Association Between Renal Function and Platelet Reactivity During Aspirin Therapy in Elderly Patients With Atherosclerotic Cardiovascular Disease

Wenyi Liang
Peking University First Hospital https://orcid.org/0000-0001-8642-9825
Peng Zhang
Peking University First Hospital
Meilin Liu (liumeilin@hotmail.com)
Department of Geriatrics, Peking University First Hospital, No. 8, Xishiku Street, Xicheng District, Beijing 100034, People's Republic of China https://orcid.org/0000-0001-9736-9864

Research article

Keywords: Age, Aspirin, Atherosclerotic cardiovascular disease, Platelet reactivity, Renal function

Posted Date: August 31st, 2020

DOI: https://doi.org/10.21203/rs.3.rs-64027/v1

Version of Record: A version of this preprint was published on January 22nd, 2021. See the published version at https://doi.org/10.1186/s12877-021-02018-y.

Abstract

Background: Aspirin is the key treatment in the secondary prevention of atherosclerotic cardiovascular disease. High on-treatment platelet reactivity (HTPR) to aspirin has been reported to partially account for the enhanced risk of thrombotic events. In particular, HTPR has been described more frequently among elderly patients. The aim of this study was to identify the clinical and biological factors associated with HTPR in a real-life elderly population.

Methods: In this retrospective study, elderly patients with atherosclerotic cardiovascular disease on regular aspirin treatment were enrolled. Cardiovascular risk factors, routine biological parameters, comorbidities, and concomitant medications were recorded. The upper quartile of the platelet aggregation rate, determined by light transmission aggregometry with arachidonic acid, was defined as the HTPR group.

Results: A total of 304 patients were included (mean age 77 ± 8 years, 76% men). Patients in the HTPR group were older than the patients in the non-HTPR group (mean age: 79 ± 7 *vs.* 76 ± 8 years, $p = 0.008$). Patients with moderately decreased estimated glomerular filtration rate (eGFR) had a higher frequency of HTPR than patients with slightly decreased eGFR or normal eGFR (35.8%, 22.5%, 12.2%, respectively, $p < 0.05$). In multivariate analysis, an independent risk factor for HTPR was the eGFR (OR: 0.984, 95% CI: 0.980-0.988, $p < 0.001$).

Conclusions: Advanced age and decreased eGFR are correlated with poor pharmacodynamic response to aspirin. Antiplatelet strategy in elderly patients with atherosclerotic cardiovascular disease should be driven by an individualized approach, especially in patients with impaired renal function.

Background

Atherosclerotic cardiovascular disease (ASCVD) includes coronary heart disease, ischemic stroke or transient ischemic attacks, and peripheral arterial disease, all of presumed atherosclerotic origin[1]. Aspirin is the key treatment in the secondary prevention of ASCVD due to its prominent antiplatelet effects[2, 3]. Aspirin inhibits cyclooxygenase (COX)-1, which mediates thromboxane A2 (TXA2) synthesis. Decreased levels of TXA2 do not activate platelets as effectively; thus, thrombus formation is impeded[4, 5].

Recent studies have shown that aspirin fails to prevent a substantial number of serious vascular events among high-risk patients[6, 7]. This has led to the introduction of the concept of high on-treatment platelet reactivity (HTPR)[8]. In particular, HTPR has been described more frequently among elderly patients, conditioned by impaired drug absorption and metabolism and by a baseline of more enhanced platelet reactivity. Most previous studies enrolled patients receiving dual antiplatelet therapy[9, 10]. However, there is evidence of overlap in the antiplatelet effects of aspirin and P2Y12 antagonists[11]. The main objective of our study was to identify routinely available clinical and biological factors associated with HTPR in a real-life elderly population of ASCVD patients receiving aspirin as monotherapy. We hypothesized that finding factors associated with HTPR can help identify high-risk patients and eventually modify antiplatelet therapy.

Methods

Study design and participants

Elderly patients on regular aspirin treatment in the Department of Geriatrics of Peking University First Hospital were enrolled from March 2014 to December 2019.

The inclusion criteria were as follows:

1. Age: ≥ 60 years;
2. Diagnosis of ASCVD, presence of at least one of the following diseases: coronary heart disease, ischemic stroke, transient ischemic attacks, and peripheral arterial disease;

3. Aspirin monotherapy was used for secondary prevention (50–100 mg daily for more than 1 month) without a change in dose within the previous month.

The exclusion criteria were as follows:

1. Use of other antithrombotic medications (including clopidogrel, ticagrelor, prasugrel, dipyridamole, warfarin, heparin, low-molecular-weight heparin and new oral anticoagulants) or nonsteroidal anti-inflammatory drugs within 1 month;
2. Severe renal dysfunction [estimated glomerular filtration rate (eGFR) < 30 ml/min/1.73 m^2] or dialysis;
3. Platelet count < 100×10^3/μL or > 450×10^3/μL;
4. A major surgical procedure or severe inflammation within 1 week;
5. History of malignant tumor, chronic inflammatory diseases, serious liver disease and autoimmune disease.

