Individualizing the Glycemic Goals

Michelle Mangual Garcia, MD
Diplomate of the American Board of Internal Medicine; Endocrinology, Diabetes and Metabolism and the American Board of Clinical Lipidology
Disclosures

• Dr. Michelle Mangual, endocrinologist, declares that she serves as a speaker and/or consultant for the following pharmaceutical companies: *Eli Lilly and Astra Zeneca.*
Objectives

• Discuss the evidence from the intensive glycemic control trials and observational studies.
• The history of the target of less than 7%.
• Glycemic goals in patients with multiple comorbidities.
• Drug selection in patients with ASCVD or heart failure.
• Glycemic goals in older patients with diabetes.
The evidence from trials and observational study

• Diabetes Control and Complications Trial
  (DCCT; 1441 participants with type 1 diabetes duration <15 years)
• The goal was to achieve glycemic control as close to normal without causing adverse events versus asymptomatic glycemic control.
• Contrast achieved: A1c ~7% versus ~9% over ~6.5 years.
A1c during DCCT and EDIC

After the trial, 96% enrolled in follow-up. A1c converged at 8%.

EDIC = Epidemiology of Diabetes Interventions and Complications

Reduction in major complications with intensive compared with Conventional during DCCT and EDIC

- At 6 years, 3 step progression of retinopathy was reduced 76%, new or progression of albuminuria was reduced 50%, neuropathy reduced 60%.
- Long term benefits over ~30 years of follow-up included 56% reduction in retinopathy, 50% reduction in nephropathy, 30% reduction in neuropathy.
DCCT/EDIC: Cumulative incidence of the first occurrence of non-fatal MI, stroke, or CV death.

Risk Reduction 57%
97% CI: 12-79
P=0.02

The evidence from trials and observational study

United Kingdom Prospective Diabetes Study
(UKPDS: 4,209 participants with new onset type 2 diabetes and FBG>108 mg/dl after 3-month dietary run in)

• Standard policy (treat for symptoms or glucose >270 mg/dl) vs intensive policy (treat with SU, insulin or metformin)
• Mean A1c contrast achieved ~7% vs ~7.9% over ~10 years.
• Clinically meaningful endpoints improved at end of randomized period.
• Additional ten years of off-trial follow-up, “Legacy Effect”
After median 8.8 years post-trial follow-up

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>RRR: 12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td><em>P:</em> 0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>RRR: 25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td><em>P:</em> 0.009</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>RRR: 16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td><em>P:</em> 0.052</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>RRR: 6%</td>
<td>13%</td>
</tr>
<tr>
<td></td>
<td><em>P:</em> 0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

## Study, Patient and HbA1c Characteristics of 5 RCTs

### Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Trial Name, Mean or median FU, number enrolled</th>
<th>Age ; Baseline</th>
<th>Diabetes Duration</th>
<th>HbA1c; Baseline (median)</th>
<th>HbA1c Achieved Intensive vs Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD 4-5 years; N=10,251</td>
<td>62 years</td>
<td>10 years</td>
<td>8.1%</td>
<td>6.4% vs 7.5%</td>
</tr>
<tr>
<td>ADVANCE 5-11 years; N=11,140</td>
<td>66 years</td>
<td>8 years</td>
<td>7.8%</td>
<td>6.4% vs 7.0%</td>
</tr>
<tr>
<td>UKPDS 33 (Insulin/SU) 11-17 years; N=3,867</td>
<td>54 years</td>
<td>Newly Dx</td>
<td>7.0%</td>
<td>7.0% vs 7.9%</td>
</tr>
<tr>
<td>UKPDS 34 (metformin) 11-18 years; N=753</td>
<td>53 years</td>
<td>Newly Dx</td>
<td>7.2%</td>
<td>7.4% vs 8.4%</td>
</tr>
<tr>
<td>VADT 6-12 years; N=1,791</td>
<td>60 years</td>
<td>12 years</td>
<td>9.4%</td>
<td>6.9% vs 8.4%</td>
</tr>
</tbody>
</table>
# Impact of Intensive Therapy for Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvascular</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>![down arrow]</td>
<td>![double-headed arrow]</td>
<td>![down arrow]</td>
</tr>
<tr>
<td>DCCT/EDIC&lt;sup&gt;*3,4&lt;/sup&gt;</td>
<td>![down arrow]</td>
<td>![double-headed arrow]</td>
<td>![down arrow]</td>
</tr>
<tr>
<td>ACCORD&lt;sup&gt;5&lt;/sup&gt;</td>
<td>![down arrow]</td>
<td>![double-headed arrow]</td>
<td>![up arrow]</td>
</tr>
<tr>
<td>ADVANCE&lt;sup&gt;6&lt;/sup&gt;</td>
<td>![down arrow]</td>
<td>![double-headed arrow]</td>
<td>![double-headed arrow]</td>
</tr>
<tr>
<td>VADT&lt;sup&gt;7&lt;/sup&gt;</td>
<td>![down arrow]</td>
<td>![double-headed arrow]</td>
<td>![double-headed arrow]</td>
</tr>
</tbody>
</table>

