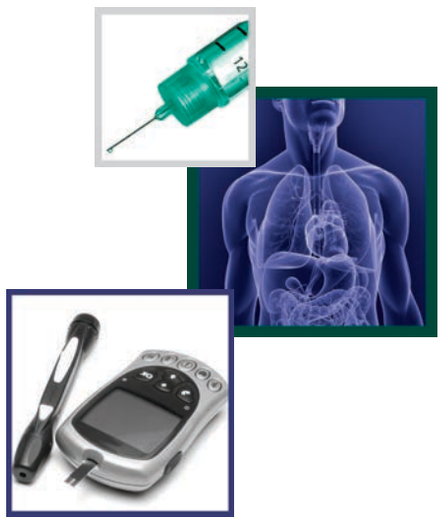
REVIEW



The 'collateral benefits' of noninsulin therapies for Type 2 diabetes

Erin D Roe[1], Natalie C Pon[2], Priscilla Hollander[3] & Philip Raskin*[4]

Practice Points

- Newer noninsulin agents to treat Type 2 diabetes offer more options for treatment intensification.
- Recent guidelines continue to emphasize a stepwise approach after metformin monotherapy is exhausted.
- When efficacy is essentially equivalent between agents, the 'collateral' effects of noninsulin agents can help clinicians craft diabetic treatments to suit patients' needs and comorbid conditions.
- Concerns about possible detrimental cardiovascular effects from sulfonylureas and thiazolidiones make incretin-based therapies (DPP-4 inhibitors and GLP-1 mimetics) more attractive in patients with risk factors.
- Thiazolidinediones increase fluid retention, which may promote decompensated congestive heart failure and diabetic macular edema in at-risk patients.
- In women with polycystic ovarian syndrome, metformin improves ovulation rates, hyperandrogenemia and hirsutism, but is generally less efficacious in achieving pregnancy compared with ovarian stimulation with clomiphene.
- Long-term use of pioglitazone has been linked to increased risk of bladder cancer in epidemiological studies; however, the mechanism remains unknown. Pancreatic cancer, meanwhile, has not been definitively linked with the use of exenatide or sitagliptin. Finally, thyroid C-cell hyperplasia and metaplasia have been observed in rodents treated with liraglutide; however, increased rates of medullary thyroid cancer have not been detected in patients treated with GLP-1 mimetics.

SUMMARY The increasing availability of non-insulin-based pharmacological therapy for Type 2 diabetes permits clinicians greater flexibility to design treatment regimens that suit individual patients' needs. Often, patients with Type 2 diabetes carry multiple comorbidities related to insulin resistance and inadequate diabetic control, which predispose to the

[1]Baylor Endocrine Center, Baylor University Medical Center, 3600 Gaston Avenue, Wadley Tower Suite 656, Dallas, TX 75246, USA
[2]University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9006, USA
[3]Baylor Endocrine Center, Baylor University Medical Center, 3600 Gaston Avenue, Wadley Tower Suite 656, Dallas, TX 75246, USA
[4]Department of Internal Medicine, University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-8858, USA
*Author for correspondence: Tel.: +1 214 648 2017; Fax: +1 214 648 4854; philip.raskin@utsouthwestern.edu

Future Medicine part of fsg

development of further complications. Currently, drug treatment effects on body weight and cardiovascular risk reduction factor most heavily in drug selection. However, more data are needed on off-target treatment effects, which can affect reproductive function, bone mineral density, retinopathy and potential cancer risk. This review outlines factors apart from glycemic control that may influence drug selection of secondary diabetes agents.

Diabetes treatment guidelines continue to advocate for metformin as the first-line agent for treatment of Type 2 diabetes [1,2]. However, in the most recent guidelines issued by the American Diabetes Association and the European Association for the Study of Diabetes, less prescriptive recommendations were offered for the secondary and tertiary agents to be employed once metformin monotherapy fails. Given that Type 2 diabetes is a progressive disease, most patients will eventually require multiple agents to maintain target glycemic levels.

For clinicians and patients, selecting secondary and tertiary agents requires consideration of the 'collateral' detrimental and beneficial effects. Common adverse side effects such as nausea may reduce food intake and provoke unintentional weight loss. Dyspepsia, meanwhile, may cause some patients to overeat to relieve discomfort, leading to unintentional weight gain. When treating Type 2 diabetes, the impact on body weight is the most significant day-to-day considerations for patients and clinicians.

Several sources acknowledge the urgent need for high-quality, comparative effectiveness research to guide diabetes treatment selection [1,2]. Patients may also hold strong feelings regarding their diabetes medications based upon material read online, or gleaned from friends, family and the experience of fellow patients. Unfortunately, the inertia to initiate insulin therapy persists both on the part of clinicians and patients [3]. Such inertia delays the steps necessary for treatment intensification and relaxes treatment goals in the name of 'individualization' when, in reality, perceived patient resistance to increasing doses or additional agents may be the underlying issue. Thus, knowledge of noninsulin therapies that can 'buy time' while preparing patients for the likelihood of insulin treatment can be particularly useful. Additionally, knowledge of the nonglycemic benefits of these oral and injectable diabetes agents factor into the decision-making process.

The addition of each non-insulin-based drug that affects glucose through different therapeutic mechanisms provides incremental improvements in overall diabetic control. Several oral agents (metformin and thiazolidinediones [TZDs]) lower exogenous insulin requirements. Novel GLP-1-based therapies, including those that work through DPP-4 inhibition, employ alternate pathways to affect diabetes progression.

The majority of non-insulin-based diabetes treatments have been approved for use in the USA in the past 15 years [2]. A summary of these agents is given in **Table 1**. For primary information on the drugs' dosing, metabolism, efficacy, side effects and interactions, we refer the reader to several excellent print and online resources [4,201]. Instead, this article examines the collateral effects of non-insulin-based therapies, with attention to insulin sensitivity, pancreatic function, body weight and composition, as well as the impacts on lipid metabolism, cardiovascular health, bone density, sex hormone and reproductive function, and potential cancer development. In the absence of major differences in HbA1c-lowering capability, these secondary effects take on increased importance during clinical decision-making.

Insulin sensitivity & β-cell preservation

Type 2 diabetes is characterized by a progressive decline in pancreatic β-cell mass and decrease in insulin secretory capacity. Comorbid obesity in Type 2 diabetes increases the insulin requirement necessary for adequate glucose disposal. Moreover, ectopic fat deposition in skeletal muscle, pancreas and liver raises insulin resistance. This mismatch between diminished endogenous insulin production in the midst of a mounting insulin requirement underlies the inevitable deterioration of glycemic control in Type 2 diabetes and the need for treatment intensification with exogenous insulin as the time from initial diagnosis increases [5]. Noninsulin treatments, as well as dietary modification, exercise and moderate weight loss, can slow the deterioration of glycemic control, maximize the effectiveness of native insulin and delay the need for exogenous insulin therapy by preserving β-cell function [6]. Meanwhile, for patients already on insulin treatment, these

Table 1. Overview of oral or injectable therapies approved for type Type 2 diabetes.

Drug class	USA regulatory approval (year)	Effect/mechanism
Biguanides (metformin)	1994	Inhibits hepatic glucose output and increases glucose uptake by skeletal muscle and fat Increases fatty acid oxidation Decreases gastrointestinal glucose absorption
Sulfonylureas (glyburide and glipizide)	1984	Binds to ATP-dependent K^+ channels on the cell membrane of pancreatic β-cells, promoting insulin secretion
Meglitinides (nateglinide, repaglinide and mitiglinide)	1997	Binds to ATP-dependent K^+ channels on the cell membrane of pancreatic β-cells, similar to sulfonylureas, increasing endogenous insulin release
Thiazolidinediones (rosiglitazone and pioglitazone)	1999	Activates PPAR-δ nuclear receptors that enhance peripheral insulin sensitivity Facilitates insulin-mediated glucose uptake and utilization
GLP-1 agonists/incretin mimetics (exenatide, once-weekly exenatide and liraglutide)	2005	Stimulates gastrointestinal GLP-1 receptors to increase glucose-dependent insulin release and reduce postprandial hyperglucagonemia Delays gastric emptying to facilitate weight loss
DPP-4 inhibitors (sitagliptin, saxaglipitin, linagliptin and vildaglipitin)	2006	Inhibits the enzyme that degrades GLP-1 and GIP, indirectly promoting postprandial insulin release and reducing postprandial glucagon secretion
Glucosidase inhibitors (acarbose, miglitol and voglibose)	1995	Pseudotetrasaccharide structure permits binding and subsequent inhibition of enzymatic activity of α-glucosidase located on the brush border of the small intestine. Inhibition of α-glucosidase prevents conversion of polysaccharides into digestible monosaccharides causing increased amounts of fermentable carbohydrates to reach the distal colon Glucose absorption is slowed and postprandial glucose excursions are attenuated
Bromocriptine-QR	2009	Immediate-release formulation that increases early morning hypothalamic dopaminergic tone, which reduces hepatic glucose output, lipolysis and sympathetic tone. Peripheral insulin resistance is reduced
Colesevelam	2008	Bile acid sequestrant that depletes hepatic lipid reserve, upregulating the hepatic enzyme, cholesterol 7-α-hydroxylase. LDL-cholesterol clearance is increased and serum triglyceride levels may increase or remain unchanged. Mechanism for blood glucose lowering is still not entirely understood

agents can reduce insulin requirements. A summary of adjunctive diabetic agents that influence insulin sensitivity and β-cell function are given in **Table 2**.

