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

Stephen Brunton, MD, FAAFP
Executive Director
Primary Care Metabolic Group
Palm Springs, CA

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

Disclosures of Interest

Advisory Board: Novo Nordisk, Janssen, Sanofi, AstraZeneca, Lilly, Boehringer Ingelheim
Speakers Bureau: Novo Nordisk, Janssen,
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?

Implications of ACCORD, ADVANCE, and VADT
Affirmed need for treatment of all vascular risk factors—not just hyperglycemia

Diet! HTN! HDL! CAD! Tobacco cessation! Weight loss! Health maintenance!

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

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

SGLT2-i with proven cardiovascular benefit
- Empagliflozin > canagliflozin

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.

**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/1.73m² 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 was reduced consistently with SGLT2-i in two trials but was a secondary outcome.

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.

Outline

The Full Range Of Therapeutic Options—Lifestyle Management, Medication and Obesity Management.

- The Foundation of Hyperglycemic Management
  - Lifestyle
  - Medical Nutrition Therapy
  - Physical activity
  - Medications
  - Metabolic Surgery
New Since 2014

SGT2 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 cardio renal 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 lixisenatide, 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

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)
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

Putting It All Together: Strategies for Implementation

Glucose-Lowering Medication in Type 2 diabetes: overall approach

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 a 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.

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

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.
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.
1. Consider choice of GLP-1 considering patient preference: A1C lowering, weight-lowering effect or frequency of injection. If CVD, consider GLP-1 RA with proven CVD benefit.

2. Consider insulin as preferred to GLP-1 RA if symptoms of hyperglycemia are present or evidence of ongoing catabolism (polyuria, polydipsia or weight loss)
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.

*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.
YOUR LIFESTYLE IS DESTROYING YOU.

THE BEST WAY TO ACHIEVE GOOD HEALTH IS TO TAKE CARE OF YOURSELF.

YOU SHOULD CHANGE YOUR EATING HABITS, AND STOP SMOKING AND DRINKING.

START AN EXERCISE PROGRAM. GET PLENTY OF REST. LEARN HOW TO HANDLE STRESS.
The position statement is available

Diabetes Care 2018;41:1-33 https://doi.org/10.2337/dc18-0033

Care.diabetesjournals.org

Thank you