Incretin-Based Therapies for the Treatment of Type 2 Diabetes: Evaluation of the Risks and Benefits

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Type 2 diabetes is a complex metabolic disorder characterized by hyperglycemia arising from a combination of insufficient insulin secretion together with resistance to insulin action. The incidence and prevalence of type 2 diabetes are rising steadily, fuelled in part by a concomitant increase in the worldwide rates of obesity. As longitudinal studies of type 2 diabetes provide evidence linking improved glycemic control with a reduction in the rates of diabetes-associated complications, there is considerable interest in the therapy of type 2 diabetes (Fig. 1), with a focus on the development and use of new agents that exhibit improved efficacy and safety relative to current available medicines.

Although the number of patients with type 2 diabetes that successfully achieve target levels of A1C is steadily improving, a substantial number of subjects continue to fall short of acceptable treatment goals, leaving them at high risk for development of diabetes-associated complications (1). More importantly, a large number of subjects with type 2 diabetes fail to achieve target values for glucose, lipids, and blood pressure, with only 12.2% of patients meeting target values despite recent improvements in therapeutic agents targeting hyperglycemia, dyslipidemia, and hypertension (2). The development of multiple new agents for the treatment of type 2 diabetes has broadened the options for patient-specific therapy. However, no currently available agents exhibit the ideal profile of exceptional glucose-lowering efficacy to safely achieve target levels of glycemia in a broad range of patients. Hence, highly efficacious agents that exhibit unimpeachable safety, excellent tolerability, and ease of administration to ensure long-term adherence and that also clearly reduce common comorbidities and complications of diabetes are clearly needed (Fig. 1). Furthermore, most patients require combination therapy to achieve effective control of their disease (3). Recommended initial therapy generally includes comprehensive lifestyle management and patient education combined with metformin therapy. Although metformin is widely accepted as the preferred agent for the initial treatment of type 2 diabetes, there remains considerable uncertainty and lack of consensus in regard to choice of additional agents that need to be added to metformin to optimize glycemic control.

Recent recommendations have highlighted the use of insulin, sulfonylureas, and thiazolidinediones as second-line therapies because of their proven efficacy in long-term outcome studies. Nevertheless, more recent studies involving intensive use of these therapies in patients with clinical cardiovascular disease or multiple risk factors to achieve lower target glucose levels were associated with hypoglycemia, bone fractures, hospitalization for congestive heart failure, weight gain, and, in some analyses, increased mortality with modest benefit on rates of myocardial infarction. This has led to a re-examination of treatment recommendations to minimize the risk of cardiovascular morbidity and mortality (3,4) and specifically an interest in incretin-based therapies in this regard.

Incretin-based therapies: mechanisms of action and benefits

The two most recently approved classes of therapeutic agents for the treatment of type 2 diabetes, glucagon-like peptide-1 (GLP-1) receptor (GLP-1R) agonists and dipeptidyl peptidase-4 inhibitors (DPP-4i), exert their actions through potentiation of incretin receptor signaling. Incretins are gut-derived hormones, principally GLP-1 and glucose-dependent insulinotropic peptide (GIP), that are secreted at low basal levels in the fasting state. Circulating levels increase rapidly and transiently following food ingestion. As native GLP-1 displays a very short circulating half-life due to renal clearance and NH_2-terminal degradation by the enzyme DPP-4, degradation-resistant GLP-1R agonists have been developed. Exendin-4, a GLP-1R agonist structurally related to the native gut peptide, was approved for the treatment of type 2 diabetes in the U.S. in April 2005 and is currently administered as a subcutaneous injection (10 μg twice daily) for use as monotherapy in subjects not achieving adequate glycemic control on lifestyle modification alone or one or more oral agents. Liraglutide is an investigational human acylated GLP-1R agonist approved in Europe that binds noncovalently to albumin and exhibits a more prolonged duration of action suitable for once daily administration. A longer-acting microsphere preparation of exenatide suitable for once weekly administration, exenatide (once weekly), has also been studied in controlled clinical trials and appears to be somewhat more effective compared with exenatide twice daily (5).

Sitagliptin was the first DPP-4i approved in the U.S. in October 2006. It exerts its glucoregulatory actions through

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Antihyperglycemic Agents in Type 2 Diabetes

Class	A1C Reduction	Hypo-Glycemia	Weight Change	CVD Risk Factors	Dosing (times/day)	Diabetes Comorbidity Contraindications
Metformin	1.5	No	Neutral	Minimal	2	Kidney, liver
Insulin, Long-acting	1.5 - 2.5	Yes	Gain	TG	1, Injected	None
Insulin, Rapid-acting	1.5 - 2.5	Yes	Gain	TG	1-4, Injected	None
Sulfonylureas	1.5	Yes	Gain	None	1	Essentially none
Thiazolidinediones	0.5 - 1.4	No	Gain	Variable	1	CHF, liver
Repaglinide	1 - 1.5	Yes	Gain	None	3	Essentially none
Nateglinide	0.5 - 0.8	Rare	Gain	None	3	Essentially none
Alpha-glucosidase Inhibitors	0.5 - 0.8	No	Neutral	Minimal	3	Essentially none
Amylin-mimetics	0.5 - 1.0	No	Loss	With weight loss	3, Injected	None
GLP-1R Agonist	0.5 - 1.0	No	Loss	With weight loss	2, Injected	Kidney
DPP-4 Inhibitor	0.6 - 0.8	No	Neutral	None	1	None
Bile acid sequestrant	0.5	No	Neutral	LDL	1-2	Severe TGs
Bromocriptine	0.7	No	Neutral	Minimal	1	Essentially none

Figure 1—*Relative comparison of properties exhibited by different classes of agents approved for the treatment of type 2 diabetes. CVD, cardiovascular disease; TG, triglycerides; CHF, congestive heart failure. A1C reduction depends on starting A1C.*

prevention of incretin degradation, leading to potentiation of GLP-1 and GIP action (6). Sitagliptin is administered as a single 100-mg daily tablet either as monotherapy or in combination therapy with oral antidiabetic agents. Sitagliptin is well tolerated and is not associated with nausea or vomiting as the levels of endogenous intact GLP-1 achieved following DPP-4 inhibition are at the upper limit of the normal physiological range; hence, it is not sufficient to induce an aversive response. Conversely, DPP-4i therapy is not associated with inhibition of gastric emptying or weight loss, and the available data suggest that long-acting GLP-1R agonists achieve more potent control of glycemia, relative to DPP-4i, due to more potent and sustained GLP-1R activation. Vildagliptin, a second DPP-4i, is approved in Europe and other countries, while saxagliptin has recently been approved in the U.S. and several other DPP-4i are under regulatory review.

GLP-1R agonists control blood glucose through regulation of islet function, principally with the stimulation of insulin and inhibition of glucagon secretion (7). Notably, these GLP-1R–dependent actions are glucose dependent, thereby minimizing the risk of hypoglycemia in the absence of concomitant sulfonylurea therapy. GLP-1R activation also inhibits gastric emptying and reduces food intake, leading to weight loss in the majority of treated subjects (8). The GLP-1R is expressed in cardiomyocytes and endothelial cells, and preclinical studies demonstrate that GLP-1R activation is associated with substantial cardioprotection and reduced infarct size in experimental models of coronary artery ischemia (9,10). Limited evidence suggests that GLP-1 may also preserve ventricular function and improve outcomes in human subjects with heart failure or myocardial infarction (11,12). Moreover, both exenatide and liraglutide reduce blood pressure, body weight, and plasma lipid profiles in subjects with type 2 diabetes (13), raising the hope that long-term treatment with these agents may reduce the incidence of cardiovascular events. Intriguingly, the GLP-1 metabolite, GLP-1 (9–36), also exerts cardioprotective actions in preclinical studies through mechanisms independent of the known GLP-1R (14); hence, ongoing research is directed at understanding the complexity of incretin biology in the cardiovascular system and the potential for incretin-based therapies to differentially modulate cardioprotective signals in the diabetic heart and blood vessel in vivo (15). The principal treatment-related adverse events associated with exenatide and liraglutide therapy are nausea and vomiting, which generally diminish over time (13). Analysis of the antidiabetic actions pursuant to GLP-1 administration has demonstrated that activation of the GLP-1R for 24 h provides more sustained and potent control of glycemia relative to shorter periods of GLP-1R agonism (16). In contrast, sustained GLP-1R activation may be associated with a modest reduction in control of postprandial glycemia (5,13), observations of interest to scientists studying the link between postprandial glucose and the development of cardiovascular morbidity and mortality. As exenatide requires twice daily administration and does not provide 24-h GLP-1R activation, there has been considerable interest in development of GLP-1R analogues with more prolonged durations of action (Fig. 2) suitable for once-daily or once-weekly administration (17). Consistent with the notion that continuous GLP-1R activation is required for optimal glucoregulation, liraglutide administered once daily and exenatide administered once weekly appear to be more potent glucose-lowering agents, relative to twice-daily exenatide (5,13). Furthermore, they seem to be associated with better tolerability and patient-reported outcomes as well as trends toward greater benefit on cardiovascular disease risk factors (Fig.

Exenatide and Long-Acting GLP-1 Agonists: *Similarities and Differences*

Properties/Effect	Exenatide[1]	Investigational >24 hr agonists[2,3]
Glucose-dependent insulin secretion and glucagon	Yes	Yes
Slows gastric emptying	Yes	Little or no
Effect on body weight	Weight loss	Weight loss
Effect on A1C	Reduction ~1%	Reduction ~1.5%
Effect on fasting glucose	Modest	Good
Effect on postprandial glucose	Good	Modest
Effect on CVD risk factors	Improve (with weight loss)	Improve
Common side effects	Nausea	Less nausea
Pancreatitis	Rare	Rare
Administration	Twice-daily	Daily or weekly
Rodent medullary thyroid cancer	Little to no signal	Signal

1. Amori RE, et al. *JAMA*. 2007; 298:194-206.
2. Exenatide LAR (once weekly): Drucker DJ, et al. *Lancet*. 2008; 372:1240-1250.
3. Liraglutide: Blonde L, et al. *Can J Diabetes*. 2008;32(suppl): A107.

Figure 2—*Comparison of features associated with exenatide twice daily versus the properties of the emerging class of long-acting GLP-1R agonists that achieve more prolonged and sustained GLP-1R activation. CVD, cardiovascular disease.*

2). There are now over a dozen long-acting investigational GLP-1R agonists being developed for the treatment of type 2 diabetes (8). Several recent reviews have emphasized the mechanisms of action and clinical results obtained in trials examining the efficacy of incretin-based therapies (8,17). Herein we examine adverse events and safety concerns associated with these agents.

Adverse events associated with GLP-1R agonists

Acute pancreatitis. Pancreatitis has been reported as a rare side effect of exenatide therapy principally through postmarketing surveillance. There are many risk factors and predisposing causes for acute pancreatitis, as well as over 200 drugs linked to the development of acute pancreatitis. The incidence of pancreatitis varies considerably among drugs, being relatively common for individuals taking 6-mercaptopurine and azathioprine (2–5%), but very uncommon for steroids and thiazide diuretics. The severity of the disease also varies; pancreatitis induced by 6-mercaptopurine is often quite severe, while that caused by cholinesterase inhibitors is usually mild. There are only two circumstances in which the mechanism of drug-induced disease is understood, drugs that cause hypertriglyceridemia (e.g., some HIV-protease inhibitors, estrogens, isotrentinoin) and drugs that are mitochondrial toxins. Drugs are not thought to cause chronic pancreatitis (with the exception of alcohol and smoking), although they have the theoretical potential to do so. Numerous animal models for pancreatitis have been developed; however, drugs that are associated with pancreatitis in humans rarely cause disease in rodents. Whether these species-specific observations reflect differences in drug metabolism, pancreatitis responses including inflammation, or the fact that some drugs may act as sensitizers and require other factors to cause disease, remains unclear.

Clinical data relating GLP-1R agonists and DPP-4i to pancreatitis come from a limited number of case reports, the U.S. Food and Drug Administration's (FDA) adverse event reporting system, and clinical trial records from pharmaceutical companies. A summary of initial 30 cases of individuals taking exenatide who developed acute pancreatitis was published in 2008 (18). The authors noted that in least 90% of these subjects, there were other factors that could predispose the individuals to pancreatitis. Rechallenge, a standard measure for assigning causality in drug-induced pancreatitis, was performed in only three patients but associated with recurrence of symptoms in each. However, the recurrence of symptoms with rechallenge was reported to occur only after weeks in some patients. In most patients with drug-induced pancreatitis, rechallenge usually causes disease within days. Subsequently, hemorrhagic pancreatitis and several deaths have been reported to the FDA in patients who previously used exenatide and similar cases but no deaths have been reported in patients treated with sitagliptin (19). A recent study used insurance records to determine that the risk of pancreatitis for subjects followed up to a year was 0.12% and 0.13% with sitagliptin and exenatide, respectively (20). These relative risks did not differ from a control cohort treated with metformin or glyburide. Data from the manufacturer of liraglutide reported a low incidence of acute pancreatitis (0.8 cases/1,000 patient-years). Notably, analysis of pancreatitis in subjects with type 2 diabetes suggests that their risk is increased threefold over nondiabetic subjects (21). Since only a fraction of this risk could be attributed to biliary pancreatitis, it seems likely that other factors such as obesity and hypertriglyceridemia might contribute to the increased risk in this population.

Several experimental studies have examined the effects of incretin-based agents on the pancreas in animal models. Koehler et al. (22) found no evidence of pancreatitis in mice treated with the GLP-1R agonist exendin-4 alone and no GLP-1R–dependent enhancement of pancreatitis responses in the caerulein-hyperstimulation model. In contrast, Nachnani et al. (23) detected histological evidence for acinar inflammation, cell drop-out and possible fibrosis and increased levels of serum lipase in Sprague-Dawley rats treated with exendin-4 for 75

days. A study by Matveyenko et al. (24) examined the effects of sitagliptin in human islet amyloid polypeptide (HIP) transgenic diabetic rats. The investigators reported that one of eight HIP rats receiving the drug developed acute pancreatitis and noted extensive pancreatic ductal proliferation and metaplasia and accompanying fibrosis in three HIP rats treated with sitagliptin. Some of the histological findings from the latter two studies were very similar, and reminiscence of changes was seen with chronic pancreatitis. The animal studies raise several confounding issues, namely might there be differences in pancreatitis responses between GLP-1R agonists and DPP-4i in humans versus rodents and in specific diabetic versus nondiabetic preclinical models? Though the relevance of the HIP transgenic rat model to human disease remains unclear, that study does suggest that DPP-4i might induce pancreatic metaplasia under specific experimental conditions. In summary, the clinical and experimental data linking GLP-1R agonists and DPP-4i to pancreatitis are still incomplete. More information is required to allow one to determine whether these agents substantially increase the risk of acute pancreatitis and whether such disease tends to be severe. However, patients receiving these medications will need to undergo continued surveillance for pancreatitis and clinicians should carefully exclude other causes of acute pancreatitis when it occurs in subjects receiving these drugs. Although the diagnosis of drug-induced pancreatitis would ideally be associated with confirmatory clinical data following drug rechallenge, physicians should exercise caution before considering a trial of drug rechallenge. As GLP-1R agonists may also affect smooth muscle responses and may regulate cholangiocyte function (25), their effects on the biliary tract and gallstone formation should also be examined.

Issues linking these agents with pancreatic metaplasia and chronic pancreatitis, as now suggested by two experimental studies, present a different challenge. Longer-term experimental studies using different GLP-1R agonists and DPP-4i in several species and experimental models of diabetes need to be undertaken to help clarify the importance of these findings. Hence, monitoring of pancreatic function and pancreatic disease in humans treated with GLP-1R agonists and DPP-4i in ongoing long-term prospective controlled clinical trials seems prudent.

Medullary thyroid cancer. Medullary thyroid carcinoma (MTC) is an uncommon neuroendocrine malignancy with an estimated U.S. annual incidence of fewer than 1,000 persons and a lifetime risk of development of 0.013% (26). When diagnosed early and still confined to the thyroid gland, the long-term survival of MTC is nearly 100% (27). About 25% of MTCs occur as part of an inherited autosomal dominant syndrome, either multiple endocrine neoplasia type II or familial MTC, and virtually all familial tumors are caused by inherited mutations in the *RET* proto-oncogene. Of sporadic MTCs, at least 40% are associated with somatic mutations and *RET*, and prognosis is worse in those mutated tumors.

The histological precursors to MTC in the inherited syndromes are well described, beginning with C-cell hyperplasia, leading to nodular C-cell hyperplasia, and then eventually to MTC. However, among the sporadically occurring MTCs, the role of this histological sequence is not defined, and the exact distinction between neoplastic and non-neoplastic C-cell hyperplasia is controversial (28,29). As a tumor derived from C-cells, MTCs generally secrete calcitonin, and high serum levels of calcitonin (>100 pg/ml) are nearly 100% specific for the presence of MTC (30,31). Nonetheless, the specificity of serum calcitonin concentrations between the upper end of the reference range and 100 pg/ml is considerably more limited. Other etiologies of mild degrees of hypercalcitoninemia include lymphocytic thyroiditis, chronic renal insufficiency, pancreatitis, hypercalcemia, hypergastrinemia (of any etiology), and even the postprandial state (31,32). Stimulation of calcitonin release with pentagastrin infusion has long been used to distinguish neoplastic from non-neoplastic causes of mild hypercalcitoninemia; however, pentagastrin is no longer available for human use in the U.S., and the diagnostic accuracy of testing with alternative stimulants such as calcium infusion remains to be established (31).

Animal models of MTC have limitations in regard to the biology and epidemiology of human MTC. Rats develop spontaneous age-related C-cell lesions at remarkably high frequency, especially nodular C-cell hyperplasia. Sporadic MTC occurs in 0.5–1% of most rat species evaluated, with increased frequency in males and with advancing age; spontaneous *RET* mutations have not been reported, and some typical histological features of human MTC are generally lacking. Mice develop spontaneous MTC less frequently, and most animal models in use are either transgenic or xenografts of the well-characterized TT cell line.

Food intake links incretin secretion with stimulation of calcitonin secretion in rodents, potentially via GLP-1 receptors expressed on rodent MTC cell lines, and GLP-1 stimulates calcitonin release in rodents in vivo (33–35). Analysis of data reported at the 2 April 2009 FDA Advisory Committee review of liraglutide revealed that preclinical toxicology studies with liraglutide reported C-cell hyperplasia and MTC with increasing exposure to liraglutide. At the highest drug exposures, MTC was reported in 14% of male and 6% of female Sprague-Dawley rats, which was above the rates observed in untreated rat controls. C-cell lesions were also reported to be more common with liraglutide in CD-1 mice, albeit at much lower frequencies; no C-cell lesions were described in the cynomologous monkey. In contrast, once-daily administration of exenatide in rodents is associated with a high frequency of nodular C-cell lesions but no carcinomas were reported (36). In safety monitoring of multiple liraglutide clinical trials, many patients with undetectable calcitonin levels before initiation of investigational (liraglutide, placebo, or active comparator) therapy were found to have levels that rose into the mid-reference normal range; rare patients developed mild hypercalcitoninemia during therapy. Across the trials, six patients were found to have C-cell findings at thyroidectomy following therapy (36). Of these patients, four were in liraglutide treatment arms, but three of these had elevated calcitonin levels before initiation of treatment. The remaining two patients were in the active comparator arms of trials, and one had an elevated calcitonin level before treatment. This single patient had MTC and was treated with an active non-GLP-1–based comparator; the patient had a markedly elevated calcitonin level before initiating non-GLP-1–based comparator therapy. All of the remaining patients who underwent thyroidectomy for hypercalcitoninemia were reported to have C-cell hyperplasia. According to the FDA briefing documents, no cases of C-cell lesions have been documented by histology in patients treated with exenatide. Several cases of papillary thyroid cancer have also been reported in the liraglutide clinical development program; however,

the small number of cases, the incidental histopathologic identification of the lesions, together with the lack of biological plausibility, suggest that this is an incidental finding not directly related to therapy with GLP-1R agonists.

In summary, rodents exposed to liraglutide and exenatide develop C-cell lesions at relatively high frequency, although the currently available data suggest that rodent MTC may be specific to long-acting GLP-1R agonists, likely due to sustained GLP-1R activation. Because of the historic difficulty of distinguishing neoplastic and non-neoplastic forms of C-cell hyperplasia in both rodents and humans, the diagnostic significance of C-cell hyperplasia is unclear. Minimal elevations of calcitonin levels are very nonspecific, and available methods of dynamic testing add little to clarify the etiologies. Given the extreme rarity of MTC in humans, the numbers of patients who would need to be treated for 10 years to yield one additional case of MTC may be extremely high (35–55,000 if risk is doubled; 10–15,000 if risk is quintupled). Moreover, the differences in rodent versus human C-cell biology with regard to responsivity to GLP-1R activation raise important questions about the suitability of mice and rats as models for understanding the effects of GLP-1R agonists on human C-cells.

Summary and conclusions

Incretin-based therapies provide new options for the treatment of type 2 diabetes and enable intensification of therapy while controlling body weight through mechanisms associated with a low rate of hypoglycemia. Investigational long-acting GLP-1R agonists require less frequent administration and appear to be more potent with respect to A1C reduction than twice-daily exenatide or once-daily sitagliptin with respect to A1C reduction. These long-acting GLP-1R agonists have considerable potential as antidiabetic therapies as they not only lower glucose as or more effectively than other noninsulin antihyperglycemic therapies, they do so in concert with weight loss, improvement in cardiovascular disease risk factors, and with very low risk of hypoglycemia. However, two safety issues have been raised—pancreatitis and medullary carcinoma of the thyroid.

The relationship between the use of incretin therapy and the development of pancreatitis remains unclear. These agents may not substantially increase the risk of acute pancreatitis in humans and might not affect the risk at all. The relevance to humans of the pancreatic metaplasia observed with these agents in two of the rodent studies is unknown. Continued clinical monitoring and more research are required to clarify the actions of GLP-1R agonists and DPP-4i on the normal and diabetic exocrine pancreas.

GLP-1R activation stimulates calcitonin secretion and promotes the development of C-cell hyperplasia and medullary thyroid cancer in rodents but not in monkeys, and the actions of GLP-1R agonists on human C-cells remain uncertain. Because of the rarity of medullary carcinoma of the thyroid and the lack of specificity of clinical markers, screening strategies, except in the setting of familial syndromes, almost certainly would be associated with an increase in morbidity and perhaps mortality as a result of false positives.

Taken together, the available evidence supports the use of incretin-based therapies for patients requiring effective control of glycemia and body weight while minimizing the risk of hypoglycemia. Ongoing scrutiny and further studies are required to clarify the potential significance of reports of pancreatic injury, including pancreatitis and metaplasia, and rodent medullary thyroid cancer for human subjects treated with GLP-1R agonists and DPP-4i.

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Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

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The consensus algorithm for the medical management of type 2 diabetes was published in August 2006 with the expectation that it would be updated, based on the availability of new interventions and new evidence to establish their clinical role. The authors continue to endorse the principles used to develop the algorithm and its major features. We are sensitive to the risks of changing the algorithm cavalierly or too frequently, without compelling new information. An update to the consensus algorithm published in January 2008 specifically addressed safety issues surrounding the thiazolidinediones. In this revision, we focus on the new classes of medications that now have more clinical data and experience.

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The epidemic of type 2 diabetes and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority (1–3). While the management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 diabetes, has historically taken center stage in the treatment of diabetes, therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, nephropathy, and neuropathy, in the setting of type 1 diabetes (4,5); in type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce microvascular complications (6–8). Intensive glycemic management resulting in lower A1C levels has also been shown to have a beneficial effect on cardiovascular disease (CVD) complications in type 1 diabetes (9,10); however, current studies have failed to demonstrate a beneficial effect of intensive diabetes therapy on CVD in type 2 diabetes (11–13).

The development of new classes of blood glucose–lowering medications to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the number of treatment options available for type 2 diabetes. Whether used alone or in combination with other blood glucose–lowering interventions, the increased number of choices available to practitioners and patients has heightened uncertainty regarding the most appropriate means of treating this widespread disease (14). Although numerous reviews on the management of type 2 diabetes have been published in recent years (15–17), practitioners are often left without a clear pathway of therapy to follow. We developed the following consensus approach to the management of hyperglycemia in the nonpregnant adult to help guide health care providers in choosing the most appropriate interventions for their patients with type 2 diabetes.

Process

The guidelines and algorithm that follow are derived from two sources. One source is the clinical trials that address the effectiveness and safety of the different modalities of therapy. Here, the writing group reviewed a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia. Unfortunately, the paucity of high-quality evidence in the form of well-controlled clinical trials that directly compare different diabetes treatment regimens remains a major impediment to recommending one class of drugs, or a particular combination of therapies, over another.

The second source of material that informed our recommendations was clinical judgement, that is, our collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes. As in all clinical decision making, an evidence-based review of

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the literature must also be supplemented by value judgements, where the benefits of treatment are weighed against risks and costs in a subjective fashion. While we realize that others may have different judgements, we believe that the recommendations made in this new iteration of our treatment algorithm will guide therapy and result in improved glycemic control and health status over time.

Glycemic goals of therapy

Controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT) (4) and the Stockholm Diabetes Study in type 1 diabetes (5) and the UK Prospective Diabetes Study (UKPDS) (6,7) and Kumamoto study (8) in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. The clinical trials, in concert with epidemiological data (18,19), support decreasing glycemia as an effective means of reducing long-term microvascular and neuropathic complications. The most appropriate target levels for blood glucose, on a day-to-day basis, and A1C, as an index of chronic glycemia, have not been systematically studied. However, both the DCCT (4) and the UKPDS (6,7) had as their goals the achievement of glycemic levels in the nondiabetic range. Neither study was able to maintain A1C levels in the nondiabetic range in their intensive treatment groups, achieving mean levels over time of ~7%, which is 4 SDs above the nondiabetic mean.

