

The Use of a Protocol for the Treatment of Deep Vein Thrombosis

An interview with Alex C. Spyropoulos, MD, Medical Director of the Clinical Thrombosis Center at Lovelace Health Systems and Clinical Assistant Professor in the Department of Medicine at the University of New Mexico in Albuquerque, New Mexico. Dr. Spyropoulos championed and cowrote the guidelines at Lovelace for the outpatient deep vein thrombosis (DVT) treatment program and perioperative bridging program for patients on chronic anticoagulant therapy. We asked Dr. Spyropoulos for his perspective on the treatment of DVT.

Background

AJMC: *What is it about the treatment/prevention of deep vein thrombosis (DVT) that attracted you to this field of treatment and research?*

Dr. Spyropoulos: This whole field is undergoing revolutionary changes at present, in terms of diagnostic and therapeutic paradigms and management issues. I was a member of the Episodes of Care team, a disease management team within Lovelace Health Systems, which is a large staff-model regional, integrated managed care organization. We developed the disease management guidelines for anticoagulation, both in terms of prevention and treatment, and we developed our institution's outpatient DVT protocol. I also became the medical director of the Anticoagulation Clinic and subsequently founded the Clinical Thrombosis Center here. This is an integrated center for the management of thromboembolic diseases.

AJMC: *How prevalent is DVT in the United States?*

Dr. Spyropoulos: Mohr et al¹ found the incidence of the disease in the United States is 1 per 1000 people, with about 48 per 100,000 presenting with DVT and 69 per 100,000 presenting with pulmonary embolism. An earlier study by Anderson et al² in 1991 showed that the prevalence of the disease is probably more than 250,000 in the United States. Remembering that two thirds of the population with the disease are largely asymptomatic, the prevalence is likely greater than 500,000, so this disease represents a national health hazard.

AJMC: *What are the risks to patients' health from DVT?*

Dr. Spyropoulos: There are both short- and long-term risks. Short-term risks include extension of the thrombus, fatal pulmonary embolic events, and early recurrence of the disease. The long-term risks include postthrombotic syndrome, pulmonary hypertension, and increased risk of late recurrence of the disease.

Treatment of DVT

AJMC: *What is the traditional therapy for DVT?*

Dr. Spyropoulos: The traditional therapy involves hospitalization of the patient, starting with inpatient unfractionated heparin. We know now that we should do this with weight-based heparin nomograms and routinely monitor patients' activated partial thromboplastin time. This is usually done for approximately 4

to 5 days with concurrent oral anticoagulant therapy, namely warfarin or warfarin-based products.

AJMC: *What are the advantages of low-molecular-weight heparin (LMWH)?*

Dr. Spyropoulos: As a class, LMWHs have at least 6 distinct advantages over unfractionated heparin. Number 1, there is less protein binding and less nonspecific binding. This translates to better bioavailability at lower doses, and also reduced heparin resistance. Number 2, there is also a longer half-life, and thus only 1 or 2 subcutaneous injections per day are needed. Third, there is a much more predictable dose-response curve, and thus no routine monitoring is needed. Fourth, the reduced effects on both the platelets and endothelium lead to reduced incidence of heparin-induced thrombocytopenia. Fifth, there may be generally less bleeding. Finally, there are reduced effects on osteoclasts, possibly leading to reduced incidence of osteopenia with long-term use.

AJMC: *Have studies examined the benefits of LMWH? If so, please describe those studies and what they found.*

Dr. Spyropoulos: There have been several studies. I separate them into 3 types: randomized controlled trials, meta-analyses, and observational studies. There are 2 key randomized controlled trials of LMWH comparing inpatient unfractionated heparin to inpatient LMWH—the Merli et al³ study in 2001, and the 1992 Hull et al⁴ study. Other key randomized controlled trials compare inpatient unfractionated heparin with mostly outpatient LMWH. The best 3 such studies are Koopman et al⁵ 1996, Levine et al⁶ 1996, and the Columbus Investigators⁷ 1997. The 2 important meta-analyses are Gould et al⁸ and Dolovich et al.⁹ The 5 observational studies that come to mind are: Wells et al,¹⁰ Harrison et al,¹¹ Pearson et al,¹² our own study,¹³ and Tillman et al.¹⁴

Merli et al³ found no statistically significant differences using the short-term

clinical end points of DVT recurrence and major bleeding when comparing inpatient unfractionated heparin, inpatient once-daily LMWH (enoxaparin), and inpatient twice-daily enoxaparin. Hull et al⁴ also found no significant statistical differences in short-term clinical outcomes—that is, venous thromboembolism recurrence and major bleeding—between inpatient unfractionated heparin and inpatient once-daily tinzaparin.

