ORIGINAL ARTICLE

Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting

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ABSTRACT

BACKGROUND

Patients' responses to oral antiplatelet therapy are subject to variation. Bedside monitoring offers the opportunity to improve outcomes after coronary stenting by individualizing therapy.

METHODS

We randomly assigned 2440 patients scheduled for coronary stenting at 38 centers to a strategy of platelet-function monitoring, with drug adjustment in patients who had a poor response to antiplatelet therapy, or to a conventional strategy without monitoring and drug adjustment. The primary end point was the composite of death, myocardial infarction, stent thrombosis, stroke, or urgent revascularization 1 year after stent implantation. For patients in the monitoring group, the VerifyNow P2Y12 and aspirin point-of-care assays were used in the catheterization laboratory before stent implantation and in the outpatient clinic 2 to 4 weeks later.

RESULTS

In the monitoring group, high platelet reactivity in patients taking clopidogrel (34.5% of patients) or aspirin (7.6%) led to the administration of an additional bolus of clopidogrel, prasugrel, or aspirin along with glycoprotein IIb/IIIa inhibitors during the procedure. The primary end point occurred in 34.6% of the patients in the monitoring group, as compared with 31.1% of those in the conventional-treatment group (hazard ratio, 1.13; 95% confidence interval [CI], 0.98 to 1.29; P=0.10). The main secondary end point, stent thrombosis or any urgent revascularization, occurred in 4.9% of the patients in the monitoring group and 4.6% of those in the conventional-treatment group (hazard ratio, 1.06; 95% CI, 0.74 to 1.52; P=0.77). The rate of major bleeding events did not differ significantly between groups.

CONCLUSIONS

This study showed no significant improvements in clinical outcomes with platelet-function monitoring and treatment adjustment for coronary stenting, as compared with standard antiplatelet therapy without monitoring. (Funded by Allies in Cardiovascular Trials Initiatives and Organized Networks and others; ARCTIC ClinicalTrials.gov number, NCT00827411.)

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Clopidogrel and aspirin play a central role in the treatment of patients undergoing percutaneous coronary intervention.[1] Up to one third of patients have inadequate platelet inhibition, with an increased risk of events.[2-5] Platelet-function testing can determine the degree of platelet reactivity during treatment at the bedside and potentially identify patients in whom adjustment of antiplatelet therapy is warranted to minimize the risks of both ischemic and bleeding complications.[6]

Cohort studies and meta-analyses have largely shown the prognostic value of high platelet reactivity during antiplatelet therapy in patients undergoing coronary stenting.[7,8] Randomized clinical trials have also shown that stronger platelet inhibition can reduce ischemic events in patients presenting with an acute coronary syndrome that is invasively managed, but this comes at the cost of more bleeding complications.[9-12] Two recent studies selected patients with high platelet reactivity during treatment with clopidogrel in order to show the superiority of stronger P2Y12 inhibition; one study was negative, and the other was interrupted prematurely.[13,14] It is unknown whether individualized antiplatelet therapy in all patients undergoing bedside testing before and after stenting can improve the long-term clinical outcome.

The Assessment by a Double Randomization of a Conventional Antiplatelet Strategy versus a Monitoring-guided Strategy for Drug-Eluting Stent Implantation and of Treatment Interruption versus Continuation One Year after Stenting (ARCTIC) study evaluated a strategy of systematic platelet-function monitoring for the purpose of adjusting treatment in patients with a poor response to aspirin, thienopyridine (clopidogrel or prasugrel), or both, as compared with a conventional approach in which similar treatment was given to all patients, without platelet-function assessment.[15]

Methods

Study Patients

In this randomized, open-label study, we recruited patients who were scheduled to undergo drug-eluting stent implantation at 38 centers in France. Exclusion criteria were primary percutaneous coronary intervention for myocardial infarction with ST-segment elevation, the planned use of glycoprotein IIb/IIIa inhibitors, long-term anticoagulation therapy, or bleeding diathesis. The study was undertaken according to the Declaration of Helsinki. The protocol was approved by the French National Institutional Ethical Review Board and has been published previously.[15] Written informed consent was obtained from all the patients.

