Establishing a predictive model for aspirin resistance in elderly Chinese patients with chronic cardiovascular disease

Jian CAO¹,*, Wei-Jun HAO²,*, Ling-Gen GAO¹, Tian-Meng CHEN¹, Lin LIU¹, Yu-Fa SUN², Guo-Liang HU¹, Yi-Xin HU¹, Li FAN¹

¹Department of Geriatric Cardiology, Chinese PLA General Hospital, Beijing, China
²Health Division of Guard Bureau, General Staff Department of Chinese PLA, Beijing, China

Abstract

Background  Resistance to anti-platelet therapy is detrimental to patients. Our aim was to establish a predictive model for aspirin resistance to identify high-risk patients and to propose appropriate intervention. Methods  Elderly patients (n = 1130) with stable chronic coronary heart disease who were taking aspirin (75 mg) for > 2 months were included. Details of their basic characteristics, laboratory test results, and medications were collected. Logistic regression analysis was performed to establish a predictive model for aspirin resistance. Risk score was finally established according to coefficient B and type of variables in logistic regression. The Hosmer–Lemeshow (HL) test and receiver operating characteristic curves were performed to respectively test the calibration and discrimination of the model. Results  Seven risk factors were included in our risk score. They were serum creatinine (> 110 μmol/L, score of 1); fasting blood glucose (> 7.0 mmol/L, score of 1); hyperlipidemia (score of 1); number of coronary arteries (2 branches, score of 2; ≥ 3 branches, score of 4); body mass index (20–25 kg/m², score of 2; > 25 kg/m², score of 4); percutaneous coronary intervention (score of 2); and smoking (score of 3). The HL test showed P ≥ 0.05 and area under the receiver operating characteristic curve ≥ 0.70. Conclusions  We explored and quantified the risk factors for aspirin resistance. Our predictive model showed good calibration and discriminative power and therefore a good foundation for the further study of patients undergoing anti-platelet therapy.

J Geriatr Cardiol 2016; 13: 458–464. doi:10.11909/j.issn.1671-5411.2016.05.003

Keywords: Aspirin resistance; Cardiovascular disease; Predictive model; Risk score

1 Introduction

Platelet activation plays a vital role in the development of cardiovascular disease (CAD). Anti-platelet therapy inhibits platelet aggregation and prevents thrombogenesis and can be used in primary and secondary prevention of CAD. However, according to clinical observations, not all patients are equally sensitive to anti-platelet therapy. Some patients still have different types of ischemic events during therapy, which is defined as anti-platelet therapy resistance.[1]

Anti-platelet therapy resistance is detrimental to patients. According to the Heart Outcomes Prevention Evaluation (HOPE) Study, patients with aspirin resistance had a 1.8-fold higher risk of the composite outcome of myocardial infarction (MI), stroke, or cardiovascular death, a two-fold higher risk of myocardial infarction, and a 3.5-fold higher risk of cardiovascular death, when compared with patients who were sensitive to aspirin.[2] A multivariate analysis revealed that aspirin resistance is an independent predictor of myonecrosis after percutaneous coronary intervention (PCI) [odds ratio (OR): 2.9; 95% confidence interval (CI): 1.2–6.9; P = 0.015].[3] In another, during follow-up, aspirin resistance was associated with an increased risk of death, myocardial infarction, or cerebrovascular accident (24% vs. 10%, hazard ratio: 3.12).[4]

Many factors may be involved in the development of anti-platelet therapy resistance. Age, diabetes and acute coronary syndrome are also predictors of anti-platelet therapy resistance.[5,6] Thus, there might be an association between risk factors and anti-platelet therapy resistance.

In our study, we established a predictive model for aspirin resistance in elderly Chinese patients, and discussed its calibration and discrimination in identifying high-risk populations.
2 Methods

2.1 Ethical approval of the study protocol

Informed consent was obtained from each patient. The study protocol conformed to the Ethical Guidelines of the 1975 Declaration of Helsinki and approved by the Scientific and Ethics Review Board of Chinese PLA General Hospital (Beijing, China).