Medical records collection

For each patient, detailed medical records were obtained from the electronic medical record system, including age, sex, smoking habit, alcohol habit, body mass index, comorbidities, concomitant medications, and usual biological parameters.

Platelet reactivity

For each patient, platelet aggregation was determined by light transmission aggregometry with arachidonic acid (LTA-AA). Platelet aggregation tests have been routinely performed for several years at our clinical laboratory by experienced technicians. Blood samples anticoagulated with 3.2% sodium citrate were centrifuged at 200 × *g* for 10 min to obtain platelet-rich plasma and further centrifuged at 2000 × *g* for 10 min to obtain platelet-poor plasma. Platelet aggregation was performed by the addition of 0.5 mg/mL arachidonic acid to platelet-rich plasma cuvette using platelet-poor plasma as a reference cuvette. The percentage of platelet aggregation was defined as the maximal light transmittance after arachidonic acid addition measured by the LBY-NJ4 platelet aggregometer (PRECIL, Beijing, China)[12].

Patient group

Patients were divided according to LTA-AA. Patients with platelet aggregation rates in quartile IV were defined as the HTPR group, whereas patients with platelet aggregation rates in quartiles I-III were defined as the non-HTPR group.

Patients were also stratified by eGFR, which was calculated using the MDRD (Modification of Diet in Renal Disease) formula[13]. The G1 group included patients with normal eGFR (eGFR ≥ 90 mL/min/1.73 m^2). The G2 group included patients with slightly decreased eGFR (eGFR 60–89 mL/min/1.73 m^2). The G3 group included patients with moderately decreased eGFR (eGFR 30–59 mL/min/1.73 m^2).

Statistical analysis

The distribution normality of each variable was tested using the Kolmogorov-Smirnov test. Continuous variables were expressed as the mean ± SD or median (interquartile range). Homogeneity of variance was tested for continuous variables. For normally distributed data, comparisons between two groups were performed by Student's unpaired *t* test, and comparisons among groups were performed using one-way ANOVA, followed by post-hoc analysis of LSD tests (if variances were equal) or Tamhane's T2 tests (if variances were unequal). The nonparametric Mann-Whitney U test or Kruskal-Wallis H test were performed if the data were nonnormal. Categorical variables were described as counts (percentages) and were tested using the chi-square test. Correction for multiple comparisons was performed using the Bonferroni-Holm correction. Correlations between quantitative variables were assessed using Pearson or Spearman correlation coefficients, as appropriate. Multivariate logistic regression analysis (forward: conditional) was performed to investigate risk factors for HTPR. After univariate analysis, variables that presented significant associations with HTPR ($p < 0.10$) were entered in the multivariate model. Differences were considered significant when $p < 0.05$ (two-tailed). The cutoff value was calculated by analyzing the receiver operating characteristic (ROC) curve. Statistical analysis was carried out using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA).

Results

Finally, 304 patients with sufficient available clinical and biological information were selected for this study. The average age was 77 ± 8 years, and 233 (76.6%) patients were males. There were 120 (39.5%) patients with age ≥ 80 years and 8 (2.6%) patients with age ≥ 90 years.

Testing of platelet aggregation

During aspirin therapy, the range of LTA-AA was from 0.84–34.91%, with a median value of 9.69% (IQR 6.80%-12.38%). There were 3 (0.99%) patients with LTA-AA > 20%. According to the aforementioned definition, there were 76 patients in the HTPR group (LTA-AA ≥ 12.38%), with a median value of 14.41% (IQR 12.94%-16.82%), and there were 228 patients in the non-HTPR group (LTA-AA < 12.38%), with a median value of 8.69% (IQR 5.83%-10.48%).

Clinical features of elderly patients with ASCVD classified by HTPR

The clinical and biological characteristics of the study participants divided according to HTPR are shown in Table 1 and Table 2. Patients in the HTPR group were older than patients in the non-HTPR group (mean age: 79 ± 7 *vs.* 76 ± 8 years, $p = 0.008$)). In terms of the ASCVD spectrum, patients in the HTPR group had an increased presence of ischemic stroke or transient ischemic attacks, and fewer patients had a history of coronary heart disease than those in the non-HTPR group ($p < 0.01$). The ratio of angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) medications was higher in the HTPR group ($p = 0.046$). There were no significant differences in daily aspirin dose between the two groups ($p > 0.05$). Patients in the HTPR group had lower levels of eGFR (average values: 65.2 *vs.* 71.8 mL/min/1.73 m^2, $p = 0.002$), indicating poorer renal function than patients in the non-HTPR group. The hemoglobin level was significantly lower in the HTPR group than that in the non-HTPR group ($p < 0.001$).

