Dama International Journal of Researchers (DIJR), ISSN: 2343-6743, ISI Impact Factor: 1.018
Vol 3, Issue 01, January, 2018, Pages 43 - 52, Available @ www.damaacademia.com

Pharmacologic Therapy of Familial Hypercholesterolemia in Cardiovascular Disease

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Abstract
Cardiovascular disease is a major health problem in almost all countries of the world and contributes to about 30 percent of all deaths in the world. Cardiovascular disease is a group of diseases caused by disorders of the heart or blood vessels. Some of the diseases included in this group include coronary heart disease, cerebrovascular disease (stroke), hypertension, peripheral vascular disease, valve disease, congenital heart disease, and heart failure. The major risk factors for cardiovascular disease that are known to date include age, sex, diabetes mellitus, dyslipidemia, smoking, physical inactivation, improper diet and alcohol consumption. Strategies for the treatment and prevention of cardiovascular disease can be highly effective and have been subjected to rigorous evaluation. The evidence base for the treatment of cardiovascular disease is stronger than for almost any other disease group.
Keyword*: cardiovascular disease, atherosclerosis, hypercholesterolemia, antihyperlipidemia*

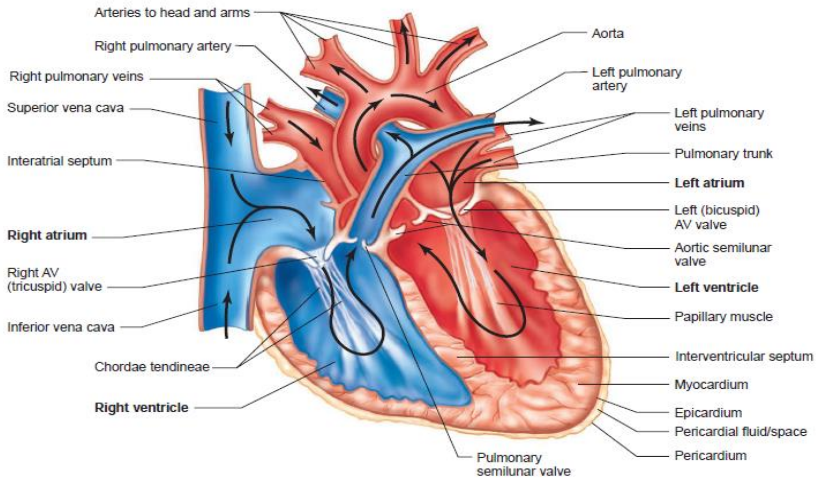
A. INTRODUCTION

Cardiovascular disease is a group of diseases caused by disorders of the heart or blood vessels. Some of the diseases included in this group include coronary heart disease, cerebrovascular disease (stroke), hypertension, peripheral vascular disease, valve disease, congenital heart disease, and heart failure.

B. ANATOMY OF HEART

The heart is a complex organ whose primary function is to pump blood through the pulmonary and systemic circulation. This organ is divided into left and right sides. Each side consists of two chambers, the atria and the ventricles, which are mainly composed of cardiac muscle cells. The thin-walled atrium works to fill or 'prepare' thick-walled vetricles, which, when contracted firmly, produce pressure that pushes blood out throughout the body (Guyton & Hall, 2014). Blood in and out of each heart chamber through separate one-way valves, which open and close alternately (ie one valve closes before the other opens) to ensure one-way flow. Blood flows into the right atrium through the superior and inferior vena cava. The left and right atrium are each connected to the ventricle via the mitral atrioventricular (AV) valve (two valve leaves) and the tricuspid (three valve leaves). AV valves are passive and close when ventricular pressure exceeds the atrial pressure. These valves are prevented from eversion into the atrium during systole by thin bundles (tendral chords) adhering between the free edge of the valve bulge and the papillary muscle, contracting during systole. The flow from the right ventricle exits through the semilunarisary pulmonary valve to the pulmonary artery, and the flow from the left ventricle enters the aorta through the semilunary aortic valve. Both semilunaris valves have three valve volumes (Guyton & Hall, 2014)

Figure 1 Parts of the heart, the arrows show the direction of blood flow



C. ANATOMY OF VASCULAR

The blood vessel is a closed system of channels that channel blood to the tissues and back to the heart. All blood flows through the lungs, but the systemic circulation is formed by many different circuits in parallel, as illustrated in the following circulation diagram (McPhee & Ganong, 2010):

