

## RESEARCH LETTER

### Hospitalization Among Patients With Atrial Fibrillation and a Recent Acute Coronary Syndrome or Percutaneous Coronary Intervention Treated With Apixaban or Aspirin Insights From the AUGUSTUS Trial

The optimal antithrombotic therapy among patients with atrial fibrillation who present with acute coronary syndrome (ACS) or require percutaneous coronary intervention (PCI) can be challenging, with combination therapy, including both dual antiplatelet therapy and oral anticoagulation, markedly increasing bleeding risk.<sup>1</sup> Recent trials with rivaroxaban<sup>2</sup> and dabigatran<sup>3</sup> have demonstrated the safety of using a non-vitamin K oral anticoagulant with a P2Y<sub>12</sub> inhibitor, without aspirin or with reduced-dose aspirin, after PCI. The AUGUSTUS trial (Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) demonstrated that apixaban resulted in less bleeding than vitamin K antagonist (VKA), with lower rates of the composite of death or all-cause hospitalization.<sup>4</sup> Rates of bleeding were higher among patients treated with aspirin than those treated with placebo, but rates of death or all-cause hospitalization were not different. This analysis evaluated rates and causes of hospitalization, a key secondary outcome, overall and by randomized treatment.

The rationale and design of the AUGUSTUS trial have been published.<sup>5</sup> Briefly, AUGUSTUS was a prospective, multicenter, 2×2 factorial trial that randomized patients with atrial fibrillation and recent ACS or PCI to apixaban or VKA and to aspirin or placebo for 6 months on background P2Y<sub>12</sub> inhibitor. The primary end point for the study was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis. Hospitalizations were classified as cardiovascular, bleeding related, or other cause by reviewers blinded to treatment assignment. The trial protocol was approved by appropriate ethics committees at participating sites, and all patients provided written informed consent before participation in the study.

All patients randomized are included and analyzed according to the intent-to-treat principle. Events were counted from the time of randomization through the 6-month visit. Hazard ratios were derived from Cox proportional hazard models using the time to the first cause-specific hospitalization. The incidence of myocardial infarction, International Society on Thrombosis and Haemostasis major bleeding, and all-cause death after bleeding-related hospitalizations are reported as frequencies and percentages of patients in patients discharged alive. Bleeding-related hospitalizations occurring within 7 days after another hospitalization are excluded from this analysis.

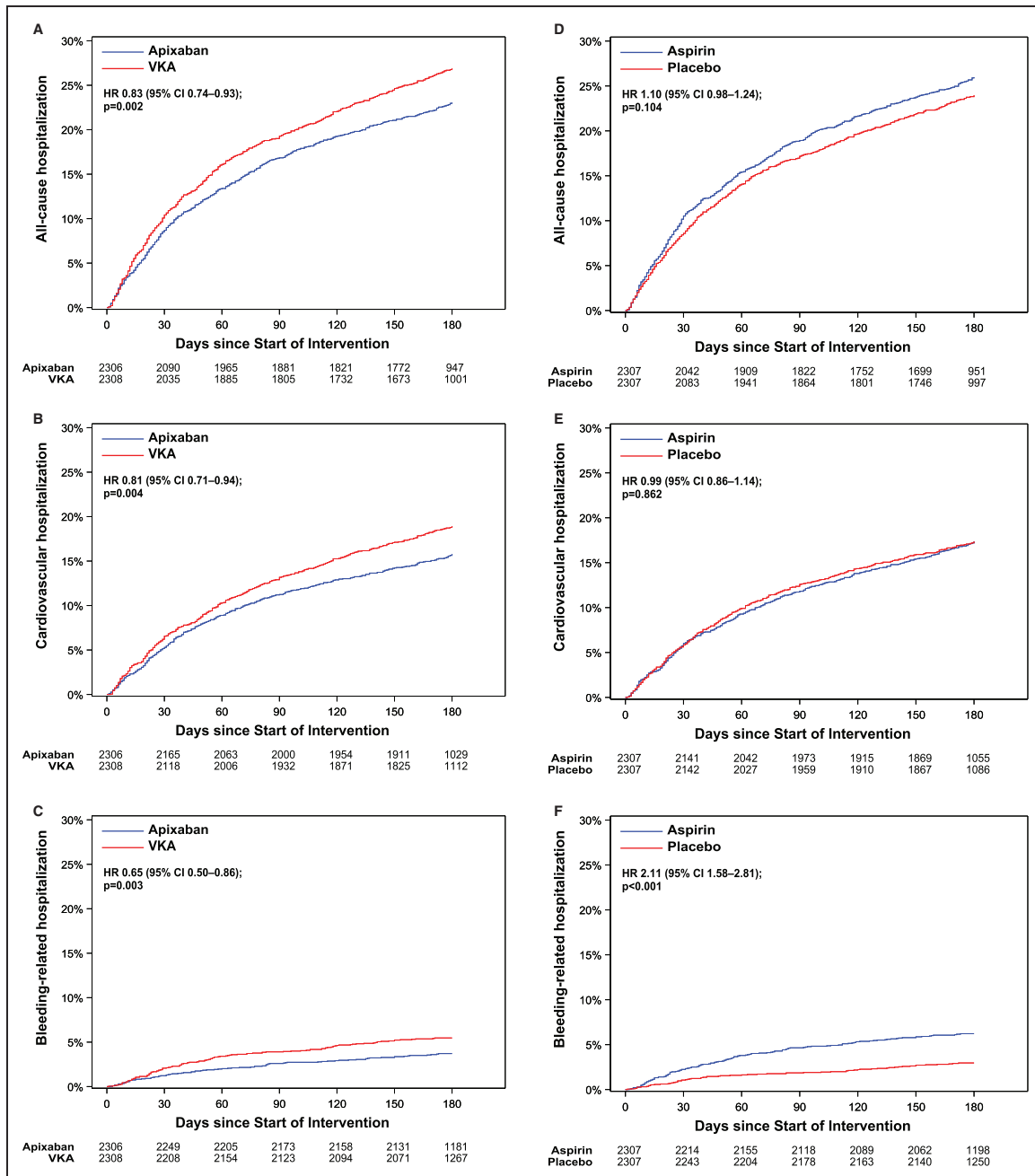
A total of 4614 patients from 492 sites in 33 countries were randomized. The median age was 71 years, and 29% were women. Thirty-seven percent had an ACS and underwent PCI; 24% had medically managed ACS; and the remaining 39% underwent elective PCI. The mean CHA<sub>2</sub>DS<sub>2</sub>-VASc score was 3.9 (SD, 1.6), and the mean HAS-BLED score was 2.9 (SD, 0.9). Clopidogrel was the P2Y<sub>12</sub> inhibitor of choice in 93% of patients.

