ORIGINAL ARTICLE

Stopping vs. Continuing Aspirin before Coronary Artery Surgery

Paul S. Myles, M.P.H., M.D., Julian A. Smith, F.R.A.C.S., Andrew Forbes, Ph.D., Brendan Silbert, M.B., B.S., Mohandas Jayarajah, M.B., B.S., Thomas Painter, M.B., Ch.B., D. James Cooper, M.D., Silvana Marasco, Ph.D., John McNeil, Ph.D., Jean S. Bussières, M.D., and Sophie Wallace, M.P.H., for the ATACAS Investigators of the ANZCA Clinical Trials Network*

ABSTRACT

BACKGROUND

Most patients with coronary artery disease receive aspirin for primary or secondary prevention of myocardial infarction, stroke, and death. Aspirin poses a risk of bleeding in patients undergoing surgery, but it is unclear whether aspirin should be stopped before coronary artery surgery.

METHODS

We used a 2-by-2 factorial trial design to randomly assign patients who were scheduled to undergo coronary artery surgery and were at risk for perioperative complications to receive aspirin or placebo and tranexamic acid or placebo. The results of the aspirin trial are reported here. Patients were randomly assigned to receive 100 mg of aspirin or matched placebo preoperatively. The primary outcome was a composite of death and thrombotic complications (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) within 30 days after surgery.

RESULTS

Among 5784 eligible patients, 2100 were enrolled; 1047 were randomly assigned to receive aspirin and 1053 to receive placebo. A primary outcome event occurred in 202 patients in the aspirin group (19.3%) and in 215 patients in the placebo group (20.4%) (relative risk, 0.94; 95% confidence interval, 0.80 to 1.12; P=0.55). Major hemorrhage leading to reoperation occurred in 1.8% of patients in the aspirin group and in 2.1% of patients in the placebo group (P=0.75), and cardiac tamponade occurred at rates of 1.1% and 0.4%, respectively (P=0.08).

CONCLUSIONS

Among patients undergoing coronary artery surgery, the administration of preoperative aspirin resulted in neither a lower risk of death or thrombotic complications nor a higher risk of bleeding than that with placebo. (Funded by the Australian National Health and Medical Research Council and others; Australia New Zealand Clinical Trials Registry number, ACTRN12605000557639.)

From the Alfred Hospital (P.S.M., D.J.C, S.M., S.W.) and Monash University (P.S.M., J.A.S., A.F., D.J.C., S.M., J.M.), Melbourne, VIC, St. Vincent's Hospital, Fitzroy, VIC (B.S.), and the Royal Adelaide Hospital, Adelaide, SA (T.P.) — all in Australia; Plymouth Medical School, Devon, United Kingdom (M.J.); and Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec, QC, Canada (J.S.B). Address reprint requests to Dr. Myles at the Department of Anaesthesia and Perioperative Medicine, Alfred Hospital, Commercial Rd., Melbourne, VIC 3004, Australia, or at p.myles@alfred.org.au.

*A list of participating centers and investigators in the Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) trial of the Australian and New Zealand College of Anaesthetists (ANZCA) Clinical Trials Network is provided in the Supplementary Appendix, available at NEJM.org.

This article was updated on February 25, 2016, at NEJM.org.

N Engl J Med 2016;374:728-37.
DOI: 10.1056/NEJMoa1507688

Most patients with coronary artery disease take aspirin for primary or secondary prevention of thrombotic events.[1] Aspirin inhibits platelet function and therefore poses an increased risk of bleeding among patients undergoing coronary artery bypass grafting (CABG),[1] although this risk appears to be small.[2-5] Until recently, it has been traditional practice in most cardiac surgical centers to have patients stop taking aspirin 5 to 7 days before surgery to reduce the risk of bleeding. However, the increased risk of surgical bleeding could be outweighed by the beneficial effect of aspirin on coronary-graft flow and on reduction in the risk of graft thrombosis,[6,7] myocardial infarction,[8] and possibly stroke.[7,9,10] Aspirin is routinely recommenced within 24 hours after CABG surgery, but this practice does not allow for the use of aspirin to help prevent thrombosis in the crucial early postoperative phase.[6] Several observational studies have shown reductions in mortality, the rate of serious complications, or both when aspirin is administered preoperatively or soon after CABG surgery.[5,9,11]

It is unclear whether aspirin should be continued or stopped in patients undergoing coronary artery surgery.[10] Conflicting guidelines from expert professional organizations highlight the dearth of data from large clinical trials and the lack of reliable recommendations.[12-16] One aim of this multicenter, double-blind, randomized trial (Aspirin and Tranexamic Acid for Coronary Artery Surgery [ATACAS]) was to determine whether aspirin would reduce the occurrence of death and thrombotic complications in at-risk patients who were undergoing coronary artery surgery.

