Heart Failure: Changing Pathways

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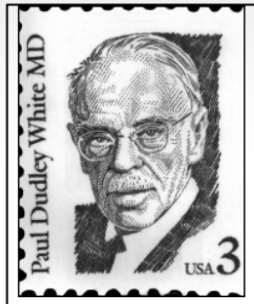
Disclosures
Research grants: Medtronic
Honoraria, speaker fees: Abbott, AstraZeneca, Medtronic, Pfizer, Pharmacosmos, Servier, Vifor

From a Terminal Diagnosis to Advances in Treatments for HF

Treatment of heart failure
From two textbooks 1929 and 1974



"…and for all this there is only digitalis and rest…"

Paul Dudley White: Textbook in Cardiology, 1929

J Willis Hurst
1920-2011

Moderately severe heart failure
- Decrease physical activity
- Institute digitalis
- Give thiazide every day plus potassium
- If not enough use furosemide and if insufficient, combine them

J W Hurst: The Heart 3rd edition, 1974

"There are decades when nothing happens, and there are weeks where decades happen"

Lenin

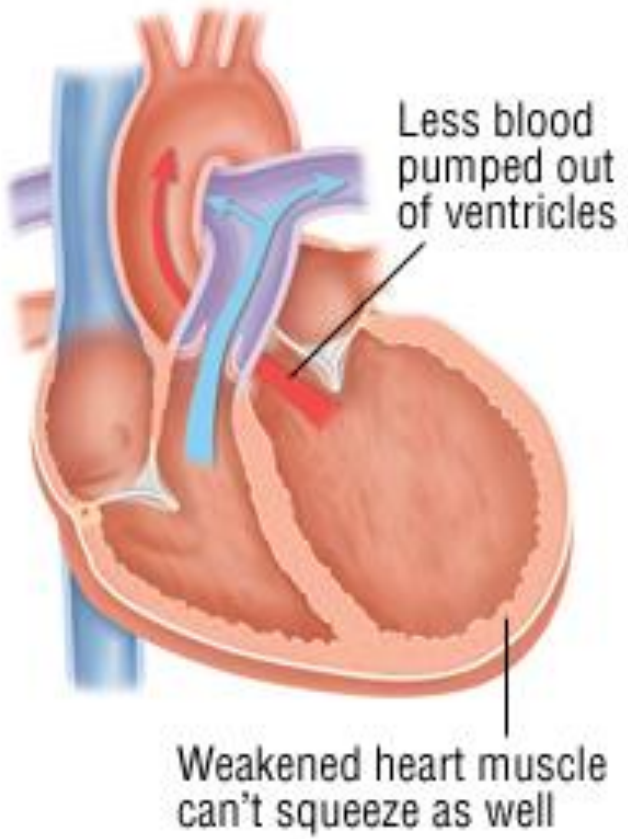
After decades of no change in the management of heart failure, there have been radical changes in the way we manage HF

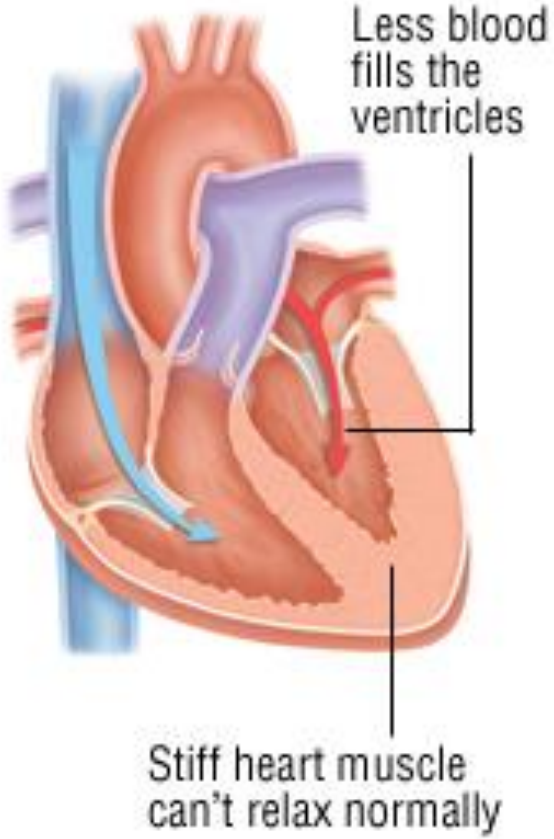
Examples, Karl Swedberg, ESC Congress.

Changing clinical pathways in HF

- Quadruple therapy
- Rapid titration
- Denovo ARNis in HFrEF
- Changing management in HFmrEF
- Changing management in HFpEF
- IV iron in heart failure
- Virtual wards for acute HF

A Simplistic View: 2 ways the myocardium can fail





"Systolic heart failure"

HF-REF

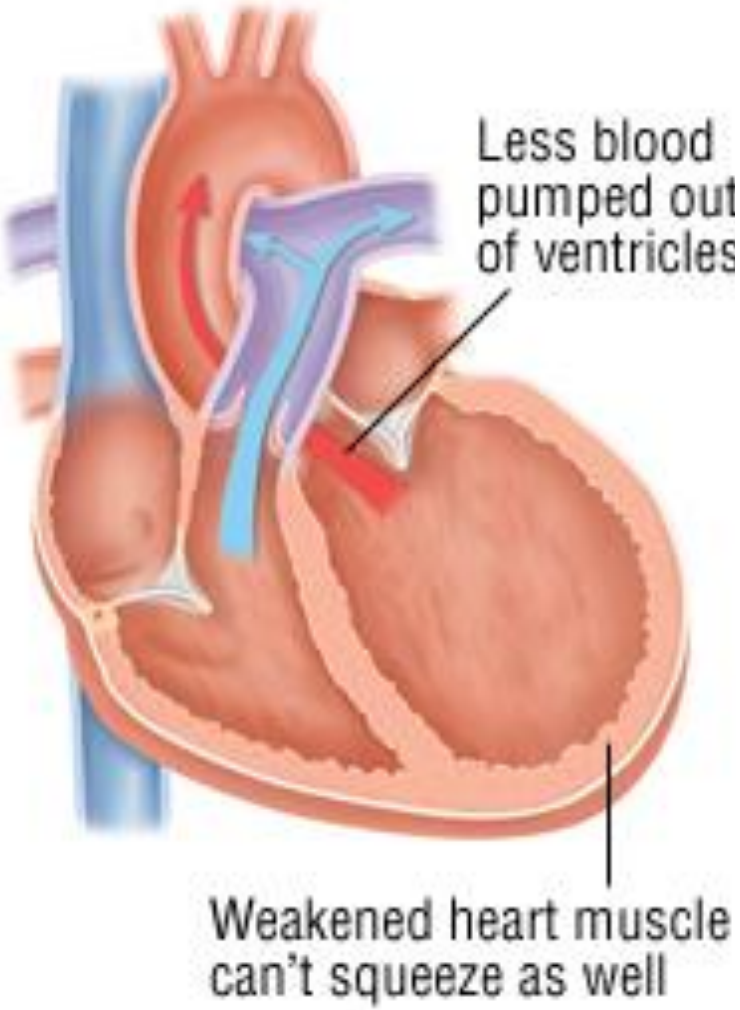
"Diastolic heart failure"

HF-PEF

Causes of HF

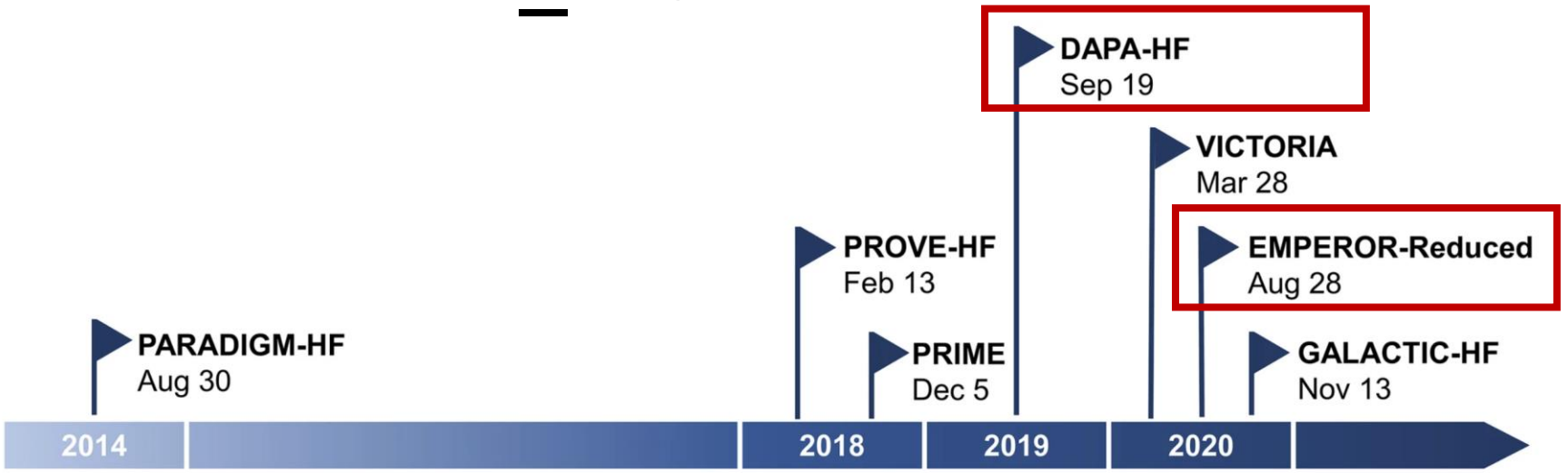
- **Ischaemic (>60%)**
- **Non-ischaemic**

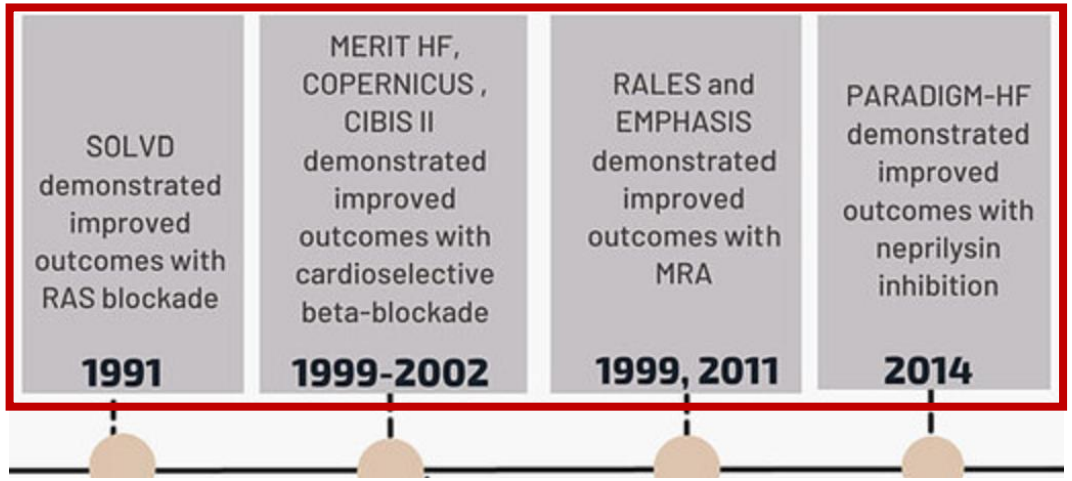
HFrEF: LVEF ≤40%



"Systolic heart failure"

HF-REF;
LVEF <40%





Subsequent to these trials we have 5 different classes of oral medications for use in Heart Failure

Dębska-Kozłowska, A., et al. *Heart Fail Rev* **27**, 419–430 (2022).

Changing clinical pathways in HF

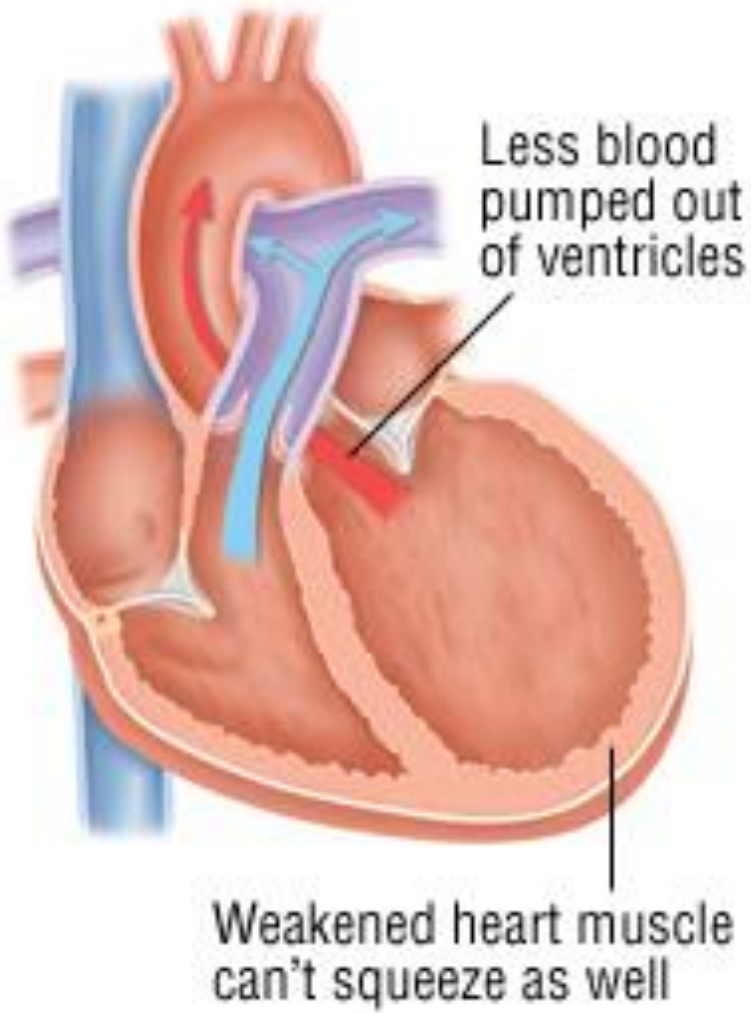
- Quadruple therapy in HFrEF
- Rapid titration in HFrEF
- Denovo ARNis in HFrEF
- Changing management in HFmrEF
- Changing management in HFpEF
- IV iron in heart failure
- Virtual wards for acute HF

Quadruple therapy is strongly recommended in HFrEF

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

Conventional drug sequencing in HFrEF:
Start low and go slow -> therapeutic inertia



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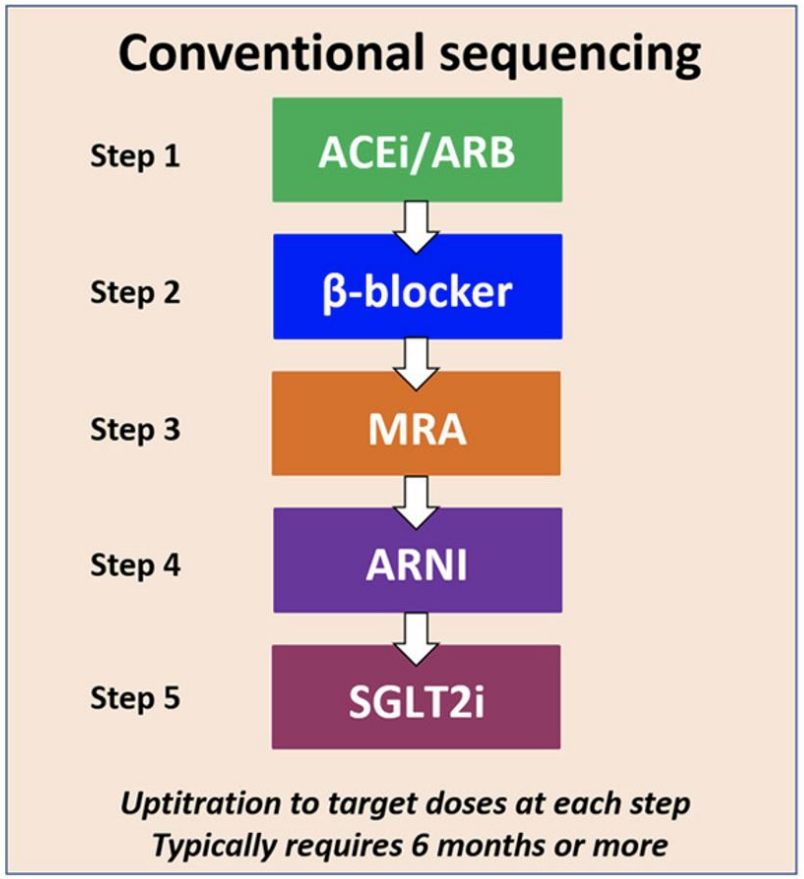


