MAYO CLINIC

REVIEW

Antithrombotic Approaches in Acute Coronary Syndromes: Optimizing Benefit vs Bleeding Risks

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Abstract

It is estimated that in the United States, each year, approximately 620,000 persons will experience an acute coronary syndrome and approximately 70% of these will have non–ST-elevation acute coronary syndrome. Cardiovascular disease still accounts for 1 of every 3 deaths in the United States, and there is an urgent need to improve the prognosis of patients presenting with acute coronary syndrome. Cardiovascular mortality and ischemic complications are common after acute coronary syndrome, and the advent of newer antithrombotic therapies has reduced ischemic complications, but at the expense of greater bleeding. The new antithrombotic agents also raise the challenge of choosing between multiple potential therapeutic combinations to minimize recurrent ischemia without a concomitant increase in bleeding, a decision that often varies according to an individual patient's relative propensity for ischemia versus hemorrhage. In this review, we will synthesize the available information to arm health care providers with the contemporary knowledge on antithrombotic therapy and individualize treatment decisions.

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It is estimated that each year in the United States, approximately 620,000 Americans have a new acute coronary event (first hospitalized myocardial infarction [MI] or coronary heart disease death) and approximately 295,000 have a recurrent event.[1] In addition to further stressing health care expenditures, which are already over capacity,[2] recurrent ischemic events remain an Achilles' heel in the management of patients with acute coronary syndromes (ACSs). Cardiovascular disease still accounts for 1 of every 3 deaths, despite a 31% decline in case-fatality rates between 2000 and 2010.[1] There is, therefore, an urgent need to improve the prognosis of patients with ischemic heart disease. The advent of newer antithrombotic therapies for patients presenting with ACS has further reduced ischemic complications, but at the expense of greater bleeding. The new antithrombotic agents also raise the challenge of choosing between multiple potential therapeutic combinations to minimize recurrent ischemia without a concomitant increase in bleeding, a decision that often varies according to an individual patient's relative propensity for ischemia versus hemorrhage. In this review, we will synthesize the available information on antithrombotic therapy to arm health care providers with the knowledge to individualize such treatment decisions.

PATHOGENESIS OF ACS

Vulnerable atherosclerotic coronary plaques form the pathologic substrate for the development of ACS.[3] Postmortem studies of culprit coronary lesions have demonstrated that more than two-thirds of events arise from disruption of a protective fibrous cap overlying a large lipid core, thereby exposing the underlying thrombogenic contents of the necrotic core to the bloodstream. Plaque rupture leads to the activation of 2 pathways. First, exposure of subendothelial matrix and vasoactive factors leads to thromboxane A2 and adenosine diphosphate (ADP) generation and activation of P2Y12 and protease-activated receptors (PAR-1). Through autocrine and paracrine mechanisms, sustained activation of glycoprotein IIb/IIIa receptors leads to platelet aggregation. In the second pathway, exposure of tissue factor leads to the activation of factors VII and X. A small amount of thrombin generation results in perpetuation of the coagulation process on the

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ARTICLE HIGHLIGHTS

- This is a contemporary review on antithrombotic therapies in patients with acute coronary syndrome.
- We provide the readers a detailed and exhaustive overview of the latest trials in this field that cover the breadth of coronary interventions, medical management, oral anticoagulation, and newer agents that are available to treat such patients.
- The review highlights flow diagrams that elucidate the duration of antithrombotic treatment. It also informs readers on which antithrombotic therapy to choose. It also gives a detailed plan on the duration of triple therapy with oral anticoagulation.

surface of platelets where a large amount of thrombus is formed.[4] Antithrombotic drugs targeting various stages of these 2 pathways have been developed to lower the ischemic risks from the prothrombotic milieu in patients presenting with ACS (Figure 1).

INTERRELATIONSHIP OF ISCHEMIA AND BLEEDING

The rate of ischemic and bleeding complications after ACS has paralleled the type and intensity of antithrombotic and anticoagulation therapy used over the past 2 decades.[6] In the 1990s, use of glycoprotein IIb/IIIa inhibitors concomitant with heparin reduced ischemia but increased major bleeding.[7,8] With less intense anticoagulation and use of dual antiplatelet therapy (DAPT) in the late 1990s (rather than glycoprotein IIb/IIIa inhibitors), bleeding complications were observed less frequently. The recent introduction of more potent antiplatelet agents has once again led to an increase in bleeding rates. Bleeding is associated with increased mortality and may directly or indirectly increase rates of MI and stent thrombosis, and bleeding avoidance strategies are associated with improved survival.[9] The increase in the ischemic risk with bleeding is not limited to the index hospitalization; a long-term hazard is noted as well.[10,11] The underlying mechanisms whereby bleeding is associated with an increase in mortality are multifactorial and include creation of a prothrombotic state, discontinuation of antiplatelet and anticoagulant therapies with resultant increase in the risk of stent thrombosis,[12] a greater prevalence of comorbidities in patients who bleed, the direct deleterious effects of anemia, and adverse effects of blood transfusions (Figure 2).[13]

ANTIPLATELET AGENTS

Mechanism of Action

Low doses of aspirin (typically 75-81 mg daily) are sufficient to irreversibly acetylate serine 530 of cyclooxygenase-1 and inhibit generation of thromboxane A2, resulting in an antiplatelet effect. The thienopyridines prasugrel and clopidogrel are prodrugs. Their active metabolites irreversibly bind to the platelet P2Y12 receptor for the platelet's life span. After intestinal absorption, clopidogrel requires 2 cytochrome P-450 (CYP)-dependent oxidation steps to generate its active compound. Conversely, prasugrel is rapidly hydrolyzed by esterases and requires only 1 additional CYP-dependent oxidation. Both clopidogrel and prasugrel may be affected by genetic polymorphisms (much more so for clopidogrel than for prasugrel) and are partially responsible for individual variability and hyporesponsiveness (Figure 3). Epigenetic factors including diabetes, smoking status, age, sex, and coadministered drugs that are metabolized by the same CYP isoenzymes as thienopyridines and ticagrelor strongly influence platelet reactivity phenotype and may influence clinical outcomes during antiplatelet therapy.

Ticagrelor is rapidly absorbed in the intestine and does not require further biotransformation for activation. It directly and reversibly binds to the platelet P2Y12 receptor. The half-life of ticagrelor is 7 to 8 hours. The recently approved agent cangrelor is an intravenous, fast-acting, reversible, and direct-acting P2Y12 inhibitor. The plasma half-life of cangrelor is approximately 3 to 5 minutes, and platelet function is restored within 1 hour of cessation of the infusion.

The glycoprotein IIb/IIIa receptor is critical to the process of platelet thrombus formation, and intravenous glycoprotein IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban) target the final pathway of platelet aggregation by competing with fibrinogen and von Willebrand factor for binding to glycoprotein IIb/IIIa receptors. Thrombin converts fibrinogen to fibrin, generating a fibrin-rich clot, and further activates platelets by binding to PAR-1 and

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