METHODS

STUDY DESIGN AND OVERSIGHT

The design of and rationale for the ATACAS trial have been published previously.[17] In brief, we used a 2-by-2 factorial design in which 2127 patients who were scheduled to undergo coronary artery surgery and were at increased risk for complications were randomly assigned to receive 100 mg of aspirin or placebo and tranexamic acid or placebo. The results of the aspirin trial are reported here. Patients were randomly assigned to receive aspirin or placebo preoperatively, with or without anxiolytic premedication, on the day of coronary artery surgery. All patients provided written informed consent. The attending anesthesiologists, surgical team, postoperative interviewers, and end-point adjudicators were unaware of the group assignments.

The study was approved by the institutional review board at each site. The members of the steering committee (see the Supplementary Appendix, available with the full text of this article at NEJM.org) designed the study and gathered and analyzed the data, prepared the manuscript, and together with their coauthors made the decision to submit the manuscript for publication. The members of the steering committee vouch for the accuracy of the data set and for adherence to the study protocol, which is available at NEJM.org. Bayer Pharma provided the 100-mg, enteric-coated aspirin used in the study and the matched placebo free of charge but did not have any role in the design of the trial, the accrual, analysis, or interpretation of the data, or the preparation of the manuscript.

A data-quality committee monitored adherence to the protocol and the completeness of the data, and a data and safety monitoring committee provided advice as to whether the trial should be stopped if there was clear evidence of benefit or harm.[17] Details on quality control regarding the study medication are provided in the Supplementary Appendix. A preliminary safety analysis of pooled data was undertaken by the data and safety monitoring committee after 824 patients were enrolled to confirm that there was no indication of an excessive risk of bleeding among the participants. Interim analyses were planned after enrollment benchmarks of 2300 patients and 3450 patients; O'Brien–Fleming stopping boundaries were used to assess efficacy, and a less stringent boundary was used to assess harm. An independent adjudication committee, whose members were unaware of group assignments, reviewed all primary outcome events and confirmed the events with the use of established definitions; details are provided in the Supplementary Appendix. Sites that recruited 30 or more participants were independently audited. A random sample of cases was reviewed to

Table 1. Characteristics of the Patients at Study Entry.*

Characteristic	Aspirin (N=1047)	Placebo (N=1053)
Age — yr	66.5±9.7	66.2±10.2
Weight — kg	85.2±16.5	86.0±17.7
Male sex — no. (%)	872 (83.3)	858 (81.5)
NYHA classification — no./total no. (%)		
I	163/1047 (15.6)	184/1053 (17.5)
II	580/1047 (55.4)	578/1053 (54.9)
III	276/1047 (26.4)	271/1052 (25.8)
IV	28/1047 (2.7)	19/1053 (1.8)
EuroSCORE for operative risk — %†	4.1±2.9	4.1±2.8
Preexisting medical condition — no. (%)		
Diabetes	347 (33.1)	368 (34.9)
Hypertension	847 (80.9)	845 (80.2)
Angina	744 (71.1)	756 (71.8)
Heart failure	136 (13.0)	133 (12.6)
Myocardial infarction within 90 days	75 (7.2)	83 (7.9)
Previous cardiac surgery	17 (1.6)	14 (1.3)
No. of coronary artery grafts		
Median	3	3
Interquartile range	2–4	2–4
Tranexamic acid received — no. (%)	521 (49.8)	526 (50.0)
Cross-clamp time — min		
Median	67	66
Interquartile range	48–91	47–91
Duration of surgery — hr	3.8±1.1	3.8±1.1
Postoperative aspirin within 24 hr — no./total no. (%)	819/1045 (78.4)	799/1052 (76.0)

* Plus–minus values are means ±SD. There were no significant differences between groups at baseline. NYHA denotes New York Heart Association.
† The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation and ranges from 0 to 100%, with higher scores indicating greater risk.[19]

verify patients' eligibility criteria, their provision of consent, and the study end points. No discrepancies were identified during these audits.

STUDY PARTICIPANTS

Eligible participants included adults who were at increased risk for major complications related to age or coexisting conditions and were about to undergo on-pump (with cardiopulmonary bypass) or off-pump (without cardiopulmonary bypass) coronary artery surgery, with or without cardiac-valve placement or another procedure. Patients were eligible for the trial if they had not been taking aspirin regularly before the trial or had stopped taking aspirin at least 4 days before CABG surgery.[1,18] Details regarding the eligibility criteria are provided in the Supplementary Appendix.

PROCEDURES

Randomization was performed with the use of a computer-generated code that was accessed by means of an automated telephone voice-recognition or Web-based service. Treatment assignment was stratified according to study site with the use of permuted blocks.

All patients received standard surgical and other perioperative care, including selection of vein and artery conduit harvesting, determination of the extent of grafting needed according to the results of coronary angiography, myocardial protection, surgical hemostasis, inotrope therapy, and postoperative care. There was no limitation to the use of postoperative aspirin or other antiplatelet therapy, and such therapy was administered in accordance with local practices.

Warfarin and clopidogrel had to be stopped at least 7 days before surgery; cessation of other antiplatelet and anticoagulant therapies was directed in accordance with local practices. In this factorial design, patients were randomly assigned, in a 1:1 ratio, to receive aspirin or placebo (administered 1 to 2 hours before surgery). We provided a guideline for the management of excessive bleeding after on-pump surgery or off-pump surgery and for blood transfusion; details are provided in the Supplementary Appendix.