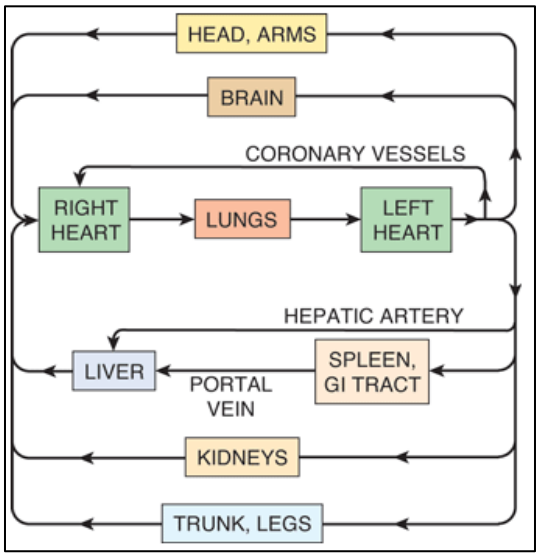


Figure 2. systemic circulation

The blood vessels in the cardiovascular system are more easily classified into arteries (which are elastic and muscular), deformed vessels (small arteries and arterioles), calpillers, venules and veins. The typical size for each type of blood vessel is described in the following figure (McPhee & Ganong, 2010). All blood vessels are coated by a layer of endothelial cells. Collectively, endothelial cells form an extraordinary organ that secretes substances that affect vessel diameter and growth, repair of injured vessels, and the formation of new vessels that carry blood to the growing tissue. The vasoactive substances produced by the endothelium generally work in paracrine to regulate local vascular tone. These include prostaglandins, such as prostacyclin, thromboxane, nitrogen oxide, and endothelin (Guyton & Hall, 2014).

D. PERIPHERAL VASCULAR DISEASE

It is a blockage or inflammatory disease that occurs in the peripheral arteries, veins or lymph glands.

Disorders of Peripheral Vascular Disease
Arterial Disease
Aterosclerosis
Arterial embolism
Atheroembolism
Vasospastic Disorders
Thromboangiitis Obliterans (Buerger's Disease)
Venous Disease
Superficial Thrombophlebitis
Deep-Vein Thrombosis
Chronic venous insufficiency
Lymphatics Disease

Lymphedema

Table 1. various peripheral vascular disorder

d.1 Atherosclerosis

d.1.1. Prevalence and Clinical Meaning

In the United States and most other developed countries, it is estimated that atherosclerosis is the underlying cause for about 50% of deaths. Almost all patients with myocardial infarction and most of those who have a stroke due to cerebrum thrombosis have arterosclerosis. Atherosclerosis is a large and medium-sized arterial disease due to the formation of a fatty lesion called atheromatous plaque on the inner surface of the artery wall. Atherosclerosis begins as a childhood with localized lipid accumulation in the arterial intima, called fatty streak. Up to middle age some of these fatty streaks develop into atherosclerotic plaques, focal lesions in which the arterial wall is clearly abnormal. Plaque may be several centimeters in size and most common in the aorta, coronary artery and internal carotid artery, and the circle of Willis. However, atherosclerosis is more common in coronary arteries that bend or branch (Henning & Ollson, 2005).

d.1.2. Pathophysiology of Atherosclerosis

The initial process in atherosclerosis is low-density lipoprotein (LDL) infiltration into the sub-thtothelial region. Endothelium is susceptible to shear stress, an interest tendency along or experiencing deformity due to blood flow. This is most evident in the branching points of the arteries, and it is here that the most optimal lipid accumulation occurs (Alkhouli, et al., 2015).

