Potential cardiovascular benefits of GLP-1 analogues: evidence and implications for type 2 diabetes management

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Glucagon-like peptide-1 (GLP-1) analogues are an injectable therapy used in the management of type 2 diabetes. These drugs seem to reduce cardiovascular risk factors and clinical trial data seems to suggest that liraglutide and semaglutide reduce cardiovascular risk in patients with type 2 diabetes and concomitant atherosclerotic cardiovascular disease. The search for agents such as these (and SGLT2 inhibitors) that not only manage diabetes but also reduce cardiovascular risk has resulted in a paradigm shift in the way diabetes can be managed.

Keywords: type 2 diabetes, GLP-1 analogues, LEADER, SUSTAIN-6, ELIXA, liraglutide, semaglutide

Introduction

Glucagon-like peptide-1 (GLP-1) receptor analogues are modified forms of the GLP-1 molecule that are structurally homologous to human GLP-1 but are resistant to degradation by the dipeptidyl peptidase-4 (DPP-4) enzyme.¹ This results in a longer duration of action. Examples of the GLP-1 analogues include: albiglutide, exenatide, liraglutide, semaglutide and lixisenitide.^{1,2} These analogues work by increasing circulating levels of GLP-1 which increases insulin secretion, decreases glucagon secretion, enhances satiety and delays gastric emptying.¹ GLP-1 analogues have been considered to be an ideal agent in the management of type 2 diabetes mellitus (T2DM) because they not only reduce blood glucose levels, have durable effects on glycaemic control and beta-cell function but also have an effect on cardiovascular risk factors.^{3,4} Table I lists the potential cardiovascular risk factors and their targets for T2DM.¹

Potential cardiovascular risk reduction benefits

The potential for cardiovascular benefits of GLP-1 analogues can be linked to their improvements in vascular endothelial function, reduction in vascular inflammatory markers, a reduction in brain natriuretic peptide levels (BNP) as well as reductions in blood pressure (BP), lipid levels and weight.

Vascular endothelial function

Data suggests that vascular endothelial dysfunction may precede clinically evident macrovascular complications.⁵⁻⁷ This is due to various factors including abnormal glucose rise and lipid metabolism and other factors. With regards to glucose rise and lipids it seems that postprandial changes in glucose levels

Table I: CVD risk factors and targets for patients with T2DM¹

Traditional CVD risk factors	Targets
Smoking	Complete cessation
Dyslipidaemia	Total cholesterol < 4.5 mmol/L LDL cholesterol < 1.8 mmol/L HDL cholesterol > 1.0 mmol/L (men) or > 1.2 mmol/L (women) Triglycerides < 1.7 mmol/L
Obesity	
Waist circumference	< 94 cm (men); < 90 cm (men of South Asian descent); < 80 cm (women)
BMI	< 25 kg/m ² *
Hypertension	
Systolic blood pressure	< 140 mmHg
Diastolic blood pressure	< 90 mmHg

* value may differ based on ethnicity

and lipid metabolism are particularly important risk factors for vascular endothelial dysfunction.⁵⁻⁷ Exenatide improves vascular endothelial dysfunction by reducing postprandial glucose excursions and prevents postprandial rises in serum triglyceride levels.^{5,8}

Vascular inflammatory markers and brain natriuretic peptide (BNP)

GLP-1 analogues like liraglutide have shown potential to reduce plasminogen activator inhibitor (PAI) levels and BNP levels.⁹ High PAI levels are known to decrease fibrinolysis and increase the risk of atherosclerosis, whilst high BNP levels are considered a risk marker for heart failure (HF). Thus GLP-1 analogues could potentially reduce the risk for atherosclerosis and HF.^{4,9} Increased GLP-1 levels reduce IL-6, prostaglandin F2α, ICAM-1,