Patient demographic and perioperative data and data on risk scores were recorded (Table 1). Twelve-lead electrocardiography was performed preoperatively, on the first, second, and third day after surgery, and at the time of hospital discharge. Blood samples were obtained at 12 to 24 hours and 48 to 72 hours after surgery to assess levels of troponin or, if unavailable, creatine kinase–myocardial band (CK-MB). Other laboratory tests were ordered if clinically indicated.

Patients were assessed daily during their hospital stay and were contacted by telephone 30 days after surgery to determine whether any of the events included in the study outcomes had occurred. Patients' medical records were also reviewed during this period.

OUTCOMES

The primary outcome of the study was a composite of death and thrombotic events (nonfatal myocardial infarction, stroke, pulmonary embolism, renal failure, or bowel infarction) during the initial 30 postoperative days. Postoperative myocardial infarction was defined according to the third universal definition[20]; further details are provided in the Supplementary Appendix. In addition, in view of the difficulty of detecting ischemic chest pain in the early postoperative period and of detecting the Q wave in patients with ventricular pacing or bundle-branch block, we defined myocardial infarction without detection of the Q wave as the presence of markedly elevated levels of at least one of the following cardiac biomarkers for at least 12 hours after isolated CABG: troponin I, more than 10 ng per milliliter [20-22]; troponin T, more than 4 ng per milliliter,[21,23] and CK-MB, more than three times the upper limit of the normal range. For consistency with the levels used in recent publications, the criterion with respect to CK-MB level was modified during the analysis to a threshold of five times the upper limit of the normal range.

The prespecified secondary outcomes were death, nonfatal myocardial infarction, major hemorrhage, cardiac tamponade, and a requirement for transfusion. Major hemorrhage was defined as any excessive bleeding leading to surgical reexploration, and tamponade was defined as the presence of typical hemodynamic or echocardiographic features and the need for surgical reexploration. An adjudication committee whose members were unaware of the group assignments assessed all major study outcomes.

SUBGROUPS

Prespecified subgroups were defined according to the following characteristics: sex, age, presence or absence of diabetes, previous or no previous myocardial infarction, presence or absence of unstable angina, operative risk (calculated with the use of the European System for Cardiac Operative Risk Evaluation [EuroSCORE], which is determined by means of a logistic-regression equation and ranges from 0 to 100%, with higher scores indicating greater risk and a score of more than 20% indicating high surgical risk), left ventricular function, risk of bleeding during surgery, on-pump or off-pump surgery, and aortic total ischemic time (the time from placement of the aortic cross-clamp to removal). Risk factors for bleeding during surgery were age over 70 years, female sex, use of low-molecular-weight heparin or an antiplatelet drug less than 5 days before surgery, renal impairment (estimated glomerular filtration rate, <60 ml per minute), and insulin-dependent diabetes. The relationship of these factors to the risk of surgical bleeding is reviewed in the Supplementary Appendix.

STATISTICAL ANALYSIS

The statistical analysis plan (including prespecified end points) was published on a publicly available trial website (www.atacas.org.au) before completion of the trial and is also provided in the Supplementary Appendix. Given a type I error rate of 0.05 and a type II error rate of 0.1, we calculated that 4484 participants would need to be enrolled for the study to detect a clinically significant difference between the aspirin group and the placebo group in the primary outcome of death or thrombotic events (7% vs. 10%); we intended to recruit a total of 4600 patients. However, we amended the protocol on July 25, 2013, because the patient enrollment rate was below expectations. The overwhelming reason was the high rate of patients who had been instructed to continue taking aspirin before coronary artery surgery, which made them ineligible for the trial (Fig. 1). In fact, the staff at many sites were interested in joining the trial but were prevented by the protocols at their institutions, which called for the maintenance of aspirin therapy before the surgery (in large part because recent guidelines recommend this practice).

A second issue was that the actual event rate for the primary outcome (pooled across groups) was higher than we had anticipated, at 19.6%, which gave the study more power than we had expected. The steering committee performed a sample-size calculation based solely on the event rate of 19.6% and postulated a 30% lower risk with aspirin than with placebo; the committee determined that for the 1880 patients enrolled at that time the trial had 96% power to detect a 30% lower risk among participants who continued to take aspirin before surgery than among those who did not take aspirin before surgery. The minimal between-group difference that could be detected with 80% power was a

