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Review

Efficacy and safety of prasugrel in acute coronary syndrome patients

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ABSTRACT

Ischemic heart disease is the primary cause of death worldwide. The pathophysiological process of cardiovascular diseases is linked to atheromatous plaque formation, while plaque rupture releases thrombogenic elements, which lead to activation of platelets, blood clotting and formation of thrombi. Platelet inhibitors are used to prevent thrombosis. The present systematic review discusses the efficacy of prasugrel in terms of platelet inhibition potential and clinical prevention of cardiovascular outcomes. The balance between reduction of ischemic events as a measure of drug efficacy and the risk of bleeding is reviewed. Other adverse events observed in patients treated with this platelet inhibitor are discussed, including hematological complications, and cutaneous and hepatic idiosyncratic reactions. The complex relationship between prasugrel use and cancer promotion is also described.

Contents

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; ADR, adverse drug reaction; CABG, coronary artery bypass surgery; CI, confidence interval; CV, cardiovascular; CYP, cytochrome p450; HOPR, high on-treatment platelet reactivity; HR, hazard ratio; HSR, hypersensitivity syndrome reaction; LD, loading dose; LTA, light transmission aggregometry; MD, maintenance dose; MFI, mean fluorescence intensity; MI, myocardial infarction; MPA, maximum platelet aggregation; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; PGE_1, prostaglandin E1; PI %, P2Y12 inhibition percentage; PPI, proton pump inhibitor; PPP, platelet poor plasma; PRI, platelet reactivity index; PRP, platelet rich plasma; PRU, P2Y12 reaction unit; RANNTES, regulated on activation, normal T cell expressed and secreted; STEMI, ST segment elevation myocardial infarction; UA, unstable angina; VASP, vasodilatator associated stimulated phospho-protein.

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Introduction

Ischemic heart disease is the primary cause of death worldwide [1]. The pathophysiological process of cardiovascular (CV) diseases is linked to atheromatous plaque formation, fibrogenesis and inflammation. This process is reviewed in detail by Binazon et al. [2]. Myocardial infarction (MI), with or without ST segment elevation, is the main subtype of acute coronary syndrome (ACS). ACS describes the sudden interruption of blood flow to the heart, characterized by the partial or complete obstruction of coronary arteries. ACS can result from the erosion and rupture of an atheromatous coronary plaque [3]. Atheromatous plaque rupture releases thrombogenic elements, which lead to platelet activation, blood clotting, and thrombi formation. Thrombus formation can prevent the flow of oxygen to the heart and can thus be responsible for myocardial ischemia and necrosis [2].

The platelet aggregation pathway is mediated by collagen, thrombin, and the binding of adenosine diphosphate (ADP) to the purinergic P2Y12 receptor on platelets. The interaction between ADP and P2Y12 leads to adenylate cyclase inhibition. Platelets are responsible for vessel occlusion, and platelet aggregation can thus lead to ischemic heart conditions. P2Y12 receptor antagonists inhibit platelet activation by ADP [2, 4]. As such, antiplatelet therapy is administered in ACS patients. The two types of P2Y12 receptor antagonists currently in use are the members of the thienopyridine family ticlopidine, clopidogrel and prasugrel, and the newer cyclopentyl triazolopyrimidine ticagrelor. Thienopyridines are irreversible P2Y12 receptor antagonists while ticagrelor binds the P2Y12 receptor reversibly. Aspirin (75–162 mg/day) in combination with clopidogrel (75 mg/day) is the current gold standard treatment in patients who underwent a CV event. Ticlopidine has been largely replaced by other platelet inhibitors due to an unfavorable safety profile [5]. Recent clinical trials have shown superior antiplatelet effects in ACS patients treated with prasugrel or ticagrelor, compared to clopidogrel. Furthermore, prasugrel and ticagrelor significantly reduce the rates of clinical end points such as CV death, nonfatal MI or nonfatal stroke. These differences were particularly evident in patients with a planned invasive strategy such as percutaneous coronary intervention (PCI) [6, 7]. This systematic review aims to present the current knowledge regarding the efficacy and the known adverse events of prasugrel (Effient®, Eli Lilly and Company) in ACS patients. Treatment strategies in patients are decided by their respective physicians after a careful consideration of benefits and risks based on a detailed medical history and known underlying diseases in each individual.

