Usefulness of Aspirin Resistance After Percutaneous Coronary Intervention for Acute Myocardial Infarction in Predicting One-Year Major Adverse Coronary Events

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Aspirin is the cornerstone of antiplatelet therapy in cardiovascular medicine and has been reported to decrease the risk of cardiovascular events by about 25% in a broad category of patients with arterial vascular disease. In recent years, much attention has been focused on the phenomenon of aspirin resistance, which may be defined as clinical or laboratory resistance. Monitoring the antiplatelet effect appears to be relevant in the presence of clinical implications, but no data are available on the possible clinical implications of the failure of aspirin to inhibit tests of platelet function in the setting of acute coronary syndromes. This study evaluated the role of aspirin resistance in the occurrence of 1-year major adverse coronary events (MACEs) in patients with acute myocardial infarction (AMI) who have undergone percutaneous coronary intervention (PCI). We prospectively evaluated 146 patients (115 men and 31 women; median age 65 years, range 30 to 84) with AMI who underwent primary PCI. Exclusion criteria were the use of glycoprotein IIb/IIIa inhibitors, hematocrit ≤30%, and a platelet count <100,000/mm³. Platelet function analyzer-100 closure times by collagen-epinephrine were used for measuring platelet function in venous blood samples obtained 12 to 15 hours after revascularization. Patients were considered aspirin resistant in the presence of a collagen-epinephrine closure time of <203 seconds. After 1-year follow-up, MACEs were recorded in 44 of 146 patients (30.1%). A significantly higher percentage of patients with MACEs had aspirin resistance (39.1% vs 23.2%, p < 0.05). A Kaplan-Meier survival curve showed that the overall risk of MACEs was significantly higher among patients with aspirin resistance (p = 0.02). A Cox regression analysis that adjusted for age, gender, traditional cardiovascular risk factors, systolic left ventricular function, number of stenosed coronary arteries, and previous AMI, PCI, or coronary artery bypass graft showed aspirin resistance to be a significant and independent risk factor for the future MACEs (hazard ratio 2.9, 95% confidence interval 1.1 to 9.2, p < 0.05). In conclusion, our data demonstrate that aspirin resistance after PCI is a significant and independent predictor of MACEs in patients with AMI undergoing primary PCI.

Methods and Results

The study population included 147 patients (31 women; median age 65 years, range 30 to 84) who were admitted to the Coronary Care Unit of the Azienda Ospedaliero, Universitaria Careggi, University of Florence (Florence, Italy) with a diagnosis of AMI. AMI was diagnosed based on an increase in creatine kinase-MB isoenzyme ≥2 times the upper normal limits (3.6 ng/ml) and/or increased cardiac troponin I levels (>0.15 ng/ml) with ≥1 of the following: acute onset of prolonged (≥20 minutes) typical ischemic chest pain; ST-segment elevation ≥1 mm in ≥2 contiguous electrocardiographic leads or ST-depression ≥0.5 mm 0.08 second after the J point in ≥2 contiguous leads, or a T-wave decrease ≥1 mm.
inversion >1 mm in leads with predominant R waves. All patients underwent coronary angiography according to the Judkins technique and primary PCI with stent implantation (bare metal stents in 82, drug-eluting stents in 76). Exclusion criteria included a history of bleeding diathesis, a platelet count ≤100,000/mm³, hematocrit ≤30%, creatinine level ≥4.0 mg/dl, and glycoprotein IIb/IIIa inhibitor use.

