Advancements in the Management of Diabetes Mellitus

Jessica Castle, MD
Harold Schnitzer Diabetes Health Center
Presenter Disclosure Information

• Consultant: Novo Nordisk, Zealand, Dexcom
• Stockholder: Pacific Diabetes Technologies
Impact of Chronic Hyperglycemia

- **Diabetic Retinopathy**: Leading cause of blindness in working age adults.
- **Diabetic Nephropathy**: Leading cause of end-stage renal disease.
- **Diabetic Neuropathy**: Leading cause of nontraumatic lower extremity amputations.
- **Stroke**: 2-fold to 4-fold increase in cardiovascular events and mortality.
- **Cardiovascular Disease**:

  - 2-fold to 4-fold increase in cardiovascular events and mortality.

American College of Physicians
Guidance Statement

- Aim to achieve an A1C 7-8% in most patients with type 2 diabetes

- Personalize goals for glycemic control

# Glycemic Control & Complications

<table>
<thead>
<tr>
<th>Type 1 Studies</th>
<th>Microvascular</th>
<th>Macrovascular</th>
<th>Mortality</th>
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<tbody>
<tr>
<td>DCCT/EDIC(^1)</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>UKPDS(^2,3)</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
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<tr>
<td>ACCORD(^4,5)</td>
<td>↓</td>
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<tr>
<td>ADVANCE(^6,7)</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<tr>
<td>VADT(^8)</td>
<td>↑</td>
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<table>
<thead>
<tr>
<th>Type 2 Studies</th>
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<tbody>
<tr>
<td>Observational Follow-up</td>
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Keep in Mind....

- A1C threshold of $\geq 6.5\%$ is strongly correlated with retinopathy
- $\sim 33\%$ of newly diagnosed patients already have complications
- Complications (particularly macrovascular) are present even in patients with pre-diabetes

Also Keep in Mind....

- Intensive group vs less intensive: 6.3-7.4% vs 7.3-8.4%
- The therapy options for type 2 diabetes have drastically changed over the past 10 years
- Sulfonylureas and insulin have a high risk of hypoglycemia
Lessons from ACCORD: Severe Hypoglycemia and Mortality Risk

<table>
<thead>
<tr>
<th></th>
<th>ACCORD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe Hypo (% / year)</td>
<td>Intensive 3.1%</td>
</tr>
<tr>
<td></td>
<td>Standard 1.1%</td>
</tr>
</tbody>
</table>

HMA = symptomatic, severe hypoglycemic event requiring medical assistance.
American College of Physicians Guidance Statement

- Consider deintensifying pharmacologic control in patients with A1C < 6.5%

- Treat to minimize symptoms related to hyperglycemia and avoid targeting an A1C in patients with a life expectancy < 10 yrs

A1C and Mean Glucose

- Data from 3 randomized clinical trials in people with type 1 or 2 diabetes (N = 387)
  - 20-78 yrs of age
  - 83% white
  - 81% type 1 diabetes

<table>
<thead>
<tr>
<th>A1C, %</th>
<th>Estimated Mean Glucose, mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>101-163</td>
</tr>
<tr>
<td>7</td>
<td>128-190</td>
</tr>
<tr>
<td>8</td>
<td>155-218</td>
</tr>
<tr>
<td>9</td>
<td>182-249</td>
</tr>
<tr>
<td>10</td>
<td>209-273</td>
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</table>

A1C Represents a Wide Range of Glucose Values

Different glucose excursions in people with A1C of 8%

<table>
<thead>
<tr>
<th>Subject</th>
<th>Lab A1c</th>
<th>Glucose Exposure</th>
<th>Glucose Ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average Glucose</td>
<td>Estimated A1c</td>
</tr>
<tr>
<td>A</td>
<td>8.0%</td>
<td>195 mg/dL</td>
<td>8.4%</td>
</tr>
<tr>
<td>B</td>
<td>8.0%</td>
<td>156 mg/dL</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

