# EMPOWER: Chương trình nghiên cứu của empagliflozin trên tim mạch-thận-chuyển hóa, gồm hơn 27,000 bệnh nhân*

## Được xem là một trong những chương trình nghiên cứu rộng lớn và đầy đủ nhất trong nhóm ức chế SGLT2i

**EMPEROR-Reduced**
Effects on HHF and CV mortality in HFrEF[1-2]
**3730 patients**

**EMPEROR-Preserved**
Effects on HHF and CV mortality in HFpEF[3-4]
**5988 patients**

**EMPERIAL-Reduced**
Effects on exercise capacity and patient-reported outcomes in HFrEF[5-6]
**312 patients**

**EMPERIAL-Preserved**
Effects on exercise capacity and patient-reported outcomes in HFpEF[6-7]
**315 patients**

**EMPULSE**
Effects of in-hospital initiation in acute HF on HF-related events and patient-reported outcomes[8]
**500 patients**

**EMPACT-MI**
Effects on HHF and mortality in post-MI patients with high risk of Heart Failure[9]
**3300 patients**

**EMPA-VISION**
Effects on cardiac Physiology and Metabolism in Patients With Heart Failure[10]
**72 patients**

**EMPA-KIDNEY**
Effects on kidney disease progression and CV death in patients with chronic kidney disease[11]
**6000 patients**

**EMPA-REG OUTCOME®**
Effects on CV morbidity and mortality in patients with high CV risk and T2D[12]
**7020 patients**

**EMPRISE**
Real world effectiveness in patients with T2D in the United States, Europe and Asia[13-15]
**230,000 patients**

*EMPRISE is an observational study and is, therefore, excluded from the total patient number. CV, cardiovascular; HHF, hospitalisation for heart failure; T2D, type 2 diabetes; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; MI, myocardial infarction

1. ClinicalTrials.gov. NCT03057977; 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. Clinicaltrials.gov. NCT03057951; 4. Anker SD *et al. Eur J Heart Fail* 2019;21:1279; 5. ClinicalTrials.gov. NCT03448419;
6. Abraham WT *et al. Eur J Heart Fail* 2019;21:932; 7. ClinicalTrials.gov. NCT03448406; 8. ClinicalTrials.gov. NCT04157751; 9. Boehringer Ingelheim Pharmaceuticals, Inc. Press release. 2020. https://www.boehringer-ingelheim.com/press-release/dcri-collaboration-empact-mi ; 10. Clinicaltrials.gov. NCT03332212; 11. ClinicalTrials.gov. NCT03594110;
12. Zinman B *et al. N Engl J Med* 2015;373:2117; 13. ClinicalTrials.gov. NCT03363464; 14. ClinicalTrials.gov. NCT03817463; 15. Patorno E *et al. Circulation* 2019;139:2822 (all websites accessed Jul 2020)

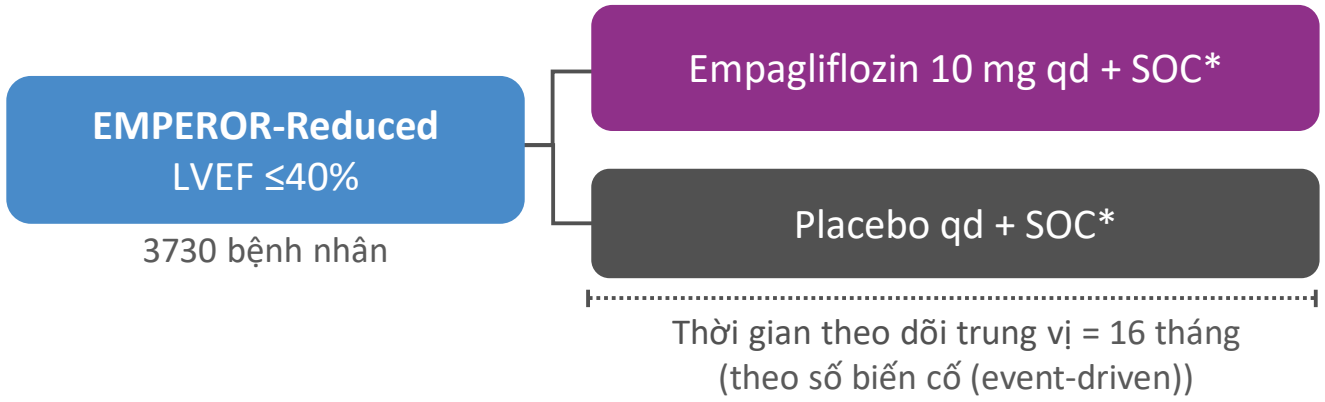
# EMPEROR-Reduced: Thiết kế nghiên cứu

## Thử nghiệm pha III mù đôi ngẫu nhiên đối chứng giả dược

**Mục tiêu:** Đánh giá tính an toàn và hiệu quả của empagliflozin so với giả dược khi thêm vào điều trị chuẩn theo hướng dẫn điều trị ở bệnh nhân suy tim phân suất tống máu giảm

**Dân số:** ĐTĐ typ 2 và không ĐTĐ typ 2, tuổi ≥18, suy tim mạn (phân độ NYHA II–IV)

### Thiết kế nghiên cứu [1–3]




### 3 Tiêu chí xác định ngay từ đầu [1,2]

1

**TIÊU CHÍ CHÍNH**

- Tử vong do tim mạch hoặc nhập viện do suy tim được thẩm định

2

3

**TIÊU CHÍ THỨ PHÁT**

- Nhập viện do suy tim lần đầu và tái nhập viện được thẩm định
- Độ giảm eGFR

* Điều trị chuẩn theo hướng dẫn điều trị (Guideline-directed medical therapy)
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate
LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; qd, once daily; SOC, standard of care; ĐTĐ, đái tháo đường

