Cardiovascular outcomes & atherosclerosis: How do GLP-1RA provide benefits?

Expanding focus for cardiologists
The diabetic patient and cardiovascular outcomes
In conjunction with the European Society of Cardiology 2020

Jorge Plutzky, MD
Director, Preventive Cardiology
Cardiovascular Division
Brigham and Women’s Hospital
Harvard Medical School
Boston, Massachusetts
jplutzky@bwh.Harvard.edu
Major GLP1-RA CVOTs

### Negative Primary Endpoint

**EXSCEL**
- MACE: Favours exenatide
- CV death
- Non-fatal stroke
- Non-fatal MI

**ELIXA**
- MACE: Favours lixisenatide
- Unstable angina
- CV death
- Fatal and non-fatal stroke
- Fatal and non-fatal MI

### Why?

**EXSCEL**
- Exenatide
- p=0.06 for superiority
- p<0.001 for noninferiority

**ELIXA**
- Lixisenatide
- p=0.81 for superiority
- p<0.001 for noninferiority

### Positive Primary Endpoint

**LEADER**
- MACE: Favours liraglutide
- CV death
- Non-fatal stroke
- Non-fatal MI

**SUSTAIN 6**
- MACE: Favours semaglutide
- CV death
- Non-fatal stroke
- Non-fatal MI

**REWIND**
- MACE: Favours dulaglutide
- CV death
- Non-fatal stroke
- Non-fatal MI

### Basis for benefit?

**Trial insights:** Pos vs Neg? Subgroups?

**Mechanistic insight:** Clinical. Preclinical

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**p-values for superiority/noninferiority are for the primary endpoint.**

Potential Factors in GLP1-RA CVOT Results
**GLP-1 RAs**

**Human GLP-1 Backbone**
- **Dulaglutide**
  - Dimeric DPP-4 resistant human GLP-1 genetically fused to the Fc domain of IgG4 ($t_{1/2} = 5$ days)
- **Liraglutide**
  - Acetylated GLP-1 analog; Acetylation allows for association with albumin ($t_{1/2} = 13$ hours)
- **Albiglutide**
  - DPP-4 resistant human GLP-1 dimer genetically fused to human albumin ($t_{1/2} = 5$ days)

**Exendin-4 Backbone**
- **Exenatide BID**
  - Synthetic exendin-4 peptide; 50% homologous to human GLP-1 and resistant to DPP-4 degradation ($t_{1/2} = 2.4$ hours)
- **Lixisenatide**
  - Synthetic exendin-4 peptide; C-terminal modification adding 6 lysine residues and removing 1 proline ($t_{1/2} = 3$ hours)
- **Exenatide QW**
  - Exenatide encased in microspheres which slowly hydrolyze and extend release ($t_{1/2} = 2.4$ hours)
<table>
<thead>
<tr>
<th></th>
<th>ELIXA</th>
<th>LEADER</th>
<th>SUSTAIN 6</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug tested</td>
<td>Lisixenatide</td>
<td>Liraglutide</td>
<td>Semaglutide</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Dose</td>
<td>20 µg/d</td>
<td>1.8 mg/d</td>
<td>0.5 or 1 mg/wk</td>
<td>1.5 mg/wk</td>
</tr>
<tr>
<td>N</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>9901</td>
</tr>
<tr>
<td>Mean age, years</td>
<td>60</td>
<td>64</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Percent women</td>
<td>31</td>
<td>36</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>Percent prior CVD</td>
<td>100</td>
<td>81</td>
<td>59</td>
<td>31</td>
</tr>
<tr>
<td>Mean BMI, kg/m²</td>
<td>30</td>
<td>33</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Mean HbA1c, %</td>
<td>7.7</td>
<td>8.7</td>
<td>8.7</td>
<td>7.3</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>MACE&lt;sup&gt;a&lt;/sup&gt; or unstable angina</td>
<td>MACE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MACE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MACE&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## LEADER: Liraglutide in Patients With T2DM and High CV Risk

