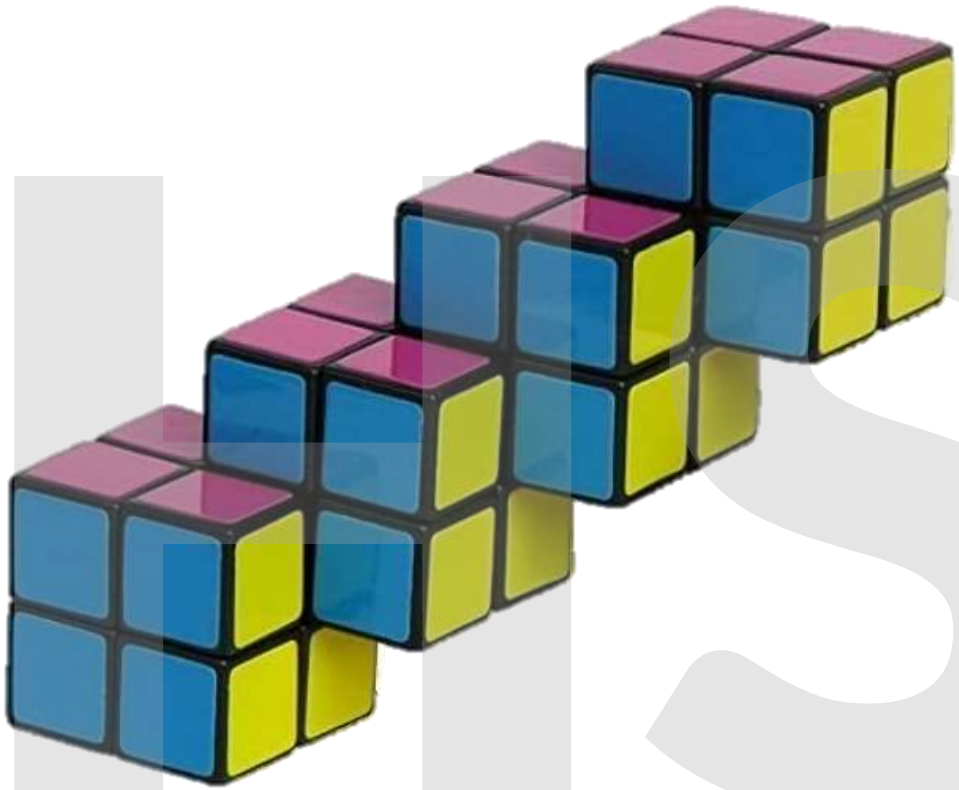
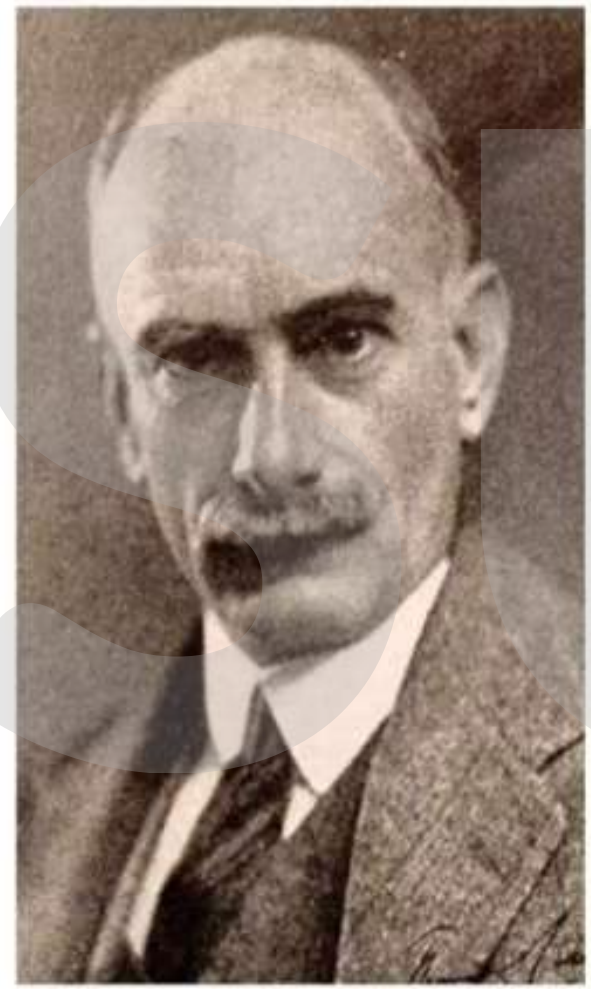
The Changing Paradigm: Implementation of Quadruple Therapy in HFrEF



Carrie Puckett, DO
Heart Failure Cardiologist
Portland VA Medical Center

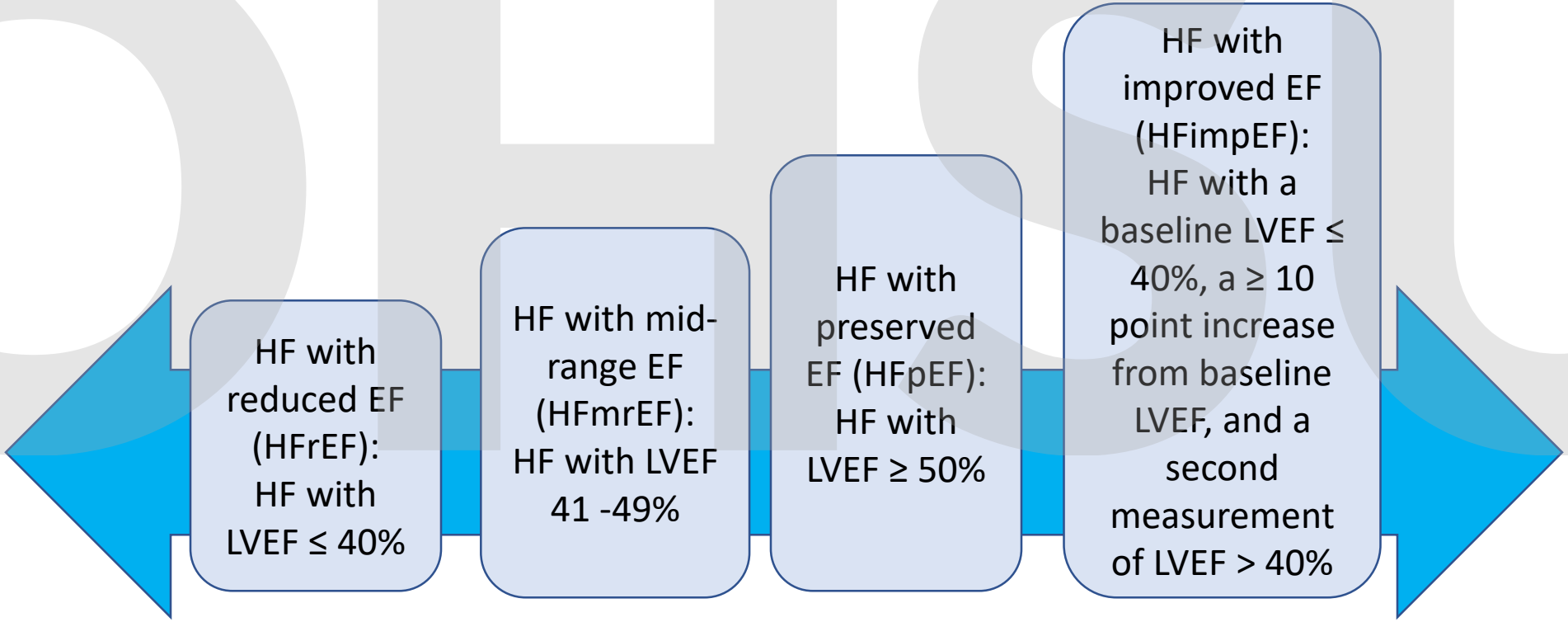
Harleen Singh, Pharm.D
Clinical Professor
UTEP School of Pharmacy

"The very essence of cardiovascular medicine is the recognition of early heart failure !



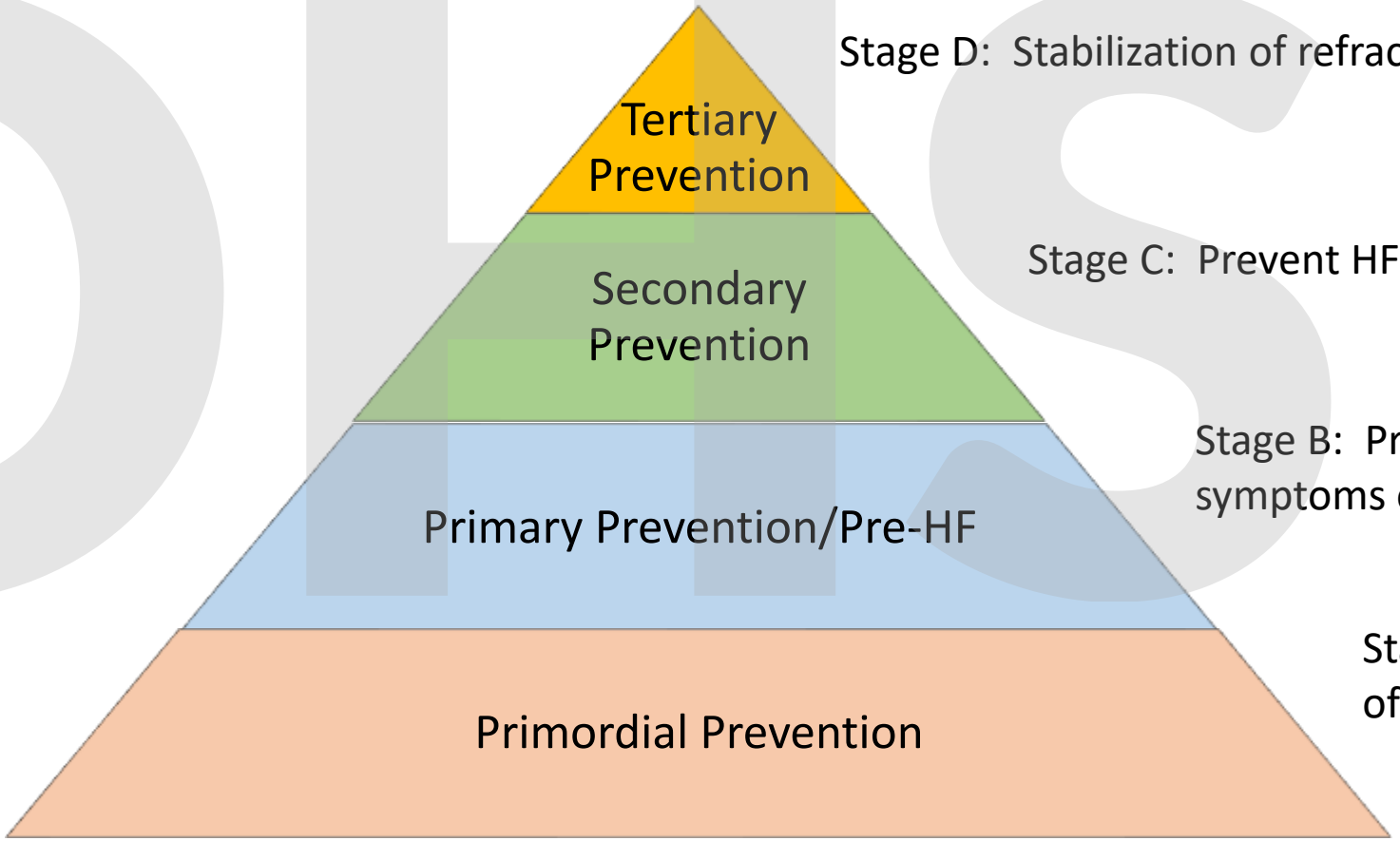
Sir Thomas Lewis 1881 –1945

Classification of Heart Failure Based on EF



Bozkurtet al. ESC 2021;23:352-380, Heidenreich et al. Circulation 2022;145:e895-e1032

