Addressing the remaining questions on SGLT2 & CKD: a review of new outcome trials

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DISCLOSURES

I am co-chair of the EMPA-KIDNEY trial, which is supported by a grant to the University of Oxford from Boehringer Ingelheim.

I do not accept personal payments (including speaker fees, honoraria, stock) from pharmaceutical companies, but I accept reimbursement of expenses arising from attending attending scientific meetings.

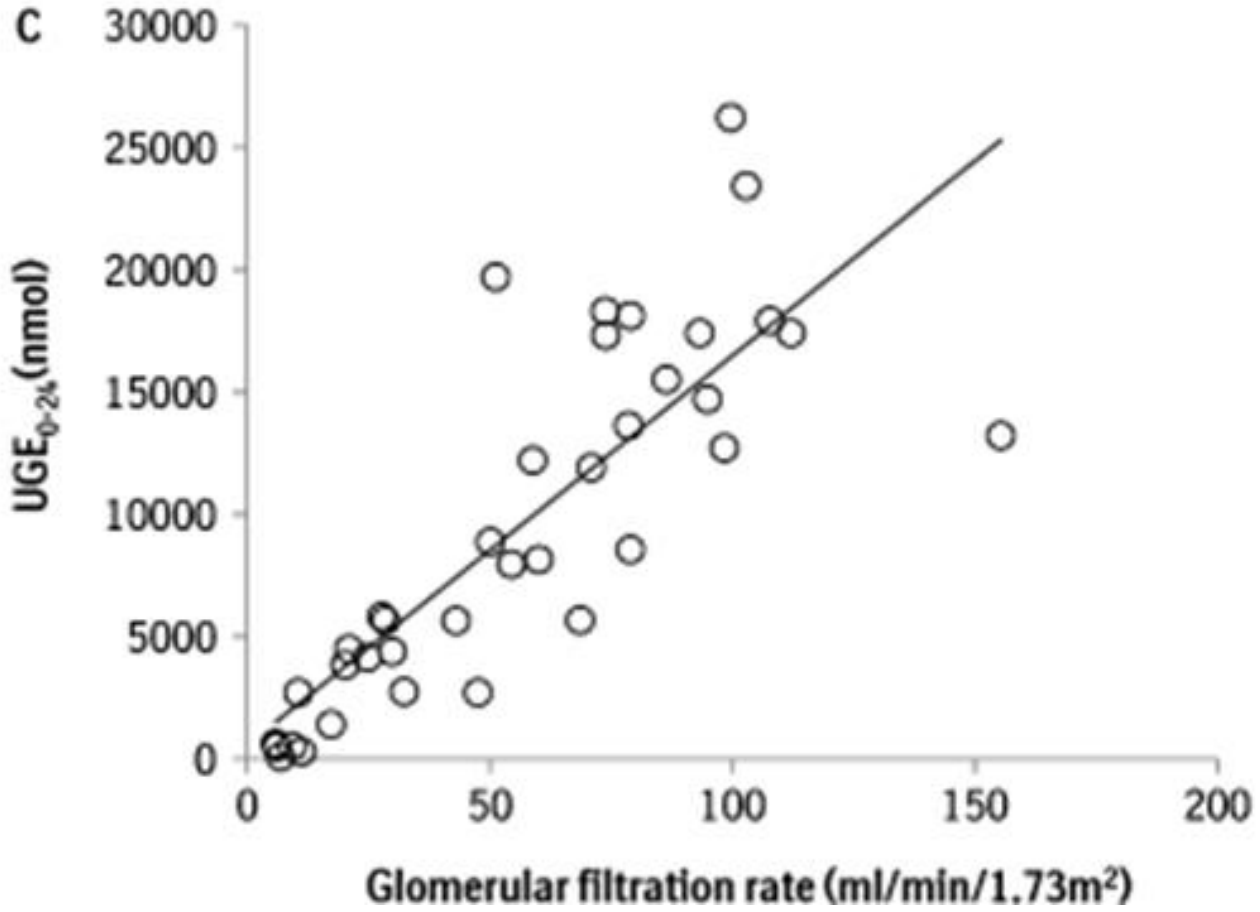
Talk outline

- What are the questions that need to be addressed before considering SGLT2-inhibition in patients with CKD?
- What will the ongoing trials tell us?
- Conclusions

What are the questions when considering SGLT2-inhibitors for patients with CKD?

