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TRANSITIONS
IN PHARMACY
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Diabetes Update: New Evidence for Insulin and Non-Insulin Agents

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Disclosure

• Alana Whittaker 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.

• Krystal Riccio 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.
Diabetes Update: New Evidence for Non-Insulin Agents

Alana Whittaker, PharmD, BCPS
Associate Professor of Pharmacy Practice
Roseman University, College of Pharmacy
Learning Objectives

Pharmacists

1. Analyze the new evidence relating to the cardiovascular outcomes of empagliflozin and liraglutide
2. Describe the new recommendations for metformin use
3. Identify specific patient population recommendations

Technicians

1. Identify the diabetic medications shown to improve cardiovascular outcomes
2. Recall updates to metformin labeling
3. List antidiabetic medications and their sites of action
1. In reviewing the evidence from empagliflozin and liraglutide and cardiovascular outcomes trials, what is TRUE regarding the reduction of cardiovascular outcomes in patients treated with empagliflozin and liraglutide?
   A. Empagliflozin and liraglutide reduced cardiovascular outcomes
   B. Empagliflozin reduced cardiovascular outcomes but liraglutide did not
   C. Liraglutide reduced cardiovascular outcomes but empagliflozin did not
   D. Liraglutide and empagliflozin did not reduce cardiovascular outcomes

2. With regard to metformin, what is the new renal function cutoff to discontinue metformin for a patient currently on therapy?
   A. eGFR < 60 ml/min/1.73 m²
   B. eGFR < 45 ml/min/1.73 m²
   C. eGFR < 30 ml/min/1.73 m²
   D. eGFR < 15 ml/min/1.73 m²
Test Questions

Technicians

1. **TRUE/FALSE:** Empagliflozin has been shown to reduce cardiovascular outcomes in type 2 diabetic patients?
   
   A. True
   
   B. False

2. **TRUE/FALSE:** Metformin must be discontinued for all patients who receive contrast dye for imaging?
   
   A. True
   
   B. False
Sites of Action of Diabetes Agents

- Amylin agonist
- Bile acid sequestrant
- GLP-1 receptor agonist
- DPP-4i
- Insulin
- Metformin
- Adipose tissue
- Blood glucose
- Muscle
- Liver
- Pancreas
- AGI
- SGLT2i
- Kidney
- SU/glinide
- TZD

### ADA Treatment Algorithm

#### Healthy eating, weight control, increased physical activity, and diabetes education

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
<th>Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>High</td>
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<tr>
<td>low risk</td>
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<td>low risk</td>
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</tr>
<tr>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
<td>GI / lactic acidosis</td>
</tr>
</tbody>
</table>

If HbA1c target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choices depend on a variety of patient and disease-specific factors):

- **Metformin +**
  - **Sulfonylurea**
    - high
    - moderate risk
  - **Thiazolidinedione**
    - high
    - edema, HF, HfSe
  - **DPP-4 inhibitor**
    - intermediate
    - low risk
  - **SGLT2 inhibitor**
    - intermediate
    - low risk
  - **GLP-1 receptor agonist**
    - high
    - low risk
  - **Insulin (basal)**
    - highest
    - hypoglycemia

If HbA1c target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choices depend on a variety of patient and disease-specific factors):

- **Metformin +**
  - **Sulfonylurea**
    - TZD
  - **Thiazolidinedione**
    - SU
  - **DPP-4 inhibitor**
    - SU
  - **SGLT2 inhibitor**
    - SU
  - **GLP-1 receptor agonist**
    - SU
  - **Insulin (basal)**
    - TZD
  - **DPP-4i**
  - **SGLT2i**
  - **GLP-1 RA**
  - **Insulin**

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1 RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulins. In refractory patients consider adding TZD or SGLT2i:

- **Metformin +**
  - Basal insulin +
  - Mealtime insulin or GLP-1 RA
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%
- Metformin
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- AGi
- SU/GLN

MONOTHERAPY*

Entry A1C ≥ 7.5%
- GLP-1 RA
- SGLT-2i
- DPP-4i
- TZD
- Basal Insulin
- Colesevelam
- Bromocriptine QR
- AGi
- SU/GLN

DUAL THERAPY*

Entry A1C > 9.0%
SYMPTOMS
- NO
- YES

DUAL Therapy
OR
TRIPLE Therapy

INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

P R O G R E S S I O N O F D I S E A S E

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

If not at goal in 3 months proceed to Dual Therapy
If not at goal in 3 months proceed to Triple Therapy
If not at goal in 3 months proceed to or intensify insulin therapy

