Chapter 11: The approach to achieving glycaemic control*

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee.

Type 2 diabetes is a heterogeneous disease, with the underlying mechanism ranging from predominantly insulin resistance with relative insulin deficiency, to predominantly an insulin secretory defect with lesser degrees of insulin resistance. The relative contribution of each abnormality varies between individuals, as well as within the same individual at different stages of the disease. People with type 2 diabetes are heterogeneous; diabetes is prevalent across all socio-economic strata, ethnic groups, age groups and weight categories, in individuals with highly variable nutrient intakes and levels of physical activity. In addition to phenotypic heterogeneity, there is genetic variability which may play a role in susceptibility, both to the disease itself or its complications. The response to treatment is heterogeneous; we see diversity in responses to the same treatments even in patients with near-identical phenotypes. It seems intuitive then, that a single uniform approach to management of such a heterogeneous disorder is unlikely to be successful. The optimal pharmacological approach to glucose control for any individual patient varies, which is why many international guidelines have endorsed individualised management, with no restriction on the choice of glucose lowering drug after initial metformin therapy.1-7 The concept of patient-centred care incorporates patients as partners in their healthcare. In practice, this means providing care that is “respectful of and responsive to individual patient preferences, needs and values, and ensures that patient values guide all clinical decisions”. These guidelines also have a broad target audience that includes health care professionals at all levels of expertise.

The SEMDSA approach to glycaemic control does not lose focus of patient-centred care but attempts to provide guidance about appropriate therapeutic choices for primary healthcare practitioners managing patients at different stages of type 2 diabetes. This is done by attempting to match the therapeutic options with the diverse clinical profiles encountered in patients, while still offering a rational approach to drug management. In the South African healthcare system, with its shortage of doctors, it is also important that nurses at primary healthcare clinics have access to medicines with the lowest probability of harm.

11.1 Factors to consider when choosing glucose lowering drugs

The factors that need to be considered when choosing appropriate pharmacologic therapies to match individual patient

Figure I: Some of the factors to consider when choosing glucose lowering drug therapy at various stages of type 2 diabetes

<table>
<thead>
<tr>
<th>Gliclazide modified release</th>
<th>Pioglitazone</th>
<th>DPP-4 inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>SGLT2 inhibitor</th>
<th>Basal insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA1c reduction</td>
<td>-0.8 to -1.0%</td>
<td>-0.8 to -1.0%</td>
<td>-0.7%</td>
<td>-0.8 to -1.2%</td>
<td>-0.8 to -1.0%</td>
</tr>
<tr>
<td>Hypoglycaemia (monotherapy)</td>
<td>Yes</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Hypoglycaemia (added to SU)</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Weight change</td>
<td>+0.0 to 1.5kg</td>
<td>+3.0 to 5.0 kg</td>
<td>Neutral</td>
<td>-3.0 kg</td>
<td>-3.0kg</td>
</tr>
<tr>
<td>Adverse events*</td>
<td>None</td>
<td>Fluid retention (oedema, CHF)</td>
<td>Heart failure with saxagliptin</td>
<td>Common – Gl upset</td>
<td>Common – GU infection Dehydration</td>
</tr>
<tr>
<td>Rare SAEs</td>
<td>None</td>
<td>Fractures, 1bladder cancer</td>
<td>Pancreatitis, pancreatic cancer</td>
<td>Pancreatitis, pancreatic cancer</td>
<td>Fractures Amputation DKA</td>
</tr>
<tr>
<td>Treatment complexity</td>
<td>Low</td>
<td>High</td>
<td>Low</td>
<td>Intermediate</td>
<td>High</td>
</tr>
<tr>
<td>Cardiovascular benefit</td>
<td>None</td>
<td>Yes, 1st and 2nd prevention</td>
<td>None</td>
<td>Yes (2nd prevention)</td>
<td>Yes (2nd prevention)</td>
</tr>
<tr>
<td>Cost*</td>
<td>&lt;R100</td>
<td>R120-180</td>
<td>R250-350</td>
<td>R650-2150</td>
<td>Unknown</td>
</tr>
<tr>
<td>Initiate at</td>
<td>1st or 2nd Line</td>
<td>1st or 2nd Line</td>
<td>1st or 2nd Line</td>
<td>3rd Line</td>
<td>2nd Line</td>
</tr>
</tbody>
</table>

