Effetti cardiovascolari dei GLP-1 RA

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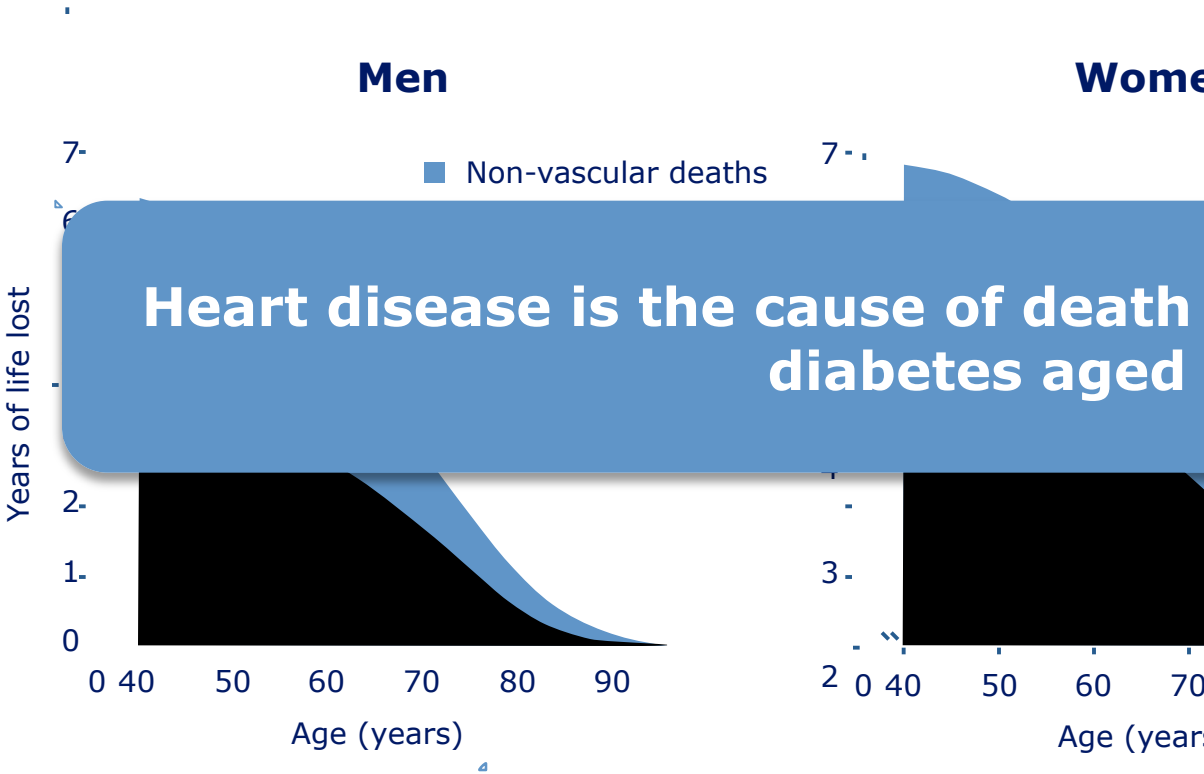
Conflitti di interesse

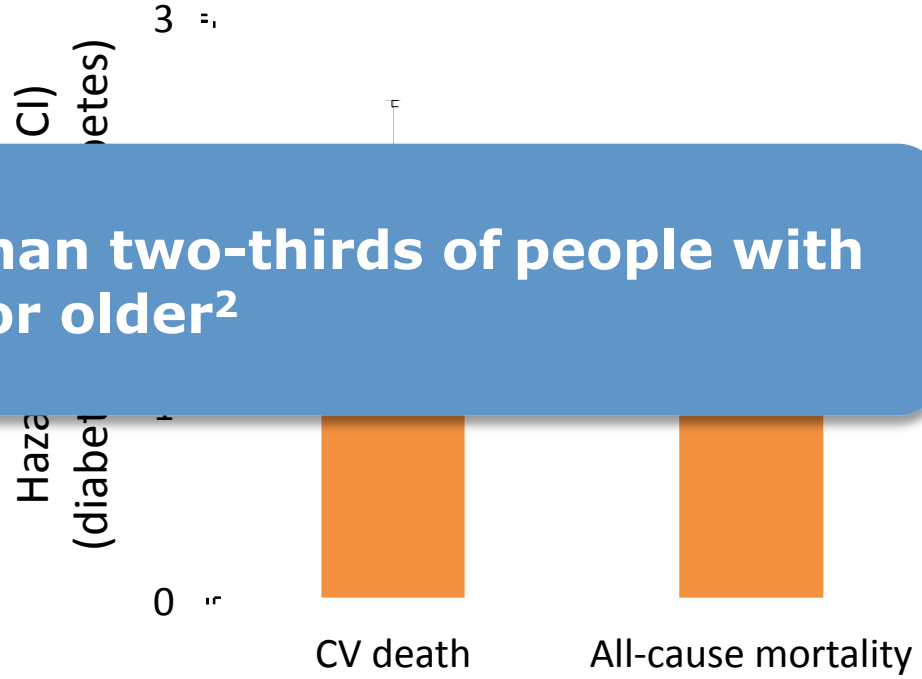
- Ai sensi dell'art. 3.3 sul conflitto di interessi, pag 17 del Regolamento Applicativo Stato-Regioni del 5/11/2009, dichiaro che negli ultimi 2 anni ho avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:
- Astra Zeneca, Boehringer, Bruno Farmaceutici, Eli Lilly, Lifescan, Menarini, Merck, Pharmexctrata, Novo Nordisk, Novartis, Sanofi, Takeda

CVD is the leading cause of death among people with diabetes

Years of life lost in people with diabetes* compared with non-diabetes peers[1]



Mortality risk associated with diabetes (n=820,900)[1]



Heart disease is the cause of death in more than two-thirds of people with diabetes aged 65 years or older[2]

In high-income countries, up to 91% of adults with diabetes have type 2 diabetes[3]

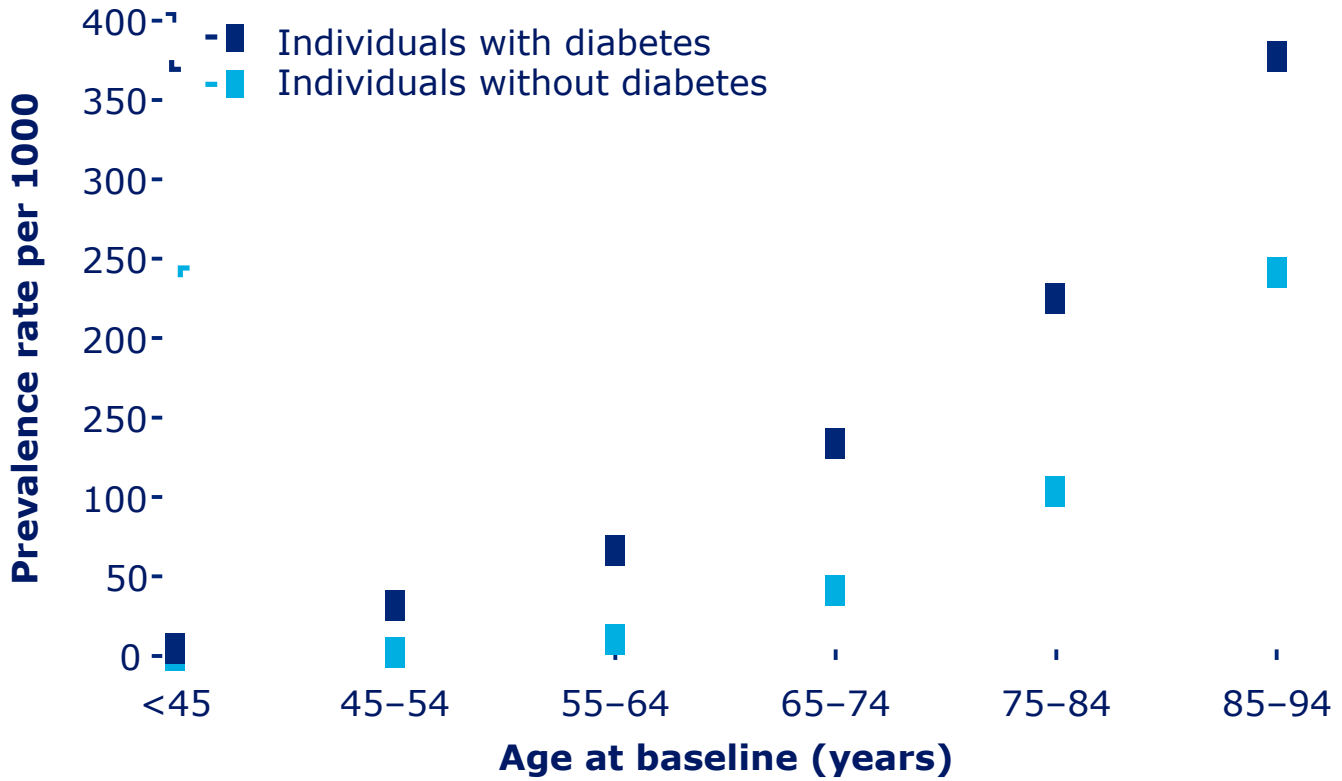
*Information on diabetes type (i.e., type 1 or 2) was generally not available, although the age of the participants suggests that the large majority with diabetes would have type 2.
CI, confidence interval; CV, cardiovascular; CVD, cardiovascular disease.

1. Seshasai SR et al. *N Engl J Med* 2011;364:829–841; 2. Centers for Disease Control and Prevention. National Diabetes Fact Sheet 2011. Available at: http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf; 3. International Diabetes Federation. *IDF Diabetes Atlas, 7th edn.* Brussels, Belgium: International Diabetes Federation, 2015. Available at: http://www.diabetesatlas.org.

Heart failure and diabetes

- Data from **The Framingham Study**[1] from 1974 suggest that “diabetes is another discrete cause of congestive heart failure and that some form of cardiomyopathy is associated with diabetes, as a result of either small vessel disease or metabolic disorders.”

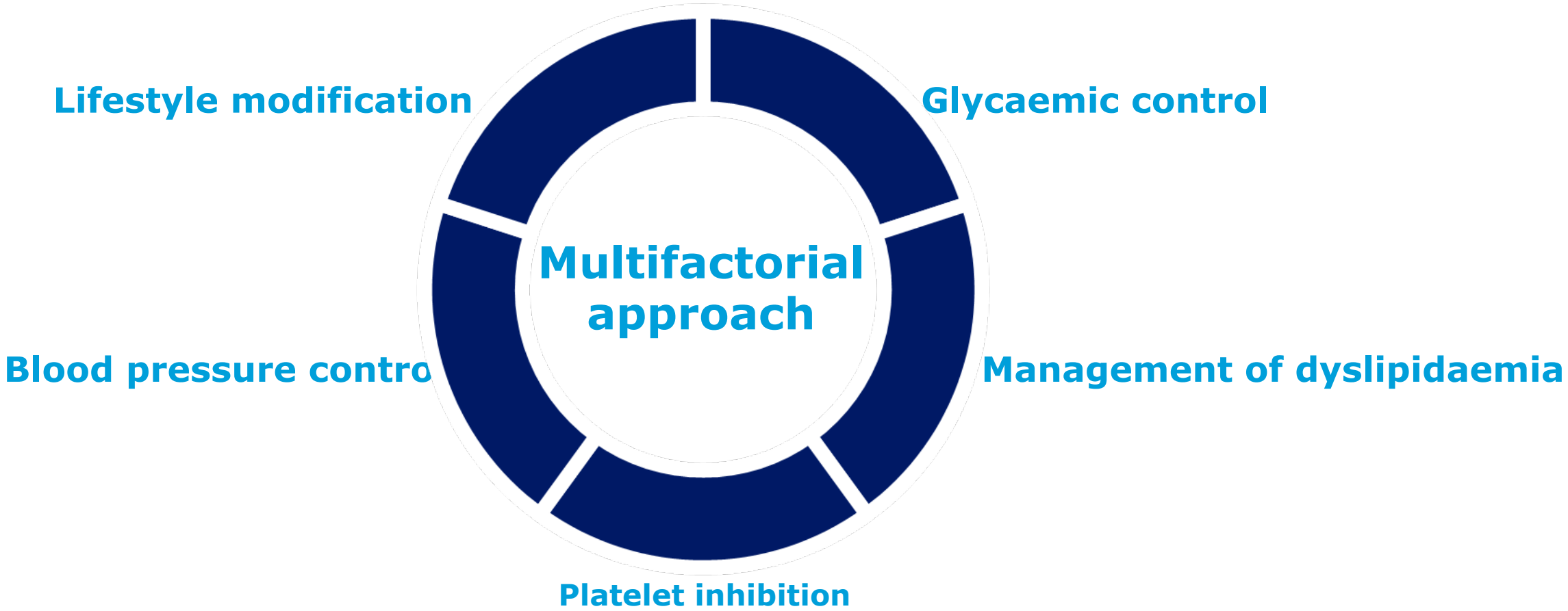
Age-associated prevalence of heart failure[2]



Diabetes is a predictor of poor clinical outcomes in HF patients[3]

1. Kannel WB *et al. Am J Cardiol* 1974;34:29–34; 2. Gilbert RE, Krum H. *Lancet* 2015;385:2107–21; 3. Bauters C *et al. Cardiovasc Diabetol*. 2003;2:1.

