

Overview of the Cardiovascular Benefit With Diabetic Agents and Novel Combination Products for Type 2 Diabetes

Candis M. Morello, PharmD, CDE

Cardiovascular (CV) disease is a common comorbidity of type 2 diabetes (T2D) and is associated with significant morbidity and mortality in this patient population.¹ Since 2008, the FDA requires all new diabetes medications to be evaluated for unacceptable increases in CV risk. Among other expectations, drug sponsors must provide an independent CV endpoints committee to prospectively, and in a blinded fashion, adjudicate CV events during phase 2 and phase 3 trials. CV events include mortality due to CV disease, myocardial infarction (MI), and stroke, and can include hospitalization for acute coronary syndrome and urgent revascularization procedures, as well as other related endpoints.

Several randomized trials suggest that liraglutide, a glucagon-like peptide-1 receptor agonist (GLP-1 RA), and empagliflozin, a sodium-glucose cotransporter-2 (SGLT-2) inhibitor, lower CV risk when added to standard care in patients with T2D with established CV disease.² Semaglutide, another promising GLP-1 RA under study in the SUSTAIN 6 trial, has demonstrated CV benefit and is being evaluated for FDA approval.³ In the CANVAS trial, canagliflozin (compared with placebo) was associated with a lower risk of CV events but a greater risk of amputation.⁴ The mechanism by which these medications exert these effects is unclear and is unlikely attributable to their modest glucose-lowering effects. However, these medications are costly and the numbers needed to treat (NNT) to benefit 1 patient are fairly large. The current American Diabetes Association and American Association of Clinical Endocrinologists/American College of Endocrinology treatment guidelines recommend considering liraglutide or empagliflozin for patients with established CV disease to reduce the risk of mortality.¹ Other incretin-based drugs, such as lixisenatide, have not demonstrated these beneficial effects, or, as in the case of some dipeptidyl peptidase-4 (DPP-4) inhibitors, have revealed an association with the development of heart failure (HF).⁵ The mechanisms of the observed CV differences between DPP-4 inhibitors and GLP-1 RAs and among individual DPP-4 inhibitors and GLP-1 RAs need further delineation and research.

Novel combination products take advantage of complementary mechanisms of action to maximize efficacy and reduce adverse

ABSTRACT

Cardiovascular (CV) disease is commonly observed in individuals with type 2 diabetes (T2D) and is associated with significant morbidity and mortality. Diabetes medications can have substantial negative or beneficial CV effects in these patients. Thus far, specific glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors have been shown to have beneficial CV effects in persons with T2D. Clinical trials are ongoing to evaluate the CV effects of investigational and recently approved diabetes medications. Additional advances through novel combination products have been shown to improve medication adherence and patient convenience. Future studies will evaluate the long-term effects of these combination products in patients with T2D.

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effects (AEs). These products offer patient convenience and can increase medication adherence. One novel combination product was recently FDA approved and several are under investigation.

Cardiovascular Risk Considerations and Diabetes Medication Concerns

HF Risk Increased

Patients with T2D are at an increased risk of developing HF; the combination of HF and diabetes substantially worsens prognosis.^{1,6} The risks of HF in diabetes are multifold and may be attributed to comorbid conditions, including myocardial ischemia, atherogenesis, coronary artery disease, hypertension, and diabetic cardiomyopathy.⁷ As a result of the FDA CV study outcomes requirements, some negative outcomes have come to light with specific DPP-4 inhibitors. The DPP-4 inhibitor class includes 4 drugs (sitagliptin, saxagliptin, linagliptin, and alogliptin), all of which decrease hyperglycemia by increasing GLP-1 and gastric inhibitory polypeptide (GIP) concentrations. These gut-derived hormones stimulate insulin secretion in a glucose-dependent manner and mildly delay gastric emptying.¹ Alogliptin and saxagliptin carry an FDA-required HF warning on prescribing information sheets. Prescribers are cautioned not to initiate these agents in patients who have HF or are at risk for HF (defined as having low estimated glomerular filtration rate, or elevated N-terminal pro b-type natriuretic peptide, or previous HF), and to discontinue an agent if HF develops.⁸⁻¹⁰

Saxagliptin

In SAVOR-TIMI 53, saxagliptin was associated with an increased risk for hospitalization for HF.¹¹ Patients at highest risk had elevated natriuretic peptide concentrations, prior history of HF, or chronic kidney disease with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min. At 24 months, 3.5% of patients in the saxagliptin group were hospitalized for HF compared with 2.8% of those in the placebo group (HR, 1.27; 95% CI, 1.07-1.51; $P = .007$), equivalent to a 27% increase in the rate of hospital admission for HF (number needed to harm [NNH]: 143 over 2 years).

