Management of Hyperglycemia in T2DM: A Patient-Centered Approach

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Johnson & Johnson Diabetes Care Companies, Wayne PA
Natural History of Type 2 Diabetes

Progression of Dysglycemia

- Prediabetes
- Type 2 Diabetes

Insulin resistance
Insulin secretion
Postprandial glucose
Fasting glucose

Prediabetes and Early Type 2 Diabetes: Generally Asymptomatic

Years to
Progression to Type 2 Diabetes Can be Prevented or Delayed
Diagnosis of Type 2 Diabetes Typically Delayed

Microvascular complications
Macrovascular complications

Adapted from Ramlo-Halsted BA, Edelman SV. Prim Care. 1999;26:771-789
Pathophysiology of Type 2 Diabetes

Inadequate Insulin Secretion
Decreased Incretin Response
Low Dopaminergic Tone
Increased Glucose Reabsorption

Excess Glucose Production
Resistance to Action of Insulin
Reduced Glucose Uptake

Polling Question

More than 50% of all non-insulin medications currently used to treat T2DM have been approved since 2000.

A. True
B. False
Diabetes Drug Classes Increasing Rapidly

- Insulin (1922)
- Sulfonylureas
- Biguanides
- \(\alpha\)-glucosidase inhibitors
- Biguanides
- TZDs
- GLP-1 Receptor Agonists
- Glinides
- DPP-4 inhibitors
- Bile acid sequestrants
- Dopamine agonists
- SGLT-2 inhibitors
Type 2 Diabetes Therapy: Sites of Action

- Pancreas: Sulfonylurea, Meglitinide, DPP-4 Inhibitor
- Brain: Bromocriptine
- Kidney: SGLT-2 inhibitor
- Adipose tissue: Glitazone
- Liver: α-glucosidase inhibitor, Bile acid sequestrant, Metformin, Glitazone
- Skeletal muscle: Glitazone

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.

## 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>
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<td>DCCT / EDIC*</td>
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<td>VADT</td>
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* in T1DM

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Kendall DM, Bergenstal RM. © International Diabetes Center 2009
ANTI-HYPERGLYCEMIC THERAPY

• Glycemic targets
  - HbA1c < 7.0% (mean PG ~150-160 mg/dl)
  - Pre-prandial PG <130 mg/dl
  - Post-prandial PG <180 mg/dl
  - Individualization is key:
    ➢ Tighter targets (6.0 - 6.5%) - younger, healthier
    ➢ Looser targets (7.5 - 8.0%⁺) - older, comorbidities, hypoglycemia prone, etc.
  - Avoidance of hypoglycemia

PG = plasma glucose

ADA-EASD Position Statement Update:
Management of Hyperglycemia in T2DM, 2015

*PG = plasma glucose*
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

PATIENT / DISEASE FEATURES

- Risks potentially associated with hypoglycemia and other drug adverse effects
- Disease duration
- Life expectancy
- Important comorbidities
- Established vascular complications
- Patient attitude and expected treatment efforts
- Resources and support system

Approach to the management of hyperglycemia

<table>
<thead>
<tr>
<th>more stringent</th>
<th>HbA1c 7%</th>
<th>less stringent</th>
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</thead>
<tbody>
<tr>
<td>low</td>
<td>high</td>
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<tr>
<td>newly diagnosed</td>
<td>long-standing</td>
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<tr>
<td>long</td>
<td>short</td>
<td></td>
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<td>absent</td>
<td>few / mild</td>
<td>severe</td>
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<tr>
<td>absent</td>
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<td>severe</td>
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<tr>
<td>highly motivated, adherent, excellent self-care capacities</td>
<td>less motivated, non-adherent, poor self-care capacities</td>
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<tr>
<td>Readily available</td>
<td>limited</td>
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Usually not modifiable

Potentially modifiable

Diabetes Care 2015;38:140-149; Diabetologia 2015;10.1077/s00125-014-3460-0
Approach to the Management of Hyperglycemia

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Risks potentially associated with hypoglycemia, other drug adverse effects
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM.

