Heart failure treatment across the spectrum of ejection fraction

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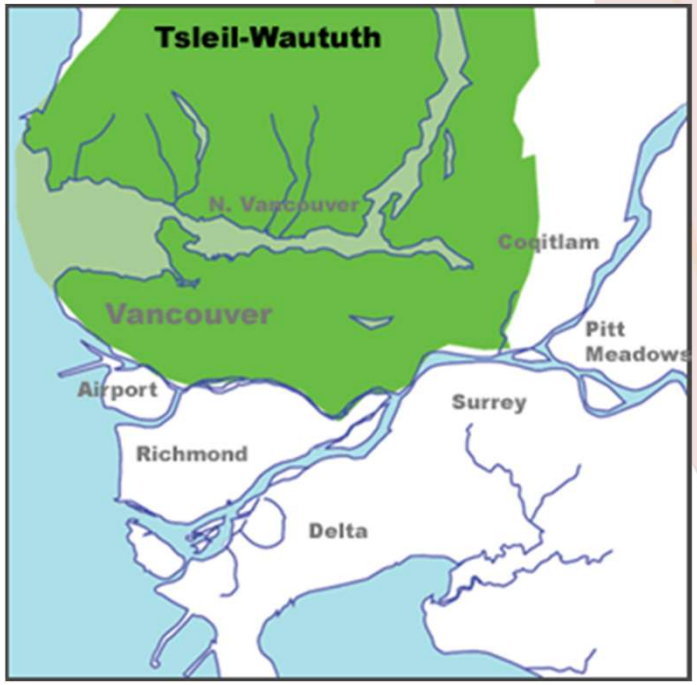
UBC

We would like to acknowledge that we are gathered today on the traditional territories of the Musqueam, Squamish and Tsleil-Waututh peoples.

Source: www.johomaps.net/na/canada/bc/vancouver/firstnations/firstnations.html



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Disclosure of Financial Support

- I am not receiving any financial support to deliver today's presentation.

Mitigation of Potential Bias

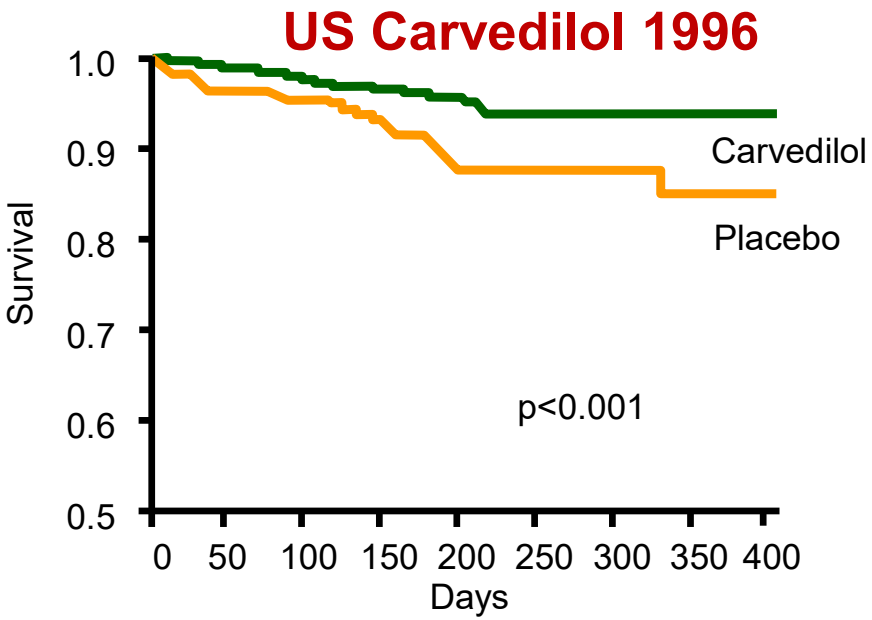
- I will only use generic names of drugs; no bias perceived
- I will not discuss off label use
- I will only use peer-reviewed literature and national specialty society recommendations

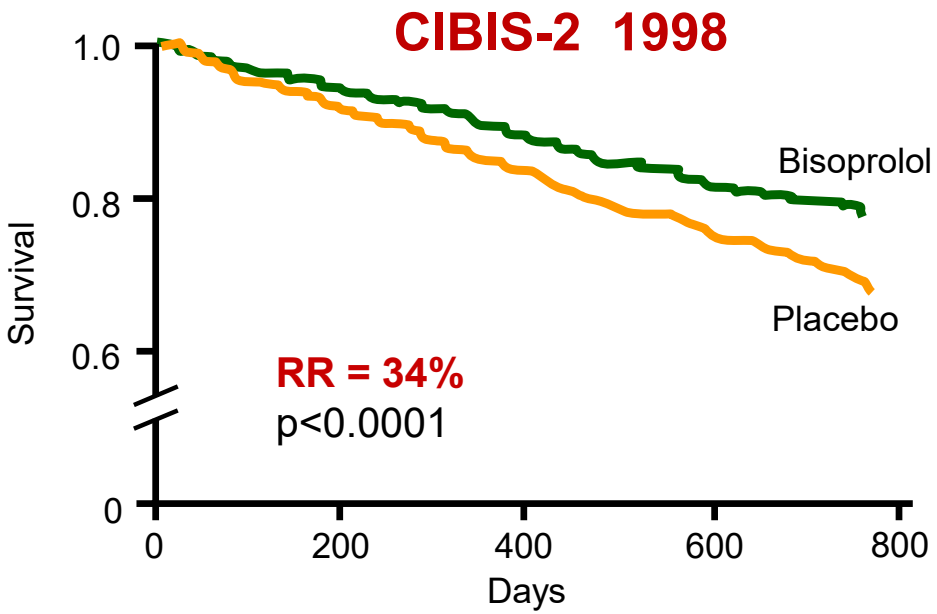
Objectives

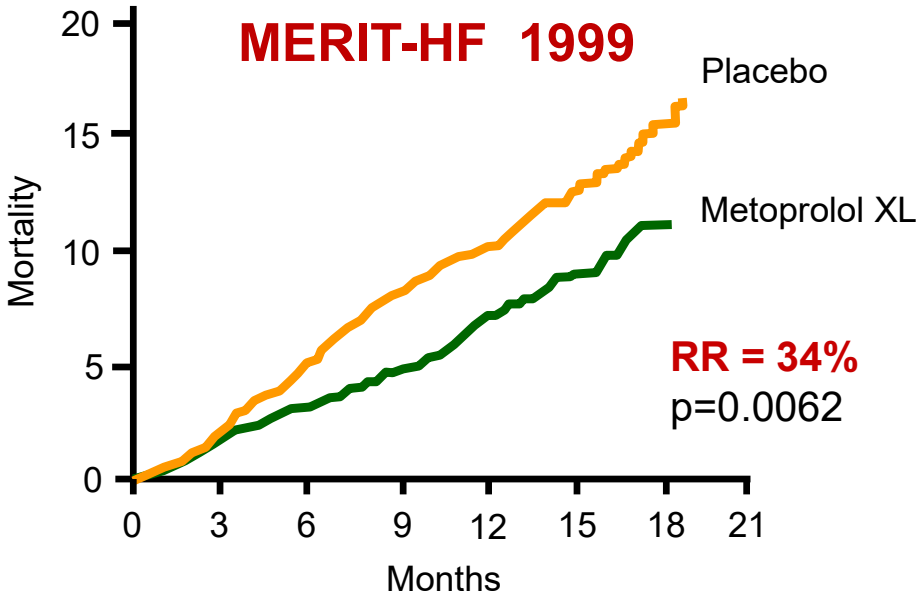
- To describe the importance and complementarity of quadruple therapy in patients with heart failure and reduced ejection fraction (HFrEF).

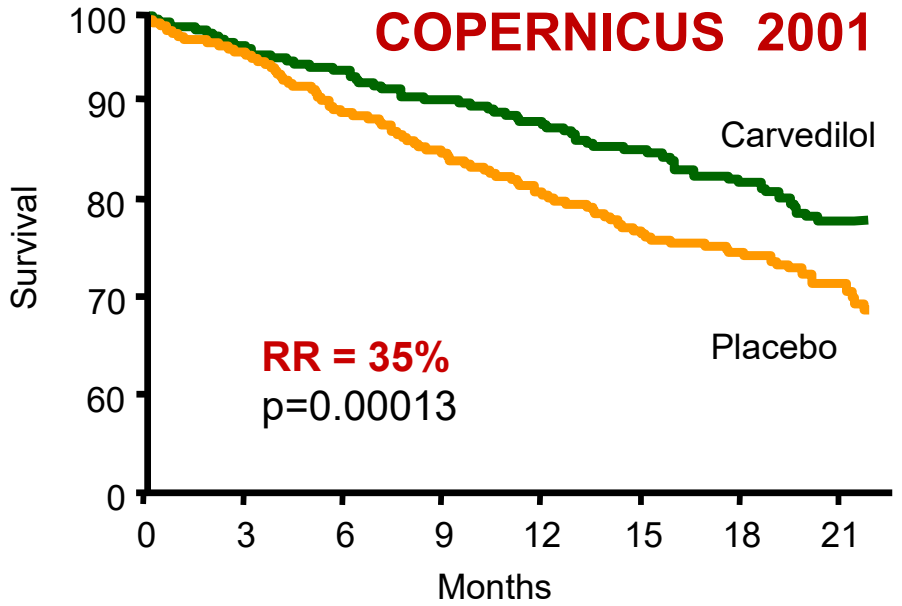
- To define heart failure with preserved ejection (HFpEF) and describe treatment options across the spectrum of ejection fraction.

Beta-blockers are the most evidence-based therapy in heart failure

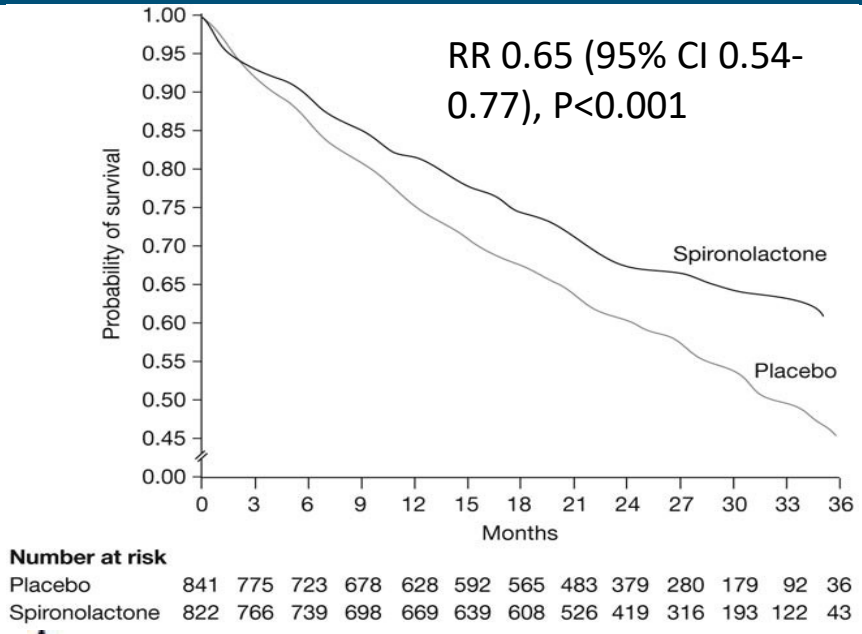


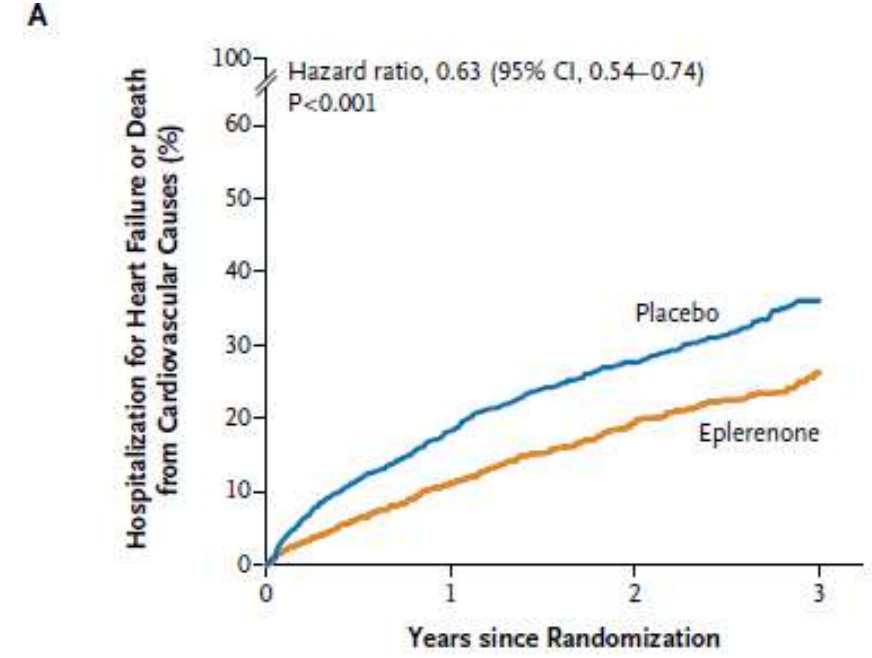






Aldosterone antagonists HF





RALES

- LVEF ≤ 35%
- NYHA IV within 6 months
- n=1663

EMPHASIS

- LVEF ≤ 35%
- NYHA II
- n=2737

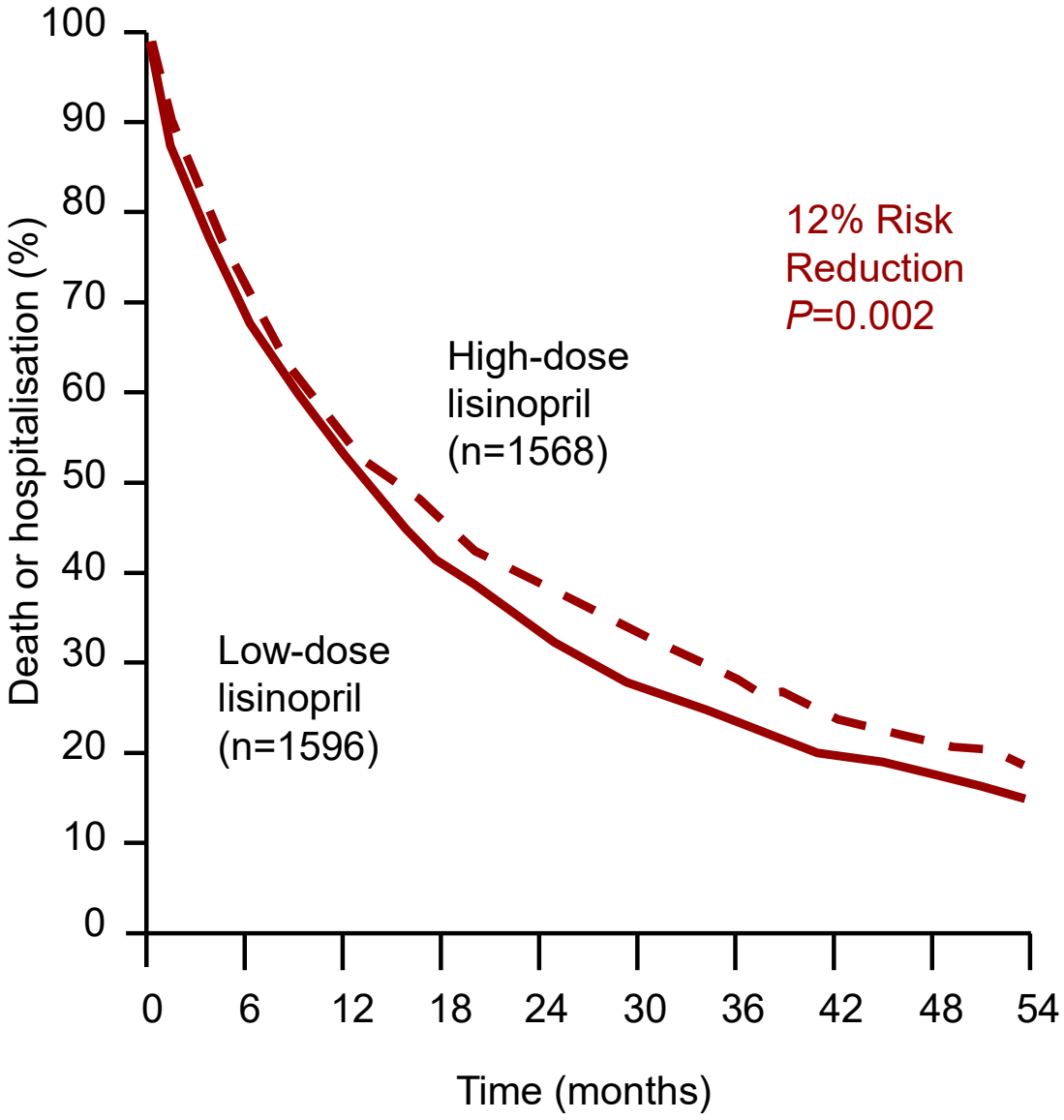
Limited benefit to high vs low dose ACEI

