All Things Insulin: Dosing, Monitoring, Titrating, Transitioning
Target Audience: Pharmacists

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Activity Type: Application-based
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Stuart Haines – declares that he has no financial or other conflicts-of-interest related to the content of this presentation

Jennifer Trujillo - declares that she serves on an advisory board for Sanofi

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All Things Insulin: Dosing, Monitoring, Titrating, Transitioning

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Attendance Code

To obtain CPE credit for this activity, you are required to actively participate in this session. The attendance code is needed to access the evaluation and CPE form for this activity. Your CPE must be filed by April ##, 2018 at 5:00 pm EDT in order to receive credit.
Learning Objectives

- Compare the characteristics of new insulin products on the market
- Explain the potential roles of recently approved insulins in the management of type 1 and type 2 diabetes
- Describe strategies to minimize insulin-induced hypoglycemia, including patient education tools
- Demonstrate how to safely switch patients among available insulin products
- Discuss management strategies when switching patients to insulin U500
When compared to insulin glargine U-100, insulin degludec U-200 is ...

A. less likely to cause nocturnal hypoglycemia in patients with type 2 diabetes
B. more likely to achieve an A1c < 7% in patients type 2 diabetes
C. more likely to achieve an A1c < 7% and a fasting BG < 100mg/dL in patients with type 1 diabetes
D. less likely to cause nocturnal hypoglycemia and weight gain in patients with type 1 diabetes
SELF-ASSESSMENT QUESTION 2

Which of the following options accurately lists medications from MOST to LEAST likely to cause hypoglycemia?

A. Insulin aspart, Insulin glargine, Regular human insulin 70/30
B. Regular human insulin 70/30, metformin, insulin glargine
C. Insulin glargine, glyburide, insulin aspart
D. Regular human insulin 70/30, glyburide, insulin glargine
Mr. B is a 55 year old man with type 2 DM who is currently taking regular human insulin U-100 40 units prior to each meal and insulin glargine U-100 80 units every 12 hours. His FBG = 174mg/dl and most recent A1c = 8.6%. Which of the following is the most appropriate medication change in this case?

A. Add pioglitazone 30mg daily
B. Increase insulin glargine U-100 dose to 100 units every 12 hours
C. Increase regular insulin U-100 dose to 50 units prior to each meal
D. Switch both insulins to regular human insulin U-500 170 units QAM and 110 units QPM
A patient with well-controlled type 2 diabetes has to switch from insulin glargine U-100 (Lantus) to insulin detemir U-100 (Levemir) because his insurance no longer covers insulin glargine. Which of the following statements is true about this scenario?

A. The patient should be instructed to reduce the dose by 20% and return for follow-up in 2 weeks.

B. This insulin switch is categorized as a “non-medical switch” because it is for reasons other than the patient’s health and safety.

C. The patient should be instructed to continue taking the same dose he was previously taking and return for follow-up in 3 months.

D. Studies have shown that this type of insulin switch does not negatively impact adherence or medication-taking behaviors in well-controlled patients.
A patient with well-controlled type 2 diabetes (A1c = 6.6%) is currently taking regular insulin u-100 6 units prior to each meal and insulin glargine u-100 74 units at bedtime. The patient states she has had several episodes of hypoglycemia over the past 3 weeks. The patient states that if she does not “eat enough or on time, I’ll go low.” Which of the following is the most appropriate action to take at this time?

A. Decrease regular insulin dose to 4 units
B. Switch regular insulin to a rapid-acting insulin product
C. Decrease insulin glargine dose to 60 units
D. Reaffirm the need to eat at least 60 grams of carbohydrates every regular 4-5 hours throughout the day
New Insulin Treatment Options
### Available Insulin Products

<table>
<thead>
<tr>
<th>Type</th>
<th>Basal Insulins</th>
<th>Prandial Insulins</th>
<th>Premixed Insulins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>• NPH U100</td>
<td>• Regular human insulin U100</td>
<td>• Regular human insulin 70/30</td>
</tr>
<tr>
<td></td>
<td>• Regular human insulin U500</td>
<td>• Regular human insulin U500</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Insulin inhalation powder</td>
<td></td>
</tr>
<tr>
<td>Analog</td>
<td>• Detimir U100</td>
<td>• Aspart U100</td>
<td>• Aspart protamine + aspart (70/30)</td>
</tr>
<tr>
<td></td>
<td>• Glargine U100</td>
<td>• Aspart U100 FIASP</td>
<td>• Lispro protamine + lispro 75/25</td>
</tr>
<tr>
<td></td>
<td>• Glargine equiv U100</td>
<td>• Lispro U100</td>
<td>• Lispro protamine + lispro 50/50</td>
</tr>
<tr>
<td></td>
<td>• Glargine U300</td>
<td>• Lispro U200</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Degludec U100</td>
<td>• Glulisine U100</td>
<td>• Insulin degludec + insulin aspart (70/30)</td>
</tr>
<tr>
<td></td>
<td>• Degludec U200</td>
<td></td>
<td></td>
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</table>