The most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is, in general, an A1C level of <7% (1). The most recent glycemic goal set by the International Diabetes Federation is an A1C level of <6.5%. The upper limit of the nondiabetic range is 6.1% (mean ± SD. A1C level of 5 ± 2%) with the DCCT/UKPDS-standardized assay, which has been promulgated through the National Glycohemoglobin Standardization Program (NGSP) and adopted by the vast majority of commercially available assays (20). Several recent clinical trials have aimed for A1C levels ≤6.5% with a variety of interventions (11,12). The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which had the primary objective of decreasing CVD with interventions aimed at achieving an A1C level of <6.0% vs. interventions aimed at achieving an A1C level of <7.9%, showed excess CVD mortality in the intensive treatment group (11). Results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial, both of which had different interventions and study populations than ACCORD, did not demonstrate any excess total or CVD mortality with intensive regimens that achieved A1C levels comparable with the 6.5% in ACCORD (12,13). However, none of the studies has demonstrated a benefit of intensive glycemic control on their primary CVD outcomes. Our consensus is that an A1C level of ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level of <7%. We are mindful that this goal is not appropriate or practical for some patients, and clinical judgement based on the potential benefits and risks of a more intensified regimen needs to be applied for every patient. Factors such as life expectancy, risk of hypoglycemia, and the presence of CVD need to be considered for every patient before intensifying the therapeutic regimen.

Assiduous attention to abnormalities other than hyperglycemia that accompany type 2 diabetes, such as hypertension and dyslipidaemia, has been shown to improve microvascular and cardiovascular complications. Readers are referred to published guidelines for a discussion of the rationale and goals of therapy for the nonglycemic risk factors, as well as recommendations on how to achieve them (1,21,22).

Principles in selecting antihyperglycemic interventions

Our choice of specific antihyperglycemic agents is predicated on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense.

Effectiveness in lowering glycaemia

Except for their differential effects on glycemia, there are insufficient data at this time to support a recommendation of one class of glucose-lowering agents, or one combination of medications, over others with regard to effects on complications. In other words, the salutary effects of therapy on long-term complications appear to be predicated predominantly on the level of glycemic control achieved rather than on any other specific attributes of the intervention(s) used to achieve glycemic goals. The UKPDS compared three classes of glucose-lowering medications (sulfonylurea, metformin, or insulin) but was unable to demonstrate clear superiority of any one drug over the others with regard to diabetes complications (6,7). However, the different classes do have variable effectiveness in decreasing glycemic levels (Table 1), and the overarching principle in selecting a particular intervention will be its ability to achieve and maintain glycemic goals. In addition to their intention-to-treat analyses demonstrating the superiority of intensive versus conventional interventions, the DCCT and UKPDS demonstrated a strong correlation between mean A1C levels over time and the development and progression of retinopathy and nephropathy (23,24). Therefore, we think it is reasonable to judge and compare blood glucose–lowering medications, as well as combinations of such agents, primarily on the basis of their capacity to decrease and maintain A1C levels and according to their safety, specific side effects, tolerability, ease of use, and expense.

Nonglycemic effects of medications

In addition to variable effects on glycemia, specific effects of individual therapies on CVD risk factors, such as hypertension or dyslipidemia, were also considered important. We also included the effects of interventions that may benefit or worsen the prospects for long-term glycemic control in our recommendations. Examples of these would be changes in body mass, insulin resistance, or insulin secretory capacity in type 2 diabetic patients.

Choosing specific diabetes interventions and their roles in treating type 2 diabetes

Numerous reviews have focused on the characteristics of the specific diabetes interventions listed below (25–34). In addition, meta-analyses and reviews have summarized and compared the glucose-lowering effectiveness and other characteristics of the medications (35–37). The aim here is to provide enough information to justify the choices of medications, the order in which they are recommended, and the use of combinations of therapies. Unfortunately, there is a dearth of high-quality studies that provide head-to-head comparisons of the ability of the medications to achieve the currently recommended glycemic levels. The authors

Table 1—*Summary of glucose-lowering interventions*

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive

[a]Repaglinide more effective in lowering A1C than nateglinide. CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction.

highly recommend that such studies be conducted. However, even in the absence of rigorous, comprehensive studies that directly compare the efficacy of all available glucose-lowering treatments and their combinations, we feel that there are enough data regarding the characteristics of the individual interventions to provide the guidelines below.

An important intervention that is likely to improve the probability that a patient will have better long-term control of diabetes is to make the diagnosis early, when the metabolic abnormalities of diabetes are usually less severe. Lower levels of glycemia at the time of initial therapy are associated with lower A1C levels over time and decreased long-term complications (38).

Lifestyle interventions

The major environmental factors that increase the risk of type 2 diabetes are overnutrition and a sedentary lifestyle, with consequent overweight and obesity (39,40). Not surprisingly, interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycemia in established type 2 diabetes (41). Unfortunately, the high rate of weight regain has limited the role of lifestyle interventions as an effective means of controlling glycemia in the long term. The most convincing long-term data indicating that weight loss effectively lowers glycemia have been generated in the follow-up of type 2 diabetic patients who have had bariatric surgery. In this setting, with a mean sustained weight loss of >20 kg, diabetes is virtually eliminated (42–45). In addition to the beneficial effects of weight loss on glycemia, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity (41,46,47). There are few adverse consequences of such life-

style interventions other than difficulty in incorporating them into usual lifestyle and sustaining them and the usually minor musculoskeletal injuries and potential problems associated with neuropathy, such as foot trauma and ulcers, that may occur as a result of increased activity. Theoretically, effective weight loss, with its pleiotropic benefits, safety profile, and low cost, should be the most cost-effective means of controlling diabetes—if it could be achieved and maintained over the long term.

Given these beneficial effects, which are usually seen rapidly—within weeks to months—and often before there has been substantial weight loss (47), a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management. Weight loss of as little as 4 kg will often ameliorate hyperglycemia. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that the large majority of patients will require the addition of medications over the course of their diabetes.

Medications

The characteristics of currently available glucose-lowering interventions, when used as monotherapy, are summarized in Table 1. The glucose-lowering effectiveness of individual therapies and combinations demonstrated in clinical trials is predicated not only on the intrinsic characteristics of the intervention but also on the duration of diabetes, baseline glycemia, previous therapy, and other factors. A major factor in selecting a class of drugs, or a specific medication within a class, to initiate therapy or when changing therapy, is the ambient level of glycemic control. When levels of glycemia are high (e.g., A1C >8.5%), classes with greater and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, are recommended; however, patients with recent-onset diabetes often respond adequately to less intensive interventions than those with longer-term disease (48). When glycemic levels are closer to the target levels (e.g., A1C <7.5%), medications with lesser potential to lower glycemia and/or a slower onset of action may be considered.

Obviously, the choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering A1C and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including side effects, tolerability, ease of use, long-term adherence, expense, and the nonglycemic effects of the medications. Type 2 diabetes is a progressive disease characterized by worsening glycemia; higher doses and additional medications are required over time if treatment goals are to be met.

Metformin. In most of the world, metformin is the only biguanide available. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower A1C levels by ~1.5 percentage points (27,49). It is generally well tolerated, with the most common adverse effects being gastrointestinal. Metformin monotherapy is not usually accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with prediabetic hyperglycemia (50). Metformin interferes with vitamin B_{12} absorption but is very rarely associated with anemia (27). The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast with many of the other blood glucose–lowering medications. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes (7), which needs to be confirmed. Renal dysfunction is considered a contraindication to metformin use because it may increase the risk of lactic acidosis, an extremely rare (less than 1 case per 100,000 treated patients) but potentially fatal complication (51). However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate falls to <30 ml/min (52).

Sulfonylureas. Sulfonylureas lower glycemia by enhancing insulin secretion. In terms of efficacy, they appear to be similar to metformin, lowering A1C levels by ~1.5 percentage points (26,49). The major adverse side effect is hypoglycemia, which can be prolonged and life threatening, but such episodes, characterized by a need for assistance, coma, or seizure, are infrequent. However, severe episodes are relatively more frequent in the elderly. Chlorpropamide and glibenclamide (known as glyburide in the U.S. and Canada), are associated with a substantially greater risk of hypoglycemia than other second-generation sulfonylureas (gliclazide, glimepiride, glipizide, and their extended formulations), which are preferable (Table 1) (53,54). In addition, weight gain of ~2 kg is common following the initiation of sulfonylurea therapy. Although the onset of the glucose-lowering effect of sulfonylurea monotherapy is relatively rapid compared with, for example, the thiazolidinediones (TZDs), maintenance of glycemic targets over time is not as good as monotherapy with a TZD or metformin (55). Sulfonylurea therapy was implicated as a potential cause of increased CVD mortality in the University Group Diabetes Program (UGDP) study (56). Concerns raised by the UGDP that sulfonylureas, as a drug class, may increase CVD mortality in type 2 diabetes were not substantiated by the UKPDS or ADVANCE study (6,12). The glycemic benefits of sulfonylureas are nearly fully realized at half-maximal doses, and higher doses should generally be avoided.

Glinides. Like the sulfonylureas, the glinides stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor (28). They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. Of the two glinides currently available in the U.S., repaglinide is almost as effective as metformin or the sulfonylureas, decreasing A1C levels by ~1.5 percentage points. Nateglinide is somewhat less effective in lowering A1C than repaglinide when used as monotherapy or in combination therapy (57,58). The risk of weight gain is similar to that for the sulfonylureas, but hypoglycemia may be less frequent, at least with nateglinide, than with some sulfonylureas (58,59).

α-Glucosidase inhibitors. α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A1C levels by 0.5–0.8 percentage points (29). Since carbohydrate is absorbed more distally, malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. In clinical trials, 25–45% of participants have discontinued α-glucosidase inhibitor use as a result of this side effect (29,60).

One clinical trial examining acarbose as a means of preventing the development of diabetes in high-risk individuals with impaired glucose tolerance showed an unexpected reduction in severe CVD outcomes

(60). This potential benefit of α-glucosidase inhibitors needs to be confirmed.

Thiazolidinediones. Thiazolidinediones (TZDs or glitazones) are peroxisome proliferator–activated receptor γ modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers") (31). The data regarding the blood glucose–lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5–1.4 percentage point decrease in A1C. The TZDs appear to have a more durable effect on glycemic control, particularly compared with sulfonylureas (55). The most common adverse effects with TZDs are weight gain and fluid retention, with peripheral edema and a twofold increased risk for congestive heart failure (61,62). There is an increase in adiposity, largely subcutaneous, with some reduction in visceral fat shown in some studies. The TZDs either have a beneficial (pioglitazone) or neutral (rosiglitazone) effect on atherogenic lipid profiles (63,64). Several meta-analyses have suggested a 30–40% relative increase in risk for myocardial infarction (65,66) with rosiglitazone. On the other hand, the Prospective Pioglitazone Clinical Trial in macrovascular events (PROactive) demonstrated no significant effects of pioglitazone compared with placebo on the primary CVD outcome (a composite of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention, and leg revascularization) after 3 years of follow-up (67). Pioglitazone was associated with a 16% reduction in death, myocardial infarction, and stroke—a controversial secondary end point reported to have marginal statistical significance (67). Meta-analyses have supported a possible beneficial effect of pioglitazone on CVD risk (68). Although the data are less than conclusive for a CVD risk with rosiglitazone or a CVD benefit with pioglitazone, we have previously advised (69) caution in using either TZD on the basis that they are both associated with increased risks of fluid retention and congestive heart failure and an increased incidence of fractures in women and perhaps in men (55,61,62,70). Although the meta-analyses discussed above are not conclusive regarding the potential cardiovascular risk associated with rosiglitazone, given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone. Currently, in the U.S., the TZDs are approved for use in combination with metformin, sulfonylureas, glinides, and insulin.

Insulin. Insulin is the oldest of the currently available medications and, therefore, the treatment with which we have the most clinical experience. It is also the most effective at lowering glycemia. Insulin can, when used in adequate doses, decrease any level of elevated A1C to, or close to, the therapeutic goal. Unlike the other blood glucose–lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Relatively large doses of insulin (≥1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower A1C to the target level. Although initial therapy is aimed at increasing basal insulin supply, usually with intermediate- or long-acting-insulins, patients may also require prandial therapy with short- or rapid-acting insulins (Fig. 1). The very rapid-acting and long-acting insulin analogues have not been shown to lower A1C levels more effectively than the older, rapid-acting or intermediate-acting formulations (71–73). Insulin therapy has beneficial effects on triacylglycerol and HDL cholesterol levels, especially in patients with poor glycemic control (74), but is associated with weight gain of ~2–4 kg, which is probably proportional to the correction of glycemia and predominantly the result of the reduction of glycosuria. Insulin therapy is also associated with hypoglycemia, albeit much less frequently than in type 1 diabetes. In clinical trials aimed at normoglycemia and achieving a mean A1C of ~7%, severe hypoglycemic episodes (defined as requiring help from another person to treat) occurred at a rate of between one and three per 100 patient-years (8,75–77), compared with 61 per 100 patient-years in the DCCT intensive therapy group (4). Insulin analogues with longer, nonpeaking profiles decrease the risk of hypoglycemia modestly compared with NPH, and analogues with very short durations of action reduce the risk of hypoglycemia compared with regular insulin (76,77).

Glucagon-like peptide-1 agonists (exenatide). Glucagon-like peptide-1 (GLP-1) 7–37, a naturally occurring peptide produced by the L-cells of the small intestine, potentiates glucose-stimulated insulin secretion. Exendin-4 has homology with the human GLP-1 sequence but has a longer circulating half-life. It binds avidly to the GLP-1 receptor on the pancreatic β-cell and augments glucose-mediated insulin secretion (32). Synthetic exendin-4 (exenatide) was approved for use in the U.S. in 2005 and is administered twice per day by subcutaneous injection. Although there are less published data on this new compound than the other blood glucose–lowering medications, exendin-4 appears to lower A1C levels by 0.5–1 percentage points, mainly by lowering postprandial blood glucose levels (78–81). Exenatide also suppresses glucagon secretion and slows gastric motility. It is not associated with hypoglycemia but causes a relatively high frequency of gastrointestinal disturbances, with 30–45% of treated patients experiencing one or more episodes of nausea, vomiting, or diarrhea (78–81). These side effects tend to abate over time. In published trials, exenatide is associated with weight loss of ~2–3 kg over 6 months, some of which may be a result of its gastrointestinal side effects. Recent reports have suggested a risk for pancreatitis associated with use of GLP agonists; however, the number of cases is very small and whether the relationship is causal or coincidental is not clear at this time. Currently, exenatide is approved for use in the U.S. with sulfonylurea, metformin, and/or a TZD. Several other GLP-1 agonists and formulations are under development.

Amylin agonists (pramlintide). Pramlintide is a synthetic analogue of the β-cell hormone amylin. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions (33). In clinical studies, A1C has been decreased by 0.5–0.7 percentage points (82). The major clinical side effects of this drug are gastrointestinal in nature. ~30% of treated participants in the clinical trials have developed nausea, but this side effect tends to abate with time on therapy. Weight loss associated with this medication is ~1–1.5 kg over 6 months; as with exenatide, some of the weight loss may be the result of gastrointestinal side effects. Currently, pramlintide is approved for use in the U.S. only as adjunctive therapy with regular insulin or rapid-acting insulin analogues.

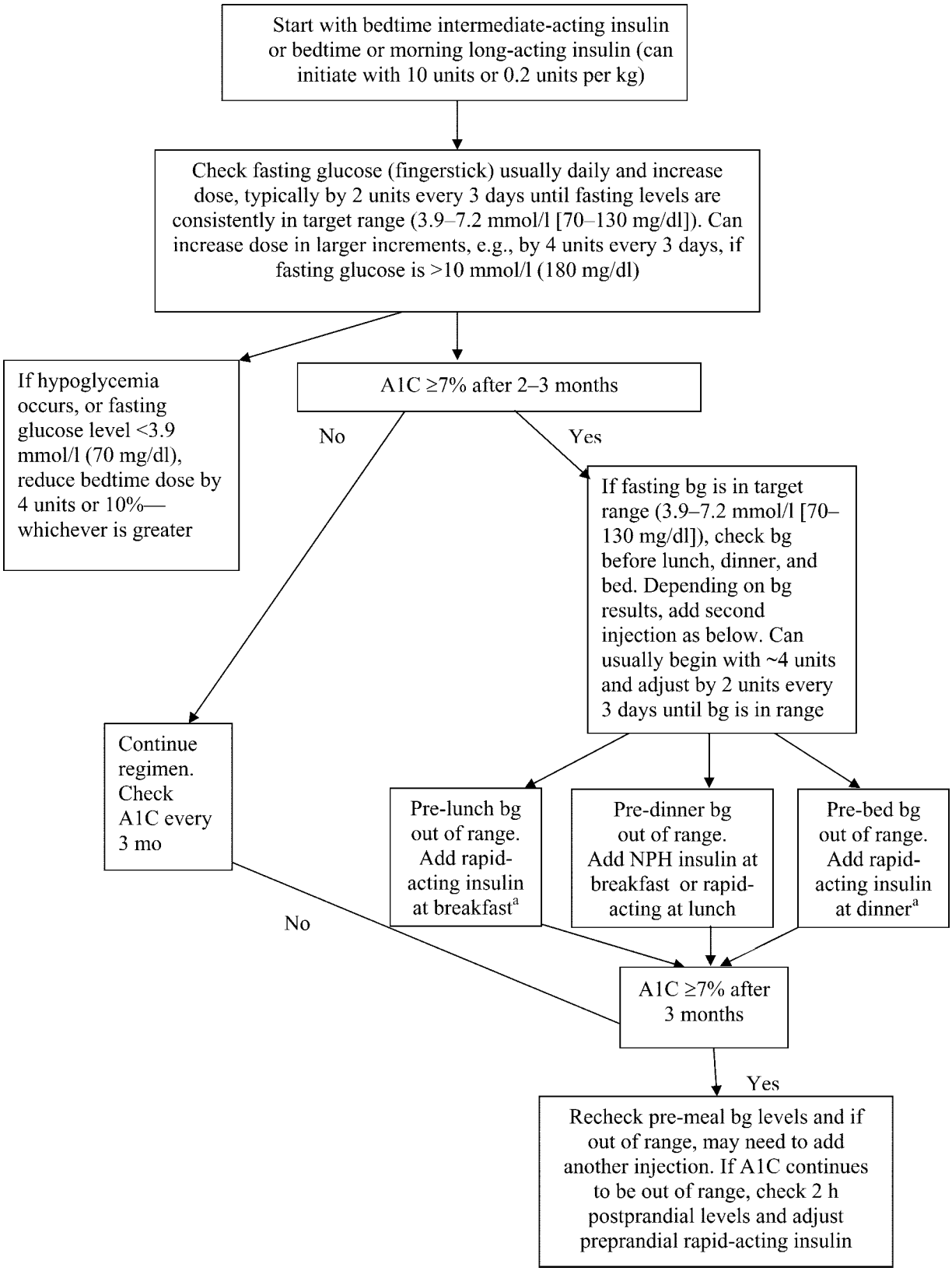

Figure 1—*Initiation and adjustment of insulin regimens. Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin. See reference 90 for more detailed instructions. [a]Premixed insulins not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner, if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available. bg, blood glucose.*

TITRATION OF METFORMIN

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5–7 days, if gastrointestinal side effects have not occurred, advance dose to 850, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.
5. Based on cost considerations, generic metformin is the first choice of therapy. A longer-acting formulation is available in some countries and can be given once per day.

Dipeptidyl peptidase four inhibitors. GLP-1 and glucose-dependent insulinotropic peptide (GIP), the main insulinotropic peptides of intestinal origin (incretins), are rapidly degraded by dipeptidyl peptidase four (DPP-4). DPP-4 is a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells (34). DPP-4 inhibitors are small molecules that enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion (83,84). The first oral DPP-4 inhibitor, sitagliptin, was approved by the Food and Drug Administration in October 2006 for use as monotherapy or in combination with metformin or TZDs. Another DPP-4 inhibitor, vildagliptin, was approved in Europe in February 2008, and several other compounds are under development. In clinical trials performed to date, DPP-4 inhibitors lower A1Clevels by 0.6–0.9 percentage points and are weight neutral and relatively well tolerated (83,84). They do not cause hypoglycemia when used as monotherapy. A fixed-dose combination pill with metformin is available. The potential for this class of compounds to interfere with immune function is of concern; an increase in upper respiratory infections has been reported (34).

How to initiate diabetes therapy and advance interventions

Except in rare circumstances, such as diabetic ketoacidosis or patients who are extremely catabolic or hyperosmolar or who are unable to hydrate themselves adequately (see SPECIAL CONSIDERATIONS/PATIENTS below), hospitalization is not required for initiation or adjustment of therapy. The patient is the key player in the diabetes care team and should be trained and empowered to adjust medications with the guidance of health care professionals to achieve glycemic goals and to prevent and treat hypoglycemia. Many patients may be managed effectively with monotherapy; however, the progressive nature of the disease will require the use of combination therapy in many, if not most, patients over time, to achieve and maintain glycemia in the target range.

The measures of glycemia that are initially targeted on a day-to-day basis are fasting and preprandial glucose levels. Self-monitoring of blood glucose (SMBG) is an important element in adjusting or adding new interventions and, in particular, in titrating insulin doses. The need for and number of required SMBG measurements are not clear (85) and are dependent on the medications used. Oral glucose-lowering regimens that do not include sulfonylureas or glinides, and are therefore not likely to cause hypoglycemia, usually do not require SMBG (86). However, SMBG may be used to determine whether therapeutic blood glucose targets are being achieved and for adjustment of treatment regimens without requiring the patient to have laboratory-based blood glucose testing. Insulin therapy requires more frequent monitoring.

The levels of plasma or capillary glucose (most meters that measure fingerstick capillary samples are adjusted to provide values equivalent to plasma glucose) that should result in long-term glycemia in the nondiabetic target range, as measured by A1C, are fasting and preprandial levels between 3.9 and 7.2 mmol/l (70 and 130 mg/dl). If A1C levels remain above the desired target despite preprandial levels that are in range, postprandial levels, usually measured 90–120 min after a meal, may be checked. They should be <10 mmol/l (180 mg/dl) to achieve A1C levels in the target range.

Attempts to achieve target glycemic levels with regimens including sulfonylureas or insulin may be associated with modest hypoglycemia, with glucose levels in the 3.1–3.9 mmol/l (55–70 mg/dl) range. These episodes are generally well tolerated, easily treated with oral carbohydrate such as glucose tablets or 120–180 ml (4–6 oz) of juice or nondiet soda, and rarely progress to more severe hypoglycemia, including loss of consciousness or seizures.

Algorithm

The algorithm (Fig. 2) takes into account the characteristics of the individual interventions, their synergies, and expense. The goal is to achieve and maintain A1C levels of <7% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. Mounting evidence suggests that aggressive lowering of glycemia, especially with insulin therapy, in newly diagnosed diabetes can result in sustained remissions, i.e., normoglycemia without need for glucose-lowering medications (87,88). Type 2 diabetes is a progressive disease (89), and patients should be informed that they are likely to require the addition of glucose-lowering medications over time.

The amylin agonists, α-glucosidase inhibitors, glinides, and DPP-4 inhibitors are not included in the two tiers of preferred agents in this algorithm, owing to their lower or equivalent overall glucose-lowering effectiveness compared with the first- and second-tier agents and/or to their limited clinical data or relative expense (Table 1). However, they may be appropriate choices in selected patients.

Tier 1: well-validated core therapies

These interventions represent the best established and most effective and cost-effective therapeutic strategy for achieving the target glycemic goals. The tier one algorithm is the preferred route of therapy for most patients with type 2 diabetes.

Step 1: lifestyle intervention and metformin. Based on the numerous demonstrated short- and long-term benefits that accrue when weight loss and increased levels of activity are achieved and maintained, as well as the cost-effectiveness of lifestyle interventions when they succeed,

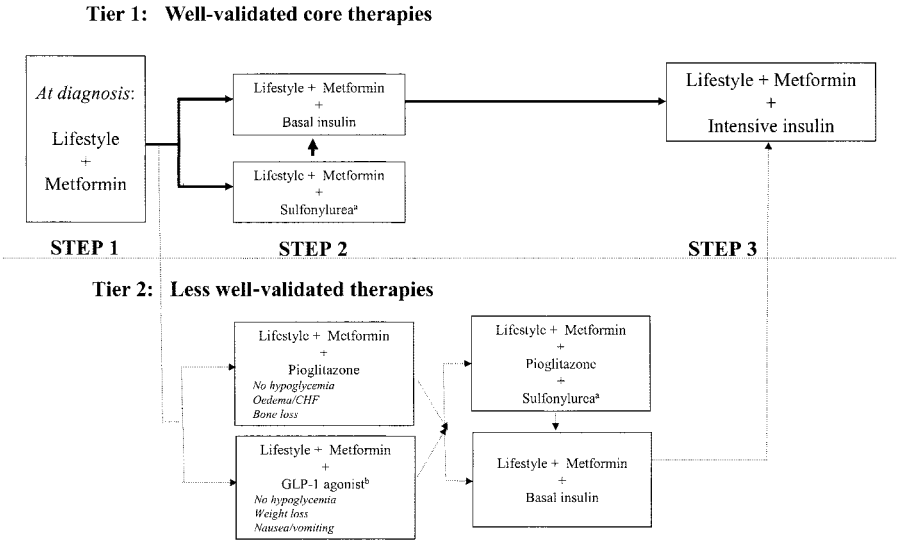

Figure 2—*Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7% and then at least every 6 months. The interventions should be changed if A1C is ≥7%. [a]Sulfonylureas other than glyburide (glyburide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. See text box, entitled* TITRATION OF METFORMIN. *See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure.*

the consensus is that lifestyle interventions should be initiated as the first step in treating new-onset type 2 diabetes (Fig. 2). These interventions should be implemented by health care professionals with appropriate training—usually registered dietitians experienced in behavioral modification—and be sensitive to ethnic and cultural differences among populations. Moreover, lifestyle interventions to improve glucose, blood pressure, and lipid levels, and to promote weight loss or at least avoid weight gain, should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used. For the 10–20% of patients with type 2 diabetes who are not obese or overweight, modification of dietary composition and activity levels may play a supporting role, but medications are still generally required early in the course of diabetes (see SPECIAL CONSIDERATIONS/PATIENTS below).

The authors recognize that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain the metabolic goals either because of failure to lose weight, weight regain, progressive disease, or a combination of factors. Therefore, our consensus is that metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis. Metformin is recommended as the initial pharmacological therapy, in the absence of specific contraindications, for its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost. Metformin treatment should be titrated to its maximally effective dose over 1–2 months, as tolerated (see text box, entitled Titration of Metformin). Rapid addition of other glucose-lowering medications should be considered in the setting of persistent symptomatic hyperglycemia.

