Needs in the Therapeutic Heart Failure Space

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CRT 19 CARDIOVASCULAR RESEARCH TECHNOLOGIES

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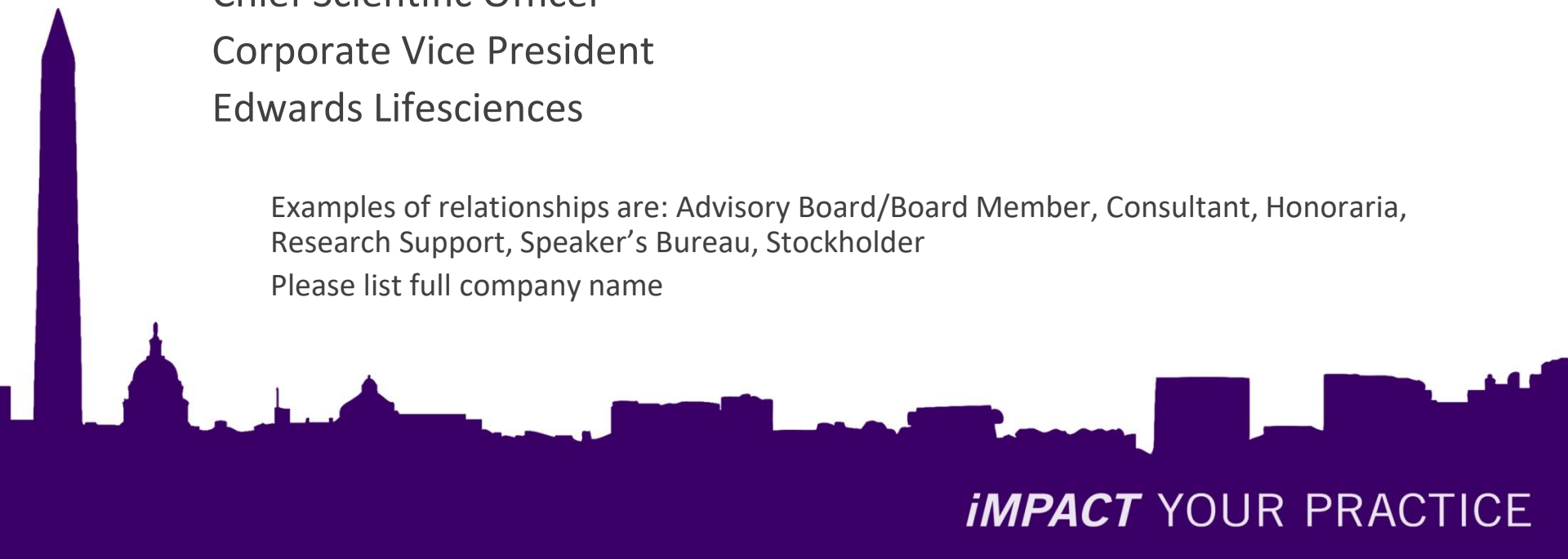
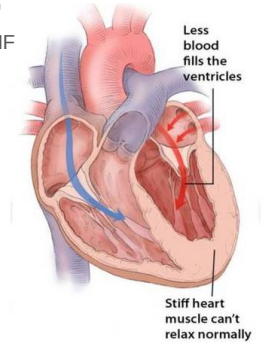
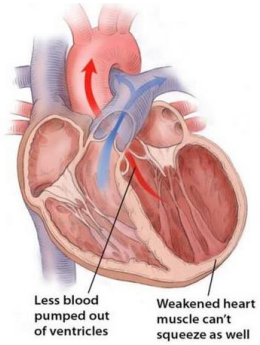


Two primary forms of heart failure



Heart failure with persevered ejection fraction or diastolic heart failure (EF > 50%)

- Associated with systemic inflammation driving arterial and myocardial stiffening
- Associated with normal left ventricular volumes and evidence of diastolic dysfunction (eg, abnormal pattern of LV filling and elevated filling pressures)
- More common in women than men
- Associated with aging and complex comorbid profiles
- No mortality signal observed in any pharma trials



Heart failure with reduced ejection fraction or systolic heart failure (EF <40%-50%)

- Driven by local cardiac injury (macro or microvascular) causing decreased cardiac output and pathologic compensatory pathways
- Characterized by increased LV volumes and reduced EF
- Higher likelihood with men
- Associated with infarctions, uncontrolled hypertension, or cardiomyopathies
- Pharma is the gold standard with several drugs with proven mortality benefit

Heart failure is the number one driver of death, hospitalizations, and costs in the Medicare population

Prevalence

6.2M (US) → **>8M** (By 2030)

Hospitalizations

~1M
US hospital admissions for Acute Decompensated Heart Failure (ADHF) as primary diagnosis

2.7M
Physician office visits with a primary diagnosis of HF

Mortality

22%
At 1 year

42.3%
At 5 years

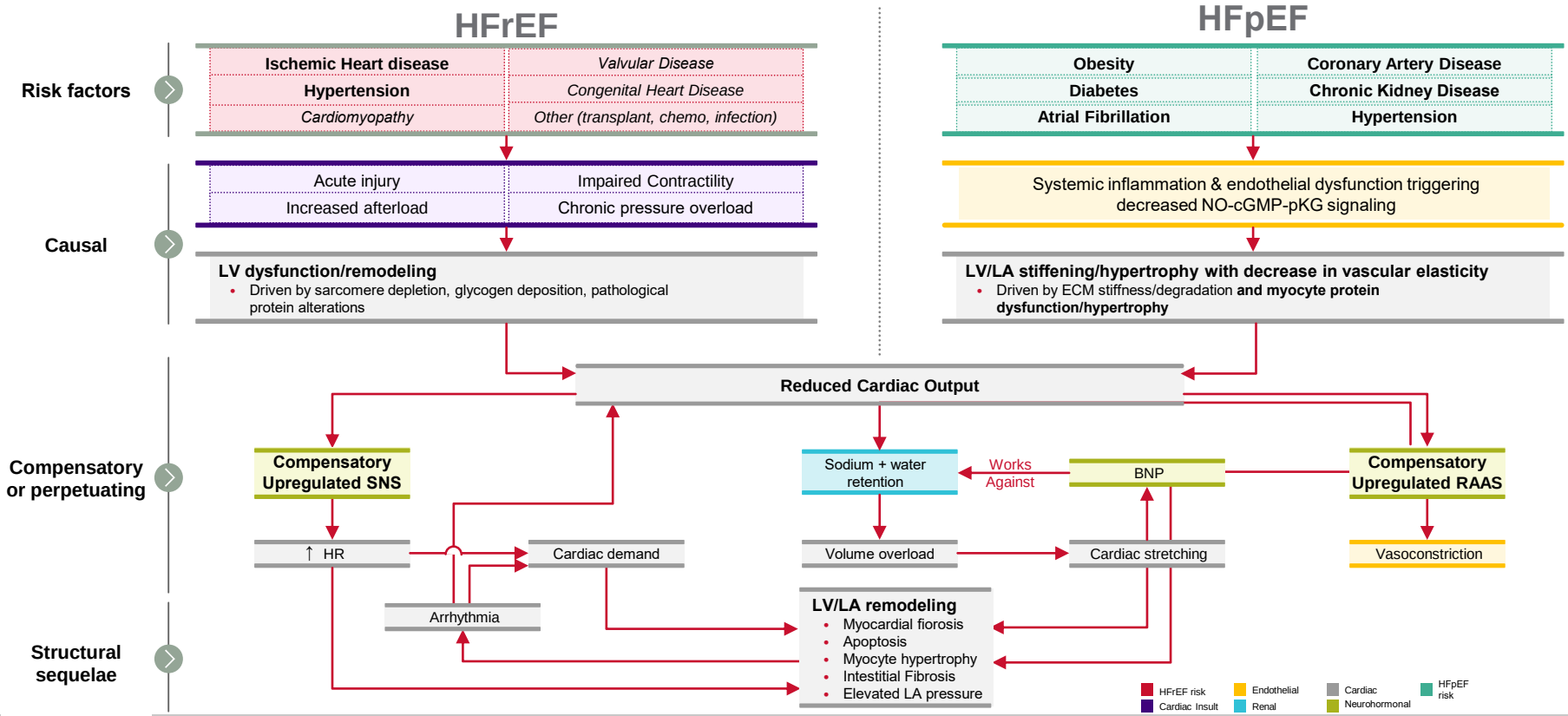
$31B direct cost to the US health system → estimated to double to $70B by 2030

