Antihyperglycemic Agents: Which One to Use
Nicole Temofonte, D.O.
August 2019

Objectives

- List the glycemic goals for nonpregnant adults with DM Type 2.
- Discuss the approach to treatment of DM Type 2.
- Identify resources for algorithms for management of DM Type 2.
- Review the classes of medications used for treatment of diabetes mellitus.
- Differentiate the different types of insulin based on onset, peak and duration of action.
- Describe approaches to selection of antihyperglycemic agents in adult patients with DM Type 2.
What is the ultimate goal?

- Achieve glycemic control with minimal side effects.
  - Achieving this goal for each individual patient is of more importance than establishing a universally accepted algorithm.

Common Themes of Algorithms

- Individualize glycemic targets for each patient
- Intensify treatment to achieve and maintain individual targets
  - Avoid clinical inertia
  - Combination therapy
  - Insulin
    - Likely eventually for many patients
    - Not a threat
    - Should not be delayed
What are the glycemic goals for nonpregnant adults with diabetes?

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>A1C</td>
<td>&lt;7.0%</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>80-130 mg/dl</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose</td>
<td>&lt;180 mg/dl</td>
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**TAILOR THERAPY FOR INDIVIDUAL PATIENTS!!!**

- Age/life expectancy
- Comorbid conditions
- Diabetes duration
- Hypoglycemia status
- Individual patient concerns
- Known CVD/advanced microvascular complications

**Depicted are patient and disease factors used to determine optimal A1C targets.**

**Approach to Individualization of Glycemic Targets**

- **Patient / Disease Features**
- **More stringent**
- **Less stringent**

<table>
<thead>
<tr>
<th>Risks potentially associated with hypoglycemia and other drug adverse effects</th>
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<tbody>
<tr>
<td>low</td>
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<tr>
<td>high</td>
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<table>
<thead>
<tr>
<th>Disease duration</th>
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<tbody>
<tr>
<td>newly diagnosed</td>
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<tr>
<td>long-standing</td>
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<table>
<thead>
<tr>
<th>Life expectancy</th>
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<tbody>
<tr>
<td>long</td>
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<tr>
<td>short</td>
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<table>
<thead>
<tr>
<th>Important comorbidities</th>
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<tbody>
<tr>
<td>absent</td>
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<tr>
<td>few / mild</td>
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<tr>
<td>severe</td>
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<table>
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<tr>
<th>Established vascular complications</th>
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<tbody>
<tr>
<td>absent</td>
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<tr>
<td>few / mild</td>
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<tr>
<td>severe</td>
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<table>
<thead>
<tr>
<th>Patient preference</th>
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<tbody>
<tr>
<td>highly motivated, excellent self-care capabilities</td>
</tr>
<tr>
<td>preference for less burdensome therapy</td>
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<table>
<thead>
<tr>
<th>Resources and support system</th>
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<tbody>
<tr>
<td>readily available</td>
</tr>
<tr>
<td>limited</td>
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</tbody>
</table>

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American Diabetes Association Clin Diabetes 2019;37:11-34
What is the approach to DM management?

- Lifestyle management
  - Diabetes Self Management Education (DSME)
  - Medical Nutrition Therapy (MNT)
  - Physical activity
  - Smoking cessation counseling
  - Psychosocial assessment and care


What is the approach to DM management?

- Lifestyle management
- Pharmacologic therapy
  - DM Type 1
    - Insulin treatment is essential for Type 1 Diabetes
      - Pramlintide
      - Pancreas and islet cell transplantation
DM Type 2 Pharmacotherapy

- Many agents
  - Oral
  - Injectable
    - Not all injectable agents are insulin!

Need to stay current

- Ever changing
- New agents
- Learn more about existing agents
- New combination formulations
Pathogenesis of type 2 diabetes: the triumvirate.

