Published in final edited form as:

Curr Hypertens Rep. 2014 August ; 16(8): 455. doi:10.1007/s11906-014-0455-7.

Blood Pressure and Cardiovascular Effects of New and Emerging Antidiabetic Agents

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Abstract

Despite remarkable declines in US cardiovascular disease morbidity and mortality over the last several decades, the prevalence of risk factors such as type 2 diabetes and hypertension remains high, associated with increasing obesity rates. Although optimal glycemic control remains a primary focus to decrease the disease burden, the FDA has issued guidance recommendations for documenting cardiovascular disease-related safety with research trials on new antidiabetic agents with more demanding requirements compared to past approval of existing therapies. This review will discuss the public health impact of type 2 diabetes, specifically with comorbid hypertension; mechanisms of action of the newest antidiabetic drug classes; and preliminary findings and potential clinical significance of the favorable blood pressure and body weight effects of the sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists; and additionally discuss two recent large cardiovascular outcome trials with dipeptidyl peptidase-4 inhibitors.

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Compliance with Ethics Guidelines

Conflict of Interest Pelbreton C. Balfour, Jr., declares that he has no conflict of interest.

Carlos J. Rodriguez has received grants from the NIH/NHLBI (R01 HL104199 and R01HL104199-03S1).

Keith C. Ferdinand has received a grant and paid travel expenses from Eli Lilly. He also has received consulting or honoraria payments from Amgen, Sanofi, Boehringer Ingelheim, Astra Zeneca, Daiichi Sankyo and Novartis. Dr. Ferdinand has also received paid travel expenses from Boehringer Ingelheim, grants from Daiichi Sankyo and lecture payments from Astra Zeneca.

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.

This article is part of the Topical Collection on *Hypertension and Obesity*

Keywords

Diabetes; Hypertension; Antidiabetic drugs; Cardiovascular disease; Sodium-glucose cotransporter 2 inhibitors; Glucagon-like peptide-1 receptor agonists; Dipeptidyl peptidase-4 inhibitors; Systolic blood pressure; Obesity

Introduction

Remarkable declines in cardiovascular disease (CVD) morbidity and mortality, including myocardial infarction and stroke, have been noted in the US over the last several decades. However, the estimated number of persons with prominent CVD risk factors, such as diabetes mellitus (DM), specifically type 2 diabetes mellitus (T2DM), and hypertension (HTN), continues to increase [1•]. Unfortunately, the synergistic effects of these potent risk factors may serve to slow or even reverse the recent gains in the US burden of CVD. Overall, patients with T2DM have approximately double the mortality risk compared to individuals without the disease, primarily driven by excess CVD [2–4]. Furthermore, this increased risk of CVD may be found with even a modest weight gain (5 kg), imparting as much as a 30 % increase in coronary heart disease (CHD) [1•, 5].

According to recent data, a total of 25.8 million children and adults (8.35 % of the population) have DM. Furthermore, the annual diabetes-related economic burden was recently estimated to be 174 billion US dollars, which includes 116 billion direct medical costs and 58 billion indirect costs (disability, work loss, premature mortality) [6]. In addition, HTN is also highly prevalent, involving over 72 million in the US, and is expected to continue to increase with aging of the post-World War II generation and persistent adverse behavioral risk factors, including high sodium, low potassium dietary patterns, physical inactivity and increasing obesity [1•, 7•, 8•]. The public health impact of these comorbid conditions is tremendous. Furthermore, like many chronic illnesses, HTN and T2DM disproportionately affect older people and have a higher prevalence among certain racial and ethnic minorities, including African Americans, Hispanics and American Indians [6].

It is well documented that the risk of CV events, particularly stroke, heart failure and chronic kidney disease, is greatly impacted by elevated BP in a strong, direct and continuous relationship, and medical therapy of elevated BP is associated with robust reductions in CV events, including 33–50 % in heart disease and stroke and 33 % in microvascular complications [6]. Approximately 67 % of adults with DM have HTN (BP ≥ 140/90 mmHg or are taking antihypertensive medications) [6], and the coexistence of hypertension and DM is associated with doubling of stroke or CVD risk [9, 10], retinopathy, a 5–6 times increased risk for end-stage renal disease and an increase in peripheral vascular disease, including lower extremity amputations [11]. This article provides a concise review on new and emerging agents for management of DM and the potentially favorable effects on systolic blood pressure and body weight.

