High prevalence of aspirin resistance in elderly patients with cardiovascular disease and metabolic syndrome

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Abstract

Background  Metabolic syndrome is known to be a prothrombotic state. We undertook this study to examine a hypothesis that aspirin resistance may be associated with metabolic syndrome, and to assess other potential determinants of aspirin resistance in patients with cardiovascular disease (CVD).

Methods  A total of 469 elderly patients with CVD were recruited. One hundred and seventy-two patients with metabolic syndrome and 297 without metabolic syndrome (control group) received daily aspirin therapy (≥75 mg) over one month. Platelet aggregation was measured by light transmission aggregometry (LTA). Aspirin resistance was defined as ≥20% arachidonic acid (AA)- and ≥70% adenosine diphosphate (ADP)-induced aggregation according to LTA. Aspirin semi-responders were defined as meeting one (but not both) of these criteria.

Results  By LTA, 38 of 469 (8.1%) patients were aspirin resistant. The prevalence of aspirin resistance was higher in the metabolic syndrome group compared with the control group [11.6% vs 6.6%, odds ratio (OR) = 2.039; 95% confidence interval (CI): 1.047–3.973]. In the multivariate logistic regression analysis, metabolic syndrome (OR = 4.951, 95% CI: 1.440–17.019, P = 0.011) was a significant risk factor for aspirin resistance.

Conclusions  A significant number of patients with CVD and metabolic syndrome are resistant to aspirin therapy. This might further increase the risk of cardiovascular morbidity and mortality in these patients.

1 Introduction

Metabolic syndrome is associated with a three times higher risk of cardiovascular disease (CVD) and an 1.8 times higher risk of cardiovascular death in the general population.[1] In patients with acute myocardial infarction, metabolic syndrome is associated with an 83% higher risk of major adverse cardiovascular events and a 1.1 times higher risk of coronary revascularization.[2] Thus aspirin use is important in these patients. However, many patients taking aspirin have suboptimal anti-platelet effects.[3,4] Lack of the expected anti-platelet effect of aspirin is known as aspirin resistance. The frequency of aspirin resistance varies widely (0.8%–70.1%) when measured by different methods.[5,6]

Unfortunately, a meta-analysis demonstrated that aspirin-resistant patients are associated with a 2.85 times higher risk of cardiovascular events, compared with aspirin-sensitive patients.[7] Possible causes of aspirin resistance include non-compliance, inadequate dose or concomitant treatment, increased platelet activity and thromboxane production, severity of CVD, smoking, hyperlipidemia, hyperglycemia, hypertension, and genetic variability.[5,6,8–10]

Given the relationship between increased adverse cardiovascular events and aspirin resistance, we hypothesized that metabolic syndrome with CVD may be associated with aspirin resistance. We undertook this study to examine a hypothesis that aspirin resistance may be associated with...
metabolic syndrome, and to assess other potential determinants of aspirin resistance in patients with CVD.

2 Methods

2.1 Ethical approval of the study protocol

This study complied with the Declaration of Helsinki. It was approved by the Scientific and Ethics Review Board of Chinese PLA General Hospital, Beijing, China. All patients provided written informed consent prior to inclusion.

