Fatal vascular outcomes following major orthopedic surgery

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Summary

Major orthopedic surgery is known to be associated with potentially serious arterial and venous vascular complications, although uncertainty exists about current event rates. Using electronic databases and investigator contact, we identified randomized and cohort studies reporting overall mortality and fatal vascular events. Where possible, studies reporting high autopsy rates (>60%) were examined. Pooled incidences were calculated from eligible studies. For *Autopsy studies*: Pooled overall mortality and fatal pulmonary embolism for patients undergoing elective hip and knee replacement without prophylaxis could not be calculated, while with prophylaxis they were 0.44% (95% confidence interval 0.02 to 0.87%) and 0.43% (0.01 to 0.85%). For patients undergoing hip fracture surgery, the corresponding rates without prophylaxis were 15.9% (14.5 to 17.3%) and 1.9% (1.4 to 2.4%). With prophylaxis, mortality and fatal pulmonary embolism rates were 8.5% (7.3 to 9.7%) and 1.0% (0.6 to 1.5%). Among *Cohort studies*: Pooled overall mortality and fatal pulmonary embolism for patients undergoing elective hip and knee replacement without prophylaxis were 0.93% (0.57 to 1.29%) and 0.36% (0.14 to 0.59%). For patients receiving prophylaxis (7 to 14 days), mortality and fatal pulmonary embolism were 0.57% (0.51 to 0.62%) and 0.18% (0.14 to 0.21%). Patients undergoing hip fracture surgery receiving prophylaxis had mortality and fatal pulmonary embolism rates of 3.2% (2.8 to 3.6%) and 0.30% (0 to 0.61%). Vascular events contributed towards approximately 50% of all deaths with similar proportions due to ischemic heart disease, cardiac failure and pulmonary embolism. In conclusion, although prophylaxis results in a reduction in overall mortality and fatal pulmonary embolism, vascular events continue to be a common cause of mortality.

Keywords

Orthopedic surgery, prophylaxis, fatal vascular outcomes

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Introduction

Currently more than two million people in the United States and Europe undergo major orthopedic surgery each year. Annual procedural numbers are increasing; a 25–35% increase in the number of elective procedures is predicted over the next 30 years (1, 2), while the number of patients undergoing hip fracture surgery is expected to triple by 2030–2050.

Major orthopedic surgery is associated with systemic activation of coagulation (3, 4) with potentially serious, and at times fatal, vascular complications, such as myocardial infarction, stroke and venous thromboembolism (5–8). Among the predominantly elderly population undergoing these procedures, coexisting cardiac, pulmonary, cerebral and renal disease are often present thus increasing the likelihood of post-operative vascular events.

Of the post-operative vascular events, venous thromboembolism is an important and well recognized cause of mortality, morbidity and hospital readmission (9). To prevent readmission for symptomatic thromboembolic events, fatalities and probable deep venous insufficiency, thromboprophylaxis is recommended in all patient groups (9). Pooled data demonstrate significant reductions in the incidence of fatal pulmonary embolism and overall mortality with the short term use of heparin based prophylaxis (10). It is plausible that the mortality reduction seen with the use of thromboprophylaxis may be due to prevention of overall vascular events. Although arterial and venous thrombosis are commonly thought to be two different disorders,

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recent evidence suggests an common pathogenic process between idiopathic venous thromboembolism and atherosclerosis (11). Furthermore, among patients undergoing major orthopedic surgery it is thought that atherosclerotic plaques may be the site for arterial thrombus formation and that bone surgery triggers arterial events in addition to venous events (3, 4), the latter having been the focus of clinical attention for many years. Data concerning arterial vascular complications following major orthopedic surgery and their sequelae are however scarce, these events have previously not been attributed to the surgical trauma *per se* and have achieved little preventative attention compared to venous events.

In order to provide estimates concerning mortality, fatal vascular outcomes (including venous and arterial events) in patients undergoing major orthopedic surgery, we undertook a review of autopsy data, unpublished source data and clinical outcome studies.

