

## PREDICTORS OF REHOSPITALIZATION FOR SYMPTOMATIC VENOUS THROMBOEMBOLISM AFTER TOTAL HIP ARTHROPLASTY

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### ABSTRACT

**Background** Recent studies have shown that symptomatic venous thromboembolism after total hip arthroplasty most commonly develops after the patient is discharged from the hospital. Risk factors associated with these symptomatic thromboembolic events are not well defined.

**Methods** Using administrative data from the California Medicare records for 1993 through 1996, we identified 297 patients 65 years of age or older who were rehospitalized for thromboembolism within three months after total hip arthroplasty. We compared demographic, surgical, and medical variables potentially associated with the development of thromboembolism in these patients and 592 unmatched controls.

**Results** A total of 89.6 percent of patients with thromboembolism and 93.8 percent of control patients were treated with pneumatic compression, warfarin, enoxaparin, or unfractionated heparin, alone or in combination. In addition, 22.2 percent and 29.7 percent, respectively, received warfarin after discharge. A body-mass index (the weight in kilograms divided by the square of the height in meters) of 25 or greater was associated with rehospitalization for thromboembolism, with an odds ratio of 2.5 (95 percent confidence interval, 1.8 to 3.4). In a multivariate model, the only prophylactic regimens associated with a reduced risk of thromboembolism were pneumatic compression in patients with body-mass indexes of less than 25 (odds ratio, 0.3; 95 percent confidence interval, 0.2 to 0.6) and warfarin treatment after discharge (odds ratio, 0.6; 95 percent confidence interval, 0.4 to 1.0).

**Conclusions** In patients who underwent total hip arthroplasty, a body-mass index of 25 or greater was associated with subsequent hospitalization for thromboembolism. Pneumatic compression in patients with a body-mass index of less than 25 and prophylaxis with warfarin after discharge were independently protective against thromboembolism. (N Engl J Med 2000;343:1758-64.)

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**E**ARLY studies of venous thromboembolism after total hip arthroplasty documented a high frequency of symptomatic complications.<sup>1,2</sup> Subsequent studies documented the efficacy of low-dose standard heparin,<sup>3</sup> pneumatic compression,<sup>4,5</sup> warfarin,<sup>6,7</sup> and low-molecular-weight heparin<sup>6,8</sup> in reducing the incidence of asymptomatic venous thrombosis, a surrogate measure of clinical thromboembolism. The use of asymptomatic venous

thrombosis as the standard to define thromboembolism improves statistical power and dramatically decreases the number of subjects required in a clinical trial,<sup>9</sup> but it may not accurately reflect symptomatic outcomes.

The three-month incidence of symptomatic thromboembolism after elective hip arthroplasty is approximately 3 to 4 percent among patients given prophylaxis with warfarin or enoxaparin during their hospital stay.<sup>10</sup> Over 75 percent of these events are diagnosed after the patient is discharged from the hospital.<sup>10,11</sup> Although prophylactic treatment with enoxaparin for three weeks after discharge reduces the incidence of venographically documented thrombosis,<sup>12,13</sup> it is not clear whether extended prophylaxis reduces the incidence of symptomatic thromboembolism.<sup>14,15</sup>

We sought to identify risk factors associated with the development of symptomatic thromboembolism after hip arthroplasty and to determine whether extended prophylaxis reduces the incidence of symptomatic thromboembolism. Therefore, we designed a large case-control study of patients who underwent total hip arthroplasty and in whom symptomatic thromboembolism developed after they were discharged from the hospital.

### METHODS

#### Study Design

Assuming that approximately 32 percent of patients who undergo hip arthroplasty are treated with warfarin after discharge,<sup>11</sup> we estimated that 250 patients with thromboembolism and 500 controls would be needed to detect a clinically meaningful 40 percent reduction in the odds of warfarin use in patients with thromboembolism as compared with controls (with a beta level of 80 percent and an alpha level of 0.05). To ensure that our study had adequate power, we decided to review the cases of approximately 300 patients with thromboembolism and 600 unmatched controls.

