Individualizing Care for Patients with Type 2 Diabetes

Disclosures
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Objectives
- Develop individualized approaches to treating patients with T2DM.
- Select appropriate treatment to optimize safe achievement of clinical targets.
- Review new and emerging therapies in the pipeline for diabetes

Individualized Therapy is based on:
- Initial A1C level
- Patient symptoms
- Patient preferences
- Clinical parameters (renal, hepatic, cv, etc.)
- Financial considerations
- Patient motivation
- Comorbid conditions/Life expectancy

Individualized Therapy: Biases
- Avoid treat to failure paradigm
- More aggressive control early in the course of disease leads to better control and more stability in control over time (initial dual combination therapy)
- Whenever possible use agents that minimize risk for hypoglycemia and weight gain
- Preservation of beta cell function should be a target of therapy
- A positive relationship with you the provider is key to successful outcomes
First Line Therapy: Metformin

- **Generic**
- Mechanism of action:
  - Increase insulin action
  - Decrease gluconeogenesis
  - Decrease glucagon secretion
- Best for:
  - Therapy-naive
  - Polycystic ovarian syndrome
- Contraindications:
  - CHF
  - Renal impairment
  - Caution in hepatic impairment
- Considerations:
  - Vitamin B12
  - Slow titration

Considerations for Selecting a Second Line Agent

- Consider pt’s starting and target A1C
- Weight loss goals
- Hypoglycemic risk
- Consider needle phobia, pt’s dexterity and eyesight
- H/O poor medication adherence when considering multiple daily dosing
- FH and PMH of contraindications

**Sulfonylureas**

- Generic
- Mechanism of action:
  - Stimulates beta cell insulin release
- Best for:
  - Low risk of hypoglycemia
  - Can tolerate mild weight gain
  - Cost
- Contraindications:
  - Caution in hepatic and renal impairment
- Considerations:
  - Fat risk
  - Bone density
  - Hypoglycemic unawareness
  - Sulfa allergy

**DPP-IV Inhibitors**

- Brand-only
- Mechanism of action:
  - Slows incretin metabolism
  - Increases insulin synthesis/release
  - Decreases glucagon levels
- Excretion:
  - Renal: sitagliptin, saxagliptin, alogliptin
  - Renal: liraglutide
- Best for:
  - Modest decrease in A1C
  - Postprandial hyperglycemia
  - Poor medication adherence
- Contraindications:
  - Dose adjustment in renal impairment (not linagliptin)
  - H/O or at risk for pancreatitis

**Second line choices**

- **Sulfonylureas**—glimepiride, glipizide, glyburide
- **DPP-IV Inhibitors**—sitagliptin, saxagliptin, alogliptin, linagliptin
- **GLP-1 Agonists**—liraglutide (qd), exenatide (bid), exenatide weekly, albiglutide (weekly), dulaglutide (weekly)
- **SGLT2 Inhibitors**—canagliflozin, dapagliflozin, empagliflozin
- **Basal Insulin**—Glargine, detemir, NPH
GLP-1 Agonist

- **Mechanism of action**
  - Augment glucose-dependent insulin secretion
  - Slow gastric emptying and increase satiety to promote weight loss
  - May increase beta cell number and function
- **Best for**
  - Weight loss
  - Appetite control
  - Poor medication adherence (liraglutide, weekly exenatide, albuglutide and dulaglutide)
- **Contraindications**
  - Gastroparesis
  - History or risk for pancreatitis
  - Prior diagnosis of islet cell tumor, thyroid CA or MEN 2
- **Considerations**
  - liraglutide and exenatide—titration
  - Weekly exenatide—depot under skin and may take 2-3 months for full efficacy

Generic

- **Mechanism of action**
  - Improve insulin sensitivity
  - Decrease hepatic glucose output
  - Decrease lipolysis (lower FFA)
- **Best for**
  - Insulin resistance
  - Potential CV benefits
  - Best record for durability
- **Contraindications**
  - CHF
  - Bladder CA
- **Considerations**
  - Edema, CHF
  - Wt. gain
  - Fracture risk, bladder cancer

SGLT-2 Inhibitors

- **Not on the 2014 ADA algorithm**
- **Brand-only**
- **Mechanism of action**
  - Blocks reabsorption of renal glucose
- **Best for**
  - Weight loss
  - Moderate A1C reduction
  - Poor medication adherence
- **Contraindications**
  - GFR < 44 (canagliflozin, empagliflozin)
  - GFR < 50 (dapagliflozin)
- **Considerations**
  - Monitor hydration
  - Monitor for hyperkalemia (canagliflozin, dapagliflozin)
  - Caution for genitourinary infections
  - No data on long term effects of glucosuria

Insulin Therapy

- **Glarine and Detemir vs NPH**
  - Slightly better A1C
  - Less weight gain
  - Less Hypoglycemia
  - More expensive

What data do you need?

