Trends in Cardiovascular Medicine 26 (2016) 321–334

Available online at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/tcm

Update on oral antithrombotic therapy for secondary prevention following non-ST segment elevation myocardial infarction

Yongwhi Park, MD, PhD[a,b], *Francesco Franchi, MD*[a], *Fabiana Rollini, MD*[a], *and Dominick J. Angiolillo, MD, PhD*[a,*,1]

[a]*University of Florida College of Medicine—Jacksonville, Jacksonville, FL*
[b]*Division of Cardiology, Department of Medicine, Gyeongsang National University Hospital, Jinju, Korea*

A B S T R A C T

Patients with non-ST segment elevation myocardial infarction (NSTEMI) are at high risk for atherothrombotic recurrences. Dual antiplatelet therapy (DAPT) with aspirin and the $P2Y_{12}$ receptor inhibitor clopidogrel significantly reduces the ischemic events in NSTEMI patients and has represented the mainstay of treatment for over a decade. However, a considerable number of patients continue to experience thrombotic complications, which may be in part due to inadequate platelet inhibition induced by this treatment regimen. This underscores the need for more potent antithrombotic treatment regimens for the long-term prevention of atherothrombotic events in NSTEMI patients. These include novel generation $P2Y_{12}$ receptor blockers, such as prasugrel and ticagrelor, or adjunctive antiplatelet or anticoagulant therapies, such as vorapaxar [a protease-activated receptors (PAR)-1 receptor inhibitor] or rivaroxaban (a factor Xa inhibitor), respectively. Since ischemic events accrue over time in NSTEMI patients, prolonging intensified antiplatelet therapy beyond 1 year has also been investigated. However, although intensified and prolonged antithrombotic treatment regimens reduce ischemic events, this occurs at the expense of an increased risk of bleeding complications. This article encompasses the current state of the art on antithrombotic therapies for the secondary prevention of atherothrombotic events in patients with NSTEMI.

Key words: Oral antithrombotic therapy, Non-ST segment elevation myocardial infarction.

Introduction

Acute coronary syndrome (ACS) is a potentially lethal condition due to sudden reduction in coronary blood flow, which is usually caused by a thrombotic occlusion of coronary arteries [1–3]. ACS is categorized into ST elevation myocardial infarction (STEMI), which has occlusive and persistent thrombus, and non-ST elevation ACS (NSTE-ACS), which usually has non-occlusive or transient thrombus [4,5]. NSTE-ACS is further subdivided into non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) according to evidence of myocardial necrosis (elevation of serum cardiac biomarkers such as troponins) [4,5]. NSTEMI is the most frequently reported among these disease entities [6]. NSTEMI is one of the leading causes of death in the United States and Europe [4–6]. Annually, more than 550,000 patients suffer

The authors have indicated there are no conflicts of interest.

* *Corresponding author*. Tel.: +1-904-244-3933; fax: +1-904-244-3102.
E-mail address: dominick.angiolillo@jax.ufl.edu (D.J. Angiolillo).

[1] Dominick J. Angiolillo has received payment as an individual for: a) Consulting fee or honorarium from Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular and PLx Pharma; b) Participation in review activities from CeloNova, Johnson & Johnson, and St. Jude Medical. Institutional payments for grants from Glaxo-Smith-Kline, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Janssen Pharmaceuticals, Inc., Osprey Medical, Inc., Novartis, CSL Behring, and Gilead.

http://dx.doi.org/10.1016/j.tcm.2015.08.002
1050-1738/

from NSTE-ACS in the United States and the incidence of the disease is ~3 per 1000 inhabitants in Europe [4,5].

In a classical concept, NSTEMI is initiated by erosion or rupture of atherosclerotic plaque and subsequent pathological coronary thrombus formation [1–3]. Therefore, suppression of thrombus formation with antithrombotic agents is the cornerstone of the acute and long-term management of NSTEMI [1]. Among the various antithrombotic regimens, dual antiplatelet therapy (DAPT) with aspirin and clopidogrel has long been a standard antithrombotic regimen in NSTEMI patients [4,5,7]. Even though DAPT significantly reduces short- and long-term thrombotic events in NSTEMI patients, ischemic recurrences, including cardiovascular mortality, remain high with a residual risk that persists even beyond 1 year [8]. These findings underscore the need for optimization of antithrombotic therapies in the post-MI setting [9]. Recent advancements in the field have led to the development of new antithrombotic treatment regimens, which have translated into further reduction of the risk of ischemic events [10]. In this review, we provide an update on oral antithrombotic therapies used for secondary prevention in patients experiencing a NSTEMI.