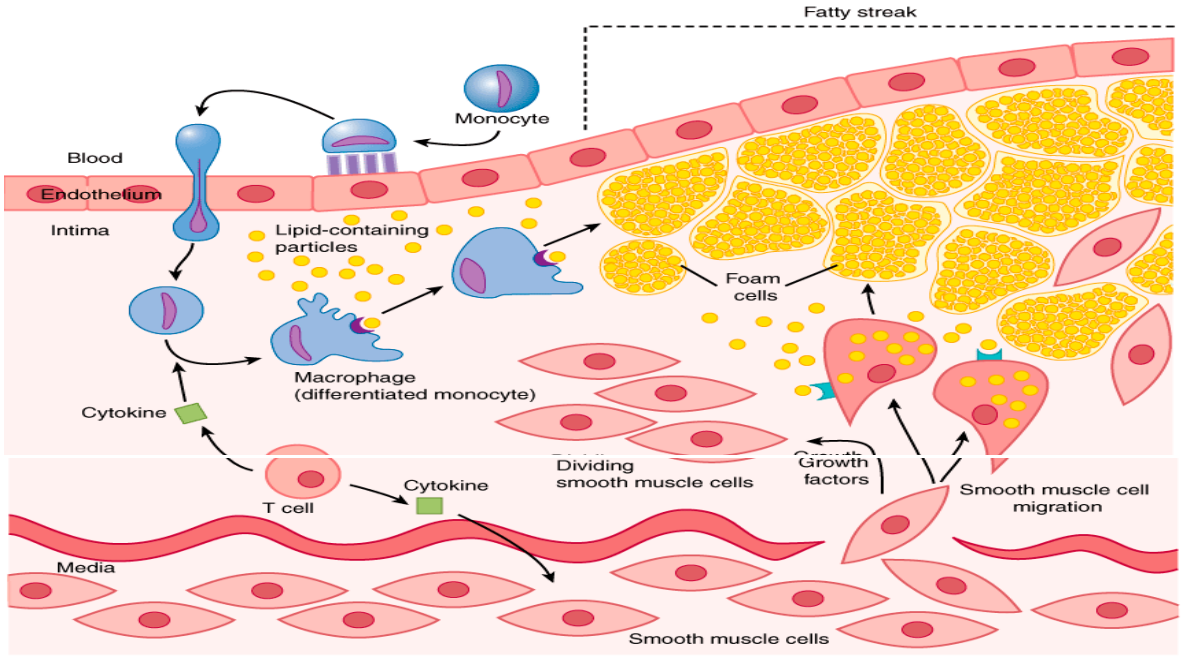


Figure 3 Pathophysiology of atherosclerosis

In the figure can be seen the formation of fatty streak in an artery. After a vascular monocyte injury binds to the endothelium and passes it to the sub-room endothelium, and turns into active tissue macrophages. Macrophages absorb low density lipoproteins (LDL) that have been oxidized and turned into foam cells. T cells secrete various cytokines, which also activate macrophages. In addition T cells also cause smooth muscle cells proliferate. Under the influence of growth, smooth muscle cells then move into subendothelial space where these cells produce collagen and absorb LDL thus increasing the population of foam cells (McPhee & Ganong, 2010).

Vascular endothelial damage subsequently increases exposure of adhesion molecules in endothelial cells and decreases the endothelial's ability to release nitric oxide (NO) and other substances that help prevent macromolecular adhesion, platelets and monocytes in the endothelium. After vascular damage occurs monocytes and lipids (mostly LDL) in circulation, begin to accumulate in places that are damaged. Monocytes through the endothelium enter the

intima layer of the vessel wall, and differentiate into macrophages which further digest and oxidize the pile of lipoproteins, so that the appearance of macrophages resembles foam (foam cells). These macrophage foam cells then unite in the blood vessels and form a visible fatty streak. Normal LDL, unlike oxidized LDL, is not fast enough absorbed by macrophages to form foam cells. Macrophages show a family of scavenger receptors that play a role in this absorption. Oxidized LDL has a number of adverse effects including stimulation of cytokine release and inhibition of NO production (Alkhouli, et al., 2015; Newby, et al., 2016).

Over time, the fatty streak becomes larger and united. The fibrous tissue and smooth muscle cells of the blood vessels around the foam cell are stimulated and move from the tunica of the media to the intima tunica, where these cells proliferate, place collagen and other matrix molecules, and play a role in determining most lesion sizes. The smooth muscle cells also absorb the oxidized LDL and become a foam cell. Lipid accumulation occurs in both the intracellular and extracellular compartments. Macrophages also release substances that give rise to inflammation and further proliferation of fibrous tissue and smooth muscle in the inner surface vessels of artery walls. The accumulation of lipid plus cell proliferation can become so large that plaque protrudes into the lumen of the artery and greatly reduces blood flow, which occasionally clogs the entire blood vessels. Even without the blockage of fibroblasts the plaque ultimately accumulates a number of dense connective tissues; sclerosis (fibrosis) becomes very large and the arteries become stiff and inflexible. Furthermore calcium salts often precipitate along with cholesterol and other lipids from plaque, which gives rise to lymph calcification that can make arteries such as stiff ducts. Both advanced stages of the disease are called "hardening of the arteries" (Alkhouli, et al., 2015; Newby, et al., 2016).

Arterosklerotic artery loses most of its distensibility, and because the area in its degeneration wall degenerates, the vessels become easily torn. On the plaque plaque into the bloodstream, a rough plaque surface may cause blood clots to form, resulting from the formation of thrombus or embolus, thereby blocking all blood flow in the arteries suddenly (Newby, et al., 2016).

