СЕРДЕЧНАЯ НЕДОСТАТОЧНОСТЬ ПРИ ДИАБЕТЕ: ОТ ПОВЫШЕННОГО РИСКА ДО ЦЕЛИ ЛЕЧЕНИЯ

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Сердечная недостаточность является одной из наиболее распространенных коморбидностей сахарного диабета 2 типа (СД2). Неадекватный гликемический контроль может ухудшать исходы сердечной недостаточности и повышать риск госпитализаций. За последнее десятилетие появилось несколько препаратов для лечения СД2, и их сердечно-сосудистая безопасность становится причиной беспокойства. По этой причине FDA поручило определить профиль сердечно-сосудистой безопасности и соотношение риск-польза для этих препаратов путем проведения специально разработанных исследований сердечно-сосудистых исходов. Несмотря на то что мы получили некоторые данные из этих исследований, ни одно из них не включало сердечную недостаточность в главные конечные точки, что отражает необходимость проведения исследований, сфокусированных на сердечной недостаточности. В данном обзоре кратко обсуждаются результаты исследования сердечно-сосудистых исходов в контексте сердечной недостаточности.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет 2 типа; сердечная недостаточность; исследования сердечно-сосудистых исходов; ингибиторы ДПП-4, ингибиторы SGLT-2; агонисты рецептора ГПП-1

HEART FAILURE IN DIABETES: FROM AN INCREASED RISK TO A TREATMENT TARGET

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Heart failure (HF) is one of the most common comorbidities of type 2 diabetes mellitus (T2DM) and poor glycaemic control can worsen the HF outcomes and increase the risk of hospitalisations. With the entry of several antihyperglycaemic agents for the management of T2DM over the last decade, there has been an increasing concern regarding the cardiovascular (CV) safety profile of these agents. In view of this, FDA mandated the demonstration of cardiovascular risk-benefit profile of these agents through specifically designed CV outcome trials. Although we have several findings from these trials, none of them included HF as a primary endpoint indicating the need of trials focusing on HF. Here, we briefly discuss the results of the CV outcome trials in the context of HF.

KEYWORDS: type 2 diabetes mellitus, heart failure, cardiovascular outcome trials, DPP-4 inhibitors, SGLT-2 inhibitors, GLP-1 receptor agonists

Heart failure (HF) and type 2 diabetes mellitus (T2DM) are clinical conditions that coexist frequently with an alarmingly increasing prevalence and economic burden. While HF is defined as a global pandemic affecting 26 million people worldwide [1], T2DM is expected to affect 642 million people by 2040 [2].

Poor glycaemic control in patients with T2DM doubles the risk of HF [3–5], and for every 1% increase in glycated haemoglobin (HbA1c), the risk of HF increases by 15% [6] and hospitalisations due to HF (hHF) by 36% [7, 8]. According to the data from REACH registry, in patients with T2DM, HF increases cardiovascular (CV) death by about 250% and hHF by about 500% [9]. Furthermore, HF in patients with T2DM is associated with poor prognosis, with a median survival of about 4 years from the time of diagnosis [10]. This indicates an urgent need for treatment strategies that prevent worsening of HF outcomes in patients with T2DM.

HEART FAILURE: SIGNS, SYMPTOMS, DIAGNOSIS AND TREATMENT STRATEGIES

Heart failure is a clinical syndrome typically characterised by symptoms and signs that result from the structural and functional abnormalities of the heart. The classic symptoms are "breathlessness (dyspnea e.g. on exertion or even at rest)", ankle swelling and fatigue that may be accompanied by signs like elevated jugular venous pressure, hepato-jugular reflux, pulmonary crackles and peripheral oedema culminating in a reduced cardiac output and/or elevated intracardiac pressures either at rest or during stress [11].

Heart failure is categorised based on ejection fraction as, patients with normal left ventricular ejection fraction (LVEF) [typically considered as ≥50% HF with preserved EF (HFpEF)], reduced LVEF [typically considered as <40%; HF with reduced EF (HFrEF)], and intermediate range of 40%–49% LVEF which is HF with a mid-range EF (HFmrEF) [11].