Step 2: addition of a second medication. If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve or sustain the glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when the target A1C level is not achieved. Another medication may also be necessary if metformin is contraindicated or not tolerated. The consensus regarding the second medication added to metformin was to choose either insulin or a sulfonylurea (Fig. 2). As discussed above, the A1C level will determine in part which agent is selected next, with consideration given to the more effective glycemia-lowering agent, insulin, for patients with an A1C level of >8.5% or with symptoms secondary to ehyperglycemia. Insulin can be initiated with a basal (intermediate- or long-acting) insulin (see Fig. 1 for suggested initial insulin regimens) (90). However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications, even if symptoms of ehyperglycemia are present (48).

Step 3: further adjustments. If lifestyle, metformin, and sulfonylurea or basal insulin do not result in achievement of target glycemia, the next step should be to start, or intensify, insulin therapy (Fig. 1). Intensification of insulin therapy usually consists of additional injections that might include a short- or rapid-acting insulin given before selected meals to reduce postprandial glucose excursions (Fig. 1). When insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be discontinued, or tapered and then discontinued, since they are not considered to be synergistic. Although addition of a third oral agent can be considered, especially if the A1C level is close to target (A1C <8.0%), this approach is usually not preferred, as it is no more effective in lowering glycemia, and is more costly, than initiating or intensifying insulin (91).

Tier 2: less well-validated therapies

In selected clinical settings, this second-tier algorithm may be considered. Specifically, when hypoglycemia is particularly undesirable (e.g., in patients who have hazardous jobs), the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. If promotion of weight loss is a major consideration and the A1C level is close to target (<8.0%), exenatide is an option. If these interventions are not effective in achieving target A1C, or are not tolerated, addition of a sulfonylurea could be considered. Alternatively, the tier two interventions should be stopped and basal insulin started.

Rationale for selecting specific combinations

More than one medication will be necessary for the majority of patients over time. Selection of the individual agents should be made on the basis of their glucose-lowering effectiveness and other characteristics listed in Table 1. However, when adding second antihyperglycemic medications, the synergy of particular combinations and other interactions should be considered. In general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. Insulin plus metformin (92) is a particularly effective means of lowering glycemia while limiting weight gain.

Special considerations/patients

In the setting of severely uncontrolled diabetes with catabolism, defined as fasting plasma glucose levels >13.9 mmol/l (250 mg/dl), random glucose levels consistently above 16.7 mmol/l (300 mg/dl), A1C above 10%, or the presence of ketonuria, or as symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy in combination with lifestyle intervention is the treatment of choice. Some patients with these characteristics will have unrecognized type 1 diabetes; others will have type 2 diabetes with severe insulin deficiency. Insulin can be titrated rapidly and is associated with the greatest likelihood of returning glucose levels rapidly to target levels. After symptoms are relieved and glucose levels decreased, oral agents can often be added and it may be possible to withdraw insulin, if preferred.

Conclusions

Type 2 diabetes is epidemic. Its long-term consequences translate into enormous human suffering and economic costs; however, much of the morbidity associated with long-term microvascular and neuropathic complications can be substantially reduced by interventions that achieve glucose levels close to the nondiabetic range. Although new classes of medications and numerous combinations have been demonstrated to lower glycemia, current-day management has failed to achieve and maintain the glycemic levels most likely to provide optimal healthcare status for people with diabetes.

Summary

The guidelines and treatment algorithm presented here emphasize the following:

- Achievement and maintenance of near normoglycaemia (A1C <7.0%)
- Initial therapy with lifestyle intervention and metformin
- Rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained
- Early addition of insulin therapy in patients who do not meet target goals

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Rationale and Strategies for Early Detection and Management of Diabetic Kidney Disease

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Diabetic kidney disease (DKD) occurs in 20% to 40% of patients with diabetes mellitus and is the leading cause of chronic kidney disease and end-stage renal disease in the United States. Despite the American Diabetes Association and the National Kidney Foundation advocating annual screening of diabetic patients, DKD remains underdiagnosed in the diabetic population. Early recognition of diabetic nephropathy by health care professionals is vital for proper management. The presence of microalbuminuria is particularly important as even low levels of dipstick-negative albuminuria indicate early disease long before a diminished glomerular filtration rate and are associated with an elevated cardiovascular disease risk. Like all forms of chronic kidney disease, DKD causes a progressive decline in renal function that, despite current treatment strategies, is largely irreversible. Many patients with DKD might be expected to develop end-stage renal disease, but many more patients will likely die of a cardiovascular event before renal replacement therapy is needed. Therefore, a renewed focus on cardiovascular risk factor reduction and a timely nephrology consultation with an emphasis on patient education is essential to proper DKD management.

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ACE = angiotensin-converting enzyme; ACR = albumin-to-creatinine ratio; ADA = American Diabetes Association; ARB = angiotensin II receptor blocker; CKD = chronic kidney disease; CVD = cardiovascular disease; DKD = diabetic kidney disease; DM = diabetes mellitus; ESRD = end-stage renal disease; GFR = glomerular filtration rate; HbA_{1c} = glycosylated hemoglobin; MDRD = Modification of Diet in Renal Disease; NKF = National Kidney Foundation; RAAS = renin-angiotensin-aldosterone system

The prevalence of both diabetes mellitus (DM) and chronic kidney disease (CKD) is steadily increasing in the United States. Current estimates suggest that 7% of the population (approximately 21 million people) have DM and that 13% of the population (approximately 26 million people) have CKD.[1,2] It may be argued that histologic findings of diabetic nephropathy, including glomerular basement membrane thickening and mesangial matrix expansion, are present in all patients with DM. However, diabetic kidney disease (DKD), defined as an elevated albumin excretion rate in a person with DM, occurs in 20% to 40% of patients with DM and is the leading cause of CKD and end-stage renal disease (ESRD) in the United States.[1,3] The increased prevalence of CKD is no doubt linked to the increased prevalence of DKD and DM, which is attributed largely to a dramatic increase in the obesity rate.[4]

In response to the growing prevalence of DKD and DM, which is increasingly recognized as an epidemic, the American Diabetes Association (ADA) and the National Kidney Foundation (NKF) have advocated annual screening for DKD in patients with DM by measuring their serum creatinine and albuminuria levels.[1,3] Despite these recommendations, DKD remains underdiagnosed in the DM population.[5-7] In a review of Medicare beneficiaries' records, proteinuria was measured in only 63% of patients with DM.[6] Furthermore, in a survey of more than 1000 primary care physicians, only 12% detected microalbuminuria in more than half of their patients with type 2 DM.[7]

Assessment of microalbuminuria is particularly important in diagnosing DKD because low levels of dipstick-negative albuminuria are an early clinical manifestation of diabetic nephropathy that may present several years before development of a diminished glomerular filtration rate (GFR). Spot urine samples have replaced the need for timed urine collections and can be used to easily identify patients with elevated albumin excretion rates by measuring the albumin-to-creatinine ratio (ACR). Once an elevated ACR has been detected, interventions should be initiated to slow the progression of DKD and possibly minimize the increased cardiovascular risk associated with DKD, a risk that exists even in the early stages of DKD.

Although DM has long been identified as a cardiovascular disease (CVD) risk equivalent, only recently has CKD been more widely recognized by primary care physicians in the United States as an independent risk factor for CVD and all-cause mortality.[8-11] In a study of more than 1 million ambulatory adult patients, the risk of a cardiovascular event and death due to any cause increased at every level of CKD below a GFR of 60 mL/min per 1.73 m^2, with a nearly 3.5-fold increased risk of a cardiovascular event and a 6-fold increased risk of death for those with a GFR of less than 15 mL/min per 1.73 m^2 (ie, CKD stage 5).[11] Furthermore, microalbuminuria alone has been associated with an increased risk of cardiovascular disease, both in patients with and without DM.[12-14] Therefore, in patients with DKD, the cardiovascular risks of DM and CKD are additive and increase as the kidney disease progresses.[15-17]

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TABLE 1. **Stages of Chronic Kidney Disease and Recommended Treatment**[a]

Stage	Description	GFR (mL/min per 1.73 m^2)	Treatment[b]
1	Kidney damage[c] with normal or elevated GFR	≥90	Manage comorbid conditions, slow progression,[d] reduce CVD risk
2	Kidney damage[c] with mildly reduced GFR	60-89	Estimate progression as follows: compare serial estimated GFRs using serum creatinine and MDRD calculation, track ACR
3	Moderately reduced GFR	30-59	Evaluate and manage complications as follows: (1) measure serum phosphorus level, consider use of phosphate binders and low-phosphorus diet; (2) measure vitamin D and parathyroid hormone levels, consider use of vitamin D supplementation; (3) measure hemoglobin, consider use of ESA
4	Severely reduced GFR	15-29	Prepare for kidney replacement therapy
5	Kidney failure (ESRD)	<15 or dialysis	Kidney replacement (if uremia present)

[a] ACR = albumin-to-creatinine ratio; CVD = cardiovascular disease; ESA = erythropoietic stimulating agent; ESRD = end-stage renal disease; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease.
[b] Includes treatments from preceding stages.
[c] Defined as abnormalities on pathologic, urine, blood, or imaging tests.
[d] Glycemic control plus angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker.
Data from *Ann Intern Med*.[9]

The current article presents results of a literature review conducted to clarify the rationale and strategies for early detection and management of DKD.

METHODS

The National Library of Medicine's PubMed database was used to conduct a review of literature published between January 1976 and June 2008. The following key terms were used in the search: *diabetes, kidney disease, microalbuminuria, glomerular filtration rate,* and *diabetic nephropathy*.

RESULTS

Overview of Renal Pathophysiology

The kidneys receive 25% of the cardiac output of blood. Although 20% of renal plasma flow (ie, approximately 180 L) is filtered through the glomerulus, only small amounts of protein can be detected in the urine.[18] Several plasma proteins are freely filtered, whereas others are prevented from crossing the glomerular filtration barrier, based on the proteins' molecular size and charge. The existence of several restrictive pores and of a glomerular charge barrier has been proposed to explain why the glomerulus is relatively impermeable to proteins of greater molecular weight (ie, >100 kDa) and to negatively charged proteins (eg, albumin).[18]

More recently, it has been suggested that, under normal conditions, a substantial amount of plasma protein, possibly at nephrotic levels, is filtered through the glomerulus, but proteinuria is prevented because of proximal tubule cell retrieval.[19] According to this idea, damage that disrupts the glomerular filtration barrier, or possibly the proximal tubular system, allows larger, negatively charged proteins that are normally contained within the serum to pass into the urine. The presence of such proteins, typically albumin, in the urine is an abnormal condition and is often one of the first signs of various forms of CKD, including DKD.

Chronic kidney disease is defined as kidney damage identified by proteinuria or by a GFR of less than 60 mL/min per 1.73 m^2 body surface area (with or without evidence of kidney damage) for 3 months or longer.[8,9] Table 1 shows the stages of CKD and the recommended treatments at each stage. In patients with DKD, the disease process begins with renal hypertrophy and hyperfiltration resulting from elevated renal plasma flow. In patients with type 1 DM and type 2 DM, hyperglycemia leads to increases in GFR of approximately 5% to 10%.[20-23] Although the mechanism is not completely understood, a correlation exists between glycosylated hemoglobin (HbA_{1c}) and GFR, and normalization of blood sugar levels has been shown to normalize GFR.[24,25] Other factors that influence hyperfiltration include increased ketone concentration, increased activity of the growth hormone/insulin-like growth factor system,[26] and disturbances in renal prostaglandins and the kallikrein-kinin system. In early-stage CKD, these abnormalities are frequently associated with enlarged kidneys.[27]

Hyperfiltration is typically followed by the loss of the negatively charged glomerular filtration barrier, allowing for negatively charged proteins, such as albumin, to pass through the glomerulus and into the urinary space. The presence of these proteins in the urinary space elevates urinary albumin excretion and produces microalbuminuria.[27] Microalbuminuria is defined as an albumin excretion rate between 30 and 300 mg per 24 hours, a range higher than the normal rate (<30 mg per 24 hours) but below the rate detectable by the standard urine dipstick method.[8] Overexcretion of albumin typically increases at a rate of 15% per year[28] and can result in macroalbuminuria (>300 mg per

24 hours) or even nephrotic-range proteinuria (>3.5 g per 24 hours).

In general, once macroalbuminuria (frank proteinuria) sets in, GFR begins to decline.[29] Progressive mesangial and interstitial capillary occlusion then occur, restricting the glomerular filtration surface and leading to a further decrease in GFR. Some proteins are reabsorbed by the renal tubules and accumulate in tubular epithelial cells. This accumulation induces the release of vasoactive and inflammatory cytokines, which damage the renal tubules and lead to tubular atrophy and interstitial fibrosis.[30] A negative feedback loop is thereby initiated, wherein increased proteinuria leads to increased tubulointerstitial injury and renal scarring, both of which further reduce GFR.[30]

Both hypertension and hyperglycemia are important in the development and progression of microalbuminuria and DKD. Table 2 presents a list of disorders associated with microalbuminuria. Several studies have shown that blood pressure elevations either precede or occur in conjunction with microalbuminuria in patients with both type 1 DM and type 2 DM.[29,31,32] Among patients with type 1 DM and DKD, those with increased urinary albumin excretion were found to be prehypertensive (120-139/80-89 mm Hg) at baseline, and their blood pressure and albuminuria levels increased in synch thereafter.[31,32] These elevations happened even though overt hypertension was not present before the onset of microalbuminuria. In patients with type 1 DM and DKD, blood pressure elevations before the onset of DM correlated with the future development of microalbuminuria.[33]

As previously mentioned, hyperglycemia can affect GFR and is necessary for the development of DKD. Likely mechanisms by which elevated glucose levels cause kidney damage include accumulation of advanced glycation end products, glucose-induced growth factor expression, and increased expression of inflammatory factors. However, hyperglycemia alone is insufficient to cause renal dysfunction.[30]

Most patients with DM never have clinically evident DKD, despite poor glycemic control. The absence of DKD in these patients suggests a genetic predisposition for DKD. The existence of such a predisposition is supported by studies showing an increased risk of nephropathy among people with a family history of the disorder.[34-36] Nevertheless, in susceptible individuals, hyperglycemia plays a crucial role in the progression of DKD from microalbuminuria to renal insufficiency and ESRD, as shown in type 1 DM by the Diabetes Control and Complications Trial[37] and in type 2 DM by the United Kingdom Prospective Diabetes Study.[38] Both these studies conclusively showed that the development and progression of DKD are strongly correlated with deficiencies in glucose control, verifying that glycemic control remains one of the cornerstones of treatment of DKD.

TABLE 2. **Disorders Associated With Microalbuminuria**

Elevated blood pressure
Dyslipidemia
Elevated fibrinogen and plasminogen activator inhibitor 1
Increased insulin resistance
Increased sodium disorders and related disorders
Increased transcapillary escape rate of albumin
Impaired basal endothelium-dependent vasorelaxation
Increased left ventricular volume
Diabetic retinopathy
Diabetic neuropathy
Peripheral vascular disease
Silent ischemic heart disease

Screening and Monitoring Techniques

The ADA recommends that both microalbuminuria and serum creatinine levels be assessed annually in patients with DM to screen for DKD.[3] For patients with type 1 DM, screening should begin 5 years after diagnosis because it takes at least that long for signs of nephropathy to develop. For patients with type 2 DM, screening should begin immediately at diagnosis because the precise onset of DM is often less clear, and the kidneys may have already sustained damage from years of undiagnosed hyperglycemia and/or hypertension.

After evidence of DKD has been detected, ongoing evaluations should be based on measurements of GFR.[3] However, in clinical practice, albuminuria is also typically measured to monitor disease progression and optimize therapy.

The following sections review the various methods used to measure GFR and albuminuria, focusing on the benefits and limitations of each.

Glomerular Filtration Rate. An index of functioning renal mass, GFR assessment is the most reliable method of detecting and monitoring renal impairment. Glomerular filtration rate can be measured directly or it can be estimated indirectly using the Modification of Diet in Renal Disease (MDRD) or Cockcroft-Gault equations. Simple measurement of serum creatinine is not recommended as an estimate of GFR because creatinine levels are greatly influenced by an individual's muscle mass, and thus simple measurements may overestimate or underestimate true GFR. Another reason that serum creatinine measurements may lead to an overestimation of GFR is that creatinine is cleared via secretion by the proximal tubule, and extrarenal excretion of creatinine is common in patients with more advanced CKD.[3,8,9]

Direct measurement of the fractional excretion of inulin, a fructose polysaccharide, is considered the criterion standard for GFR measurement. Inulin is inert, freely filtered at

the glomerulus, and neither secreted, reabsorbed, synthesized, nor metabolized by the kidneys. However, using inulin infusion to measure GFR is expensive, cumbersome, and not widely available. An alternative method for measuring GFR involves a single injection of a radioisotopic filtration marker, such as technetium Tc 99m DTPA (diethylenetriaminepentaacetic acid) or iothalamate I 125. This approach provides an accurate measure of GFR in cases of renal insufficiency, but it can overestimate GFR in healthy individuals and is also not widely available.[8,39]

The ADA and NKF recommend measuring the serum creatinine level and then using that value in either the MDRD or Cockcroft-Gault equations to estimate GFR.[1,3] Both these equations take into account variations in creatinine across age and sex, and the MDRD calculation also takes ethnicity into account.[40,41] The widely used MDRD calculation is considered more accurate than the Cockcroft-Gault equation for patients with CKD stage 2 or greater (GFR <90 mL/min per 1.73 m^2).[9] The MDRD equation was developed on the basis of direct GFR measurements and clearance of iothalamate ^{125}I in a study of 1628 patients of various ethnicities who had a variety of kidney disorders (6% had DM).[41] The MDRD was then validated in another group, consisting of more than 500 individuals.[41]

In general accuracy studies, more than 90% of GFR values estimated with the MDRD equation were within 30% of directly measured creatinine values, compared with 75% of values estimated with the Cockcroft-Gault equation.[8] Accuracy of estimates is improved if the clinical laboratory calibrates the creatinine measurement to the Cleveland Clinic's database, which includes approximately 9000 GFR measurements.[42] For this reason, many clinical laboratories are now undergoing the necessary steps to calibrate creatinine measurement.

Despite ADA and NKF recommendations, neither the MDRD calculation nor the Cockcroft-Gault equation has been validated for use in cases of diabetic nephropathy.[9] A recent accuracy study of patients with DM and microalbuminuria found that, although both the MDRD and Cockcroft-Gault equations correlated with directly measured GFR, both equations significantly underestimated the filtration rate, especially in patients with microalbuminuria.[43] The rate of renal decline was also significantly underestimated. The sensitivity of the equations to detect renal impairment was 72% for MDRD and 66% for Cockcroft-Gault. Furthermore, the use of these calculations led to accurate identification of CKD (as confirmed by a measured GFR <60 mL/min per 1.73 m^2) in only 51% (MDRD) and 66% (Cockcroft-Gault) of study participants.[43]

In a study of 169 patients with type 2 DM and macroalbuminuria, both equations underestimated GFR, although MDRD performed better than Cockcroft-Gault.[44] One study evaluated the equations by repeatedly measuring GFR with iothalamate for 10 years in 87 patients with type 2 DM and varying degrees of renal function: hyperfiltration, normal renal function, and CKD stage 2 or 3.[45] Both the MDRD and Cockcroft-Gault equations significantly underestimated GFR in patients with hyperfiltration and normal renal function. Nevertheless, in patients with CKD stage 2 or stage 3, GFR estimates made with MDRD closely matched iothalamate-determined GFR.[45]

The reason that the accuracy of the MDRD and Cockcroft-Gault equations is diminished in cases of DM is unknown. Creatinine clearance rate varies with age, sex, ethnicity, and body weight, and it is also affected by extremes of muscle mass and dietary intake. The NKF recommends that GFR be measured using direct clearance methods in patients with severe obesity, a population that includes many patients with type 2 DM but few with type 1 DM.[1] In patients with mild renal impairment (ie, CKD stage 1 or 2), the ability of the equations to estimate GFR is hampered by hypertrophy and hyperfiltration, which compensate for damaged nephrons[8] and may account for some of the observed inaccuracies.

An alternative approach being investigated is the measurement of cystatin C concentration as a surrogate for GFR. Cystatin C is a plasma protein that is freely filtered through the glomerulus and almost completely reabsorbed and catabolized by tubular cells. Several recent studies have examined the use of cystatin C concentration as an alternative method of estimating GFR. However, cystatin C is not yet used clinically because it is not widely available and is not currently recommended by either the ADA or the NKF.

Preliminary results suggest that cystatin C measurements may more accurately predict GFR than the MDRD or Cockcroft-Gault equations in patients with DM. In one study of 52 white patients with type 2 DM, the diagnostic accuracy of cystatin C measurements was 90% for identifying GFR at rates of less than 80 mL/min per 1.73 m^2, significantly greater than serum creatinine measurements alone (77%) or estimates made with the Cockcroft-Gault equation (85%).[46] A 4-year follow-up study of 30 Pima Indians with type 2 DM showed that GFR estimates based on cystatin C were numerically similar to GFR, as determined by iothalamate clearance, and that declining trends in renal function were correlated between the 2 measures (r=0.77).[47] By contrast, GFR estimates made with the MDRD or Cockcroft-Gault equation did not correlate well with iothalamate clearance (r<0.35).[47]

These provocative results await confirmation by larger studies. If the results are confirmed, cystatin C measurements may be used to arrive at more accurate assessments of CKD stage.

Albuminuria. Albuminuria can be assessed by timed collections, both overnight and 24-hour collections, and by spot urine tests used to measure ACR. Urine dipstick tests alone are not recommended for patients with DM because urinary protein levels vary with hydration and other factors, potentially leading to false-positive or false-negative results.[3]

The 24-hour timed collection of albuminuria remains the preferred method for the quantitative assessment of proteinuria; however, it is inconvenient, and over collection or under collection errors frequently result from missed or improperly timed samples. Overnight timed collections represent an alternative measure, but the shorter collection interval makes the sensitivity of overnight tests particularly vulnerable to under collection.[8]

The ADA and NKF now recommend measurement of ACR with a spot urine test to screen for diabetic nephropathy.[3] Several studies have shown clinical equivalency of ACR and 24-hour collections.[8,48-50] Both albumin and creatinine are highly soluble, and their dilution in urine is similar. Because creatinine excretion is generally constant, the ratio of albumin to creatinine accurately represents protein excretion during a 24-hour period.[8]

Several factors can increase urinary albumin over baseline values, leading to false-positive results, even when ACR is used as a measure. These factors include exercise within 24 hours of the urine test, urinary tract infection, fever, heart failure, marked hyperglycemia, marked hypertension, and protein intake. Furthermore, urinary albumin excretion has a notable intraindividual coefficient of variation, possibly as high as 40%.[51] To minimize this variability, first-morning-void urine samples are recommended. However, tests with positive results should be repeated, and a patient should not be considered to have elevated urinary albuminuria until 2 of 3 abnormal results have been obtained within a 3-month to 6-month time frame.[1,3]

Of note, a high-normal baseline level of albuminuria or a substantial increase in the level of albuminuria, even if still within the reference range, may signify future development of DKD.[52] For this reason, tests having such borderline negative results may require closer (eg, 6-month) follow-up, especially for patients at increased risk of DKD. For patients with documented renal impairment, annual evaluations of ACR should continue to assess disease progression and to monitor response to therapy (Table 1).

Rationale for Early Screening

Slowing Progression to ESRD. Diabetic kidney disease, like all forms of CKD, causes a progressive decline in renal function that may be retarded via several treatment strategies. Early recognition of DKD allows clinicians to optimize medical management and to educate patients about CKD so that patients can take measures to preserve residual renal function. Such measures may include weight loss, a low-protein diet, smoking cessation, and nephrotoxin avoidance.[53] In particular, use of nonsteroidal antiinflammatory drugs should be discouraged.

Furthermore, early awareness of DKD may prompt clinicians to adjust dosages of antidiabetes agents and to consider more frequent diagnostic tests. Metformin hydrochloride, a widely prescribed antidiabetes agent, may generate lactic acidosis in patients with an estimated GFR of less than 60 mL/min per 1.73 m^2 and should be discontinued when the patient's serum creatinine level increases higher than 1.4 mg/dL in women and 1.5 mg/dL in men.[54] In addition, use of intravenous contrast dye and oral sodium phosphate solutions may precipitate contrast-induced nephropathy or acute phosphate nephropathy, respectively, in patients with impaired renal function.

Patient Preparation in Cases of ESRD. Despite aggressive measures, ESRD may be expected to develop in many patients with DKD, and ultimately some form of long-term renal replacement therapy will be needed. In the United States, the overwhelming majority of patients with ESRD undergo hemodialysis,[55] but preemptive living-related or living-unrelated donor kidney transplant is often feasible with appropriate planning.

Preparation for renal replacement therapy requires focused patient education and timely referrals to a nephrologist, vascular surgeon, and kidney transplant center. The success of such measures begins with early DKD recognition by the primary care physician.

