ORIGINAL ARTICLE

Aspirin in Patients with Chronic Coronary Syndrome Receiving Oral Anticoagulation

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ABSTRACT

BACKGROUND

The appropriate antithrombotic regimen for patients with chronic coronary syndrome who are at high atherothrombotic risk and receiving long-term oral anticoagulation remains unknown.

METHODS

We conducted a multicenter, double-blind, randomized, placebo-controlled trial in France involving patients with chronic coronary syndrome who had undergone a previous stent implantation (>6 months before enrollment) and were at high atherothrombotic risk and currently receiving long-term oral anticoagulation. The patients were randomly assigned in a 1:1 ratio to receive aspirin (100 mg once daily) or placebo; all the patients continued to receive their current oral anticoagulation therapy. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, or acute limb ischemia. The key safety outcome was major bleeding.

RESULTS

A total of 872 patients underwent randomization; 433 were assigned to the aspirin group, and 439 to the placebo group. The trial was stopped early at the advice of the independent data and safety monitoring board after a median follow-up of 2.2 years because of an excess of deaths from any cause in the aspirin group. A primary efficacy outcome event occurred in 73 patients (16.9%) in the aspirin group and in 53 patients (12.1%) in the placebo group (adjusted hazard ratio, 1.53; 95% confidence interval [CI], 1.07 to 2.18; P=0.02). Death from any cause occurred in 58 patients (13.4%) in the aspirin group and in 37 (8.4%) in the placebo group (adjusted hazard ratio, 1.72; 95% CI, 1.14 to 2.58; P=0.01). Major bleeding occurred in 44 patients (10.2%) in the aspirin group and in 15 patients (3.4%) in the placebo group (adjusted hazard ratio, 3.35; 95% CI, 1.87 to 6.00; P<0.001). A total of 467 and 395 serious adverse events were reported in the aspirin group and placebo group, respectively.

CONCLUSIONS

Among patients with chronic coronary syndrome at high atherothrombotic risk who were receiving an oral anticoagulant, the addition of aspirin led to a higher risk of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, or acute limb ischemia than placebo, as well as higher risks of death from any cause and major bleeding. (Funded by the French Ministry of Health and Bayer Healthcare; ClinicalTrials.gov number, NCT04217447.)

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CME

Among patients with chronic coronary syndrome, formerly known as stable coronary artery disease, long-term single antiplatelet therapy is used to prevent recurrent atherothrombotic events.[1,2] Approximately 15% of these patients also receive long-term anticoagulation therapy.[3-5] Patients with both chronic coronary syndrome and an indication for oral anticoagulation therapy (often for stroke prevention when atrial fibrillation is present) are at high risk for both atherothrombotic and bleeding events.[5]

Results of several trials published within the past 7 years have shown that the risk of bleeding is higher with dual-pathway therapy with full-dose oral anticoagulants and a single antiplatelet agent than with oral anticoagulants alone.[6-10] However, these trials were open-label, included low-risk populations in which not all patients had undergone coronary-artery stent implantation, and, individually, did not show a potential benefit of dual-pathway therapy with respect to atherothrombotic events.[6-10] There is a pharmacologic rationale for combining antiplatelet therapy and oral anticoagulants in patients with chronic coronary syndrome, and several trials have suggested increased efficacy from a strategy involving dual-pathway therapy with low-dose direct oral anticoagulants and an antiplatelet agent, albeit at the expense of increased bleeding.[11,12]

Therefore, the appropriate antithrombotic regimen that should be used in patients with chronic coronary syndrome who are receiving long-term oral anticoagulants remains under debate, particularly for those with previous stent implantation in whom antiplatelet therapy may be critical to minimize the risk of stent thrombosis, as well as those at high atherothrombotic risk. Data from observational studies show that combination therapy with oral anticoagulants and a single antiplatelet agent continues to be used frequently in clinical practice.[13-16] We conducted the AQUATIC (Assessment of Quitting versus Using Aspirin Therapy in Patients with Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Oral Anticoagulation) trial to investigate the efficacy and safety of adding aspirin (100 mg once daily) to long-term oral anticoagulation therapy, as compared with oral anticoagulation therapy alone, in patients with chronic coronary syndrome who had undergone stent implantation more than 6 months before enrollment and were at high risk for atherothrombotic events.

