Lecture 1: 8:15 – 9:10 a.m.

William Polonsky, PhD, CDE, Presents:
Understanding and Addressing Problematic Adherence to Oral and Injectable Cardiometabolic Medications
Understanding and Addressing Problematic Adherence

Patients Achieving Targets: 2014


The Key Behavioral Contributor to Glycemic Control

Osborn et al, 2016

Patients Achieving Targets: 2019

Kazemian et al, 2019
Understanding and Addressing Problematic Adherence

**CLINICAL TRIAL RESULTS LOOK GOOD, BUT...**

- **GLP-1 RA (12 months):** GLP-1 RA (2600 patients)
- **DPP-4i (12 months):** DPP-4i (1889 patients)

Change in HbA1c (%)

- **Baseline HbA1c:** 8.3%
- **N=2600**
- **N=1889**
- **N=221**

**THE EFFICACY MIRAGE**

- **REAL WORLD:**
  - Efficacy unrealized

- **CLINICAL TRIAL:**
  - Efficacy realized

**POOR ADHERENCE IS THE KEY**

- **GLP-1 RA Adherence Rate in Real World:** 29%
- **GAP:**
  - Baseline characteristics, additional drug therapy

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**Change in HbA1c (%):**

- **–1.04%**
- **–0.52%**
- **–0.65%**
- **–0.51%**

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- **Medical adherence classified as poorly adherent (Percentage of days unexposed (PDU) > 80%.)**
- **NCT: unspecified number**

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**Understanding and Addressing Problematic Adherence**
Understanding and Addressing Problematic Adherence

DEFINING POOR ADHERENCE

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

PDC, proportion of days covered.


Adherence Rates for T2D Agents

PDC, proportion of days covered; SU, sulfonylurea; TZD, thiazolidinedione.


Symphony PTD Data Set; Nov 2016 – Sep 2017 - Baseline characteristics of the total cohort (N=6,086,767, No of Claims=62,224,558)

<table>
<thead>
<tr>
<th>Medication</th>
<th>1-Year Follow-up</th>
<th>2-Year Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4i</td>
<td>40.5%</td>
<td>37.8%</td>
</tr>
<tr>
<td>SU</td>
<td>34.6%</td>
<td>30.9%</td>
</tr>
<tr>
<td>TZD</td>
<td>27.9%</td>
<td>24.2%</td>
</tr>
<tr>
<td>SGLT2</td>
<td>54.4%</td>
<td>50.7%</td>
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AMONG 75,589 INSURED PATIENTS IN THE FIRST YEAR OF A COMMUNITY-BASED E-PRESCRIBING INITIATIVE

31% New E-Prescriptions Filled

Understanding and Addressing Problematic Adherence

**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

**IMPACT OF POOR ADHERENCE**

- Hospitalization risk increases with higher rates of poor adherence.
- 73% increased risk of all-cause mortality due to poor adherence to oral hypoglycemics.

Data was provided by a large, Medicare supplemental (MarketScan) database from July 1, 2009 to June 30, 2014. There were 123,235 patients with T2D aged ≥65 who received glucose-lowering agents. Comparisons between adherent (defined as PDC ≥80%) and poorly adherent (PDC <80%) were all statistically significant at P <0.001.

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.”

THE PROBLEM: FORGETFULNESS?

THE SOLUTION: ADDRESS FORGETFULNESS?
"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 BENEFITS**
- Rarely apparent
- HCP may state that long-term risks are reduced

**PERCEIVED COSTS**
- Adverse effects
- Concerns about long-term adverse effects
- Represents "sickness"

PERCEIVED TREATMENT INEFFECTICACY

Lack of tangible benefits contributes to discouragement and poor adherence


PERCEIVED TREATMENT INEFFECTICACY

Lack of tangible benefits contributes to discouragement and poor adherence


Mean Absolute Prevalence Rates of Refill Adherence (%)

Confidential
61%
65%
62%
63%
72%

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Assessing Your HCPs’ Empathy

How good was your HCP at:
1. making you feel at ease
2. letting you tell your story
3. really listening
4. being interested in you as a whole person
5. fully understanding your concerns
6. showing care and compassion
7. being positive
8. explaining things clearly
9. helping you to take control
10. making a plan of action with you

HCP Empathy and Mortality Outcomes

- 10-year follow up of patients with newly diagnosed T2D:
- “those reporting better experiences of empathy in the first 12 months after diagnosis had a significantly lower risk (40% to 50%) of all-cause mortality over the subsequent 10 years vs. those who experienced low practitioner empathy.”
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?”

SO WHAT TO DO?

1. Ask correctly
2. Forgetfulness
   - “Aside from forgetting, what else is tough about taking your meds?”
   - Anchoring strategies
SO WHAT TO DO?
1. Ask correctly
2. Forgetfulness
3. Patient-provider trust and collaboration
   - Listen, listen, listen

SO WHAT TO DO?
1. Ask correctly
2. Forgetfulness
3. Patient-provider trust
4. 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
5. Emphasize the potential long-term gains
“To live a long and healthy life, develop a chronic disease and take care of it.”
- Sir William Osler

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.

Steven V. Edelman, MD, Presents:

Effective Use of Oral Medications for Type 2 Diabetes:
Lowering Cardiovascular Risk While Improving Glycemic Control
Oral Medications for Type 2 Diabetes

**Optimal Pharmacotherapy for Hyperglycemia in Type 2 Diabetes**
- Often requires combinations of multiple agents with complementary mechanisms of action
- Should aim to achieve the best possible glycemic control with the least possible side effects
- Should help reduce ASCVD in patients at high risk or with pre-existing CVD

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**American Diabetes Association Standards of Medical Care in Diabetes - 2020**

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**Glucose-lowering medication in T2D: Overall Approach**
Key Updates to the 2018 ADA/EASD Consensus Recommendations

General Recommendations
- In appropriate, high-risk individuals with T2D, decision to treat with GLP-1 RA or SGLT-2 inhibitor to reduce MACE, HfH, CV death or CKD progression should be considered independently of baseline A1c or A1c target.
- Providers should engage in shared decision making around initial combination therapy in new onset cases of T2D.

