The American Diabetes Association’s (ADA) 2017 Standards of Care were published in *Diabetes Care* on 15 December 2016. Notable changes in the new guidelines include the recommendation of sodium-glucose cotransporter 2 (SGLT-2) inhibitor empagliflozin and glucagon-like peptide 1 (GLP-1) agonist liraglutide for type 2 diabetes (T2D) patients at high risk for cardiovascular morbidity and mortality. Data from the Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME) trial and the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) trial are now included in the section on cardiovascular disease and risk management. In addition, fixed-ratio combinations of a basal insulin and a GLP-1 agonist are included in the algorithm for combination therapy, just weeks after the first of these products, Novo Nordisk’s (Copenhagen, Denmark) Xultophy (insulin degludec/liraglutide) and Sanofi’s (Paris, France)Soliqua (insulin glargine/lixisenatide), were approved by the US Food and Drug Administration (FDA) for prescription in the US. Based on recommendations from the International Hypoglycemia Study Group, the ADA’s 2017 Standards of Care features a new classification for hypoglycemia: clinically significant hypoglycemia is now defined at blood glucose levels <54 mg/dL, whereas blood glucose levels <70 mg/dL should be used as an “alert value” to help individuals avoid more severe hypoglycemia. The ADA’s new guidelines also include a greater emphasis on cost of diabetes drugs, T2D prevention (with a push for more frequent prediabetes screenings), and psychosocial support in diabetes care, especially for adolescents and pediatric patients.

**14th Annual World Congress on Insulin Resistance, Diabetes, and Cardiovascular Disease**

The 14th Annual World Congress on Insulin Resistance, Diabetes, and Cardiovascular Disease took place in Los Angeles (CA, USA) from 1 to 3 December 2016, drawing almost 500 attendees. A presentation on the promise of fibroblast growth factor (FGF)-1 in reversing insulin resistance discussed how FGF-1 administration to genetically obese mice can normalize blood glucose levels, improve insulin sensitivity, and lower liver fat levels through action at the adipocyte FGF-1 receptor. Although FGF-1 has a short half-life when administered systemically, studies of optimized FGF-1 analogs have demonstrated the possibility of longer-term glucose-lowering effects. These analogs offer the added benefit of no thiazolidinedione (TZD)-like side effects, and could present a
management of T2D. This meeting featured a discussion of the TZD class of agents as well, and a presentation of major findings from the Insulin Resistance Intervention after Stroke (IRIS) trial. Treatment with the insulin-sensitizing TZD pioglitazone over the course of 5 years reduced the relative risk of stroke and myocardial infarction by 24% (P = 0.007), reduced the incidence of new-onset diabetes by 52% (P < 0.001), and reduced the relative risk of acute coronary syndrome by 25% compared with placebo. All participants in the IRIS trial were patients with a recent history of stroke or transient ischemic attack who were found to have insulin resistance, but who did not have diabetes (n = 3876). Thiazolidinediones have been associated with undesirable side effects, namely weight gain and edema, although this side effect profile is thought to be more benign with lower doses.

References

Company Updates

Elicelyx Therapeutics (San Diego, CA, USA) reported positive topline data from the Phase 2b dose-ranging study of metformin delayed release (DR). The drug met its primary endpoint of statistically significant reduction in HbA1c at 16 weeks. The trial enrolled 571 patients with T2D HbA1c between 7% and 10.5% who were at least 25 years old with an estimated glomerular filtration rate (eGFR) >60 mL/min per 1.73 m². Participants were randomized to daily treatment with one of four doses of metformin DR (600, 900, 1200, or 1500 mg), daily treatment with placebo, or twice-daily treatment with 1000 mg immediate-release metformin. The company announcement noted that the HbA1c efficacy of metformin DR was dose dependent, although no data were reported on the magnitude of the HbA1c reduction for the different study arms. A previous study found that the agent results in lower metformin exposure in the blood and comparable glucose-lowering efficacy to immediate-release metformin. Elicelyx plans to conduct two Phase 3 trials of metformin DR.
Company Updates

**November 21, 2016**
Novo Nordisk and Sanofi both announced the FDA approval of their basal insulin/GLP-1 agonist fixed-ratio combination products, Xultophy (insulin degludec/liraglutide) and Soliqua (insulin glargine/lixisenatide), respectively. The two therapies will now share first-to-market status in the US. Novo Nordisk’s Xultophy is launched in seven countries, not including the US, whereas Sanofi’s Soliqua is not yet available in any ex-US market (although a decision by European regulatory agencies is expected in early 2017). Soliqua was approved by the FDA for delivery through a single, prefilled SoloStar pen, despite Sanofi previously pointing to the availability of two pens with two distinct ratios as an advantage over Xultophy. Novo Nordisk’s fixed-ratio combination will also be available in a single pen.

