Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists: Is There One Better for Your Heart AND Your Wallet?

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At the end of this session, the learner will be able to:
1. Discuss diabetes guidelines and GLP-1 agents place in therapy
2. Describe purpose of cardiovascular outcome trials (CVOTs) and results for GLP-1 agents
3. Explain different economic analyses used when comparing medications and apply them to GLP-1 agents
Speaker Disclosure:
MAJ Adam B. Davies has nothing to disclose concerning possible financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation. The findings discussed in this presentation represent the views of the author, and do not necessarily reflect the views of the Department of Defense (DoD), nor the Departments of the Army, Navy, and Air Force.

Background

1. Diabetes\textsuperscript{1-2}
   a. Was 7\textsuperscript{th} leading cause of death in U.S. in 2015
   b. 30.3 million people have diabetes in U.S. (9.4\% of population)
      i. Type 1 diabetes represents 1.25 million people (\textasciitilde 5\% of population)
      ii. Type 2 diabetes represents 29.05 million people (\textasciitilde 95\% of population)
   c. Undiagnosed people represents 7.2 million of 30.3 million (\textasciitilde 25\% of population)
   d. Americans diagnosed increased four-fold between 1980 and 2014
   e. Obesity & diabetes changes in the U.S. from 1994, 2000, and 2015 are represented below in Figure 1

   ![Figure 1: Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults\textsuperscript{3}](image)

2. Cost of diabetes in U.S.\textsuperscript{1,4}
   a. Total cost of diagnosed diabetes in 2017: $327 billion
      i. $237 billion for direct medical costs
      ii. $90 billion in reduced productivity
b. Economic costs of diabetes increased by 26% from 2012 to 2017 due to increased prevalence of diabetes and increased cost per person with diabetes (adjusted for inflation)

c. Average medical expenditures were 2.3 times higher in patients with diabetes (adjusted for age group and sex)

d. Growth in diabetes prevalence and medical cost is primarily among the patient population ≥ 65 years of age

3. Military Health Benefit
a. TRICARE is the military’s health plan
b. TRICARE serves 9.5 million active duty and retired uniformed service members and their families
c. Pharmacy benefit: Three points of service (POS)
   i. Retail: ~60 thousand network locations
   ii. Mail Order: there is one mail order pharmacy
   iii. Military Treatment Facility (MTF): 708 facilities
d. Annual net pharmacy expenditures was $7.6 billion in fiscal year (FY) 18
   i. Diabetes drugs accounted for about $500 million of $7.6 billion
      1. Diabetes Non-Insulin: $328 million (4.3% of net spend)
      2. Insulin: $178 million (2.3% of net spend)

Clinical Review

1. Guidelines and recommendations for Type 2 Diabetes (T2DM)

![Figure 2: ADA and EASD Overall Approach to Glucose Lowering in T2DM](image)
a. American Diabetes Association (ADA) – Standard of Medical Care in Diabetes is guideline published annually in January with their recommendations
b. European Association for the Study of Diabetes (EASD)
c. Consensus report position statement listed in Figure 2 above is an update from previous version published in 2015

2. Facts about cardiovascular disease (CVD) and diabetes
   a. People with diabetes are two to four times more likely to die from CVD
   b. 68% of people with diabetes > 65 years old will die from CVD

3. Second-line drug classes for certain conditions & factors listed below in Table 1
   a. Red indicates the preferred class to use
   b. ADA guideline changed from 2018 to 2019 for atherosclerotic cardiovascular disease (ASCVD) recommendation in GLP-1 class
      i. 2018 guideline:
         1. benefit = liraglutide (FDA approved for CVD benefit)
         2. neutral = exenatide extended release and lixisenatide
      ii. 2019 guideline
         1. benefit = liraglutide (FDA approved for CVD benefit) > semaglutide > exenatide extended release
         2. neutral = lixisenatide

