

# Hong Kong Reference Framework for Diabetes Care for Adults in Primary Care Settings

## Revised Edition 2021

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## Preface to the First Edition

Enhancing primary care is one of the proposals put forward in the Healthcare Reform Consultation Document “Your Health, Your Life” and has received broad public support during the first stage of public consultation conducted in 2008. In recognition of this broad support for the proposals, the Working Group on Primary Care (Working Group) under the Health and Medical Development Advisory Committee and chaired by the Secretary for Food and Health was reconvened to discuss and provide strategic recommendations on enhancing and developing primary care in Hong Kong.

Four Task Forces have been established to study specific proposals set out in the Healthcare Reform Consultation Document. One of them is the Task Force on Conceptual Model and Preventive Protocols (Task Force). The Task Force makes recommendations to the Working Group on conceptual models that are evidence based with associated reference frameworks for use in the local primary care settings. The Task Force is also responsible for promulgating, maintaining and revising the models and frameworks, and the strategies to promote their adoption.

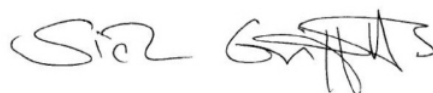
After a series of discussions with stakeholders, the Task Force has developed a basic conceptual model for the management of chronic disease using a population approach across life-course. It is based on the recognition that we need a comprehensive and continuous approach to care focused on the person to meet their needs and address their risks. The reference frameworks cover primary prevention and lifestyle changes, assessment of high risk groups, early detection and management of diseases as well as ensuring the quality of care for more complicated conditions or disabilities within the community. The need to coordinate inputs from multi-disciplinary teams, engage patients and interface with the community and other sectors is also highlighted.

To date, two reference frameworks, one on diabetes and the other on hypertension, have been developed. These reference frameworks consist of a core document supplemented by a series of different modules addressing various aspects of disease management which aim to -

- (a) provide a common reference to guide and co-ordinate care to patients from all healthcare professionals across different sectors in Hong Kong for the provision of continuous, comprehensive and evidence-based care for diabetes and hypertension in the community;
- (b) empower patients and their carers; and
- (c) raise public's awareness on the importance of preventing and properly managing these two major chronic diseases.

Drawing on international experience and best evidence, these frameworks provide general reference for practice in primary care settings to support the policy of promoting primary care within Hong Kong. However, since clinical practice and patient engagement need to keep pace with scientific advancements, in order to ensure the latest medical developments and evidence are reflected in the frameworks to provide reference for best practice, two Clinical Advisory Groups under the Task Force have been established to review and update the reference frameworks on a regular basis. The Clinical Advisory Groups are composed of experts from academia, professional organisations, private and public primary care sector and patient groups who are members of the groups in their own right, not representing organisations.

To facilitate the promulgation and adoption of the reference frameworks, support and endorsement from healthcare professionals across different sectors in Hong Kong has been and will continue to be very important. We hope that the adoption of the reference frameworks will improve patient care by facilitating co-ordination of their care, strengthen management continuity, promote evidence based effective and efficient practice, empower patients and their carers as well as enhancing public awareness about the prevention and management of these two major chronic diseases in our community.



Professor Sian GRIFFITHS  
Convenor  
Task Force on Conceptual Model and Preventive Protocols

## Key To Evidence Statements And Grades Of Recommendations<sup>#</sup>

### Levels of Evidence

1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analysis, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

<sup>#</sup> Scottish Intercollegiate Guidelines Network (SIGN) classification.

Grades of Recommendation

A	<p>At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or</p> <p>A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results</p>
B	<p>A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or</p> <p>Extrapolated evidence from studies rated as 1++ or 1+</p>
C	<p>A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or</p> <p>Extrapolated evidence from studies rated as 2++</p>
D	<p>Evidence level 3 or 4; or</p> <p>Extrapolated evidence from studies rated as 2+</p>

## Statement Of Intent

The framework is constructed from global evidence of best practice. As with all guidance it aims to support decision making, recognising that all patients are unique and have their own needs. The Task Force endeavours to provide accurate and up-to-date information. The frameworks provide support for decision making and as such are not mandatory. They should not be construed as within any legal framework, rather as guidance for professional practice. Standards of care for individual patients are determined on the basis of all the facts and circumstances involved in a particular case. They are subject to change as scientific knowledge and technology advances and patterns of care evolve. Management of diseases must be made by the appropriate primary care practitioners responsible for clinical decisions regarding a particular treatment procedure or care plan. The responsible primary care practitioners should only arrive at a particular treatment procedure or care plan following discussion with the patient on the diagnostic and treatment choices available.

## Chapter 1. Epidemiology

Diabetes mellitus is a chronic condition that occurs when there are raised levels of glucose in the blood because the body cannot produce any or enough of the hormone insulin or use insulin effectively<sup>1</sup>. There are three major types of diabetes, namely Type 1 diabetes, Type 2 diabetes, and gestational diabetes.

Type 2 diabetes is the most frequent form of diabetes among Hong Kong adults<sup>2</sup>. The majority of patients with Type 2 diabetes have insulin resistance, defined as reduced responsiveness to insulin action in peripheral tissues although insufficient insulin secretion to overcome insulin resistance remains a cardinal feature in Type 2 diabetes. This disease is currently affecting around one in 10 people in Hong Kong or about 700 000 people. From the second Population Health Survey conducted by the Department of Health, the prevalence of diabetes increased with age from 0.5% for persons aged 25-34 to 25.4% for those aged 65-84<sup>3</sup>. Around half of those suffering from diabetes were being undiagnosed<sup>3</sup>. Such findings are consistent with the observations in earlier studies<sup>4</sup>.

Diabetes is the leading cause of kidney failure, blindness, leg amputations, cardiovascular diseases and stroke<sup>5,6</sup>. Together with its chronic nature, diabetes continues to pose a significant burden to our healthcare system<sup>7</sup>. The optimal control of blood glucose level, blood pressure and dyslipidaemia in diabetic patients by a multidisciplinary team has been proven to reduce complication frequencies in randomised controlled trials and is cost-effective<sup>8a</sup>.



## Chapter 2. Population-based Intervention And Life Course Approach

In recent years, population-based approach in the control and management of chronic diseases is emphasised<sup>9,10,11</sup>. This approach seeks to embrace the whole spectrum of the problem from health promotion, disease prevention and treatment to rehabilitation. To achieve this overarching goal, a proactive approach covering primary, secondary and tertiary levels of prevention is adopted<sup>12,13</sup>. This involves promotion of healthy behaviours to reduce disease risk, early disease detection, and quality management with the ultimate goal to reduce the incidence of complications and associated morbidities and mortality.

The risks of developing chronic diseases including diabetes are influenced by factors acting at all stages of life. The effects of these modifiable risk factors accumulate with increasing age, especially in predisposed individual. Major chronic diseases often share common risk factors, e.g. undesirable environmental conditions, social deprivation, unhealthy dietary habit, physical inactivity, alcohol misuse and smoking<sup>14</sup>. Thus, it is necessary and advantageous to adopt an integrated life course approach in the prevention and control of chronic diseases based on the needs and risks of different population sub-groups to prevent the onset of diseases and reduce the rate of disease progression<sup>15</sup>. Module 1 summarises a comprehensive approach that involves different diabetes prevention or proactive management strategies that are most relevant for the different stages of the life course.

## **Chapter 3. Role Of Primary Care In The Management Of Diabetes**

Primary care is the first point of contact in the healthcare system and is easily accessible to the majority of the population. With support and training, primary care providers form a workforce in the community to deliver coordinated care to diabetic patients, especially those with clinically stable conditions, and to identify high risk subjects for referral to other experts. By applying the principle of family medicine and working in partnership with other healthcare professionals such as dietitians, nurses, occupational therapists, optometrists, pharmacists and physiotherapists, primary care practitioners are in a prime position to provide patient-centered, continuing and comprehensive care taking into account individual patients' needs and values.

In the management of chronic diseases such as diabetes, it is desirable for primary care practitioners to provide ongoing education to reduce risks, diagnose disease early, assess patients' needs, monitor treatment responses and adherence, and identify treatment barriers such as patients' concerns and misperceptions. Furthermore, they could provide holistic care by treating concurrent illnesses and co-morbidities, addressing their patients' psychosocial concerns, empowering them to change behaviour and enabling them to develop coping skills for special occasions, e.g. marriage, pregnancy, travelling and sick day management. Due to the large scope of services involved in the primary, secondary and tertiary prevention of diabetes and associated complications, multidisciplinary care targeting at interfaces between different sectors is essential. Therefore, close collaboration and coordination between primary and secondary care teams are required.

## **Chapter 4. Patient Education**

Patient education is the cornerstone of diabetes management where patients (and their carers) are empowered with appropriate knowledge and skills to live with the disease. Diabetic patients must be given basic knowledge about the nature, consequences and treatment of the diseases as well as their rights and responsibilities in terms of access to care, adherence to recommended treatment and self-management. Primary care practitioners and other care professionals should help dispel misconceptions and address patients' concern about the disease and its treatment, e.g. fear for insulin injection, and emphasise the positive aspects of the disease in terms of risk awareness, adoption of a healthy lifestyle and regular surveillance by a health care team<sup>16</sup>.

## **Chapter 5. Aim Of The Framework**

The Reference Framework for Diabetes Care in Adults in Primary Care Setting serves to provide an updated evidence-based approach and recommends core interventions to influence current practice with a view to reducing the burden of long-term complications, both microvascular and macrovascular. The Framework also aims to provide adults with or at risk of developing Type 2 diabetes with a reference for better self-management and proactive disease control.

The Framework has adopted the levels of evidence and grades of recommendations proposed by the Scottish Intercollegiate Guidelines Network (SIGN). In general, grade A recommendation is supported by level 1 evidence, whilst levels 2 and 3 evidence are considered as fair evidence.

## Chapter 6. Component 1: Prevention Of Type 2 Diabetes- Adoption Of A Healthy Lifestyle And Management Of Obesity

There are two complementary approaches to reducing the incidence of Type 2 diabetes in the population:

- The “Population approach” aims to reduce the risks across the entire population and to address the causes of chronic diseases. A small shift in the average population levels of several risk factors can lead to a large reduction in the chronic disease burden<sup>17,18</sup>.
- The “Individual-based/high-risk” approach for interventions on higher risk individuals (e.g. people with obesity or predisposing conditions, older people) has also been shown to be effective in reducing the incidence of diabetes, delaying disease onset and reducing complications<sup>19,20</sup>.

### Recommendations

**Implement interventions to reduce overweight and obesity at all stages of life to reduce future risk of diabetes.**

A

**Advise individuals at increased risk of developing Type 2 diabetes and patients with impaired glucose tolerance to maintain optimal body weight and practise healthy lifestyles.**

A

### Supporting evidence

- |   |     |
|---|-----|
| ● Overweight, general <sup>1</sup> and central obesity <sup>2</sup> are associated with increased risk of Type 2 diabetes, and interventions that affect the lifestyles of subjects at high risk of diabetes would reduce future incidence of diabetes <sup>20</sup> .  | 1++ |
| ● By changing lifestyle such as eating a balanced diet, and increasing the physical activity level, Type 2 diabetic patients in general can improve their glucose control, serum cholesterol levels and lead to a reduction in weight <sup>21,22</sup> .  | 1+  |
| ● The overall prevalence of Type 2 diabetes in the population can be reduced by lifestyle interventions targeting persons with pre-diabetes. Lifestyle interventions using dietary, or behavioral interventions produced significant weight loss among persons with pre-diabetes and a significant decrease in diabetes incidence <sup>23</sup> . | 1+  |
| ● The frequency and intensity of physical activity is inversely associated with the incidence of diabetes <sup>24,25,26</sup> .   | 1+  |

<sup>1</sup> According to the BMI classification for Chinese adults adopted by the Department of Health, overweight is defined as BMI from 23.0 kg/m<sup>2</sup> to less than 25.0 kg/m<sup>2</sup>, while obesity is defined as BMI 25.0 kg/m<sup>2</sup> or above.

<sup>2</sup> Central obesity is defined as waist circumference  $\geq 90$  cm and  $\geq 80$  cm in male and female respectively for the Chinese population.

## Chapter 7. Component 2: Early Identification Of People With Diabetes - Risk-based Screening For Type 2 Diabetes In General Population

Increased awareness of the symptoms and signs of diabetes can result in the earlier identification of people with diabetes. Primary care practitioners are also in an opportune position to adopt a risk-based approach to screen for diabetes using simple tests such as fasting plasma glucose. (Module 2)

### Recommendations

**Test individuals known to be at high risk of developing diabetes.** B

Supporting evidence

- The increase in prevalence and significant public health burden of diabetes make the test of identification of pre-diabetes and diabetes appropriate<sup>27,28,29</sup>. 2++
- Early detection of pre-diabetes and diabetes and effective interventions will prevent progression of pre-diabetes to diabetes and reduce the risk of complications of diabetes<sup>28b,30</sup>. 2++

## **Chapter 8.      Component 3: Clinical Care Of Adults With Diabetes**

Effective treatment of Type 2 diabetes can prevent or delay many of its complications. Apart from medications often needed to control blood glucose, blood pressure and blood lipids, successful management of Type 2 diabetes hinges on patients' commitment and proactive participation in self-management. The latter includes adherence to a healthy lifestyle, maintenance of optimal body weight, weight reduction if obese, and regular monitoring of blood glucose.

### **8.1      Initial assessment of adults with newly diagnosed diabetes**

Upon diagnosis of diabetes, primary care practitioners should:

- perform comprehensive assessment to detect risk factors and the presence of diabetic complications,
- review previous treatment and glycaemic control for patients with established diabetes,
- determine whether they need to be referred to a hospital/specialist service (Table 1),
- assess psychosocial aspect and need for carer support, and
- assess lifestyle behaviours including smoking habit.

Table 1. Referral to Hospital/ Specialist Service

<b>Immediate referral to hospital/ initiation of insulin therapy</b> <sup>31</sup>
(a) Who are acutely ill
(b) Who have heavy ketonuria
(c) Who have a blood glucose level $\geq 25.0$ mmol/L
(d) Who present with diabetic ketoacidosis (DKA)
(e) Who present with diabetic hyperosmolar non-ketotic syndrome (HONK)
<b>Referral to specialist</b>
(a) Young patients (age < 30 years) with diabetes
(b) Patients with features suggestive of endocrinopathies e.g. Cushing syndrome
(c) Heavy proteinuria or presence of haematuria in the absence of other complications
(d) Presence of complications
(e) Women who are pregnant

## 8.2 Initial treatment of adults with diabetes

The aim of the treatment is to treat not only hyperglycaemia but the concomitant cardiovascular risk factors including hypertension, dyslipidaemia, obesity and albuminuria. The targets of treatment are summarised at Appendix 1.

### 8.2.1 Lifestyle interventions

Adoption of a healthy lifestyle (i.e. healthy eating, regular physical activity, and abstain from smoking) is an important aspect of the management of diabetes.



**8.2.1.1 Healthy eating****Recommendations**

**Advise all patients on maintaining optimal body weight (or reducing body weight if overweight/ obese) and adopting healthy eating habit.**

**A**

## Supporting evidence

- Healthy eating is of fundamental importance as part of diabetes healthcare behaviour and has beneficial effects on weight, metabolic control and general well-being. Decrease in fasting plasma glucose is determined more by the restriction of energy intake than by the body weight<sup>32,33</sup>.
- Patients should follow a diet with balanced nutrition in accordance with the principles regarding intake of fat, carbohydrate, protein, alcohol and salt set out in Module 3.

1+

4

**8.2.1.2 Physical activity****Recommendations**

**Advise people with diabetes to increase level of physical activity and take up regular exercises. (Module 4)**

**B**

## Supporting evidence

- Regular physical activity significantly improves glycaemic control and reduces visceral adipose tissue and plasma triglycerides, but not plasma cholesterol in people with Type 2 diabetes, even without weight loss<sup>34</sup>.

2++

### **8.2.1.3 Smoking cessation**

#### **Recommendations**

**Advise all patients not to smoke.**

**A**

**Include smoking cessation counselling and other forms of treatment as a routine component of diabetes care.**

**B**

#### Supporting evidence

- Smoking is an independent risk factor for cardiovascular disease in diabetic patients<sup>35,36</sup>. 2++
- Simple advice to stop smoking given by a physician or a nurse was shown to be effective in helping patients quit smoking<sup>37,38,39</sup>. 1++

If assistance is needed, please refer to Appendix 2 for more information on smoking cessation services.

For details regarding the practical approach to help patients quit smoking, please refer to the Module on Smoking Cessation in Primary Care Settings available at [https://www.healthbureau.gov.hk/pho/rfs/english/pdf\\_viewer.html?file=download14&title=string28&titletext=string13&htmltext=string13&resources=13\\_en\\_Module\\_on\\_Smoking\\_Cessation](https://www.healthbureau.gov.hk/pho/rfs/english/pdf_viewer.html?file=download14&title=string28&titletext=string13&htmltext=string13&resources=13_en_Module_on_Smoking_Cessation)

## 8.2.2 Glucose control

### Recommendations

**Achieve optimal blood glucose control in all diabetic patients and to reduce microvascular and macrovascular complications.**

**A**

#### Supporting evidence

- Major clinical trials have shown that early implementation of aggressive glycaemic control is effective in reducing both microvascular complications as well as long-term cardiovascular risk<sup>40,41</sup>. 1+
- HbA1c goal of <7% is in adults without significant hypoglycemia.<sup>8c</sup> Even lower A1c values (say around 6.5%) can be considered for selected younger individuals with short history of diabetes and no significant cardiovascular disease, if achievable with a simple drug regimen and without significant risk of hypoglycaemia or adverse effect of treatment. A more lenient A1c target of 7 – 8.5% is more appropriate for those patients with limited life expectancy, functional impairment or significant comorbidities, older or frail patients.<sup>8d,42,43,44</sup> (Module 5) 1+
- HbA1c should be used as an indicator for blood glucose control<sup>45</sup> and the use of fructosamine as a routine substitute for HbA1c is not recommended<sup>46</sup>. 4,  
1-
- The selection of specific anti-diabetic agents is predicated on their effectiveness in lowering glucose, and extraglycaemic effects that may reduce long-term complications, safety profiles, tolerability, and expenses. (Module 6) 4
- Due to the heterogeneity of diabetic patients in terms of complications and risk factors, the treatment goal should be individualized to optimize risk-benefit ratio. 4

### 8.2.3 Self-monitoring of blood glucose

#### Recommendations

**Recommend self-monitoring of blood glucose (SMBG) to patients with type 2 diabetes who are using insulin and have been educated in appropriate alterations in insulin dose or who are at increased risk of hypoglycaemia.**

**B**

#### Supporting evidence

- Specific subgroup of patients including those who are using insulin and have been educated in appropriate alterations in insulin dose or who are at increased risk of hypoglycaemia may benefit from self-monitoring of blood glucose<sup>47</sup>.

1++

For non-insulin treated patients, the International Diabetes Federation Guideline on Self-Monitoring of Blood Glucose recommends that ‘*SMBG protocols (intensity and frequency) should be individualized to address each individual’s specific educational/ behavioural/ clinical requirements (to identify/prevent/ manage acute hyper- and hypoglycaemia) and provider requirements for data on glycaemic patterns and to monitor impact of therapeutic decision making*’<sup>48</sup>.

