American Diabetes Association
Standards of Medical Care in Diabetes
2019 Summary of Revisions

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Disclosure

Drs. Adnan Mehboob, Kandis Samuels-Leutzinger, and advisor, Dr. Hugh Bonner have no financial conflicts of interest relevant to this presentation.
Objectives

• Review the pathophysiology of type 2 diabetes mellitus.
• Review GLP-1 receptor agonists.
• Review updates in pharmacologic approaches to glycemic treatment.
• Review the SUSTAIN-6 trial.
• Review AAFP’s STEPS approach to manage hyperglycemia in patients with type 2 diabetes mellitus.
The Pathophysiology of Type 2 Diabetes Mellitus

The Ominous Octet

Thrasher J. The American Journal of Medicine 2017;130 (6S):S4-S17
Glucagon-like peptide-1 (GLP-1) receptor agonists

Hinnen D. Diabetes Spectrum 2017; 30(3):202-210
Glucagon-like peptide-1 (GLP-1) receptor agonists
1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

• Randomized, double-blind, placebo-controlled, parallel-group trial at 230 sites in 20 countries involving 3,297 patients.

• Patients were randomized in a 1:1:1:1 ratio to receive either 0.5 mg or 1.0 mg of once-weekly subcutaneous semaglutide or volume-matched placebo.

• The trial consisted of a planned observation period of 109 weeks for all patients (a 104-week treatment period with a 5-week follow-up period) in which patients who had prematurely discontinued a study treatment were also included.

• Industry sponsored study.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

• Inclusion Criteria
  • Patients with T2DM and a glycated hemoglobin level of ≥7% if they had not been treated with an antihyperglycemic drug or had been treated with no more than two oral antihyperglycemic agents, with or without basal or premixed insulin.

• Key Inclusion Criteria
  • Age ≥ 50 years with established cardiovascular disease, chronic heart failure, or chronic kidney disease of stage III or higher
  • Age ≥60 years and subclinical evidence of cardiovascular disease
    • Persistent microalbuminuria (30-299 mg/g) or proteinuria
    • Hypertension and left ventricular hypertrophy by electrocardiogram or imaging
    • Left ventricular systolic or diastolic dysfunction by imaging
    • Ankle/brachial index less than 0.9
    • Chronic renal impairment (eGFR <60 ml/min/1.73 m² per MDRD)
Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

A. Diabetic retinopathy complications

B. New or worsening nephropathy

Figure 3. Microvascular Outcomes
Kaplan-Meier plots showing time to first diabetic retinopathy complications (Panel A) and new or worsening nephropathy (Panel B).

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

Figure 2. Glycated Hemoglobin and Body Weight.
Shown are the mean values for glycated hemoglobin (Panel A) and body weight (Panel B) during the trial period. The I bars represent standard errors.
Data were estimated on the basis of scheduled visits in the full analysis set with the use of a mixed model for repeated measures with treatment group (semaglutide doses of 0.5 mg and 1.0 mg and corresponding placebo doses) and all possible combinations of stratification factors used for randomization as fixed factors.

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

Table 3. Selected Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>Semaglutide 0.5 mg (N=826)</th>
<th>Semaglutide 1.0 mg (N=822)</th>
<th>Placebo 0.5 mg (N=824)</th>
<th>Placebo 1.0 mg (N=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>740 (89.6)</td>
<td>732 (89.1)</td>
<td>748 (80.8)</td>
<td>736 (89.2)</td>
</tr>
<tr>
<td>Serious adverse event†</td>
<td>283 (35.0)</td>
<td>276 (33.6)</td>
<td>329 (39.9)</td>
<td>298 (36.1)</td>
</tr>
<tr>
<td>Severe adverse event‡</td>
<td>200 (24.2)</td>
<td>207 (25.2)</td>
<td>216 (26.2)</td>
<td>194 (23.5)</td>
</tr>
<tr>
<td>Adverse event leading to treatment discontinuation</td>
<td>95 (11.5)</td>
<td>119 (14.5)</td>
<td>47 (5.7)</td>
<td>63 (7.6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Event</th>
<th>Semaglutide 0.5 mg (N=826)</th>
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<th>Placebo 1.0 mg (N=825)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorder§</td>
<td>419 (50.7)</td>
<td>430 (52.3)</td>
<td>294 (35.7)</td>
<td>290 (35.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>148 (17.9)</td>
<td>151 (18.4)</td>
<td>98 (11.9)</td>
<td>87 (10.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>143 (17.3)</td>
<td>180 (21.9)</td>
<td>62 (7.5)</td>
<td>67 (8.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>87 (10.5)</td>
<td>122 (14.8)</td>
<td>43 (5.2)</td>
<td>34 (4.1)</td>
</tr>
<tr>
<td>Cardiac disorder§</td>
<td>173 (20.9)</td>
<td>150 (18.2)</td>
<td>189 (22.9)</td>
<td>173 (21.0)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>27 (3.3)</td>
<td>21 (2.8)</td>
<td>32 (3.9)</td>
<td>26 (3.2)</td>
</tr>
<tr>
<td>Acute pancreatitis§</td>
<td>6 (0.7)</td>
<td>3 (0.4)</td>
<td>3 (0.4)</td>
<td>9 (1.1)</td>
</tr>
</tbody>
</table>