Metformin, which has been used in Europe and Canada for over 50 years, and was approved for use in the USA in 1994, reduces insulin resistance by inhibiting hepatic glucose output and increasing glucose uptake by skeletal muscle and fat [7]. Lower circulating glucose levels improve the effects of native insulin and reduce hyperinsulinemia [8]. Additional insulin-sensitizing properties are derived from increased fatty acid oxidation [9] and decreased gastrointestinal glucose absorption [8]. It has been previously reported that combining metformin with insulin reduces insulin requirements by 27% [10]. Unlike its biguanide predecessor, phenformin, which was withdrawn from the market in the 1970s due to unacceptably high rates of lactic acidosis, metformin is considerably safer, although use with diminished renal function (males with serum creatinine levels over 1.5 mg/dl or females over 1.4 mg/dl) is associated with an increased likelihood of developing this potentially fatal side effect.

Metformin also selectively increases the incretin hormone GLP-1 in a non-glucose-dependent manner in animal studies [11], but does not appear to do this through direct stimulation of the gastrointestinal L cells that produce GLP-1 *per se* [12,13]. One theory is that metformin may increase bile acid secretion in the intestine, which stimulates bile acid receptor GPBA (TGR5) on L-cell receptors to increase GLP-1 secretion. It has been proposed that metformin may have some DPP-4-inhibiting properties. However, *in vitro* studies have disproven the hypothesis that metformin lowers DPP-4 activity directly [14–16]. Ultimately, however, metformin confers additive glycemic benefit when combined with DPP-4 agents [12].

In addition to direct glycemic effects, metformin may implicitly slow β-cell deterioration

Table 2. Oral and injectable noninsulin therapies that affect insulin sensitivity and β-cell function.

Drug class	Effect/mechanism
Biguanides (metformin)	Delays need for insulin therapy Insulin sensitizer
Insulin secretagogues	May speed-up β-cell deterioration Lower treatment durability relative to other agents
Thiazolidinediones	Slows deterioration of β-cell function more than metformin or sulfonylureas
Incretin mimetics	Protects and promotes β-cell function
DPP-4 inhibitors	Promotes postprandial insulin release May increase β-cell function

by reducing insulin demand. This was indirectly supported in the Diabetes Prevention Program, which randomized 3234 adults with prediabetes/impaired glucose tolerance (IGT) to either metformin 850 mg twice daily, intensive lifestyle modification (goal of 7% weight reduction) or combined treatment [17]. Over a median of 2.8 years, the placebo-subtracted reduction in incident diabetes was 31% (95% CI: 17–34) with metformin, 58% (95% CI: 48–66) with intensive lifestyle changes and 31% (95% CI: 24–51) with combined therapy [18]. While β-cell mass was not directly assessed in this clinical study, the results support the notion that metformin has certain disease-modifying properties, and when added early in the course of diabetes, may delay the need for insulin. Although metformin is not specifically approved for diabetes prevention, it has been shown to decrease conversion to overt diabetes in high-risk patients, as measured by improvements to fasting blood sugar, fasting insulin, BMI and lipids [19]. While lifestyle modification is more effective compared with pharmacologic therapy, it may prove difficult to achieve and provide less durable glycemic control over time.

Insulin secretagogues (sulfonylureas [SUs], e.g., glyburide and glimepiride; and meglitinides, e.g., repaglinide and nateglinide) stimulate β-cell insulin secretion in the fasting and fed states to reduce glycemia. High-glucose states (above 130 mg/dl) impair β-cell function and insulin secretion, which perpetuates hyperglycemia. Combating this acute 'glucotoxicity' enables insulin to work more effectively, enhancing insulin secretion and insulin-mediated glucose uptake. SUs may, therefore, accelerate β-cell deterioration and overall disease trajectory by necessitating the addition of exogeneous insulin therapy earlier. Combining SU and insulin therapy is generally not recommended. Once insulin demand exceeds the endogenous insulin reserve, SUs and meglitinides are ineffective, and treatment should be consolidated to insulin in combination with oral insulin sensitizers or incretin mimetics that utilize nonsecretagogue pathways [20].

Depletion of β-cell insulin secretory capacity with SUs may lower treatment durability over time compared with metformin and TZDs. The largest and longest study of Type 2 diabetes, the UK Prospective Diabetes Study (UKPDS), followed 5102 patients for a median of 10 years across 23 centers in the UK to determine whether intensive insulin treatment reduced cardiovascular and microvascular complications, and whether treatment with a SU, metformin or insulin yielded clinical advantages or disadvantages [21]. Of patients maximally treated with a SU, over half went on to require insulin during the mean 6-year follow-up period [22]. ADOPT was a double-blind study of approximately 3600 drug-naive patients randomized to maximal treatment with rosiglitazone, glyburide or metformin, and followed for a median of 4 years. Patients in the SU group required the addition of a second agent sooner than patients on metformin or rosiglitazone [23].

SU selection should take into consideration the drug's pharmacodynamic profile, and patients should be advised to administer the medication so that the peak effect coincides with maximal postprandial glucose levels in order to reduce the hypoglycemia risk [24]. One 27-week study demonstrated a lower incidence of documented hypoglycemia (3.7 vs 8.9%; odds ratio [OR]: 2.5; 95% CI: 1.4–4.7) and a reduced discontinuation rate (one vs nine patients) among those treated with gliclazide MR versus glimepiride. Gliclazide is currently marketed in most countries across the world, except for the USA. The potential for SU overdose should also be considered [25]. Over-ingestion of SU agents with

long half-lives (up to 36 h with chlorpropamide and 9–10 h with glimepiride and glyburide) can increase the risk for prolonged and erratic hypoglycemia, particularly in the elderly or those with impaired renal clearance [26]. Hospitalization and 'reversal' treatments with octreotide and supplemental dextrose may be necessary for as long as 72 h following ingestion [27].

TZDs enhance peripheral insulin resistance by facilitating insulin-mediated glucose uptake and utilization. Because it acts at the level of PPAR-γ nuclear transcription, TZD treatment may require 4–6 weeks to manifest its full effect [28]. Similar to metformin, TZDs used in conjunction with insulin therapy can reduce the amount of exogenous insulin required. In patients stabilized on continuous subcutaneous insulin infusion, the addition of troglitazone (now withdrawn from the market due to hepatotoxicity) reduced insulin requirement by 53% (48 ± 4 U/day down from 102 ± 13 U/day) compared with 31% (76 ± 13 U/day down from 110 ± 18 U/day) with metformin initiation [29]. When used in addition to premixed insulin injections twice daily, rosiglitazone treatment resulted in a 1.2% HbA1c reduction with a simultaneous reduction of insulin requirement by 12% [30]. In 2007, the US FDA warned against simultaneous use of rosiglitazone with insulin in Type 2 diabetes due to a higher risk of myocardial ischemia observed in controlled double-blind clinical trials.

TZDs also slow β-cell decline. In the DREAM trial, 982 patients randomized to ramipril, rosiglitazone or placebo underwent successive oral glucose tolerance tests over a 2-year period [31]. Rosiglitazone improved measures of insulin secretion, while ramipril showed no effect compared with baseline [32]. In a subgroup analysis, patients with IGT, or combined IGT and impaired fasting glucose benefited more from rosiglitazone therapy compared with patients with impaired fasting glucose. Similarly, pioglitazone reduced conversion from IGT to Type 2 diabetes in the ACT Now trial [33] by lowering fasting glucose, 2-h glucose tolerance levels and HbA1c compared with placebo [34]. Combined with observations from ADOPT [23], rosiglitazone monotherapy delayed the need for additional antidiabetic agents, illustrating improved β-cell preservation somewhat better than metformin and significantly better than SUs.

Incretin mimetics (i.e., exenatide, once-weekly exenatide and liraglutide) affect glucose control by activating GLP-1 receptors located in the gastrointestinal tract to promote postprandial insulin release, improve hyperglycemia-induced glucagon suppression and delay gastric emptying to lower subsequent food intake. Through vagal pathways, GLP-1 activation of hypothalamic centers reduces feeding behavior and improves satiety [35]. While sensitivity to GIP diminishes in Type 2 diabetes, responsiveness to native GLP-1 is preserved, and may be exploited with pharmacological doses to protect and promote β-cell function. In freshly isolated islet cells, GLP-1 supports β-cell morphology and function and inhibits apoptosis. When combined with intensive insulin therapy in humans, a small study (n = 8) demonstrated a three- to four-fold increased sensitivity to GIP and GLP-1, which produced higher C-peptide values during second-phase insulin release [36].

In the same pathway, DPP-4 inhibitors (i.e., sitagliptin, saxaglipitin, linagliptin and vildaglipitin) block the enzyme responsible for degradation of GLP-1 and GIP, indirectly promoting postprandial insulin release while lowering inappropriate hyperglucagonemia [37]. β-cell function, as measured by the HOMA-β index and the proinsulin:insulin ratio, improves after treatment with DPP-4 inhibitors [38–40]. In rodent studies, DPP-4 inhibition increases β-cell mass. Functional human studies demonstrate durable increases in insulin secretion for study periods as long as 2 years. Whether DPP-4 inhibition expands functional β-cell mass in humans and offers any persistent benefit after drug discontinuation is still unknown [41].

Effects on body weight & gastrointestinal function

Lifestyle modification to produce a 5–10% reduction in body weight remains a first-line recommendation for all patients newly diagnosed with Type 2 diabetes. Several non-insulin-based therapies (shown in **Table 3**) can be helpful in this regard, while others can promote further weight gain.

