New Therapies for Type 2 Diabetes

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Objectives

Background
Lifestyle Therapies
Non-Insulin Therapies
Insulin Therapies
Combined Therapies
Disparities

Financial Disclosures: None
Unlabeled/Unapproved Uses Disclosure: None

Background
Lifestyle Therapies
Non-Insulin Therapies
Insulin Therapies
Combined Therapies
Disparities
Background

30+ MILLION
Currently living
with diabetes in
the U.S.

250,000 Deaths
Related to diabetes
annually

1 in 4 People
Undiagnosed

266+ Million
Quality-adjusted years of
life lost

$237 Billion
Total annual cost of
diabetes in the U.S.

The Future

Prevalence

2017
30 Million
Americans

2030
55 Million
Americans

Costs

2017
$237 Billion
in Direct
Medical Costs

2030
$622 Billion
in Direct
Medical Costs

Death from Cardiovascular Disease in
Patients with Type 2 Diabetes vs. Matched
Controls

Lifestyle Therapies

Death per 10,000 person-years

N=457,473

Rawshami A. NEJM, 2017

Prevalence up 54%
Mortality up 38%
Costs up 53%

Background
Lifestyle Therapies
Non-Insulin Therapies
Insulin Therapies
Combined Therapies
Disparities
Lifestyle Therapy: Weight Loss

Look AHEAD – Intensive lifestyle intervention focused on physical activity, diet and weight loss
- 4.7% weight loss at 8 years
- No CVD reduction

Improvements:
- HbA1C
- Sleep Apnea
- Liver Fat
- Kidney Disease
- Decreased Meds
- Lower Costs
- Quality of Life

(Wing, NEJM, 2013)

Primary Care Led Weight Management
- T2DM dx in past 6 years, 20–65 years, BMI 27–45 kg/m2, and were not receiving insulin

Intervention
- Withdrawal of antidiabetic and antihypertensive drugs
- total diet replacement (825–853 kcal/day formula diet for 3–5 months)
- stepped food reintroduction (2–8 weeks)
- structured support for long-term weight loss maintenance

(Lean et al. Lancet, 2018)

Bariatric Surgery is Superior to Medical Therapy for T2DM

- Dixon et al. (JAMA 2008)
  - 73% of patients undergoing LAGB and 13% in lifestyle group achieved T2DM remission.
- Schauer et al. (NEJM 2012)
  - 42% after RYGB and 37% after LSG compared to 12% in intensive medical therapy and lifestyle group achieved T2DM remission (A1c<6% without diabetes medications)
- Mingrone et al. (NEJM 2012)
  - 95% after BPD and 75% after RYGB (with equivalent weight loss) compared to 0% with conventional medical therapy achieved T2DM remission (FPG <100, A1c <6.5% without diabetes medications).
- Fisher et al. (JAMA 2018)
  - 40% lower risk of incident Coronary Artery Disease

Proportion of Patients Achieving Diabetes Remission over 12-months

Adapted from Lean et al. Lancet, 2018
Non-Insulin Therapies

Cardiovascular Outcomes Trials

2008 FDA guidance mandating assessment of CV safety of all antihyperglycemic agents in RCTs

- Designed as noninferiority studies to demonstrate study drug was not associated with more MACE than placebo
- Some study designs tested for superiority if noninferiority criteria were met
- Primary endpoint: composite of cardiovascular death, nonfatal MI, and nonfatal stroke

Timeline of Currently Available Non-Insulin Medications

Timeline of Major Diabetes Outcomes Trials

Blue = Intensive vs standard control using same set of glucose-lowering agent(s)
Purple = Intensive control with a specific agent vs standard care
Red = Placebo- or active-controlled study
* = FDA-mandated cardiovascular safety trial
**Dipeptidyl peptidase IV (DPP-IV) Inhibitors**

- Blocks the breakdown of GLP-1
- Increase incretin levels (GLP-1 and GIP), increases insulin
- Inhibit glucagon release, which in turn increases insulin secretion
- CVOT Trials Neutral

**Glucagon-Like Peptide–1 (GLP-1) Agonists**

- An incretin secreted normally from intestinal cells
- Decreases blood sugar levels in a glucose-dependent manner by enhancing the secretion of insulin
- Inhibits glucagon secretion at glucose levels above fasting levels
- In the stomach it inhibits gastric emptying, acid secretion and motility collectively decreasing appetite

