Updates in Cardiovascular Risk Reduction

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No financial disclosures
Cardiovascular disease (CVD)

- Leading cause of death in U.S.
- 1 person every 36 dies from CVD
- Diabetes 2-4 fold increased risk CVD
Mr. JB is 52 year old South Asian male...
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MI 3 years ago

Triglycerides 300 mg/dL  (statin + ezetimibe)
LDL-C 130 mg/dL  (statin + ezetimibe)
Diabetes HbA1c 7.5%  (metformin)
“How can I prevent another heart attack?”

(because I don't feel I can change my lifestyle further)
Lots of CVD studies!
Cardiovascular Outcome Trials (CVOT) in type 2 diabetes

Key updates for Mr. JB

• LDL-C reduction
• Triglyceride reduction
• Type 2 diabetes CVD risk reduction

• Impact on CVD and diabetes guidelines
Lipid management – high LDL cholesterol
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

Indications
1. HoFH and HeFH
2. Established ASCVD
3. Very high risk patients

Lowers LDL 60-70%

Cost $466/mo
Mechanism of action

Monoclonal antibody to PCSK9 enzyme
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Monoclonal antibody to PCSK9 enzyme
Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors

**ODYSSEY**
Patients with ACS
LDL $\geq$70 mg/dL statin $\pm$ ezetimibe
Median f/u 2.8 years
\downarrow ASCVD 15% RRR

**FOURIER**
Patients with ASCVD
LDL $\geq$70 mg/dL statin $\pm$ ezetimibe
Median f/u 2 years
\downarrow ASCVD 15% RRR
Side effects

- Well-tolerated
- No significant muscle aches
- No major adverse events in patients with very low LDL <30 mg/dL
- Rash
Mr. JB is 52 year old South Asian male....

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Triglycerides  300 mg/dL  (statin + ezetimibe)
LDL-C        130 mg/dL  (statin + ezetimibe)
Diabetes HbA1c 7.5%  (metformin)

Start PCSK9 inhibitor because LDL ≥70 mg/dL
Lipid management – high triglycerides
prescription fish oil: Icosapent ethyl

Ethyl eicosapentaenoic acid (E-EPA)

Indications
1. TG ≥500 mg/dL (2012)
2. TG 150-499 mg/dL despite statin to reduce CV events (2019)

Reduces TG up to 33%

Cost $241/mo
31% RRR CV events

CV endpoint
-MI/stroke, CV death, revascularization/unstable angina

>8000 people statin therapy
11 countries
473 sites

45+ yo ASCVD
50+ yo DM with 1+ RF
TG ≥150-<500
LDL-C >40-≤100
on statin ≥4 weeks

Icosapent ethyl 2 g BID
Or
Placebo

Mechanism of cardiovascular benefit

Multiple atherogenic processes
- TG-rich lipoproteins
- Plaque
- Endothelium
- Anti-inflammatory
- apoB
Side effects

- Bleeding
- Atrial fib/flutter

![Atrial Fib](image-url)
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MI 3 years ago

Triglycerides 300 mg/dL (statin + ezetimibe)
LDL-C 130 mg/dL (statin + ezetimibe)
Diabetes HbA1c 7.5% (metformin)

Start Icosapent Ethyl at 2 grams BID if LDL controlled and TG remain high
CVD RISK REDUCTION IN TYPE 2 DIABETES
Sodium glucose cotransporter2 (SGLT2) inhibitors

Indications
1. Type 2 diabetes
   a. Reduce CVD risk when established CVD
   b. Reduce HF
   c. Reduce DKD
2. HFrEF reduce HF

Reduces A1c by 0.4-1.1%

Cost: $500/month

Sodium glucose cotransporter2 (SGLT2) inhibitors

### CVOTs for SGLT2 inhibitors

<table>
<thead>
<tr>
<th>CVOT</th>
<th>MACE</th>
<th>HF benefit</th>
<th>Renal benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empagliflozin</td>
<td>EMPA-REG</td>
<td>14% RR CVD</td>
<td>✔️</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>CANVAS</td>
<td>14% RR CVD</td>
<td>✔️</td>
</tr>
<tr>
<td>Dapagliflozin</td>
<td>DECLARE-TIMI</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Ertugliflozin</td>
<td>VERTIS-CV</td>
<td></td>
<td>✔️</td>
</tr>
</tbody>
</table>

Mechanism of cardiovascular benefit

- Lowers A1c
- Lowers blood pressure
- Weight loss
- Osmotic diuresis/naturesis
- Reduce oxidative stress
- Decrease vascular resistance

Side effects

- Urogenital infections
- Diabetic ketoacidosis
- Acute kidney injury
- Canagliflozin – amputation
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MI 3 years ago

