

ORIGINAL ARTICLE

Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*

ABSTRACT

BACKGROUND

Appropriate antithrombotic regimens for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) are unclear.

METHODS

In an international trial with a two-by-two factorial design, we randomly assigned patients with atrial fibrillation who had an acute coronary syndrome or had undergone PCI and were planning to take a P2Y₁₂ inhibitor to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo for 6 months. The primary outcome was major or clinically relevant nonmajor bleeding. Secondary outcomes included death or hospitalization and a composite of ischemic events.

RESULTS

Enrollment included 4614 patients from 33 countries. There were no significant interactions between the two randomization factors on the primary or secondary outcomes. Major or clinically relevant nonmajor bleeding was noted in 10.5% of the patients receiving apixaban, as compared with 14.7% of those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81; $P < 0.001$ for both noninferiority and superiority), and in 16.1% of the patients receiving aspirin, as compared with 9.0% of those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; $P < 0.001$). Patients in the apixaban group had a lower incidence of death or hospitalization than those in the vitamin K antagonist group (23.5% vs. 27.4%; hazard ratio, 0.83; 95% CI, 0.74 to 0.93; $P = 0.002$) and a similar incidence of ischemic events. Patients in the aspirin group had an incidence of death or hospitalization and of ischemic events that was similar to that in the placebo group.

CONCLUSIONS

In patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y₁₂ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in the incidence of ischemic events than regimens that included a vitamin K antagonist, aspirin, or both. (Funded by Bristol-Myers Squibb and Pfizer; AUGUSTUS ClinicalTrials.gov number, NCT02415400.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Lopes at the Duke Clinical Research Institute, 200 Morris St., Durham, NC 27701, or at renato.lopes@duke.edu.

*A complete list of the investigators in the AUGUSTUS trial is provided in the Supplementary Appendix, available at NEJM.org.

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CHOOSING ANTITHROMBOTIC THERAPY for patients with atrial fibrillation who have an acute coronary syndrome or have undergone percutaneous coronary intervention (PCI) is challenging. Oral anticoagulation is indicated to prevent stroke and systemic embolism in patients with atrial fibrillation but has not been shown to prevent stent thrombosis and is generally not indicated for secondary prevention after acute coronary syndrome.¹⁻³ Dual antiplatelet therapy is proven to reduce the incidence of recurrent ischemic events and stent thrombosis but is less effective in reducing the incidence of cardioembolic stroke associated with atrial fibrillation.^{2,4} The combination of antithrombotic agents, particularly triple therapy with oral anticoagulation and dual antiplatelet therapy, increases the risk of bleeding.⁵⁻⁷ Thus, an oral antithrombotic regimen with an acceptable benefit–risk profile would be useful in the treatment of patients with atrial fibrillation and concomitant acute coronary syndrome or PCI. Regimens including non–vitamin K antagonist oral anticoagulants appear to offer a number of advantages over vitamin K antagonists, including the potential for less bleeding.⁸

Two trials evaluated standard or reduced doses of oral anticoagulants (of dabigatran and rivaroxaban, respectively) in patients with atrial fibrillation who were undergoing PCI, and both trials showed a lower incidence of bleeding with new oral anticoagulant regimens without aspirin than with vitamin K antagonist regimens that included aspirin.^{9,10} Neither trial was designed to assess whether the lower incidence of bleeding was due to the use of the standard or reduced doses of the new oral anticoagulants or to the removal of aspirin therapy. We conducted the AUGUSTUS trial (a two-by-two factorial, randomized, controlled clinical trial) to assess the safety and efficacy of standard-dose apixaban as compared with a vitamin K antagonist and of low-dose aspirin as compared with placebo, on a background of concomitant P2Y₁₂ inhibitor therapy for 6 months in patients with atrial fibrillation and recent acute coronary syndrome or PCI.

METHODS

TRIAL OVERSIGHT

The trial was designed and led by an academic steering committee whose members were respon-

sible for the conduct of the trial. The Duke Clinical Research Institute (DCRI, Durham, NC) was the academic coordinating center. The trial was sponsored by Bristol-Myers Squibb and Pfizer. The trial protocol (available with the full text of this article at NEJM.org) and all subsequent amendments were approved by national regulatory agencies in participating countries and by institutional review boards or ethics committees at participating sites. An independent data and safety monitoring board reviewed unblinded patient-level data at regular intervals during the trial. Although Bristol-Myers Squibb assisted with data management, all the statistical analyses were performed independently at the DCRI. The initial draft of the manuscript was written by the first author and revised on the basis of comments from the other authors. All the authors vouch for the adherence of the trial to the protocol, and the first, second, and last authors vouch for the accuracy and completeness of the data and analysis. No one who is not an author contributed to writing the manuscript. The committee members and participating investigators are listed in the Supplementary Appendix, available at NEJM.org.

DESIGN

The trial rationale and design have been published previously.¹¹ In brief, AUGUSTUS was a prospective, multicenter, two-by-two factorial, randomized clinical trial comparing apixaban with a vitamin K antagonist and comparing aspirin with placebo in patients with atrial fibrillation who had a recent acute coronary syndrome or underwent PCI (or both).

TRIAL POPULATION

Patients who met all the following criteria were eligible for inclusion: an age of at least 18 years; previous, persistent, permanent, or paroxysmal atrial fibrillation and planned long-term use of an oral anticoagulant; recent acute coronary syndrome or PCI; and planned use of a P2Y₁₂ inhibitor for at least 6 months. Patients who were using anticoagulation for other conditions (e.g., prosthetic valves, venous thromboembolism, and mitral stenosis) were not eligible. Other key exclusion criteria were severe renal insufficiency, a history of intracranial hemorrhage, recent or planned coronary-artery bypass graft surgery, coagulopathy or ongoing bleeding, and contraindication to

a vitamin K antagonist, apixaban, all P2Y₁₂ inhibitors, or aspirin. All the patients provided written informed consent before enrollment.

Stroke and bleeding risks were assessed with the use of two scores (Table S1 in the Supplementary Appendix). CHA₂DS₂-VASc scores reflect the risk of stroke among patients with atrial fibrillation who are not receiving anticoagulant therapy; scores range from 0 to 9, with higher scores indicating greater risk. HAS-BLED scores reflect the risk of bleeding among patients with atrial fibrillation who are receiving anticoagulant therapy; scores range from 0 to 9, with higher scores indicating greater risk.

TRIAL REGIMEN

Patients underwent randomization within 14 days after having an acute coronary syndrome or undergoing PCI, with explicit guidance provided to enroll eligible patients and start the trial regimen as soon as possible after the index event once parenteral anticoagulation had been stopped. To be eligible, patients were required to be planning to use an approved P2Y₁₂ inhibitor for at least 6 months. The choice of P2Y₁₂ inhibitor was left to the discretion of the treating physician.

After enrollment into this trial that had a two-by-two factorial design, patients were randomly assigned by means of an interactive voice-response system to receive apixaban or a vitamin K antagonist and to receive aspirin or matching placebo. The treatment regimen comparing apixaban with a vitamin K antagonist was open-label; however, the regimen comparing aspirin with matching placebo was double-blind.

