HFpEF Masterclasses
In centers of expertise

FRANCE

7th November 2024 - DAY 1
8th November 2024 - DAY 2

Treating before knowing LVEF

Alain COHEN SOLAL
Université Paris Cité
INSERM U942
Cardiologie, Hopital Lariboisiere, Paris

theheart.org Medscape Cardiology

News > Medscape Medical News > Conference News > HFSA 2021

Ejection Fraction for Guiding HF Therapy: Forget About It?

JACC: HEART FAILURE
© 2023 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

EDITORIAL COMMENT

Exploring Ejection Fraction Range in Heart Failure Clinical Trials

Aid or Distraction for Personalized Treatment?*

European Heart Journal Supplements (2022) 24 (Supplement L), L10-L19
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suac113

ESC European Society of Cardiology

The four pillars of HFrEF therapy: is it time to treat heart failure regardless of ejection fraction?

Kieran F. Docherty[1], Antoni Bayes-Genis[2], Javed Butler[3,4], Andrew J.S. Coats[5], Mark H. Drazner[6], Emer Joyce[7,8], and Carolyn S.P. Lam[9]*

ESC Congress 2022
Barcelona

HFpEF Masterclasses

Great Debate: ejection fraction no longer determines the management of heart failure

Journal of *Cardiovascular Development and Disease*

Review

Practical Pharmacological Treatment of Heart Failure: Does Ejection Fraction Matter Anymore?

Jonathan C. H. Chan [1,2], Emily Cowley [3] and Michael Chan [2,*]

MEDPAGETODAY®

Does Ejection Fraction Matter Anymore?

— Experts debate whether familiar metric still has a place in heart failure management

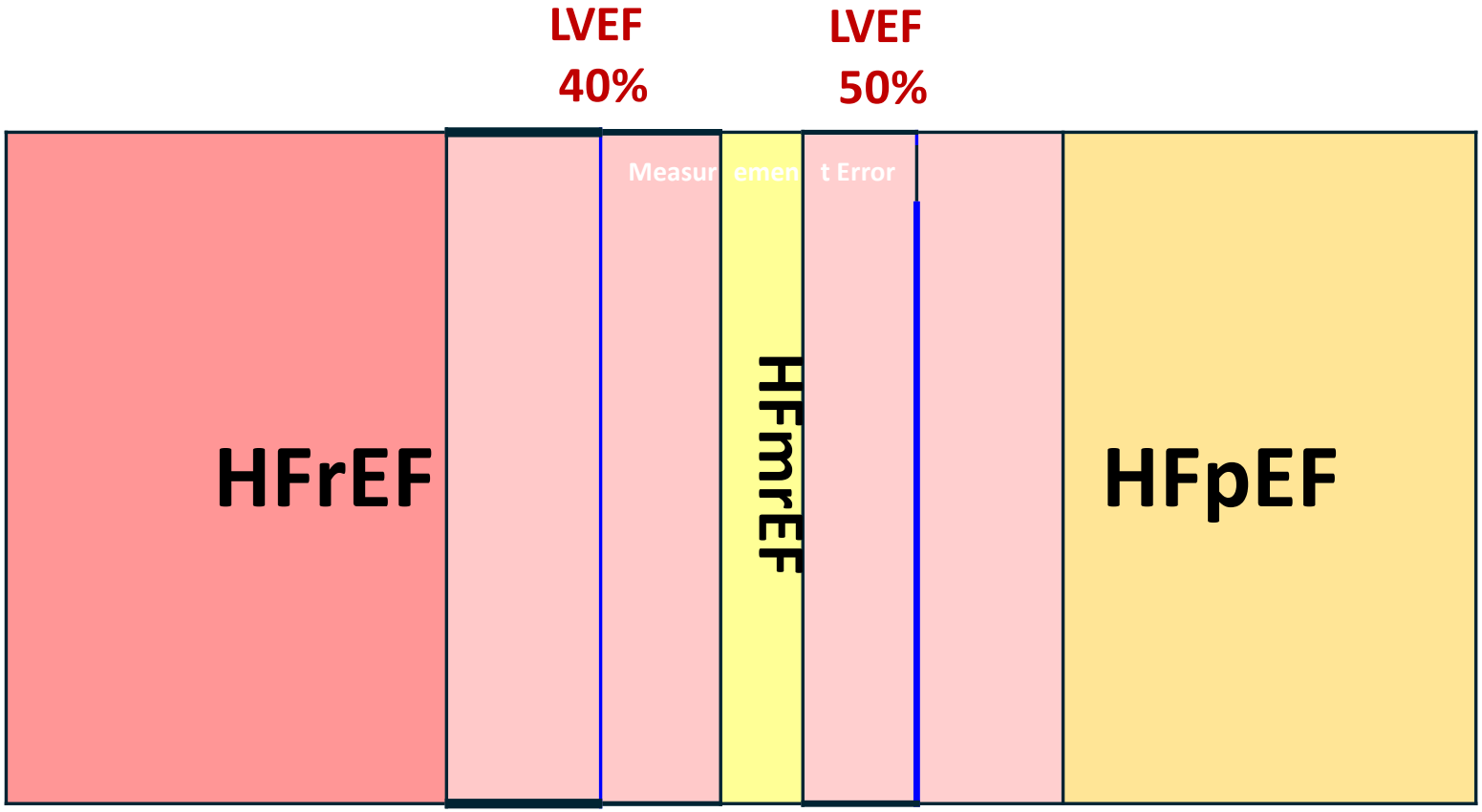
sman, Contributing Writer, MedPage Today September 2, 2020

failure specialist at the virtual meeting of the European Society of Cardiology
ated whether the role of ejection fraction calculations is relevant in the
ent of their patients.

t Pieske, MD, of Charite University Medicine, Berlin, who took the "pro"
n at the scheduled event, said, "Ejection fraction has become the single most
ant number in cardiology. We all know how to use it, how to apply it, and
interpret it. It is part of our daily life. It can be obtained using any cardiac
imaging device worldwide."

Treatment of HFpEF is based on a polytherapy based on large studies.
Enrollement – and thus implementation- has been based on the LVEF value at inclusion.
This means that we have to wait for LVEF determination before strating/optimizing therapy, given that some of them do not have indications for all LVEF strata
Which may take time in some circumstances
Studies have shown that when therapy is started early, before discharge, effectiveness is greater (ex STRONG-HF)

Is the classification of HF based upon LVEF still valid?