## Available Delivery Methods for New Insulins

<table>
<thead>
<tr>
<th>Rapid Acting Insulin</th>
<th>Vials</th>
<th>Prefilled Pens</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 Aspart (FIASP)</td>
<td>✓</td>
<td>✓ FlexTouch® Pen</td>
</tr>
<tr>
<td>U-200 Lispro</td>
<td>✓</td>
<td>✓ KwikPen®</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Long-Acting Analogs</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 Detemir</td>
<td>✓</td>
<td>✓ FlexTouch® Pen</td>
</tr>
<tr>
<td>U-100 Glargine</td>
<td>✓</td>
<td>✓ SoloStar® Pen</td>
</tr>
<tr>
<td>U-100 Glargine Equivalent</td>
<td>✗</td>
<td>✓ KwikPen®</td>
</tr>
<tr>
<td>U-100 Degludec</td>
<td>✗</td>
<td>✓ FlexTouch® Pen</td>
</tr>
<tr>
<td>U-200 Degludec</td>
<td>✗</td>
<td>✓ FlexTouch® Pen</td>
</tr>
<tr>
<td>U-300 Glargine</td>
<td>✗</td>
<td>✓ SoloStar® Pen</td>
</tr>
</tbody>
</table>

New Prandial Insulin – Ultra-Rapid Acting

- Insulin aspart
- Contains excipients nicotinamide and arginine
- Faster onset of exposure vs current aspart insulin (20.7 vs 31.6 min to reach 50% of max concentration)

In patients with type 1 diabetes:
- 50% greater glucose-lowering effect in the first 30 min after dose vs current aspart
- Significantly greater mean change in plasma glucose 2 hrs after a standard meal vs current aspart (72.36 vs 54.54 mg/dL)

Heise T, et al. Diabetes Obes Metab. 2015;17(7):682-688
New Prandial Insulin – Inhaled Insulin Powder

- Single-use cartilages of 4, 8, and 12 units
- Shorter time to peak plasma level vs subcutaneous insulins (12-15 min)
- Shorter duration of action vs subcutaneous insulins (2.5-3 hours)
- The inhaler may be used for 15 days
- The insulin powder cartridges must be stored in the refrigerator and used with 3 to 10 days after they are removed from the refrigerator
- Do not use in patients with chronic lung disease or active lung cancer
- Not recommended for active or recent smokers

See Drugs@FDA: FDA Approved Drug Products; www.accessdata.fda.gov/Scripts/cder/drugsatfda/; December 1, 2017
Case Studies
Case #1

RM is a 65 year old Lebanese man

**HPI:** Returning for a follow-up diabetes education appointment to discuss the initiation of insulin therapy. His A1C has been elevated for several months but his PCP has been putting off adding another diabetes medication.

The PCP encourages RM to lose weight and exercise. RM is worried about starting insulin. His mother had diabetes and was using insulin before she passed away.
Case #1

Past Medical History:
Type 2 diabetes x 9 years
Dyslipidemia x 9 years
Hypertension x 12 years
Obesity
Case #1

**Medications:**
- Metformin 1000mg PO twice daily
- Glipizide 20mg PO once daily
- Pioglitazone 45mg PO once daily
- Losartan 100mg PO daily
- Amlodipine 10mg PO daily
- Atorvastatin 40mg PO daily
Case #1

Social & Family Hx:

- Resides with wife; 3 grown children
- Recently retired
- Walks his dog 4-5 x /week
- Weight stable for the past year; wants to lose weight
- Never smoked, used tobacco products or illicit drugs
- Does not drink alcohol
- Father died from pancreatic cancer; mother died from CVD
- Has high deductible insurance plan
Case #1

Glucose Control History:

- A1C 9.4%
- SMBG most days before breakfast
  - Fasting 30-day average = 183 mg/dL
- 1 episode of shaking and sweating in the last month occurred midday when he was working in the yard; he did not test his blood sugar – he just ate something and his symptoms improved
Case #1

Vital Signs:

BP = 124/72   Pulse = 74, regular
Weight = 209 lbs  Height = 5’ 10”
BMI = 30.3  Temp = 98.7

Labs (drawn this morning - fasting):

