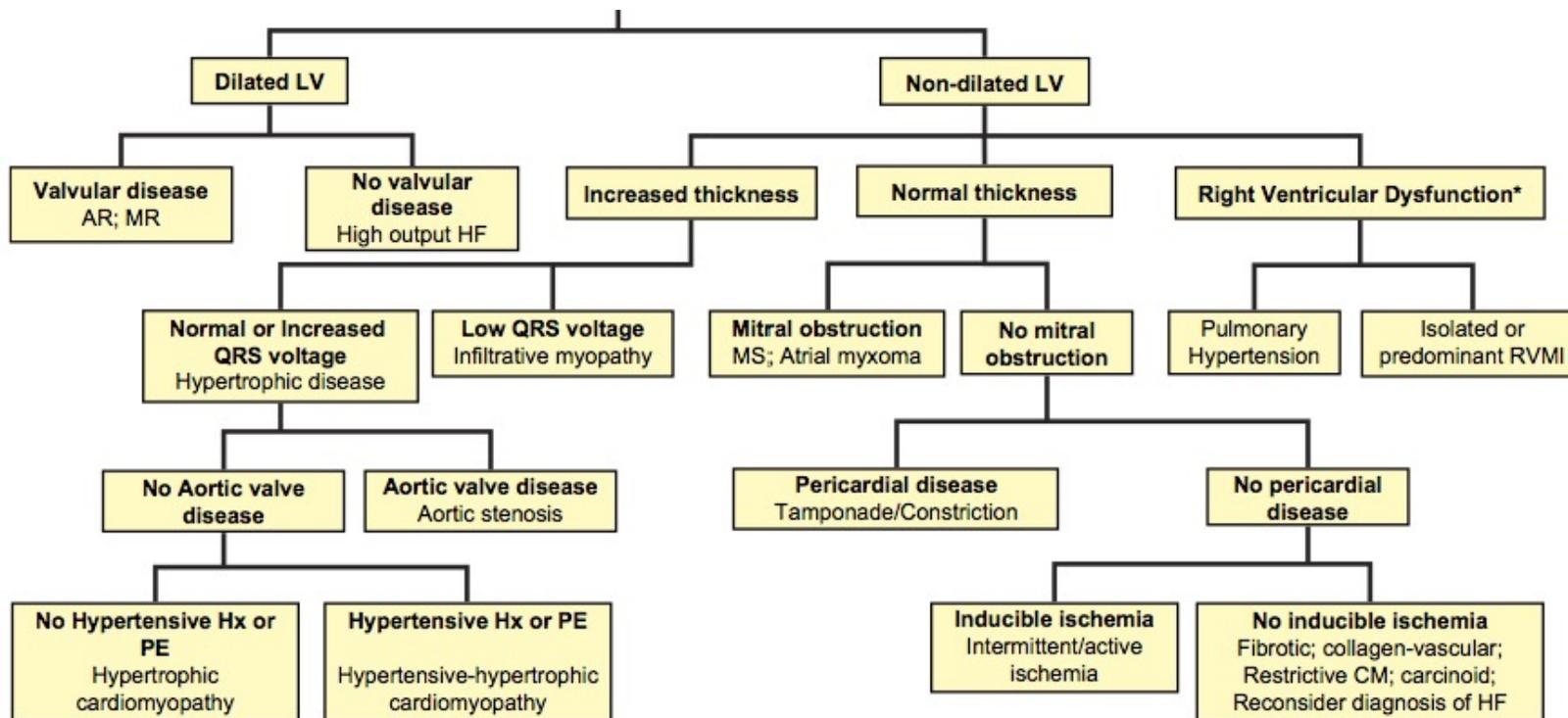


# “HFpEF” aka **it’s complicated**

Causes of “HFpEF”



