Management of Hyperglycemia in Type 2 Diabetes

Celeste C. Thomas MD, MS
Disclosures

In compliance with the accrediting board policies, the American Diabetes Association requires the following disclosure to the participants:

Celeste C. Thomas MD, MS

Disclosed no conflict of interest
PATIENT-CENTERED CARE

BACKGROUND
- Epidemiology and health care impact
- Relationship of glycemic control to outcomes
- Overview of the pathogenesis of type 2 diabetes

ANTI-HYPERGLYCEMIC THERAPY
- Glycemic targets
- Therapeutic options
  - Lifestyle
  - Oral agents & non-insulin injectables
  - Insulin


3. ANTIHYPERGLYCEMIC THERAPY
   - Implementation Strategies
     - Initial drug therapy
     - Advancing to dual combination therapy
     - Advancing to triple combination therapy
     - Transitions to and titrations of insulin

4. OTHER CONSIDERATIONS
   - Age
   - Weight
   - Sex/racial/ethnic/genetic differences
   - Comorbidities (CAD, HF, CKD, Liver disease, Hypoglycemia-prone)

5. FUTURE DIRECTIONS / RESEARCH NEEDS
Patient-Centered Approach

“...providing care that is respectful of and responsive to individual patient preferences, needs, and values - ensuring that patient values guide all clinical decisions.”

• Gauge patient’s preferred level of involvement.
• Explore, where possible, therapeutic choices. Consider using decision aids.
• Shared Decision Making – a collaborative process between patient and clinician, using best available evidence and taking into account the patient’s preferences and values
• Final decisions regarding lifestyle choices ultimately lie with the patient.

2. BACKGROUND

• Relationship of glycemic control to microvascular and macrovascular outcomes.

*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>↓↓</td>
<td>↔</td>
<td>↓↓</td>
</tr>
<tr>
<td>DCCT / EDIC*</td>
<td>↓↓</td>
<td>↔</td>
<td>↓↓</td>
</tr>
<tr>
<td>ACCORD</td>
<td>↓↓</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>↓↓</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>VADT</td>
<td>↓↓</td>
<td>↔</td>
<td>↔</td>
</tr>
</tbody>
</table>

*K in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009
2. BACKGROUND

• Overview of the pathogenesis of T2DM
  - Insulin secretory dysfunction
  - Insulin resistance (muscle, fat, liver)
  - Increased endogenous glucose production
  - Decreased incretin effect
  - Deranged adipocyte biology
Multiple, Complex Pathophysiologic Abnormalities in T2DM

Adapted from Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
Multiple, Complex Pathophysiological Abnormalities in T2DM

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
Glycemic Recommendations for Non-Pregnant Adults with Diabetes: Treatment Should be Individualized

More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.

<table>
<thead>
<tr>
<th>A1C</th>
<th>• &lt;7.0%*</th>
</tr>
</thead>
</table>
| Preprandial capillary plasma glucose | • 80–130 mg/dL*  
(4.4–7.2 mmol/L) |
| Peak postprandial capillary plasma glucose† | • <180 mg/dL*  
(<10.0 mmol/L) |

* More or less stringent glycemic goals may be appropriate for individual patients. Goals should be individualized based on duration of diabetes, age/life expectancy, comorbid conditions, known CVD or advanced microvascular complications, hypoglycemia unawareness, and individual patient considerations.
† Postprandial glucose measurements should be made 1–2 h after the beginning of the meal, generally peak levels in patients with diabetes.

# Approach to the Management of Hyperglycemia


## Approach to the Management of Hyperglycemia

<table>
<thead>
<tr>
<th>Patient / Disease Features</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks potentially associated with hypoglycemia and other drug adverse effects</td>
<td>low</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>Disease duration</td>
<td>newly diagnosed</td>
<td>long-standing</td>
<td></td>
</tr>
<tr>
<td>Life expectancy</td>
<td>long</td>
<td>short</td>
<td></td>
</tr>
<tr>
<td>Relevant comorbidities</td>
<td>absent</td>
<td>few / mid</td>
<td>severe</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>absent</td>
<td>few / mid</td>
<td>severe</td>
</tr>
<tr>
<td>Patient attitude and expected treatment efforts</td>
<td>highly motivated, advanced, excellent self-care capabilities</td>
<td>less motivated, nonadvanced, poor self-care capabilities</td>
<td></td>
</tr>
<tr>
<td>Resources and support system</td>
<td>readily available</td>
<td>limited</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Usually not mortalable</th>
<th>Potentially mortalable</th>
</tr>
</thead>
<tbody>
<tr>
<td>short</td>
<td>severe</td>
</tr>
<tr>
<td>mid</td>
<td>few</td>
</tr>
<tr>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>

