The recommendation that patients having a total hip replacement should receive pharmacological thromboprophylaxis is based on the belief that fatal pulmonary embolism is common, and that prophylaxis will decrease the death rate. To investigate these assumptions we performed a meta-analysis of all studies on hip replacement which included information about death or fatal pulmonary embolism. A total of 130 000 patients was included. The studies were so varied in content and quality that the results of our analysis must be interpreted with some caution.

The fatal pulmonary embolism rate was 0.1% to 0.2% even in patients who received no prophylaxis. This is an order of magnitude lower than that which is generally quoted, and therefore the potential benefit of prophylaxis is small and may not justify the risks. To balance the risks and benefits we must consider the overall death rate. This was 0.3% to 0.4%, and neither heparin nor any other prophylactic agent caused a significant decrease.

Our study demonstrates that there is not enough evidence in the literature to conclude that any form of pharmacological thromboprophylaxis decreases the death rate after total hip replacement. For this reason guidelines which recommend their routine use to prevent death after hip replacement are not justified.

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Despite strong pressure from both scientific and pharmaceutical sources, orthopaedic surgeons have been very slow to adopt the recommendation that all patients undergoing total hip replacement (THR) should be given some form of thromboprophylaxis (Brenkel and Clancy 1989; Laverick, Croal and Mollan 1991; Campling et al 1993; Unwin, Harries and Jones 1995).

The National Institutes of Health (NIHCC 1986), the Thromboembolic Risk Factors (Lowe et al 1992) and the European Consensus conferences (ECC 1992) all classified THR as a high-risk procedure, which implies a fatal pulmonary embolism (PE) rate of 1% to 10%. On this basis they recommend that some form of heparin should be used as prophylaxis. The risk factors for hip replacement, however, differ from those for other types of surgery (Salzman and Harris 1976; Murray, Carr and Bulstrode 1995), and it is necessary, before guidelines are agreed, that the risks and benefits of any prophylactic regime are weighed up in terms of mortality and morbidity after THR. No previous studies of mortality after THR have been large enough to compare the risks and benefits of various prophylactic regimes. The available data on the effect of prophylaxis on morbidity from thromboembolism after THR are sparse and conflicting: it is not even clear whether postphlebitic limb and leg ulcers are a genuine problem (Moore and Freeman 1993; McNally et al 1994; Warwick et al 1996), and there are no trials which have assessed the effect of prophylaxis on these outcomes. There is also a risk that prophylactic anticoagulation may increase the rate of deep infection (Kong 1995).

Many randomised controlled trials have demonstrated a significant reduction in the incidence of venographic deep-vein thrombosis (DVT) after THR when various prophylactic agents are used (Imperiale and Speroff 1994). These trials are relatively easy to perform: they require only small numbers of patients because of the high incidence of asymptomatic DVT of 40% to 80%, so that the effect observed is large. It has been assumed that this reduction in DVT rate will lead to a similar fall in the overall death rate. This may be a false assumption if fatal pulmonary embolism is not very common and does not account for most deaths, if a fall in the DVT rate is not associated with a similar fall in the fatal PE rate, or if prophylaxis increases the risk of other causes of death.

We aimed to use meta-analysis to determine as accurately as possible the actual mortality after THR and to
attempt to weigh up the risks and benefits of various types of thromboprophylaxis in terms of total mortality.

MATERIALS AND METHODS

We performed a meta-analysis of all available studies of THR in which information about overall death rate or fatal PE had been included. We searched for all papers on the outcome of THR in which the number of patients being studied and the total number of deaths or of fatal cases of PE had been reported. The Medline bibliographic database was reviewed from 1966 to 1995 to identify all the relevant English language literature. References mentioned in consensus documents, previous meta-analyses or other papers were also traced. No attempt was made to restrict the search to controlled trials or even to prospective trials. The data were used only once when the outcome of the same group of patients had been reported in more than one paper.

We recorded the year in which the trial was started, the number of patients involved, the number of cases of fatal PE and the number of deaths occurring within three months after the operation, since it is known that after THR the death rate is elevated for no more than three months (Seagroatt et al 1991). We subdivided the type of prophylaxis into six categories: none, heparin, warfarin, aspirin, dextran and others. The ‘none’ group included those given no prophylaxis, placebo, and antiembolism stockings. The ‘heparin’ group included those given any form of heparin, heparinoid or low-molecular-weight heparin prophylaxis, with or without stockings. The ‘warfarin’, ‘aspirin’ and ‘dextran’ groups were also with or without stockings. The other group included all trials in which a mixture or combination of these prophylactic regimes had been used, trials with other prophylactic agents, and trials in which the prophylactic regime was unclear. This group included patients treated by mechanical pumps as the number in this subgroup (745) was too small for a separate analysis.

