Newer Treatments for Heart Failure

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Disclosures

Research Funding: Bristol Myers Squibb

Clinical Trial Activity: Abbott, Novartis

Ownership: None

Educational Goals:

- Review the expanded indication for use of Sacubatril/Valsartan across the spectrum of LV dysfunction.
- Review the use of SGLT2 inhibitors in treatment of systolic heart failure irrespective of diabetes mellitus.
- Review the potential benefit of comprehensive disease-modifying pharmacological therapy for HF.

References

- Sacubatril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure. Circulation (2020) 141: 352-361.
- Sodium-glucose cotransporter 2 inhibitor effects on heart failure hospitalization and cardiac function: systematic review. ESC Heart Failure (2021) DOI: 10.1002/ehf2.13483
- Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomized controlled trials. The Lancet (2020) 396: 121-128.

Congestive Heart Failure-Definition

- A disorder of EITHER cardiac filling (diastole) or contraction (systole) resulting in symptoms of shortness of breath
- How do we know that the shortness of breath is due to heart failure and not another cause? What are the criteria for the diagnosis of heart failure?

Table 1. Framingham Criteria for CHF

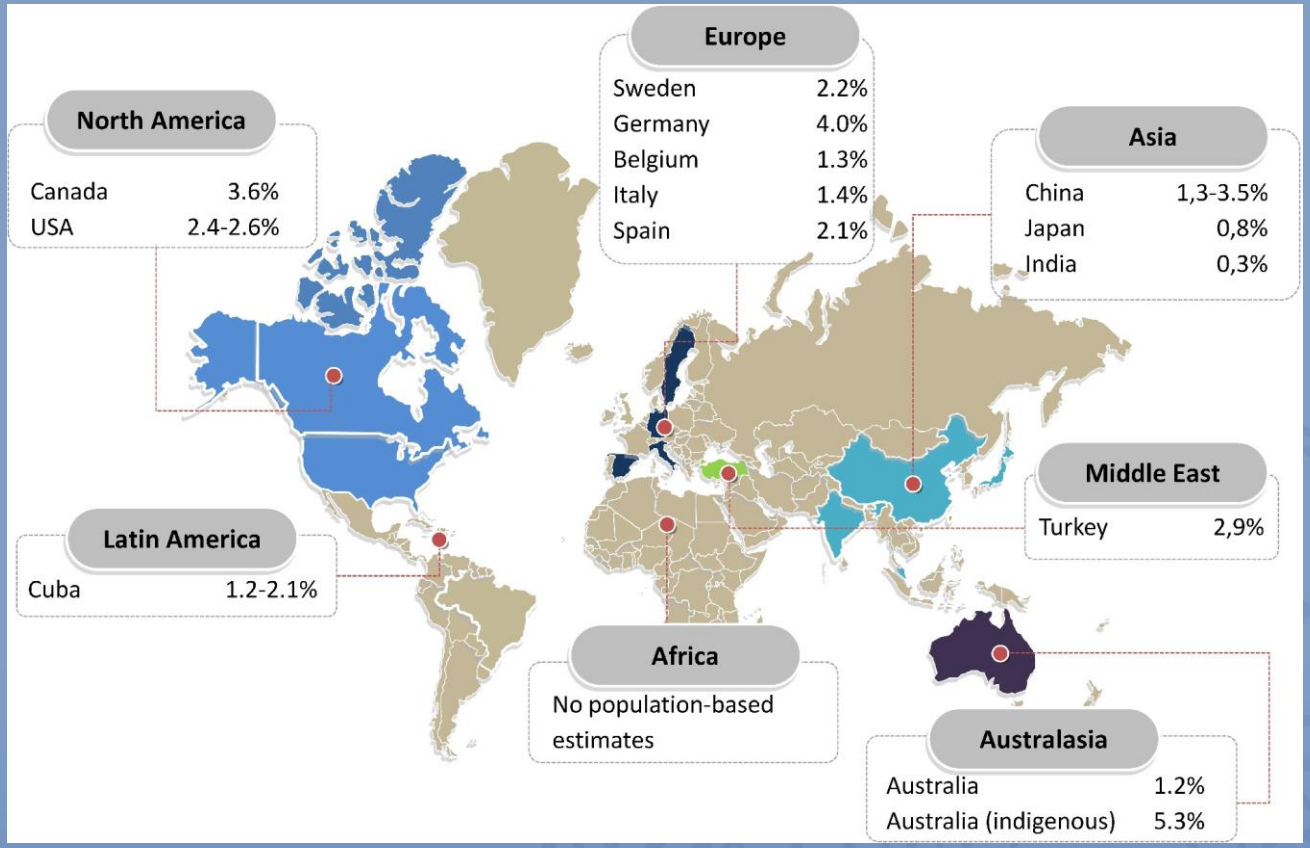
Major criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck-vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S_3 gallop
Increased venous pressure >16 cm of water
Circulation time ≥25 s
Hepatojugular reflux
Minor criteria
Ankle edema
Night cough
Dyspnea on exertion
Hepatomegaly
Pleural effusion
Vital capacity ↓1/3 from maximum
Tachycardia (range of ≥120/min)
Major or minor criteria
Weight loss ≥4.5 kg in 5 days in response to treatment

For establishing a definite diagnosis of CHF, 2 major criteria or 1 major and 2 minor criteria must be present.

