Deep vein thrombosis outcome and the level of oral anticoagulation therapy

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Objective: **The purpose of this study was to assess the rate of deep vein thrombosis (DVT) resolution and DVT outcomes as functions of the level of oral anticoagulation therapy achieved with warfarin.**
Methods: **In 33 consecutive patients, a series of 35 limbs with acute symptomatic DVT was followed throughout 1 year of anticoagulation therapy. All the patients underwent 5 days of intravenous unfractionated sodium heparin therapy that was adjusted in dose to prolong the activated thromboplastin time to 2.0 to 2.5 times the control. In addition, warfarin was administered for a period of 6 months, with a target international normalized ratio (INR) between 2.0 and 3.0. All the patients underwent venous duplex scanning and physical examination at the time of diagnosis and at 1 week, 1 month, 3 months, 6 months, and 1 year.**
Results: **At the end of the 1-year study period, the rate of complete DVT resolution was 68%. The median INR values in patients with complete DVT resolution were significantly higher than those of patients with incomplete DVT resolution after 1, 3, and 6 months of treatment with warfarin. In addition, the proportion of patients with INR values below therapeutic range was significantly higher in patients with incomplete DVT resolution than in patients with complete DVT resolution after 1, 3, and 6 months of treatment with warfarin. The presence of occlusive thrombi was associated with incomplete DVT resolution. Of the patients with occlusive thrombi, 62% had chronic venous insufficiency symptoms develop, whereas only 11% of the patients with nonocclusive thrombi ($P = .003$) had these symptoms develop.**
Conclusion: **Despite 6 months of oral anticoagulant therapy, almost one third of thrombi did not resolve completely. The INR values were significantly higher in those patients with complete DVT resolution. These results suggest that the maintenance of an INR level between 2.0 and 3.0 throughout oral anticoagulation therapy will minimize the rate of incomplete DVT resolution. (J Vasc Surg 1999;30:805-12.)**

During the last decade, the administration of heparin followed by oral anticoagulation therapy for a period of 3 to 6 months has been established as the standard treatment of lower extremity deep vein thrombosis (DVT). Traditionally, the main objectives of DVT treatment have been the prevention of death from pulmonary embolism, the reduction of morbidity from an acute event, and the minimizing of recurrences. In recent years, interest in the prevention of long-term post-thrombotic sequelae has increased because of the expanding awareness of their impact on patient quality of life and their considerable drain of health care resources.

The factors that influence the long-term clinical outcomes of DVT are not completely understood. A number of studies have shown that between 30% and 80% of patients with acute DVT will have symptoms of post-thrombotic syndrome (PTS) develop between 3 and 13 years after the initial diagnosis.[1-6] The development of chronic venous insufficiency (CVI) associated with PTS has been related to residual vein obstruction and the presence of reflux caused by valvular incompetence. In fact, approximately 30% to 50% of DVT are not completely resolved 6 to 12 months after diagnosis.[7-10] Currently, it is not possible to predict which patients will undergo complete resolution after an acute DVT or which patients will have PTS develop.

A correlation between the time needed to achieve

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Presented at the Eleventh Annual Meeting of the American Venous Forum, Dana Point, Calif, Feb 18–21, 1999.
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0741-5214/99/$8.00 + 0 **24/6/100917**

the lower limit of the activated partial thromboplastin time (aPTT) during heparin therapy and recurrent DVT has been recently documented by Hull et al.[11] However, there have been no recent studies that investigated a possible correlation between the international normalized ratio (INR) levels achieved with warfarin therapy and either DVT resolution or the development of PTS symptoms.

In this study, we prospectively assessed with serial venous duplex scanning (VDS) the degree and rate of DVT resolution during a 1-year period and correlated INR values at different time intervals with DVT outcomes.

METHODS

A series of 57 consecutive patients (22 women, 35 men) in whom acute DVT of the legs was diagnosed with duplex ultrasound scanning in our vascular laboratory were asked to participate in the study. The mean age was 65.2 ± 10.3 years (range, 45 to 87 years). The patients were referred by the physicians who were responsible for their DVT treatment. The protocol and consent forms both were approved by the hospital Institutional Review Board.

