Before and After

One of the first patients to ever receive insulin therapy
Key Messages – Insulin Therapy

• Insulin is a highly effective diabetes treatment
• Individualize treatment goals and regimens
  – Consider pathophysiology, self-care abilities, and safety
• Use pattern assessment to adjust dosing and advance therapy
• To treat Type 2 Diabetes, consider the advancement sequence recommended by nationally-recognized guidelines from basal alone to basal-bolus insulin therapy
• Recognize and address patient, provider, and practice-level barriers to insulin therapy
• Some treatment services should be provided in the practice, others obtained by consultation
Maxwell: Introduction

• 54 yo man with 11 years of T2DM. His physician just retired and he is now coming to you for ongoing medical care

• Significant past history, in addition to the diabetes, includes:
  – Hypertension: mild, well treated with an ACE-inhibitor
  – Dyslipidemia: Treated with a Statin per guidelines
  – Erectile dysfunction: Rx with PDE inhibitor
  – Background diabetic retinopathy: being monitored
  – Mild peripheral neuropathy: Regular podiatric care
Maxwell: Diabetes Treatment History

- Lifestyle Rx X 1 year
- Metformin started in year 2, continues now
- Glyburide, added in year 5, changed to glimepiride in year 6 due to hypoglycemia. Continues now
- Pioglitazone added in year 8
- SGLT2 inhibitor added 10 months ago

- With each of these changes, Maxwell achieved short-term A1C improvement, dropping into the mid 7’s, but before long it rose back up into the 8’s
Maxwell: Further Information

• Strong family history of diabetes and CV disease
• Work: Manager, large outlet of a chain of pet stores
• Concerns about finances as he has 3 children in or approaching college
• Variable activity at work, works day or evening shifts.
• No regular exercise program
• Has had multiple sessions with dietitian and feels he has optimized his nutritional program
• Does not smoke and drinks minimally on weekends
• Would like to avoid insulin – particularly if he has to give injections during work
Maxwell

• Current antidiabetes medications:
  – Metformin ER 500 mg tablets, 4 daily
  – Pioglitazone 45 mg QD
  – Glimepiride 4 mg daily
  – An SGLT-2 inhibitor

• Physical Examination
  – 6’1", 238 lbs (108 kg), BMI = 31.5
  – BP = 132/88
  – Physical examination: slightly reduced pedal pulses, and lower extremity vibratory and pin sensation, Fundi: scattered microaneurysms

• A1C: 8.7%
ARS: What is the key point about the data that you will use to determine what to do with Maxwell’s diabetes treatment?

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Post-Breakfast</th>
<th>Lunch</th>
<th>Post-Lunch</th>
<th>Supper</th>
<th>Post-Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunday</td>
<td>179</td>
<td></td>
<td></td>
<td>169</td>
<td></td>
<td></td>
<td>251</td>
</tr>
<tr>
<td>Monday</td>
<td>211</td>
<td></td>
<td></td>
<td>251</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>230</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td></td>
<td></td>
<td>159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>195</td>
<td></td>
<td></td>
<td>229</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td>202</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td>221</td>
<td></td>
<td></td>
<td>148</td>
<td></td>
<td></td>
<td>282</td>
</tr>
</tbody>
</table>

A. Insufficient data to make a proper interpretation
B. Sugars generally high
C. Fasting glucose levels are elevated
D. He likely has postprandial hyperglycemia, although we have no data
E. There could be hypoglycemia at times that are not recognized

Metformin ER 500 mg tablets, 4 daily; Glimepiride 4 mg/d; SGLT2 inhibitor
Pioglitazone 45 mg QD  A1C: 8.7%
ARS: What one of these options would be the best recommendation at this time?