2.2 Establishment of predictive model

We enrolled 1130 patients with chronic CAD and aspirin therapy (> 75 mg) for > 2 months from Wanshoulu community, Beijing, China. All the cases had complete clinical and follow-up records. All patients had prior history of cardiovascular disease as defined by previous documented coronary stenosis on cardiac catheterization of ≥ 60%, previous history of MI or stroke, or previous invasive cardiovascular revascularization procedure. All of them received a regular aspirin therapy (100 mg/day) before platelet function assays. Exclusion criteria were: thrombocytopenia (< 100,000/mm3) or thrombocytosis (> 400,000/mm3), anemia (hemoglobin < 10 g/dL), polycythemia (hematocrit > 50%), end stage renal disease, acute or chronic liver disease, hematologic diseases, malignancies and history of major surgical procedure within the last month.

Baseline characteristics were collected including age, sex, race, marital status, educational level, smoking, physical activity, body weight, blood pressure, medications and co-morbidities.

Exclusion criteria were as follows: (1) use of heparin, low molecular heparin or other anti-platelet agents within four weeks; (2) surgery within one week before study enrollment; (3) personal or family history of bleeding disorders; (4) platelet count < 150 × 10^9/L or > 450 × 10^9/L; (5) hemoglobin level < 80 g/L; (6) history of myeloproliferative diseases; (7) history of drug-induced thrombocytopenia; and (8) history of allergy to aspirin.

2.3 Sample collection

Venous blood (15 mL) was collected following overnight fasting for at least 12 h for routine blood testing, blood biochemistry, homocysteine, coagulation function, anti-thrombin III, high sensitivity C-reactive protein (hs-CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), platelet aggregation, and thrombelastography (TEG).

2.4 Light transmittance aggregometry (LTA)

Blood samples were centrifuged at 800 r/min for 5 min to obtain native platelet-rich plasma and further centrifuged at 4000 r/min for 8 min to obtain platelet-poor plasma. The platelet count was assessed using a standard cell counter. Aggregation was performed using arachidonic acid (AA, 0.5 mmol/L) and adenosine diphosphate glucose pyrophosphatase (ADP, 10 μmol/L) with a ChronoLog Aggregometer (Chronolog, Havertown, PA, USA).[7]

2.5 TEG

The TEG platelet mapping assay (Haemoscope, Niles, IL, USA) relies on the measurement of platelet function through clot strength. We used AA (1 mmol/L) as a platelet agonist to measure the degree of thromboxane (TX)A2-induced platelet aggregation, as previously described.[8]

2.6 Definition of laboratory aspirin resistance

LTA, aspirin resistance was defined as both ≥ 20% AA (0.5 mmol/L) and ≥ 70% ADP (10 μmol/L) induced aggregation. Aspirin semi-resistance was defined as either ≥ 20% AA (0.5 mmol/L) or ≥ 70% ADP (10 μmol/L) induced aggregation, but not both of them.[9,10] TEG, aspirin resistance was defined as platelet inhibition ≤ 50% induced by AA (1 mmol/L).[8]

2.7 Establishment of risk score and stratification

Risk score were finally established according to the regression coefficient and type of variables in the logistic regression model as follows: (1) definition of weight coefficient. Logistic regression coefficients of each included parameter were converted into an integer risk score by the quotient of the corresponding regression coefficient and the lowest one. The weight coefficient of the parameter with the lowest regression coefficient was defined as 1. (2) Definition of ranked score. When the parameter was binary, if the value = 0, the ranked score = 0; if the value = 1, the ranked score = 1. When the parameter was ordinal, in the lowest grade, ranked score = 0; in the second lowest grade, ranked score = 1, etc. (3) Calculation of risk score. The final score was the product of weight coefficient and ranked score. The predicted risk score for aspirin resistance was estimated by the sum of final scores.

2.8 Evaluation of predictive model

A total of 310 cases with chronic stable CAD were recruited from Chinese PLA General Hospital and enrolled in the study. All subjects received a regular aspirin therapy (100 mg/day). Baseline characteristics were collected including age, sex, race, marital status, educational level, smoking, sports, body weight, blood pressure, platelet aggregation, medications and comorbidities.

