ARThROPLASTY

Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens


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We performed a meta-analysis of modern total joint replacement (TJR) to determine the post-operative mortality and the cause of death using different thromboprophylactic regimens as follows: 1) no routine chemotherapeutic prophylaxis (NRC); 2) Potent anticoagulation (PA) (unfractionated or low-molecular-weight heparin, ximelagatran, fondaparinux or rivaroxaban); 3) Potent anticoagulation combined (PAC) with regional anaesthesia and/or pneumatic compression devices (PCDs); 4) Warfarin (W); 5) Warfarin combined (WAC) with regional anaesthesia and/or PCD; and 6) Multimodal (MM) prophylaxis, including regional anaesthesia, PCDs and aspirin in low-risk patients. Cause of death was classified as autopsy proven, clinically certain or unknown. Deaths were grouped into cardiopulmonary excluding pulmonary embolism (PE), PE, bleeding-related, gastrointestinal, central nervous system, and others (miscellaneous). Meta-analysis based on fixed effects or random effects models was used for pooling incidence data.

In all, 70 studies were included (99,441 patients; 373 deaths). The mortality was lowest in the MM (0.2%) and WC (0.2%) groups. The most frequent cause of death was cardiopulmonary (47.9%), followed by PE (25.4%) and bleeding (8.9%). The proportion of deaths due to PE was not significantly affected by the thromboprophylaxis regimen (PA, 35.5%; PAC, 28%; MM, 23.2%; and NRC, 16.3%). Fatal bleeding was higher in groups relying on the use of anticoagulation (W, 33.8%; PA, 9.4%; PAC, 10.8%) but the differences were not statistically significant.

Our study demonstrated that the routine use of PA does not reduce the overall mortality or the proportion of deaths due to PE.

During the last 20 years the incidence of fatal pulmonary embolism (PE) and mortality following total joint replacement (TJR) has decreased substantially as a result of many factors, including a better understanding of the pathophysiology and prophylaxis of post-operative thromboembolic disease, and advancements in anaesthesia, surgical technique and peri-operative care.

The need for routine pharmacological thromboprophylaxis after TJR has been questioned because post-operative PE is rare and anticoagulants increase the risk of bleeding, with its associated morbidity and mortality. The potential complications from potent anticoagulation and the increased cost could be justified if its use reduced the number of deaths due to PE, and the all-cause mortality. Whether currently used thromboprophylaxis regimens achieve these goals is debatable. Our recent meta-analysis, which investigated the incidence of all-cause mortality and symptomatic non-fatal PE in patients undergoing TJR with only three methods of thromboprophylaxis (routine use of potent anticoagulants, multimodal prophylaxis or warfarin), demonstrated that all-cause mortality was significantly lower in patients receiving multimodal prophylaxis than in the remaining two groups. Similarly, a 60% to 70% increased risk of symptomatic non-fatal PE was observed in patients receiving potent anticoagulation compared with the multimodal treatment group. This analysis was limited by two factors: first, the cause of death was not analysed; and second, only three thromboprophylaxis regimens were studied. In addition, it has recently been reported that PE is no longer the leading cause of death after TJR, even without the routine use of pharmacological prophylaxis.

We therefore conducted a second meta-analysis seeking to answer the following questions: 1) What is the mortality following modern elective TJR? 2) Is the mortality affected by the use of different thromboprophylactic regimens? 3) What are the proportions of autopsy-proven deaths, deaths in which a clinically
certain cause is reported, and deaths due to an unknown cause? 4) Are there any differences in the proportions of the individual causes of death following TJR, particularly PE, bleeding, or a combination of both, with currently used thromboprophylaxis regimens?

