# Evolution of type 2 diabetes management algorithms

## Where are we now?

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*The management of type 2 diabetes is rapidly changing to reflect increasing numbers of therapeutic agents and the clinical trials supporting their use. Management algorithms have evolved to provide up-to-date, best practice care, with particular focus on individualisation of therapy.*

**Key points**

- **Significant development has occurred in the management of type 2 diabetes over the past two decades.**
- **There is increasing emphasis on individualisation of both glycaemic targets and choice of therapy.**
- **Glycaemic targets take into account patient age, disease duration, comorbidities and patient expectations.**
- **With the expansion of available glucose-lowering agents, it is becoming increasingly important to consider patient comorbidities as well as the benefit and adverse effect profiles of pharmacotherapies.**
- **These changes have been reflected in the most recent management algorithms, most notably the ADA/EASD consensus statement of 2018.**
- **The most recent guidelines have an emphasis on considering patient comorbidities when choosing diabetes medications.**

ENDOCRINOLOGY TODAY 2019; 8(4): 26-31

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Diabetes organisations around the world have published a multitude of guidelines for many years. Early treatment algorithms were based on the evidence of a limited number of trials, but the recent expansion of cardiovascular outcome trials assessing new pharmacotherapies has led to rapid and major updates. A challenge for healthcare providers today is uncertainty in the face of a multitude of different guidelines and choice of therapy, but a common and increasingly emphasised theme across all guidelines is the importance of individualised management.

### Evolution of glycaemic targets

Achieving glycaemic control has long been viewed as the cornerstone of diabetes management. Early recommendations were formed on the basis of landmark outcome studies – the 1993 Diabetes Control and Complications Trial (DCCT)[1] and the 1998 UK Prospective Diabetes Study (UKPDS).[2] These studies showed significant reduction in microvascular complications, at the expense of increased risk of hypoglycaemia and weight gain, with intensive glycaemic control to a mean glycated haemoglobin ($HbA_{1c}$) of 7% for type 1 diabetes and type 2 diabetes, respectively. Based on these findings, international recommendations of the 1990s and early 2000s, including the 2002 American Diabetes Association (ADA) guidelines, proposed a general $HbA_{1c}$ target of less than 7%.[3]

Despite the clear benefit on microvascular complications, the effect of intensive glycaemic control on cardiovascular risk remained a subject of debate. Long-term follow-up studies of the DCCT (Epidemiology of Diabetes Interventions and Complications, EDIC) and UKPDS cohorts became available, highlighting the possible macrovascular benefit of early and sustained glycaemic control. However, new randomised trials were needed to test the possible benefits of near-normalisation of $HbA_{1c}$, leading to three further landmark studies in 2008 – the ADVANCE, VADT and ACCORD trials.[4-6] The targets of intensive glycaemic control in these studies were notable for aiming for $HbA_{1c}$ levels as low as less than 6.0%,[6] well below existing recommendations in patient populations with longer duration of disease and with higher cardiovascular risk factors than UKPDS. The result of ACCORD was of great concern, with

early termination of the trial due to increased mortality seen with the intensive control group and challenging the increasing practice at the time towards more stringent control. Subsequent exploratory analyses revealed complex relationships with hypoglycaemia, duration of diabetes, baseline glycaemic control, frailty and pre-existing cardiovascular disease. These studies prompted the ADA and American Heart Association (AHA) to propose a joint statement in 2009, emphasising the need for individualisation.[7] In particular, it stressed that targeting $HbA_{1c}$ less than 7% has well-established microvascular benefit and may have macrovascular benefit if achieved soon after diagnosis, whereas less intensive glycaemic targets may be appropriate in other settings but without detailing these modified targets.