N= 3164	HF LVEF ≤30% NYHA II-IV

Low ACEI	High ACEI
Lisinopril 2.5-5.0 mg	Lisinopril 32.5-35.0 mg

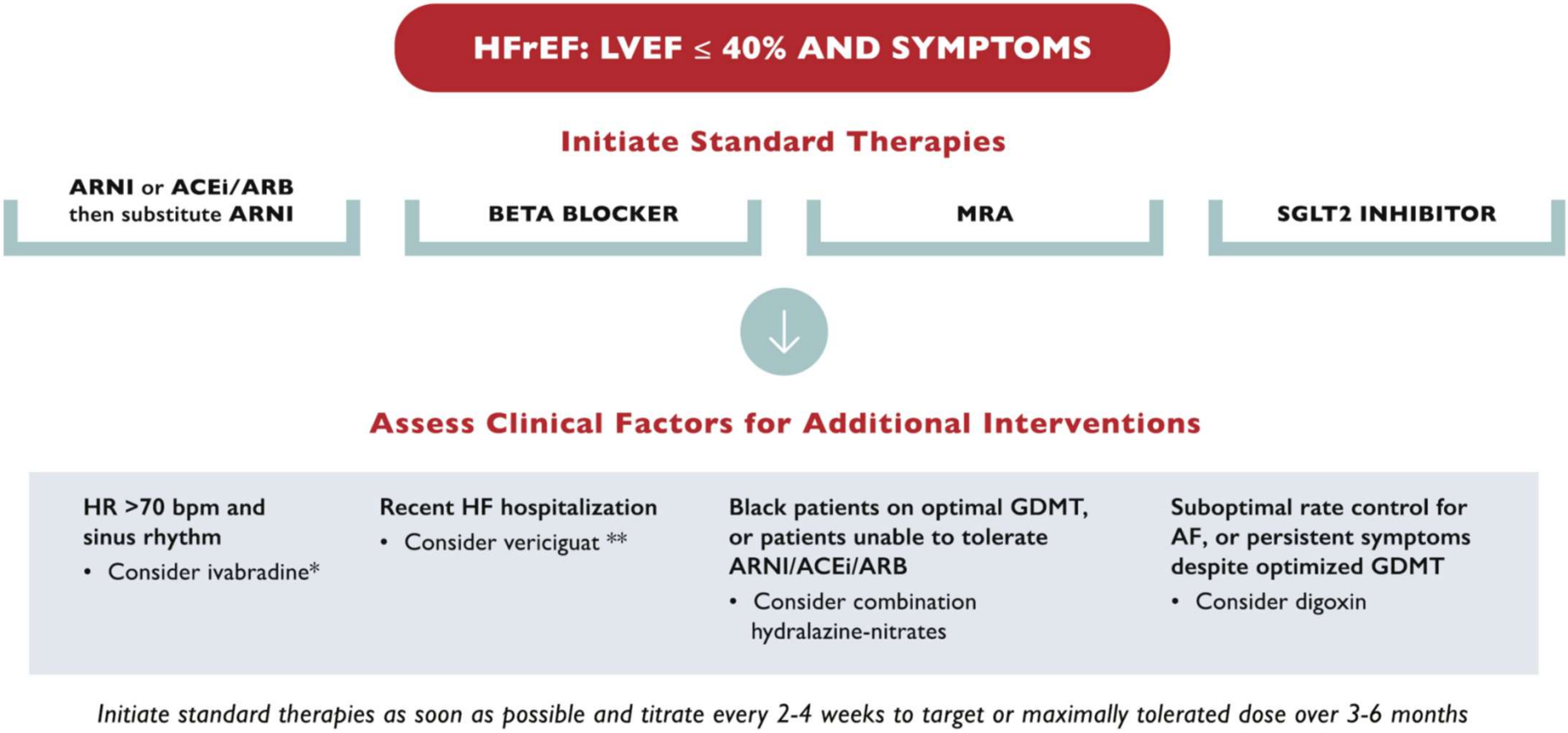
1° endpoint all cause mortality

f/u 46 median months



Packer M. Circulation 1999; 100(23):2312-2318

Heart Failure Guidelines
CCS/CHFS 2021

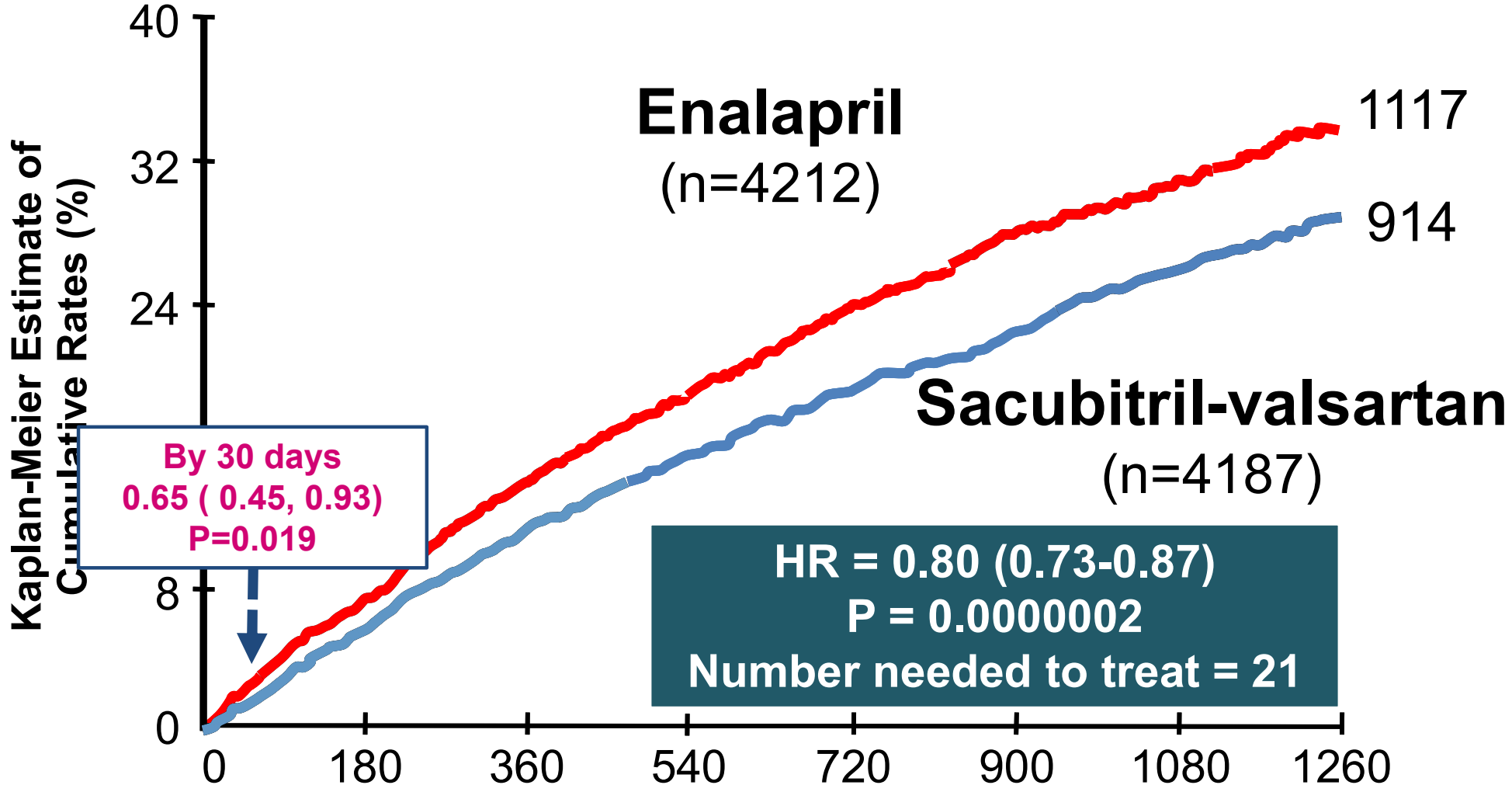


McDonald M, et al. Can J Cardiol. 2021;37:531-546

ARNI (angiotensin receptor-neprilysin inhibitor) i.e. sacubitril-valsartan

	Rec	Quality
We recommend that an ARNI be used in place of an ACEI or ARB, in patients with HFrEF, who remain symptomatic despite treatment with appropriate doses of GDMT to decrease CV death, HF hospitalizations, and symptoms	**Strong**	High
We recommend that patients admitted to hospital for acute decompensated HF with HFrEF should be switched to an ARNI, from an ACEI or ARB, when stabilized and before hospital discharge	**Strong**	Moderate
We suggest that patients admitted to hospital with a new diagnosis of HFrEF should be treated with ARNI as first-line therapy, as an alternative to either an ACEI or ARB	Weak	Moderate

PARADIGM-HF: Primary outcome CV death or HF hospitalization

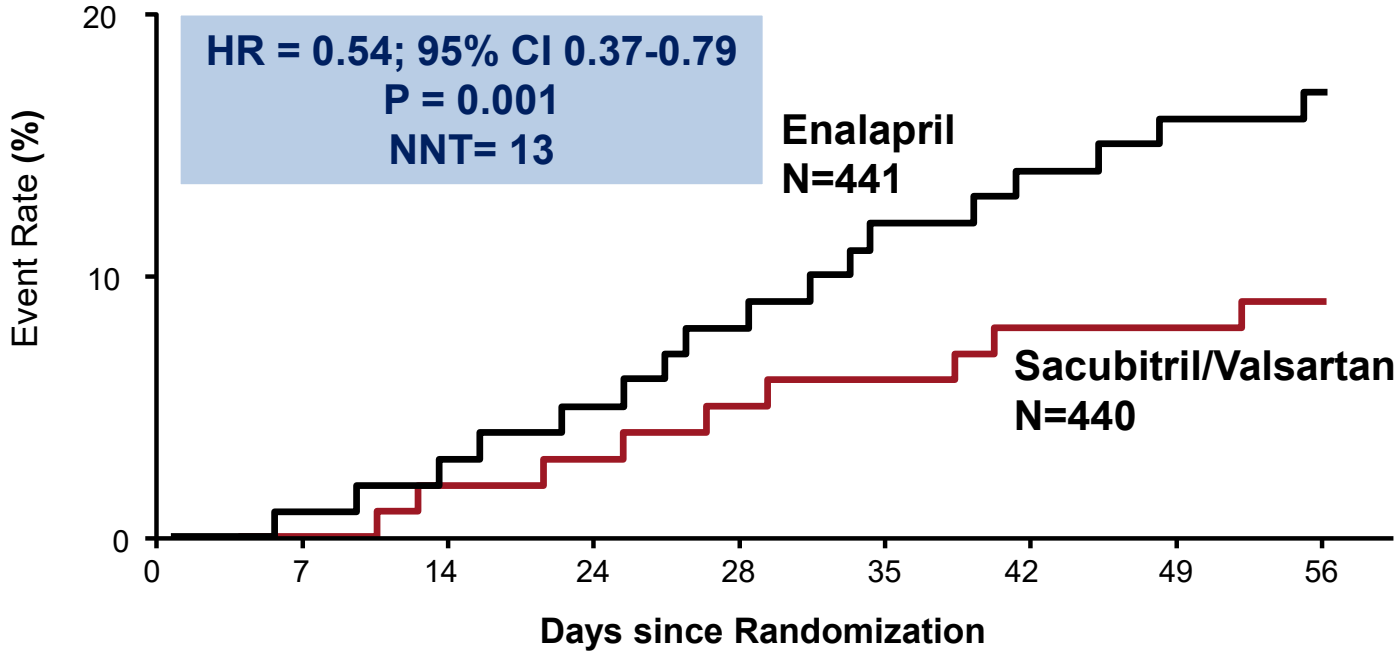


Patients at Risk

Sacubitril-val	4187	3922	3663	3018	2257	1544	896	249
Enalapril	4212	3883	3579	2922	2123	1488	853	236

PIONEER-HF: Clinical endpoints

Endpoints n (%)	Sac-val (n=440) (%)	Enalapril (n=441) (%)	RR Sac/Val vs Enalapril
Composite serious events	41 (9.3)	74 (16.8)	0.54 (0.37-0.79)
Death	10 (2.3)	15 (3.4)	0.66 (0.30-1.48)
Re-hospitalization HF	35 (8.0)	61 (13.8)	0.56 (0.37-0.84)
LVAD	1 (0.2)	1 (0.2)	0.99 (0.06-15.97)



Velazquez EJ, et al. N Engl J Med. 2018

SGLT2I recommendations 2021

	Rec	Quality
We recommend an SGLT2 inhibitor, such as dapagliflozin or empagliflozin, be used in patients with HFrEF, with or without concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of HF hospitalization and/or CV mortality	**Strong**	High

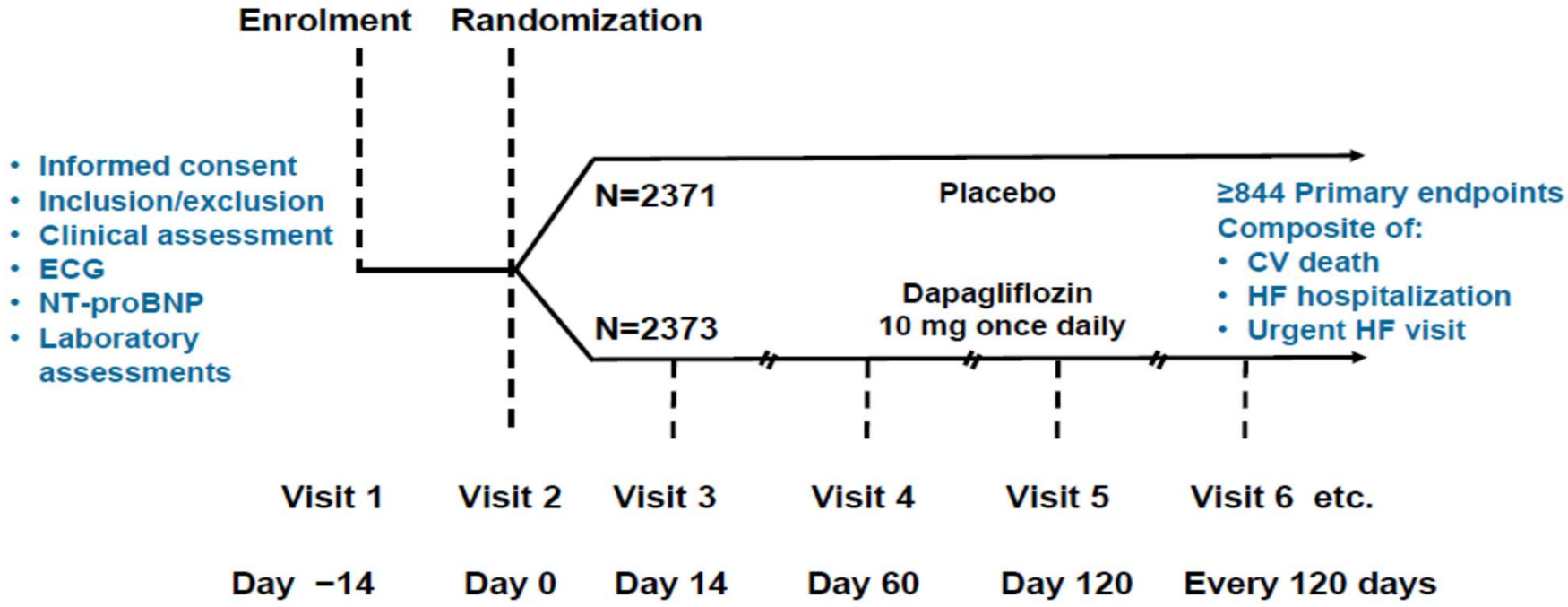
DAPA-HF: trial design

Key inclusion criteria

- HF with LVEF ≤40%
- NTproBNP ≥600 pg/ml
  - if HFH 12m ≥400 pg/mL
  - if AF/flutter ≥900 pg/mL

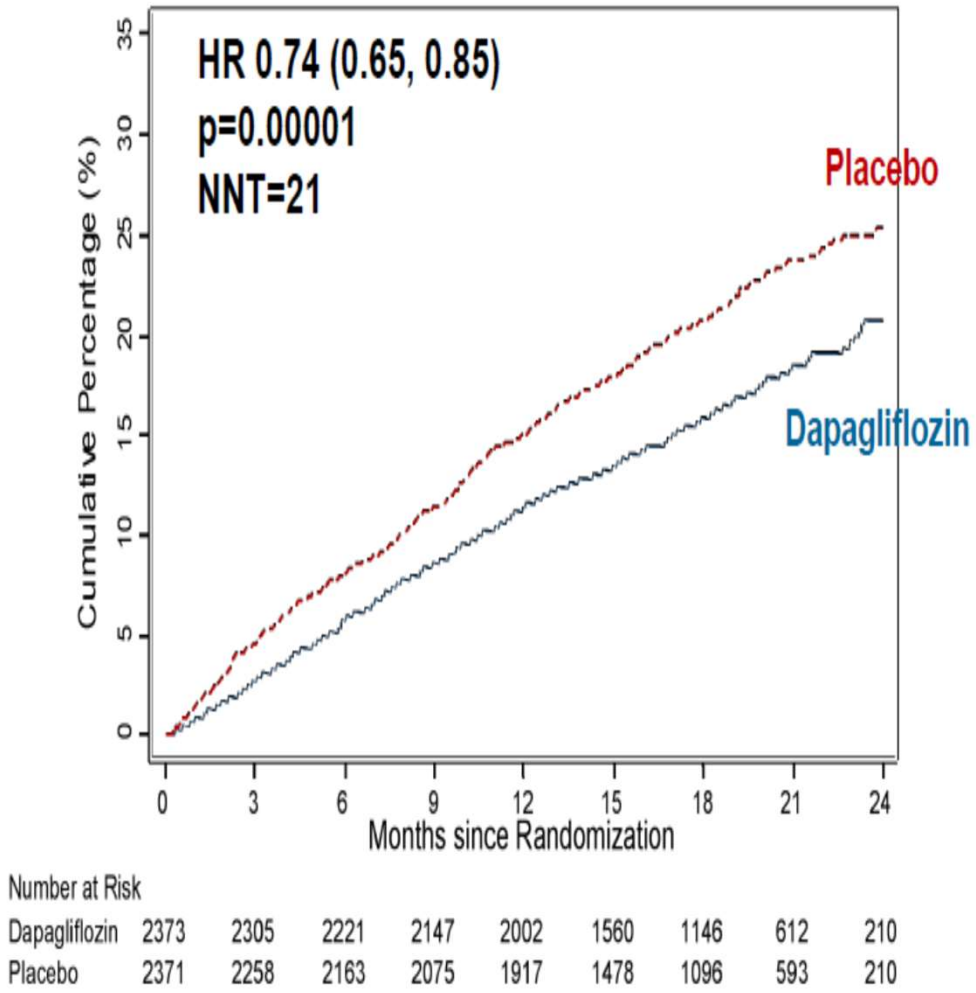
Key exclusion criteria

- eGFR <30 ml/min/1.73 m2
- Symptomatic hypotension or SBP <95 mmHg
- type 1 diabetes mellitus



