Treating Type 2 Diabetes in 2018: 
*A Medication Update*

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Disclosures

• I have no conflicts of interest to disclose

*In order to ensure clarity, given that trade names tend to dominate generic names for newer drugs (especially with patients), I will use both generic and trade names in this talk*

Objectives/Aims

• Review available algorithms for medication choice in T2DM
• Learn key points about newer, less familiar medications
• Understand the "role" each medication class can play in type 2 diabetes treatment including older, lower-cost medications
• Choose medications based on various characteristics including weight gain or loss, likelihood of hypoglycemia, cardiovascular and/or renal benefits, route of administration, and cost
Clinical Vignette

• Consider a patient in late 40s/early 50s with:
  • Type 2 diabetes for 5 years
  • Obesity
  • Hypertension
  • Dyslipidemia

• Has tried diabetes education and lifestyle interventions, on metformin 1000mg BID for 9 months, but A1c above goal

Clinical Vignette, slight twist

• Consider a patient in late 40s/early 50s with:
  • Type 2 diabetes for 5 years
  • Obesity
  • Hypertension
  • Dyslipidemia

• Refuses metformin due to diarrhea in past, on Lantus 40 units nightly and glipizide 10mg BID with A1c 9.3%
DPP-4 inhibitors

- Sitagliptin (Januvia)
- Saxagliptin (Onglyza)
- Linagliptin (Tradjenta)
- Alogliptin (Nesina)
DPP-4Is: Safety?

- “Saxagliptin, alogliptin, and sitagliptin confer neither benefit nor harm for the composite outcome of cardiovascular death, myocardial infarction, or stroke.”
- “Saxagliptin and alogliptin carry warnings of increased risk of heart failure; sitagliptin was shown to not affect heart failure risk.”

DPP-4Is: Role

- Weight-neutral, minimal hypoglycemia, oral option, well-tolerated, no up-titration
  - Reduce dose for decreased renal function
    - Except linagliptin (hepatically cleared)
  - Avoid for severe heart failure patients or those with h/o pancreatitis/tumors
  - Small reduction in A1c (0.5-0.7%)
  - $$$
- Get comfortable with: sitagliptin (Januvia)
GLP-1 receptor agonists

- Exenatide (Byetta – BID, Bydureon – QW)
- Liraglutide (Victoza – QD)
- (Tulipan with degludec – QD)
- Dulaglutide (Trulicity – QW)
- Lixisenatide (Adlyxin – QD)
- (Soliqua with glargine – QD)
- Ozempic (semaglutide – QW)

GLP-1RAs: CV, renal benefit?

- LEADER: liraglutide (Victoza)
  - “In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.”
  - “...when added to usual care, liraglutide resulted in lower rates of the development and progression of diabetic kidney disease than placebo.”

GLP-1RAs: CV benefit?

- SUSTAIN-6: semaglutide (Ozempic)
  - “In patients with type 2 diabetes who were at high cardiovascular risk, the rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than among those receiving placebo.”
    - Non-inferiority study
GLP-1RAs: CV benefit?

- EXSCEL: weekly exenatide (Bydureon)
  - "Among patients with type 2 diabetes with or without previous cardiovascular disease, the incidence of major adverse cardiovascular events did not differ significantly between patients who received exenatide and those who received placebo."


GLP-1RAs: Safety?

- Pancreatitis, pancreatic cancer risk?
  - "Of the 113 trials fulfilling inclusion criteria, 13 did not report information on pancreatitis, whereas 72 reported zero events in all treatment groups. The incidence of pancreatitis and pancreatic cancer with GLP1-RA was not significantly different from that observed in comparator arms (MH-OR [95% CI] 0.93 [0.65-1.34], p = 0.71, and 0.94 [0.52-1.70], p = 0.84, respectively), whereas, a significantly increased risk of cholecystitis (MH-OR [95% CI] 1.30 [1.01-1.68], p = 0.041) was detected."


GLP-1RAs: Safety?

**Important Safety Information**

- In animal studies, -----" caused thyroid tumors—including thyroid cancer—in some rats and mice. It is not known whether -----" causes thyroid tumors or a type of thyroid cancer called medullary thyroid cancer (MTC) in people, which may be fatal if not detected and treated early. Do not use -----" if you or any of your family members have a history of MTC or if you have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2). While taking -----", tell your doctor if you get a lump or swelling in your neck, hoarseness, trouble swallowing, or shortness of breath. These may be symptoms of thyroid cancer.
  - Liraglutide package insert
GLP-1RAs: Role

- Effective, low hypoglycemia, weight-negative option for glycemic control (especially postprandial) and weight loss,
- CV, renal benefit with liraglutide (Victoza)
- CV benefit with semaglutide (Ozempic)
- Unclear whether class effect!
- Not for those with pancreatitis/tumors or those at risk for medullary thyroid cancer
- $$$
- Get comfortable with: liraglutide (Victoza), dulaglutide (Trulicity), semaglutide (Ozempic)

SGLT-2 inhibitors

- Canagliflozin (Invokana)
- Dapagliflozin (Farxiga)
- Empagliflozin (Jardiance)
- Ertugliflozin (Steglatro)

SGLT-2Is: CV, renal benefit?

