

Selecting patients for home treatment of deep vein thrombosis: the problem of cancer

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WALTER AGENO,* LUIGI STEIDL,* CHIARA MARCHESI,*
FRANCESCO DENTALI,* VALENTINA MERA,*
ALESSANDRO SQUZZATO,* MARK A. CROWTHER,°
ACHILLE VENCO*

*Department of Internal Medicine, University of Insubria, Varese, Italy; °Department of Medicine, McMaster University, Hamilton, Ontario, Canada

Correspondence: Walter Ageno, MD, Department of Internal Medicine Ospedale di Circolo, viale Borri 57, 21100 Varese, Italy.
Phone: international +39.0332.278594. E-mail: agewal@yahoo.com

Background and Objectives. Patients with deep vein thrombosis are selected for home treatment on the basis of their clinical and social condition. Cancer is frequently associated with venous thromboembolism and is often considered an exclusion criterion for outpatient treatment. We investigated the impact of cancer on the outpatient management of venous thrombosis.

Design and Methods. We performed a prospective, cohort study on consecutive patients with objectively documented deep vein thrombosis. All were assessed for home treatment. Hospital admission was recommended in the presence of common exclusion criteria. All patients were treated with low molecular weight heparin and warfarin. Information on previous, active, or suspected cancer was collected. Recurrent thrombosis, bleeding and mortality were documented at a 3-month follow-up.

Results. One hundred patients were included; 72 were entirely treated at home (mean age: 61.2 years). There were 22 patients with known cancer: 12 (55%) were managed as outpatients (16.5% of the outpatient population) and 10 were hospitalized (36% of the inpatient population), 6 because of a poor clinical condition, 4 because further investigation of their malignancy was required. The presence of cancer and the likelihood of poor compliance were the most frequent reasons cited for in-hospital treatment. Overall, event rates at 3 months were comparable to those reported in previous studies in the outpatient population and slightly higher in the inpatient population (recurrent thrombosis 1.5% and 7%; bleeding 5.5% and 10.7%; mortality 4% and 18%, respectively).

Interpretation and Conclusions. Cancer was the most common reason cited for in-hospital treatment. Nevertheless, more than half of the patients

with known cancer were safely and effectively treated at home.

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Key words: deep vein thrombosis, cancer, outpatient treatment.

Home-treatment of deep vein thrombosis (DVT) is a common practice in many European and North American centers. Two large clinical trials^{1,2} clearly showed the efficacy and safety of the low molecular weight heparins (LMWH) in the outpatient setting, and a number of reports from clinical practice^{3,4} or further comparisons between in-hospital and home treatment⁵ have subsequently confirmed the practicality of home treatment of DVT. Despite this evidence, rates of hospitalization of patients with acute DVT vary among countries and remain high in many centers. Social and educational factors account for some cases of in-hospital treatment in patients otherwise eligible for outpatient treatment. When Tanvetyanon and Cohn⁶ applied the same criteria previously used by Wells *et al.*⁴ to select DVT patients for outpatient management in the urban Philadelphia area, they found that only 35% of the patients were eligible for home treatment as compared to 80% of patients in Wells' study. The authors attributed their findings to a higher rate of both comorbid conditions and non-compliance due, at least in part, to the lack of appropriate health insurance.

The presence of concomitant medical conditions can exclude patients from home treatment, but there is no consensus on which conditions should compel in-hospital treatment. Cancer is associated with deep vein thrombosis, and is probably the most frequently encountered concomitant disease

in patients with acute DVT.⁷ The prevalence of known cancer ranges from 10% to 20% at the time when venous thromboembolism (VTE) is diagnosed, and 4% to 10% of patients presenting with idiopathic VTE will subsequently be found to harbor a malignancy.⁸ The management of antithrombotic therapy in cancer patients is particularly difficult because of an increased risk of both bleeding and recurrent VTE.⁹ Home-treatment of patients with underlying malignancies has been reported,^{3,4,10} but the real rate of hospital admissions in patients with acute DVT and cancer is unclear. To address this lack of information, we prospectively investigated the impact of cancer on the decision to hospitalize patients with acute DVT and on their outcome with outpatient treatment.

