Aspirin Non-Responder in Thai Ischemic Stroke Patients

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Background: *An important cause of recurrent ischemic stroke is failure to prevent secondary stroke due to poor control of important stroke risk factors. One of the proposed important risk factor is aspirin resistance. The prevalence of aspirin resistance varied widely. It depended on heterogeneity in studied populations and methods of platelet functional assessment.*
Objective: *To describe the prevalence of aspirin resistance based on optical platelet aggregometry in stroke patients who attended the Neurological Institute and investigate the clinical risk factors associated with aspirin resistance.*
Material and Method: *Three hundred stable ischemic stroke patients, whose aspirin dosage varied between 60 to 325 mg/day for at least 14 days before enrollment were recruited in the present study. Demographic data, modifiable risk factors, and treatment were collected by interview and from medical records. Aspirin resistance was determined by optical platelet aggregation technique, using arachidonicacid (AA) and adenosine diphosphate (ADP) as agonists.*
Results: *The patients were classified into two groups based on their platelet aggregatometry tests (PAT). The cases group (n = 40, 13.3%) included both patients with aspirin resistance (n = 2, 0.6%) and aspirin semi-responsiveness (n = 38, 12.7%). The control group was aspirin non-resistance (n = 260, 86.7%). The cases were older (64.8 year vs. 61.26 year, p = 0.049), higher proportion of females (60% vs. 41.5%, p = 0.029), and shorter in height (159.9 CM vs. 164.1 CM, p = 0.007) than the control group. Dosage and duration of the aspirin therapy were the same in both groups. The multivariate analysis showed old age was associated with aspirin resistance.*
Conclusion: The prevalence of aspirin resistance in the present study is 0.6% (95% CI, 0.18%-1.38%). The risk factor for aspirin resistance in post stroke patients is aging. No association between duration and aspirin dosage with aspirin resistance was found. The proportion of aspirin resistance was similar to a previous study done in post myocardial infarction patients.

Keywords: *Aspirin resistance, Ischemic stroke*

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Stroke is the global second leading cause of death[1]. Recurrent stroke is a major threat to stroke patients. Previous studies of recurrent strokes reported a first year recurrence rate between 6 and 14%[2,3] and 5-year recurrent rate between 20 and 37%[3]. Despite availability of aspirin as the standard of care for prevention of recurrent ischemic strokes and attempt to control the risk factors of recurrent stroke, the incidence of recurrent ischemic strokes remained unacceptably high[4]. An important cause of recurrent ischemic stroke is inadequate control of stroke risk factors but another possible explanation is an inability to inhibit platelet aggregation by aspirin in some patients. This group of patients has been described as 'aspirin resistance'[5].

Aspirin or acetylsalicylic acid (ASA) irreversibly inhibits platelet aggregation through acetylation of platelet cyclooxygenase 1 (COX-1) enzyme, thereby inhibiting thromboxane A2 synthesis, which is a potent platelet aggregator and vasoconstrictor[6]. Based on its efficacy in prevention of secondary ischemic stroke, aspirin is widely used for secondary prevention in patients with ischemic stroke. Interestingly, the platelet response to ASA shows a high range of individual variation. Aspirin resistance has been consistently associated with an increased risk of cardiovascular events compared to patients who were sensitive to aspirin[5,7].

The prevalence of aspirin resistance varied widely, from 5 to 61%, depending on studied populations and platelet function assessment. Various factors such as genetic predisposition, female,

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smoking, cerebrovascular disease, diabetes and drug interaction, particularly the interaction of non-steroidal anti-inflammatory drugs (NSAID) with aspirin[9-11] are associated with aspirin resistance. There are several techniques to measure platelet aggregation, including optical platelet aggregometry, whole-blood aggregometry, platelet function analyzer (PFA-100w), rapid platelet function assay (Verify Now Aspirin) and urinary 11-dehydrothromboxane B2 measurement. Platelet function tests are not equally effective in measuring antiplatelet effect of aspirin and correlate poorly among each techniques[12]. Optical platelet aggregometry is the current gold standard for evaluation of aspirin resistance[13].

The aims of the present study were to assess the prevalence of aspirin resistance in stroke patients and to investigate the clinical risk factors associated with aspirin resistance, by using optical platelet aggregometry for the determination of aspirin resistance.

