Lecture 1: 8:15 – 9:15 a.m. CDT

William Polonsky, PhD, CDCES, 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
Understanding and Addressing Problematic Adherence

Patients Achieving Targets: 2019

WHY AREN'T WE SEEING DRAMATIC IMPROVEMENTS?

Kazemian et al, 2019
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

The efficacy mirage

Real world vs. clinical trial results.
POOR ADHERENCE IS THE KEY

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

REAL-WORLD RESULTS PREDICTED UNDER TYPICAL TRIAL CONDITIONS

REAL WORLDb

EXPLAINING THE GAP

ADHERENCEc

BASELINE CHARACTERISTICS, ADDITIONAL DRUG THERAPY

Change in HbA1c (%)

-1.04%

-0.52%

75%

25%

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

RCT, randomized clinical trial.

a Linear regression model fitted to estimate the change in HbA1c 1 year after initiating GLP-1 RA or DPP-4i based on baseline and treatment characteristics.

b 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. Medical adherence classified as poorly adherent if percentage of days covered (PDC) <80%.


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

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)

Tracking New E-Prescriptions for Diabetes Medications

Among 75,589 insured patients in the first year of a community-based e-prescribing initiative

Filled

Never Filled

31%

Understanding and Addressing Problematic Adherence

**Impact of Poor Adherence**

HOSPITALIZATION RISK INCREASES WITH HIGHER RATES OF POOR ADHERENCE

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.


**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

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.”
WHAT ARE WE MISSING?

THE PROBLEM: FORGETFULNESS?
THE SOLUTION: ADDRESS FORGETFULNESS?

Unintentional non-adherence to chronic prescription medications: How unintentional is it really?

Abhijit S Gadkar and Colleen A McHorney

“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

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”

PERCEIVED BENEFITS

- Rarely apparent
- HCP may state that long-term risks are reduced

PERCEIVED COSTS

PERCEIVED TREATMENT INEFFICACY

Lack of tangible benefits contributes to discouragement and poor adherence


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.

Association Between Primary Care Practitioner Empathy and Risk of Cardiovascular Events and All-Cause Mortality Among Patients With Type 2 Diabetes: A Population-Based Prospective Cohort Study

Hajira Dambha-Miller, MRCGP, PhD
Adina L. Feldman, PhD
Ann Louise Kinmonth, FRCPG

**ABSTRACT**

**PURPOSE** To examine the association between primary care practitioner (physician and nurse) empathy and incidence of cardiovascular disease (CVD) events and all-cause mortality among patients with type 2 diabetes.

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.”

Dambha-Miller et al, 2019

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!

Critical Psychosocial Issues in Diabetes
Web-based video modules

www.behavioraldiabetes.org
Lecture 2: 9:15 – 10:30 a.m. CDT

Jeremy H. Pettus, MD, Presents:

A Focus on Time in Range, Unmet Needs and 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
• New insulin and glucagon formulations
• Advances in hybrid and closed AP

Prevalence of T1D Is Increasing!

1.3 million adults in the US currently have T1D¹

• 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

¹ T1D Exchange T1D population based on company research
² www.JDRF.org
Type 1 is an Autoimmune Disease: The Immune System Attacks Healthy Beta Cells

Natural Progression is **months** to a **few years**

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**August 6, 2019**

**Teplizumab Gets Breakthrough Status for Type 1 Diabetes Prevention**

*Steve Duffy*

The Food and Drug Administration (FDA) has granted Breakthrough Therapy designation to teplizumab (PRV-031; Prevention Bio), an anti-CD3 monoclonal antibody, for the prevention or delay of clinical type 1 diabetes (T1D) in individuals at risk of developing the disease.

The designation was based on data from a recent...
You can get type 1 diabetes at any age!

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)

References:
Family History of T1D

First-degree family member with T1D

- Yes: 16%
- No: 84%


Risk of Developing Type 1 vs Type 2

<table>
<thead>
<tr>
<th>General Population</th>
<th>0.3%</th>
<th>8-11%</th>
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<tr>
<td>If you have a sibling with T1D</td>
<td>4%</td>
<td>~30%</td>
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<tr>
<td>If your mother has T1D</td>
<td>2-3%</td>
<td>~30%</td>
</tr>
<tr>
<td>If your father has T1D</td>
<td>6-8%</td>
<td>~30%</td>
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<tr>
<td>If you have an identical twin with T1D</td>
<td>~50%</td>
<td>100%</td>
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Only ~30% of Type 1s Reach ADA Goal Of An A1c Less Than 7%

A1c Goal = <8.5%
65%
A1c Goal = <8.0%
46%
A1c Goal = <7.5%
23%
20%
30%
27%
34%

Age, years
<6  6-<13  13-<20  20-<26  26-<50  50-<65  ≥ 65

A1c Goal = <7.0%


This is Type 1 Diabetes for a lot of Patients

Modal Day from 10/3/2010 12:30 AM to 10/10/2010 12:00 AM. ## With all days of the week. ## With all times of the day. ## With all glucose values.
These Patients Have the Same A1c

GV, glycemic variability

Provider CGM Overview

1. Review CGM download together with the patient, explain what you are observing
2. Look at average glucose and predicted A1c
3. Look at time in range and start with time hypoglycemic (goal < 5%)
4. Look at total time in ideal range (goal > 70%)
5. Look at 24 hour day to see when highs and lows occur
6. Look at individual days to tease out those problem areas
7. Review alert settings on the CGM. Especially if the significant other looks exhausted and has alarm PTSD
Ambulatory Glucose Profile (AGP): One Report to Rule Them All

**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

- **TAR <5%**
  - 250 mg/dl
  - 13.9 mmol/l
- **TAR <25%**
  - 180 mg/dl
  - 10.0 mmol/l
- **TIR >70%**
  - 70–180 mg/dl
  - 3.9–10.0 mmol/l
- **TBR <4%**
  - <70 mg/dl
  - <3.9 mmol/l
- **TBR <1%**
  - <54 mg/dl
  - <3.0 mmol/l

High risk individuals (with complications or comorbidities & pregnancy) have different targets.