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
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<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td></td>
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<td>Gain</td>
<td>Loss</td>
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<td>RENAL/GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Not Indicated CrCl &lt; 30</td>
<td>Not Effective with eGFR &lt; 45</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
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<td>More Hypo Risk</td>
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<td>GI Sx</td>
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<td>Possible Benefit</td>
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<td>Moderate</td>
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<td>CARDIAC</td>
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<td>Neutral</td>
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<td>Moderate Fracture Risk</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- Uncertain effect

Cardiovascular Data for Metformin, Empagliflozin and Liraglutide
Investigation into whether addition of metformin to intensive blood glucose control reduces clinical complications of diabetes in overweight patients

**Study Design**
- 1704 type 2 DM overweight patients
- 342 metformin therapy, 951 intensive therapy, 411 conventional therapy,
- 15 sites, 4 countries
- Trial: diet, sulfonylureas or insulin, metformin in overweight patients

**Aggregate Composite Outcomes**
- Any diabetes related endpoint (sudden death, death from hypo or hyperglycemia, MI, angina, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction); diabetes related death (sudden death, death from MI, stroke, PVD, renal disease, hyper or hypoglycemia; death from any cause, MI (sudden death or MI), stroke, PVD (amputation of at least one digit or death from PVD) and microvascular disease (vitreous hemorrhage, retinal photocoagulation and renal failure)

UKPDS 34

Figure 6: Incidence of clinical endpoints among patients assigned intensive control with metformin (n=342), intensive control with chlorpropamide, glibenclamide, or insulin (intensive; n=951), or conventional control (n=411).

Relative risk (RR) is for metformin or intensive group compared with conventional group.

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>p for metformin vs other intensive</th>
<th>Patients with aggregate endpoints</th>
<th>Absolute risk (events per 1000 patient-years)</th>
<th>Log-rank 2p</th>
<th>RR (95% CI)</th>
<th>Favours metformin or intensive</th>
<th>Favours conventional</th>
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</thead>
<tbody>
<tr>
<td>Any diabetes-related endpoint</td>
<td>p=0.0084</td>
<td>Metformin or intensive</td>
<td>Metformin or intensive</td>
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<td>Diabetes-related death</td>
<td>p=0.11</td>
<td>Metformin or intensive</td>
<td>Metformin or intensive</td>
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<tr>
<td>All-cause mortality</td>
<td>p=0.021</td>
<td>Metformin or intensive</td>
<td>Metformin or intensive</td>
<td></td>
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<td>Myocardial infarction</td>
<td>p=0.12</td>
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<td>Metformin or intensive</td>
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<td>Stroke</td>
<td>p=0.052</td>
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<td>Metformin or intensive</td>
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<td></td>
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<tr>
<td>Peripheral vascular disease</td>
<td>p=0.012</td>
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<td>Metformin or intensive</td>
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</tr>
<tr>
<td>Microvascular</td>
<td>p=0.39</td>
<td>Metformin or intensive</td>
<td>Metformin or intensive</td>
<td></td>
<td></td>
<td></td>
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</table>

Investigation into whether addition of metformin reduces clinical complications of diabetes in overweight patients

Study Design
- 4209 type 2 DM patients in original UKPDS, 3277 joined post trial follow-up
- 411 conventional therapy, 342 intensive therapy in metformin group
- 15 sites, 4 countries
- Original trial: diet, sulfonylureas or insulin, metformin in overweight patients
- Patients did not have to stick to original regimen in post trial follow-up

Aggregate Composite Outcomes
- Any diabetes related endpoint (sudden death, death from hypo or hyperglycemia, MI, angina, stroke, renal failure, amputation, vitreous hemorrhage, retinal photocoagulation, blindness in one eye or cataract extraction); diabetes related death (sudden death, death from MI, stroke, PVD, renal disease, hyper or hypoglycemia; death from any cause, MI (sudden death or MI), stroke, PVD (amputation of at least one digit or death from PVD) and microvascular disease (vitreous hemorrhage, retinal photocoagulation and renal failure)

10 Year Post Trial Follow-up for UKPDS

10 Year Post Trial Follow-up for UKPDS

10 Year Post Trial Follow-up for UKPDS

Metformin Effects on CV Outcomes Meta-Analysis

**Figure 1.** Trial flow diagram. RCT, randomized clinical trial.

Metformin Effects on CV Outcomes Meta-Analysis

**Figure 3.** Effect of metformin on cardiovascular events across all randomized clinical trials included in the analysis. The size of the data markers represents the relative weight of the trial according to patient-years. MH-OR, Mantel–Henzel odds ratio; CI, confidential intervals. See Appendix S1 for references [32–62].