**November 21, 2016**
Intarcia (Boston, MA, USA) announced the filing of a New Drug Application (INDA) to the FDA for ITCA 650, an implantable mini pump that offers continuous subcutaneous release of the GLP-1 agonist exenatide for 3 or 6 months (the initiation and maintenance doses, respectively). The NDA covers all aspects of ITCA 650, from extended-release exenatide to the Medici technology platform, which includes the mini pump device, high temperature stability components, and placement and removal kits for the mini pump. The company anticipates a typical 10- to 12-month review process, which means an FDA decision is expected in late 2017. It is possible that the FDA will convene an Advisory Committee meeting before making a regulatory decision, given ITCA 650’s novel delivery mechanism for a GLP-1 agonist.

**November 29, 2016**
Novo Nordisk released topline results from a Trial Comparing Cardiovascular Safety of Insulin Degludec Versus Insulin Glargine in Subjects with Type 2 Diabetes at High Risk of Cardiovascular Events (the DEVOTE trial) of Tresiba (basal insulin degludec). Tresiba met its primary endpoint by demonstrating non-inferiority to Sanofi’s Lantus (insulin glargine) for the composite outcome of three-point major adverse cardiac events (MACE; non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death). The hazard ratio was 0.91 in favor of Tresiba, although the relative risk reduction for cardiovascular events was not statistically significant. The P value was not shared. The difference in average HbA1c between Tresiba- and Lantus-treated groups was 0.01% at the end of the trial (n = 7367). This reinforces the glycemic equipoise design of the study, intended to isolate the cardiovascular effects of a drug itself, as opposed to the potential cardiovascular impact conferred by HbA1c reduction in general. The company announcement also detailed secondary endpoints from the DEVOTE trial demonstrating lower hypoglycemia rates with Tresiba than with Lantus: 27% fewer patients on Tresiba versus Lantus experienced severe hypoglycemia; there was a 40% risk reduction for an adjudicated, severe hypoglycemia event with Tresiba versus Lantus; and there was a 54% relative risk reduction for severe nocturnal hypoglycemia with Tresiba versus Lantus. All these findings were statistically significant, lending additional support to Tresiba’s hypoglycemia benefit as shown in the SWITCH 1st and SWITCH 2nd trials. Novo Nordisk is expected to report full results from DEVOTE in the first half of 2017.

**November 29, 2016**
Oramed Pharmaceuticals (Jerusalem, Israel) reported results from a Phase 1b investigation of the oral GLP-1 agonist formulation ORMD-0901 (oral exenatide). The study found the agent to be safe and well tolerated in adults with T2D, and the company announcement shared that results in the ORMD-0901 treatment arm trended towards efficacy.

**December 2, 2016**
Lilly’s (Indianapolis, IL, USA) and Boehringer Ingelheim’s (Ingelheim, Germany) SGLT-2 inhibitor Jardiance (empagliflozin) became the first T2D medication approved for the reduction of cardiovascular death in the US. The FDA approval of the expanded indication for Jardiance reflects the positive cardiovascular benefit shown in Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes (EMPA-REG OUTCOME).

**December 2, 2016**
Novo Nordisk announced positive topline results from the Phase 3b Clinical Trial Comparing Efficacy and Safety of Insulin Degludec/Liraglutide (IDegLira) Versus Basal-bolus Therapy in Subjects With Type 2 Diabetes Mellitus (DUAL VII; n = 506) for the fixed-ratio combination Xultophy (insulin degludec/liraglutide). The combination therapy demonstrated non-inferior HbA1c reduction, lower hypoglycemia risk, and greater weight loss compared with basal-bolus therapy with Sanofi’s Lantus (insulin glargine) and Novo Nordisk’s NovoLog (insulin aspart). Participants in both treatment arms experienced a mean 1.5% drop in HbA1c after...
## Company Updates

### December 2, 2016

26 weeks, from a baseline HbA1c of 8.2%. Participants treated with Xultophy experienced an 89% reduction in severe or blood glucose-confirmed hypoglycemia compared with those treated with the basal-bolus regimen. The company announcement stated that this hypoglycemia difference in favor of Xultophy was statistically significant, but did not share a P-value. The end-of-trial body weight difference between treatment arms was 3.6 kg in favor of Xultophy: participants on Xultophy experienced a mean weight loss of 0.9 kg, whereas those on basal-bolus therapy experienced a mean weight gain of 2.6 kg. Novo Nordisk further shared that the mean daily dose of Xultophy at the end of the 26-week trial was 40.1 units (40.1 units insulin and 1.4 mg liraglutide), compared with a mean daily dose of 84.6 units insulin in the basal-bolus group. The company is expected to report full results from DUAL VII in the first half of 2017.