Glucose = 194    A1C = 9.4%
BUN = 21     SCr = 1.1    eGFR > 60 ml/min
Na = 137    K = 4.7
Tchol = 156  LDL = 82    HDL = 41    Trig = 166
Case #1 - Questions

1) What insulin products are appropriate options and should be discussed with this patient?
2) Among the appropriate options, what insulin product would you recommend to this patient?
3) How would you initiate insulin therapy? (Initial dose, dose titration, patient monitoring plan)
4) Should this patient’s other antidiabetic medications be continued after insulin therapy is started?
DEBRIEF
Pharmacist’s Patient Care Process

- Collect
- Assess
- Plan
- Implement
- Follow-up: Monitor and Evaluate
Practical Considerations

- Is this the best insulin for this patient?
  - Is this an appropriate therapy for this patient? Is this the right therapy for this patient?
  - Potential benefits over alternatives
  - Mitigating adverse effects
  - Potential long term risks
- Will the patient be able to use this medication appropriately?
  - Drug administration technique
  - Initiating therapy and titrating the dose
  - Monitoring therapy
- Will the patient have access to this medication?
  - Cost issues
  - Formulary considerations
Barriers to Insulin Therapy

Patient

Provider

Health System
Insulin Pen vs. Vial/Syringe

- In 23 out of 24 studies patients preferred pen due to ease of use
- Patients report better perceived clinical efficacy
- Patients felt more confident in ability to maintain glycemic control

Address fear of needles and provide accurate education to minimize adverse effects

- Use the smallest needle (4mm)
- Do not inject through clothing
- Count to 10 before withdrawing needle
- Rotate sites (at least 1 cm)
Injection Education

- Inform patient of resources (e.g., tutorial videos)
- Educate and demonstrate process using demo pens and needles
- Have patient perform first injection in office
Pharmacokinetic Profile of Currently Available Insulins

- Rapid (aspart, lispro, glulisine, insulin human [inhaled])
- Short (regular U-100)
- Mixed short/intermediate (regular U-500)
- Intermediate (NPH)
- Long (detemir)
- Long (U-100 glargine)
- Ultra-long (degludec U-100 & U-200)
- Glargine U-300

Plasma Insulin Levels vs. Time (hr)

References:
- Flood TM. J Fam Pract. 2007; 56(suppl 1):S1-S12.
# Insulin Glargine U-300: Clinical Evidence

<table>
<thead>
<tr>
<th>Outcome</th>
<th>EDITION-1</th>
<th></th>
<th>EDITION-2</th>
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<th>EDITION-3</th>
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<tbody>
<tr>
<td></td>
<td>T2D, A1C 7%-10%, ≥42 units/day of glargine or NPH + mealtime insulin ± metformin</td>
<td></td>
<td>T2D, A1C 7%-10%, ≥42 units/day of glargine or NPH + OADs</td>
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<td>T2D, A1C 7%-11%, Insulin naive using OADs</td>
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<tr>
<td>Change in A1C from baseline (%)</td>
<td>-0.83</td>
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<td>Change in weight from baseline (kg)</td>
<td>+0.9</td>
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<td>+0.08*</td>
<td>+0.66</td>
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<td>Daily basal insulin dose at end of study (units)</td>
<td>103*</td>
<td>94</td>
<td>91*</td>
<td>82</td>
<td>59.4*</td>
<td>52</td>
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<tr>
<td>Confirmed or severe nocturnal hypoglycemia events (%)</td>
<td>36*</td>
<td>46</td>
<td>30.5*</td>
<td>41.6</td>
<td>18*</td>
<td>24</td>
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Bolli GB. Diabetes Obes Metab. 2015;17:386-94.

Noninferiority criteria met.
*P<0.05
# Insulin Degludec

<table>
<thead>
<tr>
<th>Clinical Trial (Duration)</th>
<th>Background Therapy</th>
<th>Comparator Arms</th>
<th>Change in A1C (%)</th>
<th>End of Trial Insulin Dose (units/kg)</th>
<th>Hypoglycemia (episodes per pt-year)</th>
<th>Confirmed or Severe Nocturnal Hypoglycemia (per pt-year)</th>
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<tbody>
<tr>
<td>Zinman (52 weeks)</td>
<td>Metformin (insulin naive)</td>
<td>I Deg U-100</td>
<td>-1.06</td>
<td>0.59</td>
<td>1.52</td>
<td>0.25*</td>
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<td></td>
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<td>0.60</td>
<td>1.85</td>
<td>0.39</td>
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<td>Garber (52 weeks)</td>
<td>Insulin ± OADs</td>
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<td>-1.1</td>
<td>0.75*</td>
<td>11.1*</td>
<td>1.4*</td>
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<td>-1.2</td>
<td>0.69</td>
<td>13.6</td>
<td>1.8</td>
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<td>Gough (26 weeks)</td>
<td>Metformin ± DPP-4 inhibitor (insulin naive)</td>
<td>I Deg U-200</td>
<td>-1.22</td>
<td>0.53*</td>
<td>1.22</td>
<td>0.18</td>
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<td></td>
<td>Glargine U-100</td>
<td>-1.42</td>
<td>0.60</td>
<td>1.42</td>
<td>0.28</td>
</tr>
</tbody>
</table>


Noninferiority criteria met.