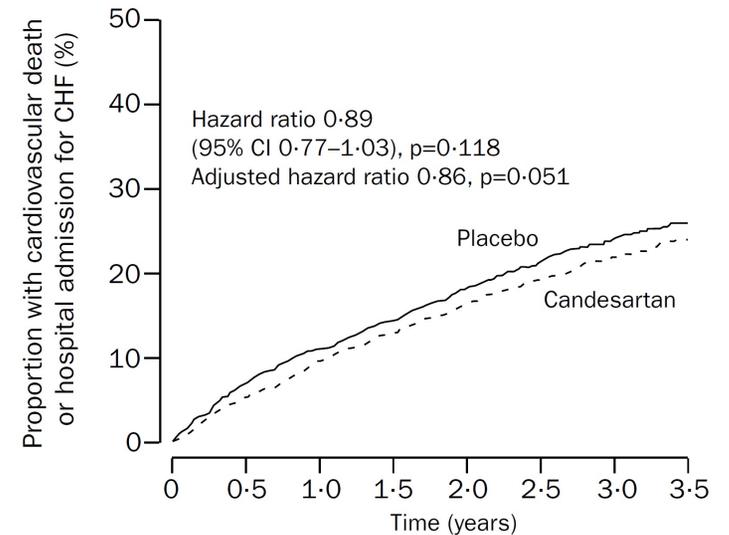
# Medications in HFpEF: **Fail Trail**

	HFrEF	HFpEF
Beta-blockers	✓	<b>X</b> SENIORS
Digoxin	✓	<b>X</b> DIG
Nitrates	✓ (+hydralazine)	<b>X</b> NEAT
Vericiguat	✓	<b>X</b> CAPACITY,VITALITY
ACEI/ARB	✓	?CHARM-Preserved <b>X</b> I-PRESERVE,PEP-HF
MRA	✓	?TOPCAT
ARNI	✓	?PARAGON-HF
SGLT2i	✓	✓EMPEROR-Preserved, SOLOIST-WHF

# \*Evidence Minute\*

## CHARM-Preserved – Candesartan in HFpEF/HFmrEF

<b>D</b>	Allocation-concealed, blinded RCT
<b>P</b>	3025 patients with symptomatic HF & EF >40% (mean 54%)
<b>I</b>	Candesartan (starting 4-8 mg/d, target 32 mg/d)
<b>C</b>	Placebo
<b>O</b>	At median 3 y <ul style="list-style-type: none"> <li>• <b>1<sup>o</sup> outcome</b> ↔ Cande 22% vs placebo 24.3%</li> <li>• <b>HF hospitalization ↓3.3%</b> (15.2% vs 18.5%)</li> </ul>

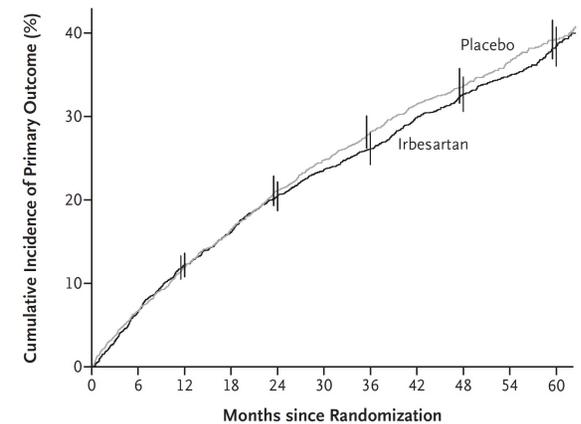


	<b>Candesartan (n=1514)</b>	<b>Placebo (n=1509)</b>	<b>p</b>
<b>Cause of discontinuation</b>			
Hypotension	37 (2.4%)	17 (1.1%)	0.009
Increase in creatinine	72 (4.8%)	36 (2.4%)	0.0005
Hyperkalaemia	22 (1.5%)	9 (0.6%)	0.029
Any adverse event or laboratory abnormality	270 (17.8%)	204 (13.5%)	0.001

# \*Evidence Minute\*

## I-PRESERVE – Irbesartan in HFpEF/HFmrEF

- D** Allocation-concealed, blinded RCT
- P** 4563 patients with symptomatic HF (NYHA 3 77%) & EF ≥45% (mean 60%)
- I** Irbesartan (starting 75 mg/d, target 300 mg/d)
- C** Placebo
- O** At mean 4.1 y
  - **1° (death/CV hospitalization)** ↔ Irbe 36% vs placebo 37%
  - **Death** ↔ (HR 1.00, 0.88-1.14)
  - **HF hospitalization** ↔ (HR 0.95, 0.81-1.10)



**Table 4. Drug Discontinuations and Adverse Events.**

Variable	Placebo (N=2061)	Irbesartan (N=2067)	P Value
	<i>no. (%)</i>		
Discontinuation of the study drug*			
Any reason	684 (33)	702 (34)	0.60
Adverse event	288 (14)	331 (16)	0.07
Patient's choice	223 (11)	208 (10)	0.43
Serious adverse event			
Hypotension	62 (3)	60 (3)	0.84
Renal failure	57 (3)	69 (3)	0.29
Hyperkalemia	9 (<1)	12 (<1)	0.34

