REVIEW

THE AMERICAN JOURNAL of MEDICINE®

Combining Antiplatelet and Antithrombotic Therapy (Triple Therapy): What Are the Risks and Benefits?

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ABSTRACT

Most patients with mechanical heart valves and many patients with atrial fibrillation will require long-term anticoagulation therapy. For patients with mechanical prosthetic valves, only warfarin is indicated. However, for patients with nonvalvular atrial fibrillation who are at increased risk for embolic stroke, one of the newer antithrombotic medications, such as rivaroxaban, dabigatran, and apixaban, also can be used. Patients with indications for antithrombotic therapy often will have coexisting vascular disease, such as coronary artery disease, requiring concomitant antiplatelet therapy with aspirin alone or more commonly with a dual antiplatelet regimen, aspirin and clopidogrel, or prasugrel or ticagrelor. The risks and benefits of this approach are still not well defined, and current guidelines have included recommendations based primarily on expert opinion.

 • *The American Journal of Medicine (2014) 127, 579-585*

KEYWORDS: Acute coronary syndrome; Anticoagulation; Antithrombotic therapy; Aspirin; Atrial fibrillation; Clopidogrel; Coronary intervention; Coronary stent; Drug-eluting stent; Platelet inhibitor; Stent; Triple therapy; Warfarin

The use of long-term oral anticoagulation is indicated in a number of different clinical situations, including atrial fibrillation with increased risk for arterial embolism and in patients with mechanical heart valves.[1] Atrial fibrillation affects more than 1% of the US population and substantially increases the risk for stroke. It is known that oral anticoagulation therapy reduces stroke incidence by two thirds compared with placebo treatment; compared with aspirin, oral anticoagulation therapy reduces the risk of stroke by 45%. The number of patients who need to be treated for 1 year with oral anticoagulation therapy to prevent 1 stroke is approximately 100. At the same time, oral anticoagulation increases the risk of major bleeding by approximately 70% compared with aspirin.[2]

Atrial fibrillation with concomitant coronary artery disease requiring percutaneous coronary intervention is present in 20% to 30% of patients with atrial fibrillation,[1] thus requiring a dual antiplatelet regimen with aspirin and clopidogrel or other adenosine diphosphate inhibitor to prevent stent thrombosis. In addition, antithrombotic therapy will be indicated in a substantial number of these individuals. The recommended length of treatment with dual antiplatelet therapy is variable, ranging from 4 weeks after bare-metal stent implantation to at least 6 to 12 months with drug-eluting stents.[3] In patients with acute coronary syndromes, clopidogrel is indicated for up to 12 months after coronary intervention. Approximately 10% of patients who undergo percutaneous coronary intervention also will have a clear indication for long-term anticoagulation therapy, for example, atrial fibrillation with increased stroke risk.[4]

The use of warfarin plus both aspirin and clopidogrel has been referred to as "triple therapy," and it represents a medical decision-making challenge, because it decreases the risk of thrombotic events together with an increased risk for bleeding complications.[3] This is especially challenging among elderly patients, in whom the risks of stroke and bleeding are higher and physicians tend to "undermedicate" because of the fear of complications, as observed in large patient databases in which less than 40% of patients aged $\geq$80 years with both coronary artery disease and atrial fibrillation with a $CHADS_2$ score $\geq$2 are prescribed warfarin for thromboembolic prophylaxis.[5]

Funding: None.

Conflict of Interest: None.

Authorship: All authors had access to the data and played a role in writing this manuscript.

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0002-9343/$ -see front matter
http://dx.doi.org/10.1016/j.amjmed.2014.02.030

Antiplatelet therapy is used for secondary prevention of ischemic events in patients with established coronary artery disease.[6] The Antithrombotic Trialist Collaboration Group meta-analysis showed that antiplatelet therapy reduces the occurrence of nonfatal myocardial infarction, stroke, or vascular events.[7] Rupture or erosion of an atherosclerotic plaque that results in partial or complete occlusion of a coronary artery is the most common mechanism responsible for acute coronary syndrome. Plaque rupture exposes the subendothelial matrix, rich in tissue factor, to the circulating blood with resultant activation and aggregation of platelets and subsequent thrombus formation. Two types of thrombi can form after plaque rupture or erosion: a platelet-rich clot, seen in patients with unstable angina/non-ST-elevation myocardial infarction, and a fibrin-rich clot, seen in patients with ST-elevation myocardial infarction.[8-10] In patients with ST-elevation myocardial infarction, management focuses on restoration of blood flow in the infarcted artery.[11] In contrast, in unstable angina/non-ST-elevation myocardial infarction, the goal of antiplatelet therapy is to prevent further thrombosis and to allow endogenous fibrinolysis to dissolve the existing thrombus and thereby reduce the degree of coronary obstruction.[12,13]

