Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)
## Writing Group

<table>
<thead>
<tr>
<th><strong>American Diabetes Association</strong></th>
<th><strong>European Assoc. for the Study of Diabetes</strong></th>
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<tbody>
<tr>
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<tr>
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<td><em>University of Pisa, Pisa, Italy</em></td>
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<tr>
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<td><em>Oxford University, Oxford, UK</em></td>
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*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
1. PATIENT-CENTERED CARE

2. BACKGROUND
   • Epidemiology and health care impact
   • Relationship of glycemic control to outcomes
   • Overview of the pathogenesis of Type 2 diabetes

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

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
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


   *Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
   *Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
1. 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.

*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
2. BACKGROUND

• Relationship of glycemic control to microvascular and macrovascular outcomes.
# 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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Kendall DM, Bergenstal RM. © International Diabetes Center 2009


* in T1DM
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 Pathophysiological Abnormalities in T2DM

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

HYPERGLYCEMIA

- GLP-1R agonists
- Glinides
- Amylin mimetics
- Insulin (pancreatic insulin secretion)
- DA agonists (pancreatic glucagon secretion)
- Metformin
- Bile acid sequestrants
- TZDs
- DA agonists
- T Z D s
- peripheral glucose uptake

- renal glucose excretion
- hepatic glucose production
- gut carbohydrate delivery & absorption

Adapted from: Inzucchi SE, Sherwin RS in: Cecil Medicine 2011
3. ANTI-HYPERGLYCEMIC THERAPY

- **Glycemic targets**
  - **HbA1c < 7.0%** (mean PG ~150-160 mg/dl [8.3-8.9 mmol/l])
  - Pre-prandial PG <130 mg/dl (7.2 mmol/l)
  - Post-prandial PG <180 mg/dl (10.0 mmol/l)

- **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**

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

HbA1c 7%

more stringent

less stringent

low

high

newly diagnosed

long-standing

long

short

absent

few / mild

severe

absent

few / mild

severe

highly motivated, adherent, excellent self-care capacities

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

Readily available

limited

Usually not modifiable

Potentially modifiable

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

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

HbA1c 7%

Absent  Few / Mild  Severe

more stringent  

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

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

Highly motivated, adherent, excellent self-care capacities

HbA1c 7%

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

more stringent

less stringent

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Figure 1. Modulation of the intensiveness of glucose lowering therapy in T2DM

*Resources and support systems* Readily available Limited

more stringent → HbA1c 7% → less stringent

POTENTIALLY MODIFIABLE

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: **Lifestyle**
  
  - Weight optimization
  
  - Healthy diet
  
  - Increased activity level


*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options:
  
  **Oral agents & non-insulin injectables**

- Metformin
- Sulfonylureas
- Thiazolidinediones
- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor agonists
- Meglitinides
- α-glucosidase inhibitors
- Colesevelam
- Dopamine-2 agonists
- Amylin mimetics


*Diabetes Care* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
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<tr>
<th>Oral Class</th>
<th>Mechanism</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| Biguanides | • Activates AMP-kinase (?other)  
• ↓ Hepatic glucose production | • Extensive experience  
• No hypoglycemia  
• Weight neutral  
• ? ↓ CVD | • Gastrointestinal  
• Lactic acidosis (rare)  
• B-12 deficiency  
• Contraindications | Low |
| Sulfonylureas | • Closes $K_{\text{ATP}}$ channels  
• ↑ Insulin secretion | • Extensive experience  
• ↓ Microvascular risk | • Hypoglycemia  
• ↑ Weight  
• Low durability  
• ? Blunts ischemic preconditioning | Low |
| Meglitinides | • Closes $K_{\text{ATP}}$ channels  
• ↑ Insulin secretion | • ↓ Postprandial glucose  
• Dosing flexibility | • Hypoglycemia  
• ↑ Weight  
• ? Blunts ischemic preconditioning  
• Dosing frequency | Mod. |
| TZDs | • PPAR-γ activator  
• ↑ Insulin sensitivity | • No hypoglycemia  
• Durability  
• ↓ TGs (pio)  
• ↑ HDL-C  
• ? ↓ CVD events (pio) | • ↑ Weight  
• Edema/heart failure  
• Bone fractures  
• ↑ LDL-C (rosi)  
• ? ↑ MI (rosi) | Low |

