Antiplatelet treatment for thromboprophylaxis: a step forward or backwards?

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A recent meta-analysis from the Antiplatelet Trialists' Collaboration recommended that antilatelet treatment either alone or, for greater effect, in addition to other proved forms of thromboprophylaxis should be considered for patients at high risk of thromboembolism. This paper argues that the current evidence does not justify the adoption of aspirin or other antiplatelet treatment for venous thromboprophylaxis, especially when more effective alternatives exist. Furthermore, several issues relating to this latest meta-analysis need to be debated.

In a critical review Thompson and Pocock in 1991 raised an important issue of whether meta-analyses can be trusted.[1] They concluded that "meta-analysis is not an exact statistical science that provides definitive simple answers to complex clinical problems. It is more appropriately viewed as a valuable objective descriptive technique, which often furnishes clear qualitative conclusions about broad treatment policies but whose quantitative results have to be interpreted cautiously." Recently, a collaborative overview of randomised trials of antiplatelet treatment published in this journal[2] came to four conclusions.

(1) A few weeks of antiplatelet treatment roughly halved the risk both of deep vein thrombosis and of pulmonary embolism in a wide range of surgical patients (and the limited evidence in immobilised medical patients was also encouraging).

(2) The absolute benefits seemed to be greater for those at higher risk—for example, those undergoing orthopaedic surgery.

(3) Antiplatelet treatment can be conveniently continued after discharge from hospital (in contrast with many other forms of prophylaxis) for as long as the risk of thromboembolism remains substantial.

(4) Antiplatelet treatment alone or, for greater effect, in addition to other proved forms of prophylaxis should be considered for patients at high risk of thromboembolism.

Our aim is to encourage constructive debate about these conclusions, taking into account the limitations of a meta-analysis. It is well established that a large number of issues concerning meta-analysis relate to difficulties in the evaluation of clinical trials particularly factors such as limited information on individual studies, "combinability," biases, confounders and effect modifiers, heterogeneity of treatment effects, effect of size (small versus large studies), and the differential qualities of studies.[3] This recent meta-analysis has also raised other important issues which need to be resolved, including the consideration of a risk-benefit assessment, the interpretation of the results, and the general recommendations which have been made. We consider that the conclusions of the antiplatelet trialists cannot be justified after taking into account many of these factors that can affect the results of a meta-analysis.

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Methodology of meta-analysis

Meta-analysis has been defined as "a statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be 'combinable.'"[3] For meta-analysis to be relevant to clinical decision making the individual studies must have enough in common for their combined evidence to be meaningfully interpreted.[1] Combinability depends on the study design, the treatments used, and the treatment effects. The last can be assessed by statistical testing for heterogeneity. Methodological problems with the studies included in the recent meta-analysis are those of design and heterogeneity of treatments and outcomes.

The studies analysed include open (unblinded) studies, those with uneven randomisation, those using unmarketed drugs, and drug company internal reports, which are not subject to peer review. Analysis of the open studies in this meta-analysis shows higher risk reductions than the blinded studies for both deep vein thrombosis and pulmonary embolism. This indicates the inherent bias of open studies. As an example, in elective orthopaedic surgery the risk reduction for blinded studies was 25·8% compared with 50% for the open studies.

Criteria for assessing the quality of studies in a reproducible and unbiased fashion have already been defined.[4] These can be applied before the inclusion of studies in a meta-analysis. Of the 16 studies included in the elective orthopaedic surgery section of this recent meta-analysis, only one fulfilled the criteria for an adequately designed clinical trial, described in the first overview of antiplatelet drugs in the prevention of thrombosis.[4] These criteria are a prospective study, concurrent controls, co-intervention, double blind, random allocation, prognostic stratification, criteria for inclusion and exclusion, defined end points, assessment of drug compliance, recording of adverse effects, appropriate statistical analysis, and feasibility. Even with the minimum criterion used in a recent meta-analysis on thromboprophylaxis, only four out of the 16 studies could be described as having sound methodology.[5]

Furthermore, some of the studies were not homogeneous with respect to populations of patients and drug treatments as described in the latest meta-analysis. For example, in the study of Chrisman *et al* the authors clearly state that they included cases of emergency trauma in their study population.[6] Patients with trauma should not have been included in the elective orthopaedic surgery group as a distinction had been made between these two groups. Also, the two studies of Hume and colleagues are said to refer to the same trial of hydroxychloroquine.[7,8] In fact the second paper contains a different double blind randomised trial of aspirin (37 patients) versus placebo (34 patients).[8] It is not clear why this study was not included in the meta-analysis. The paper by Soreff *et al* is described as a placebo controlled study in which

deep vein thrombosis is diagnosed on clinical grounds.[9] This gives seven out of 26 patients in the aspirin group and four out of 25 patients in the control group with clinically diagnosed deep vein thrombosis. In fact, this was a venographic study in which 35 out of 51 patients underwent bilateral venography. In the aspirin group 10 out of 21 patients had venographically proved deep vein thrombosis compared with five out of 14 patients in the placebo group. We are unsure why the trialists were selective with these data.