#### Definition of Patients with Thromboembolism and Controls

We selected subjects using the Medicare inpatient claims of 25,388 fee-for-service patients 65 years of age or older who underwent unilateral total hip arthroplasty (code 81.51 in the *International Classification of Diseases, 9th Revision, Clinical Modification* [ICD-9-CM])<sup>16</sup> in a California acute care hospital between January 1, 1993, and December 31, 1996. We excluded patients with hip fracture and patients likely to require long-term therapy with warfarin because of atrial fibrillation, a prosthetic heart valve, or

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venous thromboembolism during the index hospitalization or a prior hospitalization (within six months before hip surgery). We also excluded all patients who were rehospitalized and underwent surgery within 91 days after arthroplasty, unless there was an intervening admission associated with thromboembolism (ICD-9-CM codes 451.11, 451.18, 451.2, 451.81, 451.9, 453.1, 453.2, 453.8, 453.9, and 415.1). A total of 21,718 patients were eligible for selection as subjects. We defined patients with thromboembolism as eligible patients who were readmitted within 91 days after surgery with a primary or secondary diagnosis of venous thromboembolism.

We requested the records of all 436 patients with venous thromboembolism who met our case definition. Of the remaining 21,282 records, we requested a random sample of 1308 for use as controls. After three months and one or two follow-up mailings, we received 429 of the case records (98.4 percent) and 1269 of the control records (97.0 percent). We randomly selected 305 case records and 611 control records for abstraction. We excluded 7 patients with thromboembolism and 12 control patients because of incomplete records. One patient with thromboembolism and 7 con-

trol patients who received rarely used or experimental prophylactic agents were also excluded, leaving 297 patients with thromboembolism and 592 control patients.

**Data Abstraction**

Trained physicians, who were unaware of the study hypotheses, used a computerized tool to abstract independently the hospital records regarding surgery and thromboembolism. This tool was pre-tested, and sources of potential variation in responses were identified, in an initial subsample of 28 records. The items or their definitions were modified as needed. The records of 44 patients with thromboembolism and 89 control patients were reabstracted; no error was detected in 99.1 percent of the data elements.

Tables 1 and 2 summarize the abstracted information. All nurses' notes and physicians' orders were reviewed to determine whether elastic stockings or pneumatic compression had been prescribed. The types and durations of surgery were determined from the anesthesia records. The first day after surgery that the patient was ambulatory was ascertained from the physical-therapy notes. The anticipated duration of medical prophylaxis was determined from the

