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## PREVALENCE OF PERSISTENT PLATELET REACTIVITY DESPITE USE OF ASPIRIN: A SYSTEMATIC REVIEW

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## ABSTRACT

### *Background*

The absolute risk of recurrences among patients using aspirin for prevention of cardiovascular events remains high. Persistent platelet reactivity despite aspirin therapy might explain this in part. Reported prevalences of this so-called aspirin resistance vary widely between 0% and 57%. The aim of the study was to systematically review all available evidence on prevalence of aspirin resistance and to study determinants of reported prevalence.

### *Methods*

Using a predefined search strategy, we searched electronic databases MEDLINE, EMBASE, CENTRAL and Web of Science. To be included in our analysis, articles had to contain a laboratory definition of aspirin resistance, use aspirin as secondary prevention, and report associated prevalence.

### *Results*

We included 34 full-text articles and 8 meeting-abstracts. The mean prevalence of aspirin resistance was 24% (95%CI 20 to 28). After adjustment for differences in definition, used dosage and population, a statistically significant higher prevalence was found in studies with aspirin dosage  $\leq 100$  mg compared with  $\geq 300$  mg (36% (95%CI 28 to 43) versus 19% (95%CI 11 to 26),  $P < 0.0001$ ). Studies measuring platelet aggregation using light aggregometry with arachidonic acid as an agonist had a pooled unadjusted prevalence of 6% (95%CI 0 to 12). In studies using point-of-care platelet function-analyzing devices, the unadjusted prevalence was significantly higher, 26% (95%CI 21 to 31).

### *Conclusions*

Prevalences widely differ between studies reporting on aspirin resistance. Both aspirin dosage and method of defining aspirin resistance strongly influence estimated prevalence, which explains found heterogeneity among studies. On average, it appears that about one in four individuals may express biochemically defined aspirin resistance.

## INTRODUCTION

Cardiovascular diseases are the most common cause of mortality and morbidity in Western countries in the twenty-first century. In the United States, the mortality from cardiovascular diseases was nearly 40% of total mortality in 2003.<sup>1</sup> Because aggregation of platelets highly contributes to the development of cardiovascular events, inhibition of this process could play an important role in prevention of cardiovascular disease.<sup>2</sup>

Nowadays, aspirin (acetylsalicylic acid) forms the cornerstone in secondary prevention of cardiovascular events. The effect of low-dose aspirin is most likely based on the permanent inactivation of cyclooxygenase-1 (COX-1), which results in an irreversible inhibition of the production of thromboxane A<sub>2</sub> by platelets.<sup>3,4</sup> Thromboxane A<sub>2</sub> is a potent platelet activator that also causes vasoconstriction and smooth muscle proliferation.<sup>5,6</sup> A decrease in thromboxane A<sub>2</sub> leads to reduced aggregation of platelets.<sup>7</sup>

The clinical effectiveness of aspirin on the prevention of cardiovascular events has been well established. In their most recent meta-analysis of 287 randomized trials incorporating >200,000 patients, the Antithrombotic Trialists' Collaboration has documented a 22% reduction of death and serious ischemic vascular events by antiplatelet therapy compared with placebo.<sup>8</sup>

However, not all patients profit to the same extent, which could be explained by a variety of pharmacodynamic, pharmacokinetic and biochemical features.<sup>9</sup> Addressed biochemically as persistent platelet reactivity *in vitro* despite use of aspirin, this phenomenon is called aspirin resistance, although a uniform definition is lacking.<sup>10-12</sup> Based on the failure of aspirin to inhibit platelet thromboxane A<sub>2</sub> production or to inhibit tests of platelet function, a variety of laboratory tests to define and quantify aspirin resistance has been proposed. Aspirin resistance has received much attention, in both medical journals<sup>11-14</sup> and lay media.<sup>15</sup> However, both prevalence and impact of aspirin resistance are still not well known. There are only few studies on the clinical consequences of being labeled aspirin resistant.<sup>16,17</sup> Collectively, they suggest a higher recurrence rate of cardiovascular events in aspirin resistant patients. Estimates of the prevalence of aspirin resistance vary greatly, with a range from 0%<sup>18</sup> to 57%<sup>19</sup>. It is still not known which factors might influence reported prevalences.