Material and Method

A cross-sectional study was conducted at Prasat Neurological Institute, Bangkok, Thailand. Between July 2009 and August 2011, 300 patients with stable ischemic stroke[14], who received aspirin doses between 60 and 325 mg/day for at least 14 days for secondary prevention of cerebrovascular disease, were recruited in the present study. Patients with bleeding diathesis, platelet count <150,000/mm^3, hemoglobin <8 g/dl, creatinine >3 mg/dl, aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >120 IU/L, active malignancy, myeloproliferative disorder, major surgery within one week, smoking within one day, alcohol drinking within two days, current use of NSAIDS, anticoagulants, or antiplatelet drugs other than aspirin within two weeks before the enrollment were excluded from this study. The present study was approved by the ethics committee of Prasat Neurological Institute and written informed consent was obtained from all participants.

Medical records were reviewed and the following variables were assessed, age, sex, body weight, height, waist circumference, body mass index, history of smoking, alcohol drinking and exercise, underlying disease, systolic blood pressure (SBP), diastolic blood pressure (DBP), complete blood count, fasting blood sugar (FBS), HbA1C, creatinine, lipid profile, SGOT, SGPT, The Venereal Disease Research Laboratory test(VDRL), drug usage, dose and duration of aspirin administration, clinical syndrome, and the subtype of ischemic stroke. Patient compliance with aspirin was assessed by the questionnaire.

Hypertension (HT), diabetes mellitus (DM), and hyperlipidemia were diagnosed according to established criteria[15-17]. The diagnosis of carotid stenosis was made when there was 70% stenosis with the NASCET method[18]. The diagnosis of chronic kidney disease was made when the estimated glomerular filtration rate was less than 60 mL/minute per 1.73 m^2[19]. Ischemic stroke was evaluated according to the clinical syndrome by Oxfordshire community stroke project classification (OCSP)[20] as total anterior circulation infarction, partial anterior circulation infarction, lacunar infarction, posterior circulation infarction and further classified according to TOAST criteria, as large vessel infarction, small vessel (lacunar) infarction, cardioembolic, and stroke of other determined or undetermined causes[21].

Blood samples were obtained 24±2 hours after the administration of the last dose of aspirin. Platelet function was assessed by optical platelet aggregation. Platelets in platelet rich plasma (PRP) were stimulated with 10 μmol/mL of ADP and 0.5 mg/mL of arachidonic acid. Aggregation was expressed as the maximal percentage change in light transmittance from baseline, using platelet-poor plasma as a reference. All platelet aggregation tests were performed within three hours after blood collection.

Aspirin resistance or aspirin non-resistance was defined[22,23] by platelet aggregation ≥70% with 10 μmol/ml of adenosine diphosphate (ADP) and platelet aggregation ≥20% with 1.0 mg/mL of arachidonic acid measured by optical aggregometry.

Aspirin semi-responsiveness was defined as platelet aggregation ≥70% with 10 μmol/mL of ADP or platelet aggregation ≥20% with 1.0 mg/mL of arachidonic acid by optical aggregometry.

Aspirin non-resistance were defined when both above criteria were not met.

Statistical analysis

Continuous and categorical variables were expressed as mean and percentages respectively. Parametric and nonparametric comparisons of categorical and continuous variables were performed using the Chi-square test or Fisher's exact test, Student t-test, and Mann-Whitney test, as appropriate. Explanatory variables initially included in the model were those with a probability value <0.15 from the univariate analysis. A p-value less than 0.05 was the threshold of statistical significance. Statistical analysis

was performed by using SPSS 16.0 (SPSS Inc., Chicago, Ill).

Results

Three hundred patients with ischemic stroke who were taking aspirin were enrolled in the present study between July 2009 and August 2011. All participants were tested for platelet function after aspirin administration by optical platelet aggregation technique using AA and ADP as agonists. There were two (0.6%) aspirin resistance patients and 38 (12.7%) patients with aspirin semi-responsiveness. For the purpose of the present study, patients were classified into two groups, the study group included patients with aspirin resistance and aspirin semi-responsiveness (n = 40, 13.3%) and the control group included patients with aspirin non-resistance (n = 260, 86.7%).

