A Practical Approach to Managing Heart Failure in Type 2 Diabetes Mellitus

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CASE SCENARIO

A 62-year-old man was diagnosed with type 2 diabetes mellitus (T2DM) three years ago (glycated hemoglobin [A1c] 8.6%). He has been treated with lifestyle management + metformin (titrated to 2 g/day) + sulfonylurea. Currently: A1c 7.4% (7.2% 6 months ago); body mass index 31.4 kg/m^2; blood pressure 134/85 mmHg; estimated glomerular filtration rate 55 mL/min/1.73 m^2; low-density lipoprotein cholesterol 114 mg/dL; triglycerides 320 mg/dL. He now complains of occasional shortness of breath and feeling tired.

HEART FAILURE IN DIABETES MELLITUS

The treatment of patients with T2DM has generally focused on lowering the blood glucose, specifically the A1c, to 7% or lower (or some other individualized goal).[1] This focus is based on data such as those from the Framingham Heart Study showing that DM is an independent risk factor for several cardiovascular (CV) events, including heart failure (HF).[2,3] In fact, for every 1% increase in the A1c above 7.5%, there is a 15% increase in the risk of HF.[4] Moreover, the United Kingdom Prospective Diabetes Study showed that a 1% decrease in A1c results in a significantly reduced risk of microvascular and other CV complications such as HF (-16%), myocardial infarction (MI) (-14%), and stroke (-12%).[5] These data make it clear that, while lowering the blood glucose level is important, lowering CV risk is also a key treatment goal in people with T2DM.[1,6]

When it comes to reducing CV events, the focus has typically been on MI and stroke, yet, in people with T2DM, HF is the most common CV complication.[7,8] People with T2DM have more than twice the risk of HF than individuals without T2DM,[3,9,10] and up to 40% of people with HF have DM.[9,11-14] The risk of death in people with DM has been shown to be nearly 9 times higher for those with HF compared to those without HF.[15] Risk factors for HF and DM overlap and include obesity, hypertension, sleep apnea, advanced age, dyslipidemia, anemia, coronary heart disease, and chronic kidney disease.[16]

> HF is a common initial presentation of CV disease in T2DM, yet is undiagnosed in one-quarter of people with T2DM.

Not surprisingly, HF in people with T2DM often results in hospitalization,[17] with increasing mortality with repeated hospitalization.[18] Of people hospitalized for acute HF, those with DM have a worse outcome (composite of all-cause mortality, heart transplantation, and left ventricular assist device implantation) than those without DM.[19] In people with HF with preserved ejection fraction (HFpEF), ie, ejection fraction >40% (also called diastolic HF[20]), people with DM have significantly worse exercise capacity than those without DM.[21] Moreover, in people with DM vs without DM, those with HFpEF have a significantly higher risk of CV death or HF hospitalization compared with those with HF with reduced ejection fraction (HFrEF), ie, ejection fraction ≤40% (also called systolic HF[20]) (**FIGURE**).[22]

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DISCLOSURES

Dr. Butler discloses that he is on the advisory board/speakers' bureaus for Amgen, Array, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceuticals, Innolife, Janssen, Luitpold, Medtronic, Merck, Novartis, Relypsa, Stealth Peptides, scPharmaceuticals, Vifor, and ZS Pharma.

Dr. Kushner discloses that she is on the advisory board for AstraZeneca, Abbott, GlaxoSmithKline, and Janssen. She also serves on the speakers' bureaus for AstraZeneca, GlaxoSmithKline, and Janssen.

