LEADER
Liraglutide and cardiovascular outcomes in type 2 diabetes

Presented at DSBS seminar on mediation analysis
August 18th

Søren Rasmussen, Novo Nordisk

LEADER®
Liraglutide Effect and Action in Diabetes:
Evaluation of cardiovascular outcome Results

LEADER CV outcome study

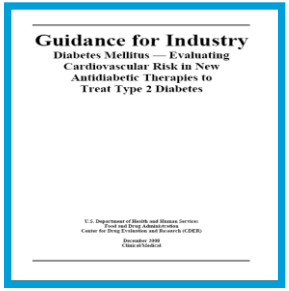
- To determine the effect and safety of liraglutide on cardiovascular outcomes in adults with T2DM that are at high risk for cardiovascular events.

- To assess the efficacy and safety with regard to clinically important events or other surrogate parameters of treatment with liraglutide compared to placebo in adults with T2DM that are at high risk for cardiovascular events.

Background

June 2007

"Rosiglitazone was associated with a significant increase in the risk of myocardial infarction…"



Dec 2008

New FDA Guidance issued
Implication for liraglutide
Retrospectively compare incidence of Major Adverse Cardiovascular Events (MACE) between liraglutide and the total comparator

Jun 2009, Jan 2010

Victoza approved by EMA and FDA.

The LEADER ® trial

(**L**iraglutide **E**ffect and **A**ction in **D**iabetes: **E**valuation of cardiovascular outcome **R**esults) is a compelling scientific opportunity that will provide new data about the GLP-1 analogue, liraglutide, and its effect on cardiovascular outcomes.

The LEADER® trial is a long-term, multi-centre, international, randomised, double-blind trial to compare liraglutide with placebo in addition to the current standard of care for type 2 diabetes. The trial will enrol 9,000 patients in more than 30 countries.

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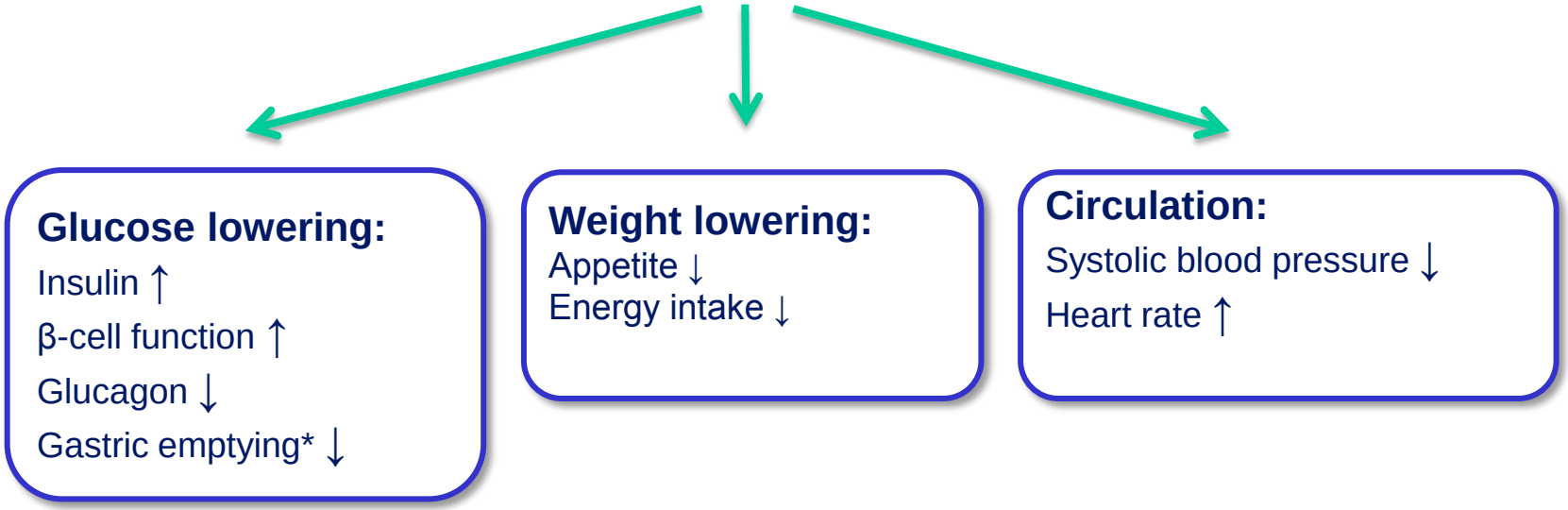
Main effects of long-acting GLP-1R agonists including liraglutide



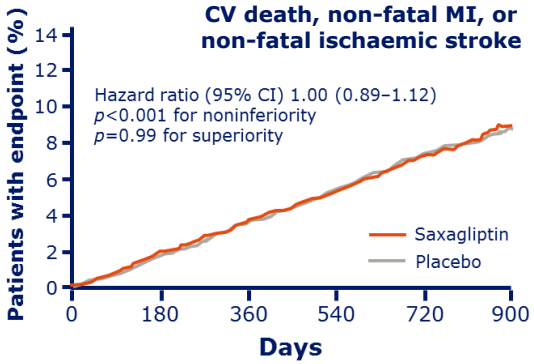
Examples of ongoing pre- and postapproval outcome studies*.

Trial name	Drug	Primary end point	No. of subjects (length of study in years)
EXAMINE	Alogliptin	MACE	5,400 (5)
CANVAS	Canagliflozin	MACE	4,500 (4)
CAROLINA	Linagliptin	MACE + unstable angina	6,000 (7)
ALECARDIO	Aleglitazar	MACE	6,000 ACS (4.5)
TECOS	Sitagliptin	MACE + unstable angina	14,000 (5)
SAVOR	Saxagliptin	MACE	16,500 (5)
EXSCEL	Exenatide LAR	MACE	12,000 (5.5)
LEADER	Liraglutide	MACE	9,000

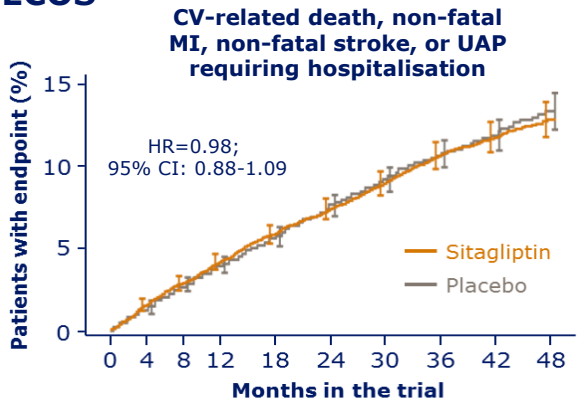
ACS, acute coronary syndrome; CANVAS, CANagliflozin cardioVascular Assessment Study; EXAMINE, Cardiovascular Outcomes Study of Alogliptin in Subjects With Type 2 Diabetes and Acute Coronary Syndrome; EXSCEL, EXenatide Study of Cardiovascular Event Lowering; LAR, long-acting release; TECOS, A Randomized, Placebo Controlled Clinical Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin in Patients with Type 2 Diabetes Mellitus and Inadequate Glycemic Control. *Accessed through http://www.clinicaltrials.gov/.

