New Therapies for Type 2 Diabetes

Joshua J. Joseph, MD
Assistant Professor of Medicine
Division of Endocrinology, Diabetes and Metabolism
The Ohio State University Wexner Medical Center

Financial Disclosures: None
Unlabeled/Unapproved Uses Disclosure: None
Objectives

Background

Lifestyle Therapies

Non-Insulin Therapies

Insulin Therapies

Combined Therapies

Disparities

Background

Lifestyle Therapies

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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

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

266+ Million
Quality-adjusted years of life lost

The Future

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>2017</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Million Americans</td>
<td>55 Million Americans</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Costs</th>
<th>2017</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$237 Billion in Direct Medical Costs</td>
<td>$622 Billion in Direct Medical Costs</td>
</tr>
</tbody>
</table>

Costs up 53%  
Mortality up 38%  
Prevalence up 54%
Death from Cardiovascular Disease in Patients with Type 2 Diabetes vs. Matched Controls

N=457,473

Lifestyle Therapies

Background

Lifestyle Therapies

Non-Insulin Therapies

Insulin Therapies

Combined Therapies

Disparities

Rawshami A, NEJM, 2017
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)

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Lifestyle Therapy: Weight Loss

- 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
Proportion of Patients Achieving Diabetes Remission over 12-months

Adapted from 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
Non-Insulin Therapies

Background

Lifestyle Therapies

Non-Insulin Therapies

Insulin Therapies

Combined Therapies

Disparities

Timeline of Currently Available Non-Insulin Medications

Exenatide 2005
Sitagliptin 2006
Saxagliptin 2009
Liraglutide 2010
Linagliptin 2011
Exenatide QW 2012

Alloglitipin 2013
Canagliflozin 2013
Dapagliflozin 2014
Empagliflozin 2014
Albiglutide 2014
Dulaglutide 2014
Semaglutide QW 2018

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 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
Elixa

Evaluation of Lixisenatide in Acute Coronary Syndrome

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.
ELIXA Trial

- 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

<table>
<thead>
<tr>
<th>ELIXA (Patients with T2D and CVD; N=6068)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>1.02 (0.89-1.17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.97 (0.85-1.10)</td>
<td>0.63</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.78-1.22)</td>
<td>0.85</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>1.03 (0.87-1.22)</td>
<td>0.71</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.12 (0.79-1.56)</td>
<td>0.54</td>
</tr>
<tr>
<td>Unstable angina</td>
<td>1.11 (0.47-2.62)</td>
<td>0.81</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.96 (0.75-1.23)</td>
<td>0.75</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.94 (0.78-1.13)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

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

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 you 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.
LEADER Trial

LEADER Trial

(N=9340)

Median follow-up: 3.5 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.87 (0.78-0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
<td>0.005</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.85 (0.74-0.97)</td>
<td>0.02</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66-0.93)</td>
<td>0.007</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.86 (0.73-1.00)</td>
<td>0.046</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>0.78 (0.67-0.92)</td>
<td>0.003</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.


LEADER Trial

- 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

SUSTAIN 6

- 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

- Statistically significant reductions in:
  - HbA1C (0.7 and 1.0%, respectively),
  - Systolic blood pressure (1.3 and 2.6 mmHg, respectively)
  - Weight (2.9 and 4.3 kg)
  - Increase in heart rate (2.0 and 2.5 bpm, respectively)

*SUSTAIN 6* Results
(N=3297)

 Median follow-up: 2.1 years

<table>
<thead>
<tr>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.74 (0.58-0.95)</td>
</tr>
<tr>
<td>Expanded composite endpoint†</td>
<td>0.88 (0.81-0.96)</td>
</tr>
<tr>
<td>All-cause death, nonfatal MI, nonfatal stroke</td>
<td>0.77 (0.61-0.97)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>1.05 (0.74-1.50)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.98 (0.65-1.48)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td>0.74 (0.51-1.08)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.61 (0.38-0.99)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>0.65 (0.50-0.86)</td>
</tr>
<tr>
<td>Retinopathy complications</td>
<td>1.76 (1.11-2.78)</td>
</tr>
<tr>
<td>New or worsening nephropathy</td>
<td>0.64 (0.46-0.88)</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)
**EXSCEL**

**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<0.001 for noninferiority, P=0.06 for superiority

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**EXSCEL**

**Median follow-up: 3.2 years**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard ratio (95% CI)</th>
<th>P value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.91 (0.83-1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.86 (0.77-0.97)</td>
<td>NS</td>
</tr>
<tr>
<td>CV death</td>
<td>0.88 (0.76-1.02)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.97 (0.85-1.10)</td>
<td></td>
</tr>
<tr>
<td>Fatal MI</td>
<td>1.29 (0.63-2.66)</td>
<td></td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>0.85 (0.70-1.03)</td>
<td></td>
</tr>
<tr>
<td>Fatal stroke</td>
<td>0.71 (0.39-1.30)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.94 (0.78-1.13)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for ACS</td>
<td>1.05 (0.94-1.18)</td>
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</tbody>
</table>

*CV death, nonfatal MI, or nonfatal stroke. †For superiority.
NS, not statistically significant based on hierarchical testing plan.
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

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

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

Adjusted mean (SE) weight (kg)
Systolic blood pressure lower with Empagliflozin

![Graph showing systolic blood pressure over weeks for Placebo, Empagliflozin 10 mg, and Empagliflozin 25 mg.]

