Type 2 Diabetes Pharmacotherapy

The Case Studies

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Brief Pathophysiology Review
Pediatric Patient with Type 2 Diabetes

- 16 years of age (identical twin)
- Positive family history of diabetes in mom
- ADHD on Concerta 54 mg, Ritalin 10 mg
- Birth Control for heavy flow, but not irregularity
- BMI: 44.8
- A1c: 7.4%

Medication consideration

- FDA approved for kids
  - Metformin: max dosing 2000 mg
  - Insulin: Lantus, Basaglar, Tresiba, Humalog, Novolog, Apidra
- And most recently approved (6/17/19) - liraglutide (Victoza)
  - potential restoration of Beta-cells
Case 1

- 26 year old Hispanic Male
- Works as a school guidance counselor
- Sees his doctor once a year
- Latest Vitals:
  - Fasting Glucose 98 mg/dL, A1c 5.7%
  - Total Cholesterol 165 mg/dL, HDL 39 mg/dL, Triglycerides 116 mg/dL, BP 157/83, BMI 26.9 (5'8", 177lbs)
Case 2 Female of childbearing age/gestational

- 36 years of age, Filipino, G3P2
  - gestational dx with 1st
    - (baby birth weight: 8lbs, 10 oz)
    - diet & exercise management (8 years ago)
  - no gestational dx with 2nd
    - (baby birth weight: 10lbs, 6oz) (4 years ago)
- Works for the government in a sedentary job
- Latest Vitals:
  - Fasting Glucose: 112 mg/dL, A1c 5.9% (up 0.2% in 6 months w/ lifestyle changes & weight loss)
  - Total Cholesterol: 183 mg/dL, HDL 44 mg/dL, Triglycerides 107 mg/dL, non-HDL 117
  - BP: 122/78
  - BMI 25.7 (5’4.5”, 152 lbs)
- Risk Factors
  - Gestational (again)
    - Previous pregnancy with GDM
    - Currently with Prediabetes
    - Filipino
    - Overweight
  - Type 2 diabetes
    - Previous history of GDM
    - Prediabetes
    - Filipino
    - Overweight
    - Potentially family history/genetics

Case 3

48 year old African American Male
- Office manager
- Married with 2 teenage sons
- PMH: type 2 diabetes for 3 years, HTN for 5 years, dyslipidemia for 5 years, ED, osteoarthritis, obesity.
- Quit smoking 3 years ago when diagnosed with diabetes
Case 3 (continued)

Current Medications:
- Metformin 1000 mg BID
- Rosuvastatin 10 mg daily
- Lisinopril/HCTZ 10/25 mg daily
- Acetaminophen 500 mg TID
- Sildenafil 50 mg PRN

Latest Vitals/Labs:
- BP 152/98, HR 68
- A1c 7.8%
- Total Cholesterol 187 mg/dL, HDL 37 mg/dL, LDL 102 mg/dL, Triglycerides 242 mg/dL
- BMI 30.4 (6'5'', 256 lbs)

ASCVD risk calculator (apps available)

10-year risk for ASCVD categories:
- Low-risk (<5%)
- Borderline risk (5% to 7.4%)
- Intermediate risk (7.5% to 19.9%)
- High risk (≥20%)

At least moderate intensity statin initiation is indicated (I, A). High-intensity statin therapy is reasonable to reduce LDL-C by ≥50%. (IIa, B-R). Addition of ezetimibe to statin therapy is also reasonable to reduce LDL-C by ≥50%.
REDUCE-IT Results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Transparent Ethyl (n=4,590)</th>
<th>Placebo (n=4,590)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td>79% (7.1)</td>
<td>80% (7.1)</td>
<td>0.97 (0.84-1.10)</td>
<td>0.45</td>
</tr>
<tr>
<td>Major secondary composite</td>
<td>429 (9.1)</td>
<td>435 (9.1)</td>
<td>0.96 (0.85-1.08)</td>
<td>0.35</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>597 (13.1)</td>
<td>607 (13.1)</td>
<td>0.97 (0.86-1.09)</td>
<td>0.57</td>
</tr>
<tr>
<td>Non-fatal ischemic stroke or cardiac effusion</td>
<td>230 (5.1)</td>
<td>236 (5.1)</td>
<td>0.96 (0.83-1.12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Any revascularization</td>
<td>231 (5.1)</td>
<td>231 (5.1)</td>
<td>0.96 (0.83-1.12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Cardiogenic death</td>
<td>137 (3.0)</td>
<td>137 (3.0)</td>
<td>0.96 (0.83-1.12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>157 (3.4)</td>
<td>158 (3.4)</td>
<td>0.96 (0.83-1.12)</td>
<td>0.54</td>
</tr>
<tr>
<td>Fatal or non-fatal stroke</td>
<td>35 (0.8)</td>
<td>35 (0.8)</td>
<td>1.00 (0.73-1.36)</td>
<td>0.91</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>316 (6.9)</td>
<td>318 (6.9)</td>
<td>0.97 (0.84-1.13)</td>
<td>0.66</td>
</tr>
</tbody>
</table>