Source: Heart Disease and Stroke Statistics – 2019 Update, American Heart Association

Key risk factors for HF are contributory and causal

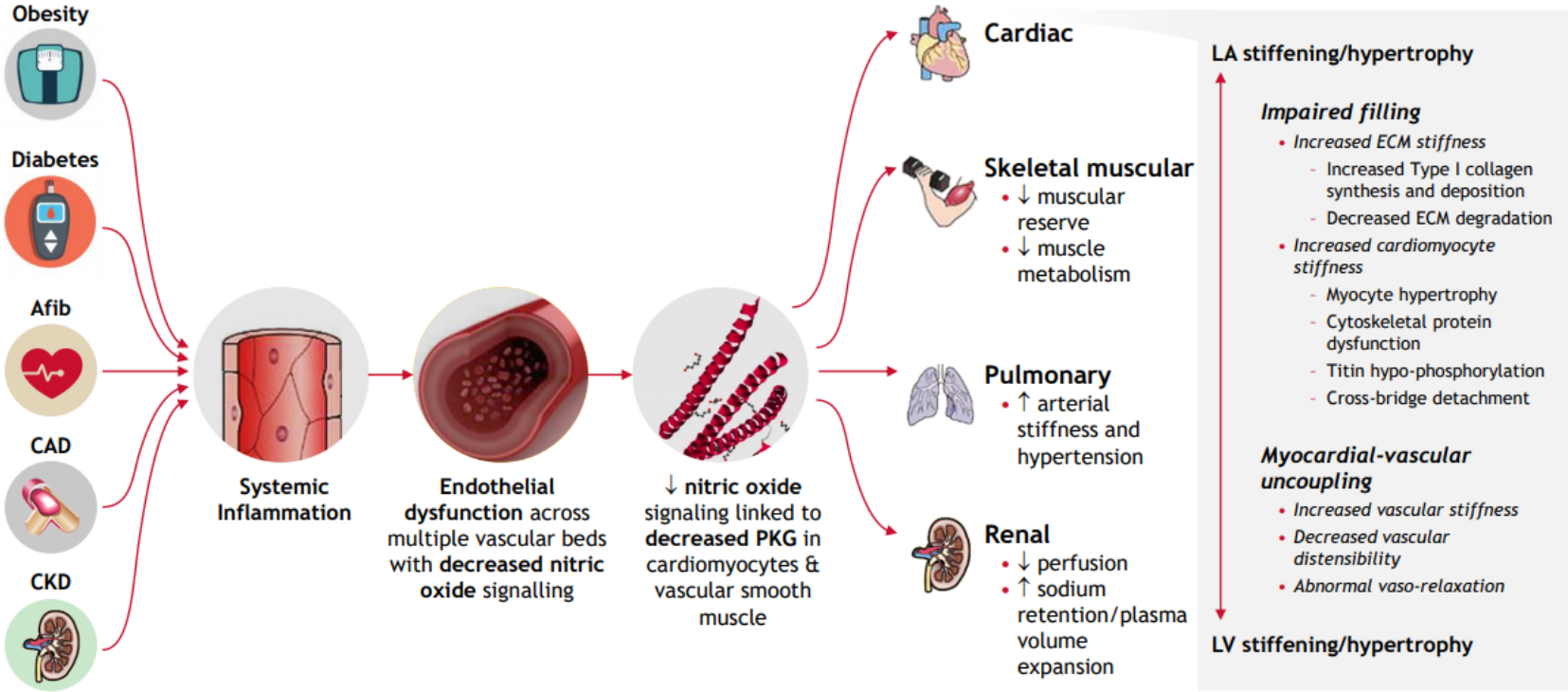
Note: HTN, hypertension, HLD, hyperlipidemia, CAD, coronary artery disease, CKD, chronic kidney disease, MI, myocardial infarction, AFIB, atrial fibrillation, PAH, pulmonary arterial HTN