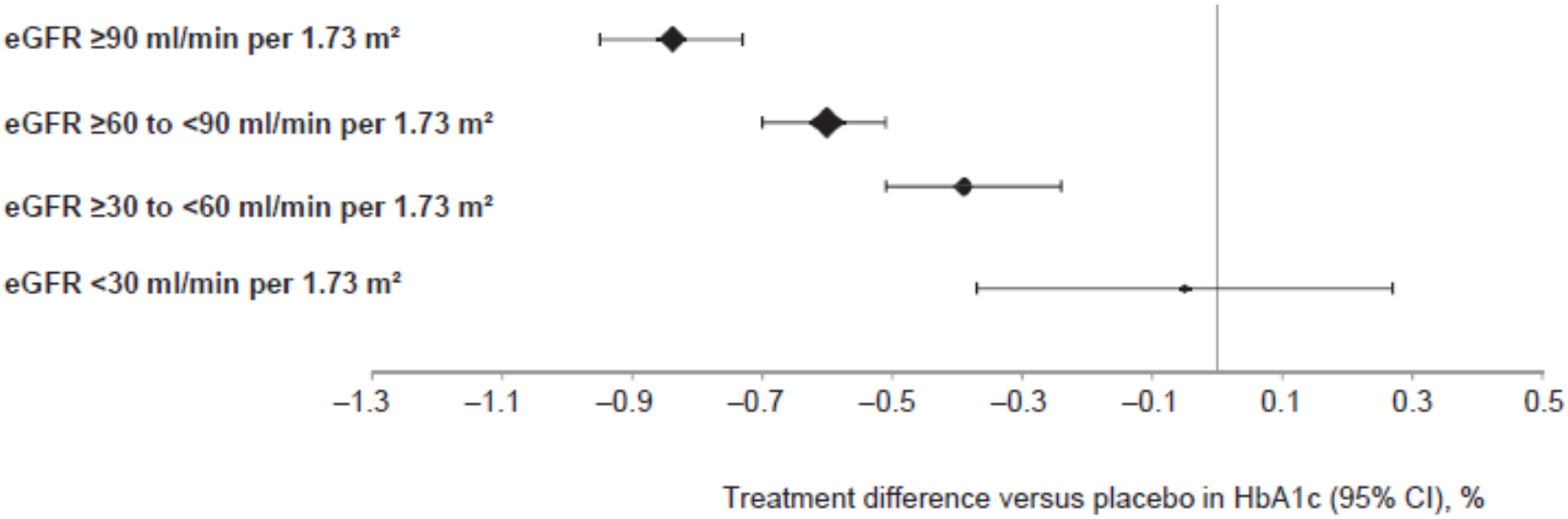
- Effects of SGLT2-inhibition as GFR declines

Effects of empagliflozin on 24 hour glycosuria at different levels of eGFR



Macha S *et al.* Diabetes, Obesity and Metabolism 2014;16:215-222

Pooled analysis of phase III trials: Effects of empagliflozin on HbA1c at low eGFR



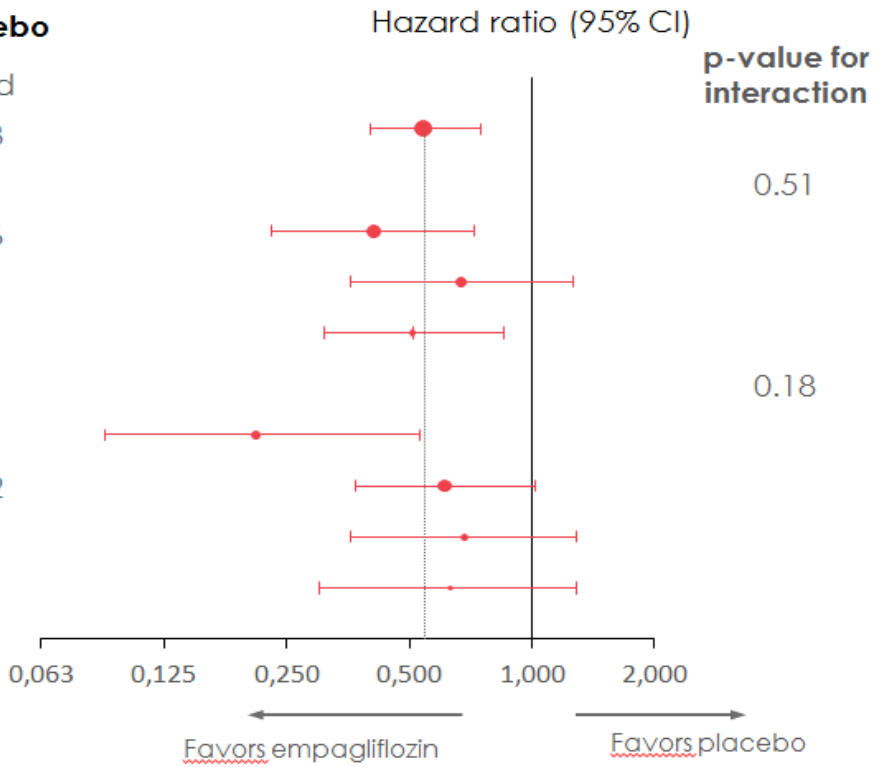
P < 0.001 for interaction between treatment and baseline eGFR.

