Type 2 Diabetes Mellitus: Update on Pharmacotherapy
No conflicts of interest
Objectives for this talk

- Update on non-insulin drug therapy for type 2 DM
- Appropriate use of insulin in type 2 DM
# ADA Treatment Goals for Glycemic Control

<table>
<thead>
<tr>
<th>General goal for non-pregnant adults</th>
<th>HbA1c &lt; 7.0% (normal &lt; 5.7%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-meal</td>
<td>80-130 mg/100 ml</td>
</tr>
<tr>
<td>Peak post-meal</td>
<td>&lt; 180 mg/100 ml</td>
</tr>
<tr>
<td>(measure 1-2 h after start of meal)</td>
<td></td>
</tr>
</tbody>
</table>

More stringent for selected Individuals:
- short duration of diabetes
- treatment with lifestyle or metformin only
- long life expectancy
- no significant cardiovascular disease.

As close to normal as possible without significant hypoglycemia

Less stringent for some patients:
- hypoglycemia unawareness
- limited life expectancy
- co-morbidity
- long hx DM with minimal complications where control has been historically difficult

HbA1c < 8.0

American Diabetes Association: Standards of Care (Diabetes Care 1, Jan. 2018 a) Online www.diabetes.org/
Metformin

- Near universal acceptance as initial drug therapy in absence of contraindication (e.g. renal failure, hypoxia) or intolerance
- Decrease hepatic glucose release and increases muscle glucose uptake
- Beneficial effects on weight and lipids
- Lack of hypoglycemia when used alone
- Generic drug with long history of use worldwide (over 50 yr)
- Evidence from several studies supports a reduction in CV events, improved carotid IMT
- UKPDS showed a significant reduction in MI and cardiac and all cause mortality by 39, 50, and 36% respectively when administered to obese patients (weight > 120% of ideal).
Initial Pharmacologic treatment

- Metformin
  - Goal achieved
  - Goal not achieved
    - Add second drug
    - Another drug
      - What drug?
Sulfonylureas

- Mechanism of action: ↑ β-cell insulin secretion by activating potassium channels
- Glipizide, Glimepiride
- Glyburide (glibenclamide) – more hypoglycemia, maybe adverse interactions with cardiac channels
- Advantages:
  - Well tolerated
  - Low cost
- Disadvantages:
  - Hypoglycemia
  - Weight gain
  - Sulfa allergy
  - May have low durability
Sulfonylureas (CV effects)

- UGDP (1970s) – increased CV mortality (controversial)
- Retrospective and some prospective analyses of databases support increased risk
- But major large scale trials (UKPDS, ADVANCE, ACCORD) do not support increased CV risk
Dipeptidyl peptidase -4 (DPP-4) inhibitors

• Several available
  – Sitagliptin (Januvia)
  – Alogliptin (Nesina)
  – Saxagliptin (Onglyza)
  – Linagliptin (Tradjenta) (no renal adjustment)

• Block degradation of endogenous GLP-1

• Not very effective in lowering A1c

• Advantages
  – Little or no hypoglycemia

• Disadvantages
  – Urticaria, angioedema
  – Pancreatitis risk
DPP-4 inhibitors (CV effects)

- Weight neutral
- Decrease TG, may reduce hsCRP, may improve endothelial function, and improve reduce ischemia-reperfusion in animals, may decrease IMT (diabetes care Dec 2015 online)
- Two large CV outcome trials in high risk patients (SAVOR-TIMI and EXAMINE) showed no difference in outcomes
  - Slight increase in hospitalization for CHF
- TECOS trial
  - 14,671 patients to add either sitagliptin or placebo, no diff in CV events (839 vs. 851)
  - No difference in hospitalization for CHF
GLP-1 agonists

- Several drugs differing in duration of action
  - Exenatide (Byetta) Short-acting BID (needs renal adjustment)
  - Long acting exenatide (Bydureon) Weekly (needs renal adjustment)
  - Lixisenatide (Lyxumia) Intermediate-acting Daily
  - Liraglutide (Victoza) Long-acting Weekly
  - Dulaglutide (Trulicity) Long-acting Weekly
  - Albiglutide (Tanzeum) Long-acting Weekly
- Activate GLP-1 receptors in pancreatic $\beta$-cell and nervous system
- $\uparrow$ glucose-induced insulin secretion, $\downarrow$ glucagon, $\downarrow$ gastric emptying,$\uparrow$ satiety
  - Decreased hepatic glucose production
  - Decreased post-prandial glucose
- Durable up to at least 3 years, may increase $\beta$-cell mass
- Mild weight loss
- Disadvantages
  - Nausea, vomiting, or diarrhea
  - Pancreatitis risk
  - Medullary thyroid tumors
GLP-1 agonists (CV effects)

