New Drugs for the Treatment of Diabetes
Part II: Incretin-Based Therapy and Beyond

Silvio E. Inzucchi, MD; Darren K. McGuire, MD, MHSc

Abstract—This is the second of a 2-part series focusing on newer therapies for type 2 diabetes and their cardiovascular implications. In the first segment, we reviewed the thiazolidinediones, highlighting emerging data concerning their cardiovascular effects, both positive and negative. Here, we present a corresponding discussion of the newest antihyperglycemic category, modulators of the incretin system, which include the glucagon-like peptide-1 mimetics and the dipeptidyl peptidase-4 inhibitors. In addition, we briefly survey several novel drug classes in development, provide summary recommendations for glucose-lowering regimens in specific patient types, underscore the importance of nonglucose cardiovascular risk reduction strategies, and comment on present and future considerations for the regulatory review of diabetes drugs. (Circulation. 2008;117:574-584.)

Key Words: coronary disease □ diabetes mellitus □ drugs □ heart failure □ incretins

A novel category of antihyperglycemic therapy based on modulation of the incretin system has recently emerged. Incretins are gut-derived peptides secreted in response to meals, specifically the presence and absorption of nutrients in the intestinal lumen.1 The major incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP). GLP-1 is produced by the neuroendocrine L cells in the distal ileum and colon; GIP is elaborated by K cells of the duodenum and jejunum. Both are released rapidly after meal intake; their secretion appears to be under neural control. Incretins stimulate insulin output from pancreatic β cells in a glucose-dependent fashion (enhancement of secretion linked to the presence of hyperglycemia). In addition, GLP-1, but not GIP, decreases pancreatic α-cell secretion of glucagon, a hormone that augments hepatic glucose production. GLP-1 also retards gastric emptying and likely has a direct suppressive effect on central appetite centers. The cardinal physiological role of the incretin system appears to be the attenuation of postprandial glucose excursions. Notably, patients with type 2 diabetes mellitus (T2DM) are partially deficient in GLP-1 secretion,2 a finding that has encouraged the development of drugs that augment GLP-1 levels or activity. Recently, however, the question of whether such incretin dysregulation is responsible for or is a consequence of the hyperglycemia in diabetes has been raised.3

The first incretin modulator class encompasses the GLP-1 analogues or mimetics, which are functional agonists of the GLP-1 receptor. The initial approved member of this class is the injectable exenatide. Incretins are rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), which is widely expressed in many tissues, including kidney, liver, lung, and the small intestine.4 As a result, the half-lives of GLP-1 and GIP are measured in minutes. Oral inhibitors of DPP-4, in essence, increase the plasma concentrations of the biologically active form of endogenously secreted incretins. The first DPP-4 inhibitor is sitagliptin; several others remain in late stages of clinical development.

GLP-1 Mimetics
Exenatide is a synthetic version of exendin-4, a peptide discovered in the salivary secretions of the reptile Heloderma suspectum (the Gila monster indigenous to the southwestern United States).1 Exenatide shares partial homology with human GLP-1 and activates human GLP-1 receptors. It is administered as a subcutaneous injection typically twice daily in doses of 5 to 10 μg. Pivotal trials have assessed its efficacy at lowering glucose in patients with T2DM in combination with metformin and/or sulfonylureas.5–7 In these investigations, exenatide resulted in a hemoglobin A1c (HbA1c) reduction of ~1.0% compared with placebo treatment, with the predominant effect on lowering postprandial glucose with less prominent reduction in fasting glucose.

Likely because of the effects of exenatide on gastric emptying and appetite, weight loss has also been demonstrated.5–7 In the placebo-controlled component of the pivotal trials, which lasted 30 weeks, mean weight reduction ranged between 1 and 3 kg compared with placebo; weight loss was most pronounced in patients with greater body mass index. In open-label extensions, weight continued to decline over 2 years of treatment, up to ~5 kg from baseline.8,9 Although

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modest, such weight reduction is an atypical feature of most antihyperglycemic drugs and exceeds that typically observed with metformin, which tends to dissipate over time.

In in vitro and animal models, GLP-1 and its analogues are associated with proliferative effects on pancreatic β cells. Progressive islet dysfunction is a recognized phenomenon in T2DM and results in the eventual loss of glycemic control over time. In addition to functional abnormalities, an actual decrease in β-cell mass also has been demonstrated, likely the result of increased apoptosis combined with decreased regeneration. Therefore, any agent that alters this balance may delay or prevent the decline in insulin secretory capacity, potentially allowing a more durable effect on glucose control than conventional agents, most of which are associated with substantial therapeutic attrition over time. This hypothetical effect of the GLP-1 mimetics, however, has not yet been demonstrated in long-term clinical trials.

Side effects of exenatide include nausea and vomiting, particularly at the initiation of therapy. Recently, postmarketing reports of pancreatitis occurring in exenatide-treated patients have emerged, with most patients having at least 1 risk factor for this condition. A causal association with exenatide is not clear. Because of its glucose-dependent effect, exenatide does not increase the risk of hypoglycemia.

Exenatide is approved solely for use in combination with metformin, a sulfonylurea, a thiazolidinedione, or the combination of metformin with a sulfonylurea, or the combination of metformin with a thiazolidinedione. Among patients with T2DM requiring insulin therapy, exenatide exhibits less potent HbA1c reduction compared with its combination with oral agents, an expected observation because such individuals tend to be more insulin deficient with less available insulin secretory reserve. Exenatide also is effective as monotherapy, but this is not an immediately attractive option for most patients, given its method of administration.

