



American Diabetes Association Consensus Algorithm for the Medical Management of Type 2 Diabetes

Issue Compiled by Erin Carlson, PharmD

The American Diabetes Association (ADA) published a new Consensus Statement titled “Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy” in the December 2008 edition of *Diabetes Care*. The original ADA consensus algorithm for the medical management of type 2 diabetes was published in August 2006, and an update to the algorithm was last published in January 2008. The newest revision focuses on the new classes of medications that now have more clinical data and experience since the 2006 consensus algorithm.

The new treatment algorithm (pg. 4) is broken down into two tiers: well-validated core therapies (tier 1) and less well validated therapies (tier 2). The tier one algorithm is the preferred route of therapy for most patients with type 2 diabetes. The algorithm emphasizes initial therapy with both lifestyle modifications and metformin. If lifestyle intervention plus the maximal tolerated dose of metformin fails to reach glycemic goals, the algorithm emphasizes early addition of a second medication within 2-3 months. Tier one options for second agents include basal insulin or a sulfonylurea added to lifestyle interventions plus metformin. Tier 1 therapies were chosen based on cost-effectiveness as well as the amount of clinical

evidence available. In the newest algorithm, the glitazones have a weaker recommendation compared to the previous algorithm. Reasons for this include:

- Glitazones are associated with increased risk of fluid retention and congestive heart failure.

ylureas.

Also, the consensus statement explicitly advises against using rosiglitazone based on potential cardiovascular risk associated with the medication, which is a new recommendation.

The tier two algorithm may be considered in selected clinical settings, specifi-

The December 2008 ADA consensus statement emphasizes four main points:

1. **Rapid** achievement and maintenance of near normal blood glucose levels (A1C < 7%)
2. Initial therapy with lifestyle intervention **PLUS** metformin
3. **Rapid** addition of medications as well as transition to new regimens if glycemic goals are not achieved or maintained
4. **Early** addition of insulin therapy in patients not at goal

- Several meta-analyses have shown an increased risk of myocardial infarction with rosiglitazone.
- They are more expensive than other available therapies such as metformin and sulfon-

cally in patients where hypoglycemia is especially undesirable. Besides the glitazones (pioglitazone), the other tier two option is the GLP-1 agonist, exenatide. The algorithm gives exenatide as an op-

(Continued on pg. 4)

Objectives:

- Understand the changes in the ADA guidelines for medical management of type 2 diabetes
- Discuss the long-term effects of intensive glucose control in type 2 diabetes based on post-trial monitoring of UKPDS
- Discuss the long-term effects of tight blood pressure control in type 2 diabetes based on post-trial monitoring of UKPDS

10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes. A Summary of the Post-trial Monitoring of Patients in the UKPDS.

By Andrew Forest, PharmD Candidate

The United Kingdom Prospective Diabetes Study (UKPDS) results were published in 1998 and showed that tight control over glucose and blood pressure in patients with type 2 diabetes mellitus significantly reduced the risk of serious complications of type 2 diabetes, such as microvascular and macrovascular disease, when compared with less-tight or conventional control. The intensive therapy group had a goal A1c of <6% and the conventional method of dietary changes had a goal of any achievable A1c.

Upon completion of the UKPDS, patients returned to community or hospital-based diabetes care according to their clinical needs; no attempt to maintain previously randomized therapies was made. The patients were seen annually for 5 years in UKPDS clinics post-trial with continued standardized collection of outcome data

and then every 3 years. This 10-year post-intervention follow-up of the UKPDS survivor cohort examined whether a continued microvascular benefit from earlier improved glycemic control was evident and whether such therapy had a long-term effect on macrovascular outcomes.

Although by the end of the 10 year follow-up most patients in all phases of the original trial were on similar therapy, and had similar A1C values, there was still significant reductions in relative risk with patients who had previously been randomized on intensive therapy compared to conventional therapy during the controlled trial of UKPDS, as seen in Table 1. Patients in the sulfonylurea and metformin intensive therapy follow-up groups maintained a significant reduction in diabetes-related death and death from

any cause compared with conventionally controlled patients. There was no significant reduction in microvascular disease in the metformin group compared conventionally controlled patients. The findings were said to be similar to those of the EDIC study, which was a follow-up study involving a cohort of patients with type 1 diabetes in the DCCT. The DCCT was a study that randomized patients with type 1 diabetes to intensive or conventional insulin control for a mean of 6.5 years; subsequently, 93% of the patients were followed for 11 years. At the end of the trial, patients in the intensive-therapy group had a significant reduction in risk of any cardiovascular event by 42%.