Randomization was stratified according to indication (acute coronary syndrome or PCI) at enrollment. In accordance with the apixaban label instructions for stroke prevention in patients with atrial fibrillation, patients who had been randomly assigned to receive apixaban were directed to take 5 mg twice daily or to take 2.5 mg twice daily if they met two or more of the following dose-reduction criteria: were at least 80 years of age, had a weight of no more than 60 kg, or had a creatinine level of at least 1.5 mg per deciliter (133 μmol per liter). Patients who had been randomly assigned to receive a vitamin K antagonist had the dose adjusted to reach a target international normalized ratio (INR) within a range of 2.0 to 3.0. Regarding the comparison of aspirin with placebo, patients

received aspirin at a dose of 81 mg or a matching placebo once daily. After 6 months, patients were transitioned from their two trial interventions to receive antiplatelet and anticoagulant therapy according to the local standard of care.

OUTCOMES

All the patients who underwent randomization were to be followed through 6 months, with an additional visit at month 7 to record transitions in antithrombotic therapy and associated outcomes. The primary outcome for both factorial comparisons was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis (ISTH). ISTH major bleeding was defined as bleeding that resulted in death, occurred in a critical organ (intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, intramuscular with compartment syndrome, or pericardial), or was associated with either a decrease in the hemoglobin level of at least 2 g per deciliter or a transfusion of at least 2 units of packed red cells.¹² Clinically relevant nonmajor bleeding was defined as bleeding that resulted in hospitalization, medical or surgical intervention for bleeding, an unscheduled clinic visit, or a change in physician-directed antithrombotic therapy. Bleeding was also classified according to the Global Use of Strategies to Open Occluded Arteries (GUSTO) and Thrombolysis in Myocardial Infarction (TIMI) definitions (see the Supplementary Appendix).^{13,14}

Secondary outcomes included the composite of death or hospitalization and the composite of death or ischemic events (stroke, myocardial infarction, stent thrombosis [definite or probable], or urgent revascularization). Exploratory outcomes included individual components of the secondary outcomes. All bleeding and ischemic events (except for urgent revascularization) were independently adjudicated by the clinical-events classification committee at the DCRI, whose members were unaware of the trial-group assignments.

STATISTICAL ANALYSIS

The trial used a factorial design to evaluate two independent hypotheses. One hypothesis was that apixaban would be at least noninferior, and possibly superior, to a vitamin K antagonist with regard to the outcome of ISTH major or clinically relevant nonmajor bleeding in patients with atrial

fibrillation and recent acute coronary syndrome or PCI and planned concomitant antiplatelet therapy. The second hypothesis was that single antiplatelet therapy with a P2Y₁₂ inhibitor would be superior to dual antiplatelet therapy with a P2Y₁₂ inhibitor and aspirin with regard to the outcome of ISTH major or clinically relevant nonmajor bleeding in patients with atrial fibrillation and recent acute coronary syndrome or PCI and planned concomitant anticoagulant therapy.

The population for the primary outcome analysis included all the patients who underwent randomization and received at least one dose of a trial drug or placebo. Events were counted from the beginning of receipt of the trial intervention through 2 days after the permanent discontinuation of the relevant drug or placebo. The population for the two secondary outcome analyses included all the patients who underwent randomization according to the randomized groups, and all events were counted from randomization through the 6-month visit.

Using a log-rank test to compare apixaban with a vitamin K antagonist, we estimated that 357 patients with primary-outcome events among 4600 patients who had undergone randomization would provide the trial with 77% power to detect a prespecified noninferiority relative margin of 1.2 at the upper one-sided 97.5% level of confidence, assuming a 1% annual loss to follow-up. Interaction between the two randomization factors (oral anticoagulant and aspirin) on the primary and secondary outcomes was assessed, with stratification according to the index event. If there was no significant interaction, the two factors were analyzed independently.

If noninferiority of apixaban as compared with a vitamin K antagonist was met, we used a prespecified hierarchical testing procedure by sequentially testing for the superiority of apixaban over a vitamin K antagonist for the following outcomes (in order): the composite of ISTH major or clinically relevant nonmajor bleeding (primary safety outcome), the composite of death or hospitalization, and the composite of death or ischemic events. If superiority was not met in any test, P values would not be reported for this or subsequent outcomes. P values were calculated for interaction tests of prespecified subgroups. Hierarchical testing was performed in the same way for aspirin as compared with placebo, except that the initial noninferiority test on the primary

outcome was omitted. All P values for superiority were two-sided.

The analysis of the time to the first primary safety outcome was performed with the use of a Cox proportional-hazards model that included anticoagulant-regimen group (apixaban or vitamin K antagonist) as a covariate, stratified according to the index event (any acute coronary syndrome or elective PCI) and the antiplatelet-regimen group (aspirin or placebo). A similar comparison was performed for the time to the first primary safety outcome for the comparison of aspirin with placebo. Denominators for presented percentages represent nonmissing values, unless otherwise indicated. All the statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From September 2015 through April 2018, a total of 4614 patients from 492 sites in 33 countries were randomly assigned to receive open-label apixaban or a vitamin K antagonist and to receive double-blind aspirin or matching placebo. The median time from the index event to randomization was 6 days (interquartile range, 3 to 10).

The characteristics of the patients at baseline were well balanced among the trial groups (Table 1). The median age among all the patients was 70.7 years, and 29.0% of the patients were women. The prevalence of hypertension involving the use of medication; diabetes; heart failure; and previous stroke, transient ischemic attack, or thromboembolism was similar in the trial groups. Among the patients who underwent randomization, 1714 of 4595 (37.3%) had acute coronary syndrome and underwent PCI, 1097 (23.9%) had medically managed acute coronary syndrome, and 1784 (38.8%) underwent elective PCI. The median CHA₂DS₂-VASc score was 4 (interquartile range, 3 to 5), and the median HAS-BLED score was 3 (interquartile range, 2 to 3). Less than one third of the patients (29.0%) had previous use of a vitamin K antagonist for 30 consecutive days at any time, and approximately half the patients (49.0%) had recently used an oral anticoagulant of any kind, which was discontinued before they underwent randomization in the trial.