Metformin's weight neutrality makes it particularly attractive as a first-line treatment for Type 2 diabetes. Additionally, metformin increases early satiety through stimulation at the GLP-1 receptor to reduce food intake [42]. Metformin-related gastrointestinal disturbances (i.e., nausea) may also reduce food intake. Conversely, measures that increase hyperinsulinemia – namely exogenous insulin or insulin secretagogues – are

Table 3. Oral and injectable noninsulin therapies that affect body weight and gastrointestinal function.

Drug class	Effect/mechanism
Biguanides (metformin)	Weight neutral Increases early satiety, may reduce food intake gastrointestinal intolerance (nauseas, diarrhea)
Insulin secretagogues	Promotes hyperinsulinemia (anabolic) Promotes weight gain Increases hypoglycemia risk; may increase hunger and food intake to defend against low blood sugar
Thiazolidinediones	Increased subcutaneous adipose tissue Mild weight gain
Incretin mimetics	Delays gastric emptying Improves satiety (reduces food intake) Promotes weight loss
DPP-4 inhibitors	Weight neutral No effect on satiety or appetite
α-glucosidase inhibitors	Weight neutral Can cause flatulence and diarrhea

anabolic and promote weight gain. In patients treated with SU monotherapy, UKPDS showed an increase of 2–4 kg over 6 years compared with patients treated with diet alone [22].

α-glucosidase inhibitors (i.e., acarbose) are also considered weight neutral. The pseudotetrasaccharide is structurally similar to oligosaccharides in dietary carbohydrates and binds with greater affinity, inhibiting the enzymatic activity of α-glucosidase contained on the brush border of the small intestine [43]. The resulting increase in fermentable carbohydrates reaching the distal colon frequently causes flatulence and diarrhea. Intestinal glucose absorption is attenuated and postprandial glucose excursions are reduced. In patients with chronic constipation, gastroparesis or functional bowel disorders, this may promote gastric motility, particularly if flatulence can be controlled by starting at the lowest dose and gradually titrating upward. Taken with a high carbohydrate meal, acarbose has also been shown to reduce GIP and lower GLP-1, but whether these changes contribute meaningfully to the drug's overall effect is uncertain [44].

The amylin analog, pramlintide complements insulin activity by reducing postprandial glucagon secretion and the amount of glucose present in circulation. Amylin also stimulates hypothalamic receptors, and replacement in both Type 1 and 2 diabetes promotes early satiety and weight loss. A pooled analysis found that pramlintide produced a placebo-corrected HbA1c difference of 0.4% among insulin-treated patients compared with placebo. Pramlintide-treated patients achieved greater mean weight reductions; overall, placebo-subtracted weight loss was 1.8 kg over the 26-week trial [45].

Incretin mimetics promote early satiety, which facilitates weight loss. The three AMIGO studies with exenatide documented weight loss of 1.6, 2.8 and 1.6 kg when combined with SU, metformin, or combined SU and metformin, respectively, over a 30-week study period [46–48]. Long-term follow-up in patients on maximally dosed metformin and exenatide showed continued weight loss of -5.3 ± 0.8 kg over 82 weeks [49]. Weight loss is equivalent for the daily and weekly formulations of exenatide [50].

For liraglutide, the LEAD studies demonstrated weight reduction when used alone or in combination with other antidiabetic agents, although use with SU or insulin tended to produce less weight loss [51–55]. Liraglutide monotherapy reduced weight by 1.85 and 2.26 kg for the 1.2 and 1.8 mg doses, respectively, compared with an increase of 1.22 kg with glimepiride [53]. However, more liraglutide-treated patients reported prolonged nausea, so it unclear whether this weight loss is a true drug treatment effect or an unintended side effect. When compared with the lipoprotein lipase inhibitor, orlistat, liraglutide produced dose-dependent weight loss of up to 7.8 kg with the 3.0 mg dose compared with 4.1 kg with maximal doses of orlistat. Overall, liraglutide produced placebo-subtracted weight loss ranging from 2.1 to 4.0 kg during the 20-week trial, as well as modest reductions in diastolic blood pressure and prevalence of prediabetes [56].

In combination with insulin and oral agents, GLP-1 agonists exert a positive effect on weight loss compared with SU-based and insulin-only regimens. Meanwhile, DPP-4 inhibitors are weight neutral and do not influence gastric emptying, satiety or appetite [57].

In addition to direct glycemic effects on the PPAR, TZDs promote differentiation of mesenchymal precursors into adipocytes. Expansion of adipose stores lowers circulating free fatty acid levels, which reduces insulin resistance and hyperinsulinemia. In nonadipose tissue, ectopic fat deposition interferes with insulin-mediated glucose uptake in skeletal muscle, while hepatic glycogen synthesis and nitric oxide generation in vascular epithelium are impaired. By reducing plasma free fatty acids, TZDs improve insulin signaling and sensitivity, but at the expense of increased body fat and

fluid retention. Fortunately, the adipose tissue expansion occurs primarily in the subcutaneous, rather than visceral depot; the latter is associated with increased cardiovascular disease risk. Total body weight gain attributable to TZD initiation is dose-dependent ranging from 1.5 to 4.0 kg.

Lipid profile improvements & hepatic effects on cholesterol metabolism

Diabetes treatment, whether through pharmacologic or intensive lifestyle modification, tends to favorably improve lipids with a few notable exceptions. Survey data from the National Health and Nutritional Education Survey (NHANES) from 1999 to 2000 found that over half of the adult patients with Type 2 diabetes had comorbid hypertension [58]. In diabetic patients with dyslipidemia, metformin treatment can lower triglyceride and total cholesterol while increasing high-density lipoprotein cholesterol [8,59,60].

Despite improved lipid metabolism, metformin has not demonstrated efficacy in reversing the fatty liver changes that often accompany Type 2 diabetes. Nonalcoholic fatty liver disease (NAFLD) is a spectrum of histological changes encompassing mild hepatocyte damage and ballooning to steatohepatitis with progressive inflammation and necrosis with or without bridging fibrosis; ultimately, culminating in cirrhosis. Biopsy results show that metformin does not reverse these histological changes and is not recommended for treatment of NAFLD [61].

TZDs, meanwhile, can reduce hepatosteatosis by as much as 50% [62]. Akyuz and colleagues followed patients for up to 1 year and observed a similar benefit on liver histology and liver function tests with rosiglitazone 4 mg daily compared with lifestyle modification through diet and exercise [62]. Another 48-week trial showed that rosiglitazone improved clinical and pathological features of hepatosteatosis and steatohepatitis [63]. Pioglitazone with diet modification has been shown to improve liver aminotransferases, hepatic fat content, histology and inflammation, but not measures of fibrosis in patients with Type 2 diabetes and NAFLD [64,65]. However, TZDs are not currently approved in the USA for the treatment of NAFLD and with rosiglitazone's subsequent market withdrawal, use of pioglitazone for this indication is still considered experimental.

Intraclass differences in PPAR affinity, in particular the α subtype, confer pioglitazone with favorable lipid effects compared with rosiglitazone [66,67]. Both rosiglitazone and pioglitazone convert small, dense, atherogenic low-density lipoprotein (LDL)-cholesterol to large, buoyant LDL particles [67]. Rosiglitazone increases LDL particles more than pioglitazone [66,68,69]. Meanwhile, HDL-cholesterol can be increased 10–20% [68]. Hypertriglyceridemia (levels over 200 mg/dl) is also improved with pioglitazone more so than rosiglitazone [66].

Additionally, the LDL-lowering agent, colesevelam (Welchol®; Daiichi Sankyo, Tokyo, Japan), has demonstrated sufficient glucose-lowering properties to gain regulatory approval for the treatment of Type 2 diabetes through mechanisms not well understood. The drug reduces HbA1c by approximately 0.5% in patients failing oral agents, and 1.0% among patients with a pretreatment HbA1c ≥8.0% compared with placebo [70]. As an add-on therapy with insulin, colesevelam yields an additional 0.5% HbA1c reduction compared with placebo [71]. Improvements in LDL cholesterol (~15%) exceed the mild nonsignificant increase in triglycerides (~7%). Furthermore, the extent of HbA1c lowering appears to correlate with an improvement in the atherogenic LDL [72].

Inflammation, endothelial dysfunction & cardiovascular health

Cardiovascular disease afflicts approximately a quarter of patients with Type 2 diabetes [58] and risk reduction, whether through pharmacologic or lifestyle interventions, is critical to improve morbidity and mortality. Metformin has proven effectiveness in the reduction of cardiovascular mortality [73,74]. The UKPDS found that metformin use in overweight patients with Type 2 diabetes reduces macrovascular morbidity and mortality compared with treatment with insulin or SUs.

Inflammatory biomarkers and acute phase proteins are increased in patients with Type 2 diabetes. Higher levels of PAI-1 predispose individuals to incident diabetes independent of BMI and insulin sensitivity [75]. Elevated PAI-1 is also associated with increased insulin resistance [76], and metformin reduces PAI-1 levels [77]. In BARI 2D, patients with Type 2 diabetes and pre-existing stable coronary artery disease were randomized to either an 'insulin-providing regimen' with exogenous insulin or SU, or an 'insulin-sensitizing regimen' with metformin or TZD. Metformin reduced PAI-1 and improved inflammatory (i.e., CRP) and fibrinolytic biomarkers (i.e., D-dimer, fibrinogen and

fibrinopeptide A) [76]. By contrast, these studies also showed consistently that metformin had marginal influence on blood pressure and heart rate [78]. Overall, metformin's cardioprotection appears mediated by its anti-inflammatory effects rather than improvements in vascular tone.