2.2 Participants

Initially, we enrolled 525 consecutive patients with CVD presenting to the outpatient clinic between April 2008 and June 2010. All patients were recruited from the Wangshoulu area of Beijing. All patients were aged ≥ 65 years and were being treated for coronary heart disease, hypertension, peripheral arterial disease or stroke; patients were on regular aspirin treatment (75–100 mg daily over one month). Exclusion criteria were as follows: patients taking clopidogrel, ticlopidine, dipyridamole or other nonsteroidal anti-inflammatory medications; administration of heparin or low-molecular-weight heparin; a major surgical procedure within 1 week of study enrolment; family or personal history of bleeding disorders; platelet count < 1.5×10^5/μL or > 4.5×10^5/μL; hemoglobin < 8 g/dL; history of myeloproliferative disorders; or history of drug-induced thrombocytopenia. Twenty-two patients had a poor compliance, 18 reported taking an inadequate dose (< 75 mg), 16 reported taking other antiplatelet medications. Thus, 469 patients were eventually included in the present study. Patients were aged ≥ 65 years and were being treated for metabolic syndrome according to a joint interim statement. Metabolic syndrome was diagnosed when three of the following five characteristics were present: abdominal obesity (waist circumference > 90 cm for men, and > 80 cm for women); triglyceride (TG) > 150 mg/dL or on treatment for hypertriglyceridemia; high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL for men, and < 50 mg/dL for women or on treatment for elevated HDL-C; blood pressure (BP) > 130/85 mmHg or on treatment for hypertension; and/or fasting glucose (FG) > 100 mg/dL or diagnosed with diabetes. There were 118 male and 54 female patients. The control group included 186 men and 101 women.

2.3 Blood sampling

After 2–12 h of aspirin ingestion, blood samples were obtained. The first 2 mL of blood drawn by venipuncture was discarded. Two tubes of whole blood, anticoagulated with 3.2% sodium citrate, were used for measurement of platelet aggregation. One tube of blood anticoagulated with CTAD (a mixture of citrate, theophylline, adenosine and dipyridamole) was used for measurements of CD62P (P-selectin) and PAC-1 (activated GP IIb/IIIa receptors). All samples were analysed within 2 h of collection.

2.4 Platelet aggregation by light transmission aggregometry

Platelet aggregation was assessed in platelet-rich plasma at 37°C by light transmission aggregometry (LTA). Samples were centrifuged at 800 r/min for 5 min to obtain native platelet-rich plasma. The platelet count was assessed using a standard cell counter. Platelet-poor plasma was obtained by centrifugation of the remaining blood at 4000 rpm at room temperature for 8 min. Aggregation was measured with a ChronoLog Aggregometer (Havertown, PA, USA). Aggregation was expressed as the maximal percentage change in light transmittance from baseline after the addition of arachidonic acid (AA; 0.5 mM) and adenosine diphosphate (ADP 10 μM) using platelet-poor plasma as a reference.

2.5 Definition of aspirin resistance

The definitions of aspirin resistance were ≥ 20% AA- and ≥ 70% ADP-induced aggregation according to LTA. Aspirin semi-responders were defined as meeting one (but not both) of the criteria described above.

2.6 Statistical analysis

Continuous variables were expressed as mean ± SD. For continuous variables, univariate analysis or Kruskal–Wallis test (if the distribution was not normal) was used to compare the three groups defined by aggregation. Student’s t-test or Mann–Whitney U two-sample test (if the distribution was not normal) was used to compare the continuous variables between the two groups. Categorical data and proportions were analyzed using the χ² test. P < 0.05 was considered significant. Parameters significantly related to the presence of aspirin resistance were determined using binary logistic regression analyses using SPSS for Windows, version 14.0 (Chicago, IL, USA).

3 Results

3.1 Patient characteristics

As shown in Table 1, there were no significant differences between patients with metabolic syndrome and the control group with regard to age, female sex, current smoking, peripheral arterial occlusive disease, and baseline platelet count. The number of patients with hypertension and diabetes among patients with metabolic syndrome was
Table 1. Demographic characteristics of the metabolic syndrome and the control group.

