Oral Antihyperglycemic Treatment Options for Type 2 Diabetes Mellitus

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KEYWORDS

• Metformin • Sulfonylureas • Thiazolidinediones
• Sodium-glucose transporter-2 inhibitors (SGLT2 inhibitors) • Colesevelam
• Bromocriptine • Type 2 diabetes mellitus

KEY POINTS

- Metformin is the best available combination of low-cost, low-risk, high-efficacy oral therapy for type 2 diabetes mellitus.
- The lowest-cost oral add-on drug to metformin is a sulfonylurea.
- A sodium-glucose transporter type 2 inhibitor, an alpha-glucosidase inhibitor, or a thiazolidinedione, is a reasonable second or tertiary add-on option.
- Alpha-glucosidase inhibitors, colesevelam, and bromocriptine mesylate are niche drugs and may have value in cardiovascular risk reduction, but more information from clinical trials and/or meta-analyses is needed.

INTRODUCTION

The worldwide epidemic of type 2 diabetes mellitus (T2DM) has made diagnosing, counseling, and prescribing for newly diagnosed patients an almost reflex process for many primary care physicians. Patients overwhelmingly prefer initial therapy to be with an oral medication, rather than an injectable (ie, insulin) and, as patient advocates, their treating physicians comply with this request. The past 20 years have transformed oral treatment options for T2DM from a single option (sulfonylureas [SUs]) to at least 9 different classes of drugs, enabling rational, individually customized combination therapy. Incretin analogues and dipeptidyl peptidase-4 (DPP-4) inhibitors are covered in detail elsewhere in this issue. This article reviews the mechanism of action, efficacy, major untoward effects, and impact of other oral therapies on T2DM and associated health risks; most notably, cardiovascular disease.

The likelihood of success for prescribed oral therapy can be estimated from simple observations and measurements at the point of care. **Box 1** emphasizes the

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Box 1
Predictors of response to oral antihyperglycemic drugs (consider initial therapy with insulin if multiple points are negative)

- Newly diagnosed T2DM
- Obesity (body mass index >30 kg/m^2)
- Absence of symptomatic diabetes mellitus (eg, rapid weight loss, severe polyuria, severe polydipsia)
- Hemoglobin A1c (HbA1c) less than 10%
- Fasting serum glucose less than 250 mg/dL
- Absence of nonfasting ketonuria

characteristics of patients likely to respond well to oral therapy for T2DM; patients who lack multiples of these characteristics are best served by an initial prescription for insulin therapy (covered in a separate article by Meah and Juneja in this issue).

Rules of thumb estimating the impact of drug monotherapy, and subsequent add-on drugs, are highlighted in **Box 2**. Available drug therapies, by class, are overviewed individually, with regard to mechanism of action, efficacy, adverse effects, and influence on cardiovascular disease and neoplasia.

METFORMIN

Metformin was first available in the United States in 1995, and was long delayed because of fear of fatal lactic acidosis, which had led to market withdrawal of another biguanide drug, phenformin, in 1970. Practitioners have learned to use the drug cautiously or not at all in patients thought to be at increased risk for lactic acidosis, including the elderly, patients with congestive heart failure (CHF), and patients with chronic kidney disease. However, it has become the number 1 most prescribed oral antihyperglycemic agent in the world, while also becoming one of the lowest-cost and lowest-risk agents available. As metformin approaches its 20th anniversary in the United States, its track record of low cost, low risk, and low frequency of troublesome side effects justifies its place as the first choice when oral therapies for T2DM are prescribed for patients. Many of the original cautions and presumed contraindications for prescribing should be relearned.

Metformin's primary action is suppression of hepatic glucose generation, and the exact molecular action is still not understood. Enhanced activity of AMP kinase (AMPK) may be either caused by a direct agonist effect on AMPK, or by suppression of hepatic mitochondrial oxidation, resulting in a higher AMP/ATP ratio, and thence secondary activation of AMPK.[1,2] An apparent insulin-sensitizing effect of metformin on muscle glucose uptake may simply be escape from the glucose toxicity phenomenon, caused by reduced endogenous glucose production.

Box 2
Anticipated efficacy of initial and add-on oral antihyperglycemic drugs

- Initial drug: ΔHbA1c = −1.5% to −2.0%
- First add-on: ΔHbA1c = −1% to −1.5%
- Second add-on: ΔHbA1c = −0.5% to −1%

Efficacy of metformin, either as a stand-alone or in combination with SU, was established in the United Kingdom Prospective Diabetes Study (UKPDS). After 3 years' usage in the UKPDS study, 79% of 207 obese patients originally randomized to metformin only were still taking the drug; only 10% required addition of another agent because of inadequate response to monotherapy. Mean hemoglobin A1c (HbA1c) at the 3-year point in the study was 7.1% for metformin only, versus 7.8% for the obese control group.[3] In a US trial, DeFronzo and Goodman[4] randomized 289 patients to metformin versus placebo, attaining a mean on-treatment HbA1c level of 7.1% versus 8.6%, in a 29-week trial.

In the UKPDS, users of metformin had significantly reduced rates of microvascular diabetic complications. A subsequent 10-year follow-up study of UKPDS patients showed risk reduction for cardiovascular disease events favoring metformin users, with relative risks versus nonusers of 0.79 for any diabetes-related end point, 0.70 for diabetes-related death, 0.73 for all-cause mortality, and 0.67 for myocardial infarction (MI).[5] Metformin plus insulin was not allowed in the UKPDS study protocol, but Hemingsen and colleagues[6] conducted a meta-analysis of 23 clinical trials totaling 2117 patients, which compared outcomes of metformin plus insulin versus insulin-only treatment regimens. The quality of evidence from these trials was generally poor, but identified significantly lower HbA1c (−0.5%), less weight gain (by 1 kg), and reduced insulin dose (by 5 units/d) in the metformin plus insulin groups, with a greater risk of hypoglycemia (odds ratio, 2.83) and no conclusive difference in cardiovascular or all-cause mortality.