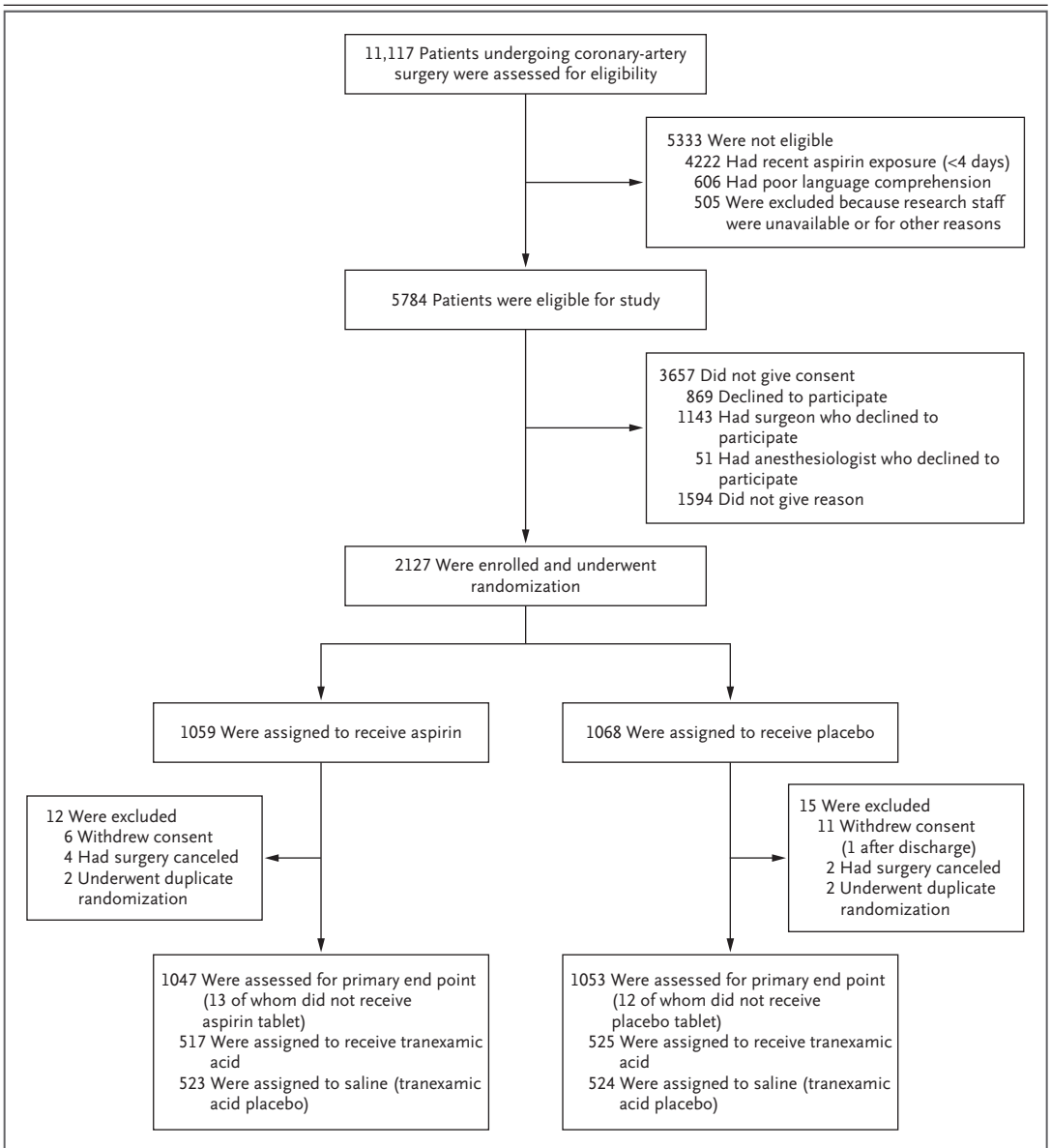

Figure 1. Enrollment, Randomization, and Assessment.

24% lower relative risk and a 5.2-percentage-point lower absolute risk with aspirin than with placebo.

The steering committee therefore elected to discontinue the aspirin group and to conduct a final comparative analysis of aspirin versus placebo; this decision was endorsed by the data and safety monitoring committee. The part of our trial that involves tranexamic acid versus placebo is continuing to the final enrollment target and will be reported at a later time. The number of patients in the aspirin group at the conclusion of that part of the study was 2127 (Fig. 1).

All patients who were randomly assigned to receive aspirin or placebo and who underwent surgery were considered to make up the intention-to-treat population for all primary and secondary analyses. Analysis of the primary and dichotomous secondary end points was performed with the use of binomial regression with a logarithmic link; the results are expressed as

risk ratios with 95% confidence intervals. Continuous secondary end points were assessed with the use of Student's t-tests or Wilcoxon rank-sum tests. Time-to-event end points were assessed with the use of the Wilcoxon–Breslow–Gehan test, with length of stay in the hospital and intensive care unit censored at 30 days, in-hospital deaths assigned the highest length of stay, and time to commencement of aspirin censored at 3 days. Analyses were repeated with adjustment for the stratification factors of site and on-pump or off-pump surgery with the use of linear or generalized linear mixed models, with site as a random effect. Results differed negligibly and only the unadjusted results are reported here. We computed differences in the primary outcome across specified subgroups by adding the appropriate interaction terms to the regression models. To determine whether the effect of aspirin over placebo varied according to whether patients were randomly assigned to tranexamic acid, an independent statistician performed a test for interaction with respect to the primary end point and the secondary end point of major hemorrhage. Results are reported only as $P>0.05$ or not in order to conceal the results for the ongoing component of the trial involving tranexamic acid. All reported P values are two-sided and have not been adjusted for multiple comparisons.