Methods

Trial Design

The AQUATIC trial was a prospective, double-blind, randomized, placebo-controlled trial that was conducted at 51 centers in France; additional details regarding the trial sites and organization are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial design has been published previously, and the protocol is available at NEJM.org.[17] Adjudication of outcomes was performed by an independent clinical end-point committee whose members were unaware of the trial-group assignments.

A Quick Take is available at NEJM.org

This trial was initiated by the investigators and was funded by a grant from the French Ministry of Health and by an unrestricted grant from Bayer Healthcare. The University Hospital of Brest (France) coordinated the trial. None of the funders had a role in the design or conduct of the trial or in the collection or management of data. The trial received approval from Comité de Protection des Personnes and Agence Nationale de Sécurité du Médicament et des Produits de Santé. The conduct of the trial was overseen by a data and safety monitoring board. The first, penultimate, and last authors designed the trial, wrote the first draft of the manuscript, and vouch for accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial Population

Patients were eligible if they were at least 18 years of age, had documented chronic coronary syndrome with previous coronary stent implantation more than 6 months before enrollment, had features of high residual atherothrombotic risk, and were receiving an oral anticoagulant (either a direct oral anticoagulant or a vitamin K antagonist) for any reason. Written informed consent was obtained from all the patients. Full details of the inclusion and exclusion criteria are provided in the Supplementary Appendix. The type and dose of oral anticoagulant was left to the investigator's discretion in accordance with formularies, drug marketing authorizations, indications, and guidelines (see the Supplementary Appendix), but the use of a direct oral anticoagulant was encouraged.

High residual atherothrombotic risk was defined by a history of percutaneous coronary inter-

vention (PCI) during an acute coronary syndrome event that involved implantation of at least one stent more than 6 months before enrollment or by a history of PCI more than 6 months before enrollment for a reason other than an acute coronary syndrome event if the patient had one or more of the following conditions: diabetes, diffuse multivessel disease (involvement of the three coronary vessels), chronic kidney disease (creatinine clearance, <50 ml per minute), a previous stent thrombosis, peripheral artery disease, or a history of complex PCI (stent implantation in the last remaining patent coronary artery or left main coronary artery, at least three stents implanted or three lesions treated, a bifurcation lesion that had been treated with two stents, a stent with a length of more than 60 mm, or chronic total coronary occlusion PCI).[2]

RANDOMIZATION AND FOLLOW-UP

Patients were randomly assigned in a 1:1 ratio to receive aspirin (100 mg once daily) or placebo. Randomization was performed in permuted blocks of four from an interactive Web-based interface and was stratified according to trial site, type of oral anticoagulant (direct oral anticoagulant or vitamin K antagonist), and baseline antithrombotic regimen at inclusion (stratum A or stratum B) to maintain balance between the trial groups. Patients who had been receiving an oral anticoagulant and a single antiplatelet agent (stratum A) were randomly assigned to continue taking the single antiplatelet agent, provided it was aspirin, or to stop taking it, whereas patients who had been receiving an oral anticoagulant alone (stratum B) were randomly assigned to start aspirin therapy or not to start aspirin therapy (Fig. S1 in the Supplementary Appendix).

Patient visits were scheduled every 6 months during follow-up (Fig. S2). All the patients were scheduled for a minimum follow-up of 24 months, with a total duration of participation ranging from 24 to 48 months, depending on the time of enrollment.

OUTCOMES

The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, or acute limb ischemia. Secondary efficacy outcomes were net adverse clinical events, defined as a composite of death from any cause, an atherothrombotic cardiovascular event, or major bleeding; death from any cause; a composite of cardiovascular death, myocardial infarction, or stroke; cardiovascular death; and an atherothrombotic cardiovascular event. The key secondary safety outcome was major bleeding according to International Society on Thrombosis and Haemostasis (ISTH) criteria.[18] A full list of the secondary and safety outcomes and all outcome definitions are provided in the Supplementary Appendix.

STATISTICAL ANALYSIS

Given the enrichment criteria targeting patients at high atherothrombotic risk,[13,14,19,20] we expected an incidence of a primary efficacy outcome event of 16% at 24 months among the patients receiving placebo and oral anticoagulation therapy, with a 25% lower hazard of this outcome among the patients receiving aspirin and oral anticoagulation therapy.[12,21] On the basis of these expectations, we calculated that 945 patients per trial group would provide the trial with 80% power at a two-sided alpha level of 0.05 to detect a hazard ratio of 0.75 in the aspirin group, as compared with the placebo group. After accounting for a 5% dropout rate, we determined that the target sample size would be 2000 patients. Additional details regarding the estimation of the sample size are provided in the Supplementary Appendix.