### 8.2.4 *Blood pressure control*

#### Recommendations

**The target blood pressure in people with diabetes is below 130/80 mm Hg.**

**A**

**Measure blood pressure at every routine diabetes visit.**

**A**

#### Supporting evidence

- Blood pressure lowering in people with diabetes reduces the risk of macrovascular and microvascular diseases<sup>49</sup>. 1+
- The lowering of blood pressure to below 130/80 mmHg is of significant benefit in people with diabetes<sup>50</sup>, particularly those with diabetic kidney disease. 1++
- Angiotensin-converting enzyme (ACE) inhibitors, calcium channel blockers, thiazides and  $\beta$ -blockers are all effective in lowering blood pressure and reducing cardiovascular events<sup>51,52</sup>. ACE inhibitors should be considered as first line therapy in patients with albuminuria for their additional benefits on renal function. Beta-blockers are not recommended as first line therapy but may be considered if patients are intolerant to ACE inhibitors or have previous heart attacks. (Module 7) 1++

### 8.2.5 *Control of lipid*

#### **Recommendations**

**Use lipid modifying drug treatment to control dyslipidemia in diabetic patients.**

**A**

#### Supporting evidence

- Lipid-lowering therapy in particular statin is highly effective in preventing cardiovascular mortality and morbidity in people with diabetes<sup>53</sup>. (Module 8)

**1+**

### 8.2.6 *Anti-platelet agents in diabetes*

#### **Recommendations**

**Use anti-platelet agents as a secondary prevention in those with a history of cardiovascular and cerebrovascular diseases e.g. myocardial infarction, peripheral vascular disease, stroke or transient ischemic attack.**

**A**

#### Supporting evidence

- Aspirin has been recommended for secondary prevention of cardiovascular events<sup>54,55,56,57</sup>.

**1++**

### 8.3 Continuing care of adults with diabetes

- Healthcare professionals should work in partnership with people who have diabetes to support them in managing their diabetic conditions, and to achieve the best possible level of blood glucose control. The risk of hypoglycaemia should also be taken into consideration.
- Once the diabetic condition is stabilised and good blood glucose control has been established, longer-term management targets for blood glucose control, weight, diet, physical activity levels, smoking cessation, blood pressure and blood lipids level should be negotiated and established with the patients. The targets should be tailored to the individual, taking account of what is possible and safe to achieve, and should be reviewed preferably at 6-monthly intervals but no more than 1 year.<sup>8c,58,59a</sup>
- All adults with diabetes should receive continuing support, including psychological support, for the rest of their life to enable them to adjust their lifestyle.
- Glycated haemoglobin (HbA1c) should be measured regularly, at 3 to 6-monthly intervals in those whose control is suboptimal, and preferably at 6-monthly intervals but no more than 1 year in those who have stable control.<sup>8c,58,59a</sup> In general, a value over treatment target calls for additional treatment (Table 2).

Table 2. HbA1c Treatment Target for Patients with Different Profile<sup>8c,59b</sup>

Patient profile	Treatment target
Adults without significant hypoglycemia	<7.0%
Patients with limited life expectancy, functional impairment or significant comorbidities, older or frail patients	7.0 – 8.5%

- All adults with diabetes should receive regular surveillance for and management of cardiovascular risk factors. This should take place at least annually in adults with Type 2 diabetes. This assessment should include:
  - calculation of body mass index (BMI) and, ideally, measurement of waist circumference (WC)
  - assessment of physical activity levels
  - dietary assessment
  - review of smoking status
  - measurement of blood pressure
  - measurement of blood lipids
- All adults with diabetes should also receive regular surveillance for the long-term complications of diabetes and for other conditions which occur more commonly in people with diabetes, such as depression. The anti-diabetic medication should also be reviewed regularly to see if adjustment of dosage is required.
- Pneumococcal vaccines and seasonal influenza vaccination are recommended for people having chronic illness such as diabetes<sup>60, 61</sup>.
- All women of childbearing age with diabetes considering motherhood should also receive continuing advice about the importance of planning their pregnancy and optimising their blood glucose control before they become pregnant. This will include the provision of advice on contraception.

#### **8.4 Detection and treatment of long-term complications**

Given the silent nature and additive effects of closely associated risk factors (blood glucose, blood lipid and blood pressure), macrovascular (stroke, peripheral vascular disease and coronary heart disease) and microvascular complications (nephropathy, renal impairment, neuropathy and retinopathy) on future cardiovascular diseases and renal event rates, periodic assessments to detect these risk factors and complications especially in those with long disease duration, presence of comorbidities, albuminuria, reduced renal function and/or poor risk factors control are of paramount importance.



### **8.4.1 Cardiovascular disease**

Macrovascular complications, namely coronary heart disease, stroke and peripheral vascular disease, are major causes of death and complications in diabetic patients.

Primary care practitioners should conduct regular assessment to detect and prevent macrovascular diseases which include:

- check for symptoms of macrovascular diseases, e.g. chest pain, transient ischaemic attack (TIA),
- palpate peripheral pulses, and
- consider conducting ECG for patients who have cardiovascular risk factors such as hypertension, dyslipidaemia, smoking, proteinuria and renal impairment even if they are asymptomatic.

### **8.4.2 Diabetic kidney disease**

Diabetic kidney disease is the commonest cause of renal failure. Early sign of diabetic kidney disease is microalbuminuria, followed by macroalbuminuria. The latter is associated with progressive deterioration in renal function with progressive rise in serum creatinine, eventually leading to renal failure and need for dialysis and transplantation. Hence primary care practitioners should ensure diabetic patients undergo regular screening for diabetic kidney disease and receive optimal management to minimise the risk of onset and progression of diabetic kidney disease. (Module 9)

### Recommendations

**Optimise glucose and blood pressure control to reduce the risk of onset and/or slow the progression of diabetic kidney disease.**

**A**

**Check the presence of microalbuminuria and serum creatinine in all Type 2 diabetic patients, starting from diagnosis and should review annually.**

**D**

**Treat diabetic patients with microalbuminuria with ACE inhibitors or Angiotensin Receptor Blockers (ARB) to reduce the progression to diabetic kidney disease if there are no contraindications.**

**A**

### Supporting evidence

- ACE inhibitors and ARB have proven significant reduction in the risk of developing microalbuminuria in patients who have diabetes with no diabetic kidney disease and have proven survival benefit in diabetic patients with diabetic kidney disease<sup>62,63,64</sup>.

**1++**

#### **8.4.3 Diabetic eye disease**

Diabetic retinopathy is one of the leading causes of blindness among adult populations. Primary risk factors for diabetic retinopathy include longer duration of disease, suboptimal blood glucose control, elevated blood pressure and dyslipidaemia. Other risk factors include pregnancy and presence of diabetic kidney disease.

Since many of these complications can be silent but are highly preventable by control of blood glucose, blood pressure and blood lipids, primary care practitioners should ensure diabetic patients undergo regular eye screening and receive proper management to reduce the risk of their occurrence and progression. (Module 10)

## Recommendations

**Achieve optimal blood glucose and blood pressure control to reduce the risk of onset and progression of diabetic retinopathy.**

**A**

**Perform eye examination in patients with Type 2 diabetes shortly after the diagnosis of diabetes and repeat annually. Examination will be required more frequently if glycaemic and blood pressure control is suboptimal.**

**B**

**Promptly refer patients with any level of macular edema, severe Non-Proliferative Diabetic Retinopathy (NPDR), or any Proliferative Diabetic Retinopathy (PDR) to an ophthalmologist.**

**A**

## Supporting evidence

- Optimal glycaemic and blood pressure control reduce the incidence and progression of diabetic retinopathy<sup>65</sup>. 1++
- Screening for diabetic retinal disease is effective in detecting unrecognised sight-threatening retinopathy<sup>66</sup>. 2++

#### **8.4.4 Diabetic foot**

Diabetic foot problems result from complex interactions between peripheral neuropathy, peripheral arterial disease and poor foot hygiene, often compounded by foot deformities and skin lesions due to poor foot care and inappropriate footwear. The loss of sweating, imbalanced foot muscle, loss of sensation and fungal infection act in multiplicative manner increases the risk of trauma and minor injury and ultimately leads to foot ulcer and poor healing. Spontaneous closure of digital blood vessels can lead to digital infarcts followed by dry gangrene.

Education on foot care, regular foot examination and aggressive treatment of foot infection and ulceration, no matter how minor, can help to prevent lower limb amputation, which is one of the most feared complications of diabetes with prolonged hospital stay and disabilities. (Module 11)

#### **Recommendations**

**Foot care education is recommended as part of a multi-disciplinary approach in all patients with diabetes.**

**B**

**Screen all patients with diabetes for foot disease annually, and refer to specialist promptly if complication is detected.**

**D**

#### Supporting evidence

- Programmes which include education with podiatrists show a positive effect on minor foot problems<sup>67,68</sup>.
- The absence of reliable symptoms and the high prevalence of asymptomatic disease make foot screening essential<sup>69</sup>.

1+,  
2++  
4

## Chapter 9. Component 4: Patient Empowerment

Empowerment of patient requires an increase of their awareness about what they can do to prevent diseases occurrence in the first instance such as living healthier lifestyles, the need for regular health checks and also the need for self-maintenance, thereby sharing with their doctors the management of their chronic diseases such as diabetes and hypertension. The healthcare professional needs to develop a working alliance with their patients to enhance and support their capacity for self-maintenance and self-care.

### Recommendations

#### **Offer structured educational intervention and lifestyle modification to all patients.**

**D**

- The purpose of education is to equip patients with knowledge and skills in diabetic self-management and thus making them capable of decision making and controlling their own health and determinants.
- Patients with diabetes should be educated about the chronic nature of diabetes and its complications, meal planning, the importance of smoking cessation, weight control, regular exercise as well as the need for periodic assessment on a long-term basis.
- Patient education programme is effective in the management of Type 2 diabetes and in the prevention of its complication in high-risk groups through the control of blood glucose, blood pressure and lipid levels.
- Education programme should be provided by appropriately trained care team including healthcare professionals with specialist training. Family members and friends of patients should also be involved.
- Patients need to be empowered to actively engage in self-management, to make informed choices and decisions that will help achieve their personal diabetic goals as well as life goals.
- The components of self-care include: adopting and maintaining a healthy lifestyle, self-monitoring, and adherence to medication.

## Chapter 10. Future Direction

Through developing and promoting the various reference frameworks, coupled with other system changes to the service delivery model for primary care, it is hoped to bring about a paradigm shift that would put a much greater emphasis on preventive care.

The reference framework is an evolving entity that will be extended and updated over time. The key to the usefulness of this reference framework is its adaptability to local structures, environments and needs. To achieve the goal of providing preventive services most effectively requires a multidisciplinary approach with concerted effort from all the stakeholders in primary care. It also involves a system adopting a more proactive approach that comprises the whole spectrum of primary, secondary and tertiary levels of prevention. It is hoped that the reference frameworks would:

- 1) Promote the family doctor concept which emphasises continuity of care, holistic care and patient-centred care.
- 2) Put greater emphasis on prevention of diseases and illnesses.
- 3) Facilitate primary care professionals to collaborate with other professionals to provide co-ordinated services.
- 4) Achieve collaboration and interfacing of service providers in the community through an integrated system.

## Appendix 1. Treatment Target Values

	<b>Ideal Control</b>	<b>Unsatisfactory control</b>
Fasting plasma glucose (mmol/L)	4-7	≥8
HbA1c (%)	<7	≥7
Body mass index (kg/m <sup>2</sup> )	<23	≥27.5
Waist circumference <sup>a</sup> for male <sup>b</sup>	<90 cm (<36 inches) and BMI<23	≥90 cm (≥36 inches)
Waist circumference for female <sup>b</sup>	<80cm (<32 inches) and BMI<23	≥80cm (≥32 inches)
Systolic blood pressure (mm Hg)	<130	≥140
Diastolic blood pressure (mm Hg)	<80	≥90
Total cholesterol (mmol/L)	<4.5	≥6.2
HDL- cholesterol for male (mmol/L)	>1.0 <sup>c</sup>	<0.9
HDL-cholesterol for female (mmol/L)	>1.3 <sup>c</sup>	<0.9
LDL- cholesterol (mmol/L)	<2.6 (<1.8 in patients with coronary heart disease)	≥3.4
Triglyceride (mmol/L)	<1.7 <sup>c</sup>	≥2.8

a “Guide to physical measurement” issued by WHO in 2008 provides reference method for measuring waist circumference:

- » Place a tape measure around the bare abdomen, just above the hip bone
- » Be sure the tape is snug, but does not compress the skin
- » The tape should be parallel to the floor, midway between the top of the iliac crest and the lower rib margin on each side
- » The patient should relax and exhale while the measurement is made

b May not be applicable to elderly age groups

c American Diabetes Association. 10. Cardiovascular disease and risk management: Standards of Medical Care in Diabetes - 2021. Diabetes Care. 2021;44(Suppl.1):S125–S150.

## Appendix 2. Smoking Cessation Services

<b>Service</b>	<b>Organisation</b>	<b>Telephone number</b>
Integrated Smoking Cessation Hotline of the Department of Health	Department of Health	1833 183 (Press 1)
Smoking Counselling and Cessation Hotline	Hospital Authority	1833 183 (Press 3), 2300 7272
HKU Youth Quitline	The University of Hong Kong	1833 183 (Press 5), 2855 9557
Tung Wah Smoking Cessation Hotline	Tung Wah Group of Hospitals	1833 183 (Press 2), 2332 8977
Pok Oi Smoking Cessation Service using Traditional Chinese Medicine	Pok Oi Hospital	1833 183 ( Press 4 ), 2607 1222



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# Module 1 Framework for Population Approach in the Prevention and Control of Diabetes across the Life Course

Age group	Lifestyle advice	Risk assessment	Early identification	Disease management	Complication monitoring	Rehabilitation care
Antenatal	<ul style="list-style-type: none"> <li>• A balanced diet</li> <li>• Regular intake of carbohydrates</li> <li>• Lower in fat</li> <li>• Plenty of fruits and vegetables</li> <li>• Regular exercise</li> </ul>	<p>Monitor risk factors for gestational diabetes:</p> <ul style="list-style-type: none"> <li>• BMI more than 30kg/m<sup>2</sup></li> <li>• Previous macrosomic baby weighting 4.5kg or more</li> <li>• Previous gestational diabetes</li> <li>• Family history of diabetes (first degree relative with diabetes)</li> </ul>	<ul style="list-style-type: none"> <li>• Assess all women for the presence of risk factors for gestational diabetes and offer 75 gram Oral Glucose Tolerance Test (OGTT) to those with risk factors</li> </ul>	<p>In women with GDM</p> <ul style="list-style-type: none"> <li>• Joint management with experts to attain stringent glycaemic, blood pressure and lipid control</li> <li>• Advice on self care</li> <li>• Early antenatal-care</li> <li>• Performance of 75 gram OGTT and risk factor assessment 6-weeks after delivery</li> <li>• Consider regular disease surveillance in women with history of GDM</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor fetal growth</li> <li>• Obstetric complications in women with GDM</li> </ul>	
Infancy	<ul style="list-style-type: none"> <li>• Breast feeding</li> <li>• Avoid obesity</li> <li>• Adequate sleep</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor weight gain</li> </ul>				
Childhood	<ul style="list-style-type: none"> <li>• Abstain from smoking</li> <li>• Regular exercise</li> <li>• Healthy eating habit</li> <li>• Adequate sleep</li> <li>• Avoid excessive intake of sugar sweetened beverages</li> <li>• Make good use of leisure time by increasing physical activities, avoid excessive time being spent on watching TV or playing computer games</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor weight for height</li> </ul>		<p>Work closely with experts to:</p> <ul style="list-style-type: none"> <li>• improve glycaemic and risk factor control</li> <li>• advise on daily living and psychological support to child and parents</li> <li>• advise on prevention and detection of ketoacidosis</li> <li>• Monitor growth and development</li> </ul>	<ul style="list-style-type: none"> <li>• Growth and development</li> <li>• Diabetic emergencies</li> </ul>	

Age group	Lifestyle advice	Risk assessment	Early identification	Disease management	Complication monitoring	Rehabilitation care
Adulthood	<ul style="list-style-type: none"> <li>● Abstain from smoking</li> <li>● Smoking cessation for smokers</li> <li>● Healthy eating habit</li> <li>● Weight management</li> <li>● Regular exercise</li> </ul>	<ul style="list-style-type: none"> <li>● Monitor BMI</li> <li>● Monitor abdominal circumference</li> <li>● Family history of diabetes</li> <li>● History of gestational diabetes</li> <li>● Presence of other risk factors (e.g. hypertension, heart disease, stroke and smoking)</li> </ul>	<ul style="list-style-type: none"> <li>● Early identification using fasting glucose or OGTT or HbA1c is suggested for all subjects aged <math>\geq 45</math> years</li> <li>● Early identification using fasting blood glucose or OGTT or HbA1c for people of all ages and have additional risk factors for diabetes (as stated in Module 2)</li> </ul>	<ul style="list-style-type: none"> <li>● Advise on self-care including self-monitoring of blood glucose as appropriate</li> <li>● Control of risk factors including blood glucose, blood pressure, blood lipid and body weight</li> <li>● Regular assessment of complications and referral to specialist care or collaborative care as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>● Avoid hypoglycaemia</li> <li>● Manage diabetic complications (e.g. retinopathy, diabetic kidney disease, neuropathy and cardiovascular diseases) in collaboration with specialists</li> </ul>	<ul style="list-style-type: none"> <li>● Optimise patient's coping skills to manage daily the presence of diabetes and its complications. e.g. myocardial infarction, cerebrovascular disease, limb amputation, blindness, renal failure</li> <li>● Provide support to carer and loved ones</li> <li>● Adopt a multidisciplinary approach in rehabilitation</li> </ul>
Elderly	<ul style="list-style-type: none"> <li>● Abstain from smoking</li> <li>● Smoking cessation for smokers</li> <li>● Healthy eating habit</li> <li>● Weight management</li> <li>● Regular exercise</li> </ul>	<ul style="list-style-type: none"> <li>● Monitor BMI</li> <li>● Monitor abdominal circumference</li> <li>● Presence of other risk factors (e.g. hypertension, heart disease, stroke and smoking)</li> </ul>	<ul style="list-style-type: none"> <li>● Screen fasting blood glucose or OGTT or HbA1c</li> </ul>	<ul style="list-style-type: none"> <li>● Advise on self-care</li> <li>● Educate carer and provide support</li> <li>● Control of risk factors including blood glucose, blood pressure and blood lipid</li> <li>● Beware of reduced renal and liver function and increased risk of drug toxicity (e.g. metformin) and hypoglycaemia</li> </ul>	<ul style="list-style-type: none"> <li>● Avoid hypoglycaemia</li> <li>● Manage diabetic complications (e.g. retinopathy, diabetic kidney disease, neuropathy and cardiovascular diseases) in collaboration with specialists</li> </ul>	<ul style="list-style-type: none"> <li>● Optimise patient's coping skills to manage daily the presence of diabetes and its complications. e.g. myocardial infarction, cerebrovascular disease, limb amputation, blindness, renal failure</li> <li>● Provide support to carer and loved ones</li> <li>● Adopt a multidisciplinary approach in rehabilitation</li> </ul>

## Module 2 Early Identification of People with Diabetes

A lot of early cases of diabetes are totally asymptomatic. Many people with diabetes will be diagnosed only if health professionals and general public remain alert to the possibility that they may have diabetes. The symptoms and signs of diabetes are summarised in Table 1.

Table 1. Symptoms and Signs of Diabetes

<b>Symptoms</b>
<ul style="list-style-type: none"><li>● Increased thirst</li><li>● Passing a lot of urine, especially at night (may lead to bedwetting in children and incontinence in older people)</li><li>● Extreme tiredness and lethargy</li><li>● Weight loss despite increased appetite</li><li>● Genital itching</li><li>● Itchy skin rash</li><li>● Blurred vision</li><li>● Tingling, pain and numbness in feet, legs or hands</li><li>● Sore or burning mouth</li></ul>
<b>Signs</b>
<ul style="list-style-type: none"><li>● Persistent or recurrent infections, such as skin infections, oral or genital thrush, mouth ulcers and urinary tract infections</li><li>● Signs of microvascular complications, such as diabetic retinopathy detected by an optometrist during a routine eye check; foot ulcers; loss of sensation in the lower limbs; or impotence</li><li>● Signs of cardiovascular disease, such as: high blood pressure; manifestations of dyslipidaemia (abnormal blood lipids), such as xanthoma; absent foot pulses</li></ul>

Diabetes can also be identified in general population by using the risk-based approach.