**TABLE 1. RESULTS OF BIVARIATE ANALYSIS OF CLINICAL VARIABLES.\***

VARIABLE	PATIENTS WITH THROMBOEMBOLISM (N=297)	CONTROLS (N=592)	ODDS RATIO (95% CI)	P VALUE
Age — yr	74.8±6.0	74.3±5.8		0.21
Age group — no. (%)				
65–74 yr	154 (51.9)	320 (54.1)	1.0	
75–84 yr	119 (40.1)	243 (41.0)	1.0 (0.8–1.4)	0.91
≥85 yr	24 (8.1)	29 (4.9)	1.7 (0.9–3.2)	0.06
Sex — no. (%)				
Female	202 (68.0)	362 (61.1)	1.4 (1.0–1.8)	0.05
Male	95 (32.0)	230 (38.9)	1.0	
Race — no. (%)				
White	282 (95.0)	552 (93.2)	1.0	
Nonwhite	15 (5.1)	40 (6.8)	0.7 (0.4–1.4)	0.32
Body-mass index†				
Mean	27.8±4.7	26.0±4.8		<0.001
≥25 — no. (%)	215 (73.1)	303 (52.1)	2.5 (1.8–3.4)	<0.001
<25 — no. (%)	79 (26.9)	279 (48.0)	1.0	
Length of stay — days	5.5±2.4	5.2±2.5		0.06
Presence of cancer — no. (%)	4 (1.3)	6 (1.0)		0.79
Arthritis diagnosis — no. (%)				
Rheumatoid arthritis	4 (1.3)	16 (2.7)	0.5 (0.1–1.5)	0.20
Osteoarthritis	293 (98.7)	576 (97.3)	1.0	
History of thromboembolism — no. (%)				
Yes	22 (7.4)	19 (3.2)	2.4 (1.2–4.7)	0.005
No	275 (92.6)	573 (96.8)	1.0	
Estrogen therapy in women — no. (%)				
Yes	53 (26.2)	88 (24.3)	1.1 (0.7–1.7)	0.61
No	149 (73.8)	274 (75.7)	1.0	
Duration of surgery — min	126±47	123±42		0.40
Type of anesthesia — no. (%)				
General	218 (73.4)	434 (73.3)	1.0	
Regional	79 (26.6)	158 (26.7)	1.0 (0.7–1.4)	0.98
Estimated blood loss — ml	584±377	548±383		0.18
Day of first ambulation after surgery — no. (%)				
Day 0 or 1	162 (54.5)	368 (62.2)	0.7 (0.5–1.0)	0.02
Day 2 or later	135 (45.5)	221 (37.3)	1.0	
Discharge destination — no. (%)				
Home	101 (34.0)	231 (39.0)	1.0	
Rehabilitation or skilled-nursing facility	196 (66.0)	361 (61.0)	1.2 (0.9–1.7)	0.14

\*Plus-minus values are means ±SD. CI denotes confidence interval.

†Data on height or weight were unavailable for 3 patients with embolism and for 10 controls.

**TABLE 2.** RESULTS OF BIVARIATE ANALYSIS OF THROMBOPROPHYLACTIC VARIABLES AT THE TIME OF SURGERY.\*

VARIABLE	PATIENTS WITH THROMBO-EMBOLISM		ODDS RATIO (95% CI)	P VALUE
	(N=297)	CONTROLS (N=592)		
	no. (%)			
No pneumatic compression				
No medical prophylaxis	31 (10.4)	37 (6.2)	1.0	
Warfarin	48 (16.2)	80 (13.5)	0.7 (0.4–1.4)	0.27
Regular heparin†	7 (2.4)	6 (1.0)	1.4 (0.4–5.3)	0.58
Enoxaparin‡	27 (9.1)	53 (9.0)	0.6 (0.3–1.3)	0.14
Pneumatic compression				
No medical prophylaxis	47 (15.8)	99 (16.7)	0.6 (0.3–1.1)	0.06
Warfarin	55 (18.5)	172 (29.1)	0.4 (0.2–0.7)	<0.001
Standard heparin§	21 (7.1)	30 (5.1)	0.8 (0.4–1.9)	0.63
Enoxaparin¶	61 (20.5)	115 (19.4)	0.6 (0.3–1.2)	0.11
Elastic thromboembolic stockings				
Yes	208 (70.0)	417 (70.4)	1.0	
No	89 (30.0)	175 (29.6)	1.0 (0.7–1.4)	0.90
Postdischarge prophylaxis with warfarin				
No	231 (77.8)	416 (70.3)	1.0	
Yes	66 (22.2)	176 (29.7)	0.7 (0.5–1.0)	0.02

\*The values for “no medical prophylaxis” include patients treated with aspirin. CI denotes confidence interval.

†These values include two patients with thromboembolism and one control who received warfarin in addition to heparin during the index hospitalization.

‡These values include five controls who received warfarin in addition to enoxaparin during the index hospitalization.

§These values include 3 patients with thromboembolism and 12 controls who received warfarin in addition to heparin during the index hospitalization.

