

# ANTIHYPERGLYCAEMICS

## KEY POINTS

Glycosylated haemoglobin levels below 7% (53 mmol/mol) as a result of antihyperglycaemic therapy are associated with increased morbidity and mortality in older people with type 2 diabetes.

In older people with type 2 diabetes, treatment should be individualised, with the aim of minimising the incidence of hypoglycaemia while also preventing symptomatic hyperglycaemia.

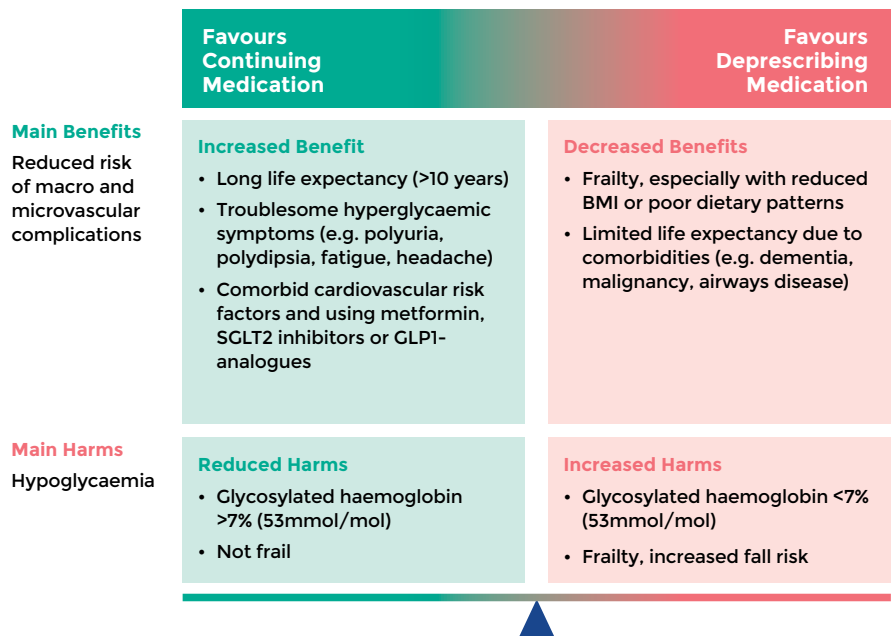
Medications that are more likely to cause hypoglycaemia are best avoided in older patients and greater care is required when using renally cleared medications.

The microvascular benefits gained from 10+ years of tight glucose control persist for many years, regardless of whether the intensity of treatment is subsequently reduced.

## CONTEXT

This guide considers the use of antihyperglycaemics to manage type 2 diabetes in older people.

## BENEFIT VERSUS HARM



## RECOMMENDED DEPRESCRIBING STRATEGY

In older people who are taking antihyperglycaemics and have an HbA1c below 7% (53mmol/mol), reduction of treatment, followed by glycaemic monitoring is often appropriate.

Patients who have or are at high risk of hypoglycaemia (due to therapy or their medical status) should have the intensity of treatment reduced.

People with a life expectancy <10 years due to age or significant comorbidities are unlikely to gain meaningful benefit from intensive glycaemic control and deprescribing should be considered.

An algorithm for the deprescribing of antihyperglycaemics is shown in **Figure 1**.