There is evidence that metformin may reduce cancer risk, possibly by ameliorating hyperinsulinemia's activation of the proneoplastic enzyme, mammalian target of rapamycin (mTOR).[7] In a 10-year follow-up study of patients with T2DM, new cancer incidence was 7.3% in users, versus 11.6% in nonusers.[8] Breast cancer incidence was significantly lower in women with T2DM who used metformin, as opposed to women who did not (odds ratio, 0.44).[9] In another study of patients with diagnosed breast cancer, complete response to neoadjuvant chemotherapy occurred in 24% of metformin-treated patients with T2DM, versus 8% of non–metformin-treated patients with T2DM, and in 16% of nondiabetic individuals.[10] A hospital-based study of pancreatic adenocarcinoma identified an odds ratio of 0.38 for metformin users. Metformin use may reduce both the incidence[11] and the prognosis of prostate cancer.[12]

The most common adverse effects limiting use of metformin are gastrointestinal, most commonly diarrhea/fecal urgency and nausea. These adverse effects are reported by up to 30% of users within the first 1 to 2 weeks of usage, but resolve in all but 5% to 10%. The adverse effects are severe enough to preclude use in approximately 5% of users[13]; in the UKPDS, 11% of patients randomized to metformin were unable to tolerate therapy.[3] Common interventions to improve tolerance of metformin include taking the medication with meals (rather than on an empty stomach), starting the medication at a low dose (500 mg, with the evening meal), and advancing the dose gradually week by week, and using an extended-release preparation. There is anecdotal evidence that these interventions help some patients, but this has not been validated by evidence from clinical trials. Metformin impairs intestinal absorption of vitamin B_{12}, and in one study vitamin B_{12} levels were 19% lower in the metformin versus the placebo group at the end of the 52-month study period. Vitamin B_{12} deficiency (serum level <150 pmol/L) occurred in 9.9% of the metformin group, versus 2.7% of the placebo group; low vitamin B_{12} (serum level 150–220 pmol/L) was found in 18.2% of the metformin group, and in 7% of the placebo group.[14] Periodic measurement of serum B_{12} levels is warranted, in the authors opinion.

Fear of lactic acidosis was a major concern when metformin first became available in the United States.[15] The estimated frequency of lactic acidosis is not in excess of 3

cases per 100,000 patients treated[16]; furthermore, a recent Cochrane Review of 347 clinical trials and observational studies concluded that, compared with other treatments for T2DM, metformin was not associated with any risk for lactic acidosis.[17] A comprehensive review by Scheen and Paquot[18] identified reduced risk for all-cause mortality in metformin users versus other T2DM treatment regimens, in the settings of stable coronary heart disease (relative risk, 0.72–0.76), following acute coronary syndrome (relative risk, 0.4–0.8), and in CHF (relative risk, 0.65–0.87). In a systematic review of observational studies numbering more than 34,000 patients with CHF, Eurich and colleagues[19] found metformin use to be associated with reduced (not increased) risk for mortality (relative risk vs nonusers, 0.80), and even when left ventricular ejection fraction was severely reduced the relative risk for mortality was not significantly different than for nonusers (0.91). Among patients with CHF and chronic kidney disease, metformin use was also associated with reduced mortality risk (relative risk, 0.81 for metformin users vs nonusers). The following recommendations for metformin use based on renal function have been offered independently by several critical reviews: no dose adjustment for estimated glomerular filtration rate (eGFR) greater than or equal to 45 mL/min/1.73 m^2; limit dose to 50% of maximum recommended for eGFR greater than or equal to 30 to less than 45 mL/min/1.73 m^2; and discontinue metformin only for eGFR less than 30 mL/min/1.73 m^2.[16,20,21] Based on the Eurich and colleagues[19] systematic review, and based on US Food and Drug Administration (FDA) change in prescribing information for metformin in 2010, CHF independent of eGFR less than 30 mL/min/1.73 m^2 should no longer be considered a contraindication to metformin use.[19]

INSULIN SECRETOGOGUES

Sulfonylureas

Until the introduction of metformin in 1995, SUs were the only oral antihyperglycemic class available in the United States. The SU class might now be considered the "Rodney Dangerfield" of oral therapies for T2DM. Like the late comedian, whose signature line bemoaned that "he got no respect at all," the SU class has been disrespected over the years for possibly increasing cardiovascular risk, and possibly accelerating pancreatic islet cell burnout. Despite the concerns, SUs remain widely prescribed, because of familiarity, relative lack of nonglycemic adverse effects, very low cost, and generally good efficacy in controlling glycemia, at least in the early phases of T2DM. The SUs prevalently used in the United States are the second-generation SUs glyburide and glipizide, and the third-generation SU, glimepiride.