The demographic characters of both groups are described in Table 1. Male to female ratio of the study group was 0.67 compared to 1.41 of the control group. Mean age of the study group was 64.8 years (ranged from 44 to 83 years) and of the control group was 61.26 years (range from 25 to 85 years). Mean height in the study group was 159.9 cm and of the control group was 164.1 cm. There was significant difference in terms of age, gender, and height between the study groups versus the control group.

Comparison of risk factors between the study group and the control group was performed. Prevalence of hypertension, DM, hyperlipidemia, ischemic heart disease, and carotid stenosis were not different between both groups.

All patients were classified according to subtype of ischemic stroke as small vessel infarction, large vessel infarction, cardioembolic and stroke of undetermined causes by using TOAST criteria. They were also classified according to clinical stroke syndrome (OCSP) as TICA, PICA, lacunar infarction and posterior circulation infarction. The result showed no statistically significant differences in ischemic stroke subtype and clinical stroke syndrome between the study group and the control group.

The risk factors for aspirin resistance were compared between the study group and the control group.

Table 1. Demographic characteristics of patients with Aspirin resistance (study group) and patients with Aspirin non-resistance (control group)

Characteristics	Study group, n = 40 (13.3%)	Control group, n = 260 (86.7%)	p-value
Age (yr; mean, SD)	64.80 (9.98)	61.26 (10.57)	0.049
Gender			
Female	24 (60.00%)	108 (41.50%)	0.029
M:F	0.67	1.41	
Height (cm; mean, SD)	159.9 (9.52)	164.1 (8.11)	0.007
Body weight (kg; mean, SD)	63.9 (12.10)	65.8 (13.70)	0.273
Body mass index (mean; SD)	24.5 (3.35)	24.4 (4.47)	0.800
Waist circumferance (inch; mean, SD)	33.18 (3.19)	33.20 (3.41)	0.964
SBP (mmHg; mean, SD)	138.33 (20.65)	138.25 (19.64)	0.984
DBP (mmHg; mean, SD)	75.02 (10.80)	77.97 (13.25)	0.182
Underlying disease			
DM	42.50%	31.50%	0.170
HT	77.50%	74.20%	0.658
Dyslipidemia	95.00%	95.80%	0.687
Subtype of ischemic stroke (TOAST criteria)			
Large vessel infarction	14 (35.00%)	86 (33.10%)	0.582
Small vessel infarction	26 (65.00%)	174 (66.90%)	0.810
Clinical syndrome			
TICA	5 (12.50%)	26 (10.00%)	0.582
Lacunar infarction	33 (82.50%)	211 (81.20%)	0.711
Posterior circulation infarction	2 (5.00%)	23 (8.80%)	0.222

TICA = total anterior circulation infarction; PICA = partial anterior circulation infarction; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 2. Baseline status and treatments between study and control group

Status and treatments	Study group (n = 40)	Control group (n = 260)	p-value
Dose of aspirin			
60-182 mg	16 (40%)	123 (47.30%)	0.388
300-325 mg	24 (60%)	137 (52.70%)	
Duration of aspirintherapy (month; median, IQR)*	12 (26.50)	11 (37.00)	0.886
Antihyperglycemicdrugs			
Sulfonylurea	8 (20.00%)	48 (18.50%)	0.816
Metformin	11 (27.50%)	63 (24.20%)	0.655
Thiazolidinedione	1 (2.50%)	11 (4.20%)	1.000
Repaglinide	1 (2.50%)	4 (1.50%)	0.514
Lipid lowering drugs			
Statin	39 (97.50%)	243 (93.50%)	0.484
Gemfibrozil	2 (5.00%)	14 (5.40%)	1.000
Ezetimibe	1 (2.50%)	2 (0.80%)	0.350
Antihypertensive drugs			
ACEI	9 (22.50%)	70 (26.90%)	0.554
ARB	2 (5.00%)	23 (8.80%)	0.550
Calcium channel blocker	19 (47.50%)	98 (37.70%)	0.236
Diuretic	3 (7.50%)	21 (8.10%)	1.000
Beta-blocker	8 (20.00%)	43 (16.50%)	0.587
Apresoline	3 (7.50%)	9 (3.50%)	0.250
Folic acid	36 (90.00%)	227 (88.00%)	1.000
FBS (mg/dl; median, IQR)	103 (21.00)	105 (29.75%)	0.615
HbA1C (mmols/l; median, IQR)	7.10 (2.65)	7.10 (1.82)	0.691
Creatinine (mg/dl; median, IQR)	0.90 (0.40)	0.90 (0.30)	0.182
Cholesterol (mg/dl; mean, SD)	160.71 (36.54)	168.93 (37.33)	0.245
HDL (mg/dl; median, IQR)	40.50 (16.25)	41 (15.00)	0.906
LDL (mg/dl; mean, SD)	88.69 (27.27)	98.35 (32.12)	0.076
Triglycerid e(mg/dl; median, IQR)	125 (68.50)	116 (92.00)	0.812
Complete blood count			
Hematocrit (%; mean, SD)	38.55 (3.78)	39.60 (4.40)	0.154
White blood cell count (cell/mcL; median, IQR)	6,850 (2,020)	7,075 (2,480)	0.544
Platelet count (platelet/mcL; median, IQR)	259,500 (84,500)	260,500 (93,250)	0.915
Mean platelet volumn (fL; mean, SD)	7.90 (1.08)	7.75 (0.85)	0.307