All the patients underwent 5 days of standard intravenous unfractionated heparin treatment adjusted in dose to prolong the aPTT between 2.0 and 2.5. After the fifth day of heparin therapy, oral sodium warfarin was initiated and continued for at least 6 months, adjusted in dose to achieve an INR level between 2.0 and 3.0. At presentation and during subsequent visits for each patient, an experienced vascular technologist filled out a questionnaire that included signs and symptoms of both DVT and PTS.

VDS was performed at patient presentation and at 1 week, 1 month, 3 months, 6 months, and 1 year thereafter. A color-coded high definition scanner (Ultramark 9 HDI, Advanced Technology Laboratories, Bothell, Wash) with a 5-MHz pulsed Doppler scan was used for all VDS. The patients were placed supine in a 10-degree to 20-degree reverse Trendelenburg position for the examination of common and superficial femoral veins. The popliteal, posterior tibial, anterior tibial, gastrocnemius, and peroneal veins were examined with the leg in a dependent position. Thrombi that extended to the popliteal, superficial femoral, common femoral, or iliac veins were reported to be proximal, and thrombi that were restricted to the calf veins (posterior tibial, gastrocnemius, soleil, peroneal, and anterior tibial) were considered to be distal. All the veins were imaged in longitudinal and transverse planes. The criteria that were indicative of DVT included absence of both spontaneous and augmented flow, presence of intraluminal echogenic material, partial or total inability to compress vein with gentle probe pressure, and dilation of the thrombosed vein. The approximate percentage of the venous lumen occluded by the thrombus was calculated and the outcomes were divided into the following four categories: worsening, no change, improvement, or complete resolution. Worsening indicated extension of the clot to other previously unaffected venous segments. No change was reported if the thrombus remained confined to the same venous segment without reduction in its size and with no recanalization. Improvement indicated signs of recanalization without complete compressibility of the venous segment with the duplex scan probe or reduction in the clot size as compared with a previous scan. A clot was considered to be completely resolved when the venous segment was fully compressible by the probe and there was complete disappearance of any echogenic intraluminal filling defect.

Statistical analysis consisted of the calculation of the average and standard deviation for normally distributed variables and the calculation of the median and 25% to 75% interquartile ranges for variables that did not pass a normality test. Accordingly, the INR results, which were not normally distributed, were compared with a nonparametric test (Mann-Whitney rank sum test). The proportions were compared with the χ^2 test or the Fisher exact test when appropriate. All the tests were two-sided, and a probability of .05 was considered to be significant.

RESULTS

Of the 57 patients who initially were recruited to participate in the study, three declined to participate, 13 dropped out during the study, five had incomplete INR data, and three died of causes other than pulmonary embolism before the completion of the 1-year follow-up period. Therefore, a total of 33 patients (17 men, 16 women) completed the study. The patients who were excluded from the analysis because of incomplete INR follow-up information were similar to the patients who were included in the study with regard to: average age at presentation (65 6 10 years and 56 6 18 years, respectively; $P = .07$), rates of proximal DVT (86% and 89%, respectively; $P = 1$) and occlusive DVT (48% and 37%, respectively; $P = .56$), and the rate of complete DVT resolution (44% and 68%, respectively; $P = .21$). Two patients had bilateral DVT, so there were 35 legs with DVT suitable for analysis. The average age of the patients was 65.9 ± 12.3 years (range, 45 to

Table I. Demographic and clinical factors at the time of deep vein thrombosis diagnosis in relation to deep vein thrombosis outcome

	Resolution (n = 22)	*Nonresolution (n = 11)*	*P value*
Age (years)	65 ± 12	67 ± 8	.13*
Male sex	10 (45%)	6 (54%)	.72†
Cancer	5 (22%)	2 (18%)	1.00†
Totally occlusive DVT	7 (32%)	9 (83%)	.01†
Proximal DVT	17 (77%)	11(100%)	.14†
Distal DVT	5 (23%)	0 (0%)	.14†
Target aPTT within 24 hours	13 (59%)	4 (36%)	.29†

DVT, Deep vein thrombosis; *aPTT,* activated partial thromboplastin time.
*Independent *t* test.
†With χ^2 test or Fisher exact test.

