Introduction, Study Rationale & Design

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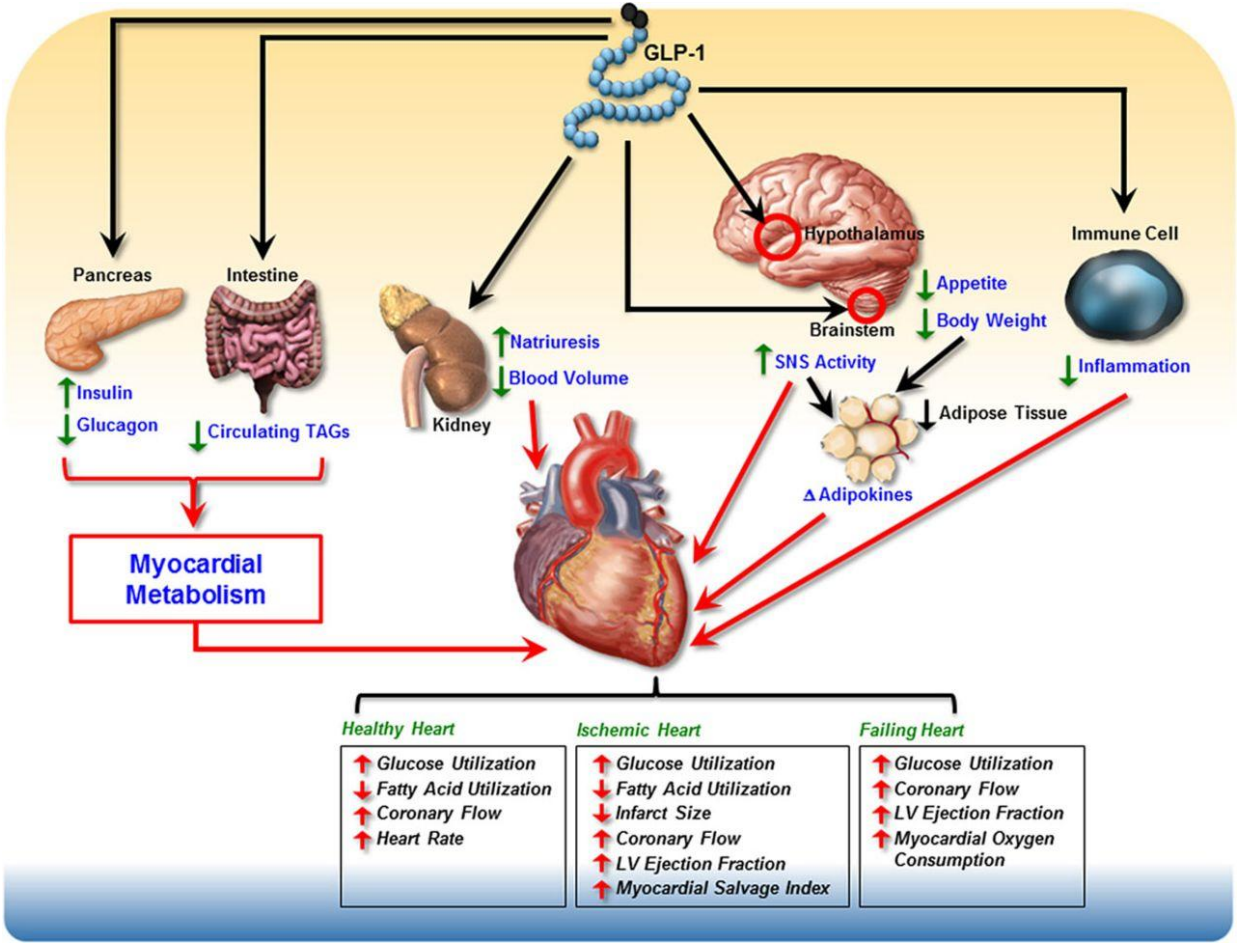
Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

UNC SCHOOL OF MEDICINE

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



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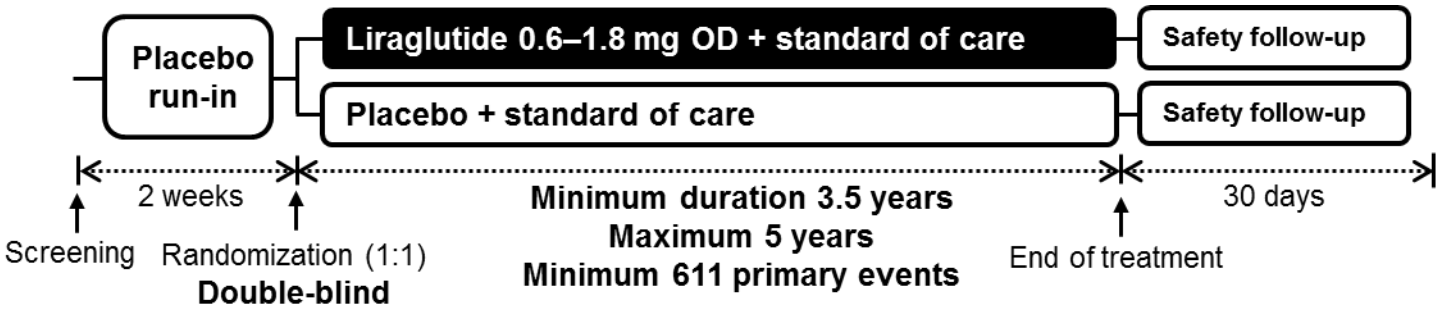

Key inclusion criteria

- 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.

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Primární a klíčové sekundární cíle

