A NEW WONDER PIL: 'GIVING TIME BACK TO CHRONIC KIDNEY PATIENTS'

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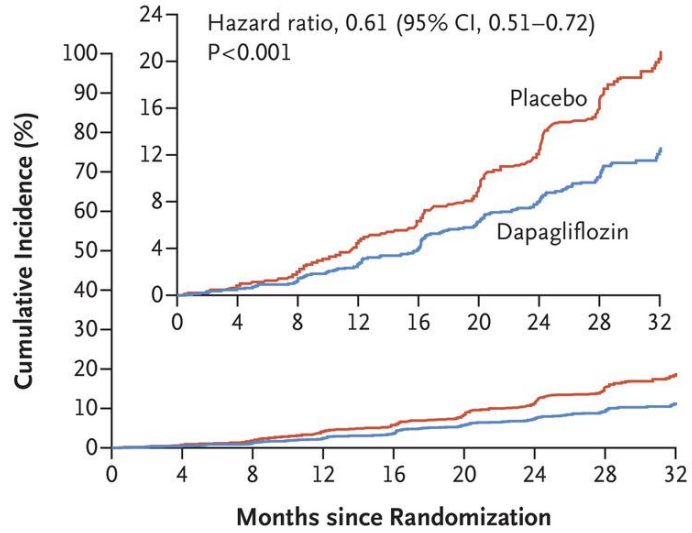
KARVA, November 19, Antwerp

The ‘Wonder Pil’ in Nephrology

SGLT2 Inhibitors

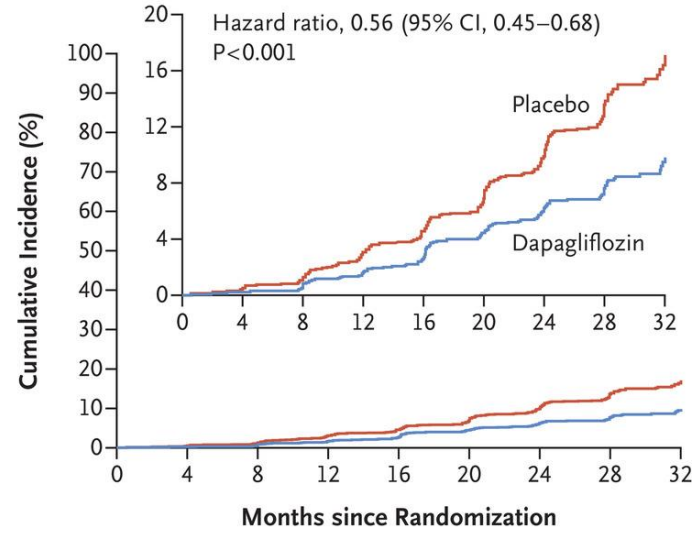
- Dapaflozine
- Canaflozine
- Empaflozine
- Ertugliflozin
- Sotagloflozin

A Primary Composite Outcome



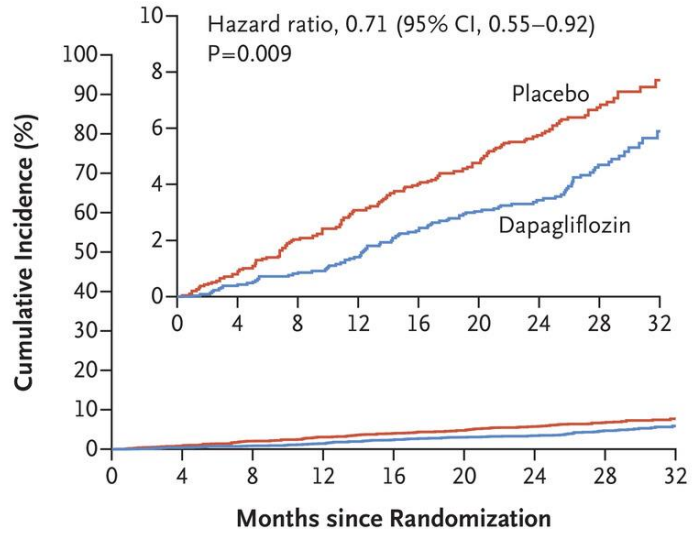
No. at Risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

B Renal-Specific Composite Outcome



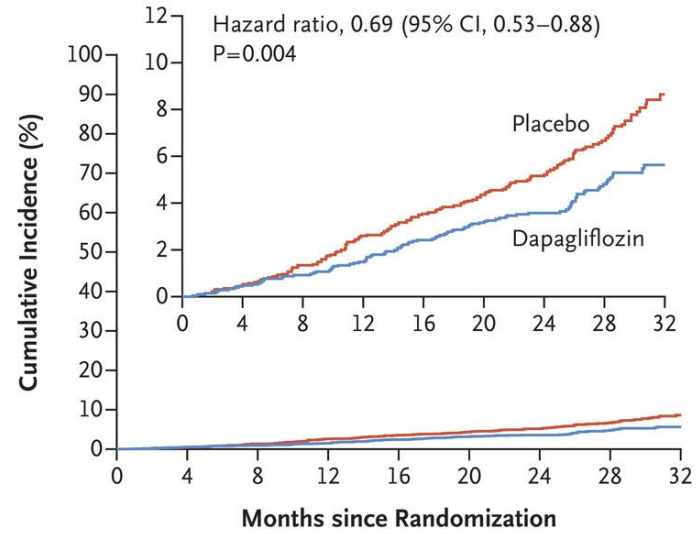
No. at Risk									
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure

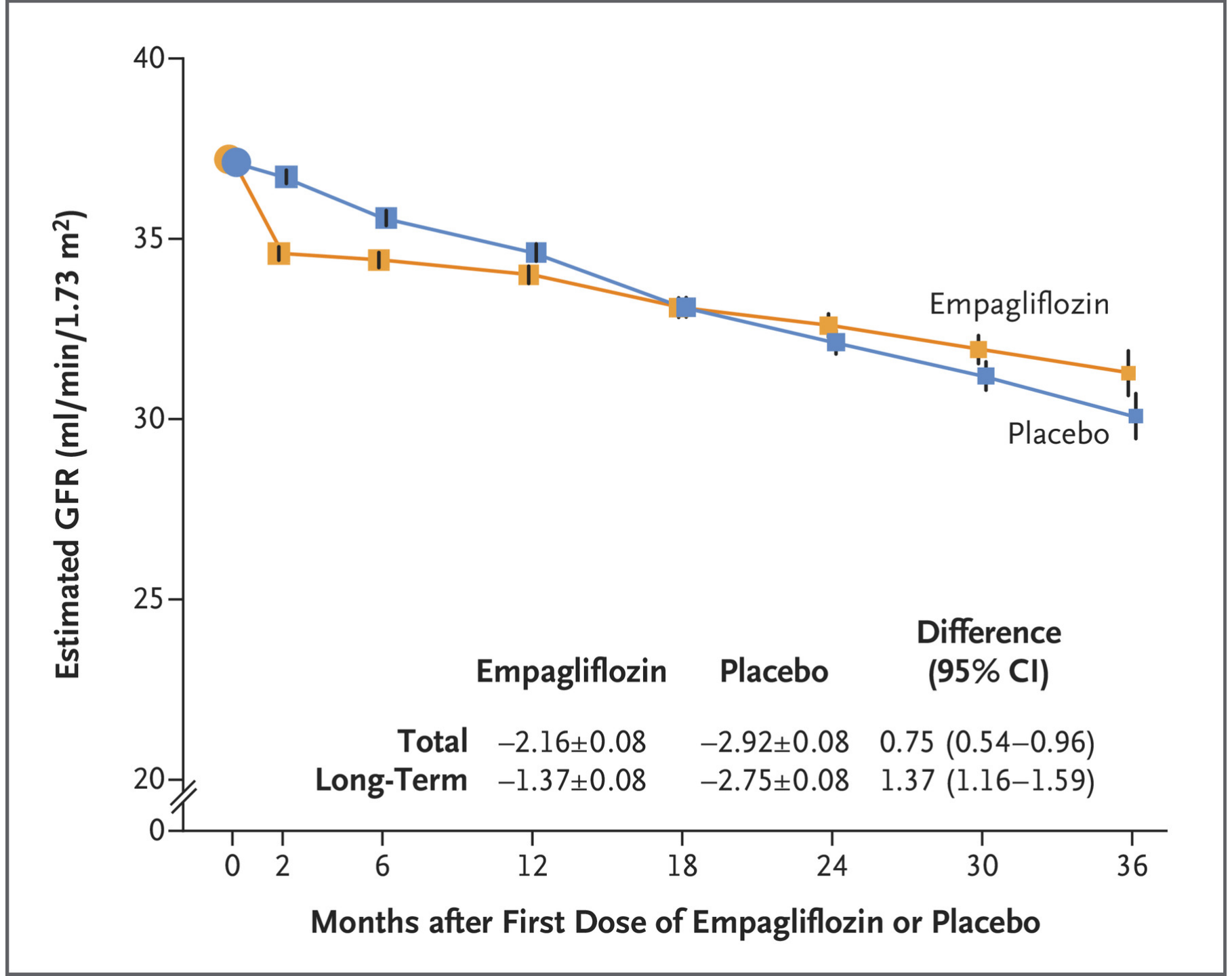


No. at Risk									
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384

D Death from Any Cause



No. at Risk									
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398


Estimated GFR (ml/min/1.73 m²)
40
35
30
25
20
0
Empagliflozin
Placebo
Empagliflozin
Placebo
Difference (95% CI)
Total
–2.16±0.08
–2.92±0.08
0.75 (0.54–0.96)
Long-Term
–1.37±0.08
–2.75±0.08
1.37 (1.16–1.59)
0
2
6
12
18
24
30
36
Months after First Dose of Empagliflozin or Placebo

A Little (recent) History

Type 2 diabetes mellitus (T2DM) is a worldwide growing public health problem

Good blood glucose control early in the disease can reduce the risk of micro- and macrovascular complications, including cardiovascular disease (CVD), diabetic nephropathy, and mortality

However, for many current blood glucose–lowering drugs, including insulin, adequate glycemic control may be difficult to establish without clinically relevant unwanted side effects, such as weight gain and hypoglycemia, and these strategies may not reduce the risk of cardiovascular complications

Since 2008, the US Food and Drug Administration (FDA) requires proof of cardiovascular safety for new glucose-lowering therapies :

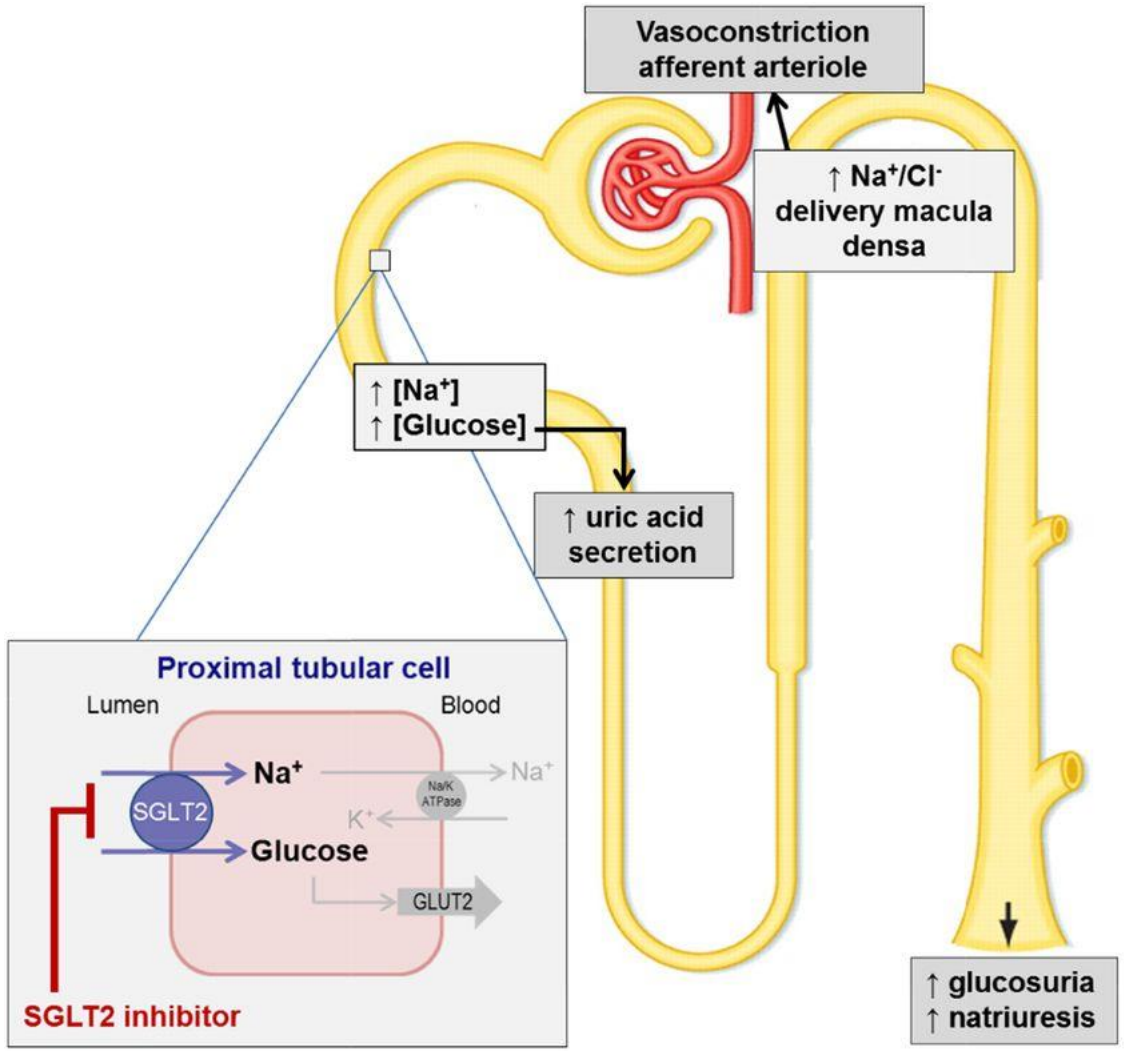
SGLT2 inhibitors were in development when the guidance came into effect .

