

Association of Laboratory-Defined Aspirin Resistance With a Higher Risk of Recurrent Cardiovascular Events

A Systematic Review and Meta-analysis

Jaapjan D. Snoep, MSc; Marcel M. C. Hovens, MD; Jeroen C. J. Eikenboom, MD, PhD; Johanna G. van der Bom, MD, PhD; Menno V. Huisman, MD, PhD

Background: The risk of recurrence of cardiovascular events among patients using aspirin (acetylsalicylic acid) for secondary prevention of such events remains high. Persistent platelet reactivity despite aspirin therapy, a laboratory-defined phenomenon called aspirin resistance (hereinafter, laboratory aspirin resistance), might explain this in part, but its actual contribution to the risk remains unclear. The objective of this study was to systematically review all available evidence on whether laboratory aspirin resistance is related to a higher risk of cardiovascular recurrent events.

Methods: Using a predefined search strategy, we searched electronic databases. To be included in our analysis, articles had to report on patients who used aspirin for secondary cardiovascular prevention, had to contain a clear description of a method to establish the effects of aspirin on platelet reactivity, and had to report recurrence rates of cardiovascular events. Odds ratios of cardiovas-

cular outcome of eligible studies were pooled in a random-effects model.

Results: We included 15 full-text articles and 1 meeting abstract. Fifteen of these studies revealed an adverse association between laboratory aspirin resistance and occurrence of cardiovascular events. The pooled odds ratio of all cardiovascular outcomes was 3.8 (95% confidence interval, 2.3-6.1) for laboratory aspirin resistance.

Conclusion: This systematic review and meta-analysis shows that patients biochemically identified as having laboratory aspirin resistance are more likely to also have "clinical resistance" to aspirin because they exhibit significantly higher risks of recurrent cardiovascular events compared with patients who are identified as (laboratory) aspirin sensitive.

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Author Affiliations:

Departments of General Internal Medicine and Endocrinology (Mr Snoep and Drs Hovens and Huisman), Hematology (Dr Eikenboom), and Clinical Epidemiology (Mr Snoep and Dr van der Bom), Leiden University Medical Center, Leiden, the Netherlands.

CARDIOVASCULAR DISEASES are the most common cause of mortality and morbidity in Western countries in the 21st century. In the United States, cardiovascular mortality contributed to nearly 40% of total mortality in 2003.¹ Because aggregation of platelets is pivotal to the development of cardiovascular events, inhibition of this process could play an important role in prevention of cardiovascular disease.²

Nowadays, aspirin (acetylsalicylic acid) forms the cornerstone in the secondary prevention of cardiovascular events. The effect of low-dose aspirin is most likely based on the permanent inactivation of cyclooxygenase 1 through the blockade of the cyclooxygenase 1 channel by the acetylation of serine residue 529, which results in an irreversible inhibition of the pro-

duction of thromboxane A₂ by platelets.³ Because thromboxane A₂ is a potent platelet activator that also causes vasoconstriction and smooth muscle proliferation, a decrease in thromboxane A₂ leads to reduced aggregation of platelets.^{3,4}



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The clinical effectiveness of aspirin in the secondary prevention of cardiovascular events has been well established. The Antithrombotic Trialists' Collaboration⁵ documented a 22% reduction in death and serious ischemic vascular events by using antiplatelet therapy compared with placebo in their most recent meta-analysis of 287 randomized trials, which comprised more than 200 000 patients.

However, not all patients benefit from aspirin to the same extent, which could be

explained by a variety of pharmacodynamic, pharmacokinetic, and biochemical features.⁶ Addressed biochemically as persistent platelet reactivity *ex vivo* despite the use of aspirin, this phenomenon is called laboratory-defined aspirin resistance (hereinafter, laboratory aspirin resistance). Based on the failure of aspirin to inhibit platelet thromboxane A₂ production or to inhibit tests of platelet function, a variety of laboratory tests to define and quantify laboratory aspirin resistance have been proposed. Yet, a uniform and agreed-on definition of laboratory aspirin resistance and its measurement is lacking.⁷⁻⁹ Laboratory aspirin resistance has received much attention in medical journals^{8,10,11} as well as in the lay media.¹²

A recent meta-analysis¹³ of studies addressing the prevalence of persistent platelet reactivity despite use of aspirin in a secondary cardiovascular prevention setting reported a mean prevalence of laboratory aspirin resistance of approximately 25%. However, the main question—whether patients who are biochemically identified as having laboratory aspirin resistance also exhibit “clinical resistance” to aspirin (ie, whether they are at a higher risk of recurrent cardiovascular events)—remains largely unanswered hitherto. To try to quantify evidence addressing this topic, we conducted a systematic review and meta-analysis of all reports, to our knowledge, on the clinical consequences of laboratory aspirin resistance among patients using aspirin for secondary prevention of cardiovascular events.

METHODS

STUDY SELECTION, QUALITY ASSESSMENT, AND DATA EXTRACTION

We used electronic databases to identify relevant reports. The following databases were searched: MEDLINE (January 1966 to October 2006), EMBASE (January 1974 to October 2006), the Cochrane Central Register of Controlled Trials (CENTRAL) (1800 to October 2006), and Web of Science (1945 to October 2006). We used predefined search terms (available from the authors) and used no language restrictions. Furthermore, we tried to iden-

tify additional studies by searching the reference lists of relevant studies and reading reviews, editorials, and letters on this topic. Authors of appropriate identified 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) included patients had established coronary artery, cerebrovascular, or peripheral artery disease; (2) patients were treated with aspirin for secondary prevention of cardiovascular events; (3) the study contained a clear description of the method used to establish the effects of aspirin on platelet reactivity to compare patients with laboratory aspirin resistance with those without; and (4) the study reported data on recurrence rates of fatal and nonfatal myocardial infarction, fatal and nonfatal stroke, or other cardiovascular outcomes as predefined by investigators. For this systematic review, we defined laboratory aspirin resistance as *ex vivo* nonresponsiveness to aspirin according to any test that reflects platelet thromboxane A₂ synthesis or platelet function.

The quality of the identified studies was assessed based largely on quality criteria concerning minimization of bias. In detail, we evaluated information regarding control for confounders, measurement of exposure, completeness of follow-up, and blinding. For case-control studies, we also assessed matching and case definition. No formal scoring system was used. Reviewers were not blinded to journal, author, or institution of publication.

We used a prespecified data collection form to extract information for each report regarding year of publication, duration, setting, and design of the study, total sample size, and study population (baseline characteristics). Concerning our research question, the following variables were collected from each selected study: the dosage of aspirin used, definitions of laboratory aspirin resistance and cardiovascular outcomes used, prevalence of laboratory aspirin resistance, and occurrence rates of cardiovascular outcomes.

Selection, quality assessment, and data extraction of studies to be included in this review were all independently performed by 2 reviewers (J.D.S. and M.M.C.H.). Disagreements were resolved by consensus and discussion with a third party (M.V.H.). The κ statistic for agreement among reviewers was performed manually for each process in the study selection. The overall κ statistic was calculated as a weighted mean of those different values.

STATISTICAL ANALYSES

To relate laboratory aspirin resistance to cardiovascular outcomes, we calculated odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for each study that reported the percentages of patients with laboratory aspirin resistance and cardiovascular events vs those without laboratory aspirin resistance with cardiovascular events. *P* values were calculated with the χ^2 test or Fisher exact test where appropriate. The ORs from cohort studies were pooled using a random-effects model.¹⁴ This rather conservative method for meta-analysis accounts for the possibility of statistical interstudy heterogeneity. To test for statistical interstudy heterogeneity, the χ^2 value was calculated for the hypothesis of homogeneity. Quantification of the effect of heterogeneity was assessed by means of the *I*² statistic, which demonstrates the percentage of total variation across studies owing to heterogeneity.

We pooled all cohort studies reporting cardiovascular outcomes, as well as several subgroups of cohort studies. These subgroups included studies reporting cardiovascular outcomes as cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, and revascularization; studies reporting on (re)occlusion after bypass grafting or angioplasty; and studies providing data on occurrence of myonecrosis represented by creatine kinase-myocardial band elevation after percutaneous coronary intervention. We assessed potential publication bias graphically, using funnel plots on ORs for laboratory aspirin resistance.

Statistical analyses were performed using Cochrane Review Manager software (version 4.2.8; Cochrane Library Software, Oxford, England). For all analyses, a level of significance of $\alpha = .05$ was used.

RESULTS

CHARACTERISTICS OF INCLUDED STUDIES

We included 15 full-text articles¹⁵⁻²⁹ and 1 meeting abstract³⁰ (**Figure 1**). Overall, the κ statistic was 0.86, indicating good interobserver agreement. Details of included studies are summarized in **Table 1** and **Table 2**. Studies are grouped according to the outcomes used. Ten studies used a composite outcome of cardiovascular events.^{15-23,30} In 4 reports, the studied outcome was (re)occlusion after bypass grafting or

angioplasty.²⁴⁻²⁷ Two studies assessed myonecrosis, defined by elevated creatine kinase–myocardial band levels, after percutaneous coronary intervention.^{28,29}

Aspirin dosages used in included studies varied from 80 to 1500 mg daily,^{15,28,30} although nearly all studies used a low to intermediate dosage of 80 to 325 mg daily.¹⁶⁻³⁰ Various methods were used to establish the effects of aspirin on platelet reactivity. Conventional optical light transmittance aggregometry was used in 5 studies.^{20,23,24,27,29} Multiple agonists were used to induce aggregation. Three studies determined levels of thromboxane B₂, which is a stable metabolite of thromboxane A₂, in plasma or urine.^{18,21,27} Five studies used the Platelet Function Analyzer 100 system (Dade Behring, Deerfield, Illinois), which measures in vitro shear-stress–induced platelet activation in terms of platelet occlusion of a membrane coated with platelet agonists.^{17,19,22,25,26} In 3 studies, platelet function was assessed with the VerifyNow Aspirin Assay (Accumetrics, San Diego, California), which measures changes in light transmittance related to the rate of aggregation, using a disposable cartridge with fibrinogen-coated beads and a platelet activator.²⁸⁻³⁰ Three studies employed other techniques.^{15,16,27} Duration of follow-up ranged from 6 to 8 hours (for the creatine kinase–myocardial band elevation) to more than 7.5 years.^{26,28}

ASSOCIATION BETWEEN LABORATORY ASPIRIN RESISTANCE AND CARDIOVASCULAR OUTCOME

The prevalence of laboratory aspirin resistance ranged from 5% to 65%.^{20,24} In the 12 studies eligible for pooling,^{15-17,20-25,27-29} comprising 1813 patients, the mean prevalence of laboratory aspirin resistance was 27%. The total variation (*I*²) among these studies, likely reflecting the aforementioned differences, was 49%, resulting in a significant statistical heterogeneity among studies (*P* = .03).

The ORs of cardiovascular outcome varied from 0.2 (95% CI, 0.0-4.5) to 14.5 (95% CI, 5.2-40.9) for laboratory aspirin resistance.^{15,25} We

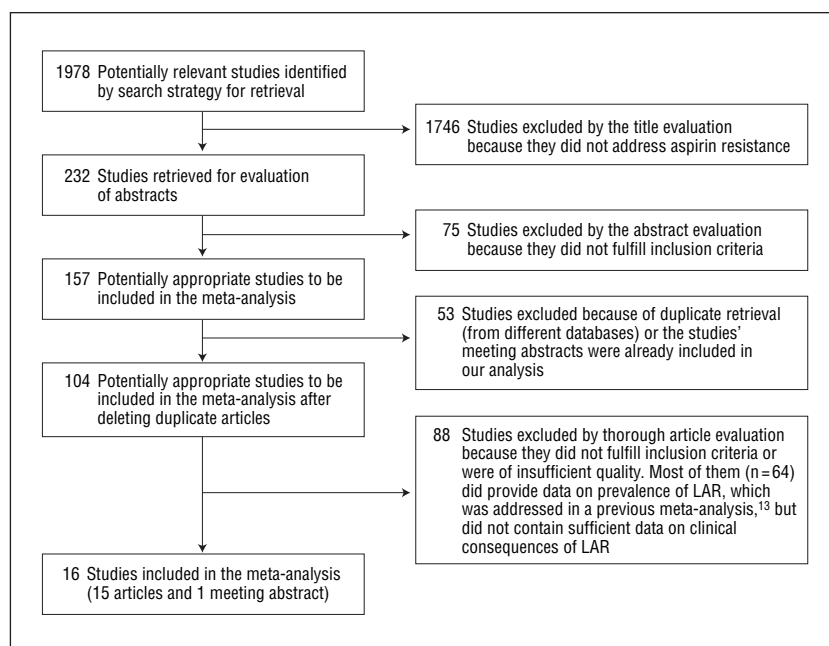


Figure 1. Flowchart of the process of study selection. LAR indicates laboratory-defined aspirin resistance.

pooled the ORs of several groups of studies, the results of which are graphically presented in **Figure 2**. When studies with cardiovascular outcomes were pooled,^{15-17,20-23} the resultant OR for laboratory aspirin resistance was 4.4 (95% CI, 2.2-8.7). In 3 cohort studies addressing (re)occlusion after interventional procedures,^{24,25,27} the pooled OR was 2.4 (95% CI, 0.4-14.3). The OR of myonecrosis after percutaneous coronary intervention was 3.1 (95% CI, 1.6-6.0).^{28,29} When all of these studies were combined, the pooled OR of cardiovascular outcome was 3.8 (95% CI, 2.3-6.1) for laboratory aspirin resistance. We also stratified the aspirin dosage used (≤ 100 mg, 101-299 mg, and ≥ 300 mg); however, no differences among the dosage groups were found.

All studies not included in the analysis because they were not a cohort study or because they did not report proportions of patients having laboratory aspirin resistance vs those without showed an association between persistent platelet reactivity despite use of aspirin and occurrence of cardiovascular events as well (Table 1 and Table 2).^{18,19,26,30}

COMMENT

We conducted a systematic review and meta-analysis to quantify evi-

dence regarding the question of whether patients with laboratory aspirin resistance have a higher risk of recurrent cardiovascular events. We showed that patients with laboratory aspirin resistance have an increased risk of cardiovascular events. Among studies eligible for meta-analysis, the pooled OR of cardiovascular outcome was 3.8 (95% CI, 2.3-6.1). The studies not included in the analysis strengthen this conclusion because they all indicate an association between persistent platelet reactivity despite use of aspirin and occurrence of cardiovascular events.

The studies in our systematic review varied in many ways. The patients included in the studies had different cardiovascular diseases and experienced a variety of risks of recurrent events. Furthermore, the studies differed in aspirin dosages used, duration of follow-up time, laboratory methods used to establish the effects of aspirin, and definition of outcome. Despite these clinical diversities and differences in method, almost all included studies suggested a positive association between the risk of cardiovascular events and the presence of laboratory aspirin resistance. We therefore decided that it could be informative to pool the findings from the cohort studies with a random-effects model,

Table 1. Details of Included Studies

Source	Design	Study Population Description	Aspirin Dosage, mg/d	Method of Assessment of LAR	Outcome	Duration of Follow-up	Comments
Grotemeyer et al, ¹⁵ 1993	Prospective cohort	Stroke (180)	1500	Platelet reactivity index > 1.25 using a technique reflecting platelet activation following blood sampling ³⁶	CV death, MI, stroke	2 y	Very heterogeneous distribution of withdrawals, LAR determined once, adh NA, adj OCs unblinded
Buchanan et al, ¹⁶ 2000	Prospective cohort	CABG (289)	325	Variation coefficient bleeding time < 26% with or without aspirin	Death, MI, stroke, graft occlusion	2 y	Bleeding time poorly established for this goal, low event rates, LAR determined once
Andersen et al, ¹⁷ 2002	Prospective cohort	CAD (71)	160	PFA-100, CEPI-CT ≤ 196 s	Nonfatal MI, stroke, revascularization	4 y	Small groups, no exclusion criteria (confounding), LAR determined once, adh NA, adj OCs unblinded
Eikelboom et al, ¹⁸ 2002	Nested case-control of HOPE study ^{37,38}	CV disease (488 cases, 488 controls)	NR	Urinary TxB ₂ : fourth quartile (most platelet activation) least sensitive	CV death, MI, stroke	5 y	Confounders in cases and controls: DM, BMI, tension, peripheral artery disease, TxB ₂ could be influenced by recent events, LAR determined once, adh NA
Grundmann et al, ¹⁹ 2003	Case-control	Stroke (35 cases, 18 controls)	100	PFA-100, CEPI-CT ≤ 165 s	Stroke, transient ischemic attack	> 2 y	Small sample size, LAR cause or result of events? LAR determined once, adh NA
Gum et al, ²⁰ 2003	Prospective cohort	CV disease (326)	325	LTA ≥ 70% (10 μmol/L ADP) and ≥ 20% (0.5 mg/mL AA)	CV death, MI, stroke	679 ± 137 d	Few patients with LAR, few events, follow-up time not specified for aspirin response, LAR determined once, adh NA
Cotter et al, ²¹ 2004	Prospective cohort	CAD (73)	100	Plasma-TxB ₂ > lowest value found in aspirin nonusers	CV death, MI, stroke, CV-related admission	1 y	Small groups, no exclusion criteria (confounding), LAR determined once
Cheng et al, ³⁰ 2005 (abstract)	Prospective cohort	CAD (422)	80-300	ASA ARU ≥ 550	Death, MI, stroke, admission for UA	NR	Follow-up time and absolute event rates NR, LAR determined once, adh NA, adj OCs unblinded
Pamukcu et al, ²² 2006	Prospective cohort	CAD (105)	100-300	PFA-100 CEPI-CT < 186 s	CV death, MI, stroke, UA	1 y	Subjective OC (UA), LAR determined once, adh NA, adj OCs unblinded
Stejskal et al, ²³ 2006	Prospective cohort	CAD (103)	100	LTA ≥ 5% (spontaneous) or ≥ 53% (3 μmol/L cationic propyl gallate)	MI, stroke, UA	4 y	Subjective OC (UA), adh NA, adj OCs unblinded
Mueller et al, ²⁴ 1997	Prospective cohort	PAD/ PTA (100) ^a	100	LTA (10 and 5 μmol/L ADP and 5 and 2 μg/mL collagen); mean, > 80% of baseline	Reocclusion	1.5 y	Reasons for exclusion NR, all patients were sensitive with AA aggregometry, making recurrence rates less related to LAR, adj OCs unblinded
Ziegler et al, ²⁵ 2002	Prospective cohort	PAD/ PTA (52) ^a	100	PFA-100, CEPI-CT ≤ 170 s	Restenosis, reocclusion	1 y	Small sample size, few nonresponders, LAR determined once, adh NA, adj OCs unblinded
Yilmaz et al, ²⁶ 2005	Case-control	CABG (14 cases, 14 controls)	Cases, 189 ± 100; controls, 214 ± 90	PFA-100, CEPI-CT ≤ 193 s	Graft occlusion	Cases vs controls: 7.5 ± 3.9 y vs 6.2 ± 2.5 y	Most cases had ACS at presentation vs stable angina in controls, LAR determined once, adh NA
Poston et al, ²⁷ 2006	Prospective cohort	CABG (225)	325	Meets 2 of 3 criteria: TEG (0.5 μmol/L AA) > 50%, LTA (1 and 5 μg/mL collagen) > 50%, plasma-TxB ₂ > 25% of baseline	Graft occlusion	30 d	Very low event rates, adh NA
Chen et al, ²⁸ 2004	Prospective cohort	PCI (151)	80-300	ASA ARU ≥ 550	Myonecrosis (CK-MB > 16 ng/mL)	6-8 h after PCI	Asian population, LAR determined once, adh NA, adj OCs unblinded
Lev et al, ²⁹ 2006	Prospective cohort	PCI (150)	81-325	Meets 2 of 3 criteria: LTA ≥ 70% (10 μmol/L ADP), LTA ≥ 20% (0.5 mg/mL AA), ASA ARU ≥ 550	Myonecrosis (CK-MB > 5.0 ng/mL)	20-24 h after PCI	CK-MB values not available for 6 patients, adj OCs unblinded

Abbreviations: AA, arachidonic acid; ACS, acute coronary syndrome; adh, adherence; adj, adjudication; ADP, adenosine diphosphate; ARU, aspirin response unit; ASA, VerifyNow Aspirin Assay (Ultegra/Verify Now; Accumetrics, San Diego, California); BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CABG, coronary artery bypass graft; CAD, coronary artery disease; CEPI-CT, collagen epinephrine closure time; CK-MB, creatine kinase-myocardial band; CV, cardiovascular; DM, diabetes mellitus; LAR, laboratory-defined aspirin resistance; LTA, light transmission aggregometry; MI, myocardial infarction; NA, not assessed; NR, not reported; OC, outcome; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PFA-100, Platelet Function Analyzer-100 system (Dade Behring, Deerfield, Illinois); PTA, percutaneous transluminal angioplasty; TEG, thromboelastography; TxB₂, thromboxane B₂; UA, unstable angina.

^aPatients with PAD undergoing PTA.

which partly accounts for the heterogeneity among the studies.¹⁴

Besides these heterogeneities, several limitations in the methods of included studies require comment. In most of the studies,^{15,17,22-25,28-30} outcomes were not adjudicated in a blinded fashion for laboratory aspirin resistance, making them more susceptible to bias. In 1 study,²⁴ 45 patients were excluded for reasons that were not mentioned, and in another study,²⁵ allocation to either aspirin or clopidogrel was not randomized but was based on patients' concerns. Moreover, use of nonsteroidal anti-inflammatory drugs, which may have differed among studies because it was not a formal exclusion criterion in 9 of them,^{15-18,21,25-27,29,30} could have influenced the prevalence of laboratory aspirin resistance.³¹⁻³³ Furthermore, laboratory aspirin resistance was only determined on a single occasion in all but 4 studies,^{23,24,27,29} which may have led to misclassification of patients. For example, persistent platelet reactivity may be more common after coronary artery bypass grafting owing to increased platelet turnover.³⁴ This temporal "resistance" was recently observed in a population of patients who had undergone coronary bypass.²⁷ Although noncompliance with treatment is an important cause of laboratory aspirin resistance,^{21,35} patient adherence to treatment was assessed in only 3 studies.^{16,21,24} Cotter et al²¹ have suggested that after exclusion of noncompliant patients, laboratory aspirin resistance is no longer related to recurrent events.

The strength of our study lies in the systematic nature of the review process. By prespecifying inclusion criteria and using a sensitive search strategy, we were able to review all retrievable studies with a minimum risk of bias. Thus, we were able to provide an extensive and, to our knowledge, complete overview of available data on cardiovascular consequences of laboratory aspirin resistance in patients with cardiovascular disease. In contrast, previous reviews included only selected studies on cardiovascular consequences of laboratory aspirin resistance. Many individual studies were

Table 2. Statistical Details of Included Studies

Source (Study Population, No.)	Patients With LAR, No. (%)	Occurrence of Cardiovascular Events			
		Patients With LAR, No. (%) ^a	Patients Without LAR, No. (%) ^a	OR (95% CI)	P Value
Grotemeyer et al, ¹⁵ 1993 (180)	60 (33)	24/60 (40)	5/114 (4)	14.5 (5.2-40.9)	< .001
Buchanan et al, ¹⁶ 2000 (289)	158 (55)	15/158 (10)	9/131 (7)	1.4 (0.6-3.4)	.42
Andersen et al, ¹⁷ 2002 (71)	25 (35)	9/25 (36)	11/46 (24)	1.8 (0.6-5.2)	.28
Eikelboom et al, ¹⁸ 2002 (448 cases, 488 controls)	NR	NR	NR	1.8 (1.2-2.9) ^b	.01
Grundmann et al, ¹⁹ 2003 (35 cases, 18 controls)	12 (23)	12/35 (34) ^c	0/18 (0) ^d	6.8 (1.8-26.2) ^e	.004
Gum et al, ²⁰ 2003 (326)	17 (5)	4/17 (24)	30/309 (10)	2.9 (0.9-9.3)	.09
Cotter et al, ²¹ 2004 (73)	21 (29)	6/21 (29)	3/52 (6)	6.5 (1.5-29.3)	.01
Cheng et al, ³⁰ 2005 (abstract) (422)	113 (27)	NR	NR	2.9 (1.5-5.7) ^f	.002
Pamukcu et al, ²² 2006 (105)	20 (19)	9/20 (45)	10/85 (12)	6.1 (2.0-18.5)	< .001
Stejskal et al, ²³ 2006 (103)	57 (55)	50/57 (88)	21/46 (46)	8.5 (3.2-22.7)	< .001
Mueller et al, ²⁴ 1997 (100)	65 (65) (after 4 wk)	8/65 (12)	0/35 (0)	10.5 (0.6-187.5)	.048
Ziegler et al, ²⁵ 2002 (52)	5 (10)	0/5 (0)	13/47 (28)	0.2 (0.0-4.5)	.31
Yilmaz et al, ²⁶ 2005 (14 cases, 14 controls)	8 (29)	7/14 (50) ^c	1/14 (7) ^c	13.0 (1.3-128.1) ^e	.03
Poston et al, ²⁷ 2006 (225) (on day 1)	22 (10)	4/22 (18)	12/203 (6)	3.5 (1.0-12.1)	.06
Chen et al, ²⁸ 2004 (151)	29 (19)	15/29 (52)	30/122 (25)	3.3 (1.4-7.6)	.004
Lev et al, ²⁹ 2006 (150)	19 (13)	7/18 (39)	23/126 (18)	2.9 (1.0-8.1)	.045

Abbreviations: CI, confidence interval; HR, hazard ratio; LAR, laboratory-defined aspirin resistance; NR, not reported; OR, odds ratio.

^aThe numerators are the patients with cardiovascular events, and the denominators are the total number of patients with and without LAR.

^bReported OR of upper vs lower quartile.

^cPrevalence of LAR in cases.

^dPrevalence of LAR in controls.

^eOdds ratio for patients with LAR.

^fOdds ratio not reported; reported as HR.

relatively small, making extrapolation difficult. However, by pooling available studies, we found a strong association between laboratory aspirin resistance and recurrent cardiovascular events.

As in all systematic reviews, our results could have been influenced by several forms of bias. However, we tried to minimize selection bias by applying no formal language restriction and including both full-text articles and meeting abstracts. Furthermore, we used a funnel plot in which there was no inverse relationship between the size of individual studies and the ORs of cardiovascular outcomes, which argues against the existence of publication

and reporting bias. However, these forms of bias could not be completely excluded owing to the relatively small number of included studies. Moreover, we assumed laboratory aspirin resistance to be a categorical variable. This may not be the case because there is no standardized definition of laboratory aspirin resistance. However, even when laboratory aspirin resistance should be seen as a continuous variable, it is likely that a categorical definition would be also predictive and that just the strength of the association might differ.

In conclusion, our systematic review and meta-analysis strongly indicates that laboratory aspirin