Randomization and Treatment Strategies

Randomization was conducted centrally with the use of an interactive voice-response system. Eligible patients were randomly assigned to a strategy of platelet-function evaluation with adjustment of antiplatelet drugs and doses in patients with an inadequate platelet-inhibitory response (monitoring group) or to a strategy of conventional treatment without platelet-function assessment (conventional-treatment group). Randomization always occurred after coronary angiography and before the intervention procedure was begun. In both groups, treatment with oral antiplatelet agents before randomization was left to the physician's discretion, but a loading dose of P2Y12 inhibitors to be administered at least 6 hours before stent implantation was recommended.

In the monitoring group, platelet-function measurements were performed for both aspirin and P2Y12 inhibitors. The same measurements were repeated 2 to 4 weeks after stent implantation in order to adjust the maintenance therapy, if necessary. Platelet-function monitoring was performed with the use of the VerifyNow assay (Accumetrics), a point-of-care platelet-function test that uses two different cartridges for aspirin and P2Y12 inhibitors. High platelet reactivity during treatment with aspirin was defined as 550 or more aspirin reaction units. High platelet reactivity during treatment with thienopyridine was defined as 235 or more platelet reaction units, 15% or less inhibition, as compared with a baseline measurement of aggregation induced by thrombin-receptor activating peptide, or both.

Before stent implantation, if high platelet reactivity during treatment with aspirin was identified, the protocol called for the administration of intravenous aspirin. If high platelet reactivity during treatment with clopidogrel was identified, the protocol called for the administration of glycoprotein IIb/IIIa inhibitors and an additional loading dose of clopidogrel (at a dose of ≥600 mg) or a loading dose of prasugrel (at a dose of 60 mg) before the procedure, followed by a daily main-

tenance dose of 150 mg of clopidogrel or 10 mg of prasugrel after the procedure. Antiplatelet therapy was not changed for patients with an adequate response.

At 14 to 30 days after stent implantation, patients with high platelet reactivity during treatment with clopidogrel were switched to prasugrel at a dose of 10 mg or received a 75-mg increase in the maintenance dose of clopidogrel; patients with low platelet reactivity during treatment with thienopyridine, defined as more than 90% inhibition, were switched to clopidogrel at a maintenance dose of 75 mg if they were receiving prasugrel at a dose of 10 mg or clopidogrel at a dose of 150 mg. For patients with an adequate response to antiplatelet therapy, no changes in treatment were made.

In the conventional-treatment group, patients underwent stent implantation without any platelet-function testing performed. The use of both aspirin and clopidogrel or prasugrel and the use of glycoprotein IIb/IIIa inhibitors were left to the physician's discretion, with the recommendation to follow the current practice and the most recent international guidelines. Prasugrel became available in France on December 28, 2009, during the conduct of the trial.

END POINTS

The primary end point was the composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis. All definitions have been described elsewhere.[15] The main secondary efficacy end point was the composite of stent thrombosis (revascularized or not) and urgent revascularization. Other prespecified end points included the composite of death, recurrent acute coronary syndrome, or stroke; the composite of death or resuscitation after cardiac arrest; the composite of death or myocardial infarction; and each individual component of the primary end point. The main safety end point was defined as a major bleeding event, according to the percutaneous coronary intervention–specific definition set in the Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients, an International Randomized Evaluation (STEEPLE) trial.[16] All events were adjudicated by an independent clinical events committee whose members were unaware of the treatment assignments.

