# Updates on Heart Failure with Reduced (HFrEF) and Preserved (HFpEF) Ejection Fractions

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**Disclosures**

Speakers Bureau – Actelion Pharmaceuticals, J&J, BI, Astra Zeneca, Pfizer and BMS

# Summary

- Background of Heart Failure
- Heart Failure With Reduced LV Function (HFrEF) Guidelines Update and What's New in 2021-2022
- Where we are at with Heart Failure with Preserved LV Function (HFpEF)and discuss the current and past clinical trials from 2003-Present

# Types of Heart Failure

**Classification of heart failure is based on which heart function or which side of the heart is most affected by the condition.**

- ***Systolic heart failure (Correct term is HFrEF)*** – failure of contraction to pump blood out of the chambers. This is measured by ejection fraction (EF) or the percentage of blood that is ejected out of the ventricle. EF <40 %

- ***Diastolic heart failure (Correct term is HFpEF)*** – failure of relaxation to fill the chambers with blood- EF is 50% or greater

- ***Heart failure with mid-range EF (Correct term is HFmrEF)*** – EF 40-49%

# Characteristics of HFpEF as Compared with Those of HFrEF

**Table 1. Characteristics of Diastolic Heart Failure as Compared with Those of Systolic Heart Failure.***

| Characteristic | Diastolic Heart Failure | Systolic Heart Failure |
|---|---|---|
| Clinical features | | |
| Symptoms (e.g., dyspnea) | Yes | Yes |
| Congestive state (e.g., edema) | Yes | Yes |
| Neurohormonal activation (e.g., brain natriuretic peptide) | Yes | Yes |
| Left ventricular structure and function | | |
| Ejection fraction | Normal | Decreased |
| Left ventricular mass | Increased | Increased |
| Relative wall thickness† | Increased | Decreased |
| End diastolic volume | Normal | Increased |
| End diastolic pressure | Increased | Increased |
| Left atrial size | Increased | Increased |
| Exercise | | |
| Exercise capacity | Decreased | Decreased |
| Cardiac output augmentation | Decreased | Decreased |
| End diastolic pressure | Increased | Increased |

* The clinical features of diastolic heart failure are similar to those of systolic heart failure, but left ventricular structure and function are distinctly different.
† The descriptor of left ventricular geometry is the relative wall thickness, defined as the ratio of left ventricular wall thickness to the radius of the left ventricular cavity.

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# 2021 ACC Expert Consensus

EXPERT CONSENSUS DECISION PATHWAY

## 2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee


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https://www.jacc.org/doi/10.1016/j.jacc.2021.11.022

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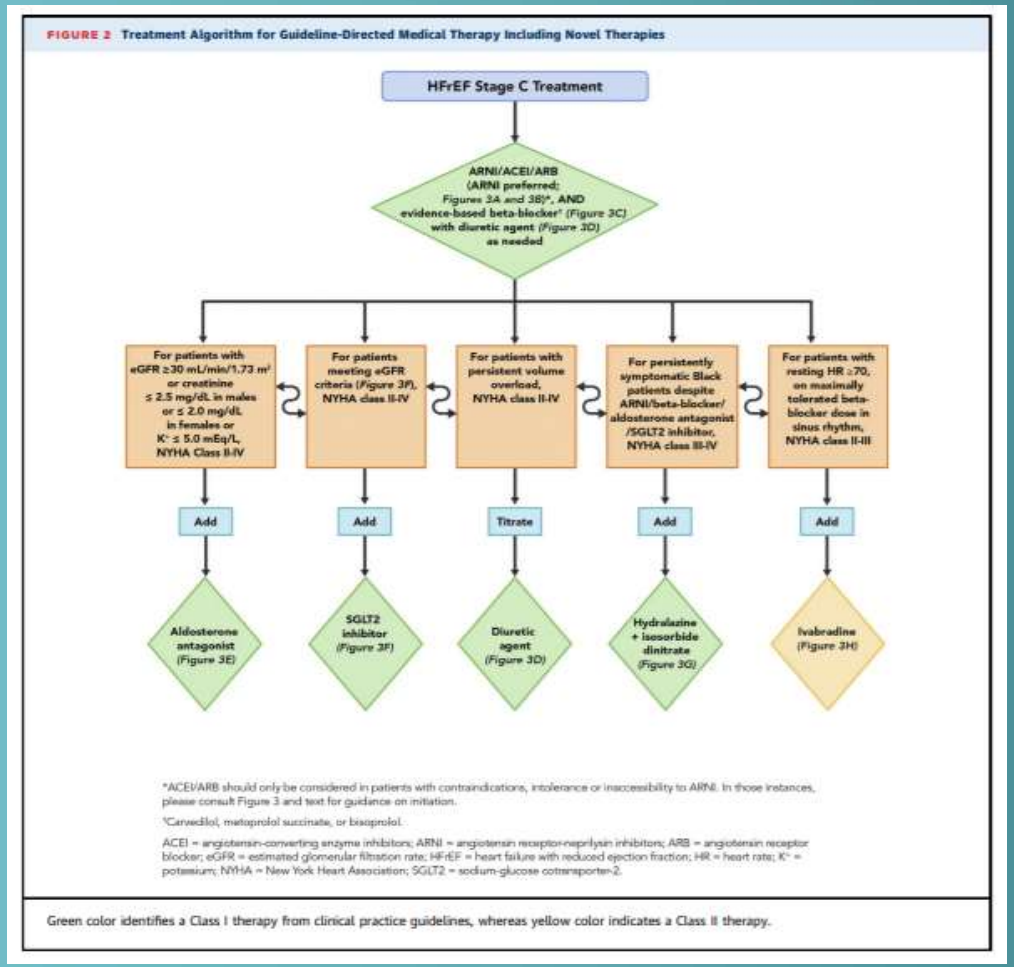
# 2021 ACC Expert Consensus



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# Therapies That Are Changing the Treatment Landscape:

## sacubitril/valsartan (ARNI)

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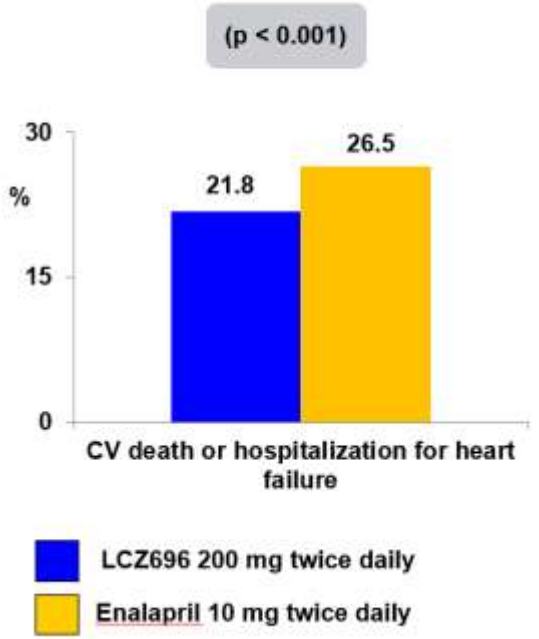
# PARADIGM-HF: Primary Endpoint of CV Death or HF Hospitalization With ARNI

## PARADIGM-HF

**Trial design:** Participants with NYHA class II-IV and LVEF ≤40% were randomized to LCZ696 200 mg twice daily (n = 4,187) vs. enalapril 10 mg twice daily (n = 4,212).




### Results

- CV death or hospitalization for heart failure: 21.8% of LCZ696 group vs. 26.5% of the enalapril group (p < 0.001)
- CV death: 13.3% vs. 16.5% (p < 0.001), respectively
- Hospitalization for HF: 12.8% vs. 15.6% (p < 0.001), respectively

### Conclusions

- Among participants with reduced EF and NYHA class II-IV symptoms, the use of LCZ696 was beneficial compared with enalapril
- LCZ696 was associated with a reduction in CV death or hospitalization for heart failure

McMurray JJ, et al. N Engl J Med 2014;371:993-1004

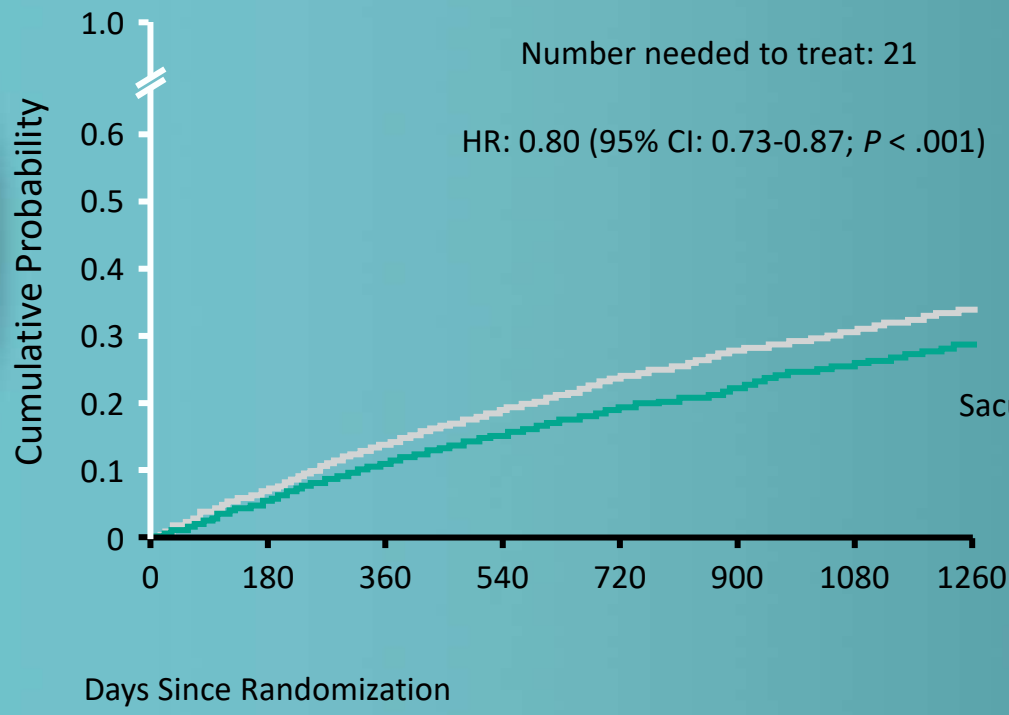


McMurray. NEJM. 2014;371:993.

# PARADIGM-HF: Primary Endpoint of CV Death or HF Hospitalization With ARNI

- Randomized trial of patients with NYHA class II-IV HF

20% relative risk reduction over median 27 mos




Number needed to treat: 21

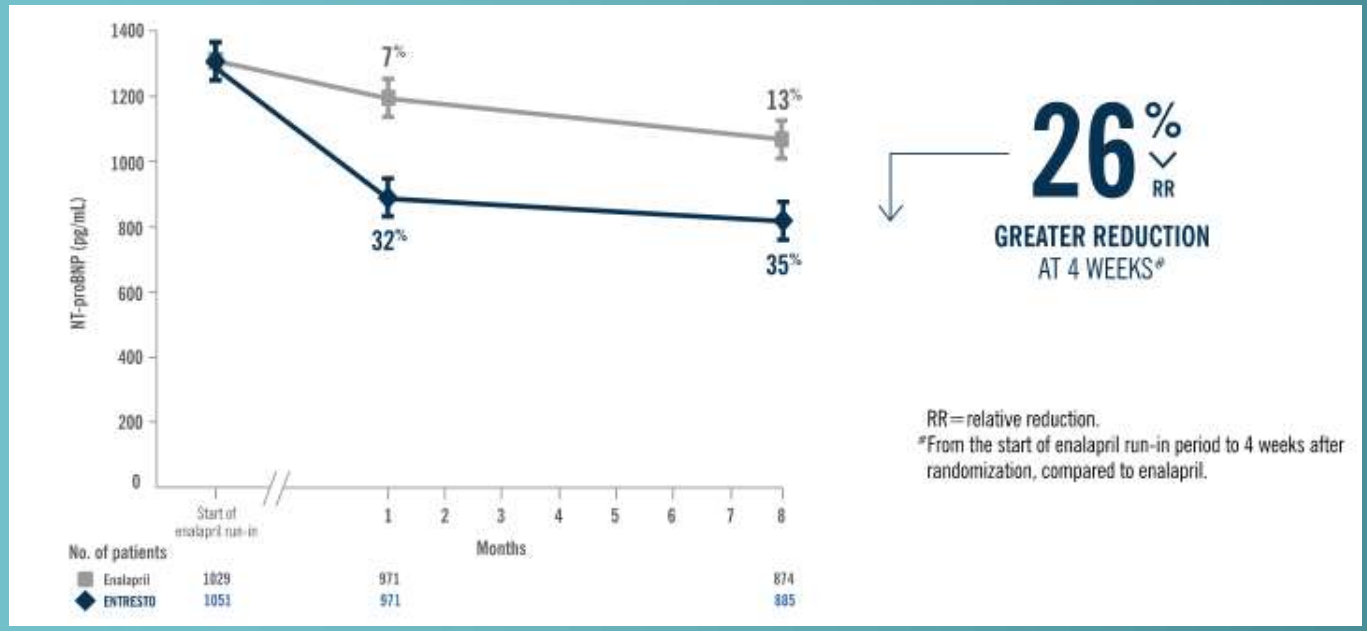
HR: 0.80 (95% CI: 0.73-0.87; *P* < .001)

Enalapril (n = 4212): 1117 events (26.5%)

Sacubitril/valsartan (n = 4187): 914 events (21.8%)

Slide credit: clinicaloptions.com

# PARADIGM-HF: Primary Endpoint of CV Death or HF Hospitalization With ARNI

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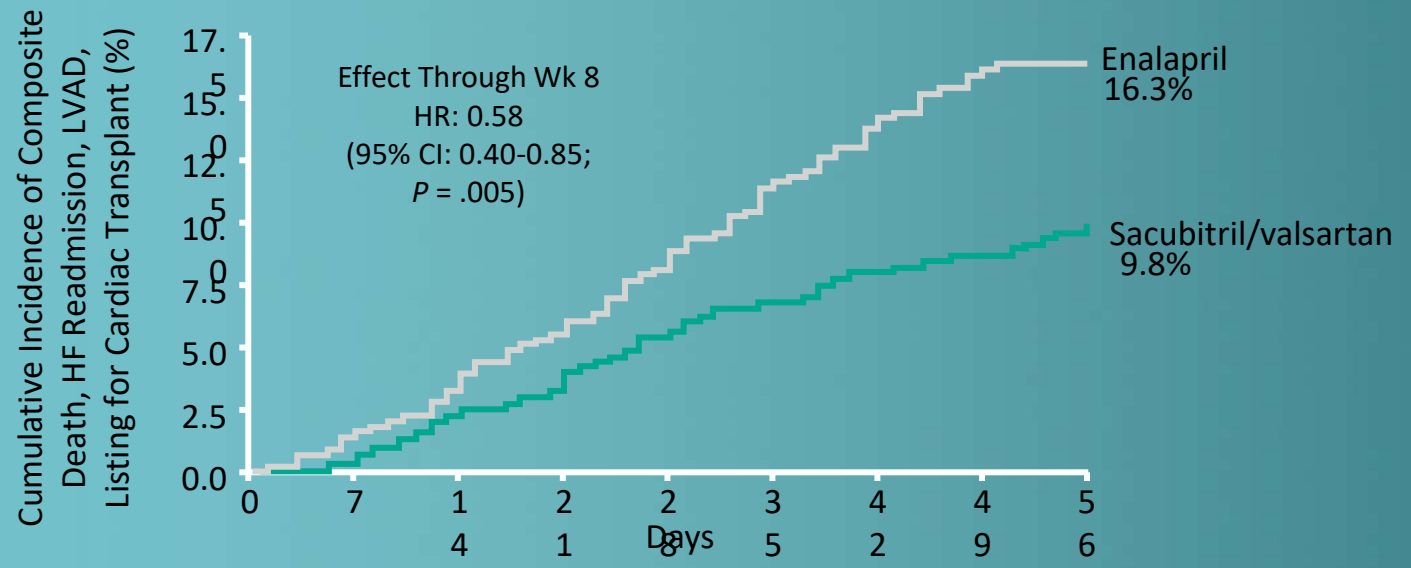
# PIONEER-HF: Composite of Death, HF Readmission, LVAD, Listing for Cardiac Transplant With ARNI

- Randomized trial of hospitalized patients with NYHA class II-IV acute HFrEF
  - ARNI started ≥ 24 hrs after admission, after patients had stabilized



# New Data and Therapies That Are Changing the Treatment Landscape:

## SGLT2 Inhibitors

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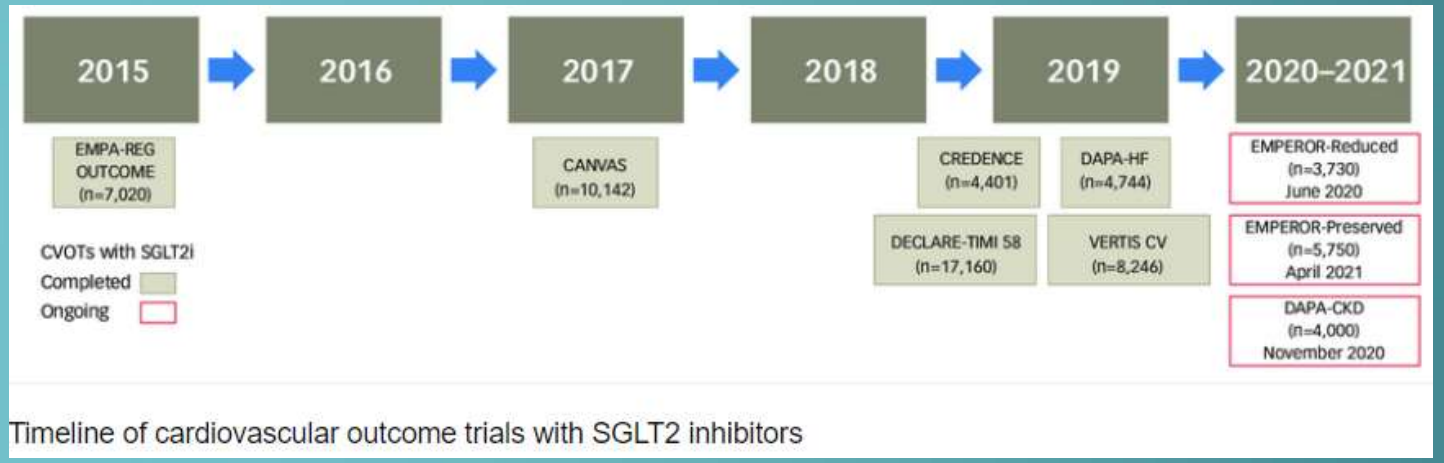
# New Data Changing the Treatment Landscape




Timeline of cardiovascular outcome trials with SGLT2 inhibitors

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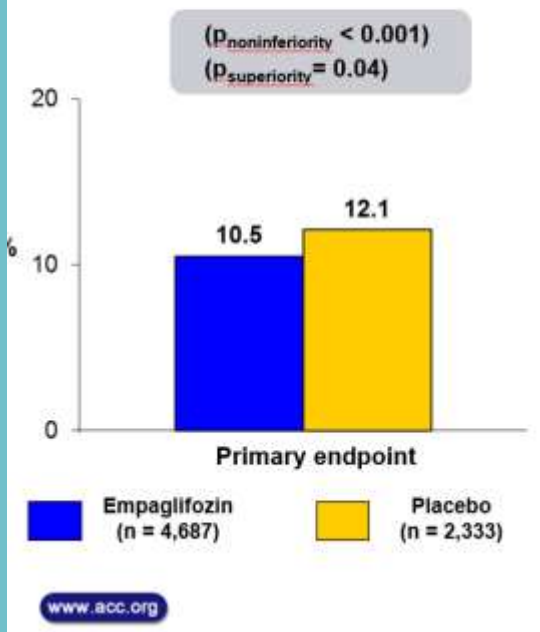
https://www.researchgate.net/figure/Timeline-of-cardiovascular-outcome-trials-with-SGLT2-inhibitors_fig2_346227048

# New Data Changing the Treatment Landscape

## EMPA-REG OUTCOME

**Trial design:** Patients with type 2 diabetes mellitus (DM2) at high risk for CV events were randomized to receive in a 1:1:1 fashion either empaglifozin 10 or 25 mg, or placebo. They were followed for 3.1 years.