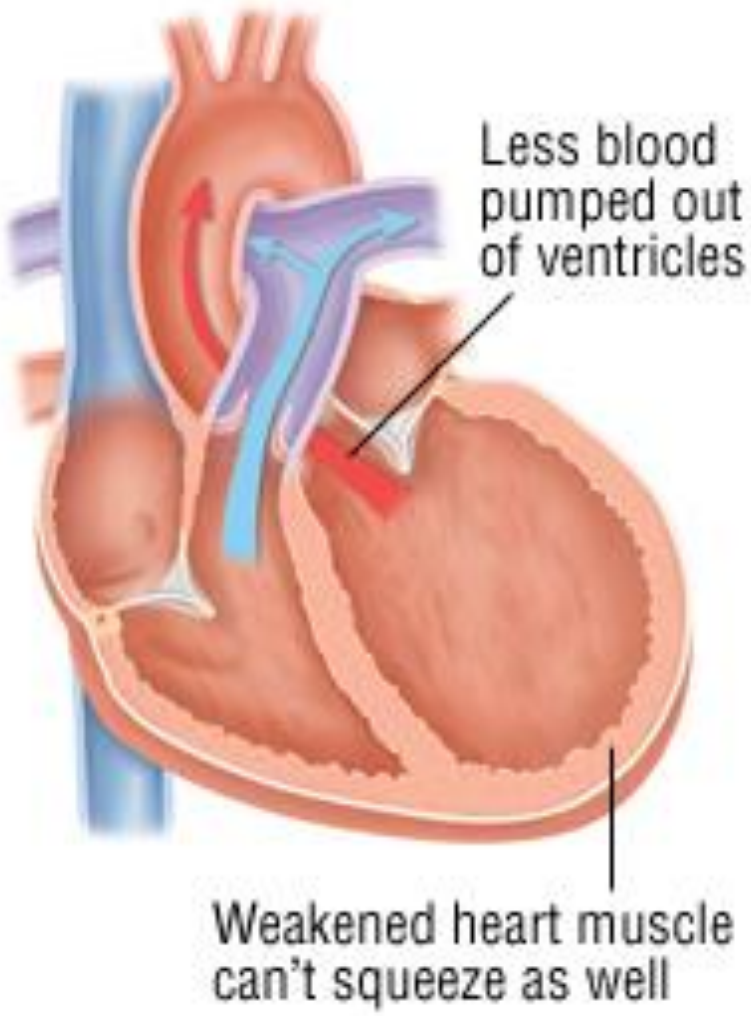
Table 8 Evidence-based doses of disease-modifying drugs in key randomized trials in patients with heart failure with reduced ejection fraction

	Starting dose	Target dose
ACE-I		
Captopril[a]	6.25 mg *t.i.d.*	50 mg *t.i.d.*
Enalapril	2.5 mg *b.i.d.*	10–20 mg *b.i.d.*
Lisinopril[b]	2.5–5 mg *o.d.*	20–35 mg *o.d.*
Ramipril	2.5 mg *b.i.d.*	5 mg *b.i.d.*
Trandolapril[a]	0.5 mg *o.d.*	4 mg *o.d.*
ARNI		
Sacubitril/valsartan	49/51 mg *b.i.d.*[c]	97/103 mg *b.i.d.*
Beta-blockers		
Bisoprolol	1.25 mg *o.d.*	10 mg *o.d.*
Carvedilol	3.125 mg *b.i.d.*	25 mg *b.i.d.*[e]
Metoprolol succinate (CR/XL)	12.5–25 mg *o.d.*	200 mg *o.d.*
Nebivolol[d]	1.25 mg *o.d.*	10 mg *o.d.*
MRA		
Eplerenone	25 mg *o.d.*	50 mg *o.d.*
Spironolactone	25 mg *o.d.*[f]	50 mg *o.d.*
SGLT2 inhibitor		
Dapagliflozin	10 mg *o.d.*	10 mg *o.d.*
Empagliflozin	10 mg *o.d.*	10 mg *o.d.*
Other agents		
Candesartan	4 mg *o.d.*	32 mg *o.d.*
Losartan	50 mg *o.d.*	150 mg *o.d.*
Valsartan	40 mg *b.i.d.*	160 mg *b.i.d.*
Ivabradine	5 mg *b.i.d.*	7.5 mg *b.i.d.*

Shah A, et al. Heart Failure: A Class Review of Pharmacotherapy. P T. 2017 Jul;42(7):464-472.

Conventional drug sequencing in HFrEF:

Why we can ill afford to start low and go slow



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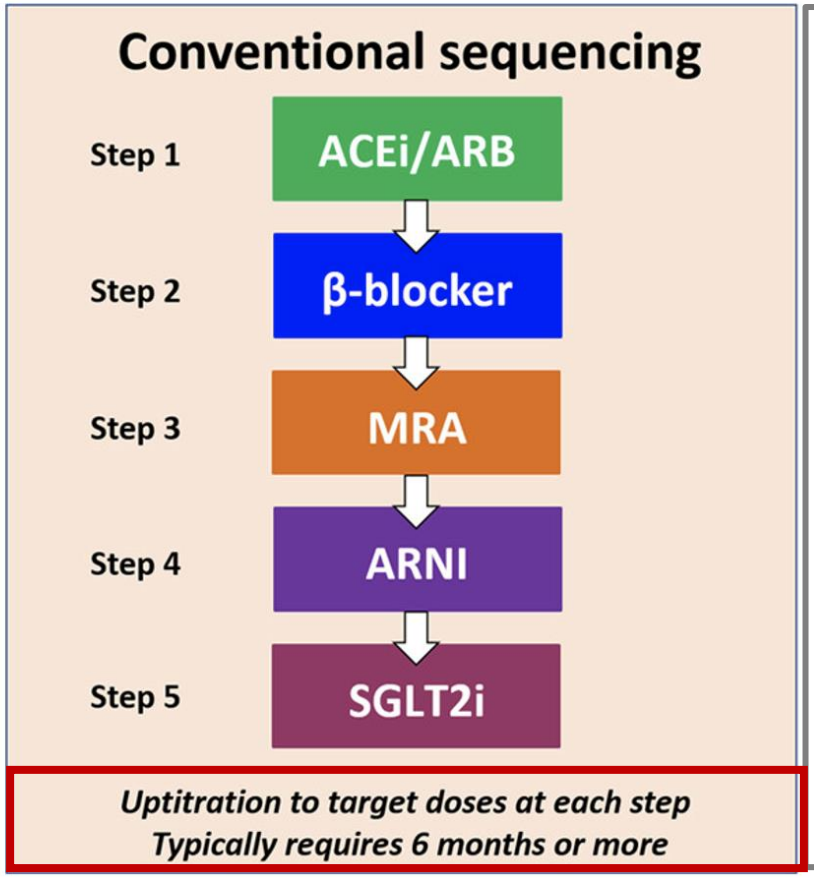
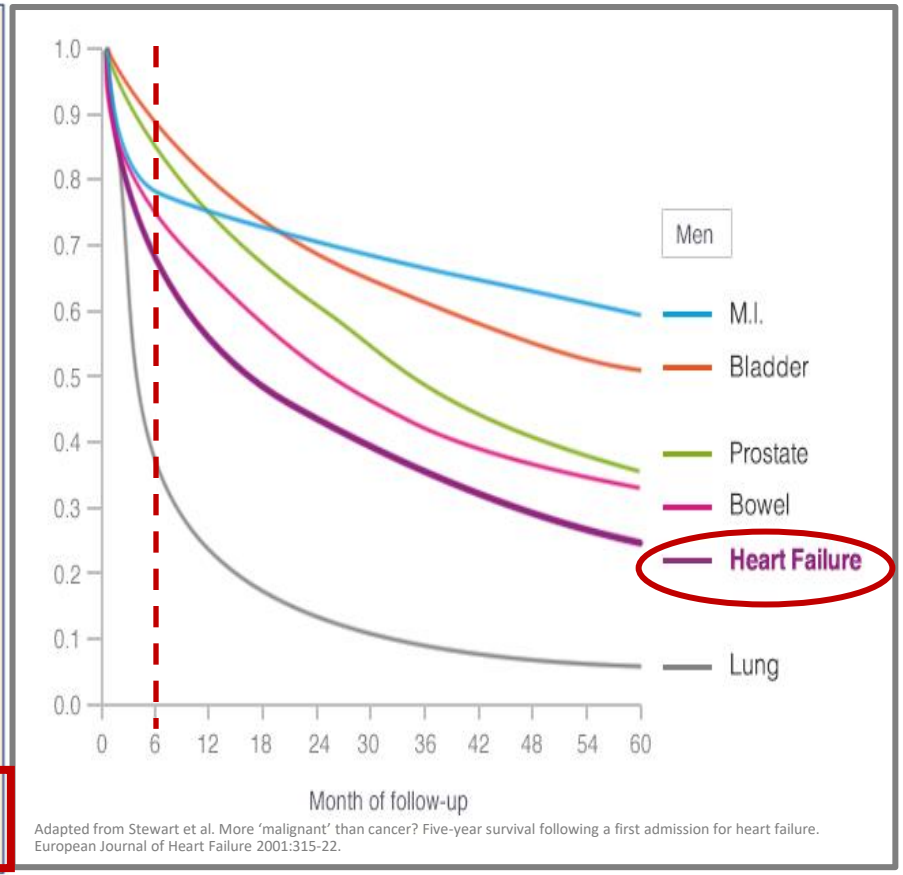
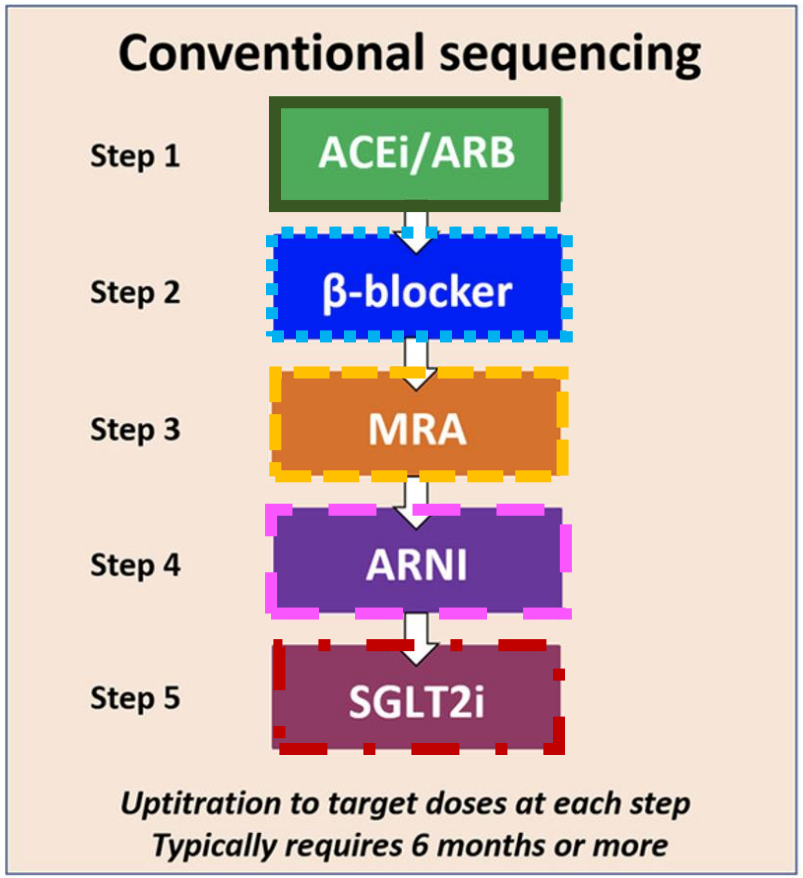


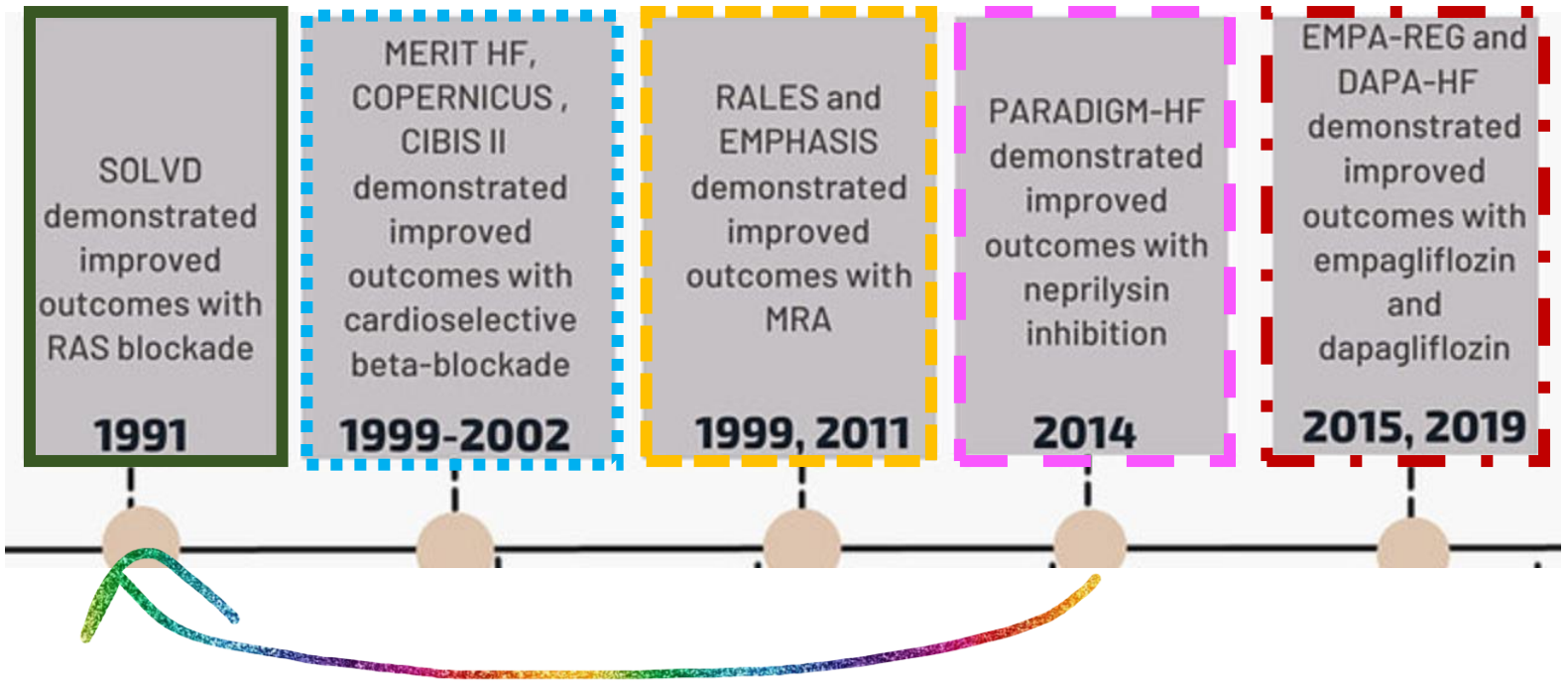


FIVE YEAR MORTALITY FOR HF WORSE THAN MI AND CANCER

Shah A, et al. Heart Failure: A Class Review of Pharmacotherapy. P T. 2017 Jul;42(7):464-472.

Rationale for historical sequencing of medications in HFrEF:

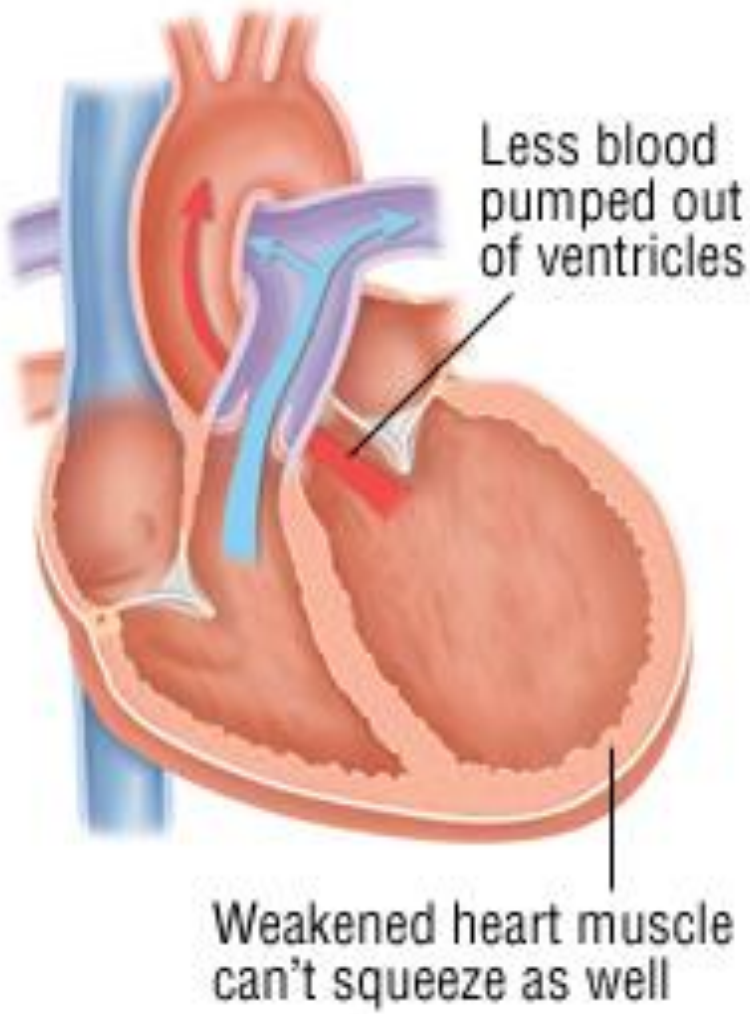




Quadruple therapy in heart failure

Shah A, et al. Heart Failure: A Class Review of Pharmacotherapy. P T. 2017 Jul;42(7):464-472.

