Achieving Antihyperglycemic Treatment Goals With Incretin-Related Therapies

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Abstract

The management of type 2 diabetes mellitus (T2DM) remains challenging. Limitations associated with many current therapies include hypoglycemia and weight gain. An increased understanding of the pathophysiology of T2DM has led to the development of incretin-related antihyperglycemic therapies. These agents enhance insulin secretion and inhibit inappropriate glucagon secretion, both in a glucose-dependent manner. As a result, they can lower blood glucose levels with a low risk of hypoglycemia or weight gain. Incretin-based therapies, the dipeptidyl peptidase 4 inhibitors and the glucagon-like peptide-1 receptor agonists, are now integrated into T2DM treatment algorithms. Trial data and clinical experience have shown that these agents are efficacious and generally well tolerated.

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For author information and disclosures, see end of text.

It is estimated that more than two-thirds of Americans are overweight or obese.[1,2] The obesity epidemic is accompanied by a parallel rise in the prevalence of type 2 diabetes mellitus (T2DM), as nearly 19 million Americans now meet the diagnostic criteria for the disease.[1] T2DM is the number 1 cause of adult blindness, end-stage kidney disease, and nontraumatic amputations.[3] Additionally, adults with diabetes are 2 to 4 times more likely to have a stroke or die from cardiovascular disease (CVD) than those without diabetes.[2] Diabetes may also be associated with an increased risk of nonvascular conditions, including certain cancers (eg, breast, liver) and other noncancerous, nonvascular disorders (eg, cognitive decline, infectious diseases).[3] Because diabetes is occurring at an earlier age, individuals are at risk of developing and experiencing complications over a greater extent of their lives.[1,2] Recent estimates indicated that diabetes and its associated complications cost the United States in excess of $174 billion per year.[4]

Diabetes Management

Interventions designed to lower glycated hemoglobin (A1C) levels have been shown to reduce rates of microvascular disease and probably macrovascular complications as well. The UK Prospective Diabetes Study (UKPDS) randomized patients to conventional care (ie, lifestyle intervention with pharmacological therapy only if hyperglycemia became severe) or intensive therapy (ie, sulfonylurea or insulin, with a subset of overweight patients randomized to metformin).[5] Not only was intensive therapy more effective in lowering blood glucose, the reduction in A1C level was associated with a significant decrease in the risk of microvascular complications (P = .029).[5] A trend toward reduced rates of macrovascular events (eg, myocardial infarction) in the intensive care group was observed, but it did not reach statistical significance.[5] In contrast, a reduced risk of any diabetes-related end point, all mortality, and CVD end points was observed in the subset of obese patients randomized to receive metformin despite only a modest decrease in mean A1C level compared with the conventional treatment (control) group.[6] A 10-year follow-up demonstrated that the relative benefit of intensive glycemic management on outcomes was maintained over a decade. Treatment with a sulfonylurea or insulin was associated with emergence of statistically significant benefits on CVD end points (P = .01) and total mortality (P = .007). CVD benefits elicited by metfor-

min therapy also persisted, despite the observation that mean A1C levels between the groups had dissipated.[7]

Several shorter-duration studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial,[8] the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) study,[9] and the Veterans Affairs Diabetes Trial (VADT),[10] reported the effects of 2 levels of glycemic control on cardiovascular end points in individuals with long-term T2DM at high risk for cardiovascular events but without overt CVD. ACCORD and VADT utilized combinations of oral agents and insulin to attempt to achieve an A1C level less than 6.0%.[8,10] ADVANCE used an initial sulfonylurea-based intervention with sequential addition or increase in dose of metformin, thiazolidinediones, acarbose, or basal insulin to try to achieve an A1C level of 6.5% or less.[9] All 3 trials failed to demonstrate a reduction in the combined cardiovascular end point. Moreover, intensive antihyperglycemic therapy in ACCORD was associated with a 22% increase in total mortality. The intensive treatment group had a 3-fold higher incidence of hypoglycemia, but investigators were unable to attribute the increased mortality to intensive treatment.[8] However, trends observed in these trials suggested that patients without overt CVD, with shorter duration of disease, and with lower baseline A1C levels benefited from intensive treatment strategies. In addition, modest improvements in some microvascular end points were also observed in these trials.

