The prognostic utility of tests of platelet function for the detection of 'aspirin resistance' in patients with established cardiovascular or cerebrovascular disease: a systematic review and economic evaluation

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Scientific summary

‘Aspirin resistance’ in patients with cardiovascular or cerebrovascular disease

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Scientific summary

Background

Aspirin is recommended in cardiovascular disease to prevent future thrombotic complications. However, not all patients benefit from being prescribed aspirin to the same extent, and the question is therefore whether or not patients who suffer events do so because of insufficient antiplatelet effect of aspirin. This systematic review assesses whether or not insufficient platelet function inhibition by aspirin, as measured by platelet function tests (PFTs), is linked to the occurrence of adverse clinical outcomes. This process was undertaken in order to ascertain the prognostic utility of the available PFTs. For the purposes of this report, those individuals prescribed aspirin and classified as having insufficient inhibition of platelet reactivity (i.e. elevated platelet reactivity), based on a PFT and threshold specified by the authors of the studies, are deemed to be 'aspirin resistant'.

Objectives

1. To review systematically the clinical evidence relating platelet function test results to the risk of adverse clinical outcome(s) in patients on aspirin therapy with established cardiovascular disease, cerebrovascular disease (CVD) or diabetes. More specifically, to determine whether or not PFT results have any utility as a prognostic factor and, should that be demonstrated, whether or not they also have any utility in identifying (diagnosing) individuals at higher risk of cardiovascular events.
2. To review systematically the evidence relating to the economic utility of PFTs in patients on aspirin therapy with established cardiovascular disease, CVD, or diabetes.
3. To undertake exploratory model-based cost-effectiveness analysis of the use of PFTs in patients on long-term aspirin therapy with investigation of the potential for populating the model with data based on the results of the systematic review outlined in objective 1.

Methods

For the systematic reviews standard methods were employed.

For the review of prognostic utility, studies were eligible for inclusion if they were prospective primary studies or systematic reviews of studies assessing PFTs in relation to clinical outcomes; were in patients aged $\geq$ 18 years on aspirin, with established cardiovascular disease, CVD, or diabetes; and included either a cyclo-oxygenase-1 enzyme-specific PFT (which measures aspirin response specifically) or a global PFT in patients receiving aspirin as the only antiplatelet therapy. Relevant clinical outcomes were vascular events, haemorrhagic events, all-cause mortality, mortality due to vascular events and composite outcomes containing the above [e.g. major adverse cardiac events (MACEs)]. Reported outcomes had to occur after the undertaking of a PFT and the post-test follow-up period had to be 7 days or longer.

Bibliographic databases (e.g. MEDLINE from inception and EMBASE from 1980, and ongoing studies and conference proceedings databases) were searched up to April 2012, and citation searching was undertaken. Study selection was performed in duplicate using predefined criteria, with recourse to full texts where necessary, and disagreements were resolved by discussion or by referral to a third reviewer. No language or publication restrictions were placed on searches or study selection.

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Risk of bias was assessed by one reviewer and independently checked by a second. Disagreements were resolved by discussion. Assessment criteria were based on criteria for checking the quality of prognostic studies and the quality assessment of diagnostic accuracy studies (revised tool) (QUADAS-2). Criteria related to the domains of patient selection, PFT, outcomes, study attrition and confounding.

Data extraction was conducted by one reviewer using a standardised, piloted data extraction form, and independently checked by a second. Disagreements were resolved through discussion or referral to a third reviewer. Data were extracted on study design and characteristics, patient characteristics, antiplatelet regimens, PFT utilised, outcome measures and length of follow-up, data required for analyses, statistical methods employed and their appropriateness.

Studies were grouped according to whether patients were prescribed monotherapy (aspirin only) or dual therapy (with a second antiplatelet agent added to aspirin) at the time of PFTs in order to distinguish between patients with different therapeutic needs. It was decided to undertake a stepwise approach to reporting and analysing studies, starting with monotherapy studies and then moving on to dual-therapy studies owing to the added complexity engendered in the latter. As prognostic utility of PFTs in patients treated with aspirin as monotherapy was not convincingly demonstrated, it was decided not to undertake analyses of the dual-therapy studies. However, all data extracted in relation to dual-therapy studies have been made available to readers via a web portal.

