IL CONCETTO DI RISCHIO GLOBALE NEL PAZIENTE CON SINDROME METABOLICA/DMT2: RISCHIO INFETTIVO, RISCHIO CARDIOVASCOLARE, RISCHIO ONCOLOGICO

PROTEZIONE DAL DANNO RENALE NEL DIABETE TIPO 2: RUOLO DEI NUOVI FARMACI

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Ancona

Disclosure

Dr Massimo Boemi has been granted as speaker by:

Eli Lilly, Novo-Nordisk, Sanofi, Boehringer-Ingelheim, Jannsen, MSD, Astra Zeneca, Novartis, Sigma-Tau

Dr Massimo Boemi has been granted as partecipant in boards/consultant by:

Eli Lilly, Novo-Nordisk, Boehringer-Ingelheim, Jannsen, Astra Zeneca

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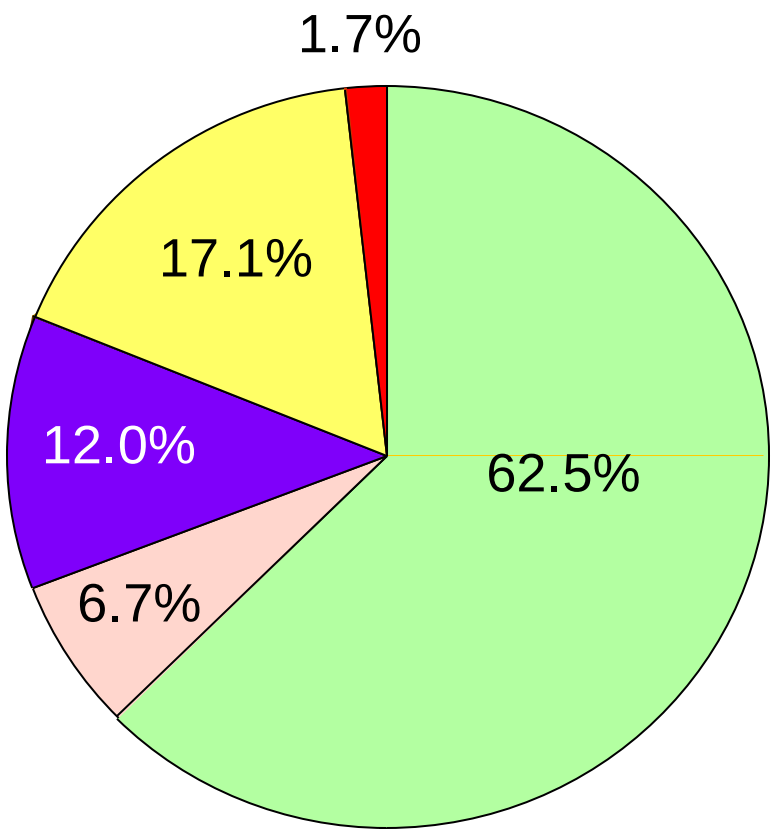
Renal dysfunction is common in patients with T2DM

The RIACE Study: 15,773 patients with T2DM



- No CKD
- CKD stage 1
- CKD stage 2
- CKD stage 3
- CKD stages 4/5

Approximately 40% of patients with T2DM show signs of CKD (stages 1-5)

Approximately 20% of patients with T2DM show signs of renal failure (eGFR <60 ml/min/1.73 m^2)

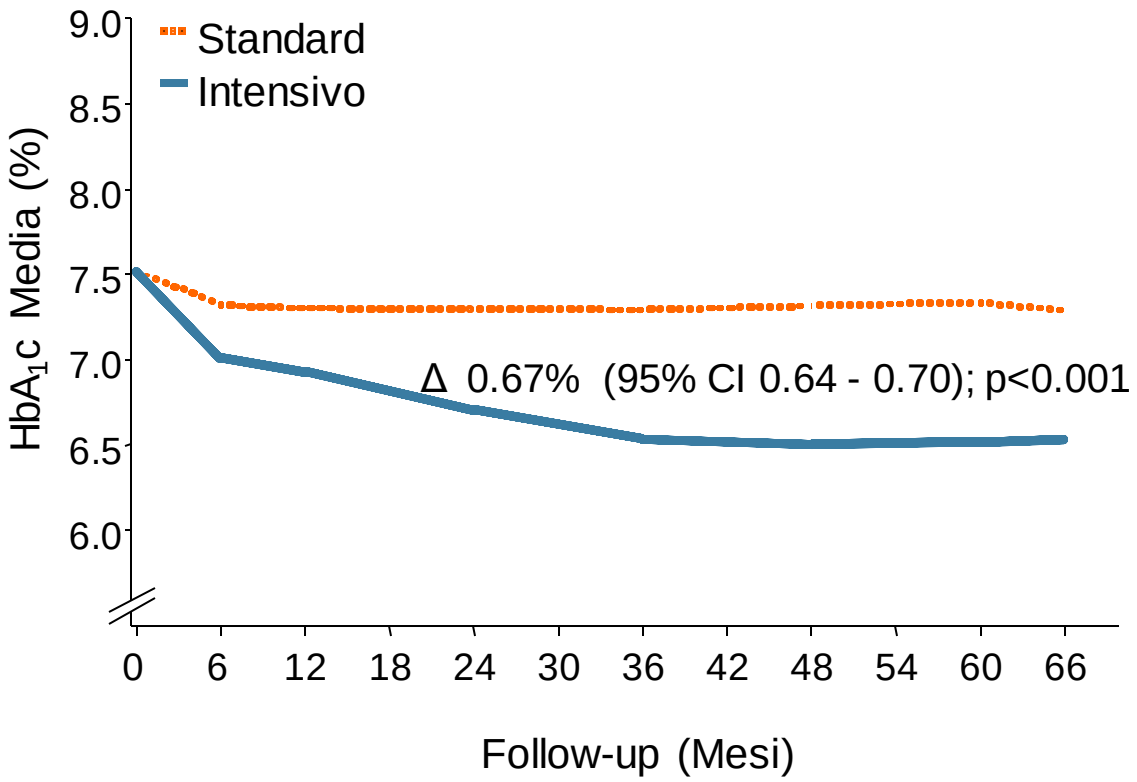
Penno G et al. J Hypertens 29: 1802-1809, 2011

Renal dysfunction is common in patients with T2DM

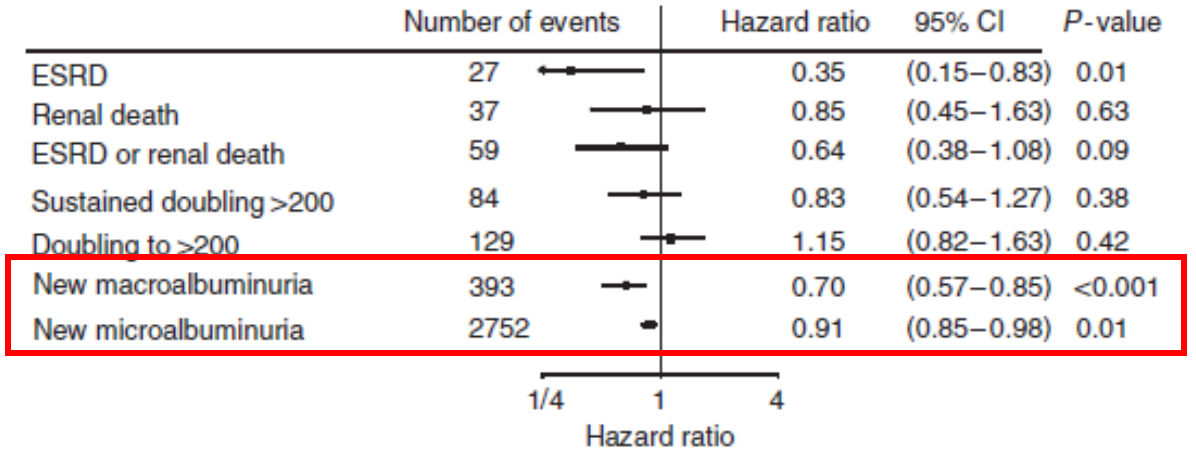
The RIACE Study: 15,773 patients with T2DM

		Albuminuria		
		Normal	Mild (micro)	Severe (macro)
eGFR ml/min/1.73 m² MDRD	>90	Stage 0 (no CKD) 62.5%	Stage 1-2 albuminuric phenotype 18.7%	
	60-89			
	45-59	Stage 3/5 NON albuminuric CKD phenotype 10.6%	Stages 3/5 albuminuric CKD phenotype 8.2%	
	30-44			
	15-30			

Penno G et al. J Hypertens 29: 1802-1809, 2011



Patel A et al., *N Engl J Med 2008*; 358(24): 2560-72



	Number of events	Hazard ratio	95% CI	*P*-value
ESRD	27	0.35	(0.15–0.83)	0.01
Renal death	37	0.85	(0.45–1.63)	0.63
ESRD or renal death	59	0.64	(0.38–1.08)	0.09
Sustained doubling >200	84	0.83	(0.54–1.27)	0.38
Doubling to >200	129	1.15	(0.82–1.63)	0.42
New macroalbuminuria	393	0.70	(0.57–0.85)	<0.001
New microalbuminuria	2752	0.91	(0.85–0.98)	0.01

Figure 2 | Summary plot showing the effects of intensive glucose lowering compared with standard glucose lowering on renal outcomes. CI, confidence interval; doubling to >200, adjudicated doubling of serum creatinine to a value over 200 μmol/l; sustained doubling >200, doubling of creatinine as above that remained at least doubled at the final available follow-up reading; ESRD, end-stage renal disease.

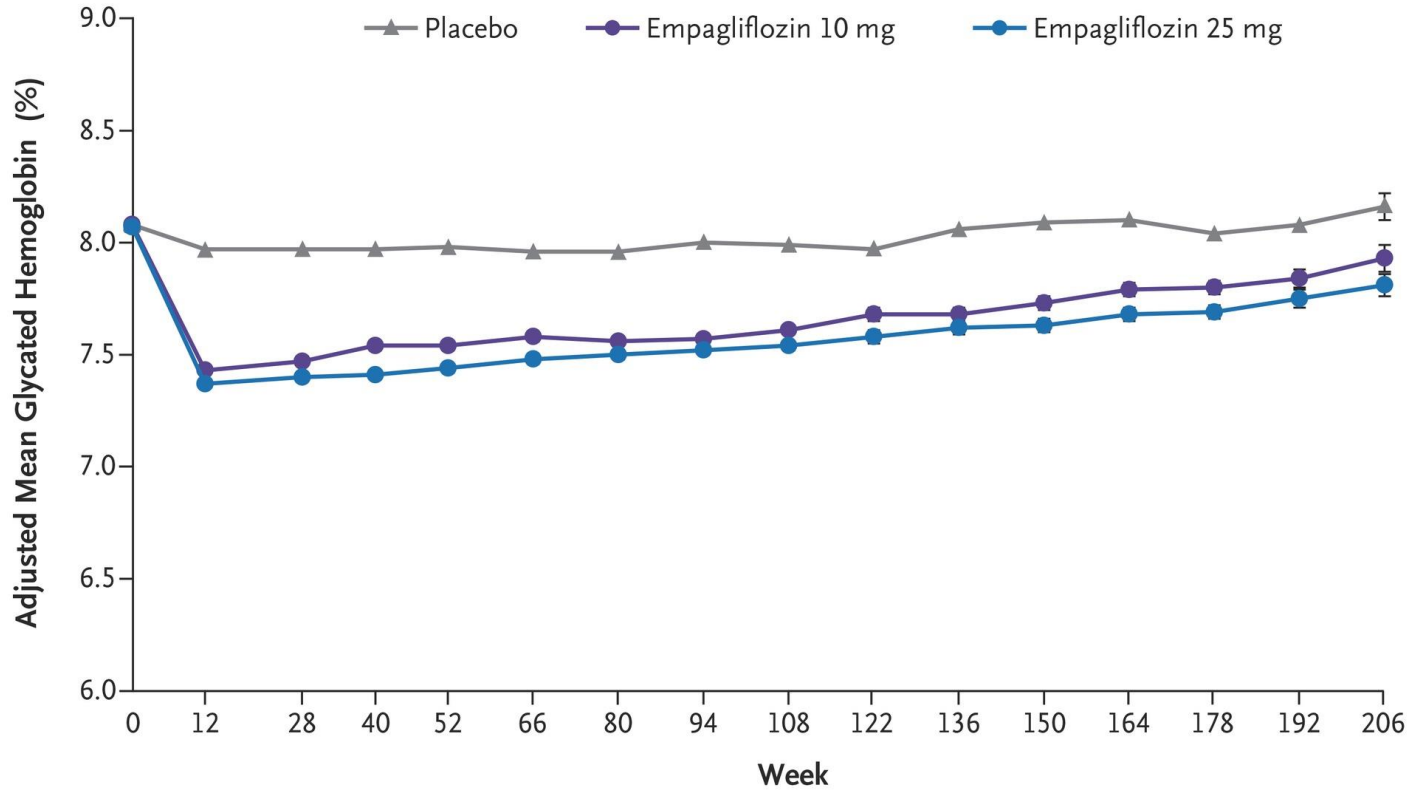
Kidney International (2013) **83,** 517–523;

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators



No. at Risk

Placebo	2294	2272	2188	2133	2113	2063	2008	1967	1741	1456	1241	1109	962	705	420	151
Empagliflozin 10 mg	2296	2272	2218	2150	2155	2108	2072	2058	1805	1520	1297	1164	1006	749	488	170
Empagliflozin 25 mg	2296	2280	2212	2152	2150	2115	2080	2044	1842	1540	1327	1190	1043	795	498	195

Methods: microvascular and renal outcomes

- Composite microvascular outcomes (secondary outcomes): initiation of retinal photocoagulation, vitreous hemorrhage, diabetes-related blindness, incident or worsening nephropathy*

  *incident or worsening nephropathy was defined as:

  – Progression to macroalbuminuria (UACR >300 mg/g) or
  – Doubling of serum creatinine accompanied by eGFR (MDRD) ≤45 mL/min/1.73m^2 or
  – Initiation of renal replacement therapy or
  – Death due to renal disease

- Prespecified Renal Endpoints in the statistical analysis plan

  - Incident or worsening nephropathy (individual components);
  - Incident or worsening nephropathy or CV death (composite)
  - doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease (composite)
  - incident albuminuria (UACR ≥30 mg/g) in patients with normoalbuminuria at baseline
  - eGFR (CKD-EPI) over time

UACR, urine albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Christoph Wanner et al. published online June 14, 2016, at NEJM.org

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

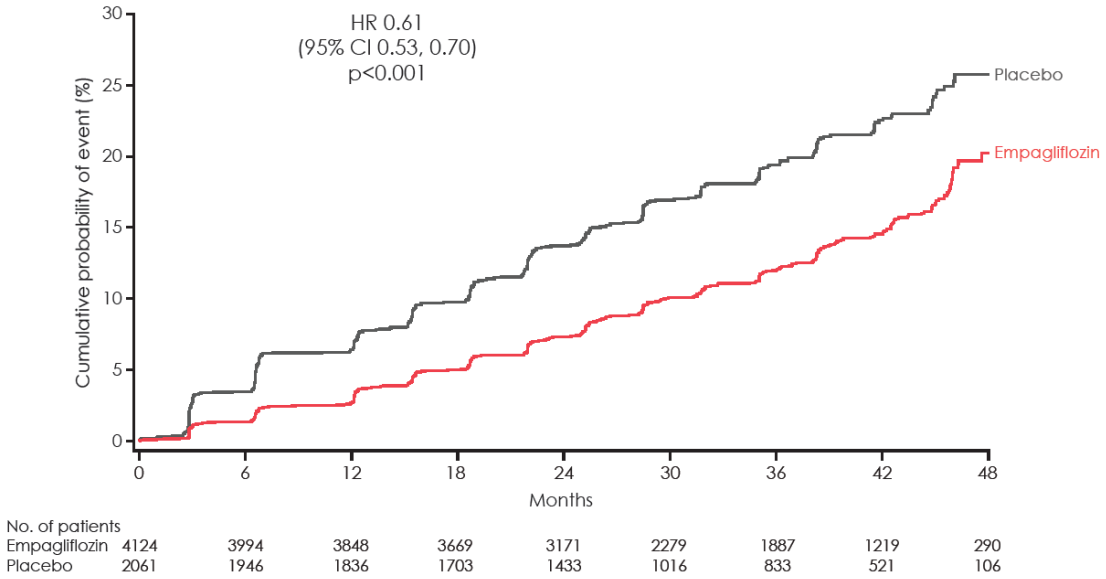
Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

N Engl J Med 2016;375:323-34.