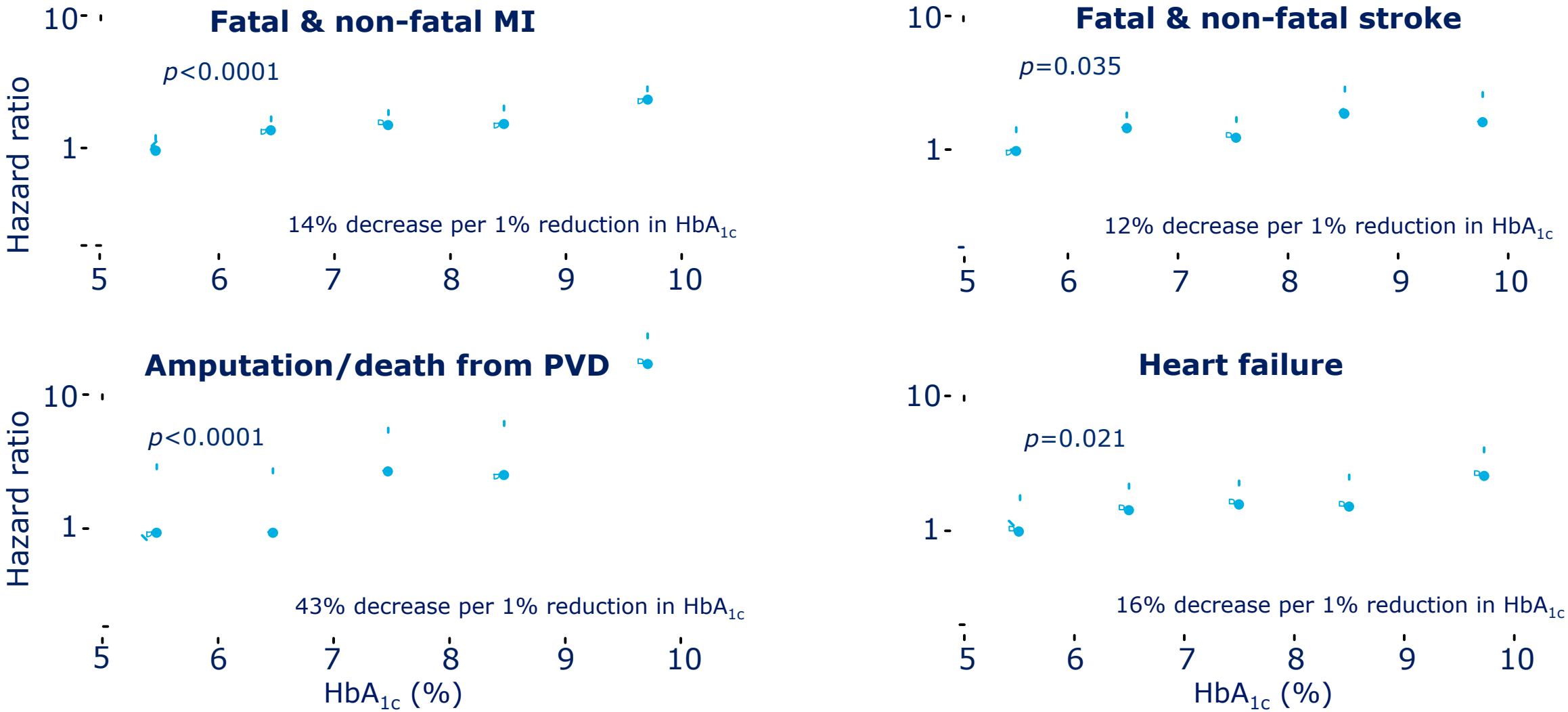
How do we modify CV risk in T2DM?



CV, cardiovascular; T2DM, type 2 diabetes mellitus.

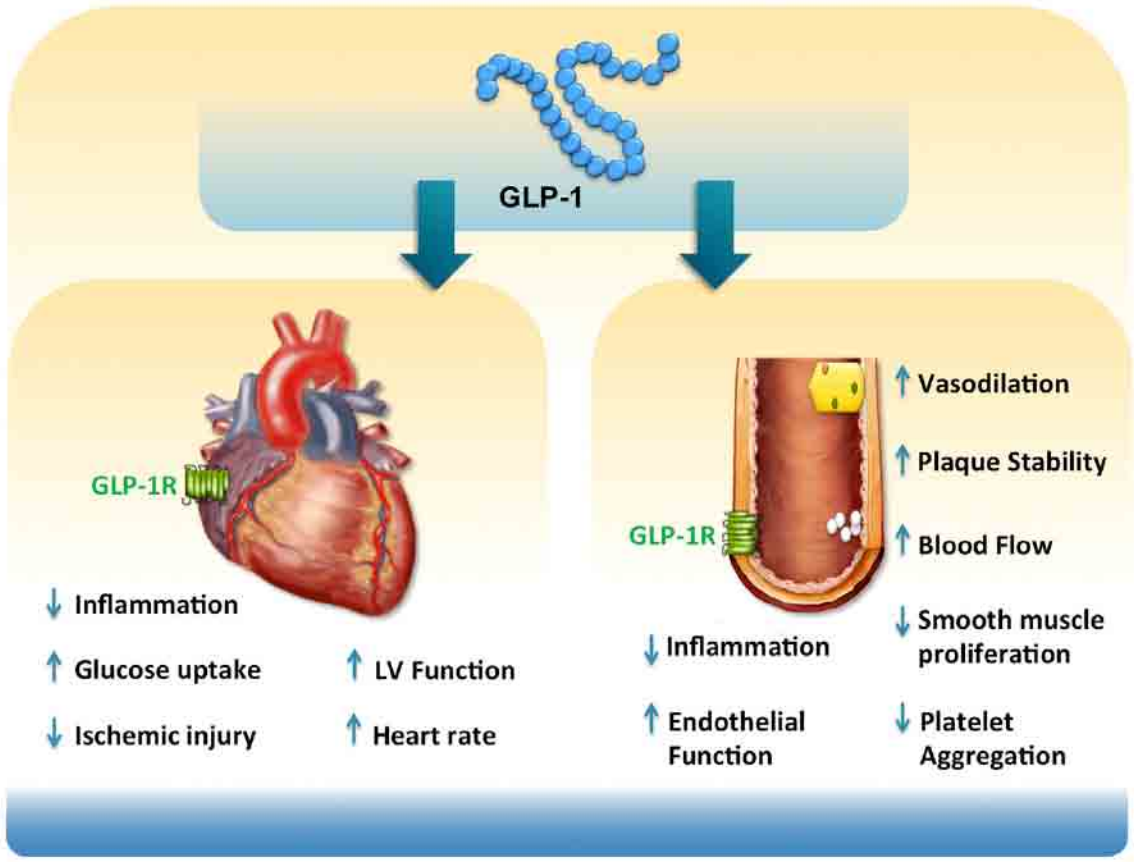
1. Rydén L et. Al. *Eur Heart J*. 2013 Oct;34(39):3035-87. 2. Fox CS et. al. *Diabetes Care* 2015 Sep;38(9):1777-803. 3. Piepoli MF et. al. *Eur Heart J*. 2016 May 23. pii: ehw106. [Epub ahead of print]

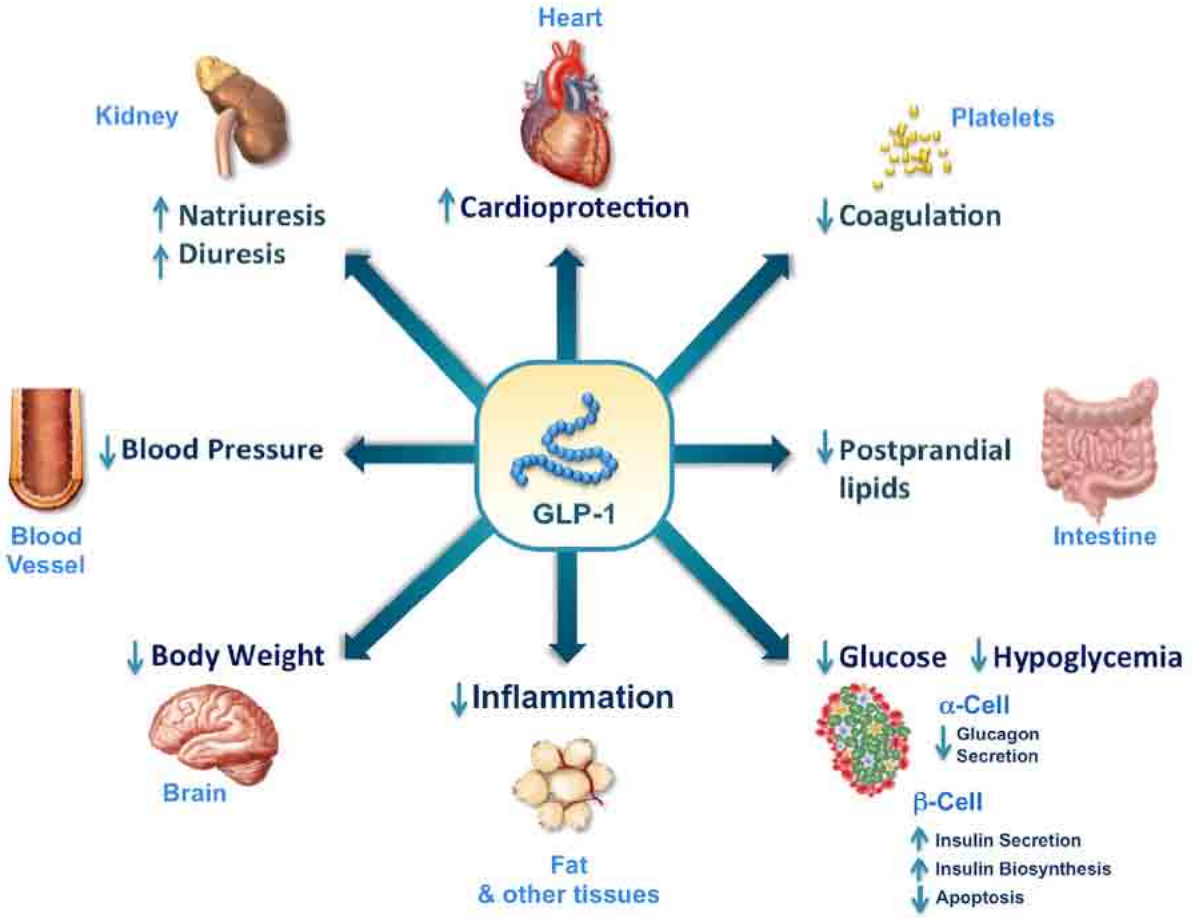
Higher HbA_{1c} predicts higher CV risk



Reference category (hazard ratio 1.0) is HbA_{1c} <6% with log linear scales.
CV, cardiovascular; HbA_{1c}, glycosylated haemoglobin; MI, myocardial infarction; PVD, peripheral vascular disease.
Stratton IM et al. *BMJ* 2000;321:405–412.

GLP-1: Beyond glucose metabolism

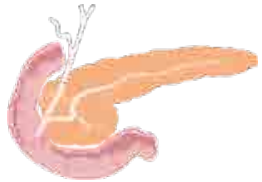




Drucker DJ, *Cell Metabolism* 2016; Epub ahead of print. DOI: http://dx.doi.org/10.1016/j.cmet.2016.06.009
Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany

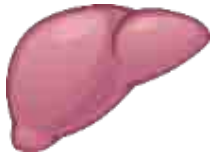
Cardiovascular actions of GLP-1 in T2DM

METABOLIC EFFECTS



↑ B-cell function

↑ Insulin secretion



↓ Glucose output

↓ Appetite

↓ Gastric emptying

IN

DIRECT CV EFFECTS

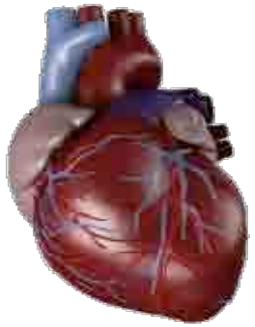
↑ Heart rate

↓ **Endothelial dysfunction**

↓ **Vessel inflammation**

↓ **Atherosclerosis**

↑ Cardiac function



GLP-1 effect on known risk factors for CVD

↓ Glucose ↓ Hypertension ↓ Dyslipidaemia ↓ Obesity

GLP-1, glucagon-like peptide-1; T2DM, type 2 diabetes mellitus

Adapted from Meier JJ et al. *Nat Rev Endocrinol* 2012;8:728–742; Nyström T et al. *Am J Physiol Endocrinol Metab* 2004;287:E1209−E1215; Song X et al. *Sci Rep* 2015;26:10202.

Recent and ongoing cardiovascular outcomes trials

Pre-approval | Post-approval

PIONEER 6
(Oral semaglutide, QD)
n=3,176; duration ~2 yrs
completion Q2 2018

SUSTAIN 6
(Semaglutide, GLP-1RA)
n=3,297; duration ~2.0 yrs
Q1 2016 – TOPLINE RESULTS

CANVAS-R
(Canagliflozin, SGLT2i)
n=5,700; duration ~3 yrs
completion Q2 2017

REWIND
(Dulaglutide, QW GLP-1RA)
n=9,622; duration ~6.5 yrs
completion Q2 2019

ALECARDIO (terminated)
(Aleglitazar, PPAR-αγ)
n=7,226; duration 2.0 yrs
Q3 2013 – **RESULTS**

EMPA-REG OUTCOME
(Empagliflozin, SGLT2i)
n=7,028; duration 3.1 yrs
Q2 2015 – **RESULTS**

CANVAS
(Canagliflozin, SGLT2i)
n=4,330; duration 4+yrs
completion Q2 2018

CREDENCE (cardio-renal)
(Canagliflozin, SGLT2i)
n=3,700; duration ~5.5 yrs
completion Q1 2019

NCT01986881
(Ertugliflozin, SGLT2i)
n=3,900; duration ~6.3 yrs
completion Q3 2021

EXAMINE
(Alogliptin, DPP4i)
n=5,380; duration 1.5 yrs
Q3 2013 – **RESULTS**

ELIXA
(Lixisenatide, GLP-1RA)
n=6,000; duration 2.1 yrs
Q1 2015 – **RESULTS**

FREEDOM
(ITCA 650, GLP-1RA in DUROS)
n=4,000; duration ~2 yrs
Q1 2016 – TOPLINE RESULTS

DECLARE-TIMI-58
(Dapagliflozin, SGLT2i)
n=17,150; duration~6 yrs
completion Q2 2019

SAVOR TIMI-53
(Saxagliptin, DPP4i)
n=16,492; duration 2.1 yrs
Q2 2013 – **RESULTS**

LEADER
(Liraglutide, GLP-1RA)
n=9,340; duration 3.5–5 yrs
Q4 2015 – **RESULTS**

EXSCEL
(Exenatide ER, QW GLP-1RA)
n=14,000; duration ~7.5 yrs
completion Q2 2018

DEVOTE
(Insulin degludec, insulin)
n=7,500; duration ~5 yrs
completion Q1 2019

HARMONY OUTCOME
(Albiglutide, QW GLP-1RA)
n~5,000; duration ~4 yrs
completion Q2 2019

