Challenges in T2DM Management: Looking Beyond the ADA/AACE Guidelines Paradigm

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Learning Objectives

• Initiate combination therapy in patients with newly diagnosed T2DM who could benefit from more intensive glycemic control
• Integrate GLP-1 RA therapy into management strategies for patients with T2DM inadequately controlled on oral agents
• Monitor PPG response to guide choices in ongoing T2DM management and better maintain glycemic control over a patient’s lifetime

GLP-1 RA = glucagon-like peptide-1 receptor agonist; PPG = postprandial glucose; T2DM = type 2 diabetes mellitus.
• More than 29 million Americans have been diagnosed with diabetes\textsuperscript{a}: 12.3% of adults\textsuperscript{1}
• Almost 2 million diagnoses each year; $245 billion in annual costs\textsuperscript{1}
• Despite increased awareness and new treatment options, progress in meeting treatment goals in T2DM is mixed\textsuperscript{2}

\textsuperscript{a}90\%-95\% of persons in the United States who have diabetes have T2DM. BP = blood pressure; LDL-C = low-density lipoprotein cholesterol.

2015 ADA and 2013 AACE Guidelines: Individualize Treatment Goals as Part of Team-Based Care

- Set patient-specific glycemic goals
  - A1C range of 6.0% to <8.0%, depending on patient age, comorbidities, duration of diabetes
- Implement lifestyle modifications, including weight loss
- CV and other risk factors: hypertension, lipids, renal impairment
- Manage patients across their life span

Collaborative, multidisciplinary teams and chronic care model to coordinate all aspects of care

ADA = American Diabetes Association; CV = cardiovascular.
Multiple Defects in T2DM Present Multiple Targets for Intervention

- 5 major classes of oral agents
- 2 types of injected agents
- Multiple options within classes
- Multiple ways to combine classes

Hyperglycemia

- Increased glucose production
- Decreased glucose uptake
- Impaired insulin secretion
- Decreased incretin effect
- Impaired insulin secretion

Sulfonylureas
Glinides
TZDs
DPP-4 inhibitors
GLP-1 RAs

DPP-4 inhibitors
GLP-1 RAs

Insulin
TZDs
Increased lipolysis

Increased glucose reabsorption via kidney
Insulin
SGLT2 inhibitors

Pancreatic β cells

DPP-4 inhibitors
GLP-1 RAs

Insulin
MET
TZDs

Insulin
MET
TZDs

Insulin
MET
TZDs

Increased hepatic glucose production

Insulin
MET
TZDs

Insulin
MET
TZDs

Neurotransmitter dysfunction

MET = metformin; TZDs = thiazolidinediones.

American Diabetes Association. DeFronzo RA. *Diabetes*. 2009;58:773-795. Copyright and all rights reserved. Material from this publication has been used with the permission of American Diabetes Association.
### Safety and Tolerability of ADA and AACE Guideline-Recommended Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>DPP-4 I</th>
<th>GLP-1 RAs</th>
<th>TZDs</th>
<th>SU/GLIN</th>
<th>SGLT2 I</th>
<th>Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypo</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/ mild</td>
<td>Neutral</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Neutral/ slight loss</td>
<td>Neutral</td>
<td>Loss</td>
<td>Gain</td>
<td>Gain</td>
<td>Loss</td>
<td>Gain</td>
</tr>
<tr>
<td><strong>Renal/GU</strong></td>
<td>Contraindicated Stages 3B-5 (except linagliptin)</td>
<td>Exenatide contraindicated CrCl &lt;30 mL/min</td>
<td>May worsen fluid retention</td>
<td>RI increases hypo risk</td>
<td>GU infections; RI lessens efficacy</td>
<td>RI increases hypo risk; fluid retention</td>
<td></td>
</tr>
<tr>
<td><strong>GI Sx</strong></td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CHF</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>CVD</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral?</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td><strong>Bone</strong></td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate bone loss</td>
<td>Neutral</td>
<td>Bone loss?</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

CHF = congestive heart failure; CrCl = creatinine clearance; CVD = CV disease; DPP-4 I = DPP-4 inhibitor; GI Sx = gastrointestinal symptoms; GU = genitourinary; Hypo = hypoglycemia; RI = renal impairment; SGLT2 I = SGLT2 inhibitor; SU/GLIN = sulfonylurea/glinide.

Case Study 1: Alice, a 45-Year-Old Woman Newly Diagnosed With T2DM

- Alice, a self-employed artist, has just acquired health insurance and presents for her first general physical in 10 years
- Job has irregular hours, requiring long commutes to clients
- Overweight (BMI = 29.7 kg/m²) and a 12-year history of hypertension (BP = 135/95 mm Hg on ACE inhibitor)
- Laboratory findings
  - A1C = 8.5%
  - FPG = 155 mg/dL
  - LDL-C = 120 mg/dL
  - eGFR = 83 mL/min/1.73²

ACE = angiotensin-converting enzyme; BMI = body mass index; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose.
Based on her presentation, what is an appropriate A1C target for Alice?

1. 6.5%
2. ≥6.5% to <7.0%
3. ≥7.0% to <7.5%
4. 7.5%

Use your keypad to vote now!
Based on her presentation, what is an appropriate A1C target for Alice?

