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Original article

Aspirin responsiveness and 6-month clinical outcome observed in a cohort study of patients with unstable angina pectoris

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Background: Whether patients with coronary heart disease (CHD) and resistance to aspirin found by in vitro tests are at a greater risk of major adverse cardiovascular events (MACEs) is controversial.

Objective: To identify any association between resistance to aspirin found by in vitro tests and MACEs in patients with unstable angina pectoris (UAP).

Methods: Previously we demonstrated that 38 of 104 patients admitted to hospital with UAP showed resistance to aspirin using whole blood aggregometry (WBA). In the present study, the same cohort was observed during a 6-month follow-up. The primary end points were MACEs, including cardiovascular death, nonfatal myocardial infarction, revascularization, stroke/transient ischemic attack, or worsening UAP that required the patient to be readmitted to hospital.

Results: During the course of 6 months, only 1 patient in the aspirin-sensitive group was lost in follow-up, and MACEs occurred in 24 patients. Patients with resistance to aspirin found by WBA did not apparently have a higher risk of MACEs compared with patients who were aspirin-sensitive (29% vs 20%, $P > 0.05$). Cox regression analysis showed that resistance to aspirin found by WBA appeared to have no significant correlation with 6-month clinical outcome (HR 1.56, 95% CI 0.70–3.48, $P > 0.05$).

Conclusion: Aspirin resistance, as defined by WBA, was not associated with an increased risk of MACEs in patients with UAP in a 6-month follow-up. Clarification of the clinical significance of aspirin responsiveness detected by platelet function tests requires further investigation in larger longitudinal studies.

Keywords: Aggregometry, antiplatelet, aspirin responsiveness, major adverse cardiovascular events, unstable angina pectoris

The antiplatelet agent, aspirin is proven to prevent vascular events in patients with a wide range of atherosclerotic diseases [1]. However, a significant proportion of patients experience ischemic events despite regular aspirin therapy [2], and platelet function tests in the laboratory have detected variable antiplatelet responsiveness in aspirin-treated patients [3]. This "aspirin resistance" includes 2 concepts: laboratory resistance and clinical resistance [4, 5]. Resistance to aspirin determined by laboratory-based tests has been used to refer to an inadequate ability of aspirin to suppress platelet aggregation in laboratory tests in vitro. Clinical resistance to aspirin has been defined mainly as failure of aspirin to protect individuals from thromboembolic vascular events. Previous studies have estimated that the prevalence of resistance to aspirin found by laboratory tests is 5.5%–45% [6, 7]. Clinical resistance to aspirin can only be diagnosed in retrospect by the occurrence of an ischemic event. Unlike clinical resistance, a diagnosis of laboratory resistance to aspirin can be made before an ischemic event occurs; this hypothetically allows patients identified with resistance to aspirin by in vitro tests to receive a more effective antiplatelet therapy. Yet, the important question—whether patients who are identified as having

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resistance to aspirin by in vitro tests are at a higher risk of vascular events (i.e. whether they also have clinical resistance to aspirin) has not been answered definitely.

Some studies have investigated the clinical consequences of resistance to aspirin in patients with stable coronary artery disease [8-10], but there has been little prospective data linking resistance to aspirin found in the laboratory and clinical outcomes found in follow-up of patients with unstable angina. In a cohort of 104 patients with unstable angina pectoris (UAP), we previously reported a 37% prevalence of resistance to aspirin detected by whole blood aggregometry [11]. In present study, we sought to determine whether this resistance to aspirin found in vitro affects the occurrence of major adverse cardiovascular events (MACEs) during a prospective 6-month follow-up of the patients with UAP.

Materials and methods

Patients

After approval of our protocols by our Institutional Review Board in accordance with the contemporary Declaration of Helsinki, we enrolled 104 consecutive patients with UAP (57 men and 47 women). Only those who had taken aspirin 100 mg daily for ≥1 week before admission were included in the study. All patients provided written informed consent for their participation. UAP was defined by the American College of Cardiology–American Heart Association 2007 Guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction [12]. Exclusion criteria included the use of different doses of aspirin; concurrent use of clopidogrel, ticlopidine, dipyridamole, or nonsteroidal anti-inflammatory drugs; myeloproliferative disease; any major surgical procedure within 1 month of enrollment; a family or personal history of bleeding disorders; platelet count $<100 \times 10^3/\mu L$ or $>300 \times 10^3/\mu L$; hemoglobin <100 g/L, or hepatic or renal insufficiency.

