Diabetes Update 2016

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Supporter

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Disclosures

• Staci-Marie Norman is a speaker for Eli Lilly and Company. Dr. Norman’s spouse is employed by Takeda Pharmaceutical Company.
• Jennifer Smith declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

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Learning Objectives

At the completion of this knowledge-based activity, participants will:

• Summarize important recent changes to the American Diabetes Association (ADA) Standards of Medical Care in Diabetes and other authoritative guidelines.
• Describe evidence regarding the risks and benefits of new and emerging medications and products for the management of patients with diabetes.
• Identify noteworthy findings from recent large clinical trials that have the potential to influence diabetes care.
• Explain how to apply emerging information to the care of patients with diabetes.
1. According to AACE 2016 ASCVD Risk Factor Modification Algorithm, which of the following is an appropriate goal for most people with diabetes?
   A. High-intensity statin therapy if > 65 yoa
   B. Goal for blood pressure is <140/90
   C. LDL-C of <70mg/dL if at very high risk for ASCVD
   D. Hemoglobin A1C goal of < 7%

2. All but the following medication can be used long-term for weight management in diabetes.
   A. Orlistat 120mg
   B. Liraglutide 1.8mg
   C. Bupropion/naltrexone 90mg/8mg
   D. Phentermine/topiramate ER 15mg/92mg

3. SGLT2 inhibitors have been associated with:
   A. joint pain
   B. heart failure
   C. euglycemic DKA
   D. worsening albuminuria

4. Which disease state should DPP-4 inhibitor treatment be used cautiously?
   A. Mild renal impairment
   B. Rheumatoid arthritis
   C. Recurrent UTI
   D. Osteoporosis

5. Which was a finding of the treatment arm in the EMPA-REG Outcome Study?
   A. Increased incidence of diabetic ketoacidosis
   B. Increased incidence of bone fractures
   C. Decreased incidence of genital infections
   D. Decreased incidence of cardiovascular death

The Good, The Bad and The Ugly
Or Is It?
New January 2016 from CDC

- Short online test
- Links to CDC National Diabetes Prevention Program
- Program provides information
  - Lifestyle change
  - Directory of CDC-recognized lifestyle change programs
  - Testimonials from participants

CDC and AMA Joined Forces

- Multi-year initiative
- Provides resources for health professionals for:
  - Screening
  - Referring to DM program
  - Feedback of patient progress in DM program

There is HOPE

- CDC published study
  - Findings suggest diabetes epidemic slowing
  - Approx. 1.7 million new cases, but first time in decades this didn’t increase
  - Overall rate of new cases slowing BUT…
    - Increased rate of diagnosis
      - Hispanic
      - African-American
      - People with less than high school education

Continued Hope

- CDC report 12/2015
  - New cases down to 1.4 million
  - Biggest decrease in
    - Men
    - Caucasian
    - Young-middle age
    - Higher educated
ADA 2016 Standards of Medical Care in Diabetes

Section 1: Strategies for Improving Care
- Recommendations on tailoring treatment to vulnerable populations
  - Food insecurity
  - Cognitive dysfunction/mental illness
  - HIV
- Discussion on disparities related to:
  - Ethnicity
  - Culture
  - Sex
  - Socioeconomic

Section 2: Classification and Diagnosis
- No diagnostic test is preferred over another
  - Fasting vs. 2-h post 75g OGTT vs. A1c
- Test all adults beginning at 45 regardless of weight
- Test asymptomatic adults of ANY AGE if overweight/obese + other risk

Section 2 continued:
- Gestational DM:
  - Test for undiagnosed DM at 1st prenatal appointment
  - Test for GDM at 24-28 weeks in no previous DM
  - Screen 6-12 weeks postpartum for persistent DM
  - History of GDM should have lifelong screening at least every 3 years
  - History of GDM found to have pre-DM – intervention with lifestyle mod. & metformin

Section 2 continued:
- Monogenic Diabetes Syndromes
  - All diagnosed before 6 months of life should have genetic testing
  - Maturity-onset diabetes of the young should be considered if
    - Mild stable fasting hyperglycemia
    - Multiple family members with DM not characteristic of T1 or T2DM
    - Refer to specialist for further evaluation