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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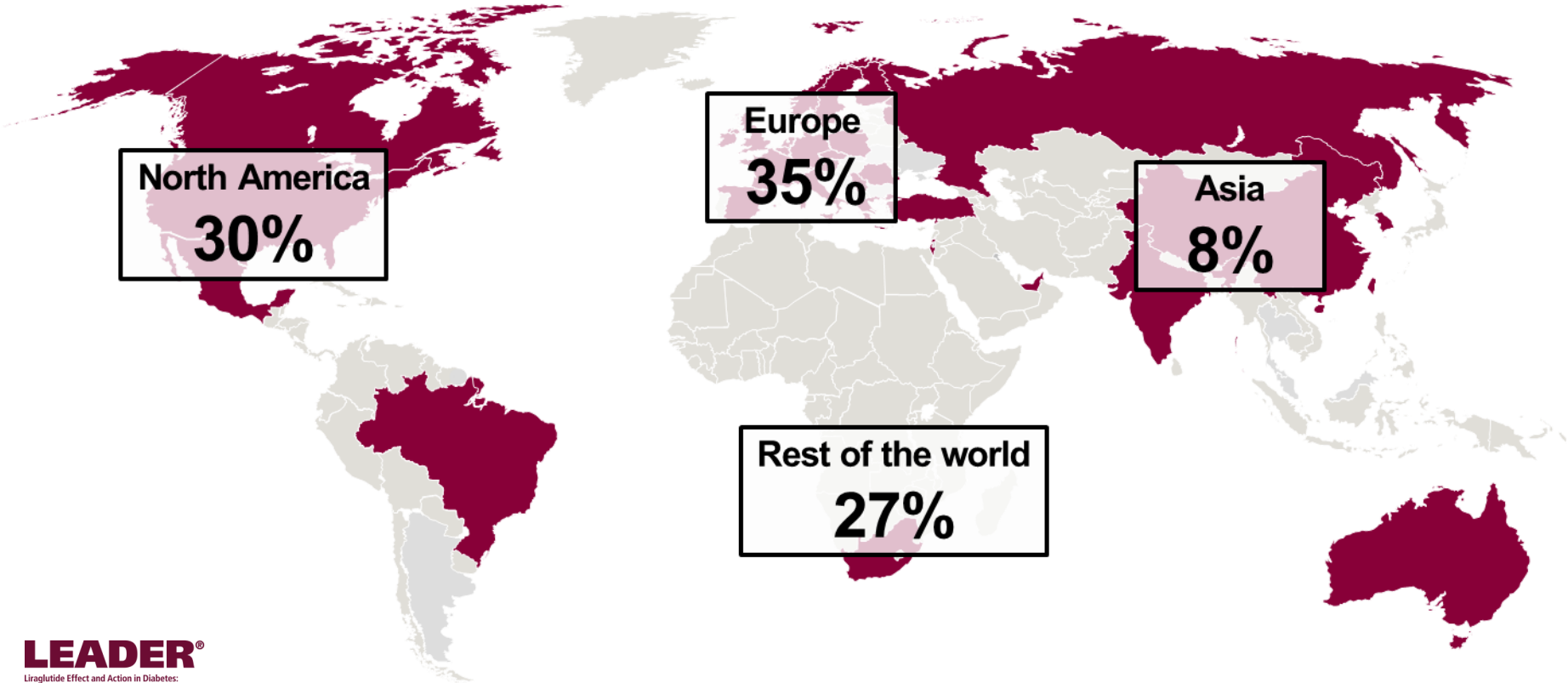

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Vstupní charakteristika

(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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Vstupní kardiovaskulární rizikový profil

	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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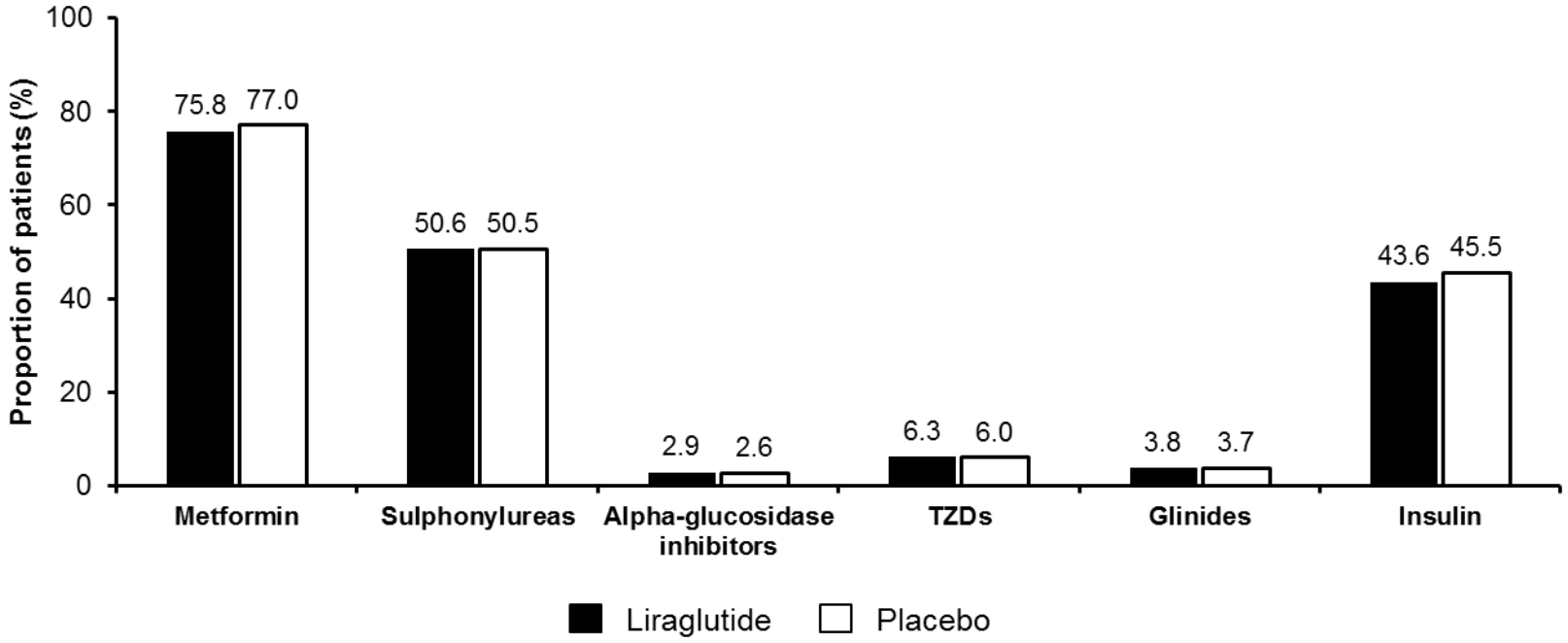
Antidiabetická terapie při vstupu



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TZD: thiazolidinediones.

