 Disclosure

“I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation.”
Pharmacist Objectives

- List the ADA and AACE glycemic recommendations for diabetes.
- Summarize the treatment approaches for Type 2 diabetes.
- Identify specific factors in diabetic medications and insulin that would influence treatment decisions and guide selection.
- Evaluate current guidelines for the prevention and management of diabetes complications.
- Explain the place in therapy for insulin pumps and continuous glucose sensors.
Technician Objectives

- Access the ADA and AACE glycemic recommendations for diabetes.
- Review the common adverse effects of diabetic medications.
- Identify the expiration for the new insulin products.
- Name the immunizations that are recommended in diabetics.
Case #1

- 45 yo male who presents to the pharmacy complaining of GI upset and diarrhea. He tests his blood sugar once a day but is unaware of his goal blood glucose levels. His current A1c is 8% and BMI is 38kg/m².

- Medications:
  - Metformin 1000mg twice a day
ADA Glycemic Recommendations

- A1C <7%
- Fasting and preprandial plasma glucose 80-130 mg/dL
- Peak postprandial plasma glucose <180 mg/dL
Patient/Disease Features

Risks associated with hypoglycemia & other drug adverse effects

Disease Duration

Life expectancy

Important comorbidities

Established vascular complications

Patient attitude & expected treatment efforts

Resources & support system

- more stringent
  - A1C 7%
  - Usually not modifiable

- less stringent
  - Potentially modifiable

low → high
newly diagnosed → long-standing
long → short
absent → Few/mild → severe
absent → Few/mild → severe
highly motivated, adherent, excellent self-care capabilities → less motivated, nonadherent, poor self-care capabilities
readily available → limited

ADA 2017
AACE Glycemic Recommendations

- A1C ≤ 6.5% for patients without concurrent serious illness and at low hypoglycemic risk

- A1C > 6.5% (up to 8%) with concurrent serious illness and at risk for hypoglycemia

- Fasting and preprandial plasma glucose <110 mg/dL

- Peak postprandial plasma glucose <140 mg/dL
Start with Monotherapy unless:

- A1C is greater than or equal to 9%, consider Dual Therapy.
- A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

### Monotherapy

<table>
<thead>
<tr>
<th>Metaformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td>COSTS</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Dual Therapy

<table>
<thead>
<tr>
<th>Metformin + Sulfonylurea</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>moderate risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>COSTS</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

### Triple Therapy

<table>
<thead>
<tr>
<th>Metformin + Sulfonylurea +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td>high</td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>edema, HF, fxs</td>
</tr>
<tr>
<td>COSTS</td>
<td>high</td>
</tr>
</tbody>
</table>

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

(See Figure 8.2)
ADA Guidelines 2017

- **Initial Therapy**: Metformin monotherapy

- **Combination Therapy**: Consider for initial therapy if $A_{1c} \geq 9\%$
  - Metformin +
    - Sulfonylurea
    - TZD
    - DPP-4 Inhibitor
    - SGLT2 Inhibitor
    - GLP-1 Receptor Agonist
    - Basal Insulin

If $A_{1c}$ target not achieved after 3 months of monotherapy
Combination Therapy

If $A_{1c}$ target not achieved after 3 months of combination therapy

Triple Therapy:
- Metformin +
  - 2 additional agents

If $A_{1c}$ target not achieved after 3 months of triple therapy

Combination Injectable Therapy
Combination Injectable Therapy

- **If on a GLP-1 RA**
  - Add basal insulin
    - Initiating basal insulin: 0.1 – 0.2 units/kg/day or 10 units/day
    - Adjust by 10-15% (2-4 units) once or twice weekly as needed

- **If on basal insulin**
  - Add GLP-1 RA, bolus mealtime insulin, or change to premixed insulin twice daily
  - Initiating bolus insulin: 4 units or 0.1 units/kg or 10% of basal dose
  - Adjust by 10-15% (1-2 units) once or twice weekly as needed

- **If on oral agents only**
  - Add basal insulin or GLP-1 RA
GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

- **Entry A1C < 7.5%**
  - **MONOTHERAPY**
    - Metformin
    - GLP-1 RA
    - SGLT-2i
    - DPP-4i
    - TZD
    - AGi
    - SU/GLN
  - If not at goal in 3 months, proceed to Dual Therapy

