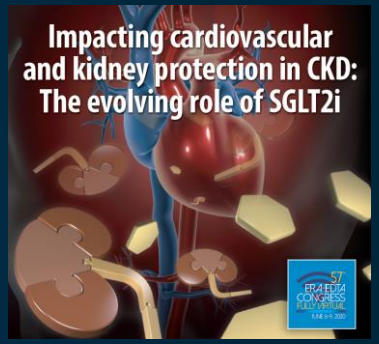
Targeting cardiovascular and kidney outcomes in CKD: Where do we stand today?



Prof. Christoph Wanner, MD
Würzburg, Germany

57TH ERA-EDTA CONGRESS FULLY VIRTUAL
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PACE-CME

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Professor Christoph Wanner, Würzburg, Germany

Presenter Disclosure

Christoph Wanner

- Grant support from Boehringer-Ingelheim (BI) to the Institution
- Honoraria from AstraZeneca, Bayer, BI, Lilly, Mundipharma, MSD

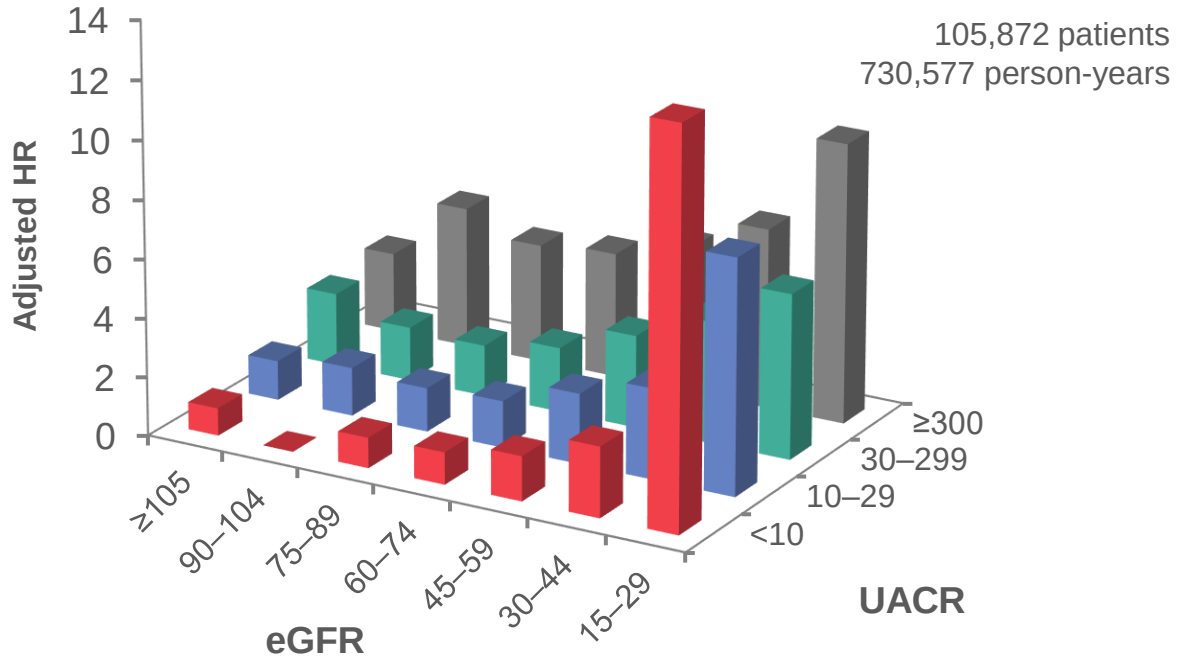
Classification of CKD

CKD is ***classified*** based on cause, Glomerular Filtration Rate - GFR category, and Albuminuria category (CGA)

GFR categories, description and range (ml/min/1.73 m²)				Albuminuria stages, description and range (mg/g)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30	30–300	>300
	G1	Normal or high	≥90			
	G2	Mild decrease	60–89			
	G3a	Mild–moderate decrease	45–59			
	G3b	Moderate–severe decrease	30–44			
	G4	Severe decrease	15–29			
	G5	Kidney failure	<15			

KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013; 3: 1–150

Risk of CV death increases as kidney function declines



Low eGFR and high UACR are *independent* predictors of CV mortality

Matsushita K et al. Lancet 2010;375:2073

67 y, male, IgAN (biopsy 8y ago)
T2DM (diagnosed 4 years ago)
CKD/DKD G3aA3
eGFR 54 ml/min/1.73m^2, UACR 1.2 mg/g
sBP 145/87 mmHg
BMI 32 kg/m^2
LDL-C 98 mg/dl
HbA1c 7.6 mg/dl
Hb 11.8 g/dl

On treatment with

ramipril 5 mg/d
amlodipine 5 mg/d
simvastatin 20 mg/d
aspirin 100 mg/d
metformin 2 g/d
DPP4i

Nonsmoker, struggles with lifestyle, reports to take 7 pills per day

Lifestyle therapy

Physical activity, nutrition, weight loss

Foundational drug therapy

Primarily for organ protection

- eGFR ≥30 mL/min/1.73m^2: choose agent & dose per eGFR
- eGFR <30 mL/min/1.73m^2: do not initiate
- Dialysis: discontinue

Primarily for glycemic control

- eGFR ≥30 mL/min/1.73m^2: dose per eGFR
- eGFR <30 mL/min/1.73m^2: discontinue
- Dialysis: discontinue

A new paradigm change in Nephrology would be ***first*** to concentrate on organ protection and ***second*** to optimise current medication and improve a reasonable well controlled metabolic profile through referral to a dietitian, diabetes educator or kidney nurse (ophthalmologist, foot care, heart specialist)
You want to see him again in three months

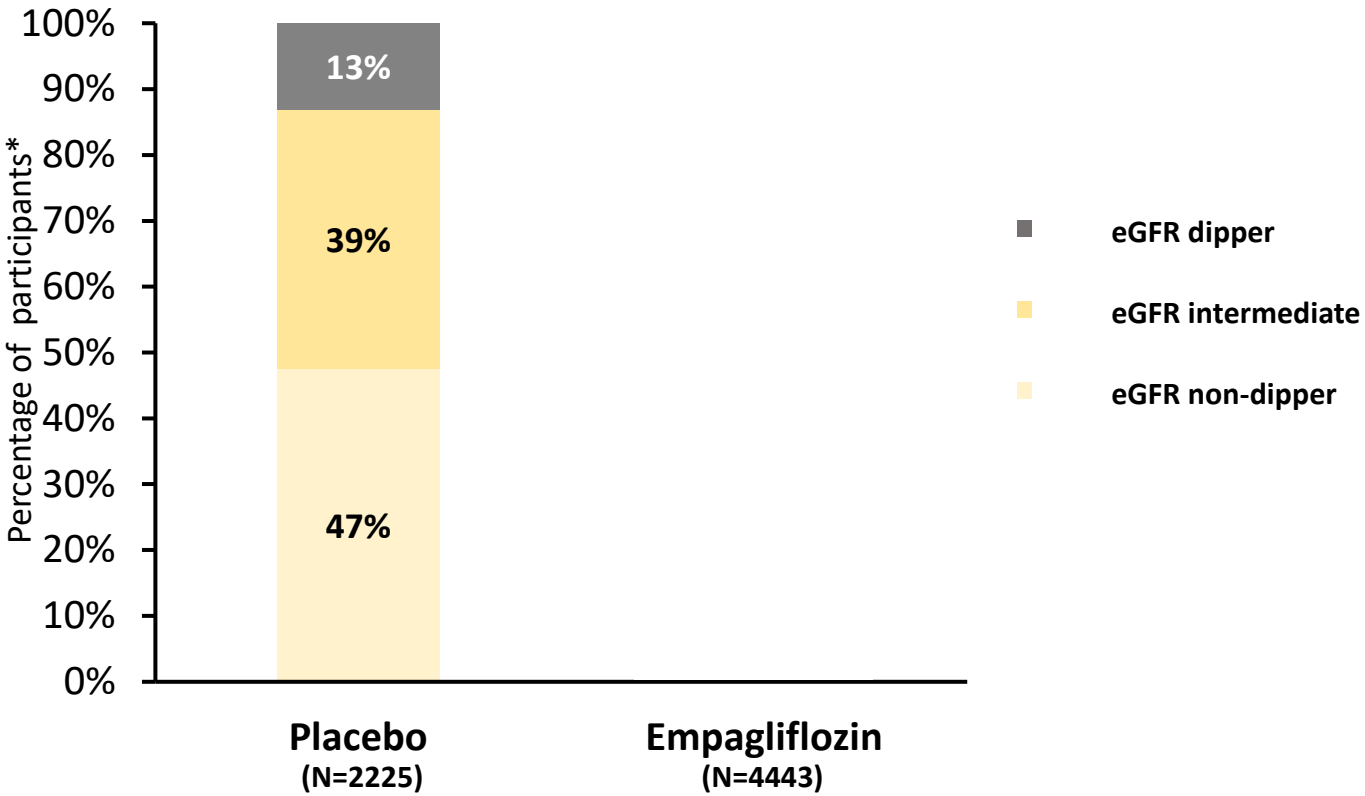
Understanding important clinical ‚concerns‘