Heart failure can be due to any abnormality of the structure, mechanical function or electrical activity of the heart and is characterised by a trajectory of deteriorating cardiac output and declining renal function leading to fluid retention, peripheral oedema and pulmonary congestion, which may result in hospitalisation and treatment with an intravenous diuretic. Factors related to T2DM, including cardioneuropathy, cardiomyopathy, microangiopathy, renal hyperfiltration, and intravascular

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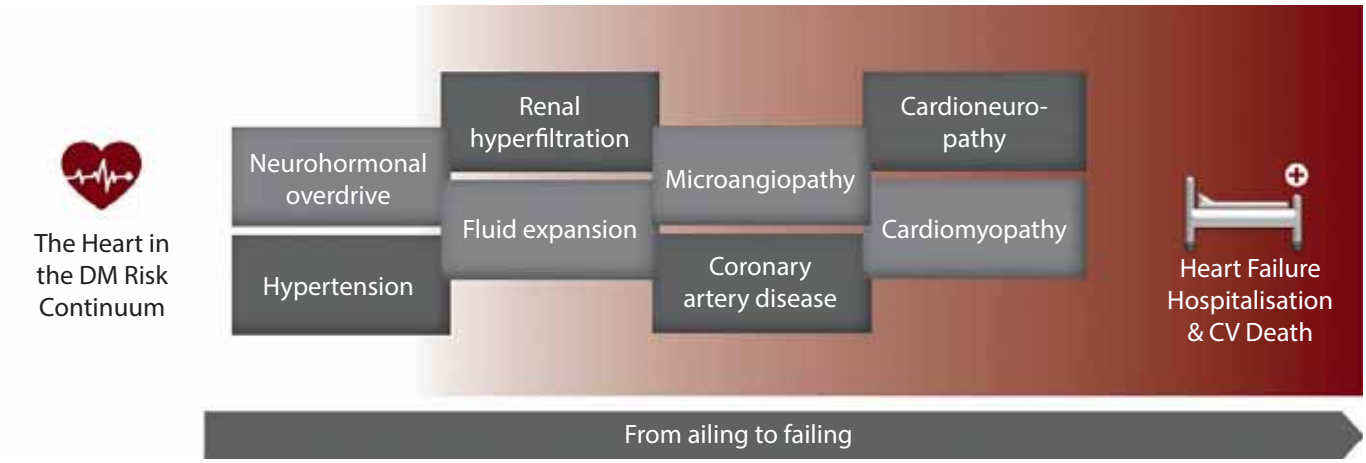

Fig. 1. The ominous octet: Contributors to a failing heart in diabetes mellitus. Notes: CV, cardiovascular; DM, diabetes mellitus. Adapted from [13].

fluid expansion, in addition to hypertension, ischaemic heart disease and sympathetic nervous system (SNS)-overdrive, all contribute to the worsening of HF [12, 13] (Figure 1).

As the symptoms of HF are often non-specific it may be difficult to differentiate them with other conditions. Signs such as the elevated jugular venous pressure, hepato-jugular reflux, and laterally displaced apical impulse are more specific; however, they may be difficult to detect and have poor reproducibility and thus need careful clinical examination. Once the signs have been determined by evaluating the clinical history and physical examination, the clinician needs to perform further diagnostic tests. The plasma concentration of natriuretic peptides (NPs) and electrocardiogram (ECG) are the preliminary tests recommended to rule out HF, but not for conclusive diagnosis. Echocardiography is the most effective and widely used test in patients with suspected HF to establish the diagnosis and proceed with the plan of treatment [11].

