



Review Article

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

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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 thrombo-

embolism. 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-

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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,

typically, 1–2% per year [3,4], which may be up to 5% per year in the elderly or those with multiple comorbidities [17,18]. For example, if the OR for harm is 1.5 (50% higher), this means if a patient's baseline risk for bleeding is estimated at 3% per year with warfarin therapy, it will be approximately 4.5% per year with combined warfarin-ASA therapy. Furthermore, there is increasing recognition as to the clinical impact of major bleeding, which is fatal in 9–10% of cases [19,20] and is associated with an increased risk for adverse cardiovascular outcomes [21,22].

The aforementioned meta-analysis also assessed the risk for major bleeding associated with combination warfarin-ASA compared with warfarin alone [10]. There was an increased risk for major bleeding with warfarin-ASA over warfarin, with an annual risk of 2.3% vs. 1.3%, a difference which is clinically significant, although it did not quite attain statistical significance (OR = 1.43; 95% CI: 1.00–2.02). Similar findings were obtained from a large community-based study [14], which found a statistically significant 2-fold higher risk for major bleeding among patients on combination warfarin-ASA compared with warfarin alone (OR = 2.06; 95% CI: 1.01–4.36).

The analysis of bleeding risk among warfarin-treated patients in the SPORTIF trial found a significantly increased risk for major bleeding compared to the risk in patients who received warfarin alone (annual risk: 3.9% vs. 2.3%, $P = 0.01$) [23]. As in the previous study, ASA therapy in the SPORTIF trial conferred a 2-fold increased risk for major bleeding among warfarin-treated patients (OR, 1.96; 1.49–2.58).

In the ASPECT-2 trial, there was a non-statistically significant increased risk for major bleeding with combination warfarin-ASA compared to warfarin alone (2% vs. 1% per patient year, respectively), although the intensity of anticoagulation was less in the ASA-treated group thereby limiting an assessment of the putative additive effect of ASA on bleeding risk. Combination warfarin-ASA therapy conferred an approximately 2-fold increase in minor-bleeding compared to warfarin alone (15% vs. 8% per patient year, $P < 0.05$). In the WARIS-II trial, there was no significant difference in bleeding between warfarin-ASA-treated and warfarin-treated patients (0.57% vs. 0.68% per year, respectively) although the overall incidence of bleeding was low at <1% per year and the possibility of more bleeding among warfarin-ASA treated patients could not be excluded.

Finally, a linked database of patients with atrial fibrillation who were receiving warfarin found that among those who were receiving combination warfarin-ASA, had a 1.8-fold increased risk for major bleeding (HR = 1.83; 95% CI: 1.72–1.96) [15]. Furthermore, this study found that combination warfarin and clopidogrel (a thienopyridine derivative with antiplatelet effects mediated by platelet ADP-receptor inhibition) conferred a substantially higher risk for bleeding compared with warfarin alone (HR = 3.08; 95% CI: 2.32–3.91); the risk of bleeding was highest in patients receiving 'triple therapy', consisting of combination warfarin-ASA-clopidogrel (HR = 4.05; 95% CI: 3.08–5.33).

Additional data as to the risks of combined ASA-dabigatran and ASA-rivaroxaban are forthcoming since up to 40% of patients were receiving

ASA in combination with a new oral anticoagulant and it is likely that the addition of ASA will confer an increase in bleeding risk [3,4].

Summary of Evidence Regarding Benefits and Risks of Warfarin-ASA Therapy

Overall, there does not appear to be compelling evidence that warfarin-ASA therapy is more effective than warfarin alone for the prevention of cardiovascular and thromboembolic outcomes but there is consistent and, perhaps, more compelling evidence that warfarin-ASA therapy increases serious bleeding, irrespective of the patient population studied (Table 1). The exception to this conclusion is patients with mechanical heart valves who, despite an increased risk for serious bleeding with combination therapy, derive a net therapeutic benefit with warfarin-ASA because the reduction in thromboembolic events outweighs the increase in the risk for serious bleeding [24,25]. In other patients such as those with chronic atrial fibrillation, which is the dominant clinical indication for long-term anticoagulant therapy, and those with chronic CAD, evidence is lacking that adding ASA to warfarin is more effective than warfarin alone to prevent stroke or other cardiovascular events.