Design and Methods

Population

Consecutive outpatients with suspected DVT referred to the Thrombosis Unit of the University Hospital of Varese, Italy between February 2000 and May 2001 were studied. All patients with objectively confirmed DVT were included and evaluated for the home treatment program. We applied the following criteria for hospital admission: poor clinical conditions related to concomitant medical disorders, illness that independently required hospitalization, high risk of bleeding or active bleeding, pain requiring parenteral narcotics, likelihood of poor compliance, refusal of home treatment, or age younger than 18 years. Family and personal history were collected to identify all potential risk factors for DVT. Recent trauma or surgery, previous episodes of VTE, known thrombophilia, previous or concomitant neoplastic, vascular, autoimmune, and inflammatory disorders were documented. Particular attention was given to previous or active cancer. Time of diagnosis, site, presence of metastases and life expectancy were also documented. Data on ongoing treatments, with special attention to contraceptive pills and hormone replacement therapy were also collected. Blood tests were performed for complete blood count, INR and activated partial thromboplastin time, renal and liver function. Patients selected for the home treatment program underwent a talk with the attending physician lasting an average of approximately 20 minutes. Patients were given an explanation of their disease and related risks and the treatment plan. After obtaining consent for outpatient treatment, patients were taught to self-inject and were given an explanation of oral anticoagulant therapy, with

particular emphasis on bleeding risks and need for regular monitoring. The same explanations were also given to hospitalized patients at discharge.

Treatment program

All patients, either hospitalized or outpatients, were treated with subcutaneous, weight-adjusted, twice daily low molecular weight heparin (Fraxiparine, Sanofi-Synthelabo, Milan or Clexane, Lepetit, Milan, Italy). Treatment was administered for a minimum of 5 days and then discontinued when the INR reached the therapeutic range (2.0 to 3.0). Warfarin was started on the same day of diagnosis or, at latest, on the following day, with a starting dose of 5 or 7.5 mg. Laboratory monitoring of the INR and subsequent dosage adjustments were performed daily for hospitalized patients, on day 3 and then according to the individual needs for the outpatients. All patients underwent blood tests for platelet count on day 5. Warfarin treatment was monitored at the local Anticoagulation Clinic and treatment was continued for a minimum of 3 months. At each attendance the occurrence of bleeding or thromboembolic events was documented. The final follow-up appointment for the study purpose was performed after 3 months. Patients who were not monitored at the local Anticoagulation Clinic were contacted on a regular basis by telephone or at a clinic visit to determine their clinical status, and to ascertain whether bleeding or thrombotic complications had occurred. All patients were instructed to report any signs or symptoms of recurrent DVT or pulmonary embolism and bleeding.

Assessments

The following characteristics of outpatients and hospitalized patients were compared: age, gender, concomitant symptomatic pulmonary embolism and risk factors for thrombosis. Reasons for hospital admission were also analyzed. The stage of cancer was compared between outpatients and inpatients and in both groups, the rates of recurrent VTE, major and minor bleeding events and death were recorded at 3 months. Recurrent DVT was defined as the detection of a new thrombus or the extension of the previous thrombus documented by compression ultrasound. For pulmonary embolism, high probability perfusion scan or positive spiral computed tomography scan was diagnostic. An intermediate probability lung scan was only considered diagnostic of acute VTE if new thrombosis was found on compression ultrasonography of the legs. Bleeding was defined as major if

Table 1. Baseline characteristics of DVT patients.

	Outpatients	Inpatients
Number	72	28
Age (mean)	61.2	68.8
Age (range)	27-91	26-88
Males	34 (52.7%)	12 (57.1%)
Concomitant pulmonary embolism	5 (6.9%)	7 (25%)

Table 2. Pathogenesis of thrombosis.

	Outpatients	Inpatients	Total
Number	72	28	100
Idiopathic	41 (57%)	10 (36%)	51
Cancer	12 (16.5%)	10 (36%)	22
Trauma	7 (9.5%)	2 (7%)	9
Oral contraceptives	5 (7%)	2 (7%)	7
Recent surgery	5 (7%)	1 (3.5%)	6
Prolonged immobilization	1 (1.5%)	2 (7%)	3
Pregnancy	1 (1.5%)	—	1
Central venous catheter	—	1 (3.5%)	1

it was overt and associated with either a decrease in hemoglobin levels of at least 2.0 g/dL or a need for the transfusion of 2 or more units of blood. Bleeding was defined as minor if it was overt but did not meet the other criteria for major bleeding. The mean age of the patients was compared by a t-test, gender and the rates of pulmonary embolism, cancer and other risk factors for thrombosis were compared by the χ^2 test.