THE NEED FOR NEW TREATMENT STRATEGIES FOR HF IN PATIENTS WITH T2DM

Beginning of a new era in diabetes research: cardiovascular outcome trials

Currently, metformin is being recommended as first-line therapy for patients with T2DM and HF who have preserved or moderately reduced renal function (i.e. estimated glomerular filtration rate >30 mL/min) whereas, sulphonylureas (SUs) and insulin could be used as a second- or third-line treatment, although their safety in HF is still inconclusive [13, 14]. These recommendations are based on the limited evidence available, as there have been no randomised controlled trials (RCTs) performed to evaluate CV safety for these traditional drugs such as metformin, insulin and SUs. A large observational study in HF demonstrated that metformin was associated with lower mortality and hHF rates compared to SUs and insulin [15]. Findings from ORIGIN study, the only RCT of insulin versus standard of care, revealed that insulin was not associated with higher rates of hHF as compared to the control group [16]. Overall, the information on these drugs is limited with regard to HF.

Following guidance by the US Food and Drug Administration (FDA) for a routinely required mandatory exclusion of CV risk of all new glucose-lowering therapies prompted by an unexpected elevated CV and HF risk seen with rosiglitazone and the dual peroxisome proliferator-activated receptor α/γ agonist muraglitazar [17, 18], a plethora of CV outcome trials (CVOTs) have emerged over the last decade. Although these studies have evaluated the effects of AHAs on HF outcomes, the data is limited to the study populations, hence more studies on HF are required to enable the clinicians to make appropriate treatment decisions.

Dipeptidyl peptidase-4 inhibitors

Three large CVOTs of dipeptidyl peptidase-4 (DPP-4) inhibitors (SAVOR-TIMI53, TECOS and EXAMINE) met the safety primary endpoint [3-point major adverse cardiac events (MACE) comprising CV disease mortality, nonfatal myocardial infarction (MI), and nonfatal stroke] of noninferiority versus placebo [19–21]. Unexpectedly, however, findings from the SAVOR-TIMI53 trial showed an increased risk of hHF in patients using saxagliptin [19], raising doubts regarding the use of these drugs in patients with HF, as the EXAMINE trial (alogliptin) disclosed a similar numerical, but nonsignificant trend [22]. However, findings from the TECOS (sitagliptin) and VIVIDD study (vildagliptin) demonstrated no increased risk of hHF [21, 23, 24]. Further, findings from several observational trials and meta-analyses conducted on hHF demonstrated a neutral effect of DPP-4 inhibitors on the risk of HF, underpinning their safety. Two large ongoing CVOTs with linagliptin, CAROLINA (https://clinicaltrials.gov/show/NCT01243424) and CARMELINA (https://clinicaltrials.gov/ct2/show/NCT01897532, publication expected in September 2018), will shed further light on the safety of DPP-4 inhibitors in HF.

Glucagon like peptide-1 receptor agonists

Findings from the ELIXA trial demonstrated that the use of lixisenatide in patients with diabetes with acute coronary syndrome showed a neutral effect on CV disease outcomes with no increase in the risk of hHF [25]. Liraglutide (LEADER trial) significantly reduced the occurrence of 3-point MACE by 13%, CV death by 22% and all-cause mortality by 15%, with no significant effect

Table 1. Cardiovascular outcomes trials with various antihyperglycaemic agents

Drug class	Drug name (trial name)	Primary outcome¶	Hospitalisation due to heart failure HR (95%CI)	Reference studies
DPP-4 inhibitors				
Completed studies	Saxagliptin (SAVOR-TIMI 53)	3-point MACE 1.00 (0.89–1.12)	1.27 (1.07–1.51)	[19]
	Sitagliptin (TECOS)	4-point MACE 0.98 (0.89–1.08)	1.00 (0.83–1.20)	[21]
	Alogliptin (EXAMINE)	3-point MACE 0.96 (95% UL ≤1.16)	1.19 (0.90–1.58)	[22]
Ongoing studies	Linagliptin (CAROLINA); NCT01243424 §Linagliptin (CARMELINA); NCT01897532			
GLP-1 receptor agonists				
Completed studies	Lixisenatide (ELIXA)	4-point MACE 1.02 (0.89–1.17)	0.96 (0.75–1.23)	[25]
	Liraglutide (LEADER)	3-point MACE 0.87 (0.78–0.97)	0.87 (0.73–1.05)	[26]
	Semaglutide (SUSTAIN-6*)	3-point MACE 0.74 (0.58–0.95)	1.11 (0.77–1.61)	[27]
	Exenatide (EXSCEL)	3-point MACE 0.91 (0.83–1.00)	0.94 (0.78–1.13)	[28]
	Exenatide (ITCA 650) (FREEDOM-CVO^)	-	-	NCT01455896
Ongoing studies	Albiglutide (HARMONY Outcomes); NCT02465515 Dulaglutide (REWIND); NCT01394952			
SGLT-2 inhibitors				
Completed studies	Empagliflozin (EMPA-REG OUTCOME)	3-point MACE 0.86 (0.74–0.99)	0.65 (0.50–0.85)	[29]
	Canagliflozin (CANVAS program)	3-point MACE 0.86 (0.75–0.97)	0.67 (0.52–0.87)	[30]
Ongoing studies	¥Dapagliflozin (DECLARE-TIMI 58); NCT01730534 Ertugliflozin (VERTIS CV); NCT01986881 Dapagliflozin (Dapa-HF); NCT03036124 Empagliflozin (EMPEROR-Reduced); NCT03057977 Empagliflozin (EMPEROR-Preserved); NCT03057951			