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Post-Breakfast</th>
<th>Lunch</th>
<th>Post-Lunch</th>
<th>Supper</th>
<th>Post-Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunday</td>
<td>179</td>
<td></td>
<td></td>
<td>169</td>
<td></td>
<td></td>
<td>251</td>
</tr>
<tr>
<td>Monday</td>
<td>211</td>
<td></td>
<td></td>
<td>251</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>230</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td></td>
<td></td>
<td>159</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>195</td>
<td></td>
<td></td>
<td>229</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td>202</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td>221</td>
<td></td>
<td></td>
<td>148</td>
<td></td>
<td></td>
<td>282</td>
</tr>
</tbody>
</table>

A. More sessions with the dietitian
B. Have him monitor at varied times, then return to reassess the patterns
C. Start on basal insulin, initially 12 units at bedtime, and titrated upward
D. Start on Premix insulin twice daily
E. Add a GLP-1 Receptor Agonist

Metformin ER 500 mg tablets, 4 daily; Glimepiride 4 mg/d; SGLT2 inhibitor Pioglitazone 45 mg QD A1C: 8.7%
Aggressive Control of Diabetes: Goals of Treatment

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>80–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>2-hour postprandial glucose</td>
<td>&lt; 180</td>
<td>&lt; 140</td>
</tr>
</tbody>
</table>

A1C is “gold standard” measure of diabetes control over previous 2–3 months

Individualizing A1C Targets for People with T2DM

ADA, EASD Position Statement. *Diabetes Care* 2015;38;1364-1379
Maxwell Started basal insulin, initially 12 units at bedtime, and titrated upward

When should you consider insulin in a person with Type 2 Diabetes?

- When a combination of non-insulin antidiabetes medications are unable to achieve A1C target
- A1C > 8.5% with two-drug therapy should receive insulin vs adding a third agent
- High fasting or postprandial glycemia
- Unacceptable side effects of other medications
- Advanced hepatic or renal disease
- Special considerations (steroids, infection, pregnancy)
- Hyperglycemia in a hospitalized patient
- “Severely” uncontrolled diabetes*

* Random Glucose > 300 mg/dL, A1C > 10%, Ketonuria, Symptomatic polyuria/polydipsia, weight loss

Maxwell Started basal insulin, initially 12 units at bedtime, and titrated upward

In Maxwell’s case...

- When a combination of non-insulin antidiabetes medications are unable to achieve A1C target
- A1C > 8.5% with two-drug therapy should receive insulin vs adding a third agent (already on 4)
- High fasting or postprandial glycemia
- Unacceptable side effects of other medications
- Advanced hepatic or renal disease
- Special considerations (steroids, infection, pregnancy)
- Hyperglycemia in a hospitalized patient
- “Severely” uncontrolled diabetes*

* Random Glucose > 300 mg/ dL, A1C > 10%, Ketonuria, Symptomatic polyuria/ polydipsia, weight loss

Pharmacokinetics Profiles of Current Insulins

PK = pharmacokinetic; NPH = neutral protamine Hagedorn.

Initiation and Titration of Basal Insulin

Bedtime or morning long-acting insulin
OR
Bedtime intermediate-acting insulin
Daily dose: 10 U or 0.1-0.2 U/kg

Check FPG daily

Adjust dose 10-15\% or 2-4 U once-twice weekly to reach FPG target 80-130 mg/dL

In the event of hypoglycemia or FPG level <80 mg/dL, reduce insulin dose by 4 U or 10-20\%

Continue regimen and check A1C every 3 months

At least 70% of subjects in each group achieved A1C ≤ 7%

*P<.001

Glargine vs NPH in Treat-To-Target
No Difference in A1C but Reduced Hypoglycemia with Glargine

756 Patients with Type 2 Diabetes on 1 or 2 Oral Agents

Glycemic Control Over Time

Hypoglycemia

PG = plasma glucose

Adapted from Riddle et al. Diabetes Care. 2003;26:3080-86.
Pharmacodynamic Profiles of Basal Insulin Analogs Glargine U-100 & Detemir U-100

T1D = type 1 diabetes; T2D = type 2 diabetes.

Pharmacodynamics of Glargine U-300 versus U-100

- The U-300 glargine has a flatter more prolonged effect
- The time it takes for 50% of the effect of a single injection
  - U-100 = 12.1 hours
  - U-300 = 16.7 hours

GIR = glucose infusion rate.