1. 6.5%
2. ≥6.5% to <7.0%
3. ≥7.0% to <7.5%
4. 7.5%

Use your keypad to vote now!

<table>
<thead>
<tr>
<th>A1C Level</th>
<th>Psychosocioeconomic Considerations</th>
<th>Hypoglycemia Risk</th>
<th>Disease Duration</th>
<th>Other Comorbidities</th>
<th>Established Vascular Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most Intensive 6.0%</td>
<td>Highly motivated, adherent, knowledgeable, excellent self-care capacities, comprehensive support systems</td>
<td>Low</td>
<td>5</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Less Intensive 7.0%</td>
<td></td>
<td>Moderate</td>
<td>10</td>
<td>Few/mild</td>
<td>Early micro</td>
</tr>
<tr>
<td>Least Intensive 8.0%</td>
<td>Less motivated, nonadherent, limited insight, poor self-care capacities, weak support systems</td>
<td>High</td>
<td>15</td>
<td>Multiple/severe</td>
<td>CV</td>
</tr>
</tbody>
</table>

EASD = European Association for the Study of Diabetes.
Using Patient Factors to Guide Glycemic Goals: Alice

- **A1C Level**
  - **Most Intensive 6.0%**
  - **Less Intensive 7.0%**
  - **Least Intensive 8.0%**

- **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

- **Hypoglycemia Risk**
  - Low
  - Moderate
  - High

- **Patient Age**
  - 40
  - 45
  - 50
  - 55
  - 60
  - 65
  - 70
  - 75

- **Disease Duration**
  - 5
  - 10
  - 15
  - 20

- **Other Comorbidities**
  - None
  - Few/mild
  - Multiple/severe

- **Established Vascular Complications**
  - None
  - Early micro
  - CV
  - Advanced micro

Cardiometabolic Risk Factor Treatment Goals in T2DM

<table>
<thead>
<tr>
<th>Blood Pressure Targets(^1,2)</th>
<th>Lipid Goals(^3)</th>
<th>Weight(^2,3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age</td>
<td>• LDL-C:</td>
<td>• Normal BMI:</td>
</tr>
<tr>
<td>• &lt;60 years:</td>
<td>• &lt;100 mg/dL,</td>
<td>&lt;25 kg/m(^2)</td>
</tr>
<tr>
<td>&lt;140/90 mm Hg</td>
<td>• moderate risk</td>
<td></td>
</tr>
<tr>
<td>• 60+ years:</td>
<td>• &lt;70 mg/dL,</td>
<td>Weight loss education,</td>
</tr>
<tr>
<td>&lt;150/90 mm Hg</td>
<td>• high risk</td>
<td>nutrition counseling</td>
</tr>
<tr>
<td>• Any age with T2DM:</td>
<td>• Non-HDL-C:</td>
<td>Increase physical activity:</td>
</tr>
<tr>
<td>&lt;140/90 mm Hg</td>
<td>• &lt;130 mg/dL,</td>
<td>30 minutes 3x a week (if</td>
</tr>
<tr>
<td>• Any age with T2DM and</td>
<td>• moderate risk</td>
<td>possible)</td>
</tr>
<tr>
<td>CKD:</td>
<td>• &lt;100 mg/dL,</td>
<td></td>
</tr>
<tr>
<td>&lt;130/80 mm Hg(^a)</td>
<td>• high risk</td>
<td>Weight loss medications:</td>
</tr>
<tr>
<td></td>
<td>• HDL-C:</td>
<td>phentermine/topiramate ER,</td>
</tr>
<tr>
<td></td>
<td>• ≥40 mg/dL (men)</td>
<td>orlistat, lorcaserin,</td>
</tr>
<tr>
<td></td>
<td>• ≥50 mg/dL (women)</td>
<td>naltrexone/bupropion,</td>
</tr>
<tr>
<td></td>
<td>• Triglycerides:</td>
<td>liraglutide</td>
</tr>
<tr>
<td></td>
<td>• &lt;150 mg/dL</td>
<td>Bariatric surgery</td>
</tr>
</tbody>
</table>

\(^a\)May be appropriate for certain patients if achieved without excess treatment burden.

CKD = chronic kidney disease; ER = extended release; HDL-C = high-density lipoprotein cholesterol.

Individualize T2DM Treatment Goals Based on Specific Patient Profiles

- Age
- Disease duration
- Other comorbid conditions: hypertension, dyslipidemia, smoking
- Hypoglycemia risk
- Patient motivation, support systems, resources

Multifactorial treatment and behavioral modification are key to glycemic control and reducing complications.
Individualize T2DM Treatment Goals Based on Specific Patient Profiles

- Age
- Disease duration
- Other comorbid conditions: hypertension, dyslipidemia, smoking
- Hypoglycemia risk
- Patient motivation, support systems, resources

Multifactorial treatment and behavioral modification are key to glycemic control and reducing complications.

ACTION ITEM:
Intensify interventions for BP, lipid lowering, smoking cessation, and A1C for patients with T2DM to reduce CV and all-cause mortality.
In addition to starting Alice on a statin to lower her LDL-C, what is your initial T2DM treatment recommendation?

