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Pharmacologic Therapy in Peripheral Artery Disease

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Abstract
Peripheral artery disease (PAD) is a common and disabling health condition affecting 20% over age 75. This disease happen in extremities, carotid artery, renalis artery, mesentrica artery. PAD could be happen because of structure or function change in vessel. Peripheral artery disease commonly caused by atherosclerotic plaque in the arteries. The most common manifestation is intermittent claudication. Complication of PAD such as critical limb ischemia, skin ulceration, gangrene, and amputation. Pharmacologic therapy is important for patient with PAD such as antihyperlipidemia and antiplatelet. Antihyperlipidemia is one most important medication for PAD. Not only pharmacologic therapy is needed but also therapeutic lifestyle changes to modify cardiovascular disease such as stop smoking, hypertension, diabetes. Optimize medication is needed to decrease morbidity an increase quality of life.

***Keyword**: Peripheral Artery Disease, Antihyperlipidemia, Antiplatelet*

A. INTRODUCTION

Peripheral artery disease (PAD) is a clinical disorder in which there is a occlusion in the arteries. Atherosclerosis is the most common cause of PAD. Other causes ; thrombosis, embolism, vasculitis, and trauma. PAD occurrence in patients >40 is higher. This disease is related with increased morbidity and reduced quality of life (Libby, 2012) (Newby, Grubb, & Bradbury, 2014)

B. ANATOMY OF ARTERY

Arteries have thicker walls than veins. Arteries's wall containing much of elastic tissue. Their primary function is conducting blood to the various organs, and the second function is to act as a pressure reservoir to maintaining blood flow through the tissue (Widmaier, Raff, & Strang, 2014)

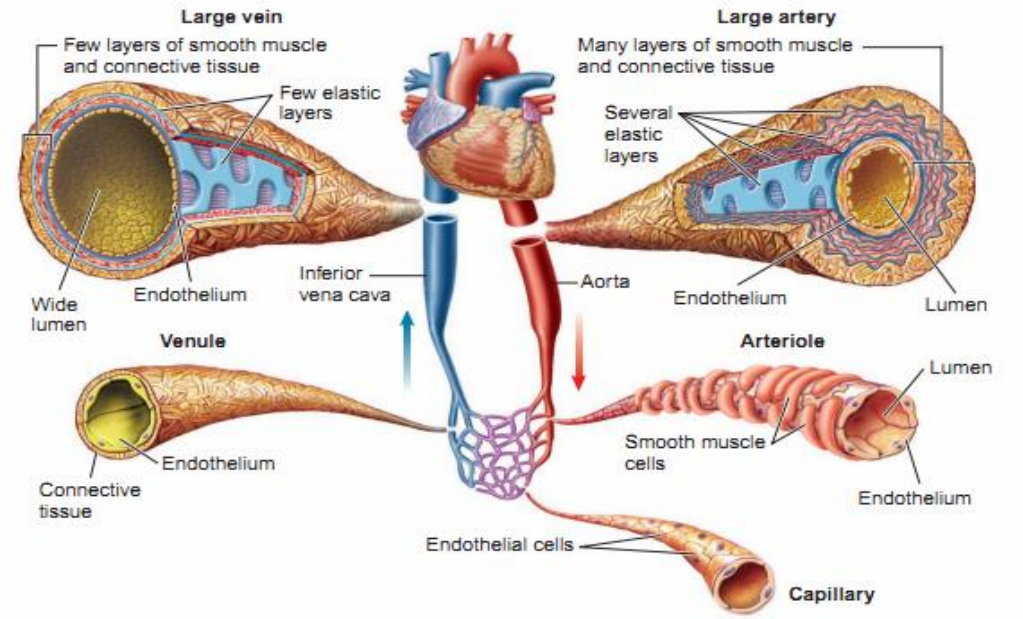

Figure 1. Anatomy of artery and vein (Widmaier, Raff, & Strang, 2014)

Walls thickness and lumen diameter of artery different with veins. Entire circulatory system has important structure called endothelium. Endothelium. Endothelial cells have many function, such as : Serve as a physical lining in vessel, serve as a permeability barrier, secrete paracrine agent such as vasodilators and vasoconstrictors, mediate angiogenesis, role in vascular remodeling, produce growth factors in response to damage, secrete substances that regulate platelet clumping, clotting and anticlotting, influence vascular smooth muscle proliferation in the disease atherosclerotic (Widmaier, Raff, & Strang, 2014)