Staging of HF



Stage D: Stabilization of refractory signs and symptoms

Stage C: Prevent HF readmissions

Stage B: Prevent signs and symptoms of HF

Stage A: Prevent development of HF risk factors

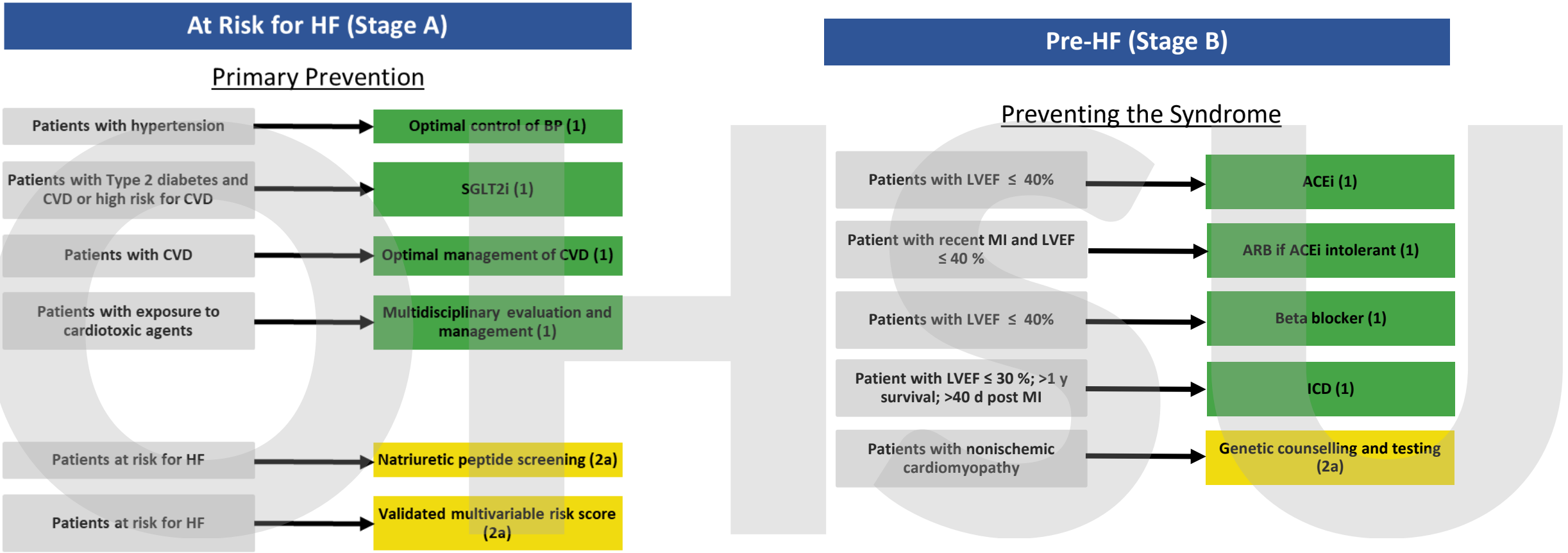
Heidenreich PA et al. J Am Coll Cardiol. 2022;79(17):e263-e421

Trajectory Of Heart Failure

New onset / de novo HF:	Worsening HF:	Improving HF:	Persistent HF:	HF in Remission:
• Newly diagnosed HF • No former history of HF	• Worsening symptom/signs/ functional capacity, and/or requiring escalation of therapies such as IV or other advanced therapies and/or hospitalization	• Improving symptoms/signs and or functional capacity	• Persistent HF with ongoing symptoms/signs and or limited functional capacity	• Resolution of symptoms and signs of HF, with resolution of previous structural/functional heart disease after a phase of symptomatic HF
			Do not use "Stable HF", instead, use "Persistent"	Do not use "Recovered HF" instead, use "HF in Remission"

Heidenreich PA et al. J Am Coll Cardiol. 2022;79(17):e263-e421

Recommendations for Patients at Risk of HF & Pre-HF

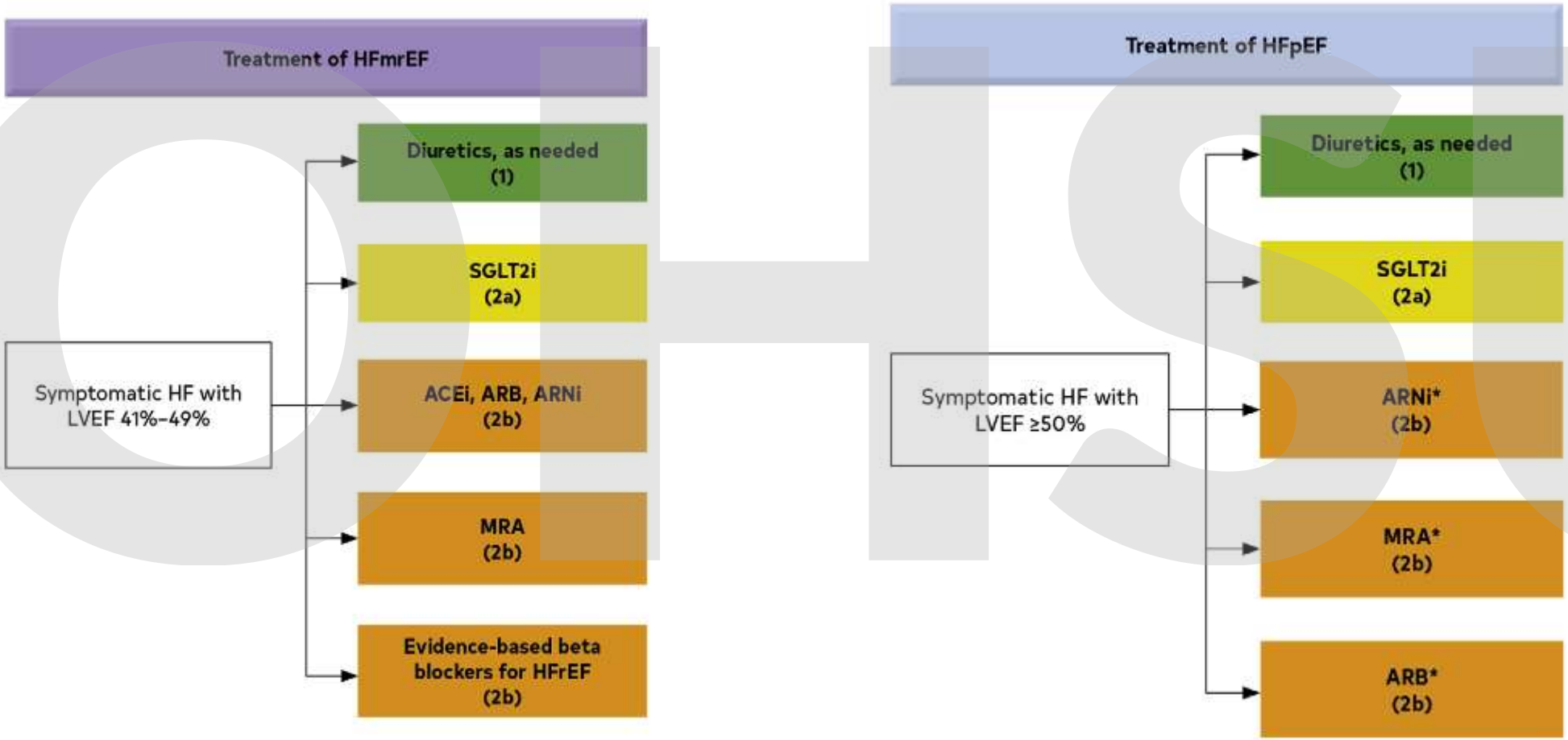


Continue Lifestyle modification and management strategies implemented in Stage A, through Stage B

Abbreviations: ACEi indicates angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; CVD, cardiovascular disease; HF, heart failure; ICD, implantable cardioverter-defibrillator; LVEF, left ventricular ejection fraction; MI, myocardial infarction; and SGLT2i, sodium glucose cotransporter 2 inhibitor.

Heidenreich PA et al. J Am Coll Cardiol. 2022;79(17):e263-e421

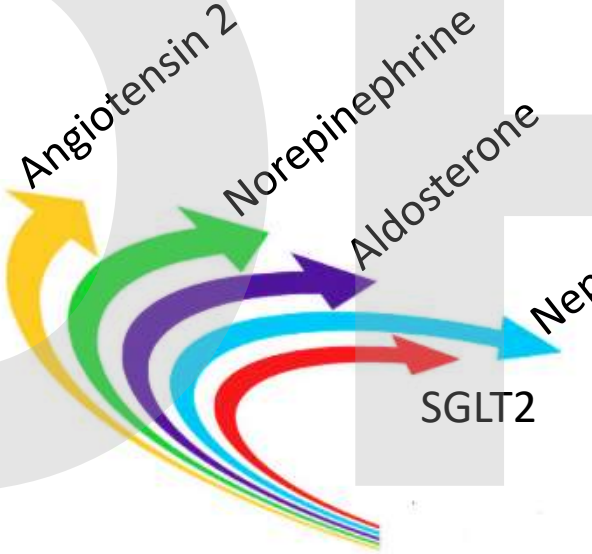
AHA/ACC/HFSA Heart Failure 2022 Guideline



Heidenreich PA et al. J Am Coll Cardiol. 2022;79(17):e263-e421

Targets for HFrEF Pharmacotherapy

5 Pathways



4 Drug Classes

ARB

ACEi

ARNI

BB

MRA

SGLT2i

3 More Drugs

Ivabradine

Hydralazine\ISDN

Vericiguat

Management of HFrEF (Stage C)

STEP 1: Initiation of Quadruple therapy*

- **ARNi /ACEI or ARB**
- **Evidence-based BB**
- **MRA**
- **SGLT2i**

Diuretics for volume management as needed

STEP 2: Titrate to target/max tolerated doses once all classes of medications are initiated

STEP 3: Reassess symptom control and LV function and consider additional therapies