Cherney *et al.* Kidney Int 2018; 93: 231-244

EMPA-REG OUTCOMES: Effect of Empagliflozin on "CKD" outcomes

Time to doubling of creatinine, RRT start or renal death

	Empagliflozin Patients analyzed	Placebo Patients analyzed	p-value for interaction
All patients	4645	2323	
Urine albumin-to-creatinine ratio			0.51
<30 mg/g	2766	1376	
≥30 to 300 mg/g	1325	671	
>300 mg/g	504	260	
Estimated glomerular filtration rate			0.18
≥90 mL/min/1.73m²	1043	486	
60 to <90 mL/min/1.73m²	2406	1232	
45 to <60 mL/min/1.73m²	822	416	
<45 mL/min/1.73m²	374	189	

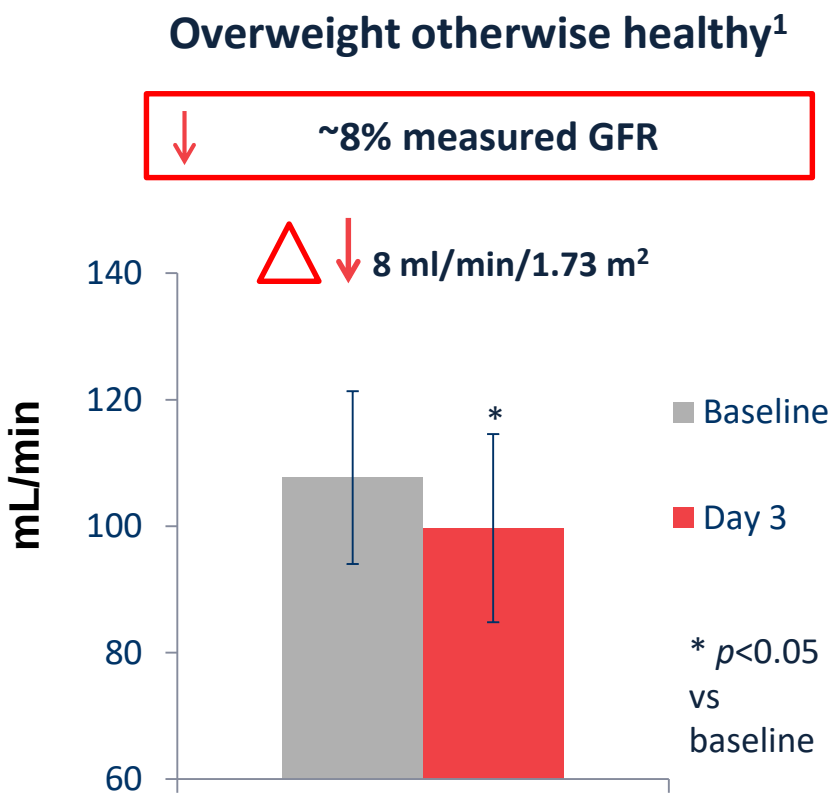


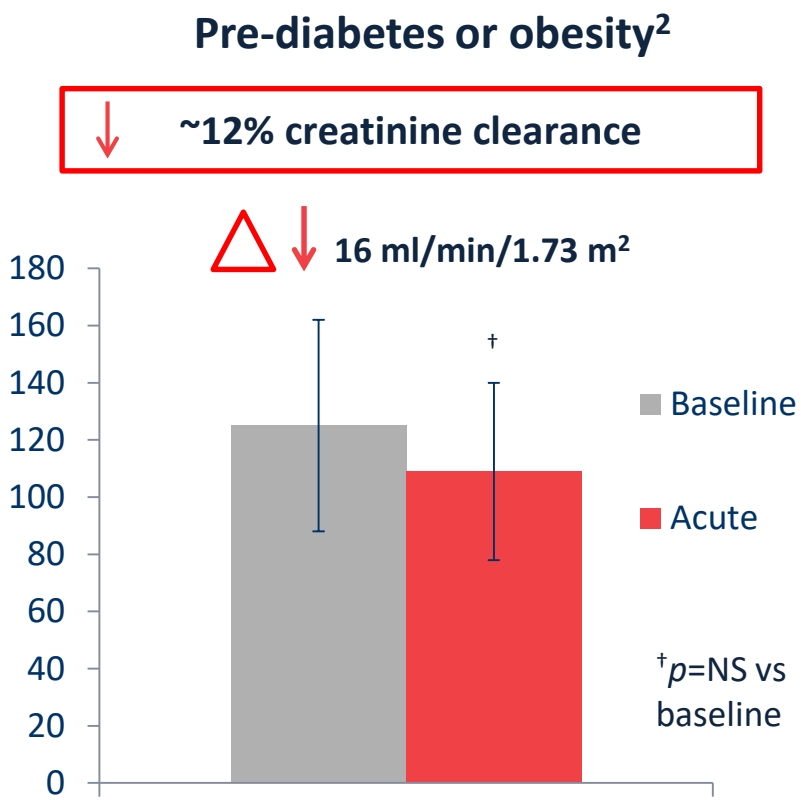
Wanner C *et al.* N Engl J Med 2016; 375:323-34

What are the questions when considering SGLT2-inhibitors for patients with CKD?

- Effects of SGLT2-inhibition as GFR declines
- Effects in people without diabetes mellitus

Evidence for effects on glomerular pressure in those without diabetes





1. Clinical trial report. Trial 1245.66. 2016. Data on file; 2. Ferrannini E *et al.* Diabetes Care 2017

Key areas of uncertainty about SGLT2-inhibitors in patients with CKD

- Efficacy
  - Effects of SGLT-inhibitors on GFR decline, and especially on ESRD outcomes
  - Effects on CV outcomes as GFR↓
  - Effects on CV and renal endpoints in patients without diabetes
- Safety
  - Magnitude of known adverse effects as GFR↓
  - Potential for unanticipated adverse effects in people with eGFR < 45 mL/min/1.73m^2

What will the ongoing trials tell us?

