Published in final edited form as:

Endocrinol Metab Clin North Am. 2013 December ; 42(4): 947–970. doi:10.1016/j.ecl.2013.06.005.

Complications of Diabetes Therapy

Sarah D. Corathers, MD^{a,b,*}, Shawn Peavie, DO^b, and Marzieh Salehi, MD, MS^b

^aDivision of Endocrinology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7012, Cincinnati, OH 45229, USA

^bDivision of Endocrinology, University of Cincinnati Medical Center, 260 Stetson, Suite 4200, Cincinnati, OH 45229, USA

Keywords

Diabetes; Treatment complications; Cardiovascular outcomes; β -cell function

INTRODUCTION AND BACKGROUND

Type 2 diabetes mellitus (T2DM) is increasingly prevalent in the United States population and is associated with significant morbidity, mortality, and rising health care costs. Microvascular^{1,2} and, to a lesser extent, macrovascular^{3,4} complications are recognized to result from uncontrolled hyperglycemia. However, intensive therapy to achieve normal glucose levels is not without risk, as demonstrated by increased rates of hypoglycemia, weight gain, and all-cause mortality rates in the intensive treatment arm of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial.⁵ In addition, observational studies indicate that the presence of diabetes increases the risk of other comorbidities such as fracture⁶ and certain cancers,^{7,8} and treatment choice may affect risk. Thus, in an effort to maintain glucose control, the clinician encounters a complex interplay of primary disease management while simultaneously seeking to avoid complications associated with glucose lowering. Given the chronic nature of diabetes management, efficacy must be balanced against side effects to achieve a tolerable long-term regimen. The goal of this review is to identify complications of non-insulin treatment of diabetes. The major classes of medication are reviewed with special attention given to patient considerations, mechanism of action, effect on weight, and cardiovascular outcomes, and additional class-specific side effects including effects on bone. In addition, effects on β -cell function are highlighted. Hypoglycemia is a recognized feature of many diabetes treatment modalities, and is not covered in depth in this article.

INSULIN SENSITIZERS

The 2 classes of drugs categorized as insulin sensitizers are biguanides (metformin) and thiazolidinediones (rosiglitazone and pioglitazone).

*Corresponding author. Division of Endocrinology, Cincinnati Children's Hospital Medical Center, 3333 Burnet Avenue, MLC 7012, Cincinnati, OH 45229. Sarah.corathers@cchmc.org.

Conflict of Interest: The authors do not have any conflict of interest to disclose.

Biguanides

Indications and patient considerations—Metformin remains the primary drug within the class of biguanides in current use, and remains the preferred initial agent for T2DM based on a recent joint statement by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) as well as the American Association of Clinical Endocrinologists (AACE).^{9–11} Metformin was approved by the Food and Drug Administration (FDA) for use in the United States in 1994 for the treatment of T2DM in adults, with a pediatric indication for children older than 10 years. Concern about risk for lactic acidosis potentiated by decreased clearance of drug led to a black-box warning for use within specific populations including those with renal or hepatic impairment, acute congestive heart failure, sepsis, dehydration, and excessive alcohol intake. In addition, it is recommended that therapy be temporarily discontinued before the administration of intravascular radiocontrast agents or surgical procedures, because of the potential for dehydration and/or kidney injury.

Mechanism of action, efficacy, and kinetics—Metformin (Glucophage) reduces fasting plasma glucose and decreases hemoglobin A_{1c} (HbA_{1c}) by approximately 1.0%.^{12,13} Although the precise mechanism of action remains uncertain, the glycemic reducing effect of metformin is primarily attributed to inhibition of hepatic glucose production and, possibly, to improved peripheral insulin sensitivity.^{12,14,15} Theories for the antihyperglycemic action of metformin include inhibition of key enzymes in gluconeogenesis,^{15–18} direct action on the insulin receptor,¹⁹ or modulation of components of the incretin axis.²⁰ The mean $t_{1/2}$ of the standard formulation is 5 hours; a sustained-release once-daily formulation is also available. Metformin is excreted unchanged in the urine, and renal clearance is the primary form of elimination of the drug.²¹

Effects on weight, cardiovascular outcomes, and risk of lactic acidosis—In the DPP (Diabetes Prevention Program) study, 3234 participants from 27 clinics in the United States were enrolled between 1996 and 1999 and randomly assigned to metformin (n = 1073) or placebo (n = 1082) treatment. Participants randomized to metformin experienced an average weight loss of 2 kg²² that was maintained following a 7- to 8-year open-label extension.²³ Among patients with established T2DM, reported weight benefits of metformin monotherapy ranged from a 0.6- to 2.9-kg reduction in treatment-naïve patients followed for up to 5 years.²⁴ Combination treatment with metformin has been also observed to mitigate weight gain associated with other agents such as sulfonylurea or thiazolidinediones.^{12,24,25}

In the 1970s phenformin, an older member of the biguanide class, was removed from the market after 306 case reports of severe lactic acidosis in patients with congestive heart failure (CHF).²⁶ Subsequently, CHF was labeled as a contraindication to biguanide therapy in general, although the reported incidence with metformin therapy remained extremely low.^{27,28} In fact, among a nested case-control series of more than 50,000 patients with T2DM, overall incidence of lactic acidosis was rare, but occurred more often in those treated with sulfonylurea (4.8 cases per 100,000 patient-years of treatment) than those in the metformin group (3.3 cases per 100,000 patient-years of treatment).²⁹ In several large observational studies in the United States and United Kingdom of patients with CHF, treatment with

metformin had no documented events of lactic acidosis.^{26,28,30} A recent meta-analysis of more than 30 clinical trials confirmed the reduction of cardiovascular mortality by metformin in comparison with any other oral diabetes agent or placebo,^{31,32} suggesting that not only is metformin safe in this population, it is likely beneficial. In 2005, the FDA removed the CHF contraindication from the product labeling, although a cautionary black-box warning remains for the increased risk of lactic acidosis among patients with concurrent CHF.²⁶ Following the recent benefit-risk analysis there are calls for urgent reassessment of the relative contraindications of metformin use, given the paucity of data supporting the incidence of lactic acidosis and the likelihood of benefit on glucose control and mortality.³³

Effects on bone and other side effects—Animal studies indicate that metformin may have a positive effect on osteoblast differentiation and a negative effect on osteoclast differentiation and bone loss.⁶ Studies of the safety and efficacy of metformin monotherapy versus a rosiglitazone/metformin combination demonstrated improved glycemic control in the combination group but a significant reduction in lumbar bone mineral density (BMD) in comparison with the metformin monotherapy group.³⁴ Moreover, studies in rodent models have shown that coadministration of metformin and rosiglitazone mitigates the adverse effects of rosiglitazone on bone.³⁵ However, data on reduction of fracture risk in patients with T2DM treated with metformin have been inconsistent.⁶

In United States clinical trials approximately 4% of patients were unable to continue metformin because of adverse effects. The most common side effect of metformin is gastrointestinal (GI), which may be transient in nature and can often be avoided with gradual dose titration and taking the drug with meals.¹⁴ In the DPP trial, through year 4 of analysis GI symptoms were significantly more common among the metformin-treated than the placebo participants (28% vs 16%). Nonserious adverse events during the DPP were uncommon and similar in the treatment and placebo groups. There were no reported serious adverse events of lactic acidosis during the nearly 18,000 patient-years of follow-up.³⁶ Additional documented side effects of metformin are rare, but include taste disturbance, decreased absorption of vitamin B₁₂ (<1 in 10,000) and rashes.^{14,26} A favorable association between metformin and a lower risk of cancer among patients with T2DM has been observed. Investigation into the anticancer properties and underlying mechanism of this effect is an area of active ongoing research.^{37–40}

Thiazolidinediones

Indications and patient considerations—Pioglitazone (Actos) and rosiglitazone (Avandia) are thiazolidinedione (TZD) drugs approved by the FDA for the treatment of T2DM. Caution is advised for use with CHF (New York Heart Association [NYHA] class I or II), and both drugs are contraindicated in advanced CHF (NYHA class III or IV). Despite demonstrated glycemic efficacy and improved insulin sensitivity, because of troublesome side effects including weight gain and fluid retention, the ADA consensus statement favors metformin over TZD for first-line treatment of impaired glucose tolerance (IGT) or impaired fasting glucose (IFG).⁴¹

Mechanism of action, efficacy, and kinetics—The TZDs are synthetic ligands for peroxisome proliferative-activated receptor gamma (PPAR γ), and are potent insulin sensitizers in muscle, liver, and adipocytes.^{42–44} Rosiglitazone and pioglitazone bind to PPAR γ , modulate the transcription of insulin-sensitive genes involved in the control of glucose and lipid metabolism,²⁶ and may have important effects on β cells. Because TZDs both improve insulin sensitivity and preserve β -cell function, they are very effective at preventing progression of IGT to T2DM and maintaining durable HbA1c reduction.⁴⁵ TZDs are extensively metabolized in the liver by the cytochrome P450 enzyme CYP2C8 and are eliminated through the feces.^{46,47} Dose adjustment of TZDs is not required for geriatric patients, or those with renal or mild hepatic impairment. However, monitoring is recommended for patients with known hepatic toxicity (alanine aminotransferase 3 time the upper limit of the reference range) or those taking concurrent strong CYP2C8 inhibitors such as gemfibrozil.

