Working Your Way through ADA’s T2D Treatment Algorithm

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Presenter Disclosure Information

• I have no disclosures

Learning Objectives

Recognize drug-specific and patient factors of antihyperglycemic agents to support patient-provider shared decision making

Demonstrate when and how to intensify therapy

Identify opportunities to refer patients to Diabetes Self-Management Education

Standards of Medical Care in Diabetes - 2019
Section 9, Pharmacologic Approaches to Glycemic Treatment

Abridged Version: Clinical Diabetes 2019
Jan:37(1):11-34.

Figure 9.1 - Glucose-lowering medication in type 2 diabetes: overall approach
Patient case: Mary

Social History
- Divorced with 2 teenage children.
- Works as an administrative assistant.
- Tried losing weight in the past but has not been successful long term.
- Tries to walk 2-3 times per week, but lacks motivation.
- She has tried to cut back on sweets, she stopped drinking soda, but still eats fast food routinely and self-identifies problems with portion control and junk food.

Patient case: Mary

History of the present illness
- 52-year-old overweight woman
- New diagnosis of type 2 diabetes based on an A1C of 8.4%
- Had prediabetes for 5 years.
- Also has hypertension and dyslipidemia, which are both well controlled with losartan 100mg once daily and atorvastatin 40mg once daily.

What is your treatment plan for Mary’s type 2 diabetes?

Vital signs:
- BP: 128/78 mmHg
- HR: 76 bpm
- Wt: 168 lb
- Ht: 5'4"
- BMI: 28.8 kg/m²

Labs:
- A1C: 8.4%
- eGFR: 68 mL/min/1.73m²
- UACR: 22 mg/g
- Tchol: 167 mg/dL
- LDL: 73 mg/dL
- HDL: 58 mg/dL
- TG: 178 mg/dL
Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes - 2019. Diabetes Care 2019; 42 (Suppl. 1): S90-S102

Figure 9.1 - Glucose-lowering medication in type 2 diabetes: overall approach

First-Line Therapy

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity) if HbA1c above target proceed as below

At diagnosis, recommended first-line therapy includes:

Metformin
Comprehensive lifestyle intervention

Pros:
• High efficacy
• May aid in weight maintenance (possibly weight loss)
• Indirect lowering of insulin levels
• Low hypoglycemia risk
• Oral administration

Cons:
• GI intolerance is common
• Potential for B12 deficiency
• Contraindicated with eGFR < 30 mL/min/1.73 m²
• Potential for metformin-associated lactic acidosis (MALA)

Metformin: Pros & Cons

Pros:
• High efficacy
• May aid in weight maintenance (possibly weight loss)
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Cons:
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• Potential for B12 deficiency
• Contraindicated with eGFR < 30 mL/min/1.73 m²
• Potential for metformin-associated lactic acidosis (MALA)

Describe 3 scenarios in which metformin monotherapy may not be the preferred first-line therapy.

Pharmacologic Therapy for Type 2 Diabetes

• Consider early introduction of insulin if:
  - evidence of ongoing catabolism
  - symptoms of hyperglycemia are present
  - when A1C levels (>10%, 86 mmol/L) or blood glucose levels (>300 mg/dL, 16.7 mmol/L) are very high.
• 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.

Metformin

• Preferred initial pharmacologic agent.
• Continue as long as it is tolerated and not contraindicated;
• Other agents, including insulin, should be added to metformin.
• Consider periodic measurement of vitamin B12 levels.
Patient case: Robert

History of the present illness
- 66-year-old man
- 3-year history of type 2 diabetes
- Also has:
  - Hypertension
  - Dyslipidemia
  - Osteoarthritis
  - Sleep apnea
  - Depression
- Had a myocardial infarction 5 years ago

Social History:
- Married and lives with his wife.
- He recently retired
- Robert and his wife travel frequently.
- They both eat out at restaurants often.
- He does not exercise.