Comparison of empagliflozin to placebo for effects on cardiovascular outcomes

**Study Design**
- 7020 type 2 DM patients with high cardiovascular risk and A1C > 7%
- 590 sites, 42 countries
- Empagliflozin 10 mg, 25 mg and placebo (pooled empagliflozin results)
- Run in period

**Primary Composite Outcomes**
- First occurrence of death from CV cause, nonfatal MI and nonfatal stroke

**Secondary Composite Outcomes**
- Events in primary composite outcomes and hospitalization for unstable angina

EMPA-REG OUTCOME Trial

Results
- Median time of exposure: 2.6 years
- Median follow-up: 3.1 years

EMPAA-REG OUTCOME Trial

A. Weight

F. Low density lipoprotein cholesterol

Conversion factor: 1 mg/dL = 0.02586 mmol/L

Zinman B et al. NEJM. 2015;373:2117-2128.
EMPA-REG OUTCOME Trial

Zinman B et al. NEJM. 2015;373:2117-2128.
EMPA-REG OUTCOME Trial

C. Systolic blood pressure

D. Diastolic blood pressure

Zinman B et al. NEJM. 2015;373:2117-2128.
EMP A-REG OUTCOME Trial

**Primary Outcome**
- Hazard ratio, 0.86 (95% CI, 0.74–0.99)
- P = 0.04 for superiority
- Patients with event (%)

**Death from Cardiovascular Causes**
- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P < 0.001
- Patients with event (%)

Zinman B et al. NEJM. 2015;373:2117-2128.
EMPA-REG OUTCOME Trial

C. Death from Any Cause
- Hazard ratio, 0.68 (95% CI, 0.57–0.82)
- P<0.001

D. Hospitalization for Heart Failure
- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P=0.002

Zinman B et al. NEJM. 2015;373:2117-2128.
LEADER Trial

Comparison of liraglutide to placebo for effects on cardiovascular outcomes

- **Study Design**
  - 9340 type 2 DM patients with high cardiovascular risk and A1C > 7%
  - 410 sites, 32 countries
  - Run in period
  - Time to event analysis

- **Primary Composite Outcomes**
  - First occurrence of death from CV cause, nonfatal MI and nonfatal stroke

- **Expanded Composite Outcomes**
  - Events in primary composite outcomes and coronary revascularization, hospital for unstable angina pectoris or heart failure

LEADER Trial

Results
- Median time of exposure: 3.5 years
- Median follow-up: 3.8 years
- Median dose of liraglutide: 1.78 mg
- Mean difference in A1C at 36 months: -0.40%, liraglutide better
- Weight loss: 2.3 kg higher in liraglutide group
- BP: systolic 1.2 mmHg and diastolic 0.6 mmHg higher in liraglutide group
- Incidence of nephropathy: (1.5 vs 1.9 per 100 patient-years) p = 0.003, liraglutide better
- Incidence of retinopathy: (0.6 vs 0.5 per 100 patient-years) p = 0.33, liraglutide worse

Marso SP et al. NEJM. 2016;311:322.
LEADER Trial

A Primary Outcome

Hazard ratio, 0.87 (95% CI, 0.78–0.97)

P<0.001 for noninferiority
P=0.01 for superiority

Patients with an Event (%)

Months since Randomization

No. at Risk
Liraglutide 4668 4593 4496 4400 4280 4172 4072 3982 1562 424
Placebo 4672 4588 4473 4352 4237 4123 4010 3914 1543 407

B Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)

P=0.007

Patients with an Event (%)

Months since Randomization

No. at Risk
Liraglutide 4668 4641 4599 4558 4505 4445 4382 4322 1723 484
Placebo 4672 4648 4601 4546 4479 4407 4338 4267 1709 465
LEADER Trial