Alogliptin

The EXAMINE trial showed that alogliptin was noninferior to placebo for major adverse cardiac event (MACE) rates (composite primary endpoint of CV death, MI, or stroke) in patients with T2D and recent acute coronary syndromes (11.3% vs 11.8%; HR, 0.96; upper boundary of the 1-sided 95% CI, 1.16).¹² Because of concerns about excessive rates of HF hospitalizations with saxagliptin, the EXAMINE trial data were assessed for hospital admission for HF.¹³ Alogliptin was not associated with increased risk of HF outcomes, such as hospital admission for HF, compared with placebo (3.1% vs 2.9%, respectively; HR, 1.07; 95% CI, 0.79-1.46). However, hospital admissions for HF occurred significantly more often in patients

without prior history of HF treated with alogliptin compared with placebo (HR, 1.76; 95% CI, 1.07-2.90; $P = .026$).¹³

HF Concerns: A DPP-4 Inhibitor Class Effect?

Randomized controlled trial (RCT) data are conflicting regarding the increased risk of HF with DPP-4 inhibitors.¹⁴ Some DPP-4 inhibitors appear to increase risk while others do not; thus, the HF concerns may not be a class effect. The TECOS trial found no association of sitagliptin with HF (relative risk [RR]: 1.00; 95% CI, 0.83-1.19).¹⁵ A recent meta-analysis evaluated 100 RCTs ($N = 79,867$), assessing the association between HF and DPP-4 inhibitors given for 24 weeks or more. Overall, 96% (1192/1244) of HF events were identified, blindly adjudicated, and required hospital admission.¹⁴ Pooled results suggest a 13% increase in HF (RR: 1.13; 95% CI, 1.01-1.26). If only the 3 large CV trials are included (SAVOR-TIMI 53, EXAMINE, and TECOS; $n = 36,543$), a similar but nonsignificant increase is observed (RR: 1.14; 95% CI, 0.97-1.32; NNH 246). SAVOR-TIMI 53 (saxagliptin) demonstrated increased HF.¹⁴ In a smaller placebo-controlled CV study of 9459 patients, 5847 received 5 mg of linagliptin once daily and experienced CV events similar to those receiving placebo ($P > .05$).¹⁶ Both linagliptin and sitagliptin appear safe to use in persons with diabetes and HF.

A mechanism for the association between DPP-4 inhibitors and HF has not been found.¹⁴ CV clinical trials to assess individual DPP-4 effects are underway; however, no large CV-safety trials comparing DPP-4 inhibitors with one another are ongoing. Therefore, results from these trials will address individual but not within-class differences. Long-term studies that include patients with HF (which may uncover higher risks) are needed to evaluate the long-term safety of these lifelong therapies.¹⁴

Two trials assessing CV effects of DPP-4 inhibitor therapy are ongoing in patients with T2D and CV disease or high CV risk. The CAROLINA (NCT01243424) trial will evaluate patients with early-onset T2D and compare linagliptin with glimepiride, each added to metformin.¹⁷ The CARMELINA (NCT01897532) trial will examine CV and renal microvascular outcomes of linagliptin in high-risk individuals with T2D.¹⁸

Recent Updates Regarding CV Benefits of Diabetic Agents

Recently, CV outcomes trials in patients with T2D receiving GLP-1 RAs, liraglutide and semaglutide (currently not FDA approved), and the SGLT-2 inhibitors, empagliflozin and canagliflozin, showed a reduction in CV events. Currently, there are no clear explanations for the unexpected findings of cardioprotection with incretin-based drugs or the SGLT-2 inhibitors, although many hypotheses exist.^{5,19} It is possible that incretin contributes to the positive CV effects by direct cardiac action of GLP-1 metabolites through GLP-1 receptor-independent pathways and of DPP-4 substrates other than GLP-1.⁵

For the SGLT-2 inhibitors, it is possible that nonglycemic effects (such as reductions in weight and blood pressure) or a shift in fuel energetics are responsible for the observed improvements.¹⁹

