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Effect of medical thromboprophylaxis on mortality from pulmonary embolus and major bleeding

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RESEARCH

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ABSTRACT

Background
Several studies have failed to discover a beneficial effect of medical thromboprophylaxis on mortality.

Aims
To examine the relative influence of acute fatal pulmonary embolism (PE) and fatal major haemorrhage on overall mortality in medical patients treated with low molecular weight heparin (LMWP) for prophylaxis.

Methods
The author compared deaths from the above factors using data from a recent Cochrane Collaboration meta-analysis. Data from trials satisfying the criteria of the Cochrane analysis plus additional exclusions to avoid bias were pooled to produce point estimates of mortality from PE and major bleeds to estimate net mortality benefit. Estimates were then subject to limited sensitivity analysis based on reported epidemiological data.

Results
Reported PE and major bleeds were 0.44 per cent and 0.27 per cent, respectively. The corresponding case-specific mortality rates were 30.8 per cent and 12.8 per cent and the relative risk reduction (RRR) for PE was 23.2 per cent. Estimated deaths from major bleeds exceeded PE deaths avoided by a small margin (3/100,000 patients given prophylaxis). This excess increased to 30/100,000 when more plausible literature values for PE case fatality rates were applied.

Conclusion
Medical thromboprophylaxis has a finely balanced effect on mortality but may increase it. Such an effect would explain the failure to discover a mortality benefit from medical thromboprophylaxis. Further work, including a formal meta-analysis and additional clinical studies, is required to confirm this picture.

Key Words
Thromboprophylaxis, low molecular weight heparin, medical patients, pulmonary embolism, haemorrhage, mortality

What this study adds:

1. What is known about this subject?
The effect of medical thromboprophylaxis on mortality is uncertain. No study has found the decrease in mortality expected from prophylaxis.

2. What new information is offered in this study?
This study extrapolates from clinical VTE and case-mortality data from a recent Cochrane Review to suggest that the likely mortality gain from reduced fatal pulmonary embolism is offset, and may be exceeded, by increased mortality from major haemorrhage.

3. What are the implications for research, policy, or practice?
There is a need for a clinical trial of the effects of medical thromboprophylaxis on clinical endpoints, including death,

and for greater emphasis in clinical practice on the effect of haemorrhage caused by low molecular weight heparin.

Background

Though randomised clinical trials of medical thromboprophylaxis using low molecular weight heparin (LMWH) have demonstrated decreased subclinical thrombotic event rates in general medical patients,[1–4] evidence is lacking for corresponding improvements in symptomatic disease[5] or in mortality.[6,7] The latter outcome is anticipated if prophylaxis reduces fatal PE as a consequence of decreased venous thrombosis. Published studies to establish whether this occurs, and all trials including mortality as a secondary endpoint, have failed to demonstrate a mortality benefit. However, all studies have been underpowered for that outcome so the results could represent false-negatives. In addition, there may be more than one determinant of mortality associated with prophylaxis. For example, a reduction in PE deaths may be partly or fully offset by increased deaths from major bleeding, a recognised adverse effect of LMWH at prophylactic dose.[8–10]

A recent Cochrane Review[11] summarised the results of medical thromboprophylaxis using heparin or LMWH on clinical endpoints from randomised clinical trials, supplementing earlier meta-analyses.[9,10,12] The review presented data for fatal and non-fatal PE and for major bleeding but not for fatal bleeding. However, the largest studies included in the Review[2,4] contain this information. Thus all the data required for the purpose of estimating overall mortality due to PE and major haemorrhage are available. It is clear that the outcome from such an exercise cannot be conclusive because the event frequency for clinical thrombotic outcomes is low, no trial has been adequately powered for clinical endpoints, and the clinical results have not been statistically significant. Nevertheless, it is legitimate to publish and examine clinical event trends for the purposes of establishing the scale of clinical outcomes, the effect of prophylaxis, and for hypothesis generation and planning future trials. No such study has been undertaken.

The author examined data from selected papers from the recent Cochrane Review[11] to derive estimates of the effect of medical thromboprophylaxis using LMWH on acute mortality. The expectation was that this exercise would provide a broad estimate, the robustness of which could be subjected to sensitivity analysis using values for important variables from elsewhere in the literature.

Methods

The balance of bleeding and PE deaths was estimated as follows. Assume a dual effect on mortality, where *N=number of eligible treated patients; P=absolute PE risk in trial patients assigned to placebo; H=prophylaxis-related major bleeds (rate with prophylaxis less the placebo rate); D_P=case-fatality rate after PE; D_H=case-fatality rate after major haemorrhage; and R=relative risk reduction for PE with prophylaxis as documented in the Cochrane Review.*

Reduction in deaths from PE with prophylaxis = $|NPD_PR|$

Increase in death from major bleeding = NHD_H

Net mortality benefit occurs if $|NPD_PR| > NHD_H$, hence if $PD_PR > HD_H$ ……. (Inequality 1)

The endpoint of the study was the direction of Inequality 1 and hence a capacity to come to a tentative conclusion as to whether there is a net decrease or increase in acute mortality with prophylaxis in medical patients, and the determinants of that conclusion. Calculations were performed on a spreadsheet (Microsoft Excel).