Treatments with RASi and SGLT2i induce an initial decline in eGFR

Although considered largely hemodynamic and reversible, this initial ‘eGFR dip’ has raised concerns in clinical practice, as it may predispose patients to acute kidney injury (AKI)

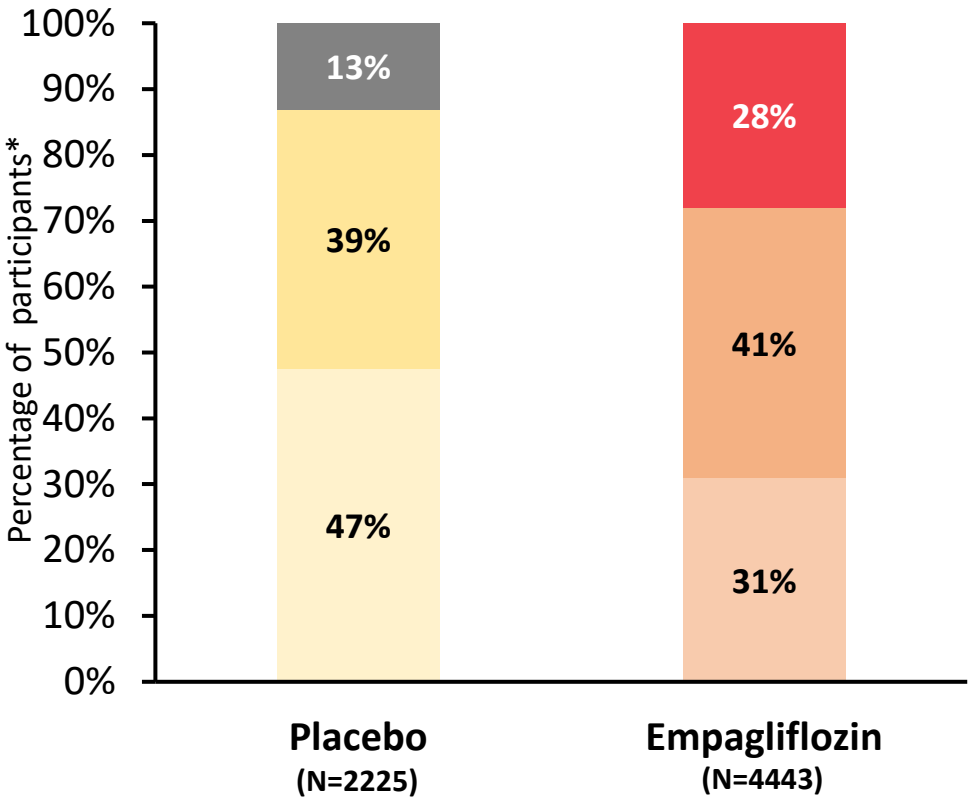
We investigated the initial ‘eGFR dip’ in the EMPA-REG OUTCOME Study