|                        | Metabolic syndrome group (n = 172) | Control group (n = 297) | P     |
|------------------------|-----------------------------------|-------------------------|-------|
| Age, yrs               | 74.27 ± 8.13                      | 73.84 ± 8.06            | 0.582 |
| Female                 | 54 (31.4%)                        | 101 (34%)               | 0.611 |
| Hypertension           | 158 (91.9%)                       | 224 (75.4%)             | 0.0001|
| Coronary artery disease| 101 (58.7%)                       | 191 (64.3%)             | 0.237 |
| Cerebrovascular disease| 71 (41.2%)                        | 115 (38.7%)             | 0.625 |
| PAOD                   | 18 (10.4%)                        | 22 (7.4%)               | 0.303 |
| Diabetes               | 91 (52.9%)                        | 122 (41.7%)             | 0.016 |
| Current smoker         | 50 (29.1%)                        | 80 (26.9%)              | 0.669 |
| Aspirin resistance     | 20 (11.6%)                        | 18 (6.6%)               | 0.036 |
| Aspirin semi-responders| 54 (31.3%)                        | 116 (39.1%)             | 0.111 |
| Aspirin resistance or  | 74 (43%)                          | 134 (45.1)              | 0.700 |
| semi-responders        |                                   |                         |       |
| Systolic BP, mmHg      | 140.57 ± 17.91                    | 133.21 ± 16.82          | 0.0001|
| Diastolic BP, mmHg     | 78.67 ± 11.07                     | 75.47 ± 8.94            | 0.003 |
| Waist, cm              | 98.22 ± 11.85                     | 66.844 ± 11.48          | 0.0001|
| Homocysteine, μmol/L   | 17.98 ± 8.57                      | 16.74 ± 8.26            | 0.141 |
| HS-CRP, mg/dL          | 0.50 ± 0.17                       | 0.46 ± 0.12             | 0.748 |
| CD62P, %               | 17.43 ± 22.78                     | 10.85 ± 14.11           | 0.0001|
| PAC-1, %               | 44.18 ± 28.53                     | 47.35 ± 27.07           | 0.244 |
| Protein C activity, %  | 115.98 ± 38.15                    | 109.13 ± 37.24          | 0.250 |
| Antithrombin III       | 104.50 ± 15.91                    | 105.34 ± 14.48          | 0.571 |
| Creatinine, μmol/L     | 80.451 ± 22.06                    | 81.58 ± 41.04           | 0.739 |
| Fasting serum glucose, | 6.31 ± 1.55                       | 5.92 ± 1.25             | 0.003 |
| mmol/L                 |                                   |                         |       |
| Total cholesterol,     | 4.99 ± 1.40                       | 4.94 ± 2.73             | 0.835 |
| mmol/L                 |                                   |                         |       |
| Triglyceride, mmol/L   | 1.78 ± 0.76                       | 1.55 ± 0.76             | 0.002 |
| HDL-C, mmol/L          | 1.24 ± 0.32                       | 1.33 ± 0.36             | 0.007 |
| LDL-C, mmol/L          | 2.89 ± 0.93                       | 2.80 ± 0.85             | 0.286 |
| Uric acid, μmol/L      | 340.35 ± 96.19                    | 320.24 ± 83.86          | 0.034 |
| Platelet count, ×10^9/μL| 209.67 ± 61.55                    | 201.663 ± 53.55         | 0.154 |
| MPV                    | 10.778 ± 1.17                     | 10.73 ± 0.86            | 0.715 |
| Medications taken      |                                   |                         |       |
| Statins                | 56 (32.6%)                        | 103 (34.7%)             | 0.686 |
| ACEIs/ARBs             | 72 (41.9%)                        | 73 (24.6%)              | 0.0001|
| CCBs                   | 100 (58.1%)                       | 135 (45.5%)             | 0.010 |
| Daily aspirin dose     |                                   |                         |       |
| 75 mg                  | 65 (37.8%)                        | 93 (31.3%)              | 0.157 |
| 100 mg                 | 107 (62.2%)                       | 204 (68.7%)             | 0.157 |

Data are presented as mean ± SD or n (%). ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index; BNP: type-B natriuretic peptide; BP: blood pressure; CCBs: calcium-channel blockers; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MPV: mean platelet volume; PAOD: peripheral arterial occlusive disease. Higher than in the control group (P = 0.0001 and P = 0.016, respectively). The group with metabolic syndrome had higher levels of systolic BP, diastolic BP, waist circumference, CD62P, FG, TG, and uric acid compared to the control group (P = 0.0001, P = 0.003, P = 0.0001, P = 0.003, P = 0.002 and P = 0.034, respectively). The control group had higher HDL-C. The control group had higher HDL-C than patients with metabolic syndrome had (P = 0.007). There were fewer patients in the control group who were receiving calcium-channel blockers and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers than in the metabolic syndrome group (P = 0.0001 and P = 0.010).

