Current Cardiology Reports (2020) 22: 105
https://doi.org/10.1007/s11886-020-01355-5

NEW THERAPIES FOR CARDIOVASCULAR DISEASE (AA BAVRY, SECTION EDITOR)

Cardiovascular Effects of Dipeptidyl Peptidase-4 Inhibitors and Glucagon-Like Peptide-1 Receptor Agonists: a Review for the General Cardiologist

Kershaw V. Patel[1] · Ashish Sarraju[2] · Ian J. Neeland[1] · Darren K. McGuire[1]

Published online: 8 August 2020

Abstract

Purpose of Review Results from cardiovascular (CV) outcome trials have revealed important insights into the CV safety and efficacy of glucose-lowering agents, including dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA).

Recent Findings Among patients with T2DM, DPP-4i have no significant effect on risk of major adverse CV events (MACE: CV death, myocardial infarction, or stroke) with mixed results regarding risk for heart failure (HF). While sitagliptin and linagliptin have neutral effects on HF risk, saxagliptin significantly increases the risk of HF. The CV safety of the GLP-1RA class of medications has been clearly demonstrated, and select agents, such as liraglutide, semaglutide, albiglutide, and dulaglutide, reduce the risk of MACE in patients with T2DM and established CV disease.

Summary CV outcome trials have demonstrated CV safety but not incremental efficacy for DPP-4i in most cases. Select GLP-1RA have proven efficacy for MACE and should be considered by cardiologists for CV risk mitigation in the care of patients with T2DM and established CV disease.

Keywords Atherosclerotic cardiovascular disease · Dipeptidyl peptidase-4 inhibitors · Glucagon-like peptide-1 receptor agonists · Heart failure · Type 2 diabetes mellitus

Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM) [1, 2]. After years of progress in T2DM management, cardiovascular (CV) complication rates remain a major clinical concern, especially in young and middle-aged adults [2]. The risk of CVD is compounded by safety concerns of specific glucose-lowering medications. For example, rosiglitazone was associated with higher risk of CVD that eventually led to restrictions of its use [3]. While prescription rates of rosiglitazone declined, new classes of glucose-lowering medications were emerging with important CV implications [4].

Dipeptidyl peptidase-4 inhibitors (DPP-4i) and glucagon-like peptide-1 receptor agonists (GLP-1RA) are incretin-based therapies approved for glycemic control since the mid-2000s [5]. Incretin hormones lower plasma glucose by stimulating glucose-dependent insulin secretion, suppressing glucagon release, and promoting satiety [6]. Dipeptidyl peptidase-4 (DPP-4) breaks down incretins and its inhibition potentiates endogenous incretin hormone effects. Pharmacologic GLP-1RA augment endogenous incretin effects and are less susceptible to DPP-4 degradation. Shortly after approval of DPP-4i and GLP-1RA as glucose-lowering agents, the United States Food and Drug Administration (US FDA) and the European

This article is part of the Topical Collection on *New Therapies for Cardiovascular Disease*

✉ Darren K. McGuire
Darren.McGuire@UTSouthwestern.edu

Kershaw V. Patel
kershawpatel@gmail.com

Ashish Sarraju
asarraju@stanford.edu

Ian J. Neeland
Ian.Neeland@UTSouthwestern.edu

[1] Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd, Dallas, TX 75390-8830, USA

[2] Division of Cardiovascular Medicine and Cardiovascular Institute, Stanford University, Stanford, CA, USA

Medicines Agency issued guidance to industry that all new glucose-lowering medications should be proven not to increase CV risk [7]. As a result, over the last decade, a series of large-scale CV outcome trials have been conducted, providing important data regarding the CV effects of glucose-lowering therapies, including the DPP-4i and GLP-1RA classes of medications.

Despite the current availability of cardioprotective medications, only about 7% of patients with T2DM and established atherosclerotic CVD (ASCVD) receive guideline-recommended optimal medical therapy, and this proportion is even lower for those treated by cardiologists [8]. Specific GLP-1RA have proven CV benefits, yet cardiologists account for less than 5% of new GLP-1RA prescriptions [9]. Cardiologists have a key role in the prevention of CVD and should consider the CV effects of glucose-lowering medications. Thus, the present review highlights the CV implications of DPP-4i and GLP-1RA for the general cardiologist.