Table 2. Risk-based Screening for Type 2 Diabetes in General Population<sup>1-5</sup>

Who should be screened	What should be done?	How often?
<p>1. Age <math>\geq</math> 45 years</p> <p>2. Anyone with any of the following risk factors for type 2 diabetes:</p> <ul style="list-style-type: none"> <li>➤ Family history (first-degree relatives) of diabetes</li> <li>➤ Overweight and obese subjects               <ul style="list-style-type: none"> <li>• BMI 23 to <math>&lt;25</math> kg/m<sup>2</sup> is classified as overweight and BMI <math>\geq</math> 25 kg/m<sup>2</sup> is classified as obese for Chinese adults living in Hong Kong. For most Asian adults including Chinese, central obesity is defined as waist circumference of <math>\geq</math> 90 cm for men and <math>\geq</math> 80 cm for women.</li> </ul> </li> <li>➤ Previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)</li> <li>➤ Hypertension</li> <li>➤ Metabolic syndrome</li> <li>➤ Clinical cardiovascular disease (e.g. coronary heart disease, stroke, peripheral vascular disease)</li> <li>➤ Presence of other cardiovascular risk factors (e.g. high LDL-C, low HDL or high TG, smoking, physical inactivity)</li> </ul>	<p><u>Fasting plasma glucose (FPG)</u></p> <ul style="list-style-type: none"> <li>● If FPG <math>&lt;</math> 5.6 mmol/L, diabetes is unlikely in low risk subjects</li> <li>● The diabetic range for FPG is <math>\geq</math> 7 mmol/L. For asymptomatic person, an additional HbA1c or plasma glucose test result with a value in the diabetic range is required (Note 1)</li> <li>● If FPG <math>\geq</math> 5.6 and <math>&lt;</math> 7 mmol/L, a 75 gram oral glucose tolerance test (OGTT) or HbA1c can be considered, particularly if there is high clinical suspicion of diabetes</li> </ul> <p><u>HbA1c (Note 2 and Note 3)</u></p> <ul style="list-style-type: none"> <li>● An HbA1c of 6.5% is recommended as the cut point for diagnosing diabetes. For asymptomatic person, an additional HbA1c or plasma glucose test result with a value in the diabetic range is required (Note 1)</li> <li>● A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests</li> </ul> <p><u>OGTT (Note 4 and Note 5)</u></p> <ul style="list-style-type: none"> <li>● The diabetic range for 2-hour post-load glucose level is <math>\geq</math> 11.1</li> </ul>	<p>If results are normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing, e.g. every 12 months, depending on initial results and risk status.</p>

<ul style="list-style-type: none"> <li>➤ Women with history of gestational diabetes mellitus / delivery of a macrosomic baby weighing <math>\geq 4</math> kg</li> <li>➤ Polycystic ovarian syndrome</li> <li>➤ Long term systemic steroid therapy</li> </ul>	<p>mmol/L. For asymptomatic person, an additional HbA1c or plasma glucose test result with a value in the diabetic range is required (Note 1)</p> <ul style="list-style-type: none"> <li>● OGTT may be considered when the FPG is 6.1 to 6.9 mmol/L and/or A1C is 6.0% to 6.4%. OGTT may also be considered when the FPG is 5.6 to 6.0 mmol/L and/or A1C is 5.5% to 5.9% and suspicion of type 2 diabetes or IGT is high</li> </ul>	
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Note 1 For symptomatic cases, FPG  $\geq 7$  mmol/L or random glucose  $\geq 11.1$  mmol/L confirms the diagnosis. The American Diabetes Association (ADA) and World Health Organization (WHO) have also adopted HbA1c  $\geq 6.5\%$  as a diagnostic criterion. Diagnosis of diabetes in an asymptomatic person should not be made on the basis of a single abnormal plasma glucose or HbA1c value. At least one additional HbA1c or plasma glucose test result with a value in the diabetic range is required. The diagnosis should be made by the best technology available, avoiding blood glucose monitoring metres and single-use HbA1c test kits.

Note 2 The use of HbA1c can avoid the problem of day-to-day variability of glucose values, and importantly it avoids the need for the person to fast and to have preceding dietary preparations. However, HbA1c may be affected by a variety of genetic, haematologic and illness-related factors. Some of the factors that influence HbA1c and its measurement are listed in Table 3.

Note 3 Measurement of HbA1c should be standardized and done in accredited laboratories under Hong Kong Laboratory Accreditation Scheme (HOKLAS) which can be found from the website [https://www.itc.gov.hk/en/quality/hkas/conformity\\_assessment\\_bodies/hoklas.html](https://www.itc.gov.hk/en/quality/hkas/conformity_assessment_bodies/hoklas.html).

Note 4 The OGTT should be performed as described by the WHO, using a glucose load containing the equivalent of 75 gram anhydrous glucose dissolved in water.

Note 5 The ADA and WHO have recommended the use of glycated haemoglobin (A1c) to screen and diagnose diabetes (A1c  $\geq 6.5\%$  indicating diabetes<sup>2,5</sup> and 5.7-6.4% indicating prediabetes<sup>2</sup>). While this strategy can mitigate the inconvenience, pre-analytical error and intra-individual variance of 75g OGTT, potential pitfalls can exist, for example in subjects with anaemia and haemoglobinopathy, and these can confound the result interpretations<sup>6</sup>.

Table 3. Some of the factors that influence HbA1c and its measurement\*  
(Adapted from Gallagher et al <sup>7</sup>)

<p><b>1. Erythropoiesis</b></p> <p><u>Increased HbA1c</u>: iron or vitamin B12 deficiency, decreased erythropoiesis. <u>Decreased HbA1c</u>: administration of erythropoietin, iron or vitamin B12; reticulocytosis, chronic liver disease.</p>
<p><b>2. Altered Haemoglobin</b></p> <p>Genetic or chemical alterations in haemoglobin: haemoglobinopathies, HbF, methaemoglobin, may increase or decrease HbA1c.</p>
<p><b>3. Glycation</b></p> <p><u>Increased HbA1c</u>: alcoholism, chronic renal failure, decreased intra-erythrocyte pH. <u>Decreased HbA1c</u>: aspirin, vitamin C and E, certain haemoglobinopathies, increased intra-erythrocyte pH. <u>Variable HbA1c</u>: genetic determinants.</p>
<p><b>4. Erythrocyte destruction</b></p> <p><u>Increased HbA1c</u>: increased erythrocyte life span: splenectomy. <u>Decreased HbA1c</u>: decreased erythrocyte life span: haemoglobinopathies, splenomegaly, rheumatoid arthritis or drugs such as antiretrovirals, ribavirin and dapsone.</p>
<p><b>5. Assays</b></p> <p><u>Increased HbA1c</u>: hyperbilirubinaemia, carbamylated haemoglobin, alcoholism, large doses of aspirin, chronic opiate use. <u>Decreased HbA1c</u>: hypertriglyceridaemia. <u>Variable HbA1c</u>: haemoglobinopathies.</p>

\* Some of the above interfering factors are “invisible” in certain of the available assays

The diagnostic criteria recommended by the WHO and ADA are summarised in Table 4 and Table 5 respectively for reference.

Table 4. WHO Recommendations for the Diagnostic Criteria for Diabetes and Intermediate Hyperglycaemia <sup>5,8</sup>

<b>Diabetes<sup>§</sup></b>	
Fasting plasma glucose	≥7.0mmol/L (126mg/dL)
2 hours plasma glucose*	<b>or</b> ≥11.1mmol/L (200mg/dL)
HbA1c <sup>#</sup>	<b>or</b> ≥6.5%
<b>Impaired Glucose Tolerance (IGT)</b>	
Fasting plasma glucose	<7.0mmol/L (126mg/dL)
2 hours plasma glucose*	<b>and</b> ≥7.8 mmol/L and <11.1mmol/L (140mg/dL and 200mg/dL)
<b>Impaired Fasting Glucose (IFG)</b>	
Fasting plasma glucose	6.1 to 6.9mmol/L (110mg/dL to 125mg/dL)
2 hours plasma glucose*	<b>and</b> (if measured) <7.8mmol/L (140mg/dL)

§ The diagnosis of diabetes in an asymptomatic person should not be made on the basis of a single abnormal plasma glucose or HbA1c value. At least one additional HbA1c or plasma glucose test result with a value in the diabetic range is required, either fasting, from a random sample, or from the oral glucose tolerance test (OGTT). The diagnosis should be made by the best technology available, avoiding blood glucose monitoring meters and single-use HbA1c test kits (except where this is the only option available or where there is a stringent quality assurance programme in place). It is advisable to use one test or the other but if both glucose and HbA1c are measured and both are “diagnostic” then the diagnosis is made. If one only is abnormal then a further abnormal test result, using the same method, is required to confirm the diagnosis.



- \* Venous plasma glucose 2 hours after ingestion of 75g oral glucose load. If 2 hours plasma glucose is not measured, status is uncertain as diabetes or IGT cannot be excluded.
- # HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardised to criteria aligned to the international reference values. A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests.

Table 5. ADA Diagnostic Criteria for DM<sup>2</sup>

1. Fasting plasma glucose $\geq 7.0$ mmol/L (126 mg/dL). Fasting is defined as no caloric intake for at least 8 hours.* <b>or</b>
2. 2 hours plasma glucose $\geq 11.1$ mmol/L (200 mg/dL) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 gram anhydrous glucose dissolved in water.* <b>or</b>
3. In a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis, a random plasma glucose $\geq 11.1$ mmol/L (200 mg/dL). <b>or</b>
4. HbA1c $\geq 6.5$ %. The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardised to the Diabetes Control and Complications Trial (DCCT) assay.*

- \* In the absence of unequivocal hyperglycaemia, the diagnosis of diabetes requires two abnormal test results in the diabetic range from the same sample (i.e. fasting plasma glucose and HbA1c from same sample) or in two separate test samples. If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. If two different tests (such as HbA1c and FPG) are both above the diagnostic threshold when analysed from the same sample or in two different test samples, this also confirms the diagnosis. On the other hand, if a patient has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with consideration of the possibility of HbA1c assay interference.

## Reference:

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Dietary management is important for people with Diabetes for blood glucose control and the prevention or delay of the onset of complications. Some people may have mistaken dietary management as dieting. Instead, the diet for people with diabetes is based on a balanced diet, which if coupled with the proper modifications, can be full of variety in food selections.

### **Key to Healthy Eating**

#### 1. Eat Regular Meals and Consistent Portions

Eating regular meals and consistent portions of carbohydrates at each meal and snack can help people with diabetes to maintain their blood glucose levels at more desirable levels. Excessive food intakes should be avoided as they can lead to hyperglycaemia (high blood glucose) and complications associated with elevated blood glucose levels. On the other hand, eating too little can lead to hypoglycaemia (low blood glucose) and cause harmful effects on health.

#### 2. Follow a Balanced Diet

Eating a balanced diet means selecting a variety of foods from different food groups, namely grains, vegetables, fruits, meat and beans, and dairy products every day in appropriate portions, and reducing the intakes of fat, sugar, and sodium, as recommended by the Food Pyramid.

#### 3. Eat More Fibre-Rich Foods

People with diabetes should select more fibre-rich foods according to the principle of healthy eating. Dietary fibre can be in the forms of soluble and insoluble fibre. Foods which are rich in soluble fibre include oatmeal, fruits, and dried beans; foods rich in insoluble fibre include whole wheat bread, vegetables, and fruits.

#### 4. Use Healthy Cooking Methods

Using healthy cooking methods can cut down the amount of fat, sugar, and sodium in the diet:

- Use vegetable oils, such as peanut oil, canola oil, etc. Avoid using animal fats, such as lard, butter, etc.
- Use low-fat cooking methods including blanching, steaming, stewing, baking, and stir-frying with little oil, etc. Avoid using high-fat cooking methods, such as pan-frying and deep-frying.
- Remove the fat and skin of meat and poultry prior to cooking to reduce the intake of fat.
- Reduce the use of sugary seasoning, such as honey, ketchup, etc.
- Use more natural, low-sugar and low-sodium seasonings, such as ginger, green onions, garlic, pepper powder, lemon juice, vinegar, etc.
- Avoid using a lot of cornstarch and flour, which are high in carbohydrates, in preparing sauces or gravies.

#### 5. Follow Own Meal Plan

- People with diabetes should not follow others' meal plans as different people have different nutritional needs. They should consult their doctor or dietitian concerning their own meal plan.
- Weight loss in obese people with diabetes can help to improve blood glucose control. They should follow the advice of medical professionals on portion control and exercise for weight management.
- Having diabetes doesn't have to mean eating the same food day after day. With a well designed meal plan, diabetic patients are able to try a great variety of foods and enjoy their favorites. The nutrition label which includes information on energy and nutrients in one serving of food is one of the useful tools for diabetic patients to make informed food choices and achieve a balanced diet. More information about nutrition label can be accessed to Centre for Food Safety web at [https://www.cfs.gov.hk/english/whatsnew/whatsnew\\_act/whatsnew\\_act\\_19\\_Nutrition\\_Labelling\\_Scheme.html](https://www.cfs.gov.hk/english/whatsnew/whatsnew_act/whatsnew_act_19_Nutrition_Labelling_Scheme.html)

## Meal Planning Approaches

All kinds of carbohydrates, including starch, fructose, and lactose, can affect blood glucose levels and should be evenly distributed in meals and snacks for blood glucose control. The common meal planning approaches are as follows:

### 1. Carbohydrate Exchange System

People with diabetes can incorporate different kinds of carbohydrate-rich foods into their meal plan using the “Carbohydrate Exchange System”. The system emphasizes the importance of the overall nutritional content of foods and encourages consistency in the timing and amount of the meals and snacks. There is the need to understand the concept of “exchanging foods”. The advice of dietitians can be sought on ways to use this system. The following examples and appendix show how different foods of similar carbohydrate content can be exchanged:

#### Example 1:

*If 10g of carbohydrate is eaten as snack, each of the following that contains 10 g of carbohydrate can be exchanged:*

*1 slice of wheat bread (thin cut, crust trimmed)  
= 4 soda crackers  
= 1 small fruit (e.g. 1 small orange, small pear, kiwifruit)*

#### Example 2:

*If 50g of carbohydrate is eaten for a meal, each of the following that contains 50g of carbohydrate can be exchanged:*

*1 2/3 bowl\* of rice, cooked (about 5 Tbsp)  
= 1 bowl\* of spaghetti, cooked  
= 1 baked potato, medium (about 240 g)*

*\*1 bowl = 300 ml*

The following foods are high in carbohydrates and may require the use of carbohydrate exchanges:

- Starchy Vegetables / Beans

Starchy vegetables, such as potatoes, yams, etc. and beans, such as black-eyed peas, kidney beans, green peas, etc. contain higher amount of carbohydrates than leafy vegetables. Using the carbohydrate exchange system can help to keep the intakes of carbohydrates consistent.

- Fruits

- Some people with diabetes are avoiding fruits as they worry that the fructose in them can affect their blood glucose levels. Fruits are rich in vitamins, minerals, anti-oxidants, and dietary fibre, which are essential for a balanced diet.
- Using the carbohydrate exchange system can make enjoying about 2 fruit exchanges daily possible. For example, 1 small orange can be exchanged with 1 small pear or 1 kiwifruit.

- Desserts

- Using the carbohydrate exchange system and nonnutritive sweetener when preparing desserts can help to satisfy the sweet tooth without adding any extra carbohydrates and energy to the meal plan.
- The carbohydrate exchange system can also be used when eating desserts that contain starchy ingredients, such as sweet potatoes, kidney beans, etc.

## 2. Carbohydrate Counting System

The “Carbohydrate Counting System” is another way of incorporating different kinds of carbohydrate-rich foods into the meal plan. To use this system, people with diabetes need to become familiar with the carbohydrate content of foods. The total carbohydrate allotment for the day must also be known. It is important not to lose sight of the overall nutritional quality of foods when counting the carbohydrates in foods. If no attention is paid to the overall nutritional quality of foods, the diet may end up being high in fat or sodium. People with diabetes should follow a balanced diet which is low in fat, sugar, sodium, and high in dietary fibre. The advice of dietitians can be sought on ways to use this system.

The local websites that provide practical dietary information for diabetic patients are:

Nutrient Information Inquiry at Centre for Food Safety website  
[http://www.cfs.gov.hk/tc\\_chi/nutrient/index.php](http://www.cfs.gov.hk/tc_chi/nutrient/index.php)

糖尿病人士健康生活網站

[http://dmcare.nur.cuhk.edu.hk/dm05.php?chapter=CH5\\_1](http://dmcare.nur.cuhk.edu.hk/dm05.php?chapter=CH5_1)

Hospital Authority Smart Patient Website

<http://www21.ha.org.hk/smartpatient/SPW/zh-hk/Disease-Information/Disease/?guid=c73a0386-fe66-42eb-a979-7619ac8359da>

Hospital Authority Hong Kong East Cluster Nutrition Information Website

[http://www3.ha.org.hk/dic/sdn\\_02\\_01.html](http://www3.ha.org.hk/dic/sdn_02_01.html)

## **Appendix: Food Exchange System**

The general recommendations aim to have a well balanced diet with appropriate amount of food containing carbohydrate (CHO) including grains, rhizome vegetables, fruits and dairy products.

Percentages of energy from CHO, protein and fat should be based on individual nutrition assessment, roughly 50% of total calorie intake from CHO. Large meals should be avoided and carbohydrate intake should be spread evenly over the day by eating 3 to 5 small meals a day. Meals should contain mostly complex carbohydrates with an emphasis on high-fibre foods such as vegetables, whole grain cereals and fruit. Simple sugar including sugar sweetened beverages (e.g. soft drinks, fruit juice) and snacks with high sugar content (e.g. cakes) should provide no more than 10% of total calorie intake.

The formula for CHO intake being: 1 portion of CHO exchange = 10 gram of CHO = 45 kcal. For example, if daily energy requirement is 1800 kcal, then 900 kcal should be from CHO which equals to 20 portions of CHO.