Ralph A. DeFronzo Diabetes 2009;58:773-795

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Ominous Octet Pathway and Agents that Target Them

Pharmacologic Therapy for Diabetes mellitus Timeline

DM Type 2 Pharmacotherapy

- Oral agents
  - Biguanides
    - Metformin (Glucophage)
    - Metformin liquid (Riomet)
    - Metformin extended release (Glucophage XR, Fortamet, Glumetza)
  - Sulfonylureas
    - Glimepiride (Amaryl)
    - Glyburide (Diabeta, Micronase)
    - Glipizide (Glucotrol, Glucotrol XL)
    - Micronized glyburide (Glynase)
  - Meglitinides
    - Repaglinide (Prandin)
    - Nateglinide (Starlix)
  - Thiazolidinediones
    - Pioglitazone (Actos)
    - Rosiglitazone (Avandia)
DM Type 2 Pharmacotherapy

- Oral agents
  - DPP-IV inhibitors
    - Sitagliptin (Januvia)
    - Saxagliptin (Onglyza)
    - Linagliptin (Tradjenta)
    - Alogliptin (Nesina)
  - Alpha-glucosidase inhibitors
    - Acarbose (Precose)
    - Miglitol (Glyset)
  - Bile acid sequestrants
    - Colesevelam (Welchol)
  - Sodium glucose co-transporter 2 (SGLT2) inhibitors
    - Canagliflozin (Invokana)
    - Dapagliflozin (Farxiga)
    - Empagliflozin (Jardiance)
    - Ertugliflozin (Steglatro)
  - Dopamine agonist
    - Bromocriptine (Cycloset)

DM Type 2 Pharmacotherapy

- Injectable agents
  - GLP-1 Agonists
    - Exenatide (Byetta)
    - Exenatide extended release (Bydureon)
    - Liraglutide (Victoza)
    - Dulaglutide (Trulicity)
    - Lixisenatide (Adlyxin)
    - Semaglutide (Ozempic)
  - Amylin analog
    - Pramlintide (Symlin)
  - Insulin (see next two slides)
DM Type 2 Pharmacotherapy

- Insulin
  - Rapid acting
    - Lispro (Humalog)
    - Aspart (Novolog)
    - Glulisine (Apidra)
    - Inhaled (Afrezza)
  - Short acting
    - Regular (Humulin R 100U)
    - Regular (Novolin R)
  - Intermediate acting
    - NPH (Humulin N)
    - NPH (Novolin N)

- Long acting
  - Glargine 100 units/ml (Lantus)
  - Detemir (Levemir)
- Ultra-long acting
  - Degludec (Tresiba)
- Mix insulin
  - 70% NPH and 30% regular (Humulin 70/30)
  - 70% NPH and 30% regular (Novolin 70/30)
  - 50% insulin lispro protamine and 50% insulin lispro (Humalog 50/50)
  - 75% insulin lispro protamine and 25% insulin lispro (Humalog 75/25)
  - 70% insulin aspart protamine and 30% insulin aspart (Novolog 70/30)
- Concentrated
  - Glargine 300 units/mL (Toujeo)
DM Type 2 Pharmacotherapy

- Metformin monotherapy should be started at diagnosis of DM Type 2 unless a patient has a contraindication
- Should be continued as long as tolerated and not contraindicated
- Other agents including insulin should be added
- Periodic measurement of vitamin B12 should be considered in patient’s with long term use especially those with anemia and/or peripheral neuropathy

Biguanides

- Metformin
  - Mechanism of action:
    - Suppresses hepatic glucose production (hepatic gluconeogenesis)
    - Increases insulin sensitivity (increase peripheral glucose uptake and utilization)


Biguanides-Metformin

**Advantages**

- Generally well tolerated
- Usually not accompanied by hypoglycemia when used as monotherapy
- Weight stability or modest weight loss
- Cost-generic available

**Disadvantages**

- Adverse gastrointestinal side effects: abdominal pain, nausea, diarrhea but generally resolve over time
- Slow titration may increase tolerability
- Reduces intestinal absorption of B12
- Most serious adverse effect is lactic acidosis although low risk (incidence 9 per 100,000 person years)
  - May be safely used in patients with eGFR ≥ 30 ml/min/1.73m²
  - REVIEW NEW LABELING GUIDELINES!
- Should be held in patients receiving intravenous contrast medium and/or undergoing a surgical procedure until stable renal function can be established
- CI in patients with factors predisposing to lactic acidosis
  - Impaired renal function eGFR<30
  - Concurrent liver disease or alcohol abuse
  - Unstable or acute heart failure
  - Past history of lactic acidosis
  - Decreased tissue perfusion or hemodynamically unstable