Materials and Methods
Identification and eligibility of relevant studies. A systematic literature review of publications in all languages from 1995 to 2009 was conducted searching Medline (23 October 2009), the Cochrane Central Register of Controlled Trials (23 October 2009) and EMBASE (27 October 2009) using the Ovid search interface to identify all studies that discussed mortality in connection with TJR where thromboprophylaxis had been used based on the following criteria: (knee prosthesis.mp or knee replacement.mp or hip arthroplasty.mp or hip replacement.mp or hip prosthesis.mp or Arthroplasty, Replacement, knee/or knee arthroplasty.mp or hip replacement.mp or hip prosthesis.mp or Arthroplasty, Replacement, Hip/or hip prosthesis/or knee prosthesis/or hip arthroplasty.mp.) AND (exp Thrombosis/pc [Prevention & Control] or exp Thromboembolism/pc [Prevention & Control] or thromboprophylaxis.mp or exp Anticoagulants/tu [Therapeutic Use]) AND exp Mortality/ or mortality.fs or death$.mp. or fatal$.mp. or mortality$.mp.

This produced 437 publications, blinded abstracts of which were reviewed independently by two authors (LAP and AGDV) to determine whether mortality and the type of thromboprophylaxis were reported. Studies with a level of evidence from I to IV were considered for inclusion. We excluded personal communications, expert opinions (level of evidence V), abstracts from meetings, registry data in which duplicate publication could not be excluded, meta-analyses, systematic reviews, studies focusing on deep-vein thrombosis (DVT) as the endpoint, and series that analysed specific cohorts (patients with cirrhosis, renal failure, morbid obesity, or exclusively bilateral TJR). We included series of elective primary and revision THR and TKR performed after 1990, as we felt that they would have used current anaesthetic, surgical and peri-operative techniques, and would have coincided with the introduction of low molecular weight heparins (LMWHs). Studies in which the form of thromboprophylaxis was not reported, and/or those in which the follow-up was less than two weeks, were excluded.

Using these criteria we identified 106 abstracts; the full texts of these studies were independently reviewed by the two authors. When some relevant information was missing we contacted the authors. Based on review of the full articles an additional 36 studies were found not to meet the inclusion criteria and were excluded, leaving 70 studies for analysis.

Data extraction. The following variables of interest were extracted: year of publication, level of evidence, date of enrolment, thromboprophylactic method, anaesthetic technique, use of pneumatic compression devices (PCDs), mean age, gender distribution, total number of patients and joint replacements, proportion of primary to revision operations, number of deaths within the first 180 days, timing and cause of death, mean follow-up, and proportion of patients lost to follow-up.

Thromboprophylactic methods: rationale and classification. The 70 publications encompassing 99 441 patients and 373 deaths were classified into seven groups based on the method of thromboprophylaxis used (Table I): 1) NRC: no routine pharmacological thromboprophylaxis;8-17 2) Potent anticoagulation (PA): unfractionated heparin, LMWH, ximelagatran, fondaparinux, or rivaroxaban as a
sole means of prophylaxis; 3) Potent anticoagulation combined (PAC) with regional anaesthesia and/or PCD; 4) Warfarin alone (W); 5) Warfarin combined (WC) with regional anaesthesia and/or PCD; 6) Multimodal (MM) prophylaxis including intention to use regional anaesthesia with or without intra-operative heparin, PCD, aspirin; 7) Aspirin and general anaesthesia.

Of the 70 studies, seven had two treatment arms, which corresponded to different thromboprophylactic regimens; the individual arms were grouped accordingly. Studies receiving W or PA were classified as WC or PAC when > 50% of the patients received regional anaesthesia and/or PCD. When these two parameters were not specified, studies were classified as W or PA, respectively. This classification of PA, PAC, W and WC groups was based on literature supporting the view that the use of regional anaesthesia is associated with a reduction in post-operative mortality compared with general anaesthesia and that PCDs substantially diminish the rate of venous thromboembolism (VTE) with or without adjuvant chemoprophylaxis.

Patients in the PA and W groups did not receive PCD. In eight out of 22 publications included in these two groups, the type of anaesthetic was not specified. In the remaining 14 publications in which the type of anaesthesia was identified, 9414 out of 13 048 (72%), patients in the PA group and 87 out of 134 (65%) patients in the W group received a general anaesthetic.

