Optimal Management of Cardiovascular Risk in Diabetes

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Jonathan Murrow MD
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Disclosures:

✓ None for Dr. Mushref
✓ Dr. Murrow reports the following: Owner, Infrared Rx.
Why Should We Care?

30.3 million people have diabetes in the US

1/10 people have diabetes

Why Should We Care?

Two thirds of diabetic patients will die of cardiovascular disease (CVD)

6/10 PEOPLE with diabetes will die of CVD

Diabetes Belt

2013 Diagnosed Diabetes Prevalence

Percentage in quintiles:
- 0–7.83
- 7.84–8.80
- 8.81–9.96
- 9.97–11.65
- ≥11.66
Life's Simple 7

- Stop smoking
- Manage blood pressure
- Reduce blood sugar
- Eat better
- Lose weight
- Get active
- Control cholesterol
Objectives:

✓ Individualize glycemic goal
✓ Apply new therapies when appropriate
✓ Importance of smoking cessation
✓ Encourage Lifestyle intervention
Patient One
Patient One:

- 60 year-old male
- Type II diabetes for 15 years
- HTN, CAD, Stroke, Diabetic neuropathy
- HbA1c 8.5%, GFR > 60
Patient One:

What is your HbA1c target to reduce further CVD?

a) Less than 10%

b) Less than 9%

c) Less than 8%

d) Less than 7%
<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Population</th>
<th>Intensive</th>
<th>Conventional</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ 20 year follow up: ↓mortality</td>
</tr>
<tr>
<td>DCCT 1993</td>
<td>Young T1DM patients</td>
<td>Achieved HgbA1C= 7.2%</td>
<td>Achieved HgbA1C=9.1%</td>
<td>✓ No CVD benefit</td>
</tr>
<tr>
<td>EDIC 2005</td>
<td>Same as DCCT</td>
<td>Same as DCCT</td>
<td>Same as DCCT</td>
<td>✓ Reduced CVD by 42%</td>
</tr>
<tr>
<td>ACCORD 2008</td>
<td>T2DM with HgbA1C≥ 7.5%, Age 40-79 with CAD</td>
<td>Achieved A1C 6.4%</td>
<td>Achieved A1C 7.5%</td>
<td>✓ No benefit in primary outcome</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ Higher CV mortality</td>
</tr>
<tr>
<td>ADVANCE 2008, Follow up 2014</td>
<td>T2DM Age ≥ 55 years</td>
<td>Achieved A1C 6.5%</td>
<td>Achieved A1C 7.3%</td>
<td>✓ No benefit in macrovascular events</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ 10 y follow up no benefit in mortality or CVD events</td>
</tr>
<tr>
<td>VADT 2009, Follow up 2015</td>
<td>T2DM Average age 60 DM for 11.5 years</td>
<td>Achieved A1C 6.9%</td>
<td>Achieved A1C 8.4%</td>
<td>✓ No initial benefit</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>✓ 10 y follow-up reduction in CVD events with no mortality benefit</td>
</tr>
</tbody>
</table>
Approach to the Management of Hyperglycemia

Patient / Disease Features | More stringent | A1C 7% | Less stringent
--- | --- | --- | ---
Risks potentially associated with hypoglycemia and other drug adverse effects | low | high
Disease duration | newly diagnosed | long-standing
Life expectancy | long | short
Important comorbidities | absent | few / mild | severe
Established vascular complications | absent | few / mild | severe
Patient attitude and expected treatment efforts | highly motivated, excellent self-care capabilities | less motivated, poor self-care capabilities
Resources and support system | readily available | limited
Back To Patient One:

- 60 years old male
- Type II DM (15 years)
- HTN, CAD, Stroke, Diabetic neuropathy
- HgbA1C 8.5%, GFR>60, BMI 28, BP 150/90
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What would you do next to lower his HbA1c below 8%?

a) Add sitagliptin
b) Add empagliflozin
c) Add liraglutide
d) Add basal insulin
New Medications:

- 2008, FDA issued a guidance for drug industry
- All new DM therapy has to prove CVD safety
- EMPA-REG and LEADER trials showed benefit!
EMP A-REG: Empagliflozin

A Primary Outcome

- Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
- P=0.04 for superiority

B Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P<0.001

EMPA-REG: Empagliflozin

LEADER: Liraglutide

A Primary Outcome

Hazard ratio, 0.87 (95% CI, 0.78–0.97)
P<0.001 for noninferiority
P=0.01 for superiority

B Death from Cardiovascular Causes

Hazard ratio, 0.78 (95% CI, 0.66–0.93)
P=0.007

LEADER: Liraglutide

E Death from Any Cause

F Hospitalization for Heart Failure

Number Needed to Treat

- **4S**
  - Simvastatin for 5.4 years
  - 1994: Pre-statin era
  - 30

- **HOPE**
  - Ramipril for 5 years
  - 2000: Pre-ACEI/ARB era, <29% statin
  - 56

- **EMPA-REG OUTCOME**
  - Empagliflozin for 3 years
  - 2015: >80% ACEI/ARB, >75% statin
  - 39

- **LEADER**
  - Liraglutide for 3.5 years
  - 2016: >90% anti-HTN, >70% statin
  - 98
New Therapies:

• Metformin is still the first line

• Both SGLTi and GLP-RA lower BP and decrease weight

• SGLT-i class effect?

