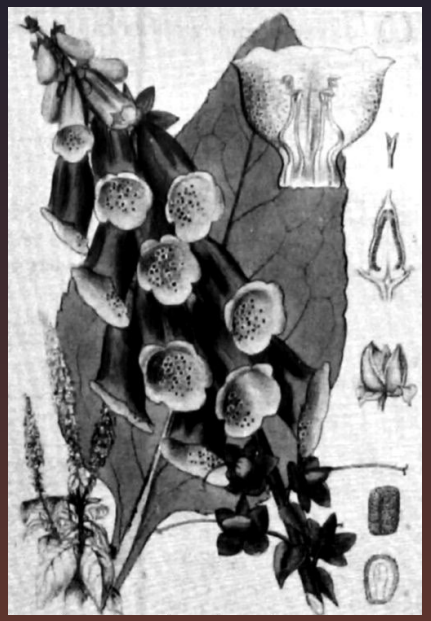
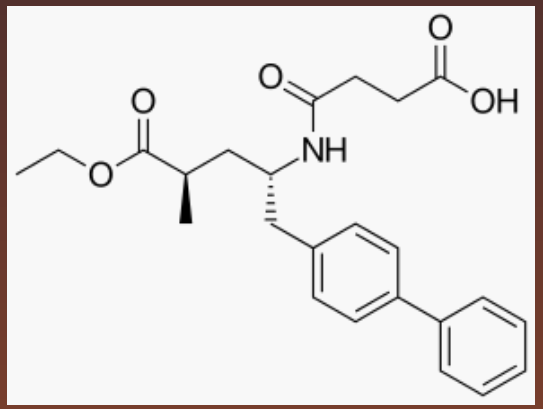
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Heart Failure
From Foxglove to PARADIGM

Bradley D. Berry, M.D.
American College of Physicians
Montana Chapter
September 17, 2022





THE INTERNATIONAL HEART INSTITUTE OF MONTANA

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

HF Incidence and Prevalence

Prevalence

- Worldwide, 23 million
- United States, 5.8 million , > 1 million Class III-IV

Incidence

- Worldwide, 2 million new cases annually
- United States, 400,000 to 700,000 new cases/year

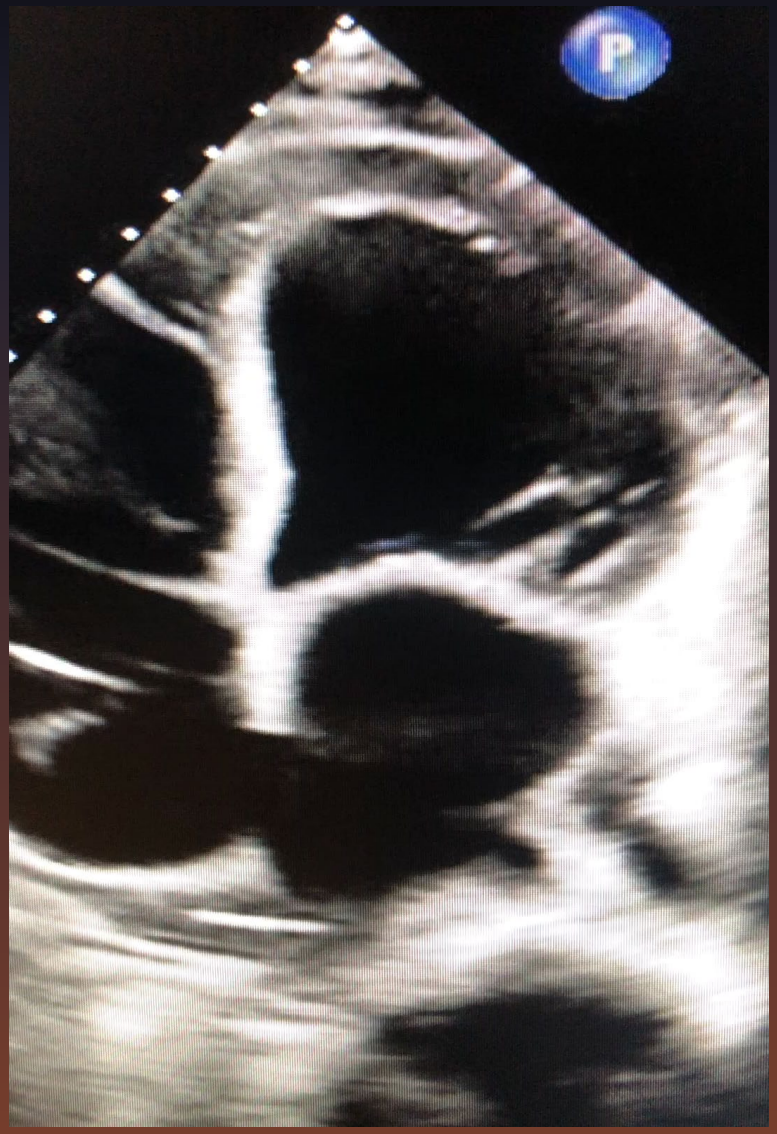
HF afflicts 1 out of every 10 over age 65 in the United States with a lifetime risk of 1 in 5

25% of people over 40 will experience HF in their lifetime

One in 9 deaths include heart failure as contributing cause

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Congestive Heart Failure



THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Congestive Heart Failure

CHF is a clinical syndrome caused inefficiency of the cardiac function or output

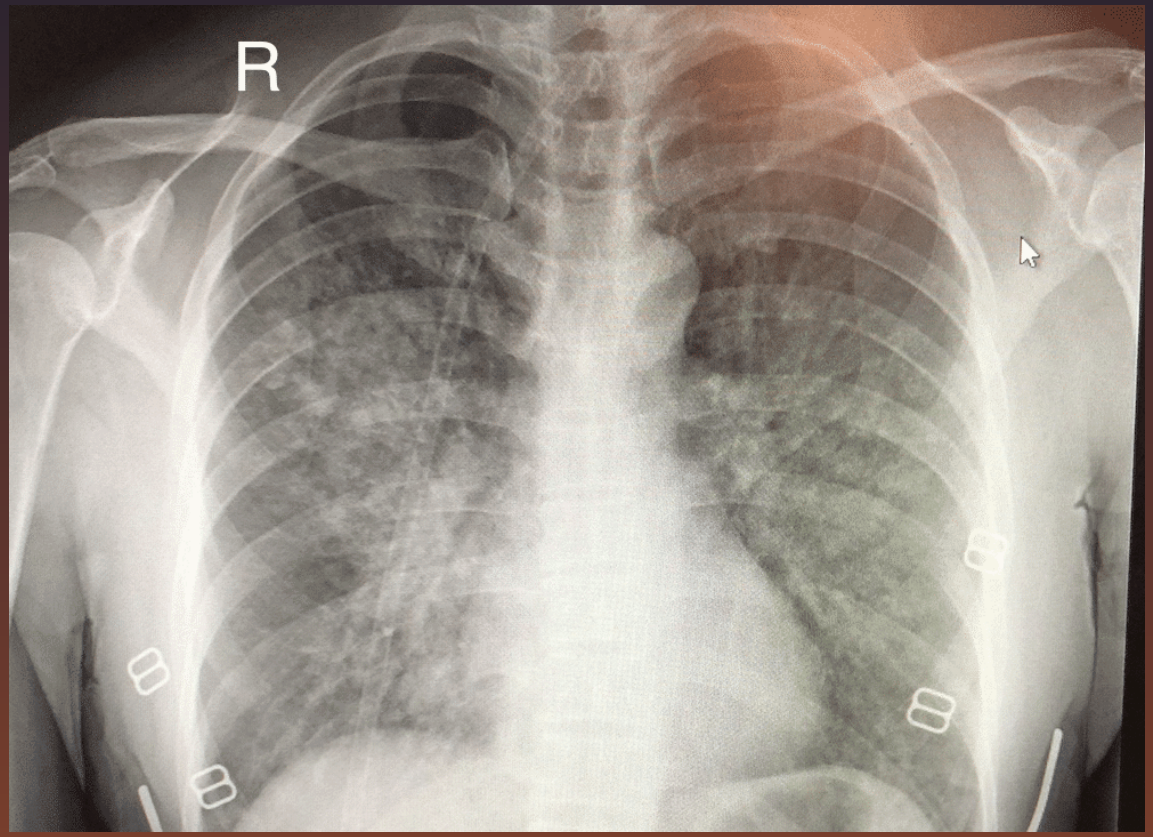
Ultimately CHF occurs when pressure elevation increases in heart

Initially LV pressure elevation leading to pulmonary edema

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Congestive Heart Failure

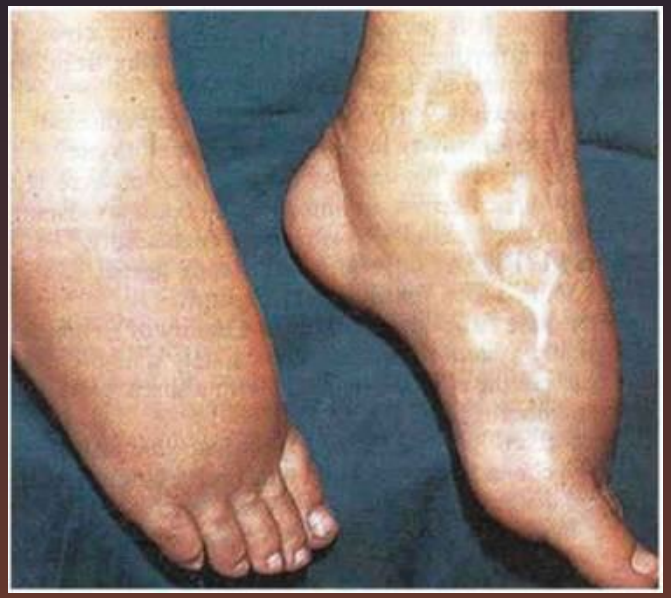
Subsequently LA Pressure rises and subsequently PCWP

