

Opinion-Leader-Meeting

**Therapeutische Innovationen
und neue Industrie-Akademia
Kooperationsmodelle**

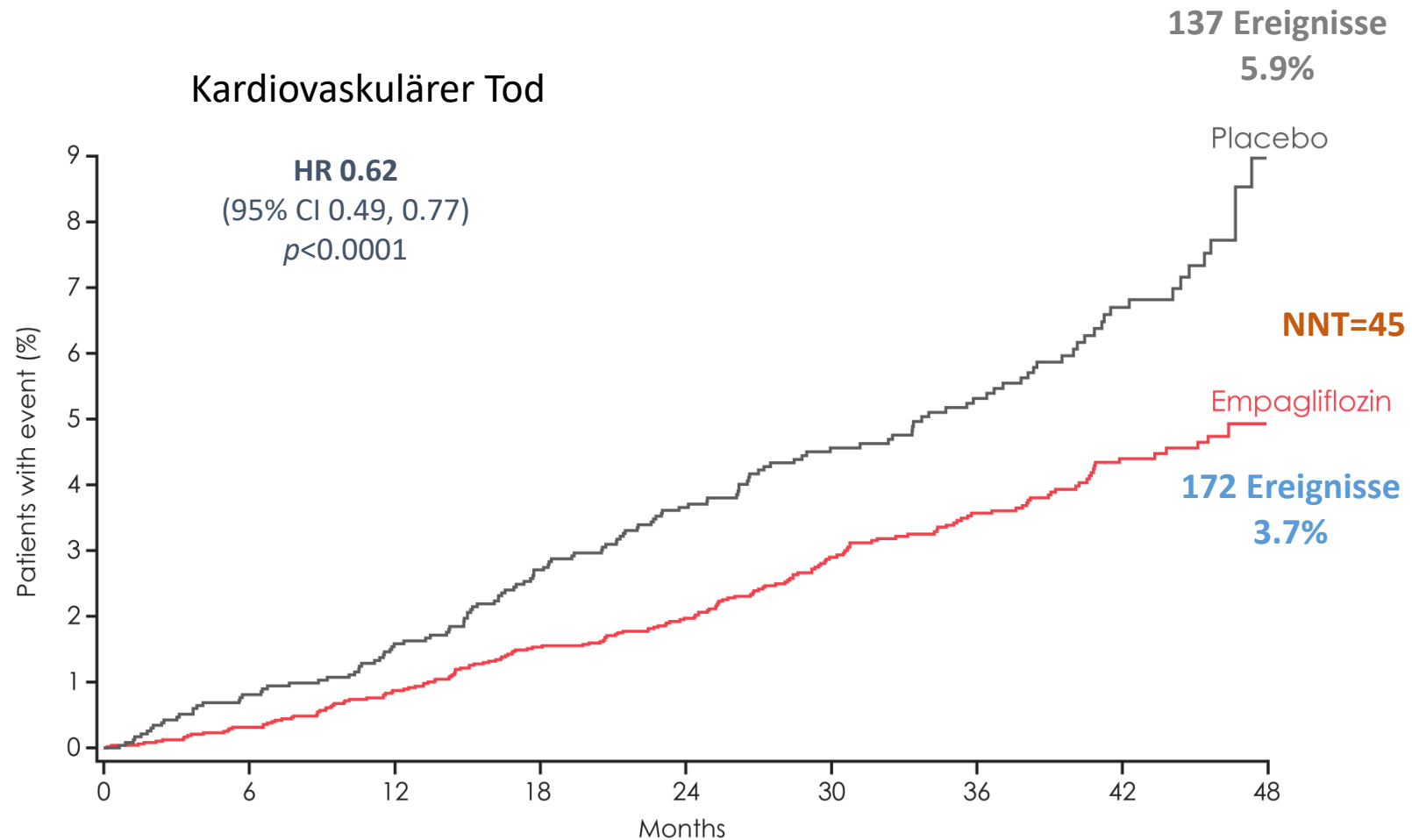
**24./25. Januar 2020
Schloss Löwenstein,
Kleinheubach**

DG&M Deutsche
Gesellschaft für
Innere Medizin

SGLT-2 Hemmer in der Diabetologie und Nephrologie

**Christoph Wanner,
Universitätsklinikum Würzburg**

2015 - EMPA-REG OUTCOME: Die große Überraschung

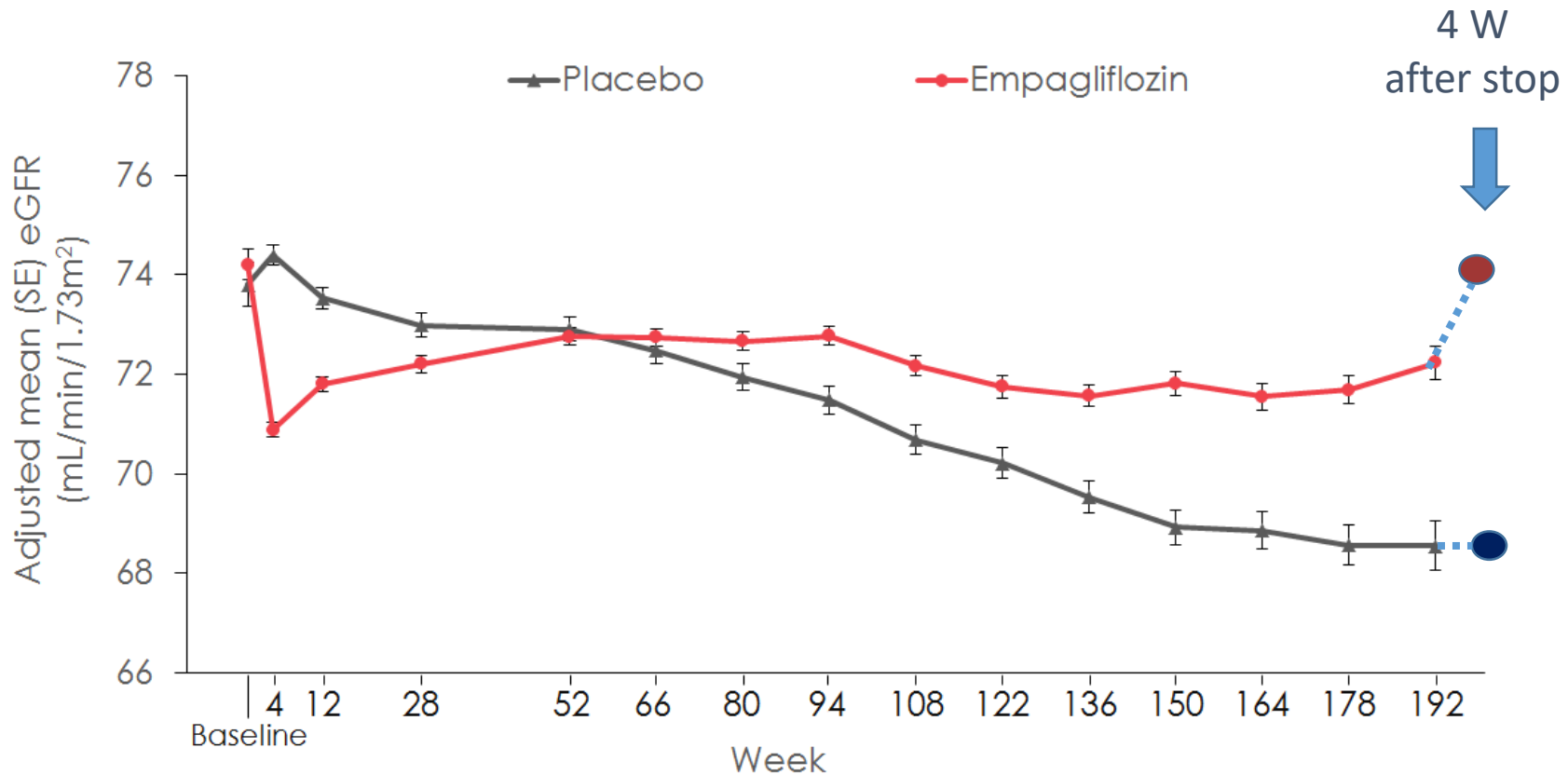


No. of patients	0	6	12	18	24	30	36	42	48
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

SGLT2i CVOTs: baseline characteristics

	EMPA-REG OUTCOME ^{®1} N=7020	DECLARE- TIMI 58 ² N=17,160	CANVAS Program ³ N=10,142
Age, y	63.1	63.8 ± 6.8	63.3 ± 8.3
Male	72%	63%	64%
Diabetes duration, y	diff terminology*	11.8 ± 7.8	13.5 ± 7.8
HbA1c, %	8.1	8.3 ± 1.2	8.2 ± 0.9
BMI, kg/m ²	30.6	32.1 ± 6.0	32.0 ± 5.9
sBP, mmHg	135.4	135 ± 15.5	137 ± 15.8
dBp, mmHg	76.7	78 ± 9.1	78 ± 9.7
UACR mg/g, median (IQR)	NR	13.1 (6, 44)	12.3 (6.7, 42)
Macroalbuminuria	769 (11.0)	1169 (6.8)	760 (7.6)
eGFR ml/min/1.73 m ²	74.0	86 ± 22	77 ± 21

