GLYCEMIC CONTROL AMONG PEOPLE AT HIGH CARDIOVASCULAR RISK

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Disclosure

Relevant Financial Relationship(s)
• None

Off Label Usage
• None
A patient revolution for careful and kind care

Why We Revolt

Victor Montori

ACC Latin America Conference 2018
55 year-old man, 1.5 years after first MI

- Sedentary, accountant, married
- Obesity (BMI 35), DM2, hypertension.
- On antiplatelet, high-dose statin
- For hypertension: beta-blocker + ACEi + diuretic
- For DM2:
  - Metformin (before MI) + sitagliptin (for 1.5 years)
  - HbA1c 7.6%, Creatinine 1.7 mg/dL
  - Last review no microvascular complications
What is appropriate for his diabetes at this point?

a) Add liraglutide to reduce his CV risk, A1c, and weight
b) Stop metformin (elevated Cr) and add insulin lantus to reduce his A1c and CV risk
c) Advice to promote activity and healthier diet and review HbA1c in 3-6 months
d) Start logging blood sugars 1-2 times per day
e) Lower the statin dose
My clinical approach

1. Promote health: diet, activity, stress, tobacco
2. Estimate and reduce CVD risk
   ✓ Statin (even high doses), aspirin
   ✓ Glucoretics? GLP-1 agonists?
   ✓ Treat hypertension
3. Glycemic control:
   – Involve patients in target (HbA1c ≤ 8%) and how
     http://diabetesdecisionaid.mayoclinic.org
   – Treat symptomatic hyper; avoid hypoglycemia
4. Failure: intensification vs. adherence
Antidiabetes agents with positive CV Outcome Trials

- Pioglitazone (IRIS)*
- Canagliflozin (CANVAS)*
- Empagliflozin (EMPA-REG)
- Dapagliflozin (DECLARE-TIMI 58)
- Liraglutide (LEADER)*
- Semaglutide (SUSTAIN-6)

* Inconsistent results within the class
EMPA-REG

- RCT at low risk of bias (blinding)
- 7028 >5y DM2 (A1c 7-10%)+ CV
- Empagliflozin (10 or 25 mg) vs. Placebo
- At 2.5y: 14% RRR in CV death, nonfatal MI, nonfatal stroke, from 12% to 10.5%
- **Certainty:** Consistent with prior trials and CANVAS (cana), but not with DECLARE (dapa), a 17160-patient 4y trial: no effect on MACE/CV death

**Empagliflozin (HbA1c 0.5%)**

<table>
<thead>
<tr>
<th>Participants with additional:</th>
<th>Placebo</th>
<th>Empagliflozin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose-lowering medications added in concordance with an escalated ‘standard of care’</td>
<td>31.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td>Insulin</td>
<td>11.5%</td>
<td>5.8%</td>
</tr>
<tr>
<td>Dipeptidyl peptidase 4-inhibitor</td>
<td>8.3%</td>
<td>5.6%</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>7.0%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Thiazolidinedione</td>
<td>2.9%</td>
<td>1.2%</td>
</tr>
</tbody>
</table>

**Concerns:** change in protocol, posthoc outcomes, 40% deaths uncertain

RCT at low risk of bias (blinding)
9340 DM2 (A1c 7-10%)+ 80% CV
Liraglutide (1.8 mg daily) vs. placebo
At 3.5y: 13% RRR in CV death, nonfatal MI, nonfatal stroke from 15% to 13%

**Concerns:** Differences between arms in diabetes treatments
Adverse effects in patients with advanced heart failure?
Class effect?
  - Exenatide weekly (EXSCEL, n=14752) Neg
  - Semaglutide weekly (SUSTAIN-6, n=3297) **Pos**
  - Lixisenatide daily (ELIXA, n=6068 ACS) Neg

Liraglutide (HbA1c 0.5%)
FDA and metformin

Obtain eGFR before starting metformin + yearly

- >45  Use (careful with contrast studies)
- 30-45  Question use
- <30  Don’t use

What is appropriate for his diabetes at this point?

a) Add liraglutide to reduce his CV risk, A1c, and weight
b) Stop metformin (elevated Cr) and add insulin lantus to reduce his A1c and CV risk
c) Advice to promote activity, stress reduction, and healthier diet and review HbA1c in 3-6 months
d) Start logging blood sugars 1-2 times per day
e) Lower the statin dose
Why not do everything to the patient?

For a patient at 30% at 10 years
- Statin low dose reduce by 25% to 22.5% (-7.5)
- Statin high dose reduce by 15% to 19.1% (-3.9)
- Aspirin reduces risk by 15%* to 16% (-3)
- Antihypertensive treatment by 20% to 13% (-3)
- Glycemic control by 15% to 11% (-2)
- Liraglutide by 13% to 9.6% (-1.4)
- Empagliflozin by 14% to 8.3% (-1.3)

20%

10%

Burden of treatment, cost to patient, and value to patient
CV risk to take low dose statins >20%

*ASCEND Trial, NEJM 379;16
Burden of treatment?

- Administration

- Side effects (worry)
  
  SGLT-2i (class effects)*
  
  - Amputations (2:1000py)
  - DKA (1:1000py)
  - Genital infex (10:1000py)

- Cost

*BMJ 2018; 363
What is the situation that requires action?

Which response makes the most intellectual, emotional, and practical sense?
Questions & Discussion