Cardiovascular Risk Associated With CKD. Previous nephropathy screening guidelines for patients with DM focused on retarding progression to ESRD. However, in addition to being a risk factor for renal failure, CKD is now widely recognized as a major risk factor for CVD.[56] In a retrospective claims-based study of more than 1 million Medicare enrollees aged 65 years and older, the risk of cardiovascular events was significantly increased in those with either CKD or DM alone, but cardiovascular risk was greatest when both conditions were present (Figure).[57] These results are supported by prospective epidemiological studies that also showed an increased risk of CVD in patients with renal insufficiency.[10,11,58,59]

Elevated cardiovascular risk occurs early in the development of CKD, as demonstrated by studies showing that even low levels of albuminuria are predictive of CVD.[12-14] Using data collected from the Heart Outcomes Prevention Evaluation study, investigators found that the relative risk of myocardial infarction, stroke, and death due to CVD in patients with microalbuminuria was 1.97 among those with DM and 1.61 among those without.[13] Independent of diabe-

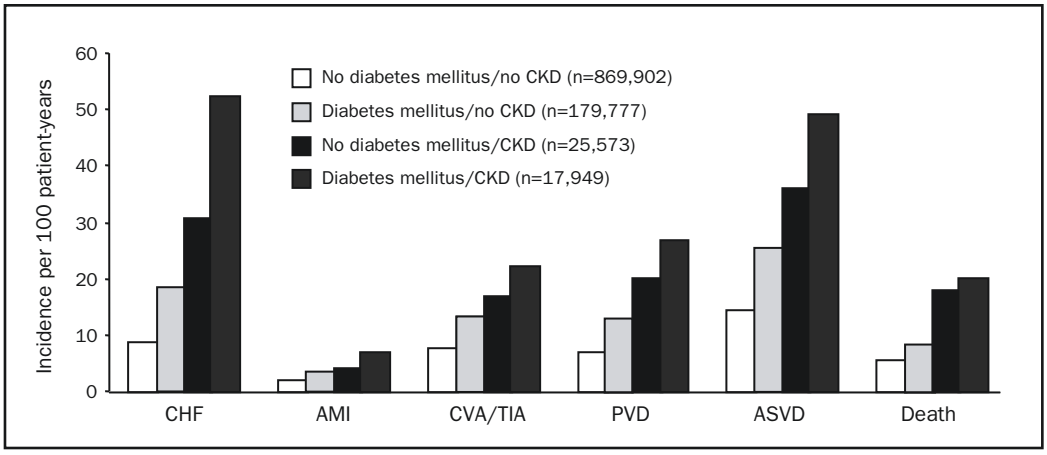

FIGURE. Rates of cardiovascular events in 2000-2001, per 100 patient-years, among individuals without diabetes mellitus or chronic kidney disease (CKD); with diabetes mellitus but without CKD; without diabetes mellitus but with CKD; and with both conditions. AMI = acute myocardial infarction; ASVD = atherosclerotic vascular disease; CHF = congestive heart failure; CVA/TIA = cerebrovascular accident/transient ischemic attack; PVD = peripheral vascular disease. Data from *J Am Soc Nephrol*.[57]

tes status, microalbuminuria was shown to be an independent, continuous risk factor for CVD. Each increase in ACR of 0.4 mg/mmol increased the risk of a cardiovascular event by 5.9%.[13]

In a study of more than 2500 men and women with no history of CVD, the relative risk of a cardiovascular event more than doubled when urinary albumin excretion was at least 15 μg/min.[12] This increased risk was found to be independent of age, creatinine clearance rate, diabetes status, hypertension, total cholesterol level, and high-density lipoprotein cholesterol level.

It is particularly striking that many patients with CKD, particularly elderly patients, may be several times more likely to die before progression to ESRD.[60] Therefore, although 26 million patients in the United States have CKD, only a fraction will develop ESRD.

Many clinicians assume that most patients with CKD die of CVD before progression to ESRD, but progression is more likely to happen in patients with DKD. Although an association exists between kidney disease and increased CVD risk, there are no controlled trials indicating whether treatment of patients with CKD improves CVD outcomes. Therefore, this association may be related to the common risk factors involved.

Treatment Strategies

CVD Risk Reduction. On the basis of these and other findings, the scientific advisory boards of the American Heart Association and NKF Kidney Disease Outcomes Quality Initiative, as well as the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, recommend that patients with DKD be considered in the highest-risk group for CVD.[56,61,62] Therefore, in addition to the slowing of kidney disease progression, treatment of patients with DKD should include efforts to manage cardiovascular risk factors such as hypertension, dyslipidemia, and hyperglycemia on the basis of the more aggressive treatment goals recommended for patients at highest risk of CVD. Specifically, in patients with DKD and CKD stages 1 to 4, recent clinical practice guidelines by the NKF Kidney Disease Outcomes Quality Initiative recommend a target blood pressure level of less than 130/80 mm Hg, a target low-density lipoprotein cholesterol level of less than 100 mg/dL, and a target HbA_{1c} level of less than 7.0%.[1]

Because most patients with DM and kidney disease also have hypertension and dyslipidemia, these treatment goals apply to most patients with DKD. However, it is important to remember that patients with advanced renal dysfunction were excluded from many of the studies on which these recommendations were based. Furthermore, targeting blood pressure, low-density lipoprotein cholesterol, and HbA_{1c} at levels lower than suggested targets or applying such target goals to patients with stage 5 CKD (ie, ESRD) may not yield additional benefit in regard to CVD risk reduction and may actually place patients at increased risk of adverse events.[63-65]

Slowing Progression of DKD. Activation of the renin-angiotensin-aldosterone system (RAAS) has long been recognized as a key regulator of CKD progression. The RAAS is capable of causing kidney damage through several mechanisms, including systemic and glomerular hypertension, increased glomerular capillary permeability, and local inflammation within the kidneys via release of several

chemokines and profibrotic cytokines.[66] Use of an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) has been shown to retard GFR decline in patients with macroalbuminuria and either type 1 or type 2 DM.[67-69] In addition, the mainstay of DKD management has long been inhibition of the RAAS with ACE inhibitors or ARBs.

However, neither ACE inhibitors nor ARBs have been shown to reverse or even stabilize GFR in patients with DKD. Although these medications significantly decrease the slope of GFR decline, the effect is often modest, with reported mean benefits of +0.8 to +1.0 mL/min per year for 3 years in patients with type 2 DM and macroalbuminuria compared with placebo.[68,69] Thus, the benefit of ACE inhibitors and ARBs in patients with DM and nonproteinuric renal disease remains unclear.

Using a combination of ACE inhibitor and ARB therapy has also been suggested for patients with DKD. However, one recent study comparing the use of ramipril (an ACE inhibitor), telmisartan (an ARB), or both showed no cardiovascular benefit from either medication or from the combination.[70] Compared with the ramipril group, the telmisartan group had a similar relative risk of renal impairment, whereas the combination-therapy group had a significant increased risk. Furthermore, the rate of renal dialysis was the same in the ramipril group and the telmisartan group but was increased in the combination-therapy group.

In addition to the use of ACE inhibitors or ARBs, blood pressure and blood glucose control aimed at targets for CVD risk reduction have been shown to slow DKD progression. Several other modifiable risk factors associated with CKD progression, including obesity, dyslipidemia, anemia, a high-protein diet, and smoking, may also be effectively targeted when treating DKD.[53] Although data are limited regarding the renal protective effects of weight loss and statin use, several recent clinical trials showed no improved cardiovascular and renal outcomes with hemoglobin normalization.[71-73]

The role of a low-protein diet is controversial for patients with DKD. High protein intake increases GFR and may induce hyperfiltration, thereby worsening glomerular injury in patients with renal disease. However, no renal benefit was observed in a randomized study of patients receiving a low-protein diet (0.58 g/kg per day) vs a usual protein diet (1.3 g/kg per day).[74] Nevertheless, most experts in DM agree that a high-protein diet may accelerate CKD progression. The ADA recommends that patients with DKD restrict their animal protein intake to less than 0.8 g/kg per day.[3]

A recent study showed reduced development of macroalbuminuria in patients with type 2 DM who were former smokers or who had never smoked compared with patients with type 2 DM who were active smokers. This finding suggests that smoking cessation may significantly impact DKD progression in patients with microalbuminuria.[75]

As renal function declines, several metabolic derangements predictably develop, including metabolic acidosis, hyperkalemia, hypocalcemia, hyperphosphatemia, hyperparathyroidism, and anemia. As noted in Table 1, when CKD progresses to stage 3 (GFR <60 mL/min per 1.73 m^2), screening and treatment for complications should commence.[9] When CKD progresses to stage 4 (GFR <30 mL/min per 1.73 m^2), preparation for renal replacement therapy should begin, and a nephrologist should be consulted.[9]

Early referrals to nephrologists are generally appropriate because a nephrologist can often help guide the management of anemia and bone mineral disease associated with CKD. A nephrologist can also provide patient education regarding lifestyle modification and renal replacement therapy options as the needs develop for such interventions.

CONCLUSION

Diabetic kidney disease is an extremely common complication of DM and is the leading cause of CKD and ESRD in the United States. The current review has presented and analyzed data primarily from studies of patients with type 2 DM. Obviously, one should not overinterpret these data when considering other specific groups of patients, such as those with type 1 DM or elderly persons, because not all the findings and outcomes may apply.

Early detection of DKD is important not only in slowing renal disease progression but also in managing cardiovascular risk. To that end and because serum creatinine measurements and estimated GFR often have normal results in early stages of DKD, health care professionals must understand the importance of measuring albumin excretion rates to effectively screen patients for DKD.

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AACE/ACE Consensus Statement

STATEMENT BY AN AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CONSENSUS PANEL ON TYPE 2 DIABETES MELLITUS: AN ALGORITHM FOR GLYCEMIC CONTROL

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AACE/ACE GLYCEMIC CONTROL ALGORITHM CONSENSUS PANEL

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ABSTRACT

This report presents an algorithm to assist primary care physicians, endocrinologists, and others in the management of adult, nonpregnant patients with type 2 diabetes mellitus. In order to minimize the risk of diabetes-related complications, the goal of therapy is to achieve a hemoglobin A1c (A1C) of 6.5% or less, with recognition of the need for individualization to minimize the risks of hypoglycemia. We provide therapeutic pathways stratified on the basis of current levels of A1C, whether the patient is receiving treatment or is drug naïve. We consider monotherapy, dual therapy, and triple therapy, including 8 major classes of medications (biguanides, dipeptidyl-peptidase-4 inhibitors, incretin mimetics, thiazolidinediones, α-glucosidase inhibitors, sulfonylureas, meglitinides, and bile acid sequestrants) and insulin therapy (basal, premixed, and multiple daily injections), with or without orally administered medications. We prioritize choices of medications according to safety, risk of hypoglycemia, efficacy, simplicity, anticipated degree of patient adherence, and cost of medications. We recommend only combinations of medications approved by the US Food and Drug Administration that provide complementary mechanisms of action. It is essential to monitor therapy with A1C and self-monitoring of blood glucose and to adjust or advance therapy frequently (every 2 to 3 months) if the appropriate goal for each patient has not been achieved. We provide a flowchart and table summarizing the major considerations. This algorithm represents a consensus of 14 highly experienced clinicians, clinical researchers, practitioners, and academicians and is based on the American Association of Clinical Endocrinologists/American College of Endocrinology Diabetes Guidelines and the recent medical literature. **(Endocr Pract. 2009;15:540-559)**

Abbreviations:
AACE = American Association of Clinical Endocrinologists; **A1C** = hemoglobin A1c; **ACCORD** = Action to Control Cardiovascular Risk in Diabetes; **ACE** = American College of Endocrinology; **ADA** = American Diabetes Association; **ADVANCE** = Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation; **AGIs** = α-glucosidase inhibitors; **DCCT/EDIC** = Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; **DPP-4** = dipeptidyl-peptidase-4; **EASD** = European Association for the Study of Diabetes; **FDA** = US Food and Drug Administration; **GLP-1** = glucagonlike peptide-1; **LDL** = low-density lipoprotein; **PROACTIVE** = Prospective Pioglitazone Clinical Trial in Macrovascular Events; **RCTs** = randomized controlled trials; **RECORD** = Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes; **SMBG** = self-monitoring of blood glucose; **TZDs** = thiazolidinediones; **UKPDS** = United Kingdom Prospective Diabetes Study; **VADT** = Veterans Affairs Diabetes Trial

INTRODUCTION

There are nearly 24 million Americans with diabetes in the United States. Every year, 1.3 million people are diagnosed with type 2 diabetes. The rapid increase in new cases of type 2 diabetes in persons 30 to 39 years of age and in children and adolescents is of special concern. This epidemic of type 2 diabetes is global and closely reflects the epidemic of overweight, obesity, metabolic syndrome, and sedentary lifestyle. An urgent need exists for an authoritative, practical algorithm for management of patients with type 2 diabetes mellitus that considers currently approved classes of medications and emphasizes safety and efficacy, while also considering secondary factors such as the cost of medications or the number of years of clinical experience with use of any specific drug. The introduction of several new classes of medications within the past few years—especially incretin-based therapies such as incretin mimetics and dipeptidyl-peptidase-4 (DPP-4) inhibitors—and the results from several recent large-scale clinical trials—Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), Veterans Affairs Diabetes Trial (VADT), Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE), and Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD)—combined with recently reported long-term follow-up results in patients in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC), the United Kingdom Prospective Diabetes Study (UKPDS), and the Steno-2 study, necessitate reevaluation of previously proposed algorithms for selection of therapies. Numerous guidelines for management of patients with diabetes are available—for example, from the American Association of Clinical Endocrinologists (AACE) (1), American Diabetes Association (ADA) Standards of Medical Care in Diabetes (2), Veterans Health Administration/US Department of Defense (VA/DOD) (3), International Diabetes Federation (4), and many others. Several of these need to be updated to reflect the recent literature and clinical experience. A few algorithms are available for that purpose: ADA/European Association for the Study of Diabetes (EASD) 2006 (5,6), ADA/EASD 2009 (7), Canadian Diabetes Association (8,9), and the American College of Endocrinology (ACE)/AACE Road Maps to Achieve Glycemic Control (10). The

cost of medications represents only a very small portion of the total cost of treatment of patients with diabetes. The major cost is related to the treatment of the complications of diabetes. We believe that identification of the safest and most efficacious agents is essential.

METHODS

AACE/ACE convened a panel of experts, including clinicians and clinical investigators, both academicians and practitioners. An algorithm was developed on the basis of the medical literature, with careful consideration of levels of evidence and evaluation for the consistency of results from multiple studies and sources; greater emphasis was placed on results from randomized controlled trials (RCTs) when available. We also considered meta-analyses, US Food and Drug Administration (FDA)-approved prescribing information, and the extensive experience, collective knowledge, and judgment of the panel members. We envisioned the need for an algorithm that reflected the best practices for expert physicians, recognizing that RCT data are not available to guide every clinical decision. Considerations were based on the AACE Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus (1), review of other guidelines (ADA Standards of Medical Care in Diabetes—2009) (2), previous algorithms—ACE/AACE Road Maps to Achieve Glycemic Control (10), ADA/EASD 2006 (5,6), ADA/EASD 2009 (7), Canadian Diabetes Association (8,9), and Inzucchi (11)—the FDA-approved prescribing information for individual agents, pharmacoepidemiologic surveillance studies, and the current literature describing relevant clinical trials: DCCT/EDIC (12), UKPDS (13), Steno-2 (14), ACCORD (15), ADVANCE (16), VADT (17), RECORD (18), PROACTIVE (19), and others.

In the development of this algorithm, we attempted to accomplish the following goals as priorities in the selection of medications:

1. minimizing risk and severity of hypoglycemia
2. minimizing risk and magnitude of weight gain
3. inclusion of major classes of FDA-approved glycemic medication, including incretin-based therapies and thiazolidinediones (TZDs)
4. selection of therapy stratified by hemoglobin A1c (A1C) and based on documented A1C-lowering potential
5. consideration of both fasting and postprandial glucose levels as end points
6. consideration of total cost of therapy to the individual and society at large, including costs related to medications, glucose monitoring requirements, hypoglycemic events, drug-related adverse events, and treatment of diabetes-associated complications

We believe that this algorithm represents the treatment preferences of most clinical endocrinologists, but in the absence of meaningful comparative data, it is not necessarily an official AACE position. Because of the insufficient number or total absence of RCTs for many combinations of therapies, the participating clinical experts used their judgment and experience. Every effort was made to achieve consensus among the panel members. Many details that could not be included in the summarizing algorithm are described in the following text.

RESULTS

Our glycemic control algorithm was developed on the basis of the principles outlined in the subsequent section.

Principles Underlying the AACE/ACE Algorithm

- Lifestyle (dietary and exercise) modifications are essential for all patients with diabetes. Reduction of obesity or overweight and adjustment to an active lifestyle can have major beneficial effects. In many cases, delaying pharmacotherapy to allow for lifestyle modifications is inappropriate because these interventions are usually not adequate. Lifestyle modification together with specific diabetes education, dietary consultation, and the introduction of a program of self-monitoring of blood glucose (SMBG) can be initiated concomitantly with medical therapy.
- Achieving an A1C of 6.5% is recommended as the primary goal, but this goal must be customized for the individual patient, with consideration of numerous factors such as comorbid conditions, duration of diabetes, history of hypoglycemia, hypoglycemia unawareness, patient education, motivation, adherence, age, limited life expectancy, and use of other medications.
- If a patient has failed to achieve the A1C goal, one can titrate dosages of medications, change regimens (add or discontinue medications), or, under some circumstances, reconsider and revise the goal.
- When combination therapy is prescribed, it is important to use classes of medications that have complementary mechanisms of action.
- Effectiveness of therapy must be evaluated frequently—for example, every 2 to 3 months—with assessment of A1C, logbook data for SMBG records, documented and suspected hypoglycemia, and other potential adverse events (weight gain, fluid retention, and hepatic, renal, or cardiac disease) as well as monitoring of comorbidities, relevant laboratory data, concomitant drug administration, diabetes-related complications, and psychosocial factors affecting patient care.
- Safety and efficacy should be given higher priorities than cost of medications per se, inasmuch as cost of medications is only a small part of the cost of care of diabetes.

- The algorithm should be as simple as possible to gain physician acceptance and improve its utility and usability in clinical practice.
- The algorithm should help educate clinicians and help guide therapy at the point of care.
- The algorithm should conform, as nearly as possible, to a consensus for current standards of care by expert endocrinologists who specialize in the management of patients with type 2 diabetes and have the broadest experience in outpatient clinical practice.
- The algorithm should be as specific as possible and provide guidance to physicians with prioritization and a rationale for selection of any particular regimen.
- Rapid-acting insulin analogues are superior to "regular human insulin" and provide a better, safer alternative.
- NPH insulin is not recommended. Use of NPH as a basal insulin has been superseded by the synthetic analogues insulin glargine and insulin detemir, which provide a relatively peakless profile for approximately 24 hours and yield better reproducibility and consistency, both between patients and within patients, and a corresponding reduction in the risk of hypoglycemia.

The Glycemic Control Algorithm

The AACE/ACE algorithm for glycemic control is presented in Figure 1.

A1C Goal

The rationale for an A1C target of 6.5% is presented in the AACE Diabetes Guidelines (2007) (1). The ACCORD and VADT studies (15,17) have confirmed that progressively lower A1C levels are associated with reduced risk of both microvascular and macrovascular complications. A recent meta-analysis of 5 prospective RCTs demonstrated a significant reduction in coronary events associated with an overall A1C of 6.6% in comparison with 7.5% (20). These studies also indicated that the risk of cardiac events and death is more common in patients with hypoglycemic episodes (and especially severe hypoglycemia) and that the benefit-to-risk ratio decreases progressively with the duration of diabetes, such that the use of intensive therapy may be at least relatively contraindicated in patients with a duration of diabetes longer than 12 years (VADT) (17). The ACCORD study (15) also suggested that excessively rapid or aggressive adjustment of therapy may be associated with increased risk. The A1C levels show an excellent correlation with the mean glucose level, but this relationship is also affected by several other factors, such as hemoglobinopathies, hemolytic anemias, varying rates of individual glycation, genetics, and the variabilities of different laboratory methods.

Frequency of Monitoring of A1C

Many physicians fail to implement the uniformly recommended guidelines to monitor A1C on a quarterly basis. Physicians are often slow in advancing therapy, relative to either dosages of medications or switching to a more efficacious therapeutic regimen in a timely manner. One of the most important aspects of the current algorithm is the strong recommendation to monitor therapy closely (every 2 to 3 months) and to intensify therapy until the goal for A1C has been achieved.

Stratification by Current A1C level

An important element of the current algorithm is the need for stratification of the therapeutic approach on the basis of the current A1C Level.

1. If the patient has an A1C value of 7.5% or lower, it may be possible to achieve a goal A1C of 6.5% with use of monotherapy. If monotherapy fails to achieve that goal, one usually progresses to dual and then to triple therapy; finally, insulin therapy should be initiated, with or without additional agents.
2. If the patient has an A1C level in the range of 7.6% to 9.0%, then one should begin with dual therapy because no single agent is likely to achieve the goal. If dual therapy fails, one can progress to triple therapy and then to insulin therapy, with or without additional orally administered agents.
3. If the patient has an A1C value of >9.0%, then the possibility of achieving a goal A1C of 6.5% is small, even if dual therapy is used. If the patient is asymptomatic, one might begin with triple therapy—for example, based on a combination of metformin and an incretin mimetic or a DPP-4 inhibitor combined with either a sulfonylurea or a TZD. If, however, the patient is symptomatic, or therapy with similar medications has failed, it is appropriate to initiate insulin therapy, either with or without additional orally administered agents.
4. When the algorithm (Fig. 1) indicates insulin therapy, one may use any of the following 4 general approaches:

    - basal insulin, using a long-acting insulin analogue (glargine, detemir), generally given once daily;
    - premixed insulins, using a rapid-acting analogue and protamine (NovoLog Mix, Humalog Mix), usually given twice daily with breakfast and dinner but occasionally used only with the largest meal;
    - basal-bolus insulin or multiple daily injections, using rapid-acting insulin analogues—aspart (NovoLog), lispro (Humalog), or glulisine (Apidra)—together with the long-acting insulin analogue glargine (Lantus) or detemir (Levemir);
    - a "prandial" insulin regimen, involving use of the rapid-acting insulin analogues, but without a basal or long-acting insulin component. This may be possible if the patient is being treated with an insulin sensitizer (metformin) that provides adequate control of fasting plasma glucose.

We do not recommend use of regular human insulin ("R"), nor of NPH insulin ("N") if possible, in view of the fact that these insulin preparations do not have a sufficiently predictable time course that adequately mimics the normal physiologic profile. As a result, the dose required to control hyperglycemia is often associated with an increased risk of hypoglycemia.

We now describe the 3 pathways within the algorithm corresponding to the 3 broad ranges of A1C: 6.5% to 7.5%, 7.6% to 9.0%, and >9.0%.

Management of Patients With A1C Levels of 6.5% to 7.5%

Monotherapy

For the patient with an A1C level within the range of 6.5% to 7.5%, it is possible that a single agent might achieve the A1C goal of 6.5%. In this setting, metformin, TZDs, DPP-4 inhibitors, and α-glucosidase inhibitors (AGIs) are recommended. Because of its safety and efficacy, metformin is the cornerstone of monotherapy and is usually the most appropriate initial choice for monotherapy unless there is a contraindication, such as renal disease, hepatic disease, gastrointestinal intolerance, or risk of lactic acidosis.

Some patients with diabetes and A1C levels of <6.5% may also be considered for pharmacotherapy. Use of an insulin secretagogue (sulfonylurea or meglitinide/"glinide") is not recommended in this A1C range. Sulfonylureas may be more potent than metformin, TZDs, DPP-4 inhibitors, or AGIs, although they have a relatively short-lived effectiveness and are associated with a substantial risk of hypoglycemia and weight gain, especially in drug-naïve patients.

The 4 agents recommended for the A1C range of 6.5% to 7.5% have a very minimal risk of hypoglycemia, especially when used as monotherapy. The TZDs require several weeks to achieve maximal benefit; likewise, their effects decline slowly after they have been discontinued. In patients with clear evidence of insulin resistance or the clinical "metabolic syndrome" and in patients with nonalcoholic fatty liver disease, TZDs may be preferred. If monotherapy is unsuccessful in achieving the A1C goal even after the dosage has been titrated appropriately, then one should advance to dual therapy.

Dual Therapy

As a result of its safety and efficacy, metformin should be the cornerstone of dual therapy for most patients. When metformin is contraindicated, a TZD may be used as the foundation for this group of options. Because metformin or a TZD will serve as an insulin sensitizer, the second component of the dual therapy is usually an incretin mimetic, DPP-4 inhibitor, glinide, or sulfonylurea. These agents are recommended in the following order: incretin mimetic, DPP-4 inhibitor, or an insulin secretagogue such as a glinide and sulfonylurea. The glucagonlike peptide-1 (GLP-1) agonist and DPP-4 inhibitors are safer than the glinide or sulfonylurea options with regard to the risk of hypoglycemia. Despite its risk of gastrointestinal side effects (which are usually transitory) and the need for twice-daily injection, the GLP-1 agonist is preferred, in view of its somewhat greater effectiveness in reducing postprandial glucose excursions relative to the DPP-4 inhibitor and the fact that approximately 30% of patients will experience considerable weight loss. The DPP-4 inhibitors are used orally once daily with excellent tolerability and no major effects on weight. Glinides are preferred relative to sulfonylureas because of the greater need for controlling postprandial glucose excursions in patients with an A1C level already below 7.5% and their relative safety. The combination of TZD with metformin has been used extensively and is efficacious, but it carries the risks of the adverse events associated with both agents. We recommend this combination with a higher priority than a glinide or sulfonylurea because of a lower risk of hypoglycemia and greater flexibility in timing of administration. One must consider the potential adverse effects of any of these medications as they apply to an individual patient (see Table 1 and Appendix 1 as well as definitive sources of prescribing information).

Two additional regimens for dual therapy are included in the algorithm: (*1*) metformin combined with colesevelam and (*2*) metformin combined with an AGI. These regimens are included because of their safety (minimal risk of hypoglycemia) and the ability of colesevelam to lower the level of low-density lipoprotein (LDL) cholesterol, although these combinations may produce some gastrointestinal side effects.

If dual therapy fails, even after each component has been titrated to its maximally effective dose (commonly, only 50% to 66% of the FDA upper limit for recommended dosage), one can advance to triple therapy or institute insulin therapy.

