Lecture 1: 8:15 – 9:10 a.m.

William Polonsky, PhD, CDE, Presents:
Communicating the Good News (Not Just the Bad News) About Diabetes:
How Evidence-Based Hope Can Promote Patient Engagement
Strategies for Promoting Behavior Change in Diabetes

Percentage of Patients Achieving ADA Treatment Targets


Number of Patients Who Avoid Sharing Information with Their HCP

Levy et al, 2018

HCP Attributions Regarding Poor Adherence in Diabetes

Edelman et al, 2012

**HCP top 5 complaints:**
1. Patients say they want to change, but are not willing to make the necessary changes
2. Not honest/Only tells me what they think I want to hear
3. Don’t listen to my advice
4. Diabetes not a priority/Uninterested in their condition/"in denial"/Don’t care/Unmotivated
5. They do not take responsibility for self-management
Strategies for Promoting Behavior Change in Diabetes

Why Avoid Sharing Information?

Table 2. Percentage of Times a Reason Was Selected for Avoiding Telling the Clinician-Collapsed Across Types of Information

<table>
<thead>
<tr>
<th>Reason</th>
<th>M (95% CI)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>I didn’t want to be judged or criticized about my behavior</td>
<td>80.8 (79.8-81.9)</td>
<td>64.1 (56.3-66.7)</td>
</tr>
<tr>
<td>I didn’t want to share how I treat my health</td>
<td>75.7 (73.5-78.0)</td>
<td>53.1 (50.5-63.8)</td>
</tr>
<tr>
<td>I was embarrassed to admit that I was not doing what I should do</td>
<td>60.9 (58.9-62.9)</td>
<td>69.5 (47.8-52.1)</td>
</tr>
<tr>
<td>I didn’t want the health care provider to think that I was a different patient</td>
<td>50.6 (48.7-52.9)</td>
<td>58.1 (56.0-59.5)</td>
</tr>
<tr>
<td>I didn’t want to take up any more of the health care provider’s time</td>
<td>45.2 (42.6-47.9)</td>
<td>35.5 (33.2-38.7)</td>
</tr>
<tr>
<td>I didn’t think I needed to</td>
<td>38.6 (36.4-40.6)</td>
<td>52.9 (39.9-56.0)</td>
</tr>
<tr>
<td>I didn’t want the health care provider to think that I was neglecting</td>
<td>37.0 (35.6-38.6)</td>
<td>50.4 (38.5-52.7)</td>
</tr>
</tbody>
</table>

Levy et al, 2018

Real Life with Diabetes

1. Living with diabetes can be tough
   - It is a time-consuming job
   - It is a balancing act that requires vigilance and an ability to deal with frustration

Russell et al, 2005
Motivation in Diabetes

- No one is unmotivated to live a long and healthy life
- The real problem: Obstacles to self-care outweigh possible benefits
  - And there are a TON of obstacles!
  - The underlying theme to most obstacles is a lack of “worthwhileness”

Lack of Worthwhileness

- An invisible and non-urgent disease

“Look, I’ll start worrying about my diabetes as soon as something falls off.”

Lack of Worthwhileness

- An invisible and non-urgent disease
- Hopelessness

“What’s the difference? This disease is going to get me no matter what I do.”
Lack of Worthwhileness

- An invisible and non-urgent disease
- Hopelessness
- Discouragement

“I did everything I was supposed to, and now you’re telling me I have to take even more medications?”

Step 1. Assess

- The informal approach:
  - “What’s one thing about diabetes that’s driving you crazy?”
- The formal approach:
  - Use self-report instruments

Diabetesdistress.org

- T1-DDS & DDS in English & Spanish
- Automatically scored, with printable reports
"It was totally unexpected and surprising. I have had diabetes for 35 years. In all that time no one has ever asked me what it was like for me to have diabetes and what it was about diabetes that I found most distressing. And even if they did ask, I doubt that they would have taken the time or had the interest to listen carefully to my answer."

Don’t try to fix your patient’s difficult feelings
Instead, acknowledge and normalize
- “Given the nature of diabetes, feeling this way is perfectly reasonable and many other people feel the same.”
Strategies for Promoting Behavior Change in Diabetes

Step 2. Respond with Empathy

Hemoglobin A1c results for 891 patients, treated between 2006-2009, by levels of their HCP's empathy

Hojat et al., 2011

Step 3. Make the Invisible Visible

<table>
<thead>
<tr>
<th>Back on Track Feedback</th>
<th>Name: Molly B.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>A1C</td>
<td></td>
</tr>
<tr>
<td>Blood Pressure</td>
<td></td>
</tr>
<tr>
<td>LDL</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Your Targets</th>
<th>Last Results</th>
<th>SAFE</th>
<th>NOT SAFE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Your score should be</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.0% or less</td>
<td>8.7%</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>130/80</td>
<td>125/75</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>100 or less</td>
<td>116</td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

Be non-judgmental.

- Fear tactics may be counterproductive:
  - “Do you want to go blind, do you?”
  - “If you don’t do better, you’ll end up on insulin. Is that what you want, is it?!”
- Rather than describing numbers as “good/bad” or “high/low”, use “safe/unsafe”.

Tests

Your Targets

Last Results

SAFE: At or better than goal

NOT SAFE: Not yet at goal

Your score should be

8.7% or less

125/75

116

Blood Pressure

LDL

Strategies for Promoting Behavior Change in Diabetes
Step 3. Make the Invisible Visible

- Be non-judgmental.
- Offer congratulations when possible.

“Your A1C is still too high. Don’t you understand the consequences? Why aren’t you working harder on this?”

VS.

“Great that you took the time to get your A1C done today. The numbers haven’t moved much, which tells us that something different is needed.”

- Provide a path forward.
  - “Let’s work together to get these important numbers to a safe place for you.”

- 248 independent samples, n = 27,372
- Fear appeal: d=0.21
- Fear appeal + efficacy message d=0.43

Tannenbaum et al, 2015
Step 4. Share the Good News

Q. Diabetes is the leading cause of adult blindness, amputation, and kidney failure. True or false?

A. False. To a large extent, it is poorly controlled diabetes that is the leading cause of adult blindness, amputation and kidney failure. Well-controlled diabetes is the leading cause of... NOTHING!

Fact Check

This doesn’t mean: good care will guarantee that you will not develop complications

This does mean: with good care, odds are good you can live a long, healthy life with diabetes

T1D Complications After 30+ Years

Deckert et al, 1978
Strategies for Promoting Behavior Change in Diabetes

T1D Complications After 30+ Years

In Summary

“Historical reports of frequencies of serious complications in T1D patients are clearly outdated ... rates of complications with "intensive" treatment, or what would now be considered the standard of care, are substantially lower than in the past. This is indeed good news that should be openly shared with the newly diagnosed patient to help alleviate fears that may accompany the diagnosis.”

Nichols, 2009

Risk Factors, Mortality, and Cardiovascular Outcomes in Patients with Type 2 Diabetes

- 271,174 T2Ds, 1,355,870 matched controls
- T2Ds “who had five risk-factor variables within target ranges appeared to have little or no excess risks of death, MIs, and stroke as compared with the general population.”

Rawshani et al., 2018
We Even Put it on Mugs!

To live a long and healthy life, develop a chronic disease and take care of it.
- Sir William Osler

Diabetes and Your Health

“We live a long and healthy life, develop a chronic disease and take care of it.”

- Sir William Osler

Step 5. Address Discouragement

- Make behavioral success easier
  - Plan for actions must be doable
  - Focus on the behavior, not the outcome
  - Collaborative agreement and commitment

“So just to make sure we’re on the same page, what’s one diabetes-related action you’re aiming to do over the next few months?”
Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation

- Taking your meds is one of the most powerful things you can do to improve your health.
- There are always pro’s and con’s; the con’s are probably not as big as you think.
- More meds doesn’t mean you’re sicker, fewer meds doesn’t mean you’re healthier.

- Provide the tools needed to be successful
  - Ongoing support

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Strategies for Promoting Behavior Change in Diabetes
Step 5. Address Discouragement

- Make behavioral success easier
- Re-frame the medication conversation
- Provide the tools needed to be successful
  - Ongoing support
  - Medications
  - Devices

QOL and CGM

<table>
<thead>
<tr>
<th></th>
<th>CGM group</th>
<th>Control group</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO-5</td>
<td>71.28 ± 14.71</td>
<td>70.47 ± 16.68</td>
<td>0.16</td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>0.90 ± 0.11</td>
<td>0.89 ± 0.10</td>
<td>0.32</td>
</tr>
<tr>
<td>Diabetes distress (EQ) Total</td>
<td>1.78 ± 0.65</td>
<td>1.61 ± 0.68</td>
<td>0.08</td>
</tr>
<tr>
<td>Emotional burden</td>
<td>2.06 ± 0.87</td>
<td>2.18 ± 0.68</td>
<td>0.06</td>
</tr>
<tr>
<td>Intercurrence</td>
<td>1.84 ± 0.81</td>
<td>1.48 ± 0.64</td>
<td>0.01</td>
</tr>
<tr>
<td>Physician</td>
<td>1.19 ± 0.63</td>
<td>1.09 ± 0.62</td>
<td>0.18</td>
</tr>
<tr>
<td>Hypoglycemic confidence (HGC)</td>
<td>3.27 ± 0.57</td>
<td>3.47 ± 0.65</td>
<td>0.08</td>
</tr>
<tr>
<td>Hypoglycemic fear (worry subscale of HPS-6)</td>
<td>15.75 ± 12.30</td>
<td>13.48 ± 10.63</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Step 6. Take Care of Yourself

- HCP burnout is much too common

Rest improves performance; nature improves happiness: Assessment of break periods on the abbreviated vigilance task

Finkbeiner et al, 2010
Step 6. Take Care of Yourself

- HCP burnout is much too common

... and although dog videos do not improve performance notably, people do report feeling better.