The Australian Diabetes Society (ADS) has recommended targets for specific subpopulations since 2009 (Table).[8] The ADS position statement agrees with the ADA's general $HbA_{1c}$ target of <7%, and suggests intensive targets for short duration of disease (≤6% for patients with diabetes controlled by lifestyle modification or metformin monotherapy, ≤6.5% for patients taking other oral therapies, and ≤7% for patients taking insulin) and recommends less stringent control ($HbA_{1c}$ ≤8%) in patients with high risk of hypoglycaemia.[8] It was not until 2012 that international guidelines began providing similarly detailed guidance on individualised $HbA_{1c}$ targets. The position statement of the ADA and European Association for the Study of Diabetes (EASD) outlined an approach to glycaemic targets, balancing the risks of hypoglycaemia, disease duration, life expectancy, comorbidities, pre-existing complications and patient attitude.[9] It proposed $HbA_{1c}$ targets that were generally consistent with the previously published ADS guidelines. The most recent ADA/EASD consensus statement, published in 2019, remains aligned with these recommendations.[10] The Royal Australian College of General Practitioners guidelines similarly note a general $HbA_{1c}$ target of less than 7% and recognise that there is not a single target suitable for all patients.[11]

**Table. Australian Diabetes Society (ADS) $HbA_{1c}$ targets for adults with type 2 diabetes**[8]

| | |
|---|---|
| **General target** | |
| Patients with type 2 diabetes where no other specific clinical details are known | ≤7.0% |
| **Targets for specific clinical situations** | |
| Diabetes of short duration and no clinical cardiovascular disease:<br>– requiring lifestyle modification ± metformin<br>– requiring any antidiabetic agents other than metformin or insulin<br>– requiring insulin | <br>≤6.0%<br>≤6.5%<br>≤7.0% |
| Pregnancy or planning pregnancy | ≤6.0% |
| Diabetes of longer duration or clinical cardiovascular disease (any therapy) | ≤7.0% |
| Recurrent severe hypoglycaemia or hypoglycaemia unawareness (any therapy) | ≤8.0% |
| Patients with major comorbidities likely to limit life expectancy (any therapy) | Symptomatic therapy of hyperglycaemia |

Adapted and summarised from: Cheung NW, Conn JJ, d'Emden MC, et al. Position statement of the Australian Diabetes Society: individualisation of glycated haemoglobin targets for adults with diabetes mellitus. *Med J Aust* 2009; 191: 339-344.

## Evolution of pharmacotherapy

Choice of pharmacotherapy was limited during the first era of guidelines of the 1990s and 2000s. For example, ADA guidelines during this period lacked a dedicated section on glucose-lowering pharmacotherapy altogether, with management recommendations focusing on lifestyle management and the screening and management of microvascular and macrovascular complications.[3,12] The 2005 International Diabetes Federation (IDF) guidelines proposed metformin as first-line therapy, sulfonylureas as second-line add-on to metformin, and thiazolidinediones as potential add-on therapy to metformin with or without sulfonylureas.[13] The 2006 and 2009 ADA/EASD consensus algorithms reinforced the role of metformin as first-line therapy, with early intensification of therapy.[14,15] Options were limited to sulfonylureas, glinides, alpha-glucosidase inhibitors, thiazolidinediones, exenatide and insulin, with dipeptidyl peptidase-4 (DPP-4) inhibitors starting to become available after 2006. Although describing the need for individualisation based on the efficacy and adverse effect profile of each class, the algorithm promoted metformin with the addition of sulfonylurea or insulin therapy as the consensus choice in most cases, with a third oral agent being considered less preferable for glycaemic control and cost-effectiveness.[14,15]

In contrast, the 2012 ADA/EASD consensus algorithm proposed a more flexible approach, with each of the available drug classes being considered a potentially equally suitable choice to add to metformin, and listing the available options and their benefit and adverse effect profiles to help guide therapy, including risk of hypoglycaemia, weight gain, gastrointestinal side effects and fluid retention.[9] The 2013 ADA guidelines expanded on this to note the importance of patient-specific comorbidities in choice of pharmacotherapy, such as using agents with a favourable metabolic profile if there is comorbid fatty liver disease or avoiding thiazolidinediones if fracture risk factors are present.[16]

