Welcome to UVM ECHO:
Treatment of Diabetes Mellitus Type II

Facilitators: Mark Pasanen MD, Liz Cote
August 27, 2020
“Introduction” to ZOOM

• Please mute microphone when not speaking
• Please use camera as much as possible
• Test both audio & video before joining
• Communicate clearly during clinic:
  • Can use “raise hand” feature to comment
  • Speak clearly
  • Use chat function for technical issues
CME disclosures

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Disclosures: None or will be resolved

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ECHO Series
Overview of Diabetes Care: ADA Guidelines
Kelsey Sheahan, MD
August 27, 2020
STANDARDS OF MEDICAL CARE IN DIABETES—2020
Diabetes: A Growing Problem

- At least **68% of people** 65 years or older with diabetes will die from some form of **heart disease**, and they are 2-4 times more likely to die from heart disease compared to those without diabetes (American Heart Association)
The Importance of Diabetes Control

• Historically we have seen convincing evidence that improved glycemic control can reduce the microvascular complications of diabetes but its effects of macrovascular complications was mixed:
  • UK Prospective Diabetes Study (UKPDS) initially found no CV mortality benefit with more intensive treatment, but 10-year follow up suggested a potential ‘legacy effect’ of early tight glycemic control leading to later reductions in MI and death (Holman et al NEJM 2008)
  • Veterans Affairs Diabetes Trial (VADT) showed no cardiovascular benefit with better glycemic control (normal HgA1c vs target 8-9%) both initially and in the long-term follow up data (Reaven et al NEJM 2019)
Diabetes Control

- Complicating this was the ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial in 2008 which found intensive glycemic control (HgA1c <6% vs 7-7.9%) had no effect on CV events and even increased mortality, with the 9 year follow up showing no mortality difference but an increase in CV related deaths in the intensive control group (Accord study group, Diabetes Care 2016)
A History of Diabetes Guidelines

• The 2017 ADA Guidelines consisted of this familiar diagram recommending metformin monotherapy and then advancing to any non-insulin medication

• This has shifted drastically given the cardiovascular outcomes trials (CVOTs) of SGLT-2i and GLP-1 RA

SGLT-2 Inhibitors

- Sodium glucose transporter 2 inhibitors (SGLT2i) inhibit these transporters that act to reabsorb glucose in the proximal tubule of the kidney.
- As we start to understand and use these medications more, they have shown favorable secondary effects on the heart, kidneys, and others.

# Summary of kidney outcomes from completed placebo-controlled SGLT2 inhibitor outcome trials in patients with Type 2 Diabetes (4-9)