* in T1DM  
Microvasc = microvascular; CVD = cardiovascular disease

Initial trial - dark grey
Long-term follow-up - light grey
ACCORD: Risk of Death over a Range of Mean A1c

Steady increase of risk from 6 to 9% A1c with intensive strategy

Excess risk of mortality with intensive strategy occurred above an A1c 7%

Riddle et al. Diabetes Care 33:983–990, 2010
Epidemiological analysis: Relative importance of risk factors for acute myocardial infarction and stroke

Epidemiological Analysis: Early glycemic control matters

Epidemiological Analysis: Early glycemic control matters

• “Among patients with newly diagnosed diabetes and 10 years of survival, HbA1c levels ≥6.5% for the 1st year after diagnosis were associated with worse outcomes. Immediate, intensive treatment for newly diagnosed patients may be necessary to avoid irremediable long-term risk for diabetic complications and mortality.”

Standards of Medical Care in Diabetes
First publication of the A1c goal <7% was in 1994

<table>
<thead>
<tr>
<th>Biochemical index</th>
<th>Nondiabetic</th>
<th>Goal</th>
<th>Action suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial glucose</td>
<td>&lt;115</td>
<td>80–120</td>
<td>&lt;80</td>
</tr>
<tr>
<td>Bedtime glucose (mg/dl)</td>
<td>&lt;120</td>
<td>100–140</td>
<td>&gt;140</td>
</tr>
<tr>
<td>Hemoglobin A₁c (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;160</td>
</tr>
</tbody>
</table>

These values are for nonpregnant individuals. "Action suggested" depends on individual patient circumstances. Hemoglobin A₁c is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, standard deviation 0.5%).
Standards of Medical Care in Diabetes
In 1997, modified to indicate “action suggested >8%”

Table 1—Glycemic control for people with diabetes

<table>
<thead>
<tr>
<th>Biochemical index</th>
<th>Nondiabetic</th>
<th>Goal</th>
<th>Action suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preprandial glucose (mg/dl)</td>
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<td>80–120</td>
<td>&lt;80</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;140</td>
</tr>
<tr>
<td>Bedtime glucose (mg/dl)</td>
<td>&lt;120</td>
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<td></td>
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</tr>
<tr>
<td>Hemoglobin A₁c (%)</td>
<td>&lt;6</td>
<td>&lt;7</td>
<td>&gt;8</td>
</tr>
</tbody>
</table>

These values are for nonpregnant individuals. “Action suggested” depends on individual patient circumstances. Such actions may include enhanced diabetes self-management education, comanagement with a diabetes team, referral to an endocrinologist, change in pharmacological therapy, initiation or increased SMBG, or more frequent contact with the patient. HbA₁c is referenced to a nondiabetic range of 4.0–6.0% (mean 5.0%, SD 0.5%).
Standards of Medical Care in Diabetes
Since 2003, the A1c goal has been <7%

Table 6—Summary of recommendations for adults with diabetes mellitus

<table>
<thead>
<tr>
<th>Glycemic control</th>
</tr>
</thead>
</table>
| A1C                                   | <7.0%*  
| Preprandial plasma glucose            | 90–130 mg/dl (5.0–7.2 mmol/l)  
| Peak postprandial plasma glucose      | <180 mg/dl (<10.0 mmol/l)  
| Blood pressure                        | <130/80 mmHg  
| Lipids                                |  
| LDL                                   | <100 mg/dl (<2.6 mmol/l)  
| Triglycerides†                        | <150 mg/dl (<1.7 mmol/l)  
| HDL                                   | >40 mg/dl (>1.1 mmol/l)†  

Key concepts in setting glycemic goals:
- Goals should be individualized
- Certain populations (children, pregnant women, and elderly) require special considerations
- Less intensive glycemic goals may be indicated in patients with severe or frequent hypoglycemia
- More intensive glycemic goals may further reduce microvascular complications at the cost of increasing hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

*Referenced to a nondiabetic range of 4.0–6.0% using a DCCT-based assay. †Current NCEP/ATP III guidelines suggest that in patients with triglycerides ≥200 mg/dl, the “non-HDL cholesterol” (total cholesterol minus HDL) be utilized. The goal is ≤130 mg/dl (53). ‡For women, it has been suggested that the HDL goal be increased by 10 mg/dl.
Guidance Statement 1: Clinicians should personalize goals for glycemic control in patients with type 2 diabetes on the basis of a discussion of benefits and harms of pharmacotherapy, patients' preferences, patients' general health and life expectancy, treatment burden, and costs of care.
Guidance Statement 2: Clinicians should aim to achieve an HbA$_{1c}$ level between 7% and 8% in most patients with type 2 diabetes.