Dipeptidyl Peptidase-4 Inhibitors

Cardiometabolic Effects

DPP-4i improve glycemic control and have modest effects on other cardiometabolic parameters, given its influence on endogenous incretins and downstream hormones [10]. Compared with placebo, DPP-4i reduce systolic BP on average by 3 mmHg and diastolic BP by 1.5 mmHg [11]. The impact of DPP-4i on weight has been inconsistent across trials, with the totality of the evidence suggesting an overall neutral effect [12]. Finally, the lipid profile of patients with T2DM who receive DPP-4i varies, with some evidence suggesting improvements in triglyceride levels [10].

Safety with Respect to Major Adverse Cardiovascular Events

Nearly 50,000 patients with T2DM have been enrolled across 5 clinical trials examining the CV effects of DPP-4i [13, 14•, 15–17]. Each of these DPP-4i trials demonstrated non-inferiority with regard to their effect on risk of major adverse cardiovascular events (MACE: a composite of CV death, non-fatal myocardial infarction, or nonfatal stroke), but there remain several important features to consider. Table 1 summarizes the results from 5 DPP-4i CV outcome trials.

EXAMINE was a CV outcome trial published in 2013 examining the CV safety of a DPP-4i alogliptin [13]. In EXAMINE, patients with T2DM who had a recent acute coronary syndrome were randomly assigned to receive either alogliptin or placebo. The risk of MACE was similar among patients in the alogliptin and placebo groups, marking alogliptin as a DPP-4i that demonstrated safety with respect to MACE. The neutral effects of the DPP-4i class of medications on MACE were confirmed in subsequent CV outcome trials, such as TECOS, which enrolled a similar study population as EXAMINE and included patients with T2DM and established ASCVD [15]. In TECOS, patients randomized to treatment with sitagliptin and placebo had similar risk of the primary composite endpoint (MACE plus hospitalization for unstable angina) as well as MACE. Similarly, saxagliptin [14•] and linagliptin [16, 17] had no significant effect on risk of MACE in lower risk study populations that included patients who had T2DM and either established ASCVD or multiple CV risk factors.

Safety Concerns for Heart Failure

While demonstrating neutral effects on the risk of MACE, a heart failure (HF) safety signal emerged for select DPP-4i. In SAVOR-TIMI 53, saxagliptin increased the rate of HF hospitalization, a risk increment evident in the first 6 months of the trial and sustained throughout the study period [14•, 19]. The higher absolute rate of hospitalization for HF in the saxagliptin versus placebo group was observed in the overall cohort as well as across key subgroups, including patients with chronic kidney disease, history of HF, and presence of multiple CV risk factors. Due in part to the increased risk of HF observed with saxagliptin, there were concerns regarding increased risk of HF associated with the entire DPP-4i class of medications, and a separate analysis of the EXAMINE trial was performed to evaluate the risk of HF in patients treated with alogliptin [18]. While the number of patients who had a hospitalization for HF was numerically higher in the alogliptin (3.1%) versus placebo group (2.9%), this difference did not achieve statistical significance. However, among patients with no prior history of HF (nearly three-quarters of the original trial population), those in the alogliptin treatment group had a 76% increased risk of developing HF compared with the placebo group. The increased risk of HF observed with saxagliptin, and numerically more HF events in the alogliptin versus placebo groups, did not translate to all of the medications in the DPP-4i class. In contrast, sitagliptin had a neutral effect on HF that was consistent for first and total hospitalizations for HF [15, 20]. Linagliptin also did not affect the risk of HF, a finding that was consistent across two CV outcome trials [16, 17].

The higher absolute number of HF hospitalizations among patients who received saxagliptin or alogliptin compared with placebo in SAVOR-TIMI 53 and EXAMINE, respectively, prompted the US FDA to convene an advisory committee to review the clinical trial data and assess the CV risk profile of these medications. As a result from the review, in April 2016, the US FDA added the potential for increased HF risk to the

Table 1 Summary of cardiovascular outcome trials examining dipeptidyl peptidase-4 inhibitors