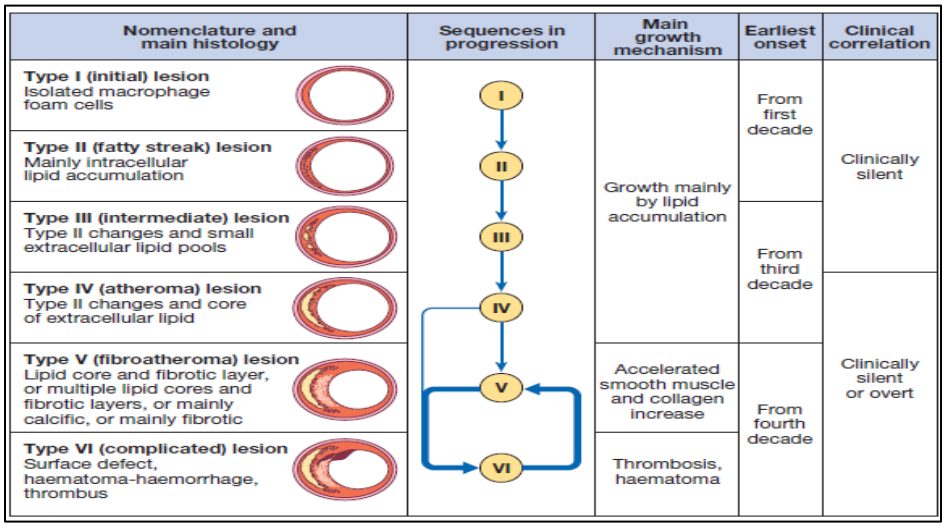


Figure 4 The six stages of atherosclerosis

d.1.3. Clinical Manifestation of Atherosclerosis

The presence of atherosclerosis in the coronary arteries will cause a decrease in blood flow to the myocardial tissue resulting in a decrease in oxygen supply. Reduced oxygen supply causes myocardium to alter aerobic metabolism to anaerobic metabolism. Anaerobic metabolism via the glycolytic pathway is very inefficient when compared with aerobic metabolism through oxidative phosphorylation and the krebs cycle. High energy decreased considerably. The end result of anaerobic metabolism, ie lactic acid, will be accumulated which decreases cell pH. The formation of high-energy phosphate decreased considerably. The end result of anaerobic metabolism, ie lactic acid, will be accumulated which decreases cell pH. The combined effects of hypoxia, reduced available energy, and acidosis rapidly impair the functioning of the left ventricle. The contraction strength of the hypoxic area of the myocardium will decrease; the fibers are shortened, and their functional ability and conduction velocity will decrease. In addition, the movement of the segment wall that undergoes ischemia becomes abnormal; the part will protrude out whenever the ventricle contracts (Henning & Ollson, 2005). Reduced power of contraction and impaired heart movement alter

hemodynamics. The change in hemodynamics varies according to the size of the ischemic segment, and the degree of reflex response to the autonomic nervous system. Reduced left ventricular function can reduce cardiac output by decreasing the stubborn output (Cardiac Output). Reduced ventricular emptying during the systolic phase increases the ventricular volume. As a result, left heart pressure will increase so that the left ventricular diastolic end pressure and pressure in the lung capillaries will also increase. Increased pressure is magnified by changes in cardiac wall power due to ischaemia. The less flexible wall further compresses the increased pressure on a particular ventricular volume. In ischemia, frequent hemodynamic manifestations are mild increases in blood pressure and heart rate before pain develops. Clearly, this pattern represents a sympathetic compensatory response to reduced myocardial function. With the onset of pain often occurs further stimulation by catecholamines

In addition to the heart, in the brain circulation, clogging of the arteries in place of atherosclerotic plaque causes a thrombotic stroke. In the abdominal aorta, atherosclerosis can cause dilatation of the aneurysm and rupture of the vessels. In the renal vessels, local constriction of one or both renal arteries causes renovascular hypertension. In the circulation of the legs, vascular insufficiency leads to intermittent claudication (fatigue and usually pain when walking and easing with rest). If circulation to a leg is severely impaired, skin ulceration may occur, and lead to long-healed lesions. Gangrene of the extremities may also occur. Although infrequent formation of clots and obstruction may occur in vessels that intestate the intestines or other body parts (Rader & Hobbs, 2013).

d.2. Arterial Embolism

Other conditions that interfere with peripheral arterial flow are caused by the presence of thrombus or vegetation in the heart or aorta, or paradoxically from the venous thrombus via intracardial right to the left shunt.

i. ***Artheroembolism:*** A part of artery blockage caused by embolization of fibrin, platelets and cholesterol debris from proximal atheromas or aneurysms. It usually appears after intraarterial instrumentation. Depending on the location of the embolism itself, it can lead to stroke, renal impairment, pain and weakness of embolored tissue. Atheroembolism in the lower limbs can cause blue toe syndrome, which can develop into necrosis and gangrene. Treatment given is usually adjunctive therapy, for recurrent events, surgery on proximal atherosclerotic vessels or aneurysm may be needed (Creager & J, 2014).

ii. ***Vasopastic Disorder:*** It is a manifestation of Raynaud's phenomenon due to cold exposure, three phases of the color response that occurs: the finger is pale, followed by cyanosis, then rubor. It is usually harmless, but it is necessary to predict the underlying disease if there is tissue necrosis, whether the disease is unilateral or develop after the age of 50 years (Creager & J, 2014).

Table 2. Raynaud's Phenomenon Classification

Primary or idiopathic Raynaud's Phenomenon	
Raynaud's disease	Primary RP or idiopathic Raynaud disease are terms to describe those patients without a definable cause for their vascular events. In this setting, RP is considered to be an exaggeration of normal
Secondary Raynaud's Phenomenon	
Collagen vascular disease	Scleroderma, systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polymyositis
Arterial occlusive disease	Atherosclerosisof the extremities, thromboangiitis obliterans, acute arterial occlusion, thoracic outlet syndrome, pulmonary hypertension.
Neurologic disorder	Intervertebral disk disease, syringomyelia, spinal cord tumors, stroke, poliomyelitis, carpal tunnel syndrome.
Hematologic abnormalities	associated with RP include cryoglobulinemia, cold agglutinin disease, paraproteinemia, **POEMS** (**P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal gammopathy, and **S**kin changes) syndrome, and cryofibrinogenemia.
Trauma	Vibration injury, hammer hand syndrome, electric shock, cold injury, typing, piano playing.

