THE OREGON STATE DRUG REVIEW©

AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

October 2013 Volume 3, Issue 4

Updates and Comparisons of Type 2 Diabetes Treatment Guidelines

By Kala Berkey and Michelle Pfeifer PharmD.Candidates 2014, Megan Herink, Pharm.D.and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

Due to the increasing prevalence of Type 2 Diabetes Mellitus (T2DM) and recent therapeutic advancements, the treatment of diabetes and its complications are constantly evolving. In response to these changes, treatment guidelines are required to be frequently updated. In 2013, the American Association of Clinical Endocrinologists (AACE) replaced the 2009 algorithm for glycemic control with a comprehensive diabetes management algorithm. This included all elements of type 2 diabetes (hyperglycemia, obesity, prediabetes, hypertension, and dyslipidemia), with limited text, followed by the release of a detailed consensus statement. In 2012, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) released a joint position statements entitled, "Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach," which described a basic algorithm for the treatment of hyperglycemia. In 2013, the ADA/EASD published its annual guideline update entitled, "Standard of Medical Care in Diabetes". This review will compare and contrast the ADA and AACE's approach to comprehensively treat T2DM and will also highlight the recent revisions for the 2013 ADA position statement.[1-3]

Glycemic Control Update

The current management of T2DM relies on patients working with clinicians to determine an appropriate hemoglobin A1c goal. Optimal glycemic goals are largely based on expert opinion, thus creating varying glycemic goals between professional organizations.[4] The AACE recommends an A1c goal of ≤6.5%, while the ADA recommends <7% for patients with no concurrent illness (cardiovascular disease [CVD], low hypoglycemic risk, long life expectancy, and short duration of diabetes).[2,3] Studies have shown more intensive strategies (A1c goals of ≤6% vs. standard strategies (A1c goal of 7-7.9%%) improve DM nephropathy progression, but have no benefit on cardiovascular outcomes, and instead have shown to increase mortality.[5-7] A slightly higher A1c target, such as 7-8%, is therefore recommended for patients with concurrent illnesses or at high risk of hypoglycemic risk by both the AACE and ADA.[2,3] In addition to fasting and 2-hour plasma glucose, the ADA included an A1c of 5.7-6.4% as a category for prediabetes, while AACE does not have an A1c as part of the diagnostic criteria for prediabetes. Its criteria include impaired glucose tolerance, impaired fasting glucose, or metabolic syndrome.

Treatment guidelines now emphasize a patient-centered approach to diabetes management.[1,3] The AACE recommendations for treatment are based on presenting A1c and do not take into account the acquisition cost of therapy.[3] They note that cost of drug is only a small factor in the overall care of a diabetic patient. However, cost should likely be a consideration as it may affect adherence and patient access to the appropriate level of care. The ADA contrasts the AACE by acknowledging that costs are a critical issue driving the selection of medication.[1]

The preferred first line therapy is metformin, along with lifestyle modifications per the ADA and AACE.[1-3] The AACE algorithm provides directed guidance on second and third line treatment options based upon expert consensus.[3] In contrast, the ADA algorithm does not recommend one therapeutic option over another for second line therapy due to lack of comparative effectiveness evidence. Treatment choice should be based on efficacy, hypoglycemic risk, weight changes, underlying comorbidity, side effects, and cost.[1] AACE recommends dual therapy if baseline A1c is ≥7.5%, while initiation of dual therapy is recommended only when baseline A1c is ≥9% per ADA.[3] Both guidelines recommend considering initial treatment with insulin in patients presenting with severe symptomatic hyperglycemia.[1,3] If the glucose level is not markedly elevated, some patients may also benefit from basal intensification with a dipeptidyl peptidase-4 inhibitor or a glucagon-like peptide-1 agonist, as this approach does not likely cause weight gain or hypoglycemia.

Hypertension Update

Managing high blood pressure (BP) in patients with diabetes is imperative in lowering cardiovascular risk and complications. According to the American Heart Association, heart disease and stroke are the number one causes of death and disability among people with T2DM.[8] However, recent evidence has challenged BP targets of <130/80 mmHg previously established for patients with T2DM.[9-11] The ADA/EASD 2013 position statement revised the target systolic blood pressure (SBP) from below 130mmHg to below 140mmHg.[2] The new target SBP goal is based on recent evidence in demonstrating a small reduction in the risk of stroke with intensive BP goal, but no evidence for decreased mortality or myocardial infarction.[9-11] There was also an increased risk of hypotension and other adverse events with the lower goal compared to the less stringent target. The ADA suggests it is reasonable to target a lower BP goals (<130/80 mmHg) in younger patients and 110-129/65-79 mmHg in pregnant women with chronic hypertension and diabetes.[2] The ADA also suggests that if a person can easily achieve a lower goal, it is likely appropriate and beneficial. A detailed review of trials involving blood pressure targets in patients with diabetes can be found in the June 2012 edition of *The Oregon State Drug Review*.[12]

