Type 2 Diabetes: Medication Management

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Disclosures

• None
Topics to Discuss:

- Review of pharmacology of medication classes, with updated information
  - Metformin
  - Sulfonylureas
  - Thiazolidinediones
  - Incretins
    - DPP-4
    - GLP-1
  - SGLT-2 inhibitors
  - Insulin

Drugs for DM Management
TYPE 2 DIABETES
12 Different Classes of Therapy

Reduce Hepatic Glucose Production
- Metformin + XR

Enhance Insulin Secretion/Effect
- Sulfonylureas
  - glipizide, glyburide, gliamepiride
- Meglitinides (short acting)
  - Repaglinide (Prandin), nateglinide (Starlix)
- Insulin injectable

Attenuate Glucose Absorption
- $\alpha$-glucosidase inhibitors
  - Acarbose (Precose)
  - Miglitol (Glyset)

Other:
- Bromocriptine
- Salsalate
- Colesevelam
- Amylin Analogs (Symlin)

Insulin Sensitizers
- Thiazolidinediones
  - Pioglitazone (Actos), Rosiglitazone (Avandia)

SGLT 2 Inhibitors
- Canagliflozin (Invokana), Dapagliflozin (Farxiga), Empagliflozin (Jardiance)

Incretin Therapies
- GLP Analogs
  - Exenatide (Byetta), XR weekly
  - Lisproglutide (Victoza), Albiglutide (Tanzeum), dulaglutide (Trulicity), lixisenatide (Adlyxin)
- DPPIV Inhibitors
  - Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Trajenta), Alogliptin (Nesina)
Case:

- 62 yo with obesity (BMI 34), type 2 diabetes for 5 yrs, no complications, HTN
- On metformin, A1c 8.5% Cr 1.6mg/dL (eGFR 45)
  - Tried glipizide in the past -> hypoglycemia
- Very limited engagement or monitoring
- Doesn’t want insulin, but willing to consider other injectables
- Questions:
  - Is the metformin safe? What to add next?

Metformin

- Mechanism of action (MOA): ↓ hepatic glucose production
- A1c lowering: 1-1.5%
- Cost: $4/month
- Pros: long experience, lack of hypoglycemia, ↓ CVD (UKPDS), ? cancer protection
- Cons: Diarrhea/cramping (?less with XR), B12 deficiency, ? lactic acidosis (very rare), cautious use with comorbidities (acidosis, hypoxia, CHF, renal insufficiency)
FDA Revises Metformin Warnings

NEW Labeling- 2016

• **Then:** Don’t use in women Cr \(\geq 1.4\text{mg/dL} \), Men \(\geq 1.5\text{mg/dL} \)

• **Now:** Before starting metformin, check eGFR
  – Contraindicated if \(<30\text{mL/min/1.73m}^2\)
  – Don’t start if between 30-45mL/min/1.73m2

• If eGFR falls to \(< 45\text{mL/min/1.73m}^2\), assess risk/benefits and consider ↓ dose

• Follow annually, or more often if at risk

www.fda.gov/drugs/drugsafety/ucm493244.htm

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Sulfonylureas

• MOA: ↑insulin secretion from beta cells

• A1c lowering: 1-2%

• Cost: Low ($4/month)

• Pros: effective, long-experience, ↓microvascular risk (UKPDS)

• Cons: **hypoglycemia, weight gain, durability,** ? blunts myocardial ischemic preconditioning
### More on Sulfonylureas

- **Beta cell burnout:**
  - ADOPT: lost glucose control at 45 months with metformin vs 33 months with glyburide
  - No difference in UKPDS
  - Over 6 yrs, 34% with SU needed insulin, c/w 27% with DPP4
- **Weight gain:** 2-5 kg on average
- **Hypoglycemia:**
  - 6x more hypoglycemia c/w other DM meds

Kahn S, NEJM 2006;355:427; UKPDS 1995;11:1249; Inzucchi S, Diab Obes Metab 2015; Cefalu W, Diab Care 2015

### Thiazolidinediones:

- **MOA:** ↑ insulin sensitivity
- **A1c lowering:** 1-1.5%
- **Cost:** low ($30/month + coupon)
- **Pros:** no hypoglycemia, durable, ↑HDL, ↓TG’s, ↓CVD events (PROactive), ?protective in steatohepatitis
- **Cons:** Fluid retention/CHF, weight gain, fractures, ↑LDL, ? MI (rosiglitazone), bladder cancer?
Pioglitazone in Steatohepatitis

- 101 pts with pre-DM or dm, biopsy-proven nonalcoholic steatohepatitis (NASH)
  - Randomized to PBO or pioglitazone 45mg/d for 18 months
- 58% achieved ↓ score of liver disease
  - 51% with resolution of NASH
- Led to reduction in A1c, fasting insulin, AST/ALT, triglycerides
- Also noted: gain of 2.5 kg, no further benefit with longer duration of treatment (up to 36 mos)

