselves from voting on sections to which their specific relationships with industry may apply; see Appendix 1 of the full guideline for detailed information. †ACC/AHA Representative. ‡ACC/AHA Joint Committee on Clinical Practice Guidelines Liaison. §ACC/AHA Task Force on Performance Measures Representative. ‖HFSA Representative.

TABLE 1 Applying American College of Cardiology/American Heart Association Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care (Updated May 2019)*

CLASS (STRENGTH) OF RECOMMENDATION	
CLASS 1 (STRONG)	**Benefit >>> Risk**
Suggested phrases for writing recommendations: • Is recommended • Is indicated/useful/effective/beneficial • Should be performed/administered/other • Comparative-Effectiveness Phrases†: – Treatment/strategy A is recommended/indicated in preference to treatment B – Treatment A should be chosen over treatment B	
CLASS 2a (MODERATE)	**Benefit >> Risk**
Suggested phrases for writing recommendations: • Is reasonable • Can be useful/effective/beneficial • Comparative-Effectiveness Phrases†: – Treatment/strategy A is probably recommended/indicated in preference to treatment B – It is reasonable to choose treatment A over treatment B	
CLASS 2b (WEAK)	**Benefit ≥ Risk**
Suggested phrases for writing recommendations: • May/might be reasonable • May/might be considered • Usefulness/effectiveness is unknown/unclear/uncertain or not well-established	
CLASS 3: No Benefit (MODERATE) **(Generally, LOE A or B use only)**	**Benefit = Risk**
Suggested phrases for writing recommendations: • Is not recommended • Is not indicated/useful/effective/beneficial • Should not be performed/administered/other	
Class 3: Harm (STRONG)	**Risk > Benefit**
Suggested phrases for writing recommendations: • Potentially harmful • Causes harm • Associated with excess morbidity/mortality • Should not be performed/administered/other	

LEVEL (QUALITY) OF EVIDENCE‡	
LEVEL A	
• High-quality evidence‡ from more than 1 RCT • Meta-analyses of high-quality RCTs • One or more RCTs corroborated by high-quality registry studies	
LEVEL B-R	**(Randomized)**
• Moderate-quality evidence‡ from 1 or more RCTs • Meta-analyses of moderate-quality RCTs	
LEVEL B-NR	**(Nonrandomized)**
• Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies • Meta-analyses of such studies	
LEVEL C-LD	**(Limited Data)**
• Randomized or nonrandomized observational or registry studies with limitations of design or execution • Meta-analyses of such studies • Physiological or mechanistic studies in human subjects	
LEVEL C-EO	**(Expert Opinion)**
• Consensus of expert opinion based on clinical experience	

COR and LOE are determined independently (any COR may be paired with any LOE).

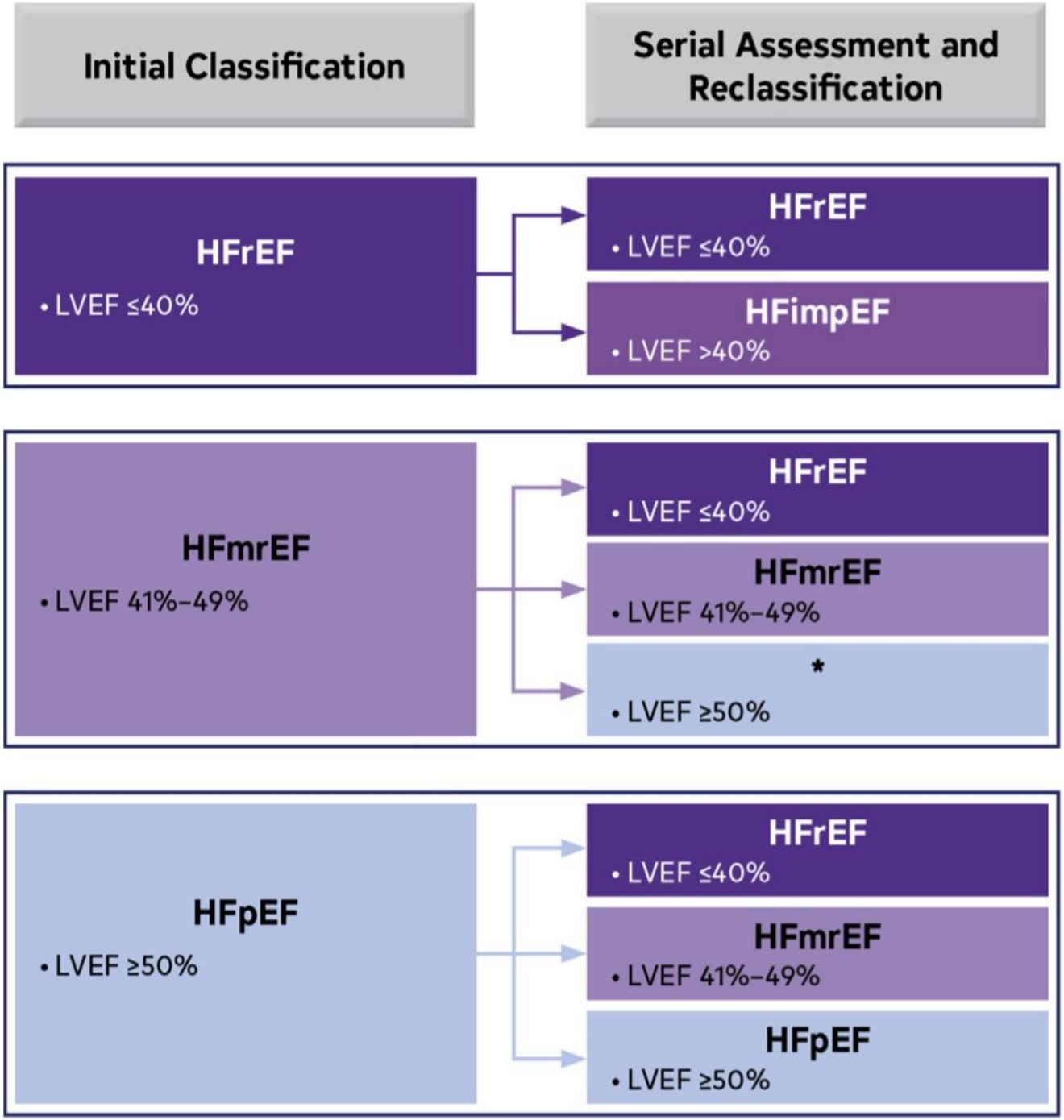
A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.


Initial Classification
Serial Assessment and Reclassification
HFrEF
• LVEF ≤40%
HFrEF
• LVEF ≤40%
HFimpEF
• LVEF >40%
HFmrEF
• LVEF 41%–49%
HFrEF
• LVEF ≤40%
HFmrEF
• LVEF 41%–49%
*
• LVEF ≥50%
HFpEF
• LVEF ≥50%
HFrEF
• LVEF ≤40%
HFmrEF
• LVEF 41%–49%
HFpEF
• LVEF ≥50%

2017 ACC/AHA/HFSA Focused Update

Recommendations for Renin-Angiotensin System Inhibition With ACE Inhibitor or ARB or ARNI (angiotensin receptor neprilysin inhibitor)

COR	LOE	Recommendations
I	ACE-I: A ARB: A ARNI: B-R	The clinical strategy of inhibition of the renin-angiotensin system with ACE inhibitors *(Level of Evidence: A)*, OR ARBs *(Level of Evidence: A)*, OR ARNI *(Level of Evidence: B-R)* in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HF*r*EF to reduce morbidity and mortality.
COR	**LOE**	**Recommendations**
I	ARNI: B-R	In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACE inhibitor or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
COR	**LOE**	**Recommendations**
III: Harm	B-R	ARNI should not be administered concomitantly with ACE inhibitors or within 36 hours of the last dose of an ACE inhibitor.
III: Harm	C-EO	ARNI should not be administered to patients with a history of angioedema.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNi, angiotensin receptor–neprilysin inhibitor; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association.

Yancy CW, Jessup M, Bozkurt B, et al. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *J Card Fail.* 2017 Apr 25. pii: S1071-9164(17)30107-0. doi: 10.1016/j.cardfail.2017.04.014.

Recommendations for Renin-Angiotensin System Inhibition With ACEi or ARB or ARNi
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with HFrEF and New York Heart Association (NYHA) class II to III symptoms, the use of ARNi is recommended to reduce morbidity and mortality (7-11).
1	A	2. In patients with previous or current symptoms of chronic HFrEF, the use of ACEi is beneficial to reduce morbidity and mortality when the use of ARNi is not feasible (12-19).
1	A	3. In patients with previous or current symptoms of chronic HFrEF who are intolerant to ACEi because of cough or angioedema and when the use of ARNi is not feasible, the use of ARB is recommended to reduce morbidity and mortality (20-24).
1	B-R	4. In patients with chronic symptomatic HFrEF NYHA class II or III who tolerate an ACEi or ARB, replacement by an ARNi is recommended to further reduce morbidity and mortality (7-11).

Recommendation for Beta Blockers
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
1	A	1. In patients with HFrEF, with current or previous symptoms, use of 1 of the 3 beta blockers proven to reduce mortality (e.g., bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations (25-27).

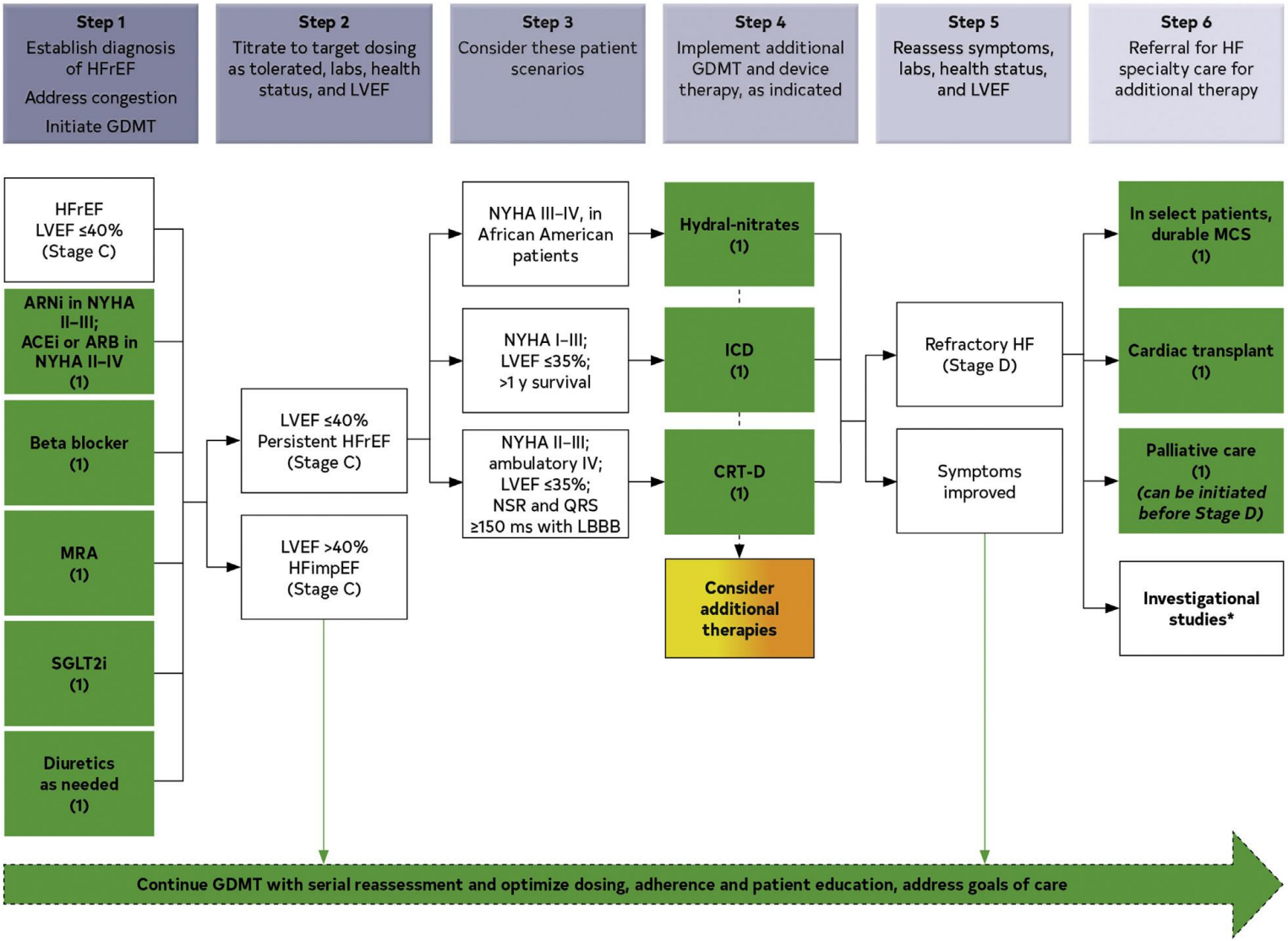
Recommendation for MRAs
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATION
1	A	1. In patients with HFrEF and NYHA class II to IV symptoms, an MRA (spironolactone or eplerenone) is recommended to reduce morbidity and mortality, if estimated glomerular filtration rate is >30 mL/min/1.73 m^2 and serum potassium is <5.0 mEq/L. Careful monitoring of potassium, renal function, and diuretic dosing should be performed at initiation and closely monitored thereafter to minimize risk of hyperkalemia and renal insufficiency (28-30).

Recommendation for SGLT2i
Referenced studies that support the recommendation are summarized in the Online Data Supplements.

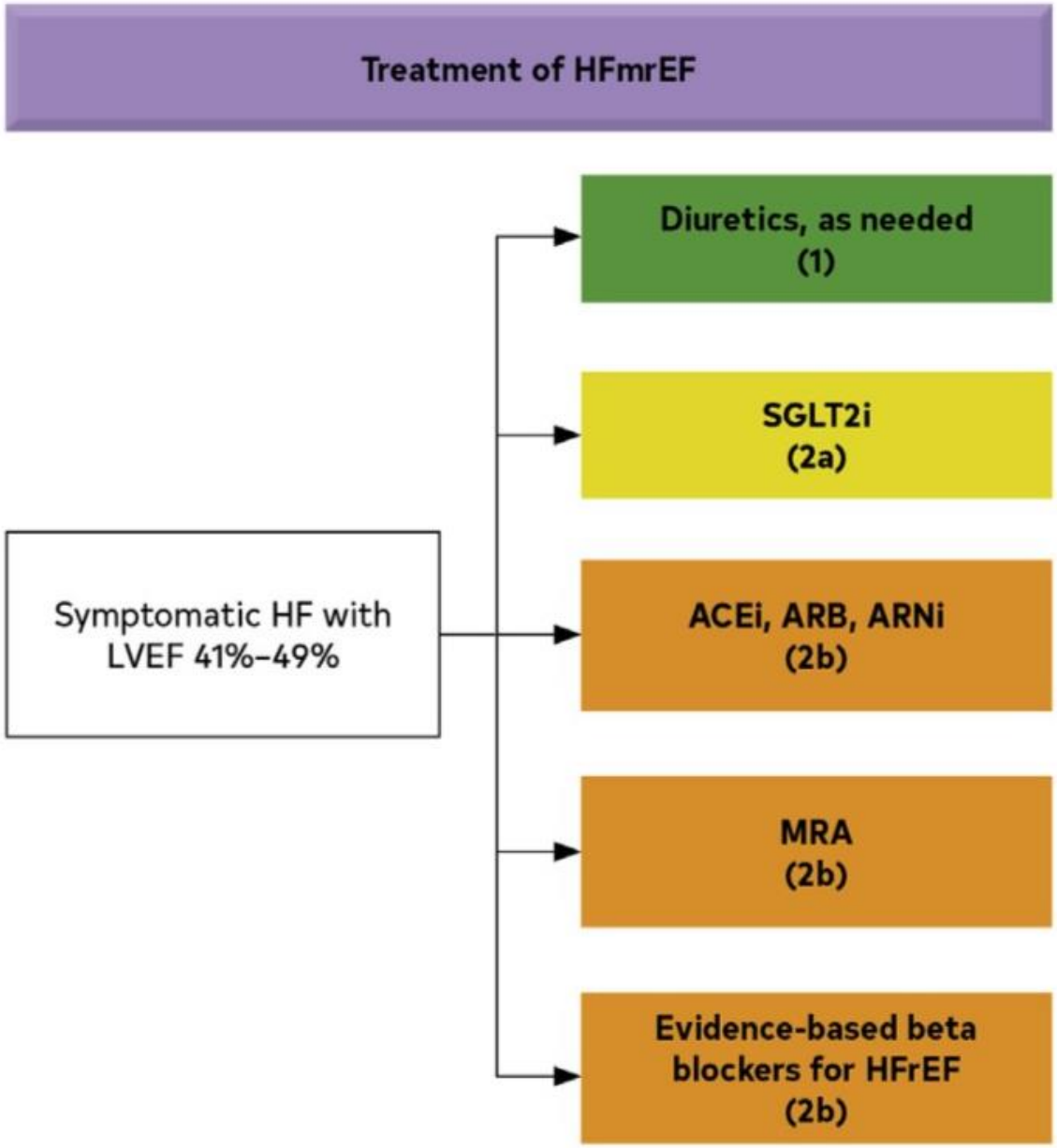
COR	LOE	RECOMMENDATION
1	A	1. In patients with symptomatic chronic HFrEF, SGLT2i are recommended to reduce hospitalization for HF and cardiovascular mortality, irrespective of the presence of type 2 diabetes (31,32).

FIGURE 1 Treatment of HFrEF Stages C and D



Recommendations for HFmrEF
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

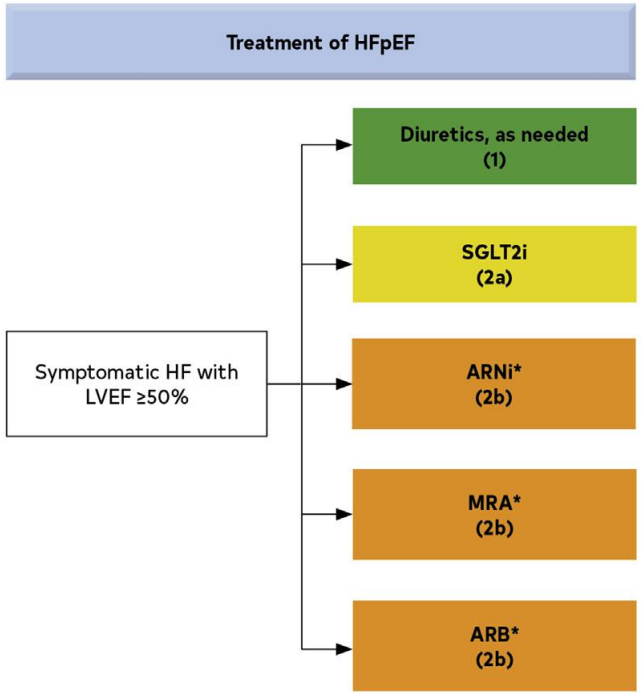
COR	LOE	RECOMMENDATIONS
2a	B-R	1. In patients with HFmrEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (33).
2b	B-NR	2. Among patients with current or previous symptomatic HFmrEF (LVEF, 41%–49%), use of evidence-based beta blockers for HFrEF, ARNi, ACEi, or ARB, and MRAs may be considered, to reduce the risk of HF hospitalization and cardiovascular mortality, particularly among patients with LVEF on the lower end of this spectrum (34-41).


