Individualized Type 2 Diabetes Management

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Disclosure of Potential Conflicts of Interest

Advisory Boards
- Abbott Diabetes Care
- Boehringer Ingelheim
- Bigfoot Biomedical
- Lilly, Livongo
- NovoNordisk
- Sanofi

Research Funding
- Dexcom
- vTv Therapeutics

Stock Options
- Mellitus Health
- Pendulum Therapeutics
- Omada Health
- Stability Health
- Livongo

Objectives

- Discuss the new treatment paradigm for the management of T2D
- Review CVOT outcomes trials on diabetes medications
- Utilize data from CGM to create individualized treatment approaches for people with diabetes
Questions

1. In a patient with new onset type 2 diabetes, CVD and an A1C of 7.5% what should be the first medication(s) used?
   A. Metformin
   B. Metformin + DPP-IV
   C. GLP-1 RA + SGLT-2
   D. Metformin + SGLT-2 (correct)

2. In the Credence Trial, of canagliflozin in people with T2DM and nephropathy what were the clinical characteristics of the individuals enrolled?
   A. eGFR <45 (correct)
   B. A/C ratio of >300 to 5,000
   C. Blood pressure of >140/90
   D. A1C 8 – 10%

3. HbA1c are useful for which of the following?
   A. Assessing frequency of hypoglycemia
   B. Measuring glycemic variability
   C. Providing an accurate mean glucose level
   D. Determining the risk for chronic complications of diabetes (correct)

Cardiovascular disease and diabetes

~65% of deaths are due to CV disease

Coronary heart disease deaths T2 to 4-fold
Cardiovascular complications of T2DM
Stroke risk T2 to 4-fold
Heart failure T2 to 5-fold


Complications Risk in Diabetes
The Impact of Intensive Glycemic Control

Relative Risk of Complications
Intensive glycemic control reduces the risk of microvascular complications early in the course of both type 1 and type 2 diabetes

Adapted from:
Summary of Major Clinical Trials in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
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<td>DCCT / EDIC</td>
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<tr>
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<tr>
<td>VADT</td>
<td>↓</td>
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Severe Hypoglycemia and Mortality Risk

<table>
<thead>
<tr>
<th>Study</th>
<th>ACCORD</th>
<th>ADVANCE</th>
<th>VADT</th>
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</thead>
<tbody>
<tr>
<td>Severe Hypo</td>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
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<tr>
<td>(%/ year)</td>
<td>3.1</td>
<td>1.1</td>
<td>0.7</td>
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<tr>
<td>Annual mortality</td>
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</table>

Case

- JR is a 60 yo male with a 6 year history of type 2 diabetes
- He has always been well controlled on metformin 1 gm BID with an A1C of 5.8 – 6.5%
- 10 years ago he had an MI from which he fully recovered
- He runs walks 5 miles daily for exercise; he eats fairly well but consumes rice/bread with most meals.
- He is on a statin, an ARB and an aspirin.
- His BP = 128/78, BMI = 23.4 kg/m², LDL = 65, eGFR = 70
- His most recent A1C is 6.1% and his blinded CGM tracing is as follows.
Type 2 Diabetes with CVD on Metformin

First-line therapy is metformin + lifestyle

Established ASCVD/HF/CKD?

Yes

No

A1C irrelevant
Start GLP-1 RA/SGLT-2 I

A1C based therapy

If High-Risk or Established ASCVD, CKD, HF

ADA. Diabetes Care 2020 Jan; 43(Supplement 1): S48-S65. https://doi.org/10.2337/dc20-S005
Considerations for Therapy

- Target additional CVD risk reduction
- Give options for therapy
- Discuss nutrition
- Watch for too much weight loss
- However, what would you do under these circumstances? Is A1C irrelevant?
  - A1C = 6.1% on a sulfonylurea agent
  - A1C = 6.1% on insulin
  - A1C = 10% with symptoms of uncontrolled diabetes

Follow-up

- Reduced metformin by 50%
- After discussion with patient started dulaglutide 0.75 mg weekly. Developed nausea/vomiting/abdominal pain.
- Switched to a low dose of a semaglutide and uptitrated to 0.5 mg weekly
- He changed his diet
- Over time he lost 12 pounds and his A1C fell to 5.1%
- His metformin was stopped.

