Effective and Timely Management of Patients with T2DM: A Case-based Approach

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Educational Objectives

- Assess the current understanding of the pathophysiology of T2DM and the targets of various anti-hyperglycemic therapies
- Target the pathophysiological disturbances in patients with T2DM using mono- or combination therapies based on their efficacy and safety
- Manage patients with T2DM optimally in accordance with the guideline recommendations

Current Understanding of the Pathophysiology of T2DM and the Targets of Available Anti-hyperglycemic Agents

The Pathophysiology of Type 2 Diabetes Includes Islet Cell Dysfunction and Insulin Resistance

Insulin and Glucagon Dynamics in Response to Meals Are Abnormal in Type 2 Diabetes

Multiple Metabolic Abnormalities Contribute to Hyperglycemia in T2DM
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Incretins

- Gut-derived hormones, secreted in response to nutrients, that potentiate insulin secretion and suppress glucagon secretion in a glucose-dependent fashion
- Many other tissue effects
- Two predominant incretins
  - Glucagon-like peptide-1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP)
- Rapidly inactivated by dipeptidyl peptidase-4
- Incretin effect is impaired in type 2 diabetes

Ingestion of food
Pancreas
Glucagon
and insulin from beta cells
GLP-1 and GIP
GI tract
Active GLP-1 & GIP
DPP-4 enzyme
Inactive GLP-1
Inactive GIP

DPP-4 Inhibitors and GLP-1 RAs: Summary of Efficacy and Other Considerations

<table>
<thead>
<tr>
<th>GLP-1 RAs</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of administration</td>
<td>Injectable</td>
</tr>
<tr>
<td>Efficacy: HbA1C reduction</td>
<td>0.5%-2.0%</td>
</tr>
<tr>
<td>Effect on weight</td>
<td>Potential for loss</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>None, unless used with secretagogue or insulin</td>
</tr>
<tr>
<td>Renal considerations</td>
<td>None</td>
</tr>
<tr>
<td>CV risk</td>
<td>CV 7, rare instance of Stevens-Johnson, no proven pancreatitis risk seen in large databases</td>
</tr>
</tbody>
</table>

Reduced Incretin Effect in Type 2 Diabetes Patients

Control Subjects
Type 2 Diabetes Patients

Incretin Therapies to Treat T2DM

Add GLP-1 analogues with longer half-life: Injectables
- Lisatglutide
- Lixisenatide (Albiglutide)
- Dulaglutide
- Exenatide
- Exenatide QW

Block DPP-4, the enzyme that degrades GLP-1:
- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

Glucose Control by the Kidney

- Gluconeogenesis
  - Proximal tubule
  - Renal contribution more substantial than previously believed
  - ~20% of post-absorptive total-body glucose release
  - ~40% of gluconeogenesis
- Reabsorption of filtered glucose
  - >99% of glucose in glomerular filtrate is reabsorbed in the proximal renal tubule
  - Sodium-coupled glucose co-transporters (SGLTs) transport glucose against gradient from lumen into epithelial cells
  - Facilitated glucose transporters (GLUTs) transport glucose down gradient to plasma

References:
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### SGLT-2 Inhibitors: FDA Approved or in Clinical Development

<table>
<thead>
<tr>
<th>Compounds in development</th>
<th>Development status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>FDA APPROVED</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>FDA APPROVED</td>
</tr>
<tr>
<td>Empagliflozin</td>
<td>FDA APPROVED</td>
</tr>
<tr>
<td>Ipragliflozin</td>
<td>US – Phase III clinical trials Approved for use in Japan</td>
</tr>
<tr>
<td>Solagliflozin (LX4211)</td>
<td>Phase III clinical trials</td>
</tr>
</tbody>
</table>

### SGLT-2 Inhibitors for Treatment of Type 2 Diabetes

**SGLT-2 inhibitors**
block reabsorption of filtered glucose in kidneys
leads to glycosuria, improved glycemic control

**Benefits**
- Insulin-independent action
- Calorie loss – possible weight loss
- Low hypoglycemia
- Complement action of other anti-diabetic agents
- Can be used regardless of diabetes duration

**Side-effects**
- Recurrent UTIs
- Genital fungal infection
- Decreased blood pressure
- Worsening of renal function
- Increased hematocrit*
- Increased LDL-C*

*S specific considerations for individuals with existing renal insufficiency, the elderly, and those receiving loop diuretics.