Section 3: Foundations of Care and Comprehensive Medical Evaluation
- Sections 3 and 4 from 2015 standards were combined
  - Reflects importance of integrating:
    - Medical evaluation
    - Patient engagement
    - Ongoing care highlighting lifestyle and behavioral modification

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Section 3 continued:
• Nutrition Recommendations Streamlined
  – Promote and support healthful eating
  – Achieve/maintain body weight goals
  – Attain glycemic, BP and lipid goals
  – Delay or prevent complications
  – Address individual nutrition needs
  – Maintain the pleasure of eating by not judging food choices
  – Provide practical tools for developing healthful eating

Section 3 continued:
• Vaccination Recommendations Streamlined
  – Provide routine vaccinations based on age
    – General public recommendations
      – Administer Hepatitis B to unvaccinated ages 19-59
      – Consider Hepatitis B vaccine to unvaccinated >60

Section 4: Prevention to Delay of T2DM
• Acknowledges the role of technology in prevention
  – Encourages use of apps and text messaging programs
    – Especially for lifestyle modification

Section 5: Glycemic Targets
• Adults over age 65 should have full access to:
  – Continuous blood glucose monitoring
  – Insulin pumps
  – In response to increased number of insulin-dependent older adults

Section 6: Obesity Management for Treatment of T2DM
• New Section combining:
  – Prior bariatric surgery recommendations
  – New comprehensive assessment of weight recommendations
    – BMI calculated, recorded and discussed at every appointment
  – New recommendations for treatment with behavior modification
    – Goal is 5% weight loss
    – High intensity intervention (>16 sessions in 6 months)
    – All diets are equally effective in achieving weight loss (same caloric intake)
    – After achieving short-term goal set long-term goal and routine monitoring (monthly)
    – High intensity lifestyle intervention can be used short term under trained practitioner

Section 6: continued
• New section
  – New recommendations for pharmacotherapy
    – Consider effect on weight when choosing glucose-lowering medications
    – Minimize medications for comorbid conditions associated with weight gain
    – BMI>27 weight loss medication may be effective with lifestyle modifications
    – If response to medication is <5% in 3 months, discontinue or try alternative
**Section 6: continued**

- New table of currently approved medications for long-term treatment
  - Orlistat (Alli and Xenical) 60 or 120mg
  - Lorcaserin (Belviq) 10mg
  - Phentermine/topiramate ER (Qsymia) all strengths
  - Naltrexone/bupropion (Contrave) 8/90mg
  - Liraglutide (Saxenda) 6mg/dL

**Section 7: Approaches to Glycemic Treatment**

- Bariatric surgery recommendations removed from this section
  - Placed in Section 6 with Obesity Treatments
- No changes to the ADA Treatment Algorithms were made

**Section 8: Cardiovascular Disease and Risk Management**

- Atherosclerotic cardiovascular disease (ASCVD) replaces CVD
- In older adults pharmacological tx to goal <130/70 not recommended
- Addition of ezetimibe (Zetia) to moderate-intensity statin
  - Proven to provide additional cardiovascular benefit
  - Good for those who may not tolerate high-intensity statin
- Table 8.1 efficacy and dose details on high/mod-intensity statin tx

**Section 8: continued**

- ASA therapy should be considered in men AND women
  - Older than 50 years of age with 1 additional risk factor
  - Based on multiple recent studies looking at risk of CAD or stroke in men vs. women or by age
  - Women with DM found to have the same if not higher risk of MI or stroke
- ASA therapy in patients <50 years of age
  - Low risk (10yr ASCVD risk <5%) ASA not recommended
  - Intermediate risk (10yr risk 5-10%) ASA use up to clinical judgement

**Section 9: Microvascular Complications & Foot Care**

- Nephropathy changed to diabetic kidney disease
- Refer for renal replacement if est. GFR <30mL/min/1.73m²
- Refer to nephrologist if:
  - Uncertain of etiology of kidney disease
  - Difficult management issues (anemia, resistant HTN…)
  - Rapidly progressing disease
- Intravitreal anti-vascular endothelial growth factor indicated for center-involved diabetic macular edema
  - More effective than laser therapy

