Symptomatic Venous Thromboembolism Uncommon without Thromboprophylaxis After Isolated Lower-Limb Fracture

The Knee-to-Ankle Fracture (KAF) Cohort Study

Rita Selby, MD, MSc, William H. Geerts, MD, Hans J. Kreder, MD, MSc, Mark A. Crowther, MD, MSc, Lisa Kaus, CRC, and Faith Sealey, RN, on behalf of the Knee-to-Ankle Fracture Cohort Study Investigators

Investigation performed at Sunnybrook Health Sciences Centre, Toronto; St. Joseph's Hospital, Hamilton; St. Michael's Hospital, Toronto; North York General Hospital, Toronto; and Toronto East General Hospital, Toronto, Ontario, Canada

Background: The prevalence of deep vein thrombosis as demonstrated by routine venography in patients with distal lower-extremity injury requiring cast immobilization or surgery is 10% to 40%. These deep vein thromboses are usually asymptomatic and distal, and the need for thromboprophylaxis in these patients is not known.

Methods: We conducted a multicenter prospective cohort study to define the prevalence of symptomatic venous thromboembolism in patients with a tibial, fibular, or ankle fracture (treated nonoperatively) or a patellar or foot fracture (treated operatively or conservatively). Consecutive patients were enrolled at five Ontario, Canada, hospitals within ninety-six hours after injury, and they were followed with a telephone interview at two, six, and twelve weeks. Thromboprophylaxis was not allowed. Suspected venous thromboembolism was investigated in a standardized manner.

Results: From August 2002 to June 2005, 1200 patients were enrolled, and a three-month follow-up was completed for 98% of them. Eighty-two percent of the patients were treated with cast or splint immobilization for an average (and standard deviation) of 42 ± 32 days. Overall, seven patients (0.6%; 95% confidence interval [CI] = 0.2% to 1.2%) had symptomatic, objectively confirmed venous thromboembolism. Two of them had proximal deep vein thrombosis; three, calf deep vein thrombosis; and two, pulmonary embolism. There were no fatal pulmonary emboli.

Conclusions: Symptomatic venous thromboembolism is an infrequent complication after fractures of the distal part of the lower limb requiring cast immobilization and managed without thromboprophylaxis. Given these estimates of symptomatic venous thromboembolism, the risk-benefit ratio and cost-effectiveness of routine anticoagulant prophylaxis are unlikely to be favorable for these patients.

Level of Evidence: Prognostic Level IV. See Instructions for Authors for a complete description of levels of evidence.

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Isolated lower-extremity fractures distal to the knee are common injuries[1,2] and constitute risk factors for venous thromboembolism[3-10]. Although studies based on sensitive screening tests such as contrast venography have suggested a 10% to 40% prevalence of deep vein thrombosis following such fractures, most of these thrombi are distal, localized, and asymptomatic and their clinical relevance is unknown[3-10]. In some centers, patients who have sustained a fracture receive several weeks of anticoagulant thromboprophylaxis on the basis of these data[11,12]. However, the risk-benefit ratio and the costs of

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this thromboprophylaxis cannot be determined unless there are reliable estimates of the prevalence of clinically important venous thromboembolism after such fractures. We conducted a multicenter, prospective cohort study to document the prevalence and predictors of symptomatic deep vein thrombosis or pulmonary embolism within three months after a lower-extremity fracture distal to the knee.