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

Characteristic	Conventional Treatment (N=1227)	Monitoring (N=1213)
Age — yr		
Median	63	63
Interquartile range	56–72	56–72
Female sex — no. (%)	247 (20.1)	223 (18.4)
Body weight — kg		
Median	78.0	78.0
Interquartile range	70.0–88.5	69.0–87.0
Medical history and risk factors — no. (%)		
Diabetes	449 (36.6)	440 (36.3)
Dyslipidemia	835 (68.1)	817 (67.4)
Hypertension	745 (60.7)	776 (64.0)
Current smoking	292 (23.8)	311 (25.6)
Prior stroke	57 (4.6)	53 (4.4)
Prior cardiovascular event — no. (%)		
Heart failure	41 (3.3)	44 (3.6)
Myocardial infarction	384 (31.3)	351 (28.9)
Percutaneous coronary intervention	545 (44.4)	505 (41.6)
Coronary-artery bypass grafting	86 (7.0)	75 (6.2)
Concomitant medication — no. (%)		
Angiotensin-converting–enzyme inhibitor	656 (53.5)	676 (55.7)
Beta-blocker	733 (59.7)	681 (56.1)
Statin	836 (68.1)	819 (67.5)
Proton-pump inhibitor	393 (32.0)	394 (32.5)
Calcium-channel blocker	252 (20.5)	268 (22.1)
Coronary intervention		
Stent implanted — no. (%)	1202 (98.0)	1189 (98.0)
No. of stents implanted		
Median	1	1
Interquartile range	1–2	1–2
Drug-eluting stent implanted — no. (%)	1188 (96.8)	1179 (97.2)
Stented vessel — no. (%)		
Left main coronary artery	45 (3.7)	42 (3.5)
Left anterior descending coronary artery	649 (52.9)	611 (50.4)
Left circumflex coronary artery	364 (29.7)	374 (30.8)
Right coronary artery	385 (31.4)	408 (33.6)
Saphenous-vein graft	13 (1.1)	9 (0.7)

* There were no significant between-group differences.

STUDY OVERSIGHT

The trial was conducted by members of the nonprofit academic research organization Allies in Cardiovascular Trials, Initiatives, and Organized

Networks (ACTION), which is based at Pitié-Salpêtrière Hospital (www.action-coeur.org). None of the funding organizations had any involvement in the design or conduct of the study, site selection, data collection, analysis of the results, or writing of the manuscript. Accumetrics was not a sponsor of the trial; all equipment and cartridges for the assays were purchased. The trial was designed and the protocol and manuscript were written by the first and last authors, who made the decision to submit the manuscript for publication; the manuscript was modified and approved by the steering committee, whose members assume responsibility for the accuracy and completeness of the report as well as its fidelity to the study protocol.

STATISTICAL ANALYSIS

We hypothesized that the annual event rate would be 15% among patients with a poor response to antiplatelet therapy and 6% among those with a good response, and we expected that one third of patients would have a poor response. Assuming this annual risk of 9% in the control group (two thirds of the patients at an event rate of 6% and one third at a rate of 15%) for the primary end

Table 2. Antiplatelet Therapy.*

Treatment	Conventional Treatment (N=1227)	Monitoring (N=1213)	P Value
Clopidogrel			
Before randomization — no. (%)			
Any treatment	1098 (89.5)	1073 (88.5)	0.42
Loading dose†	851 (69.4)	840 (69.2)	0.95
Maintenance dose‡	645 (52.6)	601 (49.5)	0.14
After randomization			
High platelet reactivity — no. (%)§	NA	419 (34.5)	—
Loading dose at time of procedure — no. (%)	125 (10.2)	307 (25.3)	<0.001
Loading dose at time of procedure — mg			0.01
Median	450	600	
Interquartile range	300–600	300–600	
Prasugrel			
Before randomization — no. (%)			
Loading dose†	9 (0.7)	7 (0.6)	0.63
Maintenance dose‡	11 (0.9)	19 (1.6)	0.13
Loading dose at time of procedure — no. (%)	4 (0.3)	15 (1.2)	0.01
Thienopyridine at discharge — no. (%)			
Any	1218 (99.3)	1197 (98.7)	0.15
Clopidogrel	1147 (93.5)	1084 (89.4)	0.003
Prasugrel	71 (5.8)	113 (9.3)	0.001
Aspirin			
Before randomization — no. (%)			
Loading dose†	375 (30.6)	362 (29.8)	0.70
Maintenance dose‡	829 (67.6)	812 (66.9)	0.74
After randomization			
High platelet reactivity — no. (%)¶	NA	92 (7.6)	NA
Intravenous loading dose or additional bolus of aspirin in patients with a poor response — no./total no. (%)¶	NA	78/92 (84.8)	NA
At discharge, in any form or dose — no. (%)	1211 (98.7)	1204 (99.3)	0.17

Table 2. (Continued.)