In one out of four studies included in the PAC group the type of anaesthetic was not described in detail; however, it was reported that most patients received regional anaesthesia. In one out of four studies included in the WC group, the type of anaesthetic was not specified but all patients received post-operative PCD. There were 24 out of 28 studies in the PAC group (24 651 patients) and three out of four studies in the WC group (1449 patients) in which there was a detailed description of the type of anaesthetic. In this subset of patients, 24 651 out of 35 292 in the PAC group (70%) and 1449 of 1907 in the WC group (76%) received regional anaesthesia.

In the MM group, aspirin was given to low-risk patients and warfarin to patients with a higher risk of thromboembolism or who were receiving anticoagulants for medical reasons before surgery. Studies using MM prophylaxis included warfarin in 1159 of 17 363 patients (6.7%). Most received regional anaesthesia; PCDs were used in eight studies, not used in three studies and not specified in one study. Intra-operative heparin was used in one study for patients undergoing THR.

**Classification of cause of death.** Cause of death was classified as 1) autopsy proven; 2) clinically certain (documented in the paper but without autopsy confirmation); or 3) unknown (cause not mentioned or reported as ‘unrelated to PE’ or ‘sudden death’ without further clarification). The reported causes of death were further classified as cardio-pulmonary, which included myocardial infarction, cardiac failure, arrhythmia, pulmonary oedema, pneumonia, fat embolism, aspiration asphyxia, cardiac or cardiopulmonary not otherwise specified; PE; bleeding (including fatal bleeding and heparin-induced thrombocytopenia and thrombosis-related deaths); gastrointestinal, excluding gastrointestinal bleeding; central nervous system, excluding central nervous system bleeding; and others (including cancer, sepsis, multiple system organ failure, acute renal failure or renal complication, ruptured aortic aneurism, and iatrogenic vascular injury).

**Methods for meta-analysis.** A number of meta-analyses were performed to pool the mortality (defined as total number of deaths divided by the total number of patients), the proportion of the different causes of death (defined as the number of deaths due to cardiopulmonary, PE, bleeding, gastrointestinal, central nervous system and other, respectively) divided by the total number of autopsy-proven and clinically certain deaths), and the proportion of autopsy-proven, clinically certain or unknown deaths. In each case, to determine the pooled proportion, the variances of the raw proportions were stabilised using a Freeman-Tukey type of arc sine square root transformation. The pooled proportions were calculated as the back-transformation of the weighted mean of the transformed proportions using DerSimonian-Laird fixed effects or random effects models. The significance of heterogeneity between studies was tested using the Q test. Random effects models were chosen if the Q test was significant. Otherwise, fixed effects models were applied. Using the test for comparing pooled estimates of the same quantity derived from separate meta-analyses, the pooled proportions were compared between the six thromboprophylaxis modalities (NRC, PA, PAC, W, WC and MM). The significance level was set at a p-value < 0.0033 by Bonferroni correction for the multiple comparisons. Publication bias in the proportion of deaths was assessed for each thromboprophylactic method using a linear regression test for funnel plot asymmetry. The forest plot method was used to present the proportions and 95% confidence intervals (CI) from individual studies, along with the pooled proportion and test for heterogeneity. There was no significant publication bias in the proportion of deaths reported. A chi-squared test was conducted to assess whether the distributions of causes of death between autopsy-proven and clinically proven were similar. All statistical analyses were conducted using the R program.