Delays in treatment intensification led to changes in the clinical pathway



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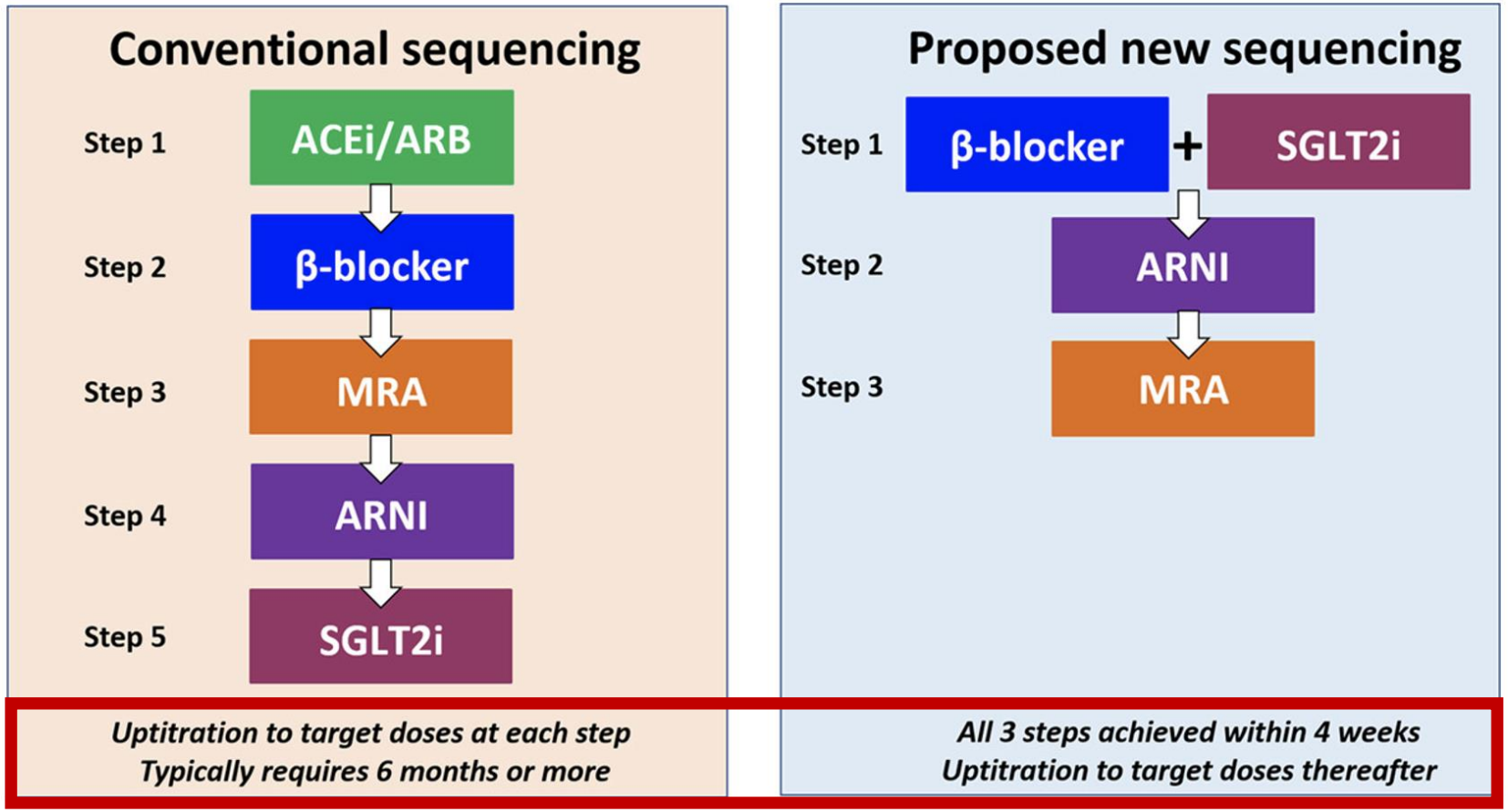
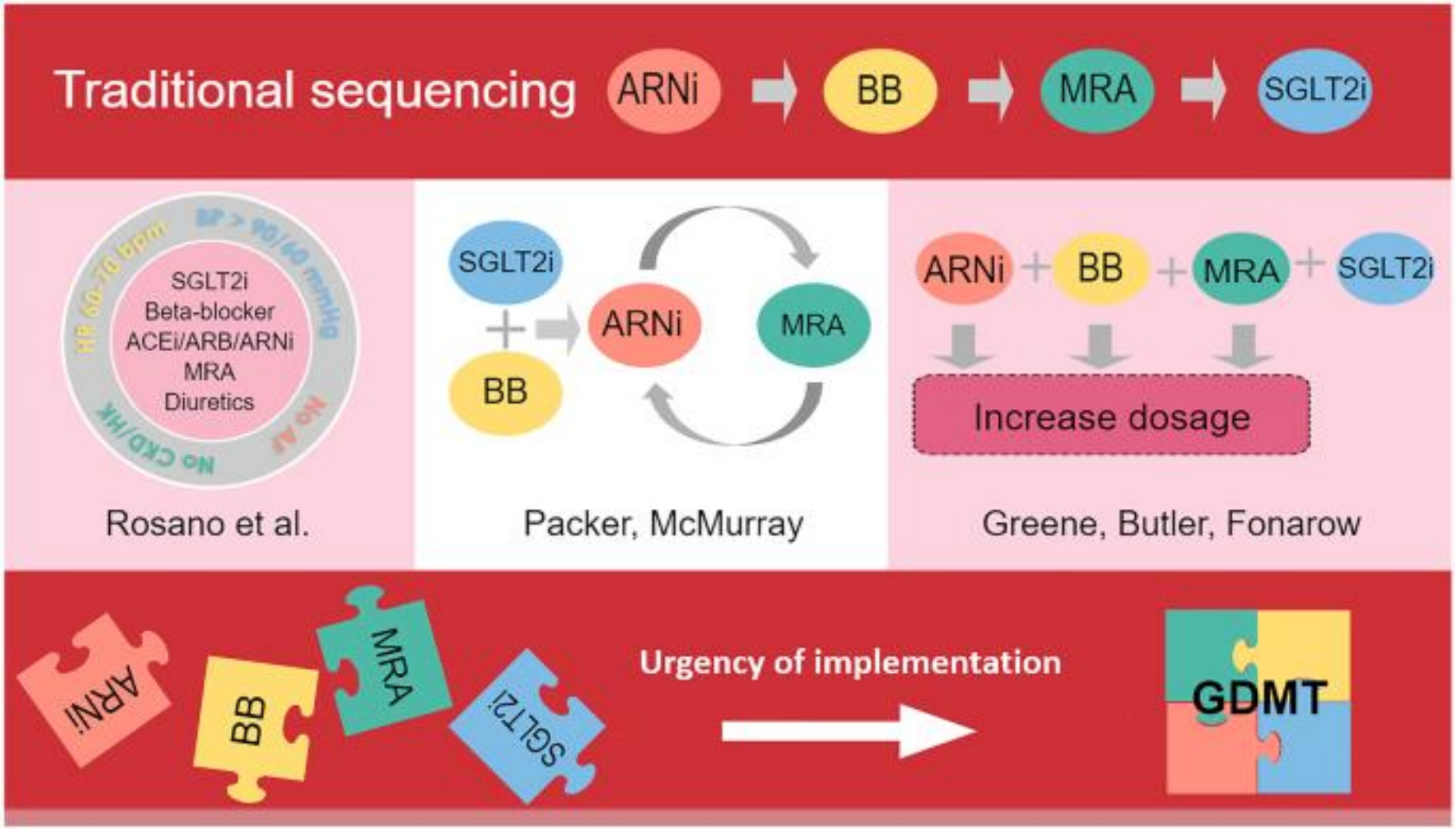
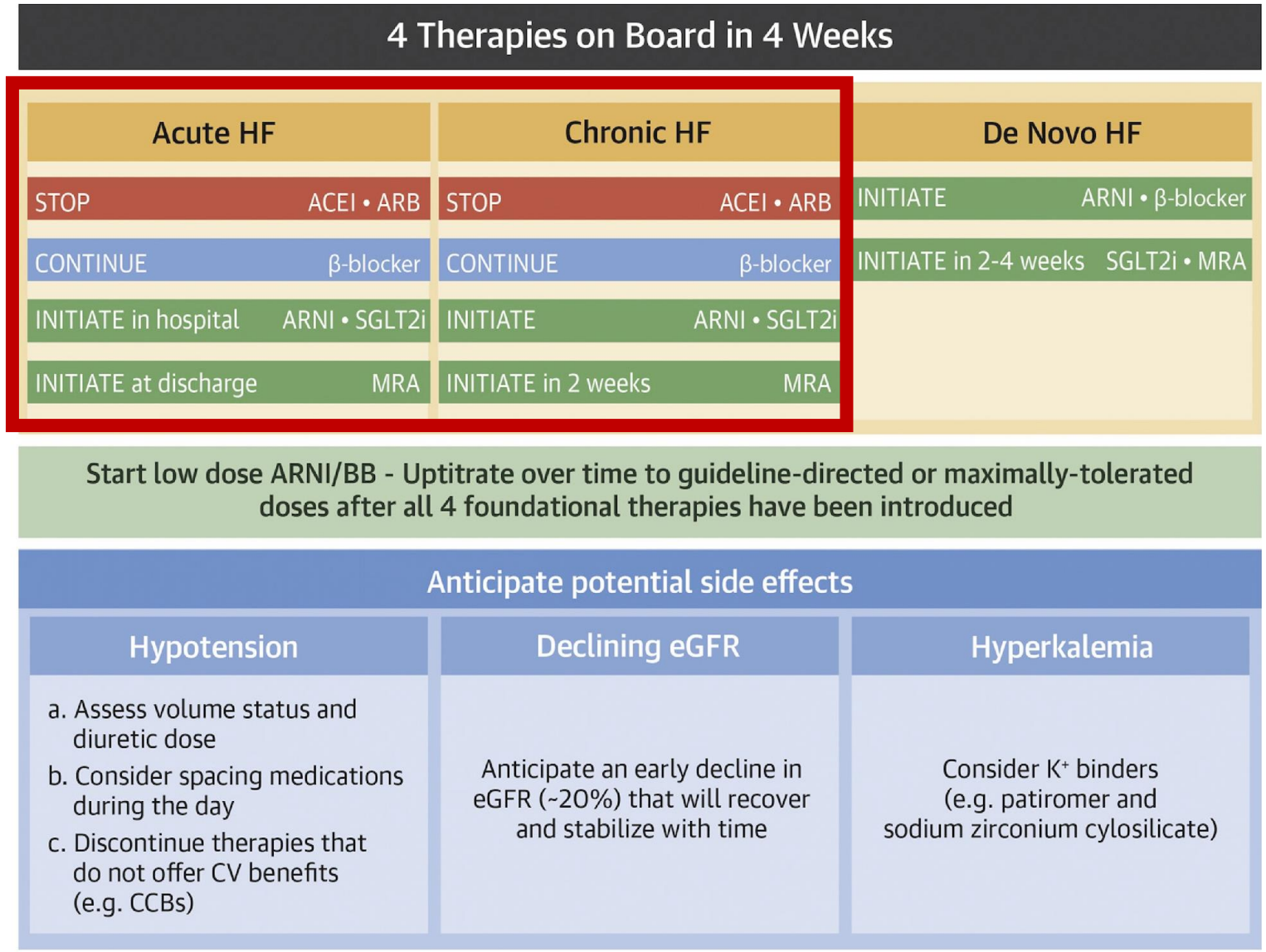


Shah A, et al. Heart Failure: A Class Review of Pharmacotherapy. P T. 2017 Jul;42(7):464-472.

Different iterations of GDMT implementation



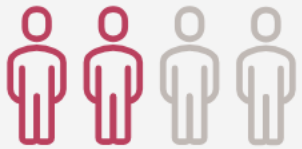
CENTRAL ILLUSTRATION Introducing Quadruple Therapy in Patients With HFrEF



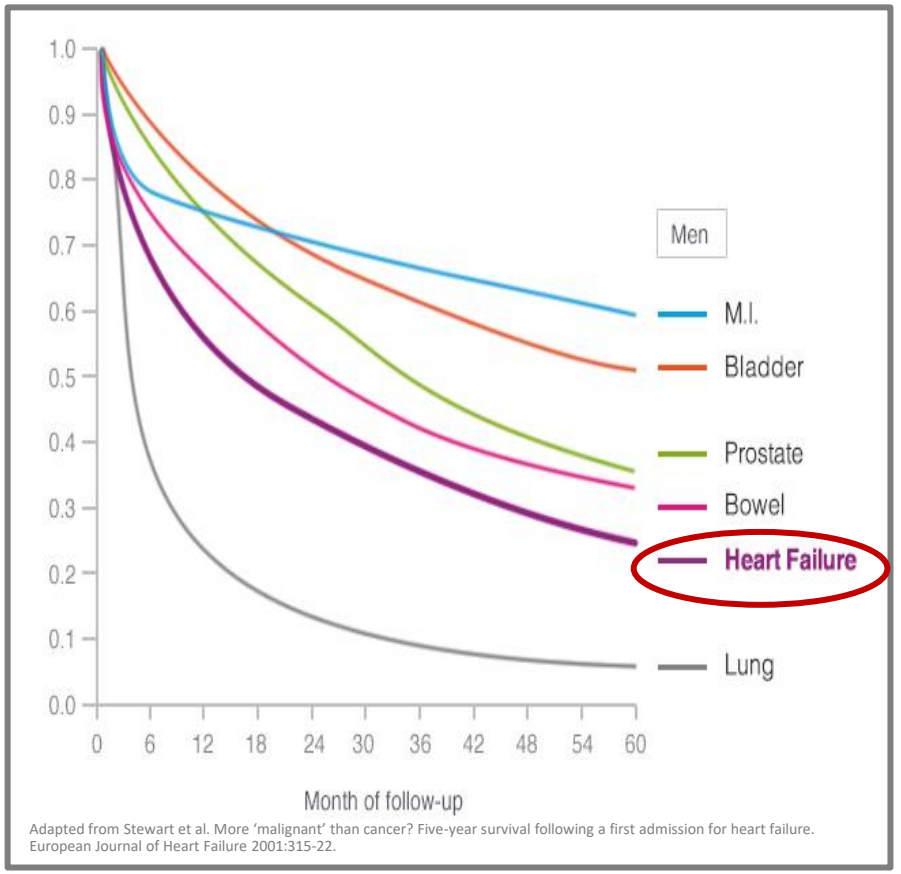
Sharma A, et al. J Am Coll Cardiol Basic Trans Science. 2022;7(5):504-517.

Heart failure has one of the highest rates of readmissions among chronic conditions

1 in 4 patients are re-admitted within **30 days** of discharge[1,2,3]



About 1 in 2 patients are re-admitted within **6 months**[4]



Adapted from Stewart et al. More 'malignant' than cancer? Five-year survival following a first admission for heart failure. European Journal of Heart Failure 2001:315-22.

FIVE YEAR MORTALITY FOR HF WORSE THAN MI AND CANCER

https://cardiothinklab.com/strong-hf-study-highlighting-benefits-of-treatment-optimisation/

Challenges of post-discharge management

Majority of heart failure patients are not closely monitored or treated with optimal doses of GDMT[5-11] after acute heart failure admission.