- **Entry A1C ≥ 7.5%**
  - **DUAL THERAPY**
    - GLP-1 RA
    - SGLT-2i
    - DPP-4i
    - TZD
    - Basal Insulin
    - Onglyza
    - Saxenda
    - Saxenda
    - Exenatide ER
    - Sitagliptin
    - Metformin
    - SU/GLN
  - If not at goal in 3 months, proceed to Triple Therapy

- **Entry A1C > 9.0%**
  - **TRIPLE THERAPY**
    - GLP-1 RA
    - SGLT-2i
    - TZD
    - Basal Insulin
    - DPP-4i
    - Onglyza
    - Saxenda
    - Saxenda
    - Exenatide ER
    - Sitagliptin
    - Metformin
    - SU/GLN
  - If not at goal in 3 months, proceed to or intensify insulin therapy

SYMPTOMS

- **NO**
- **YES**
  - DUAL Therapy
  - TRIPLE Therapy
  - INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

**LEGEND**
- Few adverse events and/or possible benefits
- Use with caution

**PROGRESSION OF DISEASE**

COPYRIGHT © 2017 AACE. MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE. DOI 10.4158/EP161682.CS

AACE 2017
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU</th>
<th>GLN</th>
<th>COLSVL</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
<td>Neutral</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Loss</td>
</tr>
<tr>
<td>RENAL / GU</td>
<td>Contraindicated if eGFR &lt; 30 mL/min/1.73 m²</td>
<td>Exenatide</td>
<td>Not Indicated CrCl &lt; 30</td>
<td>Genital Mycotic Infections</td>
<td>Not Indicated for eGFR &lt; 45 mL/min/1.73 m²</td>
<td>Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Effective in Reducing Albuminuria</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Possible Benefit of Liraglutide</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Saxagliptin and Alogliptin</td>
<td>Neutral</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>CARDIAC*</td>
<td>Neutral</td>
<td>Possible Benefit of Liraglutide</td>
<td>Possible Benefit of Empagliflozin</td>
<td>Possible Risk for Saxagliptin and Alogliptin</td>
<td>Neutral</td>
<td>Moderate</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More CHF Risk</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Canagliflozin Warning</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
<tr>
<td>KETOACIDOSIS</td>
<td>Neutral</td>
<td>Neutral</td>
<td>DKA Occurring in T2D in Various Stress Settings</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td></td>
</tr>
</tbody>
</table>

- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- ? Uncertain effect
- * FDA indication to prevent CVD death in diabetes plus prior CVD events

Copyright © 2017 AACE. May not be reproduced in any form without express written permission from AACE. DOI 10.4158/EP161682.CS
Medication Review and Updates

- Metformin
- SGLT2 inhibitors
- GLP-1 agonists
Metformin and GI intolerance

- Start with 500 mg daily or BID with meals or 850 mg once daily.

- If GI symptoms not bothersome continue to titrate up the dose every 1-2 weeks until the max dose is reached.

- If GI SE occur: Can go back down to previous dose and titrate up slower or can switch to the ER formulation.
Metformin precaution

- Temporarily withhold metformin in patients undergoing radiologic studies involving parenteral administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function
  - 48 hours before (if possible) and **48 hours after procedure**
Metformin and renal function

- **eGFR > 60 ml/min**: No CI, monitor renal function annually
- **eGFR ≥ 45 to < 60 ml/min**: continue use, monitor renal function every 3 to 6 months
- **eGFR ≥ 30 to < 45 ml/min**: If patient is currently on metformin use with caution, consider dosage reduction (50% or 50% of max dose), monitor renal function every 3 months. Do no start med if eGFR, 45 ml/min.
- **eGFR < 30 ml/min**: discontinue use
SGLT2 inhibitors

- Empagliflozin (Jardiance®)
- Canagliflozin (Invokana®)
- Dapagliflozin (Farxiga®)
Empagliflozin CV Outcomes

- EMPA-REG trial
  - Primary outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction (excluding silent MI), or nonfatal stroke
    - 10.5% vs. 12.1% (P<0.04)
    - Reduced CV events by 13%
      - Death from CV causes
        - 3.7% vs. 5.9% (P<0.001)
        - 38% relative risk reduction
      - Myocardial Infarction
        - 4.8% vs. 5.4% (P 0.23)
      - Stroke
        - 3.5% vs 3.0% (P 0.26)