The primary analysis was performed in the intention-to-treat population (all the patients who underwent randomization and provided written informed consent). The primary efficacy outcome was tested for superiority and compared between the trial groups in a survival analysis that was based on a marginal Cox frailty model clustered at the site level, with adjustment for the randomization strata (type of oral anticoagulant [vitamin K antagonist vs. direct oral anticoagulant]) and antithrombotic treatment at the time of enrollment (stratum A vs. stratum B). The primary analysis was based on the missing-at-random assumption. To assess the robustness of the primary analysis results to possible departures from the missing-at-random assumption, a sensitivity analysis was performed with pattern-

mixture models under a missing-not-at-random assumption (see the Supplementary Appendix). Under the missing-at-random assumption, missing data on the primary and secondary outcomes were imputed with a method based on multivariate imputation by chained equations. A total of 100 imputed data sets were generated from the initial data set. We analyzed each complete data set with a Cox frailty model using the marginal log-likelihood and combined the results from multivariate imputation analyses into a single inference using Rubin's rule.[22] The variables used in the imputation models were demographic data, cardiovascular risk factors, medical history at baseline, and randomization strata. Trace plots and distribution plots were created to check the accuracy of the imputations. The number and percentage of patients with missing data for each outcome are shown in Table S1. To address the issue of noncardiovascular risk as a competing risk, a cause-specific proportional-hazards model was used.[23] In addition, an analysis of complete data was performed as a sensitivity analysis (see the Supplementary Appendix). Variance components for the frailty models are shown in Table S2. The proportional-hazards assumption was assessed by graphical methods and Schoenfeld residual tests. Survival curves were derived from Kaplan–Meier estimates for the overall and stratified populations. Hazard ratios with 95% confidence intervals and P values (if appropriate) are reported. The widths of the 95% confidence intervals for the secondary efficacy outcomes that were not included in the hierarchical analysis plan were not adjusted for multiple testing and should not be used to infer definitive treatment effects.

If the primary efficacy outcome was found to be significant, the secondary efficacy outcomes were tested at a two-sided 5% significance level in the following hierarchical order: net adverse clinical events; death from any cause; a composite of cardiovascular death, myocardial infarction, or stroke; cardiovascular death; any coronary revascularization; myocardial infarction; stroke; stent thrombosis; systemic embolism; and acute limb ischemia. If an outcome was not found to be significant, only the hazard ratio and 95% confidence interval were reported for that outcome and the following outcomes in the hierarchical list. The safety analysis population included all the patients who had undergone randomization and received at least one dose of aspirin or placebo. The safety outcomes were tested at a 5% two-sided significance level without adjustment for multiplicity.

Secondary outcomes including death from any cause were analyzed by the same methods as those used in the primary analysis. Time from randomization to death due to cardiovascular causes was analyzed with noncardiovascular causes as a competing event.[23] Other time-to-event outcomes were analyzed with death as a competing event. The methods for missing data imputations and sensitivity analyses used for the primary outcome were also applied for the secondary outcomes. Sensitivity analyses were performed in the per-protocol population, which included all the patients who had undergone randomization and did not have major protocol deviations. Subgroup analyses of the primary efficacy outcome, major bleeding according to ISTH criteria, and death from any cause were performed according to prespecified clinical factors (see the Supplementary Appendix).

All statistical tests were conducted at a two-sided significance level of 0.05. All statistical analyses were performed and graphs generated with the use of SAS software, version 9.4 or later (SAS Institute).

RESULTS

POPULATION

Patients were enrolled from May 2020 through April 2024. A total of 872 patients with chronic coronary syndrome who were receiving oral anticoagulation therapy were enrolled and underwent randomization; 433 patients were assigned to receive aspirin (100 mg once daily) while continuing to receive oral anticoagulation therapy (aspirin group), and 439 patients were assigned to receive placebo while continuing oral anticoagulation therapy (placebo group) (Fig. S3).