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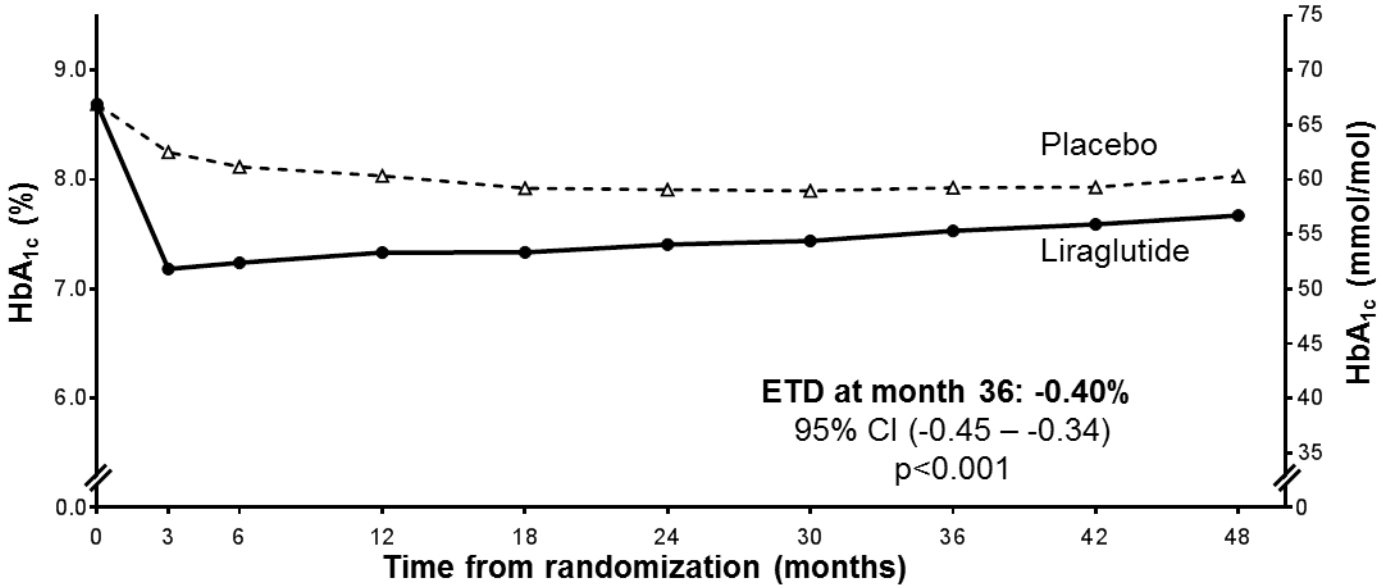
HbA_{1c}



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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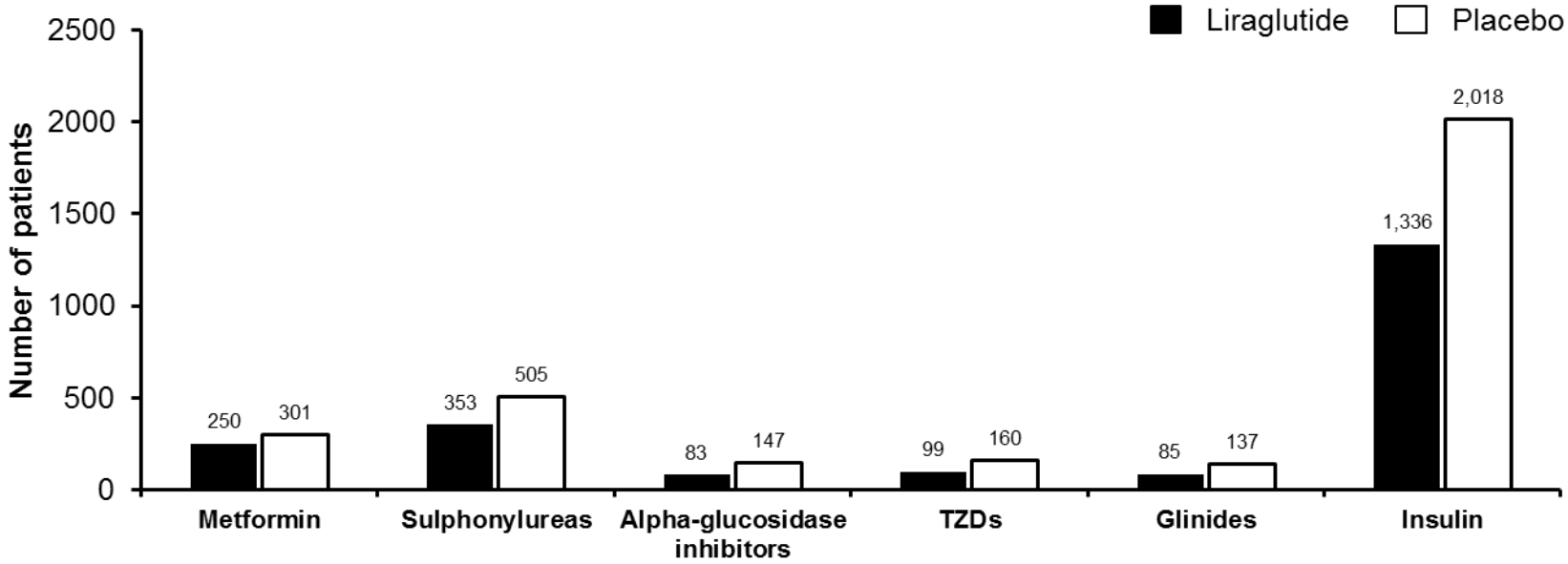
Antidiabetická medikace zavedená během studie



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

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DPP-4: dipeptidyl peptidase-4; GLP-1RA: glucagon-like peptide-1 receptor agonist; SGLT-2: sodium-glucose co-transporter-2; TZD: thiazolidinedione.