Guidance Statement 3: Clinicians should consider deintensifying pharmacologic therapy in patients with type 2 diabetes who achieve HbA$_{1c}$ levels less than 6.5%.
Who are “the many” in “a reasonable A1c goal for many nonpregnant adults is <7%”? 

- Those who already have an A1c <7% without adverse events
- Life expectancy >10 years
- People with CVD or CKD (GLP1 RA or SGLT2 inhibitors)
- Women of childbearing potential
A changing paradigm in caring for patients with type 2 diabetes and clinical CVD

<table>
<thead>
<tr>
<th>Medication</th>
<th>NNT to prevent a Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (for 5 years)</td>
<td>100</td>
</tr>
<tr>
<td>Anti-hypertensives (for 5 years)</td>
<td>125</td>
</tr>
<tr>
<td>Empagliflozin (for 3 years)</td>
<td>39</td>
</tr>
<tr>
<td>Liraglutide (for 3 years)</td>
<td>98</td>
</tr>
</tbody>
</table>

These benefits of GLP-1 receptor agonists and SGLT2 inhibitors emerged in trials were the drugs were added (versus placebo) in patients with CVD and an A1c >7%.

Drug Selection in people with ASCVD or heart failure  The new era of antidiabetic medications
The major goal of diabetes management is to prevent its complications.
# FDA-Mandated CV Outcomes Trials in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EXAMINE&lt;sup&gt;2&lt;/sup&gt;</th>
<th>TECOS&lt;sup&gt;3&lt;/sup&gt;</th>
<th>CARMELINA&lt;sup&gt;4&lt;/sup&gt;</th>
<th>CAROLINA&lt;sup&gt;5&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>glimepiride (SU)</td>
</tr>
<tr>
<td>N</td>
<td>16,492</td>
<td>5380</td>
<td>14,671</td>
<td>6979</td>
<td>6103</td>
</tr>
<tr>
<td>Results</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2018</td>
<td>2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA&lt;sup&gt;6&lt;/sup&gt;</th>
<th>LEADER&lt;sup&gt;7&lt;/sup&gt;</th>
<th>SUSTAIN 6&lt;sup&gt;8&lt;/sup&gt;</th>
<th>EXSCEL&lt;sup&gt;9&lt;/sup&gt;</th>
<th>REWIND&lt;sup&gt;10&lt;/sup&gt;</th>
<th>HARMONY&lt;sup&gt;11&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>lixisenatide</td>
<td>liraglutide</td>
<td>semaglutide</td>
<td>exenatide LR</td>
<td>dulaglutide</td>
<td>albiglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>6068</td>
<td>9340</td>
<td>3297</td>
<td>14,752</td>
<td>9901</td>
<td>9463</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG&lt;sup&gt;12&lt;/sup&gt;</th>
<th>CANVAS&lt;sup&gt;13&lt;/sup&gt;</th>
<th>(CREDENCE&lt;sup&gt;14&lt;/sup&gt;)</th>
<th>DECLARE&lt;sup&gt;15&lt;/sup&gt;</th>
<th>VERTIS CV&lt;sup&gt;16&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>7020</td>
<td>4330</td>
<td>4401</td>
<td>17,160</td>
<td>8246</td>
</tr>
<tr>
<td>Results</td>
<td>2015</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
<td>2020</td>
</tr>
</tbody>
</table>

Cardiovascular Outcome Trials for DPP4 Inhibitors

- **CVD or CRFs**
  - A1c 6.5–12.0%
  - n=16,492

- **Saxagliptin**
  - Median follow-up 2.1 years
  - CV death, non-fatal MI, or non-fatal stroke

- **Placebo**

- **Hazard Ratio**
  - 1.00
  - (95% CI 0.89, 1.12)

- **ACS**
  - A1c 6.5–11.0%
  - n=5,380

- **Alogliptin**
  - Median follow-up 1.5 years

- **Placebo**

- **CV death, non-fatal MI, or non-fatal stroke**

- **Hazard Ratio**
  - 0.96
  - (upper boundary of 1-sided repeated CI 1.15)

- **CVD**
  - A1c 6.5–8.0%
  - n=14,735

- **Sitagliptin**
  - Median follow-up 3 years
  - CV death, non-fatal MI, or non-fatal stroke, or UA requiring hospitalization

- **Placebo**

- **CV death, non-fatal MI, or non-fatal stroke**

- **Hazard Ratio**
  - 0.98
  - (95% CI 0.88, 1.09)
  - P=0.645

- **CVD or CRFs**
  - A1c 6.5–10.0%
  - n=6,979

- **Linagliptin**
  - Median follow-up 2.2 years

- **Placebo**

- **CV death, non-fatal MI, or non-fatal stroke**

- **Hazard Ratio**
  - 1.02
  - (95% CI 0.89, 1.17)