Clopidogrel was the P2Y₁₂ inhibitor used in 92.6% of the patients. A total of 229 of 2290 pa-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Apixaban (N = 2306)	Vitamin K Antagonist (N = 2308)	Aspirin (N = 2307)	Aspirin-Matched Placebo (N = 2307)	Total (N = 4614)
Age — yr					
Median	70.4	70.9	70.8	70.6	70.7
Interquartile range	64.1–77.2	64.3–77.2	64.4–77.3	63.8–77.2	64.2–77.2
Female sex — no. (%)	670 (29.1)	667 (28.9)	696 (30.2)	641 (27.8)	1337 (29.0)
Race or ethnic group — no./total no. (%)†					
White	2097/2282 (91.9)	2087/2275 (91.7)	2082/2276 (91.5)	2102/2281 (92.2)	4184/4557 (91.8)
Black	29/2282 (1.3)	30/2275 (1.3)	29/2276 (1.3)	30/2281 (1.3)	59/4557 (1.3)
Asian	70/2282 (3.1)	70/2275 (3.1)	74/2276 (3.3)	66/2281 (2.9)	140/4557 (3.1)
Native American	10/2282 (0.4)	6/2275 (0.3)	6/2276 (0.3)	10/2281 (0.4)	16/4557 (0.4)
Other	76/2282 (3.3)	82/2275 (3.6)	85/2276 (3.7)	73/2281 (3.2)	158/4557 (3.5)
Serum creatinine — no./total no. (%)‡					
<1.5 mg/dl	2101/2274 (92.4)	2051/2258 (90.8)	2078/2260 (91.9)	2074/2272 (91.3)	4152/4532 (91.6)
≥1.5 mg/dl	173/2274 (7.6)	207/2258 (9.2)	182/2260 (8.1)	198/2272 (8.7)	380/4532 (8.4)
CHA ₂ DS ₂ -VASC score¶	3.9±1.6	4.0±1.6	3.9±1.6	3.9±1.6	3.9±1.6
HAS-BLED score¶	2.9±1.0	2.9±0.9	2.8±0.9	2.9±1.0	2.9±0.9
Hypertension leading to medication use — no. (%)	2042 (88.6)	2031 (88.0)	2031 (88.0)	2042 (88.5)	4073 (88.3)
Heart failure — no. (%)	975 (42.3)	998 (43.2)	982 (42.6)	991 (43.0)	1973 (42.8)
Diabetes mellitus — no. (%)	842 (36.5)	836 (36.2)	842 (36.5)	836 (36.2)	1678 (36.4)
Stroke, TIA, or thromboembolism — no./total no. (%)	326/2289 (14.2)	307/2292 (13.4)	297/2289 (13.0)	336/2292 (14.7)	633/4581 (13.8)
Concomitant P2Y ₁₂ inhibitor at randomization — no./total no. (%)					
Clopidogrel	2105/2253 (93.4)	2060/2243 (91.8)	2075/2253 (92.1)	2090/2243 (93.2)	4165/4496 (92.6)
Prasugrel	27/2253 (1.2)	24/2243 (1.1)	31/2253 (1.4)	20/2243 (0.9)	51/4496 (1.1)
Ticagrelor	121/2253 (5.4)	159/2243 (7.1)	147/2253 (6.5)	133/2243 (5.9)	280/4496 (6.2)
Previous use of oral anticoagulant — no. (%)	1192 (51.7)	1070 (46.4)	1132 (49.1)	1130 (49.0)	2262 (49.0)
Qualifying index event — no./total no. (%)					
Acute coronary syndrome and PCI	873/2297 (38.0)	841/2298 (36.6)	844/2293 (36.8)	870/2302 (37.8)	1714/4595 (37.3)
Medically managed acute coronary syndrome	547/2297 (23.8)	550/2298 (23.9)	547/2293 (23.9)	550/2302 (23.9)	1097/4595 (23.9)
Elective PCI	877/2297 (38.2)	907/2298 (39.5)	902/2293 (39.3)	882/2302 (38.3)	1784/4595 (38.8)
No. of days from acute coronary syndrome or PCI to randomization**	6.7±4.2	6.6±4.2	6.7±4.3	6.5±4.1	6.6±4.2

* Plus-minus values are means ±SD. The characteristics of the patients at baseline were well balanced among the trial groups. PCI denotes percutaneous coronary intervention, and TIA transient ischemic attack.

† Race or ethnic group was determined by the investigator and recorded on the case-report form.

‡ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

§ CHA₂DS₂-VASC scores reflect the risk of stroke, with values ranging from 0 to 9 and with higher scores indicating greater risk (Table S1 in the Supplementary Appendix).

¶ HAS-BLED scores reflect the risk of major bleeding, with values ranging from 0 to 9 and with higher scores indicating greater risk (Table S1 in the Supplementary Appendix).

|| Shown are the numbers of patients who discontinued use of any oral anticoagulant on or before the date of randomization.

** If the patient both had acute coronary syndrome and underwent PCI within 14 days before randomization, the date of acute coronary syndrome was used.

tients (10.0%) who had been randomly assigned to receive apixaban received the dose of 2.5 mg twice daily. The median percentage of time in the therapeutic range, as calculated by the Rosendaal method,¹⁵ was 59% among patients assigned to receive a vitamin K antagonist (Table S2 in the Supplementary Appendix). The median percentage of time that patients assigned to a vitamin K antagonist had an INR above 3.0 was 3%, and the median percentage of time with an INR below 2.0 was 23% (Table S2 in the Supplementary Appendix).

Among the patients receiving oral anticoagulation, 12.7% stopped apixaban and 13.8% stopped the vitamin K antagonist before completion of the trial. Among the patients receiving aspirin or placebo, 16.9% stopped aspirin and 14.8% stopped placebo before completion of the trial (Fig. 1). A total of 13 patients (0.3%) were lost to follow-up for vital status, and the proportions were balanced among the groups (Fig. 1).

BLEEDING

No significant interaction was noted between the two randomization factors with regard to the primary outcome ($P=0.64$ for interaction) (Table S3 in the Supplementary Appendix). At 6 months, 241 of 2290 patients (10.5%) receiving apixaban had an ISTH major or clinically relevant nonmajor bleeding event, as compared with 332 of 2259 (14.7%) receiving a vitamin K antagonist, resulting in an event rate per 100 patient-years that was significantly lower among patients receiving apixaban than among those receiving a vitamin K antagonist (hazard ratio, 0.69; 95% confidence interval [CI], 0.58 to 0.81), which met the prespecified criteria for both noninferiority ($P<0.001$) and superiority ($P<0.001$) (Fig. 2A and Table 2). The number needed to treat over a period of 6 months to avoid one ISTH major or clinically relevant nonmajor bleeding event with apixaban instead of a vitamin K antagonist was 24.

In the antiplatelet-regimen comparison, 367 of 2277 patients (16.1%) receiving aspirin had an ISTH major or clinically relevant nonmajor bleeding event, as compared with 204 of 2279 (9.0%) receiving placebo. The event rate was significantly higher among those receiving aspirin than among those receiving placebo (hazard ratio, 1.89; 95% CI, 1.59 to 2.24; $P<0.001$) (Fig. 2B and Table 2). The number needed to harm over a period of 6 months

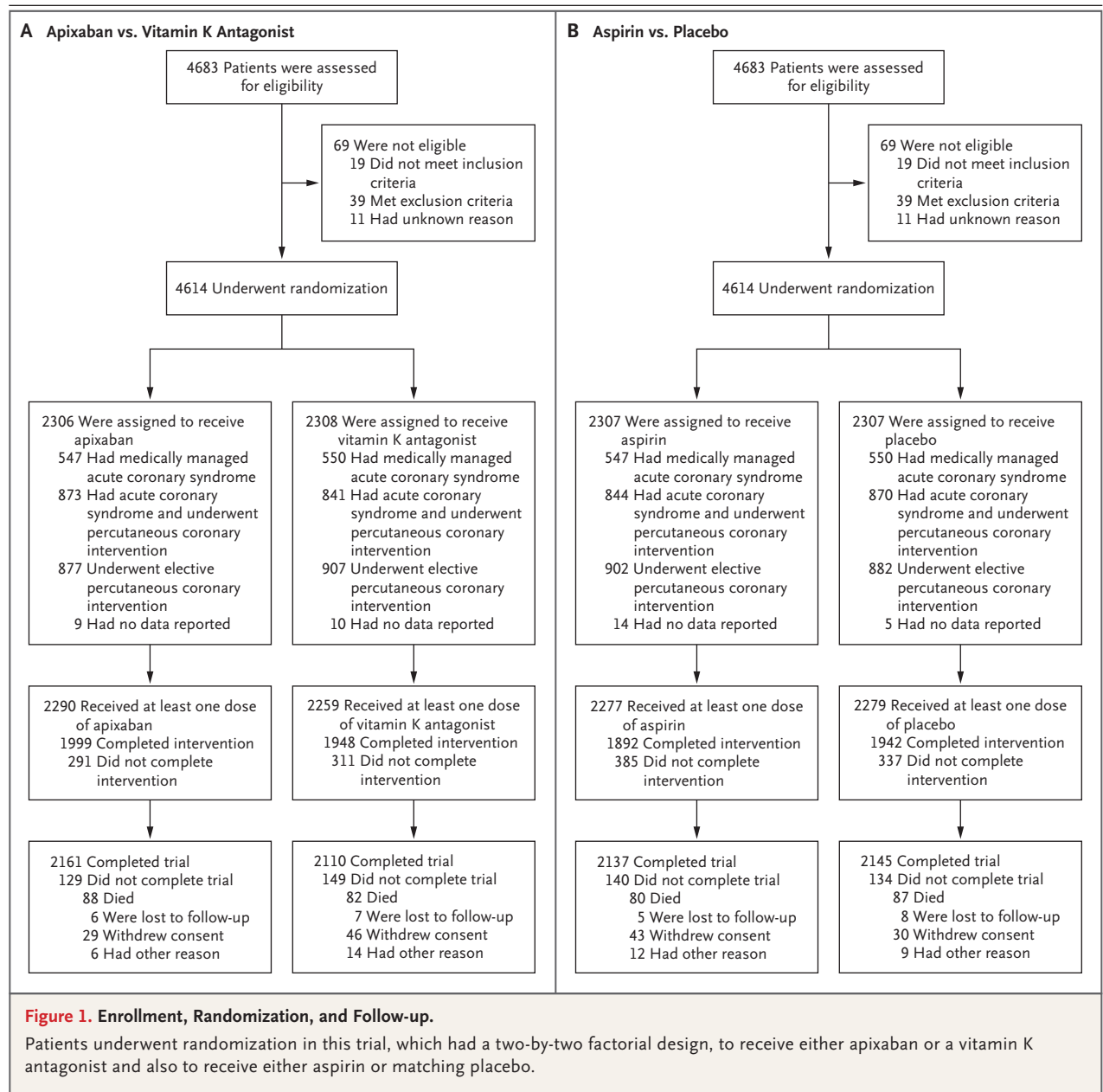
to cause one ISTH major or clinically relevant nonmajor bleeding event with aspirin instead of placebo was 14.