NEJM 2008;359:2456-67

## \*Evidence Minute\*

# TOPCAT – Spironolactone in HFpEF/HFmrEF

**D** Allocation-concealed, blinded RCT

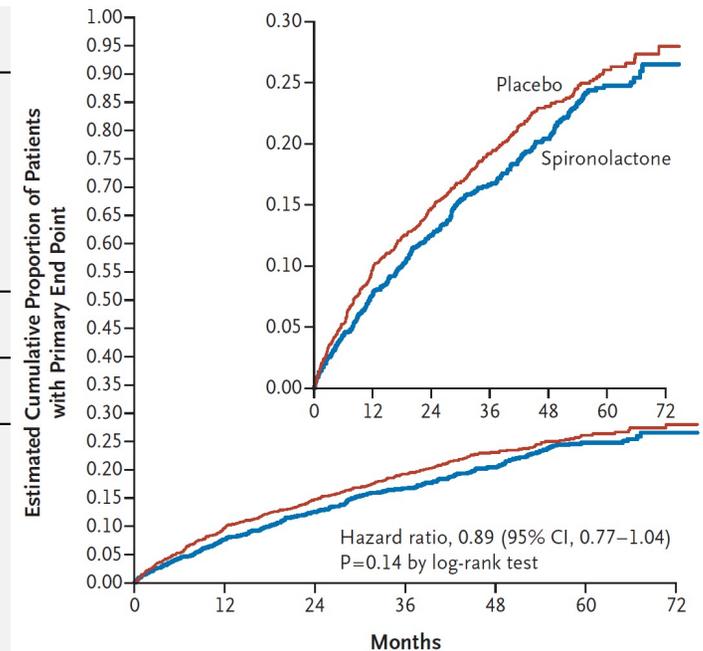
**P** 3445 patients with symptomatic HF  
& EF  $\geq$ 45% (mean 55%)  
Either HF hospitalization in last year or elevated BNP  
“Controlled” systolic BP (<140 mm Hg, or <160 with  $\geq$ 3 BP meds)

**I** Spironolactone (starting 15 mg/d, target 45 mg/d)

**C** Placebo

**O** At mean 3.3 y

- **1° (CV death/aborted cardiac arrest/HF hospitalization)**  
↔
- **HF hospitalization  $\downarrow$ 2.2%** 12% vs 14.2% (HR 0.83, 0.69-0.99)



# \*Evidence Minute\*

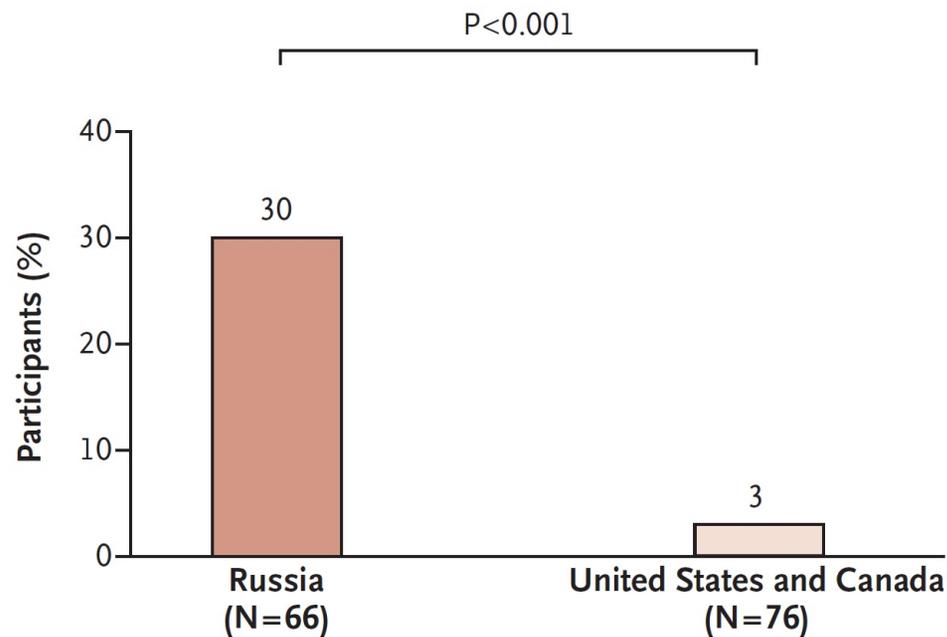
## TOPCAT controversy

Large regional differences in characteristics & outcomes of patients enrolled in Americas vs Russia/Georgia