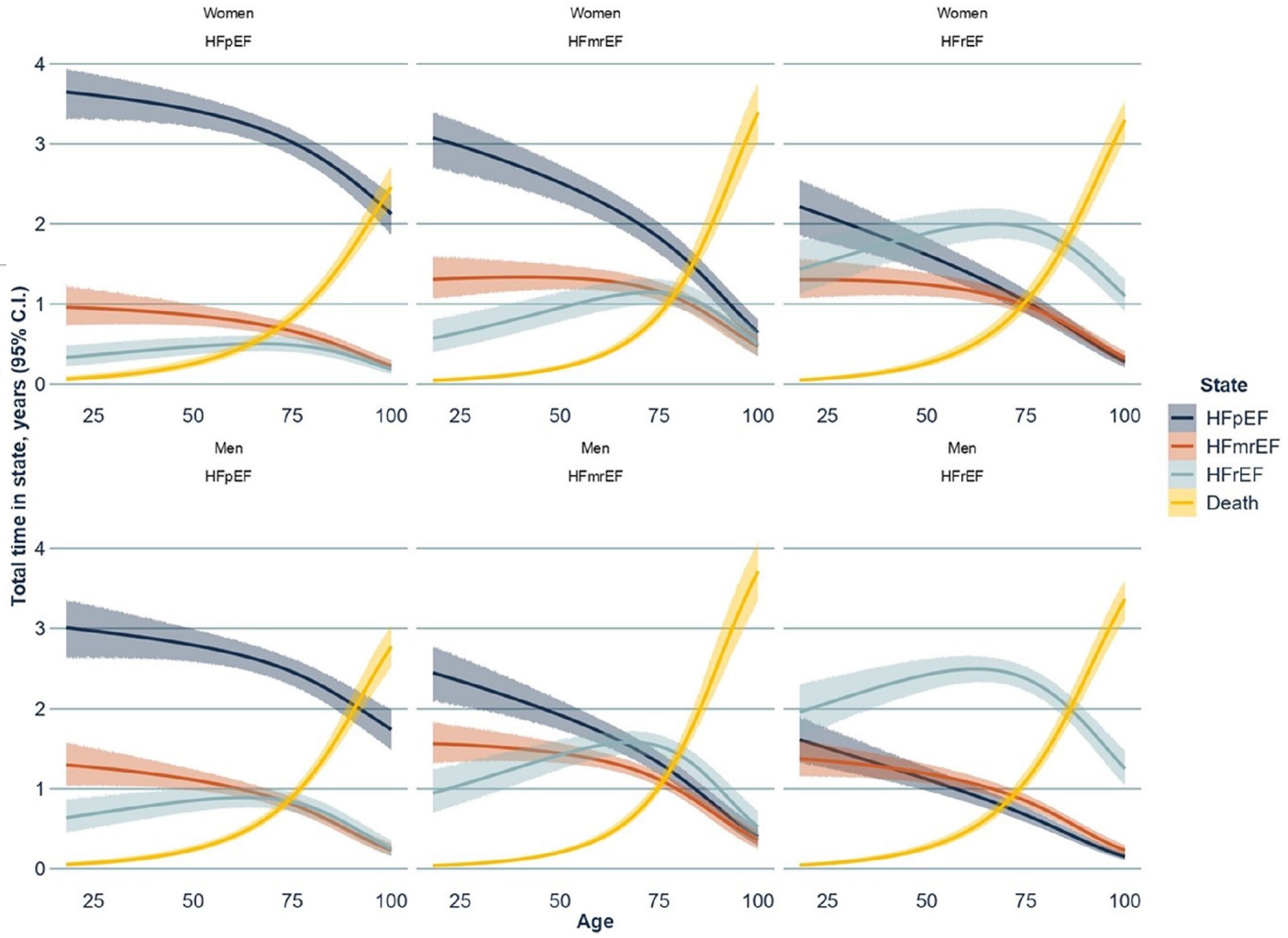


Journal of the American Heart Association

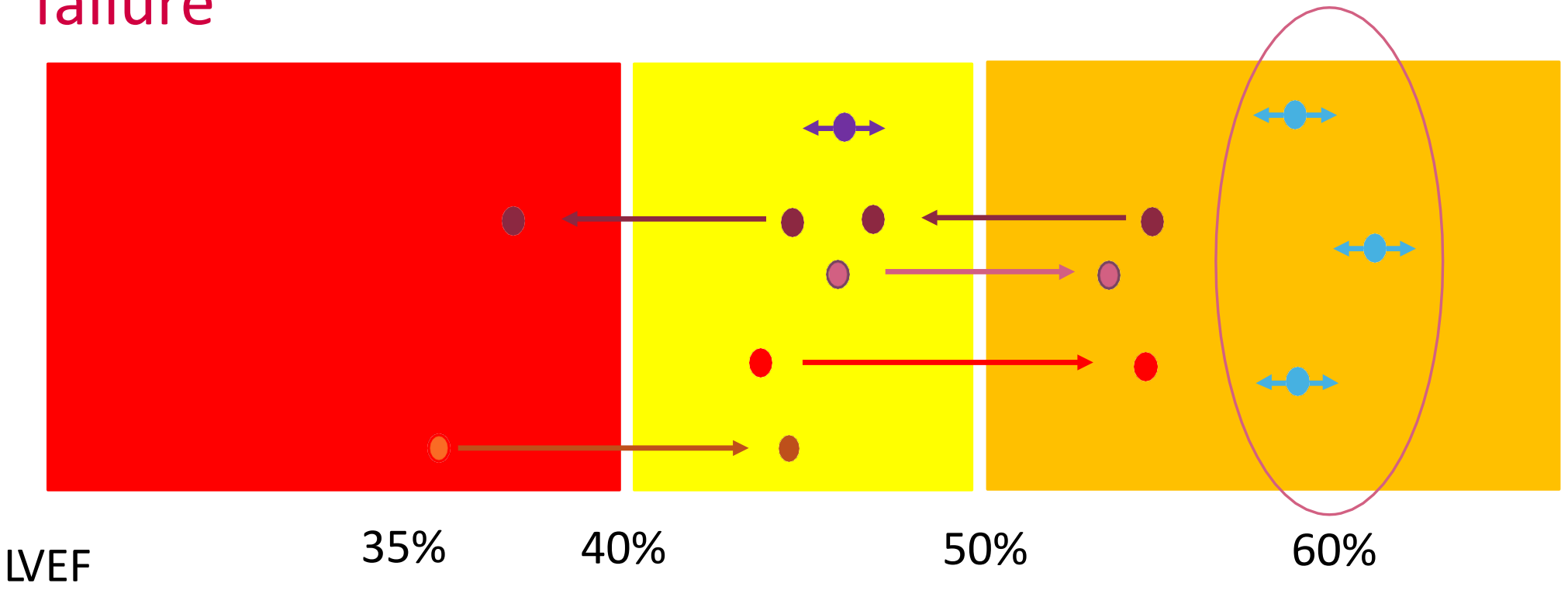
ORIGINAL RESEARCH

Usefulness of Heart Failure Categories Based on Left Ventricular Ejection Fraction

Malin Christersson, MD; Stefan Gustafsson, PhD; Erik Lampa, PhD; Matilda Almstedt, MSc; Thomas Cars, PhD; Johan Bodegård, MD, PhD; Gabriel Arefalk, MD, PhD; Johan Sundström, MD, PhD



LVEF trajectories better identify patients with heart failure



The New England
Journal of Medicine

Volume 316 JUNE 4, 1987 Number 23

EFFECTS OF ENALAPRIL ON MORTALITY IN SEVERE CONGESTIVE HEART FAILURE

Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS)

THE CONSENSUS TRIAL STUDY GROUP*

The diagnosis of congestive heart failure was based on clinical criteria: a history of heart disease with symptoms of dyspnea or fatigue or both, together with signs of fluid retention and no evidence of primary pulmonary disease. The patients were symptomatic at rest (NYHA functional class IV).

Measurements of myocardial function were not required.