Empagliflozin causes a shift towards more eGFR dippers >10%



*6,668 participants of the EMPA-REG OUTCOME® trial treated with ≥1 dose of study drug (placebo, empagliflozin 10mg or 25mg) and eGFR evaluated at baseline and week 4.
All analyses compared the placebo and pooled empagliflozin (10 mg and 25 mg) groups.

Empagliflozin causes a shift towards more eGFR dippers >10%



eGFR dipper

eGFR intermediate

eGFR non-dipper

Participants experienced an eGFR dip >30%:

- 1.4% with empagliflozin
- 0.9% with placebo

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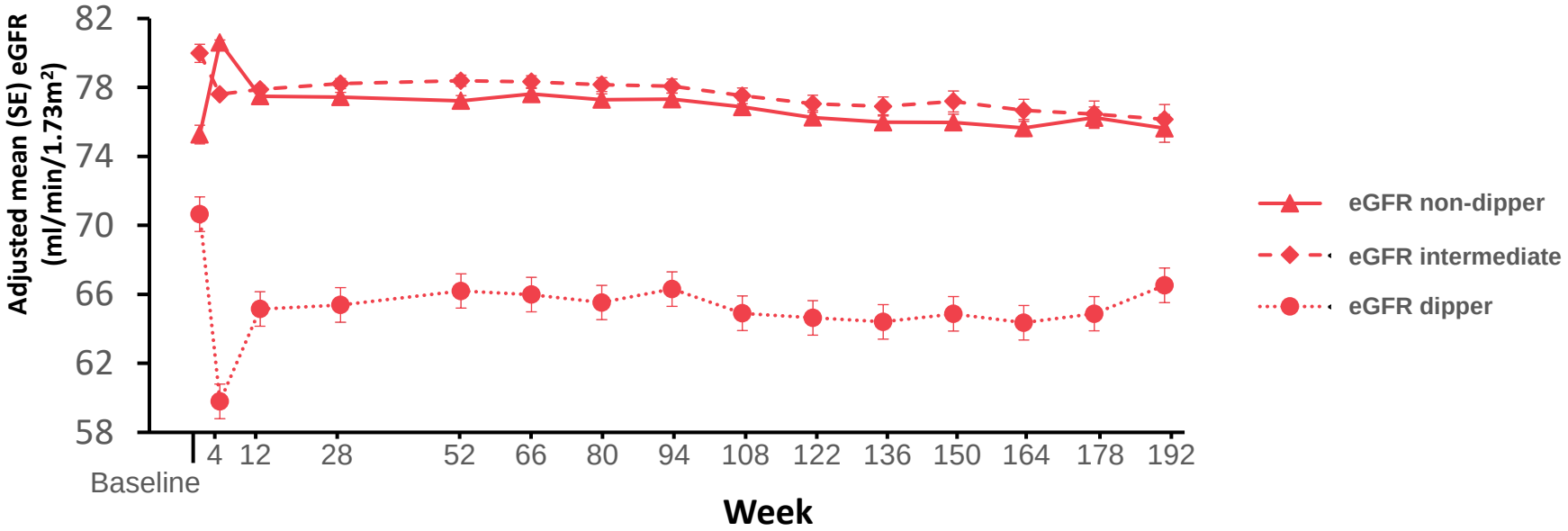
All analyses compared the placebo and pooled empagliflozin (10 mg and 25 mg) groups.