**Section 10: Older Adults**

- All recommendations are more comprehensive and focus on individualizing care based on individual
- Changes that stand out:
  - Screen for geriatric syndromes limiting activities of daily living, might affect diabetes self-management
  - High priority population for depression: screen and treat
  - Hyperglycemia should be screened for and avoided
  - Glycemic goals might reasonably be relaxed to avoid hypoglycemia
Section 10: Continued

• Changes
  – Palliative Care:
    • Strict BP control might not be necessary, even consider stopping therapy
    • Same with lipid management
  – Long-term Care:
    • DM education for staff to improve management
    • Patient needs careful assessment to est. glycemic goal based on clinical/functional status
    • End of Life:
      • Overall comfort, prevent distressing symptoms and preserve QOL is goal

Section 11: Children and Adolescents

• New recommendations for children with T2DM
  – Treatment goal same as T1DM but also includes comorbidity management
  – Obesity
  – Dyslipidemia
  – Hypertension
  – Albumin levels
  – Lifestyle modification must be priority #1
    • Family centered approach to diet and physical activity is key
    • Metformin is only oral hypoglycemic approved for children
  – Hyperlipidemia screening in T1DM has changed from 2 to 10 yoa

Section 12: Management of Diabetes in Pregnancy

• Pre-gestational Recommendation Changes
  – Family planning should be discussed and contraception used until woman is prepared for pregnancy
  – A1C <6.5% ideally to reduce risk of congenital anomalies
  – Counselling on risk of developing or progressing DM retinopathy
    • Eye exam before pregnancy or 1st trimester
    • Monitor each trimester and 1 year post-partum
  • Gestational DM
    – Lifestyle change essential component
    – Preferred medication is metformin or insulin

Section 13: Diabetes Care in the Hospital

• Consider A1C on all hyperglycemic patients with diabetes admitted
• Insulin therapy for persistent hyperglycemia >180mg/dL
  – Target for therapy is 140-180mg/dL for majority
  – Target of 110-140mg/dL for selected critically ill patients, avoid hypoglycemia
  – IV insulin infusions administered using validated protocols that allow for predefined adjustments in infusion rate based on glucose fluctuation
  – Basal + bolus correction preferred for noncritical but poor oral intake

Section 13: continued

• Sole use of sliding scale insulin is STRONGLY discouraged
• Hypoglycemia management protocol should be adopted/implemented
  – Plan for prevention should be established for each patient
  – Episodes should be documented and tracked
• Structured discharge plan should be tailored to the individual

Section 14: Diabetes Advocacy

• The ADA position statement for school age kids was revised
  – Includes all ages from preschool on up
**AACE/ACE Revisions**

**Lifestyle Therapy**

- **Nutrition**
  - Optimal weight
  - Calorie restriction
  - Plant-based diet

- **Physical Activity**
  - 150 min/week moderate exertion
  - Strength training

- **Sleep**
  - 7 hours/night

- **Behavioral Support**
  - Community engagement

- **Smoking Cessation**
  - No tobacco products

**Model of Care for Overweight/Obese Patients**

**Prediabetes Algorithm**

**AACE Treatment Algorithms**

- **Glycemic Control Algorithm**
  - No major changes
    - SGLT-2 inhibitors moved up

- **Adding/Intensifying Insulin**
  - Major change when intensifying insulin
    - SGLT-2 inhibitors or DPP-4 inhibitors can be considered

**AACE Thoughts on Blood Pressure**

- **Target** <130/80 for most
- **Less stringent goal for frail patients**
- **More intensive goal** (<120/80) if can be obtained w/o side effects
  - Benefits those at high risk for stroke
Treating Blood Pressure

- **Lifestyle therapy**
  - Weight loss
  - Sodium restriction
  - Moderate alcohol intake
  - Exercise

- **Medication**
  - ACEIs or ARBs first line in DM
  - Additional meds probably will be needed: HCTZ, CCBs or Beta Blockers
  - BP > 150/100 start with 2 agents