Disease duration

More stringent

HbA1c 7%

Less stringent

Newly diagnosed

Long-standing

Approach to the Management of Hyperglycemia
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM
Established vascular complications

Approach to the Management of Hyperglycemia

more stringent

HbA1c 7%

less stringent

Absent

Few / Mild

Severe

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM
Approach to the Management of Hyperglycemia

Patient attitude & expected treatment efforts

more stringent

HbA1c 7%

less stringent

Highly motivated, adherent, excellent self-care capacities

Less motivated, non-adherent, poor self-care capacities

Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM
American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan

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George Grunberger, MD, FACP, FACE
Guillermo Umpierrez, MD, FACP, FACE
Robert S. Zimmerman, MD, FACE

ENDOCRINE PRACTICE Vol 21 No. 4 April 2015
INDIVIDUALIZE GOALS

A1c ≤ 6.5%
For patients without concurrent serious illness and at low hypoglycemic risk

A1c > 6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
Polling Question

Which of the following statement(s) about individualization of pharmacotherapy is consistent with 2015 ADA EASD Position statement update?

A. Anti-hyperglycemic therapy includes increased activity levels
B. Insulin used to treat T2DM includes both human insulin and insulin analogues
C. Consider sex, racial, ethnic and genetic differences in management of T2DM
D. All of the above
ANTI-HYPERGLYCEMIC THERAPY

• Therapeutic options: **Lifestyle**
  
  - Weight optimization
  
  - Healthy diet
  
  - Increased activity level
### Noninsulin Agents Available for T2D

<table>
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<tr>
<th>Class</th>
<th>Primary Mechanism of Action</th>
<th>Agent(s)</th>
<th>Available as</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>α-Glucosidase inhibitors</strong></td>
<td>• Delay carbohydrate absorption from intestine</td>
<td>Acarbose</td>
<td>Precose or generic Glyset</td>
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<tr>
<td></td>
<td></td>
<td>Miglitol</td>
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<tr>
<td><strong>Amylin analogue</strong></td>
<td>• Decrease glucagon secretion</td>
<td>Pramlintide</td>
<td>Symlin</td>
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<tr>
<td></td>
<td>• Slow gastric emptying</td>
<td></td>
<td></td>
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<td></td>
<td>• Increase satiety</td>
<td></td>
<td></td>
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<tr>
<td><strong>Biguanide</strong></td>
<td>• Decrease HGP</td>
<td>Metformin</td>
<td>Glucophage or generic</td>
</tr>
<tr>
<td></td>
<td>• Increase glucose uptake in muscle</td>
<td></td>
<td></td>
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<tr>
<td><strong>Bile acid sequestrant</strong></td>
<td>• Decrease HGP?</td>
<td>Colesevelam</td>
<td>WelChol</td>
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<tr>
<td></td>
<td>• Increase incretin levels?</td>
<td></td>
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<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td>• Increase glucose-dependent insulin secretion</td>
<td>Alogliptin</td>
<td>Nesina Tradjenta</td>
</tr>
<tr>
<td></td>
<td>• Decrease glucagon secretion</td>
<td>Linagliptin</td>
<td>Onglyza</td>
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<td></td>
<td></td>
<td>Saxagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sitagliptin</td>
<td></td>
</tr>
<tr>
<td><strong>Dopamine-2 agonist</strong></td>
<td>• Activates dopaminergic receptors</td>
<td>Bromocriptine</td>
<td>Cycloset</td>
</tr>
<tr>
<td><strong>Glinides</strong></td>
<td>• Increase insulin secretion</td>
<td>Nateglinide</td>
<td>Starlix or generic Prandin</td>
</tr>
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<td></td>
<td></td>
<td>Repaglinide</td>
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DPP-4 = dipeptidyl peptidase; HGP = hepatic glucose production.