Yturralde and Gaasch (2005) Prog Cardiovasc Dis 47(5): 314-9

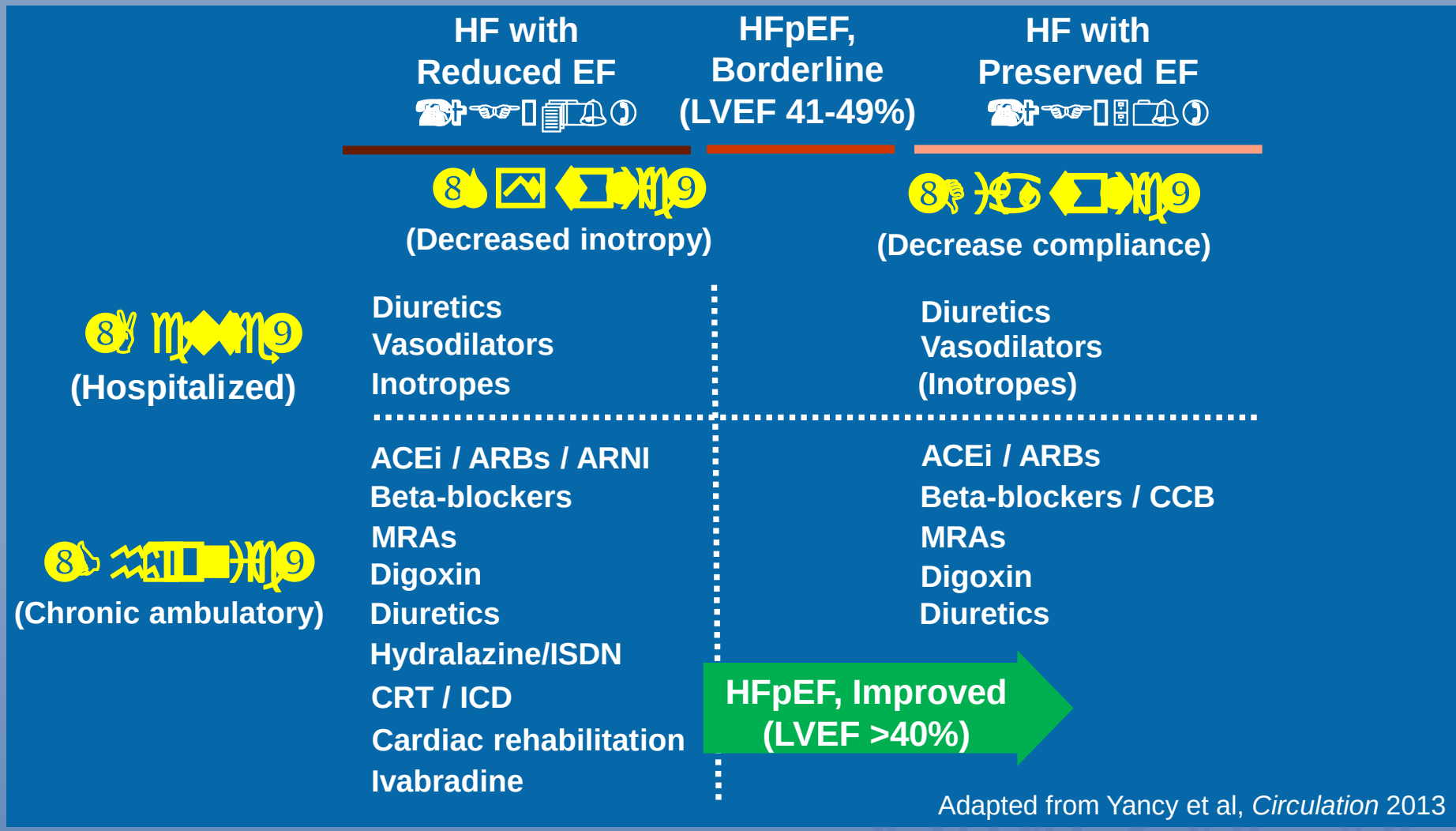
Congestive Heart Failure Epidemiology

- Six million Americans have HF, 2.5% population
- Incidence: 400,000 new cases of heart failure per year.
- Prevalence range 6-8% for individuals over age 65 years.
- Prevalence rising in young and older patients.



Circ Research (2021) 128: 1421-1434; Eur J HF (2020) 22: 1342-1356

Therapies for Heart Failure



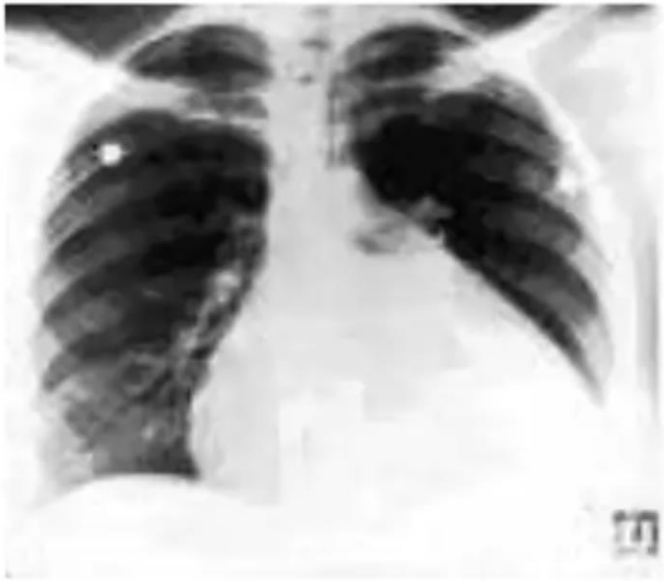
Adapted from Yancy et al, *Circulation* 2013

Illustrative Case

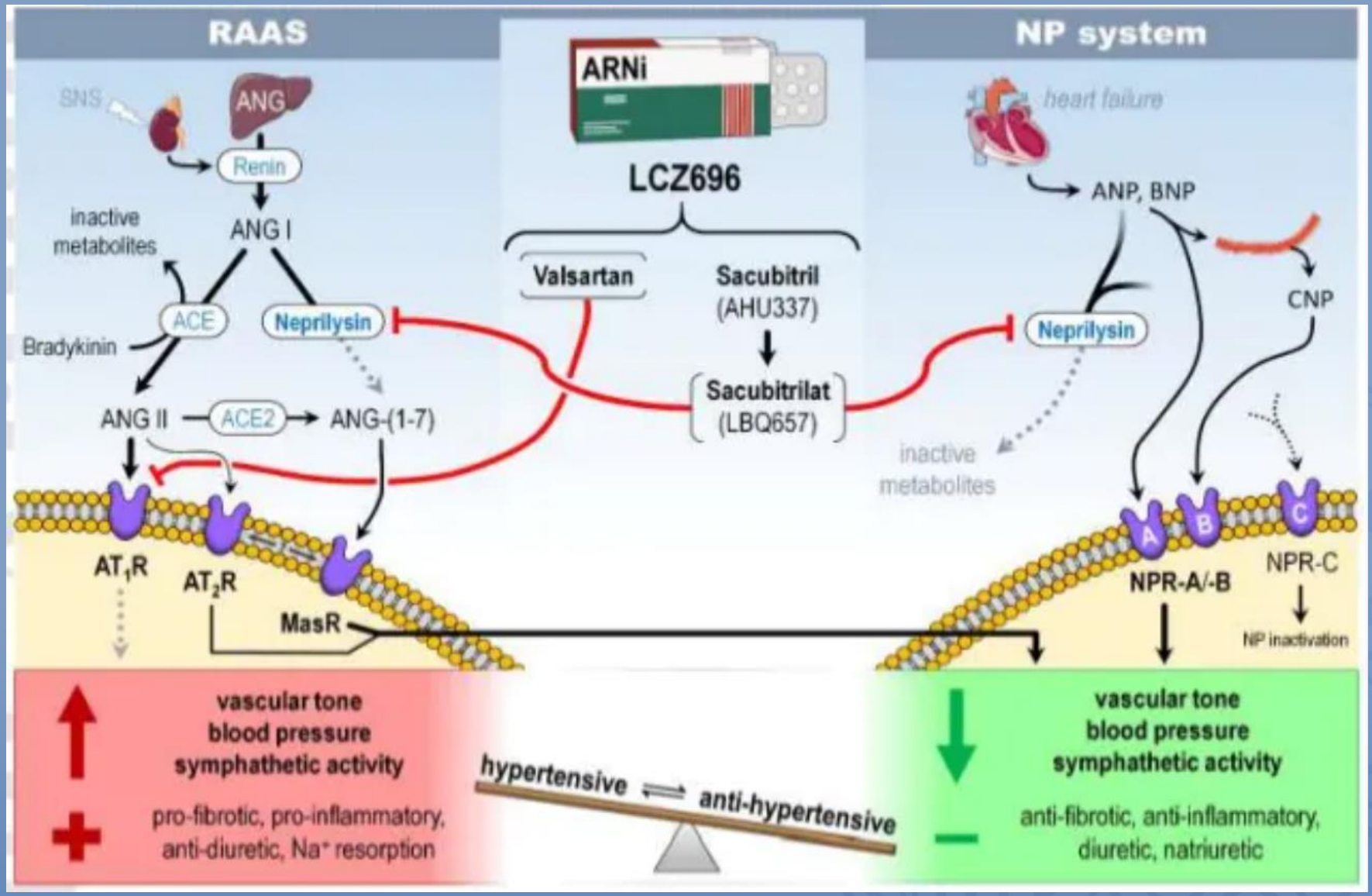
- A 63 year old woman with history of hypertension and BMI> 30 presents to your office after ER treatment for progressively worsening dyspnea. She was treated with one dose of iv furosemide in the ER resulting in improved symptoms and had BNP level 458 with TnI<0.01 x 3.
- ER started Carvedilol 6.25 mg BID, lisinopril 5 mg daily and furosemide 20 mg daily.
- She had LV EF 30-35% on echo in the ER no valvular heart disease noted. A repeat echo was obtained LV EF was 40-45% one month after ER visit.
- Na 135, Cr 1.09, eGFR > 60, Glu 122
- How could you change her medical therapy?

