Early postoperative mortality after 67,548 total hip replacements

Causes of death and thromboprophylaxis in 68 hospitals in Norway from 1987 to 1999

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ABSTRACT – **Patients in the Norwegian Arthroplasty Register with a total hip replacement (THR) have a lower long-term mortality than the age- and gender-matched Norwegian population.**

We analyzed the early postoperative mortality after 67,548 THR operations in 68 hospitals reported to the Norwegian Arthroplasty Register between 1987 and 1999. Data on deaths and causes of death were obtained from from Statistics Norway, and on thromboprophylaxis from a separate questionnaire sent to all hospitals.

During the years 1987–2000 the 68 hospitals reported use of 6 thromboprophylaxis drugs and 24 different combinations of drugs and stockings. In 1988, only 3 of 29 hospitals reported use of low molecular weight heparin (LMWH), but in 1999, 67 of the 68 hospitals used LMWH.

In the first postoperative week, the daily mortality was about 2.5 deaths per 10,000 THR patients. By the 70th postoperative day, the daily mortality had declined to about 0.57 deaths per 10,000 patients. The daily mortality of the age- and gender-matched Norwegian population was 0.95 deaths per 10,000 individuals.

Early postoperative mortality increased with age, was higher in men than women, and was usually due to vascular disease. We found only a slight reduction in the 60-day postoperative mortality during the period 1987–1999. All underlying diagnoses for a prosthesis operation had a higher 60-day postoperative mortality than primary osteoarthrosis.

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We have previously reported that total hip replacement (THR) patients have a lower long-term mortality than the age- and gender-matched Norwegian population (Lie et al. 2000). However, during the first 60 postoperative days, THR patients had a higher mortality. Thus the mortality in the early postoperative period after a THR is higher than after transurethral prostatectomy and inguinal herniorrhaphy (Seagroatt and Goldacre 1994), but lower than after coronary bypass surgery (Osswald et al. 1999). The causes of this increase and its duration are not clear. The prevention of deep venous thrombosis by thromboprophylaxis after hip surgery has been studied in several randomized clinical trials (Eriksson et al. 1991, Borris et al. 1994, Imperiale and Speroff 1994, Bergqvist et al. 1996, Planes et al. 1996, Comp et al. 1998, Colwell et al. 1999). The essential relationship between thromboprophylaxis and mortality in hip replacement surgery is still debated (Seagrott et al. 1991, Murray et al.1996, Bulstrode 1998, Salvati et al. 2000, Thomas 2000) although the relationship between heparin thromboprophylaxis and lower overall mortality and lower mortality due to pulmonary embolism in major surgery, including total hip replacement, were found 25 years ago (Kakkar et al. 1975, Collins et al. 1988).

In this observational study, we focused on the increase in mortality during the early postoperative period in 67,548 total hip replacement operations, with complete data on mortality in the early postoperative period, thromboprophylaxis in hospital and causes of death on the death certificates.

Patients and methods

The study is based on 67,548 total hip replacement (THR) operations reported to the Norwegian Arthroplasty Register from 1 September 1987 to 30 June 1999 on forms filled in by the surgeon immediately after each operation (Havelin et al. 2000). The diagnoses at hip surgery were classified as primary osteoarthrosis, rheumatoid arthritis, fracture of the femoral neck, pediatric hip diseases (dysplastic hips with or without dislocation, Perthes' disease, and slipped capital femoral epiphysis), revision surgery, and the remainder as "other diagnosis". Gender, age at operation, and surgical approach (posterolateral, lateral, or anterolateral) were also considered. Complete data for date of death of all patients were available from Statistics Norway for the early postoperative period (until 1 May 2000).

Since information on thromboprophylaxis is not routinely collected in the hip register, it was obtained by a questionnaire sent to all 68 hospitals. In this questionnaire, we asked about the type and duration of current and past thromboprophylaxis regimens during the period 1987–1999. If a hospital could not state clearly when they changed the regimen, the month or the year of change was stated as unknown.

During the observation period, 6 drugs were used for thromboprophylaxis: the low molecular weight heparins (LMWH), dalteparin (Fragmin: Pharmacia & Upjohn) or enoxaparin (Klexane: Rhône-Poulenc Rorer), heparin (Heparin: LEO), warfarin (Marevan: Nycomed Pharma), dextran (Macrodex: Medisan), and ASA (acetylsalicylic acid). Only one hospital stated that they used no thromboprophylaxis. However, at that hospital most patients had rheumatoid arthritis and were on treatment with NSAIDs (nonsteroidal antiiflamatory drugs).