**Median Duration of Follow-up**
- Randomization
- Year 1
- Year 2
- Year 3

---

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug n/N (%)</th>
<th>Placebo n/N (%)</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI</td>
<td>289/8280 (3.5%)</td>
<td>228/8212 (2.8%)</td>
<td>1.27</td>
<td>1.07, 1.51</td>
<td>.009*</td>
</tr>
<tr>
<td>(saxagliptin vs placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EXAMINE</td>
<td>106/2701 (3.9%)</td>
<td>89/2679 (3.3%)</td>
<td>1.19</td>
<td>0.89, 1.58</td>
<td>.238</td>
</tr>
<tr>
<td>(alogliptin vs placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TECOS</td>
<td>228/7332 (3.1%)</td>
<td>229/7339 (3.1%)</td>
<td>1.00</td>
<td>0.83, 1.20</td>
<td>.983</td>
</tr>
<tr>
<td>(sitagliptin vs placebo)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.

Summary: DPP4-Inhibitors Cardiovascular Outcome Trials

- All trials met the primary endpoint of demonstrating that there is no increased risk of CVD
- No benefit is apparent
- Cannot assume that this is a class effect
- There may be heterogeneity with respect to heart failure

- These large trials have been useful for evaluating other potentially beneficial effects of the drugs.
  - Decreased rates of albuminuria

- More precise estimates of the risk of other rare events
Cardiovascular benefits of GLP-1 analogs

**Liraglutide (LEADER study)**
- Cardiovascular Events: HR: 0.87 (0.78-0.97), P<0.001 for noninferiority, P=0.01 for superiority
- Death from any cause: 0.85 (0.74-0.97), p=0.02

**Semaglutide (SUSTAIN-6)**
- CV death, nonfatal MI/ stroke: HR: 0.74 (0.58-0.95), P<0.001 for noninferiority, P=0.02 for superiority

**Exenatide (weekly) (EXSCEL Study)**
- CV death, nonfatal MI/ stroke: HR: 0.91 (0.83-1.00), P<0.001 for noninferiority, P=0.06 for superiority
- Death from any cause: 0.86 (0.77-0.97)

**Dulaglutide (REWIND study)**
- 3-Point MACE: HR: 0.88 (0.79-0.99), P = 0.026
- Death from Any Cause: 0.90 (0.80-1.01), p =0.067
Cardiovascular Benefits of GLP-1 RA

<table>
<thead>
<tr>
<th>GLP1 receptor agonists</th>
<th>LEADER</th>
<th>EXSCEL</th>
<th>SUSTAIN-6</th>
<th>ELIXA</th>
<th>Harmony</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide (MR)</td>
<td>9340</td>
<td>14,752</td>
<td>3297</td>
<td>6068</td>
<td>9463</td>
<td>9901</td>
</tr>
<tr>
<td>Exenatide (s.c.)</td>
<td>72.5</td>
<td>73.1</td>
<td>83.0</td>
<td>100</td>
<td>100</td>
<td>31.5</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>3.8</td>
<td>3.2</td>
<td>2.1</td>
<td>2.1</td>
<td>1.6</td>
<td>5.4</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>1305</td>
<td>2389</td>
<td>777</td>
<td>1922</td>
<td>NA</td>
<td>853</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>23.1</td>
<td>21.6</td>
<td>24.0</td>
<td>23.2</td>
<td>23.0</td>
<td>22.2</td>
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<tr>
<td>Dulaglutide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Sample size
ASCVD%
Median fu (yr)
Hx of HF
eGFR <60 (%)