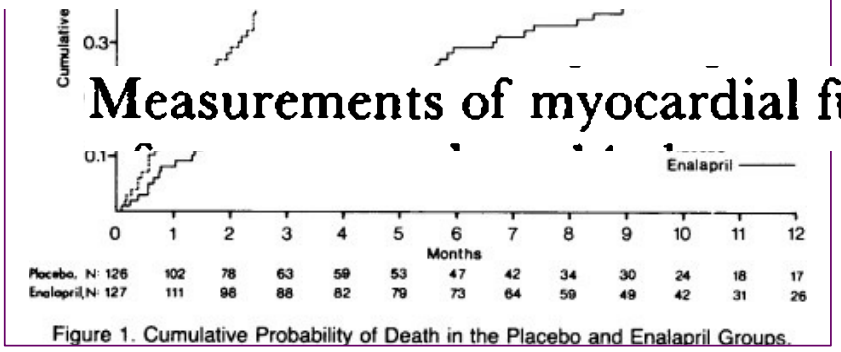
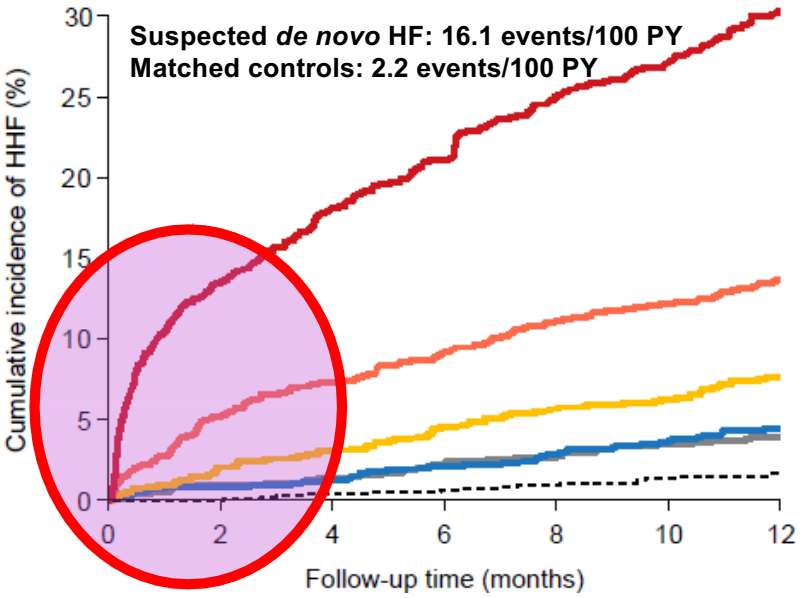


Figure 1. Cumulative Probability of Death in the Placebo and Enalapril Groups.

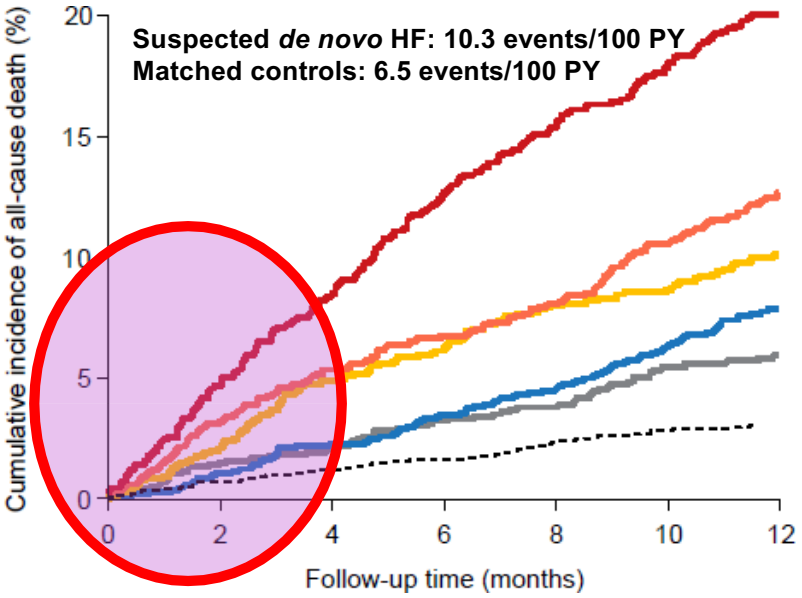
Risks in suspected *de novo* HF while waiting for an echocardiogram

REVOLUTION HF

Hospitalization for HF



All-cause death



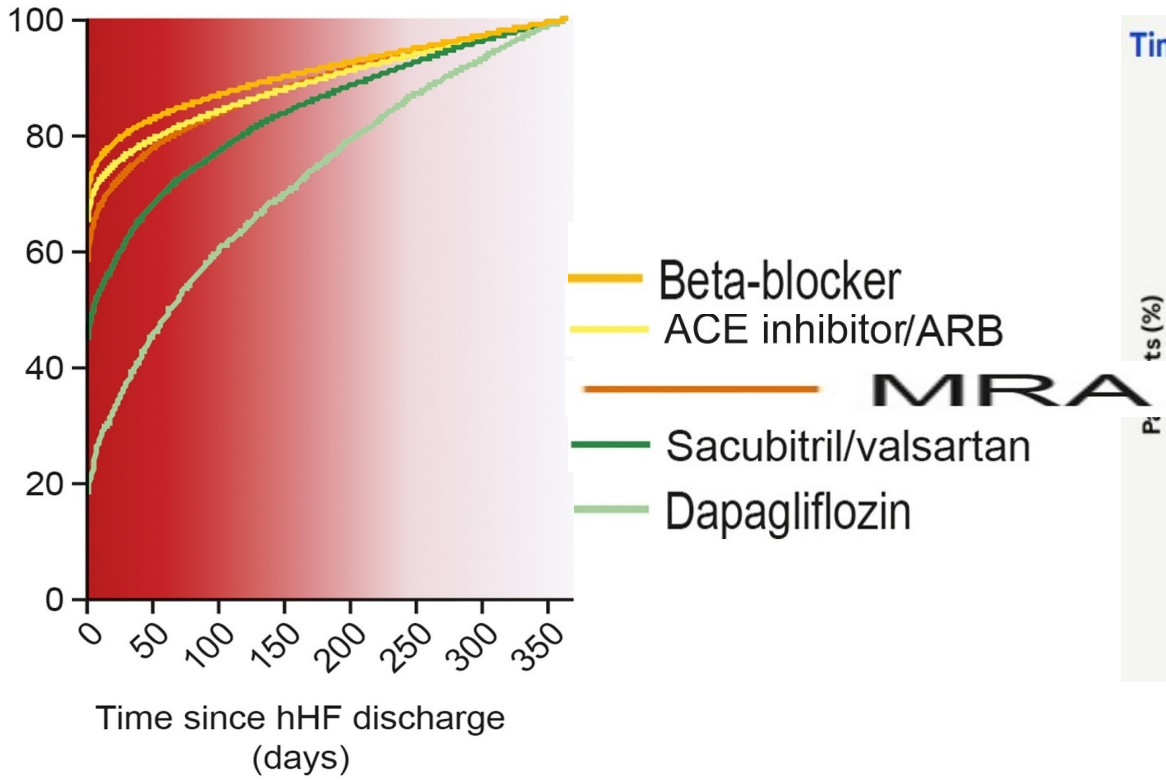
Baseline NT-proBNP

- >2000 ng/L
- 1000–2000 ng/L
- 600–1000 ng/L
- 400–600 ng/L
- 300–400 ng/L
- Matched controls

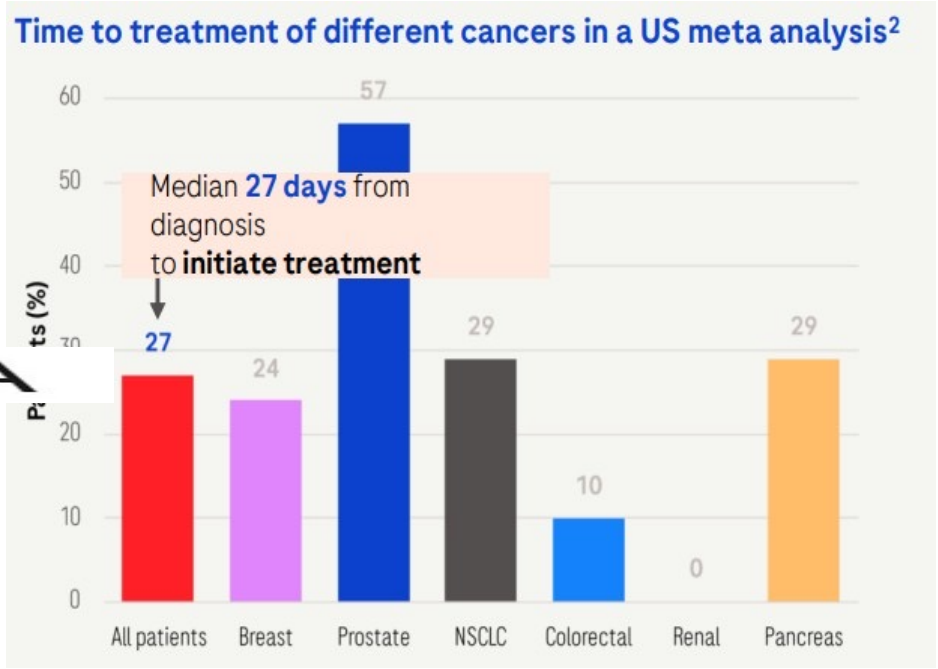
HF, heart failure; HHF, hospitalization for heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; PY, patient-years

Anderson L et al Late Breaking Trials – HFA Congress 11 May 2024

Time to treatment is unnecessarily too long



Savarese et al. Heart Failure. 2023;11:1-4.