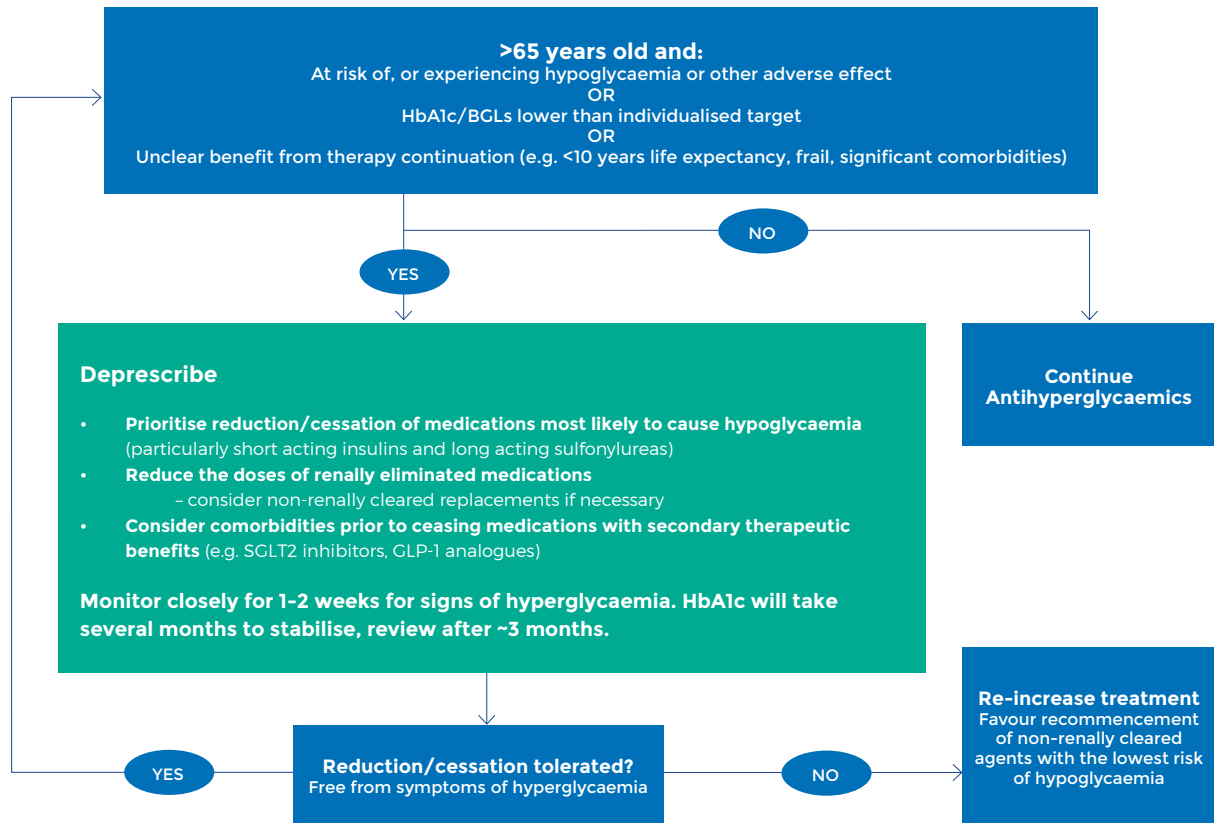


Figure 1: Algorithm for the deprescribing of antihyperglycaemic medications in older people

## BACKGROUND

Type 2 diabetes is a chronic disease characterised by deterioration of glycaemic control as a result of decreased pancreatic beta cell mass and function, on a background of insulin resistance (see **Figure 2**).<sup>1</sup> There are multiple proposed causes for this beta cell dysfunction. Metabolic changes such as consistent hyperglycaemia, obesity, and hyperlipidaemia have been suggested.<sup>2,3</sup> There is also evidence to suggest that this dysfunction may be reversible to a degree and the possibility of inducing ‘remission’ from type 2 diabetes through calorie restriction in the short term and maintained weight loss in the long term is now acknowledged.<sup>4</sup>

Intensive glycaemic control (HbA1c <7% or 53 mmol/mol) was shown in older randomised controlled trials (mainly involving the use of sulfonylureas), to reduce the incidence of microvascular complications (particularly nephropathy and retinopathy).<sup>5,6</sup> The effect of these intensive regimens on macrovascular outcomes was less favourable, however, with no apparent benefit compared with standard treatment over the short term (<6 years) and possibly even an increased risk of overall mortality.<sup>5,7,8</sup> Longer term follow-up of these studies (>10 years) suggests there may be a small, delayed benefit on cardiovascular events and mortality.<sup>9,10</sup>