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>LEADER</th>
<th>EXSCEL</th>
<th>SUSTAIN-6</th>
<th>ELIXA</th>
<th>Harmony</th>
<th>REWIND</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.87 (0.78, 0.97)</td>
<td>0.91 (0.83, 1.00)</td>
<td>0.74 (0.58, 0.95)</td>
<td>1.02 (0.89, 1.17)</td>
<td>0.78 (0.68, 0.90)</td>
<td>0.88 (0.79, 0.99)</td>
</tr>
<tr>
<td>CV Death</td>
<td>0.78 (0.66, 0.93)</td>
<td>0.88 (0.76, 1.02)</td>
<td>0.98 (0.65, 1.48)</td>
<td>0.98 (0.78, 1.22)</td>
<td>0.93 (0.73, 1.19)</td>
<td>0.91 (0.78, 1.06)</td>
</tr>
<tr>
<td>MI</td>
<td>0.88 (0.75, 1.03)</td>
<td>0.97 (0.85, 1.10)</td>
<td>0.74 (0.51, 1.08)</td>
<td>1.03 (0.87, 1.22)</td>
<td>0.75 (0.61, 0.90)</td>
<td>0.96 (0.79, 1.16)</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.89 (0.72, 1.11)</td>
<td>0.85 (0.70, 1.03)</td>
<td>0.61 (0.38, 0.99)</td>
<td>1.12 (0.79, 1.58)</td>
<td>0.86 (0.66, 1.14)</td>
<td>0.76 (0.62, 0.94)</td>
</tr>
<tr>
<td>hHF</td>
<td>0.87 (0.73, 1.05)</td>
<td>0.94 (0.78, 1.13)</td>
<td>1.11 (0.77, 1.61)</td>
<td>0.96 (0.75, 1.23)</td>
<td>0.85 (0.70, 1.04)</td>
<td>0.93 (0.77, 1.12)</td>
</tr>
<tr>
<td>All Death</td>
<td>0.85 (0.74, 0.97)</td>
<td>0.86 (0.77, 0.97)</td>
<td>1.05 (0.74, 1.50)</td>
<td>0.94 (0.78, 1.13)</td>
<td>0.95 (0.79, 1.16)</td>
<td>0.90 (0.80, 1.01)</td>
</tr>
</tbody>
</table>

Kidney Endpoint
Meta-analysis of 5 CVOTs (3 with GLP-1 RAs and 2 with SGLT-2i) in patients with history of CVD at baseline.
Meta-analysis of the 5 CVOTs in patients without history of CVD at baseline.
Proposed mechanisms of CV benefits of GLP-1 receptor agonists

FDA has granted Liraglutide, Semaglutide, and Dulaglutide Additional CV Indications

In adults with T2DM + established CVD...

- Liraglutide $\rightarrow \downarrow$ MACE
- Semaglutide $\rightarrow \downarrow$ MACE

In adults with T2DM + established CVD or high CV risk

- Dulaglutide $\rightarrow \downarrow$ MACE
CVOTs with SGLT2 inhibitors

TRIAL DESIGNS

EMPARY-REG OUTCOME

- Empagliflozin 25 mg OD
- Empagliflozin 10 mg OD
- Placebo OD

Established CVD n=7,028

CANVAS Program

- Canagliflozin OD
- Placebo OD

Established CVD or risk factors n=10,142

DECLARE-TIMI

- Dapagliflozin OD
- Placebo OD

Established CVD or risk factors n=17,160

SGLT2 Inhibitors Reduce CV Risk

Hospitalization for Heart Failure: Effects of SGLT2 Inhibitors

- EMPA-REG OUTCOME
  Empagliflozin
  - 35%
  - 9.4 vs 14.5 events/1000 p-y
  - HR 0.65 (0.50-0.85)

- CANVAS/CANVAS-R
  Canagliflozin
  - 33%
  - 5.5 vs 8.7 events/1000 p-y
  - HR 0.67 (0.52-0.87)

- DECLARE-TIMI 58
  Dapagliflozin
  - 27%
  - 6.2 vs 8.5 events/1000 p-y
  - HR 0.73 (0.61-0.88)

# Heart Failure Hospitalization By Prior Heart Failure

<table>
<thead>
<tr>
<th>Study</th>
<th>Events per 1000 Patient-Years</th>
<th>Hazard Ratio (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of HF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG Outcomes</td>
<td>40.7</td>
<td>0.75 (0.48, 1.19)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>14.1</td>
<td>0.51 (0.33, 0.78)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>27.7</td>
<td>0.73 (0.55, 0.96)</td>
</tr>
<tr>
<td>Fixed effects model for history of HF (p=0.0002)</td>
<td>0.68 (0.55, 0.83)</td>
<td></td>
</tr>
<tr>
<td><strong>No history of HF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG Outcomes</td>
<td>6.4</td>
<td>0.59 (0.43, 0.82)</td>
</tr>
<tr>
<td>CANVAS Program</td>
<td>4.3</td>
<td>0.79 (0.57, 1.09)</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>4.0</td>
<td>0.78 (0.58, 0.92)</td>
</tr>
<tr>
<td>Fixed effects model for MRF (p&lt;0.0001)</td>
<td>0.71 (0.60, 0.83)</td>
<td></td>
</tr>
</tbody>
</table>

**Heterogeneity**: $Q=1.73$, $p=0.42$, $I^2=0.0\%$
DAPA-HF Design

- Informed consent
- Inclusion/exclusion
- Clinical assessment
- ECG
- NT-proBNP
- Laboratory assessments

Enrolment

Randomization

N=2371
Placebo
≥844 Primary endpoints
Composite of:
- CV death
- HF hospitalization
- Urgent HF visit

N=2373
Dapagliflozin
10 mg once daily

Visit 1
Visit 2
Visit 3
Visit 4
Visit 5
Visit 6 etc.