Dual antiplatelet therapy with aspirin and clopidogrel after coronary intervention is superior to therapy with the combination of aspirin and oral anticoagulant.[14] Current guidelines (see next section) recommend that all patients with unstable angina/non-ST-elevation myocardial infarction should receive aspirin indefinitely (level of evidence A) and dual aspirin/clopidogrel antiplatelet therapy up to 12 months (level of evidence B) even in non-stented patients.[15]

CLINICAL SIGNIFICANCE

- The combination of chronic oral anticoagulation and antiplatelet therapy is a common therapeutic regimen encountered in the daily practice of physicians.
- It is uncertain which regimen provides the most benefit with the least rate of complications.
- We seek to describe the most appropriate therapeutic schema with a review of the most recent data available.

WHAT DO CURRENT GUIDELINES RECOMMEND?

The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines on atrial fibrillation management were recently published, and they acknowledge that no adequate studies specifically address the issue of dual antiplatelet therapy in patients who also require chronic anticoagulation because of atrial fibrillation, and recommendations are based primarily on consensus. These guidelines suggest that in patients with long-standing atrial fibrillation and moderate to high risk of thromboembolism on the basis of a Cardiac failure or dysfunction, Hypertension, Age $\geq$75 [Doubled], Diabetes, Stroke [Doubled]-Vascular disease, Age 65-74, and Sex category [female] (CHA_2DS_2-VASc) score $>$2, the maintenance regimen should be a combination of aspirin, clopidogrel, and warfarin; efforts should be directed to minimize the duration of triple therapy; and the choice of a stent should include consideration of the potential requirement for long-term anticoagulant therapy.[16] Use of dual antiplatelet therapy alone may be considered for patients with acute coronary syndrome who have atrial fibrillation and a low $CHADS_2$ score. Other authorities have suggested an antithrombotic management scheme based on the acute coronary syndrome presentation, perceived bleeding risk, and type of stent used.[3]

HOW SAFE IS IT TO USE TRIPLE THERAPY?

The risk of bleeding increases in patients receiving chronic anticoagulant therapy when an antiplatelet agent is added, for example, in patients with coronary artery disease after a coronary intervention. These are the patients in whom a medical dilemma exists, as one tries to balance the risk of thrombotic events versus the risk of bleeding complications. Unfortunately, the combination of oral anticoagulants and antiplatelet therapy is associated with a high annual risk (4%-16%) of fatal and nonfatal bleeding episodes.[1]

A retrospective trial involving 426 patients concluded that in patients with atrial fibrillation treated with percutaneous coronary intervention with or without stents who have a low risk of bleeding complications, triple-therapy regimen should be the antithrombotic drug treatment approach.[3] Orford et al[17] showed an overall bleeding rate of 9.2% with the use of triple therapy in a small group of patients. Khurram et al[18] found that in patients requiring anticoagulation therapy with warfarin, the addition of dual antiplatelet therapy was associated with a 6.6% major bleeding risk. Rogacka et al[19] found a 4.7% incidence of major bleeding complications during the triple therapy. Bleeding commonly occurred within the first month of triple therapy in the majority of patients.[19]

IS THERE BENEFIT IN USING DOUBLE THERAPY WITH REGARD TO BLEEDING RISK?

As already noted, patients receiving triple therapy are at increased risk for minor and major bleeding complications. Until recently, there has not been a controlled trial addressing this issue, with most of the recommendations and guidelines being based on retrospective studies and expert recommendations. Last year, the results of the What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing (WOEST) study were published. This was a multicenter randomized controlled trial that included patients receiving chronic anticoagulation therapy undergoing coronary artery intervention. Patients were randomized into 2 groups: warfarin plus clopidogrel and aspirin versus warfarin plus clopidogrel alone.