A Little (recent) History

2014

Inhibitors of the sodium-glucose cotransporter 2 (SGLT2-I) are a new class of **antihyperglycemic drugs**

-inhibiting renal glucose reabsorption in the early proximal tubule
  -enhancing urinary glucose excretion
  -lowering the glucose burden on the organism



Clinical findings

- ↓ Plasma glucose
- ↓ Body weight
- ↓ Blood pressure
- ↓ Plasma uric acid
- ↓ Glomerular hyperfiltration

Glucose dependent Actions of SGLT2 Inhibitors

SGLT2 I induce a sustained urinary glucose loss preventie hyperglycemia

-in T2DM decreases glycated hemoglobin (HbA1C) levels by 0.5–0.7%

-the higher the blood glucose level (and GFR), the more glucose is filtered and thus excreted in response to SGLT2 blockade.

SGLT2 I prevent hypoglycemia

-because they stop lowering blood glucose levels once the filtered glucose load falls to ~80 g/day, which can be reabsorbed by downstream SGLT1

-because they increase plasma glucagon concentrations and thereby hepatic gluconeogenesis

Glucose dependent Actions of SGLT2 Inhibitors

SGLT2 I induce Weight reduction

-Diuretic effect (osmotic diuresis and natriuresis)
-Shifting substrate utilization from carbohydrates to lipids, thereby reducing body fat, including visceral and subcutaneous fat
-Indirect improvement in beta-cell function and insulin sensitivity that is sustained)

SGLT2 I induce formation of Ketone Bodies

-Spilling glucose and calories into the urine, mimics fasting and triggers counter regulatory metabolic readjustments
-Keton bodies provide additional energy substrates to other organs)

A Little (recent) History

Since 2008, the US Food and Drug Administration (FDA) has required **proof of cardiovascular safety for new glucose-lowering therapies** :

Patients with T2DM and severe ASCVD and CV Disease were included
-Lowering the risk of Cardiovascular death, Myocardial Infarction, Stroke, and Hospitalization for Heart Failure
-Slowing the progression of established diabetic Kidney Disease

Timeline of Major SGLT2 Inhibitor Trials

- CREDENCE began before any CV outcomes trials had reported

- Renal effects were not the primary focus of the CV outcomes trials

CANVAS, DECLARE, EMPA-REG
Patient population comparison

	EMPA-REG Outcome	CANVAS Program		DECLARE (TIMI 58)
		CANVAS	CANVAS-R	
Number	7034	4339 + 5700 10039		17150
Key Inclusion	CVD (100%)	CVD (~65%) or high CVD risk (~35%)		CVD (35%) or High risk (65%)
Study Endpoints	CV Death MI Stroke	CV Death MI Stroke	Progression of albuminuria, CV Death, MI, Stroke	CV Death MI Stroke
Reporting	2015	2017	2017	2019
Median F/U	3 years	6-7 years	3 years	4-5 years

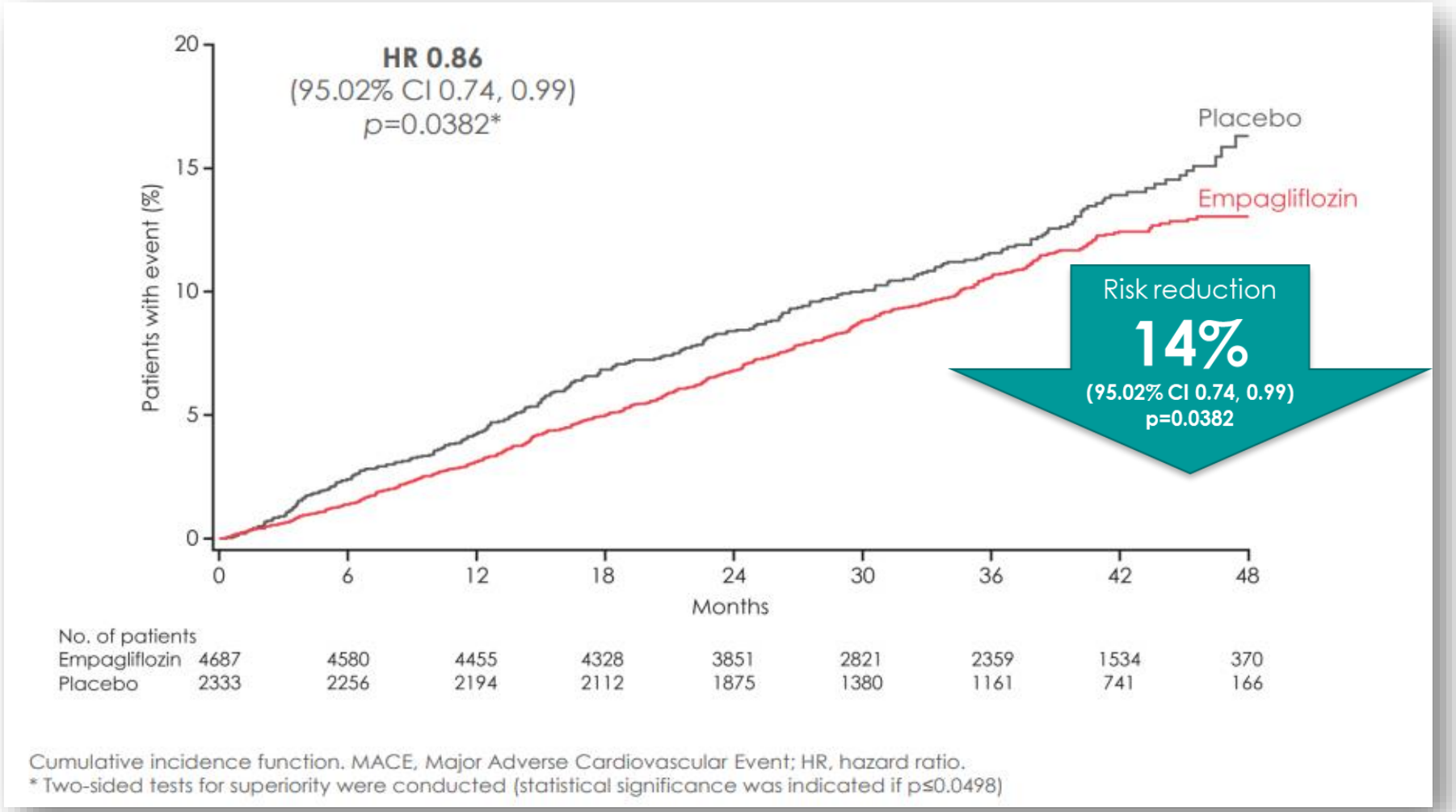
Matthews DR, Fulcher GR, Mahaffey GW, et al. The integrated results of the CANVAS program. Oral presentation at the 77th Annual Scientific Sessions of the American Diabetes Association; San Diego, California; June 12, 2017. Session 3-CT-SY26.

Adapted from Table 4, Inzucchi SE. et al (2015) *Diabetes & Vascular Disease Research*, 12(2), 90-100.

EMPA-REG

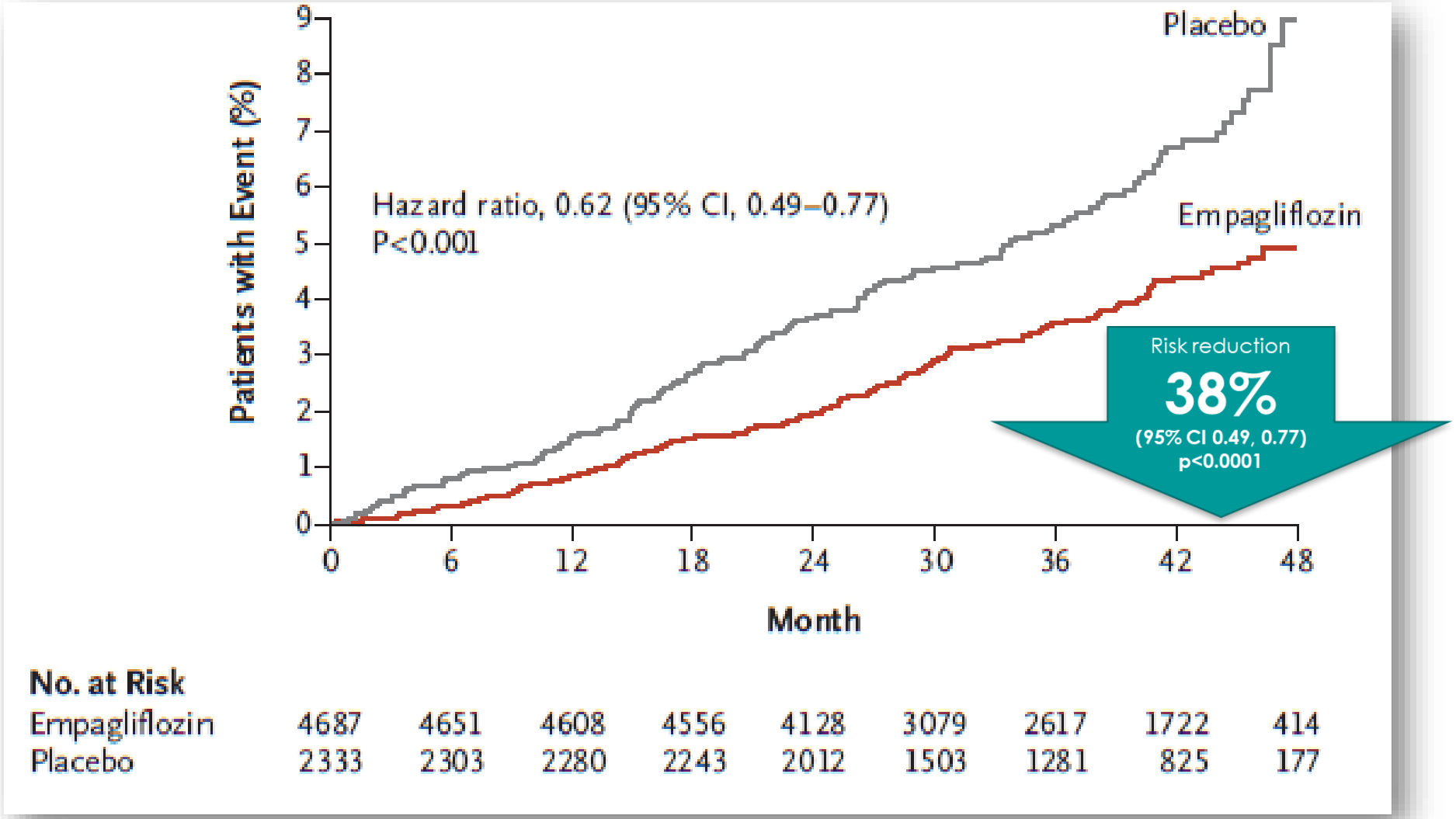
Outcome

Primary Outcome: 3-point MACE (CV death, Nonfatal MI, Nonfatal stroke)[1]



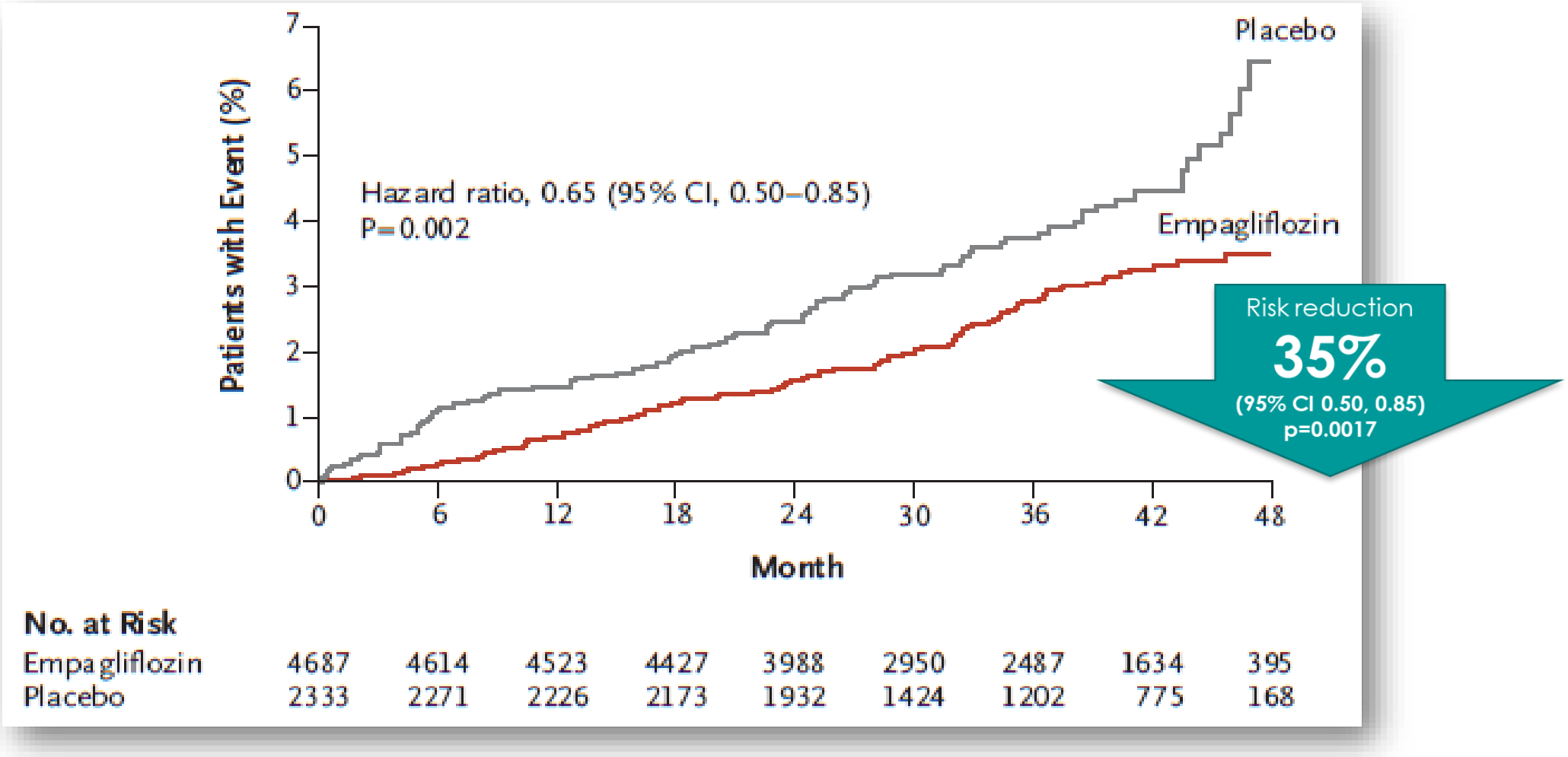
N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME®CV Death[1]