The results of this large post-trial study showed that benefits of intensive glucose control in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions.

Table 1. Outcomes for patients during follow-up

Outcome	Absolute Risk*		P-Value
	Intensive Therapy	Conventional Therapy	
Sulfonylurea group			
Any diabetes-related end point	48.1	52.2	0.04
Diabetes-related death	14.5	17	0.01
Death from any cause	26.8	30.3	0.007
Myocardial infarction	16.8	19.6	0.01
Stroke	6.3	6.9	0.39
Microvascular disease	11	14.2	0.001
Metformin group			
Any diabetes-related end point	45.7	53.9	0.01
Diabetes related death	14	18.7	0.01
Death from any cause	25.9	33.1	0.002
Myocardial infarction	14.8	21.1	0.005
Stroke	6	6.8	0.35
Microvascular disease	12.4	13.4	0.31

*Absolute risk is # of events per 1000 patient-years

Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes: A Summary of the Post-trial Monitoring of Patients in the UKPDS.

By Kaitlyn McDowell, PharmD Candidate

A follow-up study of the UKPDS, as summarized on the previous page (pg. 2), indicated that the effects of intensive glucose control during the study persisted for as long as 10 years after the completion of the study, when risk reductions for microvascular and macrovascular disease were still significant compared to those patients who had received conventional glucose-lowering therapy. The Long-Term Follow-up after Tight Control of Blood Pressure in Type 2 Diabetes trial set out to determine if tight control of blood pressure would produce a similar sustained reduction in micro- and macrovascular disease compared to less-tight blood pressure control.

This study was a 10-year follow-up of patients with hypertension who participated in the UKPDS trial. Over a 4-year period of patient randomization to the UKPDS trial, 1148 patients with hypertension (blood pressure $\geq 160/90$ mm Hg or $\geq 150/85$ mm Hg if on antihypertensive therapy) were randomized to either tight blood pressure control or less-tight blood pressure control. Patients under tight control received up to 50 mg of captopril twice daily or up to 100 mg of atenolol once daily with a target blood pressure of $<150/85$ mm Hg. Patients under less-tight control were treated with agents other than an angiotensin converting enzyme (ACE) inhibitors and beta-blockers, with a goal blood pressure of $<180/105$ mm Hg. At the end of the study, 884 of these patients were available to participate in the post-trial monitoring. At this point, patients returned to their usual physicians and no attempt was made to maintain the therapies or goals used in the UKPDS. The patients were assessed at UKPDS clinics once a year for the first five years, then by mailed questionnaire for years 6-10. Patients who were unable to attend the clinic appointments during years 1-5 were assessed through questionnaire. Data was handled on an intent-to-treat basis.

“This [study] shows the importance of intensive blood pressure control by providers in all practice settings to prevent complications in patients with type 2 diabetes.”

Each group had similar characteristics both at baseline before the UKPDS and at the start of the post-trial monitoring, including the beta-blocker group compared with the ACE inhibitor group. The only significant difference at the start of this study was that the tight-control group had significantly lower systolic and diastolic blood pressures ($p < 0.001$ each) than the less-tight control group. This difference evened out by year 2 of post-trial monitoring. By year 5 there was no significant difference in the number of anti-hypertensive agents used, use of lipid-lowering therapy, or number of patients receiving aspirin between groups. There were also no differences between groups with regards to glycated hemoglobin, fasting plasma glucose, or plasma creatinine levels throughout the study.

This study found no significant sustained effects of the tight blood pressure control used during the UKPDS. When comparing tight-control to less-tight control of blood pressure, there were no significant differences in the occurrence of microvascular disease, myocardial infarction, stroke, death, or any diabetes-related endpoint at the end of the 10-year follow-up (Table 2). Tight-control of blood pressure did show a significant risk reduction of peripheral vascular disease compared to less-tight control ($p = 0.02$). There were no significant differences in endpoints between the ACE inhibitor and beta-blocker tight-control groups.