- EMPA-REG: empagliflozin (Jardiance)
  - "Patients with type 2 diabetes at high risk for cardiovascular events who received empagliflozin, as compared with placebo, had a lower rate of the primary composite cardiovascular outcome and of death from any cause..."
  - In patients with type 2 diabetes at high cardiovascular risk, empagliflozin was associated with slower progression of kidney disease and lower rates of clinically relevant renal events than was placebo...

SGLT-2Is: CV, renal benefit?

- **CANVAS**: canagliflozin (Invokana)
  - “Patients treated with canagliflozin had a lower risk of cardiovascular events than those who received placebo...”
  - “Reduced risk of sustained loss of kidney function, attenuated eGFR decline, and a reduction in albuminuria, which supports a possible renoprotective effect...”
- **CVD-REAL Nordic**: 94% dapagliflozin (Farxiga)
  - “In a population of patients with type 2 diabetes and a broad cardiovascular risk profile, SGLT2 inhibitor use was associated with reduced cardiovascular disease and cardiovascular mortality compared with use of other glucose-lowering drugs”

### Clinical Trial Data


<table>
<thead>
<tr>
<th>Outcome</th>
<th>Canagliflozin (n=7198)</th>
<th>Placebo (n=7192)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death from cardiovascular causes, non-cardiovascular death, or stroke</td>
<td>10.9</td>
<td>13.3</td>
<td>0.84 (0.75-0.94)</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>11.6</td>
<td>12.8</td>
<td>0.90 (0.75-1.09)</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>9.7</td>
<td>11.6</td>
<td>0.83 (0.68-1.00)</td>
</tr>
<tr>
<td>Nonsudden noncardiovascular death</td>
<td>7.1</td>
<td>8.4</td>
<td>0.84 (0.71-1.00)</td>
</tr>
<tr>
<td>Acute decompensated heart failure</td>
<td>13.6</td>
<td>12.6</td>
<td>1.09 (0.97-1.23)</td>
</tr>
<tr>
<td>Hospitalization for any cause</td>
<td>18.7</td>
<td>131.1</td>
<td>0.16 (0.14-0.18)</td>
</tr>
<tr>
<td>Hospitalization for type 1 diabetes</td>
<td>9.3</td>
<td>9.7</td>
<td>0.97 (0.85-1.11)</td>
</tr>
<tr>
<td>Death from cardiovascular causes, acute hospitalization for heart failure</td>
<td>16.9</td>
<td>20.8</td>
<td>0.80 (0.67-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>17.3</td>
<td>19.3</td>
<td>0.91 (0.74-1.11)</td>
</tr>
<tr>
<td>Time to progression of albuminuria, 40% reduction in eGFR, renal replacement therapy, or renal death</td>
<td>5.5</td>
<td>9.0</td>
<td>0.49 (0.41-0.57)</td>
</tr>
</tbody>
</table>


SGLT-2Is: Safety?

- Hyperkalemia
- DKA (usually with other trigger)
  - Stop 3 days before OR
  - NO KETOGENIC DIETS
- Yeast infections > UTIs
- Foot amputations – canagliflozin (Invokana)???
SGLT-2Is: Role

- Effective, oral, weight-negative, BP-lowering option
- CV, renal benefit probably with all
- Not for those with low GFR or hyperkalemia, nor those with h/o DKA
- Monitor Cr/eGFR, K
- Start lower dose, if labs OK, increase to higher dose
- Women and uncircumcised men at higher risk of yeast infections
- Switch patients away from canagliflozin (Invokana)?
  - Especially if PAD, smokers, history of ulcers
- Get comfortable with: dapagliflozin (Farxiga), empagliflozin (Jardiance)