Table 1: Second-Line Drug Classes for Certain Conditions & Factors

<table>
<thead>
<tr>
<th>Class</th>
<th>Use for ASCVD</th>
<th>Cause Hypoglycemia</th>
<th>Weight Change</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin</td>
<td>No</td>
<td>Yes</td>
<td>Gain</td>
<td>Low (human) High (analogs)</td>
</tr>
<tr>
<td>SU</td>
<td>No</td>
<td>Yes</td>
<td>Gain</td>
<td>Low</td>
</tr>
<tr>
<td>TZD</td>
<td>No</td>
<td>No</td>
<td>Gain</td>
<td>Low</td>
</tr>
<tr>
<td>DPP4</td>
<td>No</td>
<td>No</td>
<td>Neutral</td>
<td>High</td>
</tr>
<tr>
<td>GLP-1</td>
<td>Yes*</td>
<td>No</td>
<td>Loss</td>
<td>High</td>
</tr>
<tr>
<td>SGLT2</td>
<td>Yes*</td>
<td>No</td>
<td>Loss</td>
<td>High</td>
</tr>
</tbody>
</table>

* specific agents only
ASCVD = atherosclerotic cardiovascular disease
SU = sulfonylureas  TZD = thiazolidinediones  DPP 4 = dipeptidyl peptidase-4 inhibitors
GLP-1 = glucagon-like peptide-1 receptor agonists  SGLT2 = sodium-glucose cotransporter-2 inhibitors
4. Drugs in GLP-1 Class\textsuperscript{10-14}
   a. Exenatide extended-release (Bydureon BCise) once weekly 2mg
   b. Liraglutide (Victoza) once daily 0.6 mg, 1.2 mg, and 1.8 mg
   c. Lixisenatide (Adlyxin) once daily 10 mcg and 20 mcg
   d. Semaglutide (Ozempic) once weekly 0.25 mg, 0.5 mg, and 1 mg
   e. Dulaglutide (Trulicity) once weekly 0.75 mg and 1.5 mg

5. Pathophysiologic defects in T2DM: The Ominous Octet that lead to hyperglycemia\textsuperscript{15}
   a. GI tract/decreased incretin effect (GLP-1)
   b. Islet-beta-cells/decreased insulin secretion (GLP-1)
   c. Islet-alpha-cells/increased glucagon secretion (GLP-1)
   d. Increased hepatic glucose production (HPG) (GLP-1, metformin, and thiazolidinedione)
   e. Neurotransmitter dysfunction (GLP-1)
   f. Decreased glucose uptake in muscle (metformin and thiazolidinedione)
   g. Increased glucose reabsorption in kidneys (SGLT2 inhibitors)
   h. Increased lipolysis (thiazolidinedione)

6. FDA guidance to industry\textsuperscript{16-18}
   a. Established in 2008 for new clinical studies in planning stages
      i. Sponsors should establish an independent cardiovascular (CV) endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials
      ii. Events should include cardiovascular mortality, myocardial infarction (MI), and stroke (3-point major adverse cardiovascular events [MACE]) but can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints
      iii. Trial must demonstrate that new antidiabetic therapy will not result in an unacceptable increase in cardiovascular risk
      iv. Criteria – patients at high risk for CV events (advanced disease, elderly, renal impairment), sufficient size and duration for enough CV events, and end points of at least 3-point MACE
   b. FDA advisory committee voted in October 2018 to continue CVOTs for safety (10-9 vote in favor) – called for modification to broaden population recruited to include patients without established CVD and inclusion of endpoints beyond 3-point MACE

7. GLP-1 CVOTs comparison\textsuperscript{19-25}
   a. Six trials listed below in Table 2
      i. Five completed trials and one results pending publication
      ii. Four showing superiority to placebo for primary composite endpoint
      iii. One used 4-point MACE while others used 3-point MACE
      iv. PIONEER 6 trial of oral semaglutide not included in this review
Table 2: GLP-1 CVOTs Primary Endpoints & Results (MACE = major adverse cardiovascular events)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Primary Endpoint</th>
<th>Results Summary</th>
<th>Primary Composite Outcome HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXSCEL n=14,752</td>
<td>exenatide 3.2 years</td>
<td>3P-MACE</td>
<td>Completed Apr 2017; Noninferior to placebo</td>
<td>0.91 (0.83–1.00)</td>
</tr>
<tr>
<td>LEADER n=9,340</td>
<td>liraglutide 3.8 years</td>
<td>3P-MACE</td>
<td>Completed Jan 2015; Superior to placebo in composite endpoint</td>
<td>0.87 (0.78–0.97)</td>
</tr>
<tr>
<td>ELIXA n=6,068</td>
<td>lixisenatide 2.1 years</td>
<td>4P-MACE</td>
<td>Completed Feb 2015; Noninferior to placebo</td>
<td>1.02 (0.89–1.17)</td>
</tr>
<tr>
<td>SUSTAIN-6 n=3,297</td>
<td>semaglutide 2.1 years</td>
<td>3P-MACE</td>
<td>Completed Mar 2016; Superior to placebo</td>
<td>0.74 (0.58–0.95)</td>
</tr>
<tr>
<td>HARMONY n=9,463</td>
<td>albiglutide 1.6 years</td>
<td>3P-MACE</td>
<td>Completed Mar 2018; Superior to placebo</td>
<td>0.78 (0.68–0.90)</td>
</tr>
<tr>
<td>REWIND n=9,901</td>
<td>dulaglutide &gt; 5 years</td>
<td>3P-MACE</td>
<td>Completed Aug 2018; Superior to placebo</td>
<td>Results pending Jun 2019</td>
</tr>
</tbody>
</table>