## I. 五穀類 (Grains) :

	食物	1 份份量 (1 portion)
粥 / 飯類	白飯 (Cooked Rice)	1 滿湯匙 (heaped soup spoon)
	爛飯 (Boiled rice soup) / 潮州粥 (Chiuchow style Congee)	1/3 碗 (bowl)
	白粥 (Plain congee)	1/2 碗 (bowl)
粉 / 麵類	意粉 (Spaghetti) / 通心粉 (Macaroni)	1/3 碗 (bowl)
	米粉 (Rice Noodle) / 麵 (Noodle) / 烏冬 (Udon) / 河粉 (Flat Rice Noodle)	1/5 碗 (bowl)
	蛋麵 (Egg Noodle)	1/3 碗 (bowl)
	上海麵(熟) (Cooked Shanghai Noodle)	1/4 碗 (bowl)
麵包類	方飽 (Sandwich Bread)	1/2 塊 (slice)
	生命麵包(去邊) (Crustless Garden Life Bread)	1 塊 (slice)
	麥飽(去邊) (Crustless Wheat Bread)	1/2 塊 (slice)
	豬仔飽(軟) ('Piggy' Bun)	1/3 個 (bun)
餅乾類	高纖維餅 (High Fiber Biscuit)/ 梳打餅 (Soda Biscuit) / 克力架餅 (Cracker)	2 塊 (slices)
	消化餅(低脂) (Digestive Biscuit) (Low Fat)	1 塊 (slice)
	高纖維麥餅 (Provita)	3 塊 (slices)
	馬利餅 (Marie Biscuit)	3 塊(小) / 2 塊(大) (slices)
麥皮類	麥皮(乾) (Dry Oatmeal)	2 平湯匙 (flat soup spoon)
	淡麥皮(熟) (Cooked Oatmeal)	1/2 碗 (bowl)
	粟米片 (Cornflakes)	1/2 碗 (bowl)
	全麥維 (All Bran)	3 平湯匙 (flat soup spoon)
	維他麥 (Weetabix)	1 件 (piece)
	卜卜米 (Rice Krispies)	1/2 碗 (bowl)

註：1 份五穀類食物含 10 克醣質 (1 portion of grains =10g carbohydrate)

1 碗 = 標準中型飯碗 300 毫升 (1 bowl = 300ml medium bowl)

## II. 豆類 (Beans)

食物	1 份份量 (1 portion)
栗子(大) (Chestnut – Large)	2 粒 (pieces)
蓮子 (Lotus Seed)	4 平湯匙 (flat soup spoon)
紅豆 (Red Bean) / 綠豆 (Mung Bean) / 眉豆 (Black Eyed Peas) / 赤小豆 (Semen Phaseoli)	3 平湯匙 (flat soup spoon)
青豆(熟) (Green Peas) (Cooked)	4 平湯匙 (flat soup spoon)
黑豆 (Black Bean) / 馬豆(熟) (split beans)	4 平湯匙 (flat soup spoon)
茄汁豆 (Baked beans)	4 平湯匙 (flat soup spoon)

註：1份豆類含10 克醣質 (1 portion of beans =10g carbohydrate)

## III. 高醣質蔬菜 (Rhizome Vegetables)

食物	1 份份量 (1 portion)
薯仔 (Potatoes) / 蕃薯 (Sweet Potatoes) / 芋頭 (Taro)	1 個 (雞蛋體積) (piece) (size of an egg)
慈菇 (Arrowhead)	1 個 (雞蛋體積) (piece) (size of an egg)
粟米 (Maize/Corn)	1/3 條 (piece)
粟米粒(熟) (Corn kernels)	3 平湯匙 (flat soup spoon)
蓮藕 (Lotus Root) / 紅蘿蔔 (Carrot) / 南瓜 (Pumpkin)	2 個 (雞蛋體積) (piece) (size of an egg)
馬蹄(大) (Water Chestnut - Large)	4 粒 (pieces)

註：1份高醣質蔬菜含10 克醣質 (1 portion of rhizome vegetables = 10g carbohydrate)

## IV. 奶類 (Dairy Products)

食物	1 份份量 (1 portion)
脫脂奶 (Skim Milk) / 低脂奶 (Low Fat Milk) / 鮮奶 (Fresh Milk)	1 杯 (約240毫升) (glass ~240ml)
脫脂奶粉 (Skim Milk Power) / 全脂奶粉* (Milk Power)	4 茶匙 (teaspoon)
淡奶* (Evaporated Milk)	1/3 杯 (glass) 或 6 平湯匙 (flat soup spoon)
原味低脂乳酪 (Low Fat Yogurt, Plain)	1/3 杯 (150 毫升) (glass ~150ml)
煉奶	1 湯匙 (soup spoon)
糖尿奶粉	2 殼 (scoop)

\*額外含較高脂肪 (with higher fat content)

註：1 份奶類含 12 克醣質 (1 portion of dairy product =12g of carbohydrate)

## V. 果類 (Fruits) :

食物	1 份份量 (1 portion)
橙(中) (Orange – Medium size)	1/2 個
柑(細) (Tangerine – Small size)	1 個
雪梨(中) (Pear – Medium size)	1/2 個
奇異果 (Kiwi Fruit)	1 個
蘋果(細) (Apple – Small size)	1 個
青蘋果(中) (Green Apple – Medium size)	1/2 個
啤梨(中) (Pear – Medium size)	1/2 個
西柚 (Grapefruit)	1/2 個
布祿(大)桃 (Plum - Large) / 桃駁梨 (Nectarine)	1/2 個
楊桃(13 厘米) (Starfruit – 13 cm)	1/2 個
紅柿 (Persimmon)	1/2 個
富貴柿 (Persimmon from Japan)	1/2 個
番石榴 (Guava)	1/2 個
沙田柚 (Pomelo)	2 件
菠蘿(厚 2.5 厘米) (Pineapple – 2.5cm, thick)	1 片 (slice)
芒果(中, 一邊淨肉) (Mango – Medium size, Seedless)	1/3 個
蘋果芒 (Sweet Mango)	1/6 個
香蕉 (Banana)	3 吋長 (inch) 或 1/2 條
黃帝蕉 (Emperor Banana)	1 條
大蕉 (Plantain)	1/4 條
榴槤 (Durian)	1/2 粒 (細雞蛋般體積) (size of an egg)
西梅 (Prunes)	2 粒
荔枝 (Lychee)	3 粒
提子 (Grape)	10 粒 (細) (small) 或 5 粒 (大) (large)
士多啤梨(細) (Strawberry – Small size) / 龍眼 (Longan)	8 粒
西瓜(連皮) (Water Melon with rind)	1/2 磅 (pound)
木瓜 (Papaya) / 蜜瓜 (Honeydew) / 皺皮瓜 (Cantaloupe)	1/4 磅 (pound)
哈密瓜 (Hemi Melon)	1/3 磅 (pound)
車厘子(細) (Cherry – Small size)	6 粒
火龍果 (Dragon Fruit) / 水晶梨 (Crystal Pear)	1/4 個

註：1 份水果含 10 克醣質 (1 portion of fruit = 10g of carbohydrate)

## VI. 果汁(未加糖) (Fruit juice) (without sugar additives)

食物	1 份份量 (1 portion)
鮮橙汁 (Orange Juice)	1/2 杯 (glass)
蘋果汁 (Apple Juice)	1/2 杯 (glass)
菠蘿汁 (Pineapple Juice)	1/3 杯 (glass)
西柚汁 (Grapefruit Juice)	1/2 杯 (glass)
蕃茄汁 (Tomato Juice)	1 杯 (glass)
西梅汁 (Prune Juice)	1/4 杯 (glass)
蔬菜汁 (V-8)	1 杯 (glass)

註：1 份果汁含10 克醣 (1 portion of fruit juice =10g of carbohydrate)

1 杯容量 = 240 毫升 (1 glass = 240ml)

## Reference:

1. Healthy Eating for People with Diabetes Mellitus. [Internet]. Hong Kong SAR: Elderly Health Service, Department of Health; [updated 25 Jun 2018; cited 17 May 2019]. Available from: [http://www.elderly.gov.hk/english/common\\_health\\_problems/diabetes/dmdiets.html](http://www.elderly.gov.hk/english/common_health_problems/diabetes/dmdiets.html).

## **Module 4    Recommending exercise to patients with diabetes (Adopted from Department of Health Exercise Prescription 2012 Edition)**

### **A. Effects of Exercise**

Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk, contribute to weight loss, and improve well being. Furthermore, regular exercise may prevent Type 2 Diabetes Mellitus (T2DM) in high-risk individuals. Moderate-intensity (e.g. brisk walking) to vigorous-intensity exercises of  $\geq 150$  mins per week have been proven to confer significant benefits in the prevention of T2DM onset (A risk reduction of 46 % in the Da Qing Study in mainland China, and by 58 % in the Diabetes Prevention Program in the United States.) Recent follow-up studies suggest that this risk reduction can be sustained over a prolonged period. Structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C by an average of 0.66% in people with T2DM, even with no significant change in body mass index. While higher levels of exercise intensity are associated with greater improvements in A1C and fitness, milder forms of physical activities, like yoga and tai chi, may also benefit control of blood glucose.

Progressive resistance exercise improves insulin sensitivity in older men with T2DM to the same or even greater extent as aerobic exercise. Clinical trials have provided strong evidence for the A1C-lowering value of resistance exercise in older adults with T2DM and for an additive benefit of combined aerobic and resistance exercise in adults with T2DM. Resistance exercise also enhances skeletal muscle mass and endurance, and hence may reduce the risk of fall in these elderly.

## **B. Recommendations for Exercise Prescription**

The Global Recommendations on Physical Activity for Health published by the World Health Organization in 2010 specify that adults over 18 years of age should perform at least 150 mins per week of moderate-intensity or 75 mins per week of vigorous-intensity aerobic physical activity or an equivalent combination of the two. The recommendations further suggest adults to perform muscle-strengthening activities involving all major muscle groups two or more days per week. Adults over 65 years of age are advised to follow the adult recommendations if possible or (if this is not possible) be as physically active as they are able. Studies included in the meta-analysis of effects of exercise interventions on glycaemic control had a mean number of sessions per week of 3.4, with a mean of 49 mins per session. The Diabetes Prevention Program lifestyle intervention, which involved 150 mins per week of moderate-intensity exercise, had a beneficial effect on glycaemic control in those with pre-diabetes. Therefore, it seems reasonable to recommend people with T2DM to follow the same physical activity recommendations for the general population.



The following table summarizes the exercise prescription that is recommended for patients with T2DM.

Physical Activity Profile	Recommendations*
Frequency	<ul style="list-style-type: none"> <li>• Perform moderate to vigorous aerobic exercise spread out at least 3 days during the week, with no more than two consecutive days between bouts of activity.</li> <li>• Undertake resistance exercise at least twice weekly on nonconsecutive days, but more ideally three times a week, along with regular aerobic exercise.</li> </ul>
Intensity	<ul style="list-style-type: none"> <li>• Aerobic exercise should be at least at moderate intensity (e.g. brisk walking), corresponding approximately to 40%–60% of maximal aerobic capacity (VO<sub>2</sub>max). Relatively, moderate-intensity activity could be expressed as a level of effort of 5 or 6 on a scale of 0 to 10 (where 0 is the level of effort of sitting, and 10 is maximal effort) or 50–70% of maximum heart rate.</li> <li>• Additional benefits may be gained from vigorous aerobic exercise (i.e. &gt;60% of VO<sub>2</sub>max). Relatively, vigorous-intensity activity could be expressed as a level of effort of 7 or 8 on a scale of 0 to 10 or 70–90% of maximum heart rate.</li> <li>• Resistance exercise should be moderate (&gt;50% of 1-repetition maximum, i.e. 1-RM– maximum amount of weight one can lift in a single repetition for a given exercise) or vigorous (75–80% of 1-RM) at intensity.</li> </ul>
Time	<ul style="list-style-type: none"> <li>• 20 to 60 mins per day of aerobic exercise should be performed continuously or intermittently in bouts of at least 10 mins accumulated to total 150 mins per week.</li> <li>• 3 sets of 8–10 repetitions on 8–10 exercises involving the major muscle groups may be an optimal goal for resistance exercise.</li> </ul>
Type	<ul style="list-style-type: none"> <li>• A variety of modes of aerobic exercise is recommended but any form (including brisk walking) that uses large muscle groups and causes sustained increases in heart rate (HR) is likely to be beneficial. Exercises like walking, swimming or cycling that do not impose undue stress on the feet are some appropriate choices.</li> <li>• Each session of resistance exercise should involve the major muscle groups (legs, hips, chest, back, abdomen, shoulders, and arms). According to the literature, resistance exercise programme involving a combination of bench press, leg extension, upright row, lateral pull-down, standing leg curl (ankle weights), dumbbell seated shoulder press, dumbbell seated biceps curl, dumbbell triceps kickback, and abdominal curls has been shown to improve glycaemic control in older adults with T2DM.</li> </ul>

\* Given that many patients may present with comorbidities, it may be necessary to tailor the exercise prescription accordingly.

Initial instruction and periodic supervision by a qualified exercise trainer is recommended for most persons with T2DM, particularly if they undertake resistance exercise, to ensure optimal benefits to blood glucose control, blood pressure, lipids, and cardiovascular risk and to minimize injury risk.

### **C. Rate of Progression**

Gradual progression of intensity of aerobic exercise is advisable to minimize the risk of injury, particularly if health complications are present, and to enhance compliance. Points to be taken into consideration in exercise prescription include age, ability, disease state, and individual preference of type of exercise – in general, the elderly and obese patients with T2DM take longer time for adaptation and may require slower progression, though it is advisable for the aged to be as physically active as possible.

Similarly, to avoid injury, progression of frequency and intensity of resistance exercise should occur slowly. Increases in weight or resistance are undertaken first and only once when the target number of repetitions per set can consistently be exceeded, followed by a greater number of sets and lastly by increased frequency. Early in training, each session of resistance exercise should minimally include 5–10 exercises and involve completion of 10–15 repetitions to near fatigue per set, progressing over time to heavier weights (or resistance) that can be lifted only 8–10 times. A minimum of one set of repetitions to near fatigue for each exercise, but as many as 3 to 4 sets, is recommended for optimal strength gains.

## **D. Evaluation of the diabetic patient before recommending an exercise programme**

Medical practitioners should use clinical judgment in this area. Certainly, high-risk patients should be encouraged to start with short periods of low-intensity exercise and to increase the intensity and duration slowly. Medical practitioners should assess patients for conditions that might contraindicate certain types of exercise or predispose to injury, such as uncontrolled hypertension, severe autonomic neuropathy, severe peripheral neuropathy or history of foot lesions, and unstable proliferative retinopathy as well as take into consideration patients' age and previous physical activity levels.

Exercise stress testing is not routinely recommended to detect ischaemia in asymptomatic individuals at low coronary heart disease (CHD) risk (<10 % in 10 yrs.). It is advised primarily for sedentary adults with diabetes who are at higher risk for CHD and who would like to undertake activities more intense than brisk walking, e.g. age >40, concomitant risk factors such as hypertension, microalbuminuria, etc., or presence of advanced cardiovascular or microvascular complications (e.g. retinopathy, nephropathy).

## **E. Exercise in the presence of non-optimal glycaemic control**

### 1. Hyperglycaemia.

When people with type 1 diabetes are deprived of insulin and are ketotic, exercise can worsen hyperglycaemia and ketosis; therefore, vigorous activity should be avoided in the presence of ketosis. On the other hand, T2DM subjects usually are not profoundly insulin-deficient. They do not have to postpone exercise simply because of high blood glucose (e.g.  $> 16.7$  mmol/L), as long as they feel well, and are adequately hydrated without ketosis.

### 2. Hypoglycaemia.

In individuals with T2DM performing moderate exercise, blood glucose utilization by muscles usually rises more than hepatic glucose production, and blood glucose levels tend to decline. Plasma insulin levels normally fall, however, making the risk of exercise-induced hypoglycaemia in anyone not taking insulin or insulin secretagogues very minimal, even with prolonged physical activities. In individuals taking insulin and/or insulin secretagogues (e.g. sulfonylureas like glyburide, glipizide, and glimepiride, as well as nateglinide and repaglinide), physical activity can cause hypoglycaemia if medication dose or carbohydrate consumption is not altered. For individuals on these therapies, added carbohydrate should be ingested if pre-exercise glucose levels are  $< 5.6$  mmol/L. Hypoglycaemia is rare in diabetic individuals who are not treated with insulin or insulin secretagogues, and no preventive measures for hypoglycaemia are usually advised in these cases.

## **F. Exercise in the presence of specific long-term complications of diabetes**

### **1. Retinopathy**

In the presence of proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy, vigorous aerobic or resistance exercise may be contraindicated because of the risk of triggering vitreous haemorrhage or retinal detachment.

### **2. Peripheral neuropathy**

Decreased pain sensation in the extremities results in increased risk of skin breakdown and infection and of Charcot joint destruction and this is why some prior recommendations have advised non-weight-bearing exercise for patients with severe peripheral neuropathy. Studies have shown that moderate-intensity walking may not lead to increased risk of foot ulcers or re-ulceration in those with peripheral neuropathy. Individuals with peripheral neuropathy and without acute ulceration may participate in moderate weight-bearing exercise. Comprehensive foot care including daily inspection of feet and use of proper footwear is recommended for prevention and early detection of sores or ulcers. Anyone with a foot injury or open sore should confine themselves to non-weight-bearing activities.

### **3. Autonomic neuropathy**

Autonomic neuropathy can increase the risk of exercise-induced injury or adverse events through decreased cardiac responsiveness to exercise, postural hypotension, impaired thermoregulation, impaired night vision due to impaired papillary reaction, and unpredictable carbohydrate delivery from gastroparesis predisposing to hypoglycaemia. Autonomic neuropathy is also strongly associated with cardiovascular disease in people with diabetes. People with diabetic autonomic neuropathy should be screened and receive physician approval and possibly an exercise stress test before embarking on physical activity levels more intense than usual. Exercise intensity is best prescribed using the HR reserve method with direct measurement of maximal HR.

#### 4. Albuminuria and nephropathy

Physical activity can acutely increase urinary protein excretion. However, there is no evidence that vigorous exercise increases the rate of progression of diabetic kidney disease and likely no need for any specific exercise restrictions for people with diabetic kidney disease. Exercise increases physical function and quality of life in individuals with kidney disease and may even be undertaken during dialysis sessions.

#### **Special Precautions**

- Encourage patients with T2DM to monitor their blood glucose level before and after exercise session, especially when beginning an exercise programme. This allows the patient to understand their glucose response to the particular physical activity.
- Encourage patients to keep log with the exercise intensity, duration and type. It helps them know their glucose response to the exercise sessions.
- Encourage patients to exercise with partners, especially when beginning an exercise programme until the patient know very well their glucose response to the exercise sessions.

#### **Reference:**

Recommendations for Prescribing Exercise to Patients with Diabetes. Chapter 6, The Exercise Prescription Doctor's Handbook (2012). Department of Health.

Two principal measures are available for health care providers and patients to assess the effectiveness of the management plan on glycaemic control, namely HbA1c and patient self-monitoring of blood glucose (SMBG).

### 1. HbA1c

➤ HbA1c measures glycaemic effect on haemoglobin over preceding 2-3 months and has strong predictive value for diabetes complications.

➤ HbA1c goal of <7% is in adults without significant hypoglycemia.<sup>1</sup> This target level has been shown to reduce

- microvascular<sup>2</sup> complication and
- macrovascular complication<sup>3</sup>.

A less stringent HbA1c of 7 – 8.5% target however, is more appropriate for those patients with limited life expectancy, functional impairment or significant comorbidities, older or frail patients.<sup>2,4,5,6</sup>

➤ Even lower HbA1c values (say around 6.5%) can be considered for selected younger individuals with short history of diabetes, long life expectancy, and no significant cardiovascular disease, if achievable with a simple drug regimen and without significant risk of hypoglycaemia or adverse effect of treatment. Studies show that HbA1c values closer to normal improve microvascular outcomes and reduce albuminuria<sup>2</sup>.

➤ HbA1c measured preferably half-yearly but not more than 1 year should be used as an indicator for blood glucose control<sup>1,7</sup> and the use of fructosamine as a routine substitute for HbA1c is not recommended.<sup>1,8</sup>

➤ More frequent measurements at 3 to 6-monthly intervals can be considered for those whose glycaemic control is suboptimal or during change in therapeutic regime.<sup>1</sup>

**A**  
**B**  
**C**

**B**

**D**

**D**

➤ Limitations:

- Conditions affecting red blood cell lifespan may alter HbA1c levels, for example acute or chronic blood loss, hemolysis, iron deficiency or vitamin B12 deficiency anaemia and splenectomy. Haemoglobin variants may also interfere with accurate HbA1c values.
- HbA1c is not able to give a measure of glycaemic variability or hypoglycaemia.

## 2. Self-monitoring of blood glucose (SMBG)

➤ Self monitoring of blood glucose is recommended in patients with Type 2 diabetes who are using insulin and have been educated in appropriate alterations in insulin dose or who are at increased risk of hypoglycaemia.<sup>9</sup> It helps to monitor for and prevent asymptomatic hypoglycaemia and hyperglycaemia.