Effects on weight and cardiovascular outcomes—Weight gain and fluid retention with associated edema are well-recognized side effects of TZDs.^{24,26,48–50} Initiation of TZD in the intensive treatment arm of the ACCORD trial has been described as a predominant medication-related determinant of weight gain. Patients who received combination therapy of TZD with insulin had a weight gain of 4.6 to 5.3 kg at 2 years.⁵¹ TZD-associated weight gain has been attributed to increased uptake of fatty acids and enhanced adipogenic capacity elicited by PPAR γ activation of white adipose tissue.⁴⁸

Within 2 years of approval by the FDA, reports of increased risk of heart failure associated with rosiglitazone began surfacing⁵² and by 2002, the FDA added a precaution regarding rosiglitazone-induced heart failure followed by a more stringent “restricted access program” designation in 2011 after a meta-analysis of 42 clinical trials that compared rosiglitazone with placebo, which found a statistically significant increased risk of myocardial infarction in the rosiglitazone-treated group.^{53,54} The FDA is scheduled to review a readjudication of the RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Diabetes) trial findings in June 2013.

Evidence for a strong association with heart failure appears to be a class effect of TZDs.^{55–57} However, in contrast to rosiglitazone, meta-analyses of pioglitazone suggest the possibility of ischemic cardiovascular benefit and overall reduction in mortality despite an increase in serious heart failure.⁵⁷ Systemic review and meta-analysis of 16 observational studies representing more than 800,000 TZD users reports that compared with pioglitazone, rosiglitazone is associated with a significantly increased risk of myocardial infarction (pooled odds ratio 1.2, 95% confidence interval [CI] 1.07–1.24), CHF (odds ratio 1.2, 95% CI 1.14–1.31) and overall mortality (odds ratio 1.1, 95% CI 1.09–1.20). The investigators calculate that the use of rosiglitazone would result in an annual number needed to harm (NNH) of 587 or an excess of 170 myocardial infarctions for every 100,000 patients who received rosiglitazone over pioglitazone. Use of rosiglitazone would result in an NNH of 154 for CHF, which equates to 649 excess cases for every 100,000 patients.⁵⁵

Effects on bone and other side effects—PPAR γ expression and the mechanism by which TZDs affect bone are complex and include antiosteoblastic, proadipocytic, and

proosteoclastic activities. Multiple clinical studies in patients with T2DM and polycystic ovarian syndrome, and in postmenopausal nondiabetic women indicate that both rosiglitazone and pioglitazone decrease BMD and change bone markers.⁶ Increased risk of fracture was demonstrated in posttrial analysis from ADOPT (A Diabetes Outcome Progression Trial).⁵⁸ The study was a randomized, double-blind controlled trial of 4600 individuals, designed to compare time to failure of monotherapy (defined as fasting plasma glucose >180 mg/dL) in prediabetic individuals randomly assigned to treatment with either rosiglitazone, metformin, or glyburide. Posttrial analysis of fracture rates, time to first fracture, and fracture location were analyzed after a median of 4 years of treatment. In men, there was no increased risk of fracture. However, among both premenopausal and postmenopausal women treated with rosiglitazone, the cumulative incidence of fractures was 15.1% (95% CI 11.2–19.1), whereas it was only 7.3% (95% CI 4.4–10.1) in the metformin group and 7.7% (95% CI 3.7–11.7) in the glyburide group, representing a hazard ratio of 1.8 versus 2.1 for rosiglitazone versus other therapies.⁵⁹ Subsequent meta-analysis of 10 randomized controlled trials and 2 observational studies, reflecting more than 40,000 participants, confirmed a 2-fold increased risk of fractures in women exposed to long-term TZD use, but not in men.⁶⁰ Other large-scale studies conducted in Canada, the United Kingdom, and the United States support that fracture risk is strongly associated with age and duration of TZD treatment, independent of gender. In summary, there is evidence that TZDs exert a negative effect on bone with increased risk of fracture in the following subpopulations: those with a history of prior fracture, longer duration of TZD treatment, older age, and, possibly, female predominance.⁶

Following conflicting reports, in 2012 a systematic review and meta-analysis was performed on the available studies that reported bladder cancer among adults taking either pioglitazone or rosiglitazone. In sum, a total of 3643 patients had newly diagnosed bladder cancer, for an overall incidence of 53.1 per 100,000 patient-years. All 5 studies assessing pioglitazone demonstrated an elevated risk of bladder cancer associated with pioglitazone use, whereas in the 3 studies reporting incidence of bladder cancer among rosiglitazone users, no association was found. The investigators concluded that based on a pooled estimate of 1.7 million individuals there is evidence of an increased risk of bladder cancer with pioglitazone but not with rosiglitazone.⁶¹

SECRETAGOGUES

Sulfonylureas and meglitinides, lower glucose levels by stimulating insulin secretion.

Sulfonylureas

Indications and patient considerations—Sulfonylureas are approved by the FDA for the treatment of T2DM in adults. In addition, clinical efficacy has been demonstrated in single-gene diabetes (HNF1A MODY) and permanent neonatal diabetes associated with the KCNJ11 and ABCC9 genes.⁶² Because of the risk for hypoglycemia, sulfonylureas should be used with caution in elderly, debilitated, or malnourished patients, or in patients with renal or hepatic insufficiency. In these patients the initial dosing, dose increments, and maintenance dosage should be conservative.

Mechanism of action, efficacy, and kinetics—Sulfonylureas stimulate the release of insulin secretion by binding to the sulfonylurea receptor (SUR-1), a component of the adenosine triphosphate (ATP)-sensitive potassium channel (K_{ATP}) expressed in the pancreatic β cells,⁶³ leading to calcium influx and increased responsiveness of β cells to glucose and nonglucose stimuli. These drugs lower HbA1c levels by 1% to 2%,⁶⁴ and their glycemic effect is dependent on residual β -cell function. Although the therapeutic mechanism of all sulfonylureas is similar, first-generation sulfonylureas, for example, tolbutamide (Oranase) and chlorpropamide (Diabinase), have significantly lower affinity for the SUR receptor than do second-generation sulfonylureas such as glyburide (Micronase), glipizide (Glucotrol), and glimepiride (Amaryl). This difference accounts for the greater potency and efficacy of the second-generation drugs. Most sulfonylureas are transformed by cytochrome P450 in the liver to inactive metabolites; thus, their circulatory levels can be affected by any factors modifying the cytochrome P450 system.⁶⁵ Renal excretion is important for 2 drugs in this category, glyburide and chlorpropamide, therefore they should be used with caution in patients with renal impairment.⁶⁶

Effects on weight and cardiovascular outcomes—Weight gain of 1.5 to 2.0 kg is common in the first year following initiation of sulfonylurea therapy, and typically levels off thereafter.^{2,67,68} At present, all sulfonylureas carry an FDA-required warning about the increased risk of cardiovascular death. This decision was based in part on findings from the UGDP (University Group Diabetes Program) trial, in which diabetic patients treated with tolbutamide, a first-generation sulfonylurea, experienced higher cardiovascular mortality compared with insulin or placebo.⁶⁹ However, findings from the UKPDS (United Kingdom Prospective Diabetes Study) did not reveal an increased risk of cardiovascular complications over 10 years of follow-up in patients with T2DM treated with sulfonylurea.^{2,70,71} Experimentally, sulfonylureas that bind to myocardial K_{ATP} channels have been shown to block the beneficial effects of ischemic preconditioning, which refers to a cardioprotective phenomenon recognized to reduce infarct size, augment postischemic function, and prevent arrhythmias.^{71,72} Newer sulfonylureas, such as gliclazide (Diamicron) or glimepiride, are exclusively pancreatic β -cell specific and might offer advantages over older agents. Among sulfonylurea-treated patients in a French registry of acute myocardial infarction, in-hospital mortality was significantly lower in patients receiving pancreatic cell-specific sulfonylureas (gliclazide or glimepiride) (2.7%), compared with glyburide (7.5%). Arrhythmias and ischemic complications were also markedly less frequent in patients receiving gliclazide/glimepiride (11% vs 18%).⁷³ Thus, tissue-specific effects of sulfonylureas may account for the apparent conflict of beneficial and deleterious cardiovascular outcomes reported in previous studies.

Effects on bone and other adverse effects—Results from ADOPT did not indicate adverse effects of these compounds on bone mass or fracture risk.⁵⁹ Beyond the most common side effects of hypoglycemia, other adverse effects include nausea, abdominal discomfort, headache, hypersensitivity, skin reactions (including photosensitivity), and abnormal liver function tests. Differential tissue specificity of particular sulfonylureas outside the pancreas could account for variability in complications related to these drugs. Unique to chlorpropamide is water retention and potential for hyponatremia mediated

through secretion of antidiuretic hormone.^{66,74} In addition, chlorpropamide can cause an unpleasant flushing reaction after alcohol ingestion by inhibiting the metabolism of acetaldehyde.⁷⁵

Meglitinides

Indications and patient considerations—Meglitinide analogues, nateglinide (Starlix) and repaglinide (Prandin), are approved for the treatment of T2DM in adults. Caution is recommended for moderate to severe hepatic impairment, and dose adjustment is indicated for creatinine clearance of less than 20 to 40 mL/min for repaglinide.