In contrast, the AACE 2013 consensus statement upholds the goal of <130/80 mmHg.[3] This recommendation is based on the significant reduction in fatal and non-fatal stroke (ARR 1.1%; 95% CI 0.003-0.019; p=0.01), and macroalbuminuria (ARR 2.1%; 95% CI 0.005-0.037; p=0.009) shown in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) BP trial.[9] A specific blood pressure goal in pregnancy has not been established by the AACE. [3]

Both the ADA and AACE continue to endorse the use of either an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin receptor blocker (ARB) as initial therapy for blood pressure control and stress the importance of lifestyle modifications, in addition to pharmacologic therapy.[2,3] The AACE recommends starting dual therapy (ACEi or ARB with thiazide, calcium channel blocker, or beta blocker) when initial blood pressure is >150/100 mmHg.[3] The ADA recognizes multiple-drug therapy is usually necessary to achieve blood pressure goals, but does not give a specific measurement.[2]

Dyslipidemia Update

Patients with T2DM have a significantly increased risk of CVD compared to those without. Both organizations give a target LDL-C goal of <100 mg/dL in low-moderate risk patients (DM without other CVD risk factors).[2,3] The AACE target LDL-C goal is <70 mg/dL in high risk patients (overt CVD or 1 or more CVD risk factors; family history of CHD, hypertension or on antihypertensive medication, low HDL-C, smoking).[3] The ADA's stance on lipid lowering differs, they are now emphasizing the importance of statin therapy over particular LDL goals in high-risk patients. The ADA 2013 position statement recommends statin therapy regardless of baseline lipid level in patients with overt CVD or for those without CVD who are >40 years old and have ≥1 CVD risk factors (high-risk). Statin therapy is also recommended in lower-risk patients if LDL remains above 100 mg/dl. Per the ADA, the suggested LDL goal of <70 mg/dL is optional in patients with overt CVD. In patients who cannot achieve LDL goals on maximum tolerated statin therapy, the ADA recommends an alternative goal of 30-40% reduction in LDL levels from baseline.[2]

The organizations differ in their stance on combination therapy. The AACE recommends combination therapy with ezetimibe, colesevelam, and/or niacin in patients who have not reached their LDL goal despite optimal statin therapy. It recommends adding omega-3-acid ethyl esters, and/or niacin to

lower non-HDL cholesterol or triglycerides.[3] Combination therapy with fenofibrate or niacin is not recommended by the ADA because these therapies have failed to provide any additional cardiovascular benefit above statin therapy alone, as demonstrated in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial and the Atherothrombosis Intervention in Metabolic syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial.[13-14] This is a new recommendation since the 2012 update.[15]

Weight Management Strategies

A new addition to the AACE algorithm is a section specifically focusing on the overweight/obese population, targeting weight loss strategies.[3] The focus is on a complications-centric model, as opposed to a BMI-centric model, incorporating lifestyle, medical, and surgical options. Weight loss can have a positive impact on blood glucose, lipids, and BP.[3] The AACE recommendation is a culmination of evidence from the Look Action for Health in Diabetes (Look AHEAD) and the newer weight loss pharmacotherapy clinical trials.[16-19] Although the Look AHEAD trial was terminated early due to lack of observed cardiovascular benefit, results did show that significant weight loss is associated with a significant reduction in blood pressure (-6.8/3.0 mmHg; p<0.001).[16-17] These patients were enrolled in a program of decreased caloric intake and increased physical activity.[16]

The AACE algorithm recommends phentermine, orlistat, lorcaserin, and phentermine/topiramate ER as treatment options, always as adjunct to lifestyle modification, for weight reduction.[3] In clinical trials, these drugs have shown efficacy in reducing weight compared to placebo.[18-20] However, the impact of weight loss drugs on obesity remains controversial due to lack of evidence in reducing long term macro- and microvascular complications. The newer weight loss medications, lorcaserin and phentermine/topiramate ER, were evaluated and reviewed in detail in the December 2012 edition of, *The Oregon State Drug Review.*[21] Much uncertainty remains regarding the long-term efficacy and safety of these drugs.

Other ADA Updates

In addition, many other changes resulting from new evidence were made to the ADA recommendations. The immunization section has been updated to include the new Centers for Disease Control and Prevention (CDC) recommendations for hepatitis B vaccination in patients with diabetes. This includes administering hepatitis B vaccination to unvaccinated adults with diabetes from ages 19 through 59 years, and to consider hepatitis B vaccination in all ≥60 year old patients with diabetes.[2] The CDC recommendation is a result of 29 outbreaks of hepatitis B virus that occurred in long-term care facilities and hospitals.[22]

Lastly, the recommendations for retinopathy treatment now include anti-vascular endothelial growth factor (VEGF) therapy as a treatment option for diabetic macular edema in addition to laser photocoagulation therapy. Anti-VEGF therapy has been shown to improve vision and reduce the need for laser photocoagulation in patients.[2]

