Closer Look

MEMORANDUM

ADA & EASD publish 2015 update to their position statement on type 2 diabetes management - February 13, 2015

Executive Highlights

- The ADA & EASD published an update to their 2012 type 2 diabetes position statement, reflecting new data that has emerged over the past three years.
- Major changes include: the full inclusion of SGLT-2 inhibitors, a greater role for GLP-1 agonist/ basal insulin combinations, and updated data on unanswered safety questions for incretin therapies and TZDs.

At the beginning of the New Year, the ADA and EASD jointly published an update to their widely regarded 2012 patient-centered position statement on the management of type 2 diabetes in the journal Diabetes Care. The writing committee convened between June and September 2014 to discuss new clinical data that has come to light since the publication of the initial document. The authors were careful in their introduction to the update to frame the publication as an addition rather than a replacement for the 2012 position statement; the text of the update is roughly half the length of the 2012 document.

The ADA/EASD's position statements are perhaps the most widely used type 2 diabetes management guidelines around the world, although we see alternatives such as AACE/ACE's algorithm referenced fairly frequently as well. As a result, we combed through the new document to examine the updates that the writing committee made. Big-picture, the updates to the position statement do not change the underlying focus on individualized therapy, and that the changes that were made appear to be quite logical given new data that has emerged over the past few years. With regards to unanswered safety questions for certain drug classes, the text's tone is more reassuring than alarmist. We were also glad to see occasional references to the costs of different therapeutic approaches, as this is an increasingly important factor for patients. We expect to see the update showcased at CME events over the rest of the year and referenced frequently at coming scientific and medical meetings, and are excited to hear providers' reactions. For the moment, we have been somewhat surprised with how little attention the update has received relative to its importance.

We outline a list of some of the most important changes below, and consider the drivers behind the updates as well as their possible impact for clinical care and the diabetes drug landscape.

TOP FIVE UPDATES

1. We were glad to see SGLT-2 inhibitors included in the updated guidelines. It was fairly clear over the past few years that this addition was coming, and we were particularly interested to see how the writing committee would summarize the class' characteristics in the new orange box on the flow diagram. As expected, the hypoglycemia risk was listed as "low," weight effect as "loss," and cost as "high." We were more surprised to see the characterization of the class' efficacy as only "intermediate," the same classification that DPP-4 inhibitors received and less than the "high" efficacy categorization that GLP-1 agonists, TZDs, and sulfonylureas received in the guidelines - a recent clinical review article published in *JAMA* also suggested that there was no efficacy difference between SGLT-2 inhibitors and other type 2 diabetes drug classes. Some head-to-head studies comparing SGLT-2 inhibitors and DPP-4 inhibitors have found no significant differences in efficacy, but others have found greater efficacy in terms of mean A1c reductions with SGLT-2 inhibitors and the prevailing consensus among providers appears to be that SGLT-2 inhibitors have the efficacy edge, especially in patients with minimal remaining insulin production capacity. As we receive more clinical data comparing the two classes, we imagine that there is a possibility that SGLT-2 inhibitors could

jump into the high-efficacy category in the guidelines. The list of side effects included in SGLT-2 inhibitors' box in the flow diagram included genitourinary infections and dehydration.

- **The update does designate SGLT-2 inhibitors as a potential good choice to add in patients with relatively mature type 2 diabetes who are on large doses of insulin.** In this patient group, SGLT-2 inhibitors' insulin-independent mode of action should be insulin sparing. TZDs are another insulin-sparing drug class that could be used in this patient group, but the authors note that using TZDs over SGLT-2 inhibitors would come at the expense of weight and heart failure risk. This piece of the document reinforced SGLT-2 inhibitors' strength as a class that can be used across the spectrum of type 2 diabetes patients due to its unique mechanism.

2. The end of the algorithm now includes basal insulin/GLP-1 agonist combination therapy as an alternative to MDI. In the 2012 position statement this combination received one short sentence noting that the combination "may be helpful in some patients" but that data was still accumulating. The impressive results from studies such as DUAL I for Novo Nordisk's Xultophy (insulin degludec/liraglutide) showing striking (~1.9%) A1c reductions with less hypoglycemia than insulin alone and less nausea than GLP-1 agonist monotherapy appear to have given the writing committee enough evidence to expand this sentence into an enthusiastic paragraph in the 2015 update. The authors suggest that adding GLP-1 agonists rather than prandial insulin to basal insulin is preferable in terms of weight, hypoglycemia, and possibly efficacy. As a result, the update notes that combining GLP-1 agonists with basal insulin is "arguably safer, at least for short term outcomes" vs. MDI and that it is an especially attractive option for patients with obesity those unable to handle the complexity of MDI. This part of the update reflects a big-picture trend we are noticing of increasing disillusionment with MDI's complexity and hypoglycemia risk, especially when GLP-1 agonists arguably have a much more positive benefit/risk profile.