Under development are liraglutide, a once-daily GLP-1 analogue, and exenatide LAR, a long-acting depot formulation administered once weekly. Not surprisingly, there also is some interest in using GLP-1 mimetics for weight loss in patients without diabetes, but this is not yet an approved indication.

**Cardiovascular Impact**

Weight reduction over time may have an indirect benefit on cardiovascular risk, including blood pressure, cholesterol levels, inflammatory markers, and insulin resistance. To date, however, the main metabolic benefits demonstrated from exenatide therapy have been on indexes of glycemic control. One report involving 283 patients who completed open-label extensions of various exenatide trials (total exposure, 104 weeks) suggested a modest benefit on certain cardiovascular risk factors. From baseline, the mean HbA1c change was −1.1% (95% CI, −1.3 to −1.0), with a mean weight reduction of 4.7 kg (95% CI, 5.4 to 4.0). Modest improvements in both systolic (−2.6 mm Hg; 95% CI, −4.3 to −0.9) and diastolic (−1.9 mm Hg; 95% CI, −3.0 to −0.9) blood pressures also were observed. In a separate analysis involving the same groups of patients (n=312; total drug exposure, 82 weeks), significant improvements were reported in high-density lipoprotein cholesterol (4.6 mg/dL; 95% CI, 3.7 to 5.4) and triglycerides (−38.6 mg/dL; 95% CI, −55.5 to −21.6). Because there were no control groups beyond the initial 30-week double-blind phase of these trials, the significance of these findings and their net impact on long-term cardiovascular risk remain uncertain.

Effects on the cardiovascular system with GLP-1 mimetics have centered around their potential role in heart failure (HF). GLP-1 receptors have been demonstrated in cardiac myocytes and in certain regions of the brain that regulate autonomic function. In animal models, GLP-1 receptor agonists have been reported to increase blood pressure and heart rate as a result of activation of sympathetic outflow. In addition to this chronotropic effect, a positive inotropic effect also has been attributed to direct myocardial activity. Recent evidence suggests that GLP-1 may enhance recovery of left ventricular function after transient coronary artery occlusion in an isolated rat heart model, possibly mediated through insulin-like activity in improving glucose uptake by cardiomyocytes and through the activation antiapoptotic signaling pathways shown to protect against myocardial injury. A similar benefit has been demonstrated in conscious dogs with pacing-induced cardiomyopathy. In this model, the use of GLP-1 infusion was associated with a doubling of stroke volume and an increase in cardiac output by >50%, as well as significant decreases in left ventricular end-diastolic volume. On the basis of these data, authors have proposed that GLP-1–based drugs might be useful as adjunctive therapy in patients with decompensated HF.

There is, however, a paucity of data regarding the role of GLP-1 and its analogues in humans with HF. One group administered an infusion of GLP-1 over 72 hours to 10 patients with acute myocardial infarction (AMI) and depressed left ventricular ejection fractions (<40%) after successful primary coronary intervention and compared short-term cardiac outcomes with those of 11 contemporaneous control patients. The group receiving GLP-1 experienced a significant improvement in left ventricular ejection fraction (29%±2% to 39%±2%; P<0.01) with concomitant improvements in global and regional wall motion. More recently, these same collaborators administered a 5-week infusion of GLP-1 to 12 patients with advanced HF and compared outcomes with those of 9 patients on standard therapy. GLP-1 significantly improved left ventricular ejection fraction (21%±3% to 27%±3%; P<0.01), VO₂ max (10.8±0.9 to 13.9±0.6 mL · kg⁻¹ · min⁻¹; P<0.001), 6-minute walk distance (232±15 to 286±12 m; P<0.001), and a standardized quality-of-life score. No changes were observed in the control patients in either of these unblinded investigations.

Clearly, long-term safety data are required before we fully understand any potential benefits (or risks) to the cardiovascular system from exenatide and other GLP-1–based therapies. Because exenatide is not associated with either lactic acidosis or edema formation, it may be a reasonable option in patients with HF who are difficult to manage because of current contraindications and/or precautions involving other antihyperglycemic agents (see below).
DPP-4 Inhibitors
Oral inhibitors of DPP-4 have recently become available for patients with T2DM. They decrease the activity of the enzyme >80% for up to 24 hours, thereby enhancing meal-related circulating concentrations of biologically active GLP-1 and GIP. In contrast to therapy with GLP-1 mimetics, DPP-4 inhibitors increase effective incretin levels into a more physiological range.24 Their metabolic effects include the glucose-dependent stimulation of pancreatic insulin secretion and suppression of glucagon output.25 Retardation of gastric emptying has not been demonstrated, and there are no data showing appetite or weight reduction, as reported with the GLP-1 mimetics. However, compared with sulfonylureas, thiazolidinediones, and insulin, DPP-4 inhibitors are weight neutral.