Diabetes Treatment Guidelines

Because the risk of microvascular and probably macrovascular complications increases with elevated blood glucose levels,[3] the American Diabetes Association[11] (ADA) and the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE)[12] emphasize the importance of blood glucose management efforts. However, it is also recommended that glycemic control be pursued within a multifactorial risk reduction framework that includes efforts to treat the often-associated increase in blood pressure and dyslipidemia. Thus, efforts to reduce the global CVD risk should include routine assessment and treatment of the ABCs of diabetes—A1C, Blood pressure, Cholesterol—to reach target levels.[11,12] As illustrated in the **Table**, the ADA- and AACE/ACE-recommended treatment targets for the ABCs are similar; the primary difference between the 2 is the suggested target for glycemic control for most patients (<7% for ADA[11] and ≤6.5% for AACE/ACE[12]).

Although these are evidence-based recommendations, both guidelines emphasize the need to tailor treatment to the individual patient. For example, the ADA[11] states that a glycemic target of less than 7.0% is an appropriate goal for most patients, but even lower goals may be attempted in recently diagnosed patients without CVD and at low risk of hypoglycemia if such goals can be obtained without significant hypoglycemia or other adverse consequences. On the other hand, a treatment target of greater than 7.0% may be necessary to minimize the risk of adverse events in some patients, such as those with a short life expectancy, those with a history of frequent or severe hypoglycemia or hypoglycemic unawareness, those with CVD, or those who have been unable to achieve glycemic control despite appropriate therapy. AACE/ACE guidelines make similar recommendations about individualization.[11,12]

The cornerstones of diabetes treatment continue to be diabetes self-management education as well as lifestyle modification, medical nutrition therapy, and appropriately prescribed physical activity. Compared with usual care, intensive lifestyle interventions can be associated with improvements in body weight, A1C levels, blood pressure measurements, lipid levels, and general cardiovascular fitness.[13] However, adherence to lifestyle recommendations is often challenging for patients. The National Diabetes Education Program, a joint venture of the National Institutes of Health and the Centers for Disease Control and Prevention, had a group of behavior change experts develop *Diabetes Health Sense*, which identifies over 140 resources that they believe might help patients better adhere to both lifestyle and medication recommendations.[14]

Most patients will ultimately require pharmacologic treatment in addition to lifestyle interventions to achieve their glycemic goals. Depending on the type of classification, there are now nearly a dozen classes of antihyperglycemic agents currently available; the challenge is to identify the best agent(s) and/or sequence of agents for each patient. The AACE/ACE algorithm stratifies treatment recommendations by A1C level, advocates for earlier use of combination therapy to achieve glycemic targets, and emphasizes the use of treatments with a low risk of hypoglycemia and/or weight gain.[12] Recently, the ADA, in collaboration with the European Association for the Study of Diabetes (EASD), published an updated position statement.[15] This resource has many similarities to that developed by the AACE/ACE, and both algorithms emphasize the value of incretin-related agents in reducing the risk of hypoglycemia and/or weight gain with antihyperglycemic therapy.

Unmet Needs With Antihyperglycemic Therapies

Several currently available antihyperglycemic agents, including sulfonylureas, meglitinides, insulin, and thiazoli-

Table. The ABCs of Type 2 Diabetes

Treatment Goal	AACE/ACE (2011)[12]	ADA (2012)[11]
A1C (%)	≤6.5	<7.0
Blood pressure (mm Hg)	<130/80	<130/80
Cholesterol (mg/dL)	• LDL-C level <100 (<70 an option for patients with diabetes and coronary artery disease) • HDL-C level >40 in men; >50 in women • Triglyceride level <150	• LDL-C level <100 (<70 an option for patients with diabetes and coronary artery disease) • HDL-C level >40 in men; >50 in women • Triglyceride level <150

AACE indicates American Association of Clinical Endocrinologists; ACE, American College of Endocrinology; ADA, American Diabetes Association; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

dinediones, are associated with an increased risk of hypoglycemia and/or the potential for weight gain.[16,17] Occurrence of these events may lead to suboptimal adherence, which could result in worse long-term glycemic control.

