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Review

Targeting thrombin long-term after an acute coronary syndrome: Opportunities and challenges

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ABSTRACT

Patients after an acute coronary syndrome (ACS) are at increased risk of recurrent thrombotic events, justifying the search for additional antithrombotic treatments. The pathophysiology of ACS involves arterial thrombus formation, in turn occurring because of a combination of platelet activation and fibrin formation, with thrombin playing a key role in both. Antiplatelet therapy, targeting the thromboxane pathway and the ADP $P2Y_{12}$ receptor has been widely accepted for secondary prevention after an ACS. Now, data from recent clinical trials in such patients also encourage the pursuit of inhibiting thrombin formation or thrombin-mediated platelet activation in addition to antiplatelet therapy. This "triple pathway inhibition", including inhibition of thrombin activity or thrombin receptor(s), is currently an option in pure ACS, but already a must in the setting of ACS accompanied by atrial fibrillation (AF), where anticoagulants have been shown to be much more effective than antiplatelet agents in preventing stroke. We here discuss the challenges of managing combined thrombin activity or receptor inhibition and antiplatelet therapy in all such patients. Translating this into practice still requires further studies and patient tailoring to fully exploit its potential.

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1. Introduction

Ischemic heart disease caused by coronary artery atherosclerosis is the largest single cause of death worldwide, accounting for 7.4 million deaths in 2012 (13.2% of all deaths) [1,2], and for a major healthcare burden [3,4]. The formation of a thrombus upon complications – mostly rupture or superficial erosion – of an atherosclerotic plaque results in a spectrum of clinical presentations, including unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI), which are collectively referred to as acute coronary syndromes (ACS). Patients who have experienced an ACS are at increased risk of recurrent atherothrombotic events, with mortality rates for patients presenting with STEMI and NSTEMI reported to be 4.8% and 6.2% at 6 months post-discharge follow-up and 6.5% and 9.5% at 2-years follow-up in the multinational GRACE registry [5,6]. Moreover, nearly one-fifth of patients are rehospitalized for heart disease within 6 months and approximately one-quarter for any reason within 2 years of discharge; and approximately 15% of patients undergo cardiac catheterization at both 6-months and 2-years follow-up, indicating a high incidence of recurrent events [5,6]. Because of this huge toll of mortality, morbidity and health care costs, there is continued interest in pharmacological strategies aimed at inhibiting arterial thrombus formation.

Because mechanisms underlying thrombus formation in ACS involve both platelets and fibrin, this latter produced through the action of thrombin, there is a precise rationale for tackling thrombin formation, in addition to platelets, as a preventive antithrombotic strategy. We here discuss limitations of the approach employed by the current standard of care of dual antiplatelet therapy (DAPT). We then analyse the results of recent clinical trials exploring different antithrombotic strategies for secondary prevention of recurrent events after an ACS or in the setting where inhibition of thrombin formation is demanded by the coexistence of AF, and discuss advantages and disadvantages of the various options available.

2. Pathophysiology of arterial thrombus formation

Thrombus formation in the coronary arteries is usually triggered by rupture or erosion of the fibrous cap on an atherosclerotic plaque. Platelet adhesion with von Willebrand factor (VWF) occurs through its membrane glycoprotein (GP) Ibα. This exposes thrombogenic plaque components to the bloodstream, which leads to rapid platelet adhesion and activation. In addition to platelets, however, the coagulation pathway also becomes immediately activated, leading to thrombin production, which on the one hand triggers fibrin formation, but also, on the other hand, promotes further platelet activation and recruitment. This results in the development of a thrombus rich in platelets in its initial component, but also in fibrin, providing a mesh stabilizing the structure of the thrombus, with trapped erythrocytes particularly abundant in the propagation component occurring when thrombosis becomes occlusive, as in most cases of STEMI [7]. In addition to thrombus formation from plaque disruption, thrombi may also form in coronary stents. A recent meta-analysis of 13 randomized clinical trials in 7352 patients found that bare metal and drug-eluting stents have currently similar risks of stent thrombosis (2.6% vs 2.7%; relative risk [RR] 0.97; 95% confidence interval [CI] 0.73–1.28) [8]. Current thinking before the completion of recent trials was that stent thrombosis is mostly platelet-dependent, and best counteracted with DAPT because of the poor efficacy of vitamin K antagonists (VKAs) in this setting [9]. This concept is also now undergoing re-evaluation.

