# Empaglifozina en insuficiencia cardiaca

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Lilly

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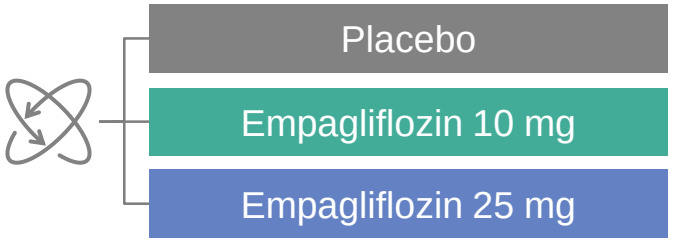
# EMPA-REG OUTCOME® was a randomised, double-blind, placebo-controlled CV outcomes trial

## Patients with T2D and established CV disease


CV disease was defined as ≥1 of the following:

- CAD
- PAD
- History of MI
- History of stroke

## Empagliflozin or placebo given on top of standard of care




**3.1 years** median observation time

## Primary endpoint: 3P-MACE

Prespecified primary endpoint components:

- CV death
- Non-fatal MI
- Non-fatal stroke

Other prespecified outcomes

- Hospitalisation for heart failure
- All-cause mortality

3P-MACE, 3-point major adverse cardiovascular events; CAD, coronary artery disease; CV, cardiovascular; MI, myocardial infarction; PAD, peripheral artery disease

Zinman B *et al. N Engl J Med* 2015;373:2117

EMPA-REG OUTCOME®

# The trial population comprised patients with T2D and established CV disease

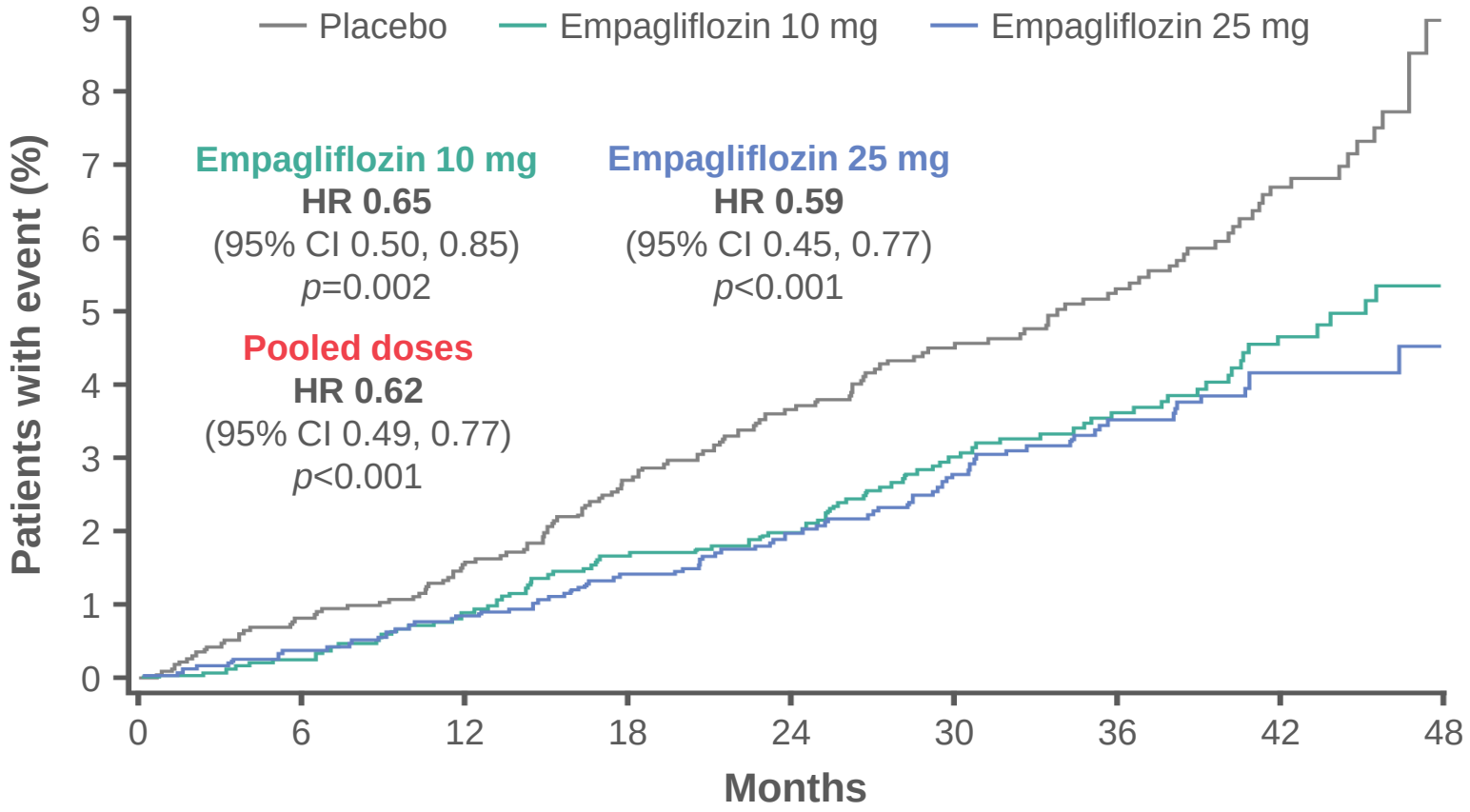
| | Placebo (n=2333) | Pooled empagliflozin (n=4867) |
|---|---|---|
| Established CV disease | 98.9 | 99.4 |
| Coronary artery disease | 75.6 | 75.7 |
| History of myocardial infarction | 46.4 | 46.7 |
| Coronary artery bypass graft | 24.1 | 25.1 |
| History of stroke | 23.7 | 23.1 |
| Peripheral artery disease | 20.5 | 20.1 |
| Heart failure* *(not an inclusion criterion)* | 10.5 | 9.9 |

- Characterisation of LV function at baseline was not performed and NT-proBNP was not measured. Not designed to determine if heart failure patients had reduced or preserved ejection fraction

Data are % in treated set
*Based on narrow standardised MedDRA query 'cardiac failure'
CV, cardiovascular; LV, left ventricular; NT-proBNP, N-terminal pro−B-type natriuretic peptide
Zinman B *et al. N Engl J Med* 2015;373:2117

EMPA-REG OUTCOME®

# Reduced risk of CV death occurred early, was sustained throughout the trial and was consistent between both doses

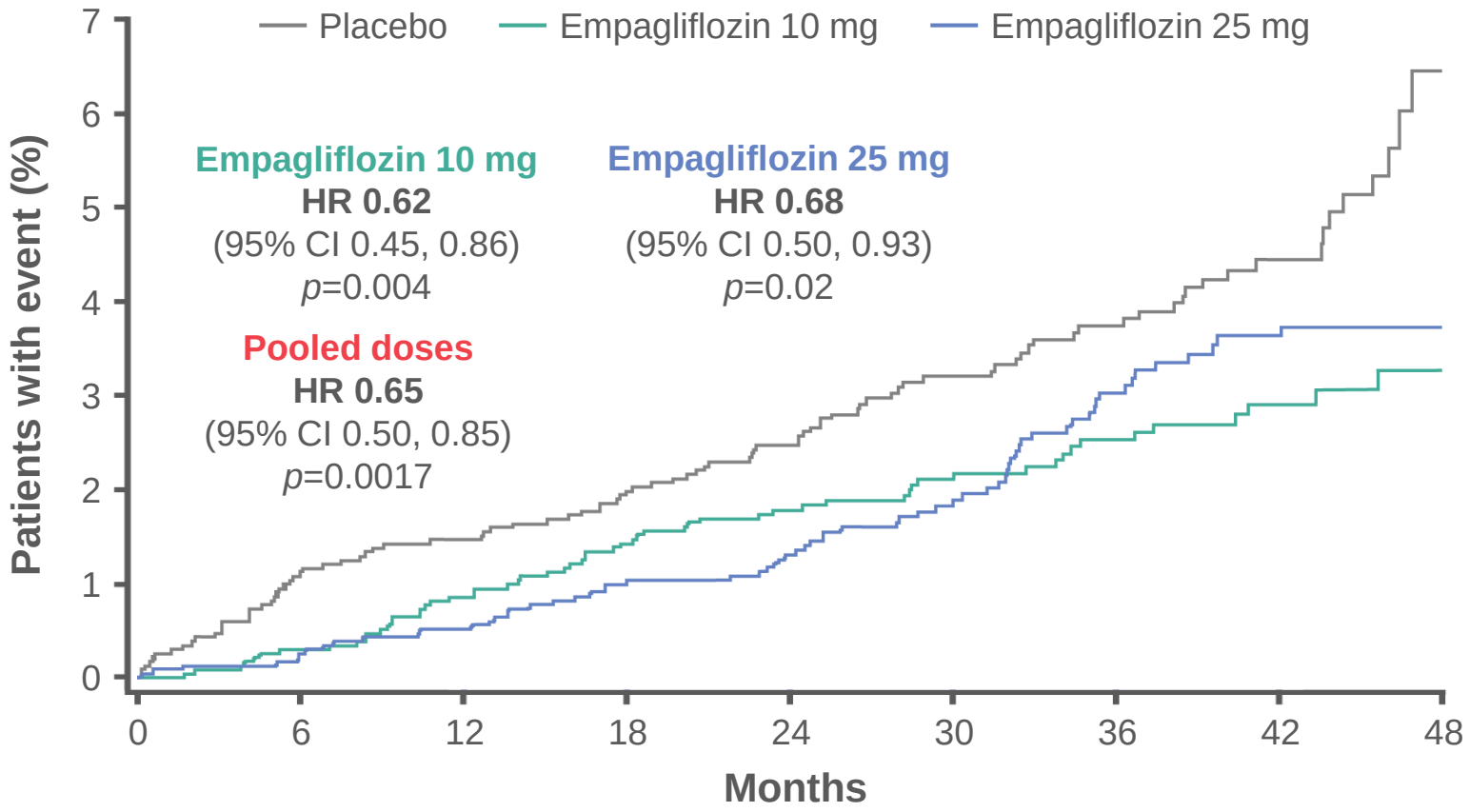



| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2333 | 2303 | 2280 | 2243 | 2012 | 1503 | 1281 | 825 | 177 |
| Empagliflozin 10 mg | 2345 | 2327 | 2305 | 2274 | 2055 | 1542 | 1303 | 847 | 201 |
| Empagliflozin 25 mg | 2342 | 2324 | 2303 | 2282 | 2073 | 1537 | 1314 | 875 | 213 |