The baseline characteristics of the patients are shown in Table 1. The mean age of the patients was 71.7 years, 85.3% were male, and 72.1% had a history of myocardial infarction. All the patients had a history of PCI, with a median interval of 3 years between the last PCI and the

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Total Population (N=872)	Oral Anticoagulant + Aspirin (N=433)	Oral Anticoagulant + Placebo (N=439)
Demographic data			
Age — yr	71.7±9.5	72.3±9.3	71.1±9.6
Male sex — no. (%)	744 (85.3)	370 (85.5)	374 (85.2)
Cardiovascular risk			
Body-mass index†			
Patients with data	857	425	432
Mean	28.4±5.1	28.3±5.3	28.5±4.9
Diabetes — no./total no. (%)	326/871 (37.4)	164/432 (38.0)	162/439 (36.9)
Current receipt of insulin therapy — no./total no. (%)	107/326 (32.8)	55/164 (33.5)	52/162 (32.1)
History of hypertension — no./total no. (%)	599/871 (68.8)	303/432 (70.1)	296/439 (67.4)
History of dyslipidemia — no./total no. (%)	615/871 (70.6)	303/432 (70.1)	312/439 (71.1)
Current smoker — no./total no. (%)	93/871 (10.7)	45/432 (10.4)	48/439 (10.9)
Medical history			
History of CABG — no./total no. (%)	89/871 (10.2)	43/432 (10.0)	46/439 (10.5)
Time since last CABG			
Patients with data	89	43	46
Median (IQR) — yr	9.0 (4.0–18.0)	9.0 (4.0–17.0)	8.5 (4.0–20.0)
History of PCI — no./total no. (%)	871/871 (100.0)	432/432 (100.0)	439/439 (100.0)
Time since last PCI			
Patients with data	844	420	424
Median (IQR) — yr	3.0 (1.0–6.0)	3.0 (1.0–6.0)	3.0 (1.0–6.0)
Last PCI between 6 and 12 mo before enrollment — no./total no. (%)	234/844 (27.7)	118/420 (28.1)	116/424 (27.4)
History of MI — no./total no. (%)	628/871 (72.1)	309/432 (71.5)	319/439 (72.7)
Time since last MI — yr			
Patients with data	589	288	301
Median (IQR) — yr	3.0 (2.0–8.0)	3.0 (2.0–8.0)	3.0 (1.0–8.0)
History of stroke — no./total no. (%)	93/871 (10.7)	39/432 (9.0)	54/439 (12.3)
History of atrial fibrillation — no./total no. (%)	775/871 (89.0)	384/432 (88.9)	391/439 (89.1)
Median CHA_2DS_2-VASc score (IQR)‡	4.0 (3.0–5.0)	4.0 (3.0–5.0)	4.0 (3.0–5.0)
History of PAD — no./total no. (%)	125/871 (14.4)	69/432 (16.0)	56/439 (12.8)
History of heart failure — no./total no. (%)	231/871 (26.5)	117/432 (27.1)	114/439 (26.0)
Laboratory value			
Hemoglobin			
Patients with data	782	393	389
Mean — g/dl	13.9±1.8	13.8±1.9	14.1±1.8
Creatinine clearance			
Patients with data	742	380	362
Mean — ml/min	71.4±26.7	70.6±26.8	72.1±26.6

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass graft surgery, IQR interquartile range, MI myocardial infarction, PAD peripheral artery disease, and PCI percutaneous coronary intervention.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ The CHA_2DS_2-VASc score is an assessment of the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke with atrial fibrillation.

time of enrollment; 27.7% of the patients had undergone their last PCI between 6 and 12 months before enrollment. Other baseline characteristics appeared to be well balanced between the trial groups.

Oral anticoagulation therapy had been prescribed because of atrial fibrillation in 89.0% of the patients, and the median CHA_2DS_2-VASc score was 4 (interquartile range, 3.0 to 5.0). The CHA_2DS_2-VASc score is an assessment of the risk of stroke among patients with atrial fibrillation; scores range from 0 to 9, with higher scores indicating a greater risk of stroke with atrial fibrillation. Other reasons for receiving an oral anticoagulant prescription are given in Table S3. Direct oral anticoagulants were used in 89.7% of the patients (62.2% received apixaban, 24.7% rivaroxaban, and 2.9% dabigatran). At baseline, 67.7% of the patients were receiving single antiplatelet therapy (stratum A), and 32.3% were not receiving antiplatelet therapy at baseline (stratum B).

EARLY TERMINATION OF THE TRIAL

Enrollment was stopped early on April 16, 2024, on the recommendation of the members of the data and safety monitoring board, who observed an excess of deaths from any cause in the aspirin group (the data and safety monitoring board met five times during the trial [see the Supplementary Appendix]). Within a month after enrollment was stopped, all the patients were contacted by telephone to stop receiving aspirin or placebo (with the antithrombotic strategy left to physician's discretion), and an additional 1-to-3-month follow-up was performed after aspirin or placebo was discontinued. The trial database was locked on May 16, 2025. The median duration of treatment was 1.7 years (interquartile range, 0.7 to 2.8), and the median follow-up was 2.2 years (interquartile range, 1.1 to 3.2).