Platelet activation is a key pathway in the development of arterial thrombosis (Fig. 1). Platelets adhere to thrombogenic plaque components and become activated. The binding of thrombin to protease-activated receptors (PARs; PAR-1 or PAR-4) on the platelet surface, causes cleavage and activation of these receptors [10–12]. This activation triggers platelets to secrete 5'-adenosine diphosphate (ADP) and to activate the arachidonic acid/thromboxane (TX) pathway. This and other platelet agonists are then able to recruit further platelets to the site of thrombus formation, with ADP-mediated activation initiated when ADP binds to $P2Y_1$ and $P2Y_{12}$ receptors on platelets, and TXA_2 binding and activating the platelet TP receptor [10,13].

The other pathway of hemostasis activated at the site of plaque rupture is thrombin formation, which is driven primarily by tissue factor through the extrinsic coagulation pathway (Fig. 1). After plaque rupture, tissue factor particles, mostly expressed by macrophage foam cells, enter the bloodstream and bind to plasma Factor VII, leading to its activation (Factor VIIa) [14]. The tissue factor-Factor VIIa complex activates Factor X to Factor Xa, which in turn forms complexes with activated Factor V to convert prothrombin into thrombin, causing a burst of thrombin that converts fibrinogen into fibrin [12–14].

The activation of the two hemostatic pathways in arterial thrombosis provides a positive feedback to both. In addition to promoting fibrin formation, the presence of thrombin is essential to the further recruitment and activation of circulating platelets at the site of thrombus formation [11]. Thus, thrombin plays a key role in the formation and stabilization of thrombi, besides also being involved in a whole array of other processes, including inflammation and protein C activation, as well as vasoconstriction [13]. Conversely, the surface of activated platelets provides the optimal site for the assembly of coagulation factors [15–17]. Therefore, inhibition of both pathways of hemostasis activation is logical and a priori promising to prevent arterial thrombosis. This has been practically explored in two different settings: stand-alone ACS, and ACS in patients with coexisting strong indications to anticoagulation, such as AF and venous thromboembolism.

3. Managing patients after an acute coronary syndrome

3.1. Current standard of care and limitations

After an ACS, current guidelines recommend DAPT with acetylsalicylic acid (ASA, aspirin) and a $P2Y_{12}$ receptor inhibitor [18–21]. Recommendations for DAPT are based on initial trials of ASA combined with ticlopidine (ISAR [22], MATTIS [23], STARS [9]). This drug combination was associated with a greater clinical benefit than ASA plus the oral anticoagulant (OAC) warfarin with regard to reduction in major cardiac events after percutaneous coronary intervention (PCI), substantially limiting stent thrombosis; and in the CURE trial with the $P2Y_{12}$ inhibitor clopidogrel [24], showing substantial reduction of events with this strategy compared with aspirin alone in NSTE-ACS, with or without revascularization interventions. Additional evidence for the benefit of dual antiplatelet therapy with aspirin and clopidogrel also accrued with the completion of the CLARITY-TIMI 28 [25] and COMMIT/CCS-2 [26] trials in the setting of ST-elevation acute myocardial infarction (STEMI) mostly treated with fibrinolysis. Based on evidence from the phase III clinical trials PLATO (which assessed DAPT with ticagrelor versus DAPT with clopidogrel; Table 1) [27] and TRITON-TIMI 38 (which assessed DAPT with prasugrel