By the time of the 2014 and 2016 ADS position statements,[17,18] 2016 RACGP guidelines[11] and the 2015 ADA/EASD consensus update,[19] sodium-glucose cotransporter-2 (SGLT-2) inhibitors had become available. These

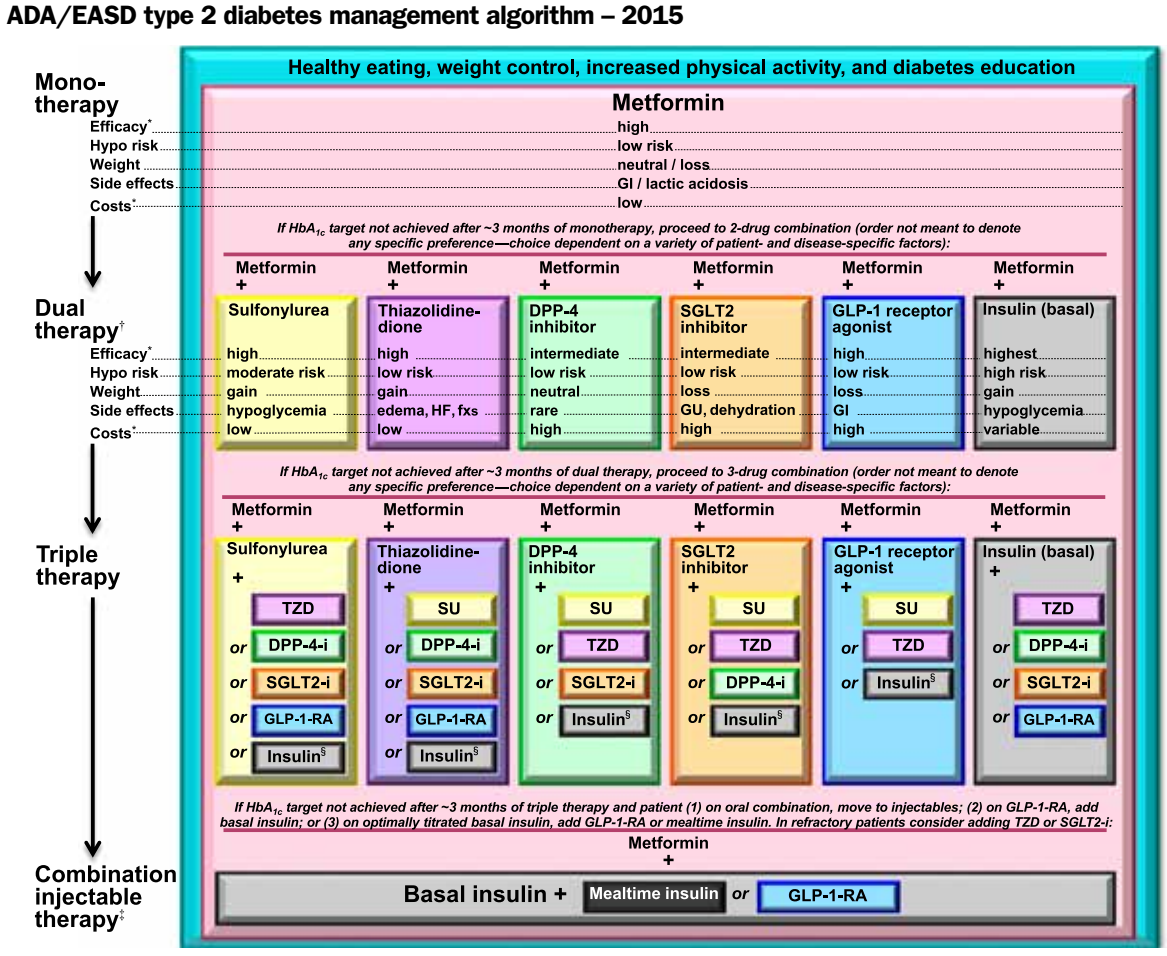


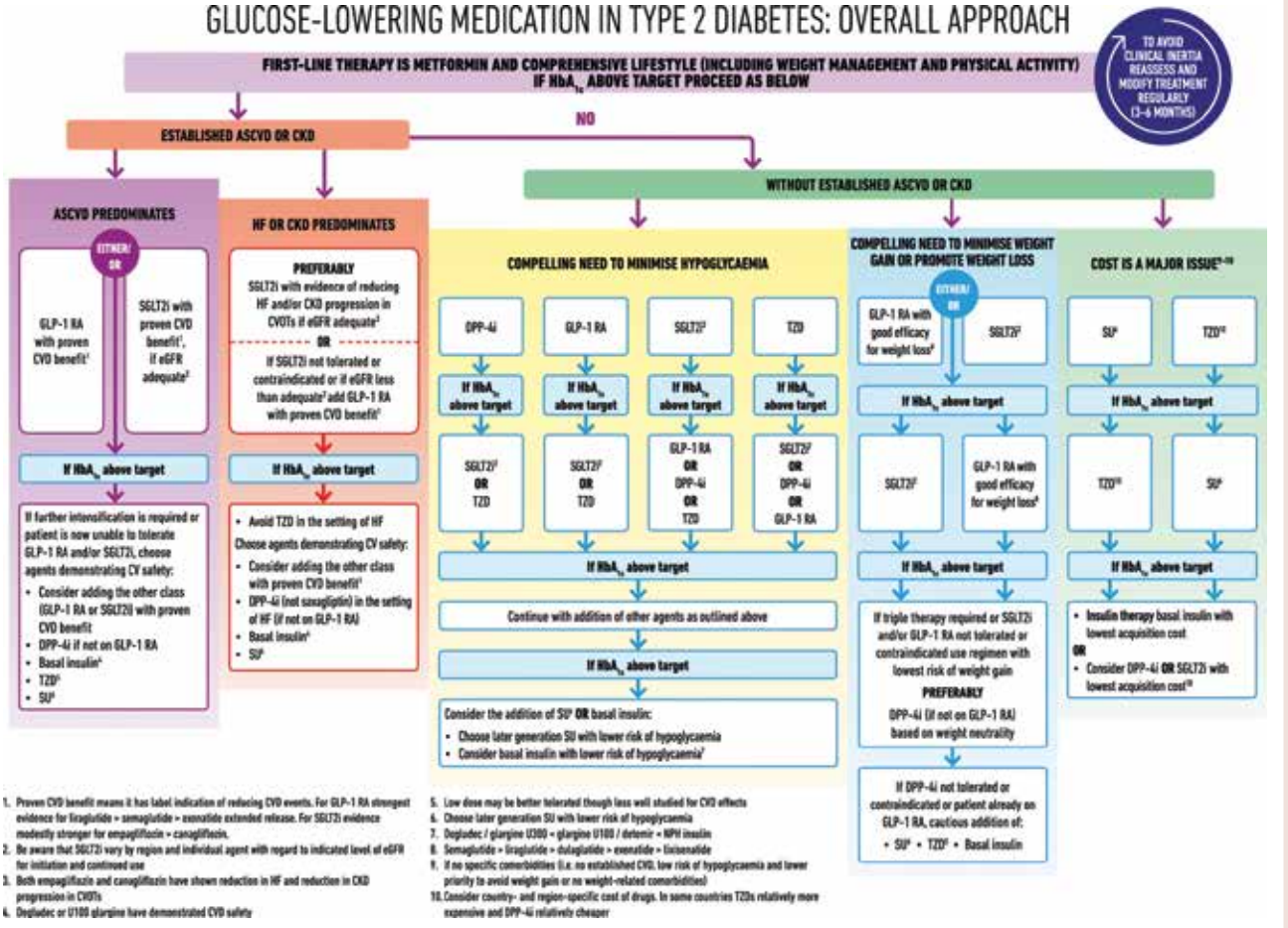

**Figure 1. Management algorithms for type 2 diabetes from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) in 2015 (left) and 2018 (right).[19,27] The differences in layout and emphasis illustrate the shift towards considering patient factors (most notably comorbidities).**

guidelines were closely aligned and continued to describe each of the individual classes as potential options without specifying patient characteristics or disease processes that would favour a particular second agent. In fact, the 2016 ADS guidelines – the most current Australian update – continue to promote sulfonylureas as the recommended second-line therapy.[18] This has led to the criticism that most major guidelines from this era could be misinterpreted as merely listing options for second- and third-line therapy rather than guiding clinicians through a patient-centric treatment algorithm.