C Nonfatal Myocardial Infarction

D Nonfatal Stroke

Marso SP et al. NEJM. 2016;311-322.
LEADER Trial

E Death from Any Cause

Hazard ratio, 0.85 (95% CI, 0.74–0.97)
P = 0.02

F Hospitalization for Heart Failure

Hazard ratio, 0.87 (95% CI, 0.73–1.05)
P = 0.14

No. at Risk
Liraglutide: 4668, 4641, 4599, 4558, 4505, 4445, 4382, 4322, 1723, 484
Placebo: 4672, 4612, 4540, 4464, 4372, 4288, 4187, 4107, 1647, 467

Months since Randomization

Patients with an Event (%)

Placebo
Liraglutide

Marso SP et al. NEJM. 2016;311-322.
Summary of Trials

UKPDS Trial
- 20 year follow-up in overweight patients only
- Reduction in diabetes related endpoints and diabetes related deaths with metformin

EMPＡ-REG OUTCOME Trial
- 3 year follow-up
- Reduction in first occurrence of death from CV cause, nonfatal MI and nonfatal stroke with empagliflozin

LEADER Trial
- 4 year follow-up
- Reduction in first occurrence of death from CV cause, nonfatal MI and nonfatal stroke with liraglutide

New Metformin Recommendations
New Metformin Recommendations

Change in renal function cutoffs

◦ Old recommendations: based on serum creatinine (contraindicated in women with Scr ≥ 1.4 mg/dL and men with Scr ≥ 1.5 mg/dL)
◦ New recommendations: based on eGFR (do not initiate if eGFR < 45/ml/min/1.73 m² and patients are already on metformin, discontinue if eGFR < 30 ml/min/1.73m²)
◦ Obtain eGFR yearly
◦ For patients on metformin if eGFR 30 – 45 ml/min/1.73 m², perform a risk/benefit analysis, if greater benefit then continue metformin

New Metformin Recommendations

Change in contrast dye recommendations

- Discontinue metformin at the time of or before an iodinated contrast dye given to patients with an eGFR between 30 and 60 mL/minute/1.73 m²; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast.

- Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Clinical Considerations

Regarding CV management for diabetics, guidelines still only recommend metformin as the hyperglycemic agent that can reduce both microvascular and macrovascular complications.

For diabetics, we primarily reduce macrovascular complications by using:
  ◦ Antiplatelets (aspirin)
  ◦ Blood pressure lowering medications
  ◦ Cholesterol lowering with statins

Test Questions

Pharmacists

1. In reviewing the evidence from empagliflozin and liraglutide and cardiovascular outcomes trials, what is TRUE regarding the reduction of cardiovascular outcomes in patients treated with empagliflozin and liraglutide?
   A. Empagliflozin and liraglutide reduced cardiovascular outcomes
   B. Empagliflozin reduced cardiovascular outcomes but liraglutide did not
   C. Liraglutide reduced cardiovascular outcomes but empagliflozin did not
   D. Liraglutide and empagliflozin did not reduce cardiovascular outcomes

2. With regard to metformin, what is the new renal function cutoff to discontinue metformin for a patient currently on therapy?
   A. eGFR < 60 ml/min/1.73 m²
   B. eGFR < 45 ml/min/1.73 m²
   C. eGFR < 30 ml/min/1.73 m²
   D. eGFR < 15 ml/min/1.73 m²
Test Questions

Technicians

1. **TRUE/FALSE**: Empagliflozin has been shown to reduce cardiovascular outcomes in type 2 diabetic patients?
   - A. True
   - B. False

2. **TRUE/FALSE**: Metformin must be discontinued for all patients who receive contrast dye for imaging?
   - A. True
   - B. False
References


Diabetes Update: New Evidence for Insulins

Krystal Riccio, PharmD, BCACP, CDE
Associate Professor of Pharmacy Practice
Roseman University, College of Pharmacy
Learning Objectives

Pharmacists
1. Describe the newer insulin products approved by the FDA
2. Evaluate the safety and efficacy of newer insulin products using trial data
3. Identify the appropriate use of these newer insulin products
4. Discuss the clinical situations or patients which may benefit from the use of these agents

Technicians
1. List the newer insulin products recently added to the US marketplace
2. Recall the delivery devices and handling recommendations for these newer insulin products
3. Identify potential situations or patients which may benefit from the use of these agents
Test Questions

