

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

Update regarding thiazolidinediones: a consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

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The consensus algorithm for the management of type 2 diabetes was developed on behalf of the American Diabetes Association and the European Association for the Study of Diabetes approximately 1 year ago (1,2). This evidence-based algorithm was developed to help guide health care providers to choose the most appropriate treatment regimens from an ever-expanding list of approved medications. The authors continue to endorse the major features of the algorithm, including the need to achieve and maintain glycemia within or as close

to the nondiabetic range as is safely possible, the initiation of lifestyle interventions and treatment with metformin at the time of diagnosis, the rapid addition of medications and transition to new regimens when target glycemia is not achieved, and the early addition of insulin therapy in patients who do not meet target A1C levels.

The availability of newly approved medications and the accrual of new clinical trial and other data should inform the algorithm. In this update, we primarily address one important issue that has re-

ceived much recent attention: our current understanding of the advantages and disadvantages of the thiazolidinediones. In addition, we have revised the original Table 1 to include the dipeptidylpeptidase-4 inhibitor sitagliptin, which was not approved by the U.S. Food and Drug Administration at the time of our original publication (Table 1).

We are mindful of the importance of not changing this consensus guideline in the absence of definitive or compelling new data. Future updates are planned to consider further revisions of the algorithm, guided by the evidence base and clinical experience with the newer classes of glucose-lowering medications.

The original consensus algorithm included the thiazolidinediones as one of three possible choices (insulin and sulfonylurea were the other two) that should be added to metformin and lifestyle intervention if target A1C levels (<7%) were not being achieved (Fig. 1). Several recent meta-analyses (3,4), together with one performed by the manufacturer (5) and one by regulatory authorities (6), have called into question the safety of rosiglitazone with regard to the risk of myocardial infarction. The putative 30–40% relative increase in risk of myocardial infarctions is based on data that are widely viewed as less than definitive; still, these data have led to the recommendation that clinicians exercise increased caution in prescribing rosiglitazone (7–10). Another recent meta-analysis of essentially the same dataset found no significantly increased risk of cardiovascular mortality owing to either rosiglitazone or pioglitazone (11). An interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) study, designed specifically to examine cardiovascular outcomes of rosiglitazone therapy, revealed no statistically significant effects on myocardial infarction (hazard ratio 1.17 [95% CI

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*Simultaneous publication: This article is being simultaneously published in 2008 in *Diabetes Care* and *Diabetologia* by the American Diabetes Association and the European Association for the Study of Diabetes.

D.M.N. has received research grants from sanofi-aventis and support for educational programs from GlaxoSmithKline and Pfizer. J.B.B. conducts research and/or serves on advisory boards under contract between the University of North Carolina and Amylin, Bristol-Myers Squibb, GlaxoSmithKline, Hoffman-LaRoche, Eli Lilly, Novo Nordisk, Merck, Novartis, Pfizer, and sanofi-aventis. M.B.D. has received research support from Eli Lilly, Merck, and Pfizer; serves on advisory boards to Amylin, GlaxoSmithKline, Merck, and sanofi-aventis; and is on speakers bureaus for Amylin, Eli Lilly, GlaxoSmithKline, and Pfizer. E.F. has received research support from AstraZeneca, Merck Sharp & Dohme, and Novartis and serves on scientific advisory boards for Amylin, AstraZeneca, GlaxoSmithKline, Roche, Merck Sharp & Dohme, Novartis, Servier, sanofi-aventis, Boehringer Ingelheim, and Takeda. R.R.H. has received grant support from Novartis, Bristol-Myers Squibb, Novo Nordisk, Pfizer, GlaxoSmithKline, and Merck and serves on scientific advisory boards for Amylin, Novartis, Eli Lilly, Merck, and sanofi-aventis. R.S. serves on advisory boards for Amylin, Bristol-Myers Squibb, Eli Lilly, Merck, and Takeda. B.Z. has received research support from Eli Lilly, GlaxoSmithKline, Novartis, and Novo Nordisk and is a member of scientific advisory boards and/or has received honoraria for speaking from Amylin, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, Merck, Novartis, Pfizer, sanofi-aventis, and Smiths Medical.

Abbreviations: CHF, congestive heart failure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

DOI: 10.2337/dc08-9016

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Table 1—Summary of glucose-lowering interventions as monotherapy

Interventions	Expected decrease in A1C (%)	Advantages	Disadvantages
Step 1: Initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in first year
Metformin	1–2	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: Additional therapy			
Insulin	1.5–3.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1–2	Inexpensive	Weight gain, hypoglycemia*
Thiazolidinediones (glitazones)	0.5–1.4	Improved lipid profile† Potential decreased risk of MI†	Fluid retention, twofold increased risk of CHF, potential increased risk of MI‡, atherogenic lipid profile, weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5§	Short duration	Three times/day dosing, expensive, hypoglycemia
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience
Sitagliptin	0.5–0.8	Weight neutral	Little experience, expensive

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide and glibenclamide [glyburide]) are more likely to cause hypoglycemia than glipizide, extended-release glipizide, glimepiride, or gliclazide. †Pioglitazone. ‡Rosiglitazone. §Repaglinide is more effective at lowering A1C than nateglinide. GI, gastrointestinal; MI, myocardial infarction.