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**ELIXA Trial**

- Patients with T2D with an MI or hospitalized for unstable angina within 180 days
- 6068 patients randomized to Lixisenatide or Placebo
- Baseline A1c 7.7%, BMI 30.1, Duration of Diabetes 9.2 years
- Tested non-inferiority and superiority to placebo
- Composite primary endpoint: CV death, non fatal MI, non fatal stroke, or hospitalization for unstable angina
- Followed for a median of 25 months

Pfeffer et al. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Symptoms. NEJM. 2015. 373, 2247-2257.
Statistically significant reductions at study end:
- Hemoglobin A1C (0.3%),
- Systolic blood pressure (0.8 mmHg), and
- Weight (0.7 kg)
- Slightly increased heart rate (0.4 bpm)

ELIXA Trial

Confirmed non-inferiority of lixisenatide to placebo in respect to primary outcome, but no superiority on any CV outcome

LEADER LIRAGLUTIDE EFFECT AND ACTION IN DIABETES: EVALUATION OF CARDIOVASCULAR OUTCOME RESULTS
LEADER Trial

- Patients with T2D and high CV risk:
  - Age >50 yo with at least 1 of the following: CAD, cerebrovascular disease, PVD, Stage III or IV CKD, Class II or III heart failure
  - Age >60 yo with at least 1 of the following: microalbuminuria, hypertension and LVH, systolic or diastolic dysfunction, or ABI <0.9
- 9340 patients randomized to liraglutide 1.8 mg daily (or highest tolerated dose) or placebo

Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM. 2016.

LEADER Trial

- Baseline A1c 8.7%, BMI 32.5, Duration of Diabetes 12.8 years
- Primary composite endpoint: First occurrence of death from cardiovascular causes, nonfatal MI, or nonfatal stroke
- Median follow up 3.8 years

Marso et al. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. NEJM. 2016.

<table>
<thead>
<tr>
<th>LEADER (N=9340)</th>
<th>Median follow-up: 3.5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>P value</td>
</tr>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.89 (0.74-0.97)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.65-0.90)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, and hospitalization for unstable angina or HF.


- Liraglutide Had Greater Benefit In:
  - < 60 yo
  - Males
  - Obesity
  - Absence of Congestive Heart Failure
  - GFR < 60
  - A1c > 8.3%
  - Presence of known Cardiovascular Disease

- NNT to prevent one death: 66
SUSTAIN 6

TRIAL TO EVALUATE CARDIOVASCULAR AND OTHER LONG-TERM OUTCOMES WITH SEMAGLUTIDE IN SUBJECTS WITH TYPE 2 DIABETES

- N=3297 patients with T2D with CVD, CHF, CKD, or age ≥60 with ≥1 CV risk factor
- 2 year duration
- Semaglutide 0.5 mg or 1.0 mg vs. Placebo
- Baseline A1c 8.7%, Duration of Diabetes 14.3 years
- 83% had established CVD and/or CKD
- Primary Outcome: 3 point MACE


SUSTAIN 6 Results (N=3297)

<table>
<thead>
<tr>
<th>Event</th>
<th>Semaglutide HR (95% CI)</th>
<th>Placebo HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.74 (0.58-0.95)</td>
<td>1.00 (0.83-1.21)</td>
<td>0.02</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.86 (0.61-1.20)</td>
<td>1.00 (0.82-1.23)</td>
<td>0.23</td>
</tr>
<tr>
<td>All-cause death, nonfatal MI, nonfatal stroke</td>
<td>0.77 (0.61-0.97)</td>
<td>1.00 (0.82-1.23)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.05 (0.74-1.50)</td>
<td>1.00 (0.75-1.38)</td>
<td>0.79</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.65-1.48)</td>
<td>1.00 (0.67-1.51)</td>
<td>0.93</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.74 (0.51-1.08)</td>
<td>1.00 (0.75-1.38)</td>
<td>0.12</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.61 (0.38-0.90)</td>
<td>1.00 (0.67-1.38)</td>
<td>0.04</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.65 (0.50-0.86)</td>
<td>1.00 (0.75-1.38)</td>
<td>0.003</td>
</tr>
<tr>
<td>Retinopathy complications</td>
<td>1.75 (1.11-2.78)</td>
<td>1.00 (0.75-1.38)</td>
<td>0.02</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>0.64 (0.46-0.89)</td>
<td>1.00 (0.75-1.38)</td>
<td>0.005</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (including silent MI), or nonfatal stroke; †CV death, nonfatal MI, nonfatal stroke, coronary or peripheral revascularization, and hospitalization for unstable angina or HF.
**SUSTAIN 6**