2.9 Statistical analyses

Categorical variables are presented as frequencies and
percentages. For the categorical variables, patient demographics between groups were compared using chi-square tests or, if expected cell frequencies were small, exact tests. Continuous variables are presented as means ± SD. Logistic regression was adopted to establish the predictive model. Variables entered into the model include: age, smoking, body mass index (BMI), blood pressure, coagulation function, serum homocysteine, anti-thrombin III, hs-CRP and NT-proBNP, history of tobacco use, diabetes, hypertension, hyperlipidemia, revascularization, MI, hemoglobin, platelet count, creatinine.

We compared the predicted percentages of aspirin resistance with the actual percentages to evaluate the calibration and discrimination of the predictive model. Calibration was tested by the Hosmer-Lemeshow (HL) test. P > 0.05 was regarded as satisfactory. Discrimination was reflected by the area under the receiver operating characteristic (ROC) curve, AUC. As AUC approached 1, the better was the discriminative power. All of the statistical analyses were performed by SPSS version 17.0.

3 Results

3.1 Patient characteristics

According to the results of both LTA and TEG, patients were grouped into aspirin resistant (AR) (n = 119), semi-AR (n = 449), and aspirin sensitive (AS) (n = 562) groups. Basic characteristics of patients are shown in Table 1. The distributions of quantitative data are shown in Table 2. For the

| Variables                        | AR (n = 119)       | Semi-AR (n = 449)  | AS (n = 562)    | P value |
|----------------------------------|--------------------|--------------------|----------------|---------|
| Age, yrs                         | 79.2 ± 10.1        | 79.8 ± 9.1         | 79.3 ± 9.4     | 0.557   |
| Smoking                          | 21                 | 114                | 123            | 0.002   |
| Female                           | 19                 | 82                 | 91             | 0.018   |
| BMI, kg/m²                       | 24.98 ± 3.56       | 24.74 ± 3.40       | 24.88 ± 3.31   | 0.664   |
| Homocysteine, μmol/L             | 13.49 ± 4.69       | 14.03 ± 6.09       | 14.56 ± 7.43   | 0.475   |
| NT-proBNP, pg/mL                 | 155.90 ± 151.80    | 205.61 ± 255.72    | 199.34 ± 257.10| 0.429   |
| hs-CRP, mg/dL                    | 6.55 ± 1.69        | 5.67 ± 1.31        | 5.77 ± 2.24    | 0.001   |
| Creatinine, μmol/L               | 85.29 ± 26.26      | 89.41 ± 39.72      | 94.65 ± 52.44  | 0.032   |
| Fasting serum glucose, mmol/L    | 6.23 ± 1.57        | 5.74 ± 1.63        | 5.69 ± 1.24    | 0.328   |
| HbA1c, %                         | 6.23 ± 1.33        | 5.89 ± 1.04        | 5.84 ± 1.07    | 0.643   |
| TC, mmol/L                       | 4.38 ± 0.99        | 4.40 ± 1.01        | 4.38 ± 2.12    | 0.026   |
| TG, mmol/L                       | 1.90 ± 1.17        | 1.70 ± 1.20        | 1.53 ± 0.80    | 0.098   |
| HDL, mmol/L                      | 1.17 ± 0.32        | 1.21 ± 0.43        | 1.28 ± 0.74    | 0.328   |
| LDL, mmol/L                      | 2.50 ± 0.83        | 2.51 ± 0.78        | 2.46 ± 0.78    | 0.061   |
| Uric acid, μmol/L                | 334.51 ± 95.92     | 336.87 ± 92.09     | 329.79 ± 86.75 | 0.168   |
| Platelet, /μL                    | 182.69 ± 56.3      | 185.72 ± 51.76     | 188.45 ± 48.41 | 0.031   |
| Hypertension                     | 32 (26.9%)         | 162 (36.1%)        | 277 (49.3%)    | 0.000   |
| Diabetes                         | 50 (42%)           | 52 (11.6%)         | 52 (9.3%)      | 0.009   |
| PAOD                             | 21 (17.6%)         | 56 (12.5%)         | 45 (8%)        | 0.337   |
| Hyperuricemia                    | 10 (8.4%)          | 34 (7.6%)          | 28 (5%)        | 0.950   |
| ≥1                               | 50 (42.0%)         | 177 (39.6%)        | 242 (43.1%)    | 0.069   |
| ≥2                               | 37 (31.1%)         | 127 (28.3%)        | 185 (32.9%)    | 0.058   |
| ≥3                               | 32 (26.9%)         | 145 (32.3%)        | 135 (24.0%)    | 0.007   |
| Left coronary artery involved    | 9 (7.6%)           | 24 (5.3%)          | 18 (3.2%)      | 0.079   |