b. Patient characteristics varied across studies and prominent characteristics are listed in Table 3 below
c. Further patient characteristics are listed in Appendix A

Table 3: GLP-1 CVOTs Prominent Patient Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EXSCEL exenatide</th>
<th>LEADER liraglutide</th>
<th>ELIXA lixisenatide</th>
<th>SUSTAIN-6 semaglutide</th>
<th>HARMONY albiglutide</th>
<th>REWIND dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>61.9 yrs</td>
<td>64.2 yrs</td>
<td>59.9 yrs</td>
<td>64.6 yrs</td>
<td>64.1 yrs</td>
<td>66 yrs</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>32.7</td>
<td>32.5</td>
<td>30.1</td>
<td>32.8</td>
<td>32.3</td>
<td>32.3</td>
</tr>
<tr>
<td>Mean duration of T2DM</td>
<td>13.1 yrs</td>
<td>12.8 yrs</td>
<td>9.2 yrs</td>
<td>13.9 yrs</td>
<td>14.1 yrs</td>
<td>&gt; 10.0 yrs</td>
</tr>
<tr>
<td>Mean A1c (SD)</td>
<td>8.1% (1.0)</td>
<td>8.7% (1.6)</td>
<td>7.7% (1.3)</td>
<td>8.7% (1.5)</td>
<td>8.7% (1.5)</td>
<td>7.3%</td>
</tr>
<tr>
<td>Previous CVD = n (%)</td>
<td>10,782 (73)</td>
<td>7,598 (81)</td>
<td>6,068 (100)</td>
<td>2,735 (83)</td>
<td>9,463 (100)</td>
<td>3,111 (31.4)</td>
</tr>
</tbody>
</table>

yrs = years  BMI = body mass index  T2DM = type 2 diabetes mellitus  SD = standard deviation  CVD = cardiovascular disease
d. Meta-analysis conducted by Bethel, et al. included four drugs

i. ELIXA CVOT results – lixisenatide once daily
   1. showed noninferiority to placebo in 3-point MACE

ii. LEADER CVOT results – liraglutide once daily
   1. showed superiority to placebo in 3-point MACE (number needed to treat [NNT] 66 in 3 years)
   2. showed noninferiority to cardiovascular mortality component of 3-point MACE
   3. showed noninferiority in all-cause mortality (NNT 98)

iii. SUSTAIN-6 CVOT results – semaglutide once weekly
   1. showed superiority to placebo in 3-point MACE (results driven by non-fatal stroke; NNT 45 in 2 years)

iv. EXSCEL CVOT results – exenatide once weekly
   1. showed noninferiority to placebo in 3-point MACE
   2. not statistically significant in all-cause mortality

v. Overall findings showed GLP-1 agents can reduce 3-point MACE and all-cause mortality (to varying degrees for individual drugs) without significant safety concerns – choice of agent can be individualized by patient’s needs

e. Individual trials (see Appendix B and C for more information)

i. HARMONY CVOT results – albiglutide once weekly
   1. showed superiority to placebo in 3-point MACE (results driven by non-fatal MI)

ii. REWIND CVOT results – dulaglutide once weekly
   1. Showed superiority to placebo in 3-point MACE (results are not published or publically available)