Notes: Outcomes reported as HR (95% CI) unless otherwise noted. ^Pre-approval trial. #Nontruncated integrated data (refer to pooled data from CANVAS, including before 20 November 2012 plus CANVAS-R). *Powered to rule out an HR upper margin ≥1.8; superiority hypothesis not prespecified. 95% UL, upper limit of 95% CI. 3-point MACE includes composite of death from CV causes, nonfatal MI, and nonfatal stroke; 4-point MACE includes hospitalisation for unstable angina in addition to components of 3-point MACE. §CARMELINA met its primary endpoint, defined as time to first occurrence of CV death, nonfatal MI or nonfatal stroke (3-point MACE), with linagliptin demonstrating similar CV safety compared with placebo (full results to be presented at the 54th European Association for the Study of Diabetes Annual Meeting in Berlin). ¥DECLARE-TIMI 58 (co-primary endpoints are the incidence CV death, MI, or ischemic stroke or the incidence of CV death or hHF), results anticipated to be read out at AHA 2018. CI, confidence interval; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; hHF, hospitalisation due to heart failure; HR, hazard ratio; MACE, major adverse cardiac events; MI, myocardial infarction; SGLT-2, sodium glucose co-transporter-2; UL, upper limit.

on nonfatal MI, stroke and hHF [26]. Similarly, SUSTAIN-6 (semaglutide) and EXSCEL (exenatide once a week) showed no adverse HF signal, though the trials differed in the primary outcome, with semaglutide demonstrating CV benefit for the primary 3-point MACE outcome [27], whereas exenatide once a week falling short of achieving that endpoint [28].

Sodium glucose co-transporter-2 inhibitors

Two large trials of sodium glucose co-transporter-2 (SGLT-2) inhibitors with empagliflozin (EMPA-REG OUTCOME trial) and canagliflozin (CANVAS) showed a significant reduction in hHF [29, 30]. The primary outcome of the EMPA-REG OUTCOME trial of 3-point MACE (composite of death from CV causes, nonfatal

MI, and nonfatal stroke) showed superiority versus placebo and noninferiority for 4-point MACE (including hospitalisation for unstable angina). Empagliflozin significantly reduced the risk of hHF by 35%, risk of CV death by 38%, and risk for all-cause mortality by 32% [29].

The CANVAS trial with canagliflozin met the prespecified noninferiority MACE endpoint and in addition demonstrated superiority over standard of care for the primary 3-point MACE outcome (Hazard ratio [HR] 0.86, 95% confidence interval [CI]: 0.75–0.97, p=0.02). In addition, hHF was reduced (HR 0.67, 95% CI: 0.52–0.87), although not rated as statistically significant due to all-cause mortality not reaching a significant difference in the predefined hierarchical statistical analysis [30].