Treatment of HFmrEF
Symptomatic HF with LVEF 41%–49%
Diuretics, as needed (1)
SGLT2i (2a)
ACEi, ARB, ARNi (2b)
MRA (2b)
Evidence-based beta blockers for HFrEF (2b)

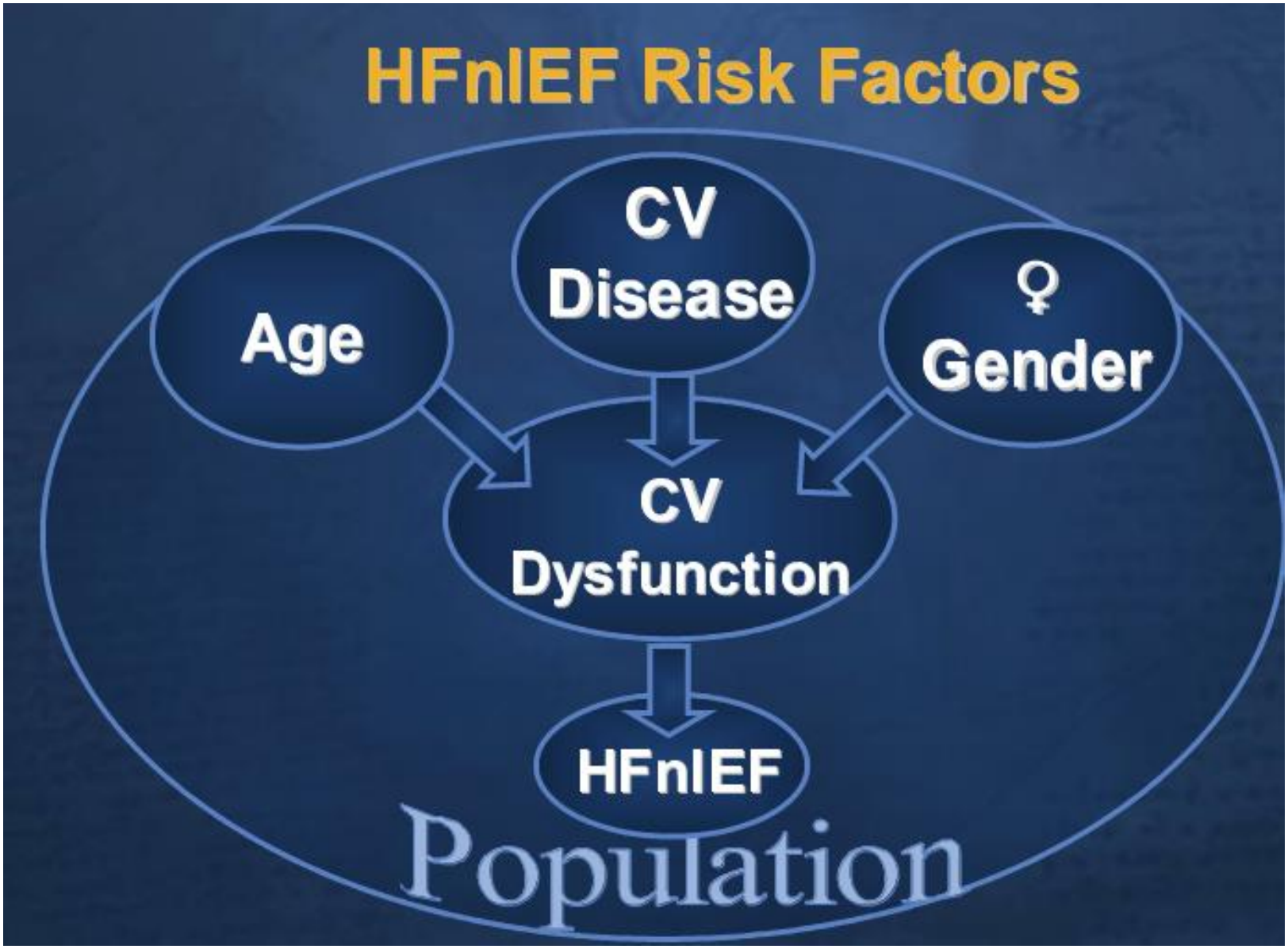
New Recommendations for HFpEF
Referenced studies that support the recommendations are summarized in the Online Data Supplements.

COR	LOE	RECOMMENDATIONS
2a	B-R	1. In patients with HFpEF, SGLT2i can be beneficial in decreasing HF hospitalizations and cardiovascular mortality (33).
2b	B-R	2. In selected patients with HFpEF, MRAs may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (38,42,43).
2b	B-R	3. In selected patients with HFpEF, ARNi may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum (35,40).

FIGURE 3 Recommendations for Patients With Preserved LVEF (≥50%)



DIASTOLIC HEART FAILURE

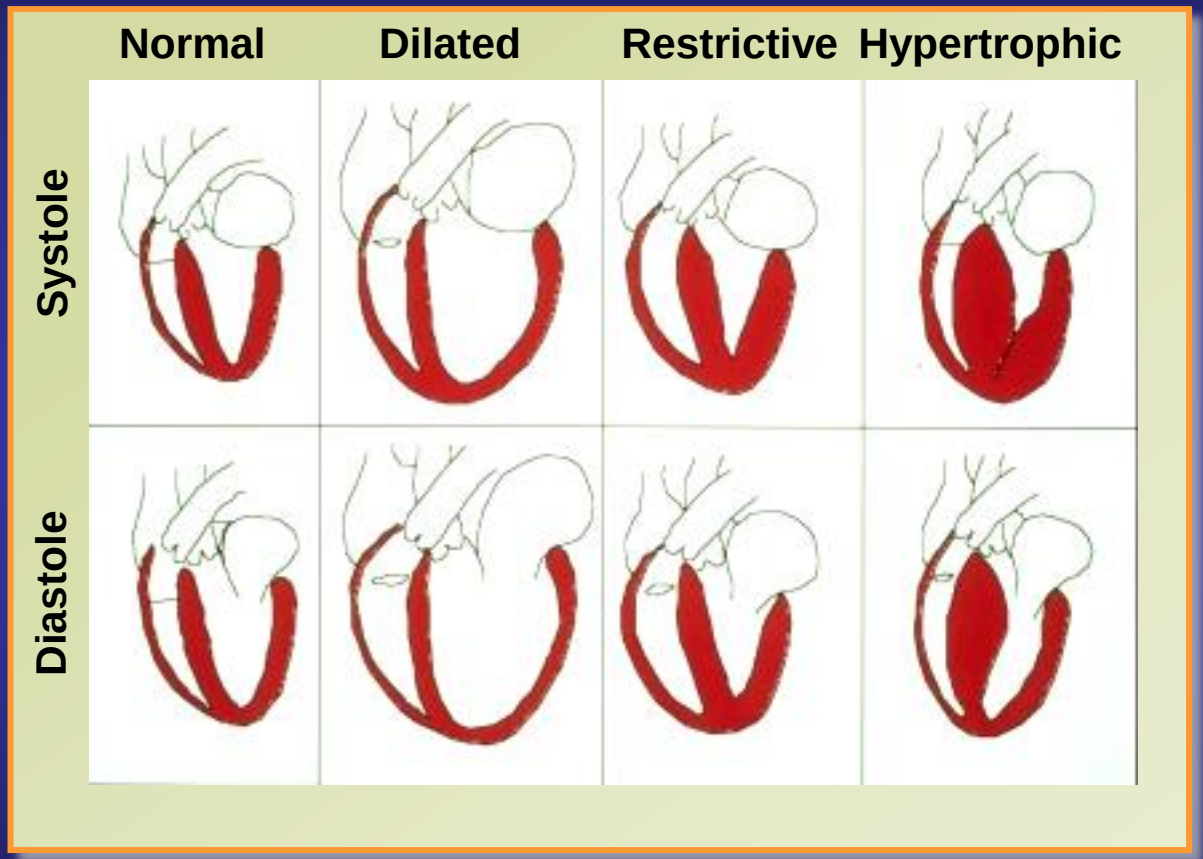

HFnlEF Risk Factors
CV Disease
Age
♀ Gender
CV Dysfunction
HFnlEF
Population

HFnlEF is due to Diastolic Dysfunction

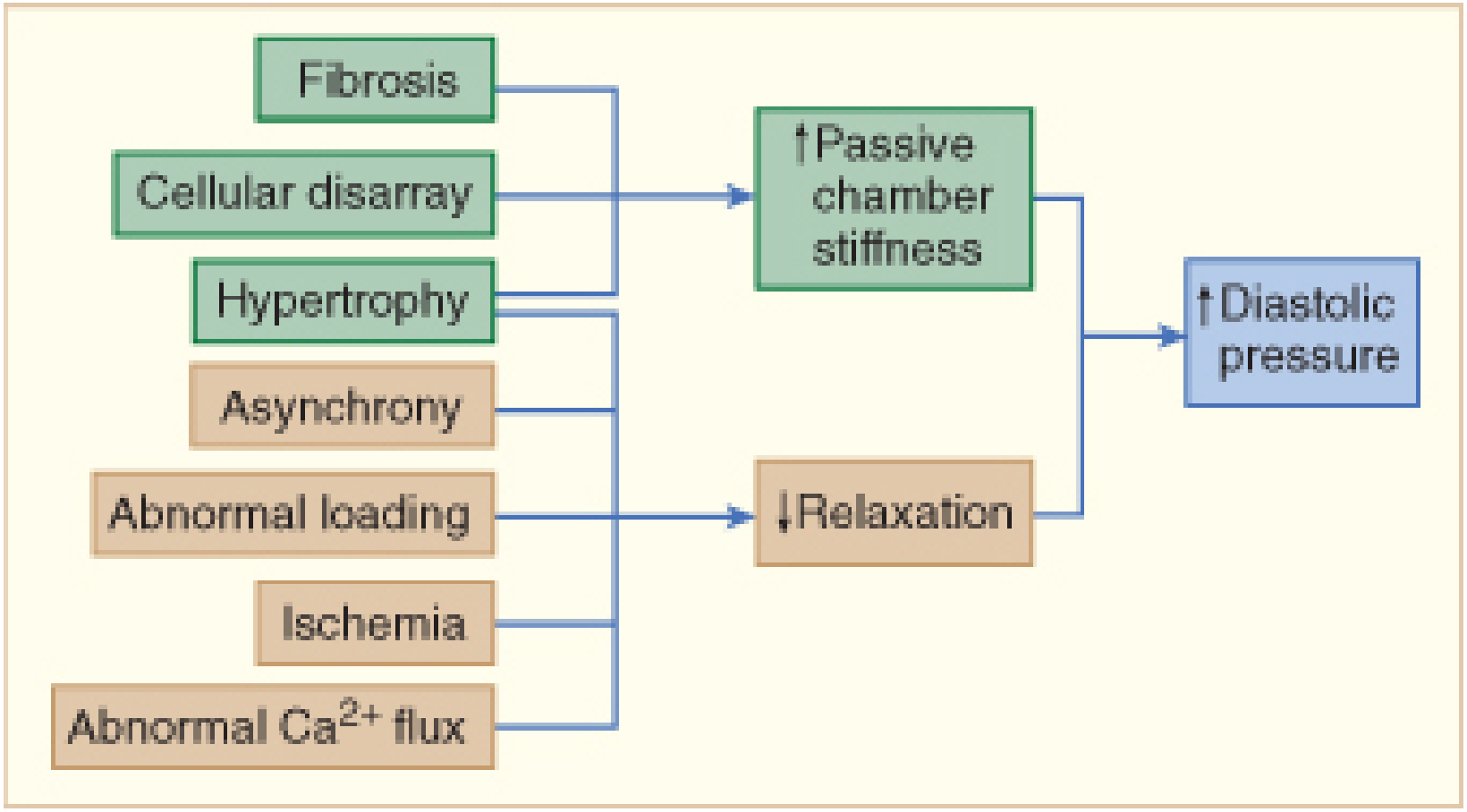
Normal	Impaired Relaxation	Reduced Compliance

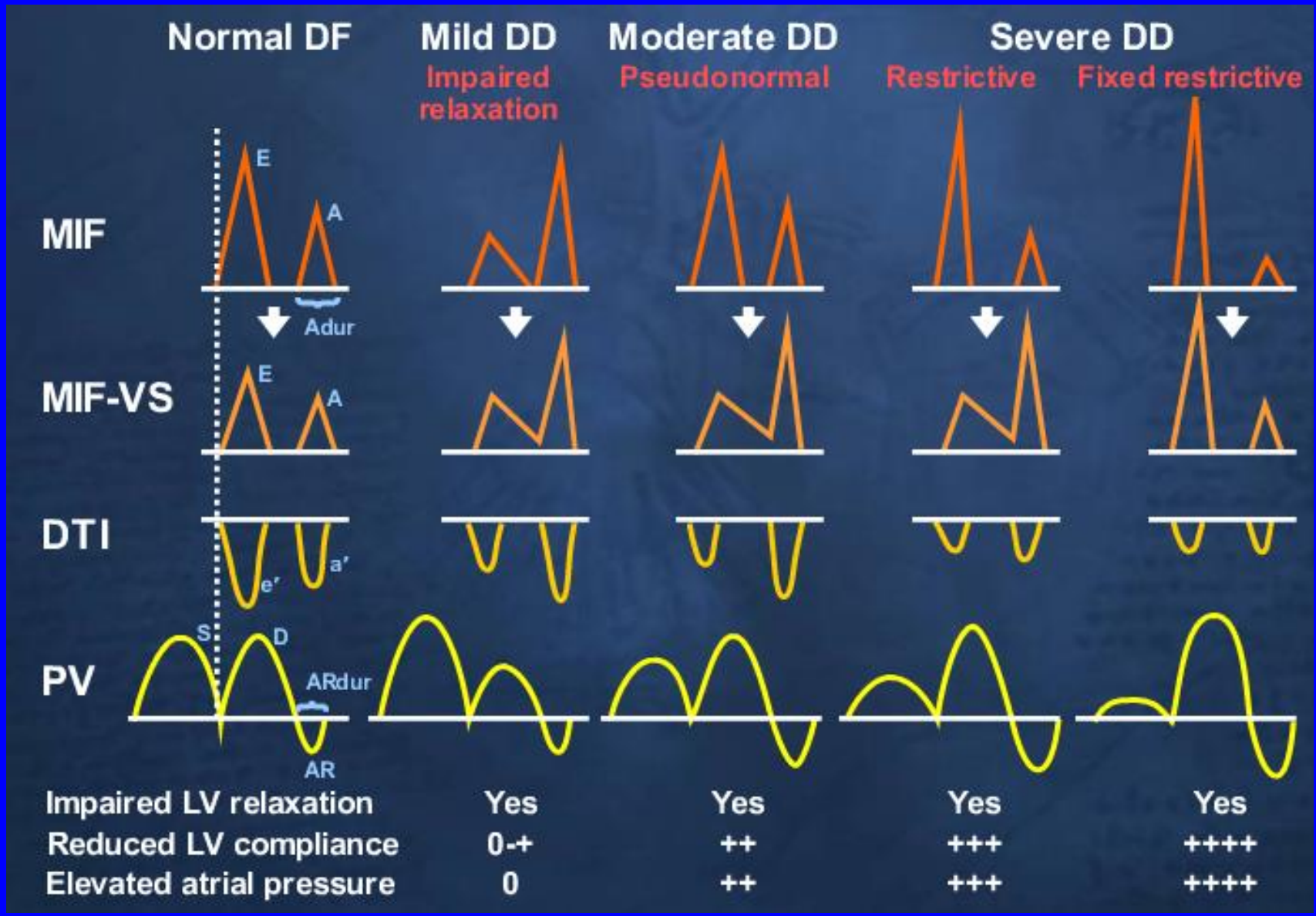
Defining Heart Failure

- HF exists when the heart is unable to pump sufficient blood to meet the metabolic needs of the body at normal filling pressures, provided the venous return to the heart is normal.[1]



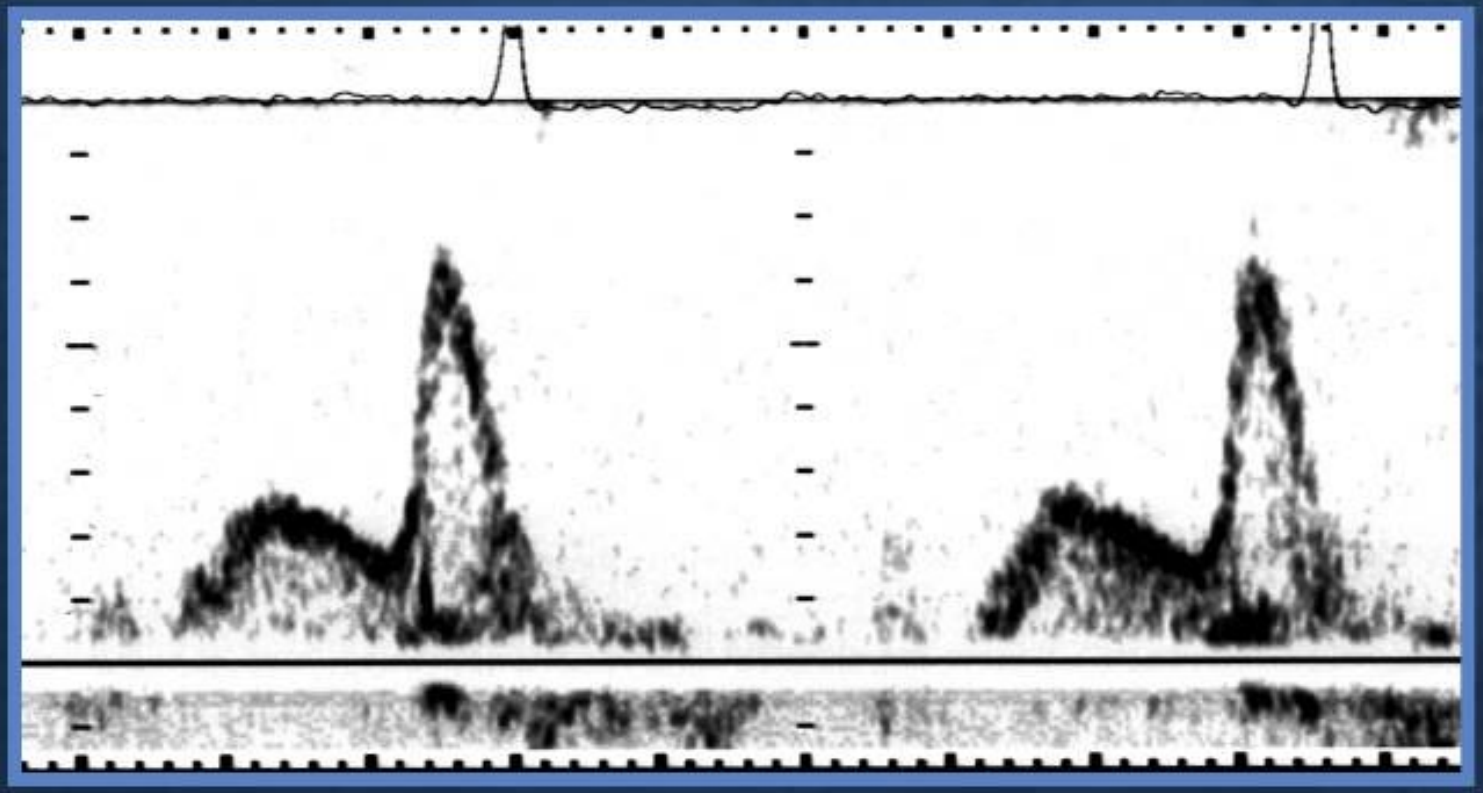
[1] Schlant RC, Sonnenblick EH. *Hurst's The Heart*. 8th ed. New York: McGraw-Hill; 1994:515-55.