Endothelium have significant role on vascular homeostasis. Endothelium release vasoactive mediators include nitric oxide and prostacyclin and endothelium-derived hyperpolarizing factor, and also vasoconstrictor include endothelin -1 dan angiotensin-II. Endothelium have important role on release inflammatory cell in thrombus formation. Endothelium release surface receptor such as E-selectin, Intercelluler adhesion molecule type 1 (ICAM-1) and endothelial cell adhesion molecule type 1 (PECAM-1) which will mediate adhesion and migration leukocyte in to subintima. Endothelium release von Willebrand factor which will stimulate thrombus formation. These process are important in atherosclerosis development and progress (Newby, Grubb, & Bradbury, 2014)

C. PATHOGENESIS OF PERIPHERAL ARTERY DISEASE

PAP caused by segmental lesions that cause stenosis or occlusion which localized to large and medium size vessels. Pathology of lesions includes atherosclerosis plaque with calcium deposition, thining of the media, patchy destruction of muscle and elastic fibers, fragmentation of the internal elastic lamina and thrombi composed of platelet and fibrin (Creager & Loscalzo, 2012)

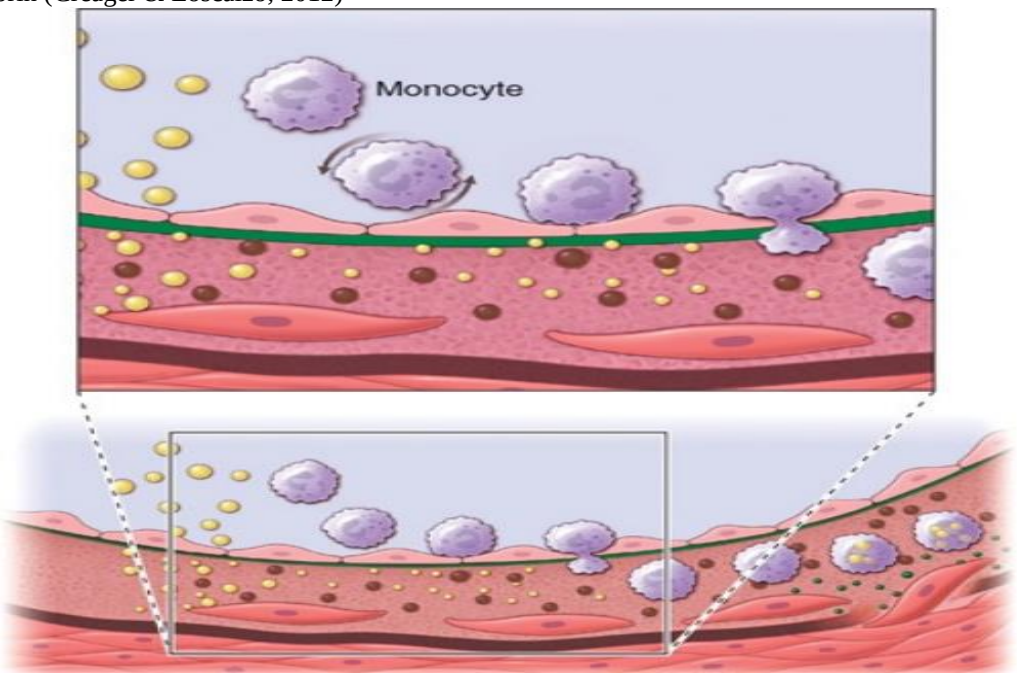

Figure 2. Atheroma formation

Lipid layers demonstrate as a early start of lesion and atherosclerosis. Lesion start from increase lipoprotein in intima. Hypercholesterolemia induce accumulation of LDL particles in the intima. Oxidative lipoprotein particles may trigger a local inflammatory response that start lesion formation. Then recruitmen of monocytes happen after adhesion leukocytes molecules on the site of a arterial lesion. Then white blood cells migrate into the intima. These mononuclear phagocytes ingest lipids and form foam cells. As the fatty streak develops into a complicated atherosclerotic lesion, smooth muscle cells migrate into internal elastic membrane and accumulate within the expanding intima, and then forms the bulk of the advanced lesion. (Libby, 2012)

