P2858
Liraglutide reduces cardiovascular events and mortality in type 2 diabetes independent of LDL cholesterol and statin use: results of the LEADER trial

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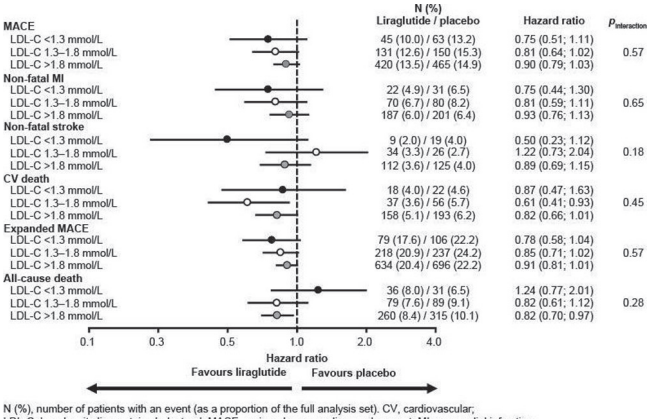
Background: The relationships among low-density lipid cholesterol (LDL-C) levels, statin use and cardiovascular (CV) outcomes are well established. In the LEADER trial, the human glucagon-like peptide 1 analogue liraglutide reduced CV events in patients with type 2 diabetes (T2D) at high CV risk.
Purpose: This post hoc analysis evaluated liraglutide effects on CV outcomes by baseline LDL-C and statin use.
Methods: LEADER (NCT01179048) studied liraglutide (1.8 mg or maximum tolerated dose) vs placebo, both in addition to standard care, in 9340 patients with T2D and high CV risk (median follow-up 3.8 years). Primary outcome: composite of CV death, non-fatal myocardial infarction, or non-fatal stroke (major adverse CV events, MACE). The key secondary expanded outcome (expanded MACE) also included hospitalisation for unstable angina or heart failure, or revascularisation. Cox regression evaluated the liraglutide effect on CV outcomes by baseline LDL-C <1.3 mmol/L, 1.3–1.8 mmol/L and >1.8 mmol/L, and statin use at baseline.
Results: In LEADER, 9187 patients had LDL-C measured: 926 (10.1%), 2021 (22.0%) and 6240 (67.9%) had baseline LDL-C <1.3 mmol/L, 1.3–1.8 mmol/L or >1.8 mmol/L, respectively. Baseline characteristics: see Table. Within the groups by LDL-C level, baseline characteristics were well-balanced across treatment groups. Liraglutide consistently reduced MACE vs placebo irrespective of baseline LDL-C (hazard ratio [HR] 0.75, 95% CI 0.51–1.11 vs HR 0.81, 95% CI 0.64–1.02 vs HR 0.90, 95% CI 0.79–1.03, p interaction=0.57). Results were similar for expanded MACE and individual MACE components (Figure). Liraglutide reduced MACE vs placebo in statin users (72%) (HR 0.83, 95% 0.73–0.94). Non-statin users (28%): HR 0.97, 95% CI 0.79–1.20 (interaction between statin and non-statin users p=0.19). Results were similar in a model adjusted for baseline characteristics.



N (%), number of patients with an event (as a proportion of the full analysis set). CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction

CV outcomes by LDL-C and treatment

Conclusions: In LEADER, liraglutide was associated with lower risk of major CV events in patients with T2D across the entire spectrum of LDL-C and statin use, with event reduction even in patients with the lowest LDL-C levels.
Funding Acknowledgements: Novo Nordisk A/S

P2859
Semaglutide consistently reduces cardiovascular risk in patients with type 2 diabetes regardless of baseline cardiovascular risk level: post hoc analyses of the SUSTAIN trial programme

