Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

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*Investigators in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51 (ATLAS ACS 2–TIMI 51) are listed in the Supplementary Appendix, available at NEJM.org.

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ABSTRACT

BACKGROUND
Acute coronary syndromes arise from coronary atherosclerosis with superimposed thrombosis. Since factor Xa plays a central role in thrombosis, the inhibition of factor Xa with low-dose rivaroxaban might improve cardiovascular outcomes in patients with a recent acute coronary syndrome.

METHODS
In this double-blind, placebo-controlled trial, we randomly assigned 15,526 patients with a recent acute coronary syndrome to receive twice-daily doses of either 2.5 mg or 5 mg of rivaroxaban or placebo for a mean of 13 months and up to 31 months. The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke.

RESULTS
Rivaroxaban significantly reduced the primary efficacy end point, as compared with placebo, with respective rates of 8.9% and 10.7% (hazard ratio in the rivaroxaban group, 0.84; 95% confidence interval [CI], 0.74 to 0.96; P=0.008), with significant improvement for both the twice-daily 2.5-mg dose (9.1% vs. 10.7%, P=0.02) and the twice-daily 5-mg dose (8.8% vs. 10.7%, P=0.03). The twice-daily 2.5-mg dose of rivaroxaban reduced the rates of death from cardiovascular causes (2.7% vs. 4.1%, P=0.002) and from any cause (2.9% vs. 4.5%, P=0.002), a survival benefit that was not seen with the twice-daily 5-mg dose. As compared with placebo, rivaroxaban increased the rates of major bleeding not related to coronary-artery bypass grafting (2.1% vs. 0.6%, P<0.001) and intracranial hemorrhage (0.6% vs. 0.2%, P=0.009), without a significant increase in fatal bleeding (0.3% vs. 0.2%, P=0.66) or other adverse events. The twice-daily 2.5-mg dose resulted in fewer fatal bleeding events than the twice-daily 5-mg dose (0.1% vs. 0.4%, P=0.04).

CONCLUSIONS
In patients with a recent acute coronary syndrome, rivaroxaban reduced the risk of the composite end point of death from cardiovascular causes, myocardial infarction, or stroke. Rivaroxaban increased the risk of major bleeding and intracranial hemorrhage but not the risk of fatal bleeding. (Funded by Johnson & Johnson and Bayer Healthcare; ATLAS ACS 2–TIMI 51 ClinicalTrials.gov number, NCT00809965.)
AFTER AN ACUTE CORONARY SYNDROME, patients remain at risk for recurrent cardiovascular events despite standard medical therapy, including long-term antiplatelet therapy with aspirin and an adenosine diphosphate–receptor inhibitor. This risk may be related in part to excess thrombin generation that persists beyond the acute presentation in such patients. As a result, there has been interest in evaluating the role of oral anticoagulants after an acute coronary syndrome. Improved cardiovascular outcomes were reported for patients who were treated with the anticoagulant warfarin in addition to aspirin. However, widespread use of long-term warfarin in such patients has been limited by challenges associated with drug administration and the risk of bleeding. Likewise, treatment with the factor IIa inhibitor ximelagatran after a myocardial infarction showed cardiovascular benefits, but the drug was associated with hepatotoxicity.

Rivaroxaban is an oral anticoagulant that directly and selectively inhibits factor Xa. Factor Xa initiates the final common pathway of the coagulation cascade and results in the formation of thrombin, which catalyzes additional coagulation-related reactions and promotes platelet activation. Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 46 (ATLAS ACS–TIMI 46; ClinicalTrials.gov number, NCT00402597) was a phase 2 dose-finding trial that enrolled 3491 patients with a recent acute coronary syndrome. Rivaroxaban was tested at total daily doses ranging from 5 to 20 mg and, as compared with placebo, reduced the composite end point of death, myocardial infarction, or stroke with the lowest hazard ratios seen at 4 weeks, at 12 weeks, and thereafter even 12 weeks.

STUDY ENROLLMENT AND RANDOMIZATION

Enrollment occurred within 7 days after hospital admission for an acute coronary syndrome. The condition of patients needed to be stabilized before enrollment, with the initial management strategies (e.g., revascularization) completed for details, see the Supplementary Appendix, available with the full text of this article at NEJM.org). All patients provided written informed consent.