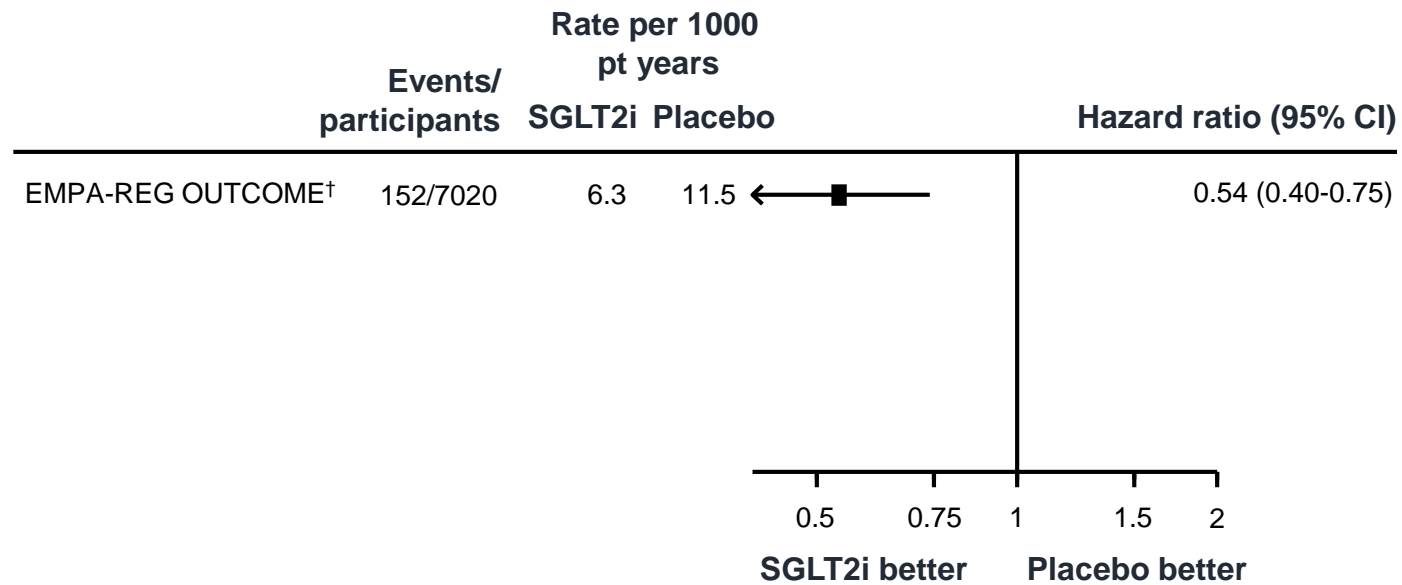
EMPA-REG Outcome: Effekte auf eGFR



Patients analyzed	Baseline	4	12	28	52	66	80	94	108	122	136	150	164	178	192
Placebo	2323			2205	2121		1927		1763		1262		977		448
Empagliflozin	4644			4451	4318		4018		3710		2654		2087		1037

EMPA-REG OUTCOME

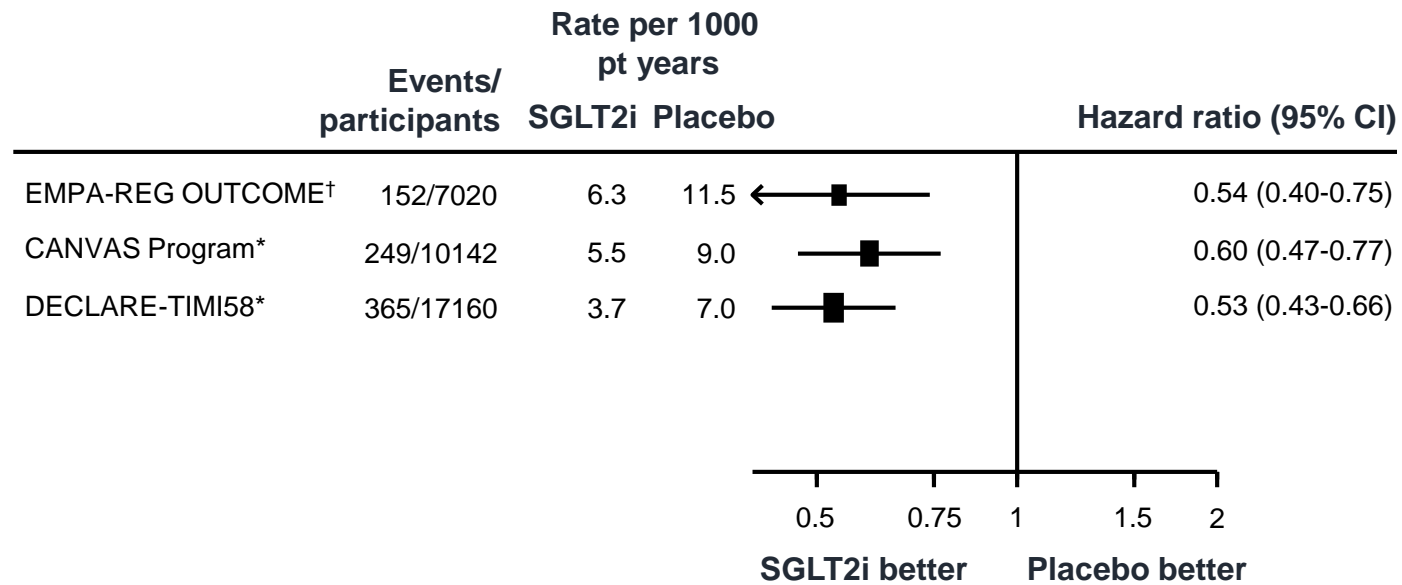
Kidney disease progression



Outcomes

† = Doubling of creatinine or ESRD

First three large SGLT2i trials in type 2 diabetes: Kidney disease progression



Outcomes

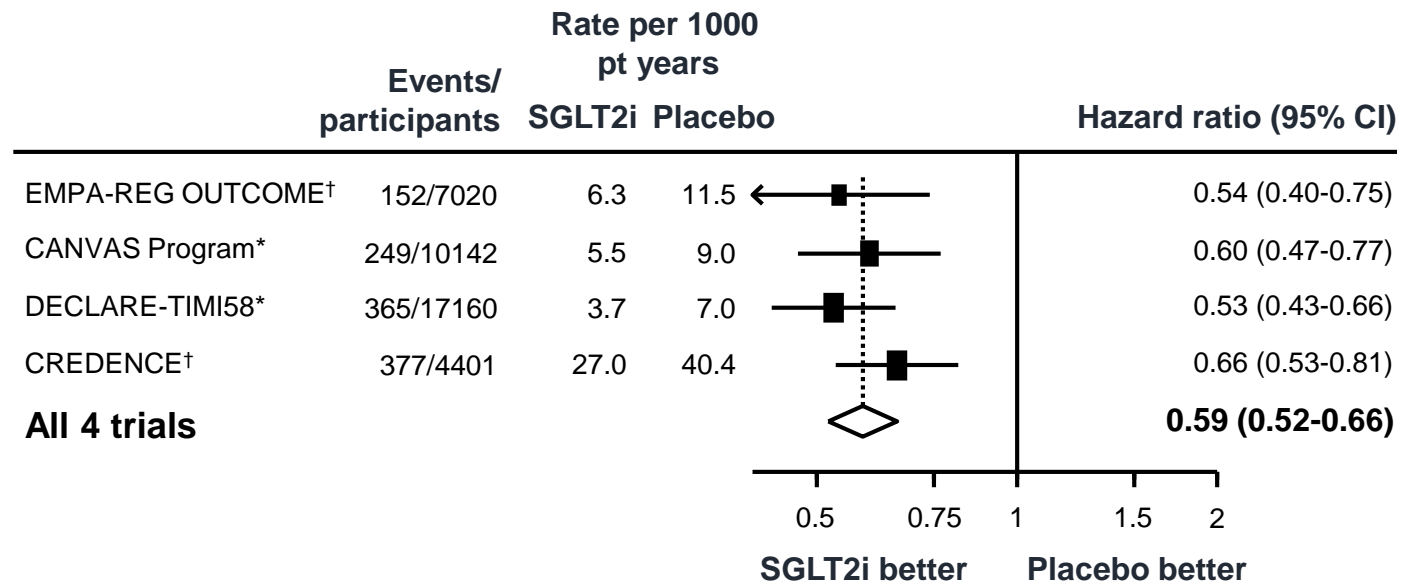
† = Doubling of creatinine or ESRD

* = 40% decline in eGFR or ESRD

SGLT2i CVOTs/Renal trials: baseline characteristics

	EMPA-REG OUTCOME ^{®1} N=7020	DECLARE- TIMI 58 ² N=17,160	CANVAS Program ³ N=10,142	CREDESCENCE ⁴ N=4401
Age, y	63.1	63.8 ± 6.8	63.3 ± 8.3	63.2 ± 9.2
Male	72%	63%	64%	66%
Diabetes duration, y	diff terminology*	11.8 ± 7.8	13.5 ± 7.8	15.8 ± 8.7
HbA1c, %	8.1	8.3 ± 1.2	8.2 ± 0.9	8.3 ± 1.3
BMI, kg/m ²	30.6	32.1 ± 6.0	32.0 ± 5.9	31.3 ± 6.2
sBP, mmHg	135.4	135 ± 15.5	137 ± 15.8	140 ± 15.6
dBp, mmHg	76.7	78 ± 9.1	78 ± 9.7	78 ± 9.4
UACR mg/g, median (IQR)	NR	13.1 (6, 44)	12.3 (6.7, 42)	927 (463, 1833)
Macroalbuminuria	769 (11.0)	1169 (6.8)	760 (7.6)	3371 (76.6) ^{§ **}
eGFR ml/min/1.73 m ²	74.0	86 ± 22	77 ± 21	56 ± 18