Medication	Clinical trial (publication year)	Participants (*n*)	Proportion with established CVD	Median f/u (year)	MACE HR (95% CI)	HF HR (95% CI)
Alogliptin [13, 18]	EXAMINE (2013)	5380	100%	1.5	0.96 (≤ 1.16)	1.07 (0.79, 1.46)
Saxagliptin [14•]	SAVOR-TIMI53 (2013)	16,492	79%	2.1	1.00 (0.89, 1.12)	1.27 (1.07, 1.51)
Sitagliptin [15]	TECOS (2015)	14,671	100%	3.0	0.99 (0.89, 1.10)	1.00 (0.83, 1.20)
Linagliptin [16, 17]	CARMELINA (2018)	6991	57%	2.2	1.02 (0.89, 1.17)	0.90 (0.74, 1.08)
	CAROLINA (2019)	6042	42%	6.3	0.98 (0.84, 1.14)	1.21 (0.92, 1.59)

MACE was defined by CV death, nonfatal MI, or nonfatal stroke

CARMELINA, Cardiovascular and Renal Microvascular Outcome Study With Linagliptin; CAROLINA, Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes; CV, cardiovascular; CVD, cardiovascular disease; EXAMINE, Examination of Cardiovascular Outcomes With Alogliptin Versus Standard of Care; HF, heart failure; MACE, major atherosclerotic cardiovascular events; MI, myocardial infarction; SAVOR-TIMI 53, Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes–Thrombolysis in Myocardial Infarction 53; TECOS, Trial Evaluating Cardiovascular Outcomes With Sitagliptin

product labels of both saxagliptin and alogliptin [21]. Despite the neutral effects of sitagliptin and linagliptin on risk of HF, the US FDA extended the HF risk warning to all members of the DPP-4i class. Several potential mechanisms have been proposed to explain the increased risk of HF with DPP-4i [22]. The adverse consequences of DPP-4i in patients with established HF with reduced ejection fraction (HFrEF) were highlighted in the VIVID trial [23]. Patients with T2DM and HF with an ejection fraction less than 40% were randomly assigned to vildagliptin or placebo for 1 year. While there was no significant difference in the primary endpoint of left ventricular ejection fraction between treatment groups, vildagliptin led to a significant increase in left ventricular end-diastolic volume, a cardiac remodeling pattern that is associated with adverse outcomes [24].

Practical Considerations

Among patients with T2DM and established ASCVD, DPP-4i are recommended as an add-on therapy to improve glycemic control after use of other guideline-recommended therapies given its established safety, but lack of efficacy, regarding risk of MACE [12]. However, saxagliptin increases the risk of hospitalization for HF and should not be prescribed to patients who have T2DM and higher risk of developing HF [14•, 19].

The DPP-4i class of medications has several distinct advantages over some other glucose-lowering medications, including the following: (1) availability as once daily tablets; (2) can be used in chronic kidney disease, although dose-adjustment is needed for select DPP-4i; and (3) generally well tolerated with few side effects, including low rates of hypoglycemia [10]. Potential complications of DPP-4i that should be considered include joint pain and pancreatitis [12].

Glucagon-like Peptide-1 Receptor Agonists

Effects on Cardiovascular Risk Factors

Originally approved by the US FDA to improve glycemic control, the GLP-1RA class of medications also notably impacts several cardiometabolic parameters including weight and lipoproteins [25]. GLP-1RA delay gastric emptying and stimulate satiety leading to weight loss. While reduction in weight observed with GLP-1RA is a class effect, liraglutide was the only agent in the class of medications evaluated extensively for this purpose and approved by the US FDA as an adjunct to diet and exercise for weight management [26]. The reduction in weight induced by GLP-1RA is accompanied by improved lipid profiles that include reductions in triglyceride and low-density lipoprotein cholesterol with an increase in high-density lipoprotein cholesterol concentrations [25].

Across multiple studies, GLP-1RA have demonstrated consistent effects on key hemodynamic measurements, including blood pressure and heart rate. Patients prescribed with GLP-1RA experience, on average, a reduction in systolic blood pressure of 2 to 3 mmHg, although the effects on diastolic blood pressure have been less consistent [27]. Potentially related to GLP-1 receptor-mediated effects on the sinoatrial node, GLP-1RA increase heart rate on average 2 to 3 beats per minute, but there is no associated risk of atrial fibrillation observed with this class of glucose-lowering medications [25, 27, 28].

Safe and Effective Therapy to Reduce the Risk of Major Adverse Cardiovascular Events

Designed to evaluate CV safety, some of the GLP-1RA CV outcome trials demonstrated significantly lower risk for MACE with select GLP-1RA. Findings from these clinical

trials led the US FDA to approve certain GLP-1RA to reduce the risk of MACE, and these cardioprotective agents have been incorporated into T2DM management guidelines. The results of 7 GLP-1RA CV outcome trials are summarized in Table 2 [29, 31•, 32–36].

