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Overview of Antiplatelet Therapy Vorapaxar in Coronary Heart Disease (Atherosclerotic Cad)

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Abstract
Coronary heart disease (CHD) mostly caused by atherosclerotic myocardium damage, disrupting coronary blood flow. In 2012, World Health Organization recorded 17.5 million deaths caused by cardiovascular disease or 31% of 56.5 million worldwide mortality. Indonesian Sample Registration System Survey in 2014 showed that CHD was the most common etiology of mortality in all spectrum of ages, following stroke, around 12.9%. CHD classified into 3 groups, unstable angina (UA), non-ST elevation segment myocardial infarction (NSTEMI), and ST elevation segment myocardial infarction (STEMI). The management of CHD consists of analgesics, antithrombotic (antiplatelet and anticoagulant), antiangina and reperfusion therapy. Aspirin and clopidogrel is the most common antiplatelet used with Percutaneous Coronary Intervention (PCI). Newly approved by FDA, Vorapaxar, is an antiplatelet in Protease-Activated Receptor-1 (PARs) class. This paper review biopharmaceutical aspects of drugs for CHD therapy. This review showed that Vorapaxar in CHD was able to decreasing mortality risk due to cardiovascular or ischemic, but in return increasing mild or heavy bleeding risk, include intracranial bleeding.
Keywords: *Coronary heart disease, antiplatelet, Vorapaxar, PAR*

I. INTRODUCTION

Coronary heart disease (CHD) is mainly caused by myocardial abnormalities due to coronary blood flow insufficiency due to arterosclerosis (Walker, *et al*., 2014). CHD is the most common form of heart disease and the leading cause of premature death in Europe, the Baltic States, Russia, North and South America, Australia and New Zealand. CHD is the number one killer in the United States and around the world. Every minute, an American dies from CHD. CHD is almost afflicted by 16 million Americans and its prevalence rises steadily with age (Ramrakha, P., 2006). In 2020 it is thought to be the leading cause of death in all regions of the world. CHD is still responsible for about one in five deaths and over 600,000 deaths per year in the United States. In the UK, 1 in 3 men and 1 in 4 women die from CHD, an estimated 330,000 people have myocardial infarction every year, and about 1.3 million people have angina. According to data from Riskerdas (2013), the highest prevalence for cardiovascular disease in Indonesia is CHD, which is 1.5%. Most age groups occur in the age group of 65-74 years (3.6%), followed by age group 75 years old (3.2%), age group 55-64 years (2.1%) and age group 35-44 years (1.3%). While according to economic status, most at lower economic level (2.1%) and lower middle (1.6%). Some of the risk factors for CHD include family history of CHD, male gender, diabetes mellitus, hypertension, smoking, drinking alcohol, psychosocial factors, abdominal obesity, lack of movement, consuming less fruits and vegetables, and hemostatic factors (Papadakis & McPhee, 2016; Walker, et al., 2014). Acute coronary syndrome (ACS), which is part of CHD, is classified into three groups: unstable angina (UA), non-ST elevation segment myocard infarction (NSTEMI), and ST elevation segment myocard infarction (STEMI). The three classifications are different in the formation of clots/blood clots in the coronary region, in which the blood clot is still in minimal size, the NSTEMI blood clot is formed in large size and almost mostly covers the coronary vessel lumen, whereas in the STEMI blood clot formed closing all the lumen of the blood vessels (Loscalzo, 2010).

II. PATHOPHYSIOLOGY

The pathophysiology of CHD can be seen in Figure II.1. Endothelial vascular damage causes some components of blood cholesterol especially Low Density Lipoprotein (LDL) to enter the endothelial layer and accumulate in it. Accumulated cholesterol undergoes oxidation or enzymatic processes. Leukocytes will enter the endothelial region of LDL accumulation in them, leukocytes will oxidize LDL phagocytosis in the tissue. Phagocytosis processes that are not well regulated can form foam cells. T lymphocytes and macrophages will be activated and joined with foam cells to perform the process of phagocytosis. The smooth muscle cells will also be activated and migrated, these cells will secrete extracellular matrices such as collagen to stabilize the formed plaques. Phagocytic cells that perform the phagocytic process will produce several inflammatory mediators such as cytokines. Cytokines induce the secretion of proteolytic enzymes that can break down or melisis extracellular matrix causing the plaque fragile and easy to experience rupture. The ruptured plaque component will be exposed to the blood component, some thrombogenic

plaque components such as collagen factor factor will activate platelets and induce the formation of thrombus or blood clots in coronary vessels (Loscalzo, 2010; Walksman *et al*, 2014; Widmaier *et al*, 2014; Heyden, R. 2016).