www.acc.org

### Results

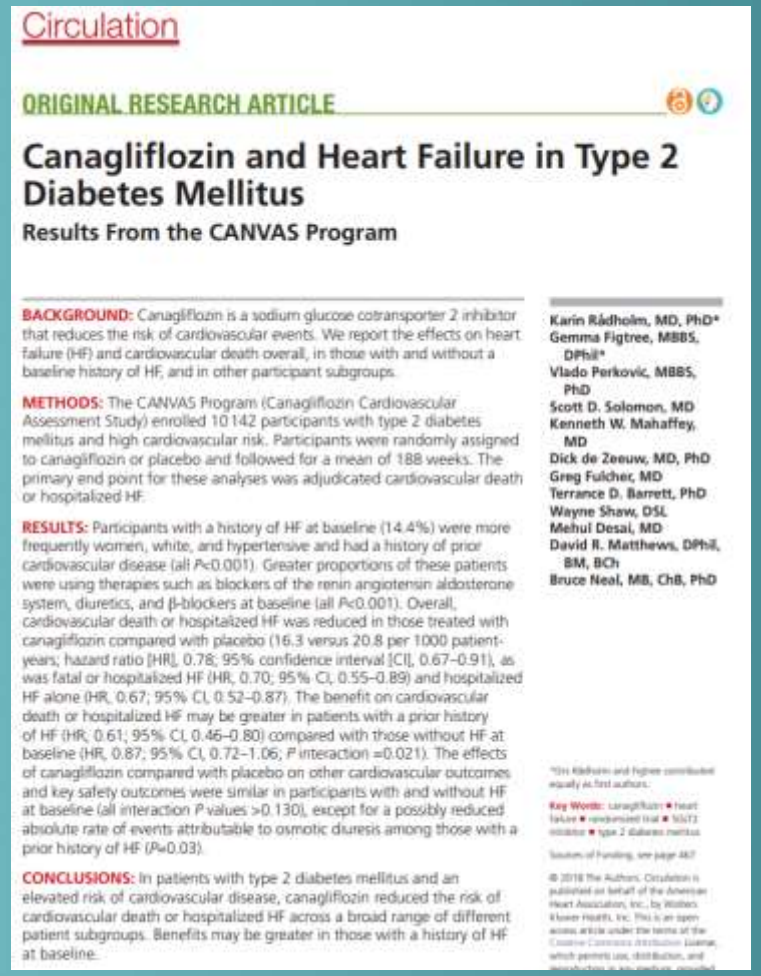
- Primary outcome, CV death/MI/stroke for empaglifozin vs. placebo: 10.5% vs. 12.1%, p < 0.001 for noninferiority; p = 0.04 for superiority
- CV death: 3.7% vs. 5.9%, p < 0.001; MI: 4.8% vs. 5.4%, p = 0.23; all stroke: 3.5% vs. 3.0%, p = 0.26; CHF hospitalization: 2.7% vs. 4.1%, p = 0.002
- HbA1c for 10 and 25 mg vs. placebo at 206 weeks: -0.24%, -0.36%, respectively

### Conclusions

- Empaglifozin, a SGLT2 inhibitor, is superior to placebo in improving glycemic control and reducing CV events in patients with DM2 and established CVD, including mortality benefit
- One of the first large-scale DM2 trials to show an improvement in hard CV outcomes with simultaneous improvements in glycemic control

Zinman B, et al. N Engl J Med 2015;373:2117-28

# New Data and Therapies That Are Changing the Treatment



Circulation

ORIGINAL RESEARCH ARTICLE

## Canagliflozin and Heart Failure in Type 2 Diabetes Mellitus

### Results From the CANVAS Program

Karin Rådholm, MD, PhD*
Gemma Figtree, MBBS, DPhil*
Vlado Perkovic, MBBS, PhD
Scott D. Solomon, MD
Kenneth W. Mahaffey, MD
Dick de Zeeuw, MD, PhD
Greg Fulcher, MD
Terrance D. Barrett, PhD
Wayne Shaw, DSL
Mehul Desai, MD
David R. Matthews, DPhil, BM, BCh
Bruce Neal, MB, ChB, PhD

**BACKGROUND:** Canagliflozin is a sodium glucose cotransporter 2 inhibitor that reduces the risk of cardiovascular events. We report the effects on heart failure (HF) and cardiovascular death overall, in those with and without a baseline history of HF, and in other participant subgroups.

**METHODS:** The CANVAS Program (Canagliflozin Cardiovascular Assessment Study) enrolled 10 142 participants with type 2 diabetes mellitus and high cardiovascular risk. Participants were randomly assigned to canagliflozin or placebo and followed for a mean of 188 weeks. The primary end point for these analyses was adjudicated cardiovascular death or hospitalized HF.

**RESULTS:** Participants with a history of HF at baseline (14.4%) were more frequently women, white, and hypertensive and had a history of prior cardiovascular disease (all $P<0.001$). Greater proportions of these patients were using therapies such as blockers of the renin angiotensin aldosterone system, diuretics, and β-blockers at baseline (all $P<0.001$). Overall, cardiovascular death or hospitalized HF was reduced in those treated with canagliflozin compared with placebo (16.3 versus 20.8 per 1000 patient-years; hazard ratio [HR], 0.78; 95% confidence interval [CI], 0.67–0.91), as was fatal or hospitalized HF (HR, 0.70; 95% CI, 0.55–0.89) and hospitalized HF alone (HR, 0.67; 95% CI, 0.52–0.87). The benefit on cardiovascular death or hospitalized HF may be greater in patients with a prior history of HF (HR, 0.61; 95% CI, 0.46–0.80) compared with those without HF at baseline (HR, 0.87; 95% CI, 0.72–1.06; $P$ interaction =0.021). The effects of canagliflozin compared with placebo on other cardiovascular outcomes and key safety outcomes were similar in participants with and without HF at baseline (all interaction $P$ values >0.130), except for a possibly reduced absolute rate of events attributable to osmotic diuresis among those with a prior history of HF ($P$=0.03).

**CONCLUSIONS:** In patients with type 2 diabetes mellitus and an elevated risk of cardiovascular disease, canagliflozin reduced the risk of cardiovascular death or hospitalized HF across a broad range of different patient subgroups. Benefits may be greater in those with a history of HF at baseline.

*Drs Rådholm and Figtree contributed equally as first authors.

Key Words: canagliflozin ■ heart failure ■ randomized trial ■ SGLT2 inhibitor ■ type 2 diabetes mellitus

Sources of Funding, see page 467



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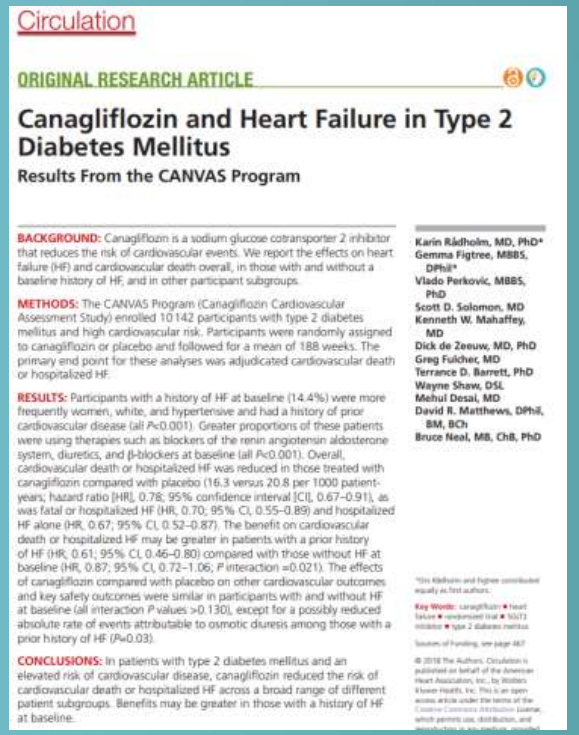
https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.034222

# New Data and Therapies That Are Changing the Treatment



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https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.118.034222

# Proposed Mechanisms of CV Benefits Observed with SGLT-2 Inhibitors

- Inhibiting SGLT2 leads to urinary glucose excretion by decreasing glucose reabsorption in the proximal tubules
- Increase sodium delivery to distal tubules
- Downstream effects
  - Osmotic diuresis without RAAS activation
  - Reductions in weight and blood pressure due to decreased plasma volume (reduced preload/afterload)
  - Decreased sympathetic activity
  - Increases in hematocrit
- Large RCTs have demonstrated decreased risk of:
  - MACE in T2D, mainly in patients with established ASCVD
  - HFH in T2D independent of history of HF or EF
  - CV death and HFH in HFrEF independent of T2D
  - Renal disease progression in CKD

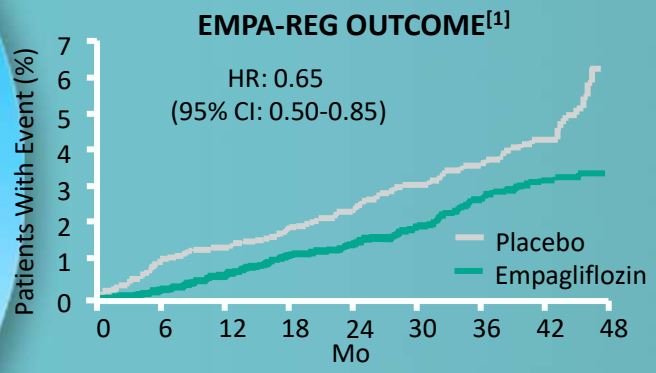


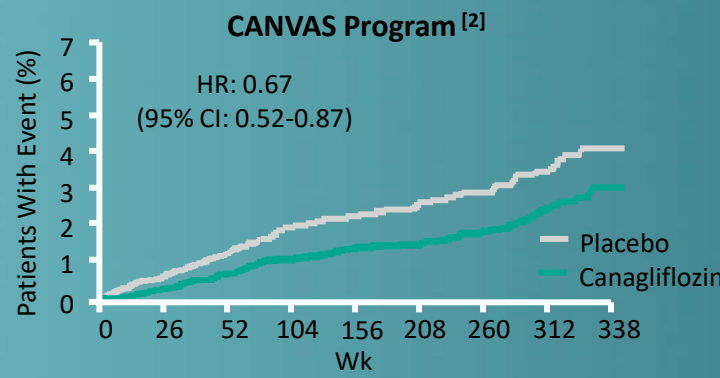
Slide credit: clinicaloptions.com

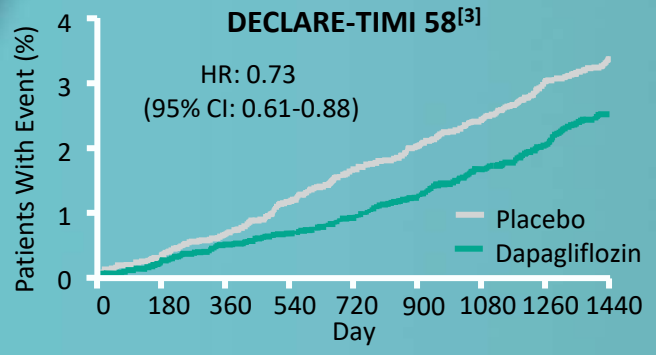
# Proposed Mechanisms of CV Benefits Observed with SGLT-2 Inhibitors

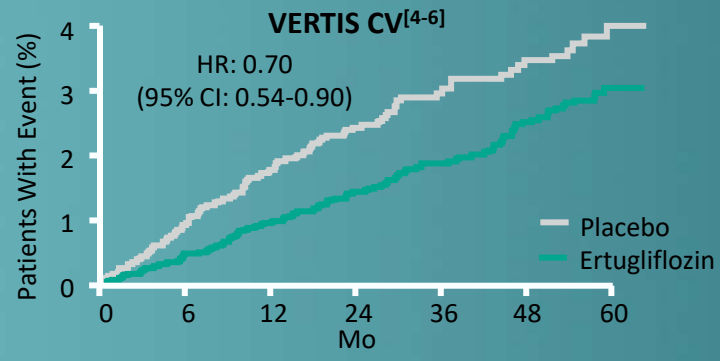
- Improved Vascular Function
  - Decreased wall stress
- Reduction in Inflammatory markers
- Reduction in oxidative stress
- Attenuation of fibrosis through inhibition of the sodium/hydrogen cotransporter
  - Decreased myocardial and renal cell death
- Shift to ketone based myocardial metabolism
  - Improved cardiac efficiency

# HFH Outcomes in SGLT2 Inhibitor CV Outcomes Trials

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# New Data and Therapies That Are Changing the Treatment Landscape:

# Treatment of HF Regardless of T2D

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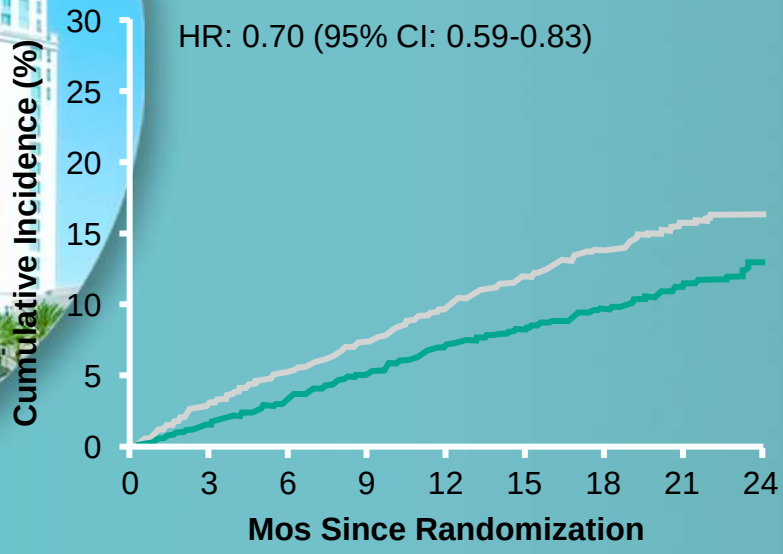
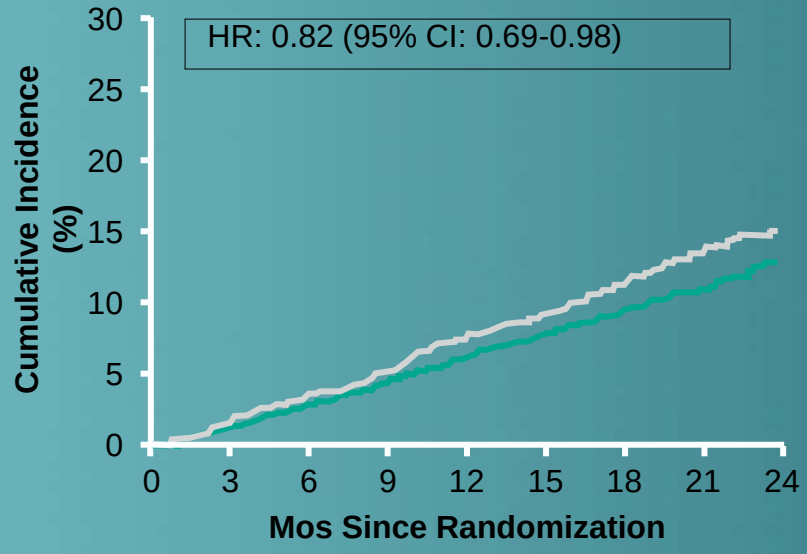
# DAPA-HF: Components of Primary Outcomes

- Randomized, double-blind, international phase III trial in patients with HF and reduced ejection fraction (N = 4744)

**Hospitalization for HF**




**Death From CV Causes**



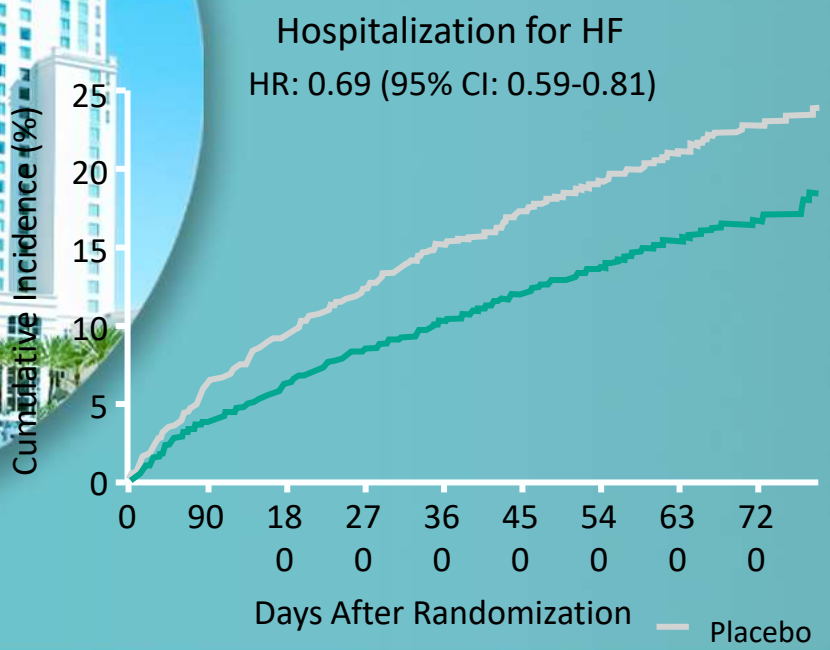

Placebo  Dapagliflozin

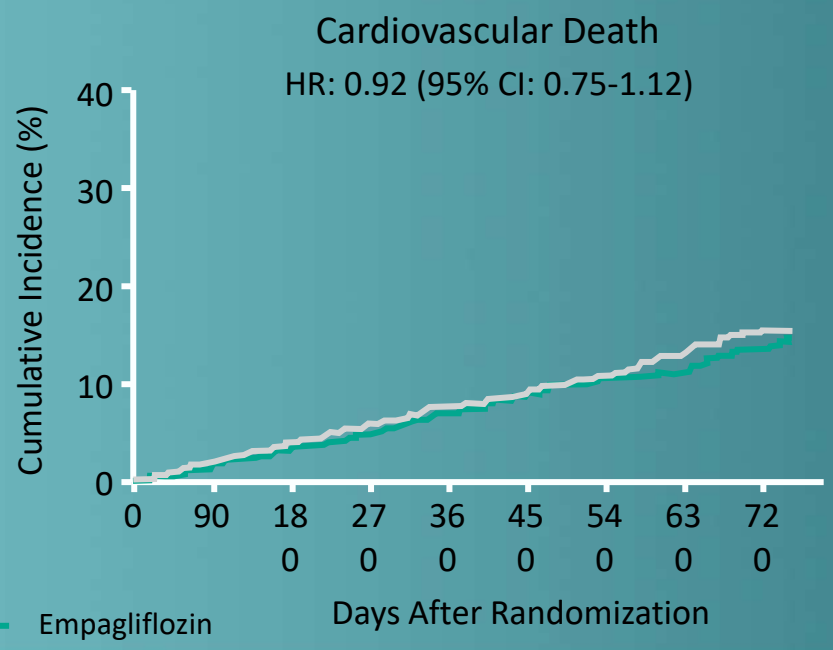


McMurray. NEJM. 2019;381:1995.
NCT03036124.

# EMPEROR-Reduced: Components of Primary Outcome

- Randomized, double-blind, international phase III trial in patients with HF and reduced ejection fraction (N = 3730)






Slide credit: clinicaloptions.com

Packer. NEJM. 2020;383:1413. NCT03057977.

# Current Recommendations for Treatment of HFrEF

Circulation

EDITORIAL

## Building the Foundation for a New Era of Quadruple Therapy in Heart Failure

Articles, see p 90 and 100

G. Michael Felker, MD, MHS

The serial development of treatments that improve morbidity and mortality in patients with chronic heart failure with reduced ejection fraction (HFrEF) is one of the great success stories of cardiovascular therapeutics. Until recently, the combination of β-blockers, renin-angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers), and mineralocorticoid receptor antagonists formed the foundation of triple therapy for heart failure (HF). These agents, each of which provides clear benefits on mortality and morbidity in patients with HFrEF, collectively came to be termed guideline-directed medical therapy (GDMT). This stable foundation of HF therapeutics was upended in 2014 by the stunning results of the PARADIGM-HF study (Prospective Comparison of ARNI With ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure), demonstrating substantial improvements in outcomes with the angiotensin receptor-neprilysin inhibitor sacubitril-valsartan above and beyond the benefits provided by the angiotensin-converting enzyme inhibitor enalapril.[1] Now, only a few years later, a remarkable data set has emerged with the sodium-glucose cotransporter-2 inhibitors (SGLT2is) in HF. Initially, the diabetes cardiovascular outcome trials provided evidence of the role of these agents in preventing incident HF in patients with type 2 diabetes mellitus. Last, the recent publication of the primary results of the DAPA-HF trial (Dapagliflozin and Prevention of Adverse-Outcomes in Heart Failure) demonstrated substantial benefits in outcomes on top of triple therapy for patients with chronic HFrEF, benefits that are remarkably similar in patients with and without diabetes mellitus.[2] So is it now time for triple therapy to evolve to quadruple therapy in patients with HFrEF?

The field of HF must now grapple with a number of questions in light of these new data in patients with established HFrEF. Is this a class effect of SGLT2is in general or specific to dapagliflozin? What about other benefits beyond morbidity and mortality? What are the specific mechanisms underlying the observed effects? And last, how should this new class of drugs be implemented, especially in groups of patients (eg, the elderly) where aggressive uptitration of triple therapy has often been a challenge? In that context, the articles by Kosiborod et al[3] and Martinez et al[4] in this issue of Circulation expand the dapagliflozin in HF story and provide greater insights into some of these critical questions.