- Achieved statistical superiority for the 3-point MACE
- Significant decrease in nonfatal stroke and a non-significant decrease in nonfatal MI (P = 0.12)
- No trend for reduction in CV death or all-cause mortality
- Significant increase in complications from retinopathy

**EXSCEL**

(EXENATIDE STUDY OF CARDIOVASCULAR EVENT LOWERING)

**Study Design**
- N=14,752 patients with T2D with or without CVD
- By design, ≥70% had CVD
- Baseline A1c 8.0%, BMI 31.8, Duration of Diabetes 12.0 years
- Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke

**Key Results**
- Median follow-up: 3.2 years
- Difference from placebo at trial end
  - A1C: −0.53%
  - Weight: −1.3 kg (P<0.001)
  - SBP: −1.6 mm Hg
- CV outcomes
  - Primary endpoint: HR 0.91 (95% CI 0.83 to 1.00); P=0.06 for superiority


**EXSCEL**

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>CV death</td>
<td>0.88 (0.76-1.02)</td>
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<td>0.88 (0.76-1.02)</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.97 (0.85-1.10)</td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1.29 (0.63-2.66)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.85 (0.70-1.03)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.71 (0.56-1.03)</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.94 (0.76-1.19)</td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>1.05 (0.84-1.32)</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke. †For superiority.*

EXSCEL

• Confirmed the noninferiority, but not superiority, of once-weekly treatment with 2 mg of the long-acting extended-release exenatide (HR 0.91 [95% CI 0.83–1.00], P = 0.06).

• The rates of CV death, fatal or nonfatal MI, fatal or nonfatal stroke, HF hospitalization, and ACS hospitalization did not differ significantly between the two treatment groups.

• Treatment adherence with weekly exenatide was low, with 43% drug discontinuation.

• Despite this limited drug exposure and a heterogeneous population of whom 27% had no history of CVD, the 3-point MACE reduction of 9% came close to reaching statistical significance, with HRs of almost all measured parameters in the direction of benefit.

HARMONY

Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial Lancet 2018

CVD 3-Point MACE Significant (Hazard ratio 0.78, 95% CI 0.68–0.90)

*Currently not on the market

Summarizing GLP-1 Trials

- HbA1c, Weight and Blood Pressure
- CV Risk (Liraglutide, Semaglutide & Albiglutide), Trend with Exenatide ER in Participants with Established CVD
- Side Effects: Mainly Gastrointestinal, Small Increase Risk of Pancreatitis
- REWIND, American Diabetes Association, 2019 (Primary Prevention?)

GLP-1 RAs Differ in Chemical Structure

Potential Indirect Cardiovascular Effects of GLP-1R Agonists

**Sodium/Glucose Cotransporter 2 (SGLT2 Inhibitors)**
- SGLT2 is responsible for 90% of the glucose reabsorption in the kidney
- Inhibition causes 50-80 grams of glucose to be eliminated in the urine per day with some water loss due to osmotic diuresis

**EMPA-REG Trial design**
- Primary outcome: 3-point MACE: Time to first occurrence of CV death, non-fatal MI or non-fatal stroke
- Key secondary outcome: 4-point MACE: Time to first occurrence of CV death, non-fatal MI, non-fatal stroke or hospitalization for unstable angina

**EMPA-REG Trial**
- Key inclusion criteria
  - Adults with type 2 diabetes
  - BMI ≤45 kg/m²
  - HbA1c 7–10%
  - ***Established cardiovascular disease***
    - Prior myocardial infarction, coronary artery disease, stroke, unstable angina or occlusive peripheral arterial disease
  - No glucose-lowering therapy for ≥12 weeks prior to randomization or no change in dose for ≥12 weeks prior to randomization or, in the case of insulin, unchanged by >10% compared to the dose at randomization
- Key exclusion criteria
  - eGFR <30 mL/min/1.73m²

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- Key exclusion criteria
  - eGFR <30 mL/min/1.73m²

**Zinman, NEJM, 2015**
Change in HbA1c greater with Empagliflozin

Mean difference at 12 weeks: -0.54% (10 mg) and -0.60% (25 mg)

Mean difference at 206 weeks: -0.24% (10 mg) and -0.36% (25 mg)

Change in Weight greater with Empagliflozin

Systolic blood pressure lower with Empagliflozin

EMPA-REG Trial

<table>
<thead>
<tr>
<th>Primary composite endpoint*</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>*CV death, nonfatal MI (excluding silent MI), or nonfatal stroke; †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; MI, myocardial infarction.

