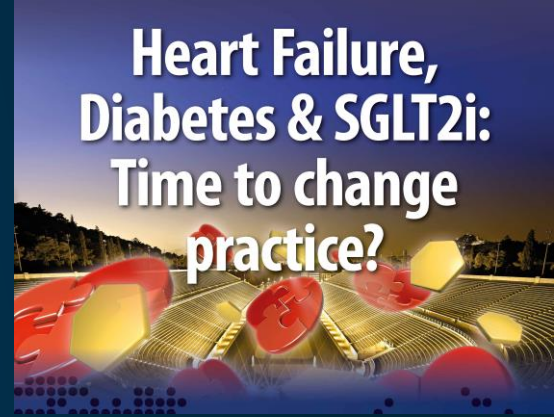


The future of SGLT2i in HF: Managing patients without T2DM?

Adriaan Voors, MD
Groningen, The Netherlands

Heart Failure,
Diabetes & SGLT2i:
Time to change
practice?



May 25, 2019 - Athens, Greece



The future of SGLT2i in HF: Managing patients without T2DM?

- Can we now routinely recommend SGLT2i in patients with DM and concomitant HF?
- Will SGLT2i work in HF patients without DM as well? Are the diuretic effects dependent on blood glucose levels?
- Which SGLT2i studies are ongoing in primary HF populations?



SGLT-2i: standard of care in DM + HF?

	EMPA-REG	CANVAS	DECLARE
N	7020	10,142	17,160
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin
Patients	T2DM with established CVD	T2DM with established CVD or multiple CV risk factors	T2DM with established CVD or multiple CV risk factors
Primary Outcome	CV death, MI, stroke	a) CV death, MI, stroke b) albuminuria	a) CV death, MI, stroke b) CV death or hHF
Primary result	HR: 0.86 P=0.04	a) HR: 0.86; P=0.016 b) HR 0.73; (0.67 - 0.79)	a) HR 0.93; P = 0.17 b) HR 0.83 ; P = 0.005
Heart Failure hospitalization	HR 0.65 (0.50 - 0.85)	HR 0.67 (0.52 - 0.87)	HR 0.73 (0.61- 0.88)

Limitations of CVOTs with SGLT2i

	EMPA-REG	CANVAS	DECLARE
N	7020	10,142	17,160
SGLT2i	Empagliflozin	Canagliflozin	Dapagliflozin
Baseline ECVD	~99%	~65%	~41%
Hf identified?	Database query; EF unknown	Physician: EF unknown	Chart review: EF known in 26%
Patients with HF	10%	14%	10%

No specific heart failure population

Low proportion of patients with established HF

Not well phenotyped

HF hospitalisation not well-adjudicated

Statins reduced HF in patients with CVD

- 4S: “Simvastatin reduces the occurrence of heart failure in patients with coronary heart disease”
- IDEAL:” Atorvastatin 80 mg was more efficient than simvastatin 20 to 40 mg in preventing development of HF in patients with previous MI.”

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rosuvastatin in Older Patients
with Systolic Heart Failure



The future of SGLT2i in HF: Managing patients without T2DM?

- Can we now routinely recommend SGLT2i in patients with DM and concomitant HF?
- Will SGLT2i work in HF patients without DM as well? Are the diuretic effects dependent on blood glucose levels?
- Which SGLT2i studies are ongoing in primary HF populations?





**SGLT2 inhibition
(Empagliflozin)**

Potential mechanisms

- blood pressure ↓
- body weight ↓
- arterial stiffness ↓
- cardiac function ↑
- cardiac oxygen demand ↓
- lack of sympathetic nerve activation
- sodium depletion
- oxidative stress ↓
- glucagon secretion ↑
- additional unknown mechanisms