Incretin-Based Therapies

Glucagon-like peptide-1 (GLP-1), one of the endogenous incretins, enhances glucose-dependent insulin secretion, suppresses excessive glucagon release, slows gastric emptying, and enhances satiety.[18] In animal models, GLP-1 also decreases beta cell apoptosis, increases beta cell proliferation, and can even lead to neogenesis of beta cells from pancreatic ductal cells.[18] Another incretin, gastric inhibitory polypeptide (GIP)—also known as glucose-dependent insulinotropic peptide—also increases insulin secretion and beta cell replication and decreases beta cell apoptosis.[18] In patients with T2DM, the "incretin effect" (greater insulin response to oral vs intravenous glucose) is markedly reduced, a pathological trait that likely plays a significant role in the inability of these patients to secrete a sufficient amount of insulin to prevent hyperglycemia following ingestion of oral glucose.[19]

While improving the impaired incretin effect is potentially useful in the treatment of T2DM, endogenous incretins are rapidly broken down by the enzyme dipeptidyl peptidase-4 (DPP-4), rendering them unsuitable as therapeutic agents because they would have to be administered by continuous intravenous or subcutaneous infusion.[18] To overcome this limitation, orally administered inhibitors of the DPP-4 enzyme and injectable GLP-1 receptor agonists resistant to DPP-4 degradation have been developed. Both classes enhance activation of GLP-1 receptors. The DPP-4 inhibitors increase endogenous levels of GLP-1 and GIP 2- to 3-fold. In contrast, GLP-1 agonists provide a 6- to 10-fold increase in pharmacologic activation of the GLP-1 receptors.[18,20]

DPP-4 Inhibitors

DPP-4 inhibitors differ from the GLP-1 receptor agonists in that they are small molecules rather than peptides; thus, they can be administered orally instead of by subcutaneous injection. DPP-4 inhibitors approved in the United States include sitagliptin, saxagliptin, and linagliptin.[21-23] These agents inhibit the degradation and inactivation of endogenous GLP-1, thereby enhancing insulin secretion and diminishing glucagon in a glucose-dependent manner. Although the DPP-4 inhibitors differ in their metabolism, excretion, and the daily dosage that is required for effective treatment, they are generally similar in their A1C-lowering efficacy and safety profile. In long-term clinical trials, DPP-4 inhibitors reduced A1C levels by 0.6% to 0.7% with a modest reduction in fasting plasma glucose level.[24-27] DPP-4 inhibitors also reduced postprandial glucose levels. These observations were substantiated by results from a meta-analysis that reported a −0.74% (95% confidence interval, −0.85% to −0.62%) placebo-subtracted reduction in A1C level following DPP-4 administration.[16] DPP-4 inhibitors are weight neutral or have minimal effects on body weight and are generally associated with a very low incidence of hypoglycemia.[24-27]

Most patients with T2DM require combinations of antihyperglycemic agents in addition to lifestyle interventions. DPP-4 inhibitors are particularly effective when administered in combination with metformin as initial combination antihyperglycemic therapy.[28,29] The additional A1C-lowering benefit observed with combined therapy can be potentially explained by both the complementary actions of the 2 classes of agents and the fact that metformin itself tends to raise GLP-1 levels. When metformin is combined with an agent that retards the degradation of the DPP-4 enzyme, raised GLP-1 levels tend to persist for a longer period.[29]

The addition of a DPP-4 inhibitor to the regimen of a patient who does not achieve target glycemic control with lifestyle interventions and metformin is recommended by both the AACE/ACE[12] algorithm and ADA/EASD guidelines[15] when it is desirable to avoid hypoglycemia and/or weight gain. Single-pill and fixed-dose combinations containing a DPP-4 inhibitor and metformin or a DPP-4 inhibitor and simvastatin are now available. Sitagliptin is

available in combination with both immediate release and extended release metformin as well as in combination with simvastatin.[30-32] Saxagliptin is approved as monotherapy and in combination with metformin HCl extended-release,[33] and linagliptin, the most recently approved DDP-4 inhibitor, is also available in combination with metformin HCl.[34] Several studies with DPP-4 inhibitors as add-on therapy to metformin have demonstrated improvement in glycemic control. Mean A1C levels are reduced by approximately 0.65% to 1% from a baseline of 7.8% to 8.4%. Furthermore, these combinations are generally well tolerated, with an adverse event profile similar to that seen in patients given metformin alone.[26,35-39]

