JACC: CARDIOVASCULAR INTERVENTIONS VOL. 3, NO. 8, 2010

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2010.05.014

Patients With Previous Definite Stent Thrombosis Have a Reduced Antiplatelet Effect of Aspirin and a Larger Fraction of Immature Platelets

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Objectives This study sought to evaluate the platelet response to aspirin and the immature platelet fraction in patients with previous stent thrombosis (ST).

Background ST is a potentially fatal complication of coronary stenting. A reduced platelet response to aspirin increases the risk of cardiovascular events.

Methods We included 117 patients previously undergoing percutaneous coronary intervention. A total of 39 patients had suffered ST and 78 patients served as controls matched at a 1:2 ratio with respect to age, sex, stent type, and percutaneous coronary intervention indication. All patients were treated with aspirin 75 mg once daily. Platelet function was assessed by multiple electrode aggregometry in citrated and hirudinized blood and by VerifyNow Aspirin Assay (Accumetrics, San Diego, California). Flow cytometric determination of the immature platelet fraction was performed to evaluate platelet turnover. Platelet activation was evaluated by soluble serum P-selectin. Compliance was confirmed by serum thromboxane B_2.

Results All patients were fully compliant, which was confirmed by suppressed levels of serum thromboxane B_2. Platelet aggregation was increased in patients with previous ST when assessed by multiple electrode aggregometry induced by collagen ($p_{citrated\ blood} = 0.003$; $p_{hirudinized\ blood} < 0.0001$) and by arachidonic acid ($p_{citrated\ blood} = 0.16$; $p_{hirudinized\ blood} = 0.04$), respectively. Similarly, platelet aggregation assessed by VerifyNow was higher in ST cases ($p = 0.12$). A trend toward an increased immature platelet fraction among cases was seen ($p = 0.13$), whereas P-selectin levels ($p = 0.56$) did not differ between groups.

Conclusions Overall, patients with previous ST had a reduced antiplatelet effect of aspirin, which might be explained by an increased platelet turnover. (J Am Coll Cardiol Intv 2010;3:828–35)

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Manuscript received March 21, 2010; revised manuscript received May 21, 2010, accepted May 31, 2010.

Stent thrombosis (ST) is a potentially fatal complication necessitating preventive dual antiplatelet therapy. Accordingly, current guidelines recommend life-long treatment with aspirin and treatment with clopidogrel for 1 to 3 or 12 months in patients with bare-metal stents (BMS) and drug-eluting stents (DES), respectively (1). The risk of definite ST is approximately 0.6% within 15-month follow-up (2). By reducing neointimal hyperplasia, DES is regarded more effective than BMS in reducing coronary restenosis, but may pre-dispose patients to ST because of incomplete endothelial coverage of the stent struts (3). Stent thrombosis might result from underexpansion or malapposition of the stent, delayed re-endothelialization, or coronary artery dissection. Other pre-disposing factors are stent length, stent type, ST-segment elevation myocardial infarction, diabetes, renal failure, a reduced response to clopidogrel, and premature discontinuation of antiplatelet therapy (3,4).

Aspirin is the mainstay of secondary antithrombotic therapy. Accordingly, low-dose aspirin reduces the risk of vascular events by approximately 32% in high-risk patients (5). Although the antithrombotic properties of aspirin are widely accepted, some patients have a lower platelet response to aspirin. The risk of recurrent vascular events is 8% to 18% within 2-year follow-up among patients on secondary preventive aspirin therapy. Two comprehensive meta-analyses (6,7) unequivocally state that a reduced platelet response to aspirin carries a 4-fold risk of cardiovascular events. Previous studies have suggested that a reduced response to aspirin predisposes specifically to ST (4,8).

The nature of a reduced aspirin response is multifactorial and might comprise clinical, biological, pharmacodynamic, and genetic elements (9). A suggested biological mechanism is based on a large fraction of immature platelets caused by an increased platelet turnover (9–13). Contrary to mature platelets, newly formed platelets express cyclooxygenase-2 (14) and contain ribonucleic acid (RNA) enabling protein synthesis, which may influence their hemostatic potential.

