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Efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing in patients after percutaneous coronary intervention: Systematic review and meta-analysis

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ABSTRACT

Background: ADP-specific platelet function assays were shown to predict thrombotic events, and might be helpful to select candidates for more potent antiplatelet therapy. We aimed to determine the efficacy and safety of giving intensified antiplatelet therapy on the basis of platelet reactivity testing for patients undergoing percutaneous coronary intervention (PCI).

Methods: Electronic databases were searched to find prospective, randomized trials that reported the clinical impact of using an intensified antiplatelet protocol (repeated loading or elevated maintenance doses of clopidogrel, prasugrel or glycoprotein IIb/IIIa inhibitor) on the basis of ADP-specific platelet reactivity testing (VerifyNow, Multiplate, VASP or light transmission aggregometry) compared to standard-dose clopidogrel. Evaluated efficacy measures included cardiovascular death, non-fatal myocardial infarction and definite/probable stent thrombosis (ST), while major bleeding events were recorded as safety endpoint.

Results: Between 2008 and 2011, 10 clinical trials comprising 4213 randomized patients were identified. Compared to standard antiplatelet therapy, the intensified protocol was associated with a significant reduction in cardiovascular mortality, ST and myocardial infarction ($p<0.01$ for all). There was no difference in the rate of major bleeding events between intensified and standard groups ($p=0.44$). Although the observed effects regarding mortality, ST and bleeding were not heterogeneous, meta-regression analysis revealed that the net clinical benefit of the intensified treatment significantly depended on the risk of ST with standard-dose clopidogrel ($p=0.023$).

Conclusion: Intensifying antiplatelet therapy on the basis of platelet reactivity testing reduces cardiovascular mortality and ST after PCI; however, the net benefit of this approach depends on the risk of ST with standard-dose clopidogrel.

1. Introduction

Administration of clopidogrel in addition to aspirin reduces thrombotic complications in patients with acute coronary syndrome (ACS) or undergoing percutaneous coronary intervention (PCI) [1,2]. However, the $P2Y_{12}$-receptor antagonist clopidogrel has several limitations including its delayed onset of action, moderate potency and large variability in terms of antiplatelet efficacy [3,4]. As a result, there remain a significant number of clopidogrel-treated patients with insufficient active metabolite generation and limited adenosine di-phosphate (ADP)-receptor inhibition [5]. Among these patients, standard doses of clopidogrel are insufficient to inhibit platelet activity resulting in a phenotype of "high on-treatment platelet reactivity" (HTPR) [5]. Numerous individual studies as well two meta-analyses have demonstrated that HTPR is strongly associated with cardiovascular death, myocardial infarction and stent thrombosis (ST) in patients undergoing

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PCI [6,7]. Just recently, a large-scale, prospective, multicenter registry involving 8575 patients confirmed these findings by showing a 3-fold higher risk for early definite or probable ST in patients with HTPR [8]. To tackle adverse clinical events associated with limitations of clopidogrel, new-generation, potent ADP-receptor antagonists were developed that provide more rapid, more potent and more reliable $P2Y_{12}$-receptor inhibition [5]. Although prasugrel and ticagrelor reduced the risk of cardiovascular death, myocardial infarction or stroke compared to clopidogrel in patients with ACS, the higher risk of bleeding coupled with a significant increase in costs remain important shortcomings with the new agents [9,10]. In this regards, platelet function assays might be helpful to select patients with inappropriate response to clopidogrel who might be ideal candidates for a more intense antiplatelet regimen. Several randomized clinical studies investigating such a strategy were published or presented recently; however, their results are controversial [11–20]. Therefore, we performed a systematic review and meta-analysis of randomized clinical trials in order to evaluate the clinical efficacy and safety of intensified antiplatelet therapy on the basis of platelet reactivity testing versus standard dose clopidogrel in PCI-treated patients with HTPR.

2. Methods

2.1. Study selection, endpoints

Electronic databases were searched for relevant articles published between January 2005 and November 2011. Search key words included the following terms: 'tailored antiplatelet treatment', 'clopidogrel resistance', 'platelet function monitoring', '150 mg clopidogrel', 'high platelet reactivity' and 'prasugrel'. We also searched the reference lists of relevant studies and reviews, editorials, and letters, together with related conference abstracts.

The main criteria for inclusion in the analysis was that a randomized clinical trial aimed to compare the clinical efficacy and/or safety of a modified antiplatelet protocol on the basis of an ADP-specific platelet function assay compared to standard dose clopidogrel in patients undergoing PCI. Studies that compared intensified protocols (higher dose, third agent, etc.) to standard care without platelet function monitoring were excluded. Similarly, studies that aimed to compare only the pharmacological efficacy of a platelet-function guided approach were also excluded. The accepted ADP-specific platelet function devices – in line with the consensus recommendation [5] – were: (a) the VerifyNow $P2Y_{12}$ assay, (b) the multiplate analyzer with ADP test, (c) flow cytometric assessment of vasodilator-stimulated phosphoprotein (VASP) phosphorylation index, and (d) conventional light transmission aggregometry with ADP used as an agonist. From one study [13] that identified and randomized both aspirin and clopidogrel non-responders, only data of patients with high on-clopidogrel platelet reactivity were included in the present meta-analysis.