**B**

➤ There is no common consensus in the use of SMBG in people with noninsulin therapies, because of inconsistent results from studies. However, the data available from randomized controlled trials suggest that SMGB is likely to be an effective self-management tool and improve glycaemic control when results are reviewed and acted upon by health care providers and/or people with diabetes to actively modify behaviour and/or adjust treatment.<sup>10,11,12,13</sup>

**B**

➤ Optimal use of SMBG requires adequate patient education given by health care professionals. Patients should be taught on the correct SMBG techniques and how to use the data to adjust food intake, exercise or pharmacological therapies. The factors affecting blood glucose results such as illness, stress, alteration of treatment regimens, food intake, exercise, problems regarding techniques of performing SMBG should be taken into account. The frequency and timing of SMBG should be addressed to the particular needs and goals of people with diabetes.<sup>1</sup> It should be individualized and negotiation is needed.



- Guideline from the International Diabetes Federation for non-insulin treated patients with type 2 diabetes recommends that low intensity SMBG should be used in early education of patients, and to be performed regularly, which can help patients understand the effects of treatment on their blood glucose levels, assist clinicians to identify post-prandial hyperglycaemia, fasting hyperglycaemia as well as asymptomatic hypoglycaemia. In addition, patients should learn to perform short-term focused SMBG, which may be useful in certain circumstances, such as when patients have symptoms of hypoglycaemia, ongoing infections, are travelling or under stress, when patients undergo adjustment of medications/nutrition/physical activity, entering new life experience, starting new jobs etc., when experiencing worsening HbA1c, or when additional information is required about nature of disease/impact of treatment, in patients who are pregnant or planning to become pregnant.<sup>10</sup>
  
- Suggested target blood glucose values<sup>14</sup>

	Target blood glucose value (mmol/L)
Preprandial/ fasting	4 - 7
Postprandial 2 hours	5 - 10

### 3. Continuous glucose monitoring (CGM)

- CGM provides immediate information about an individual's current and projected glucose level, allowing users to respond promptly to mitigate or prevent pending hypoglycemia or hyperglycemia.<sup>15</sup>
- It serves an important role in assessing the effectiveness and safety of treatment in many patients with type 1 diabetes, including prevention of hypoglycemia<sup>1</sup>, patients who are on daily multiple insulin injection, with history of asymptomatic hypoglycemia and recurrent hypoglycemia<sup>16</sup>, and in selected patients with type 2 diabetes, such as in those on intensive insulin regimens and in those on regimens associated with hypoglycemia.<sup>1</sup> However, the data on the use of CGM in type 2 diabetes patients are limited.<sup>16</sup>
- CGM devices measure the glucose content of interstitial fluid by an electrochemical enzymatic sensor inserted subcutaneously by the patient on the upper arm or abdomen and the sensor is changed every 7 to 14 days. Glucose readings are automatically transmitted to a device-specific receiver e.g. smartphone, smart watch, or other smart device.
- Many glucose meters/CGM systems provide data management features that can be downloaded onto a computer, with graphic representation of glycemic variation by time of day or over a period of weeks. Mean glucose level and time in hypoglycaemia and hyperglycaemia could be recognized and assessed glucose control of the patients.
- Contact dermatitis (both irritant and allergic) has been reported with all devices that attach to the skin.<sup>1</sup> Skin reactions should be assessed and addressed to aid in successful use of devices.<sup>17</sup>

## Reference

1. American Diabetes Association. 6. Glycemic targets: Standards of Medical Care in Diabetes - 2021. *Diabetes Care* 2021; 44(Suppl. 1):S73–S84.
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### General principles (Figure 1)

- If HbA1c<sup>a</sup> is above treatment target, consider to start metformin, early aggressive combination therapy or insulin based treatment as required in addition to lifestyle modification and self-management.
- In obese patients, avoid drugs which may cause excessive weight gain, e.g. high dose sulphonylurea, insulin or glitazone.
- Early intensive glycaemic control is critical and reduces macrovascular as well as microvascular complications in the long term.
- Treatment individualised over time to maintain an optimal balance between the benefits and risks of an intensive glucose control strategy.

### Blood glucose lowering drugs can be broadly divided into:

- Insulin sensitisers, e.g. metformin, thiazolidinediones
- Insulin secretagogues, e.g. sulphonylureas, glinides, incretin mimetics and enhancers (glucose-dependent insulin secretagogues)
- Exogenous insulin
- Drugs that modulate food absorption, e.g.  $\alpha$ -glucosidase inhibitors
- Drugs that lower glucose reabsorption by the kidneys, e.g. sodium-glucose cotransporter 2 inhibitors

### Choice of blood glucose lowering drugs should be based on

- Knowledge of the underlying pathophysiology and comorbidities
- Degree of hyperglycaemia: metformin and sulphonylureas are more effective in lowering blood glucose in general
- Risk of hypoglycaemia: high dose sulphonylureas should be avoided in patients at risk of hypoglycaemia, e.g. elderly, alcoholics, patients with renal or liver disease

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<sup>a</sup> Haemoglobin A1c (HbA1c) is a minor component of haemoglobin to which glucose is bound. HbA1c is also referred to as glycated haemoglobin. HbA1c levels depend on the blood glucose concentration. That is, the higher the blood glucose concentration, the higher the level of HbA1c. Levels of HbA1c are not influenced by daily fluctuations in blood glucose concentration but reflect the average glucose levels in the past 8 to 12 weeks. HbA1c is a useful indicator of glycaemic control and reflects the summation of fasting and post-prandial blood glucose. It is a gold standard used to monitor the effects of diet, exercise, and drug therapy in diabetic patients. In the absence of confounding factors (e.g. anaemia and haemoglobinopathy), 6% of HbA1c correlates to mean plasma glucose of 7 mmol/L while 12% of HbA1c correlates to mean plasma glucose of 16.5 mmol/L.

- Side effect profile: e.g. metformin is contraindicated in patients at risk of lactic acidosis due to reduced clearance (e.g. avoid metformin for patient with eGFR <30 ml/min/1.73m<sup>2</sup> or liver failure) or increased production of lactic acid due to hypoxia (e.g. severe heart failure or lung disease)
- Most of these drug classes have similar efficacy with greater reduction in patients with high HbA1c. In general, combination drug therapy within the same drug class is not preferred.
- Other considerations: e.g. impact on weight, patient preference and cost.

## **Dosage, efficacy and side effects of commonly used oral blood glucose lowering drugs<sup>1</sup> (Table 1)**

### **Metformin**

Metformin reduces blood glucose mainly by reducing hepatic glucose production and promoting peripheral glucose uptake. Available formulations include 250mg, 500mg, 850mg, and 1000mg tablets; 500mg, 750mg and 1000mg (extended release form) and 500mg per 5ml (liquid form). Metformin should be taken with meals and initiated at a low dose, typically 500 mg once or twice daily, in order to minimise gastrointestinal side effects<sup>2</sup>. The dose should be increased gradually to the full maximum effective dose of 1500-2000mg per day (in 2 to 3 divided doses).<sup>3</sup>

**Efficacy:** Unless contraindicated, metformin is now considered the first-line therapy along with dietary and exercise therapy. It reduces HbA1c by about 1%<sup>4</sup>. In the United Kingdom Prospective Diabetes Study (UKPDS), metformin and sulphonylurea therapy were the drugs used in the intensive treatment arm and confirmed to reduce all diabetes-related endpoint (nonfatal myocardial infarction, angina, heart failure, stroke, renal failure, amputation, vitreous haemorrhage, retinopathy, blindness, or cataract) by 21%. In obese subjects, metformin-based monotherapy reduced cardiovascular events compared to patients treated with lifestyle modification alone<sup>5</sup>. Metformin therapy is associated with some weight loss<sup>6,7,8</sup> or no weight gain which may confer additional benefits in overweight/obese subjects<sup>9</sup>.

**Adverse effects:** The most common side effect is gastrointestinal disturbances ranging from 5% to 20%, including nausea, abdominal discomfort and diarrhoea<sup>10,11</sup>. Metallic taste and decreased vitamin B12 absorption have also been reported. The possibility of vitamin B12 deficiency should be borne in mind for patients receiving high dose metformin therapy (e.g. >1.5 gram daily) on a prolonged period<sup>12</sup>. Lactic acidosis is very rare (0.4 cases /10,000 treatment years)<sup>13</sup> in the absence of risk factors or contraindications.

Contraindications: Renal insufficiency (metformin should not be used in patients with an eGFR  $<30$  ml/min/1.73m<sup>2</sup>.<sup>14</sup> Initiation of metformin in patients with an eGFR between 30 and  $<45$  ml/min/1.73m<sup>2</sup> is not recommended. For those with eGFR falls between 30 and  $<45$  ml/min/1.73m<sup>2</sup> during therapy, the benefits and risks of continuing therapy should be considered, and the dosage is suggested to be reduced to maximum 1 g/day with more cautious monitoring of renal function if metformin is continued<sup>15</sup>.), acute congestive heart failure, previous history of lactic acidosis or metabolic acidosis, impaired hepatic function, alcoholism, states with reduced peripheral circulation (e.g. dehydration) or severe infections<sup>16</sup>. It should be used with care in the elderly who often have reduced organ function<sup>17</sup>. Iodinated X-ray contrast media are not an independent risk factor for patients taking metformin, but patients who develop post-contrast acute kidney injury (AKI) while taking metformin may be susceptible to the development of lactic acidosis<sup>18</sup>. However, there are variable recommendations for patients receiving metformin and iodinated contrast imaging. For example, the metformin package insert approved by the U.S. Food and Drug Administration (FDA) stated that metformin should be discontinued at the time of or before an iodinated contrast imaging procedure in patients with an eGFR between 30 and 60 ml/min/1.73m<sup>2</sup>; in patients with a history of liver disease, alcoholism, or heart failure; or in patients who will be administered intra-arterial iodinated contrast. eGFR should be re-evaluated 48 hours after the investigation and metformin can be restarted if renal function is stable<sup>16</sup>. On the other hand, the American College of Radiology guidelines recommend that in patients with no evidence of AKI and with eGFR  $\geq 30$  ml/min/1.73m<sup>2</sup>, there is no need to discontinue metformin either prior to or following the intravenous administration of iodinated contrast media, nor is there an obligatory need to reassess the patient's renal function following the test or procedure. In patients taking metformin who are known to have acute kidney injury or severe chronic kidney disease (eGFR  $<30$  ml/min/1.73m<sup>2</sup>), or are undergoing arterial catheter studies that might result in emboli (atheromatous or other) to the renal arteries, metformin should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstated only after renal function has been re-evaluated and found to be normal<sup>18</sup>.

### **Sulphonylureas**

These drugs block potassium channels in the beta cells and enhance insulin secretion. It can be used in either monotherapy or combination therapy with other oral drugs. Once daily dosage is appropriate for most formulations whilst glibenclamide and glipizide can be given twice daily if needed. They are effective within 24 hours of initiation and reach a steady state after 1-2 weeks of therapy<sup>1</sup>. Due to the long duration of action of its metabolite, high dose glibenclamide should be avoided.

**Efficacy:** A decrease of 0.7-1.3% in HbA1c is expected<sup>4</sup>. Failure of monotherapy with sulphonylurea occurs at a rate of 5-7% annually. After 10 years of treatment, most patients require additional treatment to achieve glycaemic control<sup>19</sup>. All agents in this class have similar efficacy at equivalent doses<sup>20</sup>.

**Adverse effects:** Hypoglycaemia is the most common side effect. There is no evidence that this class of drugs worsens cardiac ischemia. Sulphonylurea and metformin were the two oral blood glucose lowering drugs used in the intensive treatment arm of the UKPDS<sup>21</sup>. After ten years of treatment, there was 0.9% difference in HbA1c between the intensive (7%) and conventional treatment group (7.9%). While intensive treatment was associated with 25% reduction in microvascular complications ( $p = 0.001$ ), the 16% risk reduction for cardiovascular events fell short of significance ( $p = 0.052$ ). However, 10 years after completion of the UKPDS, the benefits of attaining glycaemic control became evident for cardiovascular diseases with a relative risk reduction of 15% ( $p = 0.01$ )<sup>22</sup>. Mild weight gain is also commonly observed.

**Contraindications:** The drug should be used with caution in elderly patients (>80 years) and patients with liver or renal insufficiency.

### **Thiazolidinediones (TZD)**

This class of drug promotes differentiation of preadipocytes to adipocytes, reduces circulating fatty acids, shifts ectopic fat to subcutaneous fat, enhances peripheral glucose uptake and reduces insulin resistance. Pioglitazone is available in 15mg, 30mg and 45mg tablets. It could be used as monotherapy or in combination with other blood glucose lowering drugs.

**Efficacy:** HbA1c can be lowered by 0.8 to 0.9%<sup>4</sup>. It has better durability of glycaemic control<sup>23</sup> but lower efficacy in reducing blood glucose compared with sulphonylureas or metformin. Pioglitazone has been shown to reduce cardiovascular end points and hepatic steatohepatitis, but without conclusive evidence for benefit<sup>14</sup>.



Adverse effects: Fluid retention causing peripheral oedema, congestive heart failure and weight gain are common adverse effects of TZD. Long term studies have demonstrated the increased risk of heart failure. There is a small increased risk of bladder cancer associated with pioglitazone use. It is not clear if the risk increases early in treatment or only after prolonged administration<sup>24</sup>. Severe hepatic toxicity has occasionally been reported in patients taking TZD. It is recommended to measure liver function tests before initiating therapy and promptly in any patient who reports symptoms of liver injury (fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice). Therapy with TZD should not be initiated if the patient exhibits clinical evidence of active liver disease or increased serum transaminase levels (ALT >2.5X upper limit of normal at start of therapy). If the patient is found to have serum alanine aminotransferase (ALT) greater than 3 times the upper limit of the reference range during therapy, the medication should be interrupted and investigation should be done to establish the probable cause. It should not be restarted in these patients if no other cause of the abnormal liver function tests is identified<sup>25,26</sup>. Macular oedema has been reported in postmarketing experience in diabetic patients who were taking TZD. Some patients presented with blurred vision or decreased visual acuity, and most had peripheral oedema at the time macular oedema. Patients should be seen by an ophthalmologist if any visual symptoms arise during therapy and all diabetic patients should have regular ophthalmologic exams<sup>25,26</sup>. There is an increased incidence of bone fractures, particularly in females, treated with TZD. The majority of fractures occurred in hand, upper arm, or foot<sup>25,26</sup>.

Contraindications: History of congestive heart failure, history of bladder cancer or in patients with uninvestigated visible blood in the urine<sup>24</sup>, established or high risk of osteoporosis, and caution to be exercised if used together with insulin.

### **Dipeptidyl peptidase 4 – inhibitors (DPP4-I)**

This class of drugs inhibits the breakdown of glucagon-like peptide 1 (GLP-1) which is an incretin hormone produced by the L cells of the distal small intestine after food intake and gastric inhibitory polypeptide (GIP), produced by the K cells at the proximal small intestine. These gut hormones potentiate glucose-stimulated insulin secretion during meal time and also inhibit glucagon secretion, retard gastric emptying, and reduce appetite. By inhibiting the degradation of incretins, DPP4-I have weight neutral effect and low risk of hypoglycaemia. Examples of currently available DPP4-I in Hong Kong include sitagliptin, vildagliptin, linagliptin, alogliptin and saxagliptin.

**Efficacy:** This class of oral medications lowers HbA1c by 0.5-0.7%<sup>4</sup>. The drugs can be used as monotherapy or in combination with other oral blood glucose lowering drugs<sup>27,28</sup>.

**Adverse effects:** DPP4-I are usually well-tolerated. The risk of hypoglycaemia is low as the drug effect is mediated through glucose-dependent insulin secretion. Headache and nasopharyngitis occur in 1-2% patients. There are rare cases of pancreatitis associated with DPP4-I. Severe and disabling arthralgia has been reported infrequently with the use of DPP4-I. The time to onset of joint pain following initiation of drug therapy varied from 1 day to years<sup>29</sup>. Saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. It is recommended to consider discontinuing the medicine in patients who develop heart failure and monitor their diabetes control<sup>30</sup>. Cases of impaired liver function have been reported in patients taking vildagliptin and alogliptin<sup>31,32</sup>. Liver function tests should be performed prior to the initiation of treatment with vildagliptin and alogliptin<sup>31,32</sup>. It is recommended to monitor liver function at three-month intervals during the first year of therapy and periodically thereafter in patients taking vildagliptin<sup>31</sup>. Liver function tests should be measured promptly in patients who report symptoms of liver injury during the therapy. If an increase in aspartate aminotransferase (AST) or ALT of three times the upper limit of normal or greater persists, the medications should be discontinued<sup>35</sup>. Infrequent cases of bullous pemphigoid requiring hospitalization have been reported with DPP4-I use<sup>32-35</sup>.

### ***Incretin mimetics (GLP-1 analogues /GLP-1 receptor agonists)***

GLP-1 receptor agonists (GLP-1 RA) bind to the human GLP-1 receptors and result in glucose-dependent stimulation of insulin secretion and glucose-dependent suppression of glucagon secretion. Used alone or in combination with 1 or 2 blood glucose lowering drugs lead to substantial improvement of glycaemic control in certain individuals without significant increase in risk of hypoglycaemia. GLP-1 RA also have central nervous system effects to reduce appetite and increase the sense of satiety resulting in decreased food intake and weight loss. Examples of currently available GLP-1 RA in Hong Kong include liraglutide, dulaglutide, exenatide and lixisenatide.

**Efficacy:** HbA1c can be lowered by 1%<sup>4</sup>. GLP-1 RA have demonstrated cardioprotective effects in some clinical studies<sup>36</sup>.

**Adverse effects**<sup>37</sup>: The major side effects are gastrointestinal, with diarrhoea, nausea and vomiting which resolve or improve with time in most patients. However, GLP-1 RA should be avoided in patients with gastroparesis or inflammatory bowel disease due to their effects of slowed gastric emptying and potential exacerbation of disease. The other common adverse effect seen with GLP-1 RA is injection site reactions. Diabetic ketoacidosis has been reported in patients with type 2 diabetes on a combination of a GLP-1 RA and insulin who had doses of concomitant insulin rapidly reduced or discontinued<sup>38</sup>. Long-acting GLP-1 RA are contraindicated in patients with a personal or family history of medullary thyroid carcinoma and in patients with multiple neoplasia syndrome type 2.

### **Insulin**

Insulin therapy should be added if glycaemic target is not attained with combination of oral blood glucose lowering drugs. When once daily supplementary insulin is added, metformin can be continued with reduction in sulphonylurea dosage. Alternatively, if basal insulin or twice daily insulin regimen is initiated because of significant symptoms upon diagnosis, or unsatisfactory control despite optimised oral combination therapy, discontinuation of sulphonylurea is preferred while metformin is often continued for its complementary action in reducing insulin resistance<sup>39,40</sup>. (Refer to appendix of this Module for supplementary information on the use of insulin)

### **Alpha-glucosidase inhibitors**

This class of drugs inhibits the enzyme,  $\alpha$ -glucosidase, located at the intestinal brush border and thus slows the rate of intestinal glucose absorption with reduced excursion of post-prandial blood glucose level. They, however, have only modest effect on lowering fasting glucose. The most common side effects are gastrointestinal e.g. flatulence, soft stools, diarrhoea, abdominal distension and pain, and they are not to be used in patients with cirrhosis, severe renal insufficiency, history of malabsorption, inflammatory bowel disease or intestinal obstruction.