Table II: Serum lipid reductions with GLP-1 analogues²

GLP-1 analogue	LDL-C reduction (mmol/l)	Triglyceride Reduction	Total cholesterol reduction (mmol/l)
Exenatide	0.04–0.12 mmol/l	4–15%	0.009–0.3 mmol/l
Liraglutide	0.22–0.43 mmol/l	0.31–0.40 mmol/l	0.19 mmol/l

MCP-1, TNF α and inflammatory markers within monocytes. Increased GLP-1 receptor signalling has demonstrated robust cardio protection in the form of decreased infarct size, preservation of ventricular function, improved survival and reduced levels of creatinine kinase MB and hepann-1.⁴

Blood pressure and lipid levels

GLP-1 analogues have proven effects on reducing both systolic and diastolic BP and also seem to reduce serum triglyceride levels.^{2,10-12} The magnitude of change in systolic and diastolic BP seems to differ based on the GLP-1 analogue and the study but there is evidence that GLP-1 analogues reduce BP.^{1,9} Courrèges et al.⁹ noted that liraglutide reduced systolic BP (SBP) by 8 mmHg and reduced serum triglyceride levels by 22% when compared to the placebo. In other studies, liraglutide was able to reduce systolic BP between 2.5–5 mmHg from baseline depending on the dose, while diastolic BP was reduced from 0–1.7 mmHg from baseline.² Exenatide had similar effects on systolic BP reduction from 2.9–4.7 mmHg and diastolic BP from 0–1.9 mmHg in the Duration Trials.² Albiglutide reduced systolic BP by 1.5 mmHg and diastolic BP by 1 mmHg at 104 weeks in the Harmony-3 trial.¹³ It is clear that the systolic BP changes are more substantial than the diastolic BP changes which are almost negligible.

With regards to reduction in cholesterol, the reduction in triglycerides, LDL-C and total cholesterol vary depending on the type of GLP-1 analogue used and the dose being studied.² Clearly, the reduction in triglycerides seem to be the most pronounced whilst the drugs have minimal effects on total cholesterol and LDL-C.² Table II illustrates the effects of selected GLP-1 analogues on serum lipid levels

Weight loss

Obesity and abdominal obesity are cardiovascular risk factors.¹ The use of GLP-1 analogues has proven weight reduction effects.^{1,10-12,14,15} The amount of weight loss seems to vary depending on the agent used and the dose at which it is used.¹⁵ The higher the dose of the GLP-1 analogues, the greater the weight loss.² Liraglutide at a dose higher than the maximum dose used for diabetes, i.e. a dose of 3 mg daily, produced a mean weight loss of 7.2 kg at 20 weeks compared to 4.1 kg in patients who used orlistat and 2.8 kg in patients taking the placebo.¹⁶ A meta-analysis of 21 trials comparing 3 395 patients receiving a GLP-1 analogue