In Summary

- Assess
- Respond with empathy
- Make the invisible visible
- Share the good news
- Address discouragement
- Take care of yourself

Thanks for Listening!

www.behavioraldiabetes.org
Lecture 2: 11:30 – 12:30 p.m.

Irl B. Hirsch, MD, Presents:
Update and Clinical Overview of the Oral Medications for Type 2 Diabetes and Their Cardiovascular Effects
If a patient is not at goal for glycemia after comprehensive lifestyle and education management:

**Summary of new ADA treatment algorithm**
(chart in your syllabus!)

**Step 1:** Start with metformin unless contraindicated.

**Step 2:** Determine if the patient has ASCVD or CKD. If yes, use a GLP1-RA or SGLT2i with proven CV and/or CKD risk reduction.

**Step 3:** If no ASCVD or CKD:
- **Main concern is weight:** use a GLP-1RA or SGLT2i; avoid sulfonylureas, pioglitazone, and insulin.
- **Main concern is hypoglycemia:** use DPP-4i, GLP-1RA, SGLT2i or TZD; avoid sulfonylureas, pioglitazone, and insulin.
- **Main concern is access:** use SU or try to engage financial assistance programs, co-pay cards, etc.

If the additional efficacy of an injected agent is needed, GLP-1RA are preferred.

**Glucose-lowering medication in T2D: Overall approach**
Glycemic targets for patients with T2D

<table>
<thead>
<tr>
<th>Treatment Goal</th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>&lt; 7</td>
<td>≤ 6.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>80-130</td>
<td>&lt;110</td>
</tr>
<tr>
<td>Preprandial glucose (mg/dL)</td>
<td>80–130</td>
<td>&lt; 110</td>
</tr>
<tr>
<td>Postprandial glucose (mg/dL)</td>
<td>&lt; 180*</td>
<td>&lt; 140**</td>
</tr>
</tbody>
</table>

* Peak PPG; ** 2 Hr PPG


Are they realistic?

Case 1: 49-year-old male with T2D for 6 yrs

- Other medical history: central obesity, dyslipidemia, HTN and CAD s/p MI
- Family Hx: positive for T2D, obesity and CAD
- Notes: very few home glucose monitoring results
- Diabetes Meds: Metformin, SFU, DPP4i, SGLT2i, and basal insulin
- Current A1C 11.4% (10.6% 1 year ago, 10.1% 2 years ago)
- Creatinine 1.4 mg/dL, eGFR 65 mL/min/1.73 m²
- LDL 112 mg/dL, Triglycerides 296 mg/dL, HDL 21 mg/dL

What is the most likely reason why this patient has not achieved his A1c goal?

- A. He needs prandial insulin
- B. Poor adherence with his medication
- C. He does not exercise regularly
- D. His diabetes regimen is too complicated
- E. He needs a GLP-1 RA
Oral Agents

Multiple defects contribute to the pathophysiology of T2D necessitating targeted therapy

- Glucose production
- Glucose secretion
- Glucagon secretion
- Insulin resistance

hyperglycemia

DeFronzo RA. Diabetes. 2009;58(4):773-795

- Metformin (first line therapy unless contraindicated)
- Sulfonylureas, meglitinides
- Glitazones (pioglitazone, rosiglitazone)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)

NEW - GLP-1 Receptor Agonist (oral semaglutide)*
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine mesylate)*
- Alpha glucosidase inhibitors (acarbose, miglitol)*

* not discussed in detail in this presentation

Nine FDA-approved classes of oral meds for T2D

http://www.fda.gov/drugs

- Always confirm as best you can if the patient is adherent with his/her medications (check refill history)
- The higher the baseline A1C, the greater the fall in A1C with any therapeutic intervention
- Adding diabetes medication instead of switching should be the rule rather than the exception
- Address the ABCs (A1C, BP (<140/90 mm/Hg) and Cholesterol (LDL<100mg/dl or <70 if CAD present))
- Spending time with the patient and his/her support persons in meaningful shared decision-making addressing their health care priorities and concerns will improve adherence

Clinical treatment pearls

- Edelman SV (TCOYDtv). 3 September 2015. Get Type 2 Diabetes and Live Longer Because of it (video) https://www.youtube.com/watch?v=x24AbWnjVa8
**Oral Agents**

**Case 2: 69-year-old centrally obese female with T2D for 9 years**
- PMH: Obesity (BMI 34 kg/m²), HTN, dyslipidemia, OSA, breast cancer s/p lumpectomy and hormonal therapy in remission
- Family History: Both parents had type 2 diabetes
- Notes:
  - Creatinine 1.1 mg/dl, eGFR 75 mL/min/m², UACR normal (<30mg/g creatinine)
  - A1C 8.5% (above 8% for the past two years)
  - Diabetes therapy is metformin and a SFU
  - LDL 121 mg/dl, triglycerides 266 mg/dl, HDL 39 mg/dl

**What class of agent would you add to this patient’s current regimen of metformin and a SFU**

- A Thiazolidinedione (pioglitazone)
- B DPP-4 inhibitor (sita-, lina-, saxa- and aloglptin)
- C SGLT-2 inhibitor (cana-, empa-, ertu- or dapagliflozin)
- D Basal insulin given once a day
- E GLP-1 RA (liraglutide, exenatide, dulaglutide, semaglutide)

**Update on metformin, SFUs and TZDs (all generic)**

**METFORMIN**
- eGFR <60 to ≥45: OK to use full dose/monitor kidneys
- eGFR <45 to ≥30: OK to use 50% maximum dose/monitor renal function every 3-6 months (PI says yearly)
- Check B12 levels

**SFUs**
- High secondary failure rate, however when you stop them the patient’s A1C typically goes up
- Increase risk of hypoglycemia (elderly, DIO, CAD)

**TZDs (PIoglitazone)**
- Risk of bladder cancer questionable, and the risk is low (~1/5000 in the general population)
- Effective in prediabetes, best used early in the natural history (balance with potential side effects)
- Be cautious in comorbids with insulin (fluid retention)
- Contraindicated in the setting of heart failure
- Fracture risk is increased
Case 3: 62-Year-Old Native American female diagnosed with T2D at age 32
- PMH: HTN, dyslipidemia, obesity, OSA and NAFLD
- FH: T2DM, early CAD
- A1C 9.5% on maximum doses of metformin and SFU
- Occasional mild hypoglycemia
- No home glucose monitoring data
- Creatinine 1.3 mg/dl, eGFR 61 mL/min/m², BMI 39 kg/m²
- BP normally above 140/90 mmHg; on no HTN meds

What therapeutic intervention would you change/initiate if you were evaluating this patient, once you have confirmed she is adherent with her medications?

<table>
<thead>
<tr>
<th>Option</th>
<th>Therapeutic Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Add pioglitazone</td>
</tr>
<tr>
<td>B</td>
<td>Add a DPP-4 inhibitor</td>
</tr>
<tr>
<td>C</td>
<td>Add a SGLT-2 inhibitor</td>
</tr>
<tr>
<td>D</td>
<td>Add a GLP1-RA</td>
</tr>
<tr>
<td>E</td>
<td>Combination of a DPP4 inhibitor and a SGLT2 inhibitor</td>
</tr>
</tbody>
</table>

Case 3: continued

Treatment History
- A DPP-4/SGLT2 inhibitor combination pill was added to her regimen (once a day and one co-pay)
- Follow up was arranged for one month instead of the usual 3 to 4 months to confirm adherence
- She did well with a 10-pound weight loss and no hypoglycemia after the SFU dose was cut in half
- The A1C fell from 9.5% to 7.4%
- SBP decreased from 150 to 141 mmHg
- After 6 months she was started an ARB/statin combination pill to get her BP below 140/90 mmHg and her LDL <100 mg/dl
- She was resistant to starting new medication, but the combo pills helped
**Option #4: DPP-4 inhibitors**

**Mechanism of Action**

- Inhibit the enzyme, DPP-4, that normally inactivates GLP-1 and other incretins within minutes.