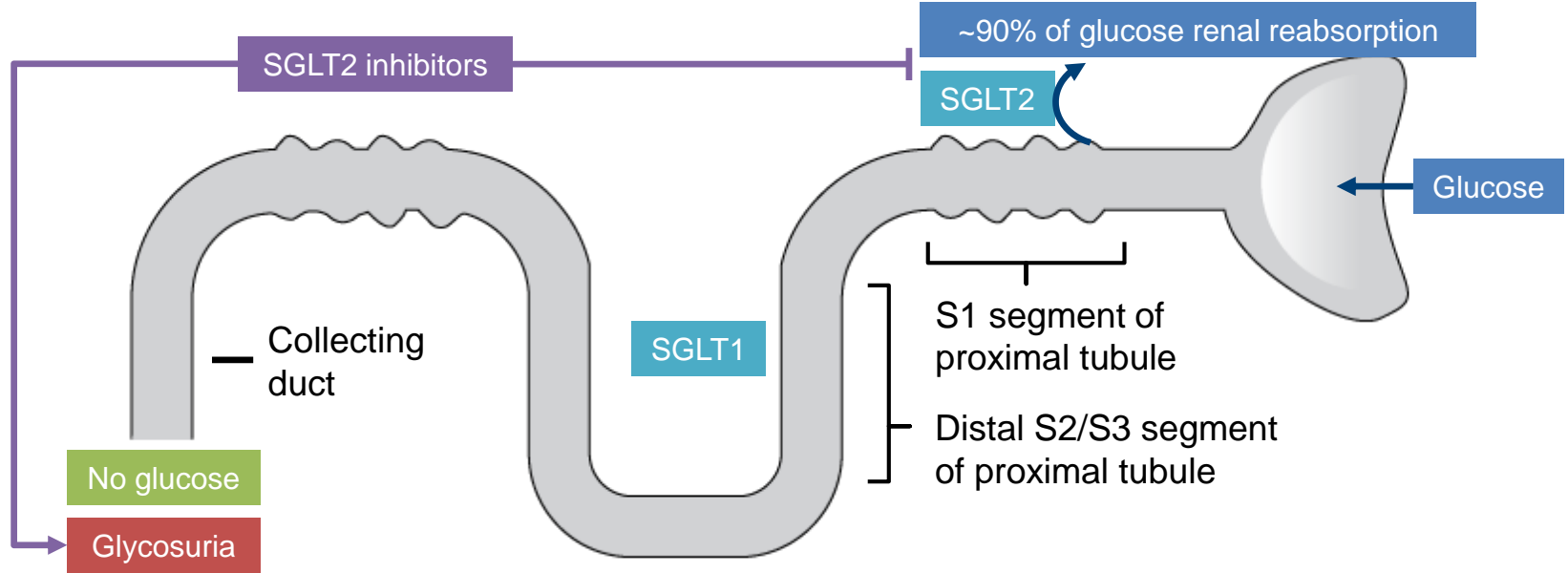
Reduction of

- CV death
- overall mortality
- HF hospitalisation

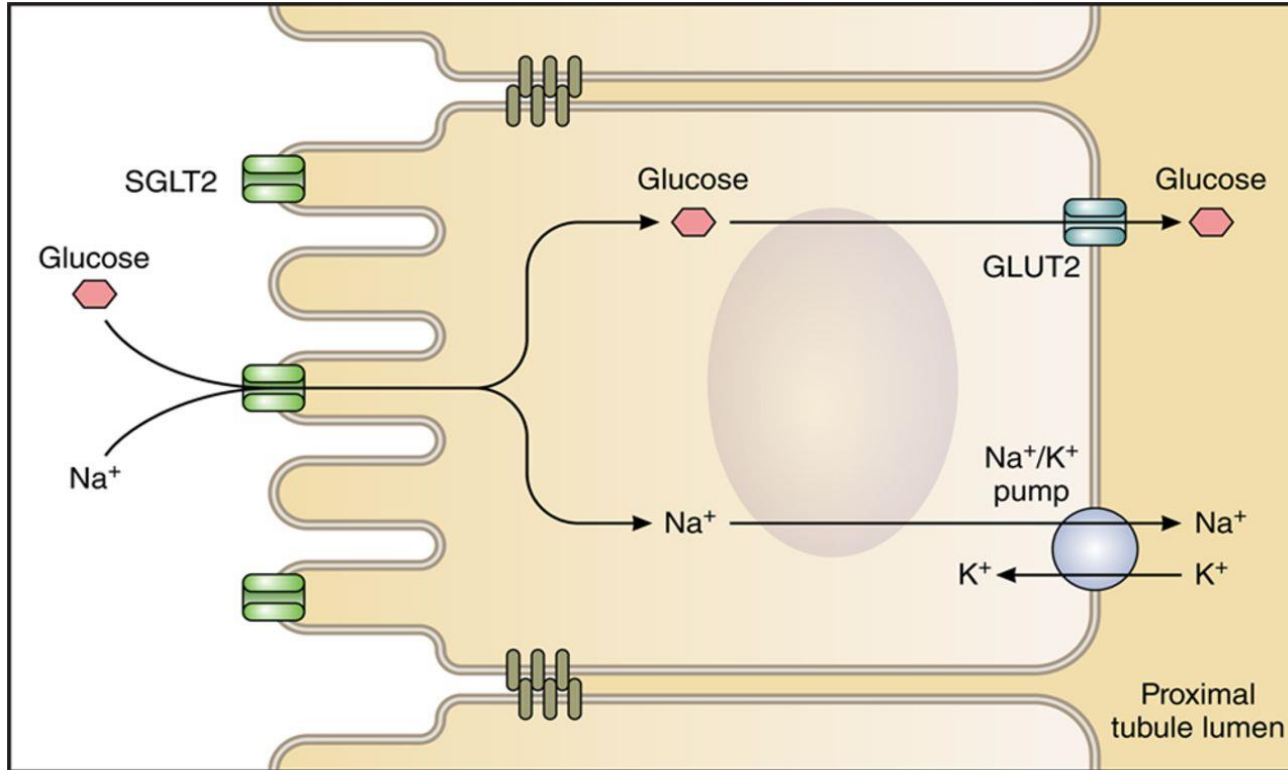
EMPA-REG OUTCOME

Marx, McGuire. Eur Heart J 2016; 37(42):3192-3200

SGLT2 inhibition



The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule



The sodium-glucose cotransporter-2 (SGLT2) mechanism in the proximal tubule