*P<0.05.
ADA/EASD Position Statement
Starting and Adjusting Basal Insulin

Start
With 10 units/day or 0.1–0.2 units/kg/day

Adjust
10%–15% or 2–4 units once or twice weekly to reach the FPG target

For Hypo
Determine cause; consider reducing dose by the greater of 4 units or 10%–20%

ADA. Diabetes Care. 2017; 40(suppl 1):S1-S112.
Continuation of Antidiabetic Agents with Insulin

- Continued use of metformin, GLP1-RA, and SGLT2 inhibitors can mitigate weight gain and may reduce the risk of hypoglycemia.

- BIDS (Bedtime insulin daytime sulfonylurea) using NPH insulin resulted in less weight gain and lower risk of hypoglycemia when compared to intensive insulin therapy but **not** when compared to basal insulin alone.

- Thiazolidinediones (TZDs) plus insulin can result in very significant weight gain and increased risk of hypoglycemia.

- In most cases, reducing medication burden and cost should be a goal — so eliminating sulfonylureas, DPP-4 inhibitors, TZDs, and meglitinides would be appropriate.

Case Study #2
Case #2
RC is a 38-year-old male

**HPI:** Returning for a follow-up appointment for his type 1 diabetes. He currently is on a basal/bolus insulin regimen with insulin glargine U-100 (Lantus) at bedtime and insulin lispro U-100 (Humalog) with each meal.

He expresses frustration with managing his diabetes. RC travels frequently for work and complains of running out of pens during business trips. He eats out frequently and occasionally forgets to take his Humalog before meals. He often ends up testing his blood glucose and bolusing after meals.
Case #2

Past Medical History:
Diabetes Type 1 x 17 years
Hypercholesterolemia
Vitamin D deficiency
Microalbuminuria
Case #2

**Medications:**

- Insulin glargine U-100 (Lantus) 40 units SC QHS
- Insulin lispro U-100 (Humalog) 15 units with each meal plus CF 50:1 (target glucose 100 mg/dL) – he uses ~55-60 units per day
- Vitamin D 1,000 units PO daily
- Lisinopril 20mg PO daily
- Rosuvastatin 20mg PO daily
Case #2

Social & Family Hx:

- Resides with wife; 2 children
- Works in sales for a large corporation
- Tries to engage in aerobic exercise 2-3 x /week; erratic times
- Travels a lot and eats out frequently; erratic times
- Weight stable for the past year but wants to lose weight
- Does not smoke tobacco or use illicit drugs
- Drinks alcohol most nights (wine with evening meal)
Case #2

Glucose Control History:

- A1C 7.9%
- SMBG before meals and at bedtime (often forgets to check before meal and will test after)
  - Overall average = 184 mg/dL
  - Fasting average = 135 mg/dL (range 72-153)
  - Pre-lunch average = 144 mg/dL (range 56-155)
  - Pre-dinner average = 141 mg/dL (range 44-201)
  - Bedtime average = 196 mg/dL (range 56-257)
- Hypoglycemia occurring 2-3 times per week; most occur in the afternoons/evening a few hours after lunch or dinner and also overnight
- Symptoms of hypoglycemia typically don’t present until glucose level is < 60 mg/dL
Case #2

Vital Signs:
BP = 126/74  Pulse = 70, regular
Weight = 184 lbs  Height = 5’ 10”
BMI = 26.4  Temp = 98.1

Labs (drawn this morning - fasting):
Glucose = 114  A1c = 7.9%
BUN = 19  SCr = 1.1  eGFR = > 60
Na = 132  K = 4.6
Tchol = 107  LDL = 55  HDL = 39  Trig = 64
Case #2 - Questions