First, Kosiborod et al[3] present a detailed analysis of the effects of dapagliflozin on health-related quality of life in the DAPA-HF study. These data are of critical importance, because improving patient-reported outcomes in HF, especially in highly symptomatic patients, is an important goal in drug development. The reported analysis from DAPA-HF shows a clinically important benefit on health-related quality of life (as measured by the well-validated Kansas City Cardiomyopathy

112 January 14, 2020 Circulation. 2020;141:112–114. DOI: 10.1161/CIRCULATIONAHA.119.044575

4 pillars of heart failure treatment - Google Search

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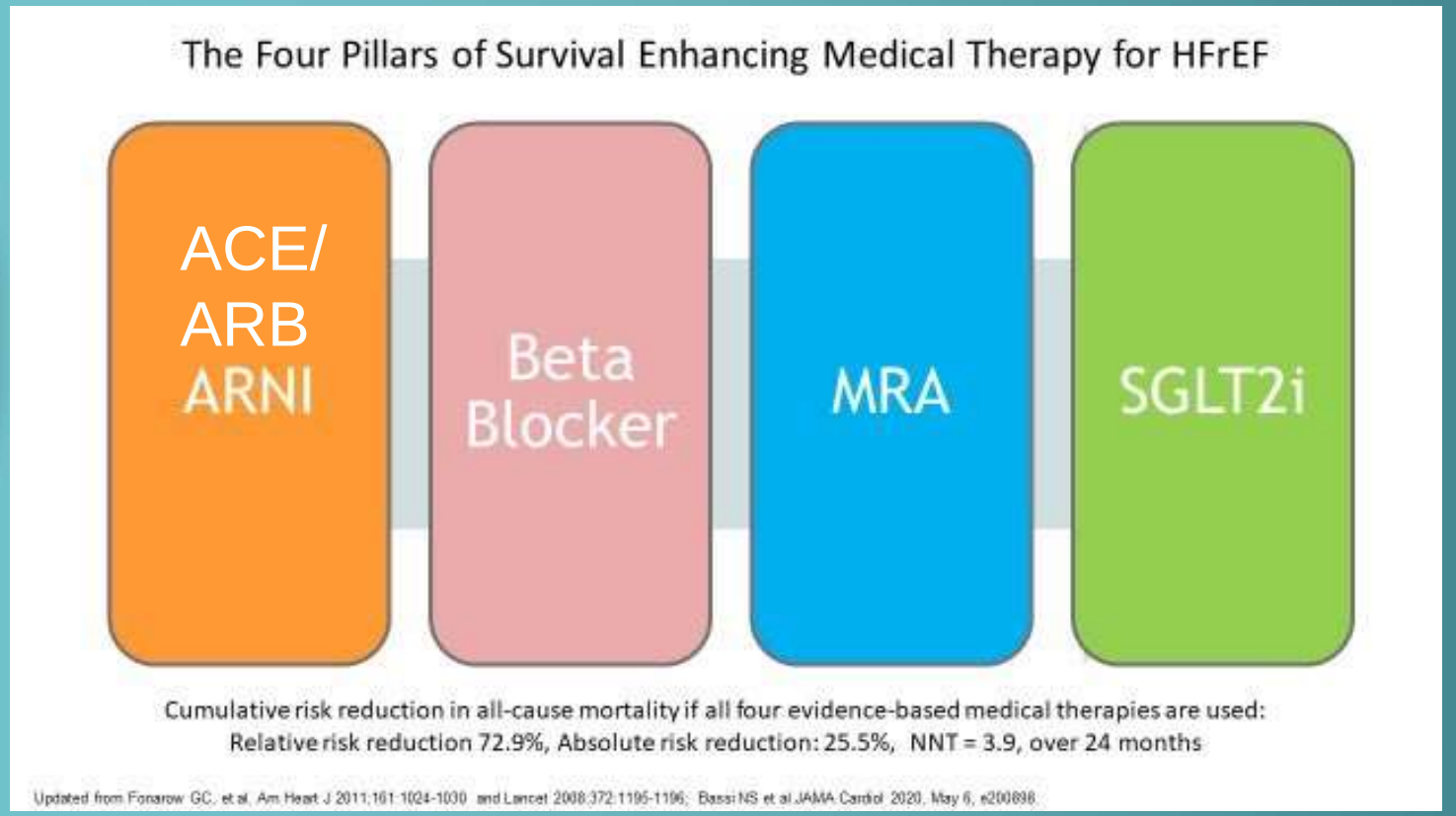
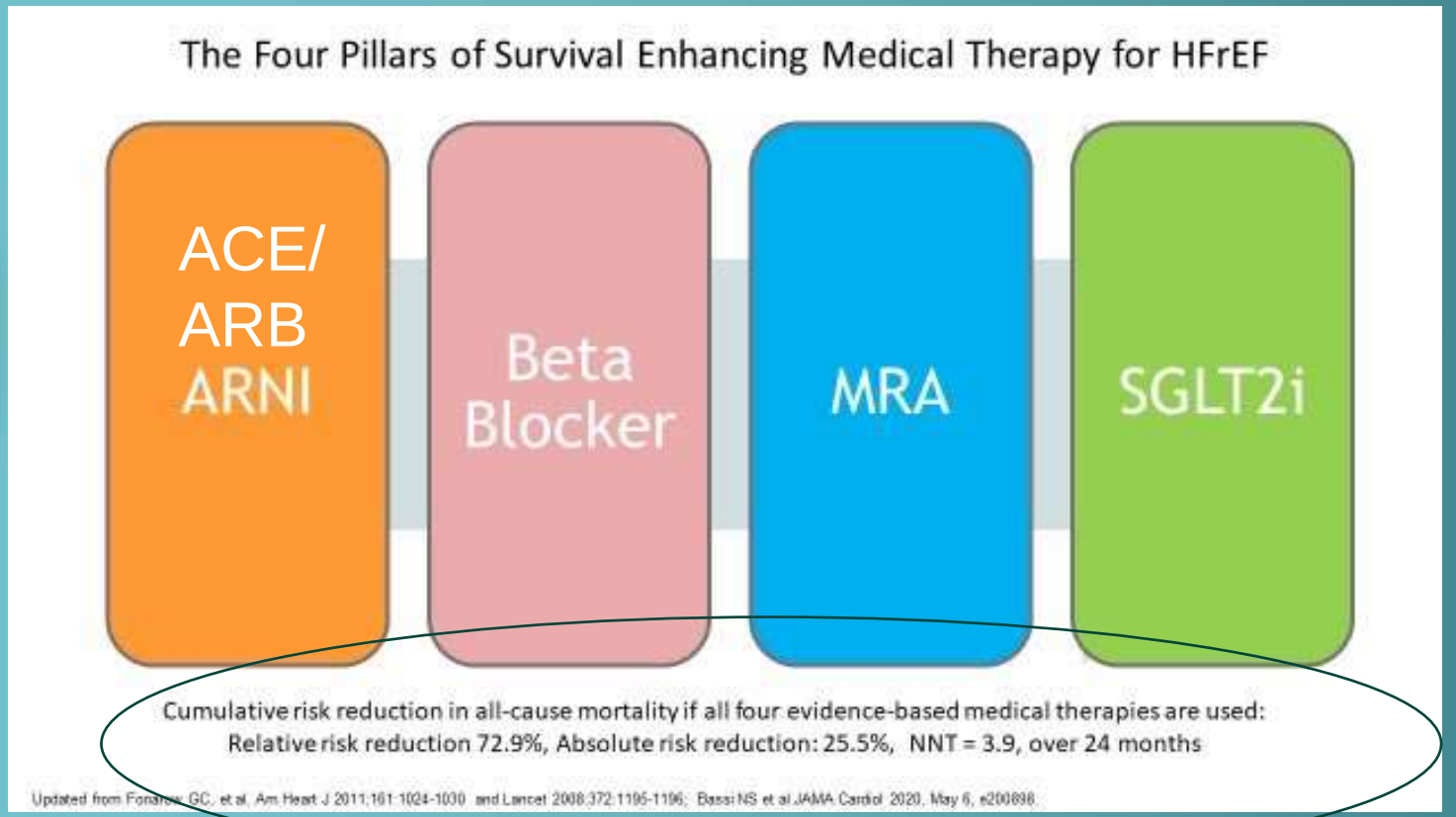
# Current Recommendations for Treatment of HFrEF



# Current Recommendations for Treatment of HFrEF



# New Data and Therapies That Are Changing the Treatment Landscape:

## HF With Preserved EF

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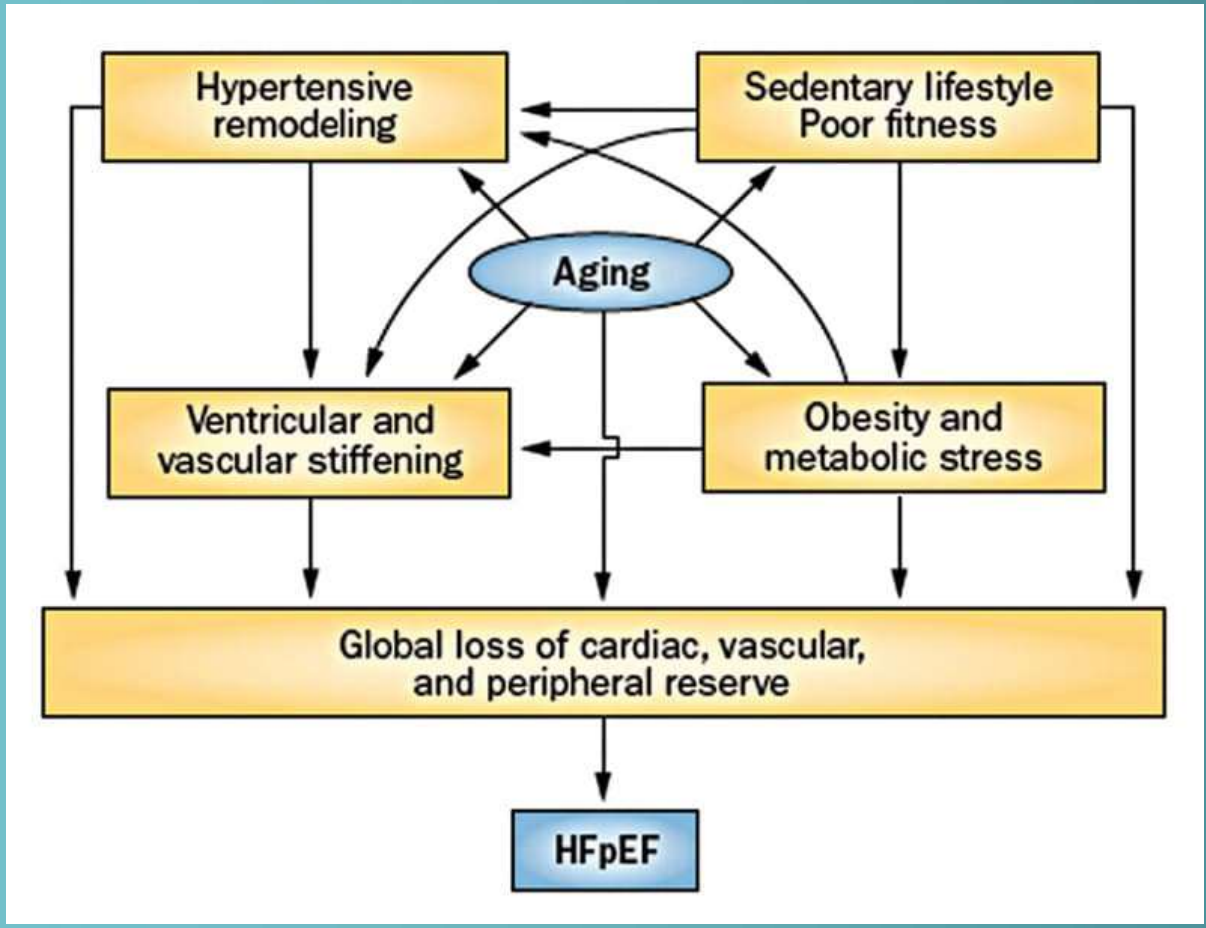
# Heart failure with preserved left ventricular function (HFpEF)

## Heart Failure with Preserved Ejection Fraction

- High rates of death and hospitalizations for HF
- High burden of debilitating symptoms and physical limitations
- No therapies with Class I recommendation in guidelines
- No therapies convincingly shown to improve health status (symptoms, physical limitations and quality of life) and exercise function

PRESERVED-HF

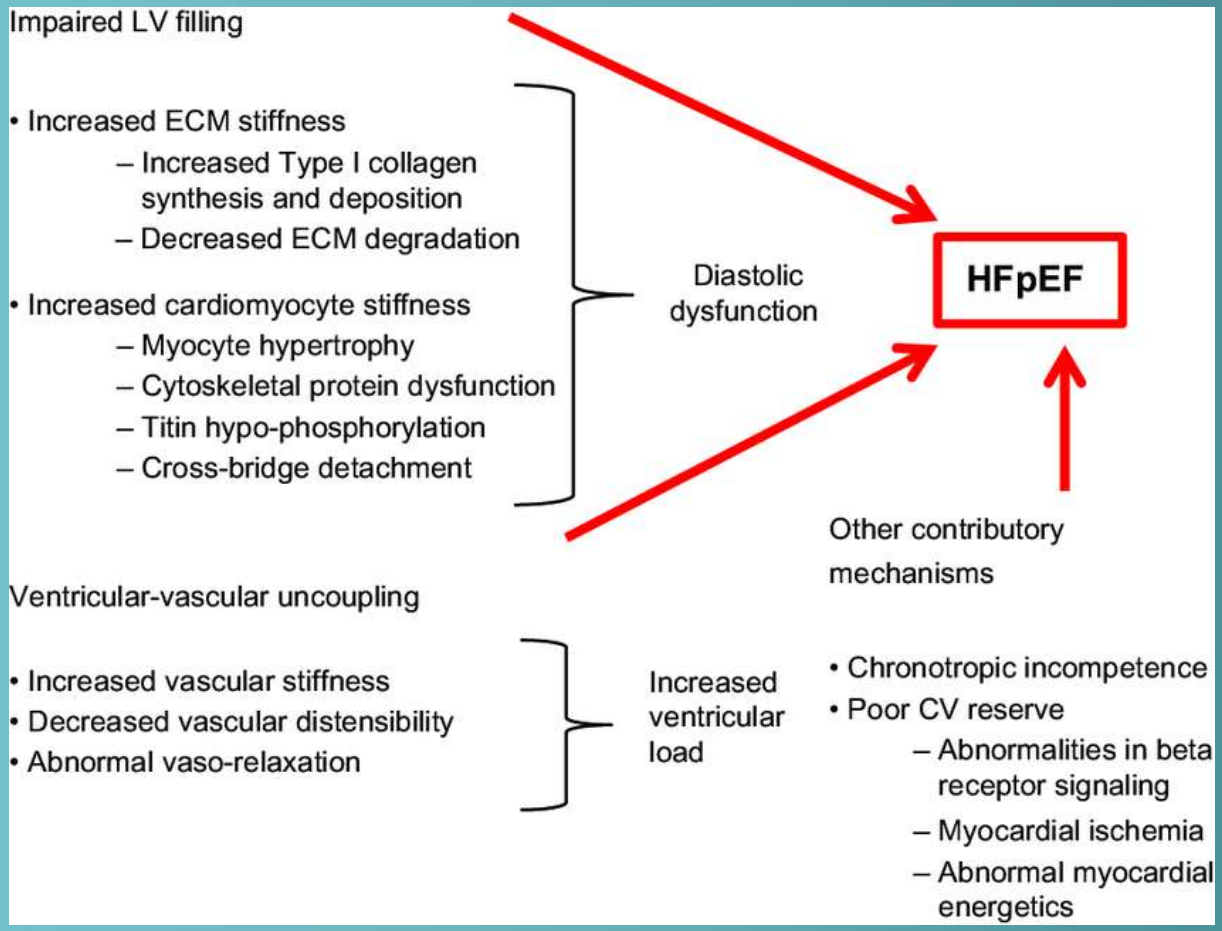
# Pathophysiology of HFpEF






https://www.google.com/search?q=dapagliflozin+the+Preserved+hf+study+ppt+slides+&tbm=isch&ved=2ahUKEwiB6_P1moj3AhUIb80KHXoYD9EQ2-cCegQIABAA&oq=dapagliflozin+the+Preserved+hf+study+ppt+slides+&gs_lcp=CgNpbWcQA1D4BljJCmDNGmgAcAB4AIABjwKIAf4FkgEFMi4xLjKYAQCgAQGqAQtnd3Mtd2l6LWltZ8ABAQ&sclient=img&ei=6iBSYoHOCYjetQb6sLylDQ&bih=754&biw=1536#imgrc=RtlBU72VTy70MM&imgdii=uOzooPAD1tZ3mM

# Pathophysiology of HFpEF






https://www.google.com/search?q=dapagliflozin+the+Preserved+hf+study+ppt+slides+&tbm=isch&ved=2ahUKEwiB6_P1moj3AhUlb80KHXoYD9EQ2-cCegQIABAA&oq=dapagliflozin+the+Preserved+hf+study+ppt+slides+&gs_lcp=CgNpbWcQA1D4BljJCmDNGmgAcAB4AIABjwKIAf4FkgEFMi4xLjKYAQCgAQGqAQtnd3Mtd2l6LWltZ8ABAQ&sclient=img&ei=6iBSYoHOCYjetQb6sLyIDQ&bih=754&biw=1536#imgrc=RtlBU72VTy70MM&imgdii=uOzooPAD1tZ3mM

# Current Recommendations for Treatment of Patients with HFpEF

## GENERAL MANAGEMENT

Current Goals of therapy — For patients with HFpEF, the goals of treatment are to reduce HF symptoms, increase functional status, and reduce the risk of hospital admission. There is no clear evidence that pharmacologic therapy, diet, or other therapies reduce the risk of mortality in patients with HFpEF.

Ongoing evaluation and monitoring
Chronic disease management
Exercise, diet, weight loss, and cardiac rehabilitation

# Current Recommendations for Treatment of Patients with HFpEF

## MANAGEMENT OF ASSOCIATED CONDITIONS

Hypertension
Atrial Fibrillation
DM
Chronic Kidney Disease
Myocardial Ischemia
Hyperlipidemia

# Current Recommendations for Treatment of Patients with HFpEF

**Beta blockers** –Beta blockers should not be used as a primary treatment for HFpEF, but beta blockers may be used to treat HFrEF, chronic coronary syndromes, to control heart rate in AF, or to treat hypertension.

**Calcium channel blockers** – In patients with HFpEF, calcium channel blockers are generally used as a third- or fourth-line therapy for hypertension.

**Nitrates** – Evidence of efficacy is lacking, and a randomized trial found that use of isosorbide mononitrate may reduce physical activity levels in patients with HFpEF.

**Phosphodiesterase-5 inhibitors** – While a prospective trial of sildenafil suggested an improvement in hemodynamic and morphologic markers of HFpEF severity, two subsequent trials of sildenafil did not show an improvement in exercise tolerance

# Current Recommendations for Treatment of Patients with HFpEF

## The dawn of a new era of targeted therapies for heart failure with preserved ejection fraction (HFpEF)

•Kenji Harada & Kazuomi Kario *Hypertension Research* **volume 45**, pages164–166 (2022)

Although effective treatments exist for heart failure with a reduced ejection fraction (HFrEF), there is a paucity of treatments with proven benefits for heart failure with a preserved ejection fraction (HFpEF). Detailed results from the phase III EMPEROR-Preserved trial were published in *The New England Journal of Medicine* on August 27, 2021 [1]. The EMPEROR-Preserved trial was a large, international, double-blind and placebo-controlled trial of empagliflozin, a sodium-glucose cotransporter 2 inhibitor (SGLT2-i), in patients with HFpEF (ejection fraction [EF] > 40%). In the trial's HFpEF patients, the SGLT2-i empagliflozin led to a 21% lower relative risk (hazard ratio [HR] 0.79, 95% confidence interval [CI]: 0.69–0.90) of the composite of cardiovascular death or hospitalization for heart failure, which was related mainly to a 29% lower risk (HR 0.73, 95% CI: 0.61–0.88) of heart failure hospitalization associated with empagliflozin treatment.

# Sodium–glucose co-transporter 2 (SGLT2) inhibitors

In patients with heart failure and reduced left ventricular ejection fraction (LVEF ≤40%; HFrEF), including those with and without type 2 diabetes, both dapagliflozin and empagliflozin reduced cardiovascular death or heart failure events when added to standard therapy.

What about patients with HFPEF?  Why is this important?

Patients with preserved (LVEF >50%) or mildly reduced ejection fraction (LVEF >40%) now represent the majority or at least half of those with heart failure

They also experience a comparable burden of poor outcomes, such as death, hospitalizations and symptom burden, as those with LVEF ≤40%; yet suffer from dearth of effective therapies.



https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2249

# Sodium–glucose co-transporter 2 (SGLT2) inhibitors

While the mechanisms by which SGLT2 inhibitors improve outcomes in heart failure continue to be investigated, they are postulated to include favorable effects on:

hemodynamics, improvement in myocardial energetics and loading conditions, favorable effects on endothelial function and inflammation, and slowing of the progression of kidney disease. These effects may collectively underlie observed early and sustained improvements in filling pressures and ventricular remodeling.

