

# *Existing HFrEF: Augmenting the SOC*

**Dr Shelley Zieroth**

**Immediate Past President, Canadian Heart Failure Society**

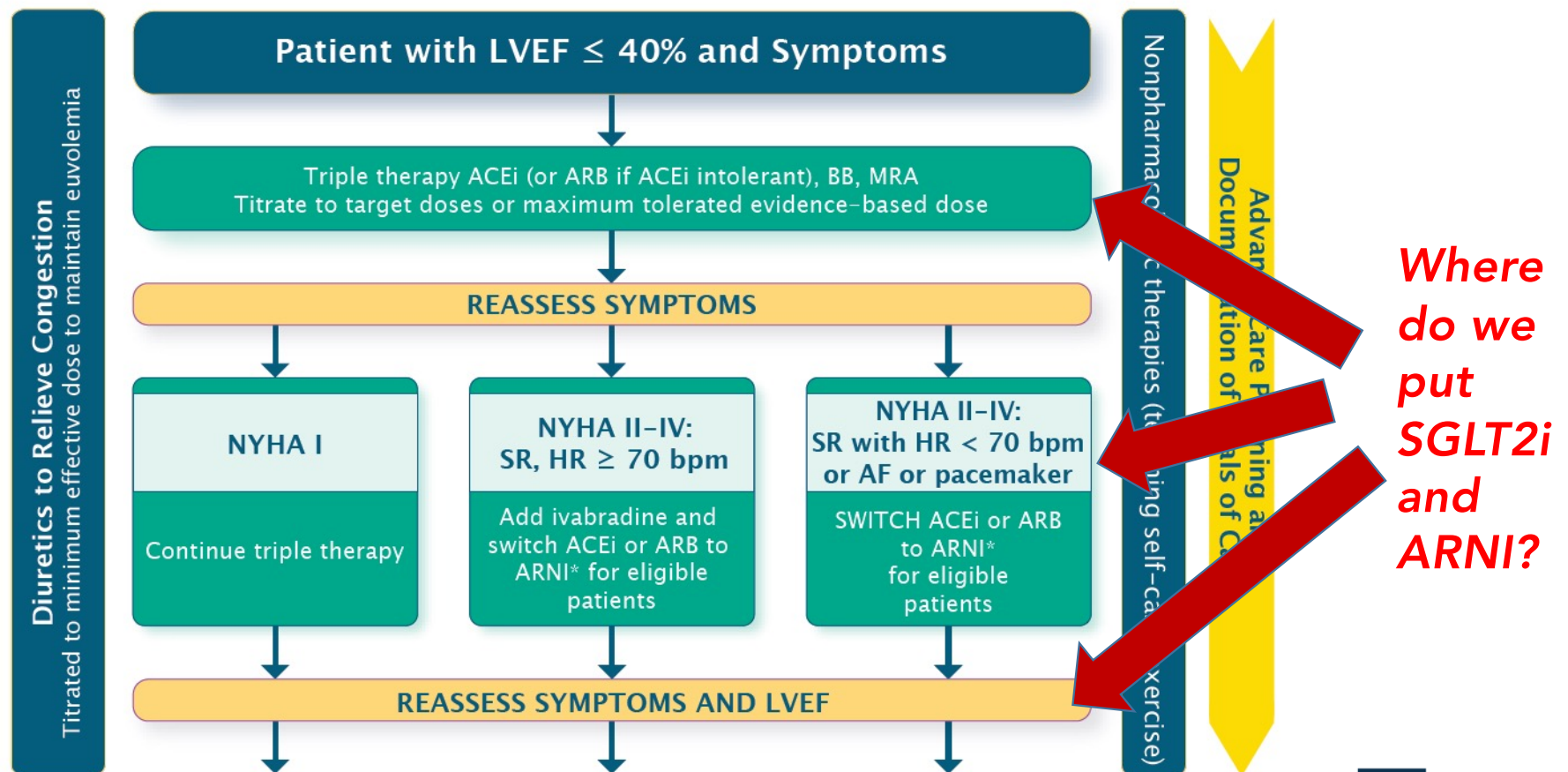
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# Disclosures

- **Grant Research/Support:** Servier, Novartis
- **Consulting Fees:** Abbott, Akcea, Astra Zeneca, Amgen, Alnylam, Boehringer Ingelheim, Eli-Lilly, Merck, Novartis, Otsuka, Pfizer, Servier, Vifor
- **Speaker Fees:** Amgen, Astra Zeneca, Boehringer Ingelheim, Eli-Lilly, Novartis, Servier, Vifor
- **Clinical Trials:** Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Eidos, Merck, Novartis
- **Steering Committee:** PARAGLIDE-HF
- **National Lead:** EMPACT-MI, EMPULSE, FINE-ARTS, DETERMINE

