A GUIDE TO

deprescribing

SULPHONYLUREAS

KEY POINTS

- **The natural history of type 2 diabetes includes gradual loss of beta cell function.**
- **Sulphonylureas are insulin secretagogues, requiring beta cell function in order to stimulate insulin secretion.**
- **Sulphonylurea failure at six years after commencement is approximately 40%.**
- **Dose reduction without an increase in blood sugar levels usually confirms lack of efficacy.**
- **Intensity of diabetes management should be reduced in frail elderly patients.**

CONTEXT

This guide considers the use of sulphonylureas in the treatment of type 2 diabetes.

RECOMMENDED DEPRESCRIBING STRATEGY

Patients who have been taking sulphonylureas for more than 10 years are likely to have limited effectiveness of the agent. If diabetes management goals are satisfactory, dose reduction (with appropriate monitoring to ensure lack of effect) with a view to cessation would be reasonable.

In patients taking sulphonylureas, who's HbA1c is below 6% (42mmol/mol) cessation, followed by appropriate monitoring would be appropriate.

Patients who have hypoglycaemia associated with their sulphonylurea should have the agent ceased.

BACKGROUND

Type 2 diabetes is a chronic disease characterised by deterioration of glycaemic control, most commonly due to loss of pancreatic beta cell mass and functions on a background of insulin resistance.[1]

There are multiple proposed causes for beta cell dysfunction in type 2 diabetes over time. Factors such as consistent hyperglycaemia, obesity, hyperlipidaemia and possibly the use of insulin secretagogues such as sulphonylureas and gliptins have been implicated.[2,3]

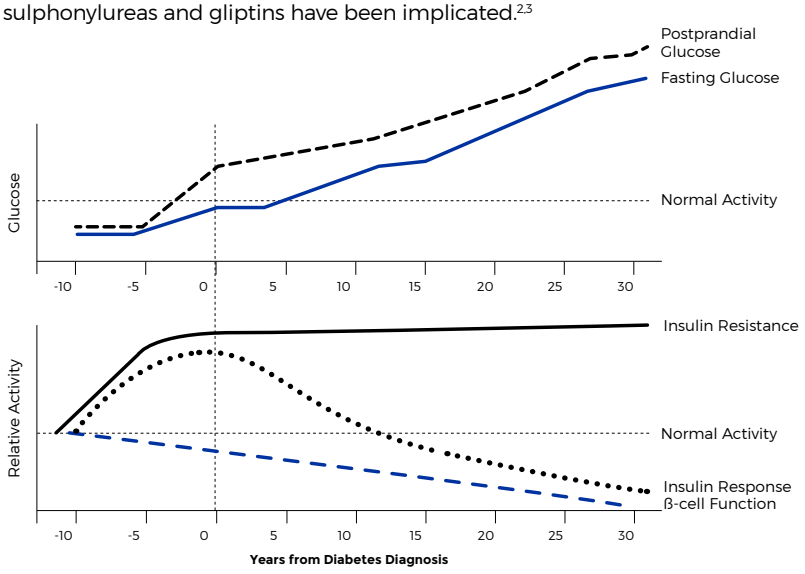


Figure 1: Natural Progression of Type 2 diabetes[1]

EFFICACY

Sulphonylureas have been considered as suitable first line or add-on therapy (to metformin) for type 2 diabetes for many decades. Sulphonylureas have been shown to be effective in the management of type 2 diabetes over periods of up to 10 years,[4] with reductions of HbA1c of approximately 1%.[5] Studies have reported varying rates of sulphonylurea "failure" where conversion to insulin was required. In the United Kingdom Prospective Diabetes Study (UKPDS), over 40% of patients who were using sulphonylureas alone required additional therapy at six years after commencement.[6] Rates of "failure" were higher for those patients with a higher blood glucose and HbA1c at commencement of treatment and also for those with a lower index of beta cell function (see **Table 1**).[6]

PARAMETER	% REQUIRING ADDITIONAL THERAPY BY 6 YEARS
Fasting Plasma Glucose (mmol/L)	
<7.8	23.0
7.8-10	38.9
>10	61.2
HbA1c (%)	
<6.8	26.4
6.8-8.6	39.9
>8.6	56.0
Beta Cell Function (%)	
>55.1	27.9
27.1-55.1	40.9
<27.1	61.6

Table 1: Sulphonylurea failure rate at six years based on parameters of patients.[6]

Sulphonylurea effectiveness seems, therefore, to decrease over time, with higher rates of failure if beta cell function is compromised.[7]

