Use of the PFA-100 closure time to predict cardiovascular events in aspirin-treated cardiovascular patients: a systematic review and meta-analysis

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CRD summary
This review concluded that a short closure time was associated with increased recurrence of ischaemic events in aspirin-treated cardiovascular patients. Given the lack of a thorough quality assessment, apparent limitations of the included studies, presence of publication bias, clinical heterogeneity between studies and the generalisation to patients with cardiovascular disease, the conclusions should be treated with some caution.

Authors' objectives
To evaluate the predictive value of platelet function by measuring closure time of a membrane aperture determined with collagen/epinephrine cartridge (PFA-100\textsuperscript{TM} CT\textsubscript{CEPI}; PFA herein) for ischaemic events in patients with symptomatic atherosclerosis treated with aspirin.

Searching
MEDLINE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for English-language publications to 2007; search terms were reported. Bibliographies of identified studies and conference abstracts were searched.

Study selection
Studies that used PFA to evaluate platelet function and used a cut-off value to define responders and non-responders for the assessment of ischaemic events in patients with symptomatic atherosclerosis treated with aspirin were eligible for inclusion. All but one study recruited patients with coronary artery disease. Where reported, mean age of participants ranged from 54 to 69. Aspirin dose was from 75mg/day to 500mg/day. CT\textsubscript{CEPI} cut off values were from 130s to 203s. The prevalence of non-responders ranged from 9.5\% to 49\%.

Two reviewers independently selected studies; disagreements were resolved by discussion.

Assessment of study quality
The authors did not state that they systematically assessed study quality, however, the blinding of biologists and clinicians was reported.

Data extraction
Data were extracted to allow the construction of a 2x2 table from which odds ratios (OR) and 95\% confidence intervals (CI) were calculated for the occurrence or recurrence of ischaemic events in aspirin non-responders (patients with a closure time equal to or less than the cut-off; short PFA) compared to aspirin responders (patients with a closure time more than the cut-off).

Two reviewers independently extracted data; disagreements were resolved by discussion.

Methods of synthesis
A pooled odds ratio and 95\% CI was calculated from the results of the prospective studies using a logarithm of the odds ratio; studies with a retrospective, case-control or cross-sectional design were analysed separately. Heterogeneity was assessed as present when the p value was 0.15 or less (method not reported); I\textsuperscript{2} was also used. Publication bias was assessed using funnel plots.

Results of the review
Fifteen studies met the inclusion criteria: seven non-prospective (n=1,466, range 28 to 588); and eight prospective (n=1,227, range 47 to 325). Blinding of both biologists and clinicians was reported in two studies, biologists only in two
studies and clinicians only in three studies.

When the results of the prospective studies were pooled, aspirin non-responders had an increased risk of recurrent ischaemic events compared to aspirin responders (OR 2.1, 95% CI 1.4 to 3.4, p<0.001; eight studies); there was no statistically significant heterogeneity observed between studies when a random-effects model was used.

Of the seven non-prospective studies, five reported a significant association between a short PFA and the occurrence of an ischaemic event. Odds ratios ranged from 1.8 (95% CI 1.0 to 3.3) to 18 (95% CI 0.99 to 327); publication bias was observed for these studies.

**Authors’ conclusions**

A short PFA was associated with increased recurrence of ischaemic events in aspirin-treated cardiovascular patients.

**CRD commentary**

The authors addressed a clear review question with appropriate inclusion criteria. Relevant sources were searched and some efforts were made to reduce publication bias. However, only English-language studies were included, so language bias could not be ruled out. Study selection and data extraction were conducted in duplicate, which reduced the potential for error and bias. There did not seem to be a systematic assessment of study quality, although blinding was considered. Although statistically significant heterogeneity was not observed in the analysis of prospective studies using a random-effects model, it was observed when a fixed-effect model was used. Clinical heterogeneity across studies was clearly evident from the tables. The conclusion drawn seemed to encompass a broader population than that evaluated in the included studies; the results of the review will be primarily generalisable to patients with coronary artery disease rather than cardiovascular patients in general. Given the lack of a thorough quality assessment, apparent limitations of the included studies, presence of publication bias, clinical heterogeneity between studies and the generalisation to patients with cardiovascular disease, the conclusions should be treated with some caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that the findings of the review need to be confirmed in stable ischaemic patients, that the need for more aggressive platelet therapy in patients treated with aspirin with low CT\textsubscript{CEPI} values required a prospective interventional study and that PFA cut-off needed to be refined.

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