All four large SGLT2i trials in type 2 diabetes: Kidney disease progression



Between trial heterogeneity **p=0.50**

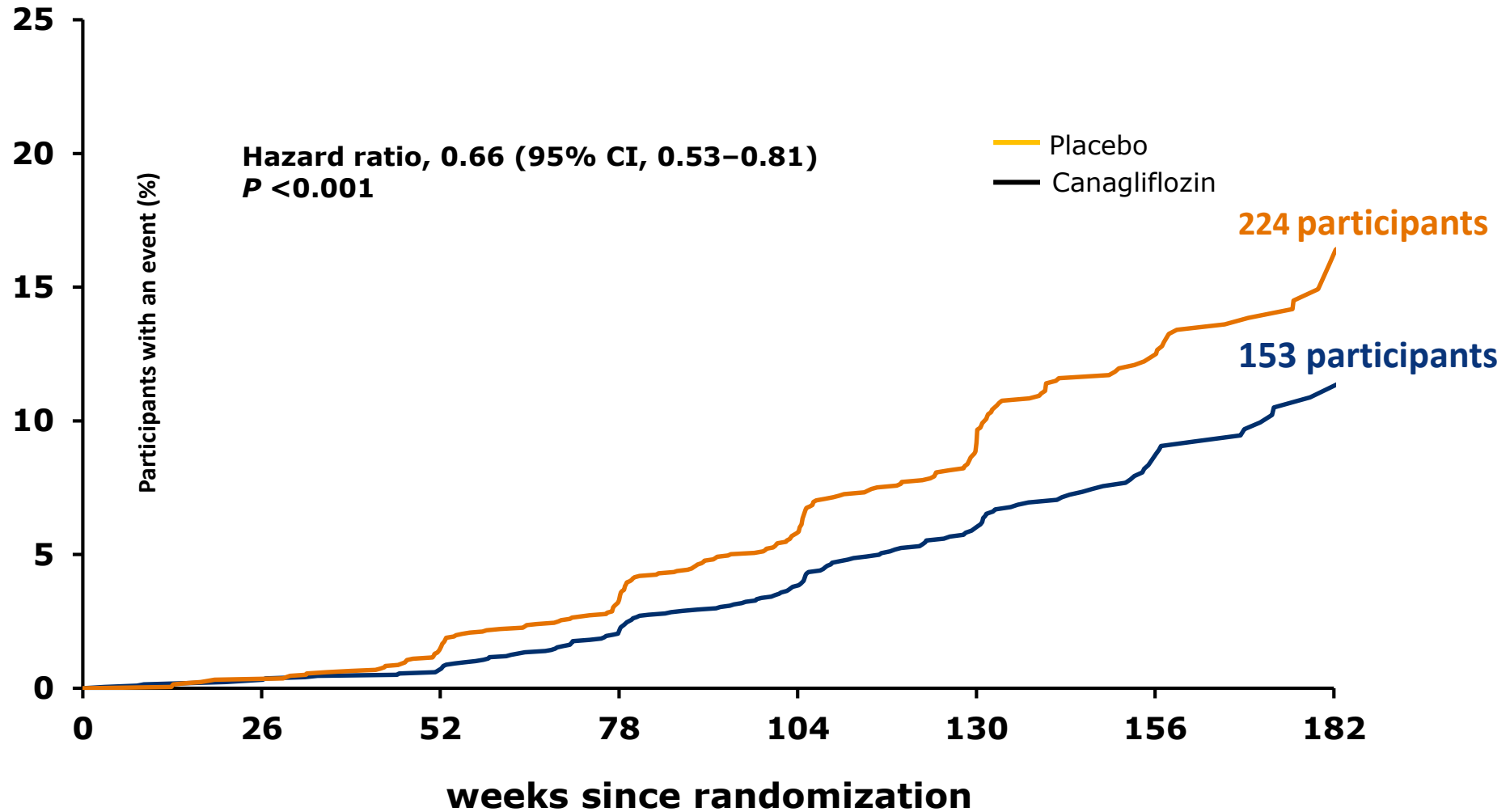
Wanner NEJM 2016; 375: 323-334; Neal NEJM 2017; 377: 644-57; Wiviott NEJM 2018; Nov 10; Percovic NEJM 2019; Apr 14.

Outcomes

[†] = Doubling of creatinine or ESRD

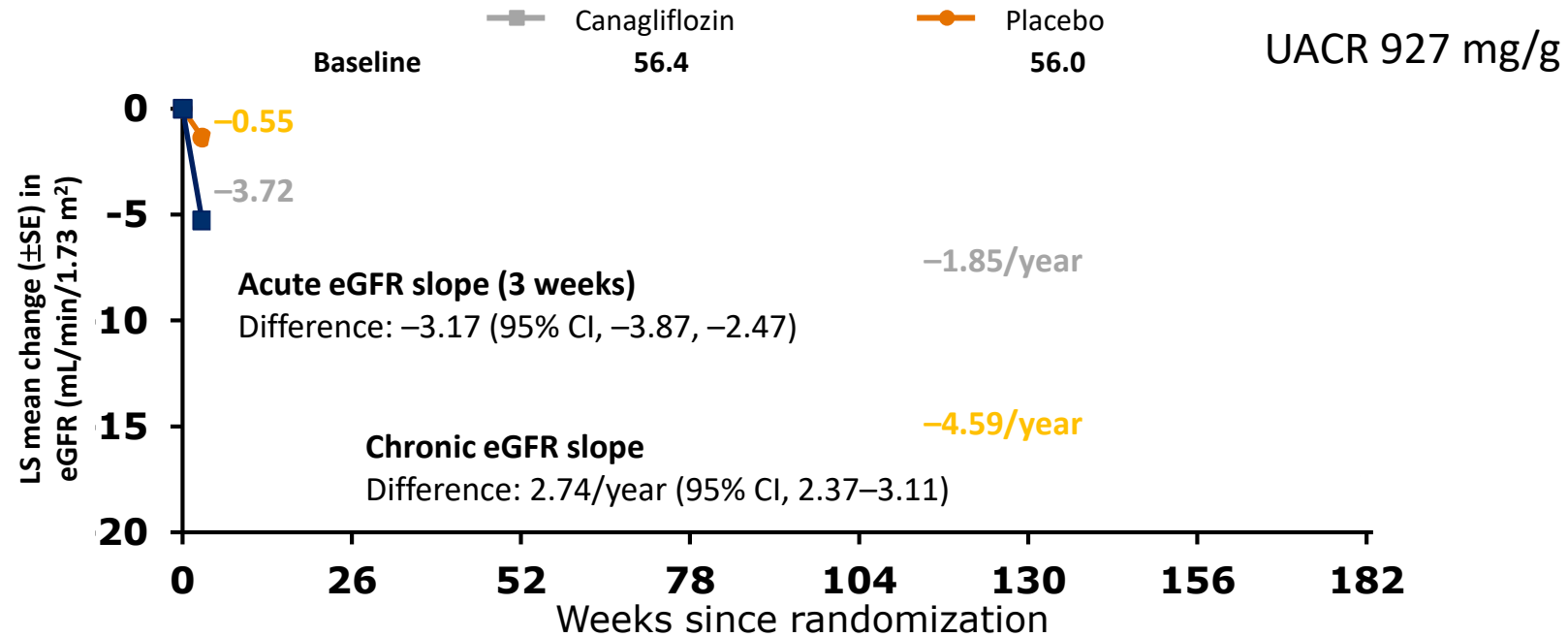
* = 40% decline in eGFR or ESRD

The Kidney Endpoint: ESKD, 2 x SCr, or renal death



No. at risk	0	26	52	78	104	130	156	182
Placebo	2199	2178	2131	2046	1724	1129	621	170
Canagliflozin	2202	2181	2144	2080	1786	1211	646	196