Canagliflozin CV Outcomes

- CANVAS trial
  - Primary outcome: composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
    - 26.9 vs 31.5 events per 1000 patient-years (p=0.02)
      - Death from cardiovascular causes
        - 4.6% vs. 4.2% (95% CI 0.75-0.97)
      - Myocardial infarction
        - 3.7% vs. 3.7% (95% CI 0.69-1.05)
      - Stroke
        - 2.7% vs. 2.7% (95% CI 0.71-1.15)
    - Hospitalization for heart failure
      - 2.1% vs. 2.8% (95% CI 0.52-0.87)
Canagliflozin Amputations

- CANVAS trial

- All amputations
  - 6.3 vs. 3.4 events per 1000 patient years (95% CI 1.41 – 2.75)
  - Leg and foot amputations (mostly toes)
  - Predisposing factors:
    - Prior amputation, peripheral vascular disease, neuropathy, and diabetic foot ulcers

Canagliflozin Bone Fractures

- CANVAS trial
  - All fractures
    - 15.4 vs 11.9 participants per 1000 patient years
    - P=0.02, 95% CI 1.04-1.52
  - Low trauma fractures
    - 11.6 vs. 9.2 participants per 1000 patient years
    - P= 0.06, 95% CI 0.99-1.52

Dapagliflozin Bladder Cancer

- 0.17% dapagliflozin vs. 0.03% placebo/comparator
- Do not use in active bladder cancer
- Risk vs. benefit with history of bladder cancer
- Less concern after subsequent studies
SGLT2 Inhibitors Safety Concerns

- **Diabetic ketoacidosis (DKA)**
  - Nausea, vomiting, abdominal pain, trouble breathing, tiredness
  - Can occur with mildly elevated blood sugars (<250 mg/dL)
  - Potential triggers: major illness, reduced food/fluid intake, reduced insulin dose
  - Consider holding drug in clinical situations that could predispose patient to DKA (e.g. prolonged fasting due to acute illness or surgery)

- **Urinary tract and mycotic infections**
  - Can lead to life-threatening:
    - Blood infections
    - Kidney infections

FDA Drug Safety Communication 2015
GLP-1 Agonists

- **Long-Acting Once Weekly**
  - Exenatide SR (Bydureon®)
  - Albiglutide (Tanzeum®)
  - Dulaglutide (Trulicity®)

- **Long-Acting Once Daily**
  - Liraglutide (Victoza®) *

- **Short-Acting Once Daily**
  - Lixisenatide (Adlyxin®) *

- **Short-Acting Twice Daily**
  - Exenatide (Byetta)

*Available in a combination product with long acting insulin
GLP-1 RA: Cardiovascular Outcomes

- LEADER Trial: Compared liraglutide to placebo
  - Primary Composite Outcome of:
    - Death from any cause*, nonfatal MI, nonfatal stroke
    - 13% vs 14.9% HR 0.87 (95% CI 0.78 – 0.97)
    - Met noninferiority (margin of 1.3) and superiority
  - Statistically significant secondary outcomes:
    - Death from any cause, Death from any cardiovascular cause, Microvascular events, Nephropathy

- EXSCEL Trial
  - Compared exenatide to placebo

GLP-1 RA: Thyroid Cancer

- **Black Box Warning:**
  - Should not be used in patients with a personal or family history of medullary thyroid cancer or multiple endocrine neoplasia syndrome type 2
  - Increased incidence in rodents, however no incidence in humans to date

- Clinical Trials and post-marketing surveillance have not shown any cases of medullary thyroid carcinomas with GLP-1 receptor agonist use
GLP-1 RA: Pancreatitis

- Should not be used in patients with a history of pancreatitis

- Retrospective observational studies have found virtually no increase of pancreatitis with incretin-based therapy
  - Lack of prospective evidence to provide sufficient data to prove a relationship between GLP-1 RA use and pancreatitis
Case #1 Update

- What would you recommend for blood glucose goals?
- What would you recommend for his GI upset and diarrhea?
- Would you add to his current regimen? What and why?
  - Things to consider
    - Efficacy
    - Cost
    - Side effects
    - Weight
    - Hypoglycemia
    - A1c level
Case #2

- 55 yo female who presents to the pharmacy with an A1c of 9%. She has frequent symptoms with increased thirst and urination. You confirm adherence with current medications.

