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Review

Does percutaneous coronary stent implantation increase platelet reactivity?

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ABSTRACT

High platelet reactivity (PR) values on treatment with clopidogrel are associated with an increased rate of thrombotic events after a percutaneous coronary intervention (PCI). However, we do not know the optimal timing of the performance of the PR measurements. Platelets might be activated during a PCI, which means that the timing of PR measurements, before or after PCI, could influence the outcome. In turn, this could lead to misinterpretation of the patient's response to antiplatelet therapy and a less accurate prediction of the patient's risk of thrombotic events during follow-up. We aimed to evaluate the effect of stent implantation on PR in patients with and without acute coronary syndromes who undergo PCI to assess the optimal timing of PR measurements. A systematic literature search was performed and the results are summarized in this review.

1. Introduction

Angioplasty with stent implantation is routinely used to treat stenoses of coronary arteries. Patients undergoing such a percutaneous coronary intervention (PCI) receive dual anti-platelet therapy (DAPT), consisting of a combination of aspirin and a $P2Y_{12}$ inhibitor, to prevent aggregation of platelets and thereby reduce the incidence of thrombotic events, particularly stent thrombosis. Clopidogrel is the most used $P2Y_{12}$ inhibitor in patients undergoing PCI. However, a large inter-individual variability in the response to clopidogrel is observed [1,2]. A multitude of studies have demonstrated that a subset of patients undergoing PCI show higher levels of platelet reactivity (PR) despite anti-platelet treatment with clopidogrel, which is called high on-treatment platelet reactivity (HPR). These patients are at an increased risk of atherothrombotic events after PCI [1,3,4]. There are several platelet function tests that can be used to measure PR [5]. However, the optimal timing for the performance of these platelet function tests is unknown. In some studies regarding PR, platelet function tests are performed before PCI [6–8], while PR is assessed after PCI in other studies [9–11].

There is a growing body of evidence that suggests that platelets are activated after PCI [12,13]. Additionally, the catheters that are used during the procedure can activate platelets within minutes after first contact [14]. The activation of platelets may be further stimulated by adenosine diphosphate (ADP), which is released from red blood cells and platelets that are damaged by contact with materials such as the stent or balloons, or by generated thrombin [15].

If PR levels which are measured early after PCI are higher than the levels measured before PCI, the actual level of platelet inhibition achieved by treatment with clopidogrel or other antiplatelet agents might be better than suggested by the PR measurement directly after PCI. Therefore, measuring PR directly after PCI might lead to misinterpretation of the patient's response to antiplatelet therapy and the patient's risk of atherothrombotic events during follow-up PCI.

The aim of this systematic review is to provide an overview of all available information regarding the influence of PCI on platelet reactivity. Furthermore, we evaluate the level of platelet reactivity over time, up to six months after PCI.

2. Methods

2.1. Criteria for considering studies in this review

2.1.1. Types of studies

This systematic search included studies in which platelet function measurements were performed on multiple time points.

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2.1.2. Types of participants

Studies with patients treated with aspirin and clopidogrel undergoing PCI with stenting were included. Adequate pre-treatment with clopidogrel at the time of blood sampling was a prerequisite for inclusion. Adequate pre-treatment was defined as a loading dose of 600 mg clopidogrel >6 h before blood sampling, 300 mg >12 hours pre-sampling, or a maintenance dose of 75 mg for >5 days for this review.

2.1.3. Types of intervention

In the studies that were included, patients underwent PCI. Platelet function assays had to be performed on multiple time points. The search included the most regularly used platelet function tests used to asses PR on clopidogrel: the VerifyNow assay, light transmission aggregometer, platelet function analyzer, Multiplate analyzer, flowcytometry (vasodilator-stimulated phosphoprotein [VASP] assay, P-selectin assay) and the thromboelastograph. By adding the search term 'platelet aggregation', we also tried to find studies using more obscure platelet function tests.

Articles were excluded based on the following criteria: 1) animal study; 2) review; 3) no platelet function measurements; 4) patients undergoing another intervention than PCI e.g. coronary artery bypass graft (CABG), stenting of cerebral or other arteries; 5) effect of other agents (no clopidogrel or other drugs in addition to clopidogrel) on platelet function; 6) studies focusing on the association of platelet function with other factors such as cigarette smoke, cannabis or different gene variants; 7) measurements around loading dose administration or with different loading concentrations; 8) the discontinuation of clopidogrel was studied; 9) platelet function assay was performed at only a single time point.

2.2. Search method

A systematic literature search of the electronic databases PubMed, EMBASE, and the Cochrane Library was performed. This search was limited to articles written in either English or Dutch. The terms 'percutaneous coronary intervention', 'PCI', and other procedures indicated with 'stent*' were used in the search as well as 'platelet function' or any of the platelet function tests described, and terms describing different forms of time indication. Detailed search strategies for PubMed, EMBASE, and the Cochrane Library are shown in Supplementary Appendix A.