- “Importantly for safety, the efficacy of SGLT2 inhibitors to increase urinary glucose excretion attenuates at lower plasma glucose levels, thereby accounting for their reduced risk of causing hypoglycemia.”
- Natriuretic effects attenuated with lower glucose levels?
- Natriuretic effects attenuated with poorer renal function?



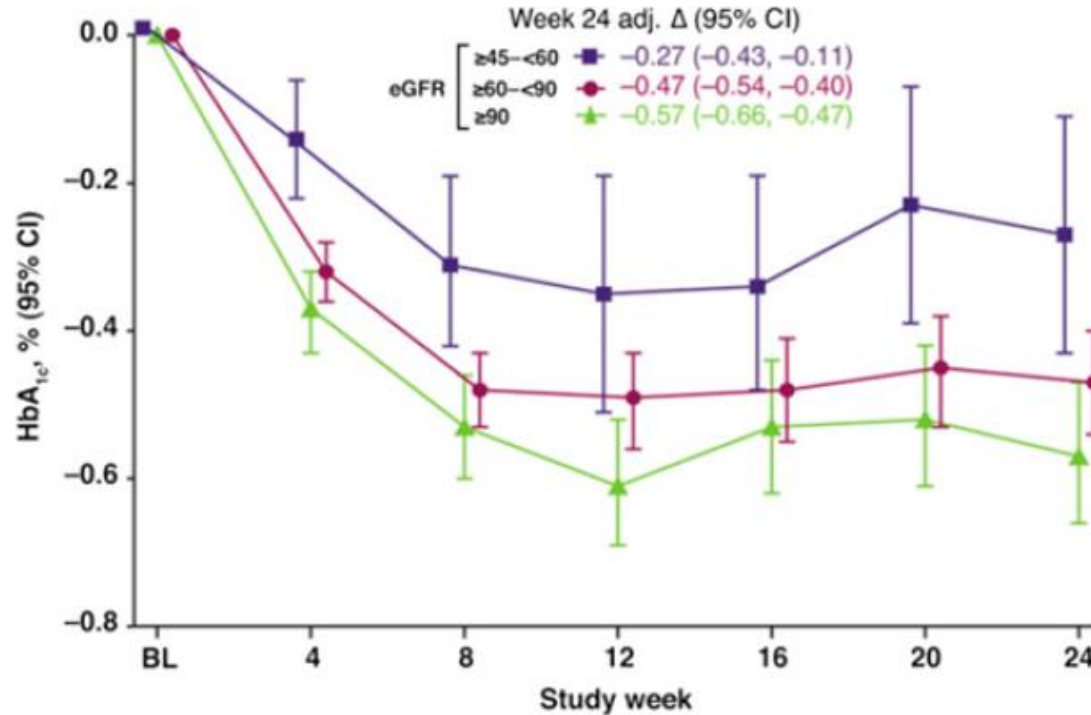
Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function