Definition of aspirin resistance

Whole blood samples were collected from every patient by antecubital venipuncture between 1 and 24 hours after administration of the most recent dose of aspirin. Aspirin resistance was measured in whole blood using electrical aggregometry (560CA, Chrono-Log; Havertown, PA, USA), as previously described. In our previous study, samples from healthy individuals who took no drugs for >7 days were assayed to determine normal reference laboratory values for whole blood aggregometry (WBA), and a reference interval from 10.4 to 18.8 Ω with 1 μg/mL collagen was accepted [11]. Increased impedance measurements after initiating coagulation with collagen are expected for individuals taking aspirin. We calculated a cut-off based on the mean impedance measured at 6 min in normal individuals, and aspirin resistance was defined as having normal impedance (impedance ≤10 Ω, the cut-off value) despite regular aspirin therapy.

Study end points

Primary end points were MACEs, including cardiovascular death, nonfatal myocardial infarction, revascularization, stroke/transient ischemic attack, or worsening UAP that required the patient to be readmitted to hospital. We defined cardiovascular death as death because of acute myocardial infarction, pump failure, or documented sudden cardiac death. We diagnosed nonfatal myocardial infarction on criteria of typical chest pain, elevated cardiac enzyme levels, and typical changes on the electrocardiogram. We defined revascularization as any unplanned percutaneous coronary intervention (PCI) performed for recurrent symptoms. We defined stroke as a neurological deficit of vascular origin ≥24 h confirmed by a brain imaging and/or a clinical diagnosis by a neurologist or an internist. We defined transient ischemic attack as a neurological symptom of vascular etiology that was resolved within 24 h.

Follow-up

Personnel conducted the clinical follow-up at 6 months by telephone contact or office visits. Personnel conducting follow-up interviews were blinded to the response to aspirin found by laboratory tests. For those patients who reached at least 1 of the primary end points, we examined hospital charts to ascertain whether the event met the criteria for a MACE as defined above.

Statistical analyses

We conducted statistical analyses using SPSS for Windows (version 13.0; SPSS Inc, Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation (SD) and categorical variables are reported as frequencies and percentages. We used a Student *t* test or Mann–Whitney *U* test to compare

continuous variables, and a chi-square test or Fisher exact test to compare categorical variables, as appropriate.

Initially, we used a bivariate Cox regression analysis with age, sex, body mass index, atrial fibrillation, traditional cardiovascular risk factors (including smoking, hypertension, diabetes, hyperlipidemia, and cerebrovascular disease), and aspirin resistance as the independent variables. All the variables with $P \leq 0.1$ were entered into the multivariate model. We then used a Cox regression model to identify independent predictors of MACEs using a stepwise model selection method with an entry of 0.05 and a stay of 0.1.

Subsequently, cumulative time-to-event-free survival curves for groups of aspirin-resistant and aspirin-sensitive patients as determined by WBA were constructed using a Kaplan–Meier method, and a log-rank sum test was used to assess significant differences between these 2 time-to-event-free survival curves. All hazard ratios are presented with their 95% confidence interval (CI). Test probabilities were two-sided, and $P < 0.05$ was considered significant.

Results

Patient characteristics

We identified 38 of 104 patients with UAP to have resistance to aspirin using WBA [11]. Only 1 patient in the aspirin-sensitive group was lost during follow up. Baseline clinical characteristics of the 103 available patients (occurrence of MACEs) are shown in **Table 1**. During the course of 6 months, MACEs occurred in 24 patients. There was no significant difference ($P > 0.05$) in the most of the clinical characteristics observed, including status of aspirin responsiveness between these 2 subgroups with (n = 24) or without (n = 79) MACEs. Patients who experienced a MACE were more likely to have a history of diabetes ($P < 0.05$) or cerebrovascular disease ($P < 0.05$).