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes (SUSTAIN-6)

• Semaglutide-treated patients had a significant 26% lower risk of the primary composite outcome of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke than did those receiving placebo.
  • This lower risk was principally driven by a significant (39%) decrease in the rate of nonfatal stroke and a nonsignificant (26%) decrease in nonfatal myocardial infarction, with no significant difference in the rate of cardiovascular death.
  • NNT to prevent one event of the primary outcome over a period of 24 months was 45 on the basis of Kaplan-Meier estimates.
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Type 2 Diabetes Therapies: A STEPS Approach

Type 2 Diabetes Therapies: A STEPS Approach

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Type 2 Diabetes Therapies: A STEPS Approach

• S: Safety
• T: Tolerability
• E: Effectiveness
• P: Price
• S: Simplicity
# Metformin

## Type 2 Diabetes Therapies: A STEPS Approach

<table>
<thead>
<tr>
<th>Drug class</th>
<th>STEPS component</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides (e.g., Glucophage)</td>
<td>Historical concern for lactic acidosis, but Cochrane review of 347 studies found no cases in 70,490 patient-years, with lactate levels similar between patients receiving metformin (Glucophage) and a control group. Should not be used in patients with estimated GFR &lt; 30 mL per minute per 1.73 m²; use caution in patients with estimated GFR of 30 to 45 mL per minute per 1.73 m²; Long-term use may be associated with vitamin B₁₂ deficiency; Safe in patients with stable CHF</td>
<td>GI effects (e.g., diarrhea, nausea, vomiting) in &lt; 10% of patients; discontinuation rate is &lt; 1%</td>
</tr>
</tbody>
</table>

## Effectiveness*

Outcomes: benefit
In 1,704 overweight patients newly diagnosed with diabetes mellitus, metformin improved rates of all-cause mortality (13.5 vs. 20.6 per 1,000 patient-years; NNT = 14), MI (11 vs. 18 per 1,000 patient-years; NNT = 14), microvascular complications (6.7 vs. 9.2 per 1,000 patient-years; NNT = 40), and any diabetes-related end point (29.8 vs. 43.3 per 1,000 patient-years; NNT = 7)

## Price†

<table>
<thead>
<tr>
<th>1,000 mg twice daily:</th>
<th>Extended-release, four 500-mg tablets once daily:</th>
</tr>
</thead>
<tbody>
<tr>
<td>$5 ($130)</td>
<td>$10 ($130)</td>
</tr>
<tr>
<td>Extended-release, two 1,000-mg tablets once daily:</td>
<td>Twice-daily oral dosing (once daily for extended-release formulation)</td>
</tr>
<tr>
<td>$730 ($6,650)</td>
<td></td>
</tr>
</tbody>
</table>

## Simplicity

Twice-daily oral dosing (once daily for extended-release formulation)

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Effectiveness

GLP-1 Receptor Agonists

Liraglutide (Victoza): in 9,340 patients with diabetes and high CV risk treated for 3.8 years, improved all-cause mortality (8.2% vs. 9.6%, NNT = 71), CV mortality (4.7% vs. 6.0%, NNT = 77), and CV events (13.0% vs. 14.9%, NNT = 53).\(^2\)

SGLT-2 Inhibitors

Empagliflozin (Jardiance): benefit

- Empagliflozin: in 7,020 patients with diabetes and high CV risk treated for 3 years, improved all-cause mortality (5.7% vs. 8.3%, NNT = 39), CV mortality (3.7% vs. 5.9%, NNT = 45), CHF hospitalizations (2.7% vs. 4.1%, NNT = 71), doubling of serum creatinine level (1.5% vs. 2.6%, NNT = 91), and need for dialysis (0.3% vs. 0.6%, NNT = 33).\(^{16,17}\)