Data are presented as mean ± SD, n or n (%). ACEIs: angiotensin-converting enzyme inhibitors; AR: aspirin resistant; ARBs: angiotensin receptor blockers; AS: aspirin sensitive; BMI: body mass index; CABG: coronary artery bypass graft; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HbA1c: Hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; PAOD: peripheral arterial occlusive disease; PCI: percutaneous coronary intervention; TC: total cholesterol; TG: triglyceride.
Table 2. Distributions of quantitative data.

| Variables                        | n (%) | Value |
|----------------------------------|-------|-------|
| Age, yrs                         |       |       |
| 41–50                            | 1 (0.08%) | 1 |
| 51–60                            | 46 (4.07%) | 2 |
| 61–70                            | 156 (13.8%) | 3 |
| 71–80                            | 335 (29.6%) | 4 |
| 81–90                            | 440 (38.9%) | 5 |
| > 90                             | 152 (13.5%) | 6 |
| BMI, kg/m²                       |       |       |
| < 20                             | 52 (4.6%) | 0 |
| 20–25                            | 531 (47.0%) | 1 |
| > 25                             | 547 (48.4%) | 2 |
| Homocysteine, μmol/L             |       |       |
| < 13.9                           | 638 (56.5%) | 0 |
| ≥ 13.9                           | 492 (43.5%) | 1 |
| NT-proBNP, pg/mL                 |       |       |
| < 95                             | 494 (43.7%) | 0 |
| 95–220                           | 391 (34.6%) | 1 |
| 221–460                          | 136 (12.0%) | 2 |
| > 460                            | 109 (9.6%) | 2 |
| hs-CRP, mg/dL                    |       |       |
| < 5                              | 506 (44.8%) | 0 |
| 5–10                             | 447 (39.6%) | 1 |
| > 10                             | 177 (15.6%) | 2 |
| Creatinine, μmol/L               |       |       |
| ≤ 110                            | 952 (84.2%) | 0 |
| > 110                            | 178 (15.8%) | 1 |
| Fasting serum glucose, mmol/L    |       |       |
| < 6.0                            | 767 (67.9%) | 0 |
| 6.1–7.0                          | 212 (18.8%) | 1 |
| > 7.0                            | 151 (13.4%) | 2 |
| HbA1c                            |       |       |
| < 6.0                            | 612 (54.1%) | 0 |
| 6.0–7.0                          | 369 (32.6%) | 1 |
| > 7.0                            | 149 (13.2%) | 2 |
| Uric acid, μmol/L                |       |       |
| < 390                            | 843 (74.6%) | 0 |
| ≥ 390                            | 287 (25.4%) | 1 |
| Platelet count, /μL              |       |       |
| < 100                            | 14 (1.2%) | 0 |
| 100–200                          | 751 (66.5%) | 1 |
| 201–300                          | 330 (29.2%) | 2 |
| > 300                            | 35 (3.1%) | 3 |
| Number of involved coronary arteries |       |       |
| 1                                | 469 (41.5%) | 1 |
| 2                                | 349 (30.9%) | 2 |
| ≥ 3                              | 312 (27.6%) | 3 |

BMI: body mass index; HbA1c: Hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; NT-proBNP: N-terminal prohormone of brain natriuretic peptide.

qualitative data (female, smoking, hypertension, diabetes, dyslipidemia, myocardial infarction, cerebral embolism, and peripheral arterial occlusive disease), if there is, value = 1; otherwise, value = 0.

