Original Investigation

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Effectiveness and Economic Impact Associated With a Program for Outpatient Management of Acute Deep Vein Thrombosis in a Group Model Health Maintenance Organization

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Abstract

Background Controlled clinical trials have demonstrated that outpatient administration of low-molecular-weight heparin to patients with acute deep vein thrombosis (DVT) provides safety and efficacy equivalent to that of traditional inpatient therapy with unfractionated heparin. Whether favorable results reported in controlled clinical trials are achievable in clinical practice is an important consideration.

Methods Appropriate patients with objectively diagnosed DVT were treated as outpatients with low-molecular-weight heparin and warfarin sodium according to an approved guideline. The primary end point for analysis consisted of objectively diagnosed symptomatic recurrent thromboembolism or major bleeding within a 90-day evaluation period. The incremental cost incurred by the organization while using the outpatient DVT treatment guideline was determined. Incremental cost savings of the outpatient DVT treatment program were determined based on the cost that would have accrued had the patient been admitted to the hospital for treatment with unfractionated heparin.

Results We enrolled 391 patients (91.4%) in the outpatient DVT treatment program. Of these, 373 (95.4%) completed 90 days of therapy without reaching the primary end point. The percentage of patients reaching the primary outcome measure (4.6%) fell within the range of patients enrolled in controlled clinical trials (3.5%-9.4%). During the 2-year program evaluation, total cost savings of $1,108,587 were realized.

Conclusions Outpatient treatment of acute DVT can be managed safely and effectively in clinical practice. The potential savings associated with outpatient DVT treatment are substantial.

TRADITIONALLY, patients with a diagnosis of acute deep vein thrombosis (DVT) have been hospitalized and treated with intravenous (IV) unfractionated heparin (UH). Long-term oral anticoagulation therapy is initiated by overlapping warfarin sodium with UH until a therapeutic international normalized ratio (INR) is achieved (minimum, 4-5 days).[1] However, evidence suggests that the initial inpatient treatment of acute DVT with low-molecular-weight heparin (LMWH) is safer and more effective than conventional UH therapy.[2-4] In addition, controlled clinical trials have demonstrated that outpatient administration of LMWH to patients with acute DVT provides safety and efficacy equivalent to that of traditional inpatient therapy with UH.[5-9] Whether favorable results reported in controlled clinical trials are achievable in clinical practice is an important consideration. We herein report the clinical and economic outcomes associated with the implementation of an outpatient DVT treatment program using LMWH in a large group model health maintenance organization (HMO).

Subjects and methods

Setting

Patients were selected from among the 340,000 members of the Kaiser Permanente Colorado Region (KPCR), a nonprofit, group-model HMO. Outpatient medical, radiology, pharmacy, and laboratory services were provided at 15 medical offices throughout the Denver, Colo, metropolitan area. Blood samples for prothrombin times were processed at a centralized in-house laboratory. Outpatient anticoagulation therapy was managed by the staff of the Clinical Pharmacy Anticoagulation Service (CPAS), which is a centralized team of pharmacy technicians and clinical pharmacists with specialty training in the coordination and management of anticoagulation therapy. All related activities and outcomes were documented in a comprehensive computerized patient monitoring system. This team of clinical pharmacy specialists was available by pager 24 hours a day, 7 days a week, to coordinate outpatient DVT therapy. Most CPAS patient care activities were conducted via the telephone. With the use of written guidelines (available on request from the authors), the CPAS acted as the agent of the referring physician and facilitated all aspects of anticoagulation therapy, including therapy initiation, patient education, laboratory monitoring, adjustment of anticoagulation medication doses, management of adverse events, and discontinuation of therapy.

Patients

We included 391 patients with a diagnosis of acute DVT from March 1, 1996, through March 31, 1998. Diagnosis of DVT was confirmed by results of objective testing (eg, ultrasonography or venography) in accordance with the approved treatment guideline. Patients were not considered candidates for outpatient therapy if hospitalization was required for concurrent symptomatic disease, if pulmonary embolism (PE) was suspected or confirmed by results of objective testing (eg, ventilation-perfusion lung scan or pulmonary angiogram), if active bleeding was present, or if pregnant.

Treatment

After the diagnosis of acute DVT, patients were referred to the CPAS for treatment. Patients received enoxaparin sodium, 1 mg/kg subcutaneously every 12 hours. Verbal and written instructions regarding the proper use of

allowed to return home. When necessary, a follow-up visit from a home health care nurse was arranged to confirm appropriate medication administration. Patients unable or unwilling to self-administer enoxaparin were temporarily admitted to a skilled nursing facility or received injections from a home health care nurse.