- **Medications:**
  - Metformin extended-release 1000mg twice a day
  - Liraglutide 1.8mg subcutaneous daily
New Insulin products

- Inhaled insulin (Afreeza®)
- Insulin degludec (Tresiba®)
- Insulin glargine 300 unit/ml (Toujeo®)
- Insulin glargine biologic (Basaglar)
- Long acting insulin combination with GLP-1 agonist
  - Insulin degludec and liraglutide (Xultophy®)
  - Insulin glargine and lixisenatide (Soliqua®)
Inhaled Regular Insulin (Afrezza®)

- Available in 4-unit, 8-unit and 12-unit single use cartridges
- Used in combination with long-acting insulin
- Contraindicated in patients with lung disease (asthma, COPD)
  - May cause bronchospasm
- Not recommended in patients who smoke or have stopped smoking < 6 months
# Inhaled Insulin (Afrezza) Dosing Chart

<table>
<thead>
<tr>
<th>Injected Mealtime Insulin Dose</th>
<th>AFREZZA Dose</th>
<th># of cartridges needed</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 unit (blue)</td>
<td>8 unit (green)</td>
</tr>
<tr>
<td>up to 4 units</td>
<td>4 units</td>
<td></td>
</tr>
<tr>
<td>5-8 units</td>
<td>8 units</td>
<td></td>
</tr>
<tr>
<td>9-12 units</td>
<td>12 units</td>
<td>+</td>
</tr>
<tr>
<td>13-16 units</td>
<td>16 units</td>
<td>or/</td>
</tr>
<tr>
<td>17-20 units</td>
<td>20 units</td>
<td>+</td>
</tr>
<tr>
<td>21-24 units</td>
<td>24 units</td>
<td></td>
</tr>
</tbody>
</table>
Long Acting Insulin

- Long acting insulin is known as basal insulin and covers insulin needs for most of the day

- Types
  - Insulin glargine 300 Units/mL (Toujeo SoloStar®)
  - Insulin degludec (Tresiba FlexTouch®)
EDITION 1 Trial - Toujeo

- Phase 3 Trial
- Insulin glargine 300 Units/mL (Toujeo) vs insulin glargine 100 Units/mL (Lantus) in T2DM
  - Glar300 proved to be noninferior to Glar100 in glycemic control
  - Confirmed hypoglycemia or Severe nocturnal hypoglycemia
    - 36% vs 46%; RR 0.79 (95% CI: 0.67 – 0.93) P = 0.0045
  - Documented symptomatic nocturnal hypoglycemia
    - 36% vs 48%

- Glar300 improved glycemic control as well as Glar100 with less nocturnal hypoglycemia and no increase in daytime hypoglycemia
EDITION 4 Trial - Toujeo

- Phase 3 Trial
- Insulin glargine 300 Units/mL (Toujeo) vs insulin glargine 100 Units/mL (Lantus) in T1DM
  - Glar300 proved to be noninferior to Glar100 in glycemic control
  - No significant difference in overall hypoglycemia, nocturnal hypoglycemia or severe hypoglycemia

- Glar300 improved glycemic control as well as Glar100 with no significant difference in hypoglycemia regardless of time of injection
SWITCH 1 Trial - Tresiba

- Compared insulin degludec (Tresiba) to insulin glargine (Lantus) in T1DM
- Patients started on degludec or glargine, then switched to other treatment
- Degludec vs. glargine during maintenance period

<table>
<thead>
<tr>
<th>Event rate per 100 pt yrs exposed</th>
<th>Degludec</th>
<th>Glargine</th>
<th>Reduction * P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypoglycemic</td>
<td>2,201</td>
<td>2,463</td>
<td>11%*</td>
</tr>
<tr>
<td>Symptomatic nocturnal hypoglycemia</td>
<td>227</td>
<td>429</td>
<td>36%*</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>69</td>
<td>92</td>
<td>35%*</td>
</tr>
</tbody>
</table>
SWITCH – 2 Trial - Tresiba