Sergei Petrykiv, C. David Sjöström,[†] Peter J. Greasley,[†] John Xu,[‡] Frederik Persson,[§] and Hiddo J.L. Heerspink**

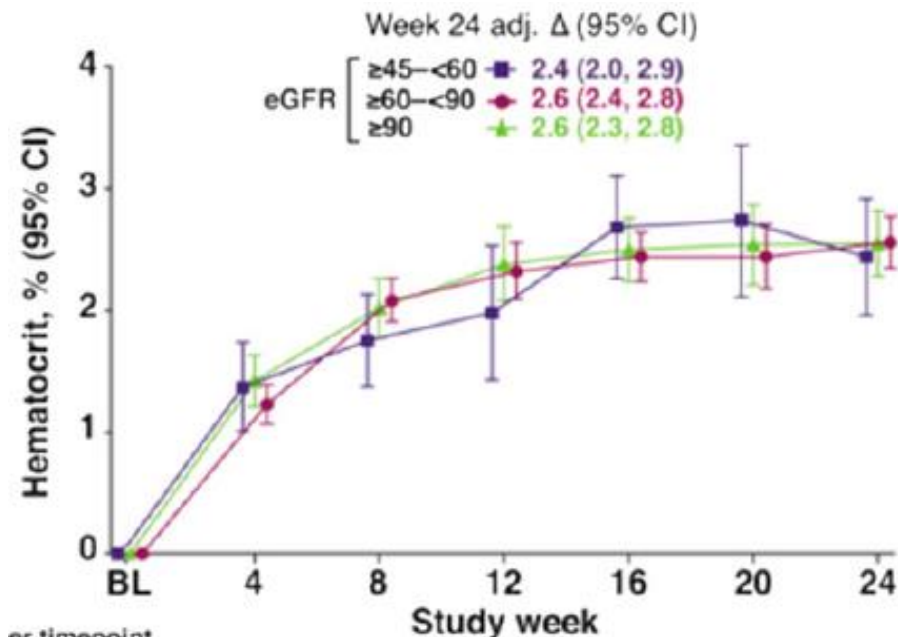
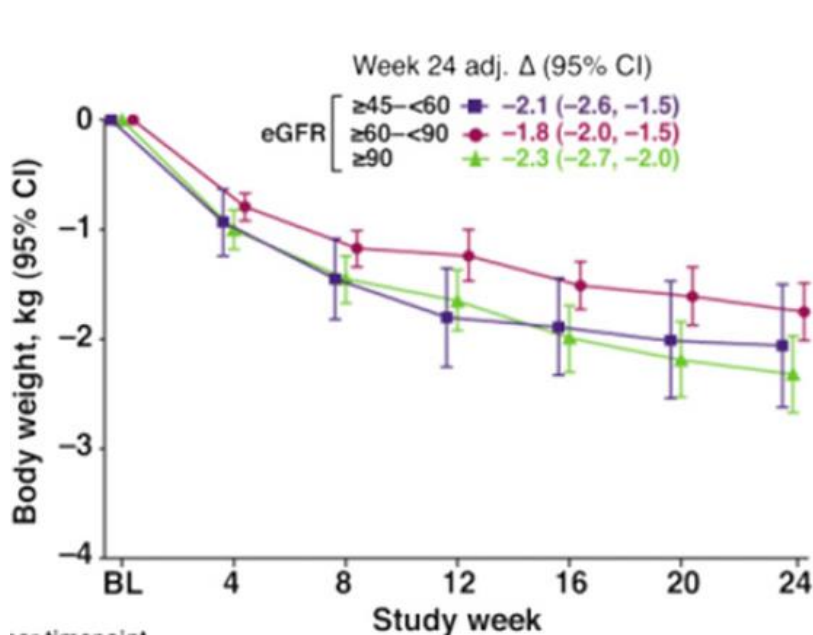
- Pooled analysis of 11 phase 3 clinical trials in T2DM
- Randomized to placebo (n=2178) or dapagliflozin 10mg(n=2226)
- Assessed changes in HbA1c, body weight, BP, hematocrit, and urinary albumin-to-creatinine ratio



The HbA_{1c}-lowering effects of dapagliflozin decrease as renal function declines



BUT: dapagliflozin reduced body weight, and caused hemoconcentration regardless of eGFR



Differential Effects of Dapagliflozin on Cardiovascular Risk Factors at Varying Degrees of Renal Function