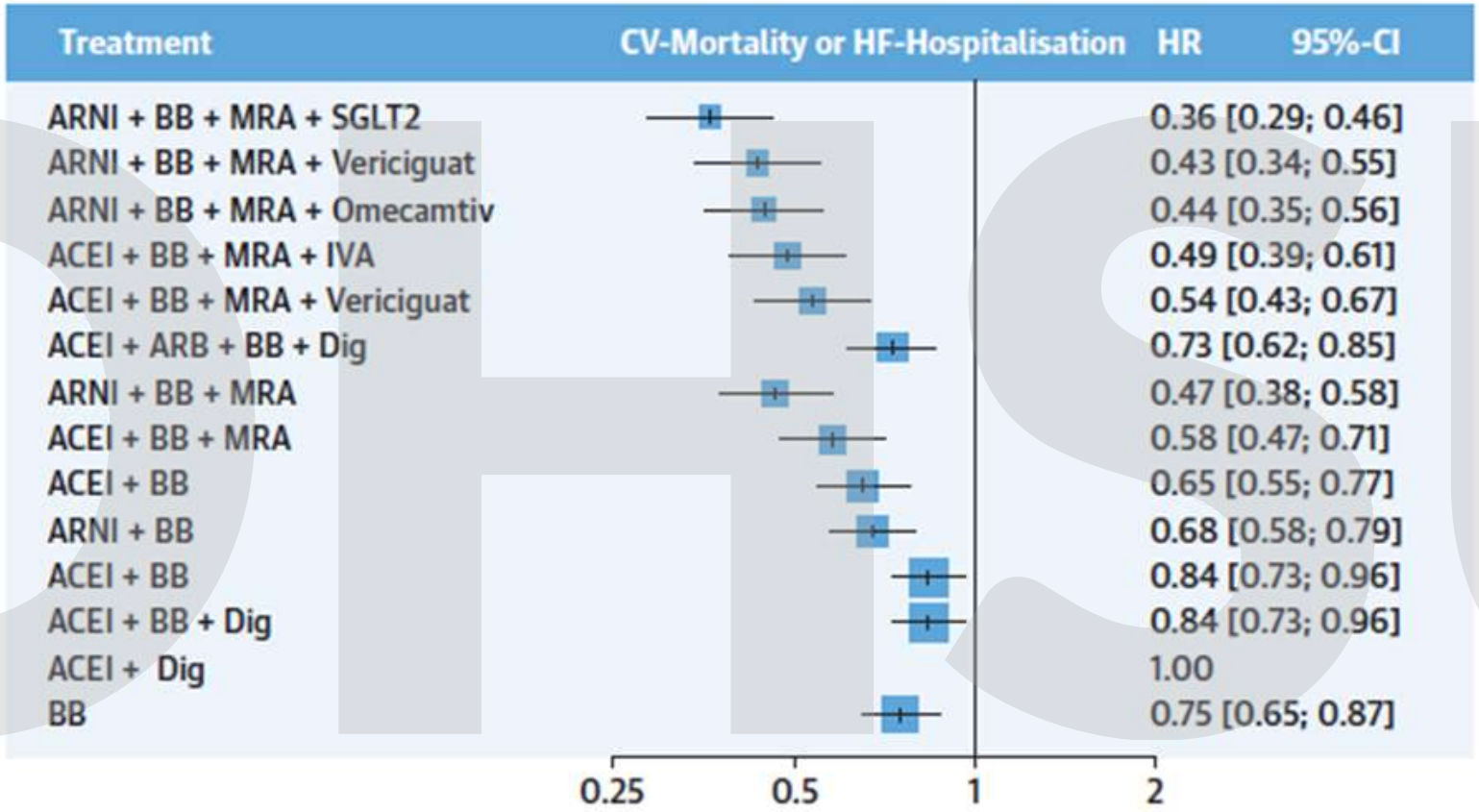
- **Hydralazine/ISDN**
  NYHA FC III-IV African American population
- **Ivabradine**
  NYHA FC II-III in NSR on max tolerated BB with HR > 70 bpm
- **Vericiguat**
  High risk NYHA FC II-IV patients with recent HF hospitalization
- **Digoxin**
  Symptomatic HF

*Medications can be started simultaneously initially (low) doses
OR
Alternatively, therapy may be started sequentially with sequence guided by patient-specific factors (without need to achieve target doses before initiating next medication)

Heidenreich PA et al. J Am Coll Cardiol. 2022;79(17):e263-e421

ARNI= angiotensin receptor neprilysin inhibitor, ACEi= angiotensin-converting enzyme inhibitor ARB, angiotensin receptor blocker, BB = beta-blocker, ISDN=isosorbide dinitrate, LVEF= left ventricular ejection fraction, MRA= mineralocorticoid receptor antagonist, NYHA= New York Heart Association, SGLT2i=sodium-glucose cotransporter2 inhibitor

Relative Risk Reduction of Combination GDMT

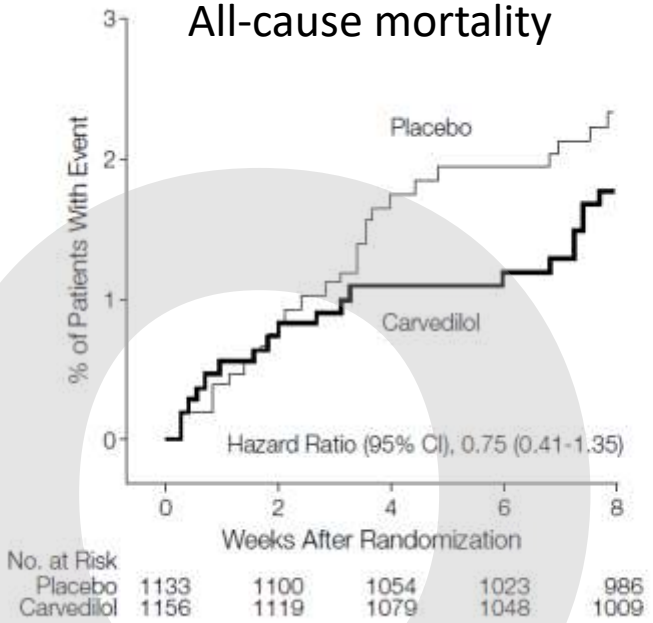


Cumulative risk reduction if all evidence based medical therapies are used: RRR 74% ARR 25.9% NNT 3.9 within 24 months to save one life.

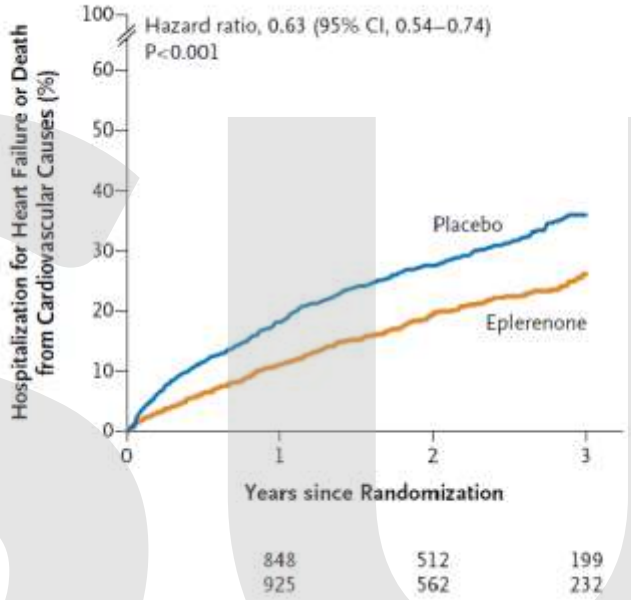
Tromp, J. et al. J Am Coll Cardiol HF. 2022;10:73-84

Timing of GDMT Benefits in HFrEF

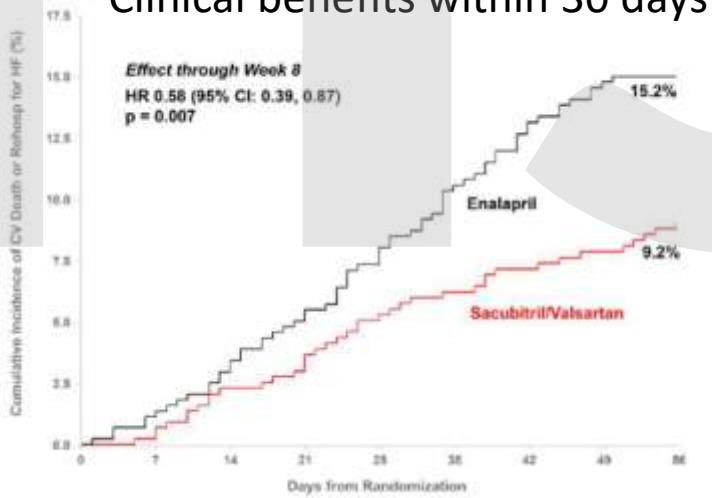
All-cause mortality



Clinical benefits within 30 days

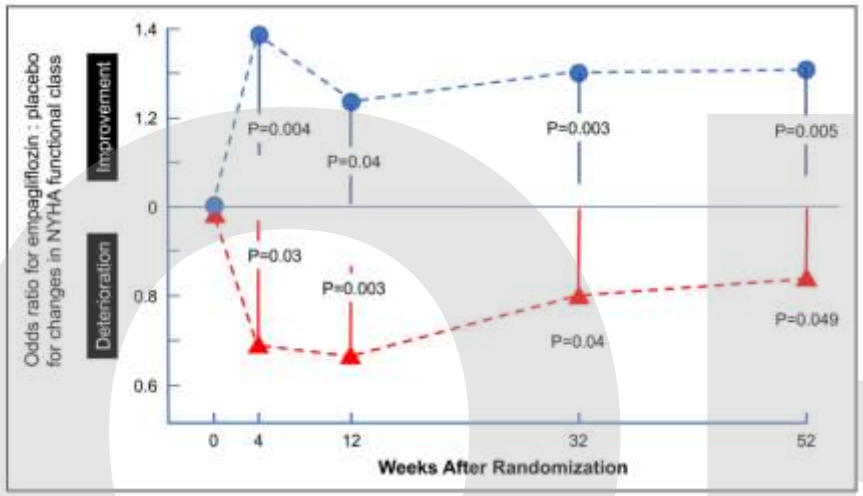


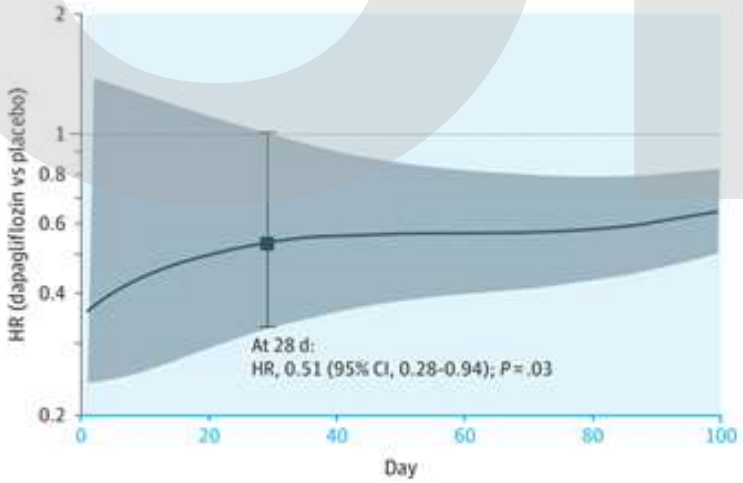
Clinical benefits within 30 days



Zannad F et al. N Engl J Med. 2011; 364:11-21; Morrow et al. *Circulation.* 2019;139:00–00; Krum H et al. JAMA. 2003;289:712-718

Timing of GDMT Benefits in HFrEF





EMPEROR- REDUCED

Combined risk of death, hospitalization for HF or an emergent/urgent HF visit; HR 0.76, 95% CI: 0.67-0.87), P <0.0001.