Boaz Hirshberg, and Arie Katz Dia Care 2013;36:S253-S258

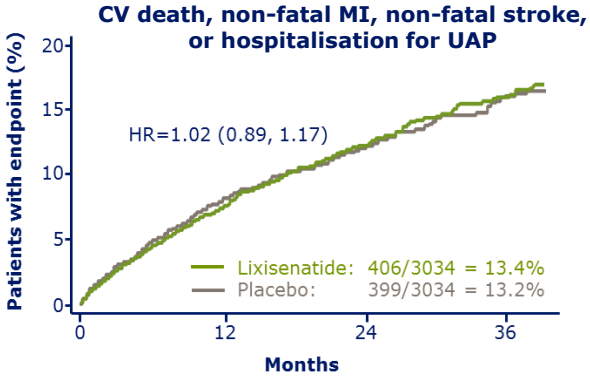
SAVOR-TIMI-53



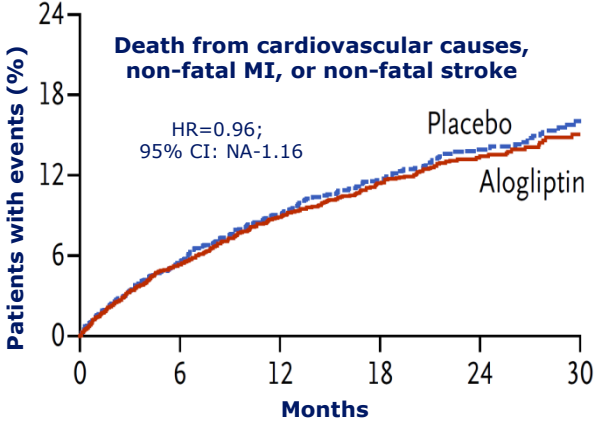
TECOS



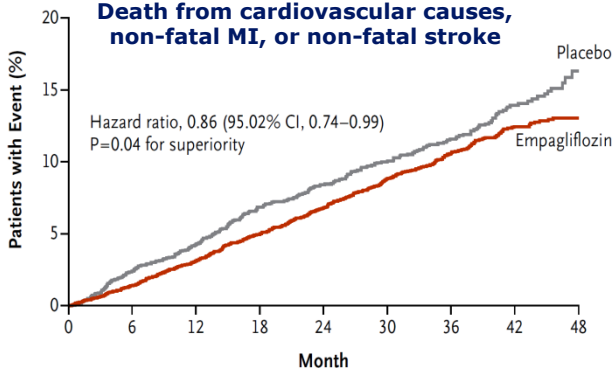
ELIXA



EXAMINE



EMPA-REG



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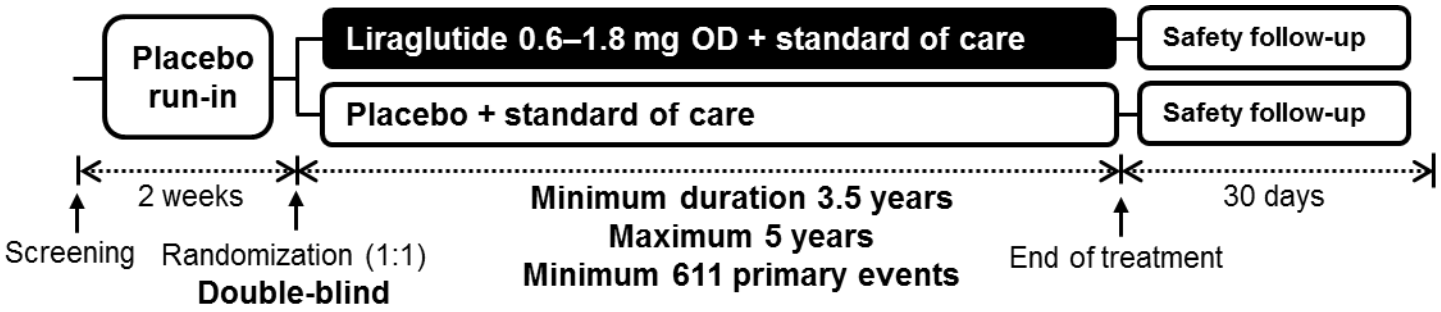
CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction; UAP, unstable angina pectoris.
Sciria *et al. N Engl J Med* 2013 Oct 3;369(14):1317–26; Zinman *et al. N Engl J Med* 2015;373:2117-28; Pfeffer *et al. N Engl J Med* 2015;373(23):2247-57;

LEADER: Study design



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

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CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Primary and key secondary outcomes

Primary outcome	**Time to first occurrence of 3-point MACE composed of** • CV death • Non-fatal MI • Non-fatal stroke
Key secondary outcomes	Time to first occurrence of • Expanded composite CV outcome (CV death, non-fatal MI, non-fatal stroke, coronary revascularization, unstable angina pectoris requiring hospitalization, or hospitalization for heart failure) • All-cause death • Each individual component of expanded composite CV outcome

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CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

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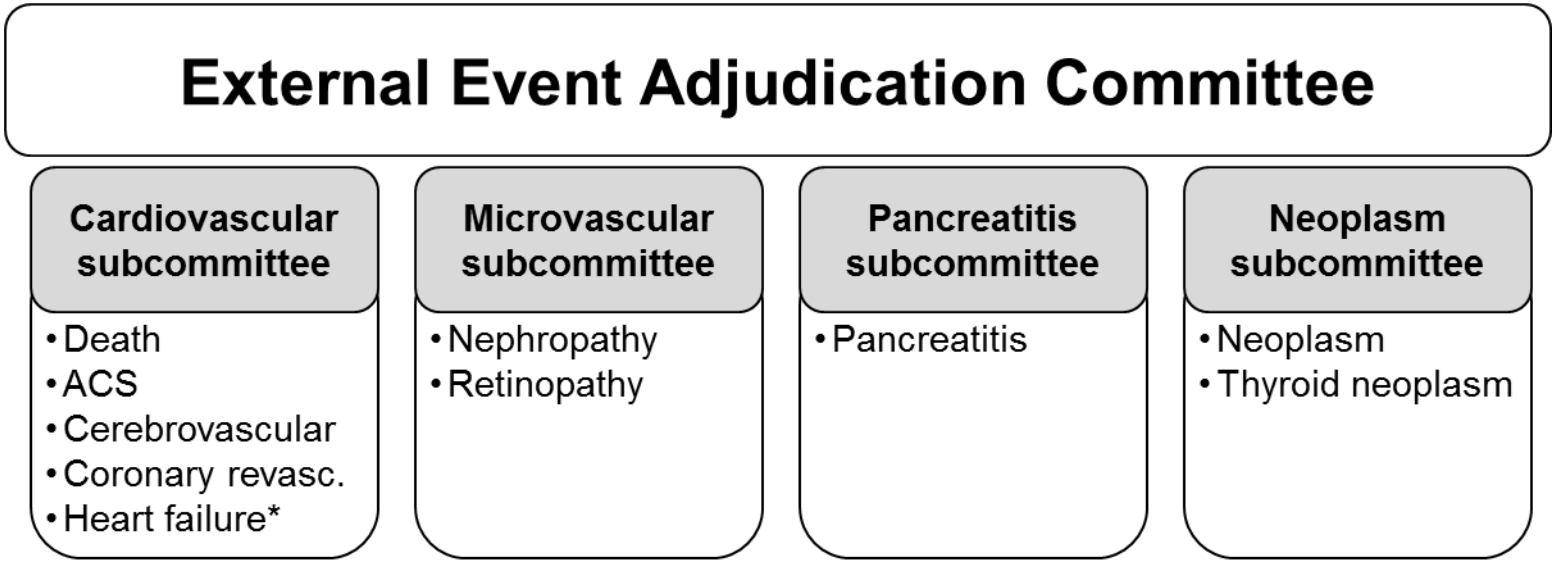
Event adjudication



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*Requiring hospitalization.
ACS: acute coronary syndrome.

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LEADER standard of care guidelines

	Treatment/Guideline
Blood glucose	• HbA_{1c} ≤7.0% (individualized depending on patient)
Blood pressure	• Target: 130/80 mmHg
Lipids	• Target LDL: <100 mg/dL (<70 mg/dL in patients with previous CV events) • Statins: recommended for all patients
Antiplatelet therapy	• Aspirin or clopidogrel (if aspirin intolerant) for patients with prior CV events (MI, CVA, or revascularization)

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CV: cardiovascular; CVA: cerebrovascular accident; HbA_{1c}: glycated hemoglobin; LDL: low-density lipoprotein; MI: myocardial infarction.

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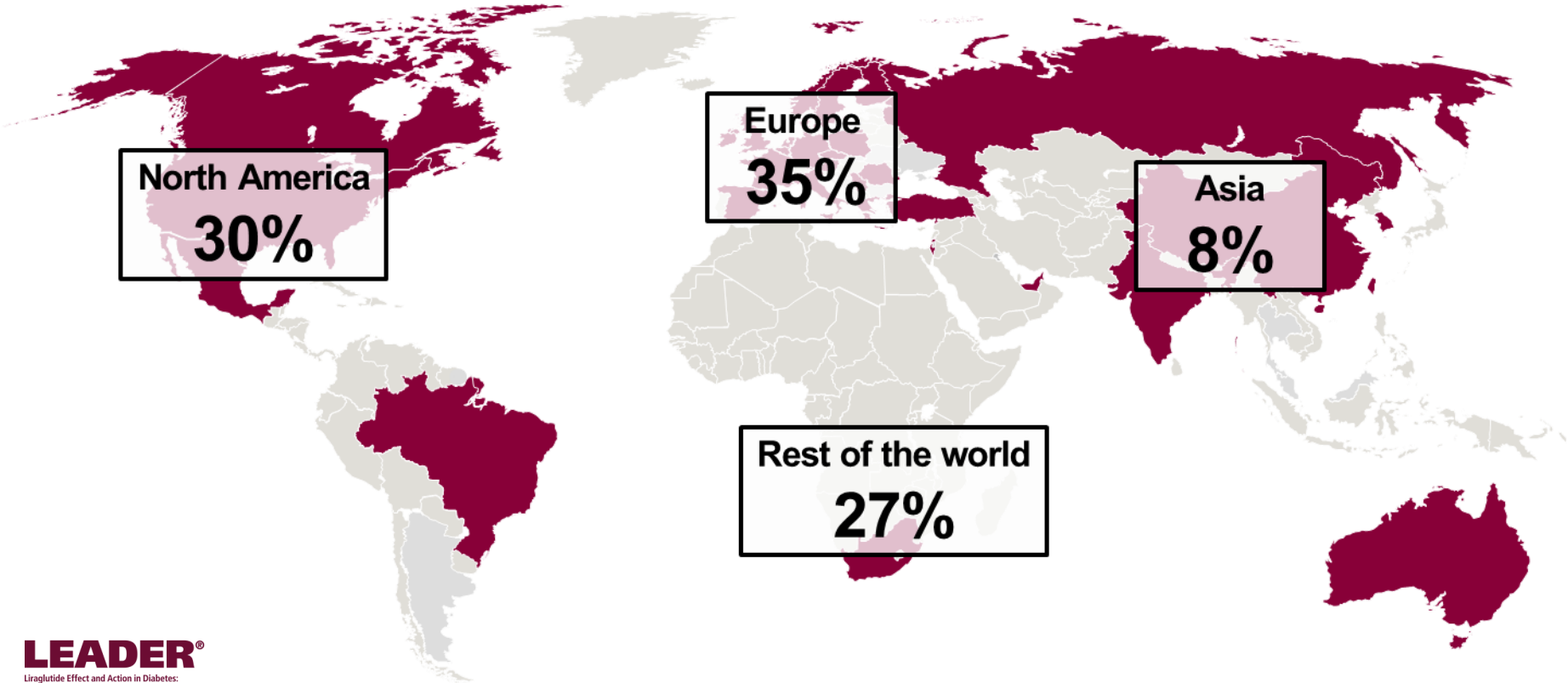
LEADER: A Global Trial