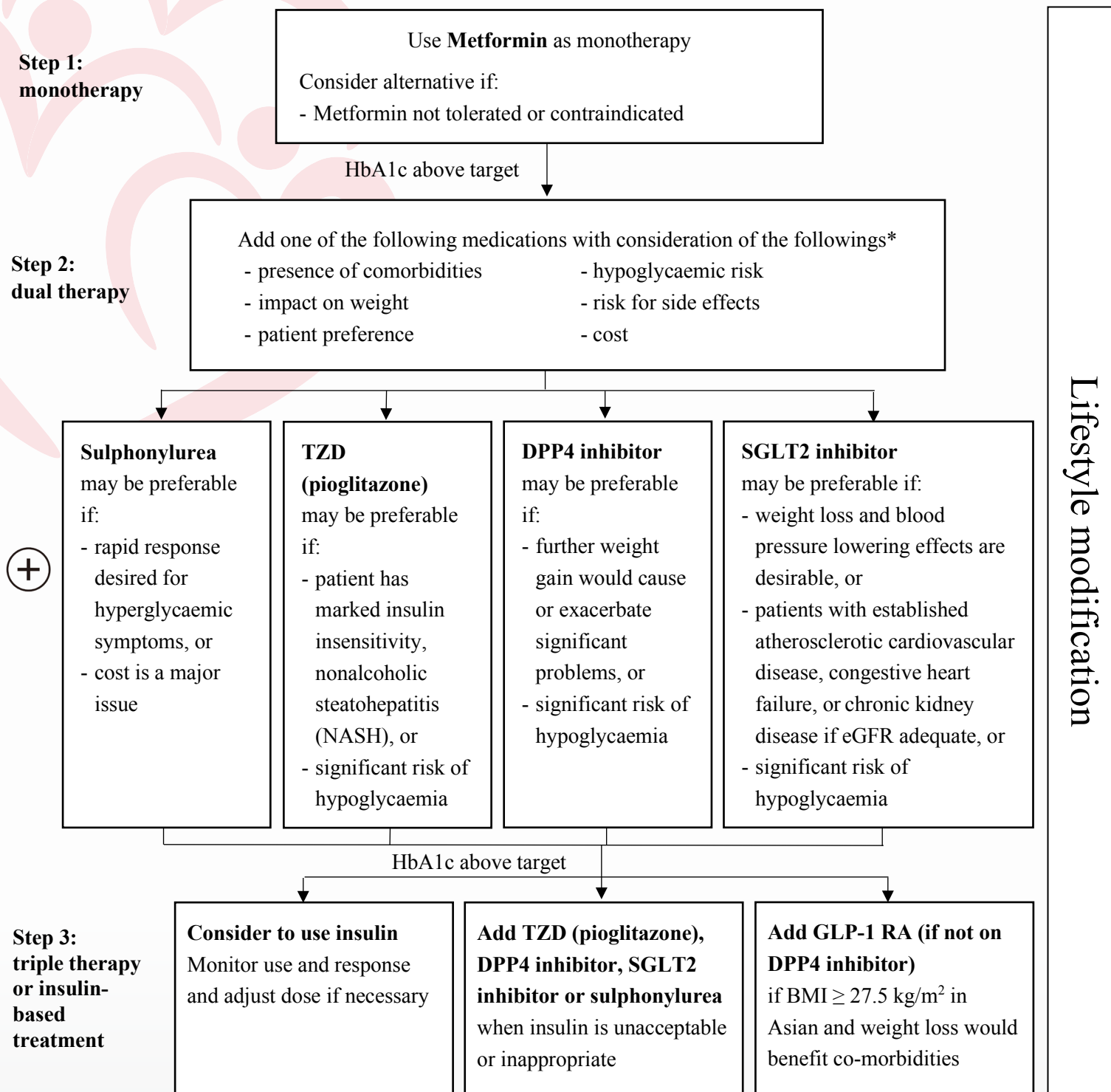
### **Sodium-glucose cotransporter 2 inhibitors (SGLT2-I)**

This class of drugs inhibit sodium glucose sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules, thus lower glucose reabsorption by the kidneys and increase glucosuria. These drugs reduce hyperglycaemia without inducing hypoglycaemia, promote weight loss (due to caloric loss and exert a modest diuretic effect with blood pressure reduction<sup>41</sup>). Examples of currently available SGLT2-I in Hong Kong include dapagliflozin, canagliflozin, empagliflozin, and ertugliflozin.

Efficacy: The efficacy is dependent on renal function. This class of oral medications has been reported to lower HbA1c by 0.4-0.7%<sup>4</sup>. A systematic review and meta-analysis of cardiovascular outcome trials showed that SGLT2 inhibitors reduced major adverse cardiovascular events by 11% with benefit only seen in patients with atherosclerotic cardiovascular disease and not in those without. They also reduced the risk of cardiovascular death or hospitalization for heart failure by 23% with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. Moreover, the risk of progression of renal disease was reduced by 45% with a similar benefit in those with and without atherosclerotic cardiovascular disease<sup>42</sup>.

Adverse effects: The risk of hypoglycaemia is low. Mild genital mycotic infections are the most common adverse events whereas the risk of urinary tract infections is only marginally increased<sup>41</sup>. Rare cases of necrotizing fasciitis of the perineum, also known as Fournier's gangrene, are reported in patients with type 2 diabetes taking SGLT2 inhibitors<sup>43</sup>. Adverse events related to volume depletion (orthostatic hypotension, acute kidney injury) are rare but may occur in fragile patients exposed to some precipitating factors<sup>41</sup>. Caution should be taken if patients have the predisposing factors to acute kidney injury which include decreased blood volume, chronic kidney insufficiency, congestive heart failure, and taking other medications such as diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and nonsteroidal anti-inflammatory drugs. Renal function should be assessed prior to initiation of SGLT2 inhibitors and monitored periodically thereafter during treatment<sup>44</sup>. Euglycemic diabetic ketoacidosis is increased with SGLT2 inhibitors, yet it remains a rare adverse event in type 2 DM patients that generally occurs in case of insulin deprivation and exposure to deleterious conditions such as post-surgery<sup>41</sup>. It is recommended to stop SGLT2 inhibitors at least 24 hours before scheduled surgery or other planned activities that might precipitate diabetic ketoacidosis, such as invasive procedures or extreme physical activity (e.g., running a marathon), and patients taking SGLT2 inhibitors should avoid excess alcohol intake and very-low-carbohydrate/ketogenic diets<sup>45</sup>. The increased risk of bone fractures and lower limb amputations was only seen with canagliflozin in CANVAS Program<sup>46</sup> but not in most other trials or observational studies with canagliflozin, dapagliflozin, and empagliflozin<sup>41,42</sup>.

Figure 1. Algorithms of drug treatment for control of hyperglycaemia



\* Refer to Table 1 and the text

(Modified from UK NICE 2015<sup>47</sup>)

**Remarks:**

- Lifestyle modification should be included in all stages of treatment
- Consider early aggressive combination therapy or insulin based treatment as required if above treatment target
- Review in 3 to 6-monthly intervals in those whose glycaemic control is suboptimal, and preferably at 6-monthly intervals but not more than 1 year in those who have stable glycaemic control.

Table 1. Mode of actions, benefits and side effects of blood glucose lowering drugs

Drugs and route of administration	Reduction in glycated haemoglobin (HbA1c in %) <sup>4</sup>	Main Mode of action	Benefits <sup>4,14,36</sup>	Side effects and limitations <sup>4,14,36</sup>
Metformin (oral)	~1	Lower production of hepatic glucose	No weight gain; reduce myocardial infarction in overweight patients; cheap	GI side effects; vitamin B12 deficiency; lactic acidosis (very rare); contraindicated with eGFR<30
Sulphonylureas (oral)	0.7-1.3	Stimulate insulin secretion	Cheap; relatively rapid blood glucose-lowering response	Hypoglycaemia, sometimes severe and of long duration; weight gain; high rate of secondary failure; renal dose adjustment required
Thiazolidinediones (oral)	0.8-0.9	Improve insulin sensitivity	Improve lipid profile and may reduce risk of CVD (pioglitazone); benefit in NASH; low risk of hypoglycaemia	Fluid retention, which can cause heart failure (rare); weight gain; risk of bone fracture; risk of bladder cancer with pioglitazone (rare); macular oedema (rare); no renal dose adjustment required but generally not recommended in renal impairment due to potential for fluid retention; expensive
$\alpha$ -glucosidase inhibitors (oral)	0.7-0.8	Retard intestinal absorption of glucose	No weight gain; low risk of hypoglycaemia	GI side effects common; multiple daily dosing required; renal dose adjustment required; expensive
Meglitinides (oral)	0.7-1.1	Stimulate insulin secretion	Short acting, less risk of hypoglycaemia compared with sulphonylureas	Multiple daily dosing with meal; weight gain; expensive
Dipeptidyl peptidase 4 inhibitors (oral)	0.5-0.7	Stimulate insulin secretion Suppress glucagon production	Low risk of hypoglycaemia; no weight gain; well tolerated	Rare potential risks of acute pancreatitis, severe joint pain, heart failure (saxagliptin and alogliptin), impaired liver function (vildagliptin and alogliptin) and bullous pemphigoid; renal dose adjustment required except linagliptin; expensive

GLP-1 receptor agonists (subcutaneous injection)	1.0	Stimulate insulin secretion Suppress glucagon production	Low risk of hypoglycaemia; promote weight loss; CV benefits in selected agents; reduce nephropathy progression with liraglutide	Experience limited; needs to be injected; GI side effects common; potential risk of thyroid C-cell tumors for long-acting GLP-1 RA; expensive
Sodium-glucose cotransporter 2 inhibitors (oral)	0.4-0.7	Lower glucose reabsorption by the kidneys	Low risk of hypoglycaemia; promote weight loss; lower blood pressure; CV benefits; renoprotective	Experience limited; genitourinary infections; DKA (rare); risk of volume depletion and hypotension; risk of bone fractures and lower limb amputations (canagliflozin); renal dose adjustment required; expensive
Subcutaneous insulin (subcutaneous injection)	0.9-1.2 or more	Stimulate peripheral glucose uptake and inhibits hepatic glucose output	Reduces severe hyperglycaemia; much experience	Weight gain; hypoglycaemia; needs to be injected; blood glucose must be monitored

GI, gastrointestinal; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; NASH, nonalcoholic steatohepatitis; MI, myocardial infarct; CV, cardiovascular; DKA, diabetic ketoacidosis

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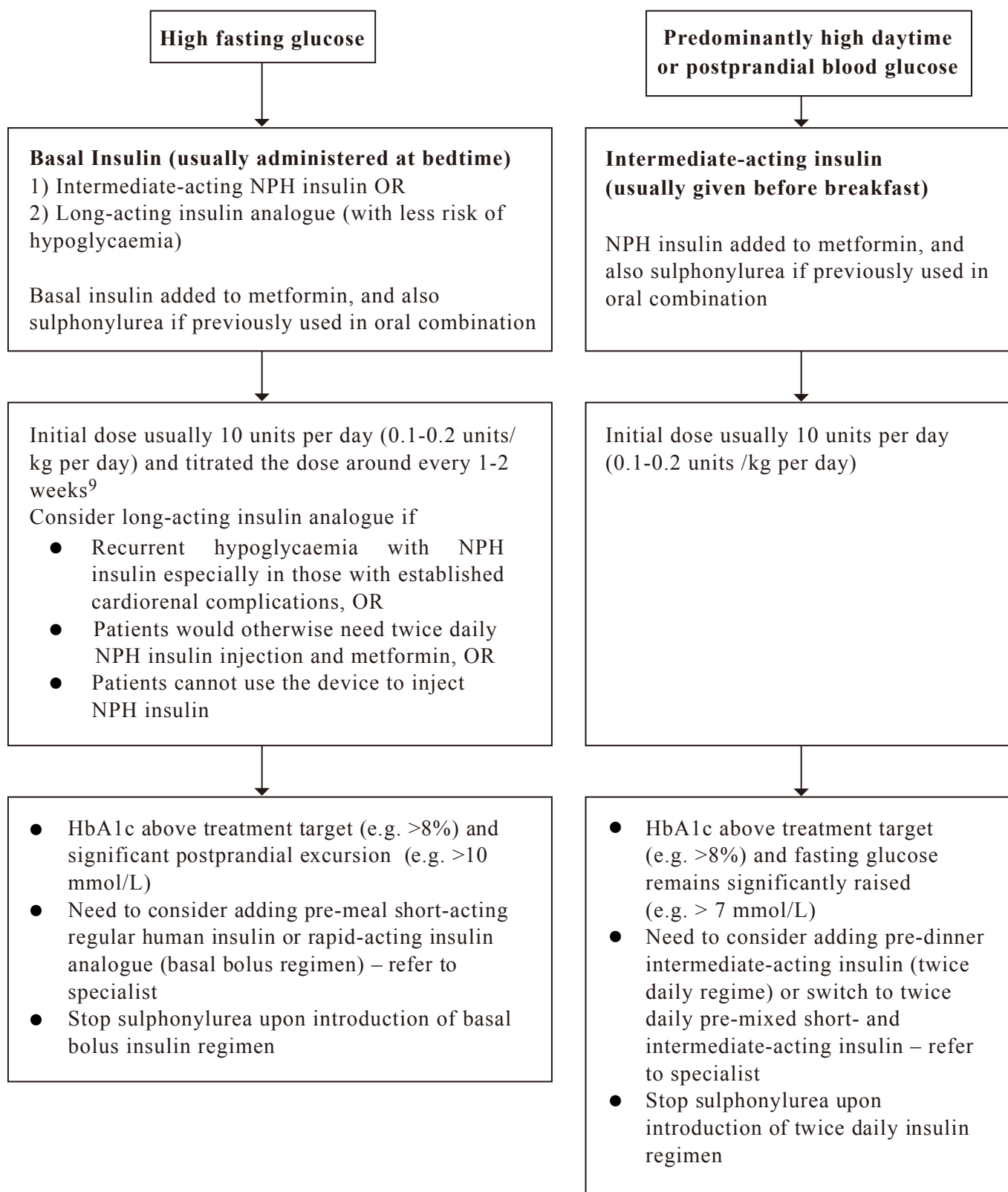


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Initiation options depend on the pattern of the patient's blood glucose levels<sup>2,8</sup>:



**Insulin Titration**

- According to latest average of 3 or more haemostix taken at specific times, be careful of hypoglycaemic value
- Titration of insulin with respective haemostix monitoring
- If total daily dose of intermediate-acting insulin exceeds 0.5 unit/kg/day, consider the need to split into twice daily regime or add short- or rapid-acting pre-meal insulin

<b>Insulin Regimen</b>	<b>Haemostix monitoring</b>
<b>Bedtime NPH or long acting</b>	Fasting
<b>Morning NPH</b>	Post breakfast; pre and post lunch; pre dinner
<b>Pre dinner NPH</b>	Fasting; post dinner; bedtime
<b>Pre meal short- or rapid-acting</b>	Post respective meal; pre next meal

Titration scale <sup>8</sup>

<b>Haemostix (mmol/L)</b>	<b>Insulin dosage (units)</b>
<4.0	-2
4.0-7.0	+0
7.1-10.0	+2
>10.0	+4

Management of oral hypoglycaemic agents upon initiation of insulin<sup>9</sup>

1. Continue with metformin
2. Avoid long acting sulphonylurea (e.g. daonil) and consider changing to a shorter acting sulphonylurea (e.g. gliclazide)
3. Gradually reduce the dose of sulphonylurea especially if high risk of hypoglycaemia
4. Consider stopping sulphonylurea if hypoglycaemia occurs or with introduction of multiple dose insulin regimen

Registered insulin products in Hong Kong can be assessed in Drug Office, Department of Health website:

[https://www.drugoffice.gov.hk/eps/do/en/healthcare\\_providers/home.html](https://www.drugoffice.gov.hk/eps/do/en/healthcare_providers/home.html)

Self-monitoring of blood glucose (SMBG) serves as an important adjunct to HbA1c because it can identify hypoglycaemia, distinguish between fasting / pre-meal and postprandial hyperglycaemia, and reveal glycaemic excursions. It also helps in adjusting medications (particularly pre-meal insulin doses), diet, and physical activity.

The optimal frequency of SMBG in type 2 DM on insulin is not clearly defined, although it has been shown that insulin-requiring type 2 DM patients who monitor at least once a day have significantly lower HbA1c values than those monitoring less than once a day and each additional monitoring per day is associated with further A1c reduction<sup>10</sup>. It is suggested in Canada that the maximum weekly frequency of SMBG for most adults with insulin-treated type 2 diabetes be up to 14 tests<sup>11</sup>.

For details of SMBG, refer to Module 5 P.2-3.

#### **Glycaemic targets**

- Fasting and pre-meal : 4-7 mmol/L
- Post meal : 5-10 mmol/L
- HbA1c < 7%

#### **Insulin Delivery**<sup>12</sup>

##### **Sites for insulin injections**

- Abdominal wall: generally fastest and most uniform rate of absorption
- Legs: slowest absorption (unless exercising), acceptable site
- Arms: not recommended

**Insulin injection devices** for subcutaneous administration include:

##### **1. Insulin syringe**

100 units, 50 units syringe

Standard needle: 8mm, 30 / 31 gauge

Short needle: 6mm 31 gauge; 5 mm 31 gauge

Insulin syringes are recommended for single use.

**2. Pen devices**

- Novopen 4 (Novo Nordisk insulins)
- Humapen (Lilly insulin)
- Solostar (Sanofi-Aventis long-acting insulin analogue)

**3. Pen needle**

- 8 or 6 mm, 30 and 31 gauge
- Short needles: 5 mm 31 gauge, 4 mm 32 gauge (latest available)
- The short (4 to 5mm) needles reduce pain and anxiety to patients and give the best outcome when injected straight into the skin at 90 degrees, without the need to pinch up skin as in the case of longer needles.

Advantages of insulin pens:

1. Easy to handle: large dose dial window and numbers make it easier for those with visual and physical disabilities (e.g. hand tremor)
2. Convenient: pen devices can be carried easily for travel
3. Multiple daily injection schedules become easier and people can be more flexible in their self management.
4. Cost-saving: the price of insulin pen needle is cheaper as compared with conventional insulin syringes

Disadvantages:

1. If the patient forgets to remove needles after use, air bubbles may get into the insulin cartridge. This may cause insulin leakage or crystal formation
2. There are more preparatory steps, and therefore the devices may not be suitable for elderly especially for those with cognitive impairment

**Subcutaneous Insulin Injection techniques:**

- Pinch up the skin fold
- Inject slowly into the subcutaneous tissue, maintain “pinch-up” throughout injection
- Inject at 45 degrees for thinner subcutaneous tissue, and 90 degrees for thicker subcutaneous tissue
- (Note: With the short 4 to 5mm needles, there is no need to pinch up skin as in the case for longer needles and injection can be done straight at 90 degrees)
- Advise the patient to press onto the injection site for ~5 seconds and avoid rubbing the injection site after withdrawing the needle

**Sharps Disposal**

Education is needed to teach patients to dispose the sharps in an approved sharps disposal container.

## **Adverse effects of insulin therapy:**

### **Hypoglycaemia <sup>12</sup>**

Insulin can cause symptomatic hypoglycaemia. Patients and their families need to be aware of the risk and be able to manage hypoglycaemia. Hypoglycaemia may arise due to excessive insulin or sulphonylurea, deficient carbohydrate intake or unaccustomed exercise. The cause needs to be identified and the episode dealt with by reinforcing education, counselling the patient and perhaps modifying treatment.

Initial management for hypoglycaemia should be by easily absorbable oral glucose or sucrose if the patient is conscious, generally amounting to 10-15 gram glucose (2-3 sugar cubes, 1/2 box fruit juice or 1/3 can of soft drink), followed by intake of additional carbohydrates (e.g. 2-3 pieces of biscuits, or 1 slice of bread) to prevent recurrence of hypoglycaemia. If the patient is unconscious, emergency call for medical assistance is required. Carers of patients on insulin and health care professionals should be familiar with the identification of hypoglycaemia and its treatment including subcutaneous glucagon administration. Glucagon 1mg should be given subcutaneously or intramuscularly. If glucagon fails to restore consciousness and a doctor is available, intravenous 50% glucose 20-30 ml can be administered. It is important to follow resuscitation with ongoing monitoring and carbohydrate intake.