OUTCOMES

A primary efficacy outcome event occurred in 73 patients (16.9%) in the aspirin group and in 53 patients (12.1%) in the placebo group (adjusted hazard ratio, 1.53; 95% confidence interval [CI], 1.07 to 2.18; P=0.02) (Table 2 and Fig. 1A). A net adverse clinical event occurred in 124 patients (28.6%) in the aspirin group and in 76 patients (17.3%) in the placebo group (hazard ratio, 1.85; 95% CI, 1.39 to 2.46; P<0.001). Death from any cause occurred in 58 patients (13.4%) in the aspirin group and in 37 patients (8.4%) in the placebo group (adjusted hazard ratio, 1.72; 95% CI, 1.14 to 2.58; P=0.01) (Table 2 and Fig. 1C). Cardiovascular death occurred in 33 patients (7.6%) in the aspirin group and in 19 patients (4.3%) in the placebo group (adjusted hazard ratio, 1.90; 95% CI, 1.07 to 3.35) (Table 2 and Fig. S4). Causes of death are summarized in Table S4. Atherothrombotic events occurred in 46 patients (10.6%) in the aspirin group and in 40 patients (9.1%) in the placebo group (adjusted hazard ratio, 1.27; 95% CI, 0.83 to 1.95) (Fig. S5). Stent thrombosis occurred in 1 patient in each group. Other secondary efficacy outcomes are shown in Table 2. The results of sensitivity analyses appeared to be consistent with those of the intention-to-treat analyses (Tables S5, S6, and S7). Subgroup analyses are shown in Figures S6, S7, and S8.

SAFETY

The safety analysis population comprised 866 patients. Major bleeding according to ISTH criteria (the key secondary safety end point) occurred in 44 patients (10.2%) in the aspirin group and 15 patients (3.4%) in the placebo group (adjusted hazard ratio, 3.35; 95% CI, 1.87 to 6.00; P<0.001) (Table 2 and Fig. 1B). Any bleeding occurred in 70 patients (16.2%) in the aspirin group and in 41 patients (9.3%) in the placebo group (adjusted hazard ratio, 1.97; 95% CI, 1.34 to 2.89; P<0.001). Other bleeding outcomes are shown in Table 2 and Tables S8A and S8B. A total of 467 serious adverse events occurred in 201 patients in the aspirin group, and 395 serious adverse events occurred in 192 patients in the placebo group (Table S9).

DISCUSSION

In this double-blind, placebo-controlled trial that was terminated early, the use of aspirin in patients with chronic coronary syndrome at high residual risk for an atherothrombotic event and currently receiving long-term oral anticoagulants increased the risk of a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, and acute limb ischemia. The use of aspirin also increased the risk of a net adverse clinical event (a composite of death from any cause, atherothrombotic cardiovascular event, or major bleeding), as well

