Rethinking the Treatment Paradigm for T2DM
AKA: Thinking Backward to Move Forward in the Management of T2DM

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Disclosures:
In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

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<th>Entity</th>
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<th>Financial Consideration</th>
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Learning Objectives:
- Discuss the American Diabetes Association Anti-hyperglycemic therapy recommendations for T2DM
- Understand the importance of co-morbidities when choosing therapy
- Review the recent CV risk reduction findings in regard to anti-hyperglycemic therapies
- Discuss how to keep the patient centered in your choice of anti-hyperglycemic medication
Second Sentence:
Ongoing patient self-management education and support are critical to preventing acute complications and reducing the risk of long-term complications.
Treatment Practice Guideline
Shortcomings: Historically
- Medication Centric
- Inattentive to Diabetes Life Cycle
- Less focused on Co-morbid conditions
- Promotes Polypharmacy

Choosing Therapy
- What are Patients Thinking?
  - Cost
  - Side Effects
  - Hassle Factors
  - Future Implications
- What are Physicians Thinking?
  - Efficacy
  - Side Effect Profile
  - Tolerability
  - Coverage

Patient Centric
- Co-Morbid Conditions
- Safety
- Economics
- Efficacy
Co-Morbid Conditions

- **Cardiovascular Risk** – Underlying CVD, Stroke, MI, PVD
- **Renal Risk** – Diabetic nephropathy, declining renal Fx
- **GI Tolerability** – Underlying GI conditions
- **Obesity**
- **Endocrine** – Thyroid, PCOS, others

**Patient Centric**

- **Obesity:** 1999-2004 (NHANES) Type 2 patients 27% overweight and 41% were obese
- **Dyslipidemia:** 1999-2004 (NHANES) 46% had elevated lipids
- **HTN:** 67% of T2DM patients were being treated or had HTN
- **Chronic Kidney Disease:** ~40% of patients with diabetes
- **Cardiovascular Disease:**
- **Depression, Sleep Disorders, Cancers**

**Safety**

- Can I take this medication with the other medications that I am already taking?
- Will this medication affect other health problems that I am having?
- I see the ads on TV. They scare me.

(NHANES) 1999-2004 14% of patients with T2DM had no co-morbidity

Patient Centric

Economics

Will my insurance cover this new medicine?
Can I afford to take this with all of my other medications?
If I get a coupon or co-pay card, how long will it last?
Is the benefit that I will get be worth the money that I am spending?

Patient

Patient Centric

Efficacy

Will it work?
Will it be worth it?

Patient

Co-Morbid Conditions

- HTN
- Hyperlipidemia
- Obesity
- Social – elderly, frail, falls risk
- CVD – stroke, MI, CAD, PVD, CHF
- CKD
- GI – GERD, Gall Bladder, NASH, Pancreatitis, IBS, Crohn’s, Ulcerative Colitis
- Endocrine – obesity, PCOS, Thyroid, Adrenal
Choosing Medications While Giving Consideration to Co-Morbid Conditions

Co-morbid Conditions

-HTN — SGLT-2 Inhibitors
  - Volume Contraction and possible hypotension need to be considered.
  - **Canagliflozin**: noted with SBP reductions of 3.3 and 5.0 mm/Hg at 26 weeks
  - **Empagliflozin**: Mean Arterial Pressure reductions of 2.3 and 2.1 mm/Hg at 24 weeks
  - **Dapagliflozin**: reduced mean seated SBP -10.4 vs -7.3 mm/Hg and mean 24 hr ambulatory SBP -9.6 vs -6.7 mm/Hg at 12 weeks


-Hyperlipidemia:
  - **SGLT-2 Class Medications**: Can cause a slight elevation in LDL Cholesterol (canagliflozin 4.5 to 8%), (dapagliflozin 2.9%), (empagliflozin 4.6, 6.5%) 3
  - **TZD Class Medications**: Pioglitazone can cause a reduction in triglycerides (-9.9% to -12.3%), HDL Cholesterol (-18.1 to -20.3%), LDL Chol increased (+5.2% to +9.0%) 4

  1. https://www.google.com/search?q=Invokana+PI&oq=Invokana+PI&aqs=chrome.0.69i59j0j69i60j0l3.2423j0j7&sourceid=chrome&ie=UTF-8
  2. https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202293s000lbl.pdf
Co-Morbid Conditions

- **Obesity:**
  - Gain:
    - SUs Class can cause weight gain
    - T2D Class can cause fluid retention and weight gain
    - Glinide Class can cause weight gain
    - Insulins
  - Neutral:
    - DPP-4i Class
    - Biguanides – metformin
  - Loss:
    - SGLT-2 Class
    - GLP-1 Class

- **Social** – elderly, frail, falls risk, isolated
  - Anything that is a hypoglycemia risk
    - SUs
    - Insulins
    - Glinides
  - Volume Depletion
    - SGLT-2s

- **Economics** –
  - Everything past metformin and SUs tend to get expensive
  - Try to simplify, limit or combine medications
  - Insured:
    - Follow formulary as much as possible
    - Use Coupon programs when you can
    - Sample Access: try to limit to extreme or emergency situations
### Cardiovascular Risk