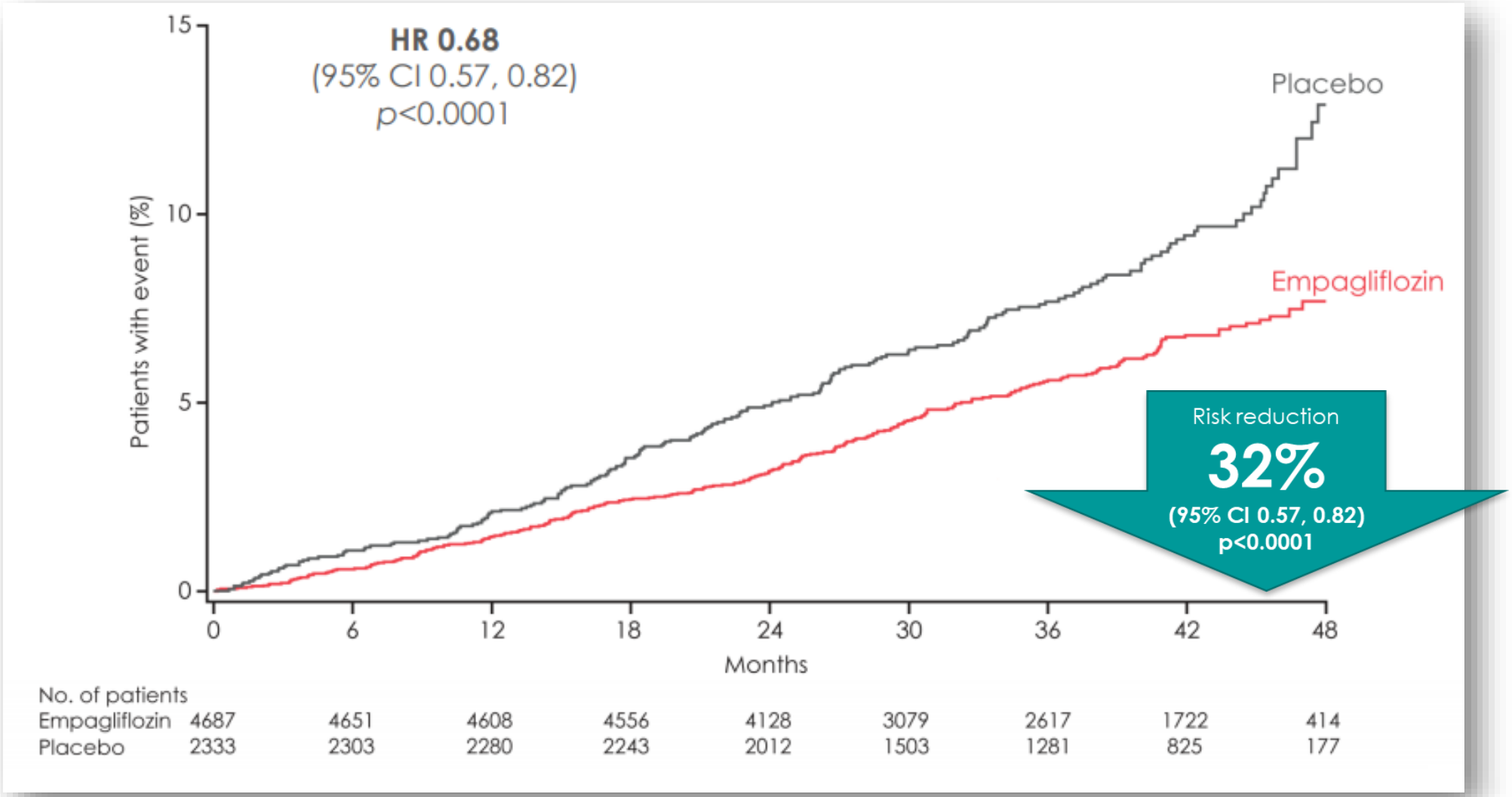
N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME® Hospitalization for Heart Failure[1]



N Engl J Med 2015; 373:2117-2128

EMPA-REG OUTCOME® All-cause Mortality[1]

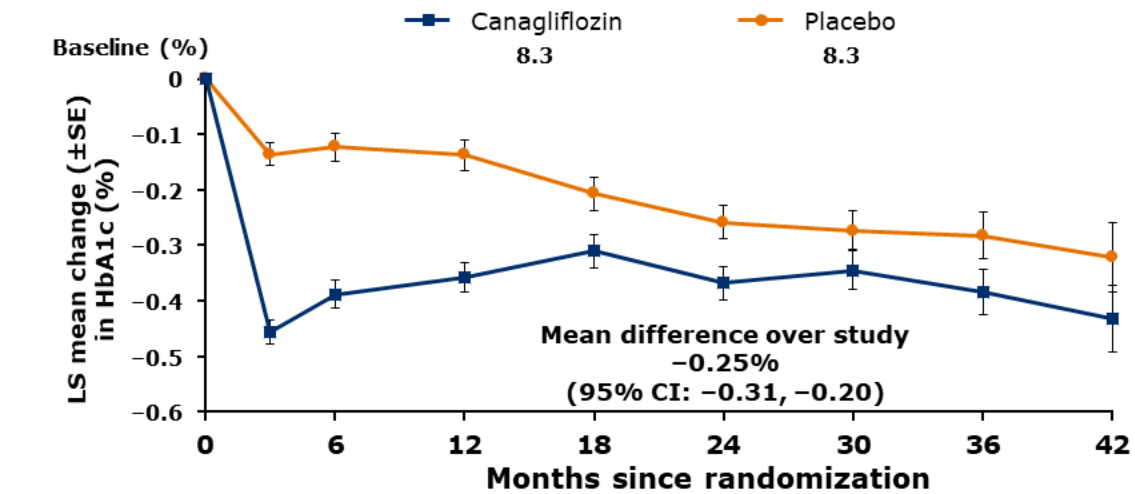


N Engl J Med 2015; 373:2117-2128

CREDENCE

Outcome

Effects on HbA1c



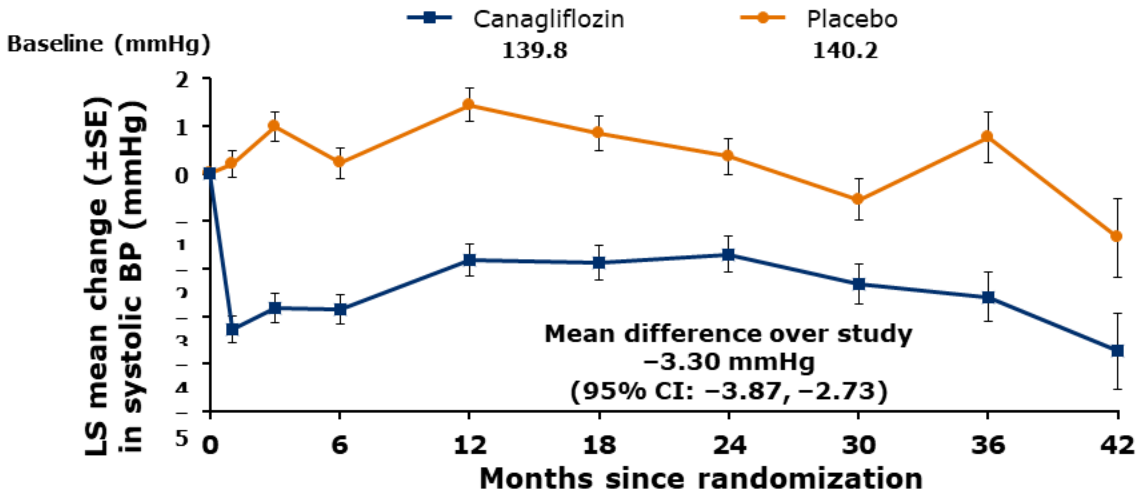
No. of participants

Placebo	2150	2103	2066	1981	1882	1728	1172	688	252
Canagliflozin	2154	2108	2074	2024	1909	1817	1254	729	274

ITT analysis

CREDENCE

Effects on Systolic BP



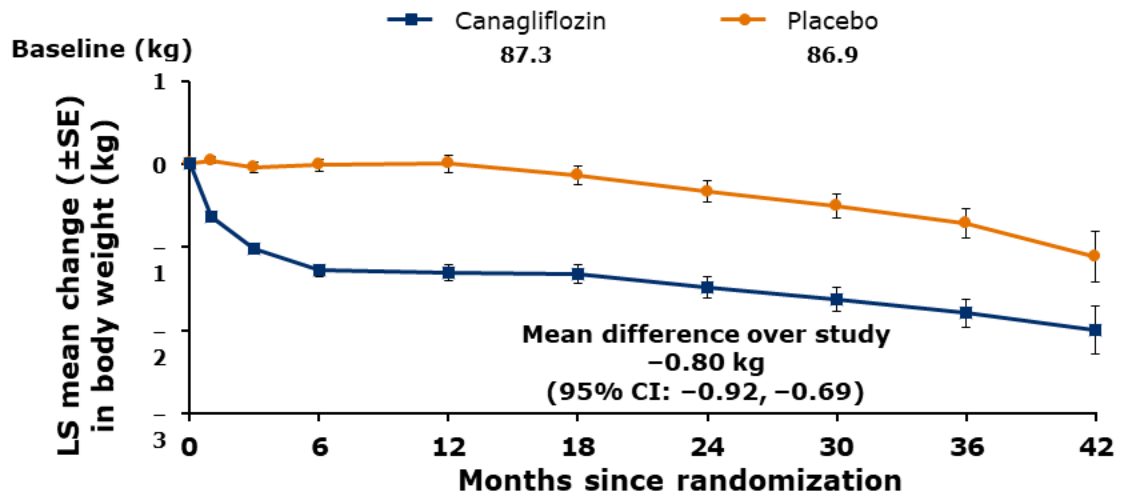
No. of participants

Placebo	2188	2131	2096	2027	1923	1766	1187	682	245
Canagliflozin	2190	2141	2096	2047	1962	1842	1261	731	264

ITT analysis

CREDENCE

Effects on Body Weight



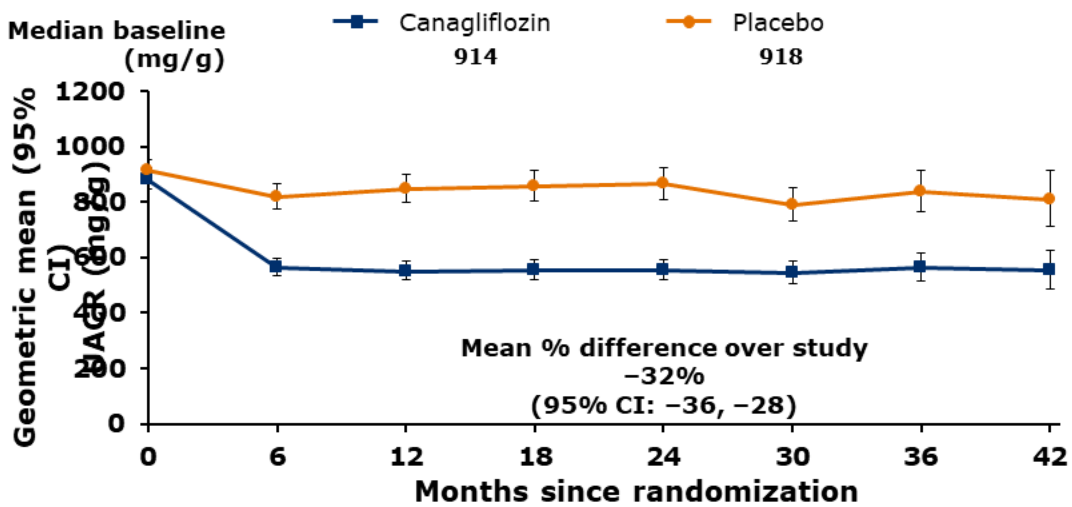
No. of participants

Placebo	2187	2126	2092	2005	1917	1750	1179	679	244
Canagliflozin	2188	2134	2091	2023	1957	1830	1256	731	263

ITT analysis

CREDENCE

Effects on Albuminuria (UACR)