### Primary Outcome: Subgroup Analysis

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Hazard ratio (95% CI)</th>
<th>p-value for interaction</th>
<th>No. of patients</th>
<th>Liraglutide no. of events/no. of patients (%)</th>
<th>Placebo no. of events/no. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary analysis</strong></td>
<td>0.87 (0.78–0.97)</td>
<td>0.84</td>
<td>9340</td>
<td>608/4668(13.0)</td>
<td>694/4672(14.9)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.88 (0.72–1.08)</td>
<td>0.84</td>
<td>3337</td>
<td>183/1657(11.0)</td>
<td>209/1680(12.4)</td>
</tr>
<tr>
<td>Male</td>
<td>0.86 (0.75–0.98)</td>
<td></td>
<td>6003</td>
<td>425/3011(14.1)</td>
<td>485/2992(16.2)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 years</td>
<td>0.78 (0.62–0.97)</td>
<td>0.27</td>
<td>2321</td>
<td>140/1197(11.7)</td>
<td>186/1124(14.8)</td>
</tr>
<tr>
<td>&gt;= 60 years</td>
<td>0.90 (0.79–1.02)</td>
<td></td>
<td>7019</td>
<td>468/3471(13.5)</td>
<td>528/3548(14.9)</td>
</tr>
<tr>
<td><strong>Geographic region</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>0.82 (0.68–0.98)</td>
<td>0.20</td>
<td>3296</td>
<td>207/1639(12.6)</td>
<td>252/1657(15.2)</td>
</tr>
<tr>
<td>North America</td>
<td>1.01 (0.84–1.22)</td>
<td></td>
<td>2847</td>
<td>212/1401(15.1)</td>
<td>216/1446(14.9)</td>
</tr>
<tr>
<td>Asia</td>
<td>0.62 (0.37–1.04)</td>
<td></td>
<td>711</td>
<td>24/360(6.7)</td>
<td>37/351(10.5)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>0.83 (0.68–1.03)</td>
<td></td>
<td>2486</td>
<td>165/1268(13.0)</td>
<td>189/1218(15.5)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.90 (0.80–1.02)</td>
<td>0.32</td>
<td>7238</td>
<td>494/3616(13.7)</td>
<td>543/3622(15.0)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>0.87 (0.59–1.27)</td>
<td></td>
<td>777</td>
<td>47/370(12.7)</td>
<td>59/407(14.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>0.70 (0.46–1.04)</td>
<td></td>
<td>936</td>
<td>40/471(8.5)</td>
<td>56/485(12.0)</td>
</tr>
<tr>
<td>Other</td>
<td>0.61 (0.37–1.00)</td>
<td></td>
<td>389</td>
<td>27/211(12.8)</td>
<td>36/176(20.2)</td>
</tr>
<tr>
<td><strong>Ethnic group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>0.74 (0.54–1.02)</td>
<td>0.30</td>
<td>1134</td>
<td>68/580(11.7)</td>
<td>86/554(15.5)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>0.89 (0.79–1.00)</td>
<td></td>
<td>8206</td>
<td>540/4088(13.2)</td>
<td>608/4118(14.8)</td>
</tr>
<tr>
<td><strong>Body mass index</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=30 kg/m²</td>
<td>0.96 (0.81–1.15)</td>
<td>0.15</td>
<td>3574</td>
<td>241/1743(13.8)</td>
<td>261/1831(14.3)</td>
</tr>
<tr>
<td>&gt;30 kg/m²</td>
<td>0.82 (0.71–0.94)</td>
<td></td>
<td>5757</td>
<td>367/2920(12.6)</td>
<td>431/2837(15.2)</td>
</tr>
</tbody>
</table>

Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. Race or ethnic group was self-reported. CI: confidence interval.
LEADER: Liraglutide in Patients With T2DM and High CV Risk