GLP-1 Receptor Agonists

Currently available GLP-1 receptor agonists include exenatide (twice-daily and once-weekly/extended-release formulations)[40,41] and liraglutide (once-daily formulation).[42] Other GLP-1 receptor agonists are presently in clinical regulatory trials. Exenatide, when administered twice daily as monotherapy, reduces A1C levels by approximately 0.7% to 1.0% from baseline in patients with baseline A1C levels of 6.5% to 10%,[40] whereas open-label comparator studies report a reduction in A1C levels of 1.1% to 1.5% from baseline A1C levels of 8.2% to 9.0%.[43,44] Reductions in A1C levels with liraglutide, observed in the LEAD (Liraglutide Effect and Action in Diabetes) clinical trial program, were 0.8% to 1.5% in patients with average baseline A1C levels of 8.2% to 8.5%.[45-51] This reduction was, in most cases, greater than or at least similar to oral comparator antihyperglycemic drugs.[43] In a head-to-head comparison of exenatide twice daily and liraglutide (LEAD-6 trial), the reduction in A1C level was 0.33% greater with liraglutide (−1.12%) compared with exenatide (−0.79%).[50,52] Reductions in fasting plasma glucose levels were also greater with liraglutide compared with exenatide (−28.8 vs −10.8 mg/dL, respectively), while weight loss was not significantly different (−3.24 vs −2.87 kg).[50,52] In most phase 3 studies with exenatide and liraglutide, weight loss ranged from 2 to 3 kg after 26 weeks of treatment (compared with placebo) and was greatest when either GLP-1 agonist was added to metformin.[43]

Slightly more patients experienced gastrointestinal side effects when treated with exenatide twice daily; 28% reported nausea, and 9.9% experienced vomiting. By comparison, 25.5% and 6.0% of patients receiving liraglutide reported nausea and vomiting, respectively.[50,52] The frequency of nausea diminished more rapidly with liraglutide than with exenatide. After 8 to 10 weeks of treatment, less than 10% of patients treated with liraglutide reported nausea, whereas nausea persisted in approximately 10% of patients in the exenatide group.[50] By week 26, 2.5% of the liraglutide group and 8.6% of the exenatide group reported nausea.[50] Approximately 60% of patients receiving exenatide and 4% to 13% of those treated with liraglutide developed antibodies.[53] Data from the LEAD-6 trial indicated that liraglutide was less immunogenic than exenatide, with less than 10% of liraglutide-treated patients developing antibodies.[53] Overall, treatment satisfaction was rated slightly higher with liraglutide than exenatide twice daily.[50,52]

Exenatide extended-release, a once-weekly formulation of exenatide, was recently introduced and approved for use in the United States. It uses slowly biodegradable polymeric microspheres, which provide a gradual, sustained release of exenatide.[41] Eventually, this polymer matrix breaks down and it is eliminated as carbon dioxide and water.[54] After subcutaneous injection of 2 mg of once-weekly exenatide, the stable drug plasma level is comparable to the peak concentrations observed after 5 to 10 weeks of therapy with exenatide in the twice-daily formulation. An exenatide plasma level of greater than 50 pg/mL, which is known to reduce fasting plasma and postprandial glucose concentration, is observed after about 2 weeks of treatment with exenatide extended-release.[55]

Extended-release exenatide has been studied in the DURATION program, a series of 6 clinical trials lasting 24 to 30 weeks.[56-60] The program included 1 monotherapy trial and the others investigated the extended-release formulation in combination with metformin, metformin with or without sulfonylureas, or the patient's usual oral diabetes medications. Comparator arms included exenatide twice daily, insulin glargine, liraglutide, metformin, sitagliptin, and pioglitazone. Mean baseline A1C levels for the study population ranged from 8.3% to 8.5%.[56-60] Overall results of the DURATION program indicated that the mean change from baseline in A1C level for patients receiving extended-release exenatide was between −1.3% and −1.9%. This reduction in A1C level was significantly greater than that observed in patients receiving twice-daily exenatide (P = .0023), sitagliptin (P = .0001), or insulin glargine (P = .01). Compared with liraglutide, exenatide once weekly failed to meet a prespecified noninferiority end point, although the difference in A1C level favoring liraglutide was only 0.2%.[60]

Injection site reactions, upper respiratory tract infections, and gastrointestinal symptoms were the most common adverse events observed in patients treated with exenatide extended-release.[56-60] Injection site reactions occurred in approximately 16% of patients given exenatide extended-release compared with 2% to 7% in those given comparators (which included exenatide twice daily) in safety and efficacy studies overall.[56-60] There were no reported episodes of major

hypoglycemia in patients treated with exenatide extended-release in the studies, and most cases of minor hypoglycemia were in patients concurrently receiving a sulfonylurea.[56-60] If a GLP-1 agonist is added to the treatment regimen of a patient receiving a sulfonylurea, a reduction in the dose of sulfonylurea should be considered to reduce the risk of hypoglycemia.[41,42,61,62]