**Results**

The pooled proportion of deaths of all patients combined was low (0.38%) and ranged from 0.2% (MM and WC groups) to 0.59% (NRC group) (Table I, Fig. 1). The pooled proportion of deaths was significantly higher in the NRC group (0.59% (95% CI 0.35 to 0.91)) than in the MM group (0.20% (95% CI 0.11 to 0.31)) (p = 0.003) (Table I, Fig. 1). There were no significant differences in the
The pooled proportion of autopsy-proven deaths of all patients combined was 17.5% and ranged from 4.5% in the W group to 55% in the NRC group. A significant difference was reached between NRC (55%) and PA (9.8%) (p < 0.001), and NRC versus PAC (9.4%) (p < 0.001). The pooled proportion of clinically certain cause of death of all patients combined was 56%, ranging from 37.3% in the NRC group to 64.7% in the MM group. No significant difference was found between the groups. The pooled proportion of unknown cause of death in all patients combined was 25.7%, ranging from 6.5% in the NRC group to 57.4% in the MM group. No significant difference was found between the groups. When patients with autopsy-proven deaths and deaths due to a clinically certain cause were combined, there was no significant difference in the proportion of patients with a reported cause of death between the groups.

When we studied the cause of death for the cohort of patients in which a cause was either reported or proven by autopsy, we found that cardiopulmonary deaths (47.9%) were more prevalent than those due to PE (25.4%), bleeding (8.9%), central nervous system (7.6%), gastrointestinal (6.3%), and others (miscellaneous) (9.8%). In the cardiopulmonary group, most patients died of a myocardial infarction (78% of autopsy-proven deaths and 70% of combined autopsy-proven and clinically certain cause of deaths). When the individual thromboprophylaxis groups were compared, we did not find a significant difference between the proportions of the different causes of death in any possible group comparison. The PA and PAC groups had the highest mortality due to PE (PA: 35.4% and PAC: 28%) and when deaths due to PE or bleeding were combined, the PA and PAC groups showed the highest mortality (PA: 44.4% and PAC: 39.6%). However, none of these differences with the rest of the groups reached significant difference.

The autopsy-proven deaths for all patients combined and for each individual group showed that cardiopulmonary complications remained the leading cause of death (Table II). The ‘other’ group included patients with autopsy-proven or clinically certain deaths due to cancer (six), sepsis (four), iatrogenic vascular injury (two), multiple system organ failure (one), acute renal failure (two) and ruptured aortic aneurysm (two). There was a similar distribution of patients who had autopsy-proven deaths and who had a clinically certain cause (Table III).

**Discussion**

In the 1960s, Sir John Charnley’s hip unit reported that most post-operative deaths occurred as a consequence of PE. He reported that the fatal PE rate diminished from 2.3% without thromboprophylaxis to 1% with the use of different pharmacological agents, including phenindione, heparin, dextran and plaquenil. Our meta-analysis shows that over the last 20 years PE has ceased to be the most frequent cause of death following TJR. Cardiopulmonary disease, excluding PE, is now more frequent. A fatal PE accounts for 25.4%
of all deaths, irrespective of the form of thromboprophylaxis.

This study has a number of limitations: first, those inherent to meta-analysis, which compares outcomes between trials. The majority of the patients in the PA and PAC groups were enrolled in randomised trials, whereas the NRC and MM groups consisted of cohort studies (consecutive series). The warfarin groups had randomised and non-randomised studies. Although randomised trials have a higher level of evidence than prospective cohorts, the randomised trials included in our study were systematically subjected to exclusion of patients at high risk of VTE, which could reduce morbidity and mortality and underestimate the mortality in a more representative population. In contrast, the consecutive cohort studies used in our analysis represent a broader cross-section of patients and are more representative of a ‘real world’ scenario. Nevertheless, all-cause mortality is a defined endpoint and unlikely to be under-reported.

Secondly, in our analysis we did not differentiate between patients undergoing THR and those undergoing TKR. The pathogenesis of DVT differs between these two procedures. In TKR a tourniquet is usually used, and consequently venous stasis occurs throughout the procedure. The risk may increase if the tourniquet causes endothelial damage. In THR, venous stasis occurs intermittently and procoagulants are forced into the venous system, predominantly during surgery on the femur. However, elective THR and TKR carry a similar rate of peri-operative mortality. Both procedures carry a bleeding risk from anticoagulation.