RESULTS

PATIENT CHARACTERISTICS

The 30-day follow-up was completed in more than 99.9% of the patients, and reported results are based on all completed cases. Patients were enrolled between March 2006 and January 2013 at 19 participating centers in five countries. Of 5784 eligible patients, 2100 patients were enrolled and assessed for the primary end point; 1047 were randomly assigned to the aspirin group and 1053 to the placebo group (Fig. 1). The mean (±SD) predicted intraoperative risk of death, calculated with the use of the EuroSCORE, was 4.1±2.8%. Approximately 75% of the patients underwent primary CABG surgery, with 97% undergoing on-pump surgery; the median number of grafts was 3, and approximately 90% of all patients had at least one internal mammary artery graft. Demographic, medical, and perioperative characteristics at baseline were similar in the two groups (Table 1, and Table S1 in the Supplementary Appendix). The median time to administration of aspirin postoperatively was 18.5 hours (interquartile range, 12.3 to 22.9) in the aspirin group and 18.8 hours (interquartile range, 13.1 to 23.5) in the placebo group.

PRIMARY OUTCOME

Death or thrombotic complications occurred within the first 30 days after surgery in 202 patients (19.3%) in the aspirin group and in 215 patients (20.4%) in the placebo group (relative risk with aspirin, 0.94; 95% confidence interval [CI], 0.80 to 1.12; $P=0.55$) (Table 2). The composite end point without the inclusion of renal failure occurred in 172 patients (16.4%) in the aspirin group and in 192 (18.3%) in the placebo group (in which the total for this comparison was 1051) (relative risk, 0.90; 95% CI, 0.75 to 1.09; $P=0.30$). There was no significant interaction between the effects of aspirin and tranexamic acid with regard to the primary end point or major hemorrhage ($P>0.05$ for each interaction).

SECONDARY OUTCOMES

Myocardial infarction was detected within the first 30 days after surgery in 144 patients (13.8%) in the aspirin group and in 166 patients (15.8%) in the placebo group (relative risk, 0.87; 95% CI, 0.71 to 1.07; $P=0.20$) (Table 2). These numbers include 15 patients in the aspirin group (1.4%) and 14 patients in the placebo group (1.3%) who underwent CABG and who were identified as having a non–Q-wave myocardial infarction solely on the basis of markedly elevated levels of troponin or cardiac enzymes.

Major hemorrhage leading to reoperation occurred in 1.8% of the patients in the aspirin group and in 2.1% of the patients in the placebo group ($P=0.75$), and cardiac tamponade occurred in 1.1% and 0.4%, respectively ($P=0.08$). The rates of death, stroke, pulmonary embolism, renal failure, and bowel infarction were similar in the two groups (Table 3). The median hospital length of stay was 7.0 days in both groups (Table 2).

SUBGROUP ANALYSES

With respect to the primary outcome, there were no significant interactions between treatment group and patients' sex, age, left ventricular function, risk of bleeding, surgical subtype, or recent exposure to aspirin (Fig. 2). Subgroup

Table 2. Outcomes.*

Event	Aspirin (N=1047)	Placebo (N=1053)	Risk Ratio (95% CI)	P Value
Primary outcome: death, myocardial infarction, stroke, renal failure, pulmonary embolism, or bowel infarction — no./total no. (%)	202/1046 (19.3)	215/1052 (20.4)	0.94 (0.80–1.12)	0.55
Death	14 (1.3)	9 (0.9)	1.56 (0.68–3.60)	0.30
Myocardial infarction	144 (13.8)	166 (15.8)	0.87 (0.71–1.07)	0.20
Stroke	14 (1.3)	12 (1.1)	1.17 (0.55–2.52)	0.70
Renal failure	49 (4.7)	41 (3.9)	1.20 (0.80–1.80)	0.39
Pulmonary embolism	8 (0.8)	10 (1.0)	0.81 (0.32–2.03)	0.81
Bowel infarction	0	2 (0.2)	—	0.50
Reoperation for hemorrhage — no. (%)	19 (1.8)	22 (2.1)	0.87 (0.47–1.60)	0.75
Cardiac tamponade — no. (%)	11 (1.1)	4 (0.4)	2.77 (0.88–8.66)	0.08
ICU stay — hr				
Initial admission			—	0.61
Median	30	29		
Interquartile range	22–64	21–64		
Total stay, including readmission			—	0.37
Median	36	30		
Interquartile range	22–69	22–67		
Duration of mechanical ventilation — hr			—	0.58
Median	9	9		
Interquartile range	6–16	6–16		
Reintubation during hospital stay — no. (%)	30 (3.5)	28 (3.3)	1.08 (0.65–1.78)	0.79
New episode of peptic ulceration — no. (%)	13 (1.2)	11 (1.0)	1.19 (0.53–2.64)	0.69
Hospital stay — days			—	0.32
Median	7	7		
Interquartile range	6–12	6–11		

* Plus–minus values are means ±SD. ICU denotes intensive care unit.

analyses and tests for interaction with respect to the secondary end points of myocardial infarction and death are provided in the Supplementary Appendix; mortality was higher among men in the aspirin group than among those in the placebo group (12 deaths vs. 3 deaths) (P=0.046 for the interaction).