Empagliflozin is not indicated in all countries for CV risk reduction
Cumulative incidence function. CV, cardiovascular
Zinman B *et al. N Engl J Med* 2015;373:2117; van de Borne P *et al. ESC-HF* 2016; poster P2231; Fitchett D *et al. J Am Coll Cardiol* 2018;23:71:364

EMPA-REG OUTCOME®

# Reduced risk of HHF occurred early, was sustained throughout the trial and was consistent between both doses




| No. at risk | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Placebo | 2333 | 2271 | 2226 | 2173 | 1932 | 1424 | 1202 | 775 | 168 |
| Empagliflozin 10 mg | 2345 | 2306 | 2256 | 2204 | 1981 | 1473 | 1240 | 804 | 188 |
| Empagliflozin 25 mg | 2342 | 2308 | 2267 | 2223 | 2007 | 1477 | 1247 | 830 | 207 |

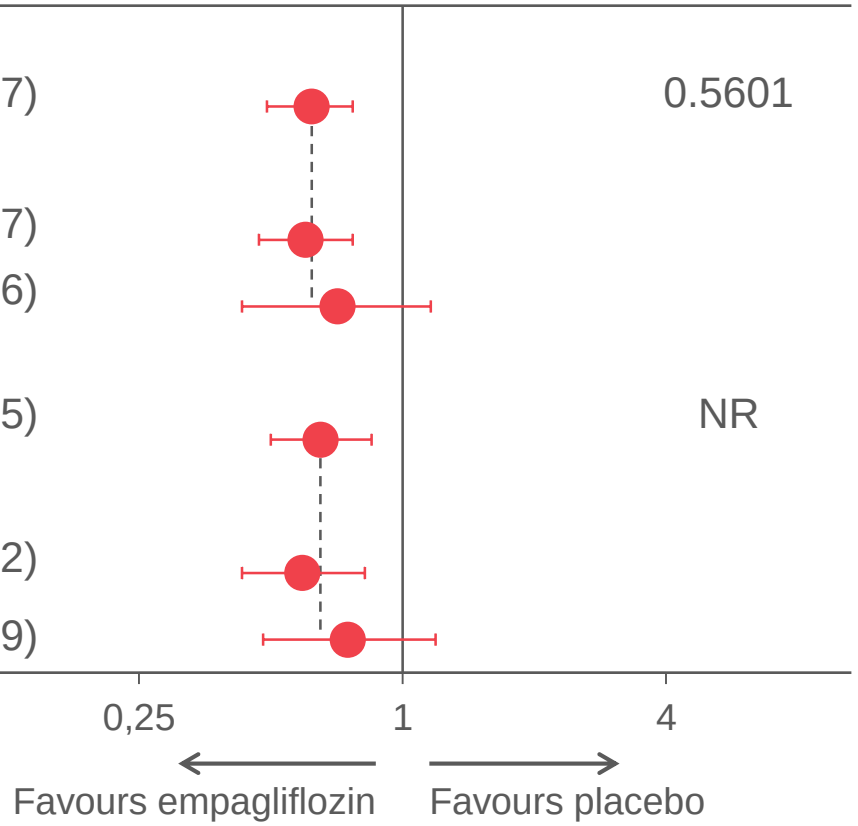
Empagliflozin is not indicated for the treatment of heart failure. HHF was a prespecified secondary outcome. Prespecified analysis. Cumulative incidence function; treated set. HHF, hospitalisation for heart failure

Zinman B *et al. N Engl J Med* 2015;373:2117; van de Borne P *et al. ESC-HF* 2016; poster P2231

EMPA-REG OUTCOME®

# The effect of empagliflozin on CV death and HHF was consistent in patients with and without HF at baseline

| | Empagliflozin | Placebo | HR (95% CI) | *p*-value for interaction |
|---|---|---|---|---|
| | n with event/N analysed (%) | | | |
| **CV death** | | | | |
| All patients | 172/4687 (3.7) | 137/2333 (5.9) | 0.62 (0.49, 0.77) | 0.5601 |
| HF at baseline | | | | |
| No | 134/4225 (3.2) | 110/2089 (5.3) | 0.60 (0.47, 0.77) | |
| Yes | 38/462 (8.2) | 27/244 (11.1) | 0.71 (0.43, 1.16) | |
| **HHF** | | | | |
| All patients | 126/4687 (2.7) | 95/2333 (4.1) | 0.65 (0.50, 0.85) | NR |
| HF at baseline | | | | |
| No | 78/4225 (1.8) | 65/2089 (3.1) | 0.59 (0.43, 0.82) | |
| Yes | 48/462 (10.4) | 30/244 (12.3) | 0.75 (0.48, 1.19) | |




Empagliflozin is not indicated for the treatment of heart failure. HHF was a prespecified secondary outcome. Cox regression analysis in patients treated with ≥1 dose of study drug. CV, cardiovascular; HF, heart failure; HHF, hospitalisation for heart failure

Fitchett DH *et al. Eur Heart J* 2016;37:1526; Zinman B *et al*. *AHA* 2016; poster S2044

EMPA-REG OUTCOME®

# EMPA-REG OUTCOME® summary

Empagliflozin in addition to standard of care **reduced CV risk and improved overall survival** in adults with **T2D** and established **CV disease**

**Relative risk reduction:**

| 3P-MACE | CV death | HHF | All-cause mortality |
|---|---|---|---|
|  |  |  |  |
| **↓14%** | **↓38%** | **↓35%** | **↓32%** |

Reduction in CV outcomes and mortality were **generally consistent across subgroups and analysis populations**

Empagliflozin is not indicated in all countries for CV risk reduction and is not indicated for the treatment of heart failure. HHF was a prespecified secondary outcome. 3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure

Zinman B *et al. N Engl J Med* 2015;373:2117; Zinman B. *EASD* 2015; oral presentation

EMPA-REG OUTCOME®

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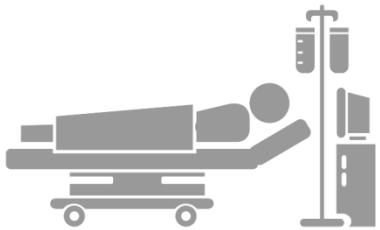
# Reduction in HHF was observed across SGLT2 inhibitor CVOTs

**HHF**



| EMPA-REG OUTCOME®[1] | CANVAS Program[2–4] | DECLARE-TIMI 58[5] |
|---|---|---|
| **35% RRR*** | **33% RRR** | **27% RRR** |
| **HR 0.65** (95% CI 0.50, 0.85) *p*=0.002† | **HR 0.67** (95% CI 0.52, 0.87)‡ | **HR 0.73** (95% CI 0.61, 0.88)‡ |

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

Empagliflozin is not indicated for the treatment of heart failure

***HHF was a prespecified secondary outcome; †Nominal *p*-value; ‡Exploratory outcome, no *p*-value is reported, only nominal effect estimate is given

CVOT, cardiovascular outcomes trial; HHF, hospitalisation for heart failure; RRR, relative risk reduction; SGLT2, sodium-glucose co-transporter-2

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Neal B *et al. N Engl J Med* 2017;377:644; 3. Mahaffey KW *et al. Circulation* 2017;137:323; 4. Rådholm K *et al. Circulation* 2018;137;458; 5. Wiviott S *et al. N Engl J Med* 2018; 2018;380:347

# Empagliflozin was the only SGLT2 inhibitor to demonstrate significant risk reduction in CV mortality

## Results were achieved on top of standard of care for CV risk reduction[1–3]

| | EMPA-REG OUTCOME®[1] (empagliflozin) | CANVAS Program[2] (canagliflozin) | DECLARE-TIMI 58[3] (dapagliflozin) |
|---|---|---|---|
| 3P-MACE (CV death, MI or stroke) | **HR 0.86** (95% CI 0.74, 0.99) *p*=0.04 | **HR 0.86** (95% CI 0.75, 0.97) *p*=0.02* | **HR 0.93** (95% CI 0.84, 1.03) *p*=0.17 |
| CV death | **HR 0.62** (95% CI 0.49, 0.77) ***p*<0.001†** | **HR 0.87** (95% CI 0.72, 1.06) | **HR 0.98** (95% CI 0.82, 1.17) |
| HHF | **HR 0.65** (95% CI 0.50, 0.85) *p*=0.002† | **HR 0.67** (95% CI 0.52, 0.87)‡ | **HR 0.73** (95% CI 0.61, 0.88)‡ |
| CV death or HHF | **HR 0.66** (95% CI 0.55, 0.79) *p*<0.001† | **HR 0.78** (95% CI 0.67, 0.91) *p*=0.002† | **HR 0.83** (95% CI 0.73, 0.95) *p*=0.005 |