Day −14
Day 0
Day 14
Day 60
Day 120
Every 120 days

McMurray et al. ESC 2019
DAPA-HF: Primary Outcome

CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65, 0.85)

p = 0.00001

NNT = 21

Placebo

Dapagliflozin

Months since Randomization

Cumulative Percentage (%)

Number at Risk

Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210

Placebo 2371 2258 2163 2075 1917 1478 1096 593 210
### DAPA-HF: Results in T2DM and Non-DM Patients

**Primary endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
</tbody>
</table>

[Graph showing HR with confidence intervals]
CREDENCE Trial: Renal outcomes in type 2 diabetes and nephropathy.

Primary Outcome:
ESKD, Doubling of Serum Creatinine, or Renal or CV Death

Hazard ratio, 0.70 (95% CI, 0.59–0.82)
P = 0.00001

340 participants
245 participants

Placebo
Canagliflozin

Proposed mechanisms of CV benefits of SGLT-2 inhibitors
FDA Granted Select SGLT2i’s Additional CV Indications

In adults with T2DM + established CVD...

• Empagliflozin ↓ risk of CV death
• Canagliflozin ↓ risk of MACE
• Canagliflozin ↓ risk of ESKD
• Dapagliflozin ↓ risk of HHF
## FDA-Mandated CV Outcomes Trials in T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>SAVOR¹</th>
<th>EXAMINE²</th>
<th>TECOS³</th>
<th>CARMELINA⁴</th>
<th>CAROLINA⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP4-i</td>
<td>saxagliptin</td>
<td>alogliptin</td>
<td>sitagliptin</td>
<td>linagliptin</td>
<td>linagliptin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>glimepiride</td>
</tr>
<tr>
<td>N</td>
<td>2013</td>
<td>2013</td>
<td>2015</td>
<td>2018</td>
<td>2018</td>
</tr>
<tr>
<td>Results</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ELIXA⁶</th>
<th>LEADER⁷</th>
<th>SUSTAIN 6⁸</th>
<th>EXSCEL⁹</th>
<th>REWIND¹⁰</th>
<th>HARMONY¹¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP1-RA</td>
<td>lixisenatide</td>
<td>liraglutide</td>
<td>semaglutide</td>
<td>exenatide</td>
<td>dulaglutide</td>
<td>albiglutide</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>2015</td>
<td>2015</td>
<td>2016</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
</tr>
<tr>
<td>Results</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>EMPA-REG¹²</th>
<th>CANVAS¹³</th>
<th>(CREDENCE¹⁴)</th>
<th>DECLARE¹⁵</th>
<th>VERTIS CV¹⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2-i</td>
<td>empagliflozin</td>
<td>canagliflozin</td>
<td>canagliflozin</td>
<td>dapagliflozin</td>
<td>ertugliflozin</td>
</tr>
<tr>
<td>Comparator</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
<td>placebo</td>
</tr>
<tr>
<td>N</td>
<td>2015</td>
<td>2017</td>
<td>2018</td>
<td>2018</td>
<td>8246</td>
</tr>
<tr>
<td>Results</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
<td>NEUTRAL</td>
</tr>
</tbody>
</table>

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Glycemic Control, Preexisting Cardiovascular Disease, and Risk of Major Cardiovascular Events in Patients with Type 2 Diabetes Mellitus: Systematic Review With Meta-Analysis of Cardiovascular Outcome Trials and Intensive Glucose Control Trials

Dario Giugliano, MD; Maria Ida Maiorino, MD, PhD; Giuseppe Bellastella, MD; Paolo Chiodini, MSc; Katherine Esposito, MD, PhD
IGCTs, CVOTs, and Risk of MACE in Patients With T2DM

<table>
<thead>
<tr>
<th>Trials</th>
<th>ΔA1C (%)</th>
<th>Hazard Ratio for MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGCTs</td>
<td>−0.90 (−1.30 to −0.50)</td>
<td>0.91 (0.84 to 0.99)</td>
</tr>
<tr>
<td>N=27 049</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVOTs</td>
<td>−0.42 (−0.53 to −0.30)</td>
<td>0.92 (0.87 to 0.96)</td>
</tr>
<tr>
<td>N=120 765</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVOTs</td>
<td>−0.90</td>
<td>0.67 (0.49 to 0.93)</td>
</tr>
<tr>
<td>meta-regression</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CVOTs indicates cardiovascular outcome trials; ΔA1C, change in glycated hemoglobin; IGCTs, intensive glucose control trials; MACE, major cardiovascular events; T2DM, type 2 diabetes mellitus.
Reduction in MACE associated with reduction in A1c in CVOTs

Figure 1. Meta-regression analysis between reduction of HbA1c and MACE risk in the 12 CVOTs. CVOT indicates cardiovascular outcome trial; HbA1c, glycated hemoglobin; HR, hazard ratio; MACE, major cardiovascular events.