- Compared insulin degludec (Tresiba) to insulin glargine (Lantus) in T2DM
- Patients started on degludec or glargine, then switched to other treatment
- Degludec vs. glargine during maintenance period

<table>
<thead>
<tr>
<th>Event rate per 100 pt yrs exposed</th>
<th>Degludec</th>
<th>Glargine</th>
<th>Reduction * P &lt; 0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic hypoglycemic</td>
<td>186</td>
<td>265</td>
<td>30%*</td>
</tr>
<tr>
<td>Symptomatic nocturnal hypoglycemia</td>
<td>55</td>
<td>94</td>
<td>42%*</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>5</td>
<td>9</td>
<td>46%</td>
</tr>
</tbody>
</table>

Long Acting Insulin Conversion

- Glargine 100u/ml (Lantus®) to Glargine 300u/ml (Toujeo®)
  - The starting dose of Toujeo® should be the same as the once daily long-acting 100u/ml injection

- Long acting insulin to insulin degludec (Tresiba®)
  - Tresiba FlexTouch® available in 100 u/ml pen and 200 u/ml pen
    - Adult patients: Start Tresiba at the same unit dose as the total daily long-acting or intermediate-acting insulin dose
    - Pediatrics: Start Tresiba at 80% of the total daily dose
Basaglar KwikPen

- Approved by the FDA as a follow-on biologic
  - Not approved by the FDA as a biosimilar to insulin glargine (Lantus)
  - Lantus was not approved under the Public Health Service Act, so there was no reference for Basaglar

- Basaglar compared to Lantus:
  - Amino acid sequence is identical
  - Very similar pharmacokinetics and pharmacodynamics (onset, peak, duration)
  - Estimated to be 20% less expensive
**Initiate Bolus Insulin**
Usually with metformin ± other noninsulin product

- **Start**: 10 U/day or 0.1 – 0.2 U/kg/day
- **Adjust**: 10-15% or 2-4 units once or twice weekly to reach FBG target
- **For hypo**: Determine & address cause; if no clear reason for hypo, ↓ dose by 4 units or 10-20%

---

If A1c not controlled, consider combination injectable therapy

**Add 1 rapid-acting Insulin injection before largest mean**

- **Start**: 4 units, 0.1 U/kg or 10% basal dose. If A1c <8%, consider ↓ basal by same amount
- **Adjust**: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo**: determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

**Add GLP-1 RA**

- If not tolerated or A1c target not reached, change to 2 injection insulin regimen
- **Adjust**: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

**Change to premixed Insulin twice daily (before breakfast and supper)**

- **Start**: Divide current basal dose into 2/3 AM, 1/3 PM or ½ AM, ½ PM
- **Adjust**: ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached
- **For hypo**: Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

ADA 2017
Add ≥2 rapid-acting Insulin injections before meals (‘basal-bolus’)

**Start:** 4 units, 0.1 U/kg, or 10% basal dose/meal. If A1c <8%, consider ↓ basal by same amount

**Adjust:** ↑ dose(s) by 1-2 units or 10-15% once or twice weekly to achieve SMBG target

**For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

**If A1c not controlled, advance to basal-bolus**

---

**If goals not met, consider changing to alternative insulin regimen**

---

**Change to premixed analog insulin 3 times daily (breakfast, lunch, supper)**

**Start:** Add additional injection before lunch

**Adjust:** ↑ doses by 1-2 units or 10-15% once or twice weekly to achieve SMBG target

**For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

---

**If A1c not controlled, advance to 3rd injection**
ALGORITHM FOR ADDING/INTENSIFYING INSULIN

START BASAL (Long-Acting Insulin)
A1C < 8%
TDD 0.1–0.2 U/kg
A1C > 8%
TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

Glycemic Control Not at Goal*

INTENSIFY (Prandial Control)
Add GLP-1 RA
Or SGLT-2i
Or DPP-4i
Add Prandial Insulin

Basal Plus 1, Plus 2, Plus 3
- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

Basal Bolus
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% or 1–2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% – 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% – 40%

*Glycemic Goal:
- <7% for most patients with T2D; fasting and premealBG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient’s age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