Oral anticoagulation therapy with warfarin was initiated on the evening of the first day of enoxaparin therapy. The initial dose of warfarin sodium was usually 5 mg/d. Patients and caregivers received verbal and written instruction regarding the use of warfarin from a KPCR pharmacist, and the CPAS reinforced all instructions. Subsequent warfarin doses were adjusted by the CPAS to achieve an INR of 2.0 to 3.0. Combined warfarin and enoxaparin therapy was continued until a therapeutic INR was achieved (minimum of 5 days).

Baseline laboratory information was obtained before the initiation of therapy and included a complete blood cell count with platelets, activated partial thromboplastin time, and INR. Subsequent INRs were measured daily, beginning on day 3 of therapy and continuing until the target INR was achieved. On approximately day 5 of therapy, a second complete blood cell count was performed to screen for heparin-induced thrombocytopenia.

Inpatients receiving IV UH and oral warfarin for treatment of acute venous thrombosis were also included in the analysis if they were discharged while receiving enoxaparin before day 4 of hospitalization. These patients received outpatient therapy to complete a minimum of 5 days of heparin therapy, continuing until a therapeutic INR was achieved.

During the first week of therapy, patients received daily telephone calls from a CPAS clinical pharmacist. During each call, patients were questioned about symptoms suggesting pulmonary embolus, bleeding, thrombosis extension, or adverse drug events. All patients were instructed to seek medical attention if they experienced worsening symptoms, chest pain, shortness of breath, uncontrolled bleeding, dizziness, or medication administration problems. Patients and caregivers were instructed regarding appropriate physical activity and elevation of the affected extremity if pain and swelling persisted. Analgesic medication was prescribed when necessary.

Data collection and analysis

Data collected at initial presentation included demographic information, risk factors for thromboembolism (obesity, history of thromboembolism, current estrogen use, history of cancer, current smoking status, recent surgery, whether the patient was nonambulatory or immobilized, recent trauma, and/or objective diagnosis of a coagulopathy), location of clot, and method of diagnosis. On day 7, the collected data included the duration of enoxaparin therapy, whether a therapeutic INR had been achieved, and indicators of health care resource utilization (medical office visits, emergency department and hospital visits, laboratory costs, medication costs, visits by a home health care nurse, and telephone contacts). Data pertaining to health care resource utilization were collected on days 7, 30, and 90 of therapy.

The primary end point for analysis was a combined event consisting of symptomatic recurrent thromboembolism (extension of DVT or PE) or major bleeding within the 90-day evaluation period. Symptomatic recurrence of thromboembolic disease was verified by objective means (eg, venous sonography, ventilation-perfusion lung scanning). *Major bleeding* was defined as bleeding that required a transfusion of 2 U of packed red blood cells or resulted in a decrease of 2 g/dL in the hemoglobin concentration, or any intracranial, retroperitoneal, or

All costs were determined from the perspective of KPCR. All direct costs for services associated with the outpatient treatment guideline were included in the analysis and inflated to 1998 US dollars by means of the medical care component of the consumer price index for all urban consumers (2.89% per year).[10] Treatment-associated costs included laboratory testing, physician visits, pharmacist or home health care nurse visits or contact time, call center contact time, urgent care visits, emergency department visits, and hospitalizations. Pharmacy costs included the acquisition cost for enoxaparin plus a calculated cost for dispensing the prescription. Vendor fees paid were used to determine costs associated with visiting nursing services, emergency department visits, and hospitalizations. Costs associated with treatment guideline development were not included in the analysis. The object of the economic evaluation was to determine the incremental cost incurred by KPCR while using the outpatient DVT treatment guideline compared with that of hospitalization for traditional UH therapy. The initial costs associated with the diagnosis of DVT (office visit, urgent care visit, or emergency department visit and diagnostic procedure) and the cost of warfarin were the same regardless of treatment location, and thus were excluded from the analysis. In addition, costs associated with non–anticoagulation-related events after day 7 of therapy were also excluded from the analysis.

To examine the robustness of the cost data, sensitivity analyses were conducted by varying the cost of enoxaparin, clinical pharmacy services, laboratory tests, clinic visits, visiting nursing services, emergency department visits, and hospitalizations in the range of 50% to 300%.[11] This range was chosen to reflect the variation in regional unit costs observed in North American centers that participated in a recent clinical trial.[12] Failure rate (thrombus extension, PE, major bleeding) was adjusted from 2.5% to 15%. In trials comparing UH with LMWH, the rates of major bleeding and recurrent thromboembolism were 1.9% and 5.4%, respectively.[13] Therefore, a failure rate of greater than 15% would be clinically unacceptable, regardless of cost savings. An analysis was conducted to determine the variables with the greatest impact on cost. These variables were used subsequently in a threshold (break-even) analysis to determine the point at which the cost of traditional UH therapy would equal that of outpatient treatment with LMWH. An additional analysis was conducted to determine the overall cost impact of increasing the length of LMWH therapy 2-fold. Incremental cost savings of the outpatient DVT treatment program were determined based on the cost KPCR would have incurred had the patient been admitted to the hospital for treatment with UH.