Giugliano, D., et al. JAHA. Volume 8, Issue 12, 18 June 2019
Treatment of Diabetes in Older Adults

An Endocrine Society Clinical Practice Guideline
• Prediabetes is highly prevalent in older people, however interventions to delay progression from prediabetes to diabetes are especially effective in this age group.

• The prevalence of type 2 diabetes increases as individuals age and exaggerates the incidence of both microvascular and macrovascular complications.

• Clinicians should perform regular screening for prediabetes and diabetes in the older population and implement interventions as indicated in this guideline.

• Given the heterogeneity of the health status of older people with diabetes the guideline emphasizes shared decision-making and provides a framework to assist healthcare providers to individualize treatment goals.
Diabetes in the older population

- Older individuals with diabetes
- Increased risk
  - Loss of independence in ADL
  - Falls
  - Hypoglycemia
  - Poor medication adherence

- Cognitive dysfunction
- Frailty
- Sarcopenia
Key Recommendation for Overall Health Assessment

• In patients aged 65 and older with diabetes, we advise assessing the patient’s overall health and personal values prior to the determination of treatment goals and strategies. (Ungraded Good Practice Statement)

### Step 1: Assessing overall health

<table>
<thead>
<tr>
<th>Overall Health Category</th>
<th>Group 1: Good Health</th>
<th>Group 2: Intermediate Health</th>
<th>Group 3: Poor Health</th>
</tr>
</thead>
</table>
|                         | No comorbidities or 1-2 non-diabetes chronic illnesses* and No ADL$^c$ impairments and $\leq$1 IADL impairment | 3 or more non-diabetes chronic illnesses* and/or Any one of the following: mild cognitive impairment or early dementia | Any one of the following:  
End-stage medical condition(s)**  
Moderate to severe dementia  
$\geq$2 ADL impairments  
Residence in a long-term nursing facility |

*Reasonable glucose target ranges and HbA1c by group*

*Does not include diabetes ** e.g. metastatic cancer, oxygen requiring COPD, ESKD on HD, advanced HF. ADL: Activities of daily living (e.g. eating, bathing, dressing) IADL: Instrumental activities of daily living (e.g. managing money, doing housework)*

Step 2: Identify HbA1c and glucose targets

<table>
<thead>
<tr>
<th>Overall Health Category</th>
<th>Group 1: Good Health</th>
<th>Group 2: Intermediate Health</th>
<th>Group 3: Poor Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of drugs that may cause hypoglycemia (e.g., insulin, sulfonylurea, glinides)</td>
<td>No</td>
<td>Fasting: 90-130 mg/dL Bedtime: 90-150 mg/dL &lt;7.5%</td>
<td>Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL &lt;8%</td>
</tr>
<tr>
<td></td>
<td>Yes&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Fasting: 90-150 mg/dL Bedtime: 100-180 mg/dL ≥7.0 and &lt;7.5%</td>
<td>Fasting: 100-150 mg/dL Bedtime: 150-180 mg/dL ≥7.5 and &lt;8.0%</td>
</tr>
</tbody>
</table>

Approach to Individualization of Glycemic Targets

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent (A1C 7%)</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
</tr>
<tr>
<td>Important comorbidities</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mild</td>
</tr>
<tr>
<td>Patient preference</td>
<td>highly motivated, excellent self-care capabilities</td>
<td>preference for less burdensome therapy</td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
</tr>
</tbody>
</table>
ADA/EASD Treatment Algorithm for T2D
ADA/EASD Treatment Algorithm for T2D

Established ASCVD or CKD

ASCVD Predominates

Either/Or

GLP-1 RA with proven CVD benefit

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA with proven CVD benefit

If HbA1c above target

Further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- Consider adding the other class (GLP-1 RA or SGLT2i) with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
- SU

If HbA1c above target

Avoid TZD in the setting of HF
Choose agents demonstrating CV safety:
- Consider adding the other class with proven CVD benefit
- DPP-4i (not saxagliptin) in the setting of HF (if not on GLP-1 RA)
- Basal insulin
- SU

HF or CKD Predominates

Preferably

SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate

OR

If SGLT2i not tolerated or contraindicated or if eGFR less than adequate add GLP-1 RA

If HbA1c above target

Without Established ASCVD or CKD

Compelling need to minimise weight gain or promote weight loss

Cost is a major issue

To avoid clinical inertia, readiness and proxy decision-making (5-6 months)
CONSIDER INDEPENDENTLY OF BASELINE A1C OR INDIVIDUALIZED A1C TARGET