*Continued on next slide*
## Noninsulin Agents Available for T2D

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| GLP-1 receptor agonists | • Increase glucose-dependent insulin secretion  
• Decrease glucagon secretion  
• Slow gastric emptying  
• Increase satiety | Albiglutide  
Dulaglutide  
Exenatide  
Exenatide XR  
Liraglutide | Tanzeum  
Trulicity  
Byetta  
Bydureon  
Victoza |
| SGLT2 inhibitors     | • Increase urinary excretion of glucose                                                   | Canagliflozin  
Dapagliflozin  
Empagliflozin | Invokana  
Farxiga  
Jardiance |
| Sulfonylureas        | • Increase insulin secretion                                                              | Glimepiride  
Glipizide  
Glyburide | Amaryl or generic  
Glucotrol or generic  
Diaβeta, Glynase,  
Micronase, or generic |
| Thiazolidinediones   | • Increase glucose uptake in muscle and fat  
• Decrease HGP                           | Pioglitazone  
Rosiglitazone | Actos  
Avandia |

GLP-1 = glucagon-like peptide; HGP = hepatic glucose production; SGLT2 = sodium glucose cotransporter 2.

ANTI-HYPERGLYCEMIC THERAPY

• Insulins

  Human Insulins
  - Neutral protamine Hagedorn (NPH)
  - Regular human insulin
  - Pre-mixed formulations

  Insulin Analogues
  - Basal analogues (glargine, detemir, degludec)
  - Rapid analogues (lispro, aspart, glulisine)
  - Pre-mixed formulations

Diabetes Care 2015;38:140-149; Diabetologia 2015;10.1077/s00125-014-3460-0
Insulin is secreted by the pancreas in a glucose-dependent manner continuously throughout the day, as well as in response to oral carbohydrate loads.
Insulin Mimics Normal Physiologic Profile

Principle of insulin use - to create as normal a glycemic profile as possible without causing unacceptable weight gain or hypoglycemia

Supplement to The Journal of the American Osteopathic Association April 2013;113(4): Supplement 2: S6–S16
Pharmacokinetic Profiles of Human Insulin and Insulin Analogs

Graph showing the insulin levels over time for different types of insulin:
- **Rapid (Lispro, Aspart, Glulisine)**
- **Short (Regular)**
- **Long (Detemir)**
- **Long (Glargine)**
- **(Degludec)**
# Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th>HYPO</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Neutral</th>
<th>Moderate to Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Contraindicated CrCl &lt; 30</td>
<td>Genital Mycotic Infections</td>
<td>Dose Adjustment May be Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>May Worsen Fluid Retention</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>
</tr>
<tr>
<td>CHF</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>CVD</td>
<td>Benefit</td>
<td>Increased LDL</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>?</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Bone Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
</tbody>
</table>

- **Green**: Few adverse events or possible benefits
- **Yellow**: Use with caution
- **Orange**: Likelihood of adverse effects

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**Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations**

- **Healthy eating, weight control, increased physical activity & diabetes education**

- **Mono-therapy**
  - Efficacy
  - Hypoglycemia risk
  - Weight
  - Side effects
  - Costs

- **Dual therapy**
  - Efficacy
  - Hypoglycemia risk
  - Weight
  - Side effects
  - Costs

- **Triple therapy**

- **Combination injectable therapy**
  - Basal Insulin
  - Mealtime Insulin
  - GLP-1-RA

---

If HbA1c target not achieved after ~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):

- **Metformin**
  - high
  - moderate risk
  - weight loss
  - GI / lactic acidosis
  - low

- **Sulfonylurea**
  - high
  - moderate risk
  - weight gain
  - hypoglycemia
  - low

- **Thiazolidinedione**
  - high
  - low risk
  - edema, HF, fx
  - low

- **DPP-4 inhibitor**
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- **SGLT2 inhibitor**
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- **GLP-1 receptor agonist**
  - high
  - low risk
  - loss
  - GI
  - high