Table III: Cardiovascular outcome trials with GLP-1 analogues

Study	Population and sample size	Primary and secondary endpoints	Results	Comments	Conclusion
ELIXA trial ¹² Randomised, double-blind, placebo-controlled, international (49 countries) multi-centre trial with a 1-week run-in phase.	Sample size: 6 068 Non-inferiority trial for primary efficacy outcome followed by superiority according to ITT analysis. Lixisenatide 20 mcg subcut vs. placebo, added to existing therapy in patients with recent acute coronary syndrome (ACS). Mean age: 60 $\pm$ 9.7 yrs. eGFR 76 $\pm$ 21 ml/min/1.73 m ² . LDL: 2.03 $\pm$ 0.9 mmol/l. SBP: 130 $\pm$ 17 mmHg. HbA1c: 7.7 $\pm$ 1.3%. BMI: 30.1 $\pm$ 5.7 kg/m ² . Duration of diabetes: 9.3 $\pm$ 8.2 yrs. Qualifying ACS events: • NSTEMI – 30%. • STEMI – 44%. • Unstable angina – 17.2%. • Unclassified – 0.2%. Background medication: • Metformin. • Insulin. • Sulphonylurea. • Thiazolidinones. • ACEI/ARB. • Beta blockers. • Statins. • Antiplatelet agents.	1. Primary endpoint Composite time to event analysis of CV death, non-fatal MI, non-fatal stroke or unstable angina. CV death. MI (all events). 2. Secondary endpoints Primary endpoint or hospitalisation for heart failure (HF). Primary endpoint, hospitalisation for HF or revascularisation. Hospitalisation for HF. All-cause mortality.	1. Primary endpoint No statistically significant difference in the hazard reduction (HR) for primary endpoint with HR 1.02 (95% CI 0.89–1.17, p < 0.01 for non-inferiority and p = 0.81 for superiority). No significant reduction in HR for CV death with HR 0.98 (95% CI 0.78–1.22, p = 0.85). No significant increase in HR for MI (all events) with HR 1.03 (95% CI 0.87–1.22, p = 0.71). 2. Secondary endpoints No significant reduction in primary endpoint or hospitalisation for HF with HR 0.97 (95% CI 0.85–1.10, p = 0.63). Neutral effect in primary endpoint, hospitalisation for HF or revascularisation with HR 1.00 (95% CI 0.90–1.11, p = 0.96). No significant reduction in hospitalisation for HF with HR 0.96 (95% CI 0.75–1.23, p = 0.75). No significant reduction in all-cause mortality with HR 0.94 (95% CI 0.78–1.13, p = 0.5).	Lixisenatide has neutral effects on CV risk. Similar rates of serious adverse events in both the lixisenatide and the control group. No significant differences between the lixisenatide group and the placebo in terms of pancreatitis, pancreatic cancer, allergic reactions. Well-designed RCT, appropriately powered with all CV outcomes pre-specified and clinically relevant with independent and blinded adjudication. 96.3% of participants in the treatment group and the 96.1% in the control group completed the study. Analysis had both intention to treat analysis and per protocol analysis. Primary composite endpoint was homogenous. However, study medication was discontinued in 27.5% of patients in the treatment group and 24% in the control group. No adjustments were made for multiplicity of exploratory outcomes thus the risk of a type 1 error was higher. The number needed to harm (NNH) over 2.1 years which will result in GIT events leading to discontinuation was 28.	Neutral CV results make the ELIXA trial similar to trials of DPP-4 inhibitors and in contrast to LEADER and SUSTAIN-6. Reasonably safe choice for patients who cannot take other recommended second-line diabetes agents. When compared to the placebo and standard of care, for every 28 patients treated with lixisenatide over 2.1 years, 1 will discontinue the use of the medication due to GIT adverse events.