Table 5—Risk reduction in four completed trials showing evidence of CV benefit

<table>
<thead>
<tr>
<th>Study</th>
<th>LEADER</th>
<th>SUSTAIN-6</th>
<th>EMPA-REG</th>
<th>OUTCOME</th>
<th>CANVAS Program (12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (bpm)</td>
<td>65 (64 to 66)</td>
<td>65 (64 to 66)</td>
<td>65 (64 to 66)</td>
<td>65 (64 to 66)</td>
<td>65 (64 to 66)</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>74 (73 to 75)</td>
<td>74 (73 to 75)</td>
<td>74 (73 to 75)</td>
<td>74 (73 to 75)</td>
<td>74 (73 to 75)</td>
</tr>
<tr>
<td>% with diabetes</td>
<td>96 (95 to 97)</td>
<td>96 (95 to 97)</td>
<td>96 (95 to 97)</td>
<td>96 (95 to 97)</td>
<td>96 (95 to 97)</td>
</tr>
<tr>
<td>% with PAD</td>
<td>20 (19 to 21)</td>
<td>20 (19 to 21)</td>
<td>20 (19 to 21)</td>
<td>20 (19 to 21)</td>
<td>20 (19 to 21)</td>
</tr>
<tr>
<td>% with history of CVD</td>
<td>40 (39 to 41)</td>
<td>40 (39 to 41)</td>
<td>40 (39 to 41)</td>
<td>40 (39 to 41)</td>
<td>40 (39 to 41)</td>
</tr>
</tbody>
</table>

Risk ratio indicates statistical significance; —, not reported; ARB, absolute risk reduction; RR, relative risk reduction.


Cost comparison: goodrx.com

- Sitagliptin/Januvia: $447 per month
- Linagliptin/Tradjenta: $429
- Exenatide/Byetta: $733
- Exenatide/Bydureon: $683
- Liraglutide/Victoza: $833
- Dulaglutide/Trulicity: $755
- Canagliflozin/Invokana: $483
- Empagliflozin/Jardiance: $483

So given the CV and renal risk reduction, along with weight reduction of SGLT2-inhibitors and GLP-1 receptor agonists...when would you use a DPP-4 inhibitor?

Honestly...probably less often now

But still a nice choice for patients who can’t tolerate others or have reduced renal function (CKD 4-5)
And should you choose SGLT-2 inhibitors first before GLP-1RAs given the cost difference?

Worth considering...

Concentrated insulin

- Human insulin (Humulin-R U-500 concentrated insulin):
  - 500 units per mL (compared to 100 units per mL)

"Regular" insulin (Humulin-R U-100) – 50 units

U-500 concentrated insulin (Humulin-R U-500) – 50 units
All insulin pens with concentrated insulin automatically account for the concentration difference

Newer basal insulins

- Glargine (Toujeo) now with a U-300 pen only
  - 450 units/pen, 3 pens/box
- Glargine (Basaglar) now 1st “biosimilar”, in pen only
  - 300 units/pen, 5 pens/box
- Degludec (Tresiba) now with U-100 or U-200 pen only
  - U-100: 300 units/pen, 5 pens/box
  - U-200: 600 units/pen, 2 pens/box
  - Much longer, flatter profile than Lantus – dosing any time of day
    - Good for forgetful patients or those with nocturnal hypoglycemia

SWITCH-2

- Degludec (Tresiba) vs. glargine (Lantus) in T2DM

Wycham C, et al. JAMA, 2017
Other new insulin pens

- Lispro (Humalog) now with a U-200 pen only
  - 600 units/pen, 2 pens/box
- Lispro biosimilar (Admelog) now with a U-100 pen as well as a 10mL vial
  - 300 units/pen, 5 pens/box
- “Fast” aspart (Fiasp) now with a U-100 pen as well as a 10mL vial
  - 300 units/pen, 5 pens/box
- Humulin-R U-500 now in a pen (in addition to vials)

Wait, is newer really better?

Lipska KJ, et al. JAMA, 2018

Wait, is newer really better?

Lipska KJ, et al. JAMA, 2018
Wait, is newer really better?

**Cost comparison: goodrx.com**

- Insulin degludec (Tresiba): 32-48 cents per unit
- Insulin glargine (Lantus, Basaglar, Toujeo): 16-22 cents per unit
- Insulin detemir (Levemir): 30-45 cents per unit
- **NovoLIN - N in vials: 2.4-2.6 cents per unit**
  - CVS, Target, Kroger, Walgreen’s, Rite-Aid, Walmart
  - **CASH PRICE, PATIENT SHOULD NOT HAVE THEM BILL INSURANCE**

**Cost comparison: goodrx.com**

- HumaLOG 75/25 mix: 19-25 cents per unit
- NovoLOG 70/30 mix: 31-38 cents per unit
- **NovoLIN 70/30 mix in vials: 2.4-2.6 cents per unit**
  - CVS, Target, Kroger, Walgreen’s, Rite-Aid, Walmart
  - **CASH PRICE, PATIENT SHOULD NOT HAVE THEM BILL INSURANCE**
Cost comparison: goodrx.com

