Update in Treatment Strategy in Type 2 Diabetes: ADA/EASD Algorithm

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Presenter Disclosure Information

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

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Consultant: None
Other: Member, ADA Professional Practice Committee
### Start with Monotherapy unless:

- A1C is greater than or equal to 8%: consider Dual Therapy.
- A1C greater than or equal to 9% (based on estimated A1C) greater than or equal to 10% (estimated A1C) or patient is markedly symptomatic: consider Combination Injectable Therapy (See Figure 8.2).

**Pharmacologic Approaches to Glycemic Treatment:**

#### Monotherapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Monotherapy</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>EFFICACY* high</td>
<td>(See Figure 8.2)</td>
</tr>
<tr>
<td></td>
<td>HYPO RISK low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WEIGHT neutral/tolerable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIDE EFFECTS GI/renal/cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COSTS* low</td>
<td></td>
</tr>
</tbody>
</table>

* If A1C target not achieved after approximately 3 months of monotherapy, consider 2-drug combination.

#### Dual Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dual Therapy</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>EFFICACY* high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HYPO RISK low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WEIGHT neutral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIDE EFFECTS GI/cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COSTS* low</td>
<td></td>
</tr>
</tbody>
</table>

* If A1C target not achieved after approximately 3 months of dual therapy, consider 3-drug combination.

#### Triple Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Triple Therapy</th>
<th>Lifestyle Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>EFFICACY* high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HYPO RISK low</td>
<td></td>
</tr>
<tr>
<td></td>
<td>WEIGHT neutral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SIDE EFFECTS GI/cardiovascular</td>
<td></td>
</tr>
<tr>
<td></td>
<td>COSTS* low</td>
<td></td>
</tr>
</tbody>
</table>

* If A1C target not achieved after approximately 3 months of triple therapy and patient on an 3-drug combination, may be beneficial to consider GLP-1 RAs (Exenatide, Liraglutide), add basal insulin, or total insulins (i.e., Aspart, Lispro, Aspart, and Lispro). Also, consider other combinations of GLP-1 RAs with basal insulin. metformin therapy should be maintained, while other drugs may be discontinued on an individual basis to avoid unnecessary toxicity or adverse effects, i.e., adding a fourth antihyperglycemic agent.

### 2017 ADA Standards of Care

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2017. Diabetes Care 2017; 40 (Suppl. 1): S64-S74
2018 ADA Standards of Care

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2018. Diabetes Care 2018; 41 (Suppl. 1): S73-S85
2018 ADA Standards of Care

At diagnosis, initiate lifestyle management, set AIC target, and initiate pharmacologic therapy based on AIC:

- **AIC is less than 5%**, consider **Monotherapy**.
- **AIC is greater than or equals 9%**, consider **Dual Therapy**.
- **AIC is greater than or equal to 10%**, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider **Combination Injectable Therapy** (See Figure B.2).

### Monotherapy

Lifestyle Management + Metformin

Initiate metformin therapy if no contraindications* (See Table B.1)

<table>
<thead>
<tr>
<th>AIC at target after 3 months of monotherapy?</th>
<th>Yes:</th>
<th>No:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Monitor AIC every 3-6 months</td>
<td>- Assess medication-taking behavior</td>
</tr>
<tr>
<td></td>
<td>- Consider Dual Therapy</td>
<td>- Consider Dual Therapy</td>
</tr>
</tbody>
</table>

### Dual Therapy

Lifestyle Management + Metformin + Additional Agent

- **A1C**
  - **Yes**: Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (See recommendations with * on p. 5/3 and Table B.1)
  - **No**: Add second agent after consideration of drug-specific effects and patient factors (See Table B.2)
Learning Objectives

This presentation will cover the following learning objectives:

1. Apply concepts of the decision cycle for patient-centered glycemic management in type 2 diabetes;
2. Recognize patient- and medication-specific factors to consider when selecting glucose lowering agents; and
• At diagnosis, recommended first-line therapy includes: *metformin* + *comprehensive lifestyle intervention*
Pharmacologic Therapy for Type 2 Diabetes

9.5 Metformin is the preferred initial pharmacologic agent for the treatment of type 2 diabetes. A

9.6 Once initiated, metformin should be continued as long as it is tolerated and not contraindicated; other agents, including insulin, should be added to metformin. A