Materials and Methods

Patients

Consecutive patients at least sixteen years of age with a radiographically confirmed unilateral or bilateral closed or open fracture of the tibia, fibula, or ankle (managed nonoperatively) or of the patella or foot (managed either surgically or nonoperatively) were identified through the hospital emergency rooms, inpatient orthopaedic surgery wards, and fracture clinics at five hospitals (three academic and two community centers; see Appendix) in Ontario, Canada, from August 2002 to June 2005, and were assessed for eligibility. Patients with a tibial, fibular, or ankle fracture that required surgical treatment were excluded as they were being screened for eligibility for a double-blind, randomized trial comparing low-molecular-weight heparin prophylaxis with a placebo[13] that was being conducted in parallel with this study. Patients who had concomitant soft-tissue, ligament, or cartilage injury were not excluded. Patients with prespecified major trauma (see Appendix) or with vascular injury requiring surgical repair were excluded from the study. Additional criteria for exclusion were an inability to enroll the patient within ninety-six hours after injury; an inability or refusal to provide consent or undergo telephone follow-up; an ongoing need for long-term anticoagulation for other indications; use of thromboprophylaxis (either anticoagulant or mechanical) for more than seventy-two hours after injury (to allow for recruitment of patients who presented over the weekend and may have received thromboprophylaxis for a brief period); an inability to receive contrast medium because of pregnancy, allergy to contrast medium, or renal failure (serum creatinine level of >300 μmol/L); active cancer or known hypercoagulability; previous deep vein thrombosis or pulmonary embolism (objectively proven or treated with anticoagulants); or previous participation in this study.

The study protocol was approved by the research ethics boards at each participating hospital, and all patients were required to provide written informed consent before participation. The study was coordinated by investigators from the Department of Medicine and Clinical Pathology at Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada (R.S., W.H.G., L.K., and F.S.). Logs of all patients screened at the participating hospitals were submitted to the coordinating center weekly.

Study Design

Eligible consenting patients were enrolled and followed prospectively for three months with telephone calls at fourteen days, six weeks, and three months after injury to determine the prevalence of symptomatic venous thromboembolism. Thromboprophylaxis, either anticoagulant or mechanical (compression stockings or pneumatic compression devices), was not allowed for the duration of the study. Aspirin and other antiplatelet agents were allowed only if they had been used before the injury for cardiac or stroke prophylaxis. Nonsteroidal anti-inflammatory agents were allowed.

Patient Assessment and Follow-up

At study entry, patients were educated and provided with information pamphlets regarding symptoms of deep vein thrombosis and pulmonary embolism. They were advised to report any concerns to the local study nurse at any time during the study period, and they were questioned about specific symptoms at each telephone follow-up contact. Suspected deep vein thrombosis and pulmonary embolism were investigated in a standardized manner with use of objective diagnostic tests (Doppler ultrasonography, lung scanning, or computed tomography [CT] pulmonary angiography) and prespecified diagnostic algorithms (see Appendix). All patients who developed objectively confirmed deep vein thrombosis or pulmonary embolism were treated with full-dose anticoagulation therapy (generally low-molecular-weight heparin followed by warfarin) for approximately three months.

TABLE I Baseline Characteristics of the Enrolled Patients (N = 1200)

Characteristic	
Mean age (range) *(yr)*	45 (16-93)
Female sex *(%)*	60
Fracture type *(%)*	
Fibular	39
Metatarsal	31
Phalangeal	12
Calcaneal, talar, and tarsal	10
Tibial	10
Patellar	5
Unilateral fracture *(%)*	99
Mechanism of injury *(%)*	
Fall	75
Sports injury	17
Motor-vehicle collision	5
Occupational	3
Nonoperative management *(%)*	93
Immobilization in cast or splint *(%)*	82
Mean duration of immobilization (and stand. dev.) *(days)*	42 ± 32

Outcome Measures

The primary outcome in the Knee-to-Ankle Fracture (KAF) Cohort Study was the occurrence of symptomatic venous thromboembolism or fatal pulmonary embolism within the three-month study period. Symptomatic deep vein thrombosis was defined as clinically suspected deep vein thrombosis confirmed by positive proximal Doppler ultrasound or contrast venography (if the Doppler ultrasound was nondiagnostic). Symptomatic pulmonary embolism was defined as clinically suspected pulmonary embolism confirmed by a high-probability ventilation/perfusion (V/Q) lung scan or positive CT pulmonary angiography, pulmonary angiography, or leg imaging. Fatal pulmonary embolism was defined as autopsy-proven pulmonary embolism; possible fatal pulmonary embolism was defined as an otherwise unexplained sudden death of a patient without an autopsy. An independent outcomes adjudication committee, which had access to pertinent clinical data and results of diagnostic tests, evaluated all cases with suspected venous thromboembolism using these prespecified adjudication criteria.