Conclusion

There are many practice guidelines and algorithms available for the treatment of diabetes mellitus. However, many of these are conflicting and vary in quality. Guidelines and algorithm updates and changes have a significant impact on clinical practice and it is therefore imperative that they be scrutinized for quality and consistency. The ADA and AACE guidelines were both appraised for quality using the AGREE II instrument. [23] The AACE guidelines scored very low in the "rigor and development" domain, which accounts for methodological quality. Rather, the recommendations were highly opinion based and thus should be interpreted with caution. In contrast, the ADA guidelines scored much better in the domain reflecting methodological quality. Both guideline development groups were comprised of members with direct ties or support to industry. Ultimately, the main goal should be to individualize care by aiming for A1c, blood pressure, and lipid goals that are safe and well tolerated so that complications related to diabetes can be minimized.

Peer Reviewed by: Kevin C.J. Yuen, MD, FRCP (UK), Oregon Health & Science University, Jonathan White, Pharm.D., BCPS, Clinical Pharmacy Specialist, Providence Medical Group

References:

1. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2012;35(6):1364–1379.
2. American Diabetes Association. Standards of Medical Care in Diabetes--2013.*Diabetes Care*. 2012;36(Supplement_1):S11–S66.
3. Garber A, Abrahamson M, Barzilay J, et al. American Association of Clinical Endocrinologists' Comprehensive Diabetes Management Algorithm 2013 Consensus Statement - Executive Summary. *EndocrPract*. 2013;19(3):536–557.
4. Handelsman Y, Mechanick JI, Blonde L, et al. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. *EndocrPr Off J Am CollEndocrinol Am AssocClinEndocrinol*. 2011;17Suppl 2:1–53.
5. Effects of Intensive Glucose Lowering in Type 2 Diabetes. *N Engl J Med*. 2008;358(24):2545–2559.
6. Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. *N Engl J Med*. 2008;358(24):2560–2572.
7. Duckworth W, Abraira C, Moritz T, et al. Glucose Control and Vascular Complications in Veterans with Type 2 Diabetes. *N Engl J Med*. 2009;360(2):129–139.
8.Cardiovascular Disease & Diabetes. Available at: http://www.heart.org/HEARTORG/Conditions/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp. Accessed July 5, 2013.
9. Effects of Intensive Blood-Pressure Control in Type 2 Diabetes Mellitus. *N Engl J Med*. 2010;362(17):1575–1585.
10. Patel A. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. *The Lancet*. 8;370(9590):829–840.
11. Cooper-DeHoff RM, Gong Y, Handberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. *JAMA*. 2010;304(1):61–68.
12. Harleen Singh, Herink M. Can the diabetic war be fought by aggressive blood pressure control? *Or State Drug Rev*. 2012;2(4). Available at: http://pharmacy.oregonstate.edu/drug_policy/sites/default/files/pages/dur_board/newsletter/osdr_articles/volume2/osdr_v2_i4.pdf.
13. Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus. *N Engl J Med*. 2010;362(17):1563–1574.
14. Niacin in Patients with Low HDL Cholesterol Levels Receiving Intensive Statin Therapy. *N Engl J Med*. 2011;365(24):2255–2267.
15. Standards of Medical Care in Diabetes—2012. *Dia Care*. 2012;35(Sup. 1):S11–S63.
16. Pi-Sunyer X, Blackburn G, Brancati FL, et al.; Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes: one-year results of the look AHEAD trial. *Diabetes Care* 2007;30:1374–1383
17. Neiberg RH, Wing RR, Bray GA, et al. Patterns of weight change associated with long-term weight change and cardiovascular disease risk factors in the Look AHEAD Study. *Obes Silver Spring Md*. 2012;20(10):2048–2056.
18. O'Neil P, Smith S, Shanahan W, et al. Randomized placebo-controlled clinical trial of lorcaserin for weight loss in type 2 diabetes mellitus: the BLOOM-DM study. *Obesity (Silver Spring, Md.)*. July 2012;20(7):1426-1436.
19. Gadde K, Allison D, Day W, et al. Effects of low-dose, controlled-release, phentermine plus topiramate combination on weight and associated comorbidities in overweight and obese adults (CONQUER): a randomised, placebo-controlled, phase 3 trial. *Lancet*. April 16, 2011;377(9774):1341-1352.
20. Torgerson J, Hauptman J, Boldrin M, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care*. January 2004;27(1):155-161.
21. Smith C, Herink M. The future of newer obesity medications.*Or State Drug Rev*. 2012;2(7):1–2.
22. Centers for Disease Control and Prevention. Use of hepatitis B vaccination for adults with diabetes mellitus: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2012;60:1709–1711
23. The AGREE Collaboration. Appraisal of Guidelines for Research and Evaluation. Available: http://www.agreetrust.org/. Accessed 2013 August 5.