1. Metformin for 3 months, reassess, adjust dose if necessary
2. Metformin for 3 months, reassess, add sulfonylurea/glinide
3. Initial combined metformin plus sulfonylurea
4. Initial combined metformin plus DPP-4 inhibitor or SGLT2 inhibitor

Use your keypad to vote now!
In addition to starting Alice on a statin to lower her LDL-C, what is your initial T2DM treatment recommendation?

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Use your keypad to vote now!
ADA 2015 and AACE 2013: Approaches to Achieving Glycemic Goals in T2DM

• ADA: based on treating to *failure* before intensifying therapy in newly diagnosed patients\(^1,2\)
  – Exception: patients presenting with A1C >9.0%
• AACE: initial combination therapy for A1C ≥7.5%\(^3\)
• Both ADA and AACE recommend:
  – Metformin as initial therapy alone or in combination with other oral or injectable agents
  • DPP-4 inhibitors, SGLT2 inhibitors, or GLP-1 RAs are optimal when weight and hypoglycemia are of concern

Rationale for Initial Dual Therapy

- T2DM natural history: progressive worsening of hyperglycemia
- Early intervention: more durable glycemic control, reduction in vascular complications\(^1\)-\(^4\)
- Initial combination of metformin + oral agents increases likelihood of achieving A1C goals by 40\%\(^5\)
- Best A1C achieved within first year of treatment predicts time to secondary failure (A1C >8.0\%)\(^2\)

<table>
<thead>
<tr>
<th>Best A1C in First Year</th>
<th>6.0%-6.9%</th>
<th>7.0%-7.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to 50% failure(^a)</td>
<td>&gt;60 months</td>
<td>≤36 months</td>
</tr>
</tbody>
</table>

\(^a\)Time until ~50\% of patients had secondary failure.

2015 ADA/EASD Position Statement: Approach to T2DM Medication Choice

Key considerations:
- Avoiding hypoglycemia and weight gain
- Side effects, costs

Healthy eating, weight control, increased physical activity

Consider initial dual therapy if A1C >9.0% at presentation
Proceed to a dual therapy if A1C not reached in ~3 months
Proceed to triple therapy if A1C is not reached in ~3 months

Oral drug classes are listed left to right, oldest to newest; injectable agents are at the far right.

http://care.diabetesjournals.org/content/38/1/140.full.pdf+html.
Characteristics of Oral Agents Available as Fixed-Dose Combinations With Metformin

<table>
<thead>
<tr>
<th>Agent</th>
<th>Δ A1C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Dosing Frequency</th>
<th>Available as FDC</th>
<th>FDC Dosing Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>−1.0 to −1.5</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Alogliptin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.5 to −0.8</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Linagliptin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.5 to −0.7</td>
<td>Once a day</td>
<td>With pioglitazone</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Saxagliptin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.7 to −0.9</td>
<td>Once a day</td>
<td>With MET ER</td>
<td>Once a day</td>
</tr>
<tr>
<td>Sitagliptin&lt;sup&gt;2&lt;/sup&gt;</td>
<td>−0.6 to −0.8</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Canagliflozin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>−0.7 to −0.8</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Dapagliflozin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>−0.5 to −0.7</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Empagliflozin&lt;sup&gt;3&lt;/sup&gt;</td>
<td>−0.6 to −0.7</td>
<td>Once a day</td>
<td>With MET</td>
<td>Twice a day</td>
</tr>
</tbody>
</table>

<sup>a</sup>Monotherapy or in combination with other oral agents, not necessarily in FDC. FDC = fixed-dose combination.

Initial Dual Therapy May Benefit β-Cell Function and Blood Pressure

- Initial dual DPP-4 inhibitor + metformin
  - Improved β-cell function and proinsulin/insulin ratio vs metformin monotherapy\(^1,2\)
  - Reduction in SBP (–5.0 mm Hg) and DBP in all groups with saxagliptin\(^1\)
- Initial dual SGLT2 inhibitor + metformin
  - Greater reductions in SBP and DBP than with metformin monotherapy:
    - –3.3 vs –1.2 mm Hg and –1.8 vs 0 mm Hg, respectively, with dapagliflozin 10 mg\(^3\)
- Initial dual TZD + metformin
  - Reductions in β-cell stress\(^4\) and greater BP control\(^5\)
- Initial dual sulfonylurea + metformin
  - Failure to prevent progressive decline in β-cell function\(^6\)

DBP = diastolic blood pressure; SBP = systolic blood pressure.

Initial Triple Therapy (Metformin, Pioglitazone, + Exenatide) vs Metformin Step Therapy

- Patients who received initial triple therapy vs step therapy (metformin then sulfonylurea then basal insulin) with target A1C of <6.5%
  - Significantly lower A1C levels (5.95% vs 6.50%)*
  - 7.5x less hypoglycemia
  - Mean 1.2-kg weight reduction vs 4.1-kg weight gain

<table>
<thead>
<tr>
<th>Benefits</th>
<th>GLP-1 RAs as a Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP reduction</td>
<td>–1 to –7 mm Hg in SBP</td>
</tr>
<tr>
<td>Weight effect</td>
<td>–1 to –4 kg (&gt; with long-acting agents)</td>
</tr>
<tr>
<td>Reduce PPG</td>
<td>–41 to –47 mg/dL (&gt; with rapid-acting agents)</td>
</tr>
</tbody>
</table>

*P < .001.