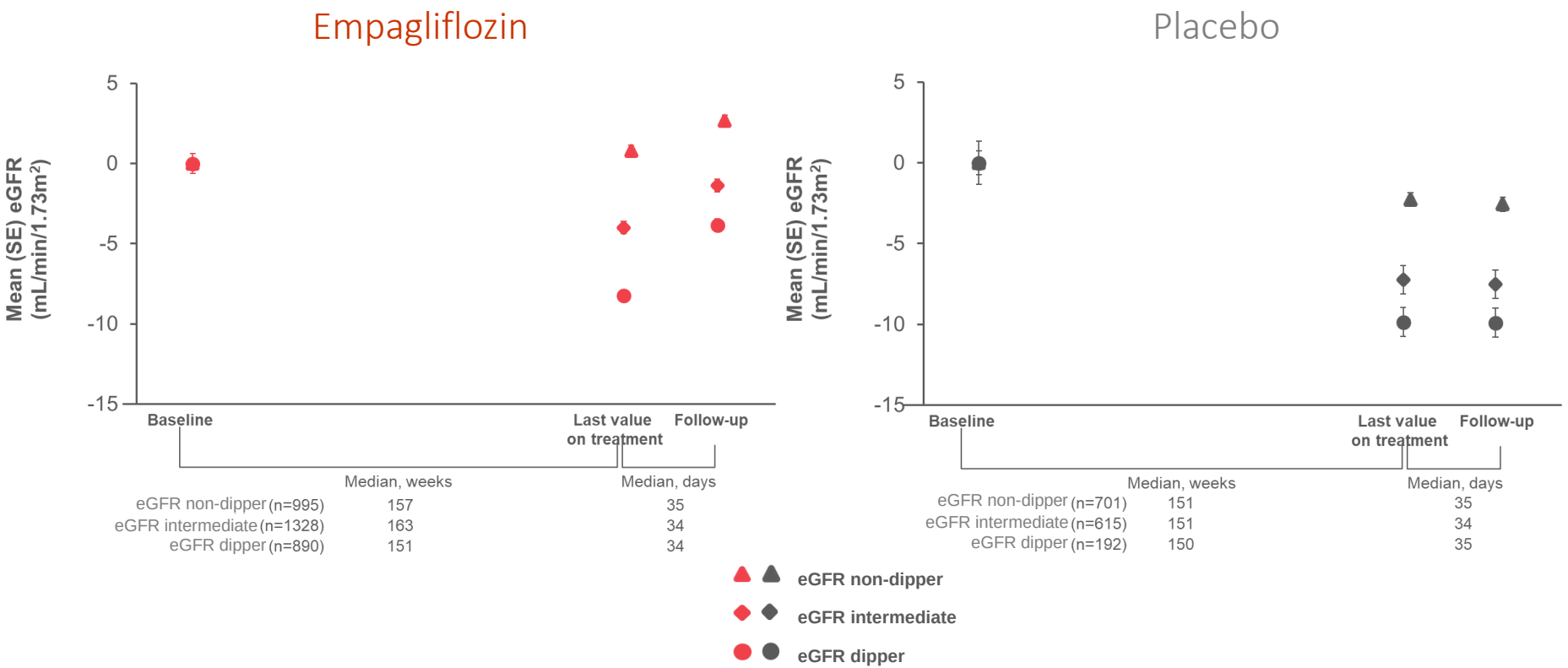
eGFR over time by initial eGFR dip categories in EMPA



eGFR non-dipper (n)	31%	7	1201	1065	866	790	686	672	555	429	358	308	268	189	108
eGFR intermediate (n)	41%	7	1607	1388	1105	1004	900	844	704	550	449	377	338	251	151
eGFR dipper (n)	28%	258	1120	928	740	655	552	528	437	349	282	233	199	143	78