GLP-1 RA Inhibitor Recommendations
- For patients with T2D and established ASCVD, where MACE is the greatest threat, the level of evidence for MACE benefit is greatest for GLP-1 RAs.
- To reduce risk of MACE, GLP-1 RA can also be considered in patients with T2D without established CVD with indicators of high risk (>55 y/o with coronary, carotid, or lower extremity artery stenosis >50%, LVH, eGFR <60 ml/min/1.73, or albuminuria).

SGLT-2 Inhibitor Recommendations
- For patients with or without established ASCVD, but with HFREF (EF <45%) or CKD (eGFR 30 to 60 ml/min/1.73 m2 or UACR >30mg/g, particularly UACR >300mg/g), the level of evidence for benefit is greatest for SGLT2 inhibitors.
- SGLT2 inhibitors are recommended in patients with T2D and HF, particularly those with HFREF, to reduce HfH, MACE, and CV death.
- SGLT2 inhibitors are recommended to prevent the progression of CKD, MACE, and CV death in patients with T2D and CKD.
- Patients with foot ulcers or at risk of amputations should only be treated with SGLT2 inhibitors after careful shared decision making around risks and benefits with comprehensive education on foot care and amputation prevention.

High CV Risk or Established ASCVD, CKD, and/or HF
Consider independently of baseline A1c or individualized A1c target.
### Oral Medications for Type 2 Diabetes

#### Compelling Need to Minimize Hypoglycemia

<table>
<thead>
<tr>
<th>DPP-4i</th>
<th>GLP-1 RA</th>
<th>SGLT2i</th>
<th>TZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If A1C above target, consider addition of SU 2 OR basal insulin.</td>
<td>2. Choose later generation SU with lower risk of hypoglycemia.</td>
<td>3. Consider basal insulin with lower risk of hypoglycemia.</td>
<td></td>
</tr>
</tbody>
</table>

#### Compelling Need to Minimize Weight Gain or Promote Weight Loss

<table>
<thead>
<tr>
<th>GLP-1 RA</th>
<th>SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If A1C above target, consider addition of GLP-1 RA with good efficacy for weight loss.</td>
<td></td>
</tr>
</tbody>
</table>

#### Second-Line Therapy for T2D if Cost if a Major Issue

<table>
<thead>
<tr>
<th>SU</th>
<th>TZD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia and lower priority to avoid weight gain or no weight-related comorbidities).</td>
<td></td>
</tr>
</tbody>
</table>

#### Hierarchy

- Degludec/glargine U300 < glargine U100/detemir < NPH insulin

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1. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
2. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.
3. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.
4. If quadruple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated, use regimen with lowest risk of weight gain. PREFERABLY DPP-4i (if not on GLP-1 RA) based on weight neutrality.
5. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
6. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.
7. Low dose may be better tolerated though less well studied for CVD effects.
8. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use.
9. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.
10. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper.

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*Note: DPP-4i: Dipeptidyl peptidase-4 inhibitor, GLP-1 RA: GLP-1 receptor agonist, SGLT2i: Sodium-glucose co-transporter 2 inhibitor, TZD: Thiazolidinedione, SU: Sulfonylurea.*
Case 1: 32-year-old male with T2D for two years

- Medical history: central obesity, dyslipidemia, HTN, and CAD s/p MI
- Family Hx: Strongly positive for T2D, obesity, and CAD
- Notes: Very few home glucose monitoring results
  - Diabetes meds: metformin, SFU, DPP-4 inh., SGLT-2 inh., and basal insulin
  - Current A1c: 11.4% (10.6% one year ago, 10.1% two years ago)
  - Creatinine: 1.4 mg/dL, eGFR 65, mL/min/1.73 m²

A He needs prandial insulin
B He needs a GLP-1RA
C Poor adherence with his medication
D His diabetes regimen is too complicated

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

“Poor Adherence” with Type 2 Medications in the Real World

Prescriptions are not always filled, taken properly, or refilled as directed

- 100
- 50%–70%
- 48%–66%
- 25%–30%
- 15%–20%

Drugs are sent
Prescriptions written
Are relayed to the pharmacy
Leave the pharmacy
Are taken properly
Are refilled

Nine FDA-Approved Classes of Oral Meds for T2D

- 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 ORALGLP-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

Clinical Treatment Pearls

- 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
- Always address the modifiable risk factors (hypertension, dyslipidemia, smoking)
- Spending time with the patient and his/her support person(s) in meaningful shared decision-making addressing their health care priorities and concerns will improve adherence

Case 2: 69-year-old centrally obese female with T2D for nine years

- Medical history: Obesity (BMI 34 kg/m²), dyslipidemia, OSA, breast cancer s/p lumpectomy and hormonal therapy remission
- Family Hx: Both parents had type 2 diabetes
- Notes:
  - eGFR 75 mL/min/m², UACR normal (<30mg/g creatinine)
  - A1C 8.5%
  - Diabetes therapy is metformin and a SFU
  - LDL 121 mg/dL, triglycerides 266 mg/dL, HDL 39 mg/dL
Oral Medications for Type 2 Diabetes 6

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 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)

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 B-12 levels

SFU
- High secondary failure rate; however, when you stop them, the patient’s A1c typically goes up
- Increase risk of hypoglycemia (elderly, CKD, CAD), weight gain

TZD (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 combo with insulin (fluid retention)
- Contraindicated in the setting of heart failure
- Weight gain
- Fracture risk is increased

Case 3: 56-year-old AA female diagnosed with type 2 diabetes at age 46

- PMH: HTN, dyslipidemia, obesity and NAFLD (non alcoholic fatty liver disease)
- A1C 9.2% on maximum doses of metformin and SFU
- Occasional mild hypoglycemia
- No home glucose monitoring data
- eGFR 50 mL/min/m², BMI 51 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?

A. Add pioglitazone
B. Add a DPP-4 inh.
C. Add a SGLT-2 inh.
D. Add a GLP-1 RA
E. Combination of a DPP-4 inh & SGLT-2 inh.

High CV Risk or Established ASCVD, CKD, and/or HF

Consider independently of baseline A1C of individualized A1C target.