ACEis, ARBs, MRAs and beta-blockers showed to improve survival rates.[12]

Factors influencing limited adherence to GDMT (Guideline Directed Medical Therapy).[13]

Physician:

1. Lack of awareness
2. Focus on treating symptoms
3. Fear of adverse effects

Patient:

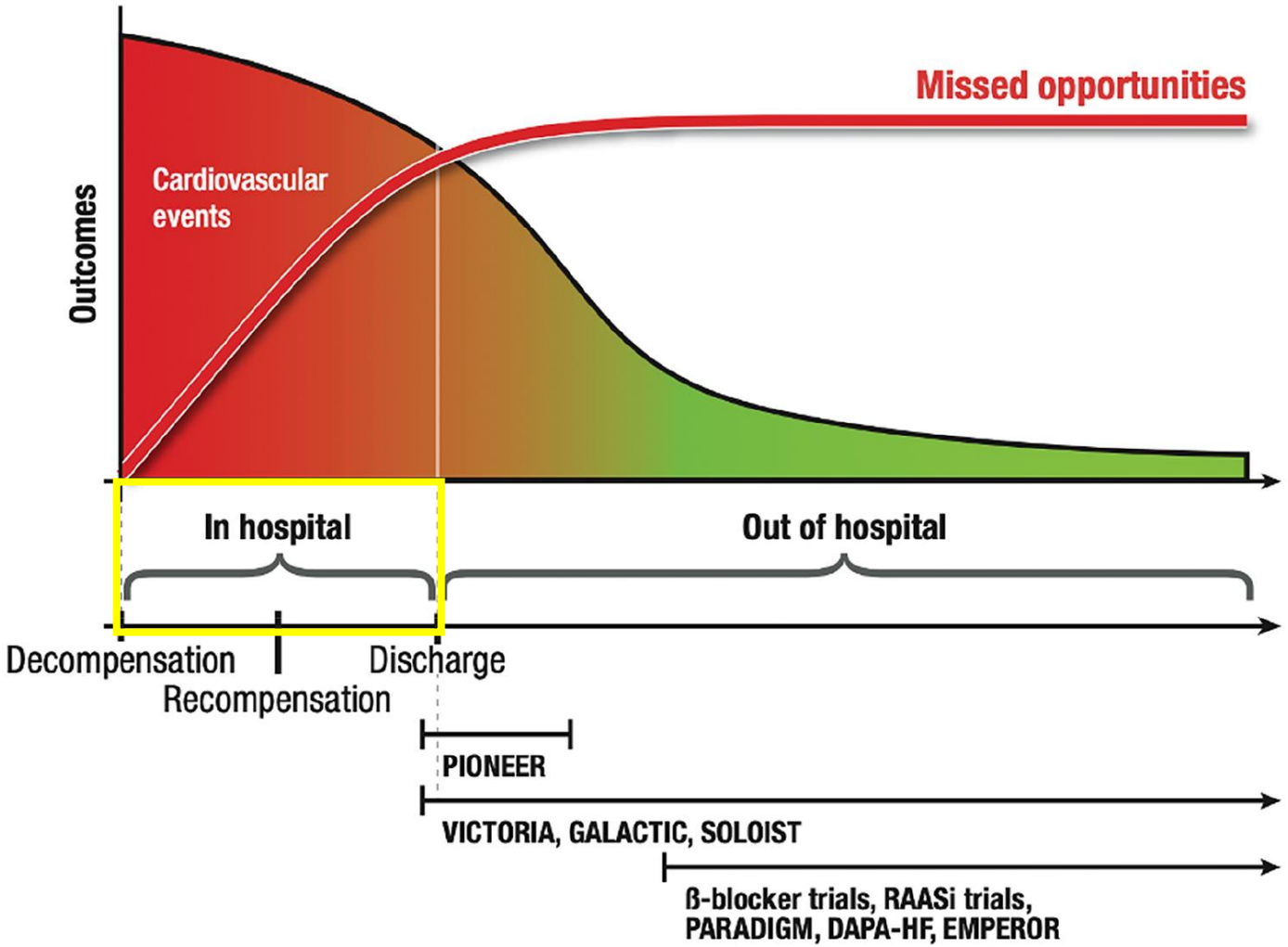
1. Age
2. Frailty and sensitivity
3. Intolerance and contraindications

Non-medical:

1. High costs
2. Limited access

https://cardiothinklab.com/strong-hf-study-highlighting-benefits-of-treatment-optimisation/

Delays in treatment initiation can cause harm in HF



Abdin, A., *et al. Clin Res Cardiol* **110**, 1150–1158 (2021).

The importance of pre-discharge and early post-discharge optimisation for AHF

Recommendation Table 3 — Recommendation for pre-discharge and early post-discharge follow-up of patients hospitalized for acute heart failure

Recommendation	Class[a]	Level[b]
An intensive strategy of initiation and rapid up-titration of evidence-based treatment before discharge and during frequent and careful follow-up visits in the first 6 weeks following a HF hospitalization is recommended to reduce the risk of HF rehospitalization or death.[c,d,e] [16]	I	B

The importance of pre-discharge and early post-discharge optimisation for AHF

StrongHF: Safety and efficacy

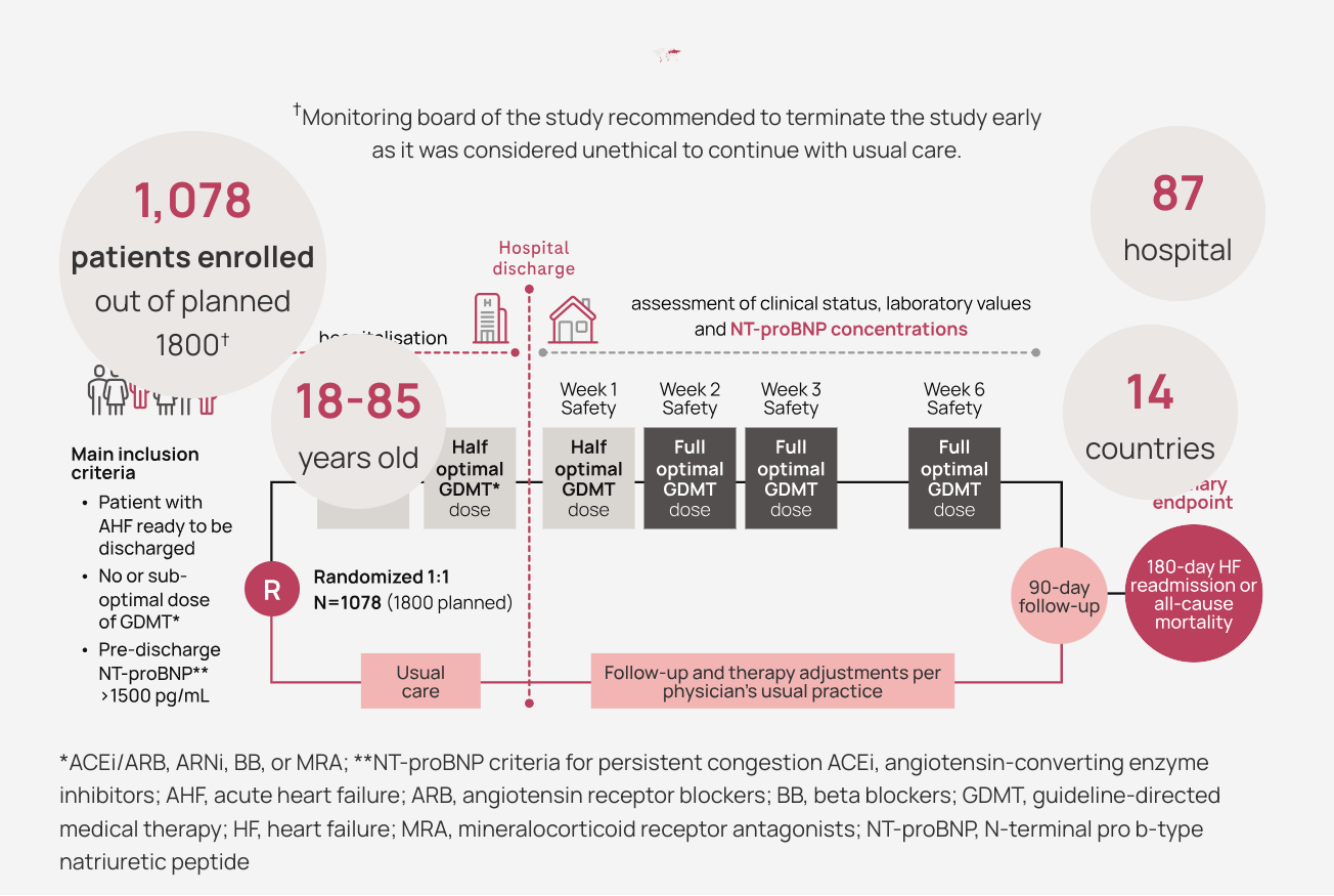
High-intensity care approach vs. Usual care

- Randomised patients hospitalised with AHF,
  - NT pro BNP >1500pg/ml
  - on no treatment or sub-optimal dose

High-intensity care approach:

- Goal of ≥50% target doses before discharge

- Full target doses attempted within 2 weeks post-dc
- Follow-up visits at 1, 2, 3, and 6 weeks



Mebazaa, Alexandre et al. The Lancet, Volume 400, Issue 10367, 1938 - 1952

Results

- Higher rates of full dose therapies in high-intensity group
- 34% relative reduction in HF readmission/death at 180 days
- 44% reduction in HF readmissions
- Similar rates of adverse events between groups

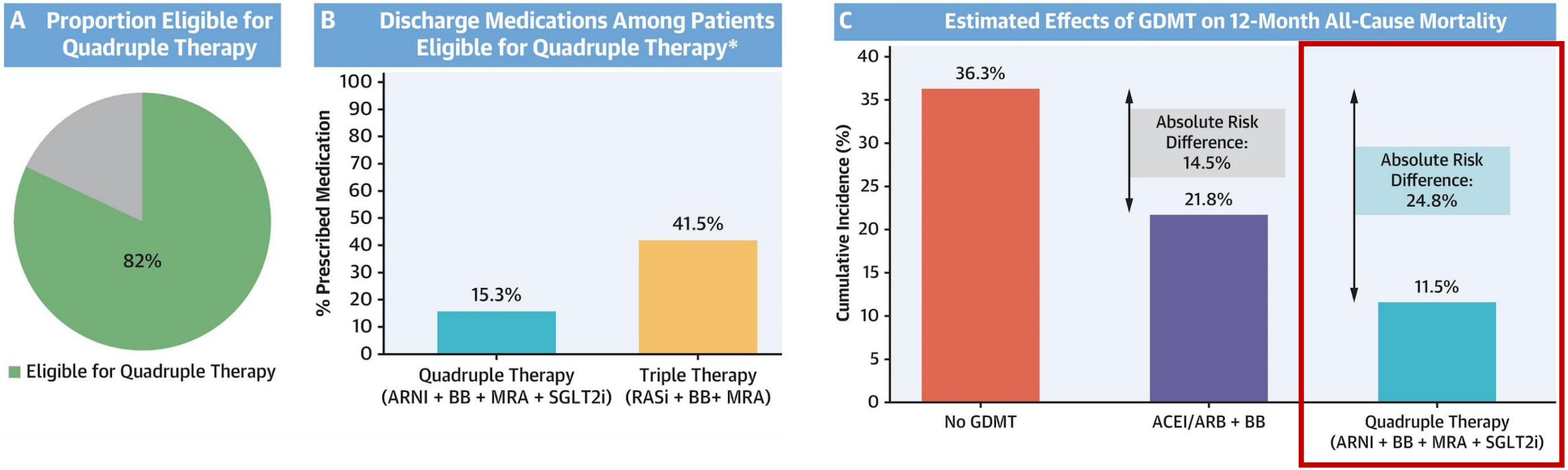
The high intensity care group: **34% relative** and **8.1% absolute risk reduction (ARR)** in the combination of death or heart failure readmission.[14]

CV (cardiovascular) death	HF readmission	All-cause death
26% lower	44% lower	16% lower

STRONG-HF study results demonstrated clear benefits for acute heart failure patients by adapting the strategy of care.

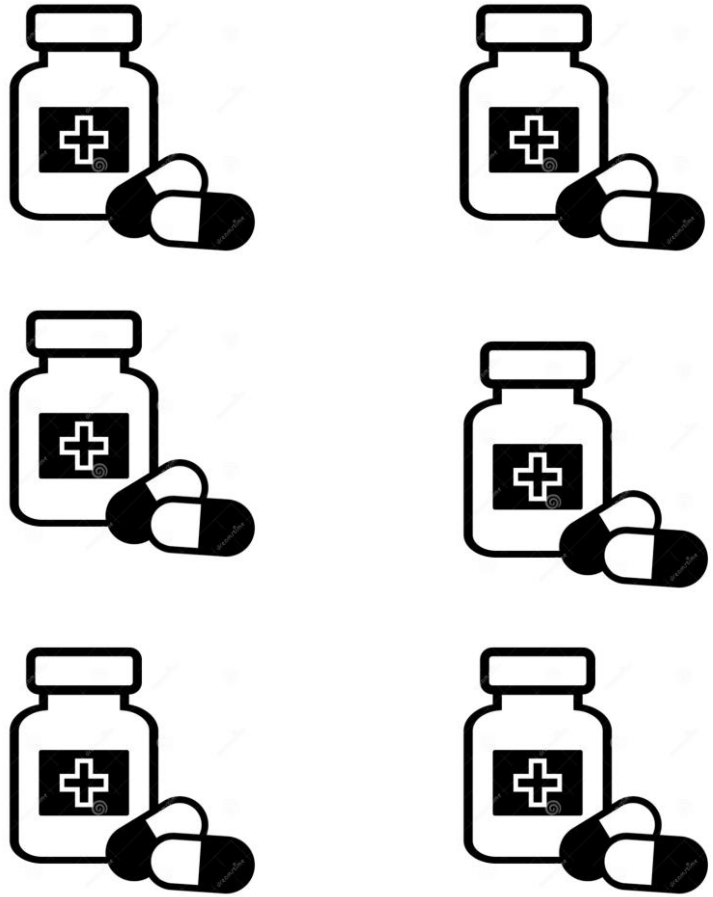
Mebazaa, Alexandre et al. The Lancet, Volume 400, Issue 10367, 1938 - 1952

Treatment Gap and Projected Clinical Benefits of Rapid Implementation of Quadruple Therapy in Newly Diagnosed HFrEF



SJ, et al. J Am Coll Cardiol HF. 2024;12(8):1365-1377.

Should we be worried about starting triple or quadruple therapy in patients hospitalised with AHF?



Up to 6 medications started in 3 days after AMI

Changing clinical pathways in HF

- Quadruple therapy
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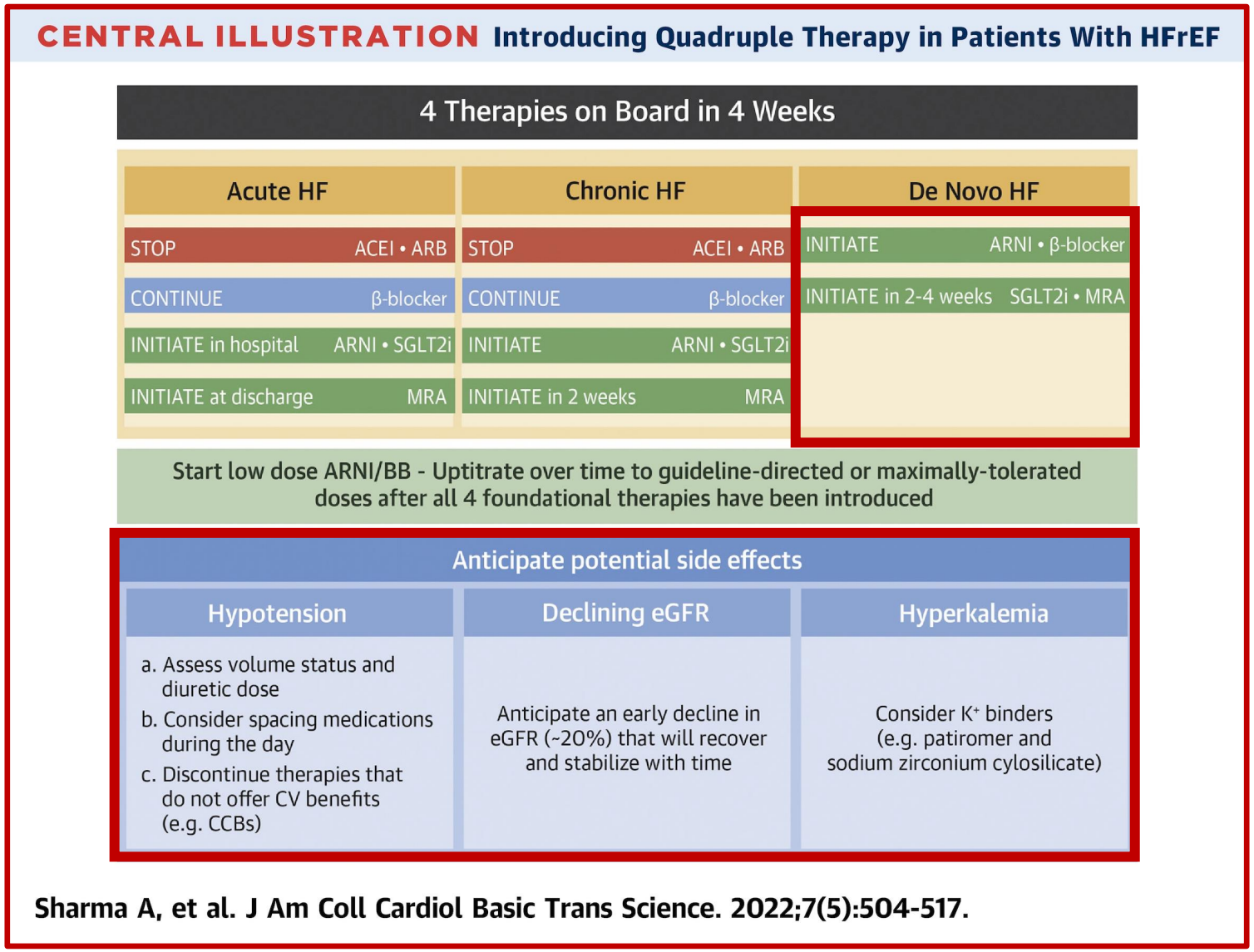
Denovo initiation of ARNi; without a run-in phase of ACE-i/ARB