In addition to the degradation of GLP-1 and GIP, the larger family of dipeptidyl peptidases also appears to play important roles in the regulation of peptide hormone signaling in a variety of tissues. DPP-8 and DPP-9, for example, are active in hematologic and immune cells.26 Accordingly, concern has been raised regarding the long-term implications of DPP-4 inhibition. The current members of this class that are either available for clinical use (sitagliptin) or in advanced phases of development (vildagliptin, saxagliptin, alogliptin) have reasonably high selectivity for DPP-4, and few adverse effects in humans have been demonstrated thus far in clinical trials.27–29

Generally speaking, the DPP-4 inhibitors are modestly effective glucose-lowering drugs. Average HbA1c reductions range between 0.6% and 0.8% compared with placebo.27–29 Notably, however, clinical trials with this drug class have involved T2DM subjects with mean HbA1c levels in the 8% range, significantly lower than in those enrolled in trials of older agents. Because mean HbA1c reduction is in part linked to the baseline glycemic status of the patient,30 the actual efficacy of these agents is best evaluated in head-to-head trials with standard antihyperglycemic drugs. These results have been mixed, with efficacy marginally lower than metformin31 but similar to rosiglitazone32 and glipizide.33 More studies are needed before the comparative effects of the DPP-4 inhibitors versus traditional antidiabetic therapies are fully understood.

Published trials with the DPP-4 inhibitors have included monotherapy27,31,32 and combination therapy with metformin,29,33 thiazolidinediones,28 or sulfonylureas.34 These constitute the current indications for sitagliptin (including add-on therapy to metformin plus a sulfonylurea), the only Food and Drug Administration (FDA)–approved DPP-4 inhibitor. It is unclear whether these agents have any role in insulin-treated T2DM patients. One study recently suggested a small benefit on HbA1c with reduced hypoglycemia risk.35

As mentioned, the DPP-4 inhibitors appear to be, at least at this early point in their development, reasonably safe medications.12 Recently, postmarketing reports of anaphylaxis, angioedema, and rashes, including Stevens-Johnson syndrome, in sitagliptin-treated patients have emerged. A causal link to the drug, however, is not known. DPP-4 inhibitors are not associated with hypoglycemia, weight gain, or edema. Few data are available concerning cardiovascular intermediate markers or clinical outcomes. Given the preliminary data concerning GLP-1 in HF, they might be considered in individuals with impaired ventricular function. However, no clinical trials using these agents have yet been reported in this or any other group of patients with cardiovascular disease (CVD).

Amylin Mimetics
Another new antihyperglycemic, used predominantly by patients with type 1 diabetes mellitus (T1DM) on intensive insulin regimens, is the injectable pramlintide. Pramlintide is a synthetic analogue of human amylin, a β-cell peptide cosecreted with insulin.36 Deficient amylin secretion is a well-recognized phenomenon in T1DM and in later-stage T2DM patients, in whom pancreatic insulin production is markedly reduced. The physiological effects of amylin, mimicked by pramlintide, are, in part, similar to those of GLP-1. However, it is not an incretin hormone. Amylin suppresses glucagon secretion from pancreatic α cells, thereby attenuating hepatic glucose production. It also delays gastric emptying and likely possesses a central effect to enhance satiety. In clinical trials, pramlintide has its predominant effect on reducing postprandial glucose fluctuations. The net effect on HbA1c is modest (−0.4% to −0.6%) compared with placebo; body weight typically decreases by 1 to 2 kg.37 Because of the effects on satiety and gastric emptying, hypoglycemia may occur in patients also receiving insulin. Accordingly, the prandial insulin dose should be preemptively reduced when pramlintide is initiated.

The role of pramlintide in the therapy of T2DM is not clear. It may be of some benefit to those already on intensive insulin regimens. Several studies have shown an efficacy similar to that in T1DM.38–40 Because pramlintide requires thrice-daily self-injections (which cannot be combined in the same syringe as insulin), it is unlikely to play a major future role in the management of T2DM. It is, however, currently under study for use as a weight loss agent in nondiabetic individuals.

There are no known cardiovascular advantages or risks from pramlintide. Control of postprandial glucose may have theoretical benefits on cardiovascular health. In addition, weight reduction may be accompanied by improvements in the overall cardiovascular risk profile, although no prominent changes have been reported in long-term clinical trials. In a 4-week study involving 18 T1DM patients intensively treated on insulin pumps, pramlintide led to a decrease in postprandial triglyceride excursions by 72% (P<0.05).41 In a separate short-term study, also in 18 patients with T1DM, pramlintide therapy was associated with a reduction in several markers of oxidative stress, including oxidized low-density lipoprotein.42 It is doubtful that any long-term cardiovascular safety data will ever emerge with what essentially is a niche medication for T2DM.

Optimal Antihyperglycemic Regimens in Patients With CVD
These 3 new drug categories have further expanded treatment options in patients with T2DM (see Table 1). Their impact, however, on the major cause of morbidity and mortality in
T2DM, namely cardiovascular complications, remains entirely unknown. Because there are few long-term data regarding the cardiovascular safety and efficacy of these agents (and most others in current use), recommendations are based on those few data available from selected investigations, consensus documents, and sound clinical judgment. Clearly, tailoring an optimal antihyperglycemic regimen for the T2DM patient with overt CVD poses unique challenges. In the following sections, we propose recommendations for the management of hyperglycemia in patients with coronary artery disease (CAD) and those with HF. They differ from the 2006 consensus algorithm from the American Diabetes Association (ADA) and European Association for the Study of Diabetes insofar as they are designed specifically for 2 important subgroups of cardiovascular patients. In addition, our guidelines integrate the incretin-modulating drugs, incorporate recent concerns regarding the thiazolidinediones, and acknowledge the widespread patient preference for noninjectable agents.