TECOS
(Sitagliptin, DPP4i)
n=14,000; duration 3 yrs
Q4 2014 – **RESULTS**

CARMELINA
(Linagliptin, DPP4i)
n=8,300; duration ~4 yrs
completion Q1 2018

CAROLINA
(Linagliptin, DPP4i vs SU)
n=6,000; duration ~8 yrs
completion Q3 2018

NCT01703208
(Omarigliptin, QW DPP4i)
n=4,000; duration ~3 yrs
completion Q3 2019

2013 **2014** **2015** **2016** **2017** **2018** **2019** **2020** **2021**

As of May 2016

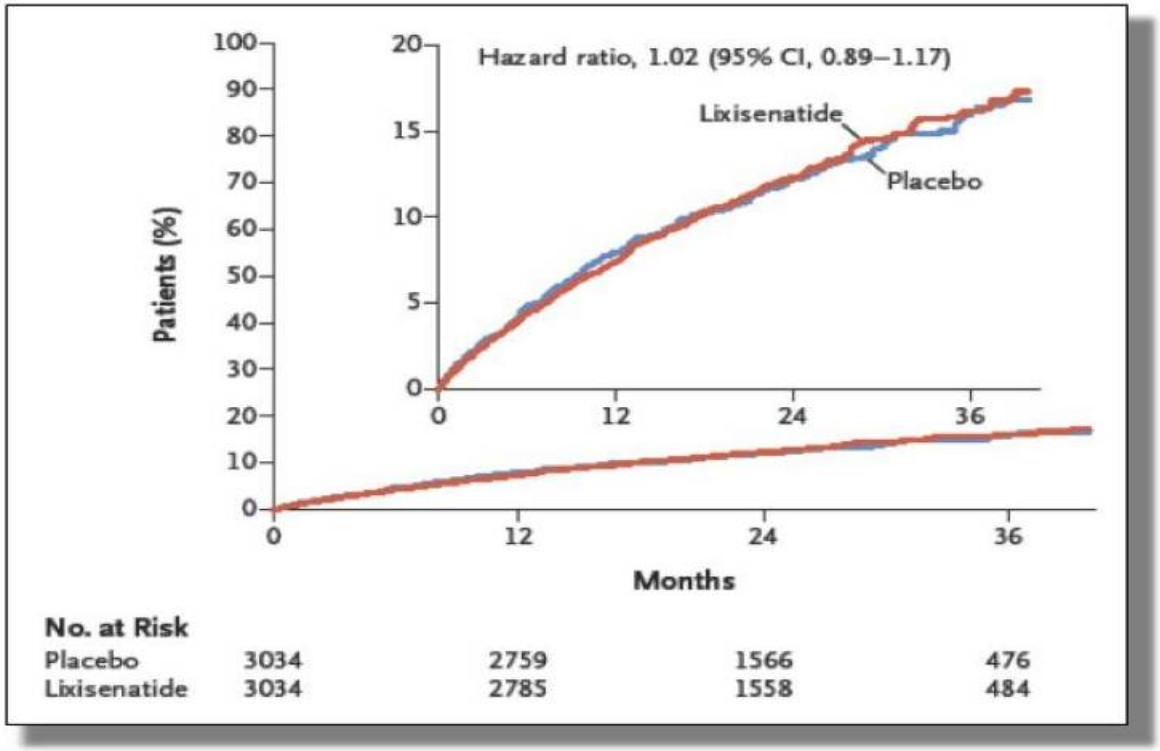
GLP1 RA and MACE

- Three cardiovascular outcome studies with different GLP1 RA and different trial population were recently published
- All the three trials (Elixa, Leader and Sustain) reached their principal endpoint (non inferiority versus placebo) with respect to major cardiovascular events
- In one of the trials, no difference across treatment groups was observed for the principal endpoint or any pre-defined secondary end point, whereas in the other two studies the incidence of major cardiovascular events was significantly reduced in the active treatment group.
- These results raised important questions about the possibility of a class effect of GLP1 receptor agonists on cardiovascular risk
- Population enrolled in CVOTs were notably different, with trials with liraglutide and semaglutide including a majority of subjects with established CVD and the trial with lixisenatide enrolling patients with a recent coronary event
- This three moleculese differ for kinetic and chemical structure: lixisenatide is a short acting analogue of exenatide, with a low homology to human GLP 1, liraglutide and semaglutide are long acting GLP 1 RA with an aminoacid sequence almost identical to the human GLP1

Elixa

Lixisenatide: effect on major cardiovascular events

Results of the ELIXA trial



Principal endpoint:
4-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death, hospitalization for unstable angina)

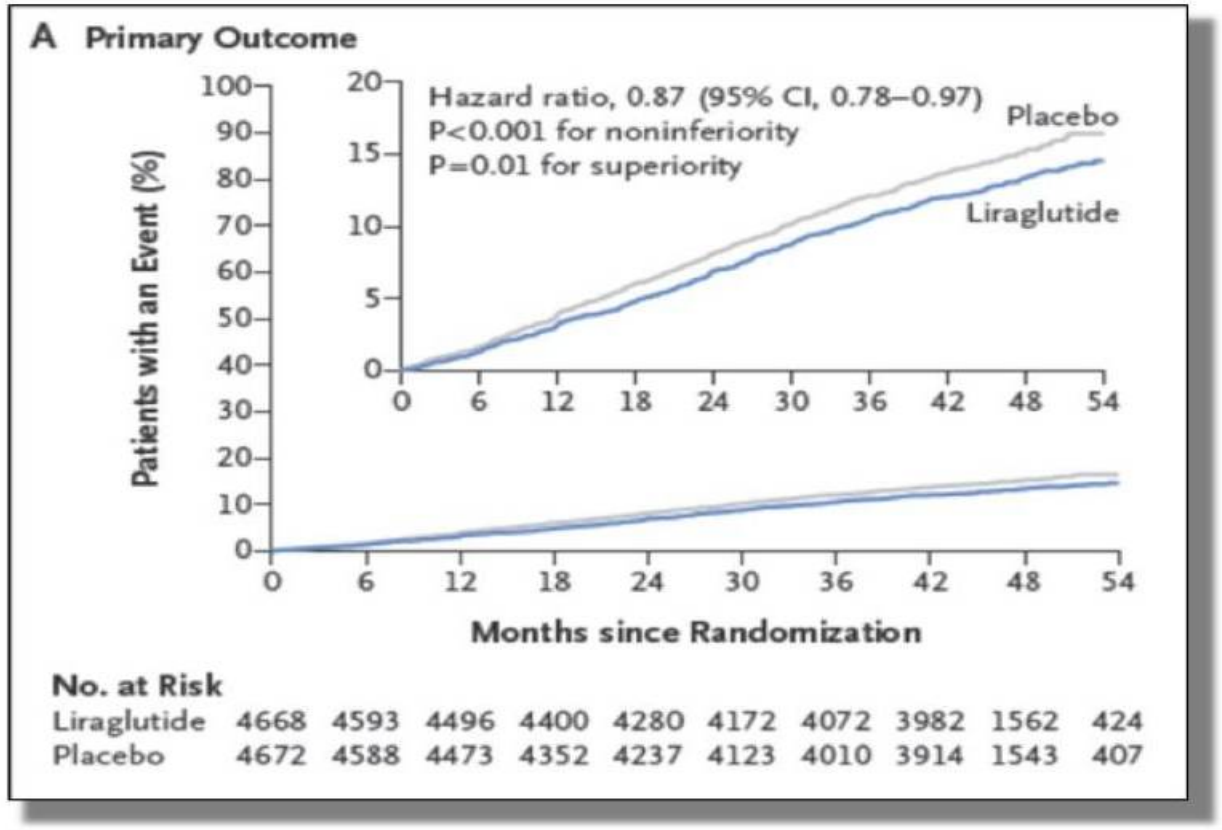
6068 T2DM patients with recent acute coronary syndrome, lixisenatide vs placebo 1:1.
Follow-up: 2.1 y

Pfeffer MA et al. *N Engl J Med* 373: 2247-57, 2015

Leader

Liraglutide: effect on major cardiovascular events

Results of the LEADER trial



Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

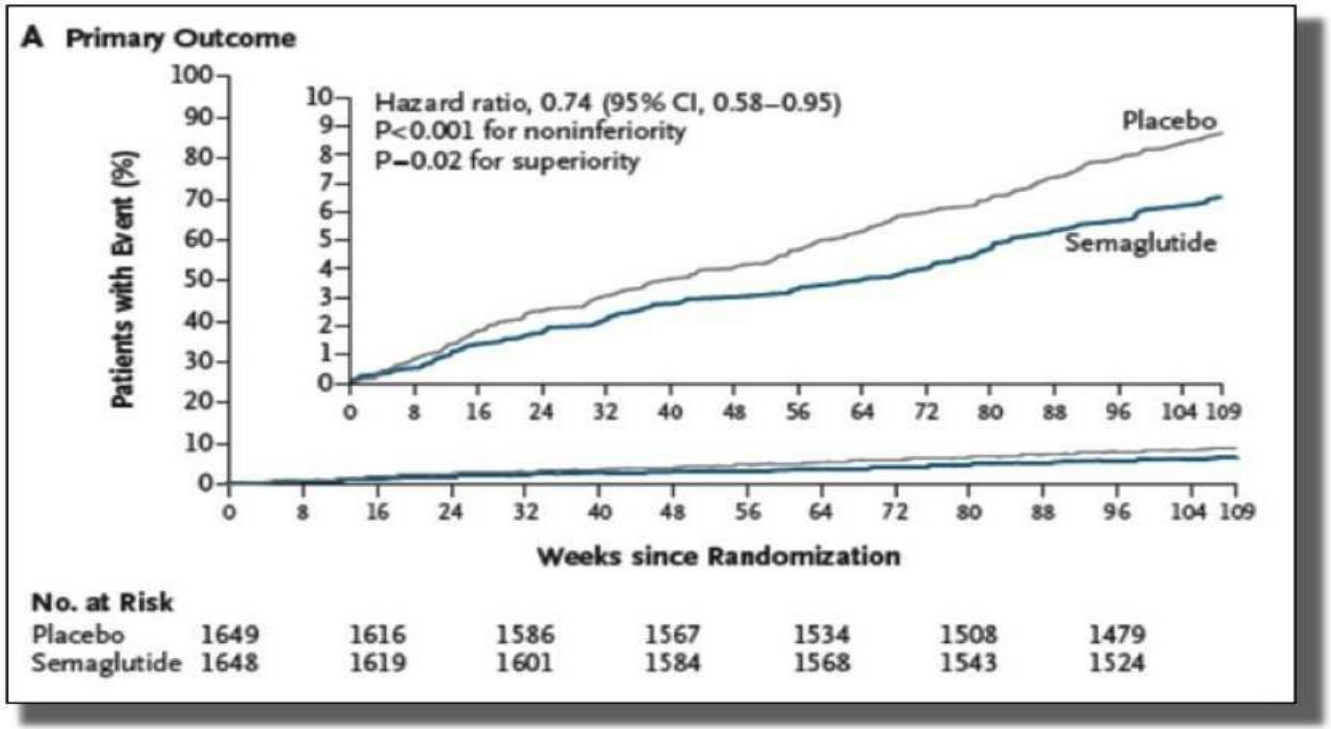
9,340 T2DM patients with prior cardiovascular disease and/or high CV risk, Liraglutide vs placebo 1:1.
Follow-up: 4 y

Marso SP et al. *N Engl J Med* 375: 311-22, 2016

Sustain

Semaglutide: effect on major cardiovascular events

Results of the SUSTAIN-6 trial

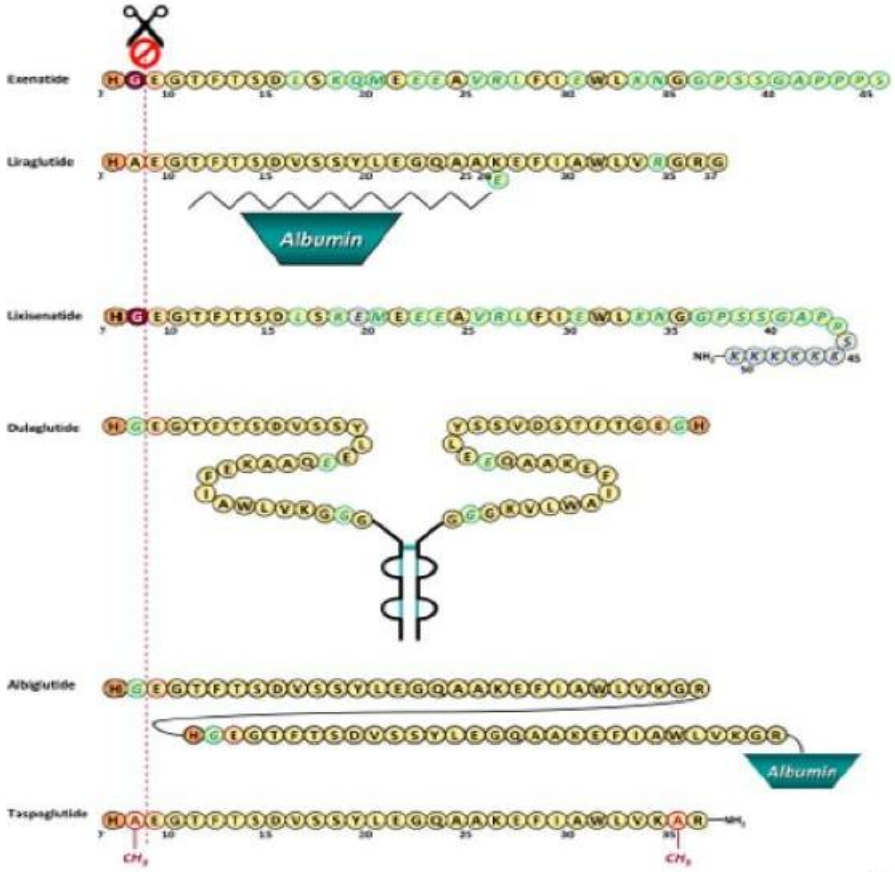


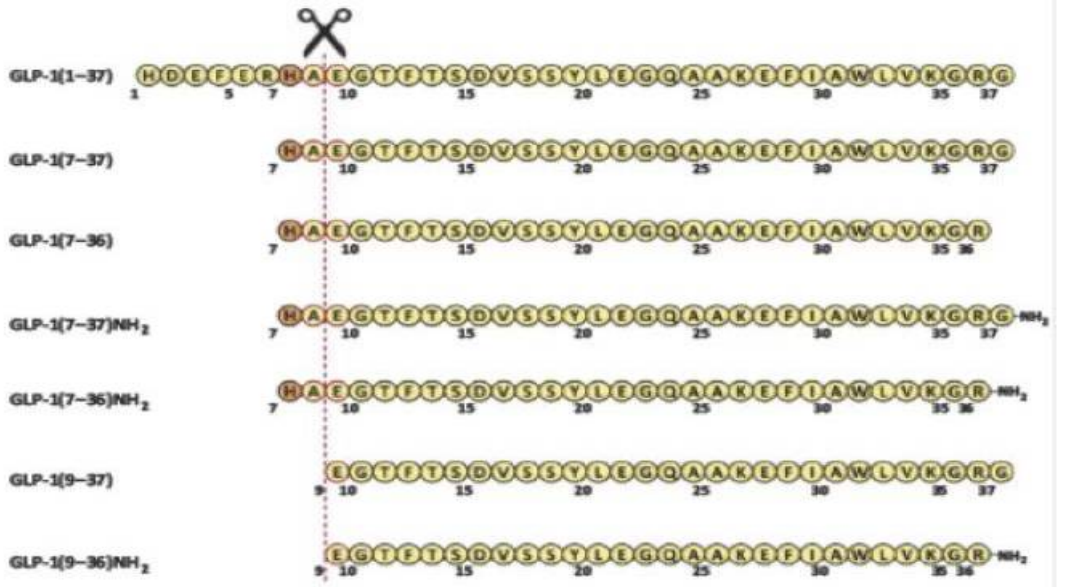
Principal endpoint:
3-point MACE
(nonfatal MI, nonfatal stroke, and cardiovascular death)

3,297 T2DM patients with prior cardiovascular disease and/or high CV risk, Semaglutide vs placebo 1:1.
Follow-up: 2 y

Marso SP et al. *N Engl J Med* 375: 1834-44, 2016

GLP1 receptor agonists





Cantini G, Mannucci E, Luconi M. *Trends Endocrinol Metab* 27: 427-38, 2016.