Therefore, there is a large and urgent unmet clinical need for efficacious and safe treatments in this vulnerable patient group.



https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2249

# Current Recommendations for Treatment of CHF

HFSA
HEART FAILURE SOCIETY OF AMERICA

JCF Journal of Cardiac Failure

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

Heidenreich PA, *et al. J Card Fail* 2022

# Current Recommendations for Treatment of CHF

1. GDMT for HFrEF includes 4 medication classes that include SGLT2i
2. SGLT2i have a 2a recommendation in HFmrEF
3. New recommendations for HFpEF for SGLT2i (2a), MRAs (2b) & ARNi (2b)
4. Improved LVEF refers to HFrEF where LVEF is now >40%; these patients should continue HFrEF treatment
5. Value statements for recommendations where high-quality, cost-effectiveness studies have been published
6. Amyloid heart disease has new recommendations for screening, testing and treatment
7. Evidence supporting increased filling pressures is important for HF diagnosis if LVEF >40%

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

HFSA HEART FAILURE SOCIETY OF AMERICA

JCF Journal of Cardiac Failure

Heidenreich PA, *et al. J Card Fail* 2022

JHFS

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HFSA HEART FAILURE SOCIETY OF AMERICA

JCF Journal of Cardiac Failure

Heidenreich PA, *et al. J Card Fail* 2022

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# New Recommendations for HFpEF

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B - R | In patients with HFpEF, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality |
| 2b | B - R | In selected patients with HFpEF, **MRAs** may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum |
| 2b | B - R | In selected patients with HFpEF, **ARNi** may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum |

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

HFSA HEART FAILURE SOCIETY OF AMERICA

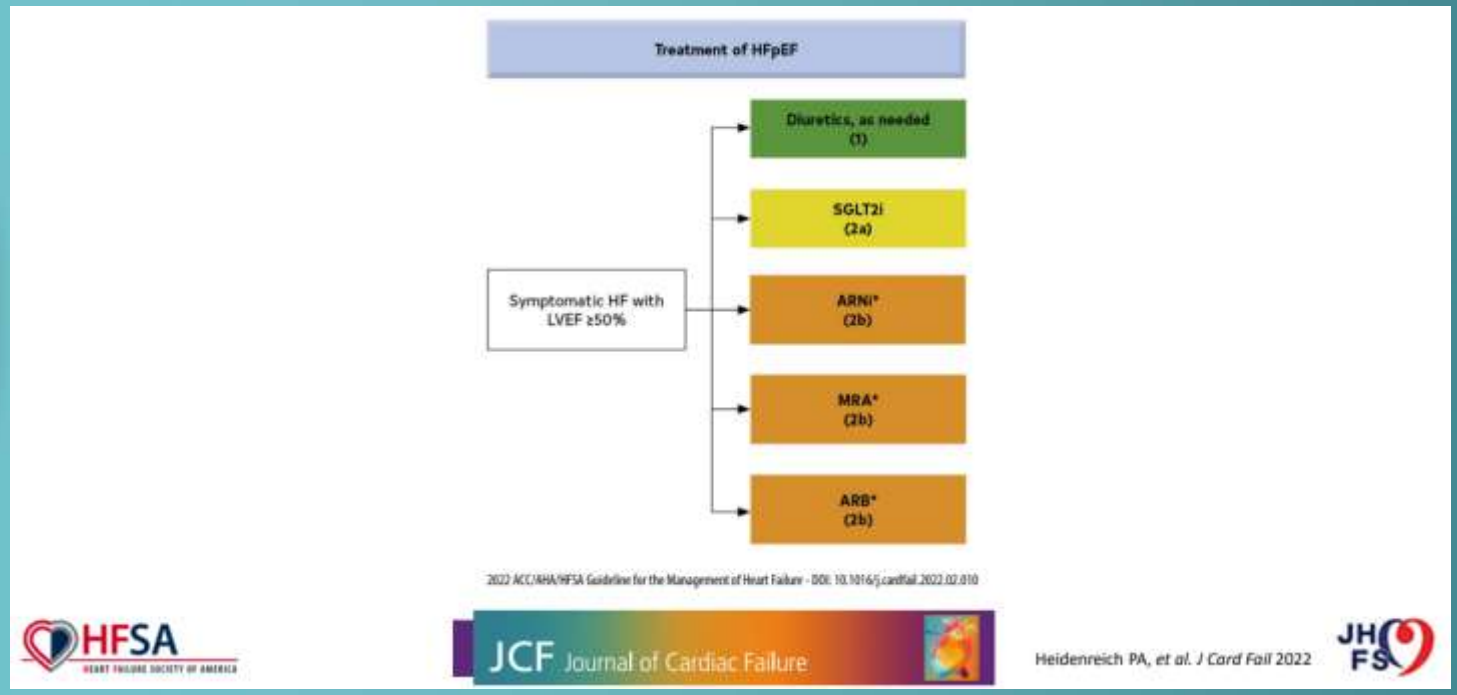
JCF Journal of Cardiac Failure

Heidenreich PA, *et al. J Card Fail* 2022

JHFS

ACOi 2023 October 11-14 Tampa • Hybrid

# New Recommendations for HFpEF




ACOi 2023 October 11-14
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# New Recommendations for HFpEF

## 2023 Focused Update of ESC Guidelines for Acute and Chronic HF: Key Points
## Aug 29, 2023

1.This 2023 Focused Update addresses changes in recommendations for the treatment of heart failure (HF) because of availability of new evidence.

2.A sodium–glucose co-transporter 2 (SGLT2) inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HF with mildly reduced ejection fraction (**HFmrEF**) to reduce the risk of HF hospitalization or cardiovascular (CV) death (Class I, level of evidence [LOE] A).

3.An SGLT2 inhibitor (dapagliflozin or empagliflozin) is recommended in patients with HF with preserved EF (**HFpEF**) to reduce the risk of HF hospitalization or CV death (Class I, LOE A).



https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2023/08/29/14/58/2023-focused-update-esc-guidelines-hf-esc-2023

# New Recommendations for HFpEF

## 2023 Focused Update of ESC Guidelines for Acute and Chronic HF: Key Points
## Aug 29, 2023

4. 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 an HF hospitalization is recommended to reduce the risk of HF rehospitalization or death (Class I, LOE B).

5. In patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), SGLT2 inhibitors (dapagliflozin or empagliflozin) are recommended to reduce the risk of HF hospitalization or CV death (Class I, LOE A).

6. In patients with T2DM and CKD, finerenone is recommended to reduce the risk of HF hospitalization (Class I, LOE A).



https://www.acc.org/Latest-in-Cardiology/ten-points-to-remember/2023/08/29/14/58/2023-focused-update-esc-guidelines-hf-esc-2023

# New Recommendations for HFpEF

What clinical trials have been done thus so far?



https://onlinelibrary.wiley.com/doi/10.1002/ejhf.2249

# Current Clinical Trials in Patients with HFpEF

CHARM PRESERVED (2003)

TOPCAT (2013)

PARAGON-HF (2019)

EMPEROR PRESERVED (2021)

PRESERVED-HF (2021)

SOLOIST-HF/ SCORED (2021)

DELIVER (2022)

VITALITY-HFpEF (2022)

FINEARTS-HF (2024)/ FIGARO- DKD (2023)

STEP-HFpEF (2023)

# CHARM PRESERVED (2003)

# CHARM PRESERVED (2003)

## CHARM-Preserved: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity - Preserved

**Purpose**

To determine whether the angiotensin II receptor blocker candesartan is beneficial in patients with chronic heart failure (CHF) and preserved left ventricular systolic function

**Reference**

**Yusuf S, Pfeffer MA, Swedberg K, et al. for the CHARM Investigators and Committees.** Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved trial. *Lancet* 2003;**362**:777–81.

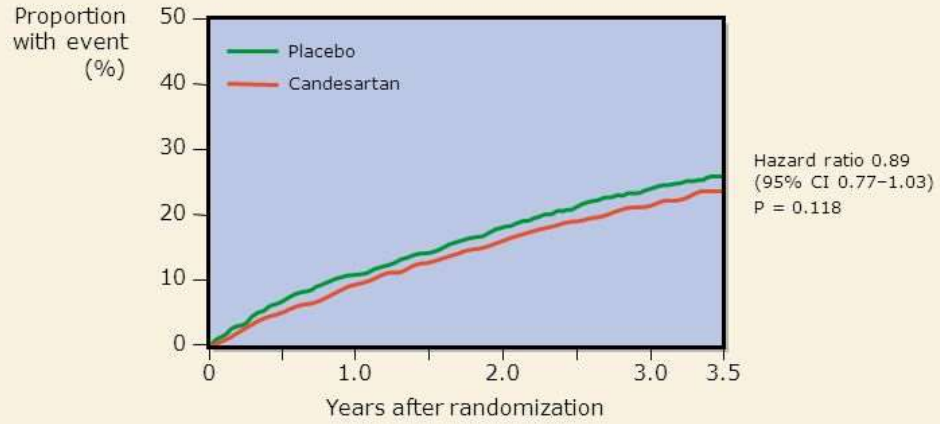


charm preserved clinical trial ppt - Google Search

# CHARM PRESERVED (2003)

## CHARM-Preserved: Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity - Preserved - *RESULTS continued* -

**Cardiovascular death or hospital admission for CHF**




Yusuf et al. *Lancet* 2003;**362**:777–81.

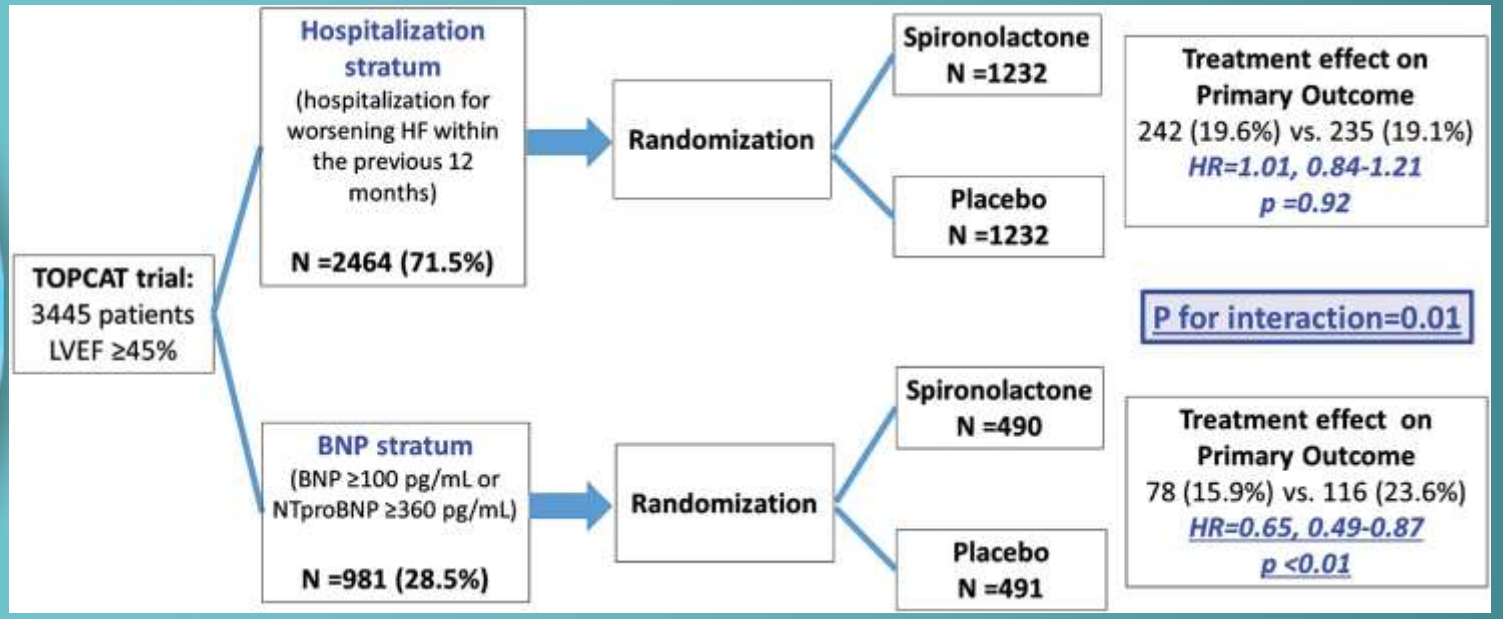
At a median follow-up of about 3 years, In patients with HFpEF and NYHA class II-IV symptoms, the addition of candesartan modestly reduced the rate of HF-related hospitalizations, but had no effect on CV mortality.



charm preserved clinical trial ppt - Google Search

# TOPCAT (2013)

# TOPCAT (2013)






https://www.google.com/search?q=clinical+trial+design+topcat+2013&source=lnms&tbm=isch&sa=X&ve

# TOPCAT (2013)

The TOPCAT trial randomly assigned 3445 patients with symptomatic HF and LVEF ≥45 percent (median 56 percent) to receive either spironolactone or placebo.

The composite primary outcome (death from cardiovascular causes, aborted cardiac arrest, or hospitalization for HF) was lower but not statistically different with spironolactone compared with placebo (18.6 and 20.4 percent, respectively; HR 0.89, 95% CI 0.77-1.04).

Hospitalization for HF was less frequent in the spironolactone group (12.0 percent) compared with the placebo group (14.2 percent; HR 0.83, 95% CI 0.69-0.99), but other components of the primary outcome occurred at similar rates in the two treatment groups. Total deaths and total hospitalizations were similar in the spironolactone and placebo groups.)

# TOPCAT (2013)

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

TOPCAT Funded by the NHLBI

**AHA Nov 18, 2013**
**Late Breaking Session**

Marc A. Pfeffer MD, PhD, on behalf of the TOPCAT Investigators

**TOPCAT Trial Executive Committee**
Inder Anand, Susan Assmann, Robin Boineau, Akshay Desai, Jerome Fleg, David Lathrop, Eldrin Lewis, Sonja McKinlay, Maureen Montrond, Marc Pfeffer, Bertram Pitt (Chair), Scott Solomon, George Sopko, Nancy Sweitzer, Song Yang.

ClinTrials.gov NCT00094302 HHS Contract # HHSN268200425207C

NIH neri BRIGHAM AND WOMEN'S HOSPITAL

TOPCAT Funded by the NHLBI

## Summary

| | Spironolactone (N = 1722) | Placebo (N = 1723) | HR (95% CI) |
|---|---|---|---|
| Primary Outcome | 320 (18.6%) 5.9/100pt-yr | 351 (20.4%) 6.6/100pt-yr | 0.89 (0.77-1.04) P=0.138 |
| Hospitalization for Heart Failure | 206 (12.0%) 3.8/100pt-yr | 245 (14.2%) 4.6/100pt-yr | 0.83 (0.69-0.99) P=0.042 Multiple HF Hosp P<0.01 |

**Conclusions:** TOPCAT population with HFpEF:

- **Rx with spironolactone did not alter the 1° composite**
- Reductions in heart failure were observed
- Use of spironolactone in these patients requires careful monitoring of $K^+$ and creatinine



https://evidence.nejm.org/doi/full/10.1056/EVIDctcs2100007

# TOPCAT (2013)

NEJM Evidence

CURRENT ISSUE RECENTLY PUBLISHED AUTHOR CENTER ABOUT

CLINICAL TRIALS CASE STUDY

Behind the Scenes of TOPCAT — Bending to Inform

Marc A. Pfeffer, M.D., Ph.D.[1] and Brian Claggett, Ph.D.[1]

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Published January 10, 2022
NEJM Evid 2022; 1 (1)
DOI: https://doi.org/10.1056/EVIDctcs2100007

Issue



https://evidence.nejm.org/doi/full/10.1056/EVIDctcs2100007

# TOPCAT (2014)

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

TOPCAT Funded by the NHLBI

**AHA Nov 18, 2014**
**Update on Randomized Trials**

**Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial**

Marc A. Pfeffer, MD, PhD; Brian Claggett, PhD; Susan F. Assmann, PhD; Robin Boineau, MD; Inder S. Anand, MD; Nadine Clausell, MD, PhD; Akshay S. Desai, MD, MPHa; Rafael Diaz, MD; Jerome L. Fleg, MD; Jean Gordeev, MD; John Heitner, MD; Eldrin F. Lewis, MD, MPH; Eileen O'Meara, MD; Jean-Lucien Rouleau, MD; Jeffrey L. Probstfield, MD; Tamar Shahrokhvili, MD, PhD; Sanjiv J. Shah, MD; Scott D. Solomon, MD; Nancy K. Sweitzer, MD, PhD; Sonja M. McKinlay, PhD; Bertram Pitt, MD
On behalf of TOPCAT Investigators

ClinTrials.gov NCT00094302 HHS Contract # HHSN268200425207C

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## Post–Hoc Analysis By Region

TOPCAT Funded by the NHLBI

- **Differences in:**
  - **Patient Populations**
  - **Prognosis**
  - **Responses to Spiro:**
    - **K+**
    - **Creatinine**
    - **Blood Pressure**

---

**Rz to spiro associated with reduced CV death and HF hospitalizations in pts from the Americas**
**(with event rates consistent with HFpEF)**

Thank you!

Circ 2014. Epub ahead of print



https://evidence.nejm.org/doi/full/10.1056/EVIDctcs2100007

# TOPCAT (2014)

Treatment Of Preserved Cardiac Function Heart Failure with an Aldosterone anTagonist (TOPCAT)

TOPCAT Funded by the NHLBI

Heart Failure Society of America

**Spironolactone metabolites in the TOPCAT trial: New insights into regional variation.**

Eileen O'Meara[1], Simon de Denus[1], Marc Pfeffer[2], Brian Claggett[2], Grégoire Leclair[1], Bertram Pitt[3], Eldrin Lewis[2], Scott Solomon[2], Jean Rouleau[1], Akshay Desai[2]

[1]Institut de Cardiologie de Montréal and Université de Montréal, Montréal, CA; [2]Cardiovascular Division, Brigham and Women's Hospital, Boston, USA; [3]Cardiology, University of Michigan, Ann Arbor, USA

The opinions expressed in this presentation have not been formally endorsed by the TOPCAT Executive Committee, the NHLBI, or contracting organizations

ClinicalTrials.gov NCT00094302 HHS Contract # HHSN268200425207C

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TOPCAT Funded by the NHLBI

## Clinical implications

- This relatively small repository uncovered further regional irregularities and unreliability of reports of study medication in Russia.
  - Impugning the veracity of the TOPCAT data from Russia
  - And by implication, Georgia.
    - Even lower event rates than Russia
    - Similar reported placebo and spironolactone doses, with less potassium response to assigned spironolactone
  - Thus, the most relevant data reflecting the impact of spironolactone in patients with HFpEF is reflected in the data from the Americas



https://evidence.nejm.org/doi/full/10.1056/EVIDctcs2100007

# TOPCAT (2014)

In subgroup analyses focused on regional effects, the efficacy of spironolactone was greater in the Americas (primary outcome 27 versus 32 percent with placebo) when compared with Russia/Georgia (9 versus 8 percent with placebo). In addition, compliance was higher in the Americas when compared with Russia/Georgia.

These differences suggest poorer adherence to the trial procedures outside of the Americas and raise questions about the veracity of the HFpEF diagnosis in this cohort as well. In a post hoc analysis of the trial that excluded Russia/Georgia, spironolactone reduced the risk of the primary outcome (27.3 versus 31.8 percent; HR 0.82, 95% CI 0.69-0.98).