1) What options are available that could address his frustrations about running out of insulin on business trips?
2) What risk factors predispose RC to hypoglycemia and what strategies could minimize insulin-induced hypoglycemia?
3) What medication changes could you recommend to RC to lower his risk of hypoglycemia?
4) What key education points should a pharmacist make to patients on insulin?
5) What is your monitoring plan? How would you determine if your recommendations (above) were beneficial and not harmful?
DEBRIEF
## Basal Insulin Pens: Practical Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Units per pen</th>
<th>Max units per injection</th>
<th>Cost per unit</th>
<th>Storage at room temp</th>
<th># of days a pen lasts if taking 40 units/day</th>
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<tbody>
<tr>
<td>NPH</td>
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<td>60</td>
<td>.30</td>
<td>14</td>
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<tr>
<td>Detemir (Levemir)</td>
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<td>.27</td>
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<tr>
<td>Glargine U-100 (Lantus)</td>
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<td>80</td>
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<td>Glargine U-300 (Toujeo)</td>
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<td>Degludec U-100 (Tresiba)</td>
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<td>56</td>
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<tr>
<td>Degludec U-200 (Tresiba)</td>
<td>600</td>
<td>160</td>
<td>.30</td>
<td>56</td>
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</table>
### Meal-time Insulin Pens: Practical Comparisons

<table>
<thead>
<tr>
<th></th>
<th>Units per pen</th>
<th>Max units per injection</th>
<th>Cost per unit</th>
<th>Storage at room temp</th>
<th># of days a pen lasts if taking 60 units/day</th>
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</thead>
<tbody>
<tr>
<td>Regular</td>
<td>--</td>
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<td>--</td>
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<td>Aspart (Novolog)</td>
<td>300</td>
<td>80</td>
<td>.33</td>
<td>28</td>
<td>5</td>
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<tr>
<td>Lispro U-100 (Humalog)</td>
<td>300</td>
<td>60</td>
<td>.33</td>
<td>28</td>
<td>5</td>
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<tr>
<td>Lispro U-200 (Humalog)</td>
<td>600</td>
<td>60</td>
<td>.33</td>
<td>28</td>
<td>10</td>
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<tr>
<td>Glulisine (Apidra)</td>
<td>300</td>
<td>80</td>
<td>.33</td>
<td>28</td>
<td>5</td>
</tr>
</tbody>
</table>
Hypoglycemia

- Plasma glucose concentration < 70 mg/dL
- Threshold for symptoms varies
- More common in type 1 diabetes
- Hypoglycemia unawareness = reduced symptoms during hypoglycemia
  - Inducible
  - Reversible
- Risks
  - Increased risk of CV events and mortality
  - Increased risk of falls in the elderly
  - Increased risk of accidental injury (e.g., driving accidents)
  - Increased risk of hospitalization
Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

Insulin Glargine U-100 vs U-300: Hypoglycemia
Meta-Analysis of EDITION Studies in T2D

Any Time of Day, 24 h
Annual Rate Ratio U300/U100,
15.22/17.73=0.86\(^b\)
(95% CI, 0.77–0.97)

Nocturnal, 00:00-05:59 h
Annual Rate Ratio U300/U100,
2.10/3.06=0.69\(^a\)
(95% CI, 0.57–0.84)

A1c, %

- Glargine U100, +0.79 kg
- Glargine U300, +0.51 kg
- LSM Difference, -0.28 kg\(^b\)

Weight gain

N=1247 patients treated with glargine U300 and 1249 treated with glargine U100 in 3 phase 3 EDITION studies.
Insulin Glargine U-100 vs U-300: Hypoglycemia

*EDITION-4 Study: T1D*

Insulin Glargine U-100 vs Insulin Degludec: Hypoglycemia

Pooled Data of Phase 3 studies in T2D

**Overall Confirmed Hypoglycemia Risk**
- Pooled basal only in T2DM: 0.83 [0.70–0.98]
- Pooled basal and basal-bolus in T2DM: 0.83 [0.74–0.94]

**Nocturnal Hypoglycemia Risk**
- Pooled basal only in T2DM: 0.64 [0.48–0.86]
- Pooled basal and basal-bolus in T2DM: 0.68 [0.57–0.82]

Pooled hypoglycemia data from 5 phase 3a trials in T2DM: 3 trials of basal degludec U100 vs glargine U100, 1 trial of basal degludec U200 vs glargine U100, 1 trial of basal-bolus degludec U100 vs glargine U100.
Insulin Glargine U-100 vs Insulin Degludec: Hypoglycemia

*SWITCH-1 Trial: T1D*

Strategies to Avoid Hypoglycemia

**Type 1 Diabetes**
- Drug selection
  - Ideal PK/PD of insulin products
- Drug dosing/administration
  - Timing of injections
  - Flexible dosing regimens
- Technology
  - Subcutaneous continuous insulin infusion (CSII)
  - Continuous glucose monitoring (CGM)
- Patient Education

**Type 2 Diabetes**
- Drug selection
  - Avoid high risk medications
- Drug dosing and administration
- Patient Education
Strategies to Avoid Hypoglycemia
Prevention: Timing is Everything