Treatment	Conventional Treatment (N=1227)	Monitoring (N=1213)	P Value
Glycoprotein IIb/IIIa–inhibitor loading at time of procedure — no. (%)	75 (6.1)	365 (30.1)	<0.001
Thienopyridine at follow-up visit between days 14 and 30 — no./total no. (%)‖			
High platelet reactivity§	NA	186/1193 (15.6)	NA
Increase in clopidogrel maintenance dose in patients with a poor response	NA	80 /186 (43.0)	NA
Prasugrel maintenance dose	71/1192 (6.0)	144/1193 (12.1)	<0.001
Aspirin at follow-up visit between days 14 and 30			
High platelet reactivity — no. (%)¶	NA	46 (3.9)	NA
Increase in maintenance dose in patients with a poor response — no./total no. (%)	NA	21/46 (45.7)	NA
Treatment at last visit — no. (%)			
Clopidogrel	1060 (86.4)	971 (80.0)	<0.001
Prasugrel	75 (6.1)	144 (11.9)	<0.001
Aspirin	1179 (96.1)	1164 (96.0)	0.87

* NA denotes not applicable.
† A loading dose was defined as a dose received within 48 hours before the procedure, unless specified as occurring at the time of the procedure.
‡ A maintenance dose was defined as a dose received for more than 7 days after the procedure.
§ Enhanced platelet reactivity during thienopyridine treatment was defined as 235 or more platelet reactivity units, 15% or less inhibition, as compared with a baseline measurement of aggregation induced by thrombin-receptor activating peptide, or both.
¶ High platelet reactivity during aspirin treatment was defined as 550 or more aspirin reactivity units.
‖ Blood samples were obtained at this visit and tested successfully with the use of the VerifyNow assay (Accumetrics) for a total of 1193 patients in the monitoring group.

point and expecting a 33% reduction in relative risk in the monitoring group (at a two-sided alpha level of 5% and a beta error of 20%), we calculated that we would need to enroll a total of 2466 patients in order to show the superiority of the strategy of monitoring and dose adjustment. Assuming a low attrition rate, we decided that 2500 patients would be needed to undergo randomization in the study. There was no sample-size reassessment.

The analysis was based on all events that occurred in the intention-to-treat population, which was defined as all patients who underwent randomization and who provided written informed consent. For patients who withdrew consent during the study, only the data collected before the day of withdrawal were included. The primary and secondary end points were analyzed with the use of a Cox model for survival analysis. Data from all patients were censored at the date of the last available information. The 95% confidence interval for the hazard ratio is presented. Nongaussian variables were summarized as medians (with interquartile ranges) and compared with the use of the Mann–Whitney test. Chi-square testing was used for frequency comparisons. All reported subgroup analyses were prespecified. Periprocedural myocardial infarction (type 4a) was defined in the protocol as a troponin level or a creatine kinase MB level 6 hours after the procedure that was more than 3 times the upper limit of the normal range.[15] Prespecified sensitivity analyses using more stringent definitions of type 4a myocardial infarction (a troponin level of 5 or 10 times the upper limit of the normal range) were performed. All tests had a two-sided significance level of 5% and were performed with the use of SAS software, version 9.2 (SAS Institute).

RESULTS

CHARACTERISTICS OF THE PATIENTS

From January 2009 through January 2011, we enrolled 2440 patients, of whom 1227 were assigned to the conventional-treatment group and 1213 to the monitoring group (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Baseline characteristics of the primary-analysis population were well matched between the two study groups (Ta-

ble 1), with 27.0% of patients presenting with an acute coronary syndrome without ST-segment elevation (327 and 330 patients in the conventional-treatment and monitoring groups, respectively). The data from patients who withdrew consent or were lost to follow-up (Fig. S1 in the Supplementary Appendix) were used up to (but not including) the date of the last contact or the date of consent withdrawal.

PLATELET REACTIVITY AND TREATMENT ADJUSTMENT

Despite adequate treatment before catheterization, approximately one third of the patients assigned to the monitoring group had high platelet reactivity during treatment with clopidogrel before stent implantation (Table 2); at the time of the procedure, 80.2% of these patients immediately received an additional loading dose of clopidogrel and 3.3% received an additional loading dose of prasugrel (Fig. S2 in the Supplementary Appendix). Prasugrel was rarely used, owing to its late availability in the trial and its off-label use in patients who were in stable condition, and it was used almost exclusively in the monitoring group. Likewise, glycoprotein IIb/IIIa inhibitors were administered after randomization five times as frequently in the monitoring group as in the conventional-treatment group, on the basis of identified resistance (P<0.001). When response to aspirin was tested before stent implantation, high platelet reactivity was rare and led to the administration of an additional bolus of intravenous aspirin in four of five patients. In the monitoring group, at the time of discharge, 9.3% of patients were being treated with prasugrel, 47.8% of those who were being treated with clopidogrel were receiving a maintenance dose of 150 mg or more, and 37.1% of those who were being treated with aspirin were receiving a dose higher than recommended (>100 mg) (Fig. S2 in the Supplementary Appendix).