### Cases in Type 2 Diabetes Management

#### Case 1: Reducing Hypoglycemic Risk

- Sophie is 87 years old and has had T2DM for 15 years
- Managed with glipizide 10mg BID since then with fairly good HbA1C levels
- Current concerns
  - Recent episodes of confusion/dizziness
  - Occasionally forgets medication and meals
  - Home glucose monitoring shows multiple hypoglycemic episodes throughout day; ? wrong dose of medication, ? missing meals

#### Case 1: Sophie

- **Physical examination**
  - Frail appearance (BMI: 19.0 kg/m²)
  - Rales at both lung bases posteriorly
  - Bilateral 1+ pitting pedal edema
- **Laboratory evaluation**
  - Random glucose: 68 mg/dL; HgbA1C: 6.1%
  - Scr 1.7; eGFR: 28 mL/min/1.73 m²

#### ADA/EASD Position Statement


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### Expected HbA1C Reduction of Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Expected HbA1C Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>1%-2%</td>
</tr>
<tr>
<td>SU (2nd Generation)</td>
<td>1%-2%</td>
</tr>
<tr>
<td>TZD</td>
<td>1%-1.5%</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>0.5%-1.5%</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>0.5%-1%</td>
</tr>
<tr>
<td>SGLT-2 inhibitor</td>
<td>0.5%-1%</td>
</tr>
</tbody>
</table>

### Case 1: Sophie

**What Should You Consider?**
- Her hypoglycemia risk
- Risk factors?
- Drug classes to avoid?
- Her renal insufficiency
- Drug classes to avoid?
- Required dose adjustments?
- Her preferences regarding route of administration

### The Association Between Medication-related Hypoglycemia and Vascular Risk

![Graph showing the association between medication-related hypoglycemia and vascular risk.]

### Sulfonylureas in Patients with Renal Impairment

- SUs are a leading cause of ER evaluations for adverse drug reactions
- Some SUs have prolonged half-life (glyburide, glimepiride)
- Some SUs have active metabolites that are renally excreted
- Safest may be glipizide (shortest acting and inactive metabolites)
- Consider glinides (e.g. repaglinide, nateglinide) – rapid-acting secretagogues
- Dose any secretagogue cautiously in CKD due to the fact that insulin itself is renally cleared

### Diabetes and Renal Impairment

- **Metformin:** contraindicated when eGFR <30, do not start if eGFR <30-45
- **SU:** dose reduction or replacement for renal insufficiency; do not use glyburide
- **Insulin:** dose reduction for renal insufficiency
- **GLP-1 receptor agonists**
  - Exenatide: do not use if eGFR <30
  - Others: use with caution
- **DPP-4 inhibitors**
  - Sitagliptin, saxagliptin, alogliptin require dose adjustment
  - Linagliptin: no dose adjustment
- **SGLT-2 inhibitors**
  - Canagliflozin: lower dose for eGFR 45-60; discontinuation not indicated if eGFR <45, discontinued <30
  - Dapagliflozin: do not initiate if eGFR <60; discontinuation if persistently <60; contraindicated in severe renal impairment, ESRD, dialysis
  - Empagliflozin: do not initiate if eGFR <45; discontinuation if persistently <45; contraindicated in severe renal impairment, ESRD, dialysis

### What about Metformin?

**FDA Changes Labeling for Metformin Use in T2DM Patients with Impaired Renal Function**

- In T2DM patients with impaired renal function, use of metformin previously contraindicated
- 2014 systemic review assessing metformin-associated lactic acidosis risk in T2DM with impaired renal function: no increased rate of lactic acidosis, along with macrovascular outcome benefit
- FDA: can use metformin safely in patients with mild renal impairment and in some with moderate renal impairment
- FDA new labeling changes
  - Obtain eGFR before starting metformin; then annually; assess more frequently if risk for renal impairment (eg, elderly)
  - Starting metformin in patients with eGFR of <60 mL/min/1.73 m²
  - Assess benefit and risk if eGFR decreases to <45 mL/min/1.73 m²; discontinue if eGFR decreases to <30 mL/min/1.73 m²

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*Images and data from various sources including Mayo Foundation for Medical Education and Research and Physicians' Desk Reference.*
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Profiles of Antidiabetic Medications

Of the recommended options for this patient, the DPP-4 inhibitor class is associated with the fewest cautions.