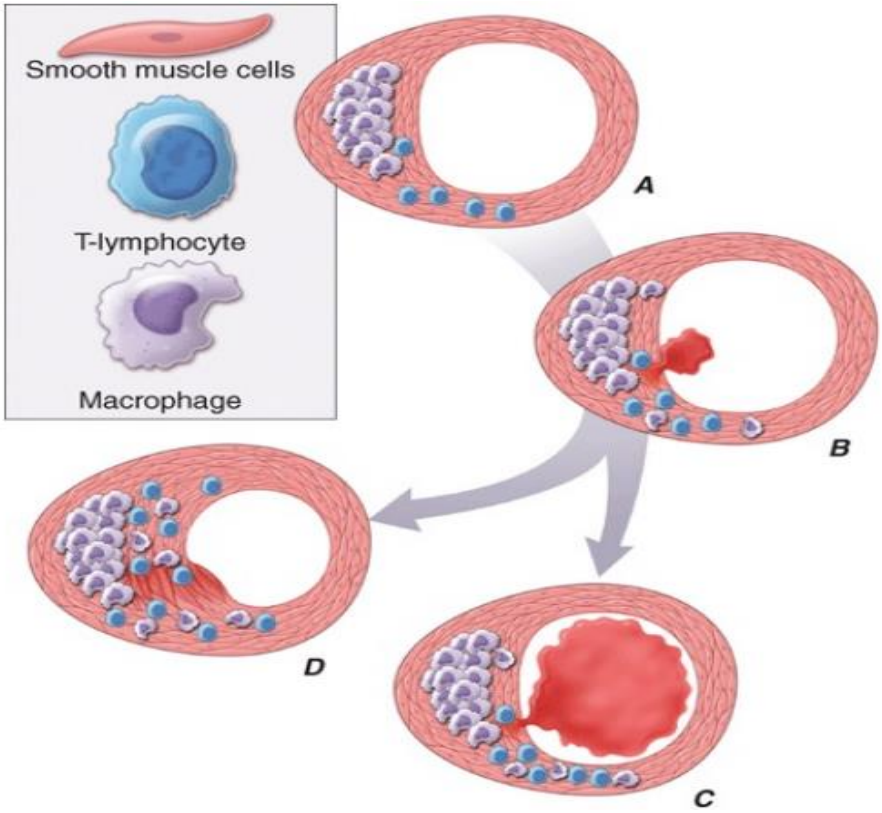

Figure 3. Plaque rupure, thrombosis, and healing (Libby, 2012)

A. Arterial remodeling during atherogenesis. On the early part of atheroma, it is growing outward in the lumen. ***B.*** Rupture of the plaque's fibrous cap causes thrombosis and then occurs arterial thrombosis because blood coagulant factors contact thrombogenic collagen in the arterial extracellular matrix and tissue factor produced by macrophage-derived foam cells in the lipid core of lesions. The normal artery wall will has fibrinolytic or antithrombotic mechanisms which will resist thrombosis and lyse clots. ***C.*** If fibrinolytic mechanism fails, it may form arterial occlusion. ***D.*** Healing and subsequent thrombin-induced fibrosis makes a fibroproliferative response which will form fibrous lesion that can produce an eccentric plaque that make a stenosis in vessel. (Libby, 2012)

D. CLINICAL MANIFESTATION

Table 1. PAP manifestation (Newby, Grubb, & Bradbury, 2014)

Chronic lower limb arterial disease	Intermittent claudication An ischaemic pain on muscles of the leg upon walking. The pain is usually felt in the calf because this affects the superficial femoral artery.
	Critical limb ischaemia an rest (night) pain, tissue loss (ulceration or gangrene),npresent for more than 2 weeks
	Diabetic vascular disease When the blood supply is adequate, then healing is difficult so dead tissue can be excised
Chronic upper limb arterial disease	Atheroembolism (blue finger syndrome) Small emboli in digital arteries and this are unilateral.
	Subclavian steal An ischaemia in vertebro-basilar, which is characterised by dizziness, cortical blindness and/or collapse.
Acute limb ischaemia	Caused by acute thrombotic occlusion

E. PHARMACOLOGIC THERAPY

a. Antihyperlipidemia

Statins reduce the risk of mortality, cardiovascular events, and stroke in patients with PAD. Patients with PAD serum LDL cholesterol target is reduced to ,2.5 mmol/L (100 mg/dL), and optimally to ,1.8 mmol/L (,70 mg/dL), or ≥50% LDL cholesterol reduction when the target level cannot be reached (Tendera, et al., 2011)