Follow-Up Blinded CGM

Image courtesy of Anne Peters, MD.
Secretion and Inactivation

Intestinal GLP-1 release

DPP-4 Inhibitors
- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

DPP-4 Inhibitors
- A1c reduction
- Weight neutral
- No hypos
- Few SE's/pill

GLP-1 Agonists
- Exenatide
- Liraglutide
- Albiglutide
- Dulaglutide
- Semaglutide

Study

CV Outcomes Trials in Diabetes: GLP1-RA

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA</th>
<th>FREEDOM CVO</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>EXSCEL 7</th>
<th>REWIND</th>
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</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>Lixi</td>
<td>ITCA-650</td>
<td>Exenatide</td>
<td>Liraglutide</td>
<td>Exenatide LR</td>
<td>Dipeptidyl peptidase 4 (DPP-4) inhibitor</td>
</tr>
<tr>
<td>N</td>
<td>6,068</td>
<td>~4,000</td>
<td>9,340</td>
<td>3,297</td>
<td>14,752</td>
<td>9,901</td>
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<tr>
<td>CVOT Outcome</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Benefit in label</td>
<td>Benefit</td>
<td>Neutral</td>
<td>Benefit</td>
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<tr>
<td>Other</td>
<td>Renal benefit</td>
<td>Worsening retinopathy</td>
<td></td>
<td></td>
<td>31% CVD; A1C = 7.3%</td>
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</table>


CV Outcomes Trials in Diabetes: GLP1-RA

Primary outcome
CV death, non-fatal myocardial infarction, or non-fatal stroke

HR: 0.87 (0.78 - 0.97)

p=0.01 by non-inferiority test

p<0.01 for superiority

Remission, with or without CV death

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24, June 13, 2016, New Orleans, LA, USA.
CV death

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Hospitalization for heart failure

The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months.

CI: confidence interval; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Time to first renal event

Macroalbuminuria, doubling of serum creatinine, ESRD, renal death

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CI: confidence interval; HR: hazard ratio.

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**SGLT-2 Inhibitors**—Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance), Eturugliflozin (Steglatro)

**Clinical Effects**
- Novel mechanism of action/oral agent
- Most will respond—action independent of beta-cell function
- A1C reduction ~1% with 2-3 kg weight loss

**Possible Side Effects and Precautions**
- Mycotic genital infections
- Findings due to volume depletion
- Don’t use if eGFR <45%
- Euglycemic DKA

**Other Features**
- Lowers BP slightly
- Raises LDL cholesterol
- Reduces CVD Risk
- Delays progression of RF

**Canagliflozin/Dapagliflozin/Empagliflozin**

**Warnings and Precautions**
- Hypoglycemia: risk with secretagogues and/or insulin
- Genital mycotic infections
- Urinary tract infection, pyelo, urosepsis
- Volume depletion/orthostatic changes
- Acute renal insufficiency/failure
- DKA
- Bladder cancer (dapagliflozin only)
- Increased fracture risk (cana)
- Increased risk for amputation (cana)

**My Approach for Prevention of Genital Mycotic Infections**

- **Female**:
  - Warn of risk; reduce sugars slowly
  - Make sure topical anti-fungal vaginal cream on hand to apply for even minimal irritation
  - If history of vaginal yeast infection, give prescription for fluconazole 150 mg q72 hours x 3

- **Male**:
  - More common in uncircumcised men
  - Discuss risk; genital hygiene
  - Make sure topical anti-fungal vaginal cream on hand to apply for even minimal irritation
  - If uncircumcised consider script for fluconazole


