General principles (Figure 1)

- If HbA1c[a] 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. α-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

[a] 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^2 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[1] (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[2]. The dose should be increased gradually to the full maximum effective dose of 1500-2000mg per day (in 2 to 3 divided doses).[3]

Efficacy: Unless contraindicated, metformin is now considered the first-line therapy along with dietary and exercise therapy. It reduces HbA1c by about 1%[4]. 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[5]. Metformin therapy is associated with some weight loss[6,7,8] or no weight gain which may confer additional benefits in overweight/ obese subjects[9].

Adverse effects: The most common side effect is gastrointestinal disturbances ranging from 5% to 20%, including nausea, abdominal discomfort and diarrhoea[10,11]. 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[12]. Lactic acidosis is very rare (0.4 cases /10,000 treatment years)[13] 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^2.[14] Initiation of metformin in patients with an eGFR between 30 and <45 ml/min/1.73m^2 is not recommended. For those with eGFR falls between 30 and <45 ml/min/1.73m^2 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[15].), 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[16]. It should be used with care in the elderly who often have reduced organ function[17]. 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[18]. 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^2; 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[16]. On the other hand, the American College of Radiology guidelines recommend that in patients with no evidence of AKI and with eGFR ≥30 ml/min/1.73m^2, 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^2), 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 reinstituted only after renal function has been re-evaluated and found to be normal[18].

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[1]. 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[4]. 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[19]. All agents in this class have similar efficacy at equivalent doses[20].

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[21]. 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% ($p = 0.01$)[22]. 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%[4]. It has better durability of glycaemic control[23] 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[14].

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[24]. 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[25,26]. 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[25,26]. 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[25,26].

Contraindications: History of congestive heart failure, history of bladder cancer or in patients with uninvestigated visible blood in the urine[24], 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%[4]. The drugs can be used as monotherapy or in combination with other oral blood glucose lowering drugs[27,28].

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[29]. 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[30]. Cases of impaired liver function have been reported in patients taking vildagliptin and alogliptin[31,32]. Liver function tests should be performed prior to the initiation of treatment with vildagliptin and alogliptin[31,32]. It is recommended to monitor liver function at three-month intervals during the first year of therapy and periodically thereafter in patients taking vildagliptin[31]. 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[35]. Infrequent cases of bullous pemphigoid requiring hospitalization have been reported with DPP4-I use[32-35].

Incretin mimectics (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%[4]. GLP-1 RA have demonstrated cardioprotective effects in some clinical studies[36].

Adverse effects[37]: 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[38]. 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[39,40]. (Refer to appendix of this Module for supplementary information on the use of insulin)

Alpha-glucosidase inhibitors

This class of drugs inhibits the enzyme, α-glucosidase, located at the intestinal brush border and thus slows the rate of intestinal glucose absorption with reduced excursion of postprandial blood glucose level. They, however, have only modest effect on lowering fasting plasma 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.