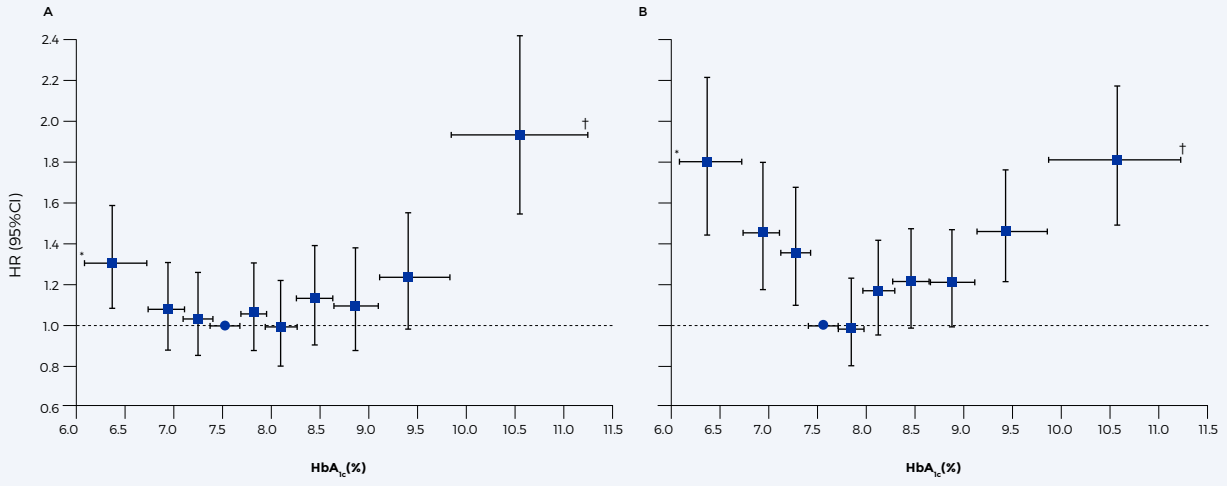
The availability of newer, effective oral agents (SGLT2 inhibitors, DPP4 inhibitors and others) has meant that many guidelines now advocate a patient centred approach to the addition of a second agent, with the choice of agent determined by comorbidities and potential impact of adverse effects (e.g. weight gain, fracture risk, risk of hypoglycaemia).[14]

DIABETES MANAGEMENT IN THE ELDERLY

While more intensive management of diabetes is associated with a lower risk of microvascular and macrovascular complications, there is a higher risk of adverse events, especially hypoglycaemia from the more intensive therapy being used (most often insulin), particularly so in the elderly patient.[4] Indeed, 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 2**).[8]

The management of diabetes in elderly patients, often with multiple comorbidities can be complicated, and there is a need to incorporate an appreciation of the impact of treatment on common syndromes and issues in the elderly (e.g. falls, urinary incontinence, sarcopenia).[9,10]

In older adults, especially with limited life expectancy, functional decline can be expected to be faster in patients with higher levels of adverse events such as hypoglycaemia. Yau et al examined the functional decline of 185 community based elderly patients (mean age 80 years) with type 2 diabetes who were approved for nursing home care.[11] They determined whether functional decline (based on reduced score on five basic activities of daily living) or death occurred over 6, 12 and 24 months and related this to the HbA1c level. At 2 years, higher HbA1c levels were associated with less functional decline or death (p for trend 0.006) (see **Figure 3** page 3). When they accounted for confounding factors (age, sex, race, baseline function, comorbid conditions, insulin use) they found that an HbA1c of 8-8.9% was associated with a lower likelihood of death or functional decline than an HbA1c of 7-7.9%.11 They suggested that guidelines that recommend an HbA1c of 8% or less for older adults with limited life expectancy may be lower than necessary to maintain function.



Adjusted hazard ratios for all-cause mortality by HbA_{1c} deciles in people given oral combination and insulin-based therapies.
Cox proportional hazards models were used, with HbA_{1c} base case scenario. Vertical error bars show 95% CIs, horizontal bars show HbA_{1c} range.
Blue circle=reference decile. *Truncated at lower quartile. †Truncated at upper quartile. Metformin plus sulphonylureas (A); and insulin-based regimens (B).

Figure 2: Relationship between HbA1c and mortality for patients taking oral hypoglycaemics (A) or insulin (B)[8]

Sussman et al.[12] examined the rates of "deintensification" of diabetic therapy in patients over 70 years old. They examined the rate of deintensification of treatment used in patients according to their HbA1c, in the categories of very low (<6%, n= 12917), moderately low (6-6.4%, n= 23,769) and not low (>6.5%, n= 143,305). Deintensification rates were 27%, 21% and 17.5% respectively.[12]

Life expectancy was estimated using the patient's age and their Charlson-Deyo score. Patients with less than 5 years of life expectancy had a 21.3% chance of diabetic therapy deintensification, those with 5 to 10 years had a 18.5% chance, and those with more than 10 years had a 17.2% chance. The authors indicated that current guidelines for management of diabetes focus on preventing underuse rather than overuse and concluded "Until guidelines and performance measures specifically call for deintensification for patients who are at risk for being harmed by overtreatment, (deintensification) rates are likely to remain low".[12]