The purpose of the present study was to evaluate the platelet response to aspirin and the fraction of immature platelets in patients with angiographically verified previous ST compared with matched controls with no history of ST.

Methods

Design. We performed a nested case-control study that included 117 patients previously undergoing percutaneous coronary intervention (PCI). We included 39 patients previously diagnosed with ST, and 78 patients with no history of ST served as controls. Cases and controls were matched at a 1:2 ratio with respect to the following risk factors for ST: age, sex, stent type, and indication for PCI.

Patients ≥18 years of age with angiographically verified coronary artery disease were included in the study. All patients underwent coronary stenting between January 1, 2002, and June 30, 2005 (referred to as index PCI), and were treated with nonenteric-coated aspirin 75 mg once daily prior to and during study participation.

Exclusion criteria were the following: aspirin intolerance, any acute or chronic disease (except for coronary artery disease), use of anticoagulants or any drugs known to affect platelet function (including clopidogrel and nonsteroidal anti-inflammatory drugs), platelet count $<120 \times 10^9$/l, any ischemic event or revascularization procedure (PCI or coronary artery bypass grafting) within the previous 12 months, and inability to give informed consent.

Written informed consent was obtained from all participants. The study was conducted in accordance with the Helsinki II declaration, and the study protocol was approved by the Central Denmark Region Committees on Biomedical Research Ethics (project #2008-0189).

Study population. Cases in our study population originate from a study conducted by Kaltoft et al. (2) that included 12,395 patients. The study evaluated mortality and cardiovascular events after coronary stenting with either BMS or DES. A total of 118 patients with previous definite ST were identified according to the Academic Research Consortium criteria (15). Diagnoses were adjudicated by a specialist committee on the basis of medical records and coronary angiographies.

Abbreviations and Acronyms

ARU = aspirin reaction units
AU = aggregation units
BMS = bare-metal stent(s)
DES = drug-eluting stent(s)
IPF = immature platelet fraction
MEA = multiple electrode aggregometry
PCI = percutaneous coronary intervention
RNA = ribonucleic acid
ST = stent thrombosis
S-TxB$_2$ = serum thromboxane B$_2$

The recruitment of patients with previous ST is described in detail in Figure 1. A total of 112 patients were alive when the present study was initiated and 57 patients accepted the invitation to participate. Of these, 18 patients were excluded due to lifelong treatment with clopidogrel or vitamin K antagonists.

Control patients were identified in the Western Danish Heart Registry and enrolled according to pre-defined inclusion and exclusion criteria. The Western Danish Heart Registry collects data on all interventions performed in interventional centers in the western part of Denmark with respect to patient and procedure characteristics.

Laboratory measurements. Standardized blood sampling was performed 1 h after aspirin ingestion. Patients were resting for 30 min before sampling. Samples were drawn from an antecubital vein into vacuum tubes through a 19-G butterfly needle using a minimum of stasis.

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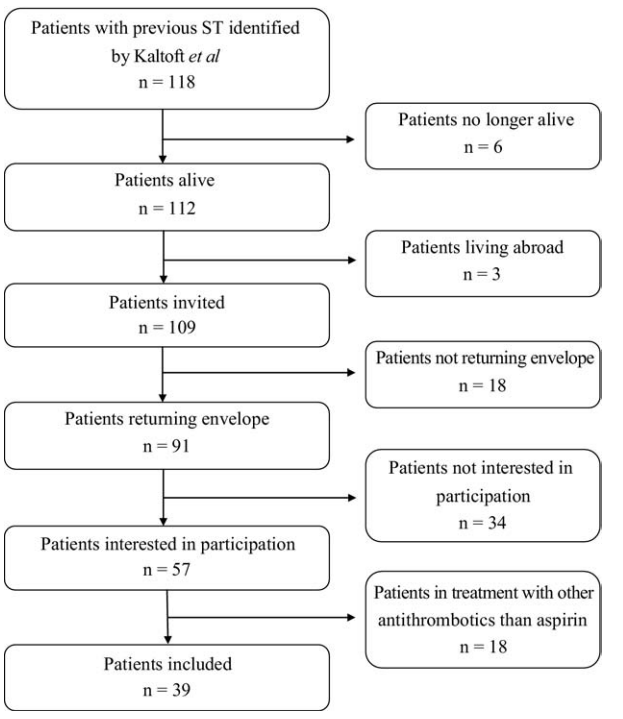

Figure 1. Flow Chart of ST Patients

Flow chart showing the inclusion of patients with previous definite stent thrombosis (ST).