3.2 Establishment of predictive model

According to logistic regression analysis, elevated serum creatinine levels, elevated fasting serum glucose levels, dyslipidemia, large number of involved coronary arteries, high BMI, PCI, and smoking were risk factors for aspirin resistance (Table 3).

\[
\text{Odds value} = \frac{e^{0.107 \times 1 + 0.207 \times 2 + 0.211 \times 3 + 0.253 \times 4 + 0.302 \times 5 + 0.361 \times 6 + 0.884}}{1 + 0.05}
\]

The percentages of aspirin resistance incidence = \[
\frac{\text{Odds value} \times 100\%}{1 + \text{Odds value}}
\]

3.3 Risk score and stratification

We converted all the quantitative data into ordinal data. Risk score was finally established according to regression coefficient and type of variables in the logistic regression model (Table 4). Scores 0–5, 6–10 and > 10 were classified into low, intermediate and high-risk groups, respectively.

3.4 Evaluation of predictive model

Three hundred and ten cases with chronic stable CAD in a hospital in Beijing were collected to evaluate the predictive model. HL test and ROC curve were performed to test calibration and discrimination of the model, respectively. The HL test \( P \) value was 0.84. AUC was 0.741 (0.712–0.771) (Figure 1). Due to HL test values of \( P > 0.05 \) and AUC > 0.70, our model showed good calibration and discriminative power.

4 Discussion

We established a predictive model for aspirin resistance in the present study. According to logistic regression analysis, elevated serum creatinine levels, elevated fasting serum glucose levels, dyslipidemia, large number of involved coronary arteries, high BMI, PCI, and smoking were risk factors for aspirin resistance. The risk score was finally established according to the regression coefficient and type of variables in the logistic regression model.

For example, in a 65-year-old man after PCI, with two branches of involved coronary arteries, BMI: 27 kg/m², normal serum lipid levels, fasting serum glucose: 7.4 mmol/L, and smoking, the steps of stratification were as follows: (1) after PCI = 2, fasting glucose levels 7.4 mmol/L = 1, BMI
Table 3. A predictive model for aspirin resistance in the elderly patients with cardiovascular disease (logistic regression analysis).

| Variables                          | B      | Wald    | P      | OR    | 95% CI  |
|------------------------------------|--------|---------|--------|-------|---------|
| Creatinine                         | 0.107  | 6.672   | 0.001  | 1.316 | 1.172–1.826 |
| Fasting serum glucose              | 0.207  | 13.533  | < 0.0001 | 1.230 | 1.121–1.402 |
| Dyslipidemia                       | 0.211  | 12.326  | < 0.0001 | 1.273 | 1.005–1.664 |
| Number of involved coronary arteries | 0.241  | 9.688   | 0.002  | 1.427 | 1.205–1.668 |
| BMI                                | 0.253  | 10.411  | 0.003  | 1.594 | 1.257–1.774 |
| PCI                                | 0.302  | 7.124   | < 0.0001 | 1.621 | 1.296–1.852 |
| Smoking                            | 0.361  | 5.568   | 0.018  | 1.438 | 1.178–1.609 |
| Constant                           | −0.884 | 3.680   | < 0.0001 |       |          |

BMI: body mass index; PCI: percutaneous coronary intervention.

Table 4. Risk score for the predictive model for aspirin resistance.

| Risk factors                          | Weight coefficient | Ranked score | Final score |
|---------------------------------------|--------------------|--------------|-------------|
| Creatinine (> 110 μmol/L)             | 1                  | 1            | 1           |
| Fasting serum glucose > 7.0           | 1                  | 1            | 1           |
| Dyslipidemia                         | 1                  | 1            | 1           |
| Number of involved coronary arteries  |                    |              |             |
| 2                                     | 2                  | 1            | 2           |
| ≥ 3                                   | 2                  | 2            | 4           |
| BMI, kg/m²                            |                    |              |             |
| 20–25                                 | 2                  | 1            | 2           |
| > 25                                  | 2                  | 2            | 4           |
| After PCI                             | 2                  | 1            | 2           |
| Smoking                              | 3                  | 1            | 3           |

BMI: body mass index; PCI: percutaneous coronary intervention.