Outcome	Americas (n=1767)			Russia/Georgia (n=1678)			P, Regional Difference*	P, Treatment-by-Region Interaction
	No. (%) With Event [Incidence Rate per 100 patient-y]		HR (95% CI) P Value	No. (%) With Event [Incidence Rate per 100 patient-y]		HR (95% CI) P Value		
	Spirolactone (n=886)	Placebo (n=881)		Spirolactone (N=836)	Placebo (N=842)			
Primary outcome	242 (27.3) [10.4] <b>↓4.5%</b>	280 (31.8) [12.6]	0.82 (0.69–0.98) 0.026	78 (9.3) [2.5]	71 (8.4) [2.3]	1.10 (0.79–1.51) 0.58	<0.001	0.12
Hyperkalemia‡ (potassium ≥5.5 mmol/L)	223 (25.2) <b>↑6.7%</b>	78 (8.9)	OR=3.46 (2.62–4.56) <0.001	99 (11.8)	79 (9.4)	OR=1.30 (0.95–1.77) 0.10	0.71	<0.001

# TOPCAT controversy: **The plot thickens**

Participants Who Reported Taking Spironolactone but Had No Detectable Canrenone Concentration



Canrenone = active metabolite of spironolactone with  $t_{1/2} \sim 16h$

# \*Evidence Minute\*

## PARAGON-HF – Sacubitril-valsartan in HFpEF/HFmEF

- D** Allocation-concealed, blinded RCT  
Active run-in phase (~16% excluded before randomized)

---

- P** n=4822 HF, EF ≥45% (median 57%)  
+ ↑ natriuretic peptides/recent HF hospitalization  
+ left atrial enlargement/LV hypertrophy on echo

---

- I** Sacubitril-valsartan 97/103 mg BID

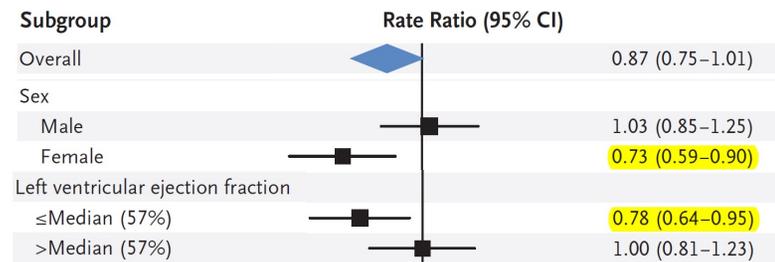
---

- C** Valsartan 160 mg BID

---

- O** At median 3 y:
  - **1° (CV death/1<sup>st</sup>+recurrent HF hospitalization)**  
↔ Sac-val 12.8%/y vs val 14.6%/y
  - **Death ↔**
  - **Clinically important QoL ↑ 33% vs 30% (OR 1.30, 1.04-1.61)**

Of 14 subgroup analyses reported, 2 focused on...