ACEI/ARB = angiotensin converting enzyme inhibitor/angiotensin receptor blockers; HDL = high density lipoprotein; LDL = low density lipoprotein; IQR = interquartile range

* Duration of aspirin therapy means the time from patients receive first dose of aspirin to follow-up.

No significant differences were found in terms of fasting serum glucose level, HbA1C level, creatinine, cholesterol level, high-density lipoprotein level (HDL), low-density lipoprotein level (LDL), triglyceride level, CBC (hematocrit, white blood cell count, platelet count, mean platelet volume), and VDRL reactivity between the study group and the control group.

Dosage of aspirin taken was compared between the study and the control groups by categorizing the dosage into two groups including low dose (60-162 mg) and high dose (300-325 mg). The results showed no significant differences in each dose of aspirin in these two groups (p = 0.388).

The duration of the aspirin therapy in the study group was longer than that of the control group, but it was not statistically significant (12 months vs. 11 months, p = 0.886).

The analysis of the accompanying drugs usage, antihypertensives, antihyperglycemics, and folic acid also showed no significant difference.

Three statistically significant factors were age, sex, and height in a univariate analysis. Furthermore,

Table 3. Factors for Aspirin resistance (multivariate logistic regression analysis)

Factors	p-value	Odds ratio (95% CI)
Age	0.040	1.040 (1.002-1.079)
Sex (female)	0.276	0.578 (0.216-1.549)
Height (cm)	0.241	0.967 (0.913-1.023)
LDL level	0.256	0.992 (0.980-1.006)
Dose of aspirin	0.989	1.005 (0.467-2.167)
Duration of aspirin therapy*	0.734	0.998 (0.984-1.011)

LDL level = lowdensity lipoprotein (mg/dl)
* Duration of aspirin therapy means the time from patients receive first dose of aspirin to follow-up.

the statistical analysis of LDL level between both groups showed that p-value nearly reached the threshold of significant difference (p = 0.076). The multivariate analysis of these factors was performed. The results showed older age was associated with aspirin resistance (Table 3).

Discussion

Aspirin is well recognized as an effective antiplatelet drug for secondary prevention in stroke patients. However, despite aspirin treatment, a number of patients experience recurrent ischemic stroke. The term "aspirin resistance" has evolved to describe the failure of aspirin to produce suppression of platelet aggregation as assessed by platelet function assays[24]. There is increasing evidence that laboratory aspirin resistance is clinically important. Gum et al[23] found a significant correlation between aspirin resistance as measured by optical platelet aggregation and the increased risks of stroke, myocardial infarction, and death. However, the clinical implications of a semi-response to aspirin have not been sufficiently studied. The previous study showed that the rate of ischemic stroke in aspirin resistance and aspirin semi-responsiveness groups was significantly higher than that of the aspirin non-resistance group[25]. This finding might indicate that aspirin semi-responsiveness was associated with an increased risk of ischemic stroke.