Methods

We conducted a literature review appertaining to the current evidence concerning fatal vascular outcomes following major orthopedic surgery. To identify relevant published studies on this topic, electronic databases (MEDLINE, EMBASE) were searched using the following terms: *autopsy, deep vein thrombosis, hip fracture surgery, myocardial infarction, pulmonary embolism, stroke, thrombosis, total knee replacement, total hip replacement, and venous thromboembolism.* Bibliographies of journal articles were hand-searched to locate additional studies and abstracts from major international meetings were reviewed. Relevance was assessed using a hierarchical approach based on title, abstract, and published or unpublished manuscripts. Several of the authors also provided unpublished source data regarding clinical outcomes. Where possible studies with high autopsy rates (>60%) were identified.

Statistical analyses

Identified studies were initially separated into the type of surgical intervention, being elective hip or knee replacement or emergency hip fracture surgery. Identified studies were further divided into whether they were randomized or cohort (prospective or retrospective observational) in design. Thereafter studies were pooled to obtain quantitative estimates of the risks of mortality and fatal vascular events according to whether prophylaxis was given or not. No differentiation was made according to the type of prophylactic agent (heparin, low-molecular weight heparin, warfarin) given. Where no difference was seen in outcomes between cohort studies and randomized trials, data was pooled. Pooled incidences were estimated by combining the data of each trial weighted firstly by the inverse of the variance (12) and secondly by the inverse of the sample size. Since the results were the same, only the first method of pooling was used. When a rate was equal to zero, the number of events equal to 0 was corrected by 0.25 to allow for the computation of the variance.

Results

Overall mortality and fatal pulmonary embolism

Autopsy studies

Mortality and fatal pulmonary embolism in patients undergoing elective joint replacement and emergency hip fracture surgery in studies where greater than 60% of patients enrolled underwent autopsy are shown in Tables 1 and 2. All studies where prophylaxis was given were randomized, whereas those evaluating outcomes in patients not receiving prophylaxis were observational in design. Only one study by Sheppeard et al. (13) was identified which dealt with patients undergoing elective hip replacement who did not receive prophylaxis. In this study, 19 out of 3016 patients (0.63%) had died by 12 months with 11 deaths (58%) due to fatal pulmonary embolism. Among patients undergoing elective hip or knee replacement who received prophylaxis, the

Table 1: Mortality and fatal pulmonary embolism following elective hip and knee replacement – autopsy studies.
*Includes observational and randomized studies with greater than 60% of patients undergoing autopsy. †Includes patients receiving low-molecular weight heparin, unfractionated heparin and warfarin. ‡ Prophylactic anticoagulation was used in approximately 20% of patients. §Based on overall population of 42,278 patients undergoing orthopedic surgery. ¶Based on fatal and contributory pulmonary embolism detected at autopsy, a further two fatal pulmonary embolism were clinically suspected as cause of death. **Based on overall study population of 23,078 patients undergoing all forms of surgery. ††A continuity correction was used (36). I/P = In-patient; NA = Not applicable; PE = Pulmonary embolism; R = Randomized; TKR = Total knee replacement; THR = Total hip replacement.

Study	Study Design	Surgical Population	Patients Operated - n	Follow Up Period	Autopsy Rate (%)	No Prophylaxis – No. /Total No. (%)			Prophylaxis† – No. /Total No. (%)		
						Mortality	Fatal PE	Fatal PE / Total Deaths	Mortality	Fatal PE	Fatal PE / Total Deaths
Sheppeard et al. 1981 (13)	RO	THR	3016‡	12 mo	448/487 (92)§	19/3016 (0.63)	11/3016 (0.4)¶	11/19 (58)	NA	NA	NA
Frostick et al. 1995 (17, 34)	R	THR	306	6 mo	3/3 (100)	NA	NA	NA	3/306 (1.0)	3/306 (1.0)	3/3 (100)
Frostick et al. 1995 (17, 34)	R	TKR	223	6 mo	4/4 (100)	NA	NA	NA	4/223 (1.8)	3/223 (1.3)	3/4 (72)
Haas et al. 2005 (35)	R	THR/ and TKR	412	14 d after prophylaxis	219/312 (70)**	NA	NA	NA	1/412 (0.24)	1/412 (0.24)	1/1 (100)
Pooled data – % (95% CI)	-		-	-	-	-	-	-	**0.44 (0.02–0.87)††**	**0.43 (0.01–0.85)††**	**84.9 (60.8–100)††**

