MEDICATION MANAGEMENT OF TYPE 2 DIABETES MELLITUS

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NYSSPA 2018 Conference

OBJECTIVES

- Review basic mechanism of action, adverse effects and efficacy of commonly used hypoglycemic agents
- Outline the current approach to medication management of Type 2 diabetes
- Review stepwise approach to second or third line medications in patients who fail metformin monotherapy
- Review current data for cardiovascular (CV) benefits with SGLT2 inhibitors (Jardiance, etc.) or GLP-1 agonists (Victoza, etc)
- Discuss the potential benefits and costs of combining a flozin and GLP-1 agonist
- Review current data regarding adverse effects of newer classes of hypoglycemic agents

GLYCEMIC GOALS

- IN general
- A1C goal <7 percent
  - (A1C levels can be higher in elderly patients)
- Fasting glucose 80 to 130 mg/dL (4.4 to 7.2 mmol/L)
- Postprandial glucose (90 to 120 minutes after a meal) less than 180 mg/dL (10 mmol/L)

GENERAL RECOMMENDATIONS FOR INITIAL DRUG SELECTION IN TYPE 2 DM

- Lifestyle modification in conjunction with
  - **Metformin** for most Type 2 DM patients in absence of contraindications
  - Severe and symptomatic hyperglycemia= insulin
    - fasting plasma glucose >250 mg/dL
    - random glucose consistently >300 mg/dL
    - A1C >9.5

GENERAL RECOMMENDATIONS FOR DRUG SELECTION WITH PERSISTENT HYPERGLYCEMIA IN TYPE 2 DM

- Failure to achieve glycemic goals within 3 months of lifestyle modifications and metformin (dosage titrated to target or as tolerated)
- Add a second agent
  - **A1C >8.5 %** or persistent symptoms of hyperglycemia
  - Insulin or a glucagon-like peptide-1 (GLP-1) receptor agonist

  - **A1C ≤8.5** percent assess patient characteristics
    - Weight issues: GLP -1 , SGLT-2 or DPP IV inhibitors
    - **CV disease**: GLP-1 receptor agonist (liraglutide or semaglutide) or sodium-glucose co-transporter 2 (SGLT2) inhibitor (empagliflozin or canagliflozin
    - Cost: SU
    - NASH: pioglitazone

PERSISTENT HYPERGLYCEMIA WITH DUAL AGENT FAILURE

- Several options (tailor to patients needs)
  - REINFORCE lifestyle modifcations
  - **Insulin (basal)**
  - Two oral agents (e.g. metformin and SU) and a GLP-1 receptor agonist
  - One oral agent (usually metformin), plus basal insulin, and a GLP-1 receptor agonist

- If adding insulin usually taper of SU
- Start with a single dose of basal insulin at am or bedtime and adjust dose according to SBGM levels every 3-4 days

ORAL HYPOGLYCEMIC AGENTS

- Metformin
- Sulfonylureas
- Short acting insulin secretagogues
- Thiazolidinediones (“glitazones)
- Alpha glucosidase inhibitors
- Dipeptidyl peptidase inhibitors (gliptins)
- Sodium glucose cotransporter 2 inhibitors

METFORMIN

- MOA: decrease hepatic glucose output by inhibiting gluconeogenesis and increases insulin-mediated glucose utilization in peripheral tissues e.g. muscle and liver

- AE:
  - The most common side effects are gastrointestinal: mild anorexia, nausea, abdominal discomfort, and soft bowel movements or diarrhea
  - B12 deficiency
  - Lactic acidosis : very rare

- Precautions and contraindications:
  - contraindicated in patients with factors predisposing to **lactic acidosis**
  - Avoid in chronic kidney disease
    - Impaired renal function (estimated glomerular filtration rate [**eGFR] <30 mL/min)**

METFORMIN

- Dosing and titration
  - 500 mg once daily with the evening meal
  - add a second 500 mg dose with breakfast.
    - increased slowly (one tablet every one to two weeks)
    - Recheck in 3 months
- Max doses (2.5 g/day)
- Metformin
  2,000 to 2,550 mg, divided BID to TID (~$10)

