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.

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

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.

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.

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.

Figure 1: Natural Progression of Type 2 diabetes
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, with reductions of HbA1c of approximately 1%. 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. 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).

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

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).

### 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. 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).

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).

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. 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 8.8-9.9% was associated with a lower likelihood of death or functional decline than an HbA1c of 7.7-7.9%. 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.

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### Table 1: Sulphonylurea failure rate at six years based on parameters of patients

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>% REQUIRING ADDITIONAL THERAPY BY 6 YEARS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Plasma Glucose (mmol/L)</td>
<td></td>
</tr>
<tr>
<td>&lt;7.8</td>
<td>23.0</td>
</tr>
<tr>
<td>7.8-10</td>
<td>38.9</td>
</tr>
<tr>
<td>&gt;10</td>
<td>61.2</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>&lt;6.8</td>
<td>26.4</td>
</tr>
<tr>
<td>6.8-8.6</td>
<td>39.9</td>
</tr>
<tr>
<td>&gt;8.6</td>
<td>56.0</td>
</tr>
<tr>
<td>Beta Cell Function (%)</td>
<td></td>
</tr>
<tr>
<td>&gt;55.1</td>
<td>279</td>
</tr>
<tr>
<td>27-55.1</td>
<td>40.9</td>
</tr>
<tr>
<td>&lt;27.1</td>
<td>61.6</td>
</tr>
</tbody>
</table>

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

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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. 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.

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

<table>
<thead>
<tr>
<th>HbA1c (%)</th>
<th>Functional Decline or Death (%)</th>
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<tbody>
<tr>
<td>&lt;7</td>
<td>0-10</td>
</tr>
<tr>
<td>7.7-9</td>
<td>10-20</td>
</tr>
<tr>
<td>8.0-9</td>
<td>20-30</td>
</tr>
<tr>
<td>&gt;9</td>
<td>30-40</td>
</tr>
</tbody>
</table>

**Figure 3:** Rate of functional decline or death at 2 years

**Figure 4:** Hypoglycaemia and frailty (Adapted)

**Risk Factors for Hypoglycaemia**
- Tight BSL Control (insulin/sulphonylurea treatment)
- Old Age (over 80yo)
- Polypharmacy
- Poor Nutrition

**Complications for Hypoglycaemia**
- Poor Nutrition / weight loss
- Cognitive impairment
- Falls / Fractures / Joint Problems
- Reduced functional status

**Complications of Frailty**
- Further risk of Hypoglycaemia
- Increased care needs / institutionalisation

**Hypoglycaemia**

**Frailty**

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. Hypoglycaemia is more common with longer acting sulphonylureas and in patients with renal dysfunction, including the elderly. 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.

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