Table 2: Mortality and fatal pulmonary embolism following hip fracture surgery – autopsy studies. *Includes observational and randomized studies with greater than 60% of patients undergoing autopsy. †Includes patients receiving low-molecular weight heparin, unfractionated heparin and warfarin. ‡ Prophylactic anticoagulation was used in approximately 20% of patients. §145 patients (8%) did not undergo surgery. ¶Based on overall study population of 23,078 patients undergoing all forms of surgery. NA = Not applicable; PE = Pulmonary embolism; PO = Prospective observational; RO = Retrospective observational; R = Randomized.

Study	Study Design	Patients Operated - n	Follow Up Period	Autopsy Rate (%)	No Prophylaxis – No. /Total No. (%)			Prophylaxis† – No. /Total No. (%)		
					Mortality	Fatal PE	Fatal PE / Total Deaths	Mortality	Fatal PE	Fatal PE / Total Deaths
Sheppeard et al. 1981 (13)	RO	928‡	12 mo	164/164 (100)	164/928 (17.7)	40/928 (4.3)‡	40/164 (24.4)	NA	NA	NA
Bergqvist and Fredin 1991 (37)	PO	806	3 mo	42/66 (64)	NA	NA	NA	66/806 (8)	8/806 (1)	8/66 (12.5)
Schroder and Andreasson 1993 (38)	RO	1,812§	3 mo	180/273 (66)	273/1,812 (15)	27/1,812 (1.5)	27/273 (9.9)	NA	NA	NA
Gruber et al. 1985 (39)	R	329	3 mo	27/40 (68)	NA	NA	NA	40/329 (12)	10/329 (3)	10/40 (25)
Frostick et al. 1995 (17, 34)	R	358	6 mo	53/53 (100)	NA	NA	NA	53/358 (14.8)	8/358 (2.2)	8/53 (15)
Haas et al. 2005 (35)	R	607	14 d after prophylaxis	219/312 (70) ¶	NA	NA	NA	37/607 (6.1)	4/607 (0.66)	4/37 (11)
Pooled data – % (95% CI)	-	-	-	-	**15.9 (14.5–17.2)**	**1.9 (1.4–2.4)**	**13.1 (10–16.3)**	**8.5 (7.3–9.7)**	**1.0 (0.6–1.5)**	**14.2 (9.4–19.1)**

pooled mortality rate was 0.44% (95% confidence interval (CI) 0.02 to 0.87%) with the vast majority of deaths (85%, 95% CI 60.8 to 100%) being due to fatal pulmonary embolism. Among patients undergoing hip fracture surgery, overall mortality was higher, the pooled rate being 15.9% (95% CI 14.5 to 17.3%) for patients not receiving prophylaxis and 8.5% (95% CI 7.3 to 9.7%) for those receiving prophylaxis. The pooled incidence of fatal pulmonary embolism was 1.9% (95% CI 1.4 to 2.4%) for patients not receiving prophylaxis and 1.0% (95% CI 0.6 to 1.5%) for those receiving prophylaxis. The contribution of fatal pulmonary embolism to overall mortality was similar (13 to 14%), irrespective of whether prophylaxis was given or not.