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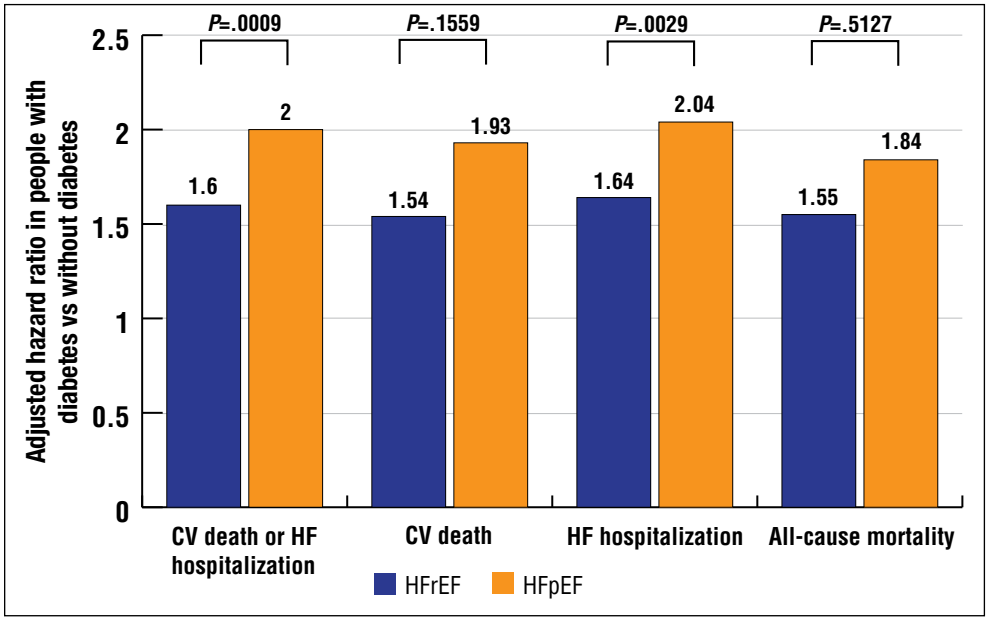
FIGURE Cardiovascular outcomes in people with type 2 diabetes mellitus and heart failure with preserved ejection fraction vs heart failure with reduced ejection fraction (HFpEF vs HFrEF)[22]



Abbreviations: CV, cardiovascular; HF, heart failure.

Among people with HFpEF, those with vs without DM have a more severe disease phenotype, more extensive comorbidities (obesity, hypertension, renal dysfunction, pulmonary disease, vascular disease), greater left ventricular hypertrophy, and higher circulating markers of vasoconstriction, oxidative stress, inflammation, and fibrosis.

INITIAL EVALUATION

Patients who present with dyspnea, fatigue, fluid retention, or other signs or symptoms suggesting HF should initially be evaluated by a thorough history and physical examination to identify cardiac and noncardiac disorders or behaviors that might cause or accelerate the development or progression of HF.[20] Initial diagnostic testing should include complete blood count, urinalysis, serum electrolytes (including calcium and magnesium), blood urea nitrogen, serum creatinine, blood glucose, fasting lipid profile, liver function tests, and thyroid-stimulating hormone. B-type natriuretic peptide (BNP) or N-terminal proBNP is useful. In addition to a 12-lead electrocardiogram, a chest X-ray should be done to assess heart size and pulmonary congestion and to rule out other diseases that may be the cause of the patient's symptoms. A 2-dimensional echocardiogram with Doppler is the most useful diagnostic test and should be performed to assess ventricular function, size, wall thickness, wall motion, and valve function. Noninvasive imaging to detect myocardial ischemia and viability is reasonable in patients with known coronary artery disease and no angina.

FDA 2008 GUIDANCE

In 2008, the US Food and Drug Administration (FDA) issued its guidance *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*, which required pharmaceutical sponsors to demonstrate that a new antihyperglycemic therapy for T2DM is not associated with an unacceptable increase in CV risk compared to placebo as part of standard care.[23] The guidance established requirements for assessing CV risk by conducting a randomized, double-blind, parallel, placebo-controlled, multicenter clinical trial. The trial is to assess CV risk using a composite of CV death, nonfatal MI, and nonfatal stroke, so-called major adverse CV events (MACE).

CARDIOVASCULAR OUTCOME TRIALS

The 2008 FDA guidance applies to all new antidiabetic therapies to treat T2DM and thus, includes dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), glucagon-like peptide-1 receptor agonists (GLP-1R agonists) except exenatide twice-daily, and sodium glucose cotransporter-2 inhibitors (SGLT-2 inhibitors).