### December 5, 2016

Novo Nordisk submitted once-weekly GLP-1 agonist semaglutide as an NDA to the FDA and as a Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA). Under a standard review process, regulatory decisions for the US and Europe are expected in late 2017. If approved, semaglutide could be the seventh or eighth GLP-1 agonist therapy available to patients with T2D, depending on the approval timeline for Intarcia’s ITCA 650 (implantable exenatide mini pump), submitted in November to the FDA. The NDA and MAA for semaglutide are based on results from the Phase 3 SUSTAIN clinical development program, including the SUSTAIN 6 trial (Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes), which showed a 26% relative risk reduction for three-point MACE (non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) with semaglutide versus placebo.9

### December 12, 2016

Lilly announced the FDA approval of Boehringer Ingelheim-partnered Synjardy XR, an extended-release version of the fixed-dose combination of the SGLT-2 inhibitor empagliflozin with metformin. Synjardy XR is now the third once-daily tablet of SGLT-2 inhibitor/metformin combination therapy available in the US, following AstraZeneca’s (London, UK) Xigduo XR (dapagliflozin/metformin extended release) and Johnson & Johnson’s (New Brunswick, NJ, USA) Invokamet XR (canagliflozin/metformin extended release). None of these three medicines is yet approved for use in Europe due to the lack of availability of extended-release metformin.

### December 14, 2016

vTv Therapeutics (High Point, NC, USA) announced positive results from a Phase 2 investigation of the oral GLP-1 agonist candidate TTP273. The 12-week trial (n = 174) found that a once-daily 150 mg dose of TTP273 led to a statistically significant, placebo-adjusted HbA1c reduction of 0.86%, whereas a twice-daily 150 mg dose led to a statistically significant, placebo-adjusted HbA1c reduction of 0.71%. On average, participants in the placebo arm of the trial experienced a 0.15% increase in HbA1c over 12 weeks. Once-daily TTP273 was associated with modest weight loss of 0.9 kg, whereas twice-daily TTP273 was associated with 0.6 kg weight loss. Neither HbA1c lowering nor weight loss seem to be dose-dependent effects of the oral GLP-1 agonist agent. The company announcement reported a lower incidence of nausea in the GLP-1 groups compared with the placebo group. No vomiting occurred in the TTP273 arms. Gastrointestinal side effects are the most common adverse events associated with currently available GLP-1 agonists.

### December 15, 2016

Lilly and Boehringer Ingelheim launched Basaglar (biosimilar insulin glargine) in the US. The product was already sold outside the US under the brand name Abasaglar. This date was scheduled for the US launch of the product through Lilly’s and Boehringer Ingelheim’s settlement of a patent infringement lawsuit over Lantus (insulin glargine) with Sanofi back in September 2015. According to Lilly management, Basaglar will be priced at a 15% discount to Sanofi’s Lantus in US pharmacies.

Lexicon Pharmaceuticals (Woodlands, TX, USA) reported positive topline data from the Phase 3 inTandem2 trial of the sodium–glucose cotransporter 1/SGLT-2 dual inhibitor sotagliflozin. The study was conducted in type 1 diabetes patients from Europe and Israel (n = 782) who were randomized to 200 mg sotagliflozin, 400 mg sotagliflozin, or placebo after insulin optimization. The 200 and 400 mg doses of the agent were associated with clinically meaningful, statistically significant, placebo-adjusted HbA1c reductions of 0.36% and 0.35% after 24 weeks, respectively (P < 0.001 for both doses). Baseline HbA1c was between 7.7% and
### Company Updates

**December 21, 2016**  
7.8% following 6 weeks of insulin optimization. Lexicon management characterized sotagliflozin as well tolerated overall. Adverse event rates were 56% in the 200 mg group, 54% in the 400 mg group, and 51% in the placebo group. Serious adverse events occurred in 4.2% of participants on 200 mg sotagliflozin, 4.2% of participants on 400 mg sotagliflozin, and 3.5% of participants on placebo. Treatment-related adverse events led to discontinuation of therapy in 2% of individuals in the 200 mg arm, 3% of individuals in the 400 mg arm, and 1.6% of individuals in the placebo arm. Two deaths occurred, both in the placebo group. Sotagliflozin caused diabetic ketoacidosis in one person in the 200 mg arm (an event rate of 0.4%) and in three people in the 400 mg arm (event rate 1.1%). Severe hypoglycemia was neither increased nor
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