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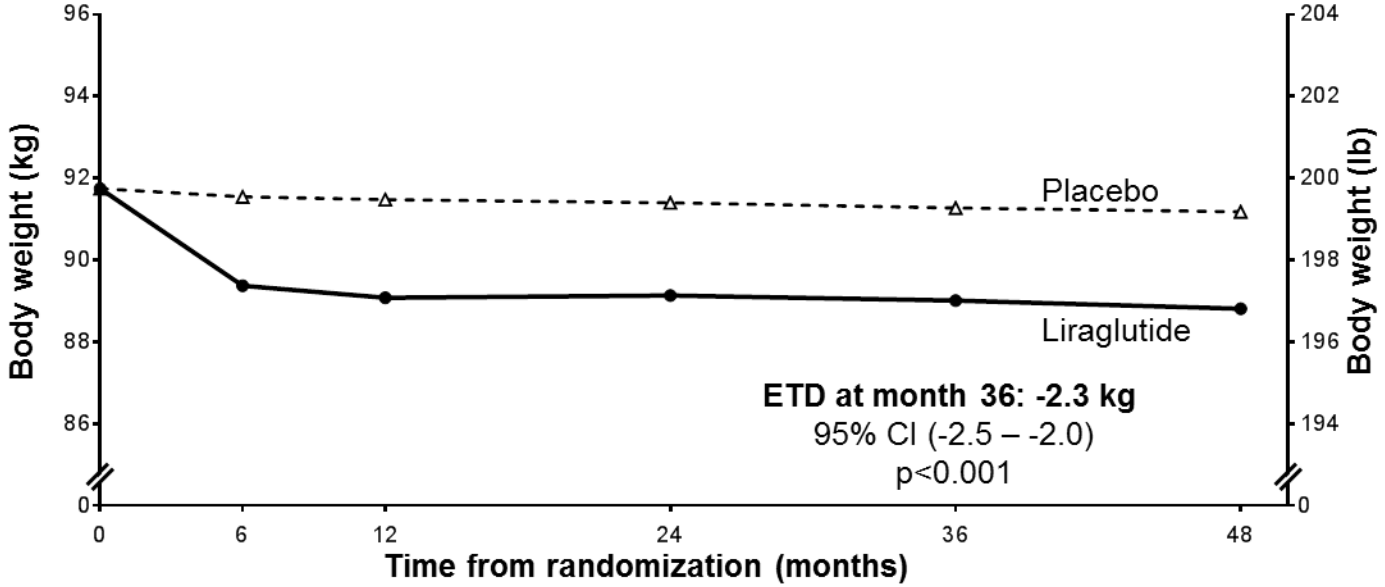
Tělesná hmotnost



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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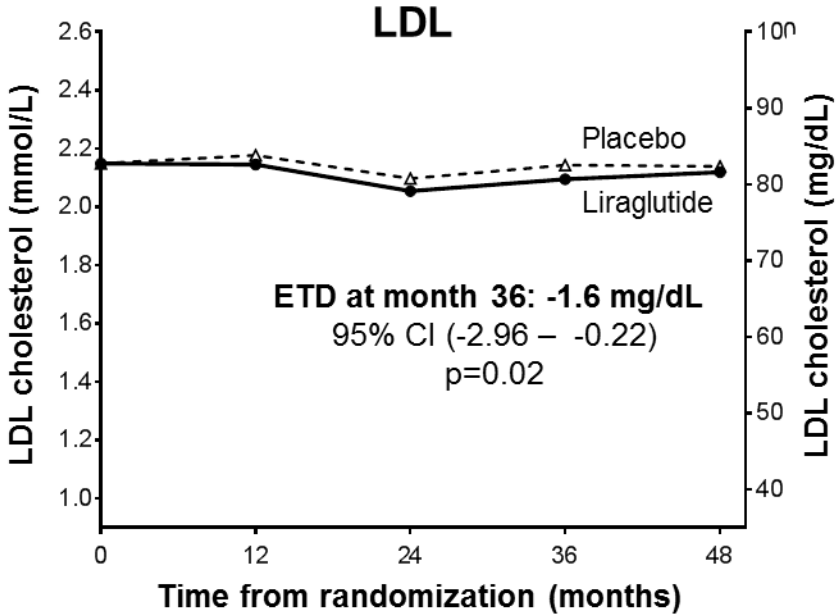
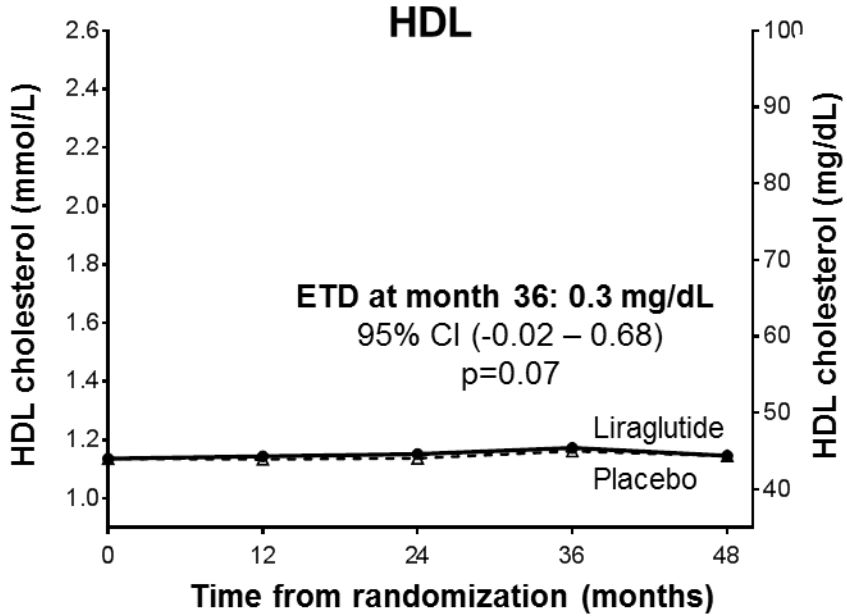
Cholesterol





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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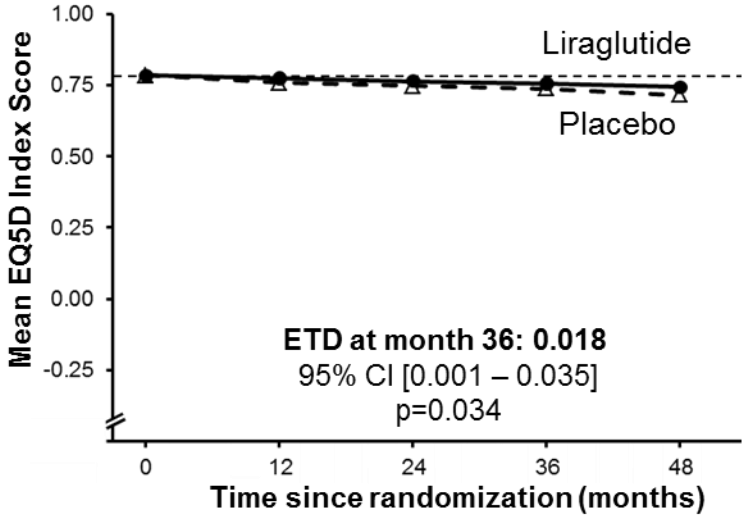
Kvalita života: EQ5D

