Review Article

Incidence, Mortality, and Risk Factors for Oral Anticoagulant–associated Intracranial Hemorrhage in Patients with Atrial Fibrillation

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Warfarin, a vitamin K epoxide reductase inhibitor, is the oral anticoagulant most commonly used to reduce the risk of stroke in patients with atrial fibrillation (AF). Warfarin has proved to be efficacious for this purpose in multiple clinical trials. However, warfarin use is laborious and associated with an increased risk of intracranial hemorrhage (ICH). Various factors increase the risk of warfarin-related ICH, including older age, intensity of anticoagulation, hypertension, and history of cerebrovascular disease. The emergence of newer classes of oral anticoagulants will offer therapeutic alternatives to reduce the risk of stroke in patients with AF. Recently, the United States Food and Drug Administration approved 3 new agents—dabigatran etexilate, a direct thrombin inhibitor, and rivaroxaban and apixaban, factor Xa inhibitors—to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF. We discuss the incidence, mortality, and risk factors predisposing to oral anticoagulant–associated ICH in patients with AF. **Key Words:** Anticoagulation—intracranial hemorrhage—atrial fibrillation—warfarin.

Introduction

Warfarin is a well-established oral anticoagulant used to reduce the risk of stroke in patients with atrial fibrillation (AF). However, warfarin use is complicated by the need for frequent monitoring, drug and dietary interactions, and a risk of major bleeding, including intracranial hemorrhage (ICH).[1] These challenges and complications have led to the development of alternative orally administered anticoagulants (OACs), including direct thrombin inhibitors and factor Xa (FXa) inhibitors, for the prevention of stroke in patients with AF. Dabigatran etexilate, a direct thrombin inhibitor, has been approved by the United States Food and Drug Administration (FDA) to reduce the risk of stroke and systemic embolism (SSE) in patients with nonvalvular atrial fibrillation (NVAF).[2] It has also been approved for the treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE) in patients who have been treated with a parenteral anticoagulant for 5-10 days, and to reduce the risk of recurrence of DVT and PE in patients who have been previously treated. Apixaban and rivaroxaban have been approved to reduce the risk of SSE in patients with NVAF. Apixaban has also been approved for the

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prophylaxis of DVT, which may lead to PE in patients who have undergone hip or knee replacement surgery.[3] Rivaroxaban has also been approved for the treatment of DVT and PE, for the reduction in the risk of recurrence of DVT and of PE, and for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.[4] Given the emergence of these new classes of OACs, it is timely to review the incidence, mortality, and risk factors for OAC-associated ICH in patients with AF. Risk factor data are derived from studies of patients receiving warfarin and may or may not apply to patients treated with new oral anticoagulants.

Efficacy of Vitamin K Antagonist in AF: Overview

AF is a common cardiac arrhythmia, particularly in the elderly. The prevalence of NVAF increases significantly with age and is observed in more than 9% of persons 80 years and older. The prevalence of AF is predicted to increase 2.5-fold over the next 50 years.[5] AF is associated with increased morbidity and mortality and is an independent risk factor for ischemic stroke. The Framingham Study showed an approximately 5-fold increased stroke risk in persons with AF and a 23.5% risk of stroke attributable to AF in persons aged 80-89 years.[6]

Warfarin, a vitamin K epoxide reductase inhibitor commonly termed a vitamin K antagonist (VKA), prevents the gamma carboxylation of the vitamin K-dependent coagulation prothrombin factors (factors II, VII, IX, and X).[7] Warfarin was first approved for clinical use as a therapeutic anticoagulant in 1954.[7] The VKA was the only class of OACs used in clinical practice until recently and has proved to be efficacious for stroke prevention.[8] The antiplatelet acetylsalicylic acid (ASA) is another oral agent commonly used for stroke risk reduction in patients with AF. It is much less effective than warfarin, and recent guidelines recommend ASA only for patients at low risk of stroke.[9]

A number of major clinical trials have established the efficacy of warfarin for stroke prevention in AF, compared with both placebo and ASA therapy (Table 1). In 1991, the Stroke Prevention in Atrial Fibrillation (SPAF) study of 1330 patients with AF demonstrated that ASA and warfarin were effective in reducing the risk of ischemic stroke in patients with AF compared with placebo.[10] However, the investigators were unable to detect a difference in the magnitude of effect between warfarin and ASA. Further evidence from a pooled analysis of 5 randomized trials of warfarin versus placebo showed a relative risk reduction of 68% favoring warfarin for stroke prevention (1889 and 1802 patient-years for warfarin and placebo, respectively).[11] The European Atrial Fibrillation Trial demonstrated the advantage of warfarin over both placebo and ASA in patients with a history of stroke or transient ischemic attack (TIA) who were deemed eligible for anticoagulation therapy, showing a 40% relative decrease in the yearly rate of stroke and related events in patients on warfarin (n = 225) compared with those on ASA (n = 230).[12] The Boston Area Anticoagulation Trial for Atrial Fibrillation; the Atrial Fibrillation, Aspirin, Anticoagulation study; and the SPAF III trial provided further evidence of the superiority of warfarin compared with ASA in risk reduction of ischemic stroke in patients with AF (Table 1).[13-15] The Atrial Fibrillation, Aspirin, Anticoagulation, Boston Area Anticoagulation Trial for Atrial Fibrillation, and Canadian Atrial Fibrillation Anticoagulation studies were terminated early because of greater than predicted reduction of events with warfarin.[16]

Incidence and Mortality of AF-associated ICH

Incidence

Although more effective for preventing stroke than ASA, warfarin is also associated with a higher risk of hemorrhage. A meta-analysis of 6 published clinical trials comparing warfarin with ASA in more than 4000 patients with AF reported that warfarin treatment in 1000 patients for 1 year would prevent 23 ischemic strokes but was associated with 9 additional major bleeds.[17] Although ICH made up only 21.9% of the major bleeding events, it accounted for more than 50% of fatal hemorrhages.[17] Nearly 70% of warfarin-related ICHs are intracerebral hemorrhages, whereas subdural hematomas account for most of the remaining intracranial bleeds.[18]

Over the past few decades, the absolute risk of intracerebral hemorrhage in patients on OAC has been estimated at approximately 1% per year,[18] but more recent studies report rates of warfarin-related intracerebral hemorrhage ranging from .3% to .6% per year.[19] A 5-year Swedish cohort study of 4434 patients receiving anticoagulation observed rates of intracerebral hemorrhage 10 times higher than the rate observed in the general population.[20]

Mortality

ICH remains one of the most feared complications of warfarin therapy because of a high mortality rate—ranging from 46% to 68%.[18] A multivariate analysis of intracerebral hemorrhage patients as part of the Genetic and Environmental Risk Factors of Hemorrhagic Stroke study showed that patients with OAC-associated intracerebral hemorrhage had higher mortality at day 1 compared with those who had intracerebral hemorrhage not associated with OAC (33.2% vs. 16.3%, $P < .001$).[21] In this study, warfarin-related intracerebral hemorrhage most commonly occurred in the cerebellum, and cerebellar intracerebral hemorrhage was associated with increased mortality compared with other intracerebral hemorrhage locations (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.2-4.0).[21]

Hematoma volume in intracerebral hemorrhage is directly related to mortality,[22] and warfarin therapy has been associated with both increased hematoma volumes and later detection in the hospital course. For example,