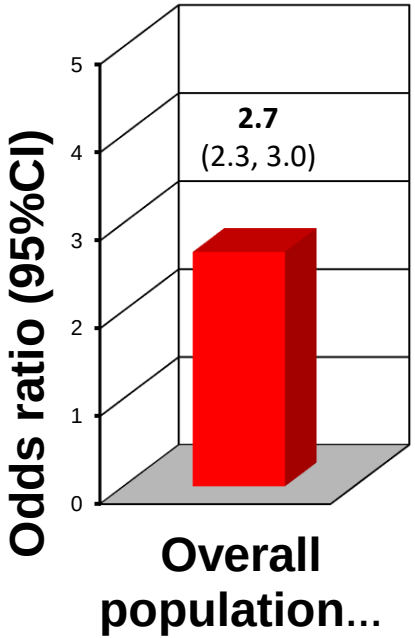
MMRM results of eGFR (CKD-EPI) on-treatment over time by categories for % change in all participants treated with at least one dose of study drug who have a baseline and week 4 value for eGFR available. Model includes baseline eGFR, baseline HbA1c as linear covariate(s) and geographical region, baseline BMI categorical, treatment, visit, visit by treatment interaction, baseline HbA1c by visit interaction, baseline eGFR by visit interaction as fixed effect(s) applied by each eGFR dipping category. MMRM, mixed-model repeated measures

Change in eGFR from baseline to last measurement during treatment and follow-up



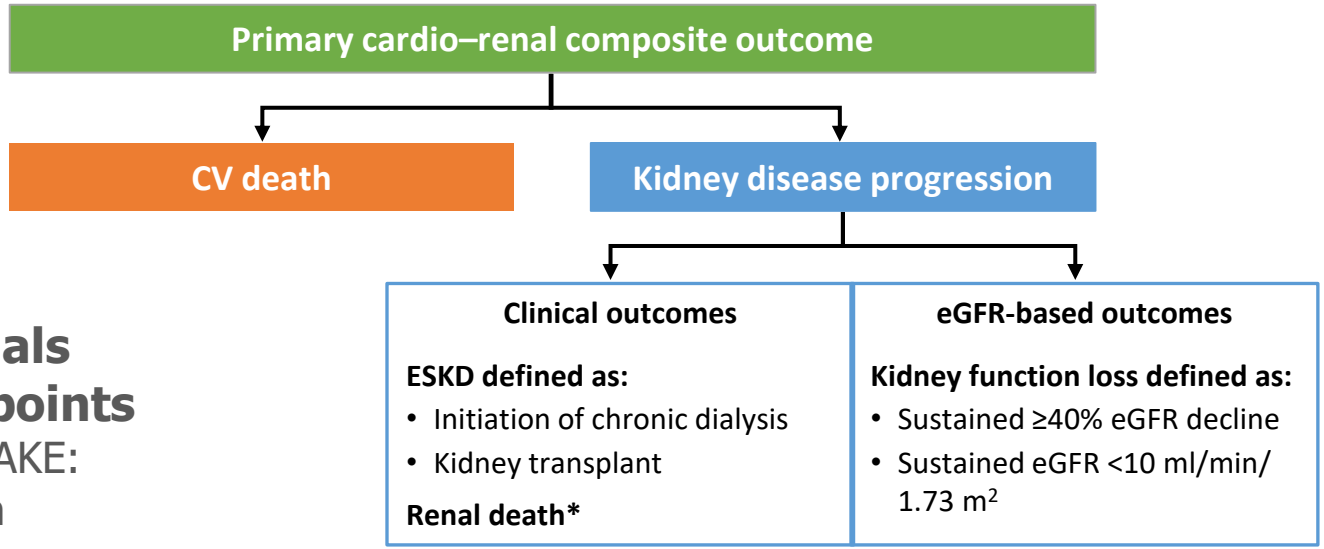
Descriptive statistics for eGFR at baseline, last value on treatment, and follow-up. Participants treated with at least one dose of study drug who have a baseline and we follow-up. eGFR (CKD-EPI)

Predicting an eGFR dip >10% with EMPA vs placebo: Odds ratio increases with diuretic use and higher KDIGO risk