Statistical Analysis

The baseline characteristics of the enrolled patients (age, sex, mechanism of injury, site of fracture, and fracture management) were analyzed with use of descriptive statistics. Since the prevalence of symptomatic venous thromboembolism after such fractures was not known, no formal sample-size calculations could be done. A convenience sample size of at least 1000 patients was agreed on by the steering committee.

Two of the investigators (R.S. and W.H.G.) developed the initial protocol, which was revised and subsequently approved by all six members of the steering committee. The steering committee supervised the trial, made the decision to stop the trial, reviewed the results, and prepared the manuscript. The outcomes adjudication committee was independent of the steering committee.

Source of Funding

This study was supported by a grant from the Canadian Institutes of Health Research-industry partnership with Pfizer Canada. Neither the Canadian Institutes of Health Research nor Pfizer Canada was involved in any aspect of protocol development, the conduct of the trial, or the decision to publish.

Results

Study Population

Over the thirty-three-month study period, 2446 consecutive patients were screened for eligibility at the five study sites by dedicated research coordinators (Fig. 1). As a result of this screening, 1246 were excluded because of an inability to contact the patient within ninety-six hours after injury (743), an inability or refusal to provide consent (236), an inability to undergo telephone follow-up (153), an ongoing need for anticoagulation for other reasons (thirty-five), use of thromboprophylaxis for more than seventy-two hours after injury (nineteen), a major injury involving other site(s) (sixteen), an inability to receive contrast medium (sixteen), active cancer (thirteen), previous deep vein thrombosis or pulmonary embolism (twelve), previous participation in this study (two), and a known molecular hypercoagulable state (one). Twelve hundred patients were enrolled, and 1179 (98.3%) of them were followed for the three months. Twenty-one patients either withdrew consent or could not be contacted for follow-up despite multiple attempts.

The baseline characteristics of the study patients are summarized in Table I. The mean age was forty-five years (range, sixteen to ninety-three years) and 60% of the cohort was female. Falls were responsible for 75% of the injuries, followed by sports injuries (17%), vehicular accidents (5%), and occupational injuries (3%). The most common fractures involved the fibula (39%), followed by metatarsals (31%), phalanges (12%), calcaneus, talus, or tarsus (10%), tibia (10%), and patella (5%). Seven percent of the patients were treated surgically, and 93% had conservative management. The majority of the patients (82%) were treated with cast or splint immobilization, and the mean duration of immobilization (and standard deviation) was 42 ± 32 days. Six patients (0.5%) received brief prophylactic anticoagulation outside of the study protocol, as they required subsequent major surgery for another reason within the study period. No patient received concomitant mechanical prophylaxis.

Venous Thromboembolism

In the group of the 1200 enrolled patients, there were thirty-nine suspected venous thromboembolism events (in thirty-seven patients); thirty-four were suspected deep vein thrombosis (in thirty-two patients) and five of these were suspected pulmonary embolism. There were seven confirmed venous thromboembolism events (0.6%; 95% confidence interval [CI] = 0.2% to 1.2%), including two proximal deep vein thromboses, three calf