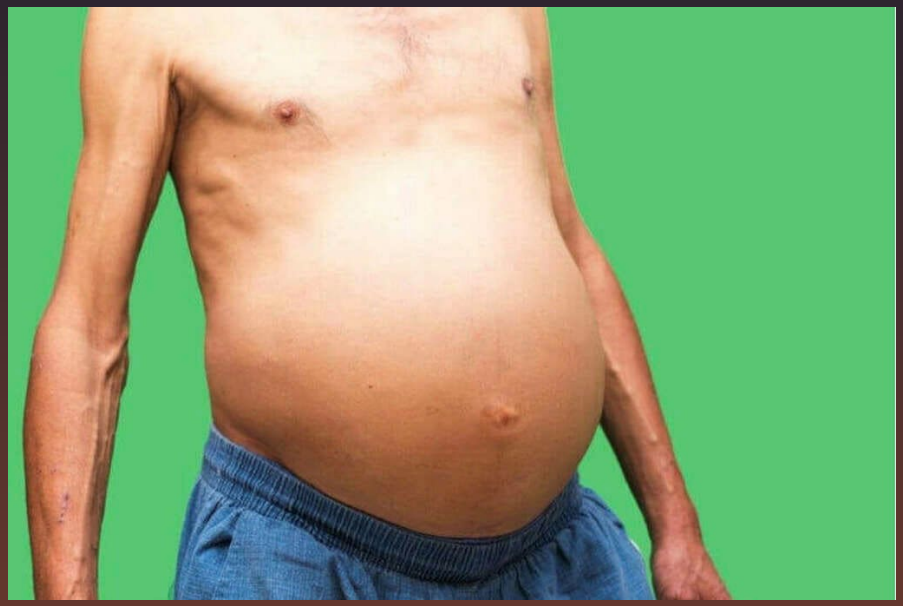


THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Congestive Heart Failure

Eventually venous pressures rise leading to elevation of right sided filling pressures





THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Congestive Heart Failure

Heart failure is a clinical syndrome

Hall mark of CHF is inappropriate sodium and fluid retention and subsequent symptoms

CHF is a clinical diagnosis, and the signs and symptoms are caused by elevated filling pressures

Congestive Heart Failure Criteria

MAJOR:

Paroxysmal nocturnal dyspnea

Orthopnea

Elevated JVP

3rd heart sound

Cardiomegaly on CXR

Pulmonary edema on CXR

> 4.5 kg weight loss w diuresis

MINOR:

Bilateral leg edema

Nocturnal cough

Hepatomegaly

Pleural effusion

Pleural effusion

Tachycardia; HR > 120 bpm

2 major or 1 major and 2 minor

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Impact of Congestive Heart Failure

12-15 million office visits for CHF annually

6.5 million hospital days annually

Heart failure costs the US an estimated $39.2 billion each year.

Hospitalization on the rise:

- Primary Diagnosis: Annual number of hospitalizations increased from 550,000 to over 1,000,000 over last 15 years
- Secondary Diagnosis: Annual number of hospitalizations increased from 1.7 to roughly 3 million over last 15 years

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Impact of Congestive Heart Failure

5-year mortality of CHF remains at or above 50% despite improvement in treatments

1-year mortality for Class III/IV heart failure is 15-30%

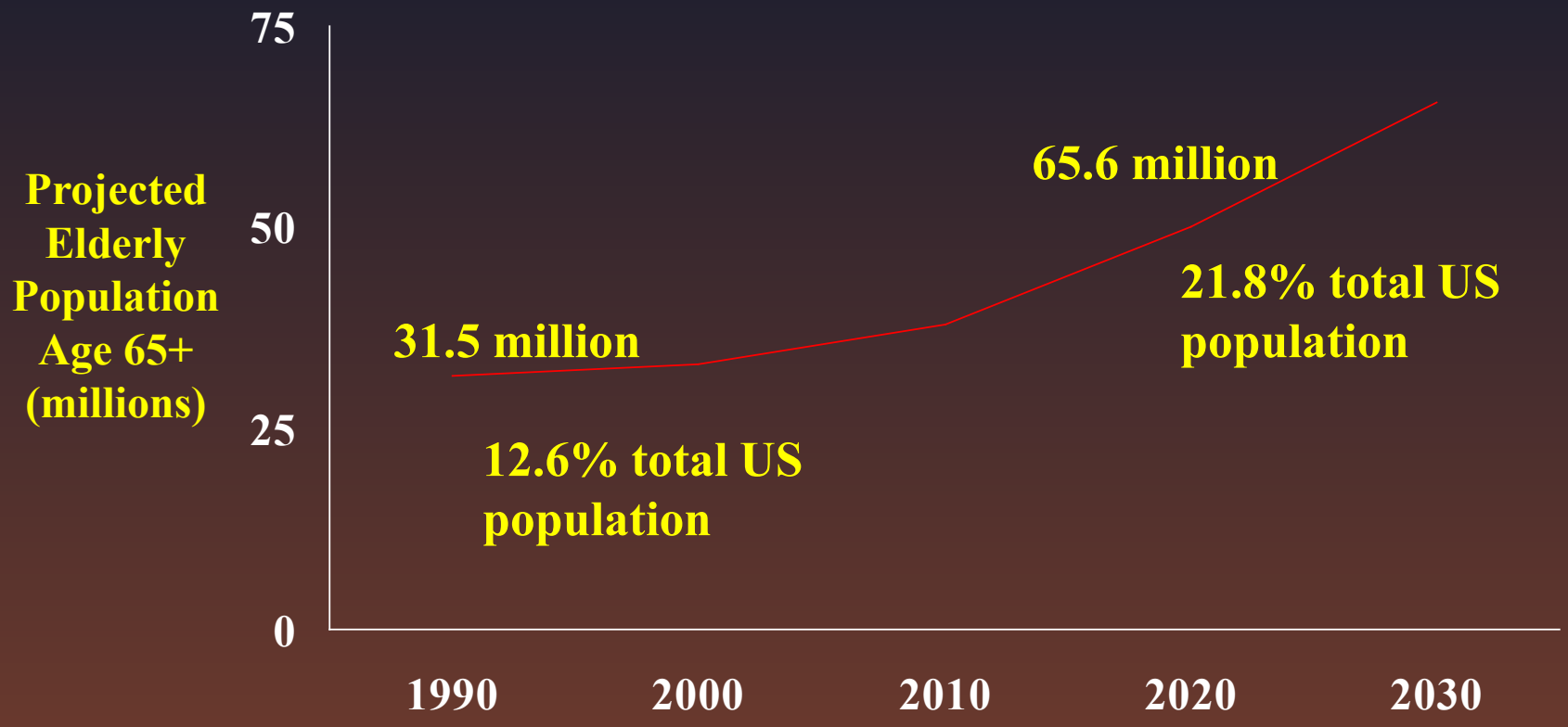
Over 300,00 deaths annually directly attributable to heart failure

