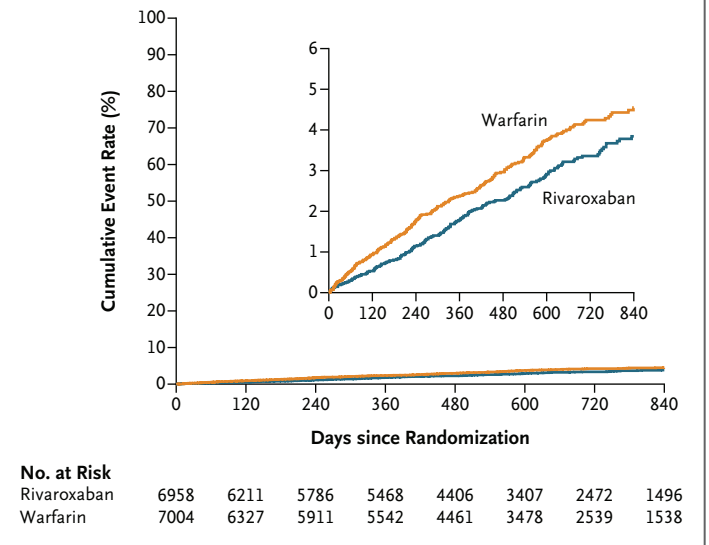

Figure 1. Cumulative Rates of the Primary End Point (Stroke or Systemic Embolism) in the Per-Protocol Population and in the Intention-to-Treat Population.

P=0.07). In addition, in the intention-to-treat analysis throughout the trial, there were 582 deaths in the rivaroxaban group and 632 deaths in the warfarin group (4.5% and 4.9% per year, respectively; hazard ratio, 0.92; 95% CI, 0.82 to 1.03; P=0.15).

SELECTED SUBGROUP ANALYSES

The effect of rivaroxaban, as compared with warfarin, in both efficacy and safety analyses was consistent across all prespecified subgroups (Fig. 3, 4, and 5 in the Supplementary Appendix). Furthermore, the effect of rivaroxaban did not differ across quartiles of the duration of time that INR values were within the therapeutic range according to study center (P=0.74 for interaction) (Table 5 in the Supplementary Appendix). Within the highest quartile according to center, the hazard ratio with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 to 1.12).

DISCUSSION

In this randomized trial, we compared rivaroxaban with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular atrial fibrillation who were at moderate-to-high risk for stroke. In both the primary analysis, which included patients in the per-protocol population, and in the intention-to-treat analysis, we found that rivaroxaban was noninferior to warfarin. In the primary safety analysis, there was no significant difference between rivaroxaban and warfarin with respect to rates of major or nonmajor clinically relevant bleeding.

As prespecified in the statistical-analysis plan, we analyzed the trial data in a variety of ways because we anticipated that some patients would discontinue the study treatment and we wished to evaluate both noninferiority and superiority. Although an intention-to-treat analysis is the standard method for assessing superiority in a randomized trial, noninferiority is best established when patients are actually taking the randomized treatment.[16-19] Thus, the primary analysis was performed in the per-protocol population during receipt of the randomly assigned therapy. In the intention-to-treat population, we found no significant between-group difference in a conventional superiority analysis. In contrast, in the analyses of patients receiving at least one dose of a study drug who were followed for events during treatment, we found that rivaroxaban was superior to warfarin. The difference between these results reflects the fact that among patients who discontinued therapy before the conclusion of the trial, no significant difference in outcomes would have been anticipated, and none was seen.

The most worrisome complication of anticoagulation is bleeding. Rates of major and nonmajor clinically relevant bleeding, the main measure of treatment safety, were similar in the rivaroxaban and warfarin groups. Bleeding that proved fatal or involved a critical anatomical site occurred less frequently in the rivaroxaban group, mainly

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because of lower rates of hemorrhagic stroke and other intracranial bleeding. In contrast, bleeding from gastrointestinal sites, including upper, lower, and rectal sites, occurred more frequently in the rivaroxaban group, as did bleeding that led to a drop in the hemoglobin level or bleeding that required transfusion. Even though patients in our trial were at increased risk for bleeding events, rates of major bleeding were similar to those in other recent studies involving patients with atrial fibrillation.[4,15,22,23]

Among patients in our study who survived and did not reach the primary end point, the rate of premature, permanent cessation of randomized treatment (14.3% in year 1) was slightly higher than in other studies (average, 11%).[15,23] This may have been a consequence of the trial's double-blind design or the inclusion of patients with more coexisting illnesses. Among patients who permanently discontinued their assigned treatment before the end of the study, only about half were treated thereafter with a vitamin K antagonist. This observation suggests that for at least some of the patients who participated in the trial, the risks of open-label therapy with currently available anticoagulants were ultimately judged to outweigh the risk of stroke or systemic embolism. Event rates were similar at 30 days and 1 year after withdrawal, suggesting that the mechanism of events did not involve hypercoagulability early after withdrawal of rivaroxaban. Events occurring at the end of the study were probably related to increased difficulty in achieving the transition from blinded trial therapy to the open-label use of a vitamin K antagonist when the patient had previously been assigned to the rivaroxaban group, since presumably many patients who had previously been assigned to the warfarin group would have already had a therapeutic INR.