The mechanism of action common to all the SU drugs involves binding to the pancreatic islet cell sulfonylurea receptor 1 (SUR1), which results in closure of the cell membrane ATP-sensitive potassium channel (K^+_{ATP}), thereby causing membrane depolarization, influx of calcium ions, and subsequent release of insulin from storage vesicles.[22,23] A Cochrane Review of clinical trial and observation study data totaling more than 22,000 patients, and including both first-generation and second-generation SUs, identified a mean 1.01% reduction in HbA1c with SU monotherapy.[24] Initiation of SU monotherapy in previously treatment-naive individuals with T2DM can be expected to produce a 1% to 2% reduction in HbA1c,[25] averaging about 1.5%.[26,27]

Based on the UKPDS trial results, slightly more than half of patients newly diagnosed with T2DM can be expected to attain a goal HbA1c less than 7% on SU monotherapy. In the UKPDS, only 24% of patients treated by intent to a goal HbA1c level of less than 7.0% were achieving that goal with SU alone after 9 years; 50% were failing to reach goal by 3 years.[28] With regard to purported accelerated burnout of islet cells

with SU therapy, some investigators have pointed out that the rate of monotherapy failure for metformin in UKPDS was similar to that for SU, suggesting that progressive loss of islet cell function is simply part of the natural history of T2DM.[29,30] In the ADOPT (A Diabetes Outcome Progression Trial) trial, monotherapy failure after 5 years of treatment was 34% for glyburide, 21% for metformin, and 15% for rosiglitazone.[31] Based on available dose-response curves, many experienced clinicians recommend a maximum clinical dose of an SU drug of approximately half the US FDA-approved maximal dose.[25,32] In one dose-response trial of glimepiride, the mean reduction in HbA1c was 1.9% at the maximal dose, 8 mg daily, and 1.8% at 4 mg daily.[33] Some investigators have suggested a tachyphylaxis response to high-dose SU, with down-regulation of SUR1 binding and signaling transduction.[34]

Efficacy of SU as add-on therapy to metformin, and thiazolidinedione (TZD) has been established, with efficacy of ΔHbA1c −0.47% to −1.3%,[27] and −1.76% to −2.68%,[35] respectively. In these studies of combination oral therapy including SU, adverse events except for hypoglycemia were similar: SU-plus groups experienced hypoglycemia about twice as often as the comparator groups (relative risk, 2.41).[27]

The most frequent serious adverse effect of SUs is hypoglycemia, occurring at a frequency of 1.7% of glimepiride users and 5% of glyburide users within the first month of therapy in one study.[25] In a German study, glyburide was responsible 6 times as often as was glimepiride for severe hypoglycemic events requiring professional care, despite many more active prescriptions in use for glimepiride.[36] Because risk for hypoglycemia is greater in persons with chronic kidney disease, all of the SUs are considered contraindicated at serum creatinine greater than 1.8 mg/dL (eGFR <30 mL/min/1.73 m^2); at any degree of impaired renal function, glipizide or glimepiride is preferred to glyburide, because of its longer half-life and inherently greater risk for hypoglycemia. Weight gain is also a frequent, possibly ubiquitous occurrence in SU-treated patients; over a 6-year period in the United Kingdom Prospective Diabetes Study, patients randomized to treatment with an SU gained a mean of 5.3 kg.[37] In the UKPDS, the prevalent SUs were chlorpropamide and glyburide; there is evidence that glimepiride may be associated with less weight gain over time than other drugs of the SU class.[25,26] Glyburide, glipizide, and glimepiride are all rated as class C in pregnancy, and glyburide has been studied and established as noninferior to insulin therapy in gestational diabetes, with no evidence of adverse fetal or maternal outcomes.[38,39]

The cardiovascular safety question that has dogged the SU class remains unresolved 43 years after the University Group Diabetes Project (UGDP) study reported a disproportionate number of acute MIs in patients receiving tolbutamide, a first-generation SU.[40] The UKPDS study partly assuaged concerns, with a nonsignificant decreased number of cardiovascular events during the original trial,[41] and a reduced rate (vs the non–SU-using usual care group) during the 10-year follow-up study, including risk ratios of 0.87 for all-cause mortality and 0.85 for MI, versus usual care.[5] However, a large retrospective cohort study of patients attending US Veterans Administration care facilities compared 98,665 veterans who received SU monotherapy with 155,025 receiving metformin monotherapy. After adjustment for confounding factors, a hazard ratio of 1.26 for glyburide versus metformin (95% confidence interval [CI], 1.16–1.37), and 1.15 for glipizide versus metformin (CI, 1.06–1.26) was identified in this study for the composite end point of acute MI, stroke, or death.[42]

It is possible that some of the disparity in cardiovascular outcomes with SU drugs can be explained by different pharmacologic properties of individual SUs. Although the various SU agents have similar agonist effects on the pancreatic islet SUR1 receptor, they differ in the degree of agonist activity on myocardial and coronary vascular SUR2 receptors.[43,44] Glipizide and glimepiride have low agonist effects on the

SUR2 receptor, whereas glyburide has significant agonist effect on SUR2. Opening of the myocardial K^+_{ATP} is important in the ischemic preconditioning phenomena, which can limit infarct size following the acute ischemic insult. Closure of this channel by activation of the SUR2 receptor is thought to interfere with ischemic preconditioning, thereby potentially extending infarct size and adversely affecting prognosis.[45] There is experimental and observational evidence to support a concept that glyburide is uniquely hazardous among the 3 SUs in common use in the United States with regard to coronary disease outcomes. In a study conducted in Taiwan, Lee and Chou[46] noted differential response to glimepiride and glyburide in both nondiabetic and diabetic patients undergoing coronary angioplasty, with lower ischemic burden scores in patients receiving glimepiride as opposed to glyburide. In a prospective study of 1310 patients admitted for acute MI over a 1-month period to French hospitals in 2005, SU use at the time of admission was not associated with an in-hospital increased risk for complications or mortality. On the contrary, SU use before admission was associated with lower mortality (3.9%) than was use of other oral agents (mortality 6.4%), insulin (mortality 9.4%), or no T2DM drug therapy (mortality 8.4%). However, the shorter-acting and more pancreatic islet–specific ATP channel agonists gliclazide and glimepiride were associated with lower in-hospital mortality (2.7%) than was the longer-acting, non–organ-specific K^+ ATP channel agonist glyburide (in-hospital mortality, 7.9%).[47]

There is controversy as to whether or not SUs are associated with increased risk for common cancers, with data from several studies summarized in **Table 1**. Taken in the aggregate, findings from these studies lead to a conclusion that, although SUs may not definitely increase the risk for malignancies, there is no evidence that they reduce cancer risk.