Fibrosis
Cellular disarray
Hypertrophy
Asynchrony
Abnormal loading
Ischemia
Abnormal Ca^{2+} flux
↑Passive chamber stiffness
↓Relaxation
↑Diastolic pressure


Normal DF
Mild DD
Impaired relaxation
Moderate DD
Pseudonormal
Severe DD
Restrictive
Fixed restrictive
MIF
E
A
Adur
MIF-VS
E
A
DTI
e'
a'
PV
S
D
ARdur
AR
Impaired LV relaxation Yes Yes Yes Yes
Reduced LV compliance 0-+ ++ +++ ++++
Elevated atrial pressure 0 ++ +++ ++++

DHF in the Community
Precipitating Factors

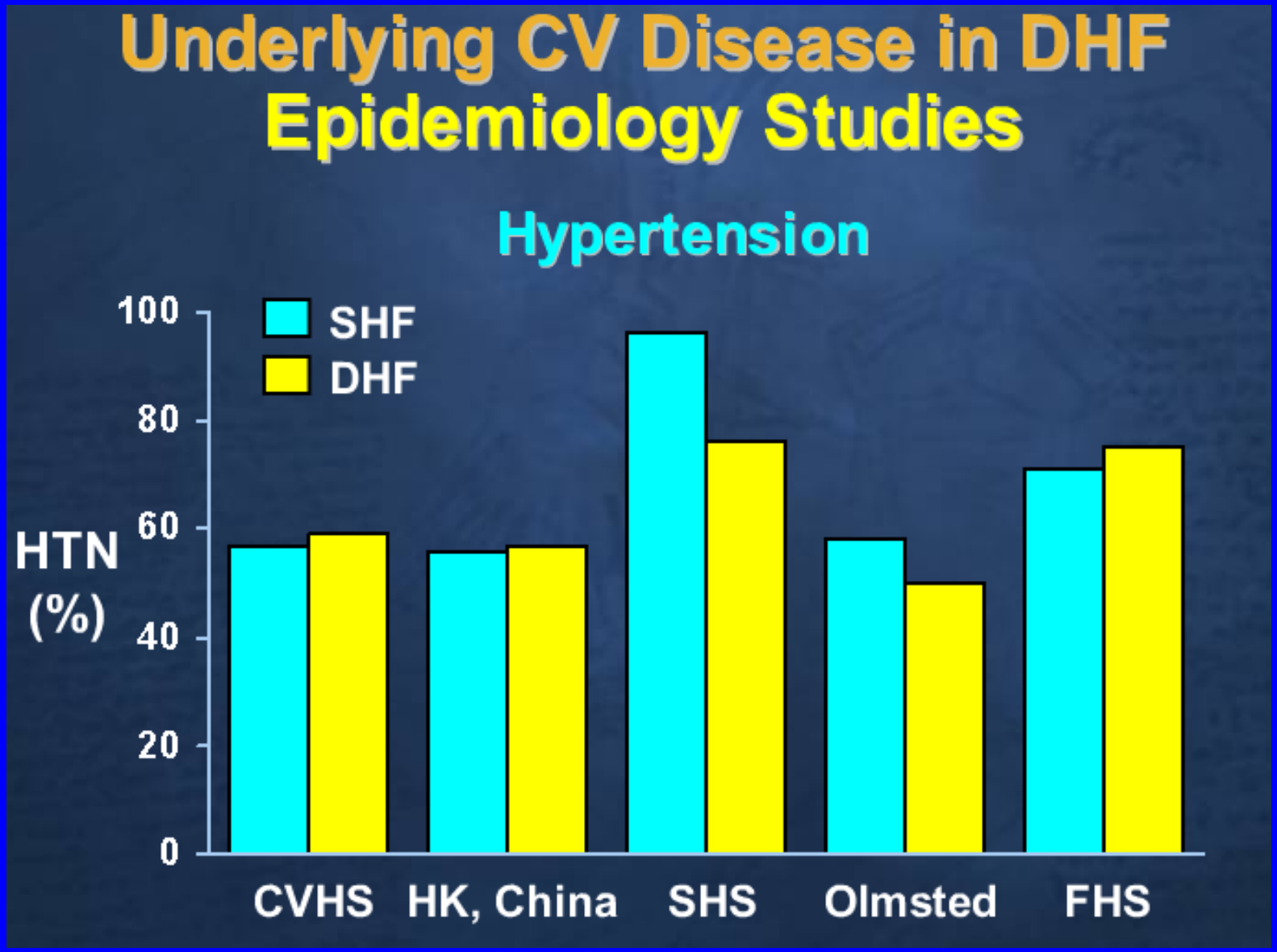
Atrial Fibrillation – 29%



Diastolic Heart Failure

- Elderly
- Women > Men
- Hx of HTN
- Present with HF symptoms

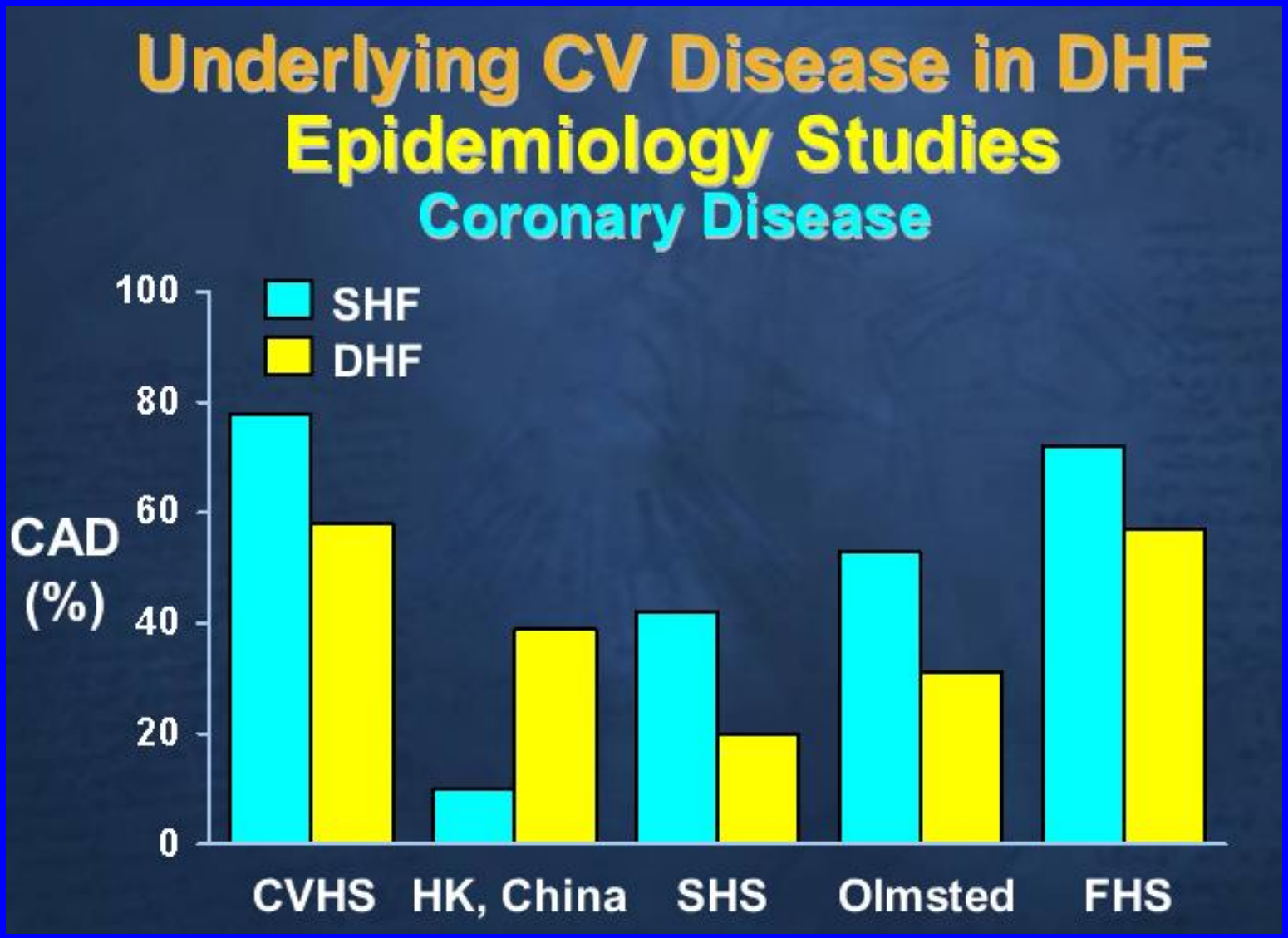
Underlying CV Disease in DHF
Epidemiology Studies



Underlying CV Disease in DHF

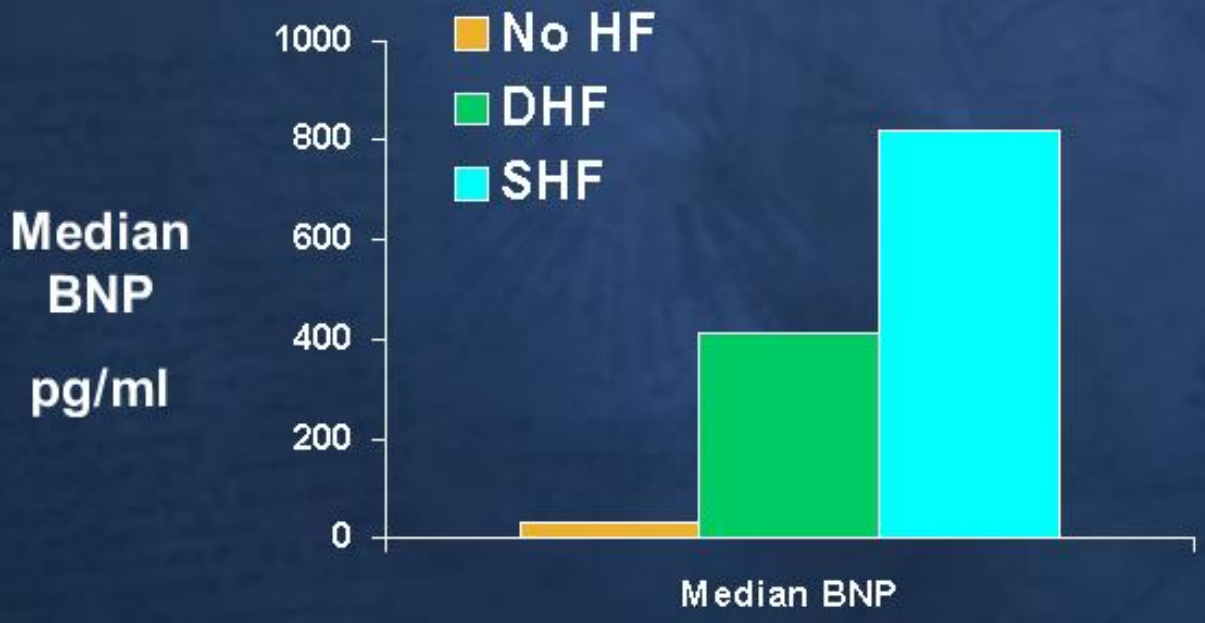
Epidemiology Studies

Coronary Disease



BNP Levels are Lower in DHF Breathing Not Properly Trial

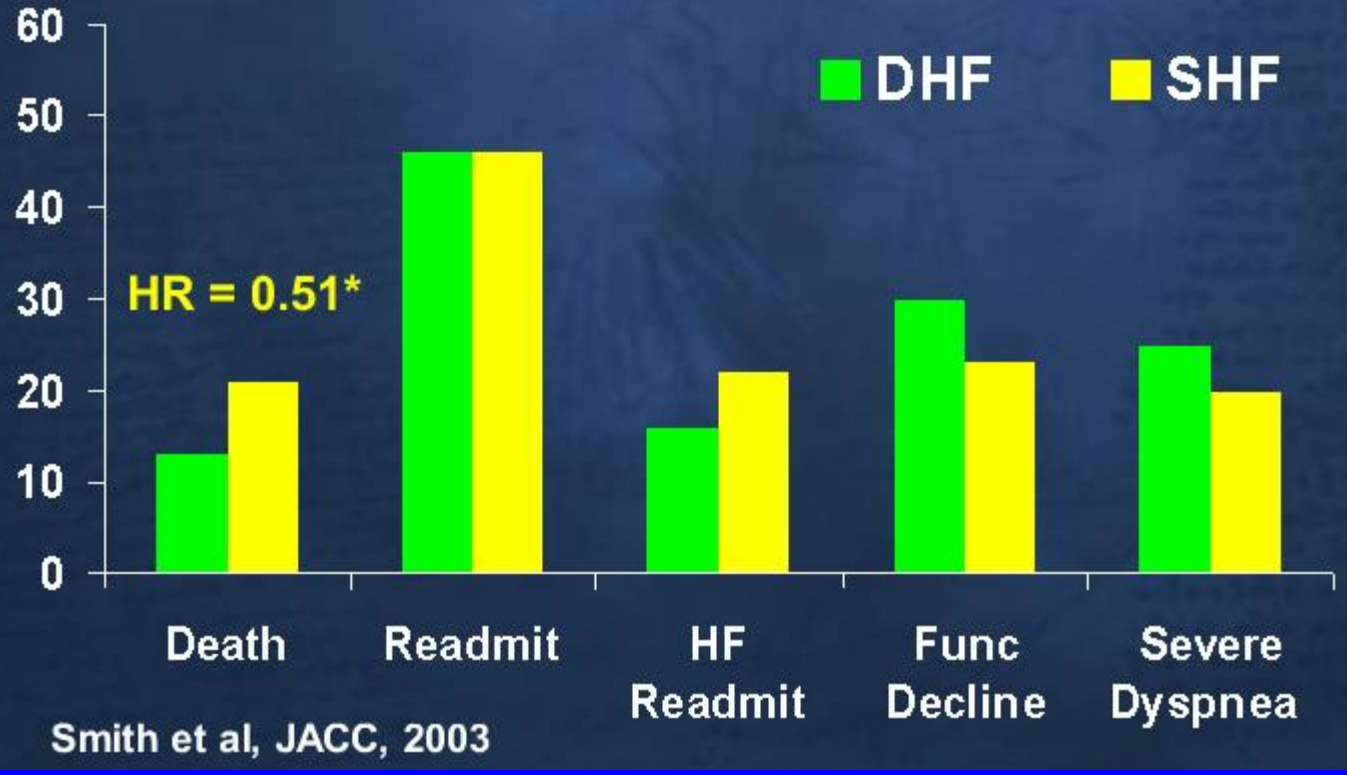
165 - NI EF; 287 - Reduced EF



Maisel et al, JACC, 2003

Mortality and Morbidity
SHF vs DHF

Prospective 6 Mo Follow-up of 413 HF pts



Smith et al, JACC, 2003

SCD in Heart Failure

- Despite improvements in medical therapy, symptomatic HF still confers a 20-25% risk of premature death in the first 2.5 years after diagnosis[1-4]
- ≈ 50% of these premature deaths are SCD (VT/VF)[1-4]

[1] SOLVD Investigators. *N Engl J Med* 1992;327:685-691.
[2] SOLVD Investigators. *N Engl J Med* 1991;325:293-302.
[3] Goldman S. *Circulation* 1993;87:V124-V131.
[4] Sweeney MO. *PACE.* 2001;24:871-888.

Relationship of SCD and Left Ventricular Dysfunction

- Reduced left ventricular ejection fraction (LVEF) remains the single most important risk factor for overall mortality and sudden cardiac death[1]
- Increased risk is measurable at ejection fractions above 30%, but an ejection fraction ≤ 30% is the single most powerful independent predictor for SCD[2]

[1] Task Force on Sudden Cardiac Death of the European Society of Cardiology. *Eur Heart J*, 2001;22:1374-1450.
Myerburg RJ, In Braunwald E, Zipes DP, Libby P, *Heart Disease, A textbook of Cardiovascular Medicine.* 6th ed. Philadelphia: W.B. Saunders, Co. 2001: 895.

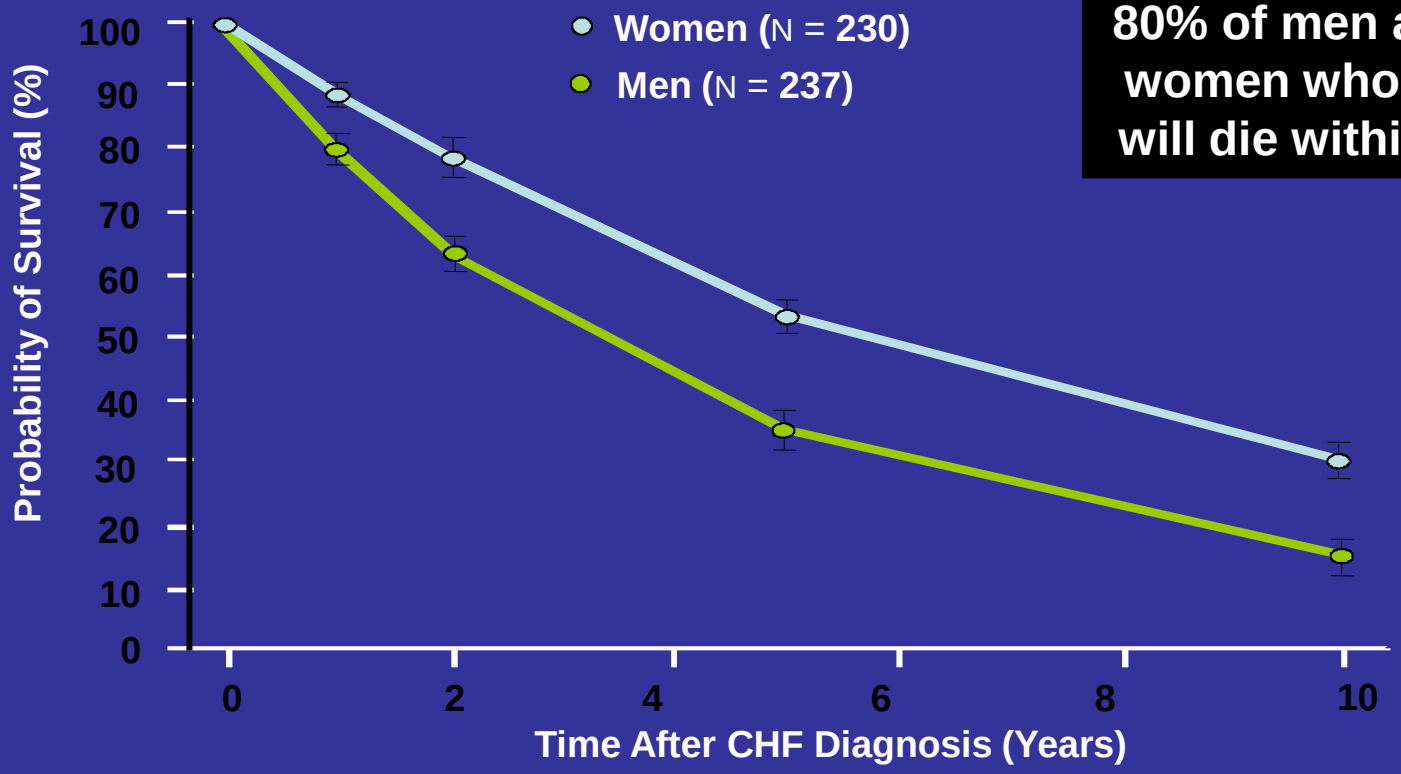
In people diagnosed with HF, sudden cardiac death occurs at

6-9 times

the rate of the general population.

American Heart Association. *Heart Disease and Stroke Statistics – 2005 Update*.

HF Patients Survival Results[1]

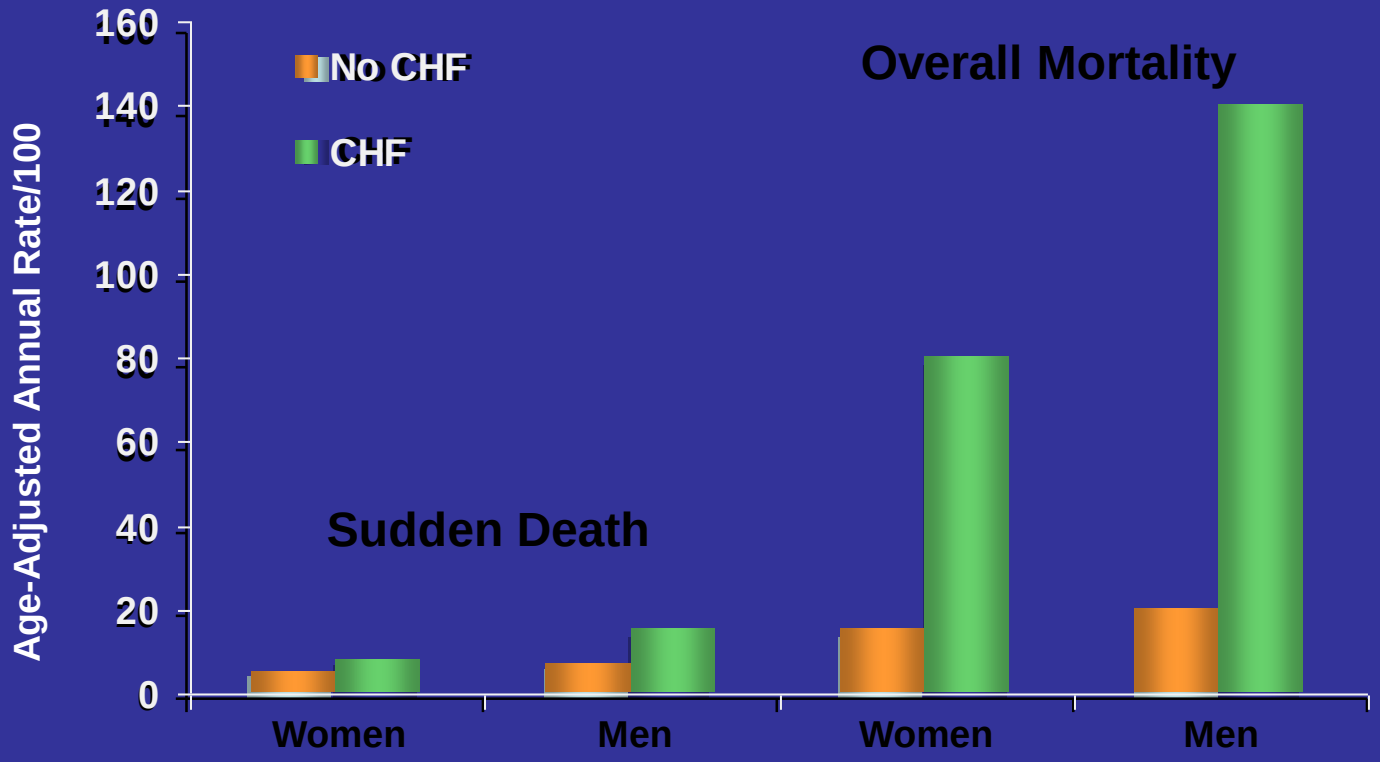


80% of men and 70% of women who have CHF will die within 8 years.[2]

[1] Framingham Heart Study (1948-1988) in Atlas of Heart Diseases.