Number one volume diagnosis in the Medicare population

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Demographic Trends

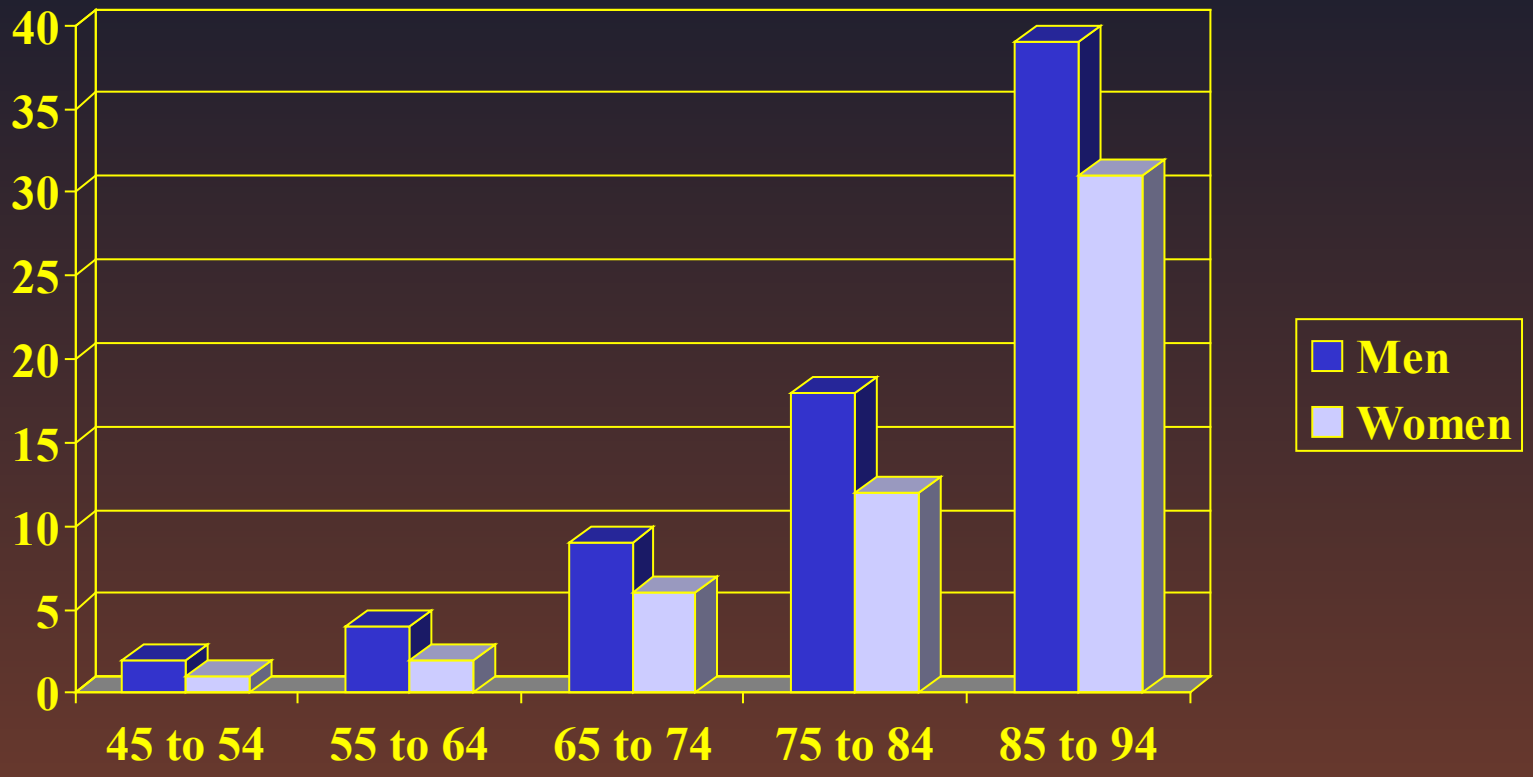
Elderly U.S. population will double with graying of "baby boomer" generation



- Cost of HF in the U.S. is estimated to be over $70 billion annually by 2030

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Incidence of Heart Failure by Age



Average annual incidence per 1000

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

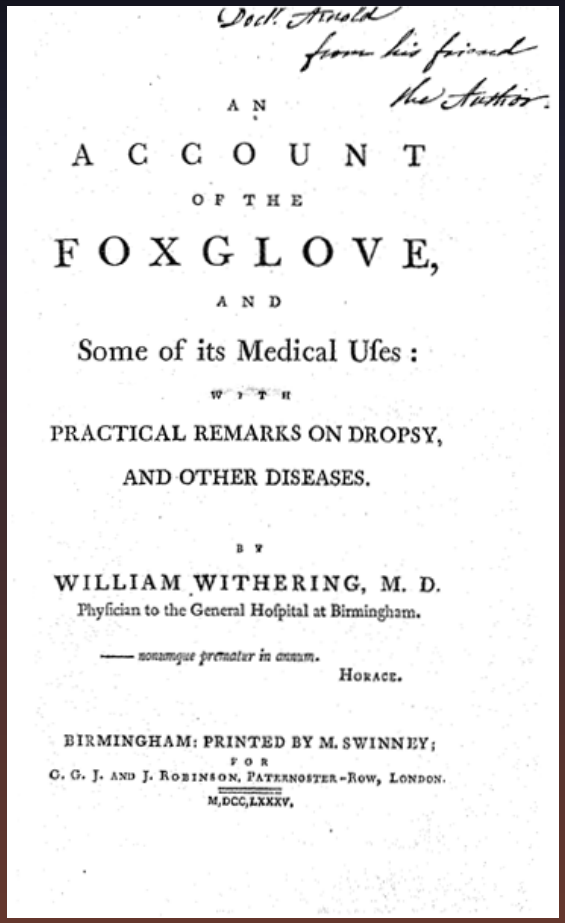
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Historical Perspective of CHF Treatment

Figure 7-1 Relief of dropsy (P Barbette, 1672).

Historical Perspective of CHF Treatment

William Withering
(1741-1799)



Dedt. Arnold
from his friend
the Author.

AN

ACCOUNT

OF THE

FOXGLOVE,

AND

Some of its Medical Uſes:

WITH

PRACTICAL REMARKS ON DROPSY,

AND OTHER DISEASES.

BY

WILLIAM WITHERING, M. D.

Phyſician to the General Hoſpital at Birmingham.

——— nonumque prematur in annum.

HORACE.

BIRMINGHAM: PRINTED BY M. SWINNEY;

FOR

G. G. J. AND J. ROBINSON, PATERNOSTER-ROW, LONDON.

M,DCC,LXXXV.

Withering W. *An Account of the Foxglove.* 1785

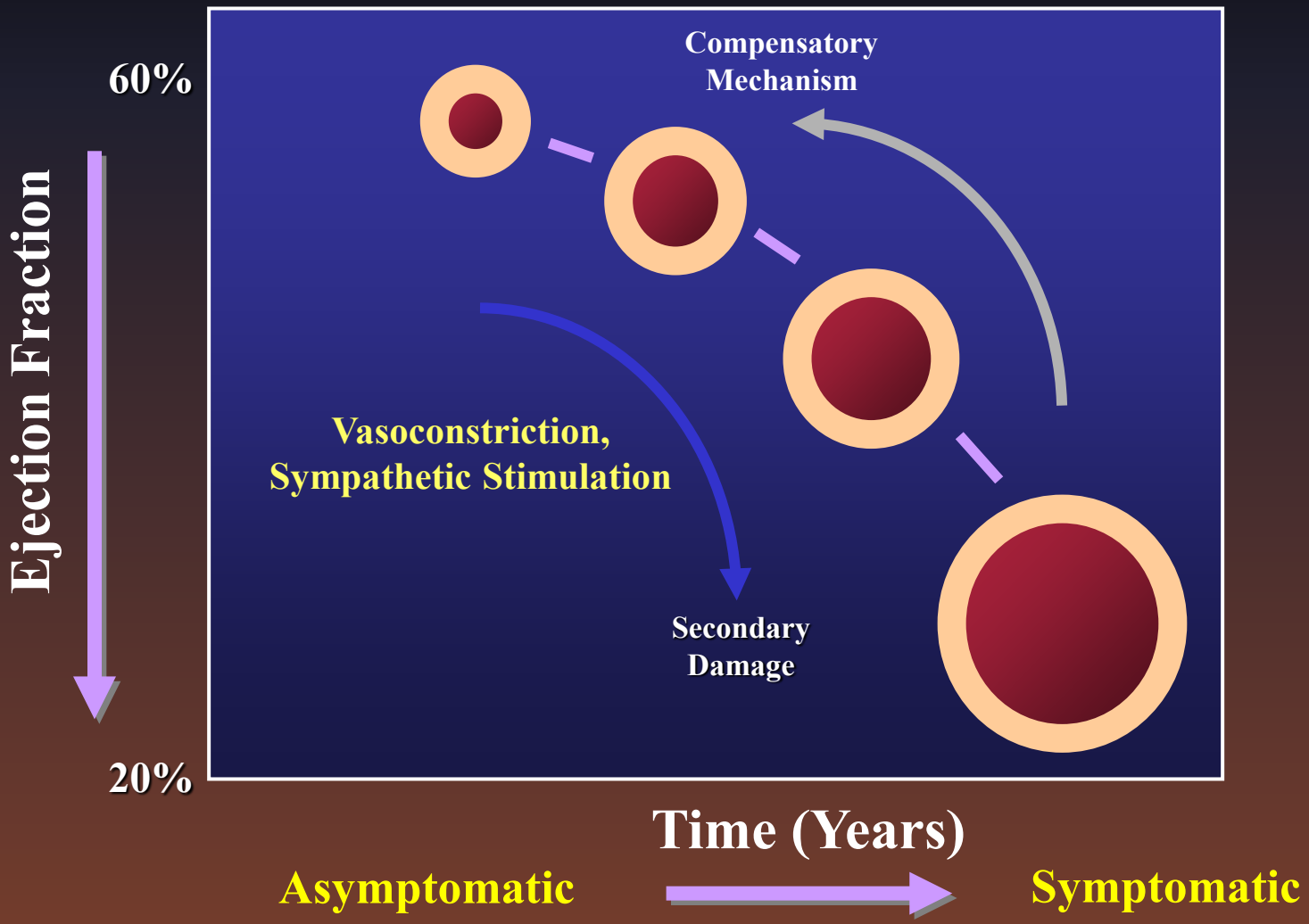
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Treatment of Heart Failure
Changing Goals for Therapy

ERA	Goal	Therapy
1970's	Symptoms	Diuretics/Dig
1980's	Hemodynamics	Inotropes/Vasodil.
1990's	Survival	ACEi/β-blocker
2000's	Remodeling	ACEi/ARB/β-blocker
		Device therapy (CRT/ICD)

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Compensation of Heart Failure Is Dependent on Neurohormonal Balance