SUs, in addition to their β-cell secretagogue function, also bind to ATP-dependent K^+ channels (K^+_{ATP}) located in several nonpancreatic tissues [79]. The myocardium and vascular smooth muscle cells contain SU receptors that differ in isoform from the subtype found in pancreatic β-cells [80]. When the myocardium is exposed to ischemia, open K^+_{ATP} channels permit ion flux, which enables protective vasodilatation and reduces myocardial damage, termed ischemic preconditioning [81]. Closure of these mitochondrial-based K^+_{ATP} channels interferes with recovery following a myocardial ischemic insult. Conversely, closing the sarcolemmal-based K^+_{ATP} channels can stabilize arrhythmogenic-prone myocardial tissue and even offer spontaneous defibrillation to protect against ventricular arrhythmias following an ischemic event [82].

Among first- and second-generation SUs, glyburide has the highest relative binding affinity for myocardial receptors. Activation of the SU receptor may increase susceptibility to and the resulting infarct size following an ischemic event [83]. Clinical data regarding this physiological observation have been mixed. While the UKPDS found no elevated cardiovascular events rate among patients on glyburide compared with other antidiabetes agents [84], other studies show an increased risk in patients on glyburide alone [85] or in conjunction with metformin [83]. Intraclass difference may also exist; the ADVANCE trial followed 11,410 patients with Type 2 diabetes with major macrovascular or microvascular disease, or at least one other cardiovascular risk factor for hypoglycemia while using gliclazide MR. Among patients who developed severe hypoglycemia, rates of subsequent major macrovascular and microvascular events, and death were higher than in patients without severe hypoglycemia [86].

Measures that improve insulin resistance translate to improvements in endothelial function and lower inflammatory markers. TZDs increase arterial vasodilatation, lowering ambulatory systolic and diastolic blood pressure readings by 3–5 mmHg [87]. PPAR-γ activation decreases production of vascular adhesion molecules and growth factors that reduce vascular smooth muscle cell and fibroblast proliferation [88–90]. TZDs also improve hypercoagulability, namely by reducing circulating fibrinogen and PAI-1 levels [91]. Additionally, cytokines and inflammatory biomarkers, particularly TNF-α and CRP, which have been shown to contribute to incident myocardial infarction, are reduced [92].

Clinically, pioglitazone's improvements in inflammation and procoagulability can be measured through reductions in carotid intimal media thickness [93], a surrogate for atherosclerotic disease progression, and in-stent restenosis following percutaneous coronary intervention [94]. While improvements in intermediary cardiovascular measures should translate to fewer cardiovascular events, TZDs have not demonstrated reductions in cardiovascular events. The PROactive study compared pioglitazone versus placebo in 5238 patients with Type 2 diabetes and established macrovascular disease over a median of 34.5 months of treatment [95]. No significant difference in clinical end points, including death, nonfatal myocardial infarction, leg amputation and acute coronary syndrome, were observed. A secondary composite end point of all-cause mortality, nonfatal myocardial infarction (excluding silent infarction) and stroke, added just prior to the study closure, showed a 16% reduction with pioglitazone treatment compared with placebo ($p < 0.027$) [96]. Interpreting the study results may be challenging due to low rates of statin use, now considered standard of care for secondary cardiovascular disease prevention. However, subsequent subset analysis failed to show cardiac risk reduction when pioglitazone was added in patients already treated with statins. Improved cardiovascular risk was associated with increased HDL after pioglitazone treatment rather than any improvement in glycemic control [97]. The RECORD trial, which randomized 4447 Type 2 diabetes patients to rosiglitazone with either metformin or SU, or metformin and SU, found no difference in cardiovascular events except for a 2.15-fold increased risk of congestive heart failure in patients using rosiglitazone [98].

TZD-mediated fluid retention and peripheral edema are mediated by PPAR-γ activation on the proximal tubule of the nephron [99]. Increased free-water retention expands blood volume, and in the absence of increased red blood cell volume may contribute to ≤1.0 mg/dl decline in hemoglobin and hematocrit within the first 12 weeks of starting TZD treatment. Peripheral edema occurs in 4–5% of patients on TZD monotherapy,

6–8% when combined with SU, and up to 15% when combined with insulin [100]. Patients with a prior history of congestive heart failure have greater risk for fluid retention and peripheral edema with TZD therapy; however, this is reversible with drug discontinuation. The PROactive trial in patients with established cardiovascular disease reported a congestive heart failure exacerbation rate of 5.7% on TZD therapy compared with 4.1% in the control population [95].

Following a 2007 meta-analysis [101], which found increased cardiovascular ischemic events in patients treated with rosiglitazone, analyses of large long-term randomized clinical trials involving rosiglitazone including ADOPT [23], DREAM [32], RECORD [98], ACCORD [102] and VADT [103] found no increased cardiovascular risk from rosiglitazone treatment [104]. However, the negative publicity prompted an FDA black box warning and cautionary warnings from several cardiology organizations [105]. Rosiglitazone is only available on a restricted basis in the USA [202] and was withdrawn from the EU, South African and New Zealand markets in 2010 and 2011.

DPP-4 inhibitor-mediated activation of GLP-1 receptors appears to promote NO-mediated vasodilation through mechanisms that are not yet well understood [106]. Clinically, this may translate to improved vascular tone, reduced ischemia reperfusion injury and improved myocardial contractile function [107]. DPP-4 inhibition also impairs cleavage of the neuropeptide Y and peptide YY; build up of intact precursors increases sensitivity to the vasoconstrictive effects of angiotensin II. GLP-1 direct agonists and DPP-4 inhibitors, to a lesser extent, show clinically meaningful blood pressure reductions in patients with Type 2 diabetes and hypertension.

DPP-4 inhibitors may confer additional cardioprotection by reducing inflammatory cytokines while upregulating immunosuppressive cytokines that block the inflammatory process, which promotes atherosclerosis. Additionally, GLP-1 receptor activation appears greater with a direct agonist compared with indirect DPP-4 inhibitors. In a small pilot study (n = 10), GLP-1 agonists demonstrated improvements in left ventricular function (left ventricular function, global wall and regional wall motion indices) in patients following angioplasty for acute myocardial infarction [108].

The newest class of oral agents for Type 2 diabetes is the sympatholytic D2 dopamine agonist, bromocriptine, an immediate-release formulation taken within 2 h of waking [109]. The drug increases early morning hypothalamic dopaminergic tone, which reduces hepatic glucose output, lipolysis and sympathetic tone. Peripheral insulin resistance is reduced [110]. Beyond trial data documenting efficacy along or with other oral antidiabetic agents, few human data are available on the drug's nonglycemic effects. The safety study conducted for FDA marketing approval showed a 40% reduction in cardiovascular end points (i.e., myocardial infarction, stroke, hospitalization for angina, hospitalization for congestive heart failure, coronary revascularization and death) compared with placebo (hazard ratio: 0.60; two-sided 95% CI: 0.37–0.96; p = 0.036) [111]. Modest improvements in blood pressure, heart rate and triglycerides were noted, which were not large enough to explain the large drop in cardiovascular events [109]. Further research is needed to elucidate the mechanism of these cardioprotective effects in humans.

Androgens & reproductive function

Although not specifically approved for the treatment of polycystic ovarian syndrome (PCOS), metformin improves ovulatory function and fecundity rates in affected patients. In women with oligomenorrhea desiring pregnancy, metformin restores menstrual frequency and normalizes ovarian hyperandrogenemia independent of weight loss [112]. One meta-analysis of 17 studies showed improved ovulation rates with metformin compared with placebo (OR: 2.94; 95% CI: 1.43–6.02) and the treatment effect appeared strongest in women resistant to clomiphene [113]. When combined with clomiphene, metformin increased ovulation frequency (OR: 4.39; 95% CI: 1.94–9.96) and odds of achieving pregnancy (OR: 2.67; 95% CI: 1.45–4.94). In head-to-head comparison, 626 women with PCOS were randomized to metformin, clomiphene or combination therapy [114]. The live birth rate was significantly lower with metformin (7.2%) compared with clomiphene (22.5%) and combination therapy (26.8%), but with higher multiple birth rates in clomiphene-treated women – 6.2% with monotherapy and 3.1% with combined therapy versus none in the metformin-treated group. A meta-analysis earlier this year also found that ovulation induction in women with PCOS was less effective with metformin compared

with clomiphene alone (OR: 0.48; 95% CI: 0.26–0.87; p = 0.01), but observed no difference in rates of pregnancy (OR: 0.94; 95% CI: 0.26–3.43) or miscarriage (OR: 0.63; 95% CI: 0.06–6.47). Meanwhile, metformin was equivalent to combined metformin and clomiphene in ovulation frequency and miscarriage rates, but inferior in achieving pregnancy [115]. Overall, combination therapy appears to outperform metformin or clomiphene alone.

Metformin-induced improvements in circulating androgen levels can also help hirsutism and acne in PCOS [116]. One study comparing metformin to an oral contraceptive containing ethinyl estradiol and cyproterone acetate found reduced hirsutism scores and improved patient self-assessment with metformin, which correlated with improved insulin sensitivity rather than with suppression of androgenic activity [117]. In nonobese girls with precocious puberty, metformin improved insulin response on glucose tolerance testing, hyperandrogenemia, hirsutism and menstrual irregularity, and these effects reverted with metformin discontinuation [118].

TZDs may also be used as insulin-sensitizers in the treatment of PCOS [119]; however, despite largely equivocal gains in insulin sensitivity, metformin promotes greater weight loss. TZDs have not been shown to improve ovulation rates. With their adverse impact on bone mineral density (which coincides with peak bone accrual for reproductive-age women) and potential teratogenic effects, TZDs are clearly inferior to metformin and are not approved for the treatment of PCOS.