Table 1. Properties of anti-hyperglycemic agents

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<th>Advantages</th>
<th>Disadvantages</th>
<th>Cost</th>
</tr>
</thead>
</table>
| α-Glucosidase inhibitors    | • Inhibits α-glucosidase  
• Slows carbohydrate digestion / absorption | • No hypoglycemia 
• Nonsystemic  
• ↓ Postprandial glucose  
• ? ↓ CVD events | • Gastrointestinal  
• Dosing frequency  
• Modest ↓ A1c | Mod.  |
| DPP-4 inhibitors            | • Inhibits DPP-4  
• Increases incretin (GLP-1, GIP) levels | • No hypoglycemia  
• Well tolerated | • Angioedema / urticaria  
• ? Pancreatitis  
• ? ↑ Heart failure | High |
| Bile acid sequestrants      | • Bind bile acids  
• ? ↓ Hepatic glucose production | • No hypoglycemia  
• ↓ LDL-C | • Gastrointestinal  
• Modest ↓ A1c  
• Dosing frequency | High |
| Dopamine-2 agonists         | • Activates DA receptor  
• Alters hypothalamic control of metabolism  
• ↑ insulin sensitivity | • No hypoglycemia  
• ? ↓ CVD events | • Modest ↓ A1c  
• Dizziness, fatigue  
• Nausea  
• Rhinitis | High |
| SGLT2 inhibitors            | • Inhibits SGLT2 in proximal nephron  
• Increases glucosuria | • ↓ Weight  
• No hypoglycemia  
• ↓ BP  
• Effective at all stages | • GU infections  
• Polyuria  
• Volume depletion  
• ↑ LDL-C  
• ↑Cr (transient) | High |

Table 1. 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>
<tbody>
<tr>
<td>Amylin mimetics</td>
<td>• Activates amylin receptor</td>
<td>• ↓ Weight</td>
<td>• Gastrointestinal</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• ↓ glucagon</td>
<td>• ↓ Postprandial glucose</td>
<td>• Modest ↓ A1c</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ gastric emptying</td>
<td></td>
<td>• Injectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ satiety</td>
<td></td>
<td>• Hypo if insulin dose not reduced</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Dosing frequency</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Training requirements</td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>• Activates GLP-1 R</td>
<td>• ↓ Weight</td>
<td>• Gastrointestinal</td>
<td>High</td>
</tr>
<tr>
<td></td>
<td>• ↑ Insulin, ↓ glucagon</td>
<td>• No hypoglycemia</td>
<td>• ? Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↓ gastric emptying</td>
<td>• ↓ Postprandial glucose</td>
<td>• ↑ Heart rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• ↑ satiety</td>
<td>• ↓ Some CV risk factors</td>
<td>• Medullary ca (rodents)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Injectable</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Training requirements</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>• Activates insulin receptor</td>
<td>• Universally effective</td>
<td>• Hypoglycemia</td>
<td>Variable</td>
</tr>
<tr>
<td></td>
<td>• Myriad</td>
<td>• Unlimited efficacy</td>
<td>• Weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• ↓ Microvascular risk</td>
<td>• ? Mitogenicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Injectable</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>• Patient reluctance</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>• Training requirements</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Properties of anti-hyperglycemic agents
Healthy eating, weight control, increased physical activity & diabetes education

Metformin

**Mono-therapy**
- **Efficacy**: high
- **Hypo risk**: low
- **Weight**: neutral/loss
- **Side effects**: GI / lactic acidosis
- **Costs**: 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 + Metformin
- Metformin + Thiazolidinediones
- Metformin + DPP-4 Inhibitor
- Metformin + SGLT2-i
- Metformin + GLP-1 RA

**Dual therapy**
- **Efficacy**: high
- **Hypo risk**: low
- **Weight**: neutral
- **Side effects**: GI
- **Costs**: low

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 + Insulin (basal) + Sulfonylurea
- Metformin + Insulin (basal) + DPP-4-i
- Metformin + Insulin (basal) + GLP-1 RA
- Metformin + Insulin (basal) + SGLT2-i