Cusi K, Annals IM 2016

Pioglitazone After Stroke/TIA

- 3876 pts with recent stroke or TIA
  - Randomized to placebo vs pioglitazone
- Diagnosed with insulin resistance using HOMA-IR index
- 1°outcome: fatal/non-fatal stroke, MI
- By 4.8 years
  - 1°outcome: 9% (pio) vs 11.8% (pbo)- HR .76
  - DM dev: 3.8% (pio) vs 7.7% (pbo)-HR .48
  - With pio more wt gain, edema and fracture

Kernan WN, NEJM 2016
## DPP 4’s

- **MOA**: Inhibitors of metabolism of GLP1/GIP to enhance incretin effect
- **A1C lowering**: .5-1%
- **Cost**: high ($370/month + coupon)
- **Pros**: less hypoglycemia unless used with SU/insulin, oral, option with renal insufficiency (linagliptin)
- **Cons**: angioedema/urticaria, ?pancreatitis, ?↑CHF

## GLP-1 Medications

- **MOA**: ↑insulin secretion, ↓glucagon, slows gastric emptying, ↑satiety
- **A1C lowering**: 1-1.5%
- **Cost**: high ($580-650/month+coupon)
- **Pros**: no hypoglycemia, weight loss, **CV benefit**
- **Cons**: injectable, pancreatitis, GI side effects, medullary thyroid cancer in animals, renal issues (exenatide)
GLP-1 Weekly

- Useful to consider in reluctant injectors
- Equivalent benefit to daily dosing
  - Wt loss, A1c lowering, hypoglycemia, SE
  - Review showed better A1c/wt loss with dulaglutide/weekly exenatide, but data biased (Zaccardi F, Ann IM 2015)
- Pick the one tolerated and affordable

SGLT2 Inhibitors:

- MOA: blocks glucose reabsorption by the kidney->glucosuria
- A1c lowering: .5-1%
- Cost: high ($400/month+coupon)
- Pros: no hypoglycemia, ↓weight, ↓BP, durable, CV benefit, renal protection
- Cons: GU infections, polyuria, volume depletion/hypotension, ↑LDL/creatinine
CV Outcomes in DM Medications

- Motivated by high prevalence of CV in diabetes + concerns raised by rosiglitazone
- FDA Guidance to Industry, 2008
  - Sponsors should demonstrate that new type 2 DM drugs should not result in unacceptable CV risk
  - Require inclusion of higher risk CV patients, be long enough to detect adverse CV effects, include in protocol and committees to evaluate

Smith RJ, Diabetes Care 2016

### Completed CV Outcome Trials

<table>
<thead>
<tr>
<th>Trial, n of subjects</th>
<th>MACE*</th>
<th>Hosp for CHF</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR-TIMI (saxagliptin), n=16,492</td>
<td>1.00 (.89-1.12)</td>
<td><strong>1.27 (1.07-1.51)</strong></td>
<td>1.11 (.96-1.27)</td>
</tr>
<tr>
<td>EXAMINE (alogliptin), n=5,380</td>
<td>.96 (.8-1.16)</td>
<td>1.19 (.9-1.58)</td>
<td>.88 (.71-1.09)</td>
</tr>
<tr>
<td>TECOS (sitagliptin), N=14,671</td>
<td>.98 (.88-1.09)</td>
<td>1.0 (.83-1.2)</td>
<td>1.01 (.9-1.14)</td>
</tr>
<tr>
<td>EMPA-REG (empagliflozin), n=7020</td>
<td>.86 (.74-.99)</td>
<td><strong>.65 (.5-.8)</strong></td>
<td><strong>.68 (.57-.82)</strong></td>
</tr>
<tr>
<td>ELIXA (lixisenatide), n=6,068</td>
<td>1.02 (.89-1.17)</td>
<td>.96 (.82-1.16)</td>
<td>.94 (.78-1.13)</td>
</tr>
<tr>
<td>LEADER (liraglutide) n=9340</td>
<td>.87 (.78-.97)</td>
<td>.87 (.73-1.05)</td>
<td><strong>.85 (.74-.97)</strong></td>
</tr>
<tr>
<td>Sustain 6 (semaglutide) n=3,297</td>
<td>.74 (.58-.95)</td>
<td>1.11 (.77-1.61)</td>
<td>1.05 (.74-1.5)</td>
</tr>
</tbody>
</table>
DPP4’s and CHF?