Koopman et al,⁵ Levine et al,⁶ and the Columbus Investigators⁷ all found no statistically significant differences between inpatient unfractionated heparin and outpatient LMWH when examining short-term clinical end points (major bleeding and DVT recurrence). Koopman et al⁵ used nadroparin as the LMWH, Levine et al⁶ used enoxaparin, and the Columbus Investigators⁷ used reviparin. In most of those studies, approximately one quarter to one third of eligible study patients were treated with some type of outpatient-based therapies.

Gould et al⁸ found a statistically significant difference in overall mortality, with a *P* value of .02, in favor of LMWHs when they were compared with unfractionated heparin. The Dolovich analysis found no statistically significant differences at a meta-analytic level between inpatient unfractionated heparin and either inpatient or outpatient LMWH when comparing the end points of DVT recurrence, major and minor bleeding, mortality, and thrombocytopenia.⁹

All 5 observational studies also found no statistically significant differences between inpatient unfractionated heparin and mostly outpatient LMWH when examining short-term triple clinical end points of DVT recurrence, major bleeding, and death. These studies were conducted in routine-care settings.

Lovelace Health System's DVT Protocol

AJMC: *How long have you been involved in the development of treatment protocols for DVT?*

Dr. Spyropoulos: Since 1996.

AJMC: Please describe the LMWH protocol designed by Lovelace Health Systems.

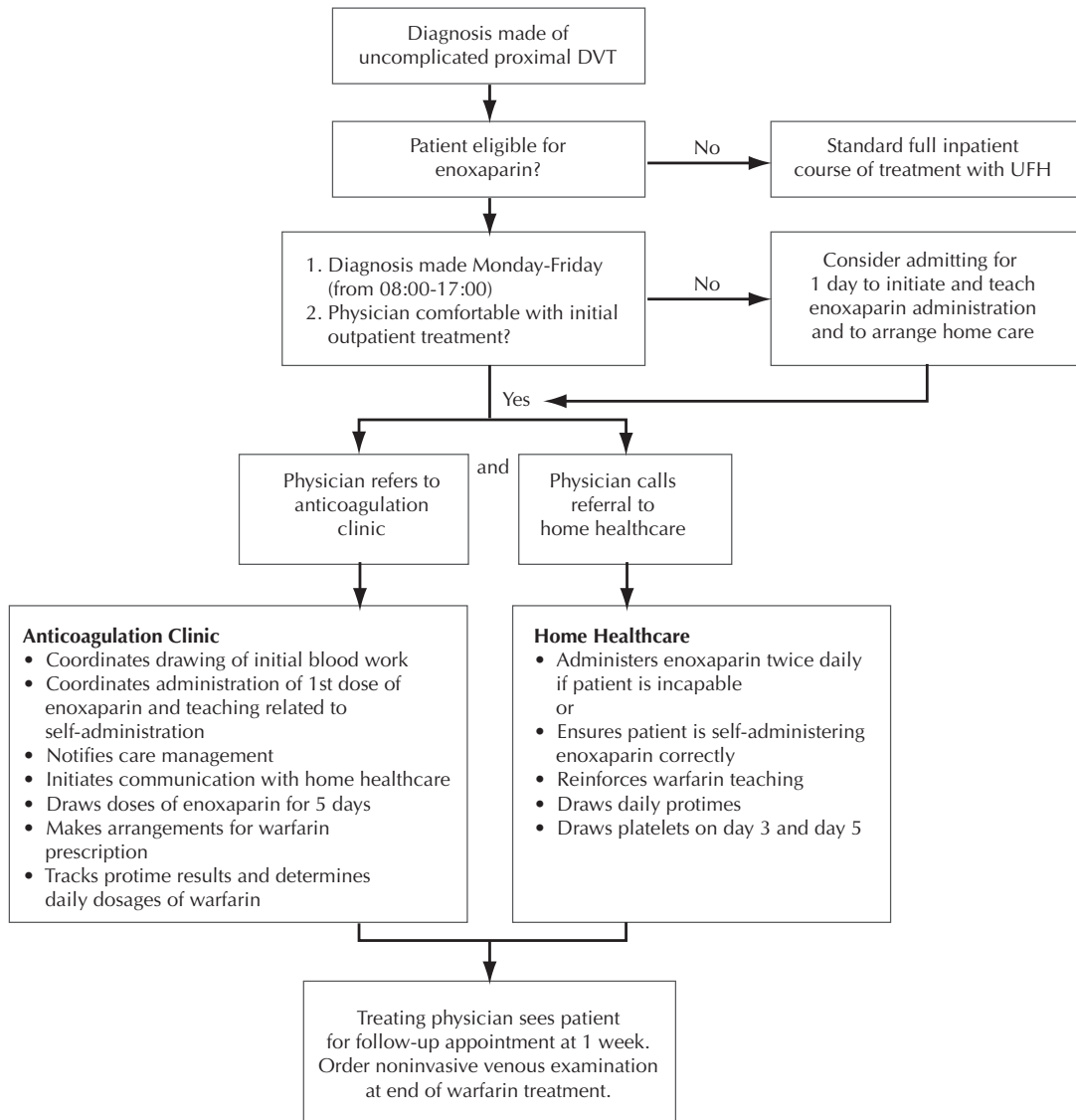
Dr. Spyropoulos: At this point, the published protocol is written for enoxaparin (Figure).¹⁵ It is our original LMWH and therefore that with which we have had the