---
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Drug Adverse Effects

Patient / Disease Features  More stringent ↔ A1C 7% → Less stringent

Risks potentially associated with hypoglycemia and other drug adverse effects

low  high

Adapted from:
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Disease Duration

Patient / Disease Features  More stringent  \( \rightarrow \) A1C 7%  \( \rightarrow \) Less stringent

Disease duration

- newly diagnosed
- long-standing

Adapted from:
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Life Expectancy

Patient / Disease Features  More stringent  ➔ A1C 7%  ➙ Less stringent

Life expectancy

long  short

Adapted from:
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Relevant Comorbidities

Patient / Disease Features

<table>
<thead>
<tr>
<th>Relevant comorbidities</th>
<th>More stringent</th>
<th>A1C 7%</th>
<th>Less stringent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Few / Mid</td>
<td></td>
<td>A1C 7%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
<td></td>
<td>A1C 7%</td>
</tr>
</tbody>
</table>

Adapted from:
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Established Vascular Complications

Patient / Disease Features  More stringent  $\Leftarrow$ A1C 7%  $\Rightarrow$ Less stringent

Established vascular complications

- absent
- few / mid
- severe

Adapted from:
Approach to the Management of Hyperglycemia By Patient/Disease Feature – Patient Attitude and Expected Treatment Efforts

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</tr>
</tbody>
</table>

Adapted from:
Approach to the Management of Hyperglycemia by Patient/Disease Feature – Resources and Support System

Patient / Disease Features | More stringent | A1C 7% | Less stringent

Resources and support system | readily available | limited

Adapted from:
Lifestyle Management

Lifestyle management is a fundamental aspect of diabetes care and includes:

- Diabetes self-management education (DSME)
- Diabetes self-management support (DSMS)
- Nutrition therapy
- Physical activity
- Smoking cessation counseling
- Psychosocial care

**ADA-EASD Position Statement Update: Anti-Hyperglycemic Therapy in T2DM**

<table>
<thead>
<tr>
<th>Therapeutic options: Oral Agents &amp; Non-Insulin Injectables</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Most Popular in the U.S. And Europe</strong></td>
</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
</tr>
<tr>
<td>DPP-4 Inhibitors</td>
</tr>
<tr>
<td>SGLT-2 Inhibitors</td>
</tr>
<tr>
<td>GLP-1 Receptor Agonists</td>
</tr>
<tr>
<td>Oral Class</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Biguanides</td>
</tr>
<tr>
<td>Sulfonylureas</td>
</tr>
<tr>
<td>Meglitinides</td>
</tr>
<tr>
<td>TZDs</td>
</tr>
</tbody>
</table>
# Properties of Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Oral Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>**A-Glucosidase</td>
<td>Inhibits a-glucosidase • Slows intestinal carbohydrate digestion / absorption</td>
<td>• Rare hypoglycemia • ↓ post-prandial glucose excursions • ↓ CVD events in prediabetes (STOP-NIDDM) • Nonsystemic</td>
<td>• Generally modest A1C efficacy • Gastrointestinal side effects • Frequent dosing schedule</td>
<td>Low to Mod.</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>Inhibits DPP-4 activity • Increases incretin (GLP-1, GIP) concentrations  • ↑ insulin secretion, ↓ glucagon secretion (glucose dependent)</td>
<td>• Rare hypoglycemia • Well tolerated</td>
<td>• Angioedema / urticaria and other immune-mediated dermatological effects • ? Acute pancreatitis • ? ↑ Heart failure hospitalizations</td>
<td>High</td>
</tr>
<tr>
<td><strong>Bile acid sequestrants</strong></td>
<td>Bind bile acids in intestinal tract, increasing hepatic bile acid production • ? ↓ Hepatic glucose production and ↑ incretin levels</td>
<td>• Rare hypoglycemia • ↓ LDL-C</td>
<td>• Modest ↓ A1C • Constipation • ↑ TGs • May ↓ absorption of other medications</td>
<td>High</td>
</tr>
<tr>
<td><strong>Dopamine-2 Agonists</strong></td>
<td>Activates DA receptor • Modulates hypothalamic regulation of metabolism • ↑ insulin sensitivity</td>
<td>• Rare hypoglycemia • ? ↓ CVD events</td>
<td>• Modest ↓ A1C efficacy • Dizziness/syncope • Nausea • Fatigue • Rhinitis</td>
<td>High</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitors</strong></td>
<td>Inhibits SGLT2 in proximal nephron • Blocks glucose reabsorption by the kidney, increasing glucosuria</td>
<td>• Rare hypoglycemia • ↓ Weight • ↓ BP • Associated with lower CVD event rate and mortality in patients with CVD</td>
<td>• GU infections • Polyuria • Volume depletion/hypotension/dizziness • ↑ LDL-C • ↑ Cr (transient) • DKA, urinary tract infections leading to urosepsis, pyelonephritis</td>
<td>High</td>
</tr>
</tbody>
</table>
## Properties of Anti-Hyperglycemic Agents