Results

During the 15-month study, we assessed 450 patients for suspected DVT: the diagnosis was objectively confirmed in 100 (22%). Of these 100, 92 had proximal vein thrombosis of the lower limbs and 8 had upper-extremity thrombi. Twelve had objectively confirmed, concomitant, symptomatic, submassive pulmonary embolism. Seventy-two patients were entirely treated at home, whereas 28 required hospitalization. Inpatients were slightly, but not significantly, older than outpatients

(68.8 compared with 61.2 years, respectively, $p = 0.0538$), with a similar age range (Table 1). There were no differences in gender between the 2 groups (Table 1). Five patients with pulmonary embolism were treated as outpatients, 7 were hospitalized because of concomitant indications: 4 had a poor clinical condition (3 had metastatic cancer), 2 were considered as potentially non-compliant, and 1 refused the home-treatment program. The suspected pathogenesis of thrombosis is summarized in Table 2. Patients with idiopathic DVT as well as patients with transient risk factors were more likely to be treated at home, whereas the prevalence of cancer and prolonged immobilization was higher among hospitalized patients. Almost half of hospital admissions were attributed to malignancies (12 patients, 43%). Six of the twelve were admitted because of metastases (predominantly to the liver) and a poor clinical condition. The other 6 were admitted for investigations of recurrent cancer or occult malignancy. Two of the six patients had previously undergone prostatectomy (3 years and 2 years before admission, respectively) for adenocarcinoma and were admitted to the hospital at the time of their presentation with acute VTE for investigation of suspected local metastases. Both had thrombi isolated to the femoral vein. The computed tomography of the lower abdomen subsequently confirmed the diagnosis of localized recurrence of prostate carcinoma. Four patients without a personal history of cancer who presented with an apparently idiopathic DVT were admitted because of suspected occult malignancy. Two of them had bilateral DVT of the lower limbs, one had a concomitant newly diagnosed microcytic anemia and one had an abnormal chest X-ray. One of these latter 2 patients had a diagnosis of rectal cancer (colonoscopy), the other lung cancer (computed tomography of the chest). The former 2 patients underwent extensive screening with negative results. Twelve patients with known malignancy, including 4 with metastatic cancer, were treated at home. None had impairment of liver or renal function. The clinical characteristics of the cancer patients are summarized in Table 3. Concomitant medical problems requiring hospital admission in patients who did not have cancer included autoimmune thrombocytopenia, chronic renal insufficiency (2 cases) and pneumonia (Table 4). Five patients were lost to follow-up at 3 months. Three were home-treated and 2 were hospitalized. In the outpatient group there was 1 case of recurrent DVT (in a non-cancer patient, 1.5%),

Table 3. Clinical characteristics of cancer patients.

	Outpatients	Inpatients
Number	12	10
Mean age	68.8	70.2
Recent diagnosis (< 1 month)	3 (25%)	2 (20%)
Metastases	4 (33%)	8 (80%)
Site		
Gastrointestinal	4 (33%)	3 (30%)
Genitourinary	2 (16.6%)	4 (40%)
Breast	2 (16.6%)	2 (20%)
Pulmonary	2 (16.6%)	1 (10%)
Lymphatic	2 (16.6%)	–
Ongoing treatment at the time of DVT diagnosis		
Chemotherapy	4 (33%)	2 (20%)
Hormone therapy	2 (16.6%)	2 (20%)
Radiotherapy	1 (8.3%)	–

Table 4. Reasons for hospital admission.

Cancer	12 (43%)*
Likelihood of poor compliance	9 (32%)
Other illness	4 (14.3%)
Need for parenteral narcotics	2 (7.2%)
Refusal of home-treatment	1 (3.5%)

*6 patients admitted because of poor clinical condition, 6 patients because of suspected underlying malignancy that was subsequently excluded in 2.

1 major bleeding (gross hematuria in a patient with known bladder cancer)(1.5%), 3 cases of minor bleeding (4%), and 3 deaths (4%), all in patients with known malignancy. In the group of hospitalized patients there were 2 episodes of recurrent VTE (one in a patient whose warfarin was stopped due to profound thrombocytopenia, and the other in a patient with known metastatic cancer, 7%), 3 cases of minor bleeding (11%) and 5 deaths (18%), all in cancer patients (Table 5).

Discussion

The results of our study confirm the crucial role of cancer in the decision of whether to hospitalize or treat at home patients presenting with acute DVT. On the one hand we demonstrated that known malignancy did not preclude the possibility of treating patients with DVT at home. After the

Table 5. Outcome results.