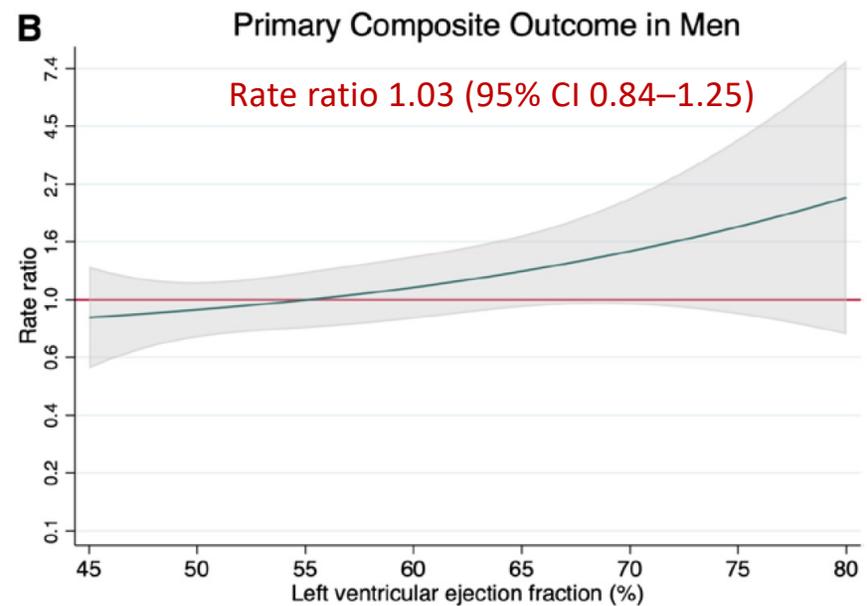
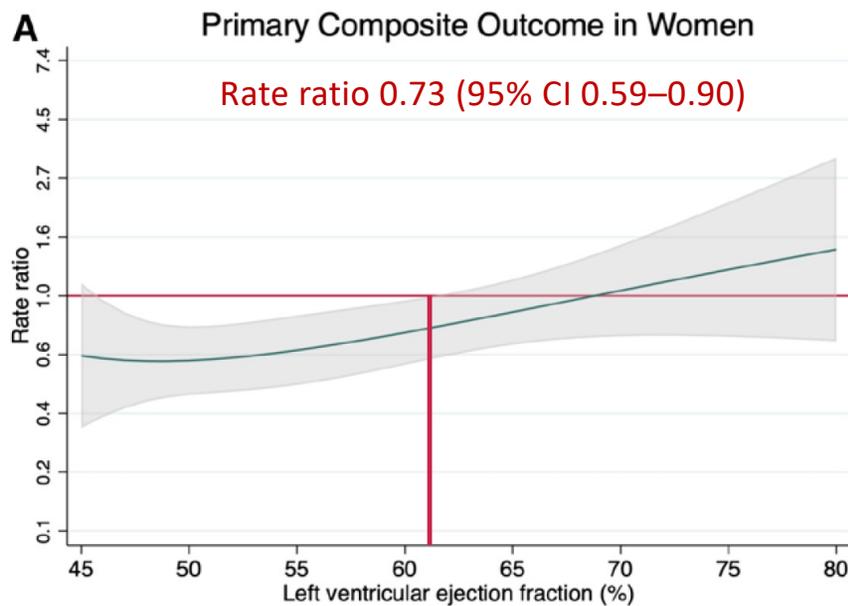
Feb 2021: FDA expanded label indication for sac-val to include any LVEF

- RECENT MAJOR CHANGES-----
- Indications and Usage, Adult Heart Failure (1.1) 2/2021
- INDICATIONS AND USAGE-----
- ENTRESTO is indicated:
- to reduce the risk of cardiovascular death and hospitalization for heart failure in adult patients with chronic heart failure. Benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal. (1.1).

# PARAGON-HF:

## Benefit probably depends on LVEF & sex

P-interaction= .017 for sex



# \*Evidence Minute\*

## EMPEROR-Preserved – SGLT2i in HFpEF/HFmrEF

**D** Allocation-concealed, blinded RCT

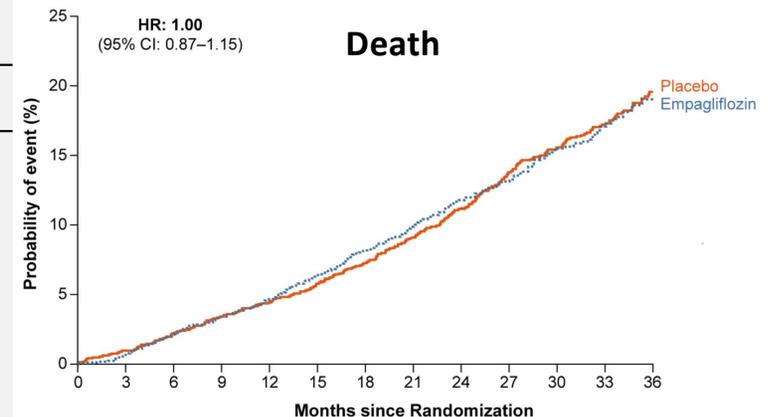
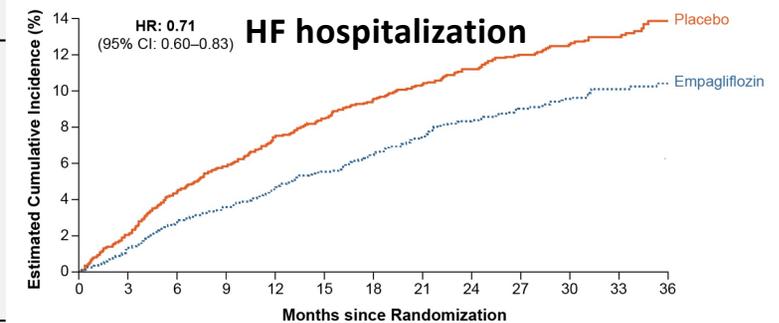
**P** n=5988 NYHA 2-4 HFpEF/mrEF (mean LVEF 54%) & no prior LVEF  $\leq$ 40%  
+ elevated NT-proBNP + (LAE/LVH on echo or recent HF hospitalization)  
Beta-blocker 86%, ACEI/ARB 79%, ARNI ~2%, MRA ~38%, digitalis 10%  
Exclusions: SBP <100, eGFR <20, type 1 diabetes, prior ketoacidosis