ASCVD or HFrEF

- Establish baseline
- Add GLP-1 RA with proven CV benefit
- Add SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate add GLP-1RA with proven CV benefit
- Avoid TZD in the setting of HF

Avoid A1C <7.5%

CKD

- Establish baseline
- Add GLP-1 RA with proven CV benefit
- Add SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate add GLP-1RA with proven CV benefit
- Avoid TZD in the setting of HF

Avoid A1C <7.5%

High CV Risk or Established ASCVD, CKD, and/or HF

- Establish baseline
- Add GLP-1 RA with proven CV benefit
- Add SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate add GLP-1RA with proven CV benefit
- Avoid TZD in the setting of HF

Avoid A1C <7.5%

ASCVD PREDOMINATES HF OR CKD PREDOMINATES

- Establish baseline
- Add GLP-1 RA with proven CV benefit
- Add SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate add GLP-1RA with proven CV benefit
- Avoid TZD in the setting of HF

Avoid A1C <7.5%

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 and engage patient
- 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 and a statin to get her BP below 140/90 mmHg and her LDL <100 mg/dl
**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 (Abo- is combined with Pio- and Lina- is combined with empaa-, new metformin XR, saxa-, dapa- tablet approved)

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**Mechanism of Action: DPP-4 Inhibitors**

**Generic and Trade Names: DPP-4 Inhibitors**

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<td>Saxagliptin</td>
<td>Onglyza</td>
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<tr>
<td>Sitagliptin</td>
<td>Januvia</td>
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Combination Pills with a DPP-4 Inhibitor

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<th>Trade Name</th>
<th>Daily Dose Range (mg)</th>
<th>Recommended Frequency</th>
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<tbody>
<tr>
<td>Sitagliptin/metformin</td>
<td>Janumet</td>
<td>50/500, 100/500</td>
<td>Twice with meals</td>
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<tr>
<td>Saxagliptin/metformin</td>
<td>Oseni</td>
<td>12.5/15, 12.5/30, 12.5/45</td>
<td>Once daily</td>
</tr>
<tr>
<td>Linagliptin/metformin</td>
<td>Jentadueto</td>
<td>2.5/500, 2.5/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Linagliptin/empagliflozin</td>
<td>Glynase</td>
<td>5/10, 5/25</td>
<td>Once daily</td>
</tr>
<tr>
<td>Linagliptin/insulin</td>
<td>Oseni</td>
<td>10 mg/5mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Linagliptin/saxagliptin</td>
<td>Oseni</td>
<td>25/15, 25/50, 25/100, 25/150, 12.5/150, 12.5/250</td>
<td>Once daily</td>
</tr>
<tr>
<td>Linagliptin/metformin</td>
<td>Kazano</td>
<td>12.5/500, 25/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Empagliflozin/linagliptin</td>
<td>Steglujan</td>
<td>5/100, 5/200</td>
<td>Once daily</td>
</tr>
<tr>
<td>Empagliflozin/linagliptin/ metformin XR</td>
<td>Glinmet XR</td>
<td>2.5/0.5/1000, 2.5/0.5/1000, 2.5/1/1000</td>
<td>Once daily</td>
</tr>
</tbody>
</table>

Newest triple combination: Empagliflozin/linagliptin/metformin (Trijardy XR)

Case 4: 70-year-old obese female with T2D for 25 years
- A1C 8.4% on maximum doses of metformin, a SFU, and a DPP-4 inh.
- Medical Hx: HTN, arthritis, recent admission for CHF
- Family Hx: Type 2 diabetes and obesity (both parents)
- Notes:
  - Fearful of injections and gaining weight BMI 31 kg/m²
  - HTN, osteoporosis, and CKD 3A (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 this patient to lower her A1c?

A. Add a TZD
B. Add a SGLT-2 inh. (cana-, dapa-, emp-, ertugliflozin)
C. Try to convince her to add a GLP-1 RA (exena-, liraglu-, dulaglu-, semaglutide)
D. Try to convince her to add a basal insulin at bedtime
Case 4 Continued

- 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%

SGLT-2 Inhibitors

**Mechanism of Action**
Reduce renal glucose reabsorption and increases urinary glucose excretion

**Benefits**
- No hypoglycemia (except when being used with SFU 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 with reduced renal function
- LDL-C increased (8% rise), HDL-C increased 10%, and TGs decreased by 25%
- Assess renal function (discussed later)
- New label warnings: DKA (discussed later), risk of amputation (discussed later), bone fractures, Fournier’s Gangrene, acute kidney injury (int)

**Clinical Pearls**
- Can now approved for renal protection and can be used with a eGFR down to 30
- Empa-Dapa and canagliflozin showed positive CVD outcomes 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: SGLT-2 Inhibitors

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

Canagliflozin:
- Suggested starting dose: 100 mg daily before first meal of day (eGFR >60 mL/min) with CKD can use to a eGFR of 30 mL/min
- 50 mg daily in placebo-controlled trials 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 mL/min)
- 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 >60 mL/min)
- Increase to 25 mg daily if tolerating and need additional glycemic control (eGFR >60 mL/min)

Ertugliflozin:
- Starting dose: 5 mg daily in morning with or without food (eGFR for both doses >60 mL/min)
- Increase to 15 mg daily if tolerating and need additional glycemic control

Oral Medications for Type 2 Diabetes
Glucose is filtered in the glomerulus.

Loop of Henle

Collecting Duct

Urine

SGLT1

Glucose reabsorbed into systemic circulation

No detectable glucose in urine

Glomerulus

Proximal Convoluted Tubule

Distal Convoluted Tubule

SGLT2

SGLT = sodium-glucose co-transporter.


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

Renal Handling of Glucose in a Non-Diabetic Patient

Adapted with permission from Abdul-Ghani, DeFronzo RA.

T2DM = type 2 diabetes mellitus.


Renal Glucose Reabsorption in Normal, T2D, 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, preeclampsia, 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 called Fournier’s gangrene

Oral Medications for Type 2 Diabetes
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

Causes of Mortality in Diabetes Over Time

Similar trends have occurred in the population without diabetes
- Vascular deaths: 30.9% (29.5-32.3)
- Cancer: 25.5% (24.3-26.8)
- Other: 43.5% (41.8-45.4)

Primary Objectives of Effective Management:

Important Basics...The 'ABCs'

- A1C %: General goal is <7% but must be individualized
- SBP mm Hg: Less than 140/90 but must be individualized
- LDL mg/dL: Less than 100 but if CAD present then less than 70, most will need a statin/ezetimibe (PCSK9 inhibitor in high risk)

Reduction of eye, kidney, nerve and heart disease by 75%!
**Blood Pressure Management**

Individualize BP Goals:
- <140/90 mmHg (10-yr CV risk <15%)
- <130/80 mmHg (10-yr CV risk >15%)

**Dyslipidemia Management**

Individualize lipid Goals:
- LDL < 100mg/dl in all PWD
- LDL < 70mg/dl if ASCVD present
- Triglycerides less than 200mg/dl
- HDL as high as you can get it!