*Side effects other than weight gain and hypoglycaemia; GI=gastrointestinal; GU= genitourinary; SU = sulphonylurea; SAEs = serious adverse events

Information represents a synthesis of data from various sources discussed in the text.

Cost is based on single exit price in the private health sector; figures may differ in the public health sector. Cost of insulin depends on dose, and excludes ancillary costs. In the 4T study basal insulin dose ranged from 0.5U/kg to 1.0U/kg from year 1 to year 3. Though evidence supporting specific insulin regimens is limited. Methods: In an open-label, controlled, multicenter trial, we randomly assigned 708 patients with a suboptimal glycated hemoglobin level (7.0 to 10.0% This translates to 40 to 80u/day for intensive basal insulin therapy in an 80kg person.

Adverse events refer to common side effects (other than weight gain and hypoglycaemia) that impact tolerability and drug discontinuation rates.

Treatment complexity considers the ease with which the drug can be prescribed, higher complexity may demand greater resources (consulting time or other resources) in screening for contraindications, educating the patient about the treatment or the patient’s required investment in complying with the treatment (e.g. injecting, SMBG and dose titration), as well as resources to monitor and treat adverse effects.
needs, fears and comorbidities are many, and are summarised in Figure I. These are also the factors that were considered when formulating the algorithm for the management of hyperglycaemia.

**a. Glycaemic targets**

The importance of individualised glycaemic targets, and the factors to consider, are covered in Chapter 8. These range from an HbA1C < 6.5% for younger newly diagnosed patients with no comorbidities and long life expectancy, to 8.5% for the frail patient with multiple comorbidities and shorter life expectancy. In general though, the glycaemic target for the majority of patients should be an HbA1C ≤ 7.0%.

**b. Glycaemic efficacy**

This is probably less of a consideration than in the past. All of the drug options are efficacious at lowering blood glucose and the reductions obtained with monotherapy are generally greater than those obtained with combination therapy for the same drug. Maximum glucose lowering efficacy is usually evident by six months. A meta-analysis of the various drug choices show that most will reduce HbA1C by approximately 0.8 to 1.2%, without much difference between all of the available agents, when added to metformin.9-12 For triple therapy (adding to metformin + sulphonylurea), the most effective 3rd line drugs appear to be basal insulin, followed by TZDs, GLP-1RA and SGLT2 inhibitors equally, with DPP-4 inhibitors having the greatest odds of treatment failure.10 Again the differences are not large.

Also, in clinical practice the range of HbA1C reduction for each drug is wide, with some patients responding very well, and others not responding at all to a particular drug. Baseline HbA1C also determines glycaemic efficacy; a 1% higher baseline HbA1C predicts an additional -0.5% HbA1C reduction at six months.12 To illustrate this point, in a study analysing patients with high baseline HbA1C, empagliflozin 25 mg reduced the HbA1C by 3.3% from a baseline HbA1C of 11.1%.13 The ability of a patient to concurrently intensify lifestyle measures is also important when intensifying drug therapy. In clinical practice, the combination of these interventions has been known to dramatically reduce HbA1C levels to an extent far greater than published mean HbA1C reductions.

The variability in glycaemic efficacy within each drug class, and between drug classes in patients with similar phenotypes, together with the small absolute differences between agents, suggests that the choice of glucose lowering drug should probably be based on other patient factors (Figure I), which are more likely to impact treatment success or failure, rather than glycaemic efficacy alone. In any event, the efficacy of any added therapy must be assessed within six months; failure to achieve the target and reduce the HbA1C by ≥ 0.5% should prompt a change to an alternative drug.