Table 2. Primary and Secondary Outcomes.*

Outcome	Total Population (N=872)	Oral Anticoagulant + Aspirin (N=433)	Oral Anticoagulant + Placebo (N=439)	Adjusted Hazard Ratio (95% CI)†‡	P Value§
		number (percent)			
Primary efficacy outcome					
Composite of cardiovascular death, MI, stroke, coronary revascularization, systemic embolism, or acute limb ischemia	126 (14.4)	73 (16.9)	53 (12.1)	1.53 (1.07–2.18)¶	0.02
Secondary efficacy outcome					
Net adverse clinical event‖	200 (22.9)	124 (28.6)	76 (17.3)	1.85 (1.39 to 2.46)	<0.001
Death from any cause	95 (10.9)	58 (13.4)	37 (8.4)	1.72 (1.14 to 2.58)	0.01
Composite of cardiovascular death, MI, or stroke	80 (9.2)	46 (10.6)	34 (7.7)	1.45 (0.93 to 2.26)¶	0.10
Cardiovascular death	52 (6.0)	33 (7.6)	19 (4.3)	1.90 (1.07 to 3.35)¶	—
Atherothrombotic cardiovascular event**	86 (9.9)	46 (10.6)	40 (9.1)	1.27 (0.83 to 1.95)††	—
Coronary revascularization	51 (5.8)	29 (6.7)	22 (5.0)	1.49 (0.86 to 2.60)††	—
MI	22 (2.5)	13 (3.0)	9 (2.1)	1.56 (0.67 to 3.62)††	—
Stroke	17 (1.9)	6 (1.4)	11 (2.5)	0.57 (0.21 to 1.54)††	—
Stent thrombosis	2 (0.2)	1 (0.2)	1 (0.2)	0.74 (0.08 to 7.22)††	—
Systemic embolism	0	0	0	—	—
Acute limb ischemia	7 (0.8)	6 (1.4)	1 (0.2)	4.15 (0.69 to 25.01)††	—
Key secondary safety outcome					
Major bleeding according to ISTH criteria	59 (6.8)	44 (10.2)	15 (3.4)	3.35 (1.87 to 6.00)‡‡	<0.001
Other secondary safety outcome					
Any bleeding according to ISTH criteria	111 (12.7)	70 (16.2)	41 (9.3)	1.97 (1.34 to 2.89)‡‡	<0.001
Major or clinically relevant nonmajor bleeding according to ISTH criteria	101 (11.6)	65 (15.0)	36 (8.2)	2.06 (1.36 to 3.11)‡‡	<0.001
Major bleeding according to TIMI criteria	30 (3.4)	23 (5.3)	7 (1.6)	3.68 (1.55 to 8.75)‡‡	0.003
Major bleeding: BARC type 3 or higher§§	52 (6.0)	40 (9.2)	12 (2.7)	3.78 (1.98 to 7.21)‡‡	<0.001

* The primary and secondary efficacy analyses were performed in the intention-to-treat population, which included all the patients who had undergone randomization. The secondary safety analyses were performed in the safety analysis population, which included all patients who had undergone randomization and received at least one dose of aspirin or placebo during the follow-up period. Outcome definitions are provided in the Supplementary Appendix. ISTH denotes International Society on Thrombosis and Haemostasis, and TIMI Thrombolysis In Myocardial Infarction.

† The analyses were adjusted for randomization strata and included trial site as a random effect. Shown are the hazard ratios and 95% confidence intervals after multiple imputation under the missing-at-random assumption.

‡ The widths of the 95% confidence intervals for the secondary efficacy outcomes that were not included in the hierarchical analysis plan have not been adjusted for multiple testing and should not be used to infer definitive treatment effects.

§ A hierarchical approach was used to control the type I error. Hypothesis testing for secondary efficacy outcomes was performed sequentially in the order listed in the statistical analysis plan, available with the protocol at NEJM.org. When a P value of 0.05 or higher was observed, the outcomes below that finding in the hierarchy were not formally tested.

¶ The analysis was conducted with a cause-specific proportional-hazards regression model with noncardiovascular death as competing risk.

‖ A net adverse clinical event was a composite of death from any cause, atherothrombotic cardiovascular event, or major bleeding.

** An atherothrombotic cardiovascular event was a composite of MI, stent thrombosis, stroke, coronary revascularization, systemic embolism, or acute limb ischemia.

†† The analysis was conducted with a cause-specific proportional-hazards regression model with death as a competing risk.

‡‡ The analysis was conducted with a cause-specific proportional-hazards regression model with death from nonbleeding causes as a competing risk.

§§ Bleeding Academic Research Consortium (BARC) types range from 0 (no bleeding) to 5 (fatal bleeding).

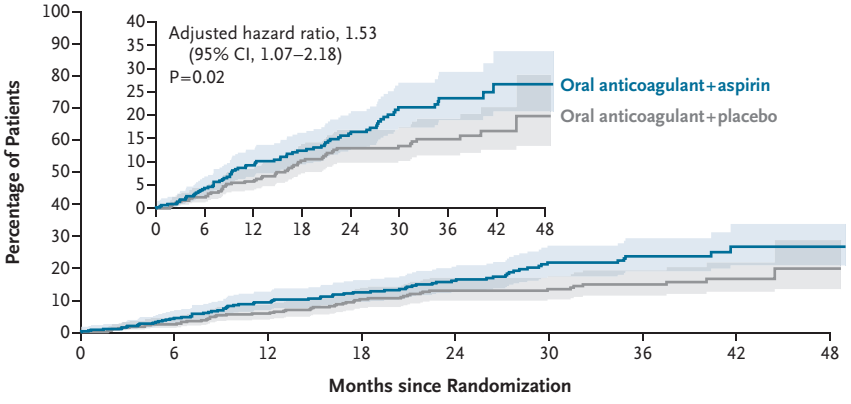
as death from any cause. The risk of bleeding was also significantly higher with aspirin than with placebo.