Khorana AA, et al. PLoS One 2019;14:e0213209.

Waiting time for echo or cardiology visit

In **Belgium**, one study showed 63% of patients in primary care with suspected HF received an echo.[17]

In **Ireland**, a study of patients with a diagnosis of HF in primary care reveals only 40% received an echo.[20]

In **Finland**, a study showed echo was only available for 32% of patients in regional hospitals, but 78% in university hospitals, and 68% in central hospitals.[16]

In the **Netherlands**, one study found that only 10% of GPs routinely perform an echo to support the diagnosis of HF.[8]

In **Germany**, a study showed only 17.2% of patients received an echo in primary care settings.[18]

In **Scotland**, only 58% of HF patients are diagnosed with an echo.[11]

Heart Failure Policy Network Report 2022

What can be given without knowing LVEF

Diuretics

ACE-I or ARB

- the scientific evidence is not strong if LVEF is > 50%

MRA ?

- Rarely an emergency
- Effective in HFrEF
- Conflicting results in HFpEF (TOPCAT ..)

What should not be given without knowing LVEF

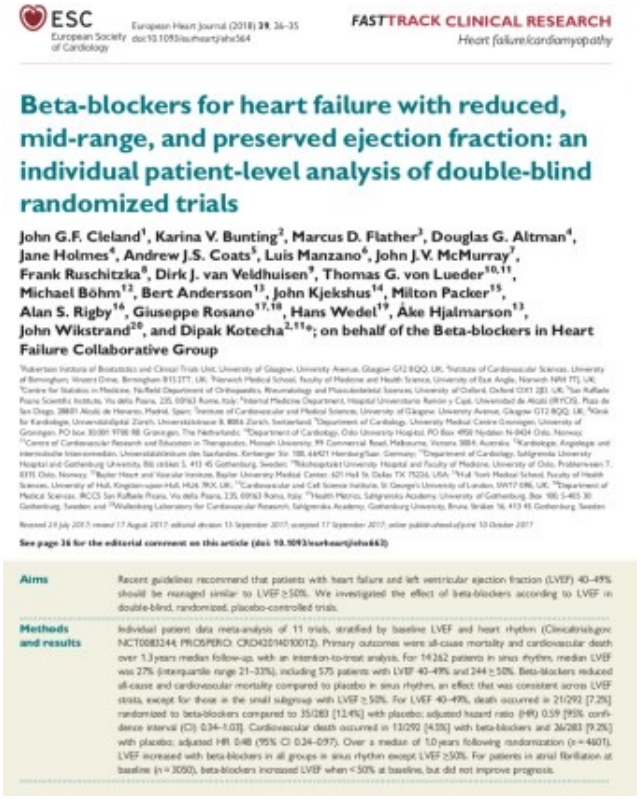
Betablockers

- Not effective in HFpEF

Sacubitril/valsartan

- No effect
- Unless when LVEF is 40-50% (HFmrEF)

Beta blockers



ESC European Society of Cardiology

European Heart Journal (2018) 39, 26–35 doi:10.1093/eurheartj/ehx564

FASTTRACK CLINICAL RESEARCH
Heart failure/cardiomyopathy

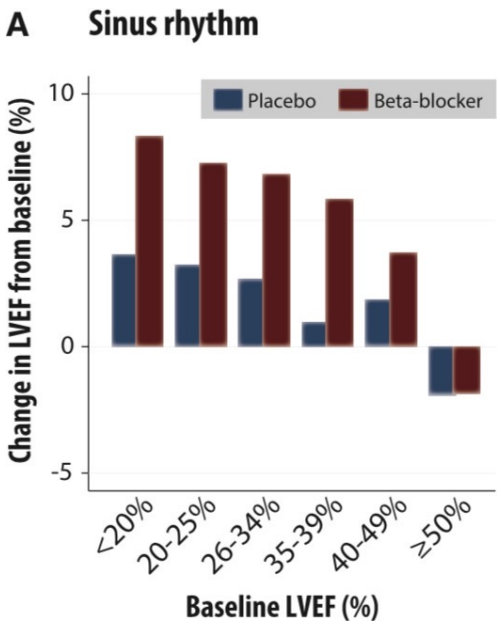
Beta-blockers for heart failure with reduced, mid-range, and preserved ejection fraction: an individual patient-level analysis of double-blind randomized trials

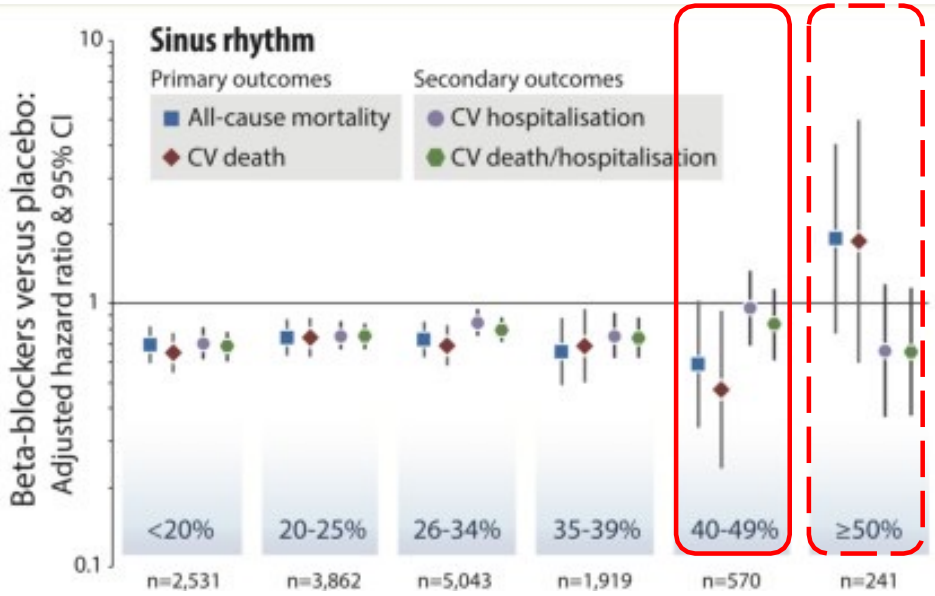
John G.F. Cleland[1], Karina V. Bunting[2], Marcus D. Flather[3], Douglas G. Altman[4], Jane Holmes[4], Andrew J.S. Coats[5], Luis Manzano[6], John J.V. McMurray[7], Frank Ruschitzka[8], Dirk J. van Veldhuisen[9], Thomas G. von Lueder[10,11], Michael Böhm[12], Bert Andersson[13], John Kjekshus[14], Milton Packer[15], Alan S. Rigby[16], Giuseppe Rosano[17,18], Hans Wedel[19], Åke Hjalmarson[13], John Wikstrand[20], and Dipak Kotecha[2,11]*; on behalf of the Beta-blockers in Heart Failure Collaborative Group

See page 36 for the editorial comment on this article (doi: 10.1093/eurheartj/ehx663)

Aims Recent guidelines recommend that patients with heart failure and left ventricular ejection fraction (LVEF) 40–49% should be managed similar to LVEF ≥50%. We investigated the effect of beta-blockers according to LVEF in double-blind, randomized, placebo-controlled trials.