- **Insulin (basal)**
  - highest
  - high risk
  - gain
  - hypoglycemia
  - variable

If HbA1c target not achieved after ~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):

- **Metformin**
  - high
  - moderate risk
  - weight loss
  - GI / lactic acidosis
  - low

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  - high
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  - high
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  - high
  - low risk
  - loss
  - GI
  - high

- **Insulin (basal)**
  - highest
  - high risk
  - gain
  - hypoglycemia
  - variable

If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2i:

- **Metformin**
  - high
  - moderate risk
  - weight loss
  - GI / lactic acidosis
  - low

- **Sulfonylurea**
  - high
  - moderate risk
  - weight gain
  - hypoglycemia
  - low

- **Thiazolidinedione**
  - high
  - low risk
  - edema, HF, fx
  - low

- **DPP-4 inhibitor**
  - intermediate
  - low risk
  - neutral
  - rare
  - high

- **SGLT2 inhibitor**
  - intermediate
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- **GLP-1 receptor agonist**
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  - highest
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  - variable
Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations
**Figure 2. Anti-hyperglycemic therapy in T2DM: General recommendations**

Healthy eating, weight control, increased physical activity & diabetes education

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<td>gain</td>
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<td>hypoglycemia</td>
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<td>low</td>
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<td>high</td>
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<td>variable</td>
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*If HbA1c target not achieved after ~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):*

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<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>DPP-4-i</td>
<td>GLP-1-RA</td>
<td>SGLT2-i</td>
<td>DPP-4-i</td>
<td>SGLT2-i</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
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<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>SGLT2-i</td>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
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<td>Insulin</td>
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<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:
### Healthy eating, weight control, increased physical activity & diabetes education

#### Metformin

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
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<td>GI/lactic acidosis</td>
<td>low</td>
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</tbody>
</table>

If HbA1c target not achieved after ~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>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
<td>Insulin (basal)</td>
</tr>
<tr>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
<td>low risk</td>
<td>low</td>
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<td>high</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>high</td>
</tr>
<tr>
<td>hypoglycemia</td>
<td>edema, HF, fx, low</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>gain</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
<td>high</td>
<td>variable</td>
<td></td>
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<td>SGLT2 Inhibitor +</td>
<td>GLP-1 Receptor Agonist +</td>
<td>Insulin (basal) +</td>
</tr>
<tr>
<td>TZD</td>
<td>SU</td>
<td>DPP-4-i</td>
<td>SGLT2-i</td>
<td>Insulin s</td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
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<td></td>
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If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:

<table>
<thead>
<tr>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal Insulin +</td>
</tr>
</tbody>
</table>

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*Diabetes Care 2015;38:140-149; Diabetologia 2015;10.1077/s00125-014-3460-0*
**Healthy eating, weight control, increased physical activity & diabetes education**

---

### Metformin

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<tr>
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<tr>
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<td>highest</td>
</tr>
<tr>
<td>moderate risk</td>
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<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
<td>gain</td>
</tr>
<tr>
<td>hypoglycemia</td>
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<td>GI</td>
<td>hypoglycemia</td>
</tr>
<tr>
<td>low</td>
<td>low</td>
<td>high</td>
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<td>variable</td>
<td></td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~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 +</th>
<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
</thead>
<tbody>
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<td>SGLT2 inhibitor</td>
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</tr>
<tr>
<td>+ TZD</td>
<td>+ SU</td>
<td>+ SU</td>
<td>+ SU</td>
<td></td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td></td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td></td>
</tr>
<tr>
<td>or Insulin§</td>
<td>or Insulin§</td>
<td>or Insulin§</td>
<td>or Insulin§</td>
<td></td>
</tr>
</tbody>
</table>

*If HbA1c target not achieved after ~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):*

