CLINICAL RESEARCH STUDY

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Mortality in Patients with Atrial Fibrillation Randomized to Edoxaban or Warfarin: Insights from the ENGAGE AF-TIMI 48 Trial

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ABSTRACT

BACKGROUND: When compared with warfarin, edoxaban significantly reduced cardiovascular mortality in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial. We studied the possible reasons leading to this reduction.

METHODS: ENGAGE AF-TIMI 48 was a double-blind, double-dummy comparison of warfarin with 2 regimens of once-daily edoxaban in 21,105 patients with atrial fibrillation followed for 2.8 years (median). Causes of deaths in the intention-to-treat population were classified as cardiovascular (including fatal bleeding and ischemic stroke), malignancy, or noncardiovascular/nonmalignancy by an independent, blinded, clinical endpoint committee. Deaths also were adjudicated as directly due to bleeding (ie, fatal), or bleeding contributing to death, or neither.

RESULTS: There were 839 total deaths (4.35%/y) in the warfarin arm, compared with 773 (3.99%/y, $P = .08$) with the higher-dose edoxaban regimen, and 737 (3.80%/y, $P = .006$) with the lower-dose edoxaban regimen. No significant differences between treatments were observed in (1) any of the 3 most common causes of cardiovascular death (sudden cardiac, heart failure, ischemic stroke), (2) fatal malignancies, (3) other noncardiovascular death. There were 124 fatal bleeds, 65 with warfarin, significantly fewer with the higher-dose ($n = 35$, $P = .003$) and lower-dose ($n = 24$, $P < .001$) edoxaban regimens. There were 101 bleeding events with warfarin that were either fatal or that contributed to death. There were significantly fewer with the higher-dose ($n = 59$, $P = .001$) and lower-dose ($n = 54$, $P < .001$) edoxaban regimens.

CONCLUSIONS: Fewer total and cardiovascular deaths were observed with edoxaban as compared with warfarin in the ENGAGE AF-TIMI 48 trial, and this predominantly resulted from the significantly lower rate of major bleeding with edoxaban. Edoxaban reduces mortality both directly (less fatal bleeding) and indirectly (fewer bleeding-related complications and interruptions in therapy after nonfatal bleeding).

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KEYWORDS: Anticoagulant; Bleeding; Death; Edoxaban; Factor Xa inhibitor; Hemorrhage; Warfarin

A systematic review of population-based studies in patients with atrial fibrillation from 21 Global Burden of Disease regions demonstrated that the overall incidence, prevalence, and mortality attributed to atrial fibrillation has increased from 1990 to 2010. This is largely due to aging of the world population, and adds to a growing and significant worldwide public health burden.[1] Although a meta-analysis of 6 trials involving 2900 patients with nonvalvular atrial fibrillation randomized to warfarin or placebo demonstrated a 26% reduction in total mortality with warfarin,[2] there was no significant reduction in total mortality with warfarin compared with antiplatelet therapy in 8 trials involving 3647 patients,[2] nor in a subsequent trial of 6706 patients

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randomized to warfarin or dual antiplatelet therapy (hazard ratio [HR] 0.99).[3] Residual mortality risk in patients with atrial fibrillation anticoagulated with warfarin has been demonstrated[4] and may be due to limitations in efficacy or increased mortality related to side effects of warfarin, or both. For example, warfarin increases the risk of major hemorrhage relative to no anti-thrombotic or aspirin. In particular, warfarin can cause intracranial hemorrhage, which is frequently fatal or severely disabling, even despite rapid reversal[5] of the anticoagulant effect with prothrombin complex concentrates.[6]

In contrast, in a meta-analysis of 4 large, randomized, warfarin-controlled trials involving 71,683 patients with atrial fibrillation, we reported that the non-vitamin K oral anticoagulants (NOACs) reduced total mortality by 10% and did not increase major bleeding as compared with warfarin.[7] In addition, NOACs demonstrated a consistent and large (approximately 50%) reduction in intracranial hemorrhage compared with warfarin across these 4 trials, whereas the observed reduction in thromboembolic events was modest and variable.[7]

