Type 2 Diabetes Management:  
Case 1: Reducing Hypoglycemic Risk  
Case 2: Reducing Cardiovascular Risk

Case 1: Sophie
- Sophie is 87 years old and has had T2DM for 15 years
- Managed with glyburide 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 – cont’d
- 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

Expected HbA1C Reduction of Antihyperglycemic Agents

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Expected HbA1C Reduction</th>
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<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>
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<td>SGLT-2 inhibitor</td>
<td>0.5%-1%</td>
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ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes; HbA1C, hemoglobin A1C; SU, sulfonylurea; TZD, thiazolidinedione; GLP, glucagon-like peptide; DPP, dipeptidyl peptidase; SGLT, sodium-glucose cotransporter.
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

Case 2: Reducing Cardiovascular Risk

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 (glyburide)
  - Safest may be glipizide (shortest acting and inactive metabolites)
  - Consider glinides (eg, repaglinide, nateglinide) – rapid-acting secretagogues
  - Dose any secretagogue cautiously in CKD due to the fact that insulin itself is renally cleared

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 systematic review assessing metformin-associated lactic acidosis risk in T2DM with impaired renal function: no increased rate of lactic acidosis, along with macromolecular 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 30 mL/min/1.73 m² is not recommended
  - Contraindicated in patients with eGFR of <30 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

Diabetes and Renal Impairment

- Metformin: contraindicated when eGFR <30, do not start if 30-45
- Dapagliflozin, do not initiate if eGFR <45; discontinue if persistently <45
- Dapagliflozin: do not initiate if eGFR <60; discontinue if persistently <45
- Empagliflozin: do not initiate if eGFR <45; discontinue if persistently <45
- Canagliflozin: lower dose for eGFR 45-60; discontinue if eGFR <45; contraindicated <30
- Sitagliptin, saxagliptin, alogliptin require dose adjustment
- Linagliptin: no dose adjustment
- GLP-1 receptor agonists
  - Exemable: do not use if eGFR <30
  - Others: use with caution
- SGLT-2 inhibitors
  - Empagliflozin: do not initiate if eGFR <45; discontinue if persistently <45
  - Canagliflozin: lower dose for eGFR 45-60; discontinue if persistently <45
  - Dapagliflozin: do not initiate if eGFR <60; discontinue if persistently <45
  - Empagliflozin: do not initiate if eGFR <45; discontinue if persistently <45
  - Sulfonylureas
  - Insulin: dose reduction for renal insufficiency
Type 2 Diabetes Management:
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Profiles of Antidiabetic Medications

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

Comparison of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>Saxagliptin</th>
<th>Linagliptin</th>
<th>Alogliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage</td>
<td>25, 50, 100 mg once daily</td>
<td>25, 50 mg once daily</td>
<td>5 mg once daily</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>12.4 h</td>
<td>2.2 to 3.8 h</td>
<td>&gt;113 h</td>
<td>21 h</td>
</tr>
<tr>
<td>24-h DPP-4 inhibition</td>
<td>&gt;90%</td>
<td>5 mg = 52%</td>
<td>&gt;90%</td>
<td>&gt;80%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Kidney poorly unchanged</td>
<td>Liver and kidney active metabolite</td>
<td>Liver =&lt;4% renal</td>
<td>Renal</td>
</tr>
<tr>
<td>Dose adjustments for renal impairment</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
</tr>
<tr>
<td>Drug interaction potential</td>
<td>Low</td>
<td>Strong CYP3A4 inhibitors</td>
<td>Strong CYP3A4 inhibitors</td>
<td>Low</td>
</tr>
</tbody>
</table>

