Lecture 1: 8:15 – 9:10 a.m.

William Polonsky, PhD, CDE, Presents:
The Efficacy Mirage in Type 2 Diabetes: Why Do Clinical Trial Results Disappear in Real-World Practice?
GLYCEMIC CONTROL, 2007-2014

HEDIS data from >1000 health plans covering >171 million lives (2014)

ONLY 40% OF PATIENTS ARE AT HbA1c <7%

HMO POPULATION

ONLY 30% OF PATIENTS ARE AT HbA1c <7%

MEDICAID POPULATION


RATES OF VERY POOR GLYCEMIC CONTROL

HEDIS data from >1000 health plans covering >171 million lives

% OF DIABETIC PATIENTS WITH VERY POOR GLYCEMIC CONTROL (HbA1c >9%) IN THE US

2005 29.7%

2014 31.1%

% OF DIABETIC PATIENTS WITH VERIF Poor GLYCEMIC CONTROL IN THE US

*In a commercial HMO population that includes either Type 1 or Type 2 diabetes.

THE KEY BEHAVIORAL CONTRIBUTOR TO GLYCEMIC CONTROL?

ALL SELF-CARE BEHAVIORS + COVARIATES

SMBG, self-monitoring of blood glucose.

aCovariates, age, gender, race, ethnicity, income, education, insurance status, insulin status and duration of diabetes. HbA1c assessed with a point-of-care device.

p < 0.05

MANY NEW T2D MEDICATION OPTIONS OVER THE LAST DECADE


Number of Treatment Options Approved

0
10
20
30
40
50

NO CHANGE IN % OF PATIENTS AT HbA1c <7%

CLINICAL TRIALS

Identified 11 pivotal randomized controlled trials with published change in HbA1c (7 GLP-1 RA [2600 patients] and 4 DPP-4i [1889 patients]).

Optum/Humedica SmartFile database (2007-2014) was used (GLP-1 RA 221 patients; DPP-4i 652 patients). Change in HbA1c measured from drug initiation to 365±90 days later.

Carls et al, 2017

DPP-4i (12 months)
GLP-1 RA (12 months)

Baseline HbA1c 8.3% 8.2% 7.8%

N=652 N=1889 N=221

8.4%

GAP

–1.0 –0.6 –1.4 –1.6 0

–0.68% –0.51% 0 –1.2 –0.4

–1.25% –0.52% –0.8 –0.2

HbA1c

CLINICAL TRIAL RESULTS LOOK GOOD, BUT...

THE EFFICACY MIRAGE

HbA1c

REAL WORLD

CLINICAL TRIAL

EFFICACY UNREALIZED
POOR ADHERENCE IS THE KEY

REAL-WORLD RESULTS PREDICTED UNDER TYPICAL TRIAL CONDITIONS

GLP-1 RA Adherence Rate in Real World = 29%

DEFINING POOR ADHERENCE

- Proportion of days covered
- Typically measured after first refill
- PDC doesn’t account for
  - Prescriptions that are never filled at all1
  - What the patient actually takes

ADHERENCE RATES FOR ORAL AGENTS ARE LESS THAN 50%
Efficacy Mirage

**Tracking New E-Prescriptions for Diabetes Medications**

Among 75,589 insured patients in the first year of a community-based e-prescribing initiative, 31% of new e-prescriptions for diabetes medications were never filled.

- Filled: 69%
- Never Filled: 31%


**Clinical Impact of Poor Adherence**

Hospitalization risk increases with higher rates of poor adherence:

- 0-19%: 37%
- 20-39%: 41%
- 40-59%: 45%
- 60-79%: 59%
- 80-100%: 56%

39% increased risk of all-cause mortality due to poor adherence to oral hypoglycemics.

- Poor adherence defined as PDC < 0.8.

*Boye KS et al. 76th ADA Scientific Sessions. June 10–14, 2016. Poster 1221-P.*

**Intervention Strategies to Address Medication Adherence**

- Written medication instructions
- Enhancing HCP adherence skills
- Goal setting
- Stimuli/prompts to take medications
- Enhancing support from significant others
- Special packaging of medications
- Self-monitoring of medication adherence
- Habit analysis and intervention

*Conn and Rupar, 2017*
INTERVENTION STRATEGIES TO ADDRESS MEDICATION ADHERENCE

- Medication side effect management
- Feedback about medication adherence
- Medication calendars
- Enhancing patient self-management skills
- Providing consequences/rewards for adherence
- Motivational interviewing
- Stress management

Conn and Rupar, 2017

EFFECTIVENESS OF CURRENT INTERVENTION STRATEGIES

Review of 771 RCTs indicate that effects are modest (Cohen’s d):
- Overall: 0.29
- Behavioral strategies: 0.33
- Addressing habits: 0.37
- No behavioral strategies: 0.28

“Much room remains for improvement.”

Conn and Rupar, 2017

THE PRESUMED PROBLEM: FORGETFUL/DISORGANIZED

Efficacy Mirage
“Patient’s medication beliefs, especially perceived need for medication and perceived medication affordability, were strong predictors of unintentional non-adherence.”

Gadkari and McHorney, 2012

“Patient’s medication beliefs, especially perceived need for medication and perceived medication affordability, were strong predictors of unintentional non-adherence.”

Gadkari and McHorney, 2012

"It’s our job to help patients live as long as possible free of CVD complications. Although most patients share that goal, we don’t always see the same pathways to get there. I want to believe that if patients knew what I know, they would take their medicine. What I’ve learned is that if I felt what they feel, I’d understand why they don’t."

Rosenbaum, 2015
**Perceived Treatment Inefficacy**

Lack of tangible benefits contributes to discouragement and poor adherence


**Co-Pays and Oral Medications**


**Lack of Physician Trust**

Differences in prevalence of poor refill adherence for any cardiometabolic medication in a cohort of 9377 patients with diabetes. Respondents were classified as poorly adherent when they had no medication supply for >20% of the observation time.


*Trust is defined using 2 items from the Trust in Physicians Scale (TIPS) modified to match the 4-point Consumer Assessment of Healthcare Providers and Systems (CAHPS) scale options during the preceding 12 months. †Shared decision-making was determined using 2 items from the interpersonal processes of care (IPC) instrument during the preceding 12 months.
Efficacy Mirage

**MEDICATION BELIEFS**

Perceived worthwhileness: Does the patient believe the benefits of the medication outweigh the costs?

- Adverse effects
- Concerns about long-term adverse effects
- Represents “sickness”
- Rarely apparent
- HCP may state that long-term risks are reduced

**PERCEIVED BENEFITS**

**PERCEIVED COSTS**


**ROY**

Takes 2 oral medications for T2D and basal insulin; his last HbA1c was 6.8%

**SAM**

Doesn’t take any medications for T2D; his last HbA1c was 9.1%

**WHO IS DOING BETTER WITH HIS DIABETES?**

ROY. How healthy you are, and your risk of complications, is *not* determined by how much medication you take. *It is your metabolic results that matter.* Even if you are not taking pills or insulin, high blood sugars will likely lead to future problems.

**WHY DO PATIENTS FEEL THIS WAY?**

- Threatening patients with medication
  - “If you can’t make some positive changes, then we’ll have no choice but to put you on more medication, and perhaps even start insulin.”
- Underlying messages
  - More medication should be avoided at all costs
  - You have failed
  - You are to be punished

SO WHAT TO DO?

1. Ask correctly
   - “Any problems taking those medications?”
   - vs.
   - “What’s one thing about taking your medications that’s been challenging?”

2. Forgetfulness
   - “Aside from forgetting, what else is tough about taking your meds?”
   - Anchoring strategies

Anchoring Medication to Daily Events

“A daily event (a meal, TV show, bedtime, brushing my teeth) reminds me.”

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Treatment complexity
   • Simplify if possible
   • Provide additional details as needed

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Treatment complexity
4. Patient-provider trust
   • Listen, listen, listen

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
3. Treatment complexity
4. Patient-provider trust
5. Talk about beliefs about diabetes and medications
Challenging Harmful Beliefs

1. Taking your medications is one of the most powerful things you can do to positively affect your health
2. Your medications are working even if you can’t feel it
3. Needing more medication isn’t your fault
4. More medication doesn’t mean you are sicker, less medication doesn’t mean you are healthier

CONCLUSIONS

Poor medication adherence:
• ... explains a great deal of the lack of glycemic progress over the past decade
• ... is commonly an attitudinal issue, not just a behavioral issue.
• ... is best addressed by considering the patient’s perspective, and encouraging a two-way conversation about the perceived pro’s and con’s of the medication.

Thanks for Listening!