**Improved TIR is Associated with Lower Microvascular Disease**

- Beck 2019 – Looked back at DCCT data for mean TIR of 7-point profiles (n=1440, 32,528 fingerstick glucose)

- **Frequency of Retinopathy**

  - Percent Time in Range (70-180 mg/dL)

DCCT = Diabetes Control and Complications Trial
Available CGM Systems

Options to Connect Directly to Smart Phone/Smart Watch

- Last 10 days
- No calibration
- No finger sticks
- Predictive low alert
- Medicare approved
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
Available CGM + Pump Systems

How Does Control IQ Keep You in Range?

- **Delivers**: Delivers an automatic correction bolus if glucose is predicted to be above 180 mg/dL.
- **Increases**: Increases basal insulin delivery if glucose is predicted to be above 160 mg/dL.
- **Maintains**: Maintains active Personal Profile settings.
- **Decreases**: Decreases basal insulin delivery if glucose is predicted to be below 112.5 mg/dL.
- **Stops**: Stops basal insulin delivery if glucose is predicted to be below 70 mg/dL.
Improved “Time in Range”

Reduced A1c

Reduced Hypoglycemia

Results
Primary Outcome Time in Range 70-180 mg/dL*

*As measured by CGM
Basal Rate Modulation Overnight to Improve Control...

AP Systems Very Effective Overnight
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)

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
Smart Pens: Same Software Programs as Pumps

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

Example of a Bionic Pancreas

2 ports for insulin and glucagon
Let’s Practice
Example Cases

Case 1:
Sam
Quick Interpretation
• Adult with T1D
• A1c ~8%
• High variability
• Minimal lows
• Most glycemic burden overnight

![Graph showing blood glucose levels over time]

- N/A
- 182 mg/dL
- 69 mg/dL
- N/A

Time in range: 79%
Sensor usage: 11.14
Case 1 Cont...

Rises around 1AM without coverage, may be a learned behavior based on experience when no snacking

- To address overnight fall in glucose, we reduced the basal 20%
- Eliminates the need for “mandatory” bedtime snack
- Over time, increased time in range

How Do you Know if the Basal Does is “Right”? 

- Check blood sugar when there is no insulin boluses in the system and no carbohydrates from last meal (e.g. 2-4 AM) and compare to morning blood sugar
- Be on the lookout for variable bedtimes
- If >30mg/dL rise in glucose raise basal insulin dose
- If >30mg/dL fall in glucose decrease basal insulin dose
Physiologic Basal

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.

Statistics for this day

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<tr>
<td>146</td>
<td>42</td>
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<tr>
<td>mg/dL</td>
<td>mg/dL</td>
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Average glucose (CGM) | Standard deviation (CGM) | Time in range

Legend

- CALIBRATIONS
- CARBS
- HEALTH
- INSULIN
- EXERCISE

---

Time after subcutaneous injection (hours)

- 0.8 units/kg
- 0.6 units/kg
- 0.4 units/kg

GIR-glucose infusion

Time since injection (Hours)
Case 1 Learning Points

- Type 1 diabetes does not require a midnight snack
- Nighttime highs SHOULD NOT reflex to increasing basal dose
- To determine if the issue is basal or bolus related, do “basal testing” as discussed
- Often, nighttime highs need to be addressed with more insulin before bed rather than changes to basal
- Newer basal insulins (Glargine U-300, Degludec U-00/U-200) are more consistent, have more flexible dosing, and less hypoglycemia

Case 2: Amelia

- Amelia is a 57 yo female with Type 1 diabetes since age 2
- Was told she needed tight glucose control to avoid complications
- Has since had a fear of HyPERglycemia and prefers to “Ride low”
- Currently on insulin pump with CGM
• Switched to Tandem CIQ

• Episodes of hypoglycemia markedly reduced...

Suspensions to Reduce Hypoglycemia
New Formulations of Glucagon

Nasal Glucagon

Pre-Filled Syringe

Auto-injector Pen

Case 2 Learning Points

• A “good” A1c doesn’t mean good control
• When you see a low A1c, look immediately at percent hypos
• Make sure these patients are on a CGM with alarms turned ON!
• Hybrid closed loop systems can help reduce hypoglycemia
• ALL type 1 patients MUST have glucagon available with loved ones trained on how to use
Case 3: Brian

Quick Interpretation
- Overall glucose just slightly below goal
- Low variability
- Hypos NOT a problem
- Spike after lunch

Top Patterns
This graph shows your data averaged over 14 days

Shark Attack
- Lows after eating are VERY common
- Can result in a “rage bolus”
- Results in lows after and getting on the rollercoaster
Postprandial Glucose bolus at - 20/0/+20 mins

What About the Low Carb Thing?

- It works
- Reduces margin of error
- Not easy to adhere to but given “Atkins craze”, lots of tips on low carb snacks/meals/etc.
- TRY it for one week to see the effect of carbs on your BG
What is Inhaled Insulin?

![Image of inhaled insulin device]

Why is it Cool?