DISCUSSION

In this trial, the use of preoperative aspirin before coronary artery surgery resulted in neither a lower risk of death or thrombotic complications than that with placebo nor a higher risk of surgical bleeding, need for transfusion, or need for reoperation. The incidence of postoperative myocardial infarction in our trial was 14.8%, an incidence that is higher than that typically seen in observational studies of CABG surgery. The increased sensitivity to the detection of small myocardial infarctions is due to the introduction of troponin surveillance and the stringent review of patients after they were accepted for participation in the trial.[23,24] However, we did limit our diagnostic criteria to the most recent universal definition of postoperative myocardial infarction, in addition to the criterion of elevated troponin levels.[20,23]

We chose to evaluate the benefits and risks

Table 3. Hemostasis, Blood Loss, and Adverse Events.*

Variable	Aspirin (N=1047)	Placebo (N=1053)	Risk Ratio (95% CI)	P Value
Total dose of protamine — mg	378±116	379±120	—	0.83
Mediastinal drainage — ml				
At 4 hr			—	0.25
Median	270	270		
Interquartile range	170–440	175–400		
At 24 hr			—	0.30
Median	780	740		
Interquartile range	530–1110	530–1050		
Total			—	0.59
Median	1015	1015		
Interquartile range	675–1550	675–1490		
Aprotinin therapy — no. (%)				
Intraoperative	4 (0.4)	2 (0.2)	2.01 (0.37–11.0)	0.76
Day 1	6 (0.6)	5 (0.5)	1.21 (0.37–3.94)	0.77
Recombinant factor VIIa therapy — no.(%)				
Intraoperative	3 (0.3)	2 (0.2)	1.51 (0.25–9.01)	0.69
Day 1	3 (0.3)	4 (0.4)	0.75 (0.17–3.36)	>0.99
Platelet transfusion — no. (%)				
Intraoperative	103 (9.8)	106 (10.1)	0.88 (0.76–1.26)	0.88
Day 1	157 (15.0)	138 (13.1)	1.14 (0.93–1.41)	0.23
Fresh-frozen plasma transfusion — no. (%)				
Intraoperative	59 (5.6)	67 (6.4)	0.89 (0.63–1.24)	0.52
Day 1	182 (17.4)	187 (17.8)	0.98 (0.81–1.18)	0.86
Red-cell transfusion — no. (%)				
Intraoperative	152 (14.5)	147 (14.0)	1.04 (0.84–1.28)	0.76
Day 1	303 (28.9)	299 (28.4)	1.02 (0.89–1.17)	0.81
Day 2 to discharge	199 (18.8)	169 (16.1)	1.19 (0.98–1.43)	0.08
Any blood transfusion within 24 hr after surgery — no. (%)	460 (43.9)	449 (42.6)	1.03 (0.93–1.14)	0.57
Lowest hemoglobin concentration — mg/liter				
Intraoperative	84.7±15.1	84.7±14.7	—	0.98
Postoperative	92.6±15.8	91.8±15.3	—	0.24
Any adverse event — no. (%)				
Intraoperative	29 (2.8)	44 (4.2)	0.66 (0.42–1.05)	0.10
Postoperative	74 (7.1)	71 (6.7)	1.05 (0.77–1.44)	0.80

* Plus–minus values are means ±SD.

Subgroup	Aspirin	Placebo	Relative Risk (95% CI)	P Value for Interaction
	no. of patients with events/total no. of patients (%)			
All patients	202/1046 (19.3)	215/1052 (20.4)	0.94 (0.80–1.12)	
Age				0.71
≤60 yr	45/290 (15.5)	58/307 (18.9)	0.82 (0.58–1.17)	
61–70 yr	72/372 (19.4)	66/350 (18.9)	1.03 (0.76–1.39)	
71–80 yr	70/319 (21.9)	70/322 (21.7)	1.01 (0.75–1.35)	
≥80 yr	15/65 (23.1)	21/73 (28.8)	0.80 (0.45–1.42)	
Sex				0.22
Male	160/872 (18.3)	175/857 (20.4)	0.90 (0.74–1.09)	
Female	42/174 (24.1)	40/195 (20.5)	1.18 (0.80–1.72)	
Diabetes mellitus				0.60
Yes	76/347 (21.9)	80/367 (21.8)	1.00 (0.76–1.33)	
No	126/699 (18.0)	135/685 (19.7)	0.91 (0.73–1.14)	
History of myocardial infarction				0.37
Yes	70/364 (19.2)	72/394 (18.3)	1.05 (0.78–1.42)	
No	132/682 (19.4)	142/658 (21.7)	0.89 (0.72–1.10)	
Unstable angina				0.69
Yes	3/21 (14.3)	5/26 (19.2)	0.74 (0.20–2.76)	
No	160/883 (18.1)	164/877 (18.7)	0.97 (0.80–1.18)	
EuroSCORE				0.55
≤4	79/541 (14.6)	86/528 (16.3)	0.90 (0.68–1.19)	
>4	81/346 (22.8)	83/368 (22.6)	1.01 (0.70–1.32)	
Surgical type				0.88
On-pump	198/1012 (19.6)	211/1021 (20.7)	0.95 (0.80–1.13)	
Off-pump	4/34 (11.8)	4/29 (13.8)	0.85 (0.23–3.11)	
Cross-clamp duration				0.40
>150 min	8/19 (42.1)	9/15 (60.0)	0.70 (0.36–1.37)	
≤150 min	109/637 (17.1)	115/642 (17.9)	0.96 (0.75–1.21)	