• Many favorable effects on CV risk factors: Decrease weight and visceral fat, decrease BP, increase urinary sodium, improved endothelial function, decrease TG, FFA levels

• LEADER trial
  – Randomized double blind trial, 9340 subjects with type 2 diabetes at high risk for CV disease or with CV disease.
  – Assessed the effect of liraglutide, a GLP-1 receptor agonist, versus placebo and standard care, on CV outcomes
  – Mean age 64 years and mean duration of diabetes 13 years.
  – Composite primary outcome (MI, stroke, or cardiovascular death) occurred in fewer participants in the treatment group (13.0%) when compared with the placebo group (14.9%) after a median follow-up of 3.8 years
  – Whether this drug class will have similar effects in lower-risk patients with diabetes remains unknown.

• SUSTAIN-6
  – Studied 2375 patients with type 2 diabetes who were at high CV risk
  – Primary outcome (MI, stroke, or cardiovascular death) occurred in 108 of 1648 patients (6.6%) in the semaglutide group and in 146 of 1649 patients (8.9%) in the placebo group (hazard ratio, p<0.001)
Sodium-glucose co-transporter-2 (SGLT2) inhibitors (SGLT2)

• Several drugs
  – Canagliflozin (Invokana)
  – Dapagliflozin (Farxiga)
  – Empagliflozin (Jardiance)

• Inhibits hSGLT2 (sodium/glucose cotransporter) in renal tubules
  – Urine glucose 60-100 mg/day
  – At base HbA1c of 8, will drop by 0.8-1.0 (similar to metformin at that base)
Sodium-glucose co-transporter-2 (SGLT2) inhibitors

- Avoid if renal dysfunction
- Advantages
  - Hypoglycemia very unusual
  - Familial renal glycosuria is a benign disease
  - Unique action, Can combine with all other agents
  - CV effects appear beneficial
- Disadvantages
  - UTIs
  - vulvovaginitis, balanitis
  - Osmotic diuresis with possible dehydration and hypotension
  - Increased hepatic glucose output
  - Risk of DKA
Sodium-glucose co-transporter-2 inhibitors (CV effects)

- By inhibiting salt reabsorption in the proximal tubule vascular volume decreases with BP drop 4-6 mmHg.
- Weight loss of 2.5 – 3.0 kg over 6-12 mos persisting for 2 years
- Small increase in LDL and HDL cholesterol
- Decrease in serum uric acid due to uric acid and glucose co-transport in proximal tubule
- Meta-analyses suggests decreased CV risk (HR 0.82)
- EMPA-REG NEJM Sept 2015
  - 7020 patients were treated (median observation time, 3.1 years).
  - HR for combined CV event favored drug over placebo at 0.82 (10.5% vs, 12.1%)
  - Decreased hospitalization for CHF (2.7% VS. 4.1%)
Cardiovascular Outcomes and Death from Any Cause.

A Primary Outcome

- Hazard ratio, 0.86 (95% CI, 0.74–0.99)
- P=0.04 for superiority

No. at Risk
- Empagliflozin: 4687, 4580, 4455, 4328, 3851, 2821, 2359, 1534, 741, 166
- Placebo: 2333, 2256, 2194, 2112, 1875, 1380, 1161, 741, 166

Month

B Death from Cardiovascular Causes

- Hazard ratio, 0.62 (95% CI, 0.49–0.77)
- P<0.001

No. at Risk
- Empagliflozin: 4687, 4516, 4608, 4556, 4128, 4128, 3079, 2617, 1722, 414
- Placebo: 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

Month

C Death from Any Cause

- Hazard ratio, 0.68 (95% CI, 0.57–0.82)
- P<0.001

No. at Risk
- Empagliflozin: 4687, 4651, 4608, 4536, 4128, 3079, 2617, 1722, 414
- Placebo: 2333, 2303, 2280, 2243, 2012, 1503, 1281, 825, 177