Methods and results Individual patient data meta-analysis of 11 trials, stratified by baseline LVEF and heart rhythm (Clinicaltrials.gov NCT00832244; PROSPERO: CRD42016040012). Primary outcomes were all-cause mortality and cardiovascular death over 1.3 years median follow-up, with an intention-to-treat analysis. For 14 262 patients in sinus rhythm, median LVEF was 27% (interquartile range 21–33%), including 575 patients with LVEF 40–49% and 244 ≥ 50%. Beta-blockers reduced all-cause and cardiovascular mortality compared to placebo in sinus rhythm, an effect that was consistent across LVEF strata, except for those in the small subgroup with LVEF ≥ 50%. For LVEF 40–49%, death occurred in 21/292 [7.2%] randomized to beta-blockers compared to 35/283 [12.4%] with placebo; adjusted hazard ratio (HR) 0.59 [95% confidence interval (CI) 0.34–1.03]. Cardiovascular death occurred in 13/292 [4.5%] with beta-blockers and 26/283 [9.2%] with placebo; adjusted HR 0.48 (95% CI 0.24–0.97). Over a median of 1.0 years following randomization (n = 4601), LVEF increased with beta-blockers in all groups in sinus rhythm except LVEF ≥50%. For patients in atrial fibrillation at baseline (n = 3050), beta-blockers increased LVEF when < 50% at baseline, but did not improve prognosis.





adjusted for age, gender, previous myocardial infarction, systolic blood pressure, heart rate, and use of angiotensin inhibitors/receptor blockers, and diuretics.

The issue is for SGLT2i

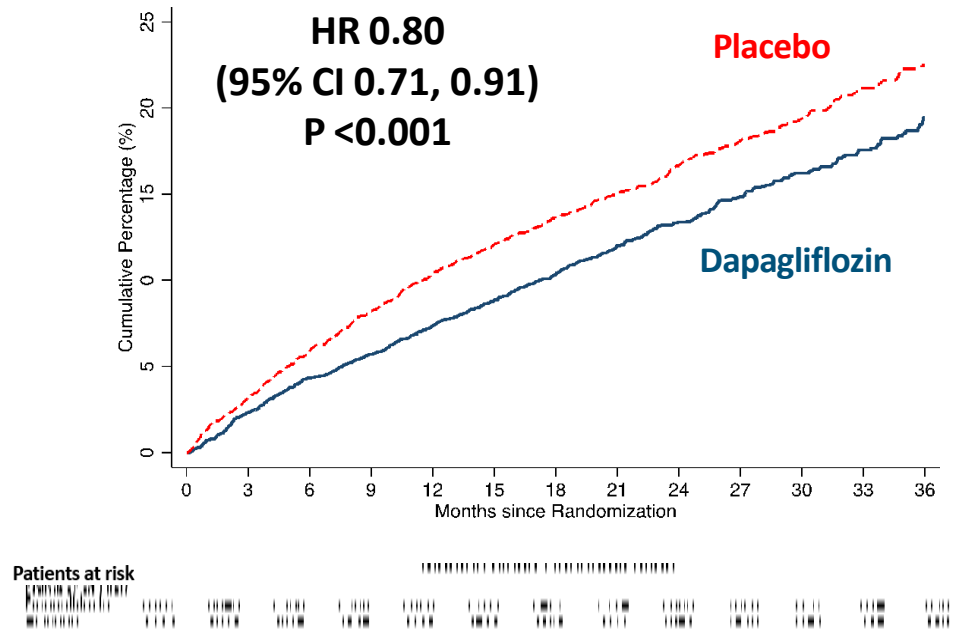
They have been found to be effective in HF whatever the level of LVEF
And safe
Their introduction does not compromise the introduction of subsequent therapies.
In HFpEF studies, their effect appears early in the first weeks
So
Should we wait LVEF determination to start ?

SGLT2 inhibitors in patients with HFmrEF and HFpEF

Patients with and <u>without</u> type 2 diabetes

DELIVER

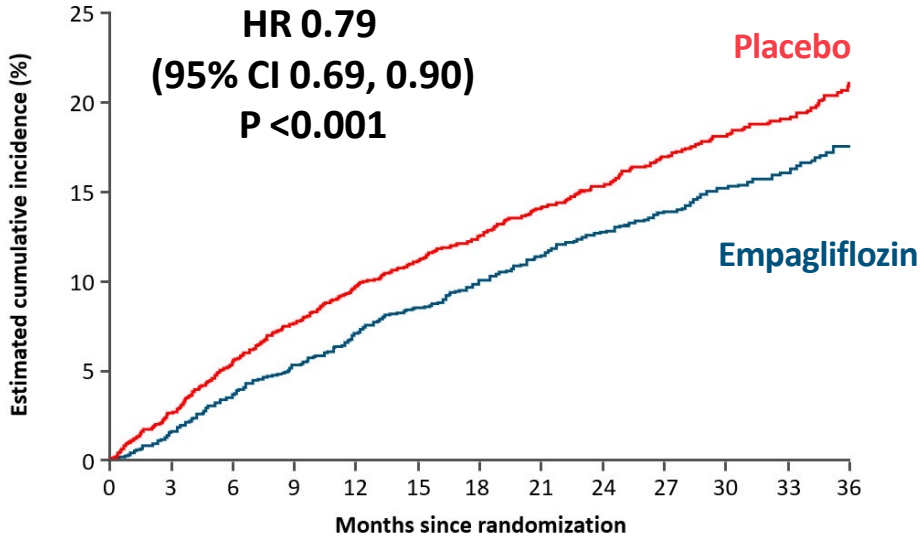
CV Death/ HF hospitalization



Solomon, McMurray, Claggett et al
N Engl J Med. 2022 Aug 27. doi: 10.1056/NEJMoa2206286

EMPEROR-Preserved

CV Death/ HF hospitalization



Patients 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

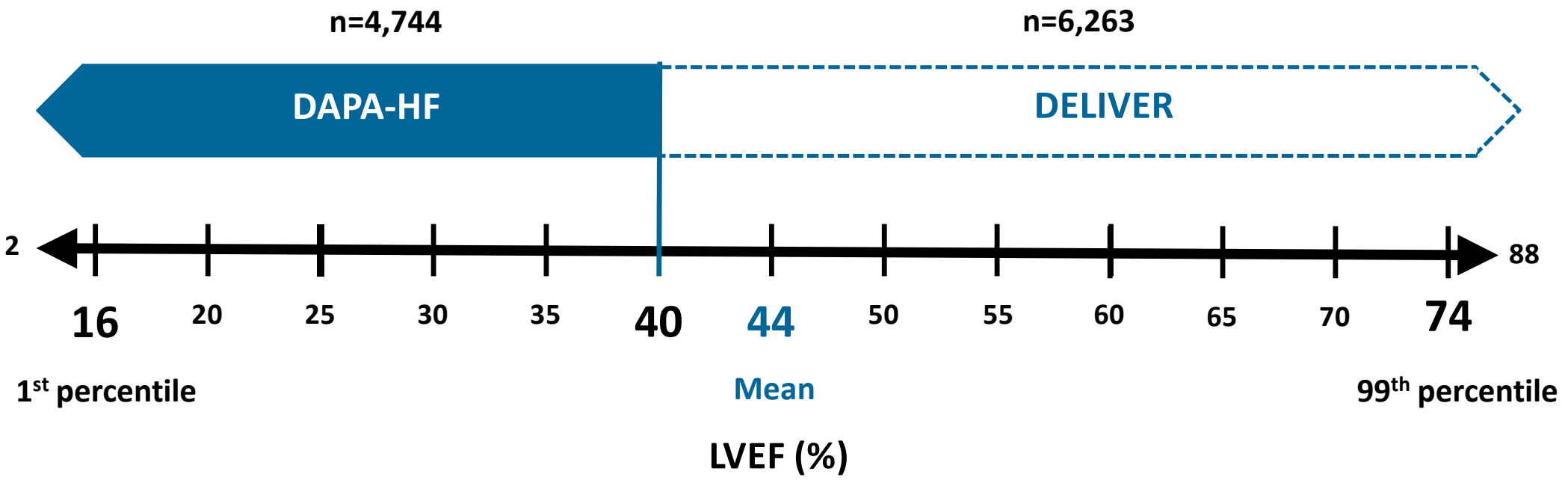
Anker, Butler, Filippatos et al
N Engl J Med. 2021; 385: 1451-1461.