### Effects on Body Weight in Combination With Other Agents

<table>
<thead>
<tr>
<th>DPP-4 Inhibitor&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Δ Weight (kg)</th>
<th>GLP-1 RA&lt;sup&gt;1,2&lt;/sup&gt;</th>
<th>Δ Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>Neutral</td>
<td>Exenatide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–0.9 to –3.1</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>Neutral</td>
<td>Exenatide ER&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–2.3 to –4.5</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Neutral</td>
<td>Liraglutide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–0.5 to –3.2</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Neutral</td>
<td>Albiglutide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–0.6 to –1.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dulaglutide&lt;sup&gt;a&lt;/sup&gt;</td>
<td>–1.0 to –1.9</td>
</tr>
</tbody>
</table>

| SGLT2 Inhibitor<sup>3</sup> | Δ Weight (kg) | • Combinations included metformin, sulfonylurea, or both  
                                |               | • Combination with metformin may augment weight loss  
                                |               | • Initial linagliptin + MET vs MET: between-group difference, –1.3 kg favoring combination<sup>4</sup> |
|-----------------------------|---------------|---------------------------------------------------------------|
| Canagliflozin<sup>b</sup>   | –1.6 to –3.8  |                                                               |
| Dapagliflozin<sup>b</sup>   | –2.0 to –4.5  |                                                               |
| Empagliflozin<sup>b</sup>   | –1.9 to –2.1  |                                                               |

<sup>a</sup>Range across studies; <sup>b</sup>Range across studies and, for each, both doses.

As well as combining agents with different mechanisms of action, clinicians should consider how treatment may affect patients’ weight, CV status, and hypoglycemic risk.

ADA and AACE emphasize choosing agents with minimal or beneficial effect on weight and hypoglycemia.

Nonglycemic effects, such as BP reduction, may provide additional benefits for patients.
Factor in Nonglycemic Effects of Treatment When Choosing Agents

- As well as combining agents with different mechanisms of action, clinicians should consider how treatment may affect patients’ weight, CV status, and hypoglycemic risk.
- ADA and AACE emphasize choosing agents with minimal or beneficial effect on weight and hypoglycemia.
- Nonglycemic effects, such as BP reduction, may provide additional benefits for patients.

**ACTION ITEM:**
Choose agents with positive or neutral effects on key patient factors, such as weight and hypoglycemic risk.
Alice initiates dual therapy with metformin + a DPP-4 inhibitor. At 3-month follow-up, her A1C is 6.7% and BMI is 28.5 kg/m². Would you:

1. Maintain her T2DM regimen and consider weight loss medication
2. Add an SGLT2 inhibitor
3. Add a long-acting GLP-1 RA
4. Stop the DPP-4 inhibitor and add an SGLT2 inhibitor
5. Stop the DPP-4 inhibitor and add a short-acting GLP-1 RA

Use your keypad to vote now!
Alice initiates dual therapy with metformin + a DPP-4 inhibitor. At 3-month follow-up, her A1C is 6.7% and BMI is 28.5 kg/m². Would you:

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Use your keypad to vote now!
AACE Guidelines Emphasize Obesity Management in T2DM

**STEP 1**
**Evaluation for Complications and Staging**

<table>
<thead>
<tr>
<th>Cardiometabolic Disease</th>
<th>Biomechanical Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Complications</td>
<td>BMI ≥ 27 with Complications</td>
</tr>
<tr>
<td>BMI 25–26.9, or BMI ≥ 27</td>
<td>Stage Severity of Complications</td>
</tr>
<tr>
<td>Low</td>
<td>Medium</td>
</tr>
<tr>
<td>High</td>
<td>(i) Therapeutic targets for improvement in complications,</td>
</tr>
<tr>
<td></td>
<td>(ii) Treatment modality and</td>
</tr>
<tr>
<td></td>
<td>(iii) Treatment intensity for weight loss based on staging</td>
</tr>
</tbody>
</table>

**STEP 2**
**Select:**

- **Lifestyle Modification:** MD/RD counseling; web/remote program; structured multidisciplinary program
- **Medical Therapy:** phentermine; orlistat; lorcaserin; phentermine/topiramate ER
- **Surgical Therapy (BMI ≥ 35):** Lap band; gastric sleeve; gastric bypass

**STEP 3**
If therapeutic targets for improvements in complications not met, intensify lifestyle and/or medical and/or surgical treatment modalities for greater weight loss

RD = registered dietitian.
AACE 2015 Position Statement: Initial Dual Therapy for A1C ≥7.5% at Presentation

*Lifestyle modification for all patients

**Disease progression**

*Order of medications listed represents suggested hierarchy of usage.
AGi = alpha-glucosidase inhibitor; GLN = glinide; QR = quick release.
Case Study 1: Conclusion

- Alice has achieved her A1C goal: tolerates combined metformin + DPP-4 inhibitor well; weight still an issue
- She admits to not contacting her CDE and not being adherent to dietary and exercise recommendations
- You set up an appointment with Alice, her CDE, and endocrinologist to assess the best approach to manage her weight
- She returns a month later: endocrinologist recommended phentermine/topiramate;¹ CDE has helped her with a practical diet and exercise program that suits her irregular work hours

CDE = certified diabetes educator.