REDUCE-IT Recommendation

- Based on findings from the Reduction of Cardiovascular Event with Icosapent Ethyl Intervention Trial (REDUCE-IT), an additional recommendation has been officially added with the March 27, 2019 Living Standards of Care update.
- In patients with ASCVD or other cardiac risk factors on a statin with controlled LDL-C, but elevated triglycerides (135-499), the addition of icosapent ethyl should be considered to reduce cardiovascular risk.

Standards of Medical Care in Diabetes - 2019, Diabetes Care 2019;42(Suppl. 1):S61-S70

Vascepa (Icosapent Ethyl)
SGLT-2 Inhibitor MOA

SGLT-2 Inhibitors

<table>
<thead>
<tr>
<th>Inovoka (canagliflozin)</th>
<th>Farxiga (dapagliflozin)</th>
<th>Jardiance (empagliflozin)</th>
<th>Steglatro (ertugliflozin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power</td>
<td>0.5 % - 1.0 % reduction in A1c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dosing</td>
<td>50 mg daily</td>
<td>5 mg daily</td>
<td>5 mg daily</td>
</tr>
<tr>
<td></td>
<td>100 mg daily</td>
<td>20 mg daily</td>
<td>15 mg daily</td>
</tr>
<tr>
<td>GFR 45-60 mL/min</td>
<td>Before breakfast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR 60 mL/min</td>
<td>Before bedtime</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADRs: Hypotension, dehydration, hyperkalemia, DKA, yeast infections/UTI

Outcomes:
- CKD, ASCVD, CHF
- CKD, ASCVD, CHF
- CKD, ASCVD, CHF
- CHF

CV Outcomes with Canagliflozin

<table>
<thead>
<tr>
<th>Primary cardiovascular outcome</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>0.86 (0.75-0.97)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0.85 (0.69-1.05)</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0.90 (0.71-1.15)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>CV death or hospitalization for heart failure</td>
<td>0.79 (0.67-0.91)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.87 (0.74-1.03)</td>
</tr>
</tbody>
</table>

Favor: Canagliflozin

Favor: Placebo

Intention-to-treat analysis.
GLP-1 Agonists

<table>
<thead>
<tr>
<th>GLP-1 Agonists</th>
<th>Power</th>
<th>Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Byetta, Bydureon (exenatide)</td>
<td>ER: 2 mg weekly</td>
<td>5-10 mcg twice a day</td>
</tr>
<tr>
<td>Victoza (liraglutide)</td>
<td>0.75-1.5 mg weekly</td>
<td>1.2-1.8 mg daily</td>
</tr>
<tr>
<td>Trulicity (dulaglutide)</td>
<td>0.5-1 mg weekly</td>
<td>0.5-1.5 mg daily</td>
</tr>
<tr>
<td>Ozempic (semaglutide)</td>
<td>10 mcg x 2 weeks, then 20 mcg daily</td>
<td></td>
</tr>
<tr>
<td>Adlyxin (lixisenatide)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADRs: GI, pancreatitis, injection site reactions