Platelet aggregation was measured with multiple electrode aggregometry (MEA) (Multiplate, Dynabyte, Munich, Germany) and with VerifyNow Aspirin Assay (Accumetrics Inc., San Diego, California). All platelet aggregation analyses were performed within 2 h of sampling. Blood was collected in 3.6-ml (for MEA) or 2.7-ml Terumo Venosafe (for VerifyNow) tubes containing 3.2% sodium citrate, and in 3-ml tubes (for MEA) containing hirudin 25 μg/ml. Collagen (1.0 μg/ml) and arachidonic acid (1.0 mmol/l) served as MEA agonists. VerifyNow inherently employs arachidonic acid as the agonist. The MEA results are expressed as area under the aggregation curve (aggregation units [AU]·min) (16), whereas VerifyNow results are expressed as aspirin reaction units (ARU) (17).

Soluble serum P-selectin was determined by enzyme-linked immunoadsorbent assay according to manufacturer's instructions (R&D Systems, Minneapolis, Minnesota). Blood was collected in nonanticoagulated glass tubes and allowed to clot at room temperature for 30 min before centrifugation for 15 min at 1,000 *g*. The supernatant serum was recovered and stored at −80°C.

The immature platelet fraction (IPF) was measured with a Sysmex XE-2100 hematology analyzer (Sysmex, Kobe, Japan) with upgraded software (XE IPF Master, Sysmex) allowing flow cytometric detection of the IPF as previously described (13,18). Briefly, platelet RNA was stained with fluorescent dyes (polymethine and oxazine) before stained cells were passed through a semiconductor diode laser beam in the flow cytometer. The resulting fluorescence intensity (RNA content) and forward light scatter (cell volume) were measured, and an algorithm integrated in the software discriminated between mature and immature platelets. The IPF was calculated as the ratio of immature platelets to the total platelet count and is given as a percentage.

Serum thromboxane B_2 (S-TxB_2) was determined according to Patrono et al. (19), with the modification that serum was collected after 1 h of clotting and that S-TxB_2 was measured by enzyme-linked immunoadsorbent assay (Cayman Chemical, Ann Arbor, Michigan). Blood was collected in nonanticoagulated glass tubes and allowed to clot at 37°C. Subsequently, it was centrifuged for 10 min at 2,600 *g* and the supernatant serum was stored at −80°C.

Compliance. Compliance was evaluated by face-to-face interviews and pill counting and confirmed by S-TxB_2 measurements. In order to optimize compliance, patients received a tablet dosage box containing 7 nonenteric-coated aspirin tablets and were instructed to save these for the last 7 days before blood sampling.

Statistics. Continuous data are presented as mean ± SD if data were normally distributed, as geometric mean with 95% confidence interval if normally distributed when log-transformed, and as medians with interquartile range (IQR) if not. Unpaired data were compared by the 2-sample *t* test if normally distributed and by the Mann-Whitney *U* test if not. Distributions of categorical variables were compared with the chi-square test and presented as absolute counts and percentages. Aggregation measures in cases and controls were compared by linear regression analysis adjusting for the matched design by using robust standard errors (vce[cluster] option in Stata [StataCorp, College Station, Texas]), and further adjusting for smoking, treatment with proton pump inhibitors, previous coronary artery bypass grafting, and diabetes. A 2-tailed probability value of $p < 0.05$ was considered statistically significant. Statistical analyses were performed using GraphPad Prism version 5.0 (GraphPad Software, La Jolla, California) and Stata version 10.0.