Summary: Reducing Hypoglycemic Risk

- Factors to consider when selecting a therapy:
  - Hypoglycemia
  - Risk factors: older age, concurrent medications (SUs, insulin), comorbidities
  - Drug classes to avoid: SUs, insulin
  - Comorbidity: Renal Insufficiency
    - Metformin contraindicated
    - SGLT-2 inhibitors not effective
    - DPP-4 inhibitors: acceptable, require dose adjustment (linagliptin exception)
    - GLP-1-RAs use cautiously
  - Route of administration: injectable vs oral

Sitagliptin vs Glipizide Added on to Metformin

<table>
<thead>
<tr>
<th></th>
<th>Baseline ± sd</th>
<th>Week 52 ± sd</th>
<th>Change in A1C from Baseline</th>
<th>Hypoglycemia</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide 10mg twice daily (n=584)</td>
<td>7.52 ± 0.85</td>
<td>6.86 ± 0.69</td>
<td>-0.67%</td>
<td>32% (857 events)</td>
<td>+1.1 kg*</td>
</tr>
<tr>
<td>Sitagliptin 100mg once daily (n=588)</td>
<td>7.48 ± 0.76</td>
<td>6.84 ± 0.68</td>
<td>-0.67%</td>
<td>5% (50 events)**</td>
<td>-1.5 kg</td>
</tr>
</tbody>
</table>

*P<0.001 between treatment

Sitagliptin vs Glipizide

Case 2: Reducing Cardiovascular Risk

Manuel is a 56-year-old man with newly diagnosed T2DM

- Physical examination
  - Patient is overweight (BMI: 31 kg/m²)
- Laboratory evaluation
  - Blood pressure: 153/87 mm Hg
  - 10-year history of uncontrolled hypertension; patient is not compliant with prescribed antihypertensive medication
  - FPG: 145 mg/dL
  - HbA1C: 8.9%
  - eGFR: 60

Case 2: Manuel – Treatment

- Patient is placed on metformin (500 mg BID) and a TZD

Case 2: Manuel – cont’d

- Patient experiences an MI
- Laboratory evaluation immediately following MI:
  - Blood pressure: 155/85 mm Hg
  - Total cholesterol: 246 mg/dL
  - HbA1C: 8.5%
  - Decline in renal function to 52
  - Also showing signs of CHF: chest pain, dyspnea, fatigue, persistent cough with phlegm production, ankle edema

- What is the next step regarding treatment for T2DM based on CV event? Would you stop the metformin and/or the TZD?
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Kosiborod M, et al.
Investigational multi-country observational study using real-world clinical practice

- Results showed dapagliflozin was associated with a lower risk of cardiovascular events, compared with placebo in patients with T2DM and high cardiovascular risk randomized to dapagliflozin vs new users of other glucose-lowering drugs.
- Rate of primary CV outcome (death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) lower with canagliflozin compared with placebo (26.9 vs 31.5 participants per 1,000 patient-years; P=0.011 for noninferiority; P=0.02 for superiority).
- Renal events (sustained 40% reduction in eGFR, need for renal-replacement therapy, or death from renal causes) occurred less frequently in patients receiving canagliflozin compared with placebo.

EMPA-REG Study
- 7,034 T2DM patients at high CVD risk randomized to empagliflozin or placebo.
- Empagliflozin reduced primary major adverse cardiac event endpoint (CV death, nonfatal myocardial infarction, nonfatal stroke) by 14%.
- 38% reduction in CV mortality.
- 35% reduction in hospitalization for heart failure.
- Multiple metabolic benefits: decreases in HbA1C, weight, and BP; increase in HDL.
- Also associated with slower progression of renal disease.