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

J. Ross Tanner, DO, FACP, Presents:
Which One, and When? Oral Medications for the Treatment of Type 2 Diabetes and Their Cardiovascular Affects
Oral Agents

Case 1: Edward
- 62 year old centrally obese male (BMI 42) with a 15-year history of type 2 diabetes also with dyslipidemia, HTN, ED, OSA, bladder cancer and CAD
- Family Hx: 3 brothers with type 2 diabetes (1 deceased/CAD)
- Notes: No home glucose monitoring data (He does not bring his meter to clinic as he “forgets” it every time)
  - Diabetes Meds: Metformin 500mg BID, glipizide 20mg BID, sitagliptin 50 mg BID, empagliflozin 10 mg QD , and glargine 100 units QHS started 6 months ago
  - Current A1c 10.5% (9.6% 1 year ago, 10.1% 2 years ago)
  - Creatinine 1.4 mg/dl, eGFR 50
  - LDL 92 mg/dl, Triglycerides 356 mg/dl, HDL 22 mg/dl

What is the most likely reason why Edward has not achieved his A1c goal?
A. He needs prandial insulin
B. He needs a GLP-1 RA
C. He is very ignorant about what to eat regarding his diabetes
D. His diabetes regimen is too complicated
E. He is most likely poorly adherent with his medications

Glycemic Target Goals for Patients with Type 2 Diabetes

<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>
Oral Agents

24-hour Glucose Profile in Patients with T2D: Both Fasting and Postprandial Glucose Contribute to the A1c

Adapted from Riddle MC. Diabetes Care. 1990;13(6):676-686. Material from this publication has been used with the permission of American Diabetes Association. Copyright and all rights reserved.

Fasting vs Postprandial Glucose: Relationship to A1C Level

FPG contribution to HbA1c is greater when HbA1c is higher
PPG contribution to HbA1c is greater when HbA1c is lower

Inflection point is ~ 8.4%

Multiple Defects Contribute to the Pathophysiology of Type 2 Diabetes Necessitating Targeted Therapy

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

Natural History of Type 2 Diabetes Is Characterized by Progressive Loss of Beta Cell Function

Macrovascular complications
Microvascular complications
Insulin resistance
Postprandial glucose
Fasting glucose

Progression of Hypoglycemia
Prediabetes
Type 2 Diabetes
Insulin resistance
Postprandial glucose
Fasting glucose

Years to Decades
Progression to Type 2 Diabetes Can be Prevented or Delayed

9 FDA-Approved Classes of Oral Medications for Type 2 Diabetes

- Metformin (first line therapy unless contraindicated)
- Sulfonylureas, meglitinides
- Glitazones (pioglitazone, rosiglitazone)
- DPP-4 inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin)
- SGLT-2 inhibitors (canagliflozin, dapagliflozin, empagliflozin, etrugslofn)
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine meslate)*
- Alpha glucosidase inhibitors (acarbose, miglitol)*

* not discussed in detail in this presentation

Clinical Treatment Pearls

- Always confirm as best you can if the patient is adherent with his 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 is the rule rather than the exception
- Always address the ABCs (A1c and Asprin 81 mg if over 50 y/o, BP <140/90 mm/Hg) and Cholesterol (LDL<100mg/dl or <70 if CAD present)
- Spending time with the patient and his support person to explain why you are starting a new medication and what benefits it will have over the long term, as well as answering any concerns will improve adherence

http://www.fda.gov
Case 2: Collin

- 52 year old centrally obese male
- 1-year history of type 2 diabetes, diagnosed with dyslipidemia and HTN
- Family History: Both Parents had type 2 diabetes, HTN and CAD
- Notes: BMI 37 (1yr ago it was 34, 2 yrs ago it was 31)
  - Diabetes therapy included only Metformin 1000 mg BID
  - Current A1c 8.5% (7.6% 6 months ago, 7.1% at diagnosis)
  - Creatinine 1.3 mg/dl, eGFR 65
  - LDL 112 mg/dl, Triglycerides 256 mg/dl, HDL 29 mg/dl

What class of agent would you add to Collin's current regimen (no one right or wrong answer)?

A. Sulfonylurea
B. DPP-4 inhibitor (sita-, saxa-, lina- or alogliptin)
C. SGLT-2 inhibitor (cana-, empa-, ertu- or dapagliflozin)
D. Basal insulin given once a day
E. GLP-1 RA (liraglutide, exenatide, dulaglutide, semaglutide)
F. Thiazolidinedione (pioglitizone)
Oral Agents

Summary Of ADA Algorithm

- **Step 1:** start with metformin unless contraindicated
- **Step 2:** Use any other option for diabetes available in the entire universe
- **Step 3:** Use any other option for diabetes available in the entire universe except what you used in steps 1 and 2
- **Step 4:** Use any other option for diabetes available in the entire universe except what you used in steps 1, 2 and 3

Is this helpful?

**Must Individualize Therapy**

**Option #1: Metformin (new info)**

- **MOA:** Reduces hepatic glucose output
- **Benefits:**
  - Significant A1c reductions (~1 to 1.5%)
  - Cost-effective for neutral effects on body weight
  - No hypoglycemia
  - Generic (low cost)
- **Concerns:**
  - GI side effects (often dose-related), sustained release formulations may help
  - Contraindicated in chronic renal insufficiency see below
  - Potential for lactic acidosis (rare)
- **Clinical Pearls:**
  - Start with low dose and up-titrate dose to improve GI tolerance or use long acting release formulation
  - eGFR <60 to ≥45 OK to use/monitor kidneys
  - eGFR <45 to ≥30 OK to use 50% maximum dose/monitor kidney function every 3 months
  - If you stop metformin, substitute with a different agent
  - Check B-12 levels

**Option #2: Insulin Secretagogues (sulfonylureas / meglitinides)**

- **Mechanism of Action:**
  - Stimulate the pancreas to secret insulin
- **Benefits:**
  - A1c reductions (~1.0 to 1.5%)
  - Quickly lower glucose/A1c
  - Generic (very low cost, pennies per day)
- **Concerns:**
  - High 2nd failure rate, however when you stop them the patient’s A1c typically goes up.
  - Weight gain
  - Increase risk of hypoglycemia (elderly, CRI, CAD)
- **Clinical Pearls:**
  - Use shorter-acting SFU (e.g., glipizide) to reduce hypoglycemia risk
  - May be more effective in lower doses as an ‘add-on’ medication (combination therapy)

Is this helpful?
**Generic and Trade Names**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nateglinide</td>
<td>Starlix</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Prandin</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>Amaryl</td>
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<tr>
<td>Glipizide</td>
<td>Glucotrol</td>
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<tr>
<td>Glyburide</td>
<td>Glucotrol XL</td>
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<tr>
<td></td>
<td>DiaBeta</td>
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<td></td>
<td>Micronase</td>
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<td>Glynase PressTab</td>
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</table>

**Option #3: Glitazones (pio-, rosiglitazone)**

*(New info in red)*

**Mechanism of Action**
- Reduce insulin resistance

**Benefits**
- No hypoglycemia
- Durable glycemic control
- Positive effect on lipids ($HDL-C$, converts small dense to large buoyant $LDL-C$)

**Concerns**
- Weight gain, edema
- Edema (precipitating CHF)
- Bone fractures primarily in Caucasian women
- Risk of bladder cancer has been disproven

**Clinical Pearls**
- Effective in prediabetes, best used early in the natural history
- Be cautious in combo with insulin (fluid retention)

**Case 3: Jamie**
- 42 year old AA obese male
- Type 2 diabetes diagnosed at age 35
- PMH: HTN, dyslipidemia
- FH: T2DM, early CAD
- A1c 8.3% on maximum doses of metformin and SFU
- No home glucose monitoring data; “forgets” his meter and log book when he comes to clinic
- Creatinine 1.4 mg/dl, eGFR 55, BMI 36
- BP normally above 140/90 mmHg; on no HTN meds
What therapeutic intervention would you change/initiate if you were evaluating Jamie once you have confirmed he is adherent with his medications?

A. Initiate basal insulin therapy
B. Add a DPP4 inhibitor
C. Add a SGLT2 inhibitor
D. Add a GLP1-RA
E. Intensify lifestyle modification and education

Case 3: Jamie (continued)

- Treatment History
  - A DPP-4 inhibitor was added to his regimen
  - He was sent to a CDE with his wife
  - Follow up was arranged for one month instead of the usual 3 to 4 months
  - Jamie did well without weight gain or hypoglycemia
  - The A1c fell to 7.4%
  - His PCP eventually started an ACE inhibitor to get his BP below 140/90 mm/Hg and a statin to get his LDL <100 mg/dl
  - It took almost 12 months to get his A1c, BP and lipids at goal as he was resistant to starting new medications.