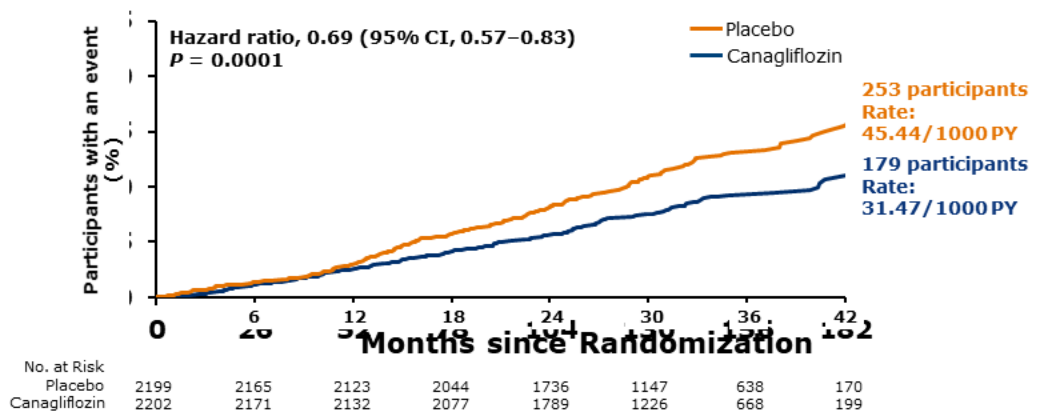


No. of participants								
Placebo	2113	2061	1986	1865	1714	1158	685	251
Canagliflozin	2114	2070	2019	1917	1819	1245	730	271

ITT analysis

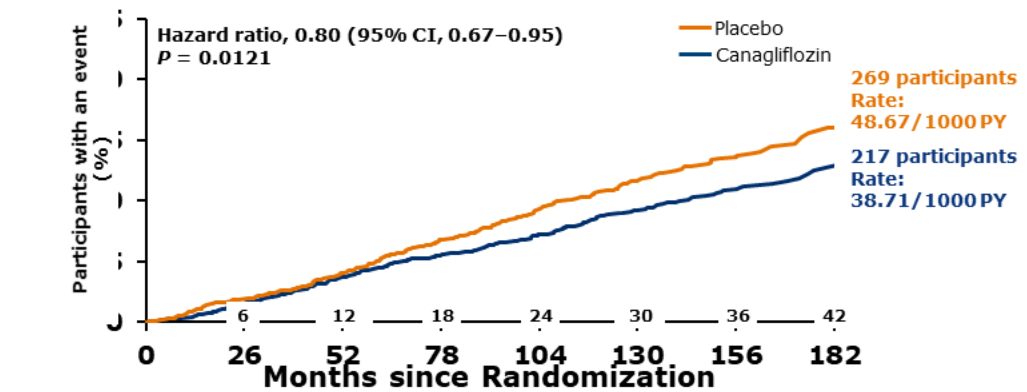
CREDENCE

CV Death or Hospitalized Heart Failure



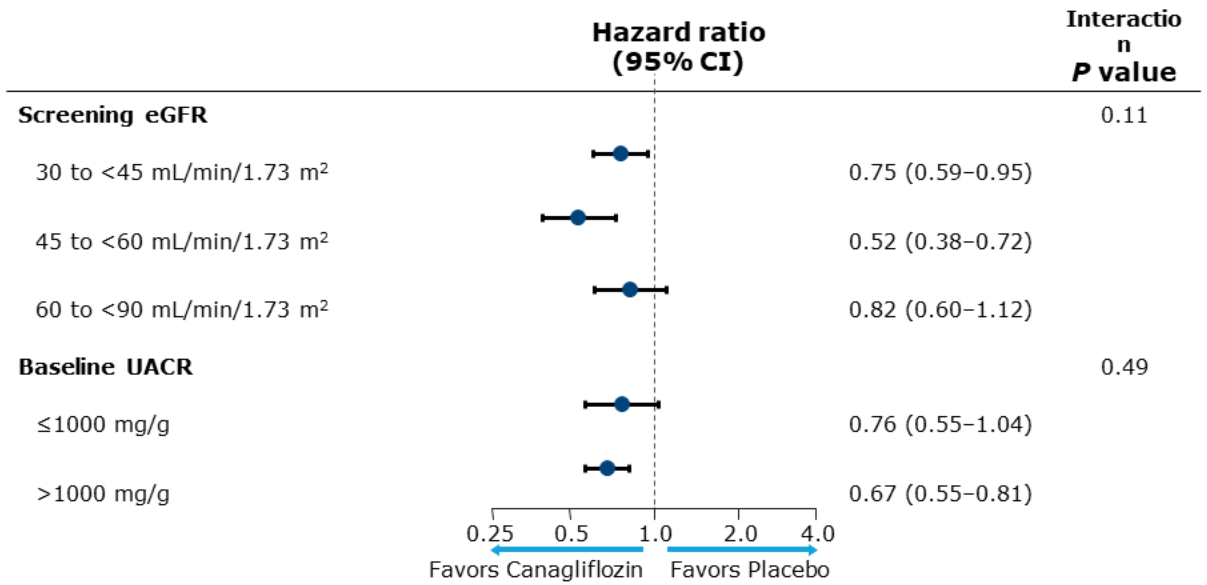
CREDENCE

Cardiovascular Death, Nonfatal Myocardial Infarction, or Nonfatal Stroke



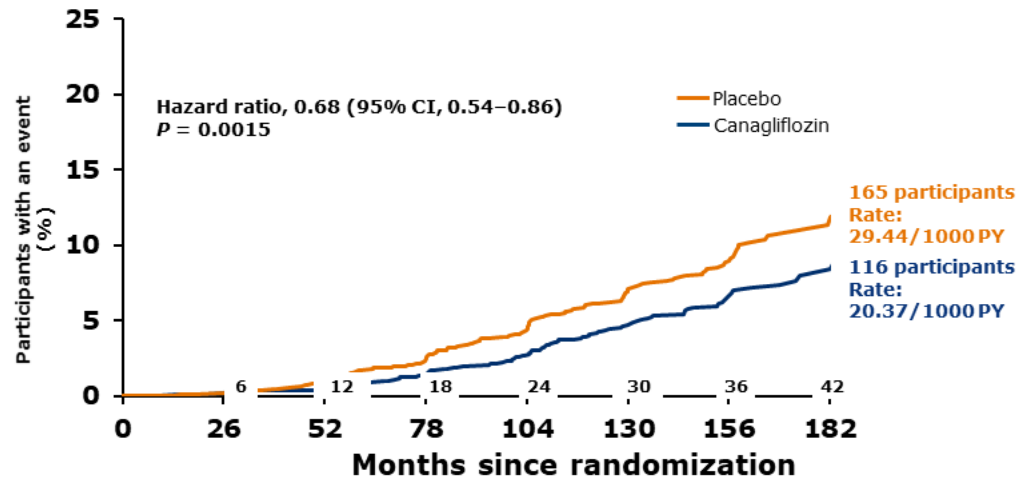
CREDENCE

Primary Outcome by Screening eGFR and Albuminuria



CREDENCE

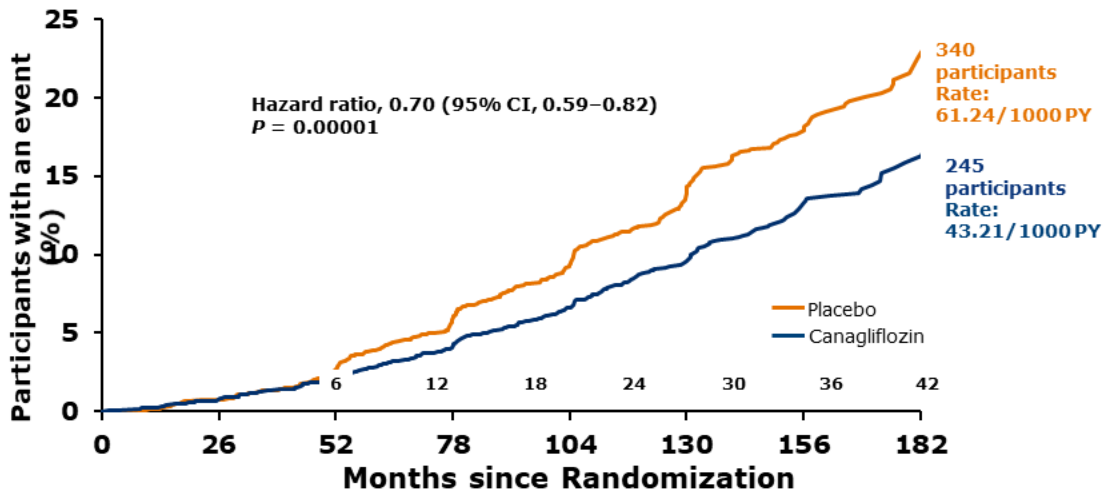
End-stage Kidney Disease (ESKD)



No. at Risk								
Placebo	2199	2182	2141	2063	1752	1152	641	178
Canagliflozin	2202	2182	2146	2091	1798	1217	654	199

CREDENCE

ESKD, Doubling of Serum Creatinine, or Renal or Cardiovascular Death (Primary Composite Outcome)



CREDENCE

EMPA-REG OUTCOME®: summary

Empagliflozin in addition to standard of care reduced CV risk and improved overall survival in adults with T2D at high CV risk[1]

14%

↓ 3P-MACE

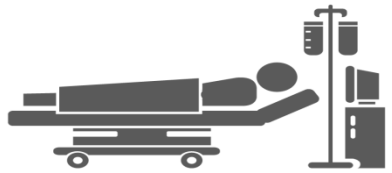
38%

↓ CV death

32%

↓ All-cause mortality

35%



↓ Heart failure hospitalisations

The overall safety profile of empagliflozin was consistent with previous clinical trials and current label information[1]

3P-MACE, 3-point major adverse cardiovascular events
Empagliflozin is not indicated for CV risk reduction. CV, cardiovascular; T2D, type 2 diabetes
1-Zinman B et al,. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. New England Journal of Medicine. 2015; 26;373(22):2117-28.

Since 2015

Implementation and Reimboursement in T2DM When GFR >60ml/min

SGLT2 I ‘prevention’ of heart failure in T2DM: also ‘treatment’ of heart failure in non T2DM?

DAPA-HF

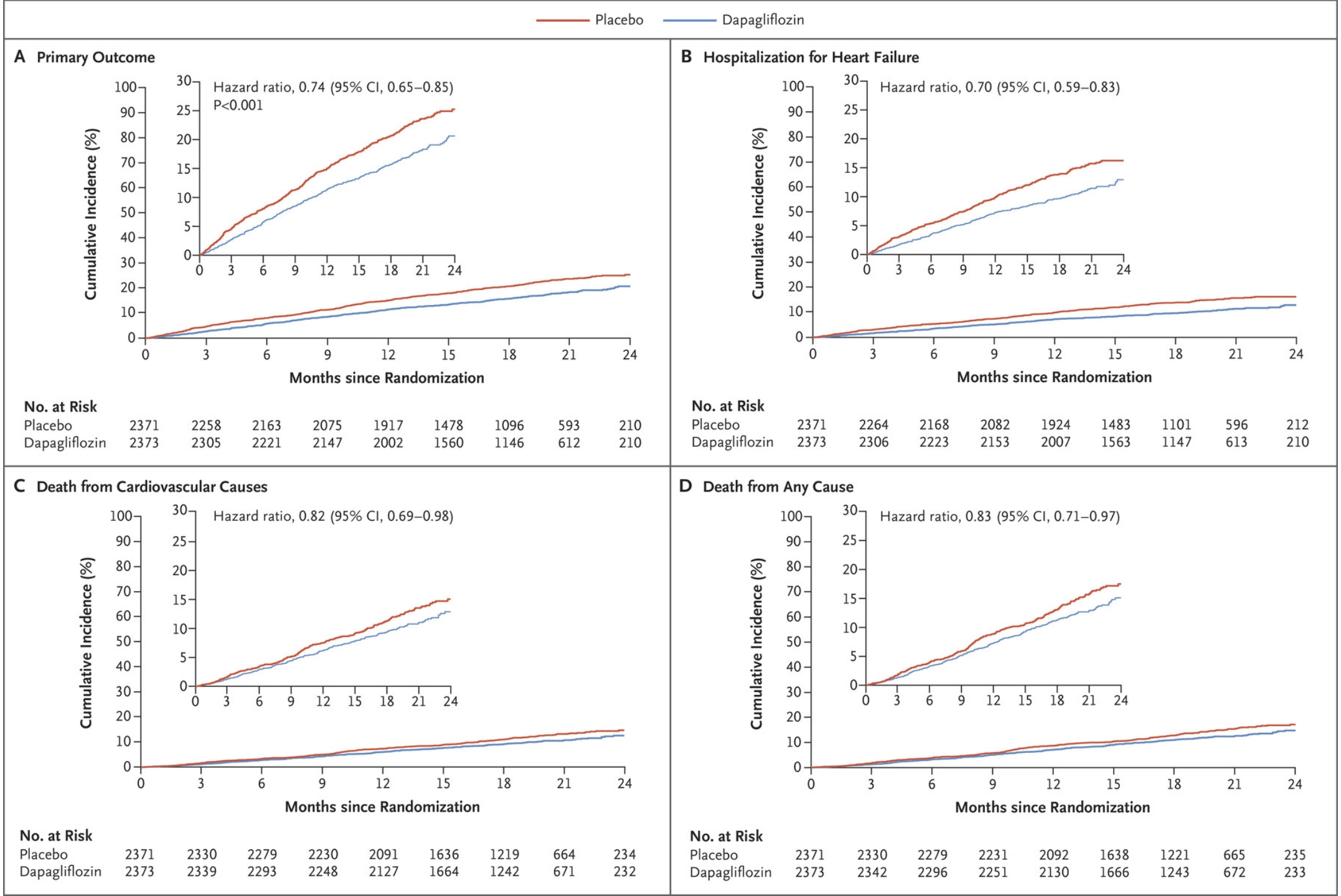
Assesment of HF as primary outcome

Inclusion of 4744 patients
Patients with and without DM

NYHA Classes II-IV HF
EF <40%
On Standard Care

DAPA-HF

Outcome


Placebo
Dapagliflozin
A Primary Outcome
Hazard ratio, 0.74 (95% CI, 0.65–0.85)
P<0.001
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210
Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210
B Hospitalization for Heart Failure
Hazard ratio, 0.70 (95% CI, 0.59–0.83)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2264 2168 2082 1924 1483 1101 596 212
Dapagliflozin 2373 2306 2223 2153 2007 1563 1147 613 210
C Death from Cardiovascular Causes
Hazard ratio, 0.82 (95% CI, 0.69–0.98)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2230 2091 1636 1219 664 234
Dapagliflozin 2373 2339 2293 2248 2127 1664 1242 671 232
D Death from Any Cause
Hazard ratio, 0.83 (95% CI, 0.71–0.97)
Cumulative Incidence (%)
Months since Randomization
No. at Risk
Placebo 2371 2330 2279 2231 2092 1638 1221 665 235
Dapagliflozin 2373 2342 2296 2251 2130 1666 1243 672 233

Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

New England Journal of medecine

November 21, 2019

HFrEF patients on SGLT2 I, in addition to excellent background therapy, was associated with a significant 26% reduction in the primary outcome of cardiovascular death or worsening heart failure and a marked improvement in quality of life parameters.

