Beyond Metformin: Safety Considerations in the Decision-Making Process for Selecting a Second Medication for Type 2 Diabetes Management

Reflections From a *Diabetes Care* Editors' Expert Forum

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EDITORS' EXPERT FORUM

The trend toward personalized management of diabetes has focused attention on the differences among available pharmacological agents in terms of mechanisms of action, efficacy, and, most important, safety. Clinicians must select from these features to develop individualized therapy regimens. In June 2013, a nine-member *Diabetes Care* Editors' Expert Forum convened to review safety evidence for six major diabetes drug classes: insulin, sulfonylureas (SUs), thiazolidinediones (TZDs), glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, and sodium glucose cotransporter 2 inhibitors. This article, an outgrowth of the forum, summarizes well-delineated and theoretical safety concerns related to these drug classes, as well as the panelists' opinions regarding their best use in patients with type 2 diabetes. All of the options appear to have reasonably wide safety margins when used appropriately. Those about which we know the most—metformin, SUs, insulin, and perhaps now also TZDs—are efficacious in most patients and can be placed into a basic initial algorithm. However, these agents leave some clinical needs unmet. Selecting next steps is a more formidable process involving newer agents that are understood less well and for which there are unresolved questions regarding risk versus benefit in certain populations. Choosing a specific agent is not as important as implementing some form of early intervention and advancing rapidly to some form of combination therapy as needed. When all options are relatively safe given the benefits they confer, therapeutic decision making must rely on a personalized approach, taking into account patients' clinical circumstances, phenotype, pathophysiological defects, preferences, abilities, and costs.

Today, there are more therapy options for managing type 2 diabetes than ever before. Primary care and specialty clinicians and the patients they advise benefit from having a wide range of interventions from which to choose in developing diabetes management plans. However, this abundance also means that therapeutic decision making has become increasingly challenging.

Recommendations published in 2012 by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) (1) set forth a flexible

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treatment algorithm that begins, in most cases, with lifestyle intervention and metformin therapy. The algorithm progresses to dual and triple therapy and, through a patient-centered, individualized decision-making process, to numerous and increasingly complex combination therapy options involving various classes of oral and injectable medications. Recent consensus guidelines from the American Association of Clinical Endocrinologists (AACE) (2) described a similar algorithm with rather aggressive A1C criteria for initiating dual therapy. Both sets of guidelines encourage consideration of individual patients' characteristics, needs, and preferences.

This trend toward a more personalized approach has focused attention on the relative differences among available pharmacological agents in terms of mechanisms of action, efficacy, and, perhaps most important, safety. It is on the basis of these differences that treatment decisions for individual patients must be made. To further this discussion, we convened a nine-member *Diabetes Care* Editors' Expert Forum in June 2013 to review the latest safety evidence for six of the major diabetes drug classes—insulin, sulfonylureas (SUs), thiazolidinediones (TZDs), glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium glucose cotransporter 2 (SGLT-2) inhibitors (Videos 1 and 2, available at http://dx.doi.org/10.2337/dc14-1395). This article summarizes both well-characterized and theoretical safety concerns related to these drug classes, as well as our opinions regarding their most efficacious use in patients with type 2 diabetes. We also provide, in Table 1, a list of key topics for discussion with patients who may be considering the use of agents in these classes.

SAFETY CONSIDERATIONS FOR THE MAJOR DRUG CLASSES FOR TYPE 2 DIABETES

Insulin

Since its discovery in 1922, insulin has been the essential treatment for type 1 diabetes and has become an important keystone of treatment for type 2 diabetes. Given the natural history of type 2 diabetes and the fact that insulin secretory deficits progress throughout the disease process, insulin is eventually required in the majority of cases. With numerous insulin formulations now available, one can design a therapy regimen that closely mimics normal physiology, offering efficacy while minimizing hypoglycemia (3). However, insulin often is initiated very late in the course of the disease (4).

Documented Safety Issues

Several concerns, both real and perceived, may explain why insulin initiation is often delayed. These include increased risks for hypoglycemia and weight gain, as well as the misperception held by some that insulin may not be appropriate in a disease not considered to be characterized by insulin deficiency, but rather by hyperinsulinemia and insulin resistance.

Although hypoglycemia is the single greatest drawback to insulin therapy, the development of basal insulin analogs has provided better opportunities for its safe and effective implementation. A 2007 Cochrane analysis (5) reviewed data on the long-acting insulin analog glargine and revealed significant reductions of ~15% in the overall risk for hypoglycemia and ~35% in the risk for nocturnal hypoglycemia compared with NPH insulin in patients with type 2 diabetes. This risk reduction appears to be limited to the long-acting analog formulations, however. A 2006 Cochrane analysis (6) comparing data on rapid-acting insulin analogs to those of regular human insulin in type 2 diabetes found little difference in hypoglycemia rates (weighted mean difference in overall hypoglycemic episodes/patient/month of –0.2 [95% CI –0.5 to 0.1] for analogs vs. regular insulin).

