Antihyperlipidemic Drugs

I-Introduction

- Plasma lipids are transported in complexes called lipoproteins . Metabolic disorders that involve elevations in any lipoprotein species are termed **hyperlipoproteinemias** or **hyperlipidemias**.
- **Atherosclerosis (ATCS)** is a disorder in which lipid deposits on the lining of the blood vessels, eventually producing degenerative changes and obstruction of blood flow. ATCS is a major contributor in the development of heart disease.
- **Triglycerides (TG)** and cholesterides are insoluble in water and must be bound to a lipid-containing protein (lipoprotein) for transportation throughout the body.
- Although several lipoproteins are found in the blood, we will focus on the low-density lipoproteins (LDL), very low-density lipoproteins (VLDL) and the high-density lipoproteins (HDL) with a simple definition of triglyceride and chylomicrons.

√- **Chylomicrons** are large triglyceride-rich lipoproteins produced in enterocytes from dietary lipids— namely, fatty acids, and cholesterol. Chylomicrons are composed of a main central lipid core that consists primarily of triglycerides, however like other lipoproteins, they carry esterified cholesterol and phospholipids.

√- **Triglycerides** (TG) are fats consisting of 3 fatty acids covalently bonded to a glycerol molecule. These fats are synthesized by the liver or, in the case of those derived from dietary sources, are ingested by the liver; the triglycerides are subsequently transported throughout the circulation by triglyceride-rich lipoproteins.

√- **Very-Low-Density Lipoproteins (VLDL)** are secreted by liver and export TGs to peripheral tissues.

√- Low-density lipoproteins (LDL) transport cholesterol to the peripheral cells. When the cells have all the cholesterol they need, the excess cholesterol is discarded into the blood. This can result in an excess of cholesterol, which can penetrate the walls of the arteries, resulting in atherosclerotic plaque formation. Elevation of the LDL increases the risk for heart disease.

√- **High-density lipoproteins (HDL)** take cholesterol from the peripheral cells and bring it to the liver, where it is metabolised and excreted. The higher the HDL, the lower the risk for development of ATCS. Therefore, it is desirable to see an increase in the HDL (the "good" lipoprotein) because of the protective nature of its properties against the development of atherosclerosis and a decrease in the LDL.

ϖ Classification of hyperlipidaemia genetic disorders:

Hyperlipidemia genetic disorders were classified to 5 categories as demonstrated in the figure below:

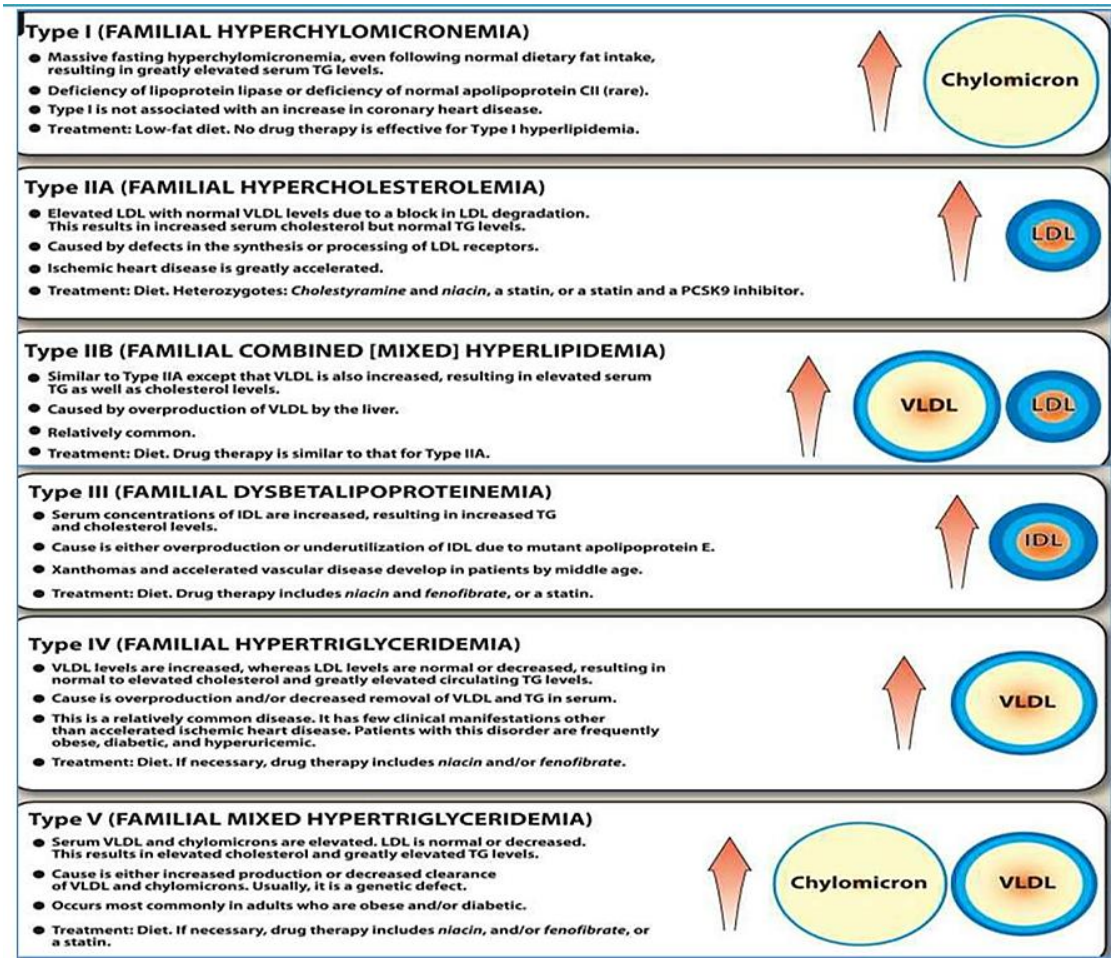

Figure 1: Characteristics of the major genetic hyperlipidemias. apo CII = apolipoprotein CII found in chylomicrons and VLDL; CM = chylomicron; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; PCSK9 = proprotein convertase subtilisin kexin type 9; TG = triglyceride; VLDL = very–low-density lipoprotein.

ϖ Drugs for Hyperlipidemia are demonstrated in the figure below:

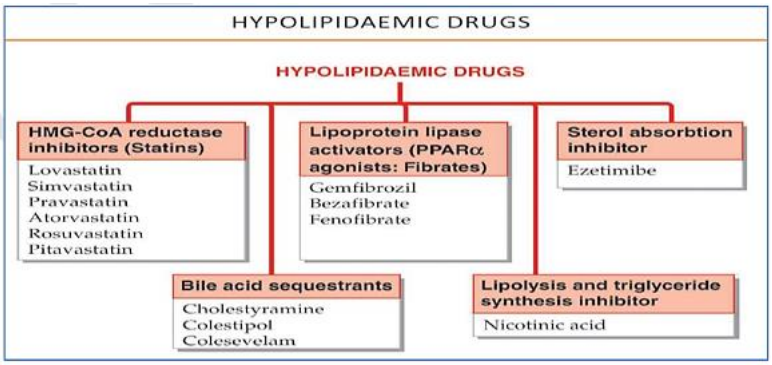

Figure 2: Characteristics of the major genetic hyperlipidemias.

1- HMG CoA reductase inhibitors:

HMG-CoA (3- hydroxy-3-methyglutaryl coenzyme A) reductase is an enzyme that is a catalyst (a substance that accelerates a chemical reaction without itself undergoing a

change) in the manufacture of cholesterol. These drugs appear to have one of two activities, namely, inhibiting the manufacture of cholesterol or promoting the breakdown of cholesterol. This drug activity lowers the blood levels of cholesterol and serum triglycerides and increases blood levels of HDLs. Examples of these drugs are Fluvastatin (Lescol), lovastatin (Mevacor), and simvastatin (Zocor). They are first line treatment for patients with elevated risk of ASCVD (atherosclerotic cardiovascular diseases) to reduce the occurrence of ASCVD events.