Month

D Hospitalization for Heart Failure

- Hazard ratio, 0.65 (95% CI, 0.50–0.85)
- P<0.002

No. at Risk
- Empagliflozin: 4687, 4614, 4523, 4427, 3988, 2950, 2487, 1634, 395
- Placebo: 2333, 2271, 2226, 2173, 1932, 1424, 1202, 775, 168

Month

DKA induced by SGLT2 inhibition

- May not be recognized as glucose may not be as high as typically seen in DKA
- Mechanism not unresolved, several hypotheses:
  - Increase in glucagon, decrease in insulin
  - Increased reabsorption of ketone with concomitant delayed clearance of ketone (may not see ketonuria)
  - Shift in substrate utilization to fatty acid with concomitant increase in ketone body production
  - Weight loss with concomitant sarcopenia
  - Associated dehydration, fluid loss (gastroenteritis) or poor fluid intake (vomiting) and infections, in a poor metabolic milieu, might also trigger this event, making the patient ketosis-prone.
SGLT2 inhibitors + Insulin

• 1402 subjects with type 1 DM on insulin randomized to sotagliflozin (400 mg per day) or placebo for 24 weeks.
• Sotagliflozin group significantly improved glycated hemoglobin (difference, −0.46 percentage points), weight (−2.98 kg), systolic BP (−3.5 mm Hg), and mean daily bolus dose of insulin (−2.8 units per day)
• The rate of diabetic ketoacidosis was higher in the sotagliflozin group than in the placebo group (3.0% [21 patients] and 0.6% [4], respectively).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Actions</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meglitinides</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>repaglinide</td>
<td>↑ β-cell insulin secretion</td>
<td>Potassium channels</td>
<td>Action focused on time of food intake</td>
<td>Not very effective Other concerns shared with sulfonylureas</td>
</tr>
<tr>
<td>nateglinide</td>
<td></td>
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<tr>
<td>Thiazolidinediones (TZDs)</td>
<td>↑ Insulin sensitivity mainly in muscle</td>
<td>Activate PPAR-γ</td>
<td>Pioglit ↑ HDL, ↓ TG No hypoglycemia</td>
<td>Any use is questionable Wt gain, edema, CHF, ↑ LDL, bone fractures, bladder CA</td>
</tr>
<tr>
<td>pioglitazone</td>
<td></td>
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<td></td>
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<tr>
<td>rosiglitazone</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>α-glucosidase Inhibitors</td>
<td>↓ intestinal glucose absorption</td>
<td>Inhibit α-glucosidase</td>
<td>Nonsystemic No hypoglycemia</td>
<td>Not very effective GI gas, diarrhea</td>
</tr>
<tr>
<td>acarbose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>miglitol</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Unclear</td>
<td>Bile acid sequestrant</td>
<td>No hypoglycemia</td>
<td>Constipation, ↑ TGS ↓ absorption of meds</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>↑ Insulin sensitivity</td>
<td>Hypothalamic dopaminergic effect</td>
<td>No hypoglycemia</td>
<td>Dizziness, syncope, nausea, fatigue, rhinitis, Long term safety?</td>
</tr>
</tbody>
</table>
Initial Pharmacologic treatment

Metformin

- Goal achieved
- Goal not achieved

Severe hyperglycemia

- Insulin
- Contraindication or intolerance to metformin

- Add second drug
- Another drug

What drug?
What drug after metformin?

- Ask what you want to accomplish (see next slide)
- Consider other possible adverse effects and contraindications
- Acceptance of injections
- Higher Hb A1c favors insulin
- Cost
<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight change</th>
<th>Cost</th>
<th>ASCVD</th>
<th>CHF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral to modest</td>
<td>Low</td>
<td>Neutral or Benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>High</td>
<td>No</td>
<td>Less</td>
<td>High</td>
<td>Neutral or Benefit</td>
<td>Neutral</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>Low *</td>
<td>No</td>
<td>Neutral</td>
<td>High</td>
<td>Neutral</td>
<td>Possible risk</td>
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<tr>
<td>SGLP-2 inhibitors</td>
<td>Intermediate</td>
<td>No</td>
<td>Less</td>
<td>High</td>
<td>Benefit</td>
<td>Benefit</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>High</td>
<td>Yes</td>
<td>More</td>
<td>Low</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>High</td>
<td>No</td>
<td>More</td>
<td>Low</td>
<td>Neutral or Benefit</td>
<td>Increased risk</td>
</tr>
<tr>
<td>Insulin</td>
<td>Highest</td>
<td>Yes</td>
<td>More</td>
<td>High</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