In the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation—Thrombolysis in Myocardial Infarction 48 (ENGAGE AF-TIMI 48) trial, the oral factor Xa inhibitor edoxaban, as compared with well-managed warfarin, was noninferior for prevention of stroke and systemic embolic events, while reducing cardiovascular mortality, major bleeding, and intracranial hemorrhage.[8] However, data regarding the causes of death and the relationship of bleeding to death with NOACs as compared with warfarin are sparse. Hence, we analyzed death in the ENGAGE AF-TIMI 48 trial to explore the factors that contributed to the improved survival observed with edoxaban.

CLINICAL SIGNIFICANCE

- An analysis of the causes of death was performed in a clinical trial of NOAC vs warfarin in patients with atrial fibrillation.
- Edoxaban reduced mortality primarily by reducing fatal intracranial bleeding.
- Edoxaban also reduced nonfatal bleeding, which indirectly may result in fewer subsequent deaths.

METHODS

The ENGAGE AF-TIMI 48 trial was a double-blind, double-dummy, randomized, controlled trial in 21,105 patients with atrial fibrillation. Details of the trial design have been previously described.[9] Briefly, patients with atrial fibrillation in the prior 12 months with a $CHADS_2$ score[10] ≥ 2 were randomized to warfarin titrated to an international normalized ratio of 2-3, a higher-dose regimen of edoxaban, or a lower-dose edoxaban regimen. The doses of edoxaban were 60 mg and 30 mg once daily in the higher-dose and lower-dose edoxaban regimen arms, respectively. In both edoxaban arms the dose was reduced by 50% if patients had any one of the following at any time during the trial: creatinine clearance <50 mg/dL, body weight ≤ 60 kg, or concomitant use of verapamil, quinidine, or dronedarone. Major exclusion criteria were high risk for bleeding, creatinine clearance <30 mL/min, need for dual antiplatelet therapy, or acute coronary syndrome or stroke within 30 days. The primary efficacy endpoint was the combination of stroke or systemic embolic events. The principal safety endpoint was major bleeding as defined by the International Society of Thrombosis and Haemostasis.[11] Patients were followed for a median of 2.8 years (interquartile range, 2.4-3.2 years). The protocol and amendments were approved by the ethics committee at each participating center. All the patients provided written, informed consent.

An independent clinical endpoint committee, blinded to treatment assignment, adjudicated all deaths and suspected cerebrovascular events, systemic embolic events, myocardial infarctions, and bleeding. In the adjudication of deaths, the clinical endpoint committee determined the primary cause of death, categorized as shown in **Table 1** (see Appendix, available online, for detailed definitions). Fatal

Table 1 Classification of Death by the Clinical Endpoint Committee

Categories of causes of death
1. Cardiovascular
   a. Fatal bleeding
      i. Intracranial hemorrhage
      ii. Extracranial bleeding
   b. Nonbleeding cardiovascular deaths
      i. Ischemic stroke
      ii. Systemic arterial embolic event
      iii. Congestive heart failure or cardiogenic shock
      iv. Directly related to coronary revascularization
      v. Dysrhythmia
      vi. Pulmonary Embolism
      vii. Sudden or unwitnessed death
      viii. Atherosclerotic vascular disease (excluding coronary artery disease)
      ix. Other
2. Malignancy
3. Other
   a. Infection
   b. Suicide
   c. Accidental/traumatic
   d. Hepatobiliary
   e. Renal
   f. Other

Relationship of death to bleeding
1. Fatal bleeding. Bleeding event led directly to death within 7 days. Cause of death must be either intracranial or extracranial bleeding.
2. Bleeding contributed to death. Bleeding was part of a causal chain resulting in death within 30 days.
3. Death unrelated to a bleeding event.