Table 1. Characteristics of the Patients at Baseline, According to the Estimated Glomerular Filtration Rate (eGFR).*

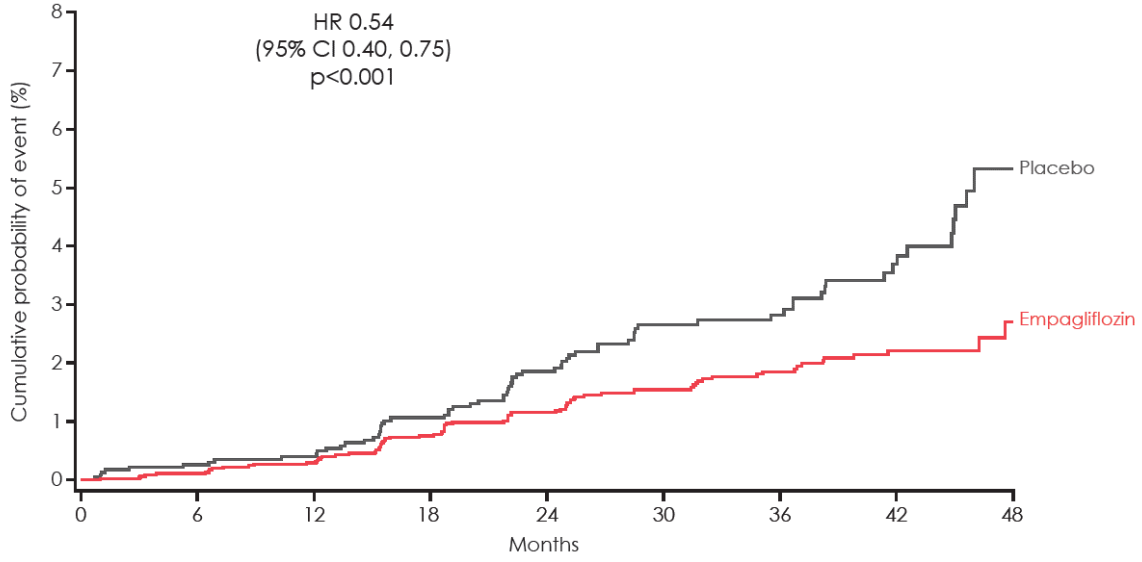
Characteristic	Patients with eGFR of 59 ml per Minute per 1.73 m^2 or Less		Patients with eGFR of 60 ml per Minute per 1.73 m^2 or More	
	Placebo (N=607)	Empagliflozin (N=1212)	Placebo (N=1726)	Empagliflozin (N=3473)
Age — yr	67.1±8.2	67.1±7.6	61.9±8.6	61.7±8.5
Male sex — no. (%)	418 (68.9)	816 (67.3)	1262 (73.1)	2518 (72.5)
Body-mass index†	30.9±5.4	31.0±5.5	30.6±5.2	30.5±5.2
Glycated hemoglobin — %‡	8.03±0.85	8.07±0.86	8.10±0.84	8.07±0.84
Interval of >10 yr since diagnosis of type 2 diabetes — no. (%)	422 (69.5)	794 (65.5)	917 (53.1)	1876 (54.0)
Blood pressure — mm Hg				
Systolic	136.4±18.7	136.1±18.0	135.6±16.7	135.0±16.6
Diastolic	74.6±10.3	74.5±9.9	77.6±10.0	77.4±9.5
Estimated glomerular filtration rate — ml/min/1.73 m^2	48.6±7.8	48.4±8.2	82.7±16.6	83.1±17.1
Urinary albumin-to-creatinine ratio — no. (%)§				
<30	283 (46.6)	566 (46.7)	1099 (63.7)	2223 (64.0)
30 to 300	205 (33.8)	411 (33.9)	470 (27.2)	926 (26.7)
>300	115 (18.9)	223 (18.4)	145 (8.4)	286 (8.2)
Cholesterol — mg/dl				
Low-density lipoprotein¶	85.0±36.1	84.4±35.8	84.8±35.1	86.5±36.0
High-density lipoprotein‖	42.9±10.7	44.2±12.5	44.4±11.5	44.7±11.7
Triglycerides — mg/dl‖	180.4±107.4	173.5±108.1	167.2±125.6	169.4±136.4
Coronary artery disease	482 (79.4)	938 (77.4)	1281 (74.2)	2606 (75.0)
History of stroke**	156 (25.7)	293 (24.2)	397 (23.0)	791 (22.8)
Peripheral artery disease††	130 (21.4)	314 (25.9)	349 (20.2)	667 (19.2)
Cardiac failure‡‡	89 (14.7)	174 (14.4)	155 (9.0)	288 (8.3)
Concomitant medication — no. (%)				
Angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker	502 (82.7)	1031 (85.1)	1366 (79.1)	2766 (79.6)
Beta-blocker	415 (68.4)	829 (68.4)	1083 (62.7)	2226 (64.1)
Diuretic	355 (58.5)	710 (58.6)	633 (36.7)	1336 (38.5)
Calcium-channel blocker	227 (37.4)	446 (36.8)	561 (32.5)	1082 (31.2)
Statin	461 (75.9)	966 (79.7)	1312 (76.0)	2663 (76.7)
Aspirin	495 (81.5)	981 (80.9)	1432 (83.0)	2894 (83.3)
Metformin	369 (60.8)	711 (58.7)	1365 (79.1)	2746 (79.1)
Sulfonylurea	234 (38.6)	480 (39.6)	758 (43.9)	1534 (44.2)
Insulin	357 (58.8)	699 (57.7)	778 (45.1)	1551 (44.7)

Incident or worsening nephropathy



No. of patients									
Empagliflozin	4124	3994	3848	3669	3171	2279	1887	1219	290
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

Doubling of serum creatinine, initiation of renal replacement therapy, or death due to renal disease



No. of patients									
Empagliflozin	4645	4500	4377	4241	3729	2715	2280	1496	360
Placebo	2323	2229	2146	2047	1771	1289	1079	680	144

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

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N Engl J Med 2016;375:323-34.

Renal Outcome Measure	Empagliflozin		Placebo		Hazard Ratio (95% CI)	P Value
	no. with event/ no. analyzed (%)	*rate/1000 patient-yr*	*no. with event/ no. analyzed (%)*	*rate/1000 patient-yr*		
Incident or worsening nephropathy or cardiovascular death	675/4170 (16.2)	60.7	497/2102 (23.6)	95.9	0.61 (0.55–0.69)	<0.001
Incident or worsening nephropathy	525/4124 (12.7)	47.8	388/2061 (18.8)	76.0	0.61 (0.53–0.70)	<0.001
Progression to macroalbuminuria	459/4091 (11.2)	41.8	330/2033 (16.2)	64.9	0.62 (0.54–0.72)	<0.001
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2	70/4645 (1.5)	5.5	60/2323 (2.6)	9.7	0.56 (0.39–0.79)	<0.001
Initiation of renal-replacement therapy	13/4687 (0.3)	1.0	14/2333 (0.6)	2.1	0.45 (0.21–0.97)	0.04
Doubling of serum creatinine level accompanied by eGFR of ≤45 ml/min/1.73 m^2, initiation of renal-replacement therapy, or death from renal disease	81/4645 (1.7)	6.3	71/2323 (3.1)	11.5	0.54 (0.40–0.75)	<0.001
Incident albuminuria in patients with a normal albumin level at baseline	1430/2779 (51.5)	252.5	703/1374 (51.2)	266.0	0.95 (0.87–1.04)	0.25

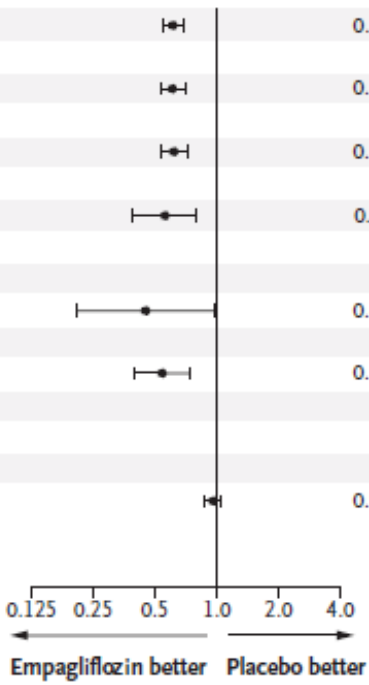
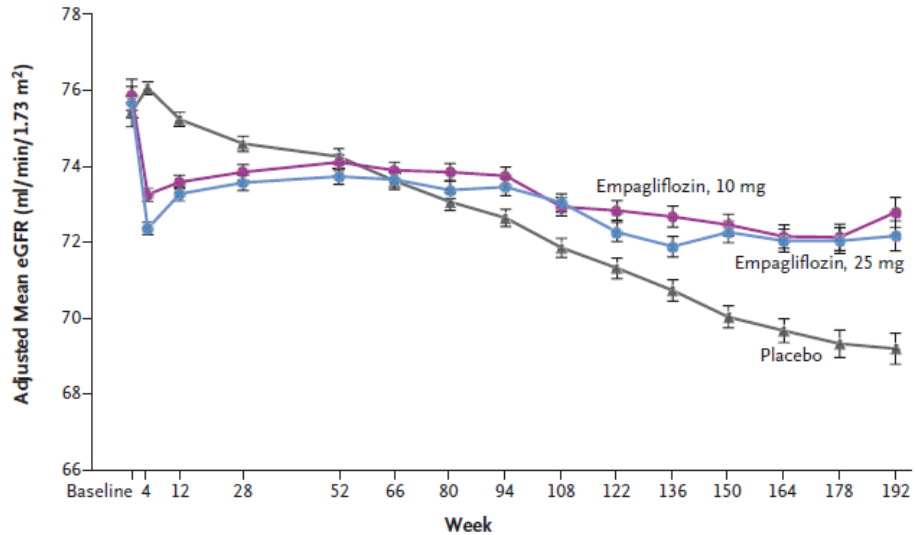


Figure 2. Risk Comparison for Seven Renal Outcomes.

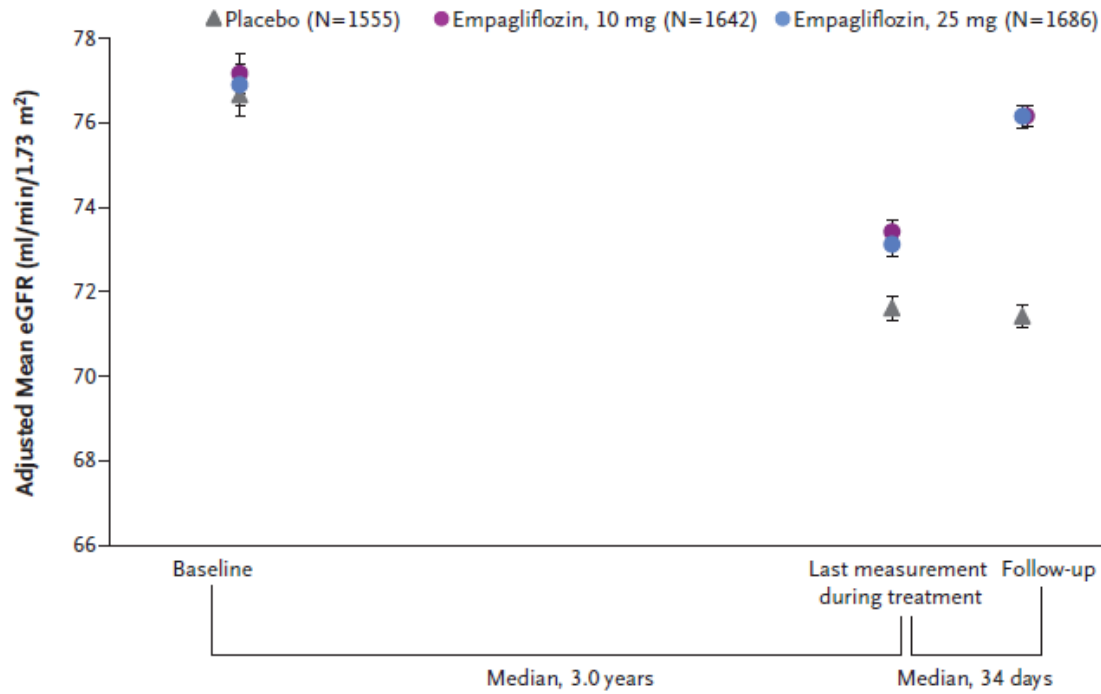
All the analyses shown were performed with the use of Cox regression in patients who received at least one dose of either empagliflozin or placebo. All the analyses were prespecified except for the composite outcome of a doubling of the serum creatinine level, the initiation of renal-replacement therapy, or death from renal disease. The abbreviation eGFR denotes estimated glomerular filtration rate.

A Change in eGFR over 192 Wk



No. at Risk															
Placebo	2323	2295	2267	2205	2121	2064	1927	1981	1763	1479	1262	1123	977	731	448
Empagliflozin, 10 mg	2322	2290	2264	2235	2162	2114	2012	2064	1839	1540	1314	1180	1024	785	513
Empagliflozin, 25 mg	2322	2288	2269	2216	2156	2111	2006	2067	1871	1563	1340	1207	1063	838	524
No. in Follow-up Analysis															
Total	7020	7020	6996	6931	6864	6765	6696	6651	6068	5114	4443	3961	3488	2707	1703

B Change in eGFR from Baseline to Last Measurement during Treatment and Follow-up



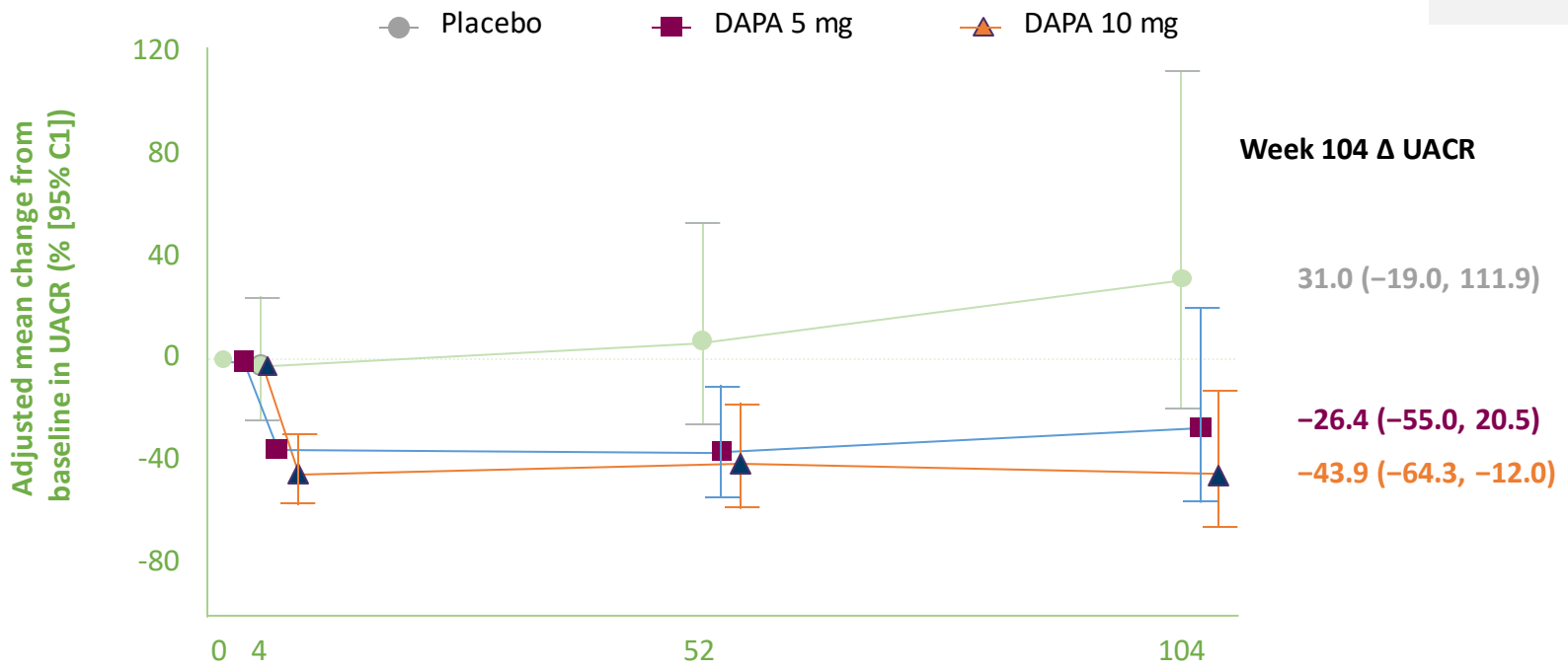
Diabetologia
DOI 10.1007/s00125-016-4017-1