Despite different drivers, compensatory/perpetuating mechanisms similar in HF

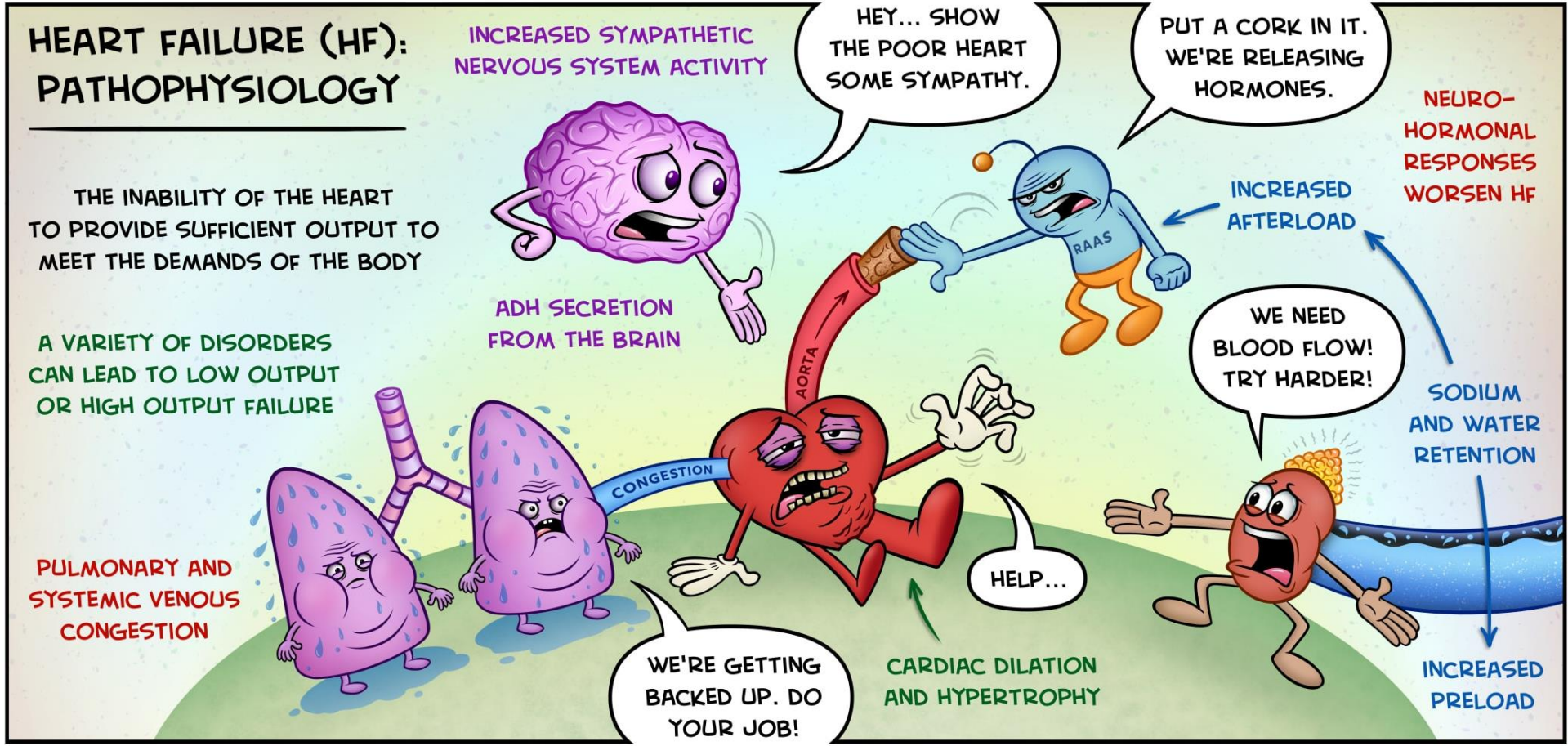


LV= left ventricular, LA= left atrial, SNS = sympathetic nervous system, RAAS = renin-angiotensin-aldosterone system , HR = heart rate, BNP = brain natriuretic peptide, NO = nitric oxide, cGMP= cyclic guanosine monophosphate, PKG = protein kinase G, ECM = extracellular matrix

Multiple co-morbidities create an inflammatory state that leads to endothelial dysfunction that drives HFpEF



Source: BCG analysis (2018)


HEART FAILURE (HF): PATHOPHYSIOLOGY
THE INABILITY OF THE HEART TO PROVIDE SUFFICIENT OUTPUT TO MEET THE DEMANDS OF THE BODY
A VARIETY OF DISORDERS CAN LEAD TO LOW OUTPUT OR HIGH OUTPUT FAILURE
PULMONARY AND SYSTEMIC VENOUS CONGESTION
INCREASED SYMPATHETIC NERVOUS SYSTEM ACTIVITY
ADH SECRETION FROM THE BRAIN
HEY... SHOW THE POOR HEART SOME SYMPATHY.
PUT A CORK IN IT. WE'RE RELEASING HORMONES.
NEURO-HORMONAL RESPONSES WORSEN HF
INCREASED AFTERLOAD
RAAS
AORTA
CONGESTION
WE NEED BLOOD FLOW! TRY HARDER!
SODIUM AND WATER RETENTION
INCREASED PRELOAD
HELP...
WE'RE GETTING BACKED UP. DO YOUR JOB!
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Current paradigm for clinical diagnosis leaves significant room for improvement

Framingham clinical criteria – key diagnostic

Two sets of criteria for HF diagnosis

Major criteria	Minor criteria
Paroxysmal nocturnal dyspnea	*Bilateral leg edema*
Orthopnea	*Nocturnal cough*
Elevated jugular venous pressure	*Dyspnea on ordinary exertion*
Third heart sound	*Hepatomegaly*
Cardiomegaly on chest x-ray	*Pleural effusion*
Pulmonary edema on chest x-ray	*Tachycardia (≥120 beats/min)*
Weight loss ≥4.5kg in 5 days in response to diuretics	*Weight loss ≥4.5kg in five days*

Diagnosis of HF requires **two major** or **one major and two minor** criteria cannot be attributed to another condition

Clinical tests can support a HF diagnosis

Supportive

Natiuretic peptide biomarkers

BNP (B-type natriuretic peptide) & NT-proBNP (N-terminal pro-B-type natriuretic peptide)

- Assist in the diagnosis or exclusion of HF as a cause of symptoms (Class I recommendation)
- Elevated levels also associated with other cardiac (i.e. VHD, afib, myocarditis, ACS) & non-cardiac causes (i.e. CKD, aging, anemia, OSA)
- Gives some impression of severity although limited tie to changes in management

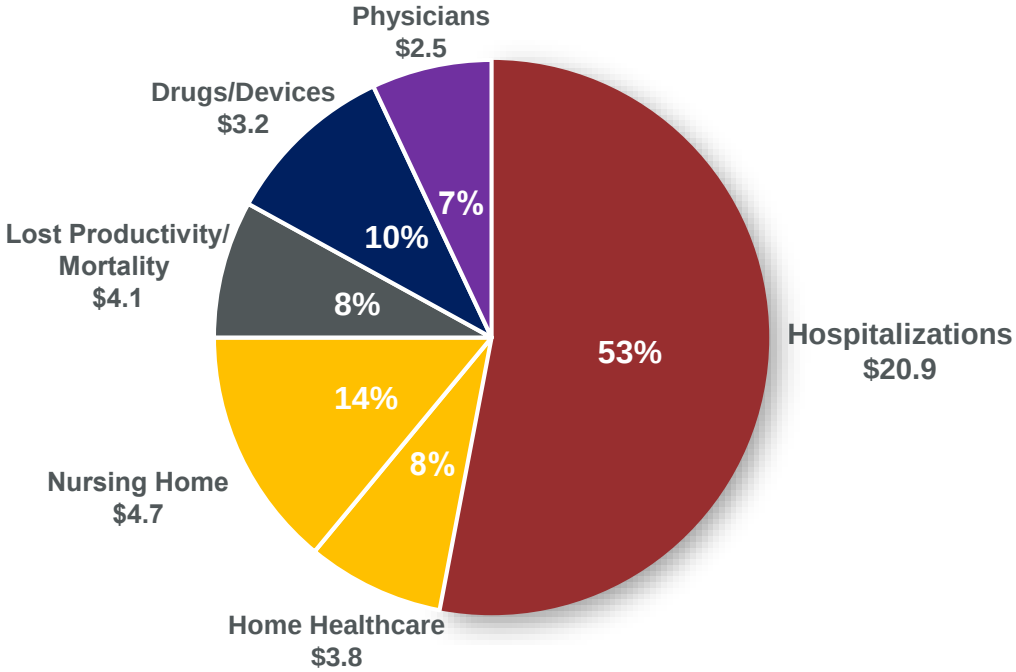
Supportive

Echocardiogram is not diagnostic

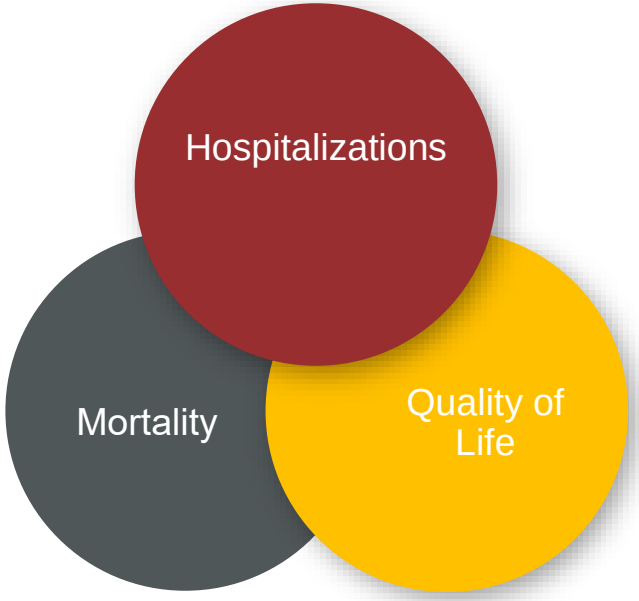
Source: 'Evaluation of patient with suspected heart failure' – Wilson S. Colucci (2018); '2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure' (2017)

Hospitalizations account for over half of the costs in Stage C/D HF and reducing them is a key priority