Cancer risk

Several diabetes agents have been linked both to increased and decreased cancer rates (shown in **Table 4**). Type 2 diabetes confers a 40% higher risk for bladder cancer compared with the general nondiabetic population [120]; however, TZDs (namely pioglitazone) add additional risk through a mechanism not yet well understood. The cumulative dose exposure to pioglitazone appears to associate with increased bladder cancer risk prompting US and Canadian regulatory warnings [121]. Pioglitazone should not be used in patients with concurrent or prior history of bladder cancer or any uninvestigated macroscopic hematuria. Screening for risk factors including age, smoking, family history, or exposures to radiation or known chemical or antineoplastic culprits should factor in the decision to start pioglitazone [203].

Epidemiologic studies of adverse event data from the FDA have signaled higher rates of pancreatic cancer in patients taking the DPP-4 inhibitor, sitagliptin, and GLP-1 analog, exenatide ($p < 0.008$ and $p < 9 \times 10^{-5}$), but no increased risk of other types of cancer [122]. It should be noted that such reporting databases do not control for other risk factors for pancreatic cancer, such as obesity, smoking and prior pancretitis, nor do they contain a representative sample of the overall population. Further analysis is still needed to define the relationship between GLP-1 agonist therapy and cancer development. Long-term safety data on to incretin-based agents are also needed.

Liraglutide causes proliferation of benign and malignant thyroid C-cell tumors in rodent studies [204]; however, no similar increases in calcitonin or medullary thyroid cancer have been documented in humans. This may be related to the reduced density of GLP-1 receptors on human C-cells compared with rodents [123].

Finally, more data continue to emerge that metformin may be protective against certain types of cancers, particularly colorectal, breast, pancreatic and liver. In breast cancer, metformin treatment was linked with a reduced risk in one recent meta-analysis [124], while another found no benefit compared with other antidiabetic agents [125]. This protective effect may be related to AMPK activation, which promotes catabolic processes and reduces energy-requiring functions including cellular proliferation.

Table 4. Oral and injectable noninsulin therapies linked to cancer incidence.

Drug class	Effect/mechanism
Metformin	Linked to protective effects in breast, colorectal, pancreatic and liver cancers
Thiazolidinediones	Increased rates of bladder cancer
Incretin mimetics	Concern for thyroid cancer
DPP-4 inhibitors	Concern for pancreatic cancer

Other notable risks

A full description of major and minor side effects for each drug class is outside the scope of this review and better covered in other sources [4,201]. Several notable side effects, however, while rare in prevalence, may still influence clinical decision-making for or against a particular drug. We have chosen to highlight several notable side effects below.

Long-term therapy with metformin has been linked to vitamin B_{12} deficiency in 10–30% of patients. The exact mechanism is not clear, but appears related to impaired calcium-dependent absorption across the ileal membrane, which may be rectified by calcium supplementation [126]. No screening guidelines exist for vitamin B_{12} levels in diabetic patients on metformin; however, clinicians should have heightened suspicion for sequelae of chronic B_{12} deficiency, including megablastic anemia, peripheral neuropathy and even increased cardiovascular risk due to elevated homocystiene levels that may result from chronic B_{12} and folate deficiencies. Other causes of B_{12} deficiency should be excluded, including pernicious anemia, malabsorption and other offending medications such as proton pump inhibitors [7].

After market introduction in 1999, TZDs have been linked to an increase in vision-compromising diabetic macular edema (DME) [127]. According to one large prospective cohort epidemiologic study, an OR of 1.6 (95% CI: 1.4–1.8) for DME was detected among patients treated with TZD compared with alternative agents despite controlling for glycemic control, regular vision screening exams and access to prescription drugs [128]. Another retrospective analysis of 103,368 patients over a 10-year period, calculated DME incidence to be 1.3% for TZD users compared with 0.2% for nonusers after controlling for body weight, HbA1c and concomitant medications, but did not account for duration of TZD exposure [129]. The degree of risk appears similarly increased for rosiglitazone and pioglitazone. A higher risk for DME was also found in patients treated with TZD combination therapy with insulin (hazard ratio: 3.0; 95% CI: 1.5–5.9) [128].

Additionally, increased fracture rates have been reported in TZD users [130]. The putative mechanism involves PPAR-γ activation, which interferes with bone marrow stem cell differentiation, promoting adipogenesis at the expense of osteoblastogenesis and new bone formation. ADOPT [23] and RECORD [98] both found elevated fracture rates in women on rosiglitazone most commonly affecting the upper limb and distal lower extremity [98]. Spine, hip and femur fractures, sites more typical for osteoporotic fractures, did not increase statistically with rosiglitazone [98]. Likewise, PERISCOPE [131] and PROactive [132] observed a similar increased risk of fracture with pioglitazone treatment. In PROactive, fractures were more common among females, primarily affecting extremities rather than the hips. In the largest meta-analysis, ten randomized controlled trials and two observational studies that followed over 45,000 patients found a higher fracture risk in women, but not men, treated with pioglitazone and rosiglitazone [133]. This gender-specific effect was subsequently countered by a UK retrospective analysis of 1020 low-trauma fractures; TZD use conferred a 2.43-fold increased fracture risk over placebo, after controlling for sex and age [134]. Thus, TZD-treated patients should have regular bone density monitoring and alternative treatments should be considered in patients with osteoporosis or prior low-trauma fractures. Currently, no recommendations exist for bone density screening in premenopausal women using TZD therapy who otherwise lack risk factors for osteoporosis.

Pancreatitis has been linked to liraglutide, exenatide and the DPP-4 inhibitor, sitagliptin. For sitagliptin, post-marketing surveillance revealed reports of acute pancreatitis requiring hospitalization [122,205]; 21% of these cases occurred during the first 30 days after drug initiation [57]. However, other retrospective studies of insurance database claims have not found an elevated risk of pancreatitis due to sitagliptan [135].

Incretin mimetics/agonists and DPP-4 inhibitors have a rare risk of hypersensitivity reactions and anaphylactoid reactions. Stevens–Johnson syndrome and acute renal failure have occurred with DPP-4 inhibitors [57,136,137].

Conclusion & future perspective

With the broader armamentarium of antidiabetic agents now available, consideration of the 'off-target' effects should factor into clinical decision-making and treatment selection. Numerous opportunities exist to select agents with complimentary nonglycemic benefits.

Lessons from rosiglitazone and other diabetic agents approved for use, only to be withdrawn from the market, remind us of the need for rigorous testing to discern side effects, particularly those resulting from long-term use. Drugs that influence glucose metabolism often influence related metabolic pathways and may carry unforeseen biologic effects – some advantageous while others are detrimental. Given the frequency of lipid disturbances and obesity in patients with Type 2 diabetes, drugs that have multiple effects are preferable; however,

caution should be exercised regarding potential cardiovascular and oncologic risks.

Financial & competing interests disclosure

P Raskin has received research support, payable to the University of Texas Southwestern Medical Center, from Amgen Inc., Andromeda Biotech Ltd, AstraZeneca Pharmaceuticals LP, Boehringer Ingelheim Pharmaceuticals, Eli Lilly & Company, Gilead Sciences Inc., Pfizer Inc. and Reata Pharmaceuticals Inc.; is an advisor for Amgen, AstraZeneca and Sanofi-Aventis US Inc.; and is on the speakers bureau for Novo Nordisk Inc. P Hollander has provided consulting services and participated in advisory boards for Novo Nordisk. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ■ of interest
- ■■ of considerable interest

1 Inzucchi SE, Bergenstal RM, Buse JB *et al.* Management of hyperglycemia 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). *Diabetes Care* 35(6), 1364–1379 (2012).

■■ **Most recent practice guidelines for the management of Type 2 diabetes.**

2 Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P. Oral pharmacologic treatment of Type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann. Intern. Med.* 156(3), 218–231 (2012).

3 Ratanawongsa N, Crosson JC, Schillinger D, Karter AJ, Saha CK, Marrero DG. Getting under the skin of clinical inertia in insulin initiation: the Translating Research Into Action for Diabetes (TRIAD) Insulin Starts Project. *Diabetes Educ.* 38(1), 94–100 (2012).

4 Brunton LL, Chabner B, Knollmann BRC. *Goodman & Gilman's The Pharmacological Basis of Therapeutics (12th Edition)*. McGraw–Hill, NY, USA (2011).

■ **Seminal pharmacology book that provides an overview of key therapuetics to treat Type 2 diabetes including their mechanisms of action and side effects.**

5 Gastaldelli A. Role of β-cell dysfunction, ectopic fat accumulation and insulin resistance in the pathogenesis of Type 2 diabetes mellitus. *Diabetes Res. Clin. Pract.* 93(Suppl. 1), S60–S65 (2011).

■ **Outlines multiple physiologic pathways that are responsible for the development and progression of Type 2 diabetes.**

6 Retnakaran R, Qi Y, Harris SB, Hanley AJ, Zinman B. Changes over time in glycemic control, insulin sensitivity, and β-cell function in response to low-dose metformin and thiazolidinedione combination therapy in patients with impaired glucose tolerance. *Diabetes Care* 34(7), 1601–1604 (2011).

7 Mazokopakis EE, Starakis IK. Recommendations for diagnosis and management of metformin-induced vitamin B_{12} (Cbl) deficiency. *Diabetes Res. Clin. Pract.* 97(3), 359–367 (2012).