To study the relation between duration of prophylaxis and mortality, we used these categories: dalteparin ($\leq$ 10 days, 11–16 days, $\geq$ 17 days), enoxaparin ($\leq$ 13 days, $\geq$ 14 days), warfarin ($\leq$ 21 days, $\geq$ 22 days), dextran ($\leq$ 4 days, $\geq$ 5 days), heparin ($\leq$ 13 days, $\geq$ 14 days) and stockings ($\leq$ 7 days, 8–30 days, $\geq$ 31 days). The differences in cut-off levels for the drugs reflected differences in the distribution of the duration of administration of the various drugs, stated on the thromboprophylaxis questionnaire.

The causes of death were available until 31 December 1995 and were coded using the ninth revision of the International Classification of Diseases (ICD-9). The mortality records were obtained from death certificates obtained from Statistics Norway. Links between the date and causes of death to the data from the Hip Register were made using the unique person identification number assigned to each inhabitant of Norway, while information from the thromboprophylaxis questionnaire was linked using the hospital identification.

We divided the cause of death for the main analyses into two distinct categories: "vascular diseases", if a vascular disease was mentioned on the mortality record (ICD-9: 390–459.9, 557.0, and 997.1) and "non-vascular diseases" in other cases (all other ICD-9 codes). We also considered the following cause of death categories: septicemia (038–038.9), neoplasms (140–239.9), ischemic heart disease (410–414.9), pulmonary embolism and pulmonary infarction (415.1), cerebrovascular disease (430–438.9), deep vein thrombosis (451.1, 451.2, 451.9, 453.9, and 459.0), pneumonia and influenza (480–487.9), thrombo-embolic complications (410, 415.1, 434.1, 434.9, 444.2, 451.1, 451.2, 451.9, 453.9, 459.0, and 557.0), bleeding (431, 432.1, 436, 459.0, 578.9, 853, and 998.1) and sudden death (798.1). The underlying cause of death could not be used, because this often, but not always, was the diagnosis for the prosthesis operation—e.g., primary osteoarthrosis. All the cause of death categories were therefore constructed according to the presence of a diagnosis anywhere on the mortality record. The same patient may therefore be listed in several cause of death categories.

Statistics

Because no censoring was present, we used ordinary logistic regression to study the mortality during 60 days. We considered combinations of thromboprophylaxis drugs and stockings, including more than 1,000 operations, used throughout the period from 1987 to 1999. In the logistic regression models, the year of operation was entered as a continuous variable, age was entered as age squared, and diagnosis was entered as a categorical variable.

Table 1. Regimens of thrombosis prophylaxis showing the number of hospitals and number of operations for various periods

Prophylaxis regimen	Number of hospitals [a]	THR operations				
		1987–1990	1991–1994	1995–1998	1999	Total
Dalteparin	21	475	3,902	5,340	606	10,323
Dalteparin+stocking	29	1,017	4,970	8,023	1,218	15,228
Dalteparin+enoxaparin	3	–	912	1,320	136	2,368
Dalteparin+dextran+stocking	4	–	406	757	184	1,347
Dalteparin+warfarin+stocking	1	–	1,021	943	211	2,175
Enoxaparin+stocking	5	127	460	443	102	1,132
Dextran+warfarin	4	1,437	433	–	–	1,870
Dextran+warfarin+stocking	3	798	327	–	–	1,125
Heparin	4	987	566	–	–	1,553
Warfarin	2	1,204	111	–	–	1,315
14 other known regimens	24	1,982	949	1,862	359	5,152
Sum of known regimens	68	8,027	14,057	18,688	2,816	43,588
Unknown regimens	52 [b]	9,561	8,031	5,961	407	23,960
Total	68	17,588	22,088	24,649	3,223	67,548

[a] Information about the hospital is available for some part of the period 1987–1999.
[b] No information on thrombosis prophylaxis regimens is available for some part of the period 1987–1999.

The mortality curves (hazard of death as a function of postoperative days) were calculated by computing the daily conditional mortality and then using a kernel smoother (normal density kernel with 14 days' bandwidth). The 95% daily score confidence limits was calculated and then smoothed with the same technique. The yearly mortality curves for age were calculated and smoothed similarly (normal density kernel with 5 years' bandwidth).