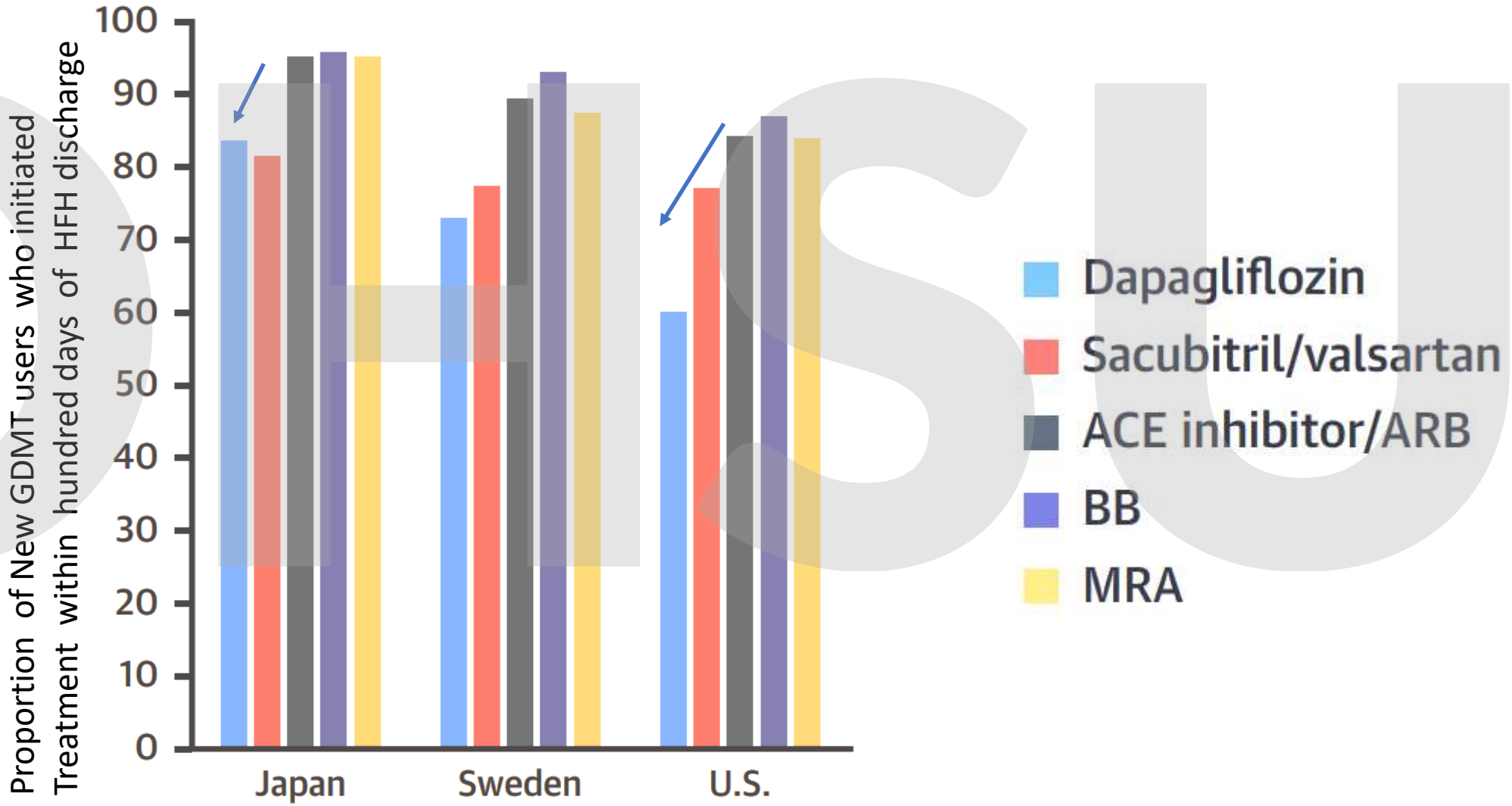
This benefit reached statistical significance at 12 days after randomization.

DAPA-HF

CV death or Hospitalization for HF or an Urgent HF visit
49% reduction in events by Day 28

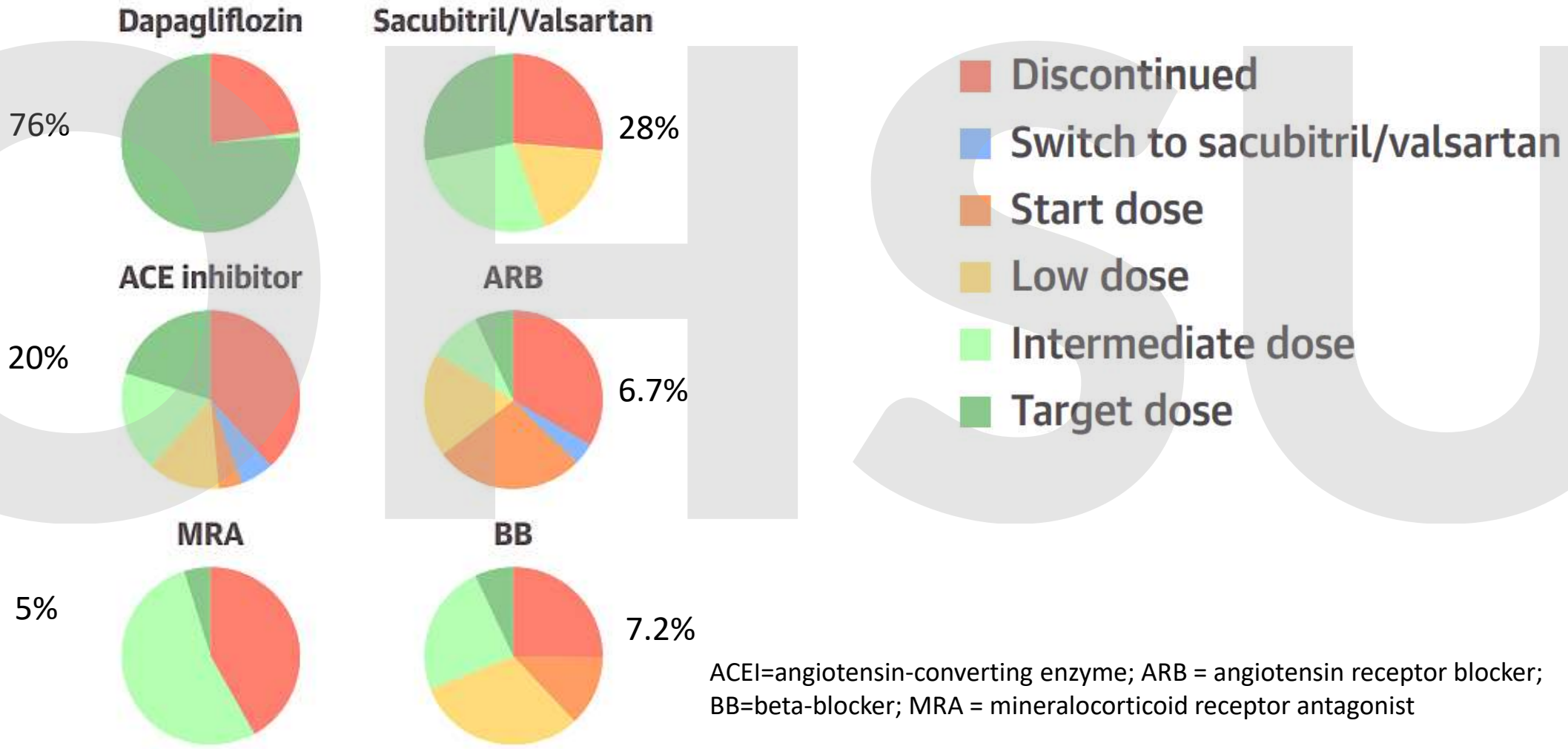
Berg DD, et al. JAMA.Cardiol ; 2021:e207585

A Multinational Observational Study: Initiation of Novel GDMT



Savarese G et al. J Am Coll Cardiol HF. 2023;11(1):1–14.

Target Doses Achieved Vs Discontinuation Rates



ACEI=angiotensin-converting enzyme; ARB = angiotensin receptor blocker; BB=beta-blocker; MRA = mineralocorticoid receptor antagonist

Savarese G, et al. J Am Coll Cardiol HF. 2023;11(1):1–14.

Challenges for Achieving Optimal Therapy in HF

- So little BP, so many drugs
- Impaired renal function
- Electrolyte imbalance and intolerance
- Multiple comorbidities
- Clinical inertia

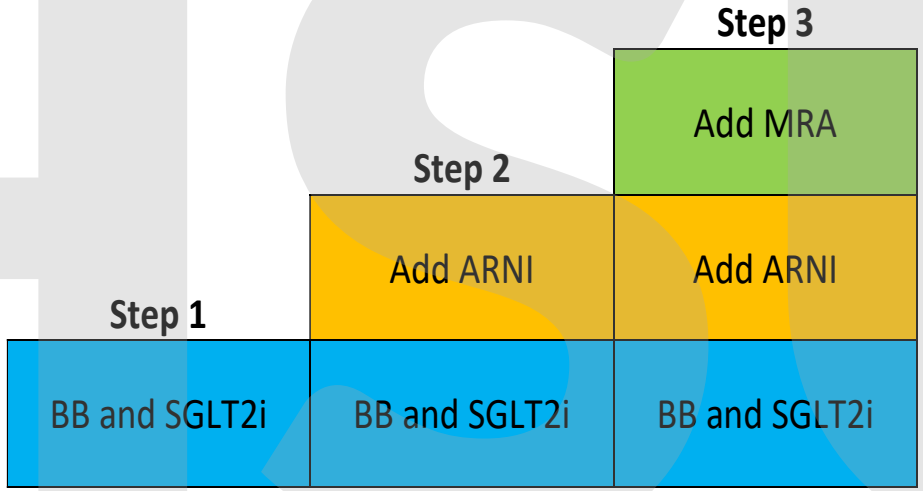
Conventional Sequencing Vs 3 Step Sequencing GDMT In HFrEF

All steps achieved within 4 weeks and up-titrated as tolerated

Conventional Sequencing

- Step 1: ACEi/ARB
- Step 2: Beta Blocker
- Step 3: MRA
- Step 4: ARNI
- Step 5: SGLT2i

6 months to reach GDMT



ARNI = angiotensin receptor neprilysin inhibitor, HFmrEF = heart failure with mildly reduce ejection fraction, MRA = mineralocorticoid receptor antagonist, SGLT2i = sodium-glucose co-transporter 2 inhibitor, HFrEF = heart failure with reduced reduce ejection

Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. *Eur J Heart Fail*. 2021;23(6):882-894.

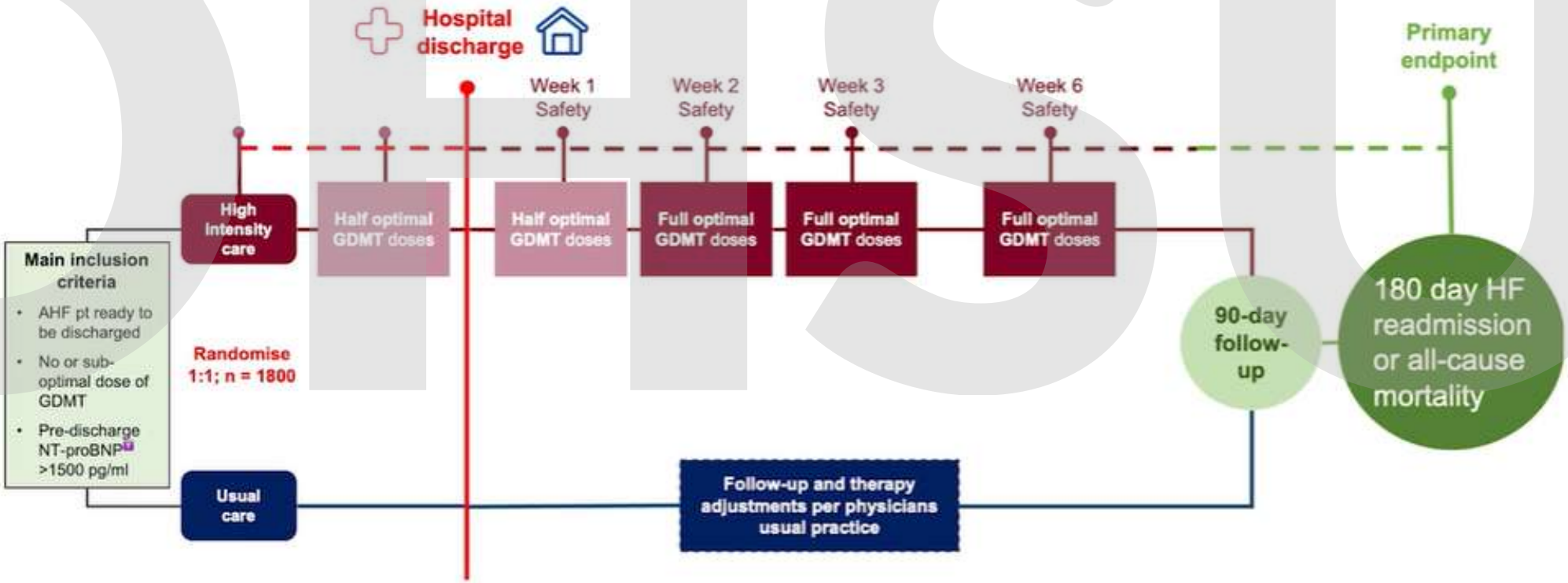
Table 3: Suggested sequencing of Guide Directed Medical Therapy				
	ARNI	BB*	MRA	SGLT2i
Day 1	Initiate low dose**	Initiate low dose	Initiate low dose	Initiate
Week 1-2	Continue	Titrate as tolerated	Continue	Continue
Week 2-4	Titrate as tolerated	Titrate as tolerated	Titrate as tolerated	Continue
Week 3-6	Titrate as tolerated	Titrate as tolerated	Continue	Continue
Beyond week 6	Continue	Continue	Continue	Continue

*beta-blocker up-titration prioritized.