Informed written consent was obtained from all patients, and the study was approved by the local ethical review board. With regard to follow-up, data were obtained by a structured telephone interview at 1 year and a clinical evaluation in case of clinical recurrences and/or new PCI. Clinical end points were a composite of MACEs, including cardiac death (defined as death from AMI, pump failure, sudden cardiac death, or death due to arrhythmias), new AMI, and target lesion revascularization for symptomatic restenosis. Restenosis was defined as a diameter stenosis ≥50% in patients needing target vessel revascularization because of symptoms or signs of ischemia. A diagnosis of cardiac death, new AMI, and target lesion revascularization for symptomatic restenosis, which determined the allocation of patients into groups with or without MACEs, was made by 2 cardiologists (CG and SV) who were unaware of the platelet function test results. Blood samples anticoagulated with 0.129 mol/L of sodium citrate (ratio 9:1) were taken from each patient 12 to 15 hours after PCI. The PFA-100 device (Dade-Behring, Marburg, Germany) was used to measure platelet function at high shear conditions on whole citrated blood. The method determines the time to occlusion of an aperture in a membrane coated with collagen and epinephrine (closure time/epinephrine). von Willebrand factor levels were measured with an enzyme-linked fluorescent assay (Biomerieux, Lyon, France). Two hundred control samples from healthy subjects who took no drugs for assay (Biomerieux, Lyon, France). Two hundred control levels were measured with an enzyme-linked fluorescent assay (Biomerieux, Lyon, France). Two hundred control samples from healthy subjects who took no drugs for

Table 1. Diabetes, number of stenosed vessels, and ejection fraction according to occurrence of MACEs are presented in Table 1. Diabetes, number of stenosed vessels, and ejection fraction were the only parameters that significantly differed according to the occurrence of MACEs. Aspirin resistance was found in 41 of 146 patients (28.0%). Long-term use of aspirin was associated with a significantly lower prevalence of aspirin resistance. Thirty-three of 46 patients were on aspirin before AMI; 21 of 33 (63.6%) had aspirin resistance compared with 20 of 113 patients (17.6%) with no previous use of aspirin (p <0.0001). None of the clinical characteristics investigated, i.e., age, gender, hypertension, smoking, diabe-

![Figure 1. Kaplan-Meier event-free rates according to response to aspirin therapy.](image-url)

Table 1 Clinical characteristics of patients according to occurrence of major adverse cardiac events

<table>
<thead>
<tr>
<th>Variable</th>
<th>MACEs</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>64.5 ± 12.2</td>
<td>63.4 ± 10.5</td>
</tr>
<tr>
<td>Men</td>
<td>31 (70.4%)</td>
<td>84 (82.3%)</td>
</tr>
<tr>
<td>Smokers</td>
<td>15 (34%)</td>
<td>44 (43.1%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>26 (59%)</td>
<td>71 (69.6%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22 (50%)</td>
<td>27 (26.4%)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>15 (34%)</td>
<td>55 (53.9%)</td>
</tr>
<tr>
<td>Ejection fraction (%)</td>
<td>44 ± 12.7</td>
<td>48.9 ± 9.3</td>
</tr>
<tr>
<td>Previous MI, PCI, coronary artery bypass graft</td>
<td>5 (11.3%)</td>
<td>15 (14.7%)</td>
</tr>
<tr>
<td>No. of stenosed coronary vessels</td>
<td>1.7 ± 0.8</td>
<td>1.4 ± 0.7</td>
</tr>
</tbody>
</table>

Clopidogrel orally before PCI and 500 mg of acetylsalicylic acid intravenously, followed by 75 mg/day of clopidogrel and 100 mg/day of aspirin. Unfractionated heparin, 70 IU/kg, was used during the procedure as an anticoagulant.

MACEs were recorded in 44 of 146 patients (30.1%): 15 cardiovascular deaths, 12 target lesion revascularizations, and 17 recurrent AMIs. Clinical characteristics of patients according to occurrence of MACEs are presented in Table 1. Diabetes, number of stenosed vessels, and ejection fraction were the only parameters that significantly differed according to the occurrence of MACEs.

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tes, and dyslipidemia, was associated with a significantly higher prevalence of aspirin resistance.