**Benefits**

- Once daily oral administration
- Virtually no side effects
- Can be added to any diabetes drug except GLP-1 RAs
- A1c reduction ~ 0.5-1% range (depends on baseline A1c)

**Concerns**

- Dose adjustment with renal insufficiency (only for sita-, saxa- and alogliptin), not for linagliptin
- Warnings and precautions: pancreatitis, heart failure, acute renal failure, angioedema, Stevens-Johnson, severe arthralgia, bullous pemphigoid

**Clinical Pearls**

- Efficacy of the DPP-4 inhibitors is similar
- All DPP-4 inhibitors come in combination pill with metformin (Alo- is combined with Pio- and Lina- is combined with empagliflozin XR, saxa-, dapa- tablet approved)

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**Mechanism of action of DPP-4 inhibitors**

- Release of active incretins GLP-1 and GIP
- Glucose uptake by peripheral tissue
- Pancreatic polypeptide release
- Hepatic glycogen production
- Glucose-dependent insulinotropic polypeptide

**Generic and trade names**

<table>
<thead>
<tr>
<th>DPP-4 inhibitors</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>Nesina</td>
<td></td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Tradjenta</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Onglyza</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Januvia</td>
<td></td>
</tr>
</tbody>
</table>
### Oral Agents

#### Generic Name | Trade Name | Daily Dose Range (mg) | Recommended Frequency
--- | --- | --- | ---
Sitagliptin/metformin | Janumet | 50/500, 50/1000 | Twice with meals
Saxagliptin/metformin | Kombiglyze XR | 5/500, 2.5/1000, 5/1000 | Once daily with evening meal
Linagliptin/metformin | Jentadueto | 2.5/500, 2.5/850, 2.5/1000 | Twice with meals
Linagliptin/empagliflozin | Glyxambi | 5/10, 5/25 | Once daily
Dapagliflozin/saxagliptin | Qtern | 10 mg/5mg | Once daily
Alogliptin/pioglitazone | Oseni | 25/15, 25/30, 25/45, 2.5/15, 2.5/30, 2.5/45 | Once daily
Alogliptin/metformin | Kazano | 12.5/500, 12.5/1000 | Twice with meals
Ertugliflozin/sitagliptin | Steglujan | 5/100, 15, 100 | Once daily
Saxagliptin/dapagliflozin/metformin XR | Qternmet XR | 2.5/2.5/1000, 2.5/5/1000, 5/5/1000, 5/10/1000 | Once daily

#### Case 4: 70-year-old obese female with T2D for 15 years
- A1C 8.4%
- On max. doses of metformin, a SFU and a DPP4-inhibitor
- Family History: Type 2 diabetes and obesity (both parents)
- Notes:
  - Very fearful of injections and gaining weight, BMI 31 kg/m²
  - HTN, osteoporosis, and CKD (creatinine 1.4 mg/dL and eGFR 58 mL/min/m²)
  - Home glucose monitoring shows FBS (147-219 mg/dL) with a few post dinner values (188 to 275 mg/dL)

#### How would you treat patient to lower her A1c?

- **A** Add a TZD
- **B** Start a SGLT-2 inhibitor (cana-, dapa-, empa-, ertugliflozin)
- **C** Try to convince her to add a GLP-1 receptor agonist (exenatide, liraglutide, dulaglutide, semaglutide)
- **D** Try to convince her to add a basal insulin at bedtime
Low dose SGLT-2i was added to her regimen and then titrated to the maximum dose after one month.

- A1C dropped to 7.3% (baseline 8.4%) and she lost 15 lbs.
- She experienced a yeast infection which was easily treated with oral fluconazole and she did not want to stop the SGLT2i.
- LDL-C increased from 100 to 108 mg/dL (8% rise), HDL-C increased 10%, and her TGs decreased by 25%.

### Option #5: SGLT-2 inhibitors

#### MOA
- Reduce renal glucose reabsorption and increases urinary glucose excretion.

#### Benefits
- No hypoglycemia (except when being used with SU or insulin).
- Mean A1c reduction ~ 1% (starting from a baseline A1c of ~8.0%).
- Weight loss (2-5% of body weight) and systolic BP reduction (2-6mmHg).

#### Concerns
- Genital mycotic infections. In women (6 to 12% higher than comparator) and in uncircumcised males (2 to 6% higher than comparator).
- Hypotension secondary to volume contraction especially in the elderly, those on loop diuretics, with reduced renal function.
- 4 to 8% elevation in LDL. (Aldosterone (LDL goes down and HDL goes up).
- Assess renal function (discussed later).
- New label warnings: DKA (discussed later), risk of amputation (discussed later), bone fractures, Fournier’s Gangrene, acute kidney injury, UI.

#### Clinical Pearls
- 1st oral medication that leads to statistically significant weight loss.
- Empa- Dapa-and canagliflozin showed positive CVD outcome trials (discussed later).
- Can be added to any other oral agent or injectable.
- Tell women to practice good hygiene and look out for yeast infections (may want to suggest to have some anti-yeast infection medication at home such as miconazole).

### Generic and trade names (dose range)

<table>
<thead>
<tr>
<th>SGLT-2 Inhibitor</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
<td>Farxiga</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>Invokana</td>
<td>Jardiance</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>Steglatro</td>
<td></td>
</tr>
</tbody>
</table>

- **Canagliflozin:**
  - Suggested starting dose: 100 mg daily before first meal of day (eGFR >45 mL/min).
  - Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min.

- **Dapagliflozin:**
  - Starting dose: 5 mg daily in morning without food (dual dose for both doses = 50 mg/mL).
  - Increase to 10 mg daily of extended and met additional glycemic control.

- **Empagliflozin:**
  - Starting dose: 10 mg daily in morning with or without food (dual dose for both doses = 50 mg/mL).
  - Increase to 25 mg daily of extended and met additional glycemic control.

- **Ertugliflozin:**
  - Starting dose: 5 mg daily in morning with or without food (dual dose for both doses = 50 mg/mL).
  - Increase to 15 mg daily of extended and met additional glycemic control.
Oral Agents

Renal glucose reabsorption in normal, T2D and with SGLT-2 inhibition

Adapted with permission from Abdul-Ghani, DeFronzo RA.


FDA Drug Safety Communication: the Prescribing Information for ALL SGLT-2 inhibitors was updated to include new Warnings and Precautions for ketoacidosis, urosepsis and pyelonephritis December 14, 2015

1. Extremely low incidence, mostly type 1's and type 2's receiving insulin
2. Complex mechanism related to paradoxical increase in glucagon promoting ketosis in the setting of glycosuria so extreme hyperglycemia is limited
3. Be especially cautious in women with a history of UTIs, pyelonephritis and/or genital mycotic infections
4. August 2018: new warning for extremely rare but serious infection: Fournier’s gangrene

What is the most common cause of death in type 2 diabetes?

A. Nephropathy including end stage renal disease requiring dialysis or transplantation
B. Complications from peripheral and autonomic neuropathy
C. Heart disease or stroke
D. Complications from obesity
E. Peripheral arterial disease

References:

What is the most common cause of death in type 2 diabetes?
Similar trends have occurred in the population without diabetes.

Vascular deaths: 30.9% (29.5-32.3)
Cancer: 26.3% (24.3-28.8)
Other: 43.5% (41.8-45.4)

**Primary objectives of effective management:**
*These are the important basics… ‘the ABCs’*

**Diabetes**
- General goal is <7% but must be individualized
- Less than 140/90 but must be individualized
- Less than 100 but if CAD present then less than 70, most will need a statin/ezetimibe (PCSK9 inhibitor in high risk)

**Blood pressure management**

Individualize BP goals:
- <140/90 mmHg (10-yr CV risk <15%)
  - Level A evidence
- <130/80 mmHg (10-yr CV risk >15%)
  - Level C evidence
PCSK9 inhibitors (evolocumab and alirocumab) if LDL not at goal on maximally tolerated statin/ezetimide

*Once-daily dosing, XL, extended release.

Impact of intensive glucose-lowering therapy in DM: Summary of major RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 38</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>‡</td>
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<tr>
<td>ACCORD</td>
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<tr>
<td>ADVANCE</td>
<td>‡</td>
<td>‡</td>
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<tr>
<td>VADT</td>
<td>‡</td>
<td>‡</td>
<td>‡</td>
</tr>
<tr>
<td>Long Term F/U</td>
<td>Initial F/U</td>
<td>Long Term F/U</td>
<td></td>
</tr>
</tbody>
</table>

Non-insulin CVOTs in T2D: DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR</th>
<th>EXAMINE</th>
<th>TECOS</th>
<th>CAROLINA</th>
<th>CARMELINA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>n</td>
<td>16,500</td>
<td>5,400</td>
<td>14,000</td>
<td>6,000</td>
<td>8,300</td>
</tr>
<tr>
<td>Results</td>
<td>June 2013</td>
<td>2015</td>
<td>2017</td>
<td>2017</td>
<td>2017</td>
</tr>
</tbody>
</table>

†‡ vs T2DM

Oral Agents

Non-insulin CVOTs in T2D: SGLT-2 inhibitors
Primarily driven by a reduction in heart failure

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>VERTIS CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2-I</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>7300</td>
<td>4300</td>
<td>22,200</td>
<td>3900</td>
</tr>
<tr>
<td>Results</td>
<td>Sept 2015 2017 2018 2020</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Non-insulin CVOTs in T2DM: GLP-1 RA
Primarily driven by a reduction in death due to cardiovascular disease

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL</th>
<th>HARMONY</th>
<th>REWIND</th>
<th>PIONEER 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>Liraglutide</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Exenatide CR</td>
<td>Dulaglutide</td>
<td>Oral semaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>16,500</td>
<td>14,000</td>
<td>6,000</td>
<td>5,400</td>
<td>9,400</td>
<td>8,300</td>
</tr>
<tr>
<td>Results</td>
<td>2016    2015 2016 2018 2019 2019</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CV death less with oral sema; no difference in non-fatal MI or non-fatal stroke. Median time in study: 15.9 months NEJM 2019;381:841-851.