HF medical treatment: Lives saved/1000/year

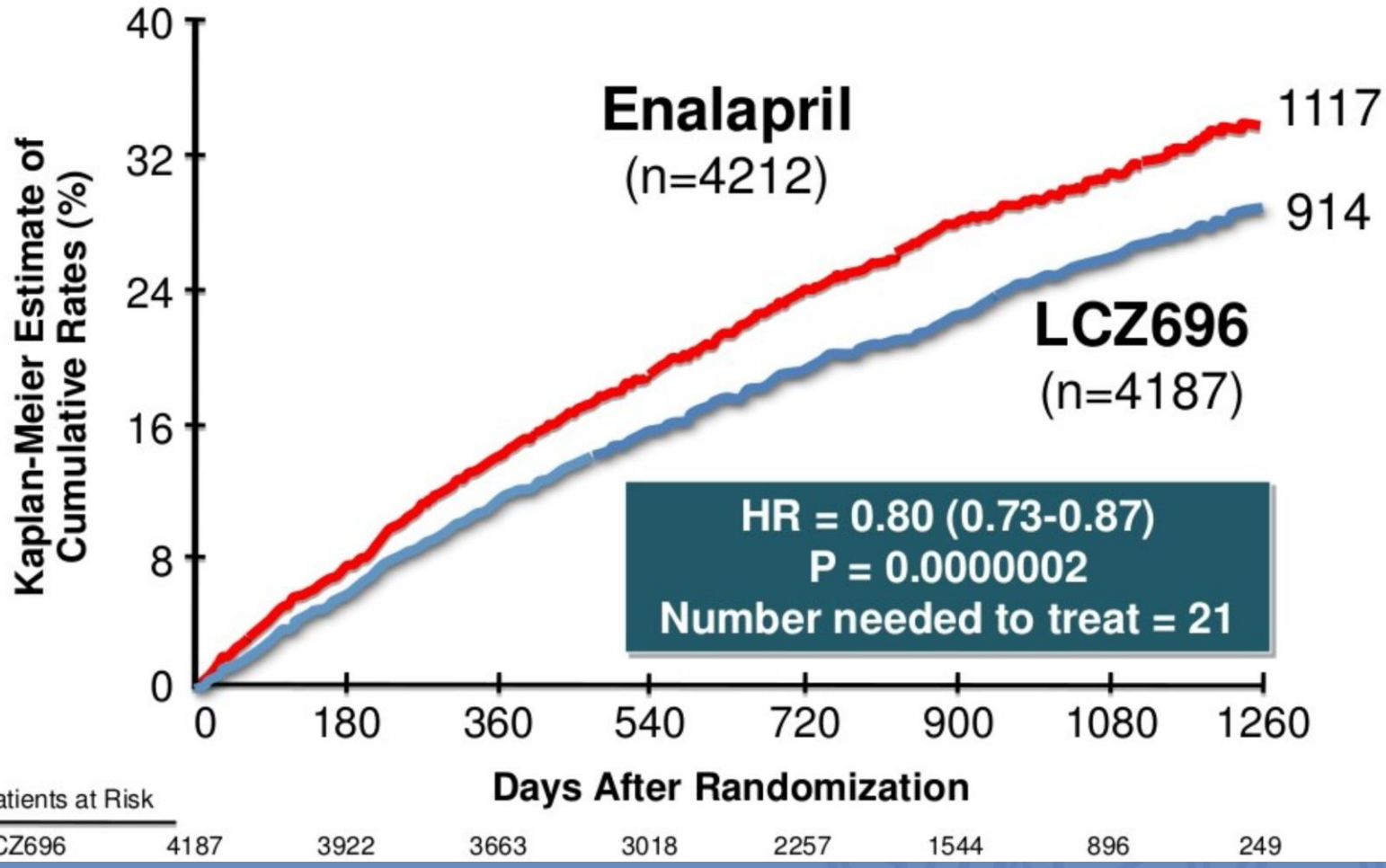
TRIAL	Lives saved/1000/year
SOLVD-P	7
SOLVD-R	17
MERIT	38
CIBIS	42
RALES	52
COPERNICUS	70



Mechanism of Action: ARNI

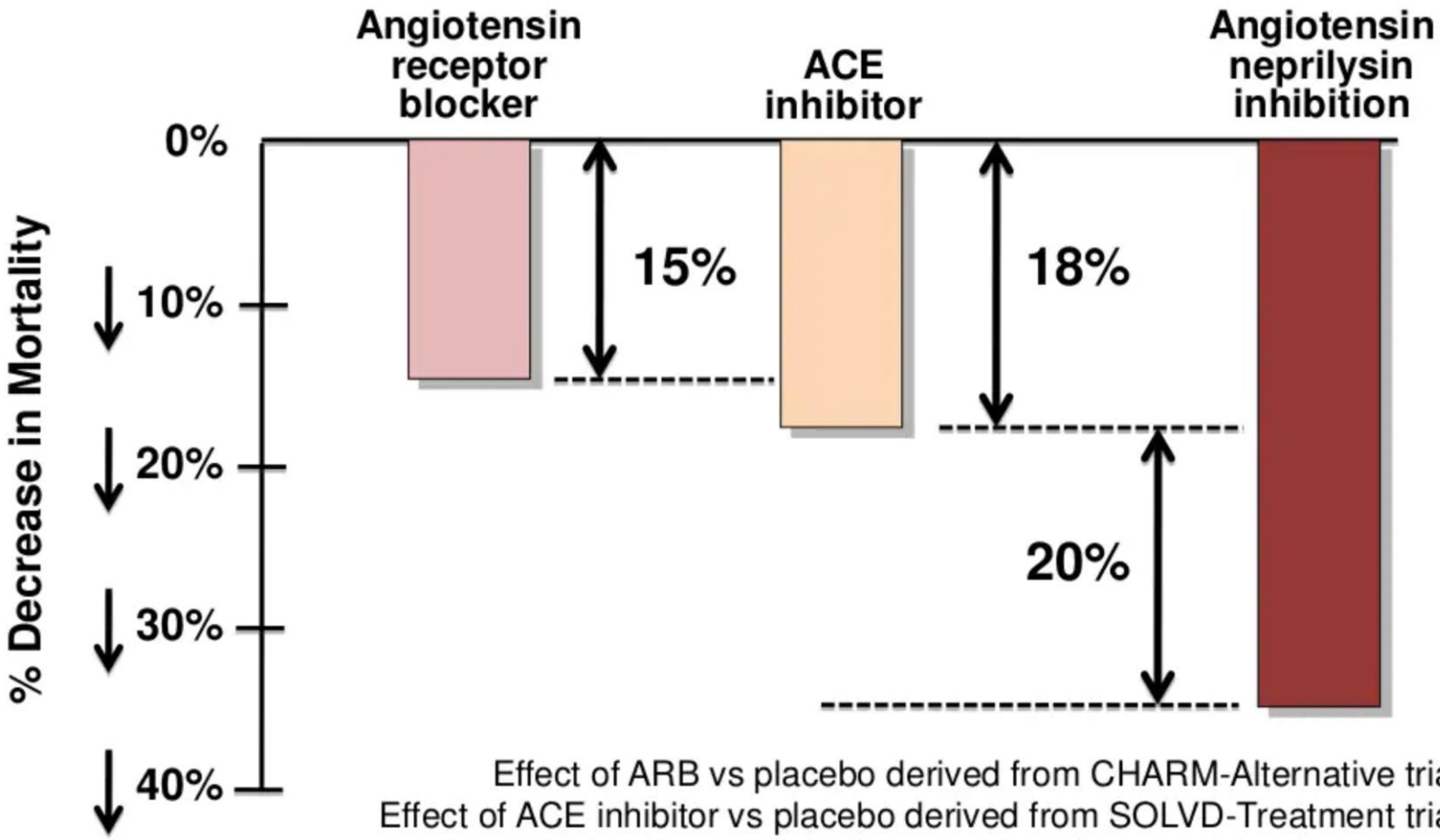


PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)



N Engl J Med (2014) 371: 993-1004

Angiotensin Neprilysin Inhibition With LCZ696 Doubles Effect on Cardiovascular Death of Current Inhibitors of the Renin-Angiotensin System



Effect of ARB vs placebo derived from CHARM-Alternative trial
Effect of ACE inhibitor vs placebo derived from SOLVD-Treatment trial
Effect of LCZ696 vs ACE inhibitor derived from PARADIGM-HF trial

Expanded Indication for Sacubatril/Valsartan Treatment

Circulation

ORIGINAL RESEARCH ARTICLE

Sacubitril/Valsartan Across the Spectrum of Ejection Fraction in Heart Failure

METHODS: We combined data from PARADIGM-HF (LVEF eligibility≤40%; n=8399) and PARAGON-HF (LVEF eligibility≥45%; n=4796) in a prespecified pooled analysis. We divided randomized patients into LVEF categories: ≤22.5% (n=1269), >22.5% to 32.5% (n=3987), >32.5% to 42.5% (n=3143), > 42.5% to 52.5% (n=1427), > 52.5% to 62.5% (n=2166), and >62.5% (n=1202). We assessed time to first cardiovascular death and HF hospitalization, its components, and total heart failure hospitlizations, all-cause mortality, and noncardiovascular mortality. Incidence rates and treatment effects were examined across categories of LVEF.