Cohort studies

Tables 3 and 4 show overall mortality and fatal pulmonary embolism events in cohort studies (elective and emergency procedures), where the cause of death was not routinely assessed by autopsy. In elective hip or knee replacement studies, the pooled overall mortality for patients not receiving prophylaxis was 0.93% (95% CI 0.57 to 1.29%) and 0.57% (95% CI 0.51 to 0.62%) for those receiving prophylaxis. The pooled incidence of fatal pulmonary embolism for patients not receiving prophylaxis was 0.36% (95% CI 0.14 to 0.59%) and 0.18% (95% CI 0.14 to 0.21%) for those receiving prophylaxis. Fatal pulmonary embolism therefore contributed towards 33 to 44% of overall morality. The duration of follow up varied between studies with out-

Table 3: Mortality and fatal pulmonary embolism following elective hip and knee replacement – cohort studies. *Includes patients receiving low-molecular weight heparin, unfractionated heparin and warfarin. †1276 cases did not use chemical prophylaxis. ‡Fatal pulmonary embolism occurred in 0.17% of patients greater than 80 years of age. §Fatal pulmonary embolism occurred in 0.08% of patients greater than 80 years of age. I/P = in-patient; NK = Not known; NA = Not applicable; PE = Pulmonary embolism; PO = Prospective observational; RO = Retrospective observational; R = Randomized; TKR = Total knee replacement; THR = Total hip replacement.

Study	Surgical Population	Patients Operated - n	Follow Up Period	No Prophylaxis – No. /Total No. (%)		Prophylaxis* – No. /Total No. (%)	
				Mortality	Fatal PE	Mortality	Fatal PE
Coventry et al. 1973 (40)	THR	2,012	NK	NK	2/62 (3.2)	NK	1/1,950 (0.05)
Seagroatt et al. 1991 (8)	THR	8,508	3 mo	NK	NK	93/8,508 (1.1)	6/8,508 (0.07)
Warwick et al. 1995 (41)	THR	1,162	3 mo	15/1,162 (1.3)	4/1,162 (0.34)	NA	NA
Ansari et al. 1997 (42)	TKR	923	3 mo	6/923 (0.65)	4/923 (0.4)	NA	NA
Fender et al. 1997 (43)	THR	1,893	42 days	7/667 (1.05)	2/667 (0.3)	10/1,226 (0.82)	2/1,226 (0.16)
National Hip Registry 2000 (44)	THR	7,134†	3 mo	NK	NK	27/7,134 (0.39)	8/7,134 (0.11)
Lubinus et al. 2001 (45)	Primary THR	4,781	I/P	NA	NA	14/4,781 (0.29)	5/4,781 (0.11)‡
Lubinus et al. 2001 (45)	Revision THR	1,248	I/P	NA	NA	9/1,248 (0.72)	4/1,248 (0.32)§
Bhatattacharyna et al. 2002 (46)	THR and TKR	10,284	I/P	NA	NA	30/10,284 (0.29)	NK
Lie et al. 2002 (7)	THR	45,767	2 mo	NA	NA	360/45,767 (0.79)	169/45,767 (0.37)
Pooled Data – % (95% CI)	-		-	**0.93 (0.57–1.29)**	**0.36 (0.14–0.59)**	**0.57 (0.51–0.62)**	**0.18 (0.14–0.21)**

Table 4: Mortality and fatal pulmonary embolism following hip fracture surgery – cohort studies. *Includes patients receiving low-molecular weight heparin, unfractionated heparin and warfarin. †Fatal Pulmonary Embolism occurred in 1.1% of patients greater than 80 years of age. I/P = In-patient; NK = Not known; NA = Not applicable; PE = Pulmonary embolism.

Study	Study Design	Patients Operated - n	Follow Up Period	No Prophylaxis– No. /Total No. (%)		Prophylaxis* – No. /Total No. (%)	
				Mortality	Fatal PE	Mortality	Fatal PE
Todd et al. 1995 (24)	Cohort	566	3 mo	NK	12/305 (4)	NK	0/261
Lubinus et al. 2001 (45)	Cohort	892	I/P	NA	NA	45/892 (5.4)	7/892 (0.78) †
Bhatattacharyna et al. 2002 (46)	Discharge survey	6,460	I/P	NA	NA	198/6,460 (3.1)	NK
Pooled Data- % (95% CI)				**-**	**-**	**3.2 (2.8–3.6)**	**0.30 (0–0.61)**

comes recorded during hospitalization and for up to 3 months following surgery. Mortality for patients undergoing hip fracture surgery was higher, being 3.2% (95% CI 2.8 to 3.6%) in two cohort studies evaluating outcomes during hospitalization. The pooled incidence of fatal pulmonary embolism was 0.3% (95% CI 0 to 0.6%), thereby contributing about 10% towards overall mortality. Overall mortality and incidence of fatal pulmonary embolism was higher among patients not receiving prophylaxis.