Among patients in the warfarin group, the proportion of time in which the intensity of anticoagulation was in the therapeutic range (mean, 55%), which was calculated from all INR values during the study and for 7 days after warfarin interruptions, was lower than in previous studies of other new anticoagulants in patients with atrial fibrillation (range, 64 to 68%). Among these trials, the only study of blinded treatment was limited to North American sites, which may have facilitated trial compliance.[15] Most earlier trials of warfarin included fewer high-risk patients,[3] and no previous studies addressed patient populations with overall levels of coexisting illnesses and geographic diversity that were similar to those of the patients in our study.[24] Significant variations in the duration of time in the therapeutic range may reflect regional differences and differential skill in managing warfarin.[25] In a recent analysis of anticoagulation management involving more than 120,000 patients in the Veterans Affairs health care system, the mean proportion of time in the therapeutic range was 58%, with significant variation across sites.[24] The efficacy of rivaroxaban, as compared with warfarin, was as favorable in centers with the best INR control as in those with poorer control.

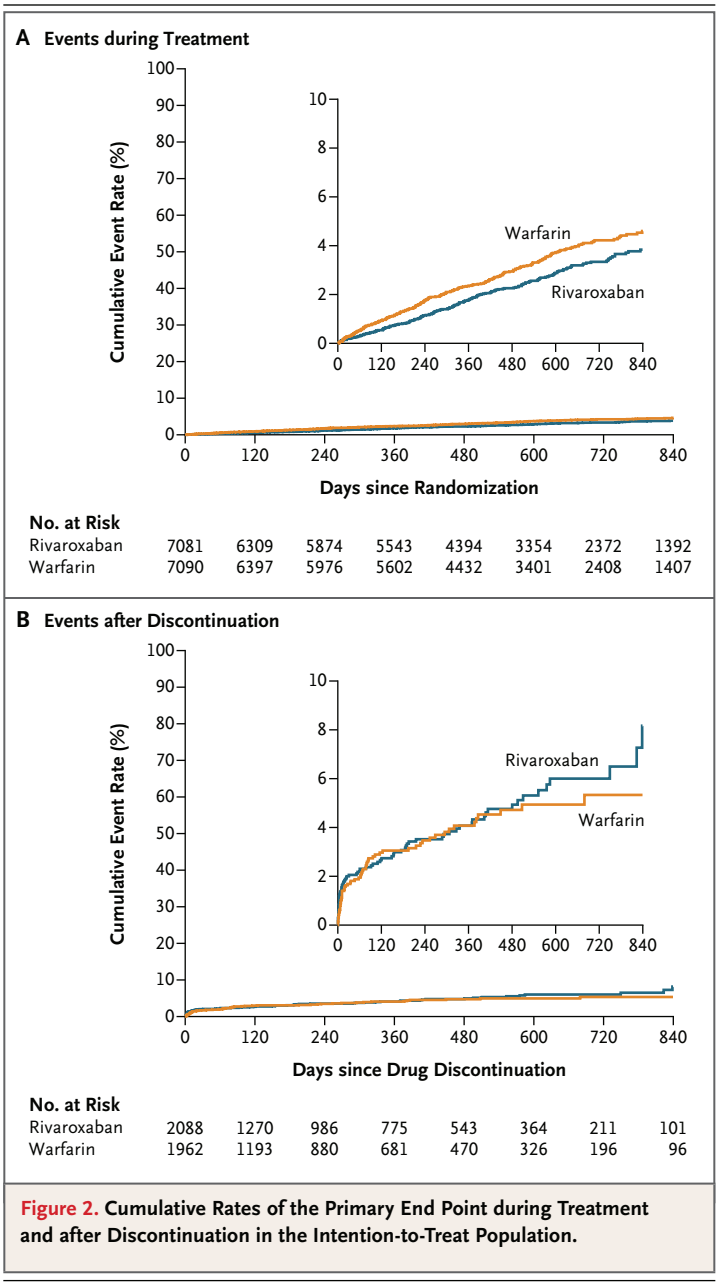

Figure 2. Cumulative Rates of the Primary End Point during Treatment and after Discontinuation in the Intention-to-Treat Population.

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