ACEi = angiotensin converting enzyme inhibitor; ARB= angiotensin receptor blocker; ARNI=angiotensin recpetor neprilysin inhibitor; MRA=mineralocorticoid receptor antagonist; and SGLT2= sodium-glucose cotransporter 2, BP=Blood pressure, K=Potassium, eGFR = estimated glomerular filtration rate,

Greene SJ, Butler J, Fonarow GC. Simultaneous or Rapid Sequence Initiation of Quadruple Medical Therapy for Heart Failure-Optimizing Therapy With the Need for Speed. *JAMA Cardiol*. 2021;6(7):743-744.

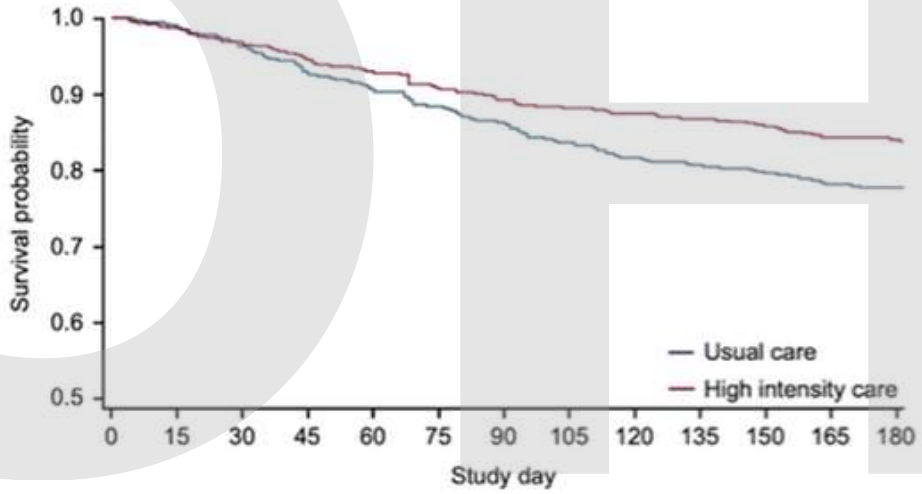
Is Rapid Up-Titration of GDMT Effective and Safe?



Mebazaa A et al. Lancet.2022

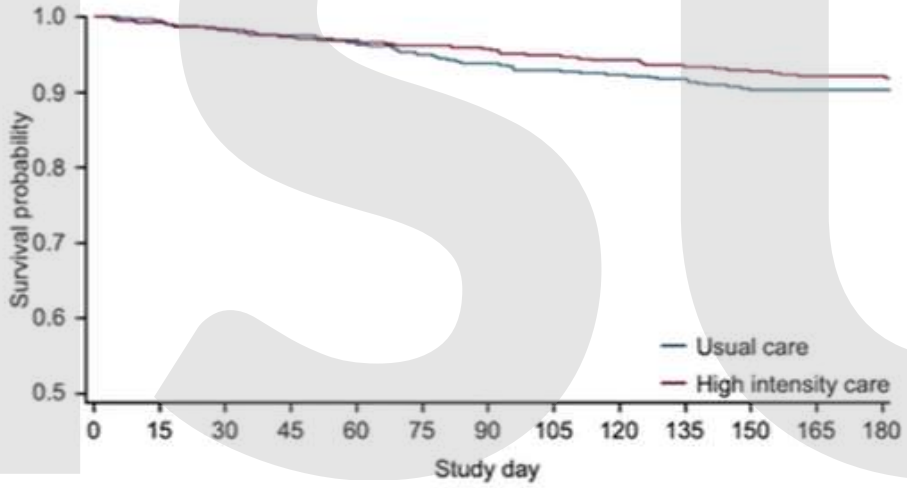
Primary Endpoint

All–cause death or HF readmission through day 180



180-day RD 7.3%, 95% CI: 2.4–12.1; p=0.0034

All- cause mortality through day 180

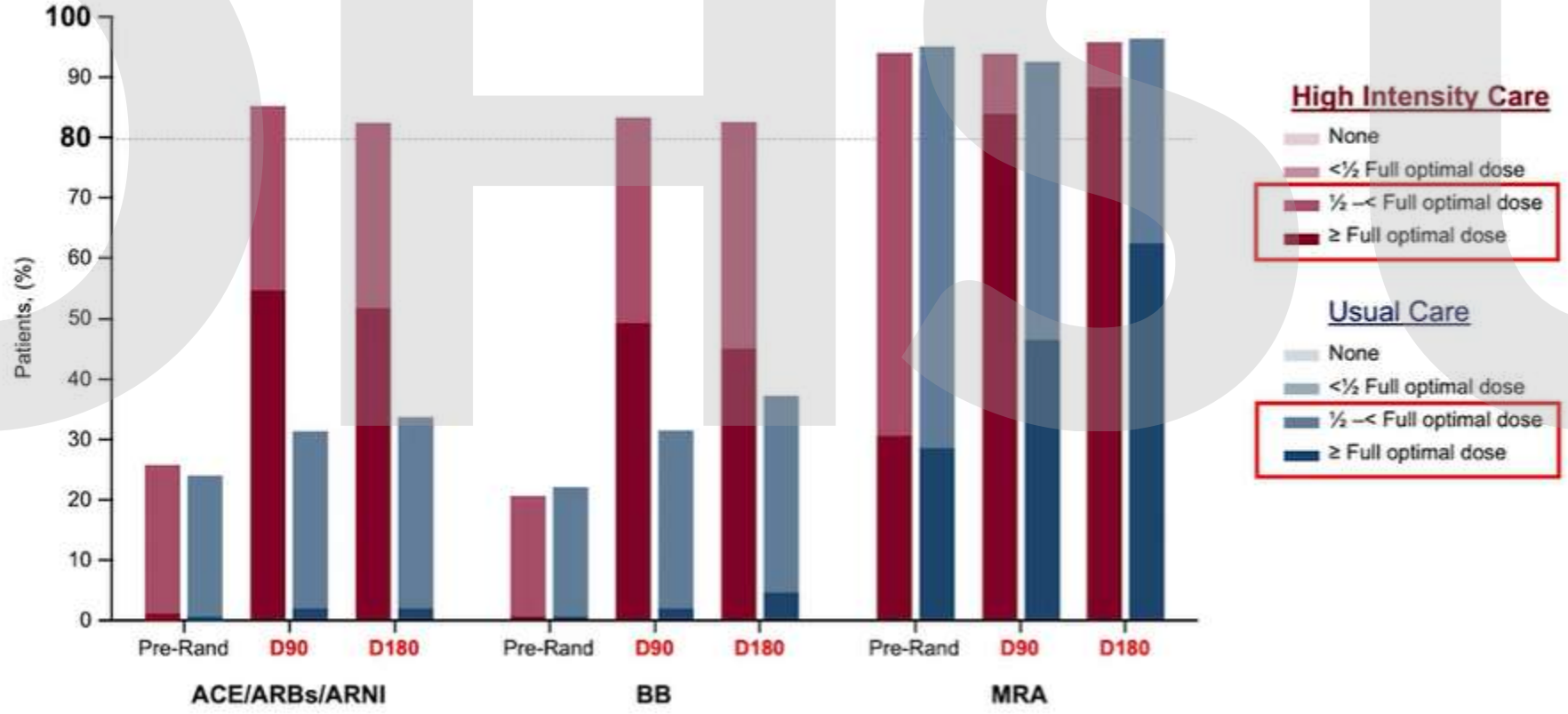


180-day RD 1.9%, 95% CI: 1.7–5.5; p=0.3068

Mebazaa A et al. Lancet.2022

Achieving Target doses

More than 80% of high intensity care: 1/2 to full dose of GDMT



Mebazaa A et al. Lancet.2022

CASE1

LM is a 64-year-old male with a past medical history significant for HFrEF (LVEF 27%), T2DM, hypertension, stage 3b CKD hyperlipidemia (LDL -c55mg/dL) and obesity (BMI 36.8kg/m^2) who presents for a follow up visit with the HF clinic. His physical exam reveals jugular vein distension 9cm H_2O and 1+bilateral pedal edema.

Medications
-Metoprolol succinate 150 mg daily -Sacubitril/valsartan49/51 bid -Rosuvastatin 20mg daily -Furosemide 20 mg daily -Aspirin 81mg daily -Metformin SA 1000 mg/day (max tolerated dose) -Glipizide XR 20mg daily

Vitals	
BP	136/84
EF	27%
Pulse	73bpm

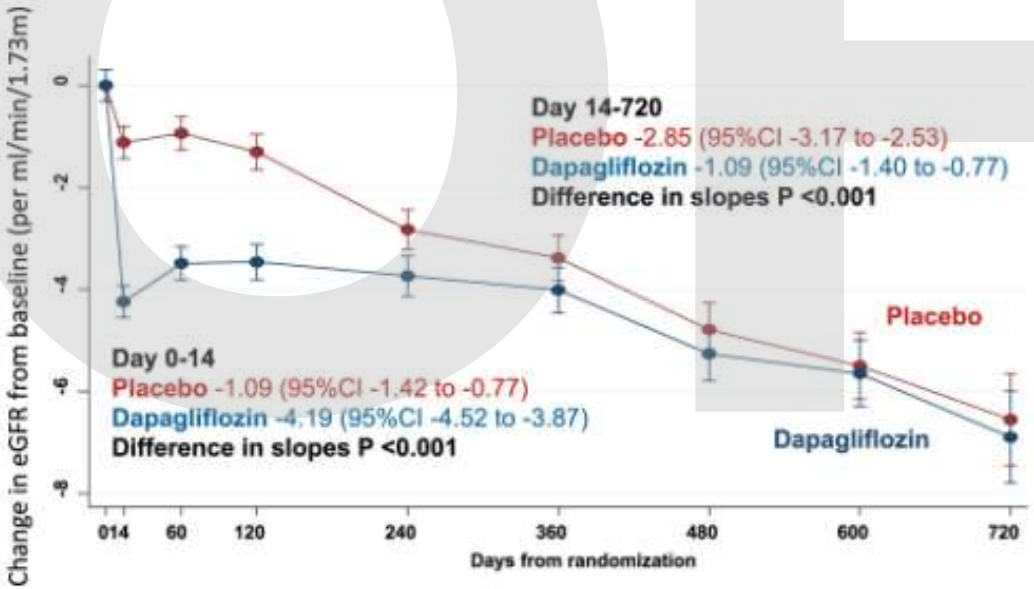
Labs (most recent)
Scr: 1.5mg/dL eGFR: 38 mL /min/1.73m A1c: 7.5% K 5.2meq/L JVP 9cm H_20

Which one of the following is the best to recommend for this patient?