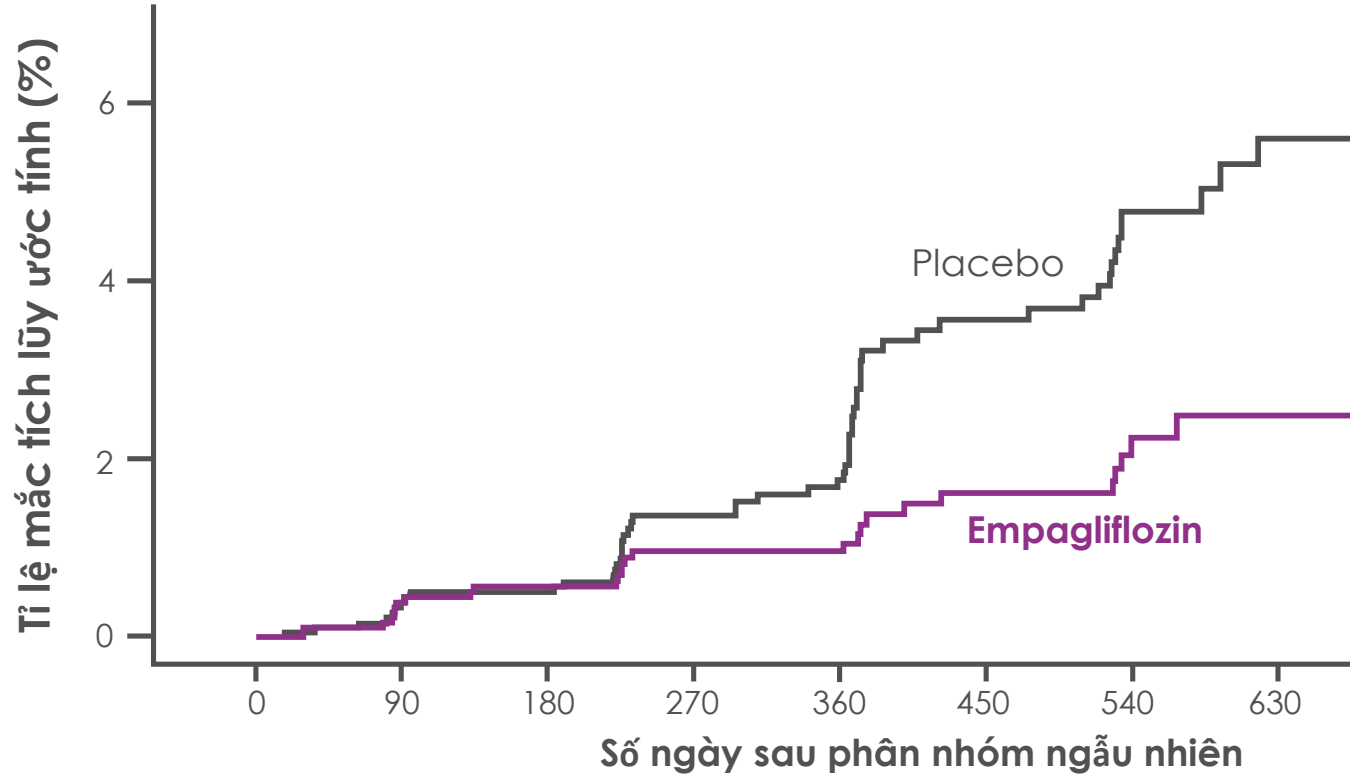
1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Packer M *et al. Eur J Heart Fail* 2019;21:1270; 3. M. Packer, S. Anker, J. Butler et al. (2020). Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. New England Journal of Medicine. doi:10.1056/nejmoa2022190

# EMPEROR-Reduced: ĐẠT CẢ 3 KẾT CỤC về hiệu quả được xác định trong kiểm định theo trình tự với p < 0.001

| | | | EMPEROR-Reduced | |
|---|---|---|---|---|
| 1 | **Tiêu chí chính:** Tử vong do tim mạch hoặc nhập viện do suy tim được thẩm định | Khẳng định* | **HR 0.75** (95% CI 0.65, 0.86) *p*<0.001 | ✓ |
| 2 | **Tiêu chí thứ phát 1:** Nhập viện do suy tim lần đầu và tái nhập viện được thẩm định | Khẳng định† | **HR 0.70** (95% CI 0.58, 0.85) *p*<0.001 | ✓ |
| 3 | **Tiêu chí thứ phát 2:** Độ giảm eGFR | Khẳng định‡ | **Khác biệt về độ dốc eGFR 1.73 ml/phút/1.73 m²/mỗi năm,** (95% CI 1.1, 2.4) *p*<0.001 | ✓ |

*Cox regression with a=0.0496; †Joint frailty model of adjudicated HHF and CV death with a=0.0496; ‡Random intercept random slope model with a=0.001
All models include covariates age, baseline eGFR, region, baseline diabetes status, sex and LVEF
CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure, LVEF, left ventricular ejection fraction
M. Packer, S. Anker, J. Butler et al. (2020). Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *New England Journal of Medicine*. doi:10.1056/nejmoa2022190

# EMPEROR-Reduced: Empagliflozin giúp giảm 50% biến cố gộp trên thận (bệnh thận giai đoạn cuối hoặc giảm eGFR kéo dài)




| BN có nguy cơ | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Placebo | 1867 | 1592 | 1501 | 1136 | 1058 | 681 | 357 | 259 |
| Empagliflozin | 1863 | 1599 | 1532 | 1155 | 1062 | 687 | 391 | 276 |

RRR 50%

ARR 1.5%

**HR 0.50**
(95% CI 0.32, 0.77)

Empagliflozin:
30 bệnh nhân có biến cố
Tỷ lệ: 1.6/100 bệnh nhân-năm
Placebo:
58 bệnh nhân có biến cố
Tỷ lệ: 3.1/100 bệnh nhân-năm

Composite renal endpoint is defined as chronic dialysis, renal transplant, sustained reduction of ≥40% eGFR or sustained eGFR <15 ml/min/1.73 m² for patients with eGFR ≥30 ml/min/1.73 m² at baseline (<10 ml/min/1.73 m² for patients with eGFR <30 ml/min/1.73 m² at baseline). Dialysis is regarded as chronic if the frequency of dialysis is twice or more per week for at least 90 days. Cox regression model including covariates age, baseline eGFR (CKD-EPI), region, baseline diabetes status, sex, and baseline LVEF.
CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LVEF, left ventricular ejection fraction; PY, patient years. ARR, absolute risk reduction; RRR, relative risk reduction
M. Packer, S. Anker, J. Butler et al. (2020). Cardiovascular and Renal Outcomes With Empagliflozin in Heart Failure. *New England Journal of Medicine*. doi:10.1056/nejmoa2022190

# Tóm tắt kết quả kết cục chính của các nghiên cứu trên HFrEF gần đây

| | Active Arm | | Placebo/comparator | | HHF+CV death* | | |
|---|---|---|---|---|---|---|---|
| | n (%) | Events/100 patient-yrs | n (%) | Events/100 patient-yrs | HR: | ARR† | NNT † |
| **EMPEROR-Reduced**[1] | 361 (19.4%) | 15.8 | 462 (24.7%) | 21 | 0.75 (0.65, 0.86) | **5.2** | **19** Over 16 months |
| **DAPA HF**[2] | 386 (16.3%) | 11.6 | 502 (21.2%) | 15.6 | 0.74 (0.65, 0.85) | **4.9** | **21** Over 18 months |
| **PARADIGM-HF**[3,4] | 914 (21.8) | 10.5 | 1117 (26.5%) | 13.2 | 0.80 (0.73, 0.87) | **4.7** | **21** Over 27 months |
| **VICTORIA**[5] | 897 (35.5%) | 33.6 | 972 (38.5%) | 37.8 | 0.90 (0.82, 0.98) | **3** | **36** Over 11 months |

**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**

*The primary end-point for DAPA-HF was a composite of worsening heart failure or CV death. An episode of worsening heart failure was defined as either an unplanned hospitalisation or as an urgent visit resulting in intravenous therapy for heart failure. †ARR and NNT information is unpublished and has been calculated. ARR was estimated as the absolute difference in the proportion of events by treatment arm. NNT=1/ARR

ARR, absolute risk reduction; HHF, hospitalisation for heart failure; NNT, number needed to treat; yrs, years