Individualizing A1C Targets


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### Hypoglycemia Risk
- Low
- Moderate
- High

### Person’s Age, yrs
- 40
- 45
- 50
- 55
- 60
- 65
- 70
- 75

### Disease Duration, yrs
- 5
- 10
- 15
- 20

### Other Comorbidities
- None
- Few/Mild
- Multiple/Severe

### Established Vascular Complications
- None
- Early Microvascular
- Advanced Microvascular

### Psychosocioeconomic Considerations
- Highly Motivated, Adherent, Knowledgeable, Excellent Self-Care Capacities, & Comprehensive Support Systems
- Less motivated, Nonadherent, Limited Insight, Poor Self-Care Capacities, & Weak Support Systems

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Multiple Outcomes to Consider When Treating Diabetes

- Cardiovascular protection
- Glycemic control
- No severe or symptomatic hypoglycemia
- No weight gain
<table>
<thead>
<tr>
<th>Parameter</th>
<th>SGLT-2 Inhibitors</th>
<th>GLP-1 Agonists</th>
<th>DPP-4 Inhibitors</th>
<th>TZDs</th>
<th>SUs</th>
<th>Insulin</th>
</tr>
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<tbody>
<tr>
<td>Efficacy</td>
<td>Intermediate</td>
<td>High</td>
<td>Intermediate</td>
<td>High</td>
<td>High</td>
<td>Highest</td>
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<tr>
<td>Hypoglycemia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Weight effect</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Gain</td>
</tr>
<tr>
<td>ASCVD benefit</td>
<td>Canagliflozin</td>
<td>Liraglutide</td>
<td>Neutral</td>
<td>Potential (pioglitazone)</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Potential risks</td>
<td>DKA, amputation, GU infection, volume depletion, hypotension, ↑ LDL</td>
<td>Thyroid C-cell tumor, GI issues, ISRs, acute pancreatitis</td>
<td>Joint pain, acute pancreatitis</td>
<td>Fluid retention, fracture, bladder cancer, ↑ LDL</td>
<td>CV mortality (based on older SU)</td>
<td>ISRs</td>
</tr>
</tbody>
</table>

Sodium/Glucose Co-transporter 2 (SGLT-2) Inhibitors

SGLT2 inhibitors suppress the action of SGLT2

Reduce glucose reabsorption

Increase urinary glucose excretion

Lost in urine

SGLT-2 Inhibitors

- FDA-approved agents: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin

Benefits

- Cardioprotective (canagliflozin, empagliflozin)
- Low risk of hypoglycemia
- Weight loss
- Decreased blood pressure

Limitations

- Genitourinary infections
- Dehydration
- Risk of diabetic ketoacidosis
- Increased risk of amputation in high-risk pts (with canagliflozin)
Cardiovascular Outcomes in Diabetes: Empagliflozin

- EMPA-REG: randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and CVD (N = 7020)

**Primary Outcome:** CV Mortality, Nonfatal MI, or Nonfatal Stroke

- HR: 0.86 (95.02% CI: 0.74-0.99)
- \( P = .04 \) for superiority

Empagliflozin and Progression of Kidney Disease in Type 2 Diabetes

- Patients with type 2 diabetes randomly assigned to empagliflozin (n=4124) or placebo (n=2061)
- Criteria included estimated GFR >30 ml/min/1.73 m²

Empagliflozin Reduced Risk of New or Worsening Nephropathy

Empagliflozin Reduced Risk of Composite of Doubling of Serum Creatinine, Need for Dialysis, or Death from Renal Disease

Cardiovascular Outcomes in Diabetes: Canagliflozin

- CANVAS/CANVAS-R: randomized, double-blind, multicenter phase III/IV trials in pts with type 2 diabetes and high CV risk (N = 10,142)

Primary Outcome: CV Mortality, Nonfatal MI, or Nonfatal Stroke

HR: 0.86 (95% CI: 0.75-0.97)