---

**Table 10.2—High-intensity and moderate-intensity statin therapy**

<table>
<thead>
<tr>
<th>High-intensity statin therapy (lowers LDL cholesterol by ≥50%)</th>
<th>Moderate-intensity statin therapy (lowers LDL cholesterol by 30-49%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin 40-80 mg</td>
<td>Atorvastatin 10-20 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg</td>
<td>Rosuvastatin 5-10 mg</td>
</tr>
<tr>
<td>PCSK9 inhibitors (evolocumab and alirocumab) if LDL not at goal on maximally tolerated statin/ezetimibe</td>
<td>Simvastatin 20-40 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 1-4 mg</td>
</tr>
</tbody>
</table>

*Once-daily dosing. XL = extended release.

---

**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>2013</td>
<td>2013</td>
<td>2015</td>
<td>2017</td>
<td>2017</td>
</tr>
</tbody>
</table>

---

**Oral Medications for Type 2 Diabetes**
Oral Medications for Type 2 Diabetes

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>22,200</td>
<td>3900</td>
<td>3900</td>
</tr>
<tr>
<td>Results</td>
<td>Sept 2015</td>
<td>2017</td>
<td>2018</td>
<td>Late 2020</td>
</tr>
</tbody>
</table>

Results Sept 2015, 2017, 2018, Late 2020

Non-Insulin CVOTs in T2D: GLP-1 RA (Primarily driven by a reduction in death due to cardiovascular disease)

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>ELIXA</th>
<th>SUSTAIN 6</th>
<th>EXCEL</th>
<th>HARMONY</th>
<th>REWIND</th>
<th>PIONEER 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RA</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Exenatide LT</td>
<td>Albiglutide</td>
<td>Dulaglutide</td>
<td>Oral semaglutide</td>
<td></td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</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>
<td>3,183</td>
</tr>
<tr>
<td>Results</td>
<td>2016</td>
<td>2015</td>
<td>2016</td>
<td>2018</td>
<td>2019</td>
<td>2019</td>
<td>2019</td>
</tr>
</tbody>
</table>

Results 2016, 2015, 2016, 2018, 2019, 2019, 2019

Non-Insulin CVOTs in T2D:

GLP-1 RA (Primarily driven by a reduction in death due to cardiovascular disease)

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).

Diabetes Medications FDA Approved for CV Risk Reduction

Empagliflozin (based on EMPA-REG data)
- to reduce the risk of cardiovascular death in adults 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
- Weight gain and hypoglycemia differences
- Regional differences
- Outcomes differ: overall mortality, non-fatal and fatal MI, stroke, etc.
- Study conduct and adherence may affect results

Diabetes Medications FDA Approved for Renal Disease

- Canagliflozin (CREDENCE study)
  - Reduce the risk of end-stage kidney disease, doubling of the serum creatinine, cardiovascular death and hospitalization for CHF in patients with type 2 diabetes with nephropathy (eGFR between 30 and 90 ml/min) and albuminuria > 300mg
- EMPA-KIDNEY: On-going

Chronic Kidney Disease in T2D
Key Principles of Management of T2D

- Glycemic targets and 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 first 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. Shared decision making is KEY!

Key Principles of Management of T2D

- GLP-1 RA are the preferred first injectable therapy over basal insulin except patients with very poor glycemia control
- 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 – 2:30 p.m.

Jeremy H. Pettus, MD, Presents:
A Focus on Time in Range, Unmet Needs and Modern Management of Type 1 Diabetes
Modern Management of Type 1 Diabetes

To Be Discussed...

- Incidence and pathophysiology
- Demographics of T1D in the U.S.
- A1c and time in range (TIR)
- Overview of pumps and CGM devices
- Interpreting CGM downloads in ~ 30 secs.
- Identifying and addressing common problems
- The importance of the trend arrows
- New insulin and glucagon formulations
- Complications of diabetes
- Advances in hybrid and closed AP

Prevalence of T1D is Increasing!

- 40,000 people diagnosed each year in U.S.\(^2\)
- 110 people are diagnosed with T1D each day
- By 2040 there will be 5 million people with T1D

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

- Natural Progression is months to a few years.
Age at Diagnosis of T1D

You can get type 1 diabetes at any age!

L.A.D.A.

Latent Autoimmune Diabetes in Adults (L.A.D.A.)

- 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)
Family History of T1D

- First-degree family member with T1D
- Yes
- No

Risk of Developing Type 1 vs Type 2

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>General Population</th>
<th>Type 1 Risk</th>
<th>Type 2 Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>If you have a sibling with T1D</td>
<td>0.3%</td>
<td>~4%</td>
<td>~30%</td>
</tr>
<tr>
<td>If your mother has T1D</td>
<td>2-3%</td>
<td>~2%</td>
<td>~30%</td>
</tr>
<tr>
<td>If your father has T1D</td>
<td>6-8%</td>
<td>~6%</td>
<td>~30%</td>
</tr>
<tr>
<td>If you have an identical twin with T1D</td>
<td>~50%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Race/Ethnicity

- White Non-Hispanic
- Black Non-Hispanic
- Hispanic or Latino
- Native Hawaiian/Other Pacific Islander
- Asian
- American Indian/Alaskan Native
- More than One Race

Only ~30% of Type 1s reach ADA goal of an A1c less than 7%

A1c Goal = <8.5%
A1c Goal = <8.0%
A1c Goal = <7.5%
A1c Goal = <7.0%

Age, years

<6 6-<13 13-<20 20-<26 26-<50 50-<65 ≥ 65

Weight

Overweight
Obese

0% 20% 40% 60% 80% 100%

<6 6-<13 13-<18 18-<26 26-<50 ≥ 50 Age (years)

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

<6 6-<13 13-<18 18-<26 26-<50 ≥ 50 Age (years)

Approximately half of people with type 1 diabetes are diagnosed as adults

Type 1 diabetes can be hereditary

Type 1 diabetes can be associated with insulin resistance

The percentage of people with type 1 diabetes is similar in Latinos, African Americans and Caucasians