U300 Glargine vs U100 Glargine in T2DM:
Meta-Analysis of Phase III Trials: Edition 1, 2, & 3

<table>
<thead>
<tr>
<th></th>
<th>Baseline to Month 6</th>
<th>RRR</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Glar U300 (N=1247)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glar U100 (N=1249)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C (%), LS mean</td>
<td>-1.02</td>
<td>~</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (kg), LS mean</td>
<td>0.51</td>
<td>35%</td>
<td>0.039</td>
</tr>
<tr>
<td>Any hypo in 24 hr*</td>
<td>67.8</td>
<td>8%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>BG ≤70 mg/dL or severe hypo*</td>
<td>15.22</td>
<td>14%</td>
<td>0.0116</td>
</tr>
<tr>
<td>Nocturnal BG ≤70 mg/dL or severe hypo*</td>
<td>2.10</td>
<td>31%</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

The number of people needed to treat with Glargine U-300 to prevent 1 BG ≤70 mg/dL or severe hypoglycemic event is 16

*Events per participant-year, people ≥1 event.
LS = least squares; RR = relative risk; BG = blood glucose; CI = confidence interval.

U-300 Insulin Glargine Dosing

• Only available in pens
  – 300 U/mL, 1.5 mL; max dose per shot of 80 units

• Insulin-Naïve Patients – Initial dosing
  – Type 1 Diabetes: Calculate total daily dose (TDD) based on 0.2–0.4 U/kg/day. Give 1/3 to 1/2 of the TDD as basal; give the remainder as a short-acting insulin divided between each meal
  – Type 2 Diabetes: Start with 0.2 U/kg/day as basal insulin once daily

• Type 1 or Type 2 Diabetes – changing from an older basal
  – Once-daily long- or intermediate-acting insulin (NPH once daily):
    • Initial dose can be the same as the once-daily long-acting dose
      – If controlled on U100 insulin glargine, a higher daily dose of U300 glargine may be needed to maintain the same level of glycemic control
  – Twice-daily NPH insulin:
    • Initial dose is 80% of the total daily NPH dosage

Pharmacodynamics of Degludec

Heise et al. Diabetes Obes Metab 2012;14:944–50

► desB30 insulin acylated (16-c fatty acid chain) at LysB29
► Half-life is ~25.4 hours, duration > 42 h
Degludec vs U100 Glargine in T2DM

Equal Efficacy, Less Nocturnal Hypoglycemia, and Less Overall Documented Hypoglycemia with Degludec

Degludec Alternating Times Achieved Comparable A1C Efficacy and Numerically Lower FPG vs Insulin Glargine U-100\(^1,2\)

### A1C (%)

<table>
<thead>
<tr>
<th></th>
<th>Degludec U-100 Alternating</th>
<th>Degludec U-100 Fixed</th>
<th>Glargine, Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C Reduction</td>
<td>-1.17</td>
<td>-1.03</td>
<td>-1.21</td>
</tr>
<tr>
<td>End of Trial</td>
<td>7.2%</td>
<td>7.3%</td>
<td>7.1%</td>
</tr>
</tbody>
</table>

### FBG (mg/dl)

<table>
<thead>
<tr>
<th></th>
<th>Degludec U-100 Alternating</th>
<th>Degludec U-100 Fixed</th>
<th>Glargine, Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBS Reduction</td>
<td>-55.0</td>
<td>-54.2</td>
<td>-47.5</td>
</tr>
<tr>
<td>End of Trial</td>
<td>105</td>
<td>105</td>
<td>112</td>
</tr>
</tbody>
</table>

Insulin Degludec met the prespecified non-inferiority margin of 0.4%

Baseline A1C: Degludec Alternating Times 8.5%; Degludec Fixed 8.4%; insulin glargine U-100 8.4%.
Baseline FPG: Degludec Alternating Times 162 mg/dL; Degludec Fixed 158 mg/dL; insulin glargine U-100 163 mg/dL.
Mean±SEM used for the full analysis set; Last observation carried forward was used for each postbaseline time point. Comparison estimates adjusted for multiple covariates.

Insulin Degludec

- Only available in pens
  - 100 U/mL (3.0 mL), max dose per injection 80 units
  - 200 U/mL (3.0 mL), max dose per injection 160 units

- Degludec U-100 pen is lime green and blue while the U-200 is green and blue with the concentration highlighted in blue

- Dosing
  - Insulin-naïve patients, start with 10 U daily
  - When converting, can start with the same unit dose as the total daily long- or intermediate-acting insulin unit dose, or consider ↓ dose by 10-20%
  - Recommended days between dose increases is 3 to 4 days

Variability of Effect

Variability in effects of an insulin can cause unexplainable variations in glucose control from day to day