When measurements of platelet reactivity were repeated 2 to 4 weeks later in the outpatient clinic, there was a reduction of approximately 50% in the percentage of patients who had a poor response to P2Y12 inhibitors (15.6%, vs. 34.5% at the time of the procedure; P<0.001) (Fig. S3 in the Supplementary Appendix). At this visit, further adjustment of antiplatelet therapy was performed for patients in the monitoring group whose results were not in the range of adequate platelet inhibition (Fig. S3 in the Supplementary Appendix). Patients in the monitoring group, as compared with those in the conventional-treatment group, were more likely to be taking a high dose of aspirin (>100 mg), a high dose of clopidogrel (≥150 mg), or prasugrel, and the differences persisted until the 1-year visit (Table 2).

Adherence to treatment was checked at each of the three follow-up visits. At the request of the regulatory authorities, antiplatelet therapies delivered to enrolled patients were recorded in a dedicated notebook.

EFFICACY END POINTS

At 1 year of follow-up, the primary end point had occurred in 34.6% of patients in the monitoring group and 31.1% of those in the conventional-treatment group (P=0.10) (Table 3 and Fig. 1A). The results were consistently similar for all secondary end points (Table 3 and Fig. 1B).

Similar results were also obtained across all subgroups for both the primary and main secondary end points (Fig. S4 in the Supplementary Appendix). The primary end point was mainly driven by the occurrence of myocardial infarction. However, prespecified sensitivity analyses with periprocedural myocardial infarction defined as a troponin level of 5 or 10 times the upper limit of the normal range confirmed the main results (Fig. S5 and S6 in the Supplementary Appendix).

SAFETY

As determined according to the STEEPLE definitions[16] used in this trial, bleeding events occurred in less than 5.0% of patients. The rate of major bleeding events did not differ significantly between the two groups (hazard ratio with monitoring, 0.70; 95% confidence interval [CI], 0.43 to 1.14). The results were similar for minor bleeding events (Table 3).

DISCUSSION

Platelet-function monitoring with adjustment of antiplatelet therapy as needed before and after stent implantation did not reduce the rate of cardiovascular events, as compared with a conventional-treatment strategy without measurement of the effect of antiplatelet drugs. The prognostic value of high platelet reactivity during treatment has been shown repeatedly,[2-6,8] leading to the rationale for individualized antiplatelet therapy. Bedside tests have previously been used as screening tools to select patients with a poor response to clopidogrel in

Table 3. Study End Points at 1 Year of Follow-up.*

End Point	Conventional Treatment (N=1227)	Monitoring (N=1213)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Ischemic				
Primary end point of death from any cause, myocardial infarction, stent thrombosis, stroke or transient ischemic attack, or urgent revascularization	382 (31.1)	420 (34.6)	1.13 (0.98–1.29)	0.10
Main secondary end point of stent thrombosis, revascularized or not, or any urgent revascularization	57 (4.6)	60 (4.9)	1.06 (0.74–1.52)	0.77
Death, recurrent acute coronary syndrome, stroke, or transient ischemic attack	86 (7.0)	100 (8.2)	1.17 (0.88–1.56)	0.28
Death or resuscitation after cardiac arrest	21 (1.7)	33 (2.7)	1.59 (0.92–2.74)	0.10
Death or myocardial infarction	353 (28.8)	385 (31.7)	1.11 (0.96–1.29)	0.15
Death	20 (1.6)	28 (2.3)	1.41 (0.79–2.50)	0.24
Myocardial infarction	348 (28.4)	368 (30.3)	1.08 (0.93–1.25)	0.32
Stent thrombosis	9 (0.7)	12 (1.0)	1.34 (0.56–3.18)	0.51
Stroke or transient ischemic attack	7 (0.6)	8 (0.7)	1.15 (0.42–3.18)	0.78
Urgent revascularization	52 (4.2)	55 (4.5)	1.06 (0.73–1.55)	0.76
Bleeding				
Major bleeding	40 (3.3)	28 (2.3)	0.70 (0.43–1.14)	0.15
Minor bleeding	21 (1.7)	12 (1.0)	0.57 (0.28–1.16)	0.12
Major or minor bleeding	55 (4.5)	38 (3.1)	0.69 (0.46–1.05)	0.08