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**Figure.** Hospitalization by anticoagulant or antiplatelet therapy.

**A**, All-cause hospitalization, apixaban vs vitamin K antagonist (VKA). **B**, Cardiovascular hospitalization, apixaban vs VKA. **C**, Bleeding-related hospitalization, apixaban vs VKA. **D**, All-cause hospitalization, aspirin vs placebo. **E**, Cardiovascular hospitalization, aspirin vs placebo. **F**, Bleeding-related hospitalization, aspirin vs placebo. HR indicates hazard ratio.

A total of 1125 patients (24.4%) were hospitalized during the study duration, and the median time from randomization to the first hospitalization was 46 days (25th–75th percentiles, 19–96 days). Among patients with hospitalizations, the median time in hospital during follow-up was 6 days (3–14 days) with 384 (34.1%) having  $\geq 2$  hospitalizations. The median length of hospitalization was 4 days (2–8 days). Among study participants, 780 patients (16.9%) had a least 1 cardiovascular hospitalization, 208 (4.5%) had a least 1

bleeding-related hospitalization, and 359 (7.8%) had at least 1 hospitalization for another cause. Patients who underwent PCI (either elective or resulting from ACS) were more likely to be hospitalized during the study period than those who presented with medically managed ACS.

Rates of hospitalization were lower among patients assigned to apixaban than those assigned to VKA (22.5% versus 26.3%; hazard ratio [HR], 0.83 [95% CI, 0.74–0.93];  $P=0.002$ ), driven by lower rates of cardiovascular

hospitalization (15.4% versus 18.5%; HR, 0.81 [95% CI, 0.71–0.94]) and bleeding-related hospitalization (3.6% versus 5.4%; HR, 0.65 [95% CI, 0.50–0.86]; Figure [A–C]). Rates of hospitalization were not different between patients assigned to aspirin and those assigned to placebo (25.4% versus 23.4%; HR, 1.10 [95% CI, 0.98–1.24]), as were rates of cardiovascular hospitalization (16.8% versus 17.0%; HR 0.99 [95% CI, 0.86–1.14]); however, rates of bleeding-related hospitalization were >2-fold higher in patients assigned to aspirin than in those assigned to placebo (6.1% versus 2.9%; HR, 2.11 [95% CI, 1.58–2.81]; Figure [D–F]).

This study has some limitations that warrant consideration. Primary causes of hospitalization were provided by the site investigators. Although they were independently classified by physician-reviewers blinded to treatment assignment, primary source documents were not reviewed. The open-label treatment with apixaban and VKA might lead to an unintentional bias to admit a patient treated with VKA compared with apixaban, especially for bleeding or cardiovascular causes. Bias is not expected for the blinded aspirin/placebo comparison, which did not demonstrate an overall difference in hospitalization. However, the increased risk of bleeding with aspirin is reflected by the increase in bleeding-related hospitalizations. Despite potential bias, adjudication of events and classification of hospitalization were blinded to treatment assignment. Finally, this analysis was based on the results of a randomized clinical trial with specific inclusion and exclusion criteria, which, despite being broad, may limit the generalizability of these results to other populations.

This prespecified analysis of the AUGUSTUS study demonstrates that the risk of rehospitalization in this patient population remains high, with  $\approx 1$  of 4 patients with atrial fibrillation with recent ACS/PCI requiring rehospitalization within 6 months of their ACS or PCI event. The risk of hospitalization was lower among patients treated with apixaban than those treated with VKA, driven by a 35% reduction in bleeding-related hospitalization and a 19% reduction in the much higher rate of cardiovascular hospitalization. Although bleeding-related hospitalization was higher among patients treated with aspirin, there was no difference in all-cause hospitalization between patients assigned to aspirin and those assigned to placebo. Our findings further support the use of apixaban over warfarin and the avoidance of aspirin to reduce bleeding on background P2Y<sub>12</sub> inhibitor in this high-risk patient population.

## ARTICLE INFORMATION

**Data Sharing:** The data, analytical methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

**Clinical Trial Registration:** URL: <https://www.clinicaltrials.gov>. Unique identifier: NCT02415400.

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