How to Use the American Diabetes Association’s Type 2 Diabetes 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
- Risk factors for hypoglycemia
- Medical 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
- Presence of 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
Glucose-Lowering Medication in Type 2 diabetes: overall approach

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

**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.

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

**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.

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Case Study #1

- **Patient:** Mr. F is a 57 year old Caucasian male, executive of an oil and gas company.
- **Diabetes Hx:** 6 years, MI 1 year ago with stents but no other complications.
- **Other Comorbidities:** BMI 30, hypertension, hyperlipidemia, gout.
- **Diabetes Meds:** metformin, saxagliptin.
- **Labs:** A1C 8.1%, anti-GAD negative, eGFR >60 ml/min/1.73m².
- **BG pattern:** fasting average 142 mg/dL, post-meal average 207 mg/dL, no hypoglycemia.
- **Patient/Provider Goals:** prevent complications, weight loss, dosing simplicity.
- **Patient Challenges:** Busy schedule with work and frequent travel, eats out a lot, no consistent exercise schedule.
Case Study #2

- **Patient:** Mrs. L is a 69 year old Hispanic female and caretaker for large family
- **Diabetes Hx:** 18 years, no retinopathy, + nephropathy with CKD3, +neuropathy, CHF with EF 40%. Med hx: SU causes hypoglycemia, SGLT2-i yeast infections, pioglitazone edema
- **Comorbidities:** BMI 34, Hypertension, Hyperlipidemia, OA both knees
- **Diabetes Meds:** metformin 500mg BID, insulin detemir 40U
- **Labs:** A1C 8.3%, eGFR 40 ml/min/1.73m²
- **BG pattern:** fasting average 145 mg/dL, post-meal average 200 mg/dL, infrequent hypoglycemia
- **Patient/Provider Goals:** prevent complications, weight loss
- **Patient Challenges:** Cultural diet high in carbs, limited in exercise by knee pain, busy family life with irregular meals

Case Study #3

- **Patient:** Mr. K is a 51 year old AA male who is a delivery man
- **Comorbidities:** BMI 29, hypertension, hyperlipidemia
- **Diabetes Hx:** 8 years, microalbumin/creatinine ratio not detected, NPR, CVA last year w/ full recovery, stopped smoking
- **Diabetes Meds:** metformin 500 mg ER 3 tabs per day, pioglitazone 30 mg daily
- **Meds:** blood pressure, statin, ASA
- **Labs:** A1C 9.5%, anti-GAD negative, eGFR >60 ml/min/1.73m²
- **BG pattern:** fasting average 145 mg/dL, post-meal average 221 mg/dL, no hypoglycemia
- **Patient/Provider Goals:** avoid further complications, support healthy eating
- **Patient Challenges:** Costs of medications, depression after recent divorce
Recommended Process for Glucose Lowering Medication Selection: Where Does New Evidence From Cardiovascular Outcome Trials Fit In?
Foundational therapy is metformin and comprehensive lifestyle management (including weight management and physical activity)

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
- Dulaglutide (soon to be published)

**SGLT2-i with proven cardiovascular benefit**
- Empagliflozin
- Canagliflozin
- Dapagliflozin

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.
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

Majority of patients did not have clinical heart failure at baseline
Recommendation:

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

Several of these medications have demonstrated renal benefit and cardiovascular benefit and should be considered as part of treatment.
CHOOSING GLUCOSE-LOWERING MEDICATION IF COMPELLING NEED TO MINIMISE WEIGHT GAIN OR PROMOTE WEIGHT LOSS

In those without established ASCVD or CKD

First-line therapy is metformin

If HbA1c ≥ 11 mmol/mol (≥ 65%) above individualised HbA1c target consider early combination therapy

- GLP-1 RA with good efficacy for weight loss
- SGLT2i if DPP4i adequate

If HbA1c above target

- GLP-1 RA with good efficacy for weight loss
- SGLT2i if DPP4i adequate

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

Implement strategies for maximising weight loss

- General lifestyle advice
- Medical nutritional therapy
- Exercise patterns
- Physical activity

- Consider medication for weight loss
- 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 metabolic surgery

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CHOOSING GLUCOSE-LOWERING MEDICATION IF COST IS A MAJOR ISSUE

In those without established ASCVD or CKD

First-line therapy is metformin

If HbA1c ≥ 11 mmol/mol (≥ 65%) above individualised HbA1c target consider early combination therapy

- SU
- TZD

If HbA1c above target

- TZD
- SU

If HbA1c above target

- Insulin therapy: Basal insulin with lowest acquisition cost
- Consider DPP-4i or SGLT2i with lowest acquisition cost

Use principles in Figure 1

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INTENSIFYING TO INJECTABLE THERAPIES

CONSIDERING ORAL THERAPY IN COMBINATION WITH INJECTABLE THERAPIES

METFORMIN
- Continue treatment with metformin

SGLT2i
- If on SGLT2i continue treatment
- Consider adding SGLT2i if:
  - Established CVD
  - If Hba1c above target or as weight reduction aid

TZD1
- Stop TZD when commencing insulin OR reduce dose

Beware:
- DKA (lactic acidosis)
- 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
- Consider stopping
- SU if prandial insulin initiated or on a premix regimen

DPP-4i
- Stop DPP-4i if GLP-1 RA initiated

1. Combinations in some countries, consider lower dose. This combination has a high risk of fluid retention and weight gain
Recommendations

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

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

The medication regimen should be reevaluated at regular intervals (every 3–6 months) and adjusted as needed to incorporate new patient factors. E

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

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.

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.

- 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 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
Thank you!