Drugs	Ergot derivatives, methysergide, β-adrenergic receptor blockers, bleomycin, vinblastine, cisplatin

management by keeping the temperature of the body extremities remain warm, not smoking. Use of dihydropyridine group calcium channel blockers (eg: nifedipine XL 30-90 mg PO qd) or α1 adrenergic antagonists (eg, prazosin 1-5 mg tid).

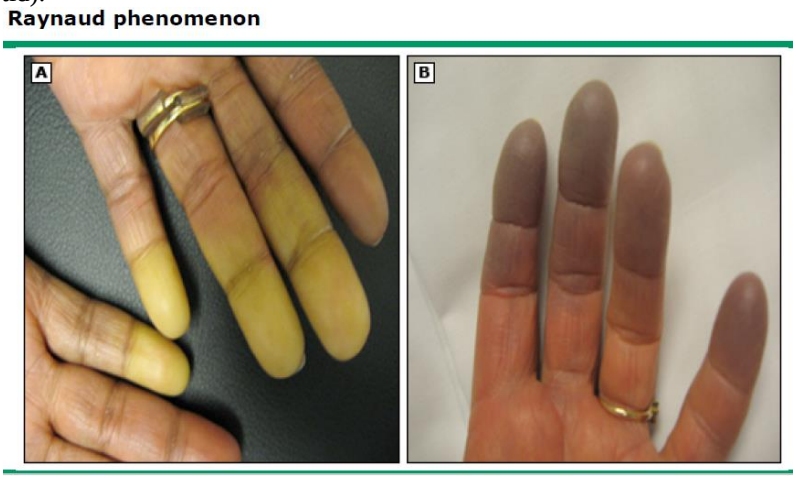


Figure A shows he borderline of some pale fingers caused by artery blockage. Figure B shows cyanosis of the fingertips caused by vasoconstriction in the thermoregulatory vessels in the skin.

Figure 5. Patient with Raynaud phenomenon

iii. ***Thromboangiitis Obliterans (Buerger's Disease):*** Muncul pada laki-laki usia muda yang merupakan perokok berat dan mempengaruhi ekstremitas bagian atas maupun bawah. Reaksi inflamasi nonatheromatosus terjadi pada vena dan arteri yang berukuran kecil yang akhirnya dapat menyebabkan *superficial thrombophlebitis* dan obstruksi arteri dengan tingkat keparahan mencapai ulser atau gangrene (Creager & J, 2014).

d.3..**Venous Disease**

i. Superficial Thrombhoplebitis: Mild disorders characterized by erythema, weakness, and edema throughout the vein. Conservative therapy can be done with a warm compress, elevate / lift the affected part, giving anti-inflammatory drugs such as aspirin. For more severe conditions such as cellulitis or lymphangitis may have the same initial symptoms but are accompanied by fever, chills, lymphadenopathy, and red lines on the surface along the inflamed lymph channels (Creager & J, 2014).

ii. Deep-Vein Thrombosis (DVT): Is a more serious condition that can cause embolism in the lungs. Especially in patients who have long bed rest, patients with diseases that lower the body's immune system, and patients with malignancy. Pain and stiffness in the veins are usually unilateral, asymptomatic, with pulmonary embolism as its main manifest. Management of DVT using systemic anticoagulants such as heparin (5000-10000 bolus units followed by IV infusion to keep aPTT 2 x normal) Giving low-molecular-weight heparin (LMWH) (eg enoxaparin 1mg / kg SC bid), followed by warfarin PO. Dose of warfarin to maintain prothrombin time INR 2.0 - 3.0. DVT can be prevented by immediate treatment, followed by surgery or with low-dose unfractionated heparin during bed rest (500 U SC bid-tid) or LMWH (eg enoxaparin 40 mg SC / day). After knee or hip surgery is continued with warfarin (INR 2.0 - 3.0). LMWH is also effective in preventing the occurrence of DVT after general surgery or bone surgery (Creager & J, 2014).

iii. Chronic Venous Insufficiency: Consequences of previous DVT or valvular venous disability result in chronic dull pain in worsening leg if standing for long periods of time, edema and varicose veins on the skin surface. May lead to erythema, hyperpigmentation, and recurrent cellulitis. The ulcer can appear on the medial and lateral malleoli. Treatment can be by using stockings for compression and elevating the feet higher (Creager & J, 2014).