EMPA-REG Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite endpoint*</td>
<td>0.86 (0.74-0.99)</td>
<td>0.04</td>
</tr>
<tr>
<td>Secondary composite endpoint†</td>
<td>0.89 (0.78-1.01)</td>
<td>0.08</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>0.68 (0.57-0.82)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>0.62 (0.49-0.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fatal or nonfatal MI</td>
<td>0.87 (0.70-1.09)</td>
<td>0.23</td>
</tr>
<tr>
<td>Hospitalization for HF</td>
<td>0.65 (0.50-0.85)</td>
<td>0.002</td>
</tr>
<tr>
<td>Hospitalization for HF or CV death</td>
<td>0.66 (0.55-0.79)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*CV death, nonfatal MI (excluding silent MI); †CV death, nonfatal MI (excluding silent MI), nonfatal stroke, and hospitalization for unstable angina.

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.

Renal Outcomes with Empagliflozin Over 3.2 Yrs

<table>
<thead>
<tr>
<th>EMPA-REG RENAL (N=7020)</th>
</tr>
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<tbody>
<tr>
<td>Incident or worsening nephropathy or CV death</td>
</tr>
<tr>
<td>Incident or worsening nephropathy</td>
</tr>
<tr>
<td>Progression to macroalbuminuria</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45</td>
</tr>
<tr>
<td>Initiation of renal replacement therapy</td>
</tr>
<tr>
<td>Doubling of SCr + eGFR ≤45, renal replacement therapy, or renal disease death</td>
</tr>
<tr>
<td>Incident albuminuria*</td>
</tr>
</tbody>
</table>

*In patients with normal albuminuria at baseline.
CI, confidence interval; CV, cardiovascular; eGFR, estimated glomerular filtration rate in mL/min/1.73 m²; HR, hazard ratio; SCr, serum creatinine.
NNT to prevent one death across landmark trials in patients with high CV risk

- Simvastatin\(^1\) for 5.4 years
  - High CV risk
  - 5% diabetes, 26% hypertension
  - Pre-statin era
  - 1994

- Ramipril\(^2\) for 5 years
  - High CV risk
  - 38% diabetes, 46% hypertension
  - Pre-ACEi/ARB era
  - 2000

- Empagliflozin for 3 years
  - T2DM with high CV risk
  - 92% hypertension
  - >75% statin
  - 2015


CANVAS PROGRAM

- Patients with type 2 diabetes
- HbA1c ≥7.0% to ≤10.5%
- eGFR ≥30 mL/min/1.73 m\(^2\)
- 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.

2-week placebo run-in

- Canagliflozin 300 mg
- Canagliflozin 100 mg
- Placebo
CANVAS PROGRAM

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

Effects on Systolic BP
Primary MACE Outcome
CV Death, Nonfatal Myocardial Infarction or Nonfatal Stroke

Hazard ratio 0.86 (95% CI, 0.75-0.97)
p < 0.0001 for noninferiority
p = 0.0158 for superiority

No. of patients
Placebo 4347 4153 2942 1240 1187 1120 789
Canagliflozin 5795 5566 4343 2555 2460 2363 1661

Summary

Hazard ratio
(95% CI)

Primary cardiovascular outcome
CV death 0.87 (0.72-1.06)
Nonfatal myocardial infarction 0.85 (0.69-1.05)
Nonfatal stroke 0.90 (0.71-1.15)
Hospitalization for heart failure 0.67 (0.52-0.87)
CV death or hospitalization for heart failure 0.78 (0.67-0.91)
All-cause mortality 0.87 (0.74-1.01)

0.5 1.0 2.0
Favors Canagliflozin
Favors Placebo
Composite of 40% Reduction in eGFR, End-stage Renal Disease, or Renal Death

<table>
<thead>
<tr>
<th>Events (n)</th>
<th>Hazard ratio 0.60 (95% CI, 0.47-0.77)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40% eGFR reduction</td>
<td>Placebo: 239, Canagliflozin: 21</td>
</tr>
</tbody>
</table>

No. of patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Placebo</th>
<th>Canagliflozin 5 mg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4347</td>
<td>5664</td>
<td>9011</td>
</tr>
</tbody>
</table>

DECLARE-TIMI 58

- 17,160 with Type 2 DM
- Established CV Disease (6974) or Multiple Risk Factors (10186)
- DAPAGLIFLOZIN 10 mg DAILY
- RANDOMIZE 1:1 DOUBLE BLIND
- All other DM Rx per treating MD
- PLACEBO
- DURATION EVENT DRIVEN ≥1390 MACE
- Follow-up visits
  - In Person Q 6 mo/ telephone Q 3 mo
- Primary EPs
  - Safety: MACE (CVD/MI/Ischemic Stroke)
  - Dual Efficacy: CVD/HHF, MACE
- Median follow up 4.2 years