The ELIXA trial randomized patients with T2DM and a recent acute coronary syndrome to once daily lixisenatide or placebo [29]. Risk of the primary composite outcome (MACE plus hospitalization for unstable angina) and MACE were similar between the lixisenatide and placebo groups [30]. Taken together, lixisenatide demonstrated safety with respect to the risk of MACE but not superiority. Similarly, CV outcome trials evaluating extended-release once weekly exenatide and oral once daily semaglutide have also ruled out excess risk of MACE in EXSCEL and PIONEER 6, respectively [33, 36]. Of note, once weekly exenatide narrowly missed the superiority margin for MACE, and the proportion of patients who died was numerically lower in the exenatide (6.9%) versus placebo group (7.9%). Furthermore, PIONEER 6 was not adequately powered to evaluate the superiority of oral semaglutide with respect to MACE.

LEADER was a landmark clinical trial published in 2016 that evaluated the CV effects of once daily liraglutide versus placebo among patients with T2DM and either established CVD or multiple CV risk factors [31•]. In LEADER, liraglutide reduced the risk of MACE by 13%, all-cause death by 15%, and death from CV causes by 22%. Liraglutide went on to become the first GLP-1RA approved by the US FDA to reduce the risk of MACE among patients with T2DM and established CVD. Subsequent CV outcome trials of select GLP-1RA demonstrated consistent superiority with respect to the risk of MACE. Compared with LEADER, SUSTAIN-6 enrolled a similar high CV risk population but included only approximately one-third of the number of participants and followed them for nearly one-half of the study duration [31•, 32]. In SUSTAIN-6, patients who were randomized to receive subcutaneous (SC) semaglutide had a significantly lower risk of MACE compared with those in the placebo group. Albiglutide and dulaglutide also significantly reduced the risk of MACE in HARMONY OUTCOMES and REWIND, respectively, but the study populations enrolled in those CV outcome trials were markedly different [34, 35]. While all patients had T2DM and established ASCVD in HARMONY OUTCOMES, the majority of patients enrolled in REWIND did not have established ASCVD. Due to the beneficial effects observed in a large primary prevention study population, dulaglutide was the first and currently only GLP-1RA approved by the US FDA to reduce the risk of MACE in patients who have T2DM with and without established CVD. Of note, the manufacturer removed albiglutide from the market.

Evidence for Incident and Prevalent Heart Failure

Most CV outcome trials examining GLP-1RA demonstrated neutral effects on risk of HF with one exception. In HARMONY OUTCOMES, albiglutide reduced the risk of HF hospitalization by 29% [30]. A pooled analysis of 7 CV outcome trials demonstrated a modest reduction in HF risk with GLP-1RA [30]. The reason for the lower risk of HF associated with GLP-1RA is unclear, but one possible explanation may be related to its beneficial effects on myocardial infarction which often precedes HF development.

Table 2 Summary of cardiovascular outcome trials examining glucagon-like peptide-1 receptor agonists

Medication	Clinical trial (publication year)	Participants (*n*)	Proportion with established CVD	Median f/u (years)	MACE HR (95% CI)	HF HR (95% CI)
Lixisenatide [29, 30]	ELIXA (2015)	6068	100%	2.1	1.02 (0.89, 1.17)	0.96 (0.75, 1.23)
Liraglutide [31•]	LEADER (2016)	9340	81%	3.8	0.87 (0.78, 0.97)	0.87 (0.73, 1.05)
Semaglutide (SC) [32]	SUSTAIN-6 (2016)	3297	83%	2.1	0.74 (0.58, 0.95)	1.11 (0.77, 1.61)
Exenatide [33]	EXSCEL (2017)	14,752	73%	3.2	0.91 (0.83, 1.00)	0.94 (0.78, 1.13)
Albiglutide [30, 34]	HARMONY OUTCOMES (2018)	9463	100%	1.6	0.78 (0.68, 0.90)	0.71 (0.53, 0.94)
Dulaglutide [35]	REWIND (2019)	9901	31%	5.4	0.88 (0.79, 0.99)	0.93 (0.77, 1.12)
Semaglutide (oral) [36]	PIONEER 6 (2019)	3183	*85%	1.3	0.79 (0.57, 1.11)	0.86 (0.48, 1.55)