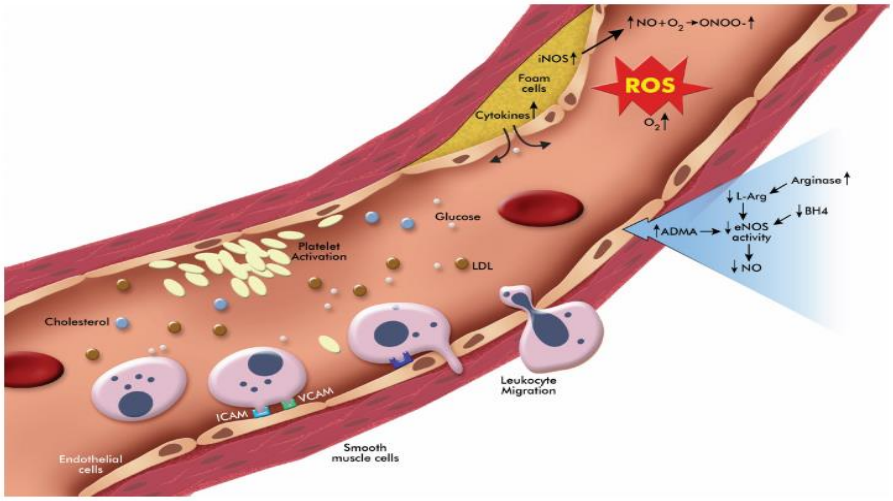

Figure 4. Effect of hyperlipidemia on vascular and endothelial (Kolluru, Bir, & Kevil, 2012)

Hyperlipidemia induce increase of LDL uptake by endothelial cell. Then foam cell produce proinflamatory cytokine released in blood flow. Increased ROS production through iNOS. Increased ROS induce decrease NO bioavailability. Decrease NO induce atherogenesis, platelet activation, an leukocyte adherence (Kolluru, Bir, & Kevil, 2012)

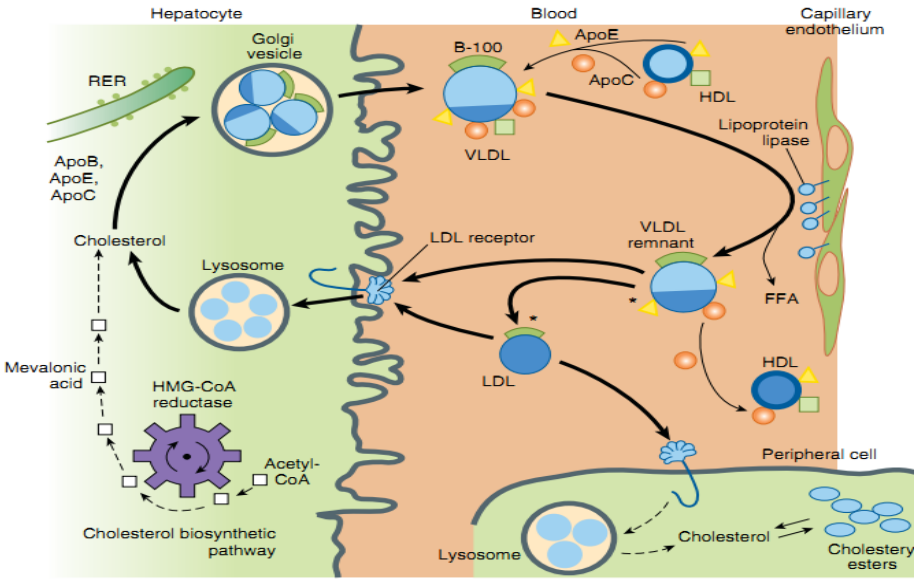

Figure 5. Lipoprotein metabolism (Malloy & Kane, 2011)

This is metabolism of lipoproteins of hepatic origin. VLDL is secreted from Golgi apparatus. They get additional apo C lipoproteins and apo E from HDL. VLDL are changed to IDL by lipolysis through lipoprotein lipase in the vessels of peripheral tissues. During the process, C lipoproteins and a portion of the apo E are given back to HDL.

Some of the IDL (VLDL remnants) are converted to LDL by losing of triglycerides and loss of apo E. LDL degradation done by endocytosis in the liver and the peripheral tissues (Malloy & Kane, 2011).