Based on low toxicity, low cost, and extensive worldwide experience, SU drugs are still deserving of a role as add-on therapy for patients failing to achieve treatment goals on regimens of 1 or 2 drugs that include metformin. Glyburide is associated with both a greater risk of hypoglycemia and greater association with complications arising from acute coronary presentations. It therefore seems prudent to preferentially use glipizide or glimepiride. It is unclear whether glyburide offers any justification for continued use, given the concerns with disproportionate risk,[51,52] except in pregnancy and in countries in which glyburide is the only available SU.

Glinides

Two drugs of the glinide class, repaglinide and nateglinide, are available for use. Like SUs, these drugs work as agonists of the SUR1 receptor, but have extremely short

Table 1
Relative risk of incident cancer with sulfonylureas (vs nonusers)

Study	Cancer Type	Number of Patients	Relative Risk
Singh et al,[48] 2013	Hepatocellular	334,307	1.61 (95% CI, 1.16–2.24)
Chang et al,[49] 2012	Any	40,970	1.08 (95% CI, 1.01–1.15)
Thakkar et al,[50] 2013	Any (meta-analysis)	315,517	1.55 (cohort studies) (95% CI, 1.48–1.63) 1.02 (case-control studies) (95% CI, 0.93–1.13) 1.17 (RCTs) (95% CI, 0.95–1.45)
Soranna et al,[7] 2012	Any (meta-analysis)	35,642	0.97 (95% CI, 0.82–1.14)

Abbreviation: RCTs, randomized controlled trials.

durations of action. They are best considered as non-SU SUs," and use is best reserved for persons responsive to SU but susceptible to fasting hypoglycemia, or for persons with true SU allergy.[53,54]

THIAZOLIDINEDIONES

If SUs are the "Rodney Dangerfield," it seems fair to label TZDs as the "Warren G. Harding" of antihyperglycemic drugs, because Harding was a US President elected largely on the basis that he looked like a president, and many TZD effects look as if they should be ideal treatment of T2DM. Rosiglitazone and pioglitazone bind to peroxisome proliferator activating receptor gamma (PPARγ) receptors to form heterodimers with retinoid-X receptors, which then bind to various response elements of the genome, resulting in transactivation of gene products enhancing insulin action, and transrepression of nuclear signal pathways generally unfavorable to insulin action (notably, nuclear factor kappa B [NF-kB]).[55,56] In adipose tissue, PPARγ activation blocks release of free fatty acids (FFAs), reduces tumor necrosis factor alpha (TNF-α), and increases adiponectin. TZDs promote expansion of the subcutaneous adipose compartment, and contraction of the visceral adipose compartment.[57] The lipid steal hypothesis suggests that increased uptake of FFAs by adipose tissue allows FFAs to escape from muscle, liver, and islet cells, resulting in improved insulin action and increased insulin secretion.[55,56]

Clinical efficacy trials of the TZD drugs have all shown significant improvement in HbA1c, as monotherapy versus placebo, or as add-on therapy to metformin, SU, and insulin regimens. Monotherapy trials of pioglitazone 15 to 45 mg produced ΔHbA1c versus placebo of up to -1.6%, at the study end points.[58] Compared with placebo as add-on therapy to metformin, pioglitazone produced ΔHbA1c up to -1.4%; as add-on therapy to SU, it produced ΔHbA1c up to -1.6%; and as add-on to insulin, it produced ΔHbA1c up to -1.0%.[58,59] Monotherapy trials of rosiglitazone 2 to 8 mg daily likewise produced ΔHbA1c of up to -1.5% versus placebo.[58] Compared with placebo as add-on therapy to metformin, SU, and insulin, rosiglitazone 2 to 8 mg daily produced ΔHbA1c up to -2.3%, -1.0%, and -1.3%, respectively.[58,59]

TZDs have shown nonglycemic pleiotropic effects on numerous surrogate markers of atherosclerotic cardiovascular disease, including reduced carotid artery intimal media thickness on carotid ultrasonography. Because of the numerous salutary effects of TZDs on markers of inflammation, thrombosis, and endothelial health (summarized in **Box 3**), the use of these agents attracted widespread interest among both researchers and clinicians interested in preventing microvascular and atherosclerotic complications of T2DM.[60–65]

Pioglitazone has shown some utility in the treatment of nonalcoholic fatty liver disease (NAFLD), which is frequently associated with T2DM, and is clinically heralded by variable transaminitis and hepatomegaly. NAFLD is now recognized as a cause of formerly cryptogenic cirrhosis. Use of both rosiglitazone and pioglitazone have been associated with net reduction in hepatic fat; in some studies, pioglitazone seems to reduce hepatic fibrosis in patients with severe NAFLD.[70]

