International Journal of Cardiology 163 (2013) 5–18

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Current antithrombotic agents for acute coronary syndromes: Focus on bleeding risk

Jean-Pierre Bassand *

Department of Cardiology, Besançon CEDEX, France

ARTICLE INFO

Article history:
Received 23 March 2010
Received in revised form 16 August 2011
Accepted 18 October 2011
Available online 17 November 2011

Keywords:
Bleeding
Acute coronary syndromes
Thrombin
PAR-1
ADP
Thromboxane A_2

ABSTRACT

The formation of an intravascular thrombus underlies the clinical symptoms associated with acute coronary syndromes (ACS). Plaque rupture signals the recruitment and activation of platelets, initiation of the coagulation cascade, and generation of thrombin, resulting in the formation of a platelet-rich thrombus. Use of antithrombotic therapy, including antiplatelet and anticoagulant agents, is a crucial element in reducing the overall morbidity and mortality in patients with ACS. Current antiplatelet and anticoagulant therapies act on distinct sites in platelet activation pathways and the coagulation cascade, but because these agents target pathways necessary for protective hemostasis, their use increases the risk for bleeding complications. Previously, bleeding was considered an unavoidable side effect of ACS management with few clinical implications; however, bleeding has since been shown to be an independent predictor of short- and long-term mortality in patients with ACS. Therefore, the prevention of bleeding has become equally as important as the prevention of further ischemic events. Strategies to limit bleeding include bleeding risk stratification, appropriate dosing of antithrombotic drugs, use of the lowest dose of aspirin with proven efficacy, avoidance of combinations of antithrombotic agents unless for a proven indication, use of drugs proven to reduce the risk of bleeding, and choice of radial access over femoral access in case of invasive strategy. In this context, several novel therapeutic approaches are currently under clinical evaluation, including new antiplatelet agents, such as protease-activated receptor 1 antagonists, and new anticoagulants, such as direct-acting antagonists of factor Xa and factor IIa (thrombin). This review discusses antiplatelet and anticoagulant treatment strategies for the management of ACS, with a particular focus on their associated bleeding risks.

1. Introduction

Acute coronary syndromes (ACS) encompass unstable angina, myocardial infarction (MI) without ST-segment elevation (non-ST-elevation MI [NSTEMI]), and MI with ST-segment elevation (ST-elevation MI [STEMI]) [1]. Given the essential role that an intravascular thrombus plays in the pathophysiology of ACS, antithrombotic therapy, including the use of antiplatelet and anticoagulant agents, is a crucial element in the management of patients with ACS [1–4]. Current antiplatelet and anticoagulant therapies act on distinct sites in platelet activation pathways and the coagulation cascade, and all are associated with bleeding risk [5,6]. Major bleeding is an independent predictor of short- and long-term mortality in patients with ACS and those undergoing percutaneous coronary intervention (PCI) [7–9]. However, even minor bleeding events are associated with a significant increase in risk of mortality [9].

Current and emerging antiplatelet agents include the cyclo-oxygenase (COX)-1 inhibitor aspirin, the $P2Y_{12}$ adenosine diphosphate (ADP) receptor antagonists clopidogrel, prasugrel, ticagrelor, and cangrelor, and the glycoprotein (GP) IIb/IIIa inhibitors eptifibatide, tirofiban, and abciximab. Antiplatelet agents increase bleeding risk by interfering with platelet activation pathways necessary for protective hemostasis [10]. Bleeding risk with aspirin and $P2Y_{12}$ receptor antagonists may be attributed to the inhibition of the essential functions of the thromboxane A_2 (TXA_2) and ADP platelet activation pathways in normal hemostasis [10]. Current injectable anticoagulants include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH; i.e., enoxaparin), the direct thrombin inhibitors (DTIs) hirudin, bivalirudin, and Argatroban, and indirect factor Xa antagonists such as fondaparinux. Currently, the only available oral anticoagulant is the vitamin K antagonist warfarin. Emerging oral anticoagulants include the direct FXa antagonists rivaroxaban and apixaban and the direct thrombin inhibitor (DTI) dabigatran. These agents inhibit the initiation or propagation of coagulation or, by targeting thrombin, inhibit fibrin formation [11]. While the use of antithrombotic agents has reduced the morbidity and mortality associated with ACS, their effects also impact hemostasis and result in increased bleeding. Novel therapies that minimize bleeding risk while providing protection against thrombotic events may improve outcomes in patients with ACS.