1. Packer M et al. N Engl J Med 2020 Aug 29; 2. McMurray JJV *et al. N Engl J Med.* 2019;381:1995; 3. McMurray JJV *et al. N Engl J Med.* 2014;371:993; Butler J *et al. Circulation.* 2020;doi: 10.1161/CIRCULATIONAHA.120.047086; 5. Armstrong PW *et al. N Engl J Med.* 2020;382:1883

# Key Medical Messages

## **EMPEROR-Reduced:** Empagliflozin reduces CV death or HHF in patients with HF and reduced EF

In EMPA-REG OUTCOME, Empagliflozin was the first and only SGLT2i to demonstrate a to-date unmatched reduction in CV death as well as HHF for people living with T2D and CVD

For HF patients with reduced EF, Empagliflozin now achieved a remarkable 25% relative risk reduction in the primary composite endpoint of CV death or HHF, on top of SOC[1]

Empagliflozin reduced first and recurrent hospitalization for HF by 30% in a confirmatory secondary endpoint. In an addition, Empagliflozin protected the kidney by significantly slowing the decline in kidney function[2] and reducing kidney outcomes [3] by 50%.

In EMPEROR-Reduced, the safety profile was similar to the known safety profile of Empagliflozin. There was no clinically meaningful increase in hypovolemia and hypotensionor hypoglycemic events.

These results underline the meaningful and preventative impact Empagliflozin has on the lives of patients across the spectrum of cardio-renal and metabolic conditions

Empagliflozin is already approved[4] for the reduction of CV death, HHF, and MACE, in addition to glycemic treatment in T2D patients with CV disease

* Unless otherwise allowed by local applicable law. [1] The study was not designed to evaluate individual components of the primary endpoint. [2] A confirmatory secondary endpoint of eGFR slope of change [3] Kidney outcomes were a composite exploratory endpoint, including chronic dialysis or renal transplant or sustained reduction of ≥ 40% eGFR(CKD-EPI) or a sustained eGFR <15 mL/min/1.73m$^2$ (for patients with baseline eGFR ≥30) or sustained eGFR <10 mL/min/1.73m$^2$ (for patients with baseline eGFR <30 mL/min/1.73m$^2$. [4]Depending on local label.

# ESC-HF position paper Oct 2020: Khuyến cáo Dapagliflozin & Empagliflozin trên BN suy tim phân suất tống máu giảm


ESC European Society of Cardiology

European Journal of Heart Failure (2020) doi:10.1002/ejhf.2026

POSITION PAPE

**Heart Failure Association of the European Society of Cardiology update on sodium–glucose co-transporter 2 inhibitors in heart failure (an update on the sodium–glucose co-transporter 2 inhibitors in heart failure: beyond glycaemic control. A position paper of the Heart Failure Association of the European Society of Cardiology)**

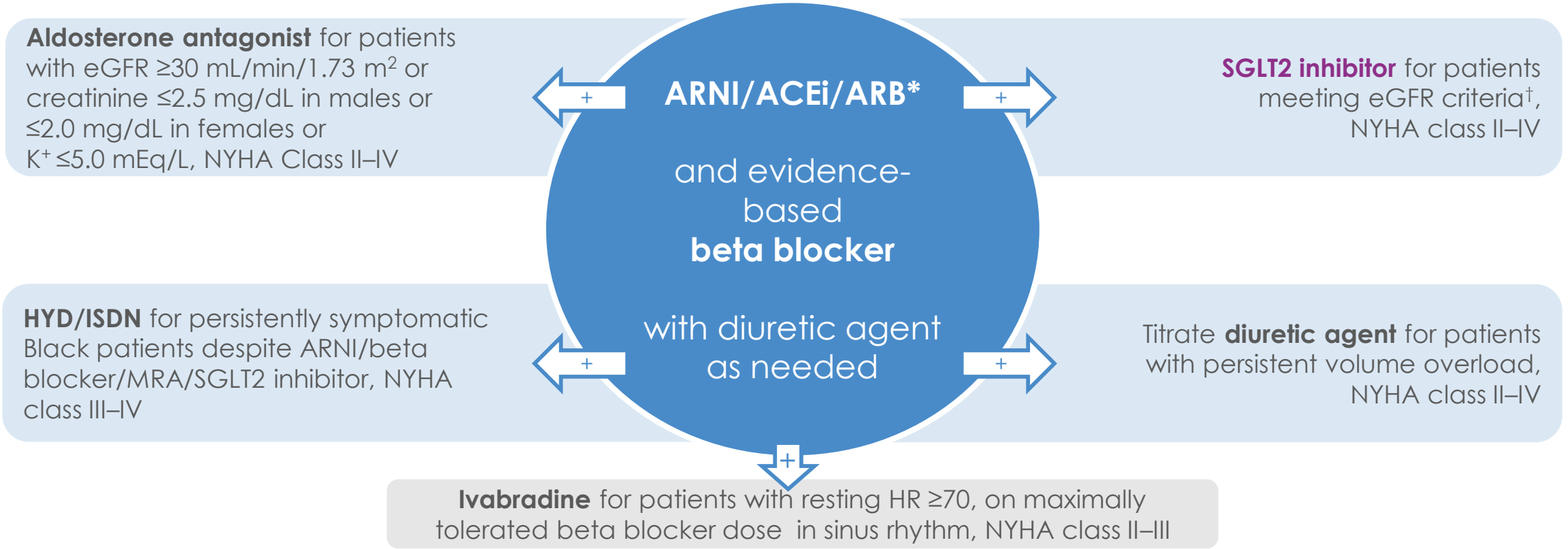
The Heart Failure Association (HFA) of the European Society of Cardiology (ESC) has recently issued a position paper on the role of sodium–glucose co-transporter 2 (SGLT2) inhibitors in heart failure (HF). The present document provides an update of the position paper, based of new clinical trial evidence. Accordingly, the following recommendations are given:

- Canagliflozin, dapagliflozin empagliflozin, or ertugliflozin have consistently demonstrated to be effective for the prevention of HF hospitalization in patients with type 2 diabetes mellitus and established cardiovascular disease or at high cardiovascular risk. The specifically listed agents are recommended.
- Dapagliflozin or empagliflozin are recommended to reduce the combined risk of HF hospitalization and cardiovascular death in symptomatic patients with HF and reduced ejection fraction, already receiving guideline-directed medical therapy, regardless of the presence of type 2 diabetes mellitus.



Eur J Heart Fail. 2020 Oct 17

# 2021 ACC Expert Consensus Treatment algorithm




*ARNI is preferred. ACEi/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI.
†Ensure eGFR ≥30 mL/min/1.73 m² (dapagliflozin) or ≥20 mL/min/1.73 m² (empagliflozin).
ACC, American College of Cardiology; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HYD/SYN, hydralazine/isosorbide dinitrate; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2.
Maddox TM *et al*. *J Am Coll Cardiol*. 2021;77:772.