8. Potential class effect of GLP-1s

a. Differences between agents:

i. Long-acting vs short-acting (dosing weekly vs daily)
ii. Large vs small molecules (small = exenatide, liraglutide, lixisenatide, and semaglutide) vs (large = albiglutide and dulaglutide)
iii. Exendin-based vs GLP-1 base (exenatide and lixisenatide ~50% amino-acid homology to human GLP-1 vs liraglutide [90%], semaglutide [94%], albiglutide [97%], and dulaglutide [90%])

b. Possible effect differences:

i. Weight loss
ii. Lowering of systolic blood pressure
iii. Changes in insulin sensitivity
iv. Improvement in lipids
v. A1c lowering
c. Proposed mechanisms of GLP-1s on reducing CV events (time to benefit approximately 12 months) listed below (see Appendix D for depiction)\(^{33}\)
   i. Modified progression of atherosclerotic vascular disease
   ii. Attenuation of cardiac and vascular inflammation
   iii. Improved vasodilation
   iv. Renal protection
   v. Reduce ectopic fat deposition

9. Overall clinical conclusion (CVOT focus)
   a. All six GLP-1 agents showed CV safety compared to placebo (this was the primary purpose of the trials per the FDA guidance)
   b. Four agents showed superiority, compared to placebo, for CV benefit in 3-point MACE primary endpoint in patients with history of ASCVD (secondary prevention)
      i. Liraglutide is only GLP-1 agent with FDA approved indication to reduce CV risk in patients with established CV disease
   c. Differences in patient populations and statistical design limitations in the CVOTs make it difficult to directly compare GLP-1 agents to each other in terms of CV benefit
   d. Various proposed mechanisms of GLP-1 agents on reducing CV events but none have shown a definitive answer and reason to having an effect for the class

### Economic Review

1. Outcomes research is defined as studies that attempt to identify, measure, and evaluate the results of healthcare services\(^{31-35}\)
   a. Extension for Community Healthcare Outcomes (ECHO) Model
      i. Economic outcomes – direct, indirect, and intangible costs compared with the consequences of medical treatment alternatives
      ii. Clinical outcomes – medical events that occur as a result of disease or treatment
      iii. Humanistic outcomes – consequences of disease or treatment on patient functional status, or quality of life, measured along several dimensions (e.g. physical functioning, social functioning, general health perceptions and well-being)
   b. Pharmacoeconomics is a division of outcomes research defined as the description and analysis of the cost of drug therapy to healthcare systems and society

2. Seven different perspectives in which analysis can be from (can have a combination of perspectives)\(^{36}\)
   a. Patient perspective – what they would pay for treatment (co-pay or out-of-pocket-costs)
b. Provider perspective – expenses associated with providing a service (it could vary depending upon private practice vs managed-care organizations (MCO) vs hospital/healthcare system)

c. Payer perspective – look at charges to healthcare products and services (are they Government, Insurer, Employer)

d. Societal perspective – this would consider the benefit to society (very broad perspective)

3. Four types of Pharmacoeconomic Analyses\textsuperscript{36-40}

a. Cost-minimization analysis (CMA)
   i. Assumes equal efficacy and cheapest alternative is preferred

b. Cost-benefit analysis (CBA)
   i. Analysis of a program, service, or treatment alternative
   ii. Both cost and benefit measured in dollars and expressed as a ratio, net benefit, or net cost

c. Cost-effectiveness analysis (CEA) see Figure 3 below for graphic of CMA and CEA
   i. Used to compare treatment alternatives with different safety and efficacy profiles
   ii. Must compare same outcome (e.g. % A1c lowering, blood pressure lowering)
   iii. Results expressed as an incremental cost-effectiveness ratio (ICER)
      1. Lower ICER = better cost-effectiveness

\[
ICER = \frac{\text{Cost (intervention A)} - \text{Cost (intervention B)}}{\text{Efficacy (intervention A)} - \text{Efficacy (intervention B)}}
\]

d. Cost-utility analysis (CUA)
   i. Similar analysis to CEA but takes into consideration patient preference or quality of life
   ii. Outcomes expressed in utilities that are weighted by patient
   iii. Compares cost, quality, and quantity of patient-years
   iv. Utility measured in quality-adjusted life years (QALYs)