Two ongoing trials will further evaluate the safety and efficacy of empagliflozin versus placebo for the reduction in primary outcomes (CV death or hHF) in patients with HFrEF (EMPEROR-Reduced; https://clinicaltrials.gov/ct2/show/NCT03057977) and HFpEF (EMPEROR-Preserved; https://clinicaltrials.gov/ct2/show/NCT03057951). Two ongoing trials with dapagliflozin, DECLARE-TIMI58 (https://clinicaltrials.gov/ct2/show/NCT01730534) and Dapa-HF (https://clinicaltrials.gov/ct2/show/NCT03036124) will be reported in November 2018 and December 2019, respectively. A list of all completed and ongoing CVOTs are presented in Table 1.

CONCLUSIONS

HF is one of the most common comorbidities of T2DM and poor glycaemic control can have direct effects on HF outcomes; thus, it is important to have a good glycaemic control to prevent or improve the CV outcomes including HF events, in patients with T2DM. The findings suggest that metformin is associated with a modest and favourable effect on HF events and insulin has a neutral effect. Although nearly all CVOTs including GLP-1 receptor agonists, DPP-4 inhibitors and SGLT-2 inhibitors had hHF as a secondary or an exploratory outcome, several important findings were revealed in these studies. Although, findings from the trials using DPP-4 inhibitors demonstrated noninferiority versus placebo of meeting the safety primary endpoint, it must be noted that an increase in hHF was observed in patients randomised to saxagliptin during first year with no significant difference thereafter. The findings from the ELIXA trial showed neutrality on CV outcomes, whereas LEADER demonstrated positive effect on the CV outcomes; however, none of them demonstrated reduction in hHF. Remarkably, the EMPA-REG OUTCOME and CANVAS trials for SGLT-2 inhibitors demonstrated a positive effect on the CV outcomes and had reduced the risk of heart failure events. Furthermore, trials specifically designed and powered to evaluate the HF outcomes may be helpful in this context as there seems to be a huge potential for undiagnosed HF in patients with diabetes mellitus, it is crucial for every endocrinologist/diabetologist to understand the basics in diagnostics and treatment of HF in cooperation with the cardiologist, in order to design a tailored glucose-lowering therapy to the individual patient (i.e. precision medicine).

ADDITIONAL INFORMATION

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СПИСОК ЛИТЕРАТУРЫ | REFERENCES