* Patients could have more than one end point.

order to evaluate different treatments. However, conflicting results of such interventions have been reported in cohort studies and randomized studies.[7,13,14,17,18] In randomized studies, the intensification of platelet inhibition in patients with a poor response to clopidogrel failed to improve outcomes when double doses of clopidogrel or prasugrel were used, whereas glycoprotein IIb/IIIa inhibition improved outcomes in these patients.[17,18] In the ARCTIC study, P2Y12 inhibition and glycoprotein IIb/IIIa inhibition were both intensified when monitoring showed a poor response to clopidogrel. In addition, patients with a poor response to aspirin were simultaneously monitored and treated. In contrast to the approaches used in previous studies, these adjustments of therapy were all begun before stent placement in order to prevent periprocedural events, were continued after the intervention, and were adjusted at 14 to 30 days to improve the long-term outcome. Nevertheless, we observed no hint of improvement in ischemic outcomes and no better safety outcomes with a strategy of monitoring and drug adjustment as compared with a conventional-treatment strategy.

Several reasons may account for the failure of individualized antiplatelet therapy to improve the outcomes of stent placement. First, previous trials have been criticized for enrolling low-risk populations,[13,14] but we enrolled a higher-risk population in the ARCTIC study, and mortality at 1 year was higher than rates usually observed among patients who undergo elective stenting.[13,14,16,19,20] Second, the percentage of patients who had a poor response to clopidogrel in our study is similar to that observed in the Gauging Responsiveness with a VerifyNow P2Y12 Assay: Impact on Thrombosis and Safety (GRAVITAS) study, but whether a different cutoff value might have been more discriminating deserves further analysis.[21] Third, the type of intervention in patients who had a poor response may be seen as heterogeneous (i.e., the dose regimen or therapy could be changed), but the ARCTIC study was a strategy trial that used all therapeutic options when the level of platelet reactivity was apparently not controlled by the ini-

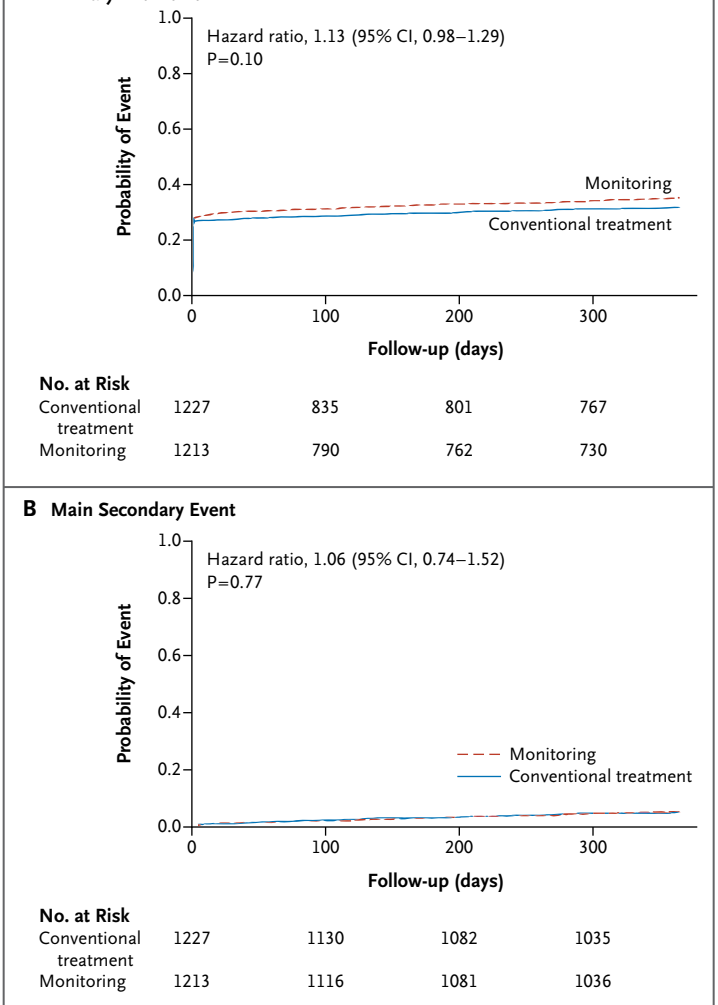

Figure 1. Proportion of Patients with Primary Outcome Events and with Main Secondary Outcome Events.