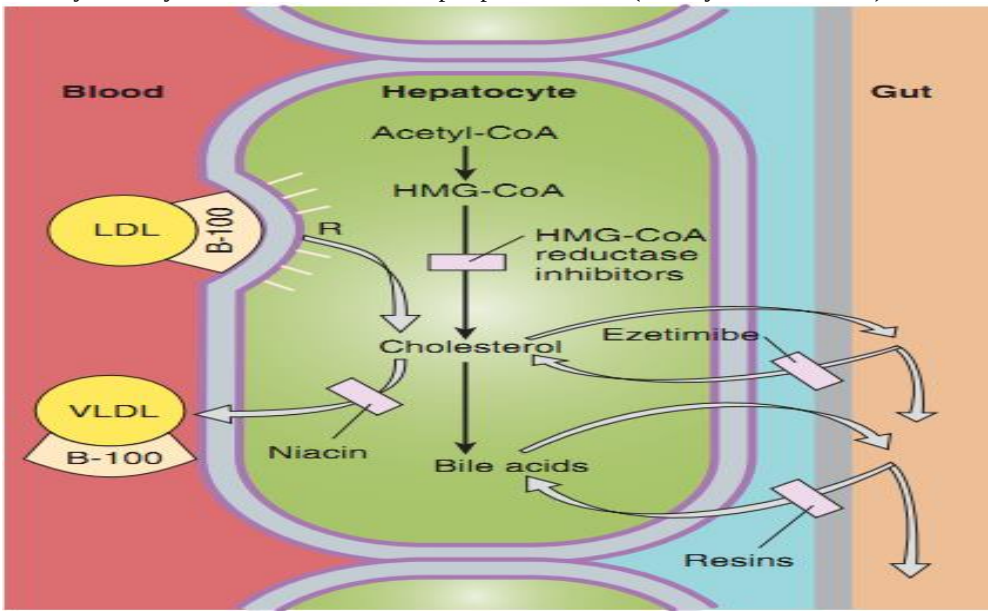

Figure 5. Anti-hyperlipidemia site of action (Malloy & Kane, 2011)

Table 3. Antihyperlipidemia (Malloy & Kane, 2011)

Golongan	Obat	Farmakologi
HMG-COA Reductase inhibitor (Statin)	Atorvastatin, Rosuvastatin, simvastatin, fluvastatin, pitavastatin	Mechanism: Increase high-affinity LDL receptors, then increase fractional catabolic rate of LDL and exctraction of LDL precursor by liver (VLDL remnant) until LDL decrease. Benefit : Decrease LDL, Decrease Trigeliseriuda, increase HDL Toxicity : Increase transaminase serum (3x), myopathi
Niacin (nicotinic Acid)		Mechanism: Inhibits VLDL secretion, until LDL production decrease. Benefit : decrease VLDL and LDL, and Lp(a), increase HDL significantly Toxicity : Increase transaminase serum (2x)
Fibric Acid derivates	Gemfibrozil, fenofibrat	Mechanism: Increase fatty acid oxidation in liver and muscle. Increase lipolysis from lipoprotein triglycerides through LPL. Decrease intraseluler lipolysis on adipose tissue. VLDL decrease, because secretion in liver decrease Benefit : decrease VLDL and LDL, increase HDL
Bile acid-binding resin	Colestipol, cholestiramin,dan colessevelan	Mechanism : increase cholesterol metabolism, increase GLP-1 secretion until incretin secretion increase Benefit : increase LDL uptake from plasma, decrease glucose concentration
Cholesterol absorption inhibitor	Ezetimibe	Mechanism: Inhibit selectively cholesterol and phytosterol absorption in intestine and inhibit cholesterol reabsorption from bile. Benefit : Decrease LDL
Cholesteryl ester transfer protein (CETP) inhibitors	Torcetrapib, anacetrapib, dalcetrapib, evacetrapib	Mechanism : Inhibit CETP so HDL can't form LDL/VLDL Benefit : decrease LDL, increase HDL Toksisitas : Increase cardiovascular event
Anti-PCKS9 antibody	Evolocumab	Mechanism: Inhibit PCKS9 so there is nodegradation of LDL receptor and LDL decrease. PCKS9 binds LDL receptor and facilitate LDL receptor degradation Benefit : decrease LDL, increase HDL significantly