Diabetes medications FDA approved for CV risk reduction

Empagliflozin (based on EMPA-REG data)
- to reduce the risk of cardiovascular death in adult patients with type 2 diabetes mellitus and established cardiovascular disease

Liraglutide (based on LEADER data)
- to reduce the risk of major adverse cardiovascular (CV) events (CV death, non-fatal myocardial infarction, or non-fatal stroke) in adults with type 2 diabetes mellitus and established CV disease

Canagliflozin (based on CANVAS program data)
- to reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
  - Semaglutide (based on SUSTAIN 6)
    - the indication of reducing the risk of major adverse cardiovascular events (MACE), including cardiovascular death, non-fatal heart attack, or non-fatal stroke in adults with type 2 diabetes and established cardiovascular disease (CVD).
Not all CVOTs are created equal

- Differences in study design: powered for safety or superiority
- Patient characteristics: age, weight, co-morbid complications, presence of CVD and risk factors
- Comparators may be different
- Weigh gain and hypoglycemia differences
- Regional differences
- Outcomes differ: overall mortality, non fatal and fatal MI, stroke, etc.
- Study conduct and adherence may effect results

Diabetes medications FDA approved for renal disease

- Canagliflozin (study = CREDENCE)
  - Reduce the risk of end-stage kidney and worsening renal function
  - EMPA-KIDNEY: on-going

Key principles of management of T2D

- Glycemic targets & glucose-lowering therapies should be individualized
- Diet, exercise and diabetes self-management education and support are the foundations of therapy
- Unless contraindicated, metformin is the preferred 1st line drug
- After metformin, the first consideration is whether the patient has established ASCVD or CKD. If not, then whether hypoglycemia, weight or financial status are dominant issues. Share decision making is key!
Key principles of management of T2D (cont.)

- GLP-1 RA are the preferred first injectable therapy
- Many patients over time will require insulin therapy alone or in combination with other agents to maintain glycemic control
- Vascular disease is the most common cause of death and prevention strategies need to be emphasized (A1C, aspirin, blood pressure, cholesterol, smoking cessation, and diabetes drugs that reduce ASCVD/heart failure)

Lecture 3: 1:15 – 2:15 p.m.

Tricia Santos Cavaiola, MD, Presents:

Practical Application of Injectable Agents:
Insulin and GLP-1 Receptor Agonists
Case 1: 60 year old male physician with type 2 diabetes for 10 years

Currently on pioglitazone, DPP-4 inhibitor and a SGLT2 inhibitor
Intolerant to metformin and has been resistant to taking insulin
History of dyslipidemia, hypertension, NASH and ED
Strong family history of type 2 diabetes
Does not smoke but “likes to indulge in Old Fashioned cocktails”
A1c 8.7%
Creatinine 1.4 eGFR 65
HGM data: FBS average 179 mg/dl SD 35 mg/dl
Bedtime average 210 mg/dl SD 76mg/dl

For The First Time A GLP1-RA
Is The Preferred Injectable Over Basal Insulin

Which of the following would you recommend for this patient?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Initiate basal insulin</td>
</tr>
<tr>
<td>B</td>
<td>Initiate a GLP-1 Receptor Agonist [RA]</td>
</tr>
<tr>
<td>C</td>
<td>Initiate premixed insulin [70/30] BID</td>
</tr>
<tr>
<td>D</td>
<td>Initiate a fixed combination of a basal insulin and a GLP-1RA</td>
</tr>
</tbody>
</table>

This exact question will be repeated at the end of the presentation
Injectable Agents

**Basal Insulin vs GLP-1 RA**

<table>
<thead>
<tr>
<th>Injectable Agent</th>
<th>Insulin: Injected once or twice a day</th>
<th>GLP-1 RA: Injectable once or once weekly and oral once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need to titrate dose</td>
<td>Targeting FBG</td>
<td>Reduced need to titrate dose to BG, but increase dose slowly to avoid GI side effects</td>
</tr>
<tr>
<td>Need to institute SMBG</td>
<td></td>
<td>&quot;No&quot; need for SMBG</td>
</tr>
<tr>
<td>Weight gain</td>
<td></td>
<td>Follow up not as crucial</td>
</tr>
<tr>
<td>Weight loss</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No Hypoglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**The Pathogenesis of Type 2 Diabetes: Insulin and Glucagon Responses are Abnormal**

**The Incretin Effect and Its Reduction in Type 2 Diabetes**

**Insulin secretion after oral versus IV glucose**

*P < .05 compared with respective value after oral load.*

*Reprinted with permission from Springer-Verlag © 1986.*

**Healthy Subjects (n = 14)**

**Type 2 Diabetes (n = 12)**

*Diabetologia. 1986;29:46-52.*
**GLP-1 Effects:**

Glucoregulatory Role of Incretins

- Promotes satiety and reduces appetite

Pancreatic beta cells:
- Enhanced glucose-dependent insulin secretion

Liver:
- Reduced hepatic glucose output

Pancreatic alpha cells:
- ↓ Postprandial glucagon secretion

Stomach:
- Helps regulate gastric emptying

GLP-1 secreted upon ingestion of food

FBG and PPG control

Adapted from:

**GLP-1 Receptor Agonists**

**Mechanism of Action**
- Mimic the effects of human GLP-1

**Benefits**
- Significant A1c reductions (1.0 to 3.0% depending on baseline)
- Shorter acting GLP-1 RAs have greater effects on PPG
- Weight loss
- No hypoglycemia
- Once daily, twice daily and once weekly formulations

**Concerns**
- GI side effects (typically nausea)
- Contraindicated in patients with a personal or family history of MTC or MEN2
- Relative contraindication in patients with a history of pancreatitis (important to know the etiology)

**Clinical Pearls**
- Ideal choice in obese patients with poor control, especially those on large doses of insulin
- "No" need to initiate or increase glucose testing
- Several with positive CVOT results

**Generic and Trade Names: GLP-1 RAs**

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
<td>Bydureon</td>
</tr>
<tr>
<td>Twice-daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
<td></td>
</tr>
<tr>
<td>Once-daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
<td></td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lixisibide</td>
<td>Adlyxin</td>
<td></td>
</tr>
<tr>
<td>Once-daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
<td></td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Semaglutide</td>
<td>Rybelsus</td>
<td></td>
</tr>
<tr>
<td>Once-daily</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Injectable Agents

Generic and Trade Names: GLP-1 RAs, Continued

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin/GLP-1 Receptor Agonist Fixed</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td></td>
</tr>
<tr>
<td>Glargine/lixisenatide</td>
<td>Soliqua</td>
</tr>
<tr>
<td>Degludec/liraglutide</td>
<td>Xultophy</td>
</tr>
<tr>
<td>both once-daily</td>
<td></td>
</tr>
</tbody>
</table>

GLP1-RAs are now recommended as the first injectable over basal insulin (unless glucose levels markedly elevated).

Established ASCVD: GLP1-RAs are recommended immediately after metformin (SGLT2 inhibitors in CHF is the major issue).

If primary concern is weight: GLP1-RAs are one of several choices preferred after metformin.

If primary concern is hypoglycemia: GLP1-RAs are one of several choices preferred after metformin.

If primary concern is access: GLP1-RAs are not generic yet, but several types of low payment plans.

Where do the GLP1-RA Class Fit in the New Treatment Guidelines?


Summary of Completed GLP-1 receptor agonists Cardiovascular Outcome Trials (CVOTs)

MACE Outcomes

- Effect on cardiovascular endpoints
- Reduction in cardiovascular events
- Significant improvement in glycemic control
- Improved weight management

*Significantly lower rates in favor of GLP1-RA treatment groups compared to placebo or comparator therapy.

<table>
<thead>
<tr>
<th>GLP1-RA</th>
<th>Effect on MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>Significant reduction in MACE</td>
</tr>
<tr>
<td>Exenatide</td>
<td>Significant reduction in MACE</td>
</tr>
<tr>
<td>Dipeptidyl peptidase-4 (DPP-4) inhibitors</td>
<td>Reduction in MACE</td>
</tr>
<tr>
<td>GLP1 agonists</td>
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<tr>
<td>GLP1 agonists</td>
<td>Reduction in MACE</td>
</tr>
</tbody>
</table>

Where do the GLP1-RA Class Fit in the New Treatment Guidelines?