Unless otherwise indicated, data are given as mean ± SD.

Results

During the 2-year evaluation period, acute DVT was diagnosed in 428 KPCR members, an annual incidence of 0.06%. A total of 391 patients (91.4%) were enrolled in the outpatient DVT treatment program. Baseline characteristics compared with those reported in selected controlled clinical trials are listed in **Table 1**. Two hundred thirty-eight patients (60.9%) had therapy initiated in the medical office; 68 (17.4%), in the emergency department; and 24 (6.1%), in a skilled nursing facility. The remaining 61 patients (15.6%) had therapy initiated in the hospital, but only 28 (7.2%) had a length of stay greater than 24 hours. The mean number of visiting nurse contacts per patient was 3.3 ± 5.0 (range, 0-28). However, less than 38% of all patients required more than a single visiting nurse contact.

Go to Figure in Article

Comparative Baseline Characteristics*

Three hundred seventy-three patients (95.4%) completed 90 days of therapy without reaching the primary end point. Time to event for the 4.6% of patients reaching a primary end point is depicted in **Figure 1**. Symptomatic extension of the initial thrombosis developed in 10 patients (2.6%) (in 1 patient, during the first 7 days of outpatient therapy). Pulmonary embolism developed in 6 patients (1.5%) (in 3, within the initial 7 days), including 1 patient who died on day 29 of therapy. Three patients (0.8%) had a major hemorrhagic episode (a gastrointestinal tract hemorrhage on day 5, a hospitalization for hematuria on day 31, and a hospitalization for calf hematoma requiring surgical intervention on day 74). No episodes of immune-mediated heparin-induced thrombocytopenia were documented. The clinical outcomes in our patient population are compared with those reported in controlled clinical trials in **Table 2**. Compared with controlled clinical trials, almost twice as many KPCR patients received their entire course of therapy in the outpatient setting (36%-49% vs 78.3%, respectively). The percentage of KPCR patients reaching the primary outcome measure (4.6%) fell within the range of patients in controlled clinical trials (3.5%-9.4%).

Go to Figure in Article

Time to event for patients reaching a primary end point.

Table 2.

Comparative 90-Day Results*

Go to Figure in Article

Comparative 90-Day Results*

Economic analysis

The mean direct cost (in 1998 US dollars) of KPCR for outpatient treatment of DVT was $1868 ± $2197 per patient (**Table 3**). When compared with hospitalization costs of inpatient UH therapy for DVT, the mean incremental cost savings associated with outpatient therapy was $2828 ± $2270 per patient. During the 2-year program evaluation, total cost savings of $1,108,587 were realized by KPCR.

Table 3.

Sensitivity analysis indicated that increasing the acquisition cost of LMWH by 300% reduced the mean cost savings to $1953 ± $2357 per patient. In comparison, increasing all other program-related costs by 300% while leaving the acquisition cost of LMWH and hospitalization cost unchanged reduced mean savings slightly to $2035 ± $2456 per patient. In addition, doubling the average length of outpatient therapy to 12 days reduced mean savings to approximately $1949 ± $2374 per patient. Threshold analysis revealed that, for the costs of inpatient treatment to be equivalent to those of outpatient treatment, LMWH acquisition costs would have to increase by 750%, or costs for inpatient therapy would have to decrease by 77%.

Comment

This analysis was designed to evaluate the effectiveness, safety, and economic impact of an outpatient treatment program for patients with a diagnosis of acute DVT. Our objectives were to determine whether outcomes from controlled clinical trials could be reproduced in an HMO setting and to determine the cost savings associated with outpatient therapy. Demographic data and overall adverse event rates were consistent with those reported in controlled clinical trials (**Table 1** and **Table 2**). Despite the less stringent inclusion and exclusion criteria applied to our patient population, the data from comparative clinical trials appear externally valid.