Left panel: Overall OR (95% CI) from logistic regression including treatment, sex, baseline BMI categorical, baseline HbA1c cat., baseline eGFR categorical, geographical region and age. Right panel: Odds Ratio (OR; 95% CI) based on multivariate logistic regression analysis following backward selection procedure given for EMPA- vs. placebo-treated participants. †prognosis of CKD progression category according to KDIGO 2012 guidelines;

Targeting CV and kidney outcomes in CKD: Where do we stand today? The design of new trials



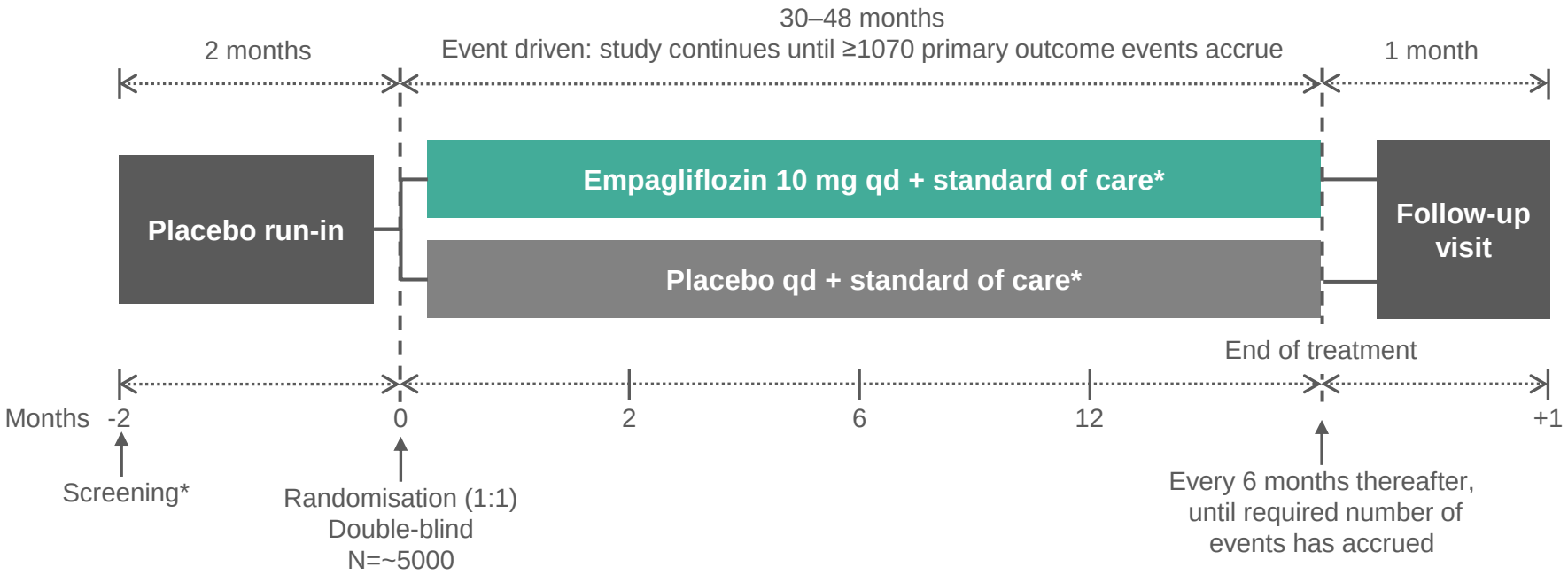
Future trials
New endpoints

4P MACE/MAKE:
- CV death
- HHF
- Kidney failure
- 40% eGFR

eGFR slopes/albuminuria

*CDISC guideline: renal death is a death determined to be caused by renal failure (eGFR <15 ml/min/1.73 m^2), with no other cause of death indicated ClinicalTrials.gov. NCT03594110 (accessed July 2018)