FDA Guidance for Industry for Evaluating CV risk in New Antidiabetic Therapies

One salient reason specific research is needed for understanding the blood pressure and overall (CV) effects of antidiabetic drugs is in response to the 2008 Food and Drug Administration (FDA) guidance for industry statement, which proposes rules for evaluating CV risk in new antidiabetic therapies to treat T2DM [12]. The 2008 guidance document issued by the Center for Drug Evaluation and Research (CDER) emerged after concerns were raised about the CV safety of drugs in this field, especially thiazolidinediones (TZDs) [13]. The FDA requests CV safety data for initial and ongoing registration of new antidiabetic compounds and recommends formation of an independent CV endpoints committee to prospectively assess CV events during all phase 2 and phase 3 trials. These events should include but not be limited to the following: CV mortality, myocardial infarction and stroke; they can include hospitalization for acute coronary syndrome and urgent revascularization procedures. In addition to demonstrating CV safety, study protocols of these trials should allow for appropriate meta-analyses of an agent's studies to be performed at the time of their completion. The FDA recommends companies exclude major adverse effect on vascular outcomes prior to registration [12].

The FDA suggest sponsors develop more stringent clinical trials that collect data on CV endpoints as well as studies that include real-world patients likely to be seen in clinical practice [12]. Although glycemic control, as measured by glycated hemoglobin levels, remains an acceptable primary efficacy endpoint for approval of diabetic drugs to treat hyperglycemia, studies will likely be longer and more expensive in order to provide sufficient data on CV risk for these new therapies. Increasingly, therefore, studies of newer antidiabetic agents are interpreted not only according to the ability to lower glucose levels, but also the effects on the CV risks of various medications, which may determine approval or availability in the US. These non-binding recommendations from the FDA have elevated control of CV risk factors as an important new standard for all antidiabetic drugs currently in development [12].

Overview of Antidiabetic Medications and Blood Pressure

As previously stated, unlike older antidiabetic agents, newer drugs will face more demanding requirements for demonstrating not only control of blood glucose levels, but also avoidance of adverse CV affects than existing medications. Although lifestyle interventions are the necessary bedrock for the control of hyperglycemia, most adults with T2DM will eventually require pharmacotherapy to achieve and maintain optimal glycemic levels [6, 14•]. Over the last decade, an increasing number of agents have been developed and are available to treat hyperglycemia. Presently, there are at least 12 classes of diabetes medications available: biguanides (metformin), thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, insulins, meglitinides, sodium-glucose cotransporter 2 inhibitors (SGLT-2), glucagon-like peptide-1 (GLP-1) receptor agonists, an amylin analog (pramlintide), alpha-glycosidase inhibitors (acarbose, miglitol), colessevalam (a bile-acid sequestrant) and bromocriptine [14•].

Several of these medication classes have been in use for many years as a single therapy or in different combination strategies [17]. Nevertheless, these older, widely prescribed agents, despite well-documented glucose-lowering effects, potentially counteract any obvious benefits in CV risk reduction. For instance, agents widely utilized in T2DM, insulin and sulfonylureas, are associated with hypoglycemia and weight gain, with no BP-lowering effects. Moreover, there are limited, if any, data confirming CV outcome benefits of insulin therapy and sulfonylureas. In addition, thiazolidinediones (TZDs) are associated with weight gain, as well as edema, and carry a known black box warning for the risk for incident heart failure in some patients with T2DM [5, 13].

Among most diabetologists and in major diabetes-related evidence-based guidelines, metformin is the consensus first-line drug for pharmacotherapy with T2DM and has documented benefits in CV outcomes, despite usually neutral body weight and blood pressure effects. However, metformin is also known to carry a black box warning, specifically for lactic acidosis in patients with predisposing factors such as renal impairment and heart failure [5].