Patients were randomly assigned in a 1:1:1 fashion to twice-daily administration of either 2.5 mg or 5.0 mg of rivaroxaban or placebo, with a maximum follow-up of 31 months. All patients were to receive standard medical therapy, including low-dose aspirin; they were to receive a thienopyridine (either clopidogrel or ticlopidine) according to the national or local guidelines. Randomization was stratified on the basis of planned use of a thienopyridine. Patients were then to be seen at 4 weeks, at 12 weeks, and thereafter every 12 weeks.

STUDY END POINTS

The primary efficacy end point was a composite of death from cardiovascular causes, myocardial infarction, or stroke (ischemic, hemorrhagic, or stroke of uncertain cause). The secondary efficacy end point was death from any cause, myocardial infarction, or stroke. Stent thrombosis was defined according to Academic Research Consortium definitions. The primary safety end point was TIMI major bleeding not related to coronary-artery bypass grafting (CABG). Complete definitions of the end points have been reported previously. A clinical-events committee whose members were unaware of study-group assignments adjudicated

STUDY POPULATION

The study included patients (≥18 years of age) who had presented with symptoms suggestive of an acute coronary syndrome and in whom an ST-segment elevation myocardial infarction (STEMI), a non–ST-segment elevation myocardial infarction (NSTEMI), or unstable angina had been diagnosed. Patients who were under 55 years of age had either diabetes mellitus or a previous myocardial infarction in addition to the index event. Key exclusion criteria included a platelet count of less than 90,000 per cubic millimeter, a hemoglobin level of less than 10 g per deciliter, or a creatinine clearance of less than 30 ml per minute at screening; clinically significant gastrointestinal bleeding within 12 months before randomization; previous intracranial hemorrhage; and previous ischemic stroke or transient ischemic attack in patients who were taking both aspirin and a thienopyridine.
all components of the key efficacy and safety end points.

**STUDY OVERSIGHT**

This randomized, double-blind, placebo-controlled, event-driven trial was designed as a collaboration between the TIMI Study Group (an academic research organization), the sponsors (Johnson & Johnson and Bayer Healthcare), and investigators from the executive and steering committees (listed in the Supplementary Appendix). The study design was approved by the appropriate national and institutional regulatory agencies and ethics committees. The study protocol is available at NEJM.org. An independent data and safety monitoring committee monitored the trial and reviewed unblinded data.

The study's sponsors coordinated data management. Statistical analyses were performed by the TIMI Study Group using an independent copy of the complete raw database. The first version of the manuscript was drafted by the academic authors of the TIMI Study Group, who take responsibility for the completeness and accuracy of the data and who made the decision to submit the manuscript for publication.

**STATISTICAL ANALYSIS**

As prespecified, efficacy analyses were performed with the use of a modified intention-to-treat approach, which included the randomized patients and the end-point events that occurred after randomization and no later than the completion of the treatment phase of the study (i.e., the global-treatment end date), 30 days after early permanent discontinuation of the study drug, or 30 days after randomization for patients who did not receive a study drug. Sensitivity efficacy analyses were conducted with the use of an intention-to-treat approach, which included the patients who underwent randomization and all end-point events occurring after randomization until the global-treatment end date. The primary safety analysis included all patients who underwent randomization and who received at least one dose of a study drug, with evaluation performed from the time of administration of the first dose of a study drug until 2 days after the discontinuation of a study drug.

We used hazard ratios and two-sided 95% confidence intervals to compare the study groups. Rates of the end points were expressed as Kaplan–Meier estimates through 24 months. Testing was prespecified to occur between the combined-dose group for rivaroxaban and placebo at an alpha level of 0.05 on the basis of the log-rank test, stratified according to the intention to use a thienopyridine. If this comparison significantly favored rivaroxaban, then each of the two doses of rivaroxaban was simultaneously compared with placebo with the use of a similar stratified log-rank test at an alpha level of 0.05 on the basis of the closed testing procedure. Results were examined according to major subgroups for general consistency of treatment effect, and interaction testing was performed.