Circulation. 2020;141:352–361. DOI: 10.1161/CIRCULATIONAHA.119.044586

Expanded Indication for Sacubatril/Valsartan Treatment

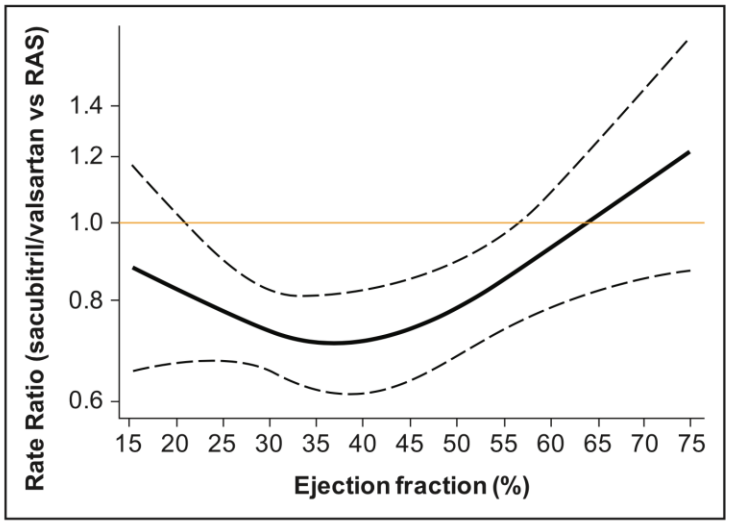


Figure 3. Treatment effects of sacubitril/valsartan vs active comparator (either enalapril or valsartan) across a range of ejection fraction for the composite of total heart failure hospitalization and cardiovascular death.
Estimated rate ratios and 95% confidence intervals obtained from negative binomial regression models with ejection fraction expressed via restricted cubic spline. RAS indicates renin-angiotensin-aldosterone–system inhibitor.

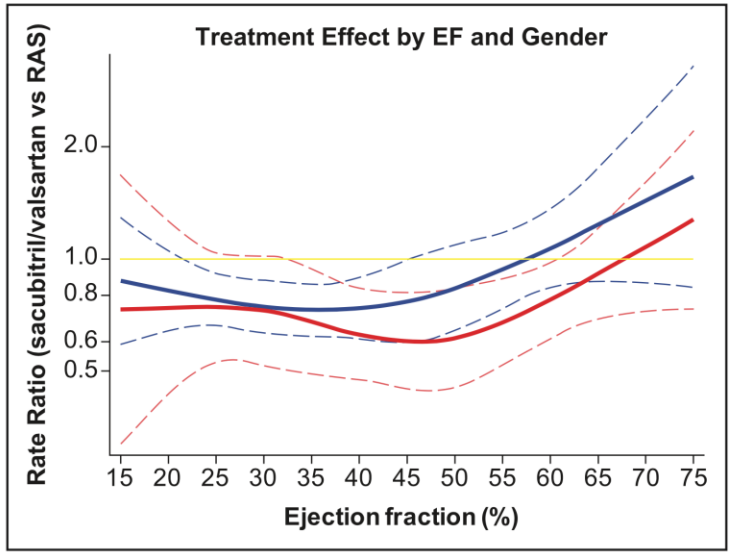
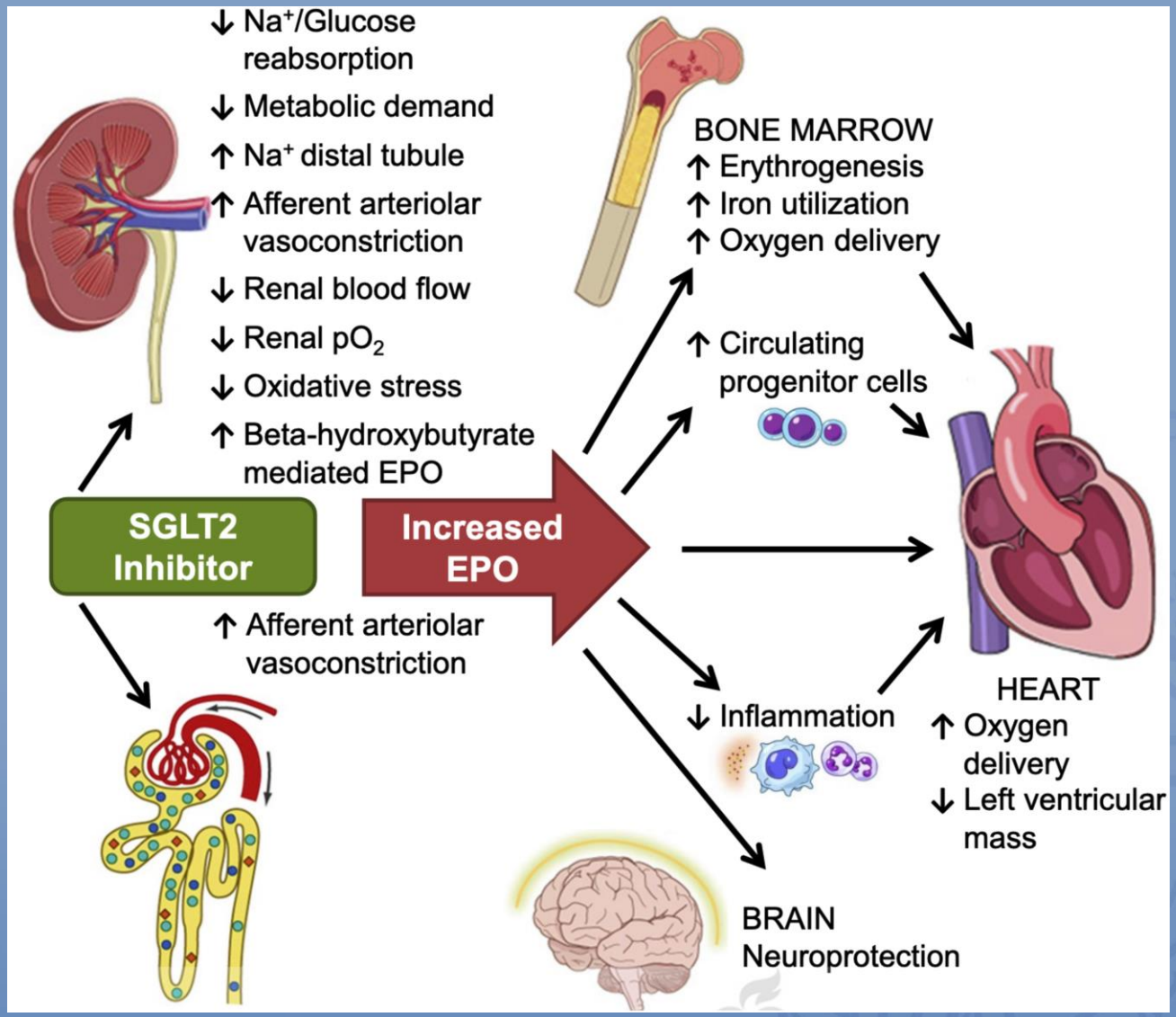


Figure 4. Continuous treatment effects of sacubitril/valsartan vs active comparator (either enalapril or valsartan) by sex.
Estimated rate ratio and 95% confidence intervals are displayed for males (blue) and females (red) separately. RAS indicates renin-angiotensin-aldosterone–system inhibitor.