Evolocumab is a monoclonal antibody for PCSK9 which reduce LDL significantly. PCSK9 binds to the LDL receptor and targets it for destruction, then it will decreased expression of LDL receptor and will increase plasma LDL cholesterol (LDL-C). Inhibiting PCSK9 will reduced serum LDL-C levels. Evolocumab is an human monoclonal antibody that will against PCSK9 and reduced serum LDL-C levels. Decrease LDL plasma will inhibit atherosclerosis progesivity (Kiyosue, Honarpour, Kurtz, Xue, Wasserman, & Hirayama, 2016)

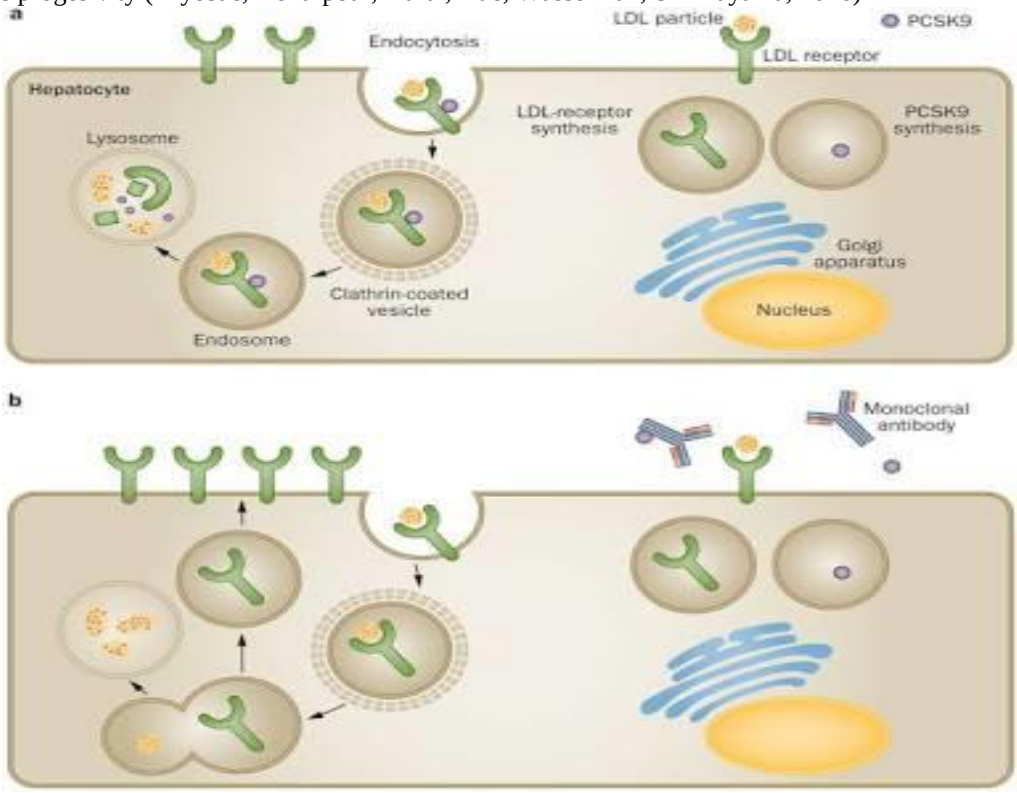

Figure 6. Evolocumab site of action (Kiyosue, Honarpour, Kurtz, Xue, Wasserman, & Hirayama, 2016)

Table 4. Evolucumab efficacy

Dosage Regimentation	Outcome	Follow up
420 mg once a month	Decrease LDL 54,6%	12 weeks
140 mg once in two week	Decrease LDL 60,4%	12 weeks
420 mg once a month	Increase HDL 7,6%	12 weeks
140 mg once in two week	Meningkatkan HDL 6,9%	12 weeks
420 mg once a month	Decrease TG 15,7%	12 weeks
140 mg once in two week	Decrease TG 17,4%	12 weeks
420 mg once a month	Decrease PCKS9 44%	12 weeks
140 mg once in two week	Decrease PCKS9 60,9%	12 weeks