The population enrolled in the AQUATIC trial was at high risk, as shown by the incidence of atherothrombotic events. Even in such a high-risk population, the risk of an atherothrombotic event (myocardial infarction, stroke, coronary revascularization, systemic embolism, or acute limb ischemia) did not appear to be reduced by adding aspirin to oral anticoagulants, and the risk of very-late stent thrombosis was very low, with only one event in each trial group. Similar to the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial,[9] the AQUATIC trial was stopped early because of a considerable excess of deaths from any cause in the aspirin plus oral anticoagulation therapy group. In addition, consistent with two previous trials,[6,9] adding aspirin to oral anticoagulants substantially increased the risk of major bleeding, regardless of the bleeding definition used. Bleeding events are associated with a higher risk of death.[19,24] Therefore, even among high-risk patients with chronic coronary syndrome and a previous stent implantation, our results do not support the use of aspirin added to oral anticoagulation therapy.

Our trial differs from previous trials that compared oral anticoagulation therapy alone with oral anticoagulation therapy plus single antiplatelet therapy in several aspects.[6-10] First, biases related to crossovers, drop-ins, event reporting, and physician behavior were minimized in our trial. Second, our trial enrolled a European population, whereas either Japanese or Korean populations were enrolled in previous trials,[6-10] which may limit the extrapolation of their results worldwide, since White and Asian populations may differ with respect to the risk of an atherothrombotic event, the risk of bleeding, and the metabolism of antithrombotic agents such as clopidogrel. In addition, the approved doses of several antithrombotic agents, including direct oral anticoagulants, differ in Japan, Korea, Europe, and the United States. Third, our trial tested specifically the addition of aspirin to oral anticoagulation therapy. In other studies,[6,8,9] $P2Y_{12}$ inhibitors (mainly clopidogrel) were allowed and used as single antiplatelet therapy in 15 to 38% of the patients. Fourth, oral anticoagulation therapy was restricted to rivaroxaban in the AFIRE trial[9] and to edoxaban in the EPIC-CAD (Edoxaban versus Edoxaban with Antiplatelet Agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease) trial[6] and PRAEDO-AF (Prospective Randomized Study of Safety Outcomes Treated with Edoxaban in Patients with Stable CAD and Atrial Fibrillation),[10] whereas all types of oral anticoagulation therapy at approved regimens were allowed in our trial (60% of the patients were treated with apixaban, 25% with rivaroxaban, 5% with dabigatran, and 10% with vitamin K antagonists). Furthermore, all the previous trials included only patients with atrial fibrillation,[6-10] whereas the indication for long-term oral anticoagulation therapy was not solely restricted to atrial fibrillation in our trial in order to address the broader issue of combination therapy in patients who are typically encountered in clinical practice. Finally, our trial focused on patients with a previous stent implantation and with additional features of high residual atherothrombotic risk — a population for which the appropriate antithrombotic regimen remains uncertain. The incidence of atherothrombotic events observed in the AQUATIC trial was seven to eight times as high as that in the previous trials.[6-10] For instance, the incidence of a composite of cardiovascular death, myocardial infarction, stroke, or systemic embolism was 1.5% in the EPIC-CAD trial,[6] 2% in PRAEDO-AF,[10] 0.9% in the AFIRE trial,[9] and 1.4% in the OAC-ALONE (Optimizing Antithrombotic Care in Patients with Atrial Fibrillation and Coronary Stent) trial,[8] whereas it was 11% in the AQUATIC trial. It is notable that all the patients in the AQUATIC trial had a history of stent implantation, whereas the incidence of previous PCI was 70% in the AFIRE trial[9] and 60% in the EPIC-CAD trial.[6] A history of myocardial infarction was present in more than 70% of the patients in the AQUATIC trial, as compared with 35% in other trials.[6-10]