DAPA-HF & DELIVER pooled dataset

Dapagliflozin 10mg once daily vs placebo

Median follow-up = 22 (IQR 17-30) months

Pooled dataset n=11,007



McMurray JJV et al Eur J Heart Fail. 2019;21:665-675 and Solomon SD et al Eur J Heart Fail 2021;23:1217-1225

nature medicine

ANALYSIS

https://doi.org/10.1038/s41591-022-01971-4

Check for updates

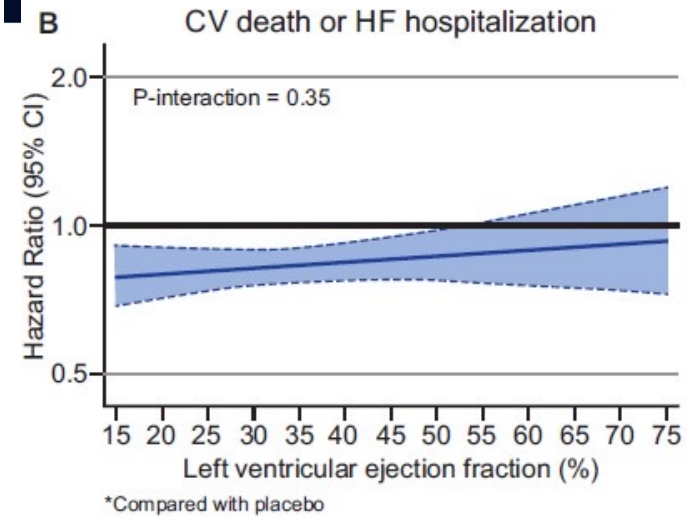
OPEN

Dapagliflozin across the range of ejection fraction in patients with heart failure: a patient-level, pooled meta-analysis of DAPA-HF and DELIVER

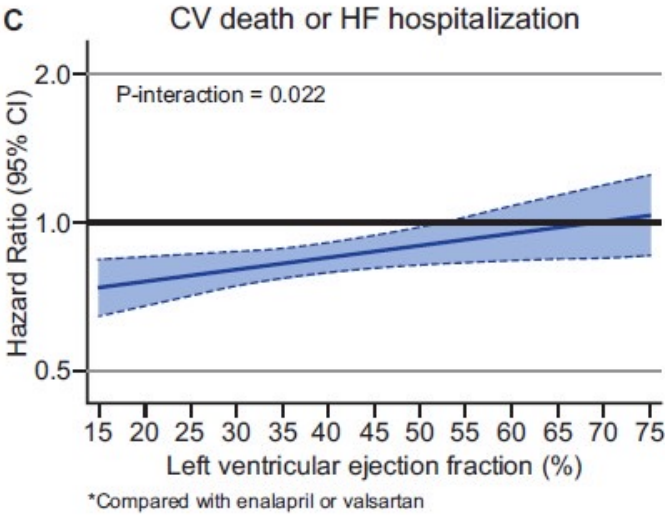
Pardeep S. Jhund[1], Toru Kondo[1], Jawad H. Butt[1], Kieran F. Docherty[1], Brian L. Claggett[2], Akshay S. Desai[2], Muthiah Vaduganathan[2], Samvel B. Gasparyan[3], Olof Bengtsson[3], Daniel Lindholm[3], Magnus Petersson[3], Anna Maria Langkilde[3], Rudolf A. de Boer[4], David DeMets[5], Adrian F. Hernandez[6], Silvio E. Inzucchi[7], Mikhail N. Kosiborod[8], Lars Køber[9], Carolyn S. P. Lam[10], Felipe A. Martinez[11], Marc S. Sabatine[12], Sanjiv J. Shah[13], Scott D. Solomon[2] and John J. V. McMurray[1]✉

Jhund PS et al Nat Med. 2022;28:1956-1964.