Option #4: DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Inhibit the enzyme, DPP-4, that normally inactivates GLP-1 and other incretins within minutes</th>
</tr>
</thead>
</table>
| 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  
                        * Rare reports of hypersensitivity skin reactions  
                        * No association or signal for pancreatitis and pancreatic cancer (2013 FDA hearing on pancreatic cancer and incretins) |
| 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) |
### Generic and Trade Names

<table>
<thead>
<tr>
<th>DPP4-Inhibitors</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alogliptin</td>
<td>Nesina</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Tradjenta</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
<td>Onglyza</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
<td>Januvia</td>
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</tbody>
</table>

### Mechanism of Action of DPP-4 Inhibitors

- **Release of active incretins (GLP-1 and GIP)**
  - GLP-1: glucagon-like peptide-1
  - GIP: glucose-dependent insulinotropic polypeptide

- **Primarily postprandial but also FBS**
  - Ingestion of food
  - Glucagon
  - Hepatic glucose production
  - GI tract
  - DPP-4 enzyme
  - Inactive GLP-1
  - Alogliptin
  - Linagliptin
  - Saxagliptin
  - Sitagliptin (DPP-4 inhibitors)

- **Insulin dependent**
  - Glucose uptake by peripheral tissue

### Combination Pills With A DPP-4 Inhibitor

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Daily Dose Range (mg)</th>
<th>Recommended Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin/metformin</td>
<td>Janumet</td>
<td>50/500, 50/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Saxagliptin/metformin</td>
<td>Kombiglyze XR</td>
<td>2.5/1000, 5/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Linagliptin/metformin</td>
<td>Jentadueto</td>
<td>2.5/500, 5/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Sitagliptin/empagliflozin</td>
<td>Glyxambi</td>
<td>5/10, 5/25</td>
<td>Once daily</td>
</tr>
<tr>
<td>Saxagliptin/saxagliptin</td>
<td>Qtern</td>
<td>10/5 mg, 10/2.5 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Alogliptin/peglizone</td>
<td>Oseni</td>
<td>15 mg, 25 mg, 37.5 mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Sitagliptin/riboglitazone</td>
<td>Kazan</td>
<td>12.5/150, 25/250</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Ertugliflozin/sitagliptin</td>
<td>Steglujan</td>
<td>5/100, 15/100</td>
<td>Once daily</td>
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</tbody>
</table>
Oral Agents

Usage and Indications
- Use with diet and exercise to improve glycemic control in type 2 diabetes
- Combination studies with SUs, WTs, pioglitazone and insulins

Dosage Administration
- Once daily, with or without food
- Tablets: 25mg, 12.5mg (CrCl <50), & 6.25mg (CrCl <30)
- Once daily, with or without food
- Tablets: 5mg
- No dose adjustment needed for renal function
- Once daily, with or without food
- Tablets: 5mg & 2.5mg (CrCl <50)
- Once daily, with or without food
- Tablets: 100mg, 50mg (CrCl <50), & 25mg (CrCl <30)

Contraindications
- Hypersensitivity (i.e., urticaria, angioedema, or bronchial hyperreactivity)
- Hypersensitivity (i.e., anaphylaxis or angioedema)

Warnings and Precautions
- When used with a SU or insulin, a lower dose of SU or insulin may be needed to reduce the risk of hypoglycemia
- Post-marketing reports of pancreatitis (D/C if suspect pancreatitis; use with caution in patients with history of pancreatitis)

Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Alogliptin</th>
<th>Linagliptin</th>
<th>Saxagliptin</th>
<th>Sitagliptin</th>
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</thead>
<tbody>
<tr>
<td>Usage and Indications</td>
<td>Combination studies with SUs, WTs, pioglitazone and insulins</td>
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<tr>
<td>Dosage Administration</td>
<td>Once daily, with or without food</td>
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<td>Tablets: 25mg, 12.5mg (CrCl &lt;50), &amp; 6.25mg (CrCl &lt;30)</td>
<td>Tablets: 5mg &amp; 2.5mg (CrCl &lt;50)</td>
<td>Tablets: 100mg, 50mg (CrCl &lt;50), &amp; 25mg (CrCl &lt;30)</td>
<td></td>
</tr>
<tr>
<td>Contraindications</td>
<td>Hypersensitivity</td>
<td>Hypersensitivity</td>
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<td>Hypersensitivity (i.e., anaphylaxis or angioedema)</td>
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</tbody>
</table>

Case 4: Susan
- 58 year old obese female
- Type 2 diabetes diagnosed 10 years ago
- A1c 8.7% (one year ago it was 8.2%) and adamantly refused any injectable agent
- On max. doses of metformin and a DPP4-inhibitor
- Family History: Type 2 diabetes and obesity (both parents)
- Notes:
  - Very fearful of injections and gaining weight
  - Normal renal function, BMI 31kg/m²
  - HGM shows FBS (137–221 mg/dl), and a few post dinner values (187 to 265mg/dl)

How would you treat Susan to lower her A1c?
- A Add a SU
- B Add a TZD
- C Start a SGLT-2 inhibitor (cana-, dapa-, empa-
- D Try to convince her to add a GLP-1 receptor agonist (exenatide, liraglutide, dulaglutide, semaglutide)
- E Try to convince her to add a basal insulin at bedtime
Oral Agents

**Option #5: SGLT-2 Inhibitors**

**Mechanism of Action**
- Reduces 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 diuretic use and in patients reduced renal function.
- 4 to 8% elevation in LDL cholesterol (TGs goes down and HDL goes up)
- Assess renal function (discussed later)
- New label warnings: DKA (discussed later)/bone fractures/risk of amputation EXCLUDED LATER WITH CVOT DATA

**Clinical Pearls**
- 1st oral medication that leads to statistically significant weight loss
- Empa-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 Monistat)

**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></td>
<td>Invokana</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td></td>
<td>Farxiga</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td></td>
<td>Jardiance</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td></td>
<td>Steglatro</td>
</tr>
</tbody>
</table>

- **Canagliflozin**:
  - Suggested starting dose 100 mg daily before first meal of day (eGFR > 45mL/min)
  - Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min
- **Dapagliflozin**:
  - Starting dose 5 mg daily in morning with or without food (eGFR for both doses > 60)
  - Increase to 10 mg daily if tolerating and need additional glycemic control
- **Empagliflozin**:
  - Starting dose 10 mg daily in morning with or without food (eGFR > 45)
  - Increase to 25 mg daily if tolerating and need additional glycemic control (eGFR > 45)
- **Ertugliflozin**:
  - Starting dose 5 mg daily in morning with or without food (eGFR for both doses > 45)
  - Increase to 15 mg daily if tolerating and need additional glycemic control

**Glucose Handling in a Non-Diabetic Individual**

- 180 g/day/1.73 m² is filtered glucose load
- SGLT-2 transports 90% of filtered glucose out of the tubular lumen

**References**
Reduced Renal Glucose Reabsorption In Type 2 Diabetes With SGLT-2 Inhibition

Renal Glucose Reabsorption In Normal, Type 2 DM And With SGLT-2 Inhibition

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
2. Many but not all of the reports for DKA were in patients with LADA
3. Be especially cautious in insulin using patients (since glucagon levels go up with SGLT2s and by lowering the insulin too much an imbalance of glucagon to insulin may occur, leading to DKA)
4. Be especially cautious in women with a history of UTIs, pyelonephritis and/or genital mycotic infections
Oral Agents

Case 4: Susan continued
- Low dose SGLT–2 inhibitor was added to her regimen and then titrated to the maximum dose after one month
- A1c dropped to 7.5% (baseline 8.7%) and she lost 15 lbs
- She was more motivated to improve her lifestyle habits and her A1c came down to 7.2% over the next 4 months
- She experienced a yeast infection which was easily treated with a topical antifungal and she did not want to stop the SGLT2 inhibitor
- She also said she had increased urination in the mornings for the first few weeks but that stopped
- LDL went from 100 to 108 mg/dL (8% rise) and her TGs dropped by 25%

Which of the following statement is true regarding SGLT-2 inhibitors?

A They are contraindicated with loop diuretics and a history of DKA
B They should not be used in women or men with a history of UTIs
C They can be used safely with pioglitazone and GLP-1 RAs
D They are approved for both type 1 and type 2 diabetes
E Men who are not circumcised should not use them

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 Stroke or cerebrovascular disease
D Complications from obesity
E Peripheral arterial disease
Causes of Mortality in Patients With Diabetes 20 years Ago: The same Trend Exists in 2017

55% Heart Disease

Most Common Causes of Death in People With Type 2 Diabetes: It is not eye, kidney or nerve disease!