Which statement about type 1 diabetes is false?
This is Type 1 Diabetes for a Lot of Patients

Glucose Variability Has an Important Impact on Patients with T1D: Both Patients Below Have the Same A1c

- Measuring A1c alone provides no information on glucose variability
- Important of avoiding extreme hyper- and dangerous hypoglycemia
- Improvement in time in range significantly reduced retinopathy and nephropathy

GV, glycemic variability


It Is All About “Time In Range” Keeping the Glucose Levels Between 70 and 180 mg/dl

1. 1st priority for your patients 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 (pump vs. MDI or multiple daily injections)
Evaluating Patients with Type 1 Diabetes

1. Review CGM download together with the patient and look at the following parameters listed here and also explained on subsequent slides: Estimated A1c (GMI) from Mean glucose, standard deviation (SD), Time in range including time in hypoglycemia and the 24 hour profile.

2. May need to look at several of the individual days to further evaluate trends on the 24 hour profile.

3. Focus in on the biggest problem and address solutions in terms of insulin dosing and timing, types and amounts of food, and time, duration and intensity of exercise, etc.

4. Always review alert settings on the CGM!

The CGM Report
Getting Oriented
- Mean glucose value
- Standard deviation (SD)
- Time in range (70-180 mg/dl)
  - Time >180 mg/dl
  - Time <70 mg/dl
- 24-hour multiday profile

CGM TIR Targets for Most with T1D and T2D
Options to Connect Directly to Smart Phone/Smart Watch

- Last 10 days
- No calibration
- No finger sticks
- Predictive low alert
- Medicare approved
Implantable CGM

- Sensor implanted under the skin
- Smart Transmitter
- Mobile App

CGM System

- 1-hour warm up
- Lasts 14 days
- Swipe to get a number
- Trend arrows
- Medicare approved
- No fingersticks
- No alerts or alarms
- No sharing features

CGM System

- Requires calibration
- Predictive low alerts
- Requires high alerts
- 6-day wear
- Need to confirm with fingerstick when dosing insulin
- No sharing capabilities

https://www.medtronic-diabetes.co.uk/minimed-system/minimed-640g-system; accessed April 2017
CGM Download

Time in Range
36%

Clinical Points?
If glucose is “all over the place”:
✓ Start with figuring out the basal dose/rate
✓ Make sure the patient is dosing for all meals and snacks
✓ Educate the patient on dosing well before the glucose level gets too high.

How to test the basal dose rate?

Which Technique is the Best Way to Test the Basal Rate/Dose in a Patient with Type 1 Diabetes?

A. Measure the fasting glucose in the morning for 5 days in a row
B. Make sure the total basal dose is approximately half of the total daily dose of insulin
C. Patient has an early dinner and does not eat until the next morning testing his/her glucose levels overnight
D. Patient has an early breakfast and tests his/her glucose levels every 2 hours until dinner
Testing the Basal Rate/Dose

Testing Overnight
1. Have an early dinner
2. Test on a night when BG is ~ 120-180mg/dl 2 hours after dinner with a horizontal trend arrow
3. Note your BG at bedtime
4. Fast until the next morning (If not on a CGM then need to test the BG every few hours)
5. BG in the morning should be about +/- 30 mg/dL from bedtime BG
6. Don’t make any decisions based on 1 day. Look for trends.

Is this T1D on too much or too little basal?

Same Patient Fasting From 9pm Until 7am

Patient's best glucose day was March 14, 2018
Patient’s glucose data was in the target range about 77% of the day.

146
42

Statistical data for this day
Average glucose
Standard deviation
Time in target

Legend:
Red:
Black:
Green:
Yellow:
Blue:
Alert and Alarm Settings:
IMPORTANT!
1. Upper limit 180 to 200 (higher in the beginning if patients A1c is high)
2. Lower limit 80mg (don’t forget about the lag time)
3. Repeat high and low alerts are important
4. Predictive high and low alerts

What can be seen in this CGM?
If there is an obvious time of day where BG is always high, consider the following:
1. Is the dose appropriate and given correctly?
   ✓ Account for all of the carbs?
   ✓ Consider a different dose or type of insulin for this meal?
   ✓ Was the dose given ahead of time?
2. Missing the dose at this time of day?
   ✓ busy at work?
   ✓ “don’t have time to bolus?”
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 content, but varying protein and fat quantities: same insulin dose:

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

Hi Dr Edelman,

I ate a slice of pizza, a protein bar, hamburger, onion rings and a beer at around 5:30. I really haven’t eaten much all day besides that. My sugar went up to around 400. I’ve taken 85 units and I’m still at 307. Normally I don’t take 85 short acting units in one day.
Snacking at Night Without Coverage

- Snacking at night without insulin coverage \(\rightarrow\) highs
- Good BG at bedtime without snacking \(\rightarrow\) hypo

Clinical Points
- A patient should not have to snack at night to prevent hypoglycemia overnight.
- If that is the case, then the basal rate/dose is too high!
- All patients need to bolus for snacks containing carbohydrates unless the glucose level is dropping.
Nocturnal Hypoglycemia

Quick Interpretation:
- A1c “great”
- Low variability
- Hypos a BIG problem
- Hypos at all time of day

Look at Alert Settings

Alert Settings for Device

Low alert set at 65
Low repeat is OFF

Alert Settings for Device

Low alert set at 65
Low repeat is OFF
Clinical Points

- Frequent hypos are extremely dangerous
- Setting the "low alert" at 75 or 80 gives the patient time to react
- Don’t forget about the lag time
- Turn on the "Repeat low alert" (~15 min). This acts like a "snooze" button to keep alarming the patient if somehow the low alert was missed the first time
- The repeat high alert is important as well

Is This Patient Under Good Control?

- 6.7% in range
- 141 mg/dl
- 55 mmol/L

Time in range:

- 31%
- 65%
- 4%
- 0%

What is Happening at 11pm?

- Patient had a pattern of nighttime highs.
- Patient's best glucose day was May 3, 2019.
- Patient's worst glucose was 171 mg/dl (9.5 mmol/L).
How do People with Type 1 Diabetes Calculate Their Insulin Doses?