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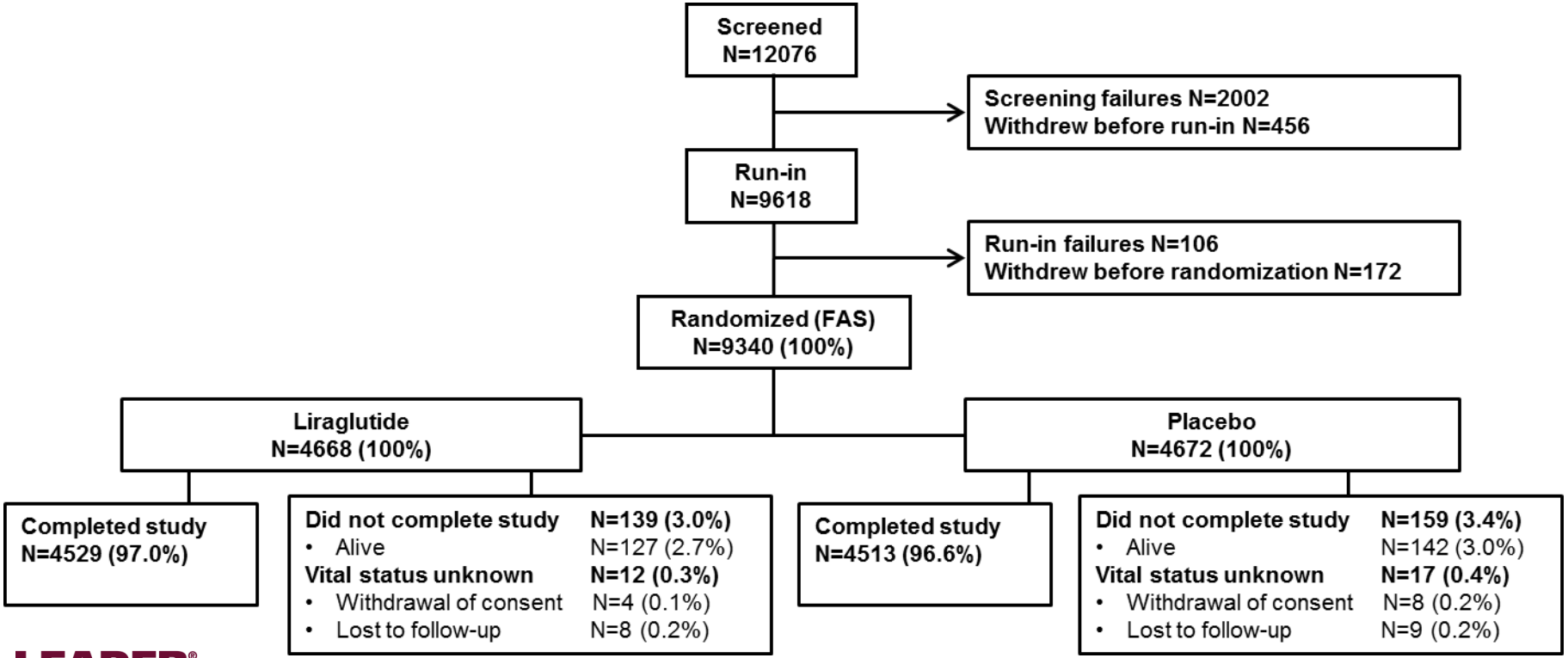
Study patient disposition



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FAS: full analysis set.

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Baseline characteristics

(mean ± SD unless stated)

	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
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)

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*Heart failure includes New York Heart Association class I, II and III. BMI: body mass index; HbA_{1c}: glycated hemoglobin.

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Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
Established CVD/CKD (age ≥50 years)	**3831 (82.1)**	**3767 (80.6)**
Prior myocardial infarction	1464 (31.4)	1400 (30.0)
Prior stroke or prior TIA	730 (15.6)	777 (16.6)
Prior revascularization	1835 (39.3)	1803 (38.6)
>50% stenosis of coronary, carotid, or lower extremity arteries	1188 (25.4)	1191 (25.5)
Documented symptomatic CHD	412 (8.8)	406 (8.7)
Documented asymptomatic cardiac ischemia	1241 (26.6)	1231 (26.3)
Chronic heart failure NYHA II – III	653 (14.0)	652 (14.0)
Chronic kidney disease (eGFR <60 mL/min/1.73m^2)	1185 (25.4)	1122 (24.0)

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Data are number of patients (%).
CHD: coronary heart disease; CKD: chronic kidney disease; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; NYHA: New York Heart Association; TIA: transient ischemic attack.

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Baseline cardiovascular risk profile

	Liraglutide (N=4668)	Placebo (N=4672)
CVD risk factors (age ≥60 years)	**837 (17.9)**	**905 (19.4)**
Microalbuminuria or proteinuria	501 (10.7)	558 (11.9)
Hypertension and left ventricular hypertrophy	248 (5.3)	251 (5.4)
Left ventricular systolic or diastolic dysfunction	203 (4.3)	191 (4.1)
Ankle/brachial index <0.9	110 (2.4)	116 (2.5)

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Data are number of patients (%).
CVD: cardiovascular disease.

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Trial follow-up and drug exposure

	Liraglutide	Placebo
Median follow-up (years)	3.84	3.84
Median time of exposure to study medication (years)	3.52	3.52
Mean proportion of time on study drug (%)*	84.0	83.0
Median (IQR) daily dose of liraglutide (mg)†	1.78 (1.54–1.79)	-

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*Excluding pre-scheduled 30 day off-treatment follow-up period.
†Including off-treatment periods.
IQR: interquartile range.

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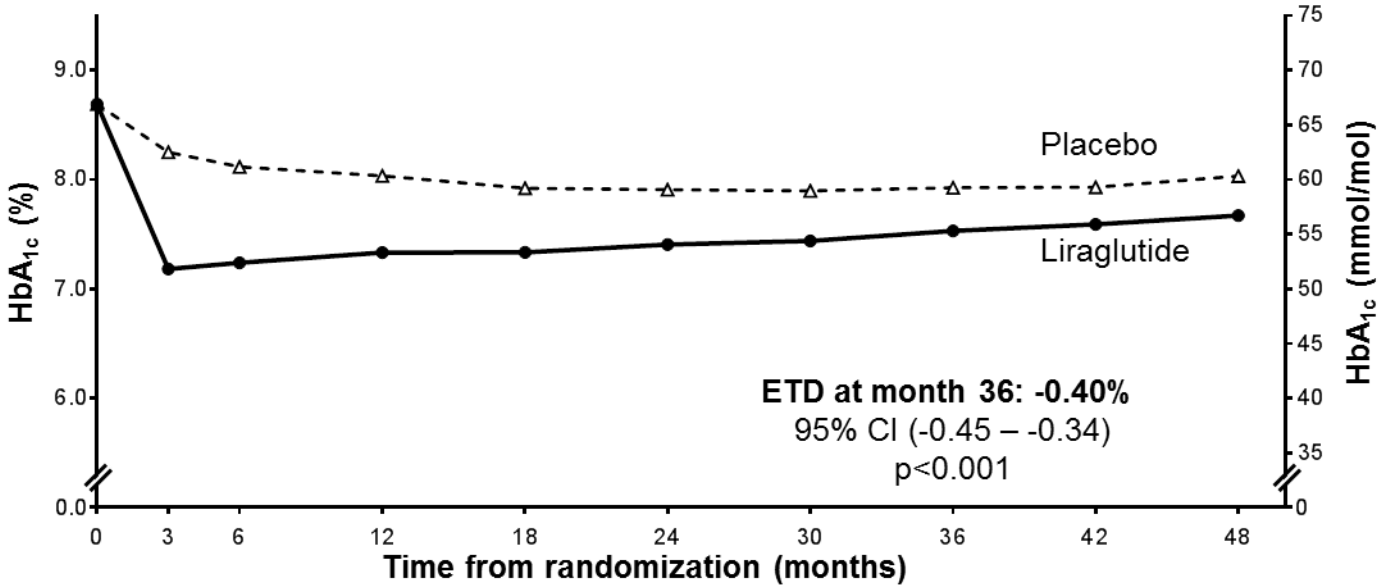
Efficacy parameters

potential mediators

HbA_{1c}



Number of patients at each visit

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

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Data are estimated mean values from randomization to month 48.
CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated hemoglobin.