Almost 80% do to any type of heart disease and stroke

Primary Objectives of Effective Management

General goal is < 7% but must be individualized

Reduction of eye, kidney, nerve and heart disease by 75%

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)
### Impact of Intensive Glucose-Lowering Therapy in DM: Summary of Major RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS 33</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓ (6.4% vs. 7.5%)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓ (6.3% vs. 7.0%)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VADT</td>
<td>↓ (6.0% vs. 8.4%)</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>


### The Etiology Of The CVOTs: a flawed meta analysis published in the NEJM by Steve Nissen and later discredited

### Large Non-Insulin CVOTs in T2DM 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>sulfonylurea</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>2013</td>
<td>2013</td>
<td>June 2015</td>
<td>2017</td>
<td>2017</td>
</tr>
</tbody>
</table>

*Adapted: Zoungas S. NEJM 2014;371:1392; Hayward RA NEJM 2015;372:23

**Large Non-Insulin CVOTs in T2DM DPP-4 Inhibitors**

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**The Etiology Of The CVOTs: a flawed meta analysis published in the NEJM by Steve Nissen and later discredited**

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**Large Non-Insulin CVOTs in T2DM DPP-4 Inhibitors**

---

**Impact of Intensive Glucose-Lowering Therapy in DM: Summary of Major RCTs**

---


### Large Non-Insulin CVOTs in T2DM

#### GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUB LARINA</th>
<th>EXSEL</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>liraglutide</td>
<td>lixisenatide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
</tr>
<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>14,000</td>
<td>6,000</td>
<td>5,400</td>
<td>8,300</td>
</tr>
<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
</tr>
</tbody>
</table>

- ** Comparator: placebo, placebo, placebo, placebo, placebo.

### Large Non-Insulin CVOTs in T2DM

#### SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>NCT01986851</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</td>
<td>2017</td>
<td>2019</td>
<td>2020</td>
</tr>
</tbody>
</table>

- ** Comparator: placebo, placebo, placebo, placebo.

### EMPA-REG CVOT: Primary outcome (3-point MACE): CV Death, Non Fatal MI and Stroke

- ** Primary Outcome:** CV Death, Non Fatal MI and Stroke
- ** P:** 0.0014
- ** P:** 0.001
- ** P:** <0.001
- ** P:** <0.002

- ** Example of how the CVOT data is reported:**

- ** Death from CV causes:** P<0.001
- ** Death from any cause:** P<0.001
- ** Hospitalizations from CHF:** P<0.002

---

**N Engl J Med 2015; 373:2117-2128**
Oral Agents

Real-World CV Study on SGLT-2 Inhibitors (CVD reduction may be a class effect?)

- CVD-REAL study assessed data from 300,000+ patients
  - 87% did not have history of CV disease
- Reduced rate of hospitalization for heart failure by 39% and all-cause mortality by 51%

https://doi.org/10.1161/CIRCULATIONAHA.117.029190
Circulation. 2017;CIRCULATIONAHA.117.029190
Originally published May 18, 2017

New FDA Indication for Diabetes Medications

- Diabetes medications FDA approved for CV risk reduction
  1. Empagliflozin (based on EMPA-REG data)
     - Reduction in risk of CV death in patients with type 2 diabetes and established CV disease
  2. Liraglutide (based on LEADER data)
     - Reduction in risk of major CV events in patients with type 2 diabetes and established CV disease
     - Canagliflozin and semaglutide under review

New FDA Warning for Diabetes Medications

- FDA warning for lower limb amputation
- 2 fold increase in amputation in the CANVAS CVOT trial.
- Relative risk 0.63 (canagliflozin) vs 0.34 (placebo) amputations per 100 patient years
- No increased risk of amputation in the phase 3 clinical trial program (~10,000 patients)
17

Oral Agents

Not All CVOTs Are Created Equal

- Differences in study design: powered for safety or superiority
- Patient characteristics: age, weight, co-morbid complications, presence of CAD
- Comparators may be different
- Weigh gain and hypoglycemia differences
- Time to first event
- Regional differences
- Outcomes differ: overall mortality, non fatal and fatal MI, stroke, etc.
- Adherence may effect results

Courtesy of Mikael Kosiborodi MD, Saint Luke’s

Key Principles of Management of Type 2 Diabetes

- Glycemic targets & glucose-lowering therapies should be individualized
- Diet, exercise and education are the foundations of therapy
- Unless contraindicated, metformin is optimal 1st line drug
- After metformin, combination therapy with 1-3 other oral and/or injectable agents; minimize side effects
- Many patients over time will require insulin therapy alone or in combination with other agents to maintain glycemic control
- CAD is the most common cause of death and prevention strategies need to be emphasized

Key Principles of Management of Type 2 Diabetes

Lecture 3: 1:15 – 2:15 p.m.

Melissa Magwire, RN, CDE, Presents:
Clinical Applications of Injectable Agents:
GLP-1 Receptor Agonists, Basal Insulin and More Intensive Regimens
Injectable Agents

Case 1: Eric
- 47 yr.-old centrally obese (BMI 32) male
- with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP-4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several times

He tests 2 to 4 times a week

<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>166 – 231 mg/dL</td>
<td>~182 mg/dL</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>143 – 197 mg/dL</td>
<td>~177 mg/dL</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>112 – 275 mg/dL</td>
<td>~213 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>159 – 231 mg/dL</td>
<td>~194 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia

Which of the following would you recommend for Eric if he were your patient?

A. Initiate basal insulin
B. Initiate a GLP-1 RA
C. Initiate a basal bolus insulin regimen
D. Initiate a fixed combination of a basal insulin and a GLP-RA

This exact question will be repeated at the end of the lecture.
### Injectable Agents

**Basal Insulin vs GLP-1 RA**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Basal Insulin</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosing frequency</td>
<td>Once or twice a day</td>
<td>Once a day or once weekly</td>
</tr>
<tr>
<td>Need to titrate dose targeting FBS</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Need to institute home glucose monitoring (SMBG)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Important to have frequent follow up when initiating basal insulin (days to weeks)</td>
<td>Yes</td>
<td>Follow up not as crucial</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No Hypoglycemia</td>
<td>No Hypoglycemia</td>
</tr>
</tbody>
</table>

---

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

- Healthy Subjects ($n=14$) vs Type 2 Diabetes ($n=12$)

---

**The Incretin Effect and Its Reduction in Type 2 Diabetes: Insulin secretion after oral versus IV glucose**

- Control Subjects vs Patients With Type 2 Diabetes
GLP-1 Effects: Glucoregulatory Role of Incretins

*GLP-1 secreted upon the ingestion of food*

- **Satiety & appetite control**
- **Pancreatic beta cells:** Enhanced glucosedependent insulin secretion
- **Liver:** Reduced hepatic glucose output
- **Pancreatic alpha cells:** Decreased postprandial glucagon secretion
- **Stomach:** Helps regulate gastric emptying

GLP-1 Effects: Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Insulin (pmol/L)</th>
<th>Glucagon (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>220</td>
<td>80</td>
<td>20</td>
</tr>
<tr>
<td>180</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>90</td>
<td>140</td>
<td>5</td>
</tr>
<tr>
<td>0</td>
<td>105</td>
<td>1</td>
</tr>
</tbody>
</table>

Placebo Glucose (mg/dL)

- 270
- 180
- 90
- 0
- -30
- 0
- 60
- 120
- 180
- 240

GLP-1 Glucose (mg/dL)

- 200
- 150
- 100
- 50
- 0
- -50
- -100
- -150
- -200
- -250

**Type 2 Diabetes (n = 10)**

- Human GLP-1 given via an insulin pump

References:

**Exenatide vs Insulin Studies:**

- **A1c and Weight**
- P=NS for A1c reductions
- P<0.05 for weight differences

**Change in Weight (lb)**

- +4.0 lb
- +5.1 lb
- -5.1 lb
- -4.9 lb
- +6.6 lb
- +5.1 lb
- +6.0 lb
- +6.4 lb

**Change in A1c (%)**

- +1.1%
- +1.4%
- +1.1%
- +1.4%
- +1.3%
- +1.6%
- +1.5%
- +1.8%
- +2.2%
- +2.5%
- +2.8%

**Exenatide vs Insulin Glargine**

- Exenatide vs Glargine + MET or SFU
- Exenatide vs Insulin + MET +/- TZD +/- SFU
- Exenatide vs Aspart 70/30

**ADA GOAL**

- -1.3%
- -0.7%
- -0.8%
- -0.9%
- -1.0%

**N=138 Crossover**

- n=36
- n=33
- n=118
- n=116
- n=253
- n=248
- n=228
- n=242

Injectable Agents 3
GLP-1 Receptor Agonists

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

**Benefits**
- Significant A1c reductions (1.0 to 2.0%)
- Shorter acting GLP-1 RAs have greater effects on PPG
- Statistically significant weight loss
- No hypoglycemia due to GLP-1 RA directly
- Once 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
- One of the most powerful agents for type 2 diabetes

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

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Bydureon</td>
</tr>
<tr>
<td></td>
<td>Byetta</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>Trulicity</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Adlyxin</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Soliqua, iGlarLixi</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Xultophy, iDegLira</td>
</tr>
</tbody>
</table>