[2] American Heart Association. *Heart Disease and Stroke Statistics—2005 Update.*

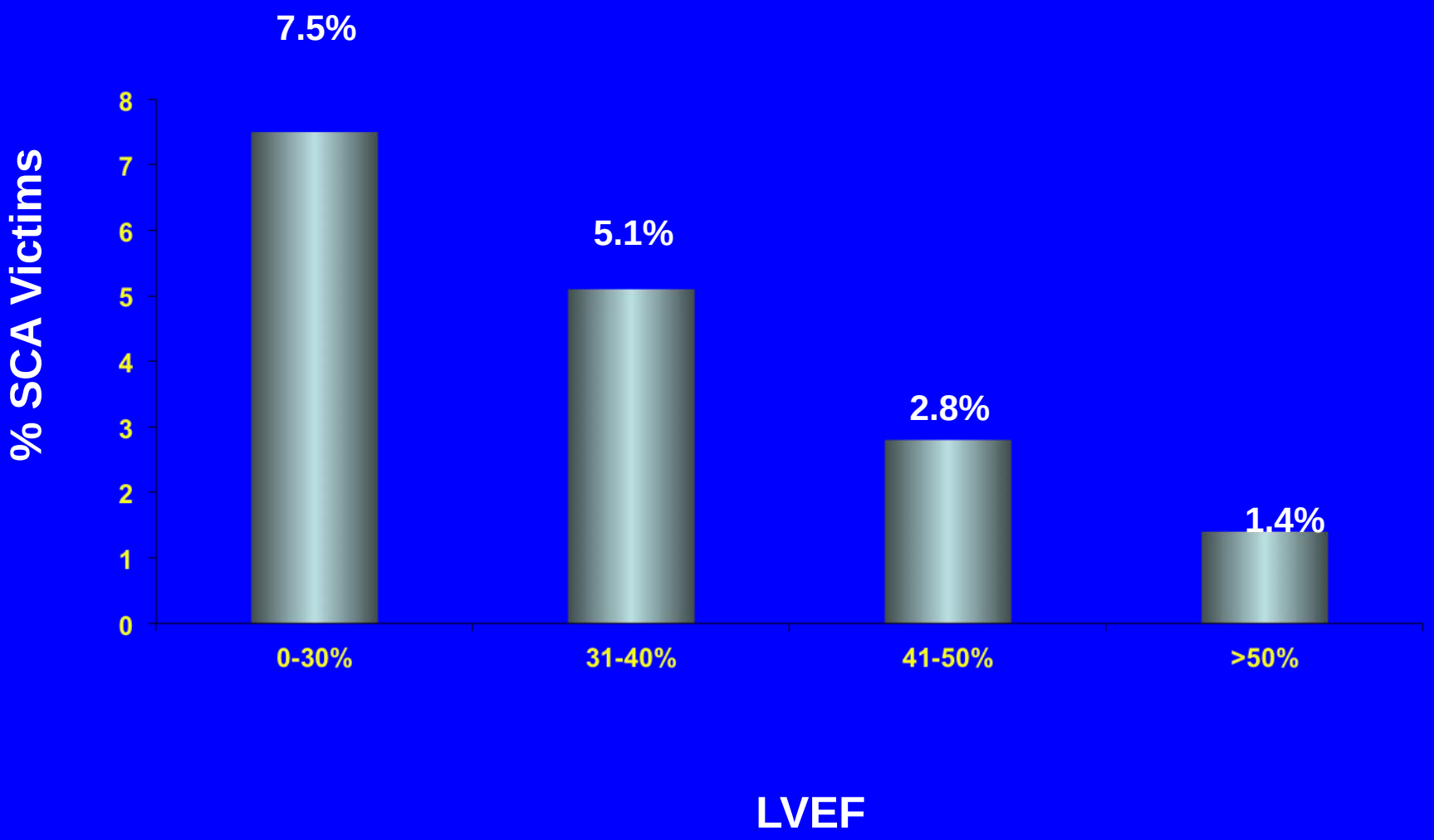
HF and Sudden Cardiac Death



CHF predicts increased sudden death and overall mortality. During a 39-year follow-up of subjects in the Framingham Heart Study, the presence of CHF significantly increased sudden death and overall mortality in both men and women.[1]

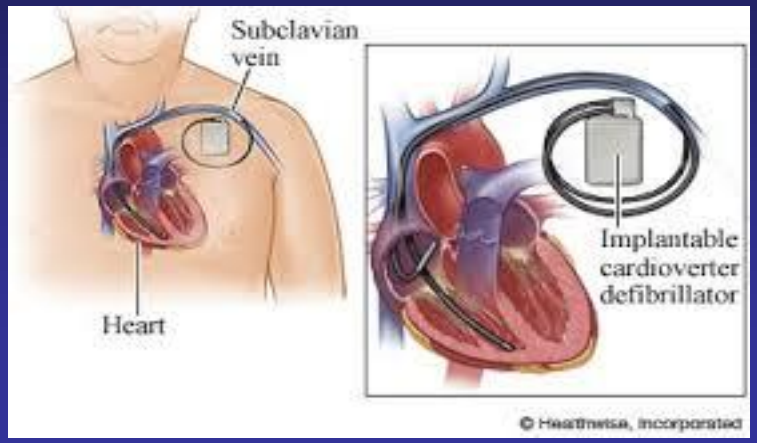
[1] Redrawn from Kannel WB. *Am Heart J.* 1998;136:205-212.

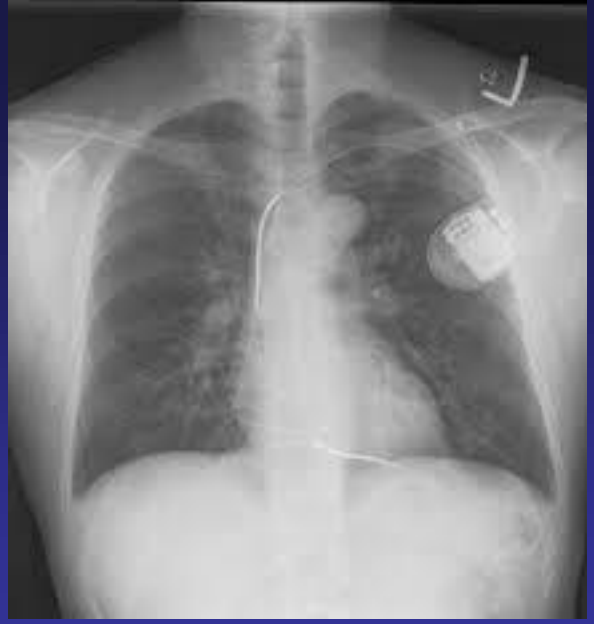
LVEF and SCA Incidence

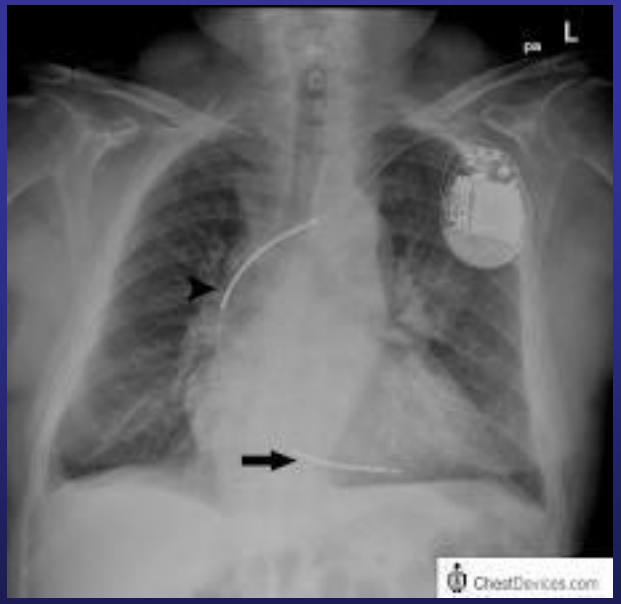


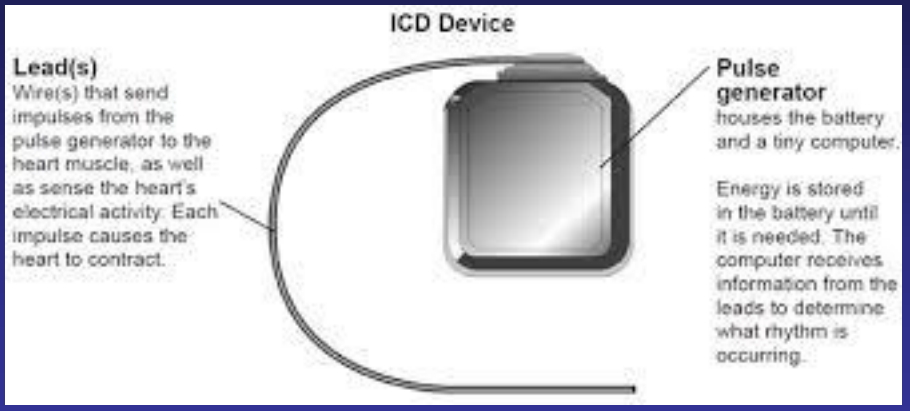
Gorgels PMA. *European Heart Journal*. 2003;24:1204-1209.

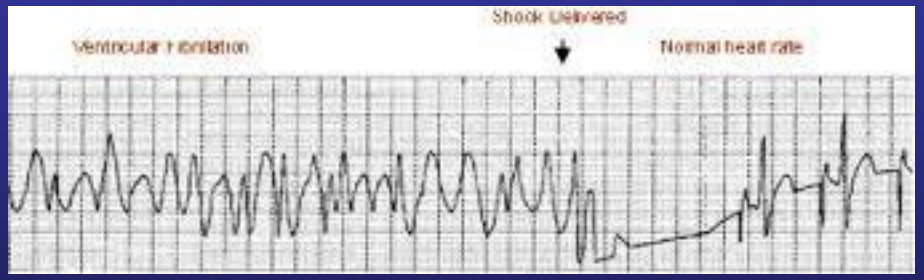
What is an ICD


Subclavian vein
Heart
Implantable cardioverter defibrillator
© Healthwise, Incorporated




L
CheatDevices.com


ICD Device
Lead(s)
Wire(s) that send impulses from the pulse generator to the heart muscle, as well as sense the heart's electrical activity. Each impulse causes the heart to contract.
Pulse generator
houses the battery and a tiny computer.
Energy is stored in the battery until it is needed. The computer receives information from the leads to determine what rhythm is occurring.


Shock Delivered
Ventricular Fibrillation
Normal heart rate

Goals of ICD Therapy

- **450,000 people suffer Sudden Death each year on a world-wide basis**
- **Only 20-30% survive**
- **In 1985, the only indication for AICD implantation was survival of 2 sudden death episodes**
- **Today, we are attempting to identify those patients at high risk for primary prevention**

Class I Indications for ICD Therapy

- **Cardiac Arrest due to VF or VT not due to a transient or reversible cause. *(A)***
- **Spontaneous sustained VT in association with structural heart disease. *(B)***
- **Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at EP study when drug therapy is ineffective not tolerated, or not preferred. *(B)***
- **Nonsustained VT with coronary disease, prior MI, LV dysfunction, and inducible VF or sustained VT at EP study that is not suppressible by a Class I antiarrhythmic drug. (MADIT I criteria) *(A)***

Class III Non-Indications for ICD Therapy

- **Syncope of undetermined cause in a patient without inducible ventricular tachyarrhythmias.** ***(C)***
- **Incessant VT or VF.** ***(C)***
- **VF or VT resulting from arrhythmias amenable to surgical or catheter ablation; for example, atrial arrhythmias associated with the Wolf-Parkinson-White syndrome, right ventricular outflow tract VT, idiopathic left ventricular tachycardia, or fascicular VT.** ***(C)***

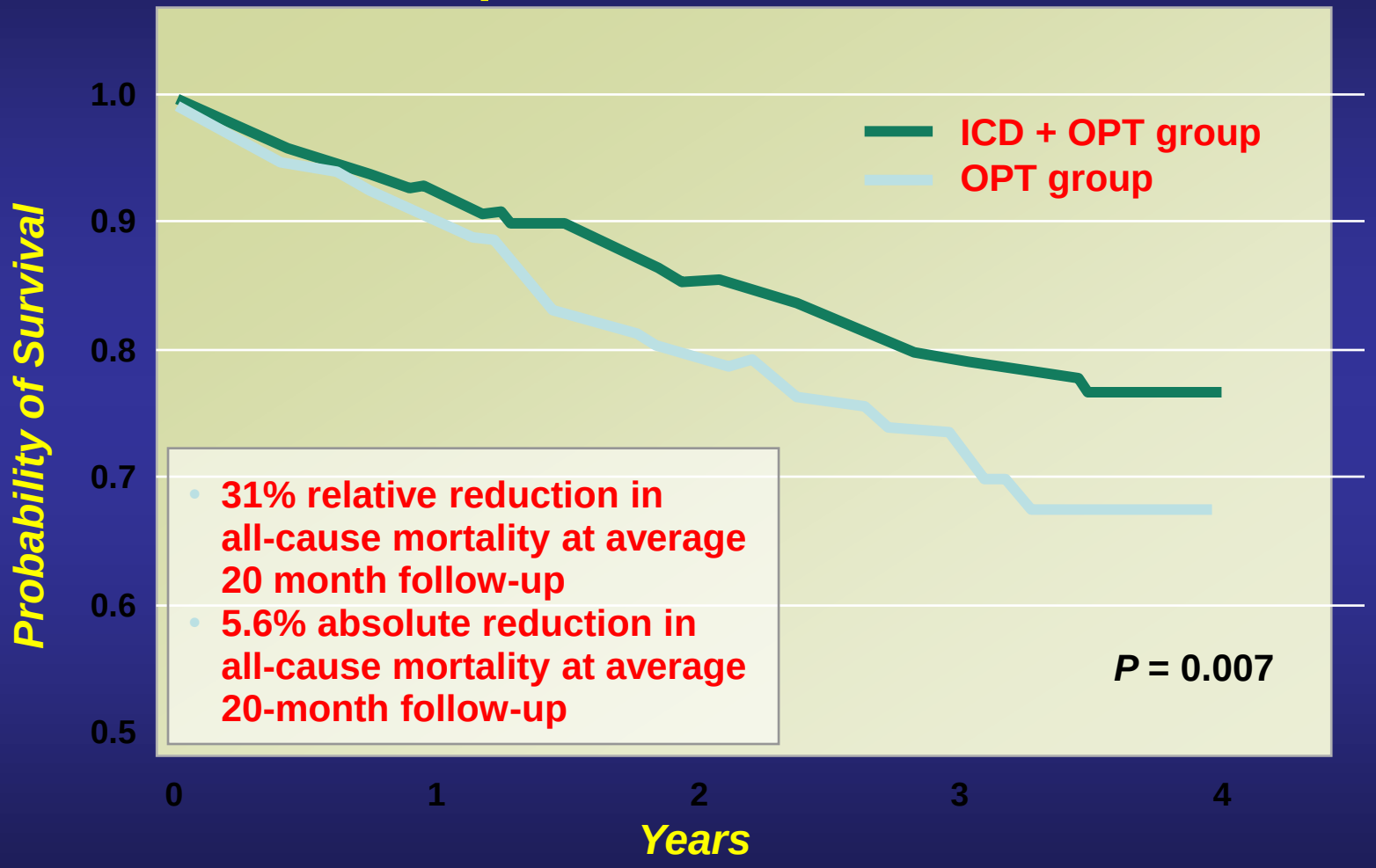
Class III Non-Indications for ICD Therapy

- **Ventricular tachyarrhythmias due to a transient or reversible disorder (eg, AMI, electrolyte imbalance, drugs, trauma).** ***(B)***

- **Significant psychiatric illnesses that may be aggravated by device implantation or may preclude systematic follow-up.** ***(C)***

- **Terminal illnesses with projected life expectancy ≤ 6 months.** ***(C)***

MADIT II: Addition of an ICD Improves Survival



Moss AJ, et al. *N Engl J Med* 2002;346:877-883. (Permission for use requested)

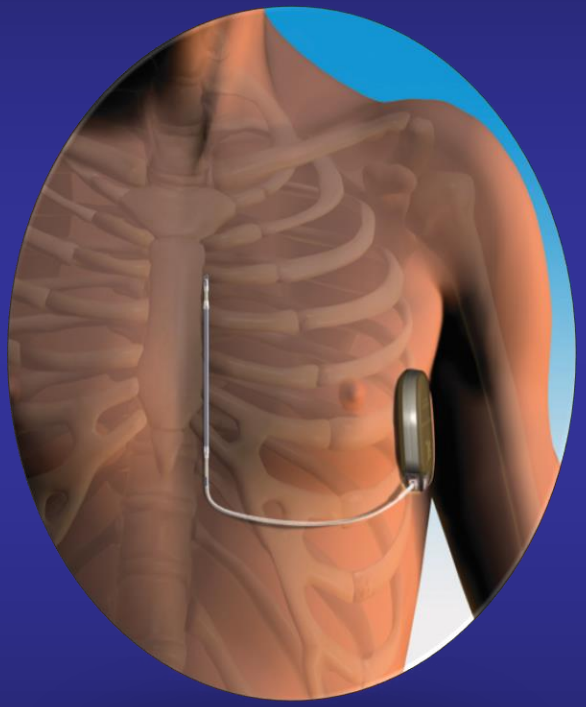
MADIT II: Conclusions

- ICD therapy improved survival when added to optimal medical therapy, compared to medical therapy alone.
- ICDs reduced mortality by 31% in patients with LVEF ≤ 30% and previous MI.
- All subgroups showed consistent results, regardless of:
  - Age
  - NYHA class
  - EF
  - QRS width
  - Gender

Moss AJ, et al. *N Engl J Med* 2002;346:877-883.

Background

- The completely Subcutaneous ICD (S-ICD) was designed to avoid the complications associated with transvenous leads.
- This device has limited pacing functionality with only transient post-shock, transthoracic pacing.
- Previous studies have largely enrolled patients with “niche” indications and relatively few co-morbidities from select, experienced centers.
- The S-ICD Post-Approval Study (PAS) was designed to evaluate a more real world US population.



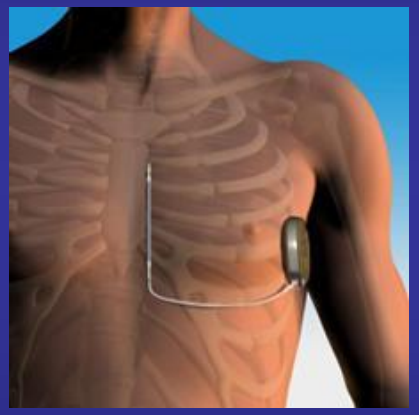
Value of a Modular CRM System

TV-ICD

mCRM™ System*

EMBLEM™ S-ICD
EMPOWER™ Modular Pacing System*

S-ICD

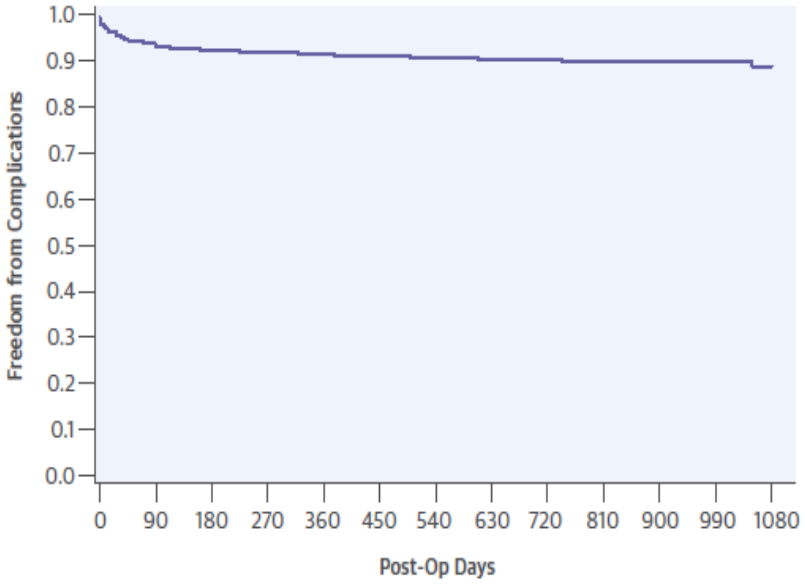


Documented need for Pacing or ATP

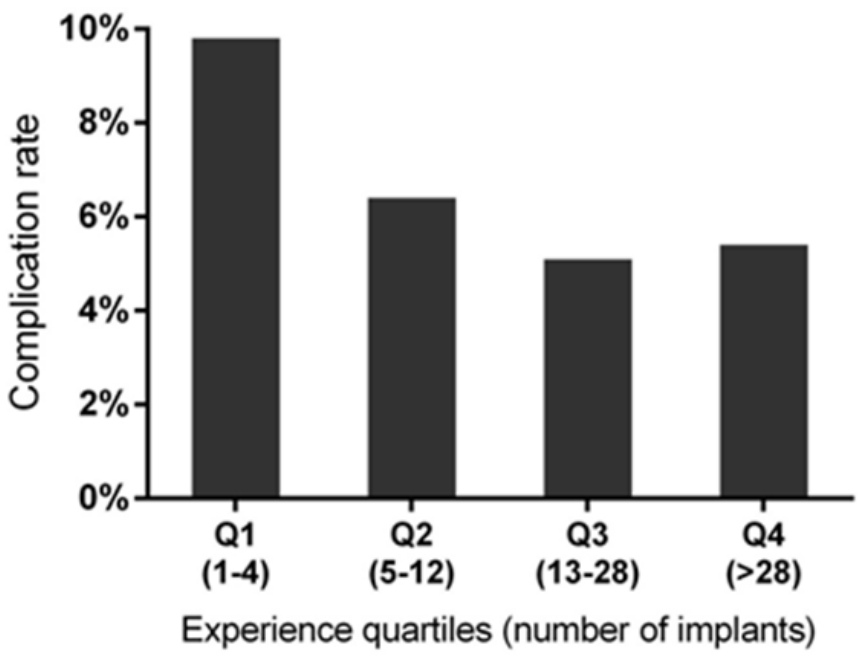
Potential need for Pacing or ATP

No need for Pacing or ATP

Long-Term Safety of the S-ICD: Freedom from Complications [1,2]



