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Diabetes and Cardiovascular Disease: The Potential Benefit of Incretin-Based Therapies

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Abstract

The health burden of type 2 diabetes mellitus continues to increase worldwide. A substantial portion of this burden is due to the development of cardiovascular disease in patients with diabetes. Recent failures of clinical trials of intensive glucose control to reduce macrovascular events, coupled with reports of potential harm of certain diabetic therapy, have led to increased scrutiny as new diabetic therapies are developed. Incretin peptides are a group of gastrointestinal proteins that regulate glucose metabolism through multiple mechanisms, and incretin-based therapies have been developed to treat type 2 diabetes. These agents include glucagon-like peptide-1 (GLP-1) and dipeptidyl peptidase-IV (DPP-IV) inhibitors. In addition to effects on glucose homeostasis, growing evidence suggest that these peptides may also affect the cardiovascular system. In this review, we discuss recent findings concerning the potential, yet untested, benefits of incretin-based pharmacotherapy in the treatment of cardiovascular disease.

Keywords

Diabetes; Glucagon-like peptide 1; DPP-IV; Incretin hormones; Cardiovascular disease

Introduction

The prevalence of type 2 diabetes mellitus continues to increase. It is estimated that approximately 7.8% of the US population, or nearly 24 million people, have diabetes [1]. Additionally, it is projected that approximately one of three individuals born in the United States in the year 2000 will develop diabetes during their lifetime [2]. Importantly, these increased rates of diabetes are not unique to the United States, but are similar across the globe. The total number of people with diabetes worldwide is projected to increase from 171 million in 2000 to 366 million in 2030 [3].

The increased prevalence of diabetes has tremendous health and financial consequences given the impact of diabetes on mortality and morbidity [1]. The age-adjusted risk of death

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among people with diabetes is approximately twice that of people without diabetes, and life expectancy is reduced 5 to 10 years among middle-aged persons with diabetes. Given the substantial health burden, the tremendous economic cost of treating diabetes is not surprising, with total (direct and indirect) annual estimated costs in the United States of approximately $174 billion. One important factor contributing the increased morbidity and mortality in diabetic individuals is the development of cardiovascular disease (CVD). In this review, we address the dangerous intersection of diabetes and CVD and discuss the potential role of incretin-based therapies in the prevention and treatment of CVD in patients with type 2 diabetes.

Diabetes and Cardiovascular Disease: Implications of Recent Clinical Trials

Multiple epidemiologic studies have established diabetes as a major risk factor for the development of all manifestations of CVD, including myocardial infarction, stroke, peripheral vascular disease, and heart failure [4–6,7•], and recent data suggest that the proportion of CVD attributable to diabetes is increasing [5]. It is estimated that CVD accounts for 65% of all deaths in persons with diabetes [1]. In a recent meta-analysis of nearly 700,000 people from 102 prospective studies, diabetes conferred an approximate twofold risk for coronary heart disease and stroke, independently from other conventional risk factors [7•]. Thus, in order to reduce the health burden of diabetes, it is necessary to aggressively prevent and treat CVD.

The etiology for the accelerated atherosclerosis and cardiovascular diseases seen in patients with diabetes is likely multifactorial [8,9]. A number of potential mechanisms have been implicated in this process, including the direct and indirect effects of hyperglycemia and advanced glycation end-products (AGEs), impaired endothelial function, increased subclinical inflammation, and abnormalities of thrombosis and fibrinolysis. Additional mechanisms include the development of atherogenic dyslipidemia, changes in adipokines, and increased levels of free fatty acids. In addition to these mechanisms, individuals with diabetes often have a clustering of additional cardiovascular risk factors closely linked to insulin resistance, including hypertension and central obesity. Efforts to lower cardiovascular risk in patients have included strategies that address several of these pathophysiologic abnormalities [4]. These strategies include lifestyle interventions to prevent obesity and physical inactivity, adequate blood pressure control, treatment of atherogenic dyslipidemia, and appropriate treatment with antiplatelet therapy [4].