Cardiovascular safety

CV outcome trials conducted in accord with the FDA guidance have been completed for 13 medications (**TABLE 1**).[24-36] The CV outcome trial for ertugliflozin is ongoing.[37] All trials involved people with established CV disease (2° prevention), while some also included patients at high CV risk (1° prevention). These and other differences in study design and patient population preclude direct comparison of these trials. All

TABLE 1 Cardiovascular outcome trials of antidiabetic medications for type 2 diabetes mellitus

	CV outcome trial(s)	Use/prevention	CV safety*	CV benefit
Dipeptidyl peptidase-4 inhibitors				
Alogliptin[24]	EXAMINE	2°	✓	
Linagliptin[25]	CARMELINA	1° & 2°	✓	
Saxagliptin[26]	SAVOR-TIMI 53	1° & 2°	✓	
Sitagliptin[27]	TECOS	1° & 2°	✓	
Glucagon-like peptide-1 receptor agonists				
Albiglutide[28]	HARMONY	2°	✓	✓
Dulaglutide[29]	REWIND	1° & 2°	✓	✓
Exenatide once-weekly[30]	EXSCEL	1° & 2°	✓	
Liraglutide[31]	LEADER	1° & 2°	✓	✓
Lixisenatide[32]	ELIXA	2°	✓	
Semaglutide[33]	SUSTAIN 6	1° & 2°	✓	✓
Sodium glucose cotransporter-2 inhibitors				
Canagliflozin[34]	CANVAS, CANVAS-R, CREDENCE	1° & 2°	✓	✓
Dapagliflozin[35]	DECLARE-TIMI 58	1° & 2°	✓	✓
Empagliflozin[36]	EMPA-REG OUTCOME	2°	✓	✓
Ertugliflozin	VERTIS CV	2°	NC	

Abbreviations: CV, cardiovascular; MI, myocardial infraction; NC, not completed.

*Non-inferior to placebo as part of standard care for the composite endpoint of CV death, non-fatal MI, and non-fatal stroke.

1°, primary prevention (ie, person who has not suffered a cardiac event) 2°, secondary prevention (ie, person who has suffered a cardiac event).

have provided reassurance that the specific DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors investigated cause no increased risk in CV safety compared to placebo as part of standard care.[24-36]

Cardiovascular benefit

The FDA guidance also provided standards whereby an antidiabetic medication could demonstrate superiority to placebo as part of standard care. Some of the antidiabetic medications have demonstrated superiority to placebo, thereby reducing CV risk (**TABLE 1**).[28,29,31,33-36] These are the GLP-1R agonists albiglutide, dulaglutide, liraglutide, and semaglutide, and the SGLT-2 inhibitors canagliflozin, dapagliflozin, and empagliflozin. These results have contributed to updated recommendations in the 2019 American Diabetes Standards of Care and the 2019 American Association of Clinical Endocrinologists/American College of Endocrinology type 2 diabetes algorithm, as well as in the 2019 American College of Cardiology/American Heart Association primary prevention of CV disease guideline, to consider the use of antidiabetic medications with a CV benefit in appropriate patients earlier in the treatment algorithm.[1,6,38] Such patients include those with established atherosclerotic CV disease, HF, or chronic kidney disease.[1] Differences among these medications with respect to their effects on CV events provide an opportunity to go beyond reducing CV risk to also selecting individualized therapy based on patient medical history, such as HF.

Hospitalization for heart failure

Of the 13 medications that have completed a CV outcome trial, empagliflozin has been reported to significantly reduce HF hospitalization (0.94 vs 1.45 events/100 patient-years; hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.50-0.85; *P*=.002) (**TABLE 2**).[28,29,31,33-36] In EMPA-REG OUTCOME, the significant reduction in HF hospitalization with empagliflozin was independent of history of prior MI and/or stroke and did not differ between women and men.[39-41]

Other SGLT-2 inhibitors also reduce HF hospitalization. In the DECLARE-TIMI 58 trial comparing dapagliflozin with placebo, dapagliflozin significantly reduced the composite endpoint of CV death or HF hospitalization (HR, 0.83; 95% CI, 0.73-0.95; *P*=.005).[35] This reduction was due to a lower rate of HF hospitalization in the dapagliflozin group (HR, 0.73; 95% CI, 0.61-0.88) as there was no difference between the groups in the rate of CV death (HR, 0.98; 95% CI, 0.82-

TABLE 2 Effect on heart failure hospitalization of antidiabetic medications for type 2 diabetes mellitus shown to reduce cardiovascular risk

	Rate of heart failure hospitalization/ 100 patient-years		Hazard ratio (95% CI)	*P*
	Active	Placebo		
Glucagon-like peptide-1 receptor agonists				
Albiglutide[28]	NR	NR	NR	NR
Dulaglutide[a,29]	0.83	0.89	0.93 (0.77-1.12)	.46
Liraglutide[31]	1.2	1.4	0.87 (0.73-1.05)	.14
Semaglutide[33]	1.76	1.61	1.11 (0.77-1.61)	.57
Sodium glucose cotransporter-2 inhibitors				
Canagliflozin[43]	0.55	0.87	0.67 (0.52-0.87)	.02
Dapagliflozin[35]	0.62	0.85	0.73 (0.61-0.88)	NR
Empagliflozin[36]	0.94	1.45	0.65 (0.50-0.85)	.002

Abbreviations: CI, confidence intervals; NR, not reported.