- **Basal Insulin**
  - Avoid “overbasalizing”
  - NPH: at bedtime instead of with dinner

- **Bolus Insulin**
  - Timing in relation to meals
  - Avoid “stacking”
  - Sick day management

- Consider timing of exercise/physical activity in relation to insulin doses

- **Sulfonylureas**
  - Avoid skipping or delaying lunch

- Tell family members and co-workers; medical alert bracelets
Detection

- Shaky
- Sweaty
- Dizzy
- Confusion and difficulty speaking
- Hungry
- Weak or tired
- Headache
- Nervous or upset
Treatment

- The 15/15 Rule
  1. Check your blood glucose. If <70 mg/dL, eat or drink 15 grams of quick-acting carbs.
  2. Wait 15 minutes.
  3. Re-check your blood glucose.
  4. If < 70 mg/dL – repeat carb and recheck in 15 minutes.
  5. If > 70 mg/dL – consume or snack or meal within 60 minutes.

- Glucagon
Case Study #3
5 minute table discussion:

List reasons why patients might switch from one insulin to another.
Case #3
JD is a 55-year-old female

- HPI: Returning for a follow-up appointment for her type 2 diabetes. JD has Type 2 diabetes. She is currently on metformin 1000mg BID, canagliflozin (Invokana) 300mg daily, and insulin glargine (Lantus) 48 units at bedtime.

- She has been fairly well controlled for years; her most recent A1C was 7.4%. She checks her blood sugar 3 times per week in the morning and has an average fasting glucose over last 30 days is 135 mg/dL.

- She has 1-2 episodes of hypoglycemia per month.

- She is adherent to all medications.
Case #3

- 3 weeks ago, JD went to her pharmacy and was told that her insurance no longer covers her insulin glargine (Lantus).

- She was sent home with a 3 month supply of insulin detemir (Levemir) with no instruction given on how to use the pens or potential dosage changes.

- Over the next few weeks, she used her usual regimen and noticed her fasting glucose numbers increase. She is frustrated and wants to go back to using insulin glargine (Lantus).
Case #3 - Questions

1) How could you improve this patient’s transition to insulin detemir (Levemir)?
   - How would you educate the patient on using insulin detemir (Levemir)?
   - What glucose changes might you predict?
   - What dose changes might be needed?
   - What monitoring would you recommend?

2) How would your recommendation change if the patient had to switch from insulin glargine U-100 (Lantus) to:
   - Insulin degludec (Tresiba)
   - Insulin glargine U-300 (Toujeo)
   - Insulin glargine U-100 (Basaglar)

3) How might non-medical switching impact patients with type 1 diabetes versus those with type 2 diabetes?
DEBRIEF
Why Switch Insulin Products?

### Medical Switching
- Regimen Complexity
- Adherence
- Hypoglycemia
- Glycemic control
- Weight
- Dose Limitations

### Non-Medical Switching
- Formulary restrictions
- Cost
- Care transitions

**Non-medical switching**: The practice in which insurers force patients to switch from their current medication to a different medication for reasons other than the patient’s health and safety.

**Non-medical switching**: A meta-analysis found that NMS was more often associated with increased medical costs and worse medication-taking behaviors, particularly in well-controlled patients.

---

Gla-100*
- Start at same dose (higher doses may be needed for patients on twice-daily dosing)
- Administer IDet once-daily with evening meal/at bedtime or twice-daily, with one dose in the morning and the other with evening meal/at bedtime/12 hours after the morning dose
- Closely monitor glycemia during switch to allow for prompt re- titration, if needed

IDet
- Start at same dose (dose may be 11–12% lower than Gla-100 discontinued dose)
- Closely monitor glycemia until steady state is reached (3–5 days)

Gla-100*
- Start at same dose (dose may be 10–18% higher than Gla-100 discontinued dose)
- Titrate no more than every 3–4 days
- Closely monitor glycemia until steady state is reached

Gla-300
- A dose change may be needed (lower doses may be needed for patients on twice-daily dosing)
- Closely monitor glycemia during switch to prevent hypoglycemia

IDeg
- Start at same dose (dose may be 20% lower than IDet discontinued dose)
- Titrate no more than every 3–4 days
- Closely monitor glycemia until steady state is reached

Gla-300
- A dose change may be needed

Gla-100*
- Start at same dose
- Titrate no more than every 3–4 days
- Closely monitor glycemia until steady state is reached

Gla-100*
- Start with 80% of Gla-300 discontinued dose

*Recommendations for switching from and to Basaglar, a follow-on of Gla-100, are the same as those for switching from and to Gla-100. The recommendations depicted in this figure are based on the guidance available in the literature and prescribing information.
Switching Insulin Products: Practical Recommendations