Mechanism of action, efficacy, and kinetics—Similar to sulfonylureas, meglitinides stimulate insulin release by inhibiting K_{ATP} channels, causing membrane depolarization, increased intracellular calcium, and insulin exocytosis. However, meglitinides have a distinct binding site of the β -cell membrane.⁷⁶ Although both drugs are rapid acting,⁷⁷ nateglinide dissociates from the receptor 90 times faster than repaglinide, indicating a very short on-and-off effect on insulin release. Nateglinide is hepatically cleared, with approximately 65% excreted in the bile and feces and 35% in the urine.⁷⁸ Repaglinide is metabolized by cytochrome P450 CYP3A4, with 90% excreted in bile and less than 10% in urine. Substances that inhibit CYP3A4 (eg, ketoconazole, steroids) may reduce repaglinide clearance, whereas drugs that induce CYP3A4 (eg, rifampin, carbamazepine) may accelerate repaglinide metabolism.⁷⁶ The efficacy of meglitinide monotherapy is similar to that of the sulfonylureas.^{79–81} Repaglinide reduces HbA1c values by 0.1% to 2.1%, and nateglinide reduces HbA1c values by 0.2% to 0.6%.⁸²

Effects on weight and cardiovascular outcomes—A Cochrane review of meglitinide analogues reports a range of weight gain from 0.7 to 2.1 kg across several trials.⁸² To date, there have been no reported significant differences in blood pressure or lipid profiles among patients treated with meglitinide.⁸³ Because the mechanism of action of meglitinides affects the ATP-dependent potassium channels, it is possible that meglitinide analogues may have an association with poorer outcomes following a myocardial infarction, similar to sulfonylureas⁷³; however, studies of long-term cardiovascular outcomes of meglitinides are lacking.

Other side effects or known complications of treatment—Similar to sulfonylureas, the most common side effect of meglitinides is mild hypoglycemia. Meglitinides have been associated with several other nonspecific side effects including dizziness, diarrhea, constipation, arthralgias, headache, and cough.^{82,84,85}

α -GLUCOSIDASE INHIBITORS

Indications and Patient Considerations

The α -glucosidase inhibitors (AGI), acarbose (Precose), miglitol (Glyset), and voglibose (Voglib), are indicated for treatment of adults with T2DM. The class is contraindicated in patients with cirrhosis, inflammatory bowel disease, colonic ulceration, intestinal obstruction, or predisposition to obstruction and diabetic ketoacidosis.

Mechanism of Action, Efficacy, and Kinetics

Relative to placebo, both acarbose and miglitol have demonstrated reduction of HbA1c to 0.5% to 0.8%.⁸⁶ AGIs lower glucose levels through reversible, competitive inhibition of pancreatic α -amylase and membrane-bound intestinal α -glucoside hydrolyases. These enzymes inhibit the conversion of complex polysaccharide carbohydrates into monosaccharides, which slows the absorption of glucose and improves postprandial glucose levels.⁸⁷ In addition, following treatment with voglibose there is a measureable increase of endogenous glucagon-like peptide⁸⁸ that may further facilitate glucose-lowering effects. Acarbose has a short $t_{1/2}$ of 2 hours; thus, to be effective it must be dosed at least 3 times daily with meals. Acarbose is metabolized within the GI tract by digestive enzymes and intestinal bacteria. The fraction that is absorbed intact is excreted by the kidneys. Therefore, use with renal impairment (creatinine clearance <25 mL/min) is not recommended for acarbose or miglitol because of the risk for increased plasma concentrations of the drug; however, voglibose is minimally excreted in the urine and therefore dose adjustment is not required. Elevated liver transaminases have been reported, and the package insert recommends reduced doses or withdrawal of treatment if abnormalities of liver enzymes develop.

Effects on Body Weight and Cardiovascular Outcomes

Meta-analysis of 41 randomized controlled trials and systematic review confirm that acarbose and miglitol are weight neutral.²⁴ The mode of action of acarbose is to diminish glucose and insulin response to meal ingestion; and lower insulin levels are proposed to explain weight neutrality.⁸⁹

Acarbose therapy has been shown to have a beneficial effect in comparison with placebo in preventing progression of an increase in carotid intimal wall thickness in patients with established coronary artery disease and either IGT or established T2DM,⁹⁰ as well as favorable effect on the level of low-density lipoprotein (LDL) and triglyceride.⁹¹ Cardiovascular outcomes were the primary end point of the multicenter, international, double-blind, randomized controlled STOP-NIDDM (Study to Prevent Non Insulin Dependent Diabetes Mellitus) trial, in which 1429 patients with IGT were randomized to either placebo or acarbose 100 mg 3 times daily, and followed for a mean of 3.3 years. At the end of the study, acarbose use was associated with 49% relative risk reduction in combined cardiovascular events (coronary heart disease, cardiovascular death, CHF, cerebrovascular event, peripheral vascular disease, and hypertension $>140/90$ mm Hg; hazard ratio [HR] 0.51, 95% CI 0.28%–0.95%; 2.5% absolute risk reduction). The major reduction was in the risk of myocardial infarction and development of hypertension.⁹²

Other Side Effects

Fermentation of an increased amount of undigested carbohydrate by bacteria in the colon accounts for the common observed side effects of abdominal pain, diarrhea, and flatulence.⁹¹ Incidence of GI side effects varies widely across international trials. In a surveillance study of 6142 patients in the United States, intolerance was 37%, compared with 13.4% of 27,803 patients from Germany and just 2% of 14,418 patients in China and other Asian countries enrolled in postmarketing studies. The difference may in part be due to dose and

titration schedules; however, given the mechanism of action it is likely that nutritional factors contribute as well. Diets higher in fiber are associated with a lower incidence of side effects. Incidence of side effects has been shown to be dose dependent, and slow titration of dose is recommended to limit the onset of unpleasant side effects.⁸⁹ Elevation of hepatic enzymes has been reported, as has one case of fulminant hepatitis with a fatal outcome. It is recommended to monitor patients with liver disease and to adjust dose or discontinue the dosing if necessary.

GLUCAGON-LIKE PEPTIDE 1-BASED DRUGS

Glucagon-like peptide 1 (GLP-1) is a gut hormone secreted in response to nutrient ingestion, which regulates postprandial glucose homeostasis. Once secreted into the circulation, GLP-1 is metabolized rapidly to inactive compounds by the action of ubiquitous enzyme dipeptidyl-peptidase 4 (DPP-4), leading to a plasma $t_{1/2}$ of 1 to 2 minutes.⁹³ Two classes of drugs in this category, GLP-1 receptor (GLP-1r) agonists and DPP-4 inhibitors, have been developed using strategies to bypass or block DPP-4 action, leading to compounds with half-lives longer than native GLP-1 or causing higher concentrations of native GLP-1 levels, respectively.

Indications and Patient Considerations

Exenatide (Byetta) was the first GLP-1r agonist to be approved in the United States in 2005, and sitagliptin (Januvia) the first DPP-4 inhibitor approved a year later. To date, liraglutide (Victoza) and exenatide long-acting release (LAR; Bydureon) from the class of GLP-1r agonists, and saxagliptin (Onglyza), linagliptin (Tadjenta), and alogliptin (Nesina) from the class of DPP-4 inhibitors, have been approved for the treatment of T2DM as an add-on to metformin, thiazolidinediones, sulfonylureas, and basal insulin, or a combination of these drugs. These drugs were recommended as second-line agents after metformin in the recent joint statement by the ADA/ESD⁹ because of the weight neutrality with DPP-4 inhibitors or weight loss with GLP-1r agonist therapy, as well as the lack of hypoglycemia with both classes of drugs. DPP-4 inhibitors, unlike the injectable GLP-1r agonists, are administered orally, which might be preferred by patients. Caution is advised for use with concurrent renal or hepatic impairment. GLP-1r agonists are contraindicated in patients with prior history of or current pancreatitis, and individual or family history of medullary thyroid cancer.

Mechanism of Action, Efficacy, and Kinetics

GLP-1 actions are mediated by binding to a specific GLP-1 receptor that is expressed on β cells, along with many other cells such as gastric and small intestinal mucosal cells, cardiac myocytes, neurons in some brain regions, and the vagus nerve.^{94,95} Administration of GLP-1 or GLP-1r agonists improves glycemia by enhancing insulin response,^{96,97} inhibiting glucagon release from pancreatic α cells,⁹⁶ delaying gastric emptying,^{98–100} inducing satiety,¹⁰¹ and lowering hepatic glucose production.¹⁰² The noninsulin effects of GLP-1 are equally essential in glycemic control, as GLP-1 infusion has been shown to normalize hyperglycemia in patients with type 1 diabetes mellitus (T1DM) and no residual β -cell function,^{103,104} even though the use of these compounds in T1DM has not been approved.

Although DPP-4 inhibitors share the insulin and glucagon effect of GLP-1r agonists, they have a trivial effect on gastric emptying.¹⁰⁵

Treatment with GLP-1r agonists leads to HbA1c reduction of 1.1% to 1.6% compared with 0.6% to 1.1% with DPP-4 inhibitors; the greatest efficacy on HbA1c and fasting plasma glucose among GLP-1r agonists was reported with long-acting agents, liraglutide (once a day) and exenatide LAR once weekly, in comparison with short-acting drugs (twice a day). Available GLP-1r agonists are excreted by the kidney; therefore, their use is not recommended in the setting of severe renal impairment. In patients with moderate renal impairment, short-acting exenatide can be used with careful optimization of the dose, but there are not enough data to support the use of long-acting GLP-1r agonists. In hepatic impairment, lack of data for the use of liraglutide limits its utility, but dose adjustment is not necessary for exenatide therapy. DPP-4 inhibitors and their metabolites have distinctive pharmacokinetic properties leading to drug-specific adverse effects in this class of drugs. Saxagliptin is excreted through renal and hepatic clearance mechanisms, whereas sitagliptin is excreted mainly through renal excretion. Therefore, dose adjustment is necessary in the setting of both moderate and severe renal impairment.^{106,107} By contrast, linagliptin is excreted mostly in feces through enterohepatic circulation, and requires no dose adjustment for renal impairment.^{106,108} Evidence regarding the use of DPP-4 inhibitors in severe hepatic failure is lacking.