Therapeutic uses:

These drugs, along with a diet restricted in saturated fat and cholesterol, are used to treat hyperlipidaemia when diet and other nonpharmacologic treatments alone have not resulted in lowered cholesterol levels.

Adverse effects:

- Elevated liver enzymes may occur with statin therapy. Therefore, liver function should be evaluated prior to starting therapy or if a patient has symptoms consistent with liver dysfunction as hepatic insufficiency can cause drug accumulation.

- Myopathy and rhabdomyolysis (disintegration of skeletal muscle) have been reported. Risk factors for rhabdomyolysis, include renal insufficiency, vitamin D deficiency, hypothyroidism, advanced age, female sex, and use of drugs that increase the risk of muscle adverse effects, such as azole antifungals and erythromycin.

- The HMG CoA reductase inhibitors may also increase the effect of warfarin. Thus, it is important to evaluate the international normalised ratio (INR) when initiating a statin or changing the dosage.

- These drugs are contraindicated during pregnancy, lactation, and active liver disease.

2-Bile Acid Sequestrants:

Cholestyramine, colestipol, and colesevelam are anion-exchange resins that bind negatively charged bile acids and bile salts in the small intestine. The resin/bile acid complex is excreted in the feces, thus lowering the bile acid concentration. This causes hepatocytes to increase conversion of cholesterol to bile acids, which are essential components of the bile. Consequently, intracellular cholesterol concentrations decrease, which activates an increased hepatic uptake of cholesterol containing LDL-C particles, leading to a decrease in plasma LDL-C.

Therapeutic uses:

The bile acid sequestrates are used as adjunctive therapy for the reduction of elevated serum cholesterol in patients with hypercholesterolemia who do not have an adequate response to a diet and exercise program.

Adverse effects:

a- A common side effects is constipation. Constipation may be severe and may occasionally result in faecal impaction. Haemorrhoids may be aggravated.

b- Additional adverse reactions include vitamin A and D deficiencies.

c- Bleeding tendencies (including gastrointestinal bleeding) caused by a depletion of vitamin K, nausea, abdominal pain, and distention.

3- Fibric Acid Derivative:

Fibric acid derivatives work in a variety of ways.

a- Clofibrate (Atromid-S), acts to stimulate the liver to increase breakdown of very–low-density lipoproteins (VLDL) to low density lipoproteins (LDL), decreasing liver synthesis of VLDL and inhibiting cholesterol formation.

b- Fenofibrate (Tricor) acts by reducing VLDL and stimulating the catabolism of TG-rich lipoproteins, resulting in a decrease in plasma TG and cholesterol.

c- Gemfibrozil (Lopid) increases the excretion of cholesterol in the feces and reduces the production of triglycerides by the liver, thus lowering serum lipid levels.

Therapeutic uses:

a- Clofibrate and gemfibrozil are used to treat individuals with very high serum triglyceride levels who present a risk of abdominal pain and pancreatitis and who do not experience a response to dietmodifications. Clofibrate is not used for the treatment of other types of hyperlipidaemia and is not thought to be effective for prevention of coronary heart disease.

b- Fenofibrate (Tricor) is used as adjunctive treatment for the reduction of LDL, total cholesterol, and triglycerides in patients with hyperlipidaemia.

Adverse effects

- Include nausea, vomiting, gastrointestinal upset, and diarrhoea.
- Clofibrate, fenofibrate, and gemfibrozil may increase cholesterol excretion into the bile, leading to cholelithiasis (stones in the gallbladder) or cholecystitis (inflammation of the gallbladder). If cholelithiasis is found, use of the drug is discontinued.
- Fenofibrate may also result in abnormal liver function tests, respiratory problems, back pain, and headache.
- Gemfibrozil may cause dyspepsia, skin rash, vertigo, and headache.