¶These values include two patients with thromboembolism and eight controls who received warfarin in addition to heparin during the index hospitalization.

||The duration of prophylaxis with warfarin was  $32.8 \pm 27$  days for patients with thromboembolism and  $20.7 \pm 21$  days for controls ( $P=0.19$ ). The mean international normalized ratio at discharge was  $1.68 \pm 0.52$  for patients with thromboembolism and  $1.80 \pm 0.61$  for controls ( $P=0.17$ ).

physicians' orders, progress notes, and pharmacy records. Objective documentation of thromboembolism required positive findings on pulmonary arteriography, ventilation–perfusion lung scanning, venography of the legs, venous ultrasonography, or impedance plethysmography.

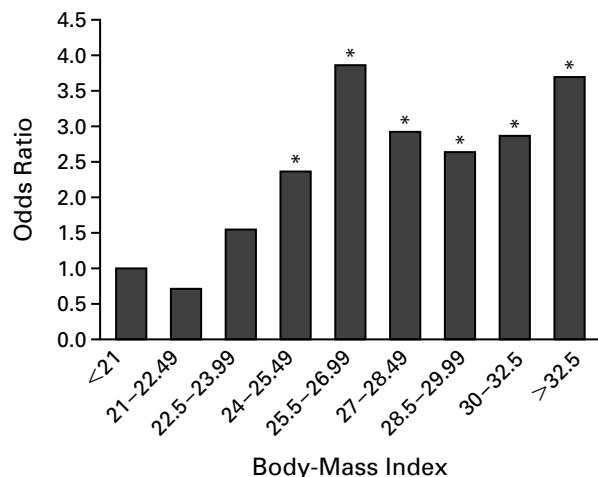
### Statistical Analysis

We categorized the body-mass index (the weight in kilograms divided by the square of the height in meters) as less than 25 or 25 or greater, the cutoff used to define overweight and obesity.<sup>17</sup> We categorized in-hospital prophylaxis as warfarin, unfractionated heparin, or low-molecular-weight heparin, either alone or in combination with pneumatic compression. Seven patients with thromboembolism and 26 controls who were treated with warfarin plus either unfractionated heparin or enoxaparin during the index hospitalization were categorized as having received in-hospital prophylaxis with heparin. All patients treated with warfarin after discharge were considered to have received postdischarge prophylaxis. We did not classify continued use of heparin or enoxaparin as postdischarge prophylaxis, because the average total duration of treatment with standard and low-molecular-weight heparin was less than seven days. Moreover, extended use of low-molecular-weight heparin was uncommon in 1995 and 1996. Because there is no evidence that aspirin provides effective prophylaxis against thromboembolism,<sup>18,19</sup> and because bivariate analysis showed no association between aspirin use and the risk of thromboembolism, patients who

received aspirin were considered to have received no prophylaxis. Patients who used elastic stockings alone were also considered to have received no prophylaxis.

For continuous variables, bivariate comparisons were made with the use of Student's *t*-test. For categorical variables, the unadjusted odds ratio and Cornfield's 95 percent confidence interval were determined.

Multivariate models were developed with the use of logistic regression. Age was categorized as 65 to 74, 75 to 84, or 85 or more years. Body-mass index was categorized as less than 25 or 25 or greater, because the odds of thromboembolism among patients with body-mass-index values of 25 or greater were relatively uniform (Fig. 1). Other potential risk factors included race (categorized as white or nonwhite); sex; type of anesthesia (general or regional); presence or absence of prior venous thromboembolism, estrogen-replacement therapy, cancer, or rheumatoid arthritis; number of days after surgery until the patient was ambulatory; and discharge destination (home or other). In-hospital prophylaxis and postdischarge prophylaxis (with warfarin) were included in the model as main effects. Potential risk factors forced into the model on the basis of prior studies included age, sex, race, type of in-hospital prophylaxis, and presence or absence of rheumatoid arthritis.<sup>20</sup> Other terms were entered in a stepwise fashion (with cutoffs of  $P \geq 0.1$  to be included and  $P > 0.05$  to be excluded). Two-way interactions involving treatment methods and key risk factors were tested. Statistical analyses were performed using the SAS-PC program (SAS



**Figure 1.** Odds Ratios for Readmission for Thromboembolism in Patients with Various Body-Mass Indexes. Asterisks indicate  $P < 0.05$  for the comparison with the group with a body-mass index of less than 21.