Clinical Observations: (*a*) prevention and treatment of heart failure; (*b*) rapid benefit, which appears to emerge within weeks of treatment initiation; (*c*) efficacy that is independent of glycemia; (*d*) reduction in hospitalization for heart failure on top of excellent(*e*) close association with renal protection; and (*f*) modest benefits on atherosclerotic outcomes.

background therapy beta-blockers, blockers of the renin-angiotensin-aldosterone system (RAAS)

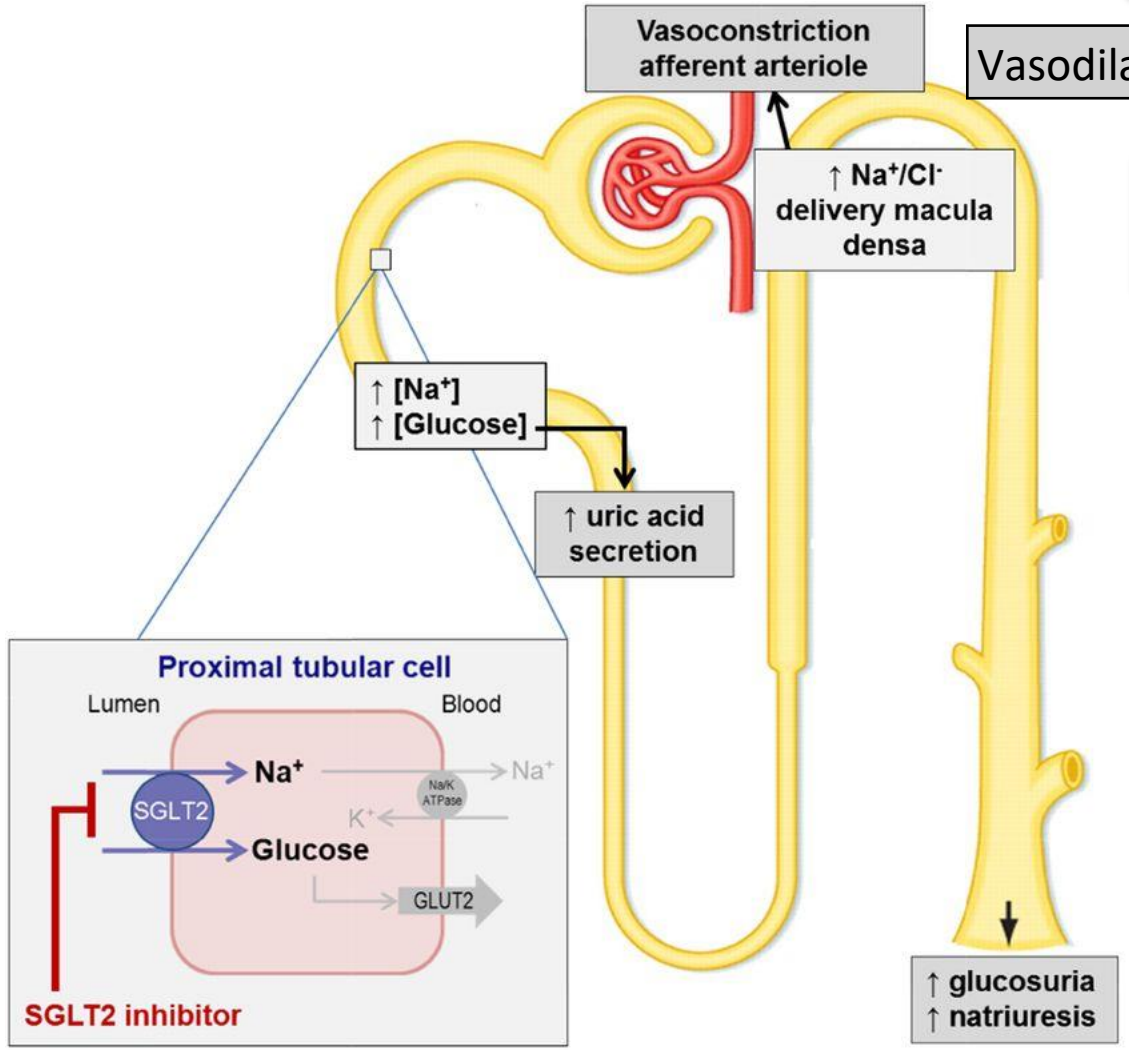
Preservation of glomerular and tubular function
By less Intraglomerular pressure and less tubular work
Less albuminuria
More O2 in cortex

Can Improve Vascular Function

Promote Cardiac Reverse Remodeling

Modulate Cardiac Inflammation and Fibrosis

attenuation of SNS activity (?)



Vasodilation efferent arteriole

More distal tubular O2 demand
and induction of ischemia: increase in EPO production

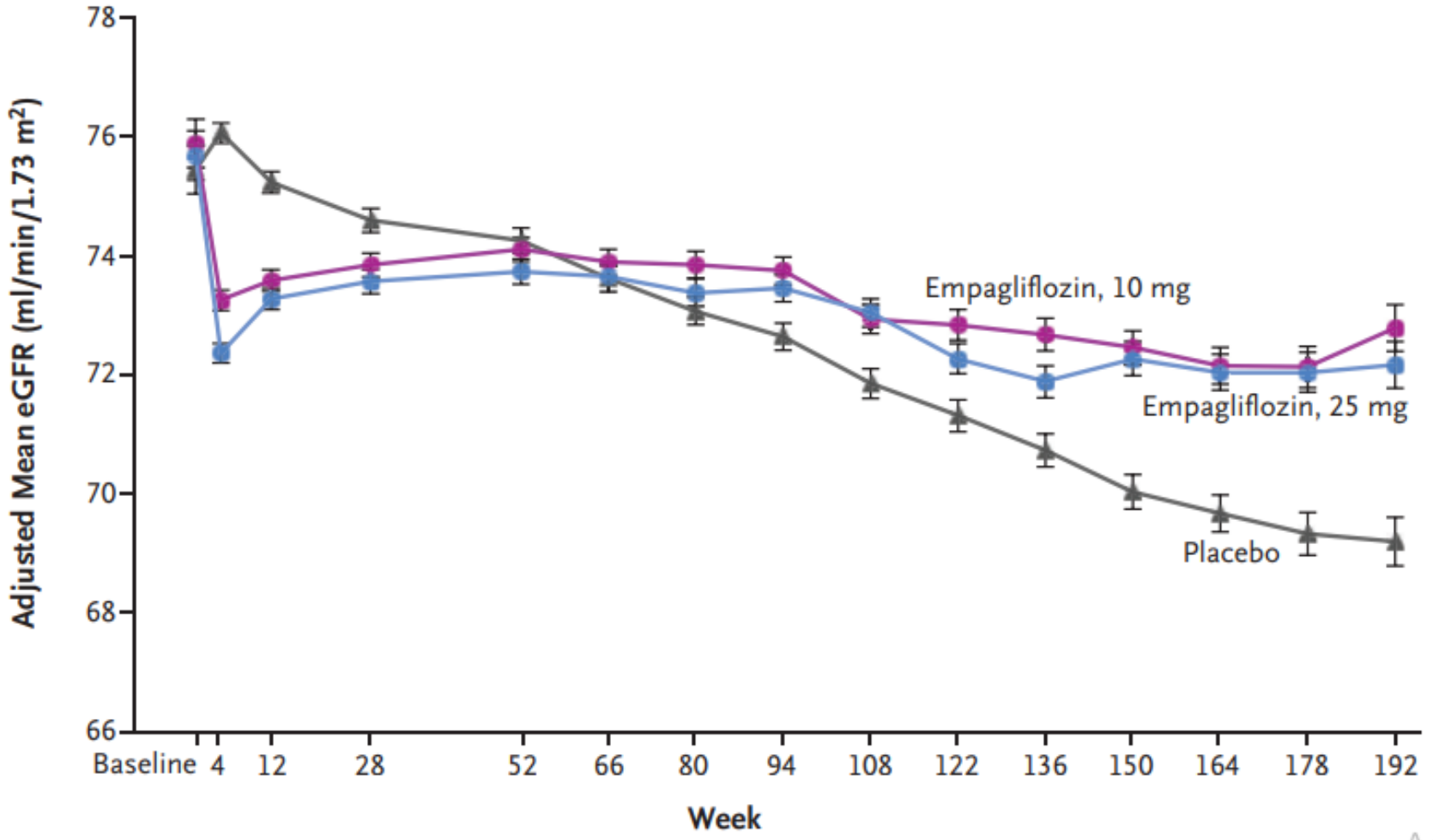
Clinical findings
↓ Plasma glucose
↓ Body weight
↓ Blood pressure
↓ Plasma uric acid
↓ Glomerular hyperfiltration

Increased kaliuresis

Glucosuria mimics fasting with ketone bodies: extra fuel

Osmotic diureses en Natriurese:
Increase sodium excretion by 15–20%
Reduction of fluidoverload > interstitial

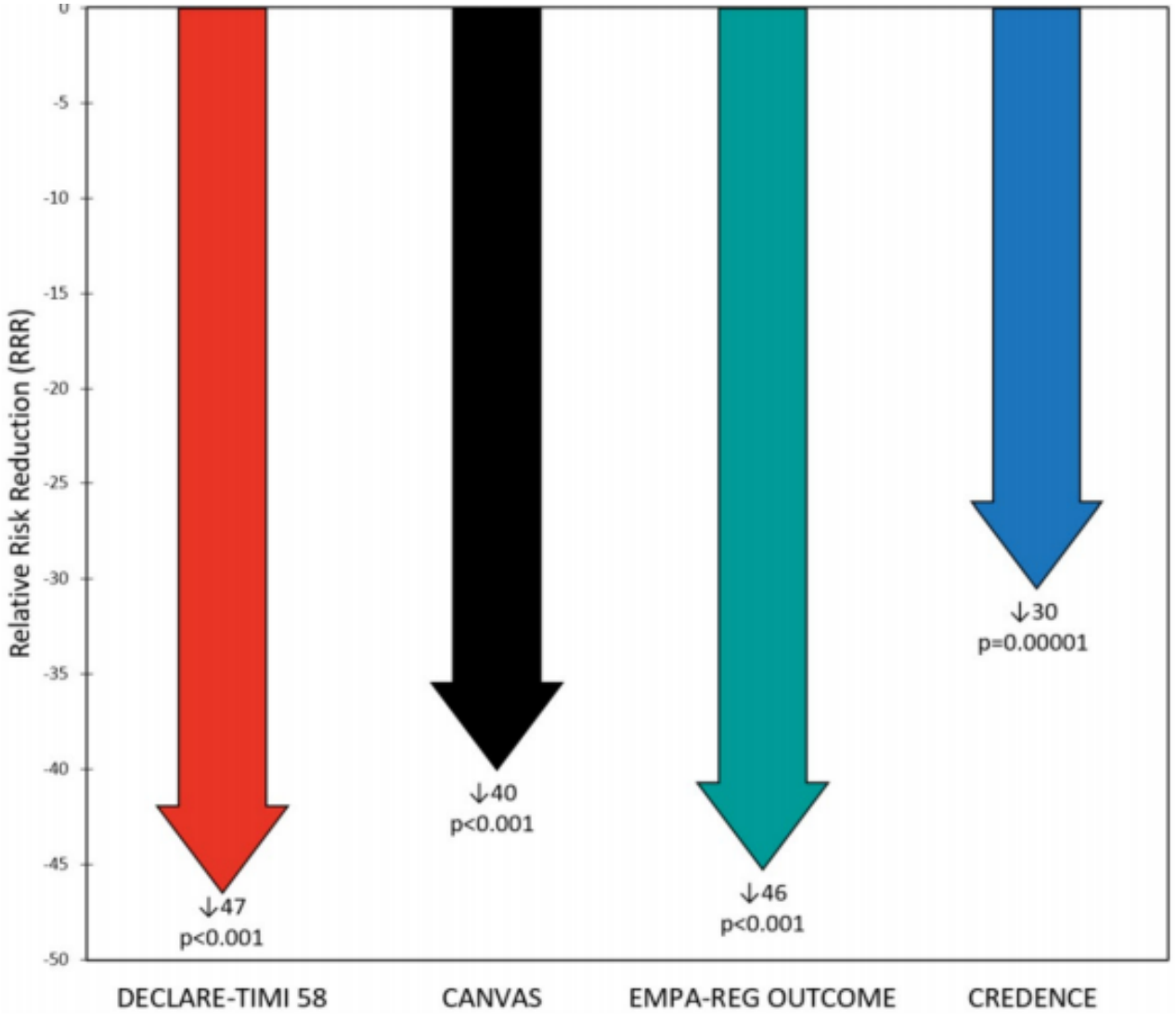
SGLT2 Inhibitors Induce a Temporary Reduction in eGFR, but Preserve Renal Function Overtime[1] (ook bij GFR <60ml/min)