* ADA classifies as intermediate, low in presenter’s experience
# High HbA1c change up to 2% (may be less), intermediate 0.5 to 1%

American Diabetes Association: Standards of Care (Diabetes Care 1, Jan. 2018 a) Online www.diabetes.org/
Insulin

Advantages

• Most effective
• “Natural”
• Once daily for many patients
• Less weight gain than TZD
• Essentially no side effects apart from hypoglycemia

Disadvantages

• Hypoglycemia
• Weight gain
• Injections
Does insulin impose CV risk or mortality?

- UK cohort study of 165,308 adults with type 2 DM. After applying structural models, insulin dose was not associated with mortality in any group. Study provides reassurance.
- In the DCCT/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort, there were fewer CV events in the intensive arm, where subjects received higher insulin doses, than in the conventional arm.
- In the UKPDS no increase in CV events was found among in individuals assigned to treatment with insulin.
- After adjustment for baseline covariates, no significant association of insulin dose with CV risk in ACCORD.

Insulin effects to keep in mind

- Insulin can increase sodium retention and stimulate the sympathetic nervous system.
- Insulin has been shown to be anti-inflammatory, antioxidant, and profibrinolytic and cardioprotective in patients with acute myocardial infarction.
- Overall, insulin does not induce ASCVD when administered properly for diabetes control in humans and lowering glucose to target range is desirable in many ways.

Mirza SA Comment, Arch Intern Med 167;858 2007
Figure 1. Schematic Time–Activity Curves for Selected Insulin Formulations.
The graph depicts time–activity profiles for selected insulin formulations. For simplicity, the known dose-dependent variability in duration of action and the wide variability in hypoglycemic effect for the selected formulations among patients are not represented. Biphasic insulin preparations are not shown.
**Figure 1. Schematic Time–Activity Curves for Selected Insulin Formulations.**
The graph depicts time–activity profiles for selected insulin formulations. For simplicity, the known dose-dependent variability in duration of action and the wide variability in hypoglycemic effect for the selected formulations among patients are not represented. Biphasic insulin preparations are not shown.
Insulin regimens

• Simple: once or twice daily
• Complex: basal and bolus Rx using multiple doses
• Choice depends on severity of diabetes
FIGURE 1. Plasma glucose and insulin concentrations in six healthy non-diabetic subjects. The shaded area represents the mean ± 1 SD. B = breakfast; L = lunch; S = supper; HS = bedtime snack. (Modified from Rizza et al.8)
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Insulin dosing in type 2 DM

- With lower A1c and relatively stable glucose, control may require only basal insulin
- Weight based (may not be the best approach)
  - Start with 10-20 units depending on A1c or 0.2 units/kg
- Can often start with a low dose, but very large amounts may eventually be needed due to resistance requiring vigorous titration.
- May need large amounts in sick patients due to stress, steroids, tube feeds, etc
- Severely insulin deficient: needs may approach like that in type 1 diabetes requiring basal/bolus regimen or insulin pump therapy
The Treat-to-Target Trial
Randomized addition of glargine or human NPH insulin to oral therapy of type 2 diabetic patients

756 subjects with type 2 DM age 55-56
Followed algorithm

Start with 10 IU/day bedtime basal insulin and adjust weekly

<table>
<thead>
<tr>
<th>Mean of self-monitored FPG values from preceding 2 days</th>
<th>Increase of insulin dosage (IU/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥180 mg/dl (10 mmol/l)</td>
<td>8</td>
</tr>
<tr>
<td>140–180 mg/dl (7.8–10.0 mmol/l)</td>
<td>6</td>
</tr>
<tr>
<td>120–140 mg/dl (6.7–7.8 mmol/l)</td>
<td>4</td>
</tr>
<tr>
<td>100–120 mg/dl (5.6–6.7 mmol/l)</td>
<td>2</td>
</tr>
</tbody>
</table>

Diabetes Care, Nov. 2003
For marked insulin deficiency approximately one-half of the total dose should be given as a basal insulin, either as once or twice per day long-acting insulin (glargine or detemir) or as twice per day intermediate-acting insulin (NPH).