**c. Hypoglycaemia**

Treatment-related hypoglycaemia is the commonest form of hypoglycaemia, and is a function of insulin or insulin sulphonylurea use. This topic is covered in Chapter 12. Hypoglycaemia is an important consideration when choosing therapies because it can have a significant negative impact on a person’s wellbeing and quality of life, and can influence adherence, compliance, and therefore the success of treatment. Severe hypoglycaemia emerges as one of the strongest risk factors for cardiovascular events and mortality, especially in those patients with higher cardiovascular risk.14-19 Independent risk factors for severe hypoglycaemia are listed in Figure II. The circumstances where the consequences of severe hypoglycaemia are sufficiently severe to warrant the avoidance of hypoglycaemia-inducing drugs are listed in Figure III.

**Figure II: Independent risk factors for severe hypoglycaemia**

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin or sulphonylurea use</td>
</tr>
<tr>
<td>Intensive glucose control</td>
</tr>
<tr>
<td>Use of 2 or more oral glucose lowering drugs</td>
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<tr>
<td>Older age</td>
</tr>
<tr>
<td>Diabetes duration</td>
</tr>
<tr>
<td>Hypoglycaemia unawareness</td>
</tr>
<tr>
<td>Impaired cognitive function</td>
</tr>
<tr>
<td>Low body mass index</td>
</tr>
<tr>
<td>Renal impairment</td>
</tr>
<tr>
<td>Microvascular complications</td>
</tr>
</tbody>
</table>

**Figure III: Circumstances where the consequences of hypoglycaemia may be catastrophic**

<table>
<thead>
<tr>
<th>Circumstances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operators of heavy machinery</td>
</tr>
<tr>
<td>Scaffold workers</td>
</tr>
<tr>
<td>Drivers of public transport or heavy duty vehicles</td>
</tr>
<tr>
<td>Airline pilots</td>
</tr>
<tr>
<td>Emergency rescue workers</td>
</tr>
<tr>
<td>People who live alone and have impaired cognition or mobility (may not be able to respond to symptoms promptly)</td>
</tr>
<tr>
<td>Hypoglycaemia unawareness</td>
</tr>
<tr>
<td>People at high fall and fracture risk</td>
</tr>
</tbody>
</table>

Recurrent hypoglycaemia may be an important impediment to achieving good glycaemic control. Patients who fear hypoglycaemia are unlikely to titrate insulin as instructed, and may also overeat for protection, setting up a vicious cycle of weight gain, hyperglycaemia and increasing insulin doses – the adage of “hypoglycaemia begets hypoglycaemia”. Patients receiving hypoglycaemic drugs must be questioned about hypoglycaemia at every visit, in order to address treatment failures. Any patient who has a severe hypoglycaemic event must be evaluated for a cause and must have their treatment reviewed. Any treatment plan should have ready access to drugs that do not cause hypoglycaemia when the circumstances demand this.

**d. Weight gain**

Weight effects of medications are considered separately because of their importance to patients’ quality of life and self-esteem, and treatment compliance. Obesity, as part of the metabolic syndrome, is a well-known cardiovascular risk factor. Weight gain after diagnosis of type 2 diabetes may also be a risk factor for cardiovascular disease but this remains to be
proven. Metformin, SGLT2 inhibitors, and GLP-1 agonists are associated with weight loss, DPP-4 inhibitors and acarbose are weight neutral, whereas sulphonylureas cause modest weight gain. Weight gain is worst with pioglitazone and insulin. Patients who experience significant weight gain (as defined by themselves) with pioglitazone or insulin are unlikely to comply with their treatment. They may be better served with a less effective treatment with better compliance. Alternative treatment options should be considered for patients who experience unacceptable weight gain.