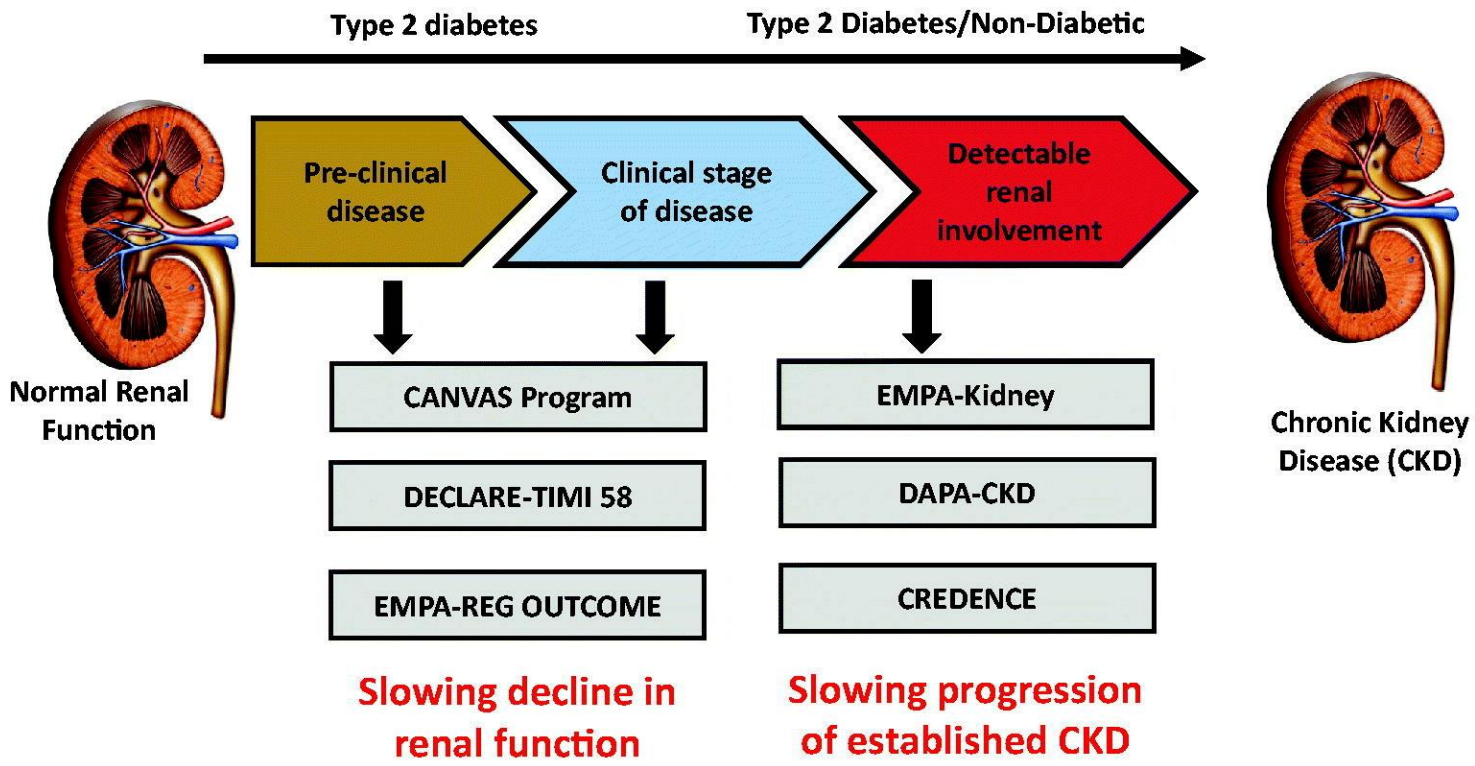
Change in eGFR over 192 Weeks

Wanner, Christoph, et al. "Empagliflozin and progression of kidney disease in type 2 diabetes." *New England Journal of Medicine* 375.4 (2016): 323-334.

Composite Renal Outcomes of SGLT2i



Kluger, Aaron Y., et al. "Class effects of SGLT2 inhibitors on cardiorenal outcomes." *Cardiovascular diabetology* 18.1 (2019): 99.


Type 2 diabetes
Type 2 Diabetes/Non-Diabetic
Pre-clinical disease
Clinical stage of disease
Detectable renal involvement
Normal Renal Function
Chronic Kidney Disease (CKD)
CANVAS Program
DECLARE-TIMI 58
EMPA-REG OUTCOME
EMPA-Kidney
DAPA-CKD
CREDENCE
Slowing decline in renal function
Slowing progression of established CKD

DAPA-CKD
EMPA-CKD
Outcome

Dapagliflozin in Patients with Chronic Kidney Disease

New England Journal
Nov 2020

Empagliflozine in Patients with Chronic Kidney Disease

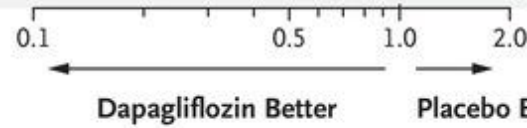
Results announced 4 November 2022
Completed final follow-up 5 July 2022
Randomisation completed 16 April 2021 with 6609 participants randomised
1st participant randomised 15 May 2019

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Dapagliflozin (N=2152)	Placebo (N=2152)
Age — yr	61.8±12.1	61.9±12.1
Female sex — no. (%)	709 (32.9)	716 (33.3)
Race — no. (%)†		
White	1124 (52.2)	1166 (54.2)
Black	104 (4.8)	87 (4.0)
Asian	749 (34.8)	718 (33.4)
Other	175 (8.1)	181 (8.4)
Weight — kg	81.5±20.1	82.0±20.9
Body-mass index‡	29.4±6.0	29.6±6.3
Current smoker — no. (%)	283 (13.2)	301 (14.0)
Blood pressure — mm Hg		
Systolic	136.7±17.5	137.4±17.3
Diastolic	77.5±10.7	77.5±10.3
Estimated GFR		
Mean — ml/min/1.73 m^2	43.2±12.3	43.0±12.4
Distribution — no. (%)		
≥60 ml/min/1.73 m^2	234 (10.9)	220 (10.2)
45 to <60 ml/min/1.73 m^2	646 (30.0)	682 (31.7)
30 to <45 ml/min/1.73 m^2	979 (45.5)	919 (42.7)
<30 ml/min/1.73 m^2	293 (13.6)	331 (15.4)
Hemoglobin — g/liter	128.6±18.1	127.9±18.0
Serum potassium — mEq/liter	4.6±0.5	4.6±0.6
Urinary albumin-to-creatinine ratio§		
Median (interquartile range)	965 (472–1903)	934 (482–1868)
>1000 — no. (%)	1048 (48.7)	1031 (47.9)
Type 2 diabetes — no. (%)	1455 (67.6)	1451 (67.4)
Cardiovascular disease — no. (%)¶	813 (37.8)	797 (37.0)
Heart failure — no. (%)	235 (10.9)	233 (10.8)
Previous medication — no. (%)		
ACE inhibitor	673 (31.3)	681 (31.6)
ARB	1444 (67.1)	1426 (66.3)
Diuretic	928 (43.1)	954 (44.3)
Statin	1395 (64.8)	1399 (65.0)

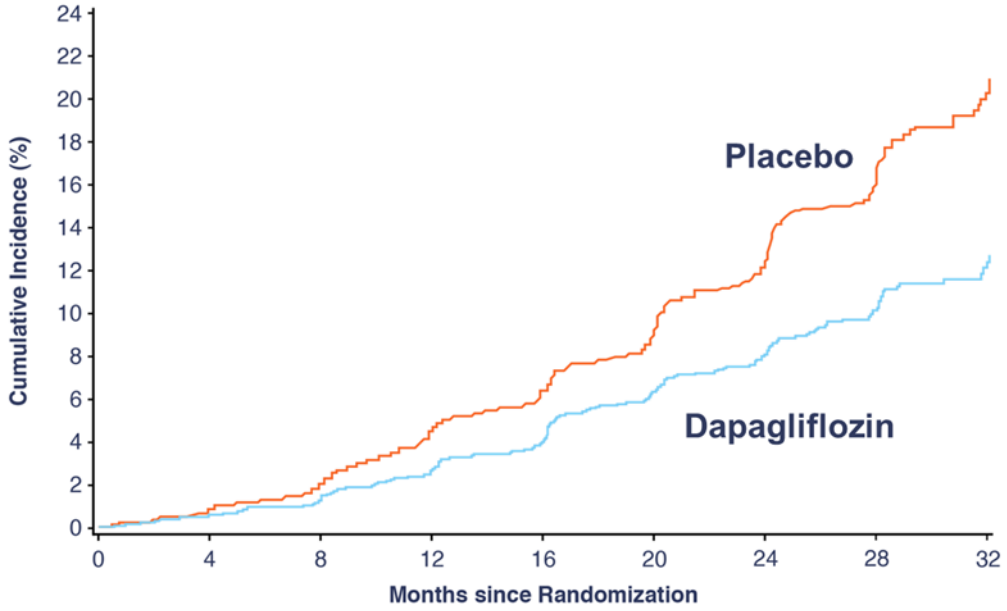
* Plus–minus values are mean ±SD. Percentages may not total 100 because of rounding. ACE denotes angiotensin-con

Subgroup	Dapagliflozin	Placebo	Hazard Ratio (95% CI)
	no. of participants/total no.		
All participants	197/2152	312/2152	0.61 (0.51–0.72)
Age			
≤65 yr	122/1247	191/1239	0.64 (0.51–0.80)
>65 yr	75/905	121/913	0.58 (0.43–0.77)
Sex			
Male	126/1443	209/1436	0.57 (0.46–0.72)
Female	71/709	103/716	0.65 (0.48–0.88)
Race			
White	110/1124	174/1166	0.62 (0.49–0.79)
Black	7/104	14/87	0.33 (0.13–0.81)
Asian	53/749	77/718	0.66 (0.46–0.93)
Other	27/175	47/181	0.54 (0.33–0.86)
Geographic region			
Asia	50/692	69/654	0.70 (0.48–1.00)
Europe	57/610	89/623	0.60 (0.43–0.85)
North America	35/401	69/412	0.51 (0.34–0.76)
Latin America	55/449	85/463	0.61 (0.43–0.86)
Type 2 diabetes			
Yes	152/1455	229/1451	0.64 (0.52–0.79)
No	45/697	83/701	0.50 (0.35–0.72)
Estimated GFR			
<45 ml/min/1.73 m^2	152/1272	217/1250	0.63 (0.51–0.78)
≥45 ml/min/1.73 m^2	45/880	95/902	0.49 (0.34–0.69)
Urinary albumin-to-creatinine ratio			
≤1000	44/1104	84/1121	0.54 (0.37–0.77)
>1000	153/1048	228/1031	0.62 (0.50–0.76)
Systolic blood pressure			
≤130 mm Hg	46/793	96/749	0.44 (0.31–0.63)
>130 mm Hg	151/1359	216/1403	0.68 (0.56–0.84)



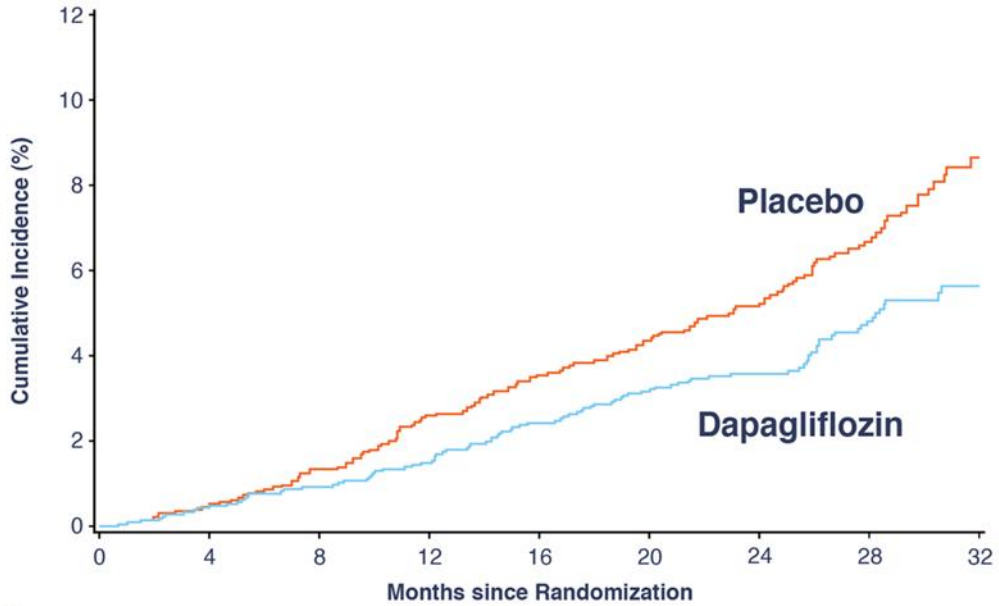
Results

Primary outcome:
Sustained ≥50% eGFR decline, end-stage kidney disease, renal or cardiovascular death



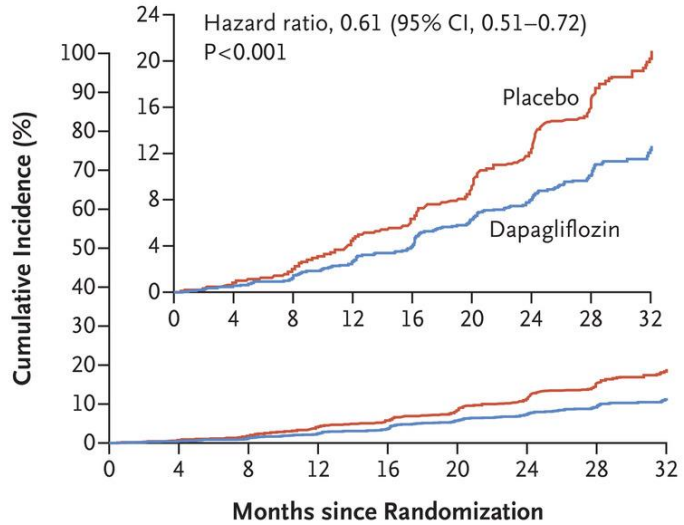
No. at Risk									
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo	2152	1993	1936	1858	1791	1664	1232	774	270

Secondary outcome:
All-cause mortality



No. at Risk									
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398
Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379