From previous studies we know that patients with coronary artery disease on aspirin therapy display an average aggregation of 430 ARU with a standard deviation of 30 assessed by VerifyNow (17). A pre-defined minimal relevant difference was set at 18 ARU. According to a 2-sided alpha level of 5% and a statistical power of 90%, an estimated sample size of 59 patients with previous ST was calculated. We were able to include 39 patients with previous ST, but compensated by matching at a 1:2 ratio.

Results

Baseline and procedure characteristics are shown in Tables 1 and 2, respectively. The groups were carefully matched with respect to age, sex, stent type, and indication for PCI. There was an excess of previous myocardial infarction and PCI in the case group, though explainable as all cases suffered an extra myocardial infarction and underwent an extra PCI as part of their event of ST. When adjusted for this extra event, the number of previous myocardial infarction and previous PCI did not differ between groups.

A higher prevalence of previous coronary artery bypass grafting was found in the case group, one of which was performed under the indication of ST. Furthermore, the use of proton pump inhibitors was somewhat higher in the case group, whereas more smokers were included in the control group. The 2 groups also significantly differed with respect to the vessel subjected to index PCI. Thus, aggregation analyses are adjusted for smoking, treatment with proton pump inhibitors, number of previous coronary artery bypass grafting, and diabetes.

Within the case population, 26 patients were on aspirin and clopidogrel at the time of ST, whereas the remaining 13 patients were on aspirin only. When explicitly asked before blood sampling, all patients confirmed they had been adherent to aspirin at the time of ST. The median time from index PCI to onset of ST was 10 (range 0 to 1,030) days.

Platelet aggregation. MEA. Analyses were completed in all patients except for 1 case in whom hirudin glasses were discarded due to passed expiration date. As shown in Figure 2, patients with previous ST had an increased platelet aggregation irrespective of the type of agonist and anticoagulant used. Whether induced by collagen (citrated blood: median 176 [IQR 117 to 255] vs. 116 [IQR 66 to 166] AU·min, $p = 0.003$; hirudinized blood: 312 [IQR 218 to 496] vs. 185 [IQR 113 to 260] AU·min, $p < 0.0001$) or by arachidonic acid (citrated blood: median 164 [IQR 102 to

Table 1. Baseline Characteristics of Study Population

	Patients With ST (n = 39)	Control Patients (n = 78)	p Value
Demographics			
Age, yrs*	63.8 (11.3)	63.7 (11.1)	NS
Male sex†	34 (87.1)	68 (87.1)	NS
Risk factors			
Smoking†			0.01
Never	26 (66.7)	29 (37.2)	
At index procedure	7 (17.9)	24 (30.8)	
Today	6 (15.4)	25 (32.1)	
Family history of IHD†	24 (61.5)	51 (65.4)	NS
Body mass index, kg/m^2‡	28.1 (26.7–29.5)	28.0 (27.3–28.8)	NS
Diabetes†	5 (12.8)	13 (16.7)	NS
Biochemistry			
Creatinine, μmol/l§	80.0 (67.5–97.5)	79.0 (67.8–88.3)	NS
Platelets, 10^9/l*	235.2 (47.8)	235.4 (47.8)	NS
Medical history			
Previous MI, n§	2 (1–2)	1 (0–1)	<0.0001
Previous PCI, n§	2 (2–3)	1 (1–2)	<0.0001
Previous CABG†	8 (20.5)	2 (2.6)	0.001
Previous stroke†	3 (7.7)	6 (7.7)	NS
Medication			
Statins†	38 (97.4)	72 (76.9)	NS
Beta-blocker†	32 (82.1)	56 (71.8)	NS
ACE inhibitor†	19 (48.7)	38 (48.7)	NS
AT-II receptor antagonist†	5 (12.8)	18 (23.1)	NS
Calcium antagonist†	7 (17.9)	19 (24.4)	NS
Diuretics†	16 (41.0)	23 (29.5)	NS
Proton pump inhibitor†	9 (23.1)	7 (9.0)	<0.05

*Mean (SD), comparison made using *t* test. †n (%), comparison made using chi-square test. ‡Geometric mean (95% confidence interval), comparison made using *t* test. §Median (interquartile range), comparison made using Mann-Whitney *U* test.