Predictors of MACEs

Hazard ratios (HRs) for bivariate and multivariate analyses of 6-month outcome are shown in **Table 2**. Diabetes (HR 2.61, 95% CI 1.04–6.58, $P < 0.05$) and cerebrovascular disease (HR 2.48, 95% CI; 1.02–6.05, $P < 0.05$) were independent predictors of adverse clinical outcomes in the 6-month follow-up. However, the study was not sufficiently powered to detect that a greater WBA impedance was associated with an increased risk of MACEs (HR 1.051, 95% CI 0.96–1.15, $P > 0.05$). The status of aspirin responsiveness (aspirin-resistant or aspirin-sensitive) seemed not to affect the 6-month clinical outcome (HR 1.56, 95% CI 0.70–3.48, $P > 0.05$) in our study cohort with UAP.

Table 1. Baseline clinical characteristics of the cohort according to the occurrence of major adverse cardiovascular events

	Total (n = 103)	Major adverse cardiovascular events		*P*
		Yes (n = 24)	No (n = 79)	
Age (y)	64.7 ± 9.4	67.3 ± 8.3	63.9 ± 9.6	0.12
Male (%)	57 (55)	14 (58)	43 (54)	0.74
Body mass index (kg/m^2)	23.1 ± 3.56	24.0 ± 3.98	22.8 ± 3.40	0.16
Atrial fibrillation (%)	20 (19)	5 (21)	15 (19)	0.84
Smoker (%)	22 (21)	3 (13)	19 (24)	0.23
Hypertension (%)	62 (60)	16 (67)	46 (58)	0.46
Diabetes* (%)	14 (14)	7 (29)	7 (9)	0.011
Hyperlipidemia (%)	12 (12)	1 (4)	11 (14)	0.19
Cerebrovascular disease* (%)	17 (17)	8 (33)	9 (11)	0.011
Impedance values (Ω)	8.3 ± 4.46	9.1 ± 4.33	8.6 ± 4.50	0.34
Aspirin resistance (%)	38 (37)	11 (46)	27 (34)	0.30

*$P < 0.05$

Table 2. Cox regression analysis: hazard ratios of major adverse cardiovascular events according to clinical characteristics, platelet aggregation function, and the status of aspirin responsiveness

	Hazard Ratio	95% CI	*P*
Bivariate analysis			
Age	1.04	0.99–1.09	0.13
Male	0.94	0.42–2.12	0.89
Body mass index	1.10	0.97–1.24	0.14
Atrial fibrillation	1.13	0.42–3.02	0.81
Smoker	0.51	0.15–1.71	0.28
Hypertension	1.40	0.60–3.27	0.44
Diabetes	3.32	1.37–8.02	0.008*
Hyperlipidemia	0.29	0.04–2.17	0.23
Cerebrovascular disease	3.10	1.32–7.26	0.009*
Impedance values	1.05	0.96–1.15	0.28
Aspirin resistance	1.56	0.70–3.48	0.28
Multivariate analysis			
Diabetes	2.61	1.04–6.58	0.04*
Cerebrovascular disease	2.48	1.02–6.05	0.046*

*$P < 0.05$

Aspirin resistance and MACEs

Cumulative time-to-event-free survival curves according to status of aspirin responsiveness are shown in **Figure 1**. In the subgroup of patients with MACEs from our previous observation, 11 patients were found to have resistance to aspirin by WBA. Two of these 11 aspirin-resistant patients died because of events of cardiovascular origin, 1 patient underwent unplanned PCI, 2 patients experienced stroke/transient ischemic attack, and 6 patients were rehospitalized with worsening UAP. The incidence of MACEs in the aspirin-resistant and aspirin-sensitive groups was 29% (11/38) and 20% (13/65), respectively. However, the Kaplan–Meier survival curve showed that the overall risk of MACEs was not significantly higher for patients with aspirin resistance found in the laboratory (log-rank chi-square = 1.25, $P = 0.26$). Hazard curves are shown in **Figure 2**, and no dramatic difference in the hazard for MACEs between these 2 groups was documented.