Five randomized, placebo-controlled trials in patients with T2D with or at risk for CV disease examined the CV safety outcomes of liraglutide, lixisenatide, dulaglutide, empagliflozin, and canagliflozin.^{2-4,20-22} The lixisenatide trial results showed a neutral effect on MACE; all other agents showed a significant reduction in CV events. Most studies showed a neutral effect of the drug on hospitalization for HF; however, empagliflozin showed a significant reduction in hospitalizations for HF.^{2-4,20-22}

GLP-1 Analogue CV Studies

LEADER

The Liraglutide Effect and Action in Diabetes: Evaluation of CV Outcome Results: A Long-Term Evaluation (LEADER) trial is a randomized double-blind trial that assessed the effect of liraglutide 0.6-1.8 mg injected subcutaneously once daily versus placebo (both plus standard care) on CV outcomes in 9340 patients with T2D at high risk for CV disease or with CV disease.³ The mean patient age was 64 years, and the mean duration of T2D was more than 12 years; 81% had established CV disease. Results showed that MACE occurred in 13.0% of patients receiving liraglutide compared with 14.9% of those receiving placebo after an average of 3.8 years of follow-up. CV-related deaths (4.7% vs 6.0%) and all-cause deaths (8.2% vs 9.6%; HR, 0.85; 95% CI, 0.74-0.97; $P = .02$) were also significantly less with liraglutide versus placebo, respectively.²⁰ The NNT to prevent 1 event in 3 years was 66 in the analysis of the primary outcome and 98 in the analysis of death from any cause. A trend toward fewer hospitalizations for HF was observed among patients receiving liraglutide versus placebo, although the difference was not significant. Significant reductions in blood pressure, body weight, and glycated hemoglobin (A1C) were also observed.²⁰

ELIXA

In contrast, the Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA) trial did not show any significant CV benefit of lixisenatide in patients with T2D.²¹ Patients ($N = 6068$) with a history of MI or hospitalization for unstable angina within the previous 180 days were randomized to receive lixisenatide 10-20 mcg daily or placebo (both plus standard care). MACE was observed in 13.4% of patients in the lixisenatide group and in 13.2% of patients in the placebo group (HR, 1.02; 95% CI, 0.89-1.17); these results supported the noninferiority of lixisenatide to placebo ($P < .001$) but not superiority ($P = .81$). The rate of hospitalization for HF and the rate of death were not significantly different with lixisenatide than placebo. Significant but moderate reductions in A1C, weight, and systolic blood pressure were also observed.²¹

CV Benefit: A GLP-1 Receptor Agonist Class Effect?

It is unknown if other GLP-1 RAs (besides lixisenatide) will have the same CV benefits as liraglutide and semaglutide (not currently FDA approved) in patients with or at high risk of CV disease or if GLP-1 RAs will have similar effects in lower-risk patients with T2D.³ A meta-analysis evaluating dulaglutide CV risk in persons ($N = 6010$) with T2D using data from safety and efficacy trials found no increase in CV risk versus placebo (HR, 0.57; adjusted 98.02% CI, 0.30-1.10).²³ Two trials of GLP-1 RA therapy are ongoing in patients with T2D and CV disease or high CV risk. The Researching CV Events with a Weekly Incretin in Diabetes (REWIND trial; NCT01394952) is assessing dulaglutide CV effects.²⁴ Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL; NCT01144338) is evaluating exenatide once weekly.²⁵ Additional data are needed for patients at lower CV risk, who are more likely to receive incretin-based drugs in the real world.⁵ Studies are needed to assess the effects of GLP-1 on non-GLP-1 RAs to determine if these are associated with CV effects. Also, the CV effects of DPP-4 substrates that differ from GLP-1 should be studied to better understand the mechanisms by which these agents exert these unexpected effects.