3.2 Aspirin resistance in patients with metabolic syndrome and controls

Aspirin resistance was defined in 20 patients with metabolic syndrome and 18 patients in the control group. The prevalence of aspirin resistance was higher in the metabolic syndrome group than the control group (11.6% vs. 6.6%, odds ratio (OR) = 2.039; 95% confidence interval (CI) = 1.047–3.973). There were no differences between patients regarding aspirin semi-responders and a combined group of aspirin resistance + aspirin semi-responders. By LTA, 38 of 469 (8.1%) patients were aspirin resistant. An additional 170 patients (36.2%) were aspirin semi-responders. Plasma protein C activity levels were higher in patients with aspirin sensitivity than in aspirin semi-responders and the combined group of aspirin resistance + aspirin semi-responders. Aspirin-sensitive patients were more likely to take statins than aspirin semi-responders and aspirin-resistant patients were (P = 0.021 and P = 0.006, respectively) (Table 2).

3.3 Multivariate logistic regression analysis

In multivariate logistic regression analysis, metabolic syndrome (OR = 4.951, 95% CI: 1.440–17.019, P = 0.011) was a significant risk factor for aspirin resistance (Table 3).

3.4 Aspirin resistance in patients with metabolic syndrome by different criteria

In patients with metabolic syndrome, aspirin resistance or aspirin semi-responders were frequently found, in descending order: 11 (55%) patients with high FG + high BP + low HDL-C; 25 (54.3%) patients with high BP + central obesity + low HDL-C; and 15 (50%) patients with high BP + high TG + low HDL-C (Table 4).

4 Discussion

In the present study, we demonstrated, for the first time,
that the prevalence of aspirin resistance by LTA in CVD patients with metabolic syndrome was 11.6%, which was higher than in the control group. One study with respect to the prevalence of aspirin resistance in 110 patients with metabolic syndrome using the platelet function analyzer (PFA-100) has been reported (21.9%).[14] The present study suggests that aspirin might not have provided adequate inhibition in one of every nine patients with CVD and metabolic syndrome. A high frequency of aspirin resistance may be anticipated in patients with metabolic syndrome, and we should pay more attention to anti-platelet therapy in these patients.

The present study showed that metabolic syndrome was a significant risk factor for aspirin resistance. Furthermore, there were more patients with metabolic syndrome among the aspirin-resistant group than the aspirin-sensitive group.

Table 2. Patient demographics by LTA.