The author selected data from placebo-controlled studies of LMWH prophylaxis within the Cochrane Review that reported both fatal and non-fatal outcomes for either PE or major bleeding.[4] The author excluded studies with potential bias and those using unfractionated heparin, which has a greater bleeding effect than LMWH[8–10] (Table 1). The author assumed that the line entries in the trial reports were not duplicated (e.g., that "major haemorrhage" does not include "fatal haemorrhage") except where indicated. Prophylaxis-specific major bleeding was defined as the difference in the rates in placebo and treatment arms. The case-fatality rates for PE and major bleeding were calculated using the data from both placebo and active-treatment groups.

To help overcome the substantial error and uncertainty inherent in estimating mortality endpoints using non-significant data from underpowered studies, the author examined the effect of varying the underlying incidence and applying literature values for case-fatality rates for PE[13–15] and major bleeding.[16–18]

Results

Table 2 shows the values for variables in the inequality obtained after the additional selection of papers from the list studied in the Cochrane Review.

Table 2: Baseline values for variables included in Inequality 1. RRR = relative risk reduction

Variable	Value
Baseline PE risk (P)	0.0044 (0.44%)
Case fatality rate after PE (D_P)	0.308 (30.8%)
RRR with prophylaxis (R)	0.232 (23.2%)
Major bleed rate with prophylaxis (H)	0.0027 (0.27%)
Case fatality rate for major bleeds (D_H)	0.128 (12.8%)
PD_PR	0.000314
HD_H	0.000345

The number of clinical events was exceedingly low: nine PE (three fatal) in 2,050 patients (0.44 per cent) given placebo in the MEDENOX and PREVENT studies, and seven (two fatal) in a similar number given LMWH prophylaxis. The number of prophylaxis-specific major bleeds was 17 (five fatal) in approximately 6,290 patients (0.27 per cent). The incidence of fatal plus non-fatal PE in non-prophylaxed patients was 0.00439 (0.44 per cent), and the effect of prophylaxis was to decrease this to 0.00337 (0.34 per cent), a relative and absolute risk reduction of 23.2 per cent and 0.1 per cent, respectively. The PE case-fatality rate was 30.8 per cent. By contrast, prophylaxis-specific rate for major bleeding was 0.00270 (0.27 per cent) and the case-fatality rate was 12.8 per cent. Thus the number of major bleeds caused by prophylaxis was 2.7 times greater than the number of PEs prevented, but a lower proportion of major bleeds were fatal.

Using the data, the values on each side of Inequality 1 are, for PD_PR, 0.000314; and for HD_H, 0.000345 (Table 2). This result indicates that deaths from major bleeds exceed deaths avoided by PE prophylaxis, to the slight extent of about three patients per 100,000 given prophylaxis. In other words, it implies a small and presumably non-significant increase in mortality caused by thromboprophylaxis in medical patients under the conditions of eligibility represented in the clinical trials contributing to the analysis.

The study case-fatality rate for PE (30.8 per cent) substantially exceeded the range found in independent literature values[13–15] (under 10 per cent) and appeared implausible. The effect of inserting values within the published range was to increase net mortality (Table 3), because the PE benefit declines. By contrast, the same rate for major bleeding was towards the upper range of published values[16–18] and decreasing this datum decreased overall mortality. The relative risk reduction (RRR) for PE appears small when compared to the RRR for asymptomatic deep venous thrombosis (about 56 per cent). Substituting that value on the basis that a relationship between the two is expected predicts a small reduction in mortality (Table 2). For the effects of other univariate sensitivity analyses, see Table 3.

Table 3: Sensitivity analysis for base-case variables in the calculation of mortality

Item	Result
Base case	+2
PE incidence halved	+19
PE incidence doubled	–28
PE incidence quadrupled	–91
Bleeding incidence halved	–14
Bleeding incidence doubled	+38
Bleeding incidence quadrupled	+107
PE case-fatality rate 0.082[13]	+26
PE case-fatality rate 0.046*	+30
Bleed case-fatality rate halved	–14
Bleed case-fatality rate doubled	+38
RRR for PE = RRR for DVT	–7

*The result is shown as the net effect on mortality, expressed as net deaths/100,000 patients selected for thromboprophylaxis as in the supporting clinical trials. Positive and negative values indicate a net increase or reduction in mortality, respectively. * = weighted average of case-fatality rates reported in references 13–15. RRR = relative risk reduction; DVT = deep vein thrombosis*

Discussion

All randomised clinical trials of medical thromboprophylaxis have had as their primary outcome sub-clinical venous thrombosis detected by imaging.[1–4] None had sufficient statistical power to detect changes in clinical events[5] or death,[6,7] but these are frequently reported as secondary endpoints and have been presented in meta-analyses,[9–12] including the Cochrane Review[11] that stimulated this work. Thus medical thromboprophylaxis relies on an unproven extrapolation from sub-clinical thrombotic events to clinical events that are exceedingly rare in medical patients. Attempts to discover a reduction in all-cause mortality arising from reduced deaths from fatal pulmonary embolus have been unsuccessful,[6–7] and several possible explanations arise. No trials or meta-analyses have had the necessary statistical power to detect clinical endpoints, and the real quantitative effect if any on mortality is uncertain. Second, anticoagulant-induced major bleeding, also a rare event whose true incidence is uncertain, but according to most analyses appears similar to the PE rate, may contribute to mortality and so offset reductions due to the effect on PE. Because both are rare, the balance of effects is not known accurately, but the possibility arises of a net

increase in mortality with prophylaxis. This possibility is supported by the present study.