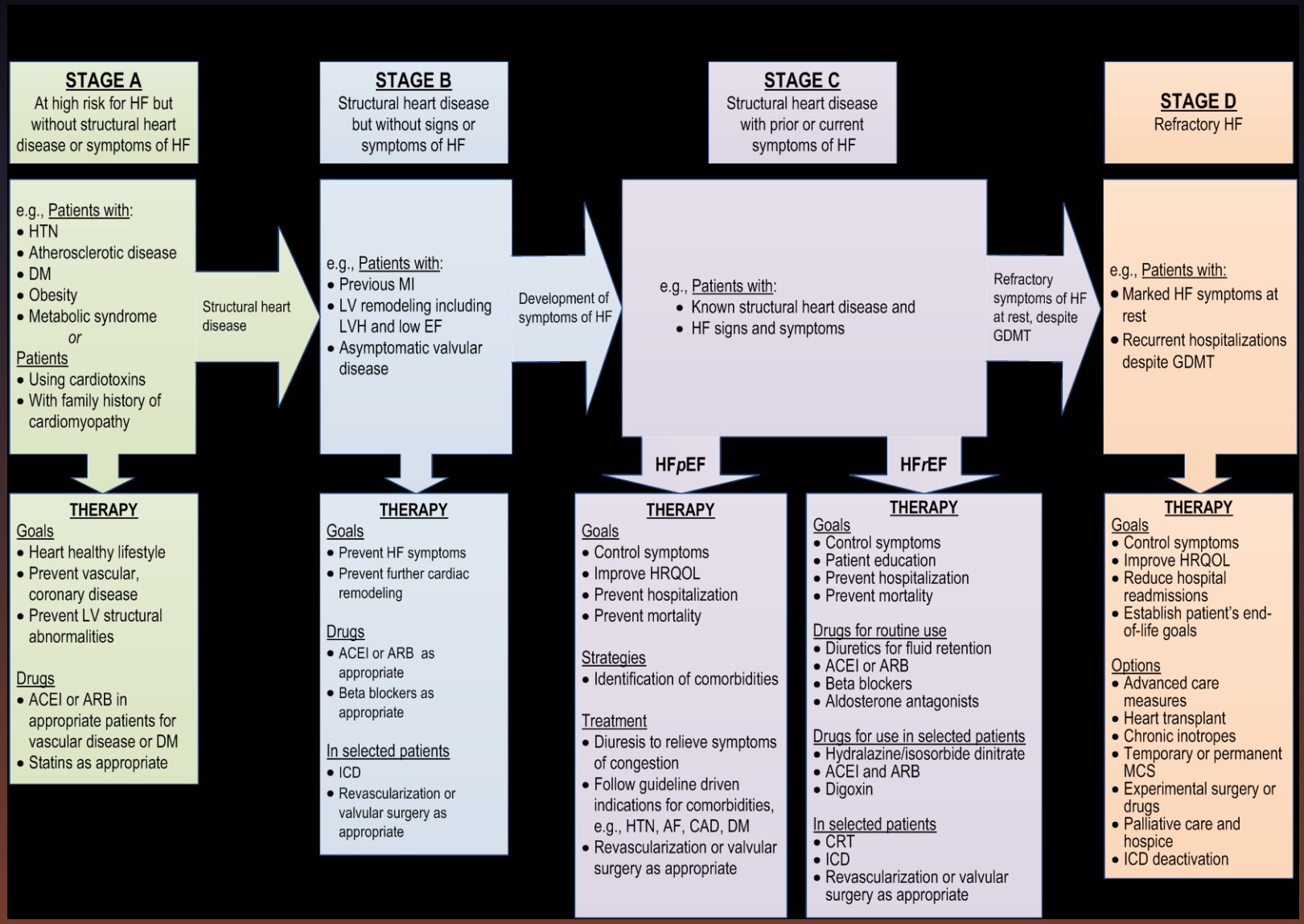
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

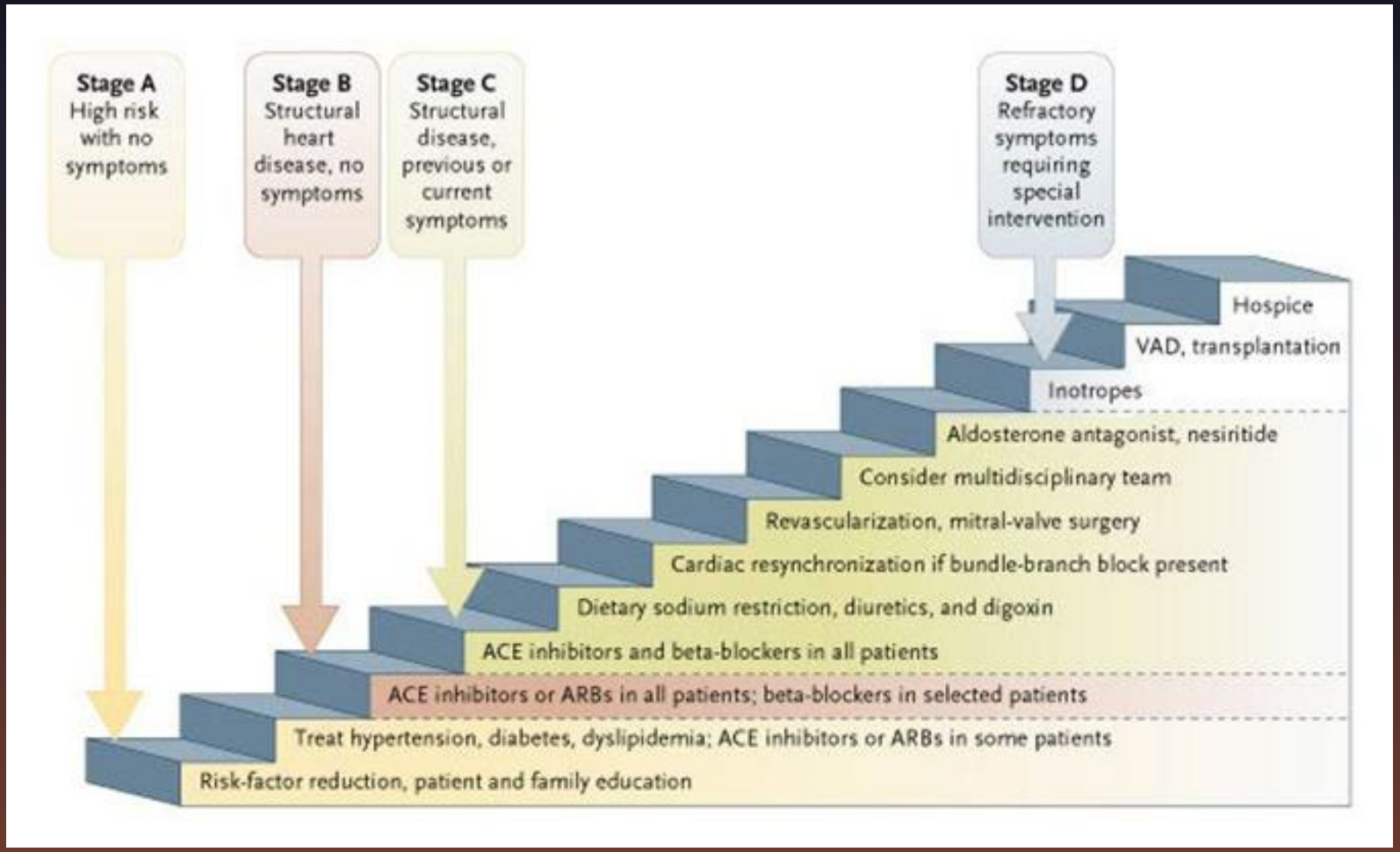
Goals in the Management of Heart Failure

- Stabilize the patient
  - Make the patient feel better
- Stabilize the disease
  - Keep the patient alive
  - Keep the patient out of the hospital
  - Keep the patient feeling better
- Disease prevention
  - Risk factor treatment

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Stages, Phenotypes and Treatment of HF