Adv Ther (2017) 34:1–40
DOI 10.1007/s12325-016-0432-4
REVIEW

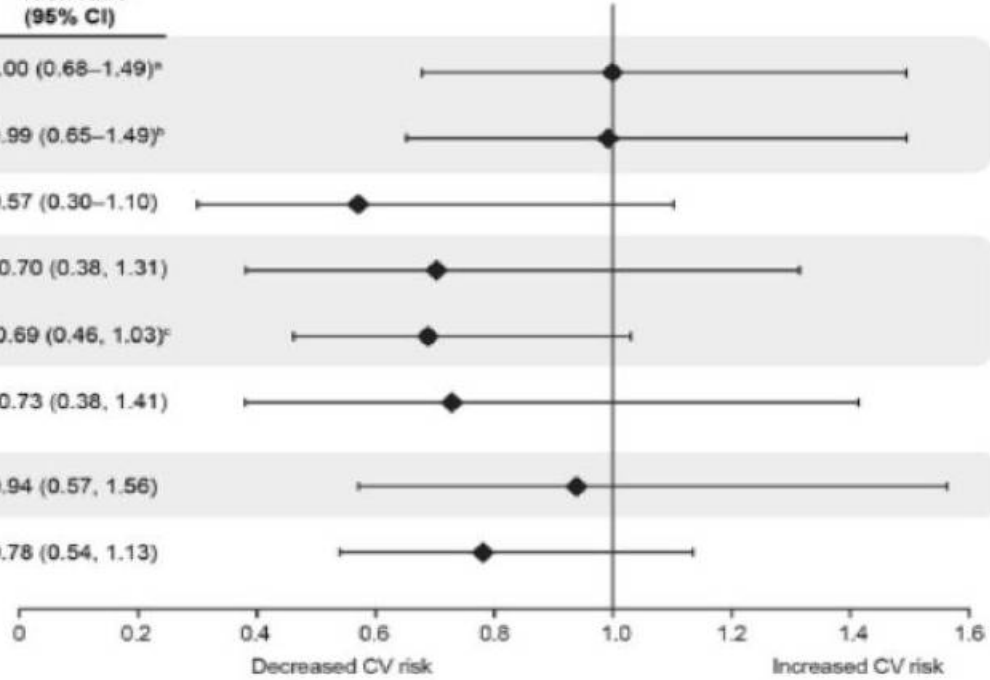
Cardiovascular Safety of Incretin-Based Therapies in Type 2 Diabetes: Systematic Review of Integrated Analyses and Randomized Controlled Trials

Edoardo Mannucci · Matteo Monami

GLP1RA: effect on major cardiovascular events

Pooled analyses of phase 2-3 trials

Drug [Reference]	Type of analysis	Primary statistical analysis	Number of patients	Risk ratio (95% CI)
Albiglutide [53]	Pooled analysis	Cox proportional hazards	5107	1.00 (0.68–1.49)[a] 0.99 (0.65–1.49)[b]
Dulaglutide [54]	Pooled analysis	Cox proportional hazards	6010	0.57 (0.30–1.10)
Exenatide twice daily [51]	Pooled analysis	Mantel–Haenszel RR	3945	0.70 (0.38, 1.31) 0.69 (0.46, 1.03)[c]
Liraglutide [50]	Pooled analysis	Incidence ratios estimated by Cochran–Mantel–Haenszel	6638	0.73 (0.38, 1.41)
Taspoglutide [52]	Pooled analysis	Peto fixed-effects OR	7056	0.94 (0.57, 1.56)
GLP-1 receptor agonists [12]	Meta-analysis	Mantel–Haenszel OR	12475	0.78 (0.54, 1.13)

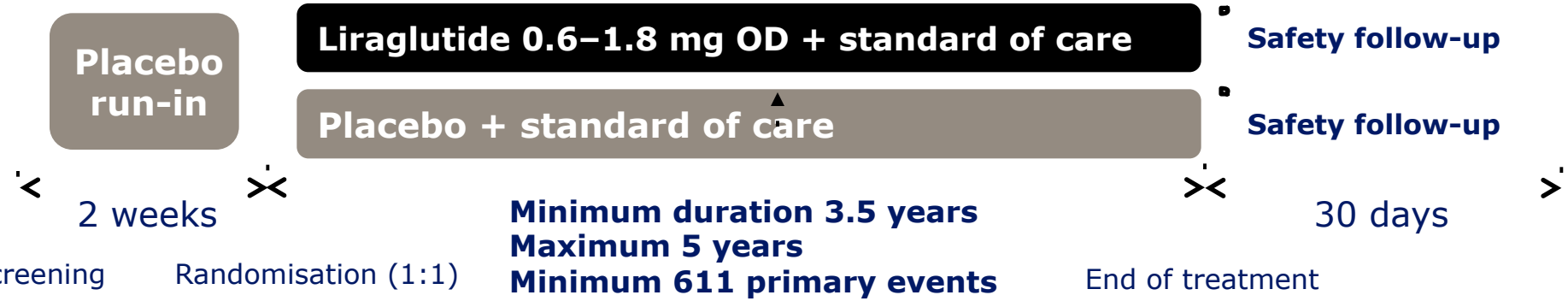


Mannucci E, Monami M. *Adv Ther* 34:1-40, 2017

LEADER: study design

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

CV, cardiovascular; HbA1c, glycosylated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T2DM, type 2 diabetes mellitus.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Primary and key secondary outcomes

Primary outcome

Time to first MACE composed of:

- CV death
- Non-fatal MI
- Non-fatal stroke

Key secondary outcomes

Time to first occurrence of:

- Expanded composite CV outcome
- All-cause death
- Clinical and metabolic outcomes
- Microvascular outcomes
- Safety outcomes

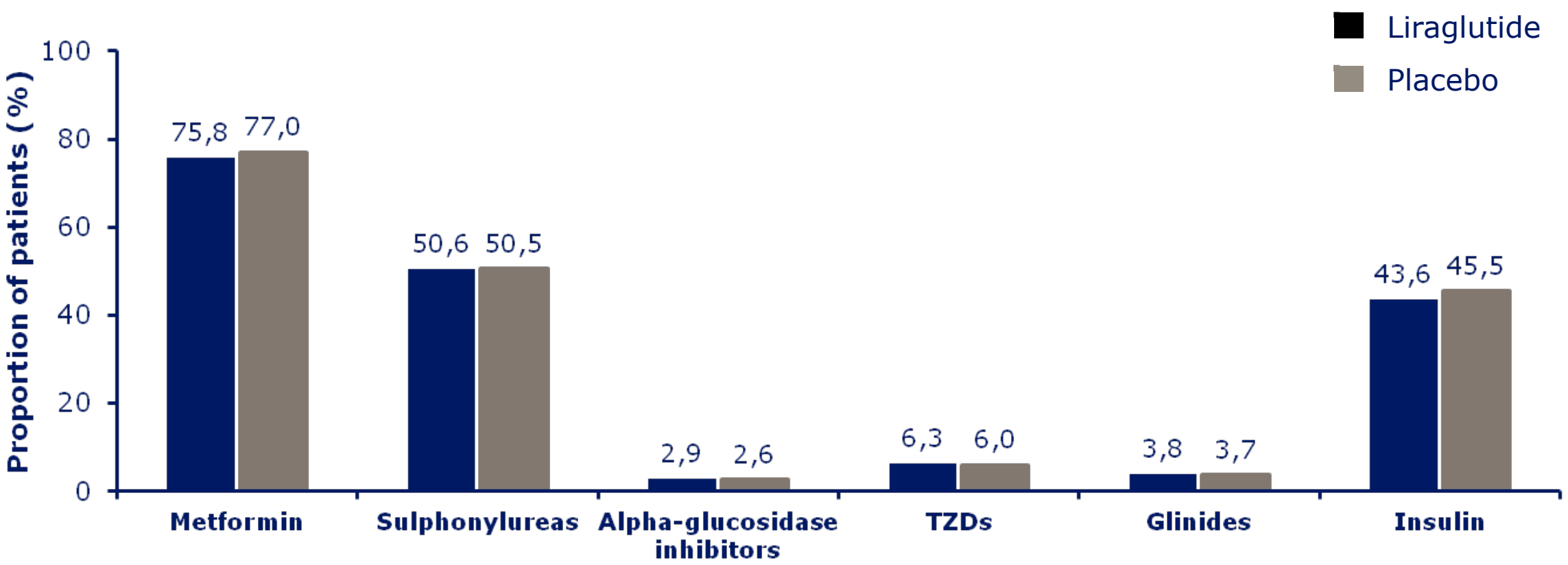
CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

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, N (%)		
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 (%)	835 (17.9)	832 (17.8)

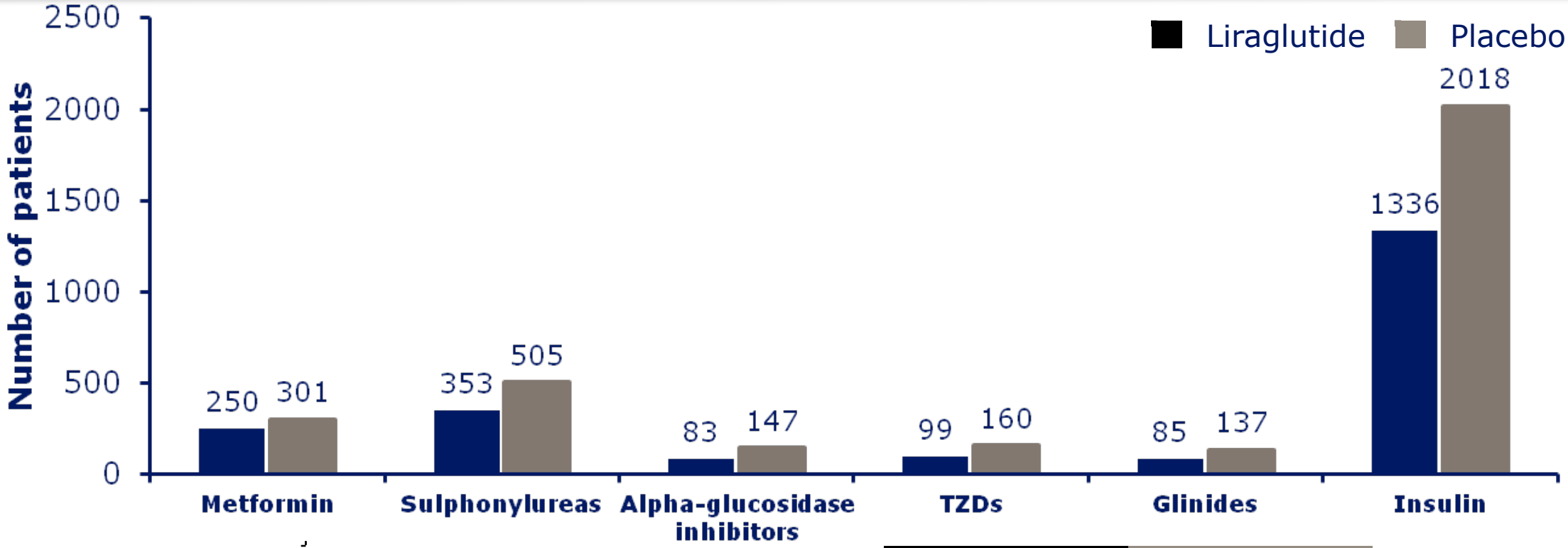
Full analysis set. Data are means ± standard deviations or number of patients (percentage of either liraglutide-treated or placebo-treated group).
Percentage data refer to proportion of patients. *Heart failure includes NYHA class I, II and III.
BMI, body mass index; HbA_{1c}, glycosylated haemoglobin; NYHA, New York Heart Association.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Antihyperglycaemic medication at baseline



TZD, thiazolidinedione.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

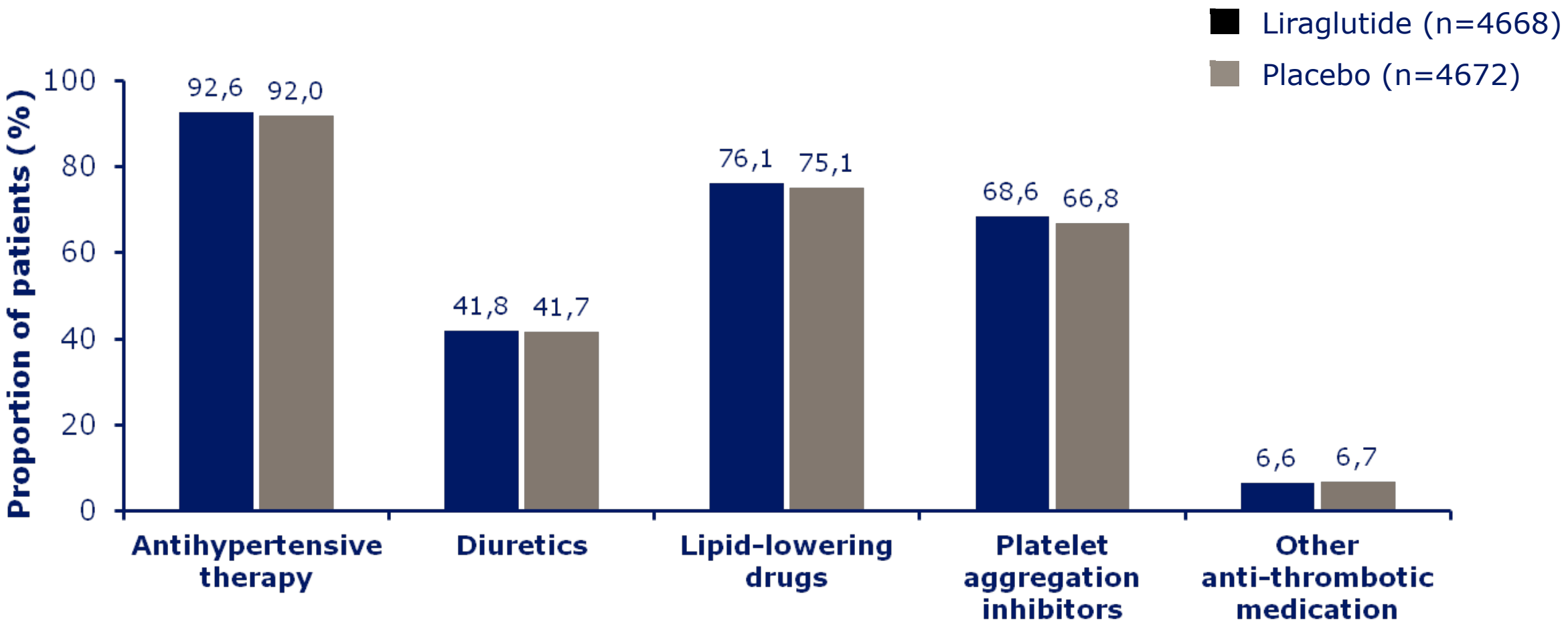
Antihyperglycaemic medications introduced during trial