The percentage of patients with a primary bleeding outcome event was highest among those receiving a vitamin K antagonist and aspirin (18.7%) and lowest among those receiving apixaban and placebo (7.3%) (Fig. 2C, and Table S4A in the Supplementary Appendix). Similar effects were observed with regard to major bleeding and to bleeding assessed with the use of other bleeding scales (Table 3). The effects of apixaban as compared with a vitamin K antagonist and of aspirin as compared with placebo were generally consistent across prespecified subgroups with regard to bleeding events (Fig. S1A and S1B in the Supplementary Appendix).

DEATH OR HOSPITALIZATION

No significant interaction was observed between the two randomization factors with regard to death or hospitalization ($P=0.21$ for interaction) (Table S3 in the Supplementary Appendix). At 6 months, 541 patients (23.5%) who had been assigned to receive apixaban had died or had been hospitalized, as compared with 632 (27.4%) who had been assigned to receive a vitamin K antagonist (Table 2). The event rate per 100 patient-years for death or hospitalization at 6 months was lower among patients assigned to receive apixaban than among those assigned to receive a vitamin K antagonist (hazard ratio, 0.83; 95% CI, 0.74 to 0.93; $P=0.002$) (Fig. 3A). The difference between groups was driven by a lower incidence of hospitalization (518 patients [22.5%] in the apixaban group vs. 607 [26.3%] in the vitamin K antagonist group) since the frequencies of death were similar. The number needed to treat over a period of 6 months to avoid one death or hospitalization with apixaban instead of a vitamin K antagonist was 26.

In the antiplatelet-regimen comparison, 604 patients (26.2%) who had been assigned to receive aspirin died or were hospitalized, as compared with 569 (24.7%) who had been assigned to receive placebo (Table 2). Patients who had been assigned to receive aspirin had an incidence of death or hospitalization at 6 months that was similar to that among patients assigned to receive placebo (hazard ratio, 1.08; 95% CI, 0.96 to 1.21) (Fig. 3B). The cumulative incidence of death or hospitalization at 6 months was highest among patients

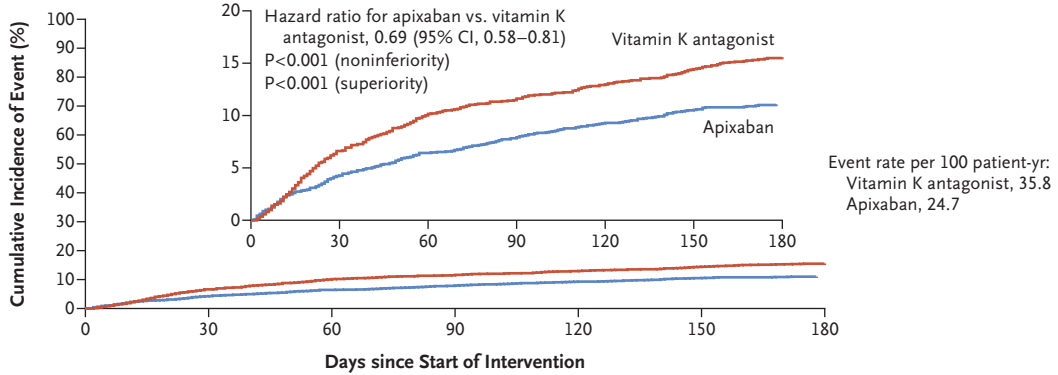


who had been assigned to receive a vitamin K antagonist and aspirin (27.5%) and lowest among those assigned to receive apixaban and placebo (22.0%) (Fig. 3C, and Table S4B in the Supplementary Appendix). The effects of apixaban as compared with a vitamin K antagonist and of aspirin as compared with placebo were generally consistent across prespecified subgroups with regard to death or hospitalization (Fig. S2A and S2B in the Supplementary Appendix).

ISCHEMIC EVENTS

No significant interaction was found between the two randomization factors with regard to death or ischemic events ($P=0.28$ for interaction) (Table S3 in the Supplementary Appendix). At 6 months, 154 patients (6.7%) who had been assigned to receive apixaban had died or had had an ischemic event — including myocardial infarction, definite or probable stent thrombosis, stroke, or urgent revascularization — as compared with 163 (7.1%)

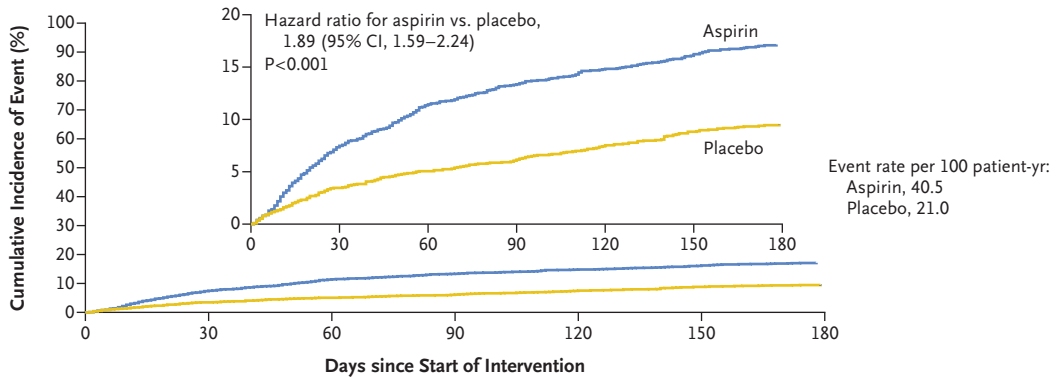
A Primary Outcome — Apixaban vs. Vitamin K Antagonist



No. at Risk

Vitamin K antagonist	2259	1984	1861	1795	1736	1686	1079
Apixaban	2290	2110	2019	1957	1902	1858	1037