b. Antiplatelet

Antiplatelet can reduce significantly the incidence of vascular death, non-fatal myocardial infarction, and non-fatal stroke by 23%. Low-dose aspirin (75–150 mg daily) was as effective as higher daily doses (Tendera, et al., 2011)
Thrombophilic risk factor related with severity of PAD such as claudication and critical limb ischemia, which fibrinogen become important factor for predicting limb ischaemia. Thrombosis define as blood clot in lumen which cause occlusion or limit blood flow. Thrombus compile of platelet, red blood cell and gather together glycoprotein, few of protein plasma, and fibrin. Platelet activation induce stimulation of thrombin, TxA-2, fibrillar collagen during atherosclerosis plaque rupture. Platelet activation has ability to adhesion on vessel walls mediated through glycoprotein platelet membrane include Ib and IIb. This facilitated factor von willebrand and fibrin interaction and

thrombosis formation. Thrombogenic factor such as fibrinogen and thrombin related with PAD status patient (Sartori, et al., 2010).

Platelet inhibitors, including aspirin and clopidogrel, will decrease the risk of adverse cardiovascular events in patients with atherosclerosis and they are recommended for PAD patients. Dual antiplatelet therapy (aspirin and clopidogrel) is not more effective than aspirin alone in decreasing cardiovascular morbidity and mortality in patients with PAD. The anticoagulant warfarin is not recommended for PAD because of its bleeding risk (Creager & Loscalzo, 2012)

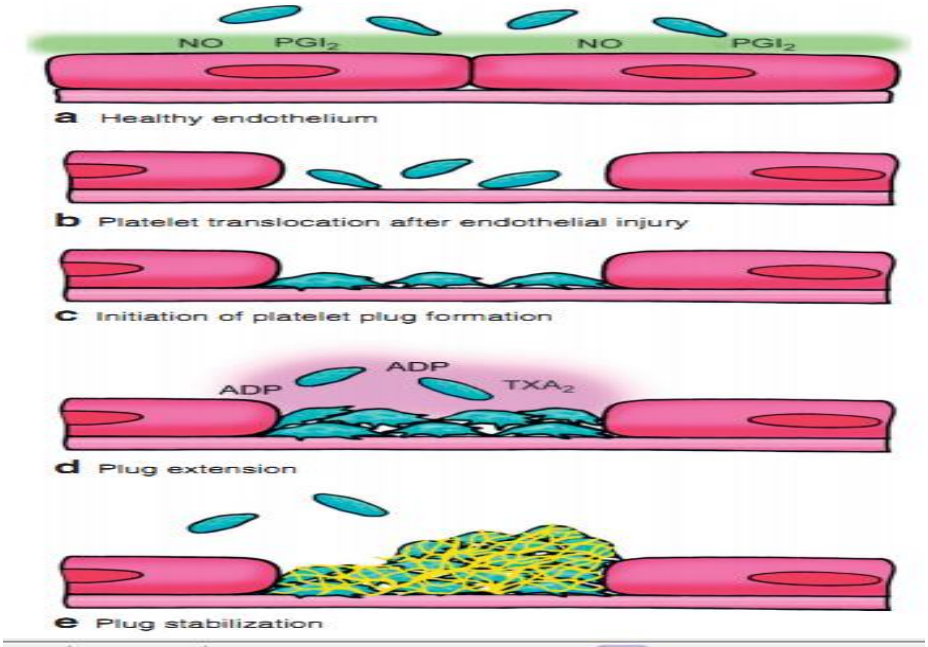

Figure 7. Thrombus formation on damaged vascular walls (endhotel) (Troxler, Dickinson, & Homer-Vanniasinkam, 2007)

a. Platelets circulate adjacent to the endothelium and there is no adhesion because it is inhibited by nitric oxide (NO) and prostacyclin (PGI2). **b** After injury occurs platelets adhere to subendothelial connective tissue. **c** Platelet spreading over subendothelium during the early phase of platelet plug formation. **d** Recruitment of further platelets by mediator release, such adenosine 5-diphosphate (ADP) and thromboxane (TXA2) form plug extension. **e** Stabilized platelet plug formed by the fibrinogen–fibrin network (Troxler, Dickinson, & Homer-Vanniasinkam, 2007)