<table>
<thead>
<tr>
<th>Intervention</th>
<th>CANVAS program (n = 10,142)</th>
<th>DECLARE-TIMI 58 (n = 17,180)</th>
<th>EMPA-REG outcome (n = 7,020)</th>
<th>CREENCE (n = 4,401)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1C inclusion criteria</strong></td>
<td>A1C 7.0-10.5%</td>
<td>A1C 6.5-12.0%</td>
<td>A1C 7.0-10.0%</td>
<td>A1C 6.5-12.0%</td>
</tr>
</tbody>
</table>
| **Additional inclusion criteria** | Preexisting cardiovascular disease if ≥30 years of age or ≥2 cardiovascular risk factors if ≥30 years of age | Preexisting cardiovascular disease or multiple risk factors for atherosclerotic cardiovascular disease | Preexisting cardiovascular disease | eGFR of 30 to <90 mL/min/1.73m²<sup>2</sup>
| | | | | UACR>300-5,000 mg/g |
| | | | | Receiving a stable dose of an ACE inhibitor or ARB for ≥14 weeks prior to randomization |
| % with history of cardiovascular disease | 85.6 | 40.6 | 99 | 50.4 |
| Mean eGFR (mL/min/1.73m²) | 76.5 | 85.3 | 74.1 | 56.2 |
| UACR group (mg/g) | <30: 70% | <30: 69% | <30: 60% | <30: 1% |
| | 30-300: 22% | 30-300: 24% | 30-300: 29% | 30-300: 11% |
| | >300: 8% | >300: 7% | >300: 11% | >300: 88% |
| **Primary outcome(s) (HR [95% CI])** | 3-point MACE 0.96 (0.75-0.97) | 3-point MACE 0.90 (0.84-1.00) | 3-point MACE 0.86 (0.74-0.99) | Primary composite kidney and cardiovascular outcome<sup>a</sup> 0.70 (0.59-0.82) |
| **Key kidney outcomes (HR [95% CI])** | Progression of albuminuria<sup>b</sup> 0.73 (0.67-0.79) | ≥40% decrease in eGFR to <60, end-stage kidney disease, or kidney-related death 0.53 (0.43-0.66) | Doubling of serum creatinine accompanied by eGFR of <45, initiation of kidney replacement therapy, or kidney-related death 0.54 (0.40-0.75) | End-stage kidney disease, doubling of serum creatinine level, or renal death 0.66 (0.53-0.81) |
| | 40% reduction in eGFR, kidney replacement therapy, or kidney-related death 0.60 (0.47-0.77) | End-stage kidney disease 0.31 (0.13-0.79) | Incident or worsening nephropathy 0.61 (0.53-0.70) | End-stage kidney disease 0.68 (0.54-0.88) |
| | | Initiation of kidney replacement therapy 0.45 (0.21-0.97) | Dialysis, kidney transplantation, or renal death 0.72 (0.54-0.97) |

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<sup>a</sup> Primary composite kidney and cardiovascular outcome includes: all-cause death, end-stage kidney disease, initiation of kidney replacement therapy, doubling of serum creatinine level, or renal death.

<sup>b</sup> Progression of albuminuria defined as 30% increase in urinary albumin excretion.

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DAPA-HF

• Secondary outcomes of CVOTs among SGLT-2i suggested benefit in reducing hospitalizations for heart failure, prompting this trial, published in 2019

• RCT of 4744 patients with NYHA class II or above with EF<40%, only 42% of patients with diabetes, treated with dapagliflozin vs placebo looking at the primary outcome of worsening heart failure, a composite of hospitalization or urgent visit requiring IV therapy for heart failure or cardiovascular death

GLP-1 Receptor Agonists

- Glucagon-like peptide 1 is an incretin hormone released from the distal ileum and colon within minutes of a meal and enhances insulin production and secretion in a glucose-dependent fashion, but also exerts many other effects including decreasing glucagon secretion, increasing glucose uptake and glycogen synthesis in peripheral tissues, delays gastric emptying and increases satiety.
## CVOTs for GLP-1 RA

<table>
<thead>
<tr>
<th>GLP-1 RA: Study name</th>
<th>No. of patients</th>
<th>Median follow-up (years)</th>
<th>% with CV disease*</th>
<th>% of statin use</th>
<th>Baseline age</th>
<th>Baseline HgA1c</th>
<th>Primary composite CV outcome HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lixisenatide: ELIXA</td>
<td>6068</td>
<td>2.1</td>
<td>100%</td>
<td>93%</td>
<td>60.3</td>
<td>7.7%</td>
<td>1.02 (0.89 to 1.17)</td>
<td>0.81</td>
</tr>
<tr>
<td>Liraglutide: LEADER</td>
<td>9340</td>
<td>3.8</td>
<td>81%</td>
<td>72%</td>
<td>64.3</td>
<td>8.7%</td>
<td>0.87 (0.78 to 0.97)</td>
<td>0.01</td>
</tr>
<tr>
<td>Semaglutide: SUSTAIN-6</td>
<td>3297</td>
<td>2.1</td>
<td>60%</td>
<td>73%</td>
<td>64.6</td>
<td>8.7%</td>
<td>0.74 (0.58 to 0.95)</td>
<td>0.02</td>
</tr>
<tr>
<td>Exenatide QW: EXSCEL</td>
<td>14752</td>
<td>3.2</td>
<td>73.1%</td>
<td>74%</td>
<td>62.0</td>
<td>8.0%</td>
<td>0.91 (0.83 to 1.00)</td>
<td>0.06</td>
</tr>
<tr>
<td>Albiglutide: Harmony</td>
<td>9463</td>
<td>1.6</td>
<td>100%</td>
<td>84%</td>
<td>64.1</td>
<td>8.7%</td>
<td>0.78 (0.68 to 0.90)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Dulaglutide: REWIND</td>
<td>9901</td>
<td>5.4</td>
<td>31.5%</td>
<td>66%</td>
<td>66.2</td>
<td>7.2%</td>
<td>0.88 (0.79 to 0.99)</td>
<td>0.026</td>
</tr>
<tr>
<td>Oral semaglutide: PIONEER 6</td>
<td>3183</td>
<td>1.3</td>
<td>84.7%</td>
<td>85%</td>
<td>66.0</td>
<td>8.2%</td>
<td>0.79 (0.57 to 1.11)</td>
<td>0.17</td>
</tr>
</tbody>
</table>

INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CHF OR CKD

CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES

- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, carotid or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
- GLP-1 RA with proven CVD benefit
- OR
- SGLT2i with proven CVD benefit if eGFR adequate

HF OR CKD PREDOMINATES

- Particularly HFpEF (LVEF <45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit
COMPPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

EITHER/ OR

GLP-1 RA with good efficacy for weight loss

SGLT2

If A1C above target

SGLT2

GLP-1 RA with good efficacy for weight loss
Poorly Controlled Diabetes

But what about patients with very poorly controlled diabetes?
A1c of 9.5%? 11%? 14%?
First Injectable Medication: GLP-1 RA

- We now have data showing that GLP-1 RA are equally efficacious if not superior to once daily insulin in HgA1c reduction, and it is recommended that these medications be the first injectable medication
  - Caveat being if A1c > 10%, BG >300 or evidence of ongoing catabolism (weight loss, symptoms), consider starting insulin early
- Meta-analysis from 2017 included 11 RCTs that evaluated GLP-1 RA versus once daily insulin

Questions?

Thank you!
Cases/HIPAA

- Names
- Address
- DOB
- Phone/Fax #
- Email address
- Social Security #
- Medical Record #
<table>
<thead>
<tr>
<th>Dates</th>
<th>Session</th>
<th>Didactic Topics (in addition to case review)</th>
</tr>
</thead>
</table>
| August 13     | TeleECHO Session #1 | • Project ECHO Orientation  
• Anatomy of an ECHO session  
• Newly diagnosed DM2  
  • Types of diabetes |
| August 27     | TeleECHO Session #2 | • Overview of Diabetic Care  
  • ADA guidelines |
| September 10  | TeleECHO Session #3 | • Approach to glycemic control  
  • Sulfonylureas, metformin  
  • Continuous Glucose Monitors (CGM) |
| September 24  | TeleECHO Session #4 | • GLP1 agonists/DPP4 inhibitors |
| October 8     | TeleECHO Session #5 | • SGLT 2 inhibitors |
| October 22    | TeleECHO Session #6 | • Insulin 101 |
| November 12   | TeleECHO Session #7 | • Advanced insulin |
| December 10   | TeleECHO Session #8 | • ASCVD prevention:  
  • Lipids, HTN, ASA |
| January 14    | TeleECHO Session #9 | • Complications:  
  • Screening  
  • Prevention |
| January 28    | TeleECHO Session #10 | • Special Populations:  
  • Elderly, pregnancy  
  • Adherence |
ECHO Reminders

• Volunteers to present cases
  • Use the case presentation form template
• Please complete evaluation forms for each session
  • CME will be processed once session evaluation form is received at UVM
• UVM Project ECHO materials available at www.vtahec.org
• Please contact us with any questions/suggestions
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  • ahec@uvm.edu