- Metformin XR
  2,000 mg to 2,500 mg, divided BID (~$120)
  - **Combination tablets of metformin and all of the oral agents are available in several doses.**

METFORMIN

- Efficacy :
  - Reduction in fasting blood glucose concentrations by approximately 20 percent and A1C by **1.5 percent**
  - Also can promote **weight loss** unlike SU and insulin

- Role in therapy : preferred for monotherapy in most patients with Type 2 DM in the absence of contraindications

METFORMIN

- Predisposing factors for lactic acidosis and metformin contraindications:
  - Impaired renal function (estimated glomerular filtration rate [eGFR] <30 mL/min)
  - Concurrent active or progressive liver disease
  - Active alcohol abuse
  - Unstable or acute heart failure at risk of hypoperfusion and hypoxemia
  - Past history of lactic acidosis during metformin therapy
  - Decreased tissue perfusion or hemodynamic instability due to infection or other causes

SULFONYLUREAS (SU):

Drugs and dosages (m/c used SU)

- Glipizide, 2.5 mg of glipizide po 30 minutes before breakfast (17$)
- Glimepiride, 1 to 2 mg with breakfast. (62$ retail)
  - the initial dose should be 1 mg daily in elderly and renal disease

MOA:

- Cause insulin secretion by binding and inhibiting K+ ATPase on beta cells causing calcium influx and **insulin secretion**

AE/ precautions and safety issues:

- primary is **hypoglycemia** –
  - counsel re: skipping meals, exercise, after hospitalization or loss of appetite, EtOH abuse
- Need functioning beta cells for efficacy and decreases over time
- Chronic kidney disease

Efficacy and role in therapy:

- Efficacy: rapidly effective with decrease in A1C % on monotherapy = **1.0 to 2.0%**
- role: add on therapy with other oral hypoglyemics
- Inexpensive

SHORT ACTING INSULIN SECRETAGOGUES

- Drugs and dosages:
  - **Repaglinide** 1 or 2 mg prior to each meal * more effective **than (average retail 310$)**
  - Nateglinide 120 mg taken immediately before each meal
- MOA:
  - Similar to SU act on beta cells K-ATPase → insulin secretion
  - Short acting given with meals for postprandial glycemic control
- AE/ precautions and safety issues:
  - Same weight gain and less hypoglycemia than SU
- Efficacy and role in therapy:
  - Efficacy of repaglinide is similar to SU
  - Safer for kidney disease
  - **Add on therapy in lieu of SU (allergy to SU) esp for postprandial control**
  - More $$ than SU

THIAZOLIDINEDIONES ("GLITAZONES, TZDS"

- Drugs and dosages:
  - Pioglitazone 15 to 30 mg daily → 45 mg (preferred due to safety profile) (18$/30days)
  - Rosiglitazone 4mg daily can increase to 8mg/day
- MOA:
  - PPAR agonists regulate gene expression leading to **increase insulin sensitivity** and glucose utilization in fat muscle and liver
- Efficacy and role in therapy:
  - May be added to other oral meds when glycemic goals are met however there are SIGNIFICANT AE and contraindications
  - Lower tier due to AE including heart failure
  - May be helpful for NASH

THIAZOLIDINEDIONES

- Not first line due to adverse effects:
  - increased risk of weight gain,
  - fluid retention
  - heart failure,
  - Fractures (caution in patients with high fracture risk e.g. postmenopausal women)
  - Potential increased risks of bladder cancer (pioglitazone)
  - Increased risk for myocardial infarction ??