# 2021 ACC Expert Consensus Treatment algorithm

**Aldosterone antagonist** for patients with eGFR ≥30 mL/min/1.73 $m^2$ 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

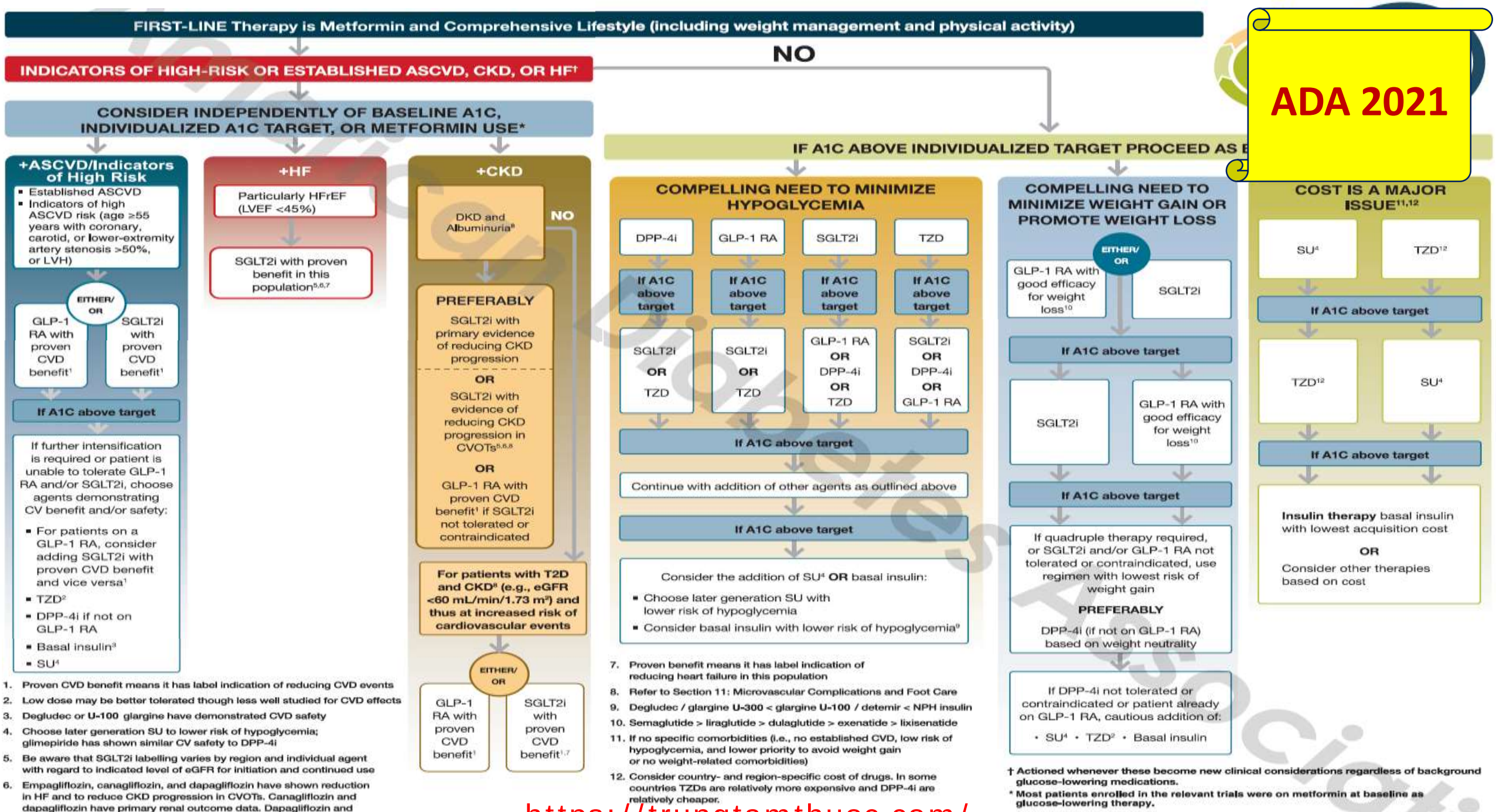
**ARNI/ACEi/ARB***

and evidence-based **beta blocker**

**SGLT2 inhibitor** for patients meeting eGFR criteria†, NYHA class II–IV

***"Based on large randomized trials for HFrEF, ARNIs, evidence-based beta blockers, aldosterone antagonists, and SGLT2 inhibitors are first-line medications for all populations"***

*ARNI is preferred. ACEi/ARB should only be considered in patients with contraindications, intolerance or inaccessibility to ARNI.
†Ensure eGFR ≥30 mL/min/1.73 $m^2$ (dapagliflozin) or ≥20 mL/min/1.73 $m^2$ (empagliflozin).
ACC, American College of Cardiology; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HR, heart rate; HYD/SYN, hydralazine/isosorbide dinitrate; MRA, mineralocorticoid receptor antagonists; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2.
Maddox TM *et al. J Am Coll Cardiol.* 2021;77:772.




1. Proven CVD benefit means it has label indication of reducing CVD events
2. Low dose may be better tolerated though less well studied for CVD effects
3. Degludec or U-100 glargine have demonstrated CVD safety
4. Choose later generation SU to lower risk of hypoglycemia; glimepiride has shown similar CV safety to DPP-4i
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population
8. Refer to Section 11: Microvascular Complications and Foot Care
9. Degludec / glargine U-300 < glargine U-100 / detemir < NPH insulin
10. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
11. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
12. Consider country- and region-specific cost of drugs. In some countries TZDs are relatively more expensive and DPP-4i are relatively cheaper.

† Actioned whenever these become new clinical considerations regardless of background glucose-lowering medications.
* Most patients enrolled in the relevant trials were on metformin at baseline as glucose-lowering therapy.

ADA 2021



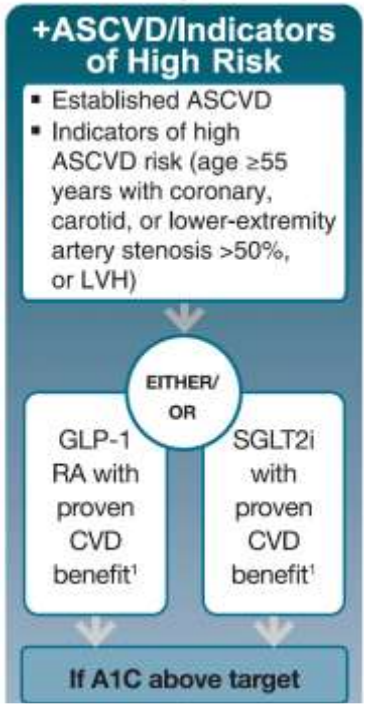
January 01 2021; volume 44 issue Supplement 1

**ADA 2021**

**FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)**

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†**

**CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE***




1. Proven CVD benefit means it has label indication of reducing CVD events

†FDA-approved for cardiovascular disease benefit.