# CCS 2017 HF Guidelines

## Therapeutic Approach to Patients With HFrEF



Ezekowitz et al. *Canadian Journal of Cardiology* 33 (2017) 1342e1433

# NYHA II Mortality Lower risk..... But Not Low Risk

Physician Inertia: We need to do better

## Heart Failure Risk Calculator

**MAGGIC**  
*Meta-Analysis Global Group  
in Chronic Heart Failure*

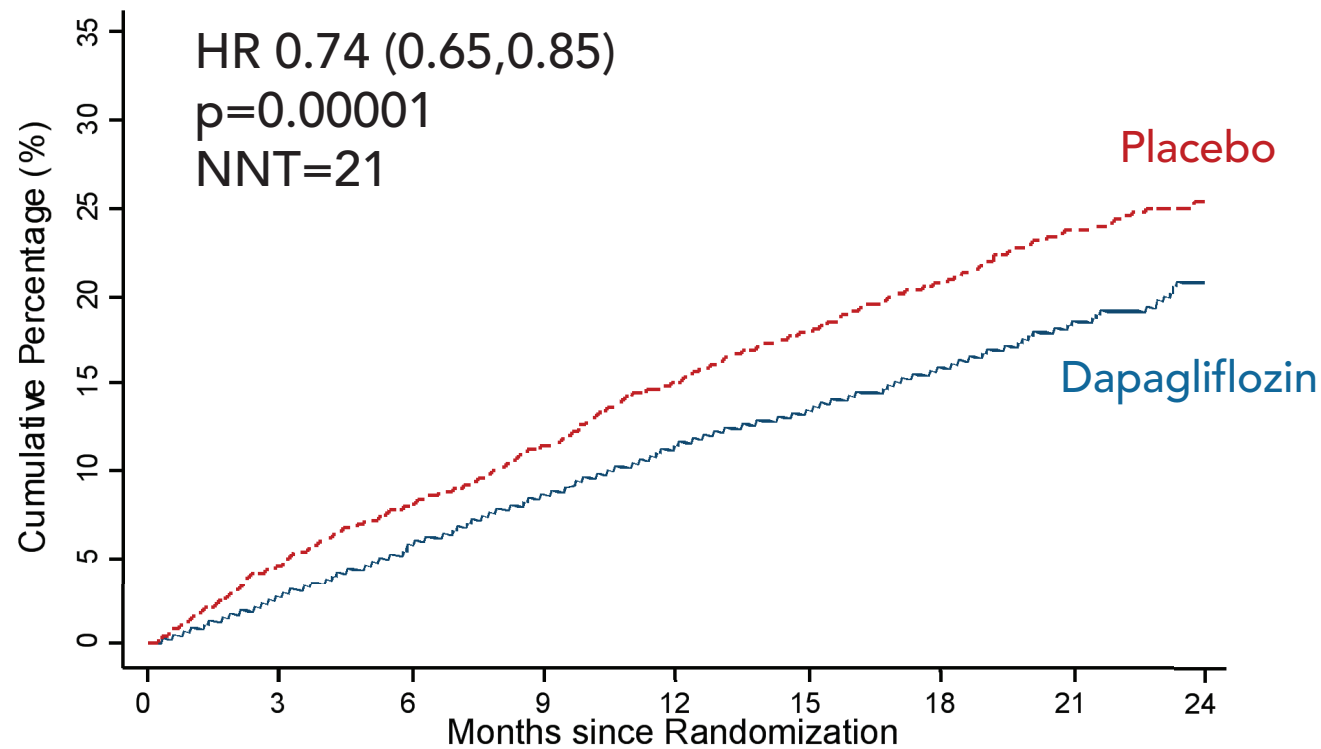
<b>Integer score: 14</b>
<b>Risk of dying within 1 year: 5.8%</b>
<b>Risk of dying within 3 years: 14.6%</b>
The patient is in the 1 <sup>st</sup> to 2 <sup>nd</sup> decile of risk in a heart failure population.

Pocock et al, *Eur Heart J* 2012

# PARADIGM SHIFTS NEW KIDS ON THE BLOCK

# DAPA-HF Primary Composite Outcome

CV Death/HF Hospitalization/Urgent HF Visit

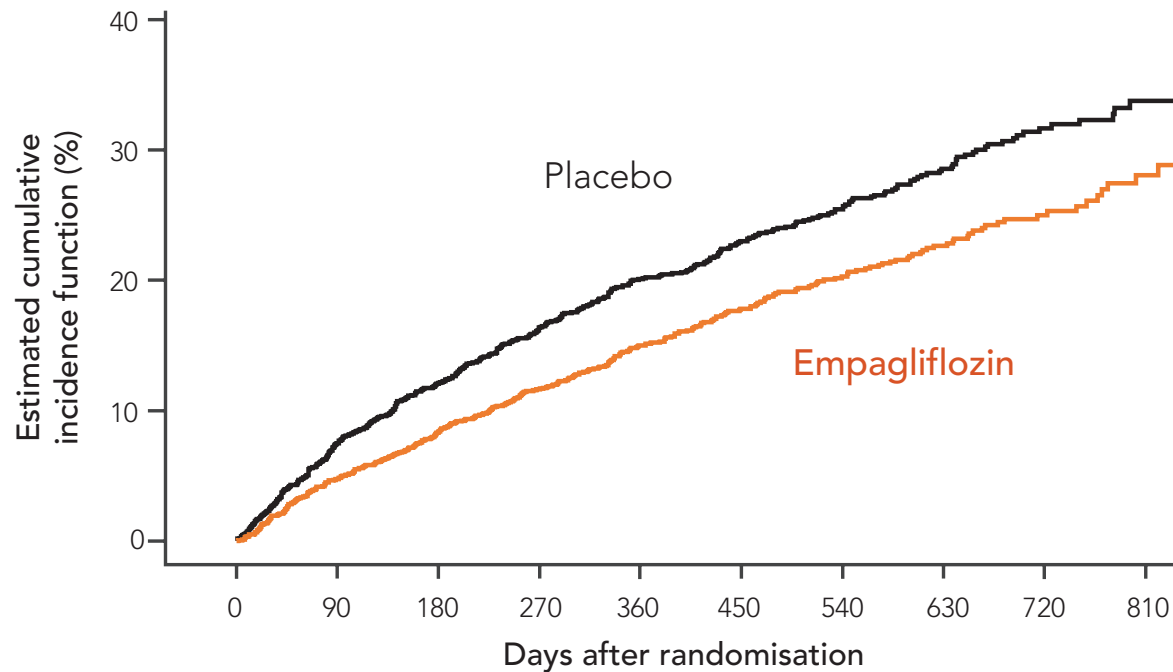


Number at Risk

Dapagliflozin	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo	2371	2258	2163	2075	1917	1478	1096	593	210

