Original Investigation

July 10, 2024

Dose Reduction of Edoxaban in Patients 80 Years and Older With Atrial Fibrillation

Post Hoc Analysis of the ENGAGE AF-TIMI 48 Randomized Clinical Trial

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JAMA Cardiol. Published online July 10, 2024. doi:10.1001/jamacardio.2024.1793

Visual Abstract

Key Points

Question Do patients 80 years and older with atrial fibrillation who are at high risk of ischemic and bleeding events benefit from lower-dose anticoagulants, even in the absence of prespecified dose-reduction criteria?

Findings In this post hoc analysis of 2966 patients with atrial fibrillation 80 years and older, major bleeding events were lower among those randomized to edoxaban, 30 mg per day, compared with either edoxaban, 60 mg per day (in patients without dose-reduction criteria), or warfarin (irrespective of dose-reduction criteria), without an offsetting increase in ischemic events.

Meaning Lower-dose anticoagulants, such as edoxaban, 30 mg once daily, may be considered in patients 80 years and older with atrial fibrillation, regardless of the presence of dose-reduction criteria.

Abstract

Importance In older patients with atrial fibrillation who take anticoagulants for stroke prevention, bleeding is increased compared with younger patients, thus, clinicians frequently prescribe lower than recommended doses in older patients despite limited randomized data.

Objective To evaluate ischemic and bleeding outcomes in patients 80 years and older with atrial fibrillation receiving edoxaban, 60 mg vs 30 mg, and edoxaban, 30 mg vs warfarin.

Design, Setting, and Participants The ENGAGE AF-TIMI 48 trial (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48) was a parallel-design, double-blind, global clinical trial that randomized patients with atrial fibrillation to either one of 2 edoxaban dosing regimens or warfarin. This secondary analysis focused on patients 80 years or older without dose-reduction criteria receiving edoxaban, 60 mg vs 30 mg, as well as patients with or without dose-reduction criteria receiving edoxaban, 30 mg, vs warfarin. Study data were analyzed between October 2022 and December 2023.

Interventions Oral edoxaban, 30 mg once daily; edoxaban, 60 mg once daily; or warfarin.

Main Outcomes and Measures Primary net clinical outcome of death, stroke or systemic embolism, and major bleeding and each individual component.

Results The current analysis included 2966 patients 80 years and older (mean [SD] age, 83 [2.7] years; 1671 male [56%]). Among 1138 patients 80 years and older without dose-reduction criteria, those receiving edoxaban, 60 mg vs 30 mg, had more major bleeding events (hazard ratio [HR], 1.57; 95% CI, 1.04-2.38; $P = .03$), particularly gastrointestinal hemorrhage (HR, 2.24; 95% CI, 1.29-3.90; $P = .004$), with no significant difference in efficacy end points. Findings were supported by analyses of endogenous factor Xa inhibition, a marker of anticoagulant effect, which was comparable between younger patients receiving edoxaban, 60 mg, and older patients receiving edoxaban, 30 mg. In 2406 patients 80 years and older with or without dose-reduction criteria, patients receiving edoxaban, 30 mg, vs warfarin had lower rates of the primary net clinical outcome (HR, 0.78; 95% CI, 0.68-0.91; $P = .001$), major bleeding (HR, 0.59; 95% CI, 0.45-0.77; $P < .001$), and death (HR, 0.83; 95% CI, 0.70-1.00; $P = .046$), whereas rates of stroke or systemic embolism were comparable.

Conclusions and Relevance In this post hoc analysis of the ENGAGE AF-TIMI 48 randomized clinical trial, in patients 80 years and older with atrial fibrillation, major bleeding events were lower in patients randomized to receive edoxaban, 30 mg per day, compared with either edoxaban, 60 mg per day (in patients without dose-reduction criteria), or warfarin (irrespective of dose-reduction status), without an offsetting increase in ischemic events. These data support the concept that lower-dose anticoagulants, such as edoxaban, 30 mg, may be considered in older patients with atrial fibrillation even in the absence of dose-reduction criteria.

Trial Registration ClinicalTrials.gov Identifier: NCT00781391

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