CONTRAINDICATIONS OF THIAZOLIDINEDIONES:

- Symptomatic heart failure (RECORD trial)
- New York Heart Association class III or IV heart failure
- Active bladder cancer or history of bladder cancer
- History of fracture or at high risk for fracture (eg, postmenopausal women with low bone mass)
- Active liver disease (liver enzymes >2.5 times above the upper reference limit)
- Type 1 diabetes
- Pregnancy

ALPHA GLUCOSIDASE INHIBITORS

- Drugs and dosages: (pricing below)
  - Acarbose 50 mg three times daily with first bite of each meal (30$/month)
  - Miglitol 25 mg 3 times daily at the start of each meal
    - Can increase after 4-8 as needed and if tolerated
- MOA:
  - inhibit gastrointestinal enzymes (alpha-glucosidases) that convert complex polysaccharide carbohydrates into monosaccharides which delays glucose absorption
- AE/ precautions and safety issues:
  - GI AE are very COMMON and can reduce compliance
    - Flatulence, diarrhea, and abdominal discomfort are dose related
- Efficacy and role in therapy:
  - Reduction in A1C by 0.4-0.9 percentage points
  - Low tier generally not used (ADA 2017)
  - More effective for postprandial glucose control

DIPEPTIDYL PEPTIDASE TYPE IV ENZYME INHIBITORS (DPP-IV INHBITORS)

- Drugs and dosages:

  - Sitagliptin100 mg once daily, (17$/pill)
  - Saxagliptin 2.5 or 5 mg once daily (16$/pill)
  - Linagliptin 5 mg once daily, eliminated via the enterohepatic system (16$/pill)
  - Alogliptin 25 mg once daily (generic and brand (7-14/pill)

  - Renal issues? **Reduce dose for GFR < or = to 45 mL/min**

DIPEPTIDYL PEPTIDASE TYPE IV ENZYME INHIBITORS (DPP-IV INHBITORS)

- MOA:
  - Inhibit enzyme which breaks down incretins eg GLP 1 and GIP
    - Incretins stimulating glucose-dependent insulin release, slow gastric emptying, and inhibit post-meal glucagon release

- AE/ precautions and safety issues:
  - **headache, nasopharyngitis, and upper respiratory tract infection are M/C**
  - ? Risk of acute pancreatitis
  - ? Increase risk of IBD
  - Skin rashes including severe hypersensitivity rx
  - MS effects and severe joint pain – monitor

- Efficacy and role in therapy
  - ? Role as combination therapy due to increase cost, modest efficacy
  - Decrease in A1C with monotherapy= 0.5%-0.8%
  - Paucity of long term clinical trial data on long-term safety, mortality, diabetic complications, or health-related quality of life.

SODIUM GLUCOSE COTRANSPORTER -2 INHIBITORS (SGLT-2 INHIBITORS, "FLOZINS"

- Drugs and dosages
  - Canagliflozin 100mg orally before the first meal of the day
    - can be increased to 300 mg daily
  - Dapagliflozin (10 mg once daily)
  - Empagliflozin 10mg (can titrate to 25mg) po once daily in am
  - Ertugliflozin 5mg→ 15 mg po once daily
- MOA: SGLT2 inhibitors promote the renal excretion of glucose by blocking glucose reabsorption in PCT
- Efficacy and role in therapy:
  - Modest efficacy SGLT2
    - reduction in A1C by approximately 0.5 to 0.7 percentage points
    - High cost and modest efficacy
    - Cardiovascular: Empagliflozin (1 trial) and canagliflozin (2 trials) decreased cardiovascular morbidity and mortality in patients with type 2 diabetes and overt CVD.
    - Modest weight loss (sustained over 2 years)
    - **Role is unclear possibly add to metformin in patients with CV disease**

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SODIUM GLUCOSE COTRANSPORTER -2 INHIBITORS (SGLT-2 INHIBITORS, "FLOZINS"

- AE and contraindications:
  - **Increase in UTIs and genital candida infections (10-15% of women)**
  - Hypotension due to MOA of drug (monitor BP closely esp in patients prone to volume depletion)
  - ? Increase in bladder cancer (postmarketing surveillance recommended by FDA)
  - Increase risk of low trauma fractures (use caution in high risk fracture patients)
  - Acute kidney injury noted in postmarketing reports ?
    - (101 cases within 1 month of drug initiation but **large analysis of users did not find increase AKI risk)**
  - *** FDA has reports of Fourniers gangrene**
  - **Reports of euglycemic DKA?**