<table>
<thead>
<tr>
<th>Injectable Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| **GLP-1 receptor agonists** | • Activates GLP-1 R  
  • ↑ Insulin, ↓ glucagon (glucose dependent),  
  • ↓ gastric emptying  
  • ↑ satiety | • Rare hypoglycemia  
  • ↓ Weight  
  • ↓ Postprandial glucose excursions  
  • ↓ Some CV risk factors  
  • Associated with lower CV event rate and mortality in patients with CVD | • Gastrointestinal side effects  
  • ↑ Heart rate  
  • ? Acute pancreatitis  
  • C-cell hyperplasia/medullary thyroid tumors in animals  
  • Injectable  
  • Training requirements | High |
| **Amylin mimetics** | • Activates amylin receptors  
  • ↓ glucagon secretion  
  • ↓ gastric emptying  
  • ↑ satiety | • ↓ Postprandial glucose  
  • ↓ Weight | • Modest ↓ A1C  
  • Gastrointestinal side effects  
  • Injectable  
  • Hypo if insulin dose not reduced  
  • Frequent dosing schedule  
  • Training requirements | High |
| **Insulin** | • Activates insulin receptor  
  • ↑ glucose disposal  
  • ↓ hepatic glucose production  
  • Suppresses ketogenesis | • Nearly universal response  
  • Theoretically unlimited efficacy  
  • ↓ Microvascular risk (UKPDS) | • Hypoglycemia  
  • Weight gain  
  • Training requirements  
  • Patient and Provider reluctance  
  • Injectable (except inhalable)  
  • Pulmonary toxicity (inhaled insulin) | High (cost is based on lowest-priced member of the class) |

*American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64-S74. *Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0*
Anti-Hyperglycemic Therapy in T2DM: General Recommendations

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 300mg/dl, or patient is markedly symptomatic, consider Combination Injectable Therapy (See Figure 8.2).

Monotherapy

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
</table>

- **Efficacy**: high
- **Hypo Risk**: low risk
- **Weight**: neutral/loss
- **Side Effects**: GI/lactic acidosis
- **Costs**: low

American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
## Anti-Hyperglycemic Therapy in T2DM: Dual Therapy

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sulfonylurea +</strong></td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td><strong>Thiazolidinedione +</strong></td>
<td>high</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>DPP-4 inhibitor +</strong></td>
<td>intermediate</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>SGLT2 inhibitor +</strong></td>
<td>intermediate</td>
<td>low risk</td>
</tr>
<tr>
<td><strong>GLP-1 receptor agonist +</strong></td>
<td>high</td>
<td>high</td>
</tr>
<tr>
<td><strong>Insulin (basal)</strong></td>
<td>highest</td>
<td>high risk</td>
</tr>
</tbody>
</table>