358 February 4, 2020 *Circulation.* 2020;141:352–361. DOI: 10.1161/CIRCULATIONAHA.119.044586

- Sacubatril/Valsartan reduces rate of HF hospitalization and CV death Across a range of LV EF up to 60%

Mechanisms of Action of SGLT2 Inhibitors



JACC: Basic and Translational Science (2020) 5: 632-644

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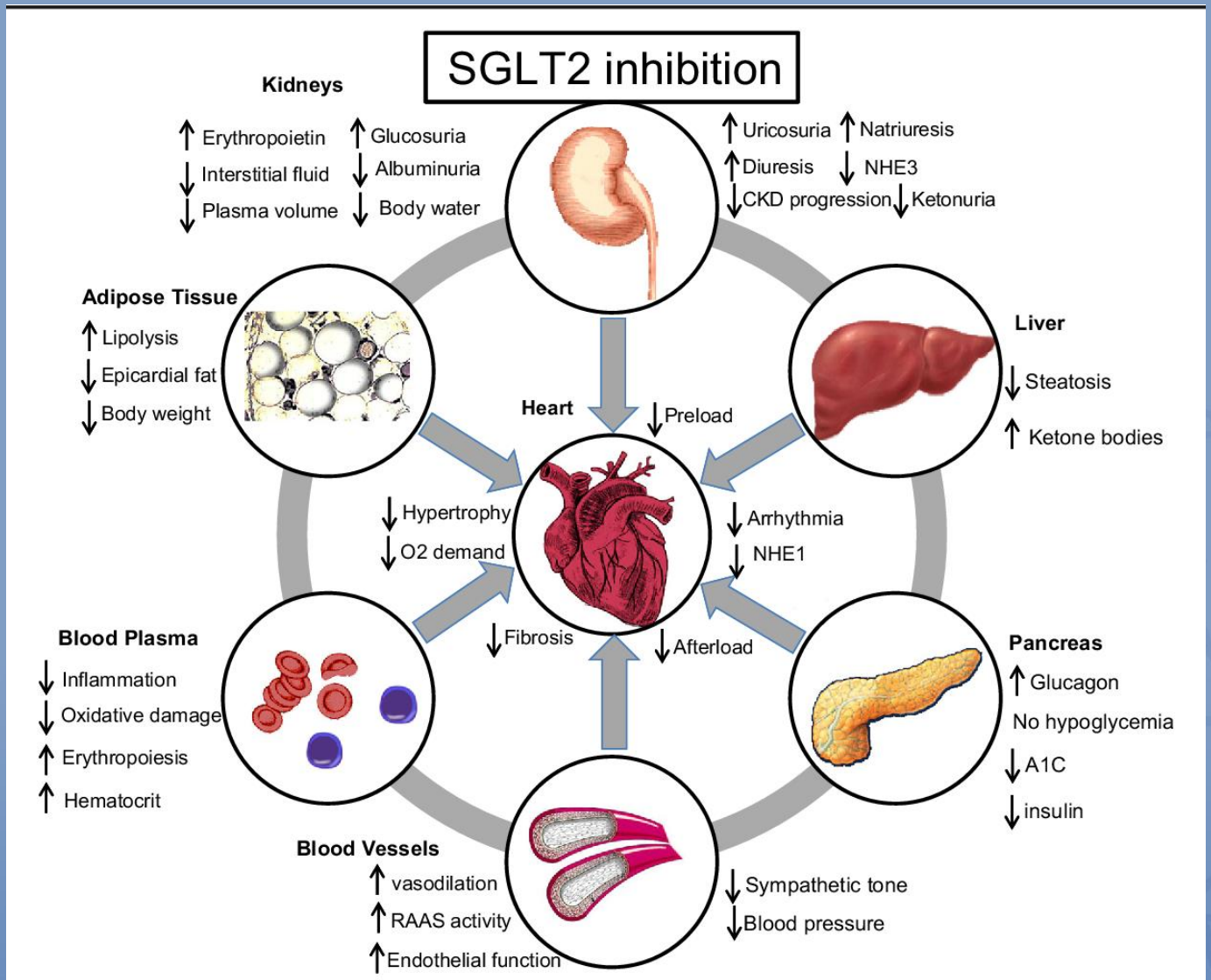
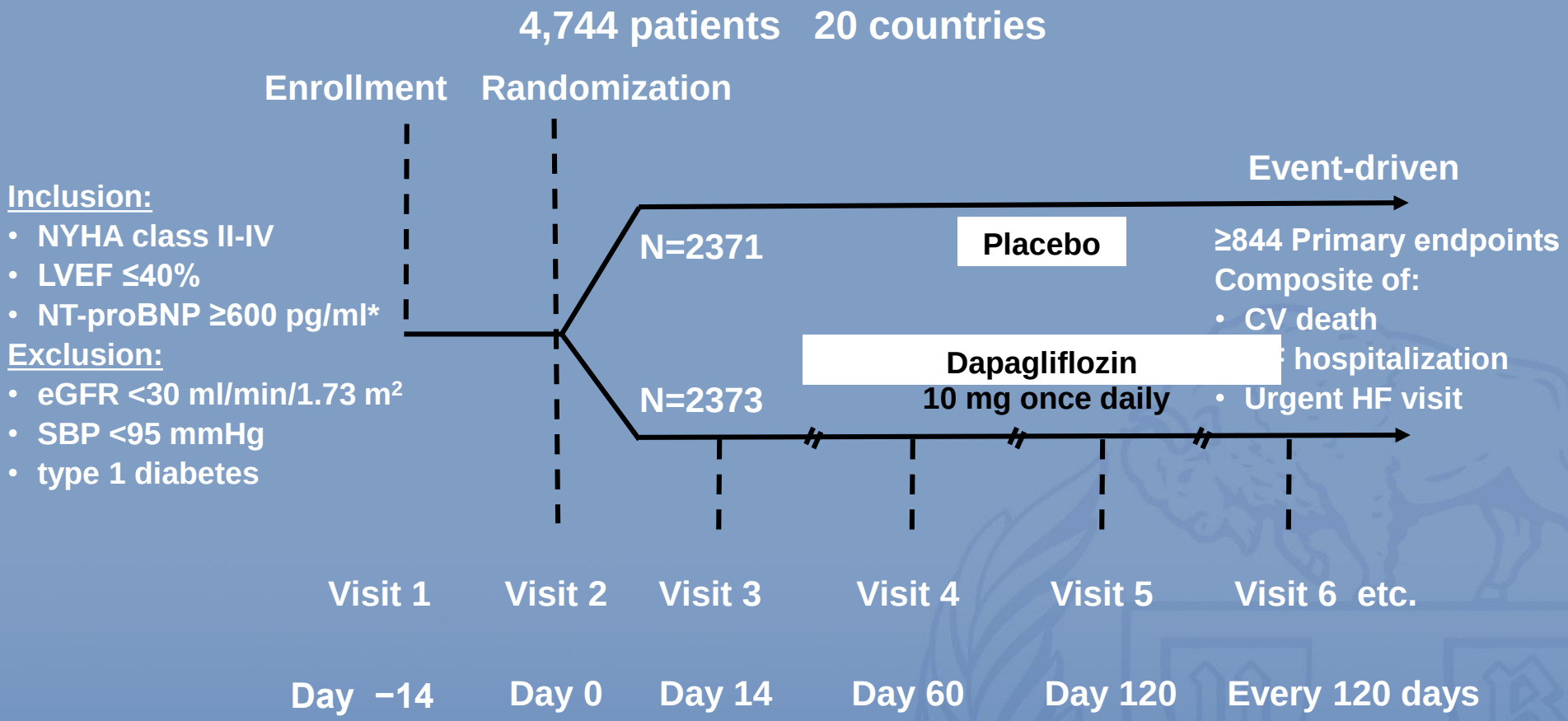


A schematic representation of the different mechanisms implicated in the cardiovascular benefits of SGLT2 inhibitors