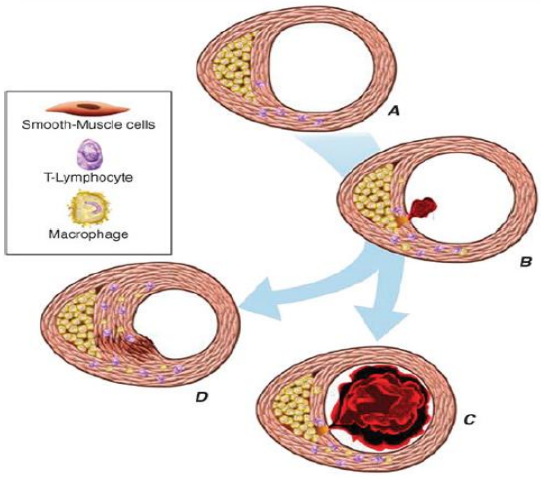

Figure II.1

Plaque rupture, thrombosis, and healing; A. Arterial remodeling during atherogenesis; B. Rupture of the plaque's fibrous cap causes thrombosis; C. When the clot over whelms the endogenous fibrinolytic mechanisms, it may propagate and lead to arterial occlusion; D. The subsequent thrombin-induced fibrosis and healing causes a fibroproliferative response that can lead to a more fibrous lesion, one that can produce an eccentric plaque that causes a hemodynamically significant stenosis.

III. CLINICAL MANIFESTATIONS AND PATHOLOGY

Table III.1 Coronary Artery Disease: Clinical Manifestations and Pathology (Walker, et al., 2014)

Clinical problem	Pathology
Stable angina	Ischaemia due to fixed atheromatous stenosis of one or more coronary arteries
Unstable angina	Ischaemia caused by dynamic obstruction of a coronary artery due to plaque rupture or erosion with superimposed thrombosis
Myocardial infarction	Myocardial necrosis caused by acute occlusion of a coronary artery due to plaque rupture or erosion with superimposed thrombosis
Heart failure	Myocardial dysfunction due to infarction or ischaemia
Arrhythmia	Altered conduction due to ischaemia or infarction
Sudden death	Ventricular arrhythmia, asystole or massive myocardial infarction

IV. MANAGEMANT OF CAD

Immediate therapy at the hospital is necessary because rapid treatment significantly reduces the risk of death or ischemic recovery by 60% with appropriate treatment. Management of therapeutic treatment may be given, among others: a. Analgesia; b. Antithrombotic (antiplatelet and anticoagulant); c. Antiangina Therapy; d. Reperfusion therapy, consisting of 1) NSTEMI, reperfusion therapy is not beneficial, and thrombolytic delivery will have a harmful effect on the patient; and 2) STEMI: Percutaneous coronary intervention (PCI) and thrombolysis (Innes & Maxwell, 2016). This article will review the biopharmaceutical aspects of drugs used in coronary heart disease, based on literature study results, with a focus on antiplatelet vorapaxar usage reviews, newly approved by the FDA in 2014.

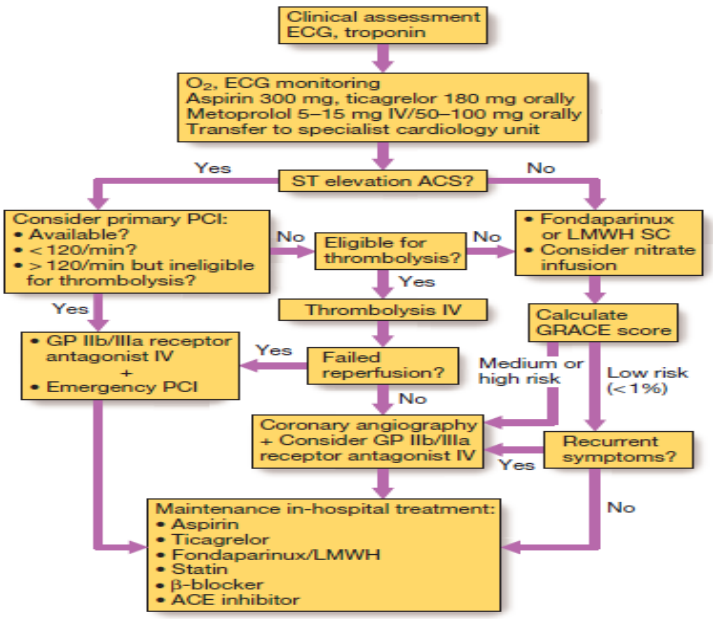

Figure IV.1 Treatment for acute coronary syndrome (ACS) (Innes & Maxwell, 2016)