Additional classes added	Liraglutide	Placebo
DPP-4 inhibitors	149	170
GLP-1RAs	87	139
SGLT-2 inhibitors	100	130

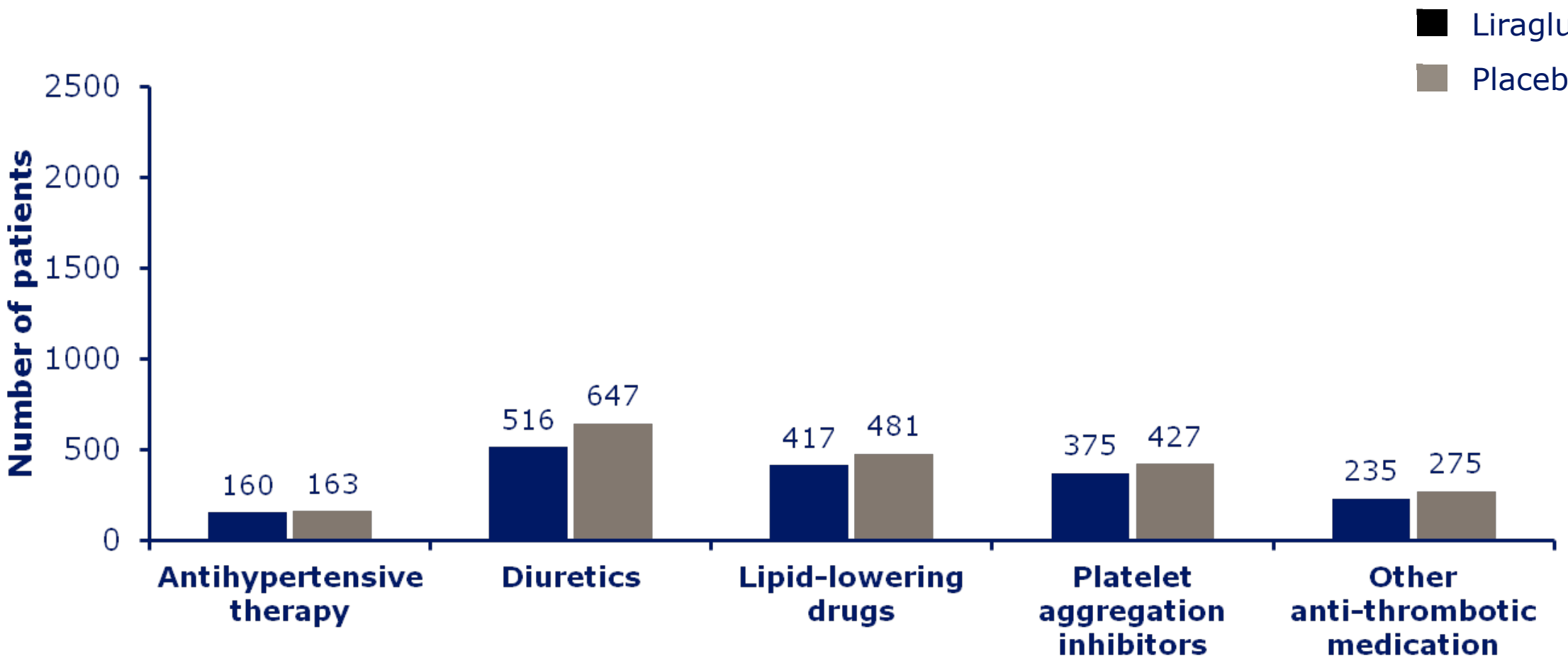
DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT-2, sodium-glucose co-transporter-2; TZD, thiazolidinedione.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Cardiovascular medication at baseline



Marso SP et al. *N Engl J Med*. 2016;375:311-22.

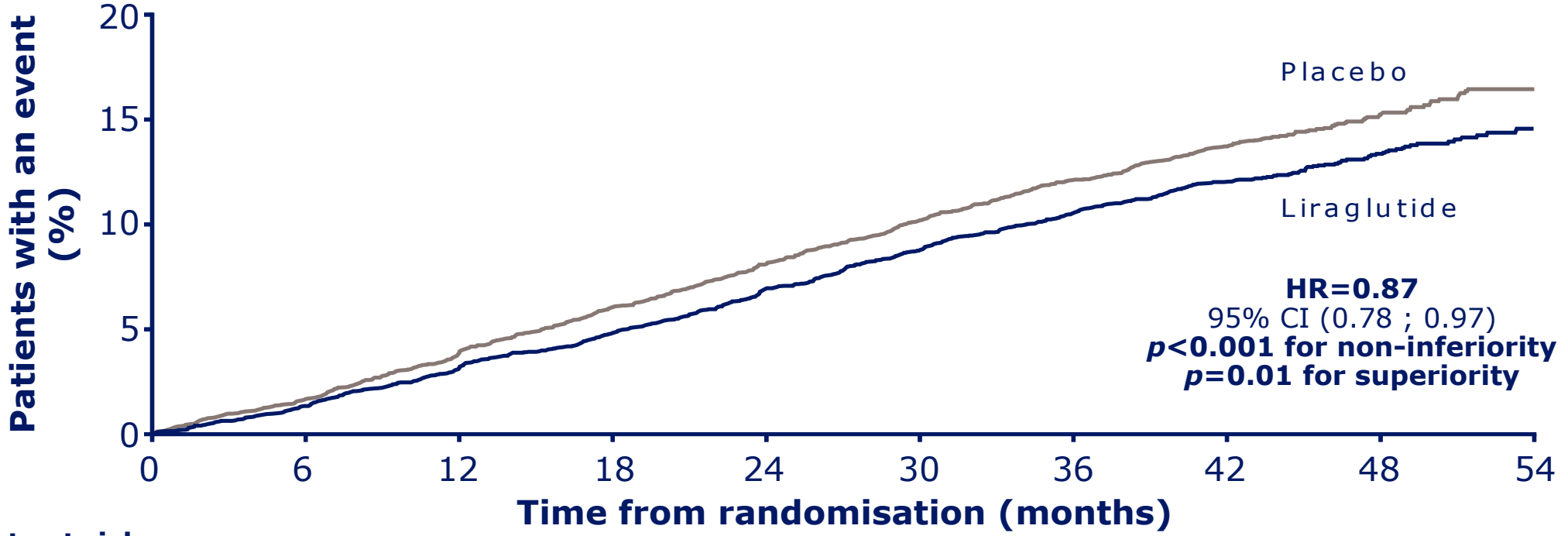
Cardiovascular medication introduced during trial



Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Primary outcome

CV death, non-fatal MI, non-fatal stroke

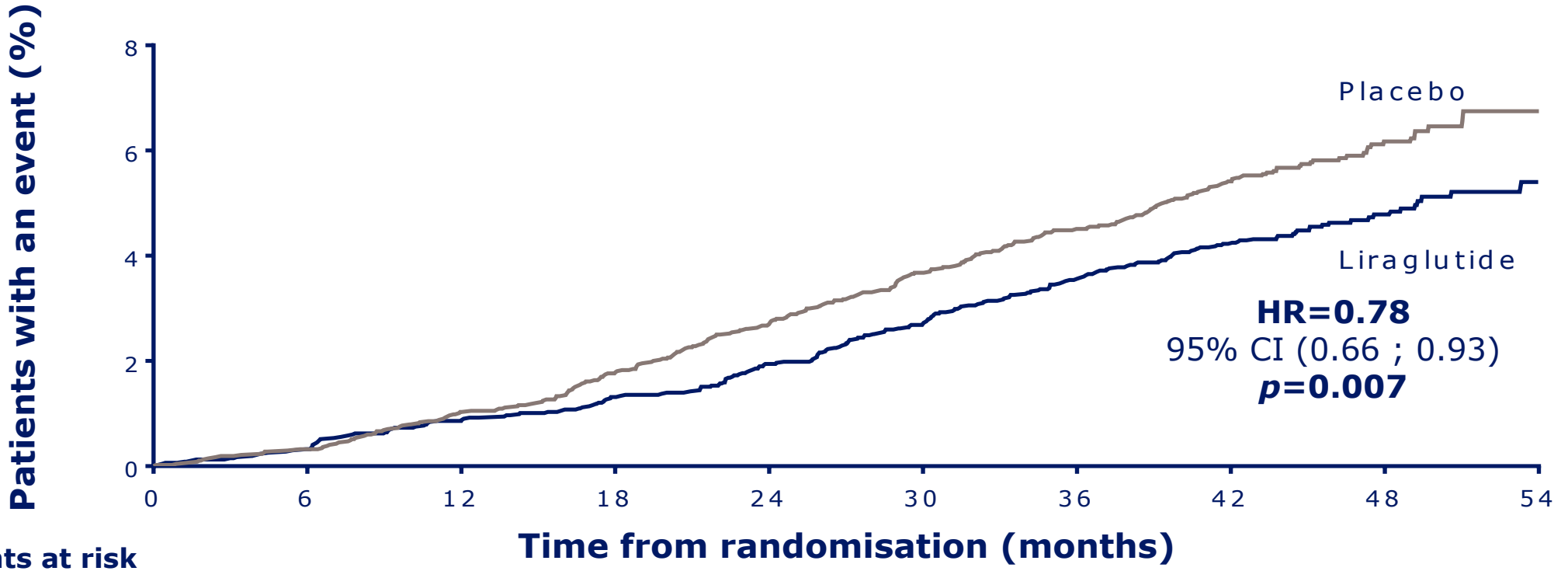


Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

CV death

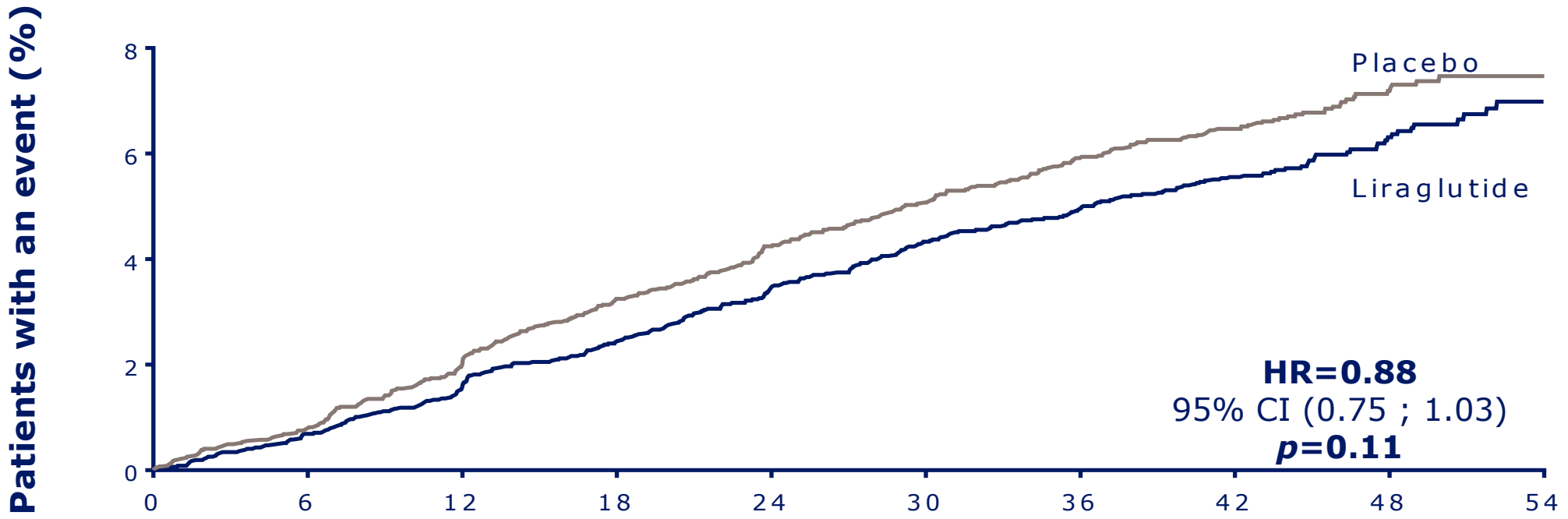


Patients at risk

Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4267	1709	465

CI, confidence interval; CV, cardiovascular; HR, hazard ratio.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Non-fatal myocardial infarction

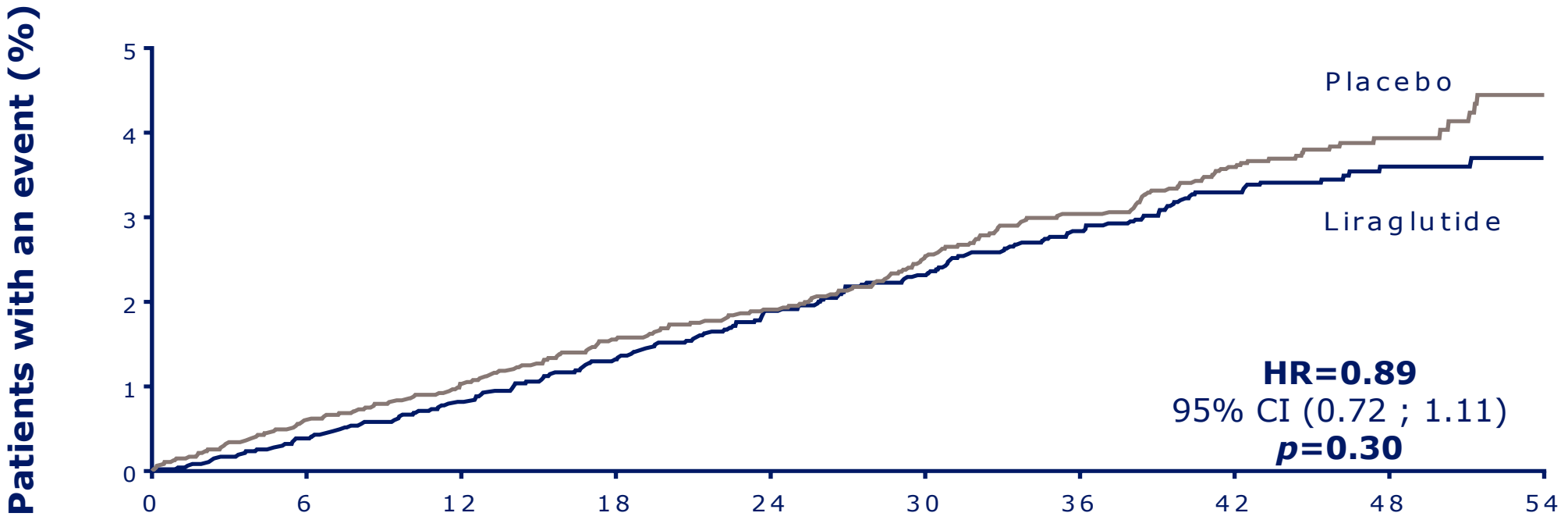


Patients at risk

Liraglutide	4668	4609	4531	4454	4359	4263	4181	4102	1619	440
Placebo	4672	4613	4513	4407	4301	4202	4103	4020	1594	424

CI, confidence interval; HR, hazard ratio.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

Non-fatal stroke



Patients at risk

Liraglutide	4668	4624	4564	4504	4426	4351	4269	4194	1662	465
Placebo	4672	4622	4558	4484	4405	4314	4228	4141	1648	445

CI, confidence interval; HR, hazard ratio.
Marso SP et al. *N Engl J Med*. 2016;375:311-22.