- No increase noted in retrospective cohort of 376,677 pts comparing risks for CHF with saxagliptin/sitagliptin (Toh et al, Annals IM 2016)
- Explanations:
  - Chance finding, differences in studies/patients enrolled, background care provided, differences in drugs

EMPA-REG OUTCOME Trial

- 7028 patients, type 2 DM + CVD
  - Followed 3.1 years
  - Empagliflozin 10mg vs 25mg vs PBO
- Primary outcome: Composite CVD death, non-fatal MI, non-fatal stroke
  - 97% completed study
- With empagliflozin:
  - ↓ rates of CV death from CV causes, CHF admits, death from any cause
  - A1c ↓ : 12 wks: -.54-.6%, 206 wks: -.24-.36%

Zinman B et al, NEJM 2015;373:2117
Results from EMPA-REG

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>RRR (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite§</td>
<td>10%</td>
<td>12%</td>
<td>13% (1 to 25)</td>
<td>63 (34 to 982)</td>
<td></td>
</tr>
<tr>
<td>CV death</td>
<td>3.7%</td>
<td>5.9%</td>
<td>37% (22 to 50)</td>
<td>46 (34 to 76)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal M (excluding silent M)</td>
<td>4.5%</td>
<td>5.2%</td>
<td>13% (9 to 29)</td>
<td>Not significant</td>
<td></td>
</tr>
<tr>
<td>Secondary composite§</td>
<td>13%</td>
<td>14%</td>
<td>10% (1 to 21)</td>
<td>Not significant†</td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>5.7%</td>
<td>8.3%</td>
<td>31% (17 to 42)</td>
<td>39 (29 to 70)</td>
<td></td>
</tr>
<tr>
<td>Adverse events**</td>
<td>90%</td>
<td>92%</td>
<td>1.6% (0.01 to 3)</td>
<td>Not significant†</td>
<td></td>
</tr>
<tr>
<td>Serious adverse events**</td>
<td>38%</td>
<td>42%</td>
<td>10% (4 to 15)</td>
<td>24 (16 to 58)</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>3.2%</td>
<td>2.6%</td>
<td>24% (8 to 66)</td>
<td>Not significant</td>
<td></td>
</tr>
</tbody>
</table>

ACP JC 1-19-16

SGLT-2’s Cardioprotective?

<table>
<thead>
<tr>
<th>Effect</th>
<th>Likelihood</th>
<th>Reason</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ↓ BG</td>
<td>Unlikely</td>
<td>BG a weak CV risk factor, benefit of A1c on CVD takes 10 yrs</td>
</tr>
<tr>
<td>- ↑ fat oxidation or ketone concentration</td>
<td>Unlikely</td>
<td>↑O2 demand per ATP generated</td>
</tr>
<tr>
<td>- Weight loss</td>
<td>Unlikely</td>
<td>Modest changes</td>
</tr>
<tr>
<td>Hemodynamic actions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ↓ BP</td>
<td>Likely</td>
<td>Proven CV protection in prior studies</td>
</tr>
<tr>
<td>- Diuretic effect</td>
<td>Likely</td>
<td>Proven against CHF in prior trials</td>
</tr>
<tr>
<td>- Impaired arterial elasticity</td>
<td>Possible</td>
<td>? Some effect of empagliflozin</td>
</tr>
<tr>
<td>- Direct effect on myocardium</td>
<td>Unlikely</td>
<td>No evidence</td>
</tr>
<tr>
<td>- Decreased sympathetic tone</td>
<td>Possible</td>
<td>No ↑ in HR with ↓ in BP and volume</td>
</tr>
</tbody>
</table>

Abdul-Ghani M, Diab Care 2016
Liraglutide and CV Outcomes

LEADER Trial: 9340 pts, followed for 3.8 yrs, randomized to liraglutide or placebo
NNT to prevent one event in 3 yrs was 66 (primary outcome), 98 (death)

In-Progress CVD Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Med</th>
<th>Planned #</th>
<th>Planned date</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUSTAIN-6</td>
<td>Semaglutide</td>
<td>3297</td>
<td>Jan 2016</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin</td>
<td>4407</td>
<td>June 2017</td>
</tr>
<tr>
<td>CARMELINA</td>
<td>Linagliptin</td>
<td>8300</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>14000</td>
<td>Jan 2018</td>
</tr>
<tr>
<td>ITCA 650</td>
<td>Exenatide</td>
<td>4000</td>
<td>July 2018</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>6000</td>
<td>Sept 2018</td>
</tr>
<tr>
<td>DECLARE-TIMI 58</td>
<td>Dapagliflozin</td>
<td>17150</td>
<td>April 2019</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>9622</td>
<td>April 2019</td>
</tr>
<tr>
<td>HARMONY</td>
<td>Albiglutide</td>
<td>9400</td>
<td>May 2019</td>
</tr>
<tr>
<td>CV OUTCOMES ERTUGLIFLOZIN</td>
<td>Ertugliflozin</td>
<td>3900</td>
<td>Oct 2020</td>
</tr>
<tr>
<td>CV OUTCOMES OMARIGLIPTIN</td>
<td>Omariglitin</td>
<td>4202</td>
<td>Dec 2020</td>
</tr>
</tbody>
</table>

Smith RJ. Diab Care 2016
Summary of CVD Data

- Studies note benefit/harm with particular medications
  - Unclear if class effect
- Many payors are responding to this data to make certain brands “preferred”
- Plenty of ongoing trials, so more to come!