Pharmacists

1. In reviewing the evidence from concentrated basal insulins compared to glargine U-100, what is TRUE regarding the HbA1c lowering effectiveness?
   A. Concentrated basal insulins are LESS effective than glargine U-100 at lowering HbA1c
   B. Concentrated basal insulins are EQUALLY effective to glargine U-100 at lowering HbA1c
   C. Concentrated basal insulins are MORE effective than glargine U-100 at lowering HbA1c
   D. Concentrated basal insulins are found to have variable HbA1c lowering potential compared to glargine U-100

2. Although all glargine and degludec insulins are labeled with a dose for dose conversion, from the evidence provided, which product will most likely require higher dosing than Lantus® after 6 months of use?
   A. Glargine U100 (Basaglar®)
   B. Glargine U300 (Toujeo®)
   C. Degludec U100 (Tresiba®)
   D. Degludec U200 (Tresiba®)
Test Questions

Technicians

1. **TRUE/FALSE**: The new glargine U100 (Basaglar®) to be released in December 2016, is bioequivalent to glargine U100 (Lantus®) AND can be interchanged in the pharmacy without contacting a prescriber?
   - A. True
   - B. False

2. What is the out of fridge expiration time for degludec U200 (Tresiba® FlexTouch®) pens?
   - A. 28 days
   - B. 36 days
   - C. 42 days
   - D. 56 days
Newly Approved Insulin Products

Bolus
- U200 insulin lispro (Humalog®)

Basal
- U100 insulin glargine (Basaglar®)
- U300 insulin glargine (Toujeo®)
- U100 insulin degludec (Tresiba®)
- U200 insulin degludec (Tresiba®)
U200 insulin lispro (Humalog Kwik Pen®)

Bolus/Mealtime Insulin

- 3mL pens = 600 units
- 2 pens per box
- 28 day out of fridge expiration
- Same KwikPen® design
  - 1 unit incremental changes

http://healthycanadians.gc.ca/
Bioequivalence Study


- Study Design
  - 38 healthy subjects
  - 8 hour euglycemic clamp study
  - 20 units U200 vs. U100 insulin lispro

- Results
  - Pharmacokinetic outcomes; CI 0.80 – 1.25
  - Pharmacodynamic outcomes; similar
  - Tolerability; similar
U200 insulin lispro (Humalog Kwik Pen®)

Bioequivalence Study

Data shown as arithmetic mean ± SE of concentrations at nominal sampling times.

Lines represent the overall LOESS smooth per treatment; symbols represent the LOESS smooth values (+SE) of glucose infusion rates at 30-minute intervals which were chosen for better graphic representation.

U200 insulin lispro (Humalog Kwik Pen®)

Bolus/Mealtime Insulin

1 unit U100 ↔ 1 unit U200

http://integrateddiabetes.com
U300 insulin glargine (Toujeo® Solostar® Pen)

Basal/Background Insulin
- Supplied in 1.5mL pens = 450 units
- Box of 3 / Box of 5
- 42 days out of fridge expiration
- Similar design to Lantus® Solostar®
  - 1 unit incremental changes
  - 80 unit maximum dial
  - Less force required for “push”
Bioequivalence Trial: U300 vs. U100 glargine

Clinical Trials: U300 glargine vs. U100 glargine

EDITION 1
- Type 2 DM; on basal & bolus insulin regimen; 6 month efficacy & safety

EDITION 2
- Type 2 DM; on basal insulin & oral medication regimen; 6 month efficacy & safety

EDITION 3
- Type 2 DM; on oral medication regimen; 6 month efficacy & safety

EDITION 4
- Type 1 DM; on basal & bolus insulin regimen; 6 month efficacy & safety
HbA1c

No statistical difference at 6 months
Dose at 6 month
Statistically different
Higher dose requirement
EDITION 2

Hypoglycemia at any time (24 hour) | Nocturnal hypoglycemia (00:00–05:59 hour) | Hypoglycemia at any time (24 hour) | Nocturnal hypoglycemia (00:00–05:59 hour)

**Any hypoglycemia**
- Baseline to month 6: RR 0.90, 95% CI 0.83–0.98
- Baseline to week 8: RR 0.77, 95% CI 0.68–0.88
- Week 9 to month 6: RR 0.91, 95% CI 0.82–1.01

**Documented symptomatic hypoglycemia (≤3.9 mmol/L [≤70 mg/dL])**
- Baseline to month 6: RR 0.86, 95% CI 0.76–0.98
- Baseline to week 8: RR 0.76, 95% CI 0.63–0.92
- Week 9 to month 6: RR 0.91, 95% CI 0.78–1.07