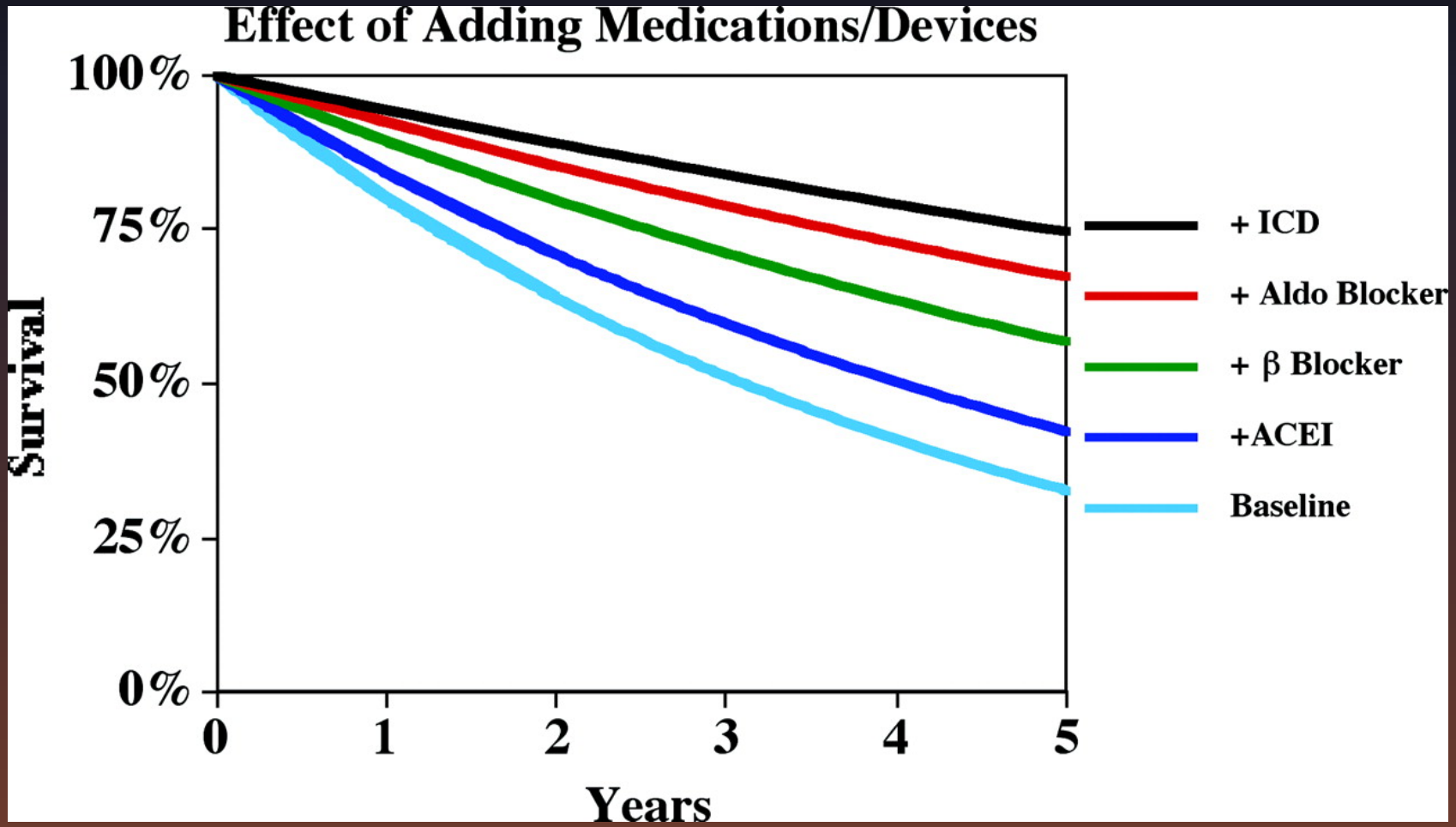



Stage A
High risk with no symptoms
Stage B
Structural heart disease, no symptoms
Stage C
Structural disease, previous or current symptoms
Stage D
Refractory symptoms requiring special intervention
Hospice
VAD, transplantation
Inotropes
Aldosterone antagonist, nesiritide
Consider multidisciplinary team
Revascularization, mitral-valve surgery
Cardiac resynchronization if bundle-branch block present
Dietary sodium restriction, diuretics, and digoxin
ACE inhibitors and beta-blockers in all patients
ACE inhibitors or ARBs in all patients; beta-blockers in selected patients
Treat hypertension, diabetes, dyslipidemia; ACE inhibitors or ARBs in some patients
Risk-factor reduction, patient and family education

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

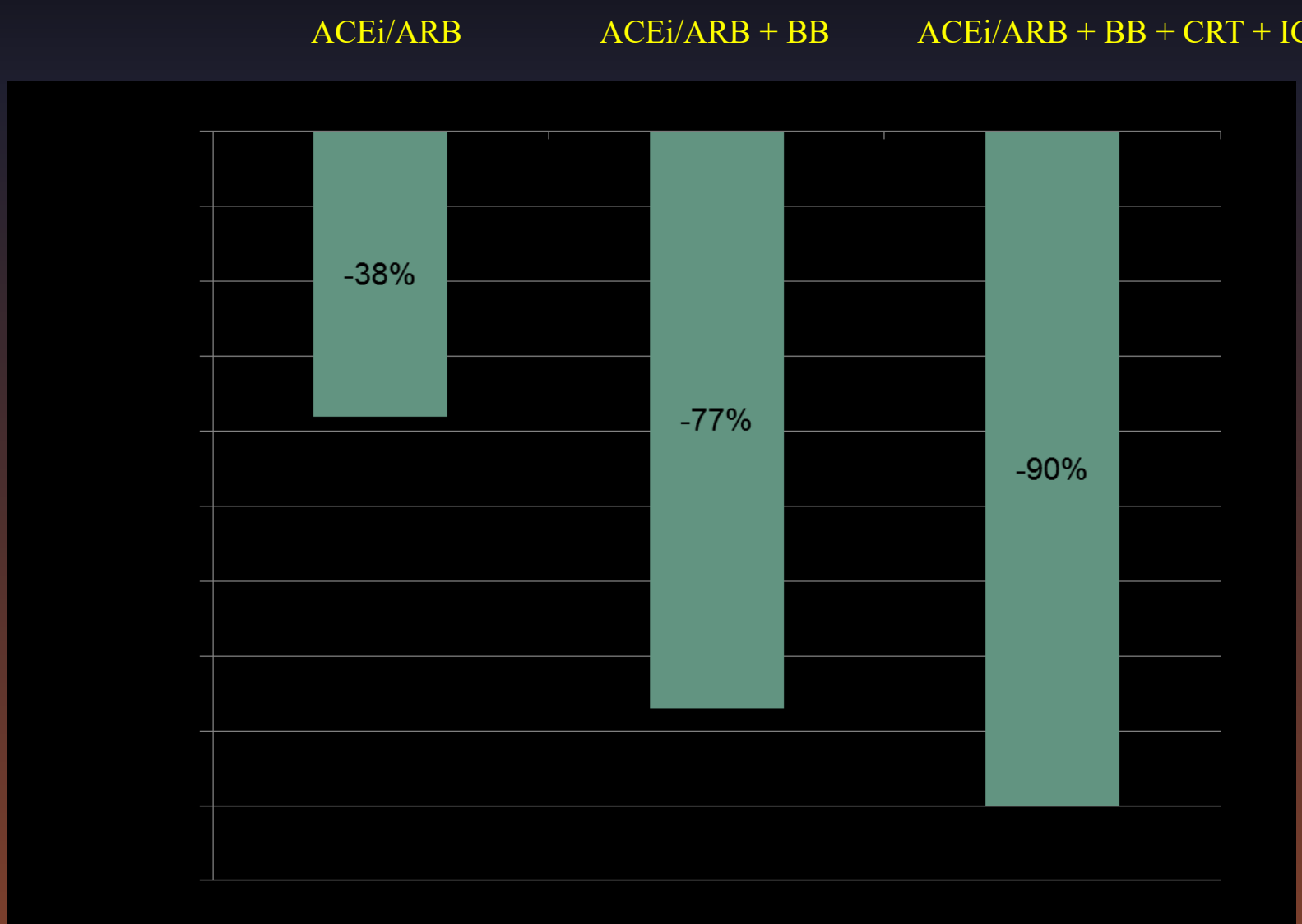
Do heart failure guidelines and guideline directed medical therapy help?

THE INTERNATIONAL HEART INSTITUTE OF MONTANA



THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Incremental Benefit with HF Therapies (Cumulative % Reduction in Odds of Death at 24 Months Associated with Sequential Treatments)



THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Vasodilators

Hydralazine-Nitrates

Angiotensin-Converting Enzyme Inhibitors

Angiotensin Receptor Antagonists

Angiotensin Receptor – Neprilysin Inhibitor

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Vasodilator therapy for patients with HFrEF

ACE inhibitors are recommended in patients with HFrEF and current or prior symptoms, unless contraindicated, to reduce morbidity and mortality.

ARBs are recommended in patients with HFrEF with current or prior symptoms ***who are ACE inhibitor-intolerant***, unless contraindicated, to reduce morbidity and mortality.