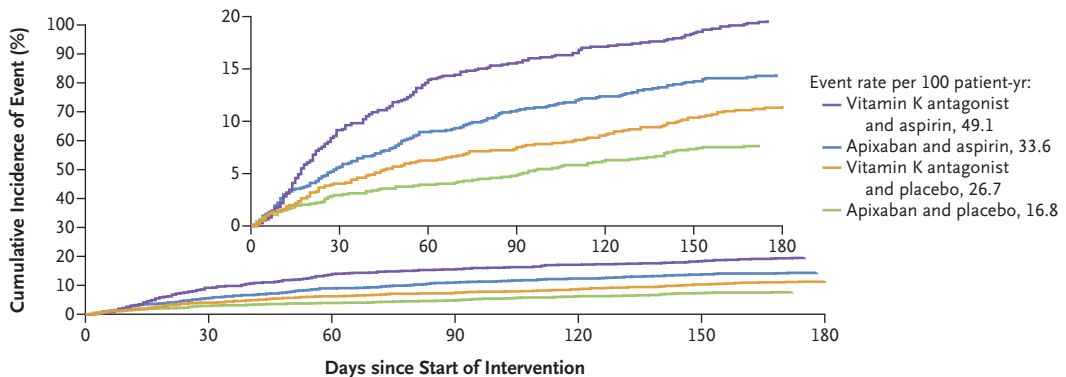
B Primary Outcome — Aspirin vs. Placebo



No. at Risk

Aspirin	2277	2003	1863	1789	1717	1674	962
Placebo	2279	2095	2006	1941	1880	1824	1079

C Primary Outcome, According to Intervention Combination



No. at Risk

Vitamin K antagonist and aspirin	1123	962	881	838	800	776	467
Apixaban and aspirin	1145	1036	975	937	903	880	485
Vitamin K antagonist and placebo	1126	1007	947	917	883	851	528
Apixaban and placebo	1143	1075	1044	1007	975	947	536

Figure 2 (facing page). Kaplan–Meier Curves for Primary Outcome of Major or Clinically Relevant Nonmajor Bleeding.

The primary outcome was major or clinically relevant nonmajor bleeding as defined by the International Society on Thrombosis and Haemostasis. Insets show the same data on an enlarged y axis.

who had been assigned to receive a vitamin K antagonist (Table 2). In the antiplatelet-regimen comparison, 149 patients (6.5%) who had been assigned to receive aspirin died or had an ischemic event, as compared with 168 (7.3%) who had been

assigned to receive placebo (Table 2). This difference was not significant, but more ischemic events occurred in the placebo group.

The overall event rates per 100 patient-years for death or ischemic events were similar in the anticoagulant-regimen and antiplatelet-regimen comparisons (Table 3). The event rate per 100 patient-years for stroke was lower among patients receiving apixaban than among those receiving a vitamin K antagonist (hazard ratio, 0.50; 95% CI, 0.26 to 0.97) (Table 3). The effects of apixaban as compared with a vitamin K antagonist and of aspirin as compared with placebo were generally consistent across prespecified subgroups with regard to

Table 2. Primary Safety and Secondary Efficacy Outcomes.*

Outcome	Apixaban	Vitamin K Antagonist	Hazard Ratio (95% CI)	P Value for Superiority
Anticoagulation-regimen comparison				
ISTH major or clinically relevant nonmajor bleeding†				
No. of patients with event/total no. (%)	241/2290 (10.5)	332/2259 (14.7)	—	—
Event rate per 100 patient-yr	24.7	35.8	0.69 (0.58–0.81)	<0.001
Death or hospitalization				
No. of patients with event/total no. (%)	541/2306 (23.5)	632/2308 (27.4)	—	—
Event rate per 100 patient-yr	57.2	69.2	0.83 (0.74–0.93)	0.002
Death or ischemic event‡				
No. of patients with event/total no. (%)	154/2306 (6.7)	163/2308 (7.1)	—	—
Event rate per 100 patient-yr	14.3	15.3	0.93 (0.75–1.16)	NS
Antiplatelet-regimen comparison				
	Aspirin	Placebo		
ISTH major or clinically relevant nonmajor bleeding				
No. of patients with event/total no. (%)	367/2277 (16.1)	204/2279 (9.0)	—	—
Event rate per 100 patient-yr	40.5	21.0	1.89 (1.59–2.24)	<0.001
Death or hospitalization§				
No. of patients with event/total no. (%)	604/2307 (26.2)	569/2307 (24.7)	—	—
Event rate per 100 patient-yr	65.7	60.6	1.08 (0.96–1.21)	NS
Death or ischemic event				
No. of patients with event/total no. (%)	149/2307 (6.5)	168/2307 (7.3)	—	—
Event rate per 100 patient-yr	13.9	15.7	0.89 (0.71–1.11)	NT

* The hazard ratios were calculated by the Cox proportional-hazards model for time to the first event, stratified according to indication at enrollment and either the antiplatelet regimen (in the analysis of the anticoagulant-regimen comparison) or the anticoagulant regimen (in the analysis of the antiplatelet-regimen comparison). All P values for superiority are two-sided. ISTH denotes International Society on Thrombosis and Haemostasis, NS not significant, and NT not tested.

† The result of the noninferiority test comparing the time to the first primary safety event in the apixaban group with that in the vitamin K antagonist group was significant ($P < 0.001$).

‡ This analysis had the first nonsignificant result in the hierarchical testing procedure for the outcomes assessed in the anticoagulant-regimen comparison.

§ This analysis had the first nonsignificant result in the hierarchical testing procedure for the outcomes assessed in the antiplatelet-regimen comparison.

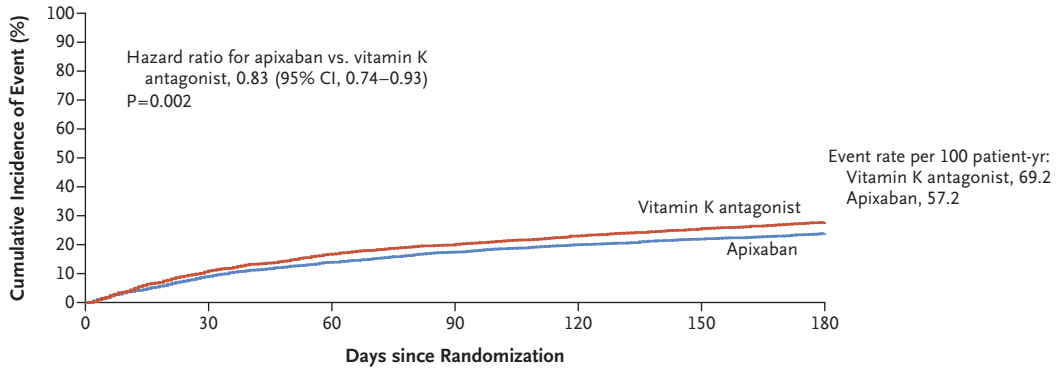
Table 3. Additional Safety and Efficacy Outcomes of Interest.*