Heart Failure burden



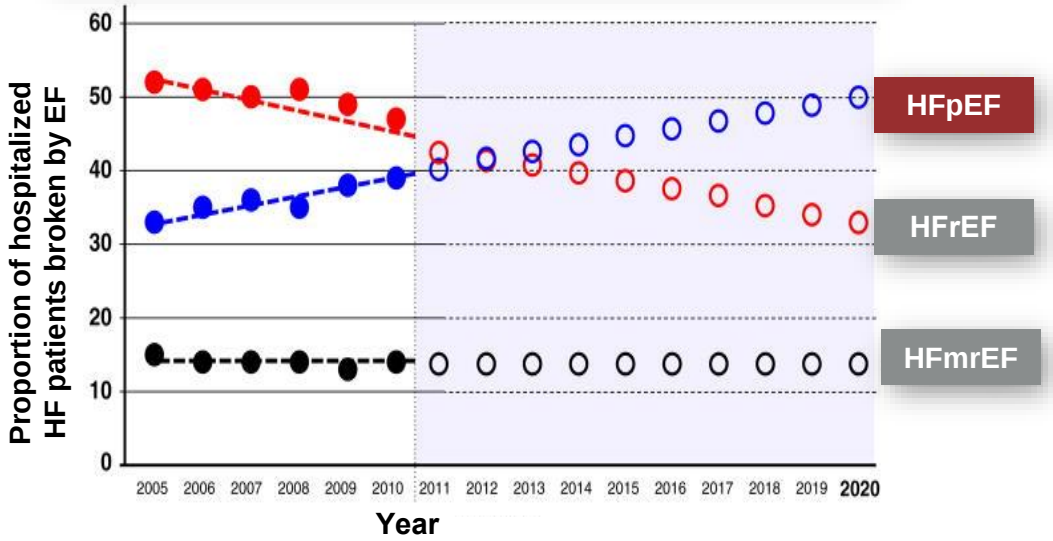
Goals of Heart Failure Therapy



Source: Heart Disease and Stroke Statistics—2010 Update

HFpEF hospitalization rate rising relative to HFrEF due to an ageing population, lesser misdiagnosis and lack of therapies

Data from a large nationwide HF hospitalization study (n>110,000)

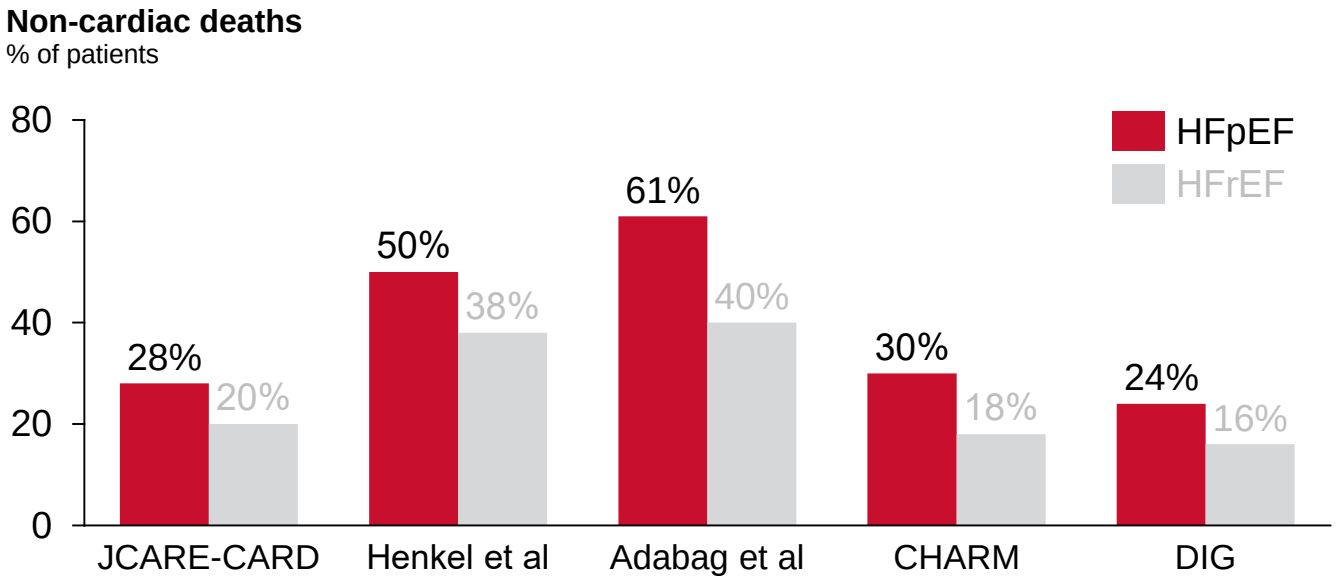


HFpEF hospitalization rates are on the rise compared to HFrEF

- Some hypothesis include:
  - Higher prevalence of HFpEF in an increasingly aging population with co-morbidities e.g., diabetes, HTN
  - Lesser rates of HFpEF misdiagnosis
  - Lower availability of drug treatments in HFpEF

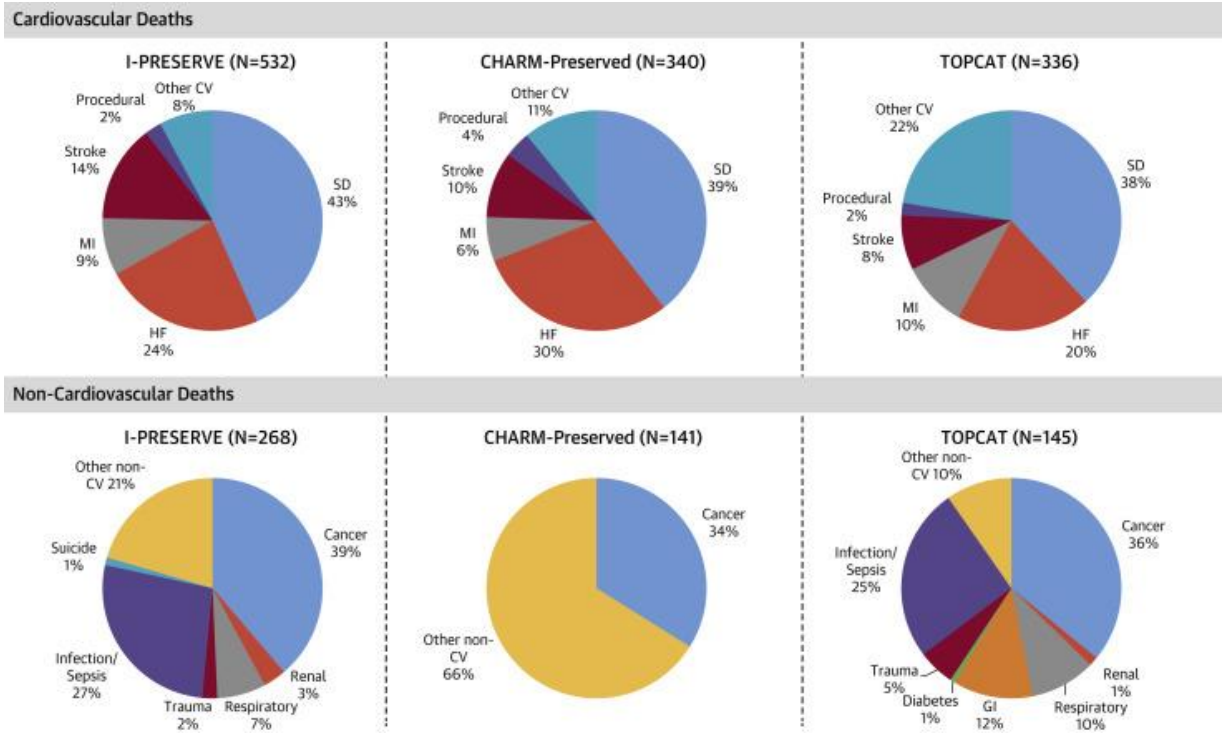
Source: Owan T et al. Trends in prevalence and outcome of heart failure with preserved ejection fraction. N Engl J Med. 2006; Get With the Guidelines-Heart Failure Registry (GWTG-HF)