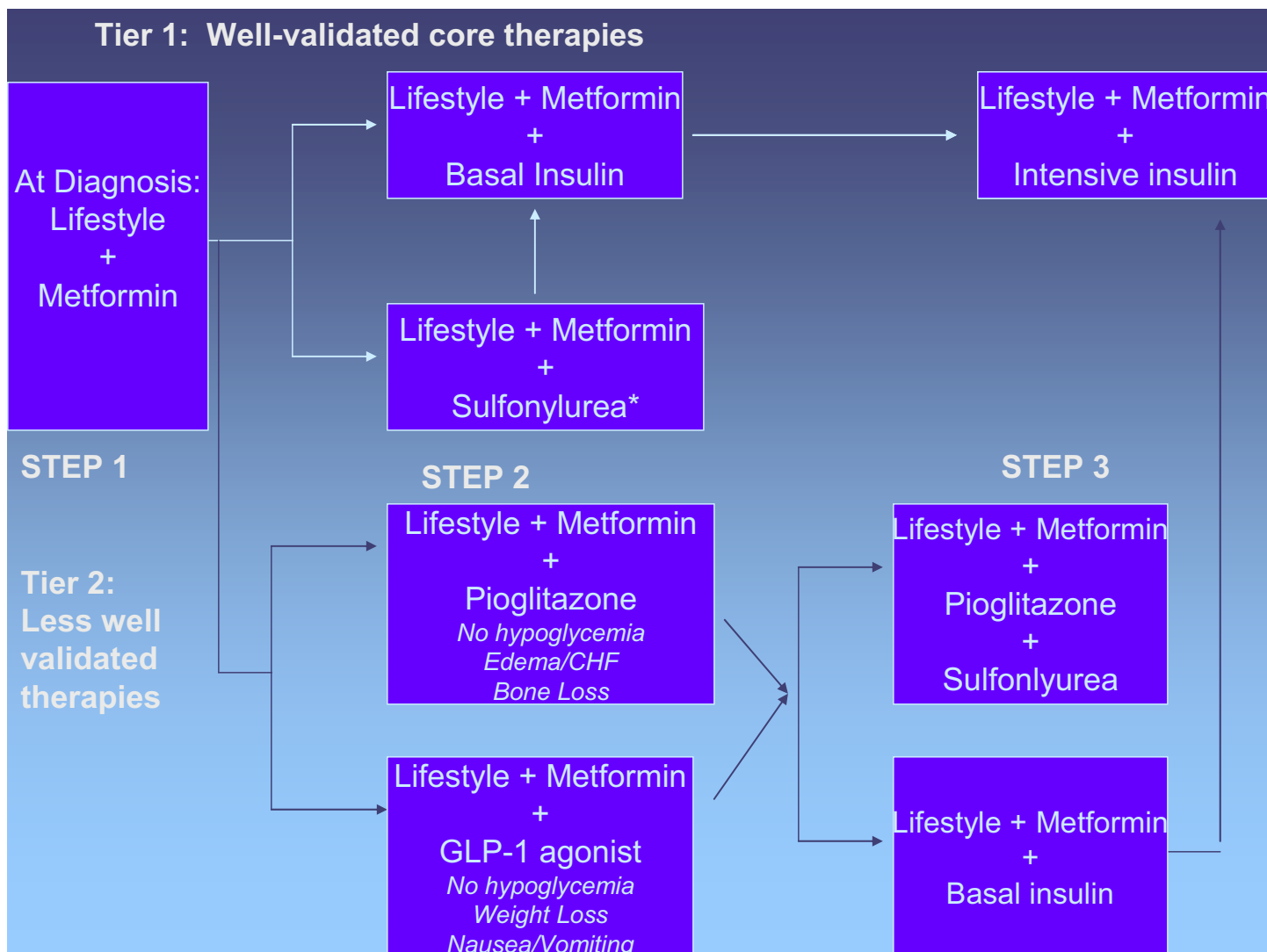
This study demonstrated that the favorable effects of tight blood pressure control used during the UKPDS in preventing micro- and macrovascular disease did not persist after patients finished the study, when their blood pressure was less tightly controlled. This shows the importance of intensive blood pressure control by providers in all practice settings to prevent complications in patients with type 2 diabetes.