1. Starts working Immediately
2. Gone by about 90 minutes
New, ”Faster Acting” Insulins

Insulin Aspart (Fiasp)  
Insulin Lispro-aabc (Lyumjev)

Insulin Aspart (Fiasp) has Lower Blood Sugars After a Meal Compared to Insulin Aspart (Novolog)

- Fiasp 21 mg/dl lower after 1 hour
- Fiasp 12 mg/dl lower after 2 hours

Graph showing change in blood sugar over time following a meal.
Insulin-Lispro-aabc (Lyumjev) also has lower blood sugars after a meal

- Lyumjev 28 mg/dl lower after 1 hour
- Lyumjev 31 mg/dl lower after 2 hour

Case 3 Learning Points

- Bolus 15-30 minutes BEFORE you eat
- Break up meal into two parts
- Try low carb
- Try inhaled insulin or newer, rapid-acting insulins
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
- New insulin and glucagon formulations
- Advances in hybrid and closed AP
Lecture 3: 11:00 – 12:30 p.m. CDT

Ian Blumer, MD, FRCPC, Presents:

Effective Use of Oral Medications for Type 2 Diabetes:
Lowering Cardiovascular Risk While Improving Glycemic Control
Treatment Should be Individualized and Defects Addressed by Agents with Complementary MOAs

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


American Diabetes Association Standards of Medical Care in Diabetes - 2020
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, hHF, 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 gravest 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 LE artery sclerosis >50%, LVH, eGFR <60 ml/min/1.73, or albuminuria.)
Key Updates to the 2018 ADA/EASD Consensus Recommendations

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 hHF, MACE and CV death
- SGLT2 inhibitors are recommended to prevent the progression of CKD, hHF, 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

Compelling Need to Minimize Hypoglycemia

If A1C above target

- DPP-4i
- GLP-1 RA
- SGLT2i
- TZD

If A1C above target

- SGLT2i OR TZD
- SGLT2i OR TZD
- GLP-1 RA OR DPP-4i OR TZD
- SGLT2i OR DPP-4i OR GLP-1 RA

If A1C above target

Continue with addition of other agents as outlined above

Hierarchy

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. Degludec / glargine U300 < glargine U100 / detemir > NPH insulin

1. Degludec / glargine U300
2. Glargine U100 / detemir
3. NPH insulin

GLP-1 RA
DPP-4i
SGLT2i
TZD
Compelling Need to Minimize Weight Gain or Promote Weight Loss

GLP-1 RA with good efficacy for weight loss

SGLT2i

If A1C above target

SGLT2i

GLP-1 RA with good efficacy for weight loss

If A1C above target

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

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA cautious addition of: ● SU3 ● TZD4 ● Basal insulin

Hierarchy

Semaglutide > Liraglutide > Dulaglutide > Exenatide > Lixisenatide

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. Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i

3. Low dose may be better tolerated though less well studied for CVD effects

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

SU3

TZD2

If A1C above target

TZD2

SU3

If A1C above target

Insulin therapy basal insulin with lowest acquisition cost

OR

Consider DPP-4i OR SGLT2i with lowest acquisition cost

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)

2. Consider country- and region-specific cost of drugs. In some countries, TZDs relatively more expensive and DPP-4i relatively cheaper

3. Chose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i
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

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

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<tr>
<td>A</td>
<td>He needs prandial insulin</td>
</tr>
<tr>
<td>B</td>
<td>He needs a GLP-1RA</td>
</tr>
<tr>
<td>C</td>
<td>Poor adherence with his medication</td>
</tr>
<tr>
<td>D</td>
<td>His diabetes regimen is too complicated</td>
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“Poor Adherence” with Type 2 Medications in the Real World

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

For every 100 Prescriptions written
- 50%–70% Are relayed to the pharmacy
- 48%–66% Leave the pharmacy
- 25%–30% Are taken properly
- 15%–20% 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 ORAL GLP-1 Receptor Agonist (oral semaglutide)
- Bile acid sequestrant (colesevelam)*
- Dopamine receptor agonists (bromocriptine mesylate)*
- Alpha glucosidase inhibitors (acarbose, miglitol)*

*not discussed in detail in this presentation

http://www.fda.gov/drugs
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

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

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Thiazolidinedione (pioglitazone)</td>
</tr>
<tr>
<td>B</td>
<td>DPP-4 inhibitor (sita-, lina-, saxa- and alogliptin)</td>
</tr>
<tr>
<td>C</td>
<td>SGLT-2 inhibitor (cana-, empa-, ertu- or dapagliflozin)</td>
</tr>
<tr>
<td>D</td>
<td>Basal insulin given once a day</td>
</tr>
<tr>
<td>E</td>
<td>GLP-1 RA (liraglutide, exenatide, dulaglutide, semaglutide)</td>
</tr>
</tbody>
</table>

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)**
- 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
- Risk of bladder cancer questionable, and the risk is low (~1/5000 in the general population)
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?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Add pioglitazone</td>
</tr>
<tr>
<td>B</td>
<td>Add a DPP-4 inh.</td>
</tr>
<tr>
<td>C</td>
<td>Add a SGLT-2 inh.</td>
</tr>
<tr>
<td>D</td>
<td>Add a GLP-1 RA</td>
</tr>
<tr>
<td>E</td>
<td>Combination of a DPP-4 inh &amp; SGLT-2 inh.</td>
</tr>
</tbody>
</table>
High CV Risk or Established ASCVD, CKD, and/or HF