Newer and emerging antidiabetic agents include the SGLT-2 inhibitors, and incretion-based medications, such as the (GLP-1) receptor agonists and DPP-4 inhibitors [15•, 16•]. Preliminary studies particularly in SGLT-2 inhibitors and GLP-1 receptor agonists have demonstrated favorable effects of these agents, in addition to glycemic control, in the reduction in blood pressure, and body weight [5, 18, 19•, 20•, 21, 22•, 23•]. Since individuals with T2DM are known to have significant management obstacles with comorbid conditions such as obesity and hypertension [6], these novel antidiabetic agents with these favorable effects on these factors may potentially have further benefits on CVD morbidity and mortality experienced by those with T2DM, although confirmatory CV outcome studies have not been completed.

Blood Pressure Effects of SGLT 2 Inhibitors

Sodium-glucose cotransporters (SGLTs) play an important role in glucose homeostasis through renal glucose reabsorption. The kidney serves to filter approximately 180 g of glucose daily in normal physiologic conditions [18], and SGLTs transport sodium and glucose into cells using the sodium gradient created by sodium/potassium ATPase pumps at the basolateral cell membranes. Glucose is then transported passively by glucose transporter 2 (GLUT2) along its concentration gradient into the interstitium with the majority of the reabsorbed glucose occurring via SGLT2. In the proximal tubule of the kidney, 90 % of renal glucose reabsorption occurs via SGLT2, while 10 % occurs via SGLT1 [18, 19•]. Moreover, human studies have demonstrated increased expression of SGLT2 in patients with T2DM when compared to healthy individuals [24]. Thus, SGLT2 inhibitors would potentially block the majority of reabsorption of filtered glucose and lower blood glucose levels.

SGLT2 inhibitors, the newest approved antidiabetic class of agents, are actually derived from one of the oldest studied compounds. The pedigree of this class dates back to 1853, when French chemists identified phlorizin, a bitter white glycoside, as a potential agent to

treat diabetes. Phlorizin was isolated from apple tree bark and inhibited both SGLT1 and SGLT2 [25]. While SGLT2 is predominantly expressed in the kidney, SGLT1 is mainly in the intestinal mucosa, and the nonspecific inhibition of phlorizin leads to malabsorption of glucose and galactose in the intestine. Hence, this agent's poor oral availability and prominent gastrointestinal side effects led to abandonment of this approach [18].

This newest class of antidiabetic drugs, SGLT2 inhibitors, blocks transport at the brush border of the proximal convoluted tubule, causing glycosuria and a subsequent decrease in blood glucose [26•]. The first SGLT2 inhibitor on the US market was canagliflozin and subsequently dapagliflozin, which was delayed because of concerns about a cancer signal. However, canagliflozin does not appear to share that risk, with no increased malignancy signal in about 8,000 person-years exposure [23•]. Currently, there are several SGLT2 inhibitors in development.

Several clinical trials involving SGLT2 inhibitors have demonstrated a favorable CV effect of blood pressure reduction and body weight [19•, 20•, 22•, 23•]. In one double-blind trial, 755 patients were randomly assigned to receive canagliflozin vs. sitagliptin, a DPP-4 inhibitor. Participants were known poorly controlled diabetics on current oral therapy. Canagliflozin demonstrated a reduction in systolic blood pressure in diabetics when compared to sitagliptin, (−5.1 mmHg vs. 0.99 mmHg, $p < 0.001$) [27•]. Additionally, two recent meta-analyses have also demonstrated favorable blood pressure effects of SGLT2 inhibitors [22•, 28•]. Clar et al. concluded that participants treated with SGLT2 inhibitors had a decrease in systolic blood pressure when the therapy was given as a single therapy or in combination with metformin [28•]. Similarly, Vasilakou et al. concluded that SGLT2 inhibitors reduce systolic blood pressure in participants when compared to placebo and to other antidiabetic medications [22•]. Overall, blood pressure appears lowered by SGLT2 inhibitors with reductions achieved comparable to those of some established antihypertensive agents in high-risk patients.

The mechanism(s) that promote the blood pressure-lowering effect of SGLT2 inhibitors may be related to osmotic diuresis with increased urinary volumes of up to 107–470 ml/24 h [18, 19•], and the loss of calories also assists with true body weight loss. In addition, changes in neurohormonal activation may result in reduced blood pressure by decreasing sodium retention and arterial stiffness (Fig. 1) [29]. Changes in diastolic blood pressure (DBP) have been smaller and inconsistent, probably reflecting lesser statistical power to detect DBP effects. The combination of decreased BP and body weight loss (beyond simply decreased volume) may result in further significant vascular protection, although CV outcome studies are pending to confirm or refute benefits [22•]. CV outcomes and safety trials are ongoing along with efforts to document CV protection for persons with diabetes (Tables 1 and 2). Fortunately, no large excess in rates of hypotension or syncope among participants in trials to date has been reported [19•, 20•].