Effects of Treatment on Weight and Cardiovascular Outcomes

GLP-1r agonist therapy results in a weight reduction of greater than 2 kg, whereas DPP-4 inhibitors are weight neutral.¹⁰⁹ Data on long-term effects of GLP-1 based drugs on cardiovascular outcomes are lacking, although these drugs may have beneficial effects on surrogate markers of cardiovascular disease. The evidence suggests that GLP-1r agonists improve systolic blood pressure^{110–112} as early as 2 weeks from initiation of treatment,¹¹³ indicating the weight-loss independence of this effect. Moreover, comparative studies of sitagliptin versus liraglutide or exenatide LAR therapy for 26 weeks have shown a greater effect on systolic and diastolic blood pressure as a result of sitagliptin treatment, whereas the effect on weight loss was trivial in comparison with GLP-1r agonist therapy.¹¹⁴ GLP-1r agonists also improve the levels of triglyceride and free fatty acid,¹¹⁵ although it is not clear whether this effect is weight independent. The evidence for antilipid effects of DPP-4 inhibitors is mixed, with neutral¹¹⁶ to favorable effects¹¹⁷ being reported on lipid profile with sitagliptin therapy.

Other Side Effects or Known Complications of Treatment

Because of glucose dependence of GLP-1 action on insulin secretion and glucagon suppression,¹¹⁸ hypoglycemia is not associated with treatment of GLP-1r agonists or DPP-4 inhibitors, unless these drugs are administered in combination with other insulin secretagogues or insulin without proper dose adjustment.^{117,119–123}

GI side effects, mainly nausea and vomiting, are the most common adverse effects associated with GLP-1r agonist therapy (30%–60%) and are the main cause for early termination of treatment with these drugs. However, nausea is mostly mild and dose

dependent, and wanes over time.^{119,120,124} Whereas nausea is less frequently reported with long-acting GLP-1r agonists compared with short-acting exenatide,^{115,125} diarrhea seems to be more frequent with long-acting agents.¹²⁵ DPP-4 inhibitors do not cause GI side effects seen with GLP-1r agonists.^{117,121–123}

The FDA has issued a warning about the potential risk of acute pancreatitis with the use of GLP-1–based drugs, given early postmarketing reports^{126,127} and findings from a recent population database study.¹²⁷ Although the causal relationship between pancreatitis and GLP-1–based drugs has not yet been established¹²⁸ and the number of cases reported with this condition is small, patients should be informed about the symptoms of acute pancreatitis, and therapy should be discontinued if these develop.

Long-acting GLP-1r agonists should also not be used in patients with any personal or family history of medullary thyroid cancer or multiple endocrine neoplasia type 2. Animal studies have suggested that liraglutide could increase the risk of C-cell hyperplasia and medullary thyroid cancer via activation of functional GLP-1rs that are expressed on thyroid C cells.^{129,130} It is noteworthy that these results were not replicated in the studies of nonhuman primates,¹³¹ nor did 2 years of treatment with liraglutide result in increased calcitonin levels.¹³¹

The wide expression of DPP-4 in different tissue cells, including T cells, has raised concerns about the potential adverse effects of DPP-4 inhibitors on immunomodulation and T-cell signaling, which need to be addressed in future studies.

AMYLIN ANALOGUES

Indications and Patient Considerations

Pramlintide (Symlin) is indicated for adjunctive use in both T1DM and T2DM in patients already taking prandial insulin. It is contraindicated in patients with a confirmed diagnosis of gastroparesis and hypoglycemia unawareness, owing to the increased risk of hypoglycemia. Dose titration is recommended, and prandial insulin doses should be reduced by 50% at the onset of therapy to limit the risk of hypoglycemia.

Mechanism of Action, Efficacy, and Kinetics

Amylin, also called islet amyloid polypeptide or diabetes-associated peptide, is produced by pancreatic β cells and is cosecreted with insulin in a 1:100 amylin/insulin ratio. Soluble amylin analogue, pramlintide acetate, is synergistic with insulin; that is, when given subcutaneously at mealtimes in combination with prandial insulin, pramlintide provides further reduction in postprandial hyperglycemia and concomitant reduction of glucagon levels in comparison with insulin monotherapy.¹³² Multiple daily dosing is required, as the $t_{1/2}$ is 48 minutes; metabolism is primarily via the kidneys. Amylin may further contribute to improved glucose levels via central anorectic effects, inhibition of ghrelin release, delayed gastric emptying, and reduced insulin dose requirements.^{133,134} A 1-year randomized controlled trial of pramlintide as adjunct to insulin therapy among patients with T1DM demonstrated reduction of HbA1c by 0.3% in the treated group compared with no change of HbA1c in the placebo group.¹³⁵

Effects of Treatment on Weight and Cardiovascular Outcomes

When pramlintide is added to basal insulin, no weight gain is observed.²⁴ In a dose-finding study with pramlintide added to a variety of insulin regimens, weight loss (−1.4 kg) was observed across the active treatment groups.¹³⁶ Pramlintide decreases the insulin requirement, thus the weight-neutral or weight-beneficial effects may be a result of the decreased weight-promoting effects of insulin. A modest and dose-dependent beneficial effect on lipid profiles has been observed in short-term studies.¹³⁷ There are no data on long-term cardiovascular outcome.

Other Side Effects

When compared with placebo, frequently reported side effects (>10% of patients) include mild to moderate hypoglycemia, nausea, vomiting, and anorexia during the first month of therapy.¹³⁸

SODIUM-GLUCOSE TRANSPORTER INHIBITORS

Indications and Patient Considerations

Sodium-glucose transporter 2 (SGLT2) inhibitors are a novel class of antidiabetes agents that exert glucose lowering primarily through effects on renal glucose handling. Several drugs in this class are in various stages of clinical development; canagliflozin (Invokana) is the first agent in this class to achieve a recent FDA approval for the treatment of T2DM. Use is contraindicated in severe renal impairment (glomerular filtration rate [GFR] <30 mL/min) or severe liver disease, and dose adjustment is advised for moderate renal impairment (GFR <45 mL/min). Monitoring for hypotension is recommended, particularly for elderly patients.

Mechanism of Action, Efficacy, and Kinetics

Under normal conditions, filtered glucose is actively reabsorbed by the sodium-glucose transporters SGLT1 and SGLT2 in the proximal tubule.¹³⁹ SGLT2 inhibitors reduce renal glucose reabsorption, resulting in increased excretion of urinary glucose and corresponding osmotic diuresis.¹⁴⁰ Completed trials of canagliflozin, dapagliflozin, and empagliflozin have demonstrated a mean reduction in HbA1c ranging from 6% to 0.9%.¹⁴¹ Patients treated for 26 weeks with canagliflozin demonstrated decreases in proinsulin/insulin and proinsulin/C-peptide ratios compared with placebo,¹³⁹ suggestive of some improvement in β -cell function. Canagliflozin is converted to inactive metabolites via *O*-glucuronidation in the liver, and excreted via feces and urine.

Effects of Treatment on Weight and Cardiovascular Outcomes

SGLT2 inhibitors have demonstrated a 2- to 3-kg weight loss in short-term (12 weeks' duration) trials.^{140–142} Fluid loss secondary to osmotic diuresis may account for early weight reduction; however, the glucose excreted in the urine as a result of SGLT2 inhibition equates to a loss of 200 to 300 calories daily,¹⁴⁰ which may provide ongoing beneficial effects on weight. A trial of dapagliflozin demonstrated a reduction in waist circumference¹⁴³ and sustained weight loss over 102 weeks when used in combination with metformin.¹⁴⁴ Reductions in systolic blood pressure up to 5 mm Hg have been described in

trials of canagliflozin¹³⁹ and dapagliflozin,¹⁴⁰ likely attributable to glycosuria-induced diuresis. A statistically significant dose-related decrease in high-density lipoprotein cholesterol was observed in the 26-week randomized controlled trial of canagliflozin,¹³⁹ with a trend toward lower triglycerides and LDL cholesterol. Data regarding cardiovascular outcomes for SGLT2 inhibitors are limited; however, a series of ongoing safety trials and the CANVAS (Canagliflozin Cardiovascular Assessment Study) are anticipated to provide additional evidence in the upcoming years.¹⁴¹

Other Side Effects

The predominant reported side effect of SGLT2 inhibitors to date are increased rates of mycotic infections (vulvovaginitis, balanitis) and, less commonly, urinary tract infections,^{139,141,144} presumably as a result of elevated urinary glucose levels.

EFFECTS ON β -CELL OUTCOMES

Once fasting hyperglycemia is detectable, β -cell function deteriorates progressively and contributes to further decline in the ability to maintain normal glycemic levels.^{145,146} Thus, preservation of β -cell function in the prediabetes state (IGT, IFG) and prevention of further loss of β -cell function once diabetes occurs is a critical aim of therapy and is an important factor for selection of antidiabetic treatment.