FDA LABEL CHANGES FOR METFORMIN*

- Before starting metformin, obtain the patient’s eGFR.
- Metformin is contraindicated in patients with an eGFR <30mL/min/1.73m2.
- Starting metformin in patients with an eGFR between 30–45mL/min/1.73m2 is not recommended.
- Obtain an eGFR at least annually in all patients taking metformin. In patients at increased risk for the development of renal impairment such as the elderly, renal function should be assessed more frequently.
- In patients taking metformin whose eGFR later falls <45mL/min/1.73m2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient’s eGFR later falls <30mL/min/1.73m2.
- Discontinue metformin at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30–60mL/min/1.73m2; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. Re-evaluate eGFR 48 hours after the imaging procedure; restart metformin if renal function is stable.

Metformin-containing Drugs: Drug Safety Communication-Revised Warnings for Certain Patients with Reduced Kidney Function Posted online 4/8/2016 www.fda.gov

Sulfonylureas (SFU)

- **First generation**: Tolbutamide, Chlorpropamide
- **Second generation**: Glyburide, Glipizide, Glimepiride
- **Mechanism of action**-
  - Known as a secretagogue-Enhance insulin secretion by inhibiting ATP-dependent potassium channels in the islet cells
  - Stimulates release of endogenous insulin
  - Glycemic benefits are nearly fully realized at half maximal doses and higher doses should generally be avoided
  - Should **not** be used in settings of advanced hepatic or renal impairment given metabolism and clearance pathways
## Sulfonylureas-Glyburide, Glipizide, Glimepiride

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Onset of glucose lowering effect is relatively rapid</td>
<td>• <strong>Hypoglycemia</strong> which can be prolonged and life threatening. Severe episodes are more likely to occur in the elderly. Glyburide is associated with a substantially greater risk of hypoglycemia than other second generation sulfonylureas (glipizide and glimepiride and their extended formulations).</td>
</tr>
<tr>
<td>• Cost-generic available</td>
<td>• Increased risk of cardiovascular mortality (based on studies with first generation)</td>
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<td></td>
<td>• <strong>Weight gain</strong> of ~2kg following initiation of therapy</td>
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<td>• Maintenance of glycemic targets over time is not as good as monotherapy with TZD or Metformin</td>
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### Meglitinides

- Repaglinide, Nateglinide

- **Mechanism of action**-
  - Also a secretagogue: Stimulate insulin secretion although bind to a different site within the sulfonylurea receptor
  - Shorter half life than the sulfonylureas and must be administered more frequently
  - Repaglinide has little renal clearance (principally metabolized in the liver)
Glinides-Repaglinide, Nateglinide

**Advantages**
- Possible less frequent hypoglycemia vs. SFU

**Disadvantages**
- Multiple daily doses
- Hypoglycemia
- Weight gain
- Cost

α-Glucosidase Inhibitors
- Acarbose, Miglitol

**Mechanism of action**
- Delay the absorption of dietary carbohydrates by inhibiting intestinal brush border α-glucosidase enzymes
- Reduce the postprandial peak in blood glucose

α-Glucosidase Inhibitors

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Lower postprandial glucose levels without causing hypoglycemia</td>
<td>• Increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms</td>
</tr>
<tr>
<td></td>
<td>• Increase aminotransferase and triglycerides</td>
</tr>
<tr>
<td></td>
<td>• Be aware of contraindications</td>
</tr>
<tr>
<td></td>
<td>• IBD</td>
</tr>
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<td></td>
<td>• Cirrhosis</td>
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<td></td>
<td>• DKA</td>
</tr>
<tr>
<td></td>
<td>• Bowel obstruction</td>
</tr>
<tr>
<td></td>
<td>• Severe digestive problems</td>
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Thiazolidinediones (TZD)

- Pioglitazone, Rosiglitazone

- **Mechanism of action**-
  - Peroxisome proliferator-activated receptor gamma (PPAR γ) modulators
  - Increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin

- Other agents typically preferred
Thiazolidinediones-Pioglitazone, Rosiglitazone

