Clinical Investigation

Aspirin Resistance Predicts Adverse Cardiovascular Events

in Patients with Symptomatic Peripheral Artery Disease

Tilak Pasala, MD, MRCP
Jennifer Soo Hoo, MD
Mary Kate Lockhart, MD
Rehan Waheed, MD
Prasanna Sengodan, MD
Jeffrey Alexander, MD
Sanjay Gandhi, MD, FSCAI

Antiplatelet therapy reduces the risk of myocardial infarction, stroke, and vascular death in patients who have symptomatic peripheral artery disease. However, a subset of patients who take aspirin continues to have recurrent cardiovascular events. There are few data on cardiovascular outcomes in patients with peripheral artery disease who manifest aspirin resistance.

Patients with peripheral artery disease on long-term aspirin therapy (≥4 wk) were tested for aspirin responsiveness by means of the VerifyNow Aspirin Assay. The mean follow-up duration was 22.6 ± 8.3 months. The primary endpoint was a composite of death, myocardial infarction, or ischemic stroke. Secondary endpoints were the incidence of vascular interventions (surgical or percutaneous), or of amputation or gangrene caused by vascular disease.

Of the 120 patients enrolled in the study, 31 (25.8%) were aspirin-resistant and 89 (74.2%) were aspirin-responsive. The primary endpoint occurred in 10 (32.3%) patients in the aspirin-resistant group and in 13 (14.6%) patients in the aspirin-responsive group (hazard ratio=2.48; 95% confidence interval, 1.08–5.66; P=*0.03). There was no significant difference in the secondary outcome of revascularization or tissue loss. By multivariate analysis, aspirin resistance and history of chronic kidney disease were the only independent predictors of long-term adverse cardiovascular events.*

Aspirin resistance is highly prevalent in patients with symptomatic peripheral artery disease and is an independent predictor of adverse cardiovascular risk. Whether intervening in these patients with additional antiplatelet therapies would improve outcomes needs to be explored. ***(Tex Heart Inst J 2016;43(6):482-7)***

Key words: *Aspirin/therapeutic use; blood platelets/drug effects; lower extremity/blood supply; peripheral vascular diseases; platelet aggregation inhibitors/therapeutic use*

From: *Departments of Cardiology (Drs. Gandhi, Lockhart, Pasala, Sengodan, Soo Hoo, and Waheed) and Vascular Surgery (Dr. Alexander), The Heart and Vascular Center, MetroHealth Medical Center; and Case Western Reserve University (Drs. Alexander, Gandhi, Pasala, Sengodan, Soo Hoo, and Waheed); Cleveland, Ohio 44109*

Address for reprints: *Sanjay Gandhi, MD, The Heart and Vascular Center, Case Western Reserve University/MetroHealth, 2500 MetroHealth Dr., Cleveland, OH 44109-1998*

E-mail: *sgandhi@metrohealth.org*

Antiplatelet therapy reduces the risk of major adverse cardiovascular events (MACE) in patients with symptomatic peripheral artery disease (PAD).[1,2] Aspirin exerts this beneficial effect by irreversible inhibition of platelet cyclooxygenase-1 (COX-1) and subsequent inhibition of thromboxane A_2 synthesis. However, its effectiveness is limited. A subset of patients who take aspirin has recurrent vascular events perhaps due to inadequate inhibition of COX-1 as measured by platelet aggregation assays or urinary 11-dehydrothromboxane B_2.[3,4] These patients have been labeled "aspirin nonresponders" or "aspirin-resistant."[5] The precise mechanism of aspirin resistance is not known, but it is associated with an increased risk of adverse clinical outcomes in patients with coronary artery disease (CAD).[6]

Patients with PAD are at high risk of adverse cardiovascular (CV) events.[7] In the PAD subgroup of the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial,[8] the risk of ischemic stroke, myocardial death, or vascular death was 4.8% per year despite the use of aspirin. Unfortunately, there are few data to enable study of the effect of aspirin resistance on MACE outcomes in patients who have symptomatic PAD. These are the patients with moderate-to-severe claudication or significant lower-extremity occlusive atherosclerotic disease, in whom the benefit of antiplatelet therapy is most likely to be seen. Mueller and colleagues[9] did find that PAD patients who failed to experience platelet inhibition by aspirin had a higher risk of repeat occlusion at 18 months after peripheral artery angioplasty.

The goal of our study was to compare, at a tertiary vascular center, MACE outcomes in patients with symptomatic PAD, on the basis of their response to aspirin.