We determined that a total of 983 primary efficacy end-point events would provide a power of approximately 96% to detect a 22.5% relative reduction between the combined-dose group receiving rivaroxaban and the placebo group with a two-sided type I error rate of 0.05. The comparison of each of the two doses of rivaroxaban with placebo had a power of approximately 90% to determine a relative risk reduction of 22.5%.

**RESULTS**

**PATIENTS**

The study was conducted from November 2008 through September 2011. A total of 15,526 patients underwent randomization at 766 sites in 44 countries. The baseline characteristics of the patients were well matched in the study groups (Table 1). The index event was a STEMI in 50.3% of the patients, an NSTEMI in 25.6%, and unstable angina in 24.0%. The median time from the index event to randomization was 4.7 days (interquartile range, 3.2 to 6.0). Background therapy included the intended use of a thienopyridine in 93% of the patients, and the mean duration of treatment with a thienopyridine was 13.3 months.

The mean duration of treatment with a study drug was 13.1 months. Among patients who received at least one dose of a study drug, premature discontinuation of treatment occurred in 26.9% of patients receiving the 2.5-mg dose of rivaroxaban, 29.4% receiving the 5-mg dose of rivaroxaban, and 26.4% receiving placebo. The most common reasons for discontinuation of rivaroxaban were adverse events and patients’ choice. During treatment, the proportions of patients who were at least 85% compliant with the study drug were 93.9% of patients receiving the 2.5-mg dose of rivaroxaban, 94.0% receiving the 5-mg dose of rivaroxaban, and 94.6% receiving placebo. The rates of withdrawal of consent from the study were...
Table 1. Baseline Characteristics of the Patients. *

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban 2.5 mg Twice Daily (N = 5174)</th>
<th>Rivaroxaban 5 mg Twice Daily (N = 5176)</th>
<th>Placebo (N = 5176)</th>
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<tbody>
<tr>
<td>Age Mean — yr</td>
<td>61.8 ± 9.2</td>
<td>61.9 ± 9.0</td>
<td>61.5 ± 9.4</td>
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<tr>
<td>≥65 yr — no. (%)</td>
<td>1905 (36.8)</td>
<td>1921 (37.1)</td>
<td>1835 (35.5)</td>
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<td>≥75 yr — no. (%)</td>
<td>466 (9.0)</td>
<td>441 (8.5)</td>
<td>498 (9.6)</td>
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<td>Male sex — no. (%)</td>
<td>3875 (74.9)</td>
<td>3843 (74.2)</td>
<td>3882 (75.0)</td>
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<td>Race — no. (%) †</td>
<td>White (73.4)</td>
<td>3815 (73.7)</td>
<td>3796 (73.3)</td>
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<td></td>
<td>Black (0.7)</td>
<td>34 (0.7)</td>
<td>39 (0.8)</td>
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<td></td>
<td>Asian (21.2)</td>
<td>1055 (20.4)</td>
<td>1075 (20.8)</td>
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<tr>
<td></td>
<td>Other (4.7)</td>
<td>272 (5.3)</td>
<td>266 (5.1)</td>
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<tr>
<td>Weight — kg</td>
<td>Median 78.0</td>
<td>Median 78.0</td>
<td>78.0</td>
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<td></td>
<td>Interquartile range 68.0–90.0</td>
<td>Interquartile range 68.0–88.0</td>
<td>68.0–88.5</td>
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<td>Creatinine clearance — ml/min ‡</td>
<td>Median 85.1</td>
<td>84.8</td>
<td>85.6</td>
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<td>Interquartile range 68.3–105.0</td>
<td>Interquartile range 68.5–104.7</td>
<td>68.1–105.1</td>
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<td>Medical history — no. (%)</td>
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<td>1403 (27.1)</td>
<td>1415 (27.3)</td>
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<td>Hypertension 3470 (67.1)</td>
<td>3499 (67.6)</td>
<td>3494 (67.5)</td>
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<td>Diabetes 1669 (32.3)</td>
<td>1648 (31.8)</td>
<td>1647 (31.8)</td>
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<td>Hypercholesterolemia 2498 (48.3)</td>
<td>2544 (49.1)</td>
<td>2496 (48.2)</td>
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<td>Index diagnosis — no. (%)</td>
<td>STEMI 2601 (50.3)</td>
<td>2584 (49.9)</td>
<td>2632 (50.9)</td>
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<td></td>
<td>NSTEMI 1321 (25.5)</td>
<td>1335 (25.8)</td>
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<td>Unstable angina 1252 (24.2)</td>
<td>1257 (24.3)</td>
<td>1221 (23.6)</td>
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<td>PCI or CABG for index event — no. (%)</td>
<td>3138 (60.6)</td>
<td>3123 (60.3)</td>
<td>3126 (60.4)</td>
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<td>Region — no. (%)</td>
<td>North America 269 (5.2)</td>
<td>293 (5.7)</td>
<td>312 (6.0)</td>
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<td></td>
<td>South America 546 (10.6)</td>
<td>581 (11.3)</td>
<td>540 (10.4)</td>
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<td>Western Europe 707 (13.7)</td>
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<td>Eastern Europe 2042 (39.5)</td>
<td>2025 (39.1)</td>
<td>2007 (38.8)</td>
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<td></td>
<td>Asia 1088 (21.0)</td>
<td>1044 (20.2)</td>
<td>1063 (20.5)</td>
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<td></td>
<td>Other 522 (10.1)</td>
<td>456 (8.8)</td>
<td>495 (9.6)</td>
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<td>Medications — no. (%)</td>
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<td>5099 (98.5)</td>
<td>5108 (98.7)</td>
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<td></td>
<td>Thienopyridine 4790 (92.6)</td>
<td>4812 (93.0)</td>
<td>4811 (92.9)</td>
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<td>Beta-blocker 3426 (66.2)</td>
<td>3394 (65.6)</td>
<td>3444 (66.5)</td>
</tr>
<tr>
<td></td>
<td>ACE inhibitor or ARB 2022 (39.1)</td>
<td>1977 (38.2)</td>
<td>2050 (39.6)</td>
</tr>
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<td></td>
<td>Statin 4304 (83.2)</td>
<td>4342 (83.9)</td>
<td>4321 (83.5)</td>
</tr>
<tr>
<td></td>
<td>Calcium-channel blocker 820 (15.8)</td>
<td>742 (14.3)</td>
<td>764 (14.8)</td>
</tr>
</tbody>
</table>