Sergei Petrykiv, C. David Sjöström,[†] Peter J. Greasley,[†] John Xu,[‡] Frederik Persson,[§] and Hiddo J.L. Heerspink**

- “This suggest that the effects of dapagliflozin are partly mediated via nonglucosuric-dependent mechanisms”



Circulation

PERSPECTIVE

Treating Heart Failure With Antihyperglycemic Medications

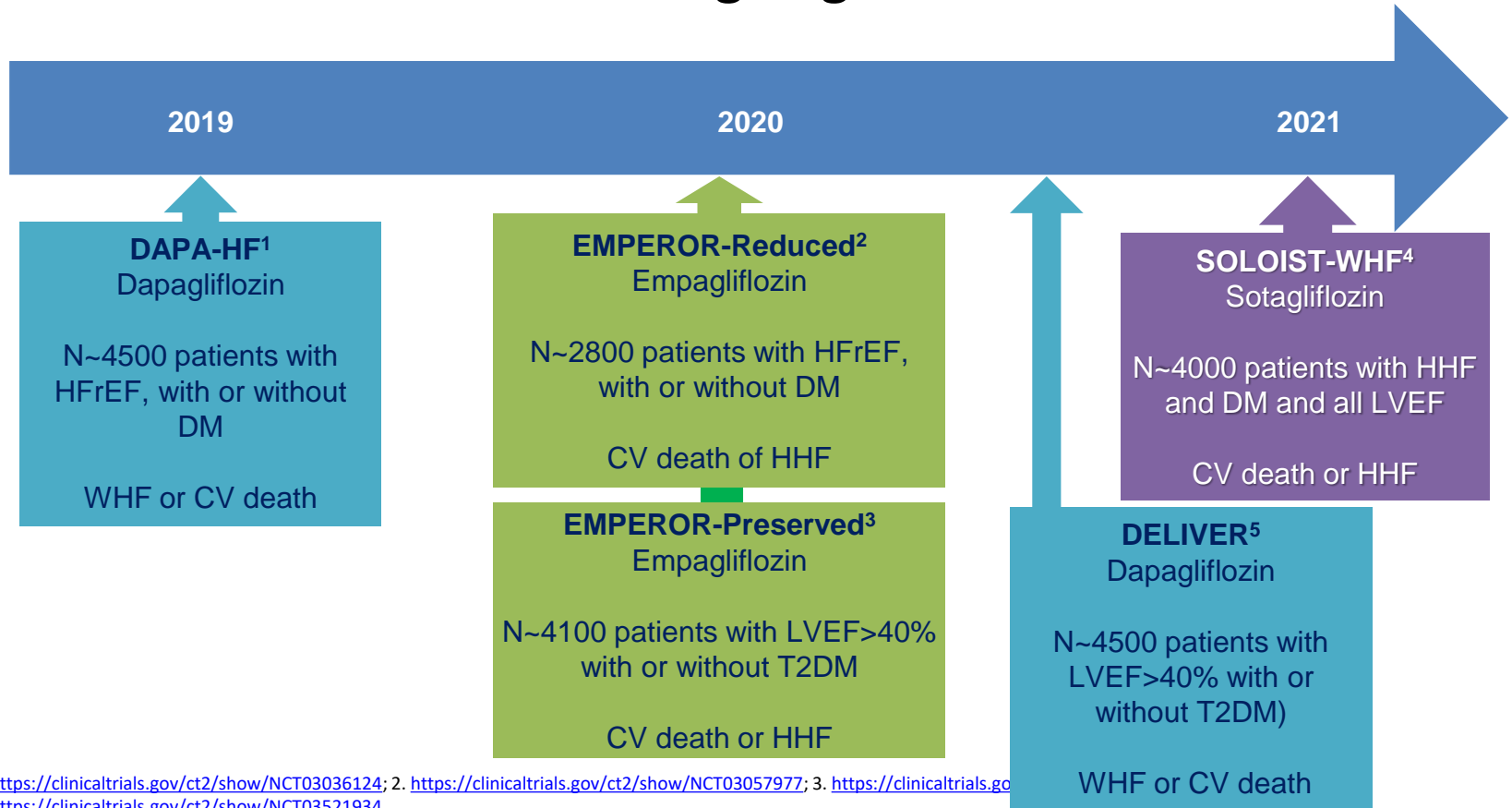
Is Now the Right Time?