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

PARADIGM-HF

Compared the angiotensin receptor valsartan combined with neprilysin inhibitor sacubitril against enalapril in patients who had heart failure with a reduced ejection fraction

Double-blind trial, randomized 8442 patients with class II, III, or IV heart failure with ejection fraction of 40% or less to receive:

- Sacubitril/valsartan (target dose of 97/103 mg twice daily)
- enalapril (target dose of 10 mg twice daily)

The primary outcome was a composite of death from cardiovascular causes or hospitalization for heart failure

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

PARADIGM-HF

Neprilysin is an endopeptidase that degrades several endogenous vasoactive peptides including:

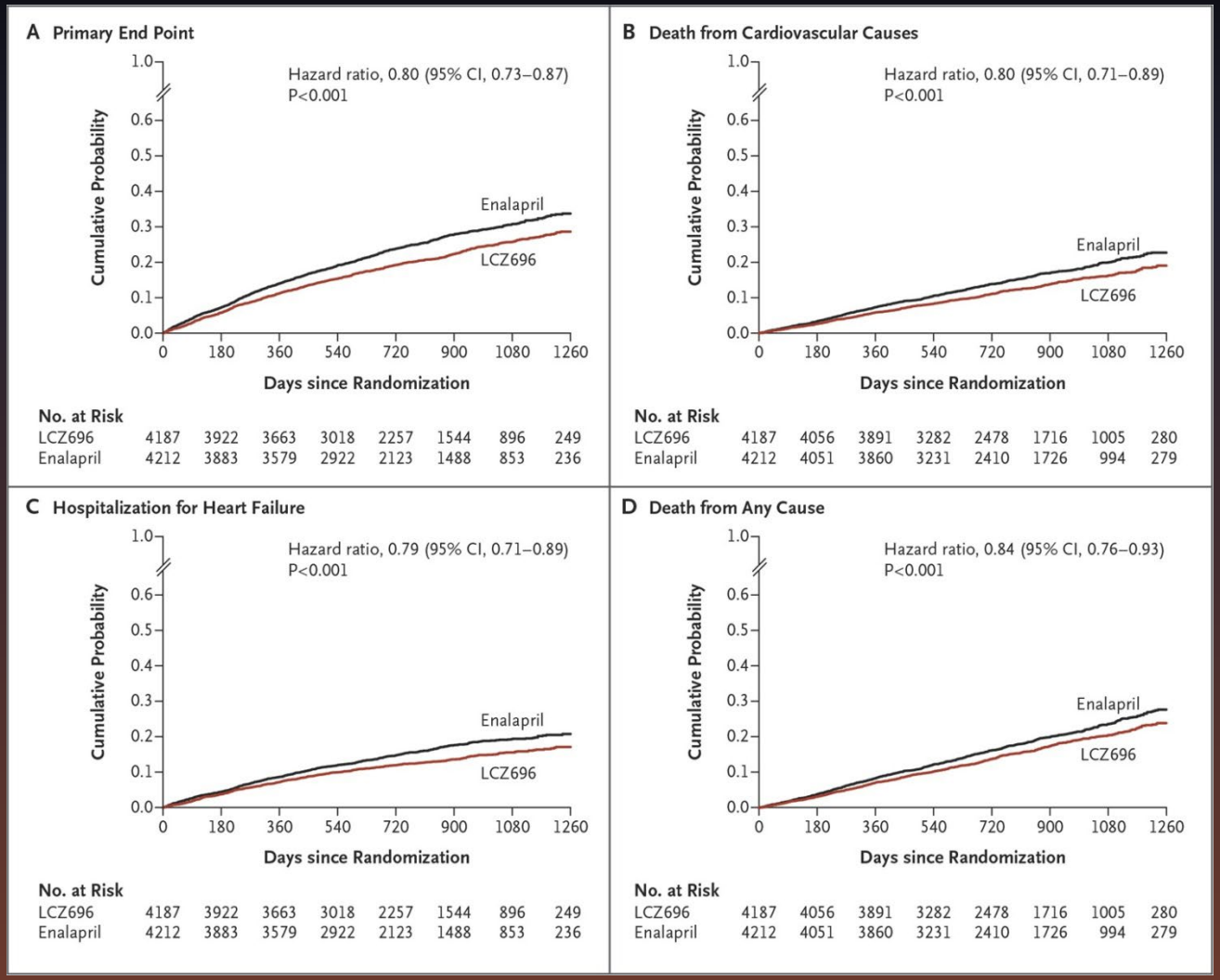
- natriuretic peptides
- bradykinin
- adrenomedullin

Inhibition of neprilysin increases the levels of vasoactive peptides that counteract neurohormonal factors that contribute to:

- vasoconstriction
- sodium retention
- and maladaptive remodeling

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Kaplan–Meier Curves for Key Study Outcomes, According to Study Group.



McMurray JJV et al. N Engl J Med 2014;371:993-1004

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Primary and Secondary Outcomes

Table 2. Primary and Secondary Outcomes.*

Outcome	LCZ696 (N=4187)	Enalapril (N=4212)	Hazard Ratio or Difference (95% CI)	P Value
Primary composite outcome — no. (%)				
Death from cardiovascular causes or first hospitalization for worsening heart failure	914 (21.8)	1117 (26.5)	0.80 (0.73–0.87)	<0.001
Death from cardiovascular causes	558 (13.3)	693 (16.5)	0.80 (0.71–0.89)	<0.001
First hospitalization for worsening heart failure	537 (12.8)	658 (15.6)	0.79 (0.71–0.89)	<0.001
Secondary outcomes — no. (%)				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76–0.93)	<0.001
Change in KCCQ clinical summary score at 8 mo†	–2.99±0.36	–4.63±0.36	1.64 (0.63–2.65)	0.001
New-onset atrial fibrillation‡	84 (3.1)	83 (3.1)	0.97 (0.72–1.31)	0.83
Decline in renal function§	94 (2.2)	108 (2.6)	0.86 (0.65–1.13)	0.28

* Hazard ratios were calculated with the use of stratified Cox proportional-hazard models. P values are two-sided and were calculated by means of a stratified log-rank test without adjustment for multiple comparisons.

† Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations associated with heart failure. The treatment effect is shown as the least-squares mean (±SE) of the between-group difference.

‡ A total of 2670 patients in the LCZ696 group and 2638 patients in the enalapril group who did not have atrial fibrillation at the randomization visit were evaluated for new-onset atrial fibrillation during the study.

§ A decline in renal function was defined as end-stage renal disease or a decrease of 50% or more in the estimated glomerular filtration rate (eGFR) from the value at randomization or a decrease in the eGFR of more than 30 ml per minute per 1.73 m^2, to less than 60 ml per minute per 1.73 m^2.

McMurray JJV et al. N Engl J Med 2014;371:993-1004

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

PARADIGM-HF

Positive results similar as compared to enalapril as enalapril was compared to placebo

- achieved results despite excellent enalapril dosing even as compared to SOLVD Trial

Cautions:

Previous trial tested neprilysin inhibitor (Omapatrilat) associated with life threatening angioedema

- In OVURTURE trial life threatening angioedema primarily in African Americans (and smokers in HTN trials)
- In PARADIGM-HF only 213 AA total in ARNI group

Current recommendation is 36 hour washout of ACEi prior to starting ARNi

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

2022 ACC/AHA/HFSA Heart Failure Guidelines

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]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Hydralazine -Nitrates

Survival benefit demonstrated against placebo but no as strong as ACE/ARB/ARNi

Key use in renal failure/renal failure exacerbation or hyperkalemia with other agents

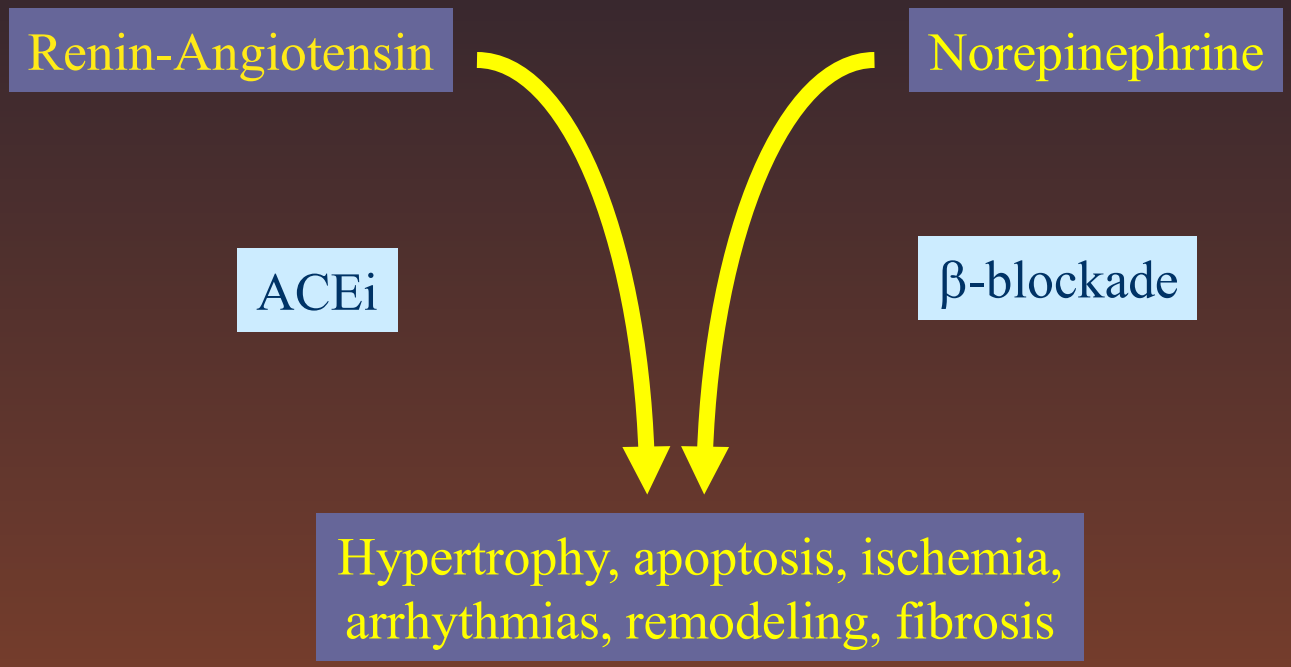
AHA/ACC class 1 recommendation:

Combination hydralazine/isosorbide dinitrate recommend for African Americans on optimal therapy with ACEi/beta blocker/aldosterone antagonism