Figure 1. ROC curve for the evaluation of the predictive model. ROC: receiver operating characteristic.

27 kg/m² = 2 × 2 = 4, smoking = 3; (2) 2 + 1 + 4 + 3 = 10; and (3) this patient should be classified into the intermediate-risk group.

Many evidence-based studies have shown that clinical risk factors, such as age, diabetes, hypertension, smoking, acute MI, and cardiac insufficiency, can predict thrombotic events in patients with coronary heart disease. Meanwhile, patients with aspirin resistance also have elevated risk for thrombotic events. Case–control studies also show that age, diabetes, and acute coronary syndrome are predictive factors for aspirin resistance. Among these risk factors, elevated serum creatinine level, elevated serum glucose level, dyslipidemia, high BMI, and smoking are consistent with the results from other countries. Large number of involved coronary arteries was not a consistent risk factor.

Smoking is a major risk factor for cardiovascular diseases. Our study indicates that smoking is also a risk factor for aspirin resistance. In men with coronary heart disease, pre-administration of aspirin failed to prevent smoking-induced platelet aggregation and release of the contents of platelet α granules. Multivariate analysis also demonstrated a strong and significant association between smoking and aspirin resistance (relative risk: 11.47, 95% CI: 6.69–18.63, P < 0.0001). The corresponding mechanism may be involved in the elevated platelet activity by smoking.

Dyslipidemia is closely related to chronic inflammation and prothrombotic state. We found that dyslipidemia is a risk factor for aspirin resistance, which is consistent with other studies. In a study exploring platelet responsiveness to aspirin in patients with hyperlipidemia, nine of 13 (69%) patients with hyperlipidemia had poor responsiveness to aspirin. Significant correlations were seen between the degree of platelet aggregation and the levels of total cholesterol (r = 0.35, P = 0.009). Recent studies have also implicated that the immunomodulatory dyad CD40/CD40L is also found on endothelial cells, smooth muscle cells, macrophages, T lymphocytes, and platelets in human atheroma. Both membrane-bound and soluble CD40L (sCD40L) interact with CD40 on vascular cells and result in inflammatory and prothrombotic responses. In vitro, oxidized-LDL promotes expression of CD40 and CD40L in human vascular cells with atheroma. In vivo,
patients with hypercholesterolemia had increased levels of sCD40L, which was also positively correlated with in vivo platelet activation, as reflected by 11-dh thromboxane B2 and P-selectin. Therefore, CD40L–CD40 interaction may play a vital role in the development of aspirin resistance in patients with hyperlipidemia. Whether drugs to treat dyslipidemia are effective for aspirin resistance need further studies.

DiMinno, et al., found that dosing schedules for aspirin that may suffice in normal circumstances are not effective in patients with diabetic angioptathy. This phenomenon may be due to a high rate of new platelets in the circulation in these patients. Many later studies have also demonstrated the close relationship between elevated serum glucose and aspirin resistance, which is consistent with our results. A correlation analysis showed that aspirin resistance was positively associated with fasting serum glucose levels ($r = 0.224, P < 0.001$) and hemoglobin A1c (HbA1c) levels ($r = 0.297, P < 0.0001$), which indicates that glycemic control influences aspirin resistance in patients with diabetes. In patients with diabetes, there is a significant correlation between TXB2 production and fasting serum glucose and HbA1c. This association suggests that hyperglycemia is a determinant of the reduced sensitivity to aspirin in diabetics. According to our study, high BMI also increased the risk of aspirin resistance. The positive correlation between BMI and aspirin resistance ($r = 0.190, P < 0.01$) has also been shown in another study. One possibility is attributed to the increase in leptin in patients with obesity, which induces hypercoagulability. Another reason is the low concentration of drug distribution. Many later studies have also demonstrated the close relationship between elevated serum glucose and aspirin resistance, which is consistent with our results.