The favorable pleiotropic effects of TZDs on multiple cardiovascular risk factors contrasts with a general lack of disease outcomes improvements. By contrast, the evidence is confluent that these drugs cause or aggravate edema and CHF. Overall, when used as monotherapy, a TZD is associated with edema in 2% to 5% of users; if combined with another oral agent, the risk increases to 6% to 8%; and, if combined with insulin, the risk is about 15%.[71] Relative risk for CHF from 17,579 patients in 3 rosiglitazone and 2 pioglitazone trials ranges from 1.41 to 7.0 versus a comparator

Box 3
Pleiotropic effects of TZDs

Antiinflammatory effects

- ↓hsCRP
- ↓TNF-α
- ↓IL-6
- ↓Vascular adhesion molecules

Antithrombotic effects

- ↓PAI-1
- ↓MMP-9

Lipid composition effects

- ↑HDLc
- ↓TG
- ↑LDL particle size (large fluffy LDLc)

Salutary vascular effects

- ↑eNOS
- ↓Smooth muscle proliferation
- ↓Systolic blood pressure
- ↓Restenosis after coronary angioplasty[66]

Abbreviations: eNOS, endothelial nitric oxide synthase; HDLc, high-density lipoprotein cholesterol; hsCRP, highly sensitive C-reactive protein; IL-6, interleukin 6; LDL, low-density lipoprotein; LDLc, low-density lipoprotein cholesterol; MMP-9, matrix metallopeptidase 9; PAI-1, plasminogen activator inhibitor-1; TG, triglycerides.
Data from Refs.[67–69]

group[71]; a meta-analysis of 7 trials totaling 20,191 participants established a relative risk for CHF of 1.72 (95% CI, 1.21–2.42) for TZD users, versus comparator groups.[72] Estimation of cardiovascular disease risk beyond edema and CHF comes from multiple clinical trials of TZDs. The diabetes reduction assessment with ramipril and rosiglitazone Medication (DREAM) trial of rosiglitazone versus placebo, in 5269 subjects with impaired glucose tolerance, showed reduced incident T2DM, but no reduction in the pooled cardiovascular outcomes of MI, stroke, and cardiovascular death. Incident CHF was greater in the rosiglitazone group, occurring in 0.5%, versus 0.1% in the placebo group.[73] The ADOPT trial, comparing magnitude and durability of response of glycemia in T2DM with rosiglitazone, metformin, or glyburide as oral monotherapy, identified rosiglitazone as the most durable response with regard to HbA1c, but it had no advantage with regard to incident cardiovascular events.[31] The RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) trial of 4447 patients T2DM compared rosiglitazone plus either metformin or SU, versus the combination of metformin and SU, specifically for cardiovascular outcomes. Analysis of RECORD trail data identified an increased risk of CHF among rosiglitazone users (hazard ratio 2.1 [95% CI, 1.35–3.27], vs nonusers), but no significant advantage with regard to microvascular disease, or cardiovascular event-related hospitalization or death.[74] A meta-analysis by Nissen, which drew heavily from unpublished clinical trials registry data, identified odds ratios of

1.43 (95% CI, 1.03–1.98; $P = .03$) for MI, and 1.64 (95% CI, 0.98–2.74; $P = .06$) for cardiovascular death for rosiglitazone use versus comparator groups in the pooled trial data.[75] With subsequent reviews reaching similar conclusions, albeit at lower magnitude of risk, rosiglitazone virtually disappeared from clinical use.

The PROspective pioglitAzone clinical trial in macroVascular events (PROActive) trial, which compared pioglitazone versus placebo as add-on therapy to existing treatment of T2DM, was specifically designed to measure rate of incident cardiovascular disease events and cardiovascular mortality in a high-risk group of patients with prior cardiovascular disease events, but there was no difference in the primary outcomes in the pioglitazone versus placebo groups.[76] Head-to-head comparison seems to favor pioglitazone rather than rosiglitazone, with regard to cardiovascular outcomes, based on data from a meta-analysis of 4 case-control and 12 retrospective cohort studies, in which relative risk for MI was 1.16 (95% CI, 1.07–1.24; $P<.001$) and relative risk of death was 1.14 (95% CI, 1.09–1.20; $P<.001$), for rosiglitazone versus pioglitazone.[77] Caution in accepting that conclusion has been urged based on methodologic flaws in many of the studies.[71] Pioglitazone, but not rosiglitazone, has been associated with an increased risk for bladder cancer; a meta-analysis by Bosetti and colleagues[78] identified a relative risk of 1.42 (95% CI, 1.17–1.72) for pioglitazone use beyond 2 years, versus never-users. No other cancer risk has thus far been linked with either rosiglitazone or pioglitazone.

TZD drugs seem to have an adverse effect on bone health. Among 666 participants with T2DM in the Health, Aging, and Body Composition observational study, self-reported TZD use in women (but not in men) was associated with annualized bone loss of −1.23% at the lumbar spine, and −0.65% at the hip by dual-energy x-ray absorptiometry (DEXA), compared with nonusers.[79] Other investigators have identified increased risk of fracture in TZD users; these studies are summarized in **Table 2**. In summary, literature to date establishes that TZD use is associated with bone loss, which translates into a roughly 50% increased risk of fracture, over time.

The increase and decrease in popularity of the TZD class represents a new age of awareness in which glycemic efficacy is no longer the sole determinant leading to drug approval, marketing, and prescribing. Henceforth, cardiovascular safety will be as important as blood glucose normalization. The TZD experience is a reminder that favorable effects on surrogate markers of disease do not necessarily translate to clinical outcomes.