Where possible, results were presented for different PFTs, different outcome measures (e.g. death, MACE) and different outcome statistics (e.g. odds ratios, hazard ratios). Adjusted and unadjusted results were also presented separately. Where more than one threshold was used (for classification of 'aspirin resistance'), results were presented for all thresholds. Methodological and clinical heterogeneity precluded pooling of results, but forest plots were used to visualise data and indicate heterogeneity between studies.

Similar review methods were employed for the review of cost-effectiveness studies. Any of the following study designs was eligible: cost–consequence analysis, cost-effectiveness analysis, cost–benefit analysis, cost–utility analysis and cost studies. Outcomes of interest were cost-effectiveness, cost estimates, utilisation estimates and quality-of-life estimates.

A speculative economic model developed as a decision tree combined with a Markov model was built to estimate the cost-effectiveness of PFTs, with the option of change in treatment based on a designation of 'aspirin resistant' compared with no testing and no change in treatment (current treatment), from a NHS and Personal Social Services perspective.

Results and discussion

Systematic review of the primary studies linking platelet function testing and future thrombotic risk

Searches identified 120 articles reporting the result(s) of one or more PFTs in relation to clinical outcome data, and these articles represented 108 separate studies. Fifty-eight studies reported on a patient group solely or predominantly receiving aspirin as monotherapy at the time of testing. The PFTs used in these studies were (i) light transmission aggregometry (LTA), (ii) VerifyNow® Aspirin (Accumetrics, Inc., San Diego, CA, USA), (iii) measurement of urinary or serum/plasma thromboxane B_2 metabolites, (iv) platelet function analyser-100 (PFA-100®; Siemens, Malvern, PA, USA), (v) whole-blood aggregometry (WBA), (vi) thromboelastography (TEG) and (vii) other miscellaneous tests.

The studies were highly heterogeneous with regard to patient groups studied, designation of 'aspirin resistance', range and definition of clinical outcomes and types of statistics reported.

Nineteen studies used LTA, mainly in stable coronary artery disease populations. The most frequently reported test threshold to define 'aspirin resistance' was 20% platelet aggregation induced by arachidonic acid, although other agonists (particularly adenosine diphosphate and collagen) were also used with different threshold levels. For the point-of-care VerifyNow® Aspirin assay, seven studies were identified. The most common threshold used to define poor response to aspirin was 550 aspirin response units, as recommended by the manufacturer. Eleven studies were identified using thromboxane metabolites to define 'aspirin resistance'. Thromboxane metabolites were measured in urine, serum or plasma, usually by enzyme immunoassay, although radioactive labelling was also reported. Methods for deriving thresholds and thresholds to define 'aspirin resistance' themselves were variable. For the PFA-100® assay, 21 studies were identified, for the most part in stable populations, although studies in acute populations contributed substantially to results. The collagen/epinephrine cartridge was used to assess platelet responses to aspirin. For WBA, eight studies were identified, all in stable disease patients except in one study. The most commonly reported agonist was arachidonic acid, although collagen was also sometimes used. The threshold to define 'aspirin resistance' was not always reported or consistent across studies. The TEG system was reported in three studies (two with a stable, one with an acute disease population), and a threshold for 'aspirin resistance' of 50% was consistently used across studies.

In general, study reporting lacked detail to assess quality criteria, regardless of the PFT used, thus hampering an overall risk-of-bias assessment. Lack of detail related in particular to blinding (to patient characteristics or of outcome assessors), loss-to-follow-up information and level of compliance with aspirin treatment. There was no consistent reporting of adjusted analyses.

Overall, there is a possible trend suggestive of more clinical events occurring in those groups of patients designated 'aspirin resistant', with some results in some studies showing statistical significance; this is the case across the majority of tests (LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement), though to a lesser extent for TEG, and with data for WBA not allowing many conclusions to be drawn. This trend is also fairly consistent across some outcomes (i.e. death, MACEs and ischaemic/thrombotic events) irrespective of test, though the direction of effect is not always consistent for different thresholds applied to the data from the same study. There are very limited data on bleeding events and thus no inference could be drawn.