# EMPEROR-Reduced: Primary Endpoint

## First Adjudicated CV Death or HFH



**HR 0.75**  
(95% CI 0.65, 0.86)  
 $p < 0.001$

Patients at risk

Placebo	1867	1715	1612	1345	1108	854	611	410	224	109
Empagliflozin	1863	1763	1677	1424	1172	909	645	423	231	101

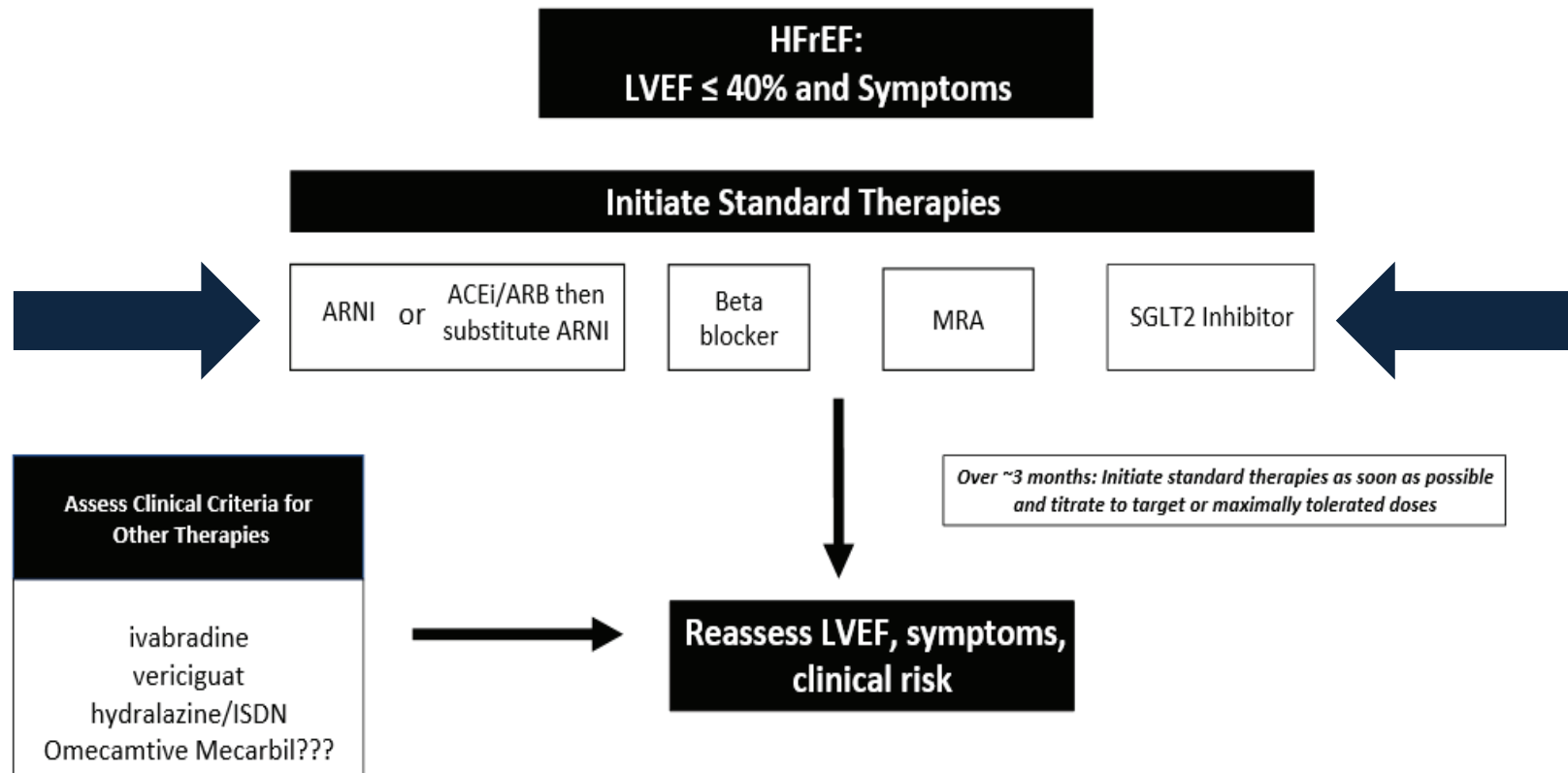
Packer M et al. *N Engl J Med* 2020. DOI:10.1056/NEJMoa2022190

SO NOW WHAT?



# Towards a New Standard of Care

In press Canadian Journal of  
Cardiology Epub date April 5<sup>th</sup>, 2021



## ← Tweet



James Januzzi Jr MD @JJheart\_doc · Jan 11

📌 2021 Update to the @ACCinTouch Expert Consensus Decision Pathway for Optimization of HFrEF Treatment.