Medications:
- Metformin 1000mg twice daily
- Lisinopril 20mg once daily
- Metoprolol XL 100mg once daily
- Rosuvastatin 20mg once daily
- Aspirin 81mg once daily
- Paroxetine 10mg once daily

Vital signs:
- BP: 136/84 mmHg
- HR: 64 bpm
- HT: 5'11"
- WT: 224 lb
- BMI: 31.2 kg/m²

Labs:
- A1C: 8.2%
- eGFR: 58 mL/min/1.73m²
- UACR: 366 mg/g
- Total: 154 mg/dL
- LDL: 69 mg/dL
- HDL: 48 mg/dL
- TG: 184 mg/dL

How would you modify Robert's type 2 diabetes treatment regimen?
**Decision Cycle for Patient-Centered Glycemic Management**

- **Assess Key Patient Characteristics**
  - Current lifestyle
  - Comorbidities (e.g., ASCVD, CKD, HF)
  - Clinical characteristics (age, HbA1c, weight)
  - Issues such as motivation and depression
  - Cultural and socio-economic context

- **Goals of Care**
  - Glycemic control
  - Reduction of complications

- **Implement Management Plan**
  - Medications
  - Lifestyle interventions

- **Agree on Management Plan**

- **Review and Agree on Management Plan**

**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**

- 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.
### Important Considerations

ASCVD is defined differently across trials
- Established CVD (e.g., MI, stroke, revascularization procedures)
- 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 true differences in the individual medications.

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### SGLT-2 Inhibitors: Pros & Cons

**Pros:**
- Intermediate efficacy
- Weight loss
- Cardiovascular (proven benefit for SGLT2 inhibitors)
- Renal benefits (empagliflozin, canagliflozin & dapagliflozin)
- Cost effectiveness
- Unique risk profile (renal, less hypoglycemia)
- Rare/Serious Safety Concerns: increased amputation risk (SGLT2 inhibitors), DKA, bone fractures (SGLT2 inhibitors)

**Potential Cons:**
- Cost
- Renal dose adjustment required (refer to individual agent prescribing information)
- GI intolerance
- Volume depletion/hypotension
- Rare/Serious Safety Concerns: increased amputation risk (SGLT2 inhibitors), DKA, bone fractures (SGLT2 inhibitors)

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### If ASCVD predominates:

- GLP-1 RA with proven cardiovascular benefit
  - Liraglutide: ↓ risk of MACE in adults with T2D and established CVD
  - Liraglutide & Dulaglutide: Superiority for MACE outcomes in large CVOTs
  - Semaglutide: Superiority for MACE outcomes in a safety CVOT

- SGLT2 inhibitor with proven cardiovascular benefit
  - Empagliflozin + canagliflozin

**SGLT-2 Inhibitors: Pros & Cons**

**Pros:**
- Intermediate efficacy
- Weight loss
- Cardiovascular & renal benefits (empagliflozin, canagliflozin & dapagliflozin)
- Oral administration
- Unique risk profile (renal, less hypoglycemia)
- Low hypoglycemia risk (monotherapy or combination with metformin)

**Potential Cons:**
- Cost
- Renal dose adjustment required (refer to individual agent prescribing information)
- Genitourinary infections
- Volume depletion/hypotension
- Rare/Serious Safety Concerns: increased amputation risk (SGLT2 inhibitors), DKA, bone fractures (SGLT2 inhibitors), pyelonephritis/urosepsis, Fournier’s gangrene

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### GLP-1 Receptor Agonists: Pros & Cons

**Pros:**
- High efficacy
- Low hypoglycemia risk (monotherapy or combination with metformin)
- Cardiovascular & renal benefits
- Weight loss

**Potential Cons:**
- Cost
- Need for renal dose adjustment
- Injectable
- GI intolerance
- Rare/Serious Safety Concerns: Thyroid C-cell tumors (long-acting agents), Acute pancreatitis

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### 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, dapagliflozin

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

**HF or CKD Predominates**

**Frequent:**
- SGLT2 with evidence of reducing HF or CKD progression in large CVOTs (empagliflozin)
  - GLP-1 RA with proven cardiovascular benefit
  - GLP-1 RA with proven cardiovascular benefit
  - GLP-1 RA with proven cardiovascular benefit

**Rare:**
- Immediate efficacy
- Weight loss
- Cardiovascular (proven benefit)
- Renal benefits (empagliflozin, canagliflozin & dapagliflozin)
- Cost effectiveness
- Unique risk profile (renal, less hypoglycemia)
- Rare/Serious Safety Concerns: increased amputation risk (SGLT2 inhibitors), DKA, bone fractures (SGLT2 inhibitors)

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**Which medication would be most supported by the ADA treatment recommendations for Robert?**

**How would your treatment plan for Robert be different if he did not have ASCVD or CKD?**
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"

**ESTABLISHED ASCVD or CKD**

**No**

**Yes**

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**DPP-4 Inhibitors: Pros & Cons**

**Pros:**
- Intermediate efficacy (preferentially target PPG)
- Low hypoglycemia risk (monotherapy or combination with metformin)
- Weight neutral
- Oral administration