Patients and Methods

Our study plan was reviewed and approved by our Institutional Review Board. From October 2008 through January 2010, all patients aged 18 years or over, diagnosed with PAD and seen in our cardiology or vascular surgery practice, were screened for participation in the study. Patients were considered to have symptomatic PAD if they met either of 2 criteria: 1) a history of intermittent claudication, rest pain, or tissue loss of presumed atherosclerotic origin, with either ankle–brachial index (ABI) <0.85, previous leg amputation, peripheral vascular surgery, or percutaneous intervention; or 2) the presence upon angiographic or computed tomographic (CT) imaging of significant lower-extremity occlusive atherosclerotic disease. Patients with PAD who had been taking aspirin at a dose ≥75 mg/d for at least 4 weeks before enrollment were included. Aspirin use was determined by patient self-report, by review of electronic medical records, or by pharmacy prescriptions at the start of the study and at subsequent follow-up. Patients were excluded for concomitant use of clopidogrel, cilostazol, or nonsteroidal anti-inflammatory drugs in the week immediately before enrollment or for an anticipated need for long-term use of these drugs, a history of vascular surgery <1 week before enrollment, a family or personal history of bleeding disorders, a hemoglobin level of <8 g/dL, or a platelet count <150 $\times 10^3/\mu L$ or >450 $\times 10^3/\mu L$. Written informed consent was obtained from all patients before enrollment.

Blood Samples. All recruited patients had blood samples collected on the day of enrollment. Whole-blood samples were drawn into a 1.8-mL, 3.2% sodium citrate vacuum tube and filled to indicate volume. After collection, the tube was gently inverted 4 or 5 times and analysis was performed within 2 hours of sample collection. We used the VerifyNow® (Ultegra) System (Accriva Diagnostics; San Diego, Calif) to test for aspirin resistance. This is a turbidimetric-based optical detection system that measures platelet-induced aggregation as an increase in light transmittance. This system uses disposable cartridges containing a lyophilized preparation of human fibrinogen-coated beads and a platelet agonist (arachidonic acid). Platelet-induced agglutination is measured as an increase in light transmittance and converted aspirin reaction units (ARUs). When compared with other platelet-function tests that use gold-standard light-transmission aggregation, VerifyNow showed the strongest positive correlation and high reproducibility.[10] Patients were divided into 2 groups: those who were aspirin-responsive, with an ARU value <550; and those who were aspirin-resistant, with an ARU value ≥550.

Clinical and demographic variables were obtained from electronic medical records and patient interviews (Table I). Study data were collected and managed with the aid of REDCap electronic data capture tools.[11]

Follow-Up Protocol. This was an observational study, and all enrolled patients were managed by the primary team and in accordance with standard practice guidelines. Follow-up was performed via telephone interviews, reviews of patient medical records every 6 months, or both—for as long as 2 years—in order to determine study endpoints. The research staff that performed follow-up interviews and chart review were blinded to aspirin-sensitivity status. Every patient had at least 6 months of follow-up data.

Endpoints. The primary endpoint was the composite of death, myocardial infarction (MI), or cerebrovascular accident (CVA). Myocardial infarction was judged to have occurred if any 2 of the following criteria were met: 1) anginal pain ≥20 min; 2) elevation of troponin I value >0.15 μg/L; 3) electrocardiographic (ECG) evidence of infarction, defined as ST-segment elevation of at least 0.1 mV (measured 0.2 s after the J point) in 2 contiguous leads; or development of new Q waves in at least 2 adjacent leads, or of a new dominant R wave in lead V_1. Ischemic stroke was defined as 1) an acute neurologic vascular event with focal signs ≥24 hr if in a new location, without evidence of intracranial hemorrhage; 2) if the event was worsening of a previous event, that previous event must have lasted at least one week, or >24 hr if accompanied by appropriate CT or magnetic resonance imaging findings. The secondary endpoint was a composite of new peripheral vascular intervention (either surgical or percutaneous) or tissue loss (either leg amputation or gangrene) due to PAD.

Statistical Analysis

All analyses were done with SPSS Advanced Statistics software version 20.0 (IBM Corporation; Endicott, NY). Categorical variables are presented as frequencies and percentages. Continuous variables are presented as mean ± SD. Baseline characteristics between groups were compared by means of the χ^2 test for categorical variables and the Student *t* test or the Wilcoxon 2-sample test (if not normally distributed) for continuous variables. Kaplan-Meier estimates that incorporated time-to-event analyses were computed for freedom from the primary endpoint of composite of death, MI, or CVA and with respect to aspirin-resistance status. In addition, the composite of "death or MI" was used as a separate endpoint. Similar analysis was done for the secondary endpoint that was a composite of new peripheral vascular intervention or tissue loss. The log-rank test was used to compare groups. The Cox proportional hazard model was used to estimate the risk of the composite endpoint of death, MI, or CVA. Variables entered into this model included age, sex, prior CAD, prior chronic kidney disease (CKD), low-density-lipoprotein cholesterol, statin usage, and aspirin-resistance status. A *P* value <0.05 was considered statistically significant.