RESEARCH LETTER

Dapagliflozin reduces albuminuria over 2 years in patients with type 2 diabetes mellitus and renal impairment

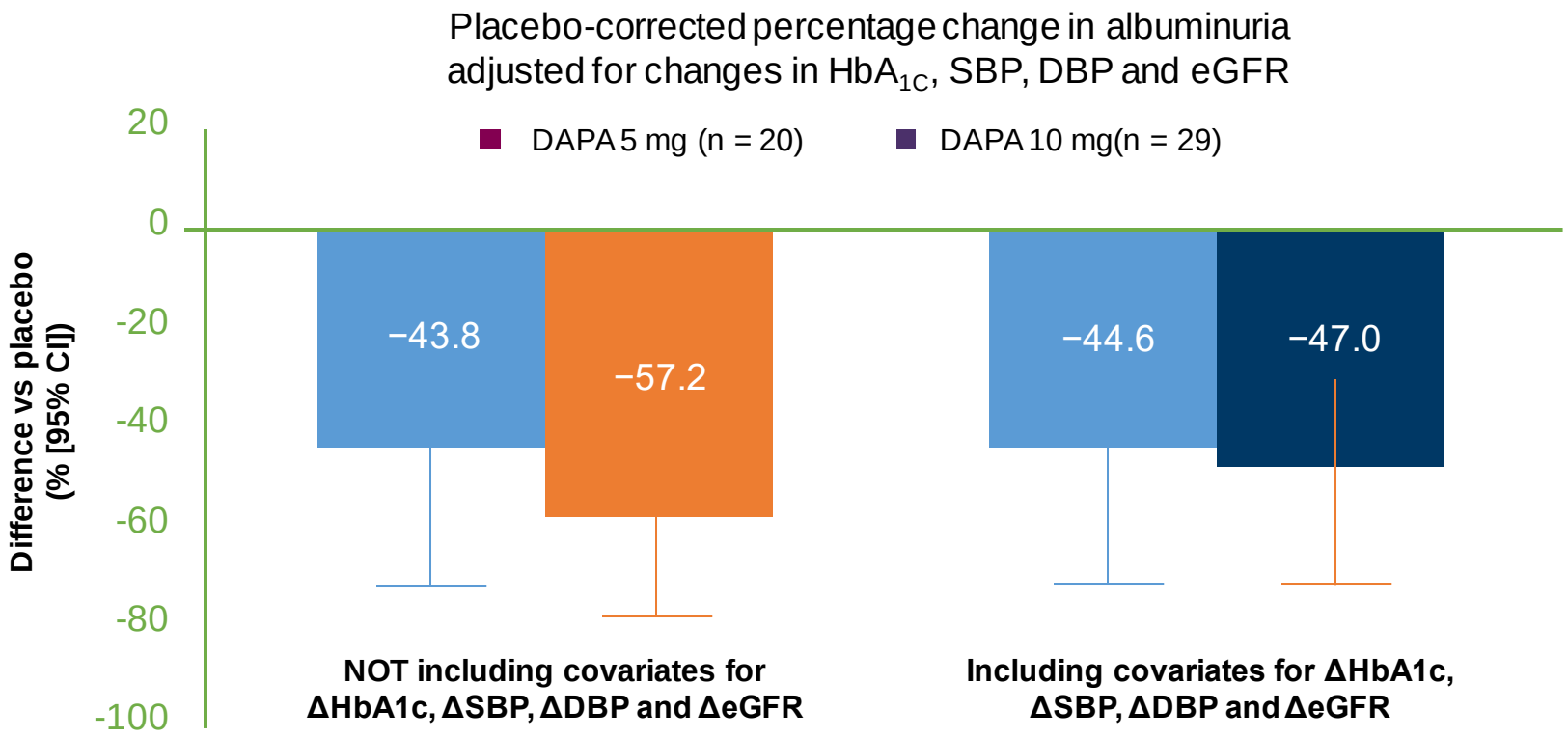
Paola Fioretto[1] · Bergur V. Stefansson[2] · Eva Johnsson[2] · Valerie A. Cain[3] · C. David Sjöström[2]

- Post-hoc analysis of data from a randomised, placebo-controlled, double blinded Phase 3 trial in patients with T2DM, CK3D and albuminuria
- 104 weeks in duration
- Patients received dapagliflozin 5 mg (n=53) or 10 mg (n=56) or placebo (n=57)



Number of Patients per Time Point					Baseline UACR
Placebo	56	49	31	25	698.0 mg/g
DAPA 5 mg	53	50	39	20	727.1 mg/g
DAPA 10 mg	56	52	40	29	604.4 mg/g

The UACR reduction by dapagliflozin is independent of changes in blood pressure, HbA_{1C} and eGFR[1]



The UACR reduction remains after adjustments for changes in blood pressure, HbA1c and eGFR indicating direct renal effect independent of changes in these variables[1]

The effect of sodium glucose cotransporter 2 inhibition with empagliflozin on microalbuminuria and macroalbuminuria in patients with type 2 diabetes

David Cherney[1,2] · Søren S. Lund[3] · Bruce A. Perkins[4] · Per-Henrik Groop[5,6,7] · Mark E. Cooper[7] · Stefan Kaspers[3] · Egon Pfarr[3] · Hans J. Woerle[3] · Maximilian von Eynatten[3]

Diabetologia (2016) 59:1860–1870

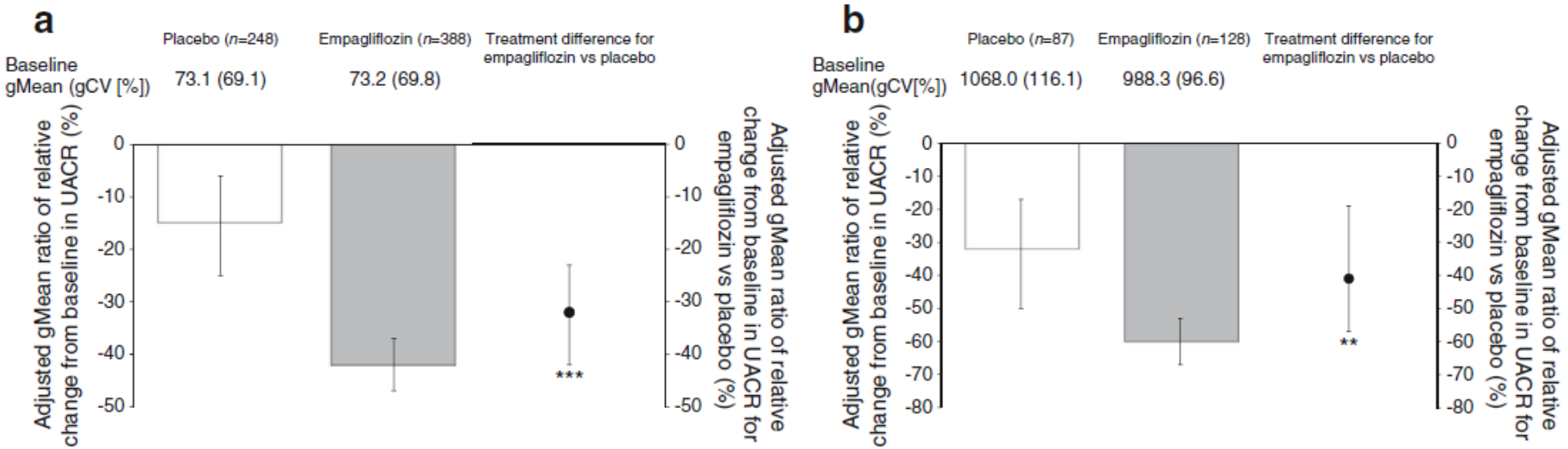
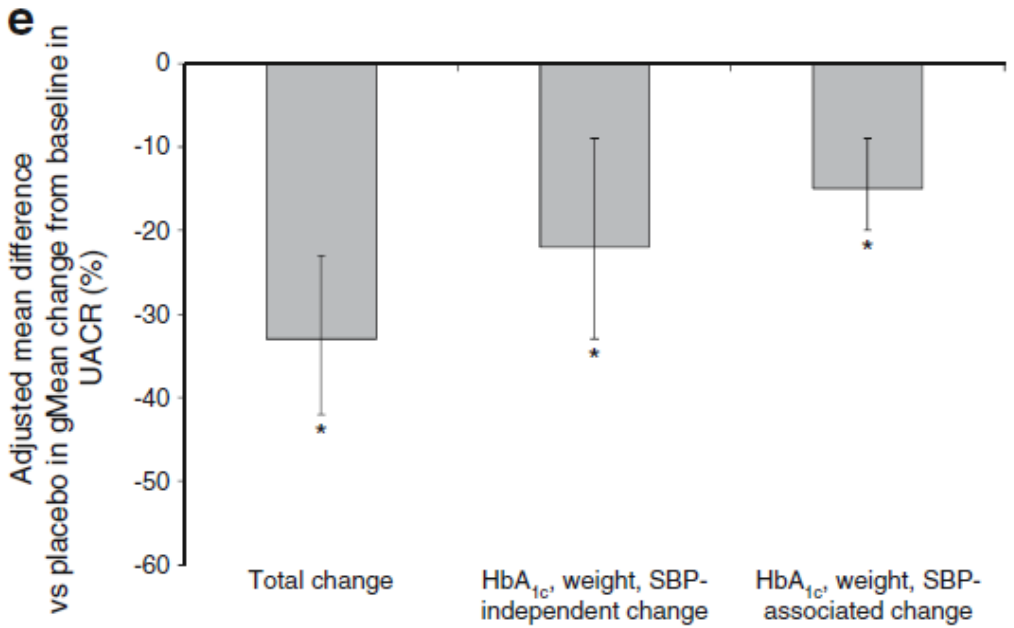
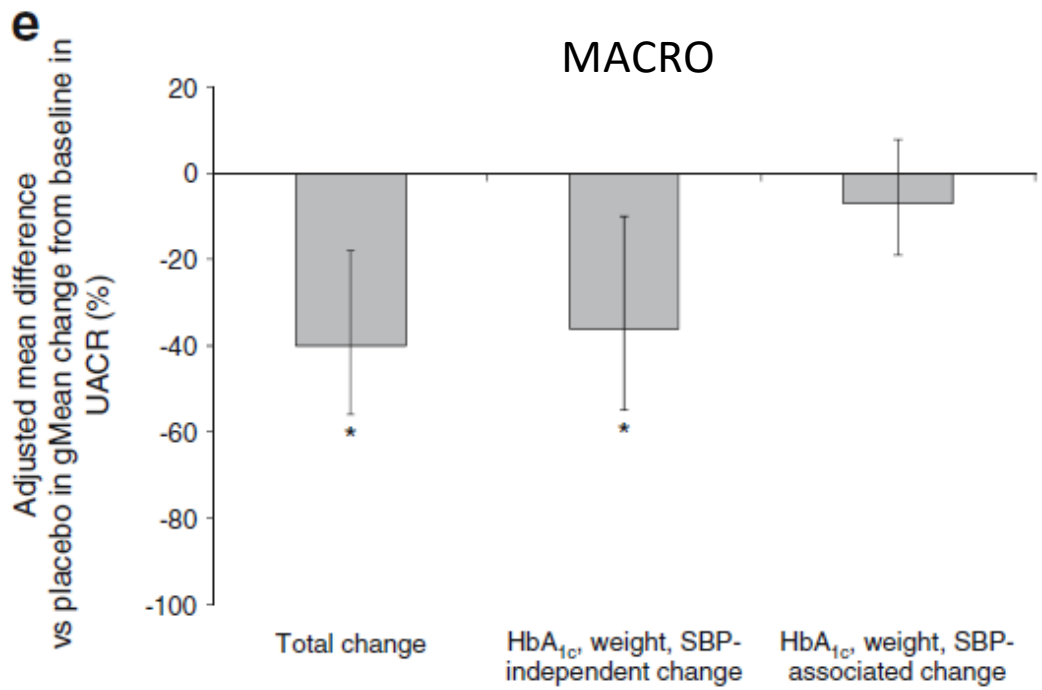


Fig. 1 Adjusted geometric mean (with 95% CI) of percentage change from baseline in UACR at week 24 in patients with microalbuminuria (**a**) or macroalbuminuria (**b**) at baseline. ANCOVA in FAS (LOCF). $^{**}p < 0.01$ and $^{***}p < 0.001$ for treatment difference between empagliflozin and placebo. gCV, geometric CV; gMean, geometric mean


e
Adjusted mean difference vs placebo in gMean change from baseline in UACR (%)
0
-10
-20
-30
-40
-50
-60
*
*
*
Total change
HbA1c, weight, SBP-independent change
HbA1c, weight, SBP-associated change

MICRO

MACRO


e
Adjusted mean difference vs placebo in gMean change from baseline in UACR (%)
20
0
-20
-40
-60
-80
-100
*
*
Total change
HbA1c, weight, SBP-independent change
HbA1c, weight, SBP-associated change

Renal Hemodynamic Effect of Sodium-Glucose Cotransporter 2 Inhibition in Patients With Type 1 Diabetes Mellitus

Circulation
2014, 129 : 5 587-597

David Z.I. Cherney, MD, PhD*; Bruce A. Perkins, MD, MPH*; Nima Soleymanlou, PhD*; Maria Maione, RN; Vesta Lai, RN; Alana Lee, RN; Nora M. Fagan, MS; Hans J. Woerle, MD; Odd Erik Johansen, MD, PhD; Uli C. Broedl, MD†; Maximilian von Eynatten, MD†

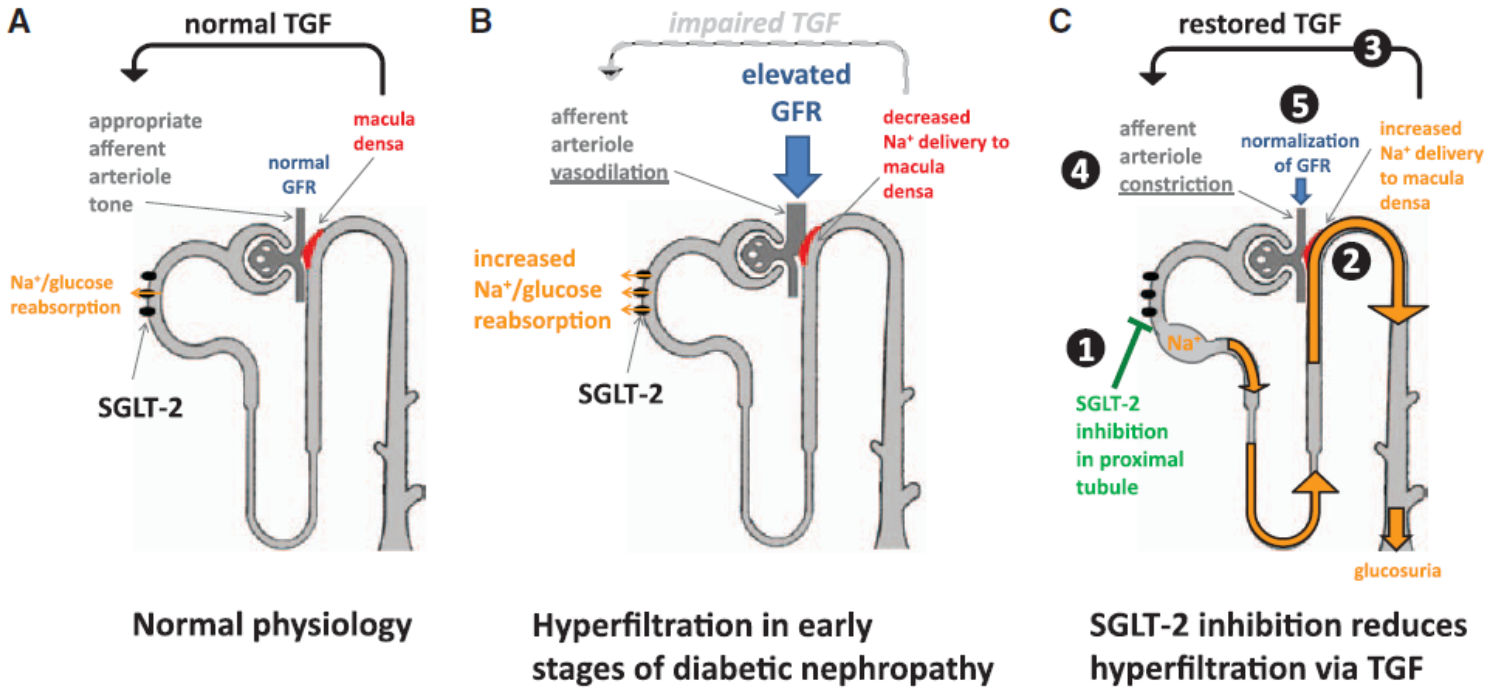


Figure 1. Postulated tubuloglomerular feedback (TGF) mechanisms in normal physiology, early stages of diabetic nephropathy, and after sodium-glucose cotransporter (SGLT) 2 inhibition. **A,** Under physiological conditions, TGF signaling maintains stable glomerular filtration rate (GFR) by modulation of preglomerular arteriole tone. In cases of conditional increases in GFR, the macula densa within the juxta-glomerular apparatus senses an increase in distal tubular sodium delivery and adjusts GFR via TGF accordingly. **B,** Under chronic hyperglycemic conditions (diabetes mellitus), increased proximal SGLT2-mediated reabsorption of sodium (Na^+) and glucose impairs this feedback mechanism. Thus, despite increased GFR the macula densa is exposed to lowered sodium concentrations. This impairment of TGF signaling likely leads to inadequate arteriole tone and increased renal perfusion. **C,** SGLT2 inhibition with empagliflozin treatment blocks proximal tubule glucose and sodium reabsorption, which leads to increased sodium delivery to the macula densa. This condition restores TGF via appropriate modulation of arteriolar tone (eg, afferent vasoconstriction), which in turn reduces renal plasma flow and hyperfiltration.