Some have advocated strict exclusion criteria when considering outpatient LMWH therapy for acute DVT.[14] Application of these exclusion criteria, specifically morbid obesity (>30% of ideal body weight) and malignant neoplasms, would have excluded 41.5% and 25.6% of our patient population, respectively. The results of this and other evaluations indicate that strict exclusion criteria are not necessary to maintain clinical outcomes similar to those achieved in controlled clinical trials.[8,15] Inclusion of patients with cancer in our program and similar programs did not increase the rates of treatment failure above those reported in controlled trials.[8,15] In fact, evidence suggests that strict exclusion criteria unnecessarily withhold LMWH therapy from patients who may benefit from it the most.[13] In a meta-analysis comparing UH with LMWH for treatment of acute DVT, Gould et al[13] reported a 9.75% absolute risk reduction in 90-day mortality in a small subset of patients with cancer who received LMWH ($P<.05$). In their 147 patients, mortality among those who received traditional inpatient therapy with UH was 25.9%, compared with 16.7% among patients treated with LMWH. Though our rate of cancer-related death (9.8%) in patients receiving LMWH was higher than in 2 of the 3 comparative trials, it is still less than what would be anticipated based on the meta-analysis mentioned above. Our results also suggest that there is no reason to withhold outpatient treatment with LMWH from this patient population.

Our results were also consistent with those reported for similar outpatient DVT treatment programs (**Table 4**).[8,15] Harrison et al[8] reported outcomes associated with consecutive outpatients with DVT who were referred to 2 thrombosis clinics. Before commencing outpatient therapy, patients were given an explanation of their disease and the treatment plan and taught to self-inject LMWH (dalteparin sodium, 100 IU/kg every 12 hours, or tinzaparin sodium, 175 IU/kg per day) by a nurse clinician. Subcutaneous LMWH therapy was continued for a minimum of 5 days and until an INR of 2.0 to 3.0 was achieved for 2 consecutive days. All patients received warfarin therapy starting within 1 day of diagnosis and continuing for at least 3 months. Patient satisfaction and comfort with home

required admission to the hospital for bleeding; and 5 patients had recurrent DVT. No economic analyses were performed.

Table 4.


Comparative 90-Day Results of Real-World Outpatient DVT Treatment Programs*

Go to Figure in Article

Comparative 90-Day Results of Real-World Outpatient DVT Treatment Programs*

The outcomes associated with an outpatient DVT treatment program using subcutaneous dalteparin sodium (100 IU/kg twice daily or 200 IU/kg once daily) have been reported by Wells et al.[15] Patients who met entry criteria self-injected LMWH or received injections from a home health care nurse. Warfarin therapy was started within 1 day of diagnosis and continued for at least 3 months. Combined LMWH and warfarin therapy continued for a minimum of 5 days. During the latter half of the study, patients with PE also were considered eligible for home treatment if they were hemodynamically stable. Of 233 patients, 194 (83.3%) completed treatment at home, and 34 of these were treated for PE. Recurrent thromboembolism occurred in 3.6% of patients (95% confidence interval, 1.5%-7.4%), and major bleeding occurred at a rate of 3.2%. Economic analyses were not performed.

Like these programs, most patient care activities in our study were provided by nonphysician health care providers (ie, pharmacists and nurses) working in close cooperation with physician partners. Our results support the effectiveness documented in these reports and also provide verification of the predicted economic benefits of outpatient therapy.[12,16] Quality of life was not measured specifically in our patient population. However, outpatient treatment for acute DVT was well received by most of our patients. Our experience is consistent with that of Harrison et al,[8] who found that 91% of patients expressed a preference for outpatient therapy.

In an inpatient clinical trial involving 432 patients, Hull et al[12] compared the costs associated with the treatment of proximal vein thrombosis using tinzaparin or UH. The average cost savings per patient treated with tinzaparin was $509 (adjusted to 1998 US dollars).[10] The authors estimated that if 37% of the patients receiving tinzaparin had been treated as outpatients, the average cost savings per patient would be approximately $1159. Using the same rationale, we calculated that if 92% of the tinzaparin-treated patients had received outpatient therapy, the adjusted cost savings would have been approximately $2165 per patient. The cost savings associated with the clinical trial of tinzaparin were therefore similar to KPCR's average cost savings of $2828 per patient.

Sensitivity and threshold analysis demonstrated that the cost savings of our program are robust (**Table 3**). The primary financial drivers of outpatient treatment appear to be the acquisition cost of LMWH and the reimbursement rate for hospitalization. However, the acquisition cost of LMWH would need to increase by 750% or the hospitalization costs associated with traditional inpatient management of DVT would need to decrease by 77% to make the cost of inpatient therapy equivalent to that of outpatient therapy. Although the cost savings associated with our program are substantial, we believe they may be underestimated. This is because our

Assuming that the costs of outpatient and inpatient therapy are similar after the first week, the cost-effectiveness of outpatient therapy would be greater if costs associated with treatment failure were limited to the initial 7 days.