[a]Heart failure hospitalization or urgent visit.

1.17). The significant reduction in the composite of CV death or HF hospitalization with dapagliflozin was consistent across several subgroups, including patients with established atherosclerotic CV disease, as well as history of HF at baseline.[35] Additional analysis showed that dapagliflozin reduced HF hospitalization both in those with and in those without HFrEF, whereas it reduced CV death only in those with HFrEF but not in those without HFrEF.[42] With respect to canagliflozin, combined analysis of CANVAS and CANVAS-R showed a similar benefit in the MACE endpoint for patients with HFrEF and HFpEF. Canagliflozin significantly lowered the risk of HF hospitalization (HR, 0.67; 95% CI, 0.52-0.87).[34,43] The reduction in HF hospitalization with canagliflozin vs placebo was significantly greater in those with a history of HF (HR 0.51, 95% CI 0.33-0.78), but not in those with no history of HF (HR,0.79; 95% CI, 0.57-1.09).[43] Further analysis of the CANVAS program showed that canagliflozin also significantly reduced the composite of fatal HF or HF hospitalization (HR, 0.70; 95% CI, 0.55-0.89).[43]

Results of the LEADER and SUSTAIN-6 trials showed liraglutide and semaglutide, respectively, did not significantly reduce the rate of HF hospitalization compared with placebo (**TABLE 2**).[31,33]

The effects of the DPP-4 inhibitor saxagliptin on HF hospitalization are also notable. Results of the SAVOR-TIMI 53 trial showed that saxagliptin was associated with a significant increase in HF hospitalization vs placebo (HR, 1.27; 95% CI, 1.07-1.51; *P*=.007).[26]

OTHER HEART FAILURE TRIALS

Other investigations outside of the CV outcome trials required by the FDA have been conducted in patients with or without DM and with or at risk of HF, many focusing on HF biomarkers. Regarding SGLT-2 inhibitors, a prospective, multicenter, open-label trial involving 58 patients with T2DM showed significant reduction in mitral inflow E and mitral e' annular velocities, indicating improved diastolic function, following 6 months of treatment with dapagliflozin.[44] Other evidence suggesting improved cardiac function with dapagliflozin includes significant reductions in the left atrial volume index and left ventricular mass index, as well as a significant reduction in B-type natriuretic peptide in patients whose level was ≥100 pg/mL at baseline. With respect to canagliflozin, another trial showed that it delays the rise in N-terminal-proB-type natriuretic peptide and high-sensitivity troponin I in 666 older adults with T2DM over 2 years.[45]

The HF effects of the GLP-1R agonists albiglutide and liraglutide have been investigated in randomized, placebo-controlled trials. Albiglutide provided no detectable effect on cardiac function or myocardial glucose use, although there

was a modest increase in peak oxygen consumption over 12 weeks in patients with stable HFrEF.[46]

Several trials involving liraglutide have been conducted, providing conflicting results. One trial involving 32 patients with T2DM and New York Heart Association class II/III HF or left ventricular ejection fraction (LVEF) ≤45% showed significant improvement in LVEF and other measures of cardiac function in patients treated with liraglutide for 52 weeks.[47] In contrast, another trial involving 241 patients (30% with T2DM, 60% with ischemic heart disease) with stable chronic HF (LVEF ≤45%) on optimal HF treatment showed liraglutide had no effect on left ventricular systolic function.[48] Moreover, liraglutide was associated with serious cardiac events (notably atrial fibrillation, ventricular tachycardia, and acute coronary syndrome) in 10% of patients. These events were not assessed in the CV outcome trial for liraglutide and merit further investigation. Another trial of patients (N=300) with or without DM recently hospitalized with HF showed the use of liraglutide for 6 months following discharge resulted in a similar percentage of patients who experienced death or HF rehospitalization as placebo.[49] In addition, the changes from baseline in LVEF, as well as left ventricular end-diastolic and -systolic volume index were similar in the 2 groups.