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

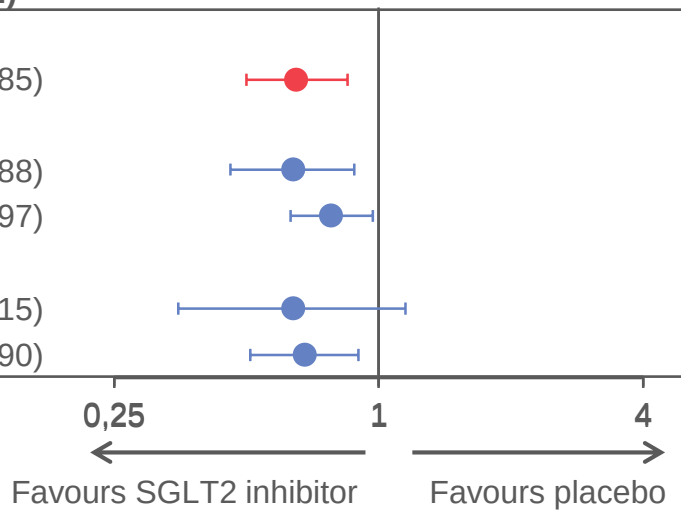
Empagliflozin is not indicated in all countries for CV risk reduction and is not indicated for the treatment of heart failure. *p*-values are for superiority

*Testing for superiority for 3P-MACE was part of the statistical analysis plan, but was not part of the hierarchical testing strategy; †Nominal *p*-value; ‡Exploratory outcome, no *p*-value is reported, only nominal effect estimate is given. 3P-MACE, 3-point major adverse cardiovascular events; CV, cardiovascular; HHF, hospitalisation for heart failure; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter-2

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Neal B *et al. N Engl J Med* 2017;377:644; 3. Wiviott S *et al. N Engl J Med* 2018; 2018;380:347

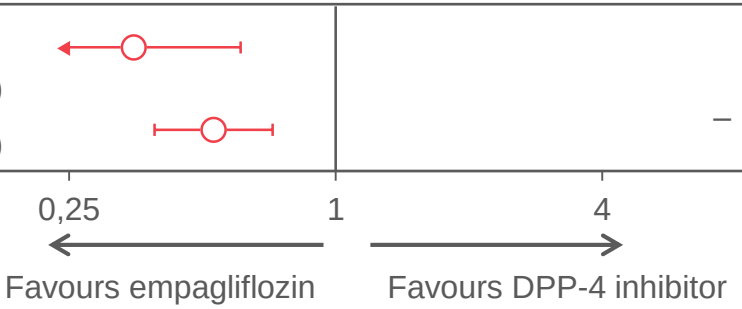
# Empagliflozin HHF results in the EMPRISE study complement those seen in SGLT2 inhibitor CVOTs

| Study | SGLT2 inhibitor n with event/N analysed (%) | Placebo n with event/N analysed (%) | HR (95% CI) | *p*-value |
|---|---|---|---|---|
| **EMPA-REG OUTCOME®[1]** | | | | |
| eCVD | 126/4687 (2.7) | 95/2333 (4.1) | 0.65 (0.50, 0.85) | <0.001 |
| **DECLARE-TIMI 58[2]** | | | | |
| MRF | 61/5108 (1.2) | 94/5078 (1.9) | 0.64 (0.46, 0.88) | 0.30* |
| ASCVD | 151/3474 (4.3) | 192/3500 (5.5) | 0.78 (0.63, 0.97) | |
| **CANVAS Program[3]** | | | | |
| MRF | – | – | 0.64 (0.35, 1.15) | 0.91* |
| eCVD | – | – | 0.68 (0.51, 0.90) | |




EMPRISE **complements** the results from EMPA-REG OUTCOME®
and indicates that the **HHF findings translate into routine clinical practice**

| | Empagliflozin | DPP-4 inhibitor | | |
|---|---|---|---|---|
| **EMPRISE[4†]** | | | | |
| Without CVD | 17/13,243 (0.1) | 47/13,243 (0.4) | 0.35 (0.20, 0.61) | – |
| With CVD | 63/4217 (1.5) | 120/4217 (2.8) | 0.53 (0.39, 0.72) | |




**Comparisons of trials should be interpreted with caution due to differences in study design, populations and methodology**. Definitions of HHF vary between studies
**p*-value for interaction; †Broad heart failure definition. See slide notes for definitions and abbreviations

1. Zinman B *et al. N Engl J Med* 2015;373:2117; 2. Wiviott S *et al. N Engl J Med* 2018; 2018;380:347;
3. Mahaffey KW *et al. Circulation* 2018:137;323; 4. Patorno E *et al. AHA* 2018; poster 1112



EMPRISE
EMPAGLIFLOZIN REAL-WORLD EFFECTIVENESS

# Contents

# Global clinical guidelines and society recommendations recognise empagliflozin for the prevention or delay of heart failure in T2D

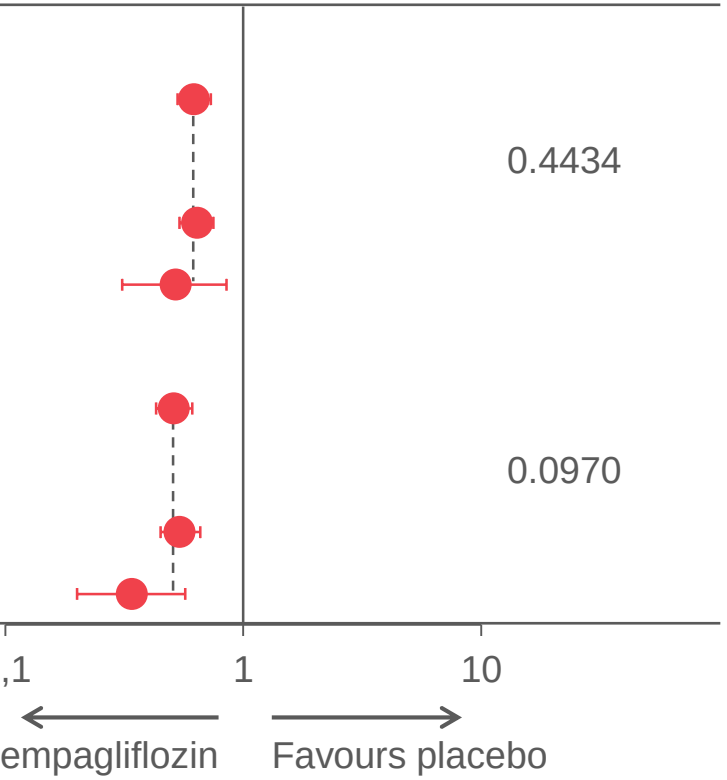
| Guideline[1–8] | Latest update | Recommendations on empagliflozin use in adult patients with T2D and CV disease |
|---|---|---|
| **Diabetes** | | |
| American Diabetes Association | Jan 2019 | To reduce the risk of MACE and CV mortality in patients with T2D and established atherosclerotic CVD[1] |
| EASD / American Diabetes Association | Oct 2018 | To be used preferentially (along with other agents with proven CV benefit) in patients with T2D where atherosclerotic CVD or CKD predominates[2] |
| Diabetes Canada / Canadian Diabetes | Apr 2018 | To reduce the risk of major CV events in adults with T2D with clinical CVD in whom glycaemic targets are not met[3] |
| AACE / ACE | Jan 2018 | To reduce CV death in patients with T2D and established CVD[4] |
| **CV disease** | | |
| American College of Cardiology | Nov 2018 | To be considered in patients with T2D and established atherosclerotic CVD to improve CV outcomes[5] |
| ESC European Society of Cardiology | Aug 2016 | To be considered early in the course of the disease to reduce CV and total mortality in patients with T2D and CVD[6] |
| **Heart failure** | | |
| Canadian Cardiovascular Society | Nov 2017 | To prevent HF-related outcomes in patients with T2D and established CVD[7] |
| Heart Failure Association of the ESC / European Society of Cardiology | May 2016 | To prevent or delay the onset of HF and prolong life in patients with T2D[8] |

**Empagliflozin is not indicated for the treatment of heart failure or kidney disease at the moment**

1. American Diabetes Association. *Diabetes Care* 2019;42:S1; 2. Davies MJ *et al. Diabetes Care* 2018;41:2669; 3. Diabetes Canada. *Can J Diabetes* 2018;42:S162; 4. Garber AJ *et al. Endocr Pract* 2018;24:91; 5. Das SR *et al. J Am Coll Cardiol* 2018;72:3200; 6. Piepoli MF *et al. Eur Heart J* 2016;37:2315; 7. Ezekowitz JA *et al. Can J Cardiol* 2017;33:1342; 8. Ponikowski P *et al. Eur Heart J* 2016;37:2129