This manuscript will provide an overview of pathways contributing to normal hemostasis and pathologic thrombosis. The mechanisms of action of antithrombotic agents that inhibit these pathways will be reviewed, and bleeding risk associated with current and emerging antiplatelet and anticoagulant therapies will be described. Finally, the relationship between bleeding risk and mortality and the clinical implications for future therapeutic approaches will be discussed. Novel strategies aiming to

* University Hospital Jean Minjoz EA 3920, 25000 Besançon CEDEX, France. Tel.: +33 381 668 539; fax: +33 381 668 582.
E-mail address: jpbassan@univ-fcomte.fr.

0167-5273/$ – see front matter © 2011 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2011.10.104

provide more comprehensive inhibition of platelet-mediated thrombosis without an incremental bleeding risk will also be considered.

2. Mechanisms of disease: pathways contributing to normal hemostasis and pathologic thrombosis

2.1. Platelet activation pathways

Upon vascular injury, circulating platelets come into contact with exposed components of the subendothelial extracellular matrix (ECM). Binding of receptors expressed on the surface of platelets to exposed collagen and von Willebrand factor (vWF) within the ECM triggers platelet adhesion, resulting in the formation of an initial platelet monolayer at the site of injury [12,13]. Additionally, ECM-mediated attachment of platelets induces the release of diffusible mediators such as ADP and TXA_2 from adherent platelets that amplify and sustain the initial platelet response [13]. ADP- and TXA_2-mediated activation of platelets occurs via G protein-coupled signaling pathways and results in the increased release of diffusible mediators, the recruitment of circulating platelets, and the formation of a hemostatic plug (Fig. 1) [12]. Additionally, collagen-mediated attachment facilitates the assembly of the prothrombinase complex on the platelet membrane, which leads to the generation of thrombin and activation of the coagulation cascade [12,14]. Thrombin also mediates cleavage of fibrinogen into fibrin, which confers mechanical stability to the developing hemostatic plug [12]. Thus, the coordinated actions of the ADP and TXA_2 platelet activation pathways, as well as thrombin-mediated conversion of fibrinogen to fibrin, are essential to hemostasis [12,13,15].

Platelet activation by ADP is mediated by the $P2Y_1$ and $P2Y_{12}$ receptors, which are coupled to Gq and Gi proteins, respectively [10]. $P2Y_{12}$ is the major receptor responsible for platelet activation by ADP; its activation inhibits adenylate cyclase, resulting in a decrease in cyclic adenosine monophosphate (cAMP), which normally acts as an inhibitor of platelet activation [10,16]. Activation of $P2Y_1$ receptors causes an increase in intracellular calcium, which is an intracellular messenger that is required for platelet activation and degranulation [10,12]. The binding of ADP to the $P2Y_{12}$ receptor results in signaling cascades that culminate in platelet aggregation and thrombus growth and stabilization [12]. The $P2Y_{12}$ receptor also participates in the amplification of platelet aggregation induced by other agents, including TXA_2 and thrombin [12]. Importantly, ADP contributes to platelet activation during protective hemostasis, during the initial formation of a platelet monolayer, and during pathologic thrombosis, when the occlusive platelet-rich thrombus is formed.