A. Count carbohydrates: “Insulin to carb” ratio (i.e. 1:15)

B. Correction factor (CF) or insulin sensitivity factor (ISF): Use when the glucose value is above a desired range (i.e. 1:40 with a goal of 120 mg/dl)

C. Trend arrows, exercise, stress, protein, fact, etc. not accounted for

Trend Arrows Define Specific Rates of Change

- Constant: Your glucose is steady (not increasing/decreasing more than 1 mg/dL, each minute)
- Slowly rising: Your glucose is rising 1-2 mg/dL, each minute
- Rising: Your glucose is rising 2-3 mg/dL, each minute
- Rapid Rising: Your glucose is rising more than 3 mg/dL, each minute
- Slowly Falling: Your glucose is falling 1-2 mg/dL, each minute
- Falling: Your glucose is falling 2-3 mg/dL, each minute
- Rapid Falling: Your glucose is falling more than 3 mg/dL, each minute

Not a rate of change intervention: The receiver cannot always calculate 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

- **3.0 units**
  - No change in calculation
- **6.8 units**
  - 140% Mean Increase
- **1.5 units**
  - 48% Mean Decrease

Adjust 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

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

- Adjust dose based on current glucose value
- Add 50 mg/dl
- Add 75 mg/dl
- Add 100 mg/dl

Wait until trend arrow becomes horizontal

Modern Management of Type 1 Diabetes

17
<table>
<thead>
<tr>
<th>Type</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast-Acting Insulin</strong></td>
<td>Regular: U-500 Regular</td>
<td>Humulin R, Novolin R</td>
</tr>
<tr>
<td></td>
<td>Aspart</td>
<td>NovoLog</td>
</tr>
<tr>
<td></td>
<td>Lispro (U-100 and U-200)</td>
<td>Fiasp, Asparil</td>
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<td></td>
<td>Lispro (U-100 and U-200)</td>
<td>Humalog</td>
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<td></td>
<td>Follow on biologic lispro</td>
<td>Afrezza</td>
</tr>
<tr>
<td><strong>Basal Insulin</strong></td>
<td>Intermediate-Acting:</td>
<td>Humulin N, Novolin NPH</td>
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<tr>
<td></td>
<td>Long-Acting:</td>
<td>Levemir</td>
</tr>
<tr>
<td></td>
<td>NPH</td>
<td>Luvas</td>
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<td></td>
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<td>Toujeo</td>
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<td>Glargine (U-100)</td>
<td>Tresiba</td>
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<td></td>
<td>Degludec (U-100/200)*</td>
<td>Basaglar</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic glargine (U-100)</td>
<td>Basaglar</td>
</tr>
</tbody>
</table>

**Inhaled Insulin**

Inhaled vs Rapid Acting Insulin

Rapid on
Rapid off

0.8 units/kg
0.6 units/kg
0.4 units/kg
New Formulations of Glucagon

Nasal Glucagon
Pre-Filled Syringe

Smart Pens: Same Software Programs as Pumps

- I:Carb ratio
- Correction factor
- Insulin log
- Cloud-based

Let Your Patients Pick the Pump

- Animas Vibe G4 (Discontinued)
- t:slim G6/X2
- 630/670G/530G
- OmniPod
- Insight
- Aviva-Combo
- Diabecare IIS
**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)

---

**How Does This Keep Your Patient in Range?**

- Auto-adjusts basal rate when in auto mode
- Target blood sugar: 120mg/dl
- Mealtime boluses required
- Sensor (needs frequent calibration to stay in auto mode)

---

**Hybrid-Closed Loop System**

- Auto-adjusts basal rate when in auto mode
- Target blood sugar: 120mg/dl
- Mealtime boluses required
- Sensor (needs frequent calibration to stay in auto mode)
How Does Control IQ Keep You in Range?

DIY Looping Hybrid Closed Loop NOT FDA Approved

- Basal rate modulator
- Communicates with certain CGM devices (no calibration needed)
- Always in auto mode
- Still need to enter carbs and give correction doses

L.L.C.
Looping Low Carbs
Advances in Complications

- Retinopathy: Anti-veg F monoclonal antibodies for DR and DME
- Diabetic Kidney Disease: SGLT-2 inhibitors
- CVD: PCSK-9 inhibitors

Approach to Reduce DKA Risk with SGLTis: STICH Protocol (applicable for DKA from any cause)

- S (Stop SGLT inhibitor)
- I (Inject bolus insulin)
- C (consume 30 g Carbohydrates)
- H (Hydrate (drink water))

An Artificial Pancreas is Coming Faster than We Thought Possible
Example of a Bionic Pancreas

- 2 ports for insulin and glucagon

CVM Readings: On and Off the Bionic Pancreas

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

To Be Discussed...

- Incidence and pathophysiology
- Demographics of T1D in the U.S.
- A1c and time in range (TIR)
- Overview of pumps and CGM devices
- Interpreting CGM downloads in ~ 30 secs.
- Identifying and addressing common problems
- The importance of the trend arrows
- New insulin and glucagon formulations
- Complications of diabetes
- Advances in hybrid and closed AP
Lecture 4: 2:30 – 3:30 p.m.

Schafer Boeder, MD, Presents:
Practical Application of Injectable Agents and Their Cardiovascular Effects:
Individualized Treatment Strategies
For The First Time A GLP1-RA Is The Preferred Injectable Over Basal Insulin

Case 1: 54 year old male with type 2 diabetes for 10 years
- History of dyslipidemia, hypertension, NAFLD
- Strong family history of type 2 diabetes
- Currently on metformin, SFU and a DPP4 inhibitor
- Recent myocardial infarction s/p 4 cardiac stent insertions
- A1c 9.3%
- Creatinine 1.3 eGFR 70
- HGM data: ranges from 82 to 379 mg/dl
- Bedtime average 210 mg/dl SD 76mg/dl
- Morning average 221 mg/dl

Which of the following would you recommend for this patient?

A. Initiate basal insulin
B. Initiate a GLP-1 Receptor Agonist (RA)
C. Initiate premixed insulin (70/30) BID
D. Initiate a fixed combination of a basal insulin and a GLP-1RA
### High CV Risk or Established ASCVD, CKD, and/or HF

Consider independently of baseline A1C or individualized A1C target.