**EMPA-REG OUTCOME: Summary**

- Empagliflozin reduced risk for 3-point MACE by 14% (superior to control)
  - Most benefits were seen only in Age >65 years old (65 was average age), Males, Caucasians and Asians, A1c <8.5%, BMI <30, GFR 60-90
  - reduced hospitalization for heart failure by 35%
  - reduced CV death by 38%: Biggest contributor was death due to heart failure
  - did not reduce the risk of MI or stroke (trend for ↑ risk)
  - was associated with an increase in genital infections but was otherwise well tolerated, 97% of subjects completed the trial.

FDA: JARDIANCE is indicated 1) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus, 2) to reduce the risk of cardiovascular death in adults with type 2 diabetes mellitus and established cardiovascular disease.

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**Renal Outcomes with Empagliflozin Over 3.2 Yrs**

| CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine. Wanner C, et al. N Engl J Med. 2016 Jun 14 |

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**CANVAS PROGRAM**

- Patients with type 2 diabetes
- HbA1c ≥7.0% to ≤10.5%
- eGFR ≥30 mL/min/1.73 m²
- Age ≥30 years and history of prior CV event
- OR
- Age ≥50 years with ≥2 CV risk factors

*Diabetes duration ≥10 years, SBP >140 mmHg on ≥1 medication, current smoker, micro- or macroalbuminuria, or HDL cholesterol <1 mmol/L.

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**NNT to prevent one death across landmark trials in patients with high CV risk**

<table>
<thead>
<tr>
<th>Simvastatin1 for 5.4 years</th>
<th>Ramipril2 for 5 years</th>
<th>Empagliflozin for 3 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>56</td>
<td>39</td>
</tr>
</tbody>
</table>

**CANVAS PROGRAM**

- Statistically significant reductions at study end:
  - Hemoglobin A1C (0.58%),
  - Weight (1.6 kg)

**Effects on Systolic BP**

Summary

<table>
<thead>
<tr>
<th>Event</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary cardiovascular outcome</td>
<td>0.86 (0.75-0.97)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.85 (0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.78 (0.67-0.91)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74-1.01)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Favoring Canagliflozin</th>
<th>Favoring Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1.0</td>
</tr>
<tr>
<td>1.0</td>
<td>2.0</td>
</tr>
</tbody>
</table>
Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>Placebo</th>
<th>Canagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
<td>229</td>
<td>229</td>
</tr>
<tr>
<td>End-stage renal disease/renal death</td>
<td>21</td>
<td>21</td>
</tr>
</tbody>
</table>

Hazard ratio 0.60 (95% CI, 0.47-0.77)

Primary Endpoints

- **CVD/HHF**
  - 4.9% vs 5.8%
  - HR 0.83 (0.73-0.95)
  - P(Superiority) 0.005

- **MACE**
  - 8.8% vs 9.4%
  - HR 0.93 (0.84-1.03)
  - P(Noninferiority) <0.001
  - P(Superiority) 0.17

Secondary Endpoints

- **1st Renal Composite EP**
  - 40% eGFR, ESRD, renal or CV death
  - 4.7% vs 5.8%
  - HR 0.81 (0.67-0.97)
  - P=0.01

- **All-Cause Mortality**
  - 4.2% vs 5.6%
  - HR 0.83 (0.73-0.94)
  - P=0.04
Summarizing SGLT2-Inhibitor Trials

- SGLT2 Inhibitors: canagliflozin (Invokana), dapagliflozin (Farxiga), empagliflozin (Jardiance), ertugliflozin (Steglatro)
- Robust effects on reducing hospitalizations for heart failure and progression of renal disease.