Despite initial beneficial therapeutic effects, metformin may not have long-term beneficial effects on β -cell function based on disease progression (failure of monotherapy to maintain goal HbA1c).⁴⁵ Sulfonylureas may have a negative effect on β -cell function, based on some in vitro studies showing that the closure of the ATP-dependent potassium channels by tolbutamide and glibenclamide may induce calcium-dependent β -cell apoptosis in rodent and human islets.^{79,81} TZDs and GLP-1-based drugs, on the other hand, may have a beneficial effect on β -cell function and may promote β -cell survival based on in vitro and animal studies.^{44,147,148} However, it is not known how much of these preclinical data could be translated to clinical outcomes given the current ability to measure β -cell mass directly in humans.

Comparative studies on the durability of glycemic reduction effects of various drugs have been used to provide information about the chronic effects of these agents on islet preservation, considering that the progressive nature of β -cell dysfunction requires a continuous intensification of treatment to maintain target glycemia. ADOPT¹⁴⁹ is the first randomized trial to compare the long-term effect of 3 conventional oral agents, glyburide, metformin, and rosiglitazone, on glucose control for a 4-year follow-up. The findings from this trial indicated that patients with early-stage T2DM receiving glyburide had the fastest decline in glycemic control and those assigned to rosiglitazone the slowest, with patients treated with metformin being somewhere in between.

Recently, findings from a randomized trial comparing the long-term effect on glucose control of adding short-acting exenatide or glimepiride to metformin therapy in approximately 10,000 patients with uncontrolled T2DM (average basal HbA1c 7.5%) showed that more patients in the glimepiride group than in the exenatide group (54% vs

41%) experienced treatment failure. In this study, the median time to inadequate glucose control and the need for alternative treatment was markedly shorter in those treated with sulfonylurea than in patients treated with a GLP-1r agonist (140 vs 180 weeks).¹⁵⁰ However, the largest risk reduction as a result of GLP-1r agonist therapy was observed in patients with higher baseline HbA1c level (>7.3%), who had the highest risk of treatment failure in general. Moreover, patients in the exenatide group had an average weight loss of 3 kg, which could contribute to treatment outcome.

Although these studies are not able to prove the beneficial effects of GLP-1-based drugs or TZDs on β -cell survival and β -cell expansion based on preclinical data, they raise the question as to whether treatment with these agents should be considered for prevention purposes, or should be initiated at an earlier stage of diabetes.

SUMMARY

T2DM is a progressive disease characterized by the need for additional antidiabetic treatments over time to maintain glycemic control at the target. A large body of evidence now supports the maintenance of glycemic control as a means of eliminating the microvascular complications of diabetes. Therefore, individualized therapy started at an earlier stage of disease, guided by the principle of “do not harm,” seems to be essential in the patient-centric, shared decision-making model of diabetes care. Long-term clinical outcome data are needed to address the differential disease-modifying effects of various antidiabetic drugs (Table 1).

REFERENCES

1. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993; 329(14):977–86. [PubMed: 8366922]
2. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998; 352(9131):837–53. [PubMed: 9742976]
3. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321(7258):405–12. [PubMed: 10938048]
4. Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008;359(15):1577–89. [PubMed: 18784090]
5. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008;358(24):2545–59. [PubMed: 18539917]
6. Lecka-Czernik B Safety of anti-diabetic therapies on bone. *Clin Rev Bone Miner Metab* 2013;11(1): 49–58. [PubMed: 23543908]
7. Giovannucci E, Harlan DM, Archer MC, et al. Diabetes and cancer: a consensus report. *Diabetes Care* 2010;33(7):1674–85. [PubMed: 20587728]
8. Larsson SC, Orsini N, Brismar K, et al. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 2006;49(12):2819–23. [PubMed: 17021919]
9. Nathan DM, Buse JB, Davidson MB, et al. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009;32(1): 193–203. [PubMed: 18945920]

10. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 2012;55(6):1577–96. [PubMed: 22526604]
11. Garber AJ, Abrahamson MJ, Barzilay JI, et al. AACE comprehensive diabetes management algorithm 2013. *Endocr Pract* 2013;19(2):327–36. [PubMed: 23598536]
12. DeFronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. *N Engl J Med* 1995;333(9):541–9. [PubMed: 7623902]
13. DeFronzo RA, Stonehouse AH, Han J, et al. Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med* 2010;27(3):309–17. [PubMed: 20536494]
14. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. *Ann Intern Med* 2002;137(1):25–33. [PubMed: 12093242]
15. Cusi K, Consoli A, DeFronzo RA. Metabolic effects of metformin on glucose and lactate metabolism in noninsulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 1996;81(11):4059–67. [PubMed: 8923861]
16. Dorella M, Giusto M, Da Tos V, et al. Improvement of insulin sensitivity by metformin treatment does not lower blood pressure of nonobese insulin-resistant hypertensive patients with normal glucose tolerance. *J Clin Endocrinol Metab* 1996;81(4):1568–74. [PubMed: 8636369]
17. Hundal RS, Krssak M, Dufour S, et al. Mechanism by which metformin reduces glucose production in type 2 diabetes. *Diabetes* 2000;49(12):2063–9. [PubMed: 11118008]
18. Natali A, Ferrannini E. Effects of metformin and thiazolidinediones on suppression of hepatic glucose production and stimulation of glucose uptake in type 2 diabetes: a systematic review. *Diabetologia* 2006;49(3):434–41. [PubMed: 16477438]
19. Gunton JE, Delhanty PJ, Takahashi S, et al. Metformin rapidly increases insulin receptor activation in human liver and signals preferentially through insulin-receptor substrate-2. *J Clin Endocrinol Metab* 2003;88(3):1323–32. [PubMed: 12629126]
20. Maida A, Lamont BJ, Cao X, et al. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor- α in mice. *Diabetologia* 2011;54(2):339–49. [PubMed: 20972533]
21. Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. *Clin Pharmacokinet* 2011;50(2):81–98. [PubMed: 21241070]
22. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346(6):393–403. [PubMed: 11832527]
23. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009;374(9702):1677–86. [PubMed: 19878986]
24. Meneghini LF, Orozco-Beltran D, Khunti K, et al. Weight beneficial treatments for type 2 diabetes. *J Clin Endocrinol Metab* 2011;96(11):3337–53. [PubMed: 21900381]
25. Phung OJ, Scholle JM, Talwar M, et al. Effect of noninsulin antidiabetic drugs added to metformin therapy on glycemic control, weight gain, and hypoglycemia in type 2 diabetes. *JAMA* 2010;303(14):1410–8. [PubMed: 20388897]
26. Wong AK, Struthers AD, Choy AM, et al. Insulin sensitization therapy and the heart: focus on metformin and thiazolidinediones. *Heart Fail Clin* 2012;8(4): 539–50. [PubMed: 22999238]
27. Salpeter SR, Greyber E, Pasternak GA, et al. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus: systematic review and meta-analysis. *Arch Intern Med* 2003;163(21):2594–602. [PubMed: 14638559]
28. Masoudi FA, Inzucchi SE, Wang Y, et al. Thiazolidinediones, metformin, and outcomes in older patients with diabetes and heart failure: an observational study. *Circulation* 2005;111(5):583–90. [PubMed: 15699279]