CVD-REAL: Data from Real-World Clinical Practice
- Investigational multi-country observational study using real-world clinical practice records from six countries (United States, United Kingdom, Germany, Sweden, Norway, and Denmark).
- Rate of CV death and hospitalization for heart failure in 309,056 patients newly initiated on any SGLT-2 inhibitor (empagliflozin, canagliflozin, dapagliflozin) vs other glucose-lowering drugs was compared to determine if benefit was seen in real-world practice and across the SGLT-2 inhibitor class.
- Results showed that compared with other agents for T2DM, the SGLT-2 inhibitor class significantly reduced the rate of hospitalization for heart failure, along with significant reductions in the rate of death from any cause.
- These results suggest that the benefits observed with empagliflozin in EMPA-REG may be a class effect applicable to a broad population of patients with T2DM in real-world practice.

CVD-REAL Nordic: Data from Real-World Clinical Practice
- This study used real-world data from clinical practice in Denmark, Norway, and Sweden to compare the incidence of CV mortality and mortality in patients (n=22,830) with T2DM at high CV risk who were new users of SGLT-2 inhibitors vs new users of other glucose-lowering agents.
- Results showed SGLT-2 inhibitor use was associated with reduced CV and CV mortality, as well as a decreased risk of severe hypoglycemia, compared with use of other glucose-lowering drugs.
- CVD-REAL Nordic trial also evaluated new users of dapagliflozin with new users of DPP-4 inhibitors in regard to the risk of major adverse cardiovascular events, hospitalization for heart failure, atrial fibrillation, and severe hypoglycemia.
- Results showed dapagliflozin was associated with a lower risk of cardiovascular events, as well as all-cause mortality, compared with DPP-4 inhibitors in a real-world clinical setting.

Large CV Outcomes Trials in Diabetes

Table: CV Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Class</th>
<th>CV ‘Advantages’</th>
<th>CV ‘Disadvantages’</th>
</tr>
</thead>
<tbody>
<tr>
<td>TZDs</td>
<td>↑ HbA1C, ↓ LDL, ↓ CRP, ↓ insulin, ↓ CV events (all-cause)</td>
<td>↑ HF, ↑ LDL, ↑ CV events (non-renal)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>↓ weight, ↓ BP, ↓ TG, ↓ CRP, ↑ direct cardiac effect</td>
<td>↑ HDL</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↑ direct cardiac effect (risk GLP-1)</td>
<td>↑ HF</td>
</tr>
</tbody>
</table>

Table: CVD-REAL: Data from Real-World Clinical Practice

- CV death, nonfatal myocardial infarction, nonfatal stroke
- Reductions in the rate of death from any cause
- Lower risk of hospitalization for heart failure
- Multiple metabolic benefits: decreases in HbA1C, weight, and BP; increase in HDL
- Also associated with slower progression of renal disease

Table: CVD-REAL Nordic: Data from Real-World Clinical Practice

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- Reductions in the rate of death from any cause
- Lower risk of hospitalization for heart failure
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- Also associated with slower progression of renal disease
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Other Considerations with SGLT-2 Inhibitors

- Genital infections
  - Patients treated with antifungal or antibiotic agents
- Fracture
  - Use of SGLT-2 inhibitors in moderate renal impairment leads to increased fractures
- Bladder cancer
  - Only seen in dapagliflozin study, groups had higher than expected risk of bladder cancer; possibly bi:GU SE led to increased cancer detection
- Serious urinary tract infections
  - FDA warning due to reported cases of urosepsis
- Ketoacidosis
  - Insulin-deficient patients at higher risk
  - 12/2015: FDA recommends stopping the drug and immediately seeking treatment for symptoms of ketoacidosis
- Acute kidney injury
  - Recent label change; 101 cases reported
- Leg/foot amputations
  - FDA warning: canagliflozin associated with increased leg/foot amputations

Liraglutide Decreases CVD in High-risk Patients with T2DM in the LEADER Trial

- 9,340 adults with T2DM at high risk of major CVD randomized to liraglutide or placebo
- Results: liraglutide reduced primary endpoint by 13% (composite outcome of first occurrence of CV death, non-fatal MI, or non-fatal stroke)
  - 15% reduction in all-cause death
  - 22% reduction in CV death
  - 14% relative risk reduction in MI
  - 14% relative risk reduction in stroke
  - 22% reduction in renal events
- Metabolic benefits: decreases in HbA1C, weight, BP