Basics of pathophysiology

The rupture, fissure, or erosion of an atherosclerotic plaque promptly activates platelets [11]. The subsequent exposure of subendothelial collagen and von Willebrand factor interact with glycoprotein (GP) Ib/V/IX and GP VI receptors on the platelet surface, which results in platelet adhesion at the site of vascular injury (Fig. 1) [11]. Initial adhesion of platelets are fortified by the activation of integrins, such as αIIbβ3 (GP IIb/IIIa) or α2β1 (GP Ia/IIa), and then form a platelet monolayer at the injured vascular wall [11]. After adhesion to the vessel wall, platelets release multiple secondary mediators, such as adenosine diphosphate (ADP), epinephrine, serotonin, thromboxane A2, and thrombin [11,12]. These mediators accelerate and amplify further recruitment of additional platelets, expression of proinflammatory molecules, and the conversion of the platelet GP IIb/IIIa receptor into its active form via intracellular signaling processes of G-protein coupled receptors (GPCRs) on the platelet surface [12]. The GP IIb/IIIa receptors mediate platelets to aggregate through fibrinogen bonds, and allow the expansion of a platelet-rich thrombus [11]. Because the activation of GPCRs by secondary mediators is the primary modulator of pathologic thrombosis, many antiplatelet agents aim to block this interaction.

A ruptured atherosclerotic plaque releases tissue factors from the subendothelium, which triggers the coagulation cascade, and downstream coagulation factors gather on the activated platelets to convert prothrombin to thrombin [13,14]. Thrombin promotes further platelet activation and thrombus formation through the activation of protease-activated

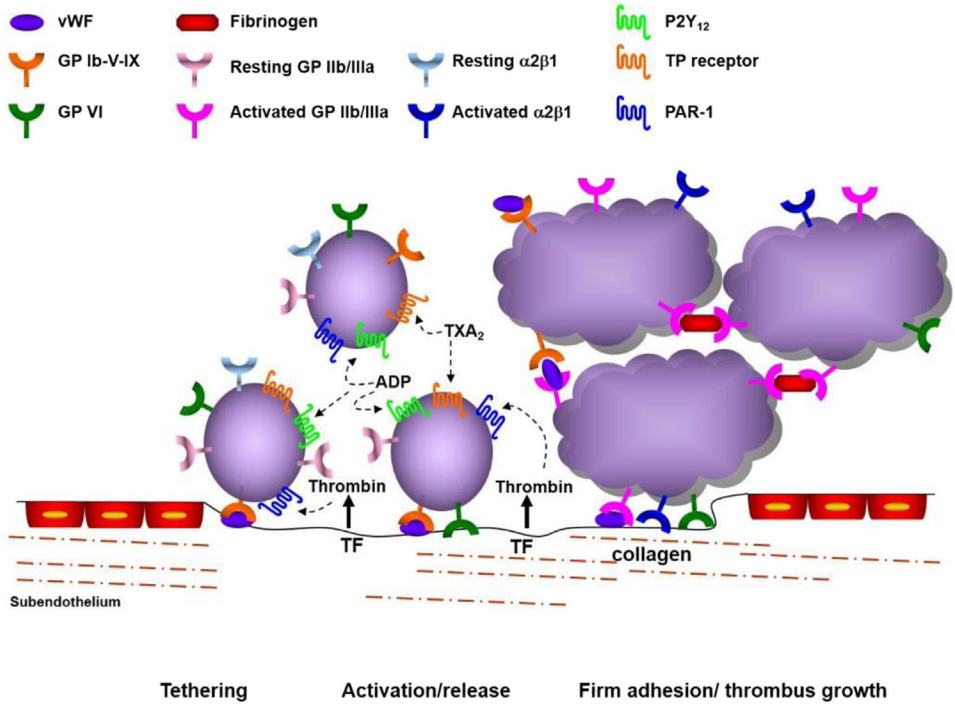

Fig. 1 – Mechanism of thrombus formation. The rupture, fissure, or erosion of atherosclerotic plaque expose subendothelial collagen and vWF. Initial platelet adhesion at the site of vascular injury is mediated by interactions between exposed collagen and platelet GP VI receptor, and between vWF and GP Ib/V/IX receptor complexes on the platelet surface. After adhesion to the vessel wall, platelets release strong activating factors (ADP, serotonin, epinephrine, thromboxane A2, and thrombin), which promote further recruitment and activation of circulating platelets. These factors also lead to changes in platelet shape, expression of proinflammatory molecules, platelet procoagulant activity, and activation of platelet integrin GP IIb/IIIa. Activated GP IIb/IIIa expands a platelet-rich thrombus by aggregating activated platelets through fibrinogen bonds. vWF = von Willebrand factor, GP = glycoprotein, PAR = protease-activated protein receptors, TP = thrombin prostanoid, TXA2 = thromboxane A2, ADP = adenosine diphosphate, TF = tissue factor. (Reproduced with permission from Angiolillo et al. [11].)