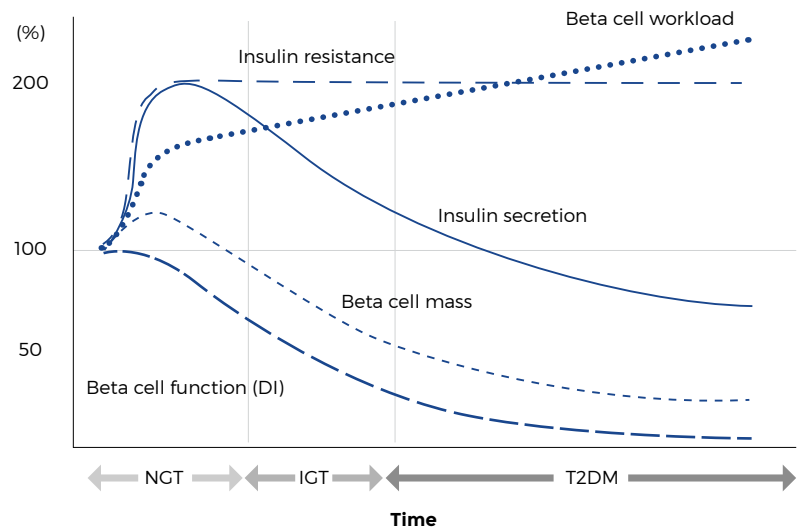


Figure 2: Change in beta cell function and during development of T2DM (Adapted from Ref 1). NGT = Normal Glucose Tolerance; IGT = Impaired Glucose Tolerance; T2DM = Type 2 Diabetes Mellitus

Intensive glycaemic control strategies (particularly with sulfonylureas and insulins) have also been shown to increase the frequency of hypoglycaemia, which is associated with poor outcomes (increased mortality, cardiovascular events, increased falls, and dementia) particularly in older people.<sup>11</sup> In a retrospective study of patients 50 years and older with diabetes, both low and high HbA1c levels were associated with increased mortality (see **Figure 3**).<sup>14</sup>

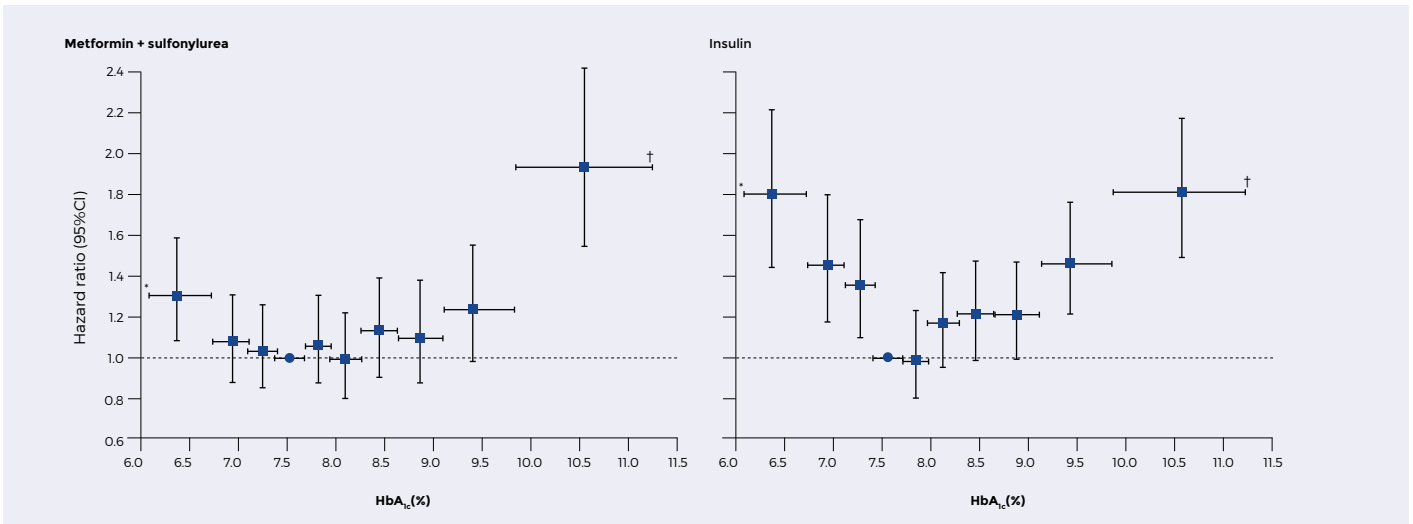


Figure 3: Relationship between HbA1c and mortality for patients taking metformin + sulfonylurea, or insulin (adapted from Ref 11)