### The Patient With CAD

Although metformin is favored by many as first-line antihyperglycemic therapy in T2DM, the only prospective data we have for this drug on cardiovascular end points come from the United Kingdom Prospective Diabetes Study (UKPDS), subjects from which made up essentially a primary prevention cohort. In a relatively small subgroup of overweight patients randomized to monotherapy with metformin, MI and death resulting from coronary heart disease were reduced by 39% (P=0.01) and 50% (P=0.02), respectively, compared with control patients receiving only dietary advice. Compared with the group of patients randomized to sulfonylureas or insulin, metformin patients also experienced fewer stroke events.

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#### Table 1. Anti-Hyperglycemic Medications for Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of Action</th>
<th>Expected HbA1c Reduction, %</th>
<th>Adverse Effects</th>
<th>Cardiovascular Issues</th>
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<tbody>
<tr>
<td><strong>Sulfonylureas</strong></td>
<td>Bind to sulfonylurea receptors on pancreatic islet cells, closing K&lt;sub&gt;ATP&lt;/sub&gt; channels, stimulating insulin release; relatively long duration of action</td>
<td>~1–2</td>
<td>Hypoglycemia, weight gain</td>
<td>Hypoglycemia may precipitate ischemia, arrhythmia; cardiac K&lt;sub&gt;ATP&lt;/sub&gt; channel closure may impair ischemic preconditioning</td>
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<td><strong>Gliburide</strong></td>
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<td><strong>Glipizide</strong></td>
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<td><strong>Glimepiride</strong></td>
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<tr>
<td><strong>Glinides</strong></td>
<td>Bind to sulfonylurea receptors on pancreatic islet cells, closing K&lt;sub&gt;ATP&lt;/sub&gt; channels, stimulating insulin release; relatively short duration of action</td>
<td>~1–2</td>
<td>Hypoglycemia, weight gain</td>
<td>Hypoglycemia may precipitate ischemia, arrhythmia; cardiac K&lt;sub&gt;ATP&lt;/sub&gt; channel closure may impair ischemic preconditioning</td>
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<td><strong>Nateglinide</strong></td>
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<td><strong>Biguanides</strong></td>
<td>Decrease hepatic glucose production</td>
<td>~1–2</td>
<td>Diarrhea, nausea, lactic acidosis, decreased B12 levels</td>
<td>May improve CVD outcomes (UKPDS); should not be used in acute or unstable HF because of lactic acidosis risk; improves postprandial glucose excursions, which are more tightly associated with CVD than fasting glucose; may reduce MI risk (STOP-NIDDM)</td>
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<td><strong>Metformin</strong></td>
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<tr>
<td><strong>α-Glucosidase inhibitors</strong></td>
<td>Slow gut carbohydrate absorption</td>
<td>~0.5–1.0</td>
<td>Gas, bloating</td>
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<td><strong>Acarbose</strong></td>
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<td><strong>Miglitol</strong></td>
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<td><strong>Thiazolidinediones</strong></td>
<td>Activate the nuclear receptor PPAR-γ, increasing peripheral insulin sensitivity; also reduces hepatic glucose production</td>
<td>~1–1.5</td>
<td>Weight gain; edema; possible bone loss in women</td>
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<td><strong>Rosiglitazone</strong></td>
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<td><strong>Pioglitazone</strong></td>
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<td><strong>Incretin modulators</strong></td>
<td>Increase glucose-dependent insulin secretion, decrease glucagon secretion, and delay gastric emptying; inhibit degradation of endogenous GLP-1 (and GIP-1), thereby enhancing these effects of these incretins (see above)</td>
<td>~1</td>
<td>Nausea, vomiting</td>
<td>Very preliminary data suggest possible benefit in patients with cardiomyopathy</td>
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<td><strong>GLP-1 mimetics</strong></td>
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<td><strong>Exenatide</strong></td>
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<td><strong>DPP-4 inhibitors</strong></td>
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<td>~0.6–0.8</td>
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<tr>
<td><strong>Sitagliptin</strong></td>
<td>Decrease glucagon secretion and delay gastric emptying</td>
<td>~0.4–0.6</td>
<td>Nausea, vomiting</td>
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<td><strong>Amylin analogues</strong></td>
<td>Decrease glucagon secretion and delay gastric emptying</td>
<td>~0.4–0.6</td>
<td>Hypoglycemia; weight gain; edema (at high doses)</td>
<td>Retrospective data in HF suggests worse clinical outcomes in HF patients who require and are treated with insulin.</td>
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<td><strong>Pramlintide</strong></td>
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<td><strong>Insulins</strong></td>
<td>Increase insulin supply</td>
<td>No limit (theoretically)</td>
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<td><strong>NPH, lente</strong></td>
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<td><strong>Regular</strong></td>
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<td><strong>Lispro, aspart, glulisine</strong></td>
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<td><strong>Premixed</strong></td>
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PPAR indicates peroxisome proliferator–activated receptor; NYHA, New York Heart Association; and NPH, neutral protamine Hagedorn.
The only randomized, double-blind, placebo-controlled study to explore the risks and benefits of a specific antihyperglycemic drug (pioglitazone) used in combination with other therapies in high-risk cardiovascular patients is the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), summarized in the first part of this series. This 3-year investigation demonstrated a modest 16% relative risk reduction (95% CI, 2 to 28; absolute risk reduction, 2.1%) in a secondary composite end point of mortality, MI, and stroke with the thiazolidinedione compared with placebo. Any benefit was at the expense of a modest increase in the diagnosis of and hospitalization for HF.