High co-morbidities in HFpEF postulated to cause a higher % of non-cardiac deaths vs. HFrEF



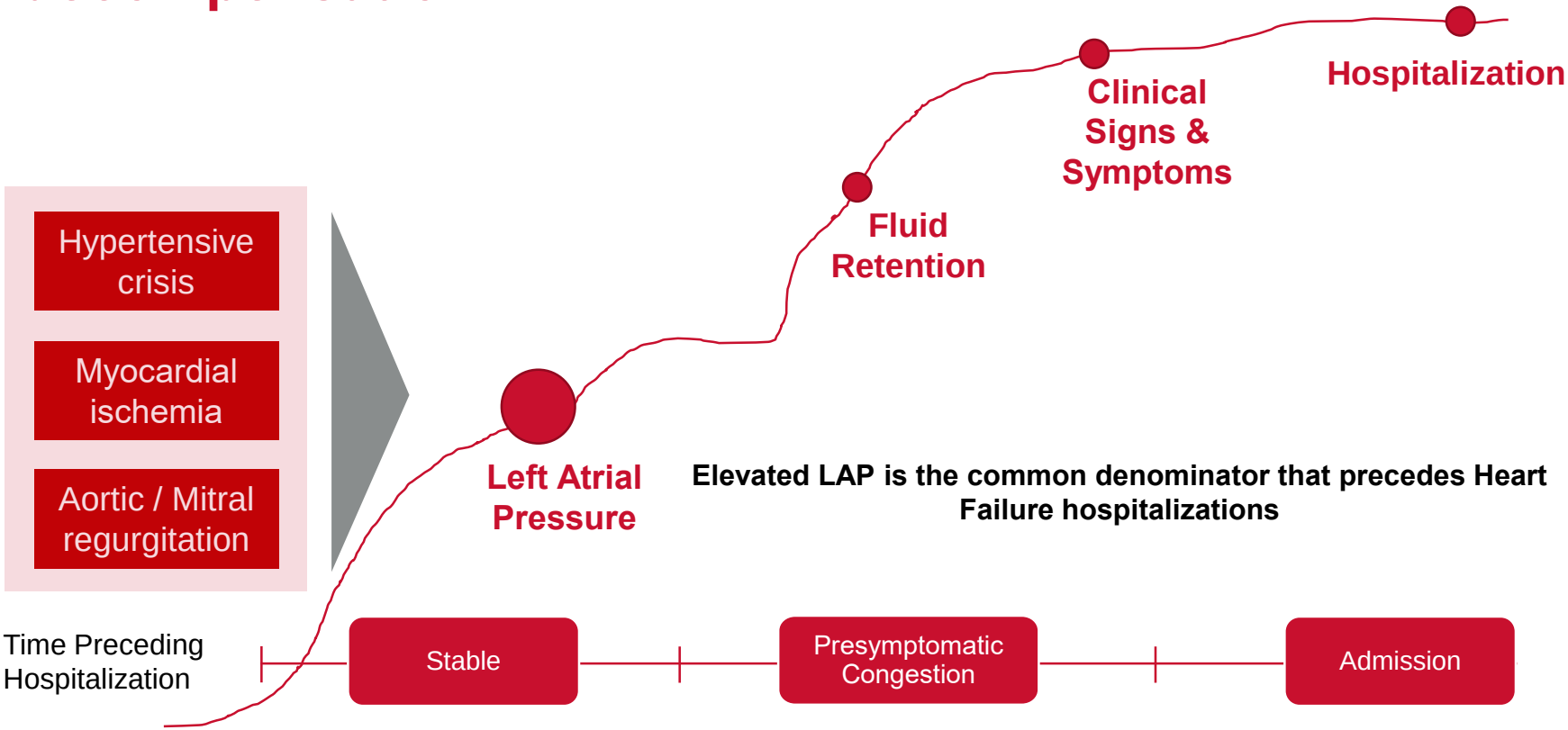
Source: Michelle M.Y. Chan, Carolyn S.P. Lam, EJHF. 2013

Cause-specific mortality in RCTs of HFpEF



Source: Vaduganathan M et al. Mode of Death in Heart Failure with Preserved Ejection Fraction. JACC 2017

Left Atrial Pressure is an early predictor of clinical decompensation



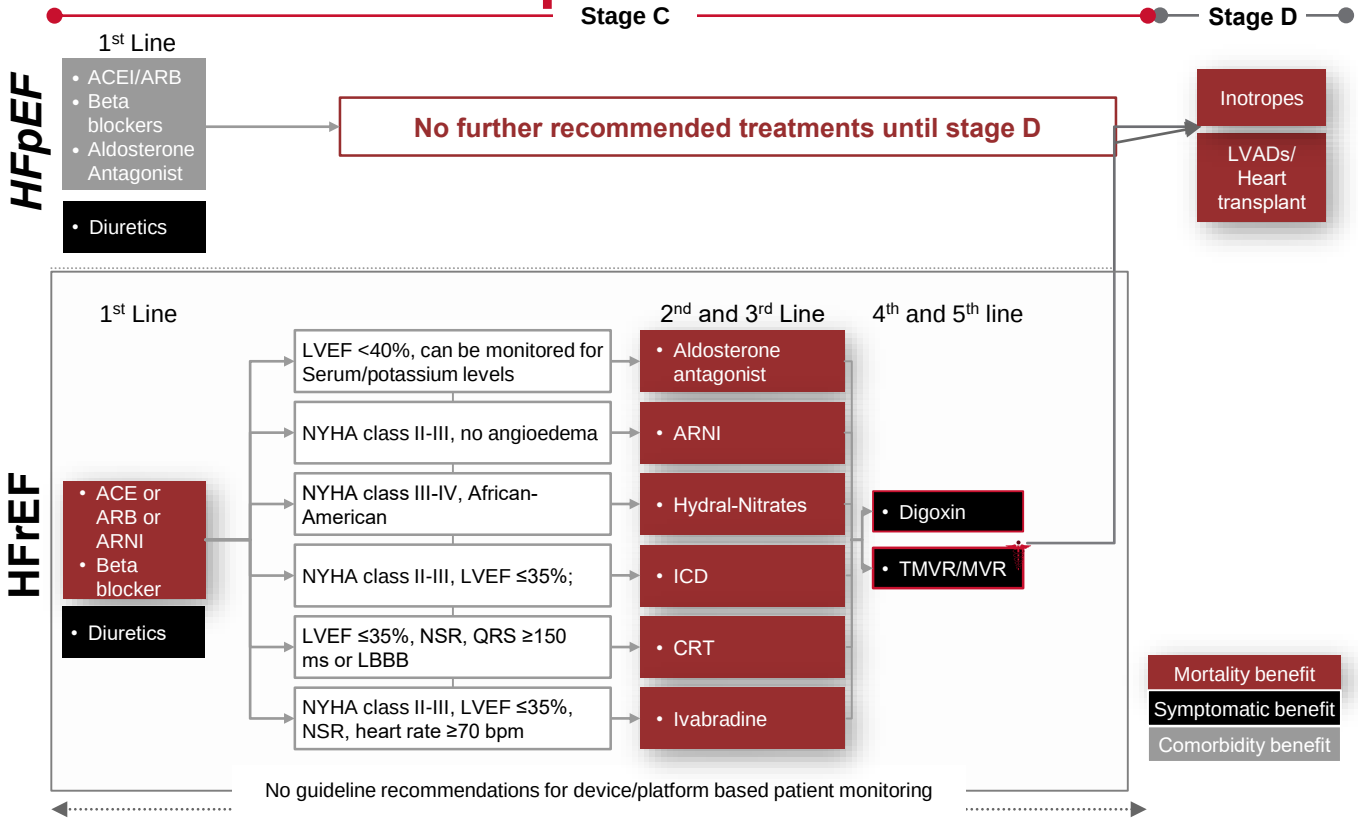
Source: Adapted from Pathophysiology of the transition from chronic compensated and acute decompensated heart failure; Adamson PB, et al. Curr Heart Fail Reports 2009