----------RECENT MAJOR CHANGES----------

Indications and Usage (1) 12/2016

----------INDICATIONS AND USAGE----------

JARDIANCE is a sodium-glucose co-transporter 2 (SGLT2) inhibitor indicated:

- as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus,
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease. (1)



January 01 2021; volume 44 issue Supplement 1

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)

**INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†**

**CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE***

**+HF**

Particularly HFrEF (LVEF <45%)

SGLT2i with proven benefit in this population[5,6,7]

**ADA 2021**

5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use
6. Empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin and dapagliflozin have primary renal outcome data. Dapagliflozin and empagliflozin have primary heart failure outcome data.
7. Proven benefit means it has label indication of reducing heart failure in this population



January 01 2021; volume 44 issue Supplement 1

# Results in context

# Trial inclusion and exclusion criteria

## Inclusion criteria

| EMPEROR-Reduced[1,2] | | DAPA-HF[3] |
|---|---|---|
| Age ≥18 years (Japan, age ≥20 years) at screening | | Age ≥18 years |
| Chronic HF NYHA class II–IV | | Chronic HF NYHA class II–IV |
| HFrEF (LVEF ≤40%) | | HFrEF (LVEF ≤40%) |
| **Elevated NT-proBNP** | | |
| **EF (%)** | **NT-proBNP (pg/ml)** Patients without AF* | **NT-proBNP ≥600 pg/ml or NT-proBNP ≥400 pg/ml in patients with HHF within 12 months** Patients without AF† |
| ≥36 to ≤40 | ≥2500 | |
| ≥31 to ≤35 | ≥1000 | |
| ≤30 | ≥600 | |
| ≤40% + HHF within 12 months | ≥600 | |
| Further inclusion criteria apply | | Further inclusion criteria apply |

**EMPEROR-Reduced**
**eGFR <20 ml/min/1.73 m²**
or requiring dialysis

**eGFR exclusion criteria**
Further exclusion criteria apply

**DAPA-HF**
**eGFR <30 ml/min/1.73 m²**
or rapidly declining renal function

***The cut off for patients with AF is doubled in EMPEROR-Reduced;** †In DAPA-HF patients with AF or atrial flutter were required to have NT-proBNP ≥900 pg/ml regardless of history of HHF
AF, atrial fibrillation; CV, cardiovascular; EF, ejection fraction; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HHF, hospitalisation for heart failure; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association

1. ClinicalTrials.gov. NCT03057977 (accessed Aug 2020); 2. Zannad F *et al*. *ESC HF* 2019; poster P1755; 3. McMurray JJV *et al*. *N Engl J Med*. 2019;381:1995

# Baseline characteristics in EMPEROR-Reduced and DAPA-HF

| | EMPEROR-Reduced[1] | | DAPA-HF[2] | |
|---|---|---|---|---|
| | Empagliflozin | Placebo | Dapagliflozin | Placebo |
| Number of participants | 1863 | 1867 | 2373 | 2371 |
| **LVEF (%), mean ± SD** | **27.7 ± 6.0** | **27.2 ± 6.1** | **31.2±6.7** | **30.9±6.9** |
| **NT-proBNP, pg/ml, median (IQR)** | **1887.0 (1077.0–3429.0)** | **1926.0 (1153.0–3525.0)** | **1428 (857-2655)** | **1446 (857-2641)** |
| **Hospitalisation for HF** | **577 (31.0%)*** | **574 (30.7%)*** | **27%** | |
| Diabetes | 927 (49.8%) | 929 (49.8%) | 1075 (45.3%) | 1064 (44.9%) |
| **ARNI** | **340 (18.3%)** | **387 (20.7%)** | **250 (10.5%)** | **258 (10.9%)** |
| **ICD or CRT-D** | **578 (31%)** | **593 (31.8%)** | **622 (26.2%)** | **620 (26.1%)** |
| **CRT-D or CRT-P** | **220 (11.8%)** | **222 (11.9%)** | **190 (8.0%)** | **164 (6.9%)** |

EMPEROR-Reduced mở rộng đối tượng BN trong Dapa-HF trên BN HFrEF nặng hơn

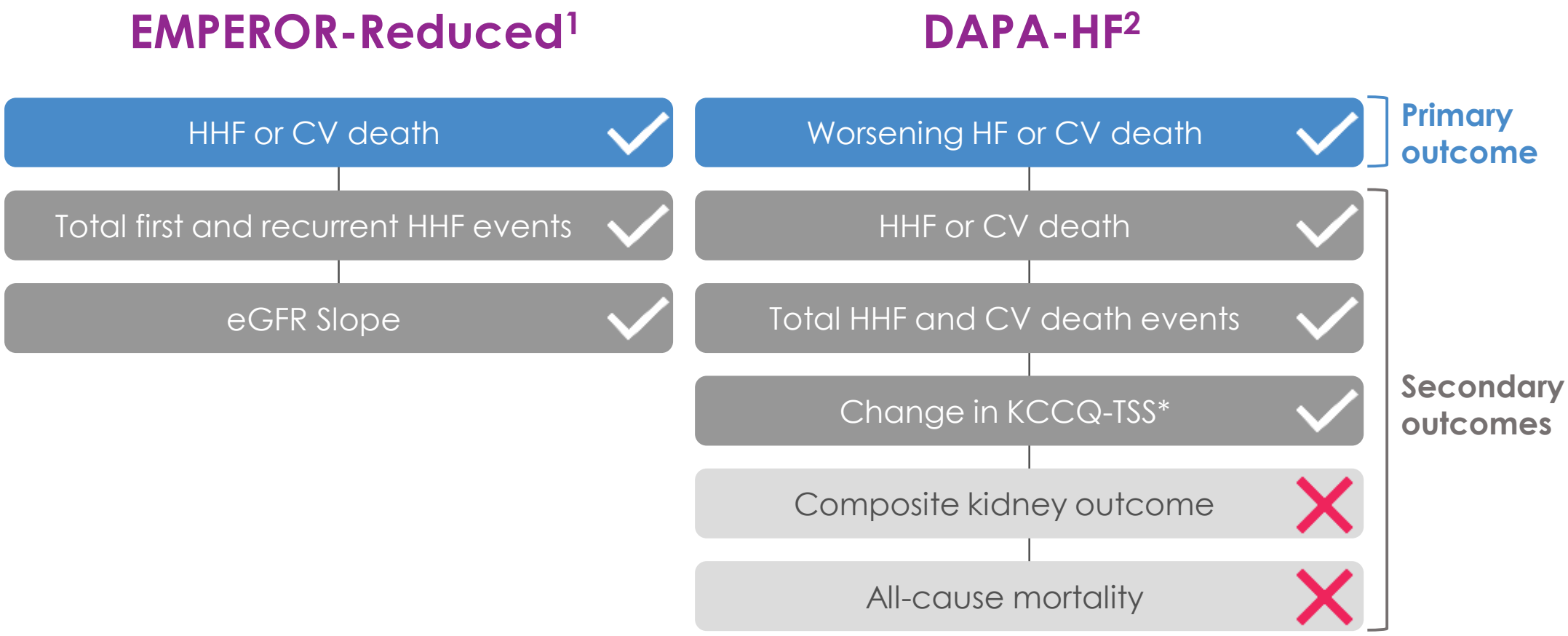
Tỉ lệ BN đạt điều trị chuẩn trong EMPEROR-Reduced > DAPA-HF

**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**

*Within 12 months. †No timeframe is specified for prior HHF history in DAPA-HF in main publication. The proportion of patients in DAPA-HF with prior HHF within 12 months was 27% overall[3]