Less effective and dose reduction in moderate CKD (GFR 45-60) and contraindicated with severe CKD (GFR <45); Has not been studied with hepatic impairment
- Side effects are UTI’s, acute kidney injury, yeast infections, increased thirst, dehydration, polyuria
- Interim clinical trial results find increased risk of leg and foot amputations. CANVAS Study of canagliflozin - mostly toe amputations
- Also possible increased risk of bone fractures and reduced BMD

New Inhibitors: ertuglifoxin (Steglatro) FDA approved for type 2 sotagliflozin (SGLT1 and SGLT2 inhibition), Type 1 indication.

SGLT2 inhibitors modulate several CV risk factors, but mechanism of cardioprotection unknown

Clinical Practice

Obese
CKD
Atherosclerosis
? Class effect

Clinical Practice

GLP-1-A
Clinical Practice

Obese
CKD
Atherosclerosis
 ethn Class effect

Overweight
Heart Failure
Nephropathy
Class effect

GLP-1-A
SGLT2-I

Insulin Therapies

Background
Lifestyle
Non-
Therapies
Therapies
Combined
Therapies
Disparities

History of Insulin

• 1910 - Sir Edward Albert Sharpey-Schafer's study of the pancreas leads him to the discovery of insulin.
• 1921 - Frederick G. Banting and student Charles Best, advised by John MacCleod at Toronto University, extract insulin from animal pancreases. James Collip purified the extract
• 1922 - Leonard Thompson, 1st successful injection and insulin commercially available in England
• 1923 - Eli Lilly and Company begins commercial production of insulin.

Natural History of T2DM

Insulin Resistance & β-Cell Function

Glucose

Years of Diabetes

• Loss of β-Cell function begins before diagnosis and progresses
• Insulin resistance doesn’t change over time (unless weight loss)

Adapted from International Diabetes Center (IDC), Minneapolis, Minnesota.
American Diabetes Association

- Consider initiating insulin therapy (with or without additional agents) in patients with newly diagnosed type 2 diabetes who are symptomatic and/or have A1C >10% and/or glucose levels > 300 mg/dL

- If noninsulin monotherapy at maximum tolerated dose does not achieve or maintain the A1C target < 7% after 3 months, add a second oral agent, a glucagon-like peptide 1 receptor agonist, or basal insulin

- For patients with type 2 diabetes who are not achieving glycemic goals, insulin therapy should not be delayed

ADA Standards of Medical Care, Diabetes Care, 2018

Complications of Hypoglycemia

- Seizures
- Ventricular Arrhythmias
- Hypokalemia
- Cardiovascular Events & Mortality
  - ADVANCE Trial: 2.9-fold increased risk of a CV event and 2.7-fold increased risk of CV Death
- Decreased Cognition and Dementia
  - 2-Fold Increased Risk of Dementia


Pharmacokinetics of Insulin Products

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Concentration</th>
<th>Duration</th>
<th>Notes</th>
<th>Start Dose</th>
<th>Convert dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>300 unit/ml</td>
<td>Long</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Lispro</td>
<td>100 unit/ml</td>
<td>Rapid</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Aspart</td>
<td>100 unit/ml</td>
<td>Intermediate</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Glulisine</td>
<td>300 unit/ml</td>
<td>Long</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Regular</td>
<td>100 unit/ml</td>
<td>Short</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Detemir</td>
<td>300 unit/ml</td>
<td>Intermediate</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
</tbody>
</table>


Pharmacokinetics of Insulin Products

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Concentration</th>
<th>Duration</th>
<th>Notes</th>
<th>Start Dose</th>
<th>Convert dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>300 unit/ml</td>
<td>Long</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Lispro</td>
<td>100 unit/ml</td>
<td>Rapid</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Aspart</td>
<td>100 unit/ml</td>
<td>Intermediate</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Glulisine</td>
<td>300 unit/ml</td>
<td>Long</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Regular</td>
<td>100 unit/ml</td>
<td>Short</td>
<td></td>
<td></td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
<tr>
<td>Detemir</td>
<td>300 unit/ml</td>
<td>Intermediate</td>
<td></td>
<td>T1 50%/T2D 4 unit/kg T2 10 U - 0.2 unit/kg Max dose 80 units Once a day sliding scale profile</td>
<td>Same as basal dose (may 10-15% more) 80% NPH dose Increase basal every other day</td>
</tr>
</tbody>
</table>

Glargine U300 (Toujeo) vs. Glargine U100 (Lantus, Basaglar)