Multitude of treatment options exist for HFrEF with a lack of standard of care for HFpEF

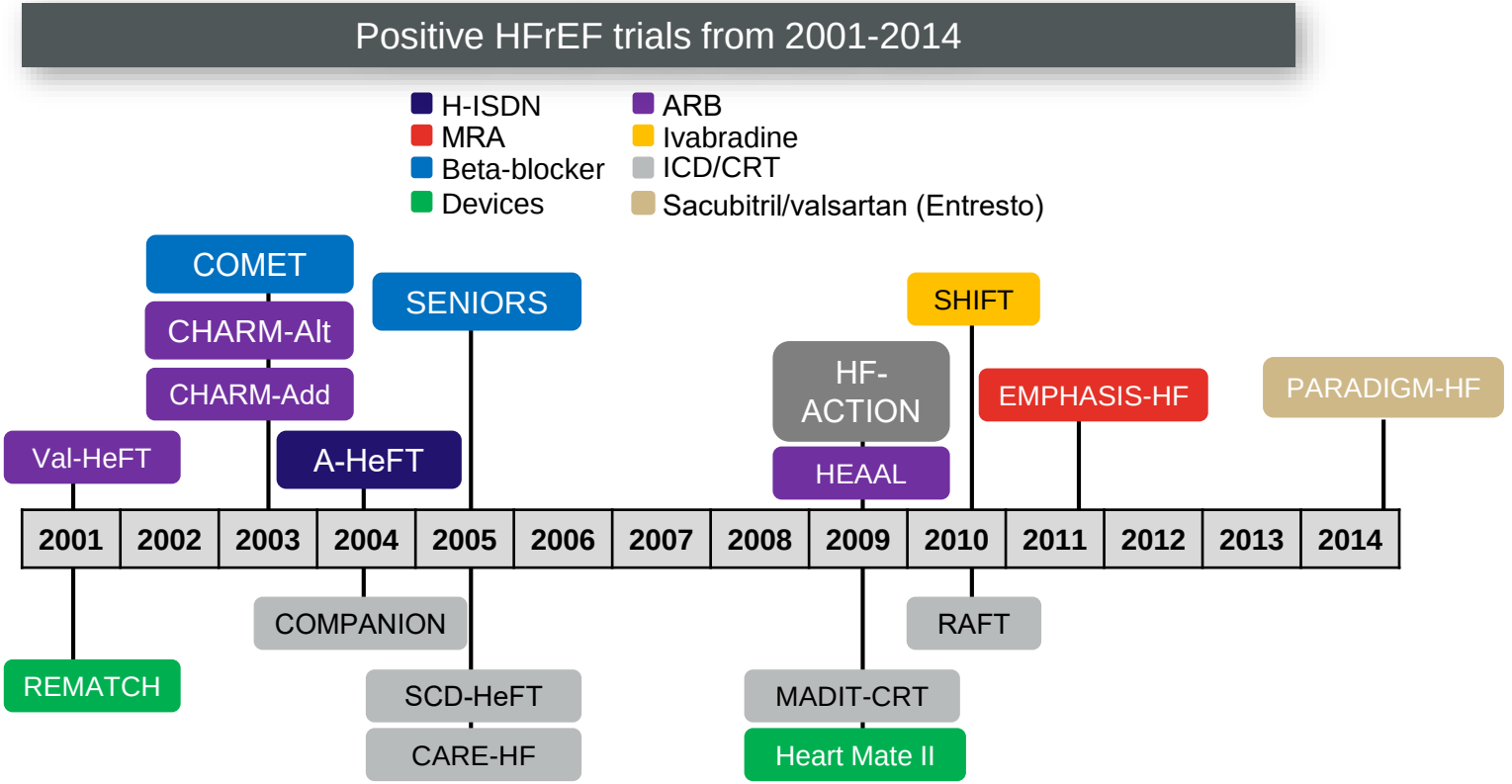
Guideline directed medical therapy (GDMT) defined by heart failure subtype

