

## Terms and Conditions

### Semantic Complexity and Aspirin Resistance

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The term *aspirin resistance* has been used to describe the occurrence of cardiovascular events despite regular aspirin intake at recommended doses.<sup>1</sup> In this context, such treatment failures resemble those with any drugs, including statins,  $\beta$ -blockers, and ACE inhibitors.<sup>2,3</sup> In secondary prevention, the clinical effectiveness of aspirin has been clearly demonstrated and is comparable to that of these other agents in that they all reduce nonfatal cardiovascular disease events by  $\approx 25\%$  to  $30\%$  and fatal events by  $\approx 15\%$  to  $20\%$  in randomized trials.<sup>3</sup> These results represent a small to moderate but clinically worthwhile reduction in risk. Conversely, they suggest that  $70\%$  to  $75\%$  of nonfatal and  $80\%$  to  $85\%$  of fatal events are not prevented by these drugs.

Mechanistic approaches to investigating aspirin resistance have relied heavily on ex vivo evaluations of platelet function. Although thrombosis is the proximate cause of virtually all occlusive vascular events,<sup>4</sup> other factors, such as vascular function,<sup>5</sup> and perhaps interactions with other blood cells, such as monocytes,<sup>6</sup> are also probably relevant. It is unknown precisely how the impact of aspirin on the ex vivo response to selected concentrations of single aggregating agonists might model its efficacy in preventing clinical events in vivo. Multiple factors may confound platelet aggregometry, including posture, time of day, smoking, exercise, and blood cholesterol.<sup>7-9</sup> Indeed, platelet aggregability may recover despite sustained inhibition of thromboxane during chronic dosing with aspirin.<sup>10</sup> The term *aspirin resistance* is insufficiently precise to offer a credible basis for clinical decision making. More usefully, the multiple potential causes of treatment failure on aspirin might be pursued and named accordingly.<sup>11</sup>

Aspirin irreversibly acetylates a serine residue at position 530 on the cyclooxygenase (COX) enzyme, thus inhibiting the first step in the transformation of arachidonic acid to the platelet agonist thromboxane  $A_2$ .<sup>12</sup> The irreversible nature of COX inhibition underlies the ability of low doses of aspirin administered chronically to inhibit platelet aggregation in vivo.<sup>13</sup> There is a nonlinear relationship of inhibition of platelet thromboxane  $A_2$  generation with inhibition of thromboxane-mediated platelet aggregation, requiring in ex-

cess of  $95\%$  inhibition to influence function.<sup>14</sup> Although inhibition of platelet COX-1 at low aspirin doses is sufficient to explain the benefits on cardiovascular disease consistently observed in randomized trials, direct comparisons of clinical efficacy with higher aspirin doses, in which other mechanisms may be operative,<sup>15</sup> have not been performed.

Aspirin resistance has relied primarily on quantitative interpretations of the impact of aspirin on platelet aggregation ex vivo,<sup>16</sup> occasionally on serum thromboxane  $B_2$ ,<sup>17</sup> and in one instance on urinary 11-dehydrothromboxane  $B_2$  excretion.<sup>18</sup> Although all of these approaches have been useful in exploring the clinical pharmacology of aspirin, none of them have been related quantitatively to clinical outcomes in individuals. Thus, the inference that a quantitative response in one of these variables to aspirin administration might predict the efficacy of aspirin in preventing a heart attack or stroke in that individual is presently unsubstantiated. Furthermore, chance, bias, and/or confounding are plausible alternative explanations for the findings from all of these studies. These limitations include technical reproducibility, adequate blinding of the investigators, assurance of compliance, and controls for recognized modifiers of the aggregation response mentioned above. Thus, it would seem premature and unwarranted to suggest that measurement of aggregation or thromboxane generation after dosing with aspirin could be used to categorize patients as "resistant" or "responsive" to aspirin in a way that reliably predicted clinical outcome and guided therapeutic decision making.

Aside from aspects of trial design and technical limitations, it is quite possible that distinct molecular mechanisms may indeed contribute to treatment failure with aspirin. These include genetic variability in the target cyclooxygenases<sup>19</sup> or indeed in proteins relevant to aspirin disposition. Although cyclooxygenase polymorphisms have been described,<sup>20</sup> they have yet to be related to clinical outcome. One plausible explanation for the occurrence of an event despite aspirin intake may relate to drug-drug interactions. For example, nonsteroidal antiinflammatory drugs may interact pharmacodynamically with aspirin, compromising its ability to sustain inhibition of platelet thromboxane formation.<sup>21</sup>

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## Epidemiological Evidence

The current totality of epidemiological evidence for aspirin resistance derives from one descriptive study, a case series,<sup>22</sup> and one observational analytic study, a prospective nested case-control study.<sup>18</sup> In a case series of 325 patients with cardiovascular disease, *ex vivo* platelet aggregation was studied after aspirin treatment in a dose of 325 mg/d for at least 7 days. Aspirin resistance was defined as having a normal aggregation response induced by collagen and/or epinephrine. In this case series, the authors reported that 6% to 10% of subjects appeared to be resistant to the antiplatelet effects of aspirin, and an additional 24% seemed to have a reduced response. This study, however, lacks a comparison group of individuals treated with other antiplatelet drugs. Thus, this descriptive study is useful to formulate but not to test hypotheses.<sup>23</sup> Furthermore, the reproducibility of this phenomenon was not established, its extension to other platelet-active drugs was not assessed, and the observations were not controlled for recognized factors that influence platelet aggregability.

A recently published nested case-control study has attracted attention.<sup>18</sup> A total of 970 patients who reported aspirin use from the Heart Outcomes Prevention Evaluation (HOPE) study had baseline measurements of urinary 11-dehydrothromboxane B<sub>2</sub>. After 5 years of follow-up, those patients with levels in the highest quartile had a significantly greater risk for a composite end point of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death (adjusted odds ratio, 1.8; 95% CI, 1.2 to 2.7), with significant increases in myocardial infarction and cardiovascular death compared with those in the lowest quartile. Compliance with aspirin was assessed by specific questioning at each follow-up visit but was not confirmed by objective measurement and was therefore subject to recall bias. In addition, the dose of aspirin being taken was not specified, nor were data available on possible drug–drug interactions. Attempts to relate analyses of a functional response to aspirin to clinical outcomes have been performed post hoc and therefore are limited in their interpretability by multiple potential sources of bias.

## Conclusions

Treatment failures occur with all drugs. Indeed, given the multiple pathways by which platelets may be activated, it is perhaps more surprising that a clinical benefit is detectable in randomized trials of cardiovascular disease<sup>24</sup> than that treatment failures complicate aspirin therapy. The current usage of the term aspirin resistance implies a linkage between a laboratory test and a clinical outcome that is presently unsubstantiated. It seems reasonable to conclude that there are subpopulations that do not respond to inhibition of serum thromboxane, to inhibition of urinary 11-dehydrothromboxane B<sub>2</sub>, or to inhibition of platelet aggregation. At present, however, there are no data that demonstrate that all 3 subsets are nonresponsive to aspirin as one might expect if there were clinical relevance. Furthermore, the available data are either descriptive or analytical data in which confounding has been inadequately controlled. Finally, the stability of the phenotype has not been demonstrated. Multiple environmental

and potentially genetic factors may contribute alone or together to cardiovascular events in patients taking aspirin. We suggest that well-controlled evaluation of factors that may modulate interindividual differences in the clinical response to all antithrombotic drugs is timely. In the absence of such data, however, clinical management of the individual might most appropriately be based on the outcome of large-scale randomized trials in appropriate patient populations. The fact that individuals develop cardiovascular disease events while taking aspirin is not surprising. What remains unclear is whether these are the very individuals who express a phenotype of defective action. If so, there would be a clinically relevant and biochemically verified mechanism of aspirin resistance. The failure to inhibit serum thromboxane, urinary 11-dehydrothromboxane B<sub>2</sub>, or platelet aggregation may turn out to be clinically meaningful, but at present, the totality of evidence is far from complete and requires further research to support any valid inferences of clinical relevance.

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