Curr Cardiol Rep (2019) 21: 130

DAPA-HF Design



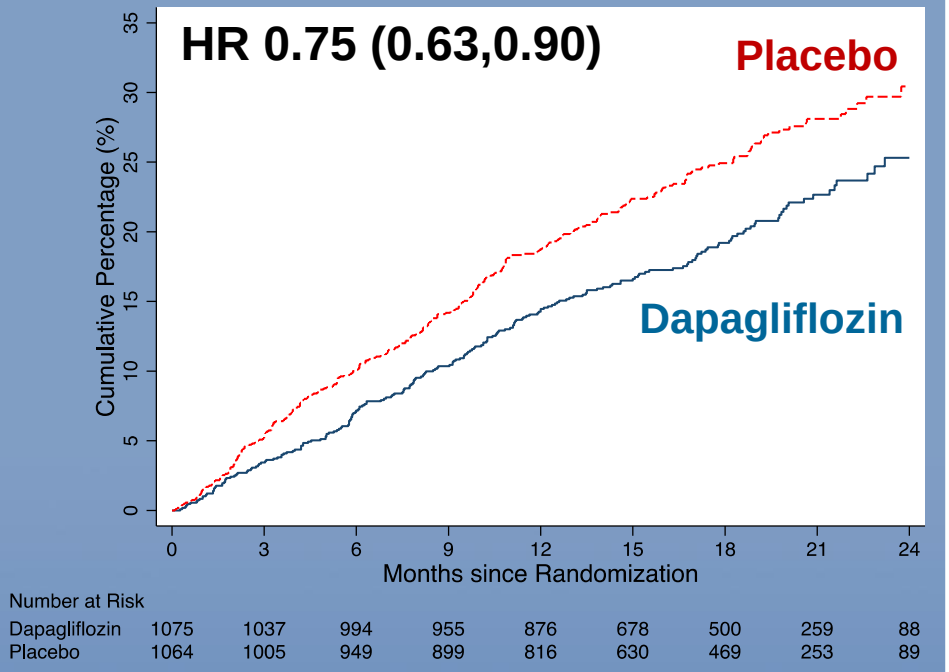
*≥400 pg/ml if HF hospitalization within ≤12 months; ≥900 pg/ml if atrial fibrillation/flutter

N Engl J Med (2019) 381: 1995-2008

Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

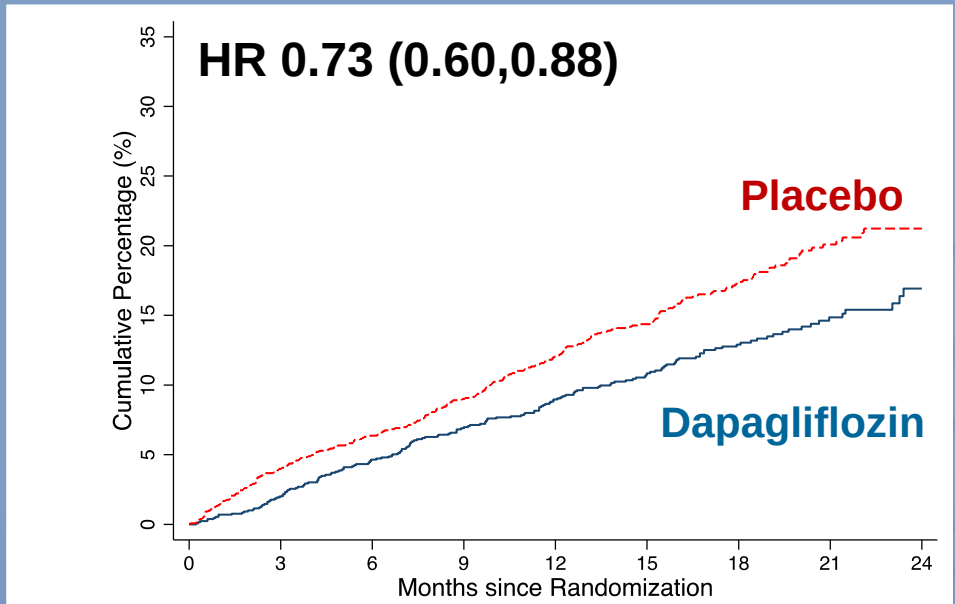
Diabetes



Number at Risk

Dapagliflozin	1075	1037	994	955	876	678	500	259	88
Placebo	1064	1005	949	899	816	630	469	253	89

No Diabetes



Number at Risk

Dapagliflozin	1298	1268	1227	1192	1126	882	646	353	122
Placebo	1307	1253	1214	1176	1101	848	627	340	121

SGLT2 Inhibition With Empagliflozin Is Effective in Heart Failure With a Reduced Ejection Fraction With or Without Diabetes

Primary Endpoint Composite of cardiovascular death or heart failure hospitalization	**25% ↓ in risk** **P < 0.001**
First Secondary Endpoint Total (first and recurrent heart failure hospitalizations)	**30% ↓ in risk** **P < 0.001**
Second Secondary Endpoint Slope of decline in glomerular filtration rate over time	**P < 0.001** **(50% ↓ in renal events)**

Also achieved success on composite renal endpoint, KCCQ clinical summary score,
and total number of hospitalizations for any reason (all nominal P < 0.01)

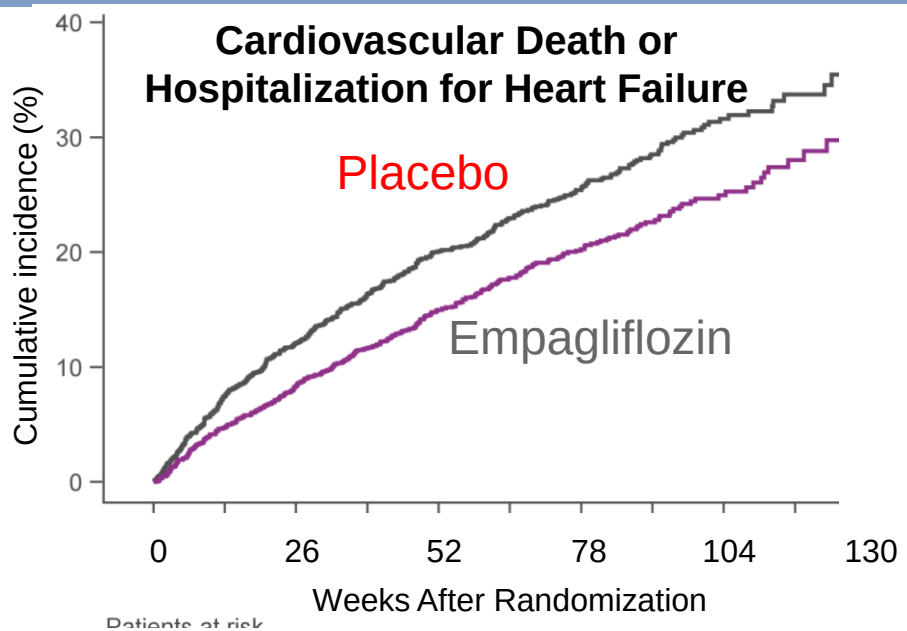
N Engl J Med (2020) 383: 1413-1424

EMPEROR-Reduced Trial

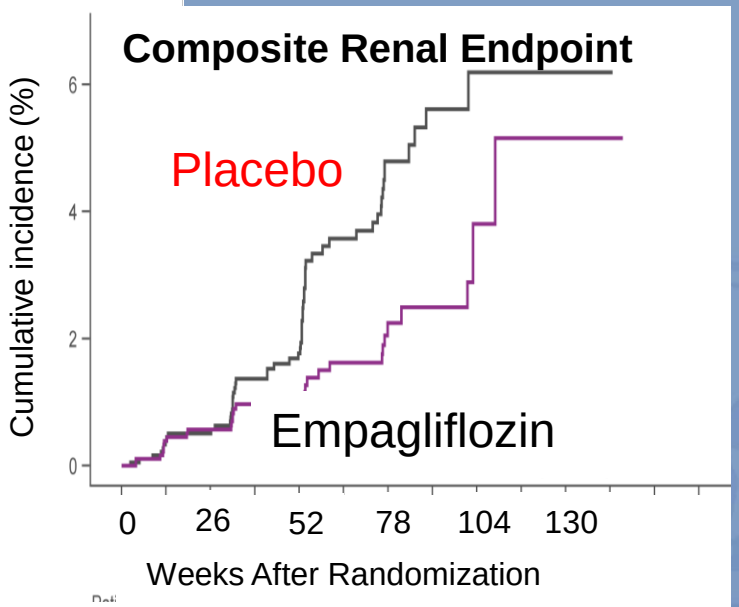
- Double-blind, placebo-controlled, randomized trial of 3730 patients in 565 centers in 20 countries
- Men and women with mild, moderate or severe heart failure due to poor systolic function of the left ventricle, who were already receiving all appropriate treatments for heart failure
- With and without type 2 diabetes (half did not have diabetes)
- Randomly assigned to placebo or empagliflozin 10 mg once daily, which was added to existing treatment. Study medication was continued for median of 16 months (up to 34 months)
- This was the second large-scale trial of a SGLT2 inhibitor in patients with a reduced ejection fraction. DAPA-HF previously reported positive results with dapagliflozin, but EMPEROR-Reduced trial studied many patients with more advanced disease.