We have quoted 95% confidence limits (CL); in subgroups in which the number of deaths occurring was small the confidence limits were determined using the Poisson distribution (Pearson and Hartley 1966). The significance of differences between subgroups was determined using the chi-squared test.

RESULTS

We identified 181 papers containing usable information about 93 000 patients (see reference list). The reports show a progressive decrease in both fatal PE and death rates over the last three decades (Table I). During the last 15 years the overall death rate has been 0.38% (CL 0.29% to 0.47%) and the fatal PE rate has been 0.11% (CL 0.07% to 0.16%) (Table I).

Additional information about the current death rate in the UK can be obtained by dividing the number of deaths (134) identified by the National Confidential Enquiry into Perioperative deaths 1991-2 (NCEPOD) (Campling et al 1993) by the number of THRs implanted during that period (38 000) (Williams et al 1994) (Table I).

The fatal PE rate, the overall death rate and the non-PE death rate for the different types of prophylaxis in studies starting in the 1970s, 80s and 90s. Differences between groups do not quite reach statistical significance (p = 0.051)

<table>
<thead>
<tr>
<th>Prophylaxis</th>
<th>Fatal PE</th>
<th>Patients</th>
<th>Rate (%)</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4</td>
<td>3432</td>
<td>0.12</td>
<td>0.03 to 0.30</td>
</tr>
<tr>
<td>Heparin</td>
<td>8</td>
<td>10 356</td>
<td>0.08</td>
<td>0.03 to 0.15</td>
</tr>
<tr>
<td>Warfarin</td>
<td>2</td>
<td>5162</td>
<td>0.04</td>
<td>0.00 to 0.14</td>
</tr>
<tr>
<td>Aspirin</td>
<td>3</td>
<td>2700</td>
<td>0.11</td>
<td>0.02 to 0.32</td>
</tr>
<tr>
<td>Dextran</td>
<td>7</td>
<td>2730</td>
<td>0.26</td>
<td>0.10 to 0.53</td>
</tr>
</tbody>
</table>

Table I. The fatal PE and death rates with confidence limits (CL) in trials starting in different decades, with the death rate in 1991-2 in the UK calculated from the number of deaths identified by the National Confidential Enquiry into Perioperative Deaths (NCEPOD) (Campling et al 1995) and the number of THRs implanted during that period (Williams et al 1994)

<table>
<thead>
<tr>
<th>Start of trial</th>
<th>Fatal PE</th>
<th>Patients</th>
<th>Rate (%)</th>
<th>95% Confidence limits</th>
<th>Deaths</th>
<th>Patients</th>
<th>Rate (%)</th>
<th>95% Confidence limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>1960s</td>
<td>129</td>
<td>20 190</td>
<td>0.64</td>
<td>0.53 to 0.75</td>
<td>237</td>
<td>21 501</td>
<td>1.10</td>
<td>0.96 to 1.24</td>
</tr>
<tr>
<td>1970s</td>
<td>143</td>
<td>40 207</td>
<td>0.36</td>
<td>0.30 to 0.41</td>
<td>434</td>
<td>39 199</td>
<td>1.11</td>
<td>1.00 to 1.21</td>
</tr>
<tr>
<td>1980s and 90s</td>
<td>27</td>
<td>23 511</td>
<td>0.11</td>
<td>0.07 to 0.16</td>
<td>69</td>
<td>18 204</td>
<td>0.38</td>
<td>0.29 to 0.47</td>
</tr>
<tr>
<td>NCEPOD</td>
<td></td>
<td>38 000</td>
<td>0.35</td>
<td>0.29 to 0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
significant decrease in the overall death rate compared with no prophylaxis. Compared with heparin the use of aspirin caused a significant decrease in non-PE deaths (p = 0.01). As a result its use tended to decrease the overall death rate, although this did not quite reach statistical significance (p = 0.052).

DISCUSSION

In the introduction to many of the papers which we reviewed, the importance of the subject was emphasised by stating that the fatal PE rate after THR is above 1%. This accepted wisdom, which is supported by the three consensus documents (NIHCC 1986; ECC 1992; Lowe et al 1992), is based on a few studies conducted mainly in the 1960s (Coventry et al 1973; Johnson, Green and Charnley 1977). Our review of a large proportion of the published data demonstrates that even in the 1960s the fatal PE rate was less than 1%. Since then it has progressively decreased and during the last 15 years has been reported to be between 0.07% and 0.16% which is an order of magnitude lower than generally perceived. Even in the subgroup of papers reporting results with no pharmacological thromboprophylaxis the rate for fatal PE is still only one or two per thousand (0.12%, CL 0.03% to 0.3%). It therefore seems likely that the progressive fall in the fatal PE rate is predominantly the result of improved surgical, anaesthetic and rehabilitation techniques rather than the increased use of thromboprophylaxis. The current fatal PE rate and therefore the potential benefit of thromboprophylaxis appear to have been grossly overestimated. The benefit may be so low that it is similar to the risks of the therapy.