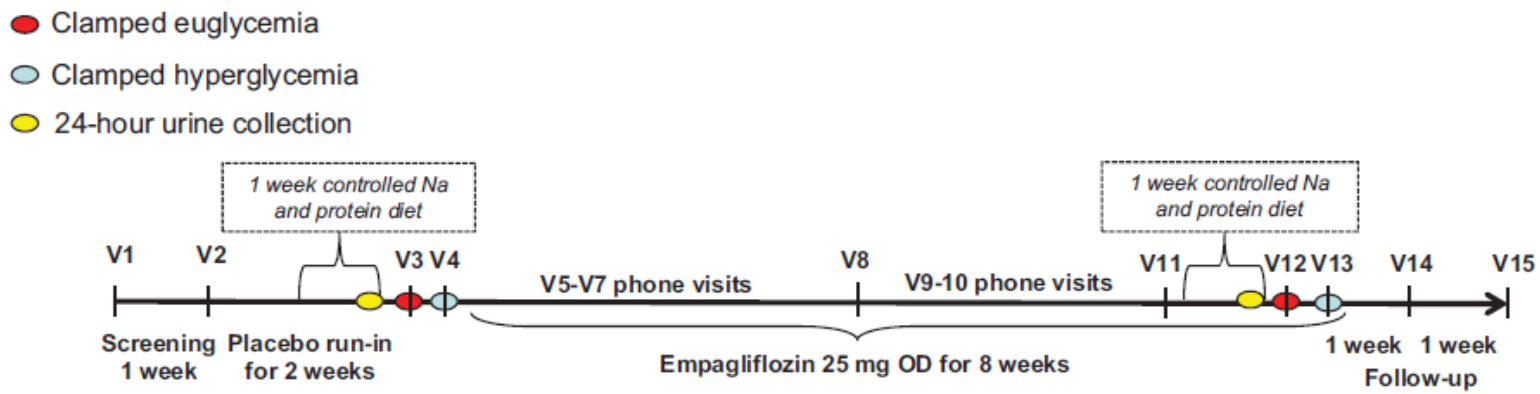


Figure 3. Study outline for renal hemodynamic function tests.

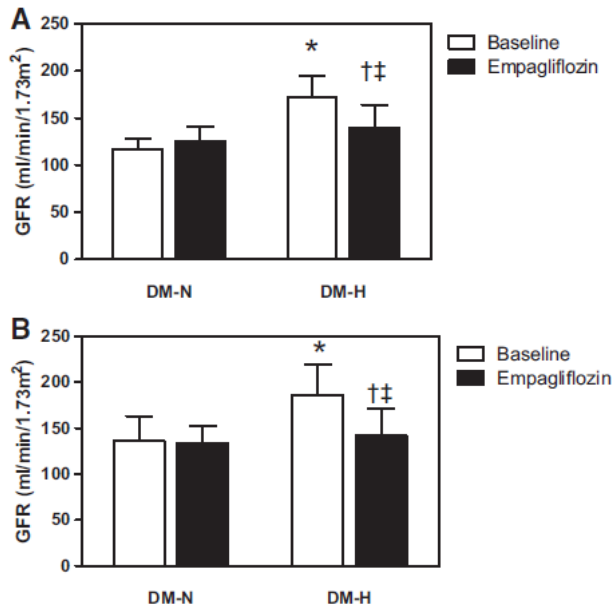


Figure 4. Glomerular filtration rate (GFR) responses to empagliflozin during clamped euglycemia (**A**) and hyperglycemia (**B**; mean±SD). *P<0.01 for baseline GFR in type 1 diabetes mellitus subjects without (T1D-N) vs with (T1D-H) renal hyperfiltration. †P<0.01 for the within-group change in GFR in T1D-H. ‡P<0.01 for the between-group effect of empagliflozin on change in GFR.

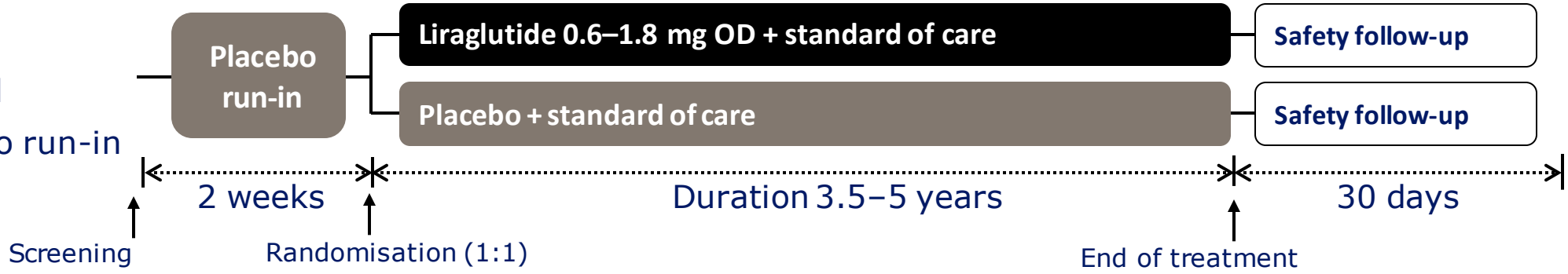
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steinberg, M.D., Mette Stockner, M.D., Bernard Zinman, M.D., Richard M. Bergenstal, M.D., and John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators*

N Engl J Med 2016;375:311-22.

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve;
- OADs and/or basal/premix insulin
- **Age ≥50 years and established CV disease or chronic renal failure**
  or
- **Age ≥60 years and risk factors for CV disease**

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

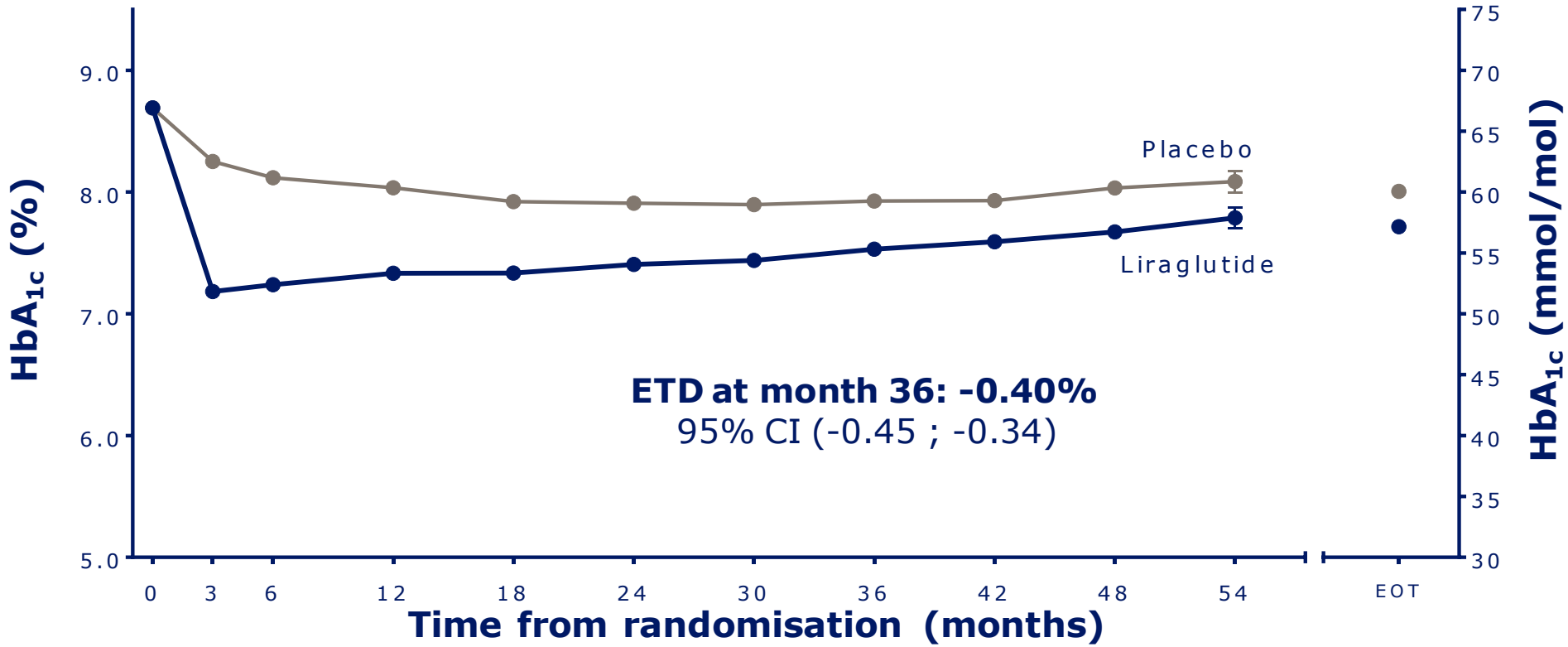
Baseline renal function

	Liraglutide (N=4668)	Placebo (N=4672)
Normal renal function (eGFR ≥90 mL/min/1.73 m^2)	1620 (34.7)	1655 (35.4)
Mild impairment (eGFR 60–89 mL/min/1.73 m^2)	1932 (41.4)	1975 (42.3)
Moderate impairment (eGFR 30–59 mL/min/1.73 m^2)	999 (21.4)	935 (20.0)
Severe impairment (eGFR <30 mL/min/1.73 m^2)	117 (2.5)	107 (2.3)

	Liraglutide	Placebo
Microalbuminuria	26.4%	26.6%
Macroalbuminuria	10.0%	11.0%
eGFR <60 mL/min/1.73 m^2	23.9%	22.3%

Full analysis set. Data are number of patients (percentage of either liraglutide-treated or placebo-treated group). Percentage data refer to proportion of patients
eGFR, estimated glomerular filtration rate.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

HbA_{1c}



Number of patients at each visit

Liraglutide	4668	4402	4355	4295	4135	4034	3877	3810	2349	809	101	3705
Placebo	4672	4413	4355	4235	4030	3905	3742	3640	2303	756	87	3561

Data are estimated mean values from randomisation to EOT.
CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; HbA_{1c}, glycosylated haemoglobin.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Table 1. Primary and Secondary Outcomes.*

Outcome	Liraglutide (N=4668)	Incidence Rate	Placebo (N=4672)	Incidence Rate	Hazard Ratio (95% CI)	P Value
	no. of patients (%)	*no. of events/ 100 patient-yr*	*no. of patients (%)*	*no. of events/ 100 patient-yr*		
Primary composite outcome†	608 (13.0)	3.4	694 (14.9)	3.9	0.87 (0.78–0.97)	0.01
Expanded composite outcome‡	948 (20.3)	5.3	1062 (22.7)	6.0	0.88 (0.81–0.96)	0.005
Death from any cause	381 (8.2)	2.1	447 (9.6)	2.5	0.85 (0.74–0.97)	0.02
Death from cardiovascular causes	219 (4.7)	1.2	278 (6.0)	1.6	0.78 (0.66–0.93)	0.007
Death from noncardiovascular causes	162 (3.5)	0.9	169 (3.6)	1.0	0.95 (0.77–1.18)	0.66
Myocardial infarction§	292 (6.3)	1.6	339 (7.3)	1.9	0.86 (0.73–1.00)	0.046
Fatal§	17 (0.4)	0.1	28 (0.6)	0.2	0.60 (0.33–1.10)	0.10
Nonfatal	281 (6.0)	1.6	317 (6.8)	1.8	0.88 (0.75–1.03)	0.11
Silent§	62 (1.3)	0.3	76 (1.6)	0.4	0.86 (0.61–1.20)	0.37
Stroke§	173 (3.7)	1.0	199 (4.3)	1.1	0.86 (0.71–1.06)	0.16
Fatal§	16 (0.3)	0.1	25 (0.5)	0.1	0.64 (0.34–1.19)	0.16
Nonfatal	159 (3.4)	0.9	177 (3.8)	1.0	0.89 (0.72–1.11)	0.30
Transient ischemic attack§	48 (1.0)	0.3	60 (1.3)	0.3	0.79 (0.54–1.16)	0.23
Coronary revascularization	405 (8.7)	2.3	441 (9.4)	2.5	0.91 (0.80–1.04)	0.18
Hospitalization for unstable angina pectoris	122 (2.6)	0.7	124 (2.7)	0.7	0.98 (0.76–1.26)	0.87
Hospitalization for heart failure	218 (4.7)	1.2	248 (5.3)	1.4	0.87 (0.73–1.05)	0.14
Microvascular event	355 (7.6)	2.0	416 (8.9)	2.3	0.84 (0.73–0.97)	0.02
Retinopathy	106 (2.3)	0.6	92 (2.0)	0.5	1.15 (0.87–1.52)	0.33
Nephropathy	268 (5.7)	1.5	337 (7.2)	1.9	0.78 (0.67–0.92)	0.003

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
‡ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
§ This analysis was not prespecified.

Microvascular event definitions

Event type		Event definition – one or more of the below
Microvascular events	**Renal**	• New onset of persistent macroalbuminuria • Persistent doubling of serum creatinine* • Need for continuous renal replacement therapy • Death due to renal disease
	Eye	• Need for retinal photocoagulation or treatment with intravitreal agents • Vitreous haemorrhage • Diabetes-related blindness

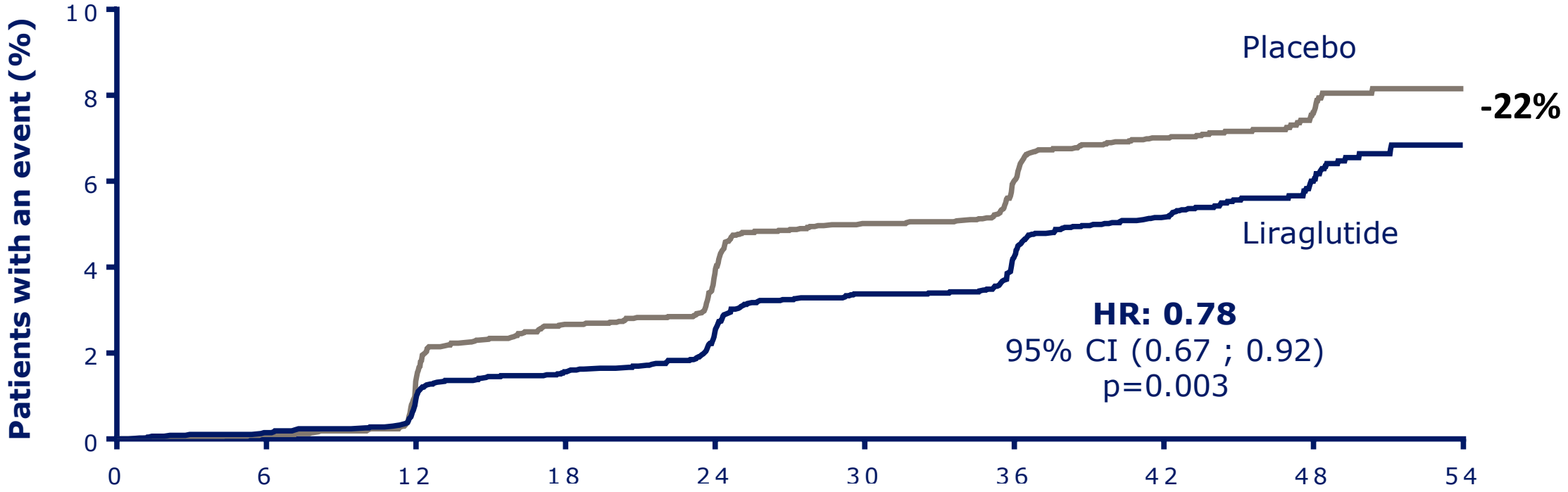
*and eGFR ≤45 mL/min/1.73 m^2 per MDRD

eGFR: estimated glomerular filtration rate; MDRD, modification of diet in renal disease.