Consider independently of baseline A1C of individualized A1C target

<table>
<thead>
<tr>
<th>ASCVD PREDOMINATES</th>
<th>HF OR CKD PREDOMINATES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Established ASCVD</td>
<td>• Particularly HFrEF (LVEF &lt;45%)</td>
</tr>
<tr>
<td>• Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis &gt;50%, or LVH)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PREFERABLY</td>
</tr>
<tr>
<td></td>
<td>SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>SGLT2i with proven CVD benefit if eGFR adequate</td>
</tr>
<tr>
<td>If A1C above target</td>
<td>If A1C above target</td>
</tr>
<tr>
<td>If further intensification is required or patients is no unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:</td>
<td>If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate² add GLP-1RA with proven CVD benefit</td>
</tr>
<tr>
<td>• For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit¹</td>
<td></td>
</tr>
<tr>
<td>• DPP4i if not on GLP-1 RA</td>
<td></td>
</tr>
<tr>
<td>• Basal insulin⁴</td>
<td></td>
</tr>
<tr>
<td>• TZD⁵</td>
<td></td>
</tr>
<tr>
<td>• SU⁶</td>
<td></td>
</tr>
<tr>
<td>• Avoid TZD in the setting of HF</td>
<td></td>
</tr>
<tr>
<td>Choose agents demonstrating CV safety</td>
<td></td>
</tr>
<tr>
<td>• For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit¹</td>
<td></td>
</tr>
<tr>
<td>• DPP4i (not saxagliptin) in the setting of HP (if not not on GLP-1 RA)</td>
<td></td>
</tr>
<tr>
<td>• Basal insulin⁴</td>
<td></td>
</tr>
<tr>
<td>• SU⁶</td>
<td></td>
</tr>
</tbody>
</table>

Case 3 Continued: Treatment History

- A DPP-4/SGLT2 inhibitor combination pill was added to her regimen (once a day and one co-pay)
- Follow up was arranged for one month instead of the usual 3 to 4 months to confirm adherence 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

<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  
                        • Warnings and precautions: pancreatitis, heart failure, acute renal failure, angioedema, Stevens-Johnson, severe arthralgia, bullous pemphigoid |
| Clinical Pearls     | • Efficacy of the DPP-4 inhibitors is similar  
                        • All DPP-4 inhibitors come in combination pill with metformin (Alo- is combined with Pio- and Lina- is combined with empa-; new metformin XR, saxa-, dapa- tablet approved) |

---

### Mechanism of Action: DPP-4 Inhibitors

**Ingestion of food** → **GI tract** → **Release of active incretins GLP-1 and GIP** → **DPP-4 enzyme** → **Inactive GLP-1** and **Inactive GIP**  

**Glucose** → **Insulin**  

**Glucagon** → **Hepatic glucose production**  

**Glucose dependent**  

**Primarily Postprandial but also FBS**  

GLP-1=glucagon-like peptide-1; GIP=glucose-dependent insulinoctropic polypeptide

---

# Generic and Trade Names: DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 Inh.</td>
<td>Alogliptin</td>
</tr>
<tr>
<td></td>
<td>Linagliptin</td>
</tr>
<tr>
<td></td>
<td>Saxagliptin</td>
</tr>
<tr>
<td></td>
<td>Sitagliptin</td>
</tr>
</tbody>
</table>

## 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 ER</td>
<td>Kombiglyze XR</td>
<td>5/500, 2.5/1000, 5/1000</td>
<td>Once daily with evening meal</td>
</tr>
<tr>
<td>Linagliptin/metformin</td>
<td>Jentadueto</td>
<td>2.5/500, 2.5/850, 2.5/1000</td>
<td>Twice with meals</td>
</tr>
<tr>
<td>Linagliptin/empagliflozin</td>
<td>Glyxambi</td>
<td>5/10, 5/25</td>
<td>Once daily</td>
</tr>
<tr>
<td>Dapagliflozin/saxagliptin</td>
<td>Qtern</td>
<td>10 mg/5mg</td>
<td>Once daily</td>
</tr>
<tr>
<td>Alogliptin/pioglitazone</td>
<td>Oseni</td>
<td>25/15, 25/30, 25/45, 12.5/15, 12.5/30, 12.5/45</td>
<td>Once daily</td>
</tr>
<tr>
<td>Alogliptin/metformin</td>
<td>Kazano</td>
<td>12.5/500, 12.5 mg/1000</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>
</tr>
<tr>
<td>Saxagliptin/dapagliflozin/metformin XR</td>
<td>Qternmet XR</td>
<td>2.5/2/5/1000, 2.5/5/1000, 5/5/1000, 5/10/1000</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?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Add a TZD</td>
</tr>
<tr>
<td>B</td>
<td>Add a SGLT-2 inh. (cana-, dapa-, empa-, ertugliflozin)</td>
</tr>
<tr>
<td>C</td>
<td>Try to convince her to add a GLP-1 RA (exena-, liraglu-, dulaglu-, semaglutide)</td>
</tr>
<tr>
<td>D</td>
<td>Try to convince her to add a basal insulin at bedtime</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Reduce renal glucose reabsorption and increases urinary glucose excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benefits</td>
<td>• No hypoglycemia (except when being used with SFU or insulin)</td>
</tr>
<tr>
<td></td>
<td>• Mean A1c reduction ~ 1% (starting from a baseline A1c of ~8.0%)</td>
</tr>
<tr>
<td></td>
<td>• Weight loss (2-5% of body weight) and systolic BP reduction (2-6mmHg)</td>
</tr>
<tr>
<td>Concerns</td>
<td>• Genital mycotic infections. In women (6 to 12% higher than comparator) and in uncircumcised males (2 to 6% higher than comparator)</td>
</tr>
<tr>
<td></td>
<td>• Hypotension secondary to volume contraction especially in the elderly, those on loop diuretic use and in patients with reduced renal function.</td>
</tr>
<tr>
<td></td>
<td>• 4 to 8% elevation in LDL cholesterol (TGs goes down and HDL goes up)</td>
</tr>
<tr>
<td></td>
<td>• Assess renal function (discussed later)</td>
</tr>
<tr>
<td></td>
<td>• New label warnings: DKA (discussed later), risk of amputation (discussed later), bone fractures, Fournier’s Gangrene, acute kidney injury, UTI</td>
</tr>
<tr>
<td>Clinical Pearls</td>
<td>• Cana now approved for renal protection and can be used with a eGFR down to 30</td>
</tr>
<tr>
<td></td>
<td>• Empa- Dapa-and canagliflozin showed positive CVD outcome trials (discussed later)</td>
</tr>
<tr>
<td></td>
<td>• Can be added to any other oral agent or injectable</td>
</tr>
<tr>
<td></td>
<td>• 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)</td>
</tr>
</tbody>
</table>