1. Ambrosy AP, Fonarow GC, Butler J, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. *J Am Coll Cardiol*. 2014;63(12):1123-1133. doi: 10.1016/j.jacc.2013.11.053
2. International Diabetes Federation. IDF Diabetes Atlas. 8th ed. Brussels: IDF; 2017.
3. Kannel WB, Hjortland M, Castelli WP. Role of diabetes in congestive heart failure: the Framingham study. *Am J Cardiol*. 1974;34(1):29-34. doi: 10.1016/0002-9149(74)90089-7
4. Thrainsdottir IS, Aspelund T, Thorgeirsson G, et al. The association between glucose abnormalities and heart failure in the population-based Reykjavik study. *Diabetes Care*. 2005;28(3):612-616. doi: 10.2337/diacare.28.3.612
5. Dei Cas A, Khan SS, Butler J, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. *JACC Heart Fail*. 2015;3(2):136-145. doi: 10.1016/j.jchf.2014.08.004
6. Erqou S, Lee CT, Suffoletto M, et al. Association between glycated haemoglobin and the risk of congestive heart failure in diabetes mellitus: systematic review and meta-analysis. *Eur J Heart Fail*. 2013;15(2):185-193. doi: 10.1093/eurjhf/hfs156
7. Bibbins-Domingo K, Lin F, Vittinghoff E, et al. Predictors of heart failure among women with coronary disease. *Circulation*. 2004;110(11):1424-1430. doi: 10.1161/01.CIR.0000141726.01302.83
8. van Melle JP, Bot M, de Jonge P, et al. Diabetes, glycemic control, and new-onset heart failure in patients with stable coronary artery disease: data from the heart and soul study. *Diabetes Care*. 2010;33(9):2084-2089. doi: 10.2337/dc10-0286
9. Cavender MA, Steg PG, Smith SC, Jr., et al. Impact of Diabetes Mellitus on Hospitalization for Heart Failure, Cardiovascular Events, and Death: Outcomes at 4 Years From the Reduction of Atherothrombosis for Continued Health (REACH) Registry. *Circulation*. 2015;132(10):923-931. doi: 10.1161/CIRCULATIONAHA.114.014796
10. Paneni F. Empagliflozin across the stages of diabetic heart disease. *Eur Heart J*. 2018;39(5):371-373. doi: 10.1093/eurheartj/ehx519
11. Ponikowski P, Voors AA, Anker SD, et al. The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2016;37:2129-2200.
12. Thomas MC. Type 2 Diabetes and Heart Failure: Challenges and Solutions. *Curr Cardiol Rev*. 2016;12(3):249-255. doi: 10.2174/1573403X12666160606120254
13. Standl E, Schnell O, McGuire DK. Heart Failure Considerations of Antihyperglycemic Medications for Type 2 Diabetes. *Circ Res*. 2016;118(11):1830-1843. doi: 10.1161/CIRCRESAHA.116.306924
14. Seferovic PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. *Eur J Heart Fail*. 2018;20(5):853-872. doi: 10.1002/ejhf.1170
15. MacDonald MR, Petrie MC, Hawkins NM, et al. Diabetes, left ventricular systolic dysfunction, and chronic heart failure. *Eur Heart J*. 2008;29(10):1224-1240. doi: 10.1093/eurheartj/ehn156
16. Gerstein HC, Bosch J, Dagenais GR, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. *N Engl J Med*. 2012;367(4):319-328. doi: 10.1056/NEJMoa1203858
17. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med*. 2007;356(24):2457-2471. doi: 10.1056/NEJMoa072761
18. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER). *Guidance for industry: diabetes mellitus—evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes*. Washington; 2008. Available at: https://www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf. Accessed Sept 2018.
19. Scirica BM, Bhatt DL, Braunwald E, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. *N Engl J Med*. 2013;369(14):1317-1326. doi: 10.1056/NEJMoa1307684
20. White WB, Cannon CP, Heller SR, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. *N Engl J Med*. 2013;369(14):1327-1335. doi: 10.1056/NEJMoa1305889
21. Green JB, Bethel MA, Armstrong PW, et al. Effect of Sitagliptin on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2015;373(3):232-242. doi: 10.1056/NEJMoa1501352
22. Zannad F, Cannon CP, Cushman WC, et al. EXAMINE Investigators. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. *Lancet*. 2015;385:2067-2076. doi: 10.1016/S0140-6736(14)62225-X
23. McGuire DK, Van de Werf F, Armstrong PW, et al. Association Between Sitagliptin Use and Heart Failure Hospitalization and Related Outcomes in Type 2 Diabetes Mellitus: Secondary Analysis of a Randomized Clinical Trial. *JAMA Cardiol*. 2016;1(2):126-135. doi: 10.1001/jamacardio.2016.0103
24. McMurray JJV, Ponikowski P, Bolli GB, et al. Effects of Vildagliptin on Ventricular Function in Patients With Type 2 Diabetes Mellitus and Heart Failure: A Randomized Placebo-Controlled Trial. *JACC Heart Fail*. 2018;6(1):8-17. doi: 10.1016/j.jchf.2017.08.004
25. Pfeffer MA, Claggett B, Diaz R, et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. *N Engl J Med*. 2015;373(23):2247-2257. doi: 10.1056/NEJMoa1509225
26. Marso SP, Daniels GH, Brown-Frandsen K, et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2016;375(4):311-322. doi: 10.1056/NEJMoa1603827
27. Marso SP, Bain SC, Consoli A, et al. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2016;375(19):1834-1844. doi: 10.1056/NEJMoa1607141
28. Holman RR, Bethel MA, Mentz RJ, et al. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. *N Engl J Med*. 2017;377(13):1228-1239. doi: 10.1056/NEJMoa1612917
29. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med*. 2015;373(22):2117-2128. doi: 10.1056/NEJMoa1504720
30. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med*. 2017;377(7):644-657. doi: 10.1056/NEJMoa1611925

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