Consider Initial Dual Therapy

- Patients who present with A1C ≥7.5%
- Achieving glycemic targets early in treatment has long-term benefits in more durable response, prevention of complications
- Combine metformin with agents that have positive effects on weight and blood pressure and will not increase hypoglycemic risk
Consider Initial Dual Therapy

- Patients who present with A1C ≥ 7.5%
- Achieving glycemic targets early in treatment has long-term benefits in more durable response, prevention of complications
- Combine metformin with agents that have positive effects on weight and blood pressure and will not increase hypoglycemic risk

ACTION ITEM:
Implement initial dual therapy for patients who present with higher A1C levels and can benefit from early, aggressive glucose control.
Case Study 2: Greg, a 62-Year-Old Man With a 10-Year History of T2DM

- Greg is a long-haul truck driver who often works through the night. He was first diagnosed with T2DM at age 52.
- He started maximum-dose metformin at diagnosis and added linagliptin 3 years ago.
- BMI = 31 kg/m²
- BP = 145/88 mm Hg on an ARB
- Glycemic and other laboratory findings
  - A1C = 8.3%
  - FPG = 130 mg/dL
  - LDL-C = 105 mg/dL on statin
  - eGFR = 58 mL/min/1.73²

ARB = angiotensin II receptor blocker.
Based on Greg’s presentation and history, what do you think is a practical A1C goal?

1. 6.0%
2. <6.5%
3. 6.5%
4. >6.5% but <7.0%
5. ≥7.0% but <7.5%

Use your keypad to vote now!
Based on Greg’s presentation and history, what do you think is a practical A1C goal?

1. 6.0%
2. <6.5%
3. 6.5%
4. >6.5% but <7.0%
5. ≥7.0% but <7.5%

Use your keypad to vote now!

A1C Level

- **Most Intensive 6.0%**
- **Less Intensive 7.0%**
- **Least Intensive 8.0%**

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

Hypoglycemia Risk

- Low
- Moderate
- High

Patient Age

- 40, 45, 50, 55, 60, 65, 70, 75

Disease Duration

- 5, 10, 15, 20

Other Comorbidities

- None
- Few/mild
- Multiple/severe

Established Vascular Complications

- None
- Early micro
- CV
- Advanced micro

Using Patient Factors to Guide Glycemic Goals: Greg

- **A1C Level**
  - Most Intensive: 6.0%
  - Less Intensive: 7.0%
  - Least Intensive: 8.0%

- **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

- **Hypoglycemia Risk**
  - Low
  - Moderate
  - High

- **Patient Age**
  - 40
  - 45
  - 50
  - 55
  - 60
  - 65
  - 70
  - 75

- **Disease Duration**
  - 5
  - 10
  - 15
  - 20

- **Other Comorbidities**
  - None
  - Few/mild
  - Multiple/severe

- **Established Vascular Complications**
  - None
  - Early micro
  - CV
  - Advanced micro

---

Based on Greg’s glycemic measures at presentation, what would be your next step?

1. With guidance from CDE, teach him to perform SMBG
2. Add basal insulin to reduce fasting glucose
3. Have him return (in a few days) 1-2 hours after lunch to measure his PPG
4. Refer him to an endocrinologist

Use your keypad to vote now!

SMBG = self monitoring of blood glucose.
Based on Greg’s glycemic measures at presentation, what would be your next step?

1. **With guidance from CDE, teach him to perform SMBG**
2. Add basal insulin to reduce fasting glucose
3. Have him return (in a few days) 1-2 hours after lunch to measure his PPG
4. Refer him to an endocrinologist

Use your keypad to vote now!

SMBG = self monitoring of blood glucose.
• PPG is not a primary target of guideline-directed antihyperglycemic therapy
• However, guidelines recommend targeting PPG when A1C remains elevated in presence of controlled FPG

<table>
<thead>
<tr>
<th>Glycemic Parameter</th>
<th>ADA 2015&lt;sup&gt;1&lt;/sup&gt;</th>
<th>AACE 2013&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Impaired (prediabetes)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Diabetes (ADA/AACE)&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>80-130 mg/dL&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤99 mg/dL</td>
<td>100-125 mg/dL</td>
<td>≥126 mg/dL</td>
</tr>
<tr>
<td>PPG</td>
<td>&lt;180 mg/dL</td>
<td>≤139 mg/dL</td>
<td>140-199 mg/dL</td>
<td>≥200 mg/dL</td>
</tr>
</tbody>
</table>

<sup>a</sup>Change from 2014 recommendation (which was 70-130 mg/dL).
Assess PPG When A1C Remains High and FPG Is Controlled

- Elevated PPG is highly prevalent among patients with T2DM and has been associated with adverse CV outcomes.
- Elevated PPG is a major contributor to residual hyperglycemia when FPG levels are controlled, especially as A1C reaches <7.5%.
- Diabetes medications have differential effects on PPG that should be considered when combining therapies to achieve glycemic goals.
Assess PPG When A1C Remains High and FPG Is Controlled

• Elevated PPG is highly prevalent among patients with T2DM and has been associated with adverse CV outcomes
• Elevated PPG is a major contributor to residual hyperglycemia when FPG levels are controlled, especially as A1C reaches <7.5%
• Diabetes medications have differential effects on PPG that should be considered when combining therapies to achieve glycemic goals

ACTION ITEM:
Assess PPG and address if elevated in patients whose A1C remains high despite adequate FPG control.
What T2DM therapy would you recommend to help Greg achieve his A1C goal?