SGLT-2 Inhibitor CV Studies

EMPA-REG OUTCOME

In the Empagliflozin CV Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME), 7020 patients with T2D and a high risk of CV disease received empagliflozin 10 mg or 25 mg daily or placebo plus standard of care.² The mean age was 63 years, 57% had diabetes for more than 10 years, and 99% had established CV disease. Significantly fewer patients receiving empagliflozin versus placebo experienced MACE (10.5% vs 12.1%), CV-related death (3.7% vs 5.9%), or all-cause death (5.7% vs 8.3%) after a median follow-up of 3.1 years. Among patients with eGFR greater than 30 mL/minute/1.73 m², adverse renal outcomes, such as incident or worsening nephropathy, serum creatinine doubling, or initiation of renal replacement therapy, occurred less frequently with empagliflozin.²⁶ Empagliflozin was associated with lower A1C, systolic blood pressure, and weight than placebo. Benefits of empagliflozin realized were similar, regardless of the 10 mg or 25 mg daily dosage used. Empagliflozin is now indicated to reduce the risk of CV death in adults with T2D and CV disease.²⁷ Nonglycemic effects of empagliflozin have been proposed. These include changes in arterial stiffness, cardiac function, cardiac oxygen demand (in the absence of sympathetic-nerve activation), and cardiorenal effects, as well as reductions in albuminuria, uric acid, weight, visceral adiposity, and blood pressure.²

CANVAS and CANVAS-R

The Canagliflozin CV Assessment Study (CANVAS) trial recruited 4330 patients with inadequately controlled T2D and increased CV risk and

randomized them to receive canagliflozin 100 mg, canagliflozin 300 mg, or placebo for an average of 2 years.^{4,22} CANVAS–Renal (CANVAS-R; N = 5812) was a sister trial to CANVAS and assessed canagliflozin's effects on albuminuria; the 2 trials' data were combined (N = 10,142).⁴ Mean baseline age was 63.3 years, the duration of diabetes was 13.5 years, and 65.6% had a preexisting history of CV disease. The primary outcome was a composite of death from CV causes, nonfatal MI, or nonfatal stroke, which was lower with canagliflozin versus placebo (occurring in 26.9 vs 31.5 participants per 1000 patient-years; HR, 0.86; 95% CI, 0.75–0.97; $P = .02$ for superiority). However, canagliflozin was also associated with a significant risk of toe or metatarsal amputations (6.3 vs 3.4 participants per 1000 patient-years; HR, 1.97; 95% CI, 1.41–2.75). The original protocol stated that if the potential for CV protection is confirmed and initial safety criteria are met, a second phase would be conducted to recruit and follow an additional 14,000 individuals to further assess CV effects. However, the planned second phase will not be undertaken.²²

CV Benefit: An SGLT-2 Inhibitor Class Effect?

Based on the CV benefit outcomes from empagliflozin and canagliflozin, there is a trend to believe that the CV benefits may be a class effect. It is unknown, however, if other SGLT-2 inhibitors will have the same effect in patients at high risk for CV disease or if empagliflozin, canagliflozin or other SGLT-2 inhibitors will have a similar effect in lower-risk patients with T2D.¹ The long-term safety and real-world impact of these agents on T2D with HF are unclear; additional studies are needed.

The Future: Ongoing Studies

DECLARE-TIMI 58 (NCT01730534) is evaluating the CV effects of dapagliflozin in patients with T2D and high risk of CV complications.²⁸ Ertugliflozin (not FDA approved) has an ongoing trial, VERTIS CV, to assess CV effects, with expected completion in 2019.²⁹ The CREDENCE trial (NCT02065791), evaluating the effects of canagliflozin on renal and CV outcomes in individuals with diabetic nephropathy, also has an expected completion date of 2019.³⁰

Additional Advances in Diabetes Management: Novel Combination Medications

Rationale for GLP-1 Receptor Analogues and Insulin Combinations

T2D is a progressive disease without a cure and is usually managed with combination therapy. Treatment intensification with insulin increases the risk of weight gain and hypoglycemia.³¹ Basal insulins are effective for controlling fasting blood glucose; however, these insulins are minimally effective for the control of postprandial blood glucose excursions. Considering the CV benefits of GLP-1 RAs, their subcutaneous administration, and additive efficacy when given in combination with insulin, it is reasonable that GLP-1 RAs would be

provided as elements in combination products. These combination products have the potential to minimize the number of injections and increase administration convenience. GLP-1 analogues stimulate glucose-dependent insulin secretion, suppress glucagon secretion, delay gastric emptying, and decrease appetite. In T2D management, insulin analogues replace depleted endogenous insulin or provide effective insulin when insulin resistance exists. Thus, combined GLP-1 analogue and insulin therapies have complementary mechanisms of action, and GLP-1 analogues coupled with basal insulin are an alternative means to intensify T2D management. Benefits include neutral weight or weight loss, less hypoglycemia, better glucose control, fewer gastrointestinal AEs, convenience, and, possibly, improved medication adherence.³² However, this combination is not without risks, such as unknown long-term tolerability, safety, and cost-effectiveness of a lifelong therapy.³¹ In addition, fixed dosing schedules and the need to titrate insulin over time need to be considered.