We also examined an independent group of people involving 310 cases with chronic, stable coronary heart disease in a Beijing hospital to evaluate our predictive model. The model showed good calibration and discriminative power in which the HL test $P > 0.05$ and AUC $> 0.70$. According to the inclusion and exclusion criteria, this predictive model was applicable to cases with chronic, stable coronary heart disease and receiving oral aspirin medication.

Acknowledgments

This work was supported by the Military Healthcare Fund 12BJZ39 (FAN L), Clinical Support Fund of Chinese PLA General Hospital 2012FC-TSYS-2019 (CAO J), the Healthcare Fund of Chinese PLA General Staff Department ZCWS14B09 (SUN Y). All authors had full access to the data and take responsibility for their integrity. All authors agree with the manuscript as written. The authors report no conflicts of interest.

References

1. Weber AA, Przyulske B, Schanz A, et al. Towards a definition of aspirin resistance: a typological approach. Platelets 2002; 13: 37–40.
2. Eikelboom JW, Hirsh J, Weitz JI, et al. Aspirin-resistant thromboxane biosynthesis and the risk of myocardial infarction, stroke, or cardiovascular death in patients at high risk for cardiovascular events. Circulation 2002; 105: 1650–1655.
3. Chen WH, Lee PY, Ng W, et al. Aspirin resistance is associated with a high incidence of myonecrosis after non-urgent percutaneous coronary intervention despite clopidogrel pretreatment. J Am Coll Cardiol. 2004; 43: 1122–1126.
4. Gum PA, Kotkje-Marchant K, Welsh PA, et al. A prospective, blinded determination of the natural history of aspirin resistance among stable patients with cardiovascular disease. J Am Coll Cardiol 2003; 41: 961–966.
5. Prabhakaran S, Wells KR, Lee VH, et al. Prevalence and risk factors for aspirin and clopidogrel resistance in cerebrovascular stenting. AJNR Am J Neuroradiol 2008; 29: 281–285.
6. Angiollo DI, Bernardo E, Ramirez C, et al. Insulin therapy is associated with platelet dysfunction in patients with type 2 diabetes mellitus on dual oral antiplatelet treatment. J Am Coll Cardiol 2006; 48: 298–304.
7. Cao J, Liu L, Fan L, et al. The prevalence, risk factors and prognosis of aspirin resistance in elderly male patients with cardiovascular disease. Aging Male 2012; 15: 140–147.
8. Tantry US, Bliedn KP, Gurbel PA. Overestimation of platelet aspirin resistance detection by thrombelastograph platelet mapping and validation by conventional aggregometry using arachidonic acid stimulation. J Am Coll Cardiol 2005; 46: 1705–1709.
9. Dussaillant NG, Zapata MM, Fardella BP, et al. Frequency and characteristics of aspirin resistance in Chilean cardiovascular patients. Rev Med Chil 2005; 133: 409–417.
10. Gum PA, Kotkje-Marchant K, Poggio ED, et al. Profile and prevalence of aspirin resistance in patients with cardiovascular disease. Am J Cardiol 2001; 88: 230–235.
11. Faraday N, Becker DM, Yanek LR, et al. Relation between atherosclerosis risk factors and aspirin resistance in a primary prevention population. Am J Cardiol 2006; 98: 774–779.
12. Liu XF, Cao J, Fan L, et al. Prevalence of and risk factors for aspirin resistance in elderly patients with coronary artery disease. J Geriatr Cardiol 2013; 10: 21–27.
13. Fan L, Cao J, Liu L, et al. Frequency, risk factors, prognosis, and genetic polymorphism of the cyclooxygenase-1 gene for aspirin resistance in elderly Chinese patients with cardiovascular disease. Gerontology 2013; 59: 122–131.
14. Tanrikulu AM, Ozben B, Koc M, et al. Aspirin resistance in patients with chronic renal failure. J Nephrol 2011; 24: 636–646.