- Canagliflozin: mixed

- Other agents: unknown

Lixisenatide (Adlyxin): in 6,068 patients with diabetes and CHD treated for 2.1 years, no benefit or harm.\(^{27}\)

All agents in this class independently produce direct weight loss.
STEPS APPROACH: An Example

<table>
<thead>
<tr>
<th>Drug class</th>
<th>STEPS component</th>
<th>Safety</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP-4 inhibitors (e.g., Januvia, Onglyza)</td>
<td></td>
<td>Pancreatitis (insufficient data to indicate causal relationship), hypoglycemia, slightly higher rates of CHF&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Rare severe arthralgias</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Effectiveness&lt;sup&gt;9&lt;/sup&gt;</th>
<th>Price†</th>
<th>Simplicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes: neutral</td>
<td>Alogliptin: NA ($90)</td>
<td>Once-daily oral dosing</td>
</tr>
<tr>
<td>Sitagliptin (Januvia): in 14,671 patients with diabetes treated for 3 years, no CV or mortality benefit or harm&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Saxagliptin: NA ($410)</td>
<td></td>
</tr>
<tr>
<td>Saxagliptin (Onglyza) and alogliptin (Nesina): short randomized controlled trials showed no CV benefit or harm&lt;sup&gt;10,31&lt;/sup&gt;</td>
<td>Sitagliptin: NA ($450)</td>
<td></td>
</tr>
</tbody>
</table>
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Type 2 Diabetes Therapies: A STEPS Approach

• SAFETY
  • Hypoglycemia
  • CKD

• SIMPLICITY
  • Frequent, complicated dosing
  • Poor memory, eyesight
  • Health literacy
## GLP-1 Receptor Agonists

<table>
<thead>
<tr>
<th>Drug class</th>
<th>STEPS component</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 receptor agonists (e.g., Victoza, Ozempic)</td>
<td>Gallstones&lt;sup&gt;22&lt;/sup&gt; Occurrence &lt; 1%: acute kidney injury, angioedema, pancreatitis (insufficient data to indicate causal relationship; 16 cases among 14,562 patients in randomized controlled trials)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Headache, diarrhea, nausea, weight loss&lt;sup&gt;24&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

### Effectiveness<sup>*</sup>

- Outcomes: benefit (some agents)
  - Liraglutide (Victoza): in 9,340 patients with diabetes and high CV risk treated for 3.8 years, improved all-cause mortality (8.2% vs. 9.6%; NNT = 71), CV mortality (4.7% vs. 6.0%; NNT = 77), and CV events (13.0% vs. 14.9%; NNT = 53)<sup>22</sup>
  - Semaglutide (Ozempic): in 3,297 patients with diabetes treated for 2.1 years, improved CV events (6.6% vs. 8.9%; NNT = 43), worsened retinal complications (RR = 1.76), and no difference in all-cause or CV mortality<sup>25</sup>
  - Exenatide weekly (Bydureon): in 14,752 patients with diabetes and high CV risk treated for 3.2 years, improved all-cause mortality (6.9% vs. 7.9%; NNT = 100); other individual and combined CV outcomes narrowly missed statistical significance for improvement<sup>26</sup>
  - Lixisenatide (Adlyxin): in 6,068 patients with diabetes and CHD treated for 2.1 years, no benefit or harm<sup>27</sup>
- All agents in this class independently produce direct weight loss

### Price<sup>†</sup>

- Liraglutide: NA ($920)
- Exenatide weekly: NA ($700)
- Exenatide twice daily (Byetta): NA ($750)
- Lixisenatide: NA ($620)

### Simplicity

- Subcutaneous injection twice daily, once daily, or once weekly

<sup>*estimated retail price based on GoodRx discount</sup>
American Academy of Family Physicians
Type 2 Diabetes Therapies: A STEPS Approach

Oral Pharmacologic Treatment of Type 2 Diabetes Mellitus: A Clinical Practice Guideline Update From the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Michael J. Barry, MD; Linda L. Humphrey, MD, MPH; and Mary Ann Forciea, MD; for the Clinical Guidelines Committee of the American College of Physicians*

ACP recommends moderate blood sugar control targets for most patients with type 2 diabetes

Philadelphia, March 6, 2018 – Patients with type 2 diabetes should be treated to achieve an A1C between 7 percent and 8 percent rather than 6.5 percent to 7 percent, the American College of Physicians (ACP) recommends in an evidence-based guidance statement published today in Annals of Internal Medicine.
References


