antagonist exendin(9-39), or inhibition of GLP-1R signaling with the PKA inhibitor H89 or by siRNA-mediated knockdown of the GLP-1R fully abolished the ability of exendin-4 to prevent apoptosis and autophagy.
Conclusion: Palmitate promotes apoptosis in hCPC, whereas oleate and EPA appear to have no impact on hCPC viability. Exendin-4 prevents the palmitate-induced abnormalities of hCPC and hCS by counteracting ceramide generation. Hence, GLP-1 and its analogues may limit the lipotoxic damage in the human heart by preserving the viability of myocardial progenitors.
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Disclosure: **R. D'Oria:** None.

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Anti-atherogenic effects of liraglutide independent of the AMPK pathway in diabetic apolipoprotein E-null mice

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Background and aims: Accumulating evidence supports the anti-atherogenic effect of glucagon like peptide (GLP)-1 in addition to its glucose lowering effect. Among various mechanisms proposed, AMP-activated protein kinase (AMPK) has been demonstrated as a central molecule mediating this effect of GLP-1. However, whether GLP-1 could suppress atherosclerosis independent of the AMPK pathway remains unclear.
Materials and methods: Male apolipoprotein E-null mice (BalBc-background) were intra-peritoneally injected with 100 mg kg^{-1} d^{-1} of streptozotocin for 5 consecutive days at 15 w/o, following which, they were again injected with streptozotocin at 50 mg kg^{-1} d^{-1} at 17 w/o. At 20 w/o, mice with blood glucose levels over 11 mmol/L were used for experiments. The diabetic mice were switched to a western diet (0.15% cholesterol and 30% fat), and were subcutaneously implanted with two osmotic pumps for agent delivery: one for saline or liraglutide 17 or 107 nmol kg^{-1} d^{-1} (low and high dose, respectively) and the other for saline or an AMPK inhibitor dorsomorphine hydrochloride (25 mg kg^{-1} d^{-1}). Thioglycolate-induced peritoneal macrophages and vessel samples were collected after 4 weeks.
Results: The diabetic mice showed severe hyperglycaemia (fasting blood glucose, 15±2 mmol/L; HbA1c, 8.9±0.4%) and dyslipidaemia (total cholesterol, 12.7±0.2 mmol/L). Although HbA1c levels tended to be lower in liraglutide-treated mice, there was no significant difference in physiological and biochemical parameters between the groups. Both doses of liraglutide reduced atherosclerotic plaque burden (oil red O staining) and intra-plaque macrophage accumulation (MOMA-2 staining) at the aortic sinus by approximately 50%. In addition, plaque area on the aortic surface was lower in liraglutide-treated mice than those in saline-treated mice. Treatment with the AMPK inhibitor enhanced atherosclerosis compared to that observed with saline treatment, without affecting physiological and biochemical parameters. In the mice co-treated with the AMPK inhibitor, anti-atherogenic effects of low-dose liraglutide were completely abolished, while those of high-dose liraglutide were preserved. In the right brachiocephalic artery, an atherosclerotic lesion-prone site, both doses of liraglutide reduced the expression of interleukin-6 and monocyte chemotactic protein-1 as assessed by real time PCR. High-dose liraglutide suppressed the expression of these molecules in the presence of the AMPK inhibitor, while low-dose liraglutide failed to do so. In the induced peritoneal macrophages, high-dose liraglutide also suppressed the expression of pro-inflammatory cytokines in the presence of the AMPK inhibitor.
Conclusion: We demonstrated that both AMPK-dependent and independent mechanisms are involved in the anti-atherogenic effects of liraglutide, and that a higher dose of liraglutide is required to exert anti-inflammatory effects independent of AMPK.
Disclosure: **M. Koshibu:** None.

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GLP-1 secretion after myocardial infarction is amplified by linagliptin and leads to improved left ventricular function and mitochondrial respiratory capacity