29. Bodmer M, Meier C, Krahenbuhl S, et al. Metformin, sulfonylureas, or other anti-diabetes drugs and the risk of lactic acidosis or hypoglycemia: a nested case-control analysis. *Diabetes Care* 2008;31(11):2086–91. [PubMed: 18782901]
30. Eurich DT, McAlister FA, Blackburn DF, et al. Benefits and harms of antidiabetic agents in patients with diabetes and heart failure: systematic review. *BMJ* 2007; 335(7618):497. [PubMed: 17761999]
31. Selvin E, Bolen S, Yeh HC, et al. Cardiovascular outcomes in trials of oral diabetes medications: a systematic review. *Arch Intern Med* 2008;168(19):2070–80. [PubMed: 18955635]
32. Lamanna C, Monami M, Marchionni N, et al. Effect of metformin on cardiovascular events and mortality: a meta-analysis of randomized clinical trials. *Diabetes Obes Metab* 2011;13(3):221–8. [PubMed: 21205121]
33. Scheen AJ, Paquot N. Metformin revisited: a critical review of the benefit-risk balance in at-risk patients with type 2 diabetes. *Diabetes Metab* 2013;39(3): 179–90. [PubMed: 23528671]
34. Borges JL, Bilezikian JP, Jones-Leone AR, et al. A randomized, parallel group, double-blind, multicentre study comparing the efficacy and safety of Avandamet (rosiglitazone/metformin) and metformin on long-term glycaemic control and bone mineral density after 80 weeks of treatment in drug-naïve type 2 diabetes mellitus patients. *Diabetes Obes Metab* 2011;13(11):1036–46. [PubMed: 21682834]
35. Sedlinsky C, Molinuevo MS, Cortizo AM, et al. Metformin prevents anti-osteogenic in vivo and ex vivo effects of rosiglitazone in rats. *Eur J Pharmacol* 2011;668(3):477–85. [PubMed: 21839072]
36. Diabetes Prevention Program Research Group. Long-term safety, tolerability, and weight loss associated with metformin in the Diabetes Prevention Program Outcomes Study. *Diabetes Care* 2012;35(4):731–7. [PubMed: 22442396]
37. Chung HH, Moon JS, Yoon JS, et al. The relationship between metformin and cancer in patients with Type 2 diabetes. *Diabetes Metab J* 2013;37(2):125–31. [PubMed: 23641353]
38. Bost F, Sahra IB, Le Marchand-Brustel Y, et al. Metformin and cancer therapy. *Curr Opin Oncol* 2012;24(1):103–8. [PubMed: 22123231]
39. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, et al. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010;9(5): 1092–9. [PubMed: 20442309]
40. Loubiere C, Dirat B, Tanti JF, et al. New perspectives for metformin in cancer therapy. *Ann Endocrinol (Paris)* 2013;74(2):130–6 [in French]. [PubMed: 23587351]
41. Nathan DM, Davidson MB, DeFronzo RA, et al. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007;30(3): 753–9. [PubMed: 17327355]
42. Molavi B, Rassouli N, Bagwe S, et al. A review of thiazolidinediones and metformin in the treatment of type 2 diabetes with focus on cardiovascular complications. *Vasc Health Risk Manag* 2007;3(6):967–73. [PubMed: 18200815]
43. Thiazolidinediones Yki-Jarvinen H. *N Engl J Med* 2004;351(11):1106–18. [PubMed: 15356308]
44. Gastaldelli A, Ferrannini E, Miyazaki Y, et al. Thiazolidinediones improve beta-cell function in type 2 diabetic patients. *Am J Physiol Endocrinol Metab* 2007; 292(3):E871–83. [PubMed: 17106061]
45. DeFronzo RA, Abdul-Ghani MA. Preservation of beta-cell function: the key to diabetes prevention. *J Clin Endocrinol Metab* 2011;96(8):2354–66. [PubMed: 21697254]
46. Budde K, Neumayer HH, Fritsche L, et al. The pharmacokinetics of pioglitazone in patients with impaired renal function. *Br J Clin Pharmacol* 2003; 55(4):368–74. [PubMed: 12680885]
47. Kirchheiner J, Thomas S, Bauer S, et al. Pharmacokinetics and pharmacodynamics of rosiglitazone in relation to CYP2C8 genotype. *Clin Pharmacol Ther* 2006;80(6):657–67. [PubMed: 17178266]
48. Ahmadian M, Suh JM, Hah N, et al. PPARgamma signaling and metabolism: the good, the bad and the future. *Nat Med* 2013;19(5):557–66. [PubMed: 23652116]
49. Tschöpe D, Hanefeld M, Meier JJ, et al. The role of co-morbidity in the selection of antidiabetic pharmacotherapy in type-2 diabetes. *Cardiovasc Diabetol* 2013; 12(1):62. [PubMed: 23574917]
50. Kung J, Henry RR. Thiazolidinedione safety. *Expert Opin Drug Saf* 2012;11(4): 565–79. [PubMed: 22616948]

51. Fonseca V, McDuffie R, Calles J, et al. Determinants of weight gain in the action to control cardiovascular risk in diabetes trial. *Diabetes Care* 2013 [Epub ahead of print].
52. Benbow A, Stewart M, Yeoman G. Thiazolidinediones for type 2 diabetes. All glitazones may exacerbate heart failure. *BMJ* 2001;322(7280):236.
53. Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N Engl J Med* 2007;356(24):2457–71. [PubMed: 17517853]
54. Khalaf KI, Taegtmeier H. After avandia: the use of antidiabetic drugs in patients with heart failure. *Tex Heart Inst J* 2012;39(2):174–8. [PubMed: 22740727]
55. Loke YK, Kwok CS, Singh S. Comparative cardiovascular effects of thiazolidinediones: systematic review and meta-analysis of observational studies. *BMJ* 2011;342:d1309. [PubMed: 21415101]
56. Singh S, Loke YK, Furberg CD. Thiazolidinediones and heart failure: a teleo-analysis. *Diabetes Care* 2007;30(8):2148–53. [PubMed: 17536074]
57. Lincoff AM, Wolski K, Nicholls SJ, et al. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA* 2007;298(10):1180–8. [PubMed: 17848652]
58. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. *N Engl J Med* 2006;355(23):2427–43. [PubMed: 17145742]
59. Kahn SE, Zinman B, Lachin JM, et al. Rosiglitazone-associated fractures in type 2 diabetes: an analysis from A Diabetes Outcome Progression Trial (ADOPT). *Diabetes Care* 2008;31(5):845–51. [PubMed: 18223031]
60. Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in type 2 diabetes: a meta-analysis. *CMAJ* 2009;180(1):32–9. [PubMed: 19073651]
61. Colmers IN, Bowker SL, Majumdar SR, et al. Use of thiazolidinediones and the risk of bladder cancer among people with type 2 diabetes: a meta-analysis. *CMAJ* 2012;184(12):E675–83. [PubMed: 22761478]
62. Klupa T, Skupien J, Malecki MT. Monogenic models: what have the single gene disorders taught us? *Curr Diab Rep* 2012;12(6):659–66. [PubMed: 22996131]
63. Aguilar-Bryan L, Nichols CG, Wechsler SW, et al. Cloning of the beta cell high-affinity sulfonylurea receptor: a regulator of insulin secretion. *Science* 1995; 268(5209):423–6. [PubMed: 7716547]
64. Hermann LS, Schersten B, Bitzen PO, et al. Therapeutic comparison of metformin and sulfonylurea, alone and in various combinations. A double-blind controlled study. *Diabetes Care* 1994;17(10):1100–9. [PubMed: 7821128]
65. Xu H, Murray M, McLachlan AJ. Influence of genetic polymorphisms on the pharmacokinetics and pharmacodynamics of sulfonylurea drugs. *Curr Drug Metab* 2009;10(6):643–58. [PubMed: 19799532]
66. Melander A Kinetics-effect relations of insulin-releasing drugs in patients with type 2 diabetes: brief overview. *Diabetes* 2004;53(Suppl 3):S151–5. [PubMed: 15561903]
67. Nathan DM, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2006;29(8):1963–72. [PubMed: 16873813]
68. Nichols GA, Gomez-Caminero A. Weight changes following the initiation of new anti-hyperglycaemic therapies. *Diabetes Obes Metab* 2007;9(1):96–102. [PubMed: 17199724]
69. Feinglos MN, Bethel MA. Therapy of type 2 diabetes, cardiovascular death, and the UGDP. *Am Heart J* 1999;138(5 Pt 1):S346–52. [PubMed: 10539796]
70. UKPDS 28: a randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Study Group *Diabetes Care* 1998;21(1):87–92.
71. Zarich SW. Does choice of antidiabetes therapy influence macrovascular outcomes? *Curr Diab Rep* 2010;10(1):24–31. [PubMed: 20425063]
72. Cleveland JC Jr, Meldrum DR, Cain BS, et al. Oral sulfonylurea hypoglycemic agents prevent ischemic preconditioning in human myocardium. Two paradoxes revisited. *Circulation* 1997;96(1):29–32. [PubMed: 9236412]

73. Zeller M, Danchin N, Simon D, et al. Impact of type of preadmission sulfonylureas on mortality and cardiovascular outcomes in diabetic patients with acute myocardial infarction. *J Clin Endocrinol Metab* 2010;95(11):4993–5002. [PubMed: 20702526]
74. Kadowaki T, Hagura R, Kajinuma H, et al. Chlorpropamide-induced hyponatremia: incidence and risk factors. *Diabetes Care* 1983;6(5):468–71. [PubMed: 6443808]
75. Groop L, Eriksson CJ, Huupponen R, et al. Roles of chlorpropamide, alcohol and acetaldehyde in determining the chlorpropamide-alcohol flush. *Diabetologia* 1984;26(1):34–8. [PubMed: 6706043]
76. Landgraf R Meglitinide analogues in the treatment of type 2 diabetes mellitus. *Drugs Aging* 2000;17(5):411–25. [PubMed: 11190420]
77. Dunning BE. New non-sulfonylurea insulin secretagogues. *Expert Opin Investig Drugs* 1997;6(8):1041–8.
78. Karara AH, Dunning BE, McLeod JF. The effect of food on the oral bioavailability and the pharmacodynamic actions of the insulinotropic agent nateglinide in healthy subjects. *J Clin Pharmacol* 1999;39(2):172–9. [PubMed: 11563410]
79. Wolffenbuttel BH, Landgraf R. A 1-year multicenter randomized double-blind comparison of repaglinide and glyburide for the treatment of type 2 diabetes. Dutch and German Repaglinide Study Group. *Diabetes Care* 1999;22(3):463–7. [PubMed: 10097930]
80. Hollander PA, Schwartz SL, Gatlin MR, et al. Importance of early insulin secretion: comparison of nateglinide and glyburide in previously diet-treated patients with type 2 diabetes. *Diabetes Care* 2001;24(6):983–8. [PubMed: 11375357]
81. Moses R, Slobodniuk R, Boyages S, et al. Effect of repaglinide addition to metformin monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 1999;22(1):119–24. [PubMed: 10333912]
82. Black C, Donnelly P, McIntyre L, et al. Meglitinide analogues for type 2 diabetes mellitus. *Cochrane Database Syst Rev* 2007;(2):CD004654. [PubMed: 17443551]
83. Eleftheriadou I, Grigoropoulou P, Katsilambros N, et al. The effects of medications used for the management of diabetes and obesity on postprandial lipid metabolism. *Curr Diabetes Rev* 2008;4(4):340–56. [PubMed: 18991602]
84. Horton ES, Foley JE, Shen SG, et al. Efficacy and tolerability of initial combination therapy with nateglinide and metformin in treatment-naïve patients with type 2 diabetes. *Curr Med Res Opin* 2004;20(6):883–9. [PubMed: 15200747]
85. Horton ES, Clinkingbeard C, Gatlin M, et al. Nateglinide alone and in combination with metformin improves glycemic control by reducing mealtime glucose levels in type 2 diabetes. *Diabetes Care* 2000;23(11):1660–5. [PubMed: 11092289]
86. van de Laar FA, Lucassen PL, Akkermans RP, et al. Alpha-glucosidase inhibitors for patients with type 2 diabetes: results from a Cochrane systematic review and meta-analysis. *Diabetes Care* 2005;28(1):154–63. [PubMed: 15616251]
87. Chiasson JL, Josse RG, Hunt JA, et al. The efficacy of acarbose in the treatment of patients with non-insulin-dependent diabetes mellitus. A multicenter controlled clinical trial. *Ann Intern Med* 1994;121(12):928–35. [PubMed: 7734015]
88. Goke B, Fuder H, Wieckhorst G, et al. Voglibose (AO-128) is an efficient alpha-glucosidase inhibitor and mobilizes the endogenous GLP-1 reserve. *Digestion* 1995;56(6):493–501. [PubMed: 8536820]
89. Rosak C, Mertes G. Critical evaluation of the role of acarbose in the treatment of diabetes: patient considerations. *Diabetes Metab Syndr Obes* 2012;5:357–67. [PubMed: 23093911]
90. Koyasu M, Ishii H, Watarai M, et al. Impact of acarbose on carotid intima-media thickness in patients with newly diagnosed impaired glucose tolerance or mild type 2 diabetes mellitus: a one-year, prospective, randomized, open-label, parallel-group study in Japanese adults with established coronary artery disease. *Clin Ther* 2010;32(9):1610–7. [PubMed: 20974318]
91. Derosa G, Maffioli P. Efficacy and safety profile evaluation of acarbose alone and in association with other antidiabetic drugs: a systematic review. *Clin Ther* 2012;34(6):1221–36. [PubMed: 22560622]