|                                               | Aspirin resistance (n = 38) | Aspirin semi-responders (n = 170) | Aspirin resistance or semi-responders (n = 208) | Aspirin Sensitive (n = 261) | P*       | P#       |
|------------------------------------------------|-----------------------------|-----------------------------------|-----------------------------------------------|-----------------------------|----------|----------|
| Age, yrs                                       | 75.13 ± 8.94                | 73.60 ± 7.89                      | 74.47 ± 8.30                                 | 73.62 ± 7.90                | 0.552    | 0.778    |
| Female                                         | 9 (23.7%)                   | 58 (34.1%)                        | 67 (32.2%)                                   | 88 (33.7%)                  | 0.439    | 0.767    |
| Metabolic syndrome                             | 20 (52.6%)                  | 54 (31.8%)                        | 74 (35.6%)                                   | 98 (37.5%)                  | 0.049    | 0.700    |
| Current smoker                                 | 14 (36.8%)                  | 50 (29.4%)                        | 64 (30.8%)                                   | 66 (25.2%)                  | 0.274    | 0.213    |
| Hypertension                                   | 31 (81.5%)                  | 137 (80.5%)                       | 168 (80.8%)                                  | 214 (81.9%)                 | 0.935    | 0.811    |
| Coronary artery disease                        | 28 (73.7%)                  | 99 (58.2%)                        | 127 (61.1%)                                  | 165 (63.2%)                 | 0.184    | 0.633    |
| Cerebrovascular disease                        | 20 (47.4%)                  | 64 (37.6%)                        | 82 (39.4%)                                   | 104 (39.8%)                 | 0.539    | 1.0      |
| Diabetes                                       | 5 (13.2%)                   | 14 (8.2%)                         | 19 (9.1%)                                    | 21 (8%)                     | 0.565    | 0.740    |
| Homocysteine, μmol/L                           | 16.52 ± 4.67                | 16.43 ± 7.63                      | 16.45 ± 7.15                                 | 17.76 ± 9.20                | 0.123    | 0.160    |
| Systolic BP, mmHg                              | 137.54 ± 21.03              | 133.93 ± 17.01                    | 134.54 ± 17.73                               | 136.46 ± 17.34              | 0.349    | 0.290    |
| Diastolic BP, mmHg                             | 78.0 ± 16.93                | 74.39 ± 16.97                     | 76.19 ± 10.12                                | 76.27 ± 19.25               | 0.316    | 0.480    |
| Waist, cm                                      | 169.7 ± 199.58              | 133.31 ± 279.74                   | 139.58 ± 267.52                              | 122.64 ± 173.24             | 0.519    | 0.436    |
| PAC-1, %                                       | 47.39 ± 29.07               | 48.31 ± 25.92                     | 48.15 ± 26.41                                | 44.53 ± 28.56               | 0.387    | 0.171    |
| CD62P, %                                       | 16.68 ± 23.87               | 12.22 ± 15.29                     | 12.98 ± 17.06                                | 13.6 ± 18.98                | 0.401    | 0.724    |
| Protein C activity, %                          | 117.08 ± 45.38              | 97.30 ± 29.72                     | 101.04 ± 33.78                               | 119 ± 38.56                 | 0.001    | 0.002    |
| Antithrombin III activity, %                   | 102.71 ± 16.28              | 105.88 ± 12.91                    | 105.3 ± 13.39                                | 104.82 ± 16.04              | 0.503    | 0.741    |
| Fasting serum glucose, mmol/L                  | 6.24 ± 1.32                 | 6.06 ± 1.49                       | 6.10 ± 1.45                                  | 6.03 ± 1.32                 | 0.684    | 0.617    |
| Total cholesterol, mmol/L                      | 4.60 ± 1.07                 | 4.84 ± 1.12                       | 4.80 ± 1.18                                  | 5.08 ± 2.97                 | 0.352    | 0.186    |
| Triglyceride, mmol/L                           | 1.72 ± 1.03                 | 2.86 ± 1.19                       | 1.68 ± 0.80                                  | 1.60 ± 0.74                 | 0.393    | 0.287    |
| Uric acid, μmol/L                              | 337.82 ± 112.27             | 330.12 ± 87.33                    | 297.00 ± 130.31                              | 324.14 ± 86.84              | 0.841    | 0.841    |
| HDL-C, mmol/L                                  | 1.25 ± 0.37                 | 1.27 ± 0.35                       | 1.26 ± 0.35                                  | 1.32 ± 0.34                 | 0.212    | 0.083    |
| LDL-C, mmol/L                                  | 2.68 ± 0.79                 | 2.84 ± 0.87                       | 2.81 ± 0.85                                  | 2.85 ± 0.90                 | 0.554    | 0.618    |
| Creatinine, μmol/L                             | 84.92 ± 24.54               | 83.79 ± 50.63                     | 83.99 ± 46.91                                | 79.5 ± 14.8                 | 0.298    | 0.122    |
| Platelet count, /μL                            | 195.68 ± 60.55              | 206.14 ± 58.56                    | 204.13 ± 58.93                               | 204.92 ± 54.93              | 0.972    | 0.884    |
| MPV                                            | 10.52 ± 2.15                | 10.74 ± 0.89                      | 10.88 ± 0.99                                 | 10.79 ± 0.85                | 0.595    | 0.390    |
| Medications taken                              |                            |                                   |                                               |                             |          |          |
| Statins                                        | 11 (28.9%)                  | 47 (27.6%)                        | 58 (27.8%)                                   | 101 (38.6%)                 | 0.021    | 0.006    |
| ACEIs/ARBs                                     | 12 (31.6%)                  | 43 (25.3%)                        | 55 (26.4%)                                   | 90 (34.5%)                  | 0.130    | 0.07     |
| CCBs                                           | 18 (47.4%)                  | 90 (52.9%)                        | 108 (51.9%)                                  | 127 (48.7%)                 | 0.644    | 0.516    |
| Daily aspirin dose                              |                            |                                   |                                               |                             |          |          |
| 75 mg                                          | 12 (31.6%)                  | 57 (33.5%)                        | 17 (34%)                                     | 86 (33%)                    | 0.972    | 1.0      |
| 100 mg                                         | 26 (68.4%)                  | 113 (66.5%)                       | 33 (66%)                                     | 175 (67%)                   | 0.972    | 1.0      |