**Confirmed (≤3.9 mmol/L [≤70 mg/dL]) or severe hypoglycemia**
- Baseline to month 6: RR 0.90, 95% CI 0.83–0.98
- Baseline to week 8: RR 0.78, 95% CI 0.69–0.89
- Week 9 to month 6: RR 0.91, 95% CI 0.82–1.02

**EDITION 3: Ratio of Annualized Event Rates**

<table>
<thead>
<tr>
<th>Week 9 – Month 6</th>
<th>Nocturnal hypoglycemia [00:00-06:00 h] RR (95% CI)</th>
<th>Hypoglycemia at any time [24 h] RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed &lt; 4 mmol/L or severe hypoglycemia</td>
<td>1.08 (0.66 – 1.77)</td>
<td>0.81 (0.60 – 1.10)</td>
</tr>
<tr>
<td>Confirmed &lt; 3 mmol/L or severe hypoglycemia</td>
<td>0.58 (0.27 – 1.24)</td>
<td>0.87 (0.49 – 1.53)</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycemia &lt; 4 mmol/L</td>
<td>1.02 (0.58 – 1.80)</td>
<td>0.70 (0.49 – 1.01)</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycemia &lt; 3 mmol/L</td>
<td>0.51 (0.23 – 1.14)</td>
<td>0.61 (0.36 – 1.05)</td>
</tr>
</tbody>
</table>

## EDITION 4: Ratio of Annualized Event Rates

<table>
<thead>
<tr>
<th></th>
<th>Nocturnal hypoglycaemia (00:00–05:59 h)</th>
<th>Hypoglycaemia at any time of day (24 h)</th>
<th>Nocturnal hypoglycaemia (00:00–05:59 h)</th>
<th>Hypoglycaemia at any time of day (24 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR  95% CI</td>
<td>RR  95% CI</td>
<td>RR  95% CI</td>
<td>RR  95% CI</td>
</tr>
<tr>
<td>Confirmed (≤3.9 mmol/l) or severe hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.98  0.64 to 1.48</td>
<td>0.75  0.57 to 0.99</td>
<td>0.98  0.64 to 1.48</td>
<td>0.75  0.57 to 0.99</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.70  0.41 to 1.18</td>
<td>0.61  0.43 to 0.86</td>
<td>0.70  0.41 to 1.18</td>
<td>0.61  0.43 to 0.86</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>1.08  0.66 to 1.77</td>
<td>0.81  0.60 to 1.10</td>
<td>1.08  0.66 to 1.77</td>
<td>0.81  0.60 to 1.10</td>
</tr>
<tr>
<td>Confirmed (&lt;3.0 mmol/l) or severe hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.61  0.33 to 1.15</td>
<td>0.75  0.47 to 1.22</td>
<td>0.61  0.33 to 1.15</td>
<td>0.75  0.47 to 1.22</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.69  0.26 to 1.86</td>
<td>0.55  0.29 to 1.02</td>
<td>0.69  0.26 to 1.86</td>
<td>0.55  0.29 to 1.02</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>0.58  0.27 to 1.24</td>
<td>0.87  0.49 to 1.53</td>
<td>0.58  0.27 to 1.24</td>
<td>0.87  0.49 to 1.53</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycaemia ≤3.9 mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.90  0.55 to 1.48</td>
<td>0.62  0.44 to 0.87</td>
<td>0.90  0.55 to 1.48</td>
<td>0.62  0.44 to 0.87</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.60  0.31 to 1.16</td>
<td>0.42  0.28 to 0.67</td>
<td>0.60  0.31 to 1.16</td>
<td>0.42  0.28 to 0.67</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>1.02  0.58 to 1.80</td>
<td>0.70  0.49 to 1.01</td>
<td>1.02  0.58 to 1.80</td>
<td>0.70  0.49 to 1.01</td>
</tr>
<tr>
<td>Documented symptomatic hypoglycaemia &lt;3.0 mmol/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to month 6</td>
<td>0.55  0.28 to 1.07</td>
<td>0.55  0.35 to 0.85</td>
<td>0.55  0.28 to 1.07</td>
<td>0.55  0.35 to 0.85</td>
</tr>
<tr>
<td>Baseline to week 8</td>
<td>0.66  0.23 to 1.92</td>
<td>0.43  0.22 to 0.85</td>
<td>0.66  0.23 to 1.92</td>
<td>0.43  0.22 to 0.85</td>
</tr>
<tr>
<td>Week 9 to month 6</td>
<td>0.51  0.23 to 1.14</td>
<td>0.61  0.36 to 1.05</td>
<td>0.51  0.23 to 1.14</td>
<td>0.61  0.36 to 1.05</td>
</tr>
</tbody>
</table>
U100 & U200 Degludec (Tresiba®)