1. Add sulfonylurea
2. Discontinue linagliptin and add a GLP-1 RA
3. Add SGLT2 inhibitor
4. Add basal insulin
5. Stop oral treatment and initiate basal insulin

Use your keypad to vote now!
What T2DM therapy would you recommend to help Greg achieve his A1C goal?

1. Add sulfonylurea
2. **Discontinue linagliptin and add a GLP-1 RA**
3. Add SGLT2 inhibitor
4. Add basal insulin
5. Stop oral treatment and initiate basal insulin

Use your keypad to vote now!

- 1: 5%
- 2: 18%
- 3: 57%
- 4: 16%
- 5: 3%
## Treatment Goals: Restore Glycemic Control; Avoid CV Complications, Hypoglycemia, and Weight Gain

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>SU</th>
<th>TZD</th>
<th>DPP-4 I</th>
<th>SGLT2 I</th>
<th>GLP-1 RA</th>
<th>Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Mod</td>
<td>Mod</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td>PPG↓</td>
<td>+</td>
<td>+</td>
<td>=</td>
<td>+++</td>
<td>+</td>
<td>++++++</td>
<td>=</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>Low</td>
<td>Mod</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Weight</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Loss</td>
<td>Loss</td>
<td>Gain</td>
</tr>
<tr>
<td>Side effects</td>
<td>GI</td>
<td>Hypo</td>
<td>Edema, HF, Fx</td>
<td>Rare</td>
<td>GMI</td>
<td>GI</td>
<td>Hypo</td>
</tr>
<tr>
<td>Effect of RI</td>
<td>Do not use in Stage 3-5 CKD</td>
<td>More hypo risk</td>
<td>May worsen fluid retention</td>
<td>Dose adj. (except linagliptin)</td>
<td>Efficacy reduced; avoid with eGFR &lt;45</td>
<td>Avoid with eGFR &lt;30 especially exenatide</td>
<td>More hypo risk</td>
</tr>
</tbody>
</table>

Fx = fractures; GMI = genital mycotic infections; HF = heart failure; Mod = moderate.

## Drug-Related Factors to Consider in Treatment Choice: Greg

<table>
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<th>Basal Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>High</td>
<td>High</td>
<td>High</td>
<td>Mod</td>
<td>Mod</td>
<td>High</td>
<td>Highest</td>
</tr>
<tr>
<td><strong>PPG ↓</strong></td>
<td>+</td>
<td>+</td>
<td>=</td>
<td>+/++</td>
<td>+</td>
<td>++/++++</td>
<td>=</td>
</tr>
<tr>
<td><strong>Hypo risk</strong></td>
<td>Low</td>
<td>Mod</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>Neutral</td>
<td>Gain</td>
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<td>Neutral</td>
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</tr>
</tbody>
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GLP-1 RAs: Clinical Characteristics and Glycemic Effects

<table>
<thead>
<tr>
<th>Dosing Frequency</th>
<th>Δ A1C (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ FPG (mg/dL)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Magnitude of PPG Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>Twice a day</td>
<td>−0.4 to −0.9</td>
<td>−18 to −25</td>
</tr>
<tr>
<td>Exenatide ER&lt;sup&gt;1-4&lt;/sup&gt;</td>
<td>Once a week</td>
<td>−1.4 to −1.9</td>
<td>−34</td>
</tr>
<tr>
<td>Liraglutide&lt;sup&gt;1,2,5&lt;/sup&gt;</td>
<td>Once a day</td>
<td>−0.6 to −1.5</td>
<td>−29 to −40</td>
</tr>
<tr>
<td>Albiglutide&lt;sup&gt;b,6,7&lt;/sup&gt;</td>
<td>Once a week</td>
<td>−0.8 to −1.0</td>
<td>−31 to −43</td>
</tr>
<tr>
<td>Dulaglutide&lt;sup&gt;b,6,7&lt;/sup&gt;</td>
<td>Once a week</td>
<td>−0.7 to −1.5</td>
<td>−13 to −43</td>
</tr>
</tbody>
</table>

<sup>a</sup>Administered as monotherapy or in combination with MET or other glucose-lowering agents;
<sup>b</sup>Neither albiglutide nor dulaglutide is recommended for first-line therapy.