The risk for hypoglycemia also appears to differ based on the type of insulin regimen used. For example, in the 4-T (Treating To Target in Type 2 Diabetes) study (7), the use of basal analog insulin was associated with fewer hypoglycemic events, whereas premixed biphasic insulin formulations carried a greater hypoglycemia risk, and the risk was higher still in regimens involving prandial analog insulin (median events/patient/year of 1.7, 3.0, and 5.7, respectively; $P < 0.001$ for the overall comparison). Of interest, the different insulin formulations are also associated with different risks for weight gain, with greater gains resulting from the use of prandial analog and premixed formulations and less from basal insulin (7).

Potential Safety Issues

Although concerning to patients and clinicians, the risks for hypoglycemia and weight gain may be managed through careful selection of insulin formulations and regimens, attention to patients' clinical circumstances, and appropriate patient education regarding hypoglycemia prevention, detection, and treatment, as well as the importance of lifestyle measures to control weight.

Does insulin use pose a potentially more serious concern with regard to the atherogenic effects of chronic hyperinsulinemia in type 2 diabetes? Most of the data on this issue have come from post hoc analyses suggesting that insulin may increase the risk for cardiovascular events (8). However, well-designed, prospective studies—most notably the ORIGIN (Outcome Reduction With Initial Glargine Intervention) trial (9), in which patients with short-duration type 2 diabetes and a high risk for cardiovascular disease (CVD) were treated with basal insulin for >6 years—have found that insulin therapy had a neutral effect on cardiovascular events compared with routine comparator therapies. The risk for severe hypoglycemia was relatively low in glargine-treated subjects but still greater than in the standard group (1.0 vs. 0.3% per year). Interestingly, the risk for cardiovascular events was increased in subjects with severe hypoglycemia and not in those with mild hypoglycemia regardless of treatment, but it was significantly higher in the standard group than in the glargine group (10).

The ORIGIN trial also helped to ease another concern: the potential of long-acting insulin analogs to increase patients' risks for developing various forms of cancer. Although previous studies (11–13) reported increased cancer rates among patients using long-acting insulin, ORIGIN investigators found a neutral effect of glargine on the risk for neoplasia, both overall and in terms of several specific types of cancer.

In the ORIGIN trial, insulin use in people with prediabetic hyperglycemia was associated with reduced or delayed conversion to overt diabetic hyperglycemia. Along with this observation, evidence is accumulating in support of the possibility of inducing remission of new-onset type 2 diabetes through early insulin

Table 1—Topics for discussion with patients (or as part of structured education programs) regarding potential adverse reactions to glucose-lowering pharmacotherapy

	Problems to address	Topics for patient education
Insulin	Late initiation of insulin treatment	Overcoming resistance to insulin therapy Careful balance of risks and benefits
	Necessity for glucose monitoring	Individualized self-monitoring plan (how frequently, what times of day)
	Dependence on integrity of insulin preparation and ascertainment of proper timing of administration into subcutaneous tissue	Proper insulin storage Proper injection technique
	Hypoglycemia	Prevention of conditions potentially leading to hypoglycemia Early recognition of hypoglycemia Self-treatment of hypoglycemia Treatment of hypoglycemia through proxies
	Weight gain	Nutritional strategies to prevent weight gain or reduce body weight
	Alternatives to progression to multiple injections after failing "bedtime" insulin treatment	Instead of meal-time insulin: Add a GLP-1 receptor agonist Add a TZD Add an SGLT-2 inhibitor
SUs	Hypoglycemia	See hypoglycemia recommendations for insulin Risk for hypoglycemia recurrence after initially successful treatment; necessity for continued surveillance
	Weight gain	See weight gain recommendations for insulin
	Concerns regarding cardiovascular risks	Balanced discussion of current evidence (pro: observational studies; con: UKPDS, ADVANCE)
TZDs	Advantage of best record for durability	Discussion of the concept of durability and its importance for the individual patient
	Advantage of potential cardiovascular benefit	Discussion of cardiovascular outcomes with pioglitazone
	Weight gain	See weight gain recommendations for insulin
	Risk for fluid retention and related adverse effects (edema, congestive heart failure, anemia)	Warning signs Screening measures Appropriate dosing
	Increased risk for fractures	Discussion of individual susceptibility for fractures Preventive measures Appropriate dosing
	Increased risk for bladder cancer	Discussion of this as an unresolved issue Information about the potential quantitative impact Screening and surveillance measures
Incretin-based therapies	Nausea, vomiting, diarrhea (GLP-1 receptor agonists only)	Rare and transient nature Possibility that drug needs to be withdrawn in a minority of patients Potential pharmacotherapy for side effects
	Injection site reactions and nodules (GLP-1 receptor agonists only)	Information about nature of this side effect (immunological responses potentially related to antibody formation) Possibility that repeated episodes may suggest the need to discontinue this treatment
	Increased risk for hospitalization for heart failure (?)	Information on recognition of symptoms Clinical significance of study findings are undetermined Caution for those at high risk
	Increased risk for acute pancreatitis (?)	Discussion of this as an unresolved issue Early signs and symptoms of pancreatitis, behavioral advice in such a case (seek medical advice, discontinue treatment) Advice for alternative treatment in the case of past episodes of pancreatitis
	Increased risk for medullary thyroid carcinoma (?)	Information about the low likelihood in the face of the rarity of this disease Advice for alternative treatment in the case of a personal or family history or with a given genetic background (multiple endocrine neoplasia syndrome type 2)