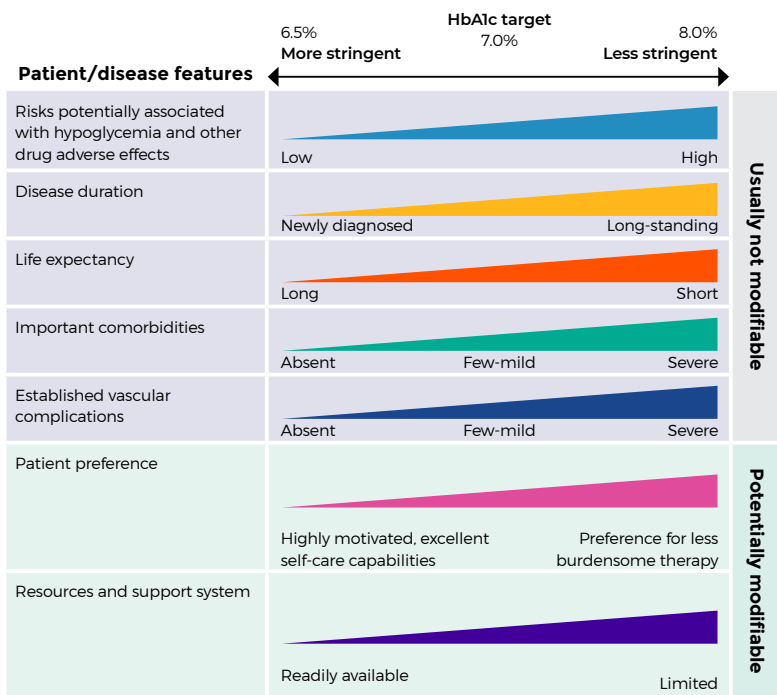


Figure 4: Approach to Individualising HbA1c Targets (adapted from Reference 13)

## TREATMENT TARGETS

Guidelines vary slightly in their recommendations on glycaemic targets. The American Diabetes Association (ADA) recommend several HbA1c targets between  $\leq 6.5\%$  and  $\leq 8\%$  depending on a number of patient characteristics (see **Figure 4**).<sup>13</sup> The American college of Physicians recommends a general target of 7-8% for most people but **avoidance of a specific HbA1c target for individuals with <10 year life expectancy due to advanced age, residence in a nursing home, or chronic conditions**, with treatment instead aimed at minimising symptomatic hyperglycaemia.<sup>14</sup>

With the recent arrival to the market of antihyperglycaemics which may provide independent benefit to cardiovascular and renal outcomes (see below), and the risks associated with targeting tight HbA1c targets in high-risk groups, the use of less intensive regimens with carefully selected medications may provide a more favourable balance of risk to benefit for many older patients.<sup>14</sup>

Medication	HbA1c reduction	Hypoglycaemia risk	Weight change	Main adverse effects	Use in renal dysfunction	Cardiovascular/mortality benefit	Renal benefit
<b>Metformin</b>	Moderate	Low	Neutral	GI upset	Reduce dose, monitor closely 15-45mL/min	Possible	No
<b>Sulfonylureas</b>	Moderate	High	Gain	Hypoglycaemia	Monitor closely	No	No
<b>Pioglitazone</b>	Low/moderate	Low	Gain	Oedema	Unchanged	Unclear	No
<b>DPP4 inhibitors</b>	Low	Low	Neutral	-	Reduce dose, except linagliptin	No	No
<b>SGLT2 inhibitors</b>	Low	Low	Loss	Genital infections	Caution	Yes	Yes
<b>GLP-1 analogues</b>	Moderate	Low	Loss	GI upset	Caution	Yes	Yes
<b>Insulin</b>	High	High	Gain	Hypoglycaemia	Unchanged	No	No