Jeffrey M. Testani, MD,
MTR

Silvio E. Inzucchi, MD
Adriaan A. Voors, MD,
PhD



Research into SGLT2 inhibition in CHRONIC heart failure is ongoing

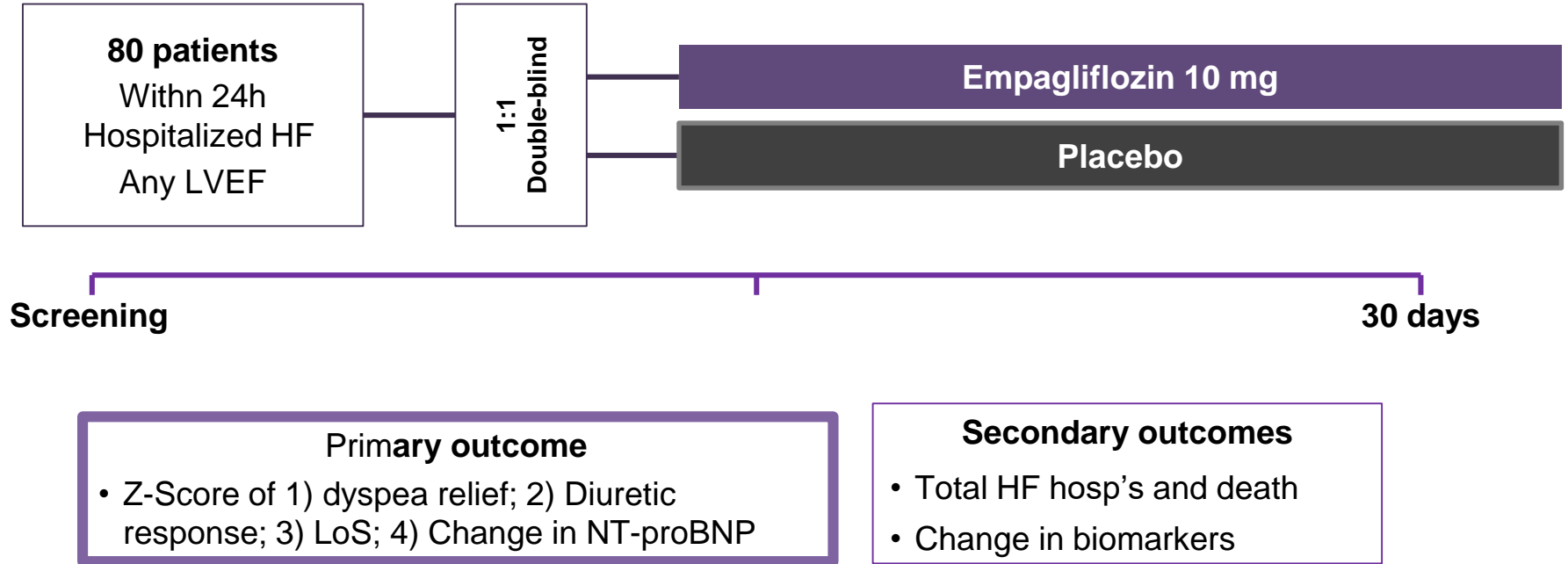


1. <https://clinicaltrials.gov/ct2/show/NCT03036124>; 2. <https://clinicaltrials.gov/ct2/show/NCT03057977>; 3. <https://clinicaltrials.gov/ct2/show/NCT03521934>

SGLT2i Exercise Study in HFpEF

EMPERIAL-Preserved	
Drug	• Empagliflozin
LVEF	• >40%
NYHA	• Class II–IV
eGFR	• ≥ 20 mL/min/1.73m ²
NT-proBNP	• >300 pg/mL –AF • >600 pg/mL +AF
Patient #	• 300
Est. Study End	• Ongoing: June 2019
Duration	• 12 weeks
1° Endpoint	• Δ 6MWT to Week 12

EMPA-RESPONSE-Acute Heart Failure Study Design



Estimated completion: 2019

The future of SGLT2i in HF: Managing patients without T2DM?

- Can we now routinely recommend SGLT2i in patients with DM and concomitant HF? **Not yet**
- Will SGLT2i work in HF patients without DM as well? **Don't know**
- Are the diuretic effects dependent on blood glucose levels? **In theory: Yes: in practice: No**
- Which SGLT2i studies are ongoing in primary HF populations? **Many!!**