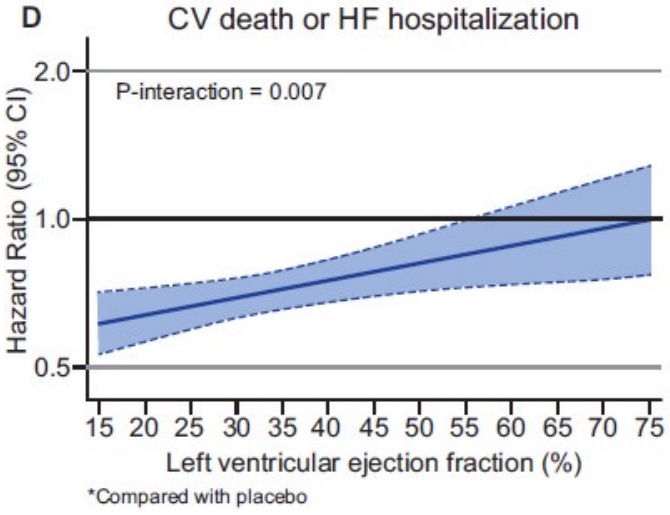
ARB



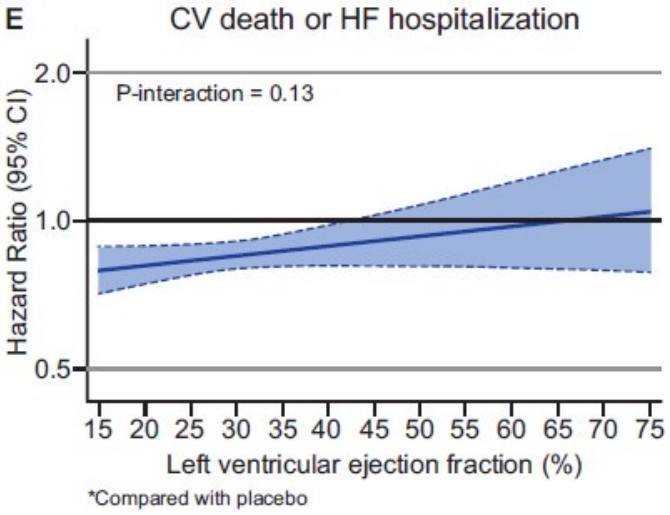
ARNI



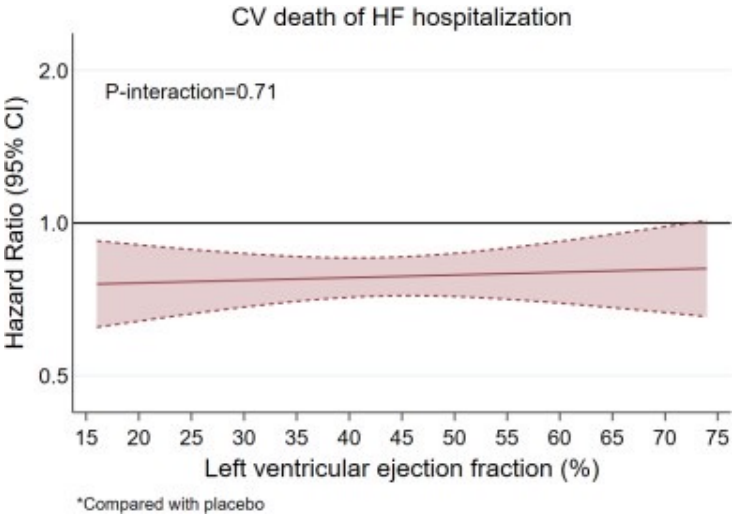
MRA



Digitalis



Dapagliflozin

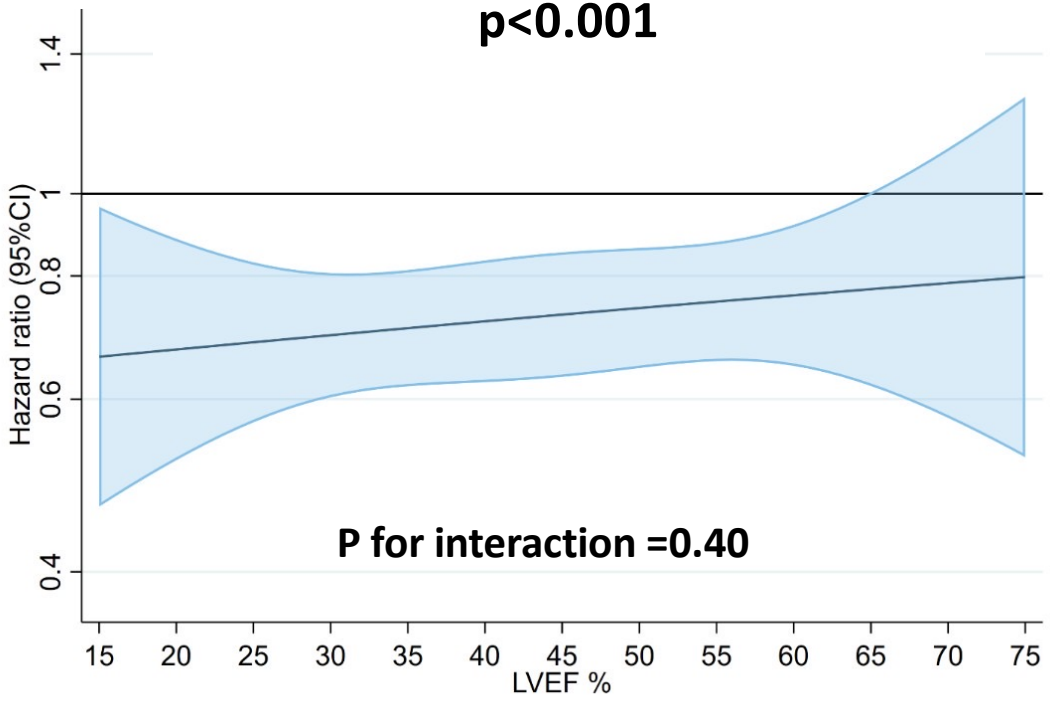


Adapted from Kondo T & McMurray Eur Heart J 2022;43: 427-429

DAPA-HF & DELIVER pooled: HF hospitalisations

First HF hospitalisation

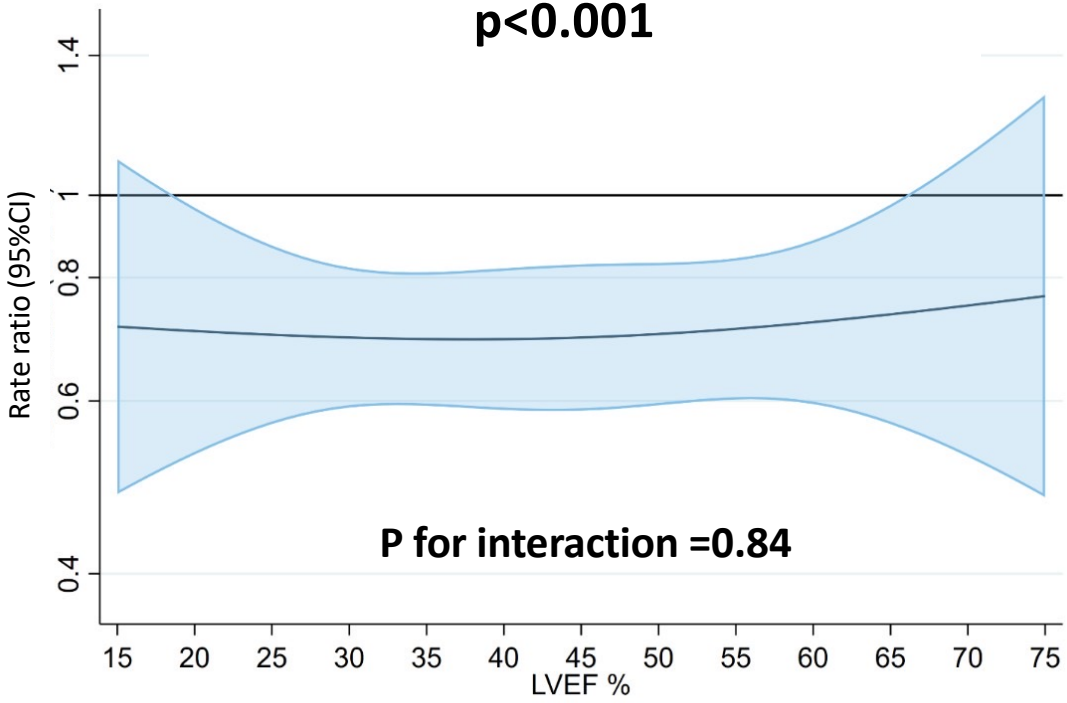
HR 0.74 (95% CI 0.66-0.82)
p<0.001



P for interaction =0.40

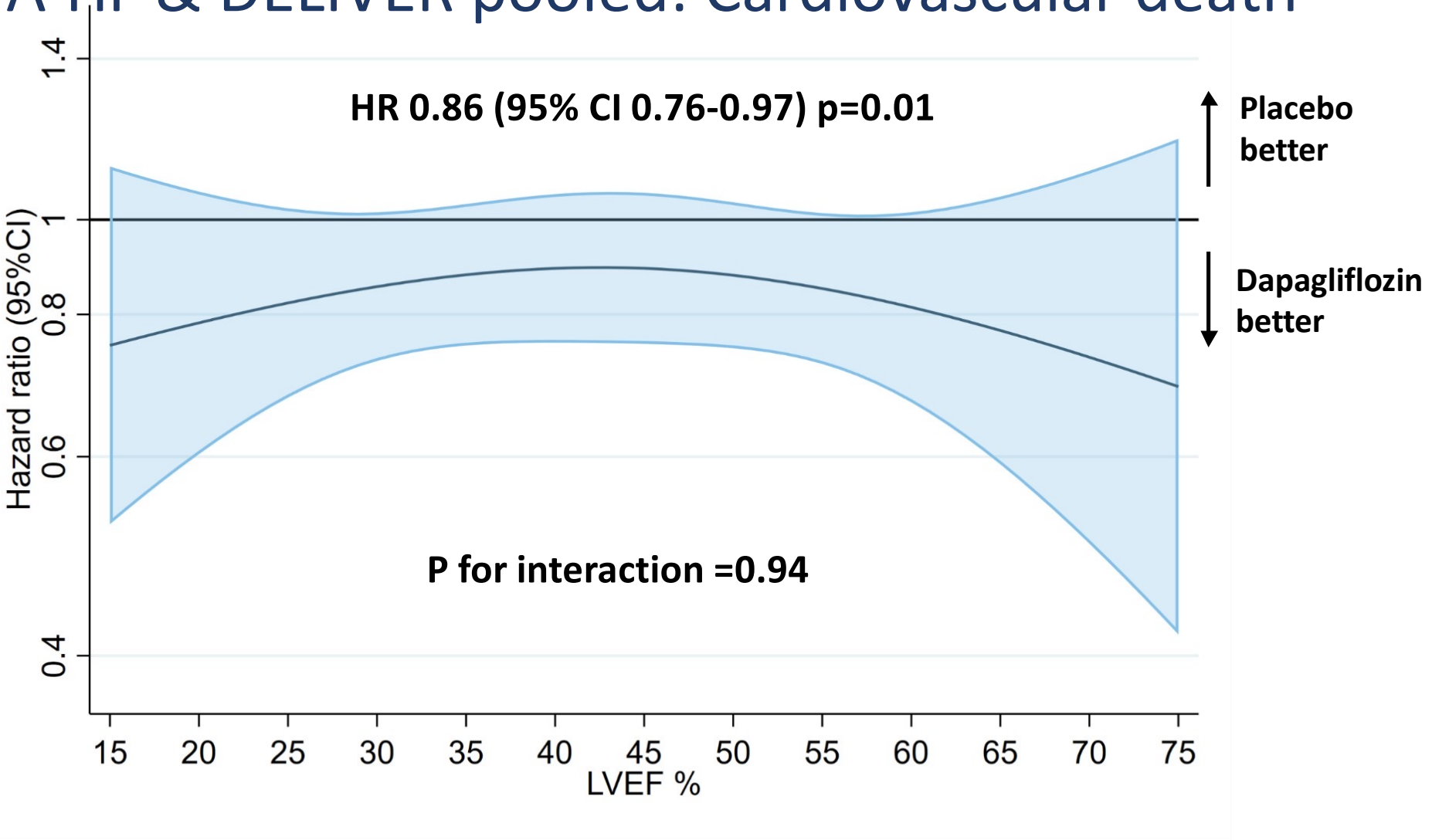
Total HF hospitalisations

RR 0.71 (95% CI 0.65-0.78)
p<0.001

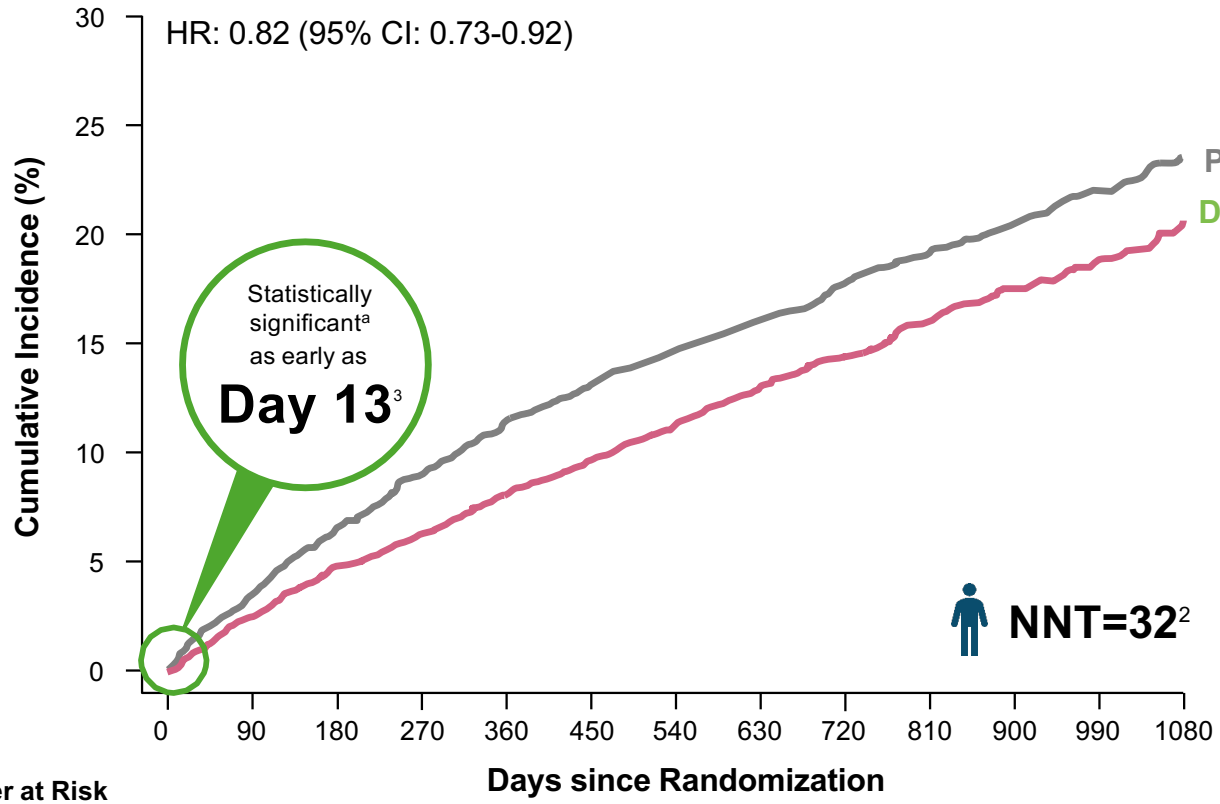


P for interaction =0.84

DAPA-HF & DELIVER pooled: Cardiovascular death



DELIVER- Primary Composite of CV Death, hHF or Urgent HF Visit



18% RRR

3.1% ARR

p=0.0008[2]

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

[a]Nominal significance at Day 13 (HR, 0.45; 95% CI, 0.20-0.99; p=0.046), with sustained statistical significance starting at Day 15.

1. Solomon SD et al. *N Engl J Med*. 2022;387(12):1089-1098; 2. Solomon SD. Presented at: ESC Congress; August 26-29, 2022; Barcelona, Spain; 3. Vaduganathan M et al. Online ahead of print. *JAMA Cardiol*. 2022.

There are arguments in favour of early treatment with SGLT2i without knowledge of LVEF

Scientific evidence
Safety, tolerability
Evidence that when not introduced during hospitalization, treatments are rarely started / increased after
