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Review Article

Combination warfarin-ASA therapy: Which patients should receive it, which patients should not, and why?

James D. Douketis *

Department of Medicine, McMaster University and St Joseph's Healthcare, Hamilton, ON, Canada

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ABSTRACT

Combination warfarin-ASA therapy is currently used in approximately 800,000 patients in North America as long-term treatment for the primary and secondary prevention of atherothrombotic and thromboembolic diseases. Despite a potentially complementary action of anticoagulant and antiplatelet drugs, the use of combination warfarin-ASA therapy is not based on compelling evidence of a net therapeutic benefit, with the exception of patients with a mechanical heart valve. On the other hand, there is more compelling and consistent evidence that combination warfarin-ASA therapy confers a 1.5- to 2.0-fold increased risk for serious bleeding compared with use of warfarin alone. In everyday practice, clinicians should combine the best available evidence with clinical judgment, considering that in most clinical scenarios, clinical practice guideline may not provide clear recommendations for patients who should, and should not, receive combination warfarin-ASA therapy. The objectives of this review are to describe which patients are receiving combined warfarin-aspirin therapy, to summarize the evidence for the therapeutic benefit and harm of combined warfarin-ASA therapy, and to suggest practical guidelines as to which patients should, and should not, receive such treatment.

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Introduction

Warfarin and acetylsalicylic acid (ASA) are widely used for the primary and secondary prevention of thromboembolic and atherothrombotic diseases in patients with chronic atrial fibrillation, coronary artery disease, valvular heart disease and venous thromboembolism. Combining these two agents is appealing because of potentially complementary antiplatelet and anticoagulant actions, which may be especially relevant for patients who have concomitant cardiovascular diseases, such as atrial fibrillation and coronary artery disease (CAD). Despite the potential therapeutic advantages of combination warfarin-ASA therapy, when multiple drugs that affect hemostasis are co-administered, this typically increases patients' risk for serious bleeding [1]. Many clinicians accept this risk of bleeding because preventing cardiovascular events is typically considered to be of paramount importance whereas bleeding is often considered a self-

* St Joseph's Healthcare Hamilton, Room F-544, 50 Charlton Ave. East, Hamilton, ON, Canada L8N 4A6. Tel.: +1 905 521 6178; fax: +1 905 521 6068.
E-mail address: jdouket@mcmaster.ca.

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limiting and treatable condition [2]. However, there is emerging evidence that combination warfarin-ASA therapy may not confer additional therapeutic benefits, except in selected patient groups, whereas the associated increase in bleeding complications is more compelling and may outweigh any potential advantages.

Addressing the putative benefits and risks of combined warfarin-ASA therapy is important because of the large number of patients who are receiving combined therapy. Among patients with chronic nonvalvular atrial fibrillation, recent large trials have found that approximately 35-40% of such patients were also receiving ASA [3,4]. This means that approximately 800,000 patients with chronic atrial fibrillation in North America alone are receiving warfarin-ASA therapy. What is, perhaps, more important is that this practice is occurring in the absence of evidence of benefit and stronger evidence for harm. Further clouding appropriate clinical management is the lack of clear guidelines as to the appropriateness of combination warfarin-ASA therapy from the American College of Chest Physicians (ACCP) Antithrombotic Consensus Guidelines and the American Heart Association/American College of Cardiology/European College of Cardiology (AHA/ACC/ESC) guidelines [5,6].

Against this background, the objectives of this review are: 1) to describe which patients are currently receiving combination warfarin-ASA therapy; 2) to summarize the evidence for the therapeutic benefits and harms of combination warfarin-ASA when compared to warfarin therapy alone; and 3) to provide practical guidelines as to which patients should receive and should not receive warfarin-ASA therapy.

Characteristics of Patients who are Receiving Combination Warfarin-ASA Therapy

The reason for the widespread use of warfarin-ASA therapy appears to be driven by the observation that warfarin-treated patients may have multiple diseases in which there is a perceived indication for both an anticoagulant and an antiplatelet drug. Thus, in a community-based study involving patients who were receiving long-term warfarin, 48% of whom had chronic atrial fibrillation, patients who were receiving warfarin-ASA therapy typically had other co-morbidities: 56% had hypertension; 35% had CAD; 27% had chronic heart failure; and 23% had diabetes [7]. In this study, CAD was the strongest predictor for combination warfarin-ASA therapy (odds ratio [OR], 7.56; 95% confidence interval [CI]: 6.50-8.82), thereby suggesting that clinicians may be adding ASA to warfarin therapy with the intent of providing a CAD-specific antithrombotic effect.