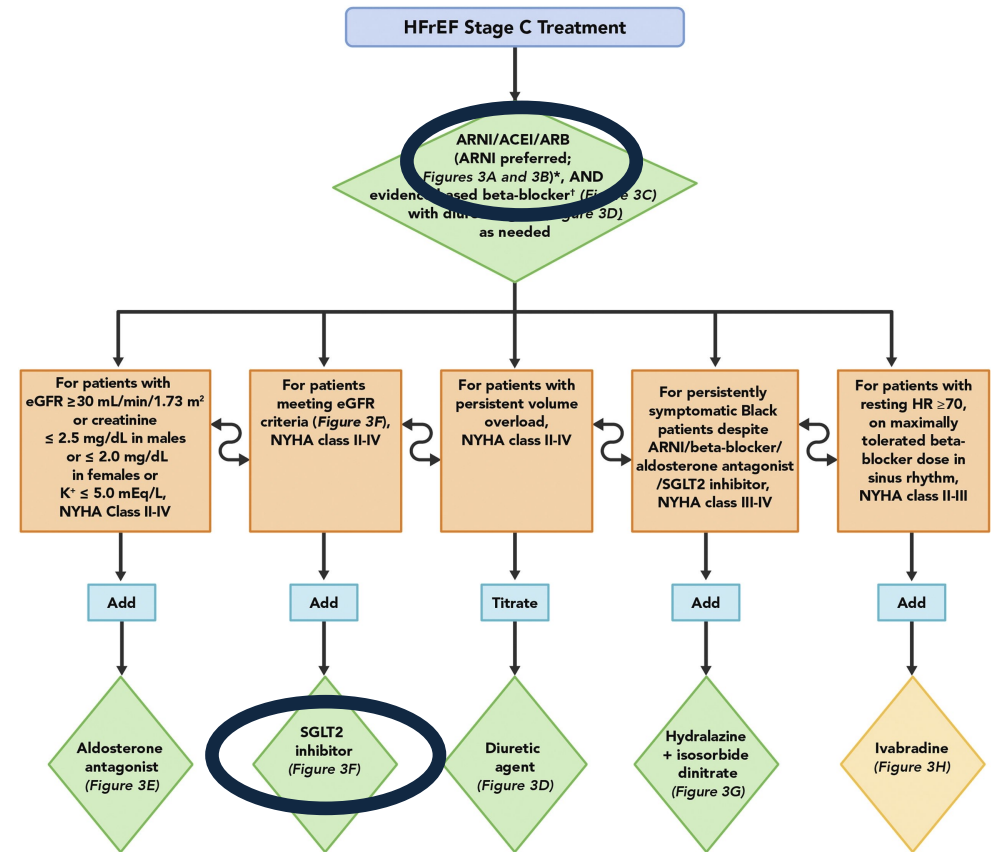
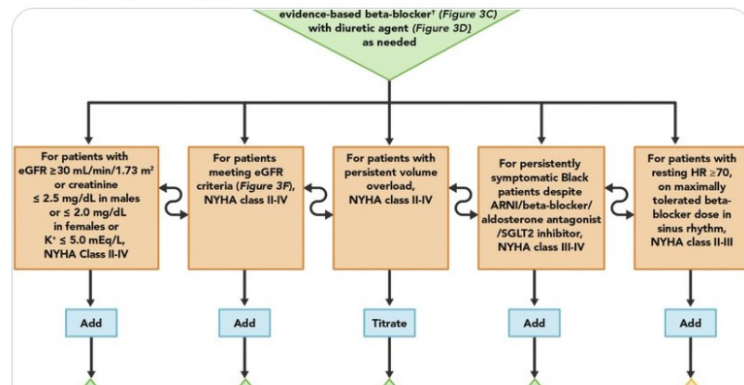
🚩 MAJOR CHANGES:

#ARNIfirst: ARNI now the foundational RASi, no pretreatment with ACE/ARB

#SGLT2i's now a part of pivotal meds

#GDMTworks #ACCBOT

[jacc.org/doi/10.1016/j.jacc.2021.01.016](https://jacc.org/doi/10.1016/j.jacc.2021.01.016)



\*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 3 and text for guidance on initiation.

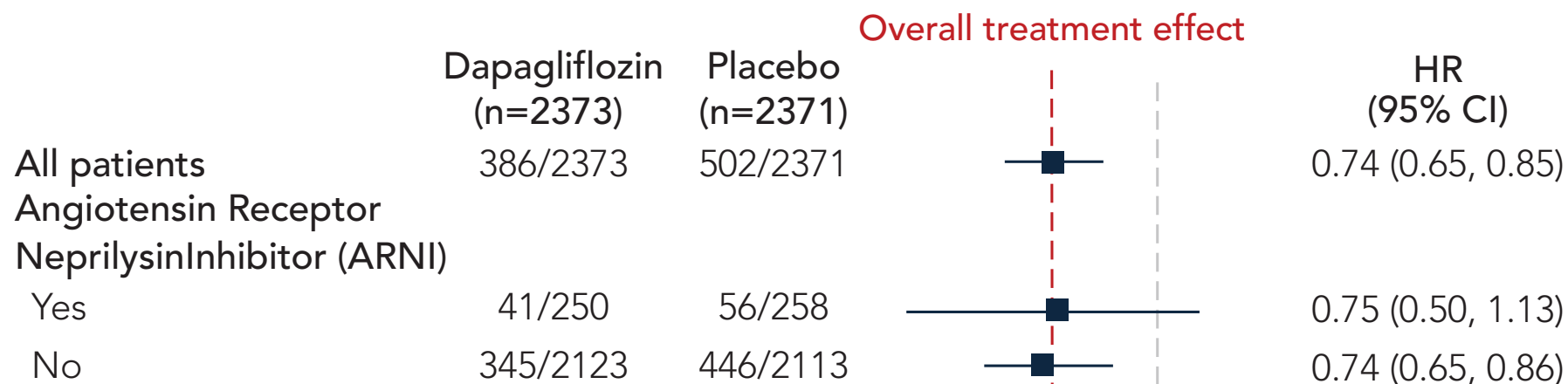
†Carvedilol, metoprolol succinate, or bisoprolol.