LEADER: Baseline characteristics

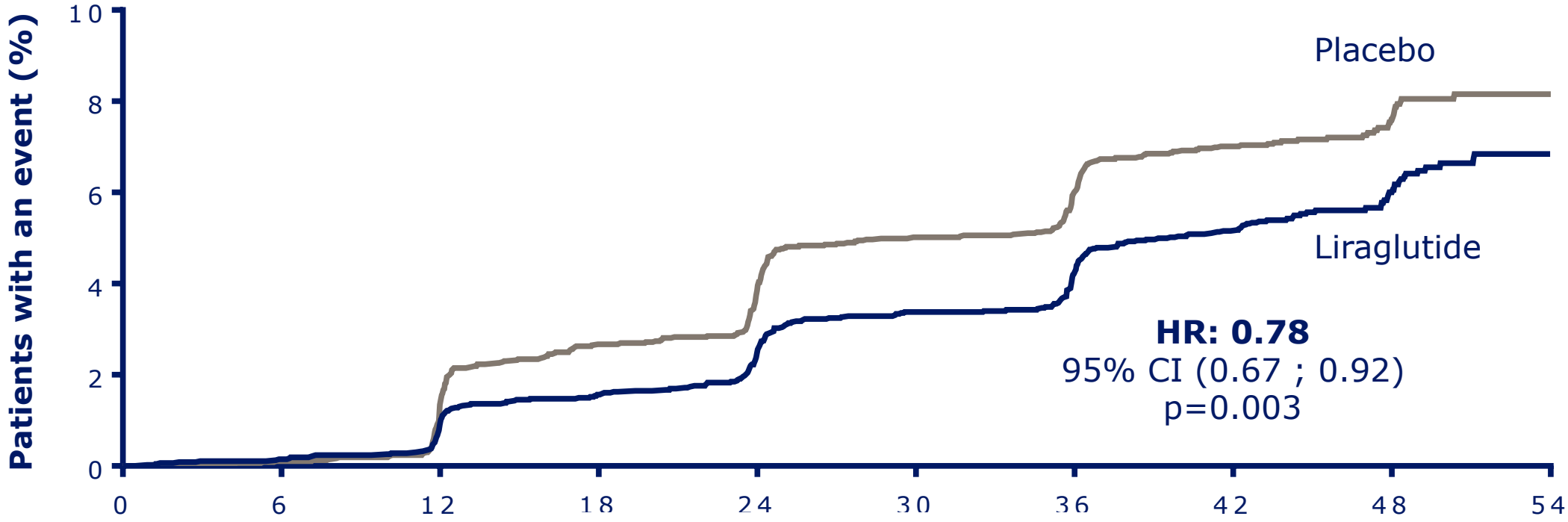
	Liraglutide (N=4668)	Placebo (N=4672)
Male sex, N (%)	3011 (64.5)	2992 (64.0)
Age, years	64.2 ± 7.2	64.4 ± 7.2
Diabetes duration, years	12.8 ± 8.0	12.9 ± 8.1
Geographic region		
Europe		.5)
North America		.0)
Asia		.5)
Rest of the world		.1)
HbA_{1c}, %		.5
BMI, kg/m^2		.3
Body weight, kg		.8
Systolic 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 (%)	835 (17.9)	832 (17.8)

	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 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; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin; NYHA, New York Heart Association.
Marso SP et al. *N Engl J Med* 2016;375:311–322; presented at ASN Kidney Week, 19 November 2016, Chicago, USA

LEADER: Time to first renal event

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



Patients at risk

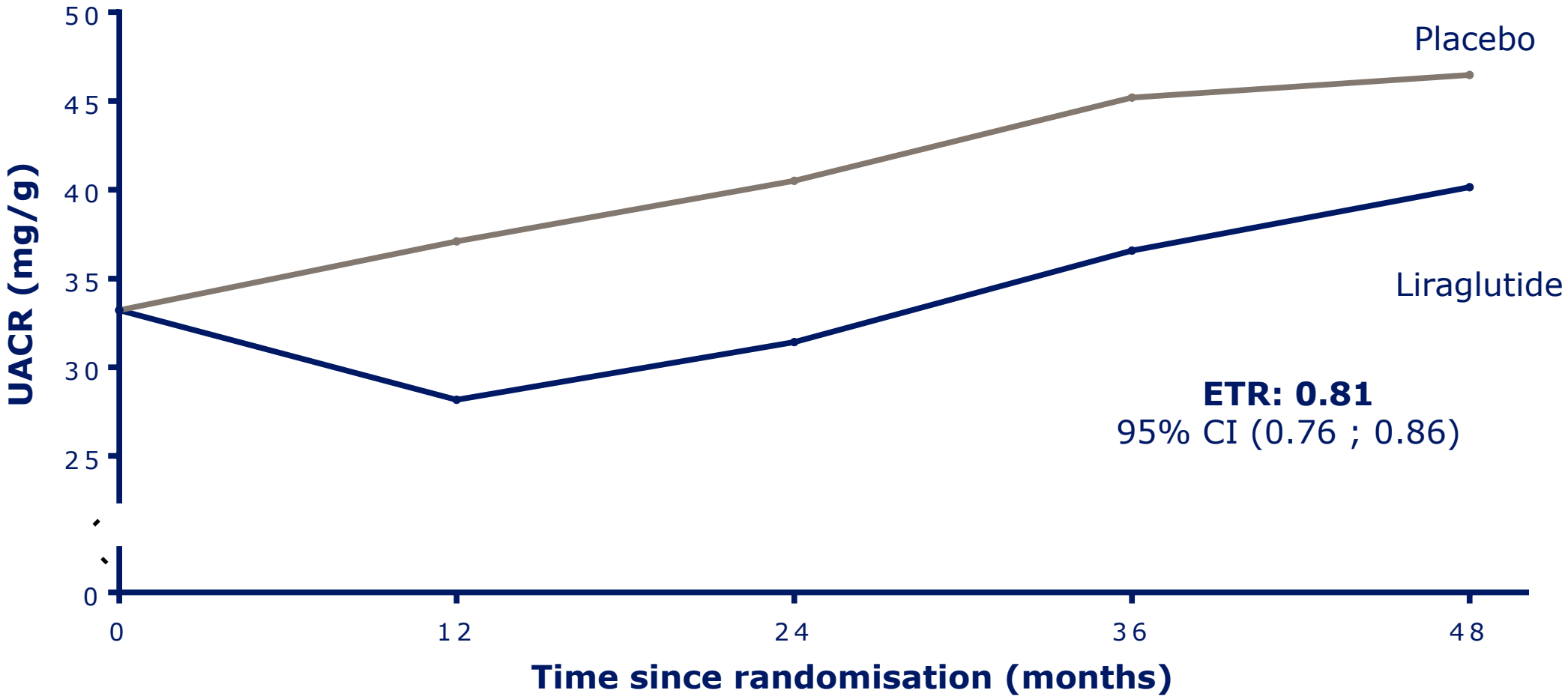
Liraglutide	4668	4635	4561	4492	4400	4304	4210	4114	1632	454
Placebo	4672	4643	4540	4428	4316	4196	4094	3990	1613	433

*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

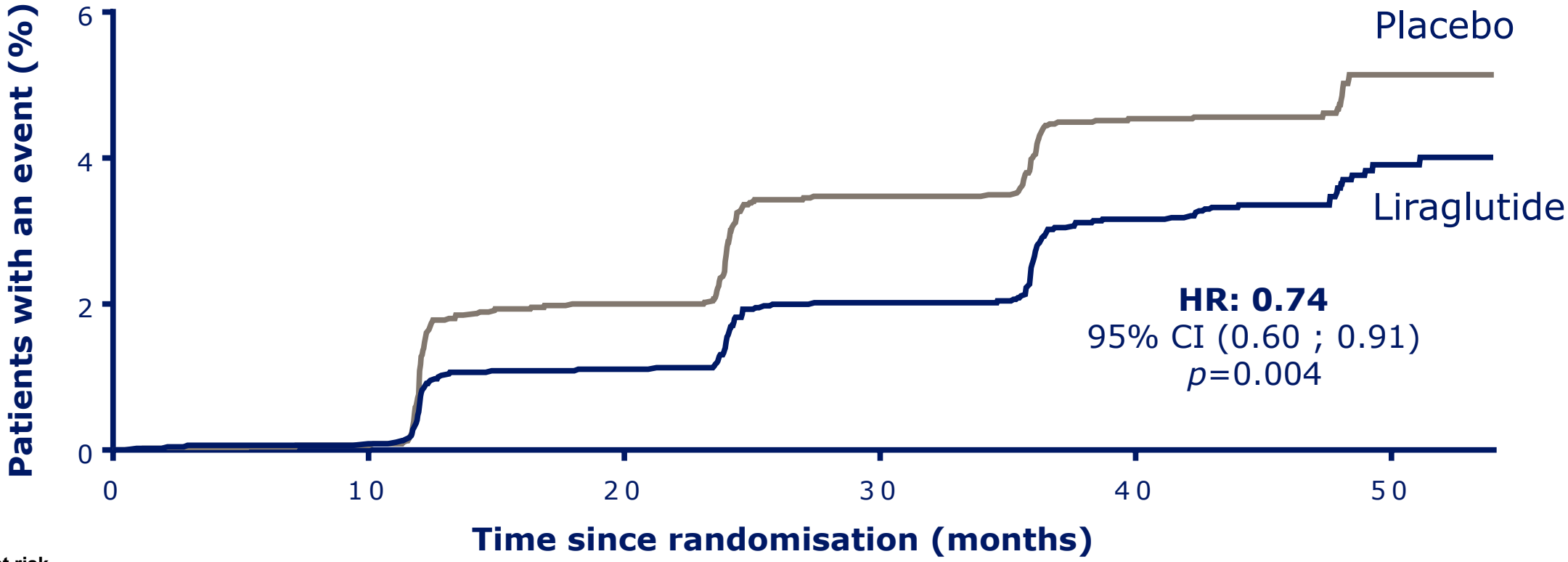
Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany.

LEADER: Urinary albumin–creatinine ratio over time



Values below LLOQ not included (app. 20% of total)
Full analysis set. Estimated geometric means
CI: confidence interval; ETR: estimated treatment ratio; LLOQ: lower limit of quantification; UACR: urinary albumin-creatinine ratio
Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany.

LEADER: Time to new onset of persistent macroalbuminuria



Patients at risk

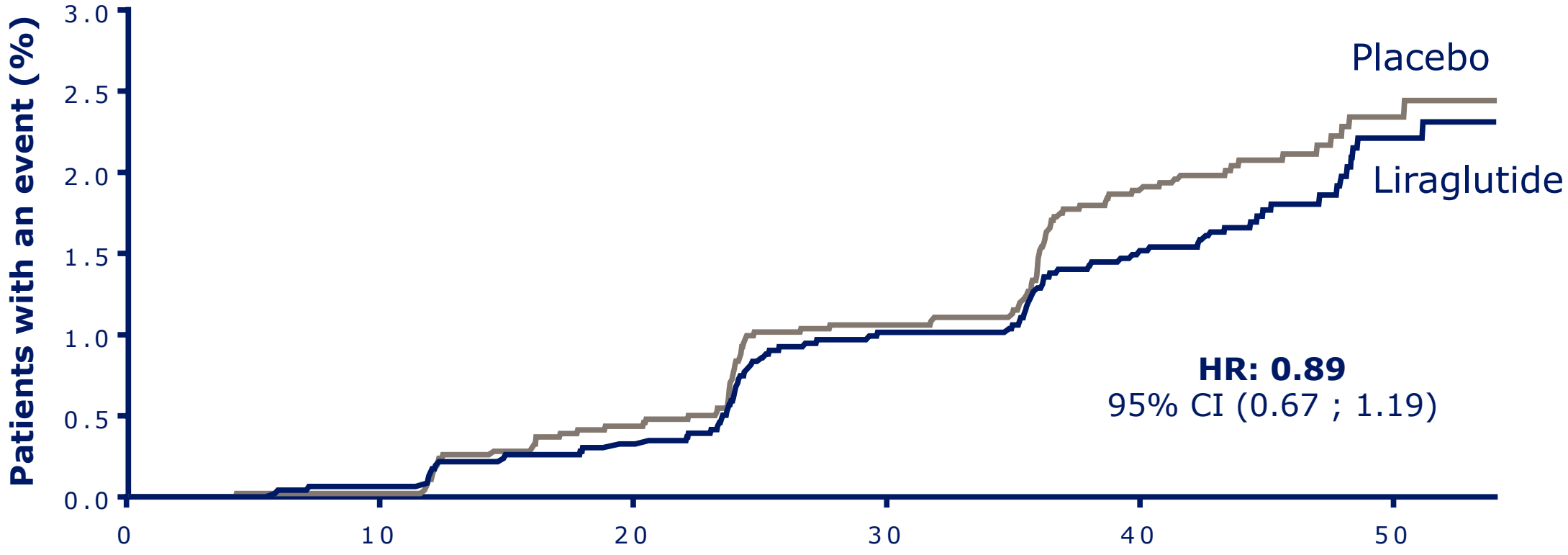
Liraglutide	4668	4606	4499	4353	4199	1006
Placebo	4672	4615	4433	4252	4094	964