Triple Therapy

We consider the following 6 options for triple therapy, which are presented in a condensed format in Figure 1:

1. Metformin + GLP-1 agonist + TZD
2. Metformin + GLP-1 agonist + glinide
3. Metformin + GLP-1 agonist + sulfonylurea
4. Metformin + DPP-4 inhibitor + TZD
5. Metformin + DPP-4 inhibitor + glinide
6. Metformin + DPP-4 inhibitor + sulfonylurea

Because of its safety and effectiveness, metformin is selected as the cornerstone for triple therapy, unless specific contraindications are present. The GLP-1 agonist, exenatide, is the second preferred component because of its safety, with nearly complete absence of hypoglycemia attributable to the fact that its stimulation of insulin is dependent on glucose, and because of its potential for

AACE/ACE DIABETES ALGORITHM *For Glycemic Control*

A1C Goal ≤ 6.5%*

LIFESTYLE MODIFICATION

A1C 6.5 – 7.5%**

Monotherapy

MET † | DPP4 [1] | GLP-1 | TZD [2] | AGI [3]

↓ *2 - 3 Mos.****

Dual Therapy

MET	+	GLP-1 or DPP4 [1]
		TZD [2]
		Glinide or SU [5]
TZD	+	GLP-1 or DPP4 [1]
MET	+	Colesevelam
		AGI [3]

↓ *2 - 3 Mos.****

Triple Therapy

MET + GLP-1 or DPP4 [1]	+	TZD [2]
		Glinide or SU [4,7]

↓ *2 - 3 Mos.****

INSULIN ± Other Agent(s) [6]

A1C 7.6 – 9.0%

Dual Therapy [8]

MET	+	GLP-1 or DPP4 [1] or TZD [2]
		SU or Glinide [4,5]

↓ *2 - 3 Mos.****

Triple Therapy [9]

MET	+	GLP-1 or DPP4 [1]	+ TZD [2]
		GLP-1 or DPP4 [1]	+ SU [7]
		TZD [2]	

↓ *2 - 3 Mos.****

INSULIN ± Other Agent(s) [6]

A1C > 9.0%

Drug Naive / *Under Treatment*

Symptoms / *No Symptoms*

INSULIN ± Other Agent(s) [6]

MET	+	GLP-1 or DPP4 [1]	± SU [7]
		TZD [2]	
		GLP-1 or DPP4 [1]	± TZD [2]

INSULIN ± Other Agent(s) [6]

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* May not be appropriate for all patients

** For patients with diabetes and A1C < 6.5%, pharmacologic Rx may be considered

*** If A1C goal not achieved safely

† Preferred initial agent

1 DPP4 if ↑ PPG and ↑ FPG or GLP-1 if ↑↑ PPG

2 TZD if metabolic syndrome and/or nonalcoholic fatty liver disease (NAFLD)

3 AGI if ↑ PPG

4 Glinide if ↑ PPG or SU if ↑ FPG

5 Low-dose secretagogue recommended

6 a) Discontinue insulin secretagogue with multidose insulin
b) Can use pramlintide with prandial insulin

7 Decrease secretagogue by 50% when added to GLP-1 or DPP-4

8 If A1C < 8.5%, combination Rx with agents that cause hypoglycemia should be used with caution

9 If A1C > 8.5%, in patients on Dual Therapy, insulin should be considered

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Fig. 1. Simplified flowchart for American Association of Clinical Endocrinologists (*AACE*)/American College of Endocrinology (*ACE*) 2009 glycemic control algorithm. Pathways are provided for patients with hemoglobin A1c (*A1C*) in 3 ranges: 6.5% to 7.5%, >7.6% to 9.0%, and >9.0%. There is a progression from monotherapy, to dual therapy, to triple therapy, to insulin therapy with or without additional agents. The order of presentation of regimens indicates general priorities that should be customized to the individual patient, with consideration of contraindications and precautions, allergies, comorbid conditions, drug-drug interactions, and drug-laboratory interactions. Physicians must be thoroughly familiar with complete prescribing information before selection of therapy. In each case, response to therapy should be monitored closely (determination of A1C every 2 to 3 months), and titration of dosages or changes of regimen should be implemented in a timely manner. *Rx* = treatment. Note accompanying Table of Annotated Abbreviations for Figure 1.

Table of Annotated Abbreviations for Figure 1[a]

Abbreviation	Class	Generic name	Trade name
AGI	α-Glucosidase inhibitor	Acarbose	Precose
		Miglitol	Glyset
DPP4	Dipeptidyl-peptidase-4 (DPP-4) inhibitor	Sitagliptin	Januvia
		Saxagliptin	Onglyza
GLP-1	Incretin mimetics (glucagonlike peptide-1 agonist)	Exenatide	Byetta
MET	Biguanide	Metformin	Metformin (generic), Glucophage XR, Glumetza, Riomet, Fortamet
SU	Sulfonylurea	Glyburide	DiaBeta, Glynase, Micronase
		Glipizide	Glipizide (generic), Glucotrol, Glucotrol XL
		Glimepiride	Amaryl
TZD	Thiazolidinedione	Rosiglitazone	Avandia
		Pioglitazone	Actos

Abbreviation	Definition	Comment
FPG	Fasting plasma glucose	After overnight fast of at least 8 hours
PPG	Postprandial glucose	2 hours after a meal

[a] The following single-tablet combinations of agents are available:
sitagliptin + metformin (Janumet), pioglitazone + metformin (ActoPlus Met),
rosiglitazone + metformin (Avandamet), repaglinide + metformin (PrandiMet),
glipizide + metformin (Metaglip and generic), and glyburide + metformin (Glucovance and generic).

TABLE 1

SUMMARY OF KEY BENEFITS AND RISKS OF MEDICATIONS

Benefits are classified according to major effects on fasting glucose, postprandial glucose, and nonalcoholic fatty liver disease (NAFLD). Eight broad categories of risks are summarized. The intensity of the background shading of the cells reflects relative importance of the benefit or risk.*

MEDICATIONS*	Metformin (MET)	DPP4 Inhibitor	GLP-1 Agonist (Incretin Mimetic)	Sulfonylurea (SU)	Glinide**	Thiazolidinedione (TZD)	Colesevelam	Alpha-glucosidase inhibitor (AGI)	Insulin	Pramlintide
BENEFITS										
Postprandial Glucose (PPG) - lowering	Mild	Moderate	Moderate to Marked	Moderate	Moderate	Mild	Mild	Moderate	Moderate to Marked	Moderate to Marked
Fasting glucose (FPG) - lowering	Moderate	Mild	Mild	Moderate	Mild	Moderate	Mild	Neutral	Moderate to Marked	Mild
Nonalcoholic fatty liver disease (NAFLD)	Mild	Neutral	Mild	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
RISKS										
Hypoglycemia	Neutral	Neutral	Neutral	Moderate	Mild	Neutral	Neutral	Neutral	Moderate to Severe	Neutral
Gastrointestinal Symptoms	Moderate	Neutral	Moderate	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Moderate
Risk of use with renal insufficiency	Severe	Reduce Dosage	Moderate	Moderate	Neutral	Mild	Neutral	Neutral	Moderate	Unknown
Contraindicated in Liver Failure or Predisposition to Lactic Acidosis	Severe	Neutral	Neutral	Moderate	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral
Heart failure / Edema	Use with caution in CHF	Neutral	Neutral	Neutral	Neutral	Mild / Moderate Contraindicated in class 3,4 CHF	Neutral	Neutral	Neutral unless with TZD	Neutral
Weight Gain	Benefit	Neutral	Benefit	Mild	Mild	Moderate	Neutral	Neutral	Mild to Moderate	Benefit
Fractures	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral
Drug-Drug interactions	Neutral	Neutral	Neutral	Moderate	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral

* *The abbreviations used here correspond to those used on the algorithm (Fig. 1).*

** *The term 'glinide' includes both repaglinide and nateglinide.*

inducing weight loss. It also has the ability to inhibit glucagon secretion in a glucose-dependent manner after consumption of meals, to increase satiety, and to delay gastric emptying. Physicians should be aware of the reported possible association of exenatide with pancreatitis and should avoid use of this drug in patients with a history of pancreatitis. A recent analysis of a very large database, however, revealed no greater incidence of pancreatitis in patients with diabetes taking exenatide in comparison with the already substantially increased incidence of this disorder in patients with diabetes. For the third member of the triple-therapy combination, one may select a TZD, glinide, or sulfonylurea. These agents are recommended in order to minimize the risk of hypoglycemia. The combination with metformin, especially when coupled with an incretin mimetic, may partially help to counteract the weight gain often associated with glinides, sulfonylureas, and TZDs.

Insulin Therapy

When triple therapy fails to achieve glycemic control, it is likely that the insulin-secretory capacity of the beta cells has been exceeded; thus, insulin therapy is needed. One can then institute therapy as basal, premixed, prandial, or basal-bolus insulin. At this point, the list of available agents to use as adjuvants to insulin is diminished. Exenatide and DPP-4 inhibitors have not been approved by the FDA for concomitant use with insulin. Agents such as colesevelam and AGIs are not likely to contribute materially to effectiveness. Sulfonylureas and glinides should be discontinued when prandial insulin is introduced, inasmuch as postprandial excursions can usually be managed better with a rapid-acting insulin analogue or a premixed insulin preparation. Use of TZDs jointly with insulin has been associated with a high probability of weight gain, fluid retention, increased risk of congestive heart failure, and significantly increased risk of fractures both in men and in women. Although some studies have been controversial, recent clinical trials—ADVANCE (16), VADT (17), and ACCORD (15)—showed no increased risk of mortality associated with rosiglitazone, and the PROACTIVE trial (19) showed a small beneficial effect of pioglitazone on cardiac events. Overall, metformin is the most commonly used and safest medication to combine with insulin.

Basal Insulin: Long-acting basal insulin is generally the initial choice for initiation of insulin therapy in the United States. Insulin glargine and insulin detemir are strongly preferred over human NPH insulin because they have relatively peakless time-action curves and a more consistent effect from day to day, resulting in a lower risk of hypoglycemia. Basal insulin therapy is generally initiated with a small arbitrary dose (usually 10 U) at bedtime. The dosage is titrated slowly (for example, an increment of 1 to 3 U) every 2 to 3 days if the fasting plasma glucose level reaches the desired target. In contrast, the dosage is reduced if the fasting plasma glucose declines below another specified threshold.

Premixed Insulins: An alternative approach to starting insulin therapy is to use premixed insulin analogues (lispro-protamine or aspart-protamine). One may initiate therapy for the major meal of the day (typically, dinner) and subsequently add another injection at the next largest meal. The insulin dose before breakfast is adjusted by measurement of the glucose level before dinner; the insulin dose before dinner is adjusted primarily by measurement of the fasting glucose concentration on the following day. Use of premixed insulin generally involves 2 injections per day rather than the 4 injections per day required for basal-bolus insulin. In general, however, with use of premixed insulin, the patient must have a fairly constant lifestyle and may have a higher risk of hypoglycemia. If the patient has failed to achieve goals for glycemia with use of a basal insulin regimen, one may institute the premixed insulin regimen with 2 injections per day.

Basal-Bolus Insulin Regimens: In comparison with premixed insulins, a basal-bolus insulin regimen involving 4 injections per day is usually more efficacious and provides greater flexibility for those patients with variable mealtimes and carbohydrate content of meals. In general, before-meal insulin doses for adults can initially be set at about 5 U per meal or about 7% of the daily dose of basal insulin. The before-meal insulin dose can be titrated upward by 2 to 3 U every 2 to 3 days on the basis of monitoring of the 2-hour postprandial glucose level and taking into account the before-meal blood glucose level for the subsequent meal. The dose should be titrated to achieve good control in terms of both the A1C level and the preprandial and postprandial glycemia.

Pramlintide

Pramlintide, an analogue of pancreatic amylin, has been used as an adjunct to prandial insulin therapy in patients with type 1 diabetes and can be helpful in patients with type 2 diabetes for control of postprandial glucose. This involves several additional carefully timed injections immediately before meals.

Insulin Pump

Some patients with type 2 diabetes using basal-bolus insulin therapy benefit from use of an insulin pump (continuous subcutaneous insulin infusion). An insulin pump can provide maximal flexibility with regard to mealtimes, size of meals, exercise, or travel.

Continuous Glucose Monitoring

Some patients with type 2 diabetes clearly benefit from use of continuous glucose monitoring (21). This can educate the patient regarding the glycemic effects of various

foods, help the patient titrate insulin, and provide warnings when the patient is experiencing hyperglycemia or hypoglycemia. Continuous glucose monitoring should be considered in patients with type 2 diabetes receiving insulin therapy whose disease is otherwise difficult to control.

Self-Monitoring of Blood Glucose

When a patient begins insulin therapy, SMBG should be increased in frequency. For patients starting basal insulin therapy at bedtime, the morning fasting blood glucose levels should be determined daily. This same approach applies for the patient initiating premixed insulin therapy before dinner. For each additional injection of insulin, SMBG should be increased in frequency to ensure successful titration of each dose.

Reinforcement of Patient Education

Advancement to insulin therapy is an important opportunity to reinforce patient education with regard to lifestyle modification, diet, exercise, weight management (weight loss or weight maintenance), and other aspects of diabetes education, including prevention, identification, and treatment of hypoglycemia. One may also reevaluate and possibly modify goals for therapy, review the needs for treatment of other commonly associated risk factors (such as hypertension, dyslipidemia, smoking, and stress), and consider therapy with low-dose aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and statins.

Management of Patients With A1C Levels of 7.6% to 9.0%

Management of patients with an A1C value in the range of 7.6% to 9.0% is similar to that just described, except that one can bypass the use of monotherapy and proceed directly to dual therapy because monotherapy is unlikely to be successful in this group. We recommend some changes, however, in the use of dual therapy or triple therapy in this group of patients in comparison with that for patients with A1C ≤7.5%, in view of the need for more efficacious therapy.

Dual Therapy

We consider the following 5 options for dual therapy in patients with this A1C range (Fig. 1):

1. Metformin + GLP-1 agonist
2. Metformin + DPP-4 inhibitor
3. Metformin + TZD
4. Metformin + sulfonylurea
5. Metformin + glinide

Metformin is again the foundation of therapy because of its safety, mechanism of action, and insulin sensitization. Usually, a GLP-1 agonist or a DPP-4 inhibitor is the preferred second component, in view of the safety and efficacy of these agents in combination with metformin. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor, in view of its somewhat greater effect on reducing postprandial glucose excursions and its potential for inducing substantial weight loss. The lower position of TZDs is attributable to their associated risks of weight gain, fluid retention, congestive heart failure, and fractures. Sulfonylureas and glinides are relegated to the lowest position because of their greater risk of inducing hypoglycemia. The relative positions for sulfonylureas and glinides are reversed in comparison with their positions in dual therapy for patients with A1C values ≤7.5%. There is a need for the greater glucose-lowering efficacy of sulfonylureas in the A1C range 7.6% to 9.0%.

Triple Therapy

When dual therapy does not achieve the A1C goal, a third agent should be added. The options for triple therapy for patients with an A1C in this range are similar to those recommended for patients with lower A1C values. We consider the following 5 options:

1. Metformin + GLP-1 agonist + TZD
2. Metformin + DPP-4 inhibitor + TZD
3. Metformin + GLP-1 agonist + sulfonylurea
4. Metformin + DPP-4 inhibitor + sulfonylurea
5. Metformin + TZD + sulfonylurea

Metformin is the foundation to which either a TZD or sulfonylurea is added, followed by incretin-based therapy—either a GLP-1 agonist or a DPP-4 inhibitor. The preference for metformin and the GLP-1 agonist or DPP-4 inhibitor is based on their safety, in view of their minimal associated risks of hypoglycemia. Similarly, TZDs are assigned a priority greater than that for a sulfonylurea because of their low risk of hypoglycemia. A GLP-1 agonist is given a higher priority than a DPP-4 inhibitor owing to its somewhat greater effect on reducing postprandial glucose excursions and the possibility that it might induce considerable weight loss. The combination of metformin, TZD, and sulfonylurea is relegated to the lowest priority because of its increased risk of weight gain for the combination of TZDs and sulfonylureas and the risk of hypoglycemia, particularly for patients at the lower end of this A1C range (~7.5%). Glinides, AGIs, and colesevelam are not considered in this A1C range, in view of their limited A1C-lowering potential.

Insulin Therapy

The considerations for insulin therapy for patients with a current A1C of 7.6% to 9.0% are similar to those discussed previously for patients with an A1C level of 6.5% to 7.5%. When transitioning to insulin from a regimen involving triple therapy, it is customary to discontinue one or more of the orally administered agents. Use of TZDs or

of sulfonylureas conjointly with insulin is associated with a risk of weight gain and fluid retention. In patients at risk, TZDs may cause or aggravate congestive heart failure, and they increase the risk of bone fractures in both women and men (22,23). Neither GLP-1 agonists nor DPP-4 inhibitors have been approved by the FDA for use with insulin. Thus, metformin is the only medication with a relatively clear indication for use in conjunction with insulin in patients with type 2 diabetes. If it becomes clear that a premixed or a basal-bolus insulin regimen is required to achieve glycemic goals, insulin secretagogues should be discontinued. Use of pramlintide should also be considered in patients with persistent postprandial hyperglycemia.

Management of Patients With A1C Levels of >9.0%

Combination Therapy

For drug-naïve patients with A1C levels of >9%, it is unlikely that use of 1, 2, or even 3 agents (other than insulin) will achieve the A1C goal of ≤6.5%. If the patient is asymptomatic, particularly with a relatively recent onset of diabetes, a good probability exists for preservation of some endogenous beta-cell function, implying that dual therapy or triple therapy may be sufficient. We consider the following 8 options:

1. Metformin + GLP-1 agonist
2. Metformin + GLP-1 agonist + sulfonylurea
3. Metformin + DPP-4 inhibitor
4. Metformin + DPP-4 inhibitor + sulfonylurea
5. Metformin + TZD
6. Metformin + TZD + sulfonylurea
7. Metformin + GLP-1 + TZD
8. Metformin + DPP-4 inhibitor + TZD

Metformin provides the foundation. One can add an incretin-based therapy (GLP-1 agonist or DPP-4 inhibitor). It may be preferable to use a GLP-1 agonist, in view of its greater effectiveness at controlling postprandial glycemia and its potential for inducing weight loss. The DPP-4 plus metformin combinations have also demonstrated a robust benefit for drug-naïve patients in this A1C range. In turn, one can add either a sulfonylurea or a TZD. The sulfonylurea is preferred here because of its somewhat greater efficacy and more rapid onset of action. In contrast, if the patient is symptomatic with polydipsia, polyuria, and weight loss, or if the patient has already been receiving treatment and regimens similar to the aforementioned ones have failed, then it is appropriate to initiate insulin therapy without delay.

Insulin Therapy

Insulin therapy for patients with A1C levels exceeding 9.0% follows the same principles as outlined previously for patients with A1C values of ≤9.0%. One can prescribe basal insulin, premixed insulins, or basal-bolus insulin.

Reversal of Glucotoxicity and Lipotoxicity

Insulin therapy, properly instituted, should lower the A1C level to close to the goal of 6.5%. In the process, it is likely that the effects of glucotoxicity and lipotoxicity on the secretory capacity of the beta cell would have been reduced or nearly eliminated. Hence, after one has achieved a meaningful reduction in A1C to a level below 7.5% with use of insulin therapy, one may then attempt use of dual therapy (as described in the foregoing material) as an adjuvant to insulin therapy, with concomitant reduction of insulin to minimize the risks of hypoglycemic events. If these efforts are successful, one can then attempt to discontinue the use of insulin therapy and consider dual therapy or triple therapy.

The AACE/ACE Glycemic Control Algorithm Consensus Panel has constructed a carefully considered rationale for the choice of each of the regimens in Figure 1 and for their order of presentation. These choices, however, are based on general principles and statistical averages for large groups of patients or based on meta-analyses of large-scale studies. When managing the individual patient, the physician must exercise judgment to weigh the benefits and risks, or the pros and cons, of each of these options. A brief useful overview of some of the core considerations for selection of agents or combinations of agents is provided in Table 1. This table is not intended to be a substitute for a comprehensive review of FDA-approved prescribing information.

Hypoglycemia

Perhaps the most important guiding principle of our current algorithm is the recognition of the importance of avoiding hypoglycemia (24-28). Severe hypoglycemia stimulates sympathetic adrenergic discharge, causing arrhythmias or autonomic dysfunction (or both), and has long been recognized to have potential for causing mortality. Hypoglycemia may have a substantial negative clinical effect, in terms of mortality, morbidity, adherence to therapy, and quality of life (24). The recently reported clinical trials of intensive therapy—ACCORD, ADVANCE, and VADT (15-17,20,29)—have shown that intensive glycemic control was associated with a 3- to 4-fold increase in the incidence of hypoglycemia. In the ACCORD study, iatrogenic hypoglycemia was associated with excess mortality in both the intensively treated group and the conventionally treated group (20,29). The risk of hypoglycemia increases with advancing age and duration of diabetes, the duration of insulin therapy (24,28), coexisting severe comorbidities, and the presence of hypoglycemia unawareness.

Insulin and sulfonylurea are the agents that most commonly cause hypoglycemia. The incidence of

hypoglycemia in insulin-treated patients with type 2 diabetes is only one-third that in patients with type 1 diabetes (27). The incidence of hypoglycemia necessitating emergency medical treatment in insulin-treated patients with type 2 diabetes approaches that observed for patients with type 1 diabetes. The glinides, repaglinide and nateglinide, are associated with a lower risk of hypoglycemia, presumably because of a more physiologic time course of action combined with somewhat lower efficacy in comparison with sulfonylureas.

For some patients, the risk of hypoglycemia may warrant specific choices of therapy and reevaluation of therapeutic goals. These patients include those who have a duration of diabetes greater than 15 years and advanced macrovascular disease, hypoglycemia unawareness, limited life expectancy, or other serious comorbidities.

DISCUSSION

The current algorithm (Fig. 1) was developed to assist primary care physicians, endocrinologists, and others in the management of patients with type 2 diabetes. In this algorithm, we consider all classes of effective drugs. We emphasize safety and the quality of glycemic control as our first priorities. Accordingly, we have given sulfonylureas much less priority because use of these agents is associated with hypoglycemia, weight gain, and limited duration of effectiveness after initiation of therapy. Placing greater emphasis on safety and ability to achieve an A1C goal of 6.5% will result in earlier and more frequent use of the incretin-based therapies—the GLP-1 agonists (incretin mimetics) and the DPP-4 inhibitors. At present, only one GLP-1 agonist (exenatide) is available. Two DPP-4 inhibitors (sitagliptin and saxagliptin) are now available. On the basis of the level of ongoing research with these 2 classes of agents, it is likely that several new agents will become available during the next few years. Our algorithm utilizes 4 types of monotherapy, 9 types of dual therapy, and 6 types of triple therapy. We consider 5 types of insulin therapy (basal, premixed, prandial, basal-bolus, and continuous subcutaneous insulin infusion), each of which can be combined with a variety of orally administered agents or with pramlintide.

This algorithm for glycemic control has the following features:

1. It favors the use of GLP-1 agonists and DPP-4 inhibitors with higher priority because of their effectiveness and overall safety profiles. In view of the millions of patients who have benefited from the use of these agents and their excellent performance in a wide range of clinical studies, in combination with the growing literature indicating the serious risks of hypoglycemia, these agents are increasingly preferred for most patients in place of sulfonylureas and glinides.
2. It moves sulfonylureas to a lower priority because of the associated risks of hypoglycemia, weight gain, and the failure of these agents to provide improved glycemic control after use for a relatively short period (1 to 2 years in typical patients).
3. It uses GLP-1 agonists (incretin mimetics) and DPP-4 inhibitors as important components of the therapeutic armamentarium.
4. It includes TZDs as "well-validated" effective agents with demonstrated extended durability of action, but with a lower priority for many patients in light of their potential adverse effects, especially when TZDs are used in combination with sulfonylureas or insulin, and the recent confirmation of previous reports of a significant increase in bone fractures associated with their use in both men and women (22,23).
5. It considers 3 other classes of agents (AGIs, colesevelam, and glinides) only for relatively narrow, well-defined clinical situations, in view of their limited efficacy. The LDL cholesterol-lowering property of colesevelam is a beneficial factor.

This algorithm is intended to provide guidance. Individual institutions, clinics, and physicians may want to modify it to incorporate their own experience and preferences, the nature of their patient populations, secondary considerations such as the availability of medications in their local formulary, and costs. They may also wish to reconsider the choice of agents for inclusion in their formulary.

CONCLUSION AND RECOMMENDATIONS

The current algorithm is intended for use in conjunction with a more detailed and comprehensive guideline—for example, the AACE Diabetes Guidelines (1) and the ACE/AACE Road Maps to Achieve Glycemic Control (10)—and with comprehensive sets of prescribing information and a compendium of drug-drug interactions. This algorithm represents a significant advance relative to most of the other available "treatment pathways" (3-9) by virtue of its inclusiveness, rationale and justification, emphasis on safety, documentation of supporting evidence, simplicity, and anticipated ease of implementation. This algorithm provides a foundation that can be modified in the future as new medications and classes of medications become available or as new data become available regarding the safety, adverse events, efficacy, and long-term outcomes associated with the medications.

APPENDIX 1

OVERVIEW OF THERAPEUTIC AGENTS

Physicians should consult the complete prescribing information and the general literature (for example, 30). The following material is offered as a brief review, a précis. A summary overview of the principal benefits and risks of the therapeutic agents used for management of type 2 diabetes is presented in Table 1 (main text). Further details are provided in the following text.

Metformin

Metformin is a biguanide that improves the effectiveness of insulin in suppressing excess hepatic glucose production, in both the fasting and the postprandial state. Metformin decreases excessive hepatic glucose production in the fasting state primarily by decreasing gluconeogenesis and, to a lesser extent, by decreasing glycogenolysis. Insulin suppression of hepatic glucose production is enhanced in the postprandial state. Thus, metformin is effective in decreasing both fasting and postprandial glucose concentrations. Decreased gastrointestinal glucose absorption, increased insulin sensitivity in peripheral tissues, and enhanced synthesis of GLP-1 may have minor roles. Metformin often has beneficial effects on components of the metabolic syndrome, including mild to moderate weight loss, improvement of the lipid profile, and improved fibrinolysis.

Metformin is effective as monotherapy and in combination with other antidiabetic agents, including sulfonylureas, TZDs, AGIs, DPP-4 inhibitors, GLP-1 agonists, and pramlintide. It can also be used in combination with insulin. Because of it relatively short duration of action, it is usually administered 2 to 3 times daily and is best tolerated if taken with meals. A long-acting, once-daily formulation is also available. The maximal recommended dosage is 2,500 mg daily, although little additional benefit is seen with dosages exceeding 2,000 mg daily.

Side effects include a metallic taste, anorexia, nausea, abdominal pain, and diarrhea. These symptoms are minimized by initiating therapy at a low dosage of 500 mg daily and gradually increasing to the maximal effective dose. Gastrointestinal side effects usually diminish with continued use, although some patients do not tolerate metformin well and discontinue the medication or fail to achieve fully effective doses.