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Table 1—Continued

	Problems to address	Topics for patient education
SGLT-2 inhibitors	Genital infections (*Candida* and other fungi)	Signs and symptoms Preventive measures (hygiene) Consider other treatments after repeated occurrence
	Urinary tract infections (bacterial)	Signs and symptoms (including those of more severe, ascending infections [urosepsis]) Preventive measures (hygiene) Consider other treatments after repeated occurrence
	Negative fluid balance	Information about potential consequences (too great a drop in blood pressure, impairment of kidney function)
	Elevated LDL cholesterol	Impact on overall cardiovascular risk Treatment options (statins, target values, careful dose-finding)
	Risk for bladder cancer	Discussion of this as an unresolved issue Information about the potential quantitative impact Screening and surveillance measures

therapy. A recent meta-analysis (14) synthesized data from studies of short-term intensive insulin therapy in newly diagnosed patients to determine its effects on insulin sensitivity and β-cell dysfunction, the two main pathophysiological defects responsible for hyperglycemia and diabetes progression. This analysis found that early introduction of insulin was associated with an improvement in both conditions.

Thus, although insulin is not without risks, its use in appropriate patients at the appropriate time does offer significant benefit. It not only improves short-term glycemic control, but also may be a viable strategy for altering the course of the disease, enabling patients to achieve a state of remission during which normoglycemia can be sustained for some time without further treatment.

Insulin: Rethinking When and How

Because most patients with type 2 diabetes continue to secrete some amount of endogenous insulin even in the late stages of the disease, initial insulin therapy usually involves a basal-only regimen aimed at suppressing overnight hepatic glucose production, thereby lowering glucose levels during sleep and between meals. In this regard, prevalent fasting hyperglycemia is perhaps the best indicator of the need for basal insulin, even when it occurs early in the disease. Other situations, such as intermittent comorbidities, surgical interventions, and pregnancy, also may call for insulin initiation, at least in the short term.

Newly diagnosed patients usually begin diabetes treatment with metformin monotherapy (or monotherapy with an SU or incretin-based agent) and progress to some form of combination oral agent therapy before starting basal insulin. However, adding basal insulin immediately after metformin may be appropriate in some cases; likewise, forgoing insulin in favor of a second or third oral agent may be reasonable (although likely more costly) for some patients. A notable exception to the standard treatment algorithm is for newly diagnosed patients with extremely poor glycemic control and a high A1C, for whom immediate insulin therapy is recommended to ameliorate glucose toxicity and related symptoms (1,2). Such patients often can substantially reduce or discontinue insulin in favor of oral agents after glycemic control stabilizes.

SUs

As the first available oral agents for glucose lowering, SUs have a 60-year record of use, second only to that of insulin. Thus, there is a substantial database from which to draw conclusions regarding their efficacy and safety (15–19). These agents stimulate endogenous insulin release in a nonglucose-mediated manner by closing ATP-sensitive potassium channels located on pancreatic β-cells (20). They are widely used in the U.S. and around the world, accounting for ~25% of newly initiated oral therapies for diabetes (21). In the U.S., they are considered one of several second-line options after metformin for most people with type 2 diabetes and a viable first-line alternative for patients who cannot take metformin (1,2).

Drugs in this class can be divided into two groups: historical agents that are no longer widely used (including carbutamide, acetohexamide, chlorpropamide, tolbutamide, and tolazamide) and currently used agents (including glyburide [also known as glibenclamide], gliclazide, glipizide, and glimepiride). Most of the historical SUs have adverse effects that have limited their use (22–24), and it has been suggested that the routine use of glyburide should also be restricted (25). Glyburide interferes with cardiac ischemic preconditioning (26); compared with the other modern SUs, it may be associated with higher mortality rates when coadministered with metformin (27) and after hospitalization for myocardial infarction (MI) (22), and it causes more hypoglycemia (28).

To our way of thinking, the ideal antihyperglycemic agent would be easy to administer, unlikely to cause symptomatic side effects that pose barriers to adherence, inexpensive, reliably efficacious, and safe. By such standards, it can be argued that the remaining modern SUs do well (although they do leave some clinical needs unmet). Glimepiride and extended-release preparations of glipizide and gliclazide can be given once daily and rarely cause symptomatic side effects other than hypoglycemia. They appear to be as effective as or more effective than other oral agents in terms of A1C reduction, life expectancy, and quality-adjusted life-years (29,30). And SUs are remarkably inexpensive compared with newer oral agents (31).

Documented Safety Issues

Hypoglycemia and weight gain are the main well-documented safety issues related to SUs (19,32). Starting an SU typically leads to a weight gain of ~2 kg depending on prior A1C level and hypoglycemia rates two to three times higher than with other agents (29). Although significant, these risks usually can be managed with appropriate patient selection, attention to dosing, and adequate patient education. Patients with compromised renal functioning are particularly susceptible to hypoglycemia from SUs; hence, their use in this population should be avoided. Allergy and other idiosyncratic effects are rare.