**Advantages**
- More durable effect on glycemic control especially when compared to sulfonylureas

**Disadvantages**
- FDA Black Box-Congestive heart failure
- Weight gain and fluid retention with peripheral edema and increased risk for CHF
- Hepatotoxicity
- Several meta analyses have suggested a 30-40% relative increase in risk for MI with rosiglitazone??
- Decrease bone density and increased fracture risk particularly in women
- "Bladder cancer? Should not be used in patients with active bladder cancer

GLP-1 Agonists

- Drugs in class:
  - Exenatide
  - Liraglutide
    - Once daily
  - Dulaglutide
    - Once weekly
  - Lixisenatide
    - Once daily
  - Semaglutide
    - Once weekly
- Subcutaneous injection
- **Mechanism of action**-
  - Secretion of insulin by pancreatic β cells in a glucose dependent manner
  - Suppresses secretion of glucagon by pancreatic α cells
  - Slows gastric emptying
  - Decreases appetite
Dipeptidyl Peptidase-4 Inhibitors
Sitagliptan, Saxagliptan, Linagliptan, Alogliptan

- **Mechanism of action** -
  - ↑ Incretins (GLP-1 and GIP) by inhibiting DPP-4 → ↑ glucose mediated insulin secretion and suppresses glucagon secretion
  - DPP-4 is the enzyme which inactivates incretins
- Weight neutral
- Low risk of hypoglycemia (if not on additional agents that can cause hypoglycemia)
- Oral

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### Dipeptidyl Peptidase-4 Inhibitors

#### Advantages
- Weight neutral
- Low risk of hypoglycemia (if not on additional agents that can cause hypoglycemia)
- Oral

#### Disadvantages
- Newer agents
- Cost
- Potential risk of acute pancreatitis and pancreatic cancer-insufficient evidence to establish causal relationship
- Mild urinary or respiratory infections
- Joint pain
- ?Heart failure? Research ongoing
  - Discontinue Saxagliptan and Alogliptan in patients who develop heart failure
- Dose adjustment in renal disease (except linagliptan)
- Monitor LFTs with alogliptin
Amylin Analogs

- Pramlintide
  - Stable analog of human amylin
  - Amylin
    - B-cell hormone co-secreted with insulin and helps regulate postprandial glucose levels
    - Type 1 DM-lack endogenous amylin
    - Type 2 DM-relative deficiency of endogenous amylin

- **Mechanism of action** -
  - Slows gastric emptying, reduces postprandial glucagon and glucose release and promotes satiety
  - Administered as subcutaneous injection before meals


<table>
<thead>
<tr>
<th><strong>Advantages</strong></th>
<th><strong>Disadvantages</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Not associated with hypoglycemia unless used in conjunction with agents that can cause hypoglycemia</td>
<td>Subcutaneous injection before all meals</td>
</tr>
<tr>
<td>Weight loss</td>
<td>Most common adverse effect is nausea</td>
</tr>
</tbody>
</table>
Sodium glucose co-transporter 2 (SGLT2) inhibitors
Canagliflozin, Dapagliflozin, Empagliflozin, Ertugliflozin

- **Mechanism of action-**
  - Inhibits SGLT2 in the proximal nephron
  - Blocks glucose reabsorption by the kidney increasing glycosuria.

When is insulin used?

- **Type 1 DM**
  - Multiple daily injections or continuous subcutaneous insulin infusion
  - Match prandial insulin to mealtime carbohydrate intake taking into account premeal blood sugar and planned physical activity

- **Type 2 DM**
Types of Insulin

- **Rapid** acting (analog)
  - Lispro (Humalog)
  - Aspart (Novolog)
  - Glulisine (Apidra)

- **Short** acting (human)
  - Regular (Humulin R, Novolin R)

- **Intermediate** acting (human)
  - NPH (Humulin NPH, Novolin NPH)

- **Long** acting (analog)
  - Gliargine (Lantus)
  - Detemir (Levemir)

Types of Insulin

- **Rapid** acting (analog)
  - Human insulin inhalation powder (Afrezza)
  
  ![Afrezza Inhaler](https://afrezza.com/uploads/hcp/holding-the-afrezza-inhaler.png)