Figure 3: Graphic Representation of CMA and CEA
4. CEA from UK
   a. Assessed cost-effectiveness of exenatide 2 mg once-weekly compared to:
      i. Dulaglutide 1.5 mg once-weekly
      ii. Liraglutide 1.2 mg once a day
      iii. Liraglutide 1.8 mg once a day
      iv. Lixisenatide 20 mcg once a day
   b. QALYs calculated with health-state utilities applied to:
      i. T2DM-related complications, weight changes, hypoglycemia, and nausea 
         (see Table 4 below)
   c. Used 40-year time horizon
   d. Applied Cardiff Diabetes Model

Table 4: Treatment Efficacy and Tolerability Applied in the Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>EQW</th>
<th>DULA</th>
<th>LIRA 1.2</th>
<th>LIRA 1.8</th>
<th>LIXI</th>
<th>NPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔHbA1c (glycosylated hemoglobin, %)</td>
<td>-1.34</td>
<td>-1.34</td>
<td>-0.96</td>
<td>-1.28</td>
<td>-0.75</td>
<td>-0.54</td>
</tr>
<tr>
<td>ΔWeight (kg)</td>
<td>-2.04</td>
<td>-2.38</td>
<td>-2.72</td>
<td>-3.09</td>
<td>-1.84</td>
<td>1.703</td>
</tr>
<tr>
<td>Discontinuation due to adverse event*</td>
<td>0.063</td>
<td>0.140</td>
<td>0.120</td>
<td>0.130</td>
<td>0.030</td>
<td>NA</td>
</tr>
<tr>
<td>Nausea as adverse event*</td>
<td>0.240</td>
<td>0.520</td>
<td>0.440</td>
<td>0.490</td>
<td>0.310</td>
<td>NA</td>
</tr>
<tr>
<td>Symptomatic hypoglycemia#</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>10.922</td>
</tr>
<tr>
<td>Severe hypoglycemia~</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Source: Kavanagh et al., except NPH

*proportion applied in the first 6-month cycle; #number of episodes per year; ~probability per 6 months.

Table 5: Cost Inputs Applied in the Model

<table>
<thead>
<tr>
<th>Drug</th>
<th>Price per pack or unit</th>
<th>Doses per pack</th>
<th>Doses per week</th>
<th>Annual cost</th>
</tr>
</thead>
</table>
| Exenatide QW          | £73.30  
£73.25  
£171.72  
£171.72  
£57.93  
—       | 4   
4   
36   
28   | 1   
1   
7   | £986.18  
£984.74  
£1,632.27  
£1,510.02  
£820.29  
£606.27  | |

Diabetes related complication:
- Fatal
- Non-fatal
- Maintenance
- Reference

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic heart disease</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>£2,505</td>
<td>—</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>—</td>
<td>£5,188</td>
</tr>
<tr>
<td>Stroke</td>
<td>—</td>
<td>£11,450</td>
</tr>
<tr>
<td>Blindness</td>
<td>—</td>
<td>£6,502</td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>—</td>
<td>£18,776</td>
</tr>
<tr>
<td>Amputation</td>
<td>—</td>
<td>£13,499</td>
</tr>
</tbody>
</table>

Severe hypoglycemic event
- Assumed to incur one GP visit

Cost includes metformin 2000 mg per day.

Cost input was based on an assumed distribution of 65% hospital treatment and 35% non-hospital treatment.
f. Utility decrements were applied in the model and can be seen in Appendix E

g. Results suggest exenatide 2 mg once-weekly is cost-effective over a lifetime horizon compared to the other four listed GLP-1 agents for treatment in T2DM adults not adequately controlled on metformin alone (see below in Table 6)

Table 6: Results (discounted) of exenatide once-weekly and comparators (PSA = probabilistic sensitivity analysis)