**I** Empagliflozin 10 mg qAM

**C** Placebo

**O** At median 2.2 y

- **1<sup>o</sup> outcome (CV death/HF hospitalization) ↓3.3%**
- **Death ↔**
- **Symptomatic hypotension ↑1.4%**
- **Genital infection ↑1.5%**
- **UTI ↑1.8%**



# EMPEROR-Preserved

## HF vs non-HF hospitalizations



**Empagliflozin**

**Placebo**

■ HF hospitalizations

■ Other hospitalizations

## \*Evidence Minute\*

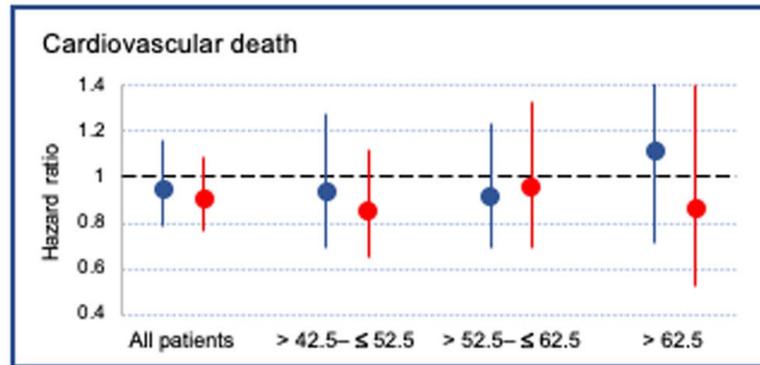
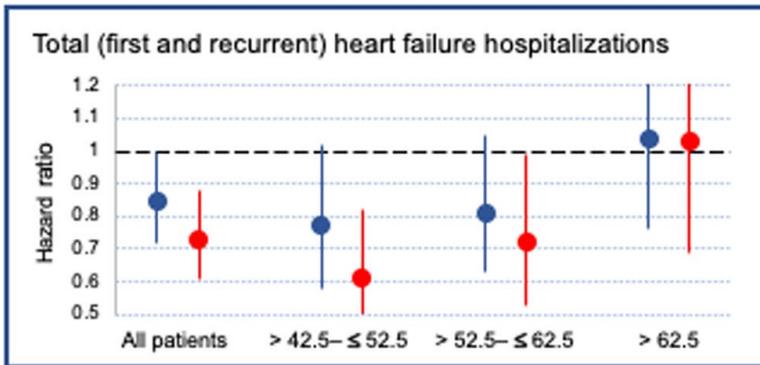
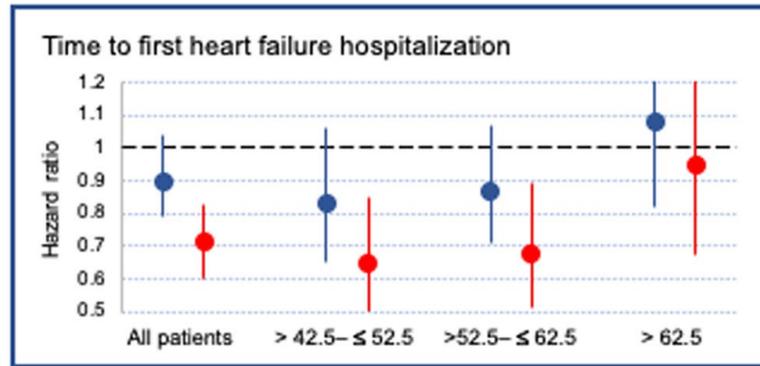
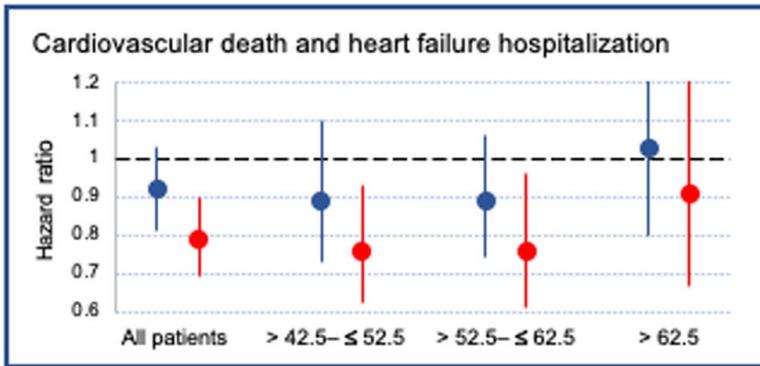
### EMPEROR-Preserved – Other outcomes