In the trials selected in this meta-analysis the main outcome variable of deep vein thrombosis showed distinct heterogeneity in all 53 studies (including general, orthopaedic, and medical patients). The general surgical trials showed even greater heterogeneity for the effect of treatment on deep vein thrombosis than did the orthopaedic studies. This is of critical importance with respect to the fixed effect method used to analyse the latest meta-analysis as this method assumes no systematic differences between the underlying true treatment effects in the individual trials.[1] When heterogeneity of treatment effect occurs the random effects model produces a more conservative assessment with wider confidence intervals than the fixed method. Many statisticians believe that the former method more accurately reflects the uncertainty of the results.[10,11]

Interpretation of results of meta-analysis

In this meta-analysis odds ratios and percentage odds ratios were calculated, but the interpretation of the results was not accurate and needs further comment. It was claimed that antiplatelet treatment roughly halved the risk of deep vein thrombosis. In fact, their results show an overall risk reduction of 26% for deep vein thrombosis in all groups (medical and surgical) and 25% for all types of surgery. For each surgical subgroup the figures were 28% for general surgery, 14% for traumatic orthopaedic, and 30% for elective orthopaedic surgery. These figures indicate a quartering rather than a halving of the risk as claimed by the trialists. The percentage odds reductions for deep vein thrombosis and pulmonary embolism were 39% and 64%, respectively. These cannot be substituted for risk reduction in studies in which events occur with high frequency such as this one. An example of the misinterpretation of these results can be seen in a recent review article in the *New England Journal of Medicine*.[12] This article stated that this recent meta-analysis "suggested that antiplatelet therapy may reduce the incidence of deep vein thrombosis and pulmonary embolism by about 40 and 60 per cent respectively." Percentage odds reductions do not equate to incidences.

The Antiplatelet Trialists' Collaboration states that the absolute benefits seem to be greater for those at higher risk—for example, those undergoing orthopaedic surgery. This is inaccurate as the benefit was least for those undergoing traumatic orthopaedic surgery. It was also stated that antiplatelet thromboprophylaxis can be conveniently continued after discharge. No trial, however, has yet been published to support this statement with respect to either efficacy or safety.

Conclusions of the meta-analysis

These conclusions have ignored the proved beneficial effects of other methods of prophylaxis. It was stated that antiplatelet treatment should be used either alone or in addition to other forms of thromboprophylaxis. The results do not indicate that antiplatelet treatment is efficient enough to be used alone. This is borne out by previous work from two of the writers of the antiplatelet trialists' papers. Collins, Peto, and coworkers undertook a meta-analysis looking at low dose heparin.[13] The results of that study showed a percentage odds reduction and risk reduction for deep vein thrombosis in general surgery of 67% and 60%, respectively, which is far superior to the 37% and 28% achieved with antiplatelet treatment. The figures for any type of surgery are equally convincing, being 68% and 58% for heparin treatment compared with 39% and 25% for antiplatelet treatment. In the light of these figures, how could antiplatelet treatment be recommended alone without a prospective comparison with standard treatment?

In many of the trials in this latest meta-analysis the authors state that they were unable to make an assessment of the safety and complications of bleeding as such data were not recorded. This information is not optional data for completeness but is absolutely essential to determine the risk-benefit ratios, which must always be clearly defined before any general recommendations are made. This is of particular importance when we consider the recommendation to use combined treatment, which is known to be associated with an increased risk of bleeding and hence may be unsafe. This is exemplified by the results of the studies that were quoted which compared aspirin and heparin with aspirin alone.[14-17] These studies did assess safety and bleeding and showed that combined treatment was associated with increased bleeding. In 534 patients, six (1·1%) major bleeds occurred in the combined treatment group compared with one (0·2%) of the 535 patients in the antiplatelet group, and the respective figures for reoperation, wound haematoma, and wound infection were 43 (8·1%) and 17 (3·2%). This point is further supported by the results of our recent multicentre trial of thromboprophylaxis in 3809 patients undergoing major abdominal surgery. We reported that the 292 patients who took antiplatelet treatment in combination with heparin treatment had an increased risk of bleeding (relative risk 1·41, 95% confidence interval 1·05 to 1·88, P=0·03).[18] Increased bleeding has also been reported with combined treatment in orthopaedic surgery.[19]