8 Bailey CJ, Turner RC. Metformin. *N. Engl. J. Med.* 334(9), 574–579 (1996).

9 Collier CA, Bruce CR, Smith AC, Lopaschuk G, Dyck DJ. Metformin counters the insulin-induced suppression of fatty acid oxidation and stimulation of triacylglycerol storage in rodent skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 291(1), E182–E189 (2006).

10 Strowig SM, Aviles-Santa ML, Raskin P. Comparison of insulin monotherapy and combination therapy with insulin and metformin or insulin and troglitazone in Type 2 diabetes. *Diabetes Care* 25(10), 1691–1698 (2002).

11 Maida A, Lamont BJ, Cao X, Drucker DJ. Metformin regulates the incretin receptor axis via a pathway dependent on peroxisome proliferator-activated receptor-α in mice. *Diabetologia* 54(2), 339–349 (2011).

12 Mulherin AJ, Oh AH, Kim H, Grieco A, Lauffer LM, Brubaker PL. Mechanisms underlying metformin-induced secretion of glucagon-like peptide-1 from the intestinal L cell. *Endocrinology* 152(12), 4610–4619 (2011).

13 Lauffer LM, Grieco A, Iakoubov R, Brubaker PL. Metformin activates the AMPK pathway and improves survival of murine and human L-cells but does not directly increase GLP-1 secretion. *Diabetologia* 51(1 Suppl.), 1–588 (2008).

14 Yasuda N, Inoue T, Nagakura T *et al.* Enhanced secretion of glucagon-like peptide 1 by biguanide compounds. *Biochem. Biophys. Res. Commun.* 298(5), 779–784 (2002).

15 Lenhard JM, Croom DK, Minnick DT. Reduced serum dipeptidyl peptidase IV after metformin and pioglitazone treatments. *Biochem. Biophys. Res. Commun.* 324(1), 92–97 (2004).

16 Hinke SA, Kuhn-Wache K, Hoffmann T, Pederson RA, Mcintosh CH, Demuth HU. Metformin effects on dipeptidylpeptidase IV degradation of glucagon-like peptide-1. *Biochem. Biophys. Res. Commun.* 291(5), 1302–1308 (2002).

17 The Diabetes Prevention Program: baseline characteristics of the randomized cohort. The Diabetes Prevention Program Research Group. *Diabetes Care* 23(11), 1619–1629 (2000).

18 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.* 346(6), 393–403 (2002).

■■ **Landmark Diabetes Prevention Program followed over 3000 nondiabetic patients treated with placebo, metformin or intensive lifestyle modification to promote 5–10% weight loss. Lifestyle modification proved more effective than metformin for risk reduction of incident diabetes.**

19 Salpeter SR, Buckley NS, Kahn JA, Salpeter EE. Meta-analysis: metformin treatment in persons at risk for diabetes mellitus. *Am. J. Med.* 121(2), 149.e2–157.e2 (2008).

20 Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with Type 2 diabetes mellitus. A randomized, controlled trial. *Ann. Intern. Med.* 130(5), 389–396 (1999).

21 American Diabetes Association. Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care* 25(Suppl. 1), S28–S32 (2002).

22 Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with Type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care* 25(2), 330–336 (2002).

23 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* 25(10), 1737–1743 (2002).

24 Owens DR, Cozma LS, Luzio SD. Early-phase prandial insulin secretion: its role in the pathogenesis of Type 2 diabetes mellitus and its modulation by repaglinide. *Diabetes Nutr. Metab.* 15(6 Suppl.), 19–27 (2002).

25 Holstein A, Hammer C, Hahn M, Kulamadayil NS, Kovacs P. Severe sulfonylurea-induced hypoglycemia: a problem of uncritical prescription and deficiencies of diabetes care in geriatric patients. *Expert Opin. Drug Saf.* 9(5), 675–681 (2010).

26 Krentz AJ, Ferner RE, Bailey CJ. Comparative tolerability profiles of oral antidiabetic agents. *Drug Saf. Int. J. Med. Toxicol. Drug Exp.* 11(4), 223–241 (1994).

27 Mclaughlin SA, Crandall CS, Mckinney PE. Octreotide: an antidote for sulfonylurea-induced hypoglycemia. *Ann. Emerg. Med.* 36(2), 133–138 (2000).

28 Yki-Jarvinen H. Thiazolidinediones. *N. Engl. J. Med.* 351(11), 1106–1118 (2004).

29 Yu JG, Kruszynska YT, Mulford MI, Olefsky JM. A comparison of troglitazone and metformin on insulin requirements in euglycemic intensively insulin-treated Type 2 diabetic patients. *Diabetes* 48(12), 2414–2421 (1999).

30 Raskin P, Rendell M, Riddle MC, Dole JF, Freed MI, Rosenstock J. A randomized trial of rosiglitazone therapy in patients with inadequately controlled insulin-treated Type 2 diabetes. *Diabetes Care* 24(7), 1226–1232 (2001).

31 Gerstein HC, Yusuf S, Bosch J *et al.* Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368(9541), 1096–1105 (2006).

32 Hanley AJ, Zinman B, Sheridan P, Yusuf S, Gerstein HC. Effect of rosiglitazone and ramipril on {β}-cell function in people with impaired glucose tolerance or impaired fasting glucose: the DREAM trial. *Diabetes Care* 33(3), 608–613 (2010).

■ **In prediabetic patients, the DREAM study found that rosiglitazone treatment improved cell function more than ramipril and slowed progression towards the development of Type 2 diabetes.**

33 Defronzo RA, Banerji M, Bray GA *et al.* Actos Now for the prevention of diabetes (ACT NOW) study. *BMC Endocr. Disord.* 9, 17 (2009).

34 Defronzo RA, Tripathy D, Schwenke DC *et al.* Pioglitazone for diabetes prevention in impaired glucose tolerance. *N. Engl. J. Med.* 364(12), 1104–1115 (2011).

35 Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 132(6), 2131–2157 (2007).

36 Hojberg PV, Vilsboll T, Rabol R *et al.* Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with Type 2 diabetes. *Diabetologia* 52(2), 199–207 (2009).

37 Hollander PA, Kushner P. Type 2 diabetes comorbidities and treatment challenges: rationale for DPP-4 inhibitors. *Postgrad. Med.* 122(3), 71–80 (2010).

38 White J. Efficacy and safety of incretin based therapies: clinical trial data. *J. Am. Pharm. Assoc.* 49(Suppl. 1), S30–S40 (2009).

39 Goldstein BJ, Feinglos MN, Lunceford JK, Johnson J, Williams-Herman DE. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with Type 2 diabetes. *Diabetes Care* 30(8), 1979–1987 (2007).

40 Ristic S, Byiers S, Foley J, Holmes D. Improved glycaemic control with dipeptidyl peptidase-4 inhibition in patients with Type 2 diabetes: vildagliptin (LAF237) dose response. *Diabetes Obes. Metab.* 7(6), 692–698 (2005).

41 Van Genugten RE, Van Raalte DH, Diamant M. Dipeptidyl peptidase-4 inhibitors and preservation of pancreatic islet-cell function: a critical appraisal of the evidence. *Diabetes Obes. Metab.* 14(2), 101–111 (2012).

42 Cho YM, Kieffer TJ. New aspects of an old drug: metformin as a glucagon-like peptide 1 (GLP-1) enhancer and sensitiser. *Diabetologia* 54(2), 219–222 (2011).

43 Bischoff H. Pharmacology of α glucosidase inhibition. *Eur. J. Clin. Investig.* 24(Suppl. 3), S3–S10 (1994).

44 Groop PH, Groop L, Totterman KJ, Fyhrquist F. Effects of acarbose on the relationship between changes in GIP and insulin responses to meals in normal subjects. *Acta Endocrinol.* 112(3), 361–366 (1986).

45 Hollander P, Maggs DG, Ruggles JA *et al.* Effect of pramlintide on weight in overweight and obese insulin-treated Type 2 diabetes patients. *Obes. Res.* 12(4), 661–668 (2004).

46 Buse JB, Henry RR, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with Type 2 diabetes. *Diabetes Care* 27(11), 2628–2635 (2004).

47 Defronzo RA, Ratner RE, Han J, Kim DD, Fineman MS, Baron AD. Effects of exenatide (exendin-4) on glycemic control and weight over 30 weeks in metformin-treated patients with Type 2 diabetes. *Diabetes Care* 28(5), 1092–1100 (2005).

48 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* 28(5), 1083–1091 (2005).

49 Ratner RE, Maggs D, Nielsen LL *et al.* Long-term effects of exenatide therapy over 82 weeks on glycaemic control and weight in over-weight metformin-treated patients with Type 2 diabetes mellitus. *Diabetes Obes. Metab.* 8(4), 419–428 (2006).

50 Blevins T, Pullman J, Malloy J *et al.* DURATION-5: exenatide once weekly resulted in greater improvements in glycemic control compared with exenatide twice daily in patients with Type 2 diabetes. *J. Clin. Endocrinol. Metab.* 96(5), 1301–1310 (2011).

51 Marre M, Shaw J, Brandle M *et al.* Liraglutide, a once-daily human GLP-1 analogue, added to a sulphonylurea over 26 weeks produces greater improvements in glycaemic and weight control compared with adding rosiglitazone or placebo in subjects with Type 2 diabetes (LEAD-1 SU). *Diabet. Med.* 26(3), 268–278 (2009).

52 Nauck M, Frid A, Hermansen K *et al.* Efficacy and safety comparison of liraglutide, glimepiride, and placebo, all in combination with metformin, in Type 2 diabetes: the LEAD (liraglutide effect and action in diabetes)-2 study. *Diabetes Care* 32(1), 84–90 (2009).