Table 1
Clinical characteristics of study participants classified by HTPR

Variables	HTPR group (N = 76)	non-HTPR group (N = 228)	*p* value
Age, years	79 ± 7	76 ± 8	0.008
Male sex, *n* (%)	54 (71.1)	179 (78.5)	0.183
Body mass index, kg/m^2	24.0 ± 2.7	24.6 ± 3.1	0.149
Systolic blood pressure, mmHg	138 ± 18	134 ± 16	0.076
Diastolic blood pressure, mmHg	71 ± 11	73 ± 11	0.164
Medical history			
Coronary heart disease, *n* (%)	59 (77.6)	210 (92.1)	0.001
PCI, *n* (%)	33 (43.4)	115 (50.4)	0.289
Ischemic stroke or TIA, *n* (%)	39 (51.3)	56 (24.6)	< 0.001
Peripheral artery stenosis, *n* (%)	7 (9.2)	29 (12.7)	0.412
Hypertension, *n* (%)	63 (80.8)	175 (75.1)	0.307
Diabetes mellitus, *n* (%)	24 (31.6)	75 (32.9)	0.832
Hyperlipidemia, *n* (%)	69 (90.8)	191 (83.8)	0.132
Smoking habits: former/current, *n* (%)	17/8 (22.4/10.5)	66/25 (28.9/11.0)	0.505
Alcoholic habits: former/current, *n* (%)	5/5 (6.5/6.5)	22/28 (9.6/12.3)	0.239
Daily aspirin dose			
100 mg, *n* (%)	65 (85.5)	196 (86.0)	0.924
50 mg or 75 mg, *n* (%)	11 (14.5)	32 (14.0)	
Medications taken			
ACEIs/ARBs, *n* (%)	48 (63.2)	114 (50.0)	0.046
Calcium-channel blockers, *n* (%)	24 (31.6)	85 (37.3)	0.369
β-blockers, *n* (%)	53 (69.7)	146 (64.0)	0.365
Nitrates, n (%)	31 (40.8)	68 (29.8)	0.077
Statins, *n* (%)	72 (94.7)	202 (88.6)	0.120
Diuretics, n (%)	11 (14.5)	33 (14.5)	0.999
Proton pump inhibitors,*n* (%)	21 (27.6)	41 (18.0)	0.071

PCI, percutaneous coronary intervention; TIA, transient ischemic attacks; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Table 2
Laboratory data of study participants classified by HTPR

Variables	HTPR group (N = 76)	non-HTPR group (N = 228)	*p* value
LTA-AA, %	14.41 (12.94–16.82)	8.69 (5.83–10.48)	< 0.001
Hemoglobin, g/dl	12.6 ± 1.6	13.4 ± 1.6	< 0.001
White blood cell count, $x10^3/\mu L$	5.9 ± 1.8	6.1 ± 1.5	0.458
Neutrophil percentage, %	61.3 ± 10.9	62.1 ± 9.5	0.507
Platelet count, $x10^3/uL$	174 ± 49	184 ± 51	0.180
Mean platelet volume, fl	8.7 ± 0.8	8.8 ± 1.2	0.334
eGFR, mL/min/1.73 m^2	65.2 ± 14.7	71.8 ± 17.3	0.002
Serum uric acid, mg/dL	5.83 ± 1.46	5.55 ± 1.27	0.112
Serum creatinine, mg/dL	1.00 (0.86–1.17)	0.98 (0.81–1.12)	0.121
Serum urea, mg/dL	39.97 ± 11.42	40.99 ± 12.92	0.556
Glycosylated hemoglobin, %	5.9 (5.6–6.7)	6.0 (5.6–6.3)	0.905
Triglycerides, mg/dL	94.8 (72.7-130.9)	102.8 (71.8-147.1)	0.436
Total cholesterol, mg/dL	133.0 (113.7-154.2)	132.7 (120.2-152.7)	0.510
HDL-C, mg/dL	41.2 ± 10.8	42.9 ± 10.5	0.243
LDL-C, mg/dL	68.2 (59.5–82.2)	70.0 (59.9–83.1)	0.666
C-reactive protein, mg/L	0.98 (0.32–3.90)	0.73 (0.35–1.70)	0.389

LTA-AA, light transmission assay with arachidonic acid; eGFR, estimated glomerular filtration rate; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.

Linear correlation analysis showed that LTA-AA was significantly correlated with age (r = 0.128, $p = 0.025$), hemoglobin (r = − 0.216, $p < 0.001$) and eGFR (r = − 0.230, $p < 0.001$) for the entire study population. Multivariate regression analysis of HTPR included the following independent variables in the model: age, systolic blood pressure, eGFR, hemoglobin, nitrate use, proton pump inhibitor (PPI) use and ACEI/ARB use. The results showed that eGFR was an independent factor associated with HTPR (OR: 0.984, 95% CI: 0.980–0.988, $p < 0.001$).