**e. Adverse effects**

Adverse effects other than hypoglycaemia and weight gain, which are considered separately, should be taken into account. Common adverse effects can limit compliance and adherence to therapy. Each patient’s potential to tolerate common adverse effects needs to be considered. Metformin has common GI side effects leading to about a 10% discontinuation rate. In the LEAD 6 trial program 15-20% of patients discontinued GLP-1RA therapy. Similarly genitourinary side effects may limit the use of SGLT2 inhibitors. Patients should be warned about the common adverse events when commencing therapy.

**f. Serious adverse events**

The rare but serious adverse events for each drug/class are discussed individually. SEMDSA has considered the impact these have on patient selection and ease of prescribing in the primary healthcare setting.

**g. Treatment complexity**

The choice of treatment considers the patient, provider and general healthcare resources that may be required for a particular therapeutic choice. The use of insulin therapy is a good example of treatment complexity. Escalation to insulin therapy is premised on information from clinical trials demonstrating equivalent and sometimes better glycaemic control than other therapeutic options. These trials often exclude patients who are unable or unwilling to perform and record frequent SMBG or to “force-titrate” insulin doses to strict glycaemic targets. These trial patients receive intensive education about insulin use, injection technique, SMBG, titration protocols and are provided with adequate supplies of insulin, needles and test strips. They also have ongoing education, very frequent clinic follow-up visits (usually two to four weeks apart) and continual, unlimited telephonic support. Translating the positive glucose control results from such trials into daily clinical practice in some/most/all primary healthcare centers may sometimes be a “mis-translation”. The patient may be given a prescription for one or other insulin, possibly with very little or no ongoing education on how to use it, with no titration instruction or protocol, perhaps a limited supply of test-strips (if at all), and no access to support for months on-end. In this regard insulin therapy could be construed as a “pseudo-escalation” of treatment. Given the relative demands of insulin initiation and titration for the patient and clinic staff, might the patient be better served with a somewhat less efficacious oral glucose lowering drug that has a lower complexity.

Other aspects of treatment complexity to be considered include assessments and counseling before and after a drug prescription in order to ensure patient safety, e.g. assessment of fracture risk for patients being considered for pioglitazone or canagliflozin treatment.

**h. Patient factors**

The entire point in considering all the features about each pharmacological agent is, of course, to find the “best-fit” for the patient. Each patient has their own needs and fears, and each has their own expectation of treatment outcomes.

**11.3 The 2017 SEMDSA approach and algorithm for the management of type 2 diabetes**

In planning the treatment algorithm, the SEMDSA Expert Committee was cognisant that the majority of type 2 diabetes patients are, and should be, managed at primary healthcare facilities. There is evidence though, that the standards of care for type 2 diabetes at all levels is not adequate, and that interventions to improve processes of care for non-communicable diseases may not be successful. The current local evidence is that 10 to 30% of patients achieve an HbA1c of <7.0% and as many as 30% have an HbA1c > 11%. It is clear that a metformin-sulphonylurea-insulin strategy is not effective in the South African primary health care setting. The purpose of this algorithm therefore is to improve glycaemic control by attempting to give primary healthcare practitioners the tools needed to achieve this in a way that is both safe and effective.

A few caveats about this algorithm need emphasizing. Firstly, it is a guideline for primary healthcare; patients managed at specialist care level often have multiple comorbidities and more severe disease requiring more complex therapies. Secondly, the algorithm applies to the stable type 2 diabetes patient who has suboptimal glycaemic control; it does not apply to the metabolically decompensated patient with severe symptomatic hyperglycaemia; those patients usually need referral for intensive management. Thirdly, it does not apply to patients with severe microvascular or macrovascular complications; these patients should also be managed under specialist supervision, and the optimal treatment options differ from this algorithm. Lastly, this can only serve as a guideline and cannot, and should not be applied rigidly to the very heterogeneous type 2 diabetes population (as discussed above). However, the suggested therapeutic options should cater for the glucose control needs of the majority of type 2 diabetes patients who are being managed appropriately in the primary healthcare setting.