Lactic acidosis is an extremely rare but serious complication of metformin use. Because metformin is primarily excreted by the kidneys, impaired renal function may result in excessive plasma concentrations of metformin and predispose to lactic acidosis. Therefore, impaired renal function is a contraindication for use of metformin. In clinical practice, this is defined as a plasma creatinine concentration of ≥1.5 mg/dL for men and ≥1.4 mg/dL for women or a creatinine clearance of <60 mL/min. Metformin is also contraindicated in patients who are at increased risk for lactic acidosis because of other conditions—for example, patients with congestive heart failure requiring pharmacologic management, elderly patients with decreased creatinine clearance, active liver disease, chronic alcohol abuse, or sepsis, or patients who have other acute illnesses with an associated risk of decreased tissue perfusion or hypoxemia. Metformin is also contraindicated during intravenous administration of radiographic contrast material, which may impair renal function.

When used as monotherapy, metformin has a very low risk of hypoglycemia. When metformin is used in combination with an insulin secretagogue or insulin, however, hypoglycemia may occur. Another rare adverse effect of metformin is megaloblastic anemia due to impaired absorption of vitamin B_{12}. This can be prevented by administration of vitamin B_{12}.

Insulin Secretagogues

Insulin secretagogues include the sulfonylureas, repaglinide, and nateglinide. Sulfonylureas stimulate the delayed, second phase of insulin secretion after meal ingestion and have little effect on first-phase insulin secretion. These characteristics may result in fasting or late postprandial hypoglycemia, which is the most severe adverse side effect of the sulfonylureas.

Repaglinide has a more rapid onset of action and a shorter duration of action in comparison with the sulfonylureas. These features result in earlier insulin secretion and a somewhat decreased risk of late postprandial hypoglycemia. For achievement of maximal benefits, however, administration before each meal is necessary. Nateglinide also has a rapid onset of action and a short duration, increases both the first and second phases of insulin secretion, and is primarily glucose dependent in its action. Like repaglinide, its major effect is to reduce postprandial hyperglycemia, and it should be administered before each meal. Most of the beneficial effects of insulin secretagogues are achieved at submaximal doses, and if adequate glucose control is not achieved, adding a second agent of a different class is generally more effective than increasing the insulin secretagogues to their maximal dosage level. The durability of effectiveness of sulfonylureas is less than with TZDs or AGIs.

The major side effect of sulfonylureas is hypoglycemia. This occurs more commonly with the long-acting sulfonylureas, chlorpropamide and glyburide, than with shorter-acting compounds. Mild to moderate weight gain is frequently observed. When sulfonylureas are used in combination with insulin or TZDs, risks of weight gain, fluid retention, and congestive heart failure are increased.

Thiazolidinediones

The TZDs first became available for treatment of patients with type 2 diabetes in the mid-1990s. The first

approved TZD, troglitazone, was associated with rare cases of liver damage, leading to liver failure and death; therefore, its use was discontinued approximately 10 years ago. The currently available TZDs, pioglitazone and rosiglitazone, are effective insulin-sensitizing agents. These agents increase the insulin sensitivity of skeletal muscle, adipose tissue, and, to a lesser extent, the liver, resulting in increased insulin-stimulated glucose uptake and metabolism and improved insulin-mediated suppression of hepatic glucose production. They also stimulate the formation of pre-adipocytes in peripheral adipose tissue, accompanied by decreases in ectopic fat deposition, plasma free fatty acid concentration, and insulin resistance.

When used as monotherapy or in combination with other antidiabetic agents (including insulin), TZDs are effective in decreasing both fasting and postprandial glucose concentrations. When used as monotherapy, they do not cause hypoglycemia. When TZDs are used with insulin secretagogues or insulin, however, hypoglycemia can occur. The major side effect of the TZDs is weight gain, due to both increased adipose tissue mass and fluid retention. Peripheral edema occurs in some patients and typically responds poorly to loop diuretics and angiotensin-converting enzyme inhibitors. Mild anemia may occur.

The TZDs not only are effective in the management of hyperglycemia but also have beneficial effects on the lipid profile, with lowering of plasma triglycerides, increasing the level of high-density lipoprotein cholesterol, and decreasing small, dense LDL cholesterol. The associated weight gain and fluid retention, however, may precipitate congestive heart failure (19). In patients with New York Heart Association class III or class IV congestive heart failure, TZDs are contraindicated. Weight gain can be a major problem for patients who are overweight or obese. An extensive but highly controversial meta-analysis suggested the possibility of increased ischemic heart disease associated with use of rosiglitazone. Subsequent, more definitive analyses, however, have indicated that rosiglitazone has no effect, positive or negative, on the occurrence of cardiovascular disease. A 1.5- to 2.5-fold increased risk of bone fractures has been documented in both men and women using TZDs (22,23).

α-Glucosidase Inhibitors

The AGIs, acarbose and miglitol, inhibit the conversion of oligosaccharides into monosaccharides at the intestinal brush border and thereby decrease the rise in plasma glucose concentrations after ingestion of complex carbohydrates. Although the main effect of AGIs is to decrease postprandial hyperglycemia in patients with type 2 diabetes, their use is also associated with a slight decrease in fasting glucose concentrations. This change is probably attributable to an overall improvement in glycemic control and reduction of glucose toxicity. They are effective as monotherapy or in combination with other antidiabetic agents, particularly if the diet contains at least 50% carbohydrate.

The major side effects of AGIs are gastrointestinal and include abdominal discomfort, increased formation of intestinal gas, and diarrhea. These adverse gastrointestinal effects are due to excessive amounts of carbohydrate reaching the large intestine and undergoing bacterial fermentation. Acarbose is not substantially absorbed from the gastrointestinal tract, whereas miglitol is absorbed rapidly and excreted by the kidneys. Acarbose, however, is metabolized by bacterial action in the colon, and its metabolites are absorbed, conjugated, and excreted in bile. Rare cases of cholestatic jaundice have been reported. Effectiveness is moderate in people consuming a typical Western diet, and AGIs are most effective when the diet contains large amounts of complex carbohydrates, as is typical of many Asian diets. The risk of hypoglycemia is minimal when AGIs are used as monotherapy. Hypoglycemia may occur when AGIs are used in combination with insulin secretagogues or insulin therapy. When hypoglycemia does occur, it must be treated with glucose, inasmuch as digestion and absorption of sucrose and complex carbohydrates are inhibited by these drugs.

Dipeptidyl-Peptidase-4 Inhibitors

The DPP-4 inhibitors decrease the metabolism of the incretin hormones, GLP-1 and gastric inhibitory polypeptide, by inhibition of the DPP-4 enzyme, which removes the 2 end-terminal amino acids and causes rapid inactivation of these gastrointestinal hormones. Active GLP-1 and gastric inhibitory polypeptide plasma levels are increased approximately 2-fold after meal ingestion. This results in increased first-phase insulin secretion, suppression of glucagon secretion in the postprandial state, and improved suppression of hepatic glucose production and peripheral glucose uptake and metabolism. Hepatic glucose production is also decreased in the fasting state; the result is lower fasting plasma glucose concentrations. Thus, the DPP-4 inhibitors decrease both fasting and postprandial glucose levels. In clinical trials, they have effectiveness similar to that of metformin and sulfonylureas. Because the effects of GLP-1 on insulin and glucagon secretion are glucose dependent, there is insignificant risk of hypoglycemia when it is used as monotherapy or in combination with metformin or a TZD. The currently available DPP-4 inhibitors, sitagliptin and saxagliptin, are conveniently administered once daily. Sitagliptin is eliminated almost entirely by the kidneys; its dosage must be reduced for patients with moderate or severe renal insufficiency. Saxagliptin is likewise primarily excreted by the kidneys but is also subject to hepatic metabolism; its dosage must be reduced only in subjects with severe renal insufficiency. No major

long-term toxicities have been reported. Rare allergic reactions have been described.

Long-Acting GLP-1 Analogues

Currently, one long-term GLP-1 analogue is available for clinical use, although several others are in various stages of development and may become available in the near future. The currently available compound, exenatide, is a biosynthetic version of a salivary peptide from a lizard, the Gila monster. Exenatide has approximately 50% homology to human GLP-1 but is highly resistant to inactivation by the DPP-4 enzyme. The binding of exenatide to the human GLP-1 receptor results in glucose-dependent stimulation of insulin secretion and glucose-dependent suppression of glucagon secretion. Exenatide is administered by injection twice daily and is effective in decreasing both fasting and postprandial plasma glucose concentrations. Exenatide has central nervous system effects to reduce appetite and increase the sense of satiety; the outcome is decreased food intake and weight loss. The major side effects are gastrointestinal, with nausea and vomiting in some patients. These effects are dose related and usually wane over time. Exenatide is administered at a low dosage (5 μg twice daily) for the first 4 weeks of treatment and then increased to a higher dosage (10 μg twice daily) after the gastrointestinal side effects have abated. Overall effectiveness is generally very good when exenatide is added to single- or dual-agent regimens involving metformin, sulfonylureas, or TZDs. Currently, exenatide is not approved for use as monotherapy or in combination with insulin.

Additional effects that have been observed with long-acting GLP-1 agonists are substantial reductions in plasma triglyceride levels, diminished liver fat content, and decreased systolic and diastolic blood pressures. To what extent these are direct effects of the drugs or are attributable to weight loss is not yet clear.

Bile Acid Sequestrants

Colesevelam is a bile acid sequestrant used primarily to treat hypercholesterolemia, either as monotherapy or in combination with hydroxymethylglutaryl-coenzyme A reductase inhibitors. Colesevelam also reduces the blood glucose level in patients with type 2 diabetes mellitus, particularly in persons inadequately controlled with metformin, a sulfonylurea, or insulin. The major side effect of colesevelam is constipation; thus, it should not be used in patients with gastroparesis or other gastrointestinal motility disorders, in patients after major gastrointestinal surgical procedures, and in others at risk for bowel obstruction. Other side effects include an increase in the level of serum triglycerides and possible malabsorption of fat-soluble vitamins.

Pramlintide

Pramlintide is a synthetic analogue that exhibits many of the properties of the natural beta-cell hormone, amylin. When injected preprandially, pramlintide lowers plasma glucagon, delays gastric emptying, and promotes satiety. The major effects are to decrease postprandial hyperglycemia and facilitate weight loss. Pramlintide can be used effectively in the treatment of obese patients with type 2 diabetes who use before-meal insulin injections, with or without orally administered antidiabetic agents. The recommended starting dose is 60 μg (10 U) injected immediately before the main meal; some patients tolerate the medication better with an initial starting dose of 30 μg (5 U) before meals. The dose should then be titrated gradually to 120 μg (20 U), as tolerated. The major side effect is nausea, which generally wanes with continued administration. Pramlintide decreases postprandial glycemic excursions and increases satiety. The dosage of the preprandial rapid-acting insulin may need to be reduced and the time of its administration may need to be delayed to compensate for the expected reduced food intake and delayed gastric emptying associated with pramlintide therapy. Hypoglycemia may also occur if pramlintide is used in combination with a sulfonylurea, and dosages may need to be adjusted appropriately.

Insulin

We consider nine types of insulin (Table A1). These can be administered in any of several regimens (Table A2). Exogenous insulin provides replacement for the deficiency of the natural hormone.

Physiology

Normally, insulin is delivered to the portal vein and thus reaches the liver within seconds. When insulin is administered subcutaneously, a very lengthy delay ensues before it dissociates from hexamer to monomer and is then absorbed into the circulation. Accordingly, regular human insulin administered subcutaneously does not mimic the normal kinetics and dynamics of endogenous insulin. As a result, regular human insulin does not provide adequate effect for control of postprandial glycemic excursions and has a propensity to cause delayed hypoglycemia.

Rapid-Acting Insulin Analogues

The rapidly acting insulin analogues lispro, aspart, and glulisine have a time course of action that closely mimics the normal physiologic features.

Premixed Insulins

Both insulin lispro and insulin aspart are available in mixtures with protamine. These premixed insulins provide a time course that is suitable for coverage for breakfast

Table A1
Outline of Various Types of Insulin

Type of insulin	Trade name	Comment
Rapid-acting insulin analogues		
Aspart	NovoLog	Superior to regular human insulin in terms of more rapid action profile with reduced risk of hypoglycemia 2-5 hours after a meal or overnight
Lispro	Humalog	
Glulisine	Apidra	
Premixed insulin/protamine		
Aspart + aspart-protamine	NovoLog Mix	Usually used twice a day before breakfast and dinner; provides postprandial coverage with 2 injections per day; less flexible than use of basal-bolus therapy with a combination of rapid-acting and long-acting analogues
Lispro + lispro-protamine	Humalog Mix	
Long-acting insulin analogues		
Glargine	Lantus	Can be used with 1 injection per day in patients with type 2 diabetes
Detemir	Levemir	Can be used with 1 injection per day in patients with type 2 diabetes; excellent reproducibility of absorption profile within individuals; possibly less weight gain than with other insulins
Not recommended		
Regular human insulin	Humulin R Novolin R	Onset of action is too slow and persistence of effect is too long to mimic a normal prandial physiologic profile; the result is impaired efficacy and increased risk of delayed hypoglycemia
NPH insulin	Humulin N Novolin N	Does not provide a sufficiently flat "peakless" basal insulin; highly variable absorption even within individuals; increased risk of hypoglycemia compared with the long-acting insulin analogues glargine or detemir

and lunch or for dinner and the overnight period. These mixtures or "biphasic insulins" do not result in 2 discrete peaks. Instead, there is a single maximum at approximately 1.5 hours, followed by a slow decline. Accordingly, they do not mimic the normal physiologic processes and are not as effective as a fully optimized basal-bolus regimen with use of rapidly acting insulin analogues and a long-acting insulin analogue. Use of mixtures of regular human insulin and NPH insulin is not recommended because the maximal activity does not occur until approximately 2 to 2.5 hours after injection.

Basal Insulin

NPH insulin shows wide variability in its absorption rate from day to day, even within individuals, and does not have a sufficiently long time course to provide a basal insulinization for a 24-hour period. It has a pronounced peak at approximately 9 hours. Accordingly, the long-acting insulin analogues glargine and detemir are strongly preferred.

The various types of insulin regimens as shown in Table A2 are discussed in the main body of the text.

Drug-Drug Interactions

Thiazide diuretics, niacin, and β-adrenergic blocking agents are well known to impair glucose homeostasis (31). Systemic administration of glucocorticoids can severely impair glucose tolerance. One should be cautious when initiating therapy with these agents in patients with diabetes and should anticipate an increased risk of hypoglycemia when one of these agents is discontinued. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have demonstrated beneficial metabolic effects.

Table A2
Summary of Insulin Regimens

Insulin regimen	Components and frequency of administration	Injections per day
Basal	Glargine or detemir (daily or twice a day)	1 or 2
Premixed	NovoLog Mix or Humalog Mix (usually twice a day; occasionally used daily or 3 times a day)	2
Prandial	NovoLog, Humalog, or Apidra (usually 3 times a day)	3
Basal-bolus (multiple daily injections)	NovoLog, Humalog, or Apidra (usually 3 times a day) in combination with glargine or detemir (daily)	4
Continuous subcutaneous insulin infusion	NovoLog, Humalog, or Apidra	Continuous

Combined use of any 2 agents that are independently capable of producing hypoglycemia is likely to increase the risk of hypoglycemia. Accordingly, it is customary to reduce the dosage of one or both agents when a second agent is added and to proceed cautiously. The most important interactions of antidiabetic agents are those among sulfonylureas, TZDs, and insulin; combined use of any 2 or all 3 of these agents may result in increased risk of weight gain, retention of fluid, and hypoglycemia.

The combination drug trimethoprim-sulfamethoxazole has been associated with a 6.6-fold increased risk of hypoglycemia (32), and case reports of extreme hypoglycemia have been reported. The "floxacin" antibiotics have been associated with a small risk of hyperglycemia and an even smaller risk of hypoglycemia (33).

There is a strong interaction of gemfibrozil with repaglinide and TZDs, resulting in considerable elevation of plasma levels of repaglinide (34) or TZDs. Fortunately, gemfibrozil is now less commonly used than in the past for management of dyslipidemia. Sulfonylureas are metabolized by CYP2C9. Thus, agents that induce or inhibit CYP2C9 can potentially affect the metabolism of sulfonylureas. Major drug-drug interactions have not been reported for nateglinide.

Metformin is eliminated by tubular secretion and glomerular filtration. Metformin may potentially compete with other cationic drugs, such as cimetidine, for renal secretion (35). In principle, rosiglitazone and pioglitazone metabolism could be affected by inhibitors or inducers of CYP2C8, but substantial drug-drug interactions have not been reported (36,37).

Acarbose and miglitol do not appear to have appreciable metabolic interactions. These drugs are associated with a small decrease in the absorption of digoxin and an increase in absorption of warfarin (38,39). Exenatide may slow absorption of some medications, such as acetaminophen and digoxin. There do not appear to be any important metabolic interactions for sitagliptin.

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The 11-β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor INCB13739 Improves Hyperglycemia in Patients With Type 2 Diabetes Inadequately Controlled by Metformin Monotherapy

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OBJECTIVE — 11-β-hydroxysteroid dehydrogenase type 1 (11βHSD1) converts inactive cortisone into active cortisol, thereby amplifying intracellular glucocorticoid action. The efficacy and safety of the 11βHSD1 inhibitor INCB13739 were assessed when added to ongoing metformin monotherapy in patients with type 2 diabetes exhibiting inadequate glycemic control (A1C 7–11%).

RESEARCH DESIGN AND METHODS — This double-blind placebo-controlled paralleled study randomized 302 patients with type 2 diabetes (mean A1C 8.3%) on metformin monotherapy (mean 1.5 g/day) to receive one of five INCB13739 doses or placebo once daily for 12 weeks. The primary end point was the change in A1C at study end. Other end points included changes in fasting glucose, lipids, weight, adverse events, and safety.

RESULTS — After 12 weeks, 200 mg of INCB13739 resulted in significant reductions in A1C (−0.6%), fasting plasma glucose (−24 mg/dl), and homeostasis model assessment–insulin resistance (HOMA-IR) (−24%) compared with placebo. Total cholesterol, LDL cholesterol, and triglycerides were all significantly decreased in hyperlipidemic patients. Body weight decreased relative to placebo after INCB13739 therapy. A reversible dose-dependent elevation in adrenocorticotrophic hormone, generally within the normal reference range, was observed. Basal cortisol homeostasis, testosterone in men, and free androgen index in women were unchanged by INCB13739. Adverse events were similar across all treatment groups.

CONCLUSIONS — INCB13739 added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone. 11βHSD1 inhibition offers a new potential approach to control glucose and cardiovascular risk factors in type 2 diabetes.

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The phenotypic similarities between obesity, type 2 diabetes, and Cushing's syndrome have sparked considerable interest in the plausible role for endogenous glucocorticoids in the pathogenesis of type 2 diabetes. 11βHSD1 is an 11β-reductase that catalyzes the intracellular conversion of inactive cortisone into active cortisol (1). 11βHSD1 is expressed in specific tissues, most notably in liver, adipose, vasculature, brain, and macrophages (2,3), where it increases intracellular cortisol levels but does not participate in adrenal cortisol biosynthesis from cholesterol. 11βHSD1 activity is elevated in adipose tissue of obese rodents and humans (4,5). Mice engineered with similarly increased adipose tissue 11βHSD1 activity exhibit increased weight and visceral fat mass, insulin resistance, hyperlipidemia, hyperphagia, and hypertension (6,7). Reduction of intracellular glucocorticoid levels via 11βHSD1 gene deletion (8–10), inhibition (11), or ectopic expression of the cortisol-inactivating enzyme 11βHSD2 in adipose tissue (12) is sufficient to drive resistance to weight gain on a high-fat diet, improve glucose tolerance and insulin sensitivity, and attenuate dyslipidemia in rodents. These data suggest that 11βHSD1 inhibition may provide a novel treatment to reduce hyperglycemia and macrovascular disease risk in type 2 diabetes.

INCB13739 is an oral and selective 11βHSD1 inhibitor being developed to treat type 2 diabetes. We conducted a 12-week dose-ranging study of INCB13739 added to ongoing metformin monotherapy in patients with type 2 diabetes to evaluate the safety and efficacy of this compound.

RESEARCH DESIGN AND METHODS

— This was a double-blind randomized paralleled trial conducted at 74 sites in the U.S. and six sites in Puerto Rico (NCT00698230). The study consisted of five periods: screening, metformin dose stabilization, 14-day pla-

cebo single-blind run-in, 12-week double-blind treatment, and 3-week off-treatment follow-up. The study was conducted pursuant to the Declaration of Helsinki and was approved by institutional review boards at participating sites. Patients provided informed consent before screening.

Patients (18–75 years) with type 2 diabetes, a BMI between 25 and 45 kg/m^2, and A1C between 7–11% while taking metformin monotherapy at a stable dose for ≥10 weeks were eligible. Exclusion criteria included a medical history of disorders involving glucocorticoid, mineralocorticoid, or androgen excess; a history of type 1 diabetes or secondary forms of diabetes; previous insulin therapy; triglycerides >500 mg/dl; and treatment with any oral, systemic, topical, or inhaled glucocorticoids, thiazolidinediones, or exenatide within 3 months of screening. No inclusion criteria were specified for cholesterol or blood pressure and patients could enter the study on (and maintain) any hypolipidemic or antihypertensive regimen.

Patients were randomized equally to once-daily INCB13739 (5, 15, 50, 100, or 200 mg) or placebo. Dose selection was based on phase 1 pharmacokinetic and pharmacodynamic data, with the goal of evaluating regimens that achieve different degrees of inhibition, from <50 to >90%, with the duration of inhibition varying across the five dose levels. Patients with a fasting plasma glucose (FPG) >270 mg/dl through week 8 or >240 mg/dl subsequently were discontinued and offered rescue therapy.

The primary end points were the change from baseline to week 12 compared with placebo in A1C, safety, and tolerability. Secondary end points included the change from baseline to week 12 compared with placebo in FPG and lipid profiles and the proportion of patients achieving an A1C ≤7% at week 12. Tertiary end points included the change from baseline in homeostasis model assessment–insulin resistance (HOMA-IR), weight, blood pressure, and the proportion of patients meeting rescue therapy criteria.

Study assessments

On-treatment study visits occurred at weeks 2, 4, 8, and 12 and a follow-up visit at week 15 off treatment. Fasting blood samples were collected after a minimum 10-h fast. Salivary samples were collected between 2200 and 2400. All assays were performed by Covance Central Labs. Monitoring for adverse events (AEs) (intensity, duration, outcome, and causality), physical examinations, vital signs, body weight and morphometrics, 12-lead electrocardiograms, and safety laboratory assessments including hematology, serum chemistry, and urinalysis were also performed.

Statistical analysis

There were 40 patients per group completing week 12 who provided 90% power to detect a mean 0.6% difference in A1C between the 200-mg group and placebo assuming an E_{max} dose-response model (13) with a half-maximal stimulation (ED_{50}) of 30 mg and an SD in A1C of 1.2%. This E_{max} model is commonly used for phase 2 dose-ranging studies and was prespecified with the following optimal linear contrast: −0.45666 (placebo), −0.31381 (5 mg), −0.12333 (15 mg), 0.168336 (50 mg), 0.312566 (100 mg), and 0.412901 (200 mg) based on the half-maximal concentration (ED_{50}) = 30 mg assumption. The study was powered for A1C alone and not for lipids or blood pressure. Two populations were prespecified: the evaluable analysis set was defined as all patients randomized who have completed the 12 weeks of study treatment with ≥80% compliance; and the full analysis set was defined as all patients randomized who have taken at least one dose of study drug with any missing week 12 data imputed by last observation carried forward. The A1C and FPG end points were prespecified to be analyzed using the evaluable analysis set; all other efficacy end points were prespecified to be analyzed using the full analysis set.

For all end points, treatment effect was assessed using a linear model with treatment as the model factor and baseline as a covariate. Changes from baseline were estimated with 90% CIs from the model.

RESULTS — The disposition of patients is in supplementary Fig. 1, found in an online appendix available at http://care.diabetesjournals.org/cgi/content/full/dc09-2315/DC1. Baseline assessments were performed in 302 patients who entered the treatment phase of the study, and 228 patients (75%) completed the 12-week treatment period. The most common reasons for discontinuation were loss to follow-up (5%), withdrawal of consent (5%), lack of efficacy (4%), noncompliance with study procedures/medication (4%), and adverse events (4%), none of which related to the dose level of study medication. The clinical characteristics of the population at baseline were similar between treatment groups (supplementary Table 1): the mean duration of diabetes was 6.2 years, BMI 32.4 kg/m^2, A1C 8.3%, and FPG 173 mg/dl.

Efficacy

At week 12, treatment with INCB13739 resulted in a dose-dependent reduction in A1C (P_{Emax} = 0.016; Table 1, Fig. 1*A*). The placebo-adjusted least-squares (LS) mean difference from baseline in A1C reached statistical significance for the 100-mg (−0.47%; $P < 0.05$) and 200-mg (−0.56%; $P < 0.01$) groups. A1C decreased compared with placebo in a time-dependent manner, reaching its maximum at week 12 (Fig. 1*B*). A greater proportion of patients (25%) randomized to 100 or 200 mg INCB13739 achieved an A1C <7% when compared with placebo (9.5%) at week 12. In a predefined subgroup analysis in patients with a baseline A1C ≥8%, the response to INCB13739 was more pronounced, with the 50-, 100-, and 200-mg groups achieving a significant ($P < 0.05$) change in A1C from baseline of −0.65 to −0.72%. The placebo-adjusted change in A1C for the 100- and 200-mg groups was greater in subjects with a baseline BMI >30 kg/m^2 (−0.53% and −0.93%, respectively) than in subjects with a baseline BMI ≤30 kg/m^2 (−0.35% and −0.17%, respectively). The number of patients requiring rescue therapy (12) did not differ significantly between treatment groups. FPG decreased in a dose- and time-dependent manner in the 100- and 200-mg treatment groups (Fig. 1*C*) and reached statistical significance ($P < 0.01$) from placebo in the 200-mg group with an LS mean difference of −24.1 mg/dl. A dose-dependent reduction in HOMA-IR was observed, reaching significance ($P < 0.05$) in the 200-mg group with an LS mean difference of −1.32 (−24%), suggesting an insulin-sensitizing mechanism of action.