No. at Risk	878	791	731	707	650	591	525	414	303	217	162	123	105
K-M Estimate (%)	99.0	93.4	92.3	92.0	91.4	90.9	90.6	90.2	90.0	89.7	89.7	89.7	88.9



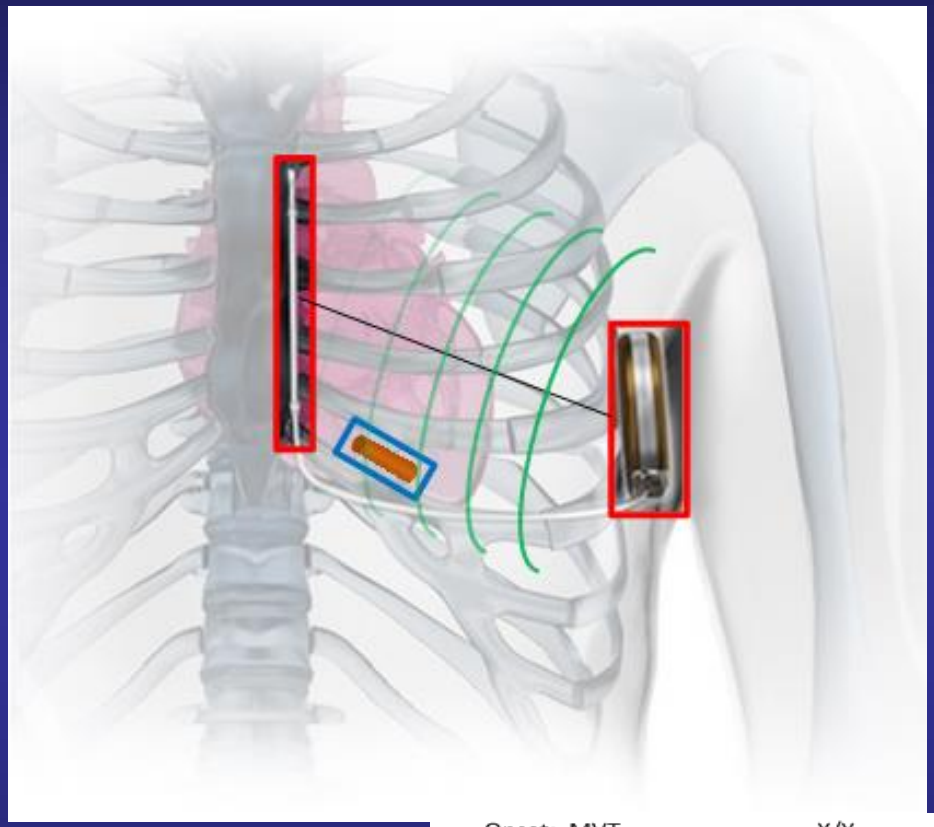
There were zero endovascular infections or S-ICD related bacteremia. The majority of the complications occurred within 30 days from implantation.

There was a learning curve associated with implantation of the S-ICD, with substantial improvement in complication rates after the 4th implant, reaching a steady-state after the 12th implant

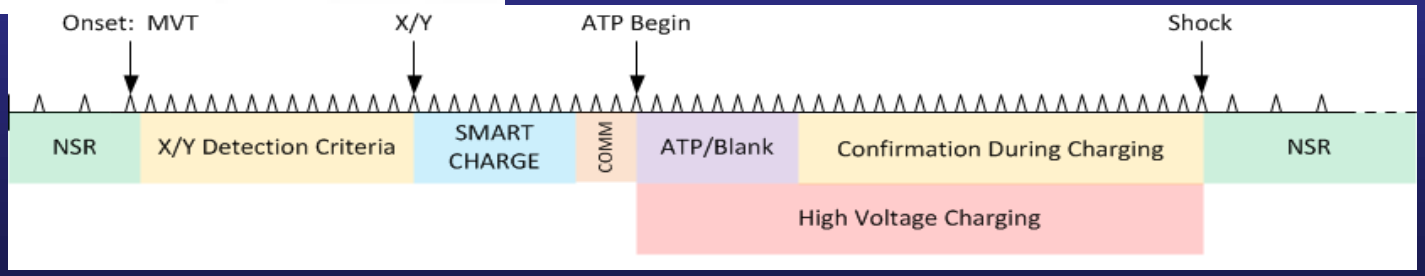
1.Burke, M.C. et al. J Am Coll Cardiol, 2015, 65(16): 1605-15

2.Knops RE, Brouwer TF, et al. Europace. 2015

Operation of the Modular CRM System



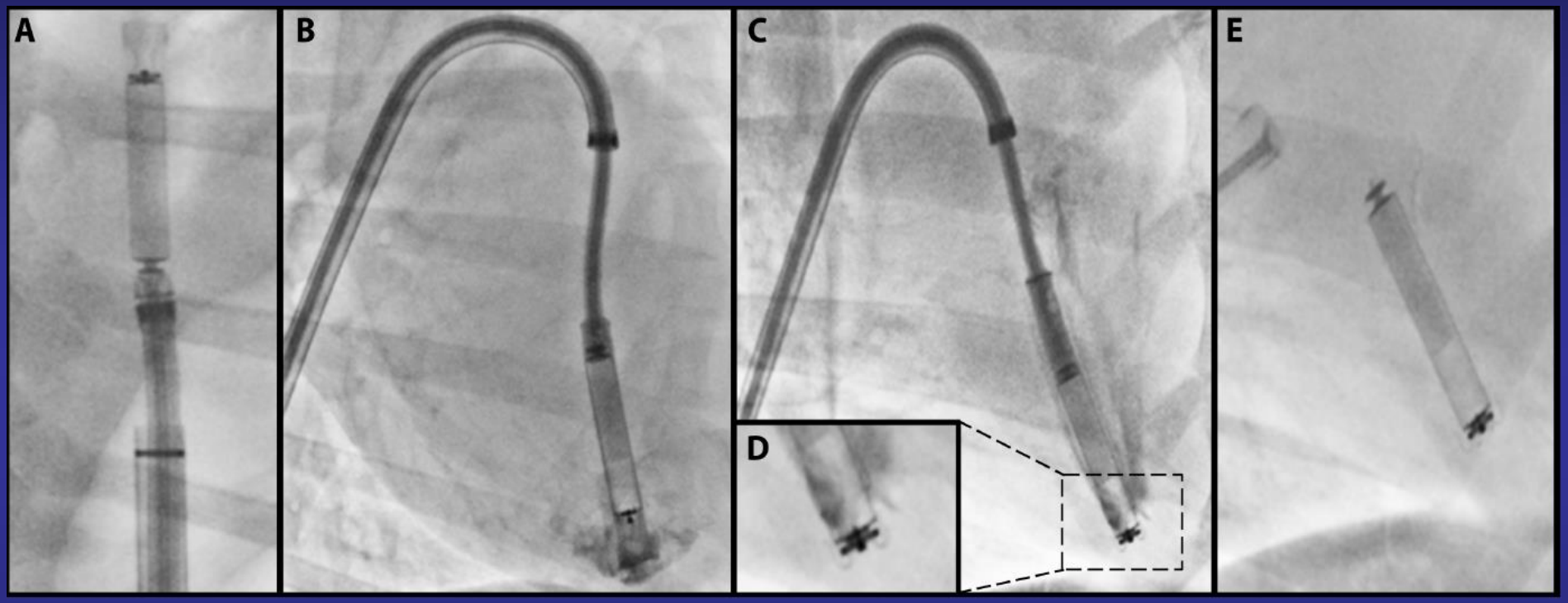
1. Leadless pacemaker designed to sense and treat bradycardia independently from the S-ICD
2. ATP schemes will be built into the leadless pacemaker, but can be activated only by the S-ICD or the programmer
3. S-ICD will continue to sense tachycardia, following which it is designed to command ATP in the leadless pacemaker prior to a shock



Example of ATP during charge in the Shock Zone

Leadless Pacemaker Platform [1,2]

Preclinical Model

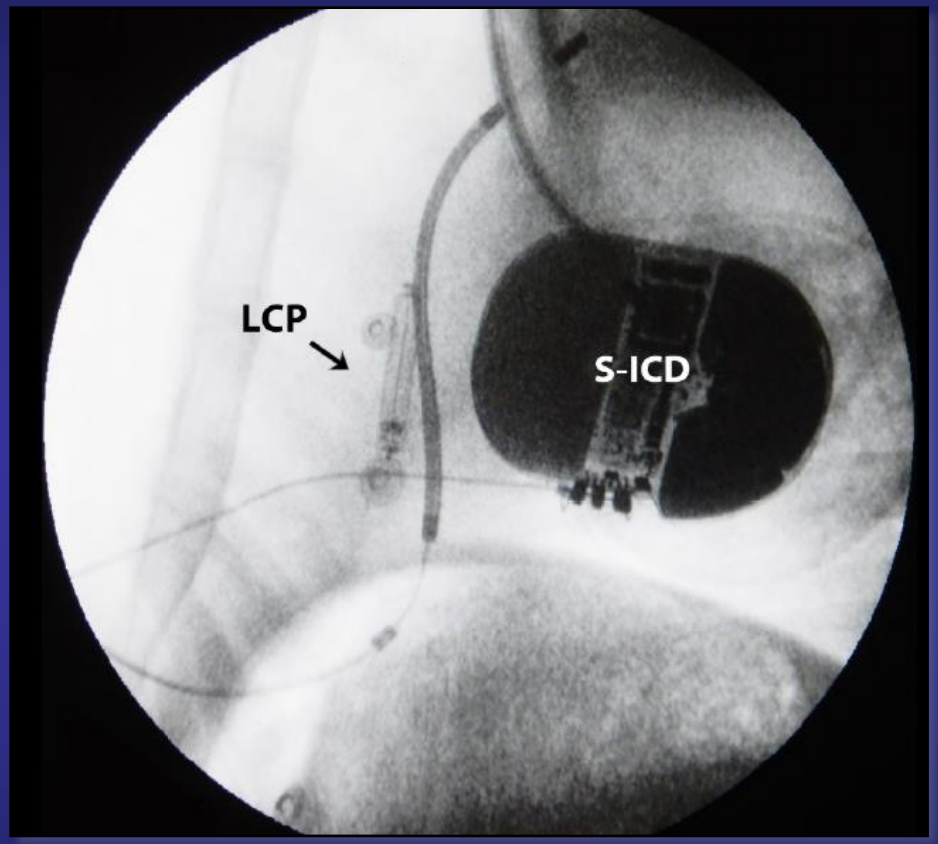


The LCP was implanted in the RV apex using a transfemoral approach and baseline performance measures were obtained [1, 2].

Images Courtesy of Dr.Tjong

1. Tjong et al, AMC Heart Center, JACC Letters, http://dx.doi.org/10.1016/j.jacc.2016.02.039
2. Tjong et al, ACC2016,Moderated Poster Session, Forst Report on Communicating Antitachycardia Pacing-Enabled Leadless Pacemaker and Subcutaneous Implantable Defibrillator

Leadless Pacemaker Platform [1,2]
Preclinical Study



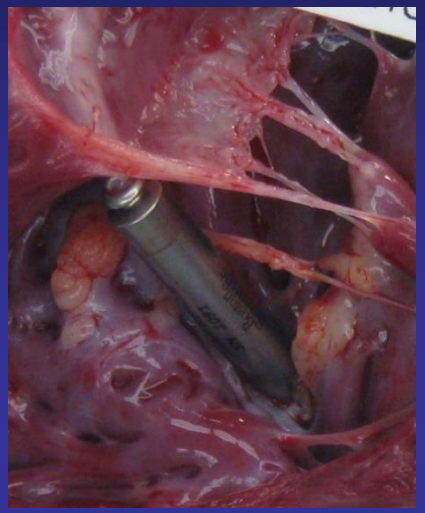
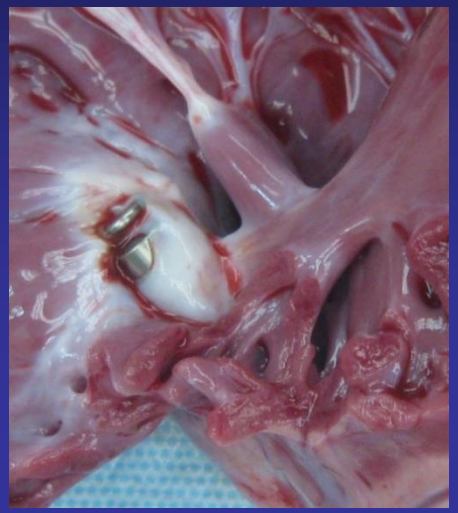
Images of the Prototype LCP, along with prototype firmware of S-ICD

Images Courtesy of Dr.Tjong

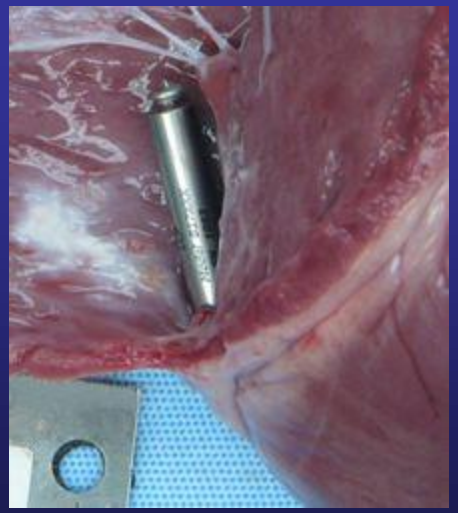
1. Tjong et al, AMC Heart Center, JACC Letters, http://dx.doi.org/10.1016/j.jacc.2016.02.039
2. Tjong et al, ACC2016,Moderated Poster Session, Forst Report on Communicating Antitachycardia Pacing-Enabled Leadless Pacemaker and Subcutaneous Implantable Defibrillator

Retrieval / Extraction Implications
Tissue Growth in Animal Models

Canine Chronic Functional*
(90 days post implant)


Ovine Chronic Functional*
(90 days post implant)


Barostim

Baroreflex Activation Therapy
Overview and Clinical Data

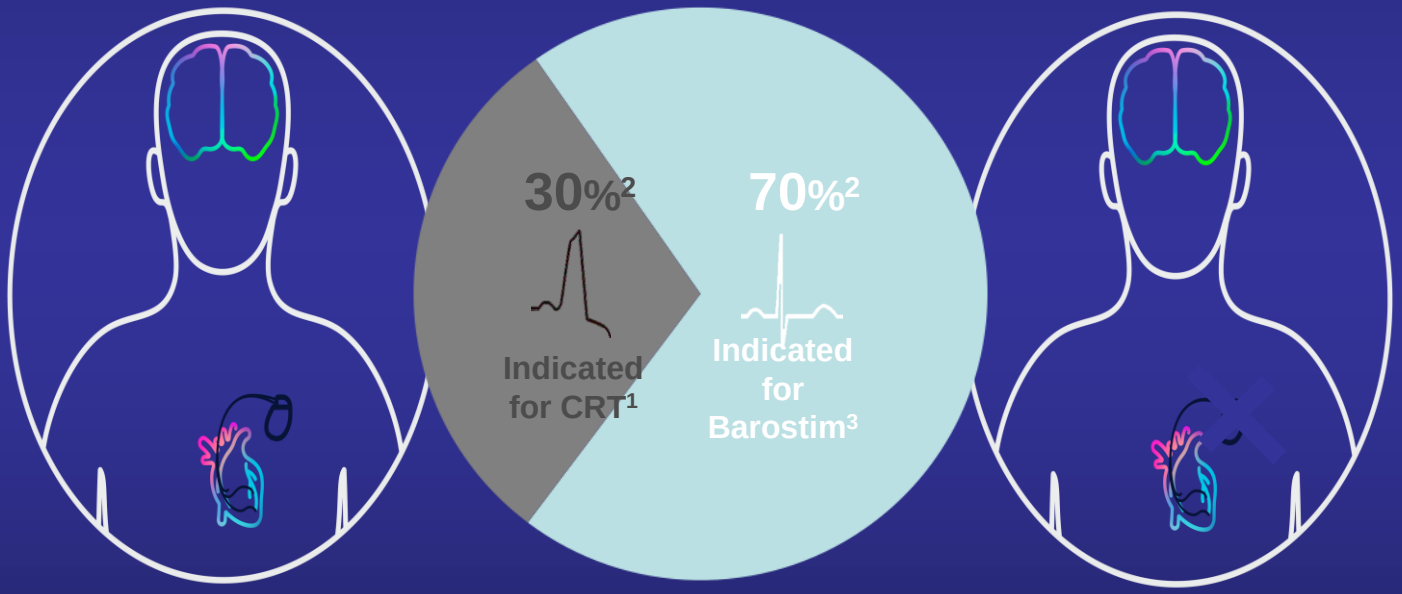
CRT is indicated for only 30% of HFrEF patients

- **Unmet Need & Indications**
- Mechanism of Action & System
- Clinical Evidence
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

NYHA II & III
EF ≤ 35%
GDMT

Indicated for CRT

Not Indicated for CRT

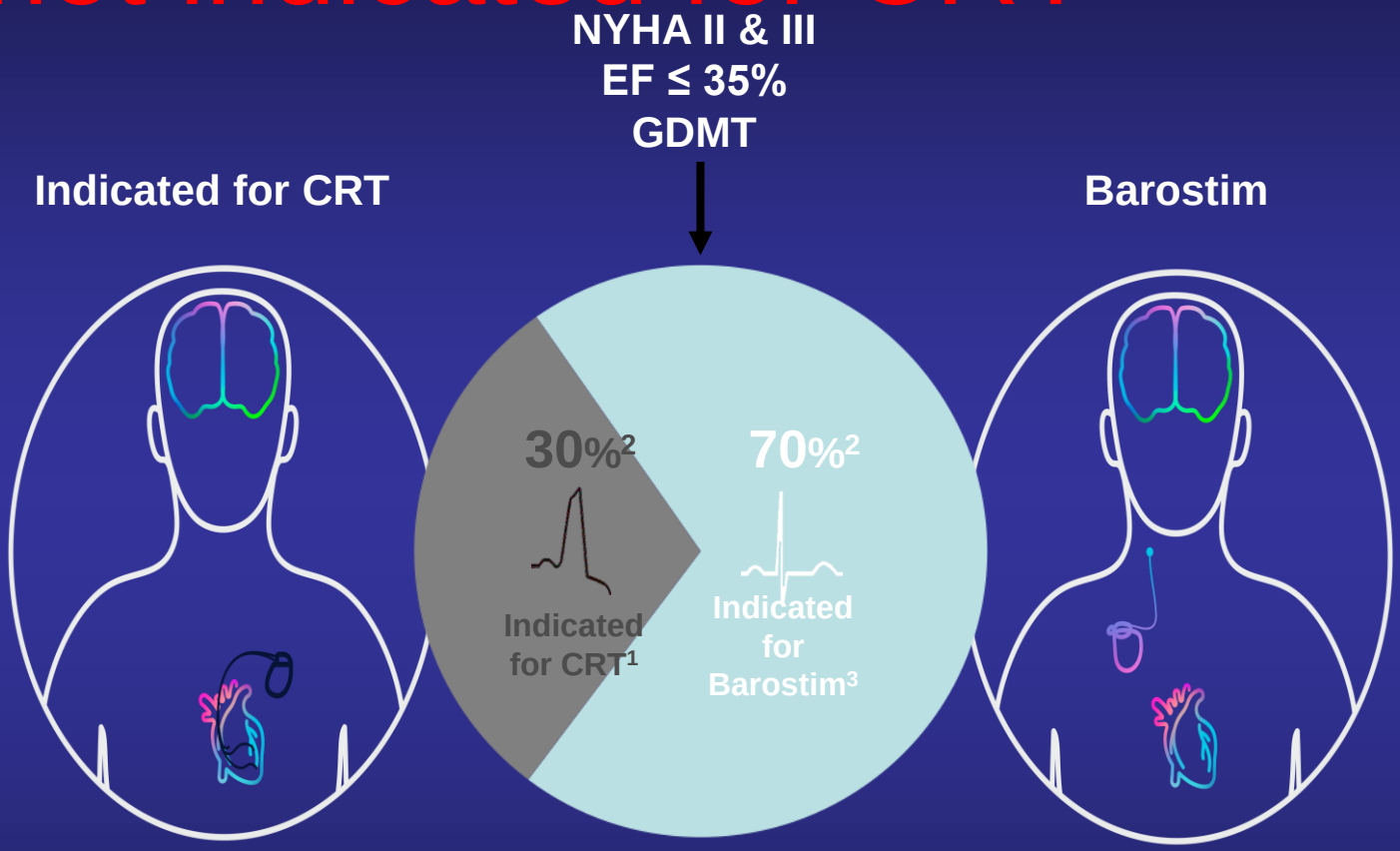


According to AHA/ACC 2013 Guidelines[1],
- QRS >= 150ms with LBBB (Class I)
- QRS > 150 w/o LBBB (Class IIa)
- QRS 120-149 w/ LBBB (Class IIa)

1. Yancy CM, et al. Circulation. 2013;128: 2013;128:e240–e327; 2. CVRx data on file.

Barostim is an option for those not indicated for CRT

- **Unmet Need & Indications**
- Mechanism of Action & System
- Clinical Evidence
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement



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1. Yancy CM, et al. Circulation. 2013;128: 2013;128:e240–e327; 2. CVRx data on file;
3. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180050. Accessed March 30, 2021

Treatment options for HFrEF patients

- **Unmet Need & Indications**
- Mechanism of Action & System
- Clinical Evidence
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

Purpose	Type	Treatment options for patients with NYHA Class II OR III, LVEF ≤ 35%[1,2]		
		QRS < 120 ms QRS 120-149 w/o LBBB	QRS ≥ 150 w/o LBBB or 120-149 w/ LBBB	QRS ≥ 150 w/ LBBB
Prevent Sudden Cardiac Death	Device	ICD		
Improve HF Symptoms and Outcomes	Drug	Guideline-Directed Medical Therapy		
	Device	**Not Indicated for CRT** **70%**	CRT "is probably indicated" 16%	CRT "is indicated" 14%

Patients with an existing CRT system that is not adequately treating their heart failure symptoms are eligible for Barostim

1. Yancy CM, et al. *Circulation.* 2013;128: 2013;128:e240–e327;
2. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180050. Accessed March 30, 2021; 3. CVRx data on file.