In a retrospective analysis of 8872 older patients with diabetes admitted for AMI, there was no clear effect on 1-year mortality with either metformin (hazard ratio [HR], 0.92; 95% CI, 0.81 to 1.06) or thiazolidinediones (HR, 0.92; 95% CI, 0.80 to 1.05) compared with a non–insulin-sensitizer regimen (ie, sulfonylureas, insulin) after controlling for multiple patient, physician, and hospital characteristics. In a small subgroup (n=139) of patients treated with both metformin and a thiazolidinedione, mortality was significantly lower at 1 year (adjusted HR, 0.52; 95% CI, 0.34 to 0.82). These observational findings require confirmation in randomized clinical trials.

On the basis of the best available evidence, as long as the patient has no active contraindications such as renal insufficiency, metformin is a logical first-line agent in T2DM patients with CAD. Of note, HF is no longer a contraindication for metformin therapy (see below). Accordingly, it may be used cautiously in patients with compensated HF, although still not in those with acute or unstable HF. On the basis of the PROactive study and a recent confirmatory meta-analysis, if required for additional glucose lowering, pioglitazone would be a reasonable option added as second line. Recent concerns regarding the safety of rosiglitazone (see part I) make it a less attractive option until more safety (and effectiveness) data become available. Clearly, patients with significant HF resulting from their coronary disease should not use thiazolidinediones (see below). Even asymptomatic patients with depressed ejection fraction or those otherwise at risk for HF should be dosed cautiously and have very careful clinical follow-up; the drug should be discontinued and treatment should be reassessed if rapid weight gain, significant edema, or respiratory decompensation occurs.

Because of persistent concerns regarding the effects of sulfonylurea drugs on cardiac ischemic preconditioning, the safety of these agents in patients with or at high risk for acute coronary complications is not clear. Glipizide and glimepiride may be safer than glyburide and the rarely used first-generation sulfonylureas because of greater inhibition of K_{ATP} channels on pancreatic β cells (which induce membrane depolarization and insulin release) versus mitochondrial K_{ATP} channels in cardiomyocytes, with a resultant lower likelihood of interfering with ischemic preconditioning. As a group, the newer nonsulfonylurea secretagogues (glinides) are not necessarily safer in this regard, although nateglinide appears to have less affinity for K_{ATP} channels in general than repaglinide. Despite these concerns, however, it should be noted that the clinical importance of this purported effect of the insulin secretagogues has never been convincingly demonstrated. Retrospective data sets regarding the relationship between sulfonylureas and adverse outcomes in patients with AMI have been conflicting, with some studies suggesting harm and others showing no differences compared with other therapies. The cardiovascular safety of the sulfonylureas, including glyburide, was actually confirmed in the primary prevention population enrolled in the UKPDS. Perhaps of greater importance than effects on ischemic preconditioning is the tendency for any insulin secretagogue to induce hypoglycemia, which may exacerbate myocardial ischemia. Accordingly, when prescribed to the patient with CAD, these drugs should be used cautiously at the lowest effective dose, with ongoing regular monitoring of the patient’s glucose levels.

An underused antihyperglycemic class, the α-glucosidase inhibitors, delays carbohydrate absorption in the proximal gut and has unique benefits on postprandial glucose, which is actually more closely aligned to cardiovascular risk than fasting glucose. Their effect on HbA1c is modest (−0.5% to 1.0%), however, and gastrointestinal side effects have limited their use. Short-term studies also have demonstrated benefits on postprandial lipemia and inflammatory markers. One diabetes prevention study involving the α-glucosidase inhibitor acarbose demonstrated an impressive 91% relative risk reduction in MI compared with the control group, although the validity of these findings is challenged by the extremely low number of MI events evaluated (12 versus 1) and 24% attrition of study treatment. These agents should be considered in patients with mild hyperglycemia, particularly when other drug options are limited because of preexisting contraindications.

Exenatide and sitagliptin, as discussed above, are newer options with few safety data in cardiovascular patients. On the other hand, there are no significant apparent cardiac-related risks with these agents. Accordingly, in the CAD patient, the former can be reasonably deployed after metformin, a sulfonylurea, or a thiazolidinedione, whereas sitagliptin may be used either as monotherapy or in similar combinations.

Insulin injections remain an option in any T2DM patient at any point in the disease course, although they are conventionally prescribed when glucose targets cannot be attained with standard oral regimens. Because insulin often leads to weight gain and because deleterious mitogenic effects with high doses have been demonstrated in animal models, concern has been raised that insulin may actually increase cardiovascular risk. Importantly, however, these concerns have never been borne out by clinical trials. For example, the Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study actually suggested that high-dose intravenous insulin administration in the hospital and multiple daily injections on discharge can reduce mortality in diabetic patients after AMI. The UKPDS also confirmed at least the cardiovascular safety of insulin therapy in T2DM. Unfortunately, because of obvious barriers, clinicians often resort to insulin too late, after hyperglycemia has been present for too long. It should instead be used sooner in those not achieving adequate glycemic control with standard regi-
men. When insulin is used, hypoglycemia should be scrupulously avoided through cautious dosing and frequent glucose monitoring. Emerging options such as inhaled insulin may overcome some of the barriers to insulin therapy, although the cost and safety of any novel delivery system require careful consideration.