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Within Subject Variability (CV% of AUC GIR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>68</td>
</tr>
<tr>
<td>Glargine U-100</td>
<td>48 – 99</td>
</tr>
<tr>
<td>Detemir</td>
<td>27</td>
</tr>
<tr>
<td>Glargine U-300</td>
<td>34.8</td>
</tr>
<tr>
<td>Degludec</td>
<td>20</td>
</tr>
</tbody>
</table>

Ultra-long Basal Insulins: Place in Therapy

- Patients who need a better basal insulin
- Often this includes people with:
  - Nocturnal hypoglycemia
  - Shift work
  - Complaints of variability of fasting glucose levels
  - Adherence issues
Switching to and from Concentrated Insulins

<table>
<thead>
<tr>
<th>Current Therapy</th>
<th>Switch to U-100 Glargine</th>
<th>Switch to U-300 Glargine</th>
<th>Switch to Degludec</th>
</tr>
</thead>
<tbody>
<tr>
<td>U-100 Glargine</td>
<td>--</td>
<td>Initial switch no dose change; likely need to up-titrate</td>
<td>Consider ↓ dose by 10%</td>
</tr>
<tr>
<td>U-300 Glargine</td>
<td>Decrease dose by 20%</td>
<td>--</td>
<td>Decrease dose by 20%</td>
</tr>
<tr>
<td>Degludec</td>
<td>Initial switch no dose change; likely need to up-titrate</td>
<td>Initial switch no dose change; likely need to up-titrate</td>
<td>--</td>
</tr>
</tbody>
</table>
Maxwell – Subsequent Events

- Saw educators to work on diet and address his barriers to using insulin.
- He agreed to start once daily glargine as a basal insulin, taken at bedtime, as he agreed that it would not impact his life and concerns too greatly.
- Pioglitazone was stopped
- The other medications continued unchanged
- Systematic Monitoring plan was initiated
Maxwell: Eight Months Later

- His basal insulin dose was titrated up to 54 units daily at bedtime (0.51 U/Kg)
- Due to occasional hypoglycemia, he changed the Glimepiride to a DPP-4 inhibitor
  - Maxwell has started exercising more and is eating better after additional sessions with Dietician
  - He has lost 4 lbs (aprox. 2 kg)
  - Weight: 234 lbs (106 kg)
  - BMI: 30.9
  - A1C: 6.9%

Metformin ER 500 mg tablets, 4 daily; DPP-4 inhibitor; SGLT2 inhibitor; Basal Insulin: 54 units q hs; A1C: 6.9% BMI: 30.9 234 lbs (106 kg)
Maxwell: What happens when his insurance company gets involved?

Maxwell’s insurance company told him that he had to change the glargine to Basaglar follow-on biologic insulin. What would you do?

A. Acquiesce and change the Rx to Basaglar
B. Fill out a PA and fight to keep him on glargine
C. Change to Levemir and hope they cover that
D. Retire from medicine, fed up with insurance company interference

Metformin ER 500 mg tablets, 4 daily; DPP-4 inhibitor; SGLT2 inhibitor; Basal Insulin: 54 units q hs; A1C: 6.9% BMI: 30.9 234 lbs (106 kg)
What is a Biosimilar?

• A biosimilar is a “copy” of a commercially-available biopharmaceutical (reference product) that no longer is protected by patent that has:
  • Undergone rigorous analytical and clinical assessment, in comparison to its reference product, 
  and
  • Been approved by a regulatory agency according to a specific pathway for biosimilar evaluation
• A biosimilar is “highly similar” to its reference product in physicochemical characteristics, efficacy, & safety

Biosimilars (Follow-on Biologics) of Insulin

- 1st follow-on biologic of insulin glargine is entering the U.S. market in December 2016
- PK & PD within regulatory parameters

Linnebjerg et al, ADA, 2014; Heise et al, ADA, 2014

LY = Lilly;   SA = Sanofi

PK = pharmacokinetics   PD = pharmacodynamics
Follow-on Biologic (biosimilar) Insulins: Potential Place in Therapy

- Patients where cost a major concern &/or required by formulary

- Issues when working with patients
  - As a substitution for the branded product, with appropriate cautions when switching from one type of insulin to another
  - While unlikely, watch for differences in immune responses
  - Monitor glucose levels more often to assess any difference of effects
  - Different administrative device may require brief education
Maxwell: Another issue