# Empagliflozin reduced the occurrence of first introduction of loop diuretic and first onset of oedema, regardless of HF status at baseline

| | Empagliflozin | Placebo | HR (95% CI) | *p*-value for subgroup interaction |
|---|---|---|---|---|
| | n with event/N analysed (%) | | | |
| **First introduction of loop diuretic** | | | | |
| All patients | 340/3962 (8.6) | 262/1969 (13.3) | 0.62 (0.53, 0.73) | |
| HF at baseline | | | | 0.4434 |
| No | 308/3724 (8.3) | 232/1835 (12.6) | 0.64 (0.54, 0.75) | |
| Yes | 32/238 (13.4) | 30/134 (22.4) | 0.52 (0.31, 0.85) | |
| **First onset of oedema** | | | | |
| All patients | 251/4687 (5.4) | 235/2333 (10.1) | 0.51 (0.43, 0.61) | |
| HF at baseline | | | | 0.0970 |
| No | 277/4225 (5.4) | 202/2089 (9.7) | 0.54 (0.45, 0.66) | |
| Yes | 24/462 (5.2) | 33/244 (13.5) | 0.34 (0.20, 0.57) | |



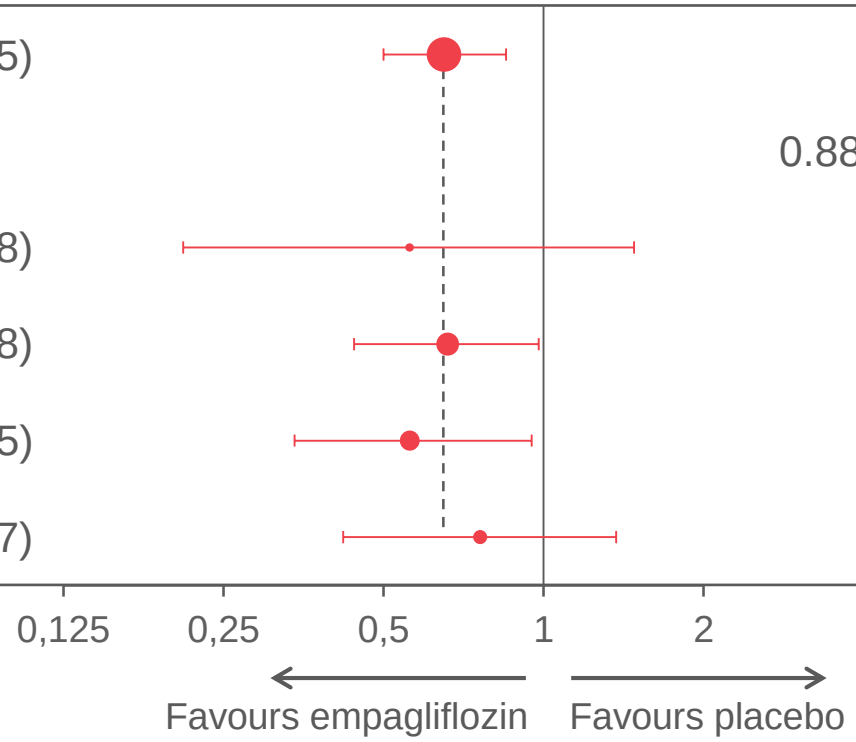

HF, heart failure

Januzzi J *et al. Eur J Heart Fail* 2019;DOI:10.1002/ejhf.1419

EMPA-REG OUTCOME®

# The effect of empagliflozin on HHF was largely independent of baseline HbA1c

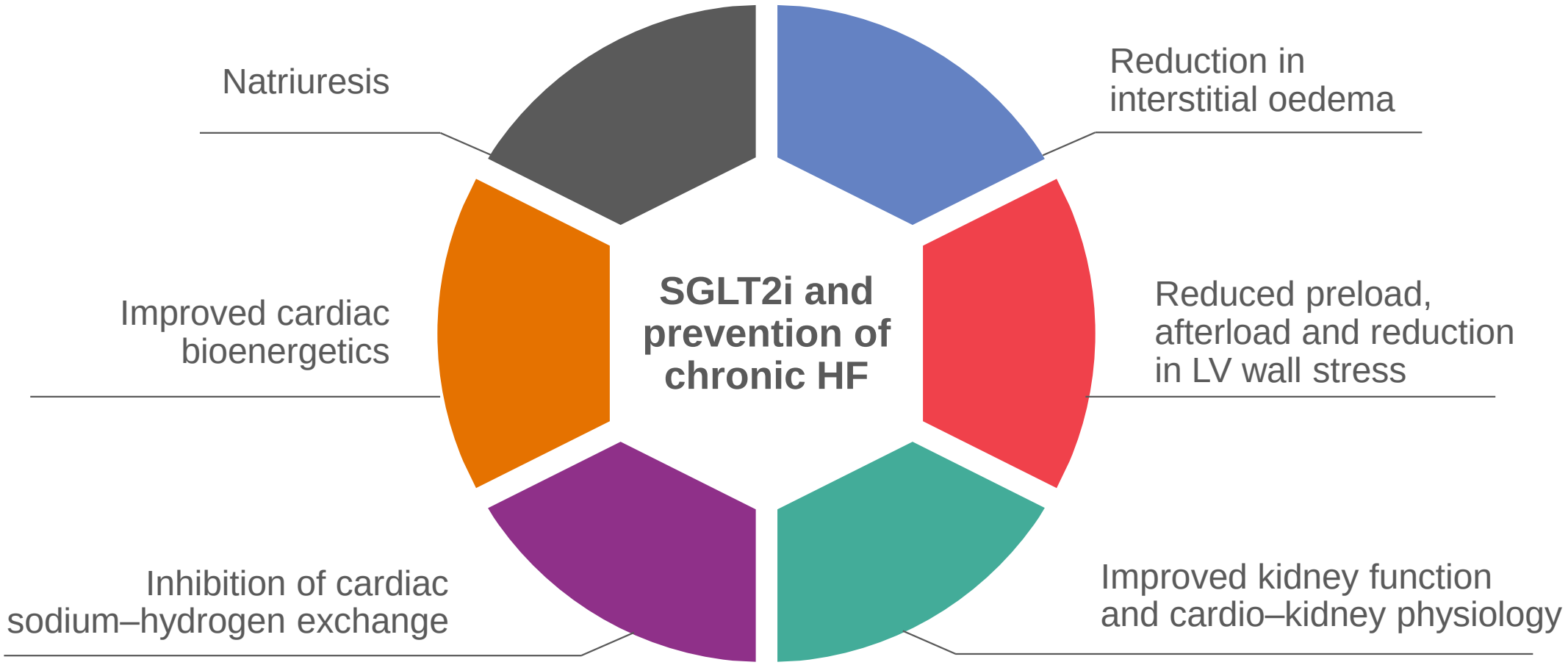
| | Empagliflozin | Placebo | | *p*-value for interaction |
|---|---|---|---|---|
| | n with event, % | | HR (95% CI) | |
| **All patients** | 2.7 | 4.1 | 0.65 (0.50, 0.85) | |
| **HbA1c at baseline** | | | | 0.8875 |
| <7.0% | 3.4 | 5.5 | 0.56 (0.21, 1.48) | |
| 7.0% to <8.0% | 2.7 | 4.2 | 0.66 (0.44, 0.98) | |
| 8.0% to <9.0% | 2.0 | 3.4 | 0.56 (0.34, 0.95) | |
| ≥9.0% | 3.6 | 4.7 | 0.76 (0.42, 1.37) | |




HHF was a prespecified secondary outcome. EMPA-REG OUTCOME® was not powered to show differences between subgroups.
Cox regression analysis in patients treated with ≥1 dose of study drug. Subgroups with HbA1c <7.0% and ≥9.0% had 95% CIs that crossed unity
HbA1c, glycated haemoglobin; HHF, hospitalisation for heart failure
Inzucchi S *et al. Circulation* 2018;138:1904

EMPA-REG OUTCOME®

# Many mechanisms may contribute to the beneficial effects on heart failure seen with empagliflozin




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

Farkouh ME & Verma S. *J Am Coll Cardiol* 2018;71:2505

# Plasma glucose remains unchanged with chronic empagliflozin treatment in patients without diabetes

| | Non-diabetes (n=25) | | T2D (n=66) | |
|---|---|---|---|---|
| | Baseline | Chronic (28 days) | Baseline | Chronic (28 days) |
| Fasting UGE (AUC), g/h | 0.02 | 5.4 | 0.02 | 9.2 |
| Plasma glucose, mmol/l | 7.1 | 7.0 | 11.1 | 9.7 |
| Plasma insulin, pmol/l | 520 | 379 | 309 | 253 |
| Plasma glucagon, pmol/l | 19 | 18 | 18 | 19 |
| Plasma βHB, mmol/l | 145 | 267 | 246 | 561 |

AUC, area under the curve; βHB, beta-hydroxybutyrate; UGE, urinary glucose excretion

Ferrannini E *et al. Diabetes* 2016;65:1190

# The empagliflozin chronic heart failure program

**Heart failure with preserved ejection fraction (HFpEF)**

LVEF >40%[1]

**Heart failure with reduced ejection fraction (HFrEF)**

LVEF ≤40%[4]

## EMPEROR PRESERVED

Outcomes trial with planned recruitment: **5500 patients**[1–3]

## EMPEROR REDUCED

Outcomes trial with planned recruitment: **3350 patients**[4,5]

## EMPERIAL PRESERVED

Functional capacity study
**300 patients**[6,7]

## EMPERIAL REDUCED

Functional capacity study
**300 patients**[8,9]

## EMPA-VISION

Mechanistic study
**86 patients**[10]