#### ASCVD PREDOMINATES
- Particularly HFrEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30mg/g, particularly UACR >300 mg/g

#### ASCVD OR CKD PREDOMINATES
- Preferably SGLT2i with evidence of reducing HF and/or CKD progression if eGFR adequate
- OR
  - If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate add GLP-1RA with proven CVD benefit
  - Avoid TZD in the setting of HF
  - Choose agents demonstrating CV safety
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit
  - DPP4i (not saxagliptin) in the setting of HP (if not on GLP-1 RA)
  - Basal insulin
  - SU

#### ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

#### Indicators of high ASCVD risk
- Preferably GLP-1 RA with proven CVD benefit
- OR
  - If GLP-1 RA is not tolerated or contraindicated or if eGFR less than adequate add SGLT2i with proven CVD benefit

#### Indicators of high ASCVD risk
- Basal insulin
- SGLT2i
- DPP4i

#### Indicators of high ASCVD risk
- SU

#### Indicators of high ASCVD risk
- Monitor for weight gain and hypoglycemia

---

### Basal Insulin vs GLP-1 RA

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>GLP-1 RA (an incretin hormone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin: Injected once or twice a day</td>
<td>GLP-1 RA: Injectable once or twice a day or once weekly and oral once daily</td>
</tr>
<tr>
<td>Need to titrate dose to achieve the desired FBS</td>
<td>Titrates to the acceptable dose to avoid based on nausea</td>
</tr>
<tr>
<td>Need to institute home glucose monitoring (SMBG)</td>
<td>“No” need for SMBG</td>
</tr>
<tr>
<td>Important to have frequent follow up when initiating basal insulin (days to weeks)</td>
<td>Follow up not as crucial</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No Hypoglycemia</td>
</tr>
</tbody>
</table>

---

### GLP-1 Effects: Glucoregulatory Role of Incretins

- **GLP-1 secreted upon the ingestion of food**
- **FBG and PPG control**

- Pancreatic beta cells: Enhanced glucose-dependent insulin secretion
- Pancreatic alpha cells: Decreased hepatic glucose output
- Liver: Reduced hepatic glucose output
- Stomach: Help regulate gastric emptying

---

**Injectable Agents and Their Cardiovascular Effects**
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>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Byetta</td>
</tr>
<tr>
<td>Twice-daily</td>
<td>Bydureon</td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
</tr>
<tr>
<td>Liraglutide</td>
<td></td>
</tr>
<tr>
<td>Once-daily</td>
<td>Victoza</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity</td>
</tr>
<tr>
<td>Once-weekly</td>
<td></td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Adlyxin</td>
</tr>
<tr>
<td>Once-daily</td>
<td></td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Ozempic</td>
</tr>
<tr>
<td>Once weekly</td>
<td></td>
</tr>
<tr>
<td>Oral Semaglutide</td>
<td>Rybelsus</td>
</tr>
<tr>
<td>Once daily</td>
<td></td>
</tr>
</tbody>
</table>

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

Injectable Agents and Their Cardiovascular Effects
Summary of Completed GLP-1 receptor agonists Cardiovascular Outcome Trials (CVOTs)

CVOTs of GLP-1 RAs (SGLT2 Inhibitors Indicated for CHF/CKD)

ITCA 650—Medical Device To Deliver a GLP-1RA (exenatide)

Not yet approved by the FDA
Case 2: 72 year old Caucasian woman with type 2 diabetes for 23 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, papillary thyroid cancer and obesity (BMI=31)
- Both parents and two siblings have type 2 diabetes and early CVD
- eGFR 65 ml/min
- Her A1c is 8.8% (Goal for this patient at least less than 8%)
- Average FBS is in the 180s (does not test at other times)

What would you recommend now for this patient?

A  Start a DPP4 inhibitor

B  Try to convince her to start basal insulin and titrate the dose to get her FBS less than 140mg/dl

C  Start a GLP1-RA

D  Initiate a fixed combination of a basal insulin and a GLP-1RA

She agreed to start a once weekly GLP-1RA (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 13 pounds and her A1c fell from 8.8% to 7.2%

Case 2 continued

<table>
<thead>
<tr>
<th></th>
<th>FBS (mg/dl)</th>
<th>PPG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before GLP-1*</td>
<td>Average 188</td>
<td></td>
</tr>
<tr>
<td>After GLP-1*</td>
<td>Average 139</td>
<td>Average 167</td>
</tr>
</tbody>
</table>
Injectable Agents and Their Cardiovascular Effects

**Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist**

**Insulin degludec/liraglutide**
- 1 dose step (unit) has 1 unit insulin degludec and 0.036 mg of liraglutide (max. dose is 50 insulin degludec/1.8 mg liraglutide)
- Injected once daily at the same time each day with or without food

**Insulin glargine/lixisenatide**
- 1 dose step (unit) has 1 unit insulin glargine and 0.33 mcg lixisenatide (max. dose is 60 insulin glargine/20 mcg lixisenatide)
- Injected once daily within one hour prior to the first meal of the day

---

**Fixed-Ratio Combination of Insulin Degludec And Liraglutide And U-100 Glargine and Lixisenatide**

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

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


---

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

Pen dose steps (units): insulin degludec = liraglutide
- 3 dose steps=10 units insulin degludec + 0.36 mg liraglutide
- 5 dose steps=20 units insulin degludec + 1.8 mg liraglutide

Starting dose:
- 1 dose step which has 16 units insulin degludec + 0.58 mg of liraglutide

Rate according to FBG, as if you were using basal insulin alone, generally 2 dose steps at a time, ideally every 3-4 days

Pen dose steps (units): insulin glargine + lixisenatide
- 5 dose steps=15 units insulin glargine + 5 mcg lixisenatide
- 10 dose steps=30 units insulin glargine + 10 mcg lixisenatide
- 30 dose steps=90 units insulin glargine + 30 mcg lixisenatide

Starting dose:
- If glargine U-100 dose is <30, start at 15 dose steps which has 150 glargine + 5mcg lixi
- If glargine U-100 dose is >30, start at 30 dose steps which has 300 glargine + 15 mcg lixi

Rate according to FBG, as if you were using basal insulin alone, generally 2-4 dose steps at a time weekly

Maximum dose is 50 units of insulin glargine and 90 mcg of lixisenatide
A1c of 8.3% at baseline drops 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%