McMurray JJV, et al. *Eur J Heart Fail*. 2019;21:665-675

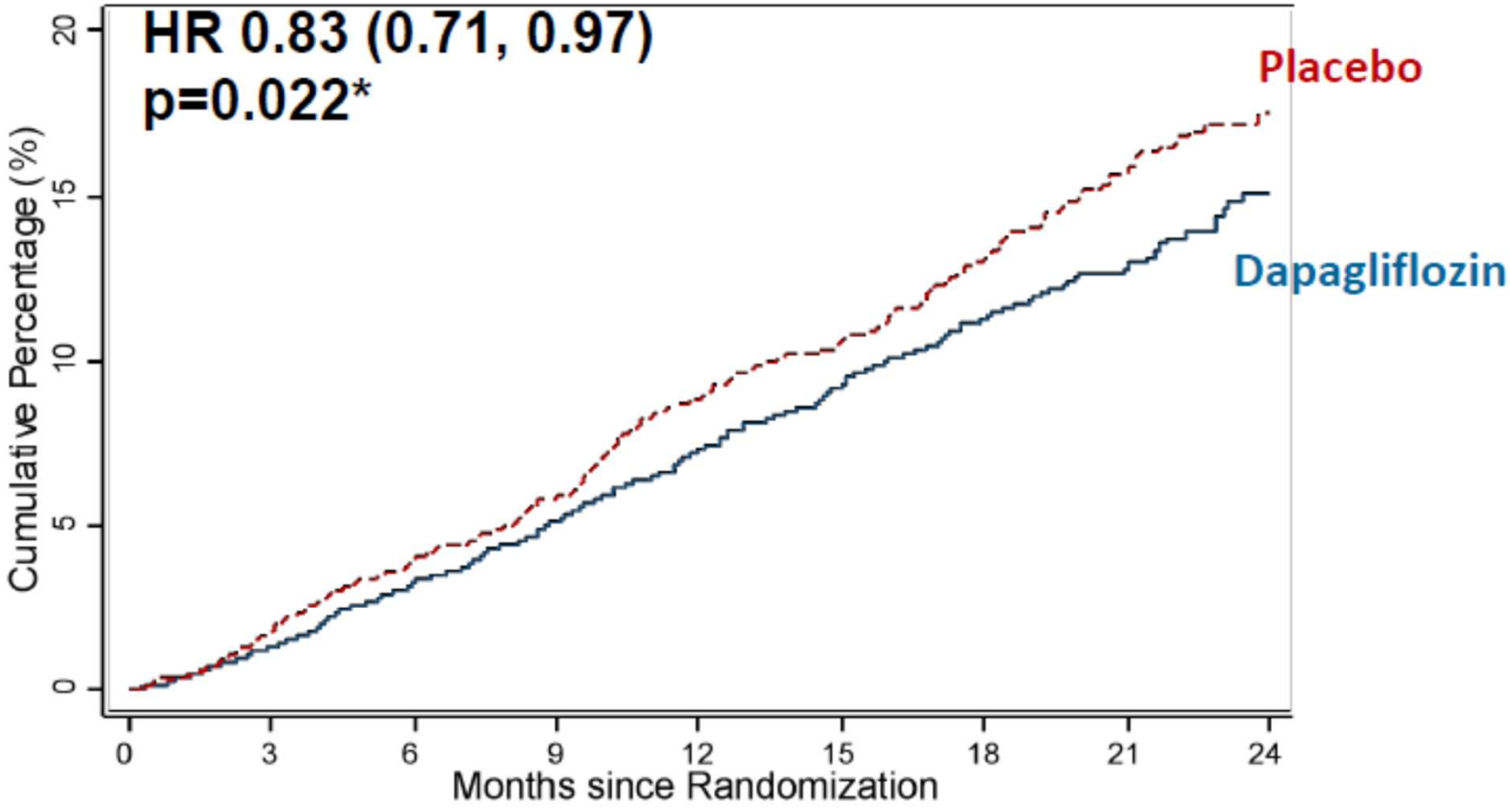
Dapagliflozin reduces CV death, HF hospitalization, urgent HF visit



Treatment (%)	Dapagliflozin n=2373	Placebo n=2371
ACEI/ARB/ARNI	94	93
ACEI	56	56
ARB	28	27
ARNI	11	11
Beta-blocker	96	96
MRA	71	71
ICD	26	26
CRT	8	7
Diuretics	93	94

McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008

Dapagliflozin reduces all-cause death



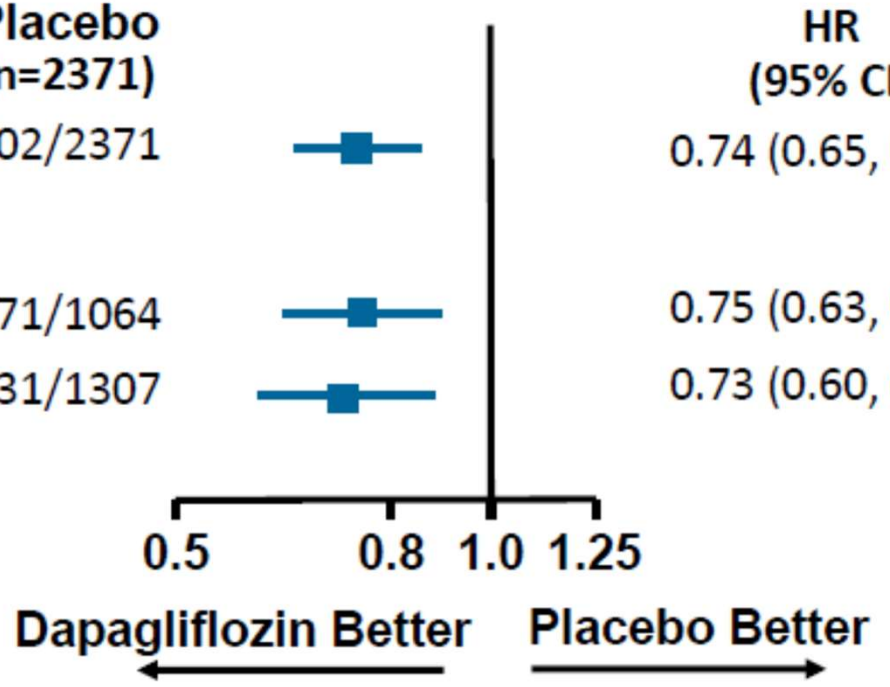
Number at Risk									
Dapagliflozin	2373	2342	2296	2251	2130	1666	1243	672	233
Placebo	2371	2330	2279	2231	2092	1638	1221	665	235

*Nominal p value

McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008

Effect independent of diabetes: primary endpoint

	Dapagliflozin (n=2373)	Placebo (n=2371)	HR (95% CI)
All patients	386/2373	502/2371	0.74 (0.65, 0.85)
Type 2 diabetes at baseline*			
Yes	215/1075	271/1064	0.75 (0.63, 0.90)
No	171/1298	231/1307	0.73 (0.60, 0.88)



McMurray JJV, et al. *N Engl J Med*. 2019;381:1995-2008

Common concern 1. Worsening renal function

History

- 61 years
- 6 months post late presentation anterior MI
- Underwent PCI
- LVEF 30%, mild MR
- ICD 6 weeks ago

Exam and labs

- HR 80
- BP 96/70
- Mild edema
- JVP 6 cm
- Sat 93%
- Crackles < 1/3

- Na 130, K+ 4.5
- Creatinine rise 155(130)
- eGFR 45

Medications

- Carvedilol 12.5 bid
- Spironolactone 12.5 od
- Enalapril 5 bid

- Furosemide 40 od

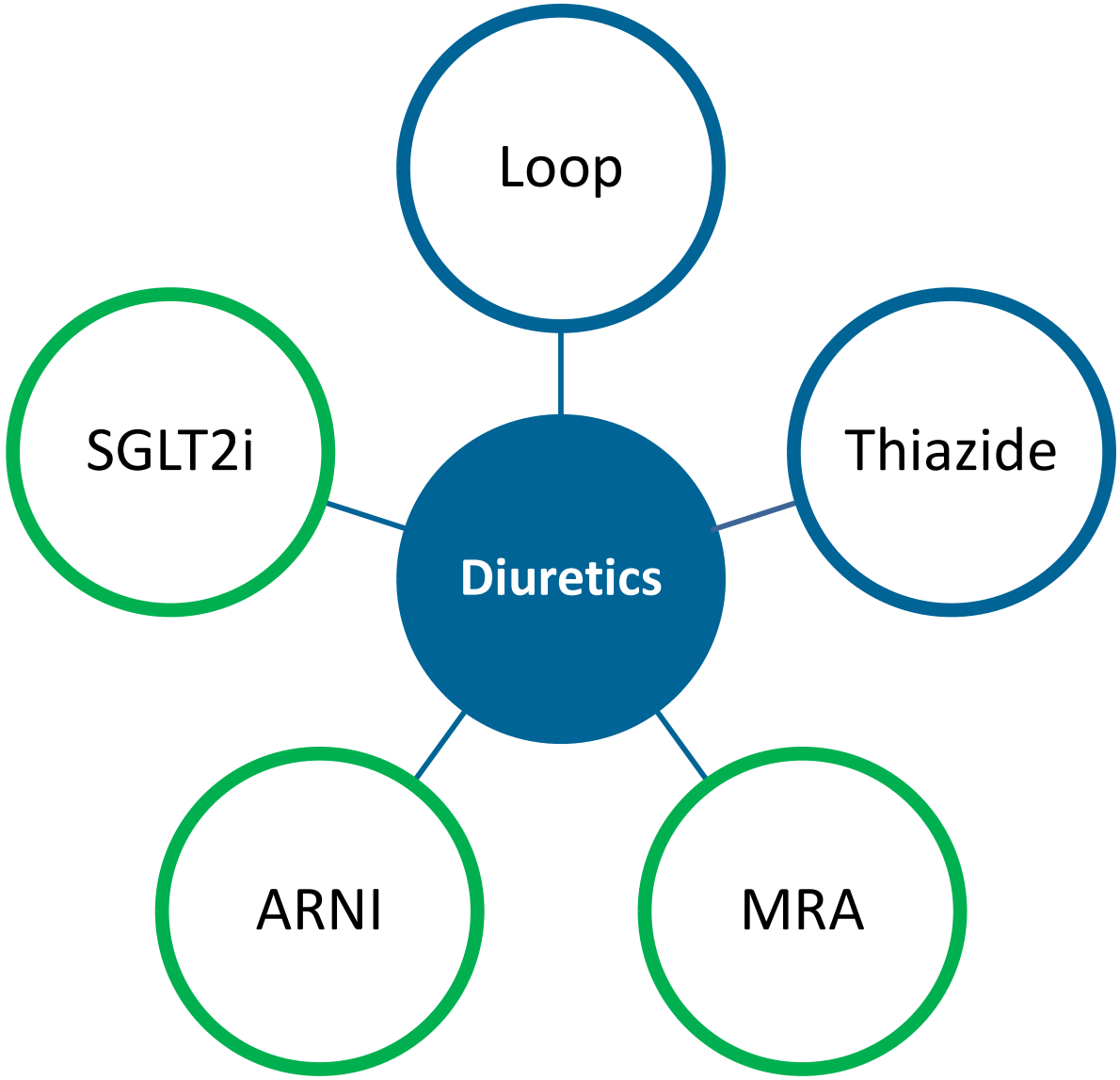
- ASA 81 od
- Clopidogrel 75 od
- Atorvastatin 80 od
- Ezetimibe 10

Question 1. What do you do?

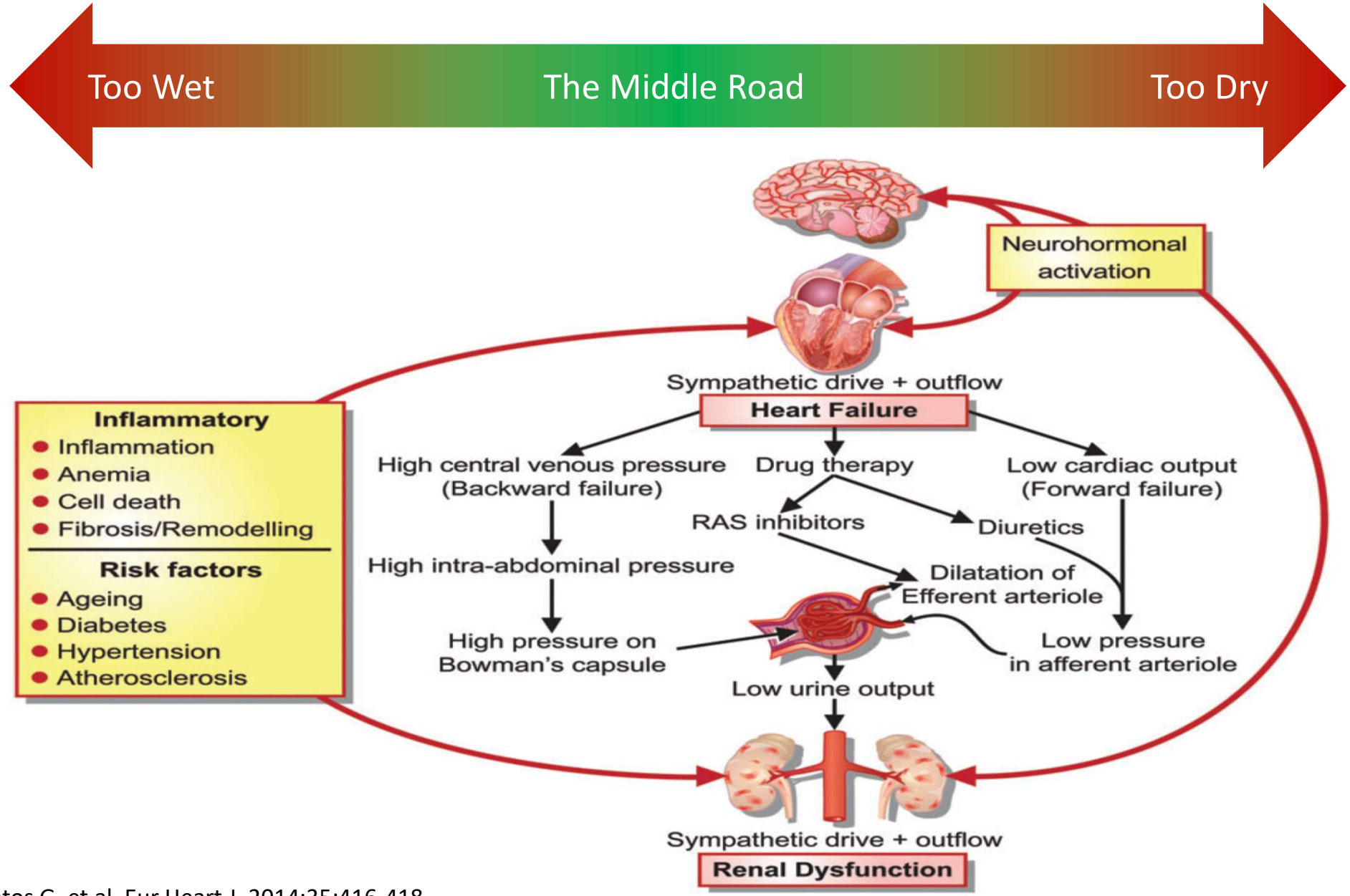
- Wet
- BP 96/70
- HR 80
- eGFR 45
- K 4.5
- Low-mid dose triple therapy

- Decrease
  - Furosemide
  - MRA
  - ACEI or beta-blocker
- Increase
  - Furosemide
  - MRA
  - ACEI or beta-blocker
- Add
  - sacubitril-valsartan
  - SGLT2I
- Increase and add
  - MRA and SGLT2I

Diuretics in HF

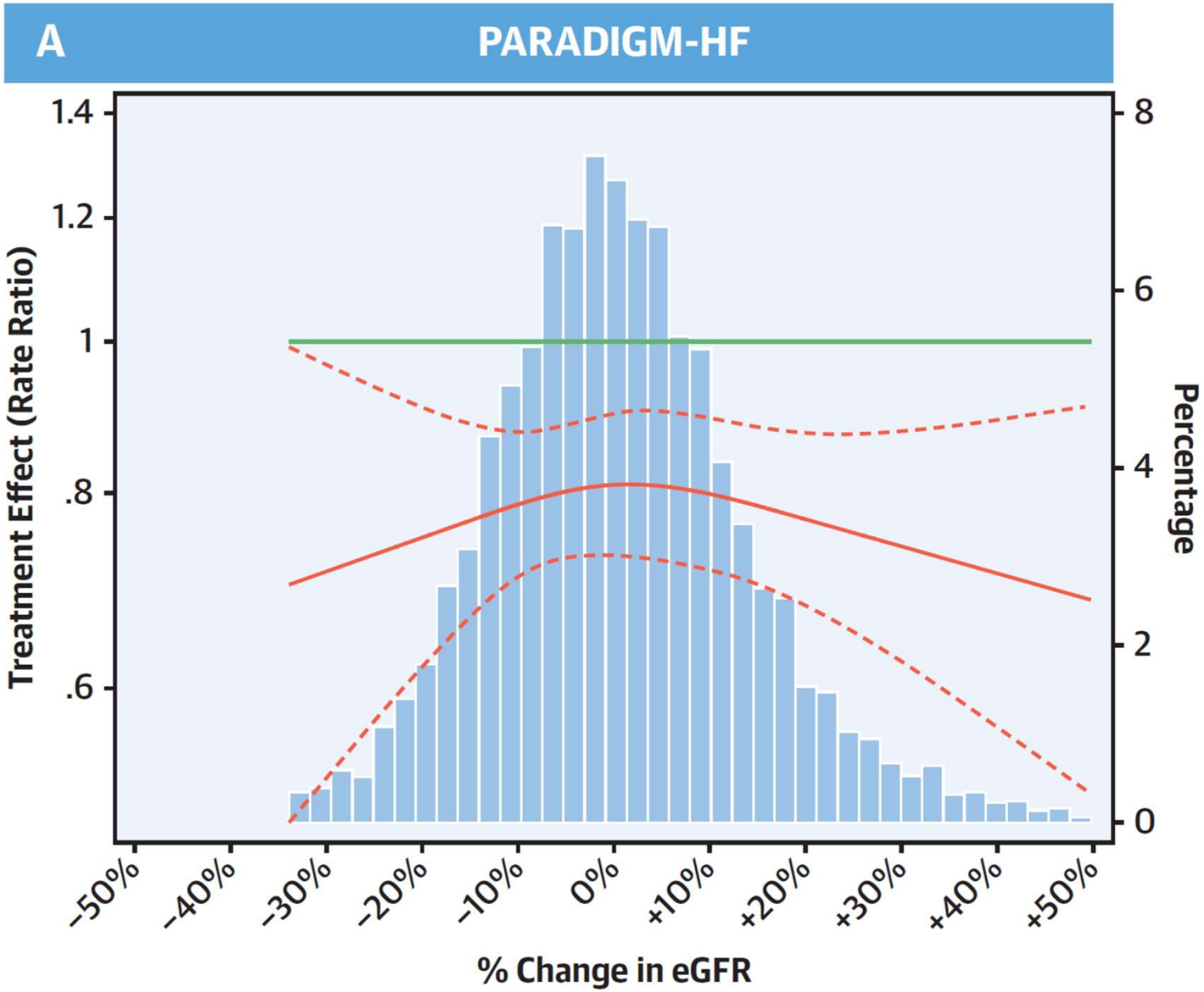


Cardiorenal syndrome



Filippatos G, et al. Eur Heart J. 2014;35:416-418

Early renal function change with GDMT: expected … and NOT a problem



Chatur S, et al. J Am Coll Cardiol. 2023;81:1443-1455

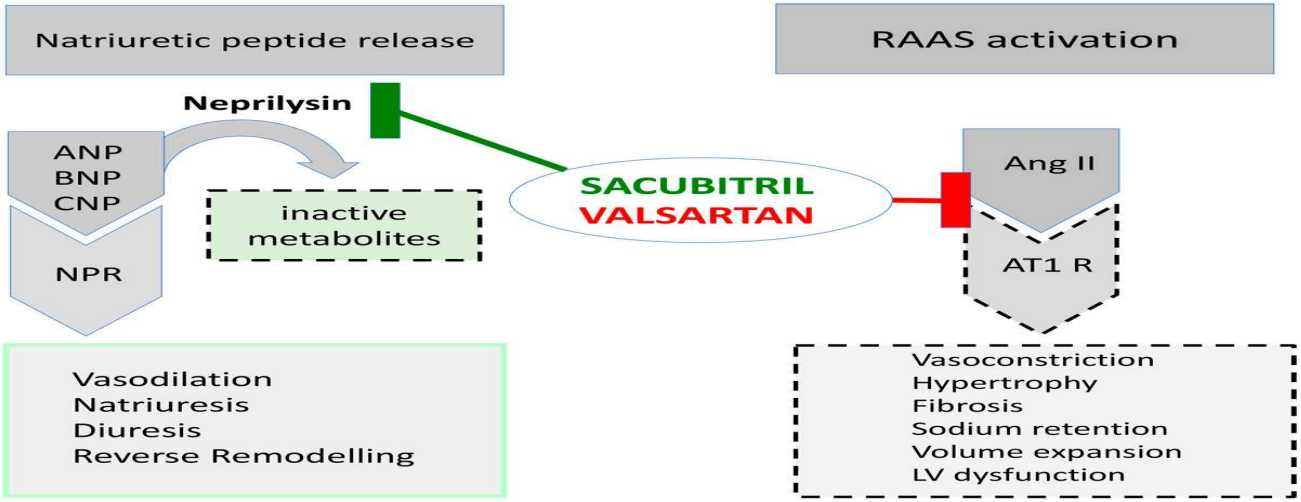
Quadruple therapy for all HFrEF: recommendations 2021