### Generic and Trade Names: SGLT-2 Inhibitors

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

**Canagliflozin:**
- Suggested starting dose: 100 mg daily before first meal of day (eGFR >45 mL/min)/with CKD can use to a eGFR of 30mL/min
- Increase to 300 mg daily if tolerating 100 mg daily and eGFR > 60 mL/min

**Dapagliflozin:**
- Starting dose: 5mg 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>45 mL/min)
- Increase to 25 mg daily if tolerating and need additional glycemic control (eGFR>45 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

---

### Renal Handling of Glucose in a Non-Diabetic Patient

- **180 g/day/1.73 m²** is filtered glucose load¹
- SGLT-2 transports 90% of filtered glucose out of the tubular lumen¹⁻⁴

**Glucose reabsorbed into systemic circulation**

**No detectable glucose in urine**

---

SGLT = sodium-glucose co-transporter.

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, urosepsis and pyelonephritis

December 14, 2015

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

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

Primary Objectives of Effective Management:
Important Basics...The ‘ABCs’

- **A1C %**
  - General goal is < 7% but must be individualized
  - Reduction of eye, kidney, nerve and heart disease by 75%

- **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)

American Diabetes Association. *Diabetes Care*. 2017;40(suppl 1)
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<70 mg/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>
</tbody>
</table>

**PCSK9 inhibitors (evolocumab and alirocumab) if LDL not at goal on maximally tolerated statin/ezetimide**

Just approved in 2020 bempedoic acid (Nexletol), first in class LDL medication

*Once-daily dosing. XL, extended release.
Management Of Hypertriglyceridemia

1. Elevated triglycerides combined with low HDL levels are part of the insulin resistant state and metabolic syndrome.
2. Diet, exercise and improved glycemic control will improve but not typically normalize elevated TG levels in type 2 DM.
3. The goal is to get the TGs to below 200mg/dl, which in turn will elevate the HDL levels.
4. Fibric acid derivatives such as fenofibrate are commonly used to treat high TGs.
5. Icosapent ethyl is an omega-3 fatty acid that has the formal indication from the FDA to reduce heart attacks and strokes in patient who have or are at risk for ASCVD.

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>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<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>June 2013</td>
<td>June 2013</td>
<td>June 2015</td>
<td>June 2017</td>
<td>June 2017</td>
</tr>
</tbody>
</table>
Non-Insulin CVOTs in T2D: SGLT-2 Inhibitors (Primarily driven by a reduction in heart failure)

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS</th>
<th>DECLARE</th>
<th>VERTIS CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT-2-i</td>
<td>empagliflozin ✓</td>
<td>canagliflozin ✓</td>
<td>dapagliflozin ✓</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo ✓</td>
<td>placebo ✓</td>
<td>placebo ✓</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>7300</td>
<td>4300</td>
<td>22,200</td>
<td>3900</td>
</tr>
<tr>
<td>Results</td>
<td>Sept 2015</td>
<td>2017</td>
<td>2018</td>
<td>Late2020</td>
</tr>
</tbody>
</table>

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>EXSCEL</th>
<th>HARMONY</th>
<th>REWIND</th>
<th>PIONEER 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>Liraglutide</td>
<td>Lixisenatide</td>
<td>Sema-glutide</td>
<td>Exenatide LR</td>
<td>Albiglutide</td>
<td>Dulaglutide</td>
<td>Oral semaglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<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>
</tbody>
</table>

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

Adapted from a slide courtesy of Silvio Inzucchi MD, Yale University
Diabetes Medications FDA Approved for CV Risk Reduction

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

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

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).

Dulaglutide (based on REWIND data)
• for the reduction of major adverse cardiovascular events (MACE) in adults with type 2 diabetes who have established cardiovascular (CV) disease or multiple cardiovascular risk factors.

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 effect results

Gautam Das, Journal of Diabetes Research & Clinical Metabolism 2015,
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

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 4: 1:00 – 2:15 p.m. CDT

Steven V. Edelman, 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?**

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

**High CV risk or established ASCVD, CKD and/or HF**

<table>
<thead>
<tr>
<th>Consider independently of baseline A1C of individualized A1C target</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ASCVD PREDOMINATES</strong></td>
</tr>
<tr>
<td>• Established ASCVD</td>
</tr>
<tr>
<td>• Indicators of high ASCVD risk (age ≥ 55 years with coronary, carotid or lower extremity artery stenosis ≥ 50%, or LVM)</td>
</tr>
<tr>
<td><strong>PREFERABLY</strong></td>
</tr>
<tr>
<td>GLP-1 RA with proven CV benefit(^1) OR SGLT2i with proven CV benefit if eGFR adequate</td>
</tr>
<tr>
<td><strong>If A1C above target</strong></td>
</tr>
<tr>
<td>If further intensification is required or patients are unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:</td>
</tr>
<tr>
<td>• For patients on a GLP-1 RA, consider adding SGLT2i with proven CV benefit(^2)</td>
</tr>
<tr>
<td>• DPP4i if not on GLP-1 RA</td>
</tr>
<tr>
<td>• Basal insulin(^3)</td>
</tr>
<tr>
<td>• TZD(^4)</td>
</tr>
<tr>
<td>• SLIP(^5)</td>
</tr>
</tbody>
</table>