Triglycerides  300 mg/dL  (statin + ezetimibe)
LDL-C  130 mg/dL  (statin + ezetimibe)
Diabetes HbA1c  7.5%  (metformin)

Start SGLT2i to improve A1c and reduce CV event risk
Glucagon-like peptide 1 receptor agonist (GLP1RA)

Indications
1. Type 2 diabetes
2. Reduce CVD risk-established CVD
3. Saxenda – obesity tx

Reduces A1c by 0.55-1.2%

Cost: $800-900/month
Glucagon-like peptide 1 receptor agonist (GLP1RA)

## CVOTs for GLP1RA

<table>
<thead>
<tr>
<th>Drug</th>
<th>CVOT</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>LEADER</td>
<td>13% RR CVD</td>
</tr>
<tr>
<td>Semaglutide (inj only)</td>
<td>SUSTAIN-6</td>
<td>24% RR CVD</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>REWIND</td>
<td>12% RR CVD</td>
</tr>
<tr>
<td>Exenatide</td>
<td>EXSCEL</td>
<td>safe</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>ELIXA</td>
<td>safe</td>
</tr>
</tbody>
</table>

Mechanism of cardiovascular benefit

- Lowers A1c
- Lowers blood pressure
- Weight loss
- Improves dyslipidemia
- Anti-inflammatory
- Improves endothelial function

Sposito et al. Cardiovasc Diabetol Dec 2018
Side effects

- GI symptoms
- Pancreatitis
- Diabetic retinopathy – injectable semaglutide
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MI 3 years ago

Triglycerides 300 mg/dL (statin + ezetimibe)
LDL-C 130 mg/dL (statin + ezetimibe)
Diabetes HbA1c 7.5% (metformin)

Start GLP1RA to improve A1c and reduce CV event risk
GUIDELINES HAVE RESPONDED
Summary

- PCSK9i recommended add on statin and ezetimibe in secondary prevention \(^1-3\)

- Very high risk patients: LDL ≥70 mg/dL as threshold for non-statin addition to statin \(^1\)

- Very high risk patients, Icosapent ethyl can be considered when TG 135-499 mg/dL despite statin therapy \(^2-4\)

- SGLT2i and GLP1RA for diabetes and ASCVD to reduce CV events, HF, and progression of kidney disease independent of A1c \(^4-5\)

1. ACC/AHA, American College of Cardiology, American Heart Association 2018 Guideline on the management of blood cholesterol
2. ESC/EAC, European Society of Cardiology, European Atherosclerosis Society Guidelines on management of dyslipidemias 2019
3. NLA Scientific Statement on the Use of Icosapent Ethyl in Statin-treated Patients with Elevated Triglycerides and High or Very High ASCVD Risk.
4. ADA, American Diabetes Association, Standards of Medical Care in Diabetes –2020
5. ACC/AHA 2020 Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients With Type 2 Diabetes
Thank you

AN OUNCE OF PREVENTION

WHERE HEALTH IS PRIMARY.
Medial follow up: 4.9 years

<table>
<thead>
<tr>
<th>Primary CV Endpoint</th>
<th>TG</th>
<th>hsCRP</th>
<th>Hosp Afib/flutter</th>
<th>Serious bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>17.2%</td>
<td>-18%</td>
<td>-13.9%</td>
<td>3.1%</td>
<td>2.7%</td>
</tr>
<tr>
<td>(HR 0.75, p&lt;0.001)</td>
<td></td>
<td></td>
<td>(p=0.004)</td>
<td>(p=0.06)</td>
</tr>
</tbody>
</table>

| 22%                 | +2.2%  | +32.2% | 2.1%             | 2.1%            |
|                     |        |        | (p=0.004)        | (p=0.06)        |

Adjunctive Therapies for ASCVD Risk Reduction in High- or Very-high-risk Statin-treated Patients Supported by RCT Evidence

Moderate or High-intensity Statin

- Ezetimibe
  - Acute coronary syndrome within 10 days (IMPROVE-IT)
  

- Icosapent Ethyl
  - Stable ASCVD; or Diabetes + ≥1 additional risk factor + TG 135-499 mg/dL (REDUCE-IT)


- PCSK9 Inhibitor
  - Stable ASCVD + additional risk factors; or ACS within 1-12 months (FOURIER, ODYSSEY-Outcomes)


Orringer et al. J Clin Lipidology Dec 2019
First-line therapy is metformin and comprehensive lifestyle management

Indications of high risk or established ASCVD, CKD, or HF

Consider independently of baseline A1c or individualized A1c target

ASCVD predominates

Preferably GLP1RA or SGLT2i with proven CV benefit

HF or CKD predominates

Preferably SGLT2i with evidence of reducing HF or CKD progression

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