P < .001 for noninferiority

P = .02 for superiority

Canagliflozin also associated with increased amputation risk, primarily at toe or metatarsal

Glucagon-like Peptide-1 (GLP-1) Agonists

GLP-1

↑ Neuroprotection
↓ Appetite
↑ Cardiac output
↓ Gastric emptying
↓ Glucagon secretion
↑ Insulin secretion
↑ Insulin biosynthesis
↓ Glucose production
↑ Glucose disposal
↑ Sodium excretion

GLP-1 Agonists

- FDA-approved agents: albiglutide, dulaglutide, exenatide, liraglutide, lixisenatide, semaglutide

**Benefits**

- Cardioprotective (liraglutide, semaglutide)
- Low risk of hypoglycemia
- Weight loss common
- Minimal/no titration

**Limitations**

- Potential side effects (e.g., nausea, vomiting, diarrhea)
- Injectable (although pain is minimal)

GLP-1 Receptor Agonists

GLP-1 receptor agonists

Short-acting
- Exenatide BID
- Lixisenatide OD
- Liraglutide OD

Long-acting
- Dulaglutide OW
- Albiglutide OW
- Semaglutide OW
- Exenatide OW

BID, twice daily; GLP-1, glucagon-like peptide-1; OD, once daily; OW, once weekly.
Cardiovascular Outcomes in Diabetes: Liraglutide

- LEADER: randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and high CV risk (N = 9340)

**Primary Outcome: CV Mortality, Nonfatal MI, or Nonfatal Stroke**

- HR: 0.87 (95% CI: 0.78-0.97)
- \( P < .001 \) for noninferiority
- \( P = .01 \) for superiority

Mann JF et al. N Engl J Med 2017;377:839-848. The primary composite renal outcome in the time-to-event analysis was a composite (Panel A) of the first occurrence of persistent macroalbuminuria (Panel B), persistent doubling of the serum creatinine level and an estimated glomerular filtration rate of 45 ml or less per minute per 1.73 m² of body-surface area (referred to as persistent doubling of the serum creatinine level; Panel C), the need for continuous renal-replacement therapy (for end-stage renal disease; Panel D), or death due to renal disease (data not shown).
Semaglutide vs Exenatide ER

813 patients with T2D
- Age ≥18 years
- HbA1c 7.0–10.5%
- Stable treatment with 1–2 OADs (metformin, thiazolidinediones, sulphonylurea)
- eGFR >60 ml/min/1.73 m²

Trial information
- Open-label, active-controlled, parallel-group, multi-centre, multi-national, two-armed trial
- Conducted at 141 sites in 12 countries in Europe, South America and USA

**HbA₁c**

ESTIMATED MEAN BY WEEK AND CHANGE FROM BASELINE AT WEEK 56

Overall mean at baseline: 8.35%

Body weight

ESTIMATED MEAN BY WEEK AND CHANGE FROM BASELINE AT WEEK 56

Overall mean at baseline: 95.79 kg

Adverse Events

Cardiovascular Outcomes in Diabetes: Semaglutide

- SUSTAIN-6: randomized, double-blind, multicenter phase III trial in pts with type 2 diabetes and high CV risk (N = 3297)

**Primary Outcome:** CV Mortality, Nonfatal MI, or Nonfatal Stroke

- HR: 0.74 (95% CI: 0.58-0.95)
- P < .001 for noninferiority
- P = .02 for superiority