Wiviott SD, Raz I...Sabatine MA, AHJ 2018
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**
- 4.3% vs 5.6%
- HR 0.76 (0.67-0.87)
- $P$<0.001

**All-Cause Mortality**
- 6.2% vs 6.6%
- HR 0.93 (0.82-1.04)
- $P$=0.20
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

Adapted from Inzucchi SE, Zinman, B, Wanner, C et al. Diab Vasc Dis Res 2015;12:90-100
Clinical Practice

Obese
CKD
Atherosclerosis
?? Class effect

GLP-1-A
Clinical Practice

Obese CKD Atherosclerosis ? Class effect

GLP-1-A SGLT2-I

Overweight Heart Failure Nephropathy Class effect

Insulin Therapies

Background Lifestyle Therapies Non-Insulin Therapies

Insulin 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

- Loss of \(\beta\)-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

Pharmacokinetics of Insulin Products

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

## 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 (0.89-0.99)</td>
<td>0.84 (0.75-0.94)</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>2</td>
<td>Basal</td>
<td>811</td>
<td>~</td>
<td>0.96 (0.89-1.02)</td>
<td>0.84 (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 (0.77-1.01)</td>
<td>0.76 (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 (0.95-1.04)</td>
<td>0.98 (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

Ritzel et al. Diabetes Obes Metab. 2015 Sep; 17(9): 859–867
Severe Hypoglycemia
SWITCH-2: Degludec vs U100 glargine

---

SWITCH 2 trial design

<table>
<thead>
<tr>
<th>Tresiba® once daily 2 AM</th>
<th>IGLAR once daily 2 AM</th>
</tr>
</thead>
<tbody>
<tr>
<td>16 week titration</td>
<td>16 week titration</td>
</tr>
<tr>
<td>16 week stable</td>
<td>16 week stable</td>
</tr>
</tbody>
</table>

Results

<table>
<thead>
<tr>
<th>Event rate per 100 patient years exposed in maintenance period</th>
<th>Tresiba®</th>
<th>IGLAR</th>
<th>Tresiba® reduction vs IGLAR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe or BG confirmed symptomatic hypoglycaemia</td>
<td>186</td>
<td>265</td>
<td>30%¹</td>
</tr>
<tr>
<td>Severe or BG confirmed symptomatic nocturnal hypoglycaemia</td>
<td>55</td>
<td>94</td>
<td>42%¹</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>5</td>
<td>9</td>
<td>46%</td>
</tr>
<tr>
<td>Severe hypoglycaemia (Full treatment period)</td>
<td>4</td>
<td>9</td>
<td>51%¹</td>
</tr>
</tbody>
</table>

*** severe - an episode requiring third-party assistance

Wysham, Effect of Insulin Degludec vs Insulin Glargine U-100 on Hypoglycemia in Patients With Type 2 Diabetes: The SWITCH 2 Randomized Clinical Trial: JAMA, 2017

---

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

## DEVOTE Study

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite¹</td>
<td>0.91</td>
<td>0.78-1.06</td>
</tr>
<tr>
<td>Expanded composite²</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>0.65-1.23</td>
</tr>
<tr>
<td>UA → hospitalization</td>
<td>0.95</td>
<td>0.68-1.31</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

[Diagram showing 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</td>
<td>mmol/L</td>
</tr>
<tr>
<td>&lt;72</td>
<td>&lt;4.0</td>
</tr>
<tr>
<td>≥72-&lt;90</td>
<td>≥4.0-&lt;5.0</td>
</tr>
<tr>
<td>&gt;90</td>
<td>&gt;5.0</td>
</tr>
</tbody>
</table>


Fasting Glucose with IDegLira

Week 26 vs. Week 52
- Week 26: p<0.0001 vs. liraglutide; p=0.1570 vs. degludec
- Week 52: p<0.0001 vs. liraglutide; p=0.1107 vs. degludec

Full analysis set. Data are mean ± SEM. Δ = Estimated treatment difference. LOCF imputation.

Week 26: p<0.0001 vs. liraglutide; p=0.1570 vs. degludec. Week 52: p<0.0001 vs. liraglutide; p=0.1107 vs. degludec.
Significant Reduction in HbA1c

Full analysis set. Data are mean ± SEM. Δ = 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 HbA$_{1c}$ Reduction

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

<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></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>

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

Zinman, NEJM, 2015; Neal, NEJM, 2017
### SGLT-2: Ethnic Variation in MACE Effect Size

<table>
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<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>

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

Zinman, NEJM, 2015; Neal, NEJM, 2017

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

<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>

**LEADER, EXSCEL, SUSTAIN-6 MACE– CV Death, nonfatal MI, or nonfatal stroke; ELIXA ns**

Marso, NEJM, 2016; Holman, NEJM, 2017
Marso, NEJM, 2016; Pfeffer, NEJM, 2015
Thank You!

Joshua J. Joseph, MD

Joseph.117@osu.edu

@joshuajosephmd