ACE = angiotensin-converting enzyme; AT-II = angiotensin-2; CABG = coronary artery bypass grafting; IHD = ischemic heart disease; MI = myocardial infarction; PCI = percutaneous coronary intervention; ST = stent thrombosis.

Table 2. Onset of ST and Procedural Characteristics of Index PCI

	Patients With ST (n = 39)	Control Patients (n = 78)	p Value
Onset of ST*			
Acute (24 h)	5 (12.8)		
Early (1 to <30 days)	16 (41.0)		
Late (30 days to 1 yr)	6 (15.4)		
Very late (≥1 yr)	12 (30.8)		
Stent type BMS*	22 (56)	44 (56)	NS
Clinical presentation*			NS
Stable AP	14 (35.9)	28 (35.9)	
Non-STEMI/UAP	8 (20.5)	16 (20.5)	
STEMI	17 (43.6)	34 (43.6)	
Lesion length, mm†	17.3 (14.1–21.1)	14.7 (13.1–16.5)	NS
Total stent length, mm†	21.3 (18.0–25.4)	17.8 (15.9–19.9)	NS
Maximum balloon diameter, mm†	3.4 (3.2–3.6)	3.4 (3.3–3.6)	NS
Maximum balloon pressure, atm†	14.0 (12.9–15.3)	14.2 (13.3–15.1)	NS
Post-PCI MLD, mm†	3.3 (3.1–3.5)	3.3 (3.2–3.5)	NS
Stenosis, % of luminal diameter‡	97.0 (90–100)	97.5 (90–100)	NS
Procedure time, min†	28.7 (23.1–35.5)	23.4 (20.4–26.8)	NS
GP IIb/IIIa inhibitor*	20 (51.3)	46 (59.0)	NS
Occluded artery*			<0.05
RCA	12 (30.1)	26 (33.3)	
LAD	24 (61.5)	32 (41.0)	
LCX	3 (7.7)	20 (25.6)	

*n (%), comparison made using chi-square test. †Geometric mean (95% confidence interval), comparison made using *t* test. ‡Median (interquartile range), comparison made using Mann-Whitney *U* test.

AP = angina pectoris; BMS = bare-metal stent(s); GP = glycoprotein; LAD = left anterior descending coronary artery; LCX = left circumflex artery; MLD = minimum luminal diameter; RCA = right coronary artery; STEMI = ST-segment elevation myocardial infarction; UAP = unstable angina pectoris; other abbreviations as in Table 1.