1. ClinicalTrials.gov. NCT03057951 (accessed Jan 2019)
2. Butler J et al. ESC-HF 2018; poster P972
3. Boehringer Ingelheim. Data on file. 2018
4. ClinicalTrials.gov. NCT03057977 (accessed Jan 2019)
5. Zannad F et al. ESC-HF 2018; poster P1755
6. ClinicalTrials.gov. NCT03448406 (accessed Jan 2019)
7. Ponikowski P et al. ESC-HF 2018; poster P302
8. ClinicalTrials.gov. NCT03448419 (accessed Jan 2019))
9. Abraham WT et al. ESC-HF 2018; poster P303
10. ClinicalTrials.gov. NCT03332212 (accessed Jan 2019)

# Contents

# The EMPEROR trial program evaluates empagliflozin in two dedicated heart failure trials

**First dedicated outcomes trials** of empagliflozin in patients with chronic heart failure

Specifically designed to prospectively address the safety and efficacy of empagliflozin in patients with heart failure, with **reduced or preserved ejection fraction**

Evaluate whether the effects on heart failure outcomes **extend to patients without diabetes**

ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); ClinicalTrials.gov. NCT03057951 (accessed Feb 2019)

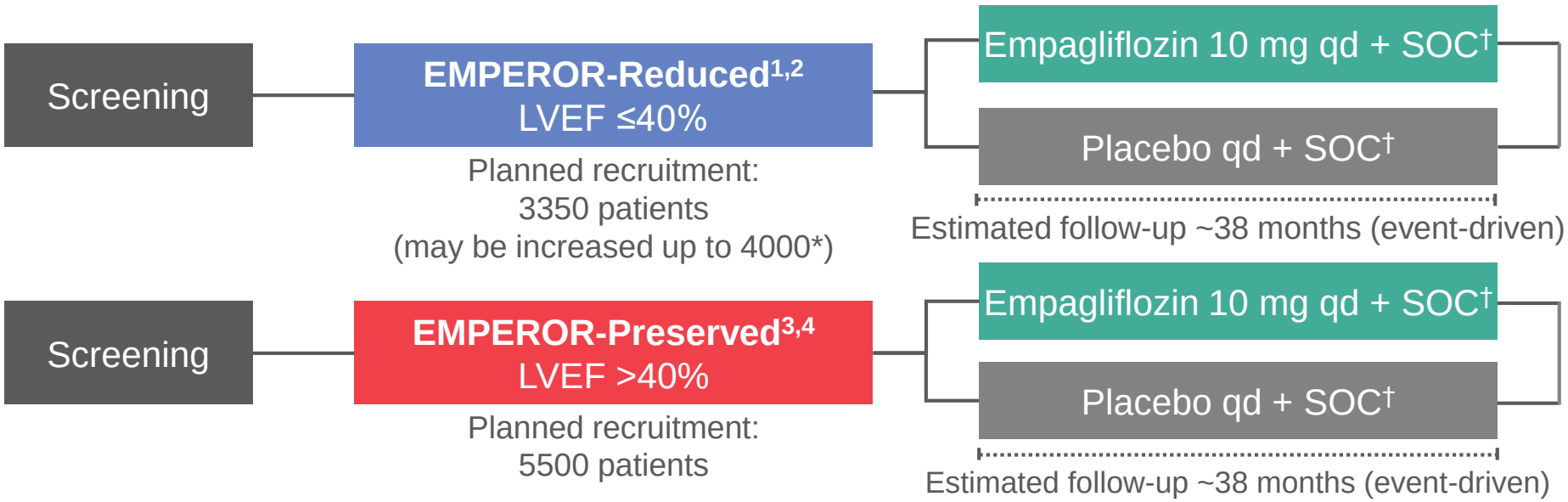


EMPEROR HEART FAILURE STUDIES

# EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials

## Phase III randomised double-blind placebo-controlled trials

**Population:** T2D and non-T2D, aged ≥18 years, chronic HF (NYHA class II–IV)




*Based on blinded assessment of event rate; †Guideline-directed medical therapy
HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SOC, standard of care
1. ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951 (accessed Feb 2019); 4. Butler J *et al. ESC-HF* 2018; poster P972



EMPEROR HEART FAILURE STUDIES

# EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials

## Trial endpoints

| | EMPEROR-Reduced[1,2] | EMPEROR-Preserved[3,4] |
|---|---|---|
| **Primary endpoint** | Time to first event of adjudicated CV death or adjudicated HHF | |
| **Secondary endpoints** | • Occurrence of adjudicated HHF (first and recurrent)<br>• Time to first adjudicated HHF<br>• Time to adjudicated CV death<br>• Time to all-cause mortality<br>• Time to onset of diabetes<br>• Occurrence of all-cause hospitalisation (first and recurrent)<br>• Change from baseline in KCCQ to Week 52<br>• eGFR (CKD-EPI equation) slope of change from baseline | |

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalisation for heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire

1. ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951 (accessed Feb 2019); 4. Butler J *et al. ESC-HF* 2018; poster P972



EMPEROR HEART FAILURE STUDIES

# EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials

## Trial inclusion criteria

| | EMPEROR-Reduced[1,2] | EMPEROR-Preserved[3,4] |
|---|---|---|
| **Inclusion criteria** | Age ≥18 years (Japan, age ≥20 years) at screening | |
| | Chronic HF NYHA class II−IV | |
| | **HFrEF (LVEF ≤40%) and elevated NT-proBNP** | **HFpEF (LVEF >40%) and elevated NT-proBNP** |
| | **EF (%)** / **NT-proBNP (pg/ml)** Patients without AF*<br>≥36 to ≤40 / ≥2500<br>≥31 to ≤35 / ≥1000<br>≤30 / ≥600<br>≤40% + HHF within 12 months / ≥600 | **NT-proBNP (pg/ml)** Patients without AF*<br>>300<br>Structural heart disease within 6 months or HHF within 12 months |
| | Dose of medical therapy for HF that is consistent with CV guidelines stable for ≥1 week prior to screening and throughout screening period | |
| | Further inclusion criteria apply | |

***The cutoff for patients *with* AF is doubled in EMPEROR-Reduced and tripled in EMPEROR-Preserved**

See slides notes for abbreviations

1. ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951 (accessed Feb 2019); 4. Butler J *et al. ESC-HF* 2018; poster P972



EMPEROR HEART FAILURE STUDIES

# EMPEROR-Reduced and EMPEROR-Preserved heart failure outcome trials

## Trial exclusion criteria

| | EMPEROR-Reduced[1,2] | EMPEROR-Preserved[3,4] |
|---|---|---|
| **Exclusion criteria** | • MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before Visit 1<br>• Heart transplant recipient, or listed for heart transplant<br>• Acute decompensated HF<br>• SBP ≥180 mmHg at Visit 2<br>• Symptomatic hypotension and/or a SBP <100 mmHg<br>• eGFR <20 ml/min/1.73 $m^2$ or requiring dialysis | |
| | Further exclusion criteria apply | |

CV, cardiovascular; eGFR, estimated glomerular filtration; HF, heart failure; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischaemic attack

1. ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); 2. Zannad F *et al. ESC-HF* 2018; poster P1755; 3. ClinicalTrials.gov. NCT03057951 (accessed Feb 2019); 4. Butler J *et al. ESC-HF* 2018; poster P972



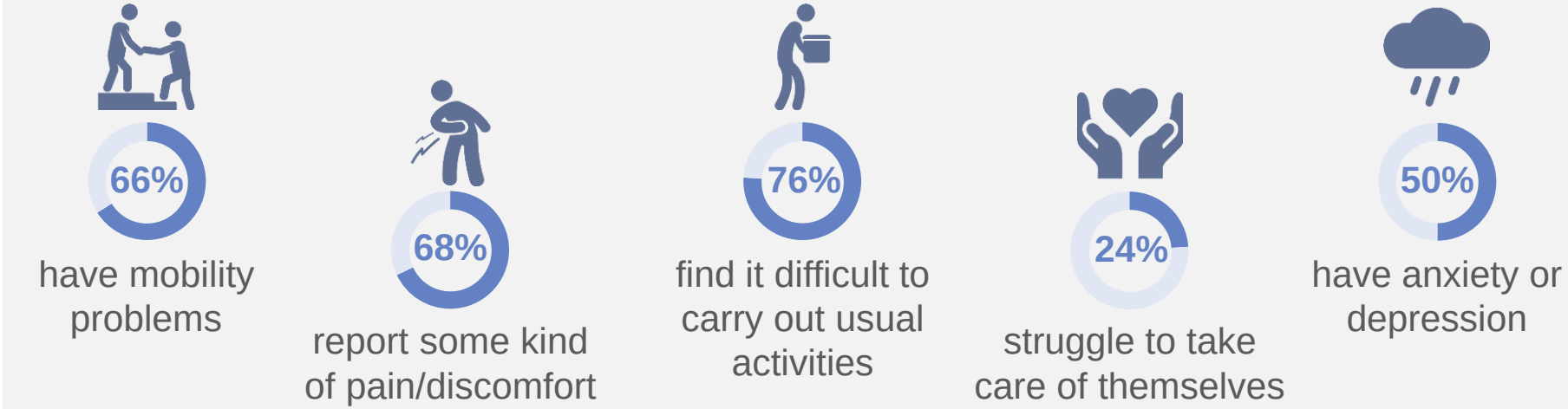
EMPEROR HEART FAILURE STUDIES

# Contents

# Background: Unmet medical need in patients with heart failure

## HF impacts patients' lives in many ways

### Physical, social and emotional impact of HF




**Improvement HF symptoms and QoL, such as physical activity, continues to be an unmet medical need in patients with HF**

