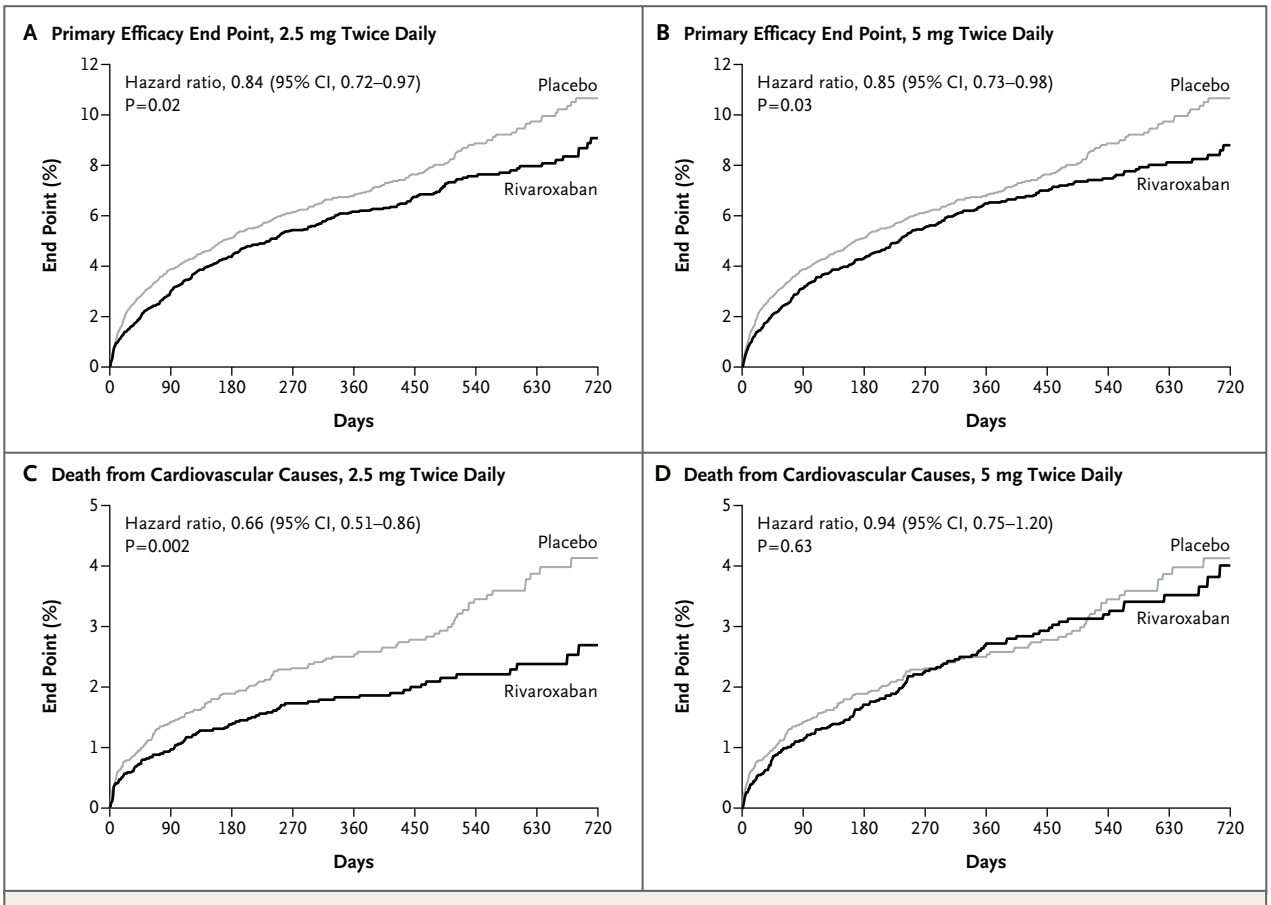

Figure 3. Cumulative Incidence of Efficacy End Points, According to Rivaroxaban Dose.

The primary efficacy end point consists of death from cardiovascular causes, myocardial infarction, or stroke. The P values are for the modified intention-to-treat analyses. The P values for the intention-to-treat analyses are P=0.007 in Panel A, P=0.01 in Panel B, P=0.005 in Panel C, and P=0.57 in Panel D.

ceiving rivaroxaban, which was expected. This increased bleeding risk was seen with the two doses of rivaroxaban, as compared with placebo, although the lower rivaroxaban dose resulted in less bleeding than the higher dose. The rates of adverse events, other than bleeding events, were similar in the combined rivaroxaban group and the placebo group.

In addition to rivaroxaban, other new factor Xa and IIa inhibitors have been evaluated in patients after an acute coronary syndrome. The phase 2 programs, which evaluated rivaroxaban, apixaban, dabigatran, and darexaban, all showed a dose-dependent increase in bleeding.[15,16] In the ATLAS ACS–TIMI 46 and Apixaban for Prevention of Acute Ischemic Events 1 (APPRAISE-1) trials (NCT00313300), rivaroxaban and apixaban also showed trends toward a reduction in cardiovascular events.[4,17] APPRAISE-2 (NCT00831441) then tested apixaban versus placebo in a phase 3 trial, which showed that the addition of 5 mg of apixaban twice daily to antiplatelet therapy in patients after an acute coronary syndrome increased the number of major bleeding events without a significant reduction in the rate of recurrent ischemic events.[18] Some of the differences in the findings between our study and APPRAISE-2 may be due in part to the patient populations. Specifically, our study was designed to exclude patients who had a history of ischemic stroke or transient ischemic attack who were to be treated with aspirin and a thienopyridine, a group that has not appeared to benefit from greater degrees of antithrombotic therapy.[19,20]

Regarding dose regimens, a 5-mg dose of apixaban twice daily was tested both in patients with atrial fibrillation in the Apixaban for Reduction in Stroke and Other Thromboembolic

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