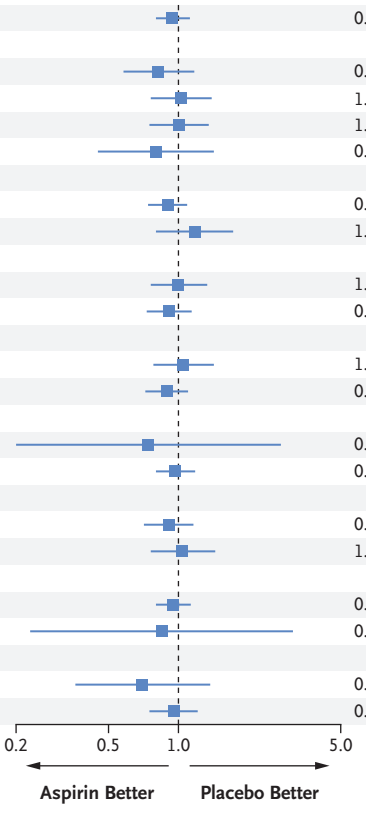

Figure 2. Subgroup Analysis of the Relative Risk of the Primary End Point with and without Preoperative Aspirin.

The European System for Cardiac Operative Risk Evaluation (EuroSCORE) is calculated by means of a logistic-regression equation and ranges from 0 to 100%, with higher scores indicating greater risk. "Off-pump" refers to surgery without cardiopulmonary bypass, and "on-pump" to surgery with cardiopulmonary bypass. Cross-clamp duration refers to the time from placement to removal of the aortic cross-clamp.

of bleeding associated with aspirin at a dose of 100 mg, a dose for which we found the strongest evidence of efficacy (at least in nonsurgical settings) balanced by a low risk of bleeding complications.[1,7,25,26] In essence, we were determining whether it was best to stop or continue aspirin in patients undergoing coronary artery surgery, since the benefits of aspirin in nonsurgical settings are well established. Stopping aspirin 5 to 7 days before surgery increases the risk of thrombosis before the benefits of bypass grafting can be achieved.[27,28] In some instances, surgery is canceled or delayed, which exposes the patient to increased thrombotic risk.

The withdrawal of aspirin to reduce the risk of bleeding in patients scheduled for surgery could be harmful.[27] The most recent meta-analysis that evaluated the use of aspirin in patients undergoing CABG surgery included 13 randomized trials with a total of 2399 participants. The authors found that the continuation of aspirin reduced the risk of perioperative myocardial infarction by nearly half.[8] However, there was evidence of increased bleeding, increased need for red-cell transfusions, and a need for surgical reexploration. Our trial results contradict some of these findings.

The absence of an adverse bleeding effect in this trial could be explained by patient selection, the low dose of aspirin used (100 mg), or the use of antifibrinolytic therapy in half the patients. Some patients — perhaps up to 25% of those undergoing coronary artery surgery — have resis-

tance to the antiplatelet effect of aspirin,[29] and this resistance mitigates the risk of bleeding. We found no indication of an interaction between aspirin and tranexamic acid with regard to the primary end point or to the risk of major hemorrhage. In conclusion, we did not find an association between aspirin and a decreased risk of death or thrombotic complications or an increased risk of bleeding after coronary artery surgery.

Supported by grants from the Australian National Health and Medical Research Council (NHMRC, ID 334015 and 1009203), the Australian and New Zealand College of Anaesthetists, and the National Institute of Health Research; Bayer Pharma, which provided the aspirin and matched placebo tablets used in the study; and by an Australian NHMRC Practitioner's Fellowship provided to Dr. Myles.

No potential conflict of interest relevant to this article was reported.

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

We thank Adam Meehan for data management, the construction of an electronic database accessible on the Web, and the provision of a telephone-based voice-recognition service that allowed for patient randomization; and Drs. Andrew Tonkin and Henry Krum and all members of the committees overseeing the trial, as well as the Australian and New Zealand College of Anaesthetists Clinical Trials Network.