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

1. TECHNOLOGY
   - Previously-approved delivery system
   - Short office procedure
   - Small micropump
   - Maintains stability at temps ≤37°C
   - Maintains stability for ≥12 months

2. MEDICINE: EXENATIDE
   - Previously-approved GLP-1
   - Exenatide
   - Glycemic control
   - Weight loss
   - Safety

Not yet approved by the FDA
Injectable Agents

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

**TECHNOLOGY**
- Previously approved delivery system
- Small micropump
  - Maintains stability at temps = 37°C
  - Maintains stability for > 12 months

**MEDICINE: EXENATIDE**
- Previously approved GLP-1 therapeutic with demonstrated:
  - Glycemic control
  - Weight loss
  - Safety

Not yet approved by the FDA

---

**Case 2: Megan**
- Megan is a 39 year old female with a 4 year history of type 2 diabetes
- On maximal doses of metformin, SFU, and a DPP-4 inhibitor
- She adamantly does not want to take insulin
- PMH: dyslipidemia, hypertension, OSA, PCOS and overweight (BMI 29)
- eGFR 75 ml/min
- Her A1c for the past 18 months has been ~8.5%

---

**What would you recommend now for Megan?**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td>Start a SGLT2 inhibitor</td>
</tr>
<tr>
<td><strong>B</strong></td>
<td>Try to convince her to start basal insulin</td>
</tr>
<tr>
<td><strong>C</strong></td>
<td>Start a GLP-1 receptor agonist and discontinue the DPP-4 inhibitor</td>
</tr>
<tr>
<td><strong>D</strong></td>
<td>Start a fixed combination of a basal insulin and a GLP-RA</td>
</tr>
</tbody>
</table>
Case 2: Megan (continued)

- She agreed to start a GLP-1-RA (Exenatide [once-weekly], Liraglutide, Dulaglutide, Semaglutide or Lixisenatide).
- If prescribing Exenatide [once-weekly], it is important to tell the patient that it takes 6–8 weeks to reach equilibration and may see skin nodules.
- She experienced no nausea or hypoglycemia. Over the next three months.
- She lost 14 pounds and her A1c fell from 8.6% to 7.3%.

What is this patient’s A1c goal?

* Increased frequency of SMBG testing not a requirement with GLP-1 receptor agonists.

---

Fixed Combinations Of Basal Insulin and GLP-1 Receptor Agonist

**Insulin Degludec/Liraglutide (Xultophy) and Insulin Glargine/Lixisenatide (Soliqua)**

1 unit of insulin degludec/liraglutide has 0.036 mg of liraglutide (maximum dose is 50 iDeg/1.8mg lira)

1 unit of insulin glargine/lixisenatide has 0.33 mcg lixisenatide (maximum dose is 60 iGlar/20 mcg lixi)

---

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

<table>
<thead>
<tr>
<th>100 units/ml of Insulin degludec</th>
<th>1.8 mg/ml of liraglutide</th>
<th>100 units/ml of Insulin glargine</th>
<th>3.3 mcg/ml of lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 units of insulin degludec has 0.16 mgs of liraglutide</td>
<td>15 units of insulin glargine has 5 mcg of lixisenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>90 units of insulin degludec has 1.8 mgs of liraglutide</td>
<td>10 units of insulin glargine has 10 mcg of lixisenatide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 units of insulin glargine has 20 mcg of lixisenatide</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Starting dose:

- 15 units of insulin degludec which has 0.56 mgs of liraglutide

Starting dose:

- If glargine U-100 dose is <30, start at 15 units of combo

- If glargine U-100 dose is >30 units, start with 50 units

Titrate as if you were using basal insulin alone

Maximum dose is 50 units of Insulin degludec and 1.8 mgs of liraglutide

Maximum dose is 60 units of Insulin glargine and 20 mcgs of lixisenatide

---

Injectable Agents 6
Injectable Agents

**Fixed-Ratio Combination of Insulin Degludec and Liraglutide**

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

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

**A1c Over Time: 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%

*p<0.0001 vs. iDeg and vs. Liraglutide*
Injectable Agents
Gastrointestinal Side Effects
Post hoc analysis: DUAL II and IV

- Subjects experiencing nausea, vomiting or diarrhea (%)
- Time since randomisation (weeks)

DUAL VII – Open-label trial comparing iDeg/Lira to basal-bolus insulin therapy (Glargine + Aspart) for 26 weeks

- iDeg/Lira was non-inferior to basal-bolus for glycemic control
  - Mean A1c reduction from 8.2 to 6.7% in both groups

- iDeg/Lira was associated with:
  - Lower insulin doses (40.1 units for iDeg/Lira group compared to 84.6 units in basal-bolus)
  - Less hypoglycemia: 89% less severe or symptomatic confirmed hypoglycemia compared to basal-bolus
  - Mean weight loss (0.9kg) versus weight gain (2.6kg) with basal-bolus

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

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

Injectable Agents
**Efficacy of Fixed-Ratio iGlarLixi in T2DM Patients Not Controlled on Basal Insulin**

T2DM patients not controlled on basal insulin + Met ± 2 OADs

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline Mean A1C (%)</th>
<th>24 Week Mean Difference</th>
<th>p-value</th>
<th>Baseline Mean A1C (%)</th>
<th>24 Week Mean Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>9.0</td>
<td>-0.52%</td>
<td>&lt;0.0001</td>
<td>7.0</td>
<td>-0.52%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12</td>
<td>8.5</td>
<td>-0.52%</td>
<td>&lt;0.0001</td>
<td>6.5</td>
<td>-0.52%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Fixed-Ratio iGlarLixi in T2DM Patients Not Controlled on Basal Insulin: Glucose and Weight Effects**

<table>
<thead>
<tr>
<th>Meal Change from Baseline (mg/dL)</th>
<th>Glargine (N = 365) Mean</th>
<th>iGlarLixi (N = 366) Mean</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>-8.1</td>
<td>-8.3</td>
<td>p = NS</td>
</tr>
<tr>
<td>2-h PPG Excursions</td>
<td>-8.4</td>
<td>-8.3</td>
<td>p &lt; 0.0001</td>
</tr>
</tbody>
</table>

**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 hypo) than adding prandial insulin.
Injectable Agents

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>Regular U-500 Regular Aspart</td>
<td>Humulin R, Novolin R</td>
<td>Humulin R U-500 Novolog Fiasp Apidra Humalog Afrezza</td>
</tr>
<tr>
<td>Faster Acting Aspart Lispro (U-100 and U-200)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulated insulin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Basal Insulin | Intermediate-Acting NPH | Long-Acting: Detemir Glargine (U-100) Glargine (U-300) Degludec (U-100/200) Follow-On Biologic Basaglar |
|--------------|-------------------------|------------------|------------------|------------------|
|              | Humulin N Novolin NPH Levemir Lantus Toujeo Tresiba | |

Time Action Profiles: Traditional Insulins

- **Rapid-acting**
  - Onset: 10-15 mins
  - Peak: 60-90 mins
  - Duration: 4-5 hr

- **Regular**
  - Onset: 30-60 mins
  - Peak: 2-4 hours
  - Duration: 5-8 hr

- **NPH**
  - Onset: 1-3 hr
  - Peak: 5-8 hours
  - Duration: 12-18 hr

- **Detemir**
  - Onset: 90 mins
  - Peak: Relatively peakless
  - Duration: 12-24 hr

- **Glargine**
  - Onset: 90 mins
  - Peak: Relatively peakless
  - Duration: 24 hr

Inhaled insulin: peak by 10-15 min, duration of 2-3 hrs.

Shortcomings of Basal Insulins Include:

- Hypoglycemia resulting in:
  - Insulin under-dosing
  - Insufficient glycemic control
- Weight gain
- Inconsistent insulin action...leading to inconsistent blood glucose levels
- Not enough flexibility with timing of injections
- Insufficient duration of action...therefore, requiring a minimum of 1 and, sometimes, 2 injections/day
- Large volume injections required for some patients
Two New Basal Insulins Recently Added To Our List Of Options

1. U-300 glargine a long-acting basal insulin
2. U-100 and U-200 degludec a long-acting basal insulin

May need 13 to 17% more than previous dose of glargine U-100 (Lantus), Beeker RH, et al. Diabetes Care. 2015;4;639-643.

GIR, mg/kg/min

Pharmacodynamics of Insulin Degludec®
U-100 and U-200 in Patients with T2DM:

Same time course of action

<table>
<thead>
<tr>
<th></th>
<th>U-100 Formulation</th>
<th>U-200 Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.8 U/kg</td>
<td>0.6 U/kg</td>
</tr>
<tr>
<td></td>
<td>0.6 U/kg</td>
<td>0.6 U/kg</td>
</tr>
<tr>
<td></td>
<td>0.4 U/kg</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacodynamics of Insulin Degludec®


PK/PD Profile with Glar U300 vs Glar U100

U300 glargine (Toujeo) has a more even and prolonged PK/PD profile.