In terms of the net therapeutic harm relating to serious bleeding associated with combined warfarin-ASA therapy, this can be estimated based on the following considerations: first, combined therapy confers a 1–2% absolute risk increase in major (serious) bleeding per year compared with warfarin alone; and, second, the case-fatality associated with each major bleed is approximately 9–10% [19,20]. Thus, for every 1,000 patients (who do not have a mechanical heart valve) treated with warfarin-ASA therapy per year, it is estimated that there would be an *additional* 10–20 major bleeds and, based on the case-fatality rate of 9–10%, an additional 1–2 deaths per year. Although these numbers seem small, they should be considered in the context of the approximately 800,000 patients in North America alone who are receiving combined warfarin-ASA therapy in the absence of a compelling evidence for a net therapeutic benefit. Thus, on a population level, combined warfarin-ASA therapy may lead to an *additional* 800 to 1,200 deaths per year in North America alone.

Recommendations from Current Clinical Practice Guidelines

As shown in Table 2, consensus groups do not provide clear guidelines aimed at the practicing clinician for the use of combination warfarin-ASA therapy outside of the context of patients with mechanical heart valves. Thus, the influential ACCP Consensus Conference on Antithrombotic and Thrombolytic Therapy (2008 Edition) states that "for high risk patients with acute myocardial infarction, including those with atrial fibrillation, we suggest the combined use of oral vitamin K antagonists (INR 2–3) plus low-dose aspirin (100 mg/d or less) for at least 3 months after the myocardial infarction (grade 2A)" [5]. Although this recommendation may apply to patients who have had an acute coronary syndrome, they do not advise

Table 1
Summary of Therapeutic Benefits and Bleeding Harm with Combination Warfarin-ASA vs. Warfarin Alone.

Clinical Outcomes: Warfarin-ASA vs. Warfarin alone	Study Type Comparing Warfarin-ASA vs. Warfarin alone			
	Meta-analysis [10]	Linked-database Study [22]	Sub-study of RCT [21]	Community-based Study [14]
Cardiovascular/Thromboembolic Outcomes				
- absolute risk difference (annual risk)	8.8% vs. 6.3%	n/a	1.5% vs. 1.7%	0.3% vs. 0.4%
- odds ratio (95% confidence interval)	0.66 (0.52–0.84) 0.99 (0.47–2.07)† 0.69 (0.35–1.36)‡	1.27 (1.14–1.40)¶	n/a	1.48 (0.43–5.08)
Major Bleeding				
- absolute risk difference (annual risk)	3.8% vs. 2.8%	6.9% vs. 3.9%	3.9% vs. 2.3%	2.0% vs. 0.9%
- NNH	100	33	63	91
- odds ratio (95% confidence interval)	1.43 (1.00–2.02)	1.83 (1.72–1.96)	1.96 (1.49–2.58)	2.06 (1.01–4.36)

Legend: † studies of patients with atrial fibrillation; ‡ studies of patients with coronary artery disease; ¶ ischemic stroke risk; n/a, not available; RCT, randomized controlled trial; NNH, number-needed-to-harm (number of patients treated per year with warfarin-ASA to cause 1 additional major bleed compared to warfarin alone).

Table 2
Clinical Practice Guideline Statements for Combination Warfarin-ASA Therapy.