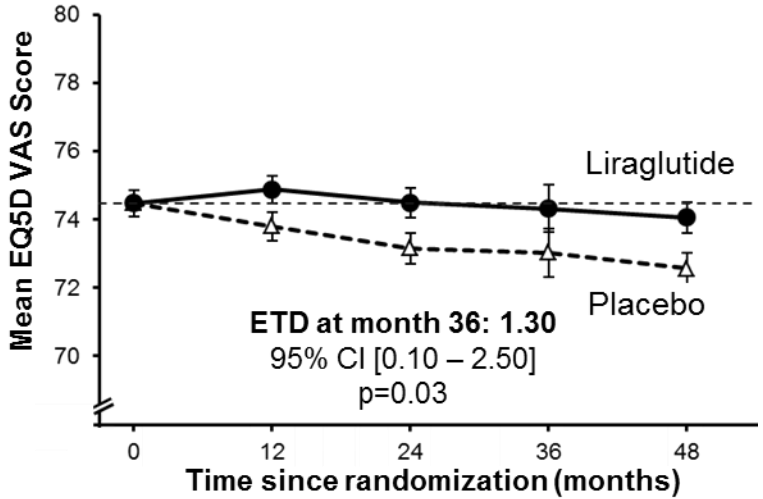
Index score



Number of patients at each visit

Liraglutide	1496	1386	1307	1219	365
Placebo	1500	1356	1269	1166	332

VAS score



Number of patients at each visit

Liraglutide	1477	1365	1290	1200	361
Placebo	1483	1339	1250	1145	323

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Full analysis set. Estimated means. Change from baseline to 3-year assessment analysed using a linear mixed model accounting for repeated measures within patients using an unstructured residual covariance matrix. Interaction between visit and respectively treatment, sex, region and antidiabetic therapy at baseline are included as fixed effects and interaction between visit and respectively baseline EQ5D Index/VAS score and age at baseline are included as covariates.
CI: confidence interval; EQ5D: EuroQol 5 Dimensions; ETD: estimated treatment difference; VAS: visual analog scale.

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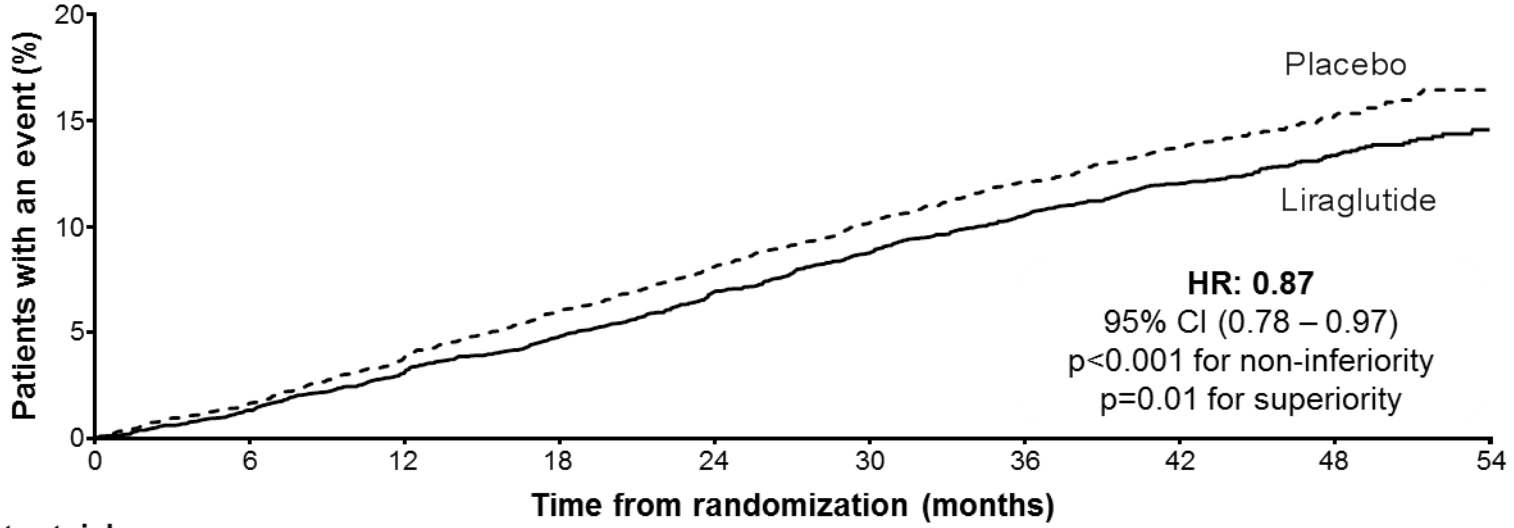
Primární cíl

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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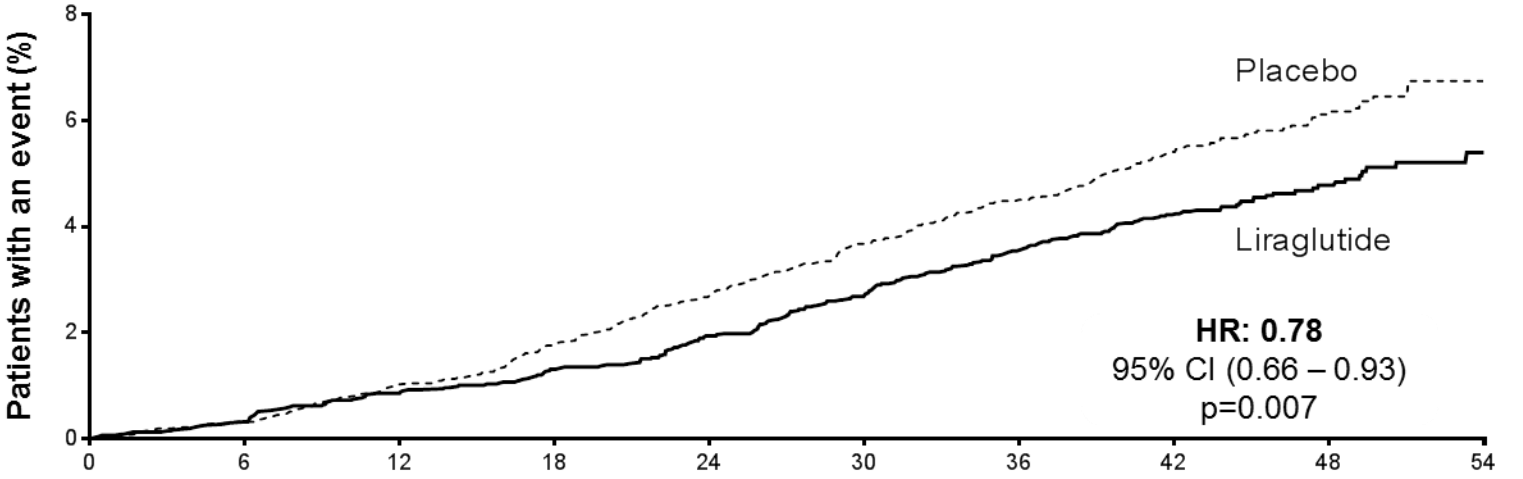
KV mortalita