# PARAGON-HF (2019)

# PARAGON-HF (2019)

Angiotensin Receptor-Neprilysin Inhibition (ARNI) in Heart Failure with Preserved Ejection Fraction

## Hypothesis

Patient's with HFpEF will have a reduction in cardiovascular (CV) mortality and heart failure (HF) hospitalizations (first and recurrent) when taking an ARNI vs valsartan.



https://www.google.com/search?q=heart+failure+with+preserved+function+ppt&source=hp&ei=LhVSYtWPJcLRtAbCn56ACA&iflsig=AHkkrS4AAAAAYIljPnL-L5qOOrD2Sus5kXShr5uZuN3t&ved=0ahUKEwjV3tndj4j3AhXCKM0KHcKPB4AQ4dUDCAk&uact=5&oq=heart+failure+with+preserved+function+ppt&gs_lcp=Cgdnd3Mtd2l6EAMyCAghEBYQHRAeMggIIRAWEB0QHjoUCAAQ6gIQtAIQigMQtwMQ1AMQ5QI6BAgAEEM6EQguEIAEELEDEIMBEMcBEKMCOgcILhDUAhBDOgsILhCABBDHARCjAjoICAAQgAQQsQM6CAguELEDEIMBOg4ILhCABBCxAxDHARCjAjoLCC4QgAQQsQMQgwE6BwgAELEDEEM6BQgAEIAEOgUIABCRAjoGCAAQFhAeOggIABAWEAoQHjoFCAAQhgNQ_QxY4klgnFJoAXAAeACAAWaIAZcWkgEENDAuMZgBAKABAbABCg&sclient=gws-wiz

# PARAGON-HF (2019)

| Primary outcome | Primary outcome results (rate ratio) |
|---|---|
| Composite cardiovascular (CV) mortality and hospitalization secondary to (HF) | Sacubitril-valsartan vs Valsartan:<br>0.87; 95% CI, 0.75 to 1.01<br><br>**p=0.06** |

# PARAGON-HF (2019)

## Secondary outcomes & results (95% CI)

*Change in NYHA class from baseline to 8 months: **OR, 1.45 (1.13-1.86)**

All-cause mortality: HR, 0.97 (0.84-1.13)

Change in KCCQ at 8 months: Difference, 1.0 (0.0-2.1)

*Renal composite outcome: **HR, 0.50 (0.33-0.77)**

*sacubitril-valsartan had significantly more patients with improved NYHA class, and less unchanged or worsened NYHA change from baseline sacubitril-valsartan had significantly less death from renal failure, ESRD, decrease in GFR < 50% from baseline

# PARAGON-HF (2019)

| Safety outcomes (p-value) | Study conclusion |
|---|---|
| *Hypotension (SBP < 100 mg Hg): **<0.001**<br><br>Elevated serum creatinine: 0.38<br><br>*Elevated serum postassium: **0.04**<br><br>*Angioedema: **0.02**<br><br>Liver-related adverse event: 0.11 | Patients with HFpEF treated with sacubitril-valsartan do not have significantly reduced risk in CV morbidity and mortality or heart failure hospitalizations (first and recurrent) to those patients taking valsartan. |



https://www.google.com/search?q=heart+failure+with+preserved+function+ppt&source=hp&ei=LhVSYtWPJcLRtAbCn56ACA&iflsig=AHkkrS4AAAAAYIljPnL-L5qOOrD2Sus5kXShr5uZuN3t&ved=0ahUKEwjV3tndj4j3AhXCKM0KHcKPB4AQ4dUDCAk&uact=5&oq=heart+failure+with+preserved+function+ppt&gs_lcp=Cgdnd3Mtd2l6EAMyCAghEBYQHRAeMggIRAWEB0QHjoUCAAQ6gIQtAIQigMQtwMQ1AMQ5QI6BAgAEEM6EQguEIAEELEDEIMBEMcBEKMCOgcILhDUAhBDOgsILhCABBDHARCjAjoICAAQgAQQsQM6CAguELEDEIMBOg4ILhCABBCxAxDHARCjAjoLCC4QgAQQsQMQgwE6BwgAELEDEEM6BQgAEIAEOgUIABCRAjoGCAAQFhAeOggIABAWEAoQHjoFCAAQhgNQ_QxY4klgnFJoAXAAeACAAWaIAZcWkgEENDAuMZgBAKABAbABCg&sclient=gws-wiz

# New Recommendations for HFpEF

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B - R | In patients with HFpEF, **SGLT2i** can be beneficial in decreasing HF hospitalizations and cardiovascular mortality |
| 2b | B - R | In selected patients with HFpEF, **MRAs** may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum |
| 2b | B - R | In selected patients with HFpEF, **ARNi** may be considered to decrease hospitalizations, particularly among patients with LVEF on the lower end of this spectrum |

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

HFSA HEART FAILURE SOCIETY OF AMERICA

JCF Journal of Cardiac Failure

Heidenreich PA, *et al. J Card Fail* 2022

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# Summary PARAGON-HF (2019)

- PARAGON-HF trial showed no significant beneficial effect of treatment with sacubitril/valsartan in the entire study cohort, the subgroup analysis indicated a potential benefit, particularly in lower EF ranges (≤ 57%) and in women.



What Type of Patients Did PARAGON-HF Select? Insights from a Real-World Prospective Cohort of Patients with Heart Failure and Preserved Ejection Fraction - PMC (nih.gov)

# EMPEROR PRESERVED (2021)

ACOi 2023 October 11-14
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# EMPEROR PRESERVED (2021)

Empagliflozin in Heart Failure with a Preserved Ejection Fraction


**BACKGROUND**
Sodium–glucose cotransporter 2 inhibitors reduce the risk of hospitalization for heart failure in patients with heart failure and a reduced ejection fraction, but their effects in patients with heart failure and a preserved ejection fraction are uncertain.

**METHODS**
In this double-blind trial, we randomly assigned 5988 patients with class II–IV heart failure and an ejection fraction of more than 40% to receive empagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

**RESULTS**
Over a median of 26.2 months, a primary outcome event occurred in 415 of 2997 patients (13.8%) in the empagliflozin group and in 511 of 2991 patients (17.1%) in the placebo group (hazard ratio, 0.79; 95% confidence interval [CI], 0.69 to 0.90; P<0.001). This effect was mainly related to a lower risk of hospitalization for heart failure in the empagliflozin group. The effects of empagliflozin appeared consistent in patients with or without diabetes. The total number of hospitalizations for heart failure was lower in the empagliflozin group than in the placebo group (407 with empagliflozin and 541 with placebo; hazard ratio, 0.73; 95% CI, 0.61 to 0.88; P<0.001). Uncomplicated genital and urinary tract infections and hypotension were reported more frequently with empagliflozin.

**CONCLUSIONS**
Empagliflozin reduced the combined risk of cardiovascular death or hospitalization for heart failure in patients with heart failure and a preserved ejection fraction, regardless of the presence or absence of diabetes.
(Funded by Boehringer Ingelheim and Eli Lilly; EMPEROR-Preserved ClinicalTrials.gov number, **NCT03057951.** . October 14, 2021

# EMPEROR PRESERVED (2021)

## EMPEROR-Preserved

### Phase III randomised double-blind placebo-controlled event driven trial

**Key Inclusion Criteria:** T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV) with LVEF >40%, elevated NT-proBNP concentrations and structural heart changes or documented HHF within 12 months.

**Key Exclusion Criteria:** Symptomatic hypotension and eGFR <20 mL/min/1.73m2.

**EMPEROR-Preserved**
LVEF >40%

Recruitment:
5988 patients

- Empagliflozin 10 mg qd†
- Placebo†

Estimated follow-up
~38 months (event-driven)

**COMPOSITE PRIMARY ENDPOINT**
Time to first event of adjudicated CV death or adjudicated HHF

**CONFIRMATORY KEY SECONDARY ENDPOINTS**
- First and recurrent adjudicated HHF events
- Slope of change in eGFR (CKD-EPI) from baseline

†Guideline-directed medical therapy

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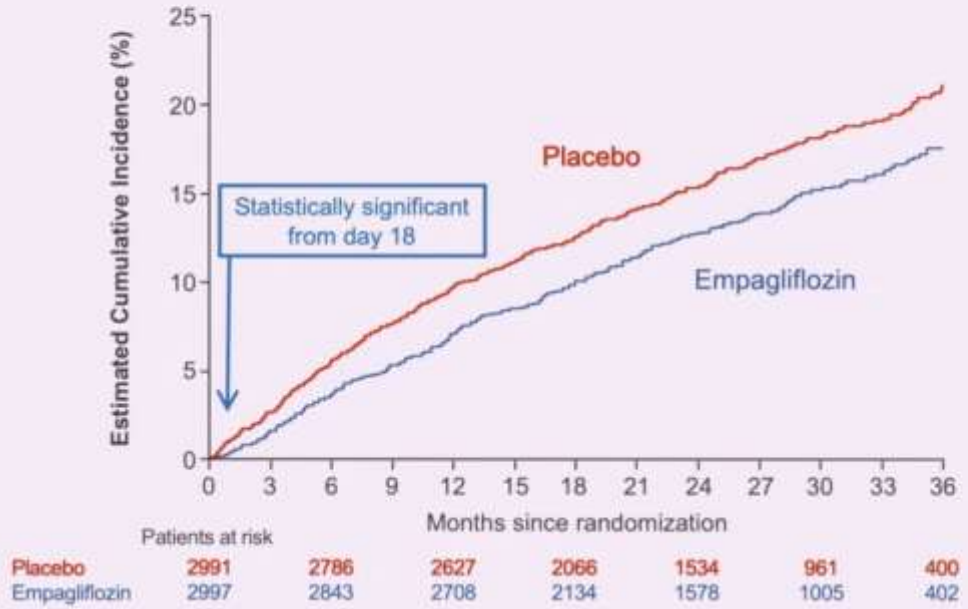
https://www.google.com/search?source=univ&tbm=isch&q=EMPERORreserved+trial+ppt+slides&fir=YgEgEc5aaU3kpM%252CX6rZG9NVDy5byM%252C_%253BIIM_iVmvlGTTwM%252Ccvdzu8A5QVSBIM%252C_%253B3Ihir97zTqsvfM%252CQHa5_uMvO-4qSM%252C_%253B3U9yGDCI27FFbM%252CaBR75Y

# EMPEROR PRESERVED (2021)

## Primary Endpoint – Composite of Cardiovascular Death or Heart Failure Hospitalization




**HR 0.79**
(95% CI 0.69, 0.90)
P = 0.0003

**Placebo:**
511 patients with event
Rate: 8.7 per 100 patient-years

**Empagliflozin:**
415 patients with event
Rate: 6.9 per 100 patient-years

RRR 21%

NNT=31
During a median trial period of 26 months.

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https://www.google.com/search?source=univ&tbm=isch&q=EMPERORreserved+trial+ppt+slides&fir=YqEgEc5aaU3kpM%252CX6rZG9NVDy5byM%252C_%253BIIM_iVmvlGTTwM%252Ccvdzu8A5QVSBIM%252C_%253B3Ihir97zTqsvfM%252CQHa5_uMvO-4gSM%252C_%253B3U9yGDCI27FFbM%252CaBR75Y

# EMPEROR PRESERVED (2021)

RESEARCH SUMMARY

## Empagliflozin in Heart Failure with a Preserved Ejection Fraction

Anker SD et al. DOI: 10.1056/NEJMoa2107038

CLINICAL PROBLEM

Treatment options for patients with heart failure and a preserved ejection fraction are limited. Sodium–glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce heart failure progression in patients with a reduced ejection fraction, but whether they improve outcomes in patients with a preserved ejection fraction is unclear.

CLINICAL TRIAL

**Design:** A multicenter, double-blind, randomized, placebo-controlled trial examined the effects of the SGLT2 inhibitor empagliflozin in patients with heart failure and a preserved ejection fraction.

**Intervention:** 5988 adults with New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction >40% were randomly assigned to receive empagliflozin (10 mg once daily) or placebo, in addition to their usual treatment. The primary outcome was a composite of cardiovascular death or hospitalization for heart failure.

RESULTS

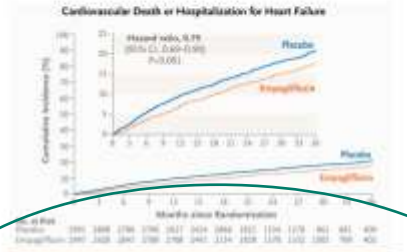
**Efficacy:** During a median follow-up of 26.2 months, a primary composite outcome event occurred significantly less often in the empagliflozin group than in the placebo group, largely owing to a decrease in hospitalizations for heart failure with empagliflozin. The benefit of empagliflozin appeared similar in patients with or without diabetes.

**Safety:** Serious adverse events occurred in 47.9% of patients in the empagliflozin group and in 51.6% of those in the placebo group. Uncomplicated genital and urinary tract infections and hypotension were more common with empagliflozin.

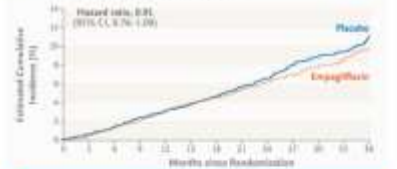
LIMITATIONS AND REMAINING QUESTIONS

- In this trial, empagliflozin did not significantly reduce the incidence of cardiovascular death alone.

Links: Full Article | NEJM Quick Take | Editorial








CONCLUSIONS

In patients with heart failure and a preserved ejection fraction, the SGLT2 inhibitor empagliflozin lowered the risk of a composite of cardiovascular death or hospitalization for heart failure, mainly owing to a reduction in hospitalizations for heart failure.

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https://www.google.com/search?source=univ&tbm=isch&q=EMPERORreserved+trial+ppt+slides&fir=YqEgEc5aaU3kpM%252CX6rZG9NVDy5byM%252C_%253BIIM_iVmvIGTTwM%252Ccvdzu8A5QVSBIM%252C_%253B3Ihir97zTqsvfM%252CQHa5_uMvO-4gSM%252C_%253B3U9yGDCl27FFbM%252CaBR75Y

# EMPEROR PRESERVED (2021)

| Efficacy Outcomes | Empagliflozin | Placebo | Hazard ratio/difference (95% confidence interval) |
|---|---|---|---|
| Death from any cause | 14.1% | 14.3% | 1.00 (0.87-1.15) |
| CV death | 7.3% | 8.2% | 0.91 (0.76-1.09) |
| Death or hospitalization | 45.2% | 47.8% | **0.92 (0.85-0.99); -2.6%** |
| Total* hospitalizations for any cause | 2566 | 2768 | 0.93 (0.85-1.01) |
| Total* HF hospitalizations | 407 | 541 | **0.73 (0.61-0.88)** |
| 1° outcome (Time to 1st HF hospitalization or CV death) | 13.8% | 17.1% | **0.79 (0.69-0.90); -3.3%** |
| 1st HF hospitalization | 8.6% | 11.8% | **0.71 (0.60-0.83); -3.2%** |
| Change in KCCQ clinical summary score at 1 y | +4.5 | +3.2 | **+1.3 (+0.45 to +2.2)** |
| eGFR mean change/y | -1.25 | -2.62 | **+1.36 (+1.06-1.66)** |

**First & recurrent*

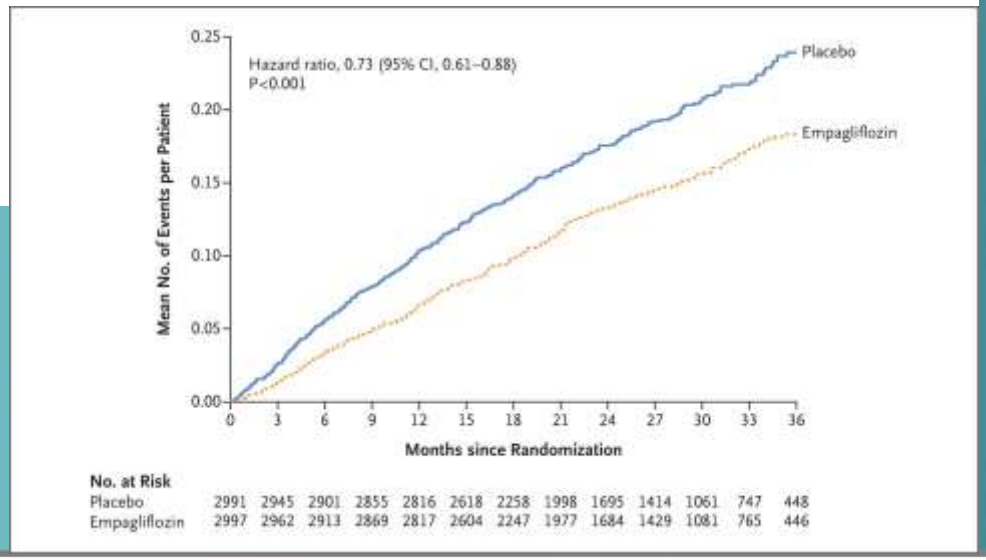


https://www.google.com/search?source=univ&tbm=isch&q=EMPERORreserved+trial+ppt+slides&fir=YqEgEc5aaU3kpM%252CX6rZG9NVDy5byM%252C_%253BIIM_iVmvIGTTwM%252Ccvdzu8A5QVSBIM%252C_%253B3Ihir97zTqsvfM%252CQHa5_uMvO-4gSM%252C_%253B3U9yGDCI27FFbM%252CaBR75Y

# EMPEROR PRESERVED (2021)

The EMPEROR-Preserved trial showed that **empagliflozin is superior to placebo in improving HF outcomes among patients with symptomatic stable HFpEF on excellent baseline GDMT, irrespective of diabetes status**.

Nov 15, 2021

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Empagliflozin in Heart Failure with a Preserved Ejection Fraction | NEJM

# PRESERVED-HF (2021)

# PRESERVED-HF (2021)

The PRESERVED-HF Study

Effects of Dapagliflozin on Symptoms and Functional Status in Patients With Heart Failure and Preserved Ejection Fraction

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# PRESERVED-HF (2021)

## Summary

- Dapagliflozin significantly improved symptoms and physical limitations in patients with HFpEF in just 12 weeks
- The treatment effect was large, clinically meaningful and statistically significant
- Effects were consistent across all key subgroups, including participants with and without Type 2 Diabetes, and those with ejection fraction above and below 60%
- Dapagliflozin well tolerated, with no new safety signals

PRESERVED-HF



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)

## What Are the Clinical Implications?

- Goals of therapy in HFpEF include reducing death and hospitalizations, and *enabling patients to feel better and do more*
- PRESERVED-HF is the first trial to demonstrate that SGLT2 inhibitor dapagliflozin significantly improves symptoms, physical limitations and 6-minute walking distance in HFpEF
  - Benefit evident at 12 weeks
- Findings highly complementary to those of large outcome trials
- Collectively, these results support the use of SGLT2 inhibitors as a new treatment option in patients with HFpEF – a morbid condition with few therapeutic options
- Important implications for guidelines, clinical practice

PRESERVED-HF

Effects of Dapagliflozin on Biomarkers, Symptoms and Functional Status in Patients with PRESERVED Ejection Fraction Heart Failure



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# SOLOIST-HF and SCORED (2021-2023)

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# SOLOIST-HF (2021)

## SOLOIST-WHF Trial Design

SOLOIST

1222 patients with diabetes and HF

Double-blind randomization in-hospital or within 3 days after discharge

- Placebo QD
- Sotagliflozin 200 mg QD[1]

Primary Endpoint: Total Events
- Cardiovascular Death
- Hospitalization for Heart Failure
- Urgent Heart Failure Visit

Median follow up duration (IQR) = 9.0 (4.9-13.4) months

**Key inclusion criteria:**
- Admission with signs and symptoms of HF
- Treatment with intravenous diuretics
- Stabilized, off oxygen, transitioning to oral diuretics
- BNP ≥150 pg/mL (≥450 pg/mL if afib) or NT-proBNP ≥600 pg/mL (≥1800 pg/mL if afib)
- Type 2 diabetes

**Key exclusion criteria:**
- End-stage HF
- Recent ACS, stroke, PCI, or CABG
- eGFR <30 mL/min/1.73m$^2$

[1]Goal of dose increase to 400 mg QD

Bhatt DL, Szarek M, Steg PG, et al., and Pitt B. *N Engl J Med.* 2020. Bhatt DL. AHA 2020, virtual.



file:///C:/Users/Chad/Desktop/8amET-SOLOIST-and-SCORED-acc-2021.pdf

# SOLOIST-HF (2021)

In the SOLOIST-HF trial, recently hospitalized patients with type 2 diabetes and either HFpEF (20 percent of patients) or HFrEF were randomly assigned to treatment with sotagliflozin (a combined SGLT2/SGLT1 inhibitor) or placebo

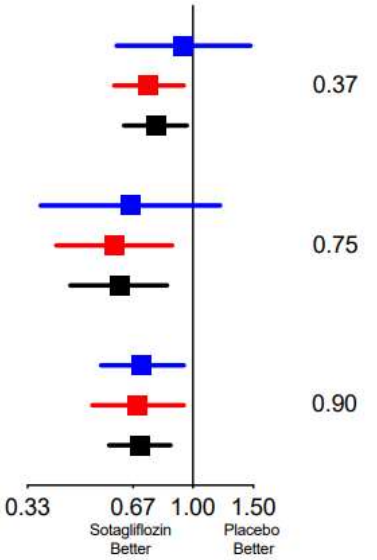
At a median follow-up of 7.7 months, the primary endpoint of cardiovascular death, hospitalization, or urgent visit for HF was lower in the sotagliflozin group (51 versus 76 events per 100 patient-years; HR 0.67, 95% CI 0.52-0.85). The effect was driven entirely by a reduction in hospitalization and urgent visits for HF (40 versus 64 events per 100 patient-years; HR 0.64, 95% CI 0.49-0.83).