Blood Pressure Effects of GLP-1 Receptor Agonists

Endogenous glucagon-like peptide-1 (GLP-1), an incretin hormone, induces glucose-dependent insulin secretion after food intake by binding to specific receptors on pancreatic

beta cells, suppresses postprandial glucagon from pancreatic alpha cells, reduces postprandial plasma glucose (PPG) concentrations by delaying gastric emptying, and diminishes appetite [5, 30, 31•]. Thus, GLP-1 maintains glucose homeostasis and is associated with weight loss [30].

Studies have shown that GLP-1 levels are reduced in individuals with T2DM [32] and is rapidly degraded by dipeptidyl peptide-1 (DPP-4) [5, 30, 31•]. One therapeutic approach has been the development of parenteral GLP-1 receptor agonists that are resistant to degradation by DPP-4. Another approach includes oral agents that are now available as DPP-4 inhibitors with a less prominent stimulant incretin effect. Hence, clinicians have options of two different treatment approaches to address the diminished GLP-1 in T2DM.

Long-acting GLP-1 receptor agonists are available, and others are under development. Two agents, exenatide and Liraglutide, are approved for treatment of T2DM in the US [33, 34]. Several trials have evaluated the efficacy of GLP-1 agonists with respect to glucose control compared with placebo and other diabetic agents [35], and recent meta-analyses have demonstrated the favorable effects of GLP-1 agonists on the reduction of body weight when compared to placebo and other diabetic agents [31•]. Also, several Liraglutide Effect and Action in Diabetes (LEAD) studies of GLP-1 receptor agonists have reported reductions in SBP [36, 37]. Liraglutide, a once-daily human analog GLP-1 receptor agonist, used in a 26-week study of patients with T2DM, produced a decline in clinic SBP from 0.6 to 3 mmHg [36]. A longer trial over 52 weeks comparing glimepiride with liraglutide demonstrated a decrease in clinic SBP of -0.7 mmHg for glimepiride, -2.1 mm for liraglutide 1.2 mg ($P=0.2912$) and -3.6 mmHg for liraglutide 1.8 mg ($P<0.0118$), respectively [37].

Robinson et al. recently published a meta-analysis focused on the effects of GLP-1 on body weight, heart rate and blood pressure. Analysis of 31 studies revealed that GLP-1 agonists reduced clinic SBP by a mean difference of -1.79 mmHg (95 % CI -2.94 to -0.64) when compared to placebo and -2.39 mmHg (95 % CI -3.35 to -1.42) compared to active control [38•]. In 22 studies, GLP-1 agonists increased the heart rate by a mean difference of 1.86 bpm (95 % CI 0.85 to 2.87) when compared to placebo and 1.90 bpm (95 % CI 1.30 to 2.50) compared to active control. These studies have not demonstrated a statistically significant reduction however in diastolic blood pressure [36, 37, 38•].

Despite apparent positive BP effects, these studies were done with clinic BP measurements, which may not accurately characterize overall blood pressure values. Potentially useful data can be obtained with ambulatory blood pressure measurements (ABPM), including more detailed hemodynamic effects, changes with administered drugs and concomitant antihypertensive medications, blood pressure-related adverse events and the timing of BP in relation to dosing. Hence, the American Society of Hypertension (ASH) position statement notes ABPM has particular utility in assessing responses in complex antihypertensive treatment regimens and for the nocturnal BP profile [39].