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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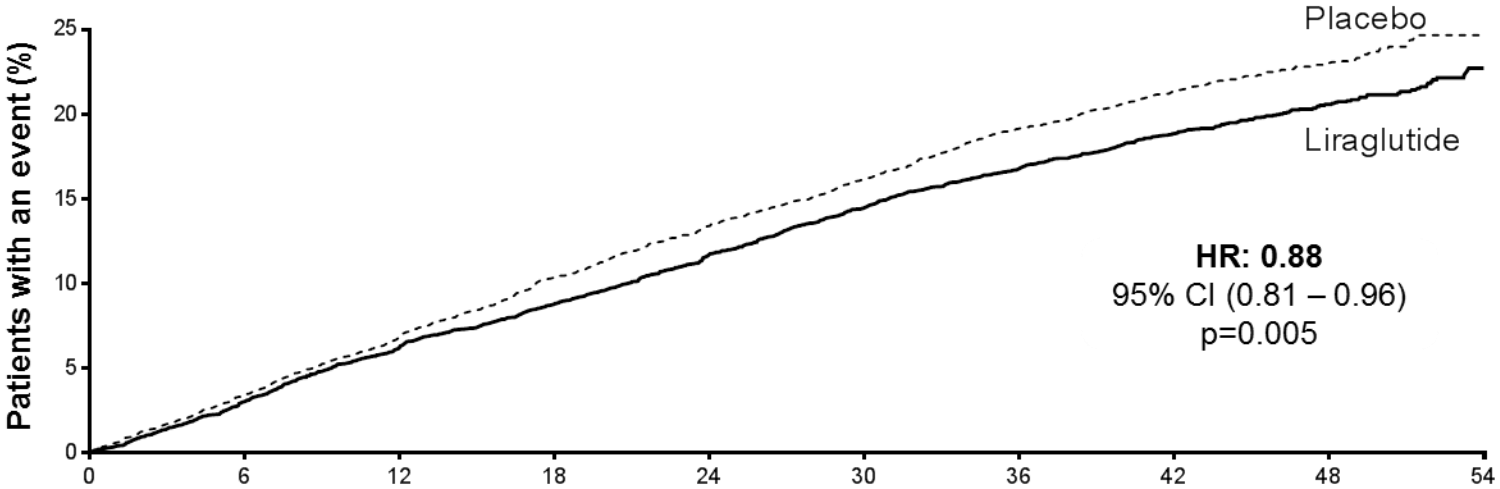
Rozšířený MACE

KV úmrtí, nefatální IM, nefatální CMP, koronární revaskularizace nebo hospitalizace pro nestabilní anginu pectoris nebo srdeční selhání



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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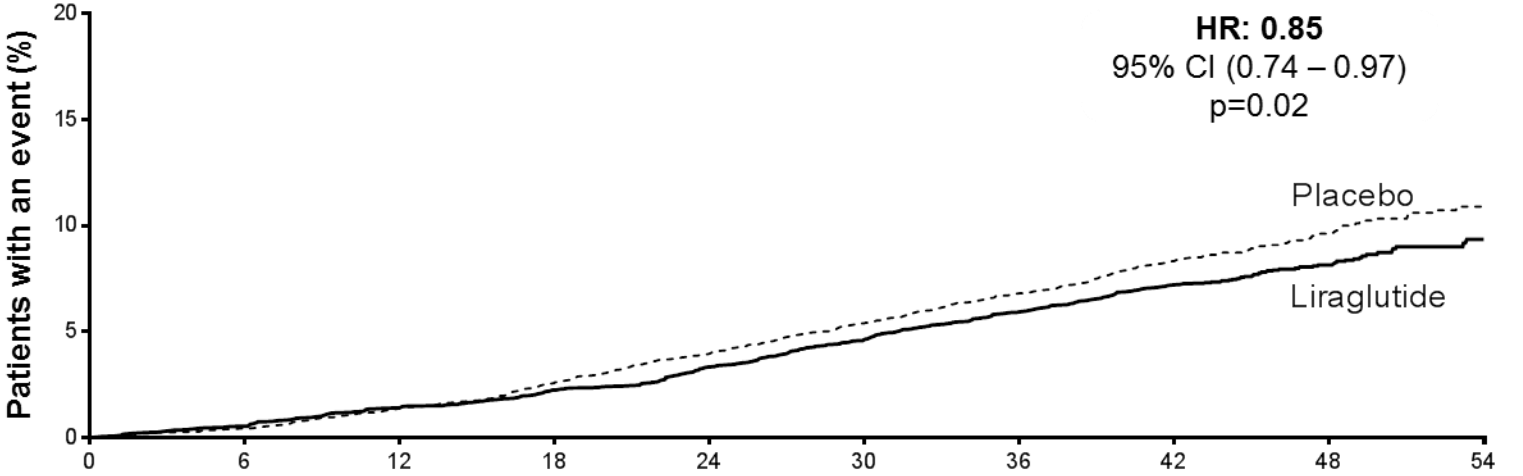
Celková mortalita



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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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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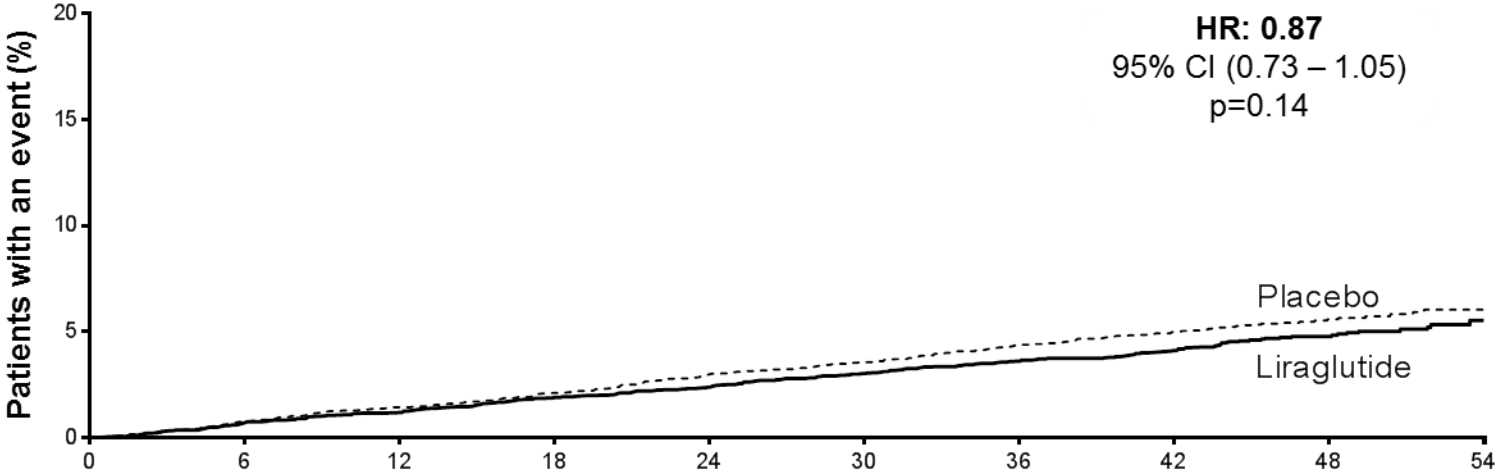
Hospitalizace pro srdeční selhání