The safety and efficacy of LMWH in the outpatient treatment of acute DVT has been demonstrated adequately in well-controlled clinical trials.[5-7] The purpose of our evaluation was to demonstrate that the results of these rigorously conducted studies were achievable in clinical practice. Our goal was to compare actual outcomes with those reported in the controlled clinical trials that were used as the basis for our outpatient DVT treatment guideline.

Levine et al[5] compared the efficacy of traditional inpatient UH (5000-U IV bolus followed by a continuous infusion) with outpatient enoxaparin sodium (1 mg/kg subcutaneously twice daily) in a multicenter, randomized controlled trial composed of 500 patients with proximal DVT. Both groups received warfarin for at least 3 months following completion of heparin therapy. The study failed to show statistically significant differences in the occurrence of recurrent thromboembolism (UH, 6.7%; enoxaparin, 5.3%; $P = .57$) or major bleeding complications (UH, 1.2%; enoxaparin, 2.0%; $P = .50$) between groups. Appropriate dosing of UH was verified by calibrating the activated partial thromboplastin time to a UH plasma concentration of 0.2 to 0.4 U/mL by means of protamine titration. The authors concluded that outpatient treatment of acute DVT appeared to be as safe and effective as inpatient therapy in the study population selected.

An international, multicenter, randomized controlled trial of 400 patients compared the efficacy of inpatient UH (5000-U IV bolus followed by an adjusted-dose continuous infusion) with outpatient nadroparin calcium (weight-based fixed dosing twice daily) in the treatment of proximal DVT.[6] The results provided additional evidence that outpatient therapy with LMWH is as safe and effective as inpatient therapy with UH. In addition to efficacy and safety, this study evaluated the patients' perceived quality of life using the Medical Outcome Study Short Form-20. The scores pertaining to mental health, thrombosis symptoms, effort to cope, and overall quality of life improved over time in both treatment groups. However, scores pertaining to physical activity and social functioning were significantly better ($P = .002$ and $P<.001$, respectively) in the LMWH group. Based on these findings, the authors concluded that outpatient treatment with LMWH provided equally effective treatment at a reduced cost with little or no measurable adverse effect on physical or mental well-being.

An open, nonrandomized multicenter trial of 434 patients further describes the efficacy and significant cost reduction of outpatient treatment of DVT.[7] Patients with an objective diagnosis of symptomatic DVT were administered dalteparin sodium, 200 IU/kg of body weight once daily. Warfarin therapy was initiated on the first day of dalteparin administration. Although not mandatory, outpatient therapy was encouraged whenever possible after a full consultation. Although most patients (80.2%) had at least part of their initial therapy as outpatients, only 44% had a hospital stay of less than 24 hours. The major reason for patients not opting for outpatient therapy concerned geographical or personal reasons (59%). The frequencies of major bleeding and recurrent venous thromboembolism were 0.9% and 1.6%, respectively. Overall, all the authors reported a 34.5% reduction in the average cost of treating DVT when compared with traditional inpatient therapy with UH. However, when the analysis was limited to patients with hospital stays of less than 24 hours, the average cost of outpatient DVT treatment was reduced by 57.4%.

Our results are limited by the observational study design and the lack of a control group. We attempted to

chose an organizational economic perspective; therefore, economic issues relevant to patients (eg, time lost from work, expenses related to travel) and society were not addressed.

Our report is, to our knowledge, the first evaluation of the clinical and financial outcomes of an outpatient acute DVT treatment program in a managed care setting. A major reason for our program's success is the continuity of care and rigorous follow-up provided by the staff of our CPAS. Patients and providers are able to contact the CPAS 24 hours a day, 7 days a week, by pager. Primary care clinical pharmacists located in the medical offices provide much of the initial patient education. The integrated structure of our group-model HMO allows improved collaboration among health care providers and ready access to medical records, pharmacy medication profiles, and laboratory test results. Our in-house outpatient pharmacies and laboratory facilities minimize logistical problems associated with dispensing anticoagulation medications and collecting laboratory specimens. Our centralized hematology laboratory allows for prompt notification of results and eliminates interlaboratory variability in INR reporting. Multidisciplinary cooperation during the development of the outpatient DVT treatment guideline also contributed to successful implementation. Although our results may not be reproducible in health care settings that are unable to support dedicated 24-hour-a-day centralized anticoagulation services, other models that optimally utilize the resources available within a given health care system have been described.[17] Our results demonstrate that outpatient treatment of acute DVT can be managed safely and effectively in clinical practice. They also demonstrate that the potential economic savings associated with outpatient DVT treatment programs are substantial.

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