- Maxwell makes the change to Basaglar.
- However, at the same time, he indicates that even before the change, and still after it, he was having occasional hypoglycemia:
  - Late morning
  - Late afternoon
  - Nocturnal; often associated with increased activity the previous day
Key aspects of Maxwell’s patterns that help guide treatment decisions:

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Post-Brkfst</th>
<th>Lunch</th>
<th>Post-Lunch</th>
<th>Supper</th>
<th>Post-Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunday</td>
<td>85</td>
<td>168</td>
<td></td>
<td></td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monday</td>
<td></td>
<td>51</td>
<td>184</td>
<td></td>
<td></td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>95</td>
<td></td>
<td>108</td>
<td>227</td>
<td></td>
<td></td>
<td>193</td>
</tr>
<tr>
<td>Wednesday</td>
<td>187</td>
<td>207</td>
<td></td>
<td></td>
<td>193</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>75</td>
<td></td>
<td>138</td>
<td>204</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td>63</td>
<td></td>
<td>166</td>
<td></td>
<td></td>
<td></td>
<td>218</td>
</tr>
<tr>
<td>Saturday</td>
<td>121</td>
<td>75</td>
<td>192</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Fasting on target
- Post breakfast and post lunch somewhat high
- Dips before lunch
- Variable at suppertime
- Elevated after supper and bedtime

Metformin ER 500 mg tablets, 4 daily; DPP-4 inhibitor; SGLT2 inhibitor; Basal Insulin (Basaglar): 54 units q hs; A1C: 6.9% BMI: 30.9 234 lbs (106 kg)
ARS: What would you recommend at this time?

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Post-Brkfst</th>
<th>Lunch</th>
<th>Post-Lunch</th>
<th>Supper</th>
<th>Post-Supper</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunday</td>
<td>85</td>
<td>168</td>
<td></td>
<td></td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monday</td>
<td></td>
<td>51</td>
<td></td>
<td>184</td>
<td></td>
<td>184</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>95</td>
<td></td>
<td></td>
<td>108</td>
<td>227</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>187</td>
<td></td>
<td>207</td>
<td></td>
<td></td>
<td>193</td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>75</td>
<td></td>
<td></td>
<td>138</td>
<td>204</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friday</td>
<td></td>
<td>63</td>
<td></td>
<td>166</td>
<td></td>
<td>218</td>
<td></td>
</tr>
<tr>
<td>Saturday</td>
<td>121</td>
<td></td>
<td>75</td>
<td>192</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

A. Reduce the Basal insulin and change to an ultralong-basal insulin type to reduce the risk of hypoglycemia
B. Add GLP-1 RA, reduce basal insulin, and stop DPP-4i
C. Add premeal insulin at suppertime, reduce basal, Stop DPP-4i
D. Change to fixed mixture insulin BID
E. Change to full basal/bolus (bolus at all 3 meals) program

Metformin ER 500 mg tablets, 4 daily; DPP-4 inhibitor; SGLT2 inhibitor; Basal Insulin (Basaglar): 54 units q hs;  A1C: 6.9%  BMI: 30.9  234 lbs (106 kg)
When It May Be Time to Stop Titrating Basal Insulin Therapy in T2DM?

• Individual is not meeting glycemic targets on basal insulin$^{1,2}$
  – A1C still not at goal with $\approx 0.5$ U/kg/day of daily basal insulin
  – A1C not at goal despite target fasting plasma glucose (FPG) with basal insulin usually due to increased PPG

• Large glucose drops overnight or between meals (suggesting excessive amounts of basal insulin)

• Nocturnal hypoglycemia$^{1,2}$

• When further increases in basal insulin result in hypoglycemia

Approach To Starting & Adjusting Insulin in T2DM

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to Glycemic Treatment. *Diabetes Care* 2016; 39 (Suppl. 1): SX
Approach To Starting & Adjusting Insulin in T2DM

**Basal insulin**
(usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine and address cause; ↓ dose by 4 U or 10–20%.