4- Niacin (nicotinic acid)

Niacin reduces LDL-C by 10% to 20% and is the most effective agent for increasing HDL-C. It also lowers triglycerides by 20% to 35% at typical doses of 1.5 to 3 g/day. Niacin can be used in combination with statins, and fixed-dose combinations of long-acting niacin

with lovastatin and simvastatin are available. Note: the addition of niacin to statin therapy has not been shown to reduce the risk of ASCVD events.

Mechanism of action

At gram doses, niacin strongly inhibits lipolysis in adipose tissue, thereby reducing production of free fatty acids. The liver normally uses circulating free fatty acids as a major precursor for TG synthesis. Reduced liver TG levels decrease hepatic VLDL production, which in turn reduces LDL-C plasma concentrations.

Adverse effects

- The most common adverse effects of niacin are an intense cutaneous flush accompanied by an uncomfortable feeling of warmth and pruritus. Administration of aspirin prior to taking niacin decreases the flush, which is prostaglandin mediated.
- Some patients also experience nausea and abdominal pain. Slow titration of the dosage or use of the sustained-release formulation of niacin reduces bothersome initial adverse effects.
- Niacin inhibits tubular secretion of uric acid and, thus, predisposes patients to hyperuricemia and gout. Impaired glucose tolerance and hepatotoxicity have also been reported.

5- Cholesterol absorption inhibitor:

- Ezetimibe selectively inhibits absorption of dietary and biliary cholesterol in the small intestine, leading to a decrease in the delivery of intestinal cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Ezetimibe lowers LDL-C by approximately 18% to 23%. Due its modest LDL-C lowering, ezetimibe is often used as an adjunct to maximally tolerated statin therapy in patients with high ASCVD risk, or in statin intolerant patients.
- Adverse effects are uncommon with the use of ezetimibe. Actions of the antihyperlipidemic drugs were summarised and demonstrated in **table 1**.

Table 1: Characteristics of antihyperlipidemic drug families. HDL = high-density lipoprotein; HMG CoA = 3 hydroxy-3-methylglutaryl coenzyme A; LDL = low-density lipoprotein.

TYPE OF DRUG	EFFECT ON LDL	EFFECT ON HDL	EFFECT ON TRIGLYCERIDES
HMG CoA reductase inhibitors (statins)	↓↓↓↓	↑↑	↓↓
Fibrates	↓	↑↑↑	↓↓↓↓
Niacin	↓↓	↑↑↑↑	↓↓↓
Bile acid sequestrants	↓↓↓	↑	↑
Cholesterol absorption inhibitor	↓	↑	↓

Drugs for Diabetes

Introduction:

The pancreas produces the peptide hormones insulin (from β cells), glucagon (fromα cells), and somatostatin (from δ cells). These hormones play an essential role in regulating metabolic activities of the body, particularly glucose homeostasis. A relative or absolute lack of insulin, as seen in diabetes mellitus, can cause serious hyperglycaemia. If untreated, retinopathy, nephropathy, neuropathy, and cardiovascular complications may result. However, administration of insulin preparations or other glucose-lowering agents can reduce morbidity and mortality associated with diabetes.

DIABETES MELLITUS

- **Diabetes** is a heterogeneous group of syndromes characterized by elevated blood glucose attributed to a relative or absolute deficiency of insulin.

- The American Diabetes Association (ADA) recognizes four clinical classifications of diabetes: type 1 diabetes (formerly insulin- dependent diabetes mellitus), type 2 diabetes (formerly non– insulin dependent diabetes mellitus), gestational diabetes, and diabetes due to other causes such as genetic defects or medications.

- Gestational diabetes (GD) is defined as carbohydrate intolerance with onset or first recognition during pregnancy. Uncontrolled GD can lead to fetal macrosomia (abnormally large body) and difficult delivery, as well as neonatal hypoglycemia. Diet, exercise, and/or insulin administration are effective in this condition. In addition, glyburide and metformin may be reasonable alternatives to insulin therapy for GD.