**Triple therapy**
- **Efficacy**: high
- **Hypo risk**: low
- **Weight**: neutral
- **Side effects**: GI
- **Costs**: low

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 SGLT2-i:
- Metformin + GLP-1 receptor agonist
- Metformin + Insulin (basal) + Glucagon-like peptide-1 receptor agonist

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

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
Healthy eating, weight control, increased physical activity & diabetes education

**Mono-therapy**

<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>
<td>GI / lactic acidosis</td>
<td>low</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):

<table>
<thead>
<tr>
<th>Metformin</th>
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<th>Metformin</th>
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<tr>
<td>Metformin</td>
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<td>+</td>
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<td>+</td>
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</table>

**Dual therapy**

<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>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
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</table>

**Triple therapy**

<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>loss</td>
<td>GU, dehydration</td>
<td>high</td>
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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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<th>Metformin</th>
<th>Metformin</th>
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<td>Metformin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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**Combination injectable therapy**

<table>
<thead>
<tr>
<th>Insulin (basal)</th>
<th>GLP-1 receptor agonist</th>
<th>DPP-4 inhibitor</th>
<th>SGLT2 inhibitor</th>
</tr>
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<tbody>
<tr>
<td>highest</td>
<td>high</td>
<td>highest</td>
<td>high</td>
</tr>
<tr>
<td>high</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
</tr>
<tr>
<td>low risk</td>
<td>loss</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td>high</td>
<td>gain</td>
<td>gain</td>
<td>gain</td>
</tr>
<tr>
<td>low</td>
<td>hypoglycemia</td>
<td>hypoglycemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

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

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
Healthy eating, weight control, increased physical activity & diabetes education

- Metformin
  - High risk
  - Low risk
  - Neutral/loss
  - GI / lactic acidosis

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 + Metformin
- Metformin + Thiazolidinedione
- Metformin + DPP-4 inhibitor
- Metformin + SGLT2 inhibitor
- Metformin + GLP-1 receptor agonist
- Metformin + Insulin (basal)

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 + Metformin + Sulfonylurea
- Metformin + Metformin + Thiazolidinedione
- Metformin + DPP-4 Inhibitor + SGLT2 Inhibitor
- Metformin + SGLT-2 Inhibitor + GLP-1 receptor agonist
- Metformin + GLP-1 receptor agonist + Insulin (basal)

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

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### Mono-therapy

<table>
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<th>Efficacy*</th>
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<th>Weight</th>
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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):

- Metformin + Sulfonylurea
- Metformin + Thiazolidinedione
- Metformin + DPP-4 inhibitor
- Metformin + SGLT2 inhibitor
- Metformin + GLP-1 receptor agonist
- Metformin + Insulin (basal)

### Dual therapy†

<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>moderate risk</td>
<td>gain</td>
<td>hypoglycemia</td>
<td>low</td>
</tr>
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</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):

- Metformin + Sulfonylurea + TZD
- Metformin + Thiazolidinedione + SU
- Metformin + SGLT2-i + GLP-1-RA
- Metformin + DPP-4 i + SU
- Metformin + GLP-1-RA + Insulin

### Triple therapy

- Metformin + GLP-1 receptor agonist + TZD
- Metformin + GLP-1 receptor agonist + DPP-4-i
- Metformin + GLP-1 receptor agonist + SGLT2-i

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 SGLT2-i:

- Metformin + Basal Insulin + Mealtime Insulin or GLP-1-RA

*Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Healthy eating, weight control, increased physical activity & diabetes education

**Metformin**

- High risk
- Low risk
- Neutral/loss
- GI / lactic acidosis
- 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):

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<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>low</td>
<td>low</td>
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<td>low</td>
<td>low</td>
<td>highest</td>
</tr>
<tr>
<td>gain</td>
<td>gain</td>
<td>rare</td>
<td>neutral</td>
<td>loss</td>
<td>high</td>
</tr>
<tr>
<td>edema, HF, fxs</td>
<td>edema, HF, fxs</td>
<td>edema, HF, fxs</td>
<td>GU, dehydration</td>
<td>GI</td>
<td>hypoglycemia</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):