**Pre-2008 → 2008 → The Present**

#### CVD – TZD’s

- **Pioglitazone – PROactive Trial**
  - 5238 Patients with evidence of macrovascular Dse.
  - 34.5 month avg. time of observation
  - **Primary Endpoint**: All-cause mortality, non-fatal MI, stroke, ACS, revascularization coronary or leg and amputation
    - HR 0.90; CI 0.80-1.02, p=0.095
  - **Secondary Endpoint**: All-cause mortality, non-fatal MI and stroke
    - HR 0.84; CI 0.72-0.98, p = 0.027


- **Rosiglitazone – RECORD Trial**
  - 4447 Patients
  - HR for CV Death 0.84; CI 0.59-1.18, MI 1.14; CI 0.80-1.63, Stroke 0.72; CI 0.49-1.06
  - Heart Failure Admission or death HR 2.10; CI 1.35-3.27
  - Increased risk of long bone Frx, mainly women
  - **Nissen Meta-analysis**
    - 42 trials, avg. age 56 y
    - Odds ratio for MI 1.43
    - Odds ratio of death 1.64

CVD – These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.

What is 3 pt. MACE:
- Cardiovascular Death
- Non-fatal MI
- Non-fatal Stroke

Study | EXAMINE | CARMELINA | SAVOR | TECOS
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<td>DPP-4I</td>
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<td>Ant. 2018</td>
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**Co-Morbid Conditions**

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<td></td>
<td></td>
<td>2016</td>
<td>2019</td>
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<td>Primary Endpoint</td>
<td>GLP-1RA</td>
<td>EXSCEL</td>
<td>LEADER</td>
<td>REWIND</td>
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<td>GLP-1RA</td>
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<td>HR</td>
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**CVD – CV Risk Reduction**
- Canagliflozin
- Empagliflozin
- Liraglutide

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**CV Risk: PVD and SGLT-2i**
- Lower Extremity Amputation
  - CANVAS Trial – higher risk of amputations at toes, feet or legs with canagliflozin (6.3 vs. 3.4 participants with amputations/1000 pt. yrs.) (HR 1.97)
  - Highest absolute risk was with patients who had a previous amputation of PVD.

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Co-morbid Conditions

- **CV Risk:** PVD and SGLT-2i
  - **Reasonable Recommendations:**
    - Diabetes Foot Exam
    - Check pulses and document
    - Hx of PVD – if questions, check Art. Duplex
    - Hx of Amputations
    - Interval Changes in Foot Health

- **CKD**
  - **Improve:**
    - ACE/ARB medication to improve renal function
    - HTN Control
    - BGM/A1c Control
  - **Cautions:**
    - Metformin
    - DPP-4’s (linagliptin ok here as it is gut cleared)
    - SGLT-2i
    - GLP-1RA

Co-Morbid Conditions

- **CKD – Stage Process 1-5 based on GFR**
  - Stage 1: 120-90 ml/min/1.73m²
  - Stage 2: 89-60 ml/min/1.73m²
  - Stage 3a: 59-45 ml/min/1.73m²
  - Stage 3b: 44-30 ml/min/1.73m²
  - Stage 4: 29-15 ml/min/1.73m²
  - Stage 5: <15 ml/min/1.73m²

  - **Cautions:**
    - Metformin
Co-Morbid Conditions

- Cautions:
  - Metformin
  - CKD – Safe Dosing for Metformin
    - Stage 3a: 59-45 ml/min/1.73m²
    - Stage 3b: 44-30 ml/min/1.73m²

- GI – GERD, Gall Bladder, NASH, Pancreatitis, IBS, Crohn’s, Ulcerative Colitis, gastroparesis
Co-Morbid Conditions

- **GI** – GERD, Gall Bladder, NASH, Pancreatitis, IBS, Crohn’s, Ulcerative Colitis, gastroparesis
- **Metformin**: GI Upset both upper and lower
- **TZD’s, GLP-1RA**: Can be beneficial with NASH
- **DPP-4i**: Small pancreatitis risk

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Co-Morbid Conditions

- **GI** – GERD, Gall Bladder, NASH, Pancreatitis, IBS, Crohn’s, Ulcerative Colitis, gastroparesis
- **GLP-1RA**: Pancreatitis contraindication
  - Hx of pancreatitis
  - Consider high triglycerides
  - Active alcoholism
  - Do not use with gastroparesis

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Co-Morbid Conditions

- **Endocrine** – obesity, PCOS
- **Obesity**:
  - Cautions: Insulins, SU’s, glinides, TZD’s
  - Beneficial: SGLT-2i, GLP-1RA
- **PCOS**: TZD’s may be of benefit here
Co-Morbid Conditions

- HTN
- Hyperlipidemia
- Obesity
- Social – elderly, frail, falls risk
- CVD – stroke, MI, CAD, PVD, CHF
- CKD
- GI – GERD, Gall Bladder, NASH, Pancreatitis, IBS, Crohn’s, Ulcerative Colitis
- Endocrine – obesity, PCOS

Putting it All Together

- Patient Cases:
  - A
  - B
  - C

Case #1:
41 year old female patient with a Dx of T2DM for the past 7 years.
Case #2:
68 year old female patient with a Dx of T2DM for the past 19 years.

Co-Morbid Conditions
- HTN
- Hyperlipidemia
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- Social – elderly, frail, falls risk
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- Endocrine – obesity, PCOS
The Standards of Medical Care in Diabetes can serve as a guide for us as we choose therapy for patients with diabetes. Co-Morbid Conditions play a critical role in the health of our patients with diabetes and their choice of medications/therapy. Specifically, consideration of CV risk for patients with diabetes is important in deciding therapy with your patient.