References:
 Holman RR, Paul SK, Bethel MA, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med.* 2008 Sep 10. [Epub ahead of print].
 Holman RR, Paul SK, Bethel MA, et al. Long-term follow-up after tight control of blood pressure in type 2 diabetes. *N Engl J Med.* 2008 Sep 10. [Epub ahead of print].

Table 2. Outcomes for Patients during Follow-up.

End Point	Percent of Patients with End Point		P-Value
	Tight Control	Less-Tight Control	
Any diabetes-related endpoint	61.5	63.6	0.31
Diabetes-related death	26.8	31.1	0.12
Death from any cause	49.2	54.1	0.18
Myocardial infarction	27.0	29.5	0.35
Stroke	11.9	14.9	0.12
Peripheral vascular disease	2.8	5.4	0.02
Microvascular disease	18.6	21.0	0.17

ADA Consensus Algorithm for the Management of Type 2 Diabetes (continued)



tion for patients in whom promotion of weight loss is a major consideration and the A1C is close to target. The third step in the algorithm for both tier one and tier two is to start or further intensify insulin therapy. This can be done by adding rapid-acting insulin before selected meals to target reduction of post-prandial blood glucose.

In the past, insulin was often seen as last

line therapy in type 2 diabetes when oral medications failed. The new ADA guidelines emphasize the importance of adding insulin **early** in therapy for type 2 diabetes in order to rapidly achieve glycemic goals. Mounting evidence suggests aggressive lowering of hyperglycemia in newly diagnosed type 2 diabetes, especially with insulin, can result in sustained normoglycemia without the need for glucose-lowering medications. Also, pa-

tients need to be educated that because diabetes is a progressive disease, and beta-cell function declines over time despite treatment, it is likely that they will require addition of glucose-lowering medications. This should not necessarily be seen as a failure on the part of the patient or provider.

Reference:
Diabetes Care, Volume 31, Number 12. December 2008.

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Continuing Education Quiz

Diabetes Dispatch: Winter 2009

- 1) Which of the following medications is **not** considered a tier 1 therapy for type 2 diabetes after metformin and lifestyle modifications fail to achieve glycemic goals?
 - a. glyburide
 - b. basal insulin
 - c. pioglitazone
 - d. none of the above

- 2) The 2008 ADA algorithm for treatment of type 2 diabetes emphasizes rapid addition of a second medication within _____ if metformin and lifestyle modifications fail.
 - a. 1-2 months
 - b. 2-3 months
 - c. 3-4 months
 - d. 4-6 months

- 3) True or False – In type 2 diabetes, pancreas beta-cell function declines despite treatment, therefore it is likely patients will eventually require insulin.

- 4) Which of the following medications is associated with weight loss in patients with type 2 diabetes:
 - a. exenatide
 - b. insulin
 - c. glimepiride
 - d. pioglitazone

- 5) Case: MC is a 70 year old male with type 2 diabetes who is currently on metformin 1000mg BID. His A1C is 8 and the physician wants to add a second drug but is concerned about hypoglycemic risk with this patient. According to the ADA algorithm, what would be an appropriate next step for this patient?
 - a. add glyburide
 - b. add exenatide
 - c. start mealtime rapid-acting insulin
 - d. add repaglinide

- 6) Which of the following is **not** a reason that the 2008 ADA guidelines have a weaker recommendation (tier 2) for the glitazones (pioglitazone) than in the past?
 - a. New studies have shown them to be ineffective at lowering glucose
 - b. Several meta-analysis have suggested increased relative risk for myocardial infarction with rosiglitazone
 - c. They are associated with increased risk of fluid retention and congestive heart failure
 - d. None of the above

- 7) True or False – The ADA Consensus Algorithm for management of type 2 diabetes emphasizes the early addition of insulin therapy in patients not at glycemic goals.

- 8) True or False – The microvascular benefits of **intensive glucose control** in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions during the UKPDS.

- 9) True or False – The macrovascular and microvascular benefits of **tight blood pressure control** in patients with type 2 diabetes were sustained for up to 10 years after the cessation of randomized interventions during the UKPDS.



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To obtain CPE credit for this lesson you must answer the questions on the quiz (70% correct required) and return the quiz. Should you score less than 70%, you will be asked to repeat the quiz. In May and

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