SODIUM-GLUCOSE TRANSPORTER TYPE 2 INHIBITORS

The concept of sodium-glucose transporter type 2 (SGLT2) inhibitors has been described as "turning symptoms into therapy"[85] for T2DM. In the proximal renal

Table 2
Relative risk of TZD use for incident fractures (vs nonusers)

Study	Number of Subjects	Relative Risk of Fracture (TZD vs Non-TZD)
Aubert et al,[80] 2010	69,047	1.39 (95% CI, 1.32–1.46)
Meier et al,[81] 2008	66,696	2.43 (95% CI, 1.49–3.45)
Dormuth et al,[82] 2009	84,000	1.28 (95% CI, 1.10–1.48)
Kahn et al,[83] 2008	1840 (ADOPT trial)	1.81 (rosiglitazone vs metformin) (95% CI, 1.17–2.80) 2.13 (rosiglitazone vs glyburide) (95% CI, 1.30–3.51)
Loke et al,[84] 2009	45,394	1.45 (95% CI, 1.18–1.79)

tubule, the SGLT2 is the predominant transport system, normally reclaiming about 144 g of filtered glucose from glomerular filtrate per 24 hours. The avidity of SGLT2-mediated glucose transport in the kidney is such that normally serum glucose must exceed 180 mg/dL for the volume of filtered glucose to exceed transport capacity and produce glucosuria. Inhibition of SGLT2 causes glycosuria at a lower level of filtered (and hence, serum) glucose and thus lowers serum glucose through increased selective glycosuria.[86]

Canagliflozin and dapagliflozin are the first two SGLT2 inhibitor drugs available in the United States. They are indicated for treatment of T2DM, based on monotherapy trials versus placebo, and as add-on therapy for patients failing to reach HbA1c treatment goals with metformin monotherapy. Monotherapy with canagliflozin produced ΔHbA1c of −0.77% to −1.03%, along with body weight change of −2.5 to −3.4 kg at doses of 100 mg and 300 mg daily, respectively, versus placebo.[87] Canagliflozin proved equal to glimepiride as add-on therapy for subjects inadequately controlled on metformin, in the CANagliflozin treatment and trial analysis-sulfonylurea (CANTATA-SU) trial, with ΔHbA1c −0.93% (vs baseline value) in the canagliflozin add-on group, and ΔHbA1c −0.81% in the glimepiride group, although on average weight changed by −3.7 kg in the canagliflozin groups and by +0.7 kg in the glimepiride group.[88] Hypoglycemia was more frequent in the glimepiride plus metformin group, whereas genital mycotic infections were more frequent in the canagliflozin plus metformin groups. Another trial examining canagliflozin versus sitagliptin as tertiary therapy for patients failing metformin plus SU slightly favored canagliflozin, with ΔHbA1c −1.03% in the canagliflozin plus SU plus metformin group, and ΔHbA1c −0.67% in the sitagliptin plus SU plus metformin group; weight changed −2.3 kg in the canagliflozin-plus group and by +0.3 kg in the sitagliptin-plus group.[89] Dapagliflozin has been studied versus placebo, as add-on therapy to metformin in inadequately controlled T2DM, with ΔHbA1c of −0.67% to −0.84% for dapagliflozin doses ranging from 2.5 to 10 mg daily, versus ΔHbA1c of +0.3% in the placebo plus metformin group. Body weight changed by −2.2 to −3.0 kg with canagliflozin plus metformin, and by −0.9 kg for placebo plus metformin, with similar frequency of adverse events.[90]

Vasilakou and colleagues[91] conducted a meta-analysis of all clinical trial data, to estimate the overall efficacy of the SGLT2 drug class, and found an overall ΔHbA1c of −0.79% in patients treated with SGLT2 monotherapy, and ΔHbA1c of −0.61% with SGLT2 as add-on therapy. Other associations with SGLT2 therapy included mean −1.8 kg weight loss, −4.5 mm Hg systolic blood pressure, and up to a 5-fold increased rate of genital mycotic infections, versus comparator groups. These investigators, and others, have been critical of missing data in trials and strong possibility of overestimation of benefit, caused by the last observation carried forward when subjects dropped out or were lost to follow-up in the trials.[91,92] It is hoped that an ongoing cardiovascular safety trial will establish long-term safety for canagliflozin[93]; dapagliflozin will be monitored closely not only for cardiovascular safety but for incident breast and bladder cancer, which was noted to have occurred more frequently in dapagliflozin users in the meta-analysis.[91] For now, SGLT2s can be viewed as equivalent to other available agents as add-on therapy to metformin, albeit at high financial cost and with increased risk for genital mycotic infections. Small but significant weight loss of up to 5 kg in the first year of therapy is expected, and risk of hypoglycemia is low. Long-term safety (benefit or noninferiority with regard to other drug classes) with regard to cardiovascular disease events and neoplasia has not yet been established.[94] Based on relative absence of long-term safety information, and high financial cost of treatment, it seems prudent to recommend SGLT2 inhibitors as third-line therapy for T2DM at the present time.

ALPHA-GLUCOSIDASE INHIBITORS

An orally administered inhibitor of intestinal alpha-glucosidases, acarbose is poorly absorbed (<1%) by the gut, and reduces peak postprandial glycemia by delaying absorption of ingested disaccharides and complex carbohydrates.[95] It has minimal effect on fasting glucose, and, when added to metformin in patients with baseline HbA1c greater than 7.0%, reduces HbA1c by approximately 0.7%.[96] Based on its mechanism of action, it has little potential for drug-induced hypoglycemia, unless used in combination with exogenously administered insulin or insulin secretogogue (SU or glinides).