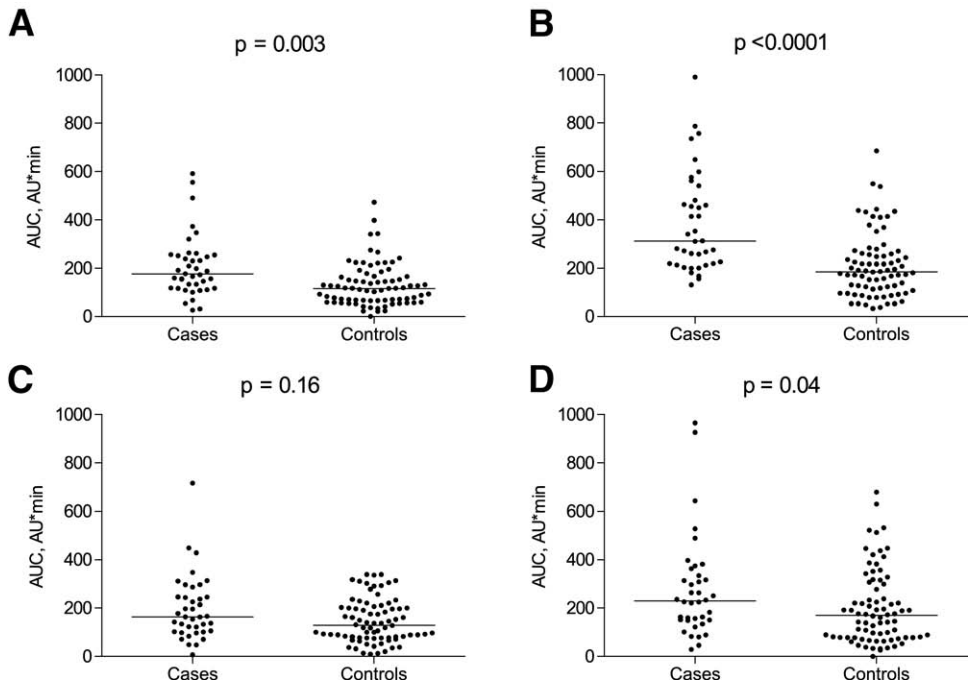

Figure 2. Platelet Aggregation by MEA

Platelet aggregation in 117 patients with coronary artery disease: 39 patients with previous stent thrombosis (cases) and 78 patients with no history of stent thrombosis (controls). Aggregation was induced by collagen 1.0 μg/ml in **(A)** citrated and **(B)** hirudinized blood as well as by arachidonic acid 1.0 mmol/l in **(C)** citrated and **(D)** hirudinized blood. AU = aggregation units; AUC = area under the aggregation curve; MEA = multiple electrode aggregometry.

246] vs. 129 [IQR 77 to 204] AU·min, p = 0.16; hirudinized blood: 230 [IQR 150 to 341] vs. 170 [IQR 78 to 301] AU·min, p = 0.04), residual platelet aggregation was higher in patients with previous ST. The difference was more pronounced, however, when aggregation was induced by collagen. We observed a more potent inhibition of platelet aggregation in citrated blood than in hirudinized blood regardless of the agonist used (all p values <0.05).

VERIFYNOW. Analyses were completed in all patients except for 2 (1 case and 1 control) in whom analyses were stopped prematurely due to instrument error messages. As shown in Figure 3, platelet aggregation was higher in patients with previous ST than in control patients (median 416 [IQR 404 to 434] ARU vs. 409 [IQR 400 to 422] ARU, p = 0.12).

Platelet activation. Soluble serum P-selectin levels did not differ between groups (mean 81.0 ± 29.8 ng/ml vs. 82.3 ± 22.4 ng/ml, p = 0.56).

Platelet turnover. Platelet turnover was assessed by the IPF as shown in Figure 4. Due to technical fallbacks, IPF measurements were only performed in 103 (88%) patients. The IPF did not significantly differ between cases (n = 25) and controls (n = 77) although a trend was seen (median: 2.7% [IQR 2.2% to 3.8%] vs. 2.3% [IQR 1.7% to 3.1%], p = 0.13).

Compliance. All patients returned empty pill boxes and claimed to be adherent to aspirin. In addition, all patients demonstrated S-TxB_2 levels (geometric mean: 1.53 (95% confidence interval: 0.67 to 2.86), range 0.139 to 18.18 ng/ml) far below the normal range of 327 ± 123 ng/ml in healthy individuals not on aspirin therapy (20) and well

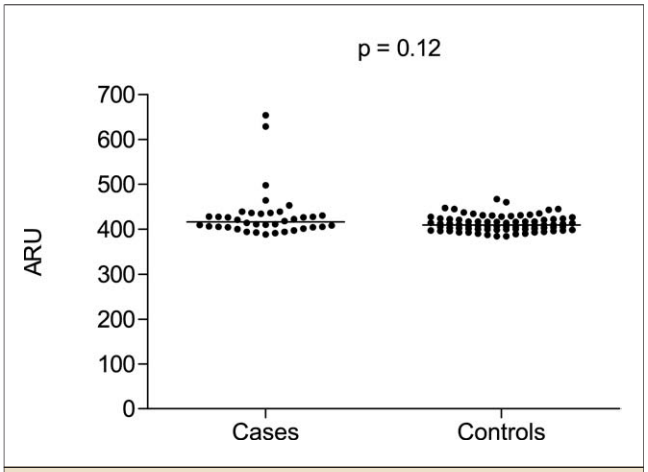

Figure 3. Platelet Aggregation by VerifyNow

Platelet aggregation in 115 patients with coronary artery disease: 38 patients with previous stent thrombosis (cases) and 77 patients with no history of stent thrombosis (controls). ARU = aspirin reaction units.