Data are presented as mean ± SD or n (%). *Comparing aspirin-resistant patients, aspirin semi-responders and aspirin-sensitive patients;#comparing combined group of aspirin-resistant patients and aspirin semi-responders with aspirin-sensitive patients. ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; BMI: body mass index; BNP: type-B natriuretic peptide; BP: blood pressure; CCBs: calcium-channel blockers; HDL-C: high-density lipoprotein cholesterol; Hs-CRP: high-sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; MPV: mean platelet volume; PAOD: peripheral arterial occlusive disease.
Table 3. Results of the multiple logistic regression analysis.

|                  | B    | SE   | Wald  | df | Sig  | Exp (B)  | 95% CI for Exp (B) |
|------------------|------|------|-------|----|------|----------|---------------------|
| Metabolic syndrome | 1.600| 0.630| 6.448 | 1  | 0.011| 4.951    | 1.440 – 17.019      |
| Statins          | -0.002| 0.008| 0.090 | 1  | 0.764| 0.998    | 0.983 – 1.013       |
| Protein C activity | -0.302| 0.647| 0.218 | 1  | 0.640| 0.739    | 0.208 – 2.626       |
| Constant         | -2.457| 1.048| 5.494 | 1  | 0.019| 0.086    |                     |

Table 4. The prevalence of aspirin resistance or semi-responders by different criteria of MS.

| Criteria                                      | Aspirin resistance | Aspirin semi-responders | Aspirin resistance or Aspirin semi-responders |
|-----------------------------------------------|--------------------|-------------------------|-----------------------------------------------|
| HFG + High BP + Low HDL-C (n = 20)            | 5 (25%)            | 6 (30%)                 | 11 (55%)                                      |
| High BP + Central obesity + Low HDL-C (n = 46) | 7 (15.2%)          | 18 (39.1%)              | 25 (54.3%)                                    |
| High BP + HTG + Low HDL-C (n = 30)            | 4 (13.3%)          | 11 (36.7%)              | 15 (50%)                                      |
| HFG + Central obesity + Low HDL-C (n = 24)    | 4 (16.7%)          | 7 (29.2%)               | 11 (45.8%)                                    |
| Low HDL-C+ + HTG + Central obesity (n = 37)   | 5 (13.5%)          | 11 (29.7%)              | 16 (43.2%)                                    |
| HFG + High BP + Central obesity (n = 63)      | 8 (12.7%)          | 19 (30.2%)              | 27 (42.9%)                                    |
| HFG + HTG + Low HDL-C (n = 17)                | 2 (11.8%)          | 5 (29.4%)               | 7 (41.2%)                                     |
| High BP+ Central obesity + HTG (n = 73)       | 7 (9.6%)           | 23 (31.5%)              | 30 (41.1%)                                    |
| HFG + High BP+ HTG (n = 33)                   | 4 (12.1%)          | 9 (27.3%)               | 13 (39.4%)                                    |
| HFG + HTG + Central obesity (n = 39)          | 4 (10.3%)          | 10 (25.6%)              | 14 (35.9%)                                    |