Indications for Barostim

Unmet Need & Indications

Mechanism of Action & System

Clinical Evidence

Patient Selection

Follow-Up & Programming

Economics & Reimbursement

Barostim Indications

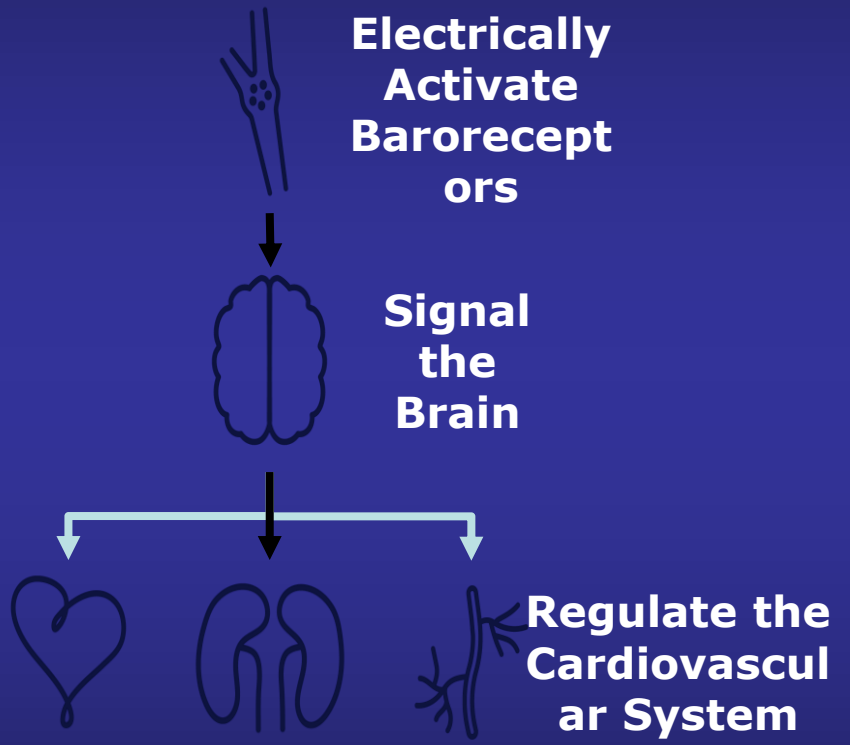
- NYHA III or NYHA II with a recent history of NYHA III
- LVEF ≤ 35%
- NT-proBNP < 1600 pg/mL
- Not indicated for CRT or not receiving adequate response from existing CRT device

No restriction on atrial arrhythmias

1. Tracy CM, et al. Circulation. 2012;126:1784-1800 2. Epstein AE, et al. J Am Coll Cardiol. 2013;61(3):e6-75 3. CVRx data on file.

Barostim rebalances the autonomic nervous system

- Unmet Need & Indications
- **Mechanism of Action & System**
- Clinical Evidence
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

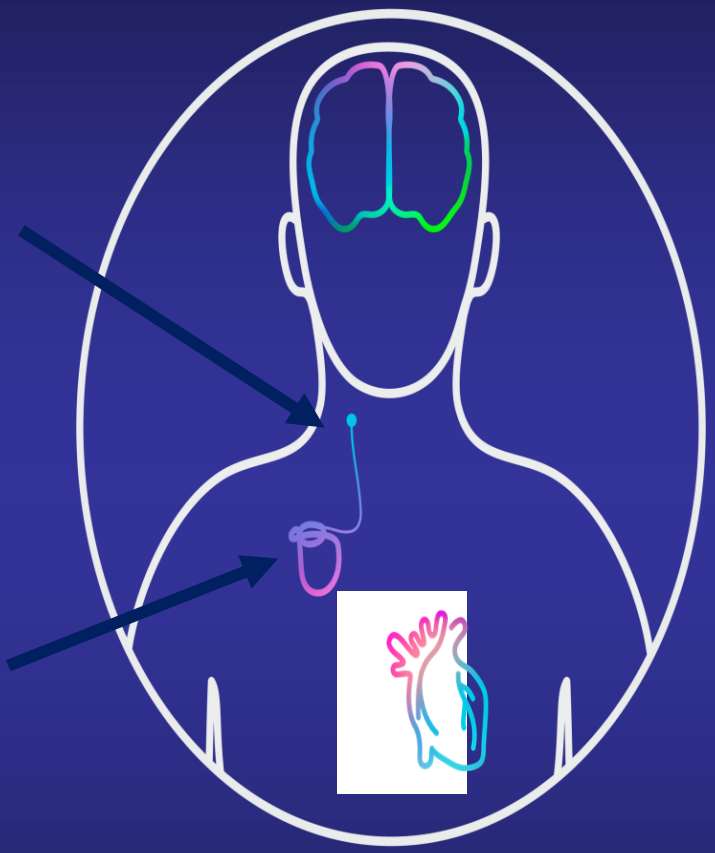


Barostim system elements

- Unmet Need & Indications
- **Mechanism of Action & System**
- Clinical Evidence
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

Create a small incision to access the carotid bifurcation and secure the electrode and lead

Tunnel the lead over the collarbone and connect to IPG in a standard device pocket



Barostim is typically implanted an a ~1 hour outpatient procedure in an OR or hybrid OR

Barostim clinical overview

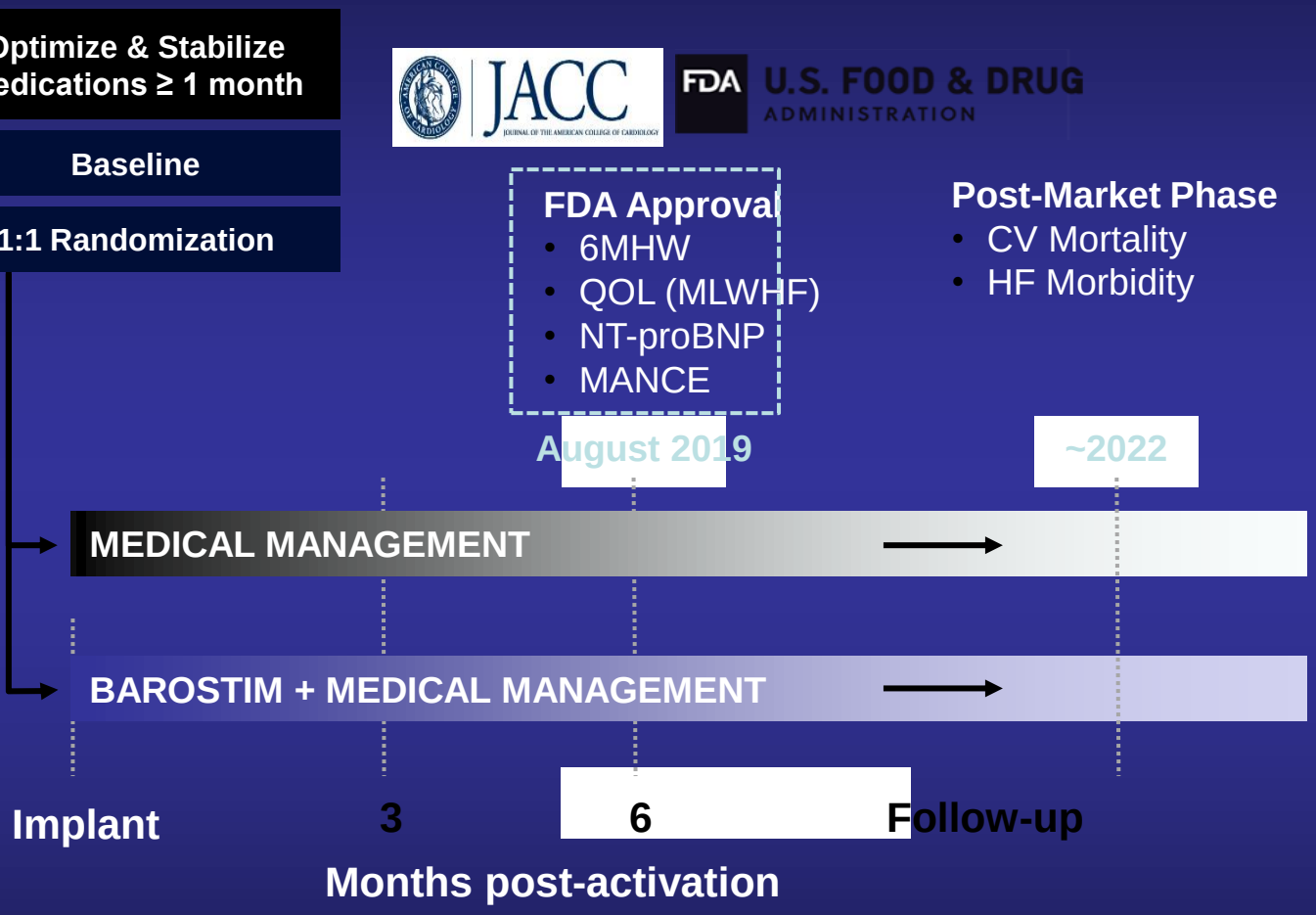
- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

	Phase I: BAT in HF[1] 1st Enrollment 12/2011	Phase II: HOPE4HF[2] 1st Enrollment 5/2012	Pivotal: BeAT-HF[3] 1st Enrollment 4/2016
Objective	• Assess safety • Demonstrate mechanism of action	• Assess safety and efficacy	• Demonstrate safety and efficacy, including morbidity & mortality • Assess health economics
Subjects	• n = 11	• n = 146	• n = 408
Outcomes	• Barostim is safe[1] • Mechanism of action demonstrated through muscle sympathetic nerve activity[1]	• Barostim is safe and effective in heart failure[2] • CE Mark Approval[4] • EAP/FDA Breakthrough Device designation[4]	• Barostim is a safe, effective, and an economically attractive solution for heart failure symptom improvement[3,5] • FDA Approval[6]

1. Gronda E, et al. Eur J Heart F
data on file.
5. Bisognano, J, et al. BMC Cardiovasc Disord 21, 155 (2021). 6..https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180050. Accessed March 30, 2021.

BeAT-HF phase III pivotal study

- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement



1. Zile MR, et al. J Am Coll Cardiol. 2020;76(1):1-13.

BeAT-HF baseline demographics

- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

	Barostim (n=130)	Control (n=134)
Demographics		
Age	62 ± 11	63 ± 10
Gender female	19%	22%
Race: Caucasian	75%	72%
Heart failure and physical status		
NYHA Class III	93%	95%
MLWHF QOL score	53 ± 24	52 ± 24
6MHW (m)	316 ± 68	294 ± 73
HR (bpm)	75 ± 10	75 ± 11
SBP (mmHg)	120 ± 17	121 ± 16
DBP (mmHg)	73 ± 10	73 ± 10
LVEF (%)	27 ± 7	28 ± 6
NT-proBNP (pg/mL) (IQR)	731 (475,1021)	765 (479, 1052)
eGFR (mL/min)	64 ± 17	62 ± 20
QRS internval	109 ± 18	111 ± 26
Previous HF hospitalization	42%	51%

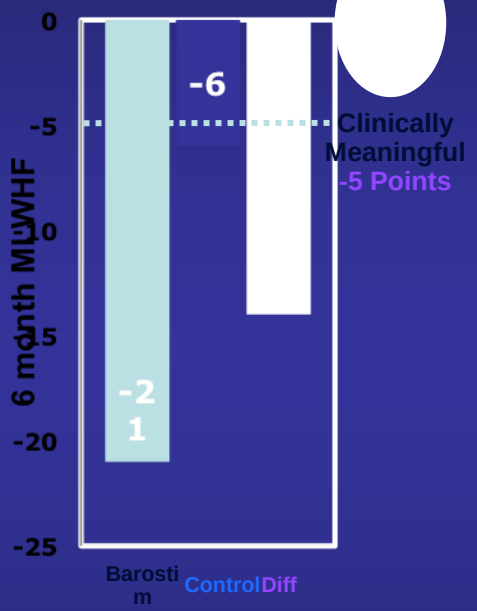
	Barostim (n=130)	Control (n=134)
Co-Morbidities		
Coronary Artery Disease	62%	69%
Atrial Fibrillation	29%	43%
Stroke or TIA	19%	22%
Chronic Kidney Disease	24%	25%
Diabetes Type II	45%	51%
Heart failure treatment		
Number of meds	3.9 ± 1.2	4.1 ± 1.4
ACE-I/ARB/ARNI	89%	84%
Beta-Blocker	95%	95%
MRA	49%	42%
Diuretic	85%	87%
Ivabradine	2.3%	4.5%
ICD	78%	79%

1. Zile MR, et al. *J Am Coll Cardiol* 2020; 76:1-13; 2. https://www.accessdata.fda.gov/cdrh_docs/pdf18/P180050b.pdf. Accessed March 27, 2021.

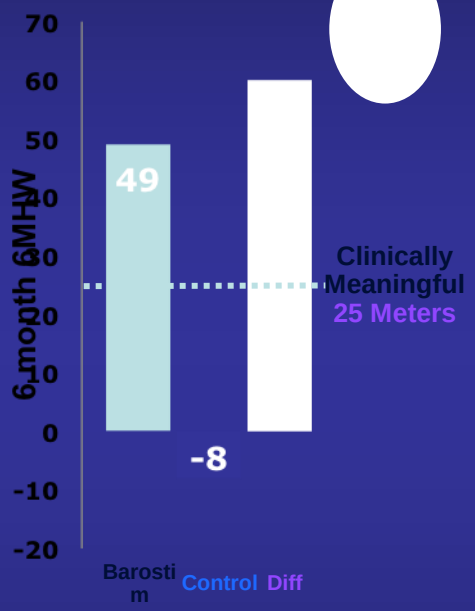
BeAT-HF symptom improvement

- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

Quality of Life (MLWHF)



Exercise capacity (6MHW)



NYHA class

CRT trial results		
CONTAK CD[3]	NYHA III or IV LVEF ≥ 35% QRS > 120ms	-11
MIRACLE[4]	NYHA III or IV LVEF ≥ 35% QRS > 130ms	-9

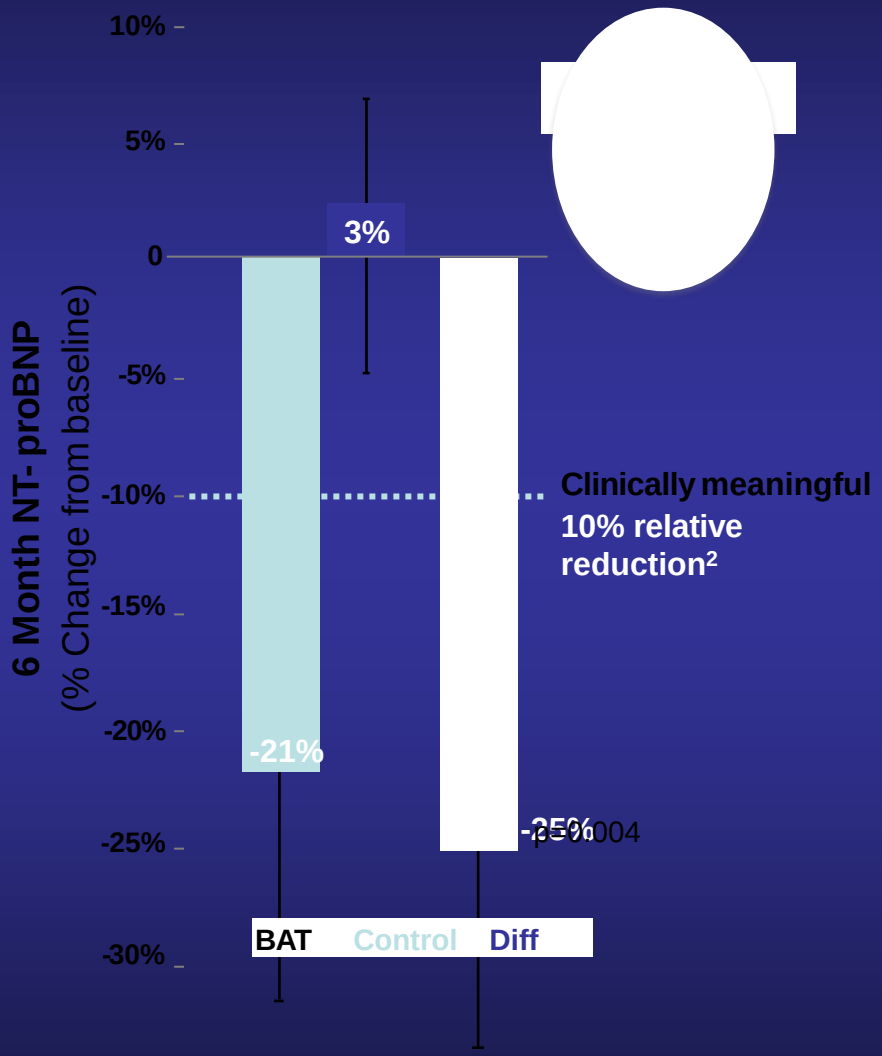
CRT trial results		
CONTAK CD[3]	NYHA III or IV LVEF ≥ 35% QRS > 120ms	39
MIRACLE[4]	NYHA III or IV LVEF ≥ 35% QRS > 130ms	29

CRT trial results		
CONTAK CD[3]	NYHA III or IV LVEF ≥ 35% QRS > 120ms	20%
MIRACLE[4]	NYHA III LVEF ≥ 35% QRS > 130ms	30%

*Data from different studies a ctly
1. Zile MR, et al. J Am Coll d F
–1459.
4. Abraham WT, et al. N Eng
5. Gremeaux V, et al. Arch P

BeAT-HF NT-proBNP reduction[1]

- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement



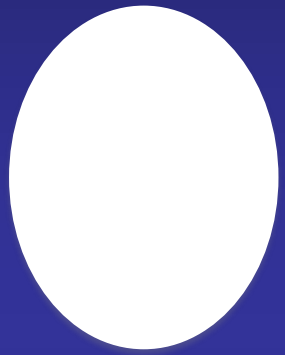
- PARADIGM-HF (ARNI) demonstrated that even a 10% reduction in NT-proBNP is associated with a significant benefit in terms of cardiovascular death or HF hospitalization[2]
- BeAT-HF hospitalization and mortality data remains blinded to support on-going post-market phase

1. Zile MR, et al. *Am Coll Cardiol* 2020;76:1-13. 2. Zile MR, et al. *J Am Coll Cardiol.* 2016;68:2425-2436.

BeAT-HF safety

- Unmet Need & Indications
- Mechanism of Action & System
- **Clinical Evidence**
- Patient Selection
- Follow-Up & Programming
- Economics & Reimbursement

MANCE-Free Rate[1]



Potential Reduction in Serious Cardiovascular Events[2]

Cardiovascular Event	Barostim (n=125)		Control (n=134)		Relative Reduction
	Number of Events	Event Rate*	Number of Events	Event Rate*	
Arrhythmias	8	0.054	18	0.109	50%
Angina/Acute MI	5	0.034	10	0.060	44%
Pre-syncope/ Syncope	2	0.014	6	0.036	63%
Total	**15**	**0.101**	**34**	**0.206**	**51%**

* Events per patient-year of follow-up

p-value=0.023
Not a powered endpoint

Heart failure hospitalization data remains blinded to support the on-going post-market outcome phase

Evaluation of other serious cardiovascular events <u>suggests</u> a reduction between treatment arms

1. Zile MR, et al. Am Coll Cardiol 2020;76:1-13; 2. Zile MR, et al. Am Coll Cardiol 2020; Supplemental Appendix Table 13.