Clinical features of elderly patients with ASCVD classified by renal function

Study participants were stratified by eGFR. Clinical and biologic characteristics with statistical significance are shown in Table 3. In all enrolled patients, 16.1% had a normal eGFR, 52.6% had a slight decrease in eGFR, and 31.3% had a moderate decrease in eGFR. LTA-AA was higher in patients with decreased eGFR than in those with normal eGFR. Patients with moderately decreased eGFR had a higher frequency of HTPR than patients with slightly decreased eGFR or normal eGFR (35.8%, 22.5%, 12.2%, respectively, $p < 0.05$). Renal function deteriorates with age. As eGFR decreased, a descending trend of diastolic blood pressure levels and hemoglobin levels, as well as an ascending trend of serum creatinine, urea and uric acid levels appeared. Patients with moderately decreased eGFR had higher MPV (mean platelet volume)/PLT (platelet count) ratios and neutrophil percentages compared to those with slightly decreased eGFR ($p < 0.05$). Compared with patients with normal eGFR, patients with moderately decreased eGFR had an increased presence of ischemic stroke/transient ischemic attack, peripheral artery stenosis and hyperlipidemia ($p < 0.05$), and the ratios of ACEIs/ARBs, statins and PPI medications were higher

($p < 0.05$). The results of ROC analysis showed that eGFR levels in all patients were calculated with 70.3 mL/min/1.73 m^2 as a cutoff value to predict HTPR, with an area under the ROC curve of 0.620 (95% CI 0.551–0.689, $p = 0.002$).

Table 3
Clinical features of study participants classified by renal function

Variables	G1 group (N = 49; eGFR ≥ 90 mL/min/1.73 m^2)	G2 group (N = 160; eGFR 60–89 mL/min/1.73 m^2)	G3 group (N = 95; eGFR 30–59 mL/min/1.73 m^2)	*P* value	*P* value		
					G1 *vs.* G2	G1 *vs.* G3	G2 *vs.* G3
eGFR, mL/min/1.73 m^2	94.5 ± 7.3	74.2 ± 8.5	50.8 ± 7.9	< 0.001	< 0.001	< 0.001	< 0.001
HTPR, *n* (%)	6 (12.2)	36 (22.5)	34 (35.8)	0.005	0.117	0.003	0.021
LTA-AA, %	7.75 ± 4.07	9.90 ± 3.83	10.92 ± 4.63	< 0.001	0.002	< 0.001	0.058
Age, years	67 ± 7	76 ± 7	82 ± 5	< 0.001	< 0.001	< 0.001	< 0.001
Diastolic blood pressure, mmHg	77 ± 11	72 ± 10	69 ± 10	< 0.001	0.007	< 0.001	0.025
Hemoglobin, g/dl	14.0 ± 1.6	13.4 ± 1.4	12.4 ± 1.7	< 0.001	0.013	< 0.001	< 0.001
Neutrophil percentage, %	61.1 ± 10.2	59.9 ± 9.4	65.6 ± 9.6	< 0.001	0.458	0.007	< 0.001
PLT, x 10^3/uL	190 ± 55	186 ± 50	169 ± 47	0.012	0.626	0.016	0.008
MPV, fl	9.4 ± 1.4	8.6 ± 1.1	8.7 ± 1.0	< 0.001	0.004	0.016	0.886
MPV/PLT ratio, fl x 10^{-3}uL	0.053 ± 0.018	0.050 ± 0.016	0.056 ± 0.018	0.031	0.248	0.393	0.009
Serum creatinine, mg/dL	0.70 (0.62–0.80)	0.95 (0.85–1.03)	1.21 (1.12–1.32)	< 0.001	< 0.001	< 0.001	< 0.001
Serum urea, mg/dL	31.9 ± 8.0	38.0 ± 9.2	47.0 ± 14.7	< 0.001	0.007	< 0.001	< 0.001
Serum uric acid, mg/dL	5.12 ± 1.32	5.52 ± 1.22	6.04 ± 1.37	< 0.001	0.059	< 0.001	0.002
C-reactive protein, mg/L	0.5 (0.3–1.3)	0.6 (0.3–1.3)	1.4 (0.7–4.1)	< 0.001	0.988	0.006	< 0.001
Medical history							
Ischemic stroke/TIA, *n* (%)	9 (18.4)	48 (30.0)	38 (40.0)	0.026	0.110	0.009	0.102
Peripheral artery stenosis, *n* (%)	0 (0)	19 (11.9)	17 (17.9)	0.007	0.011	0.002	0.182
Hypertension, *n* (%)	33 (67.3)	118 (73.8)	81 (85.3)	0.031	0.432	0.020	0.053
Hyperlipidemia, *n* (%)	35 (71.4)	137 (85.6)	88 (92.6)	0.003	0.023	0.001	0.093
Medications taken							