It had, however, also become mandatory for cardiovascular safety to be established for pharmacotherapies through cardiovascular outcome trials. While the first group of these trials indeed demonstrated the safety of all new diabetes medications introduced after rosiglitazone, more recent trials showed evidence of cardio/renal protective benefits for some SGLT-2 inhibitors and GLP-1 analogues, independent of the effect on glucose lowering. The EMPA-REG OUTCOME,[20] CANVAS[21] and DECLARE[22] trials confirmed the benefit of empagliflozin, canagliflozin and dapagliflozin, respectively, in terms of reducing 3-point MACE (a composite endpoint of cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) statistically significantly in the EMPA-REG, OUTCOME and CANVAS trials and with a very similar trend in the DECLARE study. These SGLT-2 inhibitor trials also demonstrated positive outcomes in terms of lower rates of hospitalisation for heart failure and progression of nephropathy. LEADER, SUSTAIN, HARMONY and REWIND established thecardiovascular benefit of liraglutide, semaglutide, albiglutide and dulaglutide.[23-26]

The latest 2018 ADA/EASD consensus guidelines mark a significant departure from previous updates, reflecting the proliferation of cardiovascular outcome trials and

**ADA/EASD type 2 diabetes management algorithm – 2018**






subsequent greater importance of each individual patient's disease process in choice of therapy.[27] In particular, these guidelines differentiate patients with established atherosclerotic cardiovascular disease, heart failure or chronic kidney disease, who are expected to derive significant benefit from GLP-1 agonist or SGLT-2 inhibitor therapy.[27] Even in the absence of such complications, this new guideline leads clinicians through the preferred choices of medication when avoiding hypoglycaemia or weight gain or if undue cost is the primary issue for a patient. The evolution towards the focus on comorbidities can be seen in the management algorithms (2015 and 2018) in Figure 1.[19,27] The current ADS management algorithm is shown in Figure 2.

## Other aspects of type 2 diabetes management

All guidelines, early and most recent, stress the centrality of lifestyle management in conjunction with pharmacotherapy for management of type 2 diabetes. As with pharmacotherapy, there has been increasing emphasis on individualisation of medical nutrition therapy, recognising that no single dietary pattern is superior and that it is important to select a diet that is sustainable for the individual patient. Weight management has become increasingly emphasised, with energy restriction weight management programs, pharmacotherapies and metabolic surgery having a more prominent role in more recent guidelines.[10]

The ADA, RACGP and IDF guidelines have consistently focused on the holistic nature of diabetes management, promoting multifactorial intervention to screen for and manage microvascular and macrovascular complications and cardiovascular risk factors.[10-13] Given the new tools of SGLT-2 inhibitors, GLP-1 agonists and weight management programs, identifying risk factors will have increasing impact.

# AUSTRALIAN BLOOD GLUCOSE TREATMENT ALGORITHM FOR TYPE 2 DIABETES

ads Australian Diabetes Society

**All patients should receive education regarding lifestyle measures: healthy diet, physical activity and weight control**
**Determine the individual's $HbA_{1c}$ target – this will commonly be ≤ 53 mmol/mol (7.0%).**
**If not at target, or if an $HbA_{1c}$ reduction of ≥ 0.5% is not achieved after 3 months, move down the algorithm.**

## First line: Metformin is the usual first-line therapy unless contraindicated or not tolerated

Metformin | SU | Insulin | Acarbose | DPP-4 inhibitor | SGLT2 inhibitor | TZD

**If $HbA_{1c}$ target not achieved in 3 months:**
- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

## Second line: If metformin was not used first line, add it now, if not contraindicated.
## Choice of second line agent to add to metformin should be guided by clinical factors/considerations, contraindications, side effect profile and cost.