### EFFICACY
- Sulfonylurea: high
- Thiazolidinedione: high
- DPP-4 inhibitor: intermediate
- SGLT2 inhibitor: intermediate
- GLP-1 receptor agonist: high
- Insulin (basal): highest

### HYPO RISK
- Sulfonylurea: moderate risk
- Thiazolidinedione: low risk
- DPP-4 inhibitor: low risk
- SGLT2 inhibitor: low risk
- GLP-1 receptor agonist: low risk
- Insulin (basal): high risk

### WEIGHT
- Sulfonylurea: gain
- Thiazolidinedione: gain
- DPP-4 inhibitor: neutral
- SGLT2 inhibitor: loss
- GLP-1 receptor agonist: loss
- Insulin (basal): gain

### SIDE EFFECTS
- Sulfonylurea: hypoglycemia
- Thiazolidinedione: edema, HF, fx
- DPP-4 inhibitor: rare
- SGLT2 inhibitor: GU, dehydration, fx
- GLP-1 receptor agonist: GI
- Insulin (basal): hypoglycemia

### COSTS
- Sulfonylurea: low
- Thiazolidinedione: low
- DPP-4 inhibitor: high
- SGLT2 inhibitor: high
- GLP-1 receptor agonist: high
- Insulin (basal): high

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 3-drug combination (order not meant to denote any specific preference – choice dependent on a variety of patient & disease-specific factors).
Anti-Hyperglycemic Therapy in T2DM: Triple Therapy

<table>
<thead>
<tr>
<th>Triple Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea +</td>
<td>Thiazolidinedione +</td>
<td>DPP-4 inhibitor +</td>
</tr>
<tr>
<td>TZD or DPP-4-i or SGLT2-i or GLP-1-RA</td>
<td>SU or DPP-4-i or SGLT2-i or GLP-1-RA</td>
<td>SU or TZD or SGLT2-i or Insulin</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 agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy

(See Figure 8.2)
Combination Injectable Therapy For Type 2 Diabetes

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

If goals not met, consider changing to alternative insulin regimen

American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
Choosing an Agent to Avoid Hypoglycemia

**Monotherapy**

<table>
<thead>
<tr>
<th><strong>Metformin</strong></th>
<th><strong>Lifestyle Management</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>low risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>neutral loss</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>G/I/a/lactic acidosis</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
</tr>
</tbody>
</table>

If AIC 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><strong>Sulfonylurea</strong></th>
<th><strong>Thiazolidinedione</strong></th>
<th><strong>DPP-4 inhibitor</strong></th>
<th><strong>SGLT2 inhibitor</strong></th>
<th><strong>GLP-1 receptor agonist</strong></th>
<th><strong>Insulin (basal)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efficacy</strong></td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>highest</td>
</tr>
<tr>
<td><strong>Hypo Risk</strong></td>
<td>moderate risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td><strong>Weight</strong></td>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>neutral</td>
<td>gain</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>hypoglycemia</td>
<td>edema, HF, fx</td>
<td>rare</td>
<td>GU, dehydration, fx</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>Costs</strong></td>
<td>low</td>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
</tr>
</tbody>
</table>

If AIC 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>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>TZD</strong></td>
<td>DPP-4-i</td>
<td>SU</td>
<td>SU</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or Thiazolidinedione</td>
<td>or or <strong>SGLT2-i</strong></td>
<td>or or <strong>SGLT2-i</strong></td>
<td>or or <strong>Insulin</strong></td>
<td>or <strong>GLP-1-RA</strong></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or or <strong>GLP-1-RA</strong></td>
<td>or or <strong>GLP-1-RA</strong></td>
<td>or or <strong>Insulin</strong></td>
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<td>or <strong>GLP-1-RA</strong></td>
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American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
Choosing an Agent to Avoid Weight Gain