AACE Thought on Lipids

- Intensive management is warranted to reduce risk of ASCVD
- Majority of T2D patients have ASCVD risk factors
  - Classify as high or very high risk
- Recommends LDL targets:
  - < 100 mg/dL high risk
  - < 70 mg/dL very high risk
- Non-HDL targets:
  - < 130 mg/dL high risk
  - < 100 mg/dL very high risk

Treating Hyperlipidemia

- **Lifestyle Therapy**

- **Medication**
  - Statin Primary
  - Additional agents may be necessary
    - Ezetimibe in combo with statin has proven CVD risk reduction
    - Monoclonal Antibody Inhibitors of PCSK9 Serine Protease
      - Hetero or homozygous familial hypercholesterolemia
      - Secondary prevention clinical ASCVD
  - BAS- small LDL reduction
  - Fibates- primarily triglyceride lowering
  - Niacin- most powerful for raising HDL
  - Omega-3 fish oil

AACE/ACE Take Away Message

- Lifestyle therapy is key
- A1C target must be individualized
- Targets include fasting and postprandial glucose
- Therapy should be individualized
- Minimize hypoglycemia as priority
- Minimize weight gain also priority
- Cost of medication is only part of total cost of care

Take Away Message continued

- Algorithm stratifies therapies based on initial A1C
- Combination therapy usually required
- Comprehensive management includes lipids and blood pressure
- Evaluate frequently until stable
- Therapeutic regimen should be as simple as possible
- Algorithm includes every FDA approved medication for diabetes

SAFETY COMMUNICATIONS
Multidose Diabetes Pens

“For single patient use only”

Repaglinide and Clopidogrel

• Clopidogrel inhibits CYP2C8
• May inhibit metabolism of repaglinide
• Increased risk of hypoglycemia
• Concomitant use considered contraindication by Health Canada

DPP-4 Inhibitors and Joint Pain

• New warning and precaution added to labels of all DPP-4 inhibitors
• Based on FDA Adverse Event Reporting System database and medical literature
• 33 cases of severe arthralgia (10/16/2006 – 12/31/2013)
• All individuals had decreased level of activity
• 10 required hospitalization for disabling joint pain
• Symptoms appeared within 1 day to years after starting medication. Most resolved within 1 month of discontinuation.

Canagliflozin and Bone Fractures

Increased bone fracture associated with canagliflozin

• Mean exposure time: 85 weeks
• Incidence per 100 patient-years of exposure:
  • 1.1 (placebo and active comparator)
  • 1.4 (canagliflozin 100 mg)
  • 1.5 (canagliflozin 300 mg)
• Fractures seen as early as 12 weeks of therapy initiation
• Mostly due to low trauma (falls from standing height)
• Affected upper extremities

Canagliflozin and Bone Mineral Density

• Postmarketing safety trial: 714 older individuals with uncontrolled T2DM
• Duration: 2 years
• Bone mineral density (BMD) measured by dual-energy X-ray absorptiometry

<table>
<thead>
<tr>
<th>Location</th>
<th>Canagliflozin 100 mg*</th>
<th>Canagliflozin 300 mg*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total hip</td>
<td>0.9%</td>
<td>1.2%</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Femoral neck</td>
<td>0.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>0%</td>
<td>0.4%</td>
</tr>
</tbody>
</table>

*S placebo-corrected decline in BMD

SGLT2 Inhibitors and Euglycemic DKA

• Warning based on 20 cases in the FDA Adverse Events Reporting System database from March 2013 – June 2014
• No label change at this time
• Factors identified as potential triggers:
  • Infection
  • Trauma
  • Reduced food and fluid intake
  • Reduced insulin dosage

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SGLT2-Induced Euglycemic Ketoacidosis

↑ urinary glucose excretion
↓ plasma glucose levels
↓ plasma insulin levels
↑ glucagon, lipid oxidation, and lipolysis
↑ mobilization of FFA and TG
↑ ketogenesis and β-hydroxybutyrate levels