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CRT-D, cardiac resynchronization therapy defibrillator; CRT-P cardiac resynchronization therapy pacemaker, eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter pacemaker; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–B-type natriuretic peptide; NYHA, New York Heart Association. 1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190; 2. McMurray JJV et al. N Engl J Med. 2019;381:1995; 3. McMurray JJV *et al. Eur J Heart Fail.* 2019;21:1402

# Outcome of endpoint hierarchical statistical testing: Comparison of EMPEROR-Reduced and DAPA-HF




**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**

*Change from baseline at 8 months

HF, heart failure; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; NR, not reported

1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. McMurray J.J.V. et al. *N Engl J Med* 2019;381:1995

# EMPEROR-reduced and DAPA-HF
## Summary

| | EMPEROR-Reduced[1] | | DAPA-HF[2] | |
|---|---|---|---|---|
| | N (rate per 100 PY) | HR, 95% CI, P-value | N (rate per 100 PY) | HR, 95% CI, P-value |
| Adjudicated CV death or HHF (first) | EMPA: 361 (15.8)<br>Placebo: 462 (21.0) | **HR 0.75 (0.65, 0.86)**<br>*p*<0.0001 | DAPA: 382 (11.4)<br>Placebo: 495 (15.3) | HR 0.75 (0.65, 0.86)<br>p<0.0001 |
| HHF (first) | EMPA: 246(10.7)<br>Placebo: 342 (15.5) | **HR 0.69**<br>**(0.59, 0.81)** | DAPA: 231 (6.9)<br>Placebo: 318 (9.8) | HR 0.70<br>(0.65, 0.86) |
| CV death | EMPA: 187 (7.55)<br>Placebo: 202 (8.13) | **HR 0.92**<br>**(0.75, 1.12)** | DAPA: 227 (6.5)<br>Placebo: 273(7.9) | HR 0.82<br>(0.69, 0.98) |
| All-cause mortality | EMPA: 249 (10.06)<br>Placebo: 264 (10.71) | **HR 0.92**<br>**(0.77, 1.10)** | DAPA: 276 (7.9)<br>Placebo: 329 (9.5) | HR 0.83<br>(0.71, 0.97) |



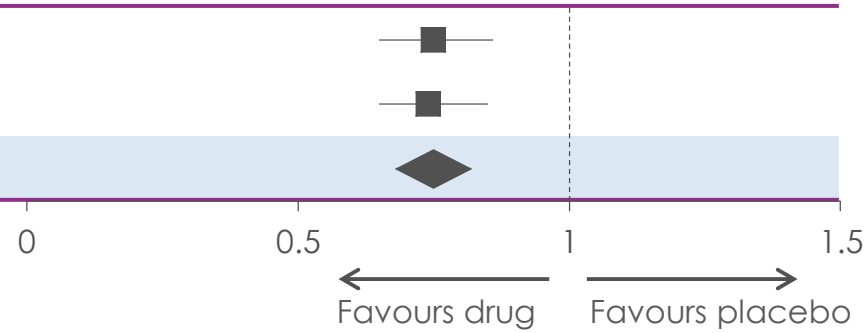
1- Packer M et al. N Engl J Med. 2020;10.1056/NEJMoa2022190; 2- McMurray JJV et al. N Engl J Med. 2019;381:1995

# Meta-analysis DAPA-HF và EMPEROR-Reduced: SGLT2i giảm 26% kết cục chính & 14% tử vong tim mạch

## Kết cục chính: Tử vong tim mạch hoặc nhập viện do suy tim

| Trial | SGLT2i, n/N (%) | Placebo, n/N (%) | HR (95% CI) |
|---|---|---|---|
| EMPEROR-Reduced | 361/1863 (19.4) | 462/1867 (24.7) | 0.75 (0.65, 0.86) |
| DAPA-HF | 386/2373 (16.3) | 502/2371 (21.2) | 0.74 (0.65, 0.85) |
| Total | | | 0.74 (0.68, 0.82) |

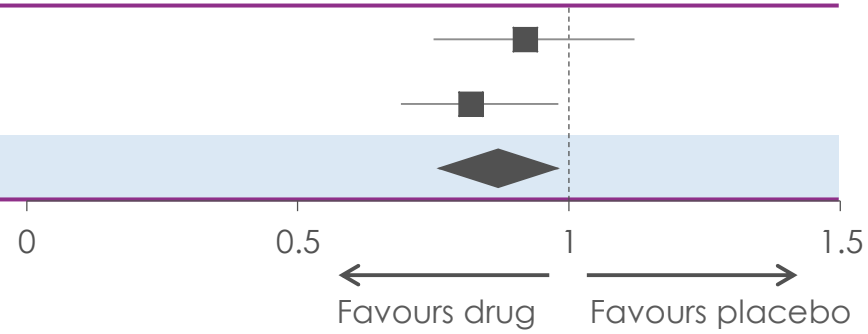
Test for overall treatment effect, $p<0.0001$
Test for heterogeneity of effect, $p=0.89$




## Tử vong tim mạch

| Trial | SGLT2i, n/N (%) | Placebo, n/N (%) | HR (95% CI) |
|---|---|---|---|
| EMPEROR-Reduced | 187/1863 (10.0) | 202/1867 (10.8) | 0.92 (0.75, 1.12) |
| DAPA-HF | 227/2373 (9.6) | 273/2371 (11.5) | 0.82 (0.69, 0.98) |
| Total | | | 0.86 (0.76, 0.98) |

Test for overall treatment effect, $p=0.027$
Test for heterogeneity of effect, $p=0.40$




HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor
1. Data on file

# Baseline characteristics: comparison of modern trials (control arms)

| | EMPEROR-Reduced[1] (placebo control arm) | DAPA-HF[2] (placebo control arm) | VICTORIA[3] (placebo control arm) | PARADIGM-HF[4–6] (enalapril active control arm) |
|---|---|---|---|---|
| **Age**, years | 66.5 | 66.5 | 67.2 | 63.8 |
| **EF** | 27% | 31% | 29% | 29% |
| **NT-proBNP**, pg/ml | 1926 | 1446 | 2821 | 1594 |
| **NYHA FC2 (or 1)** | 75% | 67% | 59% | 74% |
| **eGFR**, ml/min/1.73 $m^2$ | 62 | 66 | 62 | 70 |
| **eGFR <60 ml/min/1.73 $m^2$** | 49% | 41% | 53% | 33% |
| **ARNi use** | 21% | 11% | 15% | 0% |
| **MRA use** | 73% | 71% | 71% | 57% |
| **ICD use** | 32% | 26% | 28% | 15% |
| **CRT** | 12% | 7% | *NR* | 7% |
| **HHF 12 months** | 31%* | 27%† | 100% WHF 6 months | 42%‡ |