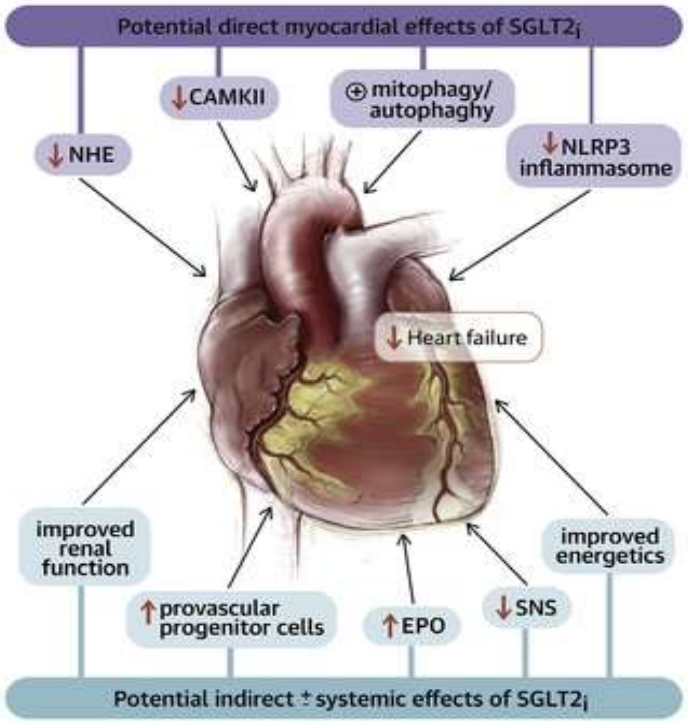
	Rec	Quality
We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories: a. ARNI (or ACEI/ARB); b. beta-blocker; c. MRA; d. SGLT2 inhibitor.	Strong	Moderate

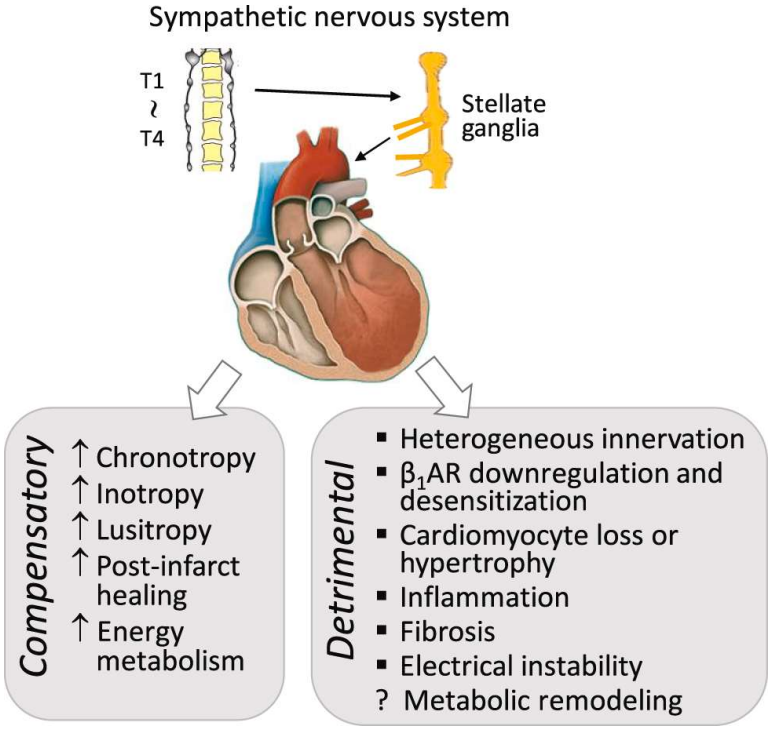
What is the effect of adding one therapy to another in HFrEF?

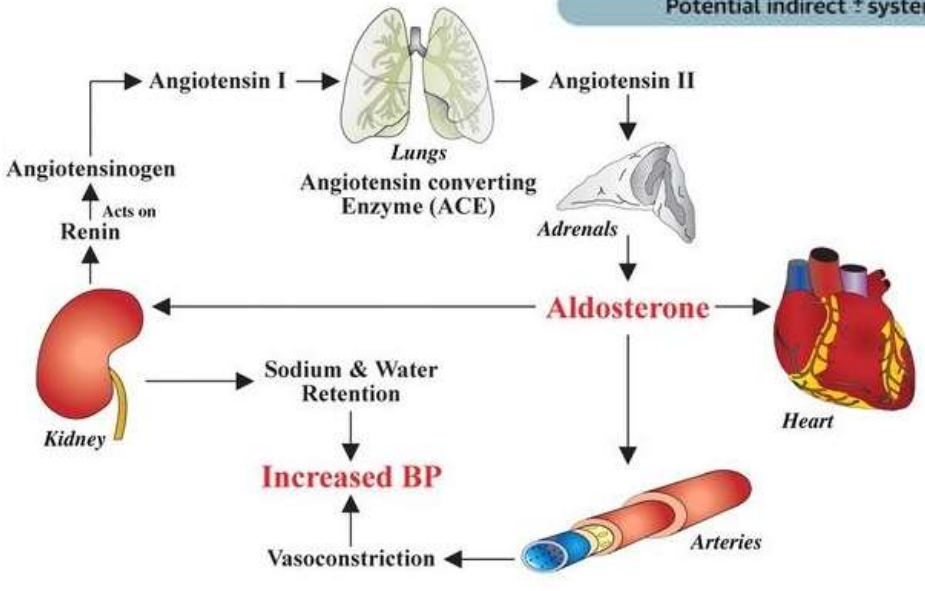
- Subtractive 1 + 1 = 0.5
- Redundant 1 + 1 = 1.0
- Partially Additive 1 + 1 = 1.5
- Fully Additive 1 + 1 = 2.0
- Synergistic 1 + 1 = 2.5

Multiple, largely non-overlapping therapeutic targets

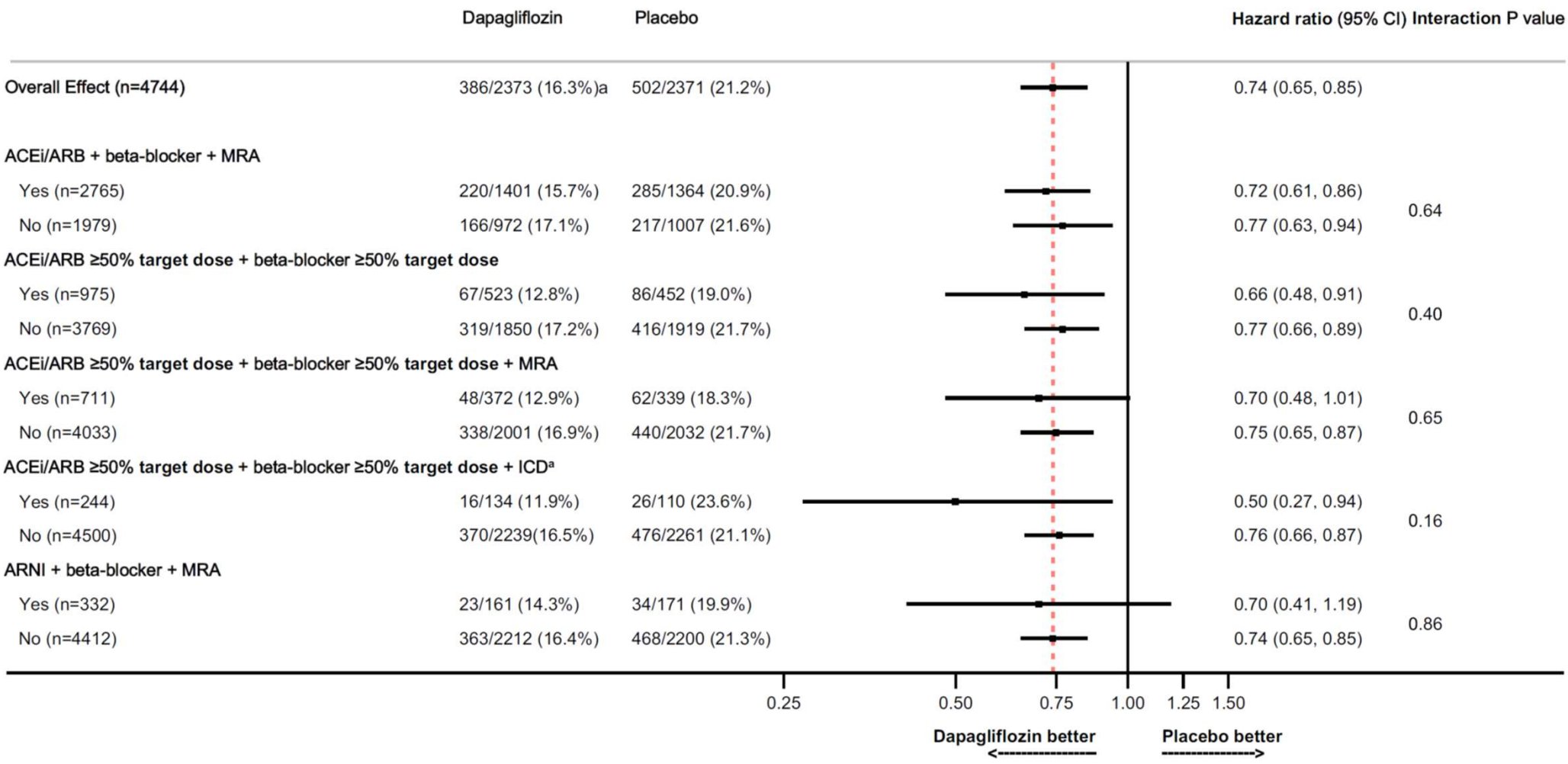






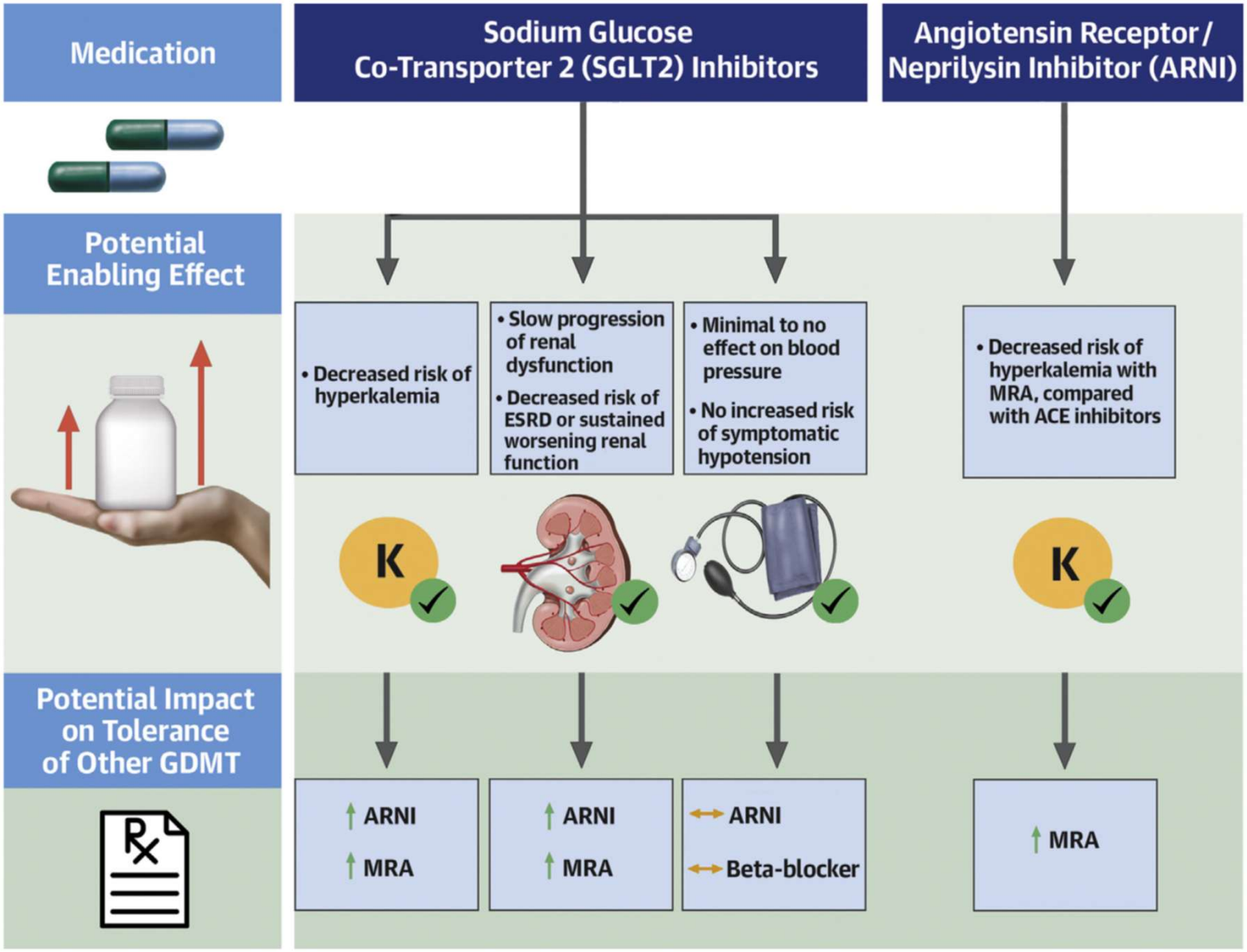


Therapies are (at least) additive



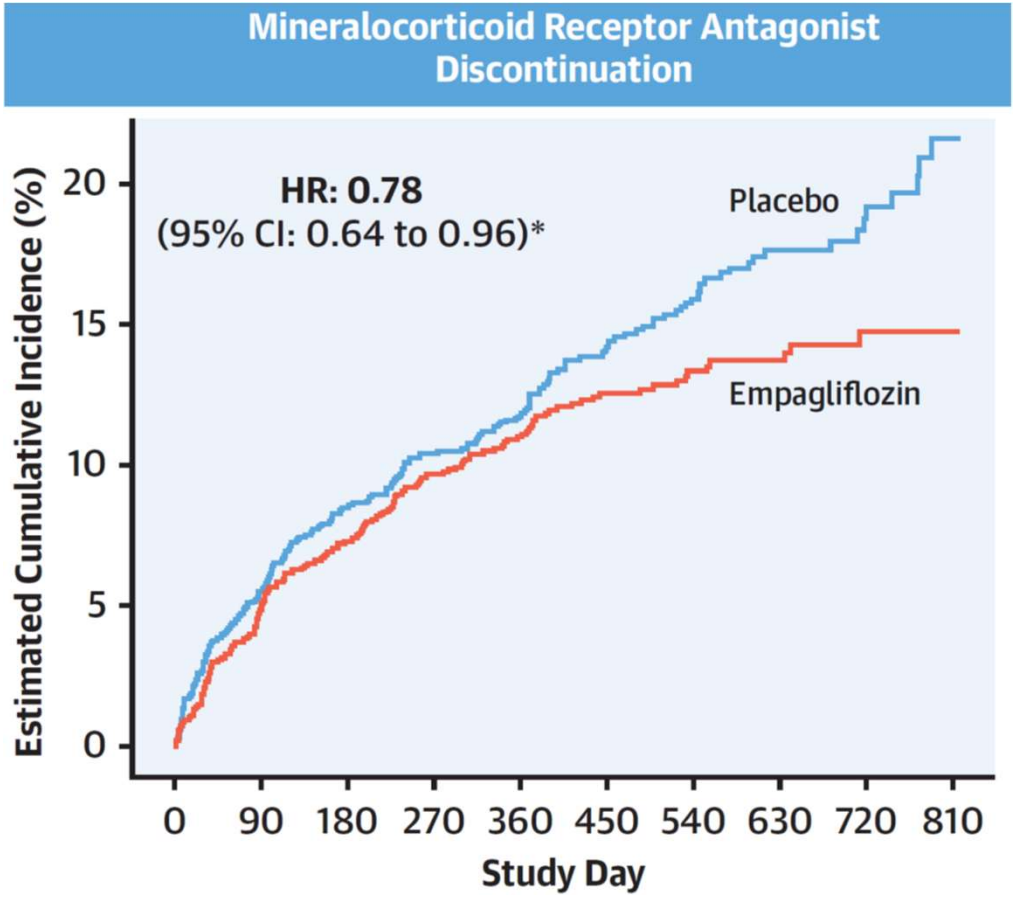
Docherty KF, et al. Eur Heart J. 2020;41:2379-2392