Case:

- 62 yo with obesity (BMI 34), type 2 diabetes for 5 yrs, no complications, HTN
- On metformin, A1c 8.5% Cr 1.6mg/dL (eGFR 45)
  - Tried glipizide in the past -> hypoglycemia
- Very limited engagement or monitoring
- Recs: continue metformin, consider adding GLP1 or sulphonylurea
Next Case:

- 68yo with type 2 dm, chronic LBP, GERD, obesity, HTN, on statin
- Meds include: glargine 75units qd
  - Intolerant of metformin, dapagliflozin caused recurrent yeast infections
- A1c now 8.7%, nl renal and liver function
- Wants better control without weight gain. *How about the one on TV?*

New insulin Options

- Degludec (*Tresiba®*):
  - Comes as U100 or U200
  - Transition 1:1 (consider 20% decrease with BID or lower A1c)
  - Dosing flexibility (not given < every 8 hours)
- U300 Glargine (*Toujeo®*):
  - Transition 1:1 from long-acting
    - Often requires dose ↑ 10-15% c/w regular glargine
  - Once daily, same time
Clinical Profiles

<table>
<thead>
<tr>
<th></th>
<th>Duration of Action</th>
<th>Half-life</th>
<th>Steady State</th>
<th>Max Dose</th>
<th>Units/pen</th>
<th>Pens/box</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>U300 Lantus</td>
<td>&gt; 30 hours</td>
<td>18-19 hrs</td>
<td>5 days</td>
<td>80 U</td>
<td>450</td>
<td>3 (1350)</td>
<td>$350</td>
</tr>
<tr>
<td>U100 Degludec</td>
<td>42 hrs</td>
<td>25 hrs</td>
<td>2-3 days</td>
<td>80 U (1U adj)</td>
<td>300</td>
<td>5 (1500)</td>
<td>$450</td>
</tr>
<tr>
<td>U200 Degludec</td>
<td>42 hrs</td>
<td>25 hrs</td>
<td>2-3 days</td>
<td>160 U (2U adj)</td>
<td>600</td>
<td>3 (1800)</td>
<td>$560</td>
</tr>
</tbody>
</table>

When to consider new insulins?

*My opinion…*

- *Degludec*: shift workers, higher dosing requirements, forgetting insulin doses, long-acting twice/day, variability thought due to long-acting
- *U300 glargine*: long-acting twice/day, forgetting insulin doses, variability thought due to long-acting
Don’t Overlook NPH and Regular Insulin

• Among privately insured adults + DM2
  – 19% using analogs in 2000, c/w 96% in 2010
  – From 2001 → 2015, lispro vials increased from $35 → $234, human insulin $20 → $131

• LOTS of marketing with insulin analogs
  – Emphasizing more physiologic, less hypoglycemia

• **No difference in A1c, no data on outcomes or complications**

Tylee T, Hirsch I, JAMA 2015

Combinations instead of bolus?

• GLP-1 or SGLT2 inhibitors
  – Effective to control BG + weight loss + ↓ hypoglycemia

• TZD also an option
  – ↑ fluid retention, weight gain when used with insulin

<table>
<thead>
<tr>
<th>GLP-1 agonists plus basal insulin (GLP-1 combination) vs other antidiabetic treatments (control) in patients with type 2 diabetes†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HbA1c level, %</td>
</tr>
<tr>
<td>Weight change, kg</td>
</tr>
</tbody>
</table>

ACP JC 1-20-16
Cost Data

Returning to Case

- 68yo with type 2 dm, chronic LBP, GERD, obesity, HTN, on statin
- Meds include: glargine 75units qd
  - Intolerant of metformin, dapagliflozin caused recurrent yeast infections
- A1c now 8.7%, nl renal and liver function

- Recs: consider GLP1
Conclusions

• DM is complicated, on so many levels
• Many new medications to choose from
  – Newer isn’t necessarily better
  • But lots of direct-to-consumer marketing, so
good to have some familiarity
• Cost an ongoing challenge
• More people have diabetes but:
  – Management is improving
  – Fewer complications

THE END