CV, cardiovascular; HF, heart failure; QoL, quality of life

Calvert MJ *et al. Eur J Heart Fail* 2005;7:243

# Background: Effect of heart failure medications on survival and functional outcomes

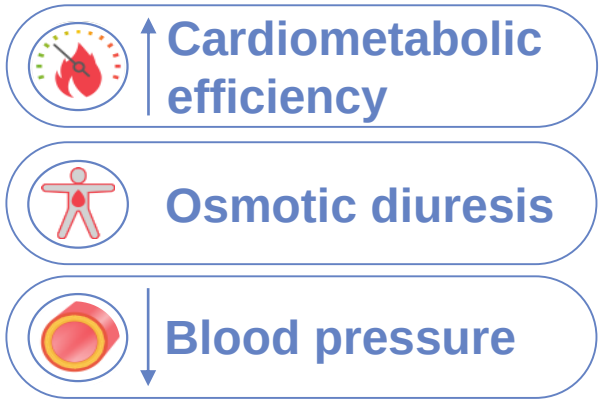
Although guideline-recommended HF therapies demonstrated benefits in survival and HHF, some have not been shown to improve patients' functional status

| | | Trial | Intervention | Significant improvement in exercise capacity (6MWT)* | Survival benefit† |
|---|---|---|---|---|---|
| HFrEF | Beta-blocker | Khand 2003[1] | Carvedilol | ✗ | ✓ |
| | Beta-blocker | Packer 1996[2] | Carvedilol | ✓ | ✓ |
| | Beta-blocker | RESOLVD 2000[3] | Metoprolol | ✗ | ✓ |
| | Beta-blocker | Genth-Zotz 2000[4] | Metoprolol | ✓ | ✓ |
| | ACEi | McKelvie 1999[5] | Enalapril | ✗ | ✓ |
| | ARB | McKelvie 1999[5] | Candesartan | ✗ | ✓ |
| | ARNI | McMurray 2014[6] | Sacubitril/valsartan | ? | ✓ |
| HFpEF | RAASi | Holland 2011[7] | RAAS inhibition | ✓ | ✗ |

*$p<0.05$; †Upper bound of the 95% CI of the odds ratio was <1
See slide notes for full list of references and abbreviations
Adapted from Wessler BS *et al. Circ Heart Fail* 2011;578:588

# Rationale and mode of action hypotheses

## The mode of action of empagliflozin suggests a potential for <u>early</u> improvement of exercise capacity and patient symptoms




- **Increased haemoglobin/oxygen-carrying capacity** (haemoconcentration ± increased synthesis)[1–8]
- **Modest osmotic diuresis** leading to haemodynamic changes and ↓ extracellular volume[1–4,11,12]
- **Blood-pressure lowering** without ↑ heart rate[6,13–15]

1. Butler J et al. Eur J Heart Fail 2017;19:1390, 2. Heise T et al. Diabetes Obes Metab 2013;15:61, 3. Heise T et al. Clin Ther 2016;38:2265, 4. Ferrannini E et al. Diabetes 2016;65:1190, 5. Lund SS et al. EASD 2015;750-P, 6. Zinman B et al. N Engl J Med 2015;373:2117 . 7. Van Beaumont W. J Appl Physiol 1972;32:712. 8: Swedberg K et al. N Engl J Med 2013;368:1210. 9: Ferrannini E et al. Clin Invest 2013;124:499. 10: Nishimura R et al. Cardiovasc Diabetol 2015;14:11. 11: Ferrannini E et al. Diabetes Care 2015;38:1730. 12: Cherney DZ et al. Circulation 2014;129:587. 13: Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance (empagliflozin) Prescribing Information. 2018. 15: Boehringer Ingelheim Pharmaceuticals, Inc. Jardiance (empagliflozin) summary of product characteristics. May 2018

# The EMPERIAL studies evaluate empagliflozin in two dedicated functional capacity studies

**First dedicated functional capacity studies** of empagliflozin designed to evaluate exercise capacity and quality of life in patients with chronic heart failure, with reduced or preserved ejection fraction

Assess the effects on functional capacity endpoints **extend to patients without diabetes**

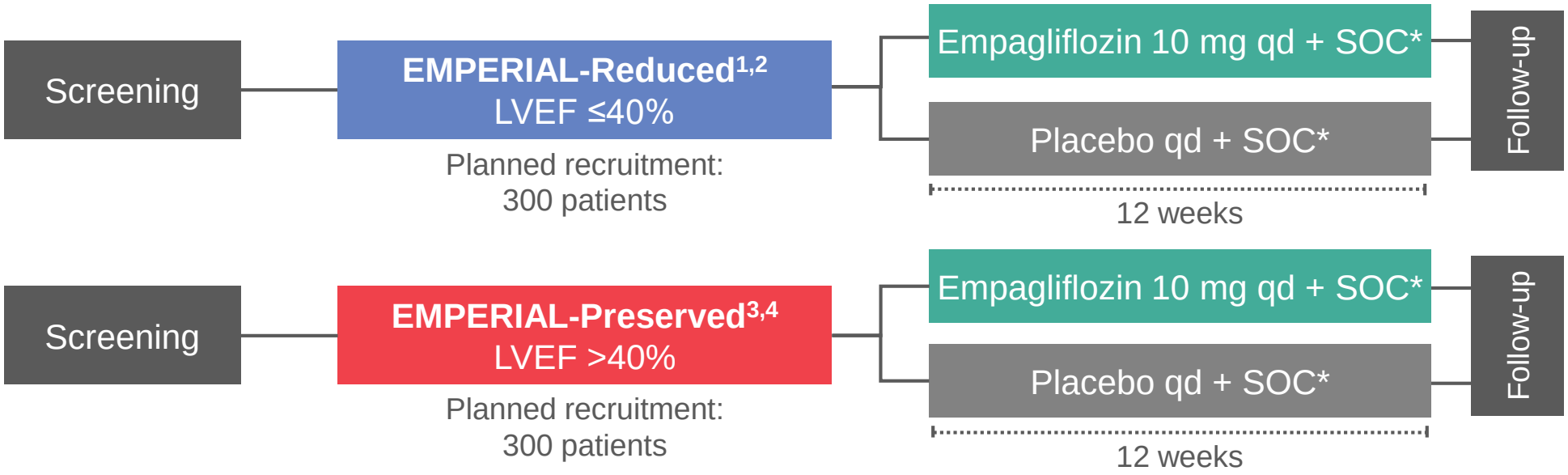
ClinicalTrials.gov. NCT03448419 (accessed Feb 2019); ClinicalTrials.gov. NCT03448406 (accessed Feb 2019)

# EMPERIAL-Reduced and EMPERIAL-Preserved studies

## International phase III randomised double-blind placebo-controlled studies

**Aim:** To evaluate the effect of empagliflozin 10 mg versus placebo on exercise ability using the **6MWT** in patients with HF with **reduced** or **preserved** ejection fraction

**Population:** Chronic HF (HFrEF or HFpEF), with or without T2D




*Guideline-directed medical therapy

6MWT, 6-minute walk test; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction; SOC, standard of care

1. ClinicalTrials.gov. NCT03448419 (accessed Feb 2019); 2. Abraham WT *et al. ESC-HF* 2018; poster P303; 3. ClinicalTrials.gov. NCT03448406 (accessed Feb 2019); 4. Ponikowski P *et al. ESC-HF* 2018; poster P302

# EMPERIAL-Reduced and EMPERIAL-Preserved studies

## Study inclusion criteria

| EMPERIAL-Reduced[1,2] | EMPERIAL-Preserved[3,4] |
|---|---|
| • Age ≥18 years<br>• Chronic HF NYHA class II−IV<br>• Walking distance in the 6MWT ≤350 m | |
| **HFrEF (LVEF ≤40%) and elevated NT-proBNP**<br>Patients without AF >450 pg/ml<br>Patients with AF >600 pg/ml | **HFpEF (LVEF >40%) and elevated NT-proBNP**<br>Patients without AF >300 pg/ml<br>Patients with AF >600 pg/ml |
| Further exclusion criteria apply | |

6MWT, 6-minute walk test; AF, atrial fibrillation; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; NT-proBNP, N terminal pro−B-type natriuretic peptide

1. ClinicalTrials.gov. NCT03448419 (accessed Feb 2019); 2. Abraham WT *et al. ESC-HF* 2018; poster P303; 3. ClinicalTrials.gov. NCT03448406 (accessed Feb 2019); 4. Ponikowski P *et al. ESC-HF* 2018; poster P302



EMPERIAL

# EMPERIAL-Reduced and EMPERIAL-Preserved studies

## Study exclusion criteria

| EMPERIAL-Reduced[1] | EMPERIAL-Preserved[2] |
|---|---|
| • MI, coronary artery bypass graft surgery or other major CV surgery, stroke or TIA ≤90 days before Visit 1<br>• Acute decompensated HF<br>• SBP ≥180 mmHg at Visit 1 or 2, or SBP >160 at both Visits 1 and 2<br>• Symptomatic hypotension and/or a SBP <100 mmHg at Visit 1 or 2<br>• eGFR <20 ml/min/1.73 $m^2$ or requiring dialysis at Visit 1<br>• Largest distance walked in the 6MWT at baseline <100 m | |
| Further exclusion criteria apply | |

6MWT, 6-minute walk test; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MI, myocardial infarction; SBP, systolic blood pressure; TIA, transient ischaemic attack