The present study investigated the prevalence and risk factors of aspirin resistance in 300 patients with ischemic stroke. The results showed that 0.6% of the patients were aspirin resistance, 12.7% of the patients were aspirin semi-responsiveness, and 86.7% of the patients were aspirin non-resistance. These results were in contrast with the previous studies showing that aspirin resistance in Thai ischemic stroke patients was 5.3 to 56%[26,27]. This may be explained by the difference in laboratory techniques, dose of aspirin and definition of aspirin resistance. In a study by Dalen, a discrepancy in the prevalence of aspirin sensitivity when using different techniques of platelet function test was found. Prevalence of aspirin sensitivity ranges from 9.5% to 35% when using the PFA-100 test, 7% to 27% with rapid platelet function assay (VerifyNow), and 0.4% to 9% with optical platelet aggregometry[28]. Besides, low prevalence of aspirin resistance was similarly reported in the present study of patients with cardiovascular disease, using similar technique of platelet function and similar definition of aspirin resistance with the present study. Singhsathitsuk et al. found that 10% of Thai patients with cardiovascular disease were aspirin semi-responsive and none was aspirin resistant[29].

The present study revealed that patients with a poor response to aspirin (study group) had a trend towards older age (64.8 year vs. 61.26 year, p = 0.049), were more likely to be female (60% vs. 41.5%, p = 0.029), and were shorter in height (159.9 cm vs. 164.1 cm, p = 0.007) as compared to the patients with aspirin non-resistance (control group). These features are in agreement with the finding by Gum et al[23]. Age and weight may also reduce the bioavailability of low-dose aspirin, mainly due to increased inactivation of acetylsalicylic acid by gastrointestinal mucosal esterases and reduced absorption of active acetylsalicylic acid[24].

To date, there is no report of the relation between the height and aspirin resistance. Calculation of body mass index was performed by using patient's height and weight, resulting in that patient's height would affect body mass index. The previous studies showed that obesity and higher body mass index were risk factors for developing aspirin resistance[30,31]. However, no significant difference of bodyweight and body mass index between patient group and control group was shown in the present study.

The previous studies demonstrated that factors associated with aspirin resistance are diabetes[32], higher Cholesterol and LDL level[33], systolic blood pressure >145 mmHg[34], and smoking[35]. However, in the present study, no association has been found. The differences of mentioned factors were not statistically significant in the present study may be due to a small sample size of the present study or other factors affecting the resistance.

The association of low aspirin dosage and aspirin resistance has been demonstrated by several

studies. An increase in the dose of aspirin was found to improve the aspirin resistance as determined by platelet aggregometry[36-38]. However, no significant difference of aspirin resistance between patients with low aspirin dosage and high aspirin dosage was demonstrated in the present study. The authors' finding was in concordance with several groups revealing that an increase in the dose of aspirin did not improve the aspirin resistance[39,40]. The meta-analysis concluded that daily aspirin doses of 75 to 150 mg seem to be as effective as higher doses for long-term treatment[41]. This shows that inadequate dose cannot explain aspirin resistance in all subjects. With regard to the management of patients with aspirin resistance, an increase in the dose of aspirin might increase the laboratory response to aspirin but there is not enough evidence in the improvement of clinical benefit.

The present study showed that duration of aspirin usage in patients with aspirin resistance was longer than that of patients with aspirin non-resistance, although not statistically significant. To date, no report has shown the association of the duration of aspirin usage and aspirin resistance yet.

The limitation of the present study was the small number of patients in the study group (n = 40), this may explain why there is no association between known risk factors and the occurrence of aspirin resistance in multivariate analysis. Some data such as life style modification, smoking, alcohol drinking, and exercise were missing because the medical records were not complete and difficulty in interviewing post stroke patients. Drug compliance is a major factors for laboratory non-response to aspirin. Aspirin compliance in the present study was based upon a response to questionnaire and not confirmed by pill count or salicylate levels. Thus, the authors could not exclude the poor compliance as the causes in some cases with aspirin resistance or semi-responsiveness.

In conclusion, the present study showed the prevalence of aspirin resistance is 0.6% and the prevalence of aspirin semi-responsiveness is 12.7%. The risk factor for aspirin resistance is older age. No association between duration and aspirin dosage with aspirin resistance. However, aspirin resistance in the laboratory testing may be associated with increased atherothrombosis. Presently, there is not enough evidence showing that increase aspirin dosage or switching to another antiplatelet with different mechanism have clinical benefit. These options should be based on clinical judgement.