82 years). No bleeding complications were encountered during the study period. During the first 24 hours of heparin therapy, 52% of the patients had aPTT values within the target range (2.0 to 2.5 times control). Seven patients underwent extended oral anticoagulation therapy for 1 year (three in the nonresolution group and four in the resolution group; $P = .67$). Otherwise, all the patients underwent 6 months of warfarin therapy.

At presentation, 18 thrombi (51%) completely occluded venous lumens. Regarding distribution within the leg, 11 clots (31.4%) were proximal without calf extension, 19 (54.2%) extended above and below the popliteal vein, and five (14.3%) were limited to the calf.

The proportion of patients with complete DVT resolution on VDS was 6% (2 of 33) at 1 week, 15% (5 of 33) at 1 month, 39% (13 of 33) at 3 months, 70% (23 of 33) at 6 months, and 70% at 1 year. There were no symptomatic DVT recurrences in veins that had clot resolution during the follow-up period. However, two patients were found to have progression on their 1-week and 3-month scans, with incomplete DVT resolution at 1 year. Of the limbs with nonocclusive DVT, 83% had complete resolution as opposed to only 38% among those with occlusive thrombi ($P = .01$). On the other hand, there were no statistically significant differences regarding DVT outcomes of proximal and distal thrombi at 1 year ($P = .14$). Eight patients had a history of previous DVT: four in the complete resolution group (17.4%) and four in the partial resolution group (33.3%; $P = .4$). Accordingly, 50% (4 of 8) of the limbs with previous DVT resolved as compared with 70.3% (19 of 27) in those patients without a history of DVT ($P = .4$). Of the two patients with bilateral thrombi, one had incomplete resolution in both limbs at 1 year and the other had complete DVT resolution in one limb and partial resolution in the contralateral limb. The limb with complete resolution had a totally occlusive thrombus on presentation that affected the posterior tibial and popliteal veins. The limb with partial resolution had a totally occlusive thrombus that extended from the calf to the common femoral vein.

Table I compares the presence of a number of factors at the time of DVT diagnosis as a function of final outcome. The only factor that was significantly more prevalent in legs with incomplete DVT resolution was the presence of occlusive thrombus on presentation.

Table II details the median and 25% to 75% interquartile range INR values initially and during the follow-up period according to complete thrombus resolution. The patients with complete DVT resolution had significantly higher INR values than did the patients with partial resolution after 1, 3, and 6 months of treatment. No significant differences in INR values were observed during the first week of warfarin treatment.

The proportion of patients with subtherapeutic INR values (<2.0) was significantly higher in the group of patients with incomplete DVT resolution at 1, 3, and 6 months after the initiation of treatment (Table III). The INR values were not significantly different throughout the study follow-up period regarding proximal thrombi or complete vessel occlusion at the time of DVT diagnosis (Tables IV and V).

One year after DVT diagnosis, deep vein reflux was detected in 25% of the limbs and PTS symptoms were reported by patients in 31% of the affected limbs. In patients with occlusive thrombi, 62.5% had symptoms of CVI develop that were suggestive of PTS versus 11% among those patients with nonocclusive thrombi ($P = .003$). The prevalence of CVI symp-

Table II. Results of serial prothrombin time tests expressed as international normalized ratio values (median and 25% to 75% interquartile ranges) in relation to deep vein thrombosis outcome

	INR results				
Outcome	*Initial*	*1 week*	*1 month**	*3 months**	*6 months†*
Resolved DVT	1.1 (1.0 to 1.2)	2.2 (1.6 to 2.5)	2.3 (2.0 to 2.8)	2.0 (1.7 to 2.5)	2.2 (1.8 to 2.5)
Not resolved DVT	1.1 (1.0 to 1.2)	1.8 (1.2 to 2.9)	1.5 (1.2 to 1.8)	1.6 (1.2 to 1.8)	1.6 (1.5 to 1.9)

INR, International normalized ratio; *DVT,* deep vein thrombosis.
* $P < .01$ with Mann-Whitney test.
† $P < .05$.