Study	Population and Sample Size	Primary and secondary endpoints	Results	Comments	Conclusion
LEADER trial ¹⁰ International, multi-centred randomised control trial. Participants were randomised to liraglutide 0.6 mg subcut daily and titrated after 2 weeks to a maximum of 1.8 mg based on tolerance (median dose 1.78 mg) or standard of care.	Sample size: 9 340 Mean age: 64.3 ± 7.2 yrs. Non-inferiority trial for primary efficacy outcome followed by superiority according to ITT analysis. Duration of diabetes: 12.8 ± 8 yrs. Average HbA1c: 8.7 ± 1.6%. BMI: 32.5 ± 6.3 kg/m ² . SBP: 135.9 ± 17.8 mmHg. DBP: 77.1 ± 10.2 mmHg. If patient did not reach recommended target for glycaemic control (HbA1c ≤ 7% or individualised target at investigator's discretion), addition of anti-hyperglycaemic agents (except GLP1-A, DPP4-I, and pramlintide) including insulin, were permitted.	<p>1. Primary endpoint Composite time to event analysis of first occurrence of death from CV causes, nonfatal MI and stroke.</p> <p>2. Expanded endpoints Death from CV causes. All-cause mortality. Non-fatal MI. Non-fatal stroke. Hospitalisation for HF.</p>	<p>1. Primary endpoint Composite outcome significantly reduced with HR = 0.87 (95% CI 0.78–0.97, <i>p</i> = 0.01 for superiority and < 0.001 for non-inferiority).</p> <p>2. Expanded endpoints Death from CV causes significantly reduced with HR = 0.78 (0.66–0.93, <i>p</i> = 0.007). All-cause mortality reduced with HR = 0.85 (95% CI 0.74–0.97, <i>p</i> = 0.02). No significant reduction in non-fatal MI HR 0.88 (95% CI 0.75–1.03, <i>p</i> = 0.11). No significant reduction in non-fatal stroke with HR = 0.89 (95% CI 0.72–1.11, <i>p</i> = 0.30). No significant reduction in hospitalisation for HF with HR = 0.87 (95% CI 0.73–1.05, <i>p</i> = 0.14).</p> <p>3. Adverse events Acute gallstone disease more common in the liraglutide group (3.1%) than the control group (1.9%) with <i>p</i> < 0.001. Nausea more common in the liraglutide group (1.6%) than the control group (0.9%) with <i>p</i> < 0.001. Diarrhoea more common in the liraglutide group (0.6%) than the control group (0.1%) with <i>p</i> < 0.001. Vomiting more common in the liraglutide group (0.7%) than the control group (< 0.1%) with <i>p</i> < 0.001. Liraglutide group suffered significantly less severe hypoglycaemia (2.4%) than the control group (3.35) with <i>p</i> < 0.02.</p>	<p>Composite endpoint reduction was driven primarily by a decrease in CV mortality as the others were non-significant. For the expanded endpoints only death from CV causes and all-cause mortality were significant. Despite a numerical increase in pancreatic carcinoma in patients using liraglutide, this result was not significant with <i>p</i> = 0.06. Control group compared to liraglutide group, received more insulin and SU. This could explain the increased incidence of hypoglycaemia in the control group. The number needed to harm for acute gallstone disease was 84 per 3.8 years. This study had the largest sample size of any CV outcome trial for a GLP-1 and the longest duration. It was a well-designed RCT that was blinded with external adjudication for all outcomes. 97% of the liraglutide group and 96.6% of the control group completed the study thus attrition was low. Results of this study indicated the use of liraglutide for CVD risk reduction can only be used in patients with established CVD disease.</p>	<p>Liraglutide was the first GLP-1 analogue to demonstrate a positive CV outcome in an RCT. Similar to other CV outcome trials like SUSTAIN-6 and ELIXA, liraglutide had a neutral effect on hospitalisation for HF. Liraglutide is a treatment option for patients with established CVD disease to reduce both CV mortality and all-cause mortality.</p>