most experience. However, we have also recently approved tinzaparin for our outpatient DVT protocol.

AJMC: How did you gain consensus for the outpatient DVT program?

Dr. Spyropoulos: The Episodes of Care team was a disease management program.

Figure. Lovelace Health Systems Protocol for Outpatient DVT Treatment



DVT = deep vein thrombosis; UFH = unfractionated heparin.

Source: This figure originally appeared in Spyropoulos AC. Outpatient-based treatment protocols in the management of venous thromboembolic disease. *Am J Manag Care* 2000;6:S1034-S1044.

In that program, we wrote the guidelines for outpatient DVT treatment at Lovelace.

AJMC: *Why has your institution focused on outpatient rather than inpatient therapy of DVT?*

Dr. Spyropoulos: Because it really represents a win-win situation. We have published data to suggest that with our own experience, we have equal or better outcomes using outpatient LMWH versus inpatient unfractionated heparin. We also have greater patient convenience, greater provider satisfaction, and significant cost savings.¹³

AJMC: *What approximate percentage of patients in Lovelace Health Systems is eligible for outpatient LMWH therapy?*

Dr. Spyropoulos: In our published work covering the period of March 1997 to August 1998, we show that approximately 61% of our total patients were eligible, of which 69% were treated exclusively as outpatients.¹⁵

AJMC: *What are the cost savings and outcome improvements that can be accrued through outpatient rather than inpatient treatment of DVT?*

Dr. Spyropoulos: There are now some good, emerging pharmacoeconomic evaluations of DVT treatment with LMWHs. I separate them into 3 designs: the pharmacoeconomic substudies of the randomized controlled trials, the decision-model analyses, and the pharmacoeconomic analyses of some of the outcome/observational studies.

In the first class, there are 3 good articles: Hull et al¹⁶ 1997, Goldhaber et al¹⁷ 1998, and O'Brien et al¹⁸ 1999. The Hull article showed about \$400 in cost savings per patient,¹⁶ whereas the Goldhaber article examined mostly outpatient LMWH and showed much more cost savings, approximately \$3685 per patient.¹⁷ O'Brien et al¹⁸ performed a subanalysis of the Levine trial and found cost savings of approximately \$3000 (Canadian dollars)

per patient when looking at outpatient-based LMWH versus inpatient unfractionated heparin.