In our study, we systematically reviewed all available evidence on the prevalence of aspirin resistance among patients using aspirin in a secondary prevention setting. Moreover, to explain potential heterogeneity, we examined whether definition used, dosage of aspirin, and clinical setting contribute to the prevalence of resistance.

## METHODS

We used electronic databases to identify relevant reports. The following databases were searched using predefined search terms (available from the authors): MEDLINE (from January 1966 to October 2005), EMBASE (from January 1974 to October 2005), the Cochrane Central Register of Controlled trials (CENTRAL) (from 1800 to 2005) and

Web of Science. We used both MeSH terms and free text words. We used no language restrictions. Furthermore, we tried to identify additional studies by searching the reference lists of relevant studies and reading reviews, editorials and letters on the topic. Authors of identified appropriate studies were contacted to obtain additional data not reported in the original article. Both full-text articles and meeting abstracts were included.

To be included in the analysis, selected studies had to meet all of the following inclusion criteria: 1) the study should be a cross-sectional survey or a cohort study that included consecutive patients; 2) the study should contain a clear definition of aspirin resistance; 3) the patients involved should use aspirin for secondary prevention cardiovascular events; 4) the study population should be well described; and 5) the study should report data on prevalence of aspirin resistance. Reviewers were not blinded to journal, author, or institution of publication.

To assess quality of identified studies, we used a prespecified data collection form to abstract information for each report regarding year of publication, duration and setting of study, study design, measurement of exposure, completeness of follow-up, blinding, case definition and matching of patients and total sample size. To answer our research question we collected data on study population, dosage of aspirin, definition of aspirin resistance, and prevalence of aspirin resistance.

Selection, quality assessment and data extraction of studies to be included in this review were all independently done by two reviewers (MMCH and JDS). Disagreements were resolved by consensus and discussion with a third party (MVH).

We performed a meta-analysis to estimate the pooled prevalence of aspirin resistance. We stratified studies based on differences in definition of aspirin resistance, population characteristics and aspirin dosage. We identified three groups based on laboratory techniques used: definitions based on measurements with the platelet function analyzer (PFA)-100, rapid platelet function assay (RPFA) and light transmission aggregometry (LTA). The PFA-100 device (Dade Behring Inc, Deerfield, IL, USA) measures in-vitro shear-stress-induced platelet activation in terms of platelet occlusion of a membrane coated with platelet agonists. Using a collagen/epinephrine cartridge (CEPI), closure times between 136 and 199 seconds formed the cut-off value to differentiate between aspirin resistance and sensitivity. The Ultegra RPFA device (Accumetrics Inc., San Diego, CA, USA) measures changes in light transmission related to the rate of aggregation, using a disposable cartridge with fibrinogen-coated beads and a platelet activator. Results are expressed as aspirin reaction units, with an aspirin responsiveness unit  $\geq 550$  indicating aspirin resistance. Light transmission aggregation (LTA) measures the increase in light transmission through a suspension of platelet-rich plasma when agonists stimulate platelet aggregation. We divided the described population into three groups. First, all trials with patients who used aspirin for secondary prophylaxis after myocardial infarction, with stable or unstable angina, and after or during revascularization were labeled as coronary artery disease (CAD) group. Second, the stroke group consisted of studies with patients with previous stroke or transient ischemic attack. Last, we defined a rest group for other patient groups, mostly consisting of patients with peripheral arterial disease or a non-specific reason for aspirin use as secondary

prevention. We categorized four dosage groups:  $\leq 100$  mg, 101 to 300 mg,  $\geq 300$  mg or no specified dosage.

Statistical analysis was based on a general linear non-parametric mixed model, which is a meta-analytical approach to explain heterogeneity among studies by modeling for available study covariates.<sup>20</sup> We performed this mixed model analysis for prevalence of aspirin resistance both with and without fixed effects for the laboratory method used to define aspirin resistance, the characteristics of the population studied and the dosage of aspirin, and with an identification number for each study as a random effect. Analyses were executed with SPSS 12.01 (SPSS Inc., Chicago, IL, USA). To quantify heterogeneity among studies, we analyzed prevalence data using generic inverse variance data entry and random effects model analysis in Review Manager 4.2.2. (Cochrane Collaboration). Quantification of the effect of heterogeneity was assessed by means of  $I^2$ , ranging from 0 to 100%.  $I^2$  demonstrates the percentage of total variation across studies due to heterogeneity.<sup>21</sup> For each process in study selection,  $\kappa$  statistics for agreement between reviewers were performed manually. The overall  $\kappa$  was calculated as a weighted mean of those values.