CREDESCENCE: Effekte auf eGFR

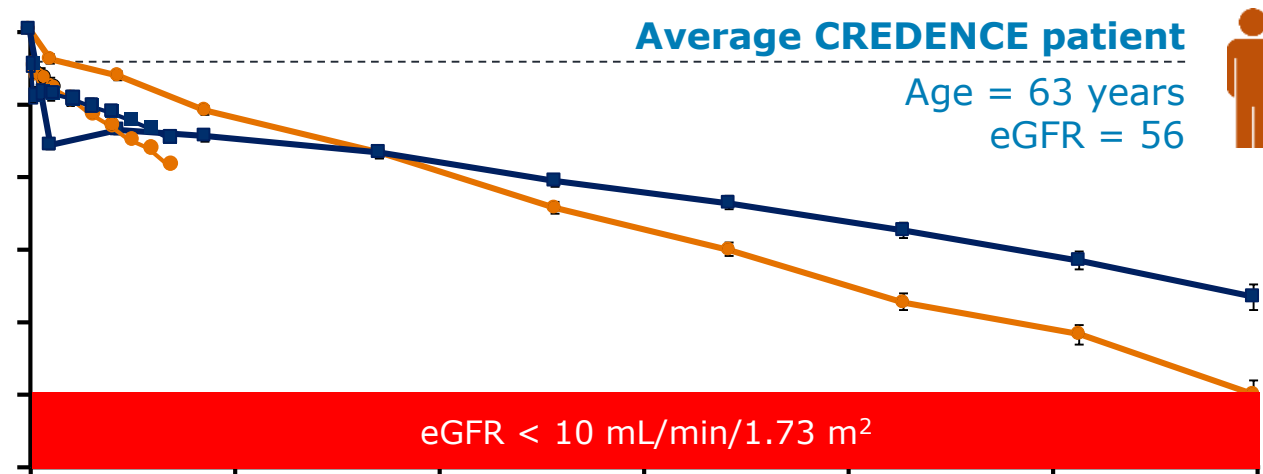


No. of Participants

Placebo	2178	2084	1985	1882	1720	1536	1006	583	210
Canagliflozin	2179	2074	2005	1919	1782	1648	1116	652	241

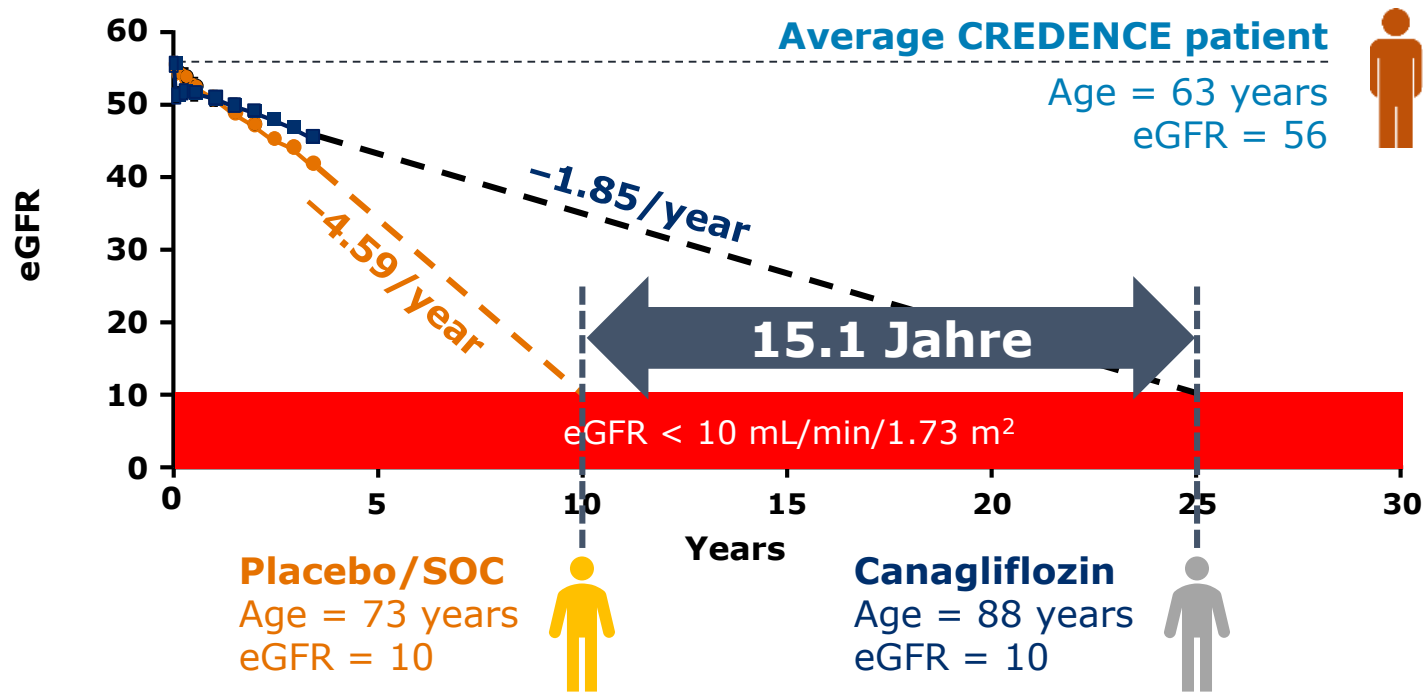
On treatment

Projizierte Effekte auf die Nierenfunktion



Intermediates Trials Renal Cardiovascular Safety

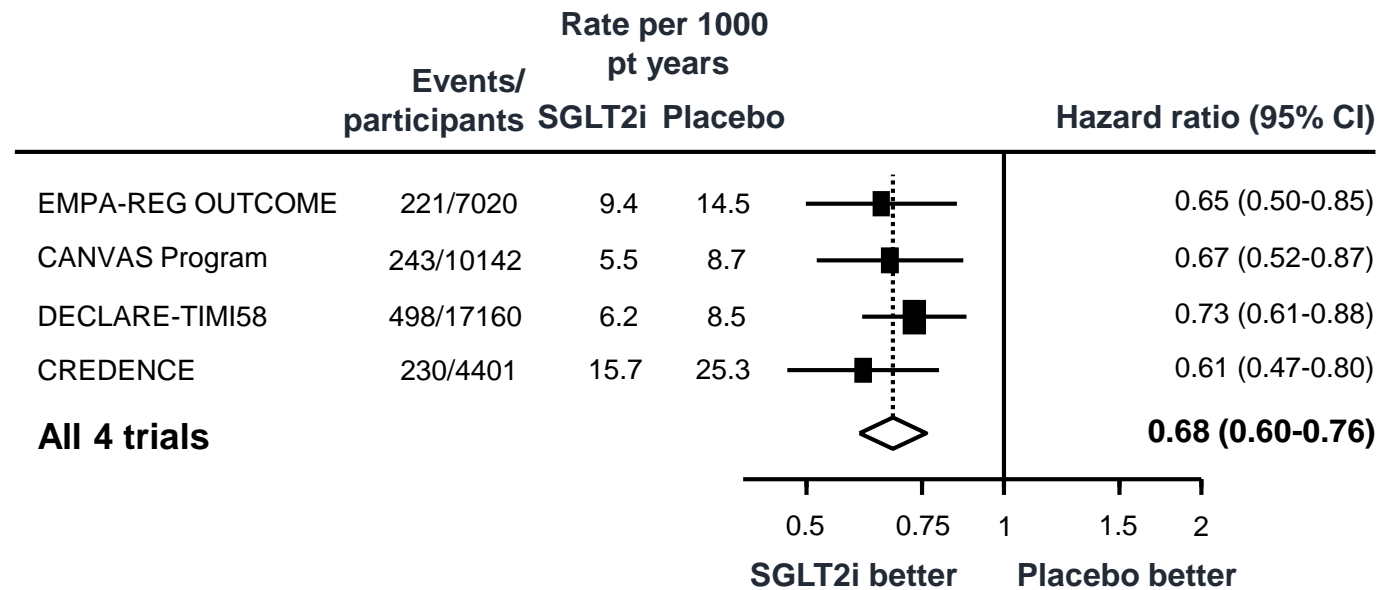
Projizierte Effekte auf die Nierenfunktion



Intermediates Trials Renal Cardiovascular Safety

Herzinsuffizienz (HRrEF/HFpEF)