# SOLOIST-HF (2021)

## Pooled Data: SOLOIST and SCORED Total CV Death, HHF, and Urgent HF Visit in 11,784 Patients

SOLOIST
SCORED

| | HR (95% CI) | $P_{interaction}$ |
|---|---|---|
| **Ejection Fraction <40%** | | |
| Female (n=482) | 0.94 (0.60, 1.47) | |
| Male (n=1276) | 0.74 (0.59, 0.94) | 0.37 |
| Overall (n=1758) | 0.78 (0.63, 0.96) | |
| **Ejection Fraction 40 to 50%** | | |
| Female (n=445) | 0.64 (0.36, 1.20) | |
| Male (n=912) | 0.59 (0.40, 0.87) | 0.75 |
| Overall (n=1357) | 0.61 (0.44, 0.84) | |
| **Ejection Fraction ≥50%** | | |
| Female (n=4439) | 0.71 (0.54, 0.94) | |
| Male (n=4230) | 0.69 (0.51, 0.94) | 0.90 |
| Overall (n=8669) | 0.70 (0.57, 0.86) | |




Bhatt DL. ACC 2021, virtual.



file:///C:/Users/Chad/Desktop/8amET-SOLOIST-and-SCORED-acc-2021.pdf

# SOLOIST-HF (2021)

## Conclusions

SOLOIST SCORED

**Sotagliflozin** robustly and significantly reduced the composite of total cardiovascular deaths, hospitalizations for heart failure, and urgent visits for heart failure across the full range of ejection fraction, including in patients with heart failure with preserved ejection fraction.

As well, in on-treatment analyses, **sotagliflozin** demonstrated a significant reduction in cardiovascular death.

These are the first randomized data from a prespecified analysis of clinical trials to show a significant effect of a therapy on heart failure with preserved ejection fraction, additionally demonstrating a consistent and significant benefit in women.

Bhatt DL. ACC 2021, virtual.

# New Recommendations for HFpEF

## FDA Update: Sotagliflozin Approved For Broad HF Treatment

**Jun 05, 2023**

**ACC News Story**

Print **Font Size** A A A

The U.S. Food and Drug Administration (FDA) on May 26 approved a new drug application submitted by Lexicon Pharmaceuticals, Inc. for sotagliflozin (Inpefa), the first dual SGLT1 and SGLT2 inhibitor for the treatment of heart failure (HF), including HF with preserved ejection fraction and HF with reduced ejection fraction.

The once-daily oral tablet is approved to reduce the risk of cardiovascular death, hospitalization for HF, and urgent HF visits in adult patients with HF or type 2 diabetes mellitus, chronic kidney disease and other cardiovascular risk factors. Approval was based on phase 3 results from the SCORED trial and the SOLOIST-WHF trial, the latter of which were presented at ACC.23/WCC in New Orleans.

Lexicon expects the new drug to be available by the end of June 2023. For more information, access the FDA approval letter or the Lexicon press release.

**Clinical Topics:** Cardiovascular Care Team, Dyslipidemia, Heart Failure and Cardiomyopathies, Lipid Metabolism, Acute Heart Failure

**Keywords:** *Tablets, Hospitalization, Renal Insufficiency, Chronic, Ventricular Dysfunction, Left, Heart Failure, Risk Factors, Cardiovascular Diseases, Consensus, United States Food and Drug Administration, Sodium-Glucose Transporter 2, Diabetes Mellitus, Type 2, Stroke Volume, Sodium-Glucose Transporter 2 Inhibitors, ACC Advocacy*

# VITALITY-HFpEF (2022)

# VITALITY-HFpEF (2022)

VITALITY -HFpEF

NCT03547583

## Vericiguat in Heart Failure with Preserved Ejection Fraction: The VITALITY-HFpEF Trial

Trial to eValuate the efficacy and safeTy of the orAL sGC stImulator vericiguaT to improve phYsical functioning in activities of daily living in patients with HFpEF

Paul W. Armstrong, MD, Carolyn S.P. Lam, MD, Kevin J. Anstrom, PhD, Justin Ezekowitz, MBBCh, Adrian F. Hernandez, MD, MHS, Christopher M. O'Connor, MD, Burkert Pieske, MD, Piotr Ponikowski, MD, PhD, Sanjiv J. Shah, MD, Scott D. Solomon, MD, Adriaan A. Voors, MD, Lilin She, PhD, Vanja Vlajnic, MS, MAS, Francine Carvalho, MD, PhD, Luke Bamber, MSc, Robert O. Blaustein, MD, PhD, Lothar Roessig, MD, and Javed Butler, MD, MPH, MBA
on behalf of the VITALITY-HFpEF Study Group

Canadian VIGOUR Centre
Bridging Hearts and Minds

Duke Clinical Research Institute



https://thecvc.ca/wp-content/uploads/2017/01/VITALITY_Primary_HFA-Discovery_June-12-2020-Session_FINAL.pdf

# VITALITY-HFpEF (2022)

Vericiguat is a soluble guanylate cyclase stimulator( sGC stimulator). In HF, sCG activity and NO bioavailability are decreased due to oxidative stress and endothelial dysfunction, resulting in myocardial and vascular dysfunction. The subsequent increase in cGMP may improve myocardial function and vascular tone



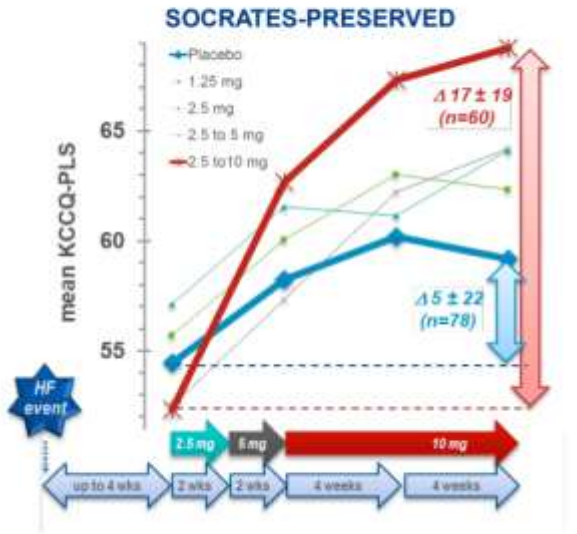
https://www.google.com/search?q=mechanism+of+action+of+vericiguat&source=hp&ei=5qdcYvGrMf2JptQPqMiusAo&iflsi

# VITALITY-HFpEF (2022)

## sGC and Physical Function in HFpEF

VITALITY -HFpEF

- Patients with HFpEF have substantially reduced functional capacity and quality of life[1]
- No treatment exists to address this major unmet need[2]
- Physiologic stimulation of sGC by NO is disrupted in HFpEF due to comorbidity-related inflammation[3]
- Soluble guanylate cyclase (sGC) has a unique mechanism enhancing heart, vessel, muscle, and renal function
- **SOCRATES-PRESERVED suggested improvement in KCCQ-PLS with vericiguat in HFpEF**




[1] Butler et al. *Circ Heart Fail*. 2016 Nov;9(11)
[2] Yancy CW et al. *J Am Coll Cardiol*. 2017 Aug 8;70(6):776-803
[3] Shah S et al. *Circulation*. 2016;134:73-90

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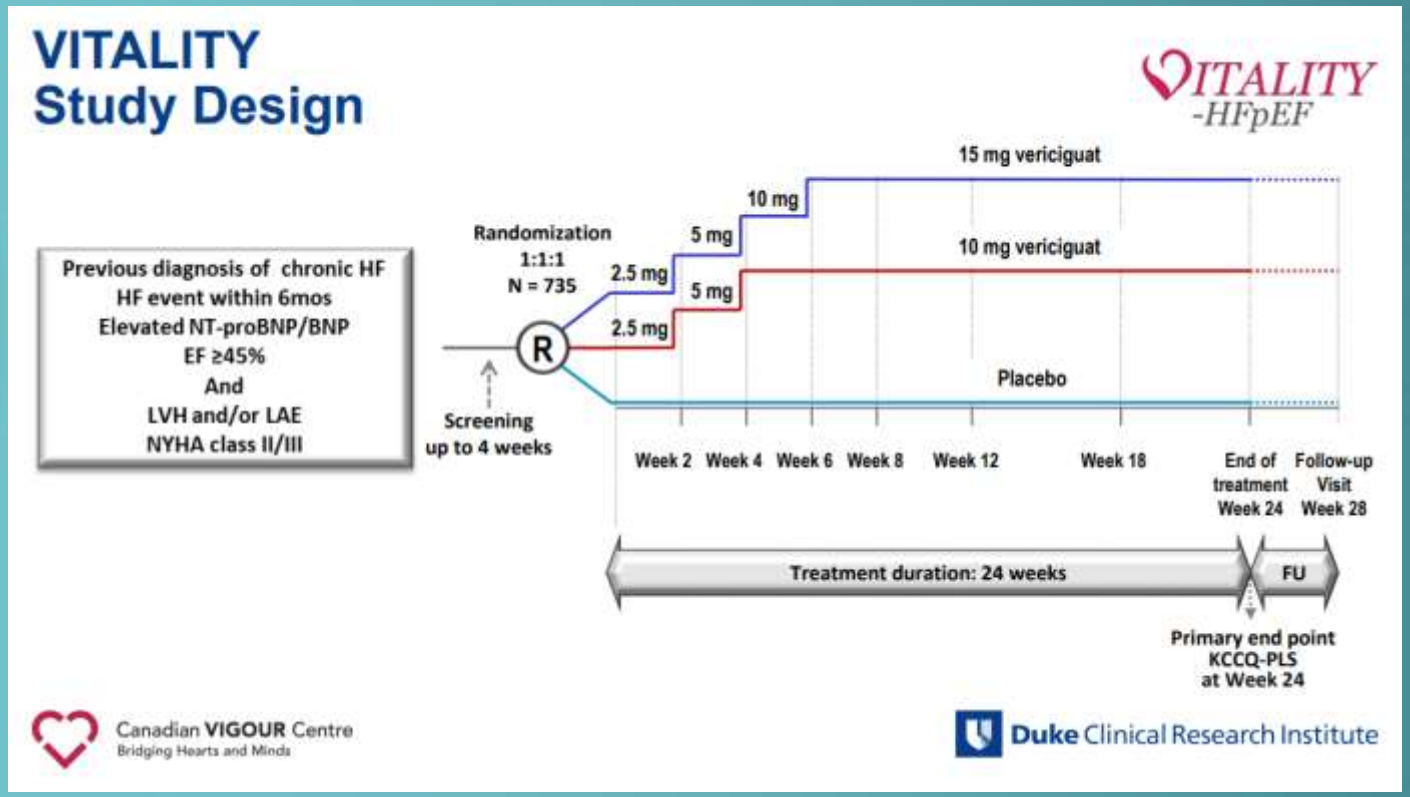
D mean ± standard deviation
Full analysis set excluding subjects with incorrectly assigned doses
Filippatos et al. Eur J Heart Fail. 2017 Jun;19(6):782-791

Duke Clinical Research Institute

https://thecvc.ca/wp-content/uploads/2017/01/VITALITY_Primary_HFA-Discovery_June-12-2020-Session_FINAL.pdf

# VITALITY-HFpEF (2022)

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https://thecvc.ca/wp-content/uploads/2017/01/VITALITY_Primary_HFA-Discovery_June-12-2020-Session_FINAL.pdf

# VITALITY-HFpEF (2022)

## Summary

VITALITY -HFpEF

- Vericiguat in target doses of 10 and 15 mg did not improve the primary outcome of KCCQ PLS nor the secondary outcome of 6-minute walking distance in a typical HFpEF population.
- Tendency for more symptomatic hypotension& syncope with both 10 and 15 mg doses suggests a pharmacodynamically active dose studied.
- Although there were more CV deaths in the vericiguat groups, the limited duration of follow up and numbers are too small for definitive conclusions.

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https://thecvc.ca/wp-content/uploads/2017/01/VITALITY_Primary_HFA-Discovery_June-12-2020-Session_FINAL.pdf

# VITALITY-HFpEF (2022)

## Conclusion

VITALITY -HFpEF

- In the VITALITY-HFpEF trial, vericiguat (10 or 15 mg) compared with placebo did not improve KCCQ PLS scores or 6MWD.
- SOCRATES PRESERVED findings were not confirmed in larger population studied with two doses for a longer time
- VITALITY aligned with prior studies of the NO-sGC-cGMP pathway that did not improve HFpEF
- Further studies are needed to identify effective interventions to improve outcomes in patients with HFpEF

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https://thecvc.ca/wp-content/uploads/2017/01/VITALITY_Primary_HFA-Discovery_June-12-2020-Session_FINAL.pdf

# DELIVER (2022)

# DELIVER (2022)

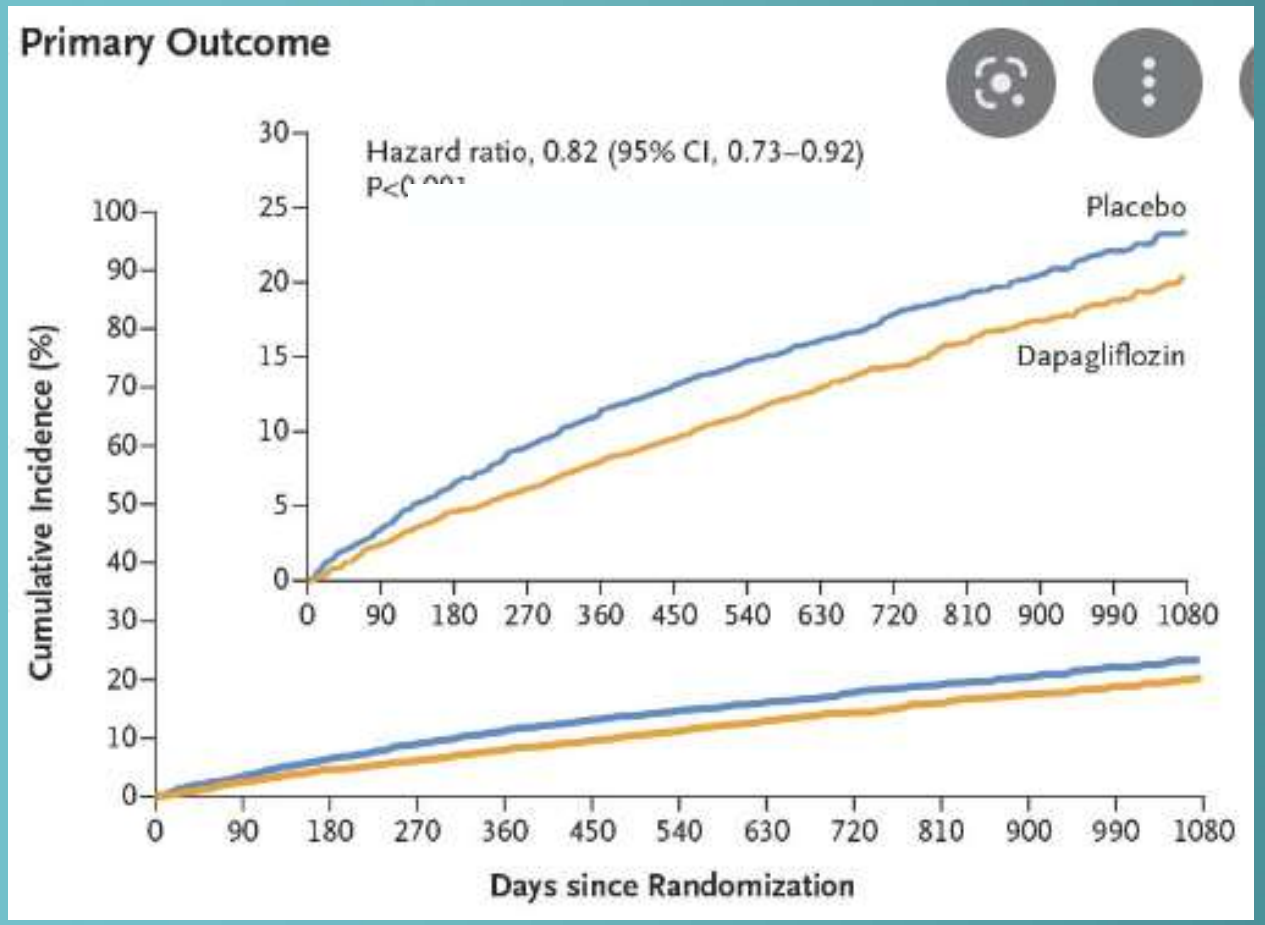
Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial

Sodium–glucose co-transporter 2 (SGLT2) inhibitors, originally developed as glucose-lowering agents, have been shown to reduce heart failure hospitalizations in patients with type 2 diabetes without established heart failure, and in patients with heart failure with and without diabetes. Their role in patients with heart failure with preserved and mildly reduced ejection fraction remains unknown.



https://doi.org/10.1002/ejhf.2249

# DELIVER (2022)

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https://www.google.com/search?q=Dapagliflozin+in+Heart+Failure+with+Mildly+Reduced+or+Preserved+Ejection+Fraction&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjR0NfulsX6AhWajYkEHQCFDxAQ_AUoAnoECAEQBA&biw=1536&bih=754&dpr=1.25#imgrc=buagKk5anhsfjM

# DELIVER (2022)

Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial

**Conclusions**

Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction.



https://doi.org/10.1002/ejhf.2249

# FINEARTS-HF (2024)

## Study Ongoing

# FINEARTS-HF (2024)

Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% (FINEARTS-HF)

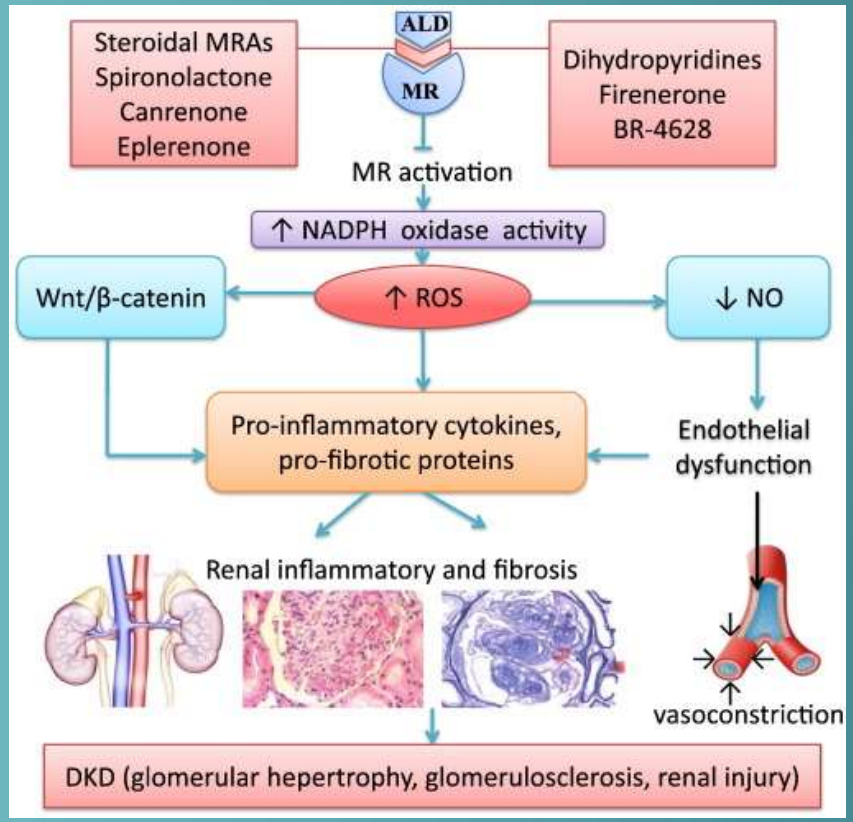


Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% - Full Text View - ClinicalTrials.gov

# FINEARTS-HF (2024)

Finerenone mechanism of action

Finerenone is a selective antagonist of the mineralocorticoid receptor (MR). Activated by aldosterone and cortisol, the nonsteroidal MRA regulates gene transcription. The overexpression of the MR is believed to contribute to fibrosis and inflammation.






Study to Evaluate the Efficacy (Effect on Disease) and Safety of Finerenone on Morbidity (Events Indicating Disease Worsening) & Mortality (Death Rate) in Participants With Heart Failure and Left Ventricular Ejection Fraction (Proportion of Blood Expelled Per Heart Stroke) Greater or Equal to 40% - Full Text View - ClinicalTrials.gov

# FIGARO-DKD (2023)

## Finerenone Reduces Risk of Incident Heart Failure in Patients With Chronic Kidney Disease and Type 2 Diabetes: Analyses From the FIGARO-DKD Trial

**Gerasimos Filippatos** ✉, **Stefan D. Anker**, **Rajiv Agarwal**, **Luis M. Ruilope**, **Peter Rossing**, **George L. Bakris**, **Christoph Tasto**, **Amer Joseph**, **Peter Kolkhof**, **Andrea Lage**, **Bertram Pitt** and **on behalf of the FIGARO-DKD Investigators**

**Originally published** 13 Nov 2021 | https://doi.org/10.1161/CIRCULATIONAHA.121.057983 | Circulation. 2022;145:437–447

Other version(s) of this article

### Abstract

#### Background:

Chronic kidney disease and type 2 diabetes are independently associated with heart failure (HF), a leading cause of morbidity and mortality. In the FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease) and FIGARO-DKD (Finerenone in Reducing Cardiovascular Mortality and Morbidity in Diabetic Kidney Disease) trials, finerenone (a selective, nonsteroidal mineralocorticoid receptor antagonist) improved cardiovascular outcomes in patients with albuminuric chronic kidney disease and type 2 diabetes. These prespecified analyses from FIGARO-DKD assessed the effect of finerenone on clinically important HF outcomes.



https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.057983

# FIGARO-DKD (2023)

**Results:**

Overall, 7352 patients were included in these analyses; 571 (7.8%) had a history of HF at baseline. New-onset HF was significantly reduced with finerenone versus placebo (1.9% versus 2.8%; hazard ratio [HR], 0.68 [95% CI, 0.50–0.93]; *P*=0.0162). In the overall population, the incidences of all HF outcomes analyzed were significantly lower with finerenone than placebo, including an 18% lower risk of cardiovascular death or first HHF (HR, 0.82 [95% CI, 0.70–0.95]; *P*=0.011), a 29% lower risk of first HHF (HR, 0.71 [95% CI, 0.56–0.90]; *P*=0.0043) and a 30% lower rate of total HHF (rate ratio, 0.70 [95% CI, 0.52–0.94]). The effects of finerenone on improving HF outcomes were not modified by a history of HF. The incidence of treatment-emergent adverse events was balanced between treatment groups.