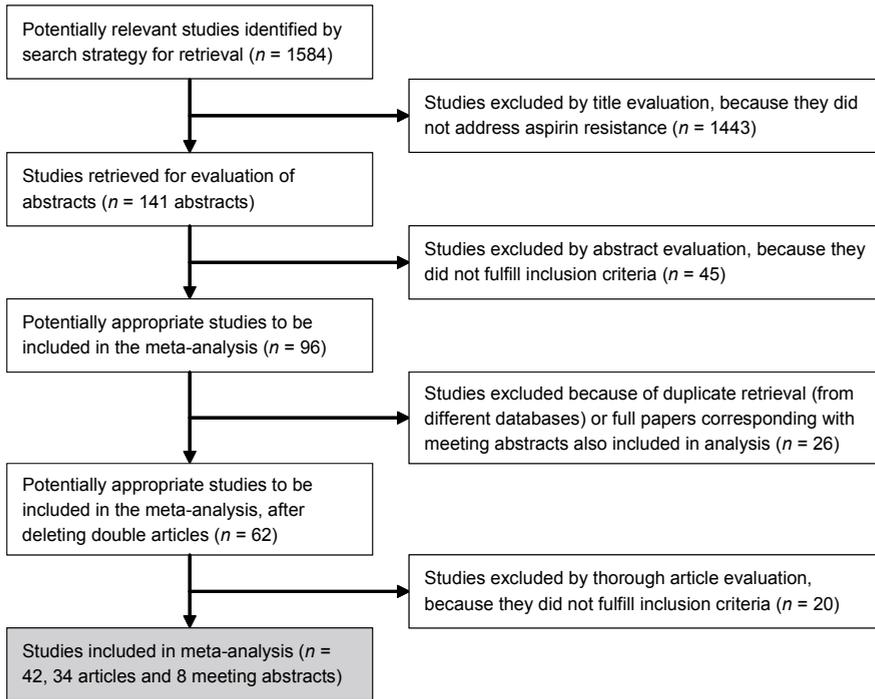
The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

## RESULTS

We included 34 full-text articles and 8 meeting abstracts<sup>22-29</sup> in our systematic review (Figure 1). Overall,  $\kappa$  statistics were 0.82, indicating good interobserver agreement. The overall prevalence, weighted for study size, was 24% (95% confidence interval (CI) 20 to 28), with ranges from 0%<sup>18</sup> to 57%.<sup>19</sup> There was a significant heterogeneity among studies ( $\chi^2$  682.87,  $P < 0.00001$ ,  $I^2$  94%). To explain this heterogeneity, we examined whether definition used, population studied and aspirin dosage contributed to prevalence of resistance. Table 1 presents overall prevalences, both unadjusted and adjusted for aforementioned study covariates.

Most included studies ( $n=22$ ) used the PFA-100 as method to determine aspirin resistance.<sup>19,23-25,27,30-46</sup> Six studies used the RPFA.<sup>37,47-51</sup> LTA was used in several studies ( $n=15$ ).<sup>18,22,26,28,29,36,37,48,52-58</sup> Among the studies using LTA, the choices of agonists and cut-off values to define aspirin resistance varied widely. A few studies ( $n=4$ ) used other methods which are less used to detect aspirin resistance than above-described techniques.<sup>19,59-61</sup> The pooled mean unadjusted prevalence among the five studies that used arachidonic acid as an agonist in LTA was 6% (95%CI 1 to 12). In studies using PFA-100 or RPFA, the pooled mean unadjusted prevalence was significantly higher, at 26% (95%CI 21 to 31,  $P < 0.0001$ ).