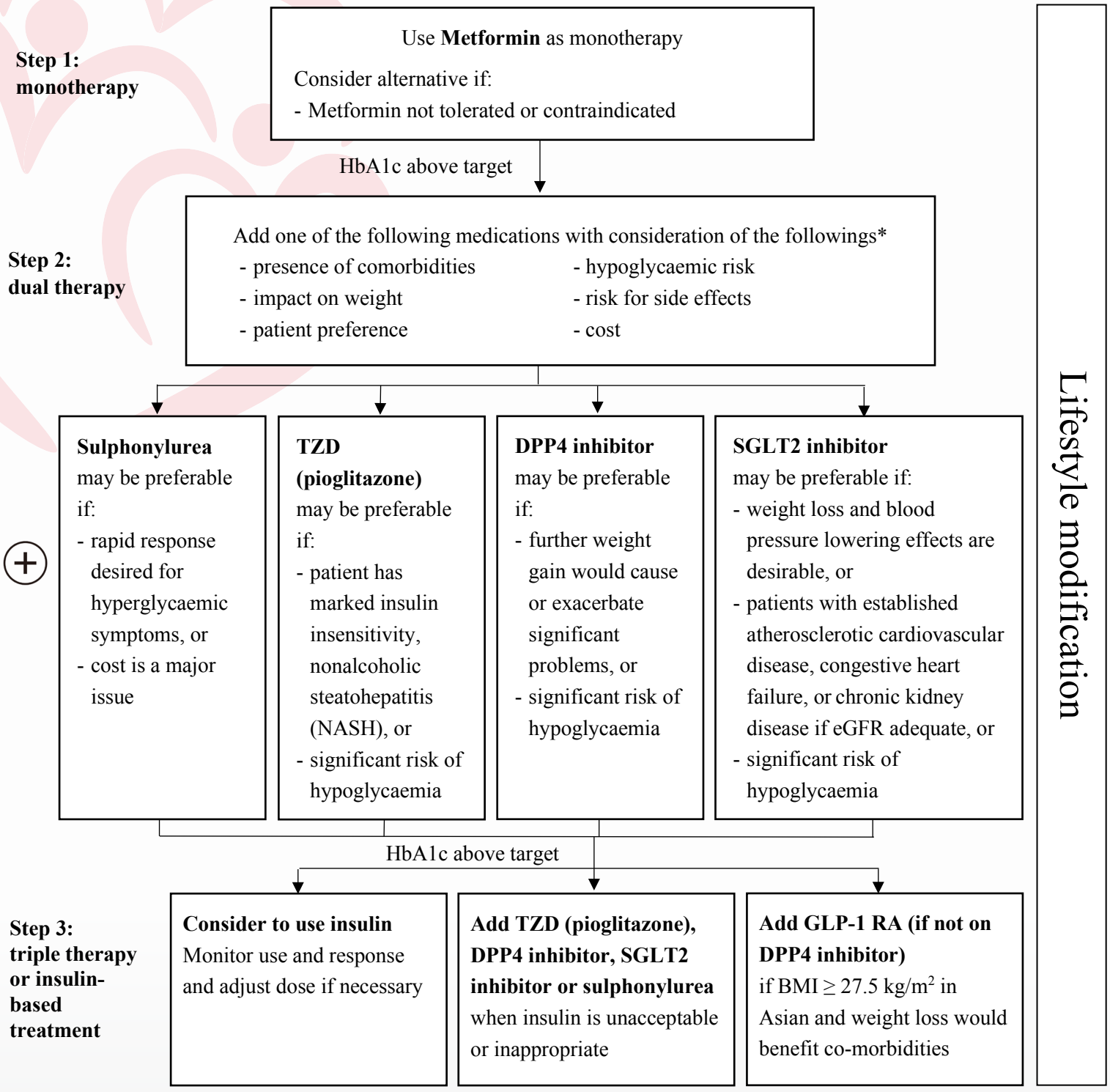
Sodium-glucose cotransporter 2 inhibitors (SGLT2-I)

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[41]. 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%[4]. 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 [42].

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[41]. 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[43]. Adverse events related to volume depletion (orthostatic hypotension, acute kidney injury) are rare but may occur in fragile patients exposed to some precipitating factors[41]. 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[44]. 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[41]. 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[45]. The increased risk of bone fractures and lower limb amputations was only seen with canagliflozin in CANVAS Program[46] but not in most other trials or observational studies with canagliflozin, dapagliflozin, and empagliflozin[41,42].