53 Garber A, Henry R, Ratner R *et al.* Liraglutide versus glimepiride monotherapy for Type 2 diabetes (LEAD3 Mono): a randomised, 52-week, Phase III, double-blind, parallel-treatment trial. *Lancet* 373(9662), 473–481 (2009).

54 Zinman B, Gerich J, Buse JB *et al.* Efficacy and safety of the human glucagon-like peptide-1 analog liraglutide in combination with metformin and thiazolidinedione in patients with Type 2 diabetes (LEAD-4 Met+TZD). *Diabetes Care* 32(7), 1224–1230 (2009).

55 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* 374(9683), 39–47 (2009).

56 Astrup A, Rossner S, Van Gaal L *et al.* Effects of liraglutide in the treatment of obesity: a randomised, double-blind, placebo-controlled study. *Lancet* 374(9701), 1606–1616 (2009).

57 Dicker D. DPP-4 inhibitors: impact on glycemic control and cardiovascular risk factors. *Diabetes Care* 34(Suppl. 2), S276–S278 (2011).

58 Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: the National Health and Nutrition Examination Survey. *Diabetes Care* 29(3), 531–537 (2006).

59 Wu MS, Johnston P, Sheu WH *et al.* Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. *Diabetes Care* 13(1), 1–8 (1990).

60 Jeppesen J, Zhou MY, Chen YD, Reaven GM. Effect of metformin on postprandial lipemia in patients with fairly to poorly controlled NIDDM. *Diabetes Care* 17(10), 1093–1099 (1994).

61 Haukeland JW, Konopski Z, Eggesbo HB *et al.* Metformin in patients with non-alcoholic fatty liver disease: a randomized, controlled trial. *Scand. J. Gastroenterol.* 44(7), 853–860 (2009).

62 Akyuz F, Demir K, Ozdil S *et al.* The effects of rosiglitazone, metformin, and diet with exercise in nonalcoholic fatty liver disease. *Digest. Dis. Sci.* 52(9), 2359–2367 (2007).

63 Brunt EM, Neuschwander-Tetri BA, Oliver D, Wehmeier KR, Bacon BR. Nonalcoholic steatohepatitis: histologic features and clinical correlations with 30 blinded biopsy specimens. *Hum. Pathol.* 35(9), 1070–1082 (2004).

64 Boettcher E, Csako G, Pucino F, Wesley R, Loomba R. Meta-analysis: pioglitazone improves liver histology and fibrosis in patients with non-alcoholic steatohepatitis. *Aliment. Pharmacol. Ther.* 35(1), 66–75 (2012).

65 Belfort R, Harrison SA, Brown K *et al.* A placebo-controlled trial of pioglitazone in subjects with nonalcoholic steatohepatitis. *N. Engl. J. Med.* 355(22), 2297–2307 (2006).

66 Goldberg RB, Kendall DM, Deeg MA *et al.* A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with Type 2 diabetes and dyslipidemia. *Diabetes Care* 28(7), 1547–1554 (2005).

67 Berneis K, Rizzo M, Stettler C *et al.* Comparative effects of rosiglitazone and pioglitazone on fasting and postprandial low-density lipoprotein size and subclasses in patients with Type 2 diabetes. *Expert Opin. Pharmacother.* 9(3), 343–349 (2008).

68 Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. *Arch. Intern. Med.* 164(19), 2097–2104 (2004).

69 Hanefeld M. The role of pioglitazone in modifying the atherogenic lipoprotein profile. *Diabetes Obes. Metab.* 11(8), 742–756 (2009).

70 Zieve FJ, Kalin MF, Schwartz SL, Jones MR, Bailey WL. Results of the glucose-lowering effect of WelChol study (GLOWS): a randomized, double-blind, placebo-controlled pilot study evaluating the effect of colesevelam hydrochloride on glycemic control in subjects with Type 2 diabetes. *Clin. Ther.* 29(1), 74–83 (2007).

71 Goldberg RB, Fonseca VA, Truitt KE, Jones MR. Efficacy and safety of colesevelam in patients with Type 2 diabetes mellitus and inadequate glycemic control receiving insulin-based therapy. *Arch. Intern. Med.* 168(14), 1531–1540 (2008).

72 Rosenson RS, Abby SL, Jones MR. Colesevelam HCl effects on atherogenic lipoprotein subclasses in subjects with Type 2 diabetes. *Atherosclerosis* 204(2), 342–344 (2009).

73 Johnson JA, Simpson SH, Toth EL, Majumdar SR. Reduced cardiovascular morbidity and mortality associated with metformin use in subjects with Type 2 diabetes. *Diabet. Med.* 22(4), 497–502 (2005).

74 Roussel R, Travert F, Pasquet B *et al.* Metformin use and mortality among patients with diabetes and atherothrombosis. *Arch. Intern. Med.* 170(21), 1892–1899 (2010).

75 Festa A, D'agostino R Jr, Tracy RP, Haffner SM. Elevated levels of acute-phase proteins and plasminogen activator inhibitor-1 predict the development of Type 2 diabetes: the insulin resistance atherosclerosis study. *Diabetes* 51(4), 1131–1137 (2002).

76 Sobel BE, Hardison RM, Genuth S *et al.* Profibrinolytic, antithrombotic, and antiinflammatory effects of an insulin-sensitizing strategy in patients in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Circulation* 124(6), 695–703 (2011).

77 Nagi DK, Yudkin JS. Effects of metformin on insulin resistance, risk factors for cardiovascular disease, and plasminogen activator inhibitor in NIDDM subjects. A study of two ethnic groups. *Diabetes Care* 16(4), 621–629 (1993).

78 Mccoy RG, Irving BA, Soop M *et al.* Effect of insulin sensitizer therapy on atherothrombotic and inflammatory profiles associated with insulin resistance. *Mayo Clin. Proc.* 87(6), 561–570 (2012).

79 Gribble FM, Reimann F. Sulphonylurea action revisited: the post-cloning era. *Diabetologia* 46(7), 875–891 (2003).

80 Quast U, Stephan D, Bieger S, Russ U. The impact of ATP-sensitive K^+ channel subtype selectivity of insulin secretagogues for the coronary vasculature and the myocardium. *Diabetes* 53(Suppl. 3), S156–S164 (2004).

81 Abdelmoneim AS, Hasenbank SE, Seubert JM, Brocks DR, Light PE, Simpson SH. Variations in tissue selectivity amongst insulin secretagogues: a systematic review. *Diabetes Obes. Metab.* 14(2), 130–138 (2012).

82 Farid TA, Nair K, Masse S *et al.* Role of KATP channels in the maintenance of ventricular fibrillation in cardiomyopathic human hearts. *Circ. Res.* 109(11), 1309–1318 (2011).

83 Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: a meta-analysis of observational studies. *Diabetes Care* 31(8), 1672–1678 (2008).

84 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* 352(9131), 837–853 (1998).

85 Simpson SH, Majumdar SR, Tsuyuki RT, Eurich DT, Johnson JA. Dose-response relation between sulfonylurea drugs and mortality in Type 2 diabetes mellitus: a population-based cohort study. *CMAJ* 174(2), 169–174 (2006).

86 Zoungas S, Patel A, Chalmers J *et al.* Severe hypoglycemia and risks of vascular events and death. *N. Engl. J. Med.* 363(15), 1410–1418 (2010).

87 Qayyum R, Adomaityte J. A meta-analysis of the effect of thiazolidinediones on blood pressure. *J. Clin. Hypertens. (Greenwich)* 8(1), 19–28 (2006).

88 Law RE, Goetze S, Xi XP *et al.* Expression and function of PPAR in rat and human vascular smooth muscle cells. Circulation 101(11), 1311–1318 (2000).

89 Lim S, Jin CJ, Kim M *et al.* PPARγ gene transfer sustains apoptosis, inhibits vascular smooth muscle cell proliferation, and reduces neointima formation after balloon injury in rats. *Arterioscler. Thromb. Vasc. Biol.* 26(4), 808–813 (2006).

90 Goetze S, Xi X, Kawano H *et al.* PPAR[γ]-ligands inhibit migration mediated by multiple chemoattractants in vascular smooth muscle cells. *J. Cardiovasc. Pharmacol.* 33(5), 798–806 (1999).

91 Kruszynska YT, Yu JG, Olefsky JM, Sobel BE. Effects of troglitazone on blood concentrations of plasminogen activator inhibitor 1 in patients with Type 2 diabetes and in lean and obese normal subjects. *Diabetes* 49(4), 633–639 (2000).

92 Qayyum R, Adomaityte J. Meta-analysis of the effect of thiazolidinediones on serum C-reactive protein levels. *Am. J. Cardiol.* 97(5), 655–658 (2006).

93 Mazzone T, Meyer PM, Feinstein SB *et al.* Effect of pioglitazone compared with glimepiride on carotid intima-media thickness in Type 2 diabetes: a randomized trial. *JAMA* 296(21), 2572–2581 (2006).

94 Patel D, Walitt B, Lindsay J, Wilensky RL. Role of pioglitazone in the prevention of restenosis and need for revascularization after bare-metal stent implantation: a meta-analysis. *JACC Cardiovasc. Interv.* 4(3), 353–360 (2011).

95 Charbonnel B, Dormandy J, Erdmann E, Massi-Benedetti M, Skene A. The prospective pioglitazone clinical trial in macrovascular events (PROactive): can pioglitazone reduce cardiovascular events in diabetes? Study design and baseline characteristics of 5238 patients. *Diabetes Care* 27(7), 1647–1653 (2004).