Outcome	Anticoagulant-Regimen Comparison			Antiplatelet-Regimen Comparison		
	Apixaban	Vitamin K Antagonist	Hazard Ratio (95% CI)	Aspirin	Placebo	Hazard Ratio (95% CI)
Safety outcomes						
No. of patients in analysis	2290	2259		2277	2279	
ISTH major bleeding						
No. of patients with event (%)	69 (3.0)	104 (4.6)	—	108 (4.7)	65 (2.9)	—
Event rate per 100 patient-yr	6.7	10.5	0.64 (0.47–0.86)	11.1	6.5	1.70 (1.25–2.31)
Clinically relevant nonmajor bleeding						
No. of patients with event (%)	180 (7.9)	246 (10.9)	—	275 (12.1)	148 (6.5)	—
Event rate per 100 patient-yr	18.2	26.1	0.69 (0.57–0.84)	30.0	15.2	1.93 (1.58–2.36)
Intracranial hemorrhage						
No. of patients with event (%)	5 (0.2)	13 (0.6)	—	8 (0.4)	10 (0.4)	—
Event rate per 100 patient-yr	0.5	1.3	0.39 (0.14–1.12)	0.8	1.0	0.82 (0.32–2.07)
GUSTO severe or moderate bleeding						
No. of patients with event (%)	41 (1.8)	68 (3.0)	—	68 (3.0)	40 (1.8)	—
Event rate per 100 patient-yr	4.0	6.8	0.58 (0.39–0.86)	6.9	4.0	1.72 (1.17–2.55)
GUSTO severe bleeding						
No. of patients with event (%)	5 (0.2)	8 (0.4)	—	7 (0.3)	6 (0.3)	—
Event rate per 100 patient-yr	0.5	0.8	0.59 (0.19–1.81)	0.7	0.6	1.19 (0.40–3.53)
GUSTO moderate bleeding						
No. of patients with event (%)	37 (1.6)	64 (2.8)	—	63 (2.8)	37 (1.6)	—
Event rate per 100 patient-yr	3.6	6.4	0.56 (0.37–0.84)	6.4	3.7	1.73 (1.15–2.59)
TIMI major or minor bleeding						
No. of patients with event (%)	96 (4.2)	132 (5.8)	—	146 (6.4)	80 (3.5)	—
Event rate per 100 patient-yr	9.5	13.5	0.70 (0.54–0.91)	15.2	8.0	1.88 (1.43–2.47)
TIMI major bleeding						
No. of patients with event (%)	38 (1.7)	48 (2.1)	—	55 (2.4)	29 (1.3)	—
Event rate per 100 patient-yr	3.7	4.8	0.78 (0.51–1.20)	5.6	2.9	1.93 (1.23–3.03)
TIMI minor bleeding						
No. of patients with event (%)	80 (3.5)	118 (5.2)	—	126 (5.5)	71 (3.1)	—
Event rate per 100 patient-yr	7.9	12.0	0.65 (0.49–0.86)	13.1	7.1	1.82 (1.36–2.44)

Efficacy outcomes						
No. of patients in analysis	2306	2308	2307	2307	2307	
Hospitalization						
No. of patients with event (%)	518 (22.5)	607 (26.3)	—	585 (25.4)	540 (23.4)	—
Event rate per 100 patient-yr	54.8	66.5	0.83 (0.74–0.93)	63.7	57.5	1.10 (0.98–1.24)
Death						
No. of patients with event (%)	77 (3.3)	74 (3.2)	—	72 (3.1)	79 (3.4)	—
Event rate per 100 patient-yr	7.0	6.7	1.03 (0.75–1.42)	6.6	7.2	0.91 (0.66–1.26)
Death from cardiovascular causes						
No. of patients with event (%)	57 (2.5)	54 (2.3)	—	53 (2.3)	58 (2.5)	—
Event rate per 100 patient-yr	5.2	4.9	1.05 (0.72–1.52)	4.8	5.3	0.92 (0.63–1.33)
Stroke						
No. of patients with event (%)	13 (0.6)	26 (1.1)	—	20 (0.9)	19 (0.8)	—
Event rate per 100 patient-yr	1.2	2.4	0.50 (0.26–0.97)	1.8	1.7	1.06 (0.56–1.98)
Myocardial infarction						
No. of patients with event (%)	72 (3.1)	80 (3.5)	—	68 (2.9)	84 (3.6)	—
Event rate per 100 patient-yr	6.6	7.4	0.89 (0.65–1.23)	6.3	7.8	0.81 (0.59–1.12)
ARC definite or probable stent thrombosis						
No. of patients with event (%)	14 (0.6)	18 (0.8)	—	11 (0.5)	21 (0.9)	—
Event rate per 100 patient-yr	1.3	1.6	0.77 (0.38–1.56)	1.0	1.9	0.52 (0.25–1.08)
Urgent revascularization						
No. of patients with event (%)	40 (1.7)	44 (1.9)	—	37 (1.6)	47 (2.0)	—
Event rate per 100 patient-yr	3.7	4.1	0.90 (0.59–1.38)	3.4	4.3	0.79 (0.51–1.21)

* Safety outcome analyses assessed the patients on an as-treated basis, and efficacy outcome analyses assessed patients according to their randomized group assignment. The hazard ratio was calculated by the Cox proportional-hazards model for time to the first event, stratified according to the indication at enrollment and either the antiplatelet regimen (in the analysis of the anticoagulant-regimen comparison) or the anticoagulant regimen (in the analysis of the antiplatelet-regimen comparison). ARC denotes Academic Research Consortium, GUSTO Global Use of Strategies to Open Occluded Arteries, and TIMI Thrombolysis in Myocardial Infarction.

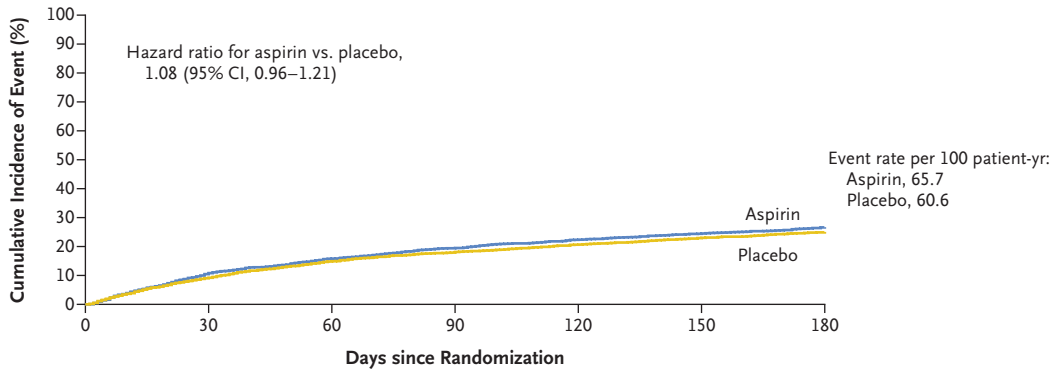
A Death or Hospitalization — Apixaban vs. Vitamin K Antagonist



No. at Risk

Vitamin K antagonist	2308	2035	1885	1805	1732	1673	1001
Apixaban	2306	2090	1965	1881	1821	1772	947

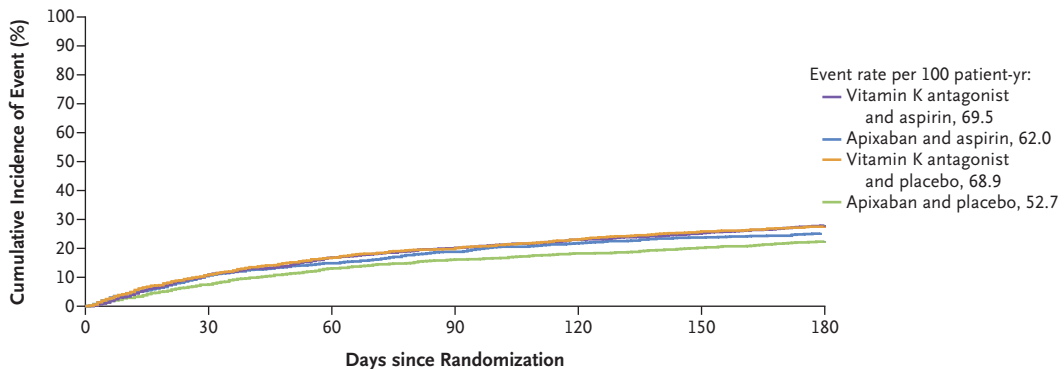
B Death or Hospitalization — Aspirin vs. Placebo