Table III. Proportion of patients with international normalized ratio results less than 2.0, between 2.0 and 3.0, and more than 3.0 in relation to deep vein thrombosis outcome

	INR < 2.0		*INR 2.0 to 3.0*		*INR > 3.0*	
	Resolved	*Nonresolved*	*Resolved*	*Nonresolved*	*Resolved*	*Nonresolved*
Initial	100% (22/22)	91% (10/11)	4% (1/22)	0% (0/11)	0% (0/22)	0% (0/11)
1 week	41% (9/22)	54% (6/11)	60% (13/22)	54% (6/11)	4.5% (1/22)	0% (0/11)
1 month	23%* (5/22)	82%* (9/11)	60% (13/22)	27% (3/11)	18% (4/22)	0% (0/11)
3 months	50%* (11/22)	91%* (10/11)	50% (11/22)	18% (2/11)	4.5% (1/22)	0% (0/11)
6 months	32%* (7/22)	82%* (9/11)	64%* (14/22)	9%* (1/11)	4.5% (1/22)	18% (2/11)

INR, International normalized ratio
* $P < .05$ with Fisher exact test.

Table IV. Results of serial prothrombin time tests expressed as international normalized ratio values (median and 25% to 75% interquartile ranges) in relation to proximal or distal deep vein thrombosis on presentation

	INR results				
Outcome	*Initial*	*1 week*	*1 month**	*3 months*	*6 months*
Proximal DVT	1.2 (1.2 to 1.2)	2.1 (1.3 to 2.4)	2.0 (1.6 to 2.3)	1.8 (1.5 to 2.2)	1.9 (1.6 to 2.5)
Distal DVT	0.9 (0.9 to 0.9)	2.2 (1.8 to 2.5)	2.8 (2.2 to 2.9)	2.1 (1.2 to 2.2)	2.5 (1.8 to 2.6)

INR, International normalized ratio; *DVT,* deep vein thrombosis.
* $P < .05$ with Fisher exact test.

toms was not significantly different between patients with proximal (34%) or distal (40%) DVT ($P = 1.0$). The most prevalent symptoms of PTS were leg edema (28.6%) and tenderness (20%). None of the patients had venous ulceration develop during the study period. The INR results were not significantly different during the follow-up period between patients who did and did not have CVI symptoms develop (Table VI). The only exception occurred in the comparison of patients with nontherapuetic INR levels and occlusive thrombi with patients who had at least two therapeutic INR levels and nonocclusive thrombi in which CVI symptoms developed in 67% (4 of 6) and 6% (1 of 16) of the patients, respectively ($P = .009$).

DISCUSSION

Most deep veins recanalize by a process of clot lysis and retraction during the first year after an episode of acute DVT. However, a significant number of thrombi remain unchanged or undergo only partial resolution. Symptomatic chronic venous disease characteristic of PTS results from persistence of obstruction to flow and from reflux caused by venous valvular incompetence.

Duplex ultrasound scanning is a useful tool for the assessment of DVT outcome. Recanalization, retraction, development of collaterals, and presence of valvular incompetence and reflux are clearly shown with this noninvasive technique. In addition to pro-

Table V. Serial prothrombin time tests expressed as international normalized ratio (median and 25% to 75% interquartile ranges) in relation to vessel occlusion at the time of deep vein thrombosis diagnosis

	INR results				
Outcome	*Initial*	*1 week*	*1 month**	*3 months*	*6 months*
Occlusive DVT	0.9 (0.9 to 0.9)	2.1 (1.4 to 2.4)	1.8 (1.4 to 2.2)	1.9 (1.4 to 2.1)	2.0 (1.6 to 2.5)
Nonocclusive DVT	1.2 (1.2 to 1.2)	2.2 (1.3 to 2.5)	2.3 (1.9 to 2.6)	1.7 (1.5 to 2.4)	2.0 (1.6 to 2.6)

INR, International normalized ratio; *DVT*, deep vein thrombosis.
**P* < .05 with Mann-Whitney test.