Worsened by ↓ insulin and ↓ CHO intake


CARDIOVASCULAR OUTCOMES STUDIES

SAVOR TIMI-53 and EXAMINE Trials

• SAVOR TIMI-53 Trial
  - Hospitalization for heart failure statistically significant (SS) in saxagliptin arm (3.5% vs 2.8%, HR 1.27, 95% CI 1.07–1.51, p=0.007)

• EXAMINE Trial
  - Increased hospitalizations for heart failure in alogliptin arm; not SS (3.9% vs 2.8%, HR 1.19, 95% CI 0.90–1.58, p=0.220)


TECOS

• 14,671 patients from 673 sites in 38 countries
  - Type 2 diabetes
  - Established CV disease
  - >50 years of age
  - HbA1C level 6.5–8.0%
• Sitagliptin or placebo added to current therapy
• Median follow-up: 3 years


TECOS: Glycemic Control

A1C mean difference: -0.29% (95% CI, -0.32 to -0.27)
  - Sitagliptin group received fewer additional antihyperglycemics (HR, 0.72; 95% CI, 0.68 to 0.77; P<0.001)
  - Sitagliptin group less likely to start long-term insulin therapy (HR, 0.70; 95% CI, 0.63 to 0.79; P<0.001)
TECOS: CV Outcomes

- Primary composite CV outcome: first confirmed event of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina -- 11.4% sitagliptin group versus 11.6% placebo
  - Non-inferiority: HR, 0.98; 95% CI, 0.88 to 1.09; P<0.001
  - Superiority: HR, 0.98; 95% CI, 0.89 to 1.10 P=0.65
- Secondary composite CV outcome: first confirmed event of CV death, nonfatal MI, or nonfatal stroke
  - Non-inferiority: HR, 0.99; 95% CI, 0.89 to 1.11; P<0.001
  - Superiority: HR, 0.99; 95% CI, 0.89 to 1.10; P=0.84

TECOS: Heart Failure

- Hospitalization for heart failure
  - 3.1% sitagliptin and placebo groups (HR, 1.00; 95% CI, 0.83 to 1.20; P=0.98)
- Composite outcome of hospitalization for heart failure or CV death
  - 7.3% sitagliptin and 7.2% placebo (HR, 1.02; 95% CI, 0.90 to 1.15; P=0.74)


FDA Advisory Panel Recommendations

Addition of a warning about potential risk for heart failure to:

- Saxagliptin-containing products
  - Safe in general population
  - Caution & additional monitoring in pts with eGFR<60 and prior history of heart failure

- Alogliptin-containing products
  - Minor concern for heart failure
  - Causal link difficult to establish

GLP-1 RA CV Safety Trials

- LEADER: liraglutide
- EXSCEL: exenatide
- REVIND: dulaglutide
- ELIXA: lixisenatide*

*New drug application (NDA) for lixisenatide accepted by FDA and awaiting review. Currently available in Europe, Japan, Australia, and Mexico.

ELIXA

- 6,068 patients from 49 countries
  - Type 2 diabetes diagnosis, acute coronary syndrome event within 70 days
  - Mean duration of diabetes: 9 years
  - Average A1C: 7.6%
  - Mean BMI: 30 kg/m²
- Lixisenatide or placebo added to current therapy
- Study duration: 2 years

ELIXA

- Primary composite outcome of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina: no difference (1.02 HR; 95% CI, 0.89-1.17)
- No difference between groups for secondary cardiovascular end points
**EMPA-REG Outcome**

- 7,020 patients from 590 sites in 42 countries
  - Established CV disease
  - A1C of 7–9% (no therapy) or 7–10% (stable therapy)
  - BMI < 45
  - eGFR ≥ 30 mL/min/1.73 m²
- Empagliflozin 10, empagliflozin 25, or placebo once daily added
- Median study duration: 3.1 years

**Zinman B, et al. NEJM. 2015;373(22):2117–28.**

<table>
<thead>
<tr>
<th>Placebo (N=2333)</th>
<th>Empagliflozin 10 (N=4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.86 (0.74–0.99)</td>
<td>&lt;0.001</td>
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</table>