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Background and aims: The incretin hormone GLP-1 holds cardioprotective efficacy and was recently found to be increased by inflammatory stimuli. This study was performed to characterize the secretion of GLP-1 in response to myocardial infarction in mice and investigate its functional relevance.
Materials and methods: Myocardial infarction (MI) was induced by permanent LAD ligation in 6 week old, male C57BL/6J mice, the dipeptidylpeptidase-4 (DPP-4) inhibitor linagliptin (3 mg/kg p.o., bid) was given for 3 days before to LAD ligation, GLP-1 and exendin-9 (both 100 nM/kg i.p.) were given for 1 day before LAD ligation, experiments were performed in wild type and GLP-1 Receptor KO mice.
Results: Myocardial infarction (MI) led to a significant increase of circulating GLP-1 concentrations (from 7.9 pM to a maximum of 20.8 pM after 6 hours; n=6; $p<0.05$ in comparison to baseline and sham control). Prevention of GLP-1 degradation by pretreatment with linagliptin increased left ventricular contractility (10101± 1690 dp/dt by Millar catheter) relative to control (7830 ± 1445 dp/dt; $p<0.05$ n=8) 6h post MI, while antagonism of the GLP-1 receptor (exendin-9; 100 nM/kg i.p., 1 day pretreatment) worsened contractility (6469 ± 944 dp/dt; $p< 0.05$ n=7). Further, linagliptin failed to improve left ventricular function in GLP-1 receptor KO mice demonstrating a GLP-1 receptor-dependent effect. Mechanistically we found linagliptin or GLP-1 pretreatment to similarly increase myocardial AMPK-activation in non-infarcted tissue (1.6 fold induction by linagliptin; $p< 0.01$ n=6; 1.5 fold induction by GLP-1; $p<0.04$ n=4;), which was associated with improved respiratory capacity of isolated mitochondria from non-infarcted myocardial tissue (2 fold induction by GLP-1; $p<0.04$ n=6; 1.7 fold induction by DPP-4 inhibition; $p< 0.04$ n=7) detected by Clark electrode.
Conclusion: Myocardial infarction is a GLP-1 secreting stimulus, which improves left ventricular function in a GLP-1 receptor dependent manner. This is amplified by linagliptin dependent DPP-4 inhibition leading to AMPK-activation and improved mitochondrial respiration of cardiomyocytes in non-infarcted tissue.
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Effect of liraglutide on physical performance in type 2 diabetes (LIPER2): a randomised, double-blind, controlled trial

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Background and aims: Preclinical studies and small clinical trials suggest that glucagon-like peptide 1 (GLP1) may have a positive effect on ventricular function. A clinical trial showed reduced cardiovascular

events in patients with type 2 diabetes treated with the GLP1 analogue liraglutide. The aim of this study was to assess the effect of liraglutide on measures of cardiac function and physical performance in patients with type 2 diabetes.

Materials and methods: LIPER 2 is a phase IV, randomized, double-blind, placebo-controlled, parallel-design trial. Patients with type 2 diabetes and an HbA1c of 7-10% on oral agents (except DPP4 inhibitors) and/or intermediate/long-acting insulin were randomised (computer-generated sequence, ratio 1:1) to receive liraglutide 1.8mg/d vs placebo for 6 months. The primary end-point was the maximal oxygen consumption (VO2 max) during a cycle ergometry. Other end-points included distance covered during a 6-min walk test, left ventricular ejection fraction and other measures of ventricular systolic and diastolic functions assessed by echocardiography (following international guidelines), heart rate, blood pressure, pro-brain natriuretic peptide, C-reactive protein, HbA1c, lipids, apolipoprotein B, body weight and waist girth. Safety end-points were also monitored. Intention to treat analysis was performed (all randomised patients included). Last observation carry forward was performed for missing data.

Results: Twenty four patients (15 women), aged 52 (11.7) years, with 8.7 (5.8) years' diabetes duration, BMI 34.98 (6.2) Kg/m^2, HbA1c 8.2 (0.68)% were randomised to liraglutide (12) or placebo. There were no differences in VO_2máx (17.98 (4.8) vs 15.90 (4.96) ml/Kg/min, p>0.1), VE/VCO2 slope (30.18 (4.8) vs 32 (4.49)), left ventricular ejection fraction, measures of diastolic function such as E/E', or in the 6 min walk test (530.7 (86) vs 503.9 (84) metres) at 6 months. There was a trend towards lower maximal systolic blood pressure during the ergometry (171.7 (24.4) vs 192.5 (25.6) mmHg, p=0.052), as well as lower HbA1c (6.7 vs 7.7% p=0.005) at the end of the study in the liraglutide group. There were no severe adverse events. All the patients receiving liraglutide (1 drop-out) and 25% of those receiving placebo reported gastro-intestinal symptoms. Amylase and lipase were higher in the treated group.

Conclusion: In this small study, liraglutide improved glycaemic control in type 2 diabetes, but did not show significant effects on physical performance or myocardial function. Gastrointestinal symptoms were very common.