Basal/Background Insulin

- **U100**
  - 1 unit dose increments
  - 80 unit maximum dial
  - 3mL pens = 300 units
  - Box of 5
  - 56 days out of fridge expiration
  - Flex Touch® design

- **U200**
  - 2 unit dose increments
  - 160 unit maximum dial
  - 3mL pens = 600 units
  - Box of 3
  - 56 days out of fridge expiration
  - Flex Touch® design

U200 degludec vs. U100 glargine
BEGIN: Basal–Bolus Type 1: 2-year results

Results at 105 weeks
- HbA1c – no statistical difference
- Insulin dose (units) – lower degludec dosing (no statistical data available)
- Hypoglycemia

<table>
<thead>
<tr>
<th>Episodes per patient-yr</th>
<th>Degludec</th>
<th>Glargine</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal Confirmed</td>
<td></td>
<td>5.3</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0.17</td>
<td>0.15</td>
<td>Non-significant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>16 – 105 weeks</th>
<th>Estimated Rate Ratio (degludec/glargine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall hypoglycemia</td>
<td>0.98 (0.8 – 1.2)</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>0.73 (0.56 – 0.94)</td>
</tr>
</tbody>
</table>

U200 degludec vs. U100 glargine
BEGIN: Basal–Bolus Type 2

Results at 52 weeks

- HbA1c – no statistical difference
- Basal Insulin Dosing: **12% difference (7.7 units/day)**

<table>
<thead>
<tr>
<th></th>
<th>Insulin degludec (U/kg; n=753)</th>
<th>Insulin glargine (U/kg; n=251)</th>
<th>Estimated treatment ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>0.45 (0.25)</td>
<td>0.44 (0.27)</td>
<td></td>
</tr>
<tr>
<td>Week 52</td>
<td>0.75 (0.43)</td>
<td>0.69 (0.40)</td>
<td>1.08 (1.01–1.15)</td>
</tr>
</tbody>
</table>

Results at 52 weeks

- Hypoglycemia

<table>
<thead>
<tr>
<th></th>
<th>Insulin degludec (n=753)</th>
<th>Insulin glargine (n=251)</th>
<th>Estimated rate ratio insulin degludec: insulin glargine (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Severe</strong>*</td>
<td>34 (5%)</td>
<td>11 (4%)</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td><strong>Overall confirmed</strong></td>
<td>609 (81%)</td>
<td>206 (82%)</td>
<td>0·82 (0·69–0·99)</td>
<td>0·0359</td>
</tr>
<tr>
<td><strong>Nocturnal confirmed</strong></td>
<td>298 (40%)</td>
<td>119 (47%)</td>
<td>0·75 (0·58–0·99)</td>
<td>0·0399</td>
</tr>
</tbody>
</table>

* Insufficient episodes for statistical assessment.

Biosimilar Insulin
U100 Glargine (Basaglar® KwikPen®)

Approved 12/15/2015
Market Release 12/15/2016

- Not approved as a “biosimilar” in the US
- Remains a branded product
- Not interchangeable with Lantus®
- Exclusivity protection

http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205692lbl.pdf
U100 Glargine (Basaglar® KwikPen®)

Basal/Background Insulin

- 3mL pens = 300 units
- 5 pens per box
- 28 day out of fridge expiration
- KwikPen® design
  - 1 unit incremental changes
Clinical Trials
U100 Glargine: Basaglar® vs. Lantus®

ELEMENT 1
- Phase III, open label, Type 1 DM on basal & bolus insulin regimen
- 52 weeks
- Safety & Efficacy

ELEMENT 2
- Phase III, open label, Type 2 DM on oral medication +/- U100 glargine
- 24 weeks
- Safety & Efficacy
Clinical Trials
U100 Glargine: Basaglar® vs. Lantus®