**Noninferiority significance:** <0.0249  
**Superiority significance:** <0.0498

**EMPA-REG Outcome**

- Individual CV outcome events were all non-significant, except:
  - Hospitalization for heart failure
  - Hospitalization for heart failure or death from CV causes (excluding fatal stroke)

**Zinman B, et al. NEJM. 2015;373(22):2117–28.**

<table>
<thead>
<tr>
<th>Placebo (N=2333)</th>
<th>Empagliflozin 25 (N=4687)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0.65 (0.50–0.85)</td>
<td>0.002</td>
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**EMPA-REG Outcome**

- Adverse events favoring empagliflozin:
  - any adverse event (P<0.001)
  - UTI in female (P<0.05)
  - acute kidney injury (P<0.05)
  - acute renal failure (P<0.01)
- Adverse events favoring placebo:
  - male and female genital infections (P<0.001)

**Zinman B, et al. NEJM. 2015;373(22):2117–28.**

**EMPA-REG Outcome – CKD Patients**

- Evaluated renal outcomes in patients with T2D and CKD:
  - New-onset or worsening nephropathy
  - Doubling of serum creatinine (+) eGFR <45 mL/min per 1.73 m²
  - Initiation of renal replacement therapy
  - Death due to renal disease

**Outcome Effect P-value**

<table>
<thead>
<tr>
<th>New-onset or worsening nephropathy</th>
<th>39% decrease in empagliflozin compared to placebo P=0.0001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite of doubling Scr, renal replacement initiation, death due to renal disease</td>
<td>46% decrease in empagliflozin compared to placebo P=0.0002</td>
</tr>
</tbody>
</table>

EMP A-REG Outcome – CKD Patients

<table>
<thead>
<tr>
<th>eGFR &lt; 60*</th>
<th>eGFR &gt;60*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: 3 point major adverse cardiac events</td>
<td>12% ↓ in empagliflozin</td>
</tr>
<tr>
<td>CV death</td>
<td>22% ↓ in empagliflozin</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>41% ↓ in empagliflozin</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>20% ↓ in empagliflozin</td>
</tr>
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* compared to placebo

Empagliflozin reduces CV morbidity and mortality in patients with T2D and various degrees of CKD.


NEW AGENTS

Available Bolus Insulin Options

- Short acting: Regular (Novolin & Humulin R)
- Rapid acting:
  - Aspart (Novolog)
  - Lispro (Humalog) **U-100 & U-200
  - Glulisine (Apidra)
- Ultra rapid acting: Inhaled (Afrezza)

Lispro U-200

- Similar efficacy to lispro U-100
- Each 3mL pen contains 600 units of insulin
- No dose conversion between U-100 and U-200

Basal Insulin Options

- Intermediate acting: Neutral protamine hagendorn (Novolin and Humulin NPH)
- Long acting:
  - Detemir (Levemir)
  - Lispro U-100 (Basaglar)
  - Lispro U-300 (Toujeo)
  - Degludec (Tresiba) U-100 & U-200

“Follow-on” Insulin Glargine

- Received tentative FDA approval in 2014 and final approval in 2015
  - Abbreviated approval pathway
  - Sufficiently similar to traditional insulin glargine U-100
- Available in pen device for adult and pediatric patients with type 1 or type 2 diabetes

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**Follow-on Glargine Safety & Efficacy**

<table>
<thead>
<tr>
<th>ELEMENT-1 (T1D)</th>
<th>ELEMENT-2 (T2D)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Non-inferiority to traditional glargine</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>535 with T1DM (adults) treated with insulin lispro</td>
</tr>
<tr>
<td><strong>Study duration</strong></td>
<td>24 week</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Non-inferiority demonstrated Mean difference 0.108% (-0.002–0.219)</td>
</tr>
<tr>
<td><strong>Adverse reactions (2%)</strong></td>
<td>Infection, nasopharyngitis, URI, hypoglycemia</td>
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**Degludec Safety & Efficacy**