Potential Safety Issues

Concerns about the potential effects of SUs on cardiovascular risk, possibly related to interference with cardiac ischemic preconditioning (33), have existed since at least 1970, with the controversial results from the University Group Diabetes Program (UGDP) (34) suggesting that tolbutamide might be associated with an increased risk for cardiovascular mortality. Attention to this issue subsided somewhat with the emergence of other SUs (35), but findings from retrospective analyses of associations between oral diabetes drugs and cardiovascular outcomes have been inconsistent (36–40).

Recent trials and analyses have been more reassuring. In 1998, the UK Prospective Diabetes Study (UKPDS) group (41) reported no difference in the rates of MI or diabetes-related death among subjects receiving chlorpropamide, glyburide, or insulin. Researchers in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trial (42) reached a similar conclusion in 2008, reporting no significant differences between intensive glucose control involving gliclazide and other drugs as required and conventional care in major macrovascular events, death from cardiovascular causes, or death from any cause. The RECORD (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) study (43) similarly found no significant differences in the risk for cardiovascular events among combination therapy with rosiglitazone and metformin, rosiglitazone and SU, or metformin and SU. Although not designed to evaluate cardiovascular outcomes, the ADOPT (A Diabetes Outcome Progression Trial) study (44), which compared the durability of effectiveness of monotherapy with metformin, rosiglitazone, or glyburide, reported nominally lower rates of cardiovascular events in patients taking glyburide than in those taking either rosiglitazone or metformin.

A 2013 meta-analysis (45) of 62 trials reporting major cardiovascular events with SUs versus various comparators has provided perhaps the best synthesis of data to date. This analysis found an overall odds ratio (OR) for major cardiovascular events with SU treatment versus comparators of 1.08 (95% CI 0.86–1.36), thus detecting no signal for cardiovascular risk. However, the authors urged cautious interpretation of their results given limitations of trial quality and potential underreporting of information on cardiovascular events and mortality.

Further evidence in support of SUs comes from modern epidemiological studies such as a recent retrospective health system database analysis from Alberta, Canada (46), which sought to determine whether patients taking SUs at the time of acute coronary syndrome were more likely to have poor outcomes. Its results indicated an adjusted OR for using versus not using an SU of 1.06 (95% CI 0.89–1.26). One possible explanation for the lack of an apparent association between the use of SUs and higher cardiovascular risk in recent studies is the decline in the use of glyburide in favor of SUs with a lower propensity to cause hypoglycemia and without significant effects on ischemic preconditioning.

SUs: a Proven and Still Valuable Option

As new drug classes have been introduced, promotional efforts have suggested that SUs are an outmoded class to be replaced by newer agents. However, we do clearly know the efficacy of these agents, just as we are aware of their limitations of hypoglycemia and weight gain. Objectively, one could argue that, given the wealth of clinical experience, new safety concerns are not likely to emerge. Although poor durability of effectiveness has been a major criticism, participants assigned to standard therapy in the ORIGIN trial, treated mainly with metformin and an SU, maintained glycemic control (average A1C 6.5%) for 6 years (9). SUs also offer the advantages of ease of administration, good tolerability, and low cost.

Still, clinicians prescribing SUs must take care to help patients avoid hypoglycemia. Appropriate patient selection is important, especially when considering SUs for patients who are elderly or frail, have a history of hypoglycemia or hypoglycemia unawareness, or have renal dysfunction or other conditions or comorbidities likely to place them at high risk. Glyburide should rarely be considered because of its greater tendency to cause hypoglycemia.

TZDs

TZDs have been a source of both enthusiasm and controversy since troglitazone, the first agent in the class, was approved in the U.S. in 1997 to address insulin resistance. This ushered in a new paradigm of treatment and was followed by rosiglitazone and pioglitazone in 1999 (47). TZDs are synthetic ligands that activate PPAR-γ nuclear receptors in adipose tissue, skeletal muscle, and the liver (48). They act primarily to improve insulin sensitivity and reduce hepatic glucose production and are, to date, the only class of agents specifically targeting insulin resistance, which is one of the primary defects in type 2 diabetes and other insulin-resistant states such as impaired glucose tolerance and polycystic ovary syndrome.

The main appeal of TZDs is their durability of effect in lowering A1C (49–52), as well as their potential to alter the natural progression of diabetes in a way that cannot be achieved with other oral agents (43,44). However, seeking this goal would necessitate initiating TZD therapy early in the course of the disease, making consideration of safety issues surrounding this drug class particularly important.

Documented Safety Issues

Troglitazone was withdrawn from the U.S. market in 2000 because of concerns regarding hepatotoxicity (53). In the mid-2000s, several articles were published suggesting that rosiglitazone was associated with excess cardiovascular events, specifically MIs. As a result, the use of rosiglitazone was tightly restricted in 2011 (54). However, the RECORD study (43), reported in 2009, had documented no increased risk for

cardiac adverse events. A recent U.S. Food and Drug Administration (FDA)–mandated readjudication of the RECORD findings (55), which confirmed no increase in overall cardiovascular risk with rosiglitazone, prompted the FDA to lift its restrictions on this agent but maintain specific warnings related to increased risks for congestive heart failure and bone fractures (56).