TABLE I. Baseline Characteristics of the 120 Patients

Variable	Aspirin-Responsive (n=89)	Aspirin-Resistant (n=31)	*P* Value
Clinical characteristics			
Age (yr)	64 ± 9.4	66.5 ± 10.7	0.21
Male	56 (62.9)	18 (58.1)	0.63
Race	—	—	0.54
White	49 (55.1)	21 (67.7)	—
Black	32 (36)	9 (29)	—
Hispanic	6 (6.7)	1 (3.2)	—
Other	2 (2.2)	0	—
Body mass index (kg/m^2)	30 ± 7.4	29.4 ± 7.8	0.73
Body surface area (m^2)	2 ± 0.3	1.9 ± 0.2	0.56
Smoking status	—	—	0.34
Current smoker	21 (23.6)	8 (25.8)	—
Former smoker	62 (69.6)	18 (58)	—
Nonsmoker	5 (5.6)	4 (12.9)	—
Diabetes mellitus	47 (52.8)	15 (12.9)	0.79
Hypertension	82 (92.1)	28 (48.3)	0.75
Hyperlipidemia	74 (83.1)	27 (87.1)	0.6
Coronary artery disease	48 (53.9)	14 (45.2)	0.4
Cerebrovascular accident	13 (14.6)	5 (16.1)	0.83
Chronic kidney disease	46 (51.6)	17 (4.8)	0.71
Congestive heart failure	22 (24.7)	10 (32.3)	0.41
Intermittent claudication or rest pain	53 (59.6)	18 (58.1)	0.83
Tissue loss or revascularization	40 (44.9)	9 (29)	0.12
Laboratory values			
Hemoglobin (g/dL)	12.5 ± 2	11.9 ± 1.9	0.14
Platelet count (×10^3/μL)	232 ± 82	236 ± 79	0.83
Serum creatinine (mg/dL)	1.4 ± 1.7	1.6 ± 1.9	0.64
Total cholesterol (mg/dL)	155 ± 41	174 ± 43	0.04
HDL cholesterol (mg/dL)	38 ± 13	39 ± 11	0.65
LDL cholesterol (mg/dL)	98 ± 35	113 ± 37	0.06
Aspirin reaction units	442 ± 44	610 ± 30	—
Medication use			
β-blocker	68 (76.4)	22 (73.3)	0.73
ACEI or ARB	68 (76.4)	21 (67.7)	0.34
Statin	76 (85.4)	30 (96.8)	0.08
Antiplatelet drug added during follow-up	5 (5.6)	1 (3.2)	0.60

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; HDL = high-density-lipoprotein; LDL = low-density-lipoprotein

Data are presented as mean ± SD or as number and percentage. $P<0.05$ was considered statistically significant.

Results

Of the 120 patients (74 men and 46 women; mean age, 64.6 ± 9.8 yr), 31 (25.8%) were identified as aspirin-resistant by means of the VerifyNow aspirin assay. Mean ARU was 610 ± 30 and 442 ± 44 in the aspirin-resistant and aspirin-responsive groups, respectively. Table I shows the baseline clinical factors, laboratory values, and medications. Mean age and the prevalence of CV risk factors were similar in the 2 groups, except for higher total cholesterol levels (174 ± 43 vs 155 ± 41 mg/dL; $P=0.04$) in the aspirin-resistant group. There were no significant differences in the histories of concomitant CAD, CKD, CVA, or congestive heart failure. Symptomatic intermittent claudication, rest pain, tissue loss, and history of vascular revascularization were also similar among the 2 groups. The addition of another antiplatelet agent during the follow-up period was infrequent and was similar in percentage of patients between the aspirin-responsive and aspirin-resistant groups (5.6% vs 3.2%, respectively; $P=0.60$).

Aspirin Resistance and Cardiovascular Events

All patients had at least 6 months of follow-up monitoring. Complete follow-up was available in 112 of 120 (93.3%) patients enrolled (90.3% in the aspirin-resistant group and 94.3% in the aspirin-responsive group) at 24 months. The primary endpoint of death, MI, or CVA occurred in 23 of 120 (19.2%) patients over a mean follow-up period of 22.6 ± 8.3 months.