LTA-AA, light transmission assay with arachidonic acid; eGFR, estimated glomerular filtration rate; PLT, platelet count; MPV, mean platelet volume; TIA, transient ischemic attacks; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Variables	G1 group (N = 49; eGFR ≥ 90 mL/min/1.73 m^2)	G2 group (N = 160; eGFR 60–89 mL/min/1.73 m^2)	G3 group (N = 95; eGFR 30–59 mL/min/1.73 m^2)	*P* value	*P* value		
					G1 *vs.* G2	G1 *vs.* G3	G2 *vs.* G3
ACEIs/ARBs, *n* (%)	20 (40.8)	83 (51.9)	59 (61.2)	0.046	0.175	0.015	0.112
Statins, *n* (%)	34 (69.4)	152 (95.0)	88 (92.6)	< 0.001	< 0.001	< 0.001	0.437
Diuretics, n (%)	5 (10.2)	17 (10.6)	22 (23.2)	0.015	0.993	0.059	0.007
Proton pump inhibitors,*n* (%)	2 (4.1)	32 (20.0)	28 (29.5)	0.002	0.008	< 0.001	0.085

LTA-AA, light transmission assay with arachidonic acid; eGFR, estimated glomerular filtration rate; PLT, platelet count; MPV, mean platelet volume; TIA, transient ischemic attacks; ACEIs, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

Discussion

The reported prevalence of patients not achieving an adequate antiplatelet effect under aspirin varies greatly, due to difference in laboratory assessment. To date, there is no universally accepted cut-off value of each method[8]. In this study, we used aggregometry tests as a surrogate measure of aspirin response, which are still considered as the gold standard for aspirin testing. LTA-AA located in the upper quartile were defined as HTPR.

HTPR has been found to be correlated with clinical events. It is of great importance to investigate the factors influencing HTPR. Elderly patients represent a challenging population for the optimal management of antiplatelet therapy. Few studies have specifically addressed the problem of platelet aggregation in elderly patients receiving antiplatelet therapy, with contrasting results[9, 14–16]. In our study, patients in the HTPR group were older. There was a positive linear correlation between age and platelet aggregation rate. However, the ADAPT-DES study addressed that despite being associated with older age, HTPR did not modify the adjusted relative risks of ischemic events associated with age[15]. Elderly patients also represent a category where other factors, such as frailty, comorbidities or lower body weight, have an intrinsic high risk of hemorrhage[17]. Indeed, future detailed mechanistic research is needed to address the relationship of platelet changes with aging and the pathophysiological basis of the antiplatelet response. At present, antiplatelet strategies in elderly patients with ASCVD should be cautiously driven by an individualized approach, balancing bleeding and thrombotic risk.

The prothrombotic status associated with aging could be even more enhanced among chronic kidney disease (CKD) patients, displaying an intrinsic higher platelet activation induced by chronic low-grade inflammation and vascular injury[18]. Even in the absence of cardiovascular disease, patients with CKD have an increased risk of thrombosis, the dominant pathophysiology of which is likely to be abnormalities of platelet function[19]. To date, few studies have been conducted regarding the role of renal function on platelet reactivity. Conflicting results were reached, and most of them were conducted among patients receiving clopidogrel in association with aspirin[20–23]. However, there is evidence of overlap in the anti-platelet effects of aspirin and P2Y12 antagonist[11]. Therefore, we aimed to evaluate the impact of renal function on HTPR in patients receiving aspirin as monotherapy. Patients with end-stage renal disease were excluded because they are likely to suffer from multiorgan damage potentially confounding the results[24]. Our study revealed that HTPR was more common in patients with mildly/moderately decreased eGFR than in those with preserved renal function. eGFR was an independent factor of HTPR. The further mechanism of platelet hyperactivity in patients with impaired renal function might be relevant to the accumulation of uremic toxins, such as indoxyl sulfate[25] and homocysteine[26]. Furthermore, pre-activation of platelets in CKD[27] may play a role in the pathogenesis of insufficient platelet inhibition by aspirin in patients with impaired kidney function.

It is well known that elevated uric acid is associated with impaired renal function. Hyperuricemia is a condition characterized by impaired nitric oxide production/endothelial dysfunction, increased vascular stiffness, inappropriate activation of the renin-

angiotensin-aldosterone system, enhanced oxidative stress, and maladaptive immune and inflammatory responses[28]. Moreover, elevated uric acid has been reported to upregulate the expression of platelet-derived growth factor and the production of tissue factor in vascular smooth muscle cells[29], which link uric acid to inflammation and therefore to platelet hyperreactivity. In this study, we found an increasing tendency of serum uric acid levels in the HTPR group, but without statistical significance, although we still know little about the mechanisms that drive these changes.