Platelet Receptor and Drug Target

Table IV.1 Platelet Receptor, Drug Target, and Adverse Effect

Platelet Receptor	Drugs	Adverse Effect
COX – 1	Aspirin	GI pain, ulceration, bleeding, angioedema, etc.
P2Y12 / ADP	Ticlopidin	Bleeding, anemia, pain, etc
	Clopidogrel	Ulceration, bleeding, pain, agranulocytosis, etc
	Prasugrel	Bleeding, anemia, pain, headache, hemolysis, etc.
	Ticagrelor	Bleeding, dyspnea, pain, headache, etc.
GPIIB/IIIa	Abciximab	Bleeding, pain, hypotension, anemia, etc.
	Tirofiban	Bleeding, pain, edema, etc.
	Eptifibatide	Bleeding, hipotension, GI hemorrhage, etc.
PAR-1	**Vorapaxar**	
	Atopaxar	

PAR 1 (Protease-activated receptor 1)

The serine protease thrombin is the most potent platelet activator and plays a critical role in thrombosis and in the maintenance of hemostasis following vascular injury. As direct thrombin inhibitors block thrombin-mediated cleavage of fibrinogen, targeting the downstream platelet thrombin receptors instead should theoretically result in a safer bleeding profile. Of the four PAR family members, only PAR1 and PAR4 are expressed on human platelets (Walksman, et al., 2014). PAR1 is the major receptor for thrombin in human platelets and has become an intensively studied antiplatelet target in clinical trials. Conversely, PAR4 is considered to be a secondary thrombin receptor due to its lower affinity for thrombin, and there has been considerably less development of PAR4 inhibitors. More recent studies have identified other proteases such as matrix metalloprotease-1 (MMP1, MMP13, plasmin, and activated protein C (APC) as direct activators of PAR1. Collagen activation of MMP1–PAR1 signaling may be an important new mechanism of platelet activation during the early steps of platelet thrombogenesis at the site of vessel injury (Walksman, et al., 2014).

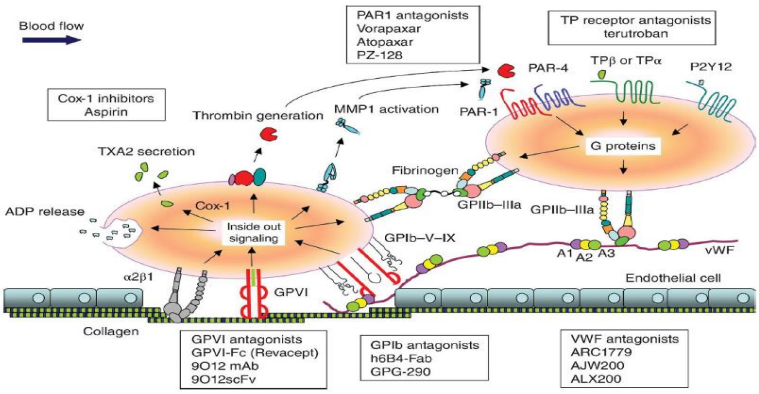

Figure IV.2

Mechanisms involved in platelet activation and emerging antiplatelet drugs. Following disruption of an atherosclerotic lesion, platelets initially adhere to exposed collagen and von Willebrand factor (vWF) from the vessel wall via GPIb–V–IX on the surface under high shear force conditions. Collagen mediates firm adhesion of platelets in a two-step mechanism in which "outside-in" signaling from the collagen receptor, GPVI, and the α2β1 integrin results in the formation of a platelet monolayer. This collagen-mediated adhesion and activation of platelets leads to the release of adenosine diphosphate (ADP) and thromboxane A2 (TXA2) production via COX-1, matrix metalloprotease-1 (MMP1) activation, and thrombin generation on the surface of activated platelets. These autocrine mediators recruit additional platelets through the major fibrinogen receptor GPIIb–IIIa and activate nearby platelets to cause platelet aggregation via G protein-coupled receptors (GPCRs), PAR1, PAR4, TP, and P2Y12 (Walksman, et al., 2014).