Generally, in the patient with CAD, the HbA1c should be maintained at <7.0% per current ADA guidelines while minimizing the risk of hypoglycemia. It is not known if more stringent control (ie, HbA1c of 6.0% to 6.5%) will improve clinical outcomes. A proposed clinical algorithm for treating hyperglycemia in the patient with T2DM and CAD is presented in Figure 1. It should be underscored that a comprehensive risk factor management strategy should be applied to any patient with diabetes, particularly those with overt CAD. In the Steno-2 study, a targeted, intensified, multifactorial approach versus conventional care was randomly assigned to 160 T2DM patients. The more aggressive, stepwise pharmacotherapeutic approach addressing hyperglycemia, hypertension/microalbuminuria, dyslipidemia, and platelet dysfunction resulted in an impressive 53% relative risk reduction in a cardiovascular composite primary outcome.

The Patient With HF

Management of the diabetic patient with HF presents an even greater challenge. Insulin resistance is associated with incident HF; conversely, HF itself is linked to various neurohumoral changes that may contribute to insulin resistance. As a result, insulin-sensitizing antihyperglycemic agents might be particularly attractive for this group of patients. However, both insulin-sensitizer classes, metformin and the thiazolidinediones, are potentially problematic in patients with ventricular dysfunction. With metformin, the concern is lactic acidosis, particularly in those with acute or advanced HF, especially when there is a severely depressed ejection fraction or hemodynamic instability or when frequent hospitalizations and/or deterioration in renal function are anticipated. Thiazolidinediones currently are not recommended in any patient with symptomatic HF and are specifically contraindicated in those with New York Heart Association class III or IV symptoms.

A recent retrospective analysis from a large Canadian healthcare database suggested decreased all-cause mortality in 1883 diabetic patients with incident HF who used metformin compared with sulfonylureas (HR, 0.70; 95% CI, 0.54 to 0.91). A second study involving 16,417 older diabetic patients discharged from US hospitals with a diagnosis of HF showed similarly improved outcomes associated not only with metformin but also, surprisingly, with thiazolidinediones. Compared with those treated with insulin and/or a sulfonylurea, an improved adjusted HR for mortality at 1 year was observed in patients prescribed either metformin (HR, 0.87; 95% CI, 0.78 to 0.97) or a thiazolidinedione (HR, 0.87; 95% CI, 0.80 to 0.94). The adjusted HR was even lower in patients prescribed both agents (0.76; 95% CI, 0.58 to 1.00). These retrospective studies, in conjunction with several editorial commentaries, may have influenced the FDA to recently request revision of the metformin product label to remove the HF contraindication. HF with specific reference to acute or unstable disease is still included in the warnings and precautions sections of the label with regard to increased risk for lactic acidosis in that setting. It is unlikely that randomized controlled trials of metformin therapy will be conducted in this group of patients because the patent protections have expired. It would therefore appear reasonable, on the basis of the best available evidence, to consider metformin in those patients with stable and compensated HF. Obviously, during any hospitalization or in the setting of any clinical deterioration, particularly when diuretic therapy is being advanced or renal function is otherwise threatened, metformin should be discontinued.

Sulfonylureas or other insulin secretagogues (ie, the glinides) could be used in this group with the same caveats expressed above concerning ischemic preconditioning and hypoglycemia risk in those with an ischemic origin of HF.

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**Figure 1.** Proposed antihyperglycemic strategy in the patient with T2DM and CAD. *Because of the risk of lactic acidosis, metformin should be avoided in patients whose CAD is complicated by acute or unstable HF. †Because of the risk of fluid retention, pioglitazone should be avoided in patients whose CAD is complicated by HF: it is contraindicated in those with New York Heart Association class III to IV symptoms. Because of recent concerns regarding the increased risk of myocardial infarction with rosiglitazone, this drug is best avoided in CAD patients until further safety data become available. ‡Secretagogues include the sulfonylureas and the nonsulfonylurea glinides. Certain sulfonfonylureas (eg, glyburide) may impair ischemic preconditioning and are probably best avoided in patients with active coronary insufficiency. §Insulin can be added to or substituted for oral agents at any point in the disease course. When more advanced regimens are used, insulin secretagogues traditionally are discontinued.
and/or whose ventricular dysfunction is accompanied by risk of arrhythmia.

Despite a paucity of clinical outcomes and safety data in patients with HF, incretin modulators such as the GLP-1 mimetics and the DPP-4 inhibitors are attractive agents because of their effects on body weight and the lack of fluid retention associated with their use. As noted, preliminary investigations suggest a possible benefit of ventricular performance from at least the GLP-1 mimetics, but of course, long-term safety and efficacy data are needed.

Insulin therapy is, again, always an option in patients failing conventional oral therapies. However, some concern has been raised by retrospective analyses suggesting increased mortality in HF patients treated with this, the most effective glucose-lowering agent. Although this observation may simply reflect confounding by underlying disease severity in patients requiring insulin (older, longer history of diabetes, with more diabetic complications), insulin increases distal nephron sodium reabsorption, contributing to expansion of intravascular volume, thus providing some pathophysiological explanation for adverse HF outcomes. Nonetheless, in patients who clearly require insulin for glycemic control, it should be provided with the same cautions previously stated.