Table 1: Features of Pharmacologic Treatments for Type 2 Diabetes

## ANTIHYPERGLYCAEMIC AGENTS

Australian guidelines for management of type 2 diabetes recommend commencing pharmacologic therapy with metformin. Addition of sulfonylureas has previously been accepted as the next step in therapy, but with the availability of newer, safer oral agents (DPP4 inhibitors, SGLT2 inhibitors, and GLP-1 analogues), a patient centred approach considering comorbidities, side effect profile, and cost is now recommended.<sup>15</sup>

The cardiovascular and renal benefits of the SGLT2 inhibitors and GLP-1 analogues demonstrated in recent trials is worth noting. A recent meta-analysis of these data reported a relative risk reduction (RRR) in atherosclerotic events of 12% and 11% with GLP-1 analogues and SGLT2 inhibitors respectively (almost all of this benefit was observed in patients with established atherosclerotic disease), a RRR of 31% in hospitalisation due to heart failure with SGLT2 inhibitors, and a RRR 18% and 38% in kidney disease progression with GLP-1 analogues and SGLT2 inhibitors respectively. SGLT2 inhibitors were also found to reduce the relative risk of worsening eGFR, end stage renal disease or renal disease associated death by 45%.<sup>16</sup> These cardiovascular and renal effects appear somewhat independent of glycaemic control.

Table 1 shows some of the key features of available treatments for diabetes.

## DIABETES MANAGEMENT IN OLDER PEOPLE

The management of diabetes in older patients, who often have multiple comorbidities, can be complicated. Risks associated with intensive glycaemic control can be significant, and the potential for long term clinical outcome benefits may be less relevant.

The presence, or tendency for hypoglycaemia in particular appears to be a major contributor to the poorer outcomes seen in intensively managed patients. A recent meta-analysis identified several adverse outcomes associated with a history of hypoglycaemia. When analysis was restricted to studies only including patients aged >65 years, risks were even higher (see Table 2).<sup>11</sup>

Presentation of hypoglycaemia differs in older people with neurological and non-specific symptoms rather than autonomic symptoms, more common.<sup>17</sup> This makes identification of hypoglycaemia more challenging in this cohort. It is also likely that asymptomatic hypoglycaemia is an under-recognised issue; incidence of this phenomenon in a recent study of adults utilising continuous glucose monitoring technology was 37%.<sup>18</sup>

Adverse Outcomes Associated With Hypoglycaemia				
Outcome	All study participants		>65 year olds	
	OR	95% CI	OR	95% CI
Cardiovascular death	<b>2.11</b>	1.55 – 2.87		
Mortality	<b>2.02</b>	1.75 – 2.32	<b>2.25</b>	1.78 – 2.83
Macrovascular complications	<b>1.81</b>	1.70 – 1.94	<b>1.88</b>	1.72 – 2.07
Falls	<b>1.78</b>	1.44 – 2.21	<b>1.98</b>	1.80 – 2.19
Microvascular complications	<b>1.77</b>	1.49 – 2.10		
Fractures	<b>1.68</b>	1.37 – 2.07		
Dementia	<b>1.50</b>	1.29 – 1.74		

Table 2: Hypoglycaemia and Adverse Outcomes (adapted from Ref 11)

In order to reduce the risk of hypoglycaemia, avoidance, or careful monitoring, of the use of insulin and/or sulfonylureas is strongly suggested. Although basal/bolus insulin regimens allow for tighter control of glycaemia, simplification of complex insulin regimens in older patients to a single once daily long-acting insulin +/- oral agents can significantly reduce the risk of hypoglycaemia and overall insulin dose, without significant deterioration in glycaemic control.<sup>19</sup>

Reduction in oral intake and change in dietary composition likely contribute to an overall reduction in the need for antihyperglycaemic therapy in older people. It is possible that metabolic changes which occur as part of the aging process also contribute. A recent observational study found 'remission' from type 2 diabetes (HbA1c <6.5% despite no treatment for >1 year) to be more common in individuals >75 years old compared with younger individuals (OR 1.48 [95% CI 1.34 to 1.62] P < 0.001), and also in those who lose a significant amount of body weight (OR 4.45 [95% CI 3.89 to 5.10] P < 0.001 for > 15kg weight loss).<sup>20</sup>