NON-INSULIN INJECTABLE HYPOGLYCEMICS: **GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS**

- Drugs and dosages: (subcutaneous injections)
  - Exenatide
    - 5 mcg -10mcg twice daily within 60 minutes prior to morning and evening meals
    - ER: 2 mg once weekly at any time of day
  - Liraglutide 0.6 mg once daily for 1 week; then increase to 1.2 mg once daily
  - Lixisenatide: 10 mcg once daily for 14 days; on day 15 increase to 20 mcg once daily. Dulaglutide SubQ: Initial: 0.75 mg once weekly; may increase to 1.5 mg once weekly
  - Semaglutide: SubQ: Initial: 0.25 mg once weekly for 4 weeks then increase to 0.5 mg once weekly for at least 4 weeks
  - **SubQ: Administer via SubQ injection in the upper arm, thigh, or abdomen; rotate injection sites.**

- MOA: bind GLP-1 receptors and stimulate **glucose-dependent insulin release**
  - Slow gastric emptying, suppress glucagon, increase satiety
  - Postprandial effects

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

- Efficacy and role in therapy:
  - All GLP-1 receptor agonists reduced (A1C) by approximately 1 percentage point
  - in combination with metformin (and/or insulin or another oral agent) for patients for persistent hyperglycemia
    - **++Weight loss** (cause weight loss beneficial for overweight and obese)
    - $$Costly
    - **CV disease may add liraglutide** to other therapies
      - LEADER Trial rate of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide v placebo
      - >9000 patients with high CV risk

GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS

- AE/ precautions and safety issues:
  - Main AE are GI, N/V/D in 10 to 50 percent of patients
  - ? Increase risk of pancreatitis (do not use in patients with h/o) assess for pancreatitis if patient has severe abd pain on GLP 1 agonist
  - Do not use Liraglutide, exenatide once weekly, and semaglutide in patients with a personal or family history of
    - medullary thyroid cancer or
    - multiple endocrine neoplasia 2A or 2B

AMYLIN ANALOG- PRAMLINITIDE

- Dosing and administration:
  - Type 1 DM: 15 mcg immediately prior to major meals; titrate in 15 mcg increments every 3 days
    - Type 2 60mcg SQ before meals (not commonly used in Type 2)
- MOA: amylin co-secreted with insulin
  - Reduces postprandial blood glucose levels by slowing gastric emptying, promoting satiety, and suppressing the abnormal postprandial rise of glucagon in patients with diabetes
- AE/ precautions and safety issues:
  - Nausea which generally improves after a month
  - SEVERE hypoglycemia start by **reducing prandial insulin by 50%** when initiating pramlinitide and adjust accordingly
- Efficacy and role in therapy: **added to prandial insulin in Type 1 or Type 2 DM** inadequately controlled with prandial insulin
  - Modest efficacy
  - Modest weight loss

Glucagon-like peptide-1 (GLP-1) agonist plus insulin combos

- Insulin degludec 100 units/mL and liraglutide 3.6 mg/mL (*Xultophy*)
- Insulin degludec 100 units/mL and liraglutide 3.6 mg/mL (*Xultophy*)
- Insulin glargine 100 units/mL and lixisenatide 33 mcg/mL (*Soliqua* [U.S.]
- **Combo products have an insulin max** of 50 units/day (*Xultophy*) and 60 units/day (*Soliqua*).