Most studies examined aspirin resistance in patients with CAD ( $n=28$ ).<sup>18,23-25,27-29,31,33,34,36,38,40,42-47,50-52,54-59</sup> The stroke group consisted of eight studies.<sup>22,30,35,37,39,53,60,61</sup> The rest group for other patient clusters, mostly consisting of patients with peripheral arterial disease or a non-specific reason for aspirin use as secondary prevention consisted of seven studies.<sup>19,26,32,35,41,48,49</sup> There was no difference in mean adjusted prevalence between the three groups.



**Figure 1** – Flow chart study selection

Reported daily aspirin dosages varied between 80 mg and 1500 mg. Ten studies used aspirin  $\leq 100$  mg,<sup>32,34,35,41,42,47,50,54,58,59</sup> 13 studies 101 to 300 mg,<sup>25,27,30-34,37-40,46,50</sup> and 13 studies  $\geq 300$  mg<sup>19,22,30,34,36,43,48,50,52,53,55,60,61</sup>. Twelve studies did not report a specific dosage.<sup>18,23,24,26,28,29,44,45,49,51,56,57</sup> Studies on aspirin resistance in users of aspirin in a dosage of  $\geq 300$  mg daily showed a significantly lower adjusted prevalence compared with studies with aspirin  $\leq 100$  mg (18.6% (95%CI 11.3 to 26.0) versus 35.6% (95%CI 28.1 to 43.2),  $P < 0.0001$ ).

## DISCUSSION

Among studies in patients using aspirin for secondary prophylaxis of arterial thromboembolism included in our meta-analysis, the overall prevalence of laboratory defined persistent platelet reactivity was approximately 25%. Prevalences widely differed between studies, which is partly explained by variance in method used to define aspirin resistance and dosage of aspirin used.

Analysis of unadjusted prevalence in studies using arachidonic acid induced LTA shows a prevalence significantly lower than the unadjusted prevalence for the point-of-care devices. LTA employing arachidonic acid as agonist is a well-established, although labor-intensive, method, reflecting biochemical action of aspirin most

**Table 1** – Prevalence of aspirin resistance

	Mean prevalence			
	Not adjusted, % (95%CI)		Adjusted*, % (95%CI)	
Overall	23.8	(19.5 to 28.0)	27.1	(21.5 to 32.6)
Definition				
PFA-100	28.1	(22.2 to 33.9)	29.0	(23.1 to 34.8)
RPFA	18.9	(12.1 to 25.8)	26.2	(18.6 to 33.9)
LTA	15.4	(7.8 to 23.0)	21.3	(15.1 to 27.5)
Rest	35.0	(6.0 to 64.0)	31.8	(21.6 to 42.0)
Population				
CAD	22.4	(17.5 to 27.4)	22.9	(17.0 to 28.7)
Stroke	26.0	(16.3 to 35.7)	32.1	(22.4 to 41.8)
Rest	27.3	(9.5 to 45.1)	26.3	(16.5 to 36.0)
Dosage				
≤100mg	27.1	(18.7 to 35.6)	35.6	(28.1 to 43.2)
101-300mg	29.6	(21.8 to 37.5)	28.2	(20.9 to 35.6)
≥300mg	21.7	(11.8 to 31.7)	18.6	(11.3 to 26.0)
Unknown	19.8	(10.7 to 28.9)	25.8	(16.2 to 35.4)

\*Adjusted for definition of aspirin resistance, study population and used dosage  
PFA-100, Platelet Function Analyzer-100 (Dade-Behring Inc., Deerfield, USA); RPFA, Rapid Platelet Function Analyzer (Ultegra, Accumetrics Inc, San Diego, USA); LTA, light transmission aggregometry; CAD, coronary artery disease

directly, because the main effect of low-dose aspirin on platelet activation is inhibition of the COX-1-dependent conversion of arachidonic acid into thromboxane  $A_2$ .<sup>3</sup> Several studies demonstrate poor concordance between PFA-100 and LTA method.<sup>36,37</sup> This discrepancy suggests that PFA-100 or RPFA measures different aspects of platelet function. Gonzalez *et al.* studied both platelet aggregation using arachidonic acid, PFA-100 closure time and markers of  $TxA_2$  production in healthy subjects on aspirin.<sup>62</sup> Although intake of 100 mg aspirin resulted in a 75% reduction in 11-dehydrothromboxane  $B_2$  in healthy subjects and all individuals displayed >90% inhibition of platelet aggregation, regression analysis revealed no association between 11-dehydrothromboxane  $B_2$  levels and PFA-100 closure times. Furthermore, increased levels of von Willebrand factor (vWF) are associated with failure to prolong PFA-100 closure time in aspirin-treated patients.<sup>32</sup> In healthy individuals, vWF plasma levels were strongly associated with CEPI closure time, but no relationship was found between closure time and platelet aggregation, suggesting that PFA-100 results reflect vWF activity more than they reflect platelet function.<sup>63</sup>