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### Triple therapy

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea</td>
<td>Thiazolidinedione</td>
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<td>SGLT2 inhibitor</td>
</tr>
<tr>
<td>+ TZD</td>
<td>+ SU</td>
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<td></td>
</tr>
<tr>
<td>or DPP-4-i</td>
<td>or DPP-4-i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td></td>
<td></td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or GLP-1-RA</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td></td>
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</tbody>
</table>

*If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2-i:*

---

### Combination injectable therapy

<table>
<thead>
<tr>
<th>Metformin +</th>
<th>Basal Insulin +</th>
<th>Mealtime Insulin</th>
<th>or</th>
<th>GLP-1-RA</th>
</tr>
</thead>
</table>

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**Diabetes Care 2015;38:140-149; Diabetologia 2015;10.1077/s00125-014-3460-0**
### Figure 2A. Anti-hyperglycemic therapy in T2DM: Avoidance of hypoglycemia

**Healthy eating, weight control, increased physical activity & diabetes education**

**Metformin**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Hypo risk</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>low risk</td>
<td>neutral/loss</td>
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</tr>
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<tr>
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<th>Metformin +</th>
<th>Metformin +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazolidinedione</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
<td>GLP-1 receptor agonist</td>
</tr>
<tr>
<td>high</td>
<td>intermediate</td>
<td>intermediate</td>
<td>high</td>
</tr>
<tr>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>gain</td>
<td>neutral</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td>edema, HF, fx</td>
<td>rare</td>
<td>GU, dehydration</td>
<td>GI</td>
</tr>
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<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Thiazolidinedione +</td>
<td>DPP-4 inhibitor</td>
<td>SGLT2 inhibitor</td>
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</tr>
<tr>
<td>or DPP-4-i</td>
<td>or TZD</td>
<td>or TZD</td>
<td>or TZD</td>
</tr>
<tr>
<td>or SGLT2-i</td>
<td>or SGLT2-i</td>
<td>or DPP-4-i</td>
<td>or insulin</td>
</tr>
<tr>
<td>or GLP-1-RA</td>
<td>or or Insulin</td>
<td>or or DPP-4-i</td>
<td>or or TZD</td>
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**Diabetes Care 2015;38:140-149; Diabetologia 2015;10.1077/s00125-014-3460-0**
Healthy eating, weight control, increased physical activity & diabetes education

Metformin

Metformin

If HbA1c target not achieved after ~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):

- Metformin + DPP-4 inhibitor
  - Efficacy: high
  - Hypo risk: low
  - Weight: neutral
  - Side effects: rare
  - Costs:
  - GI / lactic acidosis:

- Metformin + SGLT2 inhibitor
  - Efficacy: intermediate
  - Hypo risk: low
  - Weight: loss
  - Side effects: GU, dehydration
  - Costs:
  - GI:

- Metformin + GLP-1 receptor agonist
  - Efficacy: high
  - Hypo risk: low
  - Weight: loss
  - Side effects: GI
  - Costs:

If HbA1c target not achieved after ~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):

- Metformin + DPP-4 inhibitor
  - Efficacy: high
  - Hypo risk: low
  - Weight: neutral
  - Side effects: rare
  - Costs:
  - GI / lactic acidosis:

- Metformin + SGLT2 inhibitor
  - Efficacy: intermediate
  - Hypo risk: low
  - Weight: loss
  - Side effects: GU, dehydration
  - Costs:
  - GI:

- Metformin + GLP-1 receptor agonist
  - Efficacy: high
  - Hypo risk: low
  - Weight: loss
  - Side effects: GI
  - Costs:

Figure 2B. Anti-hyperglycemic therapy in T2DM: Avoidance of weight gain
Healthy eating, weight control, increased physical activity & diabetes education