Outcomes: ASCVD (ER only), ASCVD, CKD
Other considerations

- Renal prevention: ACE inhibitor
  - Current renal labs: GFR 63, albumin/creatinine 14
  - Nephrology (e)consult for Stage 2 kidney disease, near Stage 3
- Aspirin therapy?
Case 4
- 69 year old Asian Female
- Type 2 diabetes for 17 years
- Saw her CDE every year for a few years
- Needed to care for her ailing mother, and stopped seeing her PCP for a few years
- MI at age 65 when her A1c reached 10.8%
- Attended Cardiac Rehab
- Went back to seeing her PCP regularly and returned to DSMES
- Was started on insulin

Case 4 (continued)

Current Medications:
- Basaglar (glargine) 14 units at bedtime
- Lisinopril 5 mg daily
- Atorvastatin 40 mg daily
- Temazepam 15 mg at night
- Norco 5/325 mg every 6-8 hours PRN

Asian patient - geriatric

Latest Vitals:
- FPG 135, A1c 8.2%
- Ht 5'6', Wt 189 lbs, BMI 30.5
- BP 130/80, GFR 52, Cholesterol 197, HDL 46, Triglycerides 142

Currently concerned about numbness of her feet and wanting to see her grandson’s wedding
Glycemic Targets

Approach to Individualization of Glycemic Targets

- Renal or liver function
- Life expectancy
- Important comorbidities
- Life style and support
- Patient preference
- Secondary target achievement
- Prior drug treatment effects
- Use of other drugs in treatment
- Other drug interactions

Deprescribing

<table>
<thead>
<tr>
<th>65+ year old patient</th>
<th>Consider Deprescribing</th>
<th>Monitor and Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>● At risk of hypoglycemia?</td>
<td>● Reduce dose(s) or stop medication(s)</td>
<td>Daily to weekly for 2 weeks (12 weeks for TZDs)</td>
</tr>
<tr>
<td>● Experiencing, or at risk of ADRs from other diabetes medications?</td>
<td>● Switch to an alternative medication(s)</td>
<td>Signs and symptoms of hyperglycemia, hypoglycemia, other ADRs</td>
</tr>
<tr>
<td>● Unclear clinical benefits?</td>
<td>● Reduce dose(s)</td>
<td>Increase SMBG</td>
</tr>
</tbody>
</table>


Potentially Inappropriate Medications

Beers Criteria
- Sulfonylureas (except glipizide)
- Sliding scale insulin
- Benzodiazepines
- Tricyclic antidepressants
- Drug interactions
- Renally cleared medications
- Liver function

Pharmacogenomics

Other resources
- STOPP/START criteria
- www.medstopper.com
- Enlist a pharmacist for help
- Comprehensive medication review
- Drug interactions
- Cost reduction


### DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Januvia (sitagliptin)</th>
<th>Onglyza (saxagliptin)</th>
<th>Tradjenta (linagliptin)</th>
<th>Nesina (alogliptin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Power</strong></td>
<td>0.5 - 0.9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>100 mg daily</td>
<td>5 mg daily</td>
<td>5 mg daily</td>
<td>6.25-25 mg daily</td>
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<tr>
<td><strong>Renal dosing</strong></td>
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<tr>
<td><em>CrCl 31-50 mL/min:</em></td>
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<tr>
<td>50 mg daily</td>
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<tr>
<td><em>CrCl ≤ 50 mL/min:</em></td>
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<tr>
<td>12.5 mg daily</td>
<td></td>
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<tr>
<td><em>CrCl 30-59 mL/min:</em></td>
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<tr>
<td>25 mg daily</td>
<td></td>
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<tr>
<td><em>CrCl ≤ 30 mL/min:</em></td>
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<tr>
<td>25 mg daily</td>
<td></td>
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<tr>
<td><em>CrCl &lt; 30 mL/min:</em></td>
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<tr>
<td>6.25 mg daily</td>
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<tr>
<td><strong>Outcomes</strong></td>
<td>ASCVD and CKD neutral</td>
<td>ASCVD and CKD neutral</td>
<td>Possible increase CHF</td>
<td>ASCVD and CKD neutral Possible increase CHF</td>
</tr>
</tbody>
</table>

### Conclusion

- Medication management in patients with diabetes takes a patient-centered, interprofessional approach.
  - Diverse patient populations
  - Comorbidities
- Should include:
  - Ethnopharmacology into practice
  - Rational prescribing
  - Ways to address clinical inertia