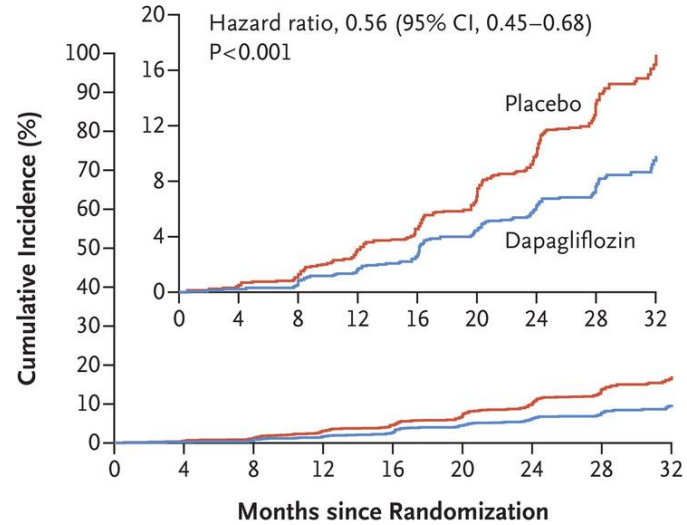
A Primary Composite Outcome



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

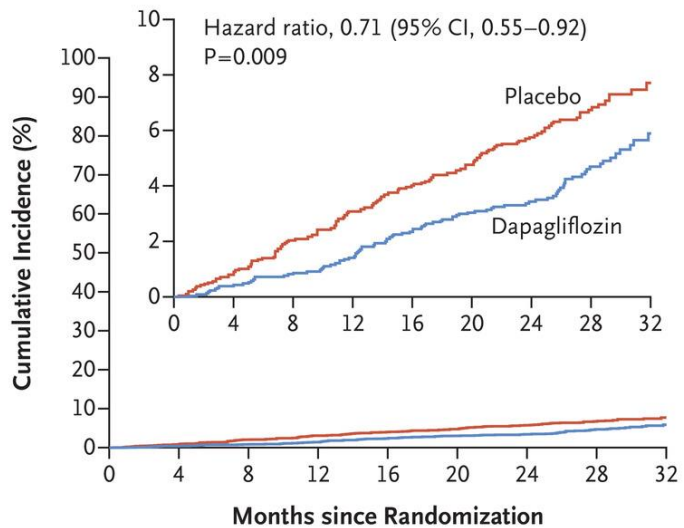
B Renal-Specific Composite Outcome



No. at Risk

Placebo	2152	1993	1936	1858	1791	1664	1232	774	270
Dapagliflozin	2152	2001	1955	1898	1841	1701	1288	831	309

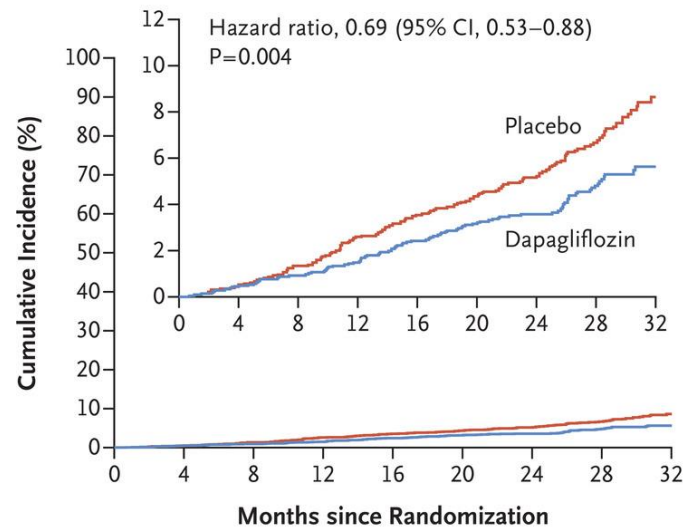
C Composite of Death from Cardiovascular Causes or Hospitalization for Heart Failure



No. at Risk

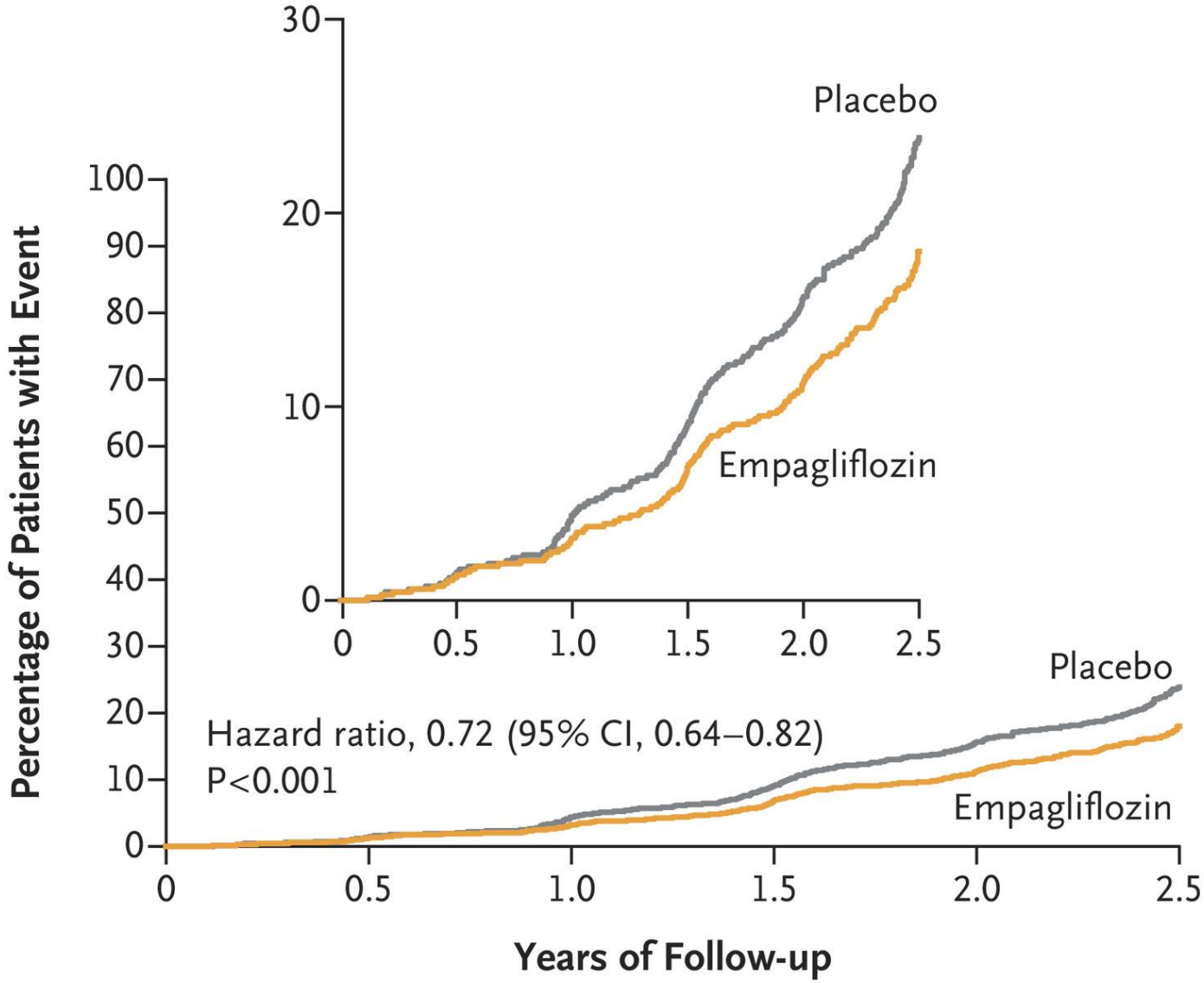
Placebo	2152	2023	1989	1957	1927	1853	1451	976	360
Dapagliflozin	2152	2035	2021	2003	1975	1895	1502	1003	384

D Death from Any Cause



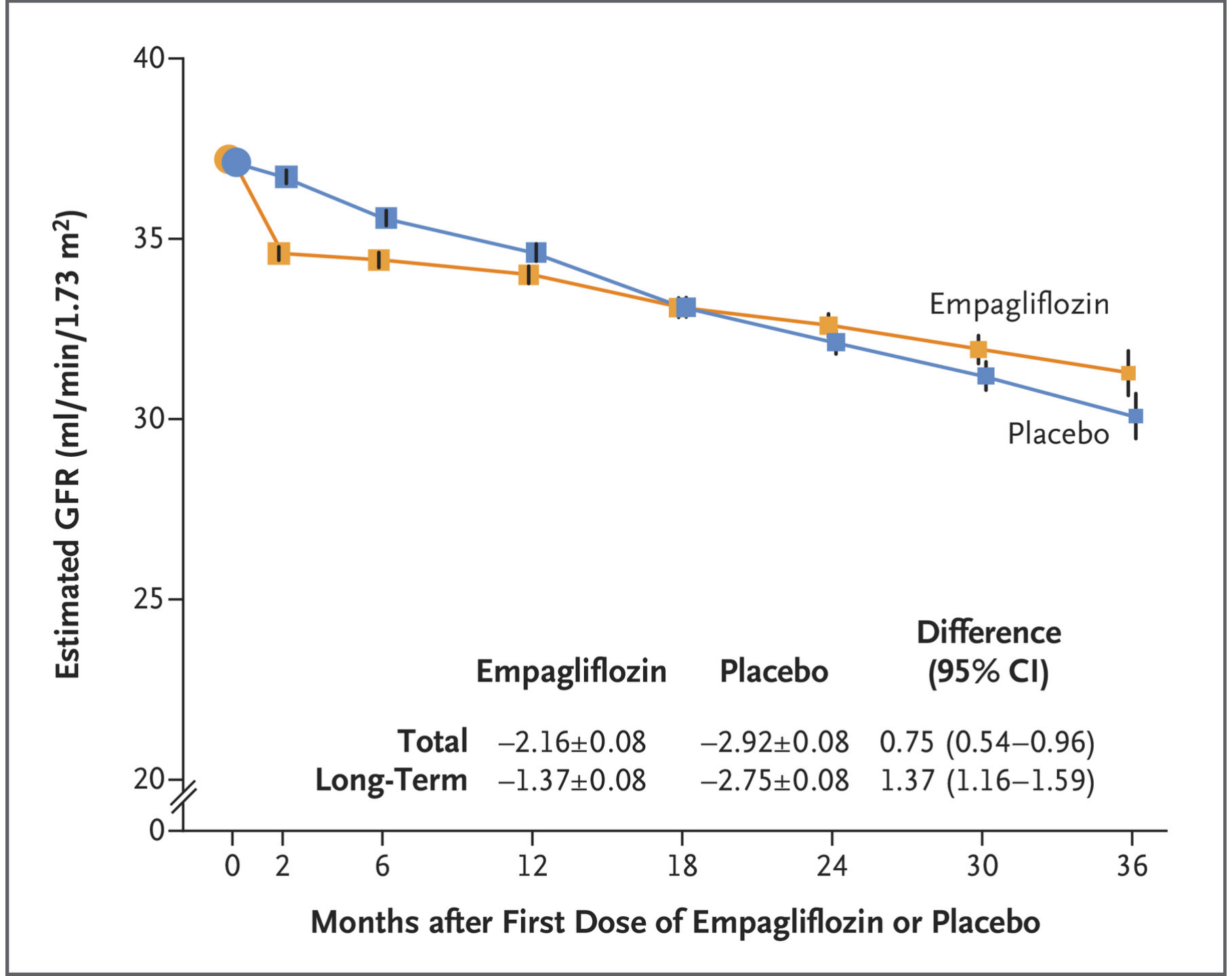
No. at Risk

Placebo	2152	2035	2018	1993	1972	1902	1502	1009	379
Dapagliflozin	2152	2039	2029	2017	1998	1925	1531	1028	398