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%	<b>0.92 (0.85-0.99); -2.6%</b>
Total* hospitalizations for any cause	2566	2768	0.93 (0.85-1.01)
Total* HF hospitalizations	407	541	<b>0.73 (0.61-0.88)</b>
1° outcome (Time to 1 <sup>st</sup> HF hospitalization or CV death)	13.8%	17.1%	<b>0.79 (0.69-0.90); -3.3%</b>
1 <sup>st</sup> HF hospitalization	8.6%	11.8%	<b>0.71 (0.60-0.83); -3.2%</b>
Change in KCCQ clinical summary score at 1 y	+4.5	+3.2	<b>+1.3 (+0.45 to +2.2)</b>
eGFR mean change/y	-1.25	-2.62	<b>+1.36 (+1.06-1.66)</b>

\*First & recurrent

NEJM 2021;385:1451-61  
Circulation 2021;144:1284-94

# EMPEROR-Preserved vs PARAGON-HF across the spectrum of HFpEF/HFmrEF



● PARAGON-HF    ● EMPEROR-Preserved

# HFpEF pharmacotherapy

## Guideline recommendations

### Canadian

2017

- **Loop diuretics** to treat congestion
- **Treat HTN** per HTN Canada
- Consider **candesartan** to reduce HF hospitalizations (Weak Recommendation; Moderate-Quality Evidence)
- Consider **MRA** if  $K<5$  &  $eGFR>30$  (Weak Recommendation; Moderate-Quality Evidence)

2020: No new recommendations

### European

(published on same weekend as EMPEROR-Preserved)

#### Recommendations for the treatment of patients with heart failure with preserved ejection fraction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Screening for, and treatment of, aetiologies, and cardiovascular and non-cardiovascular comorbidities is recommended in patients with HFpEF (see relevant sections of this document).	I	C
Diuretics are recommended in congested patients with HFpEF in order to alleviate symptoms and signs. <sup>137</sup>	I	C

*Can J Cardiol* 2017;33:1342-433

*Can J Cardiol* 2020;36:159-69

*Eur Heart J* 2021;42:3599-726

# HFmrEF pharmacotherapy

## Guideline recommendations (European)

Pharmacological treatments to be considered in patients with (NYHA class II–IV) heart failure with mildly reduced ejection fraction

Recommendations	Class <sup>a</sup>	Level <sup>b</sup>
Diuretics are recommended in patients with congestion and HFmrEF in order to alleviate symptoms and signs. <sup>137</sup>	<b>I</b>	<b>C</b>
An ACE-I may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <sup>11</sup>	<b>IIb</b>	<b>C</b>
An ARB may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <sup>245</sup>	<b>IIb</b>	<b>C</b>
A beta-blocker may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <sup>12,119</sup>	<b>IIb</b>	<b>C</b>
An MRA may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <sup>246</sup>	<b>IIb</b>	<b>C</b>
Sacubitril/valsartan may be considered for patients with HFmrEF to reduce the risk of HF hospitalization and death. <sup>13,247</sup>	<b>IIb</b>	<b>C</b>

Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated
Class II	Conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of the given treatment or procedure.	
Class IIa	Weight of evidence/opinion is in favour of usefulness/efficacy.	Should be considered
Class IIb	Usefulness/efficacy is less well established by evidence/opinion.	May be considered
Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.	
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.	
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.	