β-Blockade in the Treatment of Heart Failure

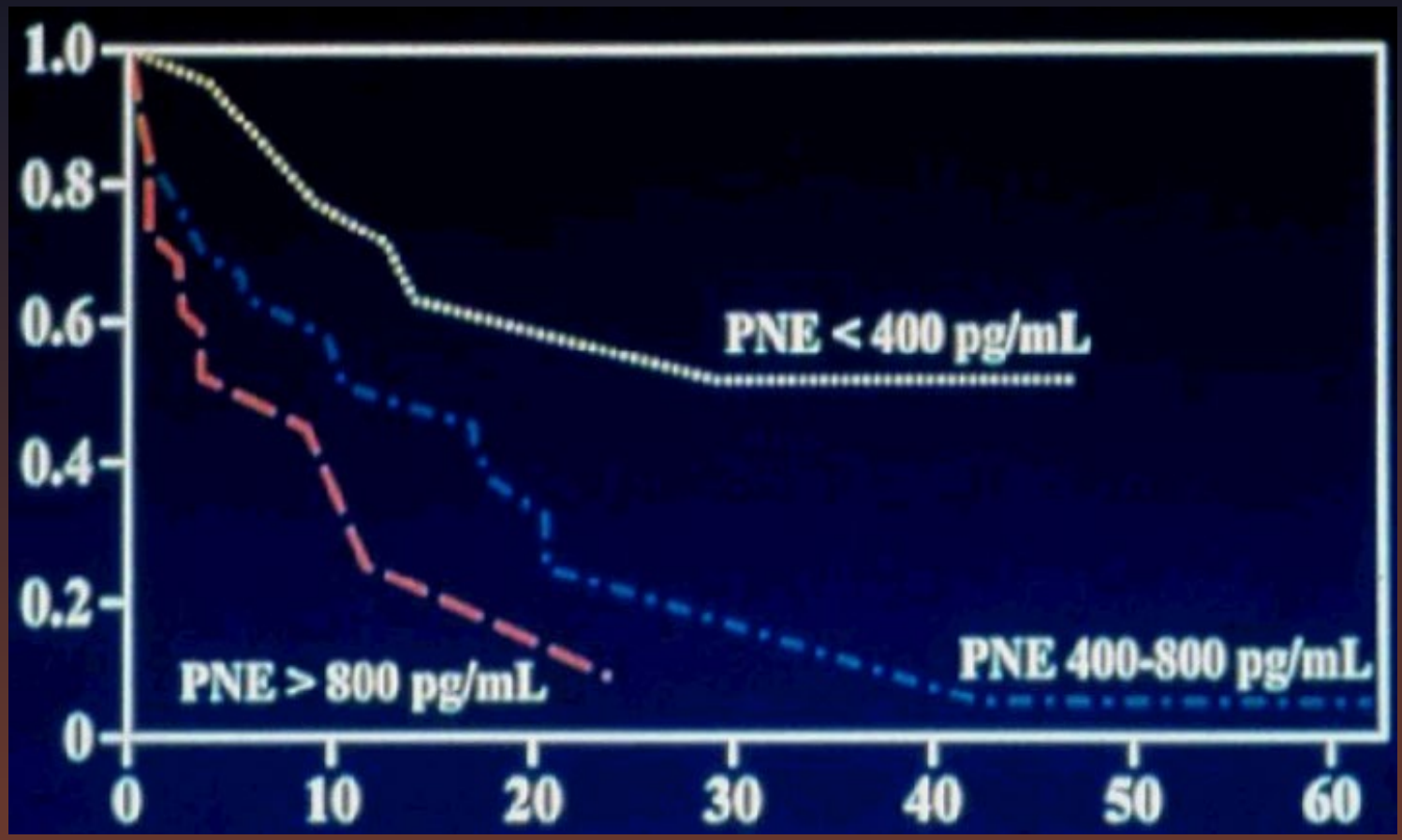
Like ACEi, β-blockers antagonize the endogenous neurohormonal system

- act primarily on the sympathetic nervous system



THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Sympathetic Activation and Increase Heart Failure Mortality



Cohn, J. *N Engl J Med.* 1984;311:819-823

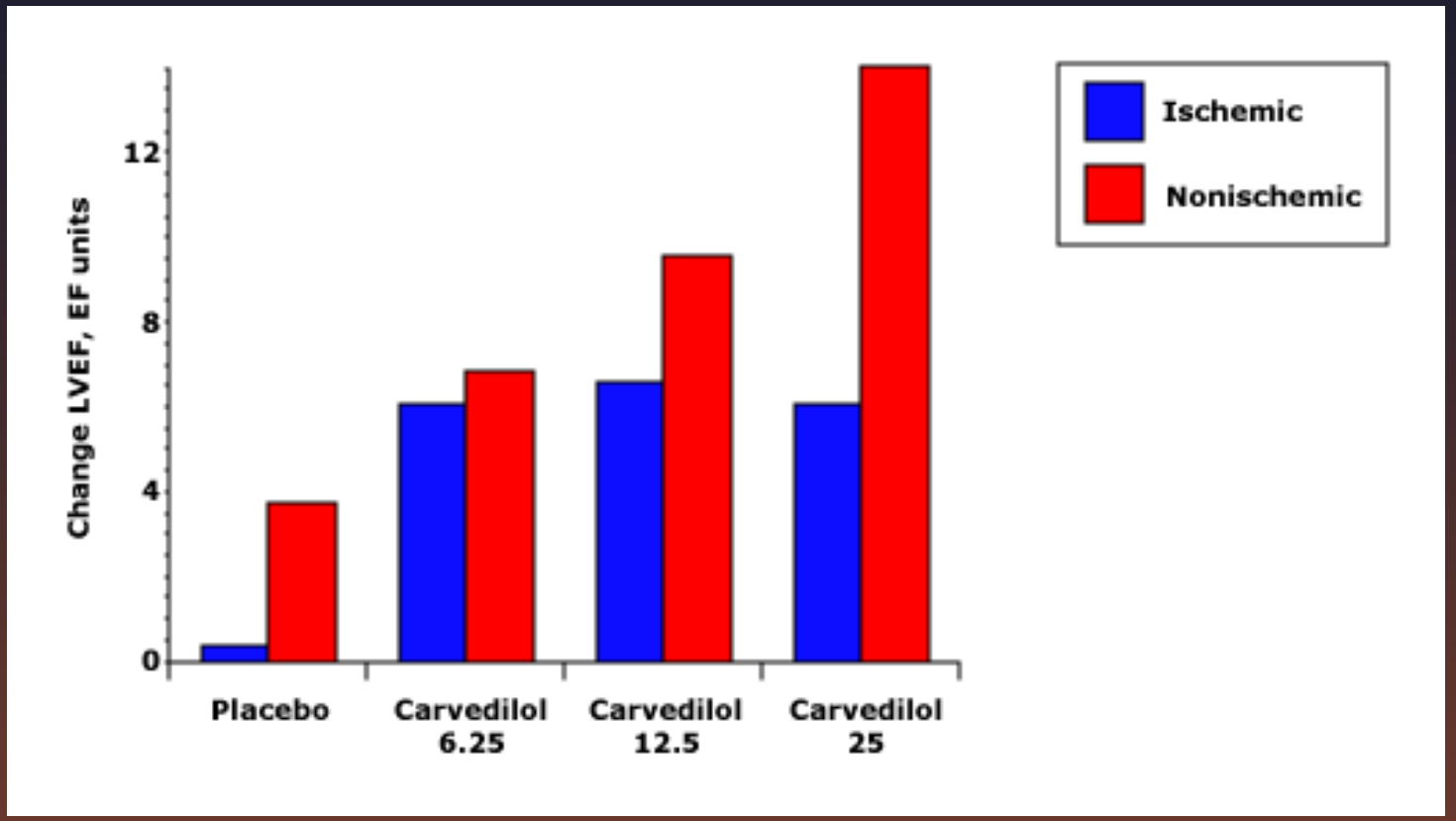
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Treatment of Heart Failure
Beta Blockers Recommendations

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 (eg, bisoprolol, carvedilol, sustained-release metoprolol succinate) is recommended to reduce mortality and hospitalizations.[25–27]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Dose-related increase in LVEF with carvedilol in nonischemic cardiomyopathy



THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Aldosterone Antagonists in Heart Failure

The spironolactone/eplerenone indicated in patients with recent or current class II/IV symptoms

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]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

All new diabetic drugs monitored for cardiac outcomes in clinical trials

Surprise findings of not only decreased CHF admission but decreased mortality

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

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]

Sodium-glucose cotransporter-2 (SGLT2) inhibitors

Empagliflozin (Jardiance)	Dapagliflozin (Farxiga)
1. NYHA II-IV: Reduce the risk of hosp for HF and CV death in patients with HFrEF, HFpEF, or HFmEF w or w/o T2DM 2. Reduce the risk of CV death in patients with T2M and established CVD 3. Treatment of T2DM	1. NYHA II-IV: Reduce the risk of hosp for HF and CV death in patients with HFrEF, HFpEF, or HFmEF in pts w or w/o T2DM 2. Reduce the risk of hospitalization for HF in pts with T2DM and established CVD or multiple CV risk factors