96 Betteridge DJ, Defronzo RA, Chilton RJ. PROactive: time for a critical appraisal. *Eur. Heart J.* 29(8), 969–983 (2008).

97 Ferrannini E, Betteridge DJ, Dormandy JA *et al.* High-density lipoprotein-cholesterol and not HbA1c was directly related to cardiovascular outcome in PROactive. *Diabetes Obes. Metab.* 13(8), 759–764 (2011).

98 Home PD, Pocock SJ, Beck-Nielsen H *et al.* Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for Type 2 diabetes (RECORD): a multicentre, randomised, open-label trial. *Lancet* 373(9681), 2125–2135 (2009).

99 Guan Y, Hao C, Cha DR *et al.* Thiazolidinediones expand body fluid volume through PPARγ stimulation of ENaC-mediated renal salt absorption. *Nat. Med.* 11(8), 861–866 (2005).

100 Karalliedde J, Buckingham RE. Thiazolidinediones and their fluid-related adverse effects: facts, fiction and putative management strategies. *Drug Saf.* 30(9), 741–753 (2007).

101 Nissen SE, Wolski K. Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *N. Engl. J. Med.* 356(24), 2457–2471 (2007).

102 Gerstein HC, Miller ME, Byington RP *et al.* Effects of intensive glucose lowering in Type 2 diabetes. *N. Engl. J. Med.* 358(24), 2545–2559 (2008).

103 Duckworth WC, Mccarren M, Abraira C. Glucose control and cardiovascular complications: the VA Diabetes Trial. *Diabetes Care* 24(5), 942–945 (2001).

104 Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA* 298(10), 1189–1195 (2007).

105 Kaul S, Bolger AF, Herrington D, Giugliano RP, Eckel RH. Thiazolidinedione drugs and cardiovascular risks: a science advisory from the American Heart Association and American College of Cardiology Foundation. *Circulation* 121(16), 1868–1877 (2010).

106 Deacon CF, Plamboeck A, Rosenkilde MM, De Heer J, Holst JJ. GIP-(3-42) does not antagonize insulinotropic effects of GIP at physiological concentrations. *Am. J. Physiol. Endocrinol. Metab.* 291(3), E468–E475 (2006).

107 Zhong J, Rao X, Rajagopalan S. An emerging role of dipeptidyl peptidase 4 (DPP4) beyond glucose control: Potential implications in cardiovascular disease. *Atherosclerosis* 226(2), 305–314 (2012).

108 Nikolaidis LA, Mankad S, Sokos GG *et al.* Effects of glucagon-like peptide-1 in patients with acute myocardial infarction and left ventricular dysfunction after successful reperfusion. *Circulation* 109(8), 962–965 (2004).

109 Defronzo RA. Bromocriptine: a sympatholytic, D2-dopamine agonist for the treatment of Type 2 diabetes. *Diabetes Care* 34(4), 789–794 (2011).

110 Kerr JL, Timpe EM, Petkewicz KA. Bromocriptine mesylate for glycemic management in Type 2 diabetes mellitus. *Ann. Pharmacother.* 44(11), 1777–1785 (2010).

111 Gaziano JM, Cincotta AH, O'Connor CM *et al.* Randomized clinical trial of quick-release bromocriptine among patients with Type 2 diabetes on overall safety and cardiovascular outcomes. *Diabetes Care* 33(7), 1503–1508 (2010).

112 Moghetti P, Castello R, Negri C *et al.* Metformin effects on clinical features, endocrine and metabolic profiles, and insulin sensitivity in polycystic ovary syndrome: a randomized, double-blind, placebo-controlled 6-month trial, followed by open, long-term clinical evaluation. *J. Clin. Endocrinol. Metab.* 85(1), 139–146 (2000).

113 Creanga AA, Bradley HM, McCormick C, Witkop CT. Use of metformin in polycystic ovary syndrome: a meta-analysis. *Obstetrics Gynecol.* 111(4), 959–968 (2008).

114 Legro RS, Barnhart HX, Schlaff WD *et al.* Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *N. Engl. J. Med.* 356(6), 551–566 (2007).

115 Xiao J, Chen S, Zhang C, Chang S. The effectiveness of metformin ovulation induction treatment in patients with PCOS: a systematic review and meta-analysis. *Gynecol. Endocrinol.* 28(12), 956–960 (2012).

116 Archer JS, Chang RJ. Hirsutism and acne in polycystic ovary syndrome. *Best Pract. Res. Clin. Obstetrics Gynaecol.* 18(5), 737–754 (2004).

117 Harborne L, Fleming R, Lyall H, Sattar N, Norman J. Metformin or antiandrogen in the treatment of hirsutism in polycystic ovary syndrome. *J. Clin. Endocrinol. Metab.* 88(9), 4116–4123 (2003).

118 Ibanez L, Valls C, Potau N, Marcos MV, De Zegher F. Sensitization to insulin in adolescent girls to normalize hirsutism, hyperandrogenism, oligomenorrhea, dyslipidemia, and hyperinsulinism after precocious pubarche. *J. Clin. Endocrinol. Metab.* 85(10), 3526–3530 (2000).

119 Sharma ST, Nestler JE. Prevention of diabetes and cardiovascular disease in women with PCOS: treatment with insulin sensitizers. *Best Pract. Res. Clin. Endocrinol. Metab.* 20(2), 245–260 (2006).

120 Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. *Diabetologia* 49(12), 2819–2823 (2006).

121 Lewis JD, Ferrara A, Peng T *et al.* Risk of bladder cancer among diabetic patients treated with pioglitazone: interim report of a longitudinal cohort study. *Diabetes Care* 34(4), 916–922 (2011).

122 Elashoff M, Matveyenko AV, Gier B, Elashoff R, Butler PC. Pancreatitis, pancreatic, and thyroid cancer with glucagon-like peptide-1-based therapies. *Gastroenterology* 141(1), 150–156 (2011).

123 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* 151(4), 1473–1486 (2010).

124 Col NF, Ochs L, Springmann V, Aragaki AK, Chlebowski RT. Metformin and breast cancer risk: a meta-analysis and critical literature review. *Breast Cancer Res. Treat.* 135(3), 639–646 (2012).

125 Stevens RJ, Ali R, Bankhead CR *et al.* Cancer outcomes and all-cause mortality in adults allocated to metformin: systematic review and collaborative meta-analysis of randomised clinical trials. *Diabetologia* 55(10), 2593–2603 (2012).

126 Bauman WA, Shaw S, Jayatilleke E, Spungen AM, Herbert V. Increased intake of calcium reverses vitamin B12 malabsorption induced by metformin. *Diabetes Care* 23(9), 1227–1231 (2000).

127 Colucciello M. Vision loss due to macular edema induced by rosiglitazone treatment of diabetes mellitus. *Arch. Ophthalmol.* 123(9), 1273–1275 (2005).

128 Fong DS, Contreras R. Glitazone use associated with diabetic macular edema. *Am. J. Ophthalmol.* 147(4), 583.e1–586.e1 (2009).

129 Idris I, Warren G, Donnelly R. Association between thiazolidinedione treatment and risk of macular edema among patients with Type 2 diabetes. *Arch. Intern. Med.* 172(13), 1005–1011 (2012).

130 Motola D, Piccinni C, Biagi C *et al.* Cardiovascular, ocular and bone adverse reactions associated with thiazolidinediones: a disproportionality analysis of the US FDA adverse event reporting system database. *Drug Saf.* 35(4), 315–323 (2012).

131 Nissen SE, Nicholls SJ, Wolski K *et al.* Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with Type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA* 299(13), 1561–1573 (2008).

132 Dormandy J, Bhattacharya M, Van Troostenburg De Bruyn AR. Safety and tolerability of pioglitazone in high-risk patients with Type 2 diabetes: an overview of data from PROactive. *Drug Saf.* 32(3), 187–202 (2009).

133 Loke YK, Singh S, Furberg CD. Long-term use of thiazolidinediones and fractures in Type 2 diabetes: a meta-analysis. *CMAJ* 180(1), 32–39 (2009).

134 Meier C, Kraenzlin ME, Bodmer M, Jick SS, Jick H, Meier CR. Use of thiazolidinediones and fracture risk. *Arch. Intern. Med.* 168(8), 820–825 (2008).

135 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* 33(11), 2349–2354 (2010).

136 Byetta®, package insert. Amylin Pharmaceuticals Inc., CA, USA.

137 Victoza®, package insert. Novo Nordisk, NJ, USA.

Websites

201 Truven Health Analytics. Micromedex® Gateway. www.thomsonhc.com/home/dispatch

■ **Leading pharmacology reference resource available online and through many libraries for clinical reference.**

202 US FDA drugs. FDA drug safety communication: reminder to healthcare providers and patients to enroll in the Avandia-Rosiglitazone Medicines Access Program (2011). www.fda.gov/Drugs/DrugSafety/ucm277629.htm

203 Health Canada. Public communication: Health Canada endorsed important safety information on ACTOS (pioglitazone hydrochloride). Potential association between ACTOS (pioglitazone hydrochloride) and bladder cancer (2012). www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/public/_2012/actos_3_pc-cp-eng.php

204 US FDA safety information. Victoza (liraglutide [rDNA origin]) injection: REMS – risk of thyroid C-cell tumors, acute pancreatitis (2011). www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm258826.htm

205 US FDA safety information. Sitagliptin (marketed as Januvia® and Janumet®) – acute pancreatitis (2009). www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm183800.htm