<table>
<thead>
<tr>
<th>EDITION Studies</th>
<th>Months</th>
<th>DM Type</th>
<th>Baseline Rx</th>
<th>N</th>
<th>HbA1c</th>
<th>Hypoglycemia (overall)</th>
<th>Hypoglycemia (nocturnal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>2</td>
<td>Basal bolus</td>
<td>807</td>
<td>~</td>
<td>0.94</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.89-0.99)</td>
<td>(0.75-0.94)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>2</td>
<td>Basal bolus</td>
<td>811</td>
<td>~</td>
<td>0.96</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.89-1.02)</td>
<td>(0.71-0.99)</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>2</td>
<td>Naïve</td>
<td>873</td>
<td>~</td>
<td>0.88</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.77-1.01)</td>
<td>(0.59-0.99)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>1</td>
<td>Basal bolus</td>
<td>559</td>
<td>~</td>
<td>1.00</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.95-1.04)</td>
<td>(0.88-1.09)</td>
</tr>
</tbody>
</table>

Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859–867

Nocturnal Hypoglycemia EDITION Trials Combined: U300 vs U100 glargine

Severe Hypoglycemia

SWITCH-2: Degludec vs U100 glargine

Cardiovascular Safety of Insulin Degludec: DEVOTE Study

7637 people with T2DM at high CV risk were randomized to standard care plus
Insulin degludec or Insulin glargine U-100
Target: FPG 71 to 90 mg/dL
Follow-up ~2 years

At baseline
Age (mean): 65.0 y
HbA1c (mean): 8.4%
Duration of T2DM (mean): 16.4 y
85.2% established CVD or moderate CKD
83.9% receiving insulin
54.8% basal-bolus

Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859–867

Wykars, Effect of insulin Degludec vs Insulin Glargine U100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial: JAMA, 2017

### DEVOTE Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite</td>
<td>0.91</td>
<td>0.78-1.06</td>
</tr>
<tr>
<td>Expanded composite</td>
<td>0.92</td>
<td>0.80-1.05</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.91</td>
<td>0.76-1.11</td>
</tr>
<tr>
<td>Non-CV death</td>
<td>0.84</td>
<td>0.60-1.16</td>
</tr>
<tr>
<td>CV death</td>
<td>0.96</td>
<td>0.76-1.21</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.85</td>
<td>0.68-1.06</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90</td>
<td>1.05-1.23</td>
</tr>
<tr>
<td>UA → hospitalization</td>
<td>0.86</td>
<td>0.68-1.13</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0.60</td>
<td>0.48-0.76</td>
</tr>
<tr>
<td>Nocturnal severe hypoglycemia</td>
<td>0.47</td>
<td>0.31-0.73</td>
</tr>
</tbody>
</table>

Degludec non-inferior to glargine for major CV events

### Combined Therapies

#### Background

#### Lifestyle Therapies

#### Non-Insulin Therapies

#### Insulin Therapies

#### Combined Therapies

#### Disparities

### Insulin Degludec + Liraglutide Combination

**Inclusion criteria**

- T2DM
- Insulin-naïve, treated with metformin ± pioglitazone
- A1C 7.0%-10.0%
- BMI ≤40 kg/m²
- Age ≥18 years

**Titration for IDeg + LIRA and IDeg**

<table>
<thead>
<tr>
<th>Mean Fasting PG</th>
<th>Dose Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>mg/dL mmol/L</td>
<td>U</td>
</tr>
<tr>
<td>&lt;72</td>
<td>+2</td>
</tr>
<tr>
<td>≥72-≤90</td>
<td>+1</td>
</tr>
<tr>
<td>&gt;90</td>
<td>+2</td>
</tr>
</tbody>
</table>

### Fasting Glucose with IDegLira

Significant Reduction in HbA1c

- Week 26  - Week 52
- iDegLira (N = 833)
- Degludec (N = 413)
- Liraglutide (N = 414)

Full analysis set. Data are mean ± SEM. ∆ = Observed change from baseline. LOCF imputation. EOT = End of treatment. *p<0.0001 vs. degludec and vs. liraglutide.

