CLOSER LOOK

MEMORANDUM

ADA publishes 2017 Standards of Care - December 16, 2016

Executive Highlights

- The ADA's 2017 Standards of Care were published yesterday in *Diabetes Care*.
- Notably, this newly-released version of the document officially recommends Lilly/BI's Jardiance (empagliflozin) and Novo Nordisk's Victoza (liraglutide) for patients with type 2 diabetes at high-risk for cardiovascular events - this is one of the biggest changes to the Standards of Care in recent history. BI's Dr. Thomas Seck, Vice President of Clinical Development and Medical Affairs, Primary Care, spoke to the national and global influence of ADA guidelines, and to what this revision really means for the role of cardioprotection in diabetes management in 2017 and beyond.
- Additional substantial revisions from the 2016 Standards of Care include the addition of basal insulin/GLP-1 agonist products in the algorithm for type 2 diabetes combination therapy (a major win for drugs approved so recently), an updated definition of clinically-meaningful hypoglycemia at blood sugar <54 mg/dl (the work of the International Hypoglycemia Study Group), a greater overall emphasis on psychosocial support for people with diabetes (a major win), and a focus on the high cost of insulin in the US.

Yesterday, the ADA released its official Standards of Care for 2017, published in Diabetes Care. *In this report, we review some of the most notable changes that have been made since the Association's 2016 Standards of Care and discuss potential implications for the field in the year ahead.*

1. The 2017 Standards of Care explicitly encourage the prescription of empagliflozin (Lilly/BI's SGLT-2 inhibitor, Jardiance) or liraglutide (Novo Nordisk's GLP-1 agonist, Victoza) to patients at high-risk for cardiovascular (CV) morbidity and mortality. Data from the EMPA-REG OUTCOME and LEADER trials is now included in the section on CV disease and risk management. This is a very big win for these compounds.

2. Fixed-ratio combinations of basal insulin/GLP-1 agonists are now considered in the recommended algorithm for combination therapy - this was fast!

3. As part of a greater emphasis on the high cost of insulin in the US, tables have been added to the 2017 Standards of Care to display the cost of insulin products (as well as non-insulin pharmacotherapies). A figure outlining recommendations for antihyperglycemic therapy in type 2 diabetes has been updated to acknowledge rising insulin prices. Another new section describes the role of biosimilar insulins in diabetes care.

4. Based on recommendations from the International Hypoglycemia Study Group, the ADA Standards of Care features a new classification for hypoglycemia: clinically-significant hypoglycemia is now defined at blood glucose <54 mg/dl, while blood glucose <70 mg/dl should be used as an "alert value." We are very glad to see the field moving away from the "mild to moderate" terminology.

5. The 2017 Standards of Care features a sharpened emphasis on type 2 diabetes prevention, starting with a push for better, more frequent prediabetes screenings. We're also very glad to see this and wonder how the field will actually make these screenings happen.

6. The need for psychosocial support in diabetes care is an overarching theme throughout the document, with particularly strong recommendations for psychosocial treatment in pediatric patients.

- **Many in the diabetes field have been eagerly awaiting guidelines updates that recommend Jardiance (empagliflozin) and Victoza (liraglutide) for the treatment of type 2 diabetes in patients at high-risk for CV death.** The ADA guidelines are among the

most influential diabetes treatment guidelines in the world - a point not lost on BI's Vice President of Clinical Development and Medical Affairs, Primary Care, Dr. Thomas Seck, who called the ADA a "clear authority in the US and worldwide." Dr. Seck continued, "there's no doubt in my mind that this is an influential guideline, and an important step toward making sure that patients are receiving appropriate medications at the appropriate time." We're very pleased by the elevated awareness of the CV benefits of empagliflozin and liraglutide that is sure to result from this update. This endorsement follows (i) compelling findings from the EMPA-REG OUTCOME and LEADER trials, respectively, (ii) the FDA approval of an expanded indication for Jardiance to include reduction of CV death, and (iii) Novo Nordisk's submission of LEADER data for inclusion on the Victoza label. Given the immense investment that goes into CVOTs (in both time and resources) we're so happy to see that positive results from these trials are making waves in FDA indications and treatment recommendations. These are essential steps to making cardioprotection a core aspect of diabetes care in real-world clinical settings.