- **Initiation:**
  - Type 1 (insulin naive): 0.2–0.4 units/kg/day—0.75 to 1 mg basal dose (TID)
  - Type 2 (insulin naive): 10 units QD

- **Titration:** every 3–4 days

- **General Dosing:**
  - Once daily anytime of day
  - Dose must be at least 8 hours apart
  - No dose conversion between U-100 and U-200

- **Stable out of refrigerator up to 56 days (8 weeks)**

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**Glargine U-300**

- More concentrated: increased dose of insulin in less volume
- Flatter and longer profile of action than glargine U-100
  - Onset of action: 6 hours
  - Maximum glucose lowering effect: up to 5 days
  - Once daily dosing

**Titrate every 5 days!**

**Glargine U-300 Safety & Efficacy**

<table>
<thead>
<tr>
<th>EDITION 1 (N=480)</th>
<th>EDITION 2 (N=811)</th>
<th>EDITION 3 (N=878)</th>
<th>EDITION 4 (N=549)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>T2D using basal (≥82 units/day) and bolus insulin</td>
<td>T2D using oral agents &amp; basal insulin (≥82 units/day)</td>
<td>T1D using basal and bolus insulin</td>
</tr>
<tr>
<td><strong>A1C reduction</strong></td>
<td>Equivalent change: -0.05% [0.11–0.01]</td>
<td>Mean diff: -0.05% [-0.14–0.12]</td>
<td>Equivalent change: 0.08% [0.09–0.17]</td>
</tr>
<tr>
<td><strong>Nocturnal hypoglycemia</strong></td>
<td>21% in U-300 (0.87–0.93)</td>
<td>23% in U-300 (0.61–0.99)</td>
<td>21% in U-300 (0.86–1.2)</td>
</tr>
</tbody>
</table>

Degludec Flexible Dosing

<table>
<thead>
<tr>
<th>Stat</th>
<th>Degludec U100 Flex Dosing Once Daily</th>
<th>Degludec Once Daily</th>
<th>Glargine U-100 Once Daily</th>
<th>Degludec Once Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEGIN FLEX</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C Change</td>
<td>-1.28%</td>
<td>-1.07%</td>
<td>-1.26%</td>
<td></td>
</tr>
<tr>
<td>Nocturnal hypoglycemia (episodes/PY)</td>
<td>0.63</td>
<td>0.56</td>
<td>0.75</td>
<td>Rate Ratio: 0.77 (0.64–1.13; p=NS)</td>
</tr>
<tr>
<td>BEGIN FLEX T1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C Change</td>
<td>-0.40</td>
<td>-0.41</td>
<td>-0.58</td>
<td>Estimated Treatment Difference: 0.13% [95% CI 0.04–0.30]</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia (episodes/PY)</td>
<td>0.62</td>
<td>0.96</td>
<td>10.0</td>
<td>Estimated Rate Ratio (Deg Flex vs. Glar): 0.60 [95% CI 0.44–0.82]</td>
</tr>
</tbody>
</table>


Basal Insulins

<table>
<thead>
<tr>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>2-4 hours</td>
<td>6-10 hours</td>
</tr>
<tr>
<td>Glargine U-100</td>
<td>5 hours</td>
<td>NA</td>
</tr>
<tr>
<td>Glargine U-300</td>
<td>6 hours</td>
<td>NA</td>
</tr>
<tr>
<td>Detemir</td>
<td>2 hours</td>
<td>NA</td>
</tr>
<tr>
<td>Degludec</td>
<td>1 hour</td>
<td>NA</td>
</tr>
</tbody>
</table>