For now, pioglitazone remains the most widely used TZD, and research suggests that its safety profile is less controversial than other agents in this class. Although the PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) trial (57), a cardiovascular outcomes randomized controlled trial (RCT), failed to meet statistical significance for a primary end point composed of numerous macrovascular outcomes, a subanalysis of a secondary end point encompassing MI, stroke, and cardiovascular death found a modest but statistically significant reduction.

Other well-recognized concerns related to the TZDs include weight gain, fluid retention leading in some cases to edema or congestive heart failure, and increased risk for bone fractures, often at peripheral sites, which is perhaps one of the greatest concerns with this class (58,59). Mechanistic studies have shown that there is a theoretical possibility that TZDs could alter the differentiation of mesenchymal stem cells toward the formation of fat and away from the formation of bone. Both RCTs (60) and pharmacoepidemiological analyses (61) have revealed an increased absolute risk for bone fractures of ~1% in men and 3% in women.

Fluid retention usually can be managed through patient counseling and careful patient selection and safely mitigated with thiazide diuretics. Although the potential for heart failure has been an important safety consideration, individual studies and meta-analyses suggest that there is a small increase in the absolute risk for heart failure requiring hospitalization but no increase in fatal heart failure (62).

TZDs also have been associated with an increased incidence of macular edema in retrospective, observational studies with an approximately twofold increased risk (63). However, this has not been consistently observed in RCTs (64). Certainly, patients treated with TZDs should have annual dilated funduscopic exams and should seek attention for more than transient visual changes.

Other common TZD side effects include anemia, rare instances of increased creatine phosphokinase (but not serious myositis), variable changes in lipids, and possible hepatic effects. The latter necessitate the avoidance of these agents in patients with substantial liver disease, although some studies have suggested that TZDs actually may be beneficial in the setting of fatty liver disease (58,59,65); furthermore, because TZDs are not excreted through the kidney, they are potentially useful for patients with chronic kidney disease. Finally, because the risk for hypoglycemia may be increased when TZDs are used in combination with insulin or insulin secretagogues, doses of these latter agents should be reduced in such circumstances.

Potential Safety Issues

As accumulating evidence lessens concern about cardiovascular risk, the main remaining potential, but as yet unproven, safety issue related to TZDs is a possible link to increased rates of bladder cancer with pioglitazone. This issue arose because of imbalances detected in the development of bladder tumors in preclinical animal studies of pioglitazone and of experimental drugs with dual PPAR-γ and PPAR-α activity (58,66). Imbalances in the number of bladder cancer cases have also been reported in some RCTs, most notably PROactive (57), which found a nonsignificant increase in bladder tumors in pioglitazone-treated patients. The most robust pharmacoepidemiological study to date (67), which is being conducted at the request of the FDA, detected no overall signal for bladder cancer risk at 5 years, but did suggest a modest increase in risk only in patients with long exposure to or on high doses of pioglitazone. However, in more recent analyses, the statistical significance of these findings disappeared by 8 years of follow-up and the cancers detected were almost all in an early stage (68).

Further study will be required to fully elucidate this potential risk. For now, prescribing information for pioglitazone suggests that it not be used in patients with a history of bladder cancer and that all patients should be instructed to seek medical attention for any urinary symptoms that may develop (58).

TZDs: Proceed With Caution

Until the issues enumerated above are put to rest, TZDs most likely will be considered as third- or fourth-line options after combinations of other agents. In such situations, the balance of benefit to risk is still quite strongly in favor of these drugs.

Incretin-Based Therapies: GLP-1 Receptor Agonists and DPP-4 Inhibitors

GLP-1 is a gut-derived incretin hormone that stimulates insulin secretion in a glucose-dependent manner, suppresses glucagon secretion similarly, slows gastric emptying, reduces appetite, and may expand β-cell mass (69). The development of two drug classes that act through stimulation of GLP-1 receptors to enhance incretin action—GLP-1 receptor agonists (incretin mimetics) and DPP-4 inhibitors (incretin enhancers)—has been an important advancement in the pharmacological treatment of type 2 diabetes (70) because these agents effectively control glycemia without causing hypoglycemia or weight gain.

GLP-1 receptor agonists are peptides that mimic native GLP-1, binding to its receptors to elicit the same effects, but at much higher pharmacological levels than the physiological profiles. Agents in the class currently available in the U.S. include exenatide twice daily, exenatide once weekly (QW), liraglutide once daily, and albiglutide QW, all of which are administered through subcutaneous injection. Other agents in development include dulaglutide QW and semaglutide QW, as well as lixisenatide once daily, which is available in Europe.

DPP-4 inhibitors act to suppress the proteolytic enzyme (i.e., DPP-4) that normally degrades endogenous GLP-1 and thereby increase the concentration of intact, biologically active GLP-1 and augment its interaction with receptors. DPP-4 inhibitors available globally and in the U.S. include alogliptin, linagliptin, saxagliptin, and sitagliptin. Vildagliptin is also globally available except in the U.S., and other DPP-4 inhibitors are available in Japan. All are administered orally.