Consensus Group (reference)	Consensus Group Statement or Commentary	Strength of Evidence
<i>Patients with a Mechanical Heart Valve</i>		
ACCP 2008 [23]	In patients with mechanical heart valves who have additional risk factors for thromboembolism, such as atrial fibrillation, hypercoagulable state, low ejection fraction, history of atherosclerotic vascular disease, we recommend the addition of low-dose ASA (50–100 mg once-daily) to long-term VKA therapy.	Grade 1B Recommendation.
ACC-AHA 2006 [24]	The addition of ASA 75–100 mg once daily to therapeutic warfarin is recommended for all patients with mechanical heart valves.	Class I recommendation; Level B Evidence
<i>Other Patient Groups</i>		
ACCP 2008 [5]	For high risk patients with acute myocardial infarction, including those with atrial fibrillation, large anterior myocardial infarction, significant heart failure, intracardiac thrombus, history of thromboembolic event, we suggest the combined use of oral VKAs (INR range: 2.0–3.0) plus low-dose ASA (100 mg once-daily or less) for at least 3 months after the myocardial infarction.	Grade 2A Recommendation
ACC-AHA-ESC 2006 [6]	For most patients with AF who have stable CAD, warfarin anticoagulation alone (INR range: 2.0–3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events.	Not applicable

Legend: AF, atrial fibrillation; ASA, acetylsalicylic acid; VKA, vitamin K antagonists; CAD, coronary artery disease.

clinicians as to whether combination warfarin-ASA therapy should be continued beyond the initial 3-month period after the acute coronary event. Furthermore, there are no guidelines about managing patients with chronic stable CAD who are receiving ASA and subsequently are diagnosed with chronic atrial fibrillation.

The ACC/AHA/ESC guidelines (2006 Edition), under the section related to management of atrial fibrillation, are somewhat more explicit, indicating that “for most patients with atrial fibrillation who have stable coronary artery disease, warfarin anticoagulation alone (target INR 2.0 to 3.0) should provide satisfactory antithrombotic prophylaxis against both cerebral and myocardial ischemic events” [6]. However, as with the ACCP guidelines, this consensus group recommendation does not directly inform clinicians about the potential therapeutic benefits and harms of combined warfarin-ASA therapy and in providing guidelines for patients with atrial fibrillation who develop an acute coronary syndrome and for ASA-treated patients with chronic CAD who develop atrial fibrillation.

Taken together, consensus guidelines are anchored on evidence-based recommendations and, therefore, it is not surprising that there are few definitive recommendations about the clinical scenarios described above. Nonetheless, the practicing clinicians who frequently assess patients in whom there is an indication for long-term warfarin and in whom co-administered ASA is being considered, there is a need to provide guidance to inform clinical practice. An attempt to address this somewhat unmet need using the available evidence on the therapeutic benefits and harms, coupled with clinical judgment, is provided in Table 3.

Managing Patients in Everyday Clinical Practice

For clinicians managing ‘real-world’ patients in whom there may be an indication for warfarin and, possibly, ASA, a suggested clinical management approaches are provided using illustrative case.

Table 3
Clinical Settings in which there is Strong, Weak or Insufficient Evidence for Therapeutic Benefit with Combination Warfarin-ASA Therapy.

Level of Evidence and Suggested Management	Clinical Setting
Strong evidence for therapeutic benefit: warfarin-ASA recommended	- mechanical mitral valve - mechanical aortic valve + risk factors for thromboembolism
Weak/insufficient evidence for therapeutic benefit: warfarin-ASA not recommended or should be considered with caution	- chronic AF alone - chronic stable CAD - chronic AF + chronic stable CAD
Insufficient evidence for therapeutic benefit but: reasonable to consider warfarin-ASA	- chronic AF (or prior VTE) + recent coronary artery stent - chronic AF (or prior VTE) + recent coronary artery bypass surgery - chronic AF (or prior VTE) + new stroke despite therapeutic INR

Legend: AF, atrial fibrillation; VKA, vitamin K antagonist; CAD, coronary artery disease; VTE, venous thromboembolism.

Clinical settings in which there is good evidence for combination warfarin-ASA therapy

Consider a 67-year old patient on long-term warfarin therapy because of valvular atrial fibrillation who undergoes mitral valve replacement with a bileaflet mechanical prosthesis. After surgery, adding ASA to warfarin is recommended because in this setting there is compelling evidence of a net therapeutic benefit with combination warfarin-ASA compared with warfarin alone. Furthermore, although the evidence for benefit is less compelling, combined warfarin-ASA therapy should be considered in patients with a mechanical aortic valves, especially those with older, caged-ball or tilting-disc, valves or in those patients with newer bileaflet valves who have additional risks for thromboembolism.