1. ClinicalTrials.gov. NCT03448419; 2. ClinicalTrials.gov. NCT03448406 (both accessed Jan 2019)



EMPERIAL

# EMPERIAL-Reduced and EMPERIAL-Preserved studies

## Study endpoints

| | EMPERIAL-Reduced[1,2] | EMPERIAL-Preserved[3,4] |
|---|---|---|
| **Primary endpoint** | Change from baseline to Week 12 in **exercise capacity (6MWT)** | |
| **Secondary endpoints** | Change from baseline to Week 12 in:<br>• KCCQ-TSS<br>• CHQ-SAS dyspnoea score<br>• Change from baseline to Week 6 in exercise capacity (6MWT)<br><br>Change from baseline to Week 12 in:<br>• Clinical congestion score<br>• PGI-S of HF symptoms<br>• PGI-S of dyspnoea<br>• PGI-C in HF symptoms<br>• PGI-C in dyspnoea<br>• NT-proBNP | |

6MWT, 6-minute walk test; CHQ-SAS, Chronic Heart Questionnaire Self-Administered Standardised; HF, heart failure; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; NT-proBNP, N terminal pro−B-type natriuretic peptide; PGI-C, Patient Global Impression of Change; PGI-S, Patient Global Impression of Severity

1. ClinicalTrials.gov. NCT03448419 (accessed Feb 2019); 2. Abraham WT *et al. ESC-HF* 2018; poster P303; 3. ClinicalTrials.gov. NCT03448406 (accessed Feb 2019); 4. Ponikowski P *et al. ESC-HF* 2018; poster P302

# 6MWT as a functional capacity endpoint

**The 6MWT is a submaximal exercise test in which the distance walked over 6 minutes is used to assess exercise capacity[1]**

- The 6MWT is a legitimate and **important therapeutic target for patients with symptomatic HF** because it represents a measure of functional status for these patients[2]
- Exertional symptoms in patients with HF usually start at a lower threshold than maximal exercise capacity[3]
  - The 6MWT is **appropriate for elderly patients** or those with considerable limitation in daily life[1,3]
  - Better reflects the **activities of daily living** [1,3]
- Distance walked during the 6MWT **correlates with symptom improvement**, **mortality** and peak $O_2$ consumption[3]
  - A 6MWT <300 m predicts a poorer outcome in stable patients with HF[4]
  - In patients evaluated for transplantation, a 6MWT <350 m has a sensitivity of 71% and specificity of 60% for predicting peak $O_2$ consumption <14 ml/kg/min[4]
- The 6MWT has been shown to be **highly reproducible** and **safe across different populations**, including patients with HF and the elderly[3]
- The 6MWT is relatively **simple**, **inexpensive** and no specific instruments are required[1,3]

6MWT, 6-minute walk test; HF, heart failure

1. Guyatt G *et al. Can Med Assoc J* 1985;132:919; 2. Wessler BS *et al. Circ Heart Fail* 2011;4:578; 3. Rostagno C *et al. Intern Emerg Med* 2007;3:205; 4. Bittner V & Singh S. The 6 Minute Walk Test. 2017 https://www.thecardiologyadvisor.com/cardiology/the-6-minute-walk-test/article/584216/ (accessed Jan 2019)

# Contents

# Potential clinical mechanisms of empagliflozin suggest it may reduce CV risk via improved cardiac energetics

## The heart converts chemical energy into mechanical energy

### Per day:

**Consumes energy-providing substrates:**

- >20 g of carbohydrates
- 30 g of fat
- Ketone bodies, amino acids
- **>35 litres of oxygen**

**Pumps 7200 litres of blood against average mean arterial pressure of 100 mmHg**

Taegtmeyer H *et al. Circ Res* 2016;118:1659

# Background: These potential mechanisms are currently under investigation

Although patients with T2D benefit from treatment with empagliflozin, physicians and researchers have set out to discover the mechanisms to explain these findings

EMPA-VISION is a **mechanistic CMR and CPET study** to assess the effects of empagliflozin on **cardiac metabolism and function** in HF patients with HFrEF and HFpEF

CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

ClinicalTrials.gov. NCT03332212 (accessed Feb 2019)

# Rationale: EMPA-VISION HF mechanistic CMR and CPET study

**Empagliflozin treatment**

May lead to:[1–6]

- Improved oxygen carrying capacity
- Improved mitochondrial function
- Improved endothelial function
- Reduced afterload

**Improved cardiac metabolism/cardiac function**

**Hypothesis**

Empagliflozin treatment improves **cardiac metabolism (energetics)** and leads to:

- Increased PCr/ATP ratio
- Improvement in cardiac function

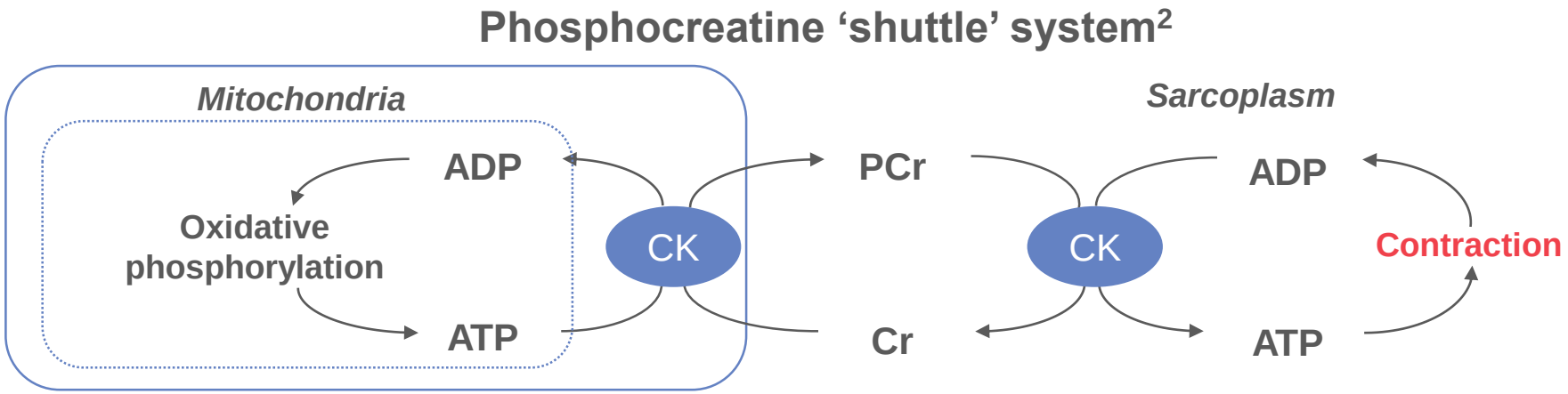
ATP, adenosine triphosphate; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; HF, heart failure; PCr, phosphocreatine

1. Chilton R *et al. Diabetes Obes Metab* 2015;17:1180; 2. Zinman B *et al*. *Stroke* 2017;48:1218; 3. Ferrannini E *et al. Diabetes* 2016;65:1190; 4. Baartscheer A *et al. Diabetologia* 2017;60:568; 5. Oelze M *et al. PLoS One* 2014;9:e112394; 6. Sebastian S *et al. Redox Biol* 2017;13:370



EMPA-VISION

# PCr/ATP ratio as a measure for cardiac energetics




Improved cardiac energetics lead to an increase in PCr/ATP ratio

Guimarães-Ferreira L. *Einstein (Sao Paulo)* 2014;12:126



EMPA-VISION

# PCr/ATP ratio as a measure of cardiac energetics

## PCr/ATP is a biomarker for HF prognosis

Decreased PCr/ATP ratios in patient with HF with dilated cardiomyopathy negatively correlate with the NYHA functional class[1]

- Better predictor of long-term survival in patients with HF compared with NYHA functional class or LVEF[1,2]

Clinical $^{31}$P-MRS studies have shown that PCr/ATP ratios decrease in advanced HF[4–6]

$^{31}$P-MRS, phosphorus 31 magnetic resonance spectroscopy; ATP, adenosine triphosphate; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PCr, phosphocreatine

1. Neubauer S *et al. Circulation* 1997;96:2190; 2. Metzler B *et al. J Cardiovasc Magn Reson* 2002;4:493;
3. Scheuermann-Freestone M *et al. Circulation* 2003;107:3040; 4. Hudsmith LE & Neubauer S. *Nat Clin Pract Cardiovasc* 2008;5(Suppl. 2):S49;
5. Hudsmith LE & Neubauer S *Am Col Cardiol Imag* 2009;2;87; 6. Phan TT *et al. J Am Coll Cardiol* 2009;54:402

# EMPA-VISION HF mechanistic CMR and CPET study: Summary

**This study will advance our understanding of:**

1. Cardiac energetics in resting/stress conditions via $^{31}$P-MRS
2. Functional capacity changes in resting/stress conditions via CPET
3. Cardiac structure, perfusion status and function measured by MRI
4. Other biomarkers of HF and metabolic changes (e.g. glucose, lipids)

It will therefore provide more insight into the mechanism of action of empagliflozin in HF