- Insulin lispro (Admelog, Humalog): 18‐30 cents per unit
- Insulin aspart (Novolog, Fiasp): 30‐38 cents per unit
- NovoLIN – R in vials: 2.4–2.6 cents per unit
  -CVS, Target, Kroger, Walgreen’s, Rite-Aid, Walmart
  - CASH PRICE, PATIENT SHOULD NOT HAVE THEM BILL INSURANCE

Older “human” insulins

- NovoLIN N and NovoLIN 70/30 are “cloudy” insulins and require mixing (roll in hand)
- NovoLIN N usually needs administered 2x/day
  - But a perfect substitute for those patients on BID basal insulin
- NovoLIN R a good choice for patients on MDI, especially higher doses/more insulin resistant
  - Have to be able to handle vials/syringes
  - >90% savings
- NovoLIN 70/30 administered pre-breakfast and pre-dinner is a great substitute for the 70/30 and 75/25 analog mixes

Lipska, Hirsch, Riddle. JAMA, 2017
How can you transition?

- Twice-daily basal analog → twice-daily NPH (NovoLIN-N) at 85-90% of prior doses

- Once daily basal analog → split into 2 doses of NPH (NovoLIN-N) at 85-90% of prior total dose

- Prandial analog → prandial regular (NovoLIN-R) same doses

- Twice-daily analog mix → twice-daily NovoLIN 70/30 same doses

- Basal-bolus changing to mix → calculate prior total daily dose (all insulin units combined), cut down 10-15%, then split into 2 doses
  - I usually start even doses, and adjust based on pre-breakfast and pre-dinner glucoses, but if they clearly eat a lot more early in day or later in day, you can dose at 60/40 or 40/60

Clinical Vignette

- Consider a patient in late 40s/early 50s with:
  - Type 2 diabetes for 5 years
  - Obesity
  - Hypertension
  - Dyslipidemia

- Has tried diabetes education and lifestyle interventions, on metformin 1000mg BID for 9 months, but A1c above goal
Options

- Sulfonylurea if patient desires least expensive option (caution re: hypoglycemia)
- SGLT-2 inhibitor (e.g., empagliflozin/Jardiance) probably a better choice than DPP-4 inhibitor (e.g., sitagliptin/Januvia) as they are at same price point but SGLT-2 inhibitor more effective at lowering A1c and provides CV and renal benefit
- GLP-1 agonist a reasonable choice if you need to lower A1c more than 1%, weight loss a strong motivator for patient

Clinical Vignette, slight twist

- Consider a patient in late 40s/early 50s with:
  - Type 2 diabetes for 5 years
  - Obesity
  - Hypertension
  - Dyslipidemia
- Refuses metformin due to diarrhea in past, on Lantus 40 units nightly and glipizide 10mg BID with A1c 9.3%

Options

- SGLT-2 inhibitor added will probably only get A1c to low-mid 8's, but better than doing nothing (and better than DPP-4 inhibitor!)
- GLP-1 agonist in place of sulfonylurea will be more costly, but provide weight loss, better A1c lowering, less hypoglycemia, potentially CV and renal protection (depending on choice)
- I would probably make that change, then titrate up basal insulin to get fasting glucose into 90-115 range (GLP-1 agonist unlikely to then dip you lower than fasting baseline)
- Adding GLP-1 agonist to basal insulin really expensive!
  - Could change basal insulin to human insulin
  - Could prescribe combination product (cheaper than sum of parts)
  - Or...another option?
Pioglitazone in place of basal insulin

Quick notes on pioglitazone

- Advantages:
  - May see A1c lowering 1-2%!
  - Once-daily oral
  - Cheap - about 30 cents a day (if you shop around)
  - Use like you'd use basal insulin or metformin
  - Less hypoglycemia than sulfonylureas (but more than other orals)
  - Secondary ischemic stroke prevention
  - Good for fatty liver

- Disadvantages:
  - Potential for weight gain and/or fluid retention
  - Avoid in patients with heart failure, other pro-edema states
  - May contribute to bone loss/osteoporosis
  - Bladder cancer warning label despite pretty good data suggesting no effect

Global Summary

- There is no one “right” way to treat type 2 diabetes

- When choosing medications, consider:
  - Burden of delivery
  - Side effect profile
  - “Side benefit” profile
  - Cost
  - Efficacy
  - Patient preference
References
