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### **Clopidogrel non-responsiveness and risk of cardiovascular morbidity. An updated meta-analysis**

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# Clopidogrel non-responsiveness and risk of cardiovascular morbidity

## An updated meta-analysis

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### Summary

We performed this meta-analysis to update the clinical evidences on the relation between clopidogrel non-responsiveness and clinical outcomes in patients with coronary artery disease (CAD) who underwent percutaneous coronary intervention. An electronic literature search through MEDLINE, EMBASE, Web of Science, and the Cochrane Library and bibliographies of retrieved articles up to January, 2009 was conducted. Studies were included if they had a cohort prospective design, if they analysed clopidogrel responsiveness in CAD patients in relation to death and/or occurrence of adverse coronary events during follow-up, and if they reported an adequate statistical analysis. Fourteen studies, totalling 4,564 CAD patients followed for a time ranging from 14 days to one year, were included. The cumulative analysis reported that residual platelet reactivity despite clopidogrel treatment was significantly associated with an increased risk of death and/or thrombotic

recurrences (odds ratio [OR] 5.67, 95% confidence interval [CI] 2.97 to 10.84;  $p < 0.00001$ ). However, four studies contributed to a consistent heterogeneity of the model and evidenced a significant risk of publication bias, so were excluded from the analysis. This exclusion, however, did not influence the overall result, by confirming the increased risk of cardiovascular recurrences for patients with a poor response to clopidogrel treatment (OR 3.58, 95%CI 2.54 to 5.05;  $p < 0.00001$ ). The present updated meta-analysis documents a significant association between residual platelet reactivity under clopidogrel treatment and recurrent cardiovascular events, so suggesting the relevance of ongoing interventional studies aimed at tailoring the antithrombotic therapy in CAD patients.

### Keywords

Clopidogrel, antiplatelet therapy, clinical recurrences, meta-analysis

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## Introduction

Large clinical trials have shown that clopidogrel significantly reduces the risk of recurrent cardiovascular events in patients with coronary artery disease (CAD) (1–5). Indeed, the standard care of patients with acute coronary syndromes who underwent percutaneous coronary intervention (PCI) is, to date, the dual therapy with aspirin and clopidogrel, that has been reported to significantly decrease the occurrence of death, myocardial infarction, and stroke compared with the use of aspirin alone (1–5). Nevertheless, a wide individual variability in response to antiplatelet medications has been recently reported (6). Furthermore, an increasing amount of data on the relation between non-responsiveness to antiplatelet therapy and clinical recurrences has been reported (7, 8). Residual platelet reactivity despite aspirin treatment has been showed to be associated with an increased risk of coronary recurrences (7). Likewise, studies reporting a similar association with clopidogrel non-responsiveness have been published (9–22). Re-

cently, Snoep et al. systematically reviewed the studies investigating the association between clopidogrel non-responsiveness and clinical outcome, by evidencing an increased risk of clinical recurrences for those with residual platelet reactivity under clopidogrel treatment (8). However, some relevant studies on this issue from then to date have been published (19–22). Therefore, we aimed this study to update the clinical evidences on the relation between clopidogrel non-responsiveness and clinical outcomes in patients with CAD who underwent PCI.

## Methods

We carried out an electronic search of MEDLINE (from 1966 to January 2009), EMBASE (from 1974 to January 2009), Science Citation Index (from 1994 to January 2009), and the Cochrane Central Register of Controlled Trials to seek for studies that investi-

gated the possible association between poor response to clopidogrel therapy and clinical events. The search was performed using a combined text word and MeSH search strategy of the terms. Relevant keywords relating to clopidogrel therapy (“clopidogrel” or “plavix” or “iscover”) were used in combination with words relating to responsiveness to the therapy (“resistance” or “resistant” or “failure” or “nonrespon\*” or “non-respon\*” or “low respon\*” or “low-respon\*”) and to the clinical consequences (“clinical consequences” or “clinical consequence” or “cardiovascular events” or “adverse events” or “recurrences” or “major adverse cardiac events” or “stent thrombosis” or “prognosis” or “outcome”). We used no language restrictions. Furthermore, we identified original articles by back-referencing from reviews, and relevant studies. We assessed the relevance of studies by using a hierarchical approach based on title, abstract, and the full manuscript.

## Inclusion criteria

We included studies that met the following criteria: (a) cohort prospective design, in which clinical outcomes in “non-responder” patients were compared with outcomes in “responder” patients; (b) patients were receiving clopidogrel therapy at the time of the index event; (c) patients were classified prospectively as clopidogrel “non-responders” or “responders” before the ascertainment of any clinical outcome; (d) definition of non-responsiveness to clopidogrel was clearly reported; (e) a measure of prospective clinical

outcome was used in both groups of patients; (f) relative risk, hazard ratio, or odds ratio (OR) and their corresponding 95% confidence intervals (CI) (or data to calculate them) were reported.

## Outcome measures

Outcomes of interest for the current meta-analysis were major adverse cardiac events (MACE), defined as any cardiovascular event (fatal and non-fatal myocardial infarction, stroke, unstable angina), death from cardiovascular causes, ischaemic recurrences (symptoms compatible with recurrent ischaemia needing new hospitalisation and coronarography), stent thrombosis occurred in CAD patients under antiplatelet therapy during follow-up.

## Data collection

All data were independently extracted by two investigators (F.S., and R.M.) through the use of a standardised data extraction tool and entered into separate databases. Results were compared, and disagreements were resolved by discussion with a third investigator (A.M.G.). The inter-observer agreement for the study selection was 0.92. For each contributing study, the following information was abstracted: leading author’s name, year of publication, age, gender, number of patients, aspirin and clopidogrel dosages, duration of follow-up, time of determination of response to clopidogrel, methods used to determine the response to the therapy and definition of clopidogrel “resistance”, number of patients with clinical events according to the quality of response to clopidogrel, OR or relative risk (RR) of cardiovascular recurrences and corresponding 95% CI, and adjustment for potential confounders.

## Statistical analysis

We pooled results from the individual studies by using Review Manager (RevMan) software for Macintosh (version 5.0) by the Cochrane Collaboration, and Statistical Package for Social Sciences (SPSS) software for Windows (version 13.0). The  $\kappa$  statistic was used to assess agreement between reviewers for study selection. The results of each study were reported as OR, RR, or dichotomous frequency data. When available, we used the results of the original studies from multivariable models with the most complete adjustment for potential confounders; the confounding variables included in this analysis are shown in Table 1. We used a random-effects model which accounts for inter-study variation and provides a more conservative effect than the fixed model. Thus, we calculated random-summary OR with 95% CI, by using inverse-variance method. The potential sources of heterogeneity were assessed by using the Cochrane’s  $Q$  test to assess between-study differences and the  $I^2$  statistic to quantify the proportion of inconsis-

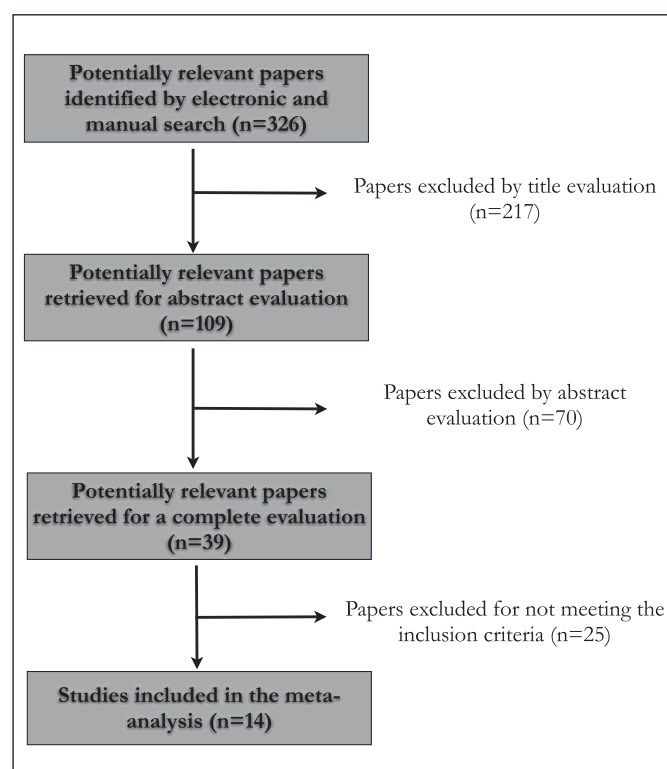


Figure 1: Flow chart of search strategy.

Table 1: Characteristics of studies included in the meta-analysis.

Source, year (reference)	Patients, n (age) Gender, n	Aspirin and clopidogrel doses (mg)	F-UP	Definition of residual platelet activity	Time of determination	Outcome, n	Cases / re-responders	Cases / non-responders	OR (95%CI)	Adjustment
Muller et al., 2003 (9)	105 CAD (age: ~ 60) 75M; 30F	Aspirin: 100 Clopidogrel: LD 600; MD 75	14 d	LTA (5, 20 $\mu$ M ADP) <10% reduction compared to baseline	4 h after LD	Subacute stent thrombosis (n=2)	0 / 93	2 / 12	44.5 (9.99–991.7)	None
Matetzky et al., 2004 (10)	60 STEMI (mean age: 58) 48M; 12F	Aspirin: LD 300; MD 200 Clopidogrel: LD 300; MD 75	6 m	LTA (5 $\mu$ M ADP) 1 <sup>st</sup> quartile of reductions compared with baseline	6 h after LD	MACE (n=8)	1 / 45	7 / 15	38.5 (4.15–357)	None
Gurbel et al., 2005 (11)	192 CAD (age: ~ 60) 108M; 84F	Aspirin: LD 325; MD: 75 Clopidogrel: LD 300 (n=75), LD 600 (n=60); MD 75	6 m	LTA (20 $\mu$ M ADP) 4 <sup>th</sup> quartile (>72%) compared to 1–3 quartiles	24 h after LD	MACE (n=38)	23 / 144	15 / 48	2.39 (1.12–5.09)	None
Cuisset et al., 2006 (12)	106 ACS (mean age: 64.2) 82M; 24F	Aspirin: 160 Clopidogrel: LD 300; MD 75	1 m	LTA (10 $\mu$ M ADP) 4 <sup>th</sup> quartile (>70%) vs. 1–3 quartiles	12 h after LD	MACE (n=12)	9 / 23	3 / 83	41.6 (4.74–364)	Age, gender, CV risk factors, heart rate, systolic blood pressure, treatment, CRP and P-selectin
Cuisset et al., 2006 (13)	292 ACS (mean age: 64.2) 222M; 70F	Aspirin: 160 Clopidogrel: LD 300 (n=146), 600 (n=146); MD 75	1 m	LTA (10 $\mu$ M ADP) >70%	12 h after LD	MACE (300 mg: n=18) (600 mg: n=7)	6 / 256 300 mg 1 / 256 600 mg	12 / 36 300 mg 6 / 22 600 mg	300 mg: 9.93 (3.19–30.90) 600 mg: 43.16 (4.89–381.10) Together: 13.82 (5.30–36.04)	Age, gender, CV risk factors, troponin elevation, ST-segment changes, LVEF, tirofiban use
Geisler et al., 2006 (14)	363 CAD (mean age: 67.5) 277M; 86F	Aspirin: 100 Clopidogrel: LD 600; MD 75	3 m	LTA (20 $\mu$ M ADP) >70%	12 h after LD	MACE (n=29)	23 / 341	6 / 22	3.71 (1.08–12.69)	Age, gender, diabetes, smoking habit, hypertension, LV dysfunction, prior ACS
Hochholzer et al., 2006 (15)	802 CAD (age: ~ 65) 627M; 175F	Aspirin: 100 Clopidogrel: LD 600; MD 75	1 m	LTA (5 $\mu$ M ADP) > median (14%)	At least 2 h after LD	MACE (n=15)	2 / 401	13 / 401	9.6 (2.1–44.3)	Age, smoking habit, hypertension, diabetes, non-left anterior descending PCI, diameter stenosis, time from clopidogrel loading
Buonamici et al., 2007 (16)	804 ACS (age: ~ 70) 602M; 202F	Aspirin: 325 Clopidogrel: LD 600; MD 75	6 m	LTA (10 $\mu$ M ADP) $\geq$ 90 <sup>th</sup> percentile of controls (70%)	12–18 h after LD	Stent thrombosis (n=25)	16 / 699	9 / 105	3.08 (1.32–7.16)	Age, previous MI, AMI, multivessel disease, total chronic occlusion, total stent length, LVEF, bifurcation lesion

Table 1: Continued

Source, year (reference)	Patients, n (age) Gender, n	Aspirin and clopidogrel doses (mg)	F-UP	Definition of residual platelet activity	Time of determination	Outcome, n	Cases / re-sponders	Cases / non-responders	OR (95%CI)	Adjustment
Frere et al., 2007 (17)	195 ACS (age: ~ 65) 158M; 37F	Aspirin: 75 Clopidogrel: LD 600; MD 75	1 m	LTA (10 µM ADP) >70%	18 h after LD	MACE (n=14)	3 / 130	11 / 65	8.62 (2.31–32.15)	None
Blindt et al., 2007 (18)	99 ACS (age: ~ 65) 74M; 25F	Aspirin: 100 Clopidogrel: LD 600 (only in case of emergency PCI; MD 75	6 m	VASP phosphorylation >48%	72–96 h after LD	Stent thrombosis (n=9)	n.d.	n.d.	1.16 (1.01–1.33)	Acute MI, ADP, main lesion length, n° of stents implanted, total stent length, maximal stent length
Price et al., 2008 (19)	317 ACS (mean age: 68) 292M; 84F	Aspirin: 325 Clopidogrel: LD 600; MD 75	6 m	VerifyNow P2Y12 PRU >235	12 h after LD	MACE (n=9)	2 / 209	7 / 108	7.17 (1.46–35.17)	None
Patti et al., 2008 (20)	160 ACS (mean age: 66) 129M; 31F	Aspirin: n.d. Clopidogrel: LD 600; MD 75	1 m	VerifyNow P2Y12 4 <sup>th</sup> quartile of PRU compared to 1–3 quartiles	8 h and 24 h after intervention	MACE (n=15)	7 / 120	8 / 40	6.1 (1.1–18.3)	Age, LVEF, glycoprotein IIb/IIIa, statin therapy
Wang et al., 2008 (21)	386 CAD (mean age 68.8) 257M; 129F	Aspirin: 300 Clopidogrel: LD 75	12 m	LTA (20 µM ADP) ≤10% of difference between aggregation at baseline and 24 h after LD	Baseline and 24 h after LD	MACE (n=31)	20 / 321	11 / 65	2.44 (1.09–5.45)	Age, gender, smoking habit, diabetes, prior CABG, MI, and PCI, renal failure, EF<30%
Marcucci et al., 2009 (22)	683 ACS (mean age: 69) 517M; 166F	Aspirin: LD 500; MD: 100–325 Clopidogrel: LD 600; MD 75	12 m	VerifyNow P2Y12 4 <sup>th</sup> quartile (PRU >258) compared to 1–3 quartiles	24 h after LD	MACE (n=51)	22 / 464	29 / 219	3.6 (1.5–9.1)	Age, CV risk factors, renal failure, LVEF <40%, multivessel disease, total stent length, bifurcation lesions, number of lesions treated and type of stent, GpIIb/IIIa

CAD, coronary artery disease; LD, loading dose; MD, maintenance dose; LTA, light-transmission aggregometry; ADP, adenosine diphosphate; STEMI, ST-elevation myocardial infarction; MACE, major adverse cardiac events; ACS, acute coronary syndromes; CV, cardiovascular; CRP, C-reactive protein; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; MI, myocardial infarction; AMI, acute myocardial infarction; VASP, vasodilator-stimulated phosphoprotein; CABG, coronary artery bypass graft.

ency across the study results. Sensitivity analyses were performed in order to determine the source of heterogeneity, according to the main characteristics of the study (loading dose of clopidogrel: 300–600 mg; duration of follow-up: <6 months–≥6 months; method used to determine clopidogrel non-responsiveness: LTA – VerifyNow; adjustment for potential confounders: yes – no). Publication bias was assessed using a funnel plot of effect size against standard error.

## Results

Database searches yielded 326 references. Exclusion of irrelevant references by title evaluation left 109 papers. After abstract evaluation additional 70 references were excluded. Moreover, after a detailed review other 25 articles were excluded because they did not fulfil our inclusion criteria. At the end of our review process 14 studies were included in the final analysis for a total of 4,564 patients (► Fig. 1). Characteristics of the included studies are presented in ► Table 1. Five studies included CAD patients (stable angina, chronic CAD) (9, 11, 14, 15, 21) while the remaining com-

prised only acute coronary syndrome patients (10, 12, 13, 16–20, 22).

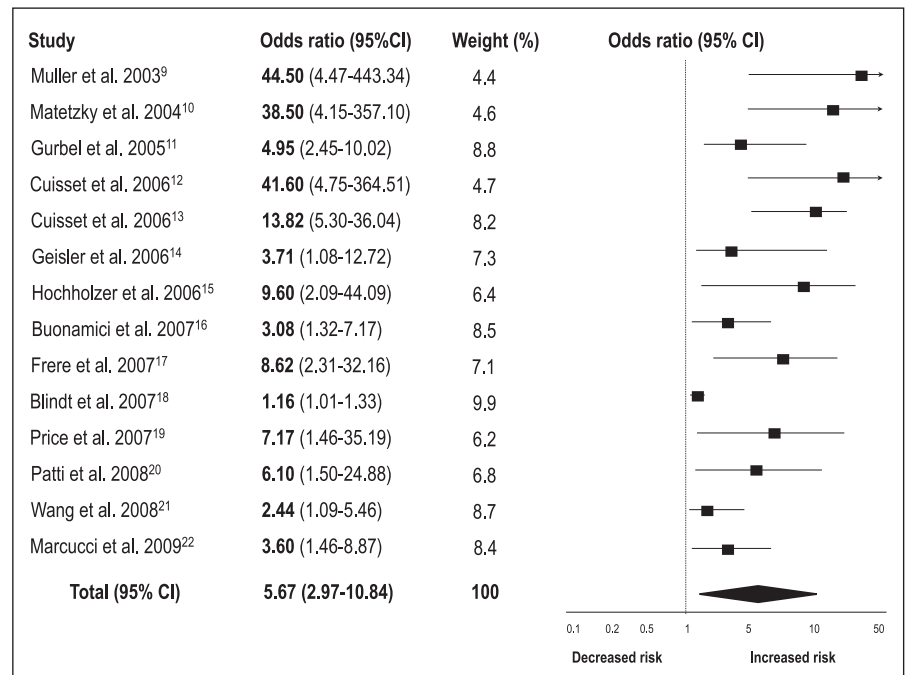
The number of participants ranged from 60 to 804, with a significantly higher prevalence of males (n=3,468; 75.9%) than females (n=1,096) and a follow-up period that ranged from 14 days to one year.

All patients were treated with aspirin with a daily dose that ranged from 75 to 325 mg. Four studies included a loading dose of

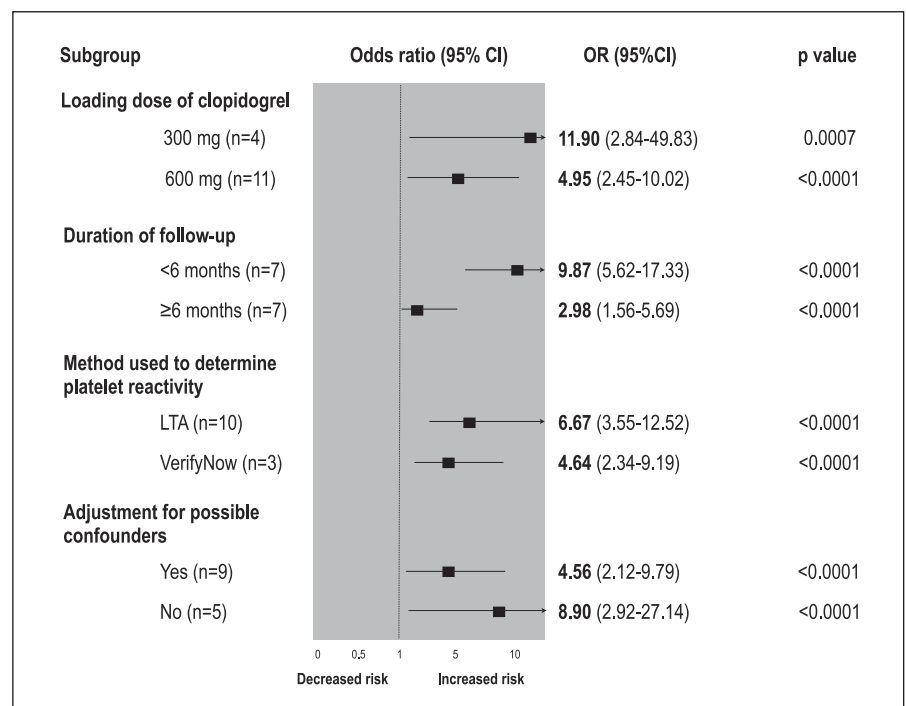
clopidogrel of 300 mg (10–13), 11 studies of 600 mg (9, 11, 13, 14–20, 22), while only one study reported a loading dose of 75 mg (21). As for the maintenance dose all the studies included a dose of 75 mg/day of clopidogrel.

A variety of assays were used to assess response to clopidogrel therapy. These included light transmission aggregometry (LTA) with the use of adenosine diphosphate as agonist with different concentration in most of them (n=10) (9–17,21), point-of-care

**Figure 2: Overall summary estimates of odds ratios and 95% confidence intervals (CI) for major adverse cardiac events in men and women with and without clopidogrel non-responsiveness.** Squares represent the effect size; extended lines, 95% CI; diamond, total effect size



**Figure 3: Sensitivity analyses on basis of dose of clopidogrel, duration of follow-up, method of diagnosis, adjustment for potential confounders.** Squares represent the effect size; extended lines, 95% confidence intervals (CI).



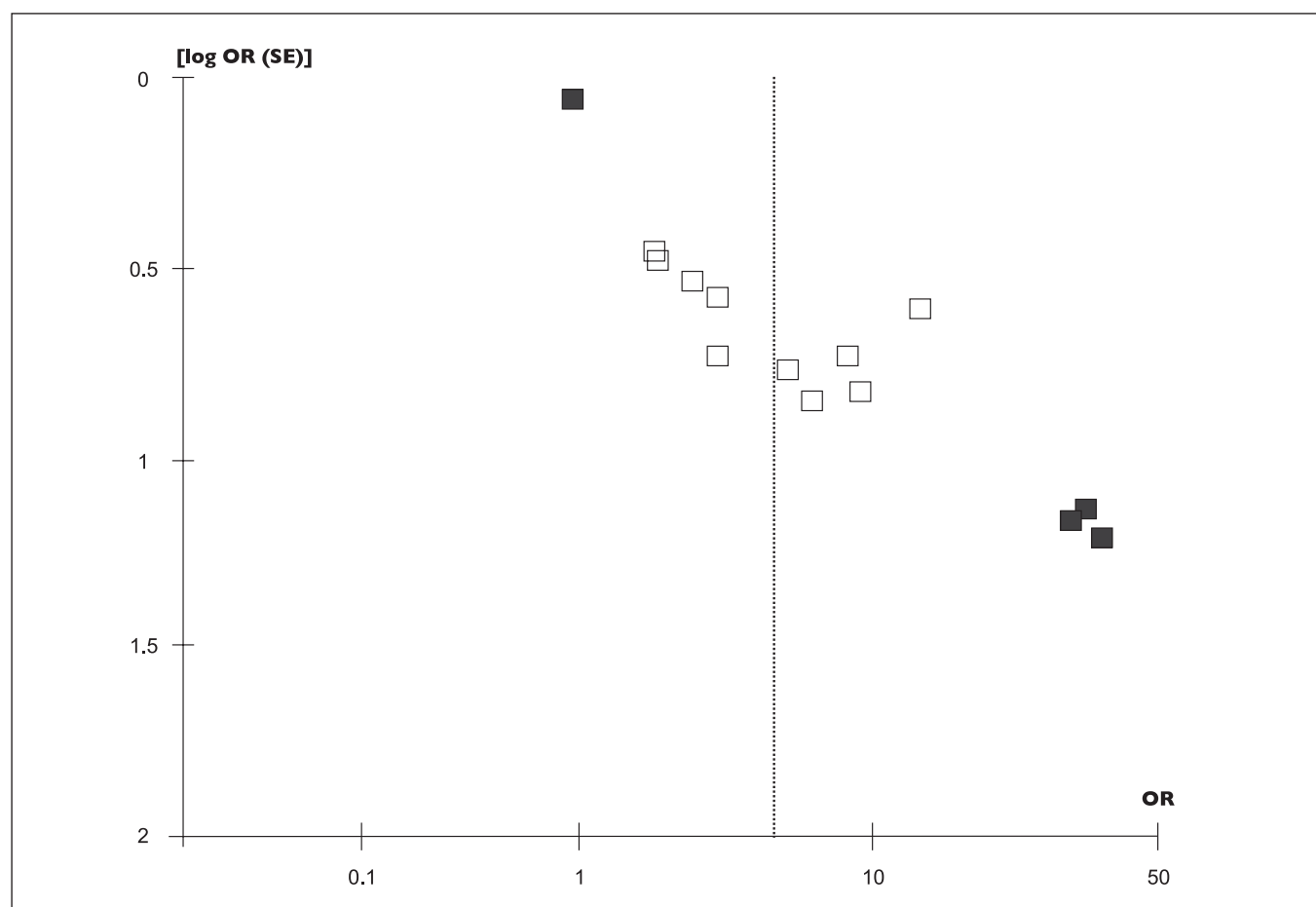
testing in three studies (19, 20, 22), and vasodilator-stimulated phosphoprotein (VASP) in one paper (18).

Overall, 1,205 out of the 4,564 patients (26.4%) were classified as clopidogrel non-responders and the remaining 3,359 (73.6%) as clopidogrel responders.

The OR under a random-effects model for cardiovascular recurrences associated with a poor response to clopidogrel in each study and overall is shown in ► Figure 2. Compared to patients showing an optimal response to antiplatelet treatment, patients with persistent platelet reactivity despite antiplatelet treatment had a significantly higher risk of death and/or ischaemic recurrences (OR 5.67, 95% CI 2.97 to 10.84;  $p < 0.00001$ ). However, a consistent degree of heterogeneity was found among the 14 included studies ( $I^2 = 86\%$ ;  $p < 0.00001$ ). All the heterogeneity was explained by studies with large RR and low number of patients and by an outlier study, that, by itself, greatly contributed (40%) to the heterogeneity of the model (9, 10, 12, 18). This paper by Blindt et al. is the only study that evaluated platelet reactivity through the VASP phosphorylation (18). But excluding these studies, indeed, the heterogeneity disappeared ( $I^2 = 0\%$ ;  $p = 0.5$ ) while the estimate of association only slightly decreased by remaining significantly associated with an increased risk of adverse clinical cardiac events (OR 3.58, 95% CI 2.54 to 5.05;  $p < 0.00001$ ).

Sensitivity analyses performed after stratification of the studies into the different variables showed statistically significant results, demonstrating that characteristics of the studies (loading dose of clopidogrel, duration of follow-up, method used to determine clopidogrel response, adjustment for potential confounders) did not influence the overall results of the meta-analysis (► Fig. 3). However, it should be noted that a greater estimate of association for some characteristics of the studies, such as a lower loading dose of clopidogrel (300 mg), a shorter period of follow-up (<6 months), or a method for determining platelet aggregation (LTA) can be detected with respect to their counterparts.

In conclusion, to evaluate the possible presence of publication bias among the included studies we performed a funnel plot of effect size versus standard error that reported a slightly asymmetrical visual examination, which is consistent with the conclusion that there were some statistical outliers. We identified these outliers as the studies previously observed to be the causes of the heterogeneity of the model (9, 10, 12, 18). Therefore, we excluded these studies from the analysis and the funnel plot showed no visual examination of publication bias (► Fig. 4).



**Figure 4:** Funnel plot of published studies of clopidogrel non-responsiveness and risk of cardiovascular morbidity. Open squares represent individual studies; black squares represent outlying studies.

## Discussion

The present updated meta-analysis conducted on a total population of over than 4,500 CAD patients who underwent a PCI showed that persistent platelet reactivity despite clopidogrel treatment confers an increased risk of recurrent adverse cardiovascular events. Indeed, patients who were classified as clopidogrel non-responders were at about a five-fold increased risk of non-fatal and fatal cardiovascular recurrences with respect to those classified as responders.

## Clinical context

Clopidogrel, in combination with aspirin, is currently the standard of care for patients undergoing PCI. Clinical trials have shown that, in high-risk patients, prolonged dual antiplatelet treatment is more effective than aspirin alone in preventing MACE (1–6). However, despite the use of such therapy, a considerable number of patients continue to have recurrent thrombotic events (9–22). Previous studies have shown a significant inter-individual variability in platelet response to clopidogrel therapy in patients with CAD, as measured by *ex vivo* platelet function assay, with up to 25% of patients classified as non-responders, and a growing degree of evidence that links the recurrence of adverse cardiac events to a poor response to clopidogrel is available (6, 8). Indeed, numerous clinical studies have demonstrated that clopidogrel non-responsiveness is associated with higher risk of cardiovascular events, including cardiac death and stent thrombosis (9–22). In addition, clopidogrel non-responsiveness has also been associated with a higher incidence of periprocedural myocardial damage, thrombotic complications, and long-term ischaemic events in patients undergoing PCI (23, 24).

A systematic review with meta-analysis on this issue has been recently published by Snoep et al. by reporting, as we do, that laboratory clopidogrel non-responsiveness is a marker of increased risk of adverse cardiovascular outcomes in patients undergoing PCI with stenting (8). In the present meta-analysis we have updated the issue by adding some very recent studies that comprised a considerable number of patients and by including (where available) in the cumulative analysis results obtained from a multivariable model that kept into account possible confounding factors of platelet aggregation. Hence, we have increased the number of the studied patients of the overall analysis and we have likely improved the quality of the included studies. However, despite strict inclusion criteria and in keeping with the previous meta-analysis we have found a statistical heterogeneity among the included studies. This finding could be strictly linked to the various methodological and clinical differences available among the included studies. To date, there is still a degree of uncertainty on how, when, and what consider as clopidogrel responders. There is not an accepted definition, and the timing as well as the methods to be used is not yet fully established.

In order to establish the nature of such heterogeneity we have identified four studies as outliers because of the low number of patients, the very large estimates of association and the possible risk of publication bias (9, 10, 12, 18). However, after exclusion of these studies a positive association between clopidogrel non-responsiveness and an increased risk of clinical recurrences still remained, thus confirming the overall result.

Actually, the mechanisms leading to a poor response to clopidogrel have not been fully elucidated and are considered to involve both acquired and genetic factors. Clopidogrel is a pro-drug, requiring biotransformation to an active metabolite by cytochrome P450 enzymes. The genes encoding these enzymes are polymorphic, and some studies reported some single nucleotide polymorphisms in these cytochromes able to confer reduced enzymatic function (25). Very recent studies showed that in patients with acute coronary syndromes treated with clopidogrel two different variants gene encoding for cytochrome P450 were differently associated with adverse clinical outcomes (26, 27). Moreover, clinical factors such as obesity, insulin resistance, and the nature of the coronary event have been found to contribute to the variability of the clopidogrel response (6). Another possible explanation of the resistance to thienopyridines could be the underdosing rather than in the inability of the drug to depress platelet function. It has been reported, indeed, that platelets of patients who responded poorly to clopidogrel were capable of being inhibited by a more potent thienopyridine such as prasugrel (6).

According to this, results from the different sensitivity analyses, although consistent with the main result of the meta-analysis, support the hypothesis that differences in response to clopidogrel partly depend on some methodological variables such as dosage, period of administration and methods used to determine platelet aggregation. Subgroup analyses, indeed, reported a greater risk of cardiovascular recurrences for patients treated with a lower loading dose of clopidogrel (300 mg vs. 600 mg), with a lesser period of treatment (<6 months vs. >6 months) and in whom platelet aggregation was established by means of a point-of-care versus a laboratory method. This is consistent with the findings reported by some clinical trials that recently showed a stronger suppression of platelet aggregation, and a reduced incidence of cardiovascular

### What is known about this topic?

- Patients with coronary artery disease and undergoing percutaneous coronary intervention are at a much greater risk of death and/or major adverse cardiac events.
- The standard care of these patients is the dual antiplatelet treatment with aspirin and clopidogrel.
- A consistent proportion of patients under antiplatelet treatment shows a clinical non-responsiveness to the therapy.

### What does this study add?

- Poor responders to clopidogrel treatment are at increased risk of cardiovascular clinical recurrences.



events, with a dosage of 600 mg of clopidogrel with respect to 300 mg (28, 29).

## Limitations of study

Some potential limitations can be detected in the present meta-analysis. First, despite augmented, the number of studies is relatively low, and thus our results have to be interpreted carefully. Second, a great heterogeneity across the studies is present by likely underestimating the overall results of the meta-analysis. On the other hand, we have performed some sensitivity analyses subgrouping studies with similar characteristics and we have reported some outlying studies within the included papers. These studies were those with greater measures of association and lower number of patients. After the exclusion, however, the overall result was confirmed. Third, publication bias in some of the included studies was supposed by means of the funnel plot.

In conclusion, our updated meta-analysis on clinical consequences of clopidogrel non-responsiveness among over than 4,500 patients followed for a period ranging from two weeks to one year after a PCI indicates that poor responders to clopidogrel are at increased risk of cardiovascular clinical recurrences with respect to those with a good response to the antiplatelet therapy.

These results suggest the need for interventional studies aimed at tailoring the antithrombotic therapy in coronary heart disease patients and need to be confirmed by further large clinical trials with standardised laboratory methods and well-defined protocols to validate the clinical relevance of such response variability to clopidogrel.

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