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

LEADER: Time to first renal event

Macroalbuminuria, doubling of serum creatinine*, ESRD, renal death



Patients at risk

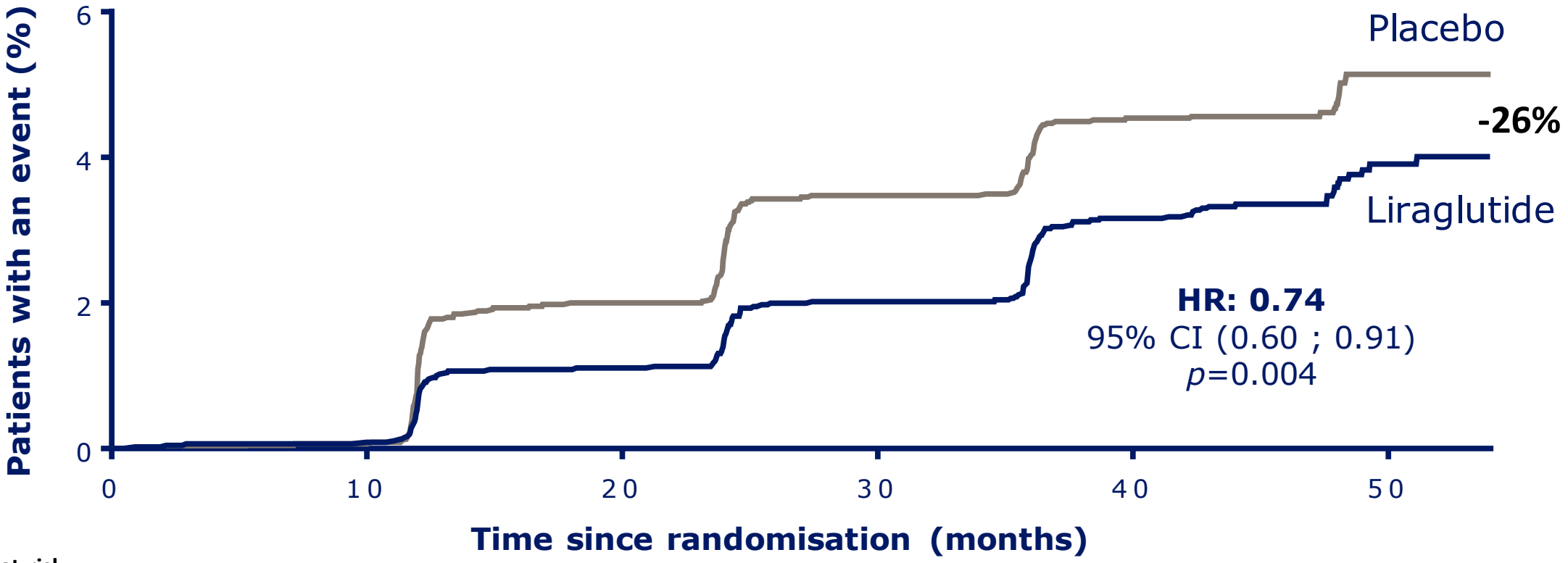
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*and eGFR ≤45 mL/min/1.73 m^2 per MDRD. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months

CI: confidence interval; ESRD: end-stage renal disease; HR: hazard ratio

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany.

LEADER: Time to new onset of persistent macroalbuminuria



Patients at risk

Liraglutide	4668	4606	4499	4353	4199	1006
Placebo	4672	4615	4433	4252	4094	964

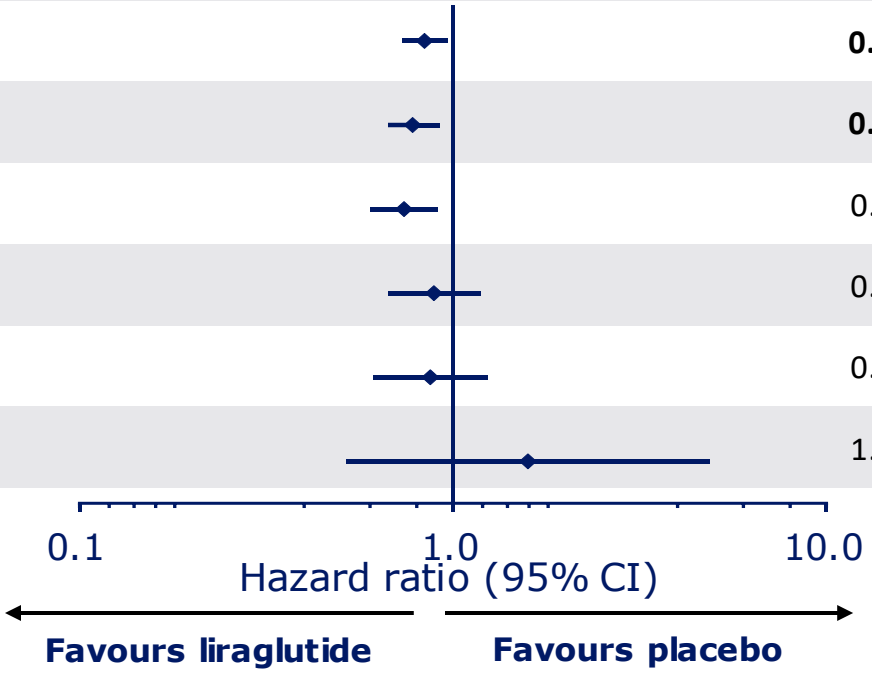
Full analysis set. EAC-confirmed index events from randomisation to follow-up. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the HRs with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months because less than 10% of the patients had an observation time beyond 54 months. Macroalbuminuria was defined as urine albumin >300 mg/g creatinine

CI, confidence interval; EAC, event adjudication committee; HR, hazard ratio

Presented at ASN Kidney Week, 19 November 2016, Chicago, USA

LEADER: Time to first microvascular endpoints

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Number of patients		**4668**	**100**	**4672**	**100**
Microvascular endpoint	**0.84 (0.73 ; 0.97)**	**355**	**7.6**	**416**	**8.9**
Nephropathy	**0.78 (0.67 ; 0.92)**	**268**	**5.7**	**337**	**7.2**
New onset of persistent macroalbuminuria*	0.74 (0.60 ; 0.91)	161	3.4	215	4.6
Persistent doubling of serum creatinine†	0.89 (0.67 ; 1.19)	87	1.9	97	2.1
Need for continuous renal replacement therapy	0.87 (0.61 ; 1.24)	56	1.2	64	1.4
Death due to renal disease	1.59 (0.52 ; 4.87)	8	0.2	5	0.1



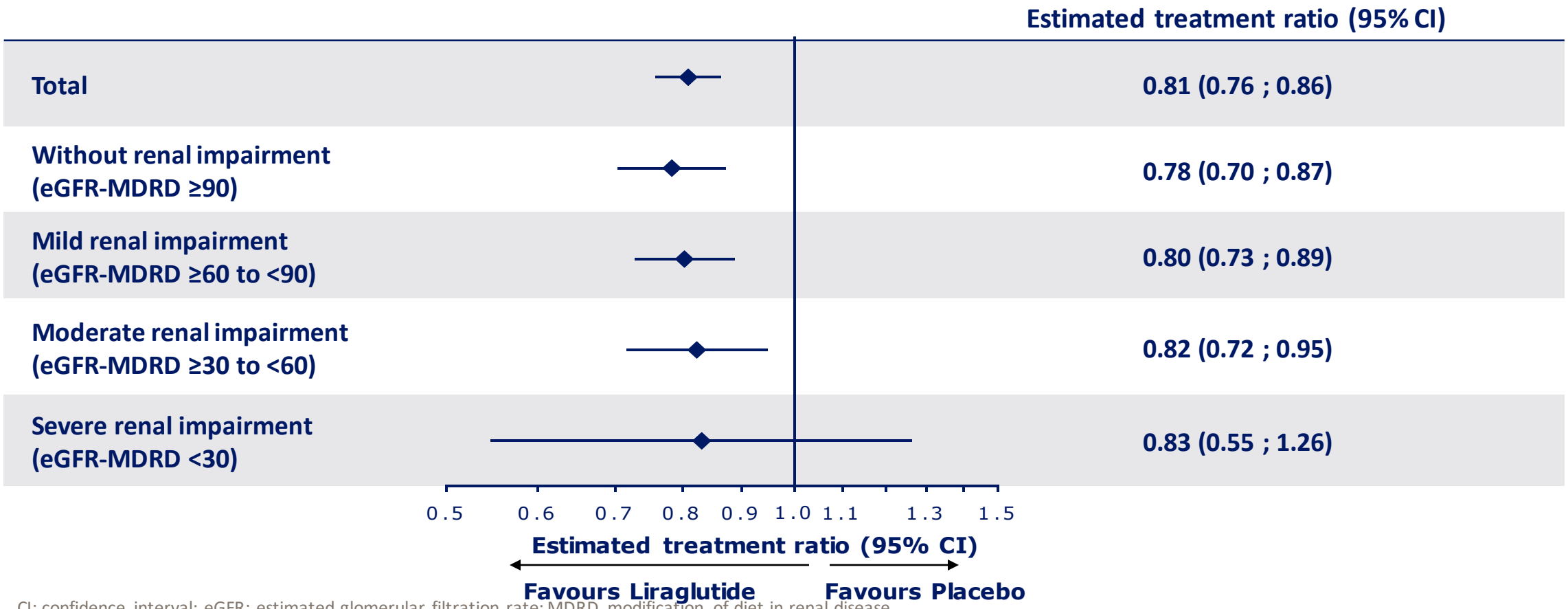
Full analysis set. EAC-confirmed microvascular events, including events with onset between date of randomisation and date of follow-up. Cox proportional-hazard model adjusted for treatment. Development of diabetes-related blindness was not analysed as an individual component as only one event was observed

*New onset of persistent macroalbuminuria: urine albumin ≥300 mg/g creatinine. †Persistent doubling of serum creatinine level and eGFR ≤45 mL/min/1.73m^2 per MDRD

CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease

Presented at ASN Kidney Week, 19 November 2016, Chicago, USA

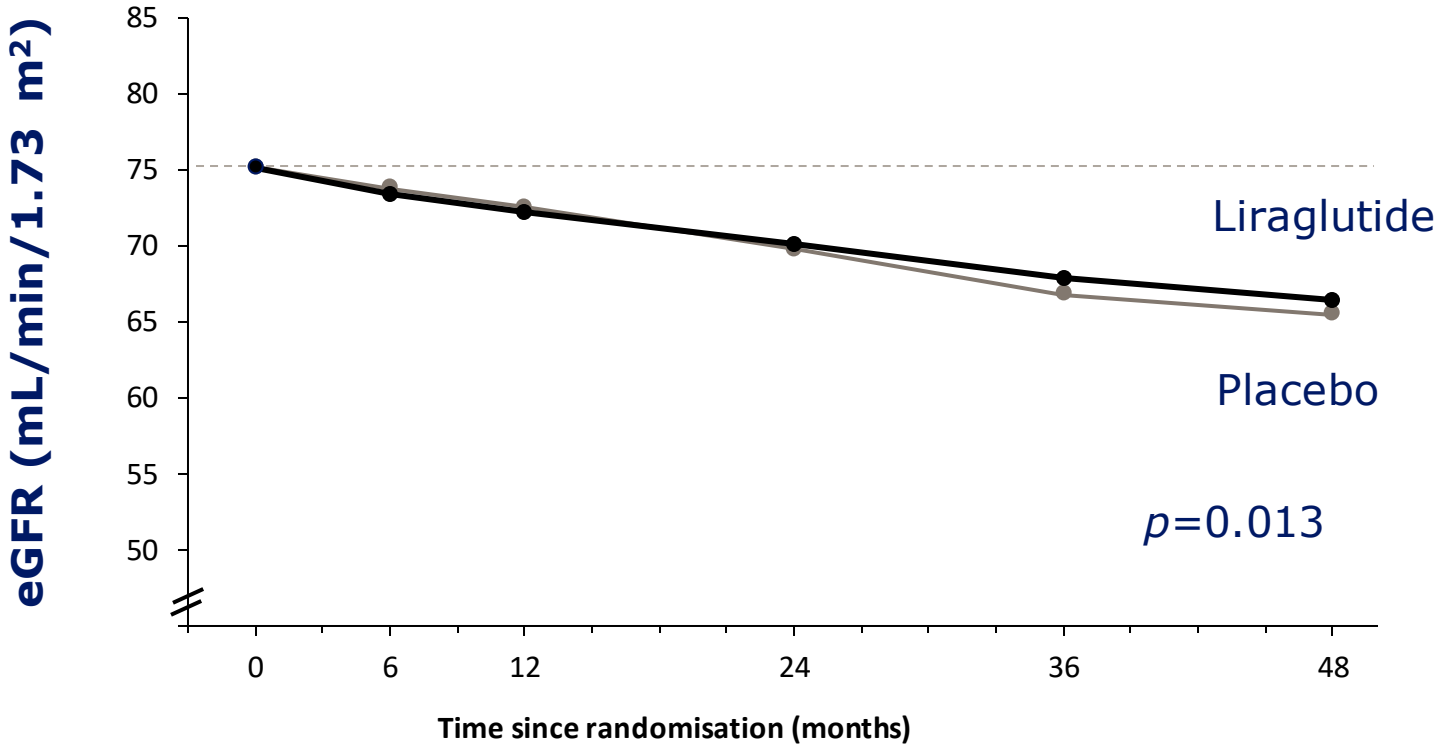
LEADER: Urinary albumin–creatinine ratio at 3 years

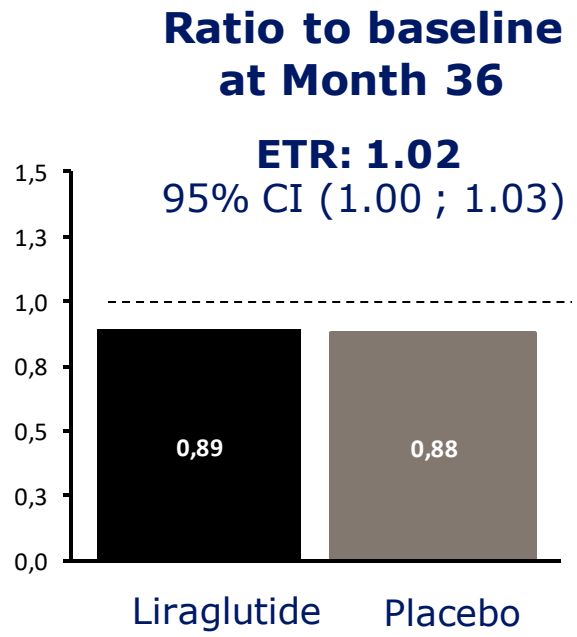


CI: confidence interval; eGFR: estimated glomerular filtration rate; MDRD, modification of diet in renal disease

Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany.