4 grosse SGLT2i Studien bei T2D: Heart failure Hospitalisierung

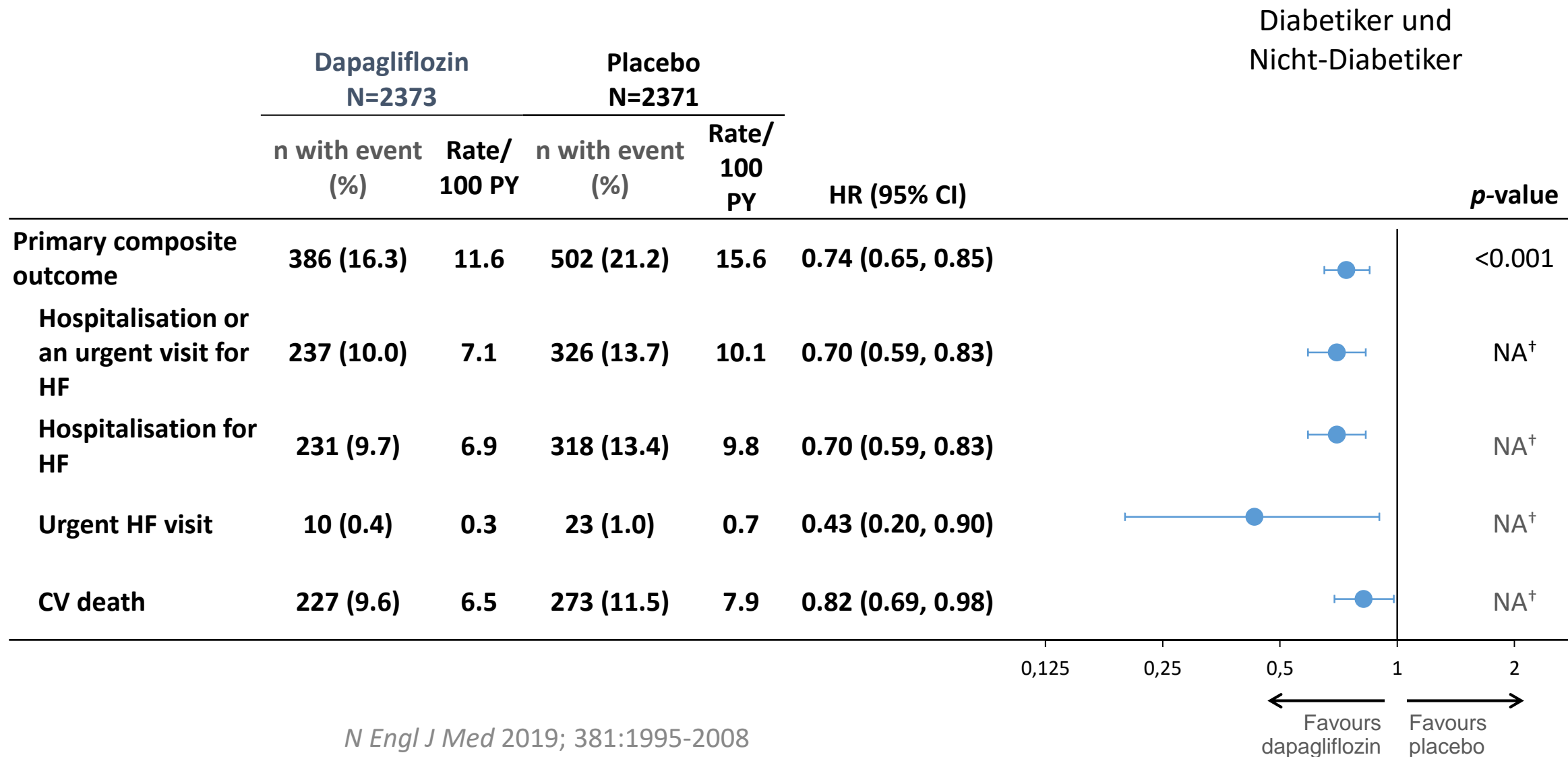


Between trial heterogeneity **p=0.72**

SGLT2i CVOTs/Renal/HF trials: baseline characteristics

	EMPA-REG OUTCOME ^{®1} N=7020	DECLARE- TIMI 58 ² N=17,160	CANVAS Program ³ N=10,142	CREDESCENCE ⁴ N=4401	DAPA-HF ⁵ N=4744
Age, y	63.1	63.8 ± 6.8	63.3 ± 8.3	63.2 ± 9.2	66.2 ± 11.0
Male	72%	63%	64%	66%	76%
Diabetes duration, y	diff terminology*	11.8 ± 7.8	13.5 ± 7.8	15.8 ± 8.7	41.8% Diabetes
HbA1c, %	8.1	8.3 ± 1.2	8.2 ± 0.9	8.3 ± 1.3	
BMI, kg/m ²	30.6	32.1 ± 6.0	32.0 ± 5.9	31.3 ± 6.2	28.2 ± 6.0
sBP, mmHg	135.4	135 ± 15.5	137 ± 15.8	140 ± 15.6	122 ± 16.3
dBp, mmHg	76.7	78 ± 9.1	78 ± 9.7	78 ± 9.4	
UACR mg/g, median (IQR)	NR	13.1 (6, 44)	12.3 (6.7, 42)	927 (463, 1833)	
Macroalbuminuria	769 (11.0)	1169 (6.8)	760 (7.6)	3371 (76.6) ^{§ **}	
eGFR ml/min/1.73 m ²	74.0	86 ± 22	77 ± 21	56 ± 18	66 ± 20

DAPA-HF: Primärer zusammengesetzter Endpunkt Verschlechterung HF oder CV Tod





Leitlinien in public review 1/2020

ANTI-HYPERGLYCEMIC THERAPIES IN PATIENTS WITH DIABETES AND CKD (SGLT2i)

Recommendation 4.2.1. In patients with Type 2 diabetes, CKD, and eGFR ≥ 30 ml/min/1.73 m², we recommend including an SGLT-2 inhibitor (SGLT2i) in the antihyperglycemic treatment regimen (1A).

Idem: Diabetes Care 2020;43 (Suppl1):S1-S213. ADA Standards of Medical Care in Diabetes 2020

T2D and atherosclerotic cardiovascular; kidney disease, or heart failure **A**

IMPACT DER OUTCOME TRIALS AUF BEHANDLUNGSLEITLINIEN

Endpunkt Studien (Outcome trials) haben **dramatisch unser Wissen verbessert** hinsichtlich non-HbA_{1c} Effekte der SGLT2 Inhibitoren

Der **CV Benefit der SGLT2 Inhibitoren** ist gut untersucht und die Verwendung dieser Substanzen wurden in Leitlinien implementiert

Die **Nieren Benefits dieser neuen Glukose senkenden Medikamente** sind beim T2D belegt, werden aber weiter ausführlich in klinischen Studien untersucht

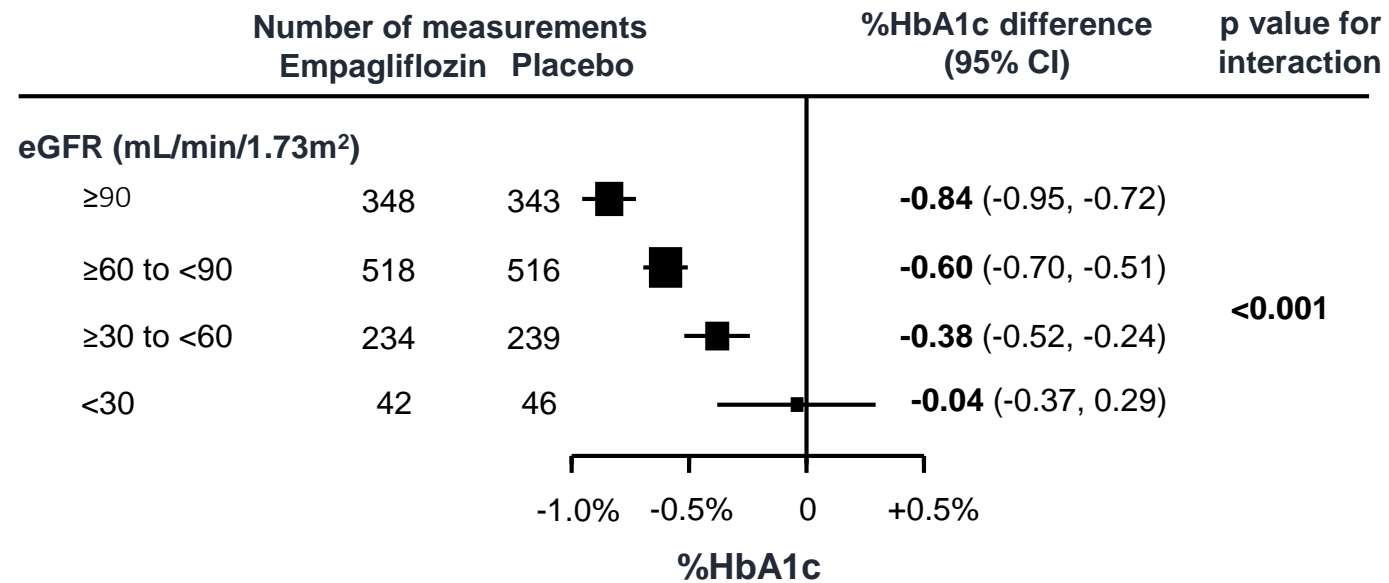
Dramatische Veränderungen für die Nephrologie

