Ceylon College of Physicians

CLINICAL PRACTICE GUIDELINES

Sri Lanka College of Endocrinologists

DIABETES MELLITUS MANAGEMENT GUIDELINES

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Abbreviations

ABI: Ankle Brachial Index

ACEI: Angiotensin Converting Enzyme Inhibitor

AIDS: Acquired Immunodeficiency Syndrome

ARB: Angiotensin Receptor Blocker

BIDS: Basal insulin day time Sulfonylurea regimen

BMI: Body Mass Index

CAD: Coronary Artery Disease

CIDP: Chronic Inflammatory Demyelinating Polyneuropathy

CKD: Chronic Kidney Disease

CLI: Critical Limb Ischemia

CV risk: Cardio Vascular risk

CVD: Cardio Vascular Disease

DCCT: Diabetes Control and Complications Trial

DKA: Diabetic Ketoacidosis

DM: Diabetes Mellitus

DPN: Diabetic Peripheral Neuropathy

DPP-4 Inhibitor: Dipeptidyl Peptidase-4 Inhibitors

DVT: Deep Vein Thrombosis

eGFR: Estimated Glomerular Filtration Rate

ESR: Erythrocyte Sedimentation Rate

ESRD: End Stage Renal Disease

FDA: Food and Drug Administration

FPG: Fasting plasma glucose

GDM: Gestational Diabetes Mellitus

GI: Gastrointestinal

GLP-1RA: Glucagon-like peptide-1 Receptor Agonist

HbA1C:Glycosylated Haemoglobin

HDL: High Density Lipoprotein

HDU: High Dependency Unit

HHS: Hyperosmolar Hyperglycaemic State

HIV: Human Immune Deficiency Virus

HONK: Hyperosmolar Non Ketotic Coma

ICU: Intensive Care Unit

IM: Intramuscular

IV: Intravenous

IADPSG: International Association of Diabetes and Pregnancy Study Groups

LDL: Low density lipoprotein

MODY: Maturity-onset diabetes of the young

NG: Nasogastric

NGSP: National Glycohemoglobin Standardization Program

NPDR: Non Proliferative Diabetic Retinopathy

NPH: Neutral Protamine Hagedorn (Isophane insulin)

OGTT: Oral Glucose Tolerance Test

PN: Peripheral Neuropathy

PG: Plasma Glucose

PPG: Postprandial Glucose

RBG: Random Blood Glucose

RDA: Recommended Daily Allowance

SBP: Systolic Blood Pressure

SGLT2 inhibitor: Sodium Glucose co Transporter 2 inhibitor

SMBG: Self Monitoring Of Blood Glucose

SNRI: Serotonin-Norepinephrine Reuptake inhibitors

T1DM: Type 1 Diabetes Mellitus

T2DM: Type 2 Diabetes Mellitus

TCA: Tricyclic Antidepressant

TG: Triglyceride

TZD: Thiazolidinediones

U:units

UACR: Urine Albumin Creatinine Ratio

VEGF: Vascular Endothelial Growth Factor

WHO: World Health Organization

TABLE OF CONTENTS

1. INTRODUCTION

This guideline is developed as a part of clinical practice guidelines produced by the Ceylon College of Physicians in collaboration with Sri Lanka College of Endocrinologists. The aim of this guideline is to guide all the doctors involved in the management of Diabetes in Sri Lanka. This is prepared according to the existing guidelines published by various international professional organizations including American Diabetes Association (ADA) and modified according to the local data to make it suitable to use in local context.

Diabetes mellitus is a metabolic disorder of multiple aetiology. The disease is characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. Continuing global pandemic of diabetes exacts huge costs both in terms of human suffering and economics. By 2040, the worldwide prevalence is projected to be 642 million, a 55% increase compared to 2015(1). Sri Lanka has not been spared from this pandemic and a similar upward trend in prevalence has been observed in local studies. Of note is a dramatic rise in urban prevalence. Overall prevalence of diabetes for Sri Lankans aged >20 years was 10.3% according to Sri Lanka diabetes and cardiovascular study (SLDCS) conducted 10 years back in 2006 with projected prevalence of 13.9% for year 2030 (2). Diabetes prevalence was reportedly higher among urban Sri Lankan population (16.8% in SLDCS and 20.3% for males and 19.3% for females in Ragama study) (2,3). Recent Colombo urban study reported a rise of urban prevalence of diabetes from 16.8% to 27.1% and a rise of prediabetes from 13.6% to 30.1% over last 10 years (2,4). Therefore an alarming increase in complications of diabetes, both microvascular disease and macrovascular disease will be seen unless urgent measures are taken to prevent them.

Diabetes Mellitus is a major risk factor for chronic kidney disease, young onset blindness and cardiovascular diseases. Considerable percentage of type 2 DM patients are unaware of the diagnosis and may have complications of diabetes at the time of diagnosis. Screening and early detection of diabetes, proper lifestyle modifications, optimizing management according to individualized targets, overall cardiovascular risk reduction, and timely referrals will help to prevent morbidity and mortality related to diabetes which is also a major burden to our country's economy.

2. CLASSIFICATION

Diabetes can be classified in to four main subtypes (5).

1. Type 1 diabetes (Type 1 DM)

Type 1 DM (T1DM) is due to absolute deficiency of insulin due to pancreatic β-cell destruction. In majority this occurs as a result of cell mediated auto-immune destruction of pancreatic β-cells. Islet cell auto antibodies, glutamic acid decarboxylase (GAD65) antibodies and auto-antibodies to insulin are some of the bio-markers present in these patients. In a small number of patients the aetiology is unknown.

2. Type 2 diabetes (Type 2 DM)

Type 2 DM (T2DM) accounts for 90-95% of all diabetic patients and is due to relative insulin deficiency along with insulin resistance. Although the exact aetiology is not clear, the risk of developing T2DM is associated with obesity and physical inactivity (Table 3). It has a strong genetic predisposition than T1DM.

3. Gestational diabetes mellitus (GDM)

GDM is diabetes diagnosed in the second or third trimester of pregnancy that is not clearly type 1 or type 2 diabetes. Women with diabetes in the first trimester of pregnancy are classified as pre- existing diabetes.

4. Specific types of diabetes

There are several specific types of diabetes such as monogenic diabetes syndromes, diseases of the pancreas and drug-induced diabetes.

- Monogenic diabetes syndromes are due defects of β cell function and include Neonatal diabetes and maturity-onset diabetes of the young (MODY)
- Diseases that involve the exocrine function of pancreas e.g. cystic fibrosis, chronic pancreatitis
- Drug-induced diabetes is due to use of diabetogenic drugs such as steroids and treatment of HIV/AIDS

Classification of diabetes is helpful in deciding on the therapy. However, there may be difficulties in determining the type of DM at the time of diagnosis e.g. type 1 DM may occur in adults and type 2 DM may be seen in children.

3. DIAGNOSIS

3.1 Diagnostic tests

Following tests can be used for diagnosis of Diabetes mellitus.

- **Fasting plasma glucose (FPG) –** Fasting is defined as no caloric intake for at least 8 hours and for maximum of 12 hours.

- **Two hour plasma glucose (2-hr PG) in 75 gm oral glucose tolerance test** (OGTT) - This test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

- **HbA1c** - Although this is convenient as it does not require fasting, it is costly and has limited availability in resource poor settings. HbA1C must be measured using a validated assay standardized to the National Glycohemoglobin Standardization Program-Diabetes Control and Complications Trial reference. Further, HbA1C levels can vary with age, ethnicity, anaemia, haemoglobinopathies, haemolysis, blood loss and in severe hepatic and renal disease.

- **Random blood sugar (RBS)** – RBS can be used for diagnosis of diabetes in the presence of symptomatic hyperglycaemia.

3.2 Criteria for diagnosis (Table 1) (5)

Table 1:Criteria for the diagnosis of diabetes
FPG >126 mg/dL (7.0 mmol/L)
OR
2-h PG >200 mg/dL (11.1 mmol/L) during an OGTT
OR
HbA1c > 6.5%.
OR
A random plasma glucose >200 mg/dL(11.1 mmol/L) in a patient with classic symptoms of hyperglycaemia or hyperglycemic crisis.

3.3 Confirmation of diagnosis

Unless a clear clinical diagnosis (patient in a hyperglycaemic crisis or with classic symptoms of hyperglycaemia) is available, diagnosis should be confirmed by repeating the same test with a new blood sample or by another test. If the patient is having discordant results from two different tests, then the test result that is above the diagnostic cut off should be repeated (5-7)).

3.4 Prediabetes

There are some individuals whose plasma glucose levels are below the diagnostic level, but too high to be considered normal. They have impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT). This situation is referred to as prediabetes and it indicates a risk of developing diabetes in future. Diagnostic criteria of prediabetes are given in table 2.

Table 2:Criteria for the diagnosis of prediabetes
FPG 100 - 125 mg/dL (5.6 – 6.9 mmol/L)
OR
2-h PG 140 -199 mg/dL (7.8-11.0 mmol/L) during an OGTT
OR
HbA1c 5.6 -6.4%

4. SCREENING FOR TYPE 2 DIABETES

Screening can detect diabetes early and may prevent adverse outcomes. T2DM may remain undiagnosed for several years because patients usually do not develop symptoms of hyperglycaemia at earlier stages. Nevertheless, patients are at risk developing long-term complications by the time of diagnosis due to exposure to chronic hyperglycaemia.

4.1. Criteria of screening for type 2 diabetes (5-7)

- All adults aged more than 40 years
- All patients who are overweight or obese and have additional risk factors for T2DM (Table 3)
- If the initial screening test is normal, testing should be repeated at a minimum of 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., patients with prediabetes should be tested yearly) and risk status (e.g. presence of multiple risk factors)

Table 3: Risk factors for Type 2 Diabetes, in addition to South Asian origin (5,6,7)
➢ Overweight and obese (BMI > 23 kg/m2)
➢ Physical inactivity
➢ First-degree relative with type 2 diabetes
➢ History of gestational diabetes or a women who delivered a baby weighing >3.5 kg
➢ History of pre diabetes (IGT or IFG or A1c 6.0 to 6.4%)
➢ Presence of CV risk factors • Hypertension (>140/90 mmHg or on therapy for hypertension) • HDL cholesterol level <35 mg/dl and/or a triglyceride level>250 mg/dl ➢ Women with polycystic ovary syndrome
➢ Other clinical conditions associated with insulin resistance (e.g. severe obesity, acanthosis nigricans)

5. CLINICAL EVALUATION

A comprehensive clinical assessment should be carried out at the first encounter of a patient with diabetes. This would provide useful information in addressing the lifestyle, behavioural, dietary and pharmaceutical interventions that are the main goals in management of the disease. Detailed medical history, physical examination and laboratory investigations should be obtained during the initial clinical assessment (Table 4).

Table 4: Clinical Evaluation

History

- Age of onset and details of first presentation e.g. asymptomatic, hyperglycaemic emergency, laboratory results
- Presence of other comorbidities: hypertension, dyslipidaemia, ischaemic heart disease, dental diseases
- Family history
- Psycho-social history
- Eating patterns, nutritional status
- History of smoking, alcohol consumption
- Review of previous treatment regimens management problems and complications
    - Blood sugar records, HbA1C records
    - Hyperglycaemic emergencies: frequency, severity, and cause
    - Hypoglycemia episodes, awareness, and frequency and causes
    - Microvascular complications: retinopathy, nephropathy, and neuropathy (sensory, autonomic including sexual dysfunction)
    - Macrovascular complications: coronary heart disease, cerebrovascular disease, and peripheral vascular disease
    - Patient's attitudes and evidence of self management
    -

Physical Examination

- Height, weight and BMI
- Acanthosis nigricans, insulin injection sites
- Blood pressure with postural measurements, peripheral pulsations esp. dorsalis pedis and posterior tibial pulses
- Fundoscopic examination
- Presence/absence of ankle reflexes, sensations including pain, proprioception, vibration, and monofilament sensation

Investigations

- Fating lipid profile
- Serum creatinine and estimated GFR
- Urine albumin-creatinine ratio
- Thyroid function test in T1DM, dyslipidaemia
- HbA1C if not done during past 3 months

6. MANAGEMENT OF TYPE 2 DIABETES MELLITUS

The main goals of management of Type 2 DM include,

1) **Life style modification and patient education**
2) **Maintenance of good glycaemic control**
3) **Multiple risk factor management**
4) **Prevention of complications**

This can be best achieved through a patient centered self-management approach with multidisciplinary support.