The results suggest that PFTs (specifically LTA, VerifyNow® Aspirin, PFA-100®, thromboxane metabolite measurement and TEG) may have some prognostic value as they are fairly consistently associated with elevated risk of cardiovascular events (MACE or death). However, as meta-analysis was not possible, no firm quantitative conclusions can be drawn as to the prognostic value. Given that the effect sizes for an association with clinical events are relatively small and highly uncertain, a determination of the diagnostic utility of PFTs (for determining if an individual is at higher risk of a clinical event) was not possible in this report.

Review of the existing systematic reviews

Fifteen systematic reviews relevant to prognostic utility were identified, and of these, four were considered methodologically more robust than the others. All four reviews found a positive association between aspirin non-responder status ('resistance') and likelihood of adverse cardiovascular outcomes, despite their differences in precise research question, range of included studies and primary outcome measures. However, these reviews had important deficiencies, variously:

- a lack of a rigorous and transparent approach to quality assessment
- insufficient comprehensiveness and a failure to account for the complexity of the field by not considering the effect of different PFTs, thresholds, etc.
- not distinguishing between adjusted and non-adjusted statistical data
- uncertainty regarding whether or not patients receiving aspirin as monotherapy and participants who received additional antiplatelet agents (most commonly dual antiplatelet therapy with aspirin and clopidogrel) were combined in the analysis

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- uncertainty over whether included studies were prospective or retrospective in design
- failure to account for the effect of non-compliance.

In this context, caution must be exercised in interpretation of the findings from these previous reviews.

Systematic review of economic evaluations and economic model

Currently, there is no existing economic evidence on the cost or cost-effectiveness of platelet function testing for 'aspirin resistance'. This report presents the first model to attempt to estimate the cost-effectiveness of a 'test and change treatment' strategy using platelet function testing to define an at-risk population. The model (based on a decision tree coupled with a Markov model) is highly speculative owing to the large degree of heterogeneity and uncertainty around the prognostic utility of PFTs, and it contains numerous assumptions. This has been addressed, where possible, by deterministic sensitivity analysis and also by taking into account the uncertainty around many of the model parameter values. In addition, further analyses have been presented to show scenarios where platelet function testing for 'aspirin resistance' and a change in treatment would not be cost-effective.

Assuming a PFT can accurately identify patients at higher risk of adverse clinical outcomes while receiving aspirin therapy as the sole antiplatelet agent and patients changed to an effective treatment, a 'test and change treatment' option is very likely to be cost-effective. Conversely, if a PFT cannot identify these patients, and a treatment change is not effective in reducing adverse clinical outcome (MACE) risk, then a 'test and change treatment' strategy is not cost-effective. The parameters with the greatest impact on model results are the proportion that are correctly identified as having a high risk of clinical outcome, the effectiveness of a change in treatment if designated 'aspirin resistant', the cost of a test and the cost of a change in treatment. The accuracy of testing, the additional risk of an adverse outcome associated with a designation of 'aspirin resistant' and the effectiveness of a change in therapy are the most uncertain. The model requires more robust data on all of these aspects.

Conclusions

The current report has demonstrated a lack of a consistent association between a laboratory designation of 'aspirin resistance' and clinical outcome, on any test and in any outcome, despite the existence of a vast number of studies which have sought to clarify this association. Although evidence indicates that some tests may have some prognostic value, methodological and clinical heterogeneity between studies and different approaches to analyses create confusion and inconsistency in prognostic results, and prevented a quantitative summary of their prognostic effect. As no large/consistent effect for prognostic utility could be shown, consideration of diagnostic utility was not meaningful.

Recommendations for future research

There is a need for large, protocol-driven and adequately powered primary studies using standardised and agreed methods of measurement to evaluate the prognostic ability of each test in the same population(s). For the tests to inform individual risk prediction, it is likely that they need to be considered in combination and alongside other prognostic factors, within a prognostic model. Once these issues have been addressed it may be possible to undertake a 'test–treat trial' using a prognostic model to tailor antiplatelet therapy to individuals.

Study registration

This study is registered as PROSPERO 2012:CRD42012002151.

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