V. NEW DRUG DEVELOPMENT

Immediate treatment of hospital admission is necessary because rapid treatment significantly reduces the risk of death or ischemic recovery by 60% with appropriate treatment (Innes & Maxwell, 2016). Platelets play an important role both in normal hemostasis and in pathologic formation of thrombus. Several large-scale clinical studies have demonstrated that inhibition of platelet aggregation results in significant reduction in mortality and morbidity due to ischemic atherothrombotic events, resulting in antiplatelet therapy being a pharmacological method in the prevention and treatment of cardiovascular, cerebrovascular and peripheral arterial disease (Papp *et al*, 2013). Vorapaxar is a newly approved FDA-approved antiplatelet drug that has a protease-activated receptor-1 inhibiting mechanism. This drug is shown to reduce cardiovascular events for patients with stable atherosclerosis with a history of myocardial disease or peripheral arterial disease in TRA2P trials. The drug is contraindicated in patients with a history of transient ischemic stroke because it leads to increased risk of intracranial haemorrhage (Papadakis & McPhee, 2016; Airoldi & Campanini, 2013). Thrombin, serine protease is the principal protease effector of the most potent coagulation cascade and platelet activator. The platelet thrombin reactions are mediated by protease activated receptors (PARs) platelets which are G protein-coupled receptors from seven-transmembrane domain superfamily receptors. The thrombin activates PAR by cleaving the peptide bond (Arg41-Ser42) at the extracellular domain receptor that produces a new N receptor of the receptor, referred to as the tethered ligand. The new "tail" of these receptors interacts with separate receptor domains and activates. To date, four sub types of PARs are: PAR-1, PAR-2, PAR-3, and PAR-4. Among these four subtypes, only PAR-1 and PAR-4 are identified in human platelets. PARs not only lie in platelets, but also elsewhere include smooth muscle cells, endothelial cells, fibroblasts, and the brain. PAR-1 is recognized as a major thrombin receptor because of its high affinity to thrombin, whereas the role of PAR-4 in humans (requiring higher thrombin concentrations) is not fully understood. An important concept behind the development of thrombin-receptor antagonists is that thrombin-mediated platelet activation is unimportant in normal hemostasis, and therefore, PAR-1 inhibition will not increase the risk of clinically significant bleeding (Airoldi & Campanini, 2013; Tello-Montoliu, A., 2010).

Tricoci. *et al* in 2012 conducted multinational, randomized, double-blind, placebo controlled studies to determine whether the addition of vorapaxar to standard therapy would be better than placebo in reducing recurrent ischemic cardiovascular events and to determine safe profiles in patients with acute coronary syndromes without ST segment elevation. The primary end point is a combination of cardiovascular death, myocardial infarction, stroke, recurrent ischemia with rehospitalization, or severe coronary revascularization. The primary end point occurred in 1,031 of 6,473 patients receiving vorapaxar versus 1,102 of 6,471 patients receiving placebo found that the addition of

vorapaxar as standard therapy did not significantly reduce primary composite endpoints but significantly increased the risk of major bleeding, including intracranial hemorrhage (Tricoci *et al*, 2012). A study conducted by Morrow, D. *et al* in 2012 was randomly assigned to 26,449 patients with a history of myocardial infarction, ischemic stroke, or peripheral artery disease getting vorapaxar (2.5 mg daily) or a suitable placebo and following them for average 30 months. The primary end point effects are cardiovascular death, myocardial infarction, or stroke. At 3 years, primary end points occurred in 1.028 patients (9.3%) in the vorapaxar group and in 1,176 patients (10.5%) in the placebo group. Severe or severe bleeding occurred in 4.2% of patients receiving vorapaxar and 2.5% of those receiving placebo. It was found that inhibition of PAR-1 with vorapaxar reduced the risk of cardiovascular or ischemic death in patients with stable atherosclerosis who received standard therapy. However, it also increases the risk of moderate or severe bleeding, including intracranial haemorrhage (Morrow *et al*, 2012).

VI. CONCLUSION

ACS is a coronary artery disease due to atheroma and its complications, especially thrombosis. Antiplatelet prevents thrombosis in ACS, eg Cox-1, P2Y12 inhibitor, Glycoprotein IIB / IIIA inhibitor. The formation of platelet plaque is influenced by many factors such as ADP, 5HT, thrombin, vWF, PDGF. Thrombin is one of the most potent platelet activators, thus inhibiting the trigger factors of CHD.

Vorapaxar is a new antiplatelet agent that selectively inhibits thrombin cellular action through FDA-approved PAR-1 antagonisms by 2014, but is not yet available in the current literature. Based on clinical trials (TRA 2P-TIMI 50 Clinical Trials), Vorapaxar reduces the risk of death from cardiovascular disease or ischemic events in patients with atherosclerosis who receive standard therapy (add therapy), but increases the risk of moderate or severe hemorrhage including intracranial hemorrhage.

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