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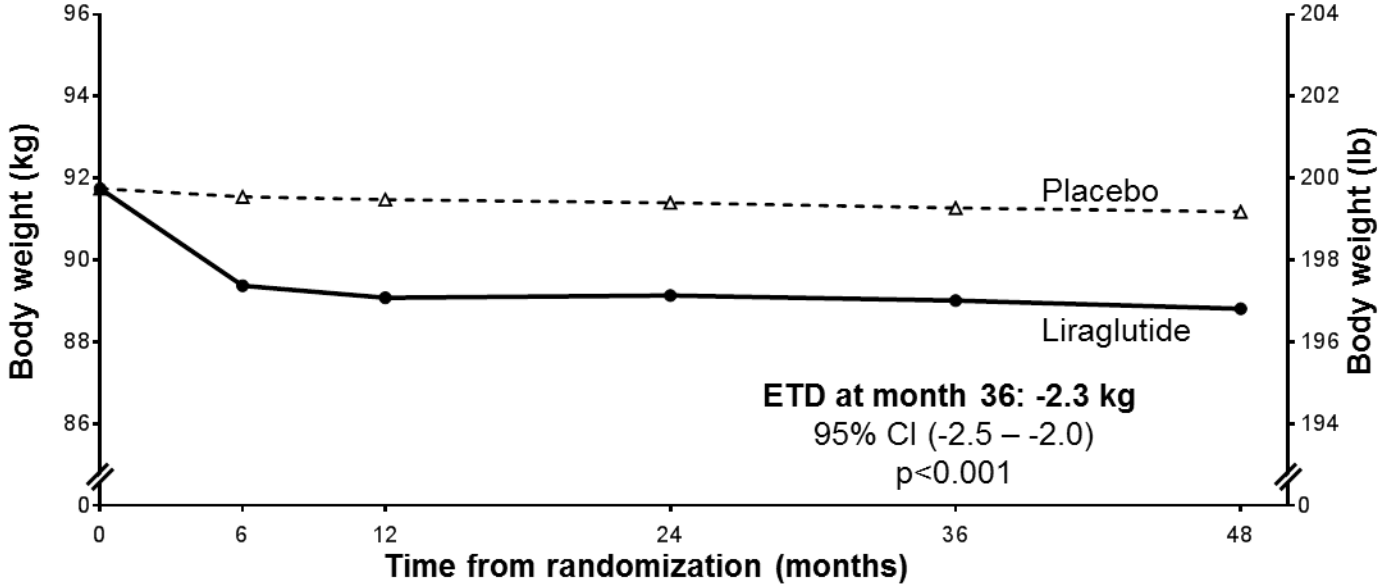
Body weight



Number of patients at each visit

Liraglutide	4667	4434	4324	4088	3835	824
Placebo	4671	4423	4285	3970	3680	766

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Data are estimated mean values from randomization to last scheduled visit for body weight measurement (month 48).
CI: confidence interval; ETD: estimated treatment difference.

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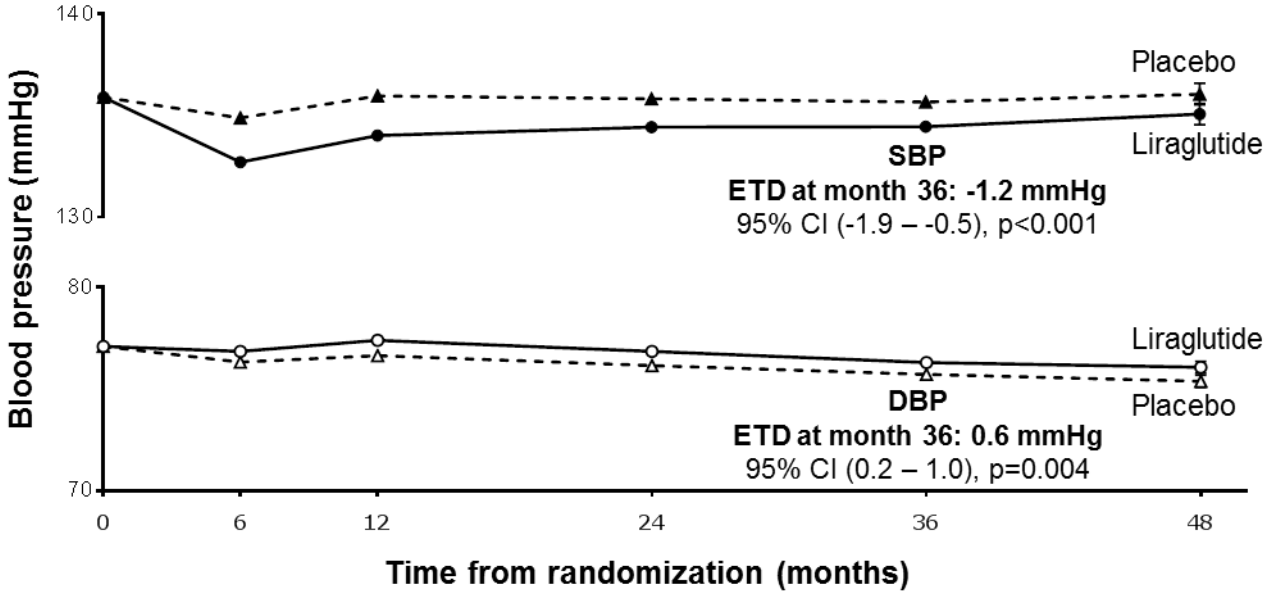
Blood pressure



Number of patients at each visit

Liraglutide	4668	4445	4332	4107	3859	823
Placebo	4672	4435	4295	3975	3699	767

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Data are estimated mean values from randomization to last scheduled visit for blood pressure measurement (month 48).
CI: confidence interval; DBP: diastolic blood pressure; ETD: estimated treatment difference; SBP: systolic blood pressure.

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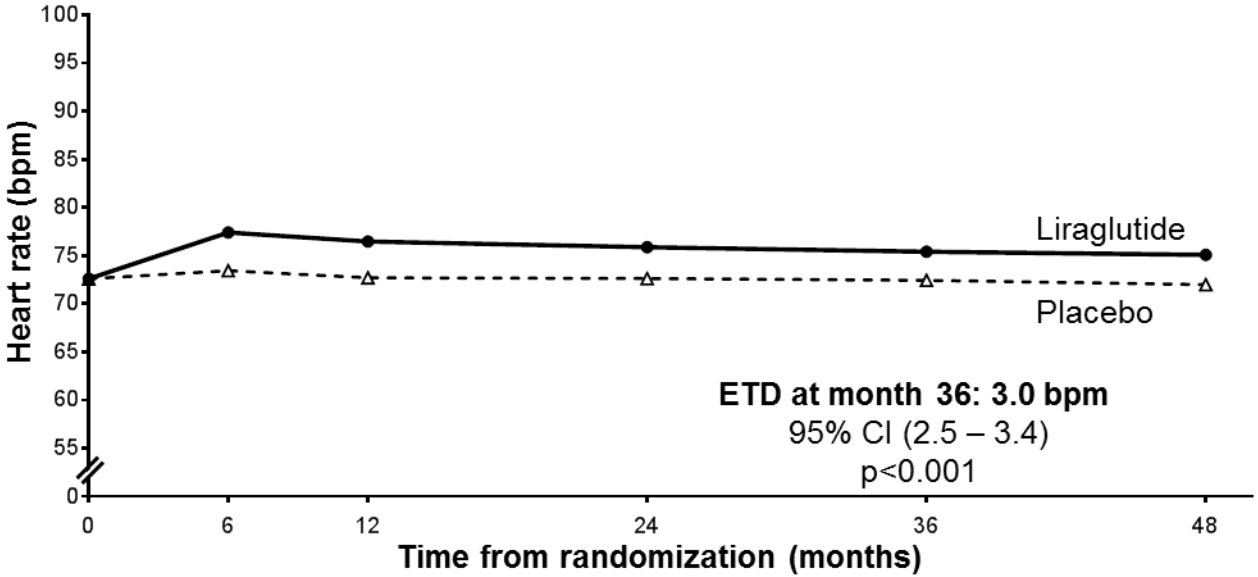
Heart rate



Number of patients at each visit

Liraglutide	4668	4442	4330	4099	3853	824
Placebo	4672	4434	4294	3971	3695	767

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Data are estimated mean values from randomization to last scheduled visit for heart rate measurement (month 48).
Bpm: beats per minute; CI: confidence interval; ETD: estimated treatment difference.