A 56 year-old female diagnosed with type 2 diabetes 6 years ago. Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, glipizide 20 mg BID and linagliptin 5 mg QD.

“Refused” to start insulin for years (afraid of weight gain), but a few months ago did try 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

Current SMBG (mg/dl) below:

<table>
<thead>
<tr>
<th>Case 3: Jennifer</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1c &gt; 8.5%</strong></td>
</tr>
<tr>
<td><strong>Pre-Breakfast</strong></td>
</tr>
<tr>
<td><strong>Pre-Lunch</strong></td>
</tr>
<tr>
<td><strong>Pre-Dinner</strong></td>
</tr>
<tr>
<td><strong>Bedtime</strong></td>
</tr>
<tr>
<td><strong>Monday</strong></td>
</tr>
<tr>
<td>211</td>
</tr>
<tr>
<td>247</td>
</tr>
<tr>
<td>181</td>
</tr>
<tr>
<td>226</td>
</tr>
<tr>
<td><strong>Tuesday</strong></td>
</tr>
<tr>
<td>211</td>
</tr>
<tr>
<td>247</td>
</tr>
<tr>
<td>181</td>
</tr>
<tr>
<td>226</td>
</tr>
<tr>
<td><strong>Wednesday</strong></td>
</tr>
<tr>
<td>211</td>
</tr>
<tr>
<td>247</td>
</tr>
<tr>
<td>181</td>
</tr>
<tr>
<td>226</td>
</tr>
<tr>
<td><strong>Thursday</strong></td>
</tr>
<tr>
<td>211</td>
</tr>
<tr>
<td>247</td>
</tr>
<tr>
<td>181</td>
</tr>
<tr>
<td>226</td>
</tr>
</tbody>
</table>

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

- A. Patient fear of insulin
- B. Health care provider inertia
- 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 at meal time when indicated. (may only needed to be given with the largest meal).
- Self-monitoring of blood glucose (SMBG) is an important tool 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)

Combination Therapy: 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)
- Slow, safe, and simple titration
- Low dosage compared to a full insulin regimen
- Limited weight gain – especially compared to insulin only regimens
- Effective improvement in glycemic control by suppressing hepatic glucose production

Case 4: Rick
- 61 yr. old overweight (BMI 30, 220lbs) male
- Type 2 diabetes diagnosed 9 years ago
- History of CAD s/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 and a DPP-4 inhibitor (100mg sitagliptin), 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

What is this patient’s A1c goal?
Case 4: Rick (continued)

- eGFR 45 ml/min, normal LFTs
- PMH: HTN, dyslipidemia, OSA, CAD, pancreatitis, ED
- Other meds: ACE inhibitor, clopidogrel, atorvastatin, HCTZ and tadalafil, carvedilol, and several vitamin supplements
- Loves to eat at fast food restaurants
- I asked him to test once a day at different times

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range (mg/dL)</th>
<th>Blood glucose average (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>148 – 229</td>
<td>~175</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>121 – 182</td>
<td>~142</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>91 – 155</td>
<td>~139</td>
</tr>
<tr>
<td>Bedtime</td>
<td>148 – 231</td>
<td>~184</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia

Which of the following would you suggest for Rick if he were your patient?

A. Work on lifestyle and no medication addition
B. Initiate basal insulin
C. Start a GLP-1 RA and stop his DPP-4 inh.
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
I asked him to test 2x/day (pre-breakfast and bedtime)
It is important to make sure the patient is not going to bed high

Pre-Breakfast 82 – 155 mg/dL (~122 mg/dL)
Pre-Lunch ---- ----
Pre-Dinner ---- ----
Bedtime 128 – 183 mg/dL (~155 mg/dL)

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 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

*Once daily may not be recommended for the new longer acting basal insulins (U300 glargine and degludec)

Second Pitfall in Initiating And 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.

†Dosage was not increased that week if there were any episodes of documented hypoglycemia (<72 mg/dL) during the preceding week.

FPG, fasting plasma glucose.


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

*Adjust dose subsequently to patient’s needs.

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.

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.


65 year old female on triple oral agent therapy (SFU, met, DPP-4 inhibitor) was started on 10 units of insulin glargine (U-100) qAM in July 2011

- FPG ~ 220 mg/dL, A1c 8.5 %, wt = 176 lb
- Insulin glargine (U-100) was titrated to 45u qAM from July 2011 to November 2011
- FPG 78–132 mg/dL, A1c = 7.4%, wt = 181 lbs, eGFR 62

Patient was asked to test more frequently than usual for 3 to 4 days before meals and bedtime (pattern testing)

<table>
<thead>
<tr>
<th>July 2011</th>
<th>November 2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c (%)</td>
<td>8.5</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>220</td>
</tr>
</tbody>
</table>

Case 4: Angela (cont)

65 year old woman on glargine (U–100) and 3 oral agents: SMBG data

<table>
<thead>
<tr>
<th></th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>101</td>
<td>124</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>132</td>
<td>146</td>
<td>109</td>
<td>214</td>
</tr>
<tr>
<td>Wednesday</td>
<td>98</td>
<td>111</td>
<td>89</td>
<td>229</td>
</tr>
<tr>
<td>Thursday</td>
<td>78</td>
<td>----</td>
<td>121</td>
<td>201</td>
</tr>
</tbody>
</table>

---- = did not test
Which of the following would you recommend for Angela at this point?

<table>
<thead>
<tr>
<th></th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>101</td>
<td>124</td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>Tuesday</td>
<td>132</td>
<td>146</td>
<td>109</td>
<td>214</td>
</tr>
<tr>
<td>Wednesday</td>
<td>98</td>
<td>111</td>
<td>89</td>
<td>229</td>
</tr>
<tr>
<td>Thursday</td>
<td>78</td>
<td></td>
<td>121</td>
<td>201</td>
</tr>
</tbody>
</table>

A. Increase basal insulin  
B. Switch to premix insulin at dinner  
C. Intensify regimen by adding rapid acting insulin at dinner  
D. SGLT-2 inhibitor

Case 5: Angela (cont)

- Dinnertime bolus added:
  - Patient was started on 5 units of rapid-acting insulin analog at dinnertime and titrated up to 15 units over a few weeks based on the bedtime blood glucose levels (initial dose can be ~10% of the total basal dose). Other options include Lispro, Aspart or Inhaled Insulin
  - The basal insulin dose (Glargine [U-100] 45 units) was titrated downward to 40 units on initiation of rapid-acting insulin based on the patient’s near normal fasting blood glucose levels in order to avoid nocturnal/fasting hypoglycemia

- SMBG values on glargine (U-100) 40 units at bedtime; Lispro 15 units pre-dinner

<table>
<thead>
<tr>
<th></th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wednesday</td>
<td>86</td>
<td></td>
<td></td>
<td>125</td>
</tr>
<tr>
<td>Thursday</td>
<td>131</td>
<td></td>
<td>143</td>
<td>188</td>
</tr>
<tr>
<td>Friday</td>
<td>98</td>
<td>122</td>
<td></td>
<td>121</td>
</tr>
<tr>
<td>Saturday</td>
<td>112</td>
<td></td>
<td>134</td>
<td>169</td>
</tr>
</tbody>
</table>

- A1c fell from 7.4% to 6.8%.
- Angela experienced occasional mild hypoglycemia.

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

- **Step 1**: U-100/300 Glargine, det., deg or NPH @ HS
- **Step 2**: Add FA analog, Inhaled Insulin, Main meal
- **Step 3**: Add FA analog, Inhaled Insulin, Next largest meal
- **Step 4**: Add FA analog, Inhaled Insulin, Last meal

Above target:
- A1c > 7.0%
- FPG > 130 mg/dL

Above target:
- A1c < 7.0%, FPG < 130 mg/dL

---

**Memoir & Kwikpen**

- NovoPen Echo & FlexTouch
- SoloStar

Convenient
Discreet
Protect insulin from light, heat and agitation

---

**Shortcomings of Existing Bolus Insulins Include**

- Not rapid enough:
  - Leading to mismatch between peak postprandial glucose and peak insulin action
  - Need to take up to ½ hour before eating
- Lasts too long...leading to delayed hypoglycemia
- Inconsistent action leading to inconsistent blood glucose levels

---

Inhaled Insulin

- Better post meal glucose values
- Less delayed hypoglycemia

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

2 hour PG levels in T1D on Pump therapy after a standardized meal comparing Aspart with Faster-Acting Aspart

Vgo Patch Pump For Type 2 diabetes

- Simple, easy to use basal-bolus insulin delivery device
- Uses a single insulin (glulisine, lispro, aspart, or Regular)
- Convenient for patients
- Fill, apply and remove every 24 hours
- No electronics, batteries, infusion sets, or programming
- Fully disposable