### **Weight gain**

Weight gain is another common adverse effect of insulin therapy. Improved glycaemic control decreases glycosuria, thereby decreasing the loss of calories through urine, also the direct lipogenic effects on adipose tissue contribute to weight gain, which can lead to increase in insulin resistance and therefore the need to step up insulin dosage.



**Lipodystrophy**

Repeated injection into the same site can cause pitting or loss of the subcutaneous adipose tissue. This is possibly due to immune complex-mediated inflammatory reaction to insulin or its excipients. Insulin absorption at the sites of lipodystrophy may be erratic and unreliable. It is best prevented by routine rotation of insulin injection sites.

**Lipohypertrophy**

This is a fatty, tumorous thickening of the subcutaneous tissue at the site of injection occurring because the patient injects into the same site day after day, and is probably a result from the local trophic action of insulin. Again, it can be obviated by regular rotation of insulin injection site, and if developed, usually will disappear over months if injections in the area are avoided.

**Endocrinologist Referral**

- **Patients with contraindication(s) in initiating insulin**
- **HbA1c not to target but insulin cannot be stepped up due to hypoglycaemia**
- **Widely fluctuating haemostix pattern/glucose profile likely requiring multiple insulin injections**
- **Complex insulin regimen not manageable in primary care setting**
- **Total daily dose of insulin >1 unit/kg (suggestive of significant insulin resistance)**

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- Hypertension is 1.5 – 2 times more prevalent in Type 2 diabetes (prevalence up to 80 % in diabetic subjects). This exacerbates the risk of cardiovascular disease by ~ two-fold.
- Drug therapy reduces the risk of cardiovascular disease and death. The United Kingdom Prospective Diabetes Study (UKPDS) has shown an 11% decrease in risk with each 10 mmHg reduction of systolic blood pressure. In the Hypertension Optimal Treatment (HOT) study, there was a 51% reduction in cardiovascular events in diabetics with target diastolic BP <80 mmHg as compared to those with target diastolic BP < 90mm Hg<sup>1,2</sup>. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure study, aggressive blood pressure control targeting a systolic blood pressure level <120 mmHg in people with type 2 DM has not been shown to yield additional cardiovascular benefits as compared to a systolic blood pressure target of <140 mmHg. Further, adverse effects were more frequent in the intensive blood pressure lowering group<sup>3</sup>.
- Thus, the target blood pressure for patients with diabetes is recommended to be below 130/80 mmHg.
- Albuminuria is a strong predictor of all-cause mortality and cardiovascular morbidity and mortality in Type 2 diabetes. Simultaneous presence of proteinuria with hypertension potentiates the mortality risk in patients with diabetes<sup>6,7</sup>.

## Treatment of hypertension:

1. Non-pharmacological measures including smoking cessation, weight reduction, moderation of alcohol consumption, reduction in salt intake and alleviation in stress.
2. Pharmacological treatment takes into consideration the drug efficacy, safety profile/side effects, and the patient's factors including co-morbidities (Table 1 and Table 2):
  - Both Angiotensin-converting enzyme inhibitor (ACEI) and Angiotensin Receptor Blockers (ARB) have been confirmed to confer additional vascular and renoprotective effects; therefore either should be included in the anti-hypertensive regime, especially for those with diabetic kidney disease. (Hope Study<sup>8,9,10,11</sup> ).
  - Most patients with diabetes and hypertension will require two or more anti-hypertensive medications to achieve blood pressure goal.
  - In the case of refractory hypertension (poor response to treatment), watch out for unsuspected secondary causes (renal or endocrine disorders), poor drug compliance, exogenous medications, and volume overload fluid status.

**Table 1. Drug Treatment for Hypertension**

Six main drug classes of anti-hypertensive drugs are available for the initiation and maintenance of blood pressure lowering therapy, but the choice of drugs is influenced by cost and many factors as illustrated below.

<b>Class of Drug</b>	<b>Compelling Indications</b>	<b>Possible Indications</b>	<b>Compelling Contraindications</b>	<b>Possible Contraindications</b>
ACE Inhibitors (ACEI)	Heart failure, Left ventricular dysfunction, Post myocardial infarction, Diabetic kidney disease	Proteinuric renal disease	Pregnancy, Bilateral renal artery stenosis, Hyperkalaemia	Renal impairment
Angiotensin II Receptor Blockers (ARB)	ACE inhibitor intolerance		Pregnancy, Bilateral renal artery stenosis, Hyperkalaemia	Renal impairment
Beta-Blockers	Angina, Post myocardial infarction, Tachyarrhythmias	Heart failure (low dose)	Asthma, chronic obstructive pulmonary disease, Heart block	Peripheral vascular disease
Calcium Channel Blockers (dihydropyridine)	Elderly patients, Isolated systolic hypertension	Angina, Peripheral vascular disease		Congestive heart failure
Calcium Channel Blockers (rate limiting, e.g. verapamil, diltiazem)	Angina		Heart block	Congestive heart failure, combination with beta-blockers
Thiazide / thiazide-like Diuretics	Heart failure, Elderly patients, Isolated systolic hypertension		Gout	Dyslipidaemia, Pregnancy, Sexually active males

**Table 2. Possible Combination and Effects of Anti-hypertensive Therapy in Diabetes**

Combination	Specific benefits	Disadvantages
ACE inhibitor + calcium-channel blocker	Calcium-channel blocker has a neutral effect on lipid and glucose metabolism. Combination of calcium-channel blocker with ACEI or ARB is effective in the treatment of diabetic hypertension.	---
Diuretic + ACE inhibitor	ACE inhibitor prevents activation of angiotensin-aldosterone system due to diuretic-induced extracellular fluid volume contraction, and helps to retain potassium	High risk of 'first dose' hypotension with ACE inhibitor in patients over treated with diuretics
Diuretic + $\beta$ -blocker	---	Possibly aggravate hyperglycaemia in Type 2 diabetes
Diuretic + calcium-channel blocker	Diuretic reduces mild ankle swelling due to calcium-channel blocker	---
$\beta$ -blocker + calcium-channel blocker	$\beta$ -blocker counteracts tachycardia due to calcium-channel blocker's vasodilator action, Effective anti-anginal therapy	May aggravate or provoke cardiac failure (both are negative inotropes)

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### Background

Accelerated atherosclerosis is multifactorial and begins years/decades prior to the diagnosis of type 2 diabetes:

- Risk for atherosclerotic events is two to four-fold greater than in non-diabetic subject.
- Responsible for 80% of diabetic mortality. (75% due to coronary heart disease and 25% due to stroke and peripheral vascular disease).
- >75% of all hospitalisations for diabetic complications<sup>1</sup>.
- In Hong Kong one-third of patients hospitalised for stroke, myocardial infarction and coronary heart failure have diabetes<sup>2,3</sup>.
- Dyslipidaemia is a major risk factor for diabetes macrovascular complications<sup>4</sup>.
- Typical characteristics of dyslipidaemia in type 2 diabetes include hypertriglyceridaemia and low HDL-Cholesterol, the LDL-Cholesterol level is similar to that in non-diabetic<sup>5</sup>, but qualitatively more atherogenic (increased glycation, triglyceride enrichment with increased proportion of small dense LDL-Cholesterol), thus leading to accelerated atherosclerosis.

### Screening

At least annual screening of lipid profile, and more frequently if needed for treatment modification.

- Optimal treatment target of various lipid components:
  - LDL-Cholesterol (LDC-C): <2.6 mmol/L  
<1.8 mmol/L (for patients with pre-existing cardiovascular diseases)
  - HDL-Cholesterol (HDL-C): >1.0 mmol/L for male  
>1.3 mmol/L for female
  - Triglyceride (TG): <1.7 mmol/L

### Management

#### *Lifestyle modification*<sup>6,7</sup>

- Reduction of dietary fat intake
- Total fat <30% of total calorie/day
- Saturated fat <7%, cholesterol <200 mg
- Avoid any trans fat

### **Drug treatment (Table 1)**

#### **(1) Statins (HMG - CoA reductase inhibitors)<sup>8-10</sup>**

- ↓ LDL-C ≥50% if high intensity and 30-50% if moderate intensity, ↓ TG 10-20%, ↑ HDL-C 1-10%<sup>7</sup>
- 25-55% risk reduction in cardiovascular diseases (coronary heart disease, stroke) in primary and secondary prevention studies
- Practical algorithm of statin usage is illustrated in Figure 1

#### **(2) Fibrates**

- ↓ TG 50%, ↑ HDL-C ≤ 20%, ↓ LDL-C ≤ 20%<sup>7</sup>
- There is no strong evidence for using fibrate therapy in primary prevention of cardiovascular disease<sup>7,12</sup>. The use of fibrates in these patients should only be considered when statins are contraindicated.
- Combination therapy of statin and fibrate is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk of rhabdomyolysis is more common with higher doses of statins and renal insufficiency and appears to be higher when statins are combined with gemfibrozil (compared with fenofibrate)<sup>12,13</sup>. Hence, gemfibrozil should not be initiated in patients on statin therapy and fenofibrate is the preferred agent when used in combination with statin but should be used with cautions and under close monitoring.

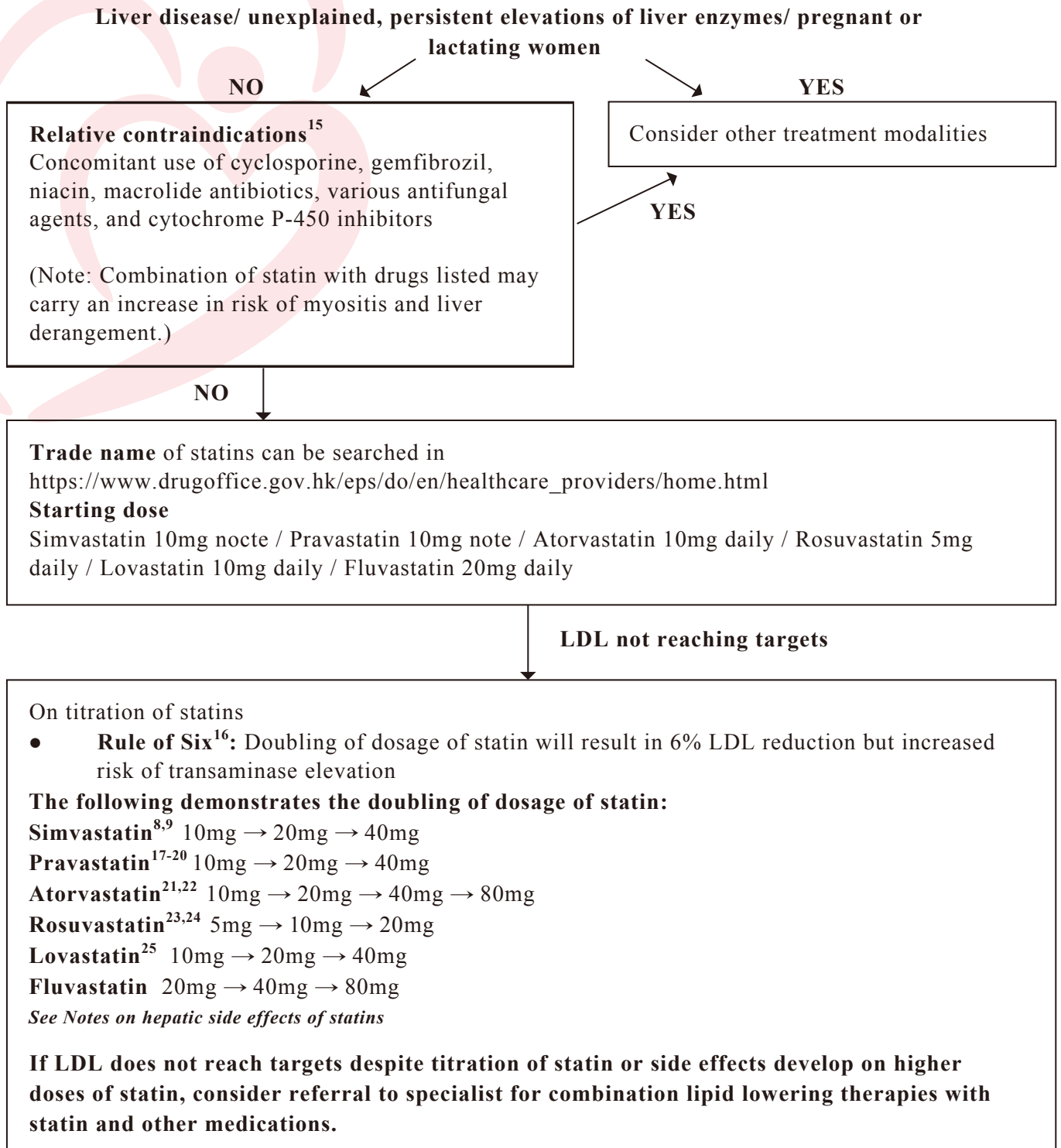
#### **(3) Ezetimibe**

- ↓ TG 8%, ↑ HDL-C 3%, ↓ LDL-C 15-22% if using ezetimibe alone. Adding ezetimibe to an ongoing statin reduces LDL-C levels by an additional 21-27%. In statin naive patients, combined therapy with ezetimibe and statin reduces LDL-C levels by around an additional 15%<sup>7</sup>.
- Can be used as an add-on drug in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose, or as an alternative to statins in patients who are intolerant of statins or with contraindications to statins<sup>7,11</sup>.
- Life-threatening liver failure with ezetimibe as monotherapy or in combination with statins is extremely rare. The addition of ezetimibe to statin therapy does not appear to increase the incidence of elevated CK levels.<sup>7</sup>

#### **(4) Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors**

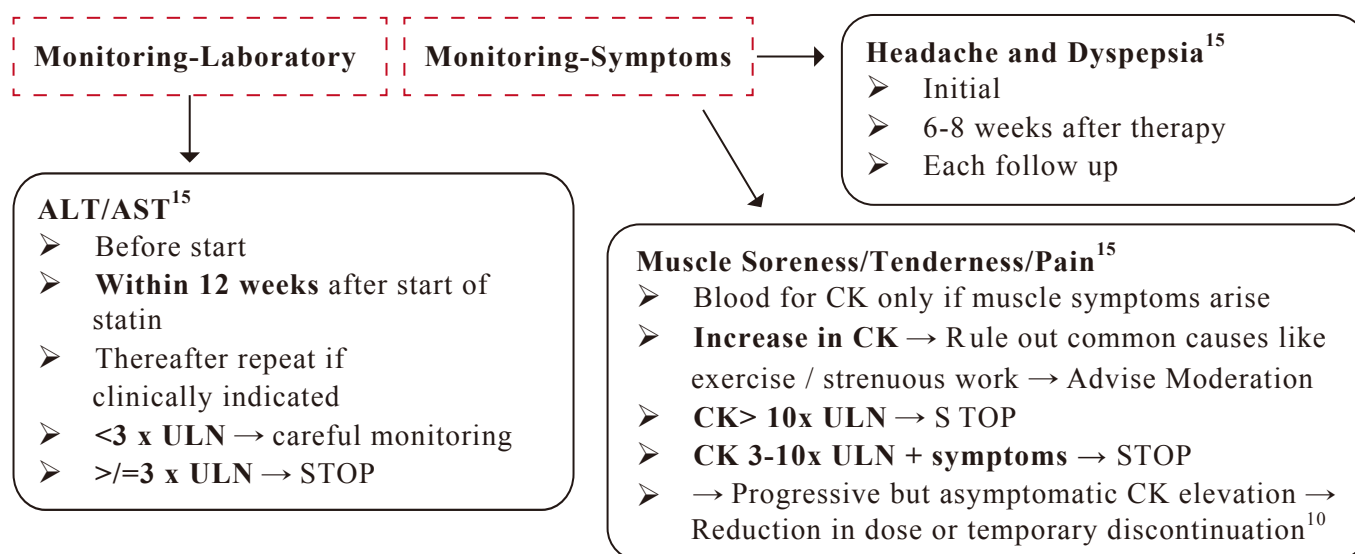
- ↓ TG 26%, ↑ HDL-C 9%, ↓ LDL-C 60%, depending on dose, largely independent of any background therapy<sup>7</sup>
- Have been approved as adjunctive therapy for patients with atherosclerotic cardiovascular disease (ASCVD) or familial hypercholesterolaemia who are receiving maximally tolerated statin therapy but require additional lowering of LDL-C<sup>12</sup>.
- Requires subcutaneous injection
- Adverse events were minimal and tolerable<sup>14</sup>. Among the most frequently reported side effects are itching at the site of injection and flu-like symptoms<sup>7</sup>.

Figure 1. Practical algorithm of statin usage



(Figure continued on next page)

Figure 1. Practical algorithm of statin usage (Continued)



**Abbreviations:**

ALT: Alanine transaminase

AST: Aspartate aminotransferase

CK: Creatine kinase

ULN: Upper limit of normal

**Notes on hepatic side effects of statin:**

- Elevated hepatic transaminase generally occurs in 0.5%-2% of cases and is dose dependent<sup>26,27</sup>, with ↑ relative risk 2 – 4 fold at higher doses of statin
- Progression to liver failure specifically due to statin is exceedingly rare if ever occurs<sup>28</sup>
- Reversal of transaminase elevation is frequently noted with a reduction in dose, and elevations do not often recur with either re-challenge or selection of another statin<sup>29,30</sup>

**Simvastatin dose limitations**

When used with simvastatin, the following medications can raise the levels of simvastatin in the body and increase the risk of myopathy. Taking no more than the recommended dose of simvastatin with these medications will help keep simvastatin levels in the body at a safer level.

<b>New simvastatin label</b>
<p>Contraindicated with simvastatin:</p> <ul style="list-style-type: none"> <li>● Itraconazole</li> <li>● Ketoconazole</li> <li>● Posaconazole (New)</li> <li>● Erythromycin</li> <li>● Clarithromycin</li> <li>● Telithromycin</li> <li>● HIV protease inhibitors</li> <li>● Nefazodone</li> <li>● Gemfibrozil</li> <li>● Cyclosporine</li> <li>● Danazol</li> </ul>
<p>Do not exceed 10 mg simvastatin daily with:</p> <ul style="list-style-type: none"> <li>● Verapamil</li> <li>● Diltiazem</li> </ul>
<p>Do not exceed 20 mg simvastatin daily with:</p> <ul style="list-style-type: none"> <li>● Amiodarone</li> <li>● Amlodipine (New)</li> <li>● Ranolazine (New)</li> </ul>
<p>Avoid large quantities of grapefruit juice (&gt;1 quart daily)</p>

FDA Drug Safety Communication: New restrictions, contraindications, and dose limitations for Zocor (simvastatin) to reduce the risk of muscle injury. 15 Dec 2011.