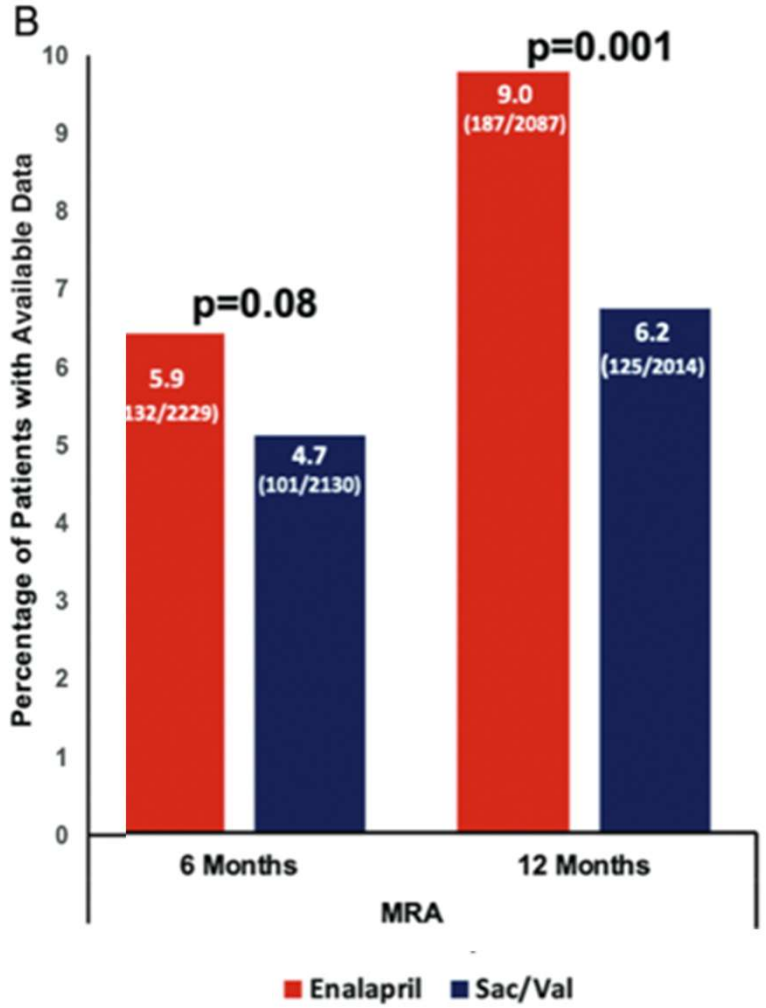
Complementarity between therapies



Greene SJ, Khan MS. J Am Coll Cardiol. 2021;77:1408-1411

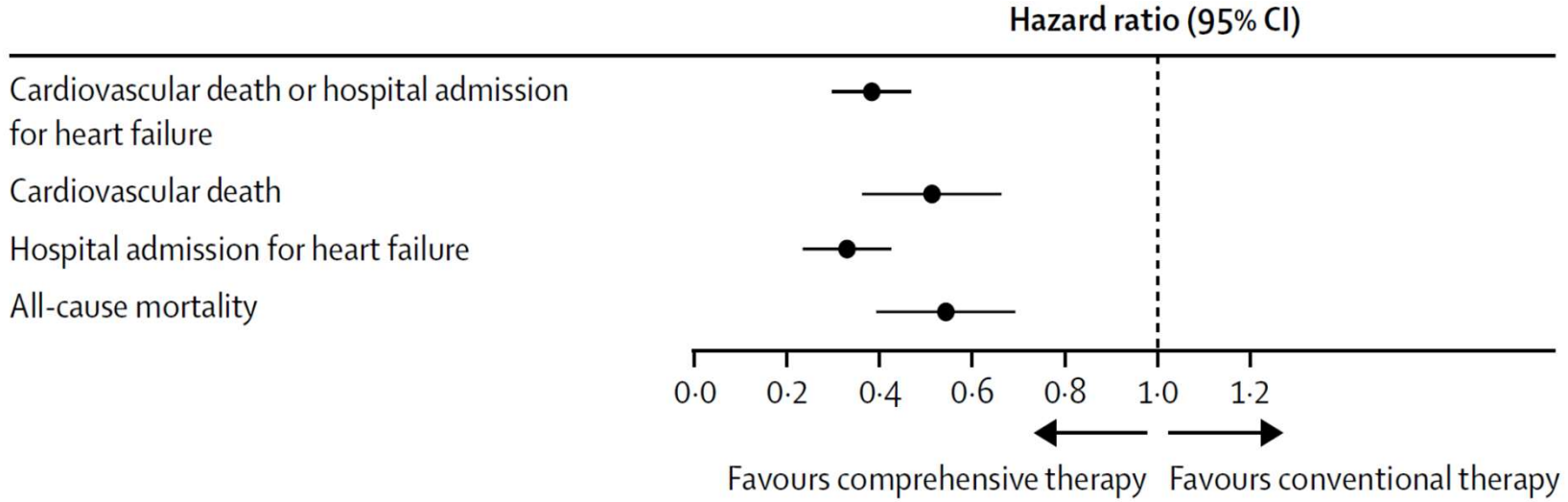
Initiating SGLT2i or switching to ARNI reduces MRA discontinuation

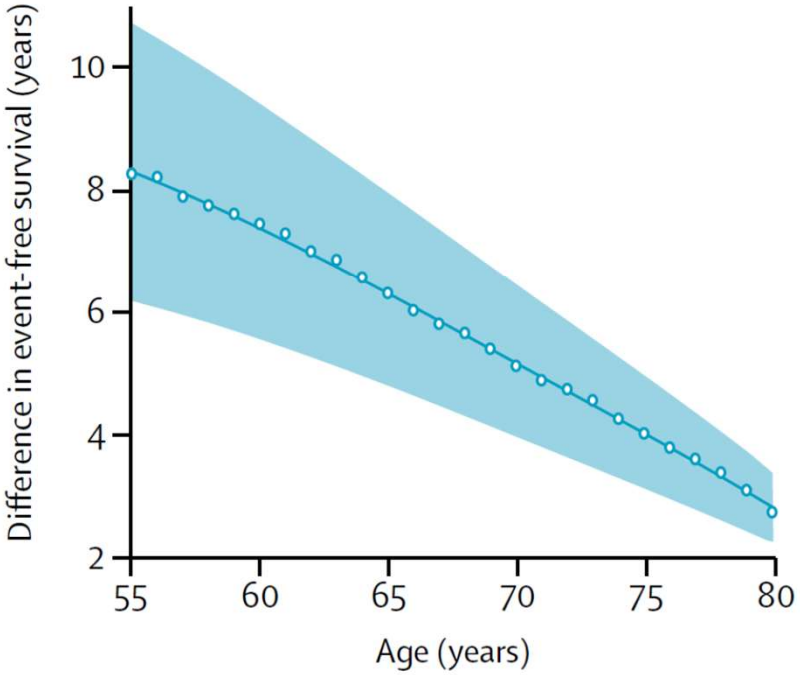


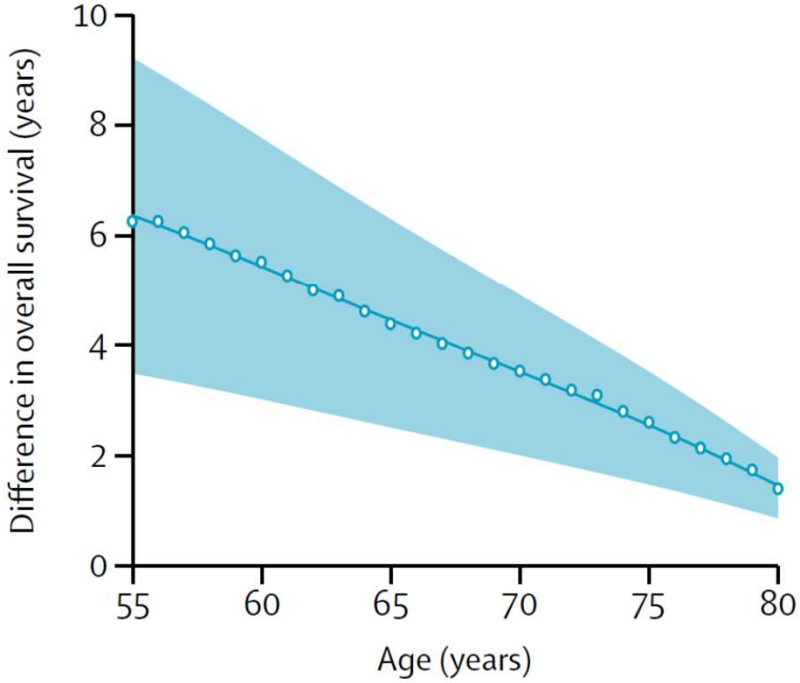


Ferreira JP, et al. J Am Coll Cardiol. 2021;77:1397-1407; Bhatt AS, et al. Eur J Heart Fail. 2021;23:1518-1524

Lifetime benefits of quadruple versus dual therapy





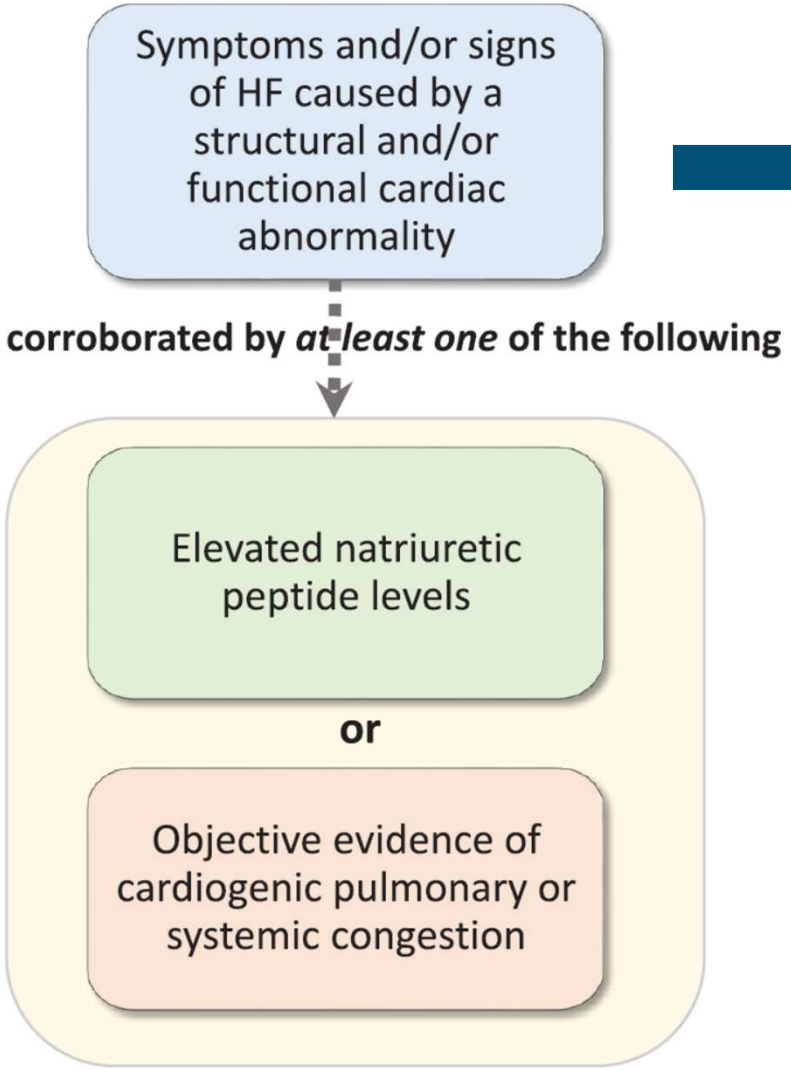


Vaduganathan M, et al. Lancet. 2020.

Key takeaways

- Maximal number of GDMT is more important than maximal doses in fewer therapies
- Multiple GDMT initiation/titration during a single visit is usually safe and well tolerated
- Worsening eGFR is common after initiation of GDMT, and is usually transient and benign
- Quadruple therapy is complementary and synergistic

What is heart failure? Universal definition HF



1. LVEF <50%

2. LVEF ≥50%

+

cardiac structural and/or functional abnormalities

Bozkurt B, et al. Eur J Heart Fail. 2021;23:352-380

HFpEF structural abnormalities

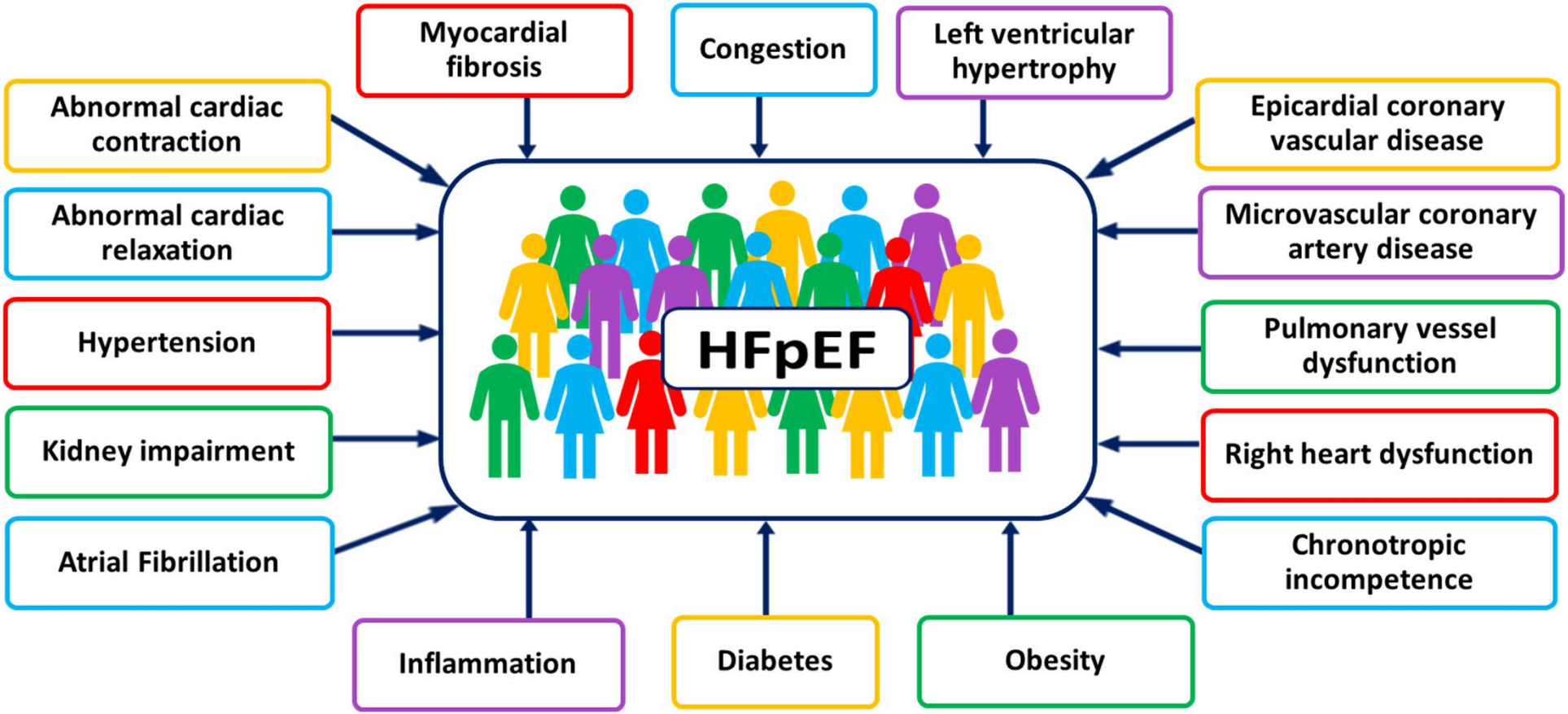
The diagnosis of HF-PEF requires three conditions:

1. Symptoms and signs of HF
2. LVEF ≥50%
3. Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised NPs

- LV mass index ≥95 g/m2 (Female), ≥115 g/m2 (Male)
- LA volume index >34 mL/m2 (SR) >40 mL/m2 (AF)
- E/e' >9
- NT-proBNP >125 (SR) or >365 (AF)
- BNP >35 (SR) or >105 (AF)
- PAP >35 mmHg