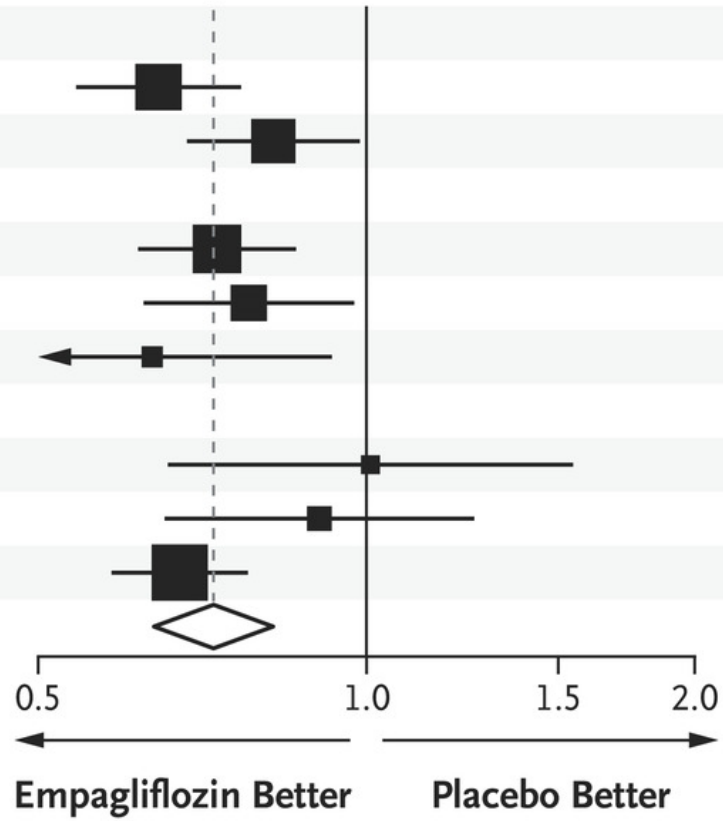


No. at Risk

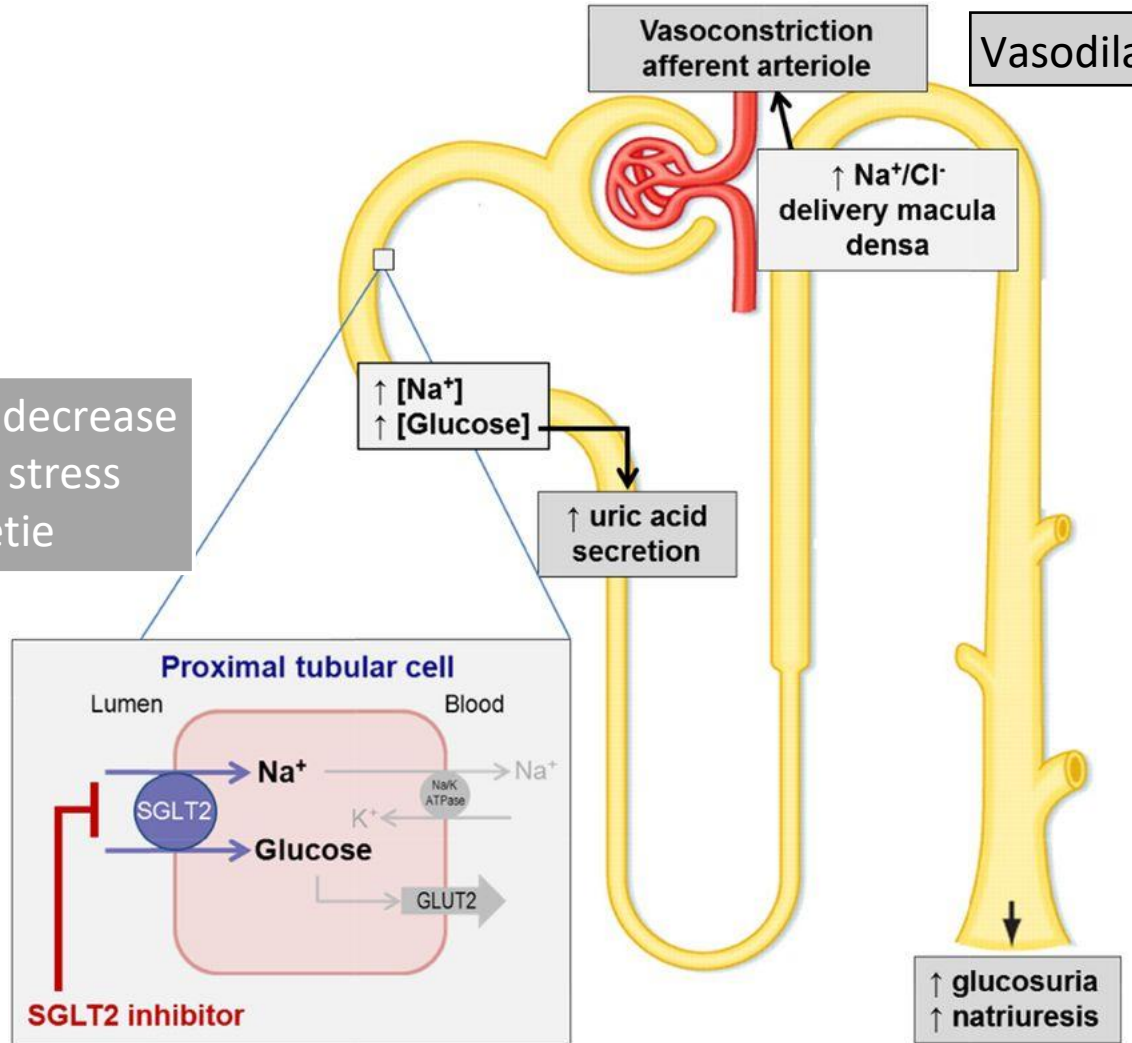
Placebo	3305	3250	3129	2243	1496	592
Empagliflozin	3304	3252	3163	2275	1538	624


Estimated GFR (ml/min/1.73 m²)
40
35
30
25
20
0
Empagliflozin
Placebo
Empagliflozin
Placebo
Difference (95% CI)
Total
–2.16±0.08
–2.92±0.08
0.75 (0.54–0.96)
Long-Term
–1.37±0.08
–2.75±0.08
1.37 (1.16–1.59)
0
2
6
12
18
24
30
36
Months after First Dose of Empagliflozin or Placebo

Subgroup	Empagliflozin	Placebo	Hazard Ratio for Progression of Kidney Disease or Death from Cardiovascular Causes (95% CI)
	no. of patients with event/total no.		
Diabetes mellitus			
Present	218/1525	306/1515	0.64 (0.54–0.77)
Absent	214/1779	252/1790	0.82 (0.68–0.99)
Estimated GFR			
<30 ml/min/1.73 m^2	247/1131	317/1151	0.73 (0.62–0.86)
≥30 to <45 ml/min/1.73 m^2	140/1467	175/1461	0.78 (0.62–0.97)
≥45 ml/min/1.73 m^2	45/706	66/693	0.64 (0.44–0.93)
Urinary albumin-to-creatinine ratio			
<30	42/665	42/663	1.01 (0.66–1.55)
≥30 to ≤300	67/927	78/937	0.91 (0.65–1.26)
>300	323/1712	438/1705	0.67 (0.58–0.78)
All patients	432/3304	558/3305	0.72 (0.64–0.82)



Preservation of glomerular and tubular function
By less Intraglomerular pressure and less tubular work
Less albuminuria
More O2 in cortex



Vasodilation efferent arteriole

More distal tubular O2 demand
and induction of ischemia: increase in EPO production

NHE3 activity decrease
Less Oxidative stress
Uric acid secretie

Clinical findings
↓ Plasma glucose
↓ Body weight
↓ Blood pressure
↓ Plasma uric acid
↓ Glomerular hyperfiltration

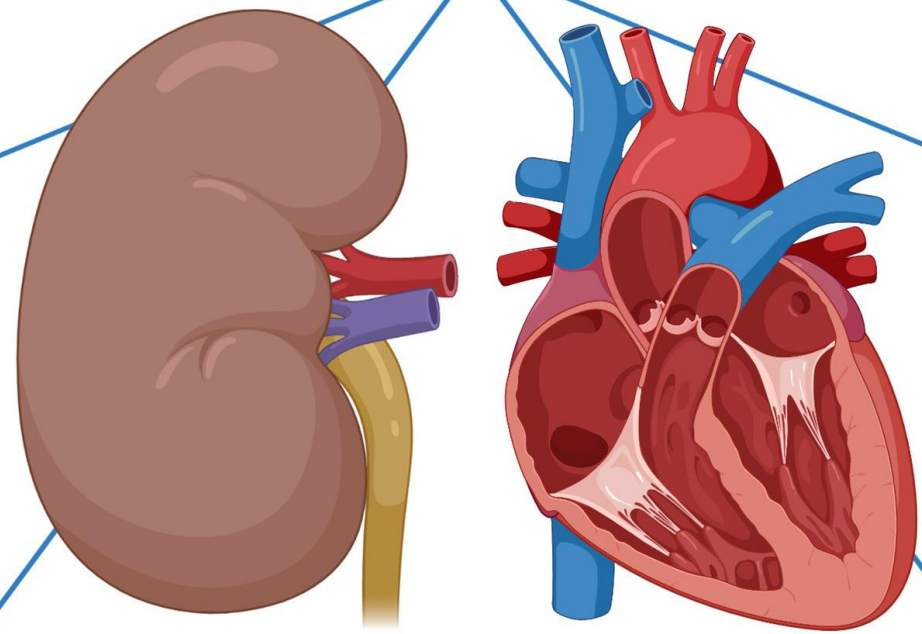
Increased kaliuresis

Reduction of fluidoverload > interstitial

Sodium glucose cotransporter 2 inhibitor mechanisms of kidney and CV protection

Hemodynamic and neurohumoral effects

- Natriuresis and blood pressure reduction
- Neutral RAAS and sympathetic activity
- Preload and afterload reduction
- Restoration of tubuloglomerular feedback
- Ventricular remodeling



Energy substrates

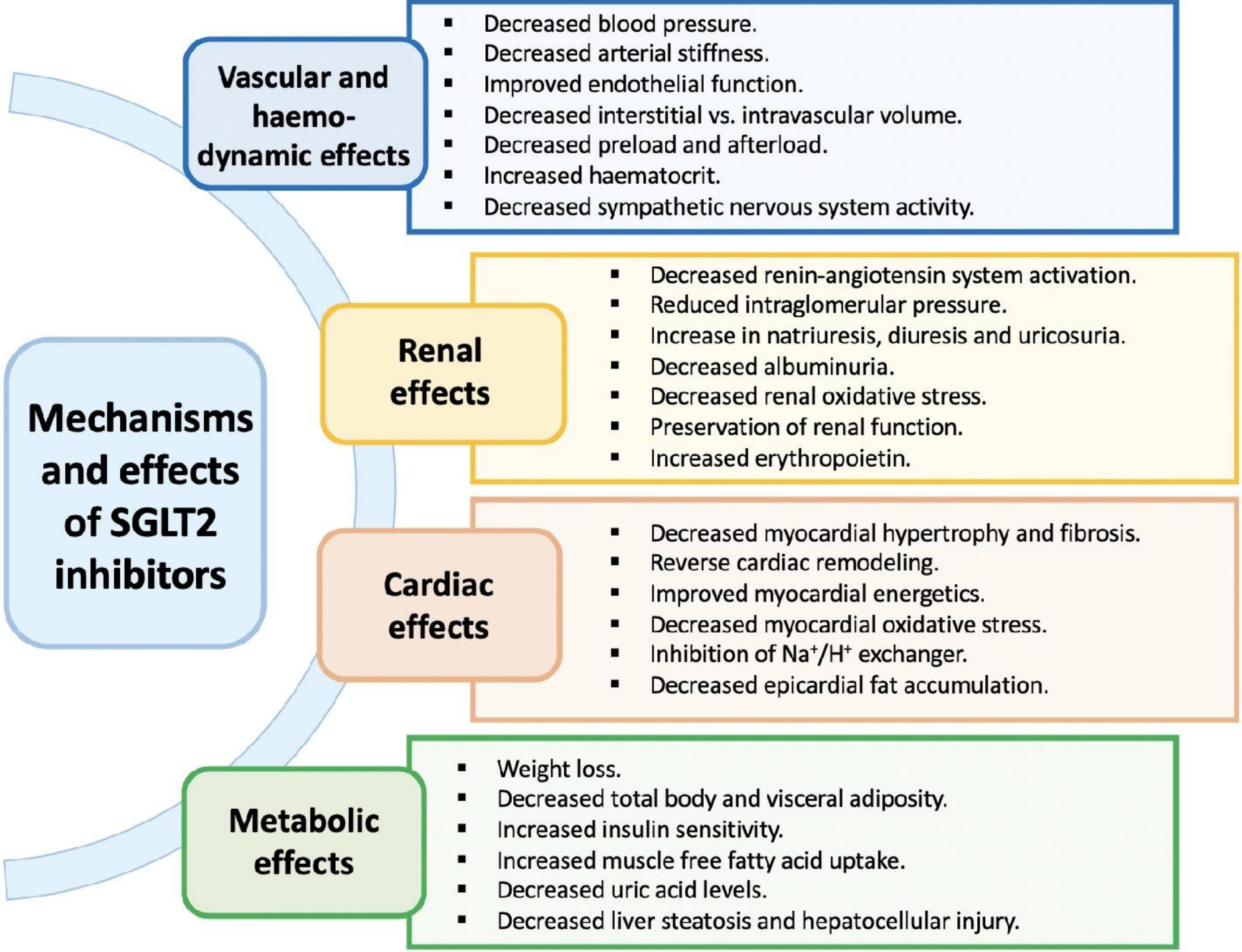
- Hyperglycemia reduction
- Reduced insulin and increased glucagon
- Increased lipolysis and ketogenesis
- Increased energy efficiency

Hematological parameters

- Increased hematocrit
- Increased EPO and reticulocyte levels
- Plasma volume contraction

Inflammation and oxidative stress

- Increased NO
- Decreased HIF1α, NOX, ROS, AGE, TGFβ, MCP-1, ICAM-1, TNFα, IL-6, NFκB


Mechanisms and effects of SGLT2 inhibitors
Vascular and haemo-dynamic effects
Decreased blood pressure.
Decreased arterial stiffness.
Improved endothelial function.
Decreased interstitial vs. intravascular volume.
Decreased preload and afterload.
Increased haematocrit.
Decreased sympathetic nervous system activity.
Renal effects
Decreased renin-angiotensin system activation.
Reduced intraglomerular pressure.
Increase in natriuresis, diuresis and uricosuria.
Decreased albuminuria.
Decreased renal oxidative stress.
Preservation of renal function.
Increased erythropoietin.
Cardiac effects
Decreased myocardial hypertrophy and fibrosis.
Reverse cardiac remodeling.
Improved myocardial energetics.
Decreased myocardial oxidative stress.
Inhibition of Na^+/H^+ exchanger.
Decreased epicardial fat accumulation.
Metabolic effects
Weight loss.
Decreased total body and visceral adiposity.
Increased insulin sensitivity.
Increased muscle free fatty acid uptake.
Decreased uric acid levels.
Decreased liver steatosis and hepatocellular injury.

ZNA Nefrologie
Koen Bouman, Mark Helbert, Koen De Boeck, Jelle Bernards
Wendy Engelen, Eric Gheuens, Ilse Muyshondt, Conny Colson, Pieter-Jan Van Gaal, Ronny Daelemans

En de collega's van GZA: Z**AS Nefrologie**

Diabetes en obesitas/metabool syndroom

- Activatie RAAS systeem met topregulatie SGLT 2
- Hyperinsulinisme en hyperglycemie: opregulatie van SGLT 2
- Opregulatie SGLT 2: ook opregulatie Na/H uitwisseling en uraatreabsorprie proximale tumulus
- Down regulatie Na/h uitwisseling: acidose en hierdoor gluconeogenese