- Useful BG monitoring data (7 point profile)
  - Cause and effect information helpful to modify behavior
  - Identify and correct recurring patterns
- What is the patient really doing
  - Does the patient have adequate education and resources to be successful
  - Labs (A1C, etc.), physical exam data

Case 1

- 64 yo Hispanic male, new onset diabetes
- A1C: 10.2%  Wt: 150 lbs  BMI: 24.2
- PMH: HTN, Hyperlipidemia
- FH: Mother – type 2 diabetes
- Meds: atorvastatin 20 mg, Lisinopril 10 mg
- Symptoms: Polydipsia, polyuria, wt. loss, fatigue
- Social: married, works as grounds keeper, drinks 64 oz sugared soda per day

What would you start this patient on as initial therapy?

- A. Metformin monotherapy
- B. Metformin + DDP-4 or GLP-1
- C. Basal insulin alone
- D. Basal insulin plus dual therapy
- E. Basal Bolus therapy
Case 1

- Begin glargine 10 units q hs with titration of increase 2 units every 3 days until FBG < 120
- Begin sitagliptin/metformin 50/500 mg bid
- Discontinue regular soda
- Referral to CDE

3 week follow-up visit – diet improved
- Still on glargine 10 units as FBG 90-110 mg/dl with this dose
- Tolerating sitagliptin/metformin 50/500 mg bid

PLAN: D/C glargine, increase sitagliptin/metformin to 50/1000 mg bid

Case 1

- 3 month follow-up: A1C 6.2%, asymptomatic
- Plan: continue sitagliptin 50/1000 mg bid, encouraged continued diet and exercise improvements
- For the subsequent 5 yrs, patient’s A1C has remained between 5.7 – 6.3%

“Overbasalization” May Lead to Inadequate Glycemic Control

- Overbasalization can be described as continued titration of basal insulin without any appreciable improvement in glucose control
- Continued titration of basal insulin may not achieve A1C goals and may require a change in treatment strategy
- Overbasalization increases the risk of adverse reactions, such as hypoglycemia


Decreasing PPG Results in Better Overall Glycemic Control

- It is clear that postprandial hyperglycemia, like prandial hyperglycemia, contributes to elevated A1C levels, with its relative contribution being higher at A1C levels that are closer to 7%.

- A1A 2013 Standards of Care

Intensification of Insulin Therapy

- Combination of Basal insulin and GLP-1 agonist found effective in meta-analysis
- Adding one dose of prandial insulin at a time can decrease the burden on the patient and lower hypoglycemia risks
- New patch/pump therapies for Type 2 patients can simplify basal/bolus regimens

FullSTEP Study

Designed to Support Multiple Intensification Options

Type 2

FullSTEP

Stepwise

- Stagger dose 4 wks.
- 1st NovoLog™ injections at last largest prandial eats
- 2nd NovoLog™ injection at largest prandial eats
- Basal-Bolus
- Basal-Bolus
- Basal-Bolus
- Basal-Bolus

Type 2 T2DM

0 NovoLog™ injections (breakfast, lunch, dinner)

Weeks 0 4 8 12
Participants:
10 12 22 32

Screening

Randomization

32 weeks treat-to-target

The FullSTEP study was a phase 3, 32-week, randomized, open-label, parallel-group, multinational, treat-to-target, noninferiority trial conducted at 150 sites across 7 countries.

Distribution of Mealtime Injections in the Stepwise Arm at End of Trial

Type 2

FullSTEP

Hypoglycemia Rates

Type 2

FullSTEP

Study Conclusions

- The stepwise regimen was noninferior to the basal-bolus regimen with respect to A1C change from baseline to 32 weeks
- There was a significantly lower rate of hypoglycemia in the stepwise arm vs the basal-bolus arm
- A higher proportion of participants withdrew from the trial in the basal-bolus arm vs the stepwise arm
- Stepwise insulin intensification was safe and achieved glycemic control
Unexplained High BG

- What are the possibilities?
  - Missed doses of oral meds/insulin
  - Inaccurate doses of insulin (vision, technique)
  - Lipohypertrophy
  - Fluid balance
  - Infection: UTI, Bronchitis, Pneumonia, Influenza, Skin, MRSA, infected diabetic foot ulcer
  - Other stress: silent MI, CHF, etc.
  - Psychosocial choices
  - Noncompliance (steroid injection, medrol dose pack)
  - Inadequate meter/strips
  - Major life stressors (family crisis, work stress, etc.)

Glucagon-like peptide-1 receptor agonist and basal insulin combination treatment for the management of type 2 diabetes: a systematic review and meta-analysis

- 15 studies, 4,348 patients
- Compared to other therapies
  - 0.44% decrease in A1C
  - ~2x greater chance of A1C < 7.0%
  - Weight decrease of 3.22 kg
- Compared to basal bolus insulin therapy
  - 0.1% reduction in A1C
  - 33% decrease in risk of hypoglycemia
  - Weight decrease of 5.4 kg

Inhaled Insulin

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In the Pipeline
- New long acting insulins
  - degludec (Novo)
  - peglispro (Lilly)
  - glargine U-300 (Sanofi)
- Lower rates of nocturnal hypoglycemia compared to glargine
- Once weekly DPP-4 oral agent (Merck)
- Oral GLP-1 therapy (Sanofi)
- New long acting insulin/GLP-1 combination products
- New Fast Acting insulin analogues

Questions and Answers

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