At 1 year of follow-up, the primary end point, a composite of death from any cause, myocardial infarction, stroke or transient ischemic attack, urgent coronary revascularization, and stent thrombosis, had occurred in 34.6% of patients in the monitoring group and in 31.1% of those in the conventional-treatment group (Panel A). Results were similar for the main secondary end point, a composite of stent thrombosis (revascularized or not) and urgent revascularization (Panel B). CI denotes confidence interval.

tial oral antiplatelet treatment. When we identified a poor response to one of the two antiplatelet agents given for stenting, several drug and dose changes were made, according to a prespecified decision algorithm, to control platelet activation and aggregation during the procedure and after discharge until the 14-day visit.[2] At this visit, another test was performed for the purpose of adjusting the maintenance therapy for the 1 year of treatment. We confirm that high platelet reactivity during treatment with aspirin is uncommon and can be overcome by the administration of an additional bolus of aspirin. In contrast, high platelet reactivity during treatment with clopidogrel is common and can be managed with an additional bolus of clopidogrel or prasugrel and by glycoprotein IIb/IIIa inhibition during the procedure. Fourth, platelet reactivity during treatment remains a surrogate end point for antiplatelet intervention studies, and our study suggests that this marker of risk has limited value in guiding therapeutic decisions. Although platelet function has been seen as a modifiable risk factor,[10,12] an absence of an association between stronger antiplatelet therapy and ischemic outcomes has also been observed elsewhere.[9,22,23] Fifth, platelet-function testing with treatment adjustment cannot affect other prognostic factors, such as adherence to treatment, procedure-related technical factors, or coexisting conditions.

We aimed to recruit a moderate-risk population, chose the best-validated platelet-function test, used well-accepted thresholds for defining a poor response to treatment, tested two pathways of platelet activation corresponding to the dual antiplatelet therapy administered in patients, assessed treatment before the stenting procedure and 2 to 4 weeks later, adjusted therapy aggressively, extended follow-up to 1 year, and had good adherence to the study protocol on the part of the investigators and the patients; however, we were unable to improve outcomes after stenting. Our study was limited by the poor positive predictive value of the assay (12.7%),[2] but we believe that other bedside tests are unlikely to perform better.[24] In addition, our study does not address the use of genetic profiling, which can now be done at the bedside.[25] We cannot exclude the possibility of a benefit of platelet-function testing in a higher-risk population, and the ongoing, randomized ANTARCTIC study (Assessment of a Normal versus Tailored Dose of Prasugrel after Stenting in Patients Aged >75 Years to Reduce the Composite of Bleeding, Stent Thrombosis and Ischemic Complications; ClinicalTrials.gov number, NCT01538446) will assess the value of platelet-function testing in older patients, with a focus on the prevention of bleeding events. An ongoing phase of the current study, ARCTIC-2, is designed to determine the most effective duration

of treatment; a second randomization for the continuation versus interruption of dual treatment occurred 1 year after the first randomization.

We also acknowledge limitations related to the design and conduct of the study. Withdrawal of consent and loss to follow-up represent a limitation, although one that is unlikely to have affected the overall results. The open-label design is a potential limitation, but this approach was the only realistic way of conducting a strategy trial with numerous interventions. The anticipated reduction in relative risk may have been overly optimistic. A posteriori calculations using the observed rate for the primary end point show that the present study would have a power of more than 95% to detect a 33% reduction in relative risk and 80% power to detect an absolute risk reduction of 5 percentage points. Other limitations are related to the failure of high-dose clopidogrel to adequately inhibit platelet function and possibly to the lack of sensitivity of the primary end point, which was driven by a high number of periprocedural myocardial infarctions.

In conclusion, our data do not support the routine use of platelet-function testing in patients undergoing coronary stenting.

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

APPENDIX

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