Most adverse events associated with exenatide extended-release observed in the DURATION program were of mild to moderate intensity, the most common being nausea, diarrhea, injection site reaction, vomiting, and headache.[56-60] Gastrointestinal symptoms were more common with exenatide extended-release than with sitagliptin, pioglitazone, or insulin glargine, but nausea and vomiting occurred less frequently with exenatide extended-release than with exenatide twice daily or liraglutide.[57,58] Injection site pruritus, erythema, and/or nodules were more frequent with exenatide extended-release than with exenatide twice daily.[56,59] Hypoglycemia was uncommon in all trials, but was more frequent in patients who were also taking a sulfonylurea.[56,59]

Use of Incretin Therapy With Insulin

Although treatment guidelines have primarily positioned the incretin-related therapies as second- or third-line agents before initiation of insulin,[11,12] the therapeutic role of these agents continues to evolve. Recent clinical studies demonstrate the efficacy and safety of combining incretin-based therapies with basal insulin.[63,64] This strategy may help to address residual postprandial hyperglycemia with a regimen that is less complex than the addition of prandial insulin. Also, data, albeit limited, from these studies suggest the benefit of optimizing a patient's own endogenous glucose-dependent insulin secretion with incretin-related therapy before adding exogenous insulin.[65-67] This may result in a lower risk of hypoglycemia and weight gain. Liraglutide and exenatide twice daily are both approved for use in combination with basal insulin.[40,42] Sitagliptin, saxagliptin, and linagliptin are also approved for use with insulin.[21-23] As noted previously, the risk of hypoglycemia may be increased with this combination. Therefore, depending on the level of glycemic control, clinicians should consider reducing the dose of insulin when adding incretin-related therapies to insulin.

Safety of the Incretins

The most commonly reported adverse events with DPP-4 inhibitors include nasopharyngitis, upper respiratory tract infection, and headaches. There have been uncommon postmarketing reports of serious allergic and hypersensitivity reactions in patients treated with DPP-4 inhibitors, including anaphylaxis, angioedema, and exfoliative skin conditions.[21-23] The most frequently reported adverse events observed in patients treated with GLP-1 receptor agonists include nausea, diarrhea, and vomiting.[40-42]

The effect of incretin therapies on the cytochrome P450(CYP) 3A4/5 metabolic pathway varies. Linagliptin is a weak to moderate inhibitor of the CYP isoenzyme CYP3A4.23 The efficacy of linagliptin-containing agents may be reduced when administered in combination (eg, with rifampin). Use of alternative treatments is strongly recommended.[23] Administration of saxagliptin with strong CYP3A4/5 inhibitors (eg, ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin) significantly increases saxagliptin concentrations.[22] Thus, the maximum recommended dose of saxagliptin is 2.5 mg once daily when coadministered with these and similar agents.[22] Liraglutide has a low potential for pharmacokinetic drug-drug interactions related to CYP isoenzymes and plasma protein binding.[42] Sitagliptin[21,30-32] and exenatide[40,41] are not inhibitors of CYP isozymes, nor are they inducers of CYP3A4.

Pancreatitis has been reported in patients receiving DPP-4 inhibitors or GLP-1 receptor agonists, but no causal relationship has been established, and people with T2DM have a 2- to 3-fold increased risk of pancreatitis.[68] Claims database analyses generally do not show an increased risk of pancreatitis with exenatide twice daily or sitagliptin versus other antihyperglycemic agents.[69-71] Preclinical studies of incretin-related therapies have yielded conflicting results and failed to reveal a mechanism linking GLP-1 activation or DPP-4 inhibition to the pathophysiology of acute pancreatitis.[69] Patients taking DPP-4 inhibitors and GLP-1 agonists should know the signs and symptoms of pancreatitis, and these agents should be discontinued if such signs and/or symptoms occur. If pancreatitis is confirmed, incretin-related agents should not be restarted. It may be reasonable to consider other classes of antihyperglycemic agents for patients with a past history of pancreatitis, but these agents should be used with caution.[20]