- If not controlled after FBG target is reached (or if dose >0.5 U/kg/day), treat PPG excursions with mealtime insulin plus GLP-1-RA (trial).
- **Add 1 rapid insulin injection before largest meal**
- **Change to premixed insulin twice daily**

American Diabetes Association Standards of Medical Care in Diabetes. Approaches to Glycemic Treatment. *Diabetes Care* 2016; 39 (Suppl. 1): SX
## Exenatide BID Added to Insulin Glargine

### Outcome | PBO | EXENATIDE BID | P-Value
---|---|---|---
Δ FPG (mg/dL)<sup>a</sup> | −27 | −29 | .63
Δ Insulin dose (U/d)<sup>b</sup> | 20 | 13 | .03
Δ Weight (kg) | 1.0 | −1.8 | < .001
Hypoglycemia<sup>c</sup> (events/patient-y) | 1.2 | 1.4 | 0.49
Discontinuation due to AEs (% of patients) | 1 | 9 | < .01

---

<sup>a</sup> Baseline FPG: 149 and 142 mg/dL for PBO and EXN BID groups, respectively.

<sup>b</sup> Baseline insulin: 47.4 and 49.5 U/d for PBO and EXN BID groups, respectively.

<sup>c</sup> 1 reported event of major hypoglycemia (PBO group).

---

![Graph showing A1C Change (%)](image)

**EXN BID or PBO Added to GLAR 30-week trial (N = 259)**

Comparison of GLP-1 RA’s vs. Prandial Insulin when used with Basal Insulin

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LIRA vs. ASPART(^1)</th>
<th>EXEN BID vs. LISPRO(^2)</th>
<th>ALBIG vs. LISPRO(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\Delta) Weight, kg</td>
<td>-2.8* 0.9</td>
<td>-2.5 2.1*</td>
<td>-0.7* 0.8</td>
</tr>
<tr>
<td>Hypoglycemia(^d)</td>
<td>1.0* 8.2</td>
<td>2.1 5.0</td>
<td>0.9 2.3</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>LIRA &gt; ASP, first 2 wks</td>
<td>2.9 0</td>
<td>11 1</td>
</tr>
<tr>
<td>Basal Insulin used</td>
<td>Degludec</td>
<td>Glargine</td>
<td>Glargine</td>
</tr>
<tr>
<td>Duration / n</td>
<td>26 weeks / 177</td>
<td>30 weeks / 637</td>
<td>26 weeks / 566</td>
</tr>
</tbody>
</table>

\(^a\) Added to DEG (26 wk; N = 177)
\(^b\) Added to GLAR (30 wk; N = 637).
\(^c\) Added to GLAR (26 wk; N = 566).
\(^d\) Rates of severe hypoglycemia were low across groups

\(P < .05\)

4. Eli Lilly and Co. Trulicity (dulaglutide) prescribing information.
5. US FDA. Drugs@FDA.
   http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
Combination Basal Insulin – GLP-1 RA Fixed Ratio Formulations

- DEG-LIRA\(^1,a,b\)
- DEG\(^1,b\)
- LIRA\(^1,b\)
- GLAR-LIXI\(^2,a,c\)
- GLAR\(^2,c\)

### Δ A1C, %

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ A1C, %</th>
<th>A1C &lt; 7%, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEG-LIRA(^1,a,b)</td>
<td>-1.9</td>
<td>81</td>
</tr>
<tr>
<td>DEG(^1,b)</td>
<td>-1.4</td>
<td>60(^d)</td>
</tr>
<tr>
<td>LIRA(^1,b)</td>
<td>-1.3</td>
<td>65(^d)</td>
</tr>
<tr>
<td>GLAR-LIXI(^2,a,c)</td>
<td>-1.8</td>
<td>84</td>
</tr>
<tr>
<td>GLAR(^2,c)</td>
<td>-1.6</td>
<td>80</td>
</tr>
</tbody>
</table>

### Δ BW, KG

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ BW, KG</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEG(^1,b)</td>
<td>-0.5</td>
</tr>
<tr>
<td>LIRA(^1,b)</td>
<td>-3.0(^d)</td>
</tr>
<tr>
<td>GLAR-LIXI(^2,a,c)</td>
<td>-1.0</td>
</tr>
</tbody>
</table>

- ≤ 3 severe hypoglycemic episodes per group
- Lower rate of hypoglycemia for LIRA vs DEG or DEG-LIRA (overall and nocturnal)\(^1\)
- Lower rate of hypoglycemia for GLAR-LIXI than for GLAR (overall)\(^2,e\)

Current GLP-1 RAs should not be mixed with or injected adjacent to insulin\(^3\)

