Welcome to UVM ECHO:
Treatment of Diabetes Mellitus Type II

Facilitators: Mark Pasanen MD, Liz Cote
December 10, 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
• We are recording the didactic section
CME disclosures

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Disclosures: None or have been resolved

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• Amy Shah, DO
• Kelsey Sheahan, MD
Atherosclerosis and Diabetes

M. H. Nathan

December 10, 2020
Multiple medications and drug adherence

![Adjusted Medication Nonadherence Costs](image)
Obviously from the Lancet-hospitalizations with DM increase with age as does CV events.
Atherosclerosis in Diabetes

- Accelerated atherosclerosis is multifactorial and begins years/decades prior to diagnosis of type 2 diabetes
- >50% of patients with newly diagnosed type 2 diabetes have CHD
- Risk for atherosclerotic events is 2- to 4-fold greater in people with diabetes than in those without diabetes
- Atherosclerosis accounts for ~65% of all diabetic mortality
  - 40% due to ischemic heart disease
  - 15% due to other heart disease
  - 10% due to cerebrovascular disease

Diabetes

Hyperglycemia, insulin resistance, and hyperinsulinemia

ASCVD
Hypertension
Metabolic disturbances
Disturbed cellular function
Structural alterations
Cardiac autonomic neuropathy
Neurohormonal activation (RAAS)

Decreased glucose oxidation
Increased FFA and lipotoxicity
Impaired calcium handling
Mitochondrial dysfunction and increased oxidative stress
Cardiomyocyte hypertrophy
AGE deposition

Fibrosis
Cardiomyocyte hypertrophy

Ischemic cardiomyopathy
Hypertensive cardiomyopathy

Diabetic cardiomyopathy

Heart failure
**Pathway for formation**

- Protein

Sugar molecule

- Schiff base

- Amadori products

- AGES

**Biological effects**

- AGES

- AGE receptor binding

- RAGE

- AGE-R1

- AGEs cross-linking to proteins

- Protein cross-linking and altered functions

- ROS generation
- Inflammation
- Metabolic and structural defect

- AGES clearance

- AGEs

- Cardiovascular Disease
- Diabetes
- Kidney disease
- Alzheimer’s Disease
- Sarcopenia
- Rheumatoid Arthritis
DM, BP and LDL cholesterol and CV events
How to screen for ASCVD

• The National Cholesterol Education Panel guidance from 2001 and the U.S. Preventive Services Task Force guideline on statin use for the primary prevention of cardiovascular disease from 2016. The article acknowledges that non-fasting total cholesterol and high-density lipoprotein cholesterol are sufficient for using most cardiovascular risk calculators, but the article is clear in both the text and Table 3 that fasting is preferred.

• Recommendations from the National Institute for Health and Care Excellence, Canadian Cardiovascular Society, and American College of Cardiology/American Heart Association all consider a non-fasting test to be an equal alternative to a fasting test for screening unless the patient is known to have significantly elevated triglycerides. I was unable to find any support in the 2016 U.S. Preventive Services Task Force guideline for the claim that fasting is preferred.

• To determine your cardiovascular risk, your doctor will consider your cholesterol test results in context with your age, sex and family history. Other risk factors, such as smoking, diabetes and high blood pressure, will be considered as well. If your risk remains uncertain, and treatment options are unclear, your healthcare professional may consider other factors and/or request a coronary artery calcium (CAC) measurement to provide greater insight into your risk and help in decision-making.
Metformin use and Heart

A. LVEDD (mm)

- eNOS −/− + Veh
- eNOS −/− + Met

Baseline: p = NS
4 Wk Post: ***

B. LVESD (mm)

- eNOS −/− + Veh
- eNOS −/− + Met

Baseline: p = NS
4 Wk Post: ***

C. Ejection Fraction (%)

- eNOS −/− + Veh
- eNOS −/− + Met

Baseline: p = NS
4 Wk Post: ***

D. Heart : Body Weight

- Sham
- eNOS−/− + Veh
- eNOS−/− + Met QD

Baseline: 5
4 Wk Post: 10

Legend: *** p < 0.001, ** p < 0.01, * p < 0.05, p = NS
Liraglutide and Empagliflozin and Cardioprotection—about 5,000 persons studied for 4 years.
**A** HbA₁c

<table>
<thead>
<tr>
<th>Months</th>
<th>Placebo</th>
<th>Dulaglutide</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>8.00</td>
<td>7.75</td>
</tr>
<tr>
<td>1</td>
<td>7.75</td>
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<tr>
<td>2</td>
<td>7.50</td>
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<tr>
<td>3</td>
<td>7.25</td>
<td>7.00</td>
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<tr>
<td>4</td>
<td>7.00</td>
<td>6.75</td>
</tr>
<tr>
<td>5</td>
<td>6.75</td>
<td>6.50</td>
</tr>
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</table>

Overall LSM difference
-0.61 (95% CI -0.65 to -0.58)
p < 0.0001

**B** Weight

<table>
<thead>
<tr>
<th>Study visit (year)</th>
<th>Mean weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>94</td>
</tr>
<tr>
<td>1</td>
<td>89</td>
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<tr>
<td>2</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>88</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>87</td>
</tr>
</tbody>
</table>

Overall LSM difference
-1.46 (95% CI -1.67 to -1.25)
p < 0.0001

**C** Systolic blood pressure

<table>
<thead>
<tr>
<th>Study visit (year)</th>
<th>Mean systolic blood pressure (mm Hg)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>140</td>
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<tr>
<td>1</td>
<td>137</td>
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<tr>
<td>2</td>
<td>136</td>
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<td>3</td>
<td>135</td>
</tr>
<tr>
<td>4</td>
<td>134</td>
</tr>
<tr>
<td>5</td>
<td>133</td>
</tr>
</tbody>
</table>