2.3. Data analysis

The screening and selection of articles was performed by two independent authors (EM and SG) based on title and abstract. When there was uncertainty about the inclusion of an article, the full text of the article was screened. The references of the relevant articles were searched for useful articles that were not in the original search. Data from conference abstracts were also screened for relevance. Any disagreements about inclusion of articles were resolved by discussion, or by asking a third reviewer (PJ) to independently screen the article.

3. Results

The search in the PubMed database, EMBASE, and the Cochrane Library was performed on 11 March 2015. The results of this literature search are depicted in Fig. 1.

Most articles were excluded because platelet function measurements were performed to show the effect of other agents (e.g. tirofiban, abciximab) on PR.

3.1. Platelet reactivity in stable patients undergoing PCI

Several studies reported a change in PR directly after stent implantation in stable patients undergoing elective PCI, as shown in Table 1. Gurbel et al. studied different dosing regimens of clopidogrel in 50 patients undergoing elective PCI and found an increase in PR 2 h after PCI measured with the light transmission aggregometer (LTA) and the VerifyNow $P2Y_{12}$ assay (VN) [16]. After the increase in PR directly after PCI, PR returned to baseline levels at 5 hours post-PCI. Kaikita et al. studied 104 elective PCI patients and showed an increase in PR as measured with the VN and LTA immediately after PCI [17].

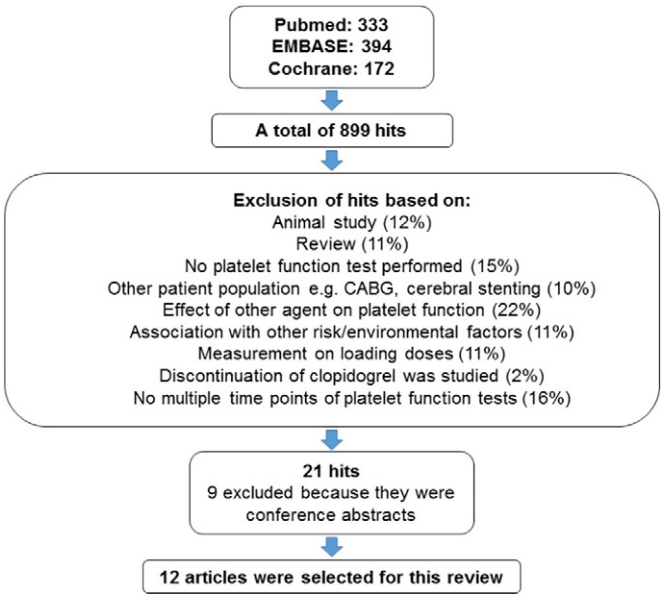

Fig. 1. Flow chart of literature search. Abbreviations: CABG = coronary artery bypass graft.

The increase in PR seems to be associated with procedural complexity. A study by Mangiacapra et al. measured PR with multiple electrode aggregometry (MEA) using the Multiplate analyzer in 65 patients with stable coronary artery disease (CAD) and observed that the increase in PR was smaller in patients undergoing angiography alone as compared to patients undergoing PCI combined with more invasive rotational atherectomy [18]. This increase in PR was also associated with total inflation time and total stent length.

PR seems to return to baseline levels after some time. A study by Siller-Matula et al. included 30 stable CAD patients undergoing PCI in which PR was assessed with the VASP-assay, platelet function analyzer (PFA) and Multiplate analyzer just after PCI and 1 day thereafter [19]. PR on clopidogrel was higher after PCI as compared to one day thereafter, indicating that there is an activation of platelets immediately after PCI and a stabilization of PR at one day after PCI. In a substudy which included 5 additional patients, PR was measured at four different time points: immediately before PCI and before heparin administration, immediately after PCI, and at 1 day and 2 days after PCI. In these additional patients, PR immediately after PCI was higher compared to all other time points, but stabilized after 1–2 days. Furthermore, Kaikita et al. also showed that after the initial increase in PR after PCI, PR stabilized to levels comparable to before PCI at 1 day, 2 days, and 28 days after PCI [17].

However, not all studies have reported stable levels of PR over a longer period of time. Campo et al. measured PR with the VerifyNow before PCI, and at 1 and 6 months after PCI in 300 patients undergoing PCI [20]. These patients showed higher PRU levels before PCI compared to 1 and 6 months after PCI. PR slightly decreased over time in this study.

Furthermore, Freynhofer et al. observed that PR as assessed with the VASP assay was higher at 6–12 h after PCI than after 1 month in