Primary Outcome: Subgroup Analysis: Cont’d

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<tr>
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<th>Placebo no. of events/no. patients (%)</th>
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<tbody>
<tr>
<td>Primary analysis</td>
<td>0.87 (0.78–0.97)</td>
<td>0.58</td>
<td>9340</td>
<td>608/4668 (13.0)</td>
<td>694/4672 (14.9)</td>
</tr>
<tr>
<td>Glycated hemoglobin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;8.3%</td>
<td>0.89 (0.76–1.05)</td>
<td></td>
<td>4768</td>
<td>289/2340 (12.4)</td>
<td>333/2428 (13.7)</td>
</tr>
<tr>
<td>&gt;8.3%</td>
<td>0.84 (0.72–0.98)</td>
<td></td>
<td>4872</td>
<td>319/2328 (13.7)</td>
<td>361/2244 (16.1)</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;11 years</td>
<td>0.82 (0.70–0.97)</td>
<td>0.42</td>
<td>4429</td>
<td>265/2216 (12.0)</td>
<td>316/2213 (14.3)</td>
</tr>
<tr>
<td>&gt;11 years</td>
<td>0.90 (0.78–1.04)</td>
<td></td>
<td>4892</td>
<td>340/2441 (13.9)</td>
<td>376/2451 (15.3)</td>
</tr>
<tr>
<td>Risk of CVD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &gt;/=50 years and established CVD/CKD</td>
<td>0.83 (0.74–0.93)</td>
<td>0.04</td>
<td>7598</td>
<td>536/3831 (14.0)</td>
<td>629/3767 (16.7)</td>
</tr>
<tr>
<td>Age &gt;/=60 years and risk factors for CVD</td>
<td>1.20 (0.86–1.87)</td>
<td></td>
<td>1742</td>
<td>72/837 (6.6)</td>
<td>65/905 (7.2)</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td></td>
<td>0.53</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.94 (0.72–1.21)</td>
<td></td>
<td>1305</td>
<td>112/653 (17.2)</td>
<td>119/652 (18.3)</td>
</tr>
<tr>
<td>No</td>
<td>0.85 (0.76–0.96)</td>
<td></td>
<td>8035</td>
<td>496/4015 (12.4)</td>
<td>575/4020 (14.3)</td>
</tr>
<tr>
<td>Antidiabetic therapy</td>
<td></td>
<td>0.73</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 OAD</td>
<td>0.75 (0.58–0.98)</td>
<td></td>
<td>1818</td>
<td>99/922 (10.7)</td>
<td>125/896 (14.0)</td>
</tr>
<tr>
<td>&gt;1 OAD</td>
<td>0.95 (0.78–1.16)</td>
<td></td>
<td>2997</td>
<td>191/1515 (12.6)</td>
<td>196/1482 (13.2)</td>
</tr>
<tr>
<td>Insulin with OAD(s)</td>
<td>0.89 (0.74–1.06)</td>
<td></td>
<td>3422</td>
<td>223/1674 (13.3)</td>
<td>259/1748 (14.8)</td>
</tr>
<tr>
<td>Insulin without OAD</td>
<td>0.86 (0.63–1.17)</td>
<td></td>
<td>737</td>
<td>71/361 (19.7)</td>
<td>86/376 (22.9)</td>
</tr>
<tr>
<td>None</td>
<td>0.73 (0.42–1.25)</td>
<td></td>
<td>366</td>
<td>24/196 (12.2)</td>
<td>28/170 (16.5)</td>
</tr>
<tr>
<td>Renal function</td>
<td></td>
<td>0.01</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60 mL/min/1.73 m²</td>
<td>0.69 (0.57–0.85)</td>
<td></td>
<td>2158</td>
<td>172/1116 (15.4)</td>
<td>223/1042 (21.4)</td>
</tr>
<tr>
<td>&gt;/=60 mL/min/1.73 m²</td>
<td>0.94 (0.83–1.07)</td>
<td></td>
<td>7182</td>
<td>436/3552 (12.3)</td>
<td>471/3630 (13.0)</td>
</tr>
</tbody>
</table>

Prespecified Cox proportional-hazard regression analyses were performed for subgroups of patients with respect to the primary outcome (first occurrence of death from CV causes, nonfatal MI, or nonfatal stroke). P values signify tests of homogeneity for between-group differences with no adjustment for multiple testing. The percentages of patients with a first primary outcome between the randomization date and the date of last follow-up are shown. There were missing data for BMI in 5 patients in the liraglutide group and 4 in the placebo group and for the duration of diabetes in 11 patients in the liraglutide group and 8 in the placebo group.
Atherosclerosis

Is atherosclerosis distinct in the context of diabetes?

Diabetic Atherosclerosis

Plutzky, Libby The Glucose Paradox, Circulation 2002
Diabetic Atherosclerosis

Pancreas

Hyper-Insulinemia

Skeletal Muscles
Insulin Resistance:
↑FFA
Hyperglycemia

Lipemia

Obesity

↑FFA

Adipocytes

TNF-α

↑CRP

Dyslipidemia
VLDL (↑TG)

↓HDL

LDL

Liver

Hypertension

Hyperglycemia

Advanced Glycation End-products

Glycated protein

Thrombosis

↑Fibrinogen

↑PAI-1

Genetic Predisposition

Circ 2002
Multiple Sites of Action of GLP-1

- Brain: 
  - Neuroprotection
  - Appetite
- Heart: 
  - Cardioprotection
  - Cardiac function
- Intestine: 
  - GLP-1
- Stomach: 
  - Gastric emptying
- Liver: 
  - Glucose production
- Pancreas: 
  - Insulin secretion
  - Glucagon secretion
  - Insulin biosynthesis
  - β-cell proliferation
  - β-cell apoptosis
- Adipose tissue: 
  - Glucose uptake and storage
- Muscle: 
  - Insulin sensitivity

Gastro 2007; 132:2131-57

Energy-dense diet and inactivity contribute to obesity, leading to ‘dysfunctional’, inflamed fat and adipokines. Adipokines, such as Adiponectin, TNF-α, and IL-6, are downregulated, whereas ICAM-1, selectins, and HSPs are upregulated, contributing to endothelial dysfunction, vascular SMCs, and inflammatory cells.

This leads to inflammation, which is associated with HTN, atherosclerosis, and CVD. Inflammation also affects the liver, leading to CRP and SAA.