ELEMENT 1
- **Efficacy** = NS Differences at 24 & 52 weeks
  - HbA1c; change from baseline HbA1c; FPG; Insulin Dose
- **Safety** = NS Differences at 24 & 52 weeks
  - Hypoglycemia rate; detectable antibodies; % insulin antibody binding; Body weight

ELEMENT 2
- **Efficacy** = NS Differences at 24 weeks
  - HbA1c, change from baseline HbA1c, FPG, Insulin Dose, and Body weight
- **Safety** = NS Differences at 24 weeks
  - Hypoglycemia rate, weight change, detectable antibodies, % insulin antibody binding
Clinical Considerations
Cost Considerations

Lispro (Humalog®) U200
- Branded
- Formulary restrictions
- Private-insured discount card ($25/mo)

Glargine (Toujeo®) U300
- Branded
- Formulary restrictions
- Private-insured/cash pay discount card ($15/mo)

Degludec (Tresiba®) U100 & U200
- Branded
- Formulary restrictions
- Private-insured discount card ($15/mo)
Consider using concentrated insulin when...

High basal dosing
- Consistent absorption curve
- Patient requires “high” units per dose
  - Degludec (Tresiba®) U200
  - Up to 160 units per injection

Need extended time outside refrigeration
- Glargine (Toujeo®) U300 = 42 days
- Degludec (Tresiba®) U200 = 56 days

Privately insured
- Formulary
- Coupon cards
!Cautions! when using concentrated insulin…

Pen Devices ONLY
  ◦ Never use pen cartridges as vials

Dose for Dose Conversions
  ◦ Concentrated glargine requires higher dosing over time

Product name/concentration confusion
  ◦ Prescriptions written for Glargine U100 not interchangeable for glargine U300
  ◦ Prescriptions written for Toujeo® cannot be substituted for Lantus®
  ◦ Degludec (Tresiba®) comes in U100 AND U200
    ◦ Degludec U100 not interchangeable for degludec U200
“Biosimilar” Limitations to impacting practice

FDA Regulations of Insulin

- **Food, Drug, and Cosmetic Act**
  - Section 505 (new drug application fast track)
  - Similar enough to comparator; “follow-on”

- **Biologics Price Competition and Innovation (BPCI) Act**
  - Section 7002(e)
  - Amended biologic definition to include proteins
  - Exclusivity terms
  - Transition period  ➔  **March 23, 2020**

- **Public Health Service Act (PHS Act)**
  - Section 351 (biologic designation)
  - No insulin approved as a biologic
  - No reference product
Test Questions

Pharmacists

1. In reviewing the evidence from concentrated basal insulins compared to glargine U-100, what is TRUE regarding the HbA1c lowering effectiveness?
   A. Concentrated basal insulins are LESS effective than glargine U-100 at lowering HbA1c
   B. Concentrated basal insulins are EQUALLY effective to glargine U-100 at lowering HbA1c
   C. Concentrated basal insulins are MORE effective than glargine U-100 at lowering HbA1c
   D. Concentrated basal insulins are found to have variable HbA1c lowering potential compared to glargine U-100

2. Although all glargine and degludec insulins are labels with a dose for dose conversion, from the evidence provided, which product will most likely require higher dosing than Lantus® after 6 months of use?
   A. Glargine U100 (Basaglar®)
   B. Glargine U300 (Toujeo®)
   C. Degludec U100 (Tresiba®)
   D. Degludec U200 (Tresiba®)
Test Questions

Technicians

1. **TRUE/FALSE**: The new glargine U100 (Basaglar®) to be released in December 2016, is bioequivalent to glargine U100 (Lantus®) AND can be interchanged in the pharmacy without contacting a prescriber?
   A. True
   B. False

2. What is the out of fridge expiration time for degludec U200 (Tresiba® FlexTouch®) pens?
   A. 28 days
   B. 36 days
   C. 42 days
   D. 56 days
References


4. Becker RHA, Dahmen R, Bergmann K, et al. New insulin glargine 300 Units/mL provides a more even activity profile and prolonged glycemic control at steady state compared with insulin glargine 100 Units/mL. *Diabetes Care*. 2015;38:637-643.


References


Questions
Alana Whittaker, PharmD, BCPS
Krystal Riccio, PharmD, BCACP, CDE
1. Write down the course code. Space has been provided in the daily program-at-a-glance sections of your program book.

2. To claim credit: Go to www.cshp.org/cpe before December 1, 2016.