IMPLICATIONS FOR PRIMARY CARE

Reducing CV risk is the key treatment objective for patients with DM. To reduce the risk of HF in patients with T2DM, several steps can be taken: (1) early recognition of HF and people at increased risk of HF; (2) optimize glycemic control; and (3) utilize and optimize medications shown to reduce HF risk, including selected medications for T2DM.

Available evidence from CV outcome trials shows that 13 of the 15 DPP-4 inhibitors, GLP-1R agonists, and SGLT-2 inhibitors currently available do not pose an increased risk of major adverse cardiovascular events. Moreover, 4 of the GLP-1R agonists (albiglutide, dulaglutide, liraglutide, semaglutide) and 3 of the SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin) are superior to placebo and significantly reduce CV risk. Of these seven medications, canagliflozin, dapagliflozin, and empagliflozin significantly reduce the occurrence of HF hospitalization. Albiglutide, liraglutide, and semaglutide provide no detectable benefit on measures of HF. Beyond individualizing treatment based on factors such as hypoglycemia and body weight, impact on CV events is now an important consideration.

CASE SCENARIO *(CONT'D)*

Following complete evaluation, the 62-year-old male patient was diagnosed with HF*p*EF. In addition to starting guideline-recommended therapy for HF*p*EF (diuretic, angiotensin receptor blocker),[20] the decision is made to discontinue the sulfonylurea (due to increasing A1c and frequent hypoglycemia) and replace with a medication shown to reduce HF hospitalization. The American Diabetes Association prefers the use of an SGLT-2 inhibitor with evidence of reducing HF, noting that empagliflozin, canagliflozin, and dapagliflozin have shown reduction in HF-related events in a CV outcome trial.[1] If an SGLT-2 inhibitor is not tolerated or is contraindicated, a GLP-1R agonist with proven CV benefit is recommended.[1] ●

REFERENCES

1. American Diabetes Association. Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S1-S193.
2. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA.* 1979;241(19):2035-2038.
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.
4. 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.
5. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ.* 2000;321(7258):405-412.
6. Garber AJ, Abrahamson MJ, Barzilay JI, et al. Consensus Statement by the American Association of Clinical Endocrinologists and American College of Endocrinology on the Comprehensive Type 2 Diabetes Management Algorithm - 2019 Executive Summary. *Endocr Pract.* 2019;25(1):69-100.
7. Foley RN, Murray AM, Li S, et al. Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. *J Am Soc Nephrol.* 2005;16(2):489-495.
8. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339(4):229-234.
9. 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.
10. Komanduri S, Jadhao Y, Guduru SS, Cheriyath P, Wert Y. Prevalence and risk factors of heart failure in the USA: NHANES 2013 - 2014 epidemiological follow-up study. *J Community Hosp Intern Med Perspect.* 2017;7(1):15-20.
11. Shah AD, Langenberg C, Rapsomaniki E, et al. Type 2 diabetes and incidence of cardiovascular diseases: a cohort study in 1.9 million people. *Lancet Diabetes Endocrinol.* 2015;3(2):105-113.
12. Nichols GA, Hillier TA, Erbey JR, Brown JB. Congestive heart failure in type 2 diabetes: prevalence, incidence, and risk factors. *Diabetes Care.* 2001;24(9):1614-1619.
13. Boonman-de Winter LJ, Rutten FH, Cramer MJ, et al. High prevalence of previously unknown heart failure and left ventricular dysfunction in patients with type 2 diabetes. *Diabetologia.* 2012;55(8):2154-2162.
14. Timmermans I, Denollet J, Pedersen SS, Meine M, Versteeg H. Patient-reported causes of heart failure in a large European sample. *Int J Cardiol.* 2018;258:179-184.
15. Bertoni AG, Hundley WG, Massing MW, Bonds DE, Burke GL, Goff DC, Jr. Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care.* 2004;27(3):699-703.
16. Thomas MC. Type 2 diabetes and heart failure: Challenges and solutions. *Curr Cardiol Rev.* 2016;12(3):249-255.
17. 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.
18. Solomon SD, Dobson J, Pocock S, et al. Influence of nonfatal hospitalization for heart failure on subsequent mortality in patients with chronic heart failure. *Circulation.* 2007;116(13):1482-1487.
19. van den Berge JC, Constantinescu AA, Boiten HJ, van Domburg RT, Deckers JW, Akkerhuis KM. Short- and long-term prognosis of patients with acute heart failure with and without diabetes: Changes over the last three decades. *Diabetes Care.* 2018;41(1):143-149.
20. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/