Acarbose was approved by the FDA for treatment of T2DM in 1996. One clinical trial compared acarbose only with SU only, and with SU plus acarbose, and found that ΔHbA1c was −0.54% for acarbose only, −0.93% for SU only, and −1.32% for acarbose plus SU.[97] Another trial compared acarbose or placebo as add-on therapy to diet only, metformin, glyburide, or insulin; at the 1-year study termination, ΔHbA1c was −0.9% for acarbose plus diet, −0.8% for acarbose plus metformin, −0.9% for acarbose plus glyburide, and −0.4% for acarbose plus insulin.[98] Adverse effects associated with acarbose were limited to flatulence, diarrhea, and abdominal cramping.

Efficacy of acarbose in the delay of onset or prevention of T2DM, and on incident cardiovascular disease events and hypertension, was established by The Study to Prevent Non–insulin-dependent Diabetes Mellitus (STOP-NIDDM) trial. This randomized, placebo-controlled study compared acarbose 100 mg 3 times a day with meals, versus placebo, on rates of incident T2DM in 1429 at-risk subjects, selected from impaired glucose tolerance on standard oral glucose tolerance testing; over a mean period of follow-up of 3.3 years, incident T2DM occurred in 32% of acarbose-treated subjects, versus 42% of placebo-treated subjects (absolute risk reduction, 10%; number needed to treat, 10).[99] Furthermore, an absolute risk reduction for new cardiovascular events of 2.5% favoring acarbose (cardiovascular disease incidence, 2.2%) versus placebo (cardiovascular disease incidence, 4.6%), and a 5.3% absolute risk reduction (adjusted by multivariate analysis) for new-onset hypertension favoring acarbose (new hypertension in 24% in 3.3 years) versus placebo (new hypertension in 33.7% in 3.3 years) were also noted in this trial.[100] No serious adverse events were reported in either study group; gastrointestinal symptoms were far more frequent in the acarbose group than in the placebo group.

Aside from flatulence and loose stool, adverse effects of acarbose are minimal. Malabsorption of iron is possible. Acarbose reduces bioavailability of metformin, and, if used in combination with metformin, markedly increases the likelihood of gastrointestinal adverse effects.[95] Contraindications to use of acarbose include severe irritable bowel syndrome, severe renal disease, and severe hepatic disease.[101]

COLESEVELAM

Bile acids are involved in glucose homeostasis signal pathways as activators of the farnesoid X receptor alpha, which is a regulator of gluconeogenesis and glucagon synthesis; bile acids may also induce glucagon-like peptide-1 production.[102] The glycemic efficacy of a bile acid sequestrant, colesevelam, was first formally tested in a randomized, placebo-controlled fashion in the glucose lowering effect of WelChol study (GLOWS) (GLP-1) trial, which showed a ΔHbA1c of −0.5% versus placebo, and also showed decreased low-density lipoprotein cholesterol (LDLc) level of −9.6% (vs baseline value), compared with +2.1% (vs baseline value) in the placebo group. Gastrointestinal symptoms, primarily constipation, were 3 times more frequent in the colesevelam group than in the placebo group.[103]

The efficacy of colesevelam as add-on therapy for T2DM was subsequently tested in clinical trials in patients receiving monotherapy with SUs, metformin, combined oral

therapies (excluding DPP-4 inhibitors), and insulin. In a 26-week clinical trial of 316 subjects at multiple centers in the United States and Mexico, patients treated with metformin or metformin plus combinations of SU, glinides, TZDs, and/or alpha-glucosidase inhibitors, were randomized to colesevelam 3.75 g per day, or placebo. At study conclusion, the colesevelam group's HbA1c level was 0.54% lower than the placebo group's; LDLc, and highly sensitive C-reactive protein (hsCRP) were also lower in the colesevelam group.[104] A 26-week multicenter trial, also including US and Mexican sites, of 461 subjects with T2DM with baseline HbA1c of 8.2%, randomized patients treated with SU or with SU plus metformin, TZD, and/or alpha-glucosidase inhibitor to receive either colesevelam 3.75 g daily or placebo. At the study's conclusion, HbA1c was 0.54% lower in the colesevelam than in the comparator groups, and LDLc level was also significantly lower.[105] A 16-week clinical trial added colesevelam or placebo to patients with mean HbA1c of 8.3% treated with insulin-based therapies, either as insulin alone or in combination with oral therapies that included metformin, SUs, or glinides, and/or a TZD. In this study of 287 randomized patients, HbA1c changed by −0.41%, and LDLc by −12.3% in the colesevelam group, whereas HbA1c changed by +0.09% and LDLc by +0.5% in the placebo group.[106]

A 2012 Cochrane Review of the available clinical trial data for colesevelam concluded that the overall strength of evidence supported adjunctive use of colesevelam, but that further research to establish long-term risks and benefits would be necessary before widespread or early use of colesevelam for glycemic control could be strongly encouraged.[107] Among other concerns, the mechanism by which colesevelam effects improved glycemia has not been elucidated. Radiolabeled tracer study of mixed meal feedings has suggested that the major action of colesevelam is to increase splanchnic sequestration of meal-derived glucose,[108] which is consistent with the clinical data from the Zieve and colleagues[103] trial, in which postprandial glycemia was significantly reduced in the colesevelam group compared with the placebo group.[103] At the present time, perhaps the best niche for colesevelam in the treatment arsenal of oral antihyperglycemic therapies is in patients adjudged to have unsatisfactory glycemic control, as well as unsatisfactory LDLc, on other well-tolerated antihyperglycemic and lipid-lowering (specifically, statin) drug therapies.[102,109,110]