d.4. Lymphedema

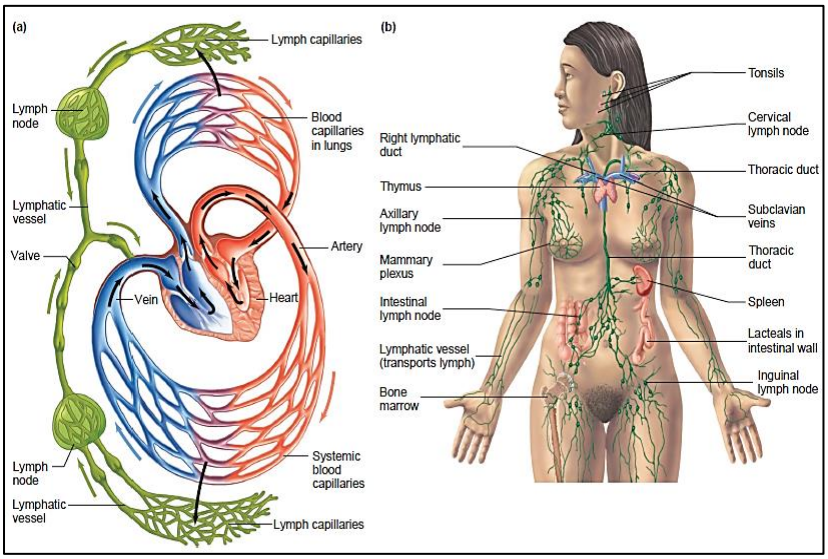


Figure 6. The lymphatic system (green) in relation to the cardiovascular system (blue and red) (a). The lymphatic system is a one-way system of interstitial fluid to the cardiovascular system. (b) Before the blood enters the subclavian vein, lymph flow through the lymph nodes in the neck, armpits, groin, and around the intestine. The lymphatic system is an additional pathway in which fluids can flow from the interstitial space into the blood. It is most important that the lymphatic system can transport proteins and large particles out of tissue space, which can not be transferred by direct absorption into the blood capillaries. The return of proteins into the blood and interstitial space is an important function, and in the absence of such function, we will die within 24 hours (Eric, et al., 2014).

Almost all body tissues have special lymph channels that drain excess fluids directly from the interstitial space. Some exceptions include skin surface area, central nervous system, muscle endomyum, and bone. But even those networks have small interstitial vessels called prelimphatic channels that can be fed by interstitial fluid. Ultimately this fluid flows into the lymph vessels or, in the brain, flows into the cerebrospinal fluid and then goes back to the blood (Eric, et al., 2014). Basically all the lymphatic vessels at the bottom of the body will eventually empty into the thoracic ducts, which further leads into the venous blood system at a meeting between the left internal jugular vein and the left subclavian vein. The lymphatic fluid from the left side of the head, left arm, and part of the thoracic region also enters the thoracic duct before it empties into the vein. The lymph fluid from the right side of the neck and head, right arm and right thorax enter the right lymphatic duct (much smaller than the thoracic ducts), which will empty into the venous blood system at the confluence between the right subclavian vein and the internal jugular vein (Eric et al., 2014).

Lymphedema is the accumulation of protein-rich interstitial fluid in the skin and subcutaneous tissue that occurs as a result of lymphatic dysfunction. Cases in which aetiology is unknown or developing as a result of congenital lymphatic dysfunction is called primary lymphedema. All forms of lymphedema occurring as a result of the blockage are referred to as secondary lymphedema (eg recurrent lymphangitis, tumors, filariasis). Usually chronic, painless edema is common in the lower extremities (Creager & J, 2014). Management with attention to foot hygiene to prevent infection, positioning the feet higher, compression stocking. Use of diuretics should be avoided to prevent intravascular volume depletion (Creager & J, 2014).

E. RISK FACTOR

Table 3. Risk factors for coronary heart disease based on the American Heart Association (AHA)

Factor risiko mayor	Factor risiko minor

Merokok	*Small LDL* particle
Hipertensi	Karakteristik etnis tertentu
Peningkatan kadar kolesterol total dan LDL	Faktor psikososial
Rendahnya kadar HDL	Peningkatan kadar trigliserida
Diabetes mellitus	Intoleransi glukosa
Meningkatnya usia	Peningkatan kadar homosistein
Obesitas	Peningkatan kadar lipoprotein (a)
Inaktivitas	Fibrinogen
Riwayat keluarga PJK	*C-reactive protein*

There are four irreversible biological risk factors: age, sex, race, and family history. The risk of coronary atherosclerosis increases with age and is generally a rare disease before the age of 40 years. But the association between age and the onset of illness may only reflect longer-term exposure to atherogenic factors (Bashore, et al., 2016). Women are relatively more rarely affected by this disease until menopause, and then become as vulnerable as men and this is thought to be by the effects of estrogen protection. African-Americans are more susceptible to atherosclerosis than whites. A positive family history of coronary heart disease (siblings or parents suffering from this disease before age 50) increases the likelihood of premature atherosclerosis. However, the relevance of genetic and environmental influences remains unknown. The genetic component may be suspected in some apparent, or rapidly progressing form of atherosclerosis, as in familial hypercholesterolemic lipid disorders. However, family history can also reflect strong environmental components, such as stressful lifestyles or obesity.

Other risk factors can still be altered, potentially slowing down the atherogenic process. These factors include elevated serum lipid levels, hypertension, smoking, impaired glucose tolerance and a diet high in saturated fats, cholesterol, and calories. Several studies have shown that high serum cholesterol and triglyceride levels can lead to the formation of arteriosclerosis. In people with arteriosclerosis, fatty fat is found throughout the depth of the intima tunica, extending to the media tunica. Cholesterol and triglycerides in the blood are encased in a fat transporting protein called lipoprotein. High-density lipoprotein (HDL) lipoproteins carry the fat out of cells to be described, and are known to be protective against arteriosclerosis. However, low density lipoprotein (LDL) lipoproteins and very low density lipoprotein (VLDL) carry fat to the body cells, including arterial endothelial cells, cholesterol oxidation and triglycerides lead to the formation of free radicals known to damage cells -sel endotel.

