Combined Targeted Approaches for the Treatment of Type 2 Diabetes: The Role of the Kidney
Faculty Affiliation

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Faculty Disclosures

- Consultant: Merck
- Contracted research: AstraZeneca, GlaxoSmithKline, Merck
Learning Objectives

- Implement current evidence-based guidelines for the detection and diagnosis of prediabetes and diabetes
- Describe the role of the kidney and SGLT2 inhibition-based therapeutic strategies
- Apply evidence-based and individualized management strategies to ensure appropriate and effective management of T2DM

SGLT2, sodium/glucose cotransporter 2; T2DM, type 2 diabetes mellitus.
Affects ~26 million individuals
  - Estimated that ~30% of adults will have diabetes by 2050
7th leading cause of death in 2012
Disease sequelae include:
  - Kidney failure, lower-limb amputations, blindness, neuropathy, cardiovascular disease (CVD), and stroke
Diabetes diagnosis continues to increase because of obesity epidemic

Macrovascular and Microvascular Complications

**Macrovascular**

- **Coronary artery disease**
  - 50% of people with T2DM die of coronary artery disease
- **Peripheral arterial disease**
  - 20-fold increase in lower-limb amputations
- **Cerebrovascular disease**
  - 150%-400% increased risk of stroke

**Microvascular**

- **Neuropathy**
  - Affects up to 50% of patients with diabetes
- **Retinopathy**
  - After 15 years, ~10% of patients with diabetes develop severe visual impairment
- **Nephropathy**
  - 10%-20% of people with T2DM die of kidney failure
CVD in T2DM

- Major cause of morbidity and mortality for individuals with diabetes
- Largest contributor to diabetes-associated direct and indirect costs
- Common T2DM comorbidities (eg, hypertension and dyslipidemia) are clear risk factors for CVD
- Diabetes confers independent risk for CVD

Guideline Recommendations for Screening and Diagnosis
ADA Guidelines for Diabetes Screening

- **Adults**
  - BMI $>25$ kg/m$^2$* with additional risk factors
  - $>45$ years of age without risk factors

- **Children and adolescents**
  - Overweight with ≥2 risk factors

- **Individuals with normal test results should follow up every 3 years**

*BMI $>23$ kg/m$^2$ for Asian Americans.

ADA, American Diabetes Association; BMI, body mass index.
## Diagnostic Criteria

### Prediabetes

<table>
<thead>
<tr>
<th>Test</th>
<th>Prediabetic Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>100-125 mg/dL (IFG)</td>
</tr>
<tr>
<td>2-hour plasma glucose (75-g OGTT)</td>
<td>140-199 mg/dL (IGT)</td>
</tr>
<tr>
<td>A1c</td>
<td>5.7%-6.4%</td>
</tr>
</tbody>
</table>

Note: For all 3 tests, risk is continuous, extending below the lower limit of the range and becoming disproportionately greater at higher ends of the range.

### Overt Diabetes

<table>
<thead>
<tr>
<th>Test</th>
<th>Threshold for Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPG</td>
<td>≥126 mg/dL</td>
</tr>
<tr>
<td>2-hour plasma glucose (75-g OGTT)</td>
<td>≥200 mg/dL</td>
</tr>
<tr>
<td>A1c</td>
<td>≥6.5%</td>
</tr>
</tbody>
</table>

Note: In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing.

FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.  
Guideline Recommendations for Management of T2DM
Glycemic Control
- Decreases onset and progression of T2DM-related microvascular complications
- Impact on cardiovascular complications remains uncertain
  - Modest long-term benefit to achievement of good glycemic control early in disease course
  - Aggressive control in older patients with advanced disease may present some risk without significant benefit

Comprehensive Cardiovascular Risk Reduction
- Reduces CVD risk in T2DM
- Significant benefits of globally addressing multiple risk factors
- Strategies
  - Smoking cessation
  - Blood pressure (BP) control
  - Lipid management (statins)
  - Antiplatelet therapy in some circumstances

### Guideline-recommended Targets for Patients with T2DM

<table>
<thead>
<tr>
<th></th>
<th>ADA</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A1c (%)</strong></td>
<td>&lt;7.0</td>
<td>&lt;6.5</td>
</tr>
<tr>
<td><strong>BP (mm Hg)</strong></td>
<td>140/90</td>
<td>130-135/80</td>
</tr>
<tr>
<td><strong>LDL-C (mg/dL)</strong></td>
<td>&lt;100</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

More or less stringent glycemic goals may be appropriate depending upon duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

AACE, American Association of Clinical Endocrinologists; LDL-C, low-density lipoprotein cholesterol.