Lower Rate of Confirmed Hypoglycemia With iDegLira vs. Basal Insulin

Safety analysis set. RR, Rate Ratio. PYE, patient-years of exposure. HbA1c and statistical analysis based on full analysis set. EOT, End of Treatment. 26 week data for 3697. *p<0.0023, p-value is not significant, **p<0.0001.

iGlarLixi Demonstrated Superior HbA1c Reduction

<table>
<thead>
<tr>
<th>Study</th>
<th>iGlarLixi</th>
<th>Lixi</th>
<th>Lantus</th>
<th>Mean (95% CI) HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening Baseline</td>
<td>8.2% (8.0%, 8.4%)</td>
<td>8.1%</td>
<td>7.2%</td>
<td>8.1% (7.9%, 8.4%)</td>
</tr>
<tr>
<td>8 weeks</td>
<td>7.8% (7.7%, 8.0%)</td>
<td>7.7%</td>
<td>6.8%</td>
<td>7.8% (7.6%, 8.1%)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>7.6% (7.4%, 7.8%)</td>
<td>7.6%</td>
<td>6.6%</td>
<td>7.7% (7.5%, 7.9%)</td>
</tr>
<tr>
<td>24 weeks</td>
<td>7.4% (7.2%, 7.7%)</td>
<td>7.5%</td>
<td>6.4%</td>
<td>7.6% (7.4%, 7.9%)</td>
</tr>
<tr>
<td>30 weeks</td>
<td>7.3% (7.1%, 7.6%)</td>
<td>7.4%</td>
<td>6.3%</td>
<td>7.5% (7.3%, 7.8%)</td>
</tr>
</tbody>
</table>

Disparities

- Background
- Lifestyle Therapies
- Non-Insulin Therapies
- Insulin Therapies
- Combined Therapy
- Disparities
### Significant Causes of Death with the Highest Black to White Disparities

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Total # of Deaths</th>
<th>Death Rates per 100,000</th>
<th>Black-White Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Black</td>
<td>White</td>
</tr>
<tr>
<td>HIV</td>
<td>6,000</td>
<td>8.3</td>
<td>1.1</td>
</tr>
<tr>
<td>Homicide</td>
<td>16,000</td>
<td>17.2</td>
<td>3.0</td>
</tr>
<tr>
<td>HTN &amp; HTN Renal Disease</td>
<td>30,000</td>
<td>15.6</td>
<td>7.4</td>
</tr>
<tr>
<td>Kidney Disease</td>
<td>6,000</td>
<td>24.6</td>
<td>12.1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>76,000</td>
<td>37.3</td>
<td>19.3</td>
</tr>
<tr>
<td>Stroke</td>
<td>133,000</td>
<td>49.7</td>
<td>35.2</td>
</tr>
<tr>
<td>Heart Disease</td>
<td>614,000</td>
<td>206.3</td>
<td>165.9</td>
</tr>
</tbody>
</table>

*Fuchs, JAMA, 2016*

### SGLT-2: Ethnic Variation in MACE Effect Size

**EMPA-REG & CANVAS – CV Death, nonfatal MI, or nonfatal stroke**

<table>
<thead>
<tr>
<th>Racial/Ethnic</th>
<th>EMPA-REG (Jardiance)</th>
<th>CANVAS (Invokana)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR</td>
</tr>
<tr>
<td>White</td>
<td>5081</td>
<td>0.88</td>
</tr>
<tr>
<td>Asian</td>
<td>1517</td>
<td>0.68</td>
</tr>
<tr>
<td>Black</td>
<td>357</td>
<td>1.48</td>
</tr>
</tbody>
</table>

*Zinman, NEJM, 2015; Neal, NEJM, 2017*

### GLP-1: Ethnic Variation in MACE Effect Size

**EMPA-REG & CANVAS – CV Death, nonfatal MI, or nonfatal stroke**

<table>
<thead>
<tr>
<th>Racial/Ethnic</th>
<th>LEADER (Victoza)</th>
<th>EXSCEL (Bydureon)</th>
<th>SUSTAIN-6 (Ozempic)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>HR</td>
<td>CI</td>
</tr>
<tr>
<td>White</td>
<td>7238</td>
<td>0.90</td>
<td>0.80–1.02</td>
</tr>
<tr>
<td>Asian</td>
<td>936</td>
<td>0.70</td>
<td>0.46–1.04</td>
</tr>
<tr>
<td>Black</td>
<td>777</td>
<td>0.87</td>
<td>0.59–1.27</td>
</tr>
</tbody>
</table>

*Marso, NEJM, 2016; Holman, NEJM, 2017*
Thank You!

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