BROMOCRIPTINE MESYLATE

Approved by FDA in 2010 for the indication of treatment of T2DM, the mechanism of action of bromocriptine mesylate (also known as bromocriptine-QR [quick release]) is largely inferred from animal studies. The drug is ingested within 2 hours of waking in the morning, with breakfast, and is rapidly cleared by first-pass action of cytochrome P450 34A (CYP34A) in the liver, with less than 10% of the ingested dose reaching the systemic circulation. It is thought to increase dopamine in the hypothalamus, thereby reducing sympathetic nervous activity, hepatic glucose production, and lipolysis, with resultant improvement in insulin sensitivity.[111]

Bromocriptine mesylate has been studied as monotherapy versus placebo, and as add-on therapy to SU, with ΔHbA1c of −0.5% to −0.7%, and also with lower FFAs and triglycerides, versus placebo.[112,113] Vinik and colleagues[114] showed similar efficacy of bromocriptine added to failing monotherapy or combined therapies with various combinations of metformin, SU, and TZDs, finding ΔHbA1c of −0.47% in the bromocriptine group, versus +0.26% in the placebo group, at 24 weeks.

A 52-week safety trial compared bromocriptine mesylate versus placebo, in randomized fashion, in 3095 subjects treated with various monotherapies, oral

combinations, or insulin alone or in combination with oral therapies, for the purpose of comparing incidence of serious adverse events in the two groups[115] Composite major adverse cardiovascular events, including MI, stroke, coronary revascularization, or hospitalization for unstable angina or CHF, occurred in 1.8% of the bromocriptine group and in 3.2% of the placebo group; a risk reduction of 40% (hazard ratio, 0.61; 95% CI, 0.38–0.97; $P = .02$).[116] Reasons for the apparent risk reduction are thought to be related to reduced sympathetic nervous system activation or to reduced circulating inflammatory markers such as hsCRP, and TNF-α, although to date such markers have not been measured in studies.[117,118] The lack of long-term efficacy data (ie, studies longer than 24 weeks), the high financial cost of bromocriptine mesylate, and a high frequency of significant adverse effects (nausea in 26%, asthenia/malaise in 15%) have led some authorities to recommend against widespread use of this therapy.[118,119] As further experience accumulates, the magnitude of benefit may allow a more optimistic benefit versus risk estimation for select patients.

SUMMARY

Table 3 provides an overview of the oral antihyperglycemic drugs reviewed in this article. A 2011 meta-analysis by Bennett and colleagues[120] found low or insufficient quality of evidence favoring an initial choice of metformin, SUs, glinides, TZDs, or

Table 3
Oral antihyperglycemic drug: suggested dosing, action, expected efficacy, and cost

Class/Drug	Suggested Dosing	Mechanism of Action	Expected ΔHbA1c (%)	Cost/ Month (US$)
Biguanide				
Metformin	500–2000 mg/d	↓Gluconeogenesis	−1 to −2	4 (generic)
Sulfonylureas				
Glipizide	2.5–10 mg/d	↑Insulin release	−1 to −2	4 (generic)
Glimepiride	1–4 mg/d			4 (generic)
Glinides				
Repaglinide	0.5–2 mg TID with meals	—	—	200 (generic)
Nateglinide	60–120 mg TID with meals	—	—	120
TZDs				
Rosiglitazone	2–4 mg/d	↓FFA release	−1 to −2	130
Pioglitazone	15–30 mg/d	↑Insulin sensitivity		45 (generic)
SGLT2s				
Canagliflozin	100–300 mg/d	↑Glycosuria	−1 to −1.5	290
Dapagliflozin	5–10 mg/d			290
Alpha-glucosidase Inhibitors				
Acarbose	25–100 mg TID with meals	↓Carbohydrate absorption	−0.5 to −1	45 (generic)
Bile Acid Sequestrants				
Colesevelam	3750 mg/d	Unclear	−0.5 to −1	335
Bromocriptine mesylate	1.6–4.8 mg/d	↑CNS dopamine	−0.5	120

Abbreviations: CNS, central nervous system; TID, 3 times a day.

Dose and price information from Anonymous. Drugs for type 2 diabetes. Treat Guidel Med Lett 2014;12(139):17–24.

DPP-4 inhibitors (alpha-glucosidase inhibitors, bromocriptine mesylate, and SGLT2 inhibitors were not included in this meta-analysis) with regard to the outcomes measures of all-cause mortality, cardiovascular events and mortality, and incidence of microvascular disease (retinopathy, nephropathy, and neuropathy) in previously healthy individuals with newly diagnosed T2DM. Likewise, the Bennett and colleagues[120] meta-analysis judged these drugs to be of roughly equal efficacy with regard to reduction of HbA1c (1%–1.6%) from the pretreatment baseline. The ADOPT clinical trial of 3 different and, at the time, popular, oral monotherapies for T2DM provides support for the consensus recommendation of metformin as first-line therapy. The ADOPT trial showed slightly superior HbA1c reduction for rosiglitazone compared with metformin, which was in turn superior to glyburide. However, significant adverse events, including edema, weight gain, and fractures, were more common in the rosiglitazone-treated patients.[31,83] The implication of this trial is that the combination of low cost, low risk, minimal adverse effects, and efficacy of metformin justifies use of this agent as the cornerstone of oral drug treatment of T2DM. Judicious use of metformin in groups formerly thought to be at high risk for lactic acidosis (ie, those with CHF, chronic kidney disease [eGFR >30 mL/min/1.73 m^2], and the elderly) may be associated with mortality benefit rather than increased risk. Secondary and tertiary add-on drug therapy should be individualized based on cost, personal preferences, and overall treatment goals, taking into account the wishes and priorities of the patient.

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