Eighteen of 41 aspirin-resistant patients (43.9%) had a subsequent MACE compared with 26 of 105 aspirin-responder patients (24.8%, \( p < 0.05 \)). In particular, 6 of 15 patients (40%) with cardiovascular death, 8 of 12 (66%) with target lesion revascularization, and 4 of 17 (23.5%) with recurrent AMI were aspirin resistant. The Kaplan-Meier survival curve showed that the overall risk of MACEs was significantly higher among patients with aspirin resistance (\( p = 0.02 \); Figure 1). In contrast, a significantly higher percentage of patients with MACEs had aspirin resistance (39.1% vs 23.2%, \( p < 0.05 \)). No significant difference in von Willebrand factor levels between patients with or without a subsequent MACE was documented (228%, range 38% to 500%, vs 221.2%, range 38% to 480%, \( p = NS \)).

A Cox regression analysis that was adjusted for age, gender, diabetes, number of stenosed coronary arteries, and ejection fraction (i.e., the parameters with a significantly higher prevalence in patients with MACEs vs patients without MACEs) showed aspirin resistance to be a significant and independent risk factor for the future occurrence of MACEs (hazard ratio 2.9, 95% confidence interval 1.1 to 9.2, \( p < 0.05 \)).

**Discussion**

In the present study, we provide the first evidence that aspirin resistance, measured after primary PCI in patients with AMI, is an independent predictor of MACEs after 1-year follow-up.

We found a high prevalence of aspirin resistance in our patients. High platelet activation in patients with AMI with respect to stable coronary artery disease may be associated with a high prevalence of aspirin resistance. A high adenosine diphosphate level in patients with AMI was hypothesized to contribute to increased platelet activity and weaker effect of aspirin.\(^{12}\) The increased prevalence of aspirin resistance in AMI could be explained by an increased activity of important feedback systems such as adenosine diphosphate and thromboxane\(^{13}\) and by an increase in von Willebrand factor released from endothelial cells under high shear stress.\(^{14}\)

The association of cardiovascular events with aspirin resistance has been previously documented in chronic coronary artery diseases\(^{5–9}\) and in patients with stent thrombosis,\(^{9,10}\) whereas no data are available, to the best of our knowledge, on patients with AMI. In 488 patients with chronic cardiovascular disease who were treated with aspirin, Eikelboom et al.\(^{7}\) documented for the first time that high levels of 11-dehydrothromboxane B\(_2\), the stable metabolite of thromboxane A\(_2\), are associated with an increased risk of MI or cardiovascular death. This result was confirmed in 326 patients with stable cardiovascular disease in whom aspirin resistance, diagnosed using platelet aggregation tests, was associated with a threefold increase in the risk of subsequent MACEs.\(^{6}\) Further, aspirin resistance in patients who underwent elective PCI was associated with a high incidence of myonecrosis after PCI and with an impaired coronary flow reserve after revascularization.\(^{5,8}\) Two retrospective studies on a limited number of patients found that those with previous stent thrombosis had an impaired response to antiplatelet therapy and an increased shear-induced platelet aggregation.\(^{6,10}\) No retrospective and prospective study evaluated the risk of subsequent events associated with aspirin resistance in acute coronary syndromes.

In our group of AMI patients who underwent primary revascularization, we evaluated platelet function in a blood sample obtained after primary PCI, so that our results would appear to be easily reproducible in a “real-world” setting, i.e., in patients admitted to a catheterization laboratory for urgent PCI. A point to be discussed is that angioplasty per se is an important prothrombotic stimulus because disruption of the atheromatous plaque causes prolonged exposure to subendothelial tissue factor, collagen fibronectin, and von Willebrand factor.\(^{15,16}\) Therefore, in our patients, platelet hyperaggregability may have resulted from the thrombotic process in the culprit vessel and platelet activation related to the revascularization procedure. Nevertheless, whatever the trigger of platelets, an impaired response to aspirin therapy seems to predict future MACEs, suggesting that it identifies a subgroup of patients at higher risk for new events. By assessing the ability of aspirin to inhibit platelet function at the time of an acute event, it is possible to select patients for whom a more intensive antiplatelet therapy might provide a better long-term benefit.

It should be emphasized that in our study, aspirin resistance was determined by a point-of-care test.\(^{2}\) Currently, platelet response to antiaggregating agents may be determined by simple and rapid methods potentially available in the coronary care unit, differently from the Born method, which is a time-consuming method requiring specialized laboratories.

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