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

**If $HbA_{1c}$ target not achieved in 3 months:**
- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

## Third line: Consider triple oral therapy or addition of GLP-1RA or insulin

DPP-4 inhibitor | SGLT2 inhibitor | SU | GLP-1RA | Insulin* | Acarbose | TZD

**If $HbA_{1c}$ target not achieved in 3 months:**
- check and review current therapies, stop any that fail to improve glycaemic control
- check patient understanding and self-management
- review use of therapies
- exclude other comorbidities/therapies impacting on glycaemic control
- reinforce lifestyle measures

**THEN**

| If on triple oral therapy | | If on GLP-1RA | | If on basal insulin* |
|---|---|---|---|---|
| Switch ≥ 1 oral agent to GLP-1RA or insulin* or another oral agent† | OR | Change to basal or premixed/ coformulated insulin* | Add basal or premixed/ coformulated insulin* | OR Add SGLT2 inhibitor or GLP-1RA or basal bolus or basal plus insulin or change to coformulated insulin |

PBS = Pharmaceutical Benefits Scheme, SU=sulfonylurea, TZD= thiazolidinedione, DPP-4 = dipeptidyl peptidase-4, GLP-1RA= glucagon like peptide 1 receptor agonist, SGLT2 = sodium glucose transporter.
**Dark blue boxes** indicate usual therapeutic strategy (order is not meant to denote any specific preference); usual refers to commonly available, evidence based, cost effective therapy.
**White boxes** indicate alternate approaches (order is not meant to denote any specific preference).
**Red outlines** indicate the classes of glucose lowering agent that include PBS subsidised products.
* Unless metformin is contraindicated, or not tolerated, it is often therapeutically useful to continue it in combination with insulin.
† Switching an oral agent is likely to have the smallest impact on glycaemia.

diabetes australia

The National Diabetes Services Scheme is an initiative of the Australian Government administered with the assistance of Diabetes Australia.

ndss national diabetes services scheme

**Figure 2. The Australian Diabetes Society management algorithm for type 2 diabetes (November 2018; available online at http://t2d.diabetessociety.com.au).**

## The future of diabetes management guidelines

With many new pharmacotherapies and cardiovascular outcome trials awaiting completion and publication, the evidence base for type 2 diabetes management algorithms will continue to grow and evolve. Even the most recent guidelines will quickly become out of date, highlighting the importance of regular updates incorporating the latest evidence. RACGP and ADS have yet to adopt the ADA and EASD approach of comorbidity-focused management, and this may underpin the next update.[11,18] In addition, the wide range of guidelines and resources available to healthcare providers can be daunting and confusing, especially when aspects of the recommendations do not align. Lastly, there is likely to be a proliferation of guidelines for niche areas in diabetes care – for example, exercise in patients with type 1 diabetes, type 2 diabetes in adolescents and young adults, diabetes in the extreme elderly, and diabetes management during Ramadan.

It may thus be helpful to establish consensus guidelines involving multiple major bodies and consolidating the recommendations in one overarching algorithm. Certain aspects of management (e.g. considering medication cost and accessibility, and the need for localisation of recommendations) may need to be released as a separate position statement by the local organisation. How feasible this is remains to be seen.

## Conclusion

The management of type 2 diabetes is a rapidly changing landscape, with many new trials and therapies on the horizon. The wealth of data from well-conducted cardiovascular outcome studies that have defined the best therapies for patients at various stages of their journey with type 2 diabetes has shifted management to an increasingly individualised, patient-focused process. Although the range of management guidelines available and the speed of development are challenges to the healthcare provider, it is important to appreciate the direction of these changes and to remain up to date with the major developments to management algorithms. The ever-increasing availability of new clinical outcome data creates challenges to learned societies developing up-to-date management guidelines. It is important that clinicians remain keep up with the major changes in these management algorithms and the issues involved in their development. **ET**

### References

A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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## Where are we now?

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