BeAT-HF conclusions

Unmet Need & Indications

Mechanism of Action & System

Clinical Evidence

Patient Selection

Follow-Up & Programming

Economics & Reimbursement

- Barostim was demonstrated to be **safe and effective for HFrEF symptoms** in the BeAT-HF study, with results published in JACC in June, 2020
- **BeAT-HF** demonstrated significant improvements and heart failure symptoms and reductions in NT-proBNP with Barostim
- **ARNI was approved for use during BeAT-HF** and 38% of BeAT-HF patients were on ARNI at 6 months. Barostim performed well even with 4x higher new medication in the Control arm.
- **Morbidity and Mortality post-market phase** of BeAT-HF enrollment completed and may lead to an expanded indication

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 76, NO. 1, 2020

ORIGINAL INVESTIGATIONS

Baroreflex Activation Therapy in Patients With Heart Failure With Reduced Ejection Fraction

Michael R. Zile, MD,[a,b] JoAnn Lindenfeld, MD,[c] Fred A. Weaver, MD,[d] Faiez Zannad, MD,[e] Elizabeth Galle, MPH,[f] Tyson Rogers, MS,[g] William T. Abraham, MD[h]

ABSTRACT

BACKGROUND This study demonstrated the safety and effectiveness of baroreflex activation therapy (BAT) in patients with heart failure with reduced ejection fraction (HFrEF).

OBJECTIVES The BeAT-HF (Baroreflex Activation Therapy for Heart Failure) trial was a multicenter, prospective, randomized, controlled trial; subjects were randomized 1:1 to receive either BAT plus optimal medical management (BAT group) or optimal medical management alone (control group).

METHODS Four patient cohorts were created from 408 randomized patients with HFrEF using the following enrollment criteria: current New York Heart Association (NYHA) functional class III or functional class II (patients who had a recent history of NYHA functional class III); ejection fraction ≤35%; stable medical management for ≥4 weeks; and no Class I indication for cardiac resynchronization therapy. Effectiveness endpoints were the change from baseline to 6 months in 6-min hall walk distance (6MHW), Minnesota Living with HF Questionnaire quality-of-life (QOL) score, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels. The safety endpoint included the major adverse neurological or cardiovascular system or procedure-related event rate (MANCE).

RESULTS Results from, timeline and rationale for, cohorts A, B, and C are presented in detail in the text. Cohort D, which represented the intended use population that reflected the U.S. Food and Drug Administration–approved instructions for use (enrollment criteria plus NT-proBNP <1,600 pg/ml), consisted of 245 patients followed-up for 6 months (120 in the BAT group and 125 in the control group). BAT was safe and significantly improved QOL, 6MHW, and NT-proBNP. In the BAT group versus the control group, QOL score decreased (Δ = −14.1; 95% confidence interval [CI]: −19 to −9; $p < 0.001$), 6MHW distance increased (Δ = 60 m; 95% CI: 40 to 80 m; $p < 0.001$), NT-proBNP decreased (Δ = −25%; 95% CI: −38% to −9%; $p = 0.004$), and the MANCE free rate was 97% (95% CI: 93% to 100%; $p < 0.001$).

CONCLUSIONS BAT was safe and significantly improved QOL, exercise capacity, and NT-proBNP. (Baroreflex Activation Therapy for Heart Failure [BeAT-HF]; NCT02627196) (J Am Coll Cardiol 2020;76:1-13) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the [a]Medical University of South Carolina, Charleston, South Carolina; [b]Ralph H. Johnson Department of Veterans Affairs Medical Center, Charleston, South Carolina; [c]Vanderbilt Heart and Vascular Institute, Nashville, Tennessee; [d]Division of Vascular Surgery and Endovascular Therapy, Keck School of Medicine, University of Southern California, Los Angeles, California; [e]Inserm Centre d'Investigation, CHU de Nancy, Institute Lorrain du Coeur et des Vaisseaux, Université de Lorraine, Nancy, France; [f]CVRx, Inc., Minneapolis, Minnesota; [g]NAMSA, Inc., Minneapolis, Minneapolis; and the [h]Division of Cardiovascular Medicine, The Ohio State University, Columbus, Ohio. This study was supported by CVRx, Inc. Dr. Zile has been a consultant to CVRx; and has received fees for being a member of the BeAT-HF trial executive steering committee. Dr. Lindenfeld has been a consultant to CVRx; has received fees for being a member of the BeAT-HF trial executive steering committee; and has been a consultant to AstraZeneca, Boehringer Ingelheim, Edwards, Impulse Dynamic, Volumetrix, Sensible Medical, and V Wave. Dr. Weaver has been

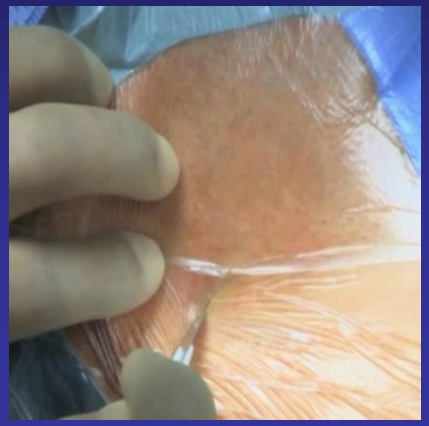
ISSN 0735-1097 https://doi.org/10.1016/j.jacc.2020.05.015

1. Zile MR, Abraham WT, et al. JACC 2020; 76: 1-13

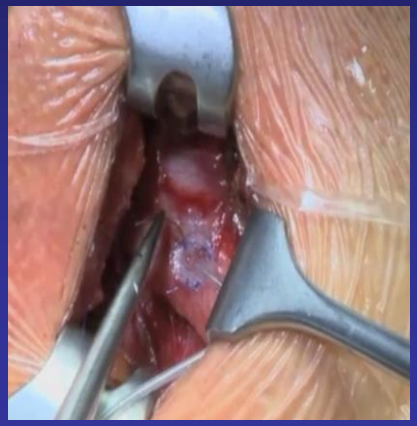
Barostim implant

- Unmet Need & Indications
- Mechanism of Action & System
- Clinical Evidence
- Patient Selection
- **Follow-Up & Programming**
- Economics & Reimbursement

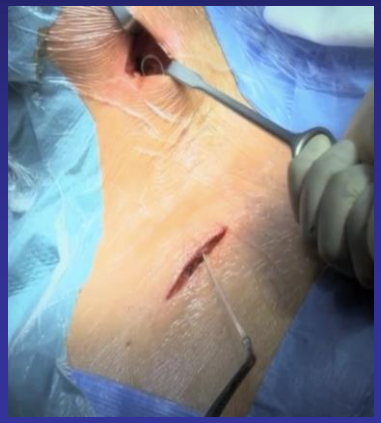
Small Incision in Neck



Electrode sutured to Carotid Artery

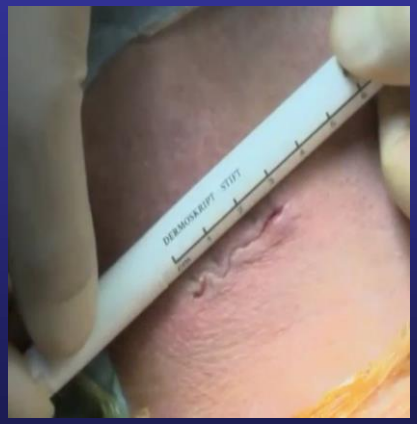


Lead tunneled to pectoral pocket



Lead connected to device and placed in pocket

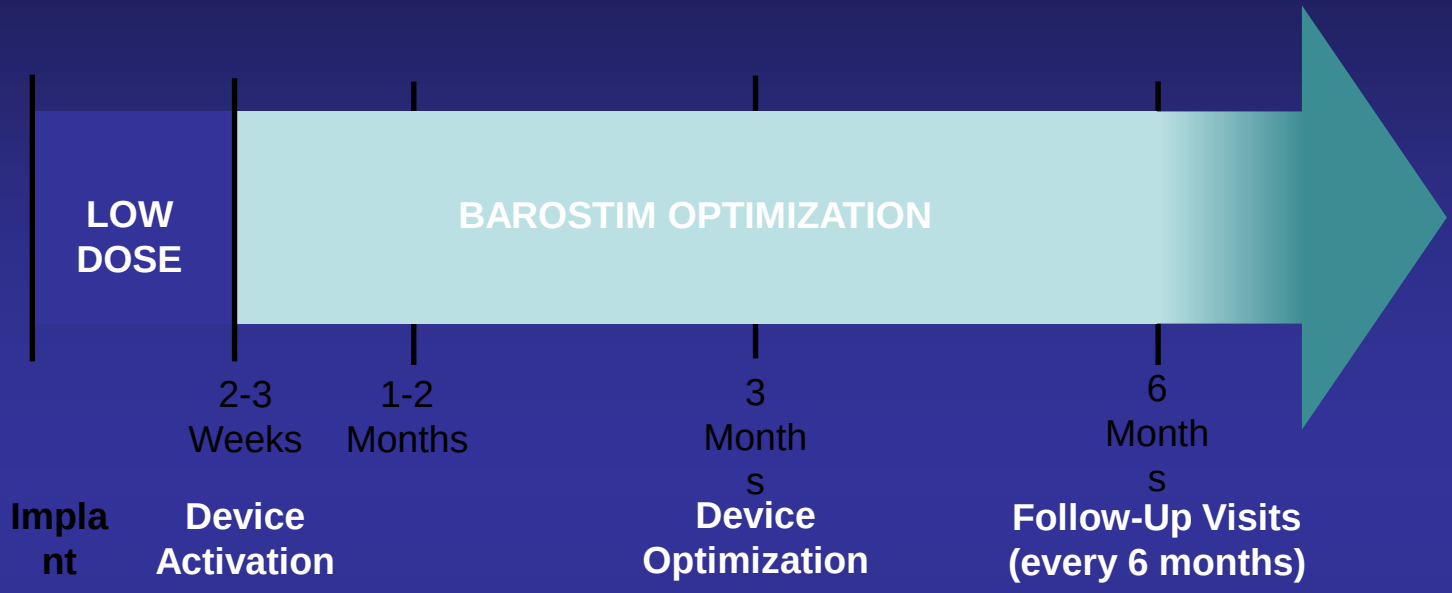
Incision in neck closed



Pocket incision closed

Follow-up programming

- Unmet Need & Indications
- Mechanism of Action & System
- Clinical Evidence
- Patient Selection
- **Follow-Up & Programming**
- Economics & Reimbursement

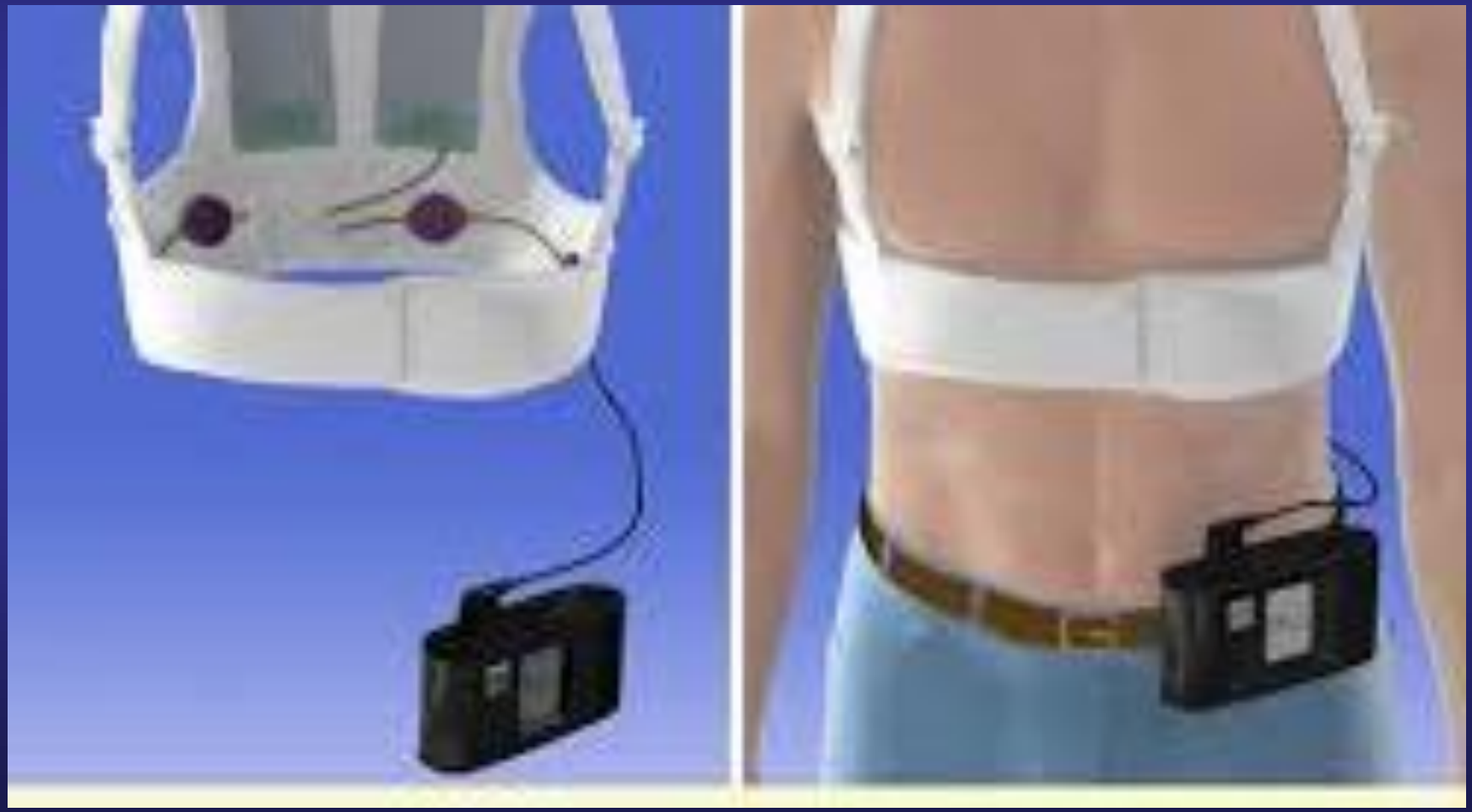


Recommended follow-up schedule:

- Activation approximately 2-3 weeks post-implant
- Optimization at 3 months and 6 months
- Follow-up visits every 6 months based on each patient's medical need

Average battery life of 5 years with no charging required

What if the patient doesn't qualify for ICD-ie too soon after MI?



Abbott

CardioMEMS™ HF System

A PERSONALIZED, PROACTIVE APPROACH TO MANAGE HF BY MONITORING PA PRESSURE

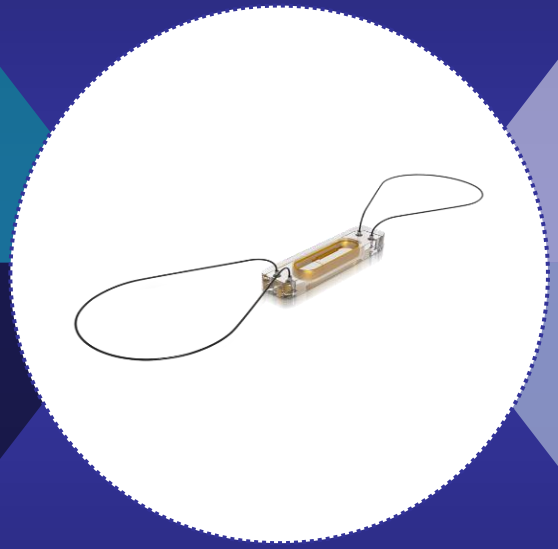
THE CARDIOMEMS HF SYSTEM DELIVERS

cardiomems™ hf System Offers New Promise

Clinical trial and early commercial use demonstrates that PA-pressure guided therapy:

Prevents Acute Decompensation

Effectively Lowers PA Pressures



Improves Quality of Life

Additionally, early commercial use offers **best practices for implementation and service management**.

Abraham WT, Lancet, 2011

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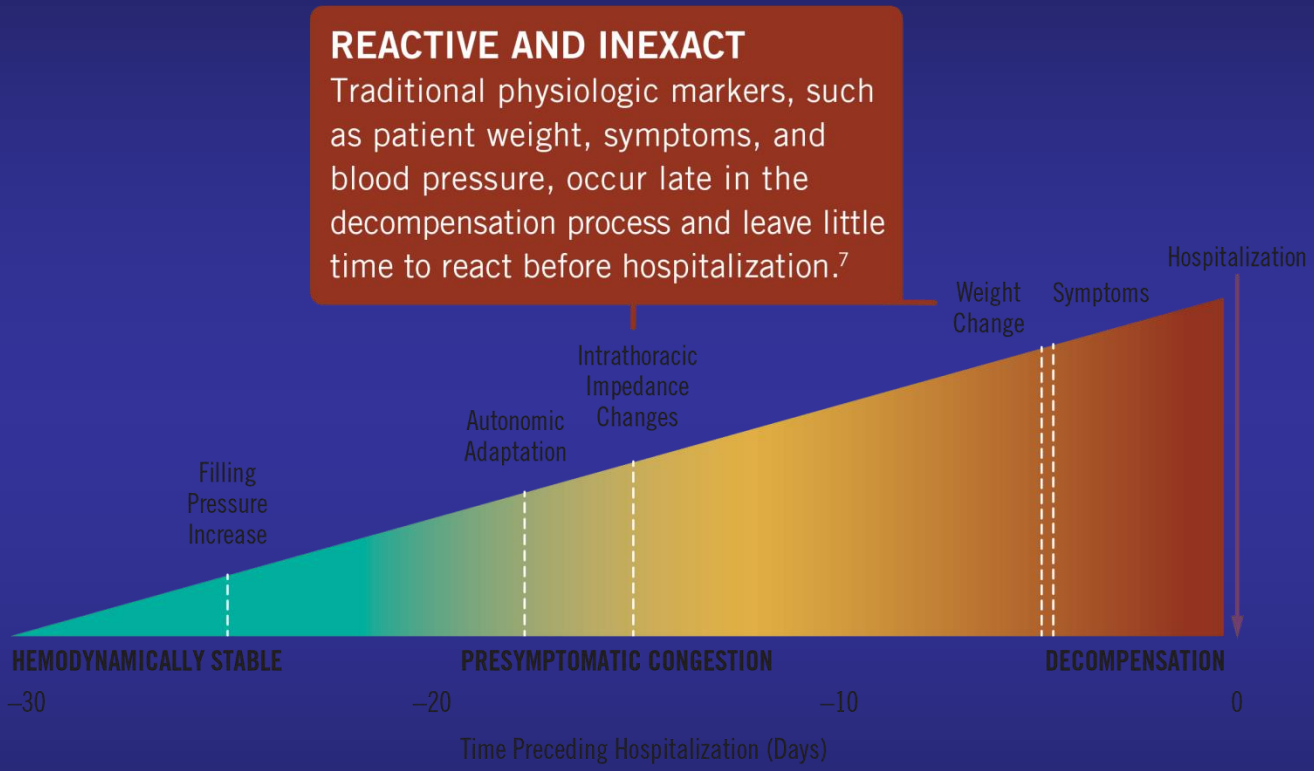
Current HF Management:

Why aren't current parameters working?



Graph adapted from Adamson PB, et al. Curr Heart Fail Reports, 2009.

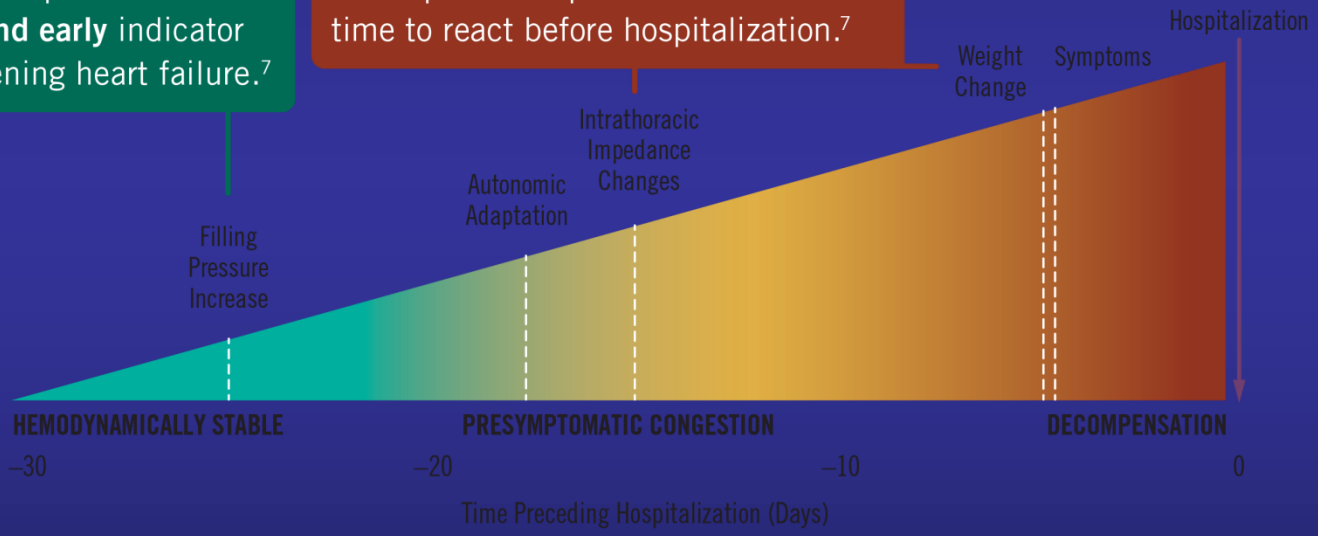
Abbott

Current HF Management:

How can we get ahead of symptoms associated with acute decompensation?