Liraglutide effect on body fat

**Change in body fat**
- **DEXA**

**Liraglutide:**
- Saxenda, 3 mg/d
- Indication: Weight loss

- **Liraglutide 1.2 mg + met**
  - Change in body fat: -1.6* (-1.1%*)
- **Liraglutide 1.8 mg + met**
  - Change in body fat: -2.4* (-1.2%*)
- **Glimepiride + met**
  - Change in body fat: +1.1 kg (+0.4%)

**Change in percentage fat** (CT)
- **Visceral**
  - Liraglutide 1.2 mg + met: -17.1
  - Liraglutide 1.8 mg + met: -16.4
  - Glimepiride + met: +3.4

- **Subcutaneous**
  - Liraglutide 1.2 mg + met: -4.8
  - Liraglutide 1.8 mg + met: -7.8* -8.5*

86% of weight loss was fat tissue (liraglutide 1.8 mg)

LEAD 2 substudy (DEXA & CT); Data are mean ±SEM; *p<0.05 vs glim+met; n=160
Jendle et al Diab Obet Met 2009
Semaglutide: A1C and Body Weight

**A1C**

- **Mean Glycated Hemoglobin**
  - Placebo, 1.0 mg
  - Placebo, 0.5 mg
  - Semaglutide, 0.5 mg
  - Semaglutide, 1.0 mg

**Mean Body Weight**

- Placebo, 1.0 mg
- Placebo, 0.5 mg
- Semaglutide, 0.5 mg
- Semaglutide, 1.0 mg

Marso SP et al. NEJM 2016.
SELECT: Secondary Prevention of CVD in Obese Subjects w/o Diabetes

Event driven 1225 first MACEs

N=17,500 patients
Male or female
≥45 years of age
BMI ≥27

Randomisation (1:1)

Established CVD as evidenced by at least one of the following:

Prior MI

Prior stroke
- Ischaemic OR
- Haemorrhagic

Symptomatic PAD
- Intermittent claudication with ankle-brachial index (ABI) < 0.85 (at rest) OR
- Peripheral arterial revascularisation procedure OR
- Amputation due to atherosclerotic disease

CV, cardiovascular; MACE, major adverse cardiovascular events; PAD, peripheral arterial disease; s.c., subcutaneous.
GLP1 Effects: Vascular

- Inflammation
- Glucose uptake
- Ischemic injury
  - ↓ Inflammation
  - ↑ Glucose uptake
  - ↓ Ischemic injury
  - ↓ LV Function
  - ↑ Heart rate

- BP
- Weight

- Vasodilation
- Plaque Stability
- Blood Flow
- Smooth muscle proliferation
- Platelet Aggregation
  - ↑ Vasodilation
  - ↑ Plaque Stability
  - ↑ Blood Flow
  - ↓ Smooth muscle proliferation
  - ↓ Platelet Aggregation

Liraglutide Attenuates Preestablished Atherosclerosis in Apolipoprotein E–Deficient Mice via Regulation of Immune Cell Phenotypes and Proinflammatory Mediators


A

HFHCD
712

HFHCD+Lir
561

338

374

187

20.8%
Unique Proteins

GLP-1R Activation

Gut
GLP-1RS

IELs
Brunner’s Glands

↓Permeability

TGs
ApoB48

↓Inflammation

↓Lipid Deposition

Anti-Atherosclerotic Effect

Independent of BW and Glucose

↓Plaque lesion development

↓Inflammatory pathways in plaque tissue

Leukocyte recruitment (IL6, IL-1RN, CCL2, OPN)
Leukocyte rolling, adhesion and extravasation (SELE, VCAM1, Cholesterol metabolism (ABCA1, PTGIS)
Extracellular matrix protein turnover (MMP3 and 13)
Plaque hemorrhage (CD163)
Cardiovascular outcomes & atherosclerosis: How do GLP-1RA provide benefits?

- The transformative clinical trial data for CV benefit with novel glucose-lowering agents like GLP1-RA forces a consideration of the mechanisms underlying these benefits, including differences among GLP1-RAs.
- Mechanistic considerations are relevant in order to understand better the disease state, better identify patients who might benefit, including from a given agent and as a means to further drug development.
- GLP1-RA CV benefits may involve improvements in CV risk factors that contribute to the complex picture of diabetic atherosclerosis, like lower blood pressure.
- Excess adiposity has been implicated extensively in CV risk; the weight loss effects of GLP1-RA may alter the effects of adipose tissue on circulating mediators involved in hypertension, inflammation, vascular reactivity.
- Preclinical models support broad effects of GLP1-RA action on inflammation and atherosclerosis, along with identifying other potential mechanisms, like gut permeability.