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 persistent doubling of serum creatinine*



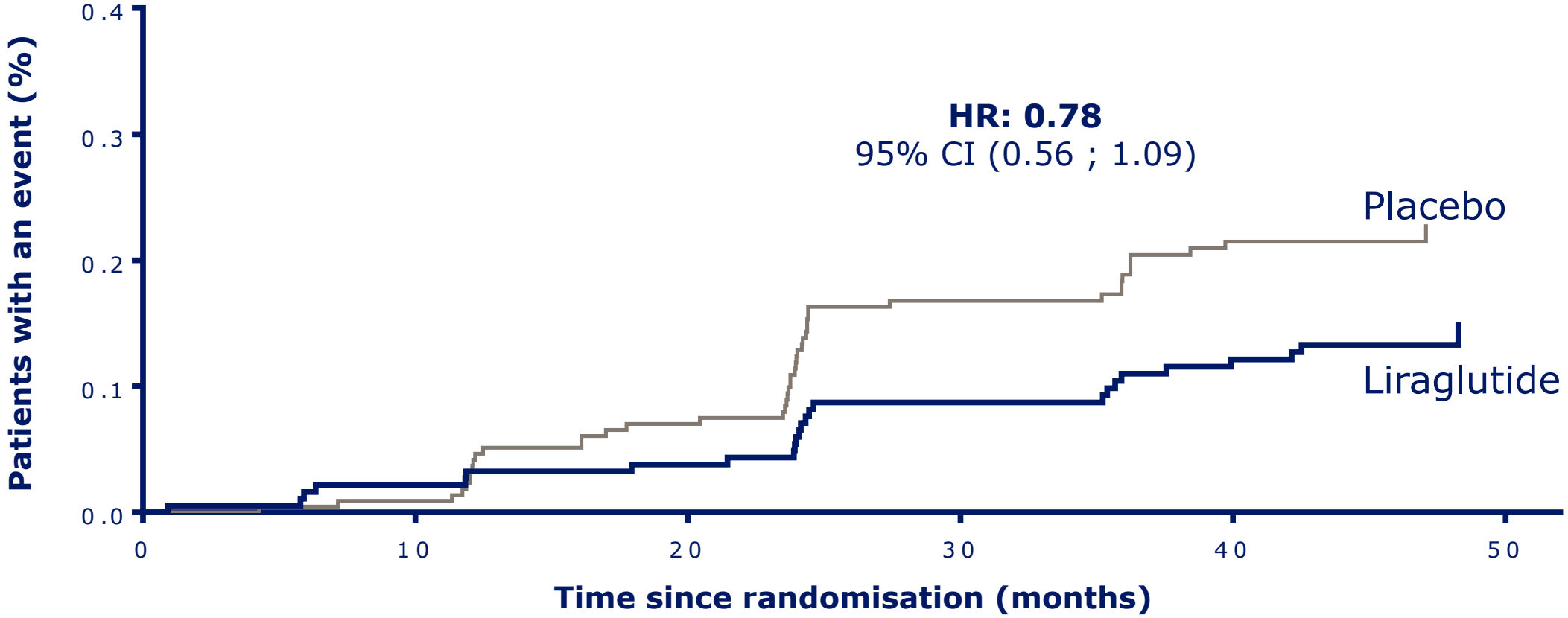
Patients at risk

Liraglutide	4668	4607	4535	4403	4279	1031
Placebo	4672	4617	4508	4367	4220	996

*And eGFR per MDRD ≤45 mL/min/1.73 m^2; 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. CI, confidence interval; EAC, event adjudication committee; eGFR, estimated glomerular filtration rate; HR, hazard ratio; MDRD, modification of diet in renal disease. Presented at ASN Kidney Week, 19 November 2016, Chicago, USA

LEADER: Time to first renal event*

eGFR <60 mL/min/1.73 m^2 and microalbuminuria subgroup



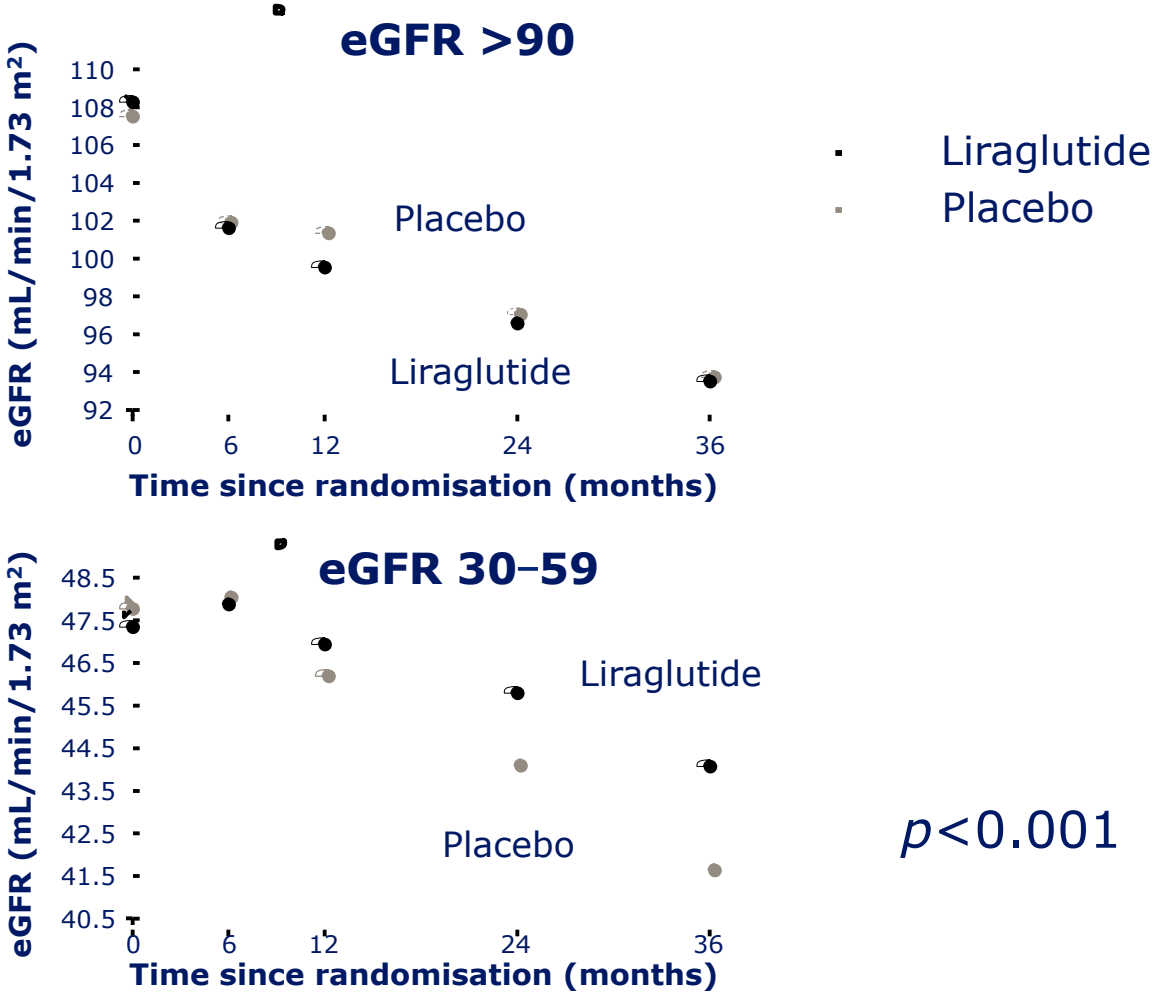
*Macroalbuminuria, doubling of serum creatinine and eGFR ≤45 mL/min/1.73 m^2 per MDRD, ESRD, renal death
Full analysis set. Observed geometric means

CI: confidence interval; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio

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

LEADER: Change in eGFR (MDRD)

Pre-defined subgroups

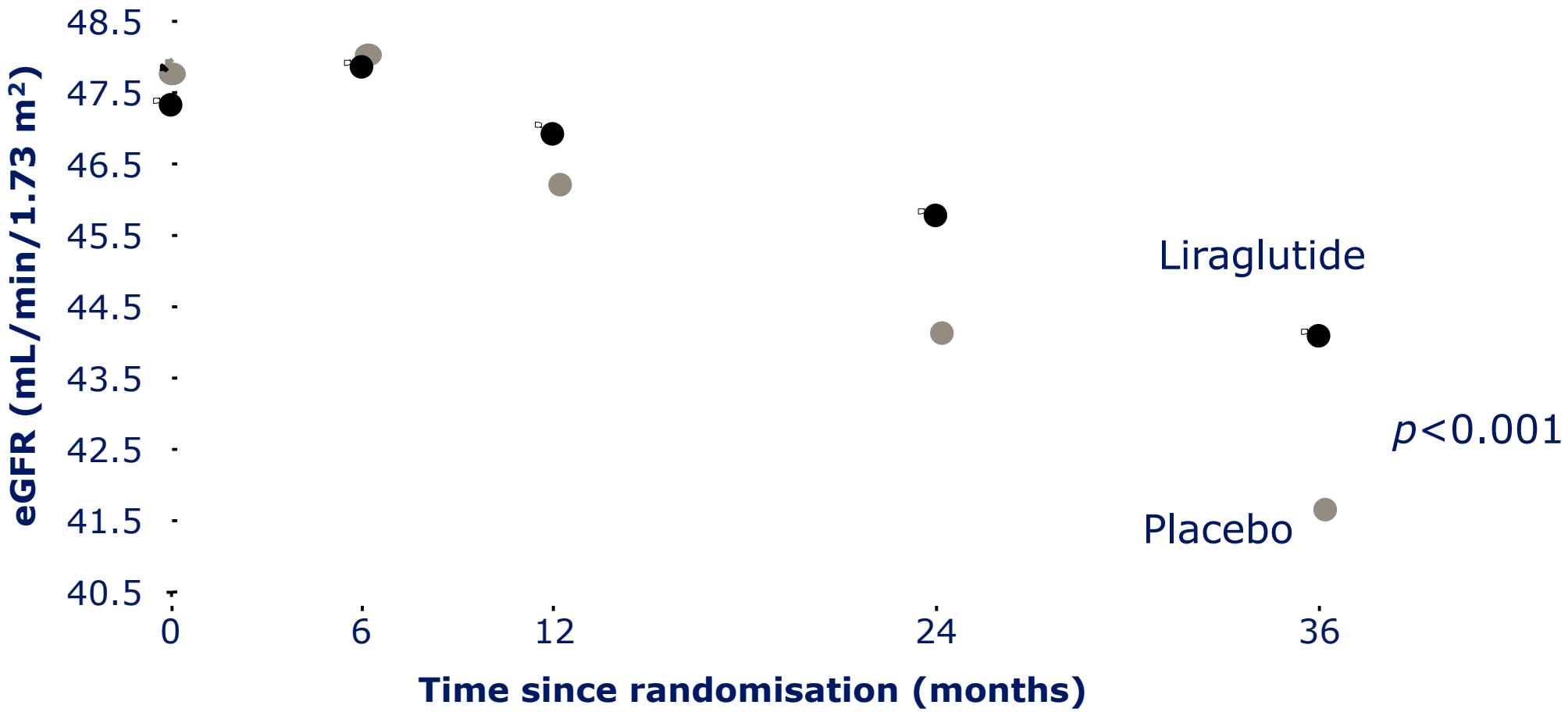


Estimated geometric means; eGFR-MDRD (mL/min/1.73 m^2), estimated glomerular filtration rate using the modification of diet in renal disease formula

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

LEADER: Change in eGFR (MDRD)

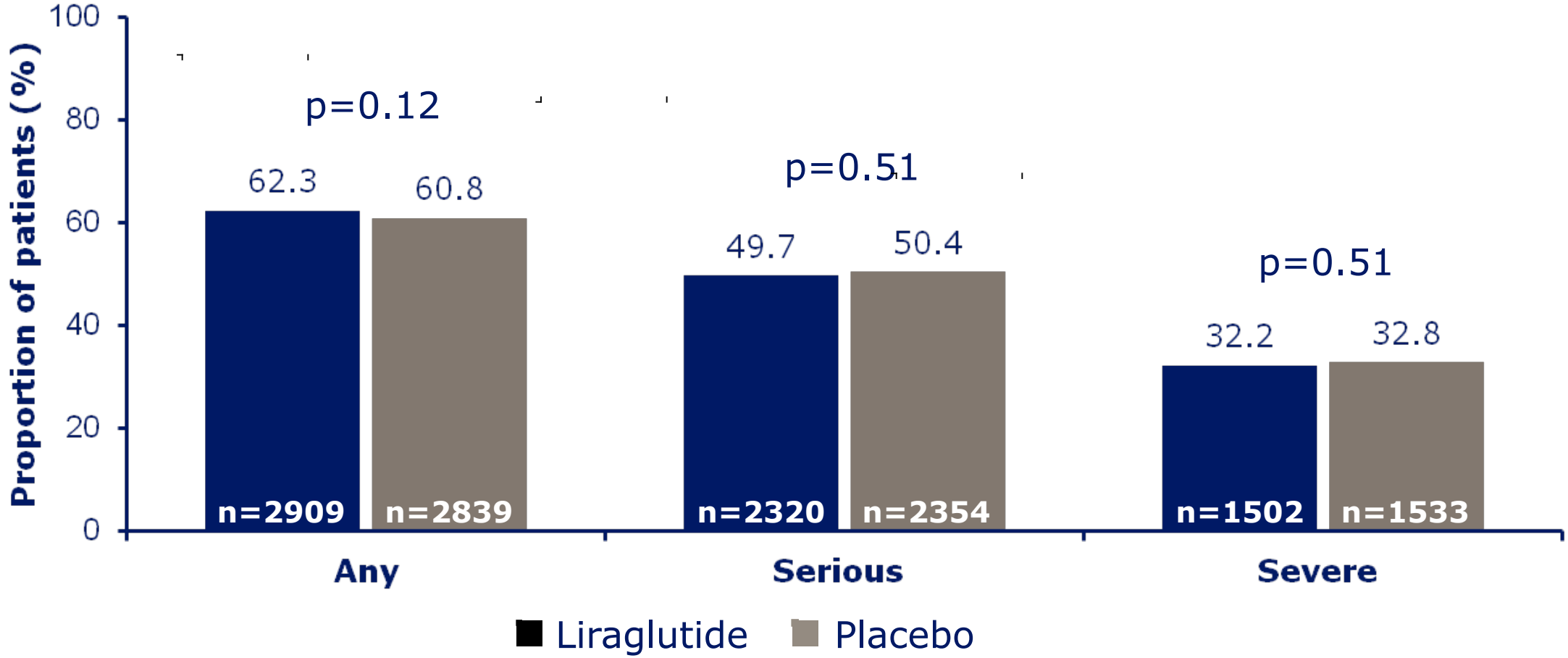
Subgroup eGFR 30–59 mL/min/1.73 m^2



Estimated geometric means; eGFR-MDRD (mL/min/1.73 m^2), estimated glomerular filtration rate using the modification of diet in renal disease formula