Cause of death

Autopsy studies

Among patients undergoing elective joint replacement only one study by Sheppeard et al. was identified where the causes of death were determined (13). In this study of over 3,000 patients (92% underwent autopsy), fatal pulmonary embolism contributed towards 58% of deaths, with a further 10% of deaths caused by heart failure. The cause of death, as determined by observational and randomized trials having high autopsy rates (>60%), among patients undergoing hip fracture surgery is shown in table 5. Pooled data indicate that vascular events contribute towards 32% of all deaths, with similar proportions of death due to pulmonary embolism (10.5%), heart failure (9.8%), and myocardial infarction (8.6%). When observational studies and randomized trials were considered separately, deaths due to heart failure were generally higher in observational studies (10.3%, 95% CI, 8.8 to 11.8%) compared with randomized trials (5.3%, 95% CI, 0.5 to 10.1%). Similarly, the pooled incidence of fatal pulmonary embolism was lower in observational studies (10.0%, 95% CI, 8.8 to 11.4%) compared with randomized trials (20.1%, 95% CI, 11.2 to 29.0%). No significant difference was seen in the incidence of myocardial infarction and pneumonia according to the nature of the study performed. Deleting individual studies did not materially alter the findings. In particular, removing the studies where follow-up was not known (14) or longer than 3 months (13), did not significantly alter the overall results.

Other studies

Several other randomized and cohort studies have examined the causes of death following major orthopedic surgery. The large Pulmonary Embolism Prevention (PEP) study, involving more than 13,000 patients undergoing hip fracture surgery and 4,000 patients undergoing hip or knee replacement, demonstrated that vascular events contribute towards a significant proportion of overall mortality (5). In total, 0.5% of patients undergoing hip or knee replacement experienced a fatal vascular event within 35 days of surgery. Vascular events accounted for 95% of all deaths recorded. In the same trial up to 4% of patients undergoing non-selected hip fracture surgery suffered fatal vascular complications during the corresponding time period, vascular events accounting for 53% of all deaths. Of the vascular deaths following hip fracture surgery (including probable but not confirmed

Table 5: Causes of death following hip fracture surgery – autopsy studies. *Includes observational and randomized studies. †Cause of death details reported in 37 patients. ‡Cause of death listed as hypertension. §Doesn't include contributory pulmonary embolism detected at autopsy. ¶Includes other cardiac, other respiratory, cancer and miscellaneous. MI = Myocardial infarction; NK = Not known, PO = Prospective observational; PE = Pulmonary embolism; R = Randomized, RO = Retrospective observational.

Study	Study Design	Patients Operated - n	Follow Up Period	Autopsy Rate (%)	Cause of Death – No. /Total No. (%)					
					MI	Heart Failure	Stroke	PE	Pneumonia	Other Causes
Sheppeard et al. 1981 (13)	RO	928	12 mo	164/164 (100)	6/164 (3.6)	36/164 (22)	4/164 (2)	40/164 (24)	47/164 (29)	31/164 (19)
Bannister et al. 1990 (47)	R	155	In-hospital	36/37 (97)†	8/37 (22)	1/37 (3)	3/37 (8)	6/37 (16)	15/37 (41)	4/37 (11)
Gruber et al. 1985 (39)	R	329	3 mo	27/40 (68)	2/40 (5)	8/40 (20)‡	0	10/40 (25)	11/40 (27.5)	9/40 (22.5)
Bergqvist and Fredin 1991 (37)	PO	806	3 mo	42/66 (64)	7/42 (16)	13/42 (31)	0	3/42 (7)§	13/42 (31)	6/42 (14)
Schroder and Andreasson 1993 (38)	RO	180	3 mo	180/273 (66)	NK	NK	NK	27/180 (14)	NK	NK
Neck of Femur Audit 1995 (16)	PO	1097	3 mo	753/1,097 (69)	79/753 (10.5)	55/753 (7.3)	52/753 (6.9)	52/753 (6.9)	224/753 (29.7)	291/753(38.6)¶
Perez et al. 1995(14)	RO	581	NK	581/581 (100)	55/581 (9)	81/581 (14)	16/581 (3)	80/581 (14)	266/581 (46)	83/581(14)
Pooled data -% (95% CI)					**8.6 (7.2–10.0)**	**9.8 (8.4–11.3)**	**3.5 (2.6–4.4)**	**10.3 (8.9–11.6)**	**35.0 (32.7–37.3)**	**22.1 (21.1–25.1)**

