CONSENSUS STATEMENT

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.

Diabetes Care 32:193–203,

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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This article is being simultaneously published in 2009 by *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.
An American Diabetes Association consensus statement represents the authors' collective analysis, evaluation, and opinion at the time of publication and does not represent official association opinion.
DOI: 10.2337/dc08-9025

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.

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