- **Dr. Seck emphasized how crucial education will be in spreading awareness of these new ADA guidelines (along with the new Jardiance indication) to cardiologists, endocrinologists, primary care physicians, and patients.** "In the end, it all comes down to education and awareness," he explained. "If you have enough time you can talk to a provider about all the data in EMPA-REG OUTCOME, but if not, you now have tremendous support from the Standards of Care plus the label update." Moreover, Dr. Seck highlighted Lilly/BI's Sweetheart campaign, which aims to educate people on the tight link between type 2 diabetes and CV disease (an association that's lost on a majority of Americans and a majority of type 2 diabetes patients themselves). We couldn't agree more that education is the critical next step here - it's fantastic progress to see the ADA recommend Jardiance and Victoza for their CV benefits, but we won't see meaningful improvements in diabetes care until all players are caught up to speed. We hope that the companies behind these products target education to cardiologists - who can now very well prescribe Jardiance and Victoza - at conferences like AHA and ACC, among other communication channels. Moreover, we're curious to see what efforts the ADA will make to spread awareness of all important updates to the Standards of Care, but especially this one given its major implications on clinical approaches to diabetes treatment.
- **Lilly has long suggested that the reflection of EMPA-REG OUTCOME results in the label for Jardiance and in diabetes treatment guidelines will serve as an inflection point in sales of Jardiance and the SGLT-2 inhibitor class as a whole.** Indeed, the company expressed high hopes for the "imminent" updating of treatment guidelines in its 2017 Financial Update yesterday and today released an announcement expressing support for the new recommendation. We also can't underestimate the power that ADA guidelines could have on payers and access - if nothing else, they offer leverage to healthcare providers and increase the chance that these advanced diabetes therapies will be reimbursed.
- **On the other hand, the inclusion of a recommendation for liraglutide therapy in patients with cardiovascular disease on the basis of the LEADER results may strike some as a bit surprising, as the results are not yet included on the label for Victoza.** We suspect Dr. Bob Ratner, the outgoing Chief Scientific Officer, wanted to make this happen and did so (today was his last day, as we understand it). Diabetes guideline committees have historically been rather conservative in their recommendations - indeed, the release of the EMPA-REG OUTCOME full results did not significantly affect recommendations for empagliflozin usage in the ADA's 2016 Standards of Care. Similarly, the 2016 update to the AACE/ACE diabetes treatment algorithm noted the EMPA-REG OUTCOME results but did not make significant changes to prescribing recommendations. We're curious if the difference in the treatment of the EMPA-REG OUTCOME and LEADER results may be traced to a greater degree of comfort with the LEADER results among those in the diabetes field due to its perceived clearer mechanism

of benefit. We've heard on the conference circuit that cardiologists are more comfortable with EMPA-REG OUTCOME than endocrinologists to some extent (and the ESC guidelines for heart failure were quick to include empagliflozin this year), while endocrinologists are more excited about the LEADER results.

    - **If we could jump on the train of less-than-conservative suggestions for a moment...we're incredibly curious to see how these agents with demonstrated CV benefit could be used in a prediabetes population to prevent CV events even earlier.** J&J has announced plans to conduct a CVOT for SGLT-2 inhibitor Invokana (canagliflozin) in a people with prediabetes, and we wonder if drugs in this class might even be investigated for their potential to prevent type 2 diabetes altogether. The most efficient way to go about this would be to investigate all SGLT-2 inhibitors in a single prevention study, though we understand that incentives may not be aligned to get companies to invest in such a trial.

- **Following the FDA approvals of Novo Nordisk's Xultophy (insulin degludec/ liraglutide) and Sanofi's Soliqua (insulin glargine/lixisenatide), the ADA now incorporates basal insulin/GLP-1 combinations in its combination therapy treatment algorithm.** As we noted in our coverage of these two drug approvals (which came within hours of each other!), this class of combination agents has been one of the most highly-anticipated in the recent history of the diabetes world. Xultophy and Soliqua have both shown impressive glucose-lowering efficacy alongside a milder side-effect profile compared to insulin or GLP-1 agonist monotherapy. Given this, we're pleased to see the ADA provide a framework for the inclusion of these options in clinical practice. We're hopeful that patients and providers duly consider a basal insulin/GLP-1 fixed-ratio combination, though how the products are priced and reimbursed in the US will have a major impact on patient access and uptake.
- **The issue of insulin pricing in the US was included, unsurprisingly.** Last month, the ADA issued a resolution calling for access to affordable insulin; it's clear this comes from the board and entire management team and staff, though we are not sure where this will head. We very much appreciate the growing acknowledgement that, increasingly, treatment decisions are based on reimbursement and access rather than clinical characteristics or HCP and/or patient preference. While this is clearly not the ideal situation - and we applaud companies that are taking action to address these issues - we believe it's important that patients and providers have as much relevant information as possible as they navigate the many diabetes drugs and drug classes (though, again, their choices matter less today, far less, than what the formularies allow). We're hopeful that the repeat emphasis on insulin pricing throughout this document will alert more healthcare professionals to the issue and will prompt providers to include cost in their discussions with patients about their treatment options.
- **The 2017 Standards of Care defines severe hypoglycemia at blood glucose <54 mg/dl, re-classifying <70 mg/dl as an "alert value" for patients and providers to prevent a hypoglycemia episode.** We recently heard Dr. Simon Heller (University of Sheffield, UK) present this recommended change to hypoglycemia classification based on the work of the International Hypoglycemia Study Group at WCPD 2016. As we've previously noted, consensus on hypoglycemia is absolutely critical for the field as we investigate new therapies - the ADA's position on hypoglycemia classification as per this newly-released document is a step toward this goal.
- **Prevention has a stronger presence in the ADA's 2017 Standards of Care, which can only be beneficial for health and health economic outcomes in the US.** The Diabetes Prevention Program (DPP) has been shown to be cost-saving, and even lower-cost translations of the DPP are forthcoming - with virtual platforms and group-based programs. With Medicare coverage of the DPP slated to start in 2018, this emphasis from the ADA on prediabetes screening (so that people at high-risk for type 2 diabetes are actually identified and enrolled in effective prevention programs) is very fitting.

- **The increased focus on psychosocial aspects to diabetes care are also extremely positive, in our view.** We've heard a consensus from thought leaders in the field that better psychosocial supports are critical to improve diabetes care - especially when you confront the fact that a majority of diabetes management is *self*-management.

-- by Payal Marathe, Helen Gao, and Kelly Close