COPYRIGHT © 2017 AACE. MAY NOT BE REPRODUCED IN ANY FORM WITHOUT EXPRESS WRITTEN PERMISSION FROM AACE. DOI 10.4158/EP161682.CS
Basal Insulin/GLP-1 agonist Combination Products

- Insulin degludec and liraglutide (Xultophy®)
  - Recommended for T2DM patients not well controlled on basal insulin (< 50 units daily) or liraglutide (≤ 1.8 mg daily)

- Insulin glargine and lixisenatide (Soliqua®)
  - Recommended for T2DM patients not well controlled on basal insulin (< 60 units daily) or lixisenatide
Soliqua®

- 3:1 ratio of insulin glargine to lixisenatide
  - Maximum dose of 60 units : 20 mcg
- If uncontrolled on <30 units of basal insulin
  - Initiate 15 units : 5 mcg
- If uncontrolled on ≥30 - 60 units of basal insulin
  - Initiate 30 units : 10 mcg
- Titrate upwards or downwards by 2-4 units every week based on targeted fasting plasma glucose
- Prime the pen before each injection with 2 units of Soliqua®
Xultophy®

- Ratio of 100 units insulin degludec : 3.6 mg liraglutide
  - Maximum dose of 50 units : 1.8 mg

- If uncontrolled on <50 units basal insulin or liraglutide
  - Initiate 16 units : 0.58 mg

- Titrate upwards or downwards by 2 units every 3-4 days based on targeted fasting plasma glucose

- Prime the pen before each injection dialed to the priming symbol on the Xultophy® pen
## Insulin Shelf Life

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled insulin (Afrezza® inhaled insulin)</td>
<td>Inhaler: 15 days</td>
</tr>
<tr>
<td></td>
<td>Unopened foil package, blister cards, and strips: 10 days</td>
</tr>
<tr>
<td></td>
<td>Opened strips: 3 days</td>
</tr>
<tr>
<td>Insulin detemir (Levemir® vials, Levemir FlexTouch®)</td>
<td>Vials, pens: 42 days</td>
</tr>
<tr>
<td>Insulin glargine (Basaglar KwikPen)</td>
<td>Pens: 28 days</td>
</tr>
</tbody>
</table>
# Insulin Shelf Life

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Expiration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin glargine (Lantus SoloSTAR®, Toujeo SoloSTAR®)</td>
<td>Pens: 28 days</td>
</tr>
<tr>
<td>Insulin degludec (Tresiba FlexTouch®)</td>
<td>Pens: 56 days</td>
</tr>
<tr>
<td>Insulin degludec and liraglutide (Xultophy®)</td>
<td>Pens: 21 days</td>
</tr>
<tr>
<td>Insulin glargine and lixisenatide (Soliqua®)</td>
<td>Pens: 14 days</td>
</tr>
</tbody>
</table>
Case #2 Update

- What would you recommend for her medication regimen?
- What key points would you counsel on based on your recommendations?
- What is the expiration of the products based on your recommendations?
Case #3

- 65 yo male with diabetes and hypertension

- **Medications:**
  - Meformin 1000mg twice a day
  - Lisinopril 20mg daily

- **Immunizations:**
  - Hepatitis B series
  - Influenza vaccine yearly
  - PPSV23 - 5 years ago
Immunizations

- Annually provide an **influenza vaccine** to all diabetic patients 6 months of age or older.

- Administer **pneumococcal polysaccharide vaccine (PPSV23)** to all diabetic patients ≥2 years of age.

- Adults ≥65 y.o., if not previously vaccinated, should receive **pneumococcal conjugate vaccine 13** (PCV13), followed by PPSV23 12 months later.

- Adults ≥65 y.o., if previously vaccinated with PPSV23, should receive a f/u ≥ 12 months later with PCV13.