• Weekly GLP-1 RA (Semaglutide, Exenatide)
Special considerations: GLP-1 receptor antagonists and SGLT2 inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>GLP-1 receptor antagonists</th>
<th>SGLT2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c reduction (%)</td>
<td>0.7–1.7</td>
<td>0.32–1.17</td>
</tr>
<tr>
<td>Target of BG lowering</td>
<td>Shorter acting, mostly postprandial BG; longer acting, target fasting and postprandial BG</td>
<td>Fasting and postprandial BG</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Weight loss (kg)</td>
<td>2–5</td>
<td>1.5–3.0</td>
</tr>
<tr>
<td>Systolic blood pressure reduction (mmHg)</td>
<td>2–5</td>
<td>3–5</td>
</tr>
</tbody>
</table>
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Patient Two
Patient Two:

• 45 years old male

• Type II Diabetes for 5 years

• HTN, LDL, Tobacco use

• HgbA1C 9%, LDL 120
Patient Two:

Which of the following the strongest predictor of death in this patient?

a) Smoking
b) Dyslipidemia
c) Uncontrolled A1c
d) Uncontrolled hypertension
Methods

Cohort of 271,174 patients with type 2 diabetes in the Swedish National Diabetes Register matched with 1,355,870 controls

Risk factors:
- elevated HbA1c
- LDL
- albuminuria
- smoking
- high blood pressure
METHODS

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Risk factors:
- elevated HbA1c
- LDL
- albuminuria
- smoking
- high blood pressure
<table>
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<tr>
<th>Intervention</th>
<th>Annual Event Rate</th>
<th>Risk Reduction</th>
<th>Number Needed to Treat (NNT)</th>
<th>NNT Range</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASPIRIN - PRIMARY</td>
<td></td>
<td></td>
<td>Insufficient evidence</td>
<td></td>
<td>USPTF 2016</td>
</tr>
<tr>
<td>ASPIRIN – SECONDARY</td>
<td>2.8%</td>
<td>0.80 (0.73–0.88)</td>
<td>201</td>
<td>134–302</td>
<td>Lancet 2009;373:1849–60</td>
</tr>
<tr>
<td>Fatal and nonfatal CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STATIN – PRIMARY</td>
<td>5.63%</td>
<td>0.72 (0.65–0.79)</td>
<td>63</td>
<td>51–81</td>
<td>Lancet 2008;371:117–25</td>
</tr>
<tr>
<td>Fatal and nonfatal CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STATIN – SECONDARY</td>
<td>10.5%</td>
<td>0.78 (0.69–0.87)</td>
<td>43</td>
<td>31–73</td>
<td>Ibid</td>
</tr>
<tr>
<td>All coronary events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCSK9 inhibitor – SECONDARY</td>
<td>11.3%</td>
<td>0.85 (0.79–0.92)</td>
<td>133</td>
<td>84–222</td>
<td>NEJM 2017;376:1713-22. (FOURIER)</td>
</tr>
<tr>
<td>CV events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statin-associated DM</td>
<td>3.5%</td>
<td>1.13 (1.03–1.23)</td>
<td>219</td>
<td>125–1000</td>
<td>Diabetes Care 2009;32:1924–1929.</td>
</tr>
<tr>
<td>BLOOD PRESSURE CONTROL</td>
<td>1.3%</td>
<td>0.89 (0.83–0.95)</td>
<td>260</td>
<td>170–640</td>
<td>JAMA. 2015;313(6):603-615</td>
</tr>
<tr>
<td>All CV events among diabetics</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</table>
Smoking Cessation

• Counselling every visit
• Nicotine replacement
• Medications

Diabetes and smoking is a bad combination.
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- HbA1c 9%, LDL 120
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He is not interested in smoking cessation but would like to change his diet. Which of the following can decrease cardiovascular events?

a) Ketogenic diet
b) Vegetarian diet
c) Mediterranean diet
d) Calorie restricted diet
e) Any weight loss will reduce CVD risk
Lifestyle Intervention: Look AHEAD trial

**A Weight**

- **Control**
- **Intervention**

Estimated Mean (kg)

- Main effect, -4 (95% CI, -5 to -3)
- P < 0.001

Lifestyle Intervention: Look AHEAD trial

- Improved most CVD risk factors

- Outcome: HR 0.83 to 1.09; P=0.51

Lifestyle Intervention: PREDIMED trial

A Primary End Point (acute myocardial infarction, stroke, or death from cardiovascular causes)

- Med diet, EVOO: hazard ratio, 0.70 (95% CI, 0.53–0.91); P=0.009
- Med diet, nuts: hazard ratio, 0.70 (95% CI, 0.53–0.94); P=0.02

<table>
<thead>
<tr>
<th>Years</th>
<th>Control diet</th>
<th>Med diet, EVOO</th>
<th>Med diet, nuts</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2450</td>
<td>2543</td>
<td>2454</td>
</tr>
<tr>
<td>1</td>
<td>2268</td>
<td>2486</td>
<td>2343</td>
</tr>
<tr>
<td>2</td>
<td>2020</td>
<td>2320</td>
<td>2093</td>
</tr>
<tr>
<td>3</td>
<td>1583</td>
<td>1987</td>
<td>1657</td>
</tr>
<tr>
<td>4</td>
<td>1268</td>
<td>1687</td>
<td>1389</td>
</tr>
<tr>
<td>5</td>
<td>946</td>
<td>1310</td>
<td>1031</td>
</tr>
</tbody>
</table>
Lifestyle Intervention:

- 5% weight loss should be recommended for overweight and obese DM patients
- Reduced calorie intake is paramount but quality of consumed fat is important
- Actively help your diabetics to quit smoking every visit
- Recommend a Mediterranean diet
- A1C<7% in young and newly diagnosed
- Add empagliflozin and liraglutide to metformin
Thank You For Listening!

Special Thanks to:
Dr. Jonathan Murrow
Dr. Catherine Apaloo