**CVOTs of GLP-1 RAs**


**ITCA 650—Medical Device To Deliver Type 2 Medication**

MEDICATION:

- Exenatide

TECHNOLOGY:

- Subcutaneous delivery system; short office procedure
- Small micropump
  - maintains stability at temps ≈37°C
  - secretes medication for >12 months

MEDICATION:

- Previously approved GLP-1 therapeutic which demonstrates:
  - glycemic control
  - weight loss
  - safety

**Case 2: 29 year old Mexican American woman with type 2 diabetes for 3 years**

- On maximal doses of metformin, SU, and a SGLT-2 inhibitor
- She adamantly does not want to take insulin for fear of weight gain
- PMH: dyslipidemia, hypertension, PCOS and obese (BMI=31)
- Both parents and two siblings have type 2 diabetes
- eGFR 75 ml/min
- Her A1c is 8.9%
What would you recommend now for this patient?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Start a DPP4 inhibitor</td>
</tr>
<tr>
<td>B</td>
<td>Try to convince her to start basal insulin</td>
</tr>
<tr>
<td>C</td>
<td>Start a GLP1-RA</td>
</tr>
<tr>
<td>D</td>
<td>Start pioglitazone</td>
</tr>
</tbody>
</table>

She agreed to start a once weekly GLP-1 RA (exenatide, dulaglutide or semaglutide).

When prescribing once-weekly GLP-1 RA, inform patient that it may take several weeks to reach equilibration and, with once-weekly exenatide, skin nodules may occur (self limited and resolve in a few days to weeks).

She experienced no nausea or hypoglycemia. Over the next three months she lost 16 pounds and her A1c fell from 8.9% to 7.2%.

Case 2 continued

### Before GLP-1*

<table>
<thead>
<tr>
<th>FBS (mg/dl)</th>
<th>PPG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 188</td>
<td>Average 265</td>
</tr>
</tbody>
</table>

### After GLP-1*

<table>
<thead>
<tr>
<th>FBS (mg/dl)</th>
<th>PPG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average 139</td>
<td>Average 167</td>
</tr>
</tbody>
</table>

Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist

- Insulin degludec/liraglutide: Xultophy
- Insulin glargine/lixisenatide: Soliqua

- 1 dose step (unit) has 1 unit insulin degludec and 0.036 mg of liraglutide (max. dose is 50 Ideg/1.8mg lira)
- Injected once daily at same time each day with or without food
- 1 dose step (unit) has 1 unit insulin glargine and 0.33 mcg lixisenatide (max. dose is 60 Iglar/20 mcg lixi)
- Injected once daily within one hour prior to the first meal of the day
Injectable Agents

**Fixed-Ratio Combination of Insulin Degludec and Liraglutide (Xultophy)**

One dose step = 1 U insulin degludec and 0.036 mg liraglutide

**Fixed-Ratio Combination of Insulin Glargine and Lixisenatide (Soliqua)**

One dose step = 1 U insulin glargine and 0.33 mcg lixisenatide

**Insulin Degludec/Liraglutide vs. Insulin Glargine/Lixisenatide**

<table>
<thead>
<tr>
<th>Pan dose steps (units): Insulin Degludec + Liraglutide (Xultophy)</th>
<th>Pan dose steps (units): Insulin Glargine + Lixisenatide (Soliqua)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 dose steps: 15 units insulin degludec + 0.5 mg of liraglutide</td>
<td>15 dose steps: 15 units insulin glargine + 0.5 mg of lixisenatide</td>
</tr>
<tr>
<td>30 dose steps: 30 units insulin degludec + 1.0 mg of liraglutide</td>
<td>30 dose steps: 30 units insulin glargine + 1.0 mg of lixisenatide</td>
</tr>
<tr>
<td>60 dose steps: 60 units insulin degludec + 1.8 mg of liraglutide</td>
<td>60 dose steps: 60 units insulin glargine + 1.8 mg of lixisenatide</td>
</tr>
</tbody>
</table>

Starting dose:
- 16 dose steps which has 16 units insulin degludec + 0.58 mg of liraglutide
- If glargine U-100 dose is <30, start at 15 dose steps which has 15 units insulin glargine + 0.5 mg of lixisenatide
- If glargine U-100 dose is >30, start at 30 dose steps which has 30 units insulin glargine + 1.0 mg of lixisenatide

**Notes:**
- If using insulin degludec alone, generally 2–4 dose steps of insulin degludec at a time, usually every 3–4 days.
- Maximum dose = 50 units of insulin degludec and 1.8 mg of liraglutide.
- Maximum dose = 60 units of insulin glargine and 2.0 mg of lixisenatide.

**References:**
**Injectable Agents**

**Insulin Degludec/Liraglutide in Type 2 Diabetes: Phase 3 Trial**

- **Patients with type 2 diabetes (n=1663)**
- **Treat to target (FPG: 72-90 mg/dL)**
- **Starting dose: 10 dose steps**
- **Dose adjustments: (2-0-2) twice weekly**

**Inclusion Criteria:**
- Type 2 diabetes
- Insulin naïve treated with metformin + pioglitazone
- A1c 7.0 – 10.0%
- BMI < 40 kg/m²
- Age > 18 years

**Buse J et al. ADA 2013. 65-OR; DUAL I**

- *insulin degludec/liraglutide one dose step=1u degludec+0.036mg lira

**A1c 8.3% to 6.4% with Insulin Degludec/Liraglutide**

- Mean values (+SEM) based on FAS and LOCF imputed data; EOT = end of trial; p-values are from an ANCOVA ADA/EASD A1c target < 7.0%; AACE A1c target < 6.5%

**Body Weight and Hypoglycemia**

- Hypoglycemia
- Increase of 4.88 lb P<0.0001
- Decrease 5.37 lb P<0.0001

**Hypoglycemia**

- 1.00
- 3.97
- 0.67
- 0.67 (0.13, 0.47)

**Body weight change**

- Increase 4.88 lb P<0.0001
- Decrease 5.37 lb P<0.0001

**Hypoglycemia**

- 1.00
- 3.97
- 0.67
- 0.67 (0.13, 0.47)

**Buse J et al. ADA 2013, 65-OR**

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Injectable Agents

Gastrointestinal Side Effects: Gradual Titration Helps

- Insulin degludec/liraglutide
- Insulin degludec/liraglutide
- Non-GLP-1 RA comparators
- Liraglutide 1.8 mg

p<0.001 significant for odds of experiencing gastrointestinal side effects for subjects on insulin degludec/liraglutide versus non-GLP-1 RA comparator

Efficacy of Fixed-Ratio insulin glargine lixisenatide in T2DM Patients Not Controlled on Basal Insulin

- T2DM patients not controlled on basal insulin + metformin (HbA1c > 7.2%)
- Mean A1C (%)
- 9.0
- 7.0
- 6.5
- 8.5
- 8.0
- Baseline
- 7.5
- Week 24
- Week 12
- Week 30

Mean A1C (%)

- Insulin glargine lixisenatide (N = 366)
- Mean difference: -0.52% (p < 0.0001)
- vs Glargine (N = 365)

Mean weight change:

- Insulin glargine lixisenatide: -0.7 kg
- Glargine: 0.7 kg

Mean weight change: -0.7 kg vs glargine -1.40 kg (p < 0.0001)

Fixed-Ratio insulin glargine lixisenatide in T2DM Patients Not Controlled on Basal Insulin: Glucose and Weight Effects

- FPG
- 2-h PPG Excursions

Mean change from baseline (mg/dL)

- Insulin glargine lixisenatide (N = 366)
- Glargine (N = 365)

p < 0.0001

A1C < 7.0% with no weight gain and no symptomatic hypoglycemia

% Patients with A1C < 7.0% at Week 30

Subjects experiencing nausea, vomiting or diarrhea (%)
Summary: Benefits for Combining GLP-1 Receptor Agonists and Basal Insulin Analogs

- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts.
- Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared to basal insulin alone.
- In the setting of inadequate control on basal insulin, adding a GLP-1RA is associated with greater benefits (weight loss and minimal hypog) than adding prandial insulin.

Generic and Trade Names: Insulin

<table>
<thead>
<tr>
<th>Fast-Acting Insulin</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>Regular regular</td>
<td>Humulin R, Novolin R</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Humulin N</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Humulin NPH</td>
</tr>
<tr>
<td></td>
<td>Faster-acting aspart</td>
<td>Humalog</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Admelog</td>
</tr>
<tr>
<td></td>
<td>Lispro (U-100 and U-200)</td>
<td>Afrezza</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lantus</td>
</tr>
<tr>
<td>Glulisine</td>
<td></td>
<td>NovoLog</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fiasp</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Apidra</td>
</tr>
<tr>
<td></td>
<td>Inhaled insulin</td>
<td>Inhaled insulin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>Intermediate-acting: NPH</th>
<th>Human R, Novolin NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long-acting: Degludec (U-100/200)</td>
<td>LevoLev</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glargine (U-300)</td>
<td>Levemir</td>
</tr>
<tr>
<td></td>
<td>Glargine (U-100)</td>
<td>Lantus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Toujeo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Basaglar</td>
</tr>
<tr>
<td>Detemir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Time Action Profiles: Traditional Insulins
Two New Basal Insulins Recently Added to Our List of Options

Both approved by the FDA and now available for patients
1. U-300 glargine a long-acting basal insulin
2. U-100 and U-200 degludec a long-acting basal insulin

Benefits Of U300 Glargine And Degludec In Type 1 Diabetes
- Less intra-subject variability
- Less hypoglycemia
- Less weight gain
- Flat, stable and prolonged action greater than 24 hours
- Tell patients it takes 4 to 5 days to reach equilibration and they may need correction doses
- 1 to 1 conversion from prior basal dose (patients switching from U100 to U300 glargine may need ~15% more)
- Both insulins come in easy to use pens

How Much Basal Insulin Will Your Patients Require?