9.7 Long-term use of metformin may be associated with biochemical vitamin B12 deficiency, and periodic measurement of vitamin B12 levels should be considered in metformin-treated patients, especially in those with anemia or peripheral neuropathy. B

9.8 The early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when A1C levels (>10% [86 mmol/mol]) or blood glucose levels (≥300 mg/dL [16.7 mmol/L]) are very high. E
Decision Cycle for Patient-Centered Glycemic Management

- Current lifestyle
- Comorbidities i.e. ASCVD\(^1\), CKD\(^2\), HF\(^3\)
- Clinical characteristics i.e. age, HbA\(_{1c}\), weight
- Issues such as motivation and depression
- Cultural and socio-economic context

Approach to Individualization of Glycemic Targets
Pharmacologic Therapy for Type 2 Diabetes

9.9 Consider initiating dual therapy in patients with newly diagnosed type 2 diabetes who have A1C ≥1.5% (12.5 mmol/mol) above their glycemic target. E

9.10 A patient-centered approach should be used to guide the choice of pharmacologic agents. Considerations include comorbidities (atherosclerotic cardiovascular disease, heart failure, chronic kidney disease), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences. E

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019;42(Suppl. 1):S90-S102
• If A1C remains above target despite recommended first-line treatment:

**Step 1:**

- Does the patient have established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)?

If the answer is “Yes”....
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102
Considerations

• ASCVD is defined differently across trials
  • Established CVD (e.g. MI, stroke, revascularization procedure)
  • Very high cardiovascular risk
• Each cardiovascular outcomes trial (CVOT), while large, is a single experiment
• It is not always clear whether differences in trial findings within a drug class are related to trial design or to true differences in the individual medications
  • Where evidence suggests a hierarchy, this is noted

If ASCVD Predominate:

- GLP-1 receptor agonist with proven cardiovascular benefit
  - Liraglutide > semaglutide > exenatide LAR

- SGLT2 inhibitor with proven cardiovascular benefit
  - Empagliflozin > canagliflozin

Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102
Among Patients with ASCVD or CKD in Whom HF or CKD Predominates:

- SGLT2 inhibitor with evidence of reducing HF and/or CKD progression
  - Empagliflozin, canagliflozin

- If SGLT2 inhibitor is not tolerated, contraindicated, or if eGFR is less than adequate, add a GLP-1 receptor agonist with proven CVD benefit

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Pharmacologic Approaches to Glycemic Treatment:
*Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102*
Pharmacologic Therapy for Type 2 Diabetes

9.11 Among patients with type 2 diabetes who have established atherosclerotic cardiovascular disease, sodium-glucose cotransporter 2 inhibitors, or glucagon-like peptide 1 receptor agonists with demonstrated cardiovascular disease benefit (Table 9.1) are recommended as part of the antihyperglycemic regimen. A

9.12 Among patients with atherosclerotic cardiovascular disease at high risk of heart failure or in whom heart failure coexists, sodium-glucose cotransporter 2 inhibitors are preferred. C

9.13 For patients with type 2 diabetes and chronic kidney disease, consider use of a sodium-glucose cotransporter 2 inhibitor or glucagon-like peptide 1 receptor agonist shown to reduce risk of chronic kidney disease progression, cardiovascular events, or both. C
• If A1C remains above target despite recommended first-line treatment:

**Step 1:**
• Does the patient have established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD)?

If the answer is “No”....
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102
• If choosing a GLP-1 receptor agonist with good efficacy for weight loss:

Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
*If no specific comorbidities (i.e., no established CVD, low risk of hypoglycemia, and lower priority to avoid weight gain or no weight-related comorbidities)
<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Efficacy</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV effects</th>
<th>Cost</th>
<th>CVD Risk</th>
<th>Renal effects</th>
<th>Additional Considerations</th>
</tr>
</thead>
</table>
| Sodium Glucose Transporter 2 Inhibitors | High | No | Neutral | Neutral | Low | Mild | Neutral | Comedication side effects common. May increase KD. Renal failure.
| GLP-1 RAs | High | No | Less | Neutral | High | Mild | Normal | Can cause weight gain. May cause fluid retention. Renal failure.
| DPP-4 Inhibitors | High | No | Neutral | Neutral | Mild | Low | Normal | Can cause weight gain. May cause fluid retention. Renal failure.
| SGLT2 Inhibitors | High | No | Neutral | Neutral | High | Low | Mild | Ketotic ketoacidosis unlikely. Renal failure.
| Insulin Analogues | High | No | Low | Neutral | High | Mild | Normal | Can cause weight gain. May cause fluid retention. Renal failure.
| Insulin Secretagogues | High | No | Low | Neutral | High | Mild | Normal | Can cause weight gain. May cause fluid retention. Renal failure.
| Sulfonylureas | High | No | Low | Neutral | High | Mild | Normal | Can cause weight gain. May cause fluid retention. Renal failure.

*For agent-specific dosing recommendations, please refer to the manufacturer’s prescribing information. HbA1c, hemoglobin A1c; CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; DKA, diabetic ketoacidosis; KD, kidney disease; GLP-1 RAs, glucagon-like peptide 1 receptor agonists; NASH, nonalcoholic steatohepatitis; SGLT2, sodium glucose cotransporter 2; SQ, subcutaneous; T2DM, type 2 diabetes.*
Figure 9.2 - Intensifying to Injectable Therapies
Pharmacologic Therapy for Type 2 Diabetes

9.14 In most patients who need the greater glucose-lowering effect of an injectable medication, glucagon-like peptide 1 receptor agonists are preferred to insulin. B
**Consensus Recommendation:** In patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are the preferred choice to insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.

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**Abd El Aziz MS et al. Diabet Obes Metab 2017;19(2):216-227**

Pharmacologic Approaches to Glycemic Treatment:
Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102
Considering Oral Therapy in Combination with Injectable Therapies

**METFORMIN**
- Continue treatment with metformin

**TZD**
- Stop TZD when commencing insulin OR reduce dose

**SGLT2i**
- If on SGLT2i, continue treatment
- Consider adding SGLT2i if
  - Established CVD
  - If HbA1c above target or as weight reduction aid

**Beware**
- DKA (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

**SULFONYLUREA**
- If on SU, stop or reduce dose by 50% when basal insulin initiated

**DPP-4i**
- Stop DPP-4i if GIP or GLP-1 RA initiated

Pharmacologic Therapy for Type 2 Diabetes

9.15 Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed. B

9.16 The medication regimen should be reevaluated at regular intervals (every 3-6 months) and adjusted as needed to incorporate new patient factors (Table 9.1). E
Overall Summary

• Patient-centered decision-making and consistent efforts at improving diet and physical activity remain the foundation of all glycemic management

• The management of hyperglycemia in type 2 diabetes has become increasingly complex with the expanding number of glucose-lowering medications available

• Initial use of metformin, followed by the addition of glucose-lowering medications based on patient co-morbidities and preferences is recommended as we await answers to the many questions that remain
ADA Standards of Care – A Living Document

• Beginning with the 2018 ADA Standards of Medical Care in Diabetes, the Standards document became a “living” document where notable updates are incorporated into the Standards

• Updates will be made in response to important events inclusive of, but not limited to:
  • Approval of new treatments (medications or devices) with the potential to impact patient care;
  • Publication of new findings that support a change to a recommendation and/or evidence level of a recommendation; or
  • Publication of a consensus document endorsed by ADA that necessitates an update of the Standards to align content of the documents

Living Standards Updates Available at: http://care.diabetesjournals.org/living-standards
ADA Standards of Care – A Living Document

All future updates to the *Standards of Medical Care in Diabetes* will be noted here.

The following 2018 updates have been incorporated into the 2019 Standards of Care:

October 5, 2018

- 8. Pharmacologic Approaches to Glycemic Treatment

April 11, 2018

- 6. Glycemic Targets
- 8. Pharmacologic Approaches to Glycemic Treatment
- 14. Diabetes Care in the Hospital
- Standards of Medical Care in Diabetes—2018 Abridged for Primary Care Providers

Living Standards Updates Available at: [http://care.diabetesjournals.org/living-standards](http://care.diabetesjournals.org/living-standards)
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Thank you