92. Chiasson JL, Josse RG, Gomis R, et al. Acarbose treatment and the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance: the STOP-NIDDM trial. *JAMA* 2003;290(4):486–94. [PubMed: 12876091]
93. Hansen L, Deacon CF, Orskov C, et al. Glucagon-like peptide-1-(7-36)amide is transformed to glucagon-like peptide-1-(9-36)amide by dipeptidyl peptidase IV in the capillaries supplying the L cells of the porcine intestine. *Endocrinology* 1999;140(11):5356–63. [PubMed: 10537167]
94. Bullock BP, Heller RS, Habener JF. Tissue distribution of messenger ribonucleic acid encoding the rat glucagon-like peptide-1 receptor. *Endocrinology* 1996; 137(7):2968–78. [PubMed: 8770921]
95. Nakagawa A, Satake H, Nakabayashi H, et al. Receptor gene expression of glucagon-like peptide-1, but not glucose-dependent insulinotropic polypeptide, in rat nodose ganglion cells. *Auton Neurosci* 2004;110(1):36–43. [PubMed: 14766323]
96. Schirra J, Nicolaus M, Roggel R, et al. Endogenous glucagon-like peptide 1 controls endocrine pancreatic secretion and antro-pyloro-duodenal motility in humans. *Gut* 2006;55(2):243–51. [PubMed: 15985560]
97. Salehi M, Vahl TP, D'Alessio DA. Regulation of islet hormone release and gastric emptying by endogenous glucagon-like peptide 1 after glucose ingestion. *J Clin Endocrinol Metab* 2008;93(12):4909–16. [PubMed: 18827000]
98. Nauck MA, Niedereichholz U, Ettl R, et al. Glucagon-like peptide 1 inhibition of gastric emptying outweighs its insulinotropic effects in healthy humans. *Am J Physiol* 1997;273(5 Pt 1):E981–8. [PubMed: 9374685]
99. Wettergren A, Schjoldager B, Mortensen PE, et al. Truncated GLP-1 (proglucagon 78-107-amide) inhibits gastric and pancreatic functions in man. *Dig Dis Sci* 1993;38(4):665–73. [PubMed: 8462365]
100. Meier JJ, Gallwitz B, Salmen S, et al. Normalization of glucose concentrations and deceleration of gastric emptying after solid meals during intravenous glucagon-like peptide 1 in patients with type 2 diabetes. *J Clin Endocrinol Metab* 2003;88(6):2719–25. [PubMed: 12788879]
101. Flint A, Raben A, Astrup A, et al. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. *J Clin Invest* 1998;101(3):515–20. [PubMed: 9449682]
102. Prigeon RL, Quddusi S, Paty B, et al. Suppression of glucose production by GLP-1 independent of islet hormones: a novel extrapancreatic effect. *Am J Physiol Endocrinol Metab* 2003;285(4):E701–7. [PubMed: 12773303]
103. Kielgast U, Holst JJ, Madsbad S. Antidiabetic actions of endogenous and exogenous GLP-1 in type 1 diabetic patients with and without residual beta-cell function. *Diabetes* 2011;60(5):1599–607. [PubMed: 21441444]
104. Creutzfeldt WO, Kleine N, Willms B, et al. Glucagonostatic actions and reduction of fasting hyperglycemia by exogenous glucagon-like peptide I(7-36) amide in type I diabetic patients. *Diabetes Care* 1996;19(6):580–6. [PubMed: 8725855]
105. Vella A, Bock G, Giesler PD, et al. Effects of dipeptidyl peptidase-4 inhibition on gastrointestinal function, meal appearance, and glucose metabolism in type 2 diabetes. *Diabetes* 2007;56(5):1475–80. [PubMed: 17303799]
106. Russell S. Incretin-based therapies for type 2 diabetes mellitus: a review of direct comparisons of efficacy, safety and patient satisfaction. *Int J Clin Pharm* 2013;35(2):159–72. [PubMed: 23263796]
107. Bergman AJ, Cote J, Yi B, et al. Effect of renal insufficiency on the pharmacokinetics of sitagliptin, a dipeptidyl peptidase-4 inhibitor. *Diabetes Care* 2007; 30(7):1862–4. [PubMed: 17468348]
108. Baetta R, Corsini A. Pharmacology of dipeptidyl peptidase-4 inhibitors: similarities and differences. *Drugs* 2011;71(11):1441–67. [PubMed: 21812507]
109. Aroda VR, Henry RR, Han J, et al. Efficacy of GLP-1 receptor agonists and DPP-4 inhibitors: meta-analysis and systematic review. *Clin Ther* 2012;34(6): 1247–1258.e22. [PubMed: 22608780]
110. Nauck MA, Duran S, Kim D, et al. A comparison of twice-daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylurea and metformin: a non-inferiority study. *Diabetologia* 2007;50(2):259–67. [PubMed: 17160407]

111. Diamant M, Van Gaal L, Stranks S, et al. Safety and efficacy of once-weekly exenatide compared with insulin glargine titrated to target in patients with type 2 diabetes over 84 weeks. *Diabetes Care* 2012;35(4):683–9. [PubMed: 22357185]
112. Bergenstal RM, Wysham C, Macconell L, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): a randomised trial. *Lancet* 2010; 376(9739):431–9. [PubMed: 20580422]
113. Gallwitz B, Vaag A, Falahati A, et al. Adding liraglutide to oral antidiabetic drug therapy: onset of treatment effects over time. *Int J Clin Pract* 2010;64(2):267–76. [PubMed: 19925617]
114. Pratley RE, Nauck M, Bailey T, et al. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. *Lancet* 2010; 375(9724):1447–56. [PubMed: 20417856]
115. Buse JB, Rosenstock J, Sesti G, et al. Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *Lancet* 2009;374(9683):39–47. [PubMed: 19515413]
116. Aschner P, Kipnes MS, Luncford JK, et al. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. *Diabetes Care* 2006;29(12):2632–7. [PubMed: 17130196]
117. Charbonnel B, Karasik A, Liu J, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. *Diabetes Care* 2006;29(12):2638–43. [PubMed: 17130197]
118. Nauck MA, Heimesaat MM, Behle K, et al. Effects of glucagon-like peptide 1 on counterregulatory hormone responses, cognitive functions, and insulin secretion during hyperinsulinemic, stepped hypoglycemic clamp experiments in healthy volunteers. *J Clin Endocrinol Metab* 2002;87(3):1239–46. [PubMed: 11889194]
119. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type 2 diabetes. *Diabetes Care* 2004;27(11):2628–35. [PubMed: 15504997]
120. Kendall DM, Riddle MC, Rosenstock J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care* 2005;28(5):1083–91. [PubMed: 15855571]
121. Raz I, Hanefeld M, Xu L, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. *Diabetologia* 2006;49(11):2564–71. [PubMed: 17001471]
122. DeFronzo RA, Hissa MN, Garber AJ, et al. The efficacy and safety of saxagliptin when added to metformin therapy in patients with inadequately controlled type 2 diabetes with metformin alone. *Diabetes Care* 2009;32(9):1649–55. [PubMed: 19478198]
123. Del Prato S, Barnett AH, Huisman H, et al. Effect of linagliptin monotherapy on glycaemic control and markers of beta-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *Diabetes Obes Metab* 2011;13(3):258–67. [PubMed: 21205122]
124. DeFronzo RA, Ratner RE, Han J, et al. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with type 2 diabetes. *Diabetes Care* 2005;28(5):1092–100. [PubMed: 15855572]
125. Drucker DJ, Buse JB, Taylor K, et al. Exenatide once weekly versus twice daily for the treatment of type 2 diabetes: a randomised, open-label, non-inferiority study. *Lancet* 2008;372(9645):1240–50. [PubMed: 18782641]
126. Elashoff M, Matveyenko AV, Gier B, et al. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 2011; 141(1):150–6. [PubMed: 21334333]
127. Singh S, Chang HY, Richards TM, et al. Glucagonlike peptide 1-based therapies and risk of hospitalization for acute pancreatitis in type 2 diabetes mellitus: a population-based matched case-control study. *JAMA Intern Med* 2013;173(7):534–9. [PubMed: 23440284]
128. Garg R, Chen W, Pendergrass M. Acute pancreatitis in type 2 diabetes treated with exenatide or sitagliptin: a retrospective observational pharmacy claims analysis. *Diabetes Care* 2010;33(11):2349–54. [PubMed: 20682680]

