Type 2 Diabetes Update 2018

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Disclosures:

- Current PI/Institutional Support only:
  - Millennium therapeutics trial for Cushing's disease
  - CHIASMA trial in Acromegaly
  - Ionis Pharmaceuticals Acromegaly Trial

Objectives

- Discuss the ACP Guidance Statement released in March and related controversy regarding A1c Goals
- Review the 4 newest classes of drugs
- Use cases to review current type 2 diabetes management options
- Use the AACE algorithm as a framework for treatment decisions (available as an app)

Case 1

- 48 year old white male, A1c is 8.5%
- Has been given diabetes education about diet and exercise
- HTN, Hyperlipidemia (both addressed appropriately)
- BMI is 35
- On metformin and glimepiride
- Commercial insurance through employer

Would you:

A. Start Basal insulin
B. Add and SGLT2i
C. Add a GLP-1 receptor agonist
D. Stop glimepiride and add an SGLT2i and a GLP-1 receptor agonist

Case 2

- 54 yo female with DM2
- No known CVD or microvascular disease
- BMI 45, A1c 8.2%
- On metformin 1000 mg bid
- GFR is over 60
- Lipids and BP adequately addressed

What would you add on next?

A. Basal Insulin
B. SGLT2i
C. GLP-1 RA
D. Triple oral therapy

Case 3

- 49 yo female
- Polydipsia, polyuria for several months
- BMI 38
- Acanthosis nigricans
- A1c is 12%

What would you initiate?

A. Basal Insulin
B. Premixed insulin
C. Basal plus insulin
D. Triple oral therapy
1. Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden and costs of care (Concurs with ADA)

ACP Guidance Statement, March 5, 2018

American College of Physicians

2. Clinicians should aim to achieve an HbA1c level between 7% and 8% in most patients with type 2 diabetes

ADA: A reasonable goal for many non-pregnant adults is 7% and less than 6.5% for selected patients. 8% may be appropriate for those with a history of severe hypoglycemia, limited life expectancy, advanced microvascular disease, extensive comorbid conditions...

ACP Guidance Statement, March 5, 2018

American College of Physicians

3. Clinicians should consider de-intensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA1c level less than 6.5%

ACP Guidance Statement, March 5, 2018

American College of Physicians

4. Clinicians should treat patients with type 2 diabetes to minimize symptoms related to hyperglycemia and avoid targeting an HbA1c level in patients with a life expectancy less than 10 years due to advanced age, residence in a nursing home, or chronic conditions (such as dementia, cancer, end-stage kidney disease, or severe COPD or CHF) because the harms outweigh the benefits in this population

ACP Guidance Statement, March 5, 2018
ACCORD Trial Summary

- Published in 2008
- 10k participants, ages 40-82
- Randomized to intensive arm (A1c goal of 6% - average was 6.4%)
- Standard arm (A1c goal 7.0-7.9% - average 7.5%)
- Designed to test if intense control would reduce heart attack, stroke, death from CVD
- Stopped 18 months early due to increased death from all causes in intensive arm

Median Glycated Hemoglobin Levels at Each Study Visit

Kaplan-Meier Curves for the Primary Outcomes and Death from Any Cause
In this study, 1791 military veterans with poorly controlled type 2 diabetes were randomly assigned to receive either standard or intensive glucose control. Other cardiovascular risk factors were treated uniformly. The glycated hemoglobin goal was an absolute reduction of 1.5 percentage points in the intensive-therapy group. There was no significant difference between the two groups for the rates of major cardiovascular events, death, or microvascular complications.

Individualization of Goals

- This is less of a concern in type 2 diabetes using agents with little to no hypoglycemia risk (true of all newer agents).
- Is a major concern in type 1 diabetes and in type 2 diabetes on multiple daily insulin injections.
- Clear barriers to tight control:
  - Inability to carb count (cannot effectively match insulin to carbohydrate intake)
  - Lack of frequent self-glucose monitoring
  - Premixed insulin (70/30, etc...) because matching insulin to carbs is not possible.

A1c Goal

- I encourage dispassionate consideration of the A1c.
- It is a statistical average.
- The lower it goes, the better the lows go.
- Certain therapies, skill sets, or self-monitoring abilities render low numbers impossible to safely achieve.
A1c Goal

- Despite higher cost of newer therapies, they tend not to cause hypoglycemia.
- In patients on agents that DO NOT cause hypoglycemia, there is probably not a lower threshold of A1c that is cause for concern.