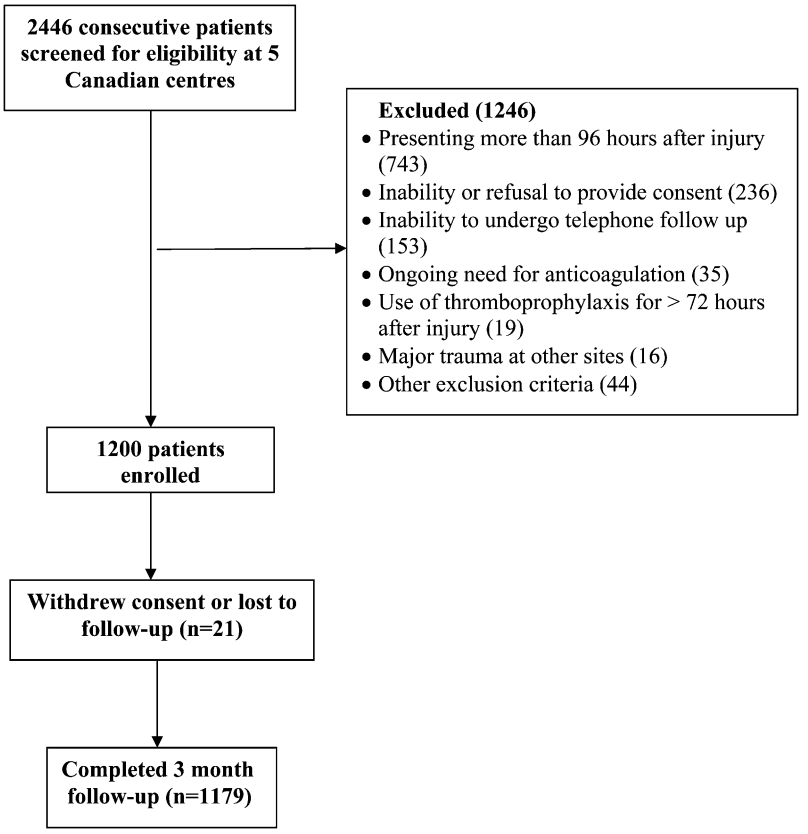

Fig. 1

Flow diagram of study population.

deep vein thromboses, and two pulmonary embolisms, as detailed in the Appendix. There was no fatal pulmonary embolism (95% CI = 0% to 0.4%). Although whole-leg ultrasounds were not allowed by the protocol for investigation for deep vein thrombosis (see Appendix), the three calf deep vein thromboses were documented in patients who underwent whole-leg ultrasound in violation of the protocol. If these three events are excluded, the prevalence decreases to 0.3% (four events). The overall event rates were too low to allow multivariate analyses for predictors of venous thromboembolism.

Discussion

To our knowledge, our investigation is the first large, rigorously conducted study that demonstrates the prevalence of symptomatic venous thromboembolism or fatal pulmonary embolism in patients with a conservatively treated tibial, fibular, or ankle fracture or a surgically or conservatively treated fracture involving the foot or patella. Patients with a surgically treated tibial, fibular, or ankle fracture were not eligible for this study as they were being screened for eligibility for another study being conducted in parallel (a double-blind, randomized trial comparing low-molecular-weight heparin prophylaxis with a placebo). Consecutive patients were screened at five hospitals (both academic and community), and 49% of the eligible patients were enrolled; complete three-month follow-up was obtained for 98% of the cohort. Only 0.5% of the patients received any anticoagulant prophylaxis at any time during the study. Suspected thromboembolic events were investigated with use of standardized algorithms for deep vein thrombosis and pulmonary embolism at all five centers. More than 80% of this cohort was treated with cast or splint immobilization, for an average of six weeks. In this cohort of 1200 patients, the prevalence of symptomatic venous thromboembolism at three months was low (<1%) and fatal pulmonary embolism did not occur.