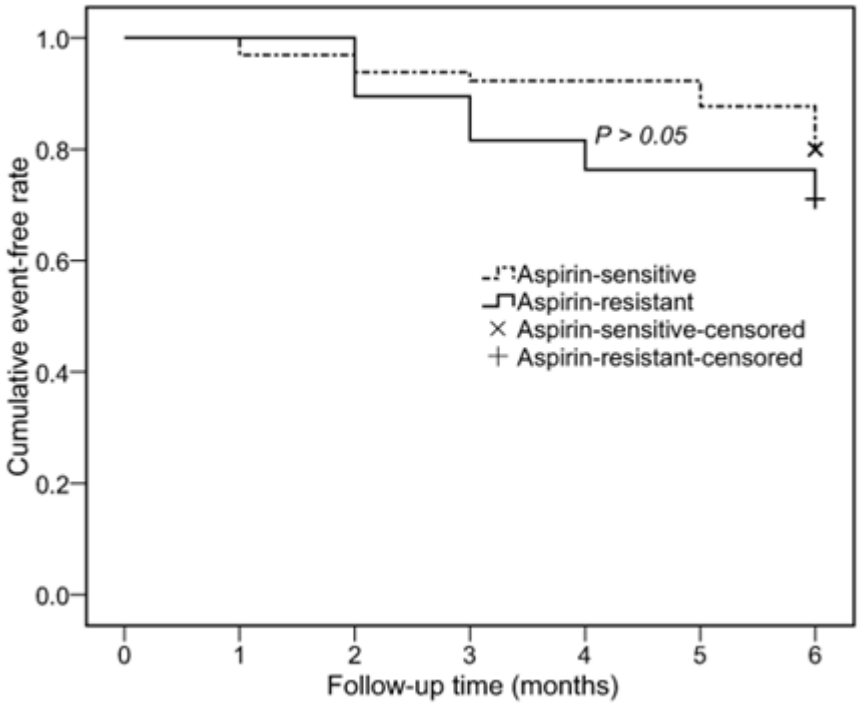

Figure 1. Cumulative time-to-event-free survival curves, log-rank chi-square = 1.25, $P = 0.26$

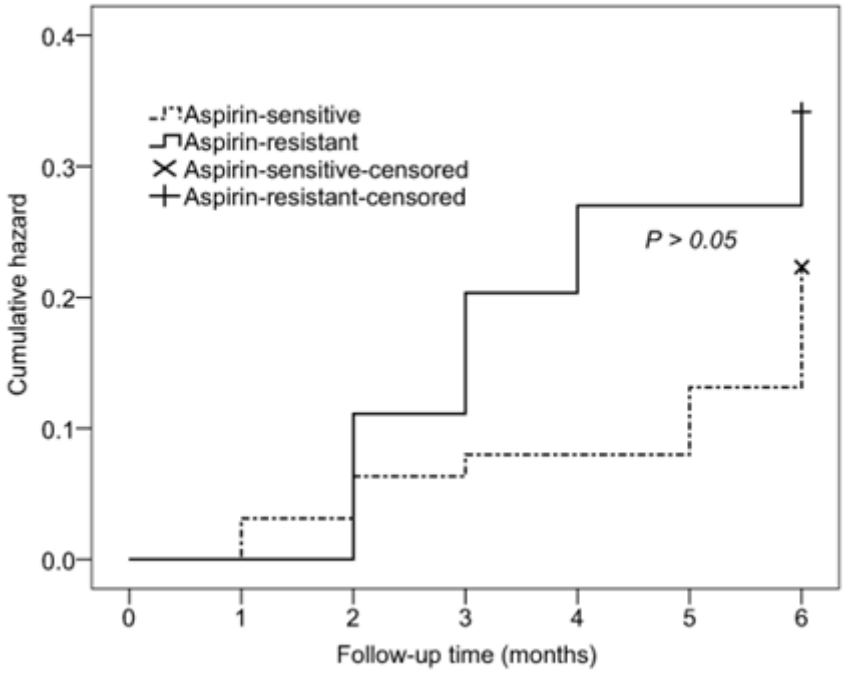

Figure 2. Cumulative hazard for major adverse cardiovascular events

Discussion

Aspirin inhibits the activation of platelets by acetylating cyclooxygenase-1 (COX-1), thus inhibiting the production of thromboxane A_2 (TXA_2) [13-15]. Resistance to aspirin detected by various platelet function tests discussed below [2-4] refers to the inability of aspirin to suppress TXA_2 production by platelets [3, 4]. Possible reasons for apparent resistance to aspirin include inadequate aspirin dose, poor compliance, drug interaction, increased platelet turnover, COX polymorphisms, and platelet activation by alternative signaling [3, 4]. Nevertheless, while the concept "resistance" is widely known, more attention should be paid to its prognostic importance.