Generally, in the patient with HF, HbA1c should be maintained at <7%, per current ADA guidelines, while minimizing fluid retention and hypoglycemia risk. It is not known whether more stringent control will improve clinical outcomes. In patients of advanced age, the benefits of tight glycemic control are less clear, and looser targets may be appropriate. A proposed, broad clinical algorithm for treating hyperglycemia in the T2DM patient with HF is shown in Figure 2.

Drugs for Diabetes: Beyond Glucose

As supported by a number of professional guidelines, the presence of diabetes warrants consideration of aggressive primary and secondary cardiovascular risk modification therapies that include but extend well beyond strategies to improve glycemic control. The foundation of such intervention remains therapeutic lifestyle change that includes dietary counseling targeted primarily at caloric restriction and weight reduction; prescription for regular leisure-time physical activity of at least 90 minutes of vigorous or 150 minutes of moderate-intensity exercise weekly, ideally on most days of the week; and smoking cessation/abstinence. In addition, evidence-based recommendations include daily aspirin therapy (81 to 325 mg) for diabetic patients >40 years of age or younger in the setting of prevalent CVD, intensive blood pressure control to <130/80 mm Hg with at least 5 classes of antihypertensive therapies proven effective among patients with diabetes, intensive management of low-density lipoprotein cholesterol to a target of at least <100 mg/dL, with an optional target of <70 mg/dL in very high-risk patients, and consideration of statin treatment for any diabetic patient >40 years of age regardless of low-density lipoprotein cholesterol concentrations. For those patients >55 years of age with either prevalent CVD or an additional cardiovascular risk factor, consideration should be given to the addition of an angiotensin-converting enzyme inhibitor regardless of blood pressure requirements.

Regulatory Oversight of Drugs for Diabetes: Past, Present, and Future

The regulatory requirement for approval of T2DM drugs has been and remains focused primarily on improved glucose control as reflected by improvements in HbA1c on the basis of a body of evidence proving benefits on the development and progression of microvascular complications, most notably retinopathy, nephropathy, and to a lesser degree, neuropathy. Given this historic focus on the prevention of microvascular disease and the paucity of clinical investigations specifically assessing the effects of diabetes drugs in large-scale cardiovascular clinical outcomes studies, the cardiovascular safety and efficacy of available glucose-lowering strategies remain to a large degree uncertain.

Given the population-attributable risk of cardiovascular complications driven by the ever-increasing global prevalence of diabetes, coupled with increased morbidity and mortality due to macrovascular disease, a critical appraisal of the present strategy of regulatory oversight of diabetes drugs is warranted. Although clearly relevant for microvascular disease risk modification, HbA1c has failed as a surrogate for clinical CVD outcomes in both directions. For example, in
the metformin UKPDS substudy, the cardiovascular benefit observed with metformin far exceeded that predicted by epidemiological modeling based on changes in HbA1c. Likewise, a number of drugs such as tolvabamide and most recently rosiglitazone that are effective at lowering HbA1c have been suggested to have neutral or deleterious effects on cardiovascular clinical risk. Therefore, HbA1c reduction appears to be neither necessary nor sufficient to affect CVD risk from glycometabolic drugs. In this context, the evolution of the regulatory paradigm toward the requirement for clinical outcomes data to support drug registration and continued approval must be considered.

Until recently, the paucity of therapeutic options for the treatment of hyperglycemia largely justified the continued reliance on the relatively modest regulatory hurdle of demonstration of glucose-lowering efficacy in the absence of a safety signal to bring new drugs to market. However, with >30 drugs representing the 9 different antihyperglycemic