	Outpatients	Inpatients
Number	72	28
Recurrent venous thromboembolism	1 (1.5%)	2 (7%)
Major bleeding	1 (1.5%)	–
Minor bleeding	3 (4.5%)	3 (11%)
Death	3 (4%)	5 (18%)

strict application of common exclusion criteria for outpatient management, we entirely treated at home more than half of the patients with VTE and concomitant malignancy (twelve out of twenty-two). Some of them had known metastases, but at the time of DVT diagnosis they were neither in poor condition nor had they concomitant indications for hospitalization. The decision on outpatient treatment was shared with the patients and was very well accepted. The presence of patients with malignancies (16.5% of the outpatient population) did not affect the rates of clinical events, which were comparable to those reported in previous, similar studies. On the other hand, cancer was also found to be the most common reason for in-hospital treatment. Almost half of hospital admissions were related to malignancies (12 patients, 43%), only 6 of the 12 actually met our predefined criteria. Six additional patients (21% of all hospitalizations) were admitted despite full eligibility for the outpatient treatment protocol because further investigation of known or suspect malignancy was felt to be required. In 4 of them, cancer was subsequently documented. Criteria that motivated hospital admission were abnormal ultrasonographic results in 4 and abnormal clinical findings in 2 patients. Abnormal ultrasonographic results were non-compressibility isolated to the common femoral vein, which has been suggested as a diagnostic marker for pelvic disease,¹¹ and bilateral DVT, for which to our knowledge no similar evidence has been conclusively reported.

Thus, when feasible, home treatment of patients with known cancer and DVT can be safe, effective and very well accepted with a potentially significant impact on quality of life. Of course, our observations are limited by the descriptive design of the study, as clear-cut conclusions can only be reached after a randomized trial comparing in-hospital and home treatment of cancer patients. Moreover, one

could argue that previous studies on outpatient management described a predictable relation between the presence of cancer and the occurrence of adverse outcomes: Harrison *et al.*³ reported that all outpatients who had recurrent VTE (5 cases) had underlying cancer, Wells *et al.*⁴ found malignancies to be the cause of 11 out of 14 recorded deaths among patients treated at home. Nevertheless, the overall rates of events remained successfully low in all studies and we have no evidence to support the hypothesis that in-hospital treatment, in particular a short hospital stay (*e.g.* 3 days), could have prevented these events.

The rate of hospital admissions related to cancer is dependent on the decision to investigate for occult malignancy routinely in all patients presenting with an idiopathic DVT. It is still unclear to what extent screening for cancer should be carried out. Routine clinical examination was shown to be of little help as compared to extensive screening.¹²⁻¹⁵ Recently, Piccioli and colleagues reported that the addition of further diagnostic tests such as computed tomography scans and endoscopy at the time of presentation with acute venous thrombosis detects the majority of hidden malignancies and reduces mortality in asymptomatic patients.¹⁶ However, if careful screening with such procedures is to be routinely performed, short-term hospitalization will be of little value: our patients spent no less than 2 weeks to complete extensive screening. Thus, we believe that only patients presenting with signs or symptoms suggestive of underlying malignancy should be considered for admission when investigation as outpatients is unfeasible.

In conclusion, we found that cancer is the most common cause of hospitalization of patients with acute venous thrombosis. However, more than half of the patients with known malignancies and acute VTE could be safely and effectively treated at home.

Contributions and Acknowledgments

WA was the major contributor to this work and was primarily responsible for it, from conception to submitted manuscript: he should be considered as the principal author. The remaining authors qualified for authorship according to the World Association of Medical Editors (WAME) criteria, and have taken specific responsibility for the following parts of the content: LS, FD, VM, AS: collection of clinical data; MAC: statistical analyses; AV had a major role as senior author in designing the study, interpreting the data and preparing the article.

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Disclosures

Conflict of interest: none.

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PEER REVIEW OUTCOMES

Manuscript processing

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What is already known on this topic

Cancer is frequently associated with venous thromboembolism and is often considered to exclude outpatient treatment.

What this study adds

The authors prospectively investigate the impact of cancer on the decision to hospitalize patients with DVT and on their outcome with outpatient treatment.

Potential implications for clinical practice

The findings indicate that more than half of the patients with known malignancies and DVT could be safely and effectively treated at home.

Vicente Vicente, Deputy Editor