No. at Risk

Aspirin	2307	2042	1909	1822	1752	1699	951
Placebo	2307	2083	1941	1864	1801	1746	997

C Death or Hospitalization, According to Intervention Combination



No. at Risk

Vitamin K antagonist and aspirin	1154	1016	939	899	864	836	492
Apixaban and aspirin	1153	1026	970	923	888	863	459
Vitamin K antagonist and placebo	1154	1019	946	906	868	837	509
Apixaban and placebo	1153	1064	995	958	933	909	488

Figure 3. Kaplan–Meier Curves for the Composite of Death or Hospitalization.

death or ischemic events (Fig. S3A and S3B in the Supplementary Appendix).

DISCUSSION

The current trial was specifically designed to assess the independent effect of anticoagulant and antiplatelet therapy in patients with atrial fibrillation and recent acute coronary syndrome or PCI who were planning to receive a P2Y₁₂ inhibitor. Apixaban led to a lower incidence of both bleeding and the composite of death or hospitalization than did a vitamin K antagonist; the latter result was driven by a lower incidence of hospitalization. The overall incidence of ischemic events was similar in the two groups. Aspirin led to a higher incidence of bleeding than placebo, and the rates of death or hospitalization and of ischemic events were similar in the two groups. A regimen of clopidogrel plus apixaban, at the dose labeled for stroke prevention, without aspirin was not associated with excess adverse events and appeared to be effective in this high-risk group of patients.

Vitamin K antagonists have not been shown to prevent stent thrombosis,¹⁶⁻¹⁸ and dual antiplatelet therapy does not provide adequate protection against strokes related to atrial fibrillation.¹⁹⁻²¹ Observational studies have shown that combined dual antiplatelet therapy and a vitamin K antagonist (i.e., triple therapy) is associated with a high risk of bleeding.⁵⁻⁷ Although there are reasons for considering the discontinuation of aspirin therapy,²² the WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial²³ showed a reduction in both bleeding and ischemic events by discontinuing aspirin in patients receiving oral anticoagulation with a vitamin K antagonist and undergoing PCI, although the trial was small and underpowered for such an analysis.

Our results confirm and extend these results in a high-risk population of patients with atrial fibrillation by showing a lower incidence of major or clinically relevant nonmajor bleeding among patients treated without aspirin than among those treated with aspirin, but we found that the incidence of ischemic events was not significantly lower among patients who did not receive aspirin. Although the choice of P2Y₁₂ inhibitor was left to the treating physician, more than 90% of the patients were treated with clopidogrel instead of the more potent agents, which is consistent with most guidance statements. We observed a greater num-

ber of coronary ischemic events among patients who did not take aspirin than among those who did, although event rates were low and the trial was not adequately powered to assess differences in individual ischemic outcomes. Although this analysis should be considered exploratory, similar trials have shown a similar pattern of numerically more coronary ischemic events when aspirin was omitted.^{9,10} Thus, when clinicians consider aspirin as a component of antithrombotic therapy after PCI in patients with atrial fibrillation, a potential small absolute decrease in the risk of coronary ischemic events needs to be weighed against a larger absolute increase in the risk of clinically significant bleeding.

Although the new oral anticoagulants have been shown to be at least as effective as vitamin K antagonists for reducing the incidence of thromboembolic events and at least as safe as vitamin K antagonists for major bleeding in patients with atrial fibrillation, patients receiving dual antiplatelet therapy were excluded from the pivotal trials of these oral agents.^{8,24-27} The PIONEER AF-PCI trial¹⁰ compared two antithrombotic regimens, involving doses of rivaroxaban lower than the dose recommended to prevent stroke risk among patients with atrial fibrillation (rivaroxaban at a dose of 15 mg daily plus a P2Y₁₂ inhibitor or rivaroxaban at a dose of 2.5 mg twice daily plus aspirin and a P2Y₁₂ inhibitor, with a switch to rivaroxaban at a dose of 15 mg daily plus aspirin when the P2Y₁₂ inhibitor was stopped), with a vitamin K antagonist plus dual antiplatelet therapy. The incidence of bleeding was significantly lower with the two rivaroxaban regimens than with a vitamin K antagonist, and there was no significant increase in the risk of ischemic events, stroke, or stent thrombosis.¹⁰ The RE-DUAL PCI trial⁹ compared two antithrombotic regimens, using approved doses of dabigatran (150 mg twice daily or 110 mg twice daily) plus a P2Y₁₂ inhibitor, with warfarin plus dual antiplatelet therapy. Again, rates of bleeding were significantly lower with each of the dabigatran-based regimens than with warfarin plus dual antiplatelet therapy, and the risk of ischemic events was not significantly higher.⁹ Both these trials compared either lower-than-approved doses of a new oral anticoagulant with a full-dose vitamin K antagonist (target INR, 2.0 to 3.0) or strategies of double therapy (new oral agent plus P2Y₁₂ inhibitor) with traditional triple therapy (oral anticoagulant plus P2Y₁₂ inhibitor plus aspirin). Given their designs, it is impossible to determine

whether the lower risk of bleeding that was seen in the new-oral-agent groups was due to the use of the new agent, the reduced dose of the agent, or the discontinuation of aspirin.

Our trial, AUGUSTUS, confirms the safety and efficacy of apixaban, as compared with a vitamin K antagonist, at a dose recommended for patients with atrial fibrillation and shows that the effect of avoiding aspirin on the incidence of bleeding events seems to be even greater than the benefit of using apixaban instead of a vitamin K antagonist. Our results concur with the current North American guidance²⁸ of recommending a new oral anticoagulant plus a P2Y₁₂ inhibitor in this population of patients, but they contrast with recent European guidance,²⁹ which still recommends triple antithrombotic therapy in these patients. Thus, our results support the use a regimen of apixaban with a P2Y₁₂ inhibitor, most commonly clopidogrel, without aspirin in a broad population of patients with atrial fibrillation and recent acute coronary syndrome or PCI.

Among patients undergoing PCI, 5 to 8% have atrial fibrillation, complicating the choice of post-PCI antithrombotic therapy.^{30,31} Our trial included patients with acute coronary syndrome, which was managed medically or with PCI, and patients who underwent elective PCI, all of whom are at high risk for both bleeding and ischemic events. The mean time from the index event to randomization was 6.6 days; treatment decisions during this time were left to the discretion of the treating physician, and many patients probably received aspirin during this time. The median CHA₂DS₂-VASc score was 4, and the median HAS-BLED score was 3. This trial shows that, after initial stabilization of the index event, the lower rates of bleeding with apixaban than with a vitamin K antagonist and of placebo than with aspirin on a background of a P2Y₁₂ inhibitor were preserved, regardless of management strategy.