| **HF OR CKD PREDOMINATES**                                    |
| • Particularly HF/EF (LVEF < 45%)                            |
| • CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR > 30 mg/g, particularly UACR > 300 mg/g |
| **PREFERABLY**                                               |
| SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate\(^6\) OR If SGLT2i is not tolerated or contraindicated or if eGFR less than adequate\(^7\) add GLP-1RA with proven CV benefit |
| **If A1C above target**                                      |
| • Avoid TZD in the setting of HF                             |
| • Choose agents demonstrating CV safety                     |
| • For patients on a SGLT2i, consider adding GLP-1 RA with proven CV benefit |
| • DPP4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA) |
| • Basal insulin\(^8\)                                        |
| • SLIP\(^9\)                                                |

1. Proven CV benefit means it has label indication of reducing CV events. 2. Be aware that SGLT2i labelling varies by region and individual agent with regard to indicated level of eGFR for initiation and continued use. 3. Empagliflozin, canagliflozin and dapagliflozin have shown reduction in HF and to reduce CKD progression in CVOTs. Canagliflozin has primary renal outcome data from CREDENCE. Dapagliflozin has primary HF outcome data from DAPA-HF. 4. Degludec and U100 glargine have demonstrated CVD safety. 5. Low dose may be better tolerated though less well studied for CVD effects. 6. Choose later generation SU to lower risk of hypoglycemia. Glimepiride has shown similar CV safety to DPP-4i.
### Basal Insulin vs GLP-1 RA

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin: Injected once or twice a day</td>
<td>GLP-1 RA: Injectable once or twice a day, injectable once weekly, or oral once daily</td>
</tr>
<tr>
<td>Need to titrate dose to achieve the desired FBS</td>
<td>Titrate to the highest acceptable dose to avoid 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: Gluco regulatory Role of Incretins

- **GLP-1 secreted upon the ingestion of food**
  - FBG and PPG control
  - Promotes satiety and reduces appetite
  - Pancreatic alpha cells: ↓ Postprandial glucagon secretion
  - Pancreatic beta cells: Enhanced glucose-dependent insulin secretion
  - Liver: Reduced hepatic glucose output
  - Stomach: Helps regulate gastric emptying

---

### GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mimic the effects of human GLP-1</td>
<td>• Significant A1c reductions (1.0 to 3.0% depending on baseline)</td>
</tr>
<tr>
<td></td>
<td>• Shorter acting GLP-1 RAs have greater effects on PPG</td>
</tr>
<tr>
<td></td>
<td>• Weight loss</td>
</tr>
<tr>
<td></td>
<td>• No hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>• Once daily, twice daily and once weekly formulations</td>
</tr>
<tr>
<td>Concerns</td>
<td>• GI side effects (typically nausea)</td>
</tr>
<tr>
<td></td>
<td>• Contraindicated in patients with a personal or family history of MTC or MEN2</td>
</tr>
<tr>
<td></td>
<td>• Relative contraindication in patients with a history of pancreatitis (important to know the etiology)</td>
</tr>
<tr>
<td>Clinical Pearls</td>
<td>• Ideal choice in obese patients with poor control, especially those on large doses of insulin</td>
</tr>
<tr>
<td></td>
<td>• “No” need to initiate or increase glucose testing</td>
</tr>
<tr>
<td></td>
<td>• Several with positive CVOT results</td>
</tr>
</tbody>
</table>

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

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

**Generic Name**
- Exenatide
- Liraglutide
- Dulaglutide
- Lixisenatide
- Semaglutide
- Oral Semaglutide

**Trade Name**
- Byetta
- Bydureon
- Victoza
- Trulicity
- Adlyxin
- Ozempic
- Rybelsus
Generic and Trade Names: GLP-1 RAs, Continued

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


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

<table>
<thead>
<tr>
<th>MACE Outcomes</th>
<th>Study Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value (superiority)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>408/3034 (13.4%)</td>
<td>399/3034 (13.2%)</td>
<td>1.02</td>
<td>0.89, 1.17</td>
<td>0.81</td>
</tr>
<tr>
<td>LEADER</td>
<td>609/4668 (13%)</td>
<td>604/4667 (14.9%)</td>
<td>0.87</td>
<td>0.78, 0.97</td>
<td>0.01*</td>
</tr>
<tr>
<td>SUSTAIN-6*</td>
<td>108/1648 (6.6%)</td>
<td>146/1649 (8.9%)</td>
<td>0.74</td>
<td>0.56, 0.95</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>EXCEL</td>
<td>839/7356 (11.4%)</td>
<td>905/7396 (12.2%)</td>
<td>0.91</td>
<td>0.63, 1.00</td>
<td>0.06</td>
</tr>
<tr>
<td>Harmony Outcomes</td>
<td>338/4731 (7.1%)</td>
<td>428/4732 (9.1%)</td>
<td>0.78</td>
<td>0.66, 0.90</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

*Superiority testing not a prespecified analysis

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

Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Study Drug</th>
<th>Placebo</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA (lixisenatide vs PBO)</td>
<td>122/2834 (4.0%)</td>
<td>127/3034 (4.2%)</td>
<td>0.96</td>
<td>0.75, 1.23</td>
</tr>
<tr>
<td>LEADER (liraglutide vs PBO)</td>
<td>218/4666 (4.7%)</td>
<td>248/4672 (5.3%)</td>
<td>0.87</td>
<td>0.73, 1.05</td>
</tr>
<tr>
<td>SUSTAIN-6 (semaglutide vs PBO)</td>
<td>62/1648 (3.7%)</td>
<td>54/1649 (3.3%)</td>
<td>1.11</td>
<td>0.77, 1.61</td>
</tr>
<tr>
<td>EXCEL (exenatide vs PBO)</td>
<td>219/7356 (3.0%)</td>
<td>231/7396 (3.1%)</td>
<td>0.94</td>
<td>0.78, 1.13</td>
</tr>
</tbody>
</table>