**Potential Cons:**
- Cost
- Need for renal dose adjustment (can still be used in ESRD)
- Potential risk for exacerbation of heart failure (saxagliptin, alogliptin)
- Rare/Serious Safety Concerns: Acute pancreatitis, joint pain

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If choosing a GLP-1 receptor agonist with good efficacy for weight loss:

- Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

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**Compelling Need to Minimize Hypoglycemia**

<table>
<thead>
<tr>
<th>Drug</th>
<th>GLP 1A</th>
<th>DPP 4I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>FPG &lt; 60</td>
<td>FPG &lt; 70</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>FPG &lt; 70</td>
<td>FPG &lt; 70</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>FPG &lt; 70</td>
<td>FPG &lt; 70</td>
</tr>
<tr>
<td>T2D</td>
<td>FPG &lt; 70</td>
<td>FPG &lt; 70</td>
</tr>
</tbody>
</table>

Consider the addition of a single agent to:
- **Counteract generation 2D with lower risk of hypoglycemia**
- **Consider individual with lower risk of hypoglycemia**

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**In Those Without Established ASCVD or CKD**

**Prior Therapy with Glucose-Lowering Agents**

- FPG > 140 mmol/L (A1C > 8.5%)
- FPG < 100 mmol/L (A1C < 7.5%)

**Weight Status**

- FPG > 140 mmol/L (A1C > 8.5%)
- FPG < 100 mmol/L (A1C < 7.5%)

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**Compelling Need to Promote Weight Loss**

- GLP 1A for good efficacy for weight loss
- T2D for GLP 1A for good efficacy for weight loss

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*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)

**COST IS A MAJOR ISSUE**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost ($)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylureas</td>
<td>31</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>66</td>
</tr>
</tbody>
</table>

**Thiazolidinediones: Pros & Cons**

**Pros:**
- High efficacy
- Low hypoglycemia risk
- Oral administration
- Low cost
- Benefit in NASH (Nonalcoholic steatohepatitis)

**Potential Cons:**
- Weight gain
- Fluid retention/edema (HF risk)
- Fractures
- Bladder Cancer (pioglitazone)

**Sulfonylureas: Pros & Cons**

**Pros:**
- High efficacy
- Oral administration
- Low cost

**Cons:**
- High hypoglycemia risk
- Weight gain

**Patient case: Maggie**

**History of the present illness**
- Maggie is an overweight (BMI 28 kg/m²)
- 60-year-old woman
- 8 year history of poorly controlled type 2 diabetes for which she takes:
  - Metformin 1000mg twice daily,
  - Glipizide 10mg once daily,
  - Sitagliptin 50mg once daily
Patient case: Maggie

- She did not tolerate canagliflozin due to recurrent yeast infections.
- Her A1C is 8.8% (target < 7.5%).
- She occasionally has blurry vision, but no other symptoms of hyperglycemia.
- She has symptomatic hypoglycemia about twice per month.
- She has CKD with reduced renal function (eGFR 40 mL/min/1.73m²) and albuminuria (UACR 450 mg/g).
- She does not have ASCVD.

Pharmacologic Therapy for Type 2 Diabetes

- 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.
- In most patients who need the greater glucose-lowering effect of an injectable medication, GLP-1 RA are preferred to insulin.

How would you modify Maggie’s treatment regimen for type 2 diabetes?

Figure 9.2 - Intensifying to Injectable Therapies
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.

Consideration of Oral Therapy in Combination with Injectable Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>SGLT2i</td>
<td>Continue if established CVD, HbA1c above target, or for weight reduction.</td>
</tr>
<tr>
<td>DPP-4i</td>
<td>Stop if GLP-1 RA initiated.</td>
</tr>
<tr>
<td>TZD</td>
<td>Stop when commencing insulin OR reduce dose.</td>
</tr>
<tr>
<td>METFORMIN</td>
<td>Continue treatment.</td>
</tr>
<tr>
<td>SU</td>
<td>Consider stopping if prandial insulin initiated or on a premix regimen.</td>
</tr>
</tbody>
</table>

Avoid Therapeutic Inertia

- Intensification of treatment for patients with type 2 diabetes not meeting treatment goals should not be delayed.
- 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).
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 and our expanding understanding of their impact on CV and renal outcomes.
- 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

- Full version available
- Abridged version for PCPs
- Standards of Care slide deck
- Free app, with interactive tools
- Pocket cards with key figures
- Free webcast for continuing education credit

Professional.Diabetes.org/SOC

Thank you