Platelet-leukocyte interactions may mitigate aspirin's suppressive effect on platelet function by enhancing thromboxane formation independent of platelet COX-1[30, 31]. Platelets might also be an amplificatory factor in various inflammatory circumstances. Activated platelets release a wide range of inflammatory mediators and induce the expression of these mediators in monocytes/macrophages and granulocytes[32]. Monocytes/macrophages are important sources of TXA2 and have the capacity to synthesize TXA2 through the COX-2 pathway, which has a higher threshold of inhibition by aspirin than the COX-1 pathway[33]. Faraday et al. demonstrated a strong association between blood leukocyte count and increased platelet reactivity in vitro and in vivo[34]. In view of this, we excluded patients with acute or chronic inflammatory diseases in our study. There were no differences in leukocyte counts, neutrophil counts or C-reactive protein levels between the HTPR group and the non-HTPR group. However, we observed significantly higher neutrophil percentages and C-reactive protein levels in patients with moderate renal impairment than in those with mild renal impairment. This may indicate the importance of chronic low-grade inflammation as a factor contributing to HTPR in CKD patients. Furthermore, higher values of MPV and MPV/PLT ratio were considered possible biomarkers in inflammatory processes, CKD and ASCVD, which is partially in line with our study[35–38].

Acid suppression with PPIs can increase the potential for mucosal esterases to hydrolyze aspirin to its inactive form. A reduction in gastric absorption thus results in an increased drug load within the small intestine, where hydrolysis by esterases prior to absorption may reduce bioavailability[39]. This could explain the finding in our study where PPI medication was more common in the HTPR group. However, the consequences of concurrent PPI therapy with aspirin are not clear, as pharmacokinetic and pharmacodynamic studies designed to address this question have been inconsistent, although the weight of evidence appears to suggest no significant interaction[40, 41]. The current evidence therefore is in favor of PPI prescription in those who are at risk of gastrointestinal bleeding, with the additional benefit that a reduction in dyspepsia may improve adherence[42, 43].

Limitations

There are several limitations in this study. First, the present data are observational, with all the inherent limitations of a retrospective analysis. We do not have baseline pretreatment data for platelet function as that would not have been feasible with this particular study design. Prospective or interventional investigations should be conducted in the future. Second, we only used LTA-AA tests as a surrogate measure of aspirin response, rather than specific assessment of its effect on the therapeutic target (*i.e.*, thromboxane B2).

Conclusions

Among elderly patients receiving antiplatelet therapy with aspirin for secondary prevention of ASCVD, advanced age was correlated with insufficient antiplatelet effects of aspirin. A significant relationship between HTPR and impaired renal function was observed. Larger trials are needed to assess the clinical impact of this finding and investigate the optimal antithrombotic regimen in elderly patients.

Abbreviations

ACEI
Angiotensin converting enzyme inhibitor; ARB:Angiotensin receptor blocker; ASCVD:Atherosclerotic cardiovascular disease; CKD:Chronic kidney disease; COX:Cyclooxygenase; eGFR:Estimated glomerular filtration rate; HTPR:High on-treatment platelet reactivity; LTA-AA:Light transmission aggregometry with arachidonic acid; MPV:Mean platelet volume; PLT:Platelet count; PPI:Proton pump inhibitor; ROC:Receiver operating characteristic; TXA2:Thromboxane A2.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

WYL: study design, obtaining funding, acquisition of data, interpretation of data, statistical analysis, drafting of the manuscript. PZ: study design, acquisition of data, interpretation of data, statistical analysis. MLL: study design, obtaining funding, interpretation of data, administrative support, revision of the manuscript, and supervision of the whole study. All authors read and approved the final manuscript.

Funding

This study was supported by the Research Foundation of Peking University First Hospital [2017QN23], the National Key Research & Development Project of China [2016YFC1301304] and the National Science & Technology Support Program of China [2012BAI37B05]. The funding body had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Availability of data and materials

The datasets used for the current study are available at the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Review Committee of Peking University First Hospital. The need for consent was waived because of the retrospective data.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Stone NJ, Robinson JG, Lichtenstein AH, Bairey MC, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889 – 934.
2. Lin TT, Lai HY, Chan KA, Yang YY, Lai CL, Lai MS. Single and dual antiplatelet therapy in elderly patients of medically managed myocardial infarction. BMC Geriatr. 2018;18(1):86.
3. Bazargani YT, Ugurlu M, de Boer A, Leufkens H, Mantel-Teeuwisse AK. Selection of essential medicines for the prevention and treatment of cardiovascular diseases in low and middle income countries. BMC Cardiovasc Disord. 2018;18(1):126.
4. Patrono C, Coller B, Dalen JE, FitzGerald GA, Fuster V, Gent M, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects. Chest. 2001;119(1 Suppl):39S–63S.
5. Patrono C. The Multifaceted Clinical Readouts of Platelet Inhibition by Low-Dose Aspirin. J Am Coll Cardiol. 2015;66(1):74–85.