Diabetes Drugs

The new
1. GLP-1s
2. SGLT-2i
3. DPP-4i
4. New insulins

The old
1. Metformin
2. Sulfonylurea
3. Insulin
4. Acarbose
5. Old insulins

The forgotten
1. Colesvelam
2. Bromocriptine
3. Pioglitazone (making a comeback?)
4. Pramlintide

The Four I’ll Cover in Detail

- All four improve glycemic control.
- None are associated with significant hypoglycemia risk.
- Pioglitazone is being revisited but does cause weight gain.
- DPP-4i are weight neutral with limited hypoglycemia.
- GLP-1 receptor agonists and SGLT-2i are associated with weight loss.
- Sulfonylureas are really not ideal second line agents (if any line).
- Poor durability of response
- Hypoglycemia
- Weight gain
- Cheap
Treatment: Metformin

- Mild insulin sensitizer, decreases glucose production in the liver
- No hypoglycemia
- Modest weight loss
- Improves cardiovascular outcomes in DM2
- Can improve fatty liver
- Use with caution in the elderly (>65), renal dysfunction, cardiopulmonary disorders (OK with stable CHF), and hepatic disease
- Stop prior to IV contrast
- Rare cases of lactic acidosis
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- Stop prior to IV contrast
- Rare cases of lactic acidosis

Thiazolidinediones: NASH Cirrhosis

- Significant evidence of benefit with TZDs
- This is a major comorbidity in DM2
- Annals of Hepatology, July-August 2017 meta analysis
- TZD showed:
  - Ballooning and fibrosis stable
  - Improved steatosis and lobular inflammation
  - Improved HDL, ALT
  - Weight similar to placebo

Treatment: Thiazolidinedione

Pioglitazone (Actos)

- Decreases insulin resistance, ↓ glucoseogenesis
- Use with caution in those at risk for heart failure
- Contraindicated in class III or IV heart failure
- May have benefits in NASH cirrhosis
- ↓ risk of MI, stroke, and death, ↓ triglycerides, ↑ HDL
- ↓1.5% A1c lowering (potent)

Fig. 5: Mechanism of action of thiazolidinediones

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Pioglitazone after Ischemic Stroke or Transient Ischemic Attack

Walter N. Kernan, M.D., Catherine M. Viscoli, Ph.D., Karen L. Furie, M.D., M.P.H., Lawrence H. Young, M.D., Anna M. Silvis, M.D., Peter D. O'Leary, M.A., Mark W. Parsons, M.D., Peter Ringleb, M.D., J. David Spence, M.D., David Tanne, M.D., David Wang, M.D., Toni R. Winder, M.D., for the IRIS Trial Investigators

N Engl J Med
Volume 374(14):1321-1331
April 7, 2016
Pioglitazone after Ischemic Stroke or TIA

- 3876 patients
- Pioglitazone or placebo
- Recent stroke
- Fatal or nonfatal stroke or MI was primary outcome
- 9% in pioglitazone group and 11.8% in placebo at 4.8 years
- Hazard ratio 0.76 (0.62-0.93), P-value 0.007

Thiazolidinediones: Risks

- Bladder cancer - verdict has swung back and forth
  - 2011 Kaiser database suggested risk
  - Subsequent analysis in JAMA of same data said no risk
  - BMJ 2016 cohort study showed risk
  - Current FDA language "may cause increase risk"
- Bone density
  - Diabetologia 2015 meta-analysis
    - Probable mild bone density loss seen in women not men
    - Increase fracture risk in women, #1614-1722
    - Caution in women.

SGLT2 Inhibitors

- Sodium glucose cotransporter 2 inhibitors
- Mechanism of action:
  - ↓ renal threshold for glucose
  - ↓ reabsorption of filtered glucose from the tubules
  - ↑ urinary glucose excretion
- Side effects:
  - UTI
  - Yeast infections
  - Lactation
  - Hypoglycemia, hypoglycemia
  - DKA
  - Amputation?

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christian Wanner, M.D., Jack K. Lachin, Ph.D., David Fitchett, M.D., Eishi Inzucchi, M.D., Stefan Hantel, Ph.D., Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

N Engl J Med
Volume 373(22):2117-2128
November 26, 2015
Study Overview

- In this study, the addition of empagliflozin, an inhibitor of sodium–glucose cotransporter 2 to standard care reduced cardiovascular morbidity and mortality in patients with type 2 diabetes at high cardiovascular risk.

Conclusions

- Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause when the study drug was added to standard care.

Received FDA approval for indication of reduction of cardiac mortality based on this trial.

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

Christoph Wanner, M.D., Silvio E. Inzucchi, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Michaela Mattheus, Dipl. Biomath., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., Bernard Zinman, M.D., for the EMPA-REG OUTCOME Investigators

Study Overview

- Among patients with type 2 diabetes at high cardiovascular risk, the rates of progression of kidney disease and clinically relevant renal events were lower among patients receiving empagliflozin, a sodium–glucose cotransporter 2 inhibitor, than among those receiving placebo.
Conclusions

- In two trials involving patients with type 2 diabetes and an elevated risk of cardiovascular disease, patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo but a greater risk of amputation, primarily at the level of the toe or metatarsal.
- 10,000 patients approximately
- Now an FDA Boxed Warning
- CANVAS: 2.8/1000 placebo vs 5.9/1000
- CANVAS-R: 4.2/1000 placebo vs 7.5/1000
- Not seen in other trials/other drugs in class

GLP-1 receptor agonists and DPP-4i: Cousins

- All given by subcutaneous injection
- Mechanism of action:
  - Potentiates insulin secretion
  - Suppresses postprandial glucagon secretion
  - Slows gastric emptying
  - Promotes satiety centrally, weight loss
  - No significant hypoglycemia
- Side effects:
  - Nausea, vomiting, diarrhea, weight loss
  - May worsen gastroparesis
  - Pancreatitis (?)