CREDENCE: key design elements

Inclusion criteria:

- Age ≥30 years (mean=63*)
- T2DM, HbA1c 6.5-12% (mean =8.3%*)
- eGFR 30-90 mL/min/1.73m^2 (mean =56*) AND uACR 300-5000 mg/g (median=927)
- Stable maximally tolerated RAS blockade

Sample size: 4401 (actual)

Comparison: Canagliflozin 100mg vs. placebo

Primary endpoint: Doubling of creatinine, ESKD, or death from renal or CV causes

Secondary endpoints: ESRD and CV or renal death; individual components of composite endpoints (2xSCr, renal death, MI, stroke, HF, UA); ΔeGFR over time; ΔUACR over time

* Jardine M et al. Am J Nephrol 2017; 46: 462-72 (design & baseline paper)

DAPA CKD: key design elements

Inclusion criteria:

- Age ≥18 years
- eGFR 25-75 mL/min/1.73m2 AND uACR 200-5000 mg/g
- Stable maximally tolerated RAS blockade, if not contraindicated

Sample size: ~4000

Comparison: Dapagliflozin 5/10 mg vs. placebo

Primary endpoint: Sustained ≥50% decline in eGFR, ESKD, or death from renal or CV causes

Secondary endpoints: Renal composite (eGFR, ESRD, or renal death), HF composite (CV death, hospitalisation for HF), all-cause mortality

EMPA-KIDNEY

The study of heart and kidney protection with empagliflozin

Study eligibility

- Age ≥18 years at Screening;
- CKD at risk of progression;
- The responsible physician(s) judge that empagliflozin (or other SGLT-2 or SGLT-1/2 inhibitor) not part of the current standard of care
- Clinically appropriate doses of RAS blockade used unless RAS blockade not tolerated or indicated