Harmony Outcomes (albiglutide vs PBO)
HR 0.85 (0.70, 1.04); p=0.113
Composite of CV death or HHF


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

TECHNOLOGY

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

MEDICATION:

EXENATIDE

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

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?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Start a DPP4 inhibitor</td>
</tr>
<tr>
<td>B</td>
<td>Try to convince her to start basal insulin and titrate the dose to get her FBS less than 140mg/dl</td>
</tr>
<tr>
<td>C</td>
<td>Start a GLP1-RA</td>
</tr>
<tr>
<td>D</td>
<td>Initiate a fixed combination of a basal insulin and a GLP-1RA</td>
</tr>
</tbody>
</table>
Case 2 continued

- 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%.

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

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

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/1.8mg liraglutide)
- Injected once daily at 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

<table>
<thead>
<tr>
<th>Pen dose steps (units): insulin degludec + liraglutide</th>
<th>Pen dose steps (units): insulin glargine + lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 dose steps=10 units insulin degludec +0.36 mgs of liraglutide</td>
<td>15 dose steps=15 units insulin glargine + 5 mcg of lixisenatide</td>
</tr>
<tr>
<td>50 dose steps=50 units insulin degludec +1.8 mgs of liraglutide</td>
<td>30 dose steps=30 units insulin glargine + 10 mcg of lixisenatide</td>
</tr>
<tr>
<td>50 dose steps=50 units insulin degludec +1.8 mgs of liraglutide</td>
<td>60 dose steps=60 units insulin glargine + 20 mcg of lixisenatide</td>
</tr>
</tbody>
</table>

Starting dose:

16 dose steps which has 16 units insulin degludec + 0.58 mgs of liraglutide

Starting dose:

If glargine U-100 dose is <30, start at 15 dose steps which has 15u glargine + 5mcg lixi

If glargine U-100 dose is >30, start at 30 dose steps which has 30u glargine + 10 mcg lixi

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

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

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 10

A1c of 8.3% at baseline drops to 6.4% with Insulin Degludec/Liraglutide

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

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%

5 6 7 8 9 10
A1c (%)

0 2 4 6 8 10 12 14 16 18 20 22 24
Time (weeks)

IDegLira (n=833)
Liraglutide (n=414)
Insulin degludec (n=413)

-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

Inclusion Criteria:
- Type 2 diabetes
- Insulin naïve
- BMI < 40 kg/m²
- Age ≥ 18 years
- A1c 7.0 – 10.0%

Mean weight values (+SEM) based on FAS and LOCF imputed; estimated treatment difference and p-values are from an ANCOVA analysis

Hypoglycemia: PG <56 mg/dL and/or requiring assistance, PYE: Patient years exposure; RR: Rate ratio: IDegLira/Comparator; p<0.05 two-sided. *p=0.002; **p<0.0001

Buse J et al. ADA 2013, 65-OR

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Insulin degludec/liraglutide Rate (episodes/PYE)</th>
<th>Insulin degludec Rate (episodes/PYE)</th>
<th>Liraglutide Rate (episodes/PYE)</th>
<th>Insulin degludec/liraglutide vs. insulin degludec RR Estimate (95% CI)</th>
<th>Insulin degludec/liraglutide vs. liraglutide RR Estimate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.80</td>
<td>2.57</td>
<td>0.22</td>
<td>0.68 (0.53; 0.87)*</td>
<td>7.61 (5.17; 11.21)**</td>
</tr>
</tbody>
</table>

Buse J et al; ADA 2013, 65-OR

Hypoglycemia: PG <56 mg/dL and/or requiring assistance, PYE: Patient years exposure; RR: Rate ratio: IDegLira/Comparator; p<0.05 two-sided. *p=0.002; **p<0.0001
Effects of insulin degludec/liraglutide in patients with poorly controlled type 2 diabetes with HbA1c >9%: analyses from the DUAL program


Gastrointestinal Side Effects: Gradual Titration Helps

Subjects experiencing nausea, vomiting or diarrhea (%)

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

Aroda et al. Diabetes 2015;64 (Suppl. 1):A235; abstract 1009-P
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 (%)

Initial Baseline

Week

Screening

8

12

24

30

Insulin glargine lixisenatide (N = 366)

Mean Difference p-value

8.5%

8.1%

7.5%

Insulin glargine lixisenatide (N = 366)

vs Glargine (N = 365)

-0.52% <0.0001

% Patients with A1C < 7.0% at Week 30

Glargine

Insulin glargine lixisenatide

30

55

20

9

A1C < 7.0% with No Wt Gain and No Symptomatic Hypoglycemia

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

Mean baseline 9.4%

Reduction in A1C from baseline to Week 30

A1C: 7.0%

SOLIQUA 100/33 (n=48)

GLP-1 RA (Lixisenatide) (n=26)

-1.7%

p<0.0001

Lantus (n=55)

-2.5%

p=0.0297

Final doses

• Combination: 45 units

• Glargine only: 44 units

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.