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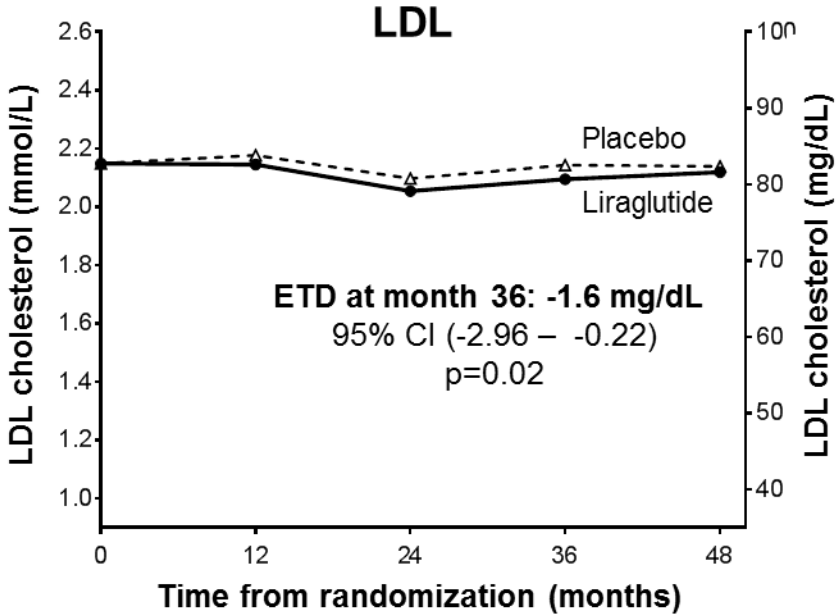
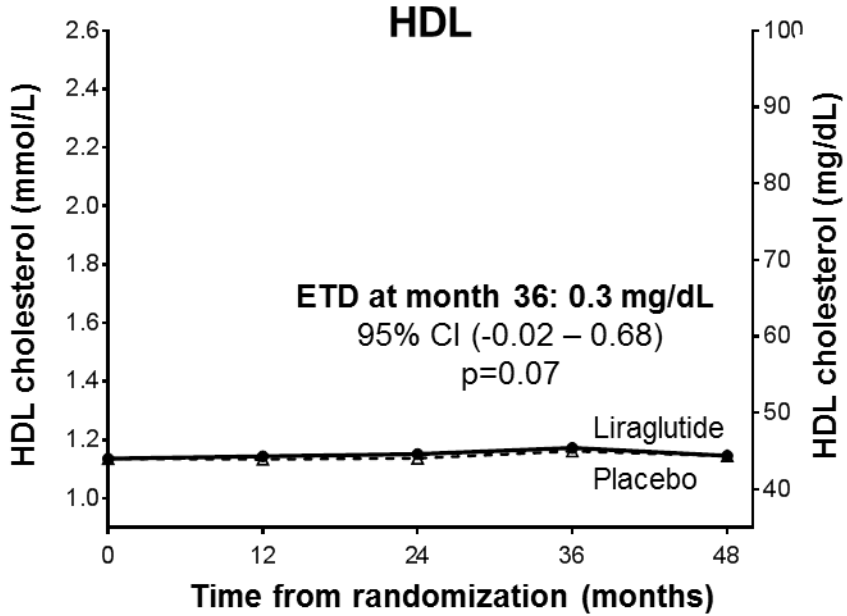
Cholesterol





Number of patients at each visit

Liraglutide	4600	4229	3975	3757	807
Placebo	4587	4165	3859	3580	747

Number of patients at each visit

Liraglutide	4600	4232	3979	3761	807
Placebo	4588	4167	3859	3581	747

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Data are observed geometric mean values from randomization to last scheduled visit for LDL and HDL cholesterol measurement (month 48).
CI: confidence interval; ETD: estimated treatment difference; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

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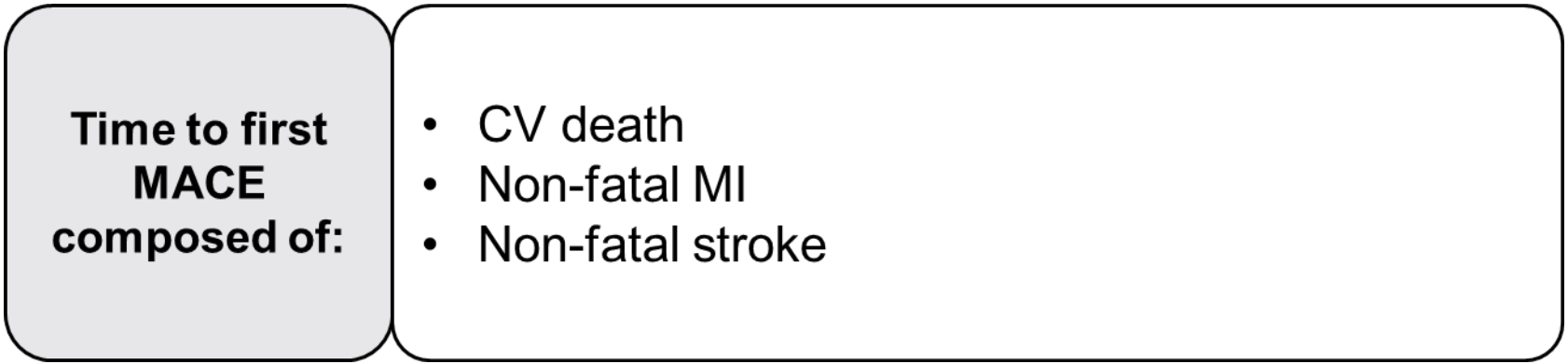
Primary outcome



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CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

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Confirmatory statistical analysis

Primary statistical analysis	Cox proportional hazard model with treatment as a covariate
Test hierarchy for the primary outcome	**1. Test of non-inferiority** • Confirmed if upper bound of the 2-sided 95% CI of the hazard ratio is below **1.30** **2. Test of superiority** • Confirmed if upper bound of the 2-sided 95% CI of the hazard ratio is below **1.00**

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CI: confidence interval; CV: cardiovascular; MACE: major adverse cardiovascular event; MI: myocardial infarction.

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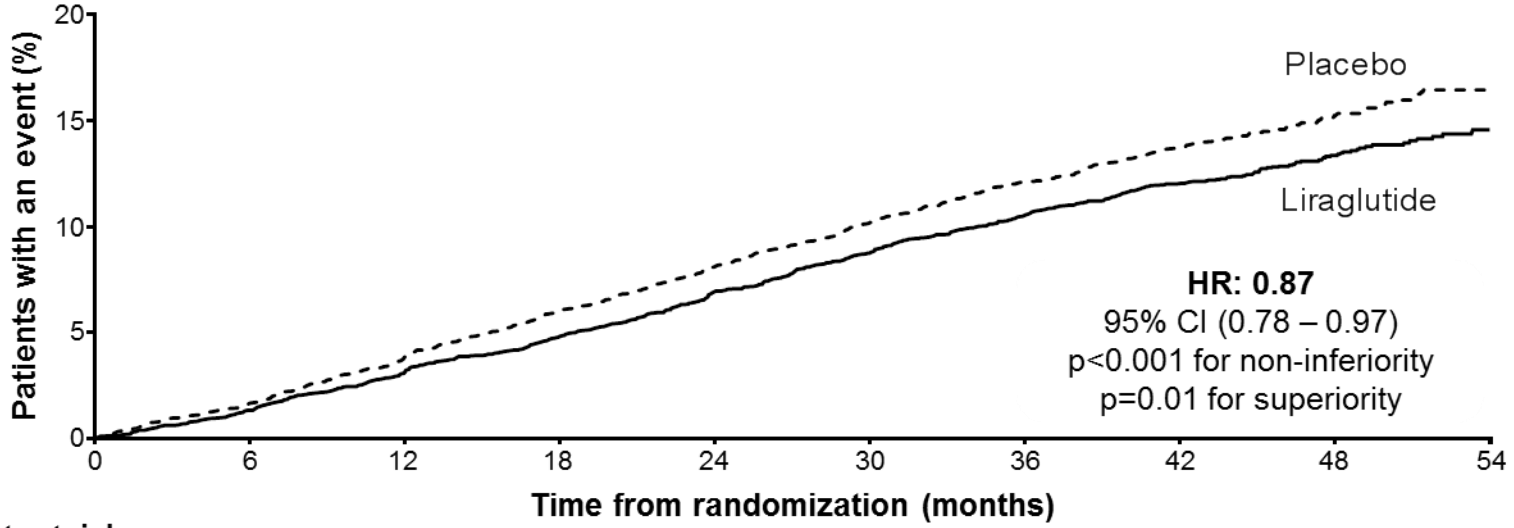
Primary outcome

CV death, non-fatal myocardial infarction, or 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

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The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios 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; CV: cardiovascular; HR: hazard ratio.

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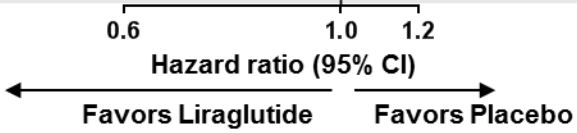
Primary outcome: Sensitivity analysis

	Hazard ratio (95% CI)	Liraglutide N	Liraglutide %	Placebo N	Placebo %
Number of patients (FAS)		**4668**	**100.0**	**4672**	**100.0**
Number of patients (PP)		**4657**	**100.0**	**4664**	**100.0**
Primary analysis (FAS)	**0.87 (0.78–0.97)**	**608**	**13.0**	**694**	**14.9**
Sensitivity analysis					
Per protocol (PP)	0.85 (0.75–0.96)	498	10.7	577	12.4
On treatment	0.83 (0.73–0.95)	443	9.5	520	11.1
On treatment + 30 days	0.82 (0.73–0.93)	480	10.3	571	12.2
Excluding events after Visit 15	0.86 (0.77–0.96)	598	12.8	690	14.8
Adjusted for additional covariates	0.87 (0.78–0.97)	605	13.0	692	14.8
Adjusted for random country effect	0.86 (0.77–0.96)	605	13.0	692	14.8
Stratified for severe renal impairment	0.87 (0.78–0.97)	608	13.0	694	14.9



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Analyzed using Cox proportional hazard regression with treatment as a fixed factor. FAS: full analysis set; PP: per protocol.