### Glycemic and Nonglycemic Effects of GLP-1 RAs

<table>
<thead>
<tr>
<th></th>
<th>Δ Weight (kg)a</th>
<th>Δ Systolic BP (mm Hg)a</th>
<th>Mild to Moderate Hypoglycemia (%)a,b</th>
<th>Severe Hypoglycemia (%)a,b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide¹</td>
<td>−0.9 to −3.1</td>
<td>−3.4 to −3.7</td>
<td>4 to 11</td>
<td>0</td>
</tr>
<tr>
<td>Exenatide ER²</td>
<td>−3.7 to −3.8</td>
<td>−4.7</td>
<td>1.3 to 14.5</td>
<td>0</td>
</tr>
<tr>
<td>Liraglutide¹</td>
<td>−1.0 to −3.2</td>
<td>−0.6 to −7.9</td>
<td>3 to 12</td>
<td>0</td>
</tr>
<tr>
<td>Albiglutide³-⁵</td>
<td>−0.6 to −1.6</td>
<td>−5.8</td>
<td>2 to 17</td>
<td>0</td>
</tr>
<tr>
<td>Dulaglutide⁶,⁷</td>
<td>−1.3 to −3.0</td>
<td>−0.6 to −3.36</td>
<td>8.7 to 10.7</td>
<td>0</td>
</tr>
</tbody>
</table>

aAdministered as monotherapy or in combination with MET or other glucose-lowering agents;  
bHigher rates are associated with combinations including sulfonylureas.  
Long-Acting GLP-1 RAs vs Basal Insulin: Glycemic and Nonglycemic Effects

<table>
<thead>
<tr>
<th></th>
<th>A1C (%)</th>
<th>FPG (mg/dL)</th>
<th>Hypo With MET/MET + SU (%)</th>
<th>Δ Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide QW¹</td>
<td>−1.50&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−37.8&lt;sup&gt;b&lt;/sup&gt;</td>
<td>~3&lt;sup&gt;c&lt;/sup&gt;/~20&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−2.6&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glargine</td>
<td>−1.30</td>
<td>−50.4</td>
<td>~19/~42</td>
<td>+1.4</td>
</tr>
<tr>
<td>Albiglutide QW²</td>
<td>−0.67</td>
<td>−15.7&lt;sup&gt;c&lt;/sup&gt;</td>
<td>1.1/18.2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>−1.06&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glargine</td>
<td>−0.79</td>
<td>−37.0</td>
<td>21.1/29.6</td>
<td>+1.57</td>
</tr>
<tr>
<td>Dulaglutide QW³</td>
<td>−1.10&lt;sup&gt;f&lt;/sup&gt;</td>
<td>−27.0&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5.6/40.0&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>−1.90&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Glargine</td>
<td>−0.60</td>
<td>−32.0</td>
<td>NR</td>
<td>+1.40</td>
</tr>
</tbody>
</table>

<sup>a</sup><i>P</i> = .017; <sup>b</sup><i>P</i> = .001; <sup>c</sup><i>P</i> < .0001; <sup>d</sup><i>P</i> = .009; <sup>e</sup><i>P</i> value not reported by background therapy; <sup>f</sup><i>P</i> values not reported; <sup>g</sup>Combined rates in clinical trials, not vs glargine.

NR = not reported; QW = once weekly.

**LEAD-5: GLP-1 RA vs Basal Insulin Provides Greater A1C and PPG Effects**

<table>
<thead>
<tr>
<th></th>
<th>A1C (%)</th>
<th>FPG (mg/dL)</th>
<th>PPG (mg/dL)</th>
<th>Hypo (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ Body Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>-1.3</td>
<td>-28.8</td>
<td>-32.4</td>
<td>27.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>Glargine</td>
<td>-1.1</td>
<td>-32.4</td>
<td>-28.8</td>
<td>28.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Placebo</td>
<td>-1.1</td>
<td>-9</td>
<td>-0.54</td>
<td>16.7</td>
<td>-0.4</td>
</tr>
<tr>
<td>&lt;i&gt;P value, liraglutide vs glargine&lt;/i&gt;</td>
<td>&lt;i&gt;.0015&lt;/i&gt;</td>
<td>NS</td>
<td>&lt;i&gt;&lt;.0001&lt;/i&gt;</td>
<td>NS</td>
<td>&lt;i&gt;&lt;.0001&lt;/i&gt;</td>
</tr>
</tbody>
</table>

Note: all patients on background MET + SU (glimepiride).
Study drug doses: liraglutide 1.8 once a day; glargine titrated to mean 24 U/day.

<sup>a</sup>Hypoglycemia rates are higher when GLP-1 RAs are added to sulfonylurea therapy. Lower doses of sulfonylurea may be needed.
NS = not significant.

Consider Adding GLP-1 RAs to Intensify Oral Therapy

- Generally provide greater overall glycemic control than basal insulin
- Long-acting GLP-1 RAs provide superior FPG control vs basal insulin
- Short-acting GLP-1 RAs provide better PPG control than basal insulin or oral agents
- Associated with weight loss, low hypoglycemia risk, and BP reductions
Consider Adding GLP-1 RAs to Intensify Oral Therapy

- Generally provide greater overall glycemic control than basal insulin
- Long-acting GLP-1 RAs provide superior FPG control vs basal insulin
- Short-acting GLP-1 RAs provide better PPG control than basal insulin or oral agents
- Associated with weight loss, low hypoglycemia risk, and BP reductions

**ACTION ITEM:**
Consider adding a GLP-1 RA when patients require additional glycemic control, especially when hypoglycemia is a major concern.
## Common Adverse Events With Incretin-Based Therapies