<table>
<thead>
<tr>
<th></th>
<th>Total lifetime cost (per patient)</th>
<th>QALYs (per patient)</th>
<th>Incremental* costs</th>
<th>Incremental* QALYs</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Base case analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>£19,930</td>
<td>11.279</td>
<td>£27 (~£30; £85)</td>
<td>0.046 (0.026; 0.056)</td>
<td>£390</td>
</tr>
<tr>
<td>Dulaglutide 1.5 mg QW</td>
<td>£19,903</td>
<td>11.233</td>
<td>£27 (~£30; £85)</td>
<td>0.040 (0.019; 0.051)</td>
<td>£1,004</td>
</tr>
<tr>
<td>Lixisenatide 1.2 mg QD</td>
<td>£19,827</td>
<td>11.177</td>
<td>£103 (£46; £160)</td>
<td>0.122 (0.090; 0.112)</td>
<td>£1,004</td>
</tr>
<tr>
<td>Lixisenatide 1.8 mg QD</td>
<td>£22,016</td>
<td>11.236</td>
<td>£2,055 (~£2,143; ~£2,028)</td>
<td>0.043 (0.034; 0.053)</td>
<td>EQW dominant</td>
</tr>
<tr>
<td>Lixisenatide 20 μg QD</td>
<td>£19,192</td>
<td>11.206</td>
<td>£738 (£681; £795)</td>
<td>0.074 (0.064; 0.083)</td>
<td>£10,002</td>
</tr>
</tbody>
</table>

| **PSA**          |                                  |                     |                    |                    |      |
| Exenatide QW     | £20,023                          | 11.500              | £667 (~£435; £482) | 0.036 (~0.072; 0.143) | £1,866 |
| Dulaglutide 1.5 mg QW | £19,957                          | 11.463              | £123 (~£964; £467) | 0.099 (0.022; 0.177) | EQW dominant |
| Lixisenatide 1.2 mg QD | £20,026                          | 11.409              | £1,467 (~£2,494; ~£1,136) | 0.021 (~0.080; 0.117) | EQW dominant |
| Lixisenatide 1.8 mg QD | £21,886                          | 11.479              | £1,163 (~£2,494; ~£1,136) | 0.021 (~0.080; 0.117) | EQW dominant |
| Lixisenatide 20 μg QD | £19,322                          | 11.418              | £701 (£286; £1,094) | 0.082 (~0.009; 0.169) | £8,599 |

*exenatide QW vs comparator.
QALYs, quality-adjusted life years; ICER, incremental cost-effectiveness ratio; EQW, exenatide QW; PSA, probabilistic sensitivity analysis. Cs are based on the mean values analysis.

h. Limitations – performed in UK (pricing different from US and might not be generalizable to our population), didn’t assess all GLP-1 agents (performed in 2016), and research was supported and funded by exenatide manufacturer (AstraZeneca Pharmaceuticals)

i. Strengths – used established model and meta-analysis data inputs, used long time horizon of 40 years, this is one of few CEAs done for GLP-1 agents

j. Overall takeaway – gives good analysis but price differences are too variable and effect overall ICER quite a bit in this model; QALYs so similar

5. Overall economic conclusion

a. GLP-1 agents can vary widely in the price (US vs UK, discounts, rebates)
b. Use of CMA indicates selection of agent with lowest cost (assumes equal efficacy)
c. CEA example indicated exenatide once-weekly to be cost-effective when compared to other four listed GLP-1 agents
d. Patient co-pays, rebates and other drug discounts should be considered when selecting agents for formulary status

Conclusion and Recommendation for Future Trials

1. Conclusions

a. Formulary management team should consider clinical and economic conclusions
b. GLP-1 agents are generally interchangeable (exception would be lixisenatide)
c. At least one GLP-1 agent should be available for patients (recommend at least two agents)

2. Recommendations for future trials

a. Should have head-to-head trials of GLP-1 agents
i. Use primary outcome of 3-point MACE
ii. Use individual composite outcomes of 3-point MACE as primary endpoints

b. Larger studies powered to allow comparison of GLP-1 agents
   i. Use individual composite outcomes of 3-point MACE as primary endpoints

c. Trials using CV events as primary prevention (no prior ASCVD history in patients)
d. CEAs comparing GLP-1 agents with focus on 3-point MACE outcomes only (cost associated with drugs and events vs probability of differences in outcomes)

References


Appendices

Appendix A: GLP-1 CVOTs Patient Characteristics Comparison\textsuperscript{19-25}