ACEI = angiotensin-converting enzyme inhibitors; ARNI = angiotensin receptor-neprilysin inhibitors; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; HFrEF = heart failure with reduced ejection fraction; HR = heart rate; K⁺ = potassium; NYHA = New York Heart Association; SGLT2 = sodium-glucose cotransporter-2.

- For patients with newly diagnosed Stage C heart failure with reduced ejection fraction (HFrEF), a beta-blocker and an angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB)/angiotensin receptor-neprilysin inhibitor (ARNI) **should be started in any order**. Each agent should be up-titrated to maximally tolerated or target dose. Initiation of a beta-blocker is better tolerated when patients are dry and an ACEI/ARB/ARNI when patients are wet.
- Only guideline-recommended beta-blockers (i.e., carvedilol, metoprolol succinate, or bisoprolol) should be used in patients with HFrEF. **Among angiotensin antagonists, ARNIs are preferred** agents. Renal function and potassium should be checked within 1-2 weeks of initiation or dose up-titration of ACEI/ARB/ARNI.
- Diuretics should be added as needed and dose should be titrated to achieve decongestion. If doses in excess of furosemide 80 mg twice daily are needed, either a different loop diuretic should be considered or a thiazide should be added.
- After initiation of beta-blocker and angiotensin antagonist, addition of an aldosterone antagonist should be considered with close monitoring of electrolytes. Sodium-glucose cotransporter-2 **(SGLT-2) inhibitors should also be considered for HFrEF** with New York Heart Association (NYHA) class II-IV patients.
- For persistently symptomatic Black patients despite above therapies, hydralazine and isosorbide dinitrate should be considered. In addition, if despite maximally tolerated beta-blocker, resting HR is  $\geq 70$  bpm in sinus rhythm, ivabradine may be considered.
- An ideal time to consider therapy **optimization is during hospitalization** for HFrEF. As an outpatient, adjustment of therapies should be considered every 2 weeks to achieve guideline-directed medical therapy (GDMT) within 3-6 months of initial diagnosis. An echocardiogram should be repeated 3-6 months after achieving target doses of therapy for consideration of an implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT).

SO HOW DO YOU DO THIS IN  
REAL LIFE?

# DAPA-HF: ARNI/no ARNI *Post Hoc* Subgroup: Primary Endpoint



P value for interaction=1.00

*The effect of dapagliflozin compared with placebo was not modified by the use or not of sacubitril/valsartan*

# EMPEROR REDUCED: Time to CV Death or HF Hospitalization (With and Without Neprilysin Inhibition)

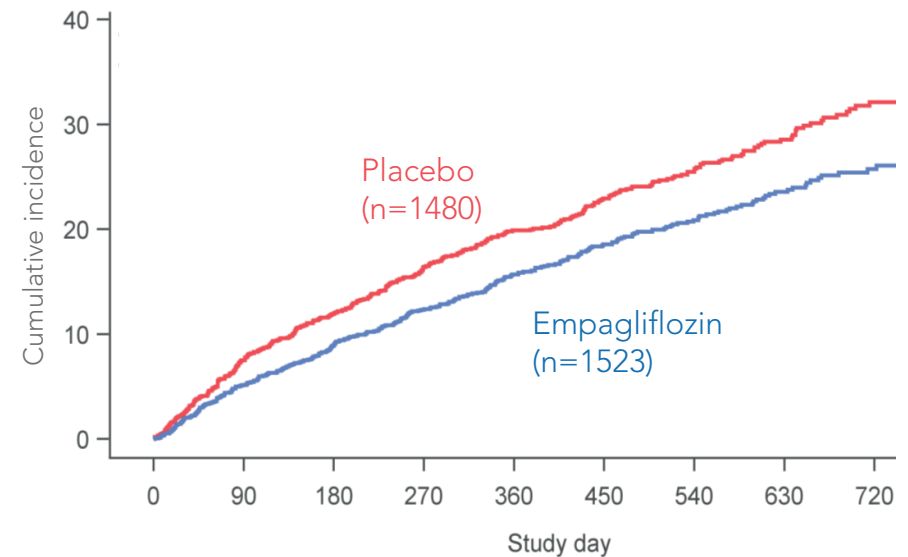
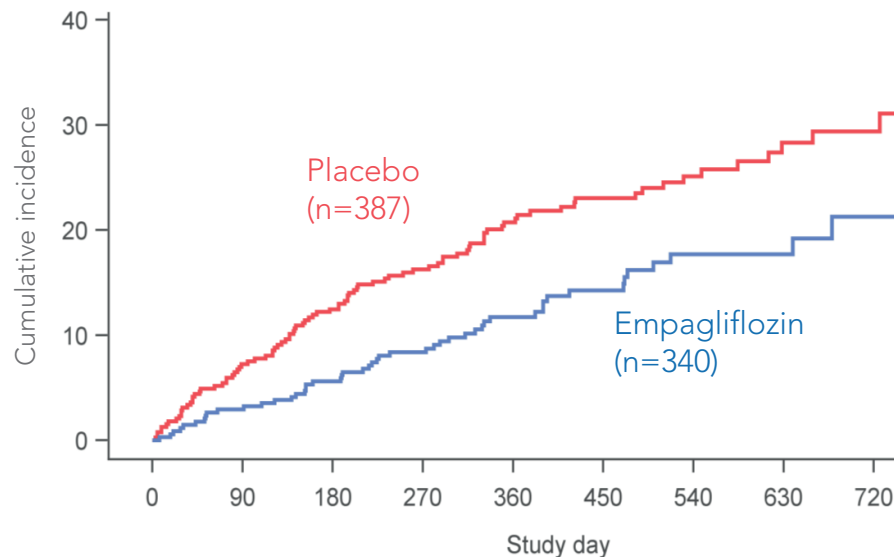
**On ARNI**