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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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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Definice mikrovaskulárních cílů

Příhoda		Definice – jeden nebo více
Mikrovasculární příhody	**Renální**	• Nový výskyt perzistentní makroalbuminurie • Perzistentní zdojnásobení sérového kreatininu • Nová potřeba trvalé terapie nahrazující ledviny • Úmrtí pro renální onemocnění
	Oční	• Potřeba fotokoaulace retiny nebo léčba intravitreální léky • Vitreální hemorrhagie • Slepota vázaná na diabetes

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Mikrovaskulární příhody

	Liraglutide (N=4668)			Placebo (N=4672)			HR	95% CI	p-value
	N	%	Rate	N	%	Rate			
Microvascular events	355	7.6	2.0	416	8.9	2.3	0.84	0.73–0.97	0.02
Renal	268	5.7	1.5	337	7.2	1.9	0.78	0.67–0.92	0.003
Eye	106	2.3	0.6	92	2.0	0.5	1.15	0.87–1.52	0.33

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%: percentage of group; CI: confidence interval; HR: hazard ratio; N: number of patients; Rate: incidence rate per 100 patient-years of observation.

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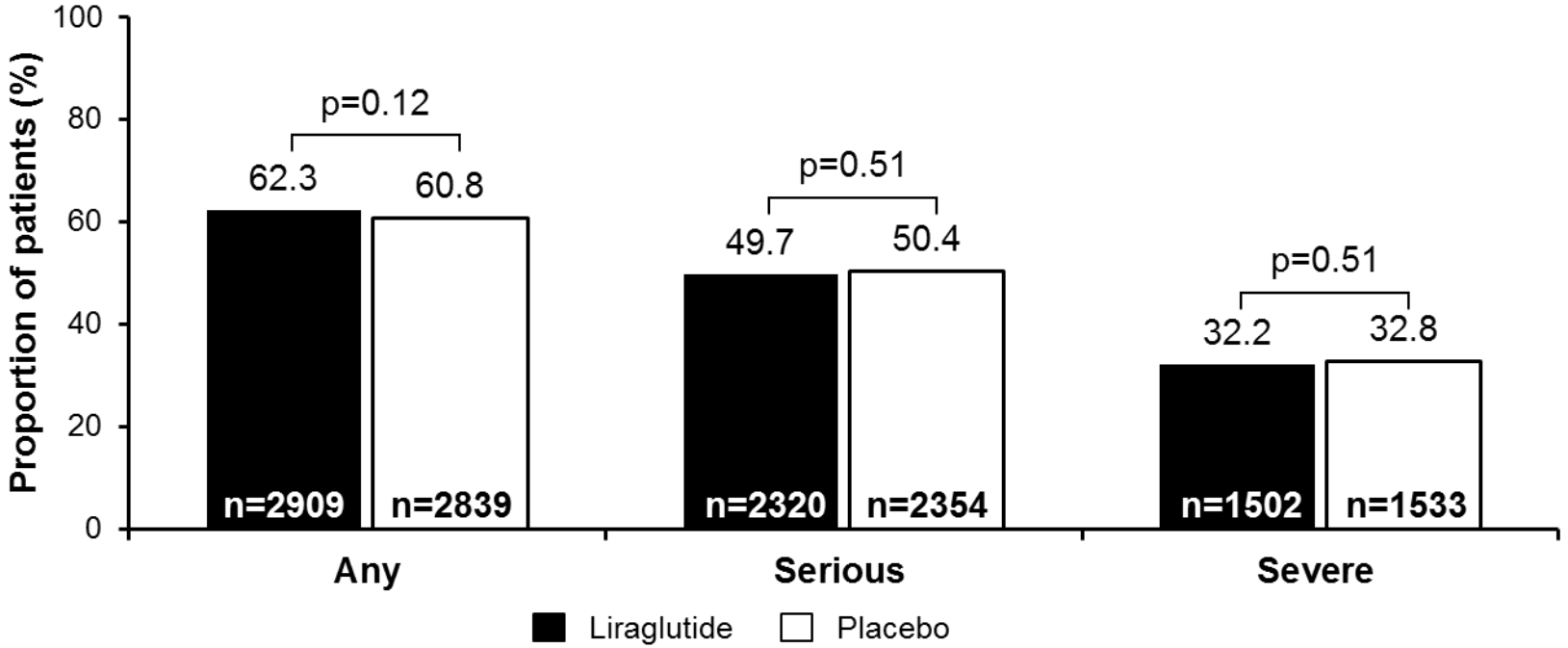
Nežádoucí účinky



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 hospitalization or prolongation of hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, important medical events that may jeopardize the patient based upon appropriate medical judgement.
- A **severe adverse event** was defined as an adverse event that resulted in considerable interference with the patient's daily activities.

N: number of patients.