**Conclusions:**

The results from these FIGARO-DKD analyses demonstrate that finerenone reduces new-onset HF and improves other HF outcomes in patients with chronic kidney disease and type 2 diabetes, irrespective of a history of HF.

**2023 Focused Update of the 2021 European Society of Cardiology (ESC)**

**In patients with T2DM and CKD, finerenone is recommended to reduce the risk of HF hospitalization (Class I, LOE A).**



https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.121.057983

# STEP-HFpEF (2023)

## Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity

Michael N. Kosiborod, M.D., Steen Z. Abildstrøm, Ph.D., Barry A. Borlaug, M.D., Javed Butler, M.D., Søren Rasmussen, Ph.D., Melanie Davies, M.D., O. Kiss, Hovingh, M.D., Ph.D., Dalane W. Kitzman, M.D., Marie L. Lindegaard, M.D., D.M.Sc., Daniël V. Verma, M.D., Ph.D., Sanjiv J. Shah, M.D., Marianne B. Treppendahl, M.D., Ph.D., et al., for the STEP-HFpEF Trial Committees and Investigators*

September 21, 2023
N Engl J Med 2023; 389:1069-1084
DOI: 10.1056/NEJMoa2306963



### Abstract

**BACKGROUND** Heart failure with preserved ejection fraction is increasing in prevalence and is associated with a high symptom burden and functional impairment, especially in persons with obesity. No therapies have been approved to target obesity-related heart failure with preserved ejection fraction.

**METHODS** We randomly assigned 529 patients who had heart failure with preserved ejection fraction and a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or higher to receive once-weekly semaglutide (2.4 mg) or placebo for 52 weeks. The dual primary end points were the change from baseline in the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS; scores range from 0 to 100, with higher scores indicating fewer symptoms and physical limitations) and the change in body weight. Confirmatory secondary end points included the change in the 6-minute walk distance; a hierarchical composite end point that included death, heart failure events, and differences in the change in the KCCQ-CSS and 6-minute walk distance; and the change in the C-reactive protein (CRP) level.

**RESULTS** The mean change in the KCCQ-CSS was 16.6 points with semaglutide and 8.7 points with placebo (estimated difference, 7.8 points; 95% confidence interval [CI], 4.8 to 10.9; P<0.001), and the mean percentage change in body weight was −13.3% with semaglutide and −2.6% with placebo (estimated difference, −10.7 percentage points; 95% CI, −11.9 to −9.4; P<0.001). The mean change in the 6-minute walk distance was 21.5 m with semaglutide and 1.2 m with placebo (estimated difference, 20.3 m; 95% CI, 8.6 to 32.1; P<0.001). In the analysis of the hierarchical composite end point, semaglutide produced more wins than placebo (win ratio, 1.72; 95% CI, 1.37 to 2.15; P<0.001). The mean percentage change in the CRP level was −43.5% with semaglutide and −7.3% with placebo (estimated treatment ratio, 0.61; 95% CI, 0.51 to 0.72; P<0.001). Serious adverse events were reported in 35 participants (13.3%) in the semaglutide group and 71 (26.7%) in the placebo group.

**CONCLUSIONS** In patients with heart failure with preserved ejection fraction and obesity, treatment with



Related Articles

EDITORIAL SEP 21, 2023
Heart Failure with Preserved Ejection Fraction — A Metabolic Disease*
Y.M. Pinto

ACOi 2023 October 11-14 Tampa • Hybrid

https://www.jwatch.org/na56490/2023/08/25/glp-1-agonist-therapy-heart-failure-with-preserved

# STEP-HFpEF (2023)

**GLP-1 Agonist Therapy for Heart Failure with Preserved Ejection Fraction and Obesity**

*Harlan M. Krumholz, MD, SM, reviewing Kosiborod MN et al. N Engl J Med 2023 Aug 25*
Interest in glucagon-like peptide-1 (GLP-1) agonists for the treatment of obesity is growing rapidly, and trials are showing cardiovascular benefit. Now, researchers report findings of an industry-sponsored, international, randomized, double-blind, placebo-controlled trial (STEP-HFpEF; NCT04788511. opens in new tab) that tested whether 2.4 mg of once-weekly subcutaneous semaglutide can improve symptoms and physical function among people with heart failure with preserved systolic function (HFpEF) and obesity.

**COMMENT**
STEP-HFpEF is another big win for semaglutide, coming on the heels of a recent announcement on August 8 that the yet-to-be-published SELECT trial, a secondary prevention trial, has shown that semaglutide can reduce the risk for major cardiovascular events in people with obesity. With STEP-HFpEF findings, we now have an evidence-based therapy for people with obesity who are suffering from HFpEF, and its side effect profile is quite reassuring. Future studies need to assess treatment in more-diverse populations, and for longer time periods. For now, this study is a major contribution and should provide hope to the many people suffering from HFpEF and obesity.

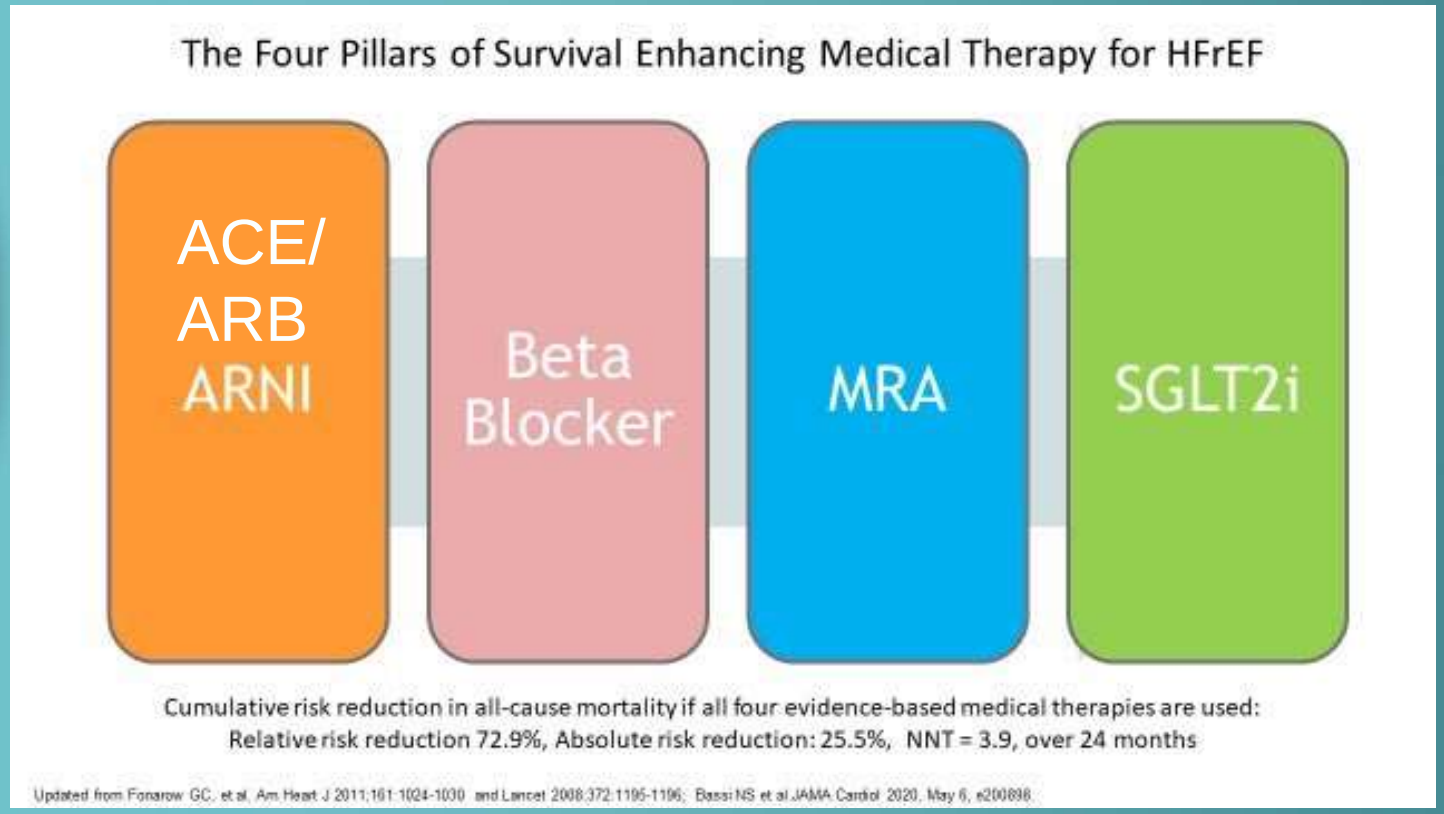
.



https://www.jwatch.org/na56490/2023/08/25/glp-1-agonist-therapy-heart-failure-with-preserved

# Summary

# Current Recommendations for Treatment of HFrEF



# Summary

In patients with HFrEF (LVEF <40 percent) Stage C Treatment

Recommend GDMT based on the 2021 ACC Expert Consensus

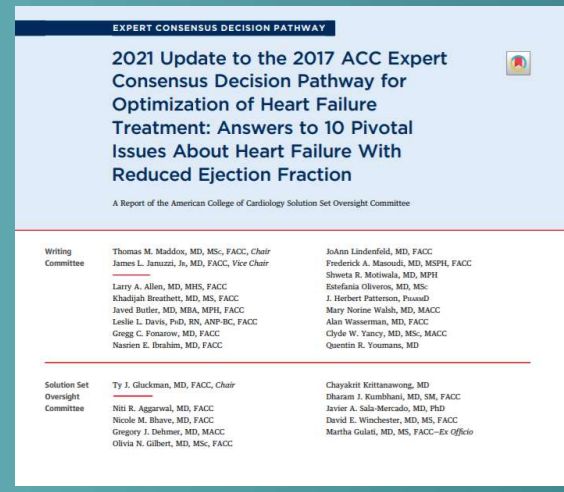
ACE/ARB/ARNI (preferred) AND Evidence based beta blocker

Then (in no particular order)

-sodium-glucose co-transporter 2 (SGLT2) inhibitor (Cr > 20)

-mineralocorticoid receptor antagonist (MRA) (Cr CL >30 Cr < 2-2.5 and K < 5)

-diuretics, ivabradine, isosorbide/hydralazine



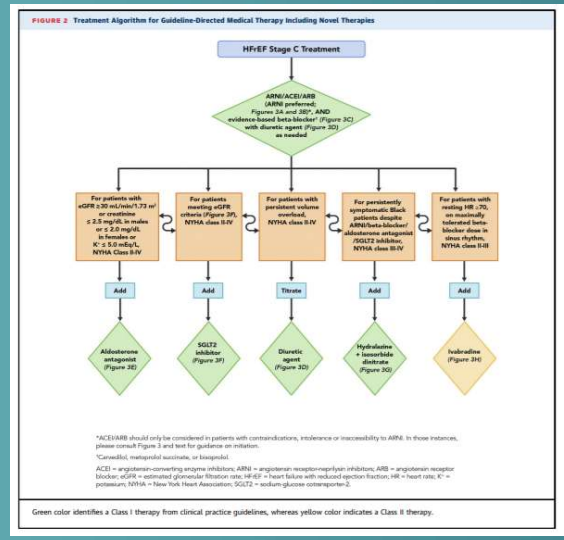
EXPERT CONSENSUS DECISION PATHWAY

2021 Update to the 2017 ACC Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment: Answers to 10 Pivotal Issues About Heart Failure With Reduced Ejection Fraction

A Report of the American College of Cardiology Solution Set Oversight Committee

Writing Committee: Thomas M. Maddox, MD, MSc, FACC, *Chair*; James L. Januzzi, Jr, MD, FACC, *Vice Chair*; Larry A. Allen, MD, MHS, FACC; Khadijah Breathett, MD, MS, FACC; Javed Butler, MD, MBA, MPH, FACC; Leslie L. Davis, PsD, RN, ANP-BC, FACC; Gregg C. Fonarow, MD, FACC; Nasrien E. Ibrahim, MD, FACC; JoAnn Lindenfeld, MD, FACC; Frederick A. Masoudi, MD, MSPH, FACC; Shweta R. Motiwala, MD, MPH; Estefania Oliveros, MD, MSc; J. Herbert Patterson, PharmD; Mary Norine Walsh, MD, MACC; Alan Wasserman, MD, FACC; Clyde W. Yancy, MD, MSc, MACC; Quentin R. Youmans, MD

Solution Set Oversight Committee: Ty J. Gluckman, MD, FACC, *Chair*; Niti R. Aggarwal, MD, FACC; Nicole M. Bhave, MD, FACC; Gregory J. Dehmer, MD, MACC; Olivia N. Gilbert, MD, MSc, FACC; Chayakrit Krittanawong, MD; Dharam J. Kumbhani, MD, SM, FACC; Javier A. Sala-Mercado, MD, PhD; David E. Winchester, MD, MS, FACC; Martha Gulati, MD, MS, FACC–*Ex Officio*

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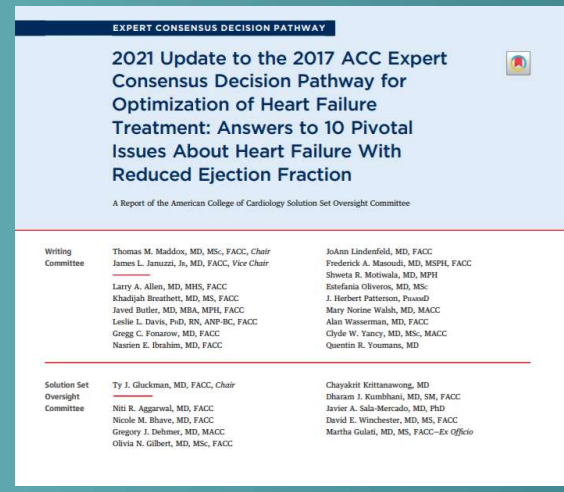
# Summary

Achieving target or max doses is not necessary before adding SGLTI

Up titration of meds should occur even if patients stable and EF improving



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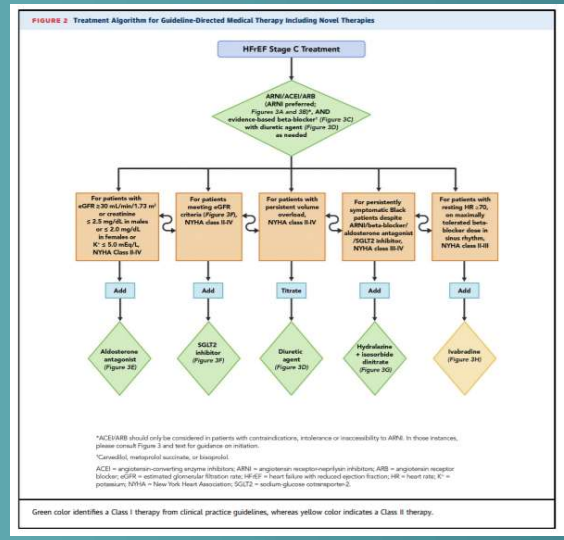

FIGURE 2 Treatment Algorithm for Guideline-Directed Medical Therapy Including Novel Therapies

HFrEF Stage C Treatment

ARNI/ACEI/ARB (ARNI preferred; Figures 2A and 2B*), AND evidence-based beta-blocker† (Figure 2C) with diuretic agent (Figure 2D) as needed

For patients with eGFR ≥ 30 mL/min/1.73 m² or creatinine ≤ 2.5 mg/dL in males or ≤ 2.0 mg/dL in females or K+ ≤ 5.0 mEq/L, NYHA Class II-IV

For patients meeting eGFR criteria (Figure 2F), NYHA class II-IV

For patients with persistent volume overload, NYHA class II-IV

For persistently symptomatic Black patients despite ARNI/beta-blocker/aldosterone antagonist /SGLT2 inhibitor, NYHA class III-IV

For patients with resting HR ≥ 70, on maximally tolerated beta-blocker dose in sinus rhythm, NYHA class II-III

Add → Aldosterone antagonist (Figure 2E)

Add → SGLT2 inhibitor (Figure 2F)

Titrate → Diuretic agent (Figure 2D)

Add → Hydralazine + isosorbide dinitrate (Figure 2G)

Add → Ivabradine (Figure 2H)

*ACEI/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI. In those instances, please consult Figure 1 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.

Green color identifies a Class I therapy from clinical practice guidelines, whereas yellow color indicates a Class II therapy.

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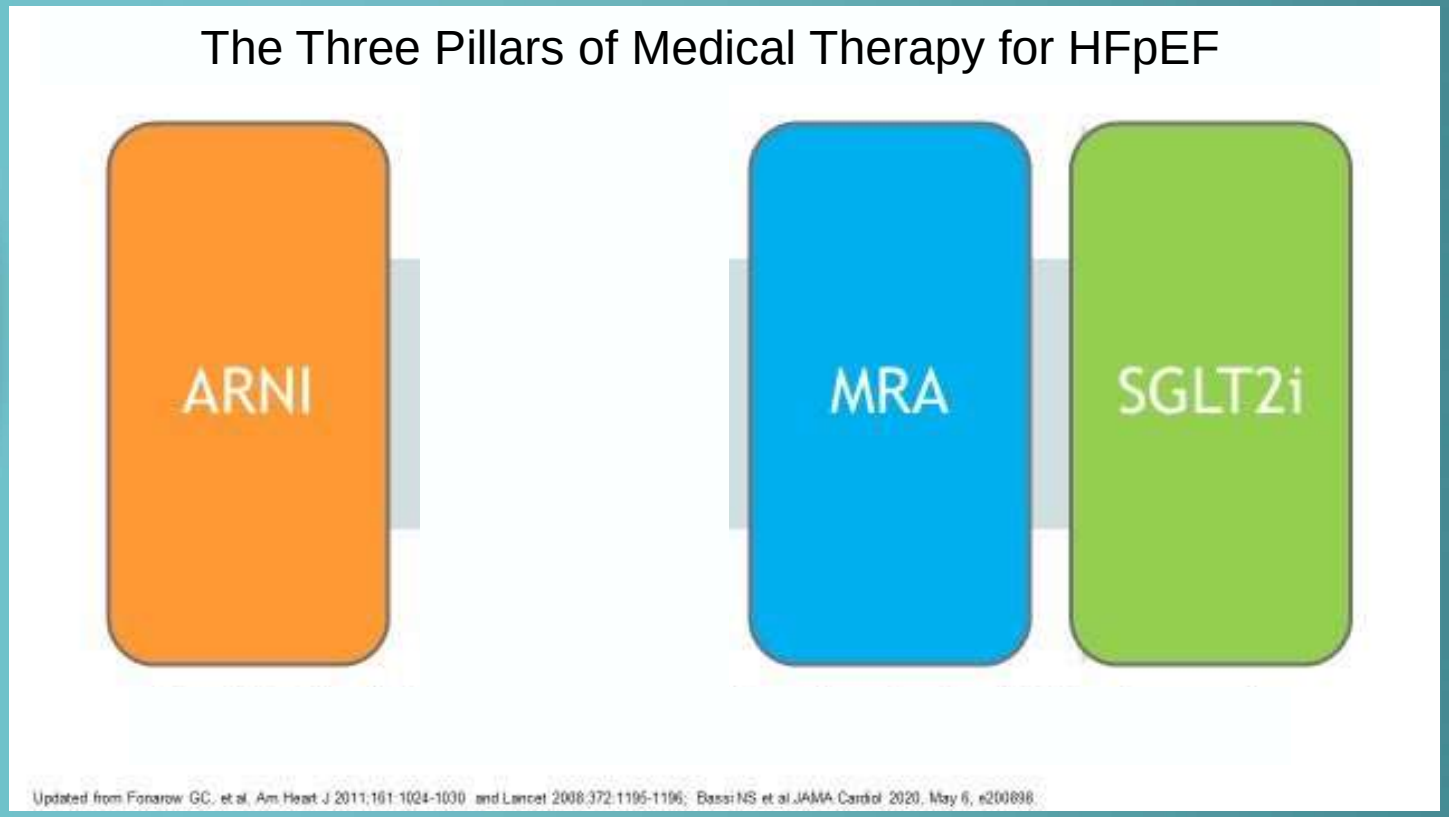
# Current Recommendations for Treatment of HFpEF



# Summary

In patients with HFpEF (LVEF ≥50 percent) who have New York Heart Association (NYHA) class II to III symptoms and who have an elevated B-type natriuretic peptide level (BNP; ie, BNP >100 pg/dL or N-terminal pro-BNP [NT-proBNP] >300 pg/dL).