events), ischemic heart disease accounted for 16% of all deaths, followed by heart failure (13%), pulmonary embolism (10%), and stroke (7%). Overall mortality was maximal within the first 35 days (6.8%), accounting for 62% of overall mortality (11%) seen after one year.

In the Norwegian hip replacement studies, involving 45,000 to 65,000 patients undergoing elective hip replacement or hip fracture surgery, three quarters of deaths were due to vascular causes (6, 7), predominantly within the first 60 days. Thromboembolic complications accounted for 47% of overall mortality, followed by deaths due to ischemic heart disease (40%) and stroke (15%). The Oxford record linkage study similarly reviewed causes of death among over 11,000 patients undergoing elective hip replacement (8). Vascular events accounted for 59% of all deaths within the first 90 days, with the majority of deaths due to ischemic heart disease (40%), followed by stroke and pulmonary embolism.

Discussion

Data from this analysis indicate that patients undergoing hip and knee replacement who receive prophylaxis have an overall mortality of 0.4 to 0.6% within 3 months of surgery. Mortality in patients undergoing hip fracture surgery is substantially higher, being 3 to 8.5% up to 6 months following surgery. For both elective and emergency procedures, overall mortality is higher among those patients not receiving prophylaxis.

Mortality following elective joint replacement appears to be maximal within the first 3 months, thereafter the mortality rate does not appear to increase by one year follow-up, the exception being patients with added comorbidities such as rheumatoid arthritis (6, 8). Mortality in patients undergoing hip fracture surgery however continues to increase with time, ranging from 5 to 18% at 3 months follow-up (5, 15–19), increasing to be 13 to 36% by one year (7, 20–25).

Further evidence indicates that there has been a reduction in mortality following elective joint replacement over the last decade. Information from the National Hospital Discharge Survey (26) and the United States Bureau of the Census Compressed Mortality File (27), were used to estimate trends in the mortality rate from hip or knee replacement in the United States from 1979 through 1998. A significant reduction in the all cause mortality rate was demonstrated, being reduced from 0.62 deaths per 100 cases of hip or knee replacement in 1990 to 0.26 deaths per 100 cases in 1998 ($P<0.0001$) (P. Stein and R. Hull, personal communication). Reductions in the population mortality rate from pulmonary embolism have been noted over the same time period (28). Although exact reasons for this decrease are unclear, improved surgical and anesthesiological techniques and widespread use of prophylaxis are likely to be contributing factors.

In our analysis of autopsy studies, vascular events accounted for approximately one third of all deaths following hip fracture surgery. With inclusion of data from the PEP study (5), the Norwegian hip replacement studies (6, 7) and the Oxford record linkage study (8), it is apparent that vascular events account for approximately 50% of all deaths, the majority of which occur within the first few months following surgery

In this analysis, the pooled fatal pulmonary embolism rate for patients undergoing elective hip or knee replacement receiving prophylaxis was 0.2 to 0.4%. This is in keeping with other estimates of fatal pulmonary embolism in patients receiving in-hospital prophylaxis, being 0.1 to 0.4% following elective hip replacement and 0.2 to 0.7% following knee replacement (9). For patients undergoing hip fracture surgery, the pooled rate for fatal pulmonary embolism for patients receiving prophylaxis was 1.0%. This higher risk of fatal pulmonary embolism may be related to a number of factors, including the preoperative non-selection of patients, the age of the patient population, multiple severe co-morbidities and a lesser pre-operative cardio-respiratory and vascular reserve (20, 22, 29).