- Administer hepatitis B vaccination to unvaccinated adults with diabetes who are aged 19-59 years -C

ADA, CDC 2017
Blood pressure control

- Patients with diabetes and hypertension should be treated to a BP goal of \(<140/90\) –A

- Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. -B

- Patients with DM and HTN should be on a regimen that includes either an ACEI or an ARB, thiazide or dihydropyridine CCB -B

ADA 2017
Antiplatelet therapy

- Use ASA (aspirin) therapy, 75-162 mg/day, as a secondary prevention strategy in patients with diabetes and Cardiovascular Disease —A

- For patients with atherosclerotic cardiovascular disease and documented aspirin allergy, clopidogrel (75 mg/day) should be used. - B

- Consider ASA, 75-162 mg/day, as primary prevention in those with diabetes who are at increased Cardiovascular Disease risk (10-year risk >10%) -C
  - Most men or women ≥ 50 years old who are not at increased risk of bleeding and have one additional major risk factor including:
    - Family history of premature CVD
    - Hypertension
    - Smoking
    - Dyslipidemia
    - Albuminuria

ADA 2017
## Statin recommendations in DM

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Factors</th>
<th>Statin Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;40 yo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors**</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>Overt ASCVD</td>
<td>High</td>
</tr>
<tr>
<td>40-75 yo</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>Overt ASCVD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASVCD and LDL &gt;50 in high intensity intolerant</td>
<td>Moderate + ezetimibe</td>
</tr>
<tr>
<td>&gt;75 yo</td>
<td>None</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>ASCVD risk factors</td>
<td>Moderate or high</td>
</tr>
<tr>
<td></td>
<td>Overt ASVCD</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>ASVCD and LDL &gt;50 in high intensity intolerant</td>
<td>Moderate + ezetimibe</td>
</tr>
</tbody>
</table>

**CVD risk factors include LDL cholesterol ≥ 100 mg/dL, HTN, smoking, CKD, albuminuria, and family hx of premature ASCVD**
## Intensity

<table>
<thead>
<tr>
<th>High-Intensity Statin Therapy</th>
<th>Moderate-Intensity Statin Therapy</th>
<th>Low-Intensity Statin Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose lowers LDL–C on average, by approximately ≥50%</td>
<td>Daily dose lowers LDL–C on average, by approximately 30% to &lt;50%</td>
<td>Daily dose lowers LDL–C on average, by &lt;30%</td>
</tr>
<tr>
<td>Atorvastatin 40–80 mg</td>
<td>Atorvastatin 10-20 mg</td>
<td>Simvastatin 10 mg</td>
</tr>
<tr>
<td>Rosuvastatin 20-40 mg (40mg not commonly used)</td>
<td>Rosuvastatin 5-10 mg</td>
<td>Pravastatin 10–20 mg</td>
</tr>
<tr>
<td></td>
<td>Simvastatin 20–40 mg</td>
<td>Lovastatin 20 mg</td>
</tr>
<tr>
<td></td>
<td>Pravastatin 40-80 mg</td>
<td>Fluvastatin 20–40 mg</td>
</tr>
<tr>
<td></td>
<td>Lovastatin 40 mg</td>
<td>Pitavastatin 1 mg</td>
</tr>
<tr>
<td></td>
<td>Fluvastatin XL 80 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluvastatin 40 mg bid</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pitavastatin 2–4 mg</td>
<td></td>
</tr>
</tbody>
</table>
Statin recommendations in DM

- For patients of all ages with diabetes and atherosclerotic cardiovascular disease, **high-intensity** statin therapy should be added to lifestyle therapy. A

- For patients with diabetes aged < 40 years with additional atherosclerotic cardiovascular disease risk factors, consider using **moderate-intensity or high-intensity statin** and lifestyle therapy. C

- For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using **moderate-intensity** statin and lifestyle therapy. A
Statin recommendations in DM

- For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using **high-intensity statin** and lifestyle therapy. **B**

- For patients with diabetes aged >75 years without additional atherosclerotic cardiovascular disease risk factors, consider using **moderate-intensity** statin therapy and lifestyle therapy. **B**

- For patients with diabetes aged >75 years with additional atherosclerotic cardiovascular disease risk factors, consider using **moderate-intensity or high-intensity** statin therapy and lifestyle therapy. **B**

ADA 2017
Case #3 Update

- What is the blood pressure goal for this patient?
- What immunizations should be given?
- Does the patient need antiplatelet therapy?
- What statin is recommended?
Case #4

- 55 yo female who presents to the pharmacy for a refill of test strips. She currently checks her blood sugars 8 times a day.