McDonagh TA, et al. Eur Heart J. 2021;42:3599-3726

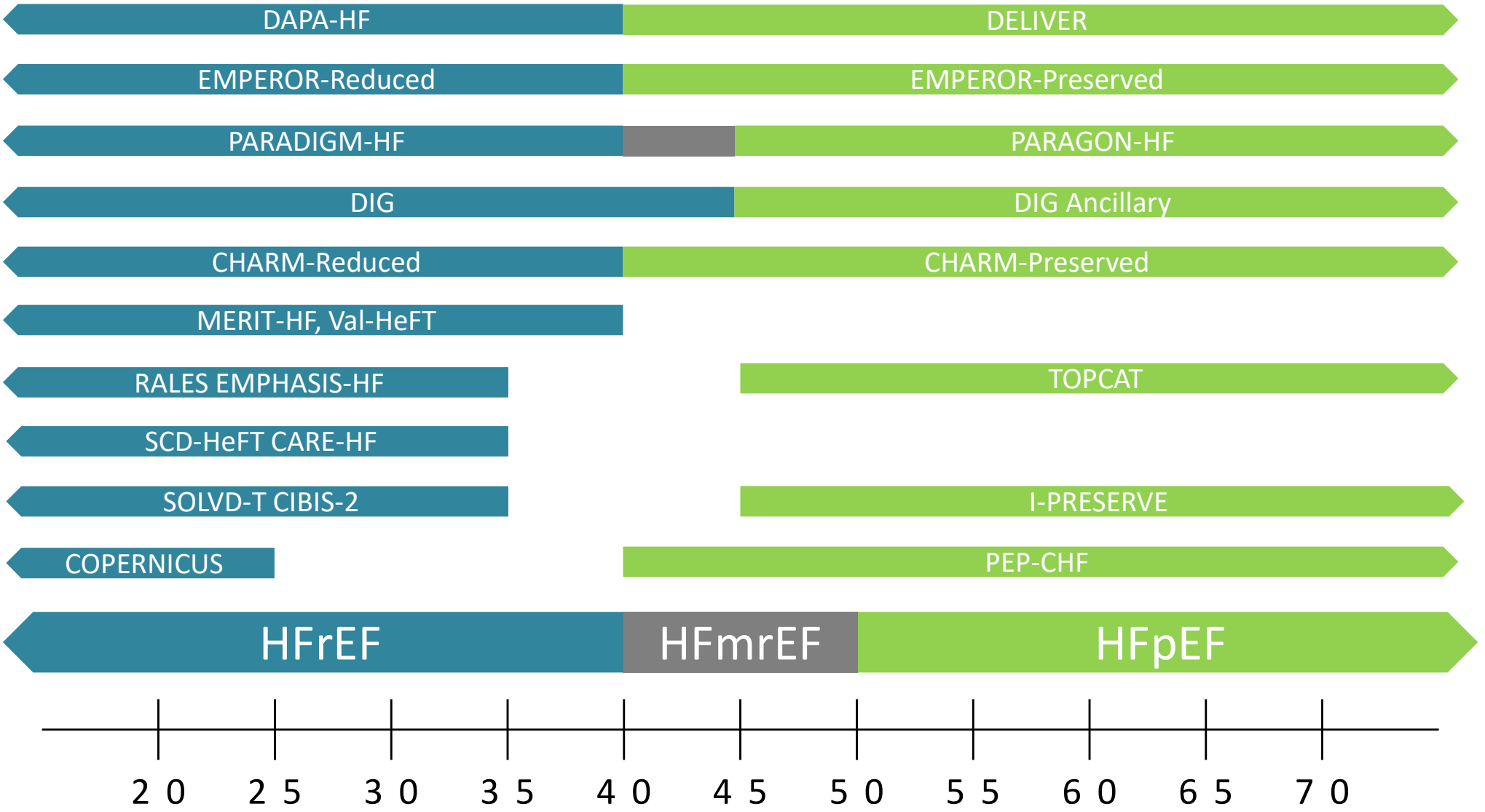
HFpEF is a complex comorbid disease



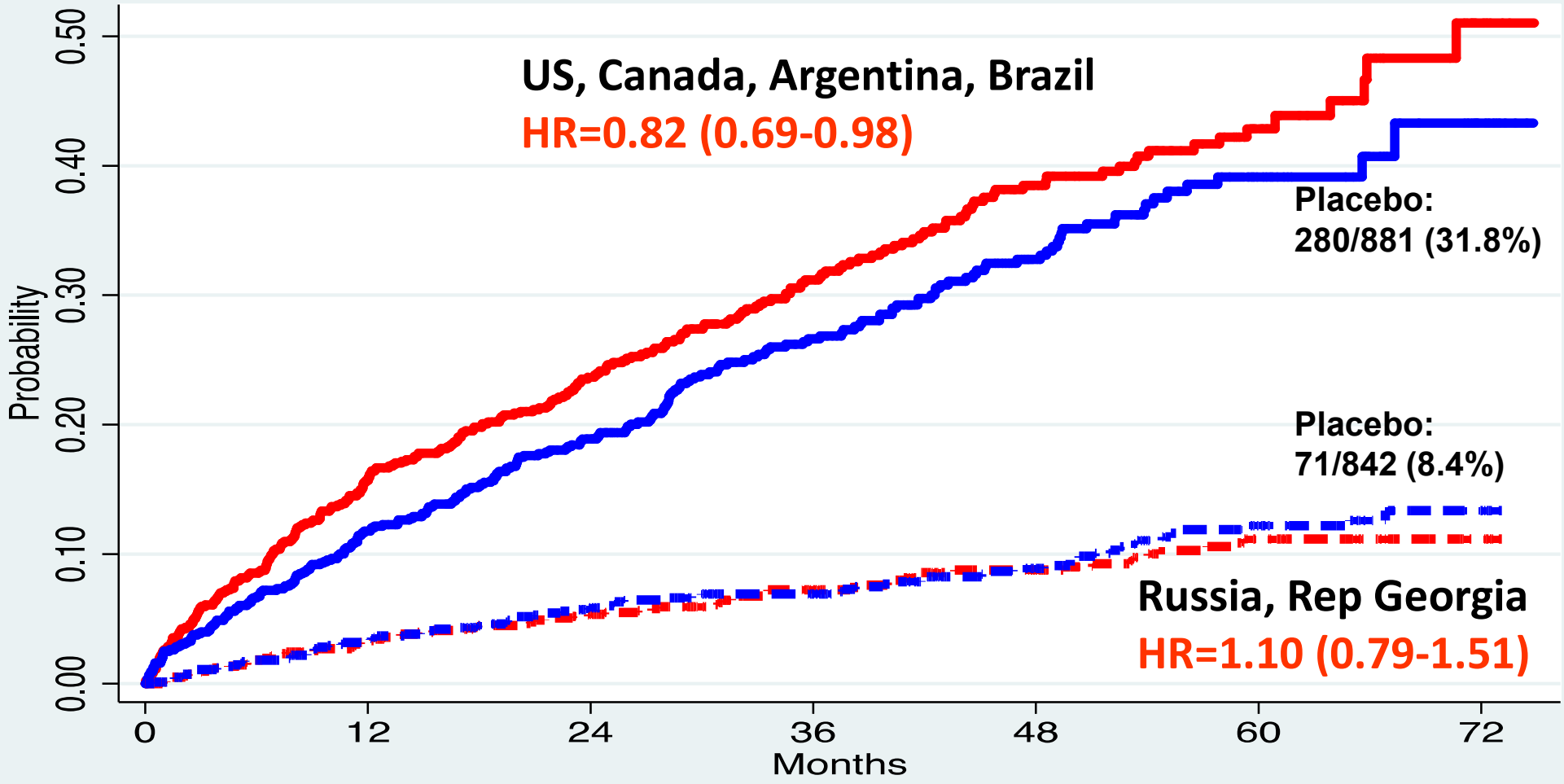
Campbell P, et al. Lancet. 2024;403:1083-1092

How did we get here?

No LVEF CONSENSUS V-HeFT



HFpEF only one treatment (Before SGLT2I): spironolactone (MRA)



- Fully adjusted model for primary endpoint including region and other variables:
  - HR 0.85, 95%CI 0.73 to 0.99, p=0.043

Common concern 2. Hyperkalemia

History

- 72 years
- HFpEF
- LVEF 51%
- T2DM 10 years
- HTN
- NSTEMI
- CKD stage 3

Exam and labs

- HR 70
- BP 125/60
- No edema
- JVP 1 cm
- BMI 33.1 kg/m2
- Euvolemia

- Na 138, K+ 4.8
- eGFR 34
- HbA1c 8.5%

Medications

- Perindopril 8 od
- Bisoprolol 5 od

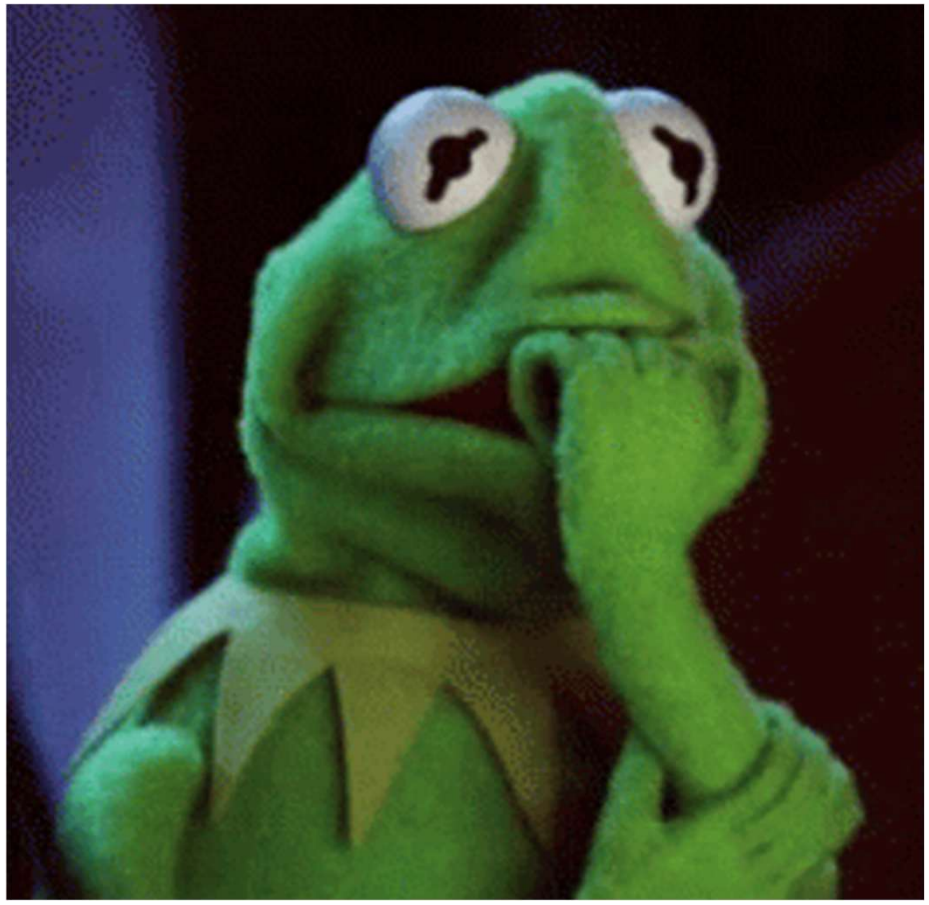
- Furosemide 40 od

- Metformin 500 bid
- Gliclazide MR 30 od

- ASA 75 od
- Clop 75 od
- Atorvastatin 80 od

You start an MRA and check labs ...

- eGFR 30 ml/min/m2
- K+ 5.8



What do you do?

- HFpEF
- Euvolemia
- eGFR 30
- K 5.8
- ACEI
- Started MRA

- Send to the ED
- Hold the MRA
- Review diet
- Review medications
- Consider an SGLT2I
- Start potassium binder

Hyperkalemia management

Severity K^+ mmol/L	Management	Monitoring
Mild 5.0 – 5.5 mmol/L	RAAS continue Potassium restriction Drugs: K^+ sparing diuretic, NSAID, K^+ supplement Hypovolemia	Routine if stable Repeat within 72 hours if medication change or upwards trend
Moderate 5.5 – 5.9 mmol/L	RAAS halve dose Or stop most recently added RAAS agent Drugs, hypovolemia Calcium polystyrene	Repeat within 72 hours Continued $K^+ > 5.5$ stop 1 RAAS agent
Severe > 5.9 mmol/L	RAAS inhibitors stop Immediate assessment 12 lead ECG Treat according protocol	Repeat 4 to 24 hours Depending on ECG and local protocol

The Canadian Cardiovascular Society Heart Failure Companion: Bridging Guidelines to Your Practice. Can J Cardiol. 2015;32(3):296-310
Canadian Cardiovascular Society Consensus Conference recommendations on heart failure update 2007. Can J Cardiol. 2007;23(1):21-45

Diet

Vegetables

- Potatoes
- Tomatoes

- Leafy greens
- Spinach
- Brussel sprouts

- Beans, lentils
- Winter squash

- Beets
- Avocado

Fruits and nuts

- Bananas
- Orange and grapefruit
- Melon
- Apricots
- Dried fruits, raisins

- Cashews
- Almonds

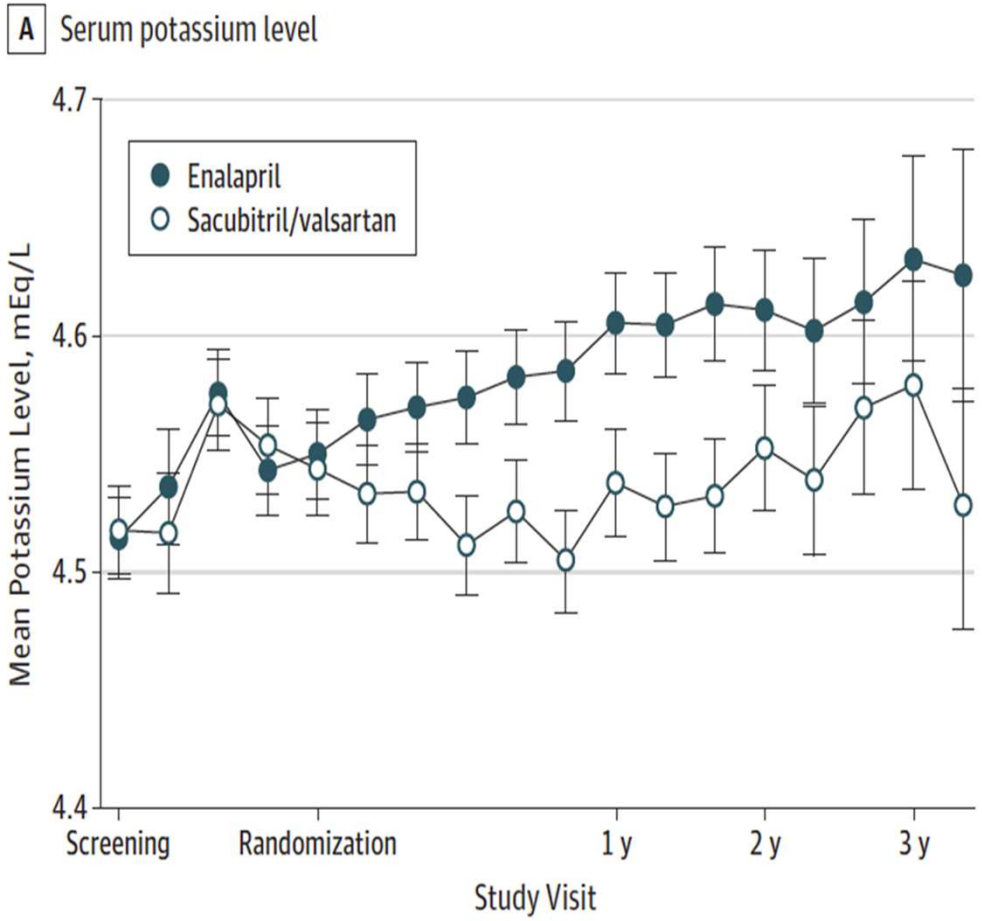
Other

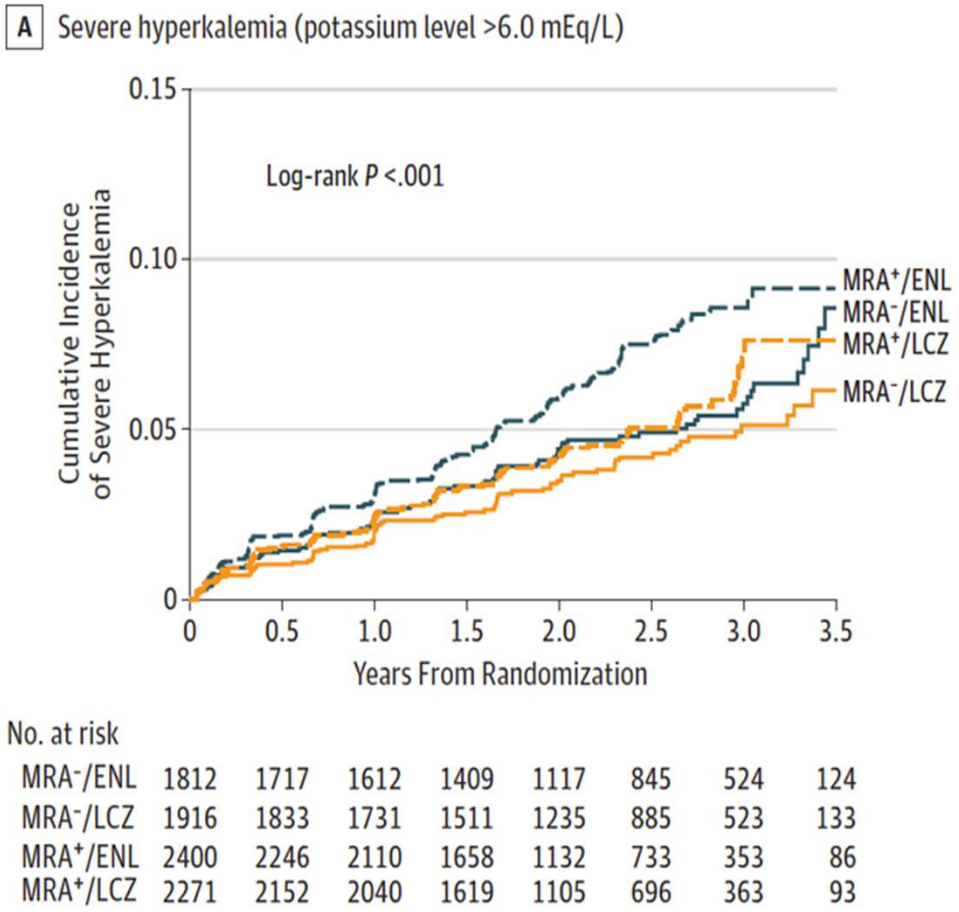
- Milk (all types)
- Yoghurt
- Granola

Medications - MRA

- MRA: The incidence of clinically significant hyperkalemia events was <1% in EPHESUS and EMPHASIS-HF, without a significant difference between Tx and placebo
- Coadministration of MRA with ACEI or ARB only mildly increases the risk of hyperkalemia
- Benefit of therapy persisted among patients who develop hyperkalemia

Risk of hyperkalemia with sacubitril-valsartan (ARNI) is lower than ACEI





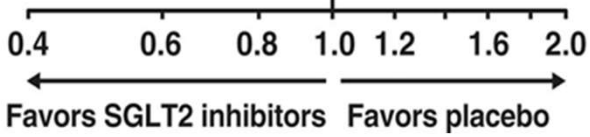
No. at risk

MRA⁻/ENL	1812	1717	1612	1409	1117	845	524	124
MRA⁻/LCZ	1916	1833	1731	1511	1235	885	523	133
MRA⁺/ENL	2400	2246	2110	1658	1132	733	353	86
MRA⁺/LCZ	2271	2152	2040	1619	1105	696	363	93

Desai et al. JAMA Cardiol. 2017 2(1):79-85

Risk of hyperkalemia is lower with concurrent SGLT2I

	SGLT2 inhibitors		Placebo		Hazard Ratio (95% CI)
	n/N	Events per 1000 patient-years	n/N	Events per 1000 patient-years	
CANVAS Program	137/5795	8.2	85/4347	9.2	0.89 (0.67, 1.17)
CREDENCE	121/2202	21.6	154/2199	27.9	0.77 (0.61, 0.98)
DAPA-CKD	159/1455	56.9	179/1451	65.3	0.88 (0.71, 1.09)
DECLARE-TIMI 58	53/8582	1.6	78/8578	2.3	0.67 (0.47, 0.95)
EMPA-REG OUTCOME	216/4687	17.2	124/2333	20.5	0.83 (0.67, 1.04)
VERTIS CV	291/5493	18.7	157/2745	21.2	0.90 (0.74, 1.09)
Overall (I^2=0.0%; $P_{heterogeneity}$=0.71)					**0.84 (0.76, 0.93)** P<0.001