Data are presented as n (%). HFG: high fasting glucose; BP: blood pressure; HTG: hypertriglyceridemia; HDL-C: high-density lipoprotein cholesterol.

Aspirin-resistant patients tended to have an increased level of diastolic BP, FG and TG, and decreased level of HDL-C compared with aspirin-sensitive patients. However, these differences were not significant. Some studies have suggested an association of aspirin resistance with smoking, hypertension, dyslipidemia, hemoglobin A1c levels, body mass index, C-reactive protein, age, and female sex. [13–18] Metabolic syndrome represents a constellation of risk factors, which include insulin resistance, dyslipidemia, hyper tension, and obesity. Metabolic syndrome may cause a high level of platelet activation. [19] We also found that patients with metabolic syndrome had higher levels of CD62P compared to the control group. In patients with metabolic syndrome, aspirin resistance or aspirin semi-responders were frequently found, in descending order: 11 (55%) patients with high FG + high BP + low HDL-C; 25 (54.3%) patients with high BP + central obesity + low HDL-C; and 15 (50%) patients with high BP + high TG + low HDL-C. Lifestyle modification remains the initial intervention of choice for patients with metabolic syndrome with subclinical atherosclerosis. Pharmacological treatment should be recommended in patients whose risk factors are not adequately decreased with therapeutic lifestyle changes. [20] Low-dose aspirin should be considered for all elderly patients (≥ 65 years old) at high Framingham risk with metabolic syndrome in the absence of contraindications. [21] We should pay more attention to patients with CVD and metabolic syndrome, and further studies are needed to focus on the relationship between aspirin resistance and metabolic syndrome.

The present study showed that plasma protein C activity levels were higher in patients with aspirin sensitivity than in aspirin semi-responders and the combined group of aspirin resistance + aspirin semi-responders. One study found that lower protein C activity and female sex were associated with critical limb ischemia in multivariate logistic regression analysis. [22] In the present study, we found that aspirin-sensitive patients were more likely to take statins than aspirin semi-responders and aspirin resistant patients were. Shen, et al. [23] also demonstrated that aspirin-resistant patients defined by whole blood platelet aggregometry had significantly higher total cholesterol and low-density lipoprotein cholesterol levels compared with aspirin-sensitive patients. Sahin, et al. [24] revealed that platelet aggregation inhibition using a modified thrombelastography showed negative correlation with hyperlipidemia. More studies have shown that concomitant use of statins improves the anti-platelet effects of aspirin. [25,26] These findings suggest that statins in patients with dyslipidemia may improve aspirin response.

The present study had two important limitations. First, the prevalence of aspirin resistance in elderly patients with metabolic syndrome was valid for the dose of 75–100 mg/day aspirin, but we did not investigate the other suggested doses of 162 and 325 mg/day. Second, the study
population was relatively small. Further studies with more subjects are required to verify the findings of the present study.

In conclusion, our findings suggest that many elderly patients with metabolic syndrome are resistant to aspirin therapy, which puts them at a higher risk of developing worse clinical events. Further studies exploring the clinical events of aspirin resistance in patients with metabolic syndrome and CVD will provide additional information for strategies for anti-platelet therapy in elderly patients with metabolic syndrome.

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