None of the three contemporary trials of the new oral anticoagulants in patients with atrial fibrillation and PCI, including AUGUSTUS, were designed to be large enough to detect small but potentially meaningful differences in the incidence of ischemic events. In the PIONEER AF-PCI trial, the ischemic event rates were similar among the groups, but the rivaroxaban doses that were tested were lower than the approved dose for stroke prevention in patients with atrial fibrillation, arousing concerns about the efficacy of these

regimens with respect to ischemic stroke.¹⁰ Although the RE-DUAL PCI trial tested doses of dabigatran that had been previously studied in the RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) trial²⁴ involving patients with atrial fibrillation, the rates of myocardial infarction and stent thrombosis were nonsignificantly higher among patients who had been randomly assigned to receive dabigatran at a dose of 110 mg twice daily without aspirin than among those who were assigned to receive warfarin plus a P2Y₁₂ inhibitor plus aspirin.⁹

Our trial used doses of apixaban with proven efficacy for stroke prevention in patients with atrial fibrillation and showed a significantly lower rate of death or hospitalization, driven by the incidence of hospitalization, and a 50% lower incidence of stroke than were observed with a vitamin K antagonist. Our trial provides reassurance that, for patients with atrial fibrillation and acute coronary syndrome or PCI who are receiving anticoagulation, the use of apixaban at a dose of 5 mg twice daily is a safe and effective regimen that is superior to a vitamin K antagonist. Finally, avoiding aspirin resulted in a 47% lower risk of bleeding than using aspirin and in a nonsignificantly higher incidence of coronary ischemic events. This finding suggests that the price for a significantly lower incidence of bleeding events without aspirin may be a modestly higher risk of coronary ischemic events.

There are limitations to our trial. The time in the therapeutic range for the patients who received a vitamin K antagonist was modestly lower than in some previous randomized trials of stroke prevention involving patients with atrial fibrillation.^{19,24-26} This finding shows real-life challenges with vitamin K antagonist treatment, especially in an international setting over a relatively short (6 month) period of time. Our trial was not designed to be large enough to detect potentially clinically important differences in less common but important individual ischemic outcomes.

In conclusion, in patients with atrial fibrillation and a recent acute coronary syndrome or PCI treated with a P2Y₁₂ inhibitor, an antithrombotic regimen that included apixaban, without aspirin, resulted in less bleeding and fewer hospitalizations without significant differences in ischemic events than regimens that included a vitamin K antagonist, aspirin, or both.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: the Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC (R.D.L., G.H., A.N.V., T.M., C.B.G., J.H.A.); Bristol-Myers Squibb, Princeton, NJ (R.A., J.L.); Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, and Cardiovascular Research Foundation, New York (R.M.); Canadian VIGOUR Centre, University of Alberta, Edmonton (S.G.G.), and the Terrence Donnelly Heart Centre, St. Michael's Hospital, University of Toronto, Toronto (S.G.G.) — both in Canada; Swiss Cardiovascular Center, Bern, Switzerland (S.W.); Vivantes Neukoelln Medical Center, Berlin (H.D.), and Heart Center Leipzig, Department of Internal Medicine–Cardiology, University of Leipzig, Leipzig (H.T.) — both in Germany; Pirogov Russian National Research Medical University, Moscow (O.A.); Instituto de Neurología Cognitiva (INECO) Neurociencias Oroño, Fundación INECO, Rosario, Argentina (M.C.B.); Hospital Israelita Albert Einstein, São Paulo (O.B.); Postgraduate Medical School, Grochowski Hospital, Warsaw, Poland (A.B.); the Department of Medical Sciences, Cardiology, and Uppsala Clinical Research Center, Uppsala University, Uppsala, Sweden (Z.H.); the National Scientific Center, Strazhesko Institute of Cardiology, Kiev, Ukraine (A.P.); University Hospitals Leuven, University of Leuven, Leuven, Belgium (P.S.); the Department of Infection, Immunity, and Cardiovascular Disease, University of Sheffield, Sheffield, United Kingdom (R.F.S.); and University of Medicine and Pharmacy Carol Davila, University and Emergency Hospital, Bucharest, Romania (D.V.).

REFERENCES

- January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol* 2019 January 21 (Epub ahead of print).
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64(24):e139-e228.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;61(4):e78-e140.
- Levenson GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2016;68:1082-115.
- Hansen ML, Sørensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med* 2010;170:1433-41.
- Lopes RD, Rao M, Simon DN, et al. Triple vs dual antithrombotic therapy in patients with atrial fibrillation and coronary artery disease. *Am J Med* 2016; 129(6):592-599.e1.
- Sørensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet* 2009;374: 1967-74.
- Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62.
- Cannon CP, Bhatt DL, Oldgren J, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med* 2017;377:1513-24.
- Gibson CM, Mehran R, Bode C, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. *N Engl J Med* 2016;375:2423-34.
- Lopes RD, Vora AN, Liaw D, et al. An open-label, 2 × 2 factorial, randomized controlled trial to evaluate the safety of apixaban vs. vitamin K antagonist and aspirin vs. placebo in patients with atrial fibrillation and acute coronary syndrome and/or percutaneous coronary intervention: rationale and design of the AUGUSTUS trial. *Am Heart J* 2018;200:17-23.
- Schulman S, Kearon C, Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of anti-hemostatic medicinal products in non-surgical patients. *J Thromb Haemost* 2005;3:692-4.
- The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329: 673-82.
- Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation* 1987;76:142-54.
- Rosendaal FR, Cannegieter SC, van der Meer FJ, Briët E. A method to determine the optimal intensity of oral anticoagulant therapy. *Thromb Haemost* 1993; 69:236-9.
- Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting: the full anticoagulation versus aspirin and ticlopidine (fantastic) study. *Circulation* 1998; 98:1597-603.
- Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. *N Engl J Med* 1998;339:1665-71.
- Rubboli A, Milandri M, Castelvetti C, Cosmi B. Meta-analysis of trials comparing oral anticoagulation and aspirin versus dual antiplatelet therapy after coronary stenting: clues for the management of patients with an indication for long-term anticoagulation undergoing coronary stenting. *Cardiology* 2005;104:101-6.
- Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet* 2006;367:1903-12.
- Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have non-valvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67.
- Mant J, Hobbs FD, Fletcher K, et al. Warfarin versus aspirin for stroke prevention in an elderly community population

- with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet* 2007;370:493-503.
22. Capodanno D, Mehran R, Valgimigli M, et al. Aspirin-free strategies in cardiovascular disease and cardioembolic stroke prevention. *Nat Rev Cardiol* 2018;15:480-96.
23. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet* 2013;381:1107-15.
24. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51.
25. Giugliano RP, Ruff CT, Braunwald E, et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104.
26. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92.
27. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91.
28. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation* 2018;138:527-36.
29. Lip GYH, Collet JP, Haude M, Huber K. Management of antithrombotic therapy in AF patients presenting with ACS and/or undergoing PCI: a summary of the joint consensus document of the European Heart Rhythm Association (EHRA), European Society of Cardiology Working Group on Thrombosis, European Association of Percutaneous Cardiovascular Inter-
- ventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), Latin America Heart Rhythm Society (LA-HRS), and Cardiac Arrhythmia Society of Southern Africa (CASSA). *Eur Heart J* 2018;39:2847-50.
30. Pérez-Gómez F, Alegría E, Berjón J, et al. Comparative effects of antiplatelet, anticoagulant, or combined therapy in patients with valvular and nonvalvular atrial fibrillation: a randomized multicenter study. *J Am Coll Cardiol* 2004;44:1557-66.
31. Wang TY, Robinson LA, Ou FS, et al. Discharge antithrombotic strategies among patients with acute coronary syndrome previously on warfarin anticoagulation: physician practice in the CRUSADE registry. *Am Heart J* 2008;155:361-8.

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