The efficacy endpoints of the analysis included (a) cardiovascular death, (b) definite or probable ST, (c) non-fatal myocardial infarction and (d) the composite of cardiovascular death, non-fatal myocardial infarction or definite/probable ST. Myocardial infarction and cardiovascular death were used according to the study definition, while definite/probable ST was defined according to the Academic Research Consortium (ARC) criteria. In case of myocardial infarction, most of the studies collected post-PCI spontaneous events (type 1), while two studies [13,14] also recorded peri-procedural myonecrosis (type 4).

The main safety endpoint was major bleeding, defined as either according to the Thrombolysis In Myocardial Infarction (TIMI) 'major' criteria or as a 'severe or moderate' bleeding according to the Global Utilization of Streptokinase and T-PA for occluded coronary arteries (GUSTO) scale. Major and minor bleeding events were defined as TIMI major and minor events, or 'any bleeding' rates. In order to assess the overall balance between thrombotic and bleeding events, the net clinical benefit (i.e. the freedom from cardiovascular death, myocardial infarction, definite/probable ST and major bleeding) was composed.

Since the length of follow-up and the duration of the intensified antiplatelet intervention may have differed between trials, the authors mandated to collect endpoints according to the following time-frame:

(a) 30 days after the initiation of the intensified treatment in case of peri-procedural glycoprotein IIb/IIIa inhibitiors (GPI) [13,14] and in case of repeated clopidogrel loading doses [11,12];
(b) until the end of the intensified protocol in trials of increased maintenance doses of clopidogrel or prasugrel [15–20].

2.2. Data abstraction and analysis

Manuscript selection and data abstraction were done independently by 2 reviewers (DA and LB). After the selection of appropriate articles, first authors were contacted to verify the validity of the dataset. Disagreements were resolved by consensus.

Statistical analysis was performed using the Review Manager 5.1.4 freeware package maintained by the Cochrane Collaboration (Review Manager [RevMan] Version 5.1 Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011). Meta-regression analyses were performed with Comprehensive Meta-Analysis 2.2.064 program package. Reported event frequencies were used to calculate odds ratios (OR) with 95% confidence intervals (CI). Since the true treatment effect of various antiplatelet protocols may have varied among the included trials, the random-effects model was used in the analysis. Compared to the fixed-effects model, the random-effects model results in wider confidence intervals and provides more conservative and robust results, better accounting for inter-study differences [21]. Heterogeneity of the trial results was quantified with the Chi^2 heterogeneity statistic, and inconsistency was assessed by means of I^2 [21]. Results were reported as the p value of the Chi^2 test (p value less than 0.05 for heterogeneous results) and percent of the I^2 [21]. Interpretation of the latter was made by assigning attributes of low, moderate, and high in case of 0–25%, 50–75% and more than 75%, respectively. Subgroup and sensitivity analysis were also performed to identify possible sources of heterogeneity. To determine the impact of baseline clinical risk of patient groups on the observed clinical benefit, rate-control meta-regression analyses were performed. In these analyzes, each study was given a specific weight corresponding to its precision and weighted least squares linear regression analysis was performed to examine the relation between outcome and the clinical parameter of the control group.

Since the results of a study might substantially influence its acceptance to peer-reviewed journals, studies with negative or inconclusive results might be neglected during the review process increasing the potential impact of small, but positive experiments. To study the relevance of such publication bias, funnel plots were constructed plotting the trial results against their precision. Egger's regression intercept was used to assess asymmetry of these funnel plots. Since this analysis requires that the effect sizes from at least 10 studies are to be included, only composite clinical endpoints were used from the meta-analysis. When Egger's test showed a significant p value, the Duval and Tweedie's trim and fill method was used to impute 'hypothetical' missing studies and to calculate adjusted versus observed ORs. Moreover, Orwin's fail-safe N was used to calculate the required number of missing studies to make the results of the original analysis clinically neutral (the pooled OR >0.85 for tailored vs. standard approach). A p value of <0.05 was considered statistically significant throughout the analyses.

3. Results

3.1. Selected studies

Between 2008 and 2011, 10 studies involving 4213 (range: 74–2214) patients qualified for the analysis (Fig. 1). The included studies varied

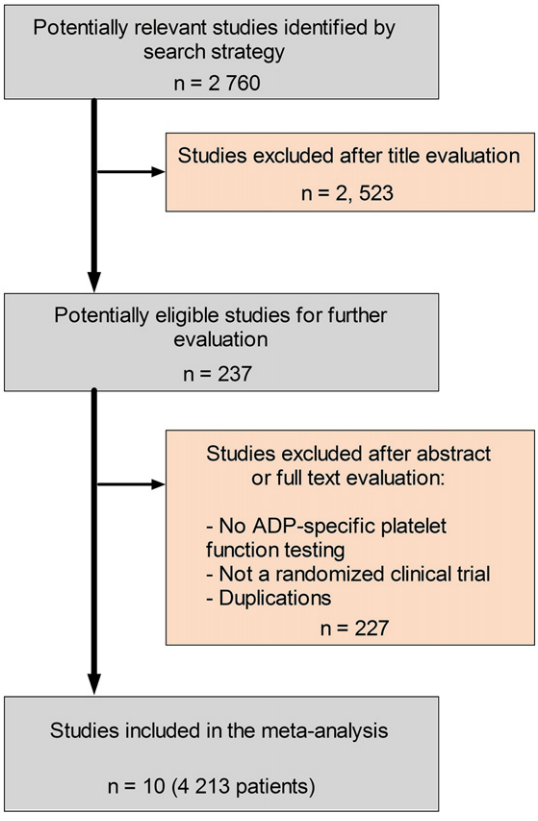

Fig. 1. Flowchart of study selection.