Platelet function is directed by three groups of substances. The first group consists of agents produced outside the platelet which interact with platelet membrane receptors, such as catecholamines, collagen, thrombin, and prostacyclin. The second group consists of agents produced inside platelet which interact with membrane receptors, such as ADP, prostaglandin D2 , prostaglandin E2 , and serotonin. The third group consist of agents produce inside the platelet which act within the platelet, such as prostaglandin endoperoxides and thromboxane A2, the cyclic nucleotides cAMP and cGMP, and calcium ion. Several targets for platelet inhibitory drugs have been identified such as, inhibition of prostaglandin synthesis (aspirin), inhibition of ADP induced platelet aggregation (clopidogrel, prasugrel, ticlopidine), and blockade of glycoprotein IIb/IIIa receptors on platelets (abciximab, tirofiban, and eptifibatide). Dipyridamole and cilostazol are additional antiplatelet drugs (Zehnder, 2011)

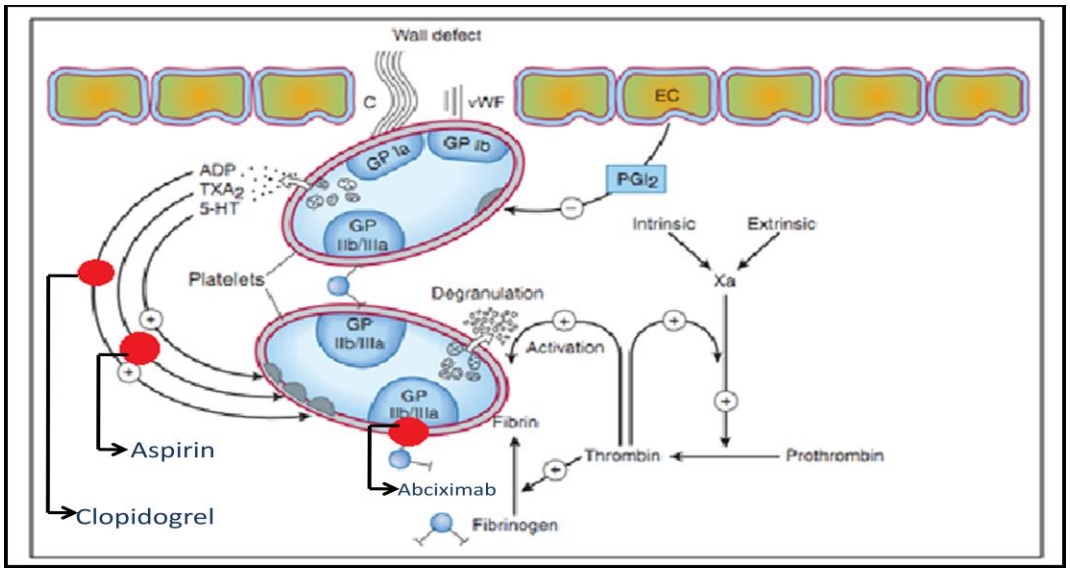

Figure 8. Antiplatelet mechanism of action (Zehnder, 2011)

When vessel wall damage thrombus form at the site of the damaged (EC, endothelial cell). Platelet membrane receptors such as glycoprotein (GP) Ia receptor, binding to collagen (C); GP Ib receptor, binding von Willebrand factor (vWF); and also GP IIb/IIIa, which binds fibrinogen. Prostacyclin (PGI2) released from the endothelium. Aggregating substances released from the degranulating platelet include adenosine diphosphate (ADP), thromboxane A 2 (TXA 2), and serotonin (5-HT) (Zehnder, 2011)

Tabel 5. Antiplatelet therapy (Zehnder, 2011)

Category	**Drug**	**Pharmacology**
Inhibit prostaglandin synthesis	Aspirin	Mechanism : Inhibit thromboxane A2 synthesis through ireversibel acetylization from COX enzym. Duration antiplatelet 7-5 hari Dosage for PAD 325 mg/day atau low dose 100mg/day
Inhibit ADP	Clopidogrel, prasurgel, ticlopidin	Mechanism : blockade ADP receptor until decrese platelet agregation Duration antiplatelet 7-5 hari Dosage clopidogrel for PAD 75mg/day

F. CONCLUSION

PAD has high morbidity and decrease patients quality of life. PAD treatment should be both lifestyle changes and pharmacologic therapy. Role of pharmacologic therapy for PAD treatment must be carefully considered. Antihyperlipidemia and antiplatelet are drug of choice for PAD. Development of utilizing antyhiperlipidemia lead to new drug approve by FDA called evolocumab. Evolucumab is monoclonal antibody of PCSK9 which significantly reduce LDL. Through its efficacy, evolocumab is reasonable to be considered as a medication for PAD patients.

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