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Absence of angioedema history

Direct initiation of an ARNI *De Novo* Without Prior Exposure to an ACE Inhibitor or ARB

- Data from clinical studies and clinical experience indicates that direct initiation of ARNi, without ACE-i/ARB pre-treatment, is **safe and effective**

PIONEER-HF (ADHF, LVEF ≤40%)

- Compared to patients on enalapril, those with denovo ARNI had:
  - **greater reduction in NT-pro BNP**
  - **Fewer re-hospitalisations for HF**
  - **comparable safety profile**

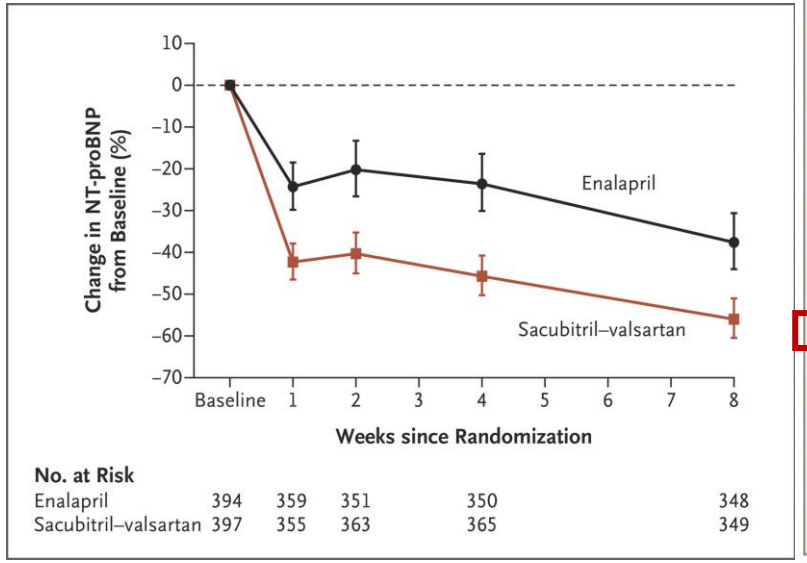

Table 2. Secondary Efficacy and Safety Outcomes.*

Outcome	Sacubitril–Valsartan (N=440)	Enalapril (N=441)	Sacubitril–Valsartan vs. Enalapril
Key safety outcomes — no. (%)			**Relative risk (95% CI)**
Worsening renal function†	60 (13.6)	65 (14.7)	0.93 (0.67 to 1.28)
Hyperkalemia	51 (11.6)	41 (9.3)	1.25 (0.84 to 1.84)
Symptomatic hypotension	66 (15.0)	56 (12.7)	1.18 (0.85 to 1.64)
Angioedema	1 (0.2)	6 (1.4)	0.17 (0.02 to 1.38)
Secondary biomarker outcomes — % (95% CI)‡			**Ratio of change (95% CI)**
Change in high-sensitivity troponin T concentration	−36.6 (−40.8 to −32.0)	−25.2 (−30.2 to −19.9)	0.85 (0.77 to 0.94)
Change in B-type natriuretic peptide concentration	−28.7 (−35.5 to −21.3)	−33.1 (−39.5 to −25.9)	1.07 (0.92 to 1.23)
Change in ratio of B-type natriuretic peptide to NT-proBNP	35.2 (28.8 to 42.0)	−8.3 (−3.6 to −12.7)	1.48 (1.38 to 1.58)
Exploratory clinical outcomes — no. (%)			**Hazard ratio (95% CI)§**
Composite of clinical events	249 (56.6)	264 (59.9)	0.93 (0.78 to 1.10)
Death	10 (2.3)	15 (3.4)	0.66 (0.30 to 1.48)
Rehospitalization for heart failure	35 (8.0)	61 (13.8)	0.56 (0.37 to 0.84)
Implantation of left ventricular assist device	1 (0.2)	1 (0.2)	0.99 (0.06 to 15.97)
Inclusion on list for heart transplantation	0	0	NA
Unplanned outpatient visit leading to use of intravenous diuretics	2 (0.5)	2 (0.5)	1.00 (0.14 to 7.07)
Use of additional drug for heart failure	78 (17.7)	84 (19.0)	0.92 (0.67 to 1.25)
Increase in dose of diuretics of >50%	218 (49.5)	222 (50.3)	0.98 (0.81 to 1.18)
Composite of serious clinical events¶	41 (9.3)	74 (16.8)	0.54 (0.37 to 0.79)

Velazquex EJ et al. N Engl J Med 2019;380:539-548

Direct Initiation of an ARNI *De Novo* Without Prior Exposure to an ACE Inhibitor or ARB

- Due to the totality of data, a *de novo* ARNI approach is now recommended in the US
  - Requires close follow-up, serial assessments (BP, U&E, K+), and consideration of the risk of hypotension
- Patient selection is key, those receiving denovo ARNI should be free from hypotension, significant renal disease and avoid frail patients.
- Entresto remains for specialist initiation only in the UK

Velazquex EJ et al. N Engl J Med 2019;380:539-548

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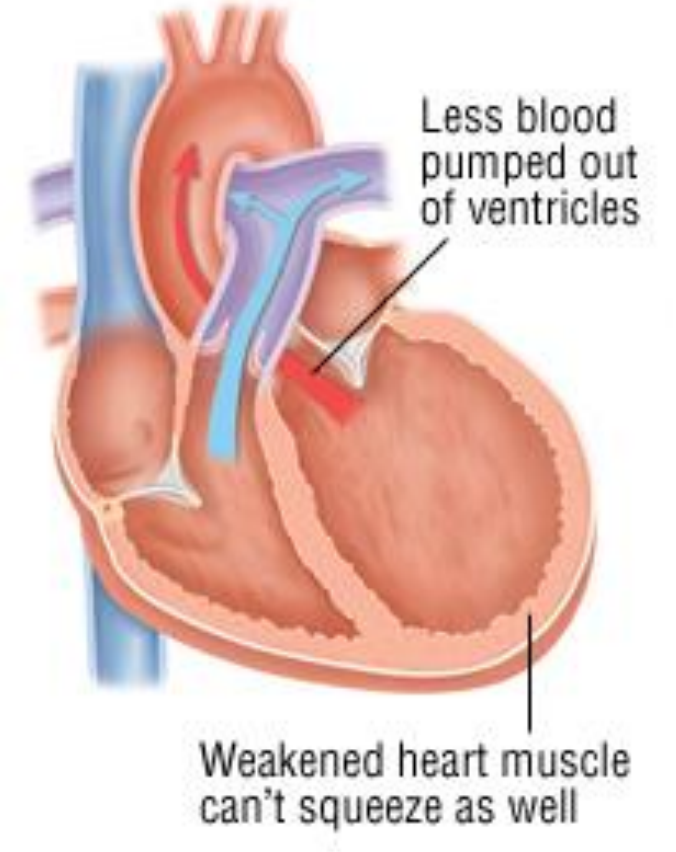
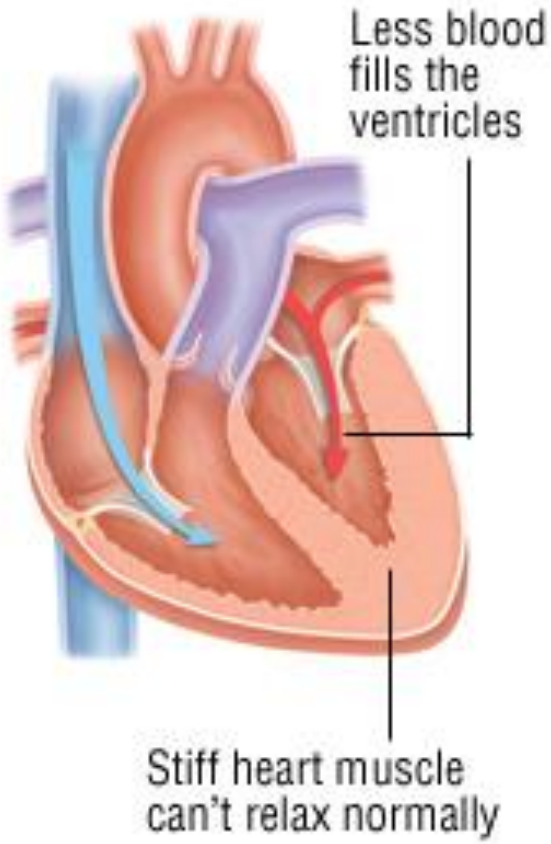


"Systolic heart failure"

HF-REF: LVEF ≤ 40%

Grey Zone

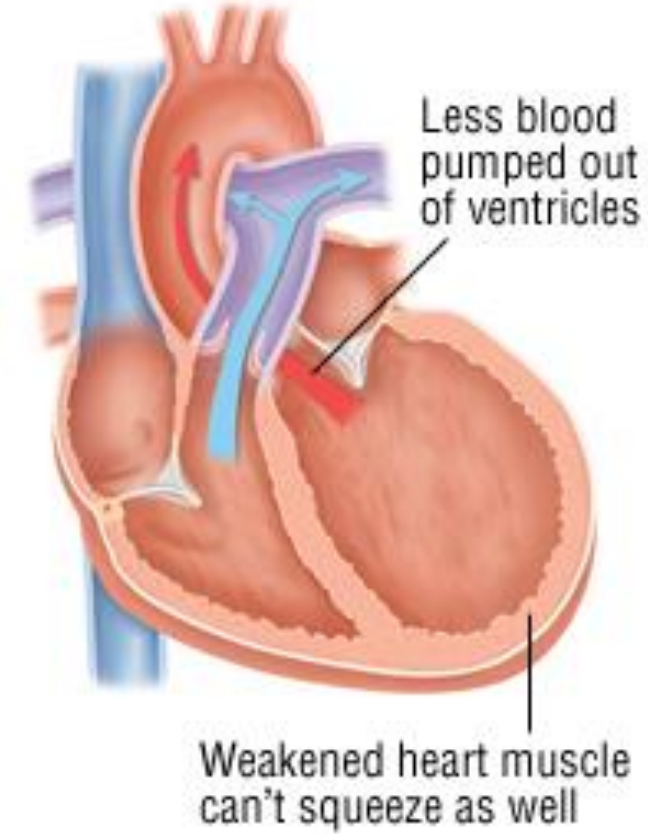
Uncertainty in the management of patients with LVEF 41-49%



"Diastolic heart failure"

HF-PEF LVEF >50%

3 main categories of HF



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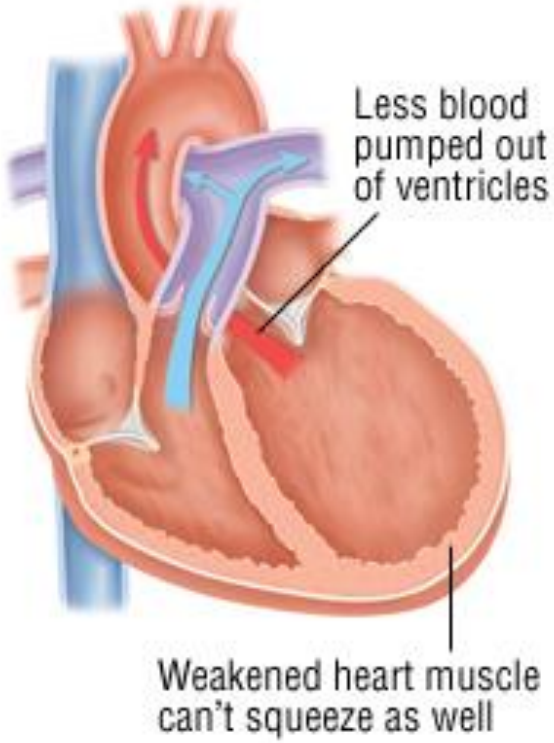
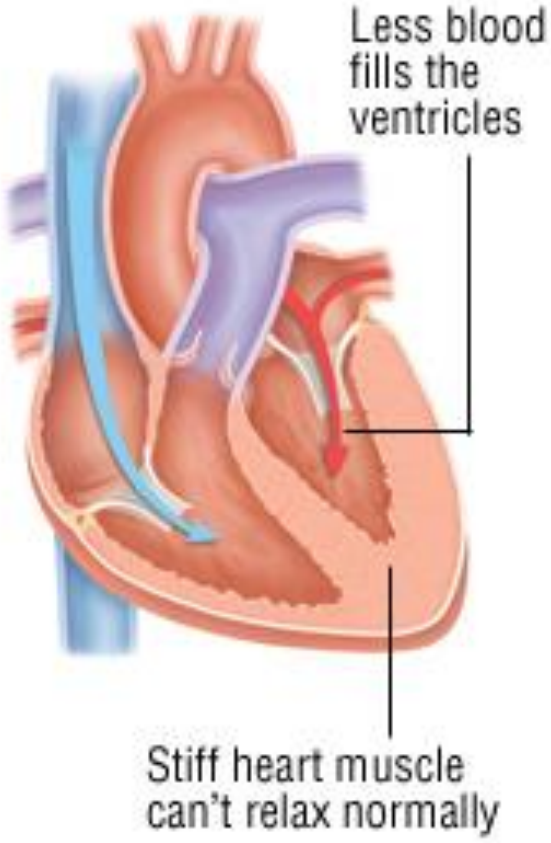


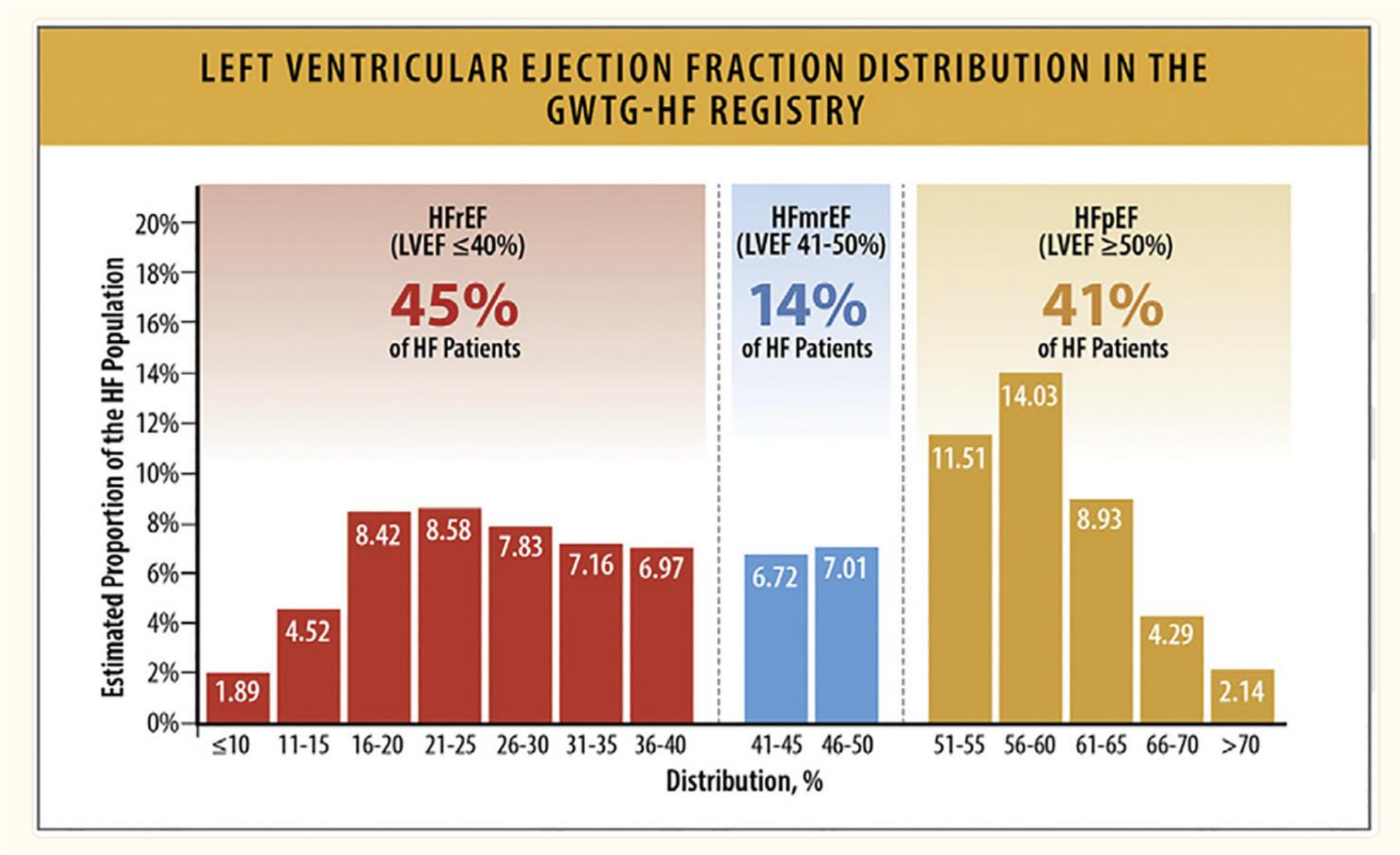
HFmREF:

LVEF 41-49%



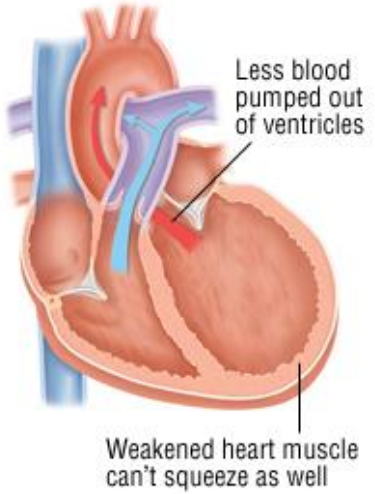
"Diastolic heart failure"

HFpEF LVEF >50%

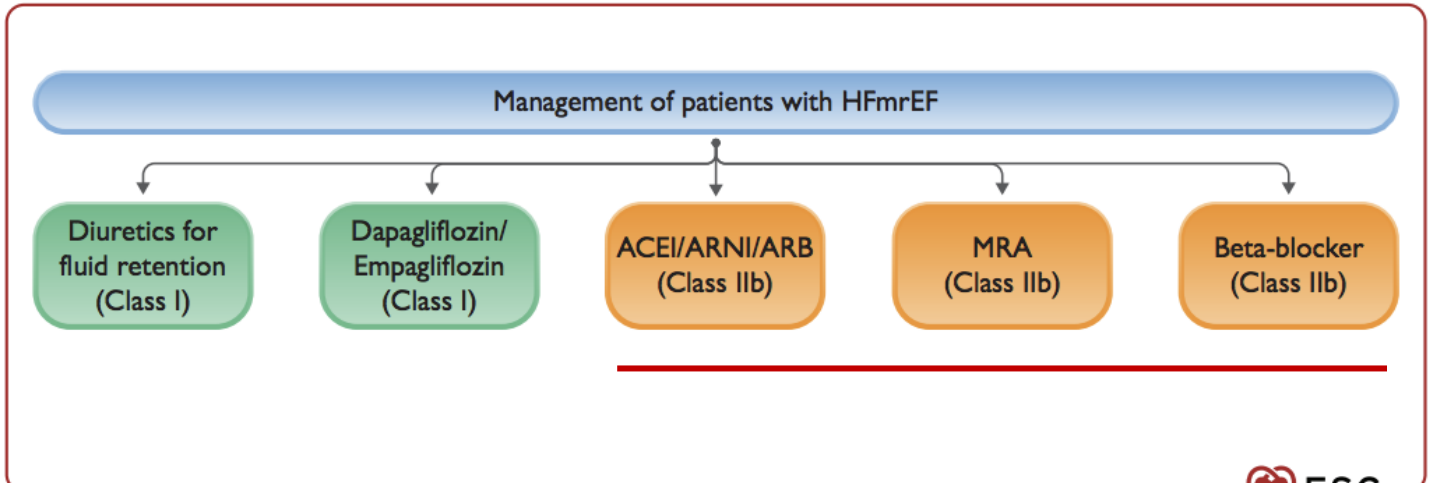


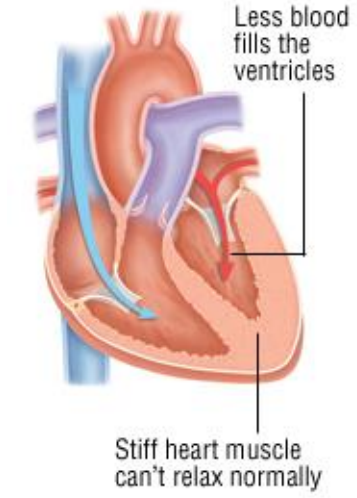
Bozkurt B, et al. J Card Fail. 2023 Oct;29(10):1412-1451.

Changing management of HF with LVEF >40%

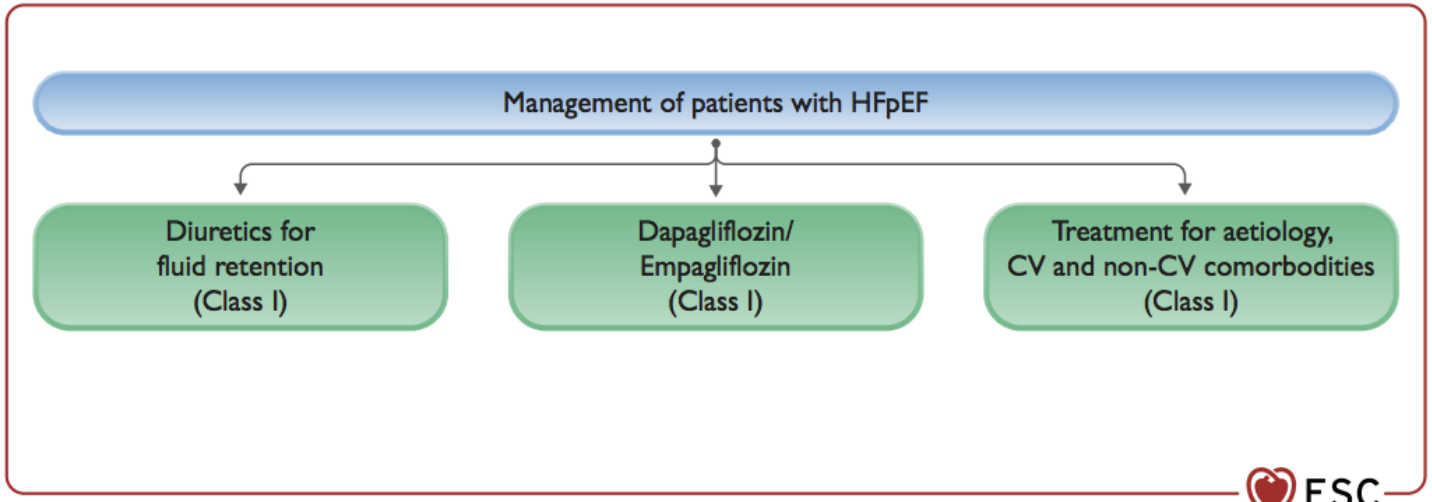


HFmrEF
LVEF 41-49%

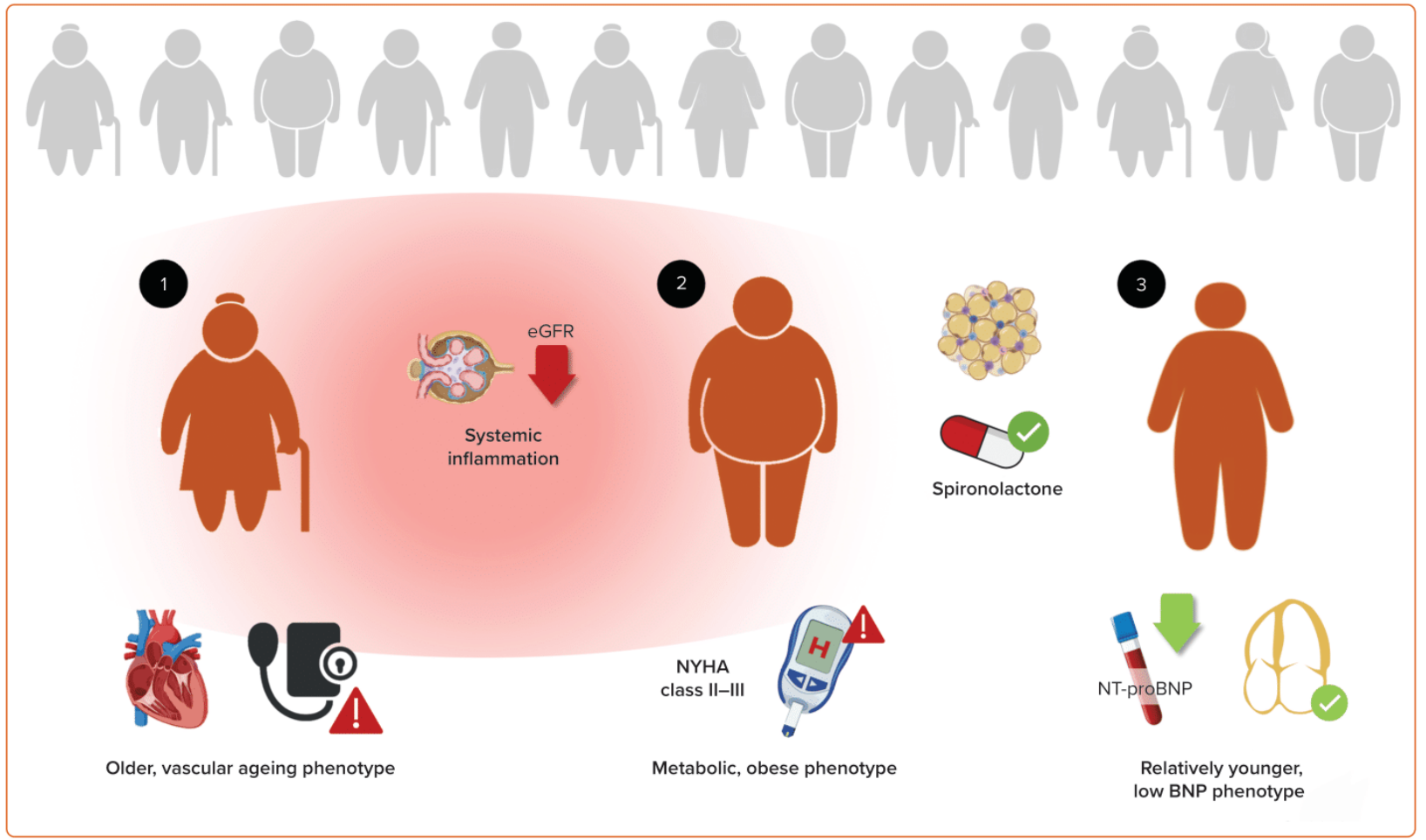




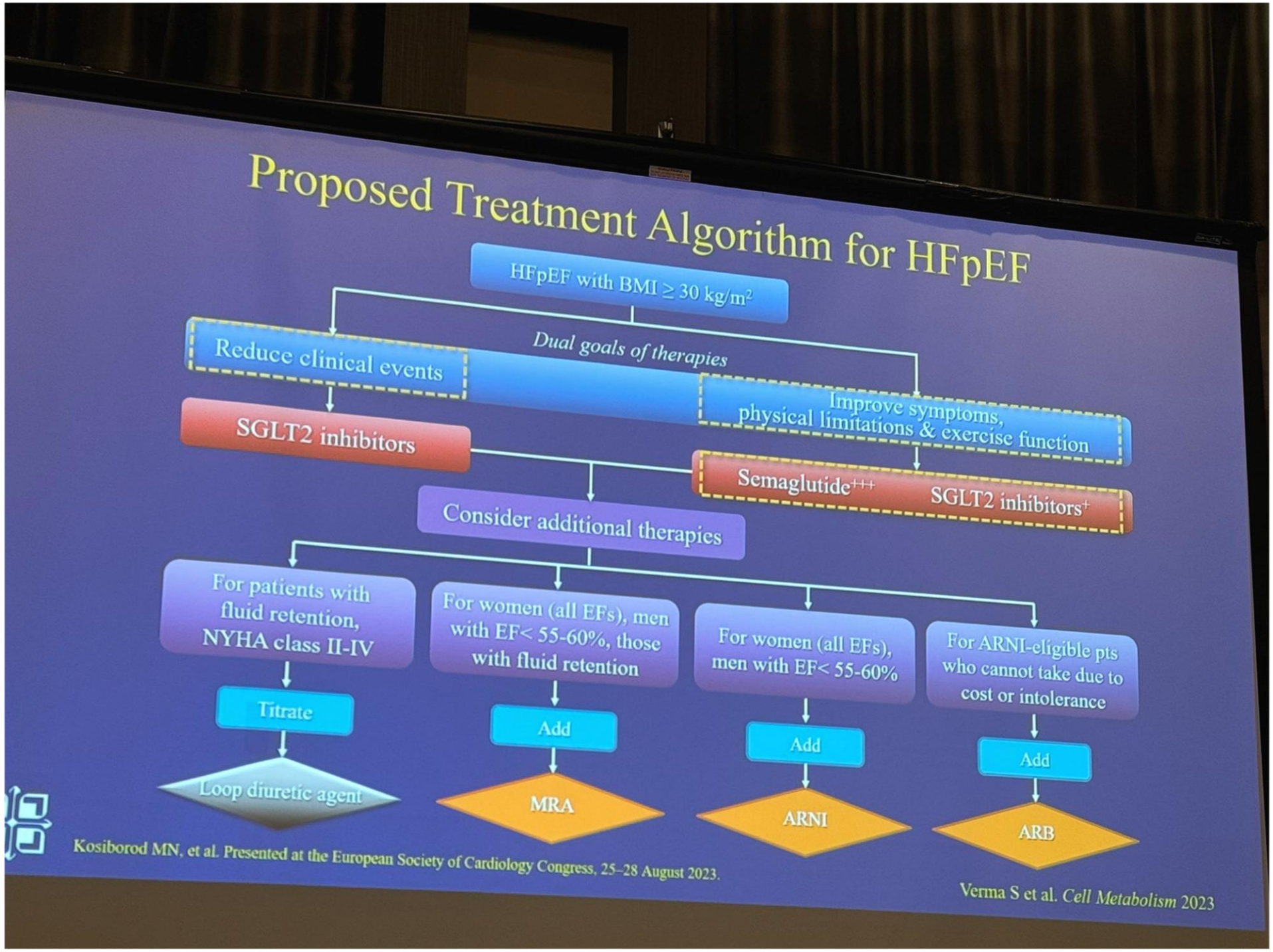
HFpEF
LVEF ≥50%



Future management of HFpEF: Phenotyping to guide optimal treatment



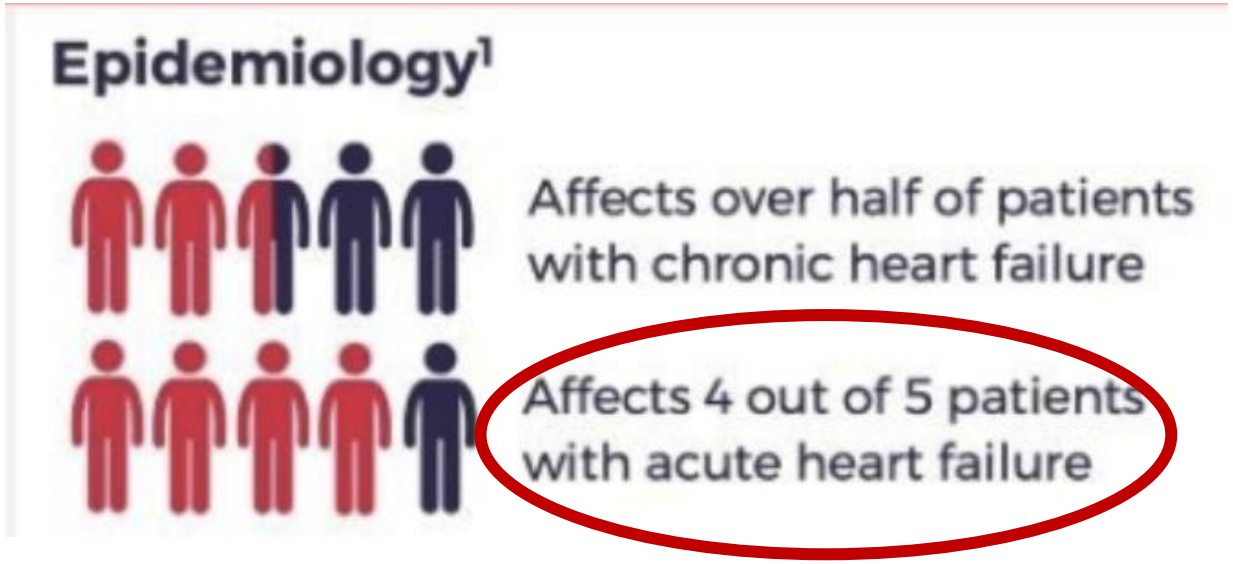
Giulio Balestrieri, et al. The Therapy and Management of Heart Failure with Preserved Ejection Fraction: New Insights on Treatment, *Cardiac Failure Review 2024;10:e05.*


Proposed Treatment Algorithm for HFpEF
HFpEF with BMI ≥ 30 kg/m²
Dual goals of therapies
Reduce clinical events
SGLT2 inhibitors
Improve symptoms, physical limitations & exercise function
Semaglutide+++
SGLT2 inhibitors+
Consider additional therapies
For patients with fluid retention, NYHA class II-IV
Titrate
Loop diuretic agent
For women (all EFs), men with EF< 55-60%, those with fluid retention
Add
MRA
For women (all EFs), men with EF< 55-60%
Add
ARNI
For ARNI-eligible pts who cannot take due to cost or intolerance
Add
ARB
Kosiborod MN, et al. Presented at the European Society of Cardiology Congress, 25–28 August 2023.
Verma S et al. Cell Metabolism 2023

Changing clinical pathways in HF

- Quadruple therapy
- Rapid titration
- Denovo ARNis in HFrEF
- Changing management in HFmrEF
- Changing management in HFpEF
- IV iron in heart failure
- Virtual wards for acute HF

Iron deficiency is one of the commonest co-morbidities in heart failure; but we seldom discuss it



Which other co-morbidity affects 4 in 5 patients admitted with acute heart failure?