A preliminary report from a phase 2 trial evaluates GLP-1 agonist effects in patients with T2DM utilizing ABPM. In this prospective study of 755 patients (NCT01149421), dulaglutide (dula), a novel, investigational, once weekly GLP-1 analog, was studied for its

effects on BP/HR using 24-h ABPM with T2DM treated with oral antihyperglycemic medications [40••]. Initial data suggest dulaglutide 1.5 mg resulted in a 2- to 3-mmHg reduction in ABPM SBP evident by 4 weeks and persisting throughout 26 weeks, also with a 3-to 4-bpm increase in 24-h HR. Biomarkers were analyzed and demonstrated no significant changes from baseline within or between dulaglutide and placebo for serum aldosterone, plasma renin activity, plasma metanephrines and normetanephrines, or NT-proBNP. Furthermore, no correlations were noted between changes in 24-h SBP and any of these analytes at 16 weeks [40••]. Although these are preliminary findings with no proven CV outcomes, the ongoing Researching Cardiovascular Events with a Weekly INcretin in Diabetes (REWIND) trial is designed to determine the effects of dulaglutide on major CV events [41].

The exact mechanism(s) of action by which GLP-1 receptor agonists affect BP remain uncertain. In rodents, GLP-1-mediated increases in HR and BP appear to involve both central and peripheral nervous system pathways, require an intact vagus nerve transmission and may involve vasopressin levels [42–45]. There may also be vasodilatation through GLP-1 receptor-dependent and independent pathways [46]. Renal effects on the BP may include diuretic and natriuretic effects. Finally, based on animal studies, activation of GLP-1 receptors in the cardiac atria promotes secretion of atrial natriuretic peptide (ANP), resulting in a reduction in blood pressure. ANP appears essential for GLP-1-stimulated urinary sodium secretion and vascular smooth muscle relaxation. ANP induces cGMP-mediated smooth muscle relaxation and natriuresis, leading to the reduction of BP [47••]. Given the potential CV effects, post-marketing surveillance is important for all of these agents. In addition, there are no data for the CV outcome benefit of potential blood pressure lowering with these two new additions to the antidiabetes armamentarium. As with SGLT2 inhibitors, there are multiple other CV outcome studies ongoing to confirm or refute CV effects of GLP-1 agonists (Table 2, Fig. 2).

DPP-4 Inhibitors: Cardiovascular Effects

As previously discussed, GLP-1 levels are reduced in individuals with T2DM, and GLP-1 is rapidly degraded by dipeptidyl peptide-1 (DPP-4) [31•, 32]. Another treatment approach to address the diminished GLP-1 in T2DM would be to target the enzymatic activity of DPP-4, thus leading to these new therapeutic agents known as DPP-4 inhibitors. DPP-4 inhibitors diminish the degradation of circulating GLP-1 by blocking the main enzymatic pathway [30]. Those presently approved in the US include alogliptin, linagliptin, saxagliptin and sitagliptin, while vildagliptin is only approved in the UK [31•].

In view of the recent FDA recommendations, greater interest has been placed on studies addressing CV outcomes with new antidiabetic agents [48]. Two recent trials have evaluated CV outcomes in patients with T2DM on therapy with DPP-4 [49••, 50••]. In patients with T2DM, major adverse CV events were not increased with either of two DPP-4 inhibitors – saxagliptin [49••] or alogliptin [50••] – versus placebo. In the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) study, however, saxagliptin was associated with a significant 27 % increased risk of hospitalizations for heart failure, a component of the pre-specified secondary endpoint [49••]. In the Examination of Cardiovascular Outcomes with Alogliptin versus Standard of

Care in Patients with Type 2 Diabetes Mellitus and Acute Coronary Syndrome (EXAMINE) study, published at the same time as SAVOR-TIMI 53, there was no reported increased risk of heart failure with alogliptin [50••]. The FDA has requested clinical trial data to conduct further analysis of saxagliptin and a potential association with increased cardiovascular risk, particularly heart failure. The findings from these analyses will be reported to the general public. At this time, the FDA recommends patients discuss further use with their physicians and both parties report side effects to the FDA MedWatch program [51].

Previous evidence has demonstrated the association of antidiabetic agents with increased HF risks such as TZDs [13] and DM as an independent risk factor for HF [52, 53]. Diabetic cardiomyopathy consists of structural abnormalities of the myocardium affecting both systolic and diastolic function and ultimately leads to HF [54–56]. Given the already increased morbidity and mortality of individuals who develop HF with underlying T2DM [55], we await the results of pending and future trials evaluating the effects on CV outcomes of these new antidiabetic agents.