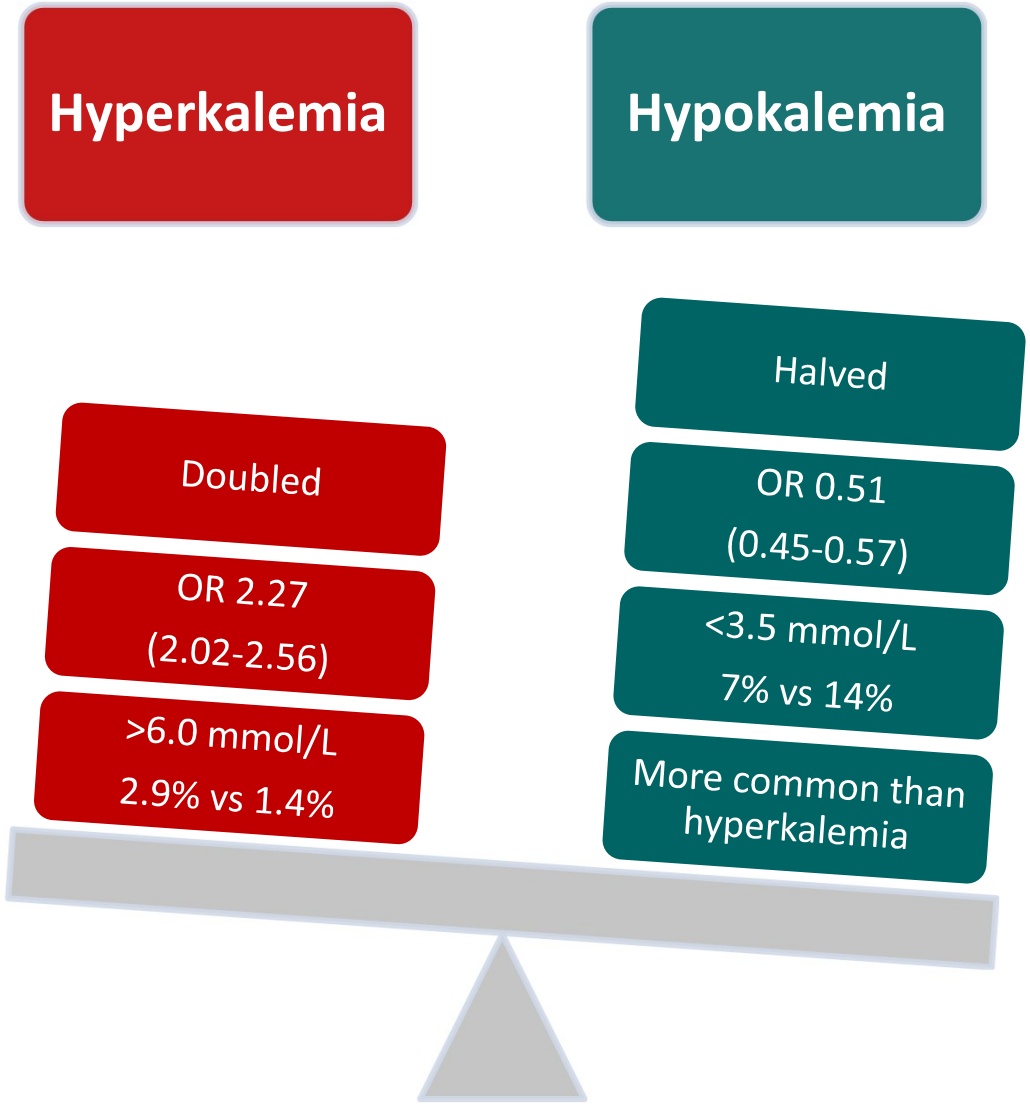


Neuen BL, et al. Circulation. 2022;145:1460-147

Potassium binders

	Sodium polystyrene sulfonate (Kayexalate)	Sodium zirconium cyclosilicate
Recommended dose	Oral: 15 g, 1–4 times daily Rectal: 30–50 g, 1–2 times daily	10 g 3 times daily for up to 48 hours Then once daily.

MRA hyper vs hypokalemia



- Meta-analysis
- 4 trials:
  - RALES (spironolactone)
  - EMPHASIS (eplerenone)
  - TOPCAT (spironolactone)
  - FINEARTS-HF (finerenone)

Jhund et al. Lancet 2024.

SGLT2I in HFpEF: Dapagliflozin (DELIVER trial)

Inclusion Criteria[1,2]

353 Sites
20 Countries

6263 Patients
- Age ≥40 with/without T2D
- Symptomatic HF
- LVEF >40%[a]
- Ambulatory or hospitalized
- Elevated NT-proBNP levels
- eGFR ≥25 mL/min/1.73 m^2

Randomized 1:1[b]
Stop when ~1117 primary events are reached

Dapagliflozin 10 mg | **Placebo**

Baseline Characteristics[2]

Older, Symptomatic Cohort

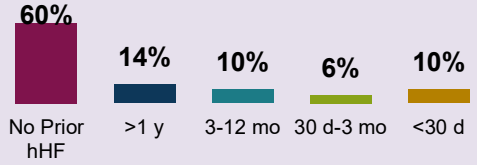
- **72 years** Mean Age
- **44%** Women
- **75%** NYHA Class II
- **25%** NYHA Class III
- **Moderate** Symptomatic Impairment[c]

High Rate of Comorbidities

- **45%** T2D
- **45%** BMI ≥30 kg/m^2
- **89%** Hypertension
- **57%** History of AF/AFL
- **51%** Coronary artery disease
- **61 mL/min/1.73 m^2** Mean eGFR

Elevated Risk

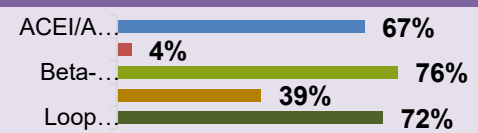
- Median NT-proBNP: **1011 pg/mL**
- **16%** enrolled during or <90 days of hospitalization
- History of hospitalization for HF:



Well-represented LVEF Groups

- Mean LVEF: **54%**
- Patients with prior LVEF ≤40%[3]: **~18%**

High Use of HF Medical Therapies



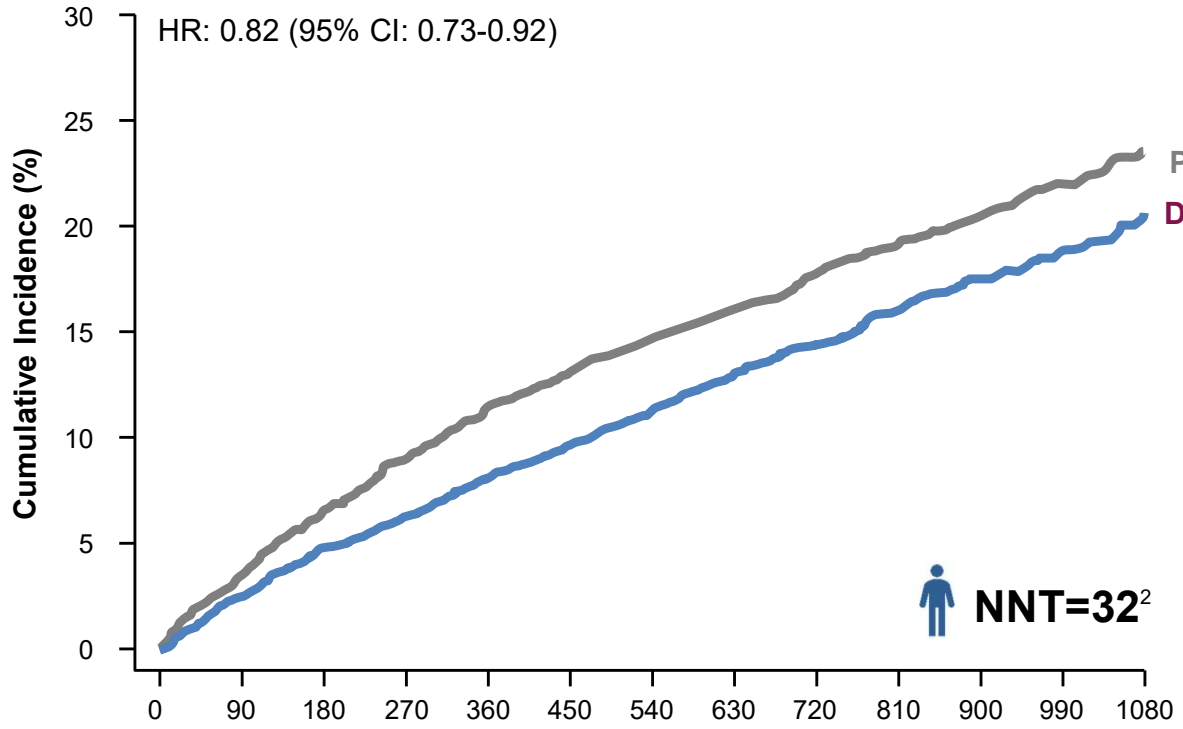
Primary Endpoint

- Time to first occurrence of any component of the composite of CV death or worsening HF events (hHF or urgent HF visit)
  - ❖ Full patient population
  - ❖ Patients with LVEF <60%

Secondary Endpoints

- Total number of HF events (first and recurrent) and CV deaths in the full patient population and in patients with LVEF <60%
- Change from baseline in KCCQ-TSS at 8 months
- Time to occurrence of CV death
- Time to occurrence of death from any cause

Primary Composite of CV Death, hHF or Urgent HF Visit

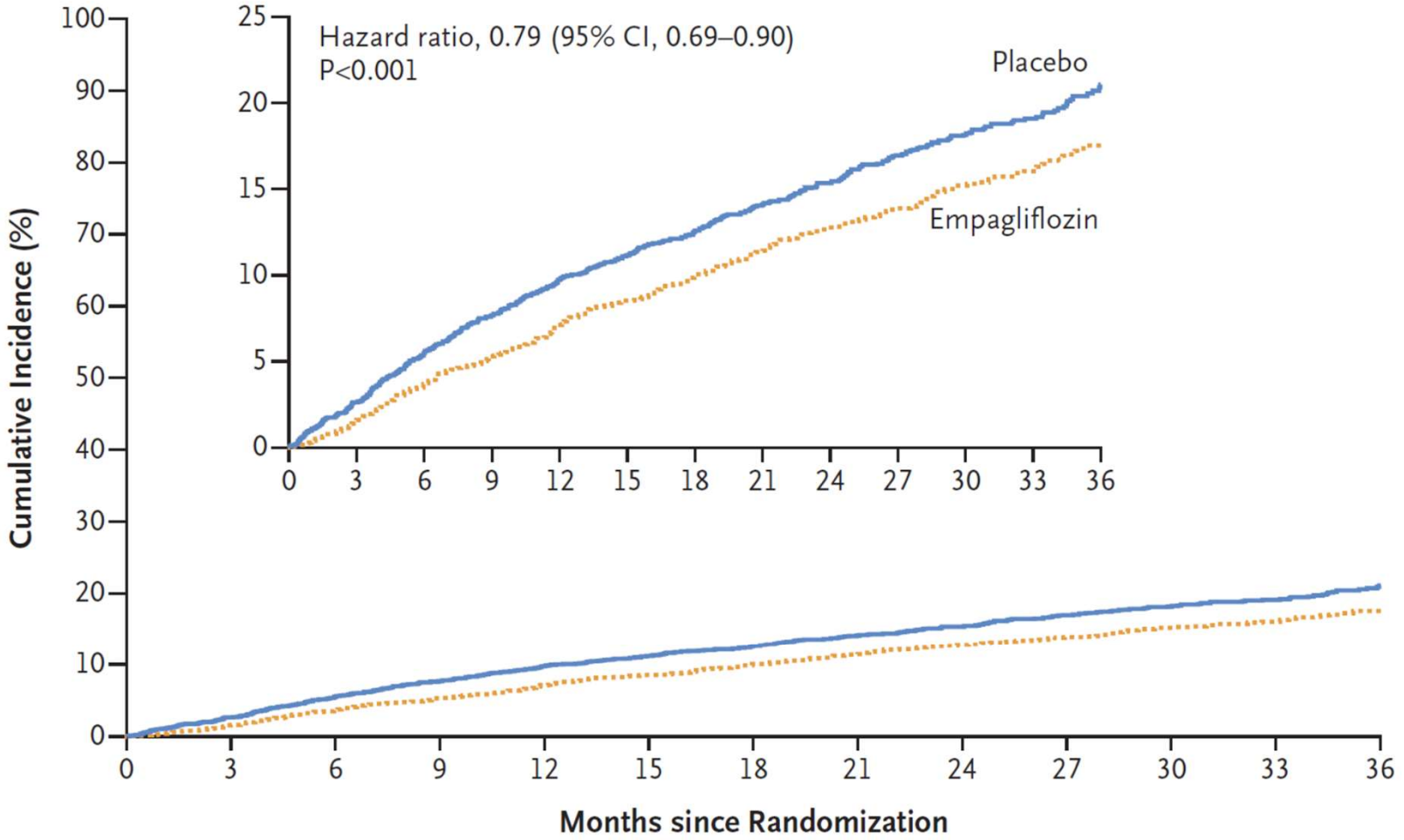


Number at Risk													
DAPA 10 mg	3131	3040	2949	2885	2807	2716	2401	2147	1982	1603	1181	801	389
Placebo	3132	3007	2896	2799	2710	2608	2318	2080	1923	1554	1140	772	383

18% RRR

3.1% ARR
p=0.0008[2]

SGLT2I in HFpEF: Empagliflozin (EMPEROR-Preserved trial)

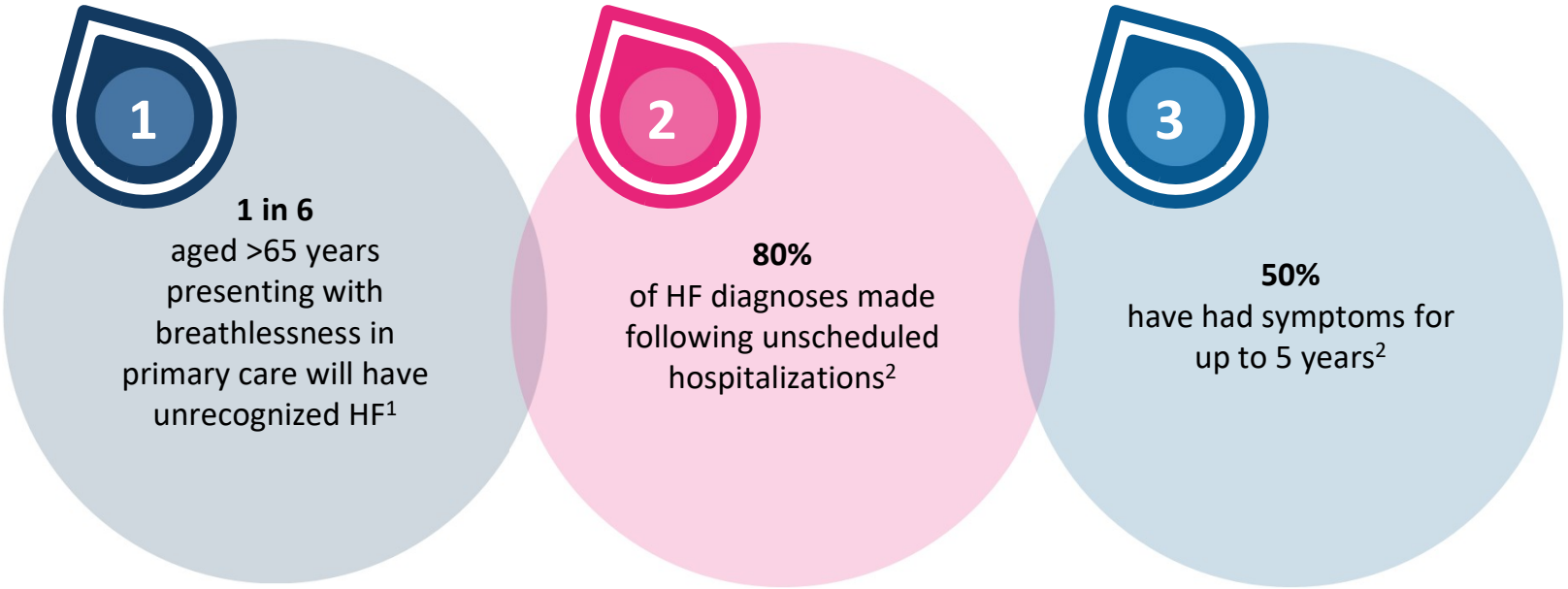


No. at Risk

Placebo	2991	2888	2786	2706	2627	2424	2066	1821	1534	1278	961	681	400
Empagliflozin	2997	2928	2843	2780	2708	2491	2134	1858	1578	1332	1005	709	402

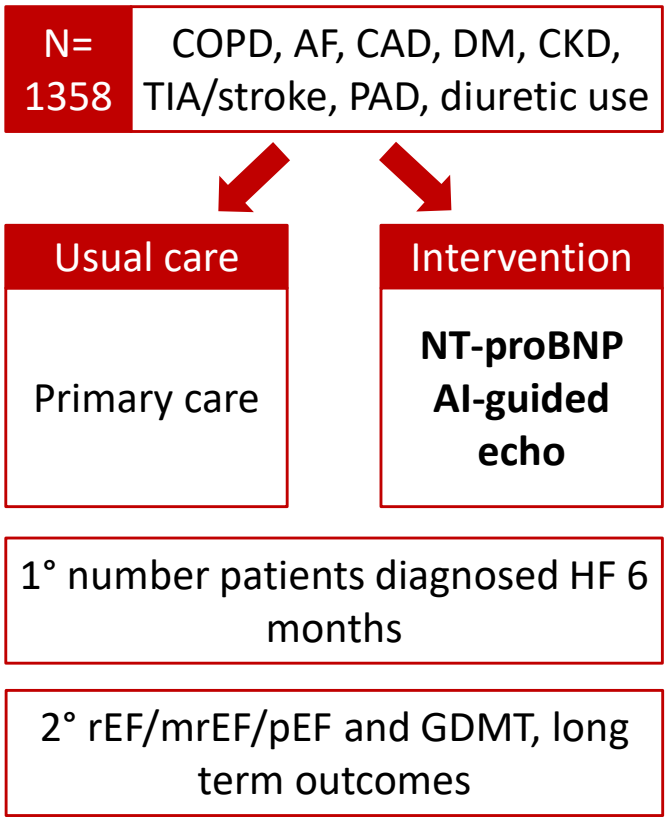
Anker SD, et al. N Engl J Med. 2021;385:1451-1461