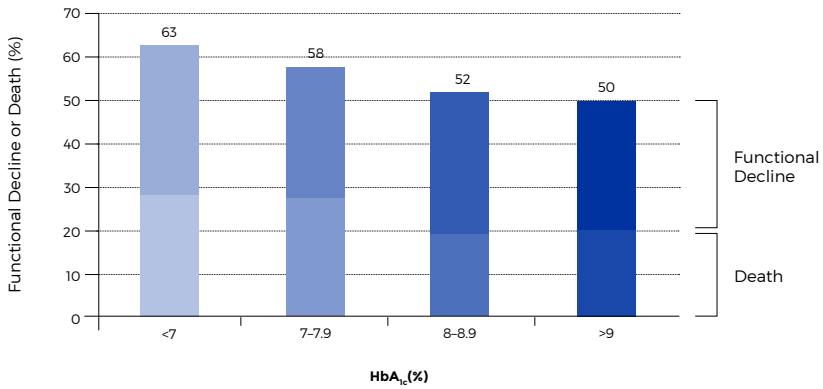


Figure 3: Rate of functional decline or death at 2 years[11]

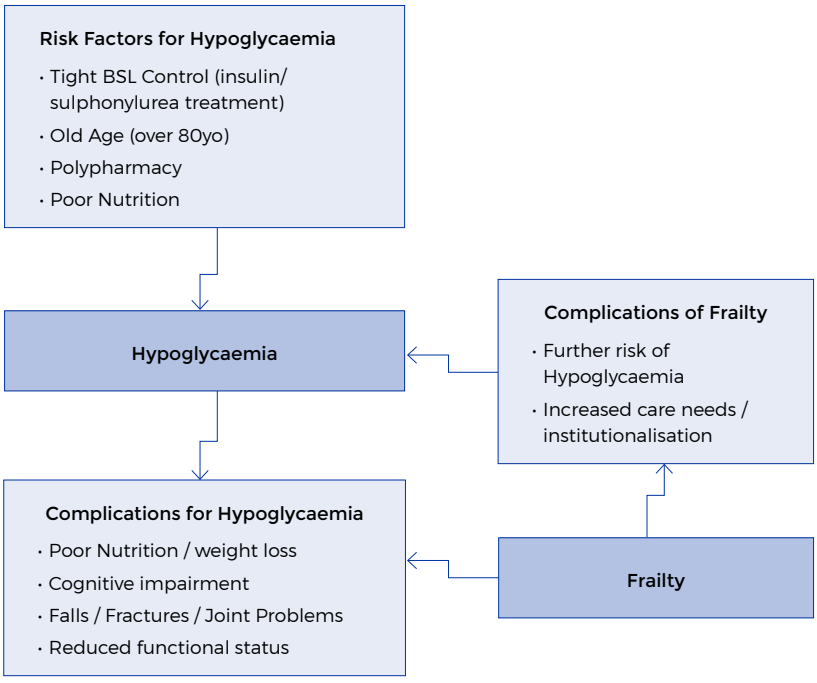


Figure 4: Hypoglycaemia and frailty[17] (Adapted)

FACTORS TO CONSIDER

IN FAVOUR OF DEPRESCRIBING

- Long duration of therapy with sulphonylureas is associated with a reduction in efficacy, most likely due to beta cell failure. In patients achieving an appropriate target HbA1c after long term use (>10 years) it is likely that the impact of the sulphonylurea is minimal and dose reduction or cessation may be possible.
- In elderly or frail patients, where the intensity of diabetic management can be reduced, reduction of any antidiabetic therapy (especially insulin or sulphonylureas which predispose to hypoglycaemia) may be appropriate.

AGAINST DEPRESCRIBING

- In people where intensive treatment of diabetes is still likely to have a long term benefit, ongoing management (which may include sulphonylureas) is appropriate.

ADVERSE EFFECTS

Sulphonylureas stimulate pancreatic secretion of insulin virtually independently of serum glucose levels. As a result hypoglycaemia can be a significant adverse event associated with sulphonylureas.[13,14] Hypoglycaemia is more common with longer acting sulphonylureas and in patients with renal dysfunction, including the elderly.[15,16]

The elderly are also more likely to suffer serious adverse consequences as a result of hypoglycaemia, and there are differences in recognising hypoglycaemia in older people. Symptoms are often non-specific or atypical (often confusion or a passive delirium) and can be misinterpreted or misdiagnosed.[17]

Hypoglycaemia from sulphonylureas is dependent on functioning beta cells, and as a result, the frequency of hypoglycaemia in patients on long term sulphonylureas reduces (as does the efficacy, see earlier).

Weight gain of ~2kg is common in patients commenced on sulphonylureas.[4]

Other adverse effects associated with sulphonylureas are occasional skin conditions (peeling of skin; skin redness, itching, or rash) or more rarely, haematological problems.

RESOURCES

- QUICK REFERENCE GUIDE
- GENERAL INFORMATION
- ALLOPURINOL
- ANTIHYPERTENSIVES
- ANTIPLATELET AGENTS
- ANTIPSYCHOTICS
- BENZODIAZEPINES
- BISPHOSPHONATES
- CHOLINESTERASE INHIBITORS
- GLAUCOMA EYE DROPS
- NSAIDS
- OPIOIDS
- PROTON PUMP INHIBITORS
- STATINS
- SULPHONYLUREAS
- VITAMIN D AND CALCIUM

AUTHORSHIP

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DISCONTINUATION SYNDROMES

None described

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