3. The ongoing discussion about metformin's use in patients with renal impairment was featured more prominently in the 2015 update than in the 2012 Position Statement. The paragraph on metformin and renal impairment was moved up from the "Comorbidities" section towards the end of the 2012 document to the top of the "Implementation Strategies" section in the update. According to the update, "there is increasing evidence that the current cut-off points for renal safety in the US ... may be overly restrictive." The authors mention recent calls for the relaxation of US guidelines to allow for metformin's use in patients with mild-to-moderate but stable chronic kidney disease (CKD). For more on this ongoing debate, read our coverage of a *JAMA* piece on the same topic by writing committee member Dr. Silvio Inzucchi (Yale University School of Medicine, New Haven, CT).

4. The overviews of other type 2 diabetes drug classes also received meaningful updates:

- **A paragraph on DPP-4 inhibitors focused on the findings of the SAVOR and EXAMINE cardiovascular outcomes trials for AZ's Onglyza (saxagliptin) and Takeda's Nesina (alogliptin), respectively.** We were glad to see the authors call out the relatively short duration of these two trials: "only slightly more than 2 years" for SAVOR and "an even shorter period (18 months)" for EXAMINE. The authors mentioned the heart failure signal seen in SAVOR but also noted that a wider database interrogation indicated no worrying signals for either overall cardiovascular disease or heart failure. The DPP-4 inhibitor paragraph ended with the cautious but appropriate recommendation that the class should be used cautiously, if at all, in patients with pre-existing heart failure; this is in line with what we have heard from KOLs at recent meetings. When the results from TECOS (for Merck's Januvia [sitagliptin]) come out at ADA we would do not believe a heart failure signal is likely to emerge given the lack of a convincing mechanistic explanation for why an true increase in risk may exist - however there is always room for surprises.
- **The language on incretin therapies and pancreatitis was more reassuring (albeit cautiously so) than the sentence on pancreatitis in the 2012 Position Statement.** Specifically, the authors note in the update that emerging data from large observational studies as well as SAVOR and EXAMINE have found no statistically significant increase in pancreatic adverse outcomes. The prescribing guidelines for GLP-1 agonists continue to recommend against their use in patients with a prior history of pancreatitis.

- **The small section on TZDs in the update noted that earlier concerns about pioglitazone and bladder cancer have largely been addressed by recent evidence.** Takeda recently submitted ten-year epidemiological results showing no association between pioglitazone and bladder cancer. The authors also note that TZDs have gone generic and therefore are more attractive from a cost perspective, although the list of side effects is still fairly significant.

5. The figure detailing the spectrum of factors that impact the individualization of therapy is now divided into "usually modifiable" and "usually not modifiable" categories. The modifiable factors are patient attitude (motivation, adherence, self-care capabilities) and the availability of resources and support systems. Non-modifiable factors include hypoglycemia risk, disease duration, life expectancy, comorbidities, and established vascular complications. This distinction will hopefully direct focus towards patient support and education to promote adherence, a key modifiable factor.

- **The figure now has the adjustable central A1c target of 7% listed in the center to provide a frame of reference.** Factors favoring more stringent goals would push the target below 7%, while a target above 7% may be appropriate for other types of patients (older, established complications, etc.). This change should hopefully help reduce some of the perceived abstractness of the individualization process for providers with relatively less familiarity with the ADA/EASD's recommended approach.

Other notable updates included: (i) mention of more concentrated insulins (i.e.: U500 insulin); (ii) a slight re-design of the diagram on insulin intensification that now allows for the progression from basal insulin directly to MDI with at least two prandial insulin injections; and (iii) a brief reference in the conclusion to the ongoing GRADE comparative effectiveness study (results not expected before 2020).

Items that were not substantially referenced included: (i) single-pill fixed-dose combinations of different oral glucose-lowering drugs; (ii) SGLT-2 inhibitors/GLP-1 agonist co-therapy, which we hear is great for many patients due to weight loss, no hypo, and strong efficacy, although high cost - there is not a large evidence base yet but there are studies ongoing; and (iii) interchangeability of drugs within a class, which is increasingly a factor due to the shift towards single-source formularies. The word "adherence" appeared only once in the text of the update and once in the figure on factors influencing the individualization of treatment - given how important adherence is for efficacy and improved outcomes, we hope to see more on adherence in the next update. We also think there is room to better flesh out some guidelines on the critical communication element between providers and patients.

The writing group for the 2015 update was the same as for the 2012 Position Statement:

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- Co-chair Dr. David Matthews (University of Oxford, Oxford, UK)
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- Dr. Anne Peters (Keck School of Medicine of the University of Southern California, Los Angeles, CA)
- Dr. Apostolos Tsapas (Aristotle University, Thessaloniki, Greece)
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