The author was aware of important statistical issues that arise when making calculations and extrapolating from rare secondary trial endpoints, where differences between active and placebo-treated groups are not statistically significant, especially when some secondary outcome data (for example, the case-fatality rate after PE) are implausible and not consistent with published literature. This study is not a meta-analysis and the results are provided as point estimates for consideration on their merits. The author took the view that if rare clinical endpoints are worthy of presentation in peer-reviewed meta-analyses, they must also assist in the drawing of tentative conclusions after secondary study. The opposing argument is that the data have such wide confidence limits that the manipulations presented here are questionable. If this view is correct, then: (a) the original data must be equally invalid and in spite of being published after peer review should not be further considered; and (b) the practice of medical prophylaxis is also invalid, since it is aimed at averting clinical events including death for which the evidence is inadequate for the same reason.[5] These uncertainties mean that distinguishing between the possibilities that thromboprophylaxis decreases, increases or has no effect on mortality in medical patients on the basis of this study is not possible.

The tentative conclusion from this work that deaths avoided from reduced PE are similar in magnitude to increased deaths from major bleeding. However, a previously unstated hypothesis for future study emerges: that medical thromboprophylaxis may have a negative action on mortality because deaths from major bleeding are greater. Previously this author has argued that the selection of patients for prophylaxis should be restricted to patients with weighty risk factors, so that these trends are influenced in favour of net benefit, and this suggestion is supported by the current work.

The case-specific mortality from PE reported in clinical trials of thromboprophylaxis studied here (30.8 per cent) is substantially greater than in recent prospective studies[13–15] (weighted average of 4.6 per cent) and hence questionable. When the lower figure is used the mortality deficit increases (Table 3). This result strengthens the hypothesis that medical thromboprophylaxis may increase mortality. However, the result must be interpreted with caution in view of the very low incidence of PE in medical patients and the possibility of bias in assigning each death as being causally related to PE. This bias, if it exists, is within the original peer-reviewed trials and meta-analyses, and does not arise from the present study.

As the author has previously documented,[19] there is intense pressure to prescribe thromboprophylaxis in Australian and overseas hospitals. Recent guidelines[20] have correctly emphasised the need to consider excluding patients with a known bleeding risk. However, this does not overcome the problem discussed here. The presence of a clinical bleeding risk (for example, thrombocytopenia), was an exclusion criterion in all the randomised trials of medical LMWH prophylaxis cited here, and hence the reported incidence of major haemorrhage is not due to administration of an anticoagulant to patients at risk of bleeding. It appears to be an inescapable side effect of LMWH, even at the lower dose used in prophylaxis, representing an idiopathic sensitivity to the drug whose effects are unpredictable. Internationally, concern has been raised that compliance with guidelines for medical thromboprophylaxis is poor,[21] and methods for improving compliance have been described.[22] If the new hypothesis generated by this study has substance, it is possible that, paradoxically, poor compliance has protected patients against increased mortality.

Conclusion

The results from selected studies included the Cochrane Review of medical thromboprophylaxis suggest that PE deaths avoided and those caused by major bleeds are of similar magnitude and that under plausible assumptions net mortality may increase. Such an effect would explain why no mortality advantage for medical thromboprophylaxis has so far been documented. There is a need for further clinical trial work to determine the effect of medical thromboprophylaxis on clinical events and mortality.

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PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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ETHICS COMMITTEE APPROVAL

As this was a review of existing literature in the public domain, no ethical approval was required for this study.

Table 1: Details of trials reported in the Cochrane Review but excluded from the present study, and reasons for the exclusions

Outcome	Publication	Inclusion	Reason for Exclusion
Non-fatal PE	Belch 1981	No	Unpaired; Unfractionated heparin
	Dahan 1986	No	Autopsy PE data only
	Fraisse 2000	No	No usable data
	Ibarra-Perez 1988	No	Unpaired; Unfractionated heparin
	MEDENOX*	Yes	
	PREVENT	Yes	
Fatal PE	Bergmann 1996	No	Autopsy data
	Dahan 1986	No	Autopsy PE data only
	Gardlund 1996	No	Unpaired; Unfractionated heparin
	Kakkar 2011	No	No usable data
	MEDENOX*	Yes	
	PREVENT	Yes	
Major bleeding	Belch 1981	No	Unfractionated heparin
	Dahan 1986	No	“Major haemorrhage” not defined
	Fraisse 2000	No	Unpaired
	Ibarra-Perez 1988	No	Unpaired; Unfractionated heparin
	Kakkar 2011	Yes	
	MEDENOX 1999	No	Unpaired
	PREVENT 2004	Yes	