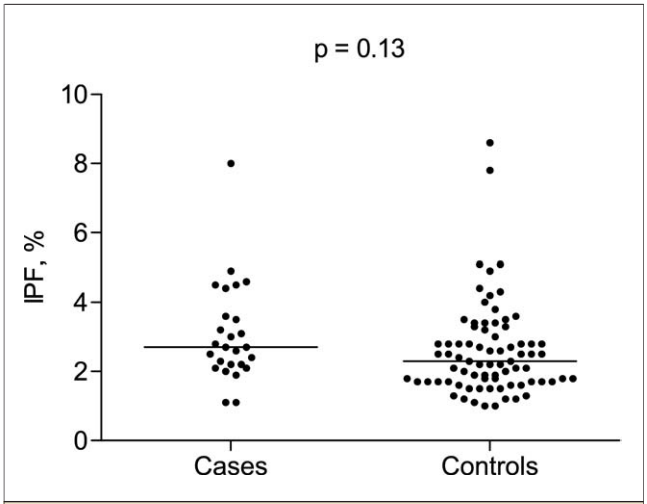

Figure 4. Immature Platelet Fraction

The immature platelet fraction (IPF) in patients with previous stent thrombosis and matched controls.

below 30 ng/ml, corresponding to a more than 95% inhibition of platelet cyclooxygenase-1 activity (21).

Discussion

We evaluated platelet aggregation in 117 patients previously subjected to coronary stenting and found an increased platelet aggregation in patients previously suffering definite ST. This finding stresses the importance of platelet aggregation in the pathophysiology of ST and may partly explain the excess of cardiovascular events in patients suffering ST.

Our study is the largest to specifically investigate the platelet response to aspirin in patients with angiographically verified ST defined according to the Academic Research Consortium criteria (15). Patients were fully compliant with aspirin monotherapy and were matched for 4 important ST risk factors. Compared with our sample size calculation, we included a larger number of control patients to compensate for the inclusion of less ST patients than expected (Fig. 1). Pinto Slottow et al. (22) evaluated the platelet response to aspirin by VerifyNow and, in agreement with our findings, reported an increased platelet aggregation in 26 patients with previous ST compared with 21 control patients. All these patients were on dual antiplatelet therapy, though.

Previously, Gum et al. (23) have shown that a reduced response to aspirin is a significant predictor of cardiovascular events in patients with coronary artery disease. Furthermore, Gori et al. (4) identified a reduced platelet response to aspirin and clopidogrel as an independent predictor of ST. In accordance with Wenaweser et al. (8), we found arachidonic acid-induced platelet aggregation by MEA to be higher in patients with previous ST than in matched controls. Similarly, in our study collagen-induced platelet aggregation by MEA was significantly higher in patients with ST.

The pathophysiology of ST partly depends on the timing of the event. Acute (24 h) and early (1 day to <30 days) ST may result from elastic recoil and platelet-dependent mural thrombus formation caused by periprocedural vessel injury or stent underexpansion, whereas late (30 days to 1 year) and very late (≥1 year) ST are often caused by chronic morphological changes as part of arterial remodeling (3). Of the 39 ST patients in our study, 21 suffered acute or early ST, whereas the remaining 18 patients suffered late or very late ST. We acknowledge that such heterogeneity likely covers different pathophysiological mechanisms, including periprocedural complications.