MACE was defined by CV death, nonfatal MI, or nonfatal stroke. *In the PIONEER 6 trial, 85% of participants were ≥ 50 years of age and had established CVD or chronic kidney disease

CV, cardiovascular; CVD, cardiovascular disease; ELIXA, Evaluation of Lixisenatide in Acute Coronary Syndrome; EXSCEL, Exenatide Study of Cardiovascular Event Lowering; HF, heart failure; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE, major atherosclerotic cardiovascular events; MI, myocardial infarction; PIONEER 6, Peptide Innovation for Early Diabetes Treatment 6; REWIND, Researching Cardiovascular Events With a Weekly Incretin in Diabetes; SC, subcutaneous; SUSTAIN-6, Trial to Evaluate Cardiovascular and Other Long-term Outcomes With Semaglutide in Subjects with Type 2 Diabetes

The number of patients with established HF enrolled in CV outcome trials examining GLP-1RA was low, but caution should be taken when prescribing these agents to patients with prevalent HF given the findings of several smaller studies [37] (reference in press). The CV effects of albiglutide were examined in a clinical trial of 82 patients with HFrEF who had no history of T2DM [38]. Albiglutide had a neutral effect on cardiac structure and systolic function and modestly improved peak oxygen consumption compared with placebo. In contrast, FIGHT and LIVE demonstrated numerically more adverse events with liraglutide versus placebo in patients who had HFrEF with and without T2DM [39, 40]. FIGHT enrolled patients with advanced HF who were recently hospitalized despite taking guideline-directed medical therapies [39]. In FIGHT, patients randomized to receive liraglutide had a greater number of rehospitalizations for HF compared with the placebo group, although this difference was not statistically significant. The LIVE trial enrolled a more stable population, but patients in the liraglutide group experienced more serious adverse cardiac events compared with the placebo group [40].

Endorsed by Society Recommendations to Lower Cardiovascular Disease Risk

The emergence of cardioprotective medications, such as GLP-1RA, coupled with the lack of consistent CV benefits of intensive glycemic control has led to a paradigm shift in T2DM management [41]. Based on the results of several CV outcome trials, recommendations for the use of GLP-1RA in T2DM have expanded from add-on therapies for glycemic control to first- and second-line agents to reduce CV risk. In patients with high-risk or established ASCVD, the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) recommend either GLP-1RA or SGLT-2 inhibitors after metformin [12]. Of particular note, recommendations for these cardioprotective agents are independent of baseline glycemic control or targets. Furthermore, GLP-1RA are preferred for patients who have higher risk of MACE versus HF in the setting of consistent and robust reduction in MACE compared with HF [12, 30].

The American College of Cardiology (ACC) recommends a similar CV risk-lowering strategy as the ADA and EASD [42]. For patients with T2DM and established ASCVD, the ACC recommends a GLP-1RA or SGLT-2 inhibitor with proven benefit plus guideline-directed medications and glucose-lowering therapy with metformin. However, concerns have been raised regarding the utility of metformin as a first-line agent for patients who have T2DM and established ASCVD or multiple CV risk factors given the lack of robust data demonstrating reduction in CV risk with metformin [43]. While most participants in CV outcome trials were receiving metformin at baseline, a substantial proportion of individuals were not. For example, approximately one-third of patients in the ELIXA trial were not taking metformin at the start of the study [29]. Furthermore, the CV benefits of GLP-1RA appear consistent regardless of background glucose-lowering therapy, including no T2DM medications, raising the question whether metformin should be first-line therapy for T2DM management [31•]. A departure from metformin as first-line therapy for T2DM is seen in a European Society of Cardiology recommendation [44]. Specifically, for patients with T2DM and either established ASCVD or at least high CV risk who are not receiving glucose-lowering medications, GLP-1RA or SGLT-2 inhibitor monotherapy is recommended as first-line therapy. However, if patients are already taking metformin, then GLP-1RA or SGLT-2 inhibitors are recommended as an add-on therapy.