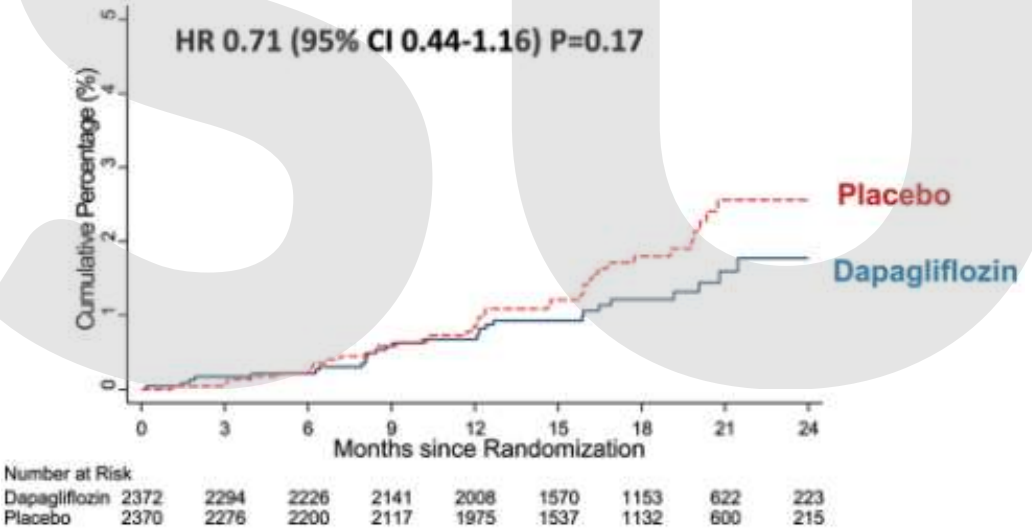
A. Initiate empagliflozin 10 mg daily.
B. Increase metoprolol succinate 200 mg daily.
C. Initiate spironolactone 25 mg daily.
D. Titrate sacubitril/valsartan 97/103 mg twice daily.

SGLT2i HF Trials: DAPA-HF

Effect of dapagliflozin on change in eGFR from Baseline



Effect of dapagliflozin on the prespecified renal composite outcome

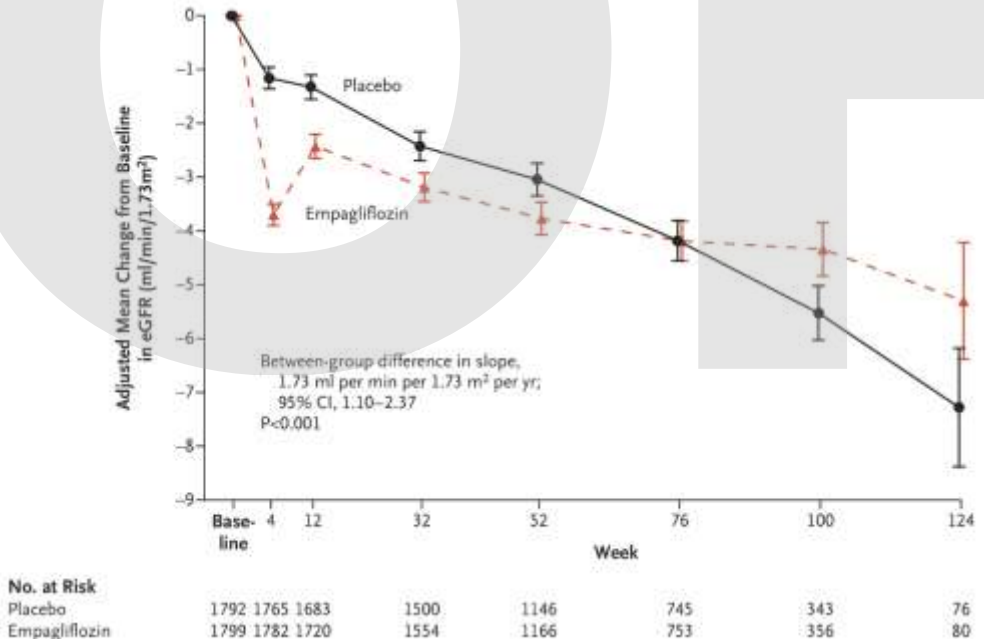


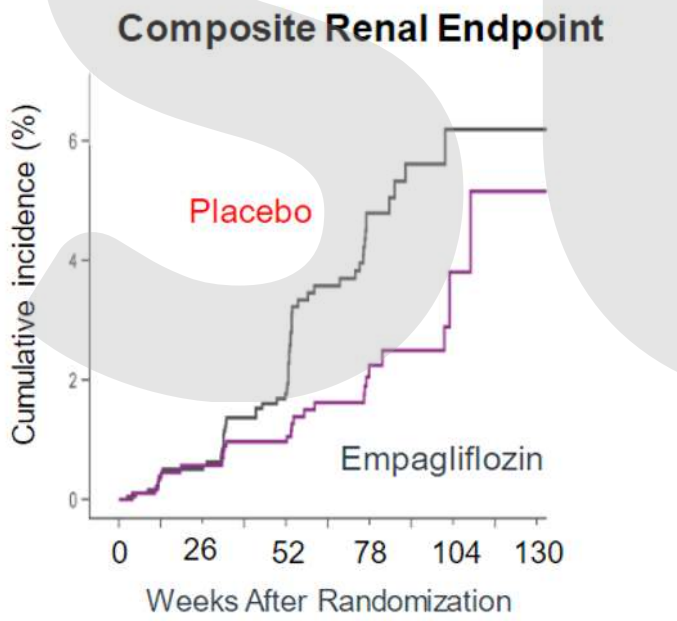
Jhund Ps et al. Circulation .2021;143:298-309

SGLT2i HF Trials: EMPEROR-Reduced

Over 16 months eGFR deteriorated by

-4.2ml/min/1.73m2 placebo vs -0.9 ml/min/1.73m^2 on empagliflozin (p<0.0001)



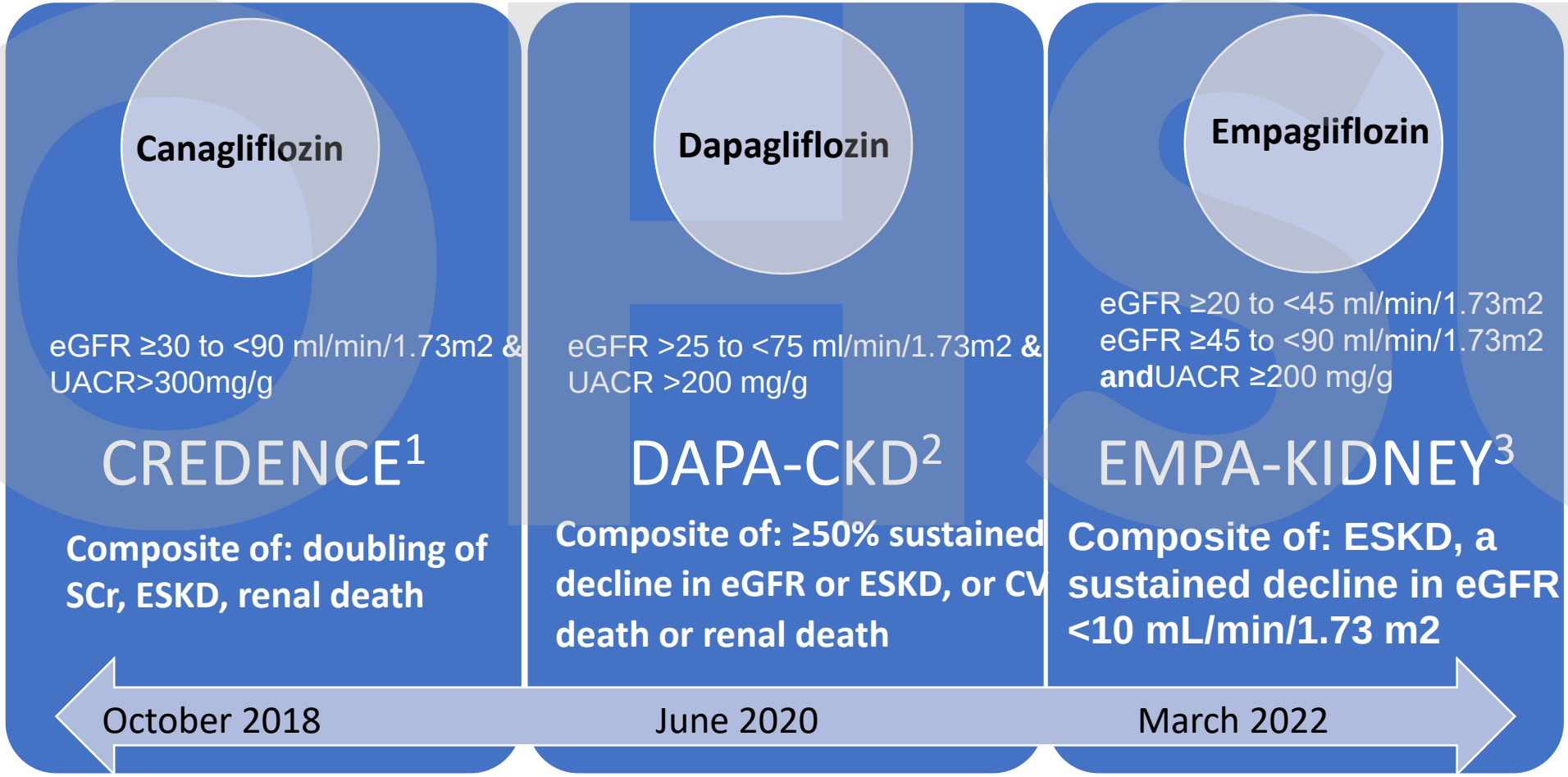


RRR 50%
ARR 1.5%

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

Packer M et al. N Engl J Med 2020;383:1413-24.

Kidney Outcomes in SGLT2i



1.Perkovic et al. NEJM. June 13, 2019 2.Heerspink HJL et al. N Engl J Med 2020;383:1436-46.3. Herrington Wget.al N Engl J Med 2023; 388:117-127.