RxList, 2014.
CV Outcomes Trials in Diabetes: SGLT-2 I

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG</th>
<th>CANVAS Program</th>
<th>DECLARE- Trial</th>
<th>VERTIS-CV</th>
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<td>SGLT-2 I</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>erasugliflozin</td>
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<tr>
<td>N</td>
<td>7028</td>
<td>10,142</td>
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<td>2017</td>
<td>2018</td>
<td>2019</td>
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<td>Benefit in label</td>
<td>Benefit</td>
<td>Pending</td>
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<tr>
<td>Other</td>
<td>Reduction in CHF Renal Benefit</td>
<td>Increased risk of amputation and fracture</td>
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</table>


EMPA-REG Trial design

- Study medication was given in addition to standard of care
- Glucose-lowering therapy was to remain unchanged for first 12 weeks
- Treatment assignment double masked
- The trial was to continue until at least 691 patients experienced an adjudicated primary outcome event

HbA1c

All patients (including those who discontinued study drug or initiated new therapies) were included in the analysis without imputation for missing data. The last available measurement was carried forward for missing data.
Systolic blood pressure

Primary outcome: 3-point MACE

CV death
Hospitalisation for heart failure

Cumulative incidence function. HR, hazard

CREDENCE: Canagliflozin and Renal Function

Is A1c Enough To Help Us Manage Patients?

- **Strengths of A1c**
  - Reflects blood glucose concentrations over ~3 months
  - Only metric of glycemic control that has been prospectively associated with chronic complications
  - Useful for assessing trends in a population over time

- **Limitations of A1c**
  - Affected by other conditions that affect red blood cell lifespan or interfere with glucose binding to hemoglobin
  - A wide range of mean glucose concentrations exist for a given HbA1c level
  - Provides no information about hypoglycemia frequency or severity
  - May under-represent the burden of hyperglycemia in African-Americans

CGM-measured Mean Glucose Versus Lab-Measured HbA1c

Data from 3 studies with Dexcom G4 (505 software)
N= 387 (315 T1D + 72 T2D)

The Value of Continuous Glucose Monitoring

Current CGM Sensors

- Dexcom G6
- Sensionics EverSense
- Abbott Libre
- Medtronic Guardian Connect
Dexcom G6 CGM System

- Factory calibrated
- Approved for nonadjunctive use (i.e., don't need to use blood glucose meter)
- 10 days of sensor use
- Measures glucose concentration every 5 min
- Has alarms for hypoglycemia and hyperglycemia thresholds and alerts for trending high or low
- Can display glucose levels on a receiver, phone, or watch
- Can 'share' glucose readings with someone else (e.g., parent, spouse)

Abbott FreeStyle Libre: Blinded and Realtime

- 14-day factory-calibrated sensor
- Approved for non-adjunctive use
- Records glucose concentration every 15 minutes
- Swipe receiver over sensor to transfer glucose data
- No alarms or alerts in original Libre (Libre 2 has optional high/low alarms)
- Remote monitoring app available

Ambulatory Glucose Profile

- Glucose Metrics
- 24 Hr Glucose Profile/Pattern
- Daily View (Calendar)
Glucose Management Indicator

**Formula to calculate GMI:**

\[
\text{GMI} = \frac{3.77 + 0.02392 \times \text{mean glucose in mg/dL}}{\text{mean glucose in mmol/L}}
\]

Enter mean glucose and select the units:

- **Calculate**

A1C = 9.0%  GMI = 10.2%

A1C = 5.7%  GMI = 6.3%

https://www.jaeb.org/gmi/

Time in Range: 70 – 180 mg/dL

A1C = 5.7%  GMI = 6.3%

A1C = 9.0%  GMI = 10.2%

T1DM: A1C = 6.8%, low variability

T1DM: A1C = 6.9%, high variability

"Do I Really Need Insulin?"

77 yo female on metformin + nateglinide
77 yo on U300 glargine 10 units qAM added

Time Spent Low

High Carb Breakfast/Basal Insulin
Conclusions

• The presence of CVD, HF and/or CKD guide the initial treatment of T2DM

• Individualization of treatment can help reduce multiple complications in people with T2DM.

• Continuous glucose monitoring can help further guide personalization of therapy.
THANK YOU