From a broader perspective, both atrial fibrillation and CAD are common diseases, with an estimated prevalence of 2.5 million people [8] and 16 million people [9], respectively, in North America. With an aging population and increasing prevalence of atrial fibrillation and CAD, the issue of whether there is a net therapeutic benefit of combination warfarin-ASA therapy over warfarin therapy alone will become increasingly relevant. Although new oral anticoagulants such as dabigatran and rivaroxaban will supplant warfarin in many patients who require long-term anticoagulation [3,4], the uncertainty as to added therapeutic benefit and probable increased bleeding risk with combination warfarin-ASA therapy will remain.

Evidence for Therapeutic Benefit with Combination Warfarin-ASA vs. Warfarin Alone

A recent meta-analysis of randomized controlled trials assessed treatment with combination warfarin-ASA compared with warfarin alone, in which patients received the same intensity of warfarin (i.e., same target international normalized ratio [INR]) in both treatment arms [10]. Ten studies were identified by a systematic review of the literature: five studies of patients with mechanical heart valves; two studies of patients with chronic atrial fibrillation; two studies of patients with CAD; and one study of patients at high risk for cardiovascular disease. The risk for cardiovascular/thromboembolic events was significantly reduced by combination warfarin-ASA therapy (OR = 0.66; 95% CI: 0.52-0.84). However, this therapeutic benefit was driven by five studies involving patients with mechanical heart valves (OR = 0.27; 95% CI: 0.15-0.49). However, there was no statistically significant risk reduction for these outcomes in the two studies of patients with atrial fibrillation (OR = 0.99; 95% CI: 0.47-2.07) and in the OR involving patients with either CAD or at high risk for cardiovascular disease (OR = 0.69; 95% CI: 0.35-1.36).

Two other randomized trials deserve mention but were excluded from this meta-analysis because different intensities of warfarin were administered in the two treatment arms. In the ASPECT-2 [11] and WARIS II [12] studies, patients with CAD were randomly allocated to receive warfarin (target INR range: 2.0-2.5) plus ASA or warfarin alone (target INR range: 3.0-4.0 in ASPECT-2 and 2.8-4.2 in WARIS-II) or ASA alone. In the ASPECT-2 trial, there was no significant differences in composite endpoint of myocardial infarction, stroke or death in patients who received combination warfarin-ASA or only warfarin (OR = 0.92; 95% CI: 0.36-1.85). In WARIS II, there was also no significant difference in the composite outcome of non-fatal re-infarction, stroke or death between warfarin-ASA-treated and warfarin-treated patients but there was a non-significant trend for a lower incidence of non-fatal re-infarction between these two groups (5.7% vs. 7.4%, respectively).

Other relevant data to assess the efficacy of combination warfarin-ASA compared with warfarin alone comes from a sub-group analysis of warfarin-treated patients in the SPORTIF trial, which compared warfarin (target INR range: 2.0-3.0) to ximelagatran for stroke prevention in patients with chronic atrial fibrillation [13]. Thus, among warfarin-treated patients there was no significant difference in the risk for coronary events (0.6% vs. 1.0% per year) or stroke (1.7% vs. 1.5%) in users of warfarin-ASA and warfarin alone.

A retrospective cohort study of over 4,500 warfarin-treated patients managed by an anticoagulation clinic is noteworthy [14]. When combination warfarin-ASA users and warfarin-only users were compared, there was no significant difference in rates of coronary events (OR = 0.99; 95% CI: 0.37-2.62) or thromboembolic events (OR = 1.48; 95% CI: 0.43-5.08) between these two patient groups despite statistical adjustment for potential confounders.

Finally, in a linked administrative database done in Denmark involving over 70,000 patients with atrial fibrillation who were receiving warfarin or combination warfarin-ASA therapy did not confer a therapeutic advantage for stroke prevention and, in fact, was associated with an increased risk for ischemic stroke compared to warfarin-only users (hazard ratio [HR] = 1.27; 95% CI: 1.14-1.40) [15].

Additional data as to the efficacy of warfarin alone to prevent acute myocardial ischemia comes from the ACTIVE-W trial which compared warfarin therapy to combination ASA-clopidogrel in patients with chronic atrial fibrillation [16]. In this study, the incidence of acute myocardial infarction was higher in patients receiving ASA-clopidogrel than warfarin-treated patients (0.86% vs. 0.55% per year; risk ratio, 1.58; 95% CI: 0.94-2.67). In the RE-LY trial, which compared warfarin to dabigatran for stroke prevention in patients with chronic atrial fibrillation, the annual risk for symptomatic acute myocardial ischemia was, as in the ACTIVE-W trial, similarly low among warfarin-treated patients (0.53% per year) [3].

Evidence for Therapeutic Harm with Combination Warfarin-ASA vs. Warfarin Alone

An assessment of treatment harm with combination warfarin-ASA and warfarin therapy should consider both relative risk increase, expressed as an odds ratio (OR) or hazard ratio (HR) and, perhaps more importantly, absolute risk increase. Thus, in patients who are receiving long-term warfarin, the risk for serious (or major) bleeding is,