In our previous study [11], we used WBA to investigate the prevalence of aspirin resistance in an group of patients with UAP, and found that among 104 patients, 38 had impedance values >10 Ω and these patients were considered aspirin resistant. In the present study, we determined the role of aspirin resistance prospectively on 6-month outcome in the same cohort (n = 103, 1 aspirin-sensitive patient lost in follow-up). The main differences between our present study and other recent studies are the methodology used to evaluate the status of aspirin responsiveness and the choice of patient population.

Various platelet function tests have been used to assess aspirin resistance [2-4], including light transmission aggregometry (LTA), Ultegra rapid platelet-function assay (RPFA), thromboelastography (TEG), and WBA. Various definitions of aspirin resistance have been applied according to the various methodologies. Traditionally, the difference in light transmission between the platelet rich plasma and platelet poor plasma can be recorded by LTA as a percentage. Using LTA, aspirin resistance is usually defined as ≥20% arachidonic acid (AA)- and ≥70% adenosine diphosphate (ADP)-induced platelet aggregation [16]. In RPFA, platelet responsiveness is expressed in aspirin response units (ARU), with a cutoff for aspirin resistance at 550 ARU [17]. Aspirin resistance is defined by TEG as ≥50% aggregation induced by AA [18]. WBA measures the change in electrical impedance between 2 electrodes placed in the whole blood samples when platelets are aggregated by an agonist [19], and seems to be better than traditional LTA to assess an antiplatelet effect [20-22] because it (1) requires a shorter time; (2) performs the test in a more physiological milieu containing red and white blood cells, which are reported to regulate platelet function; (3) has no centrifugation step, thereby avoiding injury to platelets in the sample; and (4) is more closely related to platelet function. At present, WBA is used as a measure of aspirin effect, and especially to identify patients with aspirin resistance in clinical practice [23-26]. Ivandic et al. [23] examined

collagen-induced WBA in 245 patients with stable coronary disease who were treated with 100 mg aspirin and 75 mg clopidogrel daily, and found 24 samples (10%) exhibited an impedance >8 Ω at 6 min and considered the patients providing these samples as aspirin resistant. Lordkipanidze et al. [24] found the prevalence of aspirin resistance was 18.0% by WBA. WBA was used as a reference standard to evaluate RPFA, another method used to detect aspirin resistance [25]. However, few prospective studies have determined the association between resistance to aspirin by WBA and clinical outcome. So far, Mueller et al. [26] used WBA to assess the prognostic importance of aspirin responsiveness in 100 patients with intermittent claudication treated by peripheral arterial angioplasty. During the course of 1 year, a less-than-expected effect of aspirin was independently associated with an increased risk of reocclusion following the peripheral arterial angioplasty.

Moreover, uncertainty remains regarding the measurement, interpretation, and clinical relevance of resistance to aspirin found by laboratory tests in patients with stable coronary disease [27]. In a stable population, Gum et al. [8] prospectively analyzed the natural history of aspirin resistance, subsequently documenting a greater risk of MACEs associated with aspirin resistance, consistent with a report by Chen et al. [9]. By contrast, Pamukcu et al. reported that the risk of MACEs in patients with stable coronary disease and aspirin resistance found in laboratory tests was similar to patients with aspirin-sensitive platelet aggregation [10]. However, only a couple of studies have drawn attention to the clinical importance of aspirin resistance in patients with acute coronary syndromes (ACS) [28, 29], especially in those who were diagnosed as having UAP. In their CARS study, Eccleston et al. [28] demonstrated that aspirin resistance found by LTA could predict an increased risk of an in-hospital event in patients with ACS. UAP can contribute to a higher incidence of subsequent myocardial infarct and cardiovascular death because of the instability of arteriosclerosis plaques [12]. In our previous study, the prevalence of aspirin resistance (36%) among patients with UAP [11] seemed to be higher than in those with stable coronary disease [8-10]. Whether resistance to aspirin found by laboratory tests in patients with UAP can predict an increased risk of MACEs remains unknown.