The algorithm should be interpreted in conjunction with the “Pharmacological Management” Chapters 9 and 10, which provide a summary of each drug, as well as with the recommendations for each drug below. For those wanting more detailed information, a review of each drug class is provided in the Appendix. The footnotes explain the algorithm in greater detail.
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### 2017 SEMDSA algorithm for the management of type 2 diabetes in non-pregnant adults without metabolic decompensation or cardiovascular disease

<table>
<thead>
<tr>
<th>Intensity</th>
<th>Lifestyle interventions throughout</th>
<th>Metformin</th>
<th>DPP-4 inhibitor</th>
<th>GLP-1 RA</th>
<th>SGLT2 inhibitor</th>
<th>Gliclazide MR</th>
<th>Pioglitazone</th>
<th>GLP-1 RA</th>
<th>Insulin (basal, premix, or basal-bolus)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy</td>
<td></td>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dual Therapy</td>
<td></td>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triple Therapy</td>
<td></td>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complex Therapy</td>
<td></td>
<td>Metformin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Legend**
- Preferred options are listed alphabetically.
- Alternative options (without motivation) are listed next to preferred options.
- Not recommended if HbA1c target is attainable with other agents.

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**Comparison of Injectable Therapy**
- GLP-1 RA
- Basal insulin
- SGLT2 inhibitor
- Dual therapy
- Complex therapy
Reinforce advice on diet and lifestyle at every contact.

- Insulin therapy. Decide on an individualised HbA1C target using the guidelines in Chapter 8. Monitor HbA1C every three months until the target is achieved; then every six months. Always assess the response to added treatments; if the HbA1C reduction is not >0.5% after 3-6 months, consider treatment failure and change to an alternative option.

- In newly diagnosed patients, if the HbA1C reduction is not >0.5% after 3-6 months, consider treatment failure and change to an alternative option.

- In patients with type 2 diabetes, if the HbA1C target is not achieved after three months of metformin or subsequently rises, consider adding gliclazide MR, a DPP-4 inhibitor, pioglitazone, or an SGLT2 inhibitor. If the HbA1C reduction is not >0.5% after 3-6 months, consider treatment failure and change to an alternative option.

- Consider gliclazide MR for most patients whose target is <7%. If the target is <6.5% or there are other reasons why gliclazide MR cannot be used (e.g., recurrent hypoglycaemia), then consider a DPP-4 inhibitor (or pioglitazone, or an SGLT2 inhibitor) based on the patient profile. Fixed dose combinations of a DPP-4 inhibitor + metformin may have compliance and cost advantages.

- If the HbA1C is above the individualised target (which should still be <7% for most patients) with two oral agents, consider adding either a third oral agent or an injectable agent (GLP-1 RA or basal insulin). When triple therapy is inadequate at maintaining or achieving glycaemic targets, combination injectable (complex) therapy will become necessary. Recurrent hypoglycaemia, unacceptable weight gain and treatment failure (failure to achieve an HbA1C level that is within 0.5% of the target, or to lower the HbA1C by more than 1%) with these complex therapies should warn against continuing them. The page number in the footer is not for bibliographic referencing.
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Suboptimal glycaemic control with 2 oral agents e.g. metformin + SU

Option 1
Add a 3rd oral agent (TZD, DPP-4i, SGLT2i)

Option 2
Add a GLP-1RA

Option 3
Add basal insulin Start with 10u at bedtime

Simple titration
Once weekly average of last two fasting SMBG level (use pre-prandial SMBG for premix or bolus insulin).
- If above target, +2 units
- If at target, maintain dose (usual target 4.0-7.0mmol/L)
- If below target, subtract 2 units