6. Marcucci R, Paniccia R, Antonucci E, Gori AM, Fedi S, Giglioli C, et al. Usefulness of aspirin resistance after percutaneous coronary intervention for acute myocardial infarction in predicting one-year major adverse coronary events. Am J Cardiol. 2006;98(9):1156–9.
7. Mayer K, Bernlochner I, Braun S, Schulz S, Orban M, Morath T, et al. Aspirin treatment and outcomes after percutaneous coronary intervention: results of the ISAR-ASPI registry. J Am Coll Cardiol. 2014;64(9):863–71.
8. Pettersen AA, Arnesen H, Seljeflot I. A brief review on high on-aspirin residual platelet reactivity. Vascul Pharmacol. 2015;67–69:6–9.
9. Gremmel T, Steiner S, Seidinger D, Koppensteiner R, Panzer S, Kopp CW. Adenosine diphosphate-inducible platelet reactivity shows a pronounced age dependency in the initial phase of antiplatelet therapy with clopidogrel. J Thromb Haemost. 2010;8(1):37–42.
10. Verdoia M, Pergolini P, Nardin M, Rolla R, Tonon F, Kedhi E, et al. Impact of aging on platelet reactivity in diabetic patients receiving dual antiplatelet therapy. J Thromb Thrombolysis. 2019;48(3):413–21.
11. Warner TD, Nylander S, Whatling C. Anti-platelet therapy: cyclo-oxygenase inhibition and the use of aspirin with particular regard to dual anti-platelet therapy. Br J Clin Pharmacol. 2011;72(4):619–33.
12. Zhang JW, Liu WW, McCaffrey TA, He XQ, Liang WY, Chen XH, et al. Predictors of high on-aspirin platelet reactivity in elderly patients with coronary artery disease. Clin Interv Aging. 2017;12:1271–9.
13. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247–54.
14. Verdoia M, Pergolini P, Rolla R, Nardin M, Schaffer A, Barbieri L, et al. Advanced age and high-residual platelet reactivity in patients receiving dual antiplatelet therapy with clopidogrel or ticagrelor. J Thromb Haemost. 2016;14(1):57–64.
15. Faggioni M, Redfors B, Crowley A, Claessen BE, Farhan S, Mastoris I, et al. Comparison of Age (< 75 Years Vs >/=75 Years) and Platelet Reactivity to the Risk of Thrombotic and Bleeding Events After Successful Percutaneous Coronary Intervention With Drug-Eluting Stents (from the ADAPT-DES Study). Am J Cardiol. 2020;125(5):685–93.
16. Silvain J, Cayla G, Hulot JS, Finzi J, Kerneis M, O'Connor SA, et al. High on-thienopyridine platelet reactivity in elderly coronary patients: the SENIOR-PLATELET study. Eur Heart J. 2012;33(10):1241–9.
17. Afilalo J, Alexander KP, Mack MJ, Maurer MS, Green P, Allen LA, et al. Frailty assessment in the cardiovascular care of older adults. J Am Coll Cardiol. 2014;63(8):747–62.
18. Hwang D, Park KW, Lee JM, Rhee TM, Hong MK, Jang Y, et al. Efficacy and safety of dual antiplatelet therapy after coronary stenting in patients with chronic kidney disease. Am Heart J. 2018;197:103–12.
19. Landray MJ, Wheeler DC, Lip GY, Newman DJ, Blann AD, McGlynn FJ, et al. Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. Am J Kidney Dis. 2004;43(2):244–53.
20. Polzin A, Dannenberg L, Sansone R, Levkau B, Kelm M, Hohlfeld T, et al. Antiplatelet effects of aspirin in chronic kidney disease patients. J Thromb Haemost. 2016;14(2):375–80.
21. Angiolillo DJ, Bernardo E, Capodanno D, Vivas D, Sabate M, Ferreiro JL, et al. Impact of chronic kidney disease on platelet function profiles in diabetes mellitus patients with coronary artery disease taking dual antiplatelet therapy. J Am Coll Cardiol. 2010;55(11):1139–46.
22. Feng ZM, Lin YQ, Deng BQ, Shu XR, Ke X, Nie RQ. Pharmacodynamic changes of platelet reactivity status in patients with chronic kidney disease after coronary artery stenting. Biomed Pharmacother. 2019;113:108773.
23. Barbieri L, Pergolini P, Verdoia M, Rolla R, Nardin M, Marino P, et al. Platelet reactivity in patients with impaired renal function receiving dual antiplatelet therapy with clopidogrel or ticagrelor. Vascul Pharmacol. 2016;79:11–5.
24. Jain N, Li X, Adams-Huet B, Sarode R, Toto RD, Banerjee S, et al. Differences in Whole Blood Platelet Aggregation at Baseline and in Response to Aspirin and Aspirin Plus Clopidogrel in Patients With Versus Without Chronic Kidney Disease. Am J Cardiol. 2016;117(4):656–63.