Clinical settings in which there is weak or insufficient evidence for combination warfarin-ASA therapy

Consider a 75-year old patient with nonvalvular atrial fibrillation who is not receiving warfarin and develops an acute coronary syndrome, which is treated with medical therapy alone based on the coronary disease that is not amenable to a percutaneous intervention or surgical revascularization. The patient is discharged home to receive ASA therapy, which aims to stabilize any ongoing plaque rupture and prevent coronary thrombosis, which is most likely to occur within the initial 4–12 weeks after an acute coronary syndrome. Warfarin is also commenced because of atrial fibrillation to minimize the risk for stroke. During the subsequent three months the patient has no further coronary events. It is reasonable, therefore, to use combined warfarin-ASA during the initial 3 months, but after this period ASA can be stopped given the evidence that warfarin alone is effective for chronic stable coronary artery disease. Now consider a 71-year old patient with stable CAD who is receiving long-term ASA therapy, is found to have atrial fibrillation on a routine examination and, over time, is classified as having chronic atrial fibrillation. Hypertension and heart failure are also present as comorbidities. In this case, there is a clear indication for long-term warfarin therapy alone, based on a CHADS₂ score of 2 [26]. In this patient, warfarin therapy alone should be sufficient.

Clinical settings in which, despite insufficient evidence, combination warfarin-ASA therapy may be reasonable

There are clinical settings where, despite a lack of evidence to support combined warfarin-ASA therapy, such treatment may be considered. The first is patients with chronic atrial fibrillation (or venous thromboembolism) who are receiving long-term warfarin and require placement of coronary stent. Ideally, in warfarin-treated patients who

require coronary stent placement, consideration should be given to placement of a bare-metal stent instead of a drug-eluting stent, as the later will necessitate a longer duration of 'triple therapy' consisting of combination warfarin-ASA-clopidogrel. Thus, in patients with a bare-metal stent, triple therapy would be required for 6 weeks in patients who had elective coronary stenting, and approximately 12 weeks in patients with an acute coronary syndrome who required urgent bare-metal stent placement. Thereafter, clopidogrel and ASA could be stopped assuming there are no additional coronary events [27]. On the other hand, in patients with atrial fibrillation who have a drug-eluting stent, antithrombotic management is more problematic as such patients may require 6–12 months (or longer) of triple therapy. Overall, the need to minimize the time period that patients are receiving triple antithrombotic therapy is important because of the greater than 4-fold increased risk for bleeding compared to ASA alone, as mentioned above [27]. Overall, the need to minimize the time period that patients are receiving 'triple therapy' is important because of the greater than 4-fold increased risk for bleeding compared to ASA alone [1], as previously mentioned.

In patients, who have an indication for long-term warfarin therapy and undergo coronary artery bypass graft surgery, ASA is beneficial to prevent graft thrombosis, whereas warfarin alone has not been studied. A third patient group may be patients with atrial fibrillation who develop a stroke syndrome despite therapeutic anticoagulation with warfarin, in whom the addition of ASA may mitigate the risk for recurrent stroke.

Summary

It is estimated that 800,000 patients in North America are receiving combined warfarin-ASA therapy, primarily for the presence of both chronic atrial fibrillation and CAD. Despite such widespread use of combined warfarin-ASA, there is little evidence, apart from patients with a mechanical heart valve, that combination therapy confers a therapeutic benefit compared with warfarin alone. On the other hand, there is consistent and more compelling evidence that combined warfarin-ASA therapy confers an approximately 1.5- to 2-fold increased risk for serious bleeding. Consequently, combination warfarin-ASA therapy should be used cautiously and, perhaps, should be limited to selected patients who have an acute coronary event, a recent percutaneous coronary intervention or coronary artery bypass in whom an antiplatelet drug may be of benefit to prevent acute coronary in-stent or bypass graft thrombosis. However, in patients with chronic stable CAD and chronic atrial fibrillation, in whom antiplatelet activity is less important, warfarin appears to be adequate therapy to prevent recurrent coronary and other thromboembolic events.

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