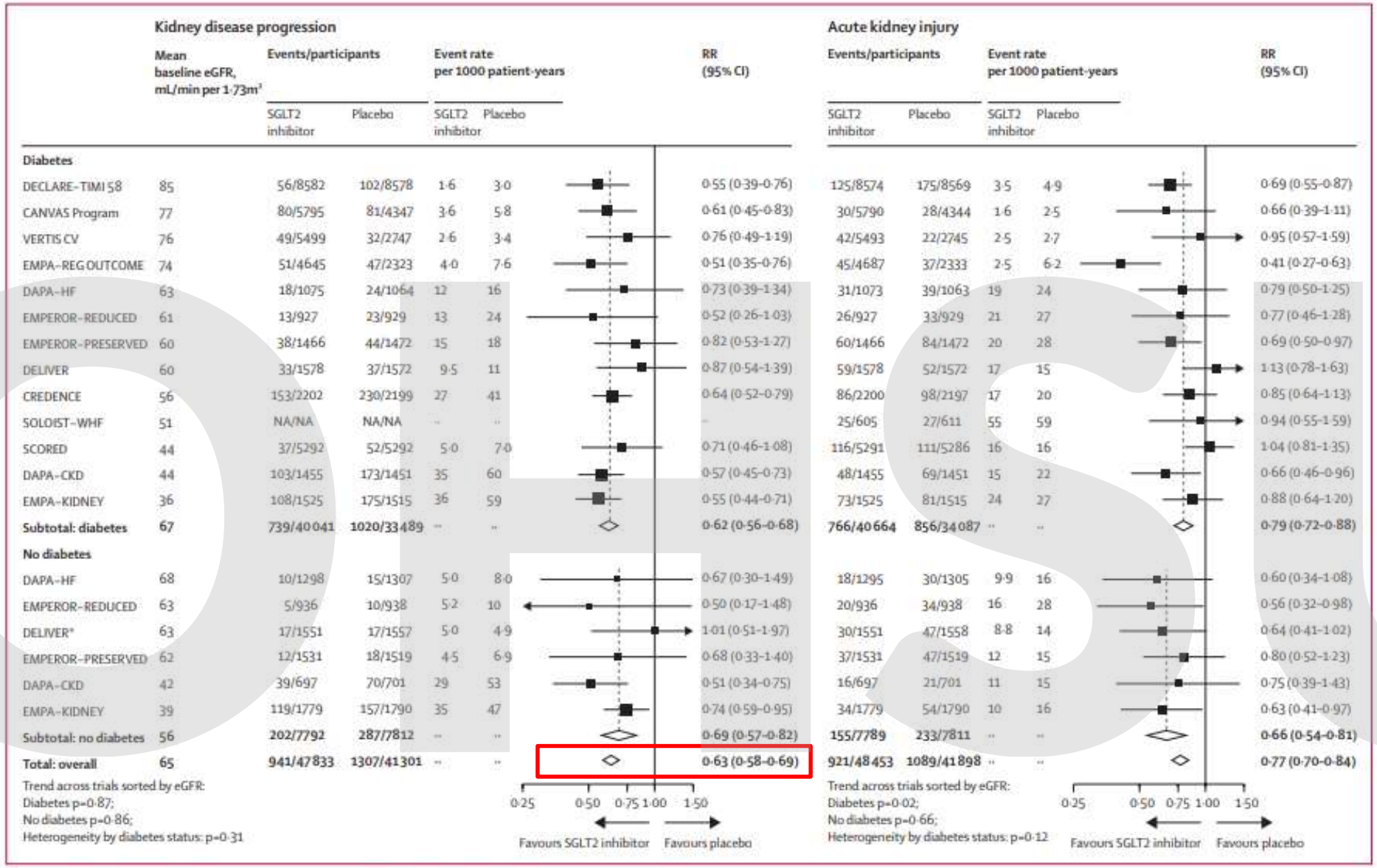


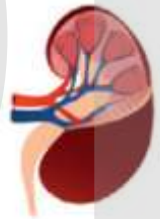
***Figure 1*: Effect of sodium glucose co-transporter-2 inhibition on kidney disease outcomes by diabetes status**

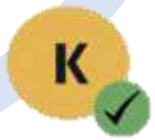
Kidney disease progression was defined as a sustained decrease in eGFR (≥50%) from randomisation, a sustained low eGFR, end-stage kidney disease, or death from kidney failure in all presented trials. Outcome definition details for each trial are provided in the appendix (pp 9–11). Rate values are not presented for the combined subtotal and total populations due to the heterogeneity in rates across the individual trials. eGFR=estimated glomerular filtration rate. RR=relative risk. SGLT2=sodium glucose co-transporter-2. NA=not available. *One participant without diabetes in DELIVER was missing a baseline creatinine measurement and was excluded.

Lancet 2022

Improving Tolerability with the other Key Medications

SGLT2i

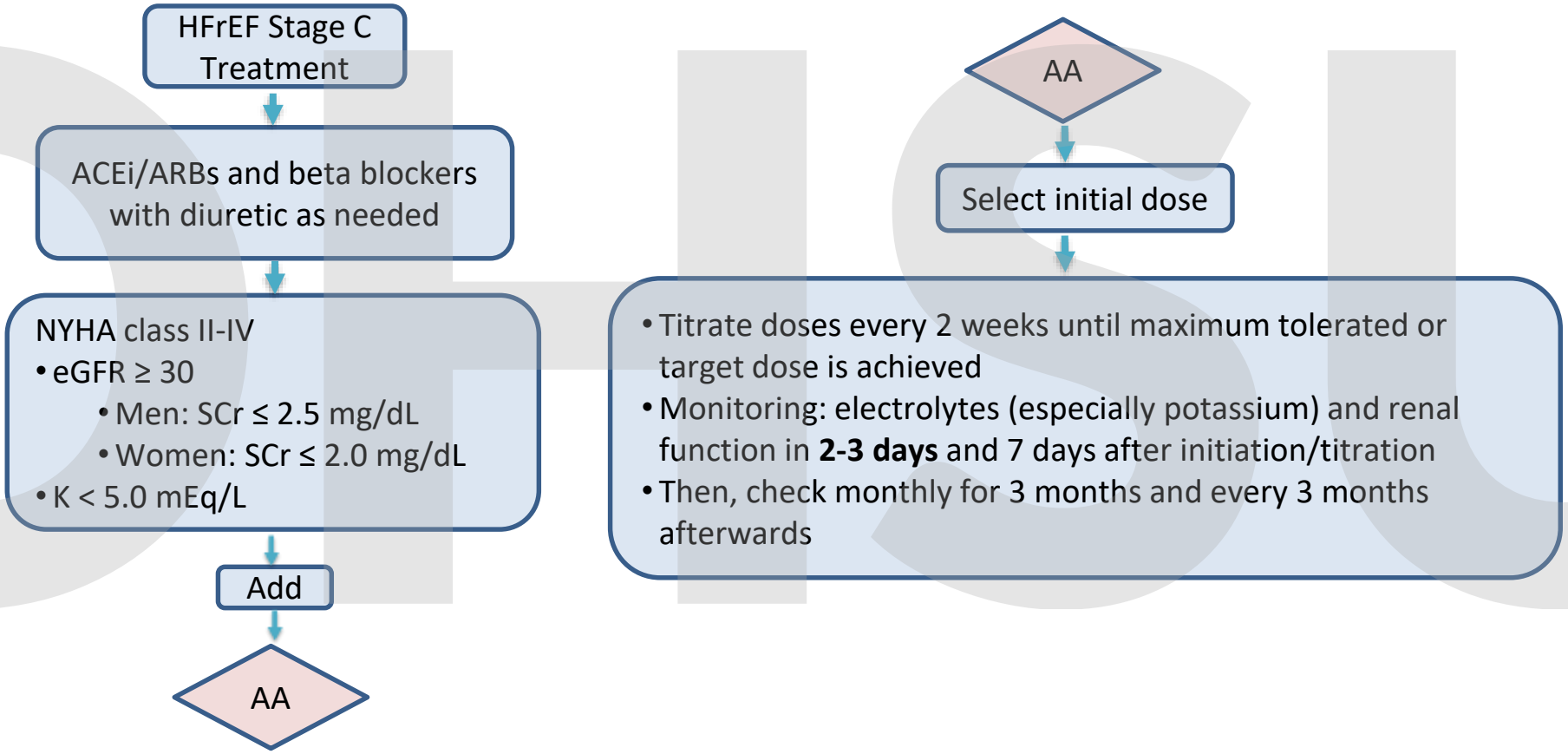




Potential enabling effects	Potential impact of tolerance on other GDMT
Minimal to no effect on BP	↔ARNI ↔MRA
Slow progression of renal dysfunction & risk of ESRD	↑ARNI ↑MRA
Decreases risk of hyperkalemia	↑ARNI ↑MRA

Greene and Khan. JACC 2021;77(11):1408-11

Aldosterone Antagonists (AA)



2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment:

Hyperkalemia Management

• Assess other medications that may increase potassium
  ○ Potassium supplements
  ○ Salt substitutes
  ○ Cyclosporin, Tacrolimus, NSAIDs, trimethoprim etc.
• Replace ACEi/ARBs by ARNi (if not yet done)
• Assess for acute increase in potassium vs. chronically elevated potassium
• Assess changes in renal function
• Identify source of Lab errors
• Educate patients and provide a list of food that are high in potassium content
• Use potassium binders

CASE1

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Medications
-Metoprolol succinate 150 mg daily -Sacubitril/valsartan49/51 bid -Rosuvastatin 20mg daily -Furosemide 20 mg daily -Aspirin 81mg daily -Metformin SA 1000 mg/day (max tolerated dose) -Glipizide XR 20mg daily

Vitals	
BP	136/84
EF	27%
Pulse	73bpm

Labs (most recent)
Scr: 1.5mg/dL eGFR: 38 mL /min/1.73m A1c: 7.5% K 5.2meq/L

Which one of the following is the best to recommend for this patient?

A. Initiate empagliflozin 10 mg daily.
B. Increase metoprolol succinate 200 mg daily.
C. Initiate spironolactone 25 mg daily.
D. Titrate sacubitril/valsartan 97/103 mg twice daily.

Glycemic Effects of SGLT-2 Inhibitors

Reduction in HgbA1c (Empa-Reg Outcome Trial 2015)

- Empagliflozin 10mg daily = HgbA1c reduced by 0.54%
- Empagliflozin 25mg daily = HgbA1c reduced by 0.6%

Hypoglycemic events

- Empa-Reg Outcome Trial (2015) :
  - Empagliflozin 27.8% vs. Placebo 27.9%

- Emperor Reduced Trial (2020) :
  - Diabetic group: Empagliflozin 2.2% vs. Placebo 2.4%
  - Non-diabetic group: Empagliflozin 0.7% vs. Placebo 0.6%

CASE 2

A 65-year-old woman presents to the HF clinic with a new diagnosis of HFrEF (EF 30%, NYHA class II). She is euvolemic on examination, complains of occasional SOB, and has slight lower extremity edema. Her PMH includes non-ischemic cardiomyopathy, obstructive sleep apnea, and iron deficiency anemia. Weight has been stable since diagnosis.

Medications
-Lisinopril 5mg daily -Amlodipine 10mg daily -Furosemide 20 mg daily

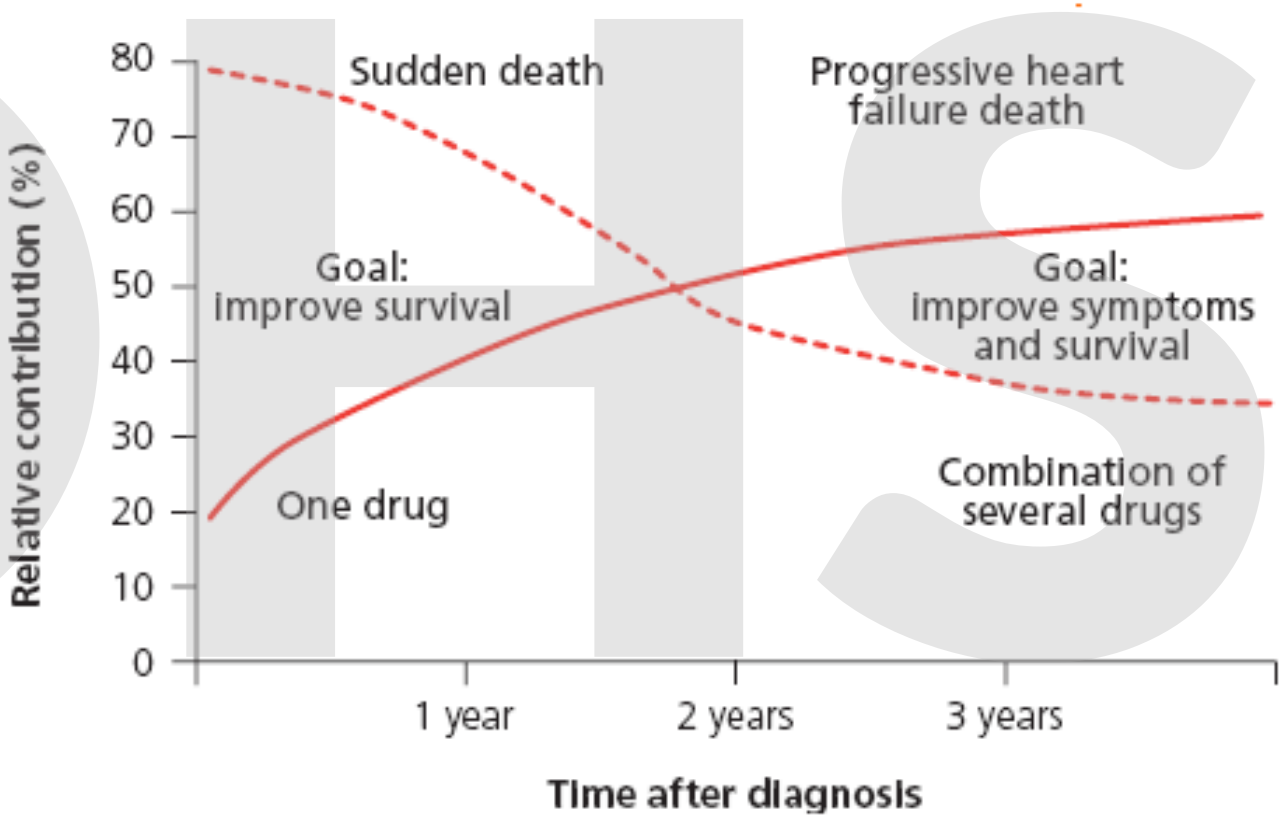
Vitals	
BP	110/77
EF	30%
HR	70 BPM

Labs (most recent)
Scr: 1.0mg/dL eGFR: 65 mL /min/1.73m K 4.3meq/L

Which one of the following is the best to recommend for this patient?