Simple rapid titration
Once daily titration according to last fasting SMBG level (use pre-prandial SMBG for premix or bolus insulin).
- If above target, +1 unit
- If at target, maintain dose (usual target 4.0-7.0mmol/L)
- If below target, subtract 2 units

Aggressive titration
Once weekly lowest of last 3 fasting SMBG readings (use pre-prandial SMBG for premix or bolus insulin)
- >10.0 mmol/L: +8u
- 8.1 to 10.0 mmol/L: +6u
- 7.0 to 8.0 mmol/L: +4u
- 5.6 to 7.0 mmol/L: +2u
- 4.0-5.5 mmol/L: maintain dose
- 3.1 to 3.9 mmol/L: -2u
- <3.1 mmol/L: -4u

Figure IV: Initiating and titrating basal insulin therapy

SU = sulphonylurea; TZD = thiazolidinedione; DPP-4i = DPP-4 inhibitor; SGLT2i = SGLT2 inhibitor; GLP-1RA = GLP-1 receptor agonist; SMBG = self-monitoring of blood glucose

§Do not combine a GLP-1RA with a DPP-4 inhibitor or SGLT2 inhibitor.

Figure V: Complex (combination injection) therapies

3 Oral anti-diabetic agents
2 Oral anti-diabetic agents + basal insulin
2 Oral anti-diabetic agents + GLP-1RA

Suboptimal glycaemic control with 3 anti-diabetic agents

Option 1
Continue metformin and add twice daily premix insulin
- Split existing basal insulin dose, or initiate 0.3u/kg; give ½ AM and ½ PM before meals.
- Set morning and evening pre-prandial SBGM targets (refer to Ch. 8).
- Titrate the morning dose to achieve the pre-supper SBGM target; titrate the evening dose to achieve the pre-breakfast SMBG target.
- Use the titration algorithms in Figure IV.

Option 2
Continue metformin and start basal-plus insulin
- Initiate and titrate basal insulin if not yet in use (refer to Appendix 10.4).
- Add 4u rapid-acting insulin before the largest meal of the day and set the appropriate pre-prandial SMBG target before the next meal (refer to Ch. 8).
- Titrate the rapid acting insulin dose to achieve the desired target; use the titration schedule in Figure IV.
- Progressively add rapid acting insulin for other meals as needed.

Option 3
Continue metformin and combine basal insulin with a GLP-1RA
- This combination can achieve similar HbA1C reductions compared to Options 1 and 2, and is preferred especially in obese patients or where weight gain has been problematic.
- Prefer exenatide if post-prandial hyperglycaemia is limiting glycaemic control.
- Prefer liraglutide if fasting hyperglycaemia is limiting control.
- Continue to titrate the basal insulin dose as per Figure IV.

Specialist referral is appropriate at any stage for suboptimal glycaemic control, problematic hypoglycaemia, unacceptable weight gain or the onset of microvascular or macrovascular complications.

GLP-1RA = GLP-1 receptor agonist; SMBG = self-monitoring of blood glucose
11.4 Recommendations for glucose lowering drugs

(Reproduced from Chapter 9)