Identifying responders and nonresponders will be a clinical practice issue. Currently, no data have been published that help determine responders. A retrospective database analysis found that exenatide and liraglutide adherence rates were less than 60%.³³ Therefore, before stopping therapy because of lack of efficacy, medication adherence should be assessed with the patient.³¹ Currently, insulin degludec/liraglutide and insulin glargine/lixisenatide are FDA approved and available as combination products. Clinical trials with GLP-1 analogues and insulin combination products demonstrate greater A1C reductions, neutral or decreased body weight, and lower rates of hypoglycemia than the individual products.^{34–36}

DUAL II and V

In the DUAL II trial, adults with T2D inadequately controlled on a GLP-1 RA (at maximum dose) and oral antidiabetic drugs (OADs) were randomized to receive degludec 50 U/liraglutide 1.8 mg once daily (n = 292) or unchanged GLP-1 RA therapy (n = 146) and continued OADs at the pretrial doses.³⁴ The reduction in A1C concentration was significantly greater with degludec/liraglutide compared with unchanged GLP-1 RA therapy (A1C change over 26 weeks from 7.8% to 6.4% with degludec/liraglutide and from 7.7% to 7.4% with unchanged GLP-1 RA therapy; $P < .001$). Patients treated with degludec/liraglutide gained weight (+2.0 kg) versus weight loss (–0.8 kg) and experienced more hypoglycemia than unchanged GLP-1 RA therapy.³⁴

In the DUAL V study, patients with uncontrolled T2D were treated with glargine 20–50 U (n = 279) versus degludec 50 U/liraglutide 1.8 mg (n = 278), both plus metformin for 26 weeks.³⁵ The mean age was 58.8 years and duration of diabetes was 11 years. A1C reduction was significantly greater with degludec/liraglutide compared with glargine (–1.81% vs –1.13%, respectively) meeting criteria for noninferiority and superiority (both $P < .001$). Treatment with degludec/liraglutide was also associated with weight loss, compared with weight gain with

glargine (−1.4 kg vs +1.8 kg, respectively; $P < .001$). Fewer confirmed hypoglycemic episodes were reported with degludec/liraglutide. Additional studies are needed to assess longer term efficacy and safety.³⁵

LixiLan

The LixiLan study compared insulin glargine (Lantus) 2 units/lixisenatide 1 mcg ($n = 161$) with glargine ($n = 162$) in insulin-naïve patients with T2D taking metformin.³⁶ The mean age was 57 years and diabetes duration was 6 to 7 years. A1C significantly decreased from 8.0% to 6.3% with glargine/lixisenatide and to 6.5% with glargine, which established statistical noninferiority and superiority of the combination product. A1C goal of <7.0% was achieved in 84% and 78% of patients, respectively; however, this was not statistically significant. Body weight decreased with the combination (−1 kg) and increased with glargine (+0.5 kg; $P < .0001$), with no difference in hypoglycemic events observed.³⁶ Additional studies are needed in different populations.

Two phase 3 trials were completed in 2015. LixiLan-O (NCT02058147) compared insulin glargine/lixisenatide with lixisenatide alone and with glargine alone (plus metformin in all groups), and LixiLan-L (NCT02058160) compared glargine/lixisenatide with glargine (with or without metformin in both groups) in patients with uncontrolled blood glucose on at least 6 months of basal insulin.³⁶

Both the DUAL and LixiLan trials demonstrated that a GLP-1 RA combined with basal insulin decreases postprandial glucose levels, lowers A1C concentrations, decreases weight, lowers basal insulin requirements, and does not increase hypoglycemic events.³¹ Future studies are needed to assess the long-term safety, efficacy, and cost-effectiveness of GLP-1 RA/basal insulin combination products.³¹