6.1. LIFE STYLE MODIFICATION & PATIENT EDUCATION

Life style modification is the key foundation for the better management of diabetes. Patient education is an essential continuous process to facilitate patient's knowledge, skills and ability necessary for self-diabetes care.

- **Medical nutrition therapy (5-7)**
  - Should be individualized.
  - Weight loss is recommended (at least 5-10%) for all overweight or obese individuals with a calorie restricted diet. All patients should attempt to have near normal body weight (BMI – 18.5-23kg/m^2)
  - Saturated fat and trans fat intake should be reduced.
  - Salt intake should be limited to less than 2.4 g sodium (i.e. 1 tea spoon of salt).

  (Refer Annexure for sample dietary plan for patient with diabetes)

- **Physical activity**
  - Increasing day to day physical activity is recommended as a more practical approach.
  - Moderate intensity aerobic physical activity (e.g. walking, cycling, swimming) is recommended.

- At least 150 min/week (e.g. brisk walk 30 minutes a day 5 days a week).
- For obese patients at least 60 minutes of exercise per a day.

- Resistance training (e.g. pushups, dumbbells) is recommended at least twice a week.
- Encourage muscle-strengthening activities that involve all major muscle groups (2 or more days per week)

- **Smoking and Alcohol**
  - All patients should be encouraged to quit smoking.
  - Alcohol is best avoided. If taken it should be less than two units per day for men and less than one unit per day for women.

6.2. GLYCAEMIC CONTROL (5-11)

6.2.1. Glycaemic Targets

Following optimal targets for glycaemic control is recommended (table 5), but each target must be individualized based on comorbid conditions, hypoglycemia unawareness, duration of diabetes, age, life expectancy, patient motivation and individual patient considerations (Figure 1). A higher glycemic target may be acceptable in elderly or those who are at risk of hypoglycaemia

Table 5: Glycaemic Targets	
HbA1c	7.0%
FPG/ Pre-prandial capillary plasma glucose	80–130mg/dL (4.4–7.2mmol/L)
Post prandial plasma glucose/ Peak post-prandial* capillary plasma glucose *(1-2 hrs after the bigining of a meal)	<180 mg/dL (<10.0 mmol/L)

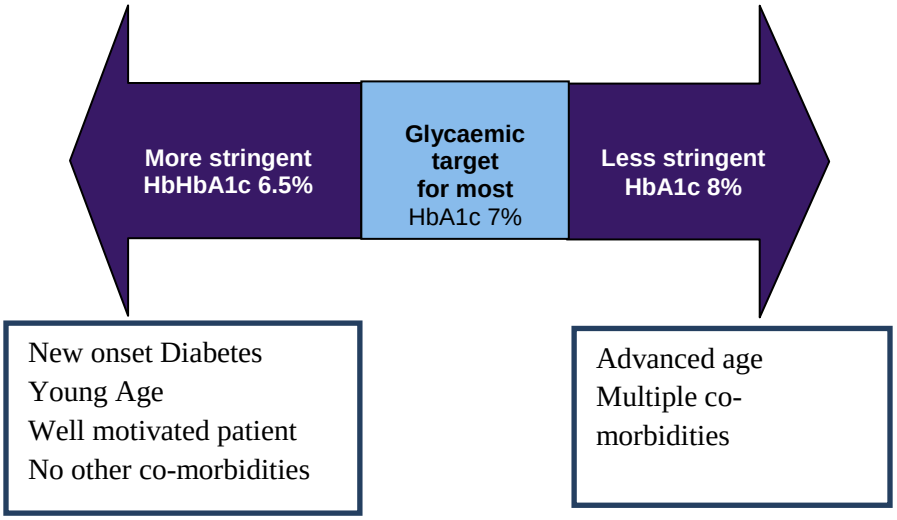


Figure 1: Individualized Glycaemic targets

6.2.2. Monitoring of glycaemic control

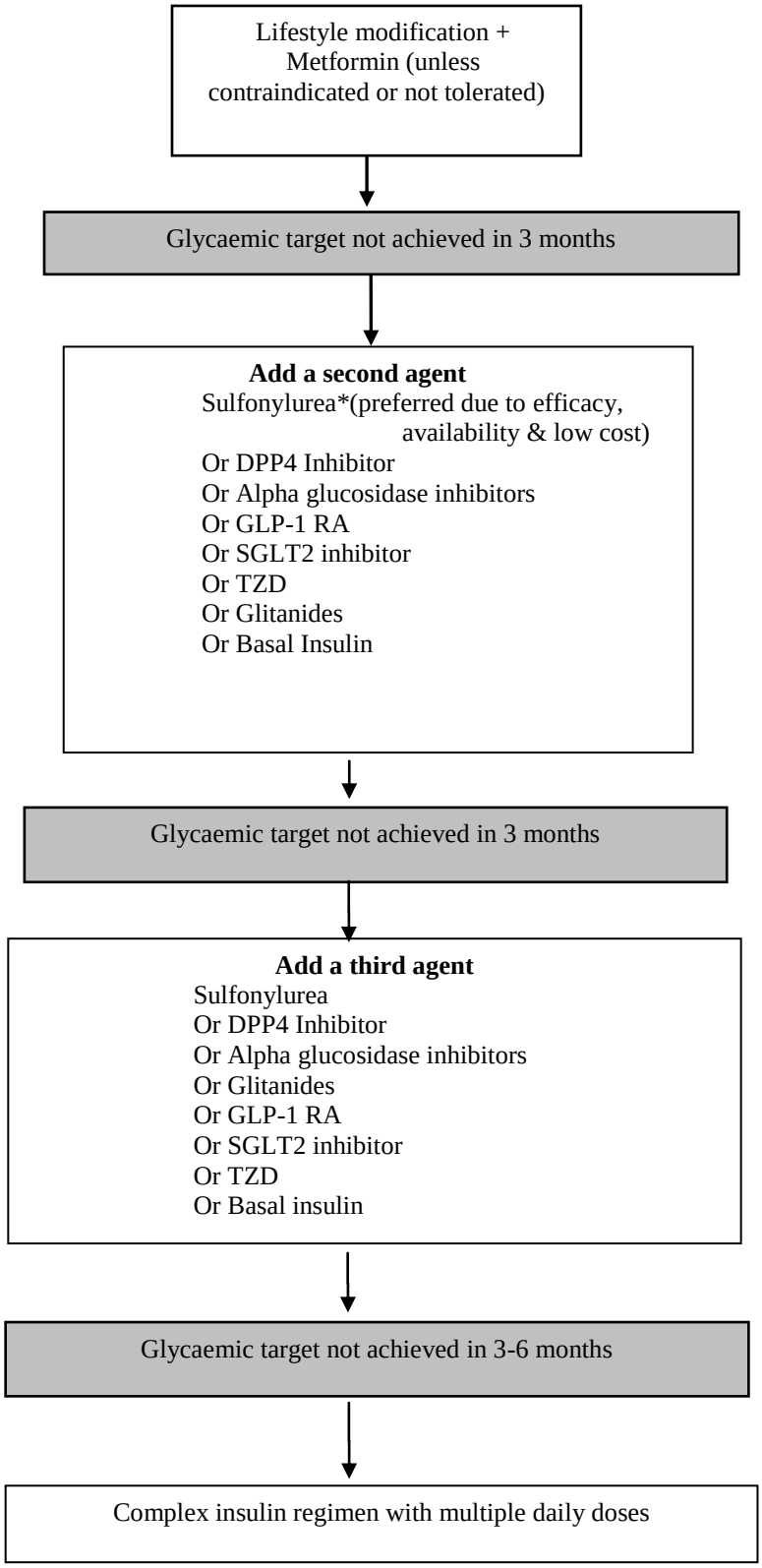
- Ideally a combination of HbA1c and self- monitoring of capillary glucose will give optimal results.
- Fasting plasma glucose and post-prandial plasma glucose are commonly used for assessment of glycaemic control in our setting due to lack of facilities for above tests.
- If HbA1c goal is not achieved despite normal fasting/pre-prandial blood sugar target, the post prandial blood glucose should be targeted.
- When the HbA1c level does not correlate with plasma glucose levels, conditions that affect red cell turn over such as anaemia, haemorrhage or haemoglobinopaties should be considered.

6.3. PHARMACOTHERAPY

6.3.1. Initiation of pharmacotherapy (Figure 2)

- At initial diagnosis, monotherapy with metformin (unless contraindicated) along with lifestyle interventions is the preferred choice as most patients cannot achieve recommended targets on lifestyle interventions alone.
- In the presence of moderate to severe hyperglycaemia at diagnosis, dual/ triple therapy or insulin may be considered.
- Insulin therapy may be required if there are severe symptoms or complications at presentation. Once the hyperglycaemia is controlled, changing over to non-insulin therapies may be possible.
- Consider timely initiation of combination therapy if monotherapy appears inadequate. The combined regimen should aim for good glycaemic efficacy, low potential for hypoglycaemia as well as weight neutrality or ideally weight loss in the obese and cost effectiveness.
- Sulphonylurea is used as the second line treatment option or as the first choice in metformin intolerant/ contraindicated patients in local setting due to absence of robust data on superiority of other agents, low cost and availability.
- Nevertheless, any combination of anti hyperglycaemic agents such as sulfonylurea, thiazolidinedione, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists, or insulin can be considered for the combination therapy.

Figure 2: ALGORITHM FOR GLUCOSE LOWERING IN TYPE 2 DM*



6.3.2. Non insulin therapies for T2DM

Brief introduction to available glucose lowering agents are given below. Refer to table 6 for dosages and adverse effects.

- ***Biguanides:*** **Metformin**

  - Metformin is the drug recommended for initial monotherapy for patients with T2DM.
  - Metformin decreases hepatic gluconeogenesis, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral uptake and utilization of glucose.
  - Metformin can be safely used down to glomerular filtration rate (GFR) of 45 mL/min/1.73 m^2 . It should be used with caution at eGFR 45-30 mL/min/1.73 m^2 with a reduced dosage.

- ***Sulphonylureas*** **(SU): Tolbutamide, Glibenclamide, Gliclazide, Glimipride & Glipizide**

  - Sulfonylureas are insulin secretogogues (stimulate insulin secretion from the pancreatic beta-cells) with well established glucose lowering efficacy and safety.
  - Individual SUs differ in their hypoglycaemic potential. Gliclazide and Glimipride has shown low hypoglycaemic events, while Glibenclamide is known to have high risk for hypoglycaemia especially in elderly.
  - SUs are linked to weight gain due to its insulinotrophic effects. But modern agents such as Glimipride, Gliclazide MR(Modified release), Glipizide ER(extended release) have shown weight neutralizing/ reducing effects.

- ***Alpha glucosidase inhibitors*****: Acarbose**
  - This drug acts by reducing post prandial glucose excursions by inhibiting gut carbohydrate digestion. This is taken before meals.

- ***Thiazolidinediones (TZD*****): Pioglitazone**

  - Pioglitazone is the only TZD used in Sri Lanka. It is known to improve insulin sensitivity in T2DM.
  - Its clinical use has become limited by the risk profile, including weight gain, worsening heart failure, macular oedema, increased fracture risk and possible risk for bladder cancer.