<table>
<thead>
<tr>
<th>Parameter</th>
<th>EXSCEL exenatide</th>
<th>LEADER lixisenatide</th>
<th>ELIXA lixisenatide</th>
<th>SUSTAIN-6 semaglutide</th>
<th>HARMONY albiglutide</th>
<th>REWIND dulaglutide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n (%)</td>
<td>9,149 (62%)</td>
<td>6,003 (64%)</td>
<td>4,207 (69%)</td>
<td>2,002 (61%)</td>
<td>6,569 (69%)</td>
<td>-</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>5,603 (38%)</td>
<td>3,337 (36%)</td>
<td>1,861 (31%)</td>
<td>1,295 (39%)</td>
<td>2,894 (31%)</td>
<td>4,589 (46.3%)</td>
</tr>
<tr>
<td>White n (%)</td>
<td>11,175 (76%)</td>
<td>7,238 (78%)</td>
<td>4,576 (75%)</td>
<td>2,736 (83%)</td>
<td>6,583 (70%)</td>
<td>-</td>
</tr>
<tr>
<td>Proportion w/HF</td>
<td>2,389 (16%)</td>
<td>1,667 (18%)</td>
<td>1,358 (22%)</td>
<td>777 (24%)</td>
<td>1,922 (20%)</td>
<td>852 (8.6)</td>
</tr>
<tr>
<td>SBP (SD)</td>
<td>135.4 (16.9)</td>
<td>135.9 (17.8)</td>
<td>129.0 (17.0)</td>
<td>135.6 (17.2)</td>
<td>134.8 (16.6)</td>
<td>137.2 (16.8)</td>
</tr>
<tr>
<td>DBP (SD)</td>
<td>78.5 (9.8)</td>
<td>77.2 (10.3)</td>
<td>-</td>
<td>77.0 (10.0)</td>
<td>76.8 (10.1)</td>
<td>78.5 (9.8)</td>
</tr>
<tr>
<td>LDL (SD)</td>
<td>2.4 (1.0)</td>
<td>2.3 (0.9)</td>
<td>2.0 (0.9)</td>
<td>2.1 (1.2)</td>
<td>-</td>
<td>2.56 (0.98)</td>
</tr>
<tr>
<td>HDL (SD)</td>
<td>1.1 (0.9)</td>
<td>1.2 (0.3)</td>
<td>1.1 (0.3)</td>
<td>1.1 (0.7)</td>
<td>-</td>
<td>1.18 (0.34)</td>
</tr>
<tr>
<td>Insulin n (%)</td>
<td>6838 (46%)</td>
<td>4159 (45%)</td>
<td>2374 (39%)</td>
<td>1913 (58%)</td>
<td>5597 (59%)</td>
<td>2398 (24.2%)</td>
</tr>
<tr>
<td>Metformin n (%)</td>
<td>11 295 (77%)</td>
<td>7136 (76%)</td>
<td>4021 (66%)</td>
<td>2414 (73%)</td>
<td>6969 (74%)</td>
<td>8016 (81%)</td>
</tr>
<tr>
<td>SU n (%)</td>
<td>5401 (37%)</td>
<td>4721 (51%)</td>
<td>2004 (33%)</td>
<td>1410 (43%)</td>
<td>2725 (29%)</td>
<td>4373 (44.2%)</td>
</tr>
<tr>
<td>TZD n (%)</td>
<td>579 (4%)</td>
<td>573 (6%)</td>
<td>95 (2%)</td>
<td>76 (2%)</td>
<td>194 (2%)</td>
<td>168 (1.7%)</td>
</tr>
<tr>
<td>DPP-4 n (%)</td>
<td>2203 (15%)</td>
<td>6 (&lt;1%)</td>
<td>NA</td>
<td>5 (&lt;1%)</td>
<td>1437 (15%)</td>
<td>88 (0.9%)</td>
</tr>
<tr>
<td>SGLT2 n (%)</td>
<td>77 (1%)</td>
<td>NA</td>
<td>NA</td>
<td>5 (&lt; 1%)</td>
<td>575 (6%)</td>
<td>12 (0.1%)</td>
</tr>
<tr>
<td>Duration of f/u γ</td>
<td>3.2 (2.2–4.4)</td>
<td>3.8 yrs</td>
<td>2.1 yrs</td>
<td>2.1 yrs</td>
<td>1.6 yrs</td>
<td>-</td>
</tr>
</tbody>
</table>