GDMT in HFpEF: diuretics

GDMT in HFrEF: ACE/ARB/ANRI, beta blocker, and diuretics

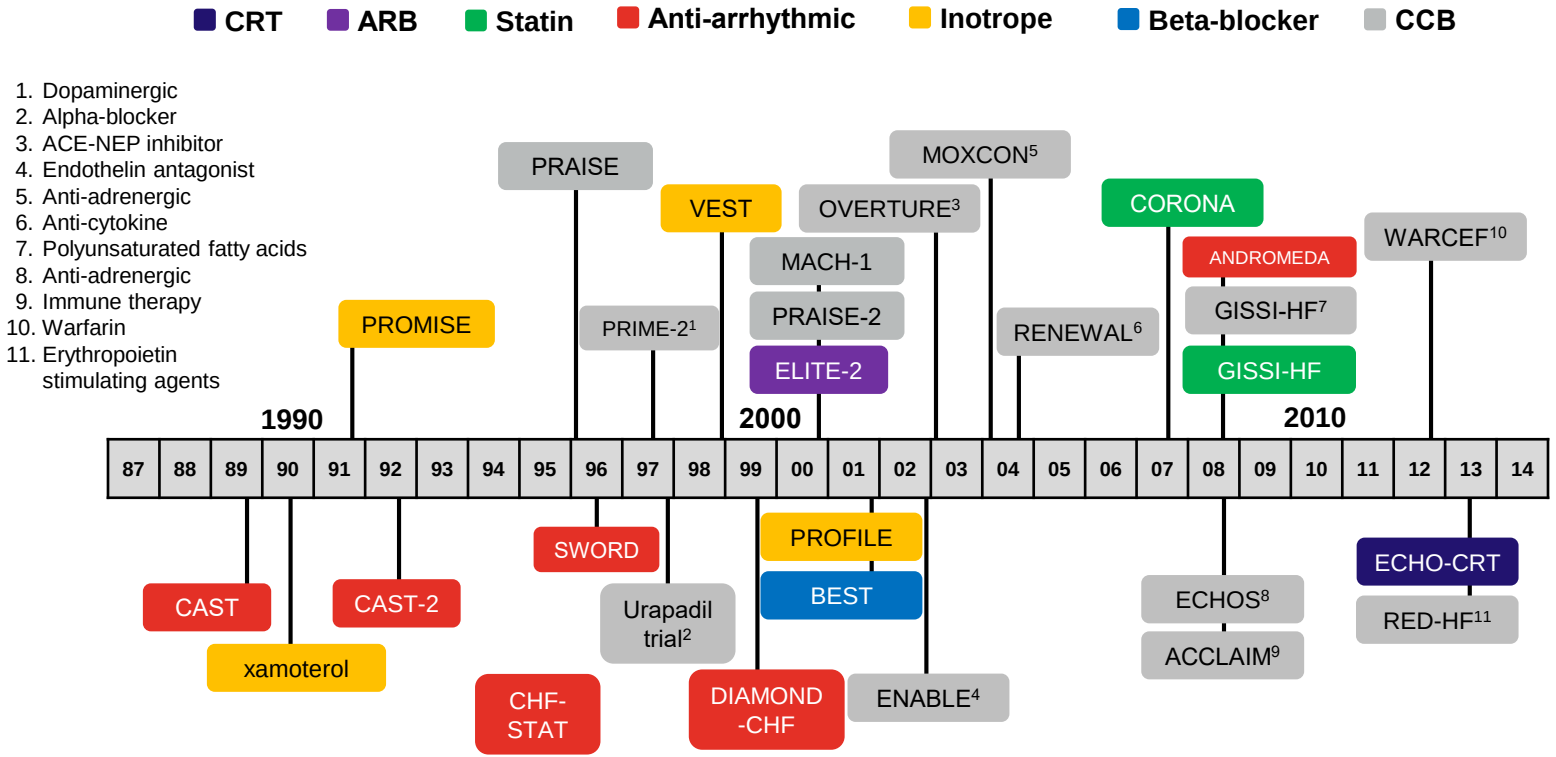


Progress made in HFrEF over the years has led to a decrease in morbidity and mortality

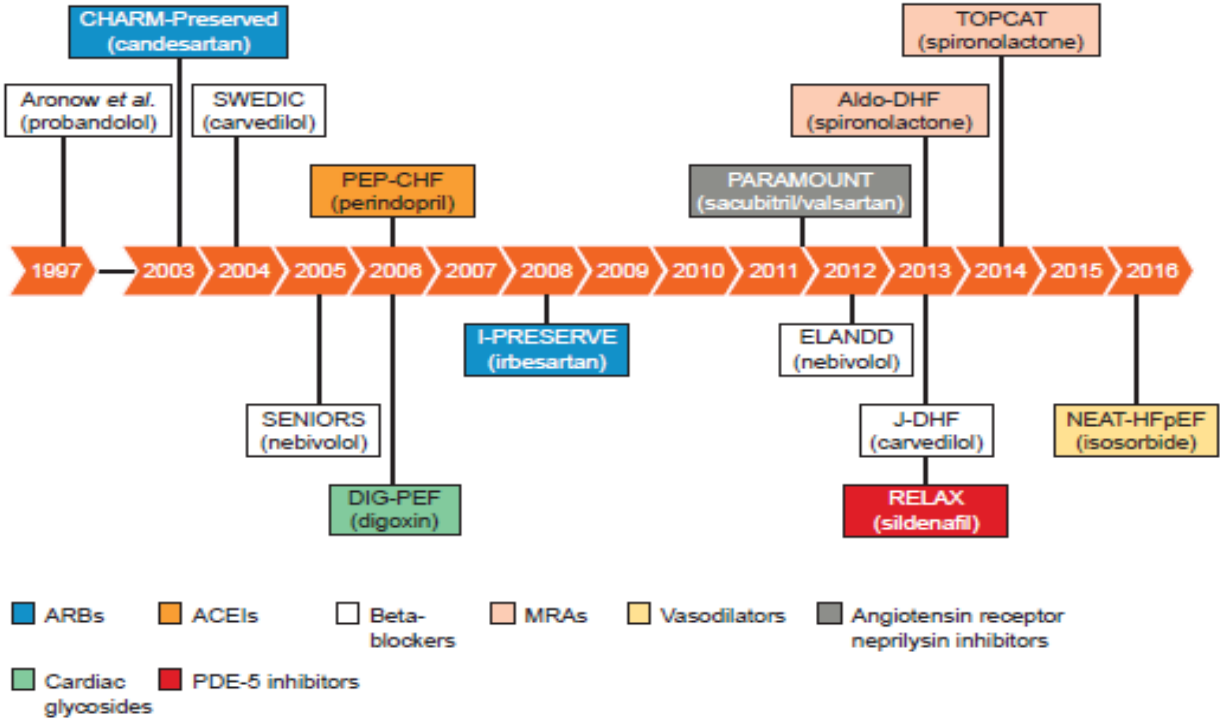


H-ISDN: Hydralazine–isosorbide dinitrate; ARB: Aldosterone receptor blocker; MRA: Mineralocorticoid receptor antagonist; ICD: Implantable cardioverter defibrillator; CRT: Cardiac resynchronization therapy

However, HFrEF trials also saw a number of early disappointments: 1987 - 2013



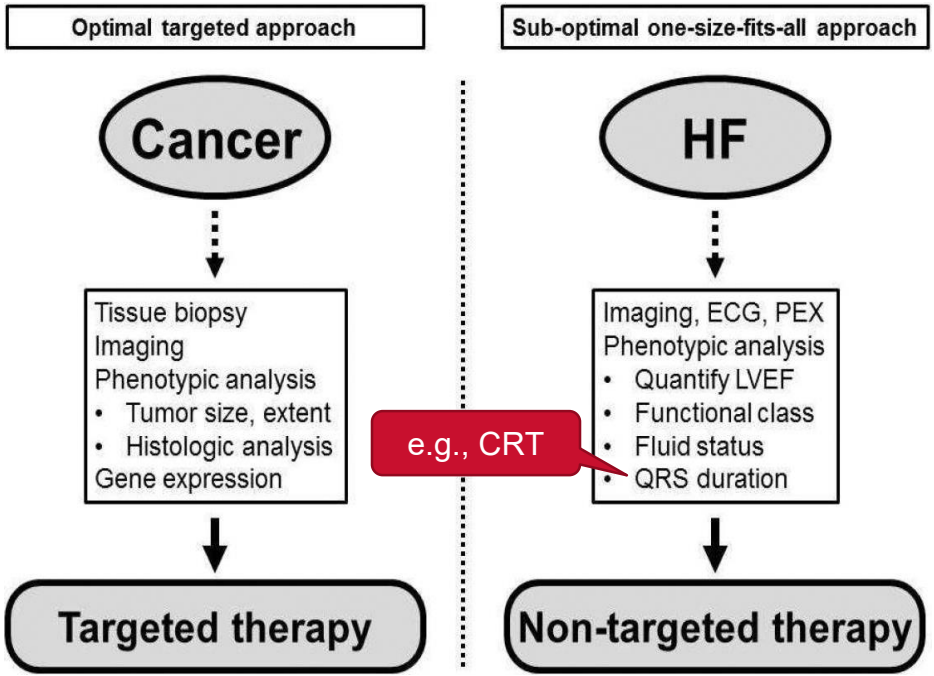
In comparison, HFpEF has been studied in fewer trials, with limited success



HFpEF's diverse etiology is similar to cancer and may require a more targeted patient classification and therapy

Challenges of treating HFpEF

- **Diverse etiology and pathophysiology** compared to HFrEF
- **Heterogeneity of HFpEF even in a single patient** may explain failure of clinical trials
- **Improved / nuanced classification** should lead to more targeted approaches and better outcomes