- ***Dipeptidyl peptidase-4 inhibitor (DPP4 Inhibitors)*:**

  Sitagliptin, Vidagliptin, Saxagliptin, Linagliptin, Alogliptin

  - DPP4 inhibitors are a group of incretin based therapy available for treatment of DM.
  - It is weight neutral and does not cause hypoglycaemia, unless used in combination with SU or insulin.

- ***Sodium glucose co-transporter inhibitors (SGLT2 inhibitors)***

  Empagliflozin, Dapagliflozin, Canagliflozin

  - SGLT2 inhibitors block the renal glucose reabsorption and causes glycosuria resulting in its glucose lowering effect.
  - Hypoglycaemia is not a significant adverse effect. Urinary tract infections and vaginal candidiasis has been commonly associated with this class of drugs.

- ***Glucagon-like peptide-1 (GLP-1)receptor agonists:***

  Exenatide , Liraglutide, Exenatide modified release, Albiglutide, Dulaglutide

  - This is a group of injectable therapy in incretin family. These are generally well tolerated, with transient mild to moderate gastrointestinal side effects at the introduction of the drug.
  - Weight loss has been shown in dose-dependent manner. No hypoglycaemic events are seen, unless in combination with other therapies. These drugs are injectable and costly.

Table 6: Non-insulin therapies for Type 2 DM

Class /compound	Dose	Advantage	Disadvantage	Reduction of HbA1c
Biguanides ➢ **Metformin**	500-2000mg in divided doses Start at a low dose after meals	Extensive experience No weight gain No hypoglycaemia Likely ↓ CVD events	GI side effects (diarrhoea, abdominal cramps) Lactic acidosis risk (extremely rare) Vitamin B12 deficiency(rare) Multiple contraindications: CKD, acidosis, hypoxia, dehydration	1-2%
Sulfonylureas ➢ **Tolbutamide** ➢ **Gliclazide** ➢ **Gliclazide MR**	500-2000mg in divided doses 40-320mg in 1-3 divided doses 30-120mg daily	Extensive experience ↓ Microvascular risk	Hypoglycaemia Weight gain ?Glibenclamide, Tolbutamide may blunt myocardial ischemic preconditioning	1-2%

➢ **Glipizide** ➢ **Glibenclamide** ➢ **Glimepiride**	2.5-20mg in divided doses 2.5-15mg daily in divided doses 1-6mg daily		Low durability	
α-Glucosidase inhibitors ➢ **Acarbose**	150-600mg in divided doses before meals	No hypoglycaemia ↓Postprandial glucose excursions ? ↓ CVD events	Gastrointestinal side effects (flatulence, diarrhoea) Frequent dosing schedule	0.5-1%
Meglitanides ➢ **Repaglnide** ➢ **Nategllinide**	0.4-4mg 60-180mg with meals	↑Insulin secretion Controls postprandial hyperglycaemia, Less weight gain in obese	Gastrointestinal side effects	~1%
DPP-4 inhibitors ➢ **Sitagliptin** ➢ **Vildagliptin** ➢ **Saxagliptin** ➢ **Linagliptin** ➢ **Alogliptin**	50 - 100mg once daily 50mg twice daily 5mg daily 5mg daily 6.25- 25mg daily	No hypoglycaemia Well tolerated Weight neutral CVD risk neutral	Generally modest HbA1c reduction and efficacy Urticaria/angioedema ? Pancreatitis	~1%
GLP1 receptor agonists ➢ **Exenatide twice daily** ➢ **Liraglutide** ➢ **Exenatide modified release** ➢ **Albiglutide** ➢ **Dulaglutide** ➢ **Lixisenatide** ➢ **Semaglutide**	5-10µg twice a day 0.6-1.8mg daily 2mg once weekly 30-50mg weekly 0.75-1.5mg weekly 20µg once daily 2.5-40mg daily	No hypoglycaemia Weight reduction ? Potential for improvedβ-cell mass/function Cardiovascular benefit (semaglutide/ liraglutide)	Gastrointestinal side effects (nausea/vomiting) C-cell hyperplasia/medullary thyroidtumours in animals Injectable Training requirements	1-1.5%
TZD ➢ **Pioglitazone**	15-30mg once daily	No hypoglycaemia Durability ↑ HDL ↓ Triglycerides ↓CVD events	Weight gain Oedema/heart failure Fractures ? ↑ Bladder cancer	0.5-1%
SGLT2 Inhibitor ➢ **Dapagliflozin** ➢ **Canagliflozin**	5-10mg once daily with/without meals 100-300mg	No hypoglycaemia ↓ Weight ↓ Blood pressure ↑HDL/↓ TG Effective at all	Increased Genitourinary infections Polyuria Euglycaemic ketoacidosis Volume depletion/	0.5-1%

➢ **Empagliflozin**	daily 10 - 25mg daily	stages of T2DM & T1DM Better cardiovascular outcome (Empagliflozin)	Hypotension/ Dizziness ↑LDL ?↑creatinine transiently	

6.3.3. Sequential insulin strategy in Type 2 DM (Figure 3)

- T2DM is a progressive disease and with time OHA may fail to achieve glycaemic targets. Insulin therapy should be promptly started in such patients.

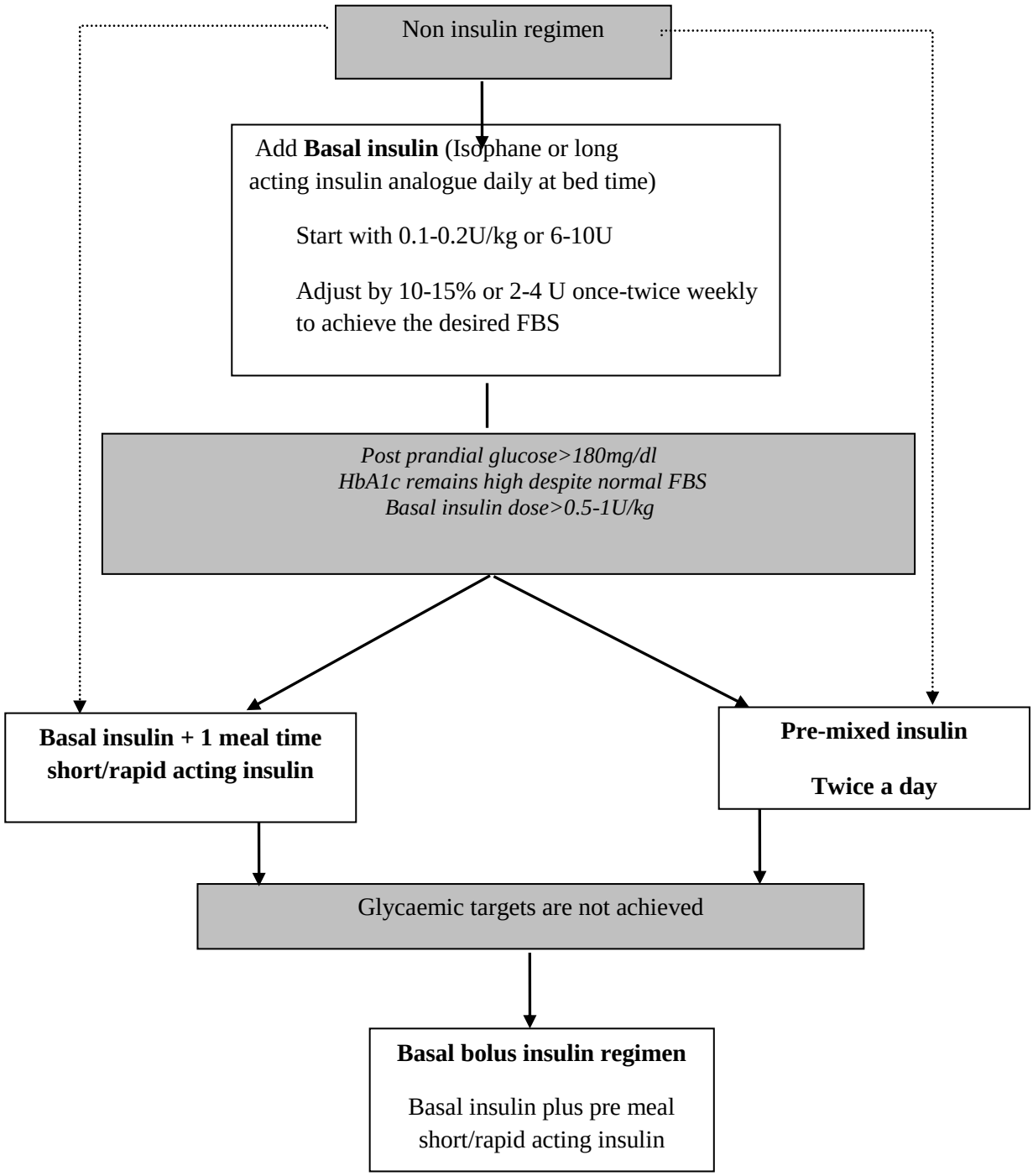
- Basal insulin (Insulin Glargine, Detemir, Isophane insulin) is recommended as add on therapy to OHAs, starting at 6-10 units or 0.1 -0.2 units/kg at bedtime. It can be adjusted by 2-4 units once or twice weekly to achieve the desired FBS. Long acting basal insulin analogues (Glargine and Detemir) have a lower risk of hypoglycaemia, but these are expensive. Intermediate acting Isophane insulin is a cheaper alternative in the local setting.

- If the post-prandial glucose (>180mg/dl) and HbA1c remains high, despite high doses of basal insulin (>0.5-1U/kg), consider adding one dose of pre-meal regular or rapid acting insulin. Premixed insulin (twice daily) either alone or in combination with OHAs can be used as an alternative regimen at this point.

- In patients who do not meet the glycaemic targets with above insulin regimens “basal-bolus” insulin therapy should be considered. Basal bolus therapy involves giving longer acting insulin during fasting state to keep the basal plasma glucose stable and giving pre meal shorter acting insulin to control the post prandial rise of plasma glucose. It is preferable to refer such patients to a diabetic clinic for advice by a specialist.

- *Refer to annexure 2 for details of insulin types*

Figure 3: SEQUENTIAL INSULIN STRATEGY IN TYPE 2 DM



6.4. PRINCIPLES OF MANAGEMENT OF PREDIABETES

- Intensive life style measures targeting weight loss of 7% of body weight significantly reduces CV risk and development of overt diabetes.
- Metformin may be considered especially for obese (BMI>35 kg/m^2), young people (less than 60 year s) and women with a history of gestational diabetes.
- Annual monitoring for the development of diabetes is recommended.
- Screening and treatment of modifiable risk factors for cardiovascular disease should be done.

6.5. MANAGEMENT OF DIABETES IN ELDERLY

- An HbA1c goal of 7-8% is adequate in most elderly and a less stringent control is recommended for those with shorter life expectancy.

- Drugs should be started at the lowest dose and titrated up gradually.

- Polypharmacy may affect compliance, cause drug interactions and worsen adverse effects such as hypoglycaemia and hypotension.

Table 7: Glycaemic recommendations for Older Adults

Patient characteristics	Cognition	Chronic illness	Functional status	Fasting/ pre prandial blood glucose mg/dl	Bedtime blood glucose mg/dl	HbA1c goal
Healthy	Intact	Few or none	Intact	90-130	90-150	< 7.5%
Complex/ Intermediate	Mild-moderate impairment	multiple	Partial dependency	90-150	100-180	<8 %
Very complex / poor health	Moderate to severe impairment	End stage	Full dependency	100-180	110-200	< 8.5%

7. MANAGEMENT OF CARDIOVASCULAR RISK FACTORS (5-7, 12-17)

Cardiovascular diseases (CVD) are the major cause of morbidity and mortality among diabetic patients; two thirds of diabetics die of cardiovascular diseases. CVD are defined as coronary artery disease (CAD) which include myocardial infarction, stable or unstable angina and coronary revascularization, stroke, transient ischaemic attack and atherosclerotic peripheral vascular disease.