The primary endpoint occurred in 10 of 31 (32.3%) patients in the aspirin-resistant group, compared to 13 of 89 (14.6%) patients in the aspirin-responsive group (hazard ratio [HR]=2.48; 95% confidence interval [CI], 1.08–5.66; *P*=0.03) (Table II). In the aspirin-resistant group, 5 (16.1%) died and 5 (16.1%) experienced MI, in comparison with 8 (9%) and 5 (5.6%), respectively, in the aspirin-responsive group. No cerebrovascular events were noted in either group at the end of follow-up. The secondary endpoint of peripheral vascular revascularization or tissue loss was the same in both groups and occurred in 25.8% of patients. Kaplan-Meier estimates for event-free survival were significantly lower in the aspirin-resistance group than in the aspirin-responsive group (Fig. 1). By multivariate analysis, aspirin resistance (HR=3.73; 95% CI, 1.43–9.81; *P*=0.007) and history of CKD (HR=3.19; 95% CI, 1.10–9.28; *P*=0.033) were the only independent predictors of long-term adverse CV events.

Discussion

In this study, we report the association between aspirin resistance in patients with symptomatic PAD and long-term adverse MACE outcomes. Aspirin resistance was observed in 26% of patients with severe or symptomatic PAD. Aspirin resistance was associated with significantly higher long-term adverse MACE outcomes than was aspirin responsiveness. There was no significant association between aspirin resistance and limb-related outcomes. Whether overcoming aspirin resistance or platelet reactivity in this cohort improves long-term adverse MACE outcomes needs to be determined.

Multiple investigators have shown reduced efficacy of aspirin due to aspirin resistance in patients with such various risk profiles as stable CAD,[12] acute stroke,[13] acute coronary syndrome,[14,15] recovery from coronary revascularization,[16] and end-stage kidney disease.[17] Krasopoulos and colleagues,[18] in a meta-analysis of 2,930 patients with CV disease from 20 studies, classified 810 patients (28%) as aspirin-resistant; CV-related events occurred in 41% of these patients. However, data are scant on the consequences of aspirin resistance on MACE outcomes in patients with PAD. Mueller and associates[9] noted that patients with intermittent claudication who failed to inhibit platelet reactivity with aspirin were more likely to experience reocclusion after peripheral intervention. Another study, of platelet responsiveness after femoropopliteal angioplasty and stenting, revealed increased event rates among patients in the 3rd and 4th quartiles.[19] In yet another study of symptomatic PAD, aspirin resistance (ARU value, ≥550) in a subset of patients undergoing point-of-care testing with VerifyNow was not associated with the combined endpoint of death, MI, stroke, major amputation, or target-vessel revascularization at 1 year.[20] However, the low event rate associated with this substudy[20] might have underpowered its abil-

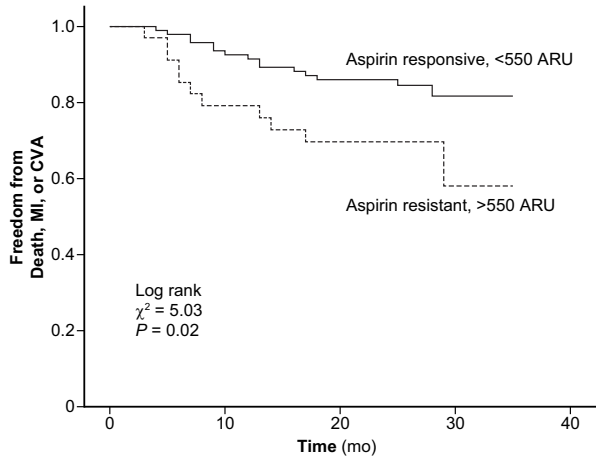

Fig. 1 *Kaplan-Meier curves for primary endpoint of death, MI, or CVA. The Kaplan-Meier estimate for event-free survival was significantly higher in the aspirin-responsive group than in the aspirin-resistant group.*

P *<0.05 was considered statistically significant.*

ARU = aspirin reaction units; CVA = cerebrovascular accident; MI = myocardial infarction

TABLE II. Time-to-Event Analyses per Aspirin Resistance

Variable	**Hazard Ratio** (95% CI)	***P* Value**
Univariate Analyses		
Death, MI, or CVA	2.48 (1.08–5.66)	0.03
Revascularization or tissue loss	0.94 (0.43–2.11)	0.89
Multivariate Analyses		
Aspirin resistance	3.73 (1.43–9.81)	0.007
Age	0.98 (0.94–1.03)	0.61
Sex	1.20 (0.46–3.14)	0.7
History of coronary artery disease	0.77 (0.29–2.05)	0.61
History of chronic kidney disease	3.19 (1.10–9.28)	0.033

CI = confidence interval; CVA = cerebrovascular disease; MI = myocardial infarction

P <0.05 was considered statistically significant.

ity to detect the effect of platelet reactivity. In our study of patients with severe or symptomatic PAD, aspirin resistance was associated with a 32% higher risk of CV events at approximately 2 years. Further multicenter studies are needed in larger cohorts to confirm (with point-of-care testing) the association between aspirin resistance and CV events in patients who have symptomatic PAD.