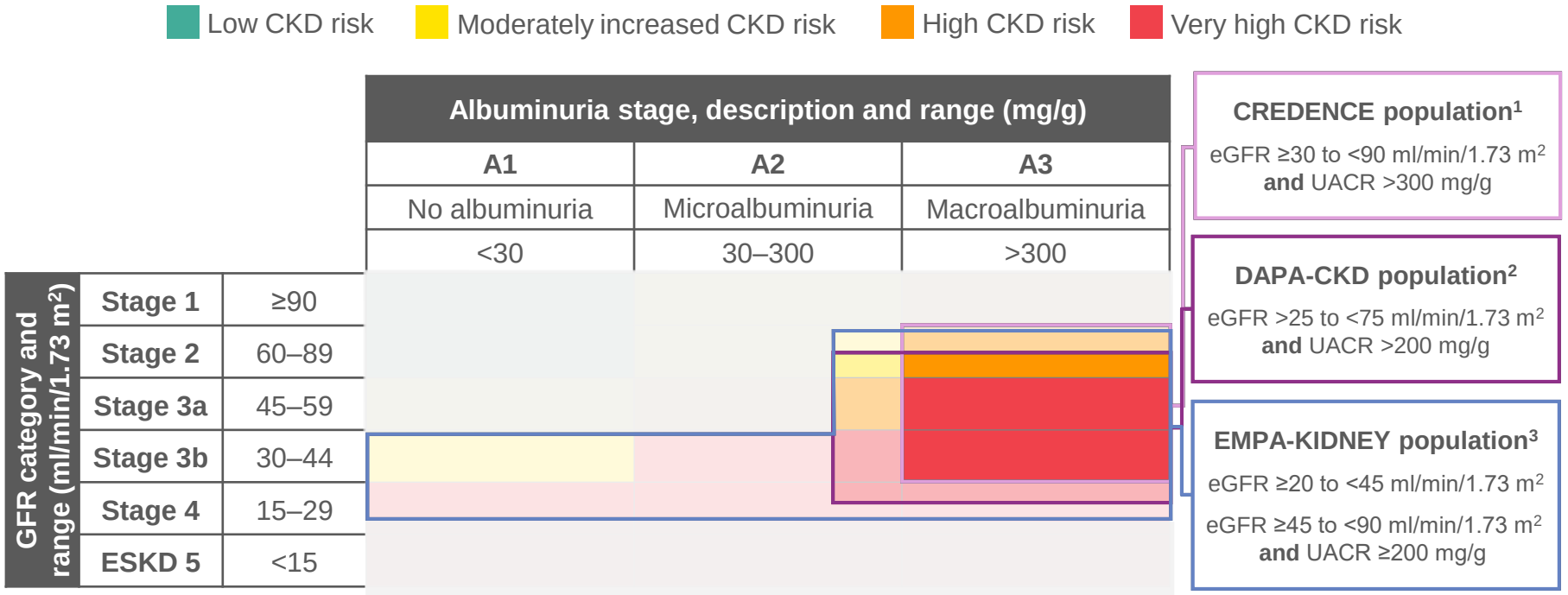
EMPA-KIDNEY is a multinational, randomised, double-blind, placebo-controlled phase III study



*Single RAS inhibition in clinical appropriate dose and management of CV risk factors and other existing comorbidities, including hypertension and diabetes
CV, cardiovascular; RAS, renin–angiotensin system
PACE-CME symposium. *ERA-EDTA* 2018
Empagliflozin ist bisher zugelassen zur Therapie des unzureichend kontrollierten Typ-2-Diabetes - siehe aktuelle Fachinformation

EMPA-KIDNEY

EMPA-KIDNEY enrols a broad CKD population



eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; UACR, urine albumin-to-creatinine ratio

Adapted from Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. *Kidney Int Suppl* 2013;3:1. 1. Jardine MJ *et al. Am J Nephrol* 2017;46:462; 2. ClinicalTrials.gov. NCT03036150 (accessed July 2018); 3. ClinicalTrials.gov. NCT03594110 (accessed July 2018)

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EMPA-KIDNEY

Thank You !