Overall, ST patients had a higher residual platelet aggregation during treatment with aspirin. Additionally, a trend toward an increased IPF was seen, although our study was not powered to detect such differences. The larger IPF indicates that an increased platelet turnover might be important for platelet aggregation and the platelet response to aspirin. Recently, a higher platelet aggregation in individuals with an increased platelet turnover has been demonstrated in healthy individuals (10,11) and in patients with acute coronary syndrome (12). Newly formed immature platelets express cyclooxygenase-2 (14) and contain RNA enabling protein synthesis, which may influence their hemostatic potential. Furthermore, the accelerated platelet turnover per se may also be important. In patients with a high platelet turnover, platelets unaffected by aspirin are introduced into the blood stream possibly causing the overall platelet inhibition to be insufficient, especially during the last hours of the dosing interval (24).

Previously, platelet aggregation in patients on dual antiplatelet therapy has been evaluated (4,25), whereas platelet aggregation in patients on aspirin monotherapy has only been sparsely investigated. Firm conclusions on the biochemical mechanisms underlying a reduced aspirin response are difficult to draw from studies evaluating patients on dual antiplatelet therapy, because several interdependent platelet activation pathways are simultaneously inhibited (26).

All patients in our study were treated with aspirin 75 mg once daily, ensuring a more than 95% inhibition of platelet cyclooxygenase-1 activity. No further increase in antiplatelet potency is obtained by dose increments, whereas the rate of bleeding complications is likely to increase (5). It remains uncertain whether a reduced platelet response to aspirin can be overcome by dose increments; however, the results of the ongoing CURRENT–OASIS 7 (Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events–Organization to Assess Strategies in Ischemic Syndromes) trial (27) are expected to shed light on this field.

In clinical practice, a reduced platelet response to aspirin is often attributable to noncompliance (28). In our study, all patients were fully compliant according to S-TxB_2, which is

regarded as the most specific test for measuring the effect of aspirin on platelets (29).

Platelet aggregation analyses by MEA were performed in both citrated and hirudinized blood, the latter of which allowed us to investigate platelet function in a Ca^{2+}- and Mg^{2+}-rich environment. Platelet aggregation was more potently inhibited under citrate preservation regardless of the agonist used, which might result from the acidification and the chelation of divalent cations caused by citrate.

The use of proton pump inhibitors was higher among patients with previous ST (Table 1). Safety concerns have arisen from reports of a potential drug interaction between clopidogrel and proton pump inhibitors (30,31). Recently, we evaluated the antiplatelet effect of aspirin in patients with coronary artery disease concomitantly treated with proton pump inhibitors (32). This study suggested that proton pump inhibitors reduce the antiplatelet effect of aspirin and, accordingly, in the present study, we adjusted for the use of proton pump inhibitors.

Standardized and highly reproducible methods are needed before platelet function testing can be adopted into clinical practice. At present, an increasingly large number of platelet function tests are available each employing a different methodological approach. Abundant data suggest that VerifyNow (33,34) and MEA (16) are among the most reliable methods for predicting cardiovascular events.

Study limitations. The retrospective nature of our study did not allow the demonstration of any causality between ST and residual platelet aggregation during treatment with aspirin. Therefore, our findings should be considered hypothesis-generating. Furthermore, a considerable number of potentially eligible patients were treated with antithrombotic drugs other than aspirin, causing potential selection bias. Accordingly, we were not able to include as many case patients as estimated by the sample size calculation. We acknowledge that the inclusion of both BMS and DES might result in several different pathophysiological mechanisms underlying our findings.

Conclusions

In our study, patients with previous ST had a higher residual platelet aggregation during treatment with aspirin than matched controls. This might be explained by an increased platelet turnover. Point-of-care platelet function testing might carry the potential to identify patients at increased risk of ST. Clinical randomized studies are needed to clarify whether optimizing antithrombotic therapy reduces the risk of cardiovascular events in high-risk patients.

Acknowledgment

The authors would like to thank Svend Juul, Associate Professor at Institute of Public Health, Department of Epidemiology, Aarhus University, Denmark, for his invaluable statistical assistance.

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Key Words: aspirin ■ immature platelets ■ platelet aggregation ■ platelet function tests ■ stent thrombosis.