* Plus–minus values are means ± SD. There were no significant differences among the three groups. ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CABG coronary-artery bypass grafting, NSTEMI, non–ST-segment elevation myocardial infarction, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.

† Race was self-reported.
‡ Creatinine clearance was calculated with the use of the Cockcroft–Gault equation.
Efficacy End Points

Rivaroxaban significantly reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates of 8.9% and 10.7%, respectively (hazard ratio, 0.84; 95% confidence interval [CI], 0.74 to 0.95; P = 0.006). In addition, rivaroxaban reduced the risk of stent thrombosis (definite, probable, or possible), as compared with placebo, with rates of 2.3% and 2.9%, respectively (hazard ratio, 0.69; 95% CI, 0.51 to 0.93; P = 0.02). The reduction in the primary efficacy end point with rivaroxaban was consistent among the subgroups except for patients with a history of stroke or transient ischemic attack (Fig. 2).

In the analysis of the two doses of rivaroxaban, each of the doses reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke, as compared with placebo, with rates in patients receiving the 2.5-mg dose of 9.1% and 10.7%, respectively (hazard ratio, 0.84; 95% CI, 0.72 to 0.97; P = 0.02) and rates in patients receiving the 5-mg dose of 8.8% and 10.7%, respectively (hazard ratio, 0.85; 95% CI, 0.73 to 0.98; P = 0.03) (Fig. 3A and 3B). The 2.5-mg dose of rivaroxaban, as compared with placebo, reduced the risk of death from cardiovascular causes (2.7% vs. 4.1%; hazard ratio, 0.66; 95% CI, 0.51 to 0.86; P = 0.002) (Fig. 3C) and the risk of death from any cause (2.9% vs. 4.5%; hazard ratio, 0.68; 95% CI, 0.53 to 0.87; P = 0.002). The 5-mg dose of rivaroxaban, as compared with placebo, did not significantly reduce the risk of death from either cardiovascular causes (hazard ratio, 0.94; P = 0.63) (Fig. 3D) or any cause (hazard ratio, 0.95; P = 0.66) and differed significantly from the 2.5-mg dose of rivaroxaban (P = 0.009 for both comparisons).