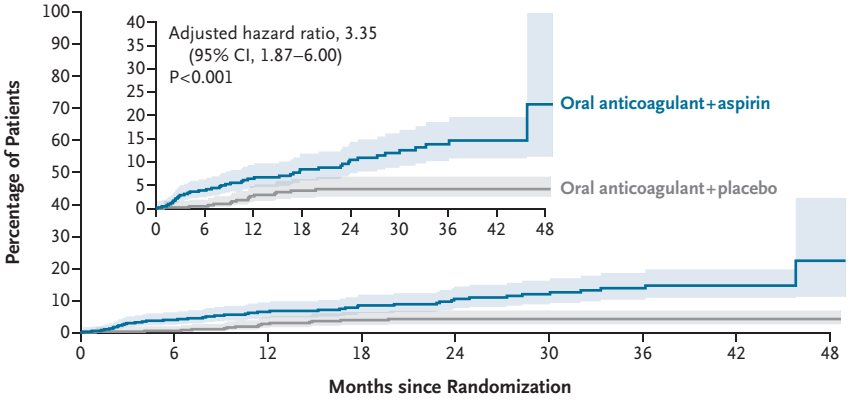
Our trial has several limitations. First, early termination of the trial might have limited the statistical power to investigate the superiority of dual-pathway therapy for atherothrombotic events. However, the incidence of atherothrombotic events was much higher than in previous studies, a finding that was consistent with the expected incidence and similar in the trial groups. Stent thrombosis occurred in only one patient in each trial

A Cardiovascular Death, MI, Stroke, Systemic Embolism, Coronary Revascularization, or Acute Limb Ischemia



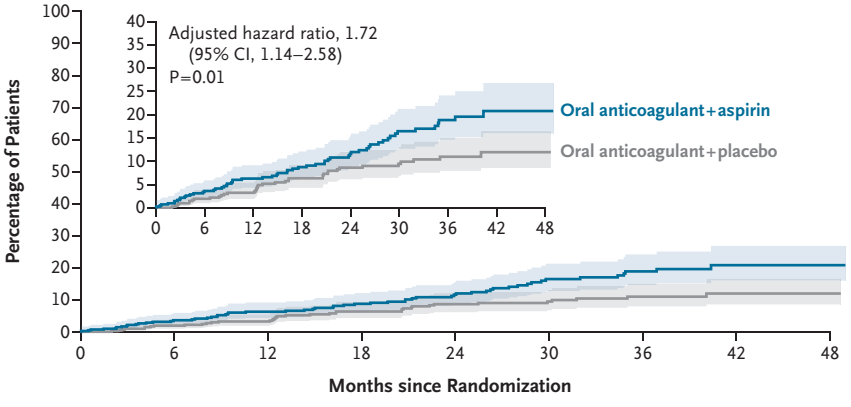
No. at Risk									
Oral anticoagulant+aspirin	433	373	311	257	206	145	109	39	4
Oral anticoagulant+placebo	439	386	340	278	238	183	129	58	2

B Major Bleeding According to ISTH Criteria



No. at Risk									
Oral anticoagulant+aspirin	429	367	307	257	206	149	109	40	4
Oral anticoagulant+placebo	437	387	345	289	248	192	139	64	3

C Death from Any Cause



No. at Risk									
Oral anticoagulant+aspirin	433	382	327	277	225	163	120	43	4
Oral anticoagulant+placebo	439	389	352	297	256	197	142	64	3

Figure 1 (facing page). Primary Efficacy and Main Secondary Outcomes.

Kaplan–Meier curves are shown for a composite of cardiovascular death, myocardial infarction (MI), stroke, systemic embolism, coronary revascularization, or acute limb ischemia (the primary efficacy outcome) (Panel A), major bleeding according to the International Society on Thrombosis and Haemostasis (ISTH) criteria (the key secondary safety outcome) (Panel B), and death from any cause (a secondary efficacy outcome) (Panel C). In each panel, the inset shows the same data on an enlarged y axis. The shaded areas indicate the 95% confidence intervals.

group. Therefore, it is very unlikely that the addition of aspirin to oral anticoagulation therapy would show superiority in a larger trial. Second, although the trial was conducted at 51 centers, all the centers were in a single country; therefore, the results may not be generalizable to other health care systems. Third, we acknowledge slow enrollment that may, at least in part, be explained by the coronavirus disease 2019 pandemic at the beginning of the trial. Besides its effect on enrollment, the pandemic period did not further affect the trial. Fourth, as in several other trials,[8-10] women were underrepresented in our trial population, which may limit the generalizability of our findings (Table S10).

Among patients with chronic coronary syndrome at high atherothrombotic risk who were receiving an oral anticoagulant, the addition of aspirin increased the risk of a composite of cardiovascular death, myocardial infarction, stroke, systemic embolism, coronary revascularization, or acute limb ischemia, as well as death from any cause and major bleeding.

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