ASCVD PREDOMINATES
- Established ASCVD
- Indicators of high ASCVD risk (age ≥55 years with coronary, cardiac, or lower extremity artery stenosis >50%, or LVH)

PREFERABLY
- GLP-1 RA with proven CVD benefit or
- SGLT2i with proven CVD benefit

If A1C above target
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a GLP-1 RA, consider adding SGLT2i with proven CVD benefit
  - DPP-4i if not on GLP-1 RA
  - Basal insulin
  - TZD
  - SU

If further intensification is required or patient is now unable to tolerate GLP-1 RA and/or SGLT2i, choose agents demonstrating CV safety:
- For patients on a GLP-1 RA, consider adding GLP-1 RA with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- TZD
- SU

HF OR CKD PREDOMINATES
- Particularly HFrEF (LVEF ≤45%)
- CKD: Specifically eGFR 30-60 mL/min/1.73 m² or UACR >30 mg/g, particularly UACR >300 mg/g

PREFERABLY
- SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate
- OR
- If SGLT2i not tolerated or contraindicated or if eGFR less than adequate, add GLP-1 RA with proven CVD benefit

If A1C above target
- Avoid TZD in the setting of HF
- Choose agents demonstrating CV safety:
  - For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit
  - DPP-4i (not saxagliptin) in the setting of HF (not on GLP-1 RA)
  - Basal insulin
  - SU

If further intensification is required or patient is now unable to tolerate SGLT2i and/or GLP-1 RA, choose agents demonstrating CV safety:
- For patients on a SGLT2i, consider adding GLP-1 RA with proven CVD benefit
- DPP-4i if not on GLP-1 RA
- Basal insulin
- SU

COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
- DPP-4i
- SGLT2i
- TZD

GLP-1 RA with good efficacy for weight loss

GLP-1 RA or DPP-4i

GLP-1 RA or DPP-4i

GLP-1 RA

If A1C above target
- SU or glargine/midazsuline
- TZD

If A1C above target
- SU or glargine/midazsuline
- TZD

COST IS A MAJOR ISSUE
- Insulin therapy: basal insulin with lowest acquisition cost
- Consider DPP-4i or SGLT2i with lowest acquisition cost

UH = Urinary Hypertension; HFrEF = Heart Failure reduced Ejection Fraction; UACR = Urinary Albumin-to-Creatinine Ratio; LVEF = Left Ventricular Ejection Fraction
GLYCEMIC CONTROL ALGORITHM

**INDIVIDUALIZE GOALS**

**A1C ≤6.5%**
For patients without concurrent serious illness and at low hypoglycemic risk

**A1C >6.5%**
For patients with concurrent serious illness and at risk for hypoglycemia

**LIFESTYLE THERAPY AND ONGOING GLUCOSE MONITORING** (CGM preferred)

**INDEPENDENT OF GLYCEMIC CONTROL, IF ESTABLISHED OR HIGH ASCVD RISK AND/OR CKD, RECOMMEND SGLT2I AND/OR LA GLP1-RA**

**Entry A1C ≥7.5% - 9.0%**

**DUAL THERAPY**
- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- SU/GLN
- Basal Insulin
- Colesvelam
- Bromocriptine QR
- AGi

**TRIPLE THERAPY**
- GLP1-RA
- SGLT2i
- TZD
- SU/GLN
- Basal Insulin
- DPP4i
- Colesvelam
- Bromocriptine QR
- AGi

**Entry A1C <7.5%**

Independent of glycemic control, if established ASCVD or high risk, CKD 3, or HFrEF, start LA GLP1-RA or SGLT2i with proven efficacy*

**MONOTHERAPY**
- Metformin
- GLP1-RA
- SGLT2i
- DPP4i
- TZD
- SU/GLN

**Entry A1C >9.0%**

**SYMPTOMS**

**NO**

DUAL Therapy

**YES**

INSULIN ± Other Agents

OR

TRIPLE Therapy

**ADD OR INTENSIFY INSULIN**

Refer to Insulin Algorithm

**LEGEND**

- ✔ Few adverse events and/or possible benefits
- ▼ Use with caution

1 Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation
2 If not at goal in 3 months, proceed to next level therapy

*CVD: congestive heart failure; HFrEF: heart failure with reduced ejection fraction; LA: long-acting (24 hour duration)

Diabetes Management Algorithm, Endocr Pract. 2020;26(No. 1) 137
Conclusions

• There are many individuals for whom an A1c <7% is clearly reasonable.
• Our best evidence suggests that the A1c level attained and how it is approached is probably the key to achieve optimal outcomes.
• The goal of an A1c less than 7% is fundamentally a tactic to achieve a strategy to minimize the risk of complications while maintaining quality of life.
• Recent CVOTs have shown benefits for patients beyond glycemic control and should be considered in certain population.
• New guidance for glycemic control in the older population is available.