Cardiovascular Protection

- In people with uncontrolled T2DM and established CV disease (or specifically to reduce CV risk), consider:
  - The oral SGLT-2 inhibitors canagliflozin or empagliflozin
  - The injectable GLP-1 agonists liraglutide or semaglutide
- Other agents are under investigation for CVD outcomes
## Cardiovascular Outcomes in Diabetes: Summary and Ongoing Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Class</th>
<th>Agent</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANVAS[1]</td>
<td>SGLT-2 inhibitor</td>
<td>Canagliflozin</td>
<td>Reduced CV events</td>
</tr>
<tr>
<td>EMPA-REG[2]</td>
<td>SGLT-2 inhibitor</td>
<td>Empagliflozin</td>
<td>Reduced CV events and CV death</td>
</tr>
<tr>
<td>LEADER[3]</td>
<td>GLP-1 agonist</td>
<td>Liraglutide</td>
<td>Reduced CV events and CV death</td>
</tr>
<tr>
<td>SUSTAIN-6[4]</td>
<td>GLP-1 agonist</td>
<td>Semaglutide</td>
<td>Reduced CV events</td>
</tr>
<tr>
<td>REWIND[6]</td>
<td>GLP-1 agonist</td>
<td>Dulaglutide</td>
<td>Expected July 2018</td>
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</tbody>
</table>
Recent advances in diabetes technology
Continuous Glucose Monitoring

- Glucose value
- Trend arrow
- Rate of change
- Trend graph

- Know where you are by how you got there AND where it's going
Dexcom G4 or G5 Mobile

And now the G6 which does not require calibration!
FreeStyle Libre

How to use the FreeStyle Libre System

1. Apply sensor with applicator
2. Scan sensor using FreeStyle Libre Reader
3. Get reading on the reader

For full instructions: www.freestylelibre.co.uk
Advanced Treatments for Diabetes: Artificial Pancreas (AP)

Computerized control of insulin ± glucagon delivery based on data from a continuous glucose sensor

*3 major delays: insulin absorption, insulin action, glucose sensing.*
MiniMed 670G: Hybrid AP System

- First FDA-approved AP system
- Hybrid indicates that meal boluses still required
- Insulin delivery is adjusted based on a PI algorithm:
  - Proportional error (distance from target)
  - Integral error (area under the curve)
  - Derivative error (rate of change)
  - Insulin-on-board safety constraints

Imagine if the heat source for your home was a mile away...

Your house would alternate between:

**Artic Freeze**

**Blazing Inferno**

Delays in insulin onset/offset lead to hyperglycemia and hypoglycemia.
OHSU Artificial Pancreas Study: 4-way Randomized Cross-over

<table>
<thead>
<tr>
<th></th>
<th>Sunday</th>
<th>Monday</th>
<th>Tuesday</th>
<th>Wednesday</th>
<th>Thursday</th>
<th>Friday</th>
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<tbody>
<tr>
<td>Current care</td>
<td></td>
<td>In clinic exercise</td>
<td></td>
<td>Home exercise</td>
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<tr>
<td>PLGS</td>
<td></td>
<td>In clinic exercise</td>
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<td>Home exercise</td>
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<tr>
<td>Insulin CL</td>
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<td>In clinic exercise</td>
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<td>Home exercise</td>
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<tr>
<td>Insulin + Glucagon CL</td>
<td>In clinic exercise</td>
<td></td>
<td>Home exercise</td>
<td></td>
<td>In clinic exercise</td>
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*Current care: patient’s usual regimen
**PLGS: predictive low glucose suspend system
***In clinic exercise: running at 60% of VO2max for 45 min
****Home exercise: exercise of subjects choice for 45 min
OHSU Artificial Pancreas Systems
Improved Time in Range (70-180 mg/dL); Glucagon Reduced Hypoglycemia

Time in range: 63.1% vs 65.2% vs 74.3% vs 72.0%

Castle, Jacobs et al. Diabetes Care, 2018, in press.
Summary

- Type 2 diabetes is a progressive disease that commonly requires multiple medications
- Consider benefits and limitations of drug choices to determine optimal choice
- Individualize glycemic targets
- There are now multiple SGLT-2 inhibitor and GLP-1 agonist options available that reduce cardiovascular risk
- CGM is available and has enabled automated insulin delivery
Thank you!