N Engl J Med (2020) 383: 1413-1424

Empagliflozin Prevented Both Serious Heart Failure and Serious Kidney Failure Events



Hazard ratio 0.75 (25% reduction in risk)
(95% CI 0.65, 0.86), P < 0.0001



Hazard ratio 0.50 (50% reduction in risk)
(95% CI 0.32, 0.77), P = 0.0019

EMPEROR-Reduced: Safety

	Empagliflozin (n=1863)	Placebo (n=1863)
Serious adverse events	772 (41.4)	896 (48.1)
Related to cardiac disorder	**500 (26.8)**	**634 (34.0)**
Related to worsening renal function	**59 (3.2)**	**95 (5.1)**
Selected adverse events of interest		
Volume depletion	197 (10.6)	184 (9.9)
Hypotension	176 (9.4)	163 (8.7)
Symptomatic hypotension	106 (5.7)	103 (5.5)
Hypoglycemia	27 (1.4)	28 (1.5)
Ketoacidosis	0 (0.0)	0 (0.0)
Urinary tract infections	91 (4.9)	83 (4.5)
Genital tract infections	31 (1.7)	12 (0.6)
Bone fractures	45 (2.4)	42 (2.3)
Lower limb amputations	13 (0.7)	10 (0.5)

N Engl J Med (2020) 383: 1413-1424

EMPEROR-Reduced Trial Has Major Implications for Clinical Practice

The EMPEROR-Reduced trial with empagliflozin (when considered together with results from the DAPA-HF trial with dapagliflozin) will have a major impact on the management of patients with chronic heart failure and a reduced ejection fraction, whether or not they have diabetes.

SGLT2 inhibitors have clinically important benefits, are given once daily, require no dose adjustment, and are well tolerated.

There is now compelling evidence that SGLT2 inhibitors should now be added to currently recommended treatments for this disease.

Sacubitril/valsartan
Beta-blockers (e.g., carvedilol)
Spironolactone and eplerenone
Empagliflozin and dapagliflozin

N Engl J Med (2020) 383: 1413-1424

Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

Muthiah Vaduganathan, Brian L Claggett, Pardeep S Jhund, Jonathan W Cunningham, João Pedro Ferreira, Faiez Zannad, Milton Packer, Gregg C Fonarow, John J V McMurray, Scott D Solomon

Methods In this cross-trial analysis, we estimated treatment effects of comprehensive disease-modifying pharmacological therapy (ARNI, β blocker, MRA, and SGLT2 inhibitor) versus conventional therapy (ACE inhibitor or ARB and β blocker) in patients with chronic HFrEF by making indirect comparisons of three pivotal trials, EMPHASIS-HF (n=2737), PARADIGM-HF (n=8399), and DAPA-HF (n=4744). Our primary endpoint was a composite of cardiovascular death or first hospital admission for heart failure; we also assessed these endpoints individually and assessed all-cause mortality. Assuming these relative treatment effects are consistent over time, we then projected incremental long-term gains in event-free survival and overall survival with comprehensive disease-modifying therapy in the control group of the EMPHASIS-HF trial (ACE inhibitor or ARB and β blocker).

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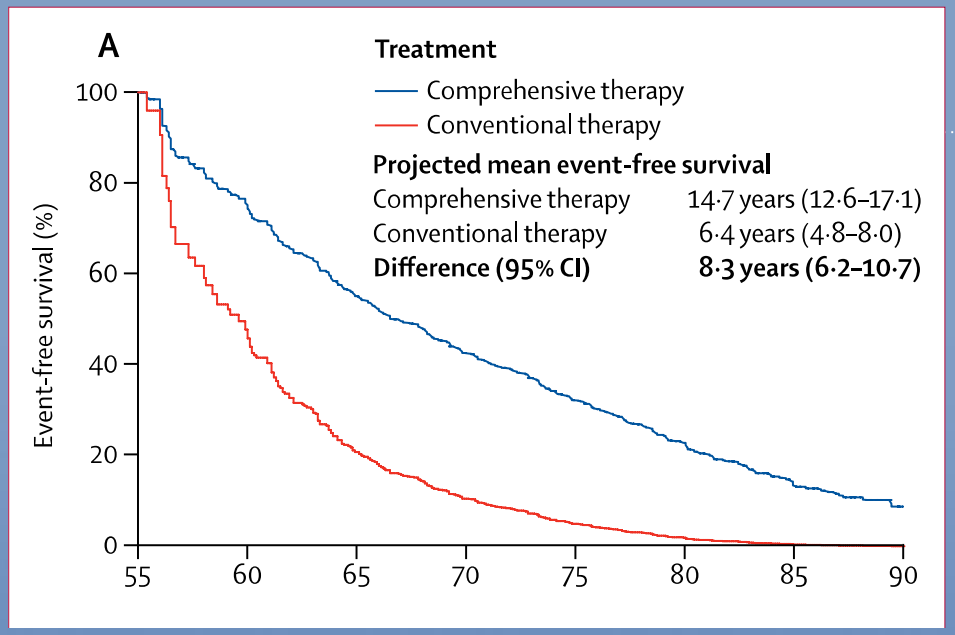

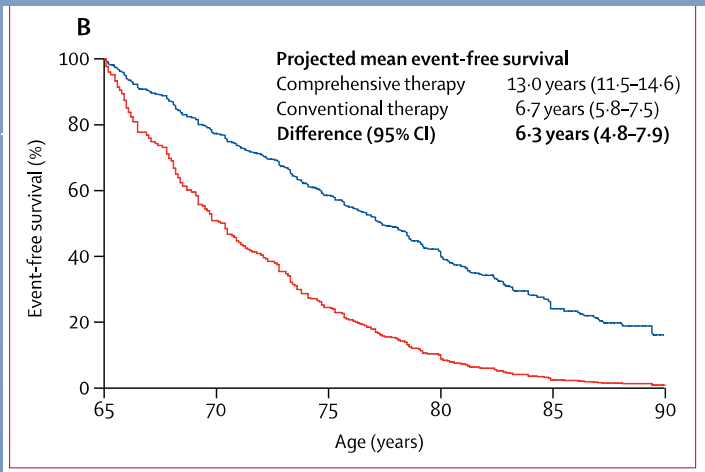

Figure 2: **Event-free survival with comprehensive disease-modifying therapy *vs* conventional therapy**

Kaplan-Meier estimated curves for patients starting at age 55 years (A) and 65 years (B) for primary endpoint event-free survival. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[6] control group) consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