The logistic regression analysis was performed in SPSS (SPSS 10.0 for Windows, SPSS Inc., Chicago, Illinois, USA), while the general additive logistic model (GAM) and the mortality curves were calculated and smoothed in S-Plus (S-Plus 2000 for Windows, MathSoft, Inc., Seattle, Washington, USA). Mortality rates for the age- and gender-matched population were calculated from the population mortality rate tables in a custom-made Fortran program.

Two sided p-values less than 0.05 were considered significant.

Results

During the years 1987–1999, 20,883 THR operations on men and 46,665 on women with a mean age of 67.7 years and 69.9 years, respectively, were reported to the Norwegian Arthroplasty Register.

Use of thromboprophylaxis regimens

Information on use of thromboprophylaxis was obtained from all 68 hospitals. However, the hospital questionnaires provided information about thromboprophylaxis during the period when 43,588 (64.5%) of the operations were done. 24 combinations of one or more of 6 thromboprophylactic drugs or use of stockings were reported for these 12 years (Table 1). No thromboprophylaxis was reported for only 371 of the 43,588 operations (0.9%). These operations, however, were on rheumatoid arthritis patients already on treatment with NSAIDs. More recently, most hospitals use a low molecular weight heparin (LMWH) alone or together with stockings. In 1999, 96.1% of the operations (67 of 68 hospitals) included a LMWH drug (Figure 1).

Mortality

The mortality for the first 20 postoperative days was 0.41% for the patients and 0.19% for the age- and gender-matched Norwegian population. In the first 60 postoperative days, the patient mortality was 0.75% and the population mortality was 0.56%. The mortality at 90 days for the patients was
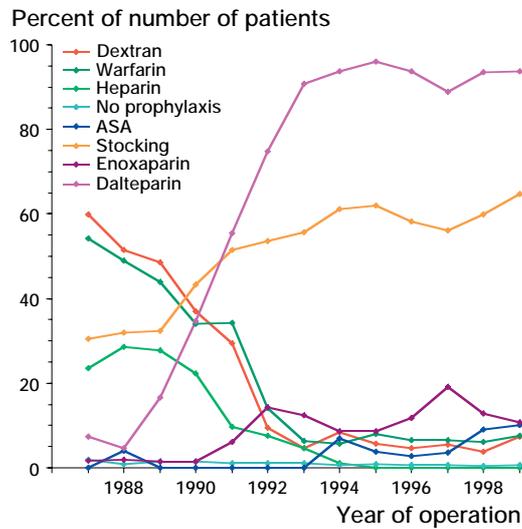
Percent of number of patients

Figure 1. The use of varous thromboprophylaxis drugs in Norway from 1987 to 1999.
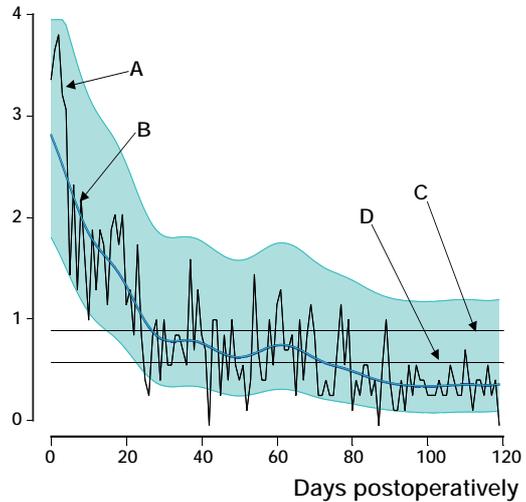
Deaths per day per 10.000

Figure 2. (A) Total daily mortality and (B) smoothed total early postoperative daily mortality (hazard) with 95% confidence limits in 67,548 total hip replacement operations. (C) Daily mortality in the age- and gender-matched population (0.95 deaths per 10,000) and (D) average patient daily mortality between days 200 and 300 (0.56 deaths per 10,000).

0.93% versus 0.83% for the population, but during the early postoperative period, the daily mortality was highest the first 20 days, and declined until the 70th postoperative day (Figure 2).

The daily mortality of THR patients decreased from about 2.5 deaths per 10,000 patients in the first postoperative week to about 0.57 deaths per 10,000 patients at 70 days postoperatively (Figure 2). The average daily mortality for the age- and gender-matched population was 0.95 deaths per 10,000.