Body weight decreased with INCB13739 treatment, with statistical significance from baseline ($P < 0.05$) achieved in the 15 (−0.6 kg), 100 (−1.1 kg), and 200 mg (−0.9 kg) treatment groups (Table 1). Waist-to-hip ratio did not change with treatment.

Plasma lipids and blood pressure were generally well controlled at baseline (supplementary Table 1). Treatment with

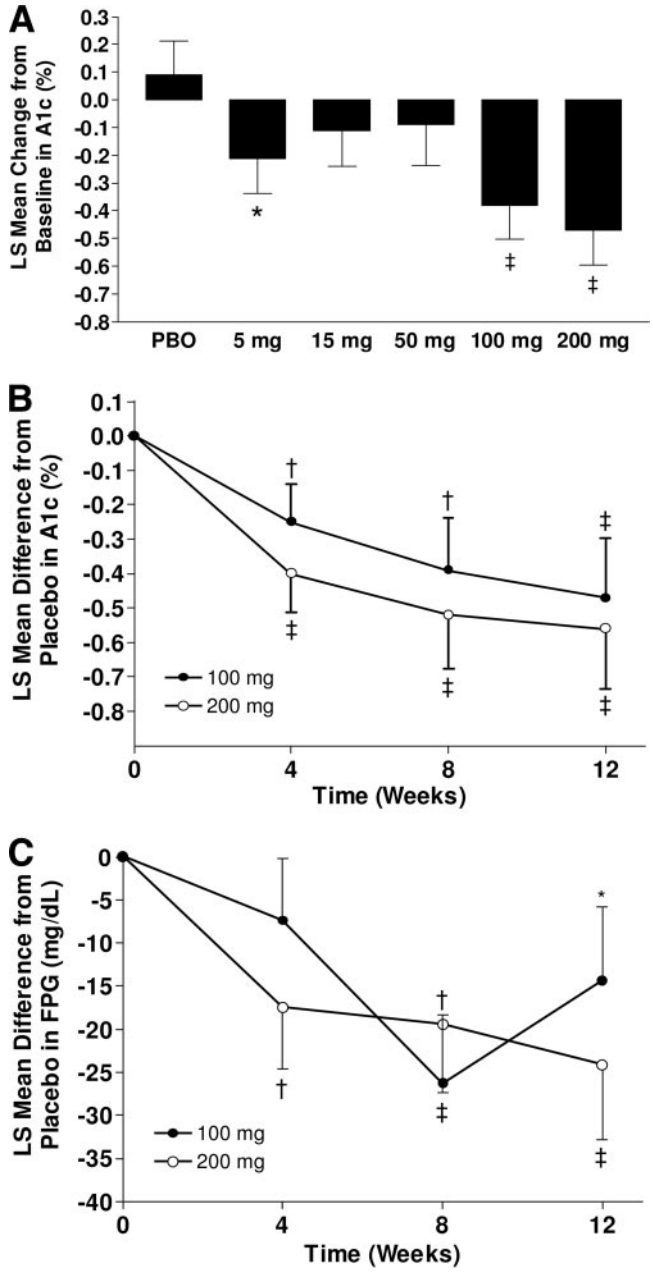

Figure 1—*Glycemic efficacy. A: LS mean (SE) change from baseline in A1C at week 12. B: LS mean difference (SE) from placebo in A1C from baseline to week 12 in the 100-mg (●) and 200-mg (○) treatment groups. C: LS mean difference (SE) from placebo in FPG from baseline to week 12 in the 100- and 200-mg treatment groups. *P < 0.1, †P < 0.05, ‡P < 0.01, active vs. placebo (PBO).*

INCB13739 resulted in a modest dose-dependent (P_{trend} = 0.026) decrease in total cholesterol, reaching a maximum of −7 mg/dl (−3%) from baseline in the 200-mg group (Table 1). In a prespecified analysis, patients with Adult Treatment Panel (ATP) III defined hyper-lipidemia (total cholesterol >200 mg/dl; LDL cholesterol >130 mg/dl) or hyper-triglyceridemia (>200 mg/dl) at baseline exhibited a greater improvement, reaching statistical significance ($P < 0.05$) in the 100-mg group for all three lipid categories (cholesterol −16 mg/dl, −6%; LDL −17 mg/dl, −10%; triglycerides −74 mg/dl, −16%). Similar responses were observed in the 200-mg group, but these did not reach significance, possibly because of the smaller size of the subgroups. Changes in HDL and free fatty acids were not significantly different between the treatment groups. Systolic and diastolic blood pressure did not change appreciably during the study.

Safety

Treatment with INCB13739 was well tolerated and AEs were reported at similar frequencies across all treatment groups (Table 2). No drug-related serious AEs occurred in the trial. One death occurred in the 200-mg group because of complications after a serious AE of acute ischemia of the lower extremities. This AE occurred ~2 weeks after the last dose of study medication in a subject with preexisting congestive heart failure and aortic valvular disease. The death was due to cardiac arrest immediately after induction of anesthesia before bilateral iliofemoral embolectomy. The AE was judged by the investigator as unrelated to study medication. No hypoglycemic events were reported during the treatment phase of the trial. The most frequent AEs reported were typical for this population and did not exhibit dose dependence. There were four reports of nausea in the 200-mg group (compared with one in the placebo group); however, all of these resolved during continued dosing and three were categorized by the investigator as unrelated to study medication. There were no clinically relevant differences between treatment groups in electrocardiograms, hematology, serum chemistry, or urinalysis.

The anticipated compensatory activation of the hypothalamic-pituitary-adrenal axis to overcome reduced cortisol regeneration on 11βHSD1 inhibition was evaluated. INCB13739 caused a dose-related increase in morning plasma ACTH and the ACTH-sensitive adrenocorticosteroid dehydroepiandrosterone sulfate (DHEAS) levels, although mean concentrations of both hormones remained within laboratory reference ranges (Table 2). ACTH and DHEAS rises after INCB13739 reached a plateau at week 4 (+102 and +54%, respectively, versus +19 and +6% in the placebo group); did not exhibit a further increase at week 12, even in the 200-mg treatment group (+114% and +55%, respectively); and returned to baseline levels by the 3-week follow-up visit (Fig. 2*A* and *B*). Morning plasma cortisol and evening salivary cortisol levels were unaltered by INCB13739 at any dose (Fig. 2*C*), suggesting that the rise in ACTH was a compensatory response.

DHEAS is a precursor for androgen biosynthesis. INCB13739 treatment resulted in a dose-related increase in morn-

Table 1—*Efficacy assessments*

	Placebo	5 mg	15 mg	50 mg	100 mg	200 mg
Baseline A1C (%)	8.3 ± 1	8.2 ± 1	8.3 ± 1	8.3 ± 1	8.2 ± 1	8.2 ± 1
A1C (%)	0.09 ± 0.1	−0.21 ± 0.1*‖	−0.11 ± 0.1	−0.09 ± 0.2	−0.38 ± 0.1†‖	−0.47 ± 0.1‡#
A1C ≥8%	−0.10 ± 0.2	−0.39 ± 0.2‖	−0.24 ± 0.2	−0.65 ± 0.3*‖	−0.72 ± 0.2†‖	−0.65 ± 0.2*#
Subgroup *n*	23	23	18	11	16	19
BMI >30 kg/m^2	0.17 ± 0.1	−0.24 ± 0.2*§	−0.10 ± 0.2	−0.25 ± 0.2*	−0.36 ± 0.2†	−0.76 ± 0.2‡#
Subgroup *n*	29	23	26	15	26	18
Baseline FPG (mg/dl)	179 ± 51	172 ± 41	175 ± 44	178 ± 53	170 ± 64	165 ± 41
FPG (mg/dl)	12.6 ± 6.1	6.0 ± 6.3	2.3 ± 6.4	−4.7 ± 7.2*	−1.6 ± 6.1*	−11.5 ± 6.2‡§
C-peptide (pmol/l)	−9.48 ± 40	−9.84 ± 41	−14.0 ± 41	−39.6 ± 45	−32.2 ± 39	−47.4 ± 40
HOMA-IR	0.25 ± 0.4	−0.29 ± 0.4	0.33 ± 0.4	−0.42 ± 0.5	−0.51 ± 0.4	−1.06 ± 0.4†‖
HOMA-B	−3.9 ± 4.1	−3.92 ± 4.2	4.78 ± 4.2	6.67 ± 4.6*	−2.35 ± 4.1	2.58 ± 4.1
Cholesterol (mg/dl)	1.2 ± 4	−0.7 ± 4	−1.2 ± 4	−3.9 ± 4	−6.6 ± 4*	−7.3 ± 4*
≥200 mg/dl	−10.0 ± 6	−11.6 ± 5	−12.4 ± 7	1.5 ± 7	−16.2 ± 5‖	−18.5 ± 6§
Subgroup *n*	19	22	14	12	28	20
LDL cholesterol (mg/dl)	2.3 ± 4	−1.2 ± 4	0.4 ± 4	−7.0 ± 4§	−4.6 ± 3§	−4.3 ± 3
≥130 mg/dl	−8.5 ± 8	−19.3 ± 8	−9.7 ± 9	−8.5 ± 13	−17.0 ± 6‖	−14.3 ± 8
Subgroup *n*	12	10	9	6	18	12
HDL cholesterol (mg/dl)	0.8 ± 1.3	−0.4 ± 1.2	1.2 ± 1.3	1.2 ± 1.4	0.4 ± 1.2	0.8 ± 1.2
<40 mg/dl	3.5 ± 1.9§	0.8 ± 2.0	2.7 ± 1.6	2.7 ± 1.7	5.0 ± 2.0	1.9 ± 1.8
Subgroup *n*	13	12	21	17	14	14
Triglyceride (mg/dl)	0.0 ± 12	−4.4 ± 12	−27.4 ± 5	−12.4 ± 13	−11.5 ± 12	−10.6 ± 12
≥200 mg/dl	−19.5 ± 28	−3.5 ± 28	−105.3 ± 31	−57.5 ± 29	−74.3 ± 27‖	−55.8 ± 29
Subgroup *n*	16	17	13	15	18	15
FFA (mmol/l)	0.0 ± 0.03	−0.03 ± 0.03	0.02 ± 0.03	−0.01 ± 0.03	−0.03 ± 0.03	0.0 ± 0.03
Systolic blood pressure (mmHg)	0.9 ± 1.6	−0.3 ± 1.5	0.17 ± 1.6	1.2 ± 1.6	0.5 ± 1.5	−0.4 ± 1.5
Diastolic blood pressure (mmHg)	1.2 ± 1.0	0.0 ± 1.0	1.4 ± 1.0	−0.2 ± 1.1	−0.5 ± 1.0	−0.8 ± 1.0
Weight (kg)	−0.2 ± 0.3	−0.5 ± 0.3§	−0.6 ± 0.4‖	0.0 ± 0.4	−1.1 ± 0.3*‖	−0.9 ± 0.3#
Waist-to-hip ratio	−0.01 ± 0.01	0.02 ± 0.01*	0.0 ± 0.01	−0.01 ± 0.01	−0.02 ± 0.01	−0.01 ± 0.01

Data are LS mean change from baseline ± SEM unless noted. *$P < 0.1$, †$P < 0.05$, ‡$P < 0.01$, active vs. PBO. §$P < 0.1$, ‖$P < 0.05$, #$P < 0.01$, week 12 vs. baseline.

ing fasting serum androstenedione (A4), although mean concentrations remained within the laboratory reference range (Table 2). In males, there were no differences between treatment groups in total testosterone, sex hormone–binding globulin (SHBG), or free androgen index (FAI). In females, total testosterone (available at baseline and week 8) increased in a dose-dependent manner with mean concentrations within the laboratory reference range. Maximal concentrations were observed in the 200-mg group (1.8 vs. 1.3 nmol/l in the placebo group; $P < 0.05$). These changes occurred alongside modest increases in SHBG (assessed at week 12), apparent in the 50- and 100-mg groups ($P < 0.05$), but not the 200-mg group. Importantly, there were no significant differences between treatment groups in calculated FAI in females (placebo = 6.9; INCB13739 range = 5.7–8.2).

CONCLUSIONS — The results from this study indicate, for the first time, that decreasing local cortisol exposure through 11βHSD1 inhibition improves hyperglycemia over 12 weeks in patients with type 2 diabetes. The addition of once-daily INCB13739 in patients inadequately controlled with metformin significantly reduced A1C, FPG, and HOMA-IR. These effects were dose dependent, and the greatest improvements were achieved at the highest dose administered (200 mg), with evidence for a more profound A1C reduction in subjects with a BMI >30 kg/m^2, compatible with elevated 11βHSD1 in adipose tissue in obesity. Preliminary data from pharmacokinetic analyses (data not shown) indicate that the 100- and 200-mg groups achieved, 4 h after administration, mean free drug exposures that reached 100 mg or exceeded 200 mg, the concentrations required to inhibit 90% of the enzyme activity in cellular assays; however, only the 200-mg group retained such a mean exposure at the end of the dosing interval. Thus, glycemic efficacy may be associated with a high degree of enzyme inhibition, and it is possible that greater glycemic improvement might be achieved with increased dose levels or frequency of administration.

Plasma lipids were generally well controlled in this population, and 30% of patients were receiving lipid-lowering medications. INCB13739 treatment resulted in a dose-dependent reduction in total cholesterol, and while of modest magnitude, these changes also associated with directional beneficial trends in LDL cholesterol and triglycerides. Of interest, patients who met ATP III criteria for "borderline high" LDL cholesterol (>130 mg/dl), total cholesterol (>200 mg/dl), or "hyper-triglyceridemia" (>200 mg/dl) exhibited a larger improvement in all three lipid parameters. The magnitude of effect was equivalent in the 100- and 200-mg groups, reaching statistical significance for the 100-mg group, which had the largest subgroup size.

INCB13739 treatment resulted in a dose-dependent modest decrease in body weight of ~1 kg at the highest dose stud-

Table 2—*End point endocrine assessments and safety summary*

	Reference range	Placebo	5 mg	15 mg	50 mg	100 mg	200 mg
Endocrinology							
ACTH	1.6–13.9 pmol/l	4.9 ± 0.9	8.3 ± 0.9‡	7.1 ± 0.9	9.2 ± 1.0‡	9.4 ± 0.9‡	11.2 ± 0.9‡
Aldosterone	111–859 pmol/l	218 ± 23	198 ± 24	208 ± 25	204 ± 28	204 ± 23	276 ± 24
Renin	3.5–65.6 pg/ml	24.9 ± 7.6	26.0 ± 7.5	38.1 ± 7.8	19.8 ± 8.7	18.7 ± 7.3	28.0 ± 7.5
DHEAS, ♂	0.14–18.73 μmol/l	4.1 ± 0.6	3.7 ± 0.6	5.2 ± 0.6	5.0 ± 0.7	5.4 ± 0.6	6.6 ± 0.7‡
DHEAS, ♀	0.19–10.61 μmol/l	2.3 ± 0.6	3.5 ± 0.7	4.2 ± 0.6†	3.4 ± 0.7	3.5 ± 0.6	4.0 ± 0.6†
A4, ♂	0.8–2.9 ng/ml	1.7 ± 0.2	1.5 ± 0.1	2.1 ± 0.2	1.7 ± 0.2	2.1 ± 0.2	2.6 ± 0.2‡
A4, ♀	<1.0–4.3 ng/ml	1.1 ± 0.2	1.6 ± 0.3	1.9 ± 0.3†	2.2 ± 0.3‡	1.6 ± 0.2	1.8 ± 0.2†
T, ♂	6.1–27.1 nmol/l	12.7 ± 0.9	11.5 ± 0.8	10.4 ± 0.9	12.0 ± 1.0	11.3 ± 0.9	13.9 ± 0.9
T[a], ♀	<0.4–2.6 nmol/l	1.3 ± 0.4	1.5 ± 0.3	1.7 ± 0.8†	1.6 ± 0.5	1.6 ± 0.6	1.8 ± 0.8†
SHBG, ♂	7–70 nmol/l	25.9 ± 3.2	29.9 ± 2.8	20.6 ± 3.1	23.5 ± 3.7	20.8 ± 3.1	29.7 ± 3.4
SHBG, ♀	15–120 nmol/l	23.0 ± 5.1	27.1 ± 6.1	30.8 ± 5.8	39.9 ± 6.4†	40.0 ± 5.1†	24.9 ± 5.1
FAI, ♂	NA	63.9 ± 5.8	43.5 ± 5.0	60.2 ± 5.5	55.8 ± 6.6	62.7 ± 5.7	53.3 ± 6.2
FAI[a], ♀	NA	6.9 ± 1.1	7.9 ± 1.3	8.2 ± 1.2	5.7 ± 1.4	7.2 ± 1.1	7.9 ± 1.1
Safety and tolerability							
≥1 AE		23 (46)	25 (49)	22 (44)	27 (57)	25 (47)	20 (39)
Rx-related*		3 (6)	8 (16)	8 (16)	9 (19)	4 (8)	5 (10)
≥1 SAE		0 (0)	1 (2)	0 (0)	0 (0)	1 (2)	1 (2)
Rx-related*		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
d/c for AE		2 (4)	2 (4)	2 (4)	3 (6)	1 (2)	1 (2)
AEs occurring in ≥3%							
Nasopharyngitis		1 (2)	4 (8)	3 (6)	5 (11)	3 (6)	1 (2)
Diarrhea		3 (6)	3 (6)	1 (2)	3 (6)	3 (6)	1 (2)
Upper respiratory tract infection		3 (6)	3 (6)	2 (4)	2 (4)	2 (4)	1 (2)
Headache		3 (6)	2 (4)	5 (10)	1 (2)	1 (2)	0 (0)
Arthralgia		0 (0)	7 (14)	1 (2)	2 (4)	0 (0)	0 (0)
Cough		0 (0)	1 (2)	2 (4)	1 (2)	3 (6)	2 (4)
Nausea		1 (2)	2 (4)	0 (0)	1 (2)	1 (2)	4 (8)

Endocrine data are week 12 LS mean ±SEM unless otherwise noted. Androgens and their precursors are categorized by sex. Central lab normal reference ranges are provided. Treatment emergent AE data are *n* (%) for all AEs or for those occurring in at least 3% of patients. A4, androstenedione; d/c, discontinuation; FAI, free androgen index; SAE, serious adverse event; T, testosterone. *Determined by the investigator to be possibly, probably, or definitely drug related. †$P < 0.05$; ‡$P < 0.01$, active vs. PBO. [a]T♀ and FAI♀ reflects week 8 concentrations.

ied. This change was time dependent and did not plateau over the 12-week treatment period (data not shown). The thiazolidinedione insulin sensitizers increase body weight through adipocyte differentiation (14,15). As cortisol can drive adipocyte differentiation and expansion (16), it is possible that attenuating cortisol signaling in adipose may decrease adipocyte size. This has been reported in preclinical models with an 11βHSD1 inhibitor (17) and suggests the potential for positive effects of INCB13739 on total body weight and/or regional adiposity with longer exposure.

INCB13739 was well tolerated at all dose levels, and there were no differences in AE frequency relative to placebo nor were there any apparent dose-dependent changes in AEs.

While 11βHSD1 is not involved in adrenal cortisol biosynthesis, 11βHSD1 activity within the splanchnic bed does contribute ~25% of total cortisol production (18). An expected consequence of 11βHSD1 inhibition is increased clearance of cortisol and compensatory hypothalamic-pituitary-adrenal axis activation to maintain blood cortisol concentrations. INCB13739 treatment did result in a dose-related increase in ACTH levels that was generally within the normal reference range. The ACTH response reached a plateau with the 50-mg dose at week 4, suggesting that the maximal response to INCB13739 had been realized. This plateau in ACTH and its rapid return to baseline levels after cessation of therapy are consistent with an adaptive endocrine process driven by reversible 11βHSD1 inhibition. Importantly, cortisol levels and circadian rhythm were unaltered by INCB13739 treatment. These data indicate normal hypothalamic-pituitary-adrenal axis function after 12 weeks of INCB13739 therapy that adjusted appropriately to the inhibition of 11βHSD1 activity to maintain basal cortisol homeostasis. The leftward shift in the ACTH dose relationship relative to efficacy might reflect a greater contribution of hepatic 11βHSD1 inhibition to splanchnic cortisol reactivation.

Aldosterone and renin were unaltered by INCB13739 treatment (Table 2), and serum electrolytes were unchanged (supplementary Table 2). Modest elevations in the androgenic precursors DHEAS and A4 paralleled changes in ACTH. Like ACTH, these changes were generally within the reference range, plateaued with respect to both dose and time, and were reversed at follow-up. The highest concentration of DHEAS observed in this study (13.2 μmol/l in males and females) is equivalent to levels observed after 50 mg/day dehydroepiandrosterone supplement use (19). In men, there was no change in plasma testosterone, SHBG, or FAI after INCB13739 treatment, consistent with the testes being the main source of androgens. In females, a modest rise in

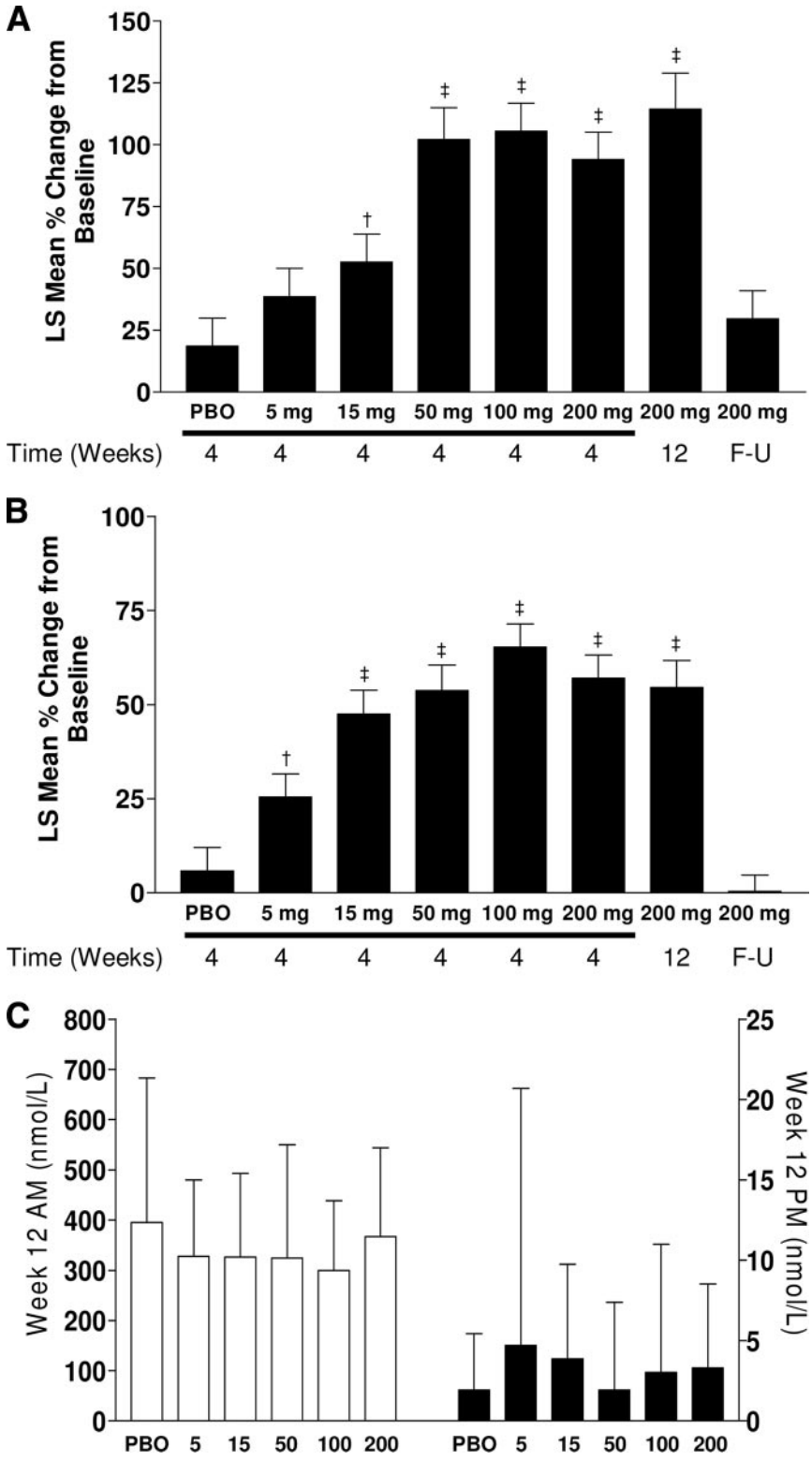

Figure 2—*Change in ACTH, DHEAS, and cortisol. A: LS mean percent (%) change (SE) from baseline in ACTH by treatment group and time on therapy. B: LS mean percent (%) change (SE) from baseline in DHEAS by treatment group and time on therapy. C: LS mean (SE) cortisol concentrations at week 12 in the morning (plasma concentrations,* □*,* left axis*) or at night (salivary concentrations,* ■*,* right axis*). F-U, follow-up. †P < 0.05, ‡P < 0.01, active vs. placebo (PBO).*

total testosterone at week 8 was observed that was paralleled by a rise in SHBG such that the resulting FAI calculation was not significantly different in any INCB13739 group compared with placebo or baseline levels. SHBG is known to increase in response to improved insulin sensitivity (20), and whether the changes observed in this study reflect this or result from more complex endocrine adaptation to small changes in total testosterone are unknown. Importantly, FAI is an accepted surrogate in clinical practice for free testosterone and a marker of biologic androgen activity in women (21). No signs or symptoms of androgen excess were observed, and longer-term studies will be required to ascertain the clinical relevance of the small androgen changes observed.

In summary, in patients with type 2 diabetes who had inadequate glycemic control with metformin alone, the addition of once-daily INCB13739 was well tolerated and resulted in significant improvements in A1C, FPG, and HOMA-IR. INCB13739 treatment decreased body weight and improved cholesterol and triglycerides in patients with hyperlipidemia at baseline. 11βHSD1 inhibition offers a new potential approach to control glucose and cardiovascular risk factors in type 2 diabetes. Further clinical characterization of INCB13739 with long-term controlled studies is warranted.