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Dual therapy†</th>
<th>Triple therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy†</td>
<td>Efficacy†</td>
<td>Efficacy†</td>
</tr>
<tr>
<td>Hypo risk</td>
<td>Hypo risk</td>
<td>Hypo risk</td>
</tr>
<tr>
<td>Weight</td>
<td>Weight</td>
<td>Weight</td>
</tr>
<tr>
<td>Side effects</td>
<td>Side effects</td>
<td>Side effects</td>
</tr>
<tr>
<td>Costs</td>
<td>Costs</td>
<td>Costs</td>
</tr>
</tbody>
</table>

**Metformin**
- high
- neutral/loss
- low

- **If HbA1c target not achieved after ~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):**
  - Metformin + Sulfonlurea
    - high
    - moderate risk
    - gain
    - hypoglycemia
    - low
  - Metformin + Thiazolidinedione
    - high
    - low risk
    - gain
    - edema, HF,fxs
    - low
  - Metformin + Insulin (basal)
    - highest
    - high risk
    - gain
    - hypoglycemia
    - variable

- **If HbA1c target not achieved after ~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):**
  - Metformin + Sulfonlurea + TZD
    - or Insulin†
  - Metformin + Thiazolidinedione + SU
    - or Insulin§
  - Metformin + Insulin (basal) + TZD

- **If HbA1c target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TZD or SGL T2i:**

Figure 2C. Anti-hyperglycemic therapy in T2DM: Minimization of costs
Figure 3. Approach to starting & adjusting insulin in T2DM

*Basal Insulin* (usually with metformin +/- other non-insulin agent)

- **Start:** 10U/day or 0.1-0.2 U/kg/day
- **Adjust:** 10-15% or 2-4 U once-twice weekly to reach FBG target.
- **For hypo:** Determine & address cause; ↓ dose by 4 units or 10-20%.
Add ≥2 rapid insulin* injections before meals ('basal-bolus')

Change to premixed insulin* twice daily

Add 1 rapid insulin* injections before largest meal

Basal Insulin
(usually with metformin +/- other non-insulin agent)

- **Start:** 10U/day or 0.1-0.2 U/kg/day
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- **For hypo:** Determine & address cause; ↓ dose by 4 units or 10-20%.

If not controlled after FBG target is reached (or if dose > 0.5 U/kg/day), treat PPG excursions with meal-time insulin. (Consider initial GLP-1-RA trial.)

Add ≥2 rapid insulin* injections before meals ('basal-bolus')!

- **Start:** 4U, 0.1 U/kg, or 10% basal dose. If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

- **Start:** 4U, 0.1 U/kg, or 10% basal dose/meal.† If A1c<8%, consider ↓ basal by same amount.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly to achieve SMBG target.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.
- **Adjust:** ↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

If not controlled, consider basal-bolus.
Add ≥2 rapid insulin* injections before meals ('basal-bolus')

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Change to premixed insulin* twice daily

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• For hypo: Determine and address cause; ↓ corresponding dose by 2-4 U or 10-20%.

Start:
Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM.

Adjust:
↑ dose by 1-2 U or 10-15% once-twice weekly until SMBG target reached.

For hypo:
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Figure 3. Approach to starting & adjusting insulin in T2DM

Add ≥2 rapid insulin* injections before meals ('basal-bolus').

Change to premixed insulin* twice daily.

Add 1 rapid insulin* injections before largest meal.

If not controlled, consider basal-bolus.

Add ≥2 rapid insulin* injections before meals ('basal-bolus').

If not controlled, consider basal-bolus.

Flexibility

More flexible

Less flexible

Complexity

Low

Moderate

High

Diabetes Care 2015;38:140; Diabetologia 2015;10.1077/s00125-014-3460-0
Polling Question

American Association of Clinical Endocrinologists (AACE) Treatment Guidelines are based on the A1c at initial entry into treatment and at all follow-up visits.

A. True
B. False
OTHER CONSIDERATIONS

• Age
• Weight
• Sex / racial / ethnic / genetic differences
• Co-morbidities
  - Coronary artery disease
  - Heart Failure
  - Chronic kidney disease
  - Liver dysfunction
  - Hypoglycemia-prone
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

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