129. Crespel A, De Boissvilliers F, Gros L, et al. Effects of glucagon and glucagon-like peptide-1-(7-36) amide on C cells from rat thyroid and medullary thyroid carcinoma CA-77 cell line. *Endocrinology* 1996;137(9):3674–80. [PubMed: 8756532]
130. Butler PC, Elashoff M, Elashoff R, et al. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care* 2013; 36(7):2118–25 [PubMed: 23645885]
131. Bjerre Knudsen L, Madsen LW, Andersen S, et al. Glucagon-like peptide-1 receptor agonists activate rodent thyroid C-cells causing calcitonin release and C-cell proliferation. *Endocrinology* 2010;151(4):1473–86. [PubMed: 20203154]
132. Adeghate E, Kalasz H. Amylin analogues in the treatment of diabetes mellitus: medicinal chemistry and structural basis of its function. *Open Med Chem J* 2011;5(Suppl 2):78–81. [PubMed: 21966328]
133. Young A Inhibition of food intake. *Adv Pharmacol* 2005;52:79–98. [PubMed: 16492542]
134. Fineman M, Weyer C, Maggs DG, et al. The human amylin analog, pramlintide, reduces postprandial hyperglucagonemia in patients with type 2 diabetes mellitus. *Horm Metab Res* 2002;34(9):504–8. [PubMed: 12384827]
135. Ratner RE, Dickey R, Fineman M, et al. Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabet Med* 2004;21(11):1204–12. [PubMed: 15498087]
136. Hollander PA, Levy P, Fineman MS, et al. Pramlintide as an adjunct to insulin therapy improves long-term glycemic and weight control in patients with type 2 diabetes: a 1-year randomized controlled trial. *Diabetes Care* 2003;26(3):784–90. [PubMed: 12610038]
137. Thompson RG, Pearson L, Schoenfeld SL, et al. Pramlintide, a synthetic analog of human amylin, improves the metabolic profile of patients with type 2 diabetes using insulin. The Pramlintide in Type 2 Diabetes Group. *Diabetes Care* 1998; 21(6):987–93. [PubMed: 9614619]
138. Singh-Franco D, Robles G, Gazze D. Pramlintide acetate injection for the treatment of type 1 and type 2 diabetes mellitus. *Clin Ther* 2007;29(4):535–62. [PubMed: 17617279]
139. Stenlof K, Cefalu WT, Kim KA, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. *Diabetes Obes Metab* 2013;15(4):372–82. [PubMed: 23279307]
140. List JF, Woo V, Morales E, et al. Sodium-glucose cotransport inhibition with dapagliflozin in type 2 diabetes. *Diabetes Care* 2009;32(4):650–7. [PubMed: 19114612]
141. Foote C, Perkovic V, Neal B. Effects of SGLT2 inhibitors on cardiovascular outcomes. *Diab Vasc Dis Res* 2012;9(2):117–23. [PubMed: 22381403]
142. Ferrannini E, Seman LJ, Seewaldt-Becker L, et al. The potent and highly selective sodium-glucose co-transporter (SGLT-2) inhibitor BI 10773 is safe and efficacious as monotherapy in patients with type 2 diabetes mellitus [abstract]. *Diabetologia* 2010;53(Suppl 2):877.
143. Bailey CJ, Gross JL, Pieters A, et al. Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial. *Lancet* 2010;375(9733):2223–33. [PubMed: 20609968]
144. Bailey CJ, Gross JL, Hennicken D, et al. Dapagliflozin add-on to metformin in type 2 diabetes inadequately controlled with metformin: a randomized, double-blind, placebo-controlled 102-week trial. *BMC Med* 2013;11:43. [PubMed: 23425012]
145. Turner RC, Cull CA, Frighi V, et al. Glycemic control with diet, sulfonylurea, metformin, or insulin in patients with type 2 diabetes mellitus: progressive requirement for multiple therapies (UKPDS 49). UK Prospective Diabetes Study (UKPDS) Group. *JAMA* 1999;281(21):2005–12. [PubMed: 10359389]
146. Levy J, Atkinson AB, Bell PM, et al. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year follow-up of the Belfast Diet Study. *Diabet Med* 1998;15(4):290–6. [PubMed: 9585393]
147. Farilla L, Bulotta A, Hirshberg B, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 2003;144(12):5149–58. [PubMed: 12960095]

148. Farilla L, Hui H, Bertolotto C, et al. Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. *Endocrinology* 2002; 143(11):4397–408. [PubMed: 12399437]
149. Viberti G, Kahn SE, Greene DA, et al. A diabetes outcome progression trial (ADOPT): an international multicenter study of the comparative efficacy of rosiglitazone, glyburide, and metformin in recently diagnosed type 2 diabetes. *Diabetes Care* 2002;25(10):1737–43. [PubMed: 12351470]
150. Gallwitz B, Guzman J, Dotta F, et al. Exenatide twice daily versus glimepiride for prevention of glycaemic deterioration in patients with type 2 diabetes with metformin failure (EUREXA): an open-label, randomised controlled trial. *Lancet* 2012;379(9833):2270–8. [PubMed: 22683137]

KEY POINTS

- The increasing incidence of diabetes over the last few decades, along with the increased pace of new antidiabetic drug development, calls for a better understanding of the efficacy, mechanism of action, and safety of these drugs.
- Current strategies for the treatment of type 2 diabetes mellitus promote the achievement of target glucose levels to minimize microvascular and macrovascular complications.
- Maintaining the glycemic control over time is a significant challenge, owing to the progressive nature of diabetes as a result of declining β -cell function.
- Given the chronic nature of diabetes management, efficacy must be balanced against side effects to achieve a tolerable long-term regimen.
- Individualized therapy started at an earlier stage of disease guided by the principle of “do not harm” seems to be essential in the patient-centric, shared decision-making model of diabetes care.

Table 1

Comparison of diabetes treatment complications and therapeutic considerations

Medication Class Examples	Dose-Adjustment Considerations	Weight Effect	CV Effects	Bone Effect	Association with Cancer	Pregnancy Category
Biguanide Metformin	Renal insufficiency Hepatic insufficiency	Neutral or loss	Neutral or possible benefit on lipid profile and CV outcomes	Neutral or possible benefit	Possible beneficial effects	B
Thiazolidinedione Rosiglitazone Pioglitazone	Caution: CHF (class I and II) Contraindication: CHF (class III and IV); concurrent use of CYP2C8 inhibitors	Gain and edema	Increased risk of CHF; rosiglitazone associated with higher risk of ischemia and CV mortality	Negative impact on BMD; increased fracture risk in select populations	Pioglitazone associated with increased risk of bladder cancer	C
Sulfonylurea Chlorpropamide, tolbutamide Glyburide, glipizide, glimepiride	Renal insufficiency (chlorpropamide, glyburide) Hepatic insufficiency Elderly or malnourished	Neutral or gain	Increased risk of CV death following myocardial infarction	No effect	Unknown	C (glyburide, class B)
Meglitinide analogues Nateglinide Repaglinide	Renal insufficiency Hepatic insufficiency Concomitant use with gemfibrozil (repaglinide) Monitor with concurrent CYP3A4 metabolized medications	Neutral or gain	No change in lipids or blood pressure	Unknown	Unknown	C
α -Glucosidase inhibitors Acarbose Miglitol Voglibose	Renal insufficiency (acarbose, miglitol) Hepatic insufficiency Contraindication: cirrhosis, inflammatory bowel disease, colonic ulceration or obstruction	Neutral	Risk reduction for myocardial infarction and hypertension	Unknown	Unknown	B
GLP-1r agonist Exenatide Liraglutide	Renal insufficiency (long-acting exenatide) Hepatic insufficiency (liraglutide) Contraindicated with prior pancreatitis	Loss or neutral	Beneficial, improves blood pressure and lipid profiles	No effect	Black-box warning for personal or family history of medullary thyroid cancer or MEN 2	C
DPP-4 analogues Saxagliptin Linagliptin Alogliptin	Renal insufficiency (saxagliptin, alogliptin) Hepatic insufficiency	Neutral	Neutral, possible beneficial effects on lipid profiles	Decreased fractures	Unknown	B
Amylin analogues Pramlintide	Reduce prandial insulin	Neutral or loss	Possible beneficial effect on lipid profiles	Unknown	Unknown	C
SGLT2 inhibitors Canagliflozin	Renal insufficiency Hepatic insufficiency	Loss or neutral	Beneficial effects on systolic blood pressure	Unknown	Unknown	C

Abbreviations: BMD, bone mineral density; CHF, congestive heart failure; CV, cardiovascular; MEN 2, multiple endocrine neoplasia type 2.