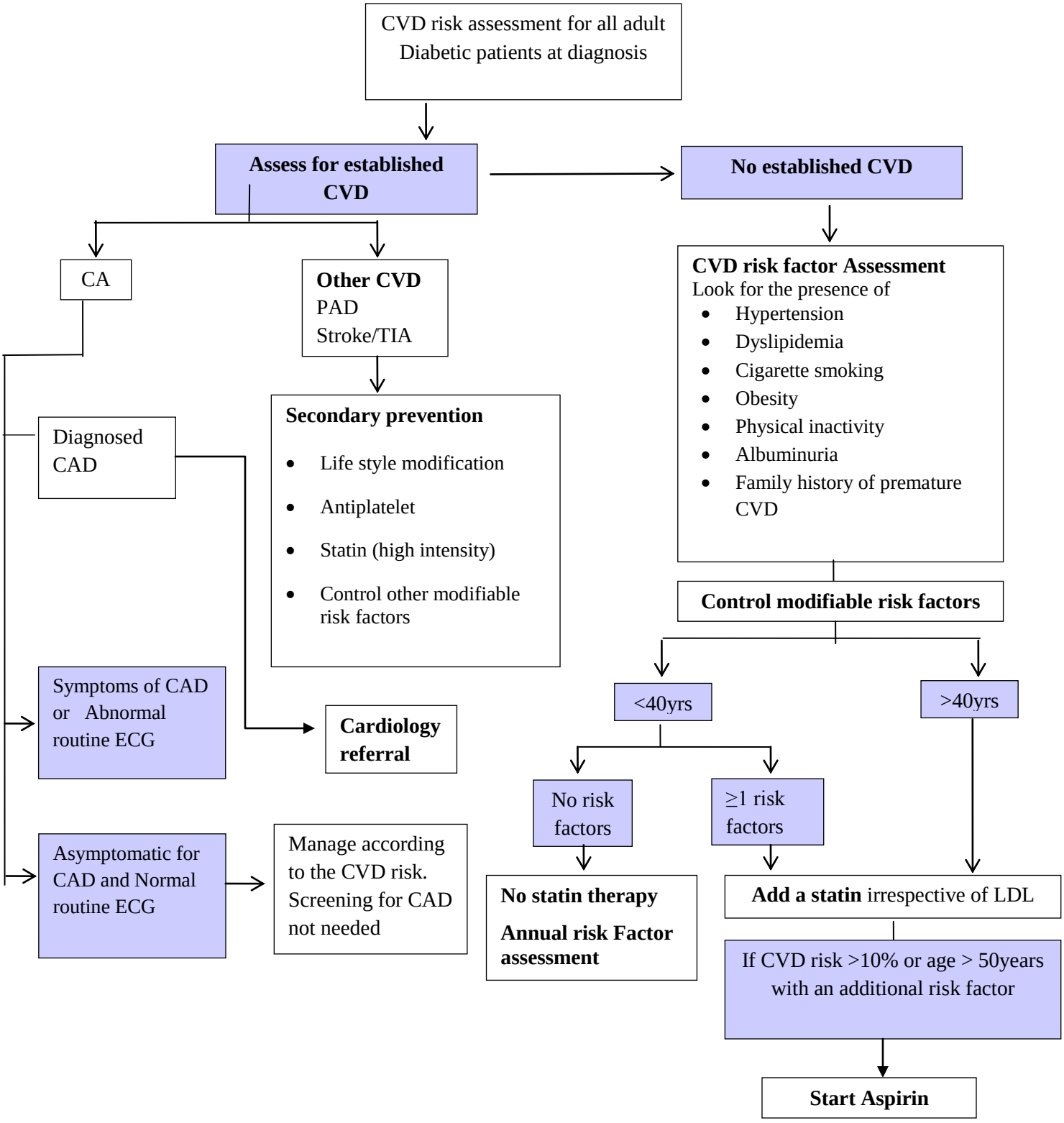
Diabetes itself is considered as a independent risk factor for CV disease. Furthermore, majority of patients with diabetes has additional cardiovascular risk factors (Table 8). Presence of additional CV risk factors exponentially increases cardiovascular morbidity and mortality.

Table 8: Definitions of CVD risk factors

Risk Factor	Evaluation
Smoking	History of current and past smoking habits/ exposure to passive smoking
Hypertension	History of hypertension on therapy Blood pressure >140/90mmHg
Dyslipidemia	LDL cholesterol >100 mg/dL (2.6 mmol/L)
Albuminuria/ microalbuminuria	UACR (>30mg/g) with otherwise normal UFR
Family history of premature cardiovascular disease	CVD in first-degree male relatives < 55 years or female relatives < 65 years.
Established Coronary artery disease	History of ischaemic heart disease
Cerebrovascular disease	History of stroke or transient ischaemic attacks
Chronic Kidney disease	abnormalities of kidney structure or function (eGFR < 60ml/min/1.73m^2), present for >3 months, with implications for health

We recommend that all patients should be evaluated for CV risk factors at the diagnosis of diabetes and annually thereafter.

Figure 4: Algorithm for management of CV risk in Diabetes



7.1. Blood pressure control

Good blood pressure control has proven to be beneficial in reducing complications of diabetes mellitus. Blood pressure should be recorded at the time of diagnosis and every routine visit. BP measurement should be carried out according to established guidelines *(Ref to Hypertension management guidelines, CCP)*

- Diabetic patients with office BP > 140/90 mmHg should be treated with life style measures and pharmacological therapy to achieve target BP less than 140/90 mmHg.
- Lower BP targets of <130/80 mmHg can be considered for younger patients, patients with albuminuria and/or chronic kidney disease.
- In older adults lowering blood pressure to <130/70 mmHg is not recommended.

Pharmacological therapy

- Drug of first choice is an angiotensin converting enzyme inhibitor (ACEi). Angiotensin receptor blocker (ARB) can be used where ACEi is not tolerated.
- A combination of drug classes (ACEI/ARB plus CCB, thiazide diuretic, beta blockers, alfa-blockers) may be necessary to achieve the blood pressure targets.
- Combination of ACEi and ARB together is not recommended due to increased incidence of hyperkalaemia and renal impairment.

7.2. Management of dyslipidaemia in diabetes

- Intensification of life style modifications addressing weight loss, dietary advice and physical activity is recommended as the initial step.
- Statin is the drug of choice to lower LDL cholesterol and to reduce the risk of CV disease. ADA Standard of Care position statement 2017 (revised) recommends high vs. moderate intensity statin therapy (Table 9) based on risk factor profile.
- Cardiovascular risk factors include LDL cholesterol ≥100mg/dl, high blood pressure, smoking, obesity and family history of premature CV disease.

Table 9: High and moderate intensity Statin therapy

Moderate intensity	High intensity
Lowers LDL cholesterol by 30% to<50% Atorvastatin 10 -20 mg Rosuvastatin 5- 10 mg Simvastatin 20 – 40 mg Pravastatin 40 – 80 mg	*Lowers LDL cholesterol by ≥ 50%* Atorvastatin 40 – 80 mg Rosuvastatin 20 – 40 mg

7.2.1. Recommendations for statins based on cardiovascular risk in people with diabetes

Age less than 40 years

- Statin therapy is not recommended for individuals with no risk factors.
- Moderate intensity statin therapy is recommended for those with other CV risk factors.
- For those who have established cardiovascular disease high intensity statin therapy is recommended.

Age - 40-75 years

- All patients even without additional risk factors will need moderate intensity statin therapy.
- Patients with cardiovascular risk factors and/or established cardiovascular disease should be given high intensity statin therapy.

Age >75years

- Limited data are available on the benefit of statin therapy in this age group. Therefore statin therapy should be individualized depending on risks and benefits.
- Individualized decision should be made in those without CV risk factors.

7.2.2. Other lipid lowering therapies

- For patients with fasting triglyceride levels >500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy with fibrates to reduce risk of pancreatitis.
- Addition of ezetimibe to moderate-intensity statin therapy can be considered in
    - high risk patients who have less than anticipated response to statins
    - Patients unable to tolerate the recommended intensity of a statin
- Combination therapy of statins with fibrates (gemfibrozil, fenofibrate) is not shown to significantly reduce the CV outcome (11) but associated with higher incidence of side effects; elevated transaminases myositis and rhabdomyolysis.

7.2.3. Follow up for lipid lowering therapy

- Lipid profile should be obtained at the time of diagnosis and any time before initiation of statin therapy. Follow up lipid profile may be helpful in monitoring compliance. However it is not always necessary once the patient is stable on therapy.
- There is no evidence to support titrating doses to achieve optimal LDL and HDL in both primary and secondary prevention of CVD.

7.2.4. Antiplatelet therapy

- Low dose aspirin therapy (75mg/day) is recommended for primary prevention of CV disease in individuals with diabetes if they have a 10-year risk of CV events over 10%.
- This will include most men and women aged 50 years or above with one or more of the major risk factors which include,
    - Smoking

- Hypertension
- Dyslipidaemia
- Family history of premature coronary artery disease
- Albuminuria

- Aspirin therapy is indicated as secondary prophylaxis for those with established cardiovascular disease.

8. MANAGEMENT OF COMPLICATIONS OF DIABETES MELLITUS (5-7, 17-25)

Tight glycaemic control from early stages of diabetes, is known to prevent and delay the progression of microvascular and macrovascular complications. Apart from glycaemic control, other factors such as adequate blood pressure control, lipid control and stopping smoking are also important in preventing complications.

Screening for microvascular complications in Type 2 DM should be started at diagnosis. Screening in type1 diabetes should be initiated after 5 years from the diagnosis. Once started,screening should be repeated at least annually.

8.1. Diabetic Neuropathy

8.1.1. Distal Symmetrical polyneuropathy (DPN)

- Assessment of DPN should include a careful history and 10-g monofilament testing with at least one of the following tests: pinprick sensation, ankle reflex or vibration perception using 128 Hz tuning fork, vibration perception threshold (using the Bio-Thesiometer)
- DPN is a diagnosis of exclusion. In all patients with diabetes and peripheral neuropathy, causes of neuropathy other than diabetes should be considered. They include, toxins, alcohol, vitamin B12 deficiency, hypothyroidism, renal disease, CIDP, malignancies (multiple myeloma, bronchogenic carcinoma), infections (leprosy, HIV), vasculitis and drugs. An alternative cause is suggested by the presence of asymmetry, high ESR, absence of other microvascular complications and rapid progression.

- Presence of peripheral neuropathy in a diabetic is a major risk factor for foot complications. Therefore, emphasis should be made on proper foot care.
- Optimal glucose control will delay the progression of DPN.
- Painful DPN is treated with the following symptomatic therapy,
    - Antidepressants - TCA, SNRI
    - Antiepileptics – pregabalin, gabapentin, phenytoin, carbamazepine
    - Topical Capsacin

8.1.2. Diabetic autonomic neuropathy

Major clinical manifestations of diabetic autonomic neuropathy are resting tachycardia, exercise intolerance, orthostatic hypotension, gastroparesis, constipation, erectile dysfunction and lack of autonomic response to hypoglycaemia.

Management of Diabetic autonomic neuropathy

- **Gastroparesis**
    - Dietary modifications: Low fat low fiber diet
    - Prokinetic drugs: Metoclopramide, Domperidone, Erythromycin
    - Others: NG drainage, Intra jejunal feeding, gastric pacemaker therapy
    - Due to side effects with long term use of metoclopramide, it should be reserved for patients with most severe symptoms unresponsive to other therapies and the duration of therapy should not exceed three months.
- **Autonomic Diarrhea**
    - Codeine, Loperamide, Antibiotics, Clonidine
- **Erectile dysfunction**
    - Phosphodiesterase inhibitors: Sildenafil, Tadalafil
    - Prostaglandins: Alprostadil
    - Vacuum devices and prosthesis
- **Postural hypotension**
    - Non pharmacological: adequate salt intake, compressive garments over the legs and abdomen, avoiding medications that aggravate hypotension, standing slowly from lying down position.