For the continuous subcutaneous delivery of insulin in pre-set basal rates and with on-demand bolus dosing for adult patients requiring insulin
Injectable Agents

**T:flex**
Holds Almost
500 Units Of Insulin

**Calibra Finesse**
Patch Pump For Type 2 diabetes

- Simple, easy to use bolus only delivery device
  - Holds 200 units
  - Delivers 2 units at a time (button)
  - Fill, apply and remove 3 days
  - No electronics, batteries, infusion sets, or programming
  - Fully disposable
- For giving a bolus of subcutaneous delivery of rapid acting insulin for type 1 and type 2 diabetes

**Case 1: Eric (Follow up!)**
- 47 yr.-old centrally obese (BMI 32) male with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several 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>166 - 231 mg/dL</td>
<td>~182 mg/dL</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>143 - 197 mg/dL</td>
<td>~177 mg/dL</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>112 - 275 mg/dL</td>
<td>~213 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>159 - 231 mg/dL</td>
<td>~194 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia

He tests 2 to 4 times a week
Which of the following would you recommend for Eric if he were your 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 RA</td>
</tr>
<tr>
<td>C</td>
<td>Initiate a basal bolus insulin regimen</td>
</tr>
<tr>
<td>D</td>
<td>Initiate a fixed combination of a basal insulin and a GLP-RA</td>
</tr>
</tbody>
</table>

Summary

- GLP-1 agonists represent a tremendous advance in the treatment of type 2 because of glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs) 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
- Patient and clinical inertia are serious problems
- Adherence and persistence needs to be addressed at every visit
Lecture 4: 2:15 – 3:15 p.m.

Steven V. Edelman, MD, Presents:
Cutting-Edge Strategies for the Treatment of People with Type 1 Diabetes
It is all about “Time In Range”: Keeping the glucose levels between 70 and 180 mg/dl

1. 1st priority is getting a CGM and educate your patients to respond to the trend arrows.
2. Bolus calculations are more than just the carbohydrates and static glucose readings.
3. In addition to getting the A1c below 7%, try to reduce the daily glucose fluctuations in your patients (hyper- and hypoglycemia).
4. The insulin regimen should mimic what happens in a non-diabetic state.

Natural History and Cause of Type 1 Diabetes

Autoimmune condition

Race/Ethnicity

Type 1 Diabetes
You can get type 1 diabetes at any age! 

Latent Autoimmune Diabetes in Adults (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)
46 year old male with the diagnosis of type 1 diabetes at age 6 (Classic presentation of DKA) 
- He has been on an insulin pump for many years 
- Over the last 8 years he has developed central obesity and his insulin requirements doubled 
- He also developed high blood pressure and dyslipidemia (triglycerides went up and his HDL when down). 
- Family history is that his father and both paternal uncles have type 2 diabetes.

What is the most likely explanation of why Phil's insulin requirements doubled later in life?

A. He developed central obesity  
B. He has both type 1 and type 2 diabetes  
C. His A1c kept rising  
D. The insulin he was receiving by mail was denatured and lost potency.
**Serum Insulin Levels in Type 1 Diabetes**

- **LisPro**
- **Regular**

Time (h) 22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00

Blood Glucose Levels

- **Lispro**
- **Regular**

Time (h) 22.00 3.00 7.00 8.00 9.00 10.00 11.00 12.00 13.00 14.00 15.00 16.00 17.00 18.00 19.00

Subcutaneous Insulin Has A Very Narrow Therapeutic Window

- Too little insulin leads to postprandial hyperglycemia
- Too much leads to hypoglycemia
- Very difficult to get it just right

Variables That Affect Glucose Levels

- Simple Carbs
- Complex Carbs
- Fatty Meal
- Fast Meal
- Gastroparesis
- Illness
- Medication
- Emotion
- Stress
- Sex
- Time change
- Caffeine
- Smoking
- French Meal
- Fatty Meal
- Exercise
- Rapid Digestion
- Constipation
- Still there the next day
- See French Meal
- Exercise
- Sustained

Excessive Glucose Fluctuations
9 subjects with type 1 diabetes
all treated with fast-acting analogues

Blinded CGM
Mean A1C=6.7%

24-hour CGMS glucose sensor data
Type 1 diabetes (N=9)

Every Day Is Different For A Person With Type 1 Diabetes
Type 1 Diabetes

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

Only ~30% Of Type 1s Reach ADA Goal Of An A1c Less Than 7%

“No Hitter”

Physiologic Insulin, Glucagon and Amylin Secretion

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

Physiologic Insulin Secretion and Glucose Levels In Healthy Subjects

Basal Glucose
Breakfast  Lunch  Dinner

Basal Insulin: HGO (40 to 60% of TTD)
Bolus Insulin (40 to 60% of TTD)

50
25
0
Insulin (μU/mL)

150
100
50
100
Glucose (mg/dL)

Breakfast  Lunch  Dinner

Basal Glucose

**Case 2: Tom**
- 36 year old male with type 1 diabetes for 20 years
- He is on a basal bolus regimen (20 units of insulin glargine at bedtime and 16 to 22 units of fast acting meal and correction boluses throughout the day.
- His correction factor is 1:40 (goal of 125) and his insulin to carbohydrate ratio is 1:12
- A1c is 7.1%, however his glucose values bounce from high to low and he is very frustrated.
- He tests his glucose value 6 to 8 times a day
- He tried to be as consistent as possible with his diet and exercise
- His wife is very supportive and he is motivated to do well

**What therapeutic intervention do you think is the most important to help Tom with his glucose control?**

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A</td>
<td>Put Tom on an insulin pump</td>
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<tr>
<td>B</td>
<td>Put Tom on a continuous glucose monitor</td>
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<tr>
<td>C</td>
<td>Split his dose of insulin glargine so that he takes 10 units BID</td>
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<tr>
<td>D</td>
<td>Send Tom to a diabetes education class</td>
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**Trade-off between Complications & Hypoglycemia**

![Graph showing the relationship between HbA1c (HbA1c %) and rate of progression of retinopathy vs. rate of severe hypoglycemia (per 100 patient years) with an inset graph showing the relative risk of retinopathy at different HbA1c levels.](image-url)

DCCT Research Group, 1993
Severe Hypoglycemia and A1C:
DCCT\* (1993), JDRF* (2008), and STAR 3* (2010) Studies

- DCCT (insulin therapy): 62 per 100 pt-yrs, A1C 6.3% ± 2.2%
- JDRF G4: 20.0 per 100 pt-yrs, A1C 6.6% ± 1.7%
- STAR 3 MD (all ages): 10.5 per 100 pt-yrs, A1C 6.9% ± 1.1%
- STAR 3 KID (all ages): 10.5 per 100 pt-yrs, A1C 7.3% ± 1.5%

530G/630G/670G Enlite
G4 & G5 Platinum
Continuous Glucose Monitoring Devices Currently Available in the United States

530G/630G/670G Enlite
G4 & G5 Platinum

**How CGM and Trending Information Can Affect Our Decisions (CF/I:CHO)**

- **Slowly rising**: Your glucose is rising 1-3 mg/dL, each minute.
- **Rising**: Your glucose is rising 2-3 mg/dL, each minute.
- **Rapidly rising**: Your glucose is rising more than 3 mg/dL, each minute.
- **Slowly falling**: Your glucose is falling 1-3 mg/dL, each minute.
- **Falling**: Your glucose is falling 2-3 mg/dL, each minute.
- **Rapidly falling**: Your glucose is falling more than 3 mg/dL, each minute.

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**Smart Phone Clarity App**

- Mean glucose value
- Standard Deviation
- Time in Range
- 24 hour multiday profile
How Do Patients with Type 1 Translate CGM Data Into Diabetes Management Decisions

300 Successful CGM Users
Mean A1c 6.9% with minimal hypoglycemia

Demographics

- 300 participants completed the survey
- 222 had type 1 diabetes
- 78 had type 2 diabetes.
- Of the participants with type 1 diabetes, the mean age was 46 ± 14 years old
- Duration of diabetes: 22±14 years
- Mean A1C (self reported) was 6.9% ± 0.8%
- Insulin delivery:
  - 75% used CSII
  - 25% used multiple daily injections

Correcting for a high BS with stable ➔

It has been 4 hours since your last dose of insulin & meal and your CGM receiver shows a value of 220 mg/dl (matching your fingerstick BG of 220 mg/dl) with arrow and trend graph flat (straight across). If you were NOT planning on eating or exercising, what dose of insulin would you give yourself to bring your glucose down to around 120mg/dl (6.7mmol/dl)?
How much insulin would you give yourself to bring your glucose down to around 120mg/dl?
(choose the closest value):

- a. 0 units
- b. 0.5 units
- c. 1-1.5 units
- d. 2-2.5 units
- e. 3-3.5 units
- f. 4-4.5 units
- g. 5-5.5 units
- h. 6-6.5 units
- i. 7-7.5 units
- j. 8-8.5 units
- k. 9 units

Mean change in Insulin Dose Based on 2 ARROWS UP: Survey of 300 CGM users

- 2.8 units
- 6.8 units

How CGM and Trending Information Can Affect Dosing Decisions

- No Change in calculation
- 14% Mean Increase
- 6.8 units
- 2.8 units
- 48% Mean Decrease
- 1.5 units
- 6.8 units
- 2.8 units

Dose Adjustment At Meal Time (➡)
Assume it is lunch time and your glucose is 110 mg/dl (6.1 mmol/L). Your trend graph and trend arrow is flat (straight across). You are eating a meal with 50 gram carbohydrates and your usual fat and protein. How much insulin would you take?