Differences in mortality for gender, age, diagnosis, year of operation and surgical approach

After adjustment for diagnosis, year of operation, and age, males had a higher mortality at 60 days than females (OR = 2.03; 95% CI (1.69, 2.43)).

All 10-year age-categories had a statistical significant difference in the 60 day mortality, as compared with the large age-category 70–80 years after adjusting for diagnosis, year of operation, and gender (< 50 years: OR = 0.16 (0.81, 0.32), 50–60 years: OR = 0.18 (0.10, 0.32), 60–70 years: OR = 0.33 (0.24, 0.44), 80–90 years: OR = 2.30 (1.88, 2.81), and ≥ 90 years: OR = 6.03 (3.63, 10.02)). Mortality curves for age showed that the postoperative mortality at 60 days increased steeply with age, from less than 0.02% below 65 years to more
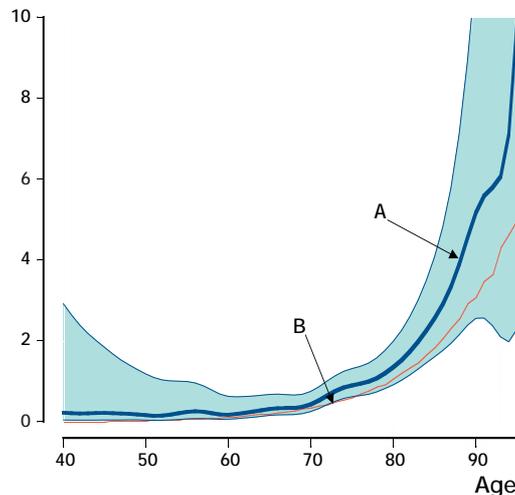
Percent mortality

Figure 3. Smoothed mortality (A) in relation to age during the first 60 postoperative days, in percent, with 95% confidence limits. (B) 60-day mortality in the age- and gender-matched population.

than 5% over 90 years. The postoperative mortality at 60 days for the age- and gender-matched population also increased, but was lower for all ages (Figure 3).
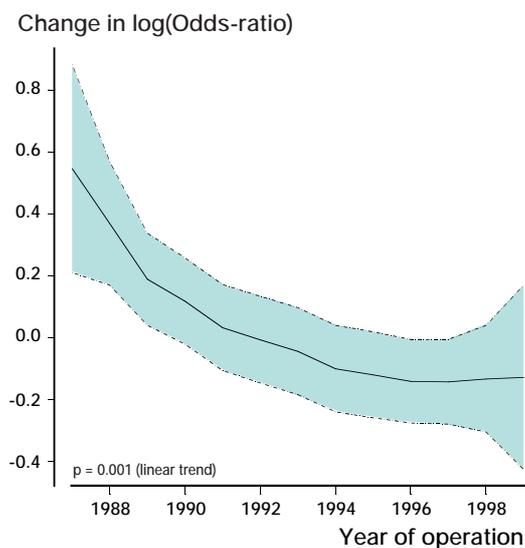
Change in log(Odds-ratio)

Figure 4. Smoothed change in log(Odds-ratio) from 1987 to 1999, adjusted for gender, age, and diagnosis in a general additive logistic model (GAM), with 95% confidence limits.
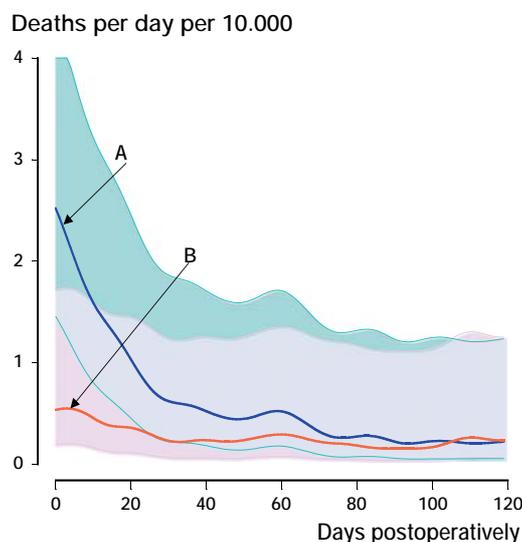
Deaths per day per 10.000

Figure 5. Smoothed total early postoperative daily mortality (hazard) for vascular diseases (A) and nonvascular diseases (B) with 95% confidence limits.