Bruno M.L. Rocha et al. JACC 2018;71:782-793

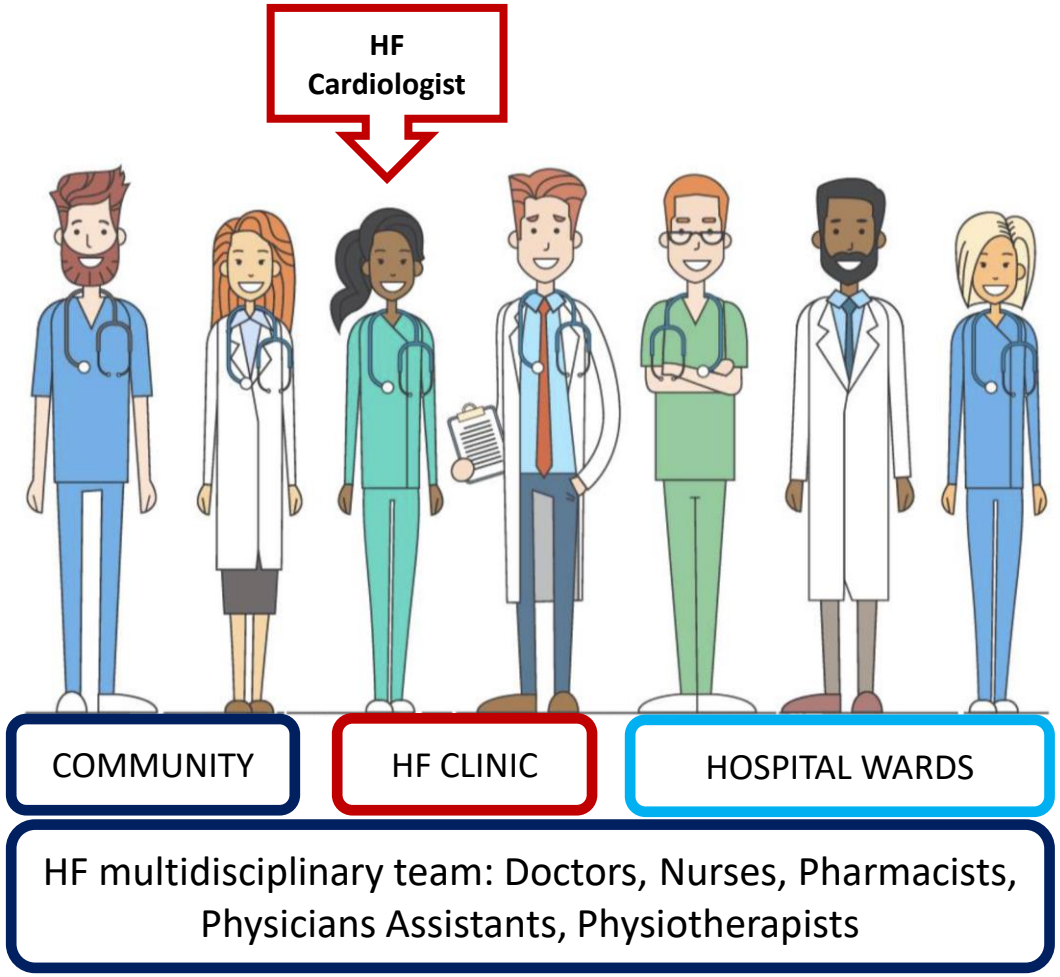
Iron deficiency; more than a co-morbidity in HF

Iron deficiency is implicated in the pathogenesis of many disease processes in heart failure

- ID is associated with impaired calcium handling and mitochondrial function[1]
- ID associated with reduced cardiac output compared to non–ID subjects[2]
- ID a key reason for lack of symptom improvement despite optimisation of guideline-directed treatments
- ID in heart failure is not benign
    - associated with more severe symptoms, higher risk of hospitalisation for heart failure, and increased mortality

1. **The Effect of Iron Deficiency on Cardiac Function and Structure in Heart Failure with Reduced Ejection Fraction** https://www.cfrjournal.com/articles/effect-iron-deficiency-cardiac-function-and-structure-heart-failure-reduced-ejection
2. Martens P, Verbrugge FH, Nijst P et al. Limited contractile reserve contributes to poor peak exercise capacity in iron-deficient heart failure. Eur J Heart Fail. 2018;20:806–8.

Using The Wrong Threshold Can Lead To Missed Opportunities For Diagnosis & Treatment Of Iron Deficiency



WHO definition of ID
Adult general population: ferritin < 15 µg/L

Different thresholds proposed diagnosing ID in patients with chronic inflammatory conditions (CKD, HF, IBD)

Absolute ID: **serum ferritin < 100 µg/L**

Functional ID: serum ferritin between 100 - 299 µg/L
+ **transferrin saturations (TSAT) < 20%**

LACK OF FAMILIARITY WITH THRESHOLDS USED TO DIAGNOSE ID IN HF -> MISSED OPPORTUNITIES

Iron deficiency; a target for treatment in HF since 2016

August 2021: ESC HF GUIDELINES

Recommended diagnostic tests in all patients with suspected chronic heart failure

Recommendations	Class[a]	Level[b]
BNP/NT-proBNP[c]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

Recommendations for management of patients with HF and iron deficiency	
It is recommended that all patients with HF are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I

When should patients with HF be tested for iron deficiency?

At initial diagnosis

Periodically thereafter

Iron deficiency; a target for treatment in HF since 2016

August 2021: ESC HF GUIDELINES

Recommended diagnostic tests in all patients with suspected chronic heart failure

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13.5 Iron deficiency and anaemia

in HFrEF, HFpEF, and AHF.[727] Oral iron therapy is not effective in

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

IV iron **Class Ia recommendation** for

1. Patients with heart failure, LVEF≤50% and ID to improve functional status and QoL

IV FDI or FCM **Class IIa recommendation** for

2. HF patients with LVEF≤50% and ID, to reduce the risk of HF hospitalisation

Despite guidelines, IV iron prescribed infrequently
Oral iron prescription is common

Follow the guidelines: systematically test & treat all eligible patients

1. Test every patient with HF for ID, initial diagnosis and annually thereafter
2. Correct hypoferraemia – in both outpatients and inpatients
3. Don't routinely prescribe oral iron in HF

It is recommended that all patients with HF are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

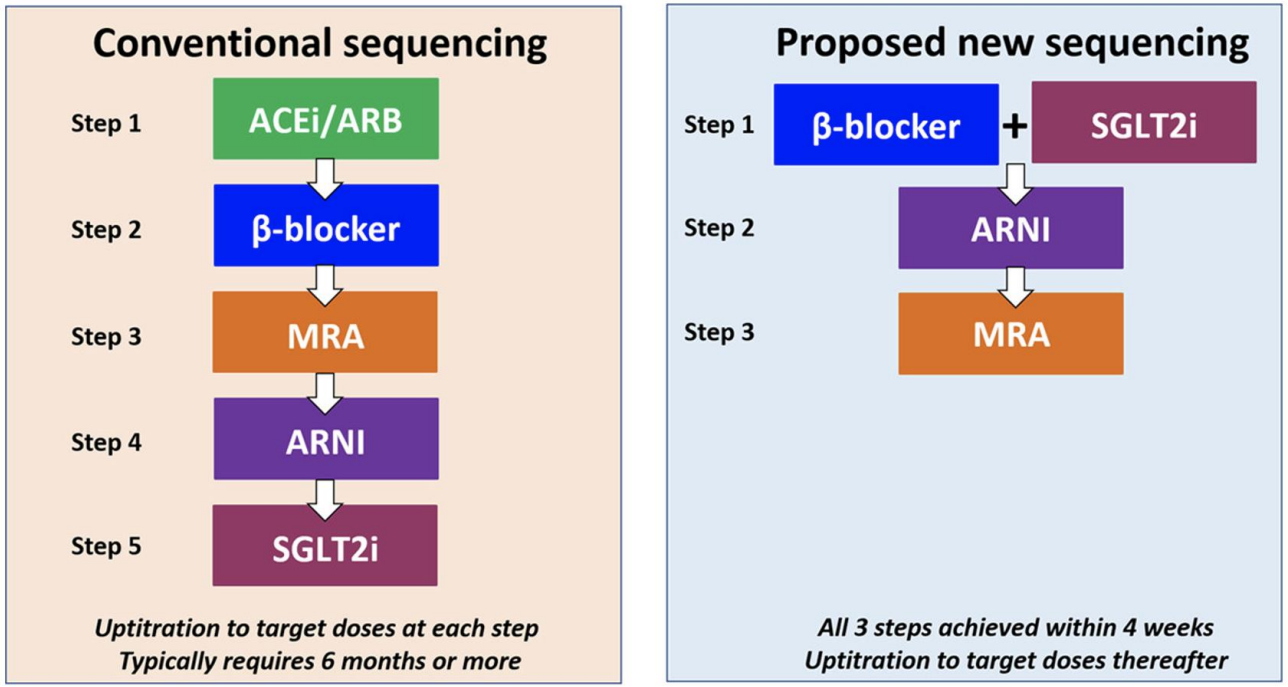
IV iron **Class Ia recommendation** for

1. Patients with heart failure, LVEF≤50% and ID to improve functional status and QoL

IV FDI or FCM **Class IIa recommendation** for

2. HF patients recently hospitalised for HF with LVEF≤50% and ID, to reduce the risk of HF hospitalisation

IV Iron treatment not subject to drug sequencing



HF patients with ID are not required to be on optimal GDMT prior to treatment with IV iron.

2023

2023 Focused Update of the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

2022

Journal of Cardiac Failure Vol. 28 No. 5 2022

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure

2021

ESC GUIDELINES

ESC European Society of Cardiology

European Heart Journal (2021) 00, 1–128 doi:10.1093/eurheartj/ehab368

2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

McMurray J and Packer M
https://doi.org/10.1161/CIRCULATIONAHA.120.052926
Circulation. 2021;143:875–877

Changing clinical pathways in HF

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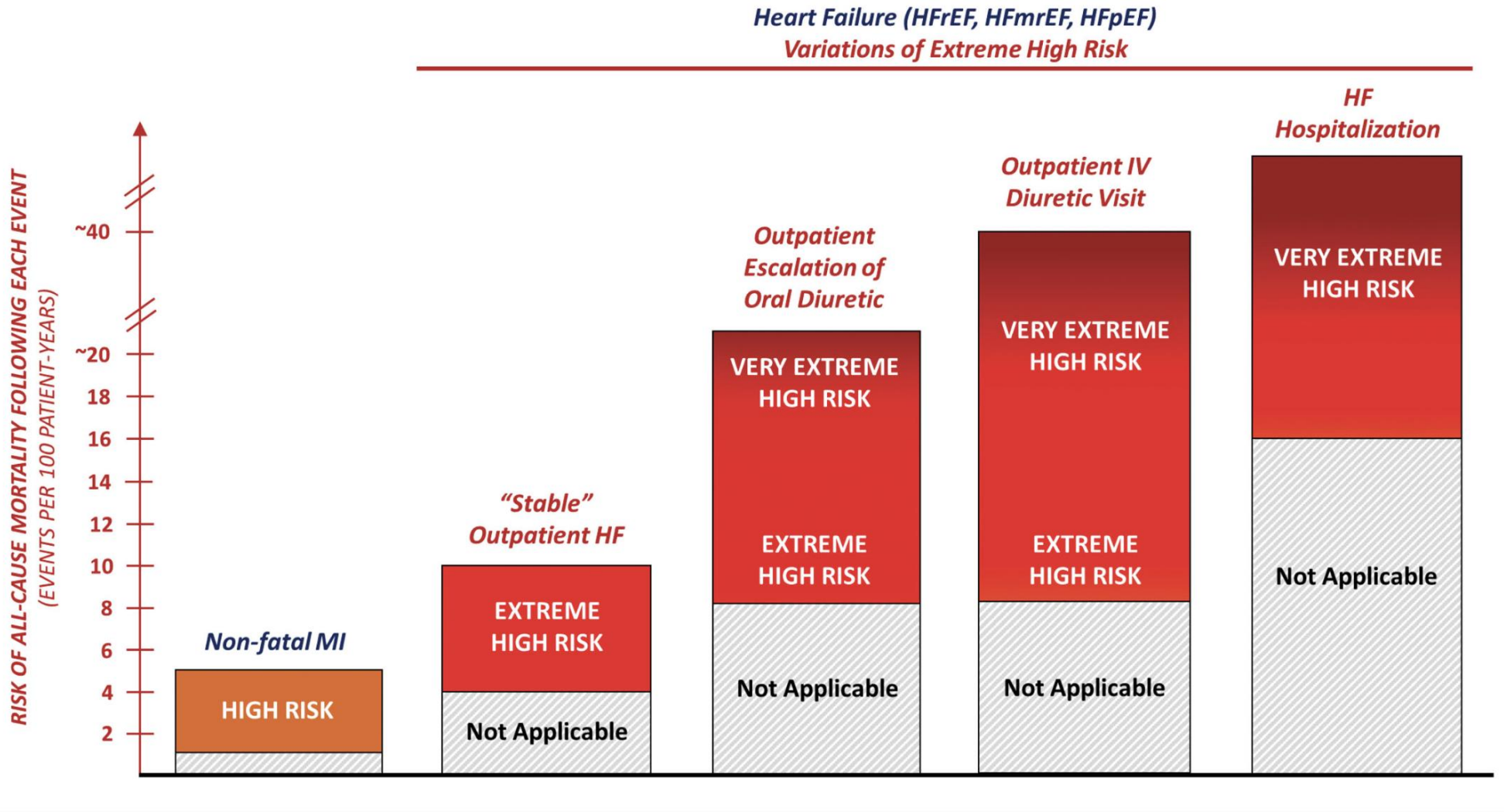
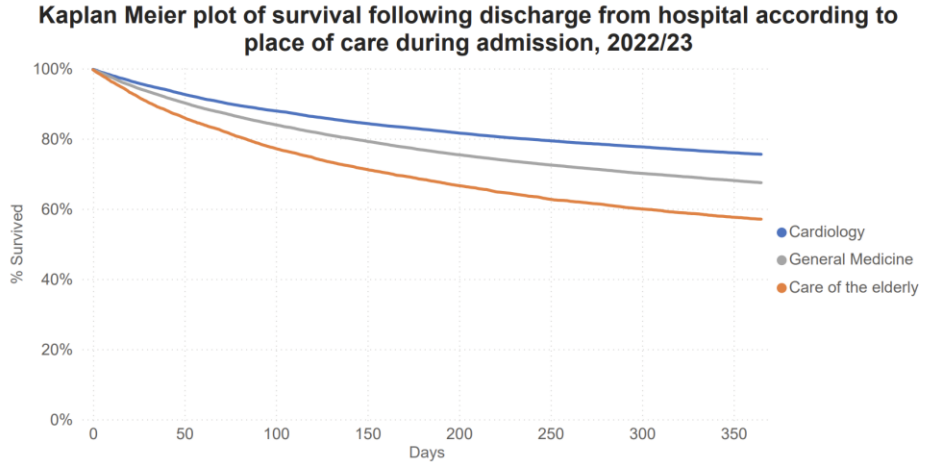
VW for HF: The importance of specialist care

Contextualising risk among individuals with worsening HF



•Sanjiv J Shah, et al. Semaglutide and diuretic use in obesity-related heart failure with preserved ejection fraction: a pooled analysis of the STEP-HFpEF and STEP-HFpEF-DM trials, European Heart Journal, **45**, 35, (3254-3269), (2024).