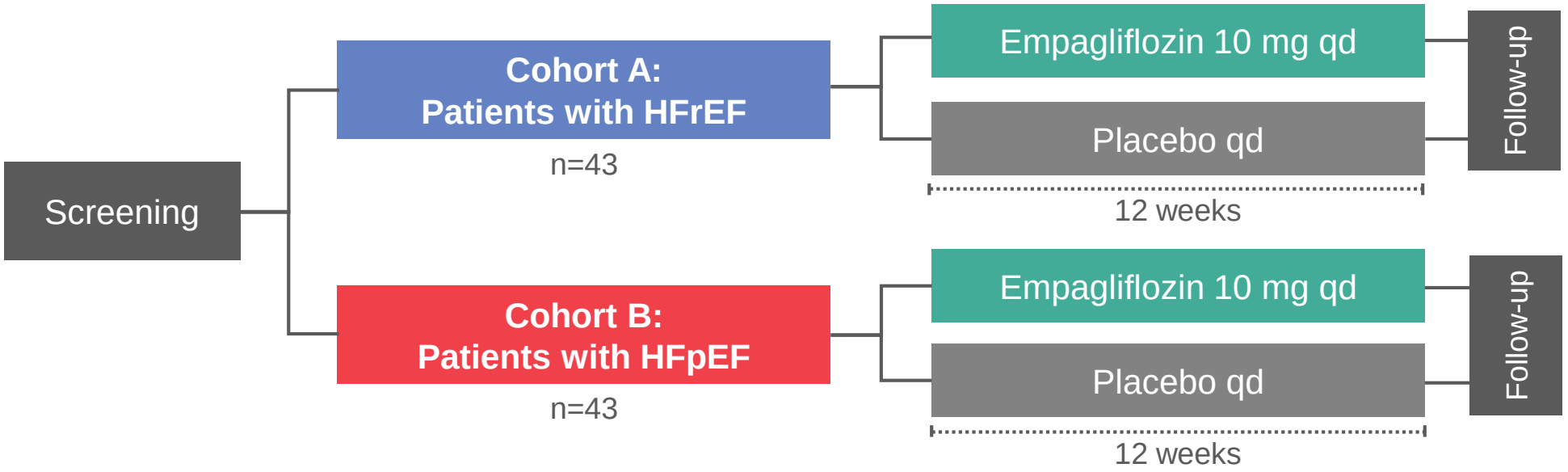
MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; $^{31}$P-MRS, phosphorus magnetic resonance spectroscopy; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; HF, heart failure
ClinicalTrials.gov. NCT03332212 (accessed Feb 2019)

# EMPA-VISION HF mechanistic CMR and CPET study: Study design

## Phase III randomised double-blind placebo-controlled study

**Aim:** A mechanistic CMR and CPET study to assess the effects of empagliflozin treatment on cardiac metabolism (energetics) and function in patients with HFpEF and HFrEF

**Population:** Chronic HF (HFrEF or HFpEF), with or without diabetes




CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise test; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction

ClinicalTrials.gov. NCT03332212 (accessed Feb 2019)

# Contents

# Dedicated HF outcomes trials with SGLT1/2 inhibitors (1/2)

| | EMPEROR-Preserved[1,2,3] | EMPEROR-Reduced[4,5] |
|---|---|---|
| **Study drug** | Empagliflozin 10 mg qd | Empagliflozin 10 mg qd |
| **Population** | HF with preserved or reduced EF, with or without T2D | |
| **Sample size** | 5500 | 3350* |
| **Key inclusion criteria** | • Chronic HF†<br>• Elevated NT-proBNP<br>• eGFR ≥20 ml/min/1.73 $m^2$ | |
| | **HFpEF (LVEF >40%)** | **HFrEF (LVEF ≤40%)** |
| **Primary endpoint** | Time to first event of adjudicated CV death or adjudicated HHF | |
| **Key secondary endpoints** | • Individual components of primary endpoint<br>• Time to all-cause mortality<br>• All-cause hospitalisation<br>• Time to first occurrence of chronic dialysis, kidney transplant, or sustained reduction of eGFR<br>• Change from baseline in KCCQ | |

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

*NT-proBNP-based enrichment of the population, with patients at higher severity of HF; †NYHA class II–IV

See notes page for abbreviations

1. ClinicalTrials.gov. NCT03057951 (accessed Feb 2019); 2. Butler J *et al. ESC-HF* 2018; poster P972; 3. Boehringer Ingelheim. Data on File. 2018;
4. ClinicalTrials.gov. NCT03057977 (accessed Feb 2019); 5. Zannad F *et al. ESC-HF* 2018; poster P1755

# Dedicated HF outcomes trials with SGLT1/2 inhibitors (2/2)

| | DELIVER[1] | DAPA-HF[2] | SOLOIST-WHF[3,4] |
|---|---|---|---|
| **Study drug** | Dapagliflozin 10 mg | Dapagliflozin 5 mg or 10 mg qd | Sotagliflozin |
| **Population** | HFpEF | HFrEF | Worsening HF in patients with T2D |
| **Sample size** | 4700 | 4744 | 6667* |
| **Key inclusion criteria** | • Symptomatic HFpEF†<br>• Elevated NT-proBNP<br>• eGFR ≥25 ml/min/1.73 $m^2$<br>• Ambulatory and hospitalised patients | • Symptomatic HFrEF*<br>• Elevated NT-proBNP<br>• eGFR ≥30 ml/min/1.73 $m^2$ | • T2D<br>• Elevated NT-proBNP<br>• Hospital admission for worsening HF and haemodynamically stable<br>• Patients with HFrEF administered beta-blockers and RAAS inhibitors (unless contraindicated) |
| | **HFpEF (LVEF >40%)** | **HFrEF (LVEF ≤40%)** | **HFpEF and HFrEF (LVEF <50%)** |
| **Primary endpoints** | Time to first occurrence of CV death, HHF or urgent HF visit | Time to first occurrence of CV death, HHF or urgent HF visit | Total number of CV death, HHF or urgent HF visit<br>Composite of ≥50% sustained eGFR decline, chronic dialysis, kidney transplant or sustained eGFR <15 ml/min/1.73 $m^2$ |
| **Key secondary endpoints** | • Total number of CV death or HHF<br>• Time to death from any cause<br>• Proportion of patients with worsened NYHA class<br>• Change from baseline in KCCQ | • Total number of CV death or HHF<br>• Time to death from any cause<br>• Composite of ≥50% sustained eGFR decline, ESKD or kidney death<br>• Change from baseline in KCCQ | • Total number of HF events<br>• Time to first composite kidney event<br>• Time to CV death in patients with LVEF <50% and total patient population<br>• Time to death from any cause in patients with LVEF <50% and total patient population |

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

*Patient numbers differ between CT.gov and EU Clinical Trials Register. See notes page for abbreviations; †NYHA class II–IV

1. ClinicalTrials.gov. NCT03619213; 2. ClinicalTrials.gov. NCT03036124; 3. ClinicalTrials.gov NCT03521934; 4. EU Clinical Trials Register 2017-003510-16. https://www.clinicaltrialsregister.eu/ctr-search/trial/2017-003510-16/SE (all accessed Feb 2019)

# Examples of SGLT2 inhibitor trials primarily focused on functional outcomes in chronic HF

| | EMPERIAL-Preserved[1] | EMPERIAL-Reduced[2] |
|---|---|---|
| **Study drug** | Empaglifozin 10 mg qd | Empagliflozin 10 mg qd |
| **Sample size** | 300 | 300 |
| **Key inclusion criteria** | • Chronic HF NYHA class II−IV<br>• Walking distance in the 6MWT ≤350 m | |
| | **HFpEF (LVEF >40%)** | **HFrEF (LVEF ≤40%)** |
| **Primary endpoint** | Change from baseline to Week 12 in **exercise capacity (6MWT)** | |
| **Key secondary endpoints** | Change from baseline to Week 12 in:<br>• KCCQ-TSS<br>• CHQ-SAS dyspnoea score | |

6MWT, 6-minute walk test; CHQ-SAS, Chronic Heart Questionnaire Self-Administered Standardised; HF, heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ-TSS, Kansas City Cardiomyopathy Questionnaire Total Symptom Score; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SGLT2, sodium-glucose co-transporter-2

1. ClinicalTrials.gov. NCT03448406; 2. ClinicalTrials.gov. NCT03448419 (both accessed Jan 2019)

# SGLT2 inhibitor trials primarily focused on mechanistic CMR and CPET study

| | EMPA-VISION HFrEF | EMPA-VISION HFpEF |
|---|---|---|
| **Primary endpoint[1]** | Change from baseline to Week 12 in **PCr/ATP ratio** in resting state measured by $^{31}$P-MRS | |
| **Exploratory endpoints[2]** | Changes from baseline to Week 12 in:<br>• PCr/ATP ratio measured by $^{31}$P-MRS during dobutamine stress<br>• Functional capacity assessed by CPET and the 6MWT<br>• Cardiac function, structure, extracellular volume and myocardial perfusion assessed by MRI<br>• Real-time cardiac function during resting/stress assessed by cine-MRI<br>• Cardiac structure and function measured by echocardiogram<br>• Myocardial fat composition measured by proton MRS<br>• Short-term QoL as measured by the EQ-5D and KCCQ questionnaires | |

6MWT, 6-minute walk test; $^{31}$P-MRS, phosphorus magnetic resonance spectroscopy; ATP, adenosine triphosphate; CMR, cardiac magnetic resonance; CPET, cardiopulmonary exercise testing; EQ-5D, European QoL-Five Dimension; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; KCCQ, Kansas City Cardiomyopathy Questionnaire; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PCr, phosphocreatine; QoL, quality of life

1. ClinicalTrials.gov. NCT03332212 (accessed Feb 2019); 2. Boehringer Ingelheim. Data on file. 2018