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Time to first event analysis

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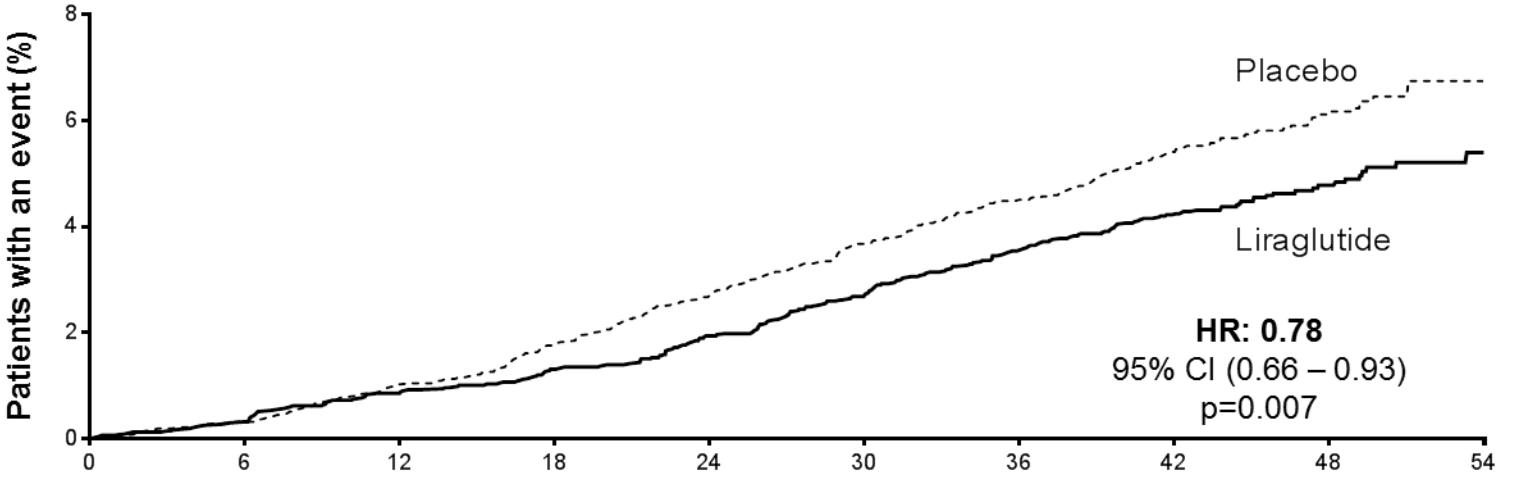
CV death



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

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The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios 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; CV: cardiovascular; HR: hazard ratio.

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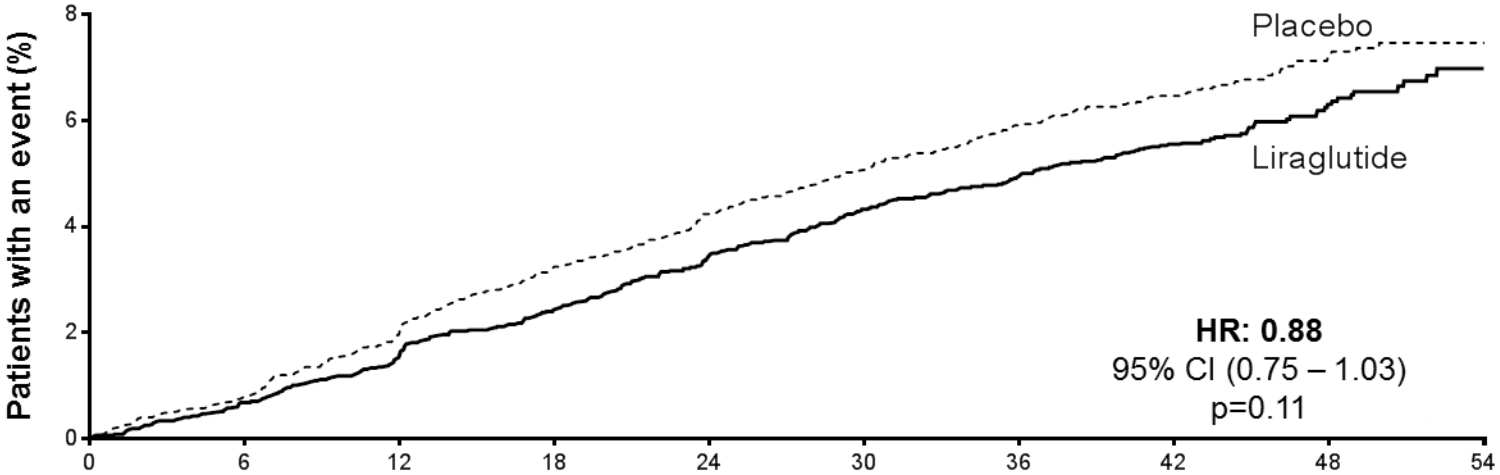
Time to non-fatal myocardial infarction



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

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Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios 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; HR: hazard ratio.

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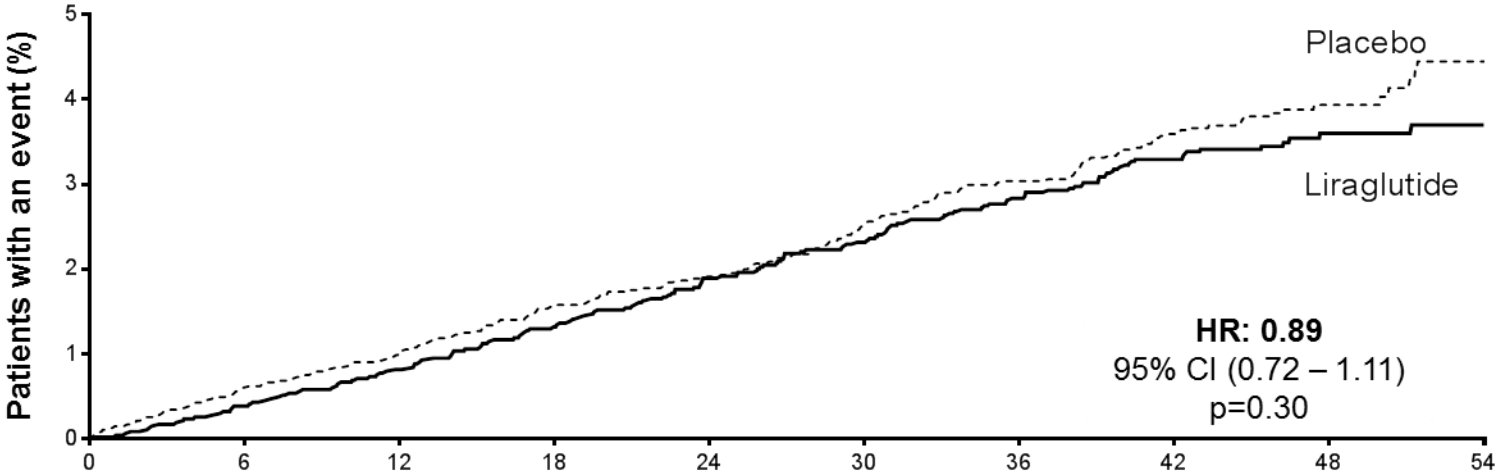
Time to non-fatal stroke



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

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Subgroup analyses of the primary outcome

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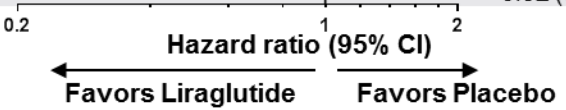
Primary outcome: Subgroup analyses

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)**
Sex		0.84			
Female	0.88 (0.72–1.08)		3337	183/1657 (11.0)	209/1680 (12.4)
Male	0.86 (0.75–0.98)		6003	425/3011 (14.1)	485/2992 (16.2)
Age		0.27			
<60 years	0.78 (0.62–0.97)		2321	140/1197 (11.7)	166/1124 (14.8)
>/= 60 years	0.90 (0.79–1.02)		7019	468/3471 (13.5)	528/3548 (14.9)
Geographic region		0.20			
Europe	0.82 (0.68–0.98)		3296	207/1639 (12.6)	252/1657 (15.2)
North America	1.01 (0.84–1.22)		2847	212/1401 (15.1)	216/1446 (14.9)
Asia	0.62 (0.37–1.04)		711	24/360 (6.7)	37/351 (10.5)
Rest of the world	0.83 (0.68–1.03)		2486	165/1268 (13.0)	189/1218 (15.5)
Race		0.32			
White	0.90 (0.80–1.02)		7238	494/3616 (13.7)	543/3622 (15.0)
Black or African American	0.87 (0.59–1.27)		777	47/370 (12.7)	59/407 (14.5)
Asian	0.70 (0.46–1.04)		936	40/471 (8.5)	56/465 (12.0)
Other	0.61 (0.37–1.00)		389	27/211 (12.8)	36/178 (20.2)
Ethnic group		0.30			
Hispanic or Latino	0.74 (0.54–1.02)		1134	68/580 (11.7)	86/554 (15.5)
Not Hispanic or Latino	0.89 (0.79–1.00)		8206	540/4088 (13.2)	608/4118 (14.8)
Body mass index		0.15			
</=30 kg/m^2	0.96 (0.81–1.15)		3574	241/1743 (13.8)	261/1831 (14.3)
>30 kg/m^2	0.82 (0.71–0.94)		5757	367/2920 (12.6)	431/2837 (15.2)



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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. Race or ethnic group was self-reported. CI: confidence interval.