Dose adjustments are required for patients with impaired renal function who are to be treated with the DPP-4 inhibitors sitagliptin[21] and saxagliptin[22] but not with linagliptin.[23] There have been postmarketing reports of renal impairment occurring in patients treated with GLP-1 receptor agonists, usually in association with nausea, vomiting, diarrhea, and/or dehydration. There is no evidence that these agents are nephrotoxic. However, exenatide, which is renally excreted, should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) and should be used with

caution in patients who underwent a renal transplant or when initiating or escalating doses in patients with moderate renal impairment (creatinine clearance 30-50 mL/min).[40,41] Liraglutide is not excreted by the kidneys, and no dose adjustments for chronic kidney disease are required. However, caution should be used when initiating or escalating doses of liraglutide in patients with renal impairment.[42]

Liraglutide[42] and exenatide extended-release[41] have caused thyroid C-cell tumors at clinically relevant exposures in rodents. It is not known whether these agents would cause thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans, because human relevance could not be determined by clinical or nonclinical studies. Rodent C-cell density, C-cell GLP-1 receptor density and responsiveness, and risk of C-cell hyperplasia and MTC are much greater than in humans.[72] The US Food and Drug Administration (FDA) concluded that increases in the incidence of carcinomas among rodents translated into a low risk for humans because statistically significant increases occurred only at drug exposure levels many times those anticipated in humans.[73] However, both GLP-1 receptor agonists are contraindicated in patients with a personal or family history of MTC or in patients with multiple endocrine neoplasia syndrome type 2, and surveillance programs including a MTC registry are ongoing.[40-42]

Cardiovascular Effects

GLP-1 receptor agonists have demonstrated beneficial effects on CVD risk factors. Results from meta-analyses have demonstrated significant reductions in weight, systolic and diastolic blood pressure measurements, and total cholesterol, low-density lipoprotein cholesterol, and triglyceride concentrations.[50,56,74] Liraglutide and exenatide have also been associated with improvements in inflammatory markers.[75,76] Although there are less data, some studies have suggested the potential for DPP-4 inhibitors to have a blood pressure benefit.[77] DPP-4 is expressed on endothelial cells and inhibition of DPP-4 within the microcirculation relaxes vascular tone via the nitric oxide system, suggesting that this class of antihyperglycemic agents might promote improvements in blood pressure.[78] However, with the exception of a single small study (N = 19) in which sitagliptin therapy in patients without diabetes was associated with a small reduction in systolic blood pressure measurements (2-3 mm Hg), as assessed by 24-hour ambulatory monitoring,[77] no consistent effect of DPP-4 agents on blood pressure has been demonstrated in humans.

DPP-4 inhibitors may also have a beneficial effect on postprandial lipid levels.[79,80] Boschmann et al have suggested that vildagliptin therapy may augment postprandial lipid mobilization and oxidation.[79] A retrospective analysis of the General Electric Centricity database (N > 500,000) indicated that patients with diabetes who were treated with sitagliptin showed decreases in low-density lipoprotein cholesterol, total cholesterol, and triglyceride levels.[81] Results of a small (N = 31) clinical trial suggested that vildagliptin improved triglyceride and apolipoprotein B metabolism after a high-fat meal in patients with T2DM.[80] In general, however, current clinical trial results are insufficiently robust to demonstrate an effect of DPP-4 inhibitors on circulating lipid concentrations in humans.

Cardiomyocytes and endothelial cells are expressed in GLP-1 receptors and preclinical studies show cardioprotection with GLP-1 receptor activation. Preliminary data suggest ventricular function preservation in individuals with heart failure or myocardial infarction.[82] Moreover, incretin-related effects, especially those of GLP-1 receptor agonists, on weight, blood pressure measurements, and lipid levels might be expected to have CVD benefits in patients with diabetes. Point estimates of cardiovascular events in regulatory trials with these agents show no evidence of increased cardiovascular risk. Indeed, the point estimates suggested decreased risk, but most estimates were not significant, possibly because of the small number of events.[83-85] FDA-mandated cardiovascular safety trials are presently ongoing with all incretin-related agents. Some of these trials are powered to potentially demonstrate cardiovascular disease benefit, and results are eagerly awaited.

Summary

Incretin dysfunction is increasingly believed to play a key role in the pathophysiology of T2DM. Two classes of agents are now available to address the abnormal incretin pathophysiology: the GLP-1 receptor agonists, which mimic the activity of endogenous GLP-1, and the DPP-4 inhibitors, which increase the endogenous levels of GLP-1. These agents beneficially affect glycemic control and body weight, and minimize the risk of hypoglycemia. Although their exact roles in the treatment of T2DM are still to be determined, both classes of incretin-related agents have been included in recent T2DM treatment algorithms.

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