Study	Population and sample size	Primary and secondary endpoints	Results	Comments	Conclusion
SUSTAIN-6 trial ¹¹ International, randomised double blind, placebo controlled trial. Patients were randomised to receive either semaglutide (0.5 mg or 1 mg) subcut once weekly or placebo.	Sample size: 2 735. Non-inferiority trial for primary efficacy outcome followed by superiority according to ITT analysis. Mean age: 64.6 ± 7.4. Duration of diabetes: 13.9 ± 8.1 yrs. Average HbA1c: 8.7 ± 1.5%. SBP: 135.6 ± 17.2 mmHg. DBP: 77.0 ± 10.0 mmHg. LDL-C: 2.12 ± 1.17 mmol/L. History of CVD (% of participants): • Ischaemic heart disease: 60.5%. • Myocardial infarction: 32.5%. • Heart failure: 23.6%. • Ischaemic stroke: 11.6%. • Haemorrhagic stroke: 3.3%. • Hypertension: 92.8%.	1. Primary endpoint Composite endpoint of time to event of either death from CV causes, non-fatal MI, non-fatal stroke. 2. Expanded endpoints Composite endpoint including: • Non-fatal MI. • Non-fatal stroke. • Revascularisation. • Death from CV causes. • Hospitalisation for unstable angina or heart failure. • All-cause mortality. • CV mortality. • Non-fatal MI. • Non-fatal stroke. • Hospitalisation for unstable angina. • Revascularisation. • Hospitalisation for HF. • Retinopathy complications. • New or worsening nephropathy.	1. Primary endpoint Composite outcome significantly reduced with HR = 0.74 (95% CI 0.58–0.95, $p = 0.02$ for superiority and < 0.001 for non-inferiority). 2. Expanded endpoints Composite outcome significantly reduced with HR = 0.74 (95% CI 0.62–0.89, $p = 0.002$). Comport of all-cause mortality, non-fatal MI or non-fatal stroke significantly reduced with HR = 0.77 (95% CI 0.61–0.97, $p = 0.03$). No significant changes in either all-cause mortality with HR = 1.05 (95% CI 0.74–1.50, $p = 0.79$) or CV mortality with HR = 0.98 (95% CI 0.65–1.48, $p = 0.92$). No significant reductions in non-fatal MIs, non-fatal strokes or hospitalisation for unstable angina. Reduction in need for revascularisation in patients using semaglutide when compared to the control with HR = 0.65 (95% CI 0.50–0.86, $p = 0.003$). No significant increase in hospitalisation for HF with HR = 1.11 (95% CI 0.77–1.61, $p = 0.57$).	NNT for semaglutide to prevent one composite outcome over 2 years was 44. Trial was powered to show non-inferiority and may have been underpowered to show superiority. Patients were followed up for a relatively short duration to truly see CVS risk reductions especially when considering that the LEADER trial took 1 year to show meaningful results. Semaglutide has similar safety profiles when compared to other GLP-1 analogues with the exception of an increased risk of retinopathy. Semaglutide 0.5 mg produced no significant reduction in systolic blood pressure but 1 mg did.	Semaglutide is the second GLP-1 analogue to demonstrate a positive CV outcome in an RCT. Similar to other CV outcome trials like LEADER and ELIXA, semaglutide had a neutral effect on hospitalisation for HF. Semaglutide is a treatment option for patients with established CVD disease to reduce both CV mortality and all-cause mortality.
3. Adverse events			Significant increase in retinopathy complications with HR = 1.76 (95% CI 1.11–2.78, $p = 0.02$). No significant differences between either group in terms of either acute pancreatitis, gallbladder disorders, pancreatic cancer or thyroid cell carcinoma.		

compared to 3 016 patients receiving different controls noted a weight reduction between 0.2–7.2 kg.¹⁷

Cardiovascular outcomes trials

There have been three large cardiovascular outcome trials of note, which investigated the cardiovascular safety of GLP-1 analogues in patients with T2DM.¹ These are discussed in significant detail in Table III.

ELIXA trial

The ELIXA trial investigating the use of lixisenatide in 6 068 patients who recently suffered an acute coronary syndrome (ACS) noted that lixisenatide had a neutral effect on cardiovascular risk.¹² The medication did not produce any significant cardiovascular risk reduction but also posed no excessive harm to patients with T2DM who had an ACS event.¹²

LEADER trial

The LEADER trial was a landmark trial in the search for a type 2 diabetic agent with potential cardiovascular risk reduction benefits. A total of 9 340 patients were randomised in a blinded manner to either a placebo group or liraglutide (at a dose 1.8 mg daily) and the cardiovascular safety of liraglutide was investigated.¹⁰ The dose of 1.8 mg of liraglutide was superior to conventional treatment and was associated with a 13% relative risk reduction in the primary composite endpoint of CV death, non-fatal MI or non-fatal stroke (3-point MACE) at a median 3.8-year follow-up compared to the placebo. Importantly, the target group selected for this trial were high cardiovascular risk patients.¹⁰