PROACTIVE AND ACTIONABLE
Real-time monitoring of PAP with the CardioMEMS™ HF system provides a **direct and early** indicator of worsening heart failure.[7]

REACTIVE AND INEXACT
Traditional physiologic markers, such as patient weight, symptoms, and blood pressure, occur late in the decompensation process and leave little time to react before hospitalization.[7]



Graph adapted from Adamson PB, et al. Curr Heart Fail Reports, 2009.

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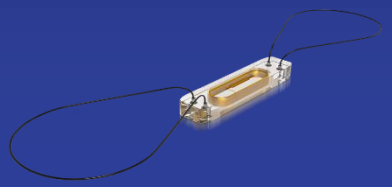
cardiomems™ HF System:

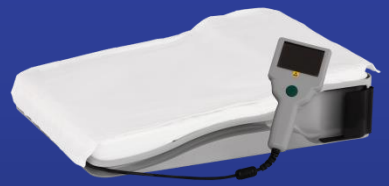
Provides clarity in the management of heart failure

Delivers insight into the early onset of worsening HF to more proactively manage HF patients and improve outcomes

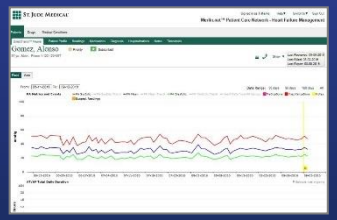
Pulmonary Artery Pressure Sensor

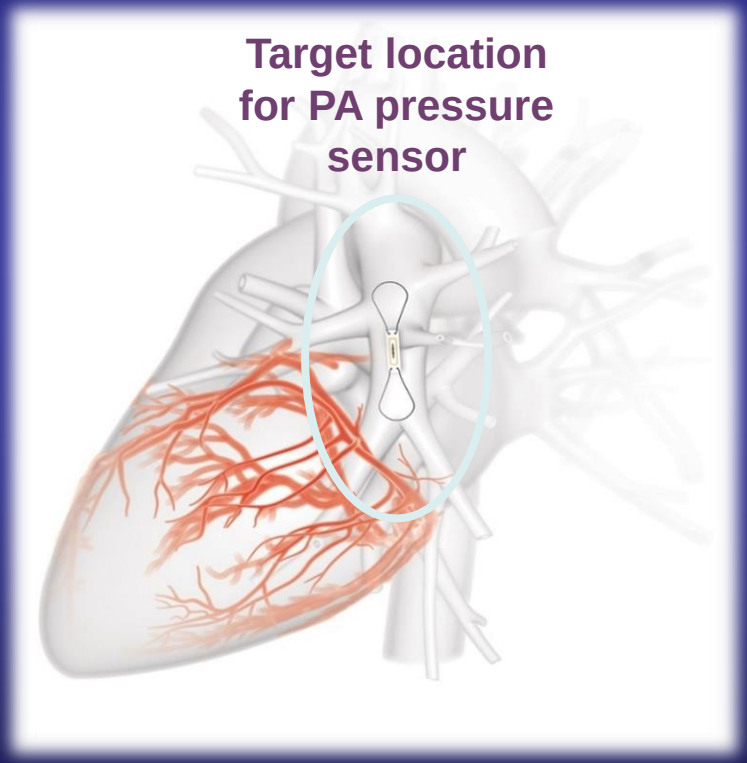


Patient Electronics System



Merlin.net™ PCN





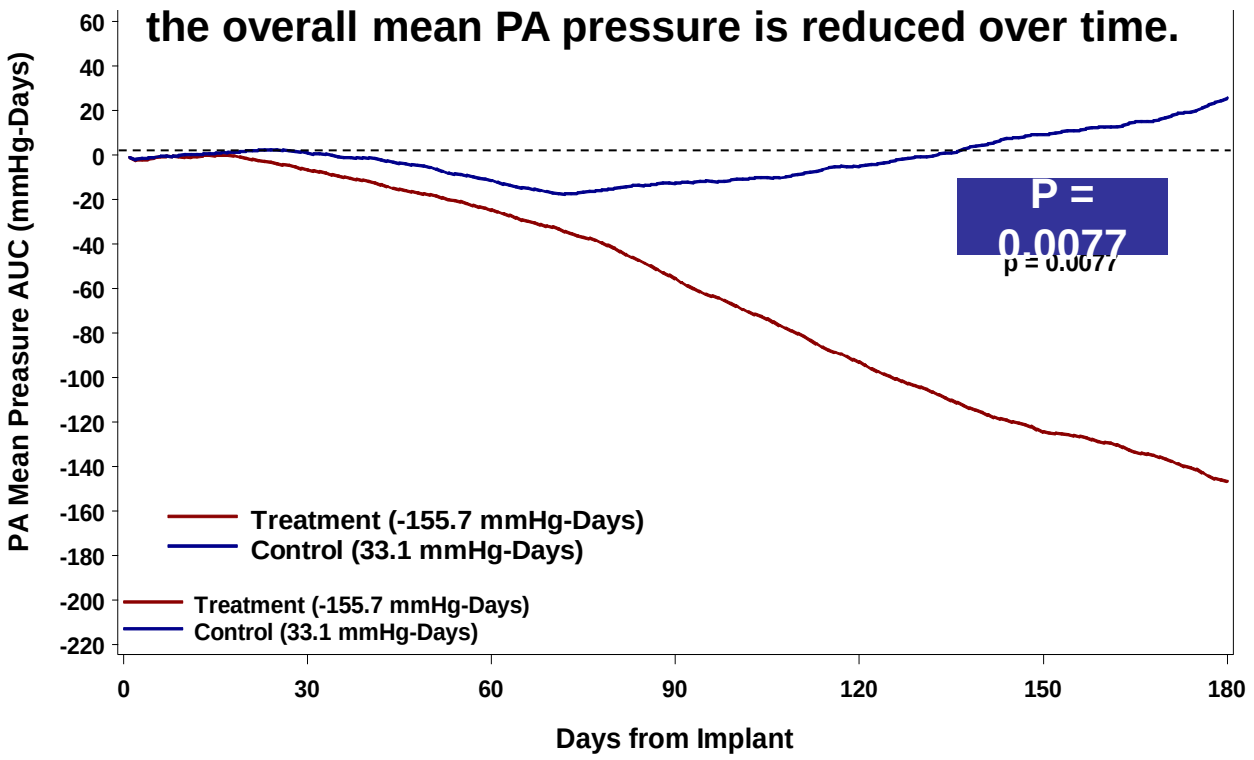
Abraham WT, Lancet, 2011

THE Champion Trial

CHAMPION Trial results:

PA PRESSURE MEAN CHANGE FROM BASELINE

PART 1: RANDOMIZED ACCESS PART 2: OPEN ACCESS



Monitoring PA pressure with the CardioMEMS™ HF System allows management of the pressure spikes that lead directly to exacerbation, as well as the long-term trends.

Abraham WT, et al. Lancet, 2011.

CardioMEMS HF System Clinical Indications

- **Indications and Usage**: The CardioMEMS HF System is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalizations.

- **Contraindications**: The CardioMEMS™ HF System is contraindicated for patients with an inability to take dual antiplatelet or anticoagulants for one month post implant.

Abbott

EVOLVING CardioMEMS™ HF SYSTEM

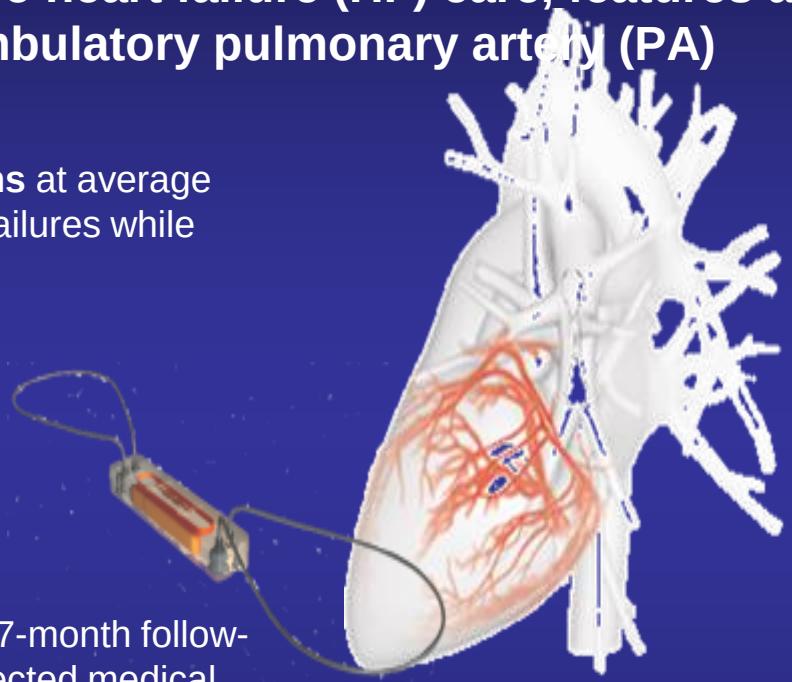
A powerful new tool for comprehensive heart failure (HF) care, features a safe, reliable sensor for measuring ambulatory pulmonary artery (PA) pressure.

33% **Reduction in HF hospital admissions** at average 15-month follow-up with zero sensor failures while 98.6% complication free[19]

78%† **Reduction in HF readmissions** among Medicare patients[24]

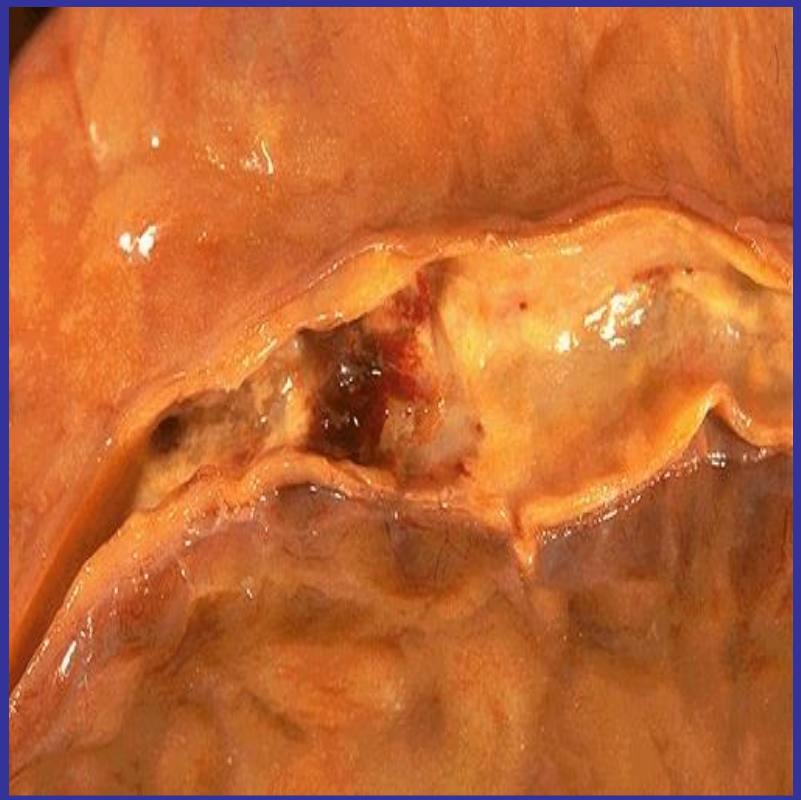
57%† **Improved survivability** at average 17-month follow-up in HFrEF patients on guideline directed medical therapy (GDMT)[25]

53%† **Improved survivability** at average 18-month follow-up in HFrEF patients on guideline directed medical therapy (GDMT) with an ICD or CRT device[26]



†Retrospective analysis from subset of CHAMPION clinical trial

you are what you eat!



AHA guidelines in HF patient

- <2000 calories/24 hrs
- Fruits and vegetables: at least 4.5 cups/d
- Fish-3 to 5 ounces servings
- Fiber rich whole grains: at least three 1 ounce equivalents
- Sodium <1.5 gm per 24 hrs
- Sugar sweetened beverages-no more than 450 calories

Dietary guidelines cont.

- Nuts, legumes and seeds: at least 4 servings/wk
- Processed meats: No more than 2 servings per week
- Saturated fat: less than 7% of total energy intake

Important Numbers to know

FACTOR	GOAL
Total Cholesterol	Less than 200 mgs/dl
LDL “bad” cholesterol	Less than 160 if at low risk, Less than 130 if intermediate risk, Less than 90 in people with known CHD
HDL “good” cholesterol	50 mgs/dl or higher
Triglycerides	Less than 150 mgs/dl
Fasting Glucose	Less than 100 mgs/dl
BMI	Less than 25 kgs/m^2
Blood Pressure	Less than 120/80, but the lower the better
Waist circumference	Less than 35 inches
Exercise	At least 30 minutes 3 times a week

Cook for lower cholesterol

- SKIM MILK DAIRY PRODUCTS: Rich in protein, calcium without being high in fat and cholesterol
- CHEESE: Have even more saturated fat than whole milk. Health options would be low-fat cottage cheese, part skim-milk mozzarella, ricotta
- EGGS: One egg yolk contains 213 mg of cholesterol. Egg whites contain no cholesterol
- MEATS: AHA recommends eating no more than 6 ounces of cooked lean meat, poultry, fish or seafood a day

Antioxidants in your diet

- Berries
- Broccoli
- Tomatoes
- Red grapes
- Garlic
- Spinach
- Tea (white, green and black)
- Carrots
- Soy
- Whole grains
- Pomegranates

Special herbs

Special herbs have antioxidants and are recommended in use with daily cooking

Black Beans

Black beans are a great source of folate, antioxidants and magnesium that increase energy and improve heart health

Red Wine

Red wine has two antioxidants: Resveratrol and catechins that improve endothelial dysfunction

Salmon

Great source of omega-3 DHA and EPA.
Recommendations are two servings of fish per week

- **Improves arterial wall strength**
- **increases HDL**
- **Decreases triglycerides**

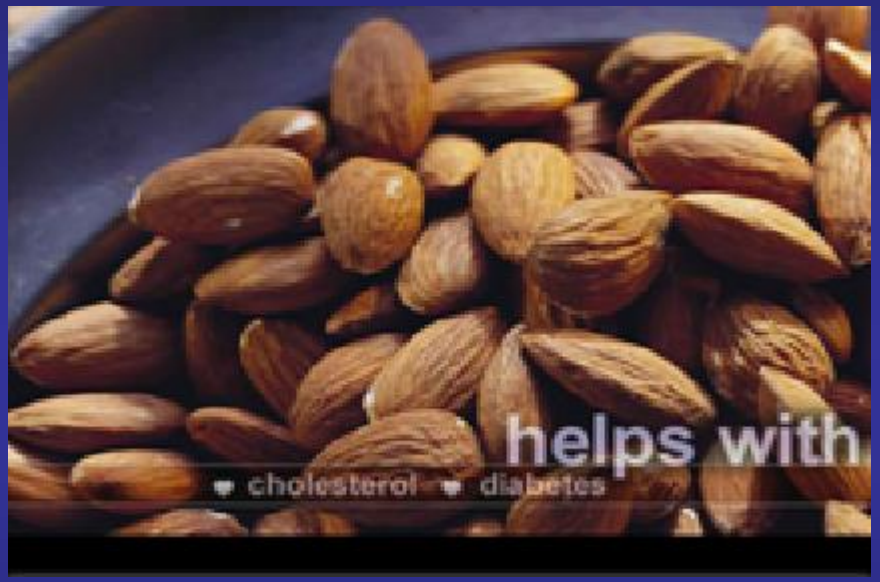
Tuna-another omega-3 source

Albacore has the most omega 3 out of all the tunas-it is cheaper than salmon and contains as much omega 3

Olive oil

-Olive oil contains polyphenols that are rich in antioxidants and improve endothelial function
-When it replaces butter, olive oil is heart healthy because polyunsaturated fats are being substituted for monounsaturated fats

Almonds



Almonds are rich in Vit E, fiber and plant sterols
They decrease LDL and increase HDL

Walnuts

Walnuts are a great source of fiber, monounsaturated fats, omega-3
Recommended amount-
1.5 ounces (a handful) daily

Tofu

- **Great substitute for red meat**

It is a soy protein that is a source of fiber

-It is lower in calories yet satisfies the hunger

Sweet red potatoes

Lower in sugar-for the diabetics
Doesn’t cause spike in glucose
It is a great source of vitamin A, lycopene and fiber

Dark leafy vegetables

Great source of vitamin A,
Vitamin K, and fiber, antioxidants
As well as magnesium

Barley

- **Barley should be substituted for rice**
- **Great source of fiber-it lowers cholesterol and improves glycemic control**

Oatmeal

-Oatmeal is a great source of fiber and keeps the stomach full for hours
-It stabilizes blood sugar levels and helps with diabetic blood glucose control
It lowers LDL and cholesterol

Flaxseed

- **Flaxseed have fiber, phytochemicals called lignans and ALA-an omega-3 fatty acid found in plants that the body converts to the more powerful Omega 3s-EPA and DHA**

Cayenne chili pepper

Cayenne chili pepper prevents
A spike in insulin and hence
Prevents glucose rise
It also increases the metabolic rate so that people can burn calories faster

Blueberries

- **Blueberries, rasberries and blackberries are strong antioxidants that contain Magnesium, fiber , potassium Folate and vitamin C**

CV risk factors between marital partners

When 1 spouse improves

his or her behavior (i.e., changes

in smoking, drinking, exercising,

or screening cholesterol) …

the other spouse is likely to

do so as well

Healthy goals post HF diagnosis

- Eliminate smoking, including exposure to secondhand smoke
- Decrease total fat in diet to 25-30% of total calories and saturated fat to less than 7%
- Decrease salt to less than 1.5 grams a day
- If dietary restrictions don't make sense, ask your cardiologist for a referral to speak to a dietitian
- Eliminate obesity
- Increase physical activity
- Get a blood pressure machine and keep a BP diary
- TAKE MEDS REGULARLY!!!!
- Weigh yourself daily-if increase weight of 1-2 within 24 hrs, possible fluid overload and signs of heart failure

Conclusion

- Heart Failure is cardiac dysfunction that is can be due to contractile dysfunction (systolic failure) or relaxation dysfunction (diastolic heart failure).
- Identification and treatment of heart failure is crucial to preventing progression and demise of the pt
- Medication therapy includes beta blockers, ACEI, ARB, diuretics, aldactone
- Cardiac resynchronization therapy promises quality of life improvement for some pts with poor systolic heart function who have been maximized on medical therapy yet are still symptomatic.
- Barostim is beneficial in pts that don't qualify for CRT

Any Questions?

Question 1

- What is HFmREF stand for
- A. heart failure with EF <40%
- B. heart failure with EF 41-49%
- C. heart failure with EF >50%
- D. heart failure with unspecified EF
- E. all of the above

Question 1

- What is HFmREF stand for
- A. heart failure with EF <40%
- B. heart failure with EF 41-49%
- C. heart failure with EF >50%
- D. heart failure with unspecified EF
- E. all of the above

Question 2

- 1. CRT is indicated in what percent of pts with HF
- A. 70%
- B. 80%
- C. 30%
- D. 10%
- E. 90%

Question 2

- 1. CRT is indicated in what percent of pts with HF
- A. 70%
- B. 80%
- C. 30%
- D. 10%
- E. 90%

Question 3

- What NYHA class is a pt with cardiac disease with marked limitation of physical activity, and fatigue. No dyspnea at rest but dyspneic with minimal physical activity
- A. NYHA class IV
- B. NYHA class II
- C. NYHA class I
- D. NYHA class III

Question 3

- What NYHA class is a pt with cardiac disease with marked limitation of physical activity, and fatigue. No dyspnea at rest but dyspneic with minimal physical activity
- A. NYHA class IV
- B. NYHA class II
- C. NYHA class I
- D. NYHA class III