The importance of glycemic control and the role of anti-glycemic therapy in reducing adverse outcomes in diabetic patients are areas of intense interest. Multiple epidemiologic studies have demonstrated an association between worse glycemic control and an increased risk of both microvascular and macrovascular adverse outcomes [7•,10]. These observational data linking worse glycemic control to higher rates cardiovascular events in diabetic patients led to several recent studies (Action to Control Cardiovascular Risk in Diabetes [ACCORD], Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Veterans Affairs Diabetes Trial [VADT]) designed to assess the strategy of intensive glucose control to normal or near normal levels in order to improve cardiovascular outcomes [11–12,13••]. Although these randomized controlled studies demonstrated reductions in microvascular complications, these studies did not demonstrate improvements in total mortality or cardiovascular mortality in individuals randomized to strategies of more intensive glucose control. Contrary, in the ACCORD trial, there was an unexpected increase in mortality in patients assigned to the intensive-treatment arm when compared to patients receiving standard care [13••]. A recent meta-analysis of randomized trials that compared clinical outcomes in patients with type 2 diabetes receiving intensive glucose control to those receiving conventional glucose control demonstrated that

intensive glucose control reduced the risk for non-fatal myocardial infarction but did not reduce the risk for cardiovascular death or all-cause mortality [14]. Reassuringly, this meta-analysis did not demonstrate the increased the mortality seen in patients randomized to intensive glucose control in the ACCORD trial.

Although several mechanisms may have contributed to the negative findings of these clinical trials, one important possibility is that the adverse consequences of hypoglycemia and limitations of current anti-diabetic therapy may have offset any potential benefit of more intensive glycemic control. In the ACCORD trial, risks of severe hypoglycemia were three times higher in those individuals randomized to intensive glucose control [13••]. Similarly, in addition to the risk of hypoglycemia, weight gain associated with insulin, sulfonylureas, and thiazolidinediones (TZDs) may offset any potential benefit. Additionally, TZDs have been associated with increased volume retention and increased risk of heart failure hospitalizations [15]. Finally, the TZD rosiglitazone has been linked to increased risk of myocardial infarction [16].

These recent failures of intensive glycemic control to reduce macrovascular events and the realization of potential harm with current diabetic therapy, such as rosiglitazone, has led to a paradigm shift to move “beyond glycemic control” as new anti-diabetic therapies are developed. This paradigm shift was highlighted in recent recommendations to industry by the US Food and Drug Administration (FDA) that new anti-diabetic therapies to treat type 2 diabetes should not result in an unacceptable increase in cardiovascular risk [17]. Incretin-based therapies represent a developing class of diabetic therapy that are currently being used and will be tested in the current environment of heightened cardiovascular safety and efficacy. There are several advantages to this class of medication that hold potential, yet untested, promise in the prevention of CVD.

Incretin-Based Therapies

Incretin System

Incretin peptides are a group of gastrointestinal proteins secreted in response to food ingestion that stimulate insulin production from the beta-cells of the pancreas [18•,19•]. The “incretin effect” refers to the observation that glucose triggers a much greater insulin secretory response when ingested orally than when administered intravenously [20]. This effect may account for up to 50% to 70% of the total insulin secreted after glucose ingestion. In humans, two molecules serve as the main incretin peptides: glucose-dependant insulinotropic polypeptide (GIP, formerly called gastric inhibitory polypeptide) and glucagon-like peptide-1 (GLP-1).

GIP is a 42-amino acid peptide secreted by intestinal K-cells, mostly in the proximal small intestine, in response to ingestion of oral intake of carbohydrates and lipids [18•,19•]. GIP augments glucose-stimulated insulin release via G-protein coupled receptors located mostly on pancreatic β-cells [21]. GIP is rapidly degraded (plasma half-life of 5–7 min) by the enzyme dipeptidyl-peptidase IV (DPP-IV) [18•]. The ubiquitous enzyme DPP-IV can be found in multiple tissues, including endothelial cells, lymphocytes, central nervous system, kidney, lung, and pancreas. DPP-IV has many substrates, including neuropeptides, cytokines, and other GI peptides [18•,19•]. Despite its relatively short half-life, GIP contributes substantially to the incretin effect seen in healthy adults. In patients with type 2 diabetes, GIP is normally secreted, but the insulinotropic effects of GIP are greatly reduced, limiting its potential in the treatment of diabetes [22].