Studies on aspirin resistance in users of aspirin with a dosage of ≥300 mg daily show a significantly lower adjusted-prevalence rate compared with studies with an aspirin dosage ≤100 mg. Consequently, our data suggest that increasing the dosage

of aspirin could reduce the prevalence of aspirin resistance. Results from other studies support this hypothesis. In a population of 102 patients with type 2 diabetes mellitus, Abaci *et al.* assessed PFA-100 closure time before and after the administration of 100 mg of aspirin.<sup>64</sup> Aspirin resistance, defined by a closure time of <300 seconds, was found in 34 of 102 patients. Prolongation of closure time of >300s was obtained in 15 of these 34 patients after additional ingestion of 300 mg of aspirin. The effect of PFA-100 guided dosage adaptation on aspirin resistance (defined by PFA-100 CEPI-closure time of <170 seconds) was studied in a population of 212 patients with CAD.<sup>65</sup> At an initial dosage of 100 mg of aspirin, 18.4% had a closure time in the normal range. After reinforcement of compliance and increase in dosage to 300 mg, only 1.4% had a closure time within the normal range. Used dosage influenced prevalence of aspirin resistance measured by RPFA as well. An aspirin dosage of  $\leq 100$  mg independently predicted presence of aspirin resistance (OR 2.2, 95% CI 1.1 to 4.4, compared with dosage of >100 mg) in a population of 468 patients with CAD.<sup>50</sup>

When an adverse relationship between aspirin resistance and risk of cardiovascular events is assumed, and aspirin dosage is a major determinant of resistance, one would expect aspirin dosage to influence the event rate in aspirin prevention trials. However, in the Antithrombotic Trialists' Collaboration meta-analysis,<sup>8</sup> in trials comparing different daily doses of aspirin versus no aspirin, dosages of 75 to 150 mg daily were at least as effective as higher daily dosages. The effects of dosages <75 mg were less certain since this regimen has been less widely assessed than dosages of 75 to 150 mg daily. Possibly, the potentially beneficial effect of aspirin dosages >150 mg daily in reducing prevalence of aspirin resistance is offset by the more profound suppression of the vasculoprotective effects of prostacyclin occurring at higher dosages of aspirin.<sup>3,66,67</sup>

The strength of our study lies in the systematic nature of the reviewing process. By prespecifying inclusion criteria and a sensitive search strategy, we were able to review all retrievable studies, with a minimum risk for bias. Thus, we were able to provide an extensive and, to our knowledge, complete overview of available data on prevalence of aspirin resistance. However, the following potential limitations to our study require comment. As in all systematic reviews, our results may have been influenced by publication bias. This could have resulted in inflated estimates of prevalence rates. Although we tried to minimize publication bias by applying no formal language restriction and including meeting abstracts, a funnel plot on all included studies suggests an inverse relationship between size of population and aspirin resistance prevalence (data not shown). On contrary, there was no difference in mean prevalence derived from studies published in peer-reviewed journals and from those published as meeting abstract. Furthermore, we could not address the effect of compliance on prevalence of aspirin resistance, since most included studies did not supply data on patient compliance. As non-compliance could lead to "aspirin resistance",<sup>55,59</sup> reported prevalences of aspirin resistance could be overestimated to some extent.

In conclusion, our systematic review on prevalence of aspirin resistance indicates that persistent platelet reactivity can be found in approximately one in four patients on aspirin therapy for secondary prevention of cardiovascular events. The biochemical method to define aspirin resistance and aspirin dosage significantly influence

prevalence of aspirin resistance. More studies are needed to determine which method is most predictive in identifying patients at high risk of cardiovascular events despite aspirin therapy. Moreover, prospective studies are needed to answer the question whether aspirin resistance could be overcome by an increase in dosage.

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