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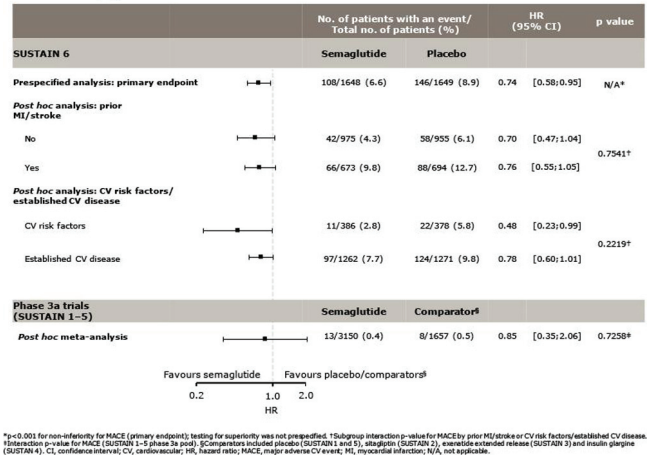
Background/Introduction: Semaglutide is a glucagon-like peptide-1 analogue for the once-weekly treatment of type 2 diabetes (T2D). Treatment with semaglutide led to significant reductions in HbA1c and body weight vs all comparators across the SUSTAIN phase 3a clinical trial programme. In SUSTAIN 6, 3,297 subjects with T2D and established cardiovascular (CV) disease or high CV risk (subclinical evidence of CV disease) were randomised to subcutaneous semaglutide (0.5 or 1.0 mg) or placebo, added to standard of care; the median duration of follow-up was 2.1 years. Semaglutide-treated patients had a significant 26% lower risk of major adverse CV events (MACE: a primary composite outcome of non-fatal myocardial infarction [MI], non-fatal stroke or CV death) vs those receiving placebo over 2 years (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.58; 0.95).
Purpose: To assess the consistency of the CV effect of semaglutide across subgroups at different CV risk levels in SUSTAIN 6. Additionally, to examine the risk of MACE in the SUSTAIN 1–5 phase 3a trials, which included subjects at lower CV risk (n=4,807).
Methods: In SUSTAIN 6, two post hoc subgroup analyses were performed, each dividing the population into two CV risk levels at baseline: 1) prior MI or stroke (yes/no); 2) CV risk factors vs established CV disease (prior stroke, ischaemic heart disease [including prior MI], peripheral arterial disease, ≥50% arterial stenosis [any artery] or heart failure). A post hoc meta-analysis of MACE in the SUSTAIN 1–5 trials was also conducted.
Results: In SUSTAIN 6, HRs for MACE were consistently below 1.0 across subgroups with no significant interactions (Figure). The HR for MACE in the SUSTAIN 1–5 trials was 0.85 (95% CI 0.35; 2.06), with the wide CI reflecting the low number of events (Figure).

Figure: Risk of major adverse cardiovascular events in SUSTAIN 6 and SUSTAIN 1–5 phase 3a trials in the SUSTAIN programme



*p<0.001 for non-inferiority for MACE (primary endpoint); testing for superiority was not prespecified. †Subgroup interaction p-value for MACE by prior MI/stroke or CV risk factors/established CV disease. ‡Interaction p-value for MACE (SUSTAIN 1–5 phase 3a pool). §Comparators included placebo (SUSTAIN 1 and 5), sitagliptin (SUSTAIN 2), exenatide extended release (SUSTAIN 3) and insulin glargine (SUSTAN 4). CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse CV event; MI, myocardial infarction; N/A, not applicable.

Conclusion: Consistent CV risk reduction with semaglutide vs comparators was observed across T2D populations at different levels of CV risk at baseline.
Funding Acknowledgements: Sponsored by Novo Nordisk A/S

P2860
MRI evaluation of the impact of metformin and dapagloflizin on epicardial adipose tissue area in prediabetes and type 2 diabetes patients

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Background: Epicardial adipose tissue (EAT) is an emerging cardio-metabolic risk factor that has been shown to correlate with adverse cardiovascular outcomes through potential local and systemic effects. Consequently, EAT has been proposed as a therapeutic target. The biguanide, metformin, and Sodium-glucose Cotransporter-2 inhibitors have been reported to improve cardiovascular outcomes. We have investigated the effects of both metformin and dapagliflozin, on EAT in patients with prediabetes and type 2 diabetes respectively.

Abstract P2858 – Table 1. Baseline characteristics by LDL-C

	Age, years		LDL, mmol/L		Statin use, n (%)		Prior CV, n (%)	
	Liraglutide	Placebo	Liraglutide	Placebo	Liraglutide	Placebo	Liraglutide	Placebo
LDL-C <1.3 mmol/L	64.9 (7.2)	64.2 (7.2)	1.0 (0.2)	1.0 (0.2)	390 (87.1%)	420 (87.9%)	214 (47.8%)	222 (46.4%)
LDL-C 1.3 to 1.8 mmol/L	64.7 (7.2)	64.7 (7.2)	1.6 (0.1)	1.6 (0.1)	926 (88.9%)	865 (88.4%)	490 (47.0%)	456 (46.6%)
LDL-C >1.8 mmol/L	63.9 (7.2)	64.3 (7.2)	2.8 (0.8)	2.8 (0.8)	2039 (65.6%)	1989 (63.5%)	1269 (40.8%)	1280 (40.9%)

Baseline characteristics based on 9187 patients with measured baseline LDL from overall LEADER population (N=9340). Values are mean (standard deviation, SD) or n (% patients within that subgroup). "Prior CV" = prior myocardial infarction or stroke.

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