Potential conflicts of interest

None.

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ภาวะดื้อยาต้านเกล็ดเลือดแอสไพรินในผู้ป่วยโรคหลอดเลือดสมอง

นฤพัชร สวนประเสริฐ, ทินนกร ยาดี, สุรัคเมธ มหาศิริมงคล, วัลยา จงเจริญประเสริฐ, ทัศนีย์ ตันติฤทธิศักดิ์

ภูมิหลัง: *สาเหตุสำคัญของการกำเริบซ้ำ ในภาวะโรคหลอดเลือดสมองตีบตันคือความล้มเหลวในการควบคุมปัจจัยเสี่ยงของภาวะโรคหลอดเลือดสมองตีบตันปัจจัยเสี่ยงหนึ่งที่สำคัญคือภาวะดื้อต่อยาแอสไพริน จากการศึกษาในอดีตพบว่าความชุกของภาวะดื้อต่อยาแอสไพรินมีความแตกต่าง และแปรปรวนสูงทั้งนี้ขึ้นอยู่กับกลุ่มประชากรที่ทำการศึกษา และวิธีการตรวจการทำงานของเกล็ดเลือดที่มีความหลากหลายในแนวทางปฏิบัติ*

วัตถุประสงค์: *เพื่อศึกษาความชุกของภาวะดื้อต่อยาแอสไพรินและปัจจัยเสี่ยงของภาวะดื้อต่อยาแอสไพรินในผู้ป่วยโรคหลอดเลือดสมองตีบตันชาวไทยที่รับการรักษาที่สถาบันประสาทวิทยา*

วัสดุและวิธีการ: *การศึกษาทำในผู้ป่วยโรคหลอดเลือดสมองตีบตันที่ได้รับยาแอสไพรินขนาด 60-325 มิลลิกรัมต่อวัน อย่างน้อย 14 วัน จำนวน 300 ราย โดยเก็บข้อมูลพื้นฐานปัจจัยเสี่ยงของภาวะดื้อต่อยาแอสไพรินและข้อมูลการรักษา โดยการสอบถามผู้ป่วยและทบทวนเวชระเบียน ผู้ป่วยได้รับการทดสอบ optical platelet aggregation test โดยใช้ arachidonic acid (AA) และ adenosine diphosphate (ADP) เป็นตัวกระตุ้นให้เกล็ดเลือดจับตัว*

ผลการศึกษา: *กลุ่มศึกษามีผู้ป่วย 40 ราย (ร้อยละ 13.3) ประกอบด้วยผู้ป่วยดื้อต่อยาแอสไพริน 2 ราย (ร้อยละ 0.6) และกึ่งดื้อต่อยาแอสไพริน 38 ราย (ร้อยละ 12.7) กลุ่มควบคุม คือผู้ป่วยที่ไม่มีภาวะดื้อต่อยาแอสไพริน 260 ราย (ร้อยละ 86.7) ผลการศึกษาพบว่ากลุ่มศึกษามีอายุสูงกว่าจำนวนเพศหญิงมากกว่าและมีส่วนสูงต่ำกว่ากลุ่มควบคุม สำหรับขนาดและระยะเวลาการใช้ยาแอสไพรินพบว่าไม่มีความแตกต่างกันในสองกลุ่มเมื่อวิเคราะห์แบบ multivariate พบว่าอายุที่มากขึ้นมีความสัมพันธ์กับภาวะดื้อต่อยาแอสไพริน*

สรุป: *ความชุกของภาวะดื้อต่อยาแอสไพรินในการศึกษานี้เท่ากับร้อยละ 6 (95% CI, 0.18%-1.38%) จากผลการศึกษาพบว่าปัจจัยเสี่ยงของภาวะดื้อต่อยาแอสไพรินได้แก่อายุที่มากขึ้นสำหรับขนาด และระยะเวลาการใช้ยาแอสไพรินพบว่าไม่มีความสัมพันธ์กับภาวะดื้อต่อยาแอสไพรินสำหรับอัตราการดื้อยาแอสไพริน ในการศึกษานี้พบว่าใกล้เคียงกับการศึกษาก่อนหน้านี้ที่ทำในผู้ป่วยโรคกล้ามเนื้อหัวใจขาดเลือด*