Chronic hypertension creates a stretching force that can damage the endothelial lining of arteries and arterioles. Stretching forces mainly arise in places where branching or bending arteries and are typical for coronary arteries, aorta, and cerebrum arteries. With tearing of the endothelial lining, recurrent damage occurs, resulting in inflammatory cycles, accumulation of white blood cells and platelets, and the formation of thrombus. Each thrombus that formed can be detached from the artery so that it becomes embolus downstream.

Smoking is a major risk factor for the occurrence of heart disease and blood vessels. People who quit smoking will reduce the risk of heart disease and blood vessels. Smoking will increase the risk of coronary heart disease and acute coronary syndrome by 2 to 3 times. The role of cigarettes in the pathogenesis of CHD is complex, including: the onset of atherosclerosis, increased thrombogenesis and vasoconstriction (including coronary artery spasm), increased blood pressure and heart rate, cardiac arrhythmia provocation, increased myocardial oxygen demand, decreased oxygen transport capacity.

Endothelial cells of the blood vessels may be infected with a virus. This viral infection will trigger an inflammatory cycle; leukocytes and platelets come into the area and form clots and scar tissue. The specific virus suspected to play a role in this theory is the sito-megalovirus, a member of the herpes virus family.

High serum iron levels are thought to damage coronary arteries or exacerbate damage caused by other things. This theory is proposed by some to explain the striking difference in the incidence of coronary artery disease between premenopausal men and women. Men usually have much higher iron levels than women who still have menstruation (Alkhouli, et al., 2015; Newby, et al., 2016).

F. FAMILIAL HYPERCHOLESTEROLEMIA

A hereditary disease that causes one to inherit the deformity of the LDL receptor gene on the surface of the cell membrane of the body, occurring in apoproteins, apoprotein receptors, or enzymes involved in lipoprotein metabolism. When this receptor is absent the liver can not absorb lipoproteins of medium density or low density lipoproteins. Without such absorption, the cholesterol engine in the liver cells becomes uncontrolled and continues to form new cholesterol. The liver no longer responds to the inhibition of feedback from an excessive amount of plasma cholesterol. As a result the amount of VLDL that is released by the liver into the plasma becomes greatly increased.
Patients with severe familial hypercholesterolemia have a cholesterol concentration of 600 to 1000mg / dl, which is four to six times the normal value. Many such patients die at less than 20 years of age, due to myocardial infarction or residual blockage of atherosclerosis throughout the body's blood vessels. Familiar heterozygous hypercholesterolemia is relatively common and occurs in 1 in 500 people. The heavier types of this disorder caused by homozygous mutations are very rare, occurring in just one out of every million births (Alkhouli, et al., 2015)

G. DEVELOPMENT OF THERAPY ON HYPERLIPIDEMIA

Treatment of hyperlipidemia aims to lower LDL cholesterol and / or triglycerides, as well as increase HDL cholesterol. There is evidence that both effects may slow or even reverse the progression of atherosclerotic lesions. Common and often used ones are (Alkhouli, et al., 2015):
Table 4 List of drugs that have been approved by the FDA and used as therapy for dyslipidemia (Rader & Hobbs, 2013).

Drugs	**Major Indication**	**Mechanism**	**Common Side Effects**
HMG-CoA reductase inhibitors (Statins)	Elevated LDL-C; Inreased CV Risk	↓ Cholesterol synthesis, ↑ Hepatic LDL receptors, ↓ VLDL production	Myalgias, arthralgias, elevated transaminases, dyspepsia
Cholesterol absorption inhibitor (Ezetimibe)	Elevated LDL-C	↓ Cholesterol absorption, ↑ LDL receptors	Elevated transaminases
Bile acid sequestrants	Elevated LDL-C	↑ Bile acid excretion and ↑ LDL receptors	Bloating, constipation, elevated triglycerides
MTP Inhibitor Lomitapide	HoFH	↓ VLDL production	Nausea, diarrhea, increased hepatic fat
apoB inhibitor Mipomersen	HoFH	↓ VLDL production	Injection site reaction, flu-like symptoms, increased hepatic fat
Nicotinic acid	Elevated LDL-C, elevated TG	↓ VLDL production	Cutaneous flushing, GI upset, elevated glucose, uric acid, and elevated liver function tests
Fibric acid derivatives	Elevated TG	↑ LPL, ↓ VLDL synthesis	Dyspepsia, myalgia, gallstones, elevated transaminases
Omega-3 fatty acids	Elevated TG	↑ TG catabolism	Dyspepsia, fishy odor to breath

Therapeutic management for familial hypercholesterolemia should focus on lifestyle management, along with maximal administration of statin therapy, often also in combination with ezetimibe or other drugs for hyperlipidemia, and assisted by apheresis lipoprotein. According to the latest ESC (European Society of Cardiology) guidelines, although various combinations of therapy have been provided, most patients with familial hypercholesterolaemia are still unable to achieve the recommended LDL-C target and are at high risk for cardiovascular disease. The following figure is the therapeutic algorithm in familial hypercholesterolemia (Cuchel, et al., 2014)