DEG=Degludec; Lira=liraglutide GLAR=Glargine Lixi=Lixisenatide

2. Rosenstock et al. *Diabetologia*. 2014;57(suppl 1) [abstract 241].
3. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

\(^a\) Not US FDA approved. \(^b\) 26-week open-label, treat-to-target RCT; N = 1663 (insulin naïve). \(^c\) 24-week open-label, treat-to-target RCT; N = 323 (insulin naïve). \(^d\) \(P < .001\) vs DEG-LIRA; \(^e\) \(P < .001\) vs GLAR-LIXI.
Combination Fixed-Ratio GLP-1 RA & Basal Insulins

- Insulin glargine combined with lixisenatide (Soliqua®)
  - 3 units / 1 mcg (Max dose 60 units & 20 mcg)

- Insulin degludec combined with liraglutide (Xultophy®)
  - 1 unit / 0.036 mg (Max dose 50 units & 1.8 mg)

- Titrate based on the fasting glucose level and the impact of basal insulin primarily
iDegLira – UK Comparative Cost-Effectiveness Study

Role for Premixed Insulin

• **Advantages**
  – Easy (no mixing, single product, pens avail.)
  – Covers insulin requirements through most of day

• **Disadvantages**
  – Not physiologic
  – Less Flexible: requires consistent meal/exercise pattern, and cannot titrate individual insulins unless custom mixed insulin is used
    – ↑ Nocturnal hypoglycemia (presupper NPH)
    – ↑ Fasting hyperglycemia (presupper NPH wears off)
  – Higher A1C (realistic goal of ≤8%)

INITIATE: Basal Analog vs Premixed Analog

Change in A1C Level From Baseline to Study End

- **Insulin Glargine + OADs**
  - Baseline: 9.8%
  - Endpoint: 7.4%
  - Change: -2.4%
  - Episodes per Patient Year: 0.7
  - P < 0.01

- **Biphasic Insulin Aspart 70/30**
  - Baseline: 9.7%
  - Endpoint: 6.9%
  - Change: -2.8%
  - Episodes per Patient Year: 3.4
  - P < 0.05

Total units = 51.3 ± 26.7 with glargine plus OADs vs. 78.5 ± 39.5 with premixed insulin

OAD = Oral antihypertlycemic agent

Comparison of Insulin Degludec/Insulin Aspart and Biphasic Insulin Aspart 30 in Uncontrolled, Insulin-Treated Type 2 Diabetes

- Graphs showing changes in HbA1c over time for IDegAsp BID and BIAsp 30 BID.

- Graph showing confirmed hypoglycemia over time for IDegAsp BID and BIAsp 30 BID with a 32% lower rate with IDegAsp, p=0.0049.

Adding Bolus Insulin: “Basal-Plus”

• Consider adding prandial (mealtime) insulin in about 3–6 months if:
  – A1C is elevated
  – Significant postprandial glucose excursions occur (> 180 mg/dL)
  – There are significant drops in glucose between meals or overnight as the basal insulin dose is increased
  – Likely needed if the total daily insulin dose exceeds 0.5 Units/kg/day.

ADA, EASD Position Statement. *Diabetes Care* 2015;38;1364-1379
Adding Bolus Insulin: “Basal-Plus”

- Add prandial insulin before meal with largest glucose excursion (>180 mg/dl) or the meal with the largest CHO content. Results are usually comparable.*

- Other meals can be covered subsequently.

- Alternatively start with coverage of all three meals at once.

- TDD: 0.3 – 0.5 U/kg; 50/50 basal/prandial

- Antihyperglycemic medications:
  - Generally, stop insulin secretagogues (SU, DPP-4 inhibitors, glinides)
  - Reduce or stop TZD’s

ADA, EASD Position Statement. *Diabetes Care* 2015;38;140-149.
AACE/ACE Comprehensive Diabetes Management Algorithm, Endocr Pract. 2015;21(No. 4)

SU = Sulfonlyurea

TDD=Total daily dose
Maxwell’s considerations: Which would you do?

A. Fixed mixture: issues with reduced flexibility and hypoglycemia risk, convenient but would have to inject presupper – issue on evening-shift days

B. Basal plus premeal insulin at one meal: Improved control, reduced hypoglycemia, could give it a breakfast so no injections during work.

