How to Use the American Diabetes Association’s Type 2 Diabetes Treatment Algorithm

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Disclosures of Interest

None
Key points to emphasize

New information -- Updated October 5, 2018 at EASD meeting in Berlin

1. Update informed by evidence generated in the past 2 years

2. Greater focus on lifestyle interventions, with increased emphasis on weight loss and obesity management, including metabolic surgery

3. Greater focus on patient related issues and self-management which have a major impact on success of any pharmacological interventions

4. Preferred choices of glucose-lowering agents driven by new evidence from CVOT and consideration of areas of major clinical need (for example weight and risk of hypoglycemia)

5. GLP-1 RAs are preferred to insulin as first injectable
Balancing Risks and Benefits for Personalized Goals

More Stringent Control
- No hypoglycemia
- Less complexity/polypharmacy
- Lifestyle or metformin only
- Short disease duration
- Long life expectancy
- No CVD

Less Stringent Control
- History of severe hypoglycemia
- High burden of therapy
- Longer disease duration
- Limited life expectancy
- Extensive co-morbidity
- CVD
Improving Glycemic Management

• Focus on treatments for glycemic control
  • Behavioral approaches
  • Medications
  • Metabolic surgery

• Addresses increasing complexity of patient centered therapeutic decisions in the context of expanding therapeutic options and new information on benefits and risks

Putting the Patient at the Center of Care
Shared decision making in type 2 diabetes

SDM can improve
- decision quality
- patient knowledge
- patient risk perception

Ethical imperative for support of patients’ autonomy
Diabetes Self-Management Education and Support (DSMES)

• Is available to patients at critical times
• Individualized to the needs of the person, including language and culture
• Structured theory-driven written curriculum with supporting materials
• Delivered in group or individual settings by trained educators
• Promote healthy eating, physical activity, good medication-taking behavior, and increase self-efficacy
• Supports person and their family in developing attitudes, beliefs, knowledge and skills to self-manage diabetes
• Includes core content and monitoring of patient progress, including health status, quality of life.
• Evidence-based

Empathic patient-centered care

• Patients with diabetes often live with multiple chronic conditions
• Providers & health care systems should prioritize the delivery of empathic, individualized patient-centered care
• To determine what is the best management option for each patient, consider each individual's
  • personal, social and biomedical context,
  • his/her values,
  • reasons he/she values the available options, and
  • relative contribution of each option in terms of benefits, harms, costs and inconveniences.
Persistence and medication adherence

• Mean medication adherence rate ≈ 75%, average proportion of patients adherent to medication < 70%.

• Adherence slightly varies between orals vs injectable therapy and individual classes

• Discontinuation rates range from 10% to 60% (both in observational studies and in clinical trials)

Clinical Inertia

Clinical inertia: failure of healthcare providers to initiate or intensify therapy when indicated, due to:

• overestimation of care provided

• use of “soft” reasons to avoid intensification of therapy

• lack of education, training, and practice organization aimed at achieving therapeutic goals
Recommended Process for Glucose Lowering Medication Selection:
Where Does New Evidence From Cardiovascular Outcome Trials Fit In?
SGLT-2 Inhibitors: Mechanism of Action

1. Normal Glucose: 90% reabsorbed, 10% filtered.
2. Type 2 Diabetes with SGLT-2i: Glucose not reabsorbed by SGLT-2, leading to increased glucose excretion in urine.

Diagram: Juxtaglomerular Complex → Proximal Convoluted Tubules → Loop of Henle → SGLT-2, SGLT-1 → Glucose reabsorption.

Note: SGLT-2 inhibitors block the reabsorption of glucose at the level of the proximal convoluted tubules, leading to increased glucose excretion in urine.
Death from cardiovascular cause: empagliflozin


The Incretin Effect

Adapted from Nauck MA, volume 63, issue 2, pages 492-498, 2016
Death from cardiovascular cause: liraglutide


Figure 1

DETECTION CYCLE FOR PATIENT-CENTRED GLYCAEMIC MANAGEMENT IN TYPE 2 DIABETES

ASSESS KEY PATIENT CHARACTERISTICS

- Current lifestyle
- Comorbidities i.e. ASCVD, CKD, HF
- Clinical characteristics i.e. age, HbA1c, weight
- Issues such as motivation and depression
- Cultural and socio-economic context
Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD

Use metformin unless contraindicated or not tolerated
If not at HbA₁c target:
- Continue metformin unless contraindicated (remember to adjust dose/stop metformin with declining eGFR)
- Add SGLT2i or GLP-1 RA with proven cardiovascular benefit¹ (See below)
If at HbA₁c target:
- If already on dual therapy, or multiple glucose-lowering therapies and not on an SGLT2i or GLP-1 RA, consider switch to one of these agents with proven cardiovascular benefit¹ (See below)
OR reconsider/lower individualised target and introduce SGLT2i or GLP-1 RA
OR reassess HbA₁c at 3 month intervals and add SGLT2i or GLP-1 RA if HbA₁c goes above target
Step 1: Assess cardiovascular disease

Presence of cardiovascular disease is compelling indication

Considerations

• ASCVD is defined differently across trials
  • Established CVD (e.g. MI, stroke, revascularization procedure)
  • Very high cardiovascular risk
• Each cardiovascular outcomes trial, 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
CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED ASCVD OR CKD

If ASCVD Predominates:

**GLP-1 RA with proven cardiovascular benefit**
- Liraglutide > semaglutide > exenatide LAR
- Recent data for dulaglutide (lower risk population)

**SGLT2-i with proven cardiovascular benefit**
- Empagliflozin > canagliflozin
- Recent data for dapagliflozin (lower risk population, heart failure hospitalization benefit)
Caveats and Questions

No evidence of CVD benefit in those at lower cardiovascular risk

The combination of SGLT2-i and GLP-1 RA has not been tested in cardiovascular outcome trials

CHOOSING GLUCOSE-LOWERING MEDICATION IN THOSE WITH ESTABLISHED HF OR CKD
Among patients with ASCVD in whom HF coexists or is of concern, SGLT2 inhibitor are recommended

**Rationale:** Patients with T2D are at increased risk for heart failure with reduced or preserved ejection fraction.

Significant, consistent reductions in hospitalization for heart failure have been seen in SGLT2-i trials.

**Caveat:** trials were not designed to adjudicate heart failure (except recent dapagliflozin study).

Majority of patients did not have clinical heart failure at baseline.

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**Consensus Recommendation:**

For patients with type 2 diabetes and CKD, with or without cardiovascular disease, consider the use of an SGLT2-i shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 RA shown to reduce CKD progression.

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment.
CKD Considerations

• For SGLT2-i, adequate eGFR differs between countries and compounds
• SGLT2-i are registered as glucose-lowering agents to be started if eGFR>45-60 ml/min/1.73m$^2$ and stopped at eGFR 45-60, as glucose-lowering effect declines with eGFR
• SGLT2-i CVOTs included patients with eGFR>30, and there were no excess adverse events in subjects with eGFR<60
• For GLP-1 RA, GI side effects increase with declining renal function
• GLP-1 RA are not recommended in end stage renal disease due to limited experience

Conclusions

An important early step in this new approach: consider the presence or absence of ASCVD, CKD and heart failure.

In patients with ASCVD, some GLP-1 RA and SGLT2-i are recommended in these patients.
Conclusions

Hospitalization for heart failure

- reduced consistently with SGLT2-i in two trials but was a secondary outcome
- reduced in a third trial as a co-primary end point

For patients with type 2 diabetes and CKD, with or without cardiovascular disease, consider the use of an SGLT2-i shown to reduce CKD progression or, if contraindicated or not preferred, a GLP-1 RA shown to reduce CKD progression

- Studies of HF or CKD as primary outcome are ongoing with SGLT2-i

Summary

Consider the presence or absence of ASCVD, CKD and HF

Start with metformin if tolerated, then:

- In patients with ASCVD a GLP-1 RA or SGLT2-i is recommended
- In patients with ASCVD and HF SGLT2-i is recommended
- In patients with CKD, with or without ASCVD consider an SGLT2-i

Agents with proven benefit are preferred

ASCVD, CKD and HF affects choice of additional glucose lowering medication
**Mark**

**Age:** 62  
**Occupation:** Sales manager  
**Diabetes Hx:** 10 years, mild neuropathy symptoms, normal dilated eye exam 6 months ago  
**Cardiovascular Hx:** M.I. 3 years ago, s/p CABG, EF 43%  
**Current Diabetes Meds:** metformin ER 1000 mg BID, glimepiride 4 mg once daily  
**Cardiovascular Meds:** statin, ARB, beta blocker, diuretic, ASA  
**A1C:** 7.9%, microalbumin/creatinine ratio 156 μg/mg, eGFR 52 ml/min/1.73m²  
**BG pattern:** fasting average 132 mg/dL, post-meal average 200s mg/dL, hypoglycemia when playing golf  
**Patient/Provider Goals:** avoid further complications, stabilize renal dysfunction, reduce post-meal BGs, dosing simplicity, play golf without hypoglycemia