Type 1 diabetes mellitus (juvenile diabetes) is characterized by beta cell destruction caused by an autoimmune-mediated processes (that may be triggered by viruses or other environmental toxins) usually leading to absolute insulin deficiency and appearance of classic symptoms of insulin deficiency (polydipsia, polyphagia, polyuria, and weight loss) (table 1). Eventually, all type1 diabetic patients will require insulin therapy to maintain normglycemia.

Type 2 diabetes accounts for greater than 90% of cases. Type 2 diabetes is influenced by genetic factors, aging, obesity, and peripheral insulin resistance, rather than autoimmune processes.

- **Cause**: Type 2 diabetes is characterized by a lack of sensitivity of target organs to insulin. In type 2 diabetes, the pancreas retains some β-cell function, but insulin secretion is insufficient to maintain glucose homeostasis in the face of increasing peripheral insulin resistance (table 1).

-**The goal** in treating type 2 diabetes is to maintain blood glucose within normal limits and to prevent the development of long-term complications.

- **Healthy life style** can help to get this goal; however, most of the patients require pharmacologic intervention with oral glucose-lowering agents. As the disease progresses, β-cell function declines and insulin therapy is often needed to achieve satisfactory glucose levels.

Table 1 : Comparison of type 1 and type 2 diabetes.

	Type 1	Type 2
Age at onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence among diagnosed diabetics	5%–10%	90%–95%
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β Cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

The blood glucose level can be monitored using different tests and the most important ones are the measuring of Plasma or Serum Glucose or the measurement of the glycosylated hemoglobin (HbA1c) as demonstrated in **table 2**.

Table 2: Diagnostic criteria for diabetes.

	Normal Glucose Tolerance, mg/dL (mMol/L)	Prediabetes	Diabetes Mellitus[2]
Fasting plasma glucose mg/dL (mmol/L)	<100 (5.6)	100–125 (5.6–6.9) (impaired fasting glucose)	≥126 (7.0)
Two hours after glucose load[1] mg/dL (mmol/L)	<140 (7.8)	≥140–199 (7.8–11.0) (impaired glucose tolerance)	≥200 (11.1)
HbA_{1c} (%) (ADA criteria)	<5.7	5.7–6.4	≥6.5

[1]Give 75 g of glucose dissolved in 300 mL of water after an overnight fast in persons who have been receiving at least 150–200 g of carbohydrate daily for 3 days before the test.
[2]A fasting plasma glucose ≥126 mg/dL (7.0 mmol) or HbA_{1c} ≥ 6.5% is diagnostic of diabetes if confirmed by repeat testing.
Symptoms and random glucose level >200 mg/dL (11.1 mmol/L) are diagnostic, and there is no need to do additional testing.

MEDICATIONS FOR HYPERGLYCEMIA

1-Insulin

Insulin is a polypeptide hormone consisting of two peptide chains that are connected by disulfide bonds. It is synthesized as a precursor (proinsulin) that undergoes proteolytic cleavage to form insulin and C-peptide, both of which are secreted by the β cells of the pancreas. Insulin secretion is most often triggered by increased blood glucose, which is taken up by the glucose transporter into the β cells of the pancreas. There, it is phosphorylated by glucokinase, which acts as a glucose sensor. The products of glucose metabolism enter the

mitochondrial respiratory chain and generate adenosine triphosphate (ATP). The rise in ATP levels causes a blockade of K+ channels, leading to membrane depolarization and an influx of Ca^{2+} . The increase in intracellular Ca2+ causes pulsatile insulin exocytosis.

Mechanism of action

Exogenous insulin is administered to replace absent insulin secretion in type 1 diabetes or to supplement insufficient insulin secretion in type 2 diabetes.

Pharmacokinetics and fate

- Human insulin is produced by recombinant DNA technology using strains of Escherichia coli or yeast that are genetically altered to contain the gene for human insulin. Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties.

- Insulin preparations vary primarily in their onset and duration of activity. For example, insulin lispro has a faster onset and shorter duration of action than regular insulin, because it does not aggregate or form complexes.

- Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various insulin preparations.

- Because insulin is a polypeptide, it is degraded in the GIT if taken orally. Therefore, it is generally administered by subcutaneous injection and inhaled insulin formulation is also available. However, in a hyperglycemic emergency, regular insulin is administered intravenously (IV).

INSULIN PREPARATIONS AND TREATMENT

Insulin preparations are classified as rapid-, short-, intermediate-, or long-acting.

Rapid-acting and short-acting insulin preparations

Four preparations fall into this category: regular insulin, insulin lispro, insulin aspart, and insulin glulisine.

- Regular insulin is a short-acting, soluble, crystalline zinc insulin while Insulin lispro, aspart, and glulisine are classified as rapid-acting insulins.
- Peak levels of rapid-acting insulins are seen at 30 to 90 minutes, as compared with 50 to 120 minutes for regular insulin.
- Rapid- or short-acting insulins are administered to mimic the prandial (mealtime) release of insulin and to control postprandial glucose. They may also be used in cases where swift correction of elevated glucose is needed.
- Rapid- and short-acting insulins are usually used in conjunction with a longer-acting basal insulin that provides control of fasting glucose.

- Regular insulin should be injected subcutaneously 30 minutes before a meal, whereas rapid-acting insulins are administered in the 15 minutes proceeding a meal or within 15 to 20 minutes after starting a meal.
- Both rapid-acting and regular insulin can be used when the IV route is needed.

Intermediate-acting insulin

- Neutral protamine Hagedorn (NPH) insulin (or insulin isophane) is an intermediate-acting insulin formed by the addition of zinc and protamine to regular insulin.
- The combination with protamine forms a complex that is less soluble, resulting in delayed absorption and a longer duration of action.
- NPH insulin is used for basal (fasting) control in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control.
- NPH insulin should be given only subcutaneously (never IV), and it should not be used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).

Long-acting insulin preparations

- Insulin glargine can be precipitated at the injection site that leads to releasing insulin over an extended period.
- It has a slower onset than NPH insulin and a flat, prolonged hypoglycemic effect with no peak.
- Insulin detemir has affinity to bind with albumin and the slow dissociation from albumin resulting in long acting properties similar to those of insulin glargine.
- As with NPH insulin, insulin glargine and insulin detemir are used for basal control and should only be administered subcutaneously.
- Neither long-acting insulin should be mixed in the same syringe with other insulins, because doing so may alter the pharmacodynamic profile.

Insulin combinations

- Various premixed combinations of human insulins, such as 70% NPH insulin plus 30% regular insulin, or 50% of each of these are also available. Use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

Insulin Delivery Systems

a- **Insulin Syringes and Needles**: Disposable plastic syringes with needles attached are available in 1-mL (100 units), 0.5-mL (50 units), and 0.3-mL (30 units) sizes.

b- **Insulin Pens**: The pens eliminate the need for carrying insulin vials and syringes. Cartridges of insulin lispro, insulin aspart, and insulin glargine are available for reusable pens.

c- **Continuous Subcutaneous** Insulin Infusion Devices (CSII, Insulin Pumps) Continuous subcutaneous insulin infusion devices are external open-loop pumps for insulin delivery. The devices have a user programmable pump that delivers individualized basal and bolus insulin. Replacement doses based on blood glucose self-monitoring results.

d- **Inhaled Insulin**: A dry powder formulation of recombinant regular insulin is now approved for use in adults with diabetes.

Side effects of insulin therapy

1- Hypoglycemia is the major risk that must be weighed against benefits of efforts to normalize glucose control. The main signs and symptoms of hypoglycaemia are: Irregular heart rhythm, fatigue, pale skin, shakiness, anxiety, sweating, hunger, irritability. If untreated, hypoglycaemia worsens and can cause confusion, abnormal behaviour or both, such as the inability to complete routine tasks. Moreover, it can cause visual disturbances, such as blurred vision, seizures and finally loss of consciousness.