This trial demonstrated that liraglutide produced a significant cardiovascular reduction in high-risk cardiovascular patients with T2DM. Liraglutide did not improve glycaemic control to any greater extent when compared to the placebo meaning the results of cardiovascular disease (CVD) risk reduction was not linked to improved glycaemia. The primary outcome was driven by a reduction in cardiovascular mortality and all-cause mortality. There were no differences in the rate of non-fatal MI, non-fatal stroke, and hospitalisation for HF, which was not dissimilar to the ELIXA or SUSTAIN-6 trial.^{10–12} The number needed to treat (NNT) to prevent one composite outcome or cardiovascular death or all-cause mortality with liraglutide 1.8 mg over 3.8 years were 66, 104 and 98 respectively.¹⁰ An important point to note is that the Kaplan Meier curve for the 3-point MACE only deviated from the control after one year.⁴

SUSTAIN-6 trial

The SUSTAIN-6 trial (a randomised controlled trial which investigated a similar cohort of patients to the LEADER trial) found that semaglutide reduced the primary composite endpoint of cardiovascular death, non-fatal MI and non-fatal stroke, at a median 2.4-year follow-up, by 26% compared to the placebo (HR 0.74; 95% CI 0.58–0.95).¹¹

Heart failure (HF) data

As discussed previously, GLP-1 analogues reduce BNP levels, which is a marker for HF,⁹ so the question becomes is there any potential reduction in HF when using GLP-1 analogues? A meta-analysis conducted by Li et al.¹⁸ of 20 randomised controlled trials noted that GLP-1 analogues had no significant effect on the incidence of HF (HR 0.62; 95% CI 0.32–1.22). This is not dissimilar to the results of the SUSTAIN-6, LEADER and ELIXA trial.^{10–12}

Overall thoughts on trial data

It is important to note that in both the LEADER and SUSTAIN-6 trial, patients without established CVD did not benefit significantly from the GLP-1 analogues used in terms of CVD risk.^{10,11} To date there are no studies published which investigated the cardiovascular outcomes of exenatide that have demonstrated significant benefit.¹ The LEADER trial has come under scrutiny by authors such as Cohen and Beckly¹⁹ who noted that patients receiving liraglutide were also on more cardio-protective medications at baseline compared to patients receiving the placebo. Considering that the population group included in this trial were patients with either established CVD or had CVD risk factors; it is not unimaginable for them to have background cardio-protective medication and with such a large sample size such differences can be expected at baseline and not be considered as significant.²⁰ Furthermore, Cohen and Beckley¹⁹ also noted that the results of the LEADER trial are incongruent with those of ELIXA. That said, Cohen and Beckley¹⁹ can be forgiven as the results of the SUSTAIN-6 trial were yet to be published. The results of SUSTAIN-6 were congruent with LEADER.¹¹

The results of these trials have forced the American Diabetes Association (ADA) to rethink its guidance regarding the management of type 2 diabetes. GLP-1 analogues and SGLT2 (sodium glucose-like transporter 2) inhibitors with proven cardiovascular risk reduction benefits are now considered as second-line added on therapy (after diet, exercise and metformin) in patients with established atherosclerotic cardiovascular disease.²¹ Additionally, GLP-1 analogues are also now considered to be the first-line injectable therapy that must be started prior to basal insulin.²¹ The South African Guidelines already acknowledge the cardiovascular benefits of certain GLP-1 analogues and it is a possibility that in a future iteration they may follow the ADA guidelines with similar recommendations.