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**Jerry**

**Age:** 51  
**Occupation:** delivery man  
**Diabetes Hx:** 8 years, microalbumin/creatinine ratio not detected, NPR, active, eats out every day  
**Cardiovascular Hx:** CVA last year (slurred speech, left-sided weakness) w/ full recovery, stopped smoking  
**Current Diabetes Meds:** metformin 500 mg ER 3 tabs per day, pioglitazone 30 mg daily  
**Cardiovascular Meds:** blood pressure, statin, ASA  
**A1C:** 9.5%, anti-GAD negative, eGFR >60 ml/min/1.73m²  
**BG pattern:** fasting average 135 mg/dL, post-meal average 221 mg/dL, no hypoglycemia  
**Patient/Provider Goals:** avoid complications, support healthy eating
The Full Range Of Therapeutic Options—Lifestyle Management, Medication and Obesity Management

Outline

The Foundation of Hyperglycemic Management

Lifestyle
• Medical Nutrition Therapy
• Physical activity
Medications
Metabolic Surgery
For Details on Each Medication Please See . . .

### New Since 2014

**Metformin**
- US and EU Labels were revised in 2016 for use when eGFR is reduced

**Insulins**
- Degludec (long acting) approved in the US (approved earlier in EU)
- Fast-acting insulin aspart approved in US and EU
- Biosimilars have become available for glargine and lispro
- Concentrated forms of several have become available

**Inhaled insulin (US)**
New Since 2014

SGLT2 Inhibitors
• Ertugliflozin approved in US and EU
• Combination products approved (with metformin or DPP4 inhibitors)
• CVOTs with empagliflozin, canagliflozin (and dapagliflozin) complete with broad benefits on cardiorenal outcomes

GLP-1 Receptor Agonists
• Two agents were approved: lixisenatide (in US 2016, EU 2013), semaglutide
• Combination products approved (with long-acting insulins)
• CVOTs with liraglutide, semaglutide and exenatide extended-release complete with cardiovascular benefits
• New safety data is reassuring regarding pancreatitis and pancreatic cancer

Outline

Lifestyle
• Medical Nutrition Therapy
• Physical activity

Medications

Metabolic Surgery
Summary

Lifestyle is the foundation*
  • Highly effective in motivated, adherent patients

Medications
  • Lots of choices
  • We hope to make it easier to navigate them
  • Safety, efficacy, cost and convenience

Metabolic surgery*
  • Consider it as very effective salvage therapy

*The only choices that can lead to disease remission

Putting It All Together: Strategies for Implementation
Glucose-Lowering Medication in Type 2 diabetes: overall approach

**Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)**

**Consensus Recommendation:**

**Metformin** is the preferred initial glucose lowering medication for most people with T2D.

This recommendation is based on the efficacy, safety, tolerability, and extensive clinical experience with this medication. Results from UKPDS showed benefits of initial treatment with metformin in clinical outcomes related to diabetes, with less hypoglycemia and weight gain than with insulin or sulfonylureas (UKPDS 34).
Consensus Recommendation:
The stepwise addition of glucose lowering medication is generally preferred to initial combination therapy.

While there is some support for initial combination therapy due to the greater initial reduction of A1C than metformin alone, there is little evidence that this approach is superior to sequential addition of medications for maintaining glycemic control, or slowing the progression of diabetes.

Since the absolute efficacy of most oral medications rarely exceeds 1% reduction in A1C, initial combination therapy should be considered in patients presenting with A1C levels more than 1.5% above their target. Fixed-dose formulations can improve medication-taking behavior when combination therapy is used and may achieve glycemic targets more rapidly.
Glucose-Lowering Medication in Type 2 Diabetes: Overall Approach

**Consensus Recommendation:**
The choice of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established **ASCVD**, other co-morbidities such as HF or CKD, and risk for specific adverse medication effects, particularly **hypoglycemia** and **weight gain**, as well as safety, tolerability, and **cost**.

**Consensus Recommendation:**
Intensification of treatment **beyond** dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on co-morbidities, as well as the burden of treatment and cost.
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those without established ASCVD or CKD

Use principles in Figure 1

Implement strategies for maximising weight loss

First-line therapy is metformin

If HbA₁c ≥ 77 mmol/mol (13.3%) above individualised HbA₁c target consider early combination therapy

If HbA₁c above target

GLP-1 RA with good efficacy for weight loss

If HbA₁c above target

SGLT2i and DPP-4i adequate

GLP-1 RA with good efficacy for weight loss

If HbA₁c above target

If triple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated use regimen with lowest risk of weight gain

PREFERABLY

DPP-4i (if not on GLP-1 RA) based on weight neutrality

If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA cautious addition of:

• SU
• TZD
• Basal insulin

Non-surgical energy restriction for weight loss

Weight loss of 15kg can lead to remission of T2DM in patient

6 years. Duration consider evidence-based weight loss programmes

Consider medication for weight loss

Consider metabolic surgery

General lifestyle advice

• Medical nutritional therapy

• Dietary patterns

• Physical activity

American Diabetes Association.

CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

In those without established ASCVD or CKD

Use principles in Figure 1

Consider additional DESMES to support weight loss/maintenance and evidence of hypoglycaemia

First-line therapy is metformin

If HbA₁c ≥ 77 mmol/mol (13.3%) above individualised HbA₁c target consider early combination therapy

If HbA₁c above target

SU

If HbA₁c above target

TZD

If HbA₁c above target

SU

1. Choose second-generation SU to minimise risk of hypoglycaemia

2. Consider country- and region-specific cost of drugs. In some countries, TZD relatively more expensive and DPP-4i relatively cheaper

3. Low-dose TZDs are better tolerated

American Diabetes Association.

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**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 hyperglycaemia, insulin is recommended.

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**Age:** 77  
**Occupation:** retired teacher  
**Diabetes Hx:** 12 years, no retinopathy, no nephropathy, no neuropathy sx, SU caused hypoglycemia, SGLT2-i yeast infections, pioglitazone edema  
**Cardiovascular History:** none  
**Current Diabetes Meds:** metformin 500mg BID, pioglitazone 30 mg daily  
**A1C:** 8.3%  
**Cardiovascular Meds:** none  
**BG pattern:** fasting average 145 mg/dL, post-meal average 200 mg/dL, infrequent hypoglycemia  
**Patient/Provider Goals:** healthy aging
**Consensus Recommendation:** Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.
Glucose-lowering Medication in Type 2 Diabetes: Overall Approach

**Consensus Recommendation:** The choice of medication added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD, other co-morbidities such as HF or CKD, and risk for specific adverse medication effects, particularly hypoglycemia and weight gain, as well as safety, tolerability, and cost.

### Figure 2

**Glucose-lowering Medication in Type 2 Diabetes: Overall Approach**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Action</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c above target</td>
<td>Add SU*</td>
<td>Consider later generation SU with lowest acquisition cost or consider DPP-4i or SGLT2i with lowest acquisition cost, if not applicable or not desired.</td>
</tr>
<tr>
<td><strong>COST IS A MAJOR ISSUE</strong>&lt;sup&gt;7,8&lt;/sup&gt;</td>
<td>If HbA1c above target</td>
<td></td>
</tr>
<tr>
<td>Add SU*</td>
<td>If HbA1c above target</td>
<td></td>
</tr>
<tr>
<td>TZD&lt;sup&gt;10&lt;/sup&gt;</td>
<td>If HbA1c above target</td>
<td></td>
</tr>
<tr>
<td>SGLT2i OR DPP-4i OR GLP-1 RA</td>
<td>If HbA1c above target</td>
<td></td>
</tr>
</tbody>
</table>

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*SU*: Sulfonylurea

*TZD*: Thiazolidinedione

*SGLT2i*: Sodium-glucose co-transporter 2 inhibitors

*GLP-1 RA*: GLP-1 receptor agonists

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<sup>7</sup> Consider SU* OR TZD OR SGLT2i OR GLP-1 RA based on patient lifestyle and individual benefit-risk profile.

<sup>8</sup> Consider DPP-4i OR SGLT2i OR GLP-1 RA based on patient lifestyle and individual benefit-risk profile.

<sup>10</sup> Consider DPP-4i OR SGLT2i OR GLP-1 RA based on patient lifestyle and individual benefit-risk profile.

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*Note: DPP-4i can be considered as initial therapy in patients with T2D without established ASCVD who do not require additional medication.
Age: 57  
Occupation: CEO of local non-for-profit  
Diabetes Hx: 6 years, no cx; struggles with weight, eating out, daily schedule  
Current Meds: metformin, saxagliptin, insulin detemir 36 units  
A1C: 8.1%, anti-GAD negative, eGFR >60 ml/min/1.73m  
BG pattern: fasting average 142 mg/dL, post-meal average 207 mg/dL, no hypoglycemia  
Patient/Provider Goals: avoid complications, facilitate weight loss, dosing simplicity

## Overall Summary

- The management of hyperglycemia in type 2 diabetes has become complex with the number of glucose-lowering medications now available.
- Patient-centered decision-making and support and consistent efforts at improving diet and exercise remain the foundation of all glycemic management.
- Initial use of metformin, followed by addition of glucose-lowering medications based on patient co-morbidities and concerns is recommended as we await answers to the many questions that remain.
The position statement is available

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dci18-0033

Care.diabetesjournals.org

Thank you