Clinical Trial Registration Number: UTN: U1111-1128-8762

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Effect of cilostazol, a phosphodiesterase III inhibitor, on coronary artery stenosis and plaque characteristics in patients with type 2 diabetes

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Background and aims: Cilostazol is an antiplatelet agent that inhibits phosphodiesterase III, increases cAMP concentrations and consequently inhibits platelet aggregation. Cilostazol also has beneficial effect on vascular smooth muscle cell, endothelial cell and lipid metabolism. Therefore, it may be effective in treatment of macrovascular complication in diabetes. We performed a prospective interventional study to evaluate the effect of cilostazol compared with aspirin in Korean diabetic patients with subclinical coronary atherosclerosis.

Materials and methods: One hundred diabetic patients (64 men, ages 60.9 ± 9.1 years) who had mild to moderate atheroma evaluated with coronary multidetector-row CT (MDCT) were randomly assigned to either cilostazol 200 mg/day (CTZ group) or aspirin 100 mg/day (ASA group) (n = 50 each) for 12 months. Coronary artery calcium score (CACS) and coronary artery stenosis and plaque volume were investigated. Primary outcome was change of coronary artery disease assessed by coronary MDCT. Secondary outcomes included change in risk factors of atherosclerosis such as glucose and lipid metabolism and inflammatory parameter.

Results: The CACS was increased in both groups (316.6 ± 525.9 to 372.2 ± 575.2 in CTZ group, p <0.05 and 328.0 ± 481.7 to 388.5 ± 515.2, p <0.05 in ASA group). In CTZ group, there was significant decrease in maximal coronary stenosis (48.1 ± 17.9 to 38.8 ± 24.6%, p = 0.010), however, there was a small insignificant decrease in ASA group (41.7 ± 14.3 to 39.5 ± 13.3%, p = 0.118). The total plaque volume decreased from 75.2 ± 53.1 to 64.8 ± 52.2 mm^3 in CTZ group and slightly decreased from 74.9 ± 56.5 to 72.4 ± 55.3 mm^3 in the ASA group (p = 0.020 and p = 0.867, respectively). Furthermore, in CTZ group, non-calcified plaque volume decreased significantly (17.6 ± 9.5 to 11.5 ± 3.6 mm^3, p = 0.037) and calcified plaque volume also decreased but statistically insignificant (59.7 ± 48.8 to 52.9 ± 47.2 mm^3, p = 0.074). However, in ASA group, there were insignificant differences both in non-calcified and calcified plaque volumes (p >0.05 for all). Triglycerides and HDL-cholesterol improved significantly in CTZ group (135.5 ± 68.3 to 114.6 ± 46.5 mg/dL, p = 0.017 in triglycerides and 47.8 ± 10.1 to 51.2 ± 10.4 mg/dL, p = 0.011 in HDL-cholesterol).

Conclusion: The present study demonstrated that cilostazol treatment decreased coronary artery plaque, particularly in noncalcified portion and improved lipid profile. Cilostazol is a potential treatment option for preventing the progression of coronary atherosclerosis in patients with diabetes.

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Disclosure: **D. Lee:** None.

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Higher one-year mortality in patients with diabetes and ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention

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Background and aims: Patients with diabetes mellitus have a worse prognosis after acute coronary syndromes than patients without diabetes. Outcomes in patients with diabetes after ST-segment elevation myocardial infarction (STEMI) in the era of modern interventional treatment and antiplatelet therapy are less well studied. The aim is to characterise outcomes and complications in a contemporary population with diabetes and STEMI undergoing primary percutaneous coronary intervention (PCI).

Materials and methods: In the registry-based randomised Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia (TASTE) trial, 7244 patients with STEMI were randomised to undergo manual thrombus aspiration followed by PCI or to undergo PCI alone. Thrombus aspiration did not affect mortality at one year in the 1005 patients (13.9%) with diabetes [Hazard ratio (HR) 1.04; CI 0.69-1.58, p=0.839]. Therefore, all patients with diabetes, irrespective of randomisation in TASTE, were studied as one cohort. All patients were followed for incidence of all-cause mortality, myocardial infarction or stent thrombosis until one year after index event. HRs were calculated using a Cox proportional hazard regression model adjusted for comorbidities.

Results: Patients with diabetes were older (mean age 67.6 vs 66.0 years, p<0.001), more often had a previous myocardial infarction (19.9 vs 10.3%, p<0.001) and undergone previous PCI (17.3 vs 8.4%, p<0.001).