- **Ultra-long** acting (analog)
  - Degludec (Tresiba)
<table>
<thead>
<tr>
<th>INSULIN</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prandial/Bolus Insulin</td>
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<td></td>
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<tr>
<td><strong>Rapid acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro (Humalog), Aspart (Novolog), Glulisine (Apidra)</td>
<td>5-15 min</td>
<td>1-1.5 hrs</td>
<td>3-4 hrs</td>
</tr>
<tr>
<td><strong>Short acting</strong></td>
<td></td>
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<tr>
<td>Regular</td>
<td>30-60 min</td>
<td>2 hrs</td>
<td>6-8 hrs</td>
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<tr>
<td><strong>Basal</strong></td>
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<tr>
<td><strong>Intermediate acting</strong></td>
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<td></td>
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</tr>
<tr>
<td>NPH</td>
<td>2-4 hrs</td>
<td>6-7 hrs</td>
<td>10-20 hrs</td>
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<tr>
<td><strong>Long acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine (Lantus)</td>
<td>1.5 hrs</td>
<td>Flat</td>
<td>~24 hrs</td>
</tr>
<tr>
<td>Detemir (Levemir)</td>
<td>1 hr</td>
<td>Flat</td>
<td>17 hrs</td>
</tr>
</tbody>
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Activity Profiles of Different Types of Insulin

https://dtc.ucsf.edu/images/charts/4.1i.jpg
Degludec

- Ultralong acting basal insulin
  - ½ life ~25 hours
  - Duration of action >42 hours
  - Glucose lowering effect is evenly distributed over 24 hour dosing interval


Concentrated insulins

<table>
<thead>
<tr>
<th></th>
<th>Human Regular U500</th>
<th>Degludec U200</th>
<th>Glargine U300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of action</td>
<td>6-10 hours</td>
<td>42 hours</td>
<td>&gt;30 hours</td>
</tr>
<tr>
<td>Half-life</td>
<td>4 hours</td>
<td>25 hours</td>
<td>18-19 hours</td>
</tr>
<tr>
<td>Steady State</td>
<td>2-3 days</td>
<td>5 days</td>
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</tbody>
</table>

ADA Guidelines: Pharmacologic Approach to Glycemic Treatment

- Focus on using an available agent that fits with patient’s preference and accessibility.
- The practitioner decides the best class for an individual.
What factors should you consider?

- Efficacy
- Presence or absence of symptoms of hyperglycemia
- HbA1C
- Side effect profile
- Hypoglycemia risk
- Effect on weight
- Cost/availability
- Durability
- Patient preference/adherence
- Patient comorbidities
- Frequency/ease of administration
- Oral vs. subcutaneous

Choice of number of agents for antihyperglycemic therapy in Type 2 DM

- Monotherapy
- Dual Therapy
- Triple Therapy
- Combination Injectable Therapy

Most patients require more than one agent

At diagnosis ➔ During treatment
Choice of number of agents for antihyperglycemic therapy in Type 2 DM

- Established ASCVD or CKD
- Compelling need to minimize hypoglycemia
- Compelling need to minimize weight gain or promote weight loss
- Cost is a major issue

*Most trials of SGLT2 and GLP-1RA required baseline HbA1c ≥ 7.5% (Example: EXICAL Trial required HbA1c ≥ 6.5%, and most patients were already on metformin as first-line therapy if tolerated and not contraindicated.*

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CV = cardiovascular; GLP-1RA = glucagon-like peptide-1 receptor agonist; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes.

Writing Committee et al. JACC 2018;Jjacc.2018.09.020
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When to initiate insulin?

- Insulin
  - Can be effective when other agents are not
  - Can be used safely when other agents cannot
  - Early initiation
    - Hyperglycemia severe
      - Blood glucose \( \geq 300 \text{ mg/dL} \) or A1C is \( \geq 10\% \)
    - Symptoms of hyperglycemia
    - Hypertriglyceridemia
    - Ketosis
    - Glucose toxicity

Goals of Insulin Therapy

- Achieve optimal glycemic control but avoid:
  - Hypoglycemia
  - Weight gain
  - Negative impact on patient’s lifestyle

- Understand the appropriate glycemic target for the individual patient
References


