SVM 2022: Updates in Vascular Disease

Real world benefits of GLP1 receptor agonists

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I do not have any relationships to report with ACCME defined ineligible companies.

I will not be discussing unlabeled/investigational uses of medical devices or pharmaceuticals during this presentation.
Objectives

- Background and overview of GLP-1 receptor agonists (GLP1RA)
- Evidence for benefits of GLP1RA
- Use of GLP1RA in the real world
GLP-1 receptor agonists (GLP1RA) increase GLP1 action to pharmacologic levels

- GLP1:
  - is an *incretin* hormone
  - is secreted by L-cells in the distal ileum and colon within minutes of nutrient ingestion
  - acts on GLP1 receptors in islet β-cells to secrete insulin and islet α-cells to suppress glucagon secretion
  - slows gastric emptying
  - promotes satiety
- The incretin effect is reduced or absent in type 2 diabetes (T2D)

Besides marked lowering of A1c, GLP1RA have potent weight loss effects

Davies M, et al. Semaglutide 2.4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomized, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397(10278):971-984.
Tirzepatide, a dual GIP/GLP1RA, vs semaglutide resulted in lower A1c and more weight loss in T2D

## GLP1RA with cardiovascular (CV) benefit

<table>
<thead>
<tr>
<th>GLP1RA</th>
<th>Dosing (mg)</th>
<th>CVOT*</th>
<th>CVOT: % with est. ASCVD</th>
<th>CVOT: duration (y)</th>
<th>MACE** reduction (%)</th>
<th>FDA indication for MACE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>SQ QD 0.6, 1.2, 1.8</td>
<td>LEADER</td>
<td>~81</td>
<td>3.8</td>
<td>13</td>
<td>T2D and established CVD</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>SQ Qwk 0.25, 0.5, 1, 2</td>
<td>SUSTAIN-6</td>
<td>83</td>
<td>2.1</td>
<td>26</td>
<td>T2D and established CVD</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>SQ Qwk 0.75, 1.5, 3, 4.5</td>
<td>REWIND</td>
<td>31</td>
<td>5.4</td>
<td>12</td>
<td>T2D and est. CVD or multiple CV risk factors</td>
</tr>
</tbody>
</table>

CVOT: cardiovascular outcome trial. MACE: major adverse cardiovascular event (nonfatal MI, nonfatal stroke, CV death)
GLP1 has direct and indirect effects in the heart and blood vessels.

GLP1 modifies CV risk through direct and indirect actions in multiple organs.
REWIND post-hoc analysis (dulaglutide) of T2D showed CV benefit w/ or w/o background metformin

Dulaglutide reduced the primary outcome whether patients were on metformin or not, at baseline

Real world evidence for effect of GLP1RA vs other glucose-lowering agents* on MACE


*except for SGLT2i
Real world evidence for effect of GLP1RA vs SGLT2i on MACE

Real world studies tend to include patients at lower CV risk

Caveats:
- Most real-world studies do not have information about diabetes duration or A1c, or other metabolic features
- Short duration of follow-up. SGLT2i exert benefits very early while benefits of GLP1RA take longer especially with lower CV risk
- Real-world studies to date do not include semaglutide or ertugliflozin use

Using GLP1RA in the real world

• Start with a GLP1RA or SGLT2i first-line in ASCVD, CKD, HF
  • Select based on individual patient characteristics and preferences
• All weekly GLP1RA can be used without dose adjustment in patients with renal impairment
• Dulaglutide and semaglutide can be used in patients with severe renal impairment
• Start with the lowest dose and uptitrate every 4 weeks as tolerated to goal dose
  • Liraglutide: 0.6 mg/day titrated Q4wk to maximum 1.8 mg QD
  • Semaglutide: 0.25 mg/wk per week titrated Q4wk to maximum 2 mg/wk
  • Dulaglutide: 0.75 mg/wk or 1.5 mg/wk titrated Q4wk to maximum 4.5 mg/wk

If starting insulin too (for symptomatic hyperglycemia) start GLP1RA as soon after basal insulin as possible

Retrospective cohort study
Uncontrolled hyperglycemia n=6339
47% male
Mean age 54 ± 11 (SD)
Weight 108 ± 26 kg
Baseline A1c 10.7% ± 1.5%
Dyslipidemia 82%
HTN 80%
CKD 26%
Neuropathy 23%
Cohorts A and B achieved control

Take-home points and conclusions

- GLP1RAs are an important class of glucose-lowering drugs with benefits for potent A1c-lowering and weight loss, and are first-line in pts w/ estab/high risk for ASCVD

- Liraglutide, semaglutide and dulaglutide lower risk of MACE by 12-26%

- Real world evidence: GLP1RAs lower risk of MACE compared with other glucose-lowering drugs.
  - SGLT2i are the exception, but this may be due to limitations of available real world data

- Tirzepatide has weight reduction effects on par with bariatric procedures but CV data will not be available until 2024