### Monotherapy

<table>
<thead>
<tr>
<th><strong>Efficacy</strong></th>
<th><strong>Hypo Risk</strong></th>
<th><strong>Weight</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low</td>
<td>neutral/loss</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
</tbody>
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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><strong>Efficacy</strong></th>
<th><strong>Hypo Risk</strong></th>
<th><strong>Weight</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
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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>
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<th><strong>Weight</strong></th>
<th><strong>Side Effects</strong></th>
<th><strong>Costs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low</td>
<td>low</td>
<td>hypoglycemia</td>
<td>high</td>
</tr>
</tbody>
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Choosing an Agent to Avoid to Minimize Cost

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low risk</td>
<td></td>
</tr>
<tr>
<td>WEIGHT</td>
<td>neutral/loss</td>
<td></td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</td>
<td></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):

<table>
<thead>
<tr>
<th>Dual Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>moderate risk</td>
<td>low risk</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>gain</td>
<td>gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>lactic acidosis</td>
<td>edema, HF, fx</td>
</tr>
<tr>
<td>COSTS*</td>
<td>low</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):

<table>
<thead>
<tr>
<th>Triple Therapy</th>
<th>Metformin +</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFFICACY*</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td>HYPO RISK</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>WEIGHT</td>
<td>high</td>
<td>gain</td>
</tr>
<tr>
<td>SIDE EFFECTS</td>
<td>lactic acidosis</td>
<td>edema, HF, fx</td>
</tr>
<tr>
<td>COSTS*</td>
<td>high</td>
<td>low</td>
</tr>
</tbody>
</table>

American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
# Therapeutic Options: Insulins

<table>
<thead>
<tr>
<th>Human Insulins</th>
<th>Insulin Analogues</th>
<th>Biosimilar Insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutral protamine Hagedorn (NPH)</td>
<td>Basal analogues (glargine, detemir, degludec)</td>
<td>Basaglar (a biosimilar version of insulin glargine); long-acting</td>
</tr>
<tr>
<td>Regular human insulin</td>
<td>Rapid analogues (lispro, aspart, glulisine)</td>
<td></td>
</tr>
<tr>
<td>Pre-mixed formulations</td>
<td>Pre-mixed formulations</td>
<td></td>
</tr>
</tbody>
</table>

*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;10.1077/s00125-014-3460-0
https://investor.lilly.com/releasedetail.cfm?ReleaseID=1004325
https://www.basaglar.com/en/
Anti-Hyperglycemic Therapy: Insulins

- Long (Detemir)
- Rapid (Lispro, Aspart, Glulisine)
- Long (Glargine)
- Short (Regular)
- Long (Degludec)
- Long (Glargine)
Approach to Starting and Adjusting Insulin in T2DM

Initiate Basal Insulin
Usually with metformin +/- other noninsulin agent

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

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
Approach to Starting and Adjusting Insulin in T2DM

Add 1 rapid-acting insulin injection before largest meal

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
If goals not met, consider changing to alternative insulin regimen

Change to premixed insulin twice daily (before breakfast and supper)

Start: Divide current basal dose into AM, 1/3 AM 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%

If A1C not controlled, advance to basal-bolus

If A1C not controlled, advance to 3rd injection

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. Diabetes Care 2017;40(Suppl. 1):S64-S74.
### Approach to Starting and Adjusting Insulin in T2DM

**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%

---

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

**Start:** Add additional injection before lunch

**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%

---

**Adapted from:**
- American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64-S74.
Other Considerations in Designing an Optimal Glucose Lowering Drug Regimen for Patients

<table>
<thead>
<tr>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
</tr>
<tr>
<td>Sex / racial / ethnic / genetic differences</td>
</tr>
</tbody>
</table>

**Comorbidities**
- Coronary artery disease
- Heart Failure
- Chronic kidney disease
- Liver dysfunction
- Hypoglycemia-prone

**Identifying and addressing barriers to medication adherence**
- Cost
- Side effects

Adapted from:
American Diabetes Association Standards of Medical Care in Diabetes. Pharmacologic Approaches to Glycemic Treatment. *Diabetes Care* 2017;40(Suppl. 1):S64-S74.
Future Directions/Research Needs

- Comparative effectiveness research
  - Focus on important clinical outcomes

- Contributions of genomic research

- Perpetual need for clinical judgment!
Key Points

Glycemic targets & BG-lowering therapies must be individualized, based on a variety of patient and disease characteristics.