**SEMDSA 2017 Recommendations for metformin**

- Initiate standard-release metformin therapy in all newly diagnosed obese patients with type 2 diabetes.
- Initiate standard-release metformin therapy in all newly diagnosed non-obese patients with type 2 diabetes.
- Dosing: Start with 500 mg once daily and up-titrate the dose slowly every 10 to 14 days until glycaemic targets are met or side effects occur. Few patients will achieve and maintain glycaemic targets with 500 mg once daily. Most patients will require 1000 – 2550 mg per day in two or three divided doses. The optimum dose for cardiovascular benefit in obese patients is 2550 mg/day (850 mg TDS).
- If gastrointestinal (GI) adverse events are limiting, try temporarily reducing or discontinuing the drug, and re-titrate when the GI disturbances resolve. The GI side-effects with metformin extended-release is not different to the standard release when used as initial therapy; however patients who switch to the extended release may have improved tolerability. If GI disturbances remain intolerable with standard metformin tablets, try switching to a metformin extended release (XR) formulation and titrate the dose every 10-14 days again.
- The extended release formulation should be dosed once daily with the evening meal at a dose not exceeding 2000 mg/day. The 2000 mg dose can be taken as 1000 mg twice a day without disadvantages if the patient so prefers. Patients not achieving their glycaemic target with 2000 mg of the extended release may benefit from switching to a higher dose of the standard release metformin.
- Monitor renal function (eGFR) in all patients at least annually. Do not exceed 1000 mg/day if the eGFR is 30-45 ml/min/1.73m². Stop metformin therapy if the eGFR is < 30 ml/min/1.73m²
- The significance of low serum vitamin B₁₂ levels associated with long-term metformin use is not known. Measure and treat whenever clinically appropriate.
- **Profile of the patient in whom metformin may not be the preferred option:**
  - Patients with irritable bowel syndrome or other chronic gastrointestinal disorders
  - Normal weight individuals who do not wish to lose weight
  - Patients at high risk for lactic acidosis (severe heart, lung, liver, renal or peripheral vascular disease)
  - There is a history of metformin intolerance.

**SEMDSA 2017 Recommendations for sulphonylureas**

- The sulphonylurea of choice should be gliclazide modified-release because:
  - It has equivalent efficacy compared to other sulphonylureas.
  - It is consistently associated with lower rates of hypoglycaemia and better cardiovascular and renal safety relative to other sulphonylureas.
  - It has proven benefits for long-term microvascular disease outcomes.
- Glibenclamide must not be used at primary care level.
- Consider gliclazide modified-release as initial monotherapy when metformin is not tolerated or is contraindicated.
- Consider gliclazide modified-release as add-on (dual therapy) to metformin (or other initial drug therapy) in most patients not achieving or maintaining their glycaemic targets.
- If not already in use, consider gliclazide modified-release as a third glucose lowering drug.
- To convert treatment from another sulphonylurea to gliclazide modified-release, use the following dose conversion:
  - Glibenclamide 5 mg = Gliclazide modified-release 30 mg
  - Glimepiride 1-2 mg = Gliclazide modified-release 30 mg
- Only continue gliclazide modified-release beyond stage 3 chronic kidney disease (when the eGFR is less 30 ml/min/m²) with specialist supervision.
- **Circumstances where gliclazide MR may be preferred to other treatment options:**
  - Gliclazide MR should be the preferred second drug for the majority of patients with type 2 diabetes.
  - At diagnosis when rapid control of hyperglycaemic symptoms is required.
- **Circumstances where gliclazide MR may not be the preferred option:**
  - The individualised glycaemic target is ≤ 6.5% (as the risk of hypoglycaemia may be unacceptably high with this target).
  - There is a history of severe hypoglycaemia or hypoglycaemia unawareness.
  - There is a history of recurrent hypoglycaemia (any degree) despite dose adjustments.
  - The risk of hypoglycaemia is high and/or its consequences are severe.
  - The patient has advanced liver disease.

**SEMDSA 2017 Recommendations for pioglitazone**

- Consider pioglitazone as initial monotherapy when metformin is contraindicated or not tolerated.
- Consider pioglitazone as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.
- Consider pioglitazone as a third non-insulin glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- **Circumstances where pioglitazone is preferred to other treatment options:**
  - The patient has advanced liver disease.
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- Gliclazide MR is contraindicated or not tolerated.
- Non-alcoholic steatohepatitis is present.
- The patient has features of severe insulin resistance.
- There is a history of previous myocardial infarction, previous stroke or chronic kidney disease stage-3 (pioglitazone offers probable benefit for secondary prevention)
- Circumstances where pioglitazone may not be the preferred option:
  - Age > 75 years old (risk of congestive heart failure (CHF), fracture and bladder cancer)
  - History of congestive heart failure.
  - History of osteoporosis.
  - History of bladder cancer, or haematuria that has not been investigated.
  - Stage-4 or worse chronic kidney disease (risk of fluid retention).
  - Patients on insulin therapy (higher risk of fluid retention and CHF).
  - Elevated liver enzymes (>2x ULN) not due to NASH.