The late/underdiagnosis of HF presents a huge problem for patients



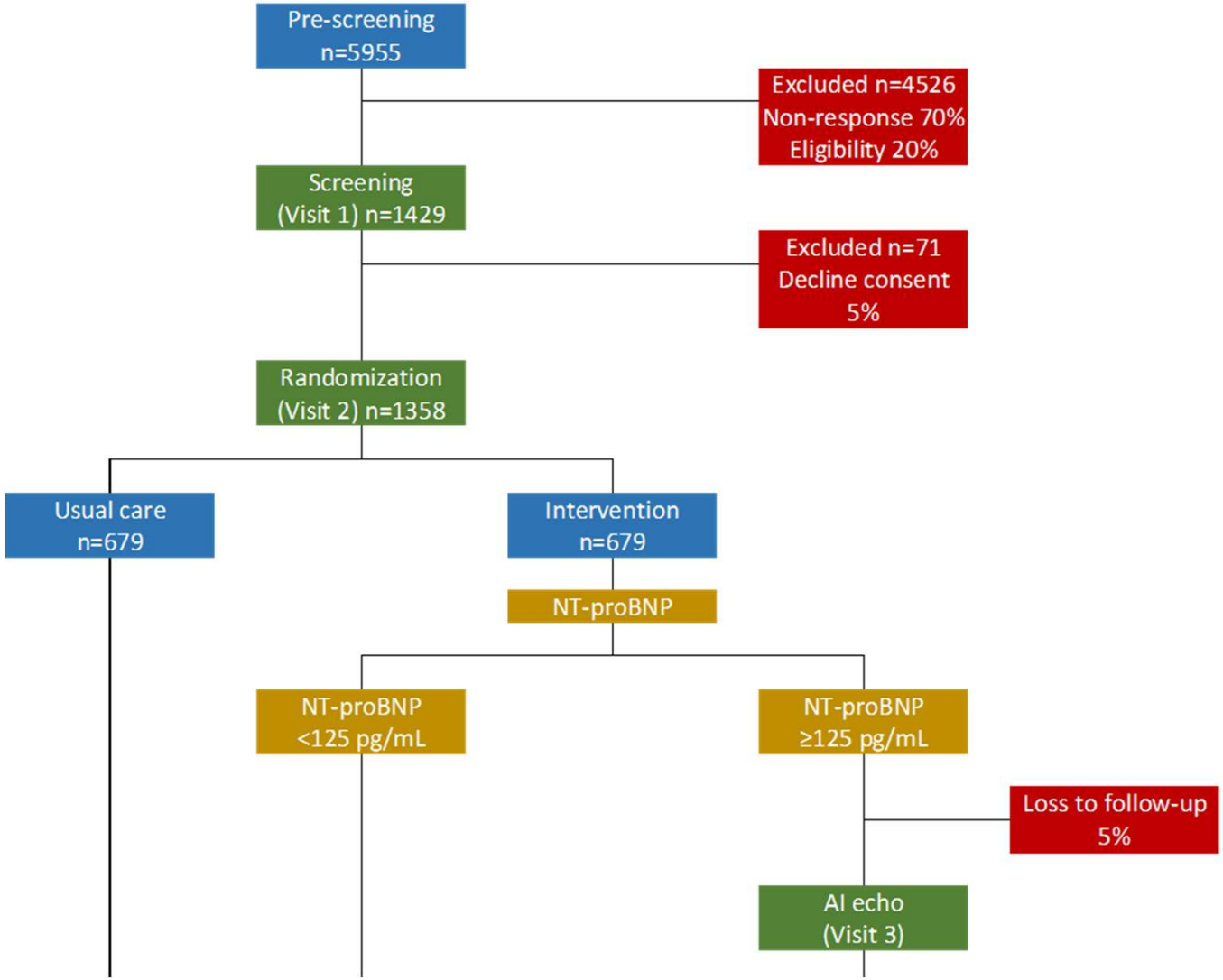
1. Van Riet EES, et al. Eur Heart J Fail 2014;16:772–777; 2. Bottle A, et al. Heart 2018;104:7:600–605

Multidisciplinary Approach for high-risk Patients Leading to Early diagnosis in Canadians with Heart Failure (MAPLE-CHF)

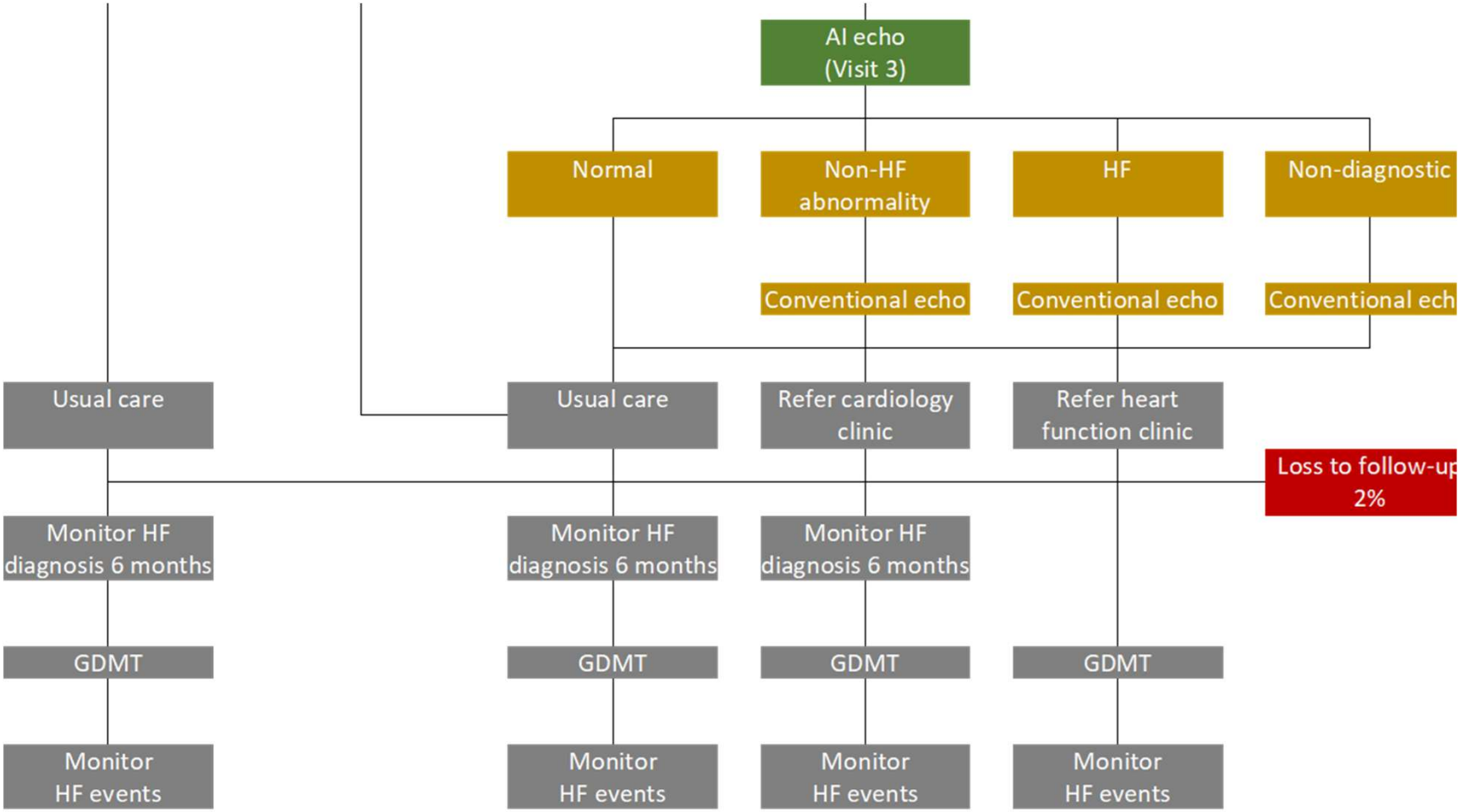


- Pre-screening through electronic health records
- NT-proBNP local labs
- AI guided acquisition and interpretation

Screening and randomization



Imaging and follow-up

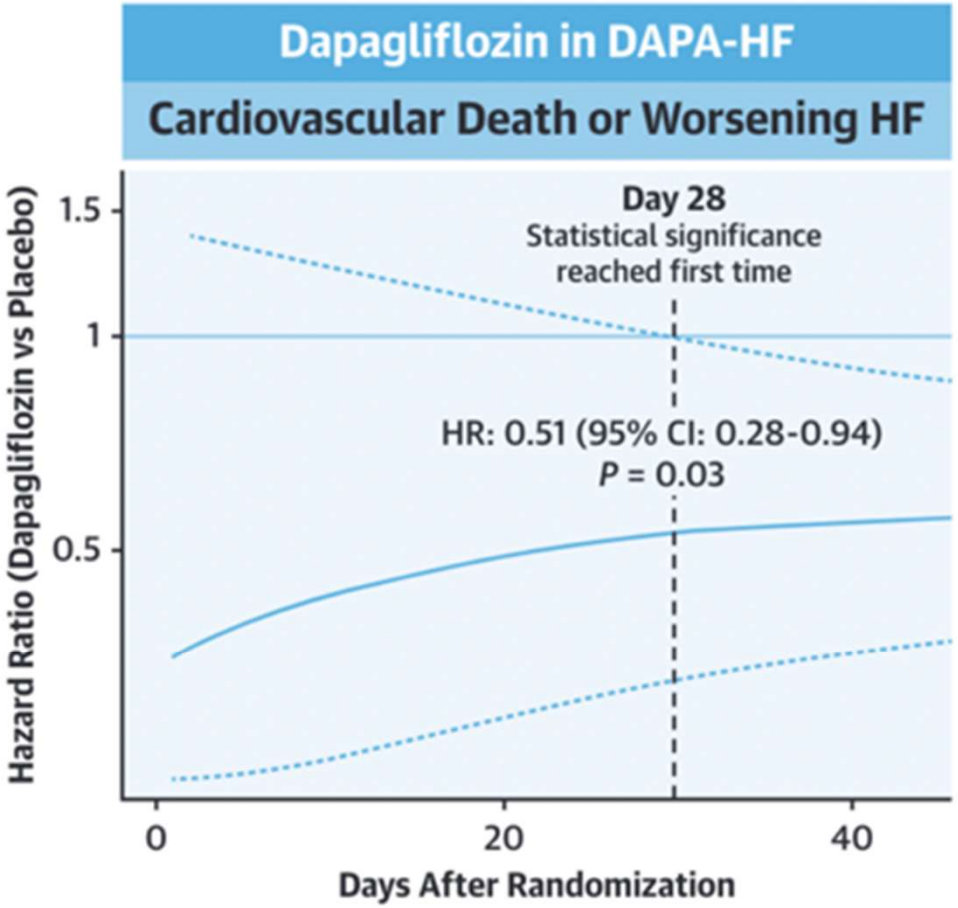


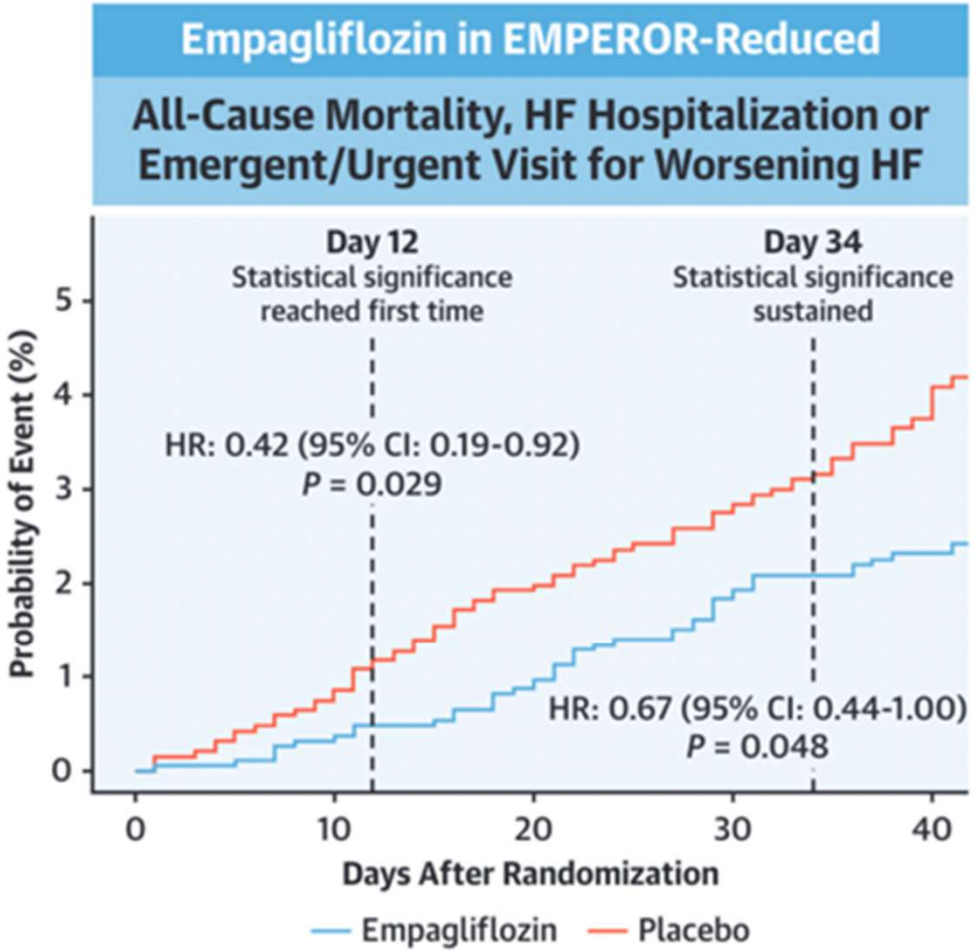
Conclusion

- HFrEF (LVEF ≤40%): quadruple therapy with ARNI, BB, MRA, and SGLT2I
- HFpEF and HFmrEF (LVEF>40%): SGLT2I and MRA
- SGLT2I and MRA are therefore used across the spectrum of ejection fraction
- Severe worsening renal function and hyperkalemia are uncommon and manageable
- To be part of MAPLE-CHF email: nat.hawkins@ubc.ca

Discussion

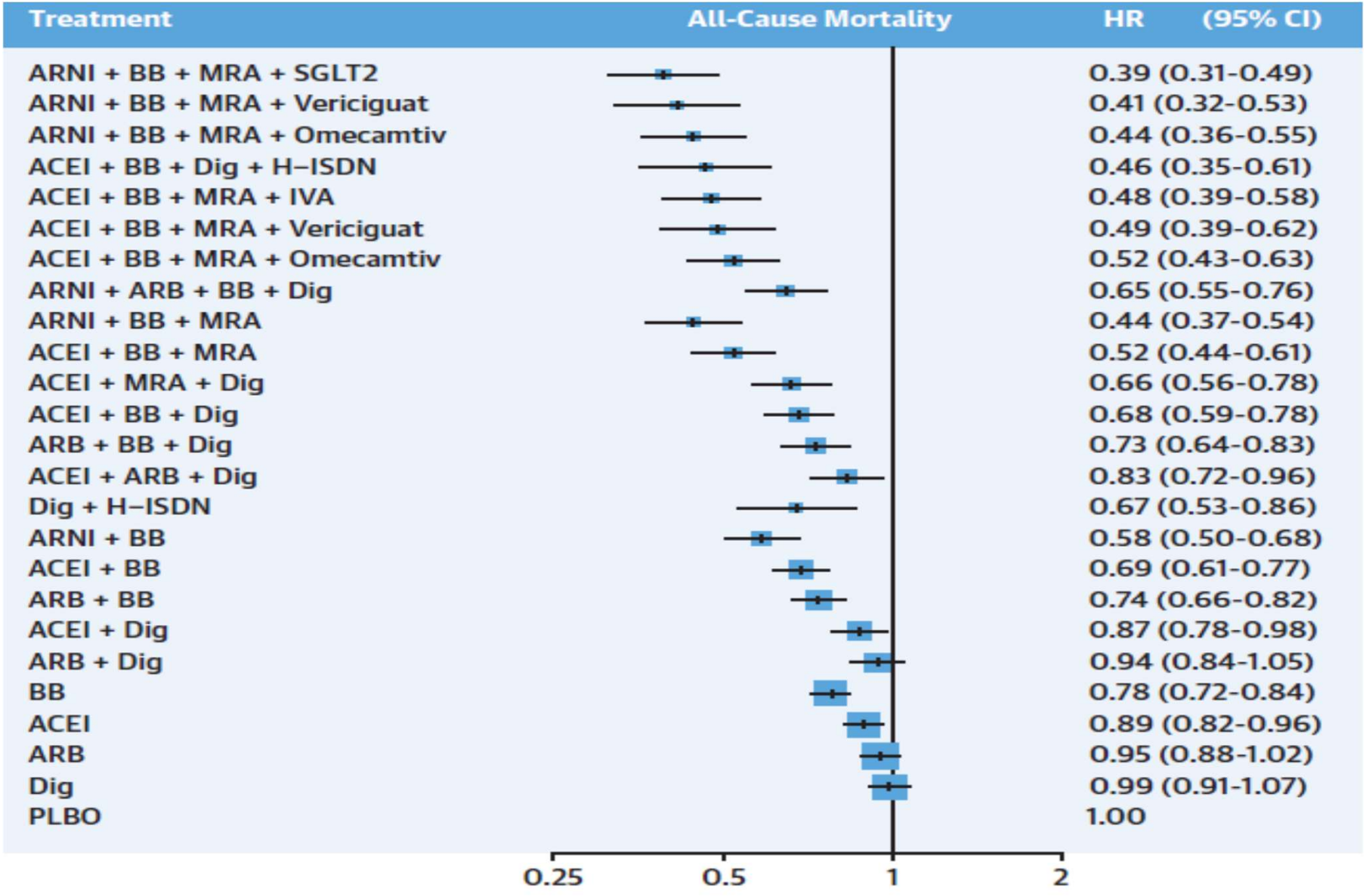
Time is of the essence: SGLT2i benefits occur very early





Berg DD, et al. JAMA Cardiol. 2021;6:499-507; Packer M, et al. Circulation. 2021;143:326-336

Quadruple therapy reduces all-cause mortality by 61% relative to placebo



Tromp J, et al. JACC Heart failure. 2022;10:73-84