**United Kingdom Prospective Diabetes Study Survivor Cohort**

**SU-INS**

- Hazard Ratio 0.4 to 1.4
- P = .52

**MET**

- Hazard Ratio 0.4 to 1.4
- P = .01

**Risk of myocardial infarction was reduced in patients treated with SU-INS (15%) or MET (33%) vs conventional therapy**.

*Conventional therapy was dietary restriction alone.
SU, sulfonylurea, INS, insulin, MET, metformin.

Risk of death from any cause was reduced in patients treated with SU-INS (13%) or MET (27%) vs conventional therapy.

*Conventional therapy was dietary restriction alone.

### Individualization of Care: ADA/EASD Position Statement

#### Approach to management of hyperglycemia:

<table>
<thead>
<tr>
<th>Patient attitude and expected treatment efforts</th>
<th>More stringent</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, nonadherent, poor self-care capacities</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Risks potentially associated with hypoglycemia, other adverse events</th>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<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>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
</tr>
</tbody>
</table>

Patients with T2DM should be provided with education and support that empowers them to self-manage their disease.

Information should emphasize the importance of the following aspects of disease management:

- Nutrition
- Physical activity
- Smoking cessation
- Psychosocial care
- Immunization

Recommendations for Dietary Modifications

- Reduce total daily calorie intake
- Reduce sodium intake: <2300 mg/day; lower for patients with hypertension
- Reduce simple carbohydrates, sugars, and high-fat foods (eliminate trans fats)
  - Limit saturated fat: <7% of calories, <20-30 g/day
  - Limit cholesterol: <200 mg/day
- Increase water-soluble fiber: 10-25 g/day
- Increase unsaturated fat and marine-based omega-3s
- Limit alcohol consumption: <1 drink day for adult women and ≤2 drinks per day for adult men

Recommendations for Physical Activity

- **Children**
  - ≥60 minutes of physical activity each day (Grade B)

- **Adults**
  - ≥150 minutes/week of moderate-intensity aerobic physical activity (50%-70% of maximum heart rate), spread over at least 3 days/week with no more than 2 consecutive days without exercise (Grade A)
  - Reduce sedentary time, particularly by breaking up extended amounts of time (>90 min) spent sitting (Grade B)
  - In the absence of contraindications, resistance training at least twice per week (Grade A)

### Vaccinations for Patients with Diabetes

<table>
<thead>
<tr>
<th>Vaccinations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine vaccinations for children and adults as for the general population</td>
<td></td>
</tr>
<tr>
<td>Annual influenza vaccine to all patients ≥6 months of age</td>
<td></td>
</tr>
<tr>
<td>PPSV23 to all patients ≥2 years of age</td>
<td></td>
</tr>
<tr>
<td>Adults ≥65 years of age not previously vaccinated, PCV13 followed by PPSV23 6-12 months after initial vaccination</td>
<td></td>
</tr>
<tr>
<td>Adults ≥65 years of age previously vaccinated with PPSV23, follow up with PCV13 ≥12 months after initial vaccination</td>
<td></td>
</tr>
<tr>
<td>HBV vaccination to unvaccinated adults 19-59 years of age</td>
<td></td>
</tr>
<tr>
<td>Consider HBV vaccination for unvaccinated adults ≥60 years of age</td>
<td></td>
</tr>
</tbody>
</table>

PPSV23, pneumococcal polysaccharide vaccine 23; PCV13, pneumococcal conjugate vaccine 13; HBV, hepatitis B.