Data on the prevalence of venous thromboembolism in patients with a distal lower-extremity fracture treated conservatively with splint or cast immobilization are very limited. Three randomized trials comparing no prophylaxis with low-molecular-weight heparin in patients with below-the-knee fracture and plaster cast immobilization, who were screened with either unilateral whole-leg Doppler ultrasound or venography, demonstrated deep vein thrombosis rates between 6% and 30%[6,14,15]. The majority of the detected thrombi were deep vein thrombi in the calf, the clinical relevance of which is uncertain. In the largest and most recent of these studies, ten of seventy-seven patients in the control group developed deep vein thrombosis, only one of which was proximal[6]. In the study by Kock et al.[15], only one proximal deep vein thrombosis and one calf deep vein thrombosis were detected in the thirty-four patients in the control arm[15]. The study by Kujath et al.[14] did not provide rates of proximal deep vein thrombosis in the enrolled patients. In a systematic review of thirteen studies that reported complications after a total of 895 tibial shaft fractures, symptomatic venous thromboembolism developed in six patients (0.7%)[16]. An observational study of 3698 patients who presented to French emergency departments with an isolated leg injury that was not surgically treated demonstrated proximal deep vein thrombosis in 0.2%, symptomatic venous thromboembolism in 1.0%, and pulmonary embolism in only a single patient (0.04%) over the three months of follow-up[12]. However, 61% of the patients in that study received thromboprophylaxis and 75% were screened with Doppler ultrasound. Two prospective studies that included a total of 300 patients with foot and ankle fractures demonstrated that calf deep vein thromboses and asymptomatic deep vein thromboses detected by routine screening tests do not progress without treatment, suggesting that these thrombi are probably not clinically important[9,10]. Additional evidence that these deep vein thrombi are not important is provided by the observation that, in seven randomized trials of patients with a distal lower-limb fracture as well as in the cohort of patients in the present study, no fatal pulmonary emboli were reported[6-8,13-15,17].

Our results provide reassurance that symptomatic and fatal venous thromboemboli are infrequent complications after these fractures without thromboprophylaxis, and they highlight the major discrepancy between studies using clinical end points and those using routine screening with either venography or whole-leg ultrasound. Despite the lack of reliable prevalence data and resulting risk-benefit estimates, routine prophylaxis with anticoagulants for four to six weeks (or for as long as a plaster cast is worn) has become the standard of practice after such fractures in some parts of the world[11]. With a venous thromboembolism prevalence of <1%, as was seen in our study, even a 1% risk of bleeding with routine anticoagulant prophylaxis[4] would render an unfavorable risk-benefit ratio and would not be cost-effective. The risk of compartment syndrome, although uncommon, also needs to be considered if patients with a lower-extremity fracture receive anticoagulant thromboprophylaxis[18]. The logistics of safely conducting an outpatient anticoagulant prophylaxis program involving daily self-injections for four to six weeks or for the entire duration of immobilization further compromise the feasibility of this strategy. We believe that mechanical prophylaxis is neither likely to be effective nor feasible in this subgroup of trauma patients.

Despite the large sample size, because of the low prevalence of symptomatic venous thromboembolism we could not identify any predictors of deep vein thrombosis or pulmonary embolism that allowed us to define a subgroup of patients at higher risk for venous thromboembolism. With such a low frequency of symptomatic venous thromboembolism in this patient population, large population-based epidemiological studies would be required to identify any putative high-risk subgroups. In the meantime, we believe that clinicians should focus on optimizing thromboprophylaxis in groups of patients with higher risks of venous thromboembolism and in whom thromboprophylaxis use is still not optimal. Although there is no specific evidence, we recommend that patients with the types of injuries in the present study should be made aware of deep vein thrombosis and pulmonary embolism as potential complications so that they may contact their health-care provider should this suspicion arise to allow timely investigation and treatment if venous thromboembolism is found.

Appendix

eA A list of the investigators and institutions participating in the KAF Cohort Study, descriptions of algorithms for investigation and treatment of clinically suspected deep vein thrombosis and pulmonary embolism, figures showing these algorithms, and tables providing the definition of major trauma and details of the confirmed venous thromboembolic events are available with the online version of this article as a data supplement at jbjs.org. ■

Rita Selby, MD, MSc
William H. Geerts, MD
Hans J. Kreder, MD, MSc
Lisa Kaus, CRC
Faith Sealey, RN
Departments of Medicine (R.S., W.H.G., L.K., and F.S.), Clinical Pathology (R.S.), and Surgery (H.J.K.), Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview Avenue, Toronto, ON M4N 3M5, Canada.
E-mail address for R. Selby: rita.selby@sunnybrook.ca

Mark A. Crowther, MD, MSc
Department of Medicine, St. Joseph's Healthcare, 50 Charlton Avenue East, McMaster University, Hamilton, ON L8N 4A6, Canada

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