- Patient education on new pen device
- Clear patient instructions on new regimen – avoid medication administration errors
- Expect changes in glycemic control
- Consider potential empiric dose adjustments
- Expect the need for dose re-titration
- Increase monitoring
- Plan for sooner follow-up
Case Study #4
Case #4

JB is a 63 year old African American male

HPI: Returning for a follow-up appointment after insulin dose adjustments. Instructed to increase insulin degludec U-200 dose from 80 units twice daily and insulin aspart dose to 44 units prior to each meal (4 weeks ago). Despite the dose increases his SMBG readings are consistently > 150mg/dL and occasionally > 250mg/dL.
Case #4

Past Medical History:
Diabetes Type 2 x 4 years
Hypertension x 7 years
Dyslipidemia x 7 years
Case #4

**Medications:**
- Metformin 1000mg PO twice daily
- Insulin degludec 80 units Sub-Q BID
- Insulin aspart 44 units Sub-AQ TID AC
- Lisinopril 40mg PO daily
- Amlodipine 10mg PO daily
- Rosuvastatin 20mg PO daily
Case #4

Social & Family Hx:

- Resides with wife; 2 grown children; 3 grandkids
- Works as a business man / executive
- Tries to engage in aerobic exercise 2-3 x /week; erratic times
- Weight stable for the past year but wants to loose weight
- Does not smoke tobacco or use illicit drugs
- Drinks alcohol most nights (wine with evening meal)
- Father died from renal failure; mother died from CVD
Case #4

Glucose Control History:

- A1C 8.7% (1 month ago)
- SMBG over the past month — performs most days before breakfast and occasionally before dinner
  - 30-day average = 191 mg/dL
  - Pre-breakfast range 139-247 mg/dL
  - Pre-dinner readings range 184 – 319 mg/dL
- He reports that his home glucose readings improved slightly after increasing insulin dose
Case #4

Vital Signs:
BP = 128/66  Pulse = 80, regular
Weight = 244 lbs  Height = 5’ 11”
BMI = 32.5  Temp = 98.4

Labs (drawn this morning - fasting):
Glucose = 158
BUN = 20  SCr = 1.7  eGFR = 65
Na = 133  K = 4.9
Tchol = 146  LDL = 63  HDL = 48  Trig = 174
Case #4 - Questions

1) What medication changes would you recommend to JB?
   a) Should an insulin sensitizing agent be added to his regimen?
   b) Should a GLP-1 receptor agonist or SGLT2 inhibitor be added to his regimen?
   c) Should metformin be continued?
   d) If you were to recommend u500 regular insulin, what dose, dosing frequency, and delivery system would you recommend?
DEBRIEF
GLP-1 RAs + Basal Insulin vs Basal-Bolus Insulin

*Meta-analysis*

### ΔA1c

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamant et al (2014)</td>
<td>-0.03 (-0.17 to 0.11)</td>
<td>32.25</td>
</tr>
<tr>
<td>Rosenstock et al (2014)</td>
<td>-0.16 (-0.33 to 0.01)</td>
<td>22.50</td>
</tr>
<tr>
<td>Shao et al (2014)</td>
<td>-0.11 (-0.23 to 0.01)</td>
<td>45.25</td>
</tr>
<tr>
<td>Overall (I²=0.0%, P=0.47)</td>
<td>-0.10 (-0.17 to -0.02)</td>
<td>100.00</td>
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</tbody>
</table>

### Hypoglycemia Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Risk (95% CI)</th>
<th>Weight, %</th>
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<tbody>
<tr>
<td>Diamant et al (2014)</td>
<td>0.70 (0.55 to 0.90)</td>
<td>50.42</td>
</tr>
<tr>
<td>Rosenstock et al (2014)</td>
<td>0.65 (0.50 to 0.83)</td>
<td>49.21</td>
</tr>
<tr>
<td>Shao et al (2014)</td>
<td>0.14 (0.01 to 2.65)</td>
<td>0.37</td>
</tr>
<tr>
<td>Overall (I²=0.0%, P=0.52)</td>
<td>0.67 (0.56 to 0.80)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

### ΔBody Weight

<table>
<thead>
<tr>
<th>Study</th>
<th>Weighted Mean Difference (95% CI)</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diamant et al (2014)</td>
<td>-4.60 (-5.33 to -3.87)</td>
<td>33.66</td>
</tr>
<tr>
<td>Rosenstock et al (2014)</td>
<td>-1.50 (-2.06 to -0.94)</td>
<td>33.81</td>
</tr>
<tr>
<td>Overall (I²=98.7%, P&lt;0.0001)</td>
<td>-5.66 (-9.80 to -1.51)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Favors GLP-1 RA + Basal Insulin

Favors Basal-Bolus Insulin

3 studies were eligible and included in the analysis.