Clinical Resource, ***Drugs for Type 2 Diabetes. Pharmacist's Letter/Prescriber's Letter.*** **July 2017.**

INSULINS: BARE BONES BASICS

INSULIN-BASICS

Preparation	Onset (hour)	Peak	duration
Rapid acting			
Lispro (Humalog)	<25min	0.5-1.5hrs	3-4 hours
Insulin aspart (Novolog)SC/IV	< 25 min	0.5-1.5 hours	3-4 hours
Insulin Glulisine *Apidra*	10 to 15 minutes	1 to 1.5 hours	3-5 hrs
SHORT ACTING: Regular insulin SC - IV	0.5-1hr	2-3	3-6

Intermediate Acting Insulin

Intermediate acting	Onset	Peak	duration
NPH and protamine analogs	2-4	6-10	10-16

INSULINS- LONG ACTING

Long acting INSULIN	Onset , h	Peak, h	Duration,h
Glargine (Lantus) or Toujeo	1	____	24hours
Insulin Detemir solution *(Levemir)*Novo Nordisk	0.8 to 2 hrs	____	Dose-dependent; 12 hours for 0.2 units/kg, 20 hours for 0.4 units/kg, up to 24 hours. Binds to albumin.

Tresiba (insulin degludec), Novo Nordisk: SC
Onset: 30 to 90 minutes
Peak: minimal 12 hours
Duration 42 hours

INITIATION OF INSULIN IN TYPE 2 DM

- Insulin may be initial therapy for severe hyperglycemia.
- Basal insulin added to other therapies
  - improve nocturnal and fasting blood glucose (FBG)
  - Dosing for insulin alone or in combination
  - initial doses:
    - NPH, detemir, or glargine is 0.2 units per kg (minimum 10 units) daily.
    - Insulin degludec is 10 units subcutaneously once daily.
    - Timing: Glargine or degludec can be given morning or at bedtime
    - Determir or NPH at bedtime

TITRATION OF INSULIN IN TYPE 2 DM: BASICS

- BASAL insulin: increase by 2 to 4 units of the basal insulin dose approximately every three days if the mean FBG is above 130 mg/dL

- If FBG is normal and A1C is elevated, check pre-lunch and/or pre-bedtime blood glucoses
  - Reinforce lifestyle modifications
  - Consider adding prandial insulin
    - Generallly 4-6 units rapid acting insulin before one or more meals
    - Increase by 2-3 units q3 days to achieve PP goals
    - Review relationship between dietary carbohydrates and insulin requirements
    - **(carb counting education)**

COST OF BASAL INSULIN

- Tresiba 50 units/day costs about $450/month...
- $400 or less for Lantus, Levemir, or Toujeo...
- $315 for Basaglar
- $40 to $200 for NPH.

COMPARISON OF BASAL INSULINS

- NPH (human insulin, intermediate acting)
  - A1C lowering
  - Hypoglycemia: slightly more compared to analogs esp in Type 1 and in type 2 on oral meds
  - Cost: significantly less than analogs (140$/10ml)

- Long-acting Analogs
  (Insulins glargine [U-100] and detemir)
  - A1C lowering: same or slightly better than NPH for Type 2 DM
  - Hypoglycemia: slightly fewer episodes than NPH
  - Cost >> $ than NPH e.g. $255.97/10 mL vial
    $383.94/5 of 3 mL SoloStar pen for Lantus

- Ultra-long acting analog (insulin degludec [Tresiba])
  - A1C lowering: same or slightly better than NPH for Type 2 DM
  - Hypoglycemia: fewer than NPH and fewer severe and nocturnal episodes than glargine
  - Cost >> $ than NPH $461.60/5 of 3 mL
    100 units/mL FlexTouch pen

REVIEW OF SELECT RECENT CLINICAL TRIAL DATA IN TYPE 2 DM

- 7028 patients with type 2 diabetes and CVD were randomly assigned to empagliflozin (10 or 25 mg) or placebo once daily
  - 3 years: primary outcome , **a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke** occurred in fewer patients assigned to empagliflozin arm than placebo
  - Fewer heart failure related hospitalizations
  - Secondary outcome: **slower progression of nephropathy** and related renal events
  - lower systolic BP
  - Limitations: very high-risk population with established CVD? Effects on patients without CVD

- Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes.
- Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE, EMPA-REG OUTCOME Investigators
- N Engl J Med. 2015;373(22):2117. Epub 2015 Sep 17.