Materials and methods

Efficacy was assessed in clinical trials comparing prasugrel and clopidogrel. The Effient product information and various Food and Drug Administration documents were consulted in order to identify adverse events and adverse drug reactions (ADR) associated with prasugrel use. A comprehensive PubMed and Google Scholar literature search was performed using the terms “prasugrel”, “P2Y12”, “assay”, “adverse event”, “adverse reactions”, as well as the name of each individual adverse event included in the Effient product information and the Food and Drug Administration documents, using articles indexed between 2005 and 2014 (Fig. 1). Each author read the publications separately and the results were discussed.

We have used the data from case reports and from five major clinical trials, namely JUMBO-TIMI 26 [8], TRITON-TIMI 38 [6], PRINCIPLE-TIMI 44 [9], TRIGGER-PCI [10] and TRILOGY ACS [11]. The characteristics and main findings of these clinical trials are summarized in Table 1. Our main focus was to compare prasugrel with clopidogrel based on the balance between superior efficacy and higher risk of bleeding, especially life-threatening or fatal bleeding.

Cardiovascular complications

CV complications often define the primary efficacy end points in acute or stable coronary disease patients treated with prasugrel. These include death from CV causes, nonfatal MI and/or nonfatal stroke in the TRITON-TIMI 38 [6], TRILOGY ACS [11] and TRIGGER-PCI trials [10], while MI, recurrent ischemia and thrombosis represented the secondary end points of the JUMBO-TIMI 26 trial [8]. In contrast to clinical end points, the PRINCIPLE-TIMI 44 trial used *in vitro* assays to measure inhibition of platelet aggregation (IPA) after administration of either loading dose (LD) or maintenance dose (MD) prasugrel in PCI patients [9]. These trials compared prasugrel with clopidogrel, with concomitant aspirin use. Prasugrel was associated with significantly lower rates of reaching the primary end point ($p < 0.001$), owing particularly to lower odds of nonfatal MI ($p < 0.001$) as well as lower odds of stent thrombosis ($p < 0.001$) compared to clopidogrel in the TRITON-TIMI

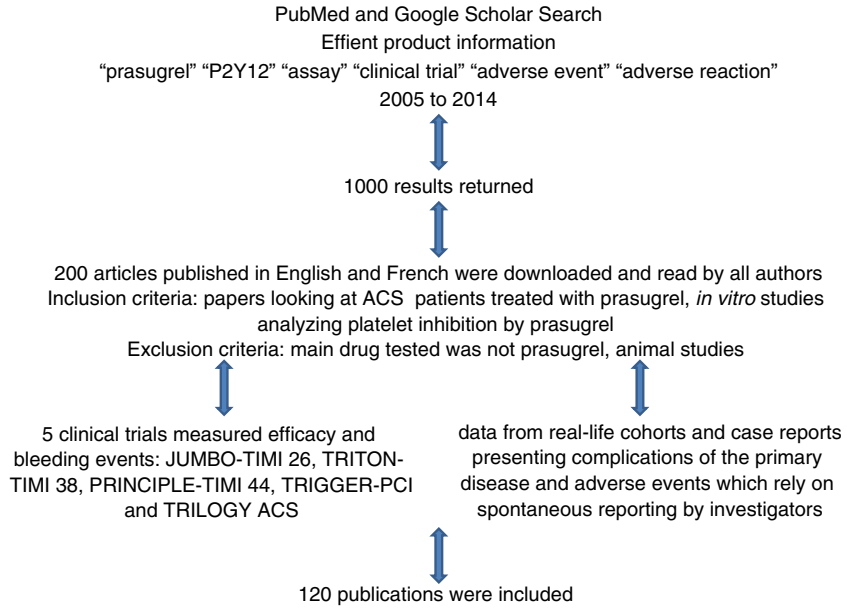

Fig. 1. Prasugrel therapy in acute coronary syndrome.