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

Adverse events

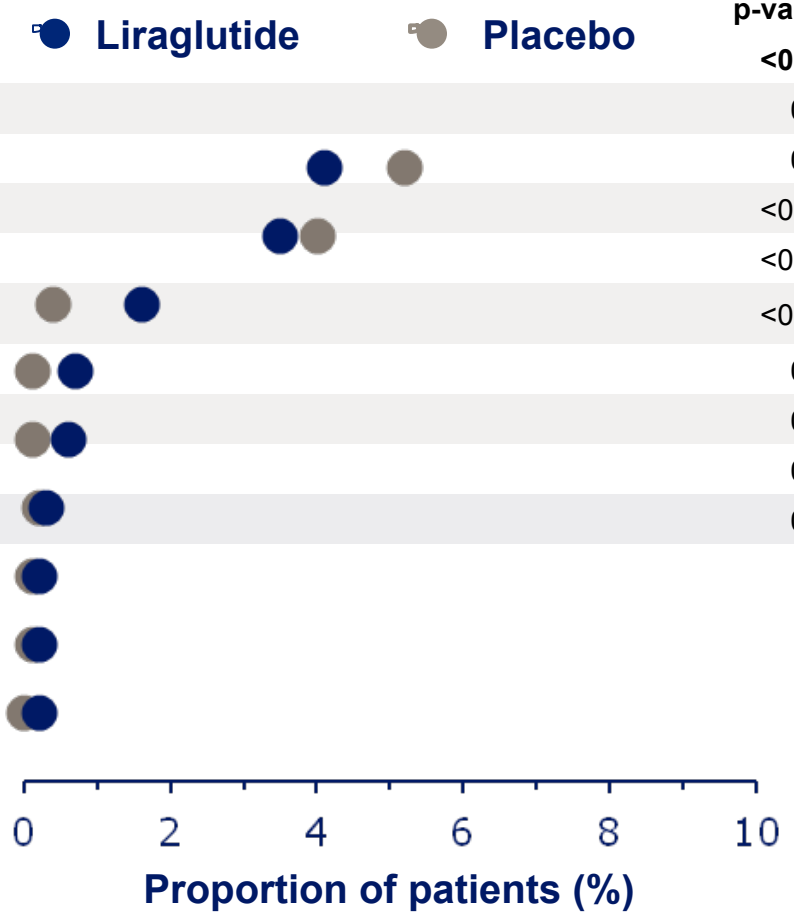


Full analysis set.
A serious adverse event was defined as an experience that at any dose resulted in any of the following: death, a life-threatening experience, in-patient hospitalisation or prolongation of hospitalisation, persistent or significant disability/incapacity, congenital anomaly/birth defect, important medical events that may jeopardise the patient based upon appropriate medical judgement. A severe adverse event was defined as a non-serious adverse event that resulted in considerable interference with the patient's daily activities. N, number of patients.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

AEs leading to permanent treatment discontinuation

-

	Liraglutide		Placebo		
	N	%	N	%	p-value*
Any adverse event	**444**	**9.5**	**339**	**7.3**	**<0.001**
Serious adverse event	192	4.1	245	5.2	0.01
Severe adverse event	164	3.5	188	4.0	0.20
Nausea	77	1.6	18	0.4	<0.001
Vomiting	31	0.7	2	<0.1	<0.001
Diarrhoea	27	0.6	5	0.1	<0.001
Lipase increased†	15	0.3	11	0.2	0.43
Abdominal pain	11	0.2	3	0.1	0.03
Decreased appetite	11	0.2	3	<0.1	0.01
Abdominal discomfort	10	0.2	0	0	0.002



*Exploratory analysis with no adjustment of p-values for multiplicity. Permanent discontinuation of the treatment regimen was indicated by the investigator in the adverse-event form. †Increased lipase levels were those that were reported by the investigator as adverse events. P values were calculated by means of Pearson's chi-square test. AE, adverse event.

Marso SP et al. *N Engl J Med* 2016; 375:311-322.

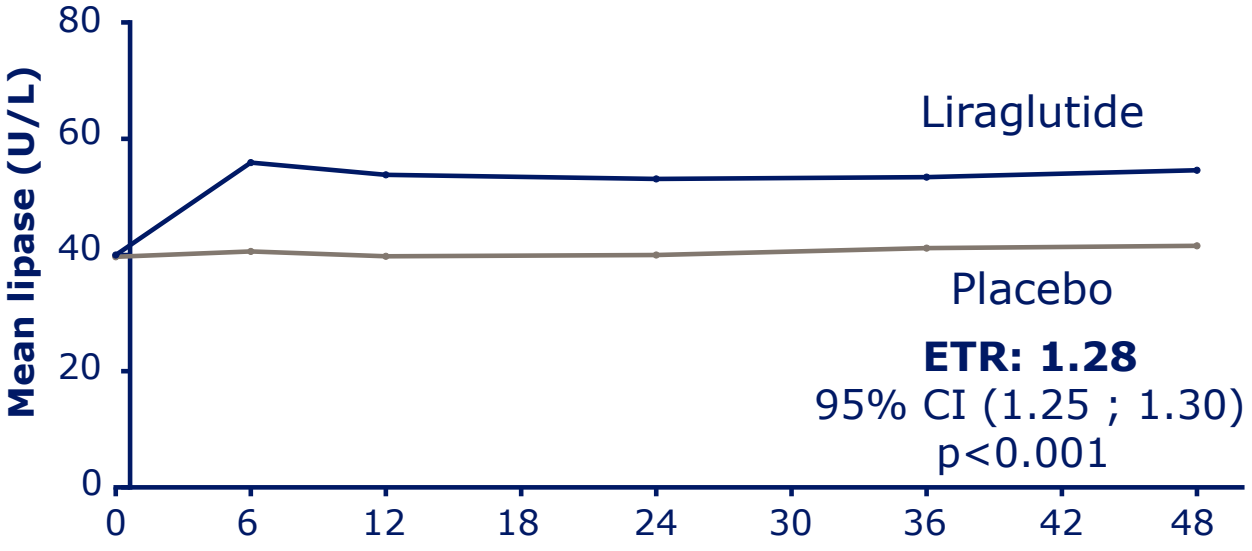
LEADER: Pancreatitis (confirmed by adjudication)

	Liraglutide		Placebo		p-value
	N	%	N	%	
Acute pancreatitis	18	0.4	23	0.5	0.44
Chronic pancreatitis	0	0.0	2	0.0	0.16

Full analysis set. The occurrence of pancreatitis was adjudicated by the event adjudication committee. P-values were calculated by means of Pearson's chi-square test
%, proportion of patients; N, number of patients.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

LEADER: Lipase and amylase over time

Lipase

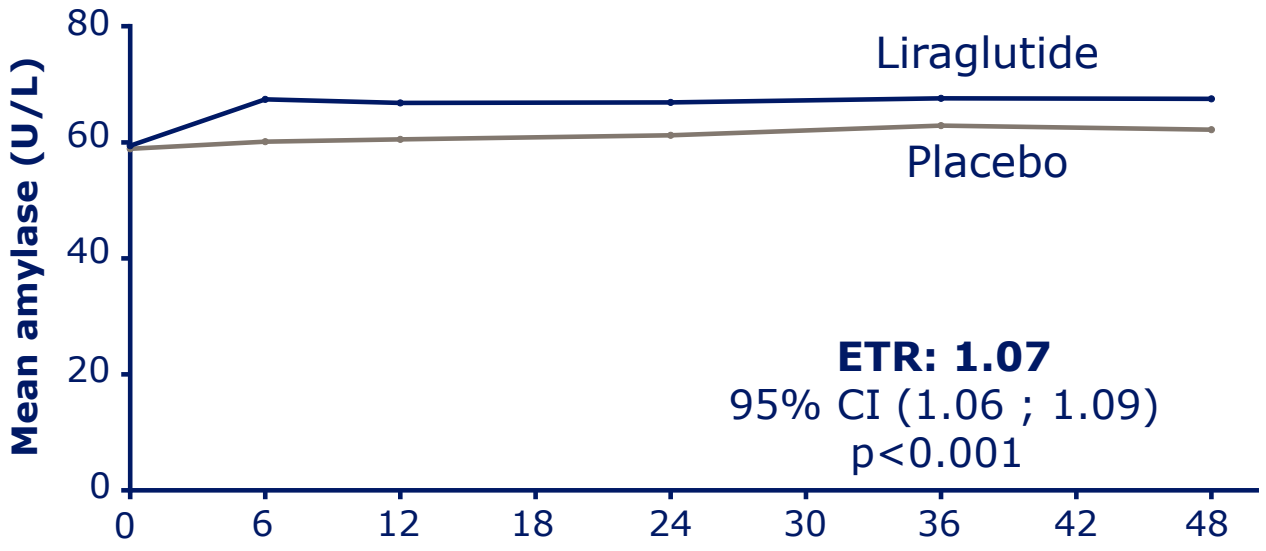


Time since randomisation (months)

Number of subjects at each visit

Lira	4578	4335	4273	4016	3800	808
Pbo	4568	4340	4230	3891	3621	752

Amylase



Time since randomisation (months)

Number of subjects at each visit

Lira	4600	4361	4289	4038	3817	814
Pbo	4590	4363	4242	3921	3642	758

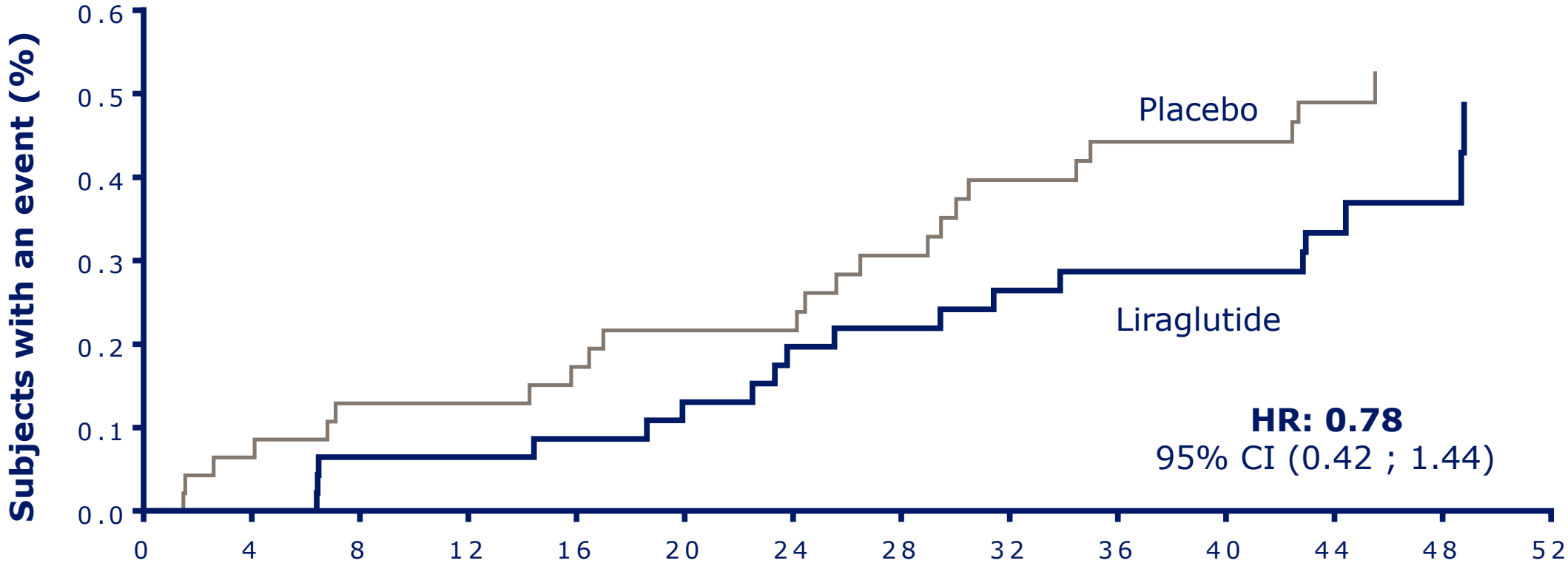
Full analysis set. Observed geometric means

Lipase UNL defined as 63 U/L; lipase LLN defined as 16 U/L. Amylase: LLN defined as 28 U/L; UNL defined as 100 U/L

ETR: estimated treatment ratio; Lira: liraglutide; LLN: lower limit of normal; Pbo: placebo; UNL: upper normal limit

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

LEADER: Time to acute pancreatitis



Subjects at risk

Liraglutide	4668	4619	4575	4496	4408	4328	1720
Placebo	4672	4628	4567	4471	4369	4272	1699

Full analysis set. Kaplan–Meier plot of time to first EAC-confirmed acute pancreatitis index event. Hazard ratio calculated using Cox analysis
CI: confidence interval; EAC: event adjudication committee; HR: hazard ratio
Presented at 52nd EASD Annual Meeting, 14 September 2016, Munich, Germany.

LEADER: Thyroid neoplasms

	Liraglutide		Placebo		
	N	%	N	%	p-value
Medullary thyroid carcinoma	0	0.0	1	<0.1	0.32

P-values were calculated by means of Pearson's chi-square test.
%, proportion of patients; N, number of patients.
Marso SP et al. *N Engl J Med* 2016; 375:311-322.

Conclusions

- Liraglutide reduced the risk of nephropathy events, cardiovascular events and all-cause mortality, relative to placebo, both in addition to standard of care
- The effect of liraglutide on the composite nephropathy outcome was driven by changes in persistent macroalbuminuria
- Liraglutide was not associated with an increased risk of renal adverse events

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

Grazie