**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**
Baseline characteristics of control arms are summarised
*Within 12 months. †No timeframe is specified for prior HHF history in DAPA-HF. The proportion of patients in DAPA-HF with prior HHF within 12 months was 27% overall[7]. ‡Refers to whole study population (study arm data not reported)
CRT, cardiac resynchronization therapy; EF, ejection fraction; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; ICD, implantable cardioverter-defibrilator; MRA, mineralocorticoid receptor antagonist; NR, not reported; NT-proBNP, N-terminal pro−B-type natriuretic peptide; NYHA FC2, New York Heart Association functional class 2; WHF, worsening heart failure

1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. McMurray JJV *et al. N Engl J Med.* 2019;381:1995; 3. Armstrong PW *et al. N Engl J Med.* 2020;382:1883;
4. McMurray JJV, *et al. N Engl J Med.* 2014;371:993; 5. Damman K *et al. J Am Coll Cardiol HF*. 2018; 6:489; 6. Solomon SD *et al. J Am Coll Cardiol HF* 2016;4:816;
7. McMurray JJV *et al. Eur J Heart Fail.* 2019;21:1402

# Primary endpoint results of modern trials

| | Active Arm | | Placebo/comparator | | HHF+CV death* | | |
|---|---|---|---|---|---|---|---|
| | n (%) | Events/100 patient-yrs | n (%) | Events/100 patient-yrs | HR: | ARR† | NNT † |
| **EMPEROR-Reduced**[1] | 361 (19.4%) | 15.8 | 462 (24.7%) | 21 | 0.75 (0.65, 0.86) | 5.2 | 19 Over 16 months |
| **DAPA HF**[2] | 386 (16.3%) | 11.6 | 502 (21.2%) | 15.6 | 0.74 (0.65, 0.85) | 4.9 | 21 Over 18 months |
| **PARADIGM-HF**[3,4] | 914 (21.8) | 10.5 | 1117 (26.5%) | 13.2 | 0.80 (0.73, 0.87) | 4.7 | 21 Over 27 months |
| **VICTORIA**[5] | 897 (35.5%) | 33.6 | 972 (38.5%) | 37.8 | 0.90 (0.82, 0.98) | 3 | 36 Over 11 months |

**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**

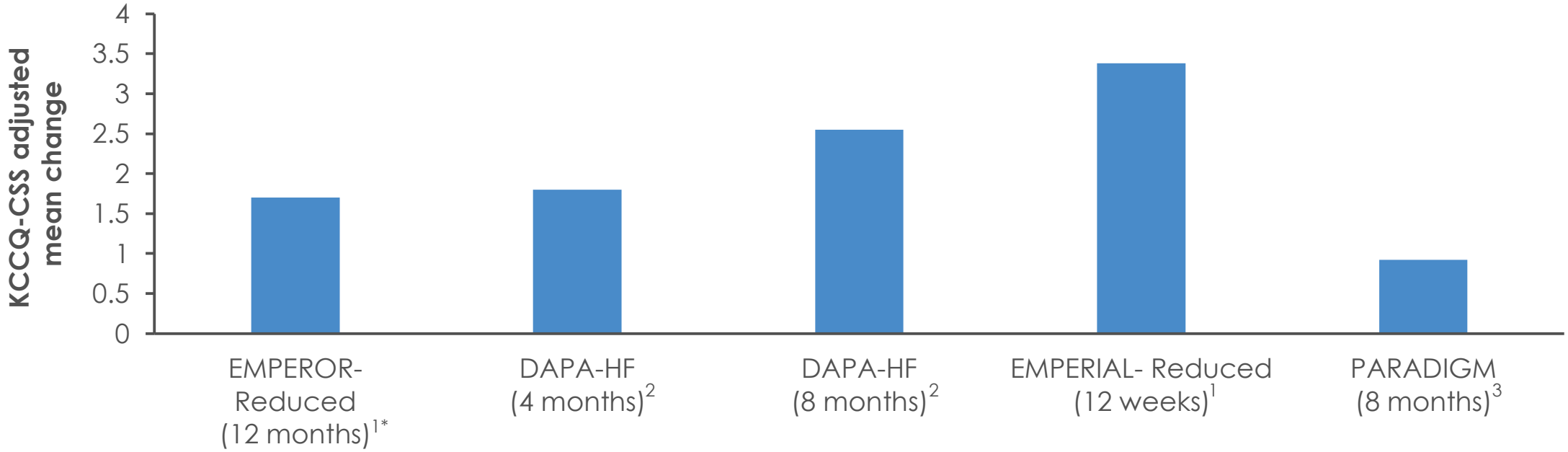
*The primary end-point for DAPA-HF was a composite of worsening heart failure or CV death. An episode of worsening heart failure was defined as either an unplanned hospitalisation or as an urgent visit resulting in intravenous therapy for heart failure. †ARR and NNT information is unpublished and has been calculated. ARR was estimated as the absolute difference in the proportion of events by treatment arm. NNT=1/ARR

ARR, absolute risk reduction; HHF, hospitalisation for heart failure; NNT, number needed to treat; yrs, years

1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. McMurray JJV *et al. N Engl J Med*. 2019;381:1995; 3. McMurray JJV, *et al. N Engl J Med*. 2014;371:993; Butler J *et al. Circulation*. 2020;doi: 10.1161/CIRCULATIONAHA.120.047086;
5. Armstrong PW *et al. N Engl J Med*. 2020;382:1883