The mechanisms of incretin-based therapies, and the clinical trials demonstrating the efficacy and safety profiles on which our understanding of them is based, have been extensively reviewed

elsewhere (70–73). Briefly, agents in both classes have been shown to lower, to varying degrees, A1C, fasting plasma glucose, and postprandial glucose. Whereas GLP-1 receptor agonists also slow the rate of gastric emptying in different degrees based on their pharmacokinetic profiles and can cause a sense of satiety leading to reduced food intake and moderate weight loss, DPP-4 inhibitors do not slow the rate of gastric emptying and are weight-neutral. Neither type of therapy increases the risk for hypoglycemia except when associated with SUs or insulin. Clinical trials of agents in both classes also have shown improvements in some surrogate markers of pancreatic β-cell function in type 2 diabetes. Both also may yield modest improvement in lipid profiles and systolic blood pressure levels, although short-term studies have shown only neutrality for cardiovascular events (74,75).

Current guidelines (1,76) recommend both types of incretin-based therapies for use as monotherapy (mostly in patients for whom metformin is not an option) and in combination with other agents (most often metformin) if, for example, treatment priorities include reducing the risk for hypoglycemia and controlling body weight.

Documented Safety Issues

The most common treatment-related adverse effects of GLP-1 receptor agonists are gastrointestinal in nature and include nausea, vomiting, and diarrhea, which are usually mild and tend to subside over time but in some patients may be intermittent and lead to eventual discontinuation (77,78). A dose-titration strategy has been found to reduce the incidence of nausea (79), but <5% of patients in clinical trials need to discontinue treatment because of such side effects (77,78). However, discontinuation rates in clinical practice are greater, mainly as a result of gastrointestinal intolerance without the type of support system typically available in clinical trials and perhaps disenchantment when these agents are initiated mainly in hopes of achieving weight loss.

Other documented but infrequent concerns with GLP-1 receptor agonists include injection site reactions (80) and, particularly with exenatide QW, the development of transient small nodules around injection sites related to the viscous nature of the formulation (81).

DPP-4 inhibitors have been shown to have a very good safety and tolerability profile similar to that of placebo (72,82). Unlike GLP-1 receptor agonists, DPP-4 inhibitors are not associated with gastrointestinal adverse events. Early signs that their use may be associated with more upper respiratory tract and urinary tract infections have not been confirmed (82,83). Evidence to date suggests that DPP-4 inhibitors do not affect cardiovascular risk with ~2 years of exposure in high-risk populations (82).

Severe hypoglycemia has not been observed in trials of any incretin-based monotherapy (77,84–90), but mild to moderate hypoglycemia has occurred in 0–12% of patients, depending on the agent studied (77,84–86,88–91). A higher hypoglycemia rate has been documented when such agents are used in combination with SUs or insulin (78,92–99); hence, decreasing the dosage of these concomitant agents is recommended.

Potential Safety Issues

Low-frequency findings of as yet unknown clinical significance have raised additional questions regarding the long-term safety of incretin-based therapies (100,101). The results of ongoing prospective studies will help to address these issues.

Heart Failure. The SAVOR (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus) study (74) found an increased rate of hospitalization for heart failure compared with standard care, although overall cardiovascular events, including heart failure, did not increase. Data from the EXAMINE (Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome) trial (75) were consistent with this observation but even less robust. Whether the effect is real and, if so, the extent of its clinical significance remains uncertain pending the completion of other studies (102,103). In the meantime, caution seems indicated in people with or at high risk for heart failure.

Acute Pancreatitis. Cases of pancreatitis have been reported in animals (104–107) and humans (108) treated with GLP-1 receptor agonists or DPP-4 inhibitors. The question of whether such cases may potentially be caused by treatment with incretin-based therapies remains unanswered.

Animal studies have been inconsistent, although most preclinical models cannot reflect the human pancreatitis model. Some have described histological changes consistent with damage to the exocrine pancreas with exenatide (104,105) and sitagliptin (107), but not with liraglutide (106). Other studies in mice have documented improvement of experimentally induced acute pancreatitis with exenatide (109) and an anti-inflammatory cytokine response with liraglutide (110).

Small imbalances in the number of cases of acute pancreatitis reported in several of the clinical development programs of incretin-based therapies led the FDA to require a warning regarding the possibility of developing acute pancreatitis and a recommendation to avoid these agents in people with a history of pancreatitis (111). Retrospective, observational studies of acute pancreatitis from incretin-based therapies have found ORs near 1, suggesting no increased risk. However, these ratios have wide CIs due to the small number of cases (112–116). Furthermore, these types of reports, obtained from insurance claims data, electronic medical records, or prescription databases, are not prospectively designed to answer specific questions regarding the safety of therapeutic interventions. Thus, any findings can only be regarded as either hypothesis-generating or merely suggestive, but certainly cannot be viewed as definitive. A single study reporting that patients taking exenatide or sitagliptin had a tenfold higher likelihood of developing pancreatitis was based on data from the FDA Adverse Event Reporting System, which is susceptible to reporting bias (117). A case-control study looking at the rate of hospitalization for pancreatitis found a higher OR among patients taking "incretin-based therapies," but yielded no significant findings for either GLP-1 receptor agonist or DPP-4 inhibitor therapy when analyzed separately (118). The possibility exists that a combination of gastrointestinal symptoms and spontaneously elevated lipase activity (as is typical for a

type 2 diabetic population [119]) were misdiagnosed as pancreatitis in at least some of these cases.