LEADER: Change in eGFR (MDRD)





Number of patients at each visit

Liraglutide	4668	4349	4288	4031	3806	812
Placebo	4672	4356	4237	3911	3634	755

Full analysis set. Estimated means ± standard error. Change from baseline to last assessment analysed using a linear mixed model for log-transformed assessment accounting for repeated measures. Analyses truncated at 48 months as <10% of patients had an observation time beyond 48 months. CI, confidence interval; eGFR, estimated glomerular filtration rate; ETR, estimated treatment ratio; MDRD, modification of diet in renal disease

Presented at ASN Kidney Week, 19 November 2016, Chicago, USA

Longitudinal Study of the Decline in Renal Function in Healthy Subjects

PLoS ONE 10(6): e0129036. doi:10.1371/

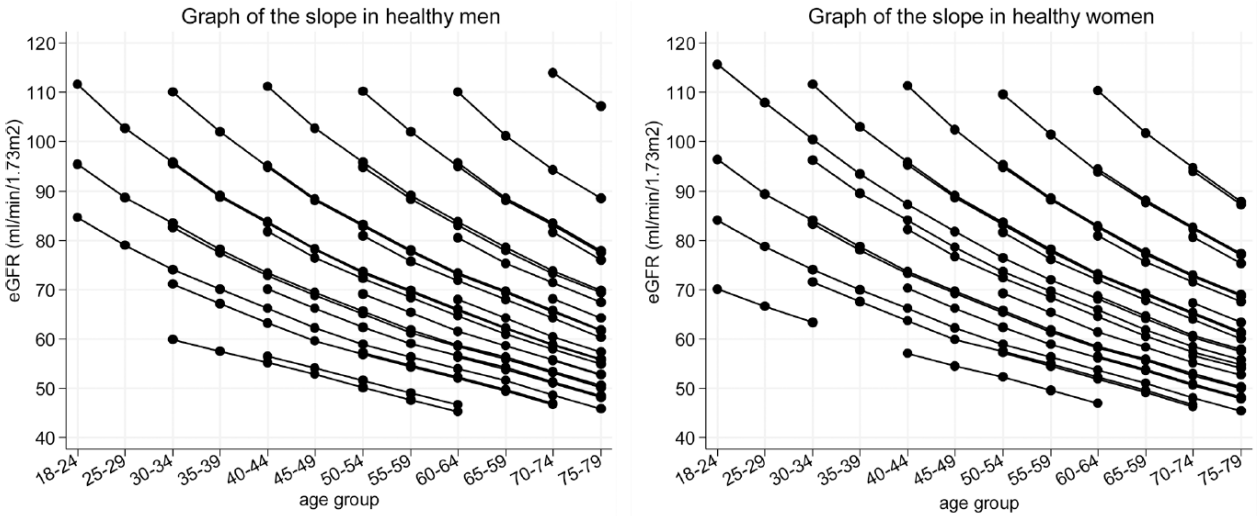


Fig 4. Graph of the slope of eGFR decline (simulated change of eGFR) in healthy men and women. The slope of eGFR decline is depicted as the inclination of each line. The trajectory of renal function based on this slope was predicted with a simulation method. The shape of the graph was gently convex downward, which matches the tendency for the slope of eGFR decline to be steeper for higher baseline eGFR and shallower for lower baseline eGFR.

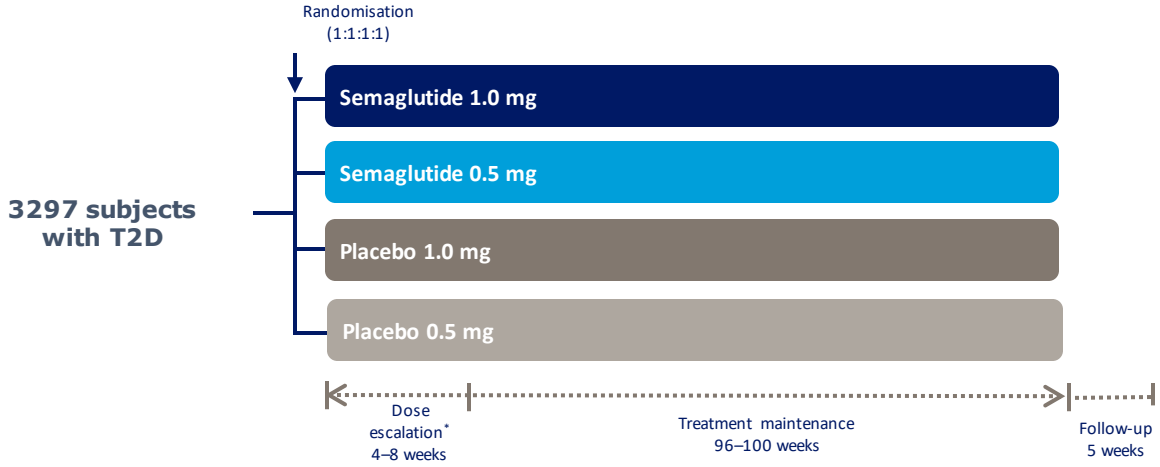
Results

In the cross-sectional study, reference values for eGFR were obtained by gender and age in 72,521 healthy subjects. The mean (±SD) eGFR was 83.7±14.7ml/min/1.73m^2. In the longitudinal study, reference values for eGFR decline rate were obtained by gender, age, and renal stage in 45,586 healthy subjects. In the same renal stage, there was little difference in the rate of decline regardless of age. The decline in eGFR depended on the renal stage and was strongly related to baseline eGFR, with a faster decline with a higher baseline eGFR and a slower decline with a lower baseline eGFR. The mean (±SD) eGFR decline rate was 1.07±0.42ml/min/1.73m^2/year (1.29±0.41%/year) in subjects with a mean eGFR of 81.5 ±11.6ml/min/1.73m^2.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

N Engl J Med 2016;375:1834-44.



Trial information

- Randomised, double-blind, placebo-controlled, four-armed parallel-group trial
- Additional glucose-lowering medication could be added to achieve glycaemic control at the discretion of investigator

Inclusion criteria

- HbA_{1c} ≥7.0%
- Previously on 0–2 OADs, basal or pre-mix insulin ± 0–2 OADs
- Age ≥50 years with established CVD (prior cardio-, cerebro- or peripheral vascular disease, chronic heart failure [NYHA class II–III]), or CKD stage 3 or worse

or

- Age ≥60 years with at least one cardiovascular risk factor

Key endpoints

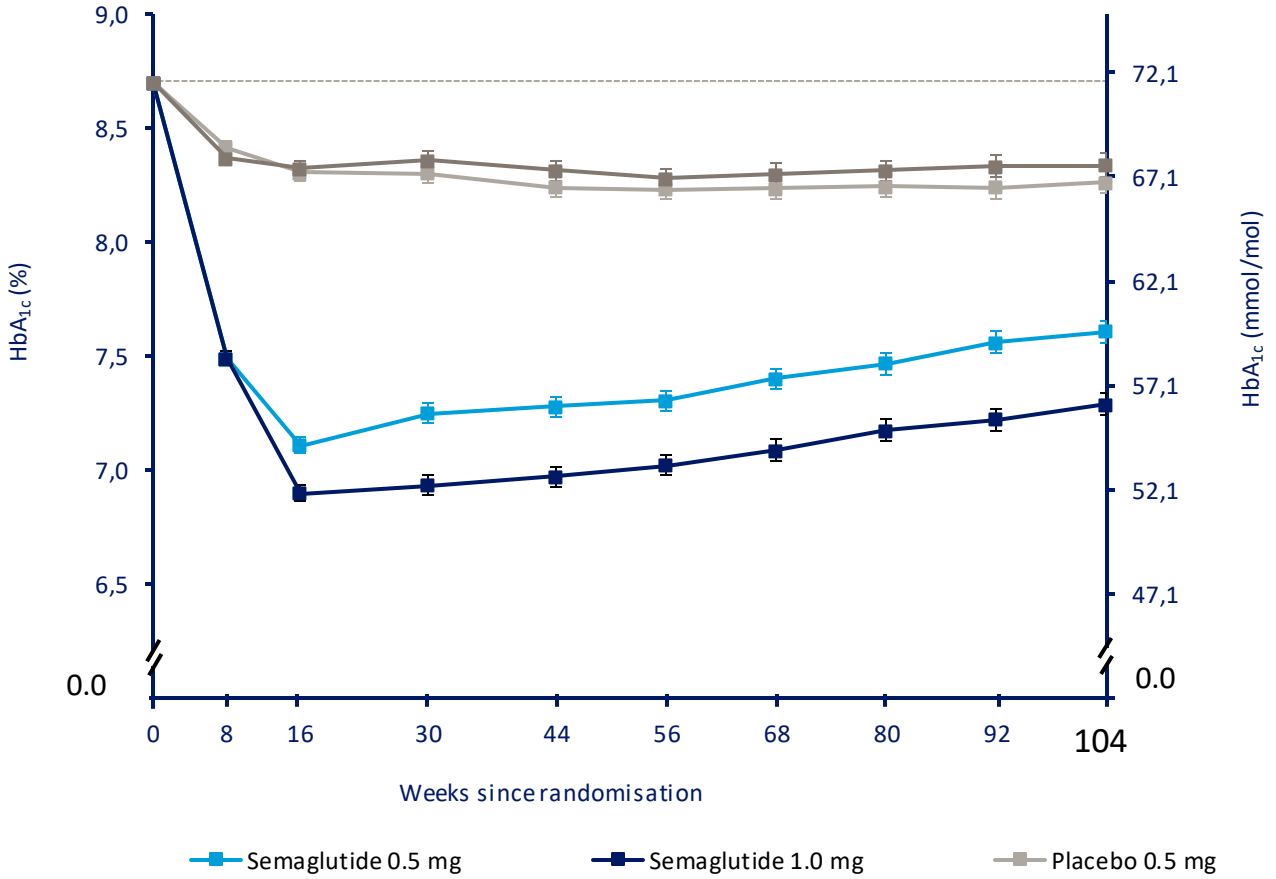
- Primary: time to first occurrence of death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke
- Secondary: time to first occurrence of revascularisation, unstable angina requiring hospitalisation, hospitalisation for heart failure, all-cause death, non-fatal MI or non-fatal stroke; time to each individual component

Baseline characteristics

	Semaglutide 0.5 mg (n=826)	Semaglutide 1.0 mg (n=822)	Placebo 0.5 mg (n=824)	Placebo 1.0 mg (n=825)	Total (N=3297)
Age (years)	64.6 (7.3)	64.7 (7.1)	64.8 (7.6)	64.4 (7.5)	64.6 (7.4)
Sex (N, %)					
Male	495 (59.9)	518 (63.0)	482 (58.5)	507 (61.5)	2002 (60.7)
Body weight (kg)*	91.8 (20.3)	92.9 (21.1)	91.8 (20.4)	91.9 (20.8)	92.1 (20.6)
Type 2 diabetes, mean (SD)					
Diabetes duration (years)	14.3 (8.2)	14.1 (8.2)	14.0 (8.5)	13.2 (7.4)	13.9 (8.1)
Glycated haemoglobin (%)	8.7 (1.4)	8.7 (1.5)	8.7 (1.5)	8.7 (1.5)	8.7 (1.5)
Cardiovascular risk factors					
Systolic blood pressure (mmHg)*	136.1 (18.0)	135.8 (17.0)	135.8 (16.2)	134.8 (17.5)	135.6 (17.2)
Diastolic blood pressure (mmHg)*	77.1 (9.8)	76.9 (10.2)	77.5 (9.9)	76.7 (10.2)	77.0 (10.0)
LDL cholesterol (mg/dl)†	81.6 (47.1)	83.3 (41.2)	80.9 (48.1)	83.6 (45.9)	82.3 (45.6)
Never smoked‡	390 (47.2)	364 (44.3)	391 (47.5)	348 (42.2)	1493 (45.3)

Table 1. *Means and standard deviations. †Geometric means and coefficients of variation. ‡Number of patients (N) and percentage (%). LDL, low-density lipoprotein; SD, standard deviation.
Marso *et al. NEJM* [in press]

Overall mean at baseline: 8.7%



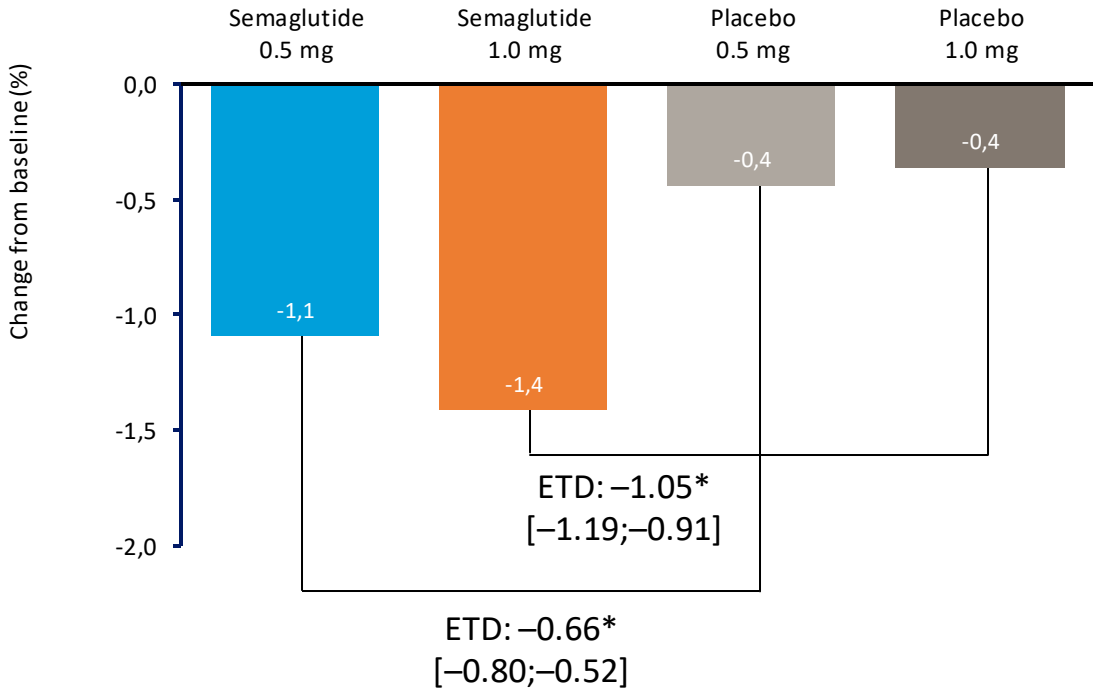


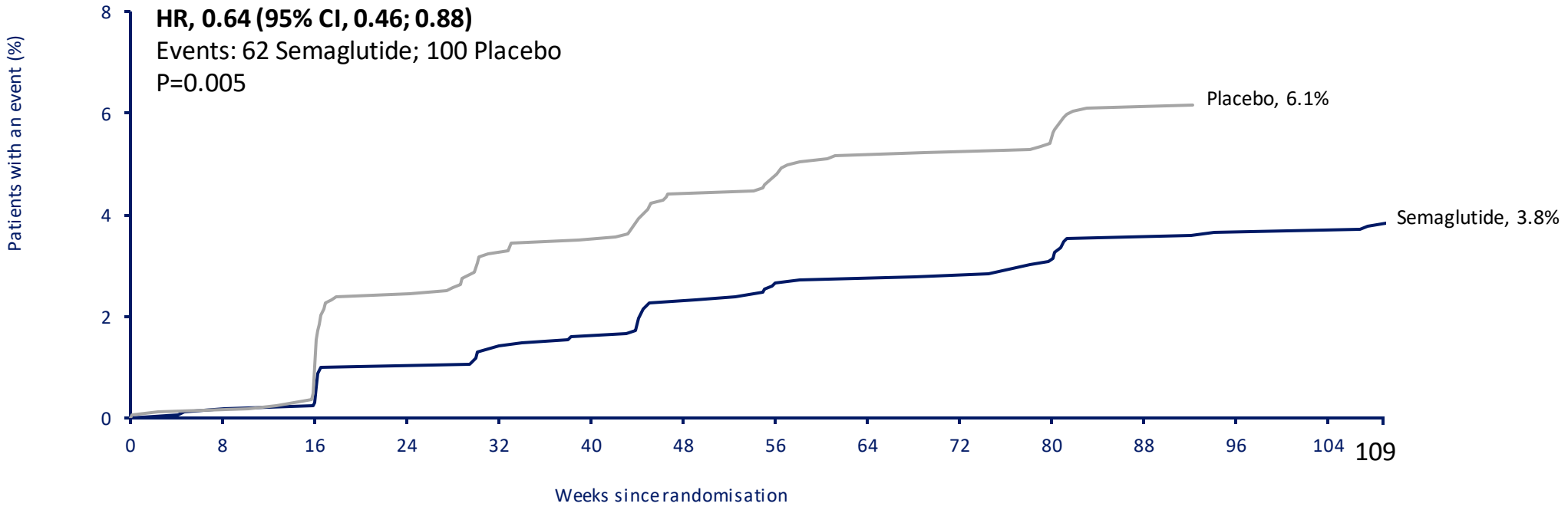
Figure 2A. Data are estimated mean plus or minus standard error of the mean based on in-trial data for scheduled visits from the full analysis set, analysed by a mixed model for repeated measures with treatment group (semaglutide 0.5 and 1.0 mg and comparable placebo doses) and stratification (9 levels) as fixed factors and the corresponding baseline value as fixed factors and the corresponding baseline value as a covariate, all nested within visit. *Indicates significance (p-value <0.0001). CI, confidence interval; ETD, estimated treatment difference.
Marso *et al. NEJM* [in press]