Diabetologen

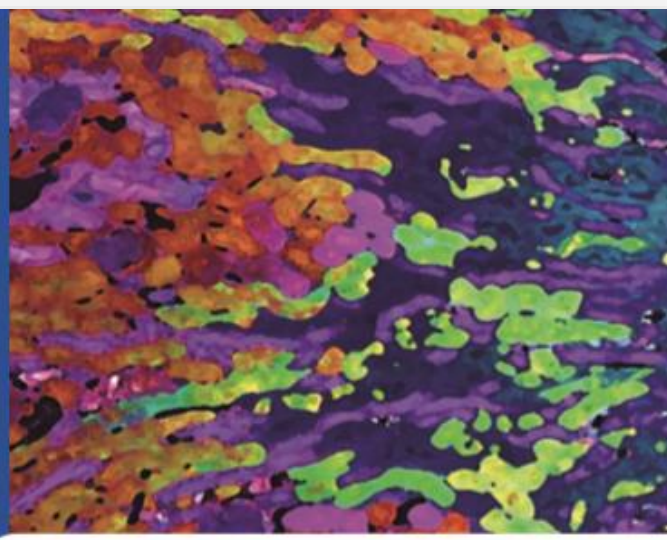
CKD is classified based on: <ul style="list-style-type: none"> • Cause (C) • GFR (G) • Albuminuria (A) 				Albuminuria categories		
				Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
GFR categories (ml/min/1.73m²) Description and range	G1	Normal or high	≥90	1 if CKD	Treat 1	Refer* 2
	G2	Mildly decreased	60-89	1 if CKD	Treat 1	Refer* 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat 3	Refer 3
	G4	Severely decreased	15-29	Refer* 3	Refer* 3	Refer 4+
	G5	Kidney failure	<15	Refer 4+	Refer 4+	Refer 4+

Nephrologen

Effects of Empagliflozin vs placebo on %HbA1c, by eGFR



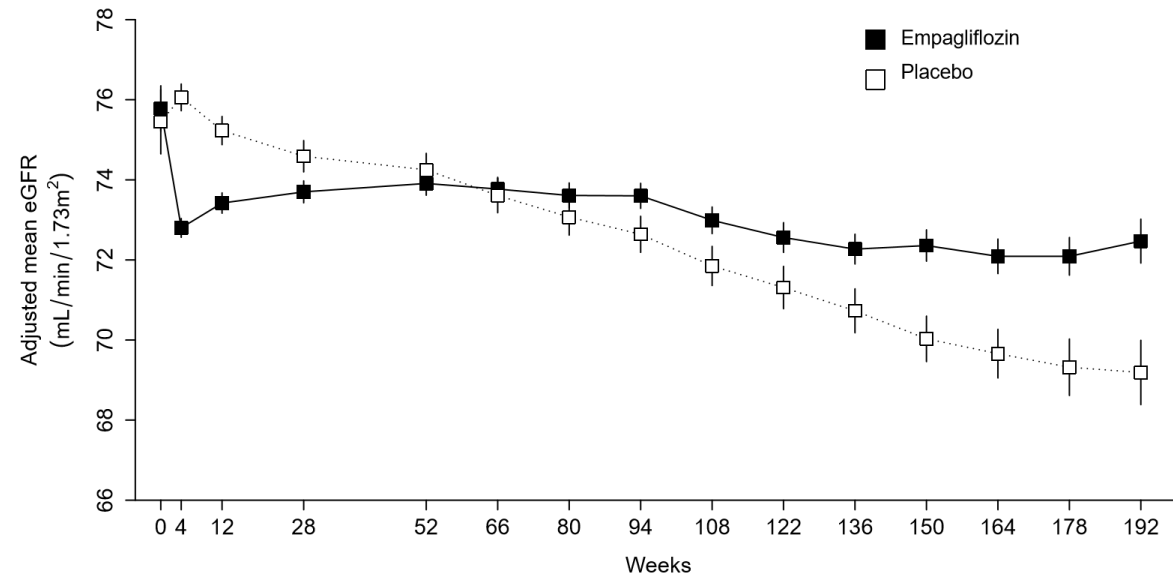
Kidney International 2018; 93: 231-244



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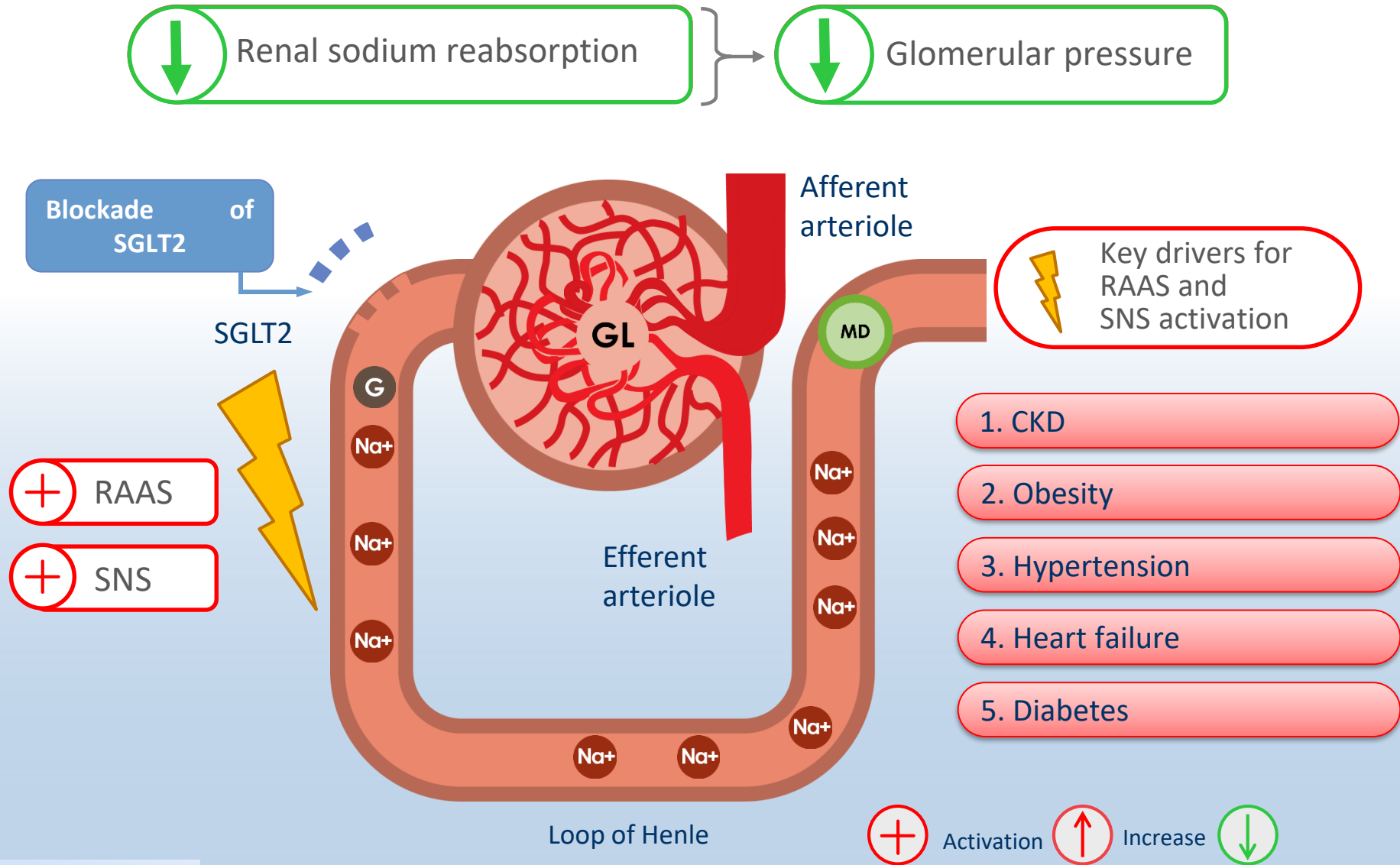
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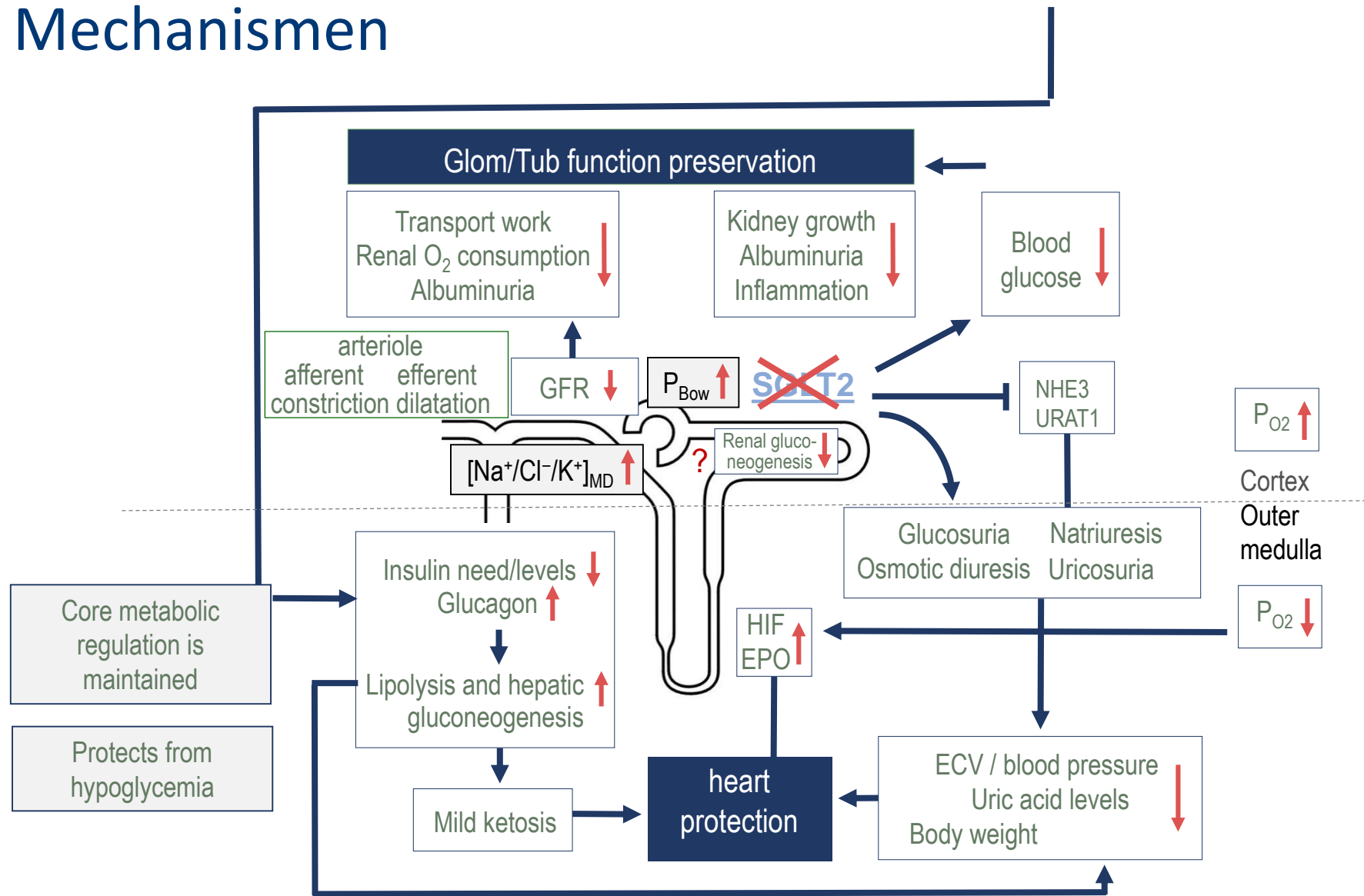
2015 Plan: Nierenstudie - 4000 T2D, 4 Jahre
Aber: CREDENCE war unterwegs
Neue Hypothesen, Machbarkeit ohne CRO