As recently recommended in this journal (120), patient-level safety data from the multiple ongoing, cardiovascular outcomes RCTs of incretin-based therapies should be combined to provide sufficient statistical power for more conclusive meta-analyses. Such efforts should yield more definitive answers regarding pancreatitis and incretin-based therapies in the coming years.

Chronic Pancreatitis and Pancreatic Cancer. Concerns have been raised regarding the potential role of incretin-based therapies in inducing chronic pancreatitis, which, in the long run, could promote preneoplastic lesions, thus raising the risk for pancreatic cancer (101). Whereas some animal studies have shown histological changes indicative of chronic pancreatitis with exenatide (104,105,107), a study of liraglutide noted pancreatitis as a rare finding unrelated to dose and with similar numbers in placebo-treated rats, mice, and monkeys (106). Recently reported tissue analysis from organ donors who had type 2 diabetes and took incretin-based agents found pancreatic abnormalities; these reports, and published reviews of them, included comments on methodological issues, as well as preexisting conditions that may have predisposed to these findings (121–123).

To date, there have been no reported cases of clinically identifiable chronic pancreatitis or pancreatic cancer arising after initiation of incretin-based therapies. However, given the relatively short time these agents have been in use and the typically slow development of pancreatic carcinomas (124), it is too early to know.

Medullary Thyroid Carcinoma. One study has shown that exposure to long-acting GLP-1 receptor agonists increased thyroid C-cell hyperplasia, adenomas, and medullary thyroid carcinomas in mice and rats (125). It is important to note, however, that such abnormalities also occur spontaneously in these species, especially in male rats, in which medullary thyroid carcinoma also developed with placebo. Rodent C-cell lines produce cyclic AMP and secrete calcitonin. Similar human cell lines do not show such effects (125), and long-term high-dose GLP-1 receptor agonist treatment in type 2 diabetic or obese humans did not elicit elevations in plasma calcitonin (126). Rodent C cells have considerably more GLP-1 receptors than their human counterparts (125). Thus, GLP-1 stimulation probably does not provoke proliferative responses in human C cells, and no such cases have been reported. Medullary thyroid carcinoma is extremely rare in humans (127).

Incretins: Safety Signals Still Require Vigilance

Although the known and anticipated benefits of incretin-based therapies appear to be substantial, the potential risks for serious rare events remain controversial and in need of further elucidation through long-term studies. Safety concerns related to alterations of the exocrine pancreas and thyroid, while deserving of further study, are not yet firmly substantiated. An excellent debate on this topic was published in a previous issue of *Diabetes Care* (100,101). The FDA and the European Medicines Agency (EMA) carefully scrutinized preclinical and clinical data on this topic and recently came to a similar conclusion that no changes in recommendations are necessary until more firm data are available (128).

SGLT-2 Inhibitors

SGLT-2 inhibitors are the newest class of medications and, as such, have the least available research and clinical data regarding their effective use and adverse effects. The mechanisms and efficacy of these agents have been reviewed elsewhere (129–131). The main advantage of SGLT-2 inhibitors is a completely different mechanism of action; they work primarily to lower the renal threshold to glucose, leading to increased glucose excretion and decreased plasma glucose levels. Because this mode of action is not dependent on insulin secretion, agents in this class can be considered for use in combination with other glucose-lowering agents throughout the course of type 2 diabetes and potentially can be a useful add-on therapy to insulin in type 1 diabetes.

The efficacy of SGLT-2 inhibitors appears to be similar to that of other antihyperglycemic agents; they significantly reduce fasting and postprandial glucose levels, leading to A1C reductions of ~0.5–1.0%. These agents also induce mild osmotic diuresis and a net loss of calories, yielding a slight reduction in blood pressure and a net weight loss. Because SGLT-2 inhibitors have no effects on glucose-dependent endogenous insulin secretion and do not completely halt glucose reabsorption, they carry a low risk for severe hypoglycemia (132–134).

Two SGLT-2 inhibitors—canagliflozin and dapagliflozin—are currently available in the U.S. and elsewhere; both are administered in once-daily oral tablets (135,136).

Empagliflozin was recently approved by the EMA, and several other SGLT-2 inhibitors are available in Japan.

Documented Safety Issues

Genital mycotic infections and urinary tract infections have been the most commonly reported adverse events associated with SGLT-2 inhibition to date (137–140). These occurrences are usually mild to moderate and responsive to treatment, and they rarely result in discontinuation of therapy (141,142). Studies have also shown that some adverse events related to osmotic diuresis (e.g., polyuria) are greater with SGLT-2 inhibitors than with placebo. In addition, there have been some unusual laboratory parameters, such as changes in hemoglobin, plasma magnesium, and blood urea nitrogen levels and, interestingly, increases in both HDL and LDL cholesterol. Furthermore, studies have documented some volume-related adverse events, such as hypotension and postural dizziness, which require further study and could have implications for the use of these agents, particularly in the elderly population (141,142). Mild hypoglycemia has been documented with concurrent use of SGLT-2 inhibitors and insulin or insulin secretagogues (134,143). Hence, reductions in the dosages of such agents are recommended when used in conjunction with SGLT-2 inhibitors (135,136).