SUSTAIN 6 Results

- 3,297 patients with T2DM received either once-weekly semaglutide (0.5 mg or 1.0 mg) or placebo
  - 83% had established CVD, CKD, or both at baseline
  - Compared with placebo, semaglutide reduced rates of CV death, nonfatal MI, or nonfatal stroke
  - 39% (significant) decrease in the rate of nonfatal stroke
  - 26% (nonsignificant) decrease in nonfatal myocardial infarction
  - Neutral outcome (2% decrease) in CV death
- Semaglutide, a once-weekly GLP-1 RA, is currently in clinical trials for T2DM management; new drug application submitted to FDA in December 2016

Other Considerations with Incretin Agents

- No added hypoglycemia unless used with secretagogue or insulin
- Pancreatitis:
  - FDA: available data do not confirm causal relationship between GLP-1 therapies and increased risk for pancreatic side effects
  - Conclusion of meta-analysis of case-controlled and retrospective cohort studies (1,324,515 patients): no suggestion that acute pancreatitis is associated
  - C-cell hyperplasia and medullary cancer in rodents
  - Side effect with GLP-1 RA: nausea/vomiting

Deciding about First Injectable Drug for Patients Not Controlled by Oral Agents

- DURATION-3 trial of once-weekly exenatide vs insulin glargine as first injectable therapy

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Basalizing</th>
<th>Long-acting</th>
<th>Very Long-acting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
<td>Exenatide</td>
<td>Liraglutide</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-5 hours</td>
<td>12-14 hours</td>
<td>&gt;1 week</td>
</tr>
<tr>
<td>Frequency of administration</td>
<td>Twice daily</td>
<td>Once daily</td>
<td>Once weekly</td>
</tr>
<tr>
<td>HbA1C reduction</td>
<td>0.7%-1.7%</td>
<td>0.8%-1.8%</td>
<td>0.8%-0.9%</td>
</tr>
<tr>
<td>SBP reduction</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Glucose sensitivity</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>Some deceleration</td>
<td>Some deceleration</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1-5 kg</td>
<td>2-4 kg</td>
<td>0.6-2.5 kg</td>
</tr>
</tbody>
</table>

Deciding about First Injectable Drug for Patients Not Controlled by Oral Agents

- DURATION-3 trial of once-weekly exenatide vs insulin glargine as first injectable therapy

<table>
<thead>
<tr>
<th>3-year endpoint</th>
<th>Exenatide (n=233)</th>
<th>Insulin glargine (n=223)</th>
<th>P*Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in A1C</td>
<td>-1.01%</td>
<td>-0.81%</td>
<td>0.03</td>
</tr>
<tr>
<td>Change in body weight</td>
<td>-5.5 lbs</td>
<td>+4.4 lbs</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypoglycemia (exposure-adjusted events)</td>
<td>0.3 events per patient-year</td>
<td>0.9 events per patient-year</td>
<td>NR</td>
</tr>
</tbody>
</table>

*P (significance level): NS = not reported.
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### Case 2: Manuel – cont’d
- Dose of metformin increased to 1000 BID
- Patient placed on liraglutide 0.6 mg per day for first 2 weeks, then increased to 1.2 mg
- Patient started on new antihypertensive medication and agent for dyslipidemia by cardiologist
- Laboratory values at 3 months:
  - Blood pressure: 135/79 mm Hg
  - Total cholesterol: 210 mg/dL
  - HbA1C: 7.9%
  - Weight loss: 18 lb

What does the endocrinologist expect of the PCP regarding the ongoing management of this patient?

### Summary: Reducing Cardiovascular Risk
Anti-hyperglycemic agents have variable effects on CV outcomes in T2DM
- **SGLT-2 inhibitors**
  - Associated with weight loss, BP reduction
  - Empaglifozin: favorable CV outcomes
- **DPP-4 inhibitors**
  - Neutral CV effects
- **GLP-1 RAs**
  - Effective lowering of A1C (except albiglutide)
  - Weight loss, BP reductions, small improvements in lipids
  - Liraglutide demonstrated CV risk reduction

### Summary
- We know from DCCT and UKPDS that sustained intensification of therapy is difficult
- Embrace ADA recommendations to reduce complications
- Don’t be afraid to consider new combinations and treatment options
- We hold the key to our patient’s success!

Thank you!