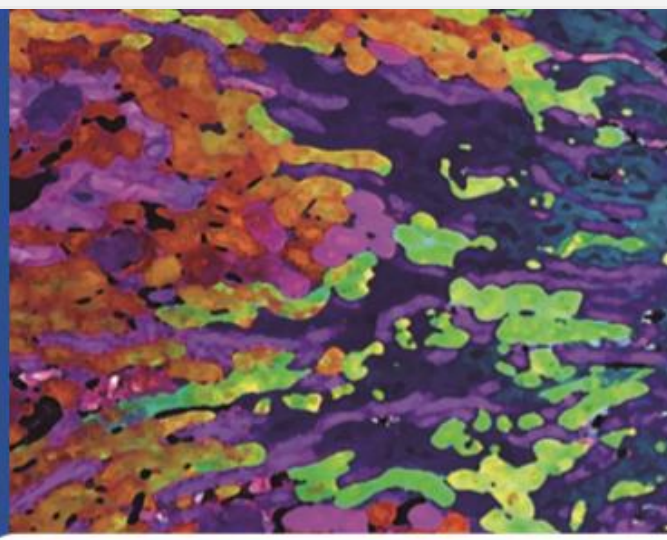
Kooperationsmodell: Boehringer-I / Akademia

Renal MOA +/- Diabetes: Increased renal sodium reabsorption



Weitere Mechanismen

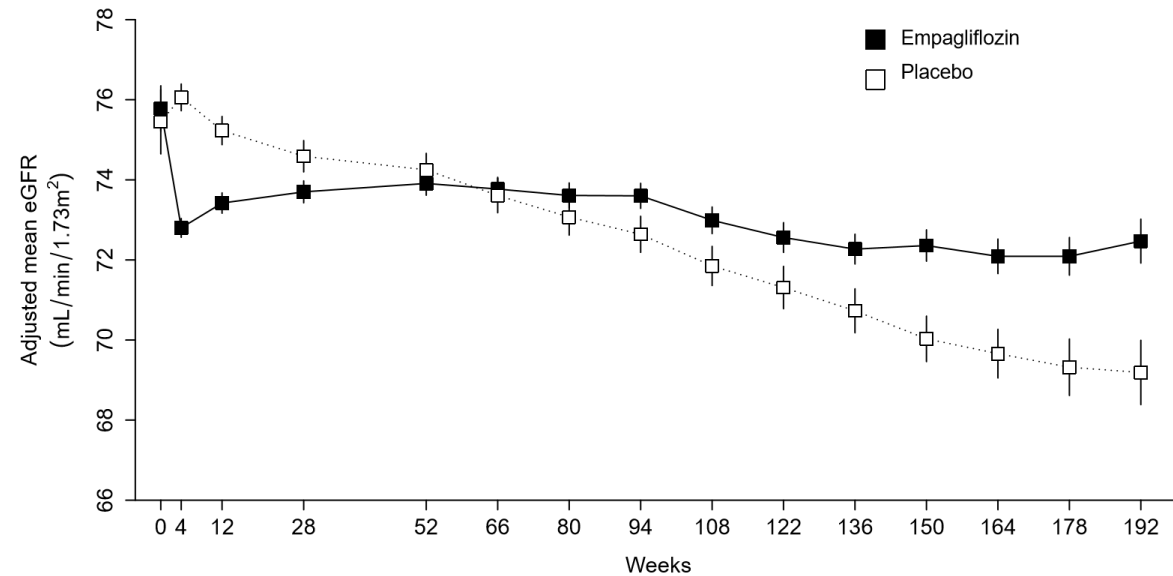




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2015 Plan: Nierenstudie - 4000 T2D, 4 Jahre
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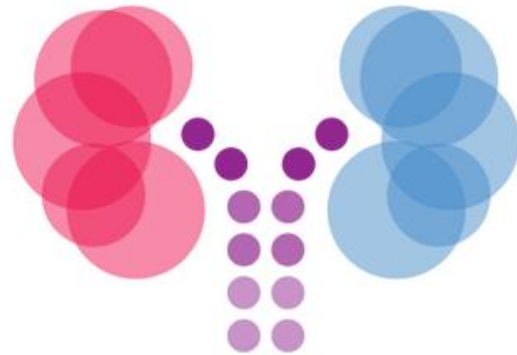
Kooperationsmodell: Boehringer-I / Akademia

Trial center in USA, Canada, UK, Australien

Boehringer Ingelheim and Lilly announce an academic collaboration with University of Oxford to investigate the effects of empagliflozin in people with chronic kidney disease

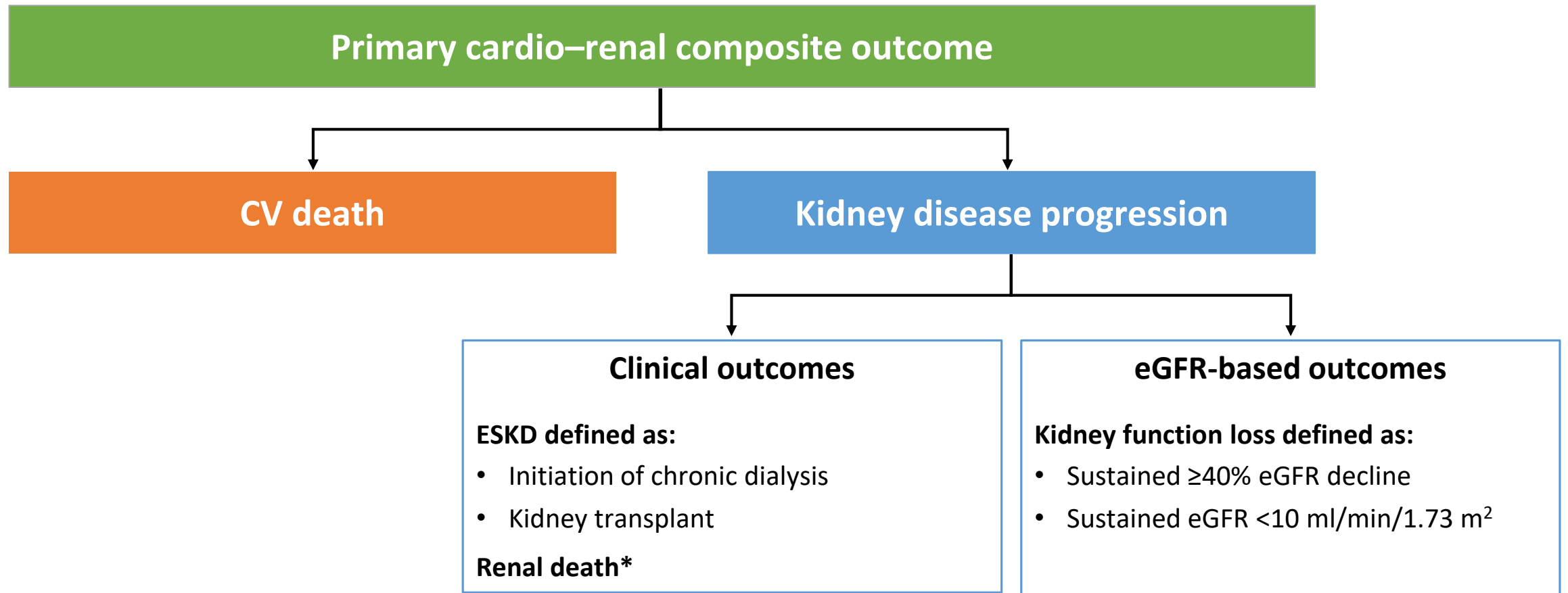
- *University of Oxford to assess effect of empagliflozin on heart and kidney disease in people with chronic kidney disease*
- *EMPA-KIDNEY will be part of the empagliflozin clinical development programme which explores the efficacy and safety of empagliflozin across a broad spectrum of patients and clinical conditions*