Safety End Points

Rivaroxaban significantly increased the rate of TIMI major bleeding that was not related to CABG, as compared with placebo, with rates of 2.1% and 0.6%, respectively (hazard ratio, 3.96; 95% CI, 2.46 to 6.38; P < 0.001) (Table 2, and Fig. 1 in the Supplementary Appendix), a finding that was also significant for the 2.5-mg and 5-mg doses of rivaroxaban (P < 0.001 for both comparisons). For TIMI major bleeding that was not related to CABG, there were no significant interactions between the measured characteristics of patients and the study group (Fig. 2 in the Supplementary Appendix). Also greater in the combined rivaroxaban group, as compared with placebo, were rates of TIMI minor bleeding (1.3% vs. 0.5%, P = 0.003), TIMI bleeding requiring medical attention (14.5% vs. 7.5%, P = <0.001), and intracranial hemorrhage (0.6% vs. 0.2%, P = 0.009) (Table 2). There was no significant difference in the rates of fatal bleeding associated with rivaroxaban as compared with placebo (0.3% vs. 0.2%, P = 0.66).
In the comparison between the two doses of rivaroxaban, the rates of TIMI major bleeding that was not related to CABG tended to be lower in patients receiving the 2.5-mg dose than in those receiving the 5-mg dose (1.8% vs. 2.4%, P = 0.12), and the lower dose resulted in significantly lower rates of TIMI minor bleeding (0.9% vs. 1.6%, P = 0.046), TIMI bleeding requiring medical attention (12.9% vs. 16.2%, P < 0.001), and fatal bleeding (0.1% vs. 0.4%, P = 0.04).

The rates of adverse events that were not related to bleeding were similar in the rivaroxaban and placebo groups (Table 1 in the Supplementary Appendix). Specifically, clinical and laboratory liver abnormalities were similar among patients treated with rivaroxaban or placebo, with alanine aminotransferase levels of more than three times the upper limit of the normal range and total bilirubin levels of more than twice the upper limit of the normal range occurring in 0.2% of patients in each study group.

**DISCUSSION**

Despite medical therapy after an acute coronary syndrome, patients continue to be at risk for recurrent cardiovascular events. In our study, rivaroxaban significantly reduced the primary efficacy end point of death from cardiovascular causes, myocardial infarction, or stroke in patients with...
Rivaroxaban and Recent Acute Coronary Syndrome

A recent acute coronary syndrome. A directionally consistent benefit was seen for the individual components of death from cardiovascular causes and myocardial infarction but not for stroke. The advantages of the addition of rivaroxaban were observed regardless of whether patients presented with a STEMI, NSTEMI, or unstable angina and across the different geographical regions. Likewise, the two doses of rivaroxaban significantly reduced the primary efficacy end point, with the twice-daily 2.5-mg dose also showing a survival benefit. In terms of safety, the two doses of rivaroxaban increased the rates of major bleeding and intracranial hemorrhage, as compared with placebo, without a significant increase in fatal bleeding. The lower dose of rivaroxaban resulted in less bleeding than the higher dose.

During the initial management of an acute coronary syndrome, parenteral anticoagulants are used in conjunction with antiplatelet agents. After hospital discharge, however, antiplatelet medications alone have served as the mainstay of antithrombotic therapy. Although secondary prevention with oral anticoagulation has shown cardiovascular benefits, the regimens have been limited by a number of constraints. We tested the anticoagulant rivaroxaban in patients with a recent acute coronary syndrome, and the study met its primary efficacy endpoint. The factor Xa inhibitor rivaroxaban has predictable pharmacokinetics and has not been associated with an increased risk of hepatotoxicity. Rivaroxaban has been evaluated in a number of clinical settings, including the prevention and treatment of venous thromboembolism and stroke prophylaxis in atrial fibrillation.