Rationale for SGLT-2 and DPP-4 Combinations

DPP-4 inhibitors increase postprandial concentrations of GLP-1 and GIP. These increases, in turn, boost glucose-dependent insulin secretion and mildly suppress glucagon secretion, slow gastric emptying, and increase satiety.^{1,37} SGLT-2 inhibitors reduce (mostly basal) glucose concentrations, independent of insulin action, by increasing renal excretion of glucose. These mechanisms of action are complementary. SGLT-2 inhibitors improve insulin sensitivity and beta-cell function but also can increase endogenous glucose production, possibly due to an increase in plasma glucagon.^{1,16} DPP-4 inhibitors reduce plasma glucagon concentrations (although not substantially). Therefore, the combination of a DPP-4 inhibitor and an SGLT-2 inhibitor may neutralize these glucogenic effects. Both drug classes have a low risk of hypoglycemia and are either weight-neutral or associated with weight loss.^{1,37}

Saxagliptin/Dapagliflozin Combination Trials

After a 4-week lead-in, a 24-week double-blind trial evaluated saxagliptin 5 mg plus dapagliflozin 10 mg ($n = 179$) versus saxagliptin

alone ($n = 176$) and dapagliflozin alone ($n = 179$), with both the combination and individual drugs added to metformin in patients with T2D poorly controlled with metformin.¹⁶ The mean baseline A1C was 8.9% and the duration of diabetes was 7.6 years. A1C change from baseline was −1.5% with saxagliptin/dapagliflozin compared with −0.9% with saxagliptin alone (difference 20.59%; $P < .0001$) and −1.2% with dapagliflozin alone (difference 20.27%; $P < .02$). More patients achieved goal A1C of <7% with saxagliptin/dapagliflozin (41%) compared with saxagliptin (18%) or dapagliflozin (22%).¹⁶

Empagliflozin/Linagliptin Combination Trials

Patients with T2D and inadequate glycemic control while on metformin received open-label empagliflozin 10 mg or 25 mg (evaluated in 2 separate studies) as add-on therapy for 16 weeks.³⁸ These patients ($N = 482$) were then randomized to a double-blind trial. Patients received add-on linagliptin 5 mg or placebo for 24 weeks. A1C significantly decreased from baseline with linagliptin compared with placebo (for empagliflozin 10 mg: −0.32%; $P = .001$; and for empagliflozin 25 mg: −0.47%; $P < .001$). This combination product is under FDA review.³⁸

The Future: Ongoing Long-Term Outcomes Trials

In addition to the trials already discussed, multiple clinical trials, underway or recently completed, are evaluating the addition of newer classes of glucose-lowering agents to standard of care and are assessing macrovascular outcomes, microvascular outcomes, or both.

TZDs and Sulfonylureas

The Thiazolidinediones or Sulfonylureas and CV Accidents Intervention Trial (TOSCA.IT) is a 4-year trial evaluating add-on pioglitazone versus add-on sulfonylurea in patients with T2D and high CV risk inadequately controlled with metformin.³⁹ The final analysis is expected in 2018 and will analyze CV and microvascular endpoints.

Comparative Effectiveness

Selecting the appropriate combination from an armamentarium of glucose-lowering drugs can be challenging without comparative effectiveness trials. Although T2D algorithms recommend various treatment combinations, few studies have directly compared these combinations. The Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE) study is an ongoing comprehensive examination of 4 classes of glucose-lowering drugs (sulfonylureas, DPP-4 inhibitors, GLP-1 RAs, and insulin) in addition to metformin.⁴⁰ GRADE ($N = 5000$) will compare the long-term glycemic control, CV risk, and microvascular complications in persons recently diagnosed with T2D. In addition, phenotypic differences that contribute to the efficacy and safety of each combination will be evaluated. The results of this study will help guide selection of individualized combination therapy regimens.⁴⁰

Conclusion

CV effects of diabetes medications can have substantial negative or beneficial effects in patients with T2D. Of the FDA-approved agents, liraglutide (a GLP-1 RA) and empagliflozin (an SGLT-2 inhibitor) appear to have the most favorable CV profile and have been shown to be cardioprotective in clinical trials. Studies are ongoing to evaluate the CV effects of recently approved and investigational diabetes medications. Novel combination products can be more effective than the individual components when added to standard of care in patients with T2D not responding to standard of care. Future studies will evaluate the long-term effects of these combinations in patients with T2D. ■

Author affiliation: Dr Morello is a professor of clinical pharmacy and associate dean for student affairs at the Skaggs School of Pharmacy and Pharmaceutical Sciences at University of California, La Jolla, CA, and a clinical pharmacist specialist at the Veterans Affairs San Diego Healthcare System in San Diego, CA.

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Address correspondence to: candismorello@ucsd.edu.

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