0.5 units per Kg or
0.23 units per pound body weight
Case 3: 66 year old obese female diagnosed with type 2 diabetes 9 years ago

Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, SGLT2 inhibitor and a DPP4 inhibitor

Her PCP started 10 units of glargine in the morning. After 3 months on 10 units she felt it “did not work” and she stopped it.

A1c > 8.5% for the past 2 years, eGFR 89, LFTs normal

Current SMBG (mg/dl) below:

<table>
<thead>
<tr>
<th>Day</th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Before</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>215</td>
<td></td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>247</td>
<td></td>
<td>174</td>
<td>196</td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td></td>
<td></td>
<td>196</td>
</tr>
<tr>
<td>Thursday</td>
<td>226</td>
<td></td>
<td>174</td>
<td></td>
</tr>
</tbody>
</table>

Which of the following is the single most likely explanation for her failure with basal insulin:

A. Poor adherence
B. Initial dose was too little
C. Inadequate titration of the glargine U-100
D. Glargine U-100 should have been given at bedtime

Initiating Insulin Therapy in Type 2 Diabetes: General Concepts

Don’t wait forever.
Address patient concerns/fears.
Consider combination therapy with oral agents.

Start with basal insulin.
Titrating the dose is essential (self titration can work well).

Use a fast-acting analog as an add on to basal dose when indicated.
(may only needed to be given with the largest meal discussed later)

Self-monitoring of blood glucose (SMBG) and CGM are important tools in motivating patients and in guiding dose adjustments.
Injectable Agents

First Goal: Correct Fasting Hyperglycemia

Second Goal: Control postprandial hyperglycemia if A1c still >7% (or above individual goal)

Adding Basal insulin to Oral Agents
An Effective Strategy to Initiate Insulin Therapy

- Only 1 injection per day is typically required
- No need for mixing different types of insulin
- Convenience (usually given at night or first thing in the morning)
- Low dosage compared to a full insulin regimen, which limits weight gain
- Effective improvement in glycemic control by suppressing hepatic glucose production

Case 4: 65 year old obese Latino with a 9 year history of type 2 diabetes

- History of CAD c/p MI 2 years ago
- Treated for 2 years with diet and exercise alone even though his A1c was above 9.5% ("did not want to take medications")
- Eventually started on metformin, sequentially followed by a sulfonylurea, DPP-4 inhibitor, and his A1c fell from 9.9% to 7.9%
- It took two years (6 clinic visits) to initiate these 3 meds and get his A1c down
Injectable Agents

Case 4: continued

- eGFR 45 ml/min
- PMH: HTN, dyslipidemia, DSA, CAD, chronic pancreatitis, ED
- Other meds: ACE inhibitor, clopidogrel, atorvastatin, HCTZ, tadalafil, carvedilol, and several vitamin supplements
- Loves to eat at fast food restaurants
- Asked to test his glucose value once a day at different times

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-breakfast</td>
<td>148 – 229 mg/dL</td>
<td>175 mg/dL</td>
</tr>
<tr>
<td>Pre-lunch</td>
<td>111 – 182 mg/dL</td>
<td>147 mg/dL</td>
</tr>
<tr>
<td>Pre-dinner</td>
<td>91 – 205 mg/dL</td>
<td>139 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>148 – 231 mg/dL</td>
<td>184 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia

Which of the following would you suggest for this patient?

A. Work on lifestyle and no medication addition
B. Initiate basal insulin
C. Start a GLP-1 RA and stop his DPP-4 inhibitor
D. Start a SGLT-2 Inhibitor

Insulin degludec U-200 was added at night (20 units) and titrated up to 120 units over the next 10 weeks.
He was asked to test 2x/day (pre-breakfast and bedtime).
It is important to make sure the patient is not going to bed high.

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-breakfast</td>
<td>82 – 110 mg/dL</td>
<td>122 mg/dL</td>
</tr>
<tr>
<td>Pre-lunch</td>
<td>82 – 110 mg/dL</td>
<td>122 mg/dL</td>
</tr>
<tr>
<td>Pre-dinner</td>
<td>82 – 110 mg/dL</td>
<td>122 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>118 – 183 mg/dL</td>
<td>155 mg/dL</td>
</tr>
</tbody>
</table>

A1c dropped to 7.1%, no hypoglycemia. Gained 2 lbs in 3 months.
Oral agents can be continued unless hypoglycemia occurs during the day, in which case the sulfonylurea should be reduced or withdrawn.
An ADA/EASD consensus algorithm for the initiation and adjustment of basal insulin:

- Start with a long-acting basal insulin
- Initiate at 10 units/day or 0.2 units/kg/day
- Check fasting glucose daily and increase dose by 2 units every 3 days until fasting is in target range (70 – 130 mg/dL)


Simple Daily Self-Titration Option* (much easier to follow by the patient than the 3 day titration)

- Increase by 1 to 2 units every 1 day until FPG ≤ 120 mg/dL

Example:
- Less than 100: decrease by 2 units
- Between 100 and 150: no change
- Over 150: increase by 2 units

The goal can be individualized

* Daily titration works well with all old and new basal insulins

Self Titration Clinic Form

Starting/Adjusting Long-Acting Basal Insulin

1. Give Basal insulin: once a day at Morning
2. Starting dose: __ units
3. Every 1 day(s), adjust your dose based on your fasting blood sugar that morning
   a. If fasting blood sugar is over __, then increase your dose by __ units
   b. If fasting blood sugar is under __, then decrease your dose by __ units
   c. If fasting blood sugar is between __ and __, then keep the same

Important:
- The presence of long acting insulin is to provide a background amount of insulin throughout the day, not at night while you sleep. It is not meant to treat high blood sugars caused by eating food, so you should not change your dose based on blood sugar readings during the day when you are eating.
Second Pitfall in Initiating/Titrating Basal Insulin
(First one is too slow titration after starting)

Not Paying Attention To Bedtime Glucose Value

1. Ask the patient to do paired testing (test at bedtime and again the next morning).
2. If the bedtime BG is high, it needs to be addressed by either lifestyle modification including reduced caloric consumption and/or post dinner exercise.
3. Other options include prandial insulin or a GLP-1 RA.

Clinical Pearls: Combination Therapy with Basal Insulin

-1- Start with 10 to 20 units (based on FBS, weight)
-2- The key to success is frequent follow up after initiation to avoid "failure" (most patients will need 40 to 70 units/day)
-3- Have the patient follow a self-titration regimen and return to clinic or follow-up in some other manner (phone, fax, email, telehealth, etc.) relatively soon
-4- You can usually limit SMBG to only once a day in the morning but check at bedtime once in awhile to make sure the pt. does not need pre-dinner fast acting insulin.

Transitioning From Basal to Basal/Bolus Insulin Therapy in Type 2 Diabetes Mellitus

(Insulin and Patch Pumps Can Improve Adherence)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lente/Lantus dose x 2</td>
<td>Add a meal analog insulin</td>
<td>Add a meal analog insulin</td>
<td>Add a meal analog insulin</td>
</tr>
<tr>
<td>dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in FPG</td>
<td>Change in FPG</td>
<td>Change in FPG</td>
<td>Change in FPG</td>
</tr>
<tr>
<td>A1c &lt; 7.0%, FPG &lt; 130 mg/dL</td>
<td>A1c &lt; 7.0%, FPG &lt; 130 mg/dL</td>
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<td>A1c &lt; 7.0%, FPG &lt; 130 mg/dL</td>
</tr>
</tbody>
</table>
Injectable Agents

68 Year Old Male On Oral Agents and Basal Insulin:
Need For Prandial Insulin Only At Dinner

Inhaled Insulin: Addresses "the needle" Issue
- Better post meal glucose values
- Less delayed hypoglycemia

Case 1: 60 year old male physician with type 2 diabetes for 10 years
- Currently on pioglitazone, DPP-4 inhibitor and a SGLT2 inhibitor
- Intolerant to metformin and has been resistant to taking insulin
- History of dyslipidemia, hypertension, NASH and ED
- Strong family history of type 2 diabetes
- Does not smoke but "likes to indulge in Old Fashions"
- A1c 8.7%
- Creatinine 1.4, eGFR 65
- HbA1c data: FBS average 179 mg/dl SD 35 mg/dl
- Bedtime average 210 mg/dl SD 76mg/dl

Currently on pioglitazone, DPP-4 inhibitor and a SGLT2 inhibitor
18

Injectable Agents

Which of the following would you recommend for this patient?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Initiate basal insulin</td>
</tr>
<tr>
<td>B</td>
<td>Initiate a GLP-1 Receptor Agonist (RA)</td>
</tr>
<tr>
<td>C</td>
<td>Initiate premixed insulin (70/30) BID</td>
</tr>
<tr>
<td>D</td>
<td>Initiate a fixed combination of a basal insulin and a GLP-1RA</td>
</tr>
</tbody>
</table>

Summary

- GLP-1 RAs represent a tremendous advance in the treatment of type 2 because of significant glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs/GLP1-RAs) is safe, effective and easy to implement
- The fixed combination of basal insulin and a GLP-1 RA has clinical advantages in terms of efficacy, reduced side effects and ease of use
- The Basal Bolus approach in type 2 diabetes does not need to be four injections per day (pens, patch pumps and inhaled insulin to improve adherence)
- Adherence and persistence needs to be addressed at every visit
Lecture 4: 2:15 – 3:15 p.m.