When Even More Insulin is Needed ...

- U-500 Regular Human Insulin
- Useful when single dose of insulin exceed 100 units or when total daily insulin requirements > 200 units
- Smaller volume allows for larger doses
- Onset similar to regular insulin (30-60 minutes) but duration similar to NPH insulin (8-12 hours)
- Typically given 2 or 3 times daily
- Total daily insulin requirements may be lower
- Now available in a 3mL disposable pen – significantly reduces the risk of dosing errors

Church T, Haines ST. Clinical Diabetes 2016; 34 (2): 97-104
U-500 Regular Insulin

- Discontinue scheduled doses of all other insulin products; correction doses using a rapid-acting insulin may be appropriate.

- Initial dose should be based on A1c and total daily dose (TDD) of insulin:
  - If A1c < 8%, reduced TDD by 10-20%
  - If A1c 8-9%, use TDD
  - If A1c > 9%, increase TDD by 10-20%

- Number of injections based on TDD
  - 200-299 units – twice daily (60%/40%)
  - 300-600 units – three times daily (40%/30%/30%)
  - > 600 units – four times daily (30%/30%/30%/10%)

Church T, Haines ST. Clinical Diabetes 2016; 34 (2): 97-104
Conclusions - Summary

- Many issues need to be carefully considered when using insulin therapy
  - Patient reluctance and clinical inertia
  - Initial treatment dose and delivery system
  - Timely titration of insulin doses
  - Safely switching between insulin products
  - Continuation of previously prescribed antidiabetic agents
  - Risk of hypoglycemia and weight gain
- Several new products make insulin delivery more convenient and may mitigate the risk of hypoglycemia and weight gain
SELF-ASSESSMENT QUESTION 1

When compared to insulin glargine U-100, insulin degludec U-200 is ...
A. less likely to cause nocturnal hypoglycemia in patients with type 2 diabetes
B. more likely to achieve an A1c < 7% in patients type 2 diabetes
C. more likely to achieve an A1c < 7% and a fasting BG < 100mg/dL in patients with type 1 diabetes
D. less likely to cause nocturnal hypoglycemia and weight gain in patients with type 1 diabetes
Which of the following options accurately lists medications from **MOST** to **LEAST** likely to cause hypoglycemia?

A. Insulin aspart, Insulin glargine, Regular human insulin 70/30
B. Regular human insulin 70/30, metformin, insulin glargine
C. Insulin glargine, glyburide, insulin aspart
D. Regular human insulin 70/30, glyburide, insulin glargine
Mr. B is a 55 year old man with type 2 DM who is currently taking regular human insulin U-100 40 units prior to each meal and insulin glargine U-100 80 units every 12 hours. His FBG = 174mg/dl and most recent A1c = 8.6%. Which of the following is the most appropriate medication change in this case?

A. Add pioglitazone 30mg daily
B. Increase insulin glargine U-100 dose to 100 units every 12 hours
C. Increase regular insulin U-100 dose to 50 units prior to each meal
D. Switch both insulins to regular human insulin U-500 170 units QAM and 110 units QPM
A patient with well-controlled type 2 diabetes has to switch from insulin glargine U-100 (Lantus) to insulin detemir U-100 (Levemir) because his insurance no longer covers insulin glargine. Which of the following statements is true about this scenario?

A. The patient should be instructed to reduce the dose by 20% and return for follow-up in 2 weeks.

B. This insulin switch is categorized as a “non-medical switch” because it is for reasons other than the patient’s health and safety.

C. The patient should be instructed to continue taking the same dose he was previously taking and return for follow-up in 3 months.

D. Studies have shown that this type of insulin switch does not negatively impact adherence or medication-taking behaviors in well-controlled patients.
SELF-ASSESSMENT QUESTION 5

A patient with well-controlled type 2 diabetes (A1c = 6.6%) is currently taking regular insulin u-100 6 units prior to each meal and insulin glargine u-100 74 units at bedtime. The patient states she has had several episodes of hypoglycemia over the past 3 weeks. The patient states that if she does not “eat enough or on time, I’ll go low.” Which of the following is the most appropriate action to take at this time?

A. Decrease regular insulin dose to 4 units
B. Switch regular insulin to a rapid-acting insulin product
C. Decrease insulin glargine dose to 60 units
D. Reaffirm the need to eat at least 60 grams of carbohydrates every regular 4-5 hours throughout the day
Questions