Newer Basal Insulin Pens At-a-Glance

<table>
<thead>
<tr>
<th>Agent</th>
<th>Units Per Pen</th>
<th>Days Stable Unrefrigerated</th>
<th>Maximum Delivery by Single Injection</th>
<th>“Hold” Injection (Seconds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine U100 (Lantus)</td>
<td>300</td>
<td>28</td>
<td>80 units</td>
<td>10</td>
</tr>
<tr>
<td>Glargine U100 (Basaglar)</td>
<td>300</td>
<td>28</td>
<td>60 units</td>
<td>5</td>
</tr>
<tr>
<td>Glargine U300 (Toujeo)*</td>
<td>450</td>
<td>42</td>
<td>80 units</td>
<td>5</td>
</tr>
<tr>
<td>Detemir U100 (Levemir)</td>
<td>300</td>
<td>42</td>
<td>80 units</td>
<td>6</td>
</tr>
<tr>
<td>Degludec U100 (Tresiba)*</td>
<td>300</td>
<td>56</td>
<td>80 units</td>
<td>6</td>
</tr>
<tr>
<td>Degludec U200 (Tresiba)*</td>
<td>600</td>
<td>56</td>
<td>160 units</td>
<td>6</td>
</tr>
</tbody>
</table>

* FDA approved in adults only

ON THE HORIZON

### Pre-Mixed Insulin

- Insulin aspart/protamine (Novolog Mix)
- Insulin lispro/protamine (Humalog Mix)
- **Insulin degludec/insulin aspart (Ryzodeg)**

### Insulin Degludec/Insulin Aspart

- First combination of basal insulin with long duration of action
- Once or twice daily dosing
- Initiation
  - T1D (insulin naive): 50% of total daily dose; give bolus at other meals
  - T2D (insulin naive): 10 units once daily
  - Conversion from pre-mixed or multiple daily injections: Divide total dose into 2 equal doses
  - Once or twice daily basal insulin: unit to unit conversion and maintain dosing schedule
- Storage: stable for 28 days out of refrigerator

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Oral and Non-Insulin Injectables

- GLP-1 RA:
  - Lixisenatide [Lyxumia] (once-daily injection)
  - Semaglutide (once-weekly injection and once-daily oral)
- DPP-4 Inhibitor:
  - Omagliplin (once-weekly oral)
- SGLT2 Inhibitor:
  - Ertugliflozin

GLP-1 RA/Basal Insulin Combos

- Lixisenatide/Glargine Fixed Ratio (LixiLan)
- Liraglutide/Degludec (Xultophy)

Single-Entity Insulin

- Faster-acting insulin aspart
- Basal insulin peglispro
- Insulin lispro
- Insulin glargine

Intranasal Glucagon

- Needle-free treatment of severe hypoglycemia
- Powder formulation in single-use, ready-to-use device

Oxyntomodulin

- Peptide hormone released from the gut post-prandially
- Activates GLP-1 and glucagon receptors
- Improves glucose tolerance and decreases weight

Key Points

- The ADA and AACE/ACE differ on the management of diabetes.
- DPP-4 inhibitors have been associated with joint pain. Use cautiously in pre-existing joint diseases.
- Heart failure associated with DPP-4 inhibitors does not appear to be a class effect.
- SGLT2 inhibitors have been associated with euglycemic ketoacidosis.
- Empagliflozin reduced CV morbidity & mortality in patients with T2DM and CVD.
- Available U-200 insulin products are for volume only. No dose conversion needed!
1. According to AACE 2016 ASCVD Risk Factor Modification Algorithm, which of the following is an appropriate goal for most people with diabetes?

A. High-intensity statin therapy if > 65 yoa
B. Goal for blood pressure is <140/90
C. LDL-C of <70mg/dL if at very high risk for ASCVD
D. Hemoglobin A1C goal of < 7%

2. All but the following medication can be used long-term for weight management in diabetes.

A. Orlistat 120mg
B. Liraglutide 1.8mg
C. Bupropion/naltrexone 90mg/8mg
D. Phentermine/topiramate ER 15mg/92mg

3. SGLT2 inhibitors have been associated with:

A. joint pain
B. heart failure
C. euglycemic DKA
D. worsening albuminuria

4. Which disease state should DPP-4 inhibitor treatment be used cautiously?

A. Mild renal impairment
B. Rheumatoid arthritis
C. Recurrent UTI
D. Osteoporosis

5. Which was a finding of the treatment arm in the EMPA-REG Outcome Study?

A. Increased incidence of diabetic ketoacidosis
B. Increased incidence of bone fractures
C. Decreased incidence of genital infections
D. Decreased incidence of cardiovascular death