Steven V. Edelman, MD, Presents:
Addressing the Therapeutic Strategies and Unmet Needs in Type 1 Diabetes
Unmet Needs in Type 1 Diabetes

- Reducing glycemic variability (GV)
- Increasing time in range (TIR)
- Reaching A1c goal without hypoglycemia
- Preventing and controlling weight gain
- Addressing cardiovascular risk factors
- Emotional burden of living with type 1 diabetes for the individual and his/her family

Glucose Variability has Important Impact on Patients with T1D: Both Patients Have the Same A1c

- Measuring A1c alone gives no information on variability
- Importance of avoiding extreme hyperglycemia and dangerous hypoglycemia
- Improvement in time in range significantly reduced retinopathy and nephropathy

Prevalence of T1D Increasing in US

- 3.3 million adults currently have T1D
- 1 million adults ≥ 20 years; not a childhood disease anymore
- 21% increase in prevalence of T1D in people < 20 years between 2001-2009
- 40,000 people diagnosed each year in U.S.
- 5 million people in U.S. expected to have T1D by 2050
Type 1 Diabetes

Type 1 is an Autoimmune Disease: The Immune System Attacks Healthy Beta Cells

Natural Progression is months to a few years

Natural History and Cause of Type 1 Diabetes
Autoimmune condition

LADA


LADA

The most missed diagnosis in diabetes
Type 1 diabetes can occur at any age
Slower beta-cell destruction (may respond briefly to oral agents)
Typically does not have features of the Metabolic Syndrome
Blood test positive for type 1 diabetes (GAD auto antibodies)

Gary Hall Jr.

Olympic Gold Medalist
World Record Holder


You can get type 1 diabetes at any age!

Age at Diagnosis of T1D

First-degree family member with T1D

Family History of T1D

Risk of Developing Type 1 vs Type 2

- General Population: 0.3% vs 8-11%
- If you have a sibling with T1D: 4% vs ~30%
- If your mother has T1D: 2 – 3% vs ~30%
- If your father has T1D: 6 – 8% vs ~30%
- If you have an identical twin with T1D: ~50% vs 100%


**Race/Ethnicity**

- White Non-Hispanic: 81%
- Black Non-Hispanic: 5%
- Hispanic or Latino: 8%
- Native Hawaiian/Other Pacific Islander: 1%
- Asian: 1%
- American Indian/Alaskan Native: 1%
- More than One Race: 1%

**Race/Ethnicity**

- CAUCASIAN
- More than One Race: 5%
- White Non-Hispanic: 19%
- Black Non-Hispanic: 13%
- Hispanic or Latino: 15%
- Native Hawaiian/Other Pacific Islander: 14%
- Asian: 13%
- American Indian/Alaskan Native: 20%
- More than One Race: 20%

**Age, years**

- <6: 32%
- 6-<13: 32%
- 13-<20: 39%
- 20-<26: 42%
- 26-<50: 65%
- ≥50: 66%

**A1c Goal**

- = <8.5%
- = <8.0%
- = <7.5%
- = <7.0%

- Only ~30% of Type 1s Reach ADA Goal of an A1c Less Than 7%
Case 1
- 36 year old male with the diagnosis of type 1 diabetes at age 6
- He has been on an insulin pump for many years
- Uses a fast acting analog in his pump
- His A1c has typically been in the 6.5 to 7.5% range
- He wears a continuous glucose monitor which gives him a mean glucose, standard deviation and TIR or time in range.
- He is frustrated with the variability of his glucose values and fluctuations.

What glycemic measurement is the most valuable to determine how his control is on a day to day basis?

A1c value  
Average glucose over the past 90 days  
Frequency of hypoglycemia  
Time in Range or TIR

Smart Phone Clarity App
- Mean glucose value
- Standard Deviation
- Time in Range
- 24 hour multiday profile
Despite Following All of the Rules

1. Unexpected highs
2. Unexpected lows
3. Carb:Insulin ratio not working consistently
4. Correction Factor not working consistently
5. Not responding to insulin and exercise consistently

G6
- No calibration required
- 10 day sensor life
- Predictive low alerts
- No interference with acetaminophen
- Auto inserter
- Medicare Approve

Eversense
Implantable Continuous Glucose Monitor
- No extra device to carry
- No weekly sensor insertion
- No open wound
- No extra device to carry
- No extra device to carry
- No extra device to carry
**Eversense Implantable CGM**

- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

---

**GUARDIAN CONNECT**

- Predictive high alerts
- Predictive low alerts
- Requires calibration
- 6-day wear
- Need to confirm with fingerstick when dosing

---

**Freestyle Libre Flash IS or Intermittent Sensing**

- 1 hour warm up time
- Lasts 14 days
- Swipe to get a number
- Trend arrows
- No calibration
- No alerts or alarms
- No sharing features
Severe Hypoglycemia Due to Too Much Insulin: 5 to 10% of all deaths in T1D


Case 2
- 25 year old female with type 1 diabetes for 5 years
- CHO to insulin ratio 15:1
- CF 1:50 goal 100 mg/dL
- Wears an insulin pump

Case (continued)
- Patient uses her bolus calculator to determining her correction dose
- Correction factor 1:50
- Target glucose 100 mg/dL
- 220 - 100 / 50 = 2.4 units
Which option below is the best suggestion for her to follow now?

A. Watch and wait (give no additional insulin)
B. Use her standing desk instead of sitting
C. Give a correction dose of at least 4 units
D. Give a correction dose of 2.4 units

A Single BS at one Point In Time Lacks Important Information

No insulin. Watch and maybe get some carbs

Pump and meter software suggests the same either way

Trend Arrows Give Important Information To The User For Treatment Decisions

- No Risk of Change Instructions. This feature cannot always indicate how fast your glucose is rising or falling.
**Mean change in Insulin Dose Based on 2 ARROWS UP: Survey of 300 CGM users**

- 3.0 units
- 6.8 units

**How CGM and Trending Information Can Affect Dosing Decisions**

- No change in calculation
  - 3.0 units

- 140% Mean Increase
  - 6.8 units

- 48% Mean Decrease
  - 1.5 units

**Adjust Correction Insulin Dose Based On Anticipated Glucose In 30 Minutes**

- Add 50 mg/dl
- Add 75 mg/dl
- Add 100 mg/dl

Wait until trend arrow becomes horizontal
Blood glucose after a meal when bolus given 20 minutes **BEFORE,** at **START,** or 20 min **AFTER** the meal

Both dietary fat and protein increase post meal glucose concentrations.

Four test breakfasts with identical carbohydrate contents, but varying protein and/or quantities of dietary fat:

- **High fat/high protein**
- **High fat/low protein**
- **Low fat/high protein**
- **Low fat/low protein**

Cobry et al, Diab Tech Therap 2010;12: 173- 177

Smart, Evans, O’Connell, McEl duf f, Lopez, Jones, Davis, King. Both Dietary Protein and Fat Increase Postprandial Glucose Excursions in Children with Type 1 Diabetes, and the Effect is Additive. Diabetes Care 2013;36:3897
64 year old male with T1D for 30 years on a T1D regimen

What is/are the possible causes of this patient's glucose profiles overnight?