15 Blann AD, Kuzniatsova N, Velu S, et al. Renal function and aspirin resistance in patients with coronary artery disease. *Thromb Res* 2012; 130: e103–e106.
16 Ajjan R, Storey RF, Grant PJ. Aspirin resistance and diabetes mellitus. *Diabetologia* 2008; 51: 385–390.
17 Gurbel PA, Blieden KP, Hiatt BL, et al. Clopidogrel for coronary stenting: response variability, drug resistance, and the effect of pretreatment platelet reactivity. *Circulation* 2003; 107: 2908–2913.
18 Lev EI, Patel RT, Maresh KJ, et al. Aspirin and clopidogrel drug response in patients undergoing percutaneous coronary intervention: the role of dual drug resistance. *J Am Coll Cardiol* 2006; 47: 27–33.
19 Karepov V, Tolpina G, Kuliczkowski W, et al. Plasma triglycerides as predictors of platelet responsiveness to aspirin in patients after first ischemic stroke. *Cerebrovasc Dis* 2008; 26: 272–276.
20 Ahmed RM, Moustafa MS, Shawky KM, et al. Obesity: is it a major risk for developing aspirin resistance in older adults? *J Am Geriatr Soc* 2012; 60: 180–182.
21 Er tugrul DT, Tutar E, Yildiz M, et al. Aspirin resistance is associated with glycemic control, the dose of aspirin, and obesity in type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2010; 95: 2897–2901.
22 Eikelboom JW, Hankey GJ, Thom J, et al. Incomplete inhibition of thromboxane biosynthesis by acetylsalicylic acid: determinants and effect on cardiovascular risk. *Circulation* 2008; 118: 1705–1712.
23 Smith CJ, Fischer TH, Heavner DL, et al. Urinary thromboxane, prostacyclin, cortisol, and 8-hydroxy-2’-deoxyguanosine in nonsmokers exposed and not exposed to environmental tobacco smoke. *Toxicol Sci* 2001; 59: 316–323.
24 Valles J, Santos MT, Fuset MP, et al. Partial inhibition of platelet thromboxane A2 synthesis by aspirin is associated with myonecrosis in patients with ST-segment elevation myocardial infarction. *Am J Cardiol* 2007; 99: 19–25.
25 Wenaweser P, Dorfler-Melly J, Imboden K, et al. Stent thrombosis is associated with an impaired response to antiplatelet therapy. *J Am Coll Cardiol* 2005; 45: 1748–1752.
26 Davis JW, Hartman CR, Lewis HD Jr., et al. Cigarette smoking–induced enhancement of platelet function: lack of prevention by aspirin in men with coronary artery disease. *J Lab Clin Med* 1985; 105: 479–483.
27 Mirkhel A, Peyster E, Sundeen J, et al. Frequency of aspirin resistance in a community hospital. *Am J Cardiol* 2006; 98: 577–579.
28 Levine PH. An acute effect of cigarette smoking on platelet function. A possible link between smoking and arterial thrombosis. *Circulation* 1973; 48: 619–623.
29 Friend M, Vucenik I, Miller M. Research pointers: Platelet responsiveness to aspirin in patients with hyperlipidaemia. *BMJ* 2003; 326: 82–83.
30 Tirmaksiz E, Pamukcu B, Oflaz H, et al. Effect of high dose statin therapy on platelet function; statins reduce aspirin-resistant platelet aggregation in patients with coronary heart disease. *J Thromb Thrombolysis* 2009; 27: 24–28.
31 Cipollone F, Mezzetti A, Porreca E, et al. Association between enhanced soluble CD40L and prothrombotic state in hypercholesterolemia: effects of statin therapy. *Circulation* 2002; 106: 399–402.
32 Schonbeck U, Gerdes N, Varo N, et al. Oxidized low-density lipoprotein augments and 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors limit CD40 and CD40L expression in human vascular cells. *Circulation* 2002; 106: 2888–2893.
33 DiMinno G, Silver MJ, Cerbone AM, et al. Trial of repeated low-dose aspirin in diabetic angiopathy. *Blood* 1986; 68: 886–891.
34 Pulcinelli FM, Biasucci LM, Riondino S, et al. COX-1 sensitivity and thromboxane A2 production in type 1 and type 2 diabetic patients under chronic aspirin treatment. *Eur Heart J* 2009; 30: 1279–1286.