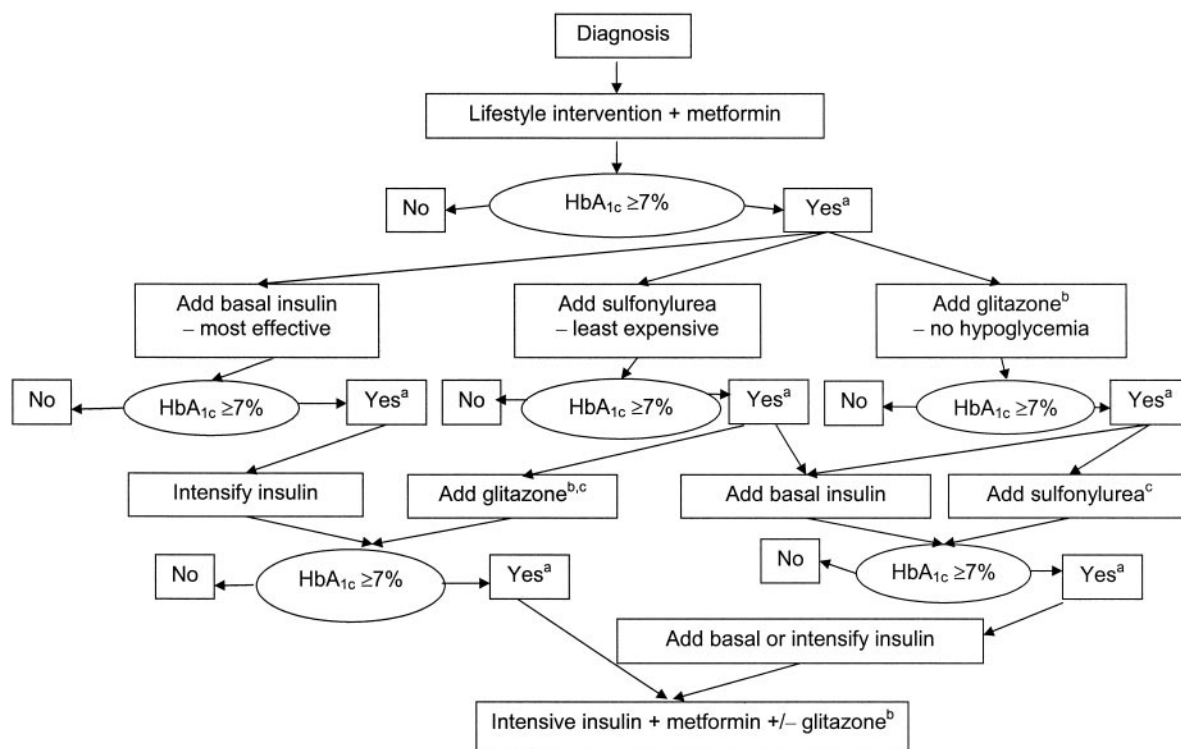


Figure 1—Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. ^aCheck A1C every 3 months until <7% and then at least every 6 months. ^bAssociated with increased risk of fluid retention, CHF, and fractures. Rosiglitazone, but probably not pioglitazone, may be associated with an increased risk of myocardial infarction. ^cAlthough three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and lower expense.

0.75–1.82]) but confirmed the risk for congestive heart failure (CHF) with rosiglitazone (2.15 [1.30–3.57]) (12). Furthermore, a meta-analysis of the clinical trial data regarding cardiovascular disease risk and pioglitazone has suggested that the drug exerts a protective effect (13).

In addition to the concern raised regarding the potential risk of myocardial infarction with rosiglitazone, the previously recognized risk of fluid retention and resultant CHF, which applies to both pioglitazone and rosiglitazone, has now been quantified as an approximate two-fold increase (11,14). These findings have led to a “black box” warning in the prescribing information for rosiglitazone regarding the risk for myocardial infarction and for both thiazolidinediones regarding the risk for CHF (15).

Both thiazolidinediones have been associated with an increased risk for fractures, particularly in women (16,17). Of note, the majority of these fractures were in the distal upper (forearm, hand, or wrist) or lower (foot, ankle, fibula, or tibia) limb, as opposed to the classic sites of osteoporotic fractures.

At this time, we do not view as definitive the clinical trial data regarding increased or decreased risk of myocardial infarctions with rosiglitazone or pioglitazone, respectively. Nor do we think that the increased risk of CHF or fractures with either of the available thiazolidinediones is of a magnitude to warrant their removal as one of the possible second-step medications in our algorithm, given that they cause hypoglycemia less frequently than other second-step drugs.

On the other hand, we do believe that the weight of the new information outlined above should prompt clinicians to consider more carefully whether to use this class of drugs versus insulin or sulfonylureas as the second step in the algorithm (Fig. 1). As with other drug classes, there may well be clinically important differences between the two drugs in this class. The current decision not to remove either or both of the thiazolidinediones from the algorithm represents a balance between the preservation of options to

treat a challenging and progressive serious disease and the recent unfavorable evidence.

In conclusion, new information suggests additional hazards associated with the use of either thiazolidinedione, and rosiglitazone in particular, may result in an increased frequency of myocardial infarctions. We therefore recommend greater caution in using the thiazolidinediones, especially in patients at risk of, or with, CHF.

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