A. Needs more basal insulin
B. Needs to be more consistent in his dinner meals/times
C. He has gastroparesis
D. All of the above

Physiologic Insulin, Glucagon and Amylin Secretion

Liver
Portal Vein
Systemic Circulation
Pancreas
Insulin
Amylin
Beta Cell
Glucagon
Alpha Cell

Physiologic Insulin Secretion and Glucose Levels in Healthy Subjects

Insulin (µU/mL)
Glucose (mg/dL)

Basal Glucose
Breakfast Lunch Dinner
0 50 100 150
Basal Insulin: HGO (40 to 60% of TTD)
Bolus Insulin (40 to 60% of TTD)

**Generic and Trade Names: Insulin**

<table>
<thead>
<tr>
<th>Fast-Acting Insulin</th>
<th>Female Name</th>
<th>Male Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular Rapid-Acting</td>
<td>Regular</td>
<td>NovoRapid</td>
</tr>
<tr>
<td>Faster-Acting Aspart</td>
<td>Aspart</td>
<td>Fiasp</td>
</tr>
<tr>
<td>Lispro (U-100 and U-200)</td>
<td>Lispro</td>
<td>Basal Bolus Lispro</td>
</tr>
</tbody>
</table>

**Basal Insulin**

<table>
<thead>
<tr>
<th>Intermediate-Acting:</th>
<th>Female Name</th>
<th>Male Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH</td>
<td>Humulin N</td>
<td>Novolin NPH</td>
</tr>
<tr>
<td>Long-Acting</td>
<td>Levemir</td>
<td>Lantus</td>
</tr>
</tbody>
</table>

**Information taken from the PDR Guide and Package Inserts**

**Inhaled Insulin**

- **Rapid on Rapid off**
  - Better post meal glucose values
  - Less delayed hypoglycemia

**Faster-Acting Aspart or Fiasp**

(addition of L-arginine and niacinamide for faster absorption)

2 hour PG levels in T1D on pump therapy after a standardized meal comparing Aspart (Novolog) with Faster Aspart (Fiasp)
Two New Basal Insulins Recently Added to Our List of Options

Both approved by the FDA and now available for patients

1. U-300 glargine a long-acting basal insulin

2. U-100 and U-200 degludec a long-acting basal insulin

Benefits Of U 300 Glargine and Degludec in Type 1 Diabetes

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- Less hypoglycemia
- Less weight gain
- Flat, stable and prolonged action greater than 24 hours
- Tell patients it takes 4 to 5 days to reach equilibration and they may need correction doses
- 1 to 1 conversion from prior basal dose (patients switching from U 100 to U 300 glargine may need ~15% more)
- Both insulins come in easy to use pens

Glucose Infusion Rate In Subjects With Type 1 Diabetes

Insulin Glargine U-300

50 T1D subjects underwent two euglycemic clamp studies after six days of receiving insulin glargine U-300

Let Your Patients Pick the Pump

Animas Vibe G4 (Discontinued)

- t:slim G6/X2
- 630/670G/530G
- Omnipod

Insulin Pumps: Advantages

- Improved glycemic control
  - More precise, physiologic insulin delivery
- Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
- "Smart features" help to estimate insulin doses and reduce errors, i.e. stacking insulin
- In some situations (but not all) freedom and flexibility in lifestyle
  - Eliminate multiple daily injections (1 stick every 3 days)
  - Very easy to respond to CGM results
  - Reduce restrictions on eating, exercise and sleeping patterns; could have the same benefits with MDI
  - Greater flexibility with sports, travel, work schedule and other activities (not with water sports)

Bolus Options With Pump Therapy

1. Standard: quickly absorbed foods
2. Square Wave: gastroparesis, fatty meals, Pramlintide (Symlin)
3. Dual Wave: combination of rapid and slowly absorbed meals
Variable Basal Rate Capability

- More precise, physiologic insulin delivery
- Greater ability to handle dawn phenomenon, stress and other conditions that alter insulin requirements
- Able to suspend and reduce basal rates to avoid hypoglycemia

Variable Basal Rate Capability

- Able to set a higher basal rate for illnesses and medications
- Able to program different sets of basal rates for different situations, ie. Work days versus weekends.
What adjustment would you suggest with this patient on a pump?

<table>
<thead>
<tr>
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<th>L</th>
<th>D</th>
<th>P</th>
<th>S</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>227</td>
<td>121</td>
<td>144</td>
<td>142</td>
</tr>
<tr>
<td>Day 2</td>
<td>203</td>
<td>152</td>
<td>144</td>
<td>161</td>
</tr>
<tr>
<td>Day 3</td>
<td>198</td>
<td>124</td>
<td>132</td>
<td>133</td>
</tr>
<tr>
<td>Day 4</td>
<td>198</td>
<td>124</td>
<td>132</td>
<td>133</td>
</tr>
</tbody>
</table>

A. Increase the insulin to carbohydrate ratio at dinner time
B. Increase the correction factor at breakfast time
C. Increase the basal rate by 20% starting at 10pm to 7am
D. Increase the basal rate by 20% starting at 3am to 7am

Testing the Basal Rate in Type 1 Diabetes

Testing Overnight
1. Ask the patient to have an early dinner, make sure the post prandial BS is between 140 and 180mg/dl (may need a correction dose) with a horizontal trend arrow
2. Fast until the next morning
3. If not on a CGM then he/she needs to test the BS every few hours

Testing During The Day (different day than testing pm)
1. Ask the patient if he/she can skip breakfast and fast as long as possible.
2. If patient wants to eat a small breakfast then make sure the post breakfast BS is between 140-180mg/dl with a horizontal trend arrow

Type 1 Diabetes
Is this T1D on too much or too little basal?

Same pt. Fasting from 9pm until 7am

32yo Male using MDI: Glargine U100 and fast acting analog

What is the best treatment option to help this patient with his overnight values?

<table>
<thead>
<tr>
<th>Option</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Decrease the basal insulin</td>
</tr>
<tr>
<td>B</td>
<td>Switch the U-100 glargine for U-300 glargine or degludec</td>
</tr>
<tr>
<td>C</td>
<td>Have a larger bedtime snack</td>
</tr>
<tr>
<td>D</td>
<td>Do not exercise after 7pm</td>
</tr>
</tbody>
</table>
Pump vs. Multiple Daily Injections?
Sensor Augmented Pumps With Newer Features May Change The Way Patients Choose

It Comes Down To Personal Choice

Medtronic 670G: Hybrid Closed Loop
- This is a basal rate modulator
- Works well overnight
- Still requires meal and correction boluses
- 4 or more fingersticks a day to stay in auto move
- Diabetes tasks during the day are not decreased
- There are more alarms
- No sharing capabilities
- Fingerstick required/boluses

DIY: Do It Yourself
Hybrid closed loop
- Old Medtronic pump/Omnipod
- Smart phone/Apple Watch
- Riley link hacking device
- Dexcom G6
- Always in auto mode
- No fingersticks
- Formal studies underway

NOT FDA APPROVED YET
Type 1 Diabetes

Tracing from Jeremy Pettus L.L.C

Looping
Low
Carbs

Time in range
“about 100%”

An Artificial Pancreas Will Bridge
The Gap Until There Is A Cure

BG mg/dL

Time

Alarm – impending hypo
No response – alarm plus insulin reduction or off/glucagon on if needed

Alarm – impending hyper
No response – alarm plus automated insulin push to bring level below threshold (glucagon off)

Resume preset basal rate

Minimize time in “Red” zones

iLet • BigFoot • Tandem • Insulet • Lilly • Medtronic • DIY Loop

Works with Dexcom G6
Upgrades via the cloud
Improve TIR
Reduce Hypos

Basal-IQ™ Technology

Predicts glucose to watch ahead
Suspends insulin to help avoid the low
Resumes insulin and glucose if needed

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Adjunctive Therapies for People with Type 1 Diabetes

- Amylin Analog (Pramlintide)
- Incretins (GLP-1 RA) *
- SGLT-2 Inhibitors *
- DPP4 Inhibitors *
- Metformin *

* Medications FDA approved only in type 2 diabetes at the current time

SGLT 1/2 Inhibitors in T1D

- There are 3 different drugs being studied in type 1 diabetes (empagliflozin, dapagliflozin and sotagliflozin)
- Sotagliflozin is the furthest along in development and will review the clinical trial data in detail
- If any are approved it would be the first oral agent for type 1 diabetes

Summarize Findings From All SGLT -1/2 Inhibitors

(difficult to make precise efficacy comparisons across trials due to design and analysis differences)

<table>
<thead>
<tr>
<th>Efficacy (placebo adjusted)</th>
<th>Highest dose*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C reduction</td>
<td>~0.4%</td>
</tr>
<tr>
<td>Time in Range (blinded CGM)</td>
<td>~3 hour increase</td>
</tr>
<tr>
<td>Time in Hypoglycemia (CGM)</td>
<td>No change or some reduction</td>
</tr>
<tr>
<td>Insulin dose</td>
<td>10-15% reduction</td>
</tr>
<tr>
<td>Weight</td>
<td>~2-3 kg reduction</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>~3-4 mm Hg reduction</td>
</tr>
<tr>
<td>Patient reported outcomes</td>
<td>Improved</td>
</tr>
</tbody>
</table>

* Lower doses retain much of the glycemic efficacy with lesser effect on weight and blood pressure

Clinically relevant adverse events include genital mycotic infections (primarily in women 12 to 15%) and DKA (3 to 4%), sometimes euglycemic DKA
The important unmet needs in T1D include improved glycemic variability (GV), increased time in range (TIR)
- Reaching A1c goal without hypoglycemia
- CGM is the standard of care for T1D
- Pumps and the newer ultra rapid and basal insulins can help improve TIR
- Adjunctive therapies can address some of the unmet needs

Summary