<http://www.fda.gov/Drugs/DrugSafety/ucm256581.htm>

Table 1. Management of diabetic dyslipidaemia<sup>12</sup>

<p>I. Lifestyle modification and glycaemic control optimisation:</p> <ul style="list-style-type: none"> <li>– Recommend lifestyle modification to improve the lipid profile and reduce the risk of developing atherosclerotic cardiovascular disease (ASCVD): <ul style="list-style-type: none"> <li>• weight loss (if indicated)</li> <li>• application of a Mediterranean diet or Dietary Approaches to Stop Hypertension (DASH) dietary pattern</li> <li>• reduction of saturated fat and trans fat</li> <li>• increase of dietary n-3 fatty acids, viscous fiber, and plant stanols/ sterols intake</li> <li>• increased physical activity</li> </ul> </li> <li>– Intensify lifestyle therapy and optimise glycaemic control for patients with elevated triglyceride levels (<math>\geq 1.7</math> mmol/L) and/or low HDL cholesterol (<math>&lt; 1.0</math> mmol/L for men, <math>&lt; 1.3</math> mmol/L for women)</li> </ul>
<p>II. LDL-C lowering and cardioprotection:</p> <ul style="list-style-type: none"> <li>– Statins are the drugs of choice in ASCVD primary and secondary prevention.</li> </ul>
<p>III. Add-on therapy in association with statins when the therapeutic target is not achieved at the maximum tolerated statin dose:</p> <ul style="list-style-type: none"> <li>– Ezetimibe, PCSK9 inhibitor<sup>12,13</sup></li> <li>– Fibrates are not recommended to be add-on drugs to statin therapy for lowering LDL-C<sup>13</sup>.</li> </ul>
<p>IV. Control of hypertriglyceridaemia:</p> <ul style="list-style-type: none"> <li>– Fasting or non-fasting triglycerides (TG) 1.7-5.6 mmol/L: <ul style="list-style-type: none"> <li>• address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise TG.</li> </ul> </li> <li>– Fasting TG levels <math>\geq 5.7</math> mmol/L: <ul style="list-style-type: none"> <li>• evaluate for secondary causes of hypertriglyceridaemia and consider medical therapy (fibrate and/or fish oil) to reduce the risk of pancreatitis.</li> <li>• if 10-year ASCVD risk is <math>\geq 7.5\%</math>, consider to initiate statin therapy or increase statin dosage. More potent statins (atorvastatin, rosuvastatin and pitavastatin) demonstrate a robust lowering of TG levels, especially at high doses and in patients with hypertriglyceridaemia<sup>7</sup>.</li> </ul> </li> <li>– Combination therapy with statin and fibrate is associated with an increased risk for abnormal transaminase levels, myositis, and rhabdomyolysis. The risk is higher when statins are combined with gemfibrozil (compared with fenofibrate). Hence, fenofibrate is the preferred agent when used in combination with statin but should be used with cautions and under close monitoring.</li> </ul>

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## Module 9 Diabetic Kidney Disease

Diabetic kidney disease is usually a clinical diagnosis made based on the presence of albuminuria and/or reduced eGFR in the absence of signs or symptoms of other primary causes of kidney damage<sup>1</sup>.

Urinary albumin-creatinine ratio (ACR) >2.5mg/mmol in men and >3.5mg/mmol in women<sup>2</sup> indicate rise in urinary albumin loss. An ACR >25mg/mmol represents a more severe and established form of renal disease and is more strongly predictive of total mortality, cardiovascular mortality and morbidity, and end-stage renal failure. Refer to nephrologists when indicated (Table 1).

**Table 1. When to refer to nephrologists**

1. When doubt exists as to the diagnosis of diabetic kidney disease. This arises with atypical features suggestive of additional or alternative renal pathology which includes history of diabetes with a very short duration, the presence of haematuria, significant renal impairment or proteinuria without other microangiopathy like diabetic retinopathy.
2. When need arises for evaluation in patients at risk of rapid progression or deterioration of renal function
3. When need arises for the planning of renal replacement therapy with patients progressing into end stage renal failure [serum creatinine over 300  $\mu\text{mol/l}$ ].

**Screening of diabetic kidney disease (Figure 1)**

- Screening for diabetic kidney disease should be performed at least annually.
- Measure random spot urine albumin creatinine ratio (ACR) and serum creatinine at least yearly. If the levels are abnormal, the test should be repeated within 3 months and more often thereafter to monitor progress.
- In patients with clinical proteinuria, especially those with short disease duration or without other microvascular complications, other causes such as urinary tract infection, severe hyperglycaemia, cardiac failure and other non-diabetes renal disease (e.g. stone and glomerulonephritis) should be excluded.

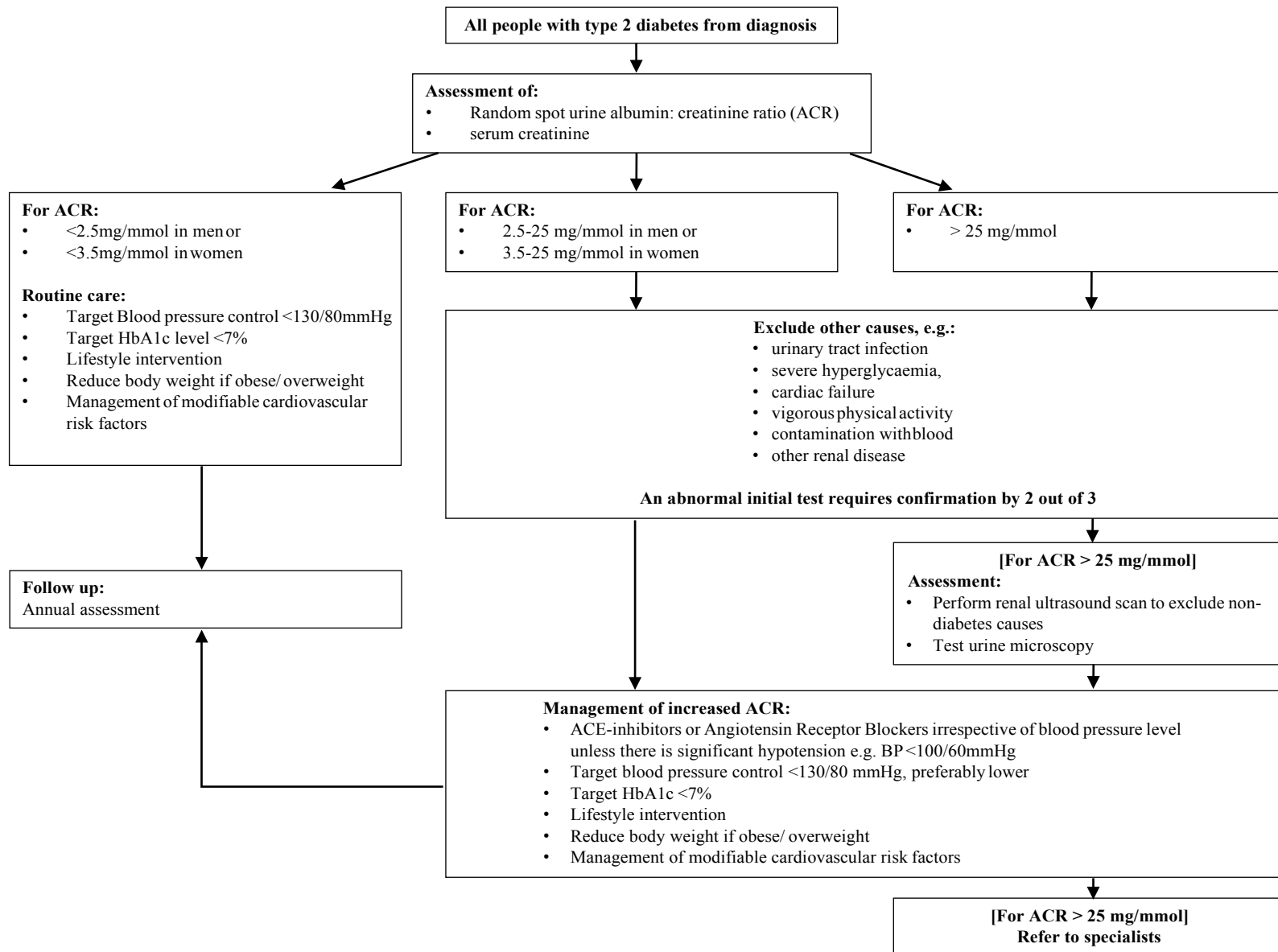
**D****D****Drug Treatment**

In the treatment of both micro- and macroalbuminuria, either Angiotensin Converting Enzyme (ACE) inhibitors or Angiotensin Receptor Blocker (ARB) should be used<sup>3,4,5</sup>.

**A**

- In the setting of albuminuria or diabetic kidney disease, in patients unable to tolerate ACE inhibitors and/or ARBs, consider the use of calcium channel blockers,  $\beta$ -blockers, or diuretics for the management of blood pressure.
- If ACE inhibitors, ARBs, or diuretics are used, monitor serum potassium levels for the development of hyperkalemia.

**Figure 1. Screening and Management of Diabetic Kidney Disease**



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### Systematic Eye examination (Figure 1)

- Patients with type 2 diabetes should have an initial dilated and proper eye examination shortly after the diagnosis of diabetes. The examination should check for visual acuity (with pin-hole if necessary), lens opacity and retinopathy<sup>1</sup>. **B**
- Retinal photography is the evidenced-based best practice and it should be carried out by experienced personnel in a programme of systematic screening for diabetic retinopathy<sup>Note,2,3,4</sup>. **B**
- For examination frequency -
  - It should be repeated annually. **B**
  - Less frequent examinations (every 2-3 years) may be considered following one or more normal eye examinations<sup>5,6</sup>. **B**
  - For patient with background retinopathy, more frequent examinations should be done if the patient is at high risk of development of diabetic retinopathy<sup>7</sup>. (Table 1) **B**
- When planning pregnancy, women with preexisting diabetes should have a comprehensive eye examination and should be counselled on the risk of development and/or progression of diabetic retinopathy. Women with diabetes who become pregnant should have a comprehensive eye examination in the first trimester and close follow-up throughout pregnancy and for one year postpartum. This guideline does not apply to women who develop gestational diabetes because such individuals are not at increased risk of diabetic retinopathy<sup>8,9</sup>. **C**

Note: Dilated direct ophthalmoscope by an experience doctor should only be used opportunistically and is not a substitute for systematic screening programme. Such opportunistic screening is an option only if systematic screening by retinal photography is not possible/ available<sup>12</sup>. **C**

## Referral

- Promptly refer patients with any level of macular edema, severe non-proliferative diabetic retinopathy (NPDR), or any proliferative diabetic retinopathy (PDR) to an ophthalmologist who is knowledgeable and experienced in the management and treatment of diabetic retinopathy<sup>10,11</sup>. (Table 2)

A

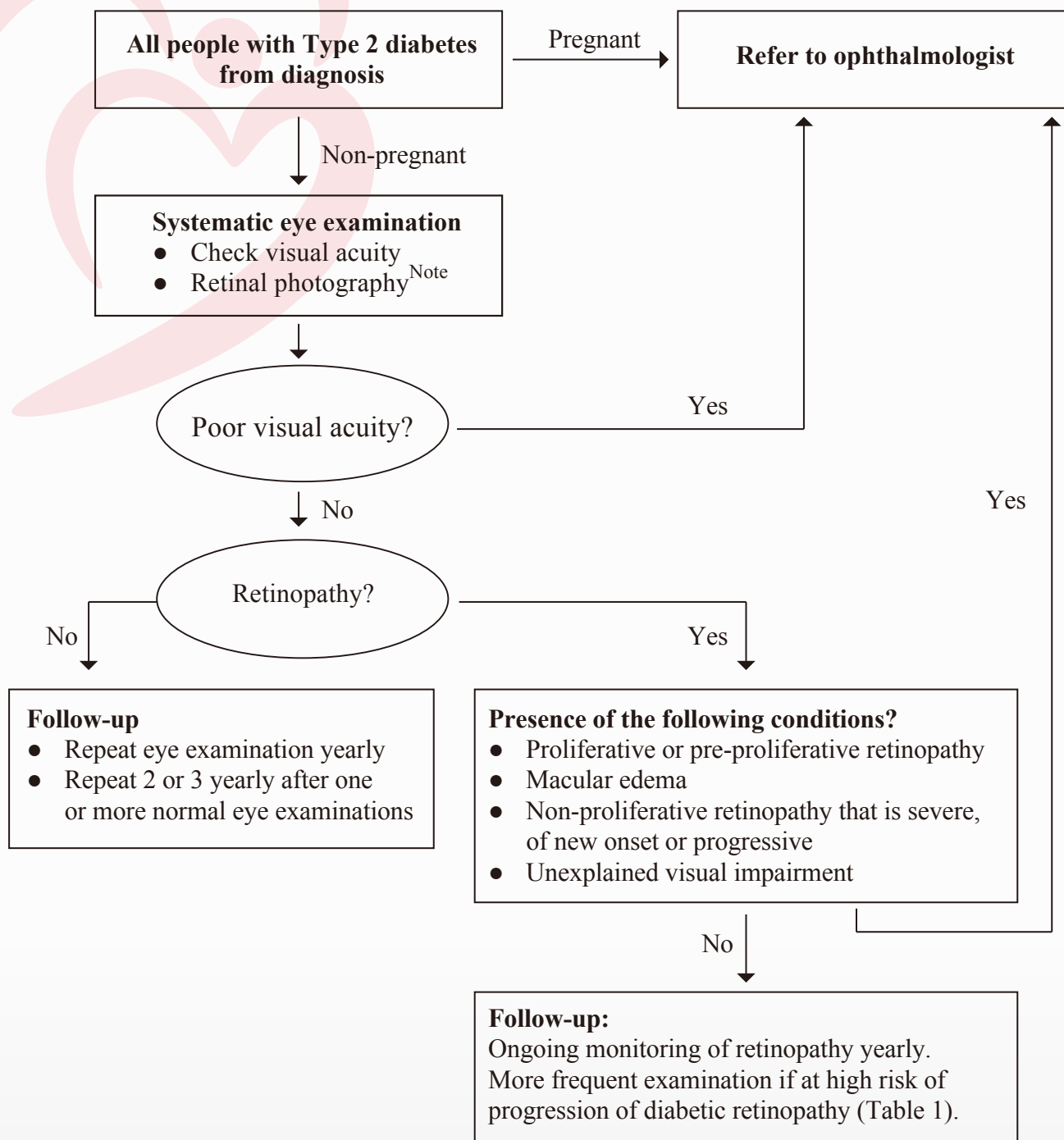
Table 1. Risk factors for diabetic retinal disease

- (a) Poor glycaemic control (HbA1c > 8%)
- (b) Poor blood pressure control
- (c) Sudden changes in visual acuity
- (d) Duration of diabetes > 10 years
- (e) Presence of microalbuminuria and proteinuria
- (f) Hyperlipidaemia
- (g) Pregnancy

Table 2. When to refer to an ophthalmologist

- Positive pregnancy test
- Proliferative or pre-proliferative retinopathy
- Macular edema
- Non-proliferative retinopathy that is severe, of new onset or progressive
- Unexplained visual impairment

Figure 1. Screening and Management of Diabetic Eye Disease



Note: Dilated direct ophthalmoscope by an experienced doctor should only be used opportunistically and is not a substitute for systematic screening programme. Such opportunistic screening is an option only if systematic screening by retinal photography is not possible/ available.



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## Module 11 Diabetic Foot Problems

### Screening and Management of Diabetic Foot Problems (Figure 1)

- All diabetic patients should have annual foot assessment. Any abnormalities, however trivial, should be treated vigorously<sup>1,2</sup>.
- The foot examination should include inspection, assessment of foot pulses, and testing for loss of protective sensation (10-g monofilament plus testing any one of the following: vibration using 128-Hz tuning fork, pinprick sensation, ankle reflexes, or vibration perception threshold)<sup>1,2</sup>.
- Check for skin cracks, infection, state of the nails, callus and deformities.
- Provide general foot self-care education to all patients with diabetes and advise on proper footwear<sup>3,4</sup>. Please visit the following website for more information: <http://www.ha.org.hk/haho/ho/hesd/101592c.htm#5>
- Refer to podiatrist for treatment of foot lesions, (e.g. callus, bunions, dystrophic nails) and additional support (e.g. prescription of custom-built footwear or orthotic insoles).
- All skin infections should be aggressively treated including frequent wound dressing, debridement and use of broad spectrum antibiotics. Glycaemic control should be optimised to promote wound healing and prevent metabolic decompensation.
- For patients with severe neuropathy, vascular insufficiency or ulcers refractive to treatment, early referral to specialists including podiatrist, vascular surgeon, endocrinologist or orthopaedic surgeon is warranted. (Table 1)

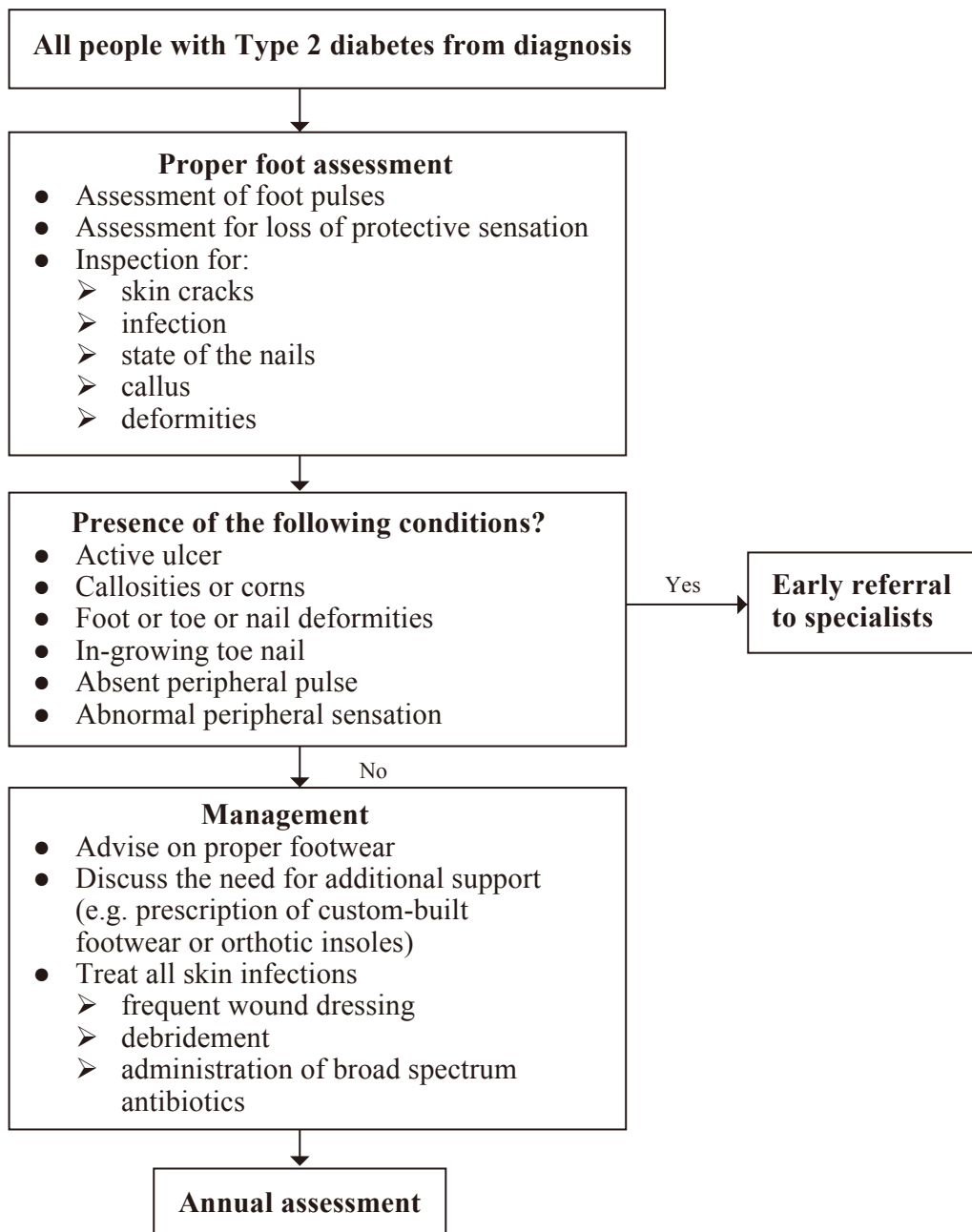
**B**

**B**

**Table 1 Criteria of referral**

- Active ulcer
- Callosities or corns
- Foot or toe or nail deformities
- In-growing toe nail
- Absent peripheral pulse
- Abnormal peripheral sensation

**Figure 1. Assessment and Management of Diabetic Foot Problems**



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