Interaction  $p=0.31$

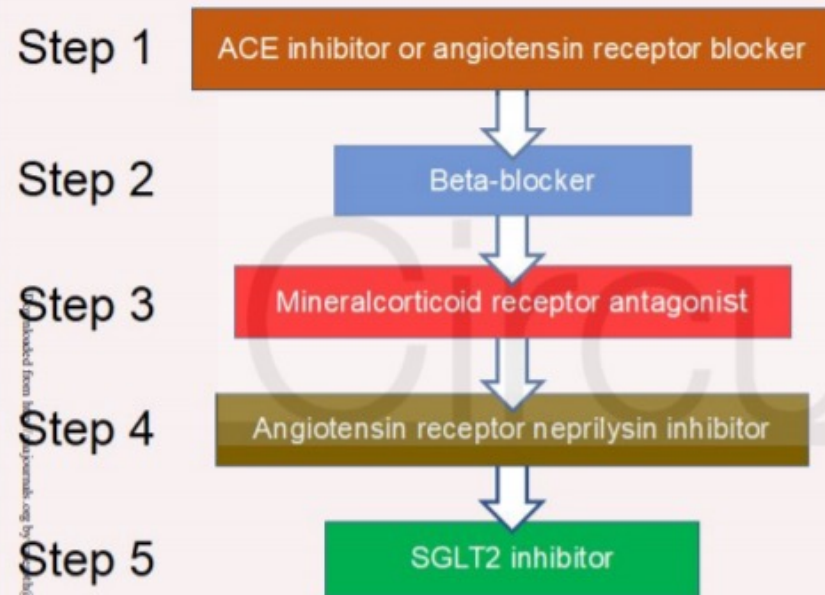
**Not on ARNI**

HR 0.64 (0.45, 0.89)

HR 0.77 (0.66, 0.90)

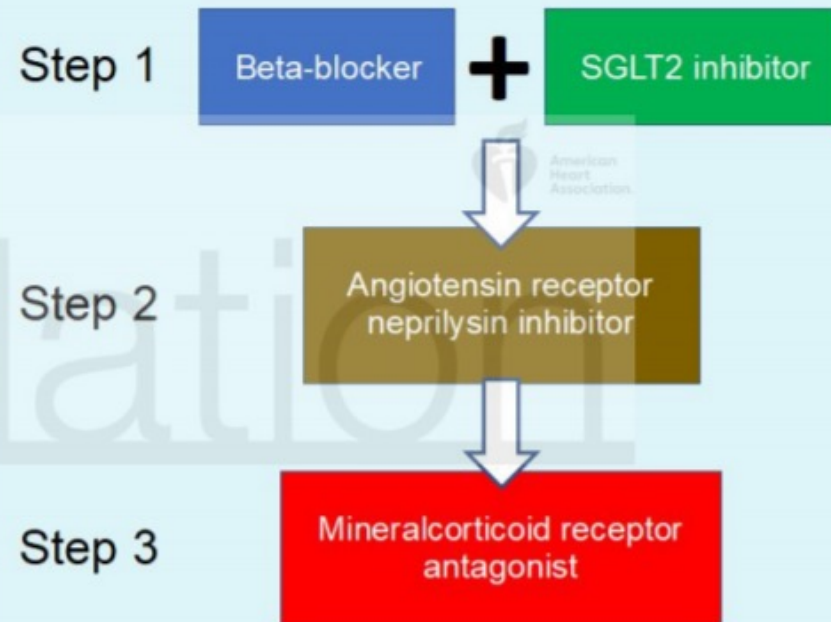


## Conventional Sequencing



*Uptitration to target doses at each step  
Typically requires 6 months or more*

## Proposed New Sequencing



*All 3 steps achieved within 4 weeks  
Uptitration to target doses thereafter*

How Should We Sequence the Treatments for Heart Failure and a Reduced Ejection Fraction? A Redefinition of Evidence-Based Medicine