Assessment of patient’s psychological and social situation

Psychosocial screening and follow-up:
- Attitudes about illness
- Expectations for medical management and outcomes
- Affect/mood
- Quality of life
- Financial, social, and emotional resources
- Psychiatric history

Routinely screen for psychosocial problems: depression, diabetes-related distress, anxiety, eating disorders, and cognitive impairment

Patients ≥65 years of age should be screened and treated for depression

Patients with comorbid depression should receive a stepwise collaborative care approach for depression management

Pharmacologic Treatment of T2DM
Hyperglycemia

- Decreased incretin effect
- Increased lipolysis
- Increased glucagon secretion
- Increased HGP
- Neurotransmitter dysfunction
- Decreased glucose uptake
- Increased glucose reabsorption

HGP, hepatic glucose production.
Pharmacologic Targeting of Pathophysiologic Disturbances in T2DM (cont’d)

GLP-1 RAs
DPP-4 inhibitors
TZDs
SUs
Meglitinides

GLP-1 RAs
DPP-4 inhibitors
Bile acid sequestrants
α-glucosidase inhibitors

TZDs

GLP-1 RAs
DPP-4 inhibitors
Amylin analogs

SGLT2 inhibitors

TZDs

MET

Recommendations for Pharmacologic Treatment Approach

- MET as first-line treatment for diagnosed patients
- If glycemic goals are unmet, add-on therapy is recommended
  - TZD
    - Pioglitazone (PIO)
  - Sulfonylurea
  - DPP-4 inhibitor
  - SGLT2 inhibitor
  - GLP-1 RA
  - INS

- Medication should be based upon individual patient characteristics:
  - Effect on glycemic control
  - Body weight
  - Risk of hypoglycemia

- With the wide spectrum of antihyperglycemic agents available, the ideal choice of therapeutic combination is not always clear

Targeting the Kidney for the Treatment of T2DM: SGLT2 Inhibition
Under normal conditions, the kidney is involved in maintaining glucose homeostasis via 3 different mechanisms:

1. Release of glucose into circulation via gluconeogenesis
2. Uptake of glucose to meet its own energy needs
3. Reabsorption of glucose from the glomerular filtrate
Glucose Reabsorption in the Kidney by SGLT2

GLUT, glucose transporter; ATP, adenosine triphosphate; ATPase, adenosine triphosphatase; S1, segment 1; S2, segment 2; S3, segment 3.

Renal Mechanisms Regulating Glucose Homeostasis Are Altered in T2DM

- Increased:
  - Threshold for glucosuria
  - Maximum glucose reabsorption
  - Renal glucose production
  - Glucose reabsorption

Therapeutic Benefits Associated with SGLT2 Inhibition

- Reduces A1c, FPG, and PPG by an INS-independent mechanism
  - Improves INS sensitivity and INS secretion (ie, correction of glucotoxicity)
- Weight loss due to renal glucose
- Reduces BP

PPG, postprandial glucose.

Case Study:
65-year-old Female
Case Study #2: 65-year-old Female
Current Exam

- Physical exam (BP higher vs last visit):
  - Height: 5’ 5”
  - Weight: 195 lb
  - BMI: 31
  - BP: 150/81

- Current medications:
  - MET extended release 2000 mg/day with evening meal

- Dietary review:
  - Consumes mostly high-fat and high-carbohydrate diet

- Activity review:
  - Limited physical activity due to arthritis of the knees
### Case Study #2: 65-year-old Female

#### Current Laboratory Results

#### Diabetes Panel

<table>
<thead>
<tr>
<th></th>
<th>Today</th>
<th>3 Months Ago</th>
<th>6 Months Ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c</td>
<td>8.2%</td>
<td>7.8%</td>
<td>7.6%</td>
</tr>
<tr>
<td>FPG</td>
<td>155 mg/dL</td>
<td>142 mg/dL</td>
<td>138 mg/dL</td>
</tr>
</tbody>
</table>

#### Lipid Panel

<table>
<thead>
<tr>
<th></th>
<th>Today</th>
<th>3 Months Ago</th>
<th>6 Months Ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>240 mg/dL</td>
<td>245 mg/dL</td>
<td>250 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>130 mg/dL</td>
<td>144 mg/dL</td>
<td>150 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>39 mg/dL</td>
<td>37 mg/dL</td>
<td>36 mg/dL</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>205 mg/dL</td>
<td>208 mg/dL</td>
<td>210 mg/dL</td>
</tr>
</tbody>
</table>

HDL-C, high-density lipoprotein cholesterol.
What are your primary goals for treatment of this patient?