Generic and Trade Names: Insulin

<table>
<thead>
<tr>
<th></th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fast-Acting Insulin</strong></td>
<td>regular</td>
<td>Humulin R, Novolin R</td>
</tr>
<tr>
<td></td>
<td>U-500 regular aspart</td>
<td>Humulin R U-500</td>
</tr>
<tr>
<td></td>
<td>faster acting aspart</td>
<td>NovoLog</td>
</tr>
<tr>
<td></td>
<td>glulisine</td>
<td>Fiasp</td>
</tr>
<tr>
<td></td>
<td>lispro (U-100 and U-200)</td>
<td>Apidra</td>
</tr>
<tr>
<td></td>
<td>Follow on biologic lispro</td>
<td>Humalog</td>
</tr>
<tr>
<td></td>
<td>inhaled insulin</td>
<td>Admelog</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Afrezza</td>
</tr>
<tr>
<td><strong>Basal Insulin</strong></td>
<td>intermediate-acting: NPH</td>
<td>Humulin N</td>
</tr>
<tr>
<td></td>
<td>long-acting: detemir</td>
<td>Novolin NPH</td>
</tr>
<tr>
<td></td>
<td>glargine (U-100)</td>
<td>Levemir</td>
</tr>
<tr>
<td></td>
<td>glargine (U-300)</td>
<td>Lantus</td>
</tr>
<tr>
<td></td>
<td>degludec (U-100/200)</td>
<td>Toujeo</td>
</tr>
<tr>
<td></td>
<td>follow-on biologic</td>
<td>Tresiba</td>
</tr>
<tr>
<td></td>
<td>glargine (U-100)</td>
<td>Basaglar</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>Rapid-acting</td>
<td>10-15 mins</td>
<td>60-90 mins</td>
<td>4-5 hrs</td>
</tr>
<tr>
<td>Regular</td>
<td>30-60 mins</td>
<td>2-4 hrs</td>
<td>5-8 hrs</td>
</tr>
<tr>
<td>NPH</td>
<td>1-3 hrs</td>
<td>5-8 hrs</td>
<td>12-18 hrs</td>
</tr>
<tr>
<td>Detemir</td>
<td>90 mins</td>
<td>Relatively peakless</td>
<td>12-24 hrs</td>
</tr>
<tr>
<td>Glargine</td>
<td>90 mins</td>
<td>Relatively peakless</td>
<td>24 hrs</td>
</tr>
</tbody>
</table>

**Inhaled insulin**: peak by 10-15 min, duration of 2-3 hrs  
**Faster-acting aspart**: onset faster, duration shorter, than rapid-acting

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### 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 to 1 conversion from prior basal dose (patients switching from U-100 to U-300 glargine may need ~15% more)
- Both insulins come in easy to use pens

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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></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>---</td>
<td>185</td>
</tr>
<tr>
<td>Tuesday</td>
<td>247</td>
<td>---</td>
<td>174</td>
<td>---</td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td>---</td>
<td>---</td>
<td>196</td>
</tr>
<tr>
<td>Thursday</td>
<td>226</td>
<td>---</td>
<td>179</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
Injectable Agents

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

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

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.


Self Titration Clinic Form

**Starting/Adjusting Long-Acting Basal Insulin**

1. Give Basal insulin once a day at Morning
2. Starting dose: 20 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 140, then increase your dose by 2
   b. If fasting blood sugar is under 90, then decrease your dose by 2
   c. If fasting blood sugar is between 90 and 140, then keep the same Lantus dose

Important:
The purpose of long active basal is to provide a background amount of insulin throughout the day and at night while you sleep. It is not meant to treat high blood sugars caused by eating food, so you should not change your dose based on blood sugar 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 canafloxacin (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>148 – 229 mg/dL</td>
<td>(175 mg/dL)</td>
</tr>
<tr>
<td>Pre- Lunch</td>
<td>111 – 182 mg/dL</td>
<td>(147 mg/dL)</td>
</tr>
<tr>
<td>Pre- Dinner</td>
<td>91 – 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

Which of the following would you suggest for this patient?

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Initiate pioglitazone</td>
</tr>
<tr>
<td>B</td>
<td>Initiate basal insulin</td>
</tr>
<tr>
<td>C</td>
<td>Start a GLP-1 RA and stop his DPP-4 inhibitor</td>
</tr>
<tr>
<td>D</td>
<td>Change to a different SGLT-2 Inhibitor</td>
</tr>
</tbody>
</table>
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>Range</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>82 – 155 mg/dL</td>
<td>(~122 mg/dL)</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>Bedtime</td>
<td>128 – 183 mg/dL</td>
<td>(~155 mg/dL)</td>
</tr>
</tbody>
</table>

- A1c dropped to 7.1%, no hypoglycemia. Gained 2 lbs in 3 months
- Oral agents can be continued unless hypoglycemia occurs during the day, in which case the sulfonylurea should be reduced or withdrawn

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.

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

Step 1
- U-100/300 glargine, det., deg or NPH @ HS
- Titration based on FPG
- All oral agents continued

Step 2
- Add FA analog
- Inhaled insulin
- Main meal
- Above target

Step 3
- Add FA analog
- Inhaled insulin
- Next largest meal
- Above target

Step 4
- Add FA analog
- Inhaled insulin
- Last meal
- Above target

A1c < 7.0%, FPG < 130 mg/dL

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)
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 diabetes because of significant glucose lowering in addition to weight loss and reducing the risk of hypoglycemia.

- Combination therapy (adding basal insulin to daytime OHAs/GLP1-RAs) is safe, effective and easy to implement.

- The fixed combination of basal insulin and a GLP-1 RA has clinical advantages in terms of efficacy, reduced side effects and ease of use.

- The Basal Bolus approach in type 2 diabetes does not need to be four injections per day (pens, patch pumps and inhaled insulin to improve adherence).

- Adherence and persistence needs to be addressed at every visit.

- Protection for ASCVD.