John J.V. McMurray and Milton Packer

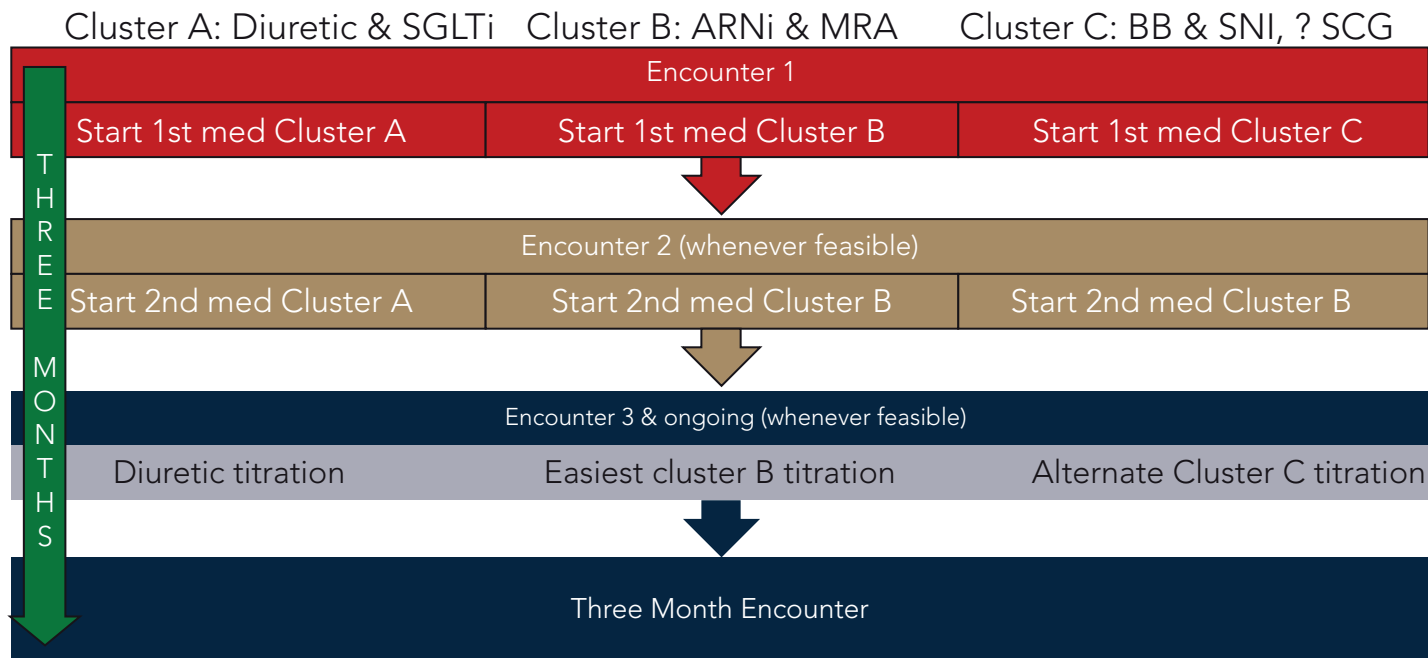
Originally published 30 Dec 2020 <https://doi.org/10.1161/CIRCULATIONAHA.120.052926>

# The Time Has Finally Come to Prioritize Drug Initiation Before Dose Titration for Patients with Heart Failure and Reduced Ejection Fraction