Thirdly, we grouped together patients receiving unfractionated heparin, LMWH, ximelagatran, fondaparinux and rivaroxaban. We believe this is justified because it would be extremely difficult to prove a difference in mortality between all drugs in the current literature. Additionally, all PA drugs carry a risk of bleeding.

Fourthly, we grouped myocardial infarction, cardiac failure, arrhythmia, pulmonary oedema, pneumonia, asphyxia, fat embolism and other cardiac-related deaths in a cardiopulmonary group. This allowed us to include deaths attributable to non-specified cardiopulmonary complications in which PE has been ruled out (15 deaths).

Fifthly, the proportion of autopsy-proven deaths varied between the different thromboprophylaxis groups. When an autopsy was not performed, the cause of death reported by the authors was used for our analysis. If only autopsy-proven deaths had been included, our analysis of 99 441 elective joint replacements and 373 deaths would have been reduced to only 64 deaths. This would have limited group comparison due to insufficient sample size. When no autopsy was performed, we carefully reviewed the description of the cause of death and used precise criteria to classify each death to the ‘clinically certain’ or the ‘unknown cause’ group. If there was ambiguity in the description of the cause of death, it was classified as ‘unknown cause’. However, there was a similar distribution
of causes of death between the autopsy-proven and clinically certain groups. Consequently, despite the limitations outlined, we believe that we were able to answer our research questions.

This study extends the observation of our previous meta-analysis by identifying the cause of mortality, whether confirmed by autopsy or by the degree of clinical certainty. This meta-analysis used different entry criteria so as to include many more patients (99 441 versus 28 038). Nevertheless, the primary observation of our previous paper was verified: namely, that symptomatic and fatal PE occurs in some patients treated with PA, and that the all-cause mortality is not reduced with the routine use of PA. The significantly higher mortality in the NRC patients compared with the MM patients suggests that the use of a multimodal approach with minimal exposure to potent anticoagulants may be beneficial in elective TJR surgery.

Previous meta-analyses have shown similar findings. Murray et al reported on all available THR studies published between the 1970s and the 1990s, encompassing a total of 130 000 patients. They reported on overall mortality, fatal PE and deaths unrelated to PE, and classified studies according to the pharmacological prophylaxis used (none, heparin/LMWH, warfarin, aspirin and dextran). There was no significant difference in the proportion of fatal PE between the groups. None of the agents caused a significant decrease in mortality (range 0.15% to 0.5%) compared to no prophylaxis. Compared with heparin, the use of aspirin caused a significant decrease in non-PE deaths.

A meta-analysis by Freedman et al reported the use of thromboprophylaxis after elective THR in RCTs published between 1966 and 1998 (52 studies involving 10 929 patients). Placebo and five prophylactic agents were evaluated (LMWH, warfarin, aspirin, low-dose heparin, and PCD). They concluded that there were no differences in the proportion of fatal PE or the all-cause mortality between the groups.7

Recently, Tasker, Harbord and Bannister performed a meta-analysis of randomised trials published between 1980 and 2005 and reported that fatal PE, other deaths, all-cause mortality and major bleeding were no different between patients who received LMWH and those in a placebo group. There was a significant reduction in non-fatal PE when LMWH was used, at the expense of a trend towards haematoma formation. They concluded that the use of PA regimens was not justified in patients without additional risk factors for thromboembolism who were undergoing THR.