A Guide for Evidence-Based Therapies

Cardiologists should consider several factors when prescribing GLP-1RA for the management of patients with T2DM and established CVD. First, GLP-1RA that have proven CV benefits should be prioritized above other agents in the class with neutral CV effects. Liraglutide, SC semaglutide, and dulaglutide are approved by the US FDA for secondary prevention of MACE based on superiority results from large CV outcome trials [31•, 32, 35]. Second, patient preference regarding route and frequency of administration of medications should be considered. All GLP-1RA are available as SC injections, and semaglutide has both a SC and oral formulation. However, SC semaglutide reduces the risk of MACE, while the CV efficacy of oral semaglutide is currently being evaluated in an ongoing trial. Additionally, the dosing frequency of cardioprotective GLP-1RA varies between once daily (liraglutide) and once weekly (SC semaglutide, albiglutide, dulaglutide) agents. Third, patients should be counseled regarding potential side effects of GLP-1RA. Diabetic retinopathy is a rare complication of GLP1-RA, especially SC semaglutide [32]. Patients with pre-existing diabetic retinopathy treated with insulin may be at particularly increased risk for complications from SC semaglutide [45]. Additionally, patients treated with GLP-1RA may experience nausea and vomiting likely related to the slowing of gastric emptying [12]. Initiation of GLP-1RA at a low dose and slow up-titration may mitigate gastrointestinal side effects.

Future Directions

Currently, there are several ongoing CV outcome trials examining the CV effects of GLP-1RA. SC semaglutide reduces the risk of MACE in patients with T2DM and established CVD, but its CV effects in patients without a history of T2DM are not well-established [32]. SELECT is a CV outcome trial currently underway evaluating the CV safety and efficacy of SC

semaglutide in patients with overweight or obesity who do not have a history of T2DM (ClinicalTrials.gov; Unique Identifier: NCT03574597). While PIONEER 6 demonstrated that oral semaglutide was non-inferior to placebo for the risk of MACE, this CV outcome trial was not powered to evaluate superiority [36]. SOUL is an ongoing clinical trial that is evaluating the CV efficacy of oral semaglutide among patients with T2DM (ClinicalTrials.gov; Unique Identifier: NCT03914326). Additionally, AMPLITUDE-O is a CV outcome trial currently underway examining the effects of efpeglenatide, a long-acting GLP-1RA, among patients with T2DM and established CVD or multiple risk factors (ClinicalTrials.gov; Unique Identifier: NCT03496298).

Conclusions

Incretin-based therapies were originally approved to lower glucose, but trial data suggest that cardiologists should consider the CV effects of DPP-4i and GLP-1RA in the management of patients with T2DM and established CVD due to select CV safety concerns and cardioprotective effects. Among patients with T2DM and established ASCVD, DPP-4i have a neutral effect on the risk of MACE. However, saxagliptin increases HF risk and should be avoided in patients with T2DM who are at high risk for developing HF. Cardiologists should consider specific agents within the GLP-1RA class of medications because of their CV risk-lowering effects. Prescription of GLP-1RA should be embraced independent of glycemic control to expand the use of cardioprotective therapies for appropriate patients with T2DM and established CVD to reduce the risk of MACE.

Funding Information Dr. Patel is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (5T32HL125247-03). Dr. Neeland reports a grant from the National Institutes of Health (K23 DK106520).