Overall LSM difference
-1.70 (95% CI -2.07 to -1.33)
p < 0.0001

**D** Heart rate

<table>
<thead>
<tr>
<th>Study visit (year)</th>
<th>Mean heart rate (beats per min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>79</td>
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<tr>
<td>1</td>
<td>79</td>
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<tr>
<td>2</td>
<td>79</td>
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<td>79</td>
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<tr>
<td>4</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
</tr>
</tbody>
</table>

Overall LSM difference
1.87 (95% CI 1.62 to 2.11)
p < 0.0001
REWRITE-almost 5,000 persons in each arm, followed 5 years

**TRULICITY CV OUTCOME TRIAL**

**PRIMARY MACE 3 RESULT**

- Dulaglutide significantly reduced the risk of Major Adverse Cardiovascular Events (MACE 3: CV death, non-fatal MI or non-fatal stroke) by 12% vs. placebo

- **p-Value:** 0.026
  - **Hazard Ratio (95% CI):** 0.88 [0.79, 0.99]

**CV OUTCOMES**

- Consistent effect across three components of MACE, greatest difference observed in Nonfatal Stroke

- **Hazard Ratio (95% CI):**
  - Nonfatal Stroke: 0.76 [0.61 - 0.95]
  - CV Death: 0.91 [0.78 - 1.06]
  - Nonfatal MI: 0.96 [0.79 - 1.16]
  - All Death: 0.90 [0.80 - 1.01]
Leader study-5,000 persons in each arm, about 4 years

Figure 1. Cumulative incidence of death from cardiovascular causes in the liraglutide group versus placebo group in the LEADER study

Cardiovascular death in LEADER

- Placebo
- Liraglutide

HR 0.78 (0.66 to 0.93), p=0.007

Hazard ratios [HR (95%CI)] based on Cox regression analysis
Adapted from reference 6
Statin use and PVOD-done in 14,000 patients in VA system
Looked for 18 yrs-about 130 type 1s, 870 type 2s and 1300 controls. Type 1s and 2s had to have age of onset > age 30.
Statin use and CV protection in DM

![Graph showing the percentage of death from other causes, cancer death, and cardiac death for Non-DM and DM patients from 1999-2004 and 2005-2010.](image)
2016 ADA guidelines for statins in DM

Table 8.1—Recommendations for statin and combination treatment in people with diabetes

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk factors</th>
<th>Recommended statin intensity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 years</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factor(s)**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40–75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ACS and LDL cholesterol $&gt;50$ mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
</tr>
<tr>
<td>&gt;75 years</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>ASCVD</td>
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<tr>
<td></td>
<td>ACS and LDL cholesterol $&gt;50$ mg/dL (1.3 mmol/L) in patients who cannot tolerate high-dose statins</td>
<td>Moderate plus ezetimibe</td>
</tr>
</tbody>
</table>

*In addition to lifestyle therapy.

**ASCVD risk factors include LDL cholesterol $\geq 100$ mg/dL (2.6 mmol/L), high blood pressure, smoking, overweight and obesity, and family history of premature ASCVD.
Statins which to use for Low, Moderate or High Protection in DM

<table>
<thead>
<tr>
<th>High</th>
<th>Moderate</th>
<th>Low</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dosage lowers LDL-C, on average, by approximately ≥ 50%</td>
<td>Daily dosage lowers LDL-C, on average, by approximately 30% to 50%</td>
<td>Daily dosage lowers LDL-C by &lt; 30% average</td>
</tr>
<tr>
<td><em><em>Atorvastatin (Lipitor®), 40</em> to 80mg</em>*</td>
<td><strong>Atorvastatin 10-20mg</strong></td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin 20-40mg</td>
<td><strong>Rosuvastatin (5) 10mg</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Simvastatin 20-40mg</strong></td>
<td>Simvastatin 10mg</td>
</tr>
<tr>
<td></td>
<td><strong>Pravastatin 40-80mg</strong></td>
<td>Pravastatin 10-20mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40mg</td>
<td>Lovastatin 20mg</td>
</tr>
<tr>
<td></td>
<td><em>Fluvastatin XL 80mg</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Fluvastatin 40mg bid</strong></td>
<td>Fluvastatin 20-40mg</td>
</tr>
<tr>
<td></td>
<td><strong>Pitavastatin 2-4mg</strong></td>
<td>Pitavastatin 1mg</td>
</tr>
</tbody>
</table>
Use of statin and Gemfibrozil

![Graph showing the comparison of major fatal or non-fatal CV events between Simva and Simva + feno. The graph indicates a 31% RRR, adjusted \( p = 0.057 \), for the high triglycerides (≥204 mg/dl) and low HDL (≤34 mg/dl) subgroup, which had a 70% higher event rate. Additionally, there was no benefit for less than moderate dyslipidemia.]
Icosapent ethyl is a type of omega-3 fatty acid, a fat found in fish oil. It is used along with a proper diet to help lower fats (triglycerides) in the blood. This medication is thought to work by decreasing the amount of triglycerides made by the body. Icosapent ethyl is also used along with certain statins such as atorvastatin, simvastatin to reduce the risk of heart attack, stroke, and certain types of chest pain that require treatment in a hospital.
Drugs to reduce LDL

Conclusion of large study—In most patients use statins for more bang for buck
Cases/HIPAA

→ stop recording

- Names
- Address
- DOB
- Phone/Fax #
- Email address
- Social Security #
- Medical Record #
<table>
<thead>
<tr>
<th>DATES (All Thursdays, 12pm to 1pm)</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
• 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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  • Elizabeth.Cote@uvm.edu
  • ahec@uvm.edu