- a. 1 unit
- b. 2 units
- c. 3 units
- d. 4 units
- e. 5 units
- f. more than 5 units

Dose Adjustment At Meal Time (➡➡)
Assume it is lunch time and your glucose is 110 mg/dl. You have 2 trend arrows pointing up. How much additional insulin would you take?

- a. Same amount of insulin as with flat trend arrow
- b. Same amount of insulin as with ➡+ 1 unit
- c. Same amount of insulin as with ➡+ 2 units
- d. Same amount of insulin as with ➡+ 3 units
- e. Same amount of insulin as with ➡+ 4 units
- f. Same amount of insulin as with ➡+ 5 units
- g. Same amount of insulin as with ➡+ 6 units
- h. Same amount of insulin as with ➡+ 7 units
- i. Same amount of insulin as with ➡+ 8 units
- j. > 8 additional units
14 Type 1 Diabetes

81% mean increase
Example: 5 units when trend arrow is flat and 9.1 units with two trend arrow going up

59% said they would allow more time between the meal bolus and eating

53% mean decrease
Example: 5 units when trend arrow is flat and 2.4 units with two trend arrows going down

65% said they would take their insulin after the meal

Dose Adjustment At Meal Time (✔️✔️)
Assume it is lunch time and your glucose is 110 mg/dl. You have 2 arrows (trend arrows) pointing down. How would this information change your dose?

5.0 units

How CGM and Trending Information Can Affect Dosing Decisions

81% Mean Increase

9.1 units

53% Mean Decrease

2.4 units
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 Postprandial Glucose Concentrations

Four test breakfasts with identical carbohydrate content, but varying protein and fat quantities: same insulin dose

Both Dietary Fat and Protein Increase Postprandial Glucose Excursions in Children with Type 1 Diabetes, and the Effect is Additive. Diabetes Care 2013;36:3897

Adjust Insulin Dose Based On Anticipated Glucose in 30 Minutes

Adjust Insulin Dose for Rising

- No Adjustment: Dose for current glucose value.
- Add 50 mg/dl
- Add 75 mg/dl
- Add 100 mg/dl
- Wait until trend arrow becomes horizontal
**Type 1 Diabetes**

**Statistical Summary**
- Glucose exposure (mean and eA1C)
- Variability (SD & IQR)
- % in target, above and below

**Visual Display**
- Modal day (14 if possible)
- 5 glucose curves
  - Median (range line)
  - 25% & 75% % (solid lines)
  - 10%, 90% (dotted lines)

**Daily View**
- Calendar format
  - Work vs. non-work
  - Weekend vs. weekday
  - Target range

**Ambulatory Glucose Profile (AGP)**

**Identifying Glycemic Trouble Spots**

**FreeStyle Libre Flash**
IS or Intermittent Sensing
- Goes on easily
- 12 hour warm up time
- Lasts 10 days
- Swipe to get a number
- Has trend arrows
- No calibration
- No alerts or alarms
- No sharing feature
Concerns To Address With CGM

- No safety concerns as more information is better than no information if CGM is accurate
- Alarm fatigue
- High and low alert settings (80 to 180mg/dl)
- High and low snooze alarms (also known as repeat high and low alerts)
- Take advantage of the Share system
- Stacking (taking multiple boluses too close in time)


Inhaled Insulin

- Better post meal glucose values
- Less delayed hypoglycemia

Rapid on
Rapid off
Faster Acting Aspart
(addition of L-arginine and niacinamide for faster absorption)

2 hour PG levels in T1D on Pump therapy after a standardized meal comparing Aspart with Faster-Acting Aspart

Scan Your Plate With Your Smart Phone App!
Integrated system

How much fast acting insulin would you recommend to a patient eating a meal with 60 grams of carbohydrates (Insulin to Carb ratio is 1 to 10), an 8 oz Filet and a salad with olives and avocados?

A 3 units
B 6 units
C 12 units
D More than 6 units
### 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

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### Newer Insulin Pumps
- Vibe G4
- t:slim G5/X2
- Med630/670G/530G
- Insulin Mgmt
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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)

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CGM Information Enables Greater Use Of Pump Features, Resulting In A1C Reduction

- Increase in boluses
- Increase use of the bolus calculator
- Increase in use of temporary basal rates
- Increase in temporary suspend
- Reduction in hypoglycemia


Variable Basal Rate Capability
(Total daily basal dose/24) - (10 to 20%)

- Basal infusion
- Breakfast
- Lunch
- Dinner
- Bolus
- Bolus
- Dual Wave Bolus

Type 1 Diabetes
Infusion Sites

- Infusion sites need to be changed every two to three days
- Quick release catheters
- Auto inserter

Disadvantages of Pump Therapy

- A disruption in short acting insulin delivery due to a dislodged catheter, blockage, or an empty reservoir can result in a fairly rapid rise in glucose concentration
  - Severe hyperglycemia
  - Ketoacidosis
- Cost of the insulin pumps
  - Pump costs approximately $3,500 to $5,000 (some pumps offer pay as you go options)
  - Monthly cost of $30 to $40 due to batteries, infusion lines, syringes, and adhesive tape
- Minor skin irritation or infections at the insulin pump catheter insertion site
  - Very occasional abscess

Basal/Bolus or MDI Insulin Regimen With Rapid and Long-Acting Analogs/Inhaled Insulin

- Glulisine
- Or Aspart
- Or Faster Acting Aspart
- Or Lispro or Inhaled Insulin
  - U-100/U-300 Clargene/Delemtor Degludec

Type 1 Diabetes

Smart Pens Now Have the Same Software Programs as Pumps

- I: Carb ratio
- Correction Factor
- Memory
- Cloud based

Testing a basal segment: Foundation of Any Insulin Regimen

https://mysugr.com/basal-rate-testing/
"Other" Therapies for People with Type 1 Diabetes

- Pramlintide
- Incretins (GLP-1 RA)*
- SGLT–2 Inhibitors*
- Inhaled Insulin

*Medications approved only type 2 diabetes at the current time

640/670G: NOT an AP

Unblinded CGM
Low glucose suspend
Predictive low feature
Hybrid Closed Loop

An Artificial Pancreas Is Coming Faster Than We Thought Possible

https://www.medtronic-diabetes.co.uk/minimed-system/minimed-640g-system; accessed April 2017
**Bionic Pancreas**

- 2 ports for insulin and glucagon

**CGM Readings On and Off the Bionic Pancreas**

- **Open Loop:** Patient on their own
- **Closed Loop:** Bionic Pancreas

**Case Jeremy**

- 35 year old male with type 1 diabetes for 20 years
- CHO to insulin ratio 10:1
- CF 1:30 goal 120 mg/dl

Post "Snack" BS of 220 mg/dL at 4:00 p.m.
(snack at 3:30 p.m., no insulin given with snack)
Case Jeremy (continued)

- Jeremy’s CGM Guidelines
  - Correction factor 1:30
  - Target glucose 120 mg/dL
  - 220-120/30 = 3.3 units

Note: A blood sugar of 220 does not lead to any symptoms

Which option below is the best suggestion for Jeremy to follow at 4:00 pm?

- A Watch and wait (give no additional insulin)
- B Walk for an hour at a brisk pace
- C Give a correction dose of 3.3 units
- D Give a correction dose greater than 3.3 units

Summary/Conclusions

- CGM will bridge the gap until a real cure for type 1 is discovered
- Numerous variables can and will affect the blood glucose levels on a daily basis
- Every day is different for a person with type 1 diabetes
- A glucose value at one point in time has limited value when dosing insulin
- Trend arrows can help PWD make better daily diabetes decisions
Summary/Conclusions

- Blinded CGM has NOT been shown to make a positive difference in Type 1 diabetes
- Rt-CGM can help lower the A1c and reduce the risk of hypoglycemia
- Education on setting and responding to alerts and alarms is important
- Rt-CGM is the standard of care in 2018 for people with type 1 diabetes on both insulin pump therapy or MDI