2- Other adverse effects include weight gain, local injection site reactions, and lipodystrophy. Lipodystrophy can be minimized by rotation of injection sites. Diabetics with renal insufficiency may require a decrease in insulin dose. Due to the potential for bronchospasm with inhaled insulin, patients with asthma, chronic obstructive pulmonary disease, and smokers should not use this formulation.

2- Glucagon-like Peptide Receptor Agonists

Oral intake of glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV. This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes. The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP 1) and glucose-dependent insulinotropic polypeptide (GIP), in response to a meal. Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion. Albiglutide and liraglutide injectable GLP-1 receptor agonists used for the treatment of type 2 diabetes. Liraglutide is also approved to reduce the risk of cardiovascular events and cardiovascular mortality in patients with type 2 diabetes and cardiovascular disease.

Mechanism of action

These agents are analogs of GLP-1 that exert their activity by improving glucose-dependent insulin secretion, slowing gastric emptying time, reducing food intake by enhancing satiety (a feeling of fullness), decreasing postprandial glucagon secretion, and promoting β-cell proliferation. Consequently, postprandial hyperglycemia is reduced, HbA1c levels decline, and weight loss may occur.

Adverse effects

The main adverse effects of the incretin mimetics consist of nausea, vomiting, diarrhea, and constipation. GLP 1 receptor agonists have been associated with pancreatitis and should be avoided in patients with chronic pancreatitis. Longer-acting agents have been associated with thyroid C-cell tumors in rodents. It is unknown if GLP-1 receptor agonists cause these tumors or thyroid carcinoma in humans, although they are contraindicated in patients with a history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2.

3- ORAL AGENTS:

- Oral agents are useful in the treatment of patients who have type 2 diabetes that is not controlled with diet. Patients who developed diabetes after age 40 and have had diabetes less than 5 years are most likely to respond well to oral glucose-lowering agents. Patients with long-standing disease may require a combination of oral agents with or without insulin to control hyperglycaemia.

- Several categories of glucose-lowering agents are available for patients with type 2 diabetes, the main categories are:

a- Agents that bind to the sulfonylurea receptor and stimulate insulin secretion (sulfonylureas and glinides).

b- - Agents that lower glucose levels by their actions on liver, muscle, and adipose tissue (biguanides, thiazolidinediones).

c- Agents that principally slow the intestinal absorption of glucose (α-glucosidase inhibitors).

A- Sulfonylureas (such as glyburide, glipizide, and glimepiride)

These agents are classified as insulin secretagogues, because they promote insulin release from the β cells of the pancreas.

Mechanism of action: The main mechanism of action includes stimulation of insulin release from the β cells of the pancreas by blocking the ATP-sensitive K+ channels, resulting in depolarization, Ca2+ influx, and insulin exocytosis.

- In addition, sulfonylureas may reduce hepatic glucose production and increase peripheral insulin sensitivity.

Adverse effects

- Adverse effects of the sulfonylureas include hypoglycemia, hyperinsulinemia, and weight gain. They should be used with caution in hepatic or renal insufficiency, since accumulation of sulfonylureas may cause hypoglycemia. Renal impairment is a particular problem for glyburide, as it may increase the duration of action and increase

the risk of hypoglycemia significantly. Glipizide or glimepiride are safer options in renal dysfunction and in elderly patients.

- Some Drugs may reduce the effects of sulfonylureas, leading to loss of glucose control such as corticosteroids while others can potentiate the effects of sulfonylureas, leading to hypoglycaemia such as chloramphenicol and Clarithromycin.

B- Glinides

This class of agents includes repaglinide and nateglinide. Glinides are also considered insulin secretagogues.

Mechanism of action:

- Like the sulfonylureas, the glinides stimulate insulin secretion. In contrast to the sulfonylureas, the glinides have a rapid onset and a short duration of action. They are particularly effective in the early release of insulin that occurs after a meal and are categorized as postprandial glucose regulators.
- Glinides should not be used in combination with sulfonylureas due to overlapping mechanisms of action.
- Glinides should be taken prior to a meal and are well absorbed after oral administration.