Conclusion of the debate

There is no doubt that meta-analysis is a powerful statistical tool. It can, however, only ever be as good as the constituent clinical trials which are used for analysis. If no attempt is made to assess the quality of trials published and then exclude those that fall short of the predefined standards, meta-analysis will surely generate data that are misleading at best and overtly dangerous at worst. What can really be recommended from this meta-analysis? Which of the 10 antiplatelet drugs should be used in which of the innumerable combinations and at what dose? One of the most effective antiplatelet regimens in elective orthopaedic surgery was aspirin 3900 mg a day.[20] This is the equivalent of three proprietary aspirin tablets four times a day, and it is difficult to believe anyone would recommend this regimen to an elderly woman about to have her hip replaced. Not surprisingly, this was associated with an 8% incidence of major gastrointestinal bleeding and a 24% incidence of tinnitus, which necessitated a reduction in the dose.

In a study of any pharmacological intervention there are always two sides to the equation. In this case the aim is the prevention of thromboembolic disease, and the risk is always that there will be increased bleeding. All clinical decisions entail some degree of risk-benefit analysis, and in orthopaedic surgery the need for effective prevention of deep vein thrombosis with minimal risk of bleeding is essential. Any clinical trial that does not disclose data regarding bleeding compli-

cations must surely be discarded. Equally, an overview which clearly states that it has used data from studies in which comparison of bleeding was not possible and then makes recommendations for clinical practice must be viewed with great caution.

In conclusion, we believe the following points should be made.

Firstly, it is time to define the minimum criteria before including studies in a meta-analysis.

Secondly, at present there is insufficient evidence to justify use of antiplatelet agents for thromboprophylaxis.

Thirdly, this meta-analysis has resulted in regressive recommendations which may lead to consideration of treatment with lesser efficacy and safety than currently available regimens with low dose heparins.

Fourthly, in view of these serious reservations we suggest that the recommendations of the antiplatelet trialists are not put into practice.

Finally, we agree that there is a need for well designed, large, blinded trials to compare antiplatelet and anticoagulant thromboprophylaxis.

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Antiplatelet therapy for thromboprophylaxis: the need for careful consideration of the evidence from randomised trials

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Venous thrombosis and pulmonary embolism remain an important cause of morbidity and mortality both in surgical patients and in immobilised medical patients.[1-5] Various thromboprophylactic treatments have, therefore, been devised to prevent or limit thromboembolism. Our previous systematic overview (or meta-analysis) of randomised trials of perioperative subcutaneous heparin found that among surgical patients such treatment can roughly halve the risk not only of deep venous thrombosis but, more importantly, of pulmonary embolism[6] (see fig 1). Subcutaneous heparin is now widely recommended for surgical or medical patients at high risk of venous occlusion.[3-5]

Prospectively defined methods for overviews (meta-analyses)

The recent Antiplatelet Trialists' Collaboration overview of the thromboprophylactic effects of antiplatelet therapy used prospectively determined criteria for trial inclusion and treatment comparisons that were similar to those of the previous heparin overview.[6-8] The aim was to include all unconfounded properly randomised trials of antiplatelet versus no antiplatelet therapy (or of one antiplatelet regimen versus another) that could have been available for review by March 1990 in which deep venous thrombosis was systematically and unbiasedly monitored. (Parts I and III of the previous overview report give a fuller description of the methods used.[1,7] The appropriateness of using "assumption free" statistical methods rather than the "random effects" model when combining trial results, as when combining results from different centres in a multicentre trial, has been discussed in detail previously.[9,10]) Such randomised trials were to be included whether or not the treatment comparison was "blinded" by placebo control. This was also the case in the heparin overview, where exclusion of informative "open" trials (in particular, the important open international multicentre trial coordinated by Professor V V Kakkar[11]) would have been equally inappropriate. Analyses confined to placebo controlled studies, which may be less subject to treatment dependent biases in the assessment of subjective outcome measures, were, however, also considered separately (but, as was shown,[1] these would not materially alter the conclusions: see below).

When the data collected did not include information about the prospectively defined outcomes of interest among all patients initially randomly assigned, extra details were sought from the principal investigators.[1,7] It was often possible to obtain such information, but when it was not the available data were to be included in the overview—unless the numbers missing were so extensive that the comparison could no longer be considered properly randomised. For example, in the study by Soreff *et al* results of venographic follow up were available for only 14 of 25 patients allocated placebo and for 21 of 26 allocated aspirin.[12] So, although the pulmonary emboli data were to be included from this study, the venographically identi-