-1.28% 7.0%
-1.44% 6.9%
-1.91% * 6.4%

*p<0.0001 vs. insulin degludec and vs. liraglutide

Body Weight and Hypoglycemia

Increase of 4.88 lb
P<0.0001

Decrease 5.37 lb
P<0.0001

Effects of insulin degludec/liraglutide in patients with poorly controlled type 2 diabetes with HbA1c >9%: analyses from the DUAL program

Frias JP et al. Diabetes 2018 Jul; 67(Supplement 1): -.
https://doi.org/10.2337/db18-1092-P

Injectable Agents and Their Cardiovascular Effects

7
Injectable Agents and Their Cardiovascular Effects

**Gastrointestinal Side Effects: Gradual Titration Helps**

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

\[ \alpha \text{non-significant for odds of experiencing gastrointestinal side effects for subjects on insulin degludec/liraglutide versus non-GLP-1 RA comparator} \]

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

- **T2DM patients not controlled on basal insulin + met 2nd OAD**
- **Mean A1C (%)**
  - Baseline: 9.0
  - Week 24: 7.0
  - Week 30: 6.5
  - Week 32: 8.0
  - Week 34: 8.5
  - Week 36: 8

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Insulin glargine lixisenatide</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>% patients</td>
<td>40%</td>
<td>30%</td>
</tr>
<tr>
<td>A1C &lt; 7.0% with No Wt Gain and No Symptomatic Hypoglycemia</td>
<td>9%</td>
<td>30%</td>
</tr>
</tbody>
</table>

**Post Hoc Analysis insulin glargine/lixisenatide In Patients With Very Poor Glycemic Control (A1c.9%). LixiLan O Study**

- **Reduction in A1C from baseline to Week 30**
  - A1C: 7.0%
  - Liixenatide: -2.9%
  - Liixenatide: -1.7%

- **Final dose lixenatide: 45 units and insulin dose 44 units**
  - Liixenatide: 2.5%
  - Liixenatide: 2.5%
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 hypoglycemia) 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>Regular</td>
<td>Humulin R</td>
<td></td>
</tr>
<tr>
<td>U-500 regular</td>
<td>Novolin R</td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>Levemir</td>
<td></td>
</tr>
<tr>
<td>lispro (U-100 and U-200)</td>
<td>Humalog</td>
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<td>Inhaled insulin</td>
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<table>
<thead>
<tr>
<th>Basal Insulin</th>
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<th>Trade Name</th>
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<tbody>
<tr>
<td>Intermediate-acting NPH</td>
<td>Humulin N</td>
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<tr>
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<td>Novolin NPH</td>
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<tr>
<td>detemir</td>
<td>Lantus</td>
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<tr>
<td>glargine (U-100)</td>
<td>Toujeo</td>
<td></td>
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<tr>
<td>glargine (U-300)</td>
<td>Tresiba</td>
<td></td>
</tr>
<tr>
<td>degludec (U-100/200)</td>
<td>Basaglar</td>
<td></td>
</tr>
</tbody>
</table>

Time Action Profiles: Traditional Insulins

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>10-15 mins</td>
<td>60-90 mins</td>
<td>4-5 hrs</td>
</tr>
<tr>
<td>NPH</td>
<td>5-9 hrs</td>
<td>5-6 hrs</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Detemir</td>
<td>90 mins</td>
<td>Relatively</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Glargine</td>
<td>90 mins</td>
<td>Relatively</td>
<td>24 hrs</td>
</tr>
</tbody>
</table>
Benefits Of U-300 Glargine And Degludec In Type 1 and Type 2 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
- 1:1 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

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, SFU and a SGLT2 inhibitor. She was intolerant to GLP-1RAs.
- Her PCP started 10 units of insulin 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>Bedtime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>211</td>
<td>---</td>
<td>185</td>
<td></td>
</tr>
<tr>
<td>Tuesday</td>
<td>247</td>
<td>174</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td>---</td>
<td>106</td>
<td></td>
</tr>
<tr>
<td>Thursday</td>
<td>226</td>
<td>179</td>
<td>---</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
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 before eating or drinking:
   a. If fasting blood sugar is over ___ mg/dL then increase your dose by __ units
   b. If fasting blood sugar is under ___ mg/dL then decrease your dose by __ units

**Important:**
- The purpose of long acting basal is to provide an adequate amount of insulin throughout the day and night while you sleep. Do not measure your blood glucose levels by eating lunch so you should not change your dose based on blood sugar numbers during the day when you are eating.

---

**Case 4: 55 year old obese Latino male with a 22 year history of type 2 diabetes**

- CKD stage 3b (eGFR 37 ml/min)
- History of ASCVD s/p MI and CHF
- HTN, dyslipidemia, OSA, NAFLD and h/o pancreatitis
- Currently treated with low dose metformin, SFU, DPP4 inhibitor and canagliiflozin (initiated by nephrology)
- A1c 8.9%

<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>130 - 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 - 155 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

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Injectable Agents and Their Cardiovascular Effects
Which of the following would you suggest for this patient?

A  Initiate pioglitazone
B  Initiate basal insulin
C  Start a GLP-1 RA and stop his DPP-4 inhibitor
D  Change to a different SGLT-2 Inhibitor

Case 4: continued

- 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>Fasting (mg/dL)</th>
<th>Pre-Breakfast</th>
<th>Pre-Lunch</th>
<th>Pre-Dinner</th>
<th>Bedtime (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>82 – 155</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>128 – 183</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</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.

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.)
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.

Injectable Agents and Their Cardiovascular Effects
Second Pitfall In Initiating/Titrating Basal Insulin
(First one is too slow titration after starting)

Not Paying Attention To
Bedtime Glucose Value So You Avoid Overbasalinization

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.

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

1. Add FA analog
2. Inhaled Insulin
3. Last meal

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

Transitioning From Basal to Basal/Bolus Insulin Therapy in Type 2 Diabetes Mellitus
(Insulin and Patch Pumps Can Improve Adherence)

Step 1
Step 2
Step 3
Step 4

U-100/300glargine, det., deg or NPH @ HS
Add FA analog
Add FA analog
Add FA analog

All oral agents continued
Inhaled Insulin
Inhaled Insulin
Inhaled Insulin

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

TCOFPediatric Endocrinology

Injectable Agents and Their Cardiovascular Effects

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 if very poor glycemic control (A1c>9%) or in addition to a GLP-1RA
- 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

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-RA) 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