C- Biguanides (Metformin, the only biguanide, which is well absorbed orally.):

Is classified as an insulin sensitizer. It increases glucose uptake and use by target tissues, thereby decreasing insulin resistance. Unlike sulfonylureas, metformin does not promote insulin secretion. Therefore, hyperinsulinemia is not a problem, and the risk of hypoglycemia is far less than that with sulfonylureas.

Mechanism of action:

- The main mechanism of action of metformin is reduction of hepatic gluconeogenesis. Also, it slows intestinal absorption of sugars and improves peripheral glucose uptake and utilization.
- Weight loss may occur because it causes loss of appetite.
- The ADA recommends metformin as the initial drug of choice for type 2 diabetes.
- Metformin may be used alone or in combination with other oral agents or insulin. However, hypoglycemia may occur when metformin is taken in combination with insulin or insulin secretagogues, so adjustment in dosage may be required.

Adverse effects:

- These are largely gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, and diarrhea).
- Metformin should be used with caution in patients older than 80 years and in those with heart failure or alcohol abuse or patients who have renal dysfunction.

- Long-term use may interfere with vitamin B12 absorption.

Other uses: metformin is effective in the treatment of polycystic ovary syndrome. It lowers insulin resistance seen in this disorder and can result in ovulation and, therefore, pregnancy.

D- Thiazolidinediones (The 2 members of this class are pioglitazone and rosiglitazone):

The thiazolidinediones (TZDs) are also insulin sensitizers. Although insulin is required for their action, the TZDs do not promote its release from the β cells, so hyperinsulinemia is not a risk.

Mechanism of action

- The TZDs lower insulin resistance by acting as agonists for the peroxisome proliferator–activated receptor-γ (PPARγ). Activation of PPARγ regulates the transcription of several insulin responsive genes, resulting in increased insulin sensitivity in adipose tissue, liver, and skeletal muscle.
- The TZDs can be used as monotherapy or in combination with other glucose-lowering agents or insulin. The dose of insulin may have to be lowered when used in combination with these agents.
- The ADA recommends pioglitazone as a 2nd or 3rd line agent for type 2 diabetes.
- TZDs are well absorbed after oral administration and no dosage adjustment is required in renal impairment.

Adverse effects:

- Liver toxicity have been reported with these drugs, and periodic monitoring of liver function is recommended.
- Weight gain can occur because TZDs may increase subcutaneous fat and cause fluid retention that can worsen heart failure. So, These drugs should be avoided in patients with severe heart failure.
- TZDs have been associated with osteopenia and increased fracture risk in women.

E- α-Glucosidase inhibitors:

Acarbose and miglitol are oral agents used for the treatment of type 2 diabetes.

Mechanism of action:

- Located in the intestinal brush border, α-glucosidase enzymes break down carbohydrates into glucose and other simple sugars that can be absorbed. Acarbose and miglitol reversibly inhibit α-glucosidase enzymes. When taken at the start of a meal, these drugs delay the digestion of carbohydrates, resulting in lower postprandial glucose levels.

- Since they do not stimulate insulin release or increase insulin sensitivity, these agents do not cause hypoglycaemia when used as monotherapy. However, when used with insulin secretagogues or insulin, hypoglycaemia may develop.

- It is important that hypoglycaemia in this context be treated with glucose rather than sucrose, because sucrase is also inhibited by these drugs. • Acarbose is poorly absorbed. It is metabolized primarily by intestinal bacteria, and some of the metabolites are absorbed and excreted into the urine.

Adverse effects:

- The major side effects are flatulence, diarrhoea, and abdominal cramping. Adverse effects limit the use of these agents in clinical practice.

- Patients with inflammatory bowel disease, colonic ulceration, or intestinal obstruction should not use these drugs.

References:

1- Katzung, B.G., 2018. Basic and clinical pharmacology. Mc Graw Hill.

2- Whalen, K., 2019. Lippincott illustrated reviews: pharmacology. Lippincott Williams & Wilkins.