- Pharmacological: fludrocortisone, Midodrine

8.2. Diabetic foot Complications

Follow up and management of diabetic foot depends on the risk category, categorized according to the presence of the following four risk factors (table 10).

- Previous ulcer or amputation
- Peripheral Artery Disease
- Current deformity /callus/ulcer
- Sensory neuropathy (see section on neuropathy assessment)

Table 10: Management of Diabetic foot complications

Risk category	Definition	Recommended action	Review
Low Risk foot	No risk factors	Foot care education Optimize metabolic control	Annual
High risk foot	1 risk factor present	Special foot wear Offer intervention Above Measures	Every 3 -6 months
Super high risk foot	Previous ulceration or amputation or 2 of other risk factors	Special foot wear Offer intervention Above Measures	Every 2 -3 months
Foot emergencies	Ulcer Injury Infection	Offer treatment appropriately. Above Measures	Every 1 -2 months

Foot care advices and patient motivation should be done regularly.

Foot care advices include,

- Use of appropriate footwear
- Avoid walking barefoot
- Keeping feet clean and dry. Application of moisturizer to prevent cracked soles
- Trimming toe nails appropriately
- Inspection of feet for early detection of complications such as infection, blisters and callus

In the presence of neuropathic ulcer and charcot foot, refer for offloading with appropriate footwear or casts.

8.3. Peripheral Arterial disease (PAD)

PAD is a marker of systemic vascular disease (MI, Stroke). A significant proportion of patients with PAD are asymptomatic.

8.3.1. Assessment of PAD

- Obtain history of claudication, rest pain.
- Examine the extremity for pulse, non-healing wounds and gangrene
- Ankle- Brachial index (ABI) is indicated in the following circumstances
    - Clinical PAD
    - Age> 50 years or < 50 years with other PAD risk factors

      (e.g: smoking, hypertension, hyperlipidemia)
- ABI may be falsely negative in calcified-poorly compressible vessels associated with diabetes and advanced age and in moderate aortoiliac stenosis
- The diagnostic criteria for PAD based on the ABI are as follows
    - Normal if 0.91–1.30
    - Mild obstruction if 0.70–0.90
    - Moderate obstruction if 0.40–0.69
    - Severe obstruction if <0.40
    - Poorly compressible if >1.30

8.3.2. Management of PAD

- Foot care advice
- Cessation of smoking
- Optimize cardiovascular risk factors
- Exercise rehabilitation-supervised treadmill walking
- Drugs – Cilostazol
- Revascularization in

- Refractory claudication
- Critical limb Ischaemia rest pain or tissue loss-non-healing ulcer/gangrene)

(Revascularization is not indicated in individuals with severe reduction in ABI <0.4 in the absence of symptoms)

8.4. Diabetic Nephropathy

- Onset and progression of nephropathy should be assessed by,
  - Spot urinary albumin to creatinine ratio -preferably in the first void sample
  - Serum creatinine with Estimated glomerular filtration rate (eGFR)
- Marked hyperglycaemia, very high blood pressure, excessive physical exercise in the previous 24 hours, urinary tract infection, fever, congestive heart failure are known to cause transient elevations in urinary albumin excretion.
- Persistent albuminuria is defined as albumin to creatinine ratio ≥ 30 mg/g continuing over 3-6 months. Treatment of persistent albuminuria retards progression to ESRD.
- In patients with renal impairment consider and exclude alternative causes (Table 11)

Table 11 : Situations where an alternative cause of renal impairment should be considered
▪ Absence of retinopathy ▪ Presence of active urine sediments ▪ Rapidly increasing proteinuria ▪ Rapidly decreasing eGFR ▪ Evidence of systemic diseases-vasculitis ▪ Evidence of urological cause -Abnormal findings on renal ultrasound ▪ Resistant hypertension ▪ > 30% reduction in eGFR after initiating ACE inhibitor or ARB therapy

8.4.1. Management of diabetic nephropathy

- Maintaining normoglycaemia is shown to delay the onset and progression of diabetic nephropathy in both Type 1 DM and Type 2 DM.

- Blood pressure targets of <140/90 mmHg (if albuminuria,< 130/80mmHg) is recommended to retard the progression of CKD. Either ACEI or ARB (in patients intolerant to ACEi) is recommended for management of albuminuria even in normotensive patients and for blood pressure reduction. Combination therapy with ACEI and ARB is not recommended.
- When eGFR is below 60 ml/min/1.73 m2, potential complications of CKD should be evaluated and managed (Table 12). These patients are best managed under specialist care.

Table 12: Management of Diabetic Nephropathy

eGFR (mL/min/1.73 m2)	Management
45–60	• Monitor eGFR 6 monthly • Monitor electrolytes, bicarbonate, hemoglobin, calcium, phosphorus and parathyroid hormone yearly • Assure vitamin D sufficiency. • Consider bone density testing
30–44	• eGFR every 3 months • Monitor electrolytes, bicarbonate, calcium, phosphorus, parathyroid hormone, hemoglobin, albumin and weight every 3–6 months. • Consider the need for dose adjustment of medications. • Assure vitamin D sufficiency • Consider bone density testing
<30	• Referral to a Nephrologist

8.5. Diabetic Retinopathy

The local prevalence of diabetic retinopathy in diagnosed patients with diabetes was found to be 27% (93.4% NPDR , 5.3% maculopathy).

Risk factors for progression of retinopathy

- Duration of diabetes
- Chronic hyperglycaemia
- High blood pressure
- Renal disease

- Hyperlipidemia
- Pregnancy

8.5.1. Screening and management of Diabetic Retinopathy

- All patients with type 2 diabetes should be screened for diabetic retinopathy at the time of diagnosis with direct ophthalmoscopy/ slit lamp and fundus lens/ mydriatic or non mydriatic fundus photography
- Management, specialist referral and follow up should be decided upon the presence and severity of diabetic retinopathy (table 13).

Table 13: Management of Diabetic Retinopathy

Stage of Retinopathy	Features	Treatment
Mild non-proliferative	Microaneurysms Cotton wool spots <5	Control risk factors
Severe non-proliferative	Increased microaneurysms Multiple hemorrhages Cotton wool spots > 5 Venous beading	Urgent ophthalmology referral Control risk factors
Proliferative	New vessels and fibrous proliferation Hemorrhages	Urgent ophthalmology referral-panretinal photocoagulation, vitreoretinal surgeries Control risk factors
Advanced diabetic eye disease -	Retinal detachment Rubeosis iris Neovascular glaucoma	Urgent ophthalmology referral-vitreoretinal surgeries Control risk factors
Maculopathy	Macular edema Ischemic maculopathy	Urgent ophthalmology referral Focal Laser photocoagulation , VEGF antibody Control risk factors

- Women with preexisting diabetes who are planning pregnancy, should have a detailed eye examination. Laser photocoagulation minimizes the risk of progression of retinopathy during pregnancy.
- Those who have become pregnant, should be examined in the first trimester with close follow-up throughout pregnancy up to 1 year postpartum

9. MANAGEMENT OF DIABETIC EMERGENCIES (5-7, 26)

9.1. Diabetes ketoacidosis

Diabetic ketoacidosis (DKA) is an acute life-threatening complication of diabetes. It occurs mainly in patients with Type 1 DM. However, DKA can complicate Type 2 DM as well. DKA is a complex disorder of metabolic state characterized by hyperglycaemia, ketoacidosis, and ketonuria due to relative or absolute insulin deficiency.

9.1.1. Diagnosis of DKA

- Ketonaemia > 3.0 mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
- Blood glucose > 11.0mmol/L or known diabetes mellitus
- Bicarbonate < 15.0mmol/L and/or venous pH < 7.3

9.1.2. Assessment of severity

The presence of one or more of the following may indicate severe DKA and should be reviewed by specialist and considered for referral to a HDU (High Dependency Unit) care

- Bicarbonate level below 5 mmol/L
- Venous/arterial pH below 7.0
- Blood ketones over 6 mmol/L
- Hypokalaemia on admission (under 3.5mmol/L)
- GCS less than 12
- Oxygen saturation below 92% on air (assuming normal baseline respiratory function)
- Systolic BP below 90mmHg
- Pulse over 100 or below 60bpm
- Anion gap above 16 [Anion Gap = (Na+ + K+) – (Cl- + HCO3-)

9.1.3. Management of DKA

9.1.3.1. Fluid replacement

Assess the severity of dehydration clinically by pulse and blood pressure. If systolic BP (SBP) on admission is below 90mmHg consider other causes of low blood pressure such as cardiogenic shock and sepsis in addition to hypovoalemia.

- Give 500ml of 0.9% sodium chloride solution over 10-15 minutes.
- If SBP remains below 90mmHg this can be repeated
- If there has been no clinical improvement reconsider other causes of hypotension and seek an immediate specialized assessment
- Once SBP above 90mmHg continue fluid replacement as shown in Table 14.

Table 14. Fluid replacement regimen for a previously well 70kg adult	
Fluid	**Volume**
0.9% sodium chloride 1L *	1000 ml over 1st hour
0.9% sodium chloride 1L with KCl	1000 ml over next 2 hours
0.9% sodium chloride 1L with KCl	1000 ml over next 2 hours
0.9% sodium chloride 1L with KCl	1000 ml over next 4 hours
0.9% sodium chloride 1L with KCl	1000 ml over next 4 hours
0.9% sodium chloride 1L with potassium chloride	1000 ml over next 6 hours
Re-assessment of cardiovascular status at 12 hours is mandatory, further fluid may be required A slower infusion rate should be considered according to age and other risk factors * Potassium chloride may be required if more than 1 liter of sodium chloride has been given already to resuscitate hypotensive patients	

Exercise caution and use central venous pressure measurements where possible to guide the rate of fluid administration in following groups of patients

- Young adults aged <25 years
- Elderly
- Pregnant
- Heart or kidney failure
- Other serious co-morbidities

When blood glucose falls below 250 mg/dl (14.0 mmol/L), commence 10% glucose given at 125ml/hour alongside the 0.9% sodium chloride solution

9.1.3.2. Insulin therapy

Intravenous insulin infusion of 0.1 units/per kilogram body weight is recommended

Monitor capillary blood glucose hourly

Metabolic treatment targets:

- Reduction of the blood ketone concentration by 0.5mmol/L/hour
- Increase the venous bicarbonate by 3.0mmol/L/hour
- Reduce capillary blood glucose by 3.0mmol/L/hour
- Maintain potassium between 4.0 and 5.5mmol/L

If these rates are not achieved, then the rate of insulin infusion should be increased

Continue insulin infusion until the ketone measurement is less than 0.6mmol/L, venous pH over 7.3 and/or venous bicarbonate over 18mmol/L (Resolution of DKA)

9.1.3.3. Potassium replacement

Although DKA patients may present with hyperkaelemia, with treatment (Fluid and insulin) potassium level falls. Table 15 will give a guide to potassium replacement.

Table 15: Principals of Potassium replacement	
Potassium level (mmol/L)	Potassium replacement in mmol/L of infusion solution (mmol/L)
Over 5.5	Nil
3.5-5.5	40
<3.5	Senior review as additional potassium may be needed.

Monitor serum potassium 2 hourly and bicarbonate levels 2 hourly during the first six hours.

9.1.3.4. Correction of acidosis

Fluid and insulin replacement usually corrects acidosis. Bicarbonate administrations is potentially dangerous and not recommended.