Table VI. Serial prothrombin time tests expressed as international normalized ratio (median and 25% to 75% interquartile ranges) in relation to symptoms of chronic venous insufficiency 1 year after deep vein thrombosis diagnosis

	INR results				
Outcome	*Initial*	*1 week*	*1 month**	*3 months*	*6 months*
No CVI symptoms	1.2 (1.2 to 1.2)	2.2 (1.3 to 2.4)	1.8 (1.5 to 2.4)	1.8 (1.5 to 2.3)	2.2 (1.7 to 2.5)
CVI symptoms	0.9 (0.9 to 0.9)	2.0 (1.4 to 2.5)	1.8 (1.4 to 2.1)	2.0 (1.5 to 2.2)	1.8 (1.4 to 2.4)

INR, International normalized ratio; *CVI*, chronic venous insufficiency.
P <.05 with Mann-Whitney test.

viding essential information on venous function, duplex ultrasound scanning can reveal the exact location of thrombi and valvular insufficiency, making it a valuable tool for the diagnosis of PTS.[12-16]

Recently, a number of studies have assessed the outcome of lower extremity DVT with serial duplex testing.[8-10,15,17-21] Although these studies reported different rates of clot resolution and development of reflux, most of them showed that recanalization is not as slow as was previously suggested and that reflux occurs in more than half of the legs with DVT. This study revealed that only 68% of thrombi undergo complete resolution within 1 year of DVT diagnosis. The most significant changes regarding DVT outcome occurred by the third month examination, and few changes occurred between the sixth and the 12th month examination. Similar results were reported by Murphy and Cronan,[8] who found that thrombus resolution, if recanalization of vein thrombi were to occur, should be evident within 6 months of the diagnosis of DVT. A different study found complete recanalization of almost all thrombosed vein segments at 1 year.[15]

Our results indicate that thrombi that completely occlude the venous lumen are associated with incomplete DVT resolution. Different results were provided by van Ramshorst et al,[9] who did not find differences in DVT regression in partially or totally occluded vessels. Regarding location of thrombi, we did not find a higher proportion of proximal DVT in patients with incomplete clot resolution as did Lea-Thomas and McCallister[22] or a faster recanalization rate among cases with distal DVT as did Franzeck et al.[6] Therefore, our results agree with the results of other investigators who have found no difference in resolution rates between different venous segments.[8,23]

In this study, early adequate anticoagulation therapy did not correlate with complete DVT resolution at 1 year because the INR levels in the first week of treatment were similar in patients with complete or incomplete thrombus resolution (Table II). Similarly, other investigators have reported no difference in early propagation of thrombi[24] or even thrombi extension[25] despite early therapeutic levels of anticoagulation therapy. Perhaps the recommended aPTT range (2 to 2.5 times control) is not as adequate as suggested because it seems to have little influence on the improvement of long-term outcomes in patients with DVT. On the other hand, a recent analysis of three trials has documented a significant association between early achievement of therapeutic aPTT and recurrent DVT.[11] In our study, however, we were more interested in the correlation of long-term oral anticoagulation therapy and DVT outcomes. Indeed, after the first month of treatment and at the 3-month and 6-month follow-up periods, the patients with complete resolution

had significantly higher INR values than did the patients without complete DVT resolution.

Recent studies have correlated DVT outcome with the degree of plasma fibrinolytic activity. Arcelus et al[10] reported higher levels of plasminogen activator inhibitor in patients with incomplete resolution. Similarly, Killewich et al[26] have reported significant enhancement of endogenous fibrinolysis, mediated by increased tissue plasminogen activator during thrombus regression.

Our results show that 62% of patients with occlusive thrombi had CVI symptoms develop as opposed to 11% in patients with nonocclusive thrombi (P = .003). Almost two thirds of the patients with a combination of subtherapeutic INR levels and occlