Systematic review and meta-analysis of outcomes after coronary revascularization procedures with regard to antiplatelet treatment and bleeding complications

Ph.D. thesis

by

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Abbreviations

ACS	-	Acute coronary syndromes
ADP	-	Adenosine diphospate receptor
AMI	-	Acute myocardial infarction
CABG	-	Coronary artery bypass graft surgery
CAD	-	Coronary artery disease
CI	-	Confidence interval
CIE	-	Composite endpoint of the reported ischemic events
CV	-	Cardiovascular death
HPR	-	High on-clopidogrel platelet reactivity
HR	-	Hazard ratio
IABP	-	Intraaortic balloon pump
IPA	-	Post-treatment platelet reactivity
LTA_{ADP}	-	ADP-stimulated light transmission aggregometry
MACCE	-	Major adverse cardiac and cerebrovascular events
MACE	-	Major adverse cardiovascular events
MD	-	Mean difference
MEA_{ADP}	-	Multiple electrode aggregometry with ADP stimuli
MI	-	Myocardial infarction
NOS	-	Newcastle-Ottawa Scale
OPCAB	-	Off pump coronary artery bypass
OR	-	Odds ratio
POBA	-	Percutaneous balloon angioplasty

PCI	-	Percutaneous coronary intervention
RBC	-	Red blood cell transfusion
ROC	-	Receiver-operating characteristic
ST	-	Stent thrombosis
STEMI	-	ST segment elevation myocardial infarction
TFPCI	-	Transfemoral coronary intervention
TRPCI	-	Transradial coronary intervention
TVR	-	Target vessel revascularization
TXA	-	Tranexamic acid
UFH	-	Unfractionated heparin
VASP	-	Flow cytometric assessment of vasodilator-stimulated phosphoprotein phosphorylation assay

1 Introduction

1.1 Short history

Meta-analysis is a statistical technique for summarising, and reviewing previously published quantitative research. Practioners, clinicians have to face an informational boom of the modern medicine. There is too much information around for people to keep up to date, on the other hand high quality information is often not easy to find. Elaborating a summary of available literature and performing a critical review of the obtained data is becoming more and more important. Using meta-analysis, a specially developed statistical armamentarium that allows cumulating the available data of independent observation, enables to analyse a wide variety of questions and allows not only a summary but also an integration of the evidences with higher statistical power and more precise effect estimates.

The first meta-analysis was performed by Karl Pearson in 1904, who analyzed the data from five studies on the correlation between the vaccination for enteric fever and its mortality. [1] He observed separate sets of data from different geographical locations. It is an early example of meta-analysis, and yet it has all the features of a correct meta-analysis. The first written work on the methodology of combining the results of different studies was given by Tippett in 1931, and then shortly by Pearson in 1933, who independently proposed a method for combining tests of statistical significance based on the product of the P values across studies. [2; 3] Also, Cochran in 1937 and Yates and Cochran in 1938 in their early work combined information across experiments in the agricultural sciences in order to derive estimates of treatment effects and test their significance. [4; 5] See also Mosteller and Bush in 1954, Glass, McGaw and Smith in 1981, then Hunter, Schmidt and Jackson in 1982, Hedges and Olkin in 1985 and Cooper and Hedges in 1994 for further investigation on the history of

meta-analysis that is widely used in epidemiology and evidence-based medicine today. [6; 7; 8; 9; 10]

1.2 Background

Coronary artery disease (CAD) is the predominant cause of heart disease and the leading cause of death worldwide. In recent decades new treatments have been developed in for its management. Coronary-artery bypass grafting (CABG), introduced in 1968, was the only method of coronary revascularization until 1977, when percutaneous balloon angioplasty (POBA) was first performed by Andreas Grüntzig, which was seen as an innovative non-surgical alternative to CABG. [11; 12] Since their inception, both techniques have undergone evolutions that have reduced rates of morbidity and mortality despite the increasing age and prevalence of co-morbidities in the patient population receiving revascularization. In the 1990s, the introduction of stents led to reduced rates of complications of POBA. Stent implantation dramatically improved the overall success rate of percutaneous coronary intervention (PCI), but some short and longer term complication has been realized. In patients after PCI, the antiplatelet therapy has radically reduced the rate of ischemic events. As acute coronary syndrome seems to be associated with a need for higher degree inhibition of platelet activation the current trends involve the use of more potent antiplatelets as well as intensified antiplatelet and anticoagulation protocols. Yet, despite these efforts acute stent thrombosis still occurs that suggest that optimal antiplatelet effect is still not achieved in a proportion of patients, while use of more aggressive regimes may encounter a higher risk for periprocedural bleeding complications. Nevertheless there is an important inter-individual difference in response to antiplatelet therapy. These differences seem to be significant in terms of the prognosis of the patient but heterogeneity in the methodology still hampers the wide-spread clinical use of these tests.

1.3 Methodical aspects of meta-analysis: selection of studies, quality assessment

1.3.1 Planning a meta-analysis

Systematic reviews aim to find and assess with statistical and analytical methods for inclusion all high quality studies addressing a question and integrate the study results into a common result. Performing a meta-analysis can be simplified to four essential stages. The first step is to define the question with excluding and including criteria for the research studies. The second is to perform a systematic search for literature in order to capture all available studies addressing the question in the medical literature. Currently keyword dependent search of electronic databases such as Pub Med, the Web of Science®, and the Cochrane Central Register of Controlled trials is used for this aim. The third step is calculation with mathematical and statistical formulas results for each study and combine them. Final step is the interpretation of the results of meta-analysis and give an answer and conclusion to the question.

1.3.2 Quality assessment

The quality of the included studies is important as it may influence the overall credibility of the meta-analysis. The inclusion criteria themselves already include some key features defining the minimal required information that qualify a report for inclusion. Randomized studies generally performed in high quality that makes their interpretation easy, however the restrictions of the involved group of patient sometimes impairs the generalization of their findings. The observational studies are less standardized consequently more heterogeneous in quality; however they reflect the praxis of the real-world circumstances. Quality assessment may also provide information about why the results of some included

studies differ from others. Similarly it is important to assess, as to whether an effect can be verified in the whole spectrum of studies or it is influenced by the application environment.

To estimate study quality scoring systems are used. Generally accepted scoring system for non-randomized studies; is the Newcastle-Ottawa Scale (NOS). The scale allocate stars, maximum of nine, for the presence of the following: 1) representativeness and 2) selection of the study, 3) ascertainment of intervention, 4) demonstration of outcome, 5) comparability (max: 2 stars), 6) assessment of outcome, 7) duration of follow-up, 8) adequacy of follow-up. An another method, which can allocate the quality of study is the less well standardized, however more detailed score, modified from Jadad et al. and Biondi-Zoccai et al. [13; 14; 15] In this scale quality is expressed on an ordinal scale, allocating 1 point for the presence of each of the following: 1) statement of objectives; 2) explicit inclusion and exclusion criteria; 3) description of interventions; 4) objective means of follow-up; 5) description of adverse events; 6) power analysis; 7) description of statistical methods; 8) multicenter design; 9) discussion of withdrawals; and 10) details of medical therapy.

1.3.3 Data structure

Data reported by the included studies may be given in different forms. This influences the statistical model selection. When the studies have a dichotomous, binary outcome the results of each study can be presented in a 2×2 table (Table 1) giving the numbers of participant who has or not the event in each of the two groups.

1. Table: Binary data

Study *i*	Event	No event	Total
Experimental	a_i	b_i	n_{1i}
Control	c_i	d_i	n_{2i}

If the reported outcome is a continuous variable, the number of patients in each of the two groups, their mean response and the standard deviation of their responses are required to perform meta-analysis (Table 2).

2. Table: Continuous data

Study *i*	Group size	Mean response	Standard deviation
Experimental	n_{1i}	m_{1i}	sd_{1i}
Control	n_{2i}	m_{2i}	sd_{2i}

There is a generic approach, for other outcomes. When study report odds or hazard ratios, after calculation it can be expressed on a log-scale with standard error, which calculable from the confidence interval. The involved patient's number can optionally be entered by the author, but are not included in the analysis. [16] (Table 3)

3. Table: Generic data

Study *i*	Estimate of effect	Standard error of estimate	Group size (experimental)	Group size (control)
	$\hat{\theta}_i$	$SE\{\hat{\theta}_i\}$	n_{1i}	n_{2i}

1.3.4 Endpoints

The endpoints of interest are typically continuous and categorical variable. A continuous variable define one points on a line and has numeric or quantitative value, which can measure length, weight or time. The categorical variable is not quantitative and has no numerical meaning. It takes a value that is one of several possible categories, like hair color or gender. In several studies the reported event frequencies are categorical variables. These are mortality, red blood cells transfusion, reoperation, cardiovascular death, definite/probable stent thrombosis and non-fatal myocardial infarction. In some cases

driven by their common pathological background or their common influence on the patients outcome composite endpoint are created. An example for the former is the major adverse cardiologic events (MACE) or the major adverse cardiac and cerebrovascular events (MACCE). These measures are of widespread use in cardiologic clinical research as hard clinical endpoint. Here cardiac mortality, myocardial infarction and cerebrovascular events are composed together based on their similar background as different manifestation of the atherosclerotic coronary disease. In studies where clinical outcome of patient after coronary interventions are followed-up the MACE is frequently amended with the number of target vessel revascularization (TVR). Recent understanding on the timing of stent thrombosis resulted in a classification that defines definite, probable and possible stent thrombosis emphasizing that some event may happen clinically unnoticed. [17] In recent studies supported by the data on relevance of bleeding events efficacy endpoints (like MACE) and safety endpoints (like bleeding) reported as a composite endpoint of net clinical outcome. [18] It is a frequently encountered problem that different studies use different endpoint criteria for the same event. An example of this is the bleeding where wide variety of bleeding criteria are available that incorporates treatment (amount of red blood cell transfusion or the surgical haemostasis required), laboratory (decrease of blood hemoglobin or hematocrit with a given level) or clinical (like in case of intracranial bleeding) characteristics. To overcome such heterogeneity review of literature can use so called consensus endpoint and subgroup analyses can be performed to ascertain as to whether the studies reporting and reporting not consensus endpoint share similar characteristics.

1.3.5 Statistical models

Meta-analysis is the use of statistical methods to combine results of individual studies. This allows making the best use of all the information. The difficulty is to integrate all those

different studies into one study. The effect size, which can be odds ratio, risk ratio, correlation coefficient, mean difference, standard mean difference is the most important value in meta-analysis. After standardization it can be comparable across studies. The number of patients varies from study to study; therefore the effect size is depending on sample size. In the analysis it can bypass with giving "weight", which dependent on deviation, to each study. The weight of each study is given by the inverse of the variance:

$$Wi = {}^{1}/_{Vi}$$

where W_i is the weight and V_i the variance of the outcome of the study. Variance defines the imprecision of the reported data, therefore if *V* is small, *W* will converge to 1, to 100% and the study will have greater weight in the final result of the analysis.

There are two statistical approaches the fixed and random effect model. Fixed effect model is based on a mathematical hypothesis that each study is evaluating a common treatment effect. That means the effect of treatment, allowing for the play of chance, was the same in all studies. Conversely the random effect model is an alternative approach that does not assume that a common or fixed treatment effect exists. This model assumes that the true treatment effects in the individual studies may be different from each other and may be influenced by chance. In studies of human population medical reports usually the more robust random effect can preferably used. Similarly, if statistical heterogeneity is high between the studies in the review, the random effects model may be better choice. [16]

The Mantel-Haenszel approach was developed by Mantel and Haenszel in 1959. [19] This method assumes a fixed effect and gives the weight of the investigated study with inverse variance approach. The Mantel-Haenszel pooled odds ratio is given by:

$$OR_{MH} = \frac{\sum w_{MH,i} OR_i}{\sum w_{MH,i}}$$

The alternative for calculation of the logarithmic (log) odds ratio, mean difference or standardized mean difference is the DerSimonian and Laird random-effects model that is given by [10]:

$$\theta \sim N(\theta, \tau^2)$$

The estimate of τ^2 is given by:

$$\hat{\tau}^2 = \max \left\{ \frac{Q - (k-1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}, o \right\}$$

where the W_i are the inverse-variance weights.

A specialized case of the random effect model is the inverse-variance method that is appropriate to pool log ORs of observational studies. The intervention effect estimate is denoted by $\hat{\theta}_i$ and the investigated studies are weighted according to the reciprocal of their variance:

$$w_i = \frac{1}{\left(SE\{\hat{\theta}_i\}\right)^2}.$$

These are combined to give a pooled estimate

$$\hat{\theta}_{IV} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i},$$

with

$$SE\{\hat{\theta}_{IV}\} = \frac{1}{\sqrt{\sum w_i}}.$$

1.3.6 Test for heterogeneity

Beside the direction, magnitude and confidence intervals of an effect estimate it is an important aspect how far the available data are heterogeneous in this aspect, and thus a conclusion how far can be generalized. The heterogeneity can be calculated with use of the following formulas:

$$Q_{MH} = \sum w_i \left(\hat{\theta}_i - \hat{\theta}_{MH}\right)^2$$

where $\hat{\theta}$ represents the log odds ratio, log risk ratio or risk difference and the W_i are the weights. The statistic I^2 is calculated as:

$$I^2 = max\left\{100\% \times \frac{Q_{MH} - (k-1)}{Q_{MH}}, 0\right\}$$

where k is the number of studies contributing to the meta-analysis.

1.3.7 Subgroup analyses

Heterogeneity of the treatment effect can be resolved with subgroup analysis. Subgroup analyses have altogether weaker statistical power as they have less case included. Thus subgroup analysis can unveil that the effect can or cannot be reproduced in certain studies, and on the other hand when subgroup analyses reveal the same characteristics in wide range of studies can underline the robustness of the data.

2 Relations of clinical outcomes, bleeding risk and antiplatelet therapy after coronary revascularizations

2.1 Transradial versus femoral percutaneous coronary intervention in acute myocardial infarction

Transradial coronary angioplasty (TRPCI) has gained widespread acceptance since its introduction by Kiemeneij and Laarman. [20] Radial access has been proven to be a highly safe and effective technique for both diagnostic- and therapeutic procedures. [13; 21] Advantages of the transradial approach over the transfemoral include safe and easy haemostasis due to compressibility of the artery, and consequent lack of need for post procedural bed rest permitting immediate ambulation, greater comfort, and earlier discharge. These have been shown to reduce the costs of hospitalization and improve quality of life for patients. [22; 23] Although it is technically more challenging, transradial intervention is feasible in the setting of acute coronary syndromes. [24; 25; 26; 27; 28; 29; 30] The major advantage of the TRPCI is the near elimination of clinically significant access site complications, even in patients at high risk (i.e. patients treated with GP IIb/IIIa inhibitors or shortly after systemic thrombolysis). Bleeding events, and the consequent need for transfusion, are independent determinants of survival in acute coronary syndromes. Their relation to short- and long-term mortality has been demonstrated in major randomized trials as well as through the evaluation of registries. [31; 32; 33; 34] Low incidence of vascular access site bleeding complications suggests that the transradial approach may be a safe alternative to the femoral technique employed in acute myocardial infarction with ST segment elevation (STEMI), particularly when an aggressive anticoagulation- and antiplatelet regimen is applied. On the contrary, the possible greater occurrence of procedural failure and longer procedural times occasioned by difficulty

in puncturing the radial artery, inability to cannulate the coronaries, or impossibility to perform the angioplasty, are factors that raise concerns as to whether radial access remains beneficial in the setting where timely reperfusion is critical, in STEMI for instance. The safety of transradial- and transfemoral PCI in AMI were compared in numerous trials; however, most of them included small patient groups. Despite consistent demonstration of lower bleeding rates, only inconclusive results are available regarding recurrent ischemic events; most of these studies were underpowered to evaluate this issue.

2.2 Outcome in patients undergoing cardiac surgery after preoperative treatment with clopidogrel

Large body of evidence supports the application of dual antiplatelet therapy (DAPT) in patients with acute coronary syndromes (ACS) and after percutaneous coronary interventions. [35; 36; 37; 38; 39] Clopidogrel, an irreversible inhibitor of the platelet P_2Y_{12} ADP-receptor, is the cornerstone of the DAPT. The inhibitory effect of clopidogrel lasts for the whole life-span of the platelet as platelets are not capable for protein synthesis. Due to the slow onset of action, clopidogrel is recommended in an oral bolus before coronary angiography to achieve rapid platelet inhibition in patients with ACS. [40; 41] In the past years, aggressive clopidogrel based antiplatelet protocols have been shown to be effective in reducing recurrent thrombo-ischemic events. [42; 43; 41; 44] This strategy is predominantly important in patients with ACS, in whom the prompt and potent antiplatelet therapy is associated with the greatest clinical benefit. Although most patients with ACS are candidates for percutaneous coronary interventions (PCI), some patients with ACS require surgical revascularization. This proportion is low among those with ST-segment elevation myocardial infarction (MI), but can reach 10% in patients with non-ST segment elevation MI. [45]

Similarly, there are also many stable angina patients taking clopidogrel before coronary artery bypass grafting (CABG) procedures due to the prior PCI or acute coronary event. As a result, the administration of clopidogrel is quite common before cardiac surgery. [46] As the impaired platelet function during CABG might be associated with higher rate of bleeding complications, it is recommended to discontinue clopidogrel for at least five days before surgery. [45] However, in certain cases, it is not possible to wait for the wash-out period, and many patients undergo surgical revascularization under the effect of clopidogrel. On the other hand some recent studies support that persisting inhibition of platelet aggregation beside the higher risk for bleeding may have beneficial effect in terms of reduction of perioperative myocardial infarction or graft patency. [34; 47; 48]

Several studies intended to clarify the potential harm and benefit associated with clopidogrel therapy prior to CABG. As these studies resulted in heterogeneous and inconclusive results currently, there is no consensus regarding the impact of clopidogrel treatment on clinical outcome after cardiac surgery. [49] Our main goal was to perform a systematic review of the literature to evaluate the impact of clopidogrel treatment on clinical outcomes in patients undergoing cardiac surgery.

2.3 Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention

Dual antiplatelet therapy with aspirin and clopidogrel reduces recurrent thrombotic events in patients after acute coronary syndrome and percutaneous coronary intervention (PCI). [35; 38] Clopidogrel is an adenosine diphospate (ADP) receptor antagonist that exerts its antiplatelet action via irreversible binding to the platelet P_2Y_{12} receptor after metabolic activation, through the cytochrome P450 enzymes. Numerous reports have found that the

antiplatelet efficacy of clopidogrel exhibits considerable inter-individual variability. [41; 50] According to our current understanding, the insufficient and highly unpredictable generation of its active metabolite is largely responsible for the inter-individual differences observed in post-treatment platelet reactivity. [51] As the active metabolite formation is influenced by genetic, clinical and pharmacological factors, the development of high on-clopidogrel platelet reactivity (HPR) is a multifactorial process. [52] As recently evidenced, low compliance is also a remarkable reason for measuring HPR in the patient. [53] Up to now, numerous in vitro or ex vivo laboratory assays have been developed to monitor on-clopidogrel platelet reactivity. [54] Using these assays, accumulating number of observational studies have found that patients with HPR have higher risk for recurrent ischemic events, including myocardial infarction and stent thrombosis (ST). [55; 39; 56; 57; 58; 59; 60; 42; 61; 62) (63; 64; 65; 66; 67; 68; 69; 70; 71; 72] However, routine platelet function testing is not yet recommended. [73] First, this is due to the somewhat arbitrary-used and non-standardized definitions for HPR. Second, the prognostic significance of HPR after PCI is unclear as prospective, adequately-powered clinical trials are lacking. Third, there is no consensus on the ideal platelet function assay to monitor on-clopidogrel platelet reactivity. In the current review and meta-analysis, we aimed to collect and summarize the available evidence regarding the prognostic significance of HPR to achieve greater statistical power and more precise estimates.

3 Aims

The main goal of the thesis to systematically overview and analyze the available medical literature, which reported clinical outcomes after revascularization procedures:

Percutaneous coronary intervention (PCI) is routinely preformed through the femoral approach, which was the gold-standard method. Nevertheless, this access route accompanies higher rate of bleeding complications. Transradial approach has a lower incidence of bleeding complications. However requires longer learning curve and might increase the procedural time and more importantly the time to reperfusion, and the rate of procedural failure. Therefore our aim was to perform a systematic review of the literature comparing the safety and efficacy of the two vascular accesses.

Antiplatelets prevent the recidive ischaemic events after PCI, but among patients, who require urgent surgical revascularization, the antiplatelet regime increases the risk of bleeding complications after operation. The higher rates of blood product transfusion may have an effect on morbidity and mortality. For that reason our aim was to evaluate the impact of preoperative administered clopidogrel on the outcome of patients referred for surgical revascularization.

Several studies reported data about insufficient clopidogrel therapy, inter-individual differences on clopidogrel responsiveness. In case of non-responsiveness the incidence of adverse event corresponds with clopidogrel naive patients. Accordingly our aim was to collect and summarize the available evidence regarding the prognostic significance of high on-clopidogrel platelet reactivity.

4 The proposed meta-analyses

4.1 Transradial PCI in acute MI

4.1.1 Search strategy

We performed a systematic review of the available literature according to the MOOSE guidelines for the conduct of meta-analyses of observational studies. [74] Relevant studies published between January 1993 and August 2009 were identified from MEDLINE®, SCOPUS®, the Web of Science® with Conference Proceedings, and the Cochrane Central Register of Controlled trials (CENTRAL) using a search strategy that combined text word and MeSH heading. Search keywords included various combinations of the following terms: "transradial", "radial access", "myocardial", "infarct*", and "coronary". No language restrictions were imposed. Furthermore, we searched reference lists of relevant studies and reading reviews and editorials on this topic. In addition, relevant abstracts and presentations from the annual meetings of the American Heart Association, the American College of Cardiology, the European Society of Cardiology and Transcatheter Cardiovascular Therapeutics were identified.

4.1.2 Selection criteria

Inclusion criteria for retrieved studies were a) controlled comparison of the radial- versus femoral approach for coronary intervention b) in acute myocardial infarction (either primary- or rescue PCI) and c) intention-to-treat analysis. Exclusion criteria were a lack of clear- and reproducible results and incomplete follow-up, and lack of clear distinction of the clinical setting of the patients included (i.e. separate data for the acute- and elective interventions included).

4.1.3 Data abstraction and validity assessment

Data abstraction was independently performed by two unblinded reviewers on pre-specified structure collection forms. Disagreements were resolved by consensus and discussion with a third party. Individual researchers were contacted in the case of incomplete reporting. The quality of study was evaluated by a third investigator according to a score, modified from Jadad et al. and Biondi-Zoccai et al. [13; 14; 15]

4.1.4 Study outcome measures

The primary clinical outcomes of interest, evaluated at the longest available follow-up, were 1) mortality; 2) major adverse cardiovascular- and cerebrovascular events (MACE), including death, recurrent myocardial infarction, emergency percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG), and stroke; 3) major bleeding (a standardized major bleeding definition was used that was adapted from the meta-analysis of Jolly et al. Briefly, major bleeding was defined as one of the following: fatal bleeding, intracranial hemorrhage, or bleeding associated with a ≥3 g/dL hemoglobin drop or requiring transfusion or requiring surgery (pseudoaneurysms requiring thrombin injection or ultrasound compression were excluded). For trials where the composite definition was not available, either transfusion rates or proportion of bleeding events associated with a ≥3 g/dL hemoglobin drop were substituted for major bleeding. Secondary procedural outcomes, pooled from individual studies when available, were: procedural time (in minutes), door-to-reperfusion time (in minutes), fluoroscopy time (in minutes), length of hospital stay (in days), and access site crossover.

4.1.5 Data analysis and synthesis

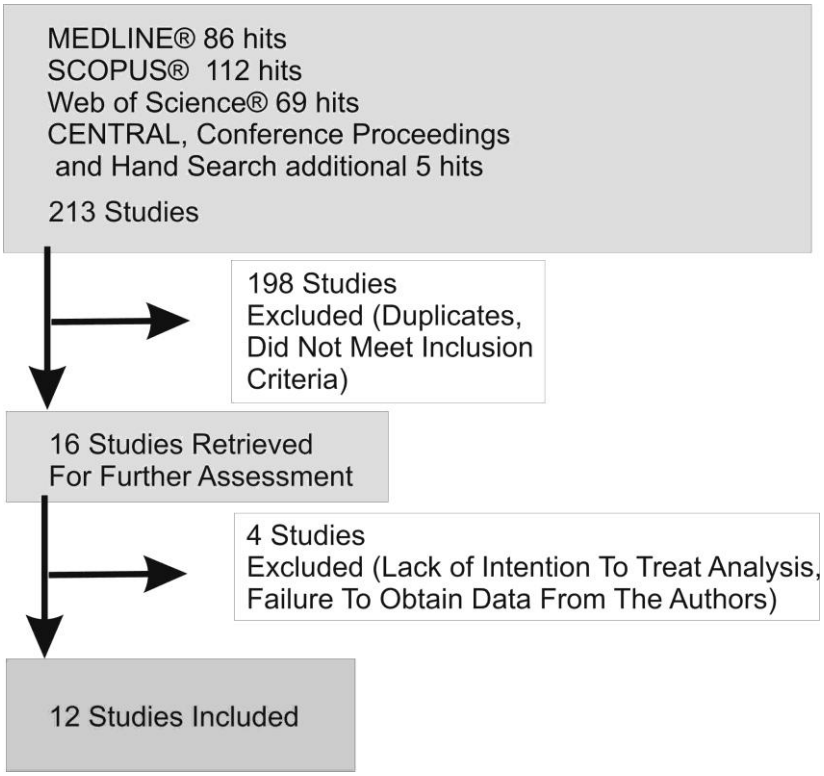
Dichotomous variables are reported as proportions and percentages, and continuous variables as mean values and standard deviation. Binary outcomes from individual studies were combined with the Mantel-Hansel fixed effect model, and the DerSimonian and Laird random effects model was used for sensitivity analysis. Continuous variables were compared with the inverse-variance method to obtain the mean difference and its confidence interval in a fixed-effect method. [75] The odds ratio (OR) and 95% confidence interval (CI) were used as summary statistics for the comparison of dichotomous variables between the radial- and femoral approaches. The mean difference (MD) and 95% CI were used for the continuous variables. Reported values were two-tailed, and hypothesis testing results were considered statistically significant at p value <0.05. Statistical analysis was performed using the Review Manager 5.0.16 developed and maintained by the Cochrane Collaboration. [75] We planned to conduct sensitivity analyses if significant heterogeneity was found (I^2) for any of the outcomes. Sensitivity- and subgroup analyses were performed using the following categories: 1) randomized and observational studies 2) primary PCI and rescue PCI (studies with >50% of the patients undergoing PCI were included in this group) 3) cohorts whose use of GP IIb/IIIa inhibitor was below and over 15% 4) quality studies whose scores were higher than median and median versus lower than median.

4.1.6 Search results and study selection

Our search detected 213 citations. These included editorials, reviews, letters, or articles regarding other aspects of the radial approach. There were 62 observational studies investigating the feasibility and safety of the radial approach in a series of patients. Moreover, we found 13 studies comparing the radial- and femoral approaches in a cohort of patients that included both elective- and acute cases without reporting separate outcomes

regarding the different settings. Twelve studies were included in the final analysis. (Figure 1) These comprised 5 randomized trials involving 516 patients: 266 of the transradial- and 250 of the transfemoral approaches. [76; 24; 77; 78; 79] Seven further reports using the registry approach of single- or dual center experiences of primary TRPCI were identified. These included 2808 cases, made up of 1212 transradial- and 1596 transfemoral interventions. [80; 81; 82; 83; 30; 84; 85] All studies were published in peer-reviewed journals. (Table 4) The mean age was 60.9 years. On average, males accounted for 77.3% of subjects. The sheath size used was predominantly 6F or 6-7F. In four studies, sheaths allowed for the vascular access were smaller, 5-6F or 5-7F; in one other, a larger size 6-8F was used. In seven reports only primary PCI cases were presented, while 3 studies included also patients after systemic thrombolysis, and 2 further reports involved only patients with rescue PCI. All studies reported that unfractionated heparin (UFH) was administered intravenously in all cases except for two where use of enoxaparine was also allowed. GP IIb/IIIa usage was allowed in ten studies; the proportion of use varied from 21.2% to 100%. (Table 4-5). All studies reported data on the in-hospital follow-up, apart from four in which follow-up data were recorded for 30 days [24; 84; 83; 79], and in one for nine months [78].

1. Figure: Flowchart of trials



4. Table: Details of trials

Study (Published year)	Methods	Number of patients	Mean age (years)	Males (%)	Rescue PCI (%)	GP IIb/IIIa (%)	Antithrombotic Treatment (LD/MD) †
TEMPURA Saito et al. (2002)	Single center randomized prospective	149	67	81.2	0	0	Ticlopidine UFH:6000 IU for males 5000 IU for females
Valsecchi et al. (2003)	Single center prospective	726	61.5	76	0	21.2	Ticlopidine UFH: 70 IU/kg*
Philippe et al. (2004)	Single center prospective	119	59.6	73.9	0	100	Clopidogrel 300/75) UFH: 70 IU/kg
RADIAL- AMI Cantor et al. (2004)	Multicenter randomized	50	55	88	66	94	Clopidogrel (300/75) UFH: all patients*, dose NA
Díaz de la Llera et al. (2004)	Single center prospective	162	57.2	85.2	17.9	67.3	Clopidogrel (300/75) UFH: 5000 IU
Kassam et al. (2004)	Dual center retrospective	111	56	79.3	100	100	Clopidogrel (300/75) UFH: 60-70 IU/kg*
Kim et al. (2005)	Single center retrospective	352	62.7	65.1	0	NA	Ticlopidine or Clopidogrel (LD:300) UFH:70 U/kg or 30 mg enoxaparin
FARMI Brasselet et al. (2007)	Single center randomized	114	59	82.4	42.1	100	Clopidogrel (300/75) UFH: 50 IU/kg (in cases w/ >75 years upper limit 4000 IU) or 30 mg enoxaparin iv. and 1mg/kg sc.
RADIAMI Chodor et al. (2007)	Single center randomized	100	59.5	68	0	43	Antiplatelets NA UFH: 70 IU/kg*
Cruden et al. (2007)	Single center retrospective	287	59	82.9	100	93	Clopidogrel (300-600/75) UFH: 5000 IU or 70 IU/kg
Yan et al. (2008)	Single center randomized,	103	70.8	74.8	0	100	Clopidogrel (600/75) UFH:70 IU/kg
Hetherington et al. (2009)	Single center retrospective	1051	63.2	71	0	92.2	Clopidogrel (600/75) UFH:70 IU/kg

Abbreviations: PCI: percutaneous coronary intervention, GP IIb/IIIa: platelet glycoprotein IIb/IIIa inhibitor, NA = not available, † aspirin plus thienopyridine, LD: loading dose, MD: maintenance dose, UFH: unfractionated, *heparin dosing monitored and adjusted to ACT

5. Table: Details of trials

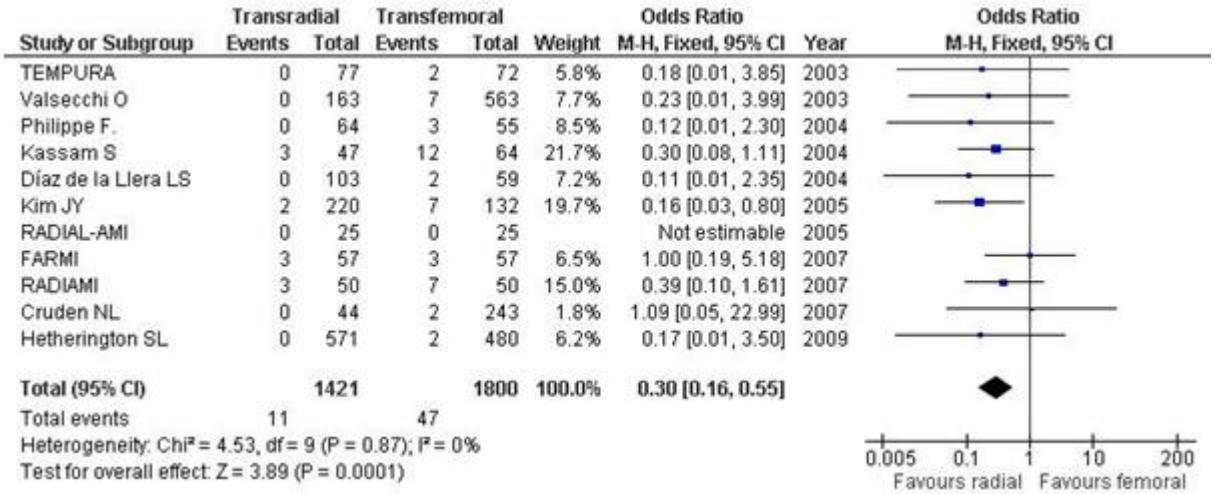
(Published year)	Sheath size	Eligibility test	Exclusion criteria	Operators experience	Follow up	Quality score
TEMPURA Saito et al. (2002)	6 F	Allen	Cardiogenic shock, thrombolytic therapy	>80% TRI cases of PCI/year	In hospital and 9 month	9
Valsecchi et al. (2003)	6 F	Allen	History of CABG with both IMA, chronic renal failure	>400 TRI cases/year	In hospital	7
Philippe et al. (2004)	5-6 F	Allen	Cardiogenic shock, history of CABG	>143 PCI cases/year	30 days	7
RADIAL- AMI Cantor et al. (2004)	6-7 F	Allen	Cardiogenic shock, contraindication of GP IIb/IIIa use	100 TRI cases	30 days	9
Díaz de la Llera et al. (2004)	6 F	Allen, Pulse oxymetry	Cardiogenic shock	Institutional#	30 days	8
Kassam et al. (2004)	5-7 F	NA	NA	Institutional	In hospital	6
Kim et al. (2005)	6-8 F	Allen	Killips state 4, history of chr. renal failure	>200 PCI cases/year	In hospital	6
FARMI Brasselet et al. (2007)	5-6 F	Allen, Pulse oxymetry	Killip state > 2, GpIIb/IIIa intolerance, history of CABG, need for IABP or PM	>100 TRI cases	In hospital	7
RADIAMI Chodor et al. (2007)	6 F	Allen, Pulse oxymetry	Killip state > 2, history of CABG, need for IABP or PM	50-100 TRI cases	In hospital	8
Cruden et al. (2007)	NA	NA	NA	>100 TRI cases/year	In hospital	5
Yan et al. (2008)	6-7 F	Allen	Cardiogenic shock, chronic renal failure	>500 TRI cases	30 days	8
Hetherington et al. (2009)	5-7 F	NA	Cardiogenic shock	NA§	In hospital	8

Abbreviations: TRI = transradial intervention, NA = not available, IABP: intra aortic balloon pump, PM: pacemaker, #: report from centers with transradial PCI expertise, applying transradial access as first choice for PCI, §: operators with different expertise included

4.1.7 Clinical results

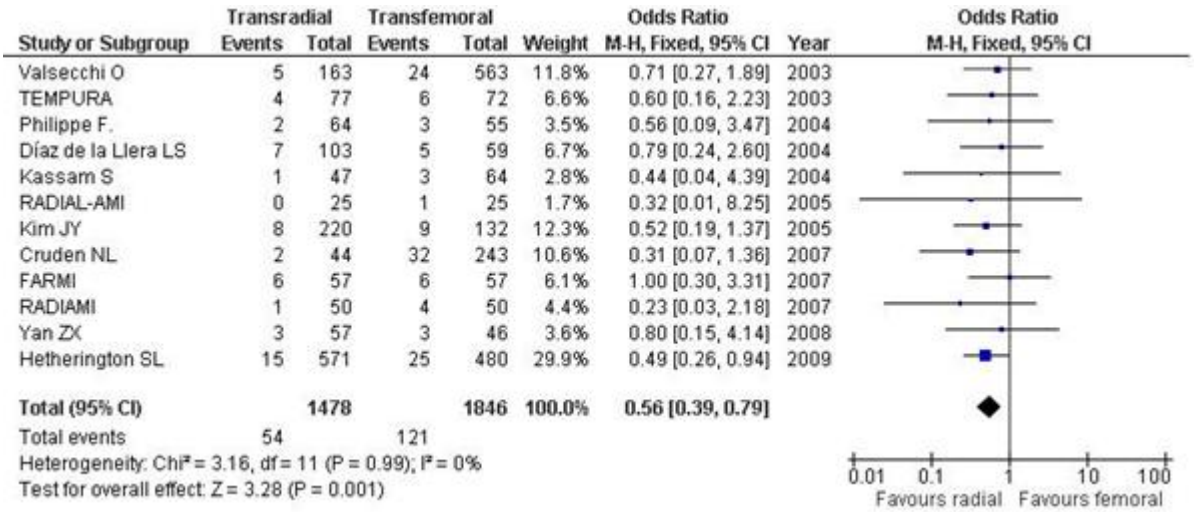
The radial approach reduced risk for major bleeding by 70% compared to TFPCI (0.77% vs 2.61%, OR: 0.30 [95% CI: 0.16, 0.55] P=0.0001; Figure 2). Reductions in the composite of death, myocardial infarction, and stroke were also significant (3.65% vs. 6.55%, OR: 0.56 [95% CI: 0.39, 0.79] P = 0.001; Figure 3). Pooling the 29 events (2.59%) of 1421 TRPCI and 55 (3.18%) of 1800 TFPCI demonstrated a significant mortality reduction in the case of TRPCI (OR: 0.54 [95% CI: 0.33, 0.86] P=0.01; Figure 4). There were no differences in procedural time and in time to reperfusion between the two access routes. Fluoroscopic times were longer in case of TRPCI; however, there was significant heterogeneity among studies in these parameters. Access site crossover was less frequent in the case of the transfemoral approach while the total hospital charge, assessed in eight studies was lower in the case of the transradial (Figure 5).

2. Figure: Overall risk of major bleeding



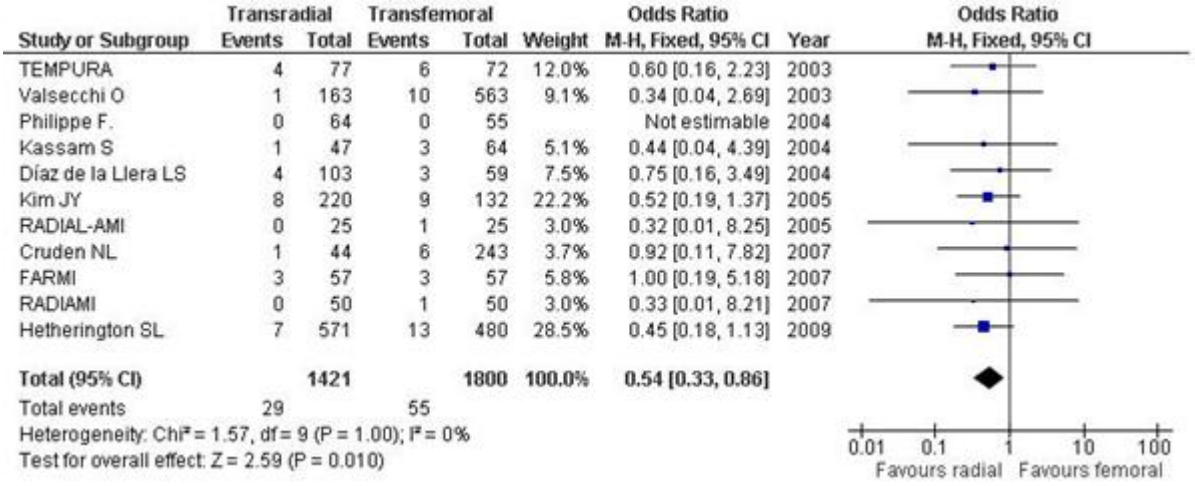
Abbreviations: CI: confidence interval; OR: odds ratio

3. Figure: Overall risk of major adverse events (MACE)



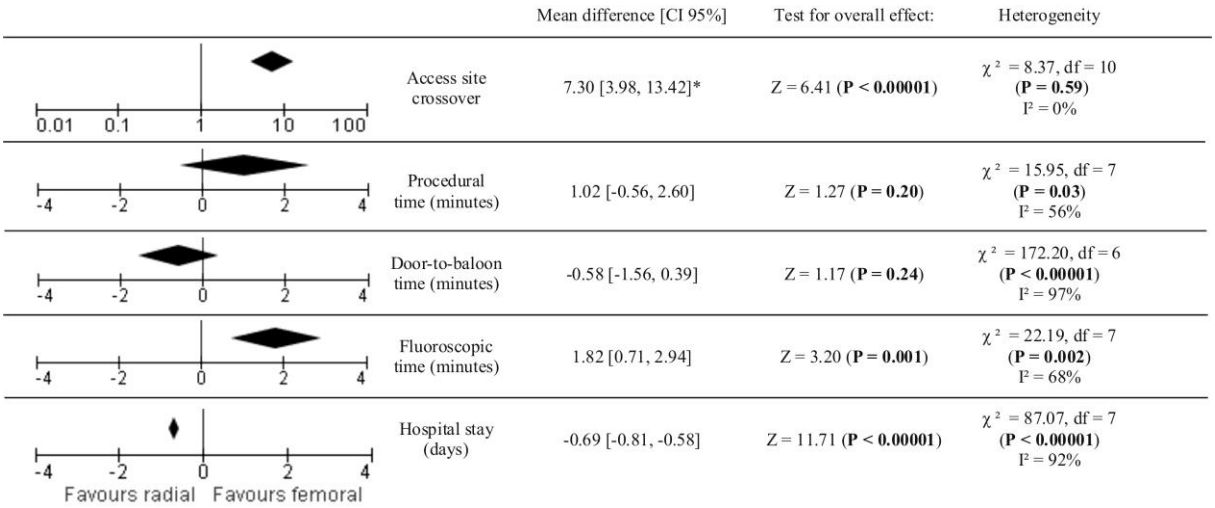
Abbreviations: CI: confidence interval; OR: odds ratio

4. Figure: Overall risk of death



Abbreviations: CI: confidence interval; OR: odds ratio

5. Figure: Summary of outcomes of secondary endpoints radial versus femoral access for coronary intervention in myocardial infarction



CI: confidence interval, * Odds ratio [CI 95%]

OR calculations were also performed according to a random effects model, yielding similar results with regard to both the direction and magnitude of overall effects. Stratification and sensitivity analysis excluding non-randomized studies showed results similar to those of the comprehensive analysis. Findings were also comparable after pre-specified stratification in studies involving high-risk patients (i.e. studies that included >30% of patients with preceding thrombolysis, and with >90% use of GP IIb/IIIa inhibitors) and higher than median versus lower than median quality studies (Table 6).

6. Table: Subgroup and sensitivity analyses

Subgroup analysis (P value)		Nr. of studies (Nr. of cases)	Odds ratio [95% Confidence interval]		
			MACE	Death	Major bleeding
Overall effect	Random effect model	11 (3324)	0.57 [0.40, 0.81]**	0.54 [0.34, 0.88]*	0.31 [0.17, 0.59]**
Randomization	Randomized studies	5 (516)	0.65 [0.32, 1.30]	0.63 [0.25, 1.58]	0.49 [0.18, 1.31]
	Non-randomized studies	7 (2808)	0.53 [0.35, 0.80]**	0.51 [0.29, 0.88]*	0.22 [0.10, 0.50]**
Rescue PCI	>30% Rescue PCI	4 (562)	0.53 [0.24, 1.17]	0.71 [0.25, 2.03]	0.49 [0.19, 1.28]
	<30% Rescue PCI	8 (2762)	0.56 [0.38, 0.83]**	0.50 [0.30, 0.85]*	0.21 [0.09, 0.48]**
GPIIb/IIIa use	>90% GPIIb/IIIa use	7 (1835)	0.53 [0.33, 0.84]**	0.54 [0.27, 1.09]	0.38 [0.16, 0.88]*
	<90% GPIIb/IIIa use	5 (1489)	0.60 [0.35, 1.01]§	0.53 [0.28, 1.00]#	0.23 [0.09, 0.56]**
Quality score	High-quality studies (QS≥7)	6 (1615)	0.54 [0.33, 0.86]*	0.51 [0.27, 0.97]*	0.31 [0.11, 0.87]*
	Low-quality studies (QS<7)	6 (1709)	0.58 [0.35, 0.97]*	0.57 [0.28, 1.13]	0.32 [0.15, 0.67]**

Abbreviations: MACE: major adverse cardiovascular and cerebrovascular events, PCI: percutaneous coronary intervention, GP IIb/IIIa: platelet glycoprotein IIb/IIIa inhibitor, QS: quality score, §: p=0.06, #: p=0.05, *: p<0.05, **: p<0.01

4.1.8 Limitations

One major drawback is that the available literature consists only of a small number of studies and these studies themselves are often small in sample. Furthermore, the observational studies on this topic did not publish adjusted odds ratios. Consequently, although pooling adjusted risk estimates could have been more appropriate, we could only perform analyses using the reported event rates. Similarly the exclusion of different patient groups which might represent an inclusion bias in most of the studies is also an important issue. Patients suffering shock and with need for intraaortic balloon pump (IABP) insertions

were generally excluded from the studies and treated via the femoral route. Indeed IABPs, percutaneous assist devices, and some novel first generation interventional devices are too large to be used via the radial artery. IABP treatment is generally started during the procedure requiring double access site, and is only rarely introduced via the same line after PCI. There is no question as to whether the use of double groin puncture increases the risk of bleeding. Conversely, it is yet to be established whether sparing the femoral puncture site for the IABP and use of the radial route for the intervention — in cases where the artery is palpable and accessible for puncture — reduces the probability of bleeding. Of note is a recent meta-analysis that raised serious concerns on the need for IABP in the setting of primary PCI, including those with cardiogenic shock. [86]

4.2 Cardiac surgery related bleeding

4.2.1 Search strategy

We performed a systematic review of the available publications according to the MOOSE guidelines, to conduct meta-analyses of observational studies. [74] PubMed and Central databases were searched for relevant studies between January 2001 and May 2010. Search key words included various combinations of the following terms: CABG, clopidogrel, prognosis, bleeding, transfusion, reoperation, and mortality. No language restriction was used. Furthermore, we searched the reference lists of relevant studies and reviews, editorials, and letters on this topic.

4.2.2 Selection criteria

We selected all relevant studies which reported clinical outcomes after cardiac surgery in the context of preoperative clopidogrel administration. The primary clinical outcomes of interest, evaluated at the longest available follow-up, were mortality, red blood cell (RBC) transfusion, major bleeding, reoperation, and myocardial infarction (MI). Major bleeding was defined as an excessive chest tube bleeding at least over 500 ml. Inclusion criteria for retrieved studies were clopidogrel treatment within 0 to 7 days before surgical revascularization. Selection and data abstraction were done independently by two reviewers on pre-specified structure collection forms. Disagreements were resolved by consensus and discussion with a third party. The Newcastle Ottawa quality scoring system was used for quality assessment of the cohort reports. [75]

4.2.3 Data analysis and synthesis

Statistical analysis was performed using the Review Manager 5.0.23 freeware package maintained by the Cochrane Collaboration. [75] Odds ratios (OR) adjusted for the relevant

clinical parameters, from individual studies, were pooled with the random-effect model with the help of generic-inverse variance-weighting. If adjusted OR was not reported, it was calculated from the reported event frequencies and pooled with the random-effect model with the help of generic-inverse variance-weighting. Heterogeneity was quantified with a Chi^2 heterogeneity statistics and by means of I^2.

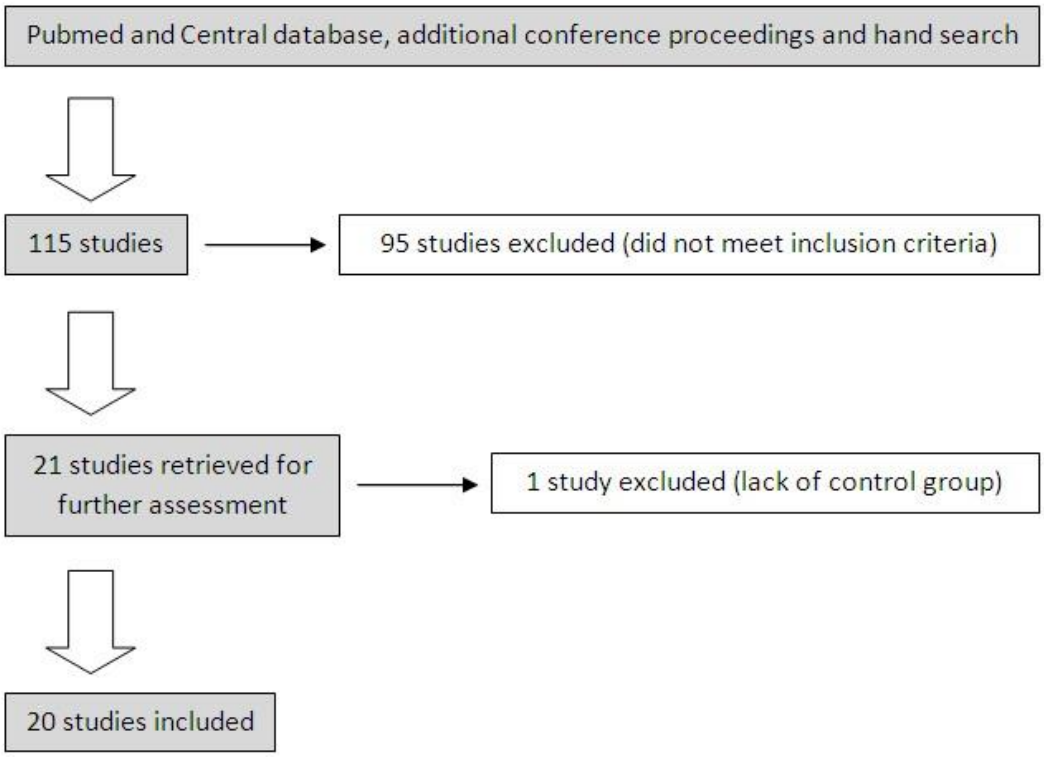
4.2.4 Search results and study selection

Our search resulted in 115 citations. These included reviews and articles that did not match our inclusion criteria. After evaluation of abstracts, twenty-one potentially appropriate studies were found. One of these had lack of controlled comparison of clopidogrel treated patients with control group and was excluded after full text evaluation. Finally, twenty articles were selected for data extraction and analysis. (Figure 6) Among these, there was one smaller randomized study involving 136 patients [87]; the further were observational trials that included 23,532 patients. Of the 20 reports, fifteen studies reported data on mortality [88; 89; 90; 91; 92; 93; 94; 95; 96; 87) (97; 98; 99; 100; 101]; fourteen reported data on the need for blood transfusion [88; 89; 90; 91; 93; 95; 96; 87; 97; 102) (98; 99; 100; 101]; 16 presented data on bleeding complications-related reoperations [88; 89; 91; 92; 93; 103; 94; 95; 96; 87) (104; 98; 105; 99; 100; 101]; 6 studies reported data on major bleeding [89; 90; 87; 100; 105; 98] and other 9 studies investigated the frequency of postoperative myocardial infarction [88; 99; 91; 93; 95; 96; 87; 104; 100]. Altogether the studies involved 23,668 patients.

The mean age was 64.27 years. On average, female gender accounted for 26.19% of the subjects. The use of off-pump coronary artery bypass grafting (OPCAB) technique was reported in 9 trials. [88; 89; 90; 94; 95; 96; 93; 98; 99] The mean rate of OPCAB was 33.1%. Glycoprotein IIb/IIIa inhibitors were administered in 6 studies. [94; 95; 96; 97; 46; 98] In further 9 reports

aprotinin usage was allowed. [89; 93; 94; 102; 46; 90; 98; 105; 99; 100] Two studies reported the use of factor VII supplementation. (93; 46) All studies reported data on the in-hospital follow-up, while in ten studies; follow-up data were available for 30 days and in one study, for one year (Table 7).

6. Figure: Flowchart of study selection



7. Table: Details of the selected trials

Study (Publication year)	Design	Number of patients	Indication for CABG	Female (%)	Mean age (yrs)	Clopidogrel therapy (%)	Clopidogrel exposure before surgery (days)	Aspirin therapy (%)	GP IIb/IIIa use (%)	Aprotinin use (%)	DM (%)	Rate of OPCAB (%)	Follow-up	Quality score
Yende (2001)	Prospective	247	All comer	35.93	63.35	20.81	NA	72.69	6.6	65.3	32.29	24.5	1 month	7
Hongo (2002)	Prospective	224	Elective	26.78	66.95	26.34	< 7	61.60	NA	NA	NA	NA	In-hospital	8
Ray (2003)	Retrospective	659	All comer	24.13	66.25	24.58	< 7	22.91	NA	§	NA	NA	In-hospital	6
Englberger (2004)	Prospective	505	All comer	22.77	67	26.93	< 3	NA	NA	100	NA	14.06	1 month	8
Karabulut (2004)	Prospective	1628	All comer	21.31	62.05	2.95	< 2	64.62	NA	NA	22.30	0	In-hospital	6
Kapetanakis (2005)	Prospective	2359	All comer	27.13	64.45	17.59	< 7	NA	NA	1.3	34.34	66.63	1 month	9
Leong (2005)	Prospective	919	All comer	23.83	63.82	9.25	< 7	71.70	1.1	NA	30.68	11.86	1 month	10
Nurozler (2005)	Prospective	182	Urgent*	26.92	63.75	42.30	< 3	64.28	NA	NA	20.33	0	In-hospital	6
CRUSADE (2006)	Prospective	2858	Urgent**	11.37	66.25	29.81	< 5 vs. >5	95.10	40.58	NA	33.41	NA	In-hospital	8
CLARITIY-TIMI 28 (2007)	Randomized	136	Urgent†	17.6	59.4	48.53	<5 vs. >5	NA	NA	NA	20.5	NA	1 month	NA
Kang (2007)	Prospective	320	All comer	28.75	65.14	20.31	<3 and <7	100	NA	NA	NA	NA	In-hospital	7

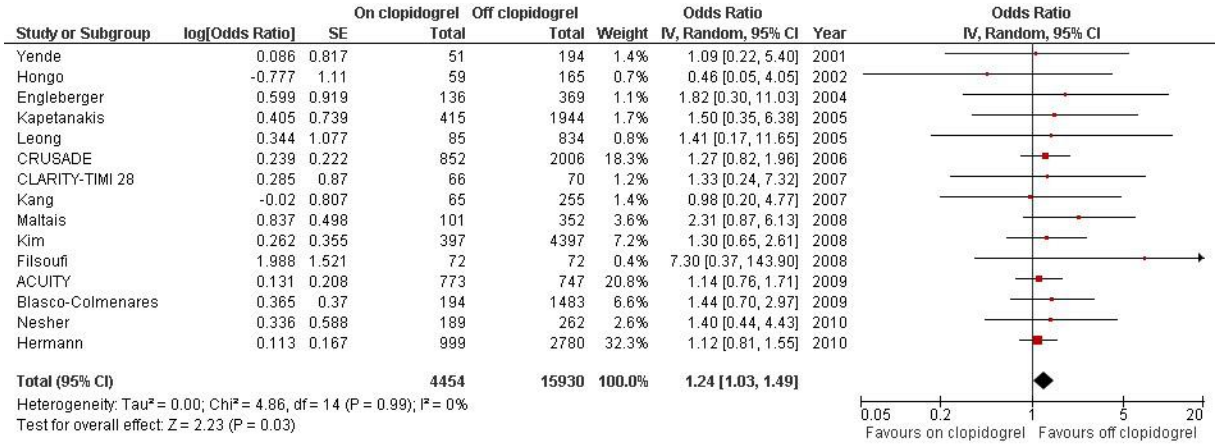
Ouattara (2007)	Prospective	217	Elective	37.06	65.5	27.65	<5	100	NA	100	35.48	0	In-hospital	7
Berger (2008)	Retrospective	596	Urgent**	31.71	64	100	<5 vs. >5	91.95	13.59	33.22	36.07	27.68	1 month	9
Filsoufi (2008)	Retrospective	144	All comer	40	63	50	<3	88.88	NA	6	50	26	In-hospital	7
Kim (2008)	Retrospective	4794	All comer	29.9	64	8.28	<5 vs. >5	NA	‡	8.76	34.8	14.5	1 month	9
Maltais (2008)	Retrospective	453	All comer	NA	64	22.29	<7	100	9.93	NA	NA	100	In-hospital	8
ACUITY (2009)	Prospective	1520	Urgent**	23.22	64.5	50.85	<5 vs. >5	97.76	NA	NA	34.01	12.7	1 year	9
Balasco-Colmenares (2009)	Retrospective	1677	All comer	27.19	65.35	13.08	<5	100	NA	NA	32.2	NA	1 month	8
Hermann (2010)	Retrospective	3779	All comer	25.06	NA	26.43	<5 vs. >5	NA	NA	10	35.48	NA	In-hospital	6
Nesher (2010)	Retrospective	451	Urgent¥	23.72	66	41.9	≤5	NA	NA	100	28.83	NA	1 month	9

Abbreviations: NA: not applicable; *: critical left main coronary artery stenosis, critical left anterior descending artery stenosis, acute coronary syndrome; **: non ST-segment elevation myocardial infarction, acute coronary syndrome; †: ST-segment elevation myocardial infarction; ¥: did not defined; §: left to the discretion of the anesthetist and surgeon; ‡: not available rate of use; yrs: year

4.2.5 Clinical results

We observed an increase in cardiovascular mortality among patients receiving clopidogrel before surgery (OR: 1.24; 95%CI: 1.03-1.49, p=0.03, Figure 7) that was not heterogeneous among studies (I^2: 0%, Chi^2: 4.68, p=0.99). Clopidogrel administration within 7 days before cardiac surgery was associated with a significant increase in the rates of RBC transfusions (OR: 1.82; 95%CI: 1.40-2.37; p<0.00001; Figure 8A) and in bleeding-triggered reoperations (OR: 2.15; 95%CI: 1.38-3.34; p<0.00001; Figure 8B). However, these outcomes showed significant heterogeneity among studies (transfusion: I^2: 84%, Chi^2: 82.52, p<0.00001; reoperation: I^2: 54%, Chi^2: 30.69, p=0.006). According to subgroup analyses, the highest risk for RBC transfusion, major bleeding or reoperation was seen if the discontinuation of clopidogrel was shorter than 3 days prior to surgery. (OR: 7.56 (95%CI: 2.38-23.99); OR: 6.62 (95%CI: 1.69-25.95) and OR: 3.40 (95%CI: 1.51-7.65), respectively). This higher risk for transfusion was less prominent when clopidogrel was discontinued earlier. In studies comparing the discontinuation before and after 5 days only a strong trend for higher rate of transfusion was found (OR: 1.36; 95%CI: 1.00-1.84; p=0.05; Table 8). Notably, Reoperation rates were significantly higher in studies published before 2006 (OR: 4.73; 95%CI: 3.01-7.45; p<0.00001; Figure 8B). There were no difference in the incidence of postoperative myocardial infarction between groups; however the pooled results were heterogeneous. (OR: 0.83; 95%CI: 0.44-1.57; p=0.57; Figure 9).

7. Figure: Overall risk of mortality

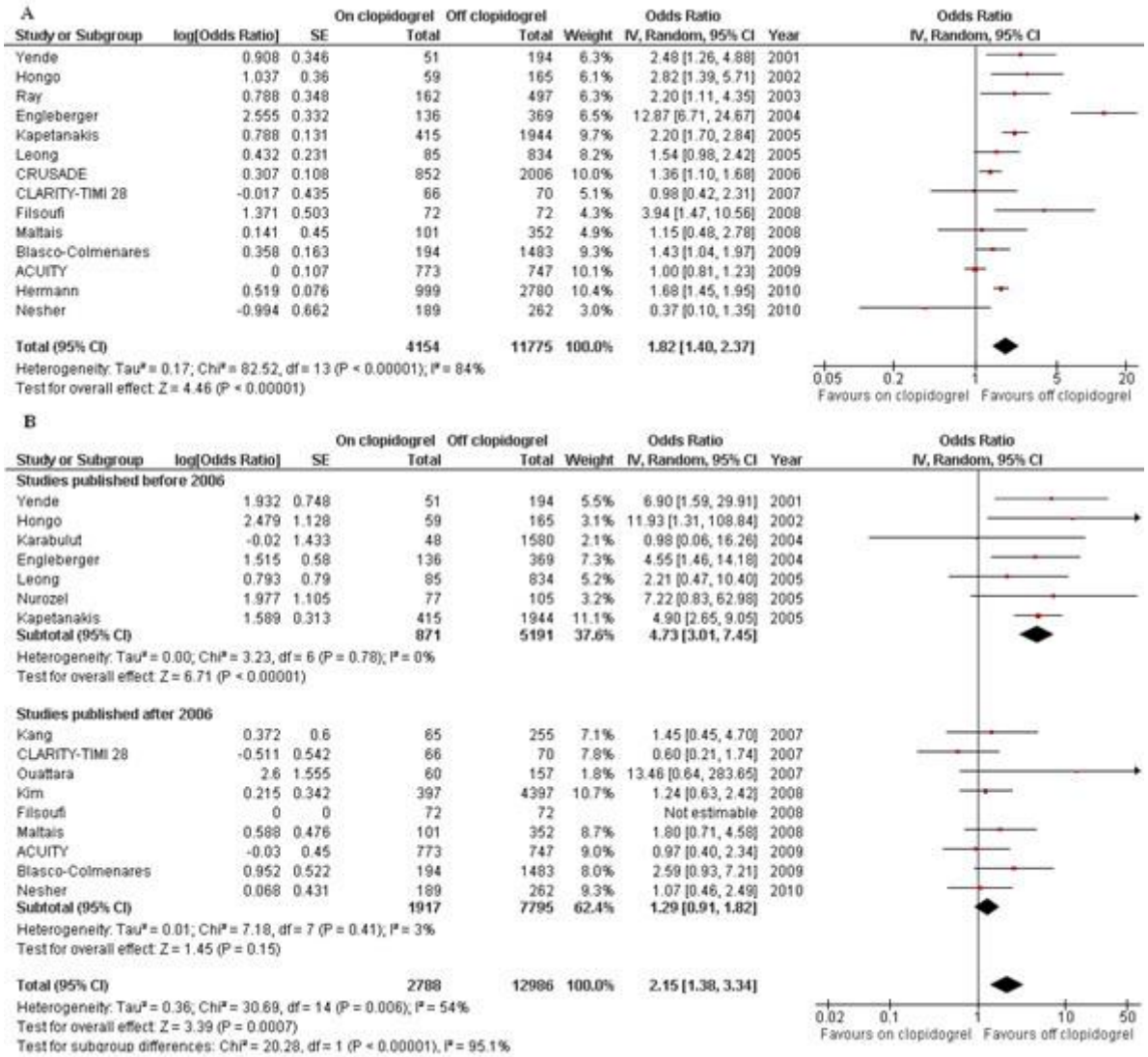


Study or Subgroup	log[Odds Ratio]	SE	On clopidogrel Total	Off clopidogrel Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Yende	0.086	0.817	51	194	1.4%	1.09 [0.22, 5.40]	2001
Hongo	-0.777	1.11	59	165	0.7%	0.46 [0.05, 4.05]	2002
Engleberger	0.599	0.919	136	369	1.1%	1.82 [0.30, 11.03]	2004
Kapetanakis	0.405	0.739	415	1944	1.7%	1.50 [0.35, 6.38]	2005
Leong	0.344	1.077	85	834	0.8%	1.41 [0.17, 11.65]	2005
CRUSADE	0.239	0.222	852	2006	18.3%	1.27 [0.82, 1.96]	2006
CLARITY-TIMI 28	0.285	0.87	66	70	1.2%	1.33 [0.24, 7.32]	2007
Kang	-0.02	0.807	65	255	1.4%	0.98 [0.20, 4.77]	2007
Maltais	0.837	0.498	101	352	3.6%	2.31 [0.87, 6.13]	2008
Kim	0.262	0.355	397	4397	7.2%	1.30 [0.65, 2.61]	2008
Filsoufi	1.988	1.521	72	72	0.4%	7.30 [0.37, 143.90]	2008
ACUITY	0.131	0.208	773	747	20.8%	1.14 [0.76, 1.71]	2009
Blasco-Colmenares	0.365	0.37	194	1483	6.6%	1.44 [0.70, 2.97]	2009
Nesher	0.336	0.588	189	262	2.6%	1.40 [0.44, 4.43]	2010
Hermann	0.113	0.167	999	2780	32.3%	1.12 [0.81, 1.55]	2010
Total (95% CI)			**4454**	**15930**	**100.0%**	**1.24 [1.03, 1.49]**	

Heterogeneity: Tau² = 0.00; Chi² = 4.86, df = 14 (P = 0.99); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)

Abbreviations: SE: standard error; CI: confidence interval

8. Figure: Overall risk of transfusion (A) and reoperation subgroup analysis (B)



A

Study or Subgroup	log[Odds Ratio]	SE	On clopidogrel Total	Off clopidogrel Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Yende	0.908	0.346	51	194	6.3%	2.48 [1.26, 4.88]	2001
Hongo	1.037	0.36	59	165	6.1%	2.82 [1.39, 5.71]	2002
Ray	0.788	0.348	162	497	6.3%	2.20 [1.11, 4.35]	2003
Engleberger	2.555	0.332	136	369	6.5%	12.87 [6.71, 24.67]	2004
Kapetanakis	0.788	0.131	415	1944	9.7%	2.20 [1.70, 2.84]	2005
Leong	0.432	0.231	85	834	8.2%	1.54 [0.98, 2.42]	2005
CRUSADE	0.307	0.108	852	2006	10.0%	1.36 [1.10, 1.68]	2006
CLARITY-TIMI 28	-0.017	0.435	66	70	5.1%	0.98 [0.42, 2.31]	2007
Filsoufi	1.371	0.503	72	72	4.3%	3.94 [1.47, 10.56]	2008
Maltais	0.141	0.45	101	352	4.9%	1.15 [0.48, 2.78]	2008
Blasco-Colmenares	0.358	0.163	194	1483	9.3%	1.43 [1.04, 1.97]	2009
ACUITY	0	0.107	773	747	10.1%	1.00 [0.81, 1.23]	2009
Hermann	0.519	0.076	999	2780	10.4%	1.68 [1.45, 1.95]	2010
Nesher	-0.994	0.662	189	262	3.0%	0.37 [0.10, 1.35]	2010
Total (95% CI)			**4154**	**11775**	**100.0%**	**1.82 [1.40, 2.37]**	

Heterogeneity: Tau² = 0.17; Chi² = 82.52, df = 13 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.46 (P < 0.00001)

B

Study or Subgroup	log[Odds Ratio]	SE	On clopidogrel Total	Off clopidogrel Total	Weight	Odds Ratio IV, Random, 95% CI	Year
Studies published before 2006							
Yende	1.932	0.748	51	194	5.5%	6.90 [1.59, 29.91]	2001
Hongo	2.479	1.128	59	165	3.1%	11.93 [1.31, 108.84]	2002
Karabulut	-0.02	1.433	48	1580	2.1%	0.98 [0.06, 16.26]	2004
Engleberger	1.515	0.58	136	369	7.3%	4.55 [1.46, 14.16]	2004
Leong	0.793	0.79	85	834	5.2%	2.21 [0.47, 10.40]	2005
Nurozel	1.977	1.105	77	105	3.2%	7.22 [0.83, 62.98]	2005
Kapetanakis	1.589	0.313	415	1944	11.1%	4.90 [2.65, 9.05]	2005
Subtotal (95% CI)			**871**	**5191**	**37.6%**	**4.73 [3.01, 7.45]**	
Heterogeneity: Tau² = 0.00; Chi² = 3.23, df = 6 (P = 0.78); I² = 0%							
Test for overall effect: Z = 6.71 (P < 0.00001)							
Studies published after 2006							
Kang	0.372	0.6	65	255	7.1%	1.45 [0.45, 4.70]	2007
CLARITY-TIMI 28	-0.511	0.542	66	70	7.8%	0.60 [0.21, 1.74]	2007
Ouattara	2.6	1.555	60	157	1.8%	13.46 [0.64, 283.65]	2007
Kim	0.215	0.342	397	4397	10.7%	1.24 [0.63, 2.42]	2008
Filsoufi	0	0	72	72		Not estimable	2008
Maltais	0.588	0.476	101	352	8.7%	1.80 [0.71, 4.58]	2008
ACUITY	-0.03	0.45	773	747	9.0%	0.97 [0.40, 2.34]	2009
Blasco-Colmenares	0.952	0.522	194	1483	8.0%	2.59 [0.93, 7.21]	2009
Nesher	0.068	0.431	189	262	9.3%	1.07 [0.46, 2.49]	2010
Subtotal (95% CI)			**1917**	**7795**	**62.4%**	**1.29 [0.91, 1.82]**	
Heterogeneity: Tau² = 0.01; Chi² = 7.18, df = 7 (P = 0.41); I² = 3%							
Test for overall effect: Z = 1.45 (P = 0.15)							
Total (95% CI)			**2788**	**12986**	**100.0%**	**2.15 [1.38, 3.34]**	

Heterogeneity: Tau² = 0.36; Chi² = 30.69, df = 14 (P = 0.006); I² = 54%
Test for overall effect: Z = 3.39 (P = 0.0007)
Test for subgroup differences: Chi² = 20.28, df = 1 (P < 0.00001), I² = 95.1%

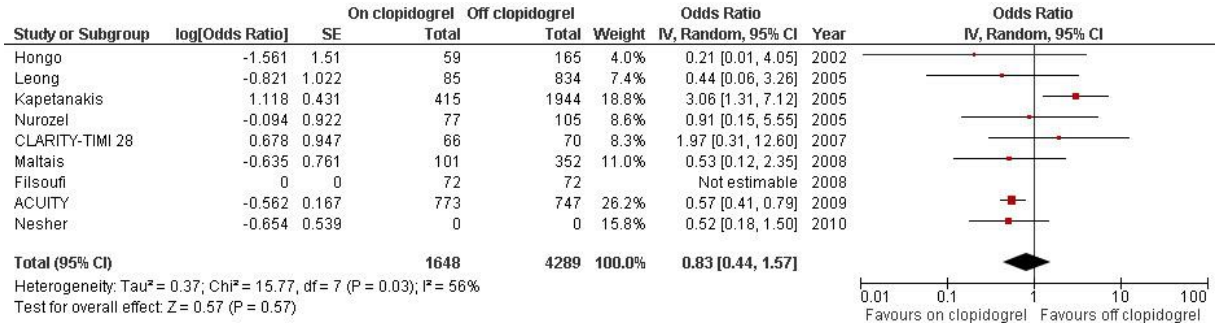
Abbreviations: SE: standard error; CI: confidence interval

8. Table: Subgroup and sensitivity analyses

Subgroup analysis (p value)		Number of studies (number of participants)	Odds ratio (95% CI)				
			RBC transfusion	Myocardial infarction	Reoperation	Mortality	Major bleeding
Discontinuation of clopidogrel prior to surgery	<3 days§	5 (2779)	7.56 [2.38, 23.99]**	0.91 [0.15, 5.55]	3.40 [1.51, 7.65]**	2.66 [0.87, 8.08]	6.62 [1.69, 25.95]**
	<5 days¥	14 (18807)	1.95 [1.31, 2.91]**	0.59 [0.44, 0.80]**	1.57 [0.99, 2.48]	1.23 [1.01, 1.49]*	1.14 [0.95, 1.37]
	<5 days vs. >5 days†	6 (7670)	1.36 [1.00, 1.84]‡	NA	1.90 [0.80, 4.49]	1.35 [0.82, 2.22]	1.32 [1.04, 1.68]*
Aprotinin use	Yes	10 (13751)	2.53 [1.57, 4.07]**	1.30 [0.23, 7.37]	2.89 [1.37, 6.10]**	1.20 [0.92, 1.58]	1.79 [0.99, 3.24]‡
	No	10 (9917)	1.32 [1.08, 1.63]**	0.59 [0.43, 0.79]**	1.63 [0.99, 2.68]‡	1.26 [0.98, 1.63]	0.98 [0.80, 1.20]
GP IIb/IIIa use	Yes	6 (9867)	1.44 [1.19, 1.75]**	0.50 [0.15, 1.64]	1.95 [1.03, 3.71]*	1.36 [0.98, 1.90]	1.73 [0.77, 3.89]
	No	14 (13801)	2.05 [1.36, 3.10]**	1.03 [0.45, 2.38]	2.19 [1.13, 4.26]*	1.16 [0.91, 1.47]	1.32 [0.91, 1.93]
OPCAB	Yes	9 (11537)	2.35 [1.33, 4.14]**	0.88 [0.31, 2.46]	2.42 [1.33, 4.38]**	1.32 [0.97, 1.79]	1.81 [0.74, 4.45]
	No	11 (12131)	1.53 [1.23, 1.89]**	0.69 [0.31, 1.52]	1.83 [0.93, 3.60]	1.19 [0.94, 1.51]	1.24 [0.91, 1.70]
Quality score	QS>7	11 (1)	1.76 [1.20, 2.59]**	0.75 [0.31, 1.81]	2.16 [1.31, 3.56]**	1.29 [1.02, 1.63]*	1.94 [0.63, 6.00]
	QS≤7	8 (71769)	2.00 [1.47, 2.72]**	0.91 [0.15, 5.55]	3.34 [1.34, 8.29]**	1.14 [0.83, 1.55]	1.38 [0.97, 1.96]

***p<.05.; ‡p=.05.; **p<.01.; §: studies with shorter than 3 days exposure vs. no clopidogrel pretreatment; ¥: studies with shorter than 5 days exposure (including the group of the <3 days vs. no clopidogrel pretreatment); †: controlled comparison of the <5 days exposure group vs. >5 days exposure group; NA: not applicable**

9. Figure: Overall risk of postoperative myocardial infarction



Abbreviations: SE: standard error; CI: confidence interval

4.2.6 Limitations

There are several obvious limitations of this study. First, the number of the high-quality, randomized clinical trials was low in the analysis. Randomized studies are usually well-balanced with regard to baseline characteristics of the enrolled patients; this is typically not the case for observational studies. Consequently, the analysis may inadvertently include some inclusion bias. In order to obviate selection bias, adjusted odds ratios are reported in some observational studies. To incorporate the adjustment, - where possible - adjusted ORs were pooled with logarithmic transformation according to a random-effect model via generic-inverse variance-weighting.

Although the rates of bleeding-related complications are easy to calculate, the indication of red blood cell transfusion and reoperation might have been very arbitrary and might have differed markedly among studies. This aspect might have been reflected in the heterogeneity of the results.

4.3 Clinical relevance of high platelet reactivity

4.3.1 Search strategy

We performed a systematic review of the available publications according to the MOOSE guidelines, to conduct meta-analyses of observational studies. [74] Pub Med and Central databases were searched for relevant articles published between January 2003 and February 2010. Search key words included various combinations of "clopidogrel" with the following terms: resistance, platelet reactivity, outcome and prognostic. No language restriction was used. We also searched the reference lists of relevant studies and reviews, editorials, and letters. In case of incomplete reporting, individual authors were contacted.

4.3.2 Selection criteria

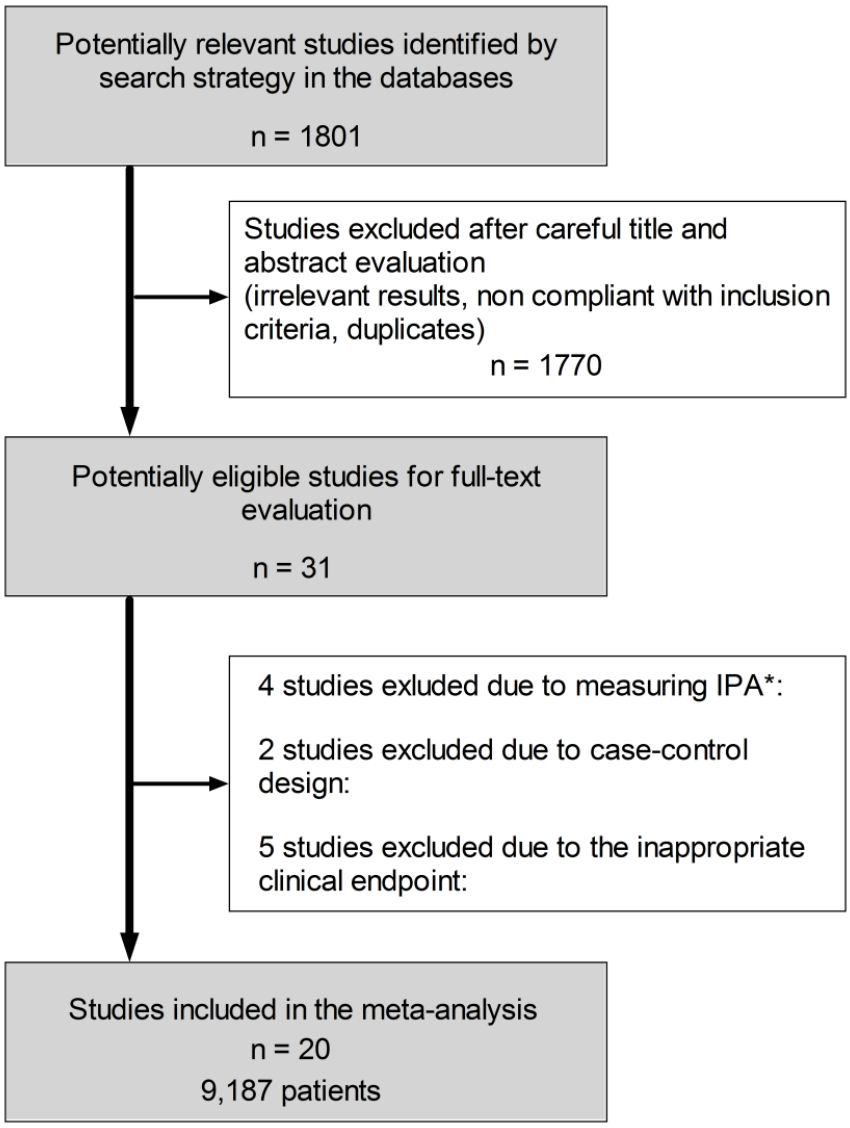
We selected all relevant studies which met the following inclusion criteria:

(1) Studies that recruited patients receiving aspirin and clopidogrel therapy after percutaneous coronary intervention (PCI);

(2) Reported an intention-to-treat analysis on the clinical impact of HPR measured by an ADP-specific platelet function assay. No case-control studies were accepted. The accepted assays included ADP-stimulated light transmission aggregometry (LTA_{ADP}), flow cytometric assessment of vasodilator-stimulated phosphoprotein phosphorylation (VASP; PLT VASP/P_2Y_{12} kit, Biocytex, Marseille, France), the VerifyNow device using P_2Y_{12} cartridge ($VerifyNow_{P2Y12}$; Accumetrics, San Diego, CA), and multiple electrode aggregometry with ADP stimuli (MEA_{ADP}; Dynabyte, Munich, Germany). In case of studies using more than one assay, two assays with the highest predictive values were selected. [58; 63; 72]

(3) All studies that measured platelet aggregation values after a loading dose or during the maintenance phase of clopidogrel therapy were eligible. Examinations that assessed responsiveness to clopidogrel, that is, a difference between baseline and post-treatment platelet reactivity (inhibition of platelet aggregation [IPA]), were excluded from the analysis. (Figure 10)

10. Figure: Flowchart of study selection



*IPA: inhibition of platelet aggregation, calculated as the baseline aggregation minus post-treatment aggregation value

The primary clinical outcomes of interest, evaluated at the longest available follow-up (during which patients were on clopidogrel treatment) were (a) cardiovascular (CV) death, (b) definite/probable stent thrombosis (ST), (c) non-fatal myocardial infarction (MI) (Type 1, 4a, 4b) and (d) a composite endpoint of the reported ischemic events (CIE) that included CV death, MI, ischemic stroke, unplanned repeat revascularization or rehospitalization for ACS. Those studies that evaluated solely periprocedural MI (Type 4b) were excluded.

4.3.3 Data abstraction and analysis

Selection and data abstraction were done independently by two reviewers on prespecified structure collection forms. Disagreements were resolved by consensus and discussion with a third party. Statistical analysis was performed using the Review Manager 5.0.22 freeware package maintained by the Cochrane Collaboration. (Review Manager [RevMan]. Version 5.0.22 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.) Hazard ratios (HR) and odds ratios (OR) adjusted for the relevant clinical parameters, from individual studies, were pooled with the random-effect model via generic-inverse variance-weighting. If the adjusted relative risk was not reported, the odd ratios were calculated from the reported event frequencies. Heterogeneity was quantified with a Chi^2 heterogeneity statistic and by means of I^2. Group comparisons in case of the prevalence of HPR were done with the Kruskal-Wallis test. A p value < than 0.05 was considered significant.

4.3.4 Study selection

Our search resulted in 1801 citations. These included reviews and articles that did not meet our inclusion criteria. After careful title and abstract evaluation, 31 potentially appropriate studies were found. After excluding case-control analyses, studies that linked clopidogrel responsiveness (baseline minus post-treatment aggregation, IPA) to clinical outcome and

studies that reported solely the rate of periprocedural myonecrosis, 20 articles including a total number of 9,187 patients were selected for full text analysis and data extraction. [55; 39; 56; 57; 58; 59; 60; 42; 61; 62) (63; 65; 64; 66; 67; 68; 69; 71; 72; 70)] (Figure 10) Out these, thirteen studies reported platelet reactivity with LTA_{ADP}, [39; 55; 56; 58; 59; 42; 61; 62; 63; 65) (64; 66; 68)] five with the $VerifyNow_{P2Y12}$ assay, (58; 60; 67; 69; 70) three used VASP phosphorylation [57; 63; 72] and two the MEA_{ADP} device [71; 72]. Major characteristics of the included studies are depicted in Table 9.

9. Table: Detailed description of the selected studies

Investigator (Publication year)	Design, patient profile	Number of patients	Laboratory methods	Selected cutoff for HPR	HPR (%)	Clopidogrel LD / MD	End point	Follow-up	Quality score†
Cuisset (2006)	RCT, NSTEMI	146*	LTA: 10µmol ADP, AGGmax	AGGmax ≥70%	15.1	600 / 75	CIE	1 month	NA
Cuisset (2006)	Prospective, NSTEMI	106	LTA: 10µmol ADP, AGGmax	Highest quartile (AGGmax ≥70%)	21.7	300 / 75	CIE	1 month	9
Geisler (2006)	Prospective, all-comer	363	LTA: 20µmol ADP, AGGmax	AGGmax ≥70%	6.1	600 / 75	D / MI / CIE	3 months	9
Hochholczer (2006)	Prospective, stable angina	802	LTA: 5µmol ADP, AGGlate	Above the median (AGGlate ≥15%)	49.3	600 / 75	D / MI / CIE	1 month	9
Angiolillo (2007)	Prospective, stable angina with DM	173	LTA: 20µmol ADP, AGGmax	Highest quartile (AGGmax ≥62%)	26.0	0 / 75	CIE	2 years	9
Bliden (2007)	Prospective stable angina	100	LTA: 5µmol ADP, AGGmax	AGGmax ≥50%	22.0	0 / 75	MI / CIE	1 year	9
Bonello (2007)	Prospective, stable/UA	144	VASP: PRI	Highest quintile (PRI >47%)	79.9	300 / 75	D / CIE	6 months	9
Buonamici (2007)	Prospective, all-comer	804	LTA: 10µmol ADP, AGGmax	AGGmax ≥70%	13.1	600 / 75	D / ST	6 months	9
Frere (2007)	Prospective, NSTEMI	195	VASP: PRI LTA:10µmol ADP, AGGmax	PRI≥53% AGGmax ≥70% (ROC-defined)	54.4 29.8	600 / 75	CIE	1 month	9
Aradi (2008)	Prospective, stable/ UA	108§	LTA: 5µmol ADP, AGGmax	Patients above the median (AGGmax >33%)	51.9	300 / 75	MI / ST / CIE	10 months	9
Patti (2008)	Prospective, all-comer	160	VerifyNow	Highest quartile (>240 PRU)	25.0	600 / 75	CIE	1 month	9

Price (2008)	Prospective, all-comer	317#	VerifyNow	≥235 PRU (ROC-defined)	34.1	600 / 75	D / MI / ST / CIE	6 months	9
Castro (2009)	Prospective, NSTEMI	161	VerifyNow	>175 PRU (ROC-defined)	39.8	300 / 75	CIE	1 year	9
Cuisset (2009)	Prospective, NSTEMI	598	LTA 10 µmol ADP, AGGmax VASP, PRI	AGGmax > 67% (ROC-defined) PRI: not reported	30.9	600 / 75	ST	1 month	9
Geisler (2009)	Prospective, all-comer	1019	LTA: 20 µmol ADP, AGGlate	Patients of the highest quartile (>42.5%)	32.3	600 / 75	D / MI ST / CIE	3 months	9
Marcucci (2009)	Prospective, ACS	683	VerifyNow	≥240 PRU (ROC-defined)	32.1	600 / 75	D / MI / CIE	1 year	9
Migliorini (2009)	Prospective, all-comer (LM)	215	LTA: 10 µmol ADP, AGGmax	AGGmax > 70%	18.6	600 / 75 or 150	D / MI ST	3 years	9
Sibbing (2009)	Prospective, all-comer	1608	MEA: AUC	Highest quintile (>416 AU)	20.1	600 / 75	D / MI ST	1 month	9
Siller-Matula (2009)	Prospective, all-comer	416	MEA: AUC VASP: PRI	AUC > 54 U PRI > 23 % (ROC-defined)	13.5 63.0	600 or 0 / 75	ST	6 months	9
Breet (2010)	Prospective, stable angina	1069	LTA: 5 µmol LTA: 20 µmol ADP, AGGmax VerifyNow	AGGmax ≥42.9% AGGmax ≥64.5% ≥236 PRU (ROC-defined)	42.4 37.3 38.6	300/75 or 600/75 or 0/75	D / MI ST /CIE	1 year	9

Abbreviations: ADP: adenosine 5'-diphosphate; AGGmax: maximal aggregation; AGGlate: late aggregation; AU: arbitrary unit; AUC: area under curve; CIE: composite ischemic events; D: cardiovascular death; DM: diabetes mellitus; LD: loading dose; LM: left main stenting; LTA: light transmission aggregometry; MEA: multiple electrode aggregometry; MI: non-fatal myocardial infarction; MD: maintenance dose; NA: not applicable; NSTEMI: non-ST-segment elevation MI; PRI: platelet reactivity index; PRU: platelet reaction unit; RCT: randomized controlled trial; ST: stent thrombosis; VASP: vasodilator-stimulated phosphoprotein phosphorylation analysis; †: New Castle Ottawa score: quality assessment of observational studies; this scoring is not applicable for randomized, controlled trials; *: data from the 600-mg loaded group, §: data from clopidogrel-treated patients, #: patients on clopidogrel for at least 6 months, UA: unstable angina

4.3.5 Prevalence of high on-clopidogrel platelet reactivity

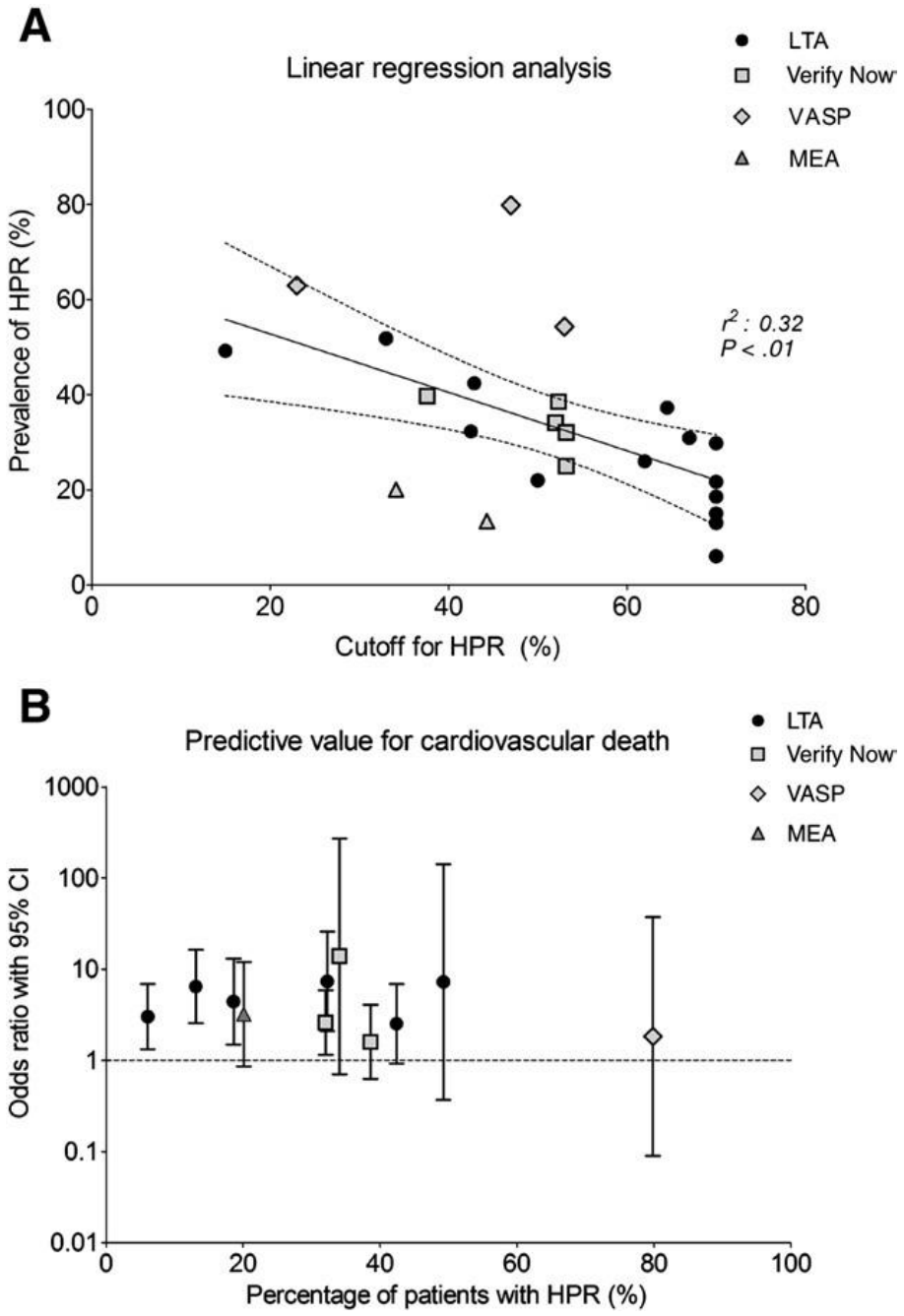
In the 20 studies, including 9,187 patients, the rate of HPR showed large heterogeneity with a mean prevalence of 32.3% (95% CI for mean: 25.9–40.5; range: 6.06-79.86). To find possible determinants of the observed heterogeneity, the prevalence of HPR was analyzed according to the following grouping factors: type of platelet function device, the selected platelet reactivity cutoff, the amount of clopidogrel loading dose, time of assessment from loading/last clopidogrel dose, proportion of acute coronary syndrome patients in each group. (Table 10) Among the recruited studies, the selected platelet reactivity cutoff and the type of the platelet function device interacted significantly with the prevalence of HPR (Kruskal-Wallis test: P=0.04 and P=0.02, respectively; Table 10). The selected cutoff was in strong, inverse correlation with the rate of HPR. (Figure 11A) Among the devices, the most P_2Y_{12}-specific assay (VASP) indicated the highest rates of HPR.

10. Table: Prevalence of high on-clopidogrel platelet reactivity (HPR)

	Mean, % (95% CI)	P
Overall	33.2 (25.9 – 40.5)	
Platelet Function Method		
MEA_{ADP}: LTA_{ADP}: $VerifyNOW_{P2Y12}$: VASP:	16.8 (-25.1 – 58.7) 28.3 (20.5 – 36.1) 33.9 (26.6 – 41.2) 65.8 (33.5 – 98.0)	*0.02*
Clopidogrel Loading Dose*		
0 mg (pre-treatment) 300 mg 600 mg	24.0 (-1.4 – 49.4) 48.3 (9.5 – 87.2) 29.2 (20.2 – 38.1)	0.27
Time to assessment from loading/last dose of clopidogrel*		
<12 h 12-18 h >18 h	31.1 (20.4 – 41.9) 28.7 (16.3 – 41.0) 33.7 (-66.3 – 133.7)	0.62
Platelet reactivity cutoff for defining HPR (tertiles†)‡		
14 – 45% 46 – 62% 63 – 70%	39.0 (25.2 – 52.8) 39.0 (22.8 – 55.2) 21.6 (12.8 – 30.3)	*0.04*
Proportion of ACS patients (tertiles)		
0 – 25% 25 – 80% 80 – 100%	37.1 (20.4 – 53.8) 27.9 (5.3 – 50.4) 32.0 (20.3 – 43.7)	0.34

Intergroup comparisons were done with the Kruskal-Wallis test. *: The POPULAR study (106) was not included as recruited patients received three different clopidogrel regimens. † For the comparison, 2 continuous variables (platelet reactivity cutoff and proportion of ACS patients) were divided into tertiles, which means dividing ordered data into 3 essentially equal-sized data subsets. ‡ Whereas LTA_{ADP} and VASP measure platelet reactivity in a 0% to 100% scale, results might range between 18 and 435 PRU in case of $VerifyNow_{P2Y12}$ and between 0 and 122 U in case of MEA_{ADP} assay according to the description of the manufacturer. Thereby, results of the $VerifyNow_{P2Y12}$ and MEA_{ADP} assays were normalized to a 0 to 100 scale, where the lowest potential value (18 PRU and 0 U) reflects 0% and the highest potential value (435 PRU and 122 U) means 100%.

11. Figure: Impact of the methodological heterogeneity in platelet aggregation tests



Impact of the methodological heterogeneity in platelet aggregation tests. A, Linear regression analysis between the selected cutoff and the prevalence rate for high platelet reactivity (HPR). Whereas LTA_{ADP} and VASP measure platelet reactivity in a 0% to 100% scale, results might range between 18 and 435 PRU in case of the $VerifyNow_{P2Y12}$ and between 0 and 122 U in case of MEA_{ADP} assay according to the description of the manufacturer. Thereby, results of the $VerifyNow_{P2Y12}$ and MEA_{ADP} assays were normalized to a 0 to 100 scale, where the lowest potential value (18 PRU and 0 U) reflects 0% and the highest potential value (435 PRU and 122 U) means 100%. B, The impact of the prevalence rate of HPR on the relative risk of CV death.

4.3.6 Prognostic significance of high on-clopidogrel platelet reactivity

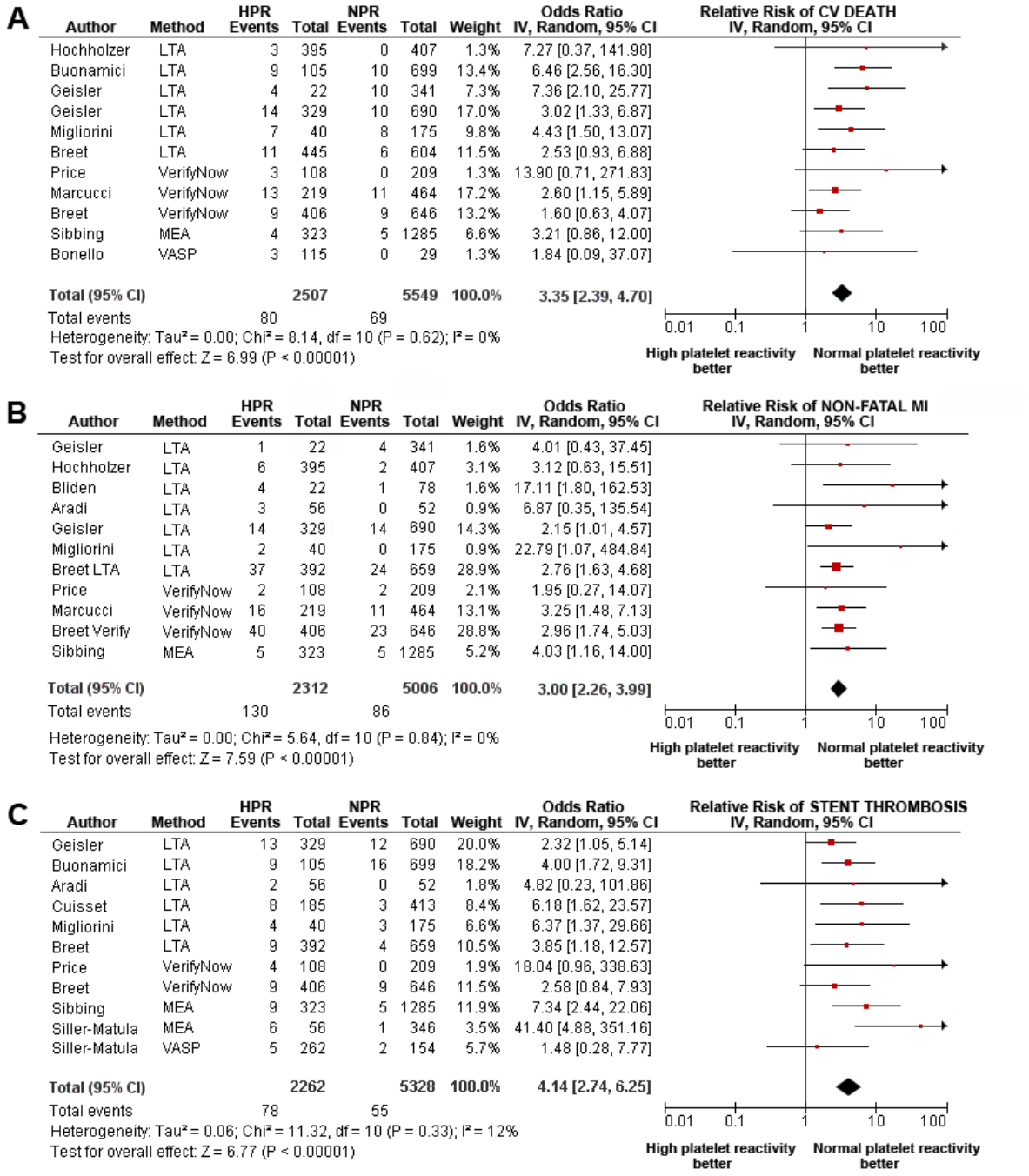
Of the 20 studies, ten reported data on cardiovascular death, [57; 58; 59; 65; 64; 66; 67; 68; 70; 71] ten on non-fatal myocardial infarction [39; 56; 58; 65; 64; 66; 70; 67; 68; 71] and nine on definite or probable stent thrombosis (ST) [39; 58; 62; 63; 64; 68; 70; 71; 72]. Moreover, there were 15 studies that reported a composite event rate of the recurrent ischemic events (CIE) in compliance with our inclusion criteria [41; 39; 56; 57; 58; 60; 42; 61; 62; 63) (65; 66; 67; 69; 70]. Based on the pooled results, HPR was associated with a significant, 3-fold increase in non-fatal MI (OR: 3.00; 95%CI: 2.26-3.99; p<0.00001; Figure 12B), a 4-fold increase in definite/probable ST (OR: 4.14; 95%CI: 2.74-6.25; p<0.0001; Figure 12C) and a 5-fold increase in the rate of composite ischemic events (OR: 4.95; 95%CI: 3.34-7.34; p<0.00001; Figure 13). Importantly, patients with HPR defined by an ADP-specific platelet function assay had a 3.4-fold increase in cardiovascular mortality compared to those with normal on-clopidogrel ADP-reactivity (OR: 3.35, 95%CI: 2.39-4.70, p<0.00001; Figure 12A). When the subgroup of studies using receiver operating characteristic (ROC)-defined cutoffs for HPR was analyzed separately, similar outputs were gained (CV death 2.34 [1.40-3.92], MI 2.89 [2.07-4.04], ST 4.75 [2.13-10.63], and CIE: 3.06 [2.07- 4.51]; P <0.001 in all cases). Although there was large methodical heterogeneity among the platelet function assays as well as in the selected cutoffs for HPR, the predicted risk for CV death, non-fatal MI and ST were not heterogeneous between studies (Figure 12). On the contrary, there was significant heterogeneity in case of the less standardized, composite end point (Figure 13).

When the predictive value of each assay was analyzed separately, only LTA-defined HPR was significantly associated with CV death, MI, and ST (death: 4.18 [2.70-6.46], MI: 2.93 [1.97-4.35], ST: 3.66 [2.32-5.78]; P<0.0001 in all cases). The VerifyNow$_{P2Y12}$ predicted CV death and MI (death: 2.28 [1.23-4.25], P=0.009; MI: 2.98 [1.94-4.58], P<0.00001), but only a trend was

observed regarding ST (4.17 [0.81-21.63], P=0.09). MEAADP significantly predicted MI and ST (MI: 4.03 [1.16-14.00], P=0.03; ST: 13.89 [2.63-73.45], P =0.002), but only a trend was observed regarding CV death (3.21 [0.86-12.00], P=0.08). Based on the results of 2 small studies, VASP-defined HPR was predictive neither for CV death (1.84 [0.09-37.07], P=0.69) nor for ST (1.48 [0.28-7.77], P =0.64).

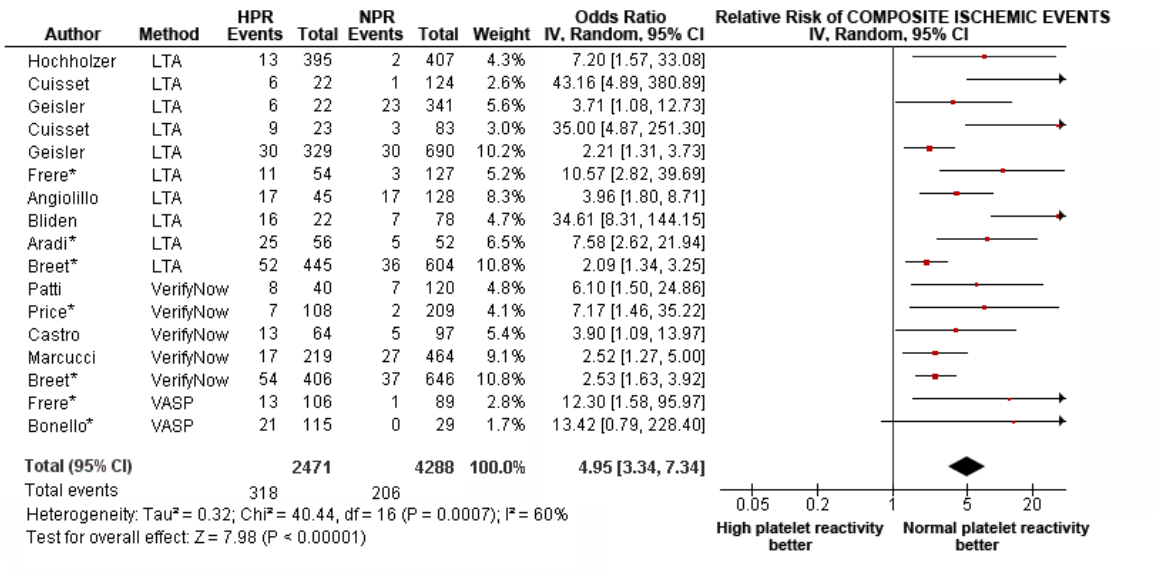
Because of the large differences in the methodology, terminology, as well as the patient selection and follow-up, we performed subgroup analyses among the studies that reported composite outcome results (Figure 14). The analysis confirmed that all of the selected ADP-specific assays were able to predict the occurrence of CIE, and the worse prognosis of patients with HPR was consistent regardless of the clinical presentation and the length of follow-up. Notably, there was significant heterogeneity in the results between studies using optical aggregometry; however, the more standardized methods, such as the VerifyNow$_{P2Y12}$ and VASP assay, showed more homogenous findings.

12. Figure: Impact of high on-clopidogrel platelet reactivity (HPR) on the occurrence of cardiovascular (CV) death (Panel A), non-fatal myocardial infarction (MI, Panel B) and definite or probable stent thrombosis (Panel C)



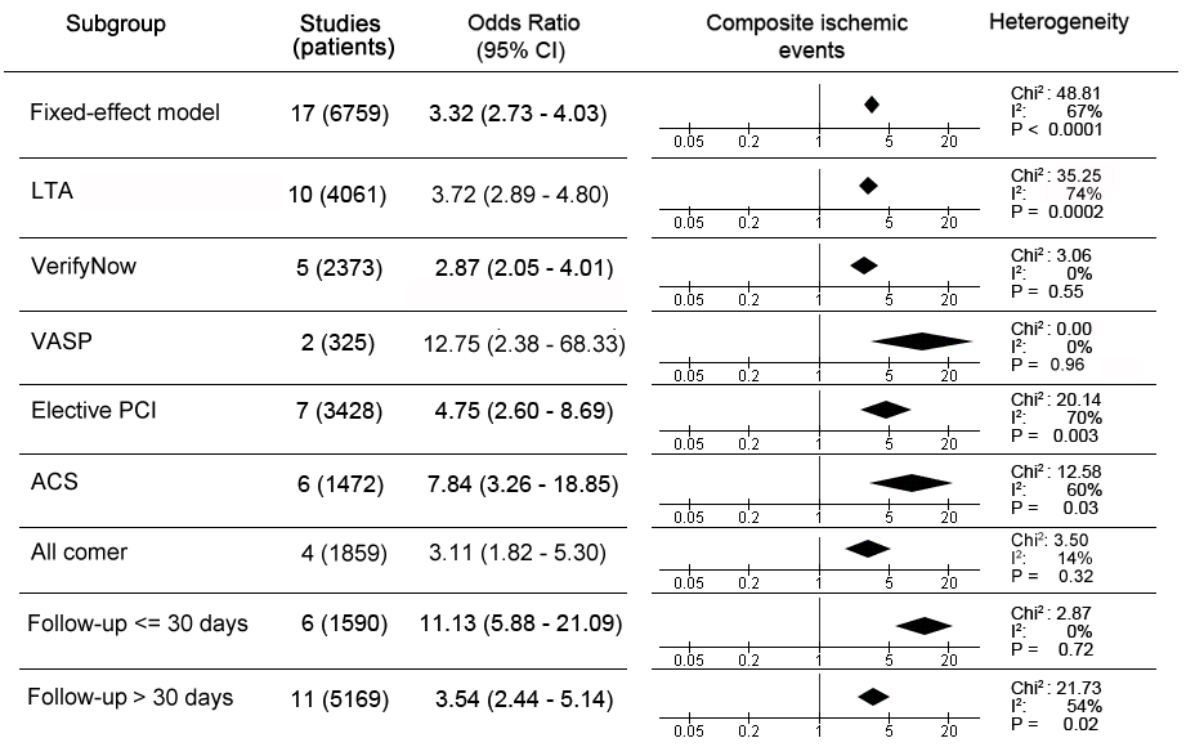
The odds ratios (OR) with 95% confidence intervals (95% CI) were calculated from event frequencies with the random-effect model via generic inverse variance-weighting. LTA: light transmission aggregometry; MEA: multiple electrode aggregometry; NPR: normal platelet reactivity; VASP: vasodilator-stimulated phosphoprotein phosphorylation assessment.

13. Figure: Impact of high on-clopidogrel platelet reactivity (HPR) on the occurrence of composite ischemic events (CIE)



Where possible, adjusted odds ratios (OR) with 95% confidence intervals (95%CI) were used in the random-effect model via generic inverse variance-weighting. *: studies not reporting adjusted OR-s. LTA: light transmission aggregometry; NPR: normal platelet reactivity; VASP: vasodilator-stimulated phosphoprotein phosphorylation assessment.

14. Figure: Sensitivity and subgroup analyses among studies that linked post-treatment platelet reactivity to the occurrence of composite ischemic events



ACS: acute coronary syndrome; LTA: light transmission aggregometry; PCI: percutaneous coronary intervention VASP: vasodilator-stimulated phosphoprotein phosphorylation

4.3.7 Limitations

Our analyses have some obvious limitations. The meta-analysis included observational studies that are usually unbalanced with regard to baseline clinical characteristics of the patients. Although observational studies could better reflect the real-world practice, lack of monitoring drug compliance, underreporting a negative result, and incomplete follow-up make their interpretation more difficult and might carry ascertainment biases. To control for possible confounding factors, adjusted risks were used where possible; and data were pooled with logarithmic transformation according to a random-effect model via generic inverse variance weighting. Although these factors might have an impact on the magnitude of the observed ORs, they did not influence the prevalence rate of HPR and were not thought to have biased the overall analysis. It is also notable that the patients were not treated uniformly regarding the loading doses of clopidogrel and that platelet function assessments were performed at different time points after PCI. One study also enabled the use of different antiplatelet strategies in the maintenance period, whereas none of the selected studies could reliably monitor compliance with the prescribed medication. In conclusion, this meta-analysis confirms that patients with HPR are at a heightened risk for CV death, MI, and ST after stent implantation. Whether HPR is a marker for adverse outcomes or a modifiable risk factor that can be diminished by more aggressive antiplatelet strategies remains to be established by the ongoing, large-scale randomized trials (ARCTIC: NCT00827411, DANTE: NCT00774475, DOSER: NCT00638326, GRAVITAS: NCT00645918, TRIGGER-PCI: NCT00910299)

5 Novel findings of the thesis

Main findings of the thesis are the followings:

Transradial percutaneous coronary intervention reduces the risk of periprocedural major bleeding and major adverse events in the ST-elevation acute myocardial infarction setting. The difference between two access routes was represented in clinically insignificant differences is procedural time and in time to reperfusion. Nevertheless the mortality significantly decreased in transradial route.

Clopidogrel pre-treatment of patients before cardiac surgery, increases the risk of major bleeding. A trend for improvement can be observed in the frequency of the need for reoperation. However perioperative care and surgical practice seems to adapt the changed medication protocol. Our meta-analysis found statistically significantly increased risk for mortality among clopidogrel pretreated patients.

High on-clopidogrel platelet reactivity, measured by an ADP-specific platelet function assay after percutaneous coronary intervention, is a strong predictor of cardiovascular death, myocardial infarction and stent thrombosis in patients after percutaneous coronary intervention. Although there were large differences in the methodology, patient selection and cutoff definition between studies, the predicted risk of cardiovascular death, myocardial infarction and stent thrombosis were not heterogeneous.

6 Discussion

The meta-analysis of studies investigating the role of vascular access site in patients with ST elevation found that transradial coronary intervention is highly effective and safe in the setting of acute myocardial infarction. We demonstrated a significant benefit of using radial access for PCI in MI with respect to major bleeding as well as in major adverse events (MACE). These findings were consistent in the setting of primary- and rescue PCI.

Bleeding events have been demonstrated to be associated with an increased risk of MACE including death and recurrent ischemic events in multiple studies. [31; 32; 107] Though the exact relation between bleeding events and higher mortality is unclear, obviating bleeding seems equally important as recurrent ischemic events after PCI. [45] Possible mechanisms of worse outcome after a bleeding event might include bleeding-induced imbalance of the coagulant/anticoagulant mechanisms, (consumption of the anticoagulant proteins, higher platelet turnover), adverse effects induced by transfusion, and premature cessation of antithrombotic/anticoagulant therapy. [21] As a consequence of the combined- and more potent anticoagulant and antiplatelet medications, bleeding is getting to be more frequent after acute intervention. Arterial puncture used for intervention is a predominant predilection site as the majority of bleeding originates from here. Reduction of the frequency of bleeding and mortality using the transradial approach has been recently demonstrated in a large registry study that included all-comers for PCI. [31] Similar reduction has been demonstrated in transradially treated cases in an observational study that included over a thousand non-ST segment elevation acute coronary syndrome patients. [108] Furthermore, two recent comprehensive meta-analyses of randomized comparisons of transradial- and transfemoral accesses demonstrated that radial access reduces bleeding

and access site complications. Neither of them found a significant link between the frequency of adverse events or mortality. It should be noted that these analyses included studies performed predominantly in elective settings and thus the benefit that the higher risk patients may have been concealed by the lower risk cases that may have formed the majority.

Distrust supported by technical difficulties, higher failure rate, and increased radiation exposure still limits general acceptance of TRPCI. This uncertainty is graver in the setting of acute MI, when the delay caused by unsuccessful arterial access may adversely affect the clinical outcome. Agostoni et al. reported reduction of the entry-site complications at the expense of more frequent entry failure requiring crossover to a second entry site with significant heterogeneity among studies. They noted that this may have been due to an initial learning curve by cardiologists employing the radial technique that was followed by a progressive equalization in technical skills for both the radial- and femoral approaches through the years. [13] In our analysis nine of the twelve studies reported an initial limit of experience of the operators. Further two reports involved PCI centers that use radial access as first choice for any type of PCI. (Table 4) Unfortunately these data are too heterogeneous and insufficient to draw further consequences regarding the transradial operator volume that is indispensible for starting a transradial primary PCI program. Additionally not only the initial learning curve but also the constant practice is important in keeping low the complication rate. Furthermore we believe that maintenance of a routine elective transradial program alongside a continuous quality assessment is an indispensible background for a safe and efficacious transradial STEMI program. Transradial primary PCI reports dominantly originate from centers of excellence and involved trained radialists and this is in line with the fact that the data on access site failure showed homogeneity

supporting that the operators included in the studies has already completed the learning curve.

In our analysis, procedural times showed significant variation among studies and TRPCI was not associated either with significantly longer procedural durations or with longer reperfusion times. This underlines the role of expertise and the notion that use of the usual access site in case of emergency might result in shorter procedural length. Altogether the heterogeneity in the different time parameters supports that other factors – most probably experience of the team and skills of the operator as well as the different local protocols – affect them more than the choice of the arterial puncture.

The main findings of the meta-analysis of studies examining the impact of perioperative clopidogrel to the outcome of heart surgery are the following. Firstly, we observed a significant increase in mortality associated with concomitant clopidogrel therapy that was consistent over the studies. Secondly, clopidogrel treatment within 7 days of cardiac surgery increases the risk of RBC transfusions and bleeding-triggered reoperations, although, there was significant heterogeneity regarding this risk among studies. Thirdly, there was no difference regarding the rates of myocardial infarction in clopidogrel-treated patients undergoing cardiac operations.

The most novel finding of this meta-analysis is the higher rate of mortality with clopidogrel after cardiac surgery. Although, this risk was homogenous over the individual studies, they were underpowered to demonstrate the excess risk, previously. The exact mechanisms are unknown, but the most evident explanation is a connection between bleeding-related complications to higher mortality. This association has been well-documented in patients after PCI and might be true for the surgical revascularization as well. [34; 109; 32; 110] One of the

included trial found that preoperative clopidogrel therapy was associated with increased risk of infections that might also contribute to the worse prognosis; however, based on our meta-analysis we can neither support nor confute this association. [101] Overall, the observed 24% increase in the relative risk of mortality is a lot smaller than the relative risk of bleeding complications whilst mortality increase was not opposed by any decrease in the rate of postoperative MI. Furthermore, as the data is originating from observational studies we cannot exclude that inclusion bias of higher rate clopidogrel use or shorter delay between cessation and operation at higher risk patients did not influence the observed higher mortality.

As expected, the meta-analysis confirmed a significant increase of bleeding-related complications among clopidogrel-pretreated patients. Bleeding events have been demonstrated to be associated with an increased risk of major adverse cardiac events including death and recurrent ischemic events in multiple studies. [33; 32] Though the exact relation between bleeding events and worse outcome is unclear, reducing bleeding seems equally important as recurrent ischemic events after CABG. [109] According to the subgroup analyses of the current study, the higher risk of bleeding-complications is not homogenous in every clinical situation. The risk for RBC transfusions is dropping with time between cessation of clopidogrel and the operation. Regarding bleeding-triggered reoperation, the higher risk was only evident in studies performed before 2006. Possible reasons for the lower reoperation rate among novel studies might include evolution in the perioperative care and adjunctive pharmacotherapy as well as in surgical practice. Altogether perioperative care and surgical practice seems to adapt to the novel circumstances when patients with higher bleeding risk are more frequently referred for cardiac surgery. Aprotinin, an antifibrinolytic serine protease inhibitor, was used for many years in elective

and urgent surgery, both routinely and selectively in patients with increased risk of bleeding. [111] Aprotinin decreased bleeding complications and reduced the need for transfusions in clopidogrel-treated patients undergoing CABG. [112] A recently published meta-analysis, which examined the efficacy of aprotinin in comparison to tranexamic acid (TXA), showed that aprotinin caused a more remarkable reduction in postoperative blood loss than TXA, and consequently fewer requirements for RBC transfusion and re-operation for bleeding. [113] It has also been shown that activated factor VII supplementation can decrease intractable bleeding in patients after cardiac surgery. [114] The fact that application of these agents may not only be beneficial in terms of reduction of bleeding is illustrated by a recently published meta-analysis proving that aprotinin increased mortality compared with TXA in cardiac surgery. [115] As a consequence of the increased frequency of end-organ damage aprotinin had been pulled from all countries and allowed only in patients without reasonable alternative therapy. In our subgroup analysis of studies applying aprotinin no benefit was demonstrable. This paradoxical relation can be explained by the observational nature of the included studies that may contain an inherent treatment bias linked to perioperative higher-risk patients.

The importance of the surgical technique on bleeding complications was well demonstrated in the CRUSADE registry and in the CURE trial. [35; 97] In these studies the strongest predictor of the RBC transfusions was the surgeon who performed the operation. There might be differences in bleeding complications between on-pump and off-pump operations, as well. Kuss et al. published a meta-analysis comparing off- and on-pump coronary artery bypass grafting, which has shown significantly increased RBC transfusion rates with the usage of cardiopulmonary bypass. [116] As off-pump CABG is getting more popular in recent years, it might influence the temporal changes in bleeding complications.

The higher mortality is exciting in the light of the introduction of novel, more potent P_2Y_{12} ADP-receptor antagonists. Prasugrel, that has been shown to decrease the risk of cardiovascular death, myocardial infarction and stroke in ACS patients after PCI, was associated with a 4.73-fold higher risk for major bleeding events in patients undergoing CABG procedures. [18] These data suggests that contrary to clopidogrel, the recommended 5-day washout period might not be sufficient in case of prasugrel. The introduction of the reversible P_2Y_{12} antagonists might change outcome of ACS patients requiring urgent bypass operations. According to the results of the PLATO trial, ticagrelor was not associated with higher risk for CABG-related bleeding complications, however, showed a significant mortality benefit compared to clopidogrel among patients with ACS. [117] These results promise that the higher mortality risk observed with irreversible ADP receptor antagonists might be opposed with ticagrelor in the future.

The main finding of the meta-analysis of platelet funcition studies after coronary stent implantation are that patients with HPR after PCI, detected by an ADPspecific laboratory assay, are at a higher risk for CV death, nonfatal MI, ST, and recurrent ischemic events. Although there were large differences in the methodology, patient selection, and cutoff definition between studies, the predicted risk of CV death, MI, and ST was not heterogeneous.

Before this meta-analysis, numerous observational studies have highlighted that those defined as clopidogrel non/low responders or with high on-treatment platelet reactivity were at higher risk for recurrent ischemic events. [42; 61; 65; 66; 55; 56; 57; 59; 63; 39) (69; 70; 60; 62; 64; 67; 68; 71; 72; 58] However, it is difficult to interpret these results because of the large methodical heterogeneity, the diverse and often arbitrarily defined cutoffs for HPR, the lack of proven

compliance, and the underpowered sample sizes. The controversy of a generally accepted, standardized, bedside test with a consensus cutoff for selecting high-risk patients hampers the current recommendation for routine platelet function testing. [73]

The findings of the current study are in line with the meta-analysis of Snoep et al published several years ago. [106] That analysis included 8 clinical studies that involved a total number of 1,205 patients. Thereby, it was underpowered to detect a clear impact on separate clinical outcomes such as CV death or MI. Moreover, it mixed studies that reported results on the inhibition of platelet aggregation values, also known as clopidogrel responsiveness, with those measuring on-treatment platelet reactivity. Using case-control studies also decreased the reliability of the analysis. Since that time, a considerably higher number of articles have been published in the topic that enabled us to evaluate not only composite but also separate clinical end points among those that measured on-treatment platelet reactivity. Not only the number of studies but also the qualities of the studies have significantly improved during this period, resulting in large-scale, prospective, adequately powered single-center experiences. [64; 67; 71; 58] Therefore, the 3-fold higher risk for nonfatal MI, the 3.4-fold increase in CV death, and the 4-fold higher rate for ST were demonstrated in almost 9,200 patients. It is also important to notice that newer, more standardized platelet function assays (eg, MEA_{ADP}, $VerifyNow_{P2Y12}$) have become available since the previous work of Snoep et al. To elucidate the differences between the available platelet function devices, the landmark POPULAR study performed a head-to-head comparison between 8 assays that monitored on-treatment platelet reactivity among 1,069 patients after elective PCI. [58] As a result, LTA_{ADP}, the $VerifyNow_{P2Y12}$ assay, and the Plateletworks device were able to discriminate between patients with and without death, nonfatal MI, definite ST, or ischemic stroke. [58] However,

the IMPACT-R, PFA collagen/ADP, and Innovance PFA_{P2Y} assays had no predictive values regarding clinical outcomes.

Although some methods such as the MEA_{ADP} and VASP assay were not tested in the study, these results emphasize that the available platelet function tests are not equal in detecting HPR or in predicting clinical outcomes. These interassays differences were suggested in prior studies that compared VASP phosphorylation with ADP-stimulated platelet aggregation measurement. According to the findings, LTA_{ADP} and MEA_{ADP} had a better predictive value than the completely P_2Y_{12} specific testing. [63; 62; 72] Although studies using VASP phosphorylation were underrepresented in the current meta-analysis, our results confirmed its poor predictive value regarding CV death and ST. One explanation for these observations is that VASP measures the degree of P_2Y_{12} receptor inhibition, but does not give a functionally relevant measure of aggregation as a whole; therefore, it fails to encompass the true extent of HPR.

Another important lesson from the POPULAR study is that there might be substantial interassay differences in the predictive values according to the exact clinical outcomes. Whereas $LTA_{ADP\ 5\ \mu mol/L}$ had the highest OR for predicting death, $LTA_{ADP\ 20\ \mu mol/L}$ had the highest OR for ST; and the Plateletworks device proved to be the best to predict MI. [58] In the current meta-analysis, LTA_{ADP} had the highest predictive value for CV death, whereas MEA_{ADP} had the greatest power to predict MI and ST. These findings widen our current view on platelet function devices and suggest that there is not one superior device; instead, there are assays that best predict a separate outcome.

In the meta-analysis, we observed large interstudy and intraassay heterogeneity in the prevalence of HPR that resulted in a range of 6% to 80%. This was largely driven by the

differences in the methodologies and in the diverse definitions of platelet reactivity cutoffs. Interestingly, the highest rates of HPR patients were observed in case of the most sensitive P_2Y_{12} receptor saturation testing (VASP), whereas whole blood aggregometry (MEA_{ADP}) identified fewer patients with HPR. The higher cutoffs in platelet reactivity also resulted in lower prevalence rates of HPR. To evaluate whether the variability in HPR carries clinical consequences, the prevalence of HPR was contrasted to the predictive values regarding CV mortality. Those studies and devices that found an unexpectedly high prevalence rate of HPR (typically higher than the mean prevalence rate of 33%) did not predict mortality (Figure 11B). It is important to emphasize that on-treatment platelet reactivity follows normal distribution; thereby, it is not possible to separate HPR patients on the basis of the laboratory assessment itself. The cutoff for HPR should be assigned on a clinically adjusted basis with ROC curve analysis, which might decrease the heterogeneity in the prevalence rate of HPR.

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9 List of publication

9.1 Topic related articles

- A. Vorobcsuk, A. Kónyi, D. Aradi, I. G. Horváth, I. Ungi, Y. Louvard, A. Komócsi. Transradial versus Transfemoral Percutaneous Coronary Intervention in Acute Myocardial Infarction. Systematic Overview and Meta-Analysis. American Heart Journal. 2009 Nov;158(5):814-21.
  (IF 4.357, 2009) (Independent citation: 6)

- D. Aradi, A. Komócsi, A. Vorobcsuk, O. Rideg, M. Tőkés-Füzesi, T. Magyarlaki, I. G. Horváth, V. Serebruany. Prognostic significance of high on-clopidogrel platelet reactivity after percutaneous coronary intervention: systematic review and meta-analysis. American Heart Journal. 2010 Sep;160(3):543-51.
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- A. Vorobcsuk, D. Aradi, K. Farkasfalvi, I.G. Horváth, A. Komócsi. Outcomes of patients receiving clopidogrel prior to cardiac surgery. International Journal of Cardiology. 2010 Nov 26. [Epub ahead of print] doi:10.1016/j.ijcard.2010.10.034.
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- A. Komócsi, A. Vorobcsuk, D. Aradi. Transradial Percutaneous Coronary Intervention in Acute Myocardial Infarction. Interventional Medicine and Applied Sciences 2010 2(2) 53-58.

9.2 Non-topic related articles

- D. Aradi; A. Vorobcsuk; T. Pintér; Zs Lenkey; I.G. Horváth; A. Komócsi. Low platelet disaggregation predicts poor response to 150 mg clopidogrel in patients with elevated platelet reactivity. Platelets 2010 Feb;21(1):1-10
  (IF 2.271, 2008)

- D. Aradi, T. Magyarlaki, M. Tőkés-Füzesi, O. Rideg, A. Vorobcsuk, A. Komócsi. Comparison of conventional aggregometry with VASP for monitoring P_2Y_{12}-specific platelet inhibition. Platelets. 2010;21(7):563-70.
  (IF 2.272, 2009)

- D. Aradi, A. Vorobcsuk, A. Komócsi. Optimizing clopidogrel therapy before stent implantation: should clinical setting be taken into account? J Am Coll Cardiol. 2008 Oct 14;52(16):1349 *letter*
  (IF 11.438, 2008)

Cumulative impact factor: 16.726 (with including IF of the letter: 28.164)

9.3 International abstracts, posters

2010

European Society of Cardiology Congress Stockholm

- Doubling the maintenance dose of clopidogrel in patients with high post-clopidogrel platelet reactivity after elective percutaneous coronary intervention: the DOSER randomized, placebo-controlled trial.
  D. Aradi, O. Rideg, T. Magyarlaki, A. Vorobcsuk, B. Magyari, T. Pintér, A. Kónyi, I.G. Horváth, A. Komócsi. Abstract No. 5340 Eur Heart J (2010) 31 (Abstract supplement), 970

EuroPCR, Congress of the European Association of Percutaneous Cardiovascular Interventions Paris

- Cardiovascular outcomes in patients with high post-clopidogrel platelet reactivity
  D. Aradi, A. Vorobcsuk, I.G. Horváth, V. Serebruany, A. Komócsi

2009 **European Society of Cardiology Congress Barcelona**

- Monitoring P_2Y_{12} receptor inhibition with light transmission aggregometry: a comparison with vasodilator stimulated phosphoprotein phosphorylation assay.

  D. Aradi, A. Vorobcsuk, M. Tőkés-Füzesi, T. Magyarlaki, I.G. Horváth, A. Komócsi. University of Pécs, Hungary Abstract No. P1317 Eur Heart J (2009) 30 (suppl 1):195

- Transradial percutaneous coronary intervention improves outcome in acute mycardial infarction. A meta-analysis.

  A. Komócsi, A. Vorobcsuk, I. Ungi*, D. Aradi, I.G. Horváth, A. Kónyi. University of Pécs, Heart Center, Pécs, Hungary,*2nd Dept. of Internal Medicine, Szeged, Hungary Abstract No. P5283 Eur Heart J (2009) 30 (suppl 1):926

2005 **18th Annual Congress – Amsterdam, Netherlands**

- Hemodynamic measurements after coronary bypass operation and intraaortic balloon pump implantation

  Sz. Czuczor, I. Győrimolnár, L. Melczer, R. Kiss, A. Vorobcsuk, L. Papp. Intensive Care Unit of Cardiac Surgery, Heart Clinic, University of Pécs, Faculty of Medicine. Intensive Care Medicine 2005 V31-211

- The effect of sterile and non-sterile towels on skin bacterial flora following iodine shower

  Sz. Czuczor, I. Győrimolnár, I. Bátai*, A. Vorobcsuk, M. Kerényi*.

  Intensive Care Unit of Cardiac Surgery, Heart Clinic, University of Pécs, Faculty of Medcine, Dept. of Anaesthesia, *Medical Microbiology, University of Pécs, Faculty of Medcine. Intensive Care Medcine 2005 V31-183

9.4 Hungarian abstracts, posters

2010 **Magyar Szívsebészeti Társaság Tudományos Kongresszusa**

- Preoperatív clopidogrel kezelés hatása a morbiditásra és mortalitásra szívműtött betegekben.
  Vorobcsuk A., Aradi D., Farkasfalvi K., Szabados S. Horváth I.G., Komócsi A.

Magyar Kardiológus Társaság Tudományos Kongresszusa

- A clopidogrel hatékonysága és a klinikai végpontok előfordulása közötti összefüggés stent implantation átesett betegeknél: a témában megjelent tanulmányok szisztematikus áttekintése és meta-analízise.
  Vorobcsuk A., Aradi D., Horváth I.G., Komócsi A.

Magyar Aneszteziológiai és Intenzív Terápiás Társaság Tudományos Kongresszusa

- Preoperatív clopidogrel kezelés hatása a klinikai végkimenetelre és a vérzéses szövõdmények elõfordulására szívsebészeti beavatkozás során: a témában megjelent tanulmányok szisztematikus áttekintése és meta-analízise.
  Vorobcsuk A., Aradi D., Farkasfalvi K., Komócsi A.

2009 **Magyar Kardiológus Társaság Tudományos Kongresszusa**

- Optikai aggregometria mérési eredményeinek összevetése specifikus P_2Y_{12} receptor gátlás áramlási citometriás meghatározásával.
  Aradi D., Vorobcsuk A., Sayour A., Magyarlaki T., Tőkés-Füzesi M., Rideg O., Horváth I.G., Komócsi A. Cardiologia Hugarica 2009; 39: A19
- Transzradiális PCI akut miokardiális infarktus ellátása során – szisztematikus irodalmi áttekintés és metaanalízis.

Komócsi A., Vorobcsuk A., Ungi I., Aradi D., Horváth I.G., Kónyi A. Cardiologia Hugarica 2009; 39: A1

2008 **Magyar Kardiológus Társaság Tudományos Kongresszusa**

- Folyamatos cardiac output monitorozás vezérelte bal kamrai elektród pozicionálás.

  Czuczor Sz., Melczer L., Kiss R., Vorobcsuk A., Harsányi K., Győrimolnár I., Papp L. Cardiologia Hugarica 2008; 38: B51

2007 **14th Annual Congress of the Hungarian Society of Cardiac Surgery**

- Effect of different type fluid loading on pulmonary permeability after cardiac surgery

  I. Győrimolnár, A. Vorobcsuk , K. Farkasfalvi, Zs. Tóth, L. Papp. University of Pécs, Heart Center, Pécs, Hungary, Cardiologia Hugarica 2007; 3: D4

2005 **Magyar Aneszteziológiai és Intenzív Terápiás Társaság 33. Nemzeti Kongresszusa és 5. Duna Kongresszus**

- Haemodinamikai mérőmódszerek alkalmazása coronária műtéten átesett betegeken intraaorticus ballon pumpa támogatás mellett.

  Vorobcsuk A., Czuczor Sz., Győrimolnár I., Melczer L., Papp L. PTE ÁOK Szívgyógyászati Klinika E 40

- Povidone-jóddal történő teljes test fürdetés hatása a bőrflórára a perioperatív szakban.

  Czuczor Sz., Győrimolnár I., Bátai I., Kiss R., Vorobcsuk A., Kerényi M. PTE ÁOK Szívgyógyászati Klinika, PTE ÁOK AITI, PTE ÁOK Microbiológiai Intézet E 41