Treatment: Incretin Mimetics (Includes GLP-1 and Amylin)

- Exenatide (Byetta), Liraglutide (Victoza): GLP-1 agonists
- Pramlintide (Symlin): Synthetic analogue of human amylin
- All given by subcutaneous injection
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  - Potentiates insulin secretion
  - Suppresses postprandial glucagon secretion
  - Slows gastric emptying
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GLP-1 Receptor Agonists: Cardiovascular Outcomes

- LEADER Trial, NEAJV:
  - Liraglutide (Victoza), 9340 patients
  - First occurrence of death from cv causes, nonfatal HF, stroke
  - Mean follow up 3.8 years
  - Primary outcome:
    - 13% reduced, 1.49% placebo (p=0.007)
    - Nonfatal HF, nonfatal stroke, hospitalization for HF non-significantly lower in tx group
Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

Steven P. Marso, M.D., Gilbert H. Daniels, M.D., Kirstine Brown-Frandsen, M.D., Peter Kristensen, M.D., E.M.B.A., Johannes F.E. Mann, M.D., Michael A. Nauck, M.D., Steven E. Nissen, M.D., Stuart Pocock, Ph.D., Neil R. Poulter, F.Med.Sci., Lasse S. Ravn, M.D., Ph.D., William M. Steenberg, M.D., Mette Stokkevold, M.D., Arne Stoffers, M.D., Richard M. Bergenstal, M.D., John B. Buse, M.D., Ph.D., for the LEADER Steering Committee on behalf of the LEADER Trial Investigators

N Engl J Med
Volume 375(4):311–322
July 28, 2016

Primary and Exploratory Outcomes.

Conclusions

• In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

GLP-1 Receptor agonists

• Summary of cardiovascular data:
  ➤ Neutral to beneficial depending on drug and trial
  ➤ No negative signals
  ➤ Concerns of pancreatitis
    ➤ No increase in LEADER trial
    ➤ Some case reports
    ➤ None of the randomized data supports it
  ➤ High triglycerides a risk factor

GLP-1 Receptor Agonists

• Weight effects:
  ➤ 1–3 kg loss depending on trial and patient population
  ➤ Differences diminish with mixed treatments
  ➤ A1c lowering
    ➤ 1–1.5%

Treatment: DPP-4 Inhibitors

Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Vildagliptin (Galvus)

• Block dipeptidyl-peptidase 4 (the enzyme that breaks down natural incretins)
  ➤ Better insulin release and blood sugar control particularly postprandial
  ➤ Rare for inulin release and blood sugar control particularly postprandial
  ➤ Side effects: minimal; UTI, sore throat, diarrhea, pancreatitis
  ➤ Weight neutral
  ➤ Many of these
Treatment: DPP-4 Inhibitors

- Not extremely potent (A1c drop is 0.5-1%)
- Linagliptin (Tradjenta) requires no adjustment for GFR which can come in handy in certain patients
- All others require renal adjustment
- Made in combination with other agents (metformin)
- Also no convincing data of pancreatitis risk
- Cardiovascular outcomes neutral

Case 1

- 48 year old white male, A1c is 8.5% 
- Has been given diabetes education about diet and exercise 
- HTN, Hyperlipidemia (both addressed appropriately) 
- BMI is 35 
- On metformin and glimepiride 
- Commercial insurance through employer 

- WOLAS prep:
  - A. Start Basal insulin 
  - B. Add an SGLT2i 
  - C. Add a DPP-4i receptor agonist 
  - D. Stop glimepiride and add an SGLT2i and a GLP-1 receptor agonist 

Case 2

- 54 yo female with DM2 
- No known CAD or microvascular disease 
- BMI 45, A1c 8.2% 
- On metformin 1000 mg bid 
  
- GFR is over 60 
- Lipids and BP adequately addressed 

- What would you add on next? 
  - A. Basal insulin 
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Case 3

- 49 yo female 
- Polydipsia, polyuria for several months 
- BMI 38 
- Acanthosis nigricans 
- A1c is 12% 

- What would you initiate? 
  - A. Basal insulin 
  - B. Premixed insulin 
  - C. Basal bolus insulin 
  - D. Triple oral therapy
Case 4

- 26 yo female, childhood cancer survivor
- Very insulin resistant, acanthosis, obese
- On U-500 insulin with very poor control
- A1c 10.2%
- High triglycerides
- NASH cirrhosis
- Would you add:
  - A. TZD
  - B. SGLT2i
  - C. DPP-4i
  - D. GLP-1 RA