The diagnosis on the THR form showed a statistically significant association with mortality during the first 60 postoperative days ($p < 0.001$). With primary osteoarthrosis as the reference diagnosis and adjusting for gender, age, and year of operation, we found that all other diagnoses had a higher mortality at 60 days; rheumatoid arthritis (OR = 2.34 (1.40, 3.92)), fracture of the femoral neck (OR = 2.68 (2.14, 3.36)), pediatric hip diseases (OR = 1,67 (1.09, 2.57)), revision surgery (OR = 1.49 (1.16, 1.93)), and "other diagnosis" (OR = 4.01 (2.84, 5.66)).

There has been a slight reduction in mortality during these 12 years with a statistically significant trend (Figure 4) ($p = 0.001$).

We found no statistically significant difference in mortality during the first 60 postoperative days using the posterolateral, lateral, or antereolateral surgical approach ($p = 0.2$).

Differences in mortality according to the type and duration of thromboprophylaxis

In a logistic regression model, we restricted the analysis to include the 10 thromboprophylaxis regimens used in more than 1,000 operations (Table 1). With dalteparin/stockings as the reference category, and adjusting for gender, age, diagnosis, and year of operation, we found a statistically significant increase in the mortality of patients in the category dalteparin/dextran/stockings (OR = 2.61 (1.60, 4.26)) and enoxaparin/stockings (OR = 1.80 (1.05, 3.10)). In an analysis of a subset of 46,087 operations due to primary coxarthrosis, only patients in the category dalteparin/dextran/ stockings (OR = 2.43 (1.17, 5.03)) showed an increase in the mortality during 60 days, as compared to dalteparin/stockings.

We found no statistically significant difference in mortality among the various duration categories of any of the thromboprophylaxis drugs, or duration of use of stockings (all $p > 0.05$). To study the duration of dalteparin prophylaxis, we considered the three categories of duration for dalteparin alone, with or without use of stockings. We found no statistically significant difference among the categories of dalteparin duration ($p = 0.5$) or for the use of stockings ($p = 0.3$).

Causes of death

Information on causes of death was available only for the years 1987–1995. The total 60-day mortality for this period was 0.79%. The increase in mortality during the early postoperative period was mainly due to vascular diseases (Figure 5). The 60-day mortality due to vascular diseases was 0.60%, while the broad category "thrombo-embolic com-

Table 2. Number of deaths and death rates during the first 60 days after surgery, 1987–1995 (n = 45,767)

Cause of death	Number of deaths	Mortality [a]
All deaths before 31 December 1995	360	7.87
All vascular causes of death	274	5.99
Ischemic heart disease	145	3.17
Pulmonary embolism and infarction	42	0.92
Cerebrovascular disease	55	1.20
Deep vein thrombosis (DVT)	13	0.28
Thrombo-embolic complications	169	3.69
Bleeding	51	1.11
Sudden death (mors subita)	32	0.70
All nonvascular causes of death	67	1.46
Neoplasms	26	0.57
Septicemia	10	0.22
Pneumonia and influenza	42	0.92

[a] Causes of death are coded according to their presence on the death record. The sum of the cause-specific mortality rates therefore exceeds the all-cause mortality.

plications" accounted for 0.37% mortality (Table 2).

We found an increase in the 60-day mortality due to vascular diseases for patients in the category dalteparin/dextran/stockings (OR = 3.26 (1.49, 7.13)) and dalteparin/warfarin/stockings (OR = 2.17 (1.11, 4.22)) in the regression analysis using combinations of drugs with more than 1,000 operations and dalteparin/stockings as the reference category (Table 1). No statistically significant time trend, in the 60-day mortality, was found for any specific cause of death (all p > 0.05).

Discussion

In this large prospective study, we found that advanced age, male gender, and an underlying diagnosis other than primary osteoarthrosis were the most important risk factors for high early mortality after surgery.

The mortality after a THR was increased mainly during the first 20 postoperative days, with a slight increase until day 70 after the operation. This accords with Seagroatt et al. (1991) who found an increase in mortality during the first 3 postoperative months, using monthly intervals in their calculation. The patient mortality during the first 60 postoperative days was 0.75%. This is similar

to the observations by Seagroatt et al. (1991), Dunsmuir et al. (1996), and Fender et al. (1997), but slightly higher than Dearborn and Harris (1998).

Our 0.75% patient mortality during the first 60 days, as compared with the 0.56% mortality of the age- and gender-matched population, gives an excess surgical mortality of 0.19%. Overall, however, THR patients have a lower long-term mortality than the age- and gender-matched population (Lie et al. 2000). If we, therefore, use the average patient mortality between day 200 and day 300 as our "baseline", the excess risk related to the operation duirng the first 60 days after surgery would be 0.42%.