<table>
<thead>
<tr>
<th>DPP-4 Inhibitors(^1)</th>
<th>GLP-1 RAs(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Upper respiratory tract infections</td>
<td>• Most common: transient nausea (generally resolves by 8 weeks)</td>
</tr>
<tr>
<td>• Nasopharyngitis</td>
<td>• Other GI effects: vomiting, diarrhea, indigestion, upper abdominal discomfort</td>
</tr>
<tr>
<td>• Headache</td>
<td>• GI effects more common with short-acting agents; titrating at initiation minimizes nausea</td>
</tr>
<tr>
<td>• Urinary tract infection</td>
<td>• Headache, dizziness, nervousness</td>
</tr>
<tr>
<td>• GI: nausea (rare)</td>
<td>• Upper respiratory infections</td>
</tr>
</tbody>
</table>

---

Incretin Therapies: Pancreatitis Update

- Meta-analysis of 55 studies with incretins: no evidence to suggest increased risk of pancreatitis\(^1\)
- Food and Drug Administration/European Medicines Agency analysis of postmarketing reports with incretin therapies\(^2\)
  - No evidence of increased rates of pancreatitis or pancreatic cancer (vs placebo) in large clinical trials
  - Causal association between pancreatitis or pancreatic cancer and incretin therapies is inconsistent with current data
- Pancreatitis continues to be considered a risk with incretin therapy and no changes in labeling have been ordered
- **Discontinue medications if signs/symptoms of pancreatitis develop; do not use if pancreatitis confirmed**

---

Incretin Therapies: Other Safety Issues

- All long-acting GLP-1 RAs contraindicated in patients with multiple endocrine neoplasia syndrome type 2 or personal/family history of medullary thyroid cancer
  - Other forms of thyroid cancer are more common but are NOT related to this specific risk
- GLP-1 RAs not recommended for patients with severe GI disease
- Postmarketing reports of hepatic failure with use of alogliptin; postmarketing reports of acute renal failure with sitagliptin

Incretin Therapies: Cardiovascular Effects

• Incretin therapies are thought to have beneficial effects on aspects of CV health
  – Reductions in SBP of 1 to 4 mm Hg\(^1\)
  – GLP-1 RAs produce beneficial changes in lipid profiles; effect of DPP-4 inhibitors not clear but may lower triglycerides\(^1\)
  – May improve endothelial function\(^2\)
• DPP-4 inhibitors do not increase risk of fatal or nonfatal cardiac events\(^3,4\)
  – Possible increase in CHF risk merits further study\(^3,5\)

SGLT2 Inhibitors: Common Adverse Events and Safety

• Most common adverse event is increase in GMI, especially in women (~10%)
  – Respond to standard therapy and are rarely recurrent
• Slight increase compared with placebo in urinary tract infections
• Potential for hypovolemic events, principally orthostatic hypotension, especially in elderly or patients with RI
• Large meta-analysis found no increase in CV events
• Should not be used in patients with active bladder cancer

SGLT2 Inhibitors: Use in Patients With Renal Impairment

- Renal function should be assessed prior to initiating therapy
  - Moderate RI and reduced GFR diminish antihyperglycemic efficacy
- Monitor and reassess renal function annually
- Dapagliflozin: not recommended with eGFR <60 mL/min/1.73 m²
- Canagliflozin
  - 100 mg limited to eGFR ≥45 mL/min/1.73 m²
  - 300 mg for eGFR ≥60 mL/min/1.73 m² and greater efficacy desired
- Empagliflozin: avoid if eGFR ≤45 mL/min/1.73 m²
- All: contraindicated at eGFR <30 mL/min/1.73 m²

Case Study 2: Conclusion

- Hypoglycemia a major concern in Greg’s job and life
- He switches from linagliptin to exenatide twice daily; should address PPG and weight
- Greg to meet regularly with CDE for nutrition counseling and to develop a plan for more regular physical activity
- 3 months later, his A1C is 7.2% and PPG is better controlled (185 mg/dL on SMBG)
- Some initial nausea but Greg is happy with treatment
- Exercising 3 times a week, has altered his diet, and has lost 15 lb
PCE Action Plan

- Intensify interventions for BP, lipid lowering, smoking cessation, and A1C for patients with T2DM to reduce CV and all-cause mortality
- Choose agents with positive or neutral effects on key patient factors, such as weight and hypoglycemic risk
- Implement initial dual therapy for patients who present with higher A1C levels and can benefit from early, aggressive glucose control
- Assess PPG and address if elevated in patients whose A1C remains high despite adequate FPG control
- Consider adding a GLP-1 RA when patients require additional glycemic control, especially when hypoglycemia is a major concern

PCE Promotes Practice Change
Q & A
What are the A1C recommendations for a patient who has 2 factors that suggest the need for a very low A1C and 2 factors that favor a higher A1C goal?
If a side effect appears on an initial 2-drug combination, how does the clinician know which one is causing the side effects?
Q & A

What is the recommendation for using metformin in patients with prediabetes?
What are the ADA guidelines for pediatric patients?
Can basal insulin and a GLP-1 RA be combined?
Q & A

Can the combination of basal insulin and a GLP-1 RA be used in a patient who has CKD stage 3 or 4?
Q & A

Are there concerns about ketoacidosis risk in patients treated with an SGLT2 inhibitor?
Can metformin be initiated as first-line therapy in patients with severe renal problems?
Would liraglutide be an appropriate treatment for a 16-year-old girl who has an A1C of 6% and weighs 260 pounds?
Is there evidence that plant-based diets, whole food diets, refined processed foods, etc, decrease inflammation and promote weight loss?