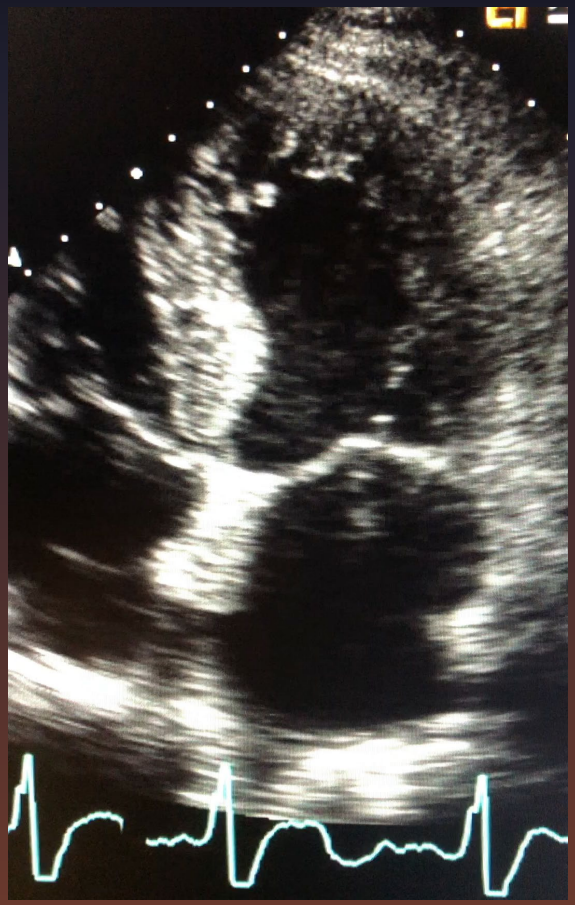
Sodium-glucose cotransporter-2 (SGLT2) inhibitors

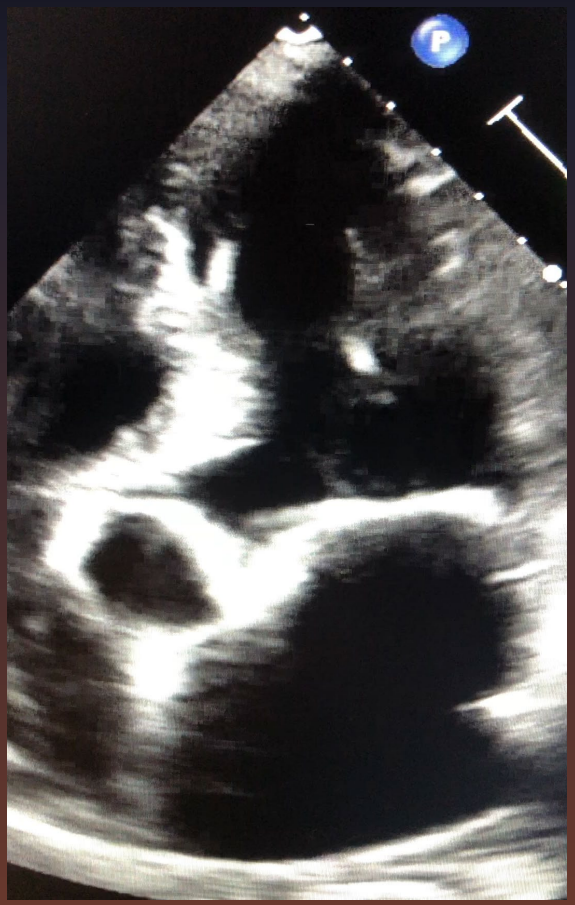
Contraindications	**1. Dialysis** **2. Anaphylactic reaction or angioedema to SGLT2i's**
Precautions	• Intravasc volume depletion esp in renal dysfunction, loop diuretic use. Monitor vol status • Ketoacidosis; avoid in T1DM, acute febrile illness, major surgery, ETOH toxicity • Hypoglycemia if used w insulin or insulin secretagogue • Serious UTI • Perineal infections or genital mycotic infections • Consider interruption 3 days prior to surgery to minimize risk of ketoacidosis • PG/Breastfeeding: not studied but risk cannot be ruled out

Failure to prescribe GDMT

Therapy	Current HF population eligible and untreated	Patient lives saved/yr
ACEi/ARB	501,767 (20.4%)	6,516
Beta blocker	361,809 (14.4%)	12,922
Aldosterone antag.	385,326 (63.9%)	21,407
Hydral/nitrate	139,797 (92.7%)	6,655
CRT	199,604 (61.2%)	8,317
ICD	852,512 (49.4%)	12,179
		Total: 67,996

THE INTERNATIONAL HEART INSTITUTE OF MONTANA





THE INTERNATIONAL HEART INSTITUTE OF MONTANA

Heart Failure Categories

Category	Ejection Fraction
HFrEF	LVEF <40%
HFmrEF	LVEF 41-49%
HFpEF	LVEF >50%

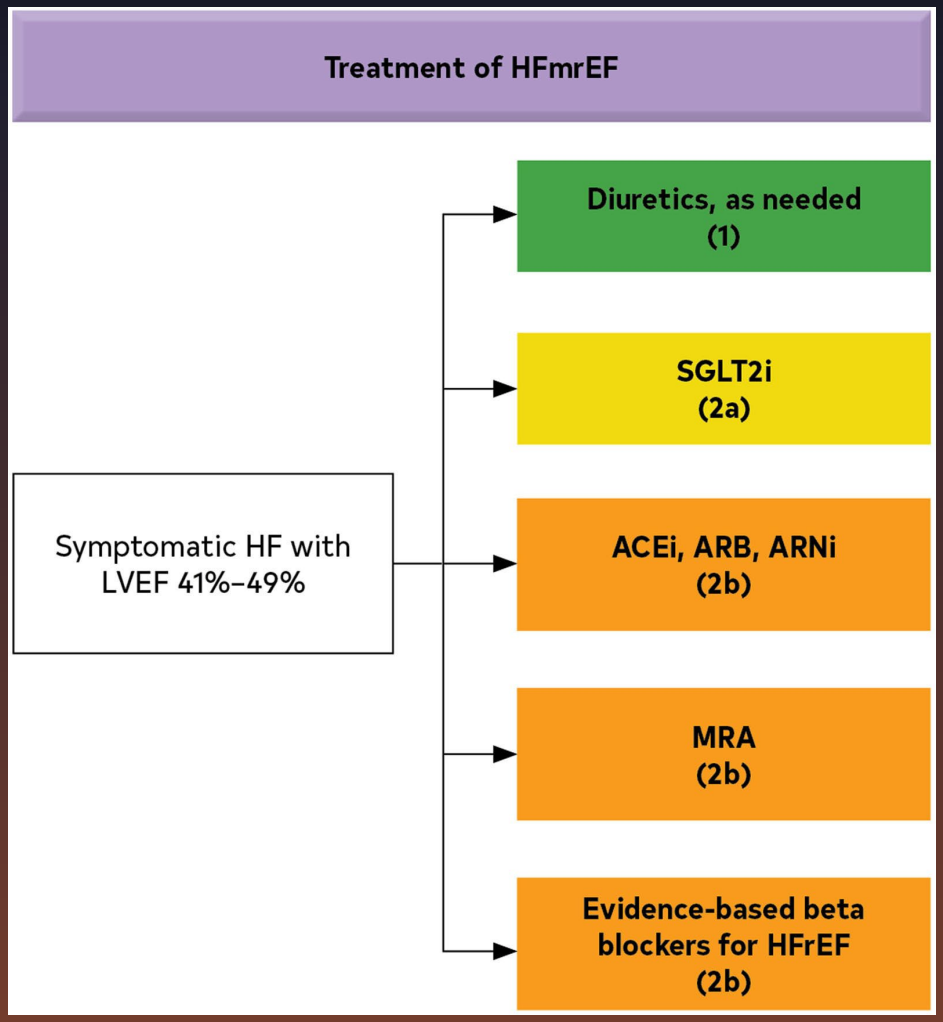
THE INTERNATIONAL HEART INSTITUTE OF MONTANA

HFmrEF

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]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

HFmrEF



HFimpEF

Heart failure with improved ejection fraction

COR	LOE	Recommendation
1	B-R	1. In patients with HFimpEF after treatment, GDMT should be continued to prevent relapse of HF and left ventricular dysfunction, even in patients who may become asymptomatic.[36]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

HFpEF

Heart failure with preserved ejection fraction
Continued recommendations

COR	LOE	Recommendations
1	C-LD	1. Patients with HFpEF and hypertension should have medication titrated to attain blood pressure targets in accordance with published clinical practice guidelines to prevent morbidity.[44–46]
2a	C-EO	2. In patients with HFpEF, management of AF can be useful to improve symptoms.
2b	B-R	3. In selected patients with HFpEF, the use of ARB may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum.[47,48]
3: No Benefit	B-R	4. In patients with HFpEF, routine use of nitrates or phosphodiesterase-5 inhibitors to increase activity or quality of life is ineffective.[49,50]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

HFpEF

Heart failure with preserved ejection fraction
New recommendations

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]

THE INTERNATIONAL HEART INSTITUTE OF MONTANA

In 2018 45% of cardiologists were 56 yo or greater

Approximately 23,000 practicing cardiologists in US

700 new cardiology graduates/year is predicted only replace approximately 50% of retiring pool annualy