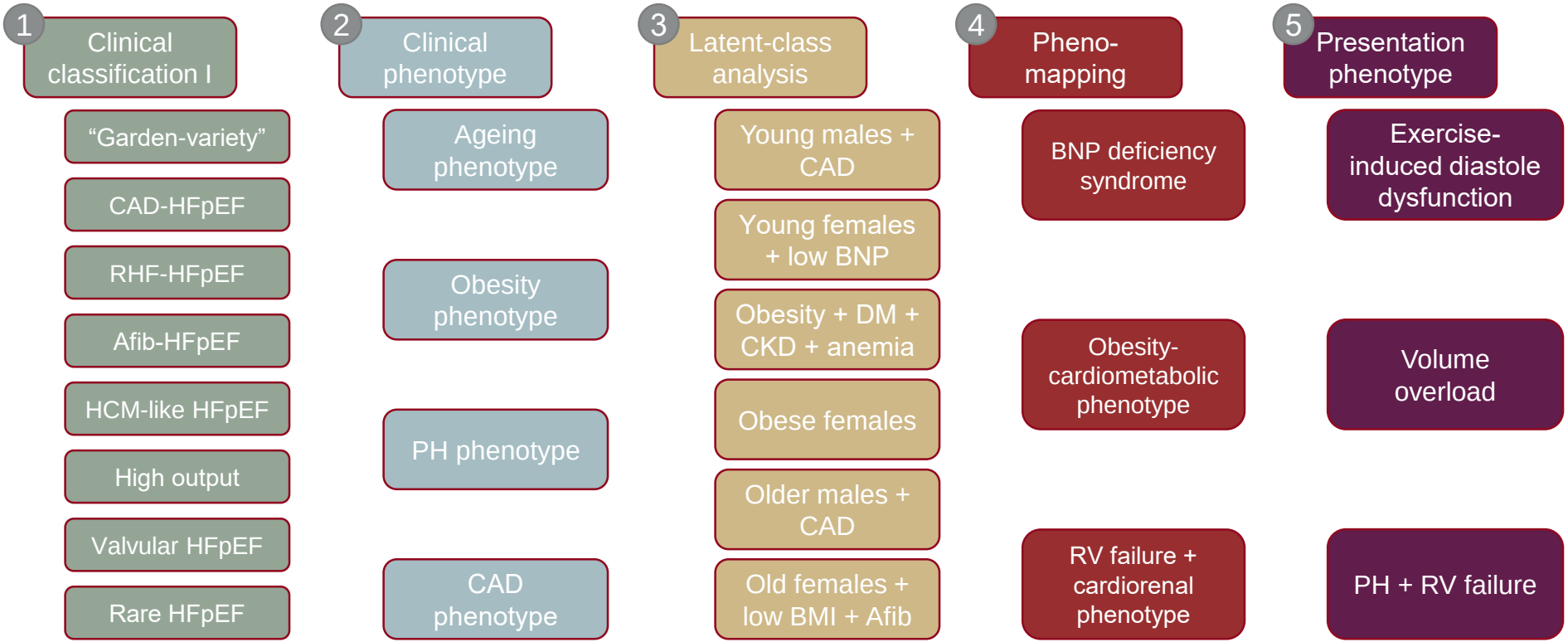
Source: Shah S et al, Heart Fail Clin.. 2014

Clinicians have proposed multiple HFpEF segmentations to better understand patient population

1. Clinical classification
2. Clinical phenotype
3. Latent-class analysis
4. Pheno-mapping
5. Presentation phenotype

Common themes amongst these classifications may help identify unmet needs and therapeutic opportunities

So what does all this mean from a clinical trial standpoint?



Negative trials in HFpEF showcase the importance of matching patient segments with interventions and endpoints

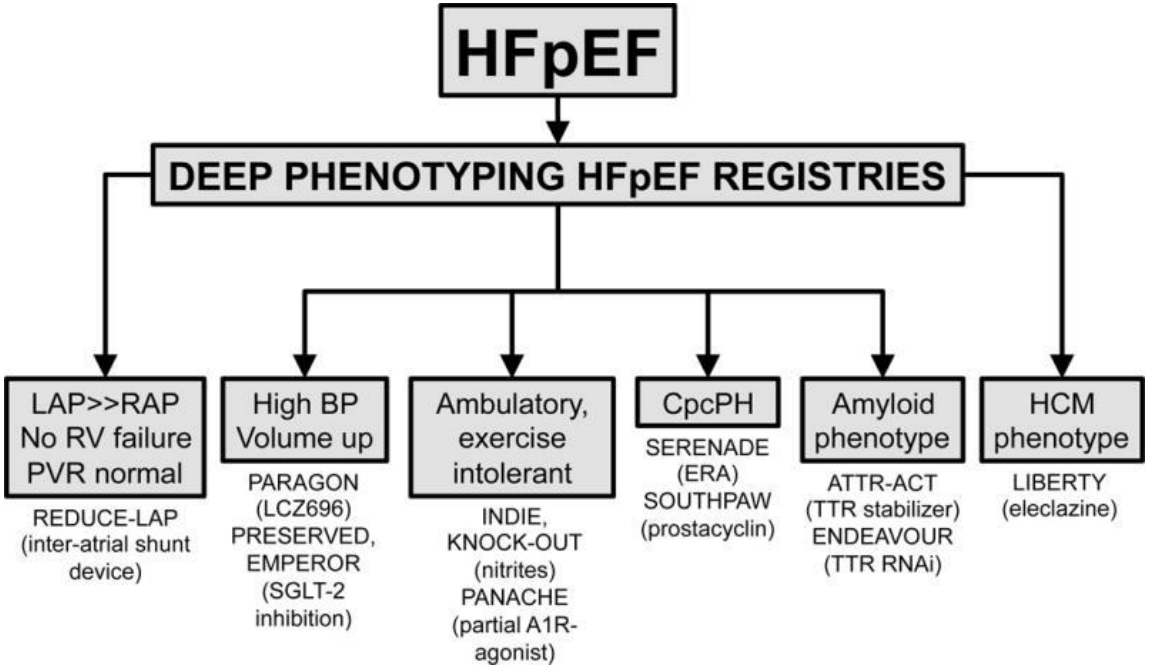
Trial	Intervention	HFpEF patient type	Primary endpoint	Trial result	Commentary
ALDO-DHF	Spironolactone	Exercise-induced DD	Peak VO2	Negative	Did not match Sprionolactone to “volume overload” patients (prior trials showed no change in exercise capacity)
ELANDD	Nerbivolol	Exercise-induced DD	6MWT	Negative	Given vasodilation effects, maybe best suited for “volume overload” patients
J-DHF	Carvedilol (low-dose)	Exercise-induced DD	Death or HFH	Negative	
RAAM-PEF	Eplerenone	Volume overload	6MWT	Negative	Right drug, right patient, wrong end-point?
RELAX	Sildenafil	Volume overload	Peak VO2	Negative	PDE5i has history of treating PAH; maybe better suited for RVD / PH patients

Source: Shah , JACC. 2013

Successful trials in HFpEF showcase the importance of matching patient segments with interventions and endpoints

Trial	Intervention	HFpEF patient type	Primary endpoint	Trial result	Commentary
Komsala et al.	Ivabradine	Exercise-induced DD	Peak VO2	Positive	Ivabridine's luscitropic effects best suited for improving exercise capacity
CHAMPION	CardioMEMS	Volume overload	HFH	Positive	Monitoring best suited to affect congestion
Guazzi et al.	Sildenafil	RHF / PH	Pulmonary Hemodynamics	Positive	PDE5 previously shown to be beneficial for PAH
Kitzman et al	Exercise testing	Exercise-induced DD	Peak VO2	Positive	Focus on exercise in patient selection / endpoint
PARAMOUNT	ARNI	Volume overload	NT-proBNP	Positive	High BNP cutoff recruitment

“Precision medicine” used in HFpEF registries: patients are deep-phenotyped and allocated to appropriate trials



Source: Shah S, JCTR. 2017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Years of
Discovery


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