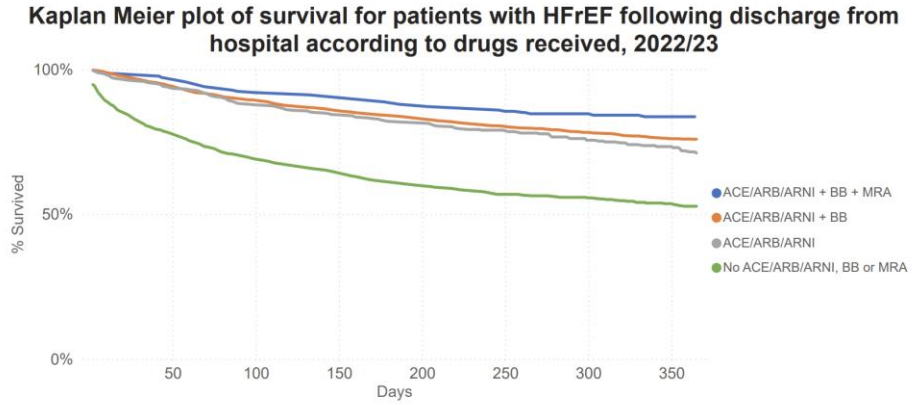
1-year survival is better for those discharged from cardiology wards



Number at risk

Cardiology	27491	25495	24181	23193	22425	20710	17161	14020
General Medicine	25174	22748	21159	19969	18966	17362	14210	11593
Care of the elderly	9483	8170	7334	6759	6309	5556	4506	3627

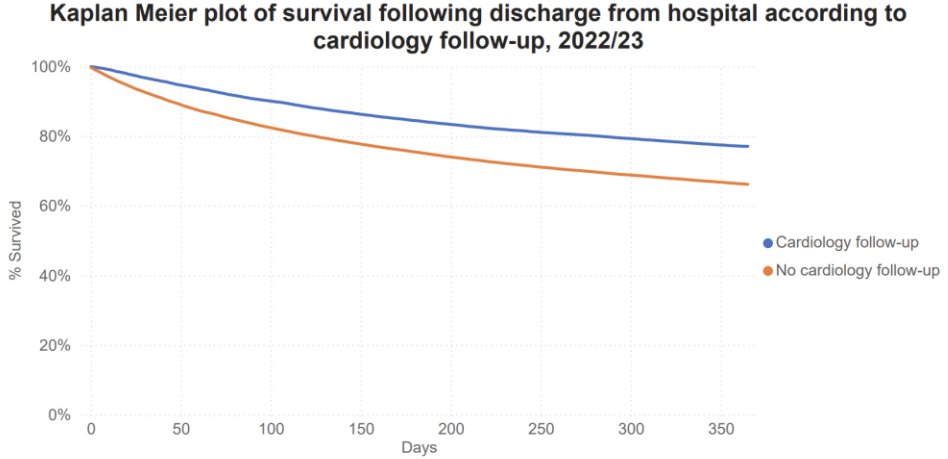
1-year survival much better for those with HFrEF discharged on all three classes of disease-modifying drugs



Number at risk

ACE/ARB/ARNI + BB + MRA	292	281	269	262	256	245	209	177
ACE/ARB/ARNI + BB	8619	8097	7665	7383	7104	6585	5393	4443
ACE/ARB/ARNI	2207	2070	1974	1891	1826	1674	1349	1100
No ACE/ARB/ARNI, BB or MRA	4334	3705	3368	3155	2954	2694	2217	1806

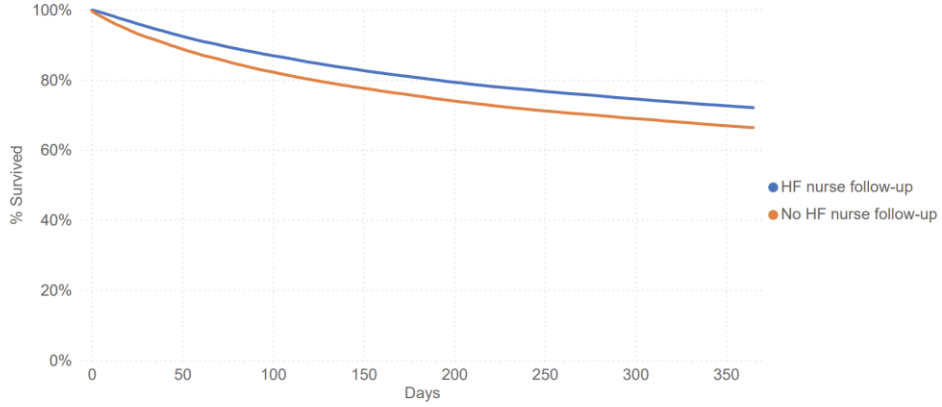
1-year survival is better for those receiving cardiology follow-up



Number at risk

Cardiology follow-up	22219	21044	20018	19181	18515	17157	14152	11488
No cardiology follow-up	47736	42571	39384	37120	35279	32109	26317	21348

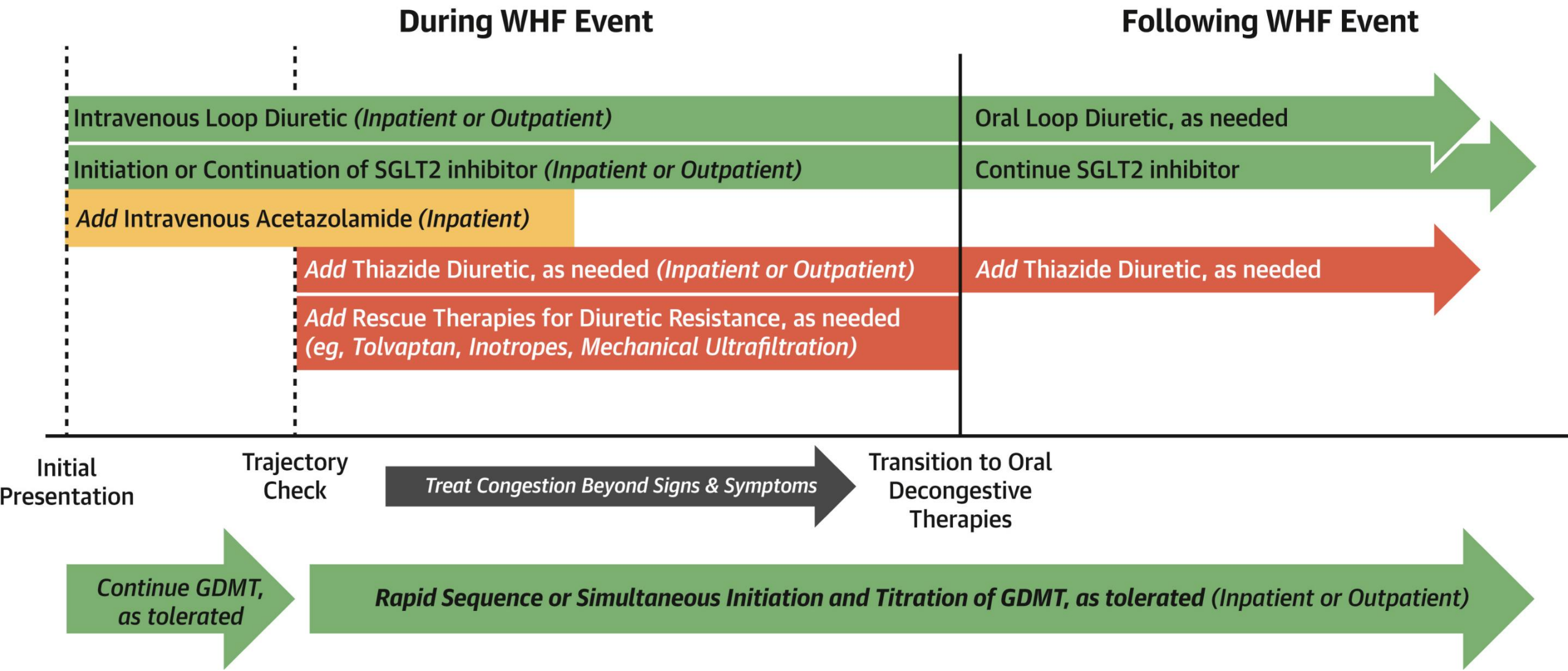
1-year survival is better for those having HF specialist nurse follow-up



Number at risk

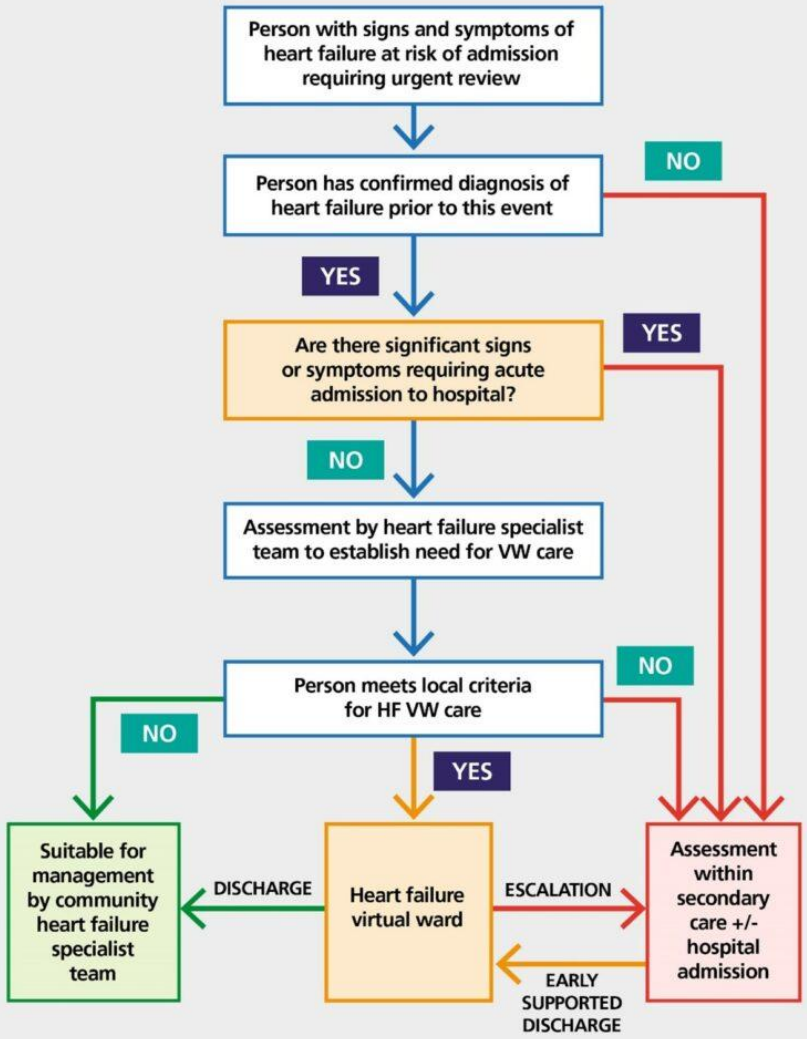
HF nurse follow-up	39029	36116	33935	32279	30930	28380	23283	18789
No HF nurse follow-up	30989	27560	25509	24058	22891	20882	17132	13985

Need for Careful Optimisation During an Episode of ADHF



Stephen J. Greene, et al. Journal of the American College of Cardiology, Volume 82, Issue 6, 2023, 559-571,

Virtual wards for the management of ADHF



Equivalence of care is a core principle of VW for HF

- Patients should be managed by HF specialists while on VW
- Pulmonary oedema or haemodynamic instability is an exclusion criteria
- Treatment should be equivalent to usual care (i.e guideline directed treatments optimised in the usual way, tests conducted in the usual way)

What do successful HF virtual wards offer?

Admissions decided by a senior clinical decision-maker, with same level of clinical assessment and decision making as if being admitted to a hospital bed.
Clearly defined criteria for triaging, admission, discharge and follow-up, including personalised and shared decision making.
Daily virtual review with HF team / MDT.
Robust provision for out-of-hours care.
Prompt access to advanced HF therapies and advance care planning when indicated

Care under a named HF specialist with clear lines of responsibility.
Access to specialist HF input from MDT including practitioners across care settings, expertise in specialist prescribing, medical, nursing, AHP and palliative care

Hybrid approach to care with face-to-face reviews and physical exams when required
Timely access to blood tests and point of care testing
Remote prescribing enabled to ensure optimisation of HF prognostic therapies.

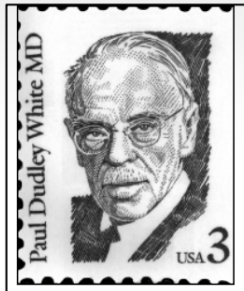
Conclusion

- Among the greatest challenges to HF care has been a culture of therapeutic hesitancy whereby
  - Clinical risk is underappreciated [1]
  - Therapeutic inertia is accepted
  - Benefits of disease modifying treatments for HF in improving health and reducing risk of death are not appreciated
- Patients are deemed “stable,” and disease modifying, lifesaving, therapies are not initiated despite patients being eligible [1]
  - New rapid sequencing protocols are designed to tackle clinical and therapeutic inertia.
  - Phenotyping and new targetted treatment options for HFmREF and pEF are designed to stabilise symptoms and reduce hospitalisations
  - IV iron carries a class 1 recommendation in patients with HF, ID and LVEF $\leq$50%, and is proven to reduce risk of re-hospitalisation for HF, but is underutilised

1. Stephen J. Greene, et al. Journal of the American College of Cardiology, Volume 82, Issue 6, 2023, 559-571,

How far we have come

Treatment of heart failure
From two textbooks 1929 and 1974



"…and for all this there is only digitalis and rest…"

Paul Dudley White: Textbook in Cardiology, 1929

J Willis Hurst
1920-2011

Moderately severe heart failure
- Decrease physical activity
- Institute digitalis
- Give thiazide every day plus potassium
- If not enough use furosemide and if insufficient, combine them

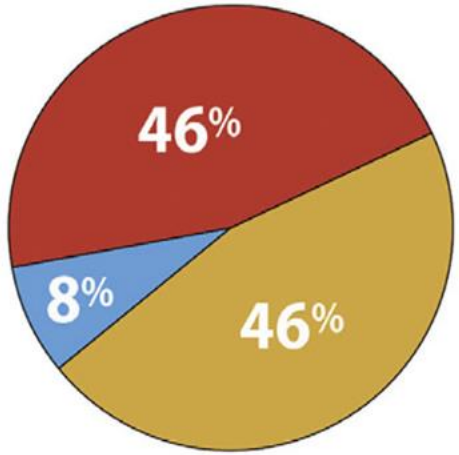
J W Hurst: The Heart 3rd edition, 1974

Oral Medical Therapy				Intravenous Medical Therapy
Quadruple Therapy				
ARNI	BB	MRA	SGLT2i	Intravenous Iron
• Prioritize initiating (at least) low doses • Prioritize initiating multiple/all medications prior to dose escalation of any one medication				• Among patients with iron deficiency (ferritin <100 μg/L, or 100-299 μg/L with transferrin saturation <20%)

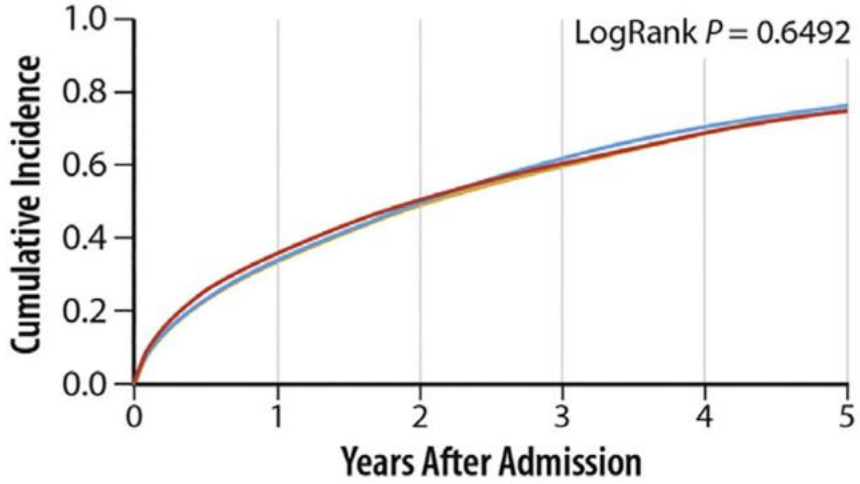
Quadruple Therapy				
↑ARNI	↑BB	↑MRA	*Continue* SGLT2i	**Strength of Recommendation and Benefit**
• Achieve maximally tolerated or target doses within 4-6 weeks • Prioritize dose escalation of BB as tolerated (strongest dose-response data) • Consider including virtual/remote visits to facilitate rapid titration • Serial laboratory monitoring of kidney function, serum potassium, and NT-proBNP during titration to confirm safety				• Proven to improve HF outcomes, including mortality • Foundational therapy for all eligible patients, as tolerated • Proven to improve HF outcomes other than mortality • Therapy should be strongly considered, as tolerated

5-YEAR OUTCOMES IN PATIENTS HOSPITALIZED WITH HF WITH PRESERVED, BORDERLINE, AND REDUCED EF

Heart Failure



5-Year Mortality



HFpEF (EF ≥50%) HFbEF (EF 41-49%) HFrEF (EF ≤40%)

Outcomes: 5-Year Event Rates (%)

	Mortality	Readmission	CV Readmission	HF Readmission	Mortality/Readmission
HFrEF	75.3	82.2	63.9	48.5	96.4
HFbEF	75.7	85.7	63.3	45.2	97.2
HFpEF	75.7	84.0	58.9	40.5	97.3