American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2013;62(16):e147-239.
21. Lindman BR, Davila-Roman VG, Mann DL, et al. Cardiovascular phenotype in HFpEF patients with or without diabetes: a RELAX trial ancillary study. *J Am Coll Cardiol.* 2014;64(6):541-549.
22. MacDonald MR, Petrie MC, Varyani F, et al. Impact of diabetes on outcomes in patients with low and preserved ejection fraction heart failure: an analysis of the Candesartan in Heart failure: Assessment of Reduction in Mortality and morbidity (CHARM) programme. *Eur Heart J.* 2008;29(11):1377-1385.
23. US Food and Drug Administration. Guidance for Industry. Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. Published 2008. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf. Accessed February 6, 2018.
24. 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.
25. Rosenstock J, Perkovic V, Johansen OE, et al. Effect of linagliptin vs placebo on major cardiovascular events in adults with type 2 diabetes and high cardiovascular and renal risk: The CARMELINA randomized clinical trial. *JAMA.* 2019;321(1):69-79.
26. 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.
27. 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.
28. Hernandez AF, Green JB, Janmohamed S, et al. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet.* 2018;392(10157):1519-1529.
29. Gerstein HC, Colhoun HM, Dagenais GR, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet.* 2019;394(10193):121-130.
30. 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.
31. 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.
32. 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.
33. 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.
34. 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.
35. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N Engl J Med.* 2019;380(4):347-357.
36. 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.
37. Cannon CP, McGuire DK, Pratley R, et al. Design and baseline characteristics of the eValuation of ERTugliflozin efflcacy and Safety CardioVascular outcomes trial (VERTIS-CV). *Am Heart J.* 2018;206:11-23.
38. Arnett DK, Blumenthal RS, Albert MA, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease. *Circulation.* 2019:Cir0000000000000678.
39. Fitchett D, Inzucchi SE, Cannon CP, et al. Empagliflozin reduced mortality and hospitalization for heart failure across the spectrum of cardiovascular risk in the EMPA-REG OUTCOME trial. *Circulation.* 2018;139(11):1384-1395.
40. Verma S, Mazer CD, Fitchett D, et al. Empagliflozin reduces cardiovascular events, mortality and renal events in participants with type 2 diabetes after coronary artery bypass graft surgery: subanalysis of the EMPA-REG OUTCOME(R) randomised trial. *Diabetologia.* 2018;61(8):1712-1723.
41. Zinman B, Inzucchi SE, Wanner C, et al. Empagliflozin in women with type 2 diabetes and cardiovascular disease - an analysis of EMPA-REG OUTCOME(R). *Diabetologia.* 2018;61(7):1522-1527.
42. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. *Circulation.* 2019;139(22):2528-2536.
43. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus. *Circulation.* 2018;138(5):458-468.
44. Soga F, Tanaka H, Tatsumi K, et al. Impact of dapagliflozin on left ventricular diastolic function of patients with type 2 diabetic mellitus with chronic heart failure. *Cardiovasc Diabetol.* 2018;17(1):132.
45. Januzzi JL, Jr., Butler J, Jarolim P, et al. Effects of canagliflozin on cardiovascular biomarkers in older adults with type 2 diabetes. *J Am Coll Cardiol.* 2017;70(6):704-712.
46. Lepore JJ, Olson E, Demopoulos L, et al. Effects of the novel long-acting GLP-1 agonist, albiglutide, on cardiac function, cardiac metabolism, and exercise capacity in patients with chronic heart failure and reduced ejection fraction. *JACC Heart Fail.* 2016;4(7):559-566.
47. Arturi F, Succurro E, Miceli S, et al. Liraglutide improves cardiac function in patients with type 2 diabetes and chronic heart failure. *Endocrine.* 2017;57(3):464-473.
48. Jorsal A, Kistorp C, Holmager P, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. *Eur J Heart Fail.* 2017;19(1):69-77.
49. Margulies KB, Hernandez AF, Redfield MM, et al. Effects of liraglutide on clinical stabilityamongpatientswithadvancedheartfailureandreducedejectionfraction:Arandomized clinical trial. *JAMA.* 2016;316(5):500-508.