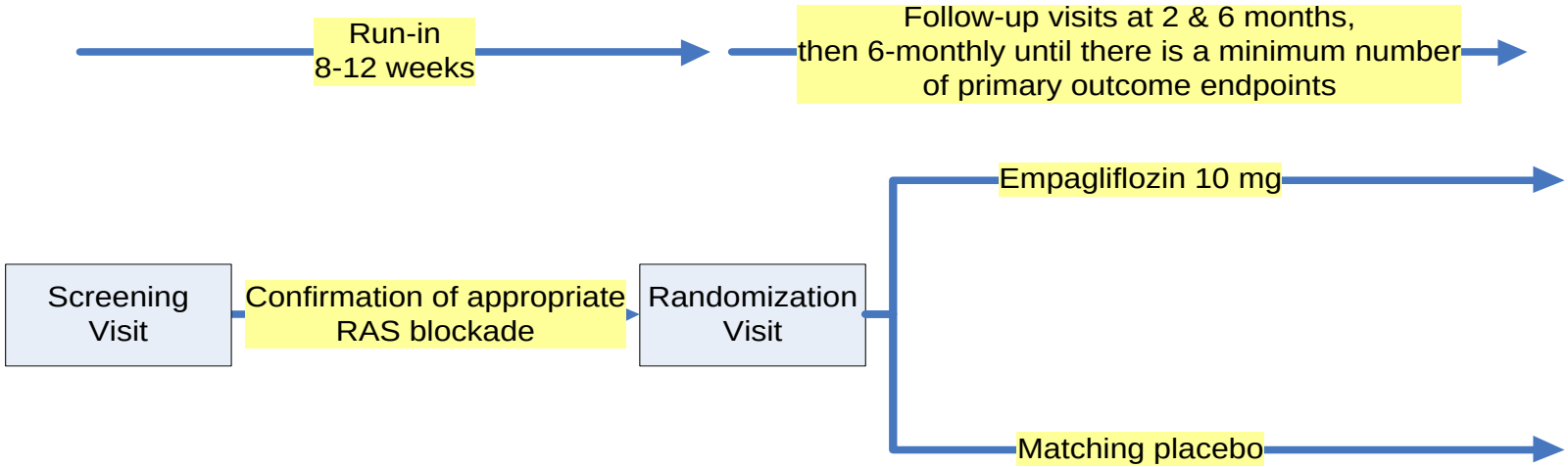
eGFR inclusion criteria

- Local laboratory results recorded ≥3 months before and at Screening:
  - eGFR ≥20 <45 mL/min/1.73m^2; OR
  - eGFR ≥45 <90 mL/min/1.73m^2; AND

    UACR ≥200 mg/g (or protein:creatinine ratio ≥300 mg/g)

- Steering Committee will monitor the numbers of people with an eGFR <45 and ≥45 (and also those with and without diabetes) to 'fine-tune' final study population

Treatment comparison



Summary of 3 ongoing trials

SGLT2-inhibitor trials in CKD: (1) INCLUSION CRITERIA

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Age	≥30	≥18	≥18
DM/non-DM	T2DM only	≥1/3 DM ≥1/3 non-DM	≥1/3 DM ≥1/3 non-DM
Renal function eGFR*/UACR	≥30 <90 (mean=56.2) AND >300mg/g	25 – 75 AND ≥ 200mg/g	(i) ≥20 <45 OR (ii) ≥45 <90 with ≥200mg/g

*mL/min/1.73m^2

SGLT2-inhibitor trials in CKD: (2) PRIMARY ENDPOINTS AND POWER

	CREDENCE	DAPA-CKD	EMPA-KIDNEY
Sample size	4401 (actual)	~4000	~5000
Primary endpoint	2 x SCr, ESKD, CV or renal death	≥50% ↓ eGFR, ESKD, or CV or renal death	≥40%↓ eGFR, ESKD, or CV or renal death
Number of primary events required	844	~600*	1070
Planned duration of follow-up	~4 years	~4 years	~3 years
RRR to be detected	20%	N/A	18%
Statistical power	90% at p=0.05	N/A	90% at p=0.05

*estimated

SGLT2-inhibitor trials in CKD: (3) SECONDARY ENDPOINTS

CREDENCE	DAPA-CKD	EMPA-KIDNEY
ESKD, renal death or CV death	≥50%↓eGFR or ESKD or renal death	<u>Key</u>: HF hospitalisation or CV death
Components of composite endpoints (2xSCr, renal death, CV death, MI, stroke, HF, UA)	CV death or HF hospitalisation	All cause hospitalisation
Change in eGFR over time	Any death	All cause mortality
Change in albuminuria over time		<u>Other</u>: Kidney disease progression
		CV death
		CV death or ESKD

Conclusions

- By 2022 we will have data on the effects of SGLT2-inhibition on ~13,500 patients with CKD, >3,000 without diabetes mellitus
- ~2,000 primary outcomes, but power for subgroups (eg, eGFR categories) for particular vascular and renal endpoints will be limited
- Potential for a major advance in management of patients with CKD