Figure 1. Algorithms of drug treatment for control of hyperglycaemia



* Refer to Table 1 and the text

(Modified from UK NICE 2015[47])

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 %)[4]**	**Main Mode of action**	**Benefits[4,14,36]**	**Side effects and limitations[4,14,36]**
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
α-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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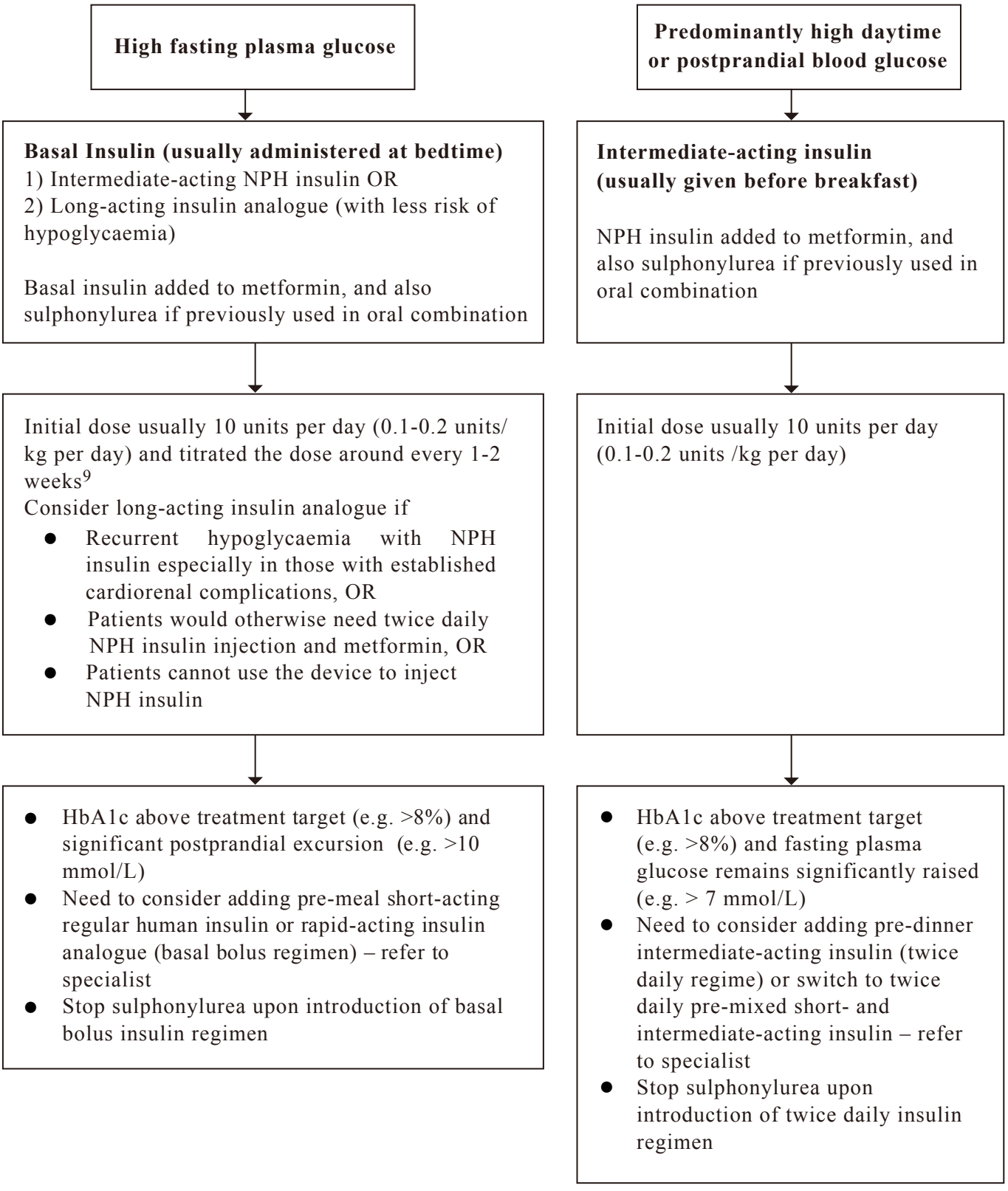
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Initiation options depend on the pattern of the patient's blood glucose levels[2,8:]



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

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

Titration scale [8]

Haemostix (mmol/L)	Insulin dosage (units)
<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[9]

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

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[10]. 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[11].

For details of SMBG, refer to Module 6 P.2-3.

Glycaemic targets

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

Insulin Delivery [12]

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 [12]

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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