Aspirin in the prevention of cardiovascular disease in type 2 diabetes

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Laboratory-defined aspirin resistance is associated with a higher risk of recurrent cardiovascular events: a systematic review and meta-analysis

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Abstract

Background: The risk of recurrences among patients using aspirin for secondary prevention of cardiovascular events remains high. Persistent platelet reactivity despite aspirin therapy, a laboratory phenomenon called aspirin resistance, might explain this in part, but its actual contribution to the risk remains unclear.

Objective: To systematically review all available evidence on the question 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 using aspirin for secondary cardiovascular prevention, to contain a clear description of a method to establish the effects of aspirin on platelet reactivity, and to report recurrence rates of cardiovascular events. Odds ratios of cardiovascular outcome of eligible studies were pooled in a random-effects model.

Results: We included fifteen full-text articles and one meeting abstract. Thirteen of these studies revealed an adverse relation between laboratory aspirin resistance and occurrence of cardiovascular events. The pooled odds ratio of all cardiovascular outcomes was 3.8 (95%CI 2.3-6.1) for aspirin resistance.

Conclusions: This systematic review and meta-analysis shows that patients biochemically labeled aspirin resistant are likely to be also “clinically resistant” as they exhibit significantly higher risks of recurrent cardiovascular events, compared with patients which are labeled sensitive.

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 of cardiovascular diseases was nearly 40% of total mortality in 2003 (1). As 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 (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 (COX-1) through blockade of the COX-channel by the acetylation of serine residue 529, which results in an irreversible inhibition of the production of thromboxane A2 by platelets (3). As 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).

The clinical effectiveness of aspirin in the secondary prevention of cardiovascular events has been well established. The Antithrombotic Trialists' Collaboration has documented a 22% reduction of death and serious ischemic vascular events by antiplatelet therapy compared with placebo, in their most recent meta-analysis of 287 randomized trials, incorporating more than 200,000 patients (5).

However, not all patients profit 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 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 aspirin resistance has been proposed. Yet, a uniform and agreed definition of aspirin resistance and its measurement is lacking (7-9). Aspirin resistance has received much attention, in both medical journals (8,10,11) and lay media (12).

A recent meta-analysis of studies addressing 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% (13). However, the main question whether patients who are biochemically labeled aspirin resistant exhibit also "clinical resistance" to aspirin, *i.e.* a higher risk of recurrent cardiovascular events, remains largely unanswered hitherto. In order to try to quantify evidence addressing this topic, we conducted a systematic review and meta-analysis of all reports on clinical consequences of laboratory aspirin resistance among patients using aspirin for secondary prevention of cardiovascular events. To this aim, we defined aspirin resistance as *ex vivo* non-responsiveness according to any test reflecting platelet thromboxane A2 synthesis or platelet function.

Methods

Selection, quality assessment and data extraction

We used electronic databases to identify relevant reports. The following databases were searched: MEDLINE (from January 1966 until October 2006), EMBASE (from January 1974 until October 2006), the Cochrane Central Register of Controlled trials (CENTRAL) (from 1800 until October 2006) and Web of Science (from 1945 until October 2006), using predefined search terms (Appendix 1). 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 this topic. Authors of appropriate identified studies were contacted to obtain additional data not reported in the original report. 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 should have established coronary artery, cerebrovascular or peripheral artery disease; 2) patients should be treated with aspirin for secondary prevention of cardiovascular events; 3) the study should contain a clear description of the method used to establish the effects of aspirin on platelet reactivity to compare aspirin resistant and non-resistant patients; and 4) the study should report data on recurrence rates of fatal and non-fatal myocardial infarction, fatal and non-fatal stroke or other cardiovascular endpoints as predefined by investigators.

The quality of the identified studies was assessed based largely on quality criteria concerning minimisation 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 and setting of study, study design, total sample size and study population (baseline characteristics). Concerning our research question, the following variables were collected from selected studies: dosage of aspirin, definition of aspirin resistance, prevalence of aspirin resistance, definition of clinical outcomes and occurrence rates of clinical outcomes.

Selection, quality assessment and data extraction of studies to be included in this review were all independently done by two reviewers (JDS and MMCH). Disagreements were resolved by consensus and discussion with a third party (MVH). *Kappa* statistics for agreement between reviewers were performed manually for each process in study selection. The overall *kappa* was calculated as a weighted mean of those different values.

Statistical analyses

To relate laboratory aspirin resistance to clinical outcomes, we calculated odds ratios with corresponding 95% confidence intervals (CI) for each study that reported the proportions of resistant and non-resistant patients with cardiovascular events. *P*-values are calculated with the χ^2-test or Fisher's exact test where appropriate. Odds ratios from cohort studies were pooled using a random-effects model (14). This rather conservative method for meta-analysis accounts for the possibility of statistical inter-study heterogeneity. To test for statistical inter-study heterogeneity, the χ^2-value was calculated for the hypothesis of homogeneity. Quantification of the effect of heterogeneity was assessed by means of I^2, which demonstrates the percentage of total variation across studies due to heterogeneity.

We pooled all cohort studies reporting cardiovascular outcomes, as well as several subgroups of cohort studies. These subgroups included studies reporting clinical

cardiovascular endpoints 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 (CK-MB) elevation after percutaneous coronary intervention. We assessed potential publication bias graphically, using funnel plots on odds ratios for aspirin resistance (15).
Analyses were performed using Cochrane Review Manager 4.2.8 (Cochrane Library Software, Oxford, U.K.). For all analyses, a level of significance of α=0.05 was used. JDS, MMCH and MVH 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.

Results

Characteristics of included studies

We included fifteen full-text articles (16-30) and one meeting abstract (31) (Figure 1). Overall, kappa statistics were 0.86, indicating good inter-observer agreement. Details of included studies are summarized in Table 1. Studies are grouped according to used endpoints. Ten studies used a composite endpoint of clinical cardiovascular events (16-24,31). In four reports, the studied outcome was (re)occlusion after bypass grafting or angioplasty (25-28). Two studies assessed myonecrosis, defined by elevated CK-MB levels, after percutaneous coronary intervention (29,30).
Used aspirin dosage varied from 80 mg to 1500 mg daily (16,29,31), though nearly all studies used a low to intermediate dosage between 80 and 325 mg (17-31). Various methods were used to establish the effects of aspirin on platelet reactivity. Conventional optical light transmittance aggregometry was used in five studies (21,24,25,28,30). Multiple agonists were used to induce aggregation. Three studies determined thromboxane B2 in plasma or urine (19,22,28), which is a stable metabolite of thromboxane A2. Five studies used the platelet function analyzer (PFA) 100 system (Dade Behring, Deerfield, Illinois, USA), which measures in vitro shear-stress-induced platelet activation in terms of platelet occlusion of a membrane coated with platelet agonists (18,20,23,26,27). In three studies platelet function was assessed with the

Ultegra/Verify Now rapid platelet function assay (RPFA, Accumetrics, San Diego, California, USA), which measures changes in light transmittance related to the rate of aggregation, using a disposable cartridge with fibrinogen-coated beads and a platelet activator (29-31). Three studies employed other techniques (16,17,28). Follow-up ranged from 6-8 hours (CK-MB elevation) to more than 7.5 years (27,29).

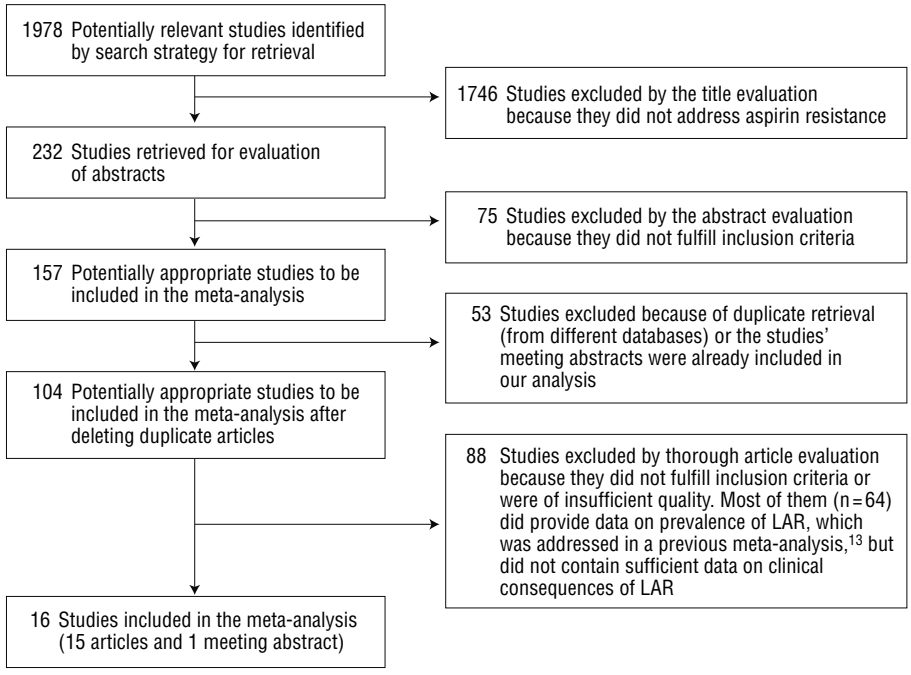

Figure 1 - Flowchart of the process of study selection

Table 1 - Details of included studies

Investigators	Design	Population, *n*	Aspirin dose (mg/d)	Assessment aspirin resistance	Outcome
Grotemeyer *et al.*, 1993[16]	Prospective cohort	Stroke 180	1500mg	Platelet reactivity index > 1.25, using a technique reflecting platelet activation following blood sampling[37]	CV death, MI, stroke
Buchanan *et al.*, 2000[17]	Prospective cohort	CABG 289	325mg	Variation coefficient bleeding time < 26% with and without aspirin	(1)Death, MI, stroke, graft occlusion
Andersen *et al.*, 2002[18]	Prospective cohort	CAD 71	160 mg	PFA-100 CEPI-CT ≤ 196s	Non-fatal MI, stroke, revascularization
Eikelboom *et al.*, 2002[19]	Nested case-control of HOPE study[38;39]	CV disease 488 cases 488 controls	Not reported	Urinary TxB_2: 4th quartile (most platelet activation) least sensitive	CV death, MI, stroke
Grundmann *et al.*, 2003[20]	Case-control	Stroke 35 cases 18 controls	100mg	PFA-100 CEPI-CT ≤ 165s	Stroke, transient ischemic attack
Gum *et al.*, 2003[21]	Prospective cohort	CV disease 326	325mg	LTA ≥ 70% (10 µmol/L ADP) and ≥ 20% (0.5 mg/mL AA)	CV death, MI, stroke
Cotter *et al.*, 2004[22]	Prospective cohort	CAD 73	100mg	Plasma-TxB_2 > lowest value found in aspirin non-users	CV death, MI, stroke, CV-related admission
Cheng *et al.*, 2005[31] (abstract)	Prospective cohort	CAD 422	80-300mg	RPFA ARU ≥ 550	Death, MI, stroke, admission for unstable angina
Pamukcu *et al.*, 2006[23]	Prospective cohort	CAD 105	100-300mg	PFA-100 CEPI-CT < 186s	CV death, MI, stroke, unstable angina
Stejskal *et al.*, 2006[24]	Prospective cohort	CAD 103	100mg	LTA ≥ 5% (spontaneous) or ≥ 53% (3µmol/L cationic propyl gallate)	MI, stroke, unstable angina
Mueller *et al.*, 1997[25]	Prospective cohort	PAD/ PTA 100	100mg	LTA (10 and 5 µmol/L ADP and 5 and 2 µg/mL collagen), on average > 80% of baseline	Reocclusion
Ziegler *et al.*, 2002[26]	Prospective cohort	PAD/ PTA 52	100mg	PFA-100 CEPI-CT ≤ 170s	Restenosis, reocclusion
Yilmaz *et al.*, 2005[27]	Case-control	CABG 14 cases 14 controls	Cases: 189 ± 100 mg, Co: 214±90mg	PFA-100 CEPI-CT ≤ 193s	Graft occlusion
Poston *et al.*, 2006[28]	Prospective cohort	CABG 225	325mg	2 of 3: TEG (0.5 µmol/L AA) > 50%, LTA (1 and 5µg/mL collagen) > 50%, Plasma-TxB_2 >25% of baseline	Graft occlusion
Chen *et al.*, 2004[29]	Prospective cohort	PCI 151	80-300mg	RPFA ARU ≥ 550	Myonecrosis (CK-MB > 16 U/L)
Lev *et al.*, 2006[30]	Prospective cohort	PCI 150	81-325mg	2 of 3: LTA ≥ 70% (10 µmol/L ADP), LTA ≥ 20% (0.5 mg/mL AA), RPFA ARU ≥ 550	Myonecrosis (CK-MB > 5.0 ng/mL)

Table 1 continued - Details of included studies

Follow-up time	Resistance, *n* (%)	Clinical consequences, resistant vs. non-resistant patients	Comments
2 years	60 (33%)	24/60 (40%) vs. 5/114 (4%) OR 14.5, 95%CI 5.2-40-9, *p*<0.0001	- Very heterogeneous distribution of withdrawals - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
2 years	158 (55%)	15/158 (10%) vs. 9/131 (7%) OR 1.4, 95%CI 0.6-3.4, *p*=0.421	- Bleeding time poorly established for this goal - Low event rates - Resistance determined once
4 years	25 (35%)	9/25 (36%) vs. 11/46 (24%) OR 1.8, 95%CI 0.6-5.2, *p*=0.280	- Small groups, no exclusion criteria (confounding) - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
5 years	Not reported	Proportions not reported Reported OR upper vs. lower quartile = 1.8, 95%CI = 1.2-2.9, *p*=0.009	- Confounders cases/controls: Diabetes, body mass index, tension, peripheral artery disease - TxB_2 could be influenced by recent events - Resistance determined once, adherence not assessed
> 2 years	12 (23%)	Cases vs. controls: 12/35 (34%) vs. 0/18 (0%) resistant OR 6.8, 95%CI 1.8-26.2, *p*=0.004	- Small sample size - Aspirin resistance cause or result of events? - Resistance determined once, adherence not assessed
679 ± 137 days	17 (5%)	4/17 (24%) vs. 30/309 (10%) OR 2.9, 95%CI 0.9-9.3, *p*=0.088	- Few patients resistant, few events - Follow-up time not specified for aspirin response - Resistance determined once, adherence not assessed
1 year	21 (29%)	6/21 (29%) vs. 3/52 (6%) OR 6.5, 95%CI 1.5-29.3, *p*=0.014	- Small groups, no exclusion criteria (confounding) - Resistance determined once
Not reported	113 (27%)	Proportions not reported Reported hazard ratio 2.9, 95%CI 1.5-5.7, *p*=0.002	- Follow-up time and absolute event rates not reported - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
1 year	20 (19%)	9/20 (45%) vs. 10/85 (12%) OR 6.1, 95%CI 2.0-18.5, *p*<0.001	- Subjective endpoint (unstable angina) - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
4 years	57 (55%)	50/57 (88%) vs. 21/46 (46%) OR 8.5, 95%CI 3.2-22.7, *p*<0.0001	- Subjective endpoint (unstable angina) - Adherence not assessed - Adjudication endpoints unblinded
1.5 years	65 (65%) (after 4 weeks)	8/65 (12%) vs. 0/35 (0%) OR 10.5, 95%CI 0.6-187.5), *p*=0.048	- Reasons for exclusion not mentioned - All patient were sensitive with AA-aggregometry, making recurrence rates less related to resistance - Adjudication endpoints unblinded
1 year	5 (10%)	0/5 (0%) vs. 13/47 (28%) OR 0.2, 95%CI 0.0-4.5, *p*=0.314	- Small sample size, few non-responders - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
Cases: 7.5± 3.9 yrs, Co: 6.2±2.5 yrs	8 (29%)	Cases vs. controls: 7/14 (50%) vs. 1/14 (7%) resistant OR 13.0, 95%CI 1.3-128.1, *p*=0.033	- Most cases had acute coronary syndrome at presentation vs. stable angina in control subjects - Resistance determined once, adherence not assessed
30 days	22 (10%) (on day 1)	4/22 (18%) vs. 12/203 (6%) OR 3.5, 95%CI 1.0-12.1, *p*=0.057	- Very low event rates - Adherence not assessed
6-8 hours after PCI	29 (19%)	15/29 (52%) vs. 30/122 (25%) OR 3.3, 95%CI 1.4-7.6, *p*=0.004	- Asian population - Resistance determined once, adherence not assessed - Adjudication endpoints unblinded
20-24 hours after PCI	19 (13%)	7/18 (38.9%) vs. 23/126 (18.3%) OR 2.9, 95%CI 1.0-8.1, *p*=0.045	- CK-MB values not available for 6 patients - Adjudication endpoints unblinded

Abbreviations: AA: arachidonic acid; ADP: adenosine diphosphate; ARU: aspirin response unit; CABG: coronary artery bypass graft; CAD: coronary artery disease; CEPI-CT: collagen epinephrine closure time; CI: confidence interval; CK-MB: creatine kinase-myocardial band, CV: cardiovascular; LTA: light transmission aggregometry; MI: myocardial infarction; OR: odds ratio; PAD: peripheral artery disease; PCI: percutaneous coronary intervention; PFA-100: platelet function analyzer-100; PTA: percutaneous transluminal angioplasty, RPFA: rapid platelet function assay; TEG: thrombelastography; TxB_2: thromboxane B_2.

Relation between laboratory aspirin resistance and cardiovascular outcome

Prevalence of laboratory aspirin resistance ranged from 5 to 65% (21,25). In the 12 studies eligible for pooling (16-18,21-26,28-30), totally including 1813 patients, the mean prevalence of aspirin resistance was 27%. The total variation between these studies, likely reflecting aforementioned differences, was 49%, resulting in a significant statistical heterogeneity among studies (p=0.03).

Odds ratios of cardiovascular outcome varied from 0.2 (95%CI 0.0-4.5) to 14.5 (95%CI 5.2-40.9) for aspirin resistance (16,26). We pooled the odds ratios of several groups of studies, which is graphically presented in Figure 2. When studies with clinical cardiovascular endpoints are pooled (16-18,21-24), the resultant odds ratio for aspirin resistance is 4.4 (95%CI 2.2-8.7). In three cohort studies addressing (re) occlusion after interventional procedures (25,26,28), the pooled odds ratio is 2.4 (95%CI 0.4-14.3). The odds ratio of myonecrosis is 3.1 (95%CI 1.6-6.0) (29,30). When all these studies are combined, the pooled odds ratio of cardiovascular outcome is 3.8 (95%CI 2.3-6.1) for aspirin resistance. We also stratified for used aspirin dosage, however, no differences between dosage groups (≤100 mg, 101-299 mg and ≥300 mg) were found. The studies not included in the analysis, for not being a cohort study or not reporting proportions of resistant and non-resistant patients, showed similar results (Table 1) (19,20,27,31).

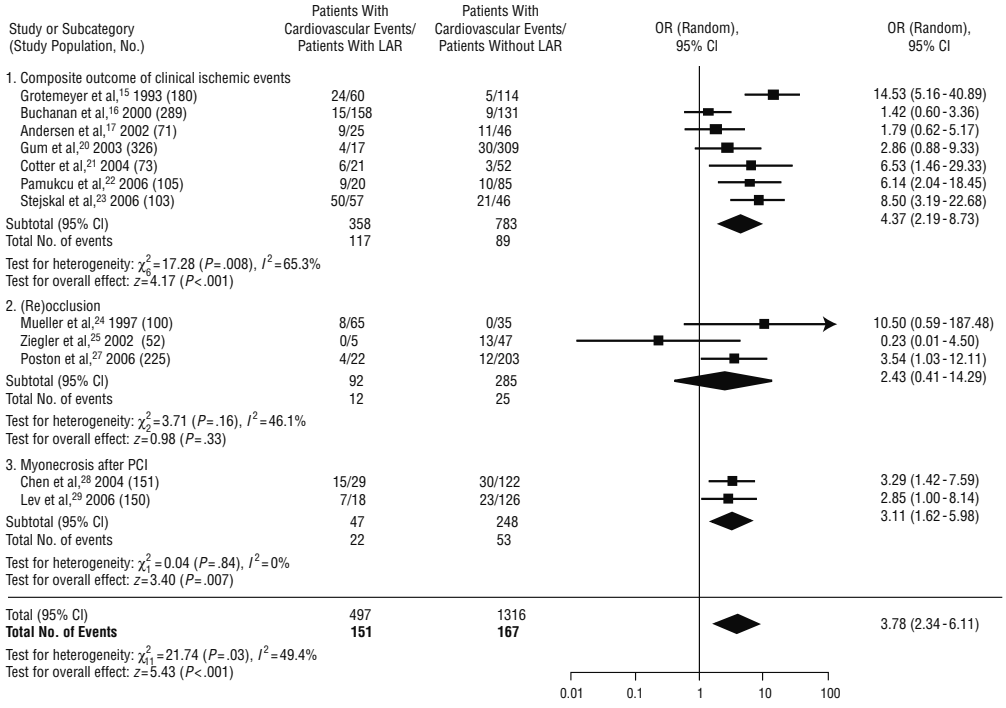

Figure 2 - Forest plots of odds ratios of cardiovascular outcome for aspirin resistance from eligible studies. In part 1, all studies with clinical cardiovascular endpoints (cardiovascular death, myocardial infarction, stroke, acute coronary syndrome and revascularization) are plotted; in part 2 studies reporting on (re)occlusion after bypass grafting or angioplasty; and in part 3 studies providing data on occurrence of myonecrosis represented by creatine kinase-myocardial band (CK-MB) elevation after percutaneous coronary intervention. In last, all studies on these cardiovascular outcomes are pooled.

Discussion

We conducted a systematic review and meta-analysis in order to quantify evidence regarding the question whether patients with laboratory-defined aspirin resistance have a higher risk of recurrent cardiovascular events. We showed that patients with laboratory aspirin resistance had an increased risk of cardiovascular events. Among studies eligible for meta-analysis, the pooled odds ratio of cardiovascular outcome was 3.8 (95%CI 2.3-6.1) and the studies not included in the analysis showed similar results (19;20;27;31).

The studies in our systematic review varied in many ways. The patients included in the studies suffered from different cardiovascular diseases and were afflicted with a variety of risks of recurrent events. Furthermore, studies differed in used aspirin dosage, follow-up time, laboratory methods to establish the effects of aspirin and definition of outcome. Despite these clinical and methodological diversities, 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, which partly accounts for the heterogeneity between the studies (14). Beside these heterogeneities, several methodological limitations of included studies require comment. In a majority of studies, endpoints were not adjudicated blinded for aspirin resistance, making them more susceptible for bias (16;18;23-26;29-31). In one study 45 patients were excluded for reasons that were not mentioned (25), and in another study allocation to either aspirin or clopidogrel was not randomized but based on complaints (26). Moreover, use of NSAIDs, which may have differed between studies as it was no formal exclusion criterion in nine studies (16-19;22;26-28;30;31), could have influenced the prevalence of aspirin resistance (32-34). Furthermore, aspirin resistance was only determined at a singular occasion in all but four studies (24;25;28;30), which may have lead to misclassification. E.g., persistent platelet reactivity may be more common after coronary artery bypass grafting, due to increased platelet turnover (35). This temporal ‘resistance’ was recently observed in a coronary bypass population (28). Though non-compliance is an important cause of aspirin resistance (22;36), patient adherence was assessed only in three studies

(17;22;25). Some have suggested that after exclusion of non-adherent patients, aspirin resistance is no longer related to recurrent events (22).

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 capable 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 clinical consequences of aspirin resistance in patients with cardiovascular disease. In contrast, previous reviews included only selected studies on clinical consequences of aspirin resistance. Many individual studies were 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 may be influenced by several forms of bias. We however tried to minimize selection bias by applying no formal language restriction and including both full-text articles and meeting abstracts. Furthermore, in a funnel plot there was no inverse relationship between size of individual studies and odds ratios of cardiovascular outcomes, which argues against existence of publication and reporting bias. However, bias these forms of bias could not be completely excluded due to the relatively small number of included studies. Moreover, we assumed aspirin resistance to be categorical variable. This may not be the case since there is no standardized definition of aspirin resistance. However, even when 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 relation might differ.

In conclusion, our systematic review and meta-analysis indicate that laboratory aspirin resistance is a clinically important phenomenon. Patients biochemically labeled aspirin resistant are likely to be also “clinically resistant” as they exhibit a strongly increased risk of recurrent cardiovascular events, compared with patients that are labeled sensitive. As cardiovascular diseases are very prevalent and associated with large mortality and morbidity, there is a clear need for future studies to thoroughly evaluate individual determinants of aspirin resistance, predictive value of the various laboratory methods and possible solutions for individual patients.

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Appendix 1

Predefined Search Terms for Electronic Databases

Medline

((“aspirin”[MeSH] OR aspirin OR aspirin* OR Acetylsalicylic Acid OR salicylate* OR salicylic*) AND (resistance OR resistant OR failure OR failing OR nonrespon* OR nonrespon*) AND (clinical consequences OR clinical consequence OR clinical implications OR clinical implication OR incidence OR prevalence OR “Treatment Outcome”[MeSH] OR “Outcome Assessment (Health Care)”[MeSH]) NOT (“insulin resistance*” OR insulin resistance)) OR ((“aspirin resistance” OR “aspirin failure” OR ((aspirin/administration and dosage OR aspirin/therapeutic use OR aspirin) AND drug resistance) OR ((resistance[title word] OR resistant[title word] OR failing[title word] OR failure[title word] OR “non responsiveness”[title word] OR non-responders[title word] OR non-response[title word] OR nonrespon*[title word]) AND aspirin[title word])) NOT “insulin resistance”)

Embase

(aspirin resistance OR ASA resistance OR aspirin failure OR resistance to aspirin).af OR ((*Acetylsalicylic Acid/ OR aspirin.ti) AND (drug resistance/ OR drug resistance.mp)) OR ((resistance.ti OR resistant.ti OR failing.ti OR failure.ti OR non responsiveness.ti OR nonrespon$.ti OR nonrespon$.ti) AND (aspirin.ti or Acetylsalicylic Acid.ti) NOT heart failure.mp)

Cochrane Central Register of Controlled Trials (Central)

(“aspirin resistance” OR “aspirin failure” OR “ASA resistance”) in All Fields OR (aspirin AND (resistance OR resistant OR failing OR failure OR “non responsiveness” OR nonresponders OR non-response OR nonrespon*)) in Record Title NOT (“insulin resistance” OR “heart failure”) in All Fields

Web of science

ti=((aspirin resistance OR aspirin failure OR resistance to aspirin OR (aspirin same resistance) OR (aspirin same failure))) NOT ts=(heart failure OR insulin resistance)