16 April 2018



EMPA-KIDNEY

The study of heart and kidney protection
with empagliflozin

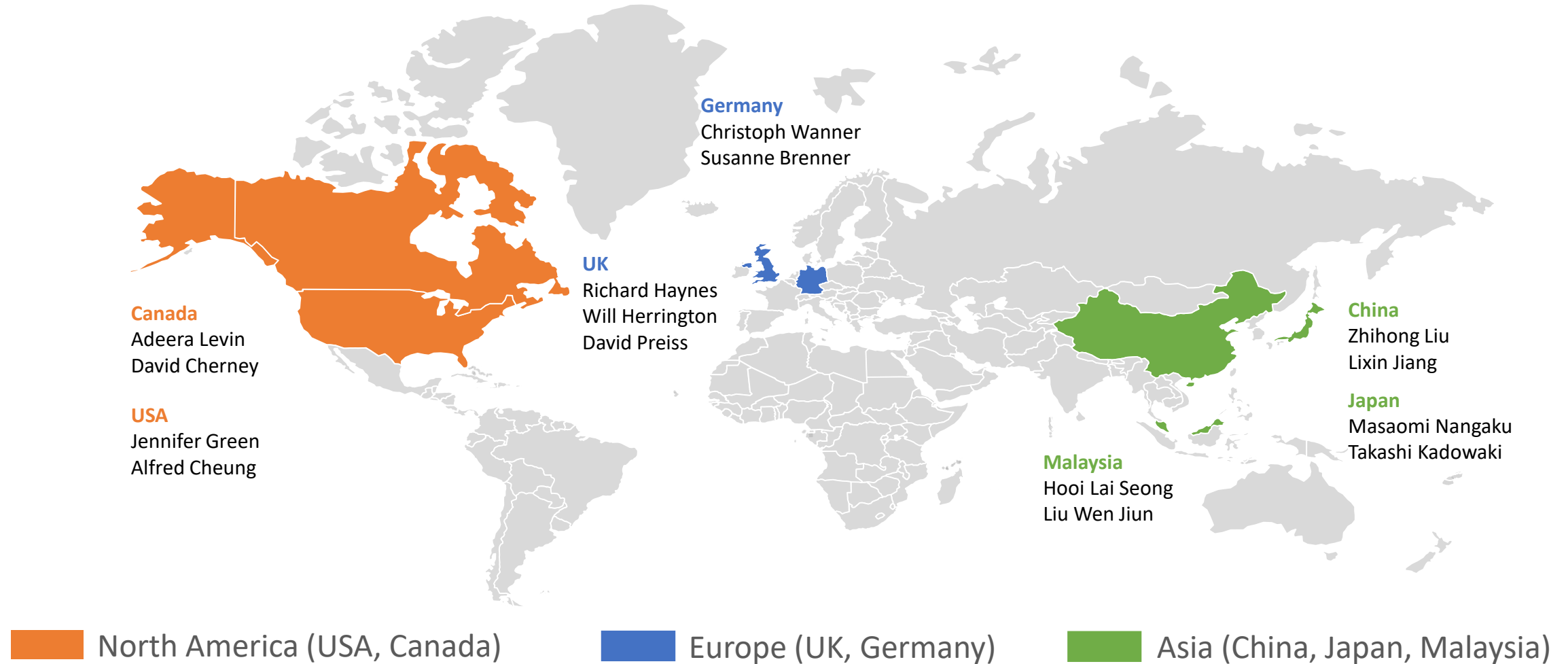


EMPA-KIDNEY (n=6000 Diabetes und Nicht-Diabetes CKD

eGFR ≥ 20 to < 45 ml/min/1.73 m²

**eGFR ≥ 45 to < 90 ml/min/1.73 m²
and UACR ≥ 200 mg/g**

EMPA-KIDNEY: International scientific and operational leaders*



Zentren in Deutschland

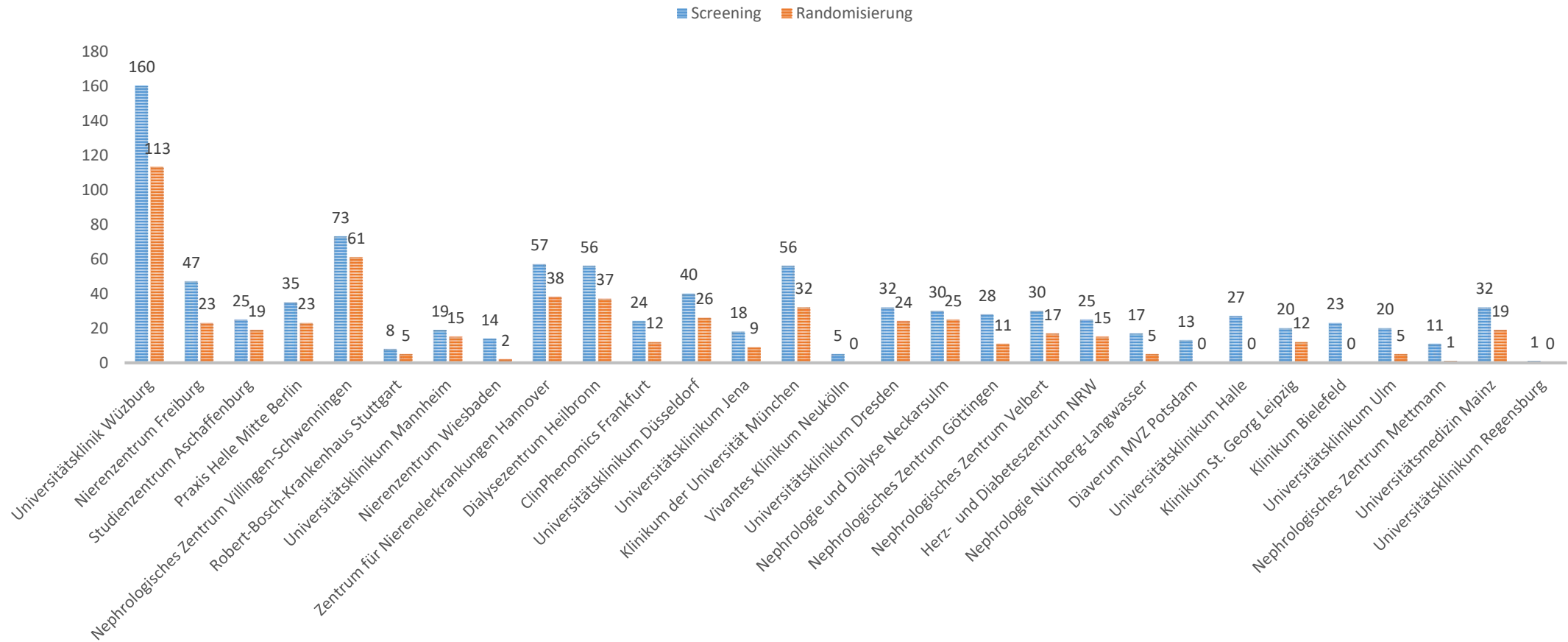


z.B. 32 Zentren

1250 Patienten

EMPA-Kidney Deutschland

Aktueller Stand Screening und Randomisierung (16.01.2020)



ONGOING AND UPCOMING KIDNEY OUTCOME TRIALS



EMPA-KIDNEY

The study of heart and kidney protection with empagliflozin



DAPACKD



CREDESCENCE

FLOW

semaglutide | renal outcomes trial



FIDELIO-DKD



**Vielen
Dank**



Glucose



Salt



Water