9.1.3.5. Assessment of resolution of ketoacidosis

- Blood ketones less than 0.6mmol/L and
- Venous pH over 7.3 (do not use bicarbonate as a surrogate at this stage because the hyperchloraemic acidosis associated with large volumes of 0.9% sodium chloride will lower bicarbonate levels)

9.1.3.6. Other key strategies

- **Identify and treat precipitating factors**
  Infections, other stresses include pancreatitis, myocardial infarction, stroke, trauma, and alcohol and drug abuse
- **Prophylaxis for DVT**

9.1.3.7. Conversion to subcutaneous insulin

Intravenous Insulin infusion should be converted to an appropriate subcutaneous regimen when DKA is resolved and the patient is ready and able to eat.

Intravenous insulin infusion should not be discontinued for at least 30 to 60 minutes after the administration of the subcutaneous dose is given with a meal.

- **Restarting subcutaneous insulin for patients already established on insulin**

The patient's previous regimen should generally be re-started if their most recent HbA1c suggests acceptable level of control i.e. HbA1c <8.0%

- **Calculating the subcutaneous insulin dose in insulin-naïve patients**

Estimate Total Daily Dose (TDD) of insulin = patient's weight x 0.5 or 0.75. (Use 0.75 units/kg for those thought to be more insulin resistant i.e. teens, obese) Calculate Basal Bolus (QDS) Regimen or twice daily (BD) regimen

9.2. Hyperosmolar hyperglycemic state (HHS)

Hyperosmolar hyperglycemic state is a life threatening metabolic derangement that occur mostly in patients with type 2 DM who have some concomitant illness that leads to reduced fluid intake. Infection is the most common preceding illness and it is usually present in older patients with type 2 DM. HHS carries a higher mortality than DKA

9.2.1.Diagnosis

- Hypovolaemia
- Marked hyperglycaemia (30 mmol/L or more) without significant ketonaemia (<3 mmol/L) or acidosis (pH>7.3, bicarbonate >15 mmol/L)
- Osmolality > 320 mOsm/kg

Alteration in mental status is common if osmolality> 330 mOsm/kg

9.2.2. Management

9.2.2.1. Fluid replacement

Fluid losses in HHS are estimated to be between 100 -220 ml/kg (6 -13 liters in a 60 kg person) with Na^+ loss (300 -780 mmol), K^+ loss (240 -360 mmol/L) and Cl^- loss (300 -900mmol)

The aim of treatment should be to replace approximately 50% of estimated fluid loss within the first 12 hours and the remainder in the following 12 hours

Use 0.9% sodium chloride solution to restore circulating volume and reverse dehydration.

Fluid replacement alone will lower blood glucose, serum sodium and osmolality

Rapid changes must be avoided – a safe rate of fall of plasma glucose of between 4 and 6 mmol/h is recommended

Measure or calculate osmolality every hour initially and the rate of fluid replacement should be adjusted to ensure a positive fluid balance sufficient to promote a gradual decline in osmolality.

The rate of fall of plasma sodium should not exceed 10 mmol/L in 24 hours

If osmolality is no longer declining despite adequate fluid replacement with 0.9% saline AND an adequate rate of fall of plasma glucose, 0.45% sodium chloride solution should be substituted

9.2.2.2.Insulin therapy

Insulin should not be started before fluid resuscitation unless there is significant ketonemia (clinical or 3β-hydroxy butyrate > 1 mmol/L)

The recommended insulin dose is intravenous insulin infusion given at 0.05 units per kg per hour.

A fall of glucose at a rate of up to 5 mmol/L per hour is ideal

Once the blood glucose has ceased to fall following initial fluid resuscitation, insulin may be started or, if already in place, the infusion rate increased by 1 unit/hr.

9.2.2.3. Potassium replacement

Hyperkaelemia and Hypokaelemiais less common than in DKA. If serum K is between 3.5 mmol/L to 5.5 mmol/L, replacement should be done with 40 mmol of KCl and if serum K >5.5 mmol/L, no replacement is indicated.

Other key strategies:

- **Identify and treat precipitating factors**

  Infections are the most common precipitating factor

- **Prophylaxis for DVT**
  As most patients are ill, dehydrated and bed bound, they are at increased risk of DVT

Other Electrolyte Imbalances

- Hypophosphatemia persisting beyond the acute phase of treatment of HHS, consider oral or IV replacement
- Magnesium replacement be considered if the patient is symptomatic

9.2.2.4. Recovery phase

Complete correction of electrolyte and osmolality abnormalities is unlikely to be achieved within 24 hours and too rapid correction may be harmful.

Early mobilization is recommended.

Intravenous insulin infusion can usually be discontinued and subcutaneous insulin can be started once patient is able to eat and drink but IV fluids may be required for longer if intake is inadequate.

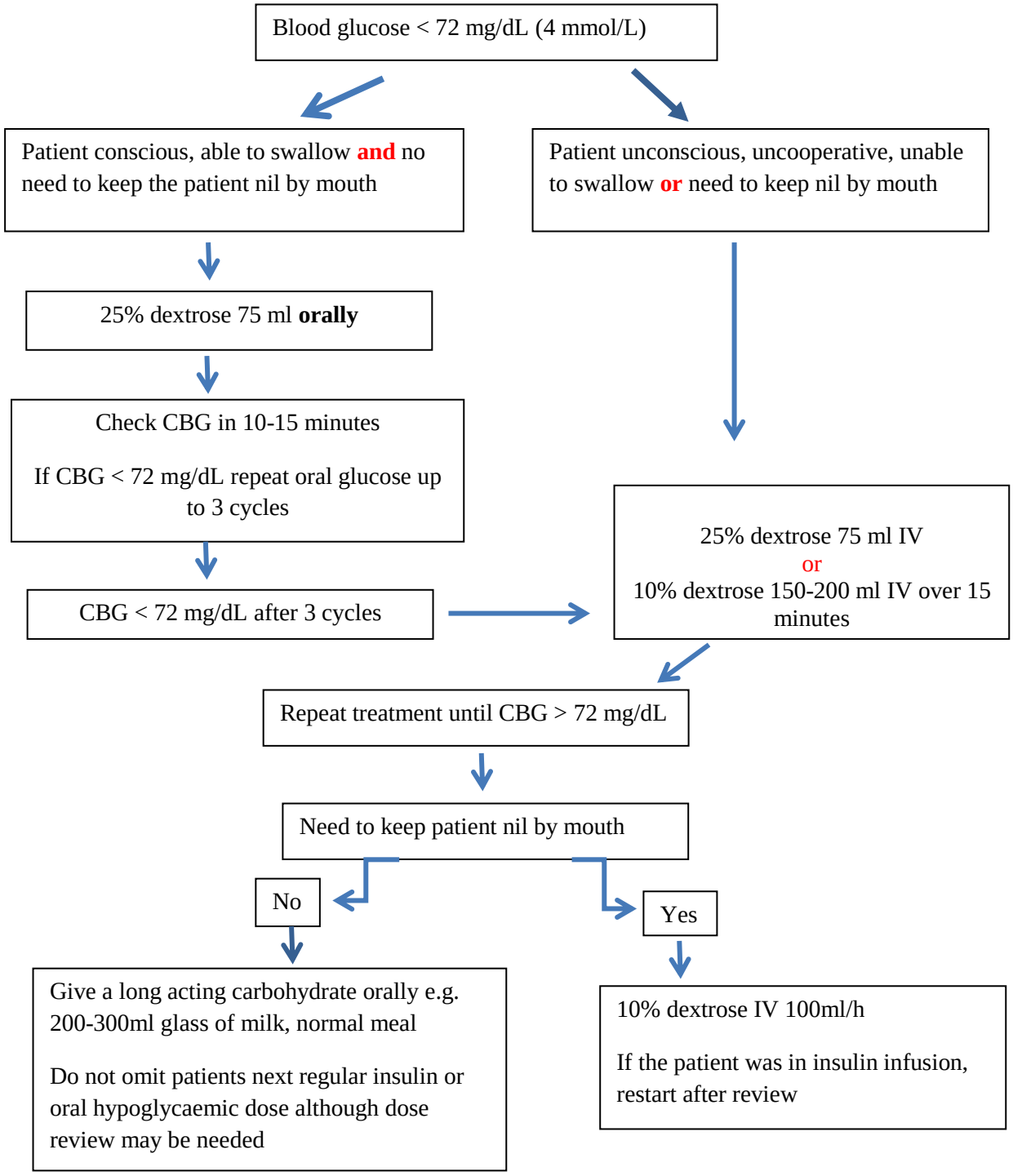
For patients with previously undiagnosed diabetes or well controlled patients on oral agents, switching from insulin to the appropriate oral hypoglycaemic agent should be considered after a period of stability (weeks or months).

7.2. Management of Hypoglycaemia (3)

Management of hypoglycaemia in the hospital setting

Hypoglycaemia is defined as blood glucose < 72 mg/dL (4 mmol/L). Any patient with blood glucose < 72 mg/dL (4 mmol/L) with or without symptoms should be treated with 15 – 20 grams of quick acting carbohydrate as soon as hypoglycaemia is diagnosed.

The type of carbohydrate and the route of administration depend on the patient's level of consciousness, ability to swallow and the need to keep the patient nil by mouth as described by the following algorithm.



Patients who experience hypoglycaemic symptoms but have a blood glucose level >72 mg/dL should be treated with a small carbohydrate snack only.

The following key points are important in management of hypoglycaemia

- Use oral glucose when possible to avoid complications of IV glucose administration and to maintain a smoother glycaemic control.
- **Avoid using 50% dextrose**. It is highly irritant and can cause serious complications. (severe thrombophlebitis and subsequent infection)
- Use a large bore cannula in a large vein when using IV dextrose
- If IV access is not available glucagon im can be given, if available.
- Do not omit next insulin or oral hypoglycaemic dose, but review the dose

Further Assessment:

- **Look for a cause for hypoglycaemia and correct it**
    - Erratic behavior – Incorrect dose/ technique, alcohol, vigorous exercises, skipping meals
    - Complication of diabetes –Renal impairment, autonomic neuropathy & hypoglycaemia unawareness
    - Other – Adrenal insufficiency
- **In the presence of hypoglycaemia unawareness or episode of severe hypoglycaemia:**
    - Re-evaluate treatment regimen
    - Insulin-treated patients: raise glycemic targets for several weeks to partially reverse hypoglycaemia unawareness and reduce recurrence

10. MANAGEMENT OF DIABETES IN SPECIAL SITUATIONS (5-7, 27-34)

10.1. Management of Diabetes in Chronic Kidney Disease

10.1.1. Measurement of Glycaemic Control

- HbA1c is affected by the severity of kidney dysfunction and the haematological complications of kidney disease.

- HbA1c is:
  - falsely decreased in haemolysis.
  - falsely elevated in acidosis and carbamylation of Hb.

- The "gold standard" is plasma glucose (FPG, PPG)
- Treatment decisions can be made by using daily glucose monitoring.

10.1.2. Pharmacological Treatment

- Clearance of many drugs and insulin is decreased by kidney disease leading to frequent hypoglycaemic episodes.
- The greatest risk is in patients with moderate to severe CKD (Stages 3–5).

Insulin

- All the available insulin preparations can be used in CKD.
- Insulin types and doses must be individualized to each patient and their level of CKD.