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The Effect of Oral Antidiabetic Agents on A1C Levels

A systematic review and meta-analysis

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OBJECTIVE — Previous reviews of the effect of oral antidiabetic (OAD) agents on A1C levels summarized studies with varying designs and methodological approaches. Using predetermined methodological criteria, we evaluated the effect of OAD agents on A1C levels.

RESEARCH DESIGN AND METHODS — The Excerpta Medica (EMBASE), the Medical Literature Analysis and Retrieval System Online (MEDLINE), and the Cochrane Central Register of Controlled Trials databases were searched from 1980 through May 2008. Reference lists from systematic reviews, meta-analyses, and clinical practice guidelines were also reviewed. Two evaluators independently selected and reviewed eligible studies.

RESULTS — A total of 61 trials reporting 103 comparisons met the selection criteria, which included 26,367 study participants, 15,760 randomized to an intervention drug(s), and 10,607 randomized to placebo. Most OAD agents lowered A1C levels by 0.5−1.25%, whereas thiazolidinediones and sulfonylureas lowered A1C levels by ~1.0–1.25%. By meta-regression, a 1% higher baseline A1C level predicted a 0.5 (95% CI 0.1–0.9) greater reduction in A1C levels after 6 months of OAD agent therapy. No clear effect of diabetes duration on the change in A1C with therapy was noted.

CONCLUSIONS — The benefit of initiating an OAD agent is most apparent within the first 4 to 6 months, with A1C levels unlikely to fall more than 1.5% on average. Pretreated A1C levels have a modest effect on the fall of A1C levels in response to treatment.

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Type 2 diabetes is a chronic, progressive disease that requires ongoing attention to lifestyle and pharmacotherapy to achieve and maintain optimal glucose control (1). Declining β-cell function and increasing insulin resistance over time lead to deteriorating glycemic control and the need for increasingly intense pharmacotherapy (1). Glycemic control is achieved by lifestyle and pharmacotherapy that targets fasting and postprandial glucose levels, as well as A1C levels—a measurement that reflects both fasting and postprandial glucose concentrations over a 3-month period (2).

Summaries of previous studies of oral antidiabetic drugs (OADs) suggest that they reduce A1C levels by 0.5–1.5% (2). However, this estimated drop in A1C was based on summaries of studies with varying designs, which may have led to over- or underestimates of the true effect of OADs. These summaries included studies with varying completeness of follow-up for both treatment and placebo groups, use of placebo control subjects, sample sizes, and durations of follow-up (3–6). We therefore completed a systematic review and meta-analysis of only those studies that met predetermined methodological criteria to estimate the effect of OADs on A1C levels.

RESEARCH DESIGN AND METHODS

Search strategy

We searched all relevant biomedical databases, including the Medical Literature Analysis and Retrieval System Online (MEDLINE), the Excerpta Medica (EMBASE), and the Cochrane Central Register of Controlled Trials. In consultation with a medical librarian, we developed a search strategy based on an analysis of medical subject headings, terms, and key text words from January 1980 to the present. A start date of January 1980 was intentionally chosen because A1C assays were becoming routinely available in the early 1980s (7). We combined terms for randomized controlled trials, placebo controlled trials, type 2 diabetes, oral hypoglycemics, OAD agents, and the classes of OADs including α-glucosidase inhibitors (acarbose and miglitol), biguanides (metformin), meglitinides (repaglinide and nateglinide), sulfonlyureas (glyburide, glimepiride, glipizide, glucotrol XL, gliclazide, and gliclazide MR), thiazolidinediones (TZDs) (rosiglitazone and pioglitazone), and dipeptidyl peptidase-4 (DPP-4) inhibitors (sitagliptin and vildagliptin) (2). Reference lists from relevant meta-analyses, systematic reviews, and clinical guidelines were also examined. Online Appendix Fig. 1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc09-1727) shows the search and selection process.

Study selection

All citations retrieved were reviewed against predetermined eligibility criteria. To be included, studies had to written in English, in a peer-reviewed journal between January 1980 and May 2008, and meet the following criteria: *1*) be a randomized, double-blind, placebo-controlled trial; *2*) report data on nonpregnant participants aged 18 and older with type 2 diabetes; *3*) report the differ-

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ential effect of the addition of an OAD versus placebo on the A1C level; *4*) report the effect of a single OAD versus placebo in subjects who were either drug naïve or on background therapy with an OAD and/or insulin; *5*) include at least 50 subjects in each arm; and *6*) report the effect of therapy on the A1C level in at least 70% of the randomized participants after a minimum of 12 weeks in every arm of the study (placebo and treatment arms). Studies were excluded if: *1*) they reported data on subjects who did not have type 2 diabetes; *2*) they reported data from first-generation sulfonylurea drugs or OADs withdrawn for safety reasons in any country; *3*) the intervention included the initiation of two OAD agents at the same time; or *4*) there was no statement that informed consent was obtained.

Data extraction

Two investigators (D.S. and K.N.) independently reviewed the titles, abstracts, and full articles for inclusion by using standardized forms. Discrepancies in eligibility were discussed between reviewers until agreement was achieved. Data abstraction was independently completed by two authors (D.S. and K.N.) and compared for accuracy. Items abstracted pertained to study characteristics, patient characteristics, and outcome results. As the main objective of this review and meta-analysis was to determine the effectiveness of OADs on A1C levels, rates of adverse events and hypoglycemia were not considered. The complete list of data abstracted is described in Online Appendix Table 1. A1C levels that were abstracted were those derived from any randomized subject who had an A1C level done within any given time interval. Unadjusted mean differences in A1C levels were collected. Authors were also contacted for further clarification regarding follow-up data at various time intervals and A1C values.

Statistical analysis

Data were categorized in the following time intervals after randomization: 12; 13–18; 19–24; 25–39; 40–47; 48–55; and 56–104 weeks. The mean difference between baseline to follow-up A1C levels at all available time intervals as well as measures of dispersion for placebo and treatment arms were recorded. If mean differences were not reported, a difference in means was calculated from the reported mean baseline and end point A1C values. A1C levels were abstracted from the text or tables, read from graphs, or computed. When more than one method for reporting the A1C level was used, the level reported in the text or table was used. When only the proportional mean decrease in A1C was provided for placebo and treatment arms, an end of study A1C level was calculated. All measures of dispersion were converted to SDs. When SDs were not reported, estimated baseline and final SDs were derived from data from other studies at the same time interval.

When more than one comparison arm was available for a specific drug and dose, a meta-analysis was completed at the reported time interval. As the focus of this review was on the glucose effect of different classes of drugs and not individual drugs, the results of different drugs and doses from the same class were meta-analyzed to yield an overall estimate. Cochran Q test and I-squared statistics were calculated for heterogeneity. If there was heterogeneity, pooled effects were calculated using a random-effects model (8).

A meta-regression analysis was also completed at each available time interval where there was sufficient data to assess the effect of baseline A1C and diabetes duration on the fall of A1C with OAD therapy. For this equation, the dependent variable was change in A1C, and the independent variables included: *1*) drug class; *2*) dose; *3*) diabetes duration; and *4*) baseline A1C. The dose variable in the regression equation was treated categorically with the starting dose coded as the baseline amount, and each doubling of a drug dose was a single increment increase. Agreement kappa statistics for each state of eligibility assessment were calculated using PC-Agree (McMaster University, Hamilton, Ontario, Canada) software. All statistical analyses were done using STATA statistical software (version 10.0) (StataCorp, College Station, TX).

RESULTS

Study and patient characteristics

A total of 61 studies comprising 103 different comparisons of OADs met the inclusion criteria. Thirty (49%) were found in EMBASE (Online Appendix references 1–30); 21 (34%) were found in the Cochrane Central Register of Controlled Trials (Online Appendix references 31–51); and 10 (16%) were found in MEDLINE (Online Appendix references 52–61). The studies were published between 1994 and 2008 with 79% of the studies published on or after 2000. Eligibility agreement was assessed between reviewers using a Cohen's κ coefficient and was 0.8 for title and abstract review and 0.8 for full article review. TZDs studies accounted for the greatest number of trials ($n = 27$), followed by DPP-4 inhibitors ($n = 26$), alpha glucosidase inhibitors ($n = 22$), biguanides ($n = 12$), meglitinides ($n = 10$), and sulfonylureas ($n = 6$). The duration of studies ranged from 12 to 156 weeks; 74% ranged from 12 to 24 weeks; 20% ranged from 25 to 52 weeks; and 6% exceeded 52 weeks. Funding sources for the trials included private for profit (73%); government, private for profit, and/or private not for profit (9%); and 18% of the studies did not report their funding source (Online Appendix Table 2).

The trials enrolled a combined total of 26,367 patients with 15,760 randomized to an intervention drug and 10,607 randomized to placebo. Background diabetes treatment in the studies included one or more OADs in 25 studies (41%); OAD plus insulin therapy in three studies (5%); and insulin only in six of the studies (10%). In 10 studies (16%), the subjects discontinued OAD therapy prior to randomization, and in 17 studies (28%), the subjects were drug naïve. Study subjects had a median age of 57 years (range 52–69 years of age) and were more likely to be male (median 57%, range 39–84). The median baseline A1C across the study populations was 8.3% (range 6.6–10%), and similar baseline A1C levels were seen across drug naïve patient groups (median 8.2, range 6.6–9.2), those on OAD(s) or discontinued OAD(s) (median 8.2, range 6.7–10) and patient populations using insulin (median 8.8, range 7.8–9.9). The median BMI was 30 (range 24–34) and the median duration of diabetes was 5 years (range 1.4–14 years of age) (Online Appendix Table 3).

OAD class effectiveness

Alpha glucosidase inhibitors. We identified 15 comparisons of acarbose and 6 comparisons of miglitol for which the effect on A1C for up to 2 years were reported (Fig. 1) (Fig. 2) (Online Appendix Figs. 2–7). All doses of both drugs, ranging from 75 to 900 mg per day, reduced A1C levels compared with placebo. Doses of 150 mg per day or higher achieved an A1C reduction of ~1% versus placebo with no evidence of an incremental effect

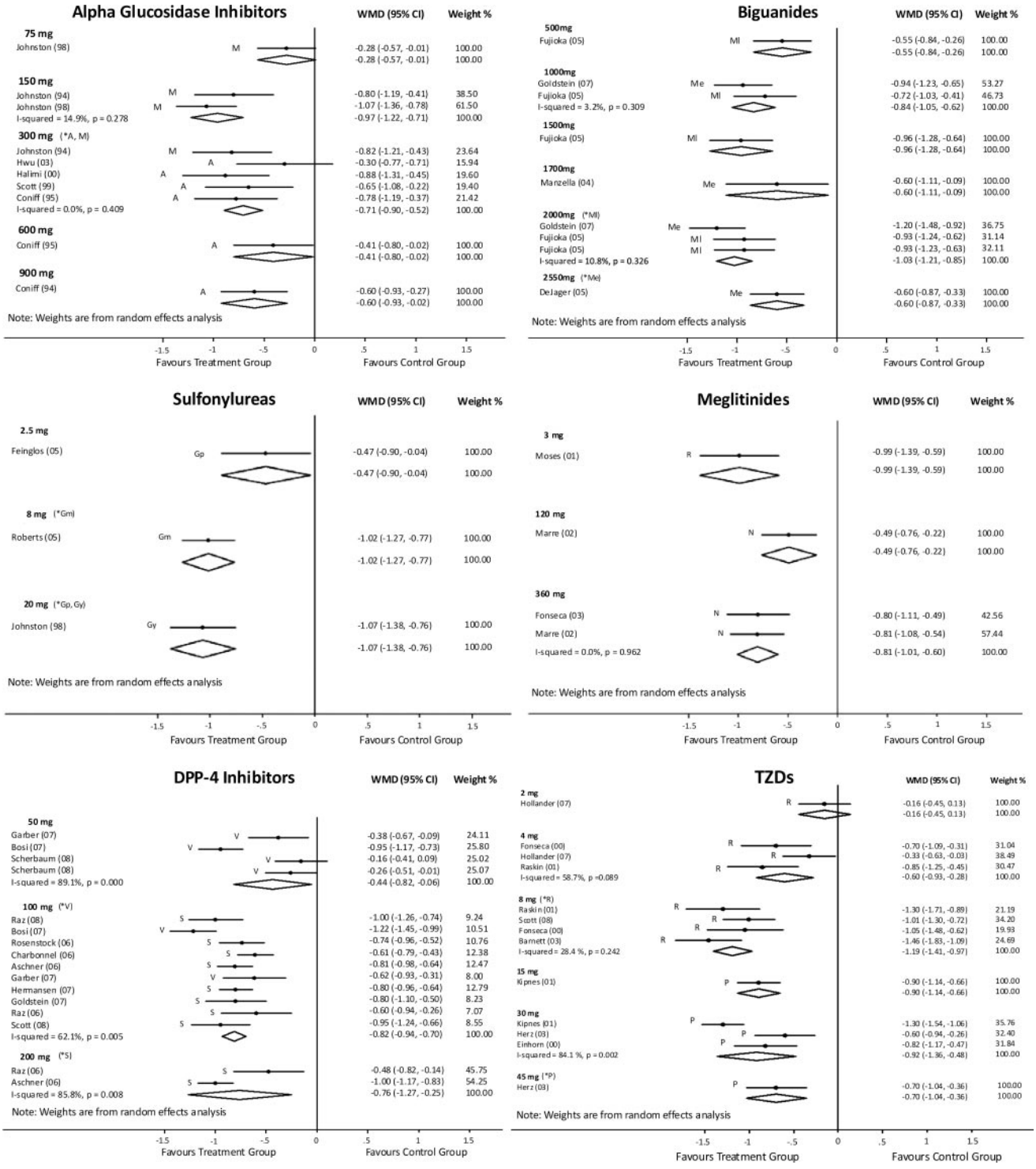

Figure 1—*Treatment effect by OAD class at 13–18 weeks. Each line represents a treatment effect (●) and 95% CIs (ends of the line). The diamond shape represents a meta-analyzed mean difference for a particular OAD class and dose. *Illustrates the generally accepted maximum daily dose. A, acarbose; Gm, glimepiride; Gp, glipizide; Gy, glyburide; M, miglitol; Me, metformin; Ml, metformin (long-acting); N, nateglinide; P, pioglitazone; R, rosiglitazone; Re, repaglinide; S, sitagliptin; V, vildagliptin.*

beyond that dose. The effect of these drugs persisted for up to 2 years (Fig. 2) (Online Appendix Figs. 2–7).

Biguanides. There were seven comparisons of metformin and five comparisons of long-acting metformin versus placebo that assessed doses ranging from 500 to 2,550 mg per day for up to 10 months (Figs. 1 and 2) (Online Appendix Figs. 3 and 4). Doses up to 1,500 mg per day reduced A1C levels by ~1% compared with placebo after 3 months of therapy. There was little evidence for additional reduction at higher doses, and the effect persisted for at least 10 months after treatment was begun.

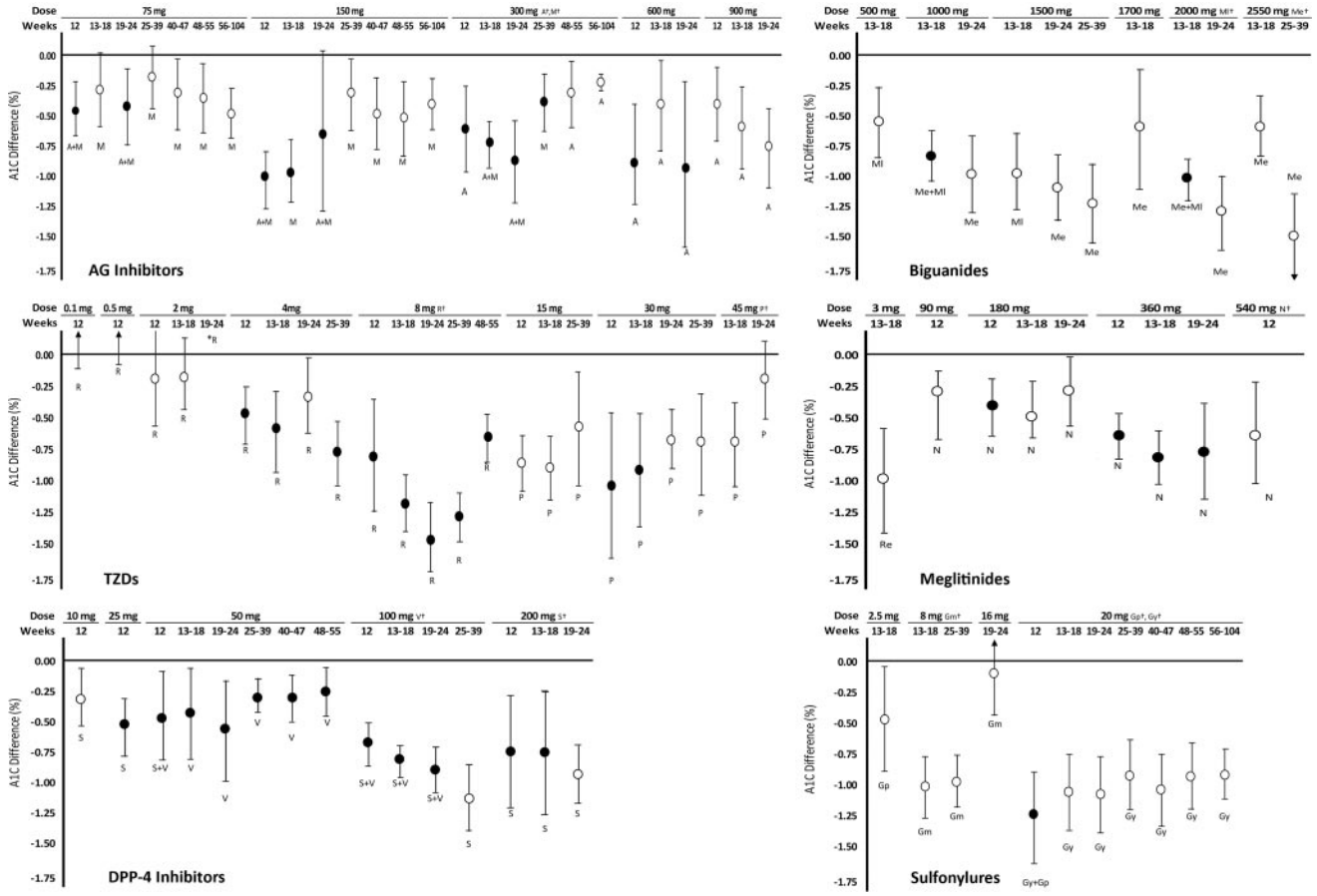

Figure 2—*Treatment effects on A1C by OAD class, dose, and time. Error bars represent 95% CIs.* ●*, represent pooled, weighted mean differences.* ○*, represent individual comparison treatment effects. *Treatment effect 1.1 (95% CI 0.8–1.4). †Illustrates the generally accepted maximum daily dose. A, acarbose; AG-α, glucosidase inhibitors; Gm, glimepiride; Gp, glipizide; Gy, glyburide; M, miglitol; Me, metformin; Ml, metformin (long-acting); N, nateglinide; P, pioglitazone; R, rosiglitazone; Re, repaglinide; S, sitagliptin; V, vildagliptin.*

DPP-4 inhibitors. A total of 19 comparisons of sitagliptin and 7 comparisons of vildagliptin were identified in which the effect on A1C for up to 1 year were reported (Figs. 1 and 2) (Online Appendix Figs. 2–6). All doses of both drugs, ranging from 10 to 200 mg per day, reduced A1C levels compared with placebo. Doses of 100 mg per day or higher achieved an A1C reduction of ~0.75% versus placebo with no evidence of an incremental effect beyond that dose.

Meglitinides. We found eight comparisons of nateglinide with doses ranging from 90 to 540 mg per day and one comparison of repaglinide at 3 mg per day versus placebo for up to 6 months in duration. Doses up to 360 mg per day reduced A1C levels by ~0.75% compared with placebo after 3 months of therapy. There was little evidence for additional reduction at higher doses (Figs. 1 and 2) (Online Appendix Figs. 2 and 3).

Sulfonylureas. Our search identified three comparisons of glipizide (doses ranging from 2.5 to 20 mg per day), two of glimepiride (doses ranging from 8 to 16 mg per day), and one of glyburide (20 mg per day) for which the effect on A1C for up to 2 years was reported (Figs. 1 and 2) (Online Appendix Figs. 2–7). As indicated in Fig. 2, doses ≥8 mg per day of glimepiride generally achieved an A1C reduction of ~1.25% versus placebo. The studies suggested that the effect of these drugs persisted for at least 2 years (Fig. 2) (Online Appendix Figs. 2–7).

TZDs. We identified 17 comparisons of rosiglitazone and 10 comparisons of pioglitazone for which the effect on A1C for up to 1 year were reported (Figs. 1 and 2) (Online Appendix Figs. 2–4, 6). One low-dose study of rosiglitazone assessing doses of 0.1, 0.5, and 2 mg per day did not show any effect on A1C levels. Daily doses of 4–8 mg of rosiglitazone and 15–45 mg of pioglitazone reduced A1C levels compared with placebo. Rosiglitazone at 8 mg per day achieved an A1C reduction of ~1.25% versus placebo, and pioglitazone at 30 mg per day achieved an A1C reduction of ~1% versus placebo (Fig. 2). The effect of these drugs persisted for at least 1 year in these studies (Fig. 2) (Online Appendix Figs. 2–4, 6).

The effect of baseline A1C and diabetes duration levels on the fall of A1C

After adjusting for drug class, dose, diabetes duration, and baseline A1C in the meta-regression analysis, the addition of an OAD led to a 0.2–0.5% greater decline for every 1% higher baseline A1C level. As noted in Table 1 (Table 1), this effect was statistically significant beyond 13 weeks. No consistent effect of diabetes duration on the change in A1C was noted. Insufficient data regarding diabetes duration precluded estimating the effect of diabetes duration and baseline A1C in studies of 40 or more weeks' duration. The effect of baseline A1C on the change in A1C with therapy could not be adjusted for changes

Table 1—*The effect of baseline A1C and diabetes duration on the fall in A1C with OAD therapy*

Follow-up time (weeks)	Comparisons (*n*)	Change in A1C (%) for every 1% higher baseline A1C (95% CI)*	Change in A1C (%) for every 1 year greater diabetes duration (95% CI)**
12	50	0.01 (−0.2 to 0.2)	−0.1 (−0.13 to −0.002)†
13–18	57	−0.2 (−0.4 to −0.05)‡	0.03 (−0.01 to −0.1)
19–24	47	−0.3 (−0.6 to −0.1)§	0.08 (0.01–0.15)¶
25–39	21	−0.5 (−0.9 to −0.1)¶	−0.03 (−0.1 to 0.1)

Estimates are derived from a meta-regression analysis that controlled for: *drug class, drug dose, and baseline A1C; **drug class, drug dose, baseline A1C, and duration of diabetes. †$P < 0.05$; ‡$P < 0.02$; §$P < 0.01$; ¶$P < 0.03$.

in the dose of insulin during the study as insulin doses were not always recorded.

CONCLUSIONS — This systematic review and meta-analysis of double-blind, randomized controlled trials that met predefined methodological criteria summarized treatment effects on A1C levels across OAD drug class, dose, and duration of therapy (Fig. 2). The greatest pooled treatment effect noted was with maximum doses of sulfonylureas after 12 weeks of therapy, followed by TZDs after 13–18 weeks of therapy. Across all OAD classes, an increase in dose yielded a further decrease in A1C initially with a maximum effect achieved by 3–6 months.

The meta-regression analysis also provided a numerical estimate of an effect that has been commented on by previous authors: higher baseline A1C levels are associated with greater declines in A1C with therapy (9). However, this effect was modest in most studies that were reviewed, such that after controlling for OAD drug class and dose, every 1% higher pretreatment A1C levels predicted a 0.5% greater fall of A1C levels after 6 months of therapy.

This review has several strengths. First, it was restricted to randomized controlled trials that met predetermined methodological criteria to minimize the potential for bias. Of note, the application of these criteria led to the exclusion of 150 out of 211 (71%) manuscripts that may otherwise have been included. Second, it entailed a comprehensive search for all currently used OAD classes for type 2 diabetes treatment. Third, the effect of OADs on A1C level was assessed at different time intervals, ranging from 12 weeks to 2 years. Finally, it focused on the effect of OAD class versus individual drugs and therefore may be relevant to new drugs from the same class.

This review has several limitations. First, most of the studies included participants with relatively newly diagnosed diabetes (median duration of diabetes of 5.2 years). As such, the review's findings may not be relevant to patients with a longer duration of diabetes or with diabetes-related complications. Second, relatively few studies were available for sulfonylureas ($n = 6$), meglitinides ($n = 10$), and biguanides ($n = 12$) thereby affecting the reliability of their respective quantitative estimates. Third, less than 30% of the reviewed papers reported the effect of therapy for periods greater than 24 weeks. Fourth, there is some statistical heterogeneity (ranging up to 90%) in the meta-analyzed results of the included studies, regardless of OAD class, drug, or dose. This heterogeneity may have been due to study differences in design, patient demographics and characteristics, duration of diabetes, and background drug therapy or confounding. Regardless of the cause, heterogeneity was managed by using a random-effects model for meta-analyses. Fifth, some of the summarized trials added oral agents to background therapy that included insulin. If investigators adjusted the dose of insulin during the trial, this may have affected the estimate of the effect of the OAD on the change in A1C. This could not be taken into consideration as insulin doses were not provided in the reports. Finally, it is possible that this review was influenced by publication bias given that studies with positive results are generally more likely to get published, resulting in an overestimate of the benefit of an OAD on A1C reduction.

In summary, the results of this systematic review and meta-analysis suggest that the initiation of an OAD in addition to current therapy yields an additional decrease in A1C level of ~1–1.25% with most of the treatment effect evident by 3–6 months of initiating OAD therapy. This effect was fairly consistent between OAD classes with sulfonylureas and TZDs having the greatest reduction in AIC. The meta-regression analysis numerically demonstrated a small effect of baseline A1C on the fall of A1C with OAD treatment. Further carefully conducted OAD trials are needed to account for *1*) combinations of OAD drug use and its impact on A1C levels; *2*) the effectiveness of long-term OAD use on A1C levels; and *3*) adverse and hypoglycemic events.

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