Potential Safety Issues

Although canagliflozin was the first SGLT-2 inhibitor to receive FDA approval, a similar agent, dapagliflozin, was approved earlier in Europe and in the U.S. in 2014 (144). Dapagliflozin's safety and effectiveness were evaluated in 16 clinical trials involving 9,400 patients with type 2 diabetes taking the agent as monotherapy or in combination with

other diabetes pharmacotherapies. These trials showed improvement in A1C and found that the most common side effects were genital fungal infections and urinary tract infections. However, because of a numerical imbalance in bladder cancers seen in dapagliflozin users, the agent is not recommended for patients with active bladder cancer (144). Similar studies of canagliflozin have not confirmed a bladder cancer effect; taken together, these studies have shown no conclusive increased risks for bladder or breast cancer (141,142).

Perhaps the greatest concern with this class of medications is simply the fact that they have not been studied long enough to reach definitive conclusions about their long-term safety, either in the general population or in specific subgroups such as the elderly. Recent studies of volume-related events in the elderly appeared to indicate that these agents remain well tolerated and beneficial even in that high-risk population (141), although further study is needed. Additional research is also needed to determine the possible effects of SGLT-2 inhibition on long-term cardiovascular risk factors and to better characterize any possible increased risks for breast or bladder cancer with long-term use. Large cardiovascular outcomes trials are under way to satisfy FDA requirements for cardiovascular safety; these trials will also provide additional data regarding renal safety and any cancer-related concerns.

SGLT-2 Inhibitors: Much Potential, Many Unanswered Questions

Through their unique focus on the kidney, SGLT-2 inhibitors have turned a condition once viewed as indicative of poor glycemic control—glucosuria—into a means of achieving decreased plasma glucose concentrations. These agents can potentially benefit any patients with diabetes who have adequate renal function. In this regard, some studies have suggested favorable effects in patients with type 1 diabetes (145,146).

In addition to their favorable effects on glucose and weight, SGLT-2 inhibitors also correct the excessive activity of sodium reabsorption that is found in type 2 diabetes and that contributes to hypertension, CVD, and other long-term consequences. In theory, then, these agents may be particularly useful in patients who are obese and hypertensive and who have some degree of established CVD.

As with the incretin-based classes, SGLT-2 inhibitors suffer from a lack of long-term clinical experience and research data, leaving numerous unanswered questions regarding their long-term safety. Although the most frequent adverse effects—genital mycotic and urinary tract infections—appear to be more an issue of patient tolerance than of safety, we await more data regarding possibly significant metabolic and other side effects, as well as further elucidation of potential cancer risks.

CONCLUSIONS

Although no pharmacological agent is without some risk, all of the options discussed above appear to have wide margins of safety when used appropriately. Many years of clinical experience with the older agents (i.e., insulin, SUs, and TZDs) and a rapidly growing understanding of the newer ones (i.e., GLP-1 receptor agonists, DPP-4 inhibitors, and SGLT-2 inhibitors) leave us better positioned than even a few years ago to help patients achieve and maintain glycemic control.

The question remaining, then, is how to determine the most appropriate role for any given agent in individual patients. Luckily, the agents and drug classes about which we have the most knowledge—metformin, SUs, insulin, and perhaps now TZDs—are quite successful in most patients and can be placed into a basic algorithm such as those recommended by ADA/EASD and AACE (1,2) and prescribed with some confidence. Selecting next steps as a patient's diabetes progresses remains a more formidable process involving newer agents that are understood less well and for which there are unresolved questions regarding risk versus benefit in certain populations.

Shedding more light on the best uses of these agents will require greater effort along two fronts. First, additional evidence is needed regarding which patients are most and least likely to benefit from each pharmacological option. Research studies must identify not only the overall effects of these agents on clinical outcomes, but also the high- and low-risk subgroups for each in terms of physiology, demographics, comorbidities, and other factors. Second, as emphasized in the ADA/EASD guidelines (1), clinicians must solicit and respect the needs and desires of patients as partners in the decision making required to most effectively manage diabetes.

Perhaps the most important message is that the selection of one agent over another is not as important as implementing some form of early intervention and advancing rapidly to some form of combination therapy as needed. Studies such as ORIGIN (9) have demonstrated that even the most conventional regimen can have excellent durability when started early. The classes of agents that have been available the longest are well-proven, cost-effective, and sensible options for many patients. For other patients, initiation of an injectable agent (early insulin in combination with metformin alone or with another oral agent or early treatment with a GLP-1 receptor agonist) may be the preferred choice.

When all options are relatively safe relative to the benefits they confer, therapeutic decision making relies more than ever on a personalized approach taking into account patients' clinical circumstances, phenotype, specific pathophysiological defects, preferences, abilities, and costs. Regardless of the specific therapy selected, the overarching goal should be to safely achieve glycemic control at the earliest possible stage with the least risk for adverse events, thereby increasing the likelihood of long-term durability of control and avoidance of complications in the future.

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