In our 6-month follow-up, patients who were found aspirin-resistant by WBA did not experience more MACEs than patients who were aspirin-sensitive, but diabetes and cerebrovascular disease were identified as independent predictors of MACEs; these latter findings are consistent with the conclusions of other large-scale clinical studies [30]. Compared with the studies of Chinese patients by Fan et al. [31] and Cao et al. [32], which demonstrated aspirin resistance found by LTA and TEG was associated with an increased risk of MACEs in elderly patients with cardiovascular disease (CVD), the unique features of our study are the use of WBA and selection of patients with UAP. WBA is a more convenient methodology than LTA and TEG, although these traditional measurements have been used in many studies of platelet aggregation. The time-consuming and cumbersome nature of LTA and TEG limit their point-of-care application. UAP is a special type of CVD because of its acute and unstable status, caused by disruption of atherosclerotic plaques with partial thrombosis, and possibly forming emboli or causing vasospasm. Antiplatelet drugs such as aspirin may help to reduce the development of plaques. Thus, information about the prognosis of UAP patients with aspirin resistance would have utility.

Although some studies support the hypothesis that aspirin-resistant patients are at a greater risk of MACEs [8, 9, 28, 29], like the present study, other studies have not found any difference in clinical outcome between patients with or without aspirin resistance [33-35]. In one of these studies, 54.7% of patients who underwent coronary artery bypass surgery were classified as aspirin resistant by bleeding times, and no significant correlation was found between aspirin resistance and thrombotic events in the follow-up period [33]. Buch et al. [34] considered that the measurement of aspirin responsiveness was not clinically important because of its lack of association with MACEs in patients undergoing PCI. Poulsen et al. [35] did not find that the presence of aspirin resistance in patients with CVD affected 1-year clinical outcome.

The issue of the clinical importance of aspirin responsiveness remains unresolved. Nevertheless, a few considerations that arose from the present study may provide some insight into apparent discrepancies between findings by other studies. The platelet activity may have varied because of the status of disease (stable or unstable); Borna et al. [36] reported that platelets were generally activated in patients with ST-elevated myocardial infarction, which resulted in a

higher incidence of aspirin resistance. These authors suggested that the increased ADP levels seen during acute myocardial ischemia contributed to the increased incidence of aspirin resistance. Rasmanis et al. [37] demonstrated that increased incidence of aspirin resistance could be explained by increased activity of positive feedback systems such as from thromboxane and prostacyclin during an acute phase. In the present study, patients with UAP were chosen and more aspirin-resistant patients were identified in our study because higher levels of endogenous platelet agonists such as ADP may activate more platelets despite regular aspirin therapy. The platelet activity of such unstable patients would return to normal when these patients recovered from the acute myocardial injury. Therefore, so-called "pseudoresistance" may exist, explaining why there was no significant association between aspirin resistance and MACEs among patients with UAP. An blinded and controlled study is necessary to verify whether "pseudoresistance" exists in patients with UAP. Moreover, there is fierce debate regarding whether aspirin-treated patients should be tested for aspirin resistance because no consistent approach to the diagnosis has been proposed [24, 38, 39]. In the present study, we used WBA to classify patients according to their aspirin responsiveness. Although the merits have been mentioned, the sensitivity and specificity of WBA in the diagnosis of aspirin resistance remain unclear [40], and WBA does not mimic the high shear environment that is present in vivo [4]. Therefore, further research is required to develop measures of platelet function that are valid, reliable, specific, and standardized.

In conclusion, in patients with UAP, aspirin resistance as determined by WBA seems not to increase the risk of MACEs. We could not completely exclude the importance of aspirin resistance as determined by WBA in clinical practice, because the observed population in the present study was relatively small. A large-scale, multi-centered, prospective, and controlled study is needed to determine the clinical importance of resistance to aspirin detected in the laboratory, and to provide evidence for optimization of antiplatelet therapy.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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