GLP-1 is a derivative of the transcription product of the proglucagon gene [18•,19•]. It is secreted in large measure from the L-cells of the distal jejunum, ileum, and colon in two

main biologically active forms, GLP-1 (7–36) amide (the major form in humans) and glycine-extended GLP-1 (7–37). GLP-1 is released within minutes of food ingestion, suggesting that this rapid release is more indirectly controlled by both neural and endocrine signaling, rather than direct stimulation of the L-cells in the gastrointestinal tract. Similar to GIP, GLP-1 is rapidly inactivated by DPP-IV; the half-life of circulating GLP-1 is 1 to 2 min. The actions of GLP-1 are felt to be predominantly mediated through GLP-1 receptors, which are expressed in the endocrine pancreas (alpha and beta-cells), gastrointestinal tract, stomach, heart, hypothalamus, kidneys, and lung. Binding of GLP-1 to the receptor leads to activation of adenyl cyclase, and leads to an increase of intracellular cyclic AMP levels [18•]. Other signaling pathways (MAP kinase, phospho-inositol-phospate [PIP3], and protein kinase [PKB]) may also be activated [21].

GLP-1 modulates various processes involved in glucose homeostasis [18•,20]. Through actions on pancreatic β-cells, GLP-1 stimulates insulin secretion in a glucose-dependent fashion, thus mitigating the potential risk of hypoglycemia. In addition to effects on insulin secretion, GLP-1 promotes glucose-stimulated insulin gene transcription and biosynthesis. Other GLP-1-mediated effects include inhibition of glucagon secretion and inhibition of gastrointestinal secretion and mobility, particularly inhibition of gastric emptying. GLP-1 has also been shown to reduce appetite and food intake and has been associated with weight loss. Finally, GLP-1 may have trophic effects on pancreatic beta-cells [23], with concurrent reduction of cellular apoptosis [24]. In patients with type 2 diabetes, the postprandial secretion of GLP-1 appears to be diminished [25], but, importantly, the effects of exogenous GLP-1 on insulin secretion, glucagon suppression, and delayed gastric emptying remain preserved.

Given these effects on glucose homeostasis, GLP-1-based therapies have been developed as potential treatment for patients with type 2 diabetes. As described above, the short half-life of native GLP-1 due to rapid degradation by DPP-IV has limited its use in the chronic treatment of type 2 diabetes, as the native peptide must be given by continuous intravenous or subcutaneous infusion. In order to overcome this limitation, inhibitors of the DPP-IV enzyme and GLP-1 receptor agonists resistant to DPP-IV have been developed.

Examples of DPP-IV inhibitors that are commercially available include sitagliptin, saxagliptin, and vildagliptin (Table 1). These agents typically result in a twofold increase in endogenous GLP-1 levels and have been associated with a 0.7% to 1% reduction in glycosylated hemoglobin (HbA1C). These agents are administered orally, are weight neutral, and generally are well tolerated.

Commercially available GLP-1 receptor agonists include exenatide and liraglutide. GLP-receptor agonists have been associated with a 0.8% to 1.1% reduction in HbA1C [26]. In contrast to the DPP-IV inhibitors, these agents may be administered at higher pharmacologic levels and lead to greater receptor activation. In addition, these agents have been associated with modest weight loss (approximately 3 kg over 6 months) [26].

Potential Cardiovascular Benefits of Incretin-Based Therapy: Beyond Glucose Control

Incretin based therapies have several attributes that may make this class of medication beneficial in the prevention and treatment of CVD when compared to other pharmacologic diabetic treatment. As opposed sulfonylureas, TZDs, and insulin, which are all associated with weight gain, DPP-IV inhibitors and GLP-1 receptor agonists are either weight-neutral or promote weight loss, respectively. In addition, incretin-based therapies have not been linked to fluid retention and/or worsening heart failure, a problem that has been reported with TZDs [15]. In addition, a growing body of literature has demonstrated a more direct

association between incretin-based therapies and modulation of both cardiovascular risk factors and cardiovascular disease states.

Dyslipidemia—Clinical studies of GLP-1 receptor agonists [26] and DPP-IV inhibitors [27] have demonstrated modest improvements in lipid panels. These improvements have included modest reduction in levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and apolipoprotein B. It is important to note, that these reductions have been modest, and not all studies have demonstrated a significant benefit [28]. Part of the association between improvements in lipid parameters and incretin-based therapy may be related to potential incretin-associated weight loss [29].