<table>
<thead>
<tr>
<th>Drug or Drug Category</th>
<th>Mechanism of Action</th>
<th>Potential Advantages</th>
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<tbody>
<tr>
<td>Ranolazine*</td>
<td>Unknown; modulation of sodium channels in pancreatic β cells may enhance glucose-stimulated insulin secretion; partial inhibition of fatty acid oxidation may shift metabolism toward glucose oxidation</td>
<td>Improves diastolic function and cardiac microvascular flow; safety demonstrated in multiple clinical trials in high-risk cardiovascular cohorts</td>
</tr>
<tr>
<td>Cannabinoid-1 receptor antagonists†</td>
<td>Blockade of the cannabinoid-1 receptor in the central nervous system that significantly affects appetite regulation; antagonism of cannabinoid-1 receptors in liver, muscle, and adipose tissue also may reduce lipogenesis and improve insulin sensitivity</td>
<td>Favorable effects on weight and accompanying metabolic features, including insulin resistance and dyslipidemia; low potential for hypoglycemia</td>
</tr>
<tr>
<td>Dual‡ or pan-PPAR agonists</td>
<td>Variable activation of the nuclear transcription factor PPAR-γ in addition to PPAR-α and/or PPAR-δ</td>
<td>Improves lipid effects, primarily triglycerides and HDL cholesterol (PPAR-α), with increased fat catabolism and weight reduction (PPAR-δ); low potential for hypoglycemia</td>
</tr>
<tr>
<td>Selective PPAR-γ modulators</td>
<td>Partial and selective activation of the nuclear transcription factor PPAR-γ</td>
<td>Tissue- and promoter-specific gene regulation, resulting in less adipogenesis and weight gain and less plasma volume expansion, with possibly reduced HF risk, vs TZDs; low potential for hypoglycemia</td>
</tr>
<tr>
<td>Colesevelam§ (a bile acid sequestrant)</td>
<td>Augmentation of intestinal bile acid excretion, secondarily increasing conversion of cholesterol to bile acids, increasing LDL clearance from the blood; mechanism responsible for glucose lowering is largely unknown</td>
<td>Simultaneously reduces LDL cholesterol levels; low potential for hypoglycemia; not absorbed, minimizing the potential for systemic toxicities</td>
</tr>
<tr>
<td>Sodium-glucose cotransporter 1 and 2 inhibitors</td>
<td>Reduction of intestinal glucose absorption by inhibition of sodium-glucose cotransporter-1 in the brush border; increase in concentration-dependent urinary glucose excretion by inhibition of sodium-glucose cotransporter 1 and 2 in the renal proximal tubule</td>
<td>Decreases postprandial hyperglycemia (sodium-glucose cotransporter-1 inhibitors); resultant negative energy balance may facilitate weight control; low potential for hypoglycemia; some sodium-glucose cotransporter-1 inhibitors are minimally absorbed, minimizing the potential for systemic toxicities</td>
</tr>
<tr>
<td>Fructose 1, 6 bisphosphatase inhibitors</td>
<td>Inhibition of the hepatic enzyme that is a key component of the gluconeogenic pathway</td>
<td>Low potential for hypoglycemia</td>
</tr>
<tr>
<td>Glucokinase activators</td>
<td>Stimulation of a key enzyme in liver to increase hepatic glucose metabolism and in pancreatic β cells to increase insulin secretion</td>
<td>Complementary mechanisms of action</td>
</tr>
<tr>
<td>11β-Hydroxysteroid dehydrogenase 1 inhibitors</td>
<td>Inhibition of the enzyme that regenerates cortisol from inactive cortisone in liver and adipose tissue, thereby improving insulin sensitivity at these sites</td>
<td>Reduces insulin resistance; possible lipid lowering and weight reduction; low potential for hypoglycemia</td>
</tr>
<tr>
<td>Protein tyrosine phosphatase 1B inhibitors</td>
<td>Inhibition of a protein in muscle and liver that down-regulates insulin signaling, thereby improving insulin sensitivity</td>
<td>Reduces insulin resistance; low potential for hypoglycemia</td>
</tr>
<tr>
<td>Acetyl-CoA carboxylase-1 and -2 inhibitors</td>
<td>Reduction in malonyl-CoA production, with subsequent increase in fatty acid oxidation in liver and adipose tissue (acetyl-CoA carboxylase-1 or skeletal muscle and cardiac tissue (acetyl-CoA carboxylase-2)</td>
<td>Reduces insulin resistance, body fat content, and body weight; low potential for hypoglycemia; possible cardiac benefits</td>
</tr>
<tr>
<td>Glucagon receptor antagonists</td>
<td>Blockade of the effect of glucagon in liver to stimulate hepatic glucose production</td>
<td>Low potential for hypoglycemia</td>
</tr>
</tbody>
</table>

PPAR indicates peroxisome proliferator–activated receptor; HDL, high-density lipoprotein; TZD, thiazolidinedione; LDL, low-density lipoprotein; and CoA, coenzyme A.

*Currently approved by the FDA as an antianginal drug.
†Recently, the first member of this class, rimonabant, was denied FDA approval as a weight loss agent because of concerns regarding psychiatric adverse effects (depression).
‡Two initial members of this class, muraglitazar (increased cardiovascular events) and tesaglitazar (decreased renal function), were dropped in late stages of clinical development because of potential toxicities.
§Currently approved by the FDA as a cholesterol-lowering drug.

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classes currently available and at least 12 novel classes of medications being evaluated in clinical testing (Table 2), such urgency no longer exists. In addition, with the increased efficiency of large-scale clinical trials driven by advances in technology and development of international collaborative research networks, the regulation of diabetes drugs needs to be reconsidered, with some requirement to demonstrate efficacy on clinical cardiovascular outcomes. As recently been demonstrated in the diabetes field with rosiglitazone and in the lipid field with the failure of torcetrapib, the reliance on intermediate CVD biomarkers for drug development and clinical decision making is imperfect at best.

Valid arguments can be made that registration requirements for proof of clinical efficacy would hinder the present rapid development of novel compounds and potentially delay the availability of new drugs with purported improved efficacy, tolerability, and/or safety profiles. In this light, perhaps the most rational first step would be to continue to regulate the approval of new drugs with existing criteria but require outcomes studies to be executed and results reported within an enforceable timeline after registration. Beyond this point, continued approval would be jeopardized if such projects are not completed or if they failed to demonstrate improved clinical outcomes or acceptable safety profiles. Some difficult questions arise, however, if such an approach were to be adopted. Whose responsibility are these studies? Who should bear their cost? Clearly, creative solutions and continued partnership between industry, regulatory agencies, and academia are required to further develop these new paradigms, with the common ultimate goal of improving the health of patients with diabetes.

Disclosures
Dr Inzucchi reports having received grant/research support and/or honoraria from or having been a consultant for Eli Lilly, Takeda Pharmaceuticals North America, Merck and Co, Novartis, Nordisk, and Pfizer. Dr McGuire reports having received grant/research support and/or honoraria from or having been a consultant for GlaxoSmithKline, Takeda Pharmaceuticals North America, Pfizer, and Johnson & Johnson.

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