Only one dosage for SGLT2i (no titration)
What is important for treatment introduction and titration is BP, renal function, kalaemia .. Not LVEF …

There are arguments against

Studies have been done with SGLT2i ***ON TOP*** of other therapies, not immediately

For all other drugs

The ***intensity*** of treatment may depend on LVEF value

Do we treat with similar doses patients with LVEF of 20% or 60% …

No reason to wait for an echocardiogram before starting SGLT2i and diuretics

HFrEF	Class/ level[a]
Dapagliflozin/ empagliflozin[1]	**1A**
ACEi/ARNI[1,b]	**1A**
Beta blocker[1]	**1A**
MRA[1]	**1A**
Loop diuretic for fluid retention[1]	1

HFmrEF	Class/ level[a]
Dapagliflozin/ empagliflozin[2]	**1A**
Diuretics for fluid retention[1]	1

HFpEF	Class/ level[a]
Dapagliflozin/ empagliflozin[2]	**1A**
Diuretics for fluid retention[1]	1
Treatment for etiology and CV and non-CV comorbidities[1]	1

- [a]Number indicates class of recommendation, letter indicates level of evidence; [b]ARNI used as a replacement for ACE inhibitor

1. McDonagh TA, et al. *Eur Heart J* 2021;42:3599–3726; 2. McDonagh TA, et al. *Eur Heart J* 2023;44:3627–3639

In practice

One generally start diuretics and RAS antagonists before knowing LVEF
Betablockers and S/V introduction need knowledge of LVEF
MRA too (unless hypokalaemia)
SGLT2i may be introduced early, without knowledge of LVEF, given their safety and the fact that they do not jeopardize subsequent therapy