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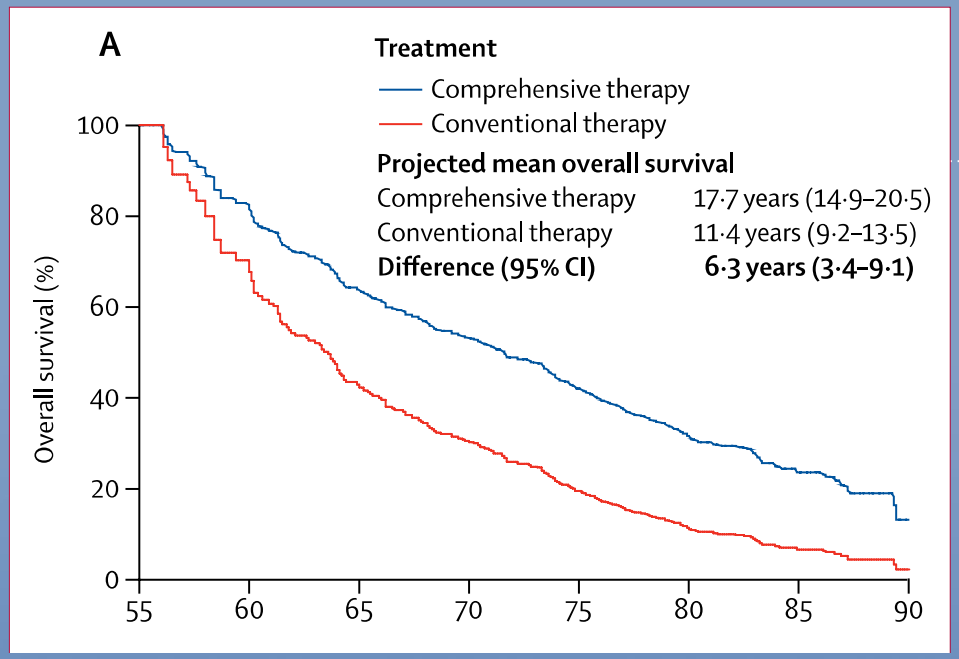

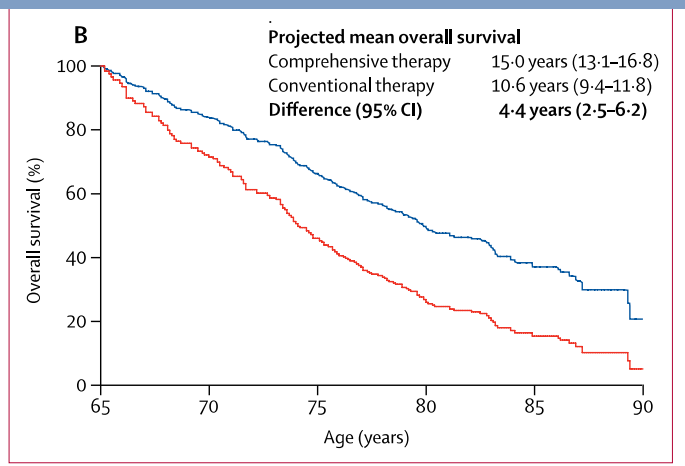

Figure 3: **Long-term overall survival with comprehensive disease-modifying therapy *vs* conventional therapy**
Kaplan-Meier estimated curves for patients starting at age 55 years (A) and 65 years (B) for overall survival. Residual lifespan was estimated using the area under the survival curve up to a maximum of 90 years. Comprehensive therapy (simulated) consisted of an ARNI, β blocker, MRA, and SGLT2 inhibitor; conventional therapy (EMPHASIS-HF[6] control group) consisted of an ACE inhibitor or ARB and β blocker. ACE inhibitor=angiotensin-converting enzyme inhibitor. ARB=angiotensin receptor blocker. ARNI=angiotensin receptor–neprilysin inhibitor. MRA=mineralocorticoid receptor antagonist. SGLT2 inhibitor=sodium/glucose cotransporter 2 inhibitor.

Illustrative Case

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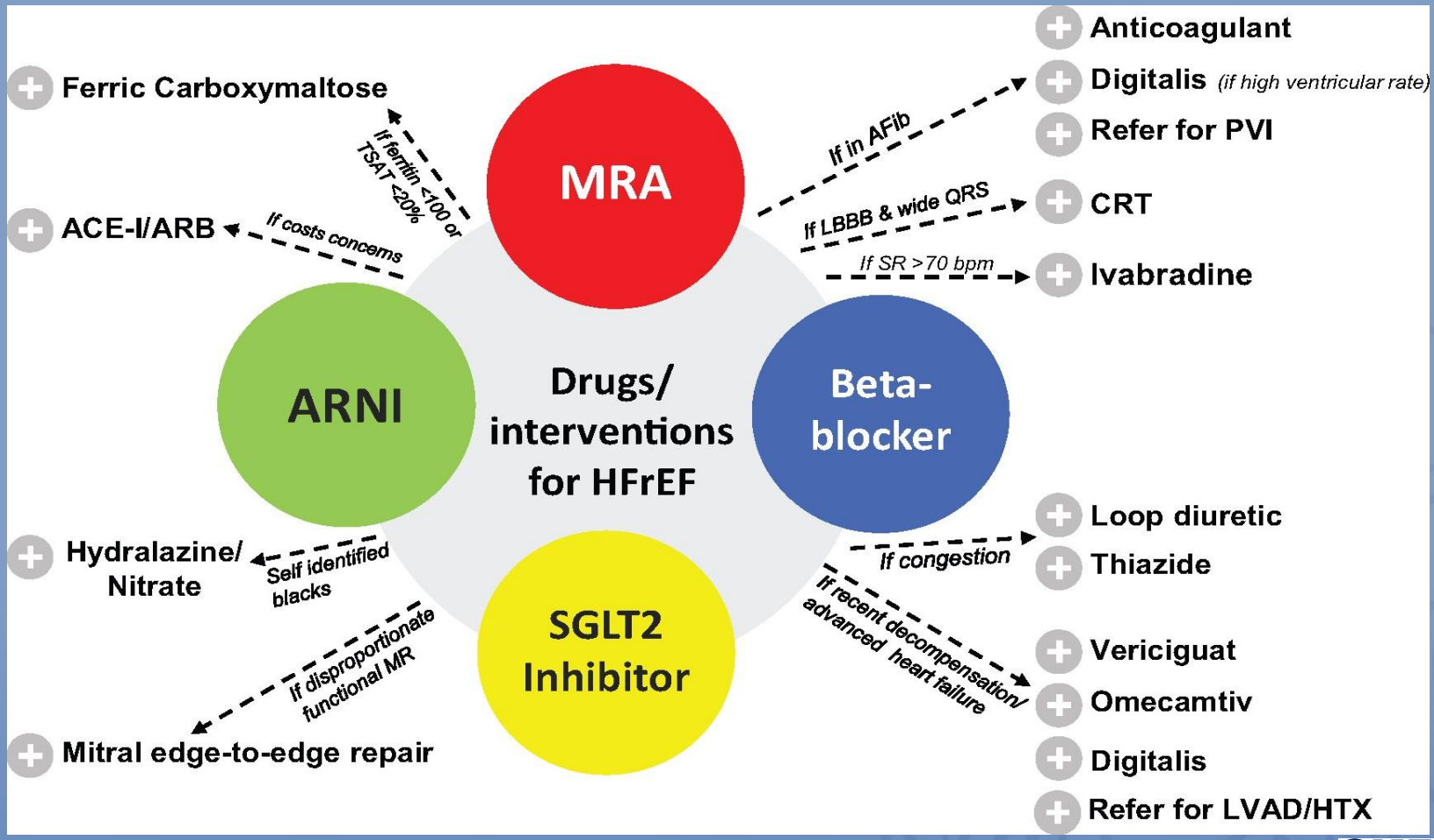
- She had LV EF 30-35% on echo in the ER no valvular heart disease noted. A repeat echo was obtained LV EF was 40-45% one month after ER visit.
- Na 135, Cr 1.09, eGFR > 60, Glu 122
- How could you change her medical therapy?

Illustrative Case-Changes to Medical Therapy

- Change Lisinopril to Entresto 24/26 mg BID
- Add Spironolactone or Eplerinone
- Consider addition of SGLT2 inhibitor if other changes well tolerated
- Encourage coronary angiography and exercise/weight loss program
- Cardiac rehabilitation to facilitate

Drug, interventional, and device treatment for heart failure with reduced ejection fraction (HFrEF)

ESC European Society of Cardiology



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Questions?

Thank you for your attention