Expanded MACE
All-cause death
Hospitalization for HF

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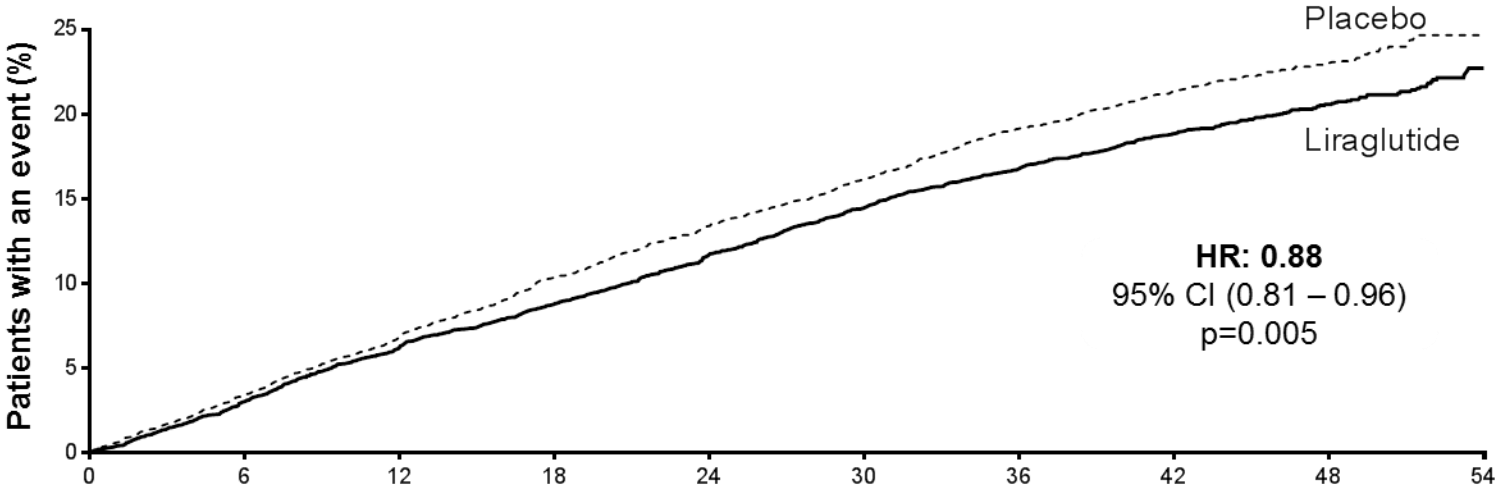
Expanded MACE

CV death, non-fatal MI, non-fatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure



Patients at risk

Liraglutide	4668	4515	4356	4221	4063	3914	3793	3682	1452	395
Placebo	4672	4506	4336	4157	4002	3857	3697	3581	1410	366

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The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios 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; CV: cardiovascular; HR: hazard ratio; MACE: major adverse cardiovascular event; MI: myocardial infarction.

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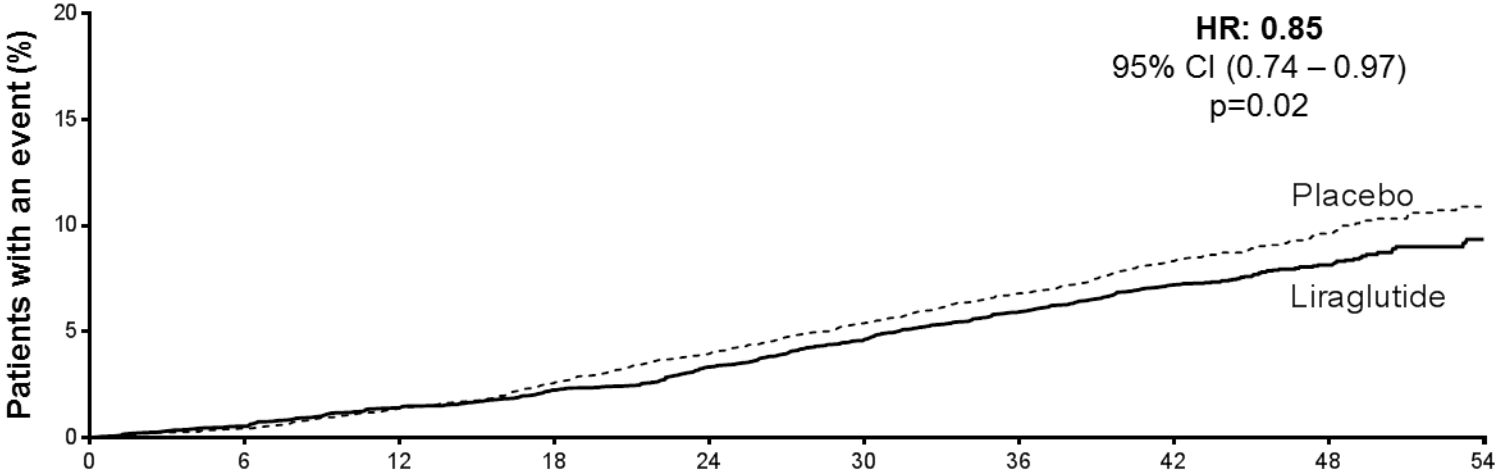
All-cause death



Patients at risk										
Liraglutide	4668	4641	4599	4558	4505	4445	4382	4322	1723	484
Placebo	4672	4648	4601	4546	4479	4407	4338	4268	1709	465

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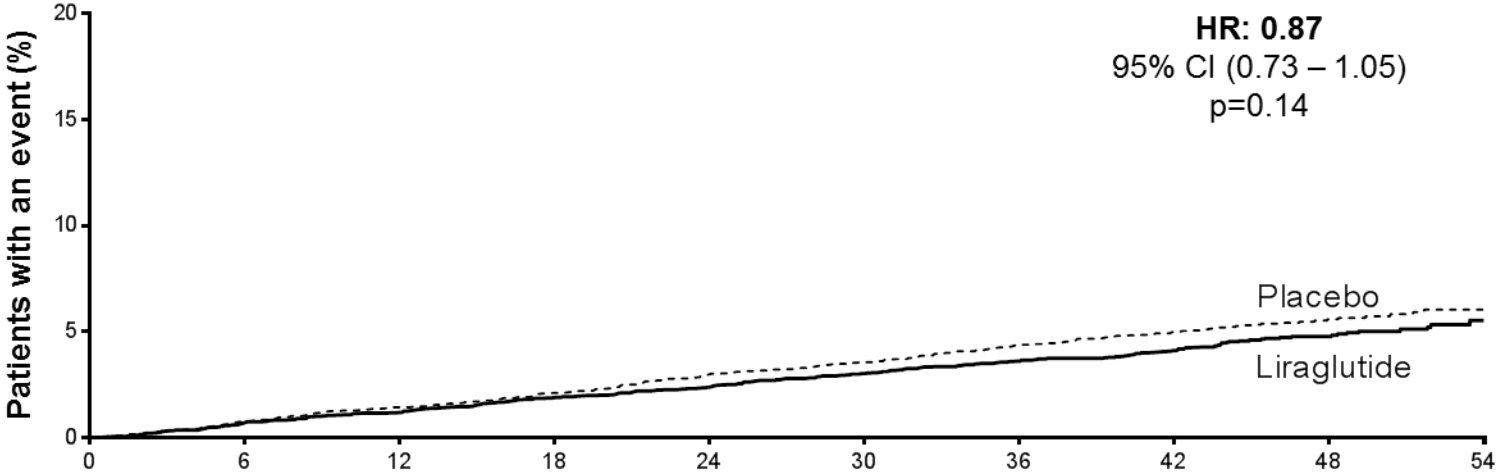
Hospitalization for heart failure



Patients at risk										
Liraglutide	4668	4612	4550	4483	4414	4337	4258	4185	1662	467
Placebo	4672	4612	4540	4464	4372	4288	4187	4107	1647	442

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Mediation analysis

perspectives in CV outcome studies

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Evaluation of cardiovascular outcome Results

Mediation analysis

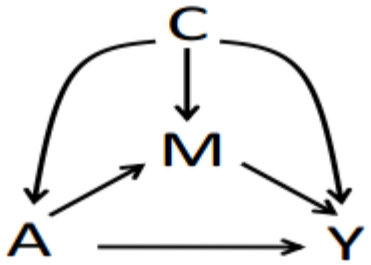
In mediation, we consider an intermediate variable, called the *mediator*, that helps explain how or why an independent variable influences an outcome. In the context of a treatment study, it is often of great interest to identify and study the mechanisms by which an intervention achieves its effect.

With mediation analysis, we gain insight and acquire understanding about the mechanism of action of pharmacological treatments……

Gunzler et al: Shanghai Arch Psychiatry. 2013 Dec; 25(6): 390–394.