# Effects on KCCQ-CSS: SGLT2 inhibitors and ARNI

## EMPEROR-Reduced showed comparable effects to EMPERIAL-Reduced and dapagliflozin trials



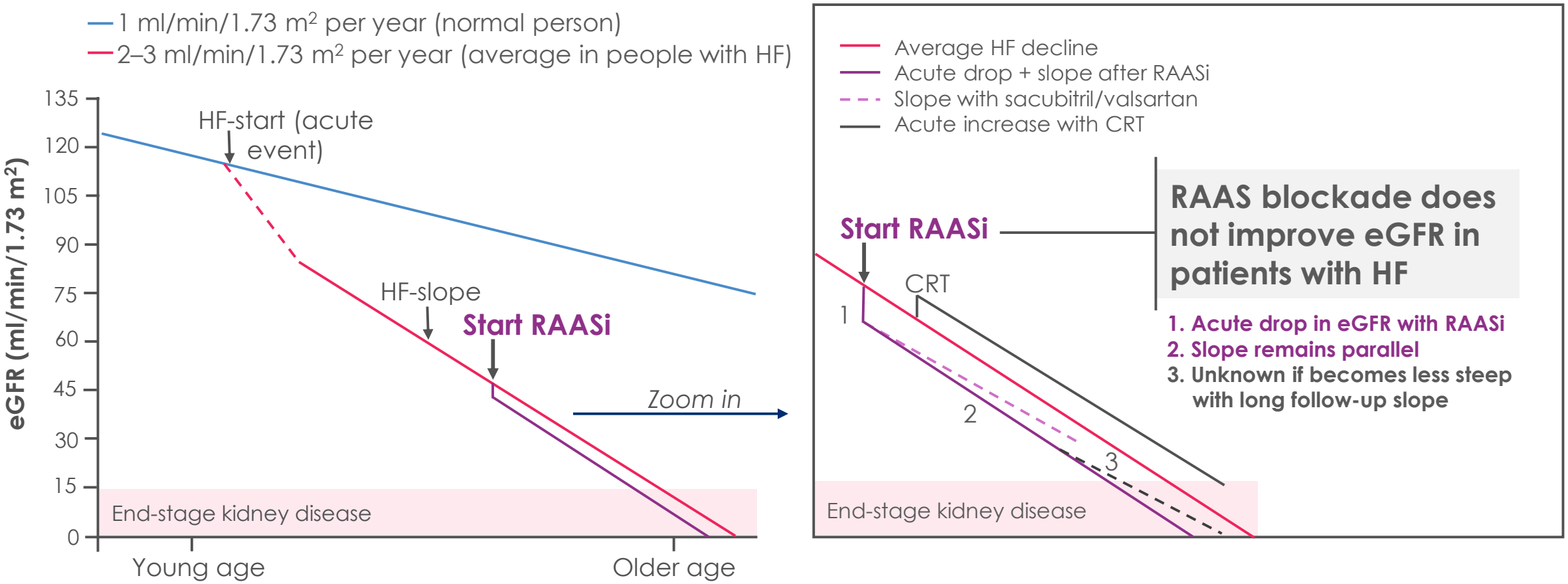

Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology
SGLT2 inhibitor trials difference in change in scores vs placebo are shown. PARADIGM trial difference of sacubitril valsartan vs enalapril. *On treatment
KCCQ, Kansas City Cardiomyopathy Questionnaire; CSS, Clinical summary score; ARNI, angiotensin receptor neprilysin inhibitor; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose co-transporter-2



1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. Kosiborod M, et al. *Circulation*. 2020;141:90-99.; 3. Lewis EF. *Circ Heart Fail*. 2017;10:e003430

# No treatment options have been identified that provide sufficient kidney protection in patients with heart failure

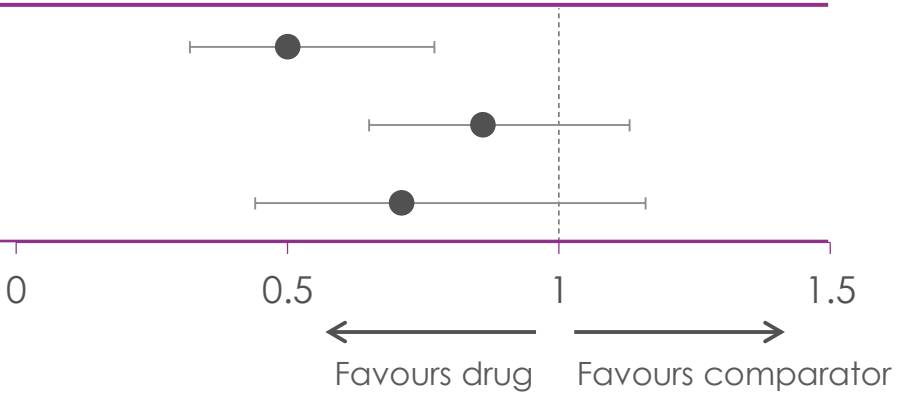
## Kidney function in patients with HF following treatment initiation




CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; RAASi, renin–angiotensin–aldosterone system inhibitor
Adapted from Mullens W *et al. Eur J Heart Fail*. 2020;22:584

# Composite kidney outcomes: end stage renal disease, sustained and profound decrease in eGFR

| Trial | HR | 95% CI |
|---|---|---|
| EMPEROR-Reduced[1] | 0.50 | (0.32, 0.77) |
| PARADIGM-HF[2] | 0.86 | (0.65, 1.13) |
| DAPA-HF[3] | 0.71 | (0.44, 1.16) |




**Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology**

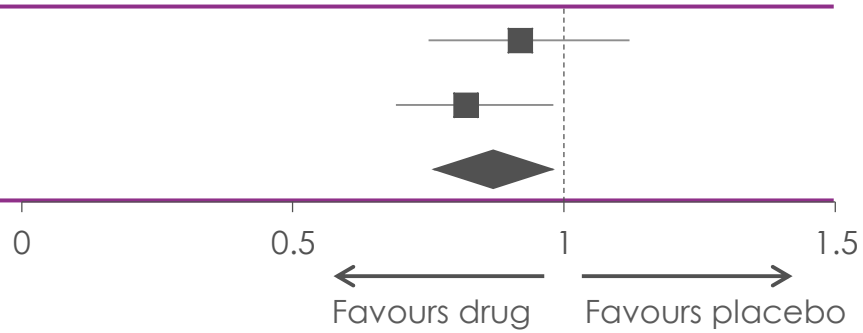
eGFR, estimated glomerular filtration rate

1. Packer et al. NEJM 2020. DOI: 10.1056/NEJMoa2022190.; 2. McMurray J.J.V. *et al. N Engl J Med* 2014;371:993-1004; 3. McMurray J.J.V. *et al. N Engl J Med* . 2019;381:1995

# Meta-analysis of DAPA-HF and EMPEROR-Reduced

## CV death

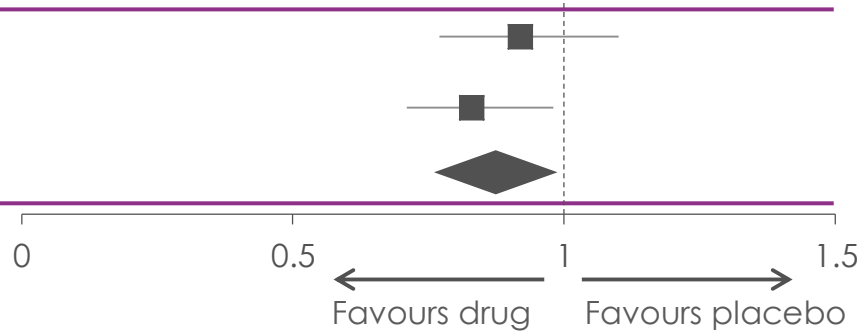
| Trial | SGLT2i, n/N (%) | Placebo, n/N (%) | HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| EMPEROR-Reduced | 187/1863 (10.0) | 202/1867 (10.8) | 0.92 (0.75, 1.12) | |
| DAPA-HF | 227/2373 (9.6) | 273/2371 (11.5) | 0.82 (0.69, 0.98) | |
| Total | | | 0.86 (0.76, 0.98) | |




Test for overall treatment effect, *p*=0.027
Test for heterogeneity of effect, *p*=0.40

## All-cause death

| Trial | SGLT2i, n/N (%) | Placebo, n/N (%) | HR (95% CI) | HR (95% CI) |
|---|---|---|---|---|
| EMPEROR-Reduced | 249/1863 (13.4) | 266/1867 (14.2) | 0.92 (0.77, 1.10) | |
| DAPA-HF | 276/2373 (11.6) | 329/2371 (13.9) | 0.83 (0.71, 0.97) | |
| Total | | | 0.87 (0.77, 0.98) | |




Test for overall treatment effect, *p*=0.018
Test for heterogeneity of effect, *p*=0.39

HF, heart failure; SGLT2i, sodium-glucose co-transporter-2 inhibitor

Zannad et al. The Lancet 2020. DOI:10.1016/S0140-6736(20)31824-9