Compliance with Ethical Standards

Conflict of Interest Dr. Neeland reports receiving fees for consulting and serving on the advisory board from Boehringer Ingelheim/Lilly Alliance and AMRA Medical and a research grant from Novo Nordisk. Dr. McGuire reports honoraria for trial leadership from AstraZeneca, Sanofi Aventis, Janssen Research and Development LLC, Boehringer Ingelheim, Merck Sharp & Dohme Co., Pfizer, Novo Nordisk, Lexicon, Eisai Inc., GlaxoSmithKline, Esperion, and Lilly US and honoraria for consulting for Afimmune, AstraZeneca, Sanofi Aventis, Lilly US, Boehringer Ingelheim, Merck & Co., Pfizer, Novo Nordisk, Metavant, and Applied Therapeutics. Drs. Patel and Sarraju have no conflicts to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Gregg EW, Cheng YJ, Srinivasan M, Lin J, Geiss LS, Albright AL, et al. Trends in cause-specific mortality among adults with and without diagnosed diabetes in the USA: an epidemiological analysis of linked national survey and vital statistics data. Lancet. 2018;391(10138):2430–40. https://doi.org/10.1016/S0140-6736(18)30314-3.
2. Gregg EW, Hora I, Benoit SR. Resurgence in diabetes-related complications. JAMA. 2019;321(19):1867–8. https://doi.org/10.1001/jama.2019.3471.
3. 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):2457–71. https://doi.org/10.1056/NEJMoa072761.
4. Hampp C, Borders-Hemphill V, Moeny DG, Wysowski DK. Use of antidiabetic drugs in the U.S., 2003-2012. Diabetes Care. 2014;37(5):1367–74. https://doi.org/10.2337/dc13-2289.
5. White JR Jr. A brief history of the development of diabetes medications. Diabetes Spectr. 2014;27(2):82–6. https://doi.org/10.2337/diaspect.27.2.82.
6. Ussher JR, Drucker DJ. Cardiovascular actions of incretin-based therapies. Circ Res. 2014;114(11):1788–803. https://doi.org/10.1161/CIRCRESAHA.114.301958.
7. Patel KV, de Albuquerque RN, McGuire DK. Diabetes medications and cardiovascular outcome trials: lessons learned. Cleve Clin J Med. 2017;84(10):759–67. https://doi.org/10.3949/ccjm.84gr.17006.
8. Arnold SV, de Lemos JA, Rosenson RS, Ballantyne CM, Liu Y, Mues KE, et al. Use of guideline-recommended risk reduction strategies among patients with diabetes and atherosclerotic cardiovascular disease. Circulation. 2019;140(7):618–20. https://doi.org/10.1161/CIRCULATIONAHA.119.041730.
9. Vaduganathan M, Patel RB, Singh A, McCarthy CP, Qamar A, Januzzi JL Jr, et al. Prescription of glucagon-like peptide-1 receptor agonists by cardiologists. J Am Coll Cardiol. 2019;73(12):1596–8. https://doi.org/10.1016/j.jacc.2019.01.029.
10. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA. 2007;298(2):194–206. https://doi.org/10.1001/jama.298.2.194.
11. Zhang X, Zhao Q. Effects of dipeptidyl peptidase-4 inhibitors on blood pressure in patients with type 2 diabetes: a systematic review and meta-analysis. J Hypertens. 2016;34(2):167–75. https://doi.org/10.1097/HJH.0000000000000782.
12. American DA. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S98–S110. https://doi.org/10.2337/dc20-S009.
13. White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369(14):1327–35. https://doi.org/10.1056/NEJMoa1305889.
14.• Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369(14):1317–26. https://doi.org/10.1056/NEJMoa1307684 **This CV outcome trial demonstrated that saxagliptin was non-inferior to placebo for the risk of MACE but increased the risk of HF among patients with T2DM and either established ASCVD or multiple CV risk factors**.

15. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373(3):232–42. https://doi.org/10.1056/NEJMoa1501352.
16. Rosenstock J, Perkovic V, Johansen OE, Cooper ME, Kahn SE, Marx N, 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. https://doi.org/10.1001/jama.2018.18269.
17. Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA. 2019. https://doi.org/10.1001/jama.2019.13772.
18. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, et al. 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(9982):2067–76. https://doi.org/10.1016/S0140-6736(14)62225-X.
19. Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation. 2014;130(18):1579–88. https://doi.org/10.1161/CIRCULATIONAHA.114.010389.
20. McGuire DK, Van de Werf F, Armstrong PW, Standl E, Koglin J, Green JB, 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):126–35. https://doi.org/10.1001/jamacardio.2016.0103.
21. US Food and Drug Administration. FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-adds-warnings-about-heart-failure-risk-labels-type-2-diabetes. Accessed May 28, 2020.
22. Packer M. Do DPP-4 inhibitors cause heart failure events by promoting adrenergically mediated cardiotoxicity? Clues from laboratory models and clinical trials. Circ Res. 2018;122(7):928–32. https://doi.org/10.1161/CIRCRESAHA.118.312673.
23. McMurray JJV, Ponikowski P, Bolli GB, Lukashevich V, Kozlovski P, Kothny W, 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. https://doi.org/10.1016/j.jchf.2017.08.004.
24. Konstam MA, Udelson JE, Anand IS, Cohn JN. Ventricular remodeling in heart failure: a credible surrogate endpoint. J Card Fail. 2003;9(5):350–3. https://doi.org/10.1054/j.cardfail.2003.09.001.
25. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular actions and clinical outcomes with glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors. Circulation. 2017;136(9):849–70. https://doi.org/10.1161/CIRCULATIONAHA.117.028136.
26. Mehta A, Marso SP, Neeland IJ. Liraglutide for weight management: a critical review of the evidence. Obes Sci Pract. 2017;3(1):3–14. https://doi.org/10.1002/osp4.84.
27. Sun F, Wu S, Guo S, Yu K, Yang Z, Li L, et al. Impact of GLP-1 receptor agonists on blood pressure, heart rate and hypertension among patients with type 2 diabetes: a systematic review and network meta-analysis. Diabetes Res Clin Pract. 2015;110(1):26–37. https://doi.org/10.1016/j.diabres.2015.07.015.
28. Monami M, Nreu B, Scatena A, Giannini S, Andreozzi F, Sesti G, et al. Glucagon-like peptide-1 receptor agonists and atrial fibrillation: a systematic review and meta-analysis of randomised controlled trials. J Endocrinol Investig. 2017;40(11):1251–8. https://doi.org/10.1007/s40618-017-0698-7.
29. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Kober LV, et al. Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. N Engl J Med. 2015;373(23):2247–57. https://doi.org/10.1056/NEJMoa1509225.
30. Kristensen SL, Rorth R, Jhund PS, Docherty KF, Sattar N, Preiss D, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet Diabetes Endocrinol. 2019;7(10):776–85. https://doi.org/10.1016/S2213-8587(19)30249-9.
31.• Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311–22. https://doi.org/10.1056/NEJMoa1603827 **This was the first CV outcome trial to demonstrate a reduction in risk of MACE with a GLP-1RA among patients who had T2DM with prevalent CVD or multiple CV risk factors**.
32. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375(19):1834–44. https://doi.org/10.1056/NEJMoa1607141.
33. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, et al. Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2017;377(13):1228–39. https://doi.org/10.1056/NEJMoa1612917.
34. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB Sr, Granger CB, Jones NP, 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):1519–29. https://doi.org/10.1016/S0140-6736(18)32261-X.
35. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet. 2019;394(10193):121–30. https://doi.org/10.1016/S0140-6736(19)31149-3.
36. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2019;381(9):841–51. https://doi.org/10.1056/NEJMoa1901118.
37. Greene SJ, Vaduganathan M, Khan MS, Bakris GL, Weir MR, Seltzer JH, et al. Prevalent and incident heart failure in cardiovascular outcome trials of patients with type 2 diabetes. J Am Coll Cardiol. 2018;71(12):1379–90. https://doi.org/10.1016/j.jacc.2018.01.047.
38. Lepore JJ, Olson E, Demopoulos L, Haws T, Fang Z, Barbour AM, 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):559–66. https://doi.org/10.1016/j.jchf.2016.01.008.
39. Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA. 2016;316(5):500–8. https://doi.org/10.1001/jama.2016.10260.
40. Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, 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. https://doi.org/10.1002/ejhf.657.

41. Patel KV, McGuire DK. Long-term follow-up of intensive glycaemic control in type 2 diabetes. Nat Rev Cardiol. 2019;16(9):517–8. https://doi.org/10.1038/s41569-019-0241-y.
42. Das SR, Everett BM, Birtcher KK, Brown JM, Cefalu WT, Januzzi JL Jr, et al. 2018 ACC expert consensus decision pathway on novel therapies for cardiovascular risk reduction in patients with type 2 diabetes and atherosclerotic cardiovascular disease: a report of the American College of Cardiology Task Force on expert consensus decision pathways. J Am Coll Cardiol. 2018;72(24):3200–23. https://doi.org/10.1016/j.jacc.2018.09.020.
43. Harrington JL, de Albuquerque Rocha N, Patel KV, Verma S, McGuire DK. Should metformin remain first-line medical therapy for patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease? An alternative approach. Curr Diab Rep 2018;18(9):64. https://doi.org/10.1007/s11892-018-1035-z.
44. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020;41(2):255–323. https://doi.org/10.1093/eurheartj/ehz486.
45. Vilsboll T, Bain SC, Leiter LA, Lingvay I, Matthews D, Simo R, et al. Semaglutide, reduction in glycated haemoglobin and the risk of diabetic retinopathy. Diabetes Obes Metab. 2018;20(4):889–97. https://doi.org/10.1111/dom.13172.