C. Add a GLP-1 RA: Glucose-dependent insulin secretion and weight-beneficial, side effects of GLP-1 RA’s

D. Just go directly to a full basal/bolus program: Maximum flexibility and diabetes control, but needs frequent injections with weight gain and hypoglycemia potential

Metformin ER 500 mg tablets, 4 daily; DPP-4 inhibitor; SGLT2 inhibitor; Basal Insulin (Basaglar): 54 units q hs; A1C: 6.9% BMI: 30.9 234 lbs (106 kg)
Advancing Therapy Using Basal-Plus Dosing

- Choose a target meal to initiate prandial coverage
  - Breakfast or the largest meal of the day

- Start 4–6 units of a rapid-acting insulin analog 10–15 minutes before the meal

- Adjust prandial insulin dose based on
  - 2-h PPG target <180 mg/dL
  - Next preprandial or HS BG target <130 mg/dL

- If A1C remains above target, add second prandial dose

- Usually need about 8–12 units of prandial insulin to cover meal(s)

- **Basal-bolus dosing**
  - ~50% bolus insulin and ~50% basal insulin

---

HS = at bedtime; PPG = postprandial glucose

Physiologic Insulin Regimens with basal insulin plus rapid-acting insulin dosing before each meal

- Premeal insulin dosing by algorithmic scale or, preferably, carbohydrate counting
- Checking blood glucose 4 to 6 times a day
- CHO counting or consistent CHO Intake
- Surveillance and risk for hypoglycemia
- Record keeping: “Monitoring” rather than just “checking”
- Likely recalculate doses when advancing from basal-plus, not just adding another injection
Sample Insulin Adjustment Algorithm: Premeal Rapid-Acting and Bedtime Basal Insulin

An option for determining premeal insulin doses if carbohydrate counting is not possible.

<table>
<thead>
<tr>
<th>Rapid-Acting Insulin BLOOD GLUCOSE</th>
<th>BREAKFAST</th>
<th>LUNCH</th>
<th>SUPPER</th>
<th>BED</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 70*</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>71 – 100</td>
<td>3</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>101 – 150</td>
<td>4</td>
<td>7</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>151 – 200</td>
<td>5</td>
<td>8</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>201 – 250</td>
<td>6</td>
<td>9</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>251 – 300</td>
<td>7</td>
<td>10</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>301 – 400</td>
<td>8</td>
<td>11</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>OVER 400</td>
<td>9</td>
<td>12</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Basal Insulin</td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
</tbody>
</table>

*Treat with food first, retest, then use algorithmic dose.
Carbohydrate Counting

• Two factors primarily govern premeal insulin doses:
  – Grams of carbohydrate
  – Correction doses if premeal hyperglycemia is present

• Two calculations are useful for initial dosing:
  – Carbohydrate coverage: Total daily insulin dose (TDD) divided into 500 gives the approximate number of carb grams that 1 unit of rapid acting insulin will “cover.”
  – Correction dose: Divide the TDD into 1500. Usually initially target a glucose of 120 mg/dL

• Comparable control, but less weight gain than with algorithms*

Insulin Pumps

Accu-Chek Aviva Combo

Medtronic 530G with Enlite

Animas One Touch Vibe

Omni Pod

Tandem t-slim

Patch Pumps for Type 2 Diabetes
External Insulin Pump Using Rapid Acting Insulin

- **Insulin Bolus Doses**
- **Insulin Basal**
CGM Devices

MiniMed 630G

DexCom G5
Continuous Glucose Monitoring Provides a More Comprehensive Picture of the Patterns

Fingerstick Blood Glucoses (Type 1)
CGM Software Report
FDA News Release

FDA expands indication for continuous glucose monitoring system, first to replace fingerstick testing for diabetes treatment decisions

For Immediate Release
December 20, 2016
Take-Away Messages

• Treatment goals, program design, and monitoring recommendations must be individualized

• Sequential advancement of insulin treatment designs is an important part of that individualized approach to therapy

• Basal-bolus regimens require more injections but provide better insulin coverage and glycemic control

➤ Don’t delay initiation of insulin: Self-assess office capabilities in the context of insulin treatment support
“Insulin is a remedy for the wise and not the foolish, be they patients or doctors. Everyone knows it requires brains to live long with diabetes, but to use insulin successfully requires more brains.”

- Elliott P. Joslin, MD, ScD
- *Diabetic Manual*, 1959