The 2 significant decision-model analyses are Rodger et al¹⁹ 1998 and Gould et al²⁰ 1999. These analyses also found cost savings, ranging from approximately \$700 (US) to \$1400 (Canadian) per patient when various assumptions of outpatient LMWH were modeled.

But I think what is the most reflective of real-world expectations are the third class of studies, the pharmacoeconomic analyses of outcome/observational studies. The 2 best ones were that of my own group¹³ and by Tillman et al.¹⁴ Both were done in a managed care setting and both found remarkably similar results. We found about \$2500 of cost savings per patient when using prefilled syringes of LMWH¹³ and Tillman et al¹⁴ found approximately \$2800 of cost savings per patient. We were comparing mostly outpatient LMWH (enoxaparin) and inpatient unfractionated heparin.

AJMC: *What are the main keys to the success of this program?*

Dr. Spyropoulos: There are 4 major determinants of successful implementation of an outpatient DVT treatment program. The first is the use of protocols using LMWH with patient-selection criteria and risk-stratification strategies, whether explicit or implicit. The second is a dedicated anticoagulation management service or equivalent, with home health service support. The third is a single physician or group of physicians who have developed expertise using LMWH. The fourth and last is a data-tracking system.

AJMC: *When did you implement this program and what have the results been to date?*

Dr. Spyropoulos: The program was implemented in March 1997. The published results, from March 1997 to August 1998, reflect our experience with 102 patients. We found an approximately 0%

major bleeding rate and a 1.9% DVT recurrence rate. From that experience, I can say that since March 1997 we have treated approximately 400 patients with our outpatient DVT program, and we have had a major bleeding rate of less than 1% and a DVT recurrence rate of less than 3%.

AJMC: *How does Lovelace Health System's experience with LMWH for the treatment of DVT compare with that of other centers?*

Dr. Spyropoulos: It has more stringent and explicit clinical and psychosocial exclusionary risk factors. We therefore have slightly reduced eligibility compared with other centers. Our eligibility is approximately 60%, whereas other centers have eligibility of more than 75%, according to their published data. However, to date we have had excellent clinical outcomes. What we have found is that our patient bed-day rate with our outpatient DVT program went from an average of 5.3 to 0.79 days.

Future Directions

AJMC: *It has been said that optimum dosing and duration of prophylaxis remain uncertain and that the true cost of prophylaxis will not be known until we have a better sense of what they are. Do you agree?*

Dr. Spyropoulos: Yes, I agree. The main thing is we have the PRIME (Prevention of Thromboembolism in Medical Patients with Enoxaparin)²¹ and PRINCE (Thromboembolism Prevention in Cardiopulmonary Diseases with Enoxaparin)²² studies. We also now have the MEDENOX (Prophylaxis of VTE in Medical Patients with Enoxaparin) study, or Samama et al study.²³ The one thing that these studies show is that there are a priori defined high-risk groups among medical patients who are in need of pharmacologic prophylaxis. Indeed, the MEDENOX study showed a 66% reduction in proximal DVT occurrences at study day 110, with statistically significant differ-

ences when comparing enoxaparin 40 mg once daily to placebo.²³ There were also no statistically significant differences between major bleeding rates and thrombocytopenia rates. Although there were no statistically significant differences between the 2 groups in mortality, the mortality curves by day 110 seem to indicate a trend toward reduction in mortality in the 40-mg enoxaparin group. Further randomized controlled trials (ie, Level 1 studies) need to be done in the areas of dosing and prophylaxis.

AJMC: *Theoretically speaking, identifying at-risk patients could eliminate the occurrence of DVT. Do you think this is an area that should be studied more extensively?*

Dr. Spyropoulos: Yes. What we need to have is better explicit risk-stratification schemes. We need better identification of patient risk factors and more explicit risk-benefit strategies using pharmacologic prophylaxis—that is, the reduction of DVT recurrence versus the risk of bleeding with these therapies—and in general, better epidemiologic data.

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