What adjustments would you make to the patient’s treatment plan?
  - Increase MET dose to maximum daily dose?
  - Add a second medication? If so, what medication would you recommend?

How can you address the need to make lifestyle modifications?
SGLT2 Inhibitors Currently Approved for T2DM Treatment
**Currently Approved SGLT2 Inhibitors**

<table>
<thead>
<tr>
<th>SGLT2 Inhibitor</th>
<th>Initial Dose</th>
<th>Max Dose*</th>
<th>Renal Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canagliflozin (CANA)</td>
<td>100 mg qd</td>
<td>300 mg qd</td>
<td>• eGFR ≥45–&lt;60 mL/min/1.73 m²: 100 mg CANA qd</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR &lt;45 mL/min/1.73 m²: Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR &lt;30 mL/min/1.73 m²: Contraindicated</td>
</tr>
<tr>
<td>Dapagliflozin (DAPA)</td>
<td>5 mg qd</td>
<td>10 mg qd</td>
<td>• eGFR &lt;60 mL/min/1.73 m²: Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR &lt;30 mL/min/1.73 m²: Contraindicated</td>
</tr>
<tr>
<td>Empagliflozin (EMPA)</td>
<td>10 mg qd</td>
<td>25 mg qd</td>
<td>• eGFR &lt;45 mL/min/1.73 m²: Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR &lt;30 mL/min/1.73 m²: Contraindicated</td>
</tr>
</tbody>
</table>

*May be prescribed for patients requiring better glycemic control if agent is well tolerated.
qd, once per day; eGFR, estimated glomerular filtration rate.
Combination Therapy with SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>SGLT2 Inhibitor</th>
<th>Previously Studied Therapeutic Combinations</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dual Therapy</td>
<td>Triple Therapy</td>
</tr>
<tr>
<td>CANA</td>
<td>MET Sulfonylurea</td>
<td>MET and sulfonylurea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MET and PIO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INS ± other AHAs</td>
</tr>
<tr>
<td>DAPA</td>
<td>MET Sulfonylurea</td>
<td>MET and sulfonylurea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MET and DPP-4 inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>INS ± other AHAs</td>
</tr>
<tr>
<td>EMPA</td>
<td>MET PIO Sulfonylurea</td>
<td>MET and sulfonylurea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PIO ± MET</td>
</tr>
</tbody>
</table>

AHAs, antihyperglycemic agents.  
Wilding JP. *Metabolism.* 2014;63(10):1228-1237.
## Currently Approved Fixed-dose SGLT2 Inhibitor Combination Therapies

<table>
<thead>
<tr>
<th>Combination</th>
<th>Initial Dose</th>
<th>Maximum Daily Dose</th>
<th>Renal Dose Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CANA/ MET</td>
<td>50/500–150/500 mg bid with meals</td>
<td>300/2000 mg</td>
<td>• eGFR $\geq 45$–$&lt;60$ mL/min/1.73 m²: Adjust to 50 mg CANA bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR $&lt;45$ mL/min/1.73 m²: Contraindicated</td>
</tr>
<tr>
<td>DAPA/ MET</td>
<td>5/500–10/1000 mg qd in the morning</td>
<td>10/2000 mg</td>
<td>• eGFR $&lt;60$ mL/min/1.73 m²: Contraindicated</td>
</tr>
<tr>
<td>EMPA/ linagliptin</td>
<td>10/5 mg qd in the morning, with or without food</td>
<td>25/5 mg</td>
<td>• eGFR $&lt;45$ mL/min/1.73 m²: Not recommended</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• eGFR $&lt;30$ mL/min/1.73 m²: Contraindicated</td>
</tr>
</tbody>
</table>

Efficacy of SGLT2 Inhibition
Overview of SGLT2 Inhibitor Glycemic Efficacy: Changes in Baseline A1c Level

*Doses evaluated in studies cited: CANA=100 or 300 mg, DAPA=5 or 10 mg, EMPA=10 or 25 mg.

MONO, monotherapy; GLIM, glimepiride; SITA, sitagliptin; PBO, placebo.