Our study was specifically designed to test two low doses of rivaroxaban in patients with a recent acute coronary syndrome. The 2.5-mg dose of rivaroxaban reduced the primary efficacy end point, as compared with placebo, and also reduced the risk of death from cardiovascular causes (relative reduction, 34%; absolute reduction, 1.4 percentage points) and from any cause.
The 2.5-mg dose of rivaroxaban showed a nonsignificant but directionally consistent benefit for myocardial infarction and a significant reduction in the risk of stent thrombosis, a finding that suggests that enhanced thrombin activity may play a role in these events. Thus, when viewed as long-term therapy after an acute coronary syndrome, the addition of very-low-dose rivaroxaban appears to be an attractive option.

Previous studies have tested rivaroxaban against an active comparator (e.g., warfarin or enoxaparin), and in general the bleeding rates between the two study groups have been similar. In our study, in which the comparator was placebo, the rates of bleeding were significantly higher in patients re-

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### Figure 2. Risks of the Primary Efficacy End Point, According to Major Subgroup.

The primary efficacy end point consists of death from cardiovascular causes, myocardial infarction, or stroke. Among the patients who had a history of stroke or transient ischemic attack, 198 received aspirin only and 217 received aspirin and a thienopyridine. The latter was a deviation from the study protocol. NSTEMI denotes non–ST-segment elevation myocardial infarction, STEMI ST-segment elevation myocardial infarction, and TIA transient ischemic attack.
Receiving 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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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**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.
Events in Atrial Fibrillation (ARISTOTLE) trial (NCT00412984) and in those with an acute coronary syndrome in APPRAISE-2. In the trials evaluating rivaroxaban for stroke prophylaxis in patients with atrial fibrillation or treatment of venous thromboembolism, most patients received at least 20 mg per day. In our study, the tested doses of rivaroxaban were a quarter or one half of the 20-mg dose. Ultimately, the lower dose of rivaroxaban, but not the higher dose, resulted in a survival benefit. This observation is explained in part by the numerical increase in fatal bleeding associated with the higher dose of rivaroxaban. However, other consequences of nonfatal bleeding may also have contributed to this finding. Within ATLAS ACS–TIMI 46 and RUBY-1 (a phase 2 evaluation of darexaban vs. placebo in patients after an acute coronary syndrome) (NCT00994292), inverse dose–response relationships with cardiovascular events were also observed. Therefore, our study, in conjunction with the important observations from APPRAISE-2, ATLAS ACS-TIMI 46, and RUBY-1 suggests that in patients with a recent acute coronary syndrome, very low doses of an oral anticoagulant appear to be most favorable.

In conclusion, treatment with rivaroxaban reduced the risk of death from cardiovascular causes, myocardial infarction, or stroke in patients across the spectrum of acute coronary syndromes. This beneficial effect was accompanied by increased rates of bleeding. However, there was no significant increase in the rate of fatal bleeding, and the twice-daily 2.5-mg dose of rivaroxaban reduced overall and cardiovascular mortality. Thus, the addition of very-low-dose anticoagulation with rivaroxaban may represent a new treatment strategy in patients with a recent acute coronary syndrome.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

APPENDIX

The authors’ affiliations are as follows: the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Brigham and Women’s Hospital and Harvard Medical School (L.L.M., E.B., S.D.W., D.L.B., S.A.M., C.M.G.); the Veterans Affairs Boston Healthcare System (D.L.B.) — all in Boston; the Department of Cardiology, University Hospital Jean Minjoz, Besançon, France (J.-P.B.); University Hospital Freiburg, Freiburg (C.B.), and Bayer Healthcare, Wuppertal (N.C.-B.) — both in Germany; Johnson & Johnson Pharmaceutical Research and Development, Raritan (P.B., A.N.P., X.S.), and Newark Beth Israel Medical Center, Newark (M.C.) — both in New Jersey; the Centre for Cardiovascular Science, Edinburgh University and Royal Infirmary, Edinburgh (K.A.A.F.); Tokai University School of Medicine, Tokyo (S.G.); the University of Vermont/Fletcher Allen Health Care, Burlington (D.S.); and Radboud University Nijmegen Medical Center, Nijmegen, the Netherlands (F.W.A.V.).

REFERENCES

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