CANAGLIFLOZIN TRIALS ON CARDIOVASCULAR, RENAL, AND SAFETY OUTCOMES

- > 10,000 patients with type 2DM and high CV risk (mean f/u 3.6 years) randomly assigned to canagliflozin or placebo
  - primary outcome , **a composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke** occurred in fewer patients assigned to canagliflozin arm than placebo
  - Similar to empagliflozin, no statistically significant reduction in individual components
- all cause death and death from CV disease was not statistically significant
- Reduction in heart failure related hospitalizations
- Secondary outcome of progression of albuminuria lower in cana vs placebo group

- **Increased risk of amputations (lower limb)**
-

- Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes.
- Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group

GLP-1 agonists and CV Outcomes

- LEADER trial > 9000 patients with type 2 diabetes and CVD or high CV risk there was a reduction in primary outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke with **liraglutide** vs PB
- SUSTAIN-6 trial: > 3000 patients rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving **semaglutide** than among those receiving placebo
  - lower systolic BP
- no significant difference in these primary CV outcomes in lixisenatide or exenatide

GLP-1 agonists and SGLT 2 inhibitors: to combine or not to combine?

Liraglutide and empagliflozin lower CV risk and death

- Both reduce weight and lower systolic BP
- Cost is high
- Efficacy is modest
- Jury is out if additive effects on CV outcomes so choose additive therapies based on cost, comorbidities and risk for hypoglycemia

NEW ADA/EASD GUIDANCE ON DIABETES: ASSESS CV STATUS FIRST

- Current updates to the 2015 ADA/EASD Management of Hyperglycemia in Type 2 Diabetes statement
- Assess cardiovascular disease (CVD) status, other comorbidities, and patient preferences
  - METFORMIN still comes out on top
  - Then, if ASCVD predominates,
    - a GLP-1 receptor agonist with proven CVD benefit
    - or SGLT2 inhibitor with proven CVD benefit (provided the patient has adequate kidney function
    - liraglutide is preferred among GLP-1 receptor agonists based on the LEADER trial, and
    - empagliflozin among SGLT2 inhibitors based on EMPA-REG OUTCOME
  - Heart failure and Type 2 DM:
    - SGLT2 inhibitor with CT supportive data or GLP-1 agonist with proven CVD benefit

HEMOGLOBIN A1C GOALS

- **Overall Goals**
  - AACE supports an A1C goal of ≤6.5% for most patients
  - A goal of >6.5% (up to 8%; see below) if the lower target cannot be achieved without adverse outcomes
  - A less stringent A1C of 7.0 to 8.0% is appropriate for patients with a
    - history of severe hypoglycemia,
    - limited life expectancy,
    - advanced renal disease or macrovascular complications,
    - extensive comorbid conditions, or
    - long-standing T2D in which the A1C goal has been difficult to attain despite intensive efforts

A1C and Medication

HEMOGLOBIN A1C AND MEDICATION

- Initial A1C< 9% monotherapy

- IF A1C is ≥9% (75 mmol/mol), consider initiating dual combination therapy
  - combination insulin injectable therapy when blood glucose is ≥300 mg/dL (16.7 mmol/L) or
- A1C is ≥10% (86 mmol/mol) or
- if the patient has symptoms of hyperglycemia (i.e., polyuria or polydipsia)

THANK YOU FOR YOUR ATTENTION!

REFERENCES

- Clinical Resource, Drugs for Type 2 Diabetes. Pharmacist's Letter/Prescriber's Letter. July 2017.
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- Standards of Medical Care in Diabetes—2018. Diabetes Care Jan 2018, 41 (Supplement 1) S1-S2; DOI: 10.2337/dc18-Sint01
- **Pharmacologic Approaches to Glycemic Treatment : *Standards of Medical Care in Diabetes—2018*.** American Diabetes Association. Diabetes Care 2018 Jan; 41(Supplement 1): S73-S85.https://doi.org/10.2337/dc18-S008