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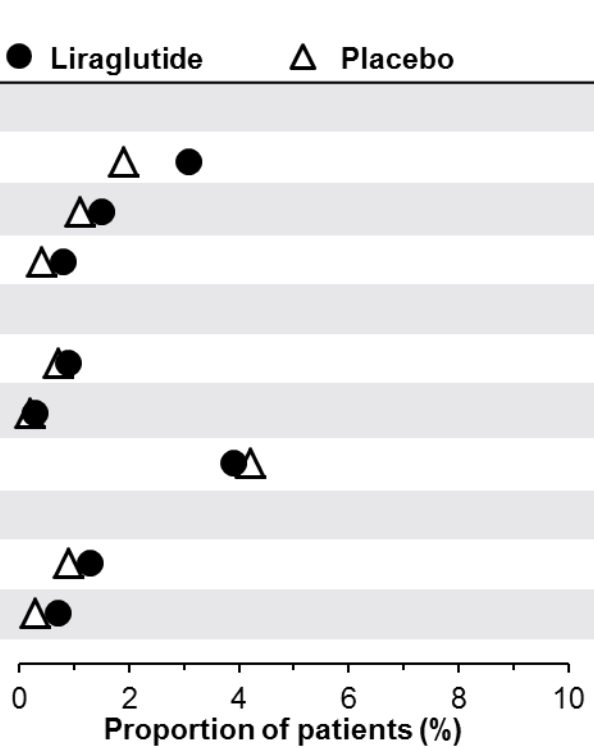
Selected adverse events of special interest

	Number of patients		p-value
	Liraglutide	Placebo	
Gallstone disease			
Acute gallstone disease	145	90	<0.001
Cholelithiasis	68	50	0.09
Acute cholecystitis	36	21	0.046
Thyroid events			
Hypothyroidism	44	33	0.21
Hyperthyroidism	13	8	0.27
Diabetic foot ulcer	181	198	0.38
Immunogenicity events			
Allergic reactions	59	44	0.14
Injection site reactions	32	12	0.002



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Serious adverse events and nonserious medical events of special interest were identified by search in the Medical Dictionary for Regulatory Activities, version 18.0, or by "action to trial product: trial product permanently discontinued due to adverse event."
P-values were calculated by means of Pearson's chi-square test.

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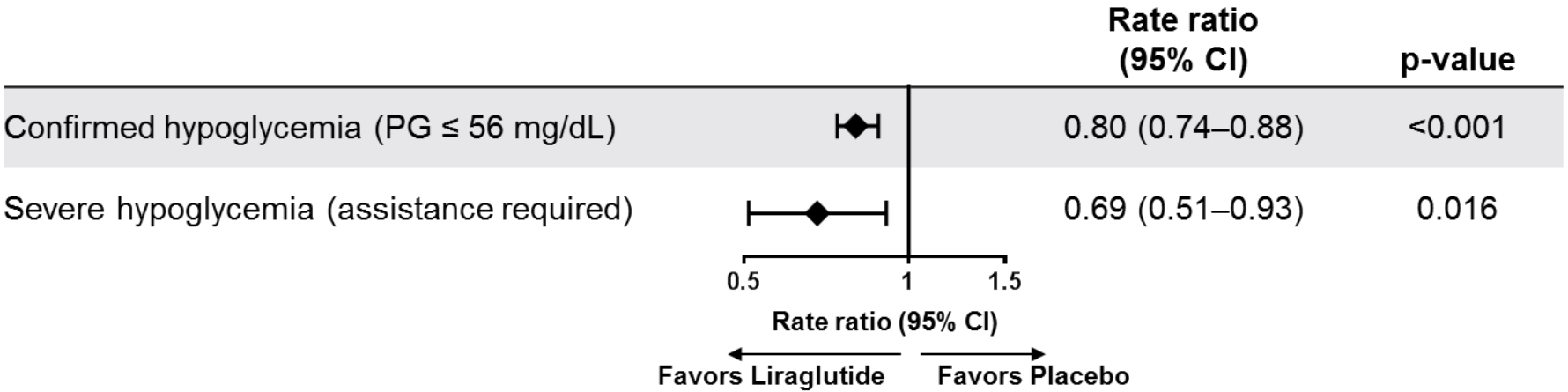
Hypoglykémie



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Confirmed hypoglycemia was defined as plasma glucose level of less than 56 mg per deciliter (3.1 mmol per liter) or a severe event. Severe hypoglycemia was defined as hypoglycemia for which the patient required assistance from a third party. Analyzed using a negative binomial regression model.
CI: confidence interval; PG: plasma glucose.

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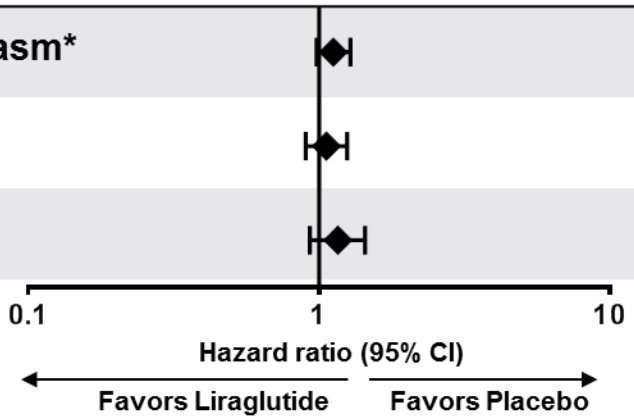
Novotvary

Confirmed by adjudication

	Hazard ratio (95% CI)	Liraglutide		Placebo	
		N	%	N	%
Any neoplasm*	1.12 (0.98–1.28)	**470**	**10.1**	**419**	**9.0**
Malignant	1.06 (0.90–1.25)	296	6.3	279	6.0
Benign	1.16 (0.93–1.44)	168	3.6	145	3.1



*EAC-confirmed neoplasms with EAC onset date from randomization date to follow-up; includes malignant, pre-malignant, benign and unspecified neoplasms. Neoplasms were adjudicated by the event adjudication committee. This committee interpreted neoplastic growth as clonal disorders that grow in an autonomous manner. The abnormality of clonal disorder may not always have been identified nor could autonomous growth always be determined, but both were considered to be fundamental aspects of neoplastic growth. Cox proportional hazard regression model adjusted for treatment.
%: proportion of patients; CI: confidence interval; EAC: Event Adjudication Committee; N: number of patients.

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LEADER: Souhrn (1)

- Liraglutide snížil riziko primárního 3-stupňového MACE o 13%

- Liraglutide snížil rizika kompozitních mikrovaskulárních endpotinů zejména snížením nové a perzistentní makroalbuminurie
- Liraglutid snížil HbA_{1c}, hmotnost a bylo při něm méně hypoglykémií

- Liraglutide byl všeobecně dobře tolerovaný

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HbA_{1c}: glycated hemoglobin; MACE: major adverse cardiovascular event.

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LEADER: Souhrn (2)

- Nebylo více pancreatitid, ale bylo zvýšení akutní lithiázy
- Nebylo zvýšení hospitalizací pro srdeční selhání
- Liraglutid snížil riziko celkového úmrtí o 15%
- Liraglutid snížil riziko KV úmrtí o 22%

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

CV: cardiovascular.

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