It is not always possible to determine if a death is caused by pulmonary embolus and as a result the rate for fatal PE may be inaccurate (Fitts et al 1964). It is therefore important to determine the overall death rate. This sets an upper limit to the fatal PE rate, and is also essential to balance the risks and benefits (Warwick and Freeman 1995).

Our meta-analysis suggests that the overall death rate is 0.38% (CL 0.29% to 0.47%). In the papers which we reviewed the deaths were assessed for different periods after the THR, high-risk patients were often excluded, and many of the studies came from centres of excellence. It could therefore be argued that the meta-analysis gives a false impression of the overall death rate after THR. A further potential bias is that in many of the trials the patients were screened by venography. A positive result may have resulted in the patient being formally anticoagulated which may have influenced the mortality. The death rate calculated from NCEPOD data and national statistics (0.35%, CL 0.29% to 0.41%, Table I), however, is similar to that found in our meta-analysis (0.38%, CL 0.29% to 0.47%). This suggests that the potential biases in the meta-analysis are not important and that a combination of both sets of data may give a better estimate of the current overall death rate after THR: this estimate is 0.36% (CL 0.31% to 0.41%).

To extract as much data from the literature as possible we undertook an opportunist meta-analysis (Rosendaal 1994) which was not restricted to randomised controlled trials. An opportunist meta-analysis includes data from studies in which the primary aim is different from the aim of the meta-analysis: we investigated death rates although many of the papers were studies of rates of DVT. Such an opportunist meta-analysis minimises some of the potential weaknesses of formal meta-analysis, such as publication bias against negative results or commercial bias against unfavourable results. Classical meta-analysis combines data from randomised controlled trials which compare the same pair of treatments. In our meta-analysis data were pooled from trials involving many different comparisons. This type of meta-analysis has previously been used to study thromboprophylaxis after THR (Imperiale and Speroff 1994) and the results must be interpreted with considerable caution, since pooling is based on the assumption that patients and their management are similar in different studies. For example, if the type of prophylaxis changed with time then an observed difference between prophylactic regimes may be explained by a progressive decrease in mortality rather than a real difference between the regimes.

Despite using all the relevant data from a large number of papers, we have been unable to draw any firm statistical conclusions about the type of thromboprophylaxis which should be used, and even whether it should be used at all. To demonstrate a significant reduction in the incidence of
fatal PE would require about 30,000 patients in each arm of a trial (Murray et al 1995; Warwick, Williams and Bannister 1995), which is substantially more than the number of patients in each of our meta-analyses.

If no pharmacological thromboprophylaxis is used the fatal PE rate after THR appears to be about 0.12%. Previous meta-analyses from all fields of medicine and surgery have suggested that both heparin and aspirin cause a substantial decrease in this rate (Collins et al 1988; APT 1994b). If we assume that prophylaxis is effective at preventing fatal PE after THR then our data would suggest that such prophylaxis would not decrease the fatal PE rate after THR by more than 0.05%. Anticoagulants do have a complication rate although the death rate from these complications is not known (Kong 1995; Warwick and Freeman 1995). If the death rate due to anticoagulant complications is 0.05% or more then the use of these agents will actually cause harm. The best method to assess whether a prophylactic agent is useful is to consider the overall death rate: this takes into account both risks and complications (Warwick and Freeman 1995). In our meta-analysis neither heparin nor any other prophylactic agent caused a significant decrease in overall death rate compared with no prophylaxis. There is therefore as yet no good evidence that any pharmacological agent does more good than harm after prophylaxis. There is therefore as yet no good evidence that any pharmacological agent does more good than harm after prophylaxis.

If, despite the finding that no agent significantly decreases the overall death rate, orthopaedic surgeons feel that they should use some form of pharmacological prophylaxis then it would seem appropriate to compare different agents. Heparin has the most evidence suggesting that it should decrease the fatal PE rate (NIHCC 1986; ECC 1992; Lowe et al 1992). Aspirin may be a better option, however, as this meta-analysis suggests that, compared with heparin, aspirin causes a decrease in non-PE deaths, and as a result shows a tendency to decrease the overall death rate. There is also evidence from large trials unrelated to hip replacement that aspirin prevents non-PE deaths (APT 1994a).

We believe that in future pharmaceutical companies and others concerned with the study of thromboembolism should put the subject into perspective by using up-to-date, reliable data based on large numbers of patients. Every effort should be made to avoid the assumption, until clear evidence is available to the contrary, that a reduction in DVT rate will automatically reduce the overall death rate. Even for elective total hip replacement, for which there are large numbers of outcome studies of a common and reasonably standard procedure, there is still not enough information on which to draw up guidelines on thromboprophylaxis. Until a randomised controlled trial of adequate size can be performed, using morbidity and mortality as the main outcome measures, the problem is likely to remain unresolved.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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