Oral agents

Table 16 :Oral hypoglycaemic agents in Diabetic Nephropathy

Class	Drug	CKD *Stage 3–5*	Dialysis	Complication
Biguanides	Metformin	eGFF 30-45mL/min/1.73 m2 max. dose 1,000mg/day eGFR <30 mL/min/1.73 m2 – discontinue	Avoid	Lactic acidosis
Sulphonylures	Tolbutamide	Use with caution	Avoid	Hypoglycaemia
	Glibenclamide	Avoid	Avoid	Hypoglycaemia

	Glipizide	No dose adjustment	No dose adjustment	
	Gliclazide	No dose adjustment	No dose adjustment	
	Glimepiride	Low dose: 1 mg/day	Avoid	Hypoglycemia
α-Glucosidase inhibitors	Acarbose	Avoid if Serum Creatinine> 2 mg/dl	Avoid	Possible hepatic toxicity
TZD	Pioglitazone	No dose adjustment	No dose adjustment	Fluid retention Fracture risk
DPP-4 inhibitors	Linagliptin	No dose adjustment	No dose adjustment	
	Sitagliptin	GFR 30–50 ml/min - ↓25% GFR < 30 ml/min - ↓ 50%	Reduce by 50%	Hypoglycaemia
	Vildagliptin	Reduce dose to 50 mg/d	Reduce dose to 50 mg/d with caution	Hypoglycaemia
	Saxagliptin	2.5mg/d if eGFR < 30ml/min	Reduce to 2.5mg/d	Hypoglycaemia
	Alogliptin	eGFR 30–59: 12.5 mg daily eGFR<30: 6.25 mg daily	Reduce to 6.25mg/d	Hypoglycaemia
SGLT2 inhibitors	Dapagliflozin Canagliflozin Empagliflozin	Not Recommended	Contraindicated	Not effective May worsen CKD
Incretin mimetic	Exenatide	eGFR 30–50: use caution Avoid if GFR < 30	Avoid if GFR < 30	Hypoglycaemia
	Liraglutide	No dose adjustment	No dose adjustment	
	Albiglutide	Limited experience	Limited experience	
	Dulaglutide	Limited experience	Limited experience	

10.2. Management of Diabetes in patients with heart failure

- Since 2008 FDA has recommended to conduct cardiovascular safety trials for all new anti-diabetic drugs.
- Selection of anti-diabetic medications has to be done cautiously in patients with heart failure, due to the risk of fluid retention caused by certain drugs and the risk of lactic acidosis in decompensate state.
- Dose adjustment or complete withdrawal of some drugs is necessary in parallel to the severity of cardiac failure (Table 17).

Table 17:HypoglycaemicAgents in Heart failure				
Class	Drug	NYHA 1-2	NYHA 3-4	Complications/ Special remarks
Biguanides	Metformin	can be used provided eGFR>30ml /min/1.73m^2	Avoid	Discontinue during episodes of acute heart failure due to the risk of lactic acidosis
Sulphonylurea	Glibenclamide/ glimepiride	Limited data Available. use with caution	Limited data Available. use with caution	
	Gliclazide / Glipizide/Tolbutamide	No dose adjustment	use with caution	
Thiazolidinedione	Pioglitazone	Better avoided	Contraindicated	Worsen heart failure by fluid retention and increased hospitalization.
α-glucosidase inhibitors	Acarbose	Safe. But can lead to malabsorption of cardiac drugs	Safe. But can lead to malabsorption of cardiac drugs	Interact with drug absorption
Meglitinides	Repaglinide nateglinide	No safety data available. Better avoided	No safety data available. Better avoided	
DPP 4 inhibitors	Sitagliptin	No dose adjustment	No dose adjustment	No added risk of worsening of heart failure
	Saxagliptin	Use with caution	Use with caution	Increased hospitalization due to heart failure reported.
	Vildagliptin Alogliptin	No dose adjustment	No dose adjustment	
GLP-1	Exenatide Liraglutide Albiglutide Dulaglutide	Safe to use	Safe to use	
SGLT 2 inhibitors	Empagliflozin Canagliflozin Dapagliflocin	Safe to use	Safe to use	
Insulin		Safe to use	Safe to use. Be cautious of fluid retention	

10.3. Management of diabetes in patients with liver dysfunction

- The liver is a primary site of drug metabolism and the impairment of drug metabolism is proportional to the liver dysfunction.
- Risk of hypoglycaemia and lactic acidosis is increased in severe liver dysfunction
- Therefore selection of antidiabetic drugs and their dose adjustments should be done according to the severity of liver disease (Table 18).

Table18:Hypoglycaemic agents in Liver dysfunction

Class	Drug	Mild to moderate liver disease	Severe liver Disease/ liver failure	Complications/ Special remarks
Biguanides	Metformin	Safe to use with dose adjustment	Avoid	Risk of lactic acidosis specially in patients who continue to ingest alcohol
Sulphonylurea	Glibenclamide/ glimepiride /Glipizide	Avoid	Avoid	Risk of Hypoglycaemia
	Gliclazide / Tolbutamide	Use with caution	avoid	Risk of Hypoglycaemia
Thiazolidinedione	pioglitazone	Avoid	Avoid	Can cause liver injury and elevation of LFTs, monitor liver enzymes
α-glucosidase inhibitors	Acarbose	Safe to use	Use with caution	May reduce blood ammonia levels. Can be used in low-grade hepatic encephalopathy
Meglitinides	Repaglinide nateglinide	Use with caution	Avoid	Risk of Hypoglycaemia
DPP 4 inhibitors	Sitagliptin	Safe to use	No safety data	Eliminated by kidney
	Saxagliptin	Use with dose adjustment	Avoid	Eliminated by liver
	Vildagliptin Alogliptin	No safety data	No safety data	
GLP-1	Exenatide Liraglutide Albiglutide Dulaglutide	Use with caution	Avoid	
SGLT 2 inhibitors	Empagliflozin Canagliflozin Dapagliflocin	No dose adjustment	Avoid	
Insulin		Safe to use. May need dose adjustment	Use with caution	Careful glucose monitoring and frequent dose adjustments needed

10.4. Peri-operative Care in a Diabetic Patient

- Elective surgery should be postponed whenever possible if glycaemic control is poor (HbA1c ≥ 9%).
- Blood glucose should be kept between 80-180 mg/dl during the peri-operative period
- Preoperative risk assessment should be done for patients at high risk for ischemic heart disease and those with autonomic neuropathy or renal failure.
- Patients who undergo minor surgery which require fasting should omit their morning oral hypoglycemic medication.
- Patients on Insulin should be on long acting basal insulin given in the morning.
- Patients undergoing major surgery may require insulin – glucose infusion during surgery as well as during post operative period until oral intake is resumed.
- Once patient has resumed oral feeding blood glucose can be controlled by basal long acting insulin plus short acting insulin at meal times.

10.6. Management of Diabetes in acute illness

- All patients admitted to hospital should have their blood glucose tested.
- Hyperglycaemia in the hospital may be due to previously known diabetes, previously undiagnosed diabetes, or stress-related hyperglycaemia.
- Blood glucose levels persistently higher than 140 mg/dL (7.8 mmol/ L) should be considered for treatment in hospitalized patients.
- HbA1C values > 6.5% suggests undiagnosed diabetes that preceded hospitalization.

Non- critically ill patients

- Individualized care under a specialist is recommended.
- Basal insulin or a basal plus bolus correction insulin regimen is preferred.
    - Total daily dose of insulin:

      0.5–0.7 units/kg for Type 1 DM

      0.4–1.0 units/kg or more for patients having Type 2 DM

- Use 50% of the calculated daily dose as basal insulin (divided in two doses if Isophane insulin is used) and rest as premeal bolus in divided doses.
- If the premeal glucose is high extra dose of bolus insulin can be given (Correction-dose of insulin).
- Traditional sliding scale insulin regimens are no longer recommended and when used as sole therapy, result in large swings in blood glucose levels.

- Continuation of home regimens including oral antihyperglycemic medications may be appropriate in selected stable patients taking normal meals at regular meals under specialist advice.

  Blood Glucose Targets

Premeal	<140 mg/dL(7.8 mmol/L)
RBG	< 180 mg/dL(10 mmol/L)

- Hypoglycaemia should be avoided and treatment regimen should be modified when blood glucose values are <70 mg/dL (3.9 mmol/L).

Critically ill patients

- In critically ill ICU patients, insulin infusion should be started if blood glucose levels is>180 mg/dL
- Blood glucose levels should be maintained between 140 and 180 mg/dL (7.8–10.0 mmol/L) while the lower limit is preferred.
- In selected patients lower blood glucose target (<140mg/dL) may be appropriate. However targets less than 110 mg/dL (6.1mmol/L) are not recommended.
- Transition from IV insulin infusion to subcutaneous insulin:
  - Calculate total daily dose used in infusion(Calculate the total insulin dose given for the last 6 hours and multiply it by four to get the daily requirement) and give it as basal bolus regimen
  - Continue infusion for another 1–2 h after the first subcutaneous dose.

able 20: **I.V. Insulin protocol for ICU Patients**[5]				
Blood glucose (mg/dL)	**Insulin infusion(units/hour)**			
	A1	**A2**	**A3**	**A4**
<100	**0**	**0**	**0**	**0**
100-109	**0**	**0**	**0.5**	**1**
110-119	**0.5**	**1**	**2**	**3**
120-149	**1**	**1.5**	**3**	**5**
150-179	**1.5**	**2**	**4**	**7**
180-209	**2**	**3**	**5**	**9**
210-239	**2**	**4**	**6**	**12**
240-269	**3**	**5**	**8**	**6**
270-299	**3**	**6**	**10**	**20**
300 - 329	**4**	**7**	**12**	**24**
330-359	**4**	**8**	**14**	**28**
>360	**6**	**12**	**16**	**28**

- Glycaemic target- 140-180mg/dL (Not less than 110mg/dL)
- Standard infusion: 100 units of insulin/100 mL 0.9% NaCl via infusion device (1units/1mL)
- Enough glucose must be provided to avoid starvation ketosis and prevent hypoglycaemia: At least 5-10g of glucose/hour (**D5W:** 5% Dextrose in water or **D5W.NS:** 5% Dextrose in normal saline at 100–200mL/hour or equivalent,TPN, enteral feeding, etc.)
- Starting the Infusion: Once BG> 120 mg/dl
    - Algorithm 1: Start here for most patients.
    - Algorithm 2: start here if receiving glucocorticoids, previously on high total daily dose of insulin etc.
- Moving from Algorithm to Algorithm:
    - Moving Up: if the blood glucose is above the goal range & does not change by at least 60mg/dL within 1 hour.
    - Moving Down: When glucose is <110 mg/dL for 2hrs or decreases >60 mg/dl in 1 hour
- Patient Monitoring:Do hourly capillary glucose until glucose is within goal and may extend to 2-4 hourly if stable.
- Treatment of hypoglycaemia (blood glucose<70mg/dL)

- Stop insulin infusion drip and give IV 50% Dextrose(Awake-25ml, Not awake-50ml)
- Recheck blood glucose every 20min and repeat 25mL of 50% dextrose
- Restart insulin infusion once blood glucose is >110mg/dL for 2 checks
- Restart drip with lower algorithm

This algorithm is not intended to be used for those individuals with Type 1 DM, diabetic ketoacidosis or hyperglycaemic hyperosmolar states.

10.5. Diabetes in Pregnancy (5,6)

Tight glycaemic control in the first trimester is crucial to prevent fetal congenital malformations. Therefore preconception planning is of vital importance.

All Sri Lankan pregnant women should initially undergo screening for preexisting diabetes at Anti Natal Clinic booking visit by HBA1c or fasting blood glucose.

10.5.1. Diagnosis of Diabetes in Pregnancy

All pregnant women who attend the booking visit should be screened for diabetes in pregnancy with 2hr 75 g OGTT. If the screening test becomes negative, those women should be retested at a POA of 24 -28 weeks.

IADPSG recommended diagnostic criteria (2hr 75 g OGTT) for diagnosis

Fasting plasma glucose:	≥92 mg/dl (5.1 mmol/L)
One hour plasma glucose	≥180 mg/dl (10 mmol/L)
2 hr plasma glucose:	≥153 mg/dl (8.5 mmol/L)

10.5.2. Pre-pregnancy counselling and workup in Pre existing Diabetes

- Achieve the best possible glycaemic control before conception.
- Target HbA1c is <6.5%.
- Women with an elevated HbA1c value above 8.0% should be discouraged from becoming pregnant until their control can be improved and appropriate contraceptive advice should be provided.
- Initiate insulin to get ideal control
- Use of metformin should be under specialist care.
- Assess established diabetes complications before conception.