Glargine or detemir can be given either at bedtime or in the morning. May need to change to BID.

Bolus insulin is given as short or rapid-acting insulin, divided before meals. The pre-meal dosing is determined by the pre-meal glucose level, meal size and content, as well as activity and exercise pattern.
Adjust for exercise

• Match food to activity - Take enough extra food to balance out activity
• Take additional food during and/or after activity
• Reduce insulin if the goal is weight loss
Types of insulin

- Non-analog (biosynthetic human insulin) sold as Humulin N or Humulin R, Novolin N or Novolin R
  - N = NPH, R = regular
- Commonly used analogs
  - Long acting: glargine, detemir
  - Fast acting: lispro, aspart, glulisine
- Newer insulin preparations
  - U-500 vial or pen form
  - U-300 glargine (sold as Toujeo)
  - U-200 lispro
  - Degludec: extra long acting (sold as Tresiba)
  - Inhaled (sold as Afrezza)
- Pre-mixed long acting/short acting, 50-75/25-50
Degludec (Tresiba)

- Duration 42h, onset 30-90
- Administered daily
- Modified insulin that has one single amino acid deleted in comparison to human insulin, and is conjugated to hexadecanedioic acid via gamma-L-glutamyl spacer at the amino acid lysine at position B29.
- BEGIN Basal-Bolus Type 2 trial (755 pts on degludec, 251 on glargine), less hypoglycemia and less nocturnal hypoglycemia, otherwise non-inferior to glargine
U-500 insulin

- 500 units/ml (as opposed to 100 units/ml for U-100 insulin)
- There are no U-500 syringes so, e.g. 25 units drawn in a U-100 syringe will deliver 125 units of insulin.
- Formulated as regular insulin but duration longer than regular
- Generally used in multiple doses pre-meals and sometimes HS – but does not match well to meal glucose absorption
- Can be used in pumps

Prescribing information, Eli Lilly Co, Indianapolis, IN
U-500 regular insulin

- Sold as Humulin R U-500
- Now approved in pen form
  - Do not convert dosing
  - Pen can deliver up to 300 units in a single injection
Other concentrated insulins

• U-300 glargine (Toujeo)
• U-200 lispro
• Degludec available as U-100 or U-200
S.C. Insulin Pumps (CSII)

- Use estimated as about 40% of patients with type 1 DM in the USA and with increasing frequency in type 2 DM.
- Can be used with a real-time S.C. sensor but (currently) does not act on monitored blood glucose except in limited fashion.
- Does require calibration using fingerstick recordings.
- Requires pump needle insertion recommended every three days.
- Advantages: Convenient, better control of basal insulin, can use a square wave, can be linked to sensors
- Indications: Type 1 or Type 2 with substantial insulin deficiency. Educated patient able to use pump effectively.
1963
First insulin pump
Basal and bolus infusions used.
Continuous subcutaneous insulin infusion
The MiniMed 670G is FDA approved for people with type 1 diabetes ages 14 and over, though a pediatric study (7-13 year olds) is currently underway to investigate an expansion in how it can be prescribed.

The device cannot be used in children less than seven years old and those on less than eight units of insulin per day.
The Artificial Pancreas

HOW IT WORKS: THE ARTIFICIAL PANCREAS

Three main components make up the artificial pancreas system: a continuous glucose sensor, a monitor that displays blood-sugar levels and an insulin pump. Spaghetti-thin tubing inserted just beneath the skin delivers insulin to the body. For dual hormone systems that deliver both insulin and glucagon, one cell-phone-sized device would have two leads into the skin. An algorithm in the monitor assesses blood-sugar levels continuously, adjusting hormone levels automatically. Both the sensor and the pump connect to the monitor wirelessly.

For the future
Mean (SD) of venous PG (A), CGMG (B), insulin and glucagon doses (C), plasma insulin levels (D), and glucagon levels (E) for all experiments. 6 subjects, followed 48h q 15 min venous blood measurement.