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=398)</td>
<td>7.52 ± 0.85</td>
<td>6.86 ± 0.69</td>
<td>-0.67%</td>
<td>32% (55 events)</td>
<td>+1.1 kg*</td>
</tr>
<tr>
<td>Sitagliptin 100mg once daily (n=588)</td>
<td>7.48 ± 0.70</td>
<td>6.84 ± 0.65</td>
<td>-0.67%</td>
<td>7% (50 events)*</td>
<td>-1.5 kg</td>
</tr>
</tbody>
</table>

*P<0.001 between treatments


Summary

- 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

Case 2: Manuel

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: Reducing Cardiovascular Risk
Type 2 Diabetes Management:
Case 1: Reducing Hypoglycemic Risk
Case 2: Reducing Cardiovascular Risk

ADA/EASD Position Statement

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 S2
- Also showing signs of CHF: chest pain, dyspnea, fatigue, persistent cough with plethrm 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?

T2DM Agents:
CV Advantages and Disadvantages

<table>
<thead>
<tr>
<th>Class</th>
<th>CV 'Advantages'</th>
<th>CV 'Disadvantages'</th>
</tr>
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<tbody>
<tr>
<td>SUs</td>
<td></td>
<td>↑ CV events ischemic preconditioning</td>
</tr>
<tr>
<td>Biguanides</td>
<td>↓ LDL, ↓ CRP, ↓ insulin</td>
<td></td>
</tr>
<tr>
<td>TZDs</td>
<td>↑ HDL, ↓ TG, ↓ insulin, ↓ CRP, ↓ CVD events (pio)</td>
<td>↑ HF, ↑ LDL, ↑TVD events (rosi)</td>
</tr>
<tr>
<td>GLP-1 RAs</td>
<td>↓ weight, ↓ BP, ↓ TG, ↓ CRP, ↓ direct cardiac effect</td>
<td>↑ HF</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↓ direct cardiac effect (via GLP-1)</td>
<td>↑ HF</td>
</tr>
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Large CV Outcomes Trials in Diabetes

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

Other Considerations with SGLT-2 Inhibitors

- Patients treated with antifungal or antibiotic agents
- Genital infections
- Fracture
- Deceleration
- Reduction
- DURATION
- Short
- +4.4 lbs
- Reduction
- Strong
- Once daily
- NR
- No added hypoglycemia unless used with secretagogue or insulin
- Acute kidney injury
- Reversal of change: 101 cases reported
- Leg/foot amputations
- Risk increased, liraglutide associated with increased leg/foot amputations

Short-, Long-, and Very Long-acting GLP-1 RAs

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<th>Short-acting</th>
<th>Long-acting</th>
<th>Very Long-acting</th>
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<tr>
<td>Compounds</td>
<td>Exenatide</td>
<td>Liraglutide</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td>Half-life</td>
<td>2 hours</td>
<td>57 hours</td>
<td>~1 week</td>
</tr>
<tr>
<td>Fasting</td>
<td>1.7%</td>
<td>1.8%</td>
<td>0.9%</td>
</tr>
<tr>
<td>BP hyperglycemia</td>
<td>Strong</td>
<td>Strong</td>
<td>Strong</td>
</tr>
<tr>
<td>Gluagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.5 kg</td>
<td>2.5 kg</td>
<td>5 kg</td>
</tr>
<tr>
<td>Body weight</td>
<td>0.3%</td>
<td>0.7%</td>
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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

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

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<th>Insulin glargine (n=223)</th>
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<td>Change in A1C</td>
<td>-0.1%</td>
<td>-0.81%</td>
<td>0.03</td>
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<td>Change in body weight</td>
<td>-5.5 lbs</td>
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<td>Hypoglycemia (episodes-adjusted events)</td>
<td>0.3 events per patient-year</td>
<td>0.9 events per patient-year</td>
<td>NR</td>
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Is insulin the best choice for this overweight patient, with CV history and increased hypoglycemia risk?
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

Antihyperglycemic agents have variable effects on CV outcomes in T2DM

- SGLT-2 inhibitors
  - Associated with weight loss, BP reduction
  - Empagliflozin: 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