Conclusion

The increased risk of CV morbidity and mortality with current therapies remains a public health burden in patients with T2DM and HTN. Individuals frequently have management obstacles with optimal glycemic control, maintaining excess body weight and reducing blood pressure. Current evidence suggests that newer agents such as SGLT-2 inhibitors and GLP-1 receptor agonists have favorable effects on lowering blood pressure, while DPP-4 inhibitors have few if any effects on blood pressure. Individuals with T2DM may potentially benefit from SGLT-2 inhibitors and GLP-1 receptor agonists that not only control hyperglycemia but also address increased body weight and elevated blood pressure. Although recently the CV safety of DPP-4 inhibitors has been shown, concerns regarding the effects on HF still remain. Future clinical trials are necessary to address the CV risk and long-term outcomes of these newer antidiabetic agent effects, especially in view of the apparent beneficial data with SGLT 2 inhibitors and GLP-1 agonists.

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Fig. 1.

Physiological mechanisms implicated in arterial stiffness-lowering effects with sodium glucose cotransport-2 inhibition. (Used with permission from Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, Woerle HJ, von Eynatten M, Broedl UC (2014). The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovascular Diabetology*, 13(1), 28)

Fig. 2.

Schematic mechanism for GLP-1 regulation of blood pressure. After activation of atrial cardiomyocyte GLP-1R agonists such as liraglutide or exenatide, increased amounts of cAMP promote Epac2 membrane translocation, which then mediates ANP release from the large dense core vesicle (LDCV). ANP induces cGMP-mediated smooth muscle relaxation and natriuresis, leading to a reduction of blood pressure. (Used with permission from Kim M, Platt MJ, Shibasaki T, Quaggin SE, Backx PH, Seino S, Simpson JA, Drucker DJ. GLP-1 receptor activation and Epac2 link atrial natriuretic peptide secretion to control of blood pressure. *Nat Med.* 2013;19:567–575)

Table 1

Ongoing cardiovascular outcome trials of SGLT2 inhibitors

Trial/drug	N	Status
CANVAS (NCT01032629) Canagliflozin vs. PBO	4,330	Phase III
DECLARE-TIMI58 (NCT01730534) Dapagliflozin vs. PBO	22,200	Phase III
Efficacy and Safety in Patients with T2DM and CVD (NCT01042977) Dapagliflozin vs. PBO	964	Phase III
Efficacy and Safety in Patients with T2DM, CVD, and HTN (NCT01031680) Dapagliflozin vs. PBO	922	Phase III
BI 10773 (Empagliflozin) CVD Outcome Event Trial in T2DM Patients (NCT01131676) Empagliflozin vs. PBO	7,000	Phase III

Notes: Identified from clinicaltrials.gov April 2014.

Abbreviations: SGLT=sodium-glucose cotransporters; N=number of estimated participants; CANVAS=CANagliflozin cardioVascular Assessment Study; DECLARE-TIMI58=Multicenter Trial to Evaluate the Effect of Dapagliflozin on the Incidence of Cardiovascular Events. T2DM= Type 2 Diabetes Mellitus; CVD=cardiovascular disease; PBO=placebo; HTN=hypertension

Table 2**Ongoing Cardiovascular Outcome Trials of GLP-1 receptor agonists**

Trial/drug	N	Status
LEADER (NCT01179048) Liraglutide once daily vs. PBO	9,340	Phase III
EXSCEL (NCT01144338) Exenatide once weekly vs. PBO	14,000	Phase IV
ELIXA NCT01147250 Lixisenatide vs. PBO	6,000	Phase III
SUSTAIN-6 (NCT01720446) Semaglutide vs. PBO	3,260	Phase III
REWIND (NCT01394952) Dulaglutide vs. PBO	9,622	Phase III

Notes: Identified from clinicaltrials.gov April 2014.

Abbreviations: GLP-1 = glucagon-like peptide-1; N = number of estimated participants; EXSCEL = Exenatide Study of Cardiovascular Event Lowering; LEADER = Liraglutide Effect and Action on Diabetes: Evaluation of Cardiovascular Outcome Results; ELIXA = Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide); SUSTAIN-6 = Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects With Type 2 Diabetes; REWIND = Researching Cardiovascular Events With a Weekly Incretin in Diabetes. PBO = placebo.