Pooled data show that pulmonary embolism contributes to approximately 10 to 14% of all deaths following hip fracture surgery with similar proportions due to other fatal vascular events. For patients undergoing elective procedures, where overall mortality rate is much lower due to the predominantly selected and medically optimized population, pulmonary embolism contributes to a substantially higher proportion (85%) of deaths. Haake and Berkmann in their review of autopsy studies showed similar findings, fatal pulmonary embolism accounting for 67% for all deaths in patients undergoing hip replacement and 38% of all deaths in patients undergoing hip fracture surgery (29).

This analysis predominantly presents information concerning outcomes following the use of short term (7 to 10 days) prophylaxis. Mortality and the risk of fatal vascular events are however recognized to remain elevated for several months following hospital discharge (6). Studies evaluating non-fatal outcomes show a similar prolonged period of risk, varying according to the type of surgery performed. Venous thromboembolism following knee replacement usually occurs in the period immediately following surgery (9 to 16 days), which extends out to several weeks post surgery (27 to 36 days) for those undergoing hip fracture surgery or hip replacement (30, 31).

While clinical attention is often focused on prevention of mortality and fatal pulmonary embolism, randomized clinical trials evaluating prophylactic therapies predominantly report the incidence of objectively confirmed subclinical (silent) deep-vein thrombosis. These subclinical deep-vein thrombi are usually treated with therapeutic anticoagulation, thereby altering the natural history of thromboembolic events and limiting any assessment of the potential benefits in preventing fatal outcomes. In addition, the role that prophylactic therapy may play in preventing arterial vascular events following major orthopedic surgery is rarely assessed in most trials. Future evaluation of overall vascular morbidity and mortality may provide additional information concerning the effect of antithrombotic therapies on reducing arterial and venous events.

Our study has several potential limitations. First, pooled data were derived from a wide spectrum of randomized controlled trials and cohort studies with different designs and goals. In an effort to minimize uncertainty in event rates, we attempted to use studies in which patients underwent autopsy to determine the cause of death in conjunction with large cohort studies that were methodologically robust and reflect current surgical practice. Second, despite an extensive literature search for published and

unpublished data, a paucity of data exists concerning the causes of fatal outcomes, making it difficult to precisely assess event rates. Many studies did not report clinical outcomes and our figures may indeed underestimate the actual numbers seen in clinical practice. In particular, in cohort studies pulmonary embolism is often clinically misdiagnosed and underestimated as a cause of death due to its clinically ambiguous presentation, and as such, death certificates are notoriously unreliable (32, 33). These studies are open label, often without central blinded adjudication of events or systematic clinical follow up. Third, the length of follow up varied greatly depending on the studies considered. Therefore, a longer duration of follow-up will lead to higher number of fatal outcomes. Fourthly, methodological differences are recognized in any studies evaluating the cause of death. In observational studies, cardiac insufficiency is likely to be overdiagnosed while fatal pulmonary embolism events are underdiagnosed due to their silent nature prior to death. Although autopsy studies will eliminate much of this uncertainty surrounding the cause of death limitations exist in the manner in which they are performed. Last, the lack of autopsy data in patients undergoing elective hip and knee replacement did not allow us draw any firm conclusions concerning the main causes of death in these population groups.

In summary, despite thromboprophylaxis being associated with a reduction in overall mortality and fatal pulmonary embolism, vascular events continue to be a common cause of death. The incidence of fatal pulmonary embolism (autopsy proven) among patients undergoing hip fracture surgery remains especially high at 1%. The findings reaffirm previous study results and demonstrate the contribution of vascular events toward overall mortality. Further progress towards reducing overall vascular mortality, especially among hip fracture surgery procedures, may involve alternative methods or longer durations of prophylaxis.

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