Institute, Cary, N.C.). The study was approved by the human subjects committee of the University of California, Davis.

**RESULTS**

**Hospitalization for Thromboembolism**

Among the 297 patients who were hospitalized with a diagnosis of postoperative venous thromboembolism, 203 (68.4 percent) had venous thrombosis alone and 94 (31.6 percent) had pulmonary embolism.

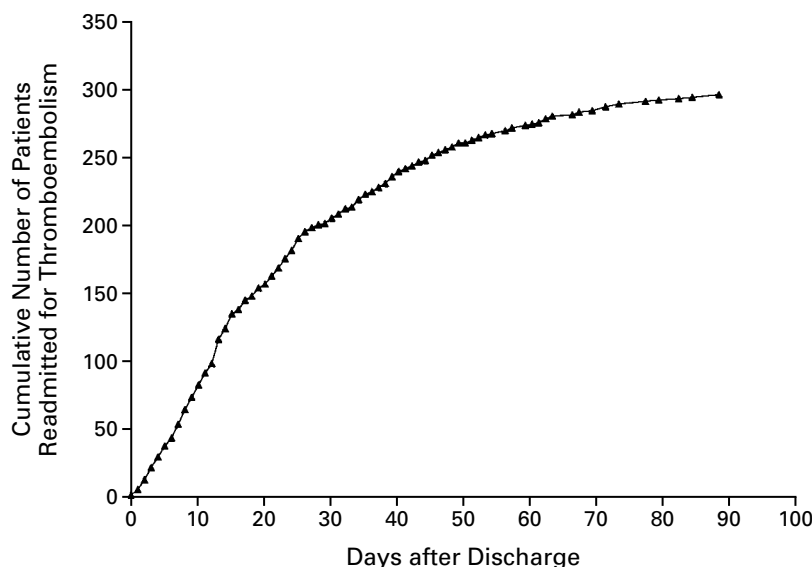
Symptoms were recorded for 284 (95.6 percent) of the patients, a report or note indicated that thromboembolism was objectively confirmed in 285 (96.0 percent), and anticoagulant treatment was administered to 293 (98.7 percent). Of the four untreated patients, one died of acute pulmonary embolism (discovered at autopsy), and the remaining three had active bleeding.

At the time of admission for venous thromboembolism, 49 patients were receiving warfarin and 19 were receiving standard heparin or enoxaparin. An international normalized ratio was recorded at the time of admission in 45 of the 49 patients treated with warfarin. The median international normalized ratio was 1.4, and 29 of the 45 patients (64 percent) had a ratio of less than 2.0. Figure 2 shows the cumulative incidence of readmissions for thromboembolism.

**Hospitalization for Surgery**

Table 1 shows the results of bivariate analysis of clinical risk factors. A body-mass index of 25 or greater was associated with an odds ratio of 2.5 for thromboembolism (95 percent confidence interval, 1.8 to 3.4). In a multivariate analysis the odds ratio was 1.8 (95 percent confidence interval, 1.1 to 2.9;  $P = 0.03$ ). The relation between body-mass index and the odds of thromboembolism is shown in Figure 1, with a body-mass index of less than 21 as the reference category.