## Cluster Titration: Treatment of Heart Failure with LVEF < 40%

FACE TO FACE RED

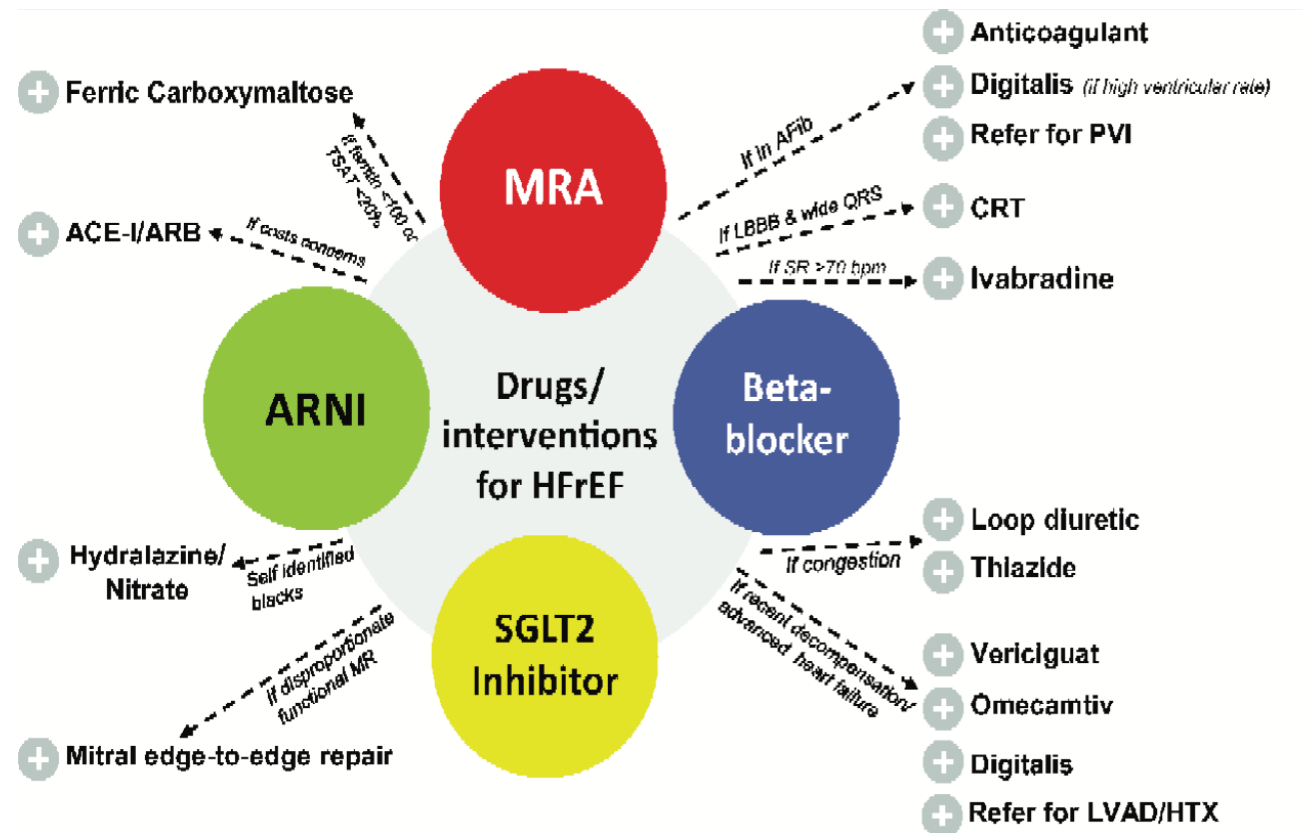
OFFLINE/PHONE/APP VISIT YELLOW







# THE FANTASTIC FOUR!!!!!!



Johann Bauersachs, Heart failure drug treatment: the fantastic four, *European Heart Journal*, 2021;, ehaa1012, <https://doi.org/10.1093/eurheartj/ehaa1012>



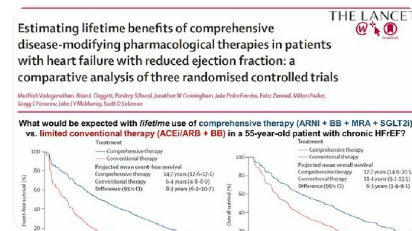
Muthu Vaduganathan @mv... · 5d ✓

How do you communicate the expected lifetime benefits of HF therapies?

New data in @TheLancet from 3 RCTs (#EMPHASISHF #PARADIGMHF #DAPAHF) estimate up to \*6 years\* of survival gains.

Combination ARNI+BB+MRA+SGLT2i = new therapeutic standard in HFrEF.

[thelancet.com/journals/lancet...](https://thelancet.com/journals/lancet...)



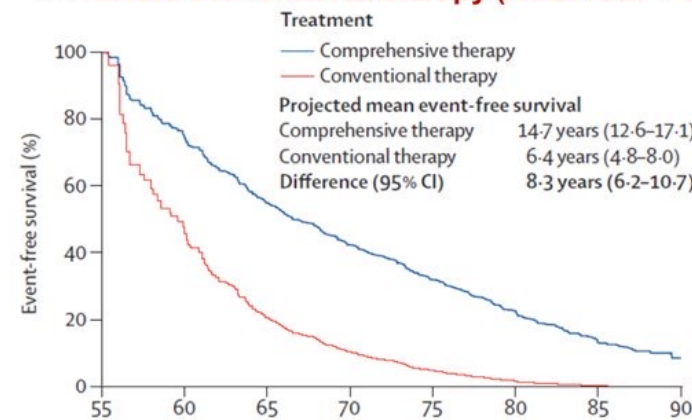
You and 9 others



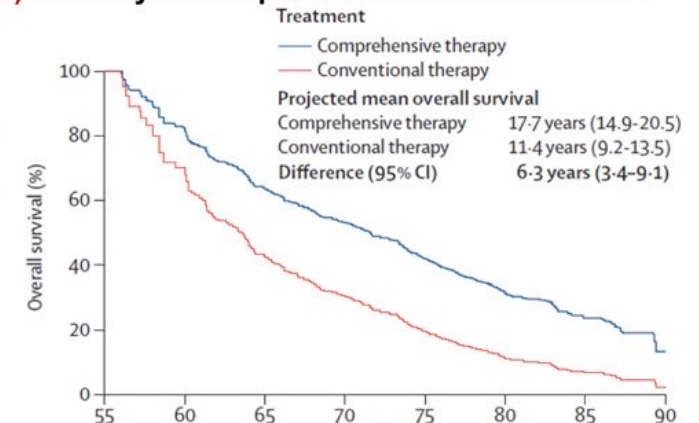
## Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: a comparative analysis of three randomised controlled trials

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

What would be expected with *lifetime* use of **comprehensive therapy (ARNI + BB + MRA + SGLT2i)** vs. **limited conventional therapy (ACEi/ARB + BB)** in a 55-year-old patient with chronic HFrEF?



**8 additional years free from CV death or HF hospitalization**



**6 additional years of overall survival**

[https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30748-0/fulltext#articleInformation](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30748-0/fulltext#articleInformation)

## QUANTIFYING THE BURDEN OF HFrEF



**Gregg Fonarow MD**

@gcfmd

Replying to @OKiamanesh @ShelleyZieroth and 15 others

The current use rate of ARNI + BB + MRA + SGLT2i for HFrEF is <4%. That is >10 million life-years that will be lost, but could be saved, if there was optimal and equitable implementation.

None

ARNI (vs imp

Beta Blo

Aldoster

SGLT2 in

Mortality

5.0%

5.2%

5.4%

5.5%

5.5%

Cumulative risk red

Relative risk reduction 72.9%, Absolute risk reduction: 25.5%, NNT = 3.9

therapies are used:

Updated from Fonarow GC, et al. Am Heart J 2011;161:1024-1030 and Lancet 2008;372:1195-1196.

# Summary

- GDMT for HFrEF has evolved
- In hospital initiation of newer HF therapies should be considered
- You should be using caremaps or pathways to insure treatment with GDMT
- QUADRUPLE THERAPY
- More changes coming:
  - Vericiguat – “5-Alive”
  - Omecamtiv Mecarbil