The various surgical approaches to the hip joint can cause differences in blood flow to the lower extremities, which in turn may lead to differences in the risk of developing venous thrombosis. However, we found no statistically significant difference in mortality in these surgical approaches.

Vascular causes of death were commonest, with the subcategory thromboembolic complications as the most frequent cause. The cause of death information from death records is known to be inaccurate (Karwinski 1993), but may be of interest for a crude classification of vascular and non-vascular deaths, although only 20% of the cases were autopsied.

We studied many total hip replacement (THR) operations with accurate information about the time of death, age, gender, and underlying diagnosis for surgery. Our data on thromboprophylaxis, however, were based on retrospective hospital reports of standard regimens, and should be interpreted with caution. Based on the hospital questionnaires, practically all patients received some sort of thromboprophylaxis. They showed that the patients had been given some sort of thromboprophylaxis. We were therefore unable to compare use versus non-use of thromboprophylaxis.

During the study, the prophylaxis regimen policy was changed. While low molecular weight heparin (LMWH) was used by 3 of 29 hospitals in 1988, it was used by 67 of 68 hospitals in the first half of 1999. We observed a slight reduction in the 60-day postoperative mortality from 1987 to 1999. Other factors related to surgery have also changed during this period. Improved methods of anesthesia are assumed to be associated with a reduction in

deep venous thrombosis (Salvati et al. 2000), and a shorter postoperative recovery time.

We compared mortality among various thromboprophylaxis regimens and found several statistically significant deviations from the reference group of dalteparin combined with stockings. Mortality in hospitals reporting use of the combination dalteparin/dextran/stockings and enoxaparin/stockings was higher than with the combination dalteparin/stockings. If the endpoint was mortality due to vascular deaths, the combination dalteparin/dextran/stockings and dalteparin/warfarin/stockings had a higher mortality than dalteparin/stockings. Since we collected the data on thromboprophylaxis retrospectively from each hospital, and not prospectively on the individual patient level as with the other variables in the study, these results on the type of thromboprophylaxis should be interpreted with caution. The differences between the above regimens may be correct—i.e., caused by pharmacological differences or pharmacological interactions. However, several hospital-related confounding factors may be involved since the combination dalteparin/dextran/stockings was mainly used by 2 hospitals (93% of the operations) and the combination dalteparin/warfarin/stockings was used in only one hospital. However, we did not check patient morbidity and potential statistical artifacts due to multiple testing. All these factors contribute to the uncertainty of the results.

We found no statistically significant difference in mortality among the various duration categories of any of the thromboprophylaxis regimens or time using the stockings. Since the data on duration of thromboprophylaxis were collected in the same way as the type of thromboprophylaxis, they must be interpreted with caution and could not be used to assess the duration of prophylaxis.

The effect and duration of thromboprophylaxis treatment must be established in randomized trials. This study, however, gives good baseline estimates on mortality for other studies. Since the incidence of venous thrombosis after a THR-operation is high (10–80%) (Mohr et al. 1993, Dahl et al. 1997, Bulstrode 1998), it is a suitable outcome variable for randomized trials evaluating thromboprophylaxis (Eriksson et al. 1991, Borris et al. 1994, Imperiale and Speroff 1994, Bergqvist et al. 1996, Planes et al. 1996, Comp et al. 1998,

Colwell et al. 1999, Freedman et al. 2000, Prentice 2000). In contrast, mortality after total hip replacement operations is low. Therefore, many patients are needed to obtain statistically significant effects (Fender et al. 1997, Collins et al. 1988, O'Brian et al. 2000). Few randomized clinical trials large enough to show statistically significant differences in total mortality between thromboprophylaxis regimens during the early postoperative period will probably be done. If our estimate of mortality due to thrombo-embolic complications is correct (0.37%), about 30,000 patients are needed to test a 50% reduction in mortality between two thromboprophylaxis policies.

In conclusion, gender, age, and diagnosis were the most important factors associated with an increase in early mortality in this prospective study. The daily mortality was highest during the first 20 days, and remained slightly increased until the 70th postoperative day. Recently almost all hospitals have changed to a regimen including low molecular weight heparin (LMWH). We found a slight reduction in the 60-day postoperative mortality during the period 1987–1999.

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