Recommend treatment with both a sodium-glucose co-transporter 2 (SGLT2) inhibitor and a mineralocorticoid receptor antagonist (MRA) rather than:

-or other agents (eg, ARNI or ARB)

- rather than non HFpEF-specific therapy or either treatment alone

# Summary

In patients with preexisting therapies for diabetes and/or chronic kidney disease (CKD) is guided by the following general principles:

Recommend starting an SGLT2 inhibitor first and then add the MRA two weeks later if the patient tolerates initial therapy.

Consider monotherapy if HF symptoms resolve or if the BNP decreases in response to initial therapy.

No direct data to suggest that use of both therapies has an additive effect in reducing the risk of HF hospitalization.

# Summary

Regardless of which agent is used first, monitor for intolerance to the initial agent for approximately two weeks before starting a second agent.

In patients in whom starting an SGLT2 inhibitor or an MRA would interfere with an existing treatment, start a HFpEF-specific therapy if the benefit of the HFpEF-specific therapy is greater than the benefit of the therapy that it would replace.

# Thank You For Your Attention!

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# PRESERVED-HF (2021)

## Inclusion Criteria

- HF with NYHA class II-IV symptoms (with or without T2D)
- Left Ventricular Ejection Fraction ≥ 45%
- NTproBNP ≥ 225 pg/mL (or BNP ≥ 75 pg/mL)*
- Requirement for diuretic therapy
- At least one of the following
  - Recent HF hospitalization or urgent HF visit requiring IV diuretic
  - Elevated filling pressures by right or left heart catheterization
  - Structural heart disease by echocardiography

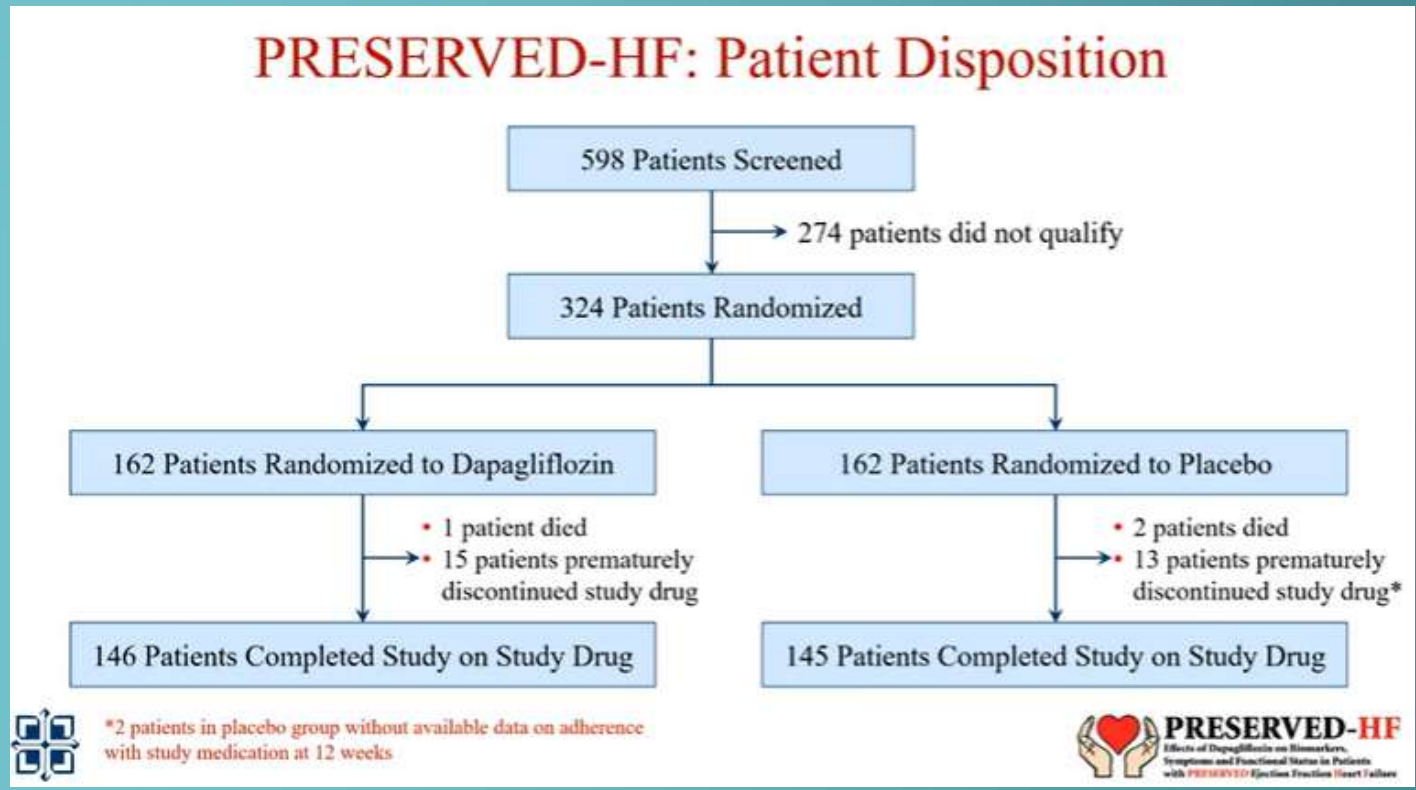
*in patients with Atrial Fibrillation, NTproBNP ≥ 375 pg/mL or BNP ≥ 100 pg/mL

PRESERVED-HF



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)

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The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)

## Baseline Characteristics

| Baseline Characteristics | Dapagliflozin (n = 162) | Placebo (n = 162) | P-Value |
|---|---|---|---|
| **Demographics** | | | |
| Age (years) | 69 (64, 77) | 71 (63, 78) | 0.44 |
| Women | 92 (57%) | 92 (57%) | 1.00 |
| White | 108 (67%) | 109 (69%) | 0.91 |
| African American | 50 (31%) | 47 (30%) | |
| **Medical History** | | | |
| Duration of Heart Failure (years) | 3.0 (1.1, 6.5) | 3.2 (1.0, 6.6) | 0.20 |
| Prior Hospitalization for Heart Failure | 98 (61%) | 83 (51%) | 0.09 |
| Ejection Fraction (%) | 60 (55, 65) | 60 (54, 65) | 0.89 |
| Ischemic Heart Disease | 32 (20%) | 31 (19%) | 0.89 |
| Type 2 Diabetes | 90 (56%) | 91 (56%) | 0.91 |
| Atrial Fibrillation | 82 (51%) | 89 (55%) | 0.44 |
| ICD | 7 (4%) | 9 (6%) | 0.61 |

PRESERVED-HF



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)

## Baseline Characteristics

*Baseline HF/CV Medications*

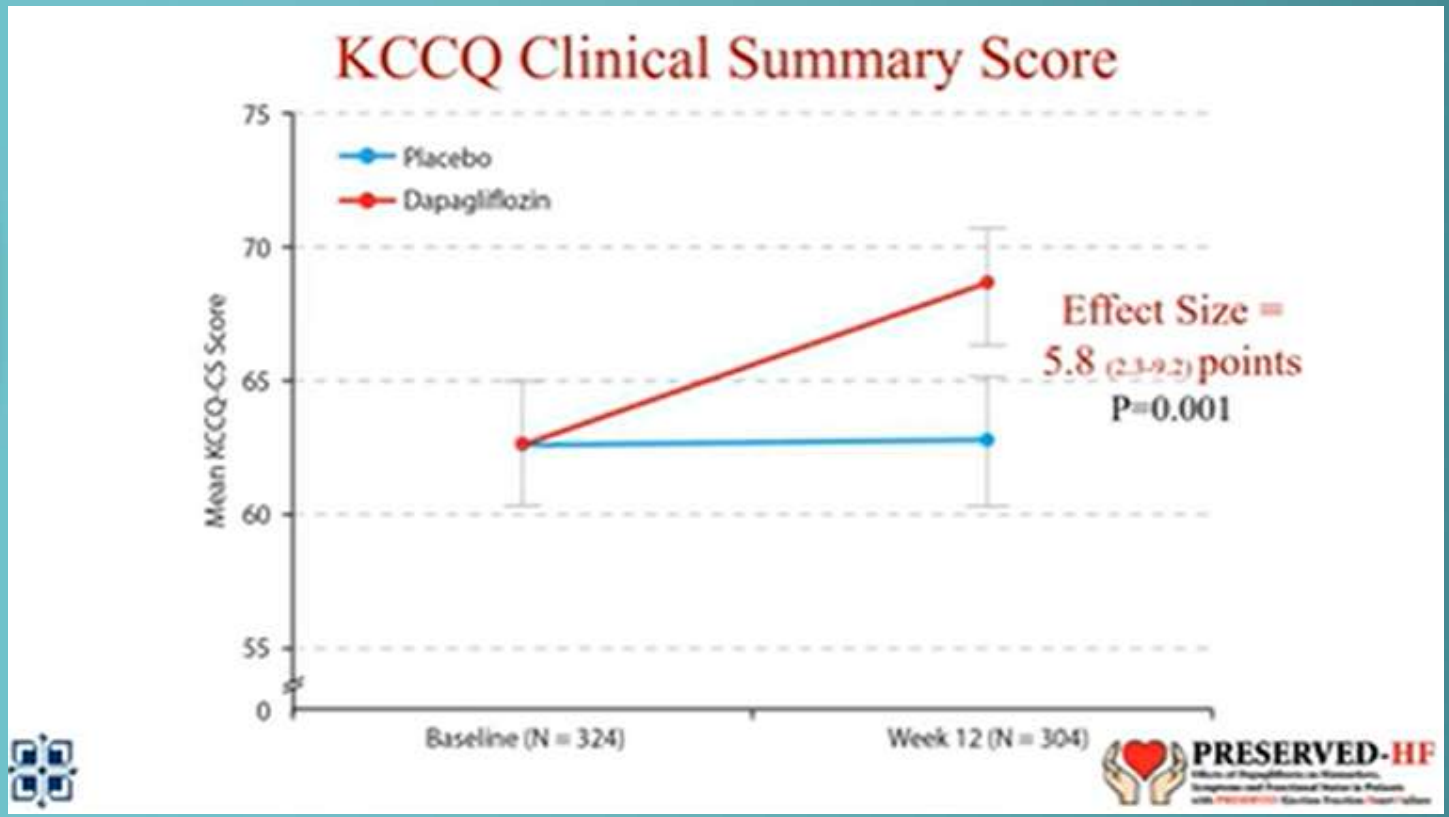
| Baseline Characteristics | Dapagliflozin (n = 162) | Placebo (n = 162) | P-Value |
|---|---|---|---|
| **Baseline HF/CV Medications** | | | |
| ACE Inhibitor/ARB | 98 (61%) | 98 (61%) | 1.00 |
| ARNI | 2 (1.2%) | 3 (1.9%) | |
| Beta Blockers | 119 (74%) | 116 (72%) | 0.71 |
| Hydralazine | 25 (15%) | 18 (11%) | 0.25 |
| Long Acting Nitrates | 34 (21%) | 27 (17%) | 0.32 |
| MRA | 50 (31%) | 68 (42%) | 0.04 |
| Loop Diuretics | 151 (93%) | 135 (83%) | 0.01 |
| Lipid Lowering Agents | 132 (82%) | 127 (78%) | 0.49 |
| Anticoagulant Agents | 71 (44%) | 84 (52%) | 0.15 |

PRESERVED-HF



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)






The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# PRESERVED-HF (2021)

## Safety*

| | Dapagliflozin (n = 162) | Placebo (n = 162) |
|---|---|---|
| All reported adverse events | 44 (27%) | 38 (24%) |
| Serious adverse event | 31 (19%) | 22 (14% ) |
| Adverse events resulting in discontinuation of study medication | 18 (11%) | 15 (9%) |
| Drug adverse events | 7 (4%) | 8 (5%) |
| All cause death | 1 (0.6%) | 2 (1.2%) |
| Non-fatal MI | 0 (0%) | 1 (0.6%) |
| Stroke | 0 (0.0%) | 1 (0.6%) |
| Acute kidney injury | 5 (3%) | 5 (3%) |
| Diabetic ketoacidosis | 0 (0%) | 0 (0%) |
| Volume depletion events | 11 (7%) | 7 (4%) |
| Severe hypoglycemic events | 0 (0%) | 0 (0%) |
| Lower limb amputations | 0 (0%) | 0 (0%) |

*patients with events

PRESERVED-HF



The PRESERVED-HF Study – Main Study Presentation and Discussion | USC Journal

# DELIVER (2022)

## CENTRAL ILLUSTRATION: Baseline Characteristics of Participants Enrolled in DELIVER

### The DELIVER Trial

6,263 participants with symptomatic HF and LVEF >40%

353 sites across 20 countries worldwide

Randomized to dapagliflozin 10 mg once daily or matching placebo

**Older symptomatic cohort**
- Age 72 ± 10 years
- 44% women
- 75% NYHA class II

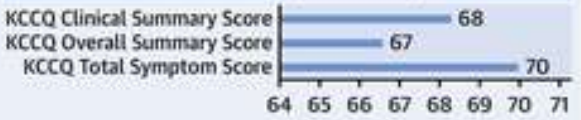
**Elevated risk**
- Median NT-proBNP 1,011 pg/mL
- 16% enrolled during or within 90 days of hospitalization

**High proportion of comorbidities**
- 45% T2D
- 45% BMI ≥30 kg/m²
- 57% with history of AF/AFL

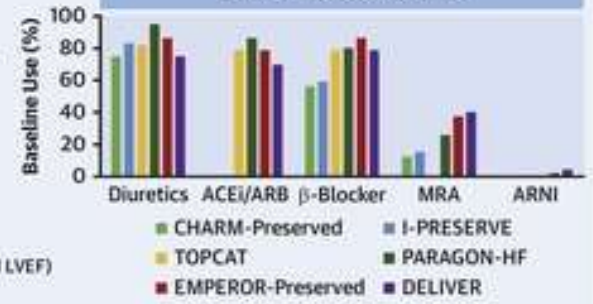
**Well-represented LVEF groups**
- LVEF 41%–49%: 34%
- LVEF 50%–59%: 36%
- LVEF ≥60%: 30%

(including 18% with HF improved LVEF)

**Moderate Baseline Symptomatic Impairment**




**High Use of HF Medical Therapies, Aligned With Other Contemporary Trials**




DELIVER is the largest and broadest clinical trial of this population to date and enrolled high-risk, well-treated patients with HF with mildly reduced and preserved LVEF. *(Clinical Trial Registration: NCT03619213; Funded by AstraZeneca)*

Solomon, S.D. et al. J Am Coll Cardiol HF. 2022;10(3):184–197.



https://www.jacc.org/doi/pdf/10.1016/j.jchf.2021.11.006

# DELIVER (2022)

Dapagliflozin in heart failure with preserved and mildly reduced ejection fraction: rationale and design of the DELIVER trial

Methods
Dapagliflozin Evaluation to Improve the LIVEs of Patients With PReserved Ejection Fraction Heart Failure (DELIVER) is an international, multicentre, parallel group, event-driven, randomized, double-blind trial in patients with chronic heart failure and left ventricular ejection fraction (LVEF) >40%, comparing the effect of dapagliflozin 10 mg once daily, vs. placebo, in addition to standard of care. Patients with or without diabetes, with signs and symptoms of heart failure, a LVEF >40%, elevation in natriuretic peptides and evidence of structural heart disease are eligible.

The primary endpoint is time-to-first cardiovascular death or worsening heart failure event (heart failure hospitalization or urgent heart failure visit), and will be assessed in dual primary analyses – the full population and in those with LVEF <60%. The study is event-driven and will target 1117 primary events. A total of 6263 patients have been randomized.



https://doi.org/10.1002/ejhf.2249

# DELIVER (2022)

## Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Solomon SD et al. DOI: 10.1056/NEJMoa2206286

**CLINICAL PROBLEM**

Clinical guidelines recommend the use of sodium–glucose cotransporter 2 (SGLT2) inhibitors in patients with chronic heart failure and a reduced ejection fraction (a left ventricular ejection fraction of ≤40%), but the benefits in patients with a higher ejection fraction are less certain.

**CLINICAL TRIAL**

**Design:** An international, double-blind, randomized, placebo-controlled trial examined the efficacy and safety of the SGLT2 inhibitor dapagliflozin in patients with stabilized heart failure and a mildly reduced or preserved ejection fraction.

**Intervention:** 6263 patients 40 years of age or older with a left ventricular ejection fraction of more than 40% were assigned to receive either dapagliflozin (10 mg once daily) or placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (an unplanned hospitalization for heart failure or an urgent visit for heart failure) or cardiovascular death.

**RESULTS**

**Efficacy:** Overall, during a median follow-up of 2.3 years, a primary-outcome event occurred in significantly fewer patients in the dapagliflozin group than in the placebo group. A similar benefit was observed in a subgroup of patients with a left ventricular ejection fraction of less than 60%.

**Safety:** The incidence of serious adverse events was similar in the two groups.

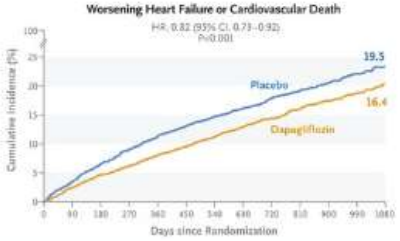
**LIMITATIONS AND REMAINING QUESTIONS**

- Less than 5% of the patients enrolled were Black.
- All the subgroups were underpowered, so findings within subgroups should be interpreted with caution.
- Trials in higher-risk populations, or of longer duration, are needed to better assess the benefits of dapagliflozin with respect to mortality.

Links: Full Article | NEJM Quick Take | Editorial

**Dapagliflozin**
10 mg daily
Usual therapy

**Placebo**
Daily
Usual therapy





**CONCLUSIONS**

The SGLT2 inhibitor dapagliflozin reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction, with no excess of adverse events.



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https://www.google.com/search?q=Dapagliflozin+in+Heart+Failure+with+Mildly+Reduced+or+Preserved+Ejection+Fraction&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjR0NfulsX6AhWajYkEHQCFDxAQ_AUoAnoECAEQBA&biw=1536&bih=754&dpr=1.25#imgrc=-3pQhYqE0bDxyM

# DELIVER (2022)

## Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction

Scott D. Solomon, M.D., John J. V. McMurray, M.D., Brian Claggett, Ph.D., Rudolf A. de Boer, M.D., David DeMets, Ph.D., Adrian F. Hernandez, M.D., Silvio E. Inzucchi, M.D., Mikhail N. Kosiborod, M.D., Carolyn S.P. Lam, M.D., Felipe Martinez, M.D., Sanjiv J. Shah, M.D., Akshay S. Desai, M.D., et al., for the DELIVER Trial Committees and Investigators*

September 22, 2022

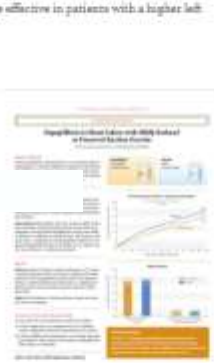

### Abstract

**BACKGROUND** Sodium–glucose cotransporter 2 (SGLT2) inhibitors reduce the risk of hospitalization for heart failure and cardiovascular death among patients with chronic heart failure and a left ventricular ejection fraction of 40% or less. Whether SGLT2 inhibitors are effective in patients with a higher left ventricular ejection fraction remains less certain.

**METHODS** We randomly assigned 6263 patients with heart failure and a left ventricular ejection fraction of more than 40% to receive dapagliflozin (at a dose of 10 mg once daily) or matching placebo, in addition to usual therapy. The primary outcome was a composite of worsening heart failure (which was defined as either an unplanned hosp
visit for heart fai
assessed in a time-to-event analysis.

**RESULTS** Over a median of 2.3 years, the primary outcome occurred in 512 of 3131 patients (16.4%) in the dapagliflozin group and in 610 of 3132 patients (19.5%) in the placebo group (hazard ratio, 0.82; 95% confidence interval [CI], 0.73 to 0.92; P=0.001). Worsening heart failure occurred in 368 patients (11.8%) in the dapagliflozin group and in 455 patients (14.5%) in the placebo group (hazard ratio, 0.79; 95% CI, 0.69 to 0.91); cardiovascular death occurred in 231 patients (7.4%) and 261 patients (8.3%), respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05). Total events and symptom burden were lower in the dapagliflozin group than in the placebo group. Results were similar among patients with a left ventricular ejection fraction of 60% or more and those with a left ventricular ejection fraction of less than 60%, and results were similar in prespecified subgroups, including patients with or without diabetes. The incidence of adverse events was similar in the two groups.

**CONCLUSIONS** Dapagliflozin reduced the combined risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction. (Funded by AstraZeneca; DELIVER ClinicalTrials.gov number, NCT03619213.)



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