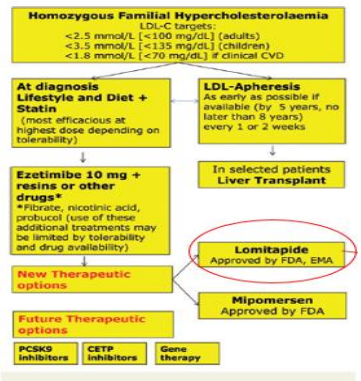


Figure 7. Familial homozygous therapy algorithm of hypercholesterolemia according to ESC (European Society of Cardiology) 2014. From the research publication in 2014 three new drugs were found to decrease LDL-C levels, namely lomitapide, mipomersen and protein convertase substilisin / kexin type 9 (PCSK9). Lomitapide is an oral drug that can inhibit microsomal triglyceride transfer protein (MTP) which can significantly decrease LDL-C concentration. MTP is a lipid transfer protein found in the hepatic and intestinal cellular reticulum, serves to facilitate the secretion of apolipoprotein B (apo B). In the liver itself MTP mediates the transfer of triglycerides and cholesterol ester to apo B-100 to form very-low-density-lipoprotein (VLDL). In intestinal MTP can bind to apo B-48 and produce kilomycron particles. Inhibition of the synthesis of kilomikron and VLDL causes the decrease of LDL-C in plasma (Reiner, 2015).

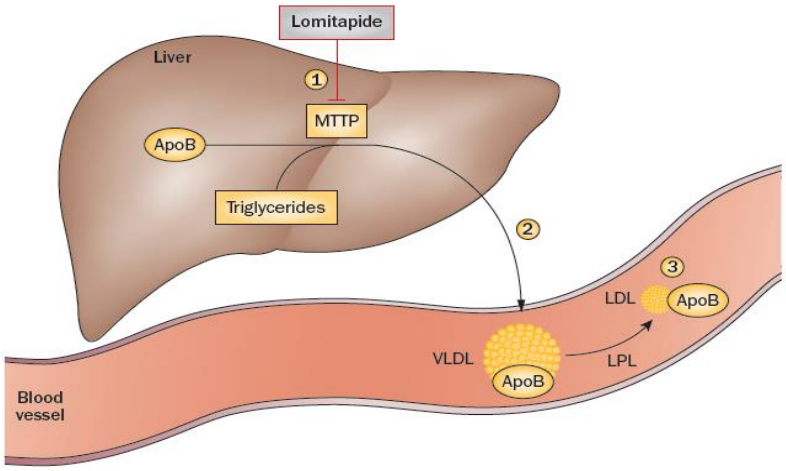


Figure 8 Lomitapide work mechanism.

Lomitapide inhibits MTTP activity (1) thereby inhibiting triglyceride loading to apoB and formation of VLDL particles. As a result, the secretion of VLDL from hepatocytes (2) decreases, resulting in a decrease in the production of LDL particles (3) and decreased levels of LDL-C in the blood. The efficacy and safety of microsomal triglyceride inhibitors (oral lomitapide) have been evaluated in three small clinical studies:

i. In a study of six patients with homozygous familial hypercholesterolaemia, lomitapide (starting dose between 0.03 and 1.0 mg per kilogram body weight per day) decreased (LDLC) by 51% and apolipoprotein B by 56% from baseline (Rosenson, et al., 2017).
ii. A further phase 2 study, concerned with lomitapide side effects. In this study, 64 patients with moderate hypercholesterolaemia (LDL 130-250) were randomly assigned to ezetimibe, increasing the dose of lomitapide (5, 7, 10 mg / day), or ezetimibe + increasing lomitapide dose. After 32 weeks LDL fell by 20, 30 (with lomitapide 10 mg), and 46 mg in 3 groups (sequence). Lomitapide also decreases HDL by 6% and apo-B by 24% (Rosenson, et al., 2017).

iii. In a phase 3, non-randomized, open-label study, 29 patients with familial hypercholesterolemia homozygous diagnosis aged 18 and routine underwent apheresis. After 26 weeks of therapy, LDL-C decreased 50% from the baseline (from 336 to 166 mg / dL [8.7 mmpl / L to 4.3 mmol / L]) (Rosenson, et al., 2017).

iv Of the three studies the most common side effects were gastrointestinal discomfort, elevated hepatic aminotransferase (about 40%), and hepatic fat accumulation (about 8%). These side effects arise depending on the dose. With regard to hepatic fat accumulation, one study showed a stabilization at 30% after three years of treatment (Rosenson, et al., 2017).

The advantages of lomitapide as a novel agent of familial hypercholesterolemia therapy compared with mipomersen and PCSK9 inhibitors are lomitapide can be used orally, where other agents should be administered by subcutaneous injection. So there are often side effects at the site of injection, discomfort in patients and decreased adherence in patients undergoing therapy (Davis & Miyares, 2014).

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