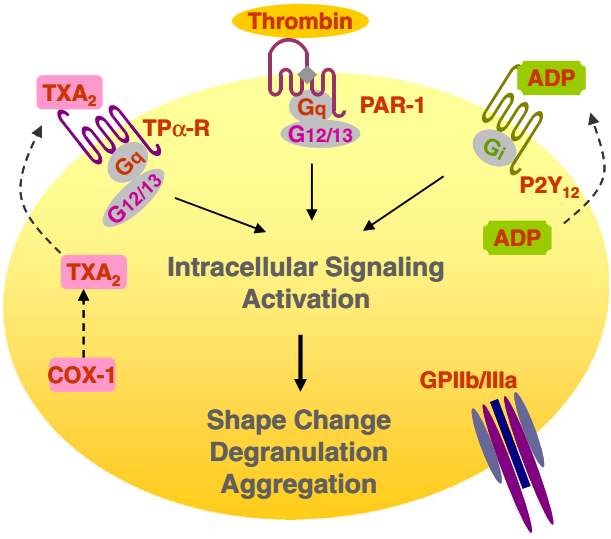

Fig. 1. Platelet activation pathways stimulated by thromboxane A_2 (TXA_2), adenosine diphosphate (ADP), and thrombin [15]. *Abbreviations*: COX = cyclo-oxygenase; GP = glycoprotein; PAR-1 = protease-activated receptor 1.

TXA_2 is synthesized by activated platelets from arachidonic acid via the COX pathway [12]. TXA_2 diffuses across the platelet membrane and activates one of two splice variants of the TXA_2 receptor: TPα (the major receptor responsible for platelet activation) or TPβ, which differ in their cytoplasmic tails and association with G proteins [17]. Activation of either receptor leads to the activation of phospholipase C, ultimately resulting in an increase of intracellular calcium [10]. Activation by TXA_2 results in changes in platelet shape and enhancement of recruitment and aggregation of platelets to the primary platelet plug [12]. TXA_2 also activates platelets during both protective hemostasis and pathologic thrombus formation.

Thrombin is generated at sites of vascular injury, where it acts as a potent activator of platelets [12,18]. Thrombin induces pro-coagulant activity on the surface of platelets, resulting in the additional generation of thrombin [18]. Platelet responses to thrombin are mediated primarily through the G protein-coupled protease-activated receptor (PAR)-1. PAR-1 is activated by thrombin-mediated cleavage of its N-terminal peptide, which then serves as a "tethered ligand" for PAR-1 activation [19]. Human platelets express both PAR-1 and PAR-4; however, PAR-4 requires higher concentrations of thrombin for activation [19]. Activation of signaling pathways associated with PAR-1 leads to increased levels of intracellular calcium and decreased levels of cAMP [10]. Thrombin-mediated platelet activation contributes to pathologic thrombosis through the formation of an occlusive platelet-rich thrombus but may not be required for protective hemostasis. Thrombin-mediated cleavage of fibrinogen to fibrin is more important for hemostasis than thrombin-mediated platelet activation, as suggested by a substantially more dramatic bleeding phenotype in mice lacking fibrinogen compared with mice lacking the thrombin receptor [19,20]. Other studies have shown that inhibition of PAR-1 selectively interferes with platelet deposition at sites of arterial injury and subsequent thrombus growth without affecting bleeding time or coagulation parameters [21,22]. These findings suggest that PAR-1 inhibition should not interfere with primary hemostasis but should abrogate thrombus propagation.

Thus, multiple pathways contribute to platelet activation [10]. All agonists increase levels of intracellular calcium and decrease levels of cAMP, ultimately stimulating the conversion of the platelet integrin GP IIb/IIIa (αIIbβ3) from an inactive to an active state [10]. This allows the binding of GP IIb/IIIa to extracellular ligands, including fibrinogen and vWF, and subsequent platelet aggregation. A positive feedback mechanism further increases the formation and release of ADP and TXA_2 and production of thrombin [10].

2.2. The coagulation cascade

After vascular injury, the initiation of coagulation is triggered by the formation of a complex between tissue factor and factor VIIa, which then activates factor IX and factor X (Fig. 2). Activated factor IX binds activated factor VIII, forming the intrinsic tenase complex that activates factor X [23]. The prothrombinase complex is formed by activated factor X and activated factor V and converts prothrombin (factor II) to thrombin (factor IIa). Thrombin converts fibrinogen to a fibrin monomer. Fibrin monomers then polymerize to form a fibrin mesh that is cross-linked and stabilized by activated factor XIII. Through a positive feedback mechanism, thrombin is further generated by activation of factor V and factor VIII [23]. Thrombin also activates factors V, VIII, and XI, which leads to further thrombin generation [24]. Clot formation is regulated by several endogenous anticoagulants, including the protein C and protein S systems, tissue factor pathway inhibitor, and antithrombin, which confine the hemostatic plug to the site of vessel injury [24].