Peri-operative bleeding has consistently been noted to be a side effect of PA, and this was verified in this meta-analysis. Bleeding was a cause of death in the PA group verified both clinically and at autopsy. The risk of fatal bleeding is lowest in the NRC and MM groups, proven both by clinical certainty and at autopsy. Brown conducted a quantitative systematic review of the randomised control trials cited by the American College of Chest Physician (ACCP) Guidelines for VTE prophylaxis after major orthopaedic surgery (THR, TKR and hip fracture surgery). Brown’s findings negate the ACCP guideline’s statement that there is no evidence that aspirin is effective in reducing VTE events after major orthopaedic surgery. In fact, it was shown that the use of warfarin, LMWH and pentasaccharides after major orthopaedic surgery significantly increased the risk of post-operative bleeding, without reducing clinically relevant symptomatic DVT, PE, and fatal PE rates compared to aspirin. Our analyses and conclusions support the view that the routine use of PA may not save lives and may increase morbidity and mortality owing to the associated unwanted increased risk of bleeding.4-6

The major cause of death following modern TJR is cardiopulmonary disease, which includes predominantly myocardial infarction, pneumonia, and other cardiac conditions such as congestive heart failure. This begs the question whether aspirin is more appropriate to use than agents such as W or PA, which presumably act on the venous system rather than on the arterial system. In addition, we have previously shown that aspirin prevents the development of heterotopic ossification. Our findings are similar to those of Gandhi et al, who retrospectively investigated the in-hospital incidence, timing and mortality of myocardial infarction in patients undergoing TJR. They found that the incidence of peri-operative myocardial infarction was 1.8% and the in-hospital mortality rate due to myocardial infarction was 0.2%. Our results are also in line with those of Gill, Mills and Joshi. They followed 3048 consecutive patients after TKR and found that the in-hospital and 90-day mortality was respectively 0.36% and 0.46%. The leading cause of death was cardiac related and ranged between 0.2% and 0.29%. Death related to PE ranged from 0.03% to 0.16%.

Two recent studies also showed that myocardial infarction was the most frequent cause of death. Both studies used PCDs and the patients were followed for three months. One study followed 2153 patients after THR and TKR; of the eight autopsy-proven deaths, five (62.5%) were the result of myocardial infarction. The other study followed 1727 patients after THR; there were seven (0.41%) deaths from myocardial infarction, four (0.23%) resulting from cerebrovascular events and two (0.12%) due to PE. Four other patients (0.23%) died of non-vascular causes.

The ACCP guidelines and other regulatory bodies have recommended the routine use of PA after THR and TKR. However, our research suggests that these recommendations are inappropriate. PA has never been shown to reduce the rate of symptomatic fatal PE or all-cause mortality following elective TJR, and its adoption was based exclusively upon DVT rates. Our current and earlier studies demonstrated no reduction in the proportion of deaths or in non-fatal or fatal PE with PA compared to
multimodal thromboprophylaxis. Our results support the conclusions of the study by Jameson et al., who demonstrated in 219 602 patients that the use of LMWH promulgated by the National Institute for Clinical Excellence in the United Kingdom in 2007 increased the 90-day VTE rate in THR patients and did not improve the VTE rate in TKR patients. There was an increase in complications, particularly thrombocytopenia. However, it is conceivable that the selective use of these potent anticoagulants could diminish the overall risk of bleeding.

The data presented in our analysis in the context of the previously discussed limitations demonstrate that mortality following modern elective TJR is low and unlikely to be affected by current thromboprophylactic regimens. Further, we have shown that the routine use of PA with or without regional anaesthesia and/or pneumatic compression devices does not diminish the overall mortality or the proportion of deaths due to PE. The routine use of PA in modern elective total joint arthroplasty seems to be unjustified.

Supplementary material

A PRISMA flow diagram detailing the meta-analysis, sets of funnel plots showing the proportion of deaths in each of the thromboprophylaxis groups, and three tables detailing i) pooled proportions (%) and 95% confidence intervals (CI) of types of death in each thromboprophylaxis group, ii) number, pooled proportions (%) and 95% confidence intervals (95% CI) for cause of death in each thromboprophylaxis group (based on the total number of autopsy-proven and clinically certain deaths), and iii) cause of death for patients with autopsy-proven and clinically certain death in the cardiopulmonary group, are available with the electronic version of this article on our website at www.jbjs.org.uk

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References