Microvascular outcomes

	Semaglutide No. (%)	Semaglutide Incidence rate per 100 PYR	Placebo No. (%)	Placebo Incidence rate per 100 PYR	HR (95% CI)		P value
Retinopathy complications	50 (3.0)	1.49	29 (1.8)	0.86	1.76	1.11; 2.78	0.02
Need for retinal photocoagulation	38 (2.3)	1.13	20 (1.2)	0.59	1.91	1.11; 3.28	0.02
Vitreous haemorrhage	16 (1.0)	0.47	7 (0.4)	0.21	2.29	0.94; 5.57	0.07
Need for treatment with intravitreal agent	16 (1.0)	0.47	13 (0.8)	0.38	1.25	0.59; 2.56	0.58
Onset of diabetes-related blindness	5 (0.3)	0.15	1 (0.1)	0.03	5.01	0.59; 42.88	0.14
New or worsening nephropathy	62 (3.8)	1.86	100 (6.1)	3.06	0.64	0.46; 0.88	0.005
Persistent macroalbuminuria	44 (2.7)	1.31	81 (4.9)	2.47	0.54	0.37; 0.77	0.001
Persistent doubling of serum creatinine level and creatinine clearance per MDRD <45 ml/min/1.73m2	18 (1.1)	0.53	14 (0.8)	0.41	1.28	0.64; 2.58	0.48
Need for continuous renal-replacement therapy	11 (0.7)	0.32	12 (0.7)	0.35	0.91	0.40; 2.07	0.83

Supplementary Table 9. †The primary composite outcome in the time-to-event analysis consisted of the first occurrence of either death from cardiovascular causes, non-fatal myocardial infarction or non-fatal stroke. ‡The expanded composite outcome included death from cardiovascular causes, non-fatal myocardial infarction, non-fatal stroke, revascularisation (coronary and peripheral), hospitalisation for unstable angina or heart failure. CI, confidence interval; HR, hazard ratio; PYR, patient years of risk time (time from randomisation until first event or censoring).
Marso *et al. NEJM* [in press]

New or worsening nephropathy



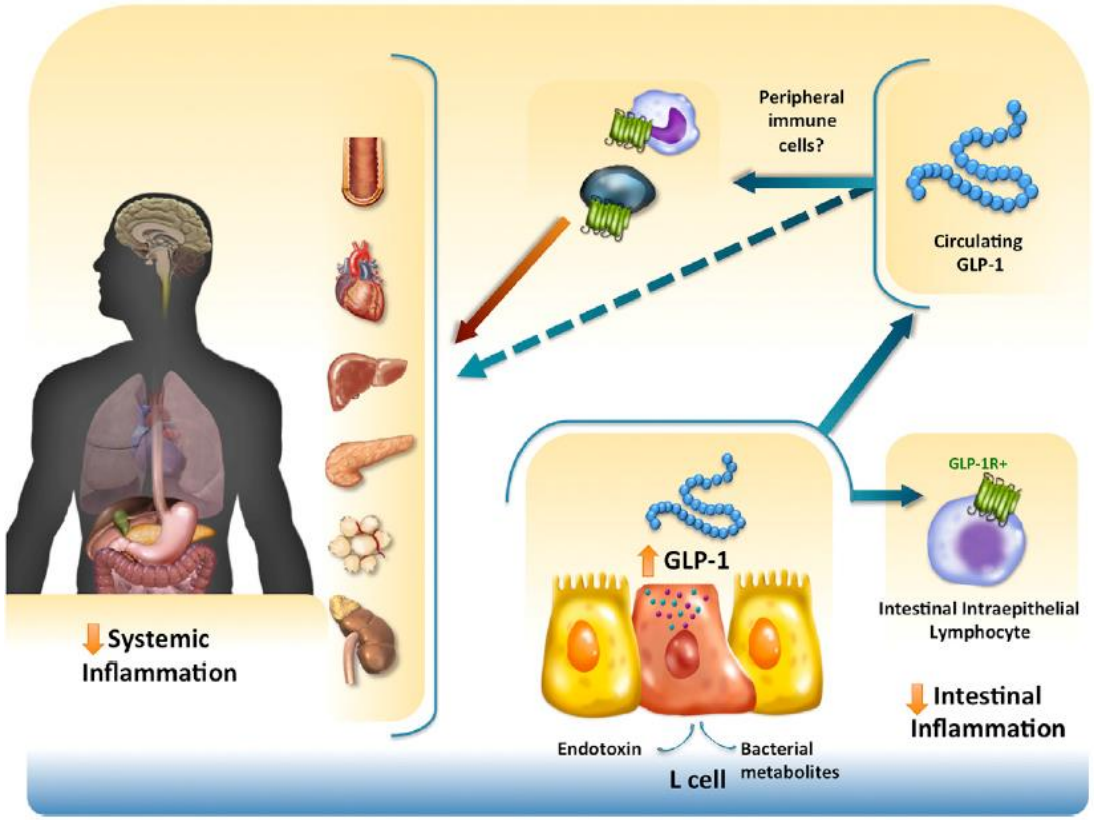
Number of patients at risk

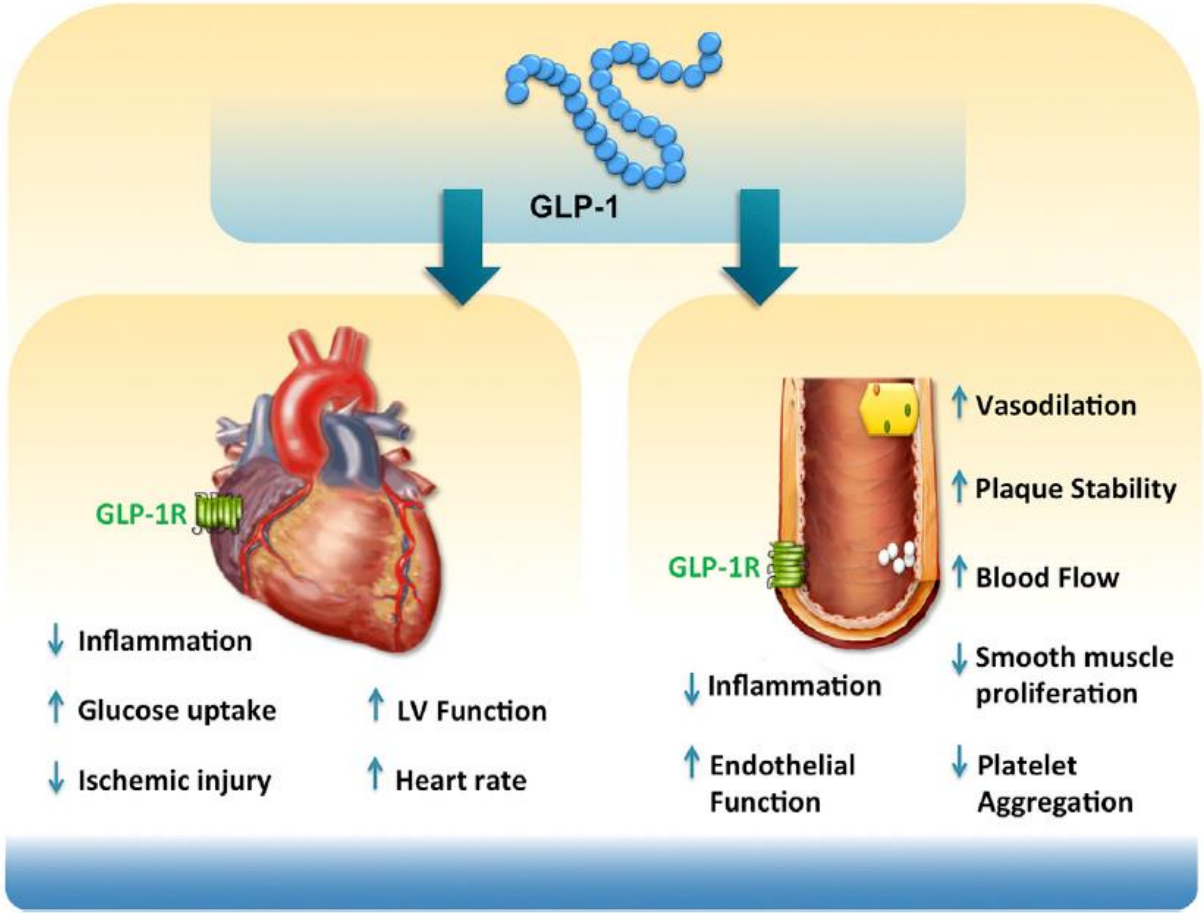
Semaglutide	**1648**	**1630**	**1605**	**1580**	**1563**	**1541**	**1525**	**1518**
Placebo	**1649**	**1629**	**1570**	**1545**	**1518**	**1498**	**1471**	**1465**

Supplementary Figure 5B. Kaplan Meier plot for time from randomisation to first EAC-confirmed new or worsening nephropathy using 'in-trial' data from subjects in the full analysis set. HR is from a proportional hazard model. CI, confidence interval; EAC, (external) event adjudication committee; HR, hazard ratio.
Marso *et al*. *NEJM* [in press]

The Cardiovascular Biology of Glucagon-like Peptide-1

Daniel J. Drucker[1,*]





Società Italiana di Diabetologia

POSITION STATEMENT

Farmaci ipoglicemizzanti, malattie cardiovascolari e renali

Enzo Bonora, Antonio Bossi, Daniela Bruttomesso, Angelo De Pascale, Gabriella Gruden, Davide Lauro, Frida Leonetti, Edoardo Mannucci, Roberto Miccoli, Annalisa Natalicchio, Gianluca Perseghin, Francesco Purrello, Ferdinando Sasso, Giorgio Sesti

Box 5 *- Empagliflozin e liraglutide oltre a benefici cardiovascolari, hanno determinato, indipendentemente dagli effetti sulla glicemia, importanti benefici renali. In virtù di ciò, quanto meno in soggetti con pregressa malattia cardiovascolare, empagliflozin o liraglutide dovrebbero essere considerate utili nella nefroprotezione. E' possibile che i benefici di empagliflozin si estendano anche agli altri inibitori di SGLT-2, e che quelli di liraglutide siano condivisi anche da altri agonisti del recettore di GLP-1 ma ciò deve essere ancora verificato con studi clinici di outcome renale attualmente in corso.*

PROTEZIONE DAL DANNO RENALE NEL DIABETE TIPO 2: RUOLO DEI NUOVI FARMACI

Grazie della vostra attenzione

Chronic kidney disease in type 2 diabetes: Lessons from the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicentre Study

G. Pugliese [a,*], A. Solini [b], E. Bonora [c], C. Fondelli [d], E. Orsi [e], A. Nicolucci [f], G. Penno [b] for the RIACE Study Group[1]

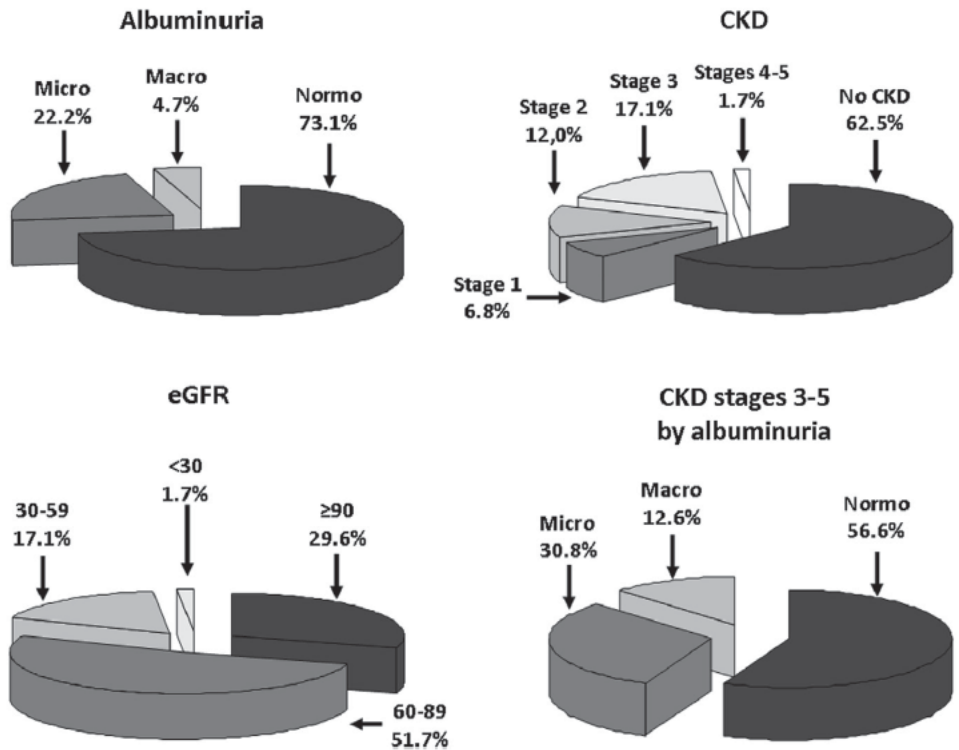


Figure 1 Prevalence of albuminuria and eGFR (ml/min/1.73 m^2) categoried and CKD stages (with stratification of subjects with Stages 3–5 CKD by albuminuria) in the RIACE cohort. Categories of albuminuria (mg/24 h or mg/g creatinine): normoalbuminuria < 30; microalbuminuria 30–299; macroalbuminuria > 300.

Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 815–822

Intensive glucose control improves kidney outcomes in patients with type 2 diabetes

Kidney International (2013) **83,** 517–523;

Vlado Perkovic[1], Hiddo Lambers Heerspink[2], John Chalmers[1], Mark Woodward[1,3], Min Jun[1], Qiang Li[1], Stephen MacMahon[1,4], Mark E. Cooper[5], Pavel Hamet[6], Michel Marre[7], Carl Erik Mogensen[8], Neil Poulter[9], Giuseppe Mancia[10], Alan Cass[1], Anushka Patel[1] and Sophia Zoungas[1,11], for the ADVANCE Collaborative Group

Table 2 | Effects of intensive compared with standard glucose control on albuminuria

Outcome	Intensive, *n* (%)	Standard, *n* (%)	Hazard ratio (95% confidence interval)	*P*-value
New-onset microalbuminuria	1318 (33.5)	1434 (36.3)	0.91 (0.85–0.98)	0.012
New-onset macroalbuminuria	162 (3.0)	231 (4.3)	0.70 (0.57–0.85)	0.0004
Progression of albuminuria by ⩾1 stage[a]	1298 (23.3)	1410 (25.3)	0.90 (0.84–0.97)	0.0077
Regression of albuminuria by ⩾1 stage[b]	1003 (61.2)	914 (56.3)	1.15 (1.05–1.26)	0.0020
Regression to normoalbuminuria	922 (56.3)	814 (50.2)	1.20 (1.09–1.31)	0.0002

[a]From normoalbuminuria to either microalbuminuria or macroalbuminuria, or from microalbuminuria to macroalbuminuria.
[b]From macroalbuminuria or microalbuminuria to normoalbuminuria, or from macroalbuminuria to microalbuminuria.

Prognosis of CKD by GFR and albuminuria category

Prognosis of CKD by GFR and Albuminuria Categories: KDIGO 2012

GFR categories (ml/min/ 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.