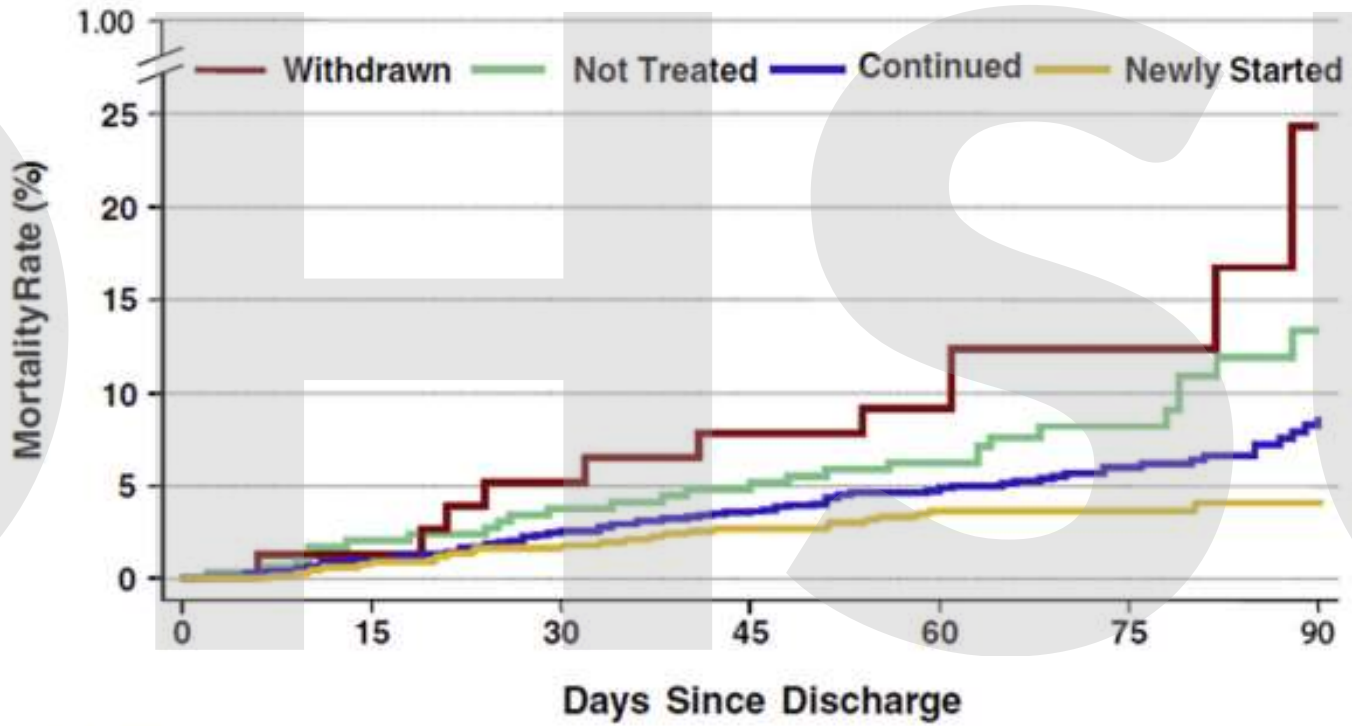
A. Add metoprolol succinate 12.5mg daily and discontinue amlodipine.
B. Switch lisinopril to sacubitril/valsartan 24/26 twice daily.
C. Increase lisinopril 10 mg daily.
D. Add spironolactone 12.5 mg daily.

Early Versus Late Stages of Chronic Heart Failure



Willenheimer R et al.B.J Cardiol2005;12:448–454

Post–Discharge Survival by Beta–Blocker Treatment Group



Patients at risk:							
Withdrawn	79	77	73	68	66	26	10
Not Treated	303	275	269	262	242	114	51
Continued	1350	1303	1268	1236	1123	536	224
NewlyStarted	632	609	591	575	531	274	110

Fonarow et al. JACC 2008

CASE 2

A 65-year-old woman presents to the HF clinic with a new diagnosis of HFrEF (EF 30%, NYHA class II). She is euvolemic on examination, complains of occasional SOB, and has slight lower extremity edema. Her PMH includes non-ischemic cardiomyopathy, obstructive sleep apnea, and iron deficiency anemia. Her weight has been stable since diagnosis.

Medications
-Lisinopril 5mg daily -Amlodipine 10mg daily -Furosemide 20 mg daily

Vitals	
BP	110/77
EF	30%
HR	70 bpm

Labs (most recent)
Scr: 1.0mg/dL eGFR: 65 mL /min/1.73m K 4.3meq/L

Which one of the following is the best to recommend for this patient?

A. Add metoprolol succinate 12.5mg daily and discontinue amlodipine
B. Switch lisinopril to sacubitril/valsartan 24/26 twice daily
C. Increase lisinopril 10 mg daily
D. Add spironolactone 12.5 mg daily

CASE 3

A 76-year-old woman who presents with mild exertional dyspnea and dizziness, which she noticed recently while walking. She becomes SOB when walking on hills but still walks about ¼ mile per day. She believes her symptoms of dizziness started with initiation of sacubitril/valsartan 24/26 mg twice daily. She really enjoys her morning walking routine and wants to know if she can stop sacubitril/valsartan. She has had mild pedal edema in the evenings for many years. She has a history of HFrEF, HTN, MI 2 years ago, depression, GERD, and hyperlipidemia. She is negative for orthostatic vital signs.

Medications
• Carvedilol 12.5 mg twice daily • Sacubitril/valsartan 24/26 twice daily • Torsemide 20 mg daily • Aspirin 81 mg daily • Simvastatin 20 mg at bedtime

Vitals	
BP	110/78
EF	35%
HR	80 BPM

Labs (most recent)
Scr: 1.2mg/dL eGFR: 60 mL /min/1.73m K 4.5meq/L

What is the best recommendation for this patient currently?

A. Switch from carvedilol to metoprolol succinate 100mg daily and monitor BP and symptoms.

B. Stop sacubitril/valsartan 24/26 twice daily and monitor BP and symptoms.

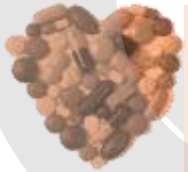
C. Increase her fluid intake which will help with her symptoms of dizziness.

D. Make no changes to her medications.

Hypotension Etiology

Hypovolemia secondary to diuretics

Low cardiac output



HF medications

Autonomic dysfunction

Non-HF medications

Non-cardiac Hypovolemia

Cautela et al. ESC 2020;22:1357-1365

Angiotensin-Converting Enzyme Inhibitors

CONSENSUS:5.5% incidence requiring discontinuation.

SOLVD: 2x more common in ACEI group (14%)

Factors associated: hyponatremia, recent diuretic augmentation

No defined BP.

Temporary reduction rather than withdrawal.

Angiotensin II Receptor Blockers

CHARM-Alt: 9/10 tolerated ARB when pt previously had hypotension with ACEI.

Val-HeFT: Valsartan effect on morbidity/mortality similar across all baseline SBP categories

Angiotensin Receptor-Neprilysin Inhibitor

PARADIGM-HF: hypotension was common. Occurred with 13.4% but only 2.7% had SPB<90 w/ symptoms.

- Action: Reduced or temporarily stopped ARNi, waited for spontaneous improvement (34%), or changed other meds. Only 2.2% permanent dc.

- Pts with lower BP received comparable benefits from ARNI.

PIONEER-HF: Similar rates of hypotension when initiated with acute decompensated HF. SBP >100mmHg

Cautela et al. Euro J of HF202022;1357-1365

Beta Blockers

MOCHA: Dose related improvement in LV function as well as dose reduced mortality/hospitalization with carvedilol.

COPERNICUS: those with lowest BP experienced the greatest benefit from the medication.

Only saw BP transient.

Beta blocker trials showed low discontinuation rates for hypotension (0.3-0.6%)

Mineralocorticoid Receptor Antagonists

RALES: No difference in BP reported in two groups (placebo).

EPHESUS and EMPHSASIS-HF: non-significant lower BP.

-Hypotension is infrequent.

Sodium-Glucose Co-Transporter 2 Inhibitors

DAPA-HF: Mean SBP drop only 1.3mmHg. Older pts had similar BP drop and derived benefit.

EMPEROR Reduced: No significant difference in SBP vs placebo.

Loop Diuretics

Dosage should be adjusted based on congestion.

Hypovolemia is primary cause for hypotension with these agents.

Filling pressures need to be considered prior to titration of other GDMT because if hypovolemia more likely to have more drastic impact on blood pressure (ie ARNI).

Cautela et al. Euro J of HF202022;1357-1365

Take Away from Trial Data

- Most evidence regarding low BP in HF is taken from trials.
  - May not be represented by real life patients
  - Less baseline hypotension
- Clinical judgement fueled characterization of hypotension rather than pre-defined BP thresholds.
  - Lack of consensus and makes clinical application difficult
- Low BP was relevant when associated with symptoms.
  - Symptoms should guide management!
- Studies showed that those with lowest baseline BP drew similar if not greater treatment benefits
  - Suggests the short-term BP lowering effect are compensated by long term beneficial systemic effects.

Cautela et al. Euro J of HF 2020 22, 1357-1365

Management of Hypotension in HF patients
Asymptomatic Hypotension • No action is required, provided there is no evidence of organ hypoperfusion • With improvement of HF status with GDMT and/or CRT, BP profile usually improves
Symptomatic Hypotension • Use flexible diuretic dosing or reduce doses when no signs of congestion • Avoid/discontinue non-HFrEF BP lowering medical therapies (α-blockers, calcium channel blockers, nitrates) • Transition agents within a class (e.g. Carvedilol to Metoprolol) • Consider separate timing of medications that may cause hypotension • Assess non-cardiovascular causes of hypotension • Initiate and up titrate GDMT slowly with close follow-up and monitoring • Check for orthostasis. Patients with postural hypotension should be set up with compression stockings. • Consider cardiac rehabilitation
BP = blood pressure, CRT = cardiac resynchronization therapy, GDMT = guideline directed medical therapy, HF = heart failure, non-HFrEF = non heart failure with reduced ejection fraction.

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D. Make no changes to her medications

Summary

- Contemporary evidence suggests that there have been limited attempts to titrate disease-modifying therapies for HFrEF
- New guidelines propose a new set of recommendations and expand treatment options for a broad range of LVEF based on contemporary evidence
- Quadruple therapy [a combination of ACE/ARB/ARNi (ARNi preferred), evidence-based beta-blockers, MRA, and SGLT2i] is the new standard for HFrEF and associated with greatest improvement in clinical outcomes
- The optimal approach is to utilize each GDMT demonstrated to reduce all-cause mortality in combination and titrate to maximally tolerated dosed without delay
- Simultaneous or sequential strategies can be used to initiate or titrate GDMT based on patient specific factors (BP, kidney function and electrolytes)