Conclusions

It is clear that GLP-1 analogues have pleiotropic effects that extend to aspects of cardiovascular risk reduction and also reduce cardiovascular risk factors such as BP, cholesterol and weight. They also have effects on endothelial function and vascular inflammatory markers. They signal a potential for CVD risk reduction. Whilst the ELIXA trial demonstrated CVD risk neutrality for lixisenatide, the LEADER and SUSTAIN-6 trials demonstrated distinct CVD risk reduction benefits with liraglutide and semaglutide respectively. However, this was only in patients with established CVD. The results of these

studies prompted the ADA to change their guidelines and ask practitioners to consider the use of GLP-1 analogues in patients with established atherosclerotic CVD if they fail on lifestyle modification and metformin.

Acknowledgements

I would like to acknowledge the kind assistance of Miss NK Hassim for helping to review this manuscript.

References

1. The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee. The 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA. 2017;21(1) (Supplement 1):S1-196.
2. Prasad-Reddy L, Isaacs D. A clinical review of GLP-1 receptor agonists: efficacy and safety in diabetes and beyond. *Drugs Context*. 2015 Jul 9;4:212283. <https://doi.org/10.7573/dic.212283>. eCollection 2015. Review. PubMed PMID: 26213556; PubMed Central PMCID: PMC4509428.
3. DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. *Diabetes Care*. 2013 Aug;36 Suppl 2:S127-38. <https://doi.org/10.2337/dcS13-2011>. PubMed PMID: 23882037; PubMed Central PMCID: PMC3920797.
4. DeFronzo RA. Combination therapy with GLP-1 receptor agonist and SGLT2 inhibitor. *Diabetes Obes Metab*. 2017 Oct;19(10):1353-1362. <https://doi.org/10.1111/dom.12982>. Epub 2017 Jun 7. Review. PubMed PMID: 28432726; PubMed Central PMCID: PMC5643008.
5. Torimoto K, Okada Y, Mori H, et al. Effects of exenatide on postprandial vascular endothelial dysfunction in type 2 diabetes mellitus. *Cardiovasc Diabetol*. 2015 Feb 18;14:25. <https://doi.org/10.1186/s12933-015-0188-1>. PubMed PMID: 25849903; PubMed Central PMCID: PMC4339392.
6. Ceriello A, Assaloni R, Da Ros R, et al. Effect of atorvastatin and irbesartan, alone and in combination, on postprandial endothelial dysfunction, oxidative stress, and inflammation in type 2 diabetic patients. *Circulation*. 2005 May 17;111(19):2518-24. Epub 2005 May 2. PubMed PMID: 15867169.
7. Xu J, Zou MH. Molecular insights and therapeutic targets for diabetic endothelial dysfunction. *Circulation*. 2009 Sep 29;120(13):1266-86. <https://doi.org/10.1161/CIRCULATIONAHA.108.835223>. Review. PubMed PMID: 19786641; PubMed Central PMCID: PMC2910587.
8. Koska J, Schwartz EA, Mullin MP, Schwenke DC, Reaven PD. Improvement of postprandial endothelial function after a single dose of exenatide in individuals with impaired glucose tolerance and recent-onset type 2 diabetes. *Diabetes Care*. 2010 May;33(5):1028-30. <https://doi.org/10.2337/dc09-1961>. Epub 2010 Mar 3. PubMed PMID: 20200309; PubMed Central PMCID: PMC2858168.
9. Courrèges J-P, Vilsbøll T, Zdravkovic M, et al. Beneficial effects of once-daily liraglutide, a human glucagon-like peptide-1 analogue, on cardiovascular risk biomarkers in patients with Type 2 diabetes. *Diabet Med*. 2008 Sep;25(9):1129-31. <https://doi.org/10.1111/j.1464-5491.2008.02484.x>. PMID: 19183322; PMCID: PMC2592347.
10. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, Nissen SE, Pocock S, Poulter NR, Ravn LS, Steinberg WM, Stockner M, Zinman B, Bergenstal RM, Buse JB; LEADER Steering Committee; LEADER Trial Investigators. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016 Jul 28;375(4):311-22. <https://doi.org/10.1056/NEJMoa1603827>. Epub 2016 Jun 13. PubMed PMID: 27295427; PubMed Central PMCID: PMC4985288.
11. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016 Nov 10;375(19):1834-1844. Epub 2016 Sep 15. PubMed PMID: 27633186.
12. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, Lawson FC, Ping L, Wei X, Lewis EF, Maggioni AP, McMurray JJ, Probstfield JL, Riddle MC, Solomon SD, Tardif JC; ELIXA Investigators. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015 Dec 3;373(23):2247-57. <https://doi.org/10.1056/NEJMoa1509225>. PubMed PMID: 26630143.
13. Åhrén B, Johnson SL, Stewart M, Cirkel DT, Yang F, Perry C, Feinglos MN; HARMONY 3 Study Group. HARMONY 3: 104-week randomized, double-blind, placebo- and active-controlled trial assessing the efficacy and safety of albiglutide compared with placebo, sitagliptin, and glimepiride in patients with type 2 diabetes taking metformin. *Diabetes Care*. 2014 Aug;37(8):2141-8. <https://doi.org/10.2337/dc14-0024>. Epub 2014 Jun 4. PubMed PMID: 24898304.
14. Davies MJ, Bergenstal R, Bode B, Kushner RF, Lewin A, Skjøth TV, Andreasen AH, Jensen CB, DeFronzo RA; NN8022-1922 Study Group. Efficacy of Liraglutide for Weight Loss Among Patients With Type 2 Diabetes: The SCALE Diabetes Randomized Clinical Trial. *JAMA*. 2015 Aug 18;314(7):687-99. <https://doi.org/10.1001/jama.2015.9676>. Erratum in: *JAMA*. 2016 Jan 5;315(1):90. PubMed PMID: 26284720.
15. Potts JE, Gray LJ, Brady EM, et al. The effect of glucagon-like peptide 1 receptor agonists on weight loss in type 2 diabetes: a systematic review and mixed treatment comparison meta-analysis. *PLoS One*. 2015 Jun 29;10(6):e0126769. <https://doi.org/10.1371/journal.pone.0126769>. eCollection 2015. Review. PubMed PMID: 26121478; PubMed Central PMCID: PMC4487255.
16. Astrup A, Rössner S, Van Gaal L, Rissanen A, Niskanen L, Al Hakim M, Madsen J, Rasmussen MF, Lean ME; NN8022-1807 Study Group. Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet*. 2009 Nov 7;374(9701):1606-16. [https://doi.org/10.1016/S0140-6736\(09\)61375-1](https://doi.org/10.1016/S0140-6736(09)61375-1). Epub 2009 Oct 23. Erratum in: *Lancet*. 2010 Mar 20;375(9719):984. PubMed PMID:19853906.
17. Vilsbøll T, Christensen M, Junker AE, Knop FK, Gluud LL. Effects of glucagon-like peptide-1 receptor agonists on weight loss: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2012 Jan 10;344:d7771. <https://doi.org/10.1136/bmj.d7771>. Review. PubMed PMID: 22236411; PubMed Central PMCID: PMC3256253.
18. Li L, Li S, Liu J, et al. Glucagon-like peptide-1 receptor agonists and heart failure in type 2 diabetes: systematic review and meta-analysis of randomized and observational studies. *BMC Cardiovasc Disord*. 2016 May 11;16:91. <https://doi.org/10.1186/s12872-016-0260-0>. PMID: 27169565; PMCID: PMC4863354.
19. Cohen S, Beckley J. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016 Nov 3;375(18):1797-1799. <https://doi.org/10.1056/NEJMc1611289>.
20. Buse JB. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med*. 2016 Nov 3;375(18):1797-1799. <https://doi.org/10.1056/NEJMc1611289>.
21. American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2019. *Diabetes Care*. 2019 Jan;42(Suppl 1):S90-S102. <https://doi.org/10.2337/dc19-S009>. Review. PubMed PMID: 30559235.