The mean ( $\pm$ SD) dose of standard heparin was  $10,422 \pm 4490$  IU per day in patients with thromboembolism and  $11,000 \pm 2260$  IU per day in controls ( $P = 0.6$ ). The mean dose of enoxaparin was  $59 \pm 4.5$  mg per day in patients with thromboembolism and



**Figure 2.** Time of Readmission for Thromboembolism in the 297 Patients with Thromboembolism.

60±2.4 mg per day in controls (P=0.3). The expected total durations of heparin therapy were also similar: 6.6±3.2 days in patients with thromboembolism and 6.8±5.4 days in controls (P=0.9).

Bivariate analysis revealed that the use of pneumatic compression significantly reduced the risk of thromboembolism (odds ratio, 0.7; 95 percent confidence interval, 0.5 to 0.9). Table 2 shows the results of bivariate analysis of in-hospital thromboprophylaxis stratified according to the use or nonuse of pneumatic compression.

The results of risk-adjusted multivariate modeling are shown in Table 3. Independent predictors of thromboembolism included an age of at least 85 years (as compared with an age of 65 to 74 years), female sex, a history of thromboembolism, and a body-mass index of 25 or greater. Factors associated with protection against thromboembolism were initial ambulation before day 2 after surgery, use of pneumatic compression (among patients with a body-mass index of <25), and use of warfarin after discharge. A significant interaction was found between pneumatic compression and body-mass index (P<0.03). Among patients treated with pneumatic compression, there was a significant reduction in the odds of thromboembolism only among those with a body-mass index

of less than 25 (odds ratio, 0.3; 95 percent confidence interval, 0.2 to 0.6). Medical prophylaxis with standard heparin, enoxaparin, or warfarin during the index hospitalization was not associated with a reduced risk of rehospitalization due to thromboembolism. This was true regardless of the use of pneumatic compression or body-mass index. Interactions between body-mass index and types of medical prophylaxis were not significant.

## DISCUSSION

The use of longitudinal California Medicare data allowed us to identify risk factors associated with symptomatic thromboembolism in a large, representative sample of patients who underwent hip arthroplasty. We found that the use of pneumatic compression was associated with a significant reduction in the risk of symptomatic thromboembolism; however, this effect was found only in patients with a body-mass index of less than 25. Also noteworthy were the findings that female sex and a higher body-mass index were each associated with a significantly higher risk of symptomatic thromboembolism. Protective factors included ambulation before day 2 after surgery and use of warfarin after discharge from the hospital.

Given that immobilization is a well-known risk factor associated with venous thrombosis,<sup>9,21</sup> the finding that early ambulation was associated with a lower risk of thromboembolism is not surprising. Other studies have noted a trend over time toward earlier mobilization of patients,<sup>22</sup> and delayed weight bearing is known to be associated with an increased risk of venous thrombosis.<sup>23</sup>

Most clinical studies that have assessed the efficacy of pneumatic compression either have not analyzed the effect of weight or body-mass index<sup>5,24-28</sup> or have restricted the analysis to patients with a body-mass index of 30 or greater.<sup>29</sup> Further studies are needed to confirm the finding that pneumatic compression is significantly more effective in patients with a lower body-mass index.

A higher body-mass index was an independent predictor of symptomatic thromboembolism. Obesity is generally acknowledged as a risk factor for venous thrombosis, and two recent studies of patients undergoing hip arthroplasty reported associations between a body-mass index of greater than 30 and the development of symptomatic<sup>10</sup> or venographically detected thromboembolism.<sup>30</sup> It is tempting to speculate that obesity is associated with inflammation, which may be the primary stimulus for the development of thromboembolism.<sup>31-34</sup>

Obesity is also associated with reduced fibrinolysis,<sup>35</sup> and the effectiveness of pneumatic compression appears to be due to an enhancement of systemic fibrinolysis.<sup>36</sup> Taken together, these observations provide a plausible explanation for our findings. In overweight or obese patients, the stimulation of fibrinolysis asso-