Hypertension—GLP-1 agonists have been implicated in the reduction of systolic blood pressure [30,31•]. In a meta-analysis of six trials, exenatide was associated with a reduction of 2 to 4 mmHg in systolic blood pressure (SBP) when compared to placebo or insulin therapy [31•]. In this meta-analysis, the reduction in SBP was greatest in those with high baseline blood pressure and was not significant in patients with normal blood pressure at baseline. Similarly, liraglutide has been associated with an SBP reduction of 2 to 3 mmHg when compared to glimepiride [30]. Although weight loss may contribute to these reductions in SBP, the meta-analysis of exenatide trials demonstrated only a weak correlation between SBP reduction and weight loss [31•]. Similarly, the reductions in SBP seem to occur prior to the onset of significant weight loss [30]. Other potential explanations for a reduction in SBP include increased excretion of sodium [32] or improved endothelial function [33].

Endothelial Function—Vascular endothelial dysfunction is strongly associated with diabetes and insulin resistance and represents an early manifestation of atherosclerosis. Several studies have demonstrated potential benefits of incretin-based therapies on endothelial function. GLP-1 has been shown to improve endothelial-dependent vasodilation in a small study of patients with type 2 diabetes [33]. In addition to vascular reactivity, GLP-1 has been associated with a reduction in inflammatory markers and adhesion molecules that may adversely affect endothelial function. For example, treatment with the GLP-1 receptor agonist exendin-4 reduced monocyte/macrophage accumulation in the arterial wall of mice by inhibiting the inflammatory response in macrophages [34]. Exendin-4 appears to regulate this inflammatory response via the cAMP/PKA pathway, which subsequently inhibits pro-inflammatory cytokines such as tumor necrosis factor-α and monocyte chemoattractant protein-1 [34]. Liraglutide has also been shown to inhibit tumor necrosis factor-α or hyperglycemia-mediated induction of plasminogen-activator inhibitor type-1, intercellular adhesion molecule-1, vascular cell adhesion molecule-1, mRNA, and protein expression in human vascular endothelial cell lines [35].

Preliminary data also suggest potential benefits of DPP-IV inhibitors on endothelial function. DPP-IV inhibition by vildagliptin has been shown to reduce endothelial senescence in a diabetic rat model through the activation of protein kinase A and induction of antioxidant genes [36]. Additionally, a non-randomized study of 32 patients with type 2 diabetes demonstrated that inhibition of DPP-IV by sitagliptin for 4 weeks was associated with increased circulating endothelial progenitor cells (EPCs), a finding felt to be related to up-regulation of stromal-derived factor-1α by DPP-IV inhibition [37]. Given the potential protective vascular effects of EPCs and reduced EPCs in patients with diabetes [38], such effects may translate to favorable outcomes.

Coronary Artery Disease/Myocardial Infarction—As described above, GLP-1 may affect the development of atherosclerosis by improving many of the cardiovascular risk factors associated with the development of coronary artery disease (CAD). In addition,

GLP-1-based therapies may have beneficial effects in the setting of ischemia and myocardial infarction. GLP-1 has been shown to be cardioprotective in a rat model of myocardial ischemia and reperfusion/injury through multiple prosurvival kinases [39].

Similarly, both exenatide [40] and liraglutide [41•] have been shown to reduce infarct size in porcine models and mice models of acute myocardial infarction, respectively. In addition to reduced infarct size, treatment with exenatide prior to coronary artery ligation and subsequent reperfusion prevented the deterioration of systolic and diastolic cardiac function and was associated with reduced markers of nuclear oxidative stress and increased expression of the pro-survival kinase phosphorylated Akt [40]. In the study of liraglutide, 7-day pre-treatment with liraglutide modulated the expression and activity of cardioprotective genes and led to improvement in cardiomyocyte survival [41•]. Interestingly, in this study, liraglutide conferred cardioprotection and survival advantages over metformin, despite equivalent glycemic control [41•].