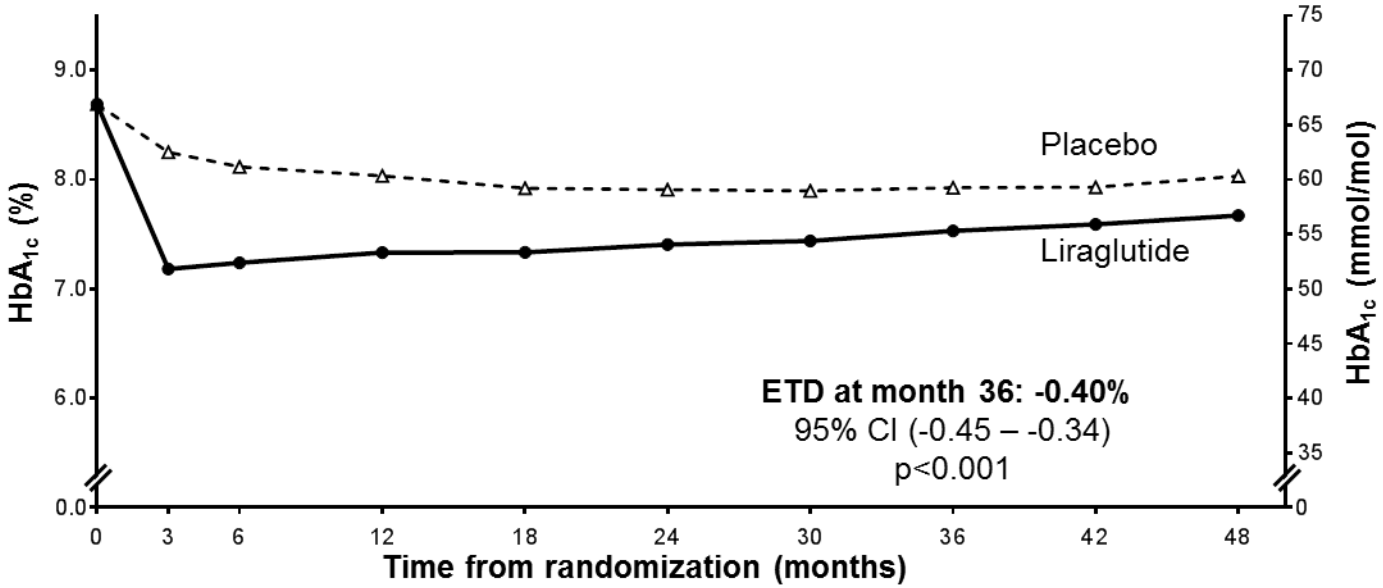
Objective of the mediation analyses

- To explore how the positive effect of liraglutide on CV outcomes is influenced by effects through the trial



A:exposure, M: Mediator, C: confounder, Y: outcome

HbA_{1c}



Number of patients at each visit

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

Data are estimated mean values from randomization to month 48.
CI: confidence interval; ETD: estimated treatment difference; HbA_{1c}: glycated hemoglobin.

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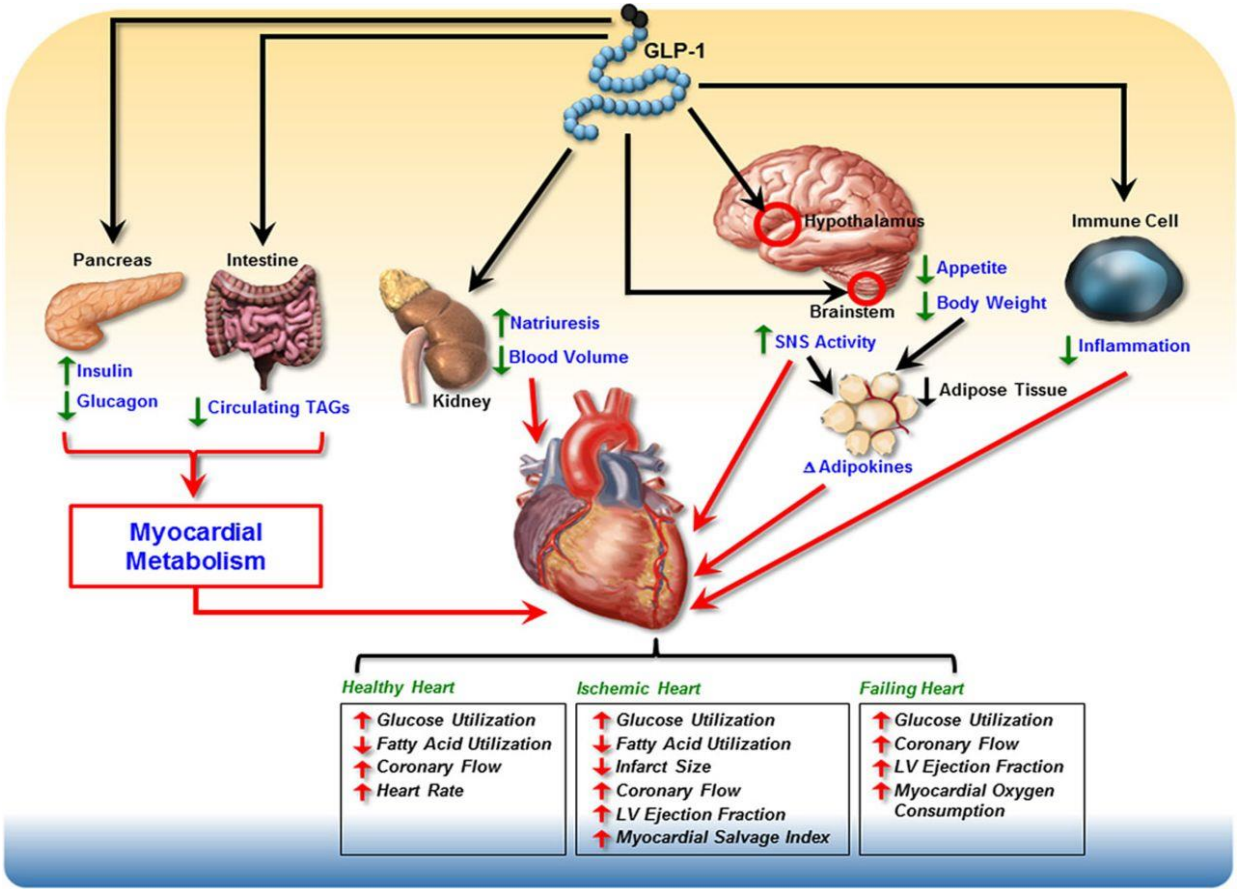
Mode of action - cardiovascular outcome



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Ussher JR, Drucker DJ. *Circ Res* 2014;114:1788–803.
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Objectives (cont.)

- Which variables mediates the effect of liraglutide?
  - How much of the effect of liraglutide on first MACE is mediated by e.g. reduction in HbA1c from baseline
- Insight in “mode of action” ~ how can the CV protective effect be explained?
  - which variables mediates the effect of treatment?
  - are the variables related to mode of action
- “Acute effect” versus “chronic effect”
  - How to differentiate (if possible)
  - Change from baseline <> absolute (mean) values

Limitations

- There is no unified approach for assessing mediation
  - Wanderweele & Lange
    - Based on counterfactual approach as seen in works from Pearl / Robbins

- Estimation cannot be employed in standard software without doing advanced programming
  - SAS macros

- Computation of confidence intervals are quite cumbersome (and somehow approximate)
  - Delta methods
  - Bootstrapping
  - MCMC?

- Cox regression in mediation analysis
  - Rare event assumption; proportion of events < 10 %
    - LEADER; primary outcome: 14% Components of primary outcome: < 10%

Direct and indirect effect – counterfactual approach

- Natural direct effects (NDE) is the effect of changing the exposure relative to the direct pathway, but keeping exposure constant relative to the indirect pathway through the mediator; i.e. Y_L (M_p) versus Y_P (M_p)

- Natural indirect effects (NIE) is the effect of changing the exposure relative to the indirect pathway, but keeping exposure constant relative to the direct pathway; i.e. Y_L (M_L) vs. Y_L (M_P)

- Total effects (TE) denotes the effect of changing the exposure; that is comparing Y_L (M_L) vs. Y_P (M_P)

Proportion mediated

- Total effect equals the natural indirect effect + natural direct effect
- Proportion (%) mediated:
  - Indirect effect / total effect *100%
  - Quite complicated formulas according to the type of regression applied
    - Example; Cox regression with a continuous mediator
  -

$$\log\left\{\lambda_{T_{aM_a}}(t|c)\right\} - \log\left\{\lambda_{T_{aM_{a^*}}}(t|c)\right\} = (\gamma_2\beta_1+\gamma_3\beta_1 a)(a-a^*)$$
$$\log\left\{\lambda_{T_{aM_{a^*}}}(t|c)\right\} - \log\left\{\lambda_{T_{a^*M_{a^*}}}(t|c)\right\} = \left\{\gamma_1+\gamma_3\left(\beta_0+\beta_1 a^*+\beta_2' c+\gamma_2\sigma^2\right)\right\}(a-a^*)+0.5\gamma_3^2\sigma^2\left(a^2-a^{*2}\right)$$

VanderWeele. T.J. (2015). Explanation in Causal Inference: Methods for Mediation and Interaction,

Challenges in LEADER study

- Cox regression
  - The preferred regression method
- Time varying mediators
  - e.g. HbA1c at different visits
- Time varying confounders
  - e.g. concomitant medication (start and stop dates)
- Interactions
  - Modifications of mediators by exposure

A simple setup of an mediator analysis - 1

- Change in HbA1c until visit 60 (6 months) as mediator
- Events before the actual visit is censored
  - To keep the direction in the causality
  - <100 events censored due to this
  - Baseline measurements is entered as a covariate
- Variables of interest
  - Direct effect attenuated ~ HR towards 1 ?
  - High proportion mediated ?

A simple setup of an mediator analysis - 2

- Change in HbA1c until event/censoring as mediator
  - May be interpreted as an ‘acute effect’
  - Baseline as confounder

- <Weighted> mean of HbA1c until event/censoring as mediator
  - May be interpreted as an ‘chronic effect’

- Variables of interest

  - Direct effect attenuated ~ HR towards 1 ?
  - High proportion mediated ?

Summary

- Liraglutide associated with CV benefits
- Mediation analysis can potentially support suggestions for biological pathways
  - Mode of action
  - Only variables measured can be used
- No unified approach yet established
- Looking forward to the next presentations!