Significant de-escalation of therapy and even complete withdrawal of antihyperglycaemic therapy may be possible in the very old. Small trials demonstrating this concept have been conducted.<sup>21,22</sup> In one trial, a group of nursing home residents (mean age 86.5 years, mean body weight 88kg) had all antihyperglycaemic treatment withdrawn with mean HbA1c increasing by only 0.3% over the subsequent 12 months (6.2% to 6.5%).<sup>21</sup>

The relationship between glycaemic control and mortality is complicated by many factors. Avoidance of hypoglycaemia and significant variability in glycaemic control is likely more important than treatment to target. The choice of antihyperglycaemic agent is also now recognised as more important than in the past, with the SGLT2 inhibitors and GLP-1 analogues providing mortality benefit in certain cohorts irrespective of HbA1c control.

RACGP guidelines have recently been updated and now include a section on managing diabetes in older people and residential aged care facilities. Recommendations include:<sup>15</sup>

- Over-treatment of diabetes is common in older adults and should be avoided
- De-intensification (or simplification) of complex regimens is recommended to reduce the risk of hypoglycaemia in older adults, if achievable within the individualised HbA1c target

### IS THERE A "LEGACY EFFECT" OF GOOD GLYCAEMIC CONTROL?

The United Kingdom Diabetes Prevention Study (UKPDS) compared intensive control with less intensive control of glycaemia in type 2 diabetes for a period of 10 years.<sup>23</sup> They found a reduction in microvascular complications and the results of this study have guided treatment for the last two decades.

A 10 year follow-up of survivors of the study showed interesting results implicating a legacy effect of good glycaemic control. At the completion of the 10 year intensive treatment options (either sulfonylurea/insulin or metformin) patients returned to "usual care" and were monitored for outcomes for a further 10 years.<sup>24</sup> Although the glycosylated haemoglobin levels of patients in the intensive treatment arms rapidly returned to those seen in the usual treatment arms, the rate of microvascular complications in the patient who had previously had intensive treatment remained lower for an average follow-up of 7.7 years. The authors conclude that there is "...a sustained legacy effect of an intensive glucose-control strategy that appears to be longer than previously reported."<sup>24</sup>

The implication of these results is that decreasing the intensity of glycaemic control later in the course of type 2 diabetes is unlikely to worsen microvascular outcomes in the short term.

## FACTORS TO CONSIDER

### IN FAVOUR OF DEPRESCRIBING

Hypoglycaemia is associated with negative outcomes in older adults. Medications which cause hypoglycaemia (especially insulin or sulfonylureas) should be reviewed and de-escalation/deprescribing considered. Changing from short acting insulins to longer acting insulins may help minimise risks associated with treatment.

Low HbA1c levels are associated with poorer outcomes in older people. When HbA1c is <7.0% deprescribing is often appropriate.

People with <10 year life expectancy are unlikely to benefit from an approach that targets a specific HbA1c as microvascular complications usually take > 10 years to develop. There is a legacy effect gained from appropriate treatment early in the course of the disease.

### AGAINST DEPRESCRIBING

In people with > 10 year life expectancy where intensive treatment of diabetes is still likely to have a long term benefit, continuation of treatment (which may include sulfonylureas and/or insulin) is likely to be appropriate.

The cardiovascular and renal benefits of SGLT2 inhibitors and GLP-1 analogues mean they are indicated for reasons beyond glycaemic control in many individuals. These comorbidities (e.g. heart failure with SGLT2 inhibitors) should be considered prior to deprescribing.

In the absence of a specific HbA1c target in older patients, avoidance of symptoms associated with hyperglycaemia (e.g. polyuria, polydipsia, fatigue, headache) is a priority. Continuation of well tolerated antihyperglycaemic therapy is often appropriate for this purpose.

## DISCONTINUATION SYNDROMES

Hyperglycaemia is possible following a decrease or discontinuation of antihyperglycaemic agents. This would generally be apparent within 1-2 weeks of discontinuation and may require an increase or recommencement of therapy. A period of blood glucose monitoring following changes is suggested, with HbA1c to be tested 3 months after any medication change if clinically appropriate.

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