The effects of incretin-based therapies in humans with established CAD have been limited. In a non-randomized study of 10 patients with acute myocardial infarction and severe left ventricular (LV) systolic dysfunction (LV ejection fraction <40%), a 72-hour continuous infusion of GLP-1 (1.5 pmol/kg per minute) started shortly after successful percutaneous coronary intervention was associated with significant improvements in LV ejection fraction (from 29% to 39%) and both global and regional wall motion when compared to 11 control patients [42]. Similarly, in another randomized, double-blind, placebo-controlled study of 20 patients with coronary heart disease and preserved LV function who were scheduled to undergo coronary artery bypass grafting (CABG), continuous infusion of GLP-1 (1.5 pmol/kg/min) beginning 12 h before CABG and continued for 48-hours after surgery was associated with less need for inotropic support and better glycemic control than patients receiving insulin alone [43]. Finally, a more recent human study also suggested potential benefit with the DPP-IV inhibitor sitagliptin [44]. In a pilot study of 14 patients with CAD and preserved LV function who were awaiting revascularization, sitagliptin improved global and regional LV performance in response to dobutamine stress testing and mitigated post-ischemic stunning when compared with placebo.

Heart Failure—GLP-1-based therapies have shown potential promise in animal models of heart failure and limited human studies. GLP-1 receptors are present in the heart, and a potential physiologic function to this receptor was demonstrated in a mouse model where genetic disruption of the GLP-1 receptor was associated with phenotype characteristics of diastolic heart failure, including increased LV wall thickness, smaller LV chamber dimensions, and increased LV end-diastolic pressure [45]. Forty-eight hour continuous GLP-1 infusion has also been associated with improvements in myocardial glucose uptake and improvements in LV and systemic hemodynamics in conscious dogs with dilated cardiomyopathy due to rapid pacing [46]. Of note, in this study of canine dilated cardiomyopathy, beneficial cardiac and hemodynamic effects were seen with both GLP-1 (7–36) amide and, the metabolite GLP-1 (9–36) (generated by the breakdown of GLP-1 (7–36) by DPP-IV) [46]. A subsequent study, in a similar canine heart failure model, demonstrated that 48-hour infusion of GLP-1 (7–36) stimulated myocardial glucose uptake through a p38α MAP kinase-mediated and nitric oxide-dependent mechanism and that the increased myocardial uptake was not dependent on adenyl cyclase or Akt [47]. Finally, when administered continuously over a 3-month period in spontaneously hypertensive, heart-failure-prone rats, GLP-1 (7–36) was associated with improved survival and associated preserved LV function, increased myocardial glucose uptake, and reduced myocyte apoptosis [48•].

Limited human studies of GLP-1-based therapies have also shown potential promise in heart failure patients. As described above, a 72-hour continuous infusion of GLP-1 in survivors of acute myocardial infarction complicated by severe LV dysfunction was associated with significant improvements in LV ejection fraction [42]. Similarly, in a non-randomized study of 12 patients with New York Heart Association (NYHA) class III/IV HF, a continuous infusion of GLP-1 (2.5 pmol/kg/min) for 12 weeks improved LV ejection fraction (21% to 27%), VO_2 max, and 6-minute walk compared to nine HF patients on standard therapy [49]. Conclusions from these studies in HF populations have been limited due to the small sample sizes and largely non-randomized nature of the studies.

Unresolved Questions and Future Directions

Despite the growing body of literature regarding the potential benefits of incretin-based therapy in the prevention and treatment of CVD, several limitations exist and deserve future studies. Most importantly, large, randomized, blinded clinical trials assessing the impact of incretin-based therapies in the prevention and treatment of CVD have not been performed. To date, human studies examining cardiovascular effects have been small, mostly open-label, and have focused on surrogate endpoints. Recent lessons from studies of glycemic control [13], diabetic therapy [16], and other surrogate markers demonstrate the need for large clinical trials to asses both safety and efficacy of diabetic treatment and define the benefit to risk ratio. Fortunately, several of these trials with incretin-based therapies are ongoing or being planned (Table 2).

In addition, mechanistic studies need to be completed to compare potential differences between the different available therapies (native GLP-1, GLP-1 analogues, and DPP-IV inhibitors). For example, some of the cardioprotective and vasodilatory actions of GLP-1 appear to be mediated by both GLP-1 (7–36) and the metabolite GLP-1 (9–36), which is formed when GLP-1 (7–36) is degraded by DPP-IV [50•]. The implications of these findings on the potential effects of GLP-1 receptor analogues and DPP-IV inhibitors require future studies. Finally, given the ubiquitous nature of DPP-IV, large studies of DPP-IV inhibitors need to be performed to ensure that there are no adverse off-target effects; to date, the safety profile appears acceptable.