Diet, exercise, & education: foundation of any T2DM therapy program

Unless contraindicated, metformin remains the optimal first-line drug.

- After metformin, data are limited. Combination therapy with 1-2 other oral / injectable agents is reasonable. Try to minimize side effects.
- Ultimately, many patients will require insulin therapy alone or in combination with other agents to maintain BG control.
- All treatment decisions should be made in conjunction with the patient (focusing on his or her preferences, needs & values.)

Comprehensive CV risk reduction - a major focus of therapy

*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
*Diabetes Care* 2015;38:140-149; American Diabetes Association Standards of Medical Care in Diabetes.
Case Study: Introduction

- Mrs. G, a 58-year-old African American female, has had type 2 diabetes for 8 years
- She is currently being treated for hypertension (12 years) and dyslipidemia (10 years)
- She is concerned about her uncontrolled blood glucose level, a recent increase in weight (5 lbs)
- She is a non-smoker and only occasionally consumes alcohol
- Walks 15-20 minutes, three times a week
- Her diet has improved over the last 5 years after consultation with a registered dietitian, but she admits to having a “sweet tooth”
Case Study (cont’d)

- **Physical exam:**
  - General examination normal, No pallor, cyanosis, clubbing or lymphadenopathy
  - Height, 5’2” (157 cm); weight, 152 lbs (69 kg)
  - BMI, 27.8 kg/m²
  - BP, 132/86 mmHg
  - Pulse 80/min, regular, peripheral pulses well felt
  - Systemic examination- normal
  - Foot examination is normal
  - Fundus examination : Grade I non proliferative diabetic retinopathy

- **Medication history:** Glimepiride 2 mg daily BID • Metformin sustained release preparations 1000 mg daily • Telmisartan 40 mg daily • Atorvastatin 10 mg at night • Aspirin 75 mg at night

(Continued…)

American Diabetes Association
## Case Study (cont’d)

### Lab results (recent):

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C</td>
<td>8%</td>
</tr>
<tr>
<td>FPG</td>
<td>130 mg/dL</td>
</tr>
<tr>
<td>2-hour postprandial (dinner)</td>
<td>252 mg/dL</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>197 mg/dL</td>
</tr>
<tr>
<td>HDL-C</td>
<td>35 mg/dL</td>
</tr>
<tr>
<td>LDL-C</td>
<td>101 mg/dL</td>
</tr>
<tr>
<td>TG</td>
<td>147 mg/dL</td>
</tr>
<tr>
<td>Blood Urea Nitrogen</td>
<td>19 mg/dL</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.3 mg/dL</td>
</tr>
<tr>
<td>Urine routine</td>
<td>Sugar, ketones, negative</td>
</tr>
</tbody>
</table>
From the lab results, which plasma glucose patterns of hyperglycemia are present?

A. Fasting
B. Preprandial
C. Postprandial
D. Nocturnal
E. B and C above
Case Study: Discussion Question

A drug from which of the following drug classes could you consider to intensify Mrs. G’s treatment to manage her postprandial hyperglycemia?

A. GLP-1 receptor agonist
B. DPP-4 inhibitor
C. SGLT2 inhibitor
D. Basal insulin
E. A, B, C, or D above
Case Study: Think-Pair-Share

• Do you agree with introducing a GLP-1 receptor agonist to Mrs. G’s treatment plan?

• Is there another option you would have tried first?

• Would you discontinue the sulfonylurea or add the GLP-1 receptor agonist to the metformin/sulfonylurea?
Helpful Resources
Guidelines

• Full version
• Abridged version for PCPs
• Free app
• Pocket cards with key figures
• Free webcast for continuing education credit

Professional.Diabetes.org/SOC
Professional Education

- Live programs
- Online self-assessment programs
- Online webcasts

Professional.Diabetes.org/CE
Diabetes Self-Management Education

- Find a recognized Diabetes Self-Management program
- Become a recognized DSME program
- Tools and resources for DSME programs
- Online education documentation tools

Professional.Diabetes.org/ERP
Professional Membership

• Journals
• Meeting, book and journal discounts
• Career center
• Quarterly member newsletter

Professional.Diabetes.org/membership
Thank You!