- Detailed renal and retinal assessment

- Stop ACE inhibitors, ARBs, Statins, fibrates and niacin before conception or as soon as pregnancy is confirmed.
- Alternative antihypertensive agents suitable for use during pregnancy (Nifedepine, Methyldopa, Prazosin, Hydralazine and Labetalol) should be substituted.
- Women with diabetes with unplanned or unexpected pregnancy, should be referred to a specialist immediately

10.5.3. Management of Diabetes during Pregnancy

- Encourage self-monitoring of blood glucose levels - both fasting and postprandial, preferably 2 h after a meal.

Table 19: Capillary blood glucose targets in GDM

Timing	Target in mg/dl
Premeal	≤95 mg/dl
1 h after a meal	≤140mg/dl
2 h after a meal	≤120 mg/dl

- Women with insulin-treated diabetes should test blood glucose levels at bed time as well.

1. Lifestyle management

Medical Nutrition Therapy

- Advice should be individualized and should be administered by a nutritionist/dietician.
- Calorie requirement in pregnancy is 30 Kcal/kg/day and in overweight pregnant ladies, it is 25 kcal/kg/day or less.
- Women with pre-existing diabetes who had previous nutritional advice need to be revised and reviewed during pregnancy.
- Dietary advices should be reemphasized at each clinic visit.

Exercise

- A minimum of 30 minutes exercise on most days of the week is recommended during a normal pregnancy (e.g. walking, swimming, cycling and aerobics).

2. Insulin use during pregnancy

- Lifestyle measures may be adequate in some, while others may need insulin from the beginning.
- Pre-mixed or basal bolus regimens are the most suitable.
- Women on insulin should be advised of the risks of hypoglycaemia particularly in the first trimester.

3. Oral glucose-lowering agents in pregnancy

- Metformin can be used with caution under specialist care in pregnancy and breastfeeding
- All other oral hypoglycaemic agents should be discontinued before pregnancy and substituted with insulin.

4. After delivery

- Women with preexisting diabetes before conception:
    - Require lower doses of insulin post partum.
    - Should be counseled on contraception and pre-conception care.

- Women with gestational diabetes:
    - Could discontinue hypoglycaemic treatment.
    - At discharge, reinforce lifestyle modification.
    - Screen for persistent diabetes at 6–12 weeks postpartum, using OGTT
    - Re screen annually
    - Those who have pre diabetes should receive lifestyle interventions or metformin to prevent diabetes.

Annexure 1: Sample meal plans for patients with diabetes

Meal plan-1 (1800 kcal)
For weight maintenance in most

Breakfast
Non-fat milk 1 cup (morning tea)
Rice 2 cups
Non-starchy vegetables 3 cups
Fish / Meat 1-2 pieces
Or
Green gram / Chick peas 2 cups with "Lunumiris"

Morning snack
Fruits 1 cup (e.g. 1 small banana)

Lunch
Rice 2 cups

Non-starchy vegetables 3 cups
Fish / Meat 1-2 pieces

Afternoon snack
Non-fat milk 1 cup
Fruits 1 cup or 2 sugar-free biscuits

Dinner
Red string hoppers – 5-7
Non-starchy vegetables 2 cups
Dhal ½ cup
Or
Rice 2 cups
Non-starchy vegetables 2 cups
Fish / Meat 1-2 pieces

Late night snack
Non-fat milk 2 cups or 2 sugar-free biscuits or fruits 1 cup

Meal plan-2 (1300 kcal)
For weight loss in most

Breakfast
Non-fat milk 1 cup (morning tea)
Rice 1 cup
Non-starchy vegetables 3 cups*
Fish / Meat 1 piece
Or
Green gram / Chick peas 1 cup with "Lunumiris"

Morning snack
Fruits 1 cup (e.g. 1 small banana)

Lunch
Rice 1 cup

Non-starchy vegetables 3 cups*
Fish / Meat 1 piece

Afternoon snack
Non-fat milk 1 cup
Fruits 1 cup or 2 sugar-free biscuits

Dinner
Red string hoppers – 3-5
Non-starchy vegetables 2 cups*
Dhal ½ cup
Or
Rice 1 cup
Non-starchy vegetables 2 cups*
Fish / Meat 1 piece

Late night snack
Non-fat milk 1 cup or 2 sugar-free biscuits

* Vegetables should be cooked without coconut milk
be cooked without coconut milk

Annexure 2 : Different Insulin types

Insulin type	Onset of action	Peak action	Duration of action	Colour
Ultra short acting/ Rapid acting insulin analogue: insulin lispro, insulin aspart, insulin glulisine Usually taken before or with a meal to cover the post prandial blood sugar elevation	<15 min	1-2 hrs	4-6 hrs	Clear
Short acting Insulin: Regular Human Insulin Taken 30 min before meal to cover the post prandial blood sugar elevation	½-1 hr	2-4hrs	6-8hrs	Clear
Intermediate acting: NPH Often combined with rapid or short acting insulin (Pre-Mixed insulin) and taken twice a day Can be used as a basal insulin at initiation of insulin therapy(Single bed time dose)	1-2 hr	6-10 hrs	>12 hrs	Cloudy
Long Acting: Insulin Glargin, Insulin Detemir, Insulin Degludec Usually used as a basal insulin and given once or twice daily Can be combined with short/ rapid acting insulin	3-4 hrs	No defined peak	12->24hrs	Clear

References

1. International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation, 2015. http://www.diabetesatlas.org

2. Katulanda P, Constantine GR, Mahesh JG, Sheriff R, Seneviratne RDA, Wijeratne S et al. Prevalence and projections of diabetes and pre-diabetes in adults in Sri Lanka—Sri Lanka Diabetes, Cardiovascular Study (SLDCS). Diabet Med 2008; 25: 1062– 1069.

3. Pinidiyapathirage MJ,Kasturiratne A, Ranawaka UK, Gunasekara D, Wijekoon N, Medagoda1 K, etal.The burden of diabetes mellitus and impaired fasting glucose in an urban population of Sri Lanka. Diabet Med.2013;30:326–332.

4. Gunawardane PTK, Somasundaram NP, Thalagala N, Fernando KRAS. The prevalence of diabetes, pre diabetes and obesity among adults living in an urban setting in Colombo, Sri Lanka. Endocrine society of Sri Lanka, annual academic sessions- Abstracts. 2014:49.

5. American Diabetes Association. Standards of medical care in diabetes 2017. Diabetes Care 2017; 40(Suppl. 1):S1–S129.

6. Diabetes Mellitus - Glycaemic control: Sri Lanka College of Endocrinologist's Clinical guidelines. 2nd ed. 2015.

7. Somasundaram N P, Somasundaram G. Companian to clinical Diabetology. 3rd ed. 2015.

8. Diabetes UP. Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with Type 2 DM (UKPDS 34). lancet. 1998;352:854-65.

9. Uk P. Intensive blood-glucose control with sulfonureas or insulin compared with conventional treatment and risk of complications in patients with type II diabetes. Lancet. 1998;352:837-53.

10. Points E, ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with Type 2 DM. New England journal of medicine. 2008 Jun 12;358:2560-72.

11. Ismail-Beigi F, Craven T, Banerji MA, Basile J, Calles J, Cohen RM, Cuddihy R, Cushman WC, Genuth S, Grimm RH, Hamilton BP. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial. The Lancet. 2010 Aug 13;376(9739):419-30.

12. Rydén L, Grant PJ, Anker SD, BerneC, Cosentino F et al. ESC Guidelines on diabetes, prediabetes& cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-

diabetes and diabetes, cardiovascular diseases of the European Society of Cardiology (ESC). Eur Heart J. 2013 Oct;34(39):3035-87.

13. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002; 106:3143.

14. Michael Pignone, Mark J. Alberts, John A. Colwell. AHA Guideline on the Assessment of Cardiovascular Risk: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014;129:S49-S73.

15. Edward W. Gregg, Silvio E. Inzucchi, Mark E. Molitch, John M.Morton, Robert E. Standards of Medical Care in Diabetes—2015. Diabetes Care 2015;38(Suppl. 1)

16. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline; A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

17. Nather A, Soegondo S, Adam JM, Nair HK, Zulkilfly AH, Villa MA, Tongson LS, Yeng BC, Wijeyaratne M, Somasundaram N, Mutirangura P. Best practice guidelines for ASEANPlus: Management of diabetic foot wounds. Sri Lanka Journal of Diabetes Endocrinology and Metabolism. 2015 Jul 10;5(1).

18. Katulanda P, Ranasinghe P, Jayawardena R. Prevalence of retinopathy among adults with self-reported diabetes mellitus: the Sri Lanka diabetes and Cardiovascular Study. BMC ophthalmology. 2014 Aug 20;14(1):1.

19. Diabetes Control and Complications Trial Research Group. Effect of pregnancy on microvascular complications in the diabetes control and complications trial. The Diabetes Control and Complications Trial Research Group. Diabetes care. 2000 Aug 1;23(8):1084-91.

20. Peripheral IO. Peripheral arterial disease in people with diabetes. Diabetes care. 2003 Dec;26(12):3333.

21. Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM. Management of patients with peripheral artery disease (compilation of 2005 and 2011 ACCF/AHA guideline recommendations). Circulation. 2013 Apr 2;127(13):1425-43.

22. Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, Hogg RJ, Perrone RD, Lau J, Eknoyan G. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Annals of internal medicine. 2003 Jul 15;139(2):137-47.

23. Control TD, Group CD. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. Kidney International. 1995 Jun 30;47(6):1703-20.

24. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. New England Journal of Medicine. 1993 Nov 11;329(20):1456-62.

25. Nelson RG, Knowler WC, Pettitt JD, Bennett PH, National Diabetes Data Group. Kidney diseases in diabetes. In: Diabetes in America. Bethesda, Md: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 1995:349–400.

26. Dhatariya K, Savage M, Claydon A, Dyer P, Evans P, Khan A. Joint British Diabetes Societies Inpatient Care Group. The management of diabetic ketoacidosis in adults. Update: September. 2013 Sep.

27. Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, Danchin N, Deaton C, Escaned J, Hammes HP, Huikuri H, Marre M. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. European heart journal. 2013 Oct 14;34(39):3035-87.

28. Silvio E. Inzucch. Metformin and Heart Failure.*Diabetes Care* 2005 Oct; 28(10): 2585-2587.

29. Masoudi FA, Inzucchi SE, Wang Y, Havranek EP, Foody JM, Krumholz HM. Thiazolidinediones, Metformin, and outcomes in older patients with Diabetes and Heart Failure an observational study. Circulation. 2005 Feb 8;111(5):583-90.

30. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, Josse R, Kaufman KD, Koglin J, Korn S, Lachin JM. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. New England Journal of Medicine. 2015 Jul 16;373(3):232-42.

31. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. New England Journal of Medicine. 2013 Oct 3;369(14):1317-26.

32. Zannad F, Cannon CP, Cushman WC, Bakris GL, Menon V, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Lam H. Heart failure and mortality outcomes in patients with type 2 diabetes taking alogliptin versus placebo in EXAMINE: a multicentre, randomised, double-blind trial. The Lancet. 2015 May 29;385(9982):2067-76.

33. Hamed AE, Abas B, Shaltout I, Esmt G, Gomez R, et al. (2015) Managing Diabetes and Liver Disease Association, Guidelines (Consensus) Development. J Endocrinol Diabetes Obes 3(3): 1073

34. Tolman KG, Fonseca V, Dalpiaz A, Tan MH. Spectrum of liver disease in type 2 diabetes and management of patients with diabetes and liver disease. Diabetes care. 2007 Mar 1;30(3):734-43.