25. Yang K, Du C, Wang X, Li F, Xu Y, Wang S, et al. Indoxyl sulfate induces platelet hyperactivity and contributes to chronic kidney disease-associated thrombosis in mice. Blood. 2017;129(19):2667–79.
26. Verdoia M, Rolla R, Negro F, Tonon F, Pergolini P, Nardin M, et al. Homocysteine levels and platelet reactivity in coronary artery disease patients treated with ticagrelor. Nutr Metab Cardiovasc Dis. 2020;30(2):292–9.
27. Gremmel T, Muller M, Steiner S, Seidinger D, Koppensteiner R, Kopp CW, et al. Chronic kidney disease is associated with increased platelet activation and poor response to antiplatelet therapy. Nephrol Dial Transplant. 2013;28(8):2116–22.
28. Chaudhary K, Malhotra K, Sowers J, Aroor A. Uric Acid - key ingredient in the recipe for cardiorenal metabolic syndrome. Cardiorenal Med. 2013;3(3):208–20.
29. Chitalia VC, Shivanna S, Martorell J, Balcells M, Bosch I, Kolandaivelu K, et al. Uremic serum and solutes increase post-vascular interventional thrombotic risk through altered stability of smooth muscle cell tissue factor. Circulation. 2013;127(3):365–76.
30. McKee SA, Sane DC, Deliargyris EN. Aspirin resistance in cardiovascular disease: a review of prevalence, mechanisms, and clinical significance. Thromb Haemost. 2002;88(5):711–5.
31. Hankey GJ, Eikelboom JW. Aspirin resistance. Lancet. 2006;367(9510):606–17.
32. Aukrust P, Damas JK, Solum NO. Soluble CD40 ligand and platelets: self-perpetuating pathogenic loop in thrombosis and inflammation? J Am Coll Cardiol. 2004;43(12):2326–8.
33. Du G, Lin Q, Wang J. A brief review on the mechanisms of aspirin resistance. Int J Cardiol. 2016;220:21–6.
34. Faraday N, Yanek LR, Vaidya D, Kral B, Qayyum R, Herrera-Galeano JE, et al. Leukocyte count is associated with increased platelet reactivity and diminished response to aspirin in healthy individuals with a family history of coronary artery disease. Thromb Res. 2009;124(3):311–7.
35. Staszewski J, Pogoda A, Data K, Walczak K, Nowocien M, Frankowska E, et al. The mean platelet volume on admission predicts unfavorable stroke outcomes in patients treated with IV thrombolysis. Clin Interv Aging. 2019;14:493–503.
36. Korniluk A, Koper-Lenkiewicz OM, Kaminska J, Kemona H, Dymicka-Piekarska V. Mean Platelet Volume (MPV): New Perspectives for an Old Marker in the Course and Prognosis of Inflammatory Conditions. Mediators Inflamm. 2019;2019:9213074.
37. Ucar H, Gur M, Koyunsever NY, Seker T, Turkoglu C, Kaypakli O, et al. Mean platelet volume is independently associated with renal dysfunction in stable coronary artery disease. Platelets. 2014;25(4):274–8.
38. Guenancia C, Hachet O, Stamboul K, Bejot Y, Leclercq T, Garnier F, et al. Incremental predictive value of mean platelet volume/platelet count ratio in in-hospital stroke after acute myocardial infarction. Platelets. 2017;28(1):54–9.
39. Floyd CN, Ferro A. Mechanisms of aspirin resistance. Pharmacol Ther. 2014;141(1):69–78.
40. Adamopoulos AB, Sakizlis GN, Nasothimiou EG, Anastasopoulou I, Anastasakou E, Kotsi P, et al. Do proton pump inhibitors attenuate the effect of aspirin on platelet aggregation? A randomized crossover study. J Cardiovasc Pharmacol. 2009;54(2):163–8.
41. Wurtz M, Grove EL, Kristensen SD, Hvas AM. The antiplatelet effect of aspirin is reduced by proton pump inhibitors in patients with coronary artery disease. Heart. 2010;96(5):368–71.
42. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 Expert Consensus Document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents. Circulation. 2010;122(24):2619–33.
43. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020;41(3):407–77.