**TABLE 3. RESULTS OF MULTIVARIATE ANALYSIS OF VARIABLES ASSOCIATED WITH THROMBOEMBOLISM.\***

VARIABLE	ODDS RATIO (95% CI)	P VALUE
Age		
<75 yr	1.0	
75-84 yr	1.1 (0.8-1.5)	0.71
≥85 yr	2.1 (1.1-3.9)	0.02
Female sex	1.4 (1.0-1.9)	0.04
Nonwhite race	0.9 (0.4-2.2)	0.84
Ambulation before day 2 after surgery	0.7 (0.5-0.9)	0.007
History of thromboembolism	3.4 (1.7-7.0)	0.001
Rheumatoid arthritis	0.6 (0.2-1.8)	0.38
Body-mass index ≥25	1.8 (1.1-2.9)	0.03
Thromboprophylaxis		
Standard heparin	1.5 (0.8-2.7)	0.23
Enoxaparin	0.9 (0.6-1.4)	0.70
Warfarin (in-hospital only)	0.9 (0.6-1.4)	0.57
Pneumatic compression†		
Body-mass index <25‡	0.3 (0.2-0.6)	<0.001
Body-mass index ≥25§	0.7 (0.5-1.1)	0.16
Warfarin (postdischarge)	0.6 (0.4-1.0)	0.04

\*Records of 8 patients with thromboembolism and 36 controls were missing one or more values (model  $\chi^2=90.9$ , C statistic = 0.69).

†P<0.03 for the interaction between body-mass index and pneumatic compression.

‡The reference group had a body-mass index of less than 25 and no pneumatic compression.

§The reference group had a body-mass index of 25 or greater and no pneumatic compression.

ciated with pneumatic compression may not be sufficient to overcome the enhancement of blood coagulation associated with surgery and immobilization.

The failure of in-hospital prophylaxis with standard heparin, enoxaparin, or warfarin to be associated with a significant reduction in the risk of thromboembolism was not expected. This finding may in part reflect a type II error, given the relatively small number of patients who received each type of medical prophylaxis. In addition, a short course of medical prophylaxis may simply be insufficient to prevent late symptomatic thromboembolism. It should be stressed that we analyzed only symptomatic thromboembolism that was diagnosed after discharge from the hospital. Medical prophylaxis may reduce the incidence of symptomatic thromboembolism that develops during the initial hospitalization, which accounts for approximately 20 to 25 percent of all cases of symptomatic thromboembolism.<sup>10,11</sup> The apparent benefit of post-discharge prophylaxis with warfarin could have been underestimated if a greater proportion of the patients with thromboembolism than of the controls received inadequate anticoagulant therapy.<sup>37</sup> Unfortunately, comparative data specifying the adequacy of warfarin therapy could not be obtained.

Potential sources of bias in this case-control study include diagnostic bias and selection bias. Because it may be difficult to determine whether compression of a vein is complete in the leg of an extremely obese person,<sup>38</sup> the incidence of false positive ultrasonographic findings may be increased in very large patients. If only high-risk patients were treated with warfarin after discharge from the hospital, the observed effect of postdischarge prophylaxis with warfarin might have been reduced. Because of these potential biases, our findings should be corroborated in randomized trials or by careful meta-analysis of existing data.

Our findings are likely to apply to the majority of patients undergoing elective hip-replacement surgery, since most hip-arthroplasty surgery is performed in patients over the age of 65.<sup>39</sup> The prevalence of prophylaxis against thromboembolism in the control group, 93.8 percent, was similar to the prevalence of 93 percent reported by orthopedic surgeons in Massachusetts.<sup>40</sup> The 2.1 percent incidence of symptomatic thromboembolism that we observed over a period of three months is in accord with the rates reported in other large studies.<sup>10,41</sup> Finally, the time course of postdischarge events (Fig. 2) is similar to that previously reported.<sup>11</sup> To further reduce the incidence of symptomatic thromboembolism, efforts need to focus on improving the effectiveness of in-hospital as well as postdischarge thromboprophylaxis in overweight patients.

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