The RIACE (Renal Insufficiency and Cardiovascular Events) study

15,773 patients with type 2 diabetes from Italy

Stages of "Diabetic nephropathy"	
Normo	73,1%
Micro	22,2%
Macro	4,7%

eGFR strata (ml/min/1.73 m^2)	
≥90	29,6%
60-89	51,7%
30-59	17,1%
<30	1,7%

MDRD

NKF's KDOQI CKD stages	
No CKD	62,5%
Stage 1 ≥90*	6,7%
Stage 2 60-89*	12,0%
Stage 3 30-59	17,1%
Stages 4, 5 <30	1,7%

* Plus "kidney damage"

Penno G et al. J Hypertens 29: 1802-1809, 2011

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Maximilian von Eynatten, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators*

New England Journal of Medicine

2016

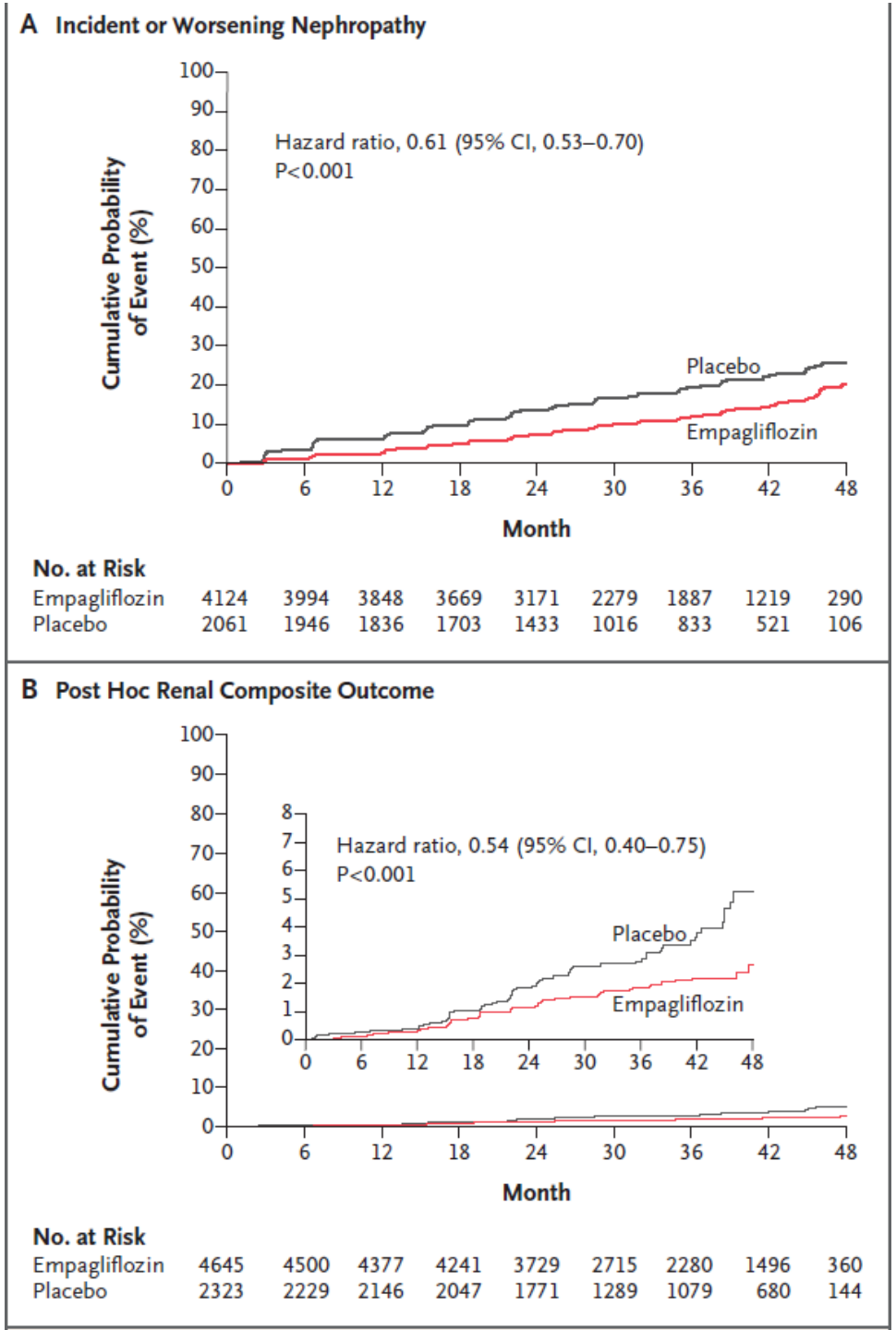
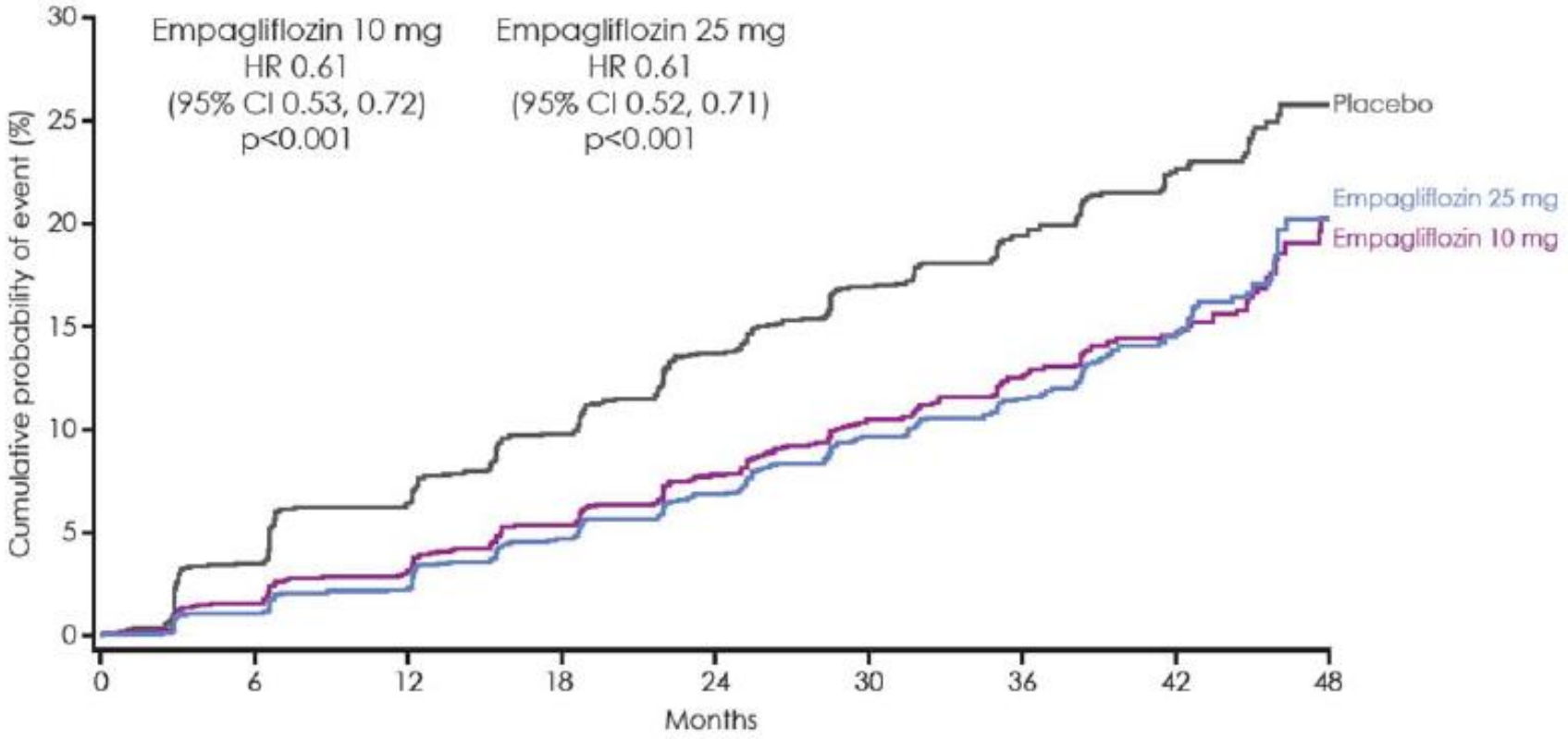


Figure S2. Incident or worsening nephropathy with empagliflozin 10 mg, empagliflozin 25 mg and placebo

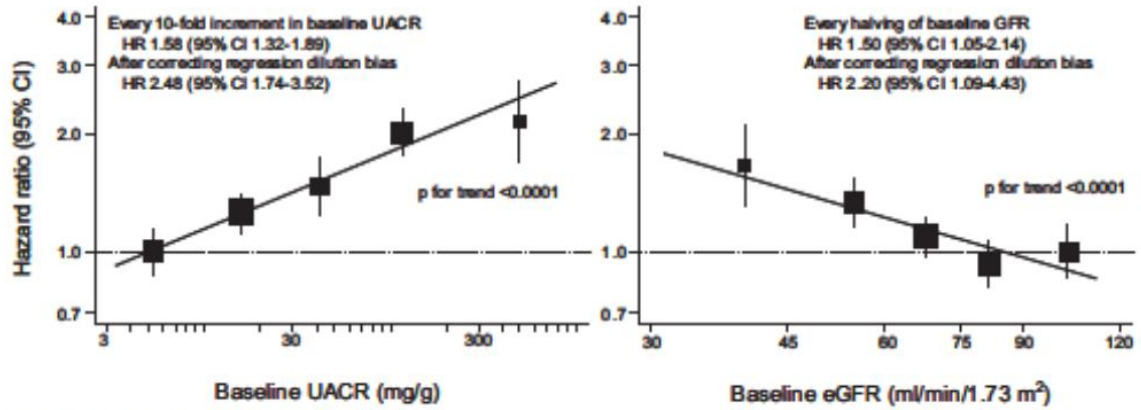


No. of patients									
Empagliflozin 10 mg	2055	1991	1912	1825	1571	1122	922	593	136
Empagliflozin 25 mg	2069	2003	1936	1844	1600	1157	965	626	154
Placebo	2061	1946	1836	1703	1433	1016	833	521	106

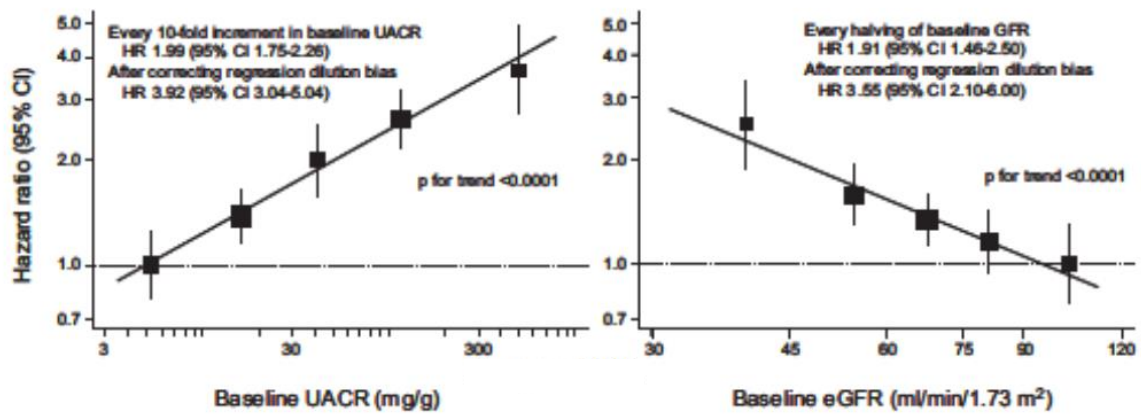
Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

Toshiharu Ninomiya,* Vlado Perkovic,* Bastiaan E. de Galan,*† Sophia Zoungas,* Avinesh Pillai,* Meg Jardine,* Anushka Patel,* Alan Cass,* Bruce Neal,* Neil Poulter,‡ Carl-Erik Mogensen,§ Mark Cooper,‖ Michel Marre,¶ Bryan Williams,** Pavel Hamet,†† Giuseppe Mancia,‡‡ Mark Woodward,*§§ Stephen MacMahon,* and John Chalmers,* on behalf of the ADVANCE Collaborative Group

Cardiovascular events



Cardiovascular death



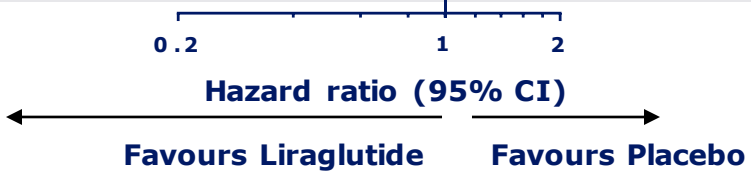
Baseline characteristics

	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe	1639 (35.1)	1657 (35.5)
North America	1401 (30.0)	1446 (31.0)
Asia	360 (7.7)	351 (7.5)
Rest of the world	1268 (27.2)	1218 (26.1)
HbA_{1c}, %	8.7 ± 1.6	8.7 ± 1.5
BMI, kg/m^2	32.5 ± 6.3	32.5 ± 6.3
Body weight, kg	91.9 ±21.2	91.6 ± 20.8
Systolic blood pressure, mmHg	135.9 ± 17.8	135.9 ± 17.7
Diastolic blood pressure, mmHg	77.2 ± 10.3	77.0 ± 10.1
Heart failure*, N (%) NYHA I,II,III.	835 (17.9)	832 (17.8)

Full analysis set. Data are means ± standard deviations or number of patients (percentage of either liraglutide-treated or placebo-treated group). Percentage data refer to proportion of patients. *Heart failure includes NYHA class I, II and III.
BMI, body mass index; HbA_{1c}, glycosylated haemoglobin; NYHA, New York Heart Association.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Primary outcome: Subgroup analyses

Subgroup	Hazard ratio (95% CI)	p-value for interaction	No. of patients	Liraglutide no. of events/no. of patients (%)	Placebo no. of events/no. of patients (%)
Primary analysis	**0.87 (0.78 ; 0.97)**		**9340**	**608/4668 (13.0)**	**694/4672 (14.9)**
Renal function		0.01			
<60 mL/min/1.73 m^2	**0.69 (0.57 ; 0.85)**		2158	172/1116 (15.4)	223/1042 (21.4)
>/=60 mL/min/1.73 m^2	0.94 (0.83 ; 1.07)		7182	436/3552 (12.3)	471/3630 (13.0)
Renal function		0.93			
<30 mL/min/1.73 m^2	0.89 (0.51 ; 1.54)		224	25/117 (21.4)	26/107 (24.3)
>/=30 mL/min/1.73 m^2	0.87 (0.77 ; 0.97)		9116	583/4551 (12.8)	668/4565 (14.6)



Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. Renal function was assessed by means of the estimated glomerular filtration rate, as calculated by the Modification of Diet in Renal Disease equation.
CI, confidence interval.
Marso SP et al. *N Engl J Med* 2016. In press.

Figure S4. Incident or worsening nephropathy with empagliflozin and placebo in patients with prevalent kidney disease defined as eGFR (MDRD) <60 mL/min/1.73m^2 and/or macroalbuminuria (urine albumin-to-creatinine ratio >300 mg/g) at baseline

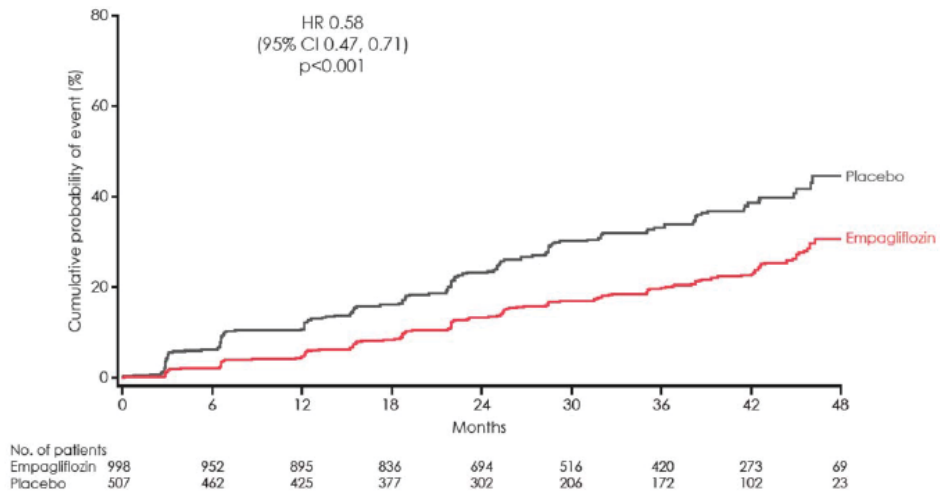


Figure S5. Composite of doubling of serum creatinine (accompanied by eGFR [MDRD] ≤45 ml/min/1.73m^2), initiation of renal replacement therapy, or death due to renal disease in patients with macroalbuminuria (urine albumin-to-creatinine ratio >300 mg/g) at baseline