CLOSER LOOK

MEMORANDUM

## AACE/ACE publish updated type 2 diabetes management algorithm - January 6, 2016

**Executive Highlights**

- AACE/ACE published an updated version of its type 2 diabetes management algorithm yesterday in the journal *Endocrine Practice*.
- The most substantial change from the 2015 algorithm is the addition of a new Lifestyle Therapy section.
- The algorithm mentions a "possible benefit" of SGLT-2 inhibitors on cardiovascular disease following the EMPA-REG OUTCOME results but does not make any major changes to prescribing recommendations.

*AACE/ACE published an updated version of its type 2 diabetes management algorithm yesterday in the journal Endocrine Practice. The algorithm and accompanying executive summary are intended to supplement the organization's full 2015 clinical practice guidelines published last April. Along with the ADA/EASD position statement (most recently updated in February 2015), the AACE/ACE algorithm is one of the most widely referenced sets of guidelines for type 2 diabetes management in the US. In conversations with us, Dr. Timothy Garvey (University of Alabama, Birmingham, AL) and Dr. Alan Garber (Baylor College of Medicine, Houston, TX) noted that the organizations plan to update the guidelines once a year.*

*The most substantial change in the 2016 algorithm is the addition of a new Lifestyle Therapy section. The section provides recommendations for nutrition, physical activity, sleep, behavioral support, and smoking cessation interventions, stratified by burden of obesity and related complications. We are very pleased to see this addition, as we feel that lifestyle intervention is often underemphasized in more product-focused conference sessions. We particularly applaud AACE/ACE for addressing aspects of lifestyle like sleep and mental health that are not always considered in traditional weight loss programs. Mental health is underfunded in virtually ever therapeutic area and we hope greater visibility by AACE will help. We are fairly impressed with the specificity of the recommendations as well, and we hope future iterations will provide even more explicit guidance for clinicians on implementation.*

*Aside from this new section, the type 2 diabetes treatment algorithm itself is mostly unchanged from the 2015 version. The latest version mentions a "possible benefit" of SGLT-2 inhibitors on cardiovascular disease following the positive EMPA-REG OUTCOME results for Lilly/BI's Jardiance (empagliflozin). The algorithm also does take a more flexible approach to insulin intensification, now providing guidelines for "basal plus one, plus two, plus three" therapy in addition to basal bolus therapy. We've heard very good things about SGLT-2 and basal insulin in particular (as well as GLP-1) and it's good to see more room for different combinations. It also addresses the management of other cardiovascular risk factors like blood pressure and lipids more explicitly than in the past and includes PCSK9 inhibitors as a new option for LDL lowering in patients with type 2 diabetes.*

- **The new Lifestyle Therapy section provides specific recommendations for five categories of lifestyle interventions.** The recommendations increase in intensity for patients with more severe obesity and obesity-related complications.

| Category | Baseline Interventions | More Intense Interventions |
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| Nutrition | Plant-based diet with limited saturated fat and no trans fat<br>Aim to maintain optimal weight<br>Calorie restriction with goal of 5-10% weight reduction if BMI ≥25 kg/m² | Structured counseling<br>Meal replacement |
| Physical Activity | 150 min/week of moderate exertion plus strength training | Structured program<br>Medical evaluation/supervision for patients with contraindications/limitations on physical activity |
| Sleep | Seven hours per night | Screening for obstructive sleep apnea |
| Behavioral Support | Community engagement<br>Screening for anxiety and depression | Referral to mental health professional<br>Cognitive behavioral therapy |
| Smoking Cessation | No tobacco products | Structured programs |

- **Dr. Garber characterized the lifestyle section as an important addition to the guidelines that is too often overlooked in current practice.** He stated that this section represented a conscious decision by AACE/ACE to be more prescriptive (as it is with pharmacotherapy recommendations) rather than "assuming everyone knows something about lifestyle." He particularly emphasized the importance of family support and the role of relationships in lifestyle therapy. For example, beginning a weight loss program could be quite emotionally loaded for someone whose spouse is also overweight. Dr. Garber suggested that while helping patients implement lifestyle interventions is "everyone's job," these guidelines are aimed primarily at PCPs, as endocrinologists are hopefully more familiar with the latest evidence.
- **The new algorithm incorporates the EMPA-REG OUTCOME results to some extent but makes no major changes to prescribing recommendations, even for the specific population group tested (we would not have expected more).** The algorithm mentions a "possible benefit" of SGLT-2 inhibitors on cardiovascular disease but does not refer to a benefit on specific endpoints like reduced hospitalization for heart failure. Dr. Garber suggested that the reduction in hospitalization for heart failure could not be listed as a benefit because it was not part of the study's prespecified primary endpoint; he noted that the same reasoning could apply to a future FDA decision on a label update as well.. Overall, it appears that AACE/ACE wants to wait for more CV outcomes data on other SGLT-2 inhibitors before making any significant changes to prescribing recommendations. Dr. Garvey agreed with this assessment, stating that more trials are needed to confirm a beneficial effect and that even within EMPA-REG OUTCOME, some beneficial findings were observed sooner than expected. This conservative approach is understandable although we would've liked to seen some acknowledgement or characterization of the population group tested in EMPA-REG OUTCOME and acknowledgement of results. We assume the ADA/ EASD guidelines committee will take a similar conservative-for-now approach.
- **The 2016 guidelines appear to place a greater emphasis on broad cardiovascular risk reduction.** Unlike the 2015 version, the "guiding principles" section of the 2016 algorithm lists lipid and blood pressure therapies as part of comprehensive type 2 diabetes management - this is great to see. The 2016 version also classifies all patients with type 2 diabetes as "high" risk for cardiovascular disease and those with additional risk factors as "very high" risk. Patients were

classified as "moderate" and "high" risk, respectively, in previous versions. The latest algorithm also includes the new PCSK9 inhibitor class as an option for LDL lowering in patients with type 2 diabetes - we are very interested to see how many people with diabetes qualify for these drugs based on their current indications and insurance coverage.

- **While there were no major changes to the type 2 diabetes drug sections of the algorithm, there were a few adjustments:**
    - **More flexibility around insulin intensification:** The latest algorithm provides recommendations for the more gradual "basal plus one, plus two, plus three" therapy in addition to basal bolus therapy - this is in keeping with the call for more personalized therapy and we are glad to see it. Both versions also include GLP-1 agonists and potentially oral options as alternative ways to intensify prandial control.
    - **A slight boost for TZDs in the hierarchy of monotherapy options:** TZDs are now listed ahead of alpha glucosidase inhibitors as a preferred first-line option, though they still rank below metformin, GLP-1 agonists, SGLT-2 inhibitors, and DPP-4 inhibitors. This makes sense in our view given the side effect profile was so troubling.
    - **Removal of fluid retention warnings for TZDs and insulin.** We assume this represents a decision that these statements were redundant with other categories (like weight gain) rather than a response to new evidence.
- **The new algorithm includes a more streamlined "principles" section, with additional details reserved for the executive summary.** We see this as a wise move, as the current list of 13 one- or two-line items is much more approachable than the longer previous version. The new version also uses slightly softer language on cost. While the previous version led with the statement that "safety and efficacy should be given higher priorities than initial acquisition cost," the current version relegates that line to the executive summary. The main message highlighted in the streamlined list is that initial acquisition cost should be considered as one component of the total cost of care.

*-- by Emily Regier and Kelly Close*