Conclusions

The prevalence of type 2 diabetes continues to increase, seemingly unabated. The incretin-based therapies have several potential advantages when compared to other diabetic pharmacotherapy, including lower risks of hypoglycemia and less weight gain. In addition to beneficial effects on glucose homeostasis, a growing body of literature suggests potential benefits of this class of medication in the prevention and treatment of cardiovascular disease, the major contributor to increased morbidity and mortality in patients with diabetes. As we strive to lower the burden of cardiovascular disease in this population, future studies are necessary to assess cardiovascular safety and efficacy of these agents in patients with type 2 diabetes.

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Table 1

Examples of incretin-based therapies

Drug	Manufacturer	Availability
DPP-IV inhibitors		
Linagliptin	Boehringer Ingelheim	Currently in phase III
Dutogliptin	Phenomix Corporation	Currently in phase III
Alogliptin	Takeda Pharmaceuticals Company	Currently in phase III
Sitagliptin	Merck & Co.	Available in US, Europe, and Japan
Saxagliptin	Bristol-Myers Squibb	Available in US, Europe, and Japan
Vildagliptin	Novartis	Available in Europe and Australia
GLP-1 receptor agonists		
Albiglutide	GlaxoSmithKline	Currently in phase III
Taspoglutide	Ipsen and Roche	Currently in phase III
Lixasenatide	Sanofi-Aventis	Currently in phase III
Exenatide	Amylin Pharmaceuticals and Eli Lilly and Company	Available in US, Europe, and Japan
Liraglutide	Novo Nordisk	Available in US, Europe, and Japan

DPP-IV dipeptidyl-peptidase-IV; *GLP-1* glucagon-like peptide 1

Table 2

Selected ongoing large-scale, prospective clinical trials

Drug	Study	Estimated enrollment
DPP-IV inhibitors		
Alogliptin	Cardiovascular Outcomes Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE): a randomized, double-blind, placebo-control trial to evaluate time to composite CV event following the addition of alogliptin to standard therapy in subjects with T2DM and ACS	5400
Sitagliptin	Sitagliptin Cardiovascular Outcome Study (TECOS): a randomized, placebo-control trial to evaluate the incidence of CV events when sitagliptin is added to standard therapy in patients with T2DM (HbA1Cs 6.5– 8.0%) and CV disease	14,000
Saxagliptin	Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Medications to Other Diabetes Medications (SAVOR-TIMI 53): a randomized, placebo-controlled, phase IV trial to evaluate the incidence of CV events (as well as safety) when saxagliptin is added to standard therapy in patients with T2DM and CV disease	12,000
Saxagliptin	Comparison of Risk of Major Cardiovascular Events Between Patients With Type 2 Diabetes Exposed to Saxagliptin and those Exposed to Other Oral Antidiabetic Treatments: an observational, cohort study to evaluate compare the incidence of major CV events among patients with T2DM who are new users of saxagliptin and those who are new users of other anti-diabetic drugs	180,000
Vildagliptin	Effect of Vildagliptin on Left Ventricular Function in Patients With Type 2 Diabetes and Congestive Heart Failure: a randomized, placebo-control trial to evaluate the effect (as well as safety and efficacy) of vildagliptin on LV function in patients with T2DM and CHF (NYHA class I–III) by showing that vildagliptin is at least not inferior to placebo with respect to change in LVEF	490
GLP-1 receptor agonists		
Taspoglutide	A Study of Taspoglutide in Patient with Inadequately Controlled Diabetes Mellitus Type 2 and Cardiovascular Disease: a randomized, placebo-controlled trial to assess the time to CV event following the start of taspoglutide and standard therapy (CV and Glycemic) to subjects with uncontrolled T2DM and established CV disease	2000
Exenatide	Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): a randomized, placebo-controlled trial to evaluate time to first confirmed CV event	9500
Liraglutide	Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER): a randomized, placebo-controlled trial to assess time to CV event following the addition of liraglutide to standard therapy in subjects with T2DM and CV disease or chronic kidney disease or specific CV risk factors.	8754
Lixasenatide	Evaluation of CV outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment with AVE0010 (Lixasenatide) (ELIXA)	6000

ACS acute coronary syndrome; *CHF* congestive heart failure; *CV* cardiovascular; *LVEF* left ventricular ejection fraction; *NYHA* New York Heart Association; *T2DM* type 2 diabetes mellitus