SEMDSA 2017 Recommendations for DPP-4 inhibitors

- Consider a DPP-4 inhibitor as initial monotherapy when metformin is contraindicated or not tolerated.
- Consider a DPP-4 inhibitor as add-on to metformin or other initial drug therapy, in selected patients not achieving or maintaining their glycaemic targets.
- Consider a DPP-4 inhibitor as the third glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- Combination DPP-4 inhibitor and insulin therapy should be initiated at specialist level.
- Be aware of dose adjustments for chronic kidney disease.
- Circumstances where a DPP-4 inhibitor may be preferred to other treatment options:
  - As the 2nd add-on drug when gliclazide MR is contraindicated or not tolerated.
  - As the 3rd add on drug for most patients if HbA1c targets are potentially achievable.
  - Older patients with multiple comorbidities.
  - Patients with stage-4 chronic kidney disease (can be used without risk of hypoglycaemia).
  - If a fixed-dose combination tablet will improve adherence, compliance and/or cost-effectiveness.
- Circumstances where a DPP-4 inhibitor may not be the preferred option:
  - Very high HbA1c and the glycemic target is not likely to be achieved with a DPP-4 inhibitor.
  - History of pancreatitis or pancreatic tumour.
  - History of heart failure or high risk of heart failure (saxagliptin).
- Liver disease: moderate (do not use saxagliptin or vildagliptin) or severe (do not any DPP-4 inhibitor).

SEMDSA 2017 Recommendations for GLP-1 receptor agonists (GLP-1RA)

- Consider a GLP-1RA injectable as the third glucose lowering drug (triple therapy) in overweight and obese patients when glycaemic targets are not being achieved or maintained.
- Consider adding a GLP-1RA to existing basal insulin therapy (with oral therapies) as an alternative to intensifying the insulin regimen, especially when weight gain and/or hypoglycaemia is a limiting factor.
- Escalate the dose of GLP-1RA slowly to minimise side-effects.
- Circumstances where a GLP-1RA may be preferred to other treatment options:
  - Overweight and obese patients
  - Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options.
  - HbA1c is very high (GLP-1RA and insulin are the most effective glucose lowering drugs for most patients).
  - Patients with established cardiovascular disease (liraglutide benefit); to be managed at specialist care level.

SEMDSA 2017 Recommendations for SGLT2 inhibitors

- Do not use SGLT2 inhibitors as initial monotherapy
- Consider an SGLT2 inhibitor as add-on (dual therapy) to metformin (or other initial drug therapy) in selected patients not achieving or maintaining their glycaemic targets.
- Consider an SGLT2 inhibitor as the 3rd glucose lowering drug in selected patients not achieving or maintaining their glycaemic targets on an existing oral two-drug regimen.
- Circumstances where an SGLT2 inhibitor may be preferred to other treatment options:
  - Overweight and obese patients.
  - Weight gain or hypoglycaemia has been, or is likely to be problematic with other treatment options.
  - Patients with established cardiovascular disease (empagliflozin benefit); to be managed at specialist care level.
- Circumstances where an SGLT2 inhibitor may not be the preferred option:
  - Patients with recurrent mycotic genital infections or urinary tract infections.
  - Patients at risk for dehydration and hypotension.
  - Patients at high risk for stroke, fracture (canagliflozin), amputation (canagliflozin), bladder cancer (dapagliflozin) or ketoacidosis (refer to drug review).
• Do not initiate SGLT2 inhibitors when the eGFR is < 60 ml/min/m².

• Stop all SGLT2 inhibitors when the eGFR is < 45 ml/min/m².

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References