The mechanism of aspirin resistance remains unclear, but high platelet reactivity seems to be associated with poor prognosis.[6] Poor patient compliance is a factor frequently associated with aspirin resistance, and with adverse MACE outcomes.[21] In our study, we took every precaution to ascertain patients' compliance with the medication regimen. Patients' compliance was monitored through telephone enquiry, checking of pharmacy prescriptions, or review of the electronic charts at baseline and at follow-up. Only 2 patients from the aspirin-responsive group had stopped taking aspirin for more than 4 weeks. Other possible explanations for resistance include COX-1 or COX-2–related residual thromboxane production, genetic polymorphisms of P1A/A2, polymorphism of genes involved in thromboxane biosynthesis, and increased platelet turnover as seen in such clinical conditions as acute coronary syndrome, coronary artery bypass grafting, and stent thrombosis.[5]

Aspirin did not improve CV risk in patients with asymptomatic PAD free of clinical CV disease.[22] However, aspirin was associated with reduced CV events in patients with symptomatic PAD—including those with intermittent claudication or critical limb ischemia, prior lower-extremity revascularization (endovascular or surgical), or prior amputation for lower-extremity ischemia.[23] In our population, approximately 60% of patients had intermittent claudication or rest pain, 40% had a history of tissue loss or revascularization, and about half had a history of CAD, representing a high-risk milieu. In this high-risk subset, aspirin resistance as noted by VerifyNow appears to predict the risk of CV events. We noticed that the curves in the Kaplan-Meier graph started to separate after 5 to 6 months. Although that observation was interesting, it more likely was an event born of chance than of any specific pathophysiologic effect.

The tests for measuring platelet reactivity are variable, and there is uncertainty in their clinical meaning. However, we used an easily available point-of-care biochemical test (VerifyNow) to evaluate platelet aggregation as a measure of aspirin resistance. In comparison with other platelet-function tests, the VerifyNow assay showed the strongest correlation with the gold-standard LTA and produced the lowest coefficients of variation for duplicate measurements.[10]

Although point-of-care testing of aspirin response has been shown to correlate with risk of adverse clinical outcomes, there is lack of evidence to justify routine use of point-of-care testing, because the clinical implications for altering therapy are uncertain. The clinical effectiveness of tailoring antiplatelet therapy in patients undergoing percutaneous coronary intervention, on the basis of a laboratory finding of aspirin resistance, failed to show benefit.[24] In a recent cohort study—by means of propensity analysis—of patients with symptomatic PAD, aspirin or clopidogrel resistance was not associated with adverse clinical events, although dual-antiplatelet therapy was associated with reduced MACE, in comparison with aspirin therapy alone.[20] Whereas dual-antiplatelet therapy might be beneficial overall, whether it adds additional benefit in patients with aspirin resistance is unclear. Future studies are necessary to determine if there is a role for point-of-care testing in patients with PAD, and whether dose escalation or substitution of alternative antiplatelet agents like clopidogrel, ticagrelor, or prasugrel improves outcomes.

Study Limitations

Our study has several limitations. We used a small sample of patients at a single institution. A large multicenter study to confirm these findings would be helpful. Aspirin compliance was not confirmed with salicylate levels or pill counts and was checked via telephone enquiry, pharmacy prescriptions, or review of electronic medical records—methods that might not have been adequate. We chose to perform single testing with VerifyNow, instead of laboratory-based aggregation studies, to evaluate aspirin resistance. Our testing might not have accounted for non-COX-1–related antiplatelet effects. However, at this time there is no consensus on an optimal test for aspirin resistance, and VerifyNow remains a reliable option given its strong correlation with gold-standard LTA and its correlation with MACE outcomes.

Variability in platelet responsiveness to aspirin over time was not taken into account.[25] Our study did not show traditional risk factors as independent factors of CV risk, which more likely would reflect the study's lack of power.

Conclusion

We conclude that aspirin resistance as determined by the VerifyNow System is highly prevalent among patients with symptomatic PAD. This test for aspirin resistance is an independent predictor of adverse CV events in these patients. Further studies with large sample sizes are needed to validate point-of-care testing for aspirin resistance in patients with symptomatic PAD and to evaluate the possible role of altering therapy in this population.

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