- Medications:
  - Insulin glargine 80 units twice a day
  - Insulin aspart 25 units three times a day with meals
Insulin pumps

- Benefits of pump
- Ideal candidates
- Important insulin pump basics
Insulin Pump Benefits

- Improved glycemic control
  - Decreased risk of hypoglycemia
  - Less hyperglycemia
- Decreased insulin requirements
- Increased flexibility
- Improved quality of life
- Decreased hospitalizations and overall cost of health care
Study results

- Medtronic 670g in 12,389 patient days of use in Type 1 DM
- Change in A1c
  - Baseline - 7.4±0.9%
  - Study End - 6.9±0.6%
- Severe hypoglycemia
  - No cases
- DKA
  - No cases
Pharmacist Collaboration with Transition to Pump Therapy

- 25 patients with Type 1 or 2 diabetes
- HbA1c reduced from 8.69% to 7.52% (p<0.001)
- Fewer clinic visits 5.09 vs 3.78 (P=0.009)
- Patient comfort level (p<0.001)
Insulin Pumps – Ideal Candidates

- Motivated, knowledgeable in DM self-care
- Self-monitors blood glucose
- Carbohydrate counting
- Problem solver
- Emotionally stable
Important Insulin Pump Basics

- Most patients use rapid acting U-100 insulin (aspart, lispro, glulisine)
- Patients need to have a back-up supply of insulin and syringes/pens
- Encourage proper site rotation
- Stability of insulin in pump
- Understand how to handle pumps during hospitalizations/surgery
Continuous Glucose Monitor Important Points

- Blood sugar trends
- Calibration
- Importance of blood glucose and sensor glucose
- Data patterns
- Alerts/Alarms
DIAMOND Trial - CGM

- 158 patients with Type 1 diabetes on multiple injections
- A1c reduction from baseline to 24 weeks reduced by 1.0% (P<.001)
- Median duration of hypoglycemia was 43 min/day in CGM vs 80 min/day in control group

Medicare Guidelines for Self Monitoring Blood Glucose

- Oral medications or diet controlled
  - Test blood sugars once a day

- Insulin
  - Test blood sugars three times a day

- Exceptions for Medical Necessity

- Therapeutic Continuous Glucose Monitor (CGM)
Case #4 Update

- Would she benefit from an insulin pump and CGM?
- What insulin would she use in her pump?
- Would her total daily dose of insulin increase or decrease?
Pharmacist Post-Assessment

Which of the following are ADA glycemic goals for diabetes?

A. Peak postprandial plasma glucose <180 mg/dL
B. Fasting and preprandial plasma glucose 80-130 mg/dL
C. A1c < 7% for most patients
D. All of the above
Pharmacist Post-Assessment

What medication is first line for the treatment of Type 2 diabetes in a patient with normal kidney function and an A1c of 8 percent?

A. Glipizide  
B. Metformin  
C. Insulin  
D. None of the above
Pharmacist Post-Assessment

A pneumococcal polysaccharide vaccine (PPSV23) should be administered to all diabetic patients ≥2 years of age who do not have contraindications every 5 years.

A. True
B. False
Pharmacist Post-Assessment

Insulin pumps and continuous glucose monitoring devices should be recommended for all diabetic patients.

A. True
B. False
Pharmacist Post-Assessment

Which of the following insulins has the lowest incidence of hypoglycemia?

A. Insulin degludec
B. Insulin glargine
C. Insulin aspart
D. None of the above
Which of the following are ADA glycemic goals for diabetes?

A. Peak postprandial plasma glucose <180 mg/dL
B. Fasting and preprandial plasma glucose 80-130 mg/dL
C. A1c < 7% for most patients
D. All of the above
Technician Post-Assessment

Which of the following medications has an expiration date of 56 days?

A. Insulin glargine
B. Insulin degludec
C. Insulin detemir
D. All of the above
Which of the following is a common adverse effect from metformin?

A. Hypoglycemia
B. Weight gain
C. GI intolerance
D. None of the above
Influenza vaccine is recommended yearly in diabetics >6 months old with no contraindications.

A. True
B. False
Questions
References

- Home PD, Bergenstal RM, Bolli GB, et al. New insulin glargine 300 units/mL versus glargine 100 units/mL in people with type 1 diabetes: a randomized, phase 3a, open-label clinical trial (EDITION 4). Diabetes Care. 2015;38(12):2217-25.
References

Images References