REFERENCES

1. Awtry EH, Loscalzo J. Aspirin. Circulation 2000;101:1206-18.
2. Serebruany VL, Malinin AI, Eisert RM, Sane DC. Risk of bleeding complications with antiplatelet agents: meta-analysis of 338,191 patients enrolled in 50 randomized controlled trials. Am J Hematol 2004; 75:40-7.
3. Parr KG, Patel MA, Dekker R, et al. Multivariate predictors of blood product use in cardiac surgery. J Cardiothorac Vasc Anesth 2003;17:176-81.
4. Jacob M, Smedira N, Blackstone E, Williams S, Cho L. Effect of timing of chronic preoperative aspirin discontinuation on morbidity and mortality in coronary artery bypass surgery. Circulation 2011;123:577-83.
5. Dacey LJ, Munoz JJ, Johnson ER, et al. Effect of preoperative aspirin use on mortality in coronary artery bypass grafting patients. Ann Thorac Surg 2000;70: 1986-90.
6. Goldman S, Copeland J, Moritz T, et al. Improvement in early saphenous vein graft patency after coronary artery bypass surgery with antiplatelet therapy: results of a Veterans Administration Cooperative Study. Circulation 1988;77:1324-32.
7. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002;324:71-86.
8. Hastings SLM, Myles P, McIlroy D. Aspirin and coronary artery surgery: a systematic review and meta-analysis. Br J Anaesth 2015;115:376-85.
9. Mangano DT. Aspirin and mortality from coronary bypass surgery. N Engl J Med 2002;347:1309-17.
10. Myles PS. Stopping aspirin before coronary artery surgery: between the devil and the deep blue sea. Circulation 2011; 123:571-3.
11. Bybee KA, Powell BD, Valeti U, et al. Preoperative aspirin therapy is associated with improved postoperative outcomes in patients undergoing coronary artery bypass grafting. Circulation 2005;112:Suppl: I286-92.
12. Douketis JD, Berger PB, Dunn AS, et al. The perioperative management of antithrombotic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008;133:Suppl:299S-339S.
13. Bell AD, Roussin A, Cartier R, et al. The use of antiplatelet therapy in the outpatient setting: Canadian Cardiovascular Society guidelines. Can J Cardiol 2011;27: Suppl A:S1-59.
14. Society of Thoracic Surgeons Blood Conservation Guideline Task Force, Society of Cardiovascular Anesthesiologists Special Task Force on Blood Transfusion, International Consortium for Evidence Based Perfusion. 2011 Update to the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologists blood conservation clinical practice guidelines. Ann Thorac Surg 2011;91:944-82.
15. Ferraris VA, Ferraris SP, Moliterno DJ, et al. The Society of Thoracic Surgeons practice guideline series: aspirin and other antiplatelet agents during operative coronary revascularization (executive summary). Ann Thorac Surg 2005;79:1454-61.
16. Hillis LD, Smith PK, Anderson JL, et al. 2011 ACCF/AHA guideline for coronary artery bypass graft surgery: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Thorac Cardiovasc Surg 2012;143:4-34.
17. Myles PS, Smith J, Knight J, et al. Aspirin and Tranexamic Acid for Coronary Artery Surgery (ATACAS) Trial: rationale and design. Am Heart J 2008;155:224-30.
18. Cahill RA, McGreal GT, Crowe BH, et al. Duration of increased bleeding tendency after cessation of aspirin therapy. J Am Coll Surg 2005;200:564-73.
19. Nashef SA, Roques F, Hammill BG, et al. Validation of European System for Cardiac Operative Risk Evaluation (EuroSCORE) in North American cardiac surgery. Eur J Cardiothorac Surg 2002;22:101-5.
20. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. Circulation 2012;126:2020-35.
21. Thielmann M, Massoudy P, Schmermund A, et al. Diagnostic discrimination between graft-related and non-graft-related perioperative myocardial infarction with cardiac troponin I after coronary artery bypass surgery. Eur Heart J 2005;26:2440-7.
22. Mohammed AA, Agnihotri AK, van Kimmenade RR, et al. Prospective, comprehensive assessment of cardiac troponin T testing after coronary artery bypass graft surgery. Circulation 2009;120:843-50.
23. Fransen EJ, Diris JH, Maessen JG, Hermens WT, van Dieijen-Visser MP. Evaluation of "new" cardiac markers for ruling out myocardial infarction after coronary artery bypass grafting. Chest 2002;122:1316-21.
24. Wong CK, White HD. Implications of the new definition of myocardial infarction. Postgrad Med J 2005;81:552-5.
25. Sun JC, Whitlock R, Cheng J, et al. The effect of pre-operative aspirin on bleeding, transfusion, myocardial infarction, and mortality in coronary artery bypass surgery: a systematic review of randomized and observational studies. Eur Heart J 2008;29:1057-71.
26. Peters RJ, Mehta SR, Fox KA, et al. Effects of aspirin dose when used alone or in combination with clopidogrel in patients with acute coronary syndromes: observations from the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) study. Circulation 2003;108:1682-7.
27. Collet JP, Montalescot G, Blanchet B, et al. Impact of prior use or recent withdrawal of oral antiplatelet agents on acute coronary syndromes. Circulation 2004;110:2361-7.
28. Ferrari E, Benhamou M, Cerboni P, Marcel B. Coronary syndromes following aspirin withdrawal: a special risk for late stent thrombosis. J Am Coll Cardiol 2005; 45:456-9.
29. Petricevic M, Biocina B, Konosic S, Ivancan V. Impact of aspirin resistance on antiplatelet therapy management after coronary artery surgery. Eur J Cardiothorac Surg 2012;42:760-1.