JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 68, NO. 11, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.07.714

EDITORIAL COMMENT

Atrial Fibrillation and Fall Risk

What Are the Treatment Implications?*

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A recent report from the National Safety Council cited falls as a major cause of accidental deaths in the United States, representing an increase of 63% over the previous decade (1). Falls from a standing position are a frequent cause of injury, particularly among older adults. Data from a high-volume trauma center found that 8% of trauma admissions were due to falls from standing (2). Warfarin use was found in this study to be an independent risk factor for mortality. In this issue of the *Journal*, Steffel et al. (3) confirm the vulnerability of individuals at high risk of falls who were enrolled in the ENGAGE AF-TIMI 48 (Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis In Myocardial Infarction 48) study. Using pre-specified criteria, patients categorized as high fall risk experienced higher rates of major bleeding, bone fracture, and mortality. Of note, the authors found no differences in ischemic stroke, intracranial hemorrhage, or fatal hemorrhage, which raises important questions about cause-specific mortality in this high- risk group of patients.

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Fall risk and bleeding risk are the reasons physicians most often cite for not prescribing anticoagulant therapy for stroke prevention in atrial fibrillation (4). As acknowledged by the authors, they were unable to address the question of anticoagulation as stroke prophylaxis because all the patients received anticoagulant therapy. Although not a randomized assessment, Gage et al. (5) concluded that stroke prevention weighed in favor of anticoagulation for patients who were prone to fall, despite an increased risk of intracranial hemorrhage due to the high risk of ischemic stroke in these patients. The 30-day mortality of atrial-fibrillation-associated ischemic stroke is 24%. Individuals in the high fall risk subgroup of the ENGAGE atrial fibrillation trial had a mean CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes mellitus, Prior stroke, transient ischemic attack [TIA], or thromboembolism, Vascular disease, Age 65-74 years, Sex category [female]) score of 5.1, were older, more often female, and more often had a history of stroke or TIA (41.3% vs. 27.7%, respectively). The rate of intracranial hemorrhage was 0.89%. The expected average rate of ischemic stroke without anticoagulation therapy for this subgroup would be approximately 8%. As was seen with bleeding risk scores, the risk of falls likely also parallels the risk of ischemic stroke. Autonomic dysregulation, sarcopenia, and sensory impairments increase with age. These age-related factors are compounded by medication-induced postural effects of drugs used to treat hypertension and heart failure. Given the morbidity and mortality of ischemic stroke, interventions to reduce fall risk should be the focus as opposed to withholding anticoagulant therapy (6,7).

The optimal choice of anticoagulant for patients who are prone to falling cannot be definitively answered by this study, as high fall risk patients were not randomized. Biologically, the non-vitamin K oral anticoagulants (NOACs) should have an advantage as their mode of action does not affect factor VII; initiation of the coagulation cascade and hemostasis occurs when tissue factor binds to factor VIIa (8). Vitamin K antagonists prevent the activation of factors II, VII, IX, and X. In addition, the shorter half-lives of the NOACs may help to limit hemorrhage in the setting of tissue injury. Despite the small number of events, dabigatran was associated with fewer traumatic intracranial hemorrhages (11 patients with

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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each dose) compared with warfarin (24 patients; $p < 0.05$) in the RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial (9). As stated by Steffel et al. (3), data from ENGAGE AF suggest a greater absolute risk reduction with edoxaban than with warfarin for the high fall risk subgroup, but the small numbers and wide confidence intervals preclude definitive conclusion and recommendation. A meta-analysis of the 4 pivotal atrial fibrillation trials with this subgroup as the focus would be a logical next step.

Other questions remain unanswered. Given the touted deleterious effects of warfarin on bone metabolism, it was anticipated that NOACs might reduce fracture risk. However, the relatively short interval of drug exposure in a randomized trial may not be adequate to address this question. Because the authors found no differences in ischemic stroke, myocardial infarction, intracranial hemorrhage, or fatal hemorrhage between the high fall risk group and those individuals who were not categorized as such, more data are needed for the specific cause of death, particularly if related to cessation of antithrombotic therapy.

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KEY WORDS anticoagulation therapy, atrial fibrillation, fall injury, warfarin