<table>
<thead>
<tr>
<th>Metformin +</th>
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<th>Metformin +</th>
</tr>
</thead>
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</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>DPP-4-i</td>
<td>SU</td>
<td>TZD</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>SGLT2-i</td>
<td>SU</td>
<td>TZD</td>
<td>SU</td>
<td>TZD</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>GLP-1-RA</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
<td>Insulin</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
</tr>
<tr>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</td>
<td>or</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:

- Metformin +
- Combination injectable therapy:
  - Basal Insulin + Mealtime Insulin or GLP-1-RA

*Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442*
Healthy eating, weight control, increased physical activity & diabetes education

Metformin

- High efficacy
- Low risk of hypoglycemia
- Neutral/low risk of weight gain
- GI/lactic acidosis neutral/loss
- Low cost

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 + Thiazolidinedione (TZD)
- Metformin + DPP-4 inhibitor
- Metformin + SGLT2 inhibitor
- Metformin + GLP-1 receptor agonist

- High efficacy
- Low risk of hypoglycemia
- Neutral/low risk of weight gain
- GI/lactic acidosis neutral/low risk
- Low cost

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 + Thiazolidinedione + DPP-4 inhibitor
- Metformin + Thiazolidinedione + SGLT2 inhibitor
- Metformin + Thiazolidinedione + GLP-1 receptor agonist
- Metformin + SGLT2 inhibitor + DPP-4 inhibitor
- Metformin + SGLT2 inhibitor + TZD
- Metformin + GLP-1 receptor agonist + TZD

- High efficacy
- Low risk of hypoglycemia
- Neutral/low risk of weight gain
- GI/lactic acidosis neutral/low risk
- Low cost

Figure 2A. Anti-hyperglycemic therapy in T2DM: Avoidance of hypoglycemia

Diabetes Care 2015;38:140-149; Diabetologia 2015;58:429-442
Healthy eating, weight control, increased physical activity & diabetes education

**Mono-therapy**
- **Metformin**
  - Efficacy: high
  - Hypo risk: low risk
  - Weight: neutral/loss
  - Side effects: GI/lactic acidosis
  - Costs: 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):*

**Dual therapy**

**Triple therapy**

*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):*

---

**Figure 2B. Anti-hyperglycemic therapy in T2DM:**

**Avoidance of weight gain**

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
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</td>
<td>neutral/loss</td>
<td>GI / lactic acidosis</td>
<td>low</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):

- **Metformin** + Thiazolidinedione
- **Metformin** + Sulfonlurea
- **Metformin** + DPP-4 Inhibitor
- **Metformin** + GLP-1-RA
- **Metformin** + Insulin (basal)
- **Metformin** + Basal Insulin + Sulfonylurea
- **Metformin** + Basal Insulin + GLP-1-RA
- **Metformin** + Basal Insulin + SGLT-2 Inhibitor

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
- **Metformin** + Thiazolidinedione + SU
- **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 T2-i:

**Fig 2C. Anti-hyperglycemic therapy in T2DM:**

**Minimization of costs**

*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
3. ANTI-HYPERGLYCEMIC THERAPY

• Therapeutic options: 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* 2012;35:1364–1379; *Diabetologia* 2012;55:1577–1596
*Diabetes Care* 2015;38:140-149; *Diabetologia* 2015;58:429-442
3. ANTI-HYPERGLYCEMIC THERAPY

- Therapeutic options: *Insulins*

![Graph showing insulin levels over time for different types of insulins.](image)
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-twelce weekly to reach FBG target.
- **For hypo**: Determine & address cause; 
  ↓ dose by 4 units or 10-20%.

Diabetes Care 2015;38:140-149;
Diabetologia 2015;58:429-442
Add ≥ 2 rapid insulin* injections before meals ("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.

Add 1 rapid insulin* injections before largest meal

- **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.

Change to premixed insulin* twice daily

- **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.

**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%.

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.)

**Figure 3. Approach to starting & adjusting insulin in T2DM**
Add ≥2 rapid insulin* injections before meals (‘basal-bolus’)
4. OTHER CONSIDERATIONS

- Age
- Weight
- Sex / racial / ethnic / genetic differences
- Comorbidities
  - Coronary artery disease
  - Heart Failure
  - Chronic kidney disease
  - Liver dysfunction
  - Hypoglycemia-prone
4. 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 2015;38:140-149; Diabetologia 2015;58:429-442