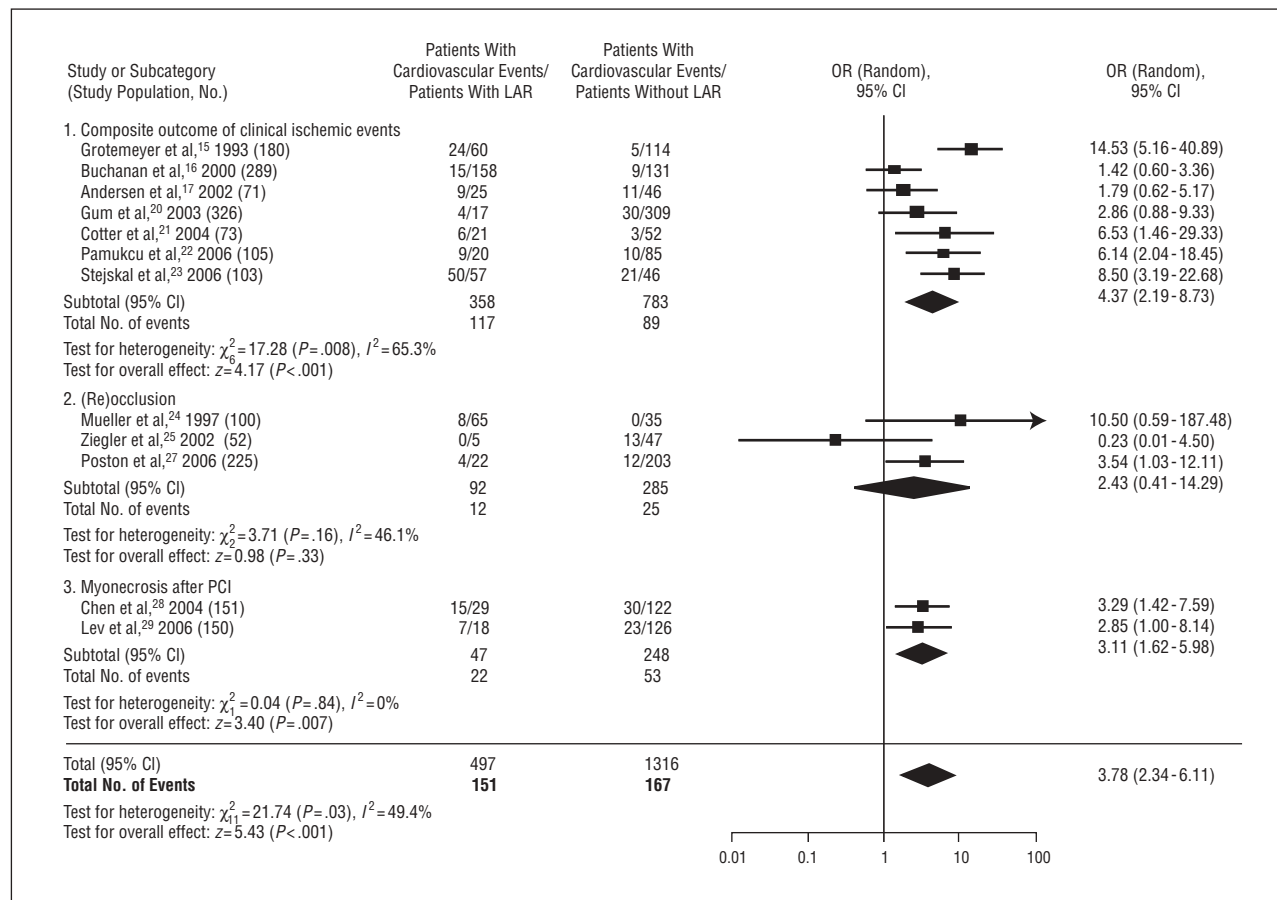


Figure 2. Forest plots of odds ratios (ORs) of the cardiovascular outcome for patients with laboratory-defined aspirin resistance (LAR) vs those without LAR from eligible studies. Studies are grouped by the outcome parameter used: group 1 presents a composite outcome of clinical ischemic events, including cardiovascular death, myocardial infarction, stroke, acute coronary syndrome, and revascularization procedure; group 2, (re)occlusion after bypass grafting or angioplasty; and group 3, myonecrosis after percutaneous coronary intervention (PCI), represented by a creatine kinase–myocardial band elevation. In the lower part of the figure, all studies on these cardiovascular outcomes are pooled together. The black squares represent ORs for the association between aspirin resistance and cardiovascular outcomes of individual studies. The size of the squares corresponds to the weight of the study in the meta-analysis. Horizontal lines represent corresponding 95% confidence intervals (CIs). The CIs of the totals are indicated by the black diamonds.

resistance is a clinically important phenomenon. Patients biochemically identified as having laboratory aspirin resistance are more likely to also have clinical resistance to aspirin because they exhibit a considerably increased risk of recurrent cardiovascular events compared with patients identified as (laboratory) aspirin sensitive. Because cardiovascular diseases are very prevalent and associated with considerable mortality and morbidity, there is a clear need for future studies to thoroughly evaluate individual determinants of laboratory aspirin resistance, predictive value of the various laboratory methods, and possible solutions for individual patients.

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Correspondence: Jaapjan D. Snoep, MSc, Department of Clinical Epidemiology, Leiden University Medical Center, C-09-P, PO Box 9600, 2300 RC Leiden, the Netherlands (j.d.snoep@lumc.nl).

Author Contributions: Mr Snoep and Drs Hovens and Huisman had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Snoep, Hovens, Eikenboom, and Huisman. *Acquisition of data:* Snoep and Hovens. *Analysis and interpretation of data:* Snoep, Hovens, Eikenboom, van der Bom, and Huisman. *Drafting of the manuscript:* Snoep. *Critical revision of the manuscript for important intellectual content:* Hovens, Eikenboom, van der Bom, and Huisman. *Statistical analysis:* Snoep. *Study supervi-*

sion: Eikenboom, van der Bom, and Huisman.

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