Appendix B: HARMONY CVOT\textsuperscript{24}

**Albiglutide: HARMONY outcomes**

**Time to first occurrence of CV death, MI or stroke**

![Graph showing time to first occurrence of CV death, MI or stroke](image)

- HR: 0.78
- 95% CI: 0.68; 0.90
- Event rate per 100 person-years: albiglutide 4.57; placebo 5.87
- *p* < 0.0001 for non-inferiority
- *p* = 0.0006 for superiority

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Time from randomisation (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide</td>
<td>4731 4613 4503 4239 3148 2142 1064 -</td>
</tr>
<tr>
<td>Placebo</td>
<td>4732 4603 4469 4208 3074 2077 1030 -</td>
</tr>
</tbody>
</table>
HARMONY OUTCOMES
Secondary endpoints and all-cause death

<table>
<thead>
<tr>
<th>3-point MACE (primary outcome)</th>
<th>Albglutide (N=4731)</th>
<th>Placebo (N=4732)</th>
<th>Hazard ratio (95% CI)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-point MACE*</td>
<td>373</td>
<td>468</td>
<td>0.78 (0.68; 0.90)</td>
<td>&lt;0.0001; 0.0006</td>
</tr>
<tr>
<td>CV death</td>
<td>122</td>
<td>130</td>
<td>0.93 (0.73; 1.19)</td>
<td>0.578</td>
</tr>
<tr>
<td><strong>Myocardial infarction</strong></td>
<td>181</td>
<td>240</td>
<td><strong>0.75 (0.61; 0.90)</strong></td>
<td>0.003</td>
</tr>
<tr>
<td>Stroke</td>
<td>94</td>
<td>108</td>
<td>0.86 (0.66; 1.14)</td>
<td>0.300</td>
</tr>
<tr>
<td>CV death or hospitalisation for HF</td>
<td>188</td>
<td>218</td>
<td>0.85 (0.70; 1.04)</td>
<td>0.113</td>
</tr>
<tr>
<td>All-cause death</td>
<td>196</td>
<td>205</td>
<td><strong>0.95 (0.79; 1.16)</strong></td>
<td>0.644</td>
</tr>
</tbody>
</table>

*CV death, myocardial infarction, stroke and urgent revascularisation for unstable angina;

Appendix C: REWIND CVOT²⁵

**Dulaglutide: REWIND**

“Dulaglutide significantly reduced major adverse cardiovascular events (MACE), a composite endpoint of cardiovascular (CV) death, non-fatal myocardial infarction (heart attack) or non-fatal stroke, meeting the primary efficacy objective in the precedent-setting REWIND trial”
Potential mechanisms mediating a beneficial effect of glucagon-like peptide-1 (GLP-1) receptor agonists on reducing cardiovascular events. Effects of diabetes mellitus-related parameters (glycemic control, avoidance of [severe] hypoglycemia), cardiovascular risk factors (body weight, blood pressure, lipoproteins/lipids), and interactions with GLP-1 receptors in the cardiovascular system (potentially leading to improved endothelial function/vasodilation, improved cardiac function under conditions of coronary ischemia, and anti-inflammatory/anti-atherosclerotic effects) have to be considered. CV indicates cardiovascular.
### Appendix E: Utility Decrements Applied in the Model

<table>
<thead>
<tr>
<th>Event</th>
<th>Utility decrement</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes-related complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>0.090</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.055</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.108</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>Stroke</td>
<td>0.164</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>Amputation</td>
<td>0.280</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>Blindness</td>
<td>0.074</td>
<td>Clarke <em>et al.</em></td>
</tr>
<tr>
<td>End stage renal disease</td>
<td>0.263</td>
<td>Currie <em>et al.</em></td>
</tr>
<tr>
<td><strong>Hypoglycemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>0.0142</td>
<td>Currie <em>et al.</em></td>
</tr>
<tr>
<td>Severe</td>
<td>0.047</td>
<td>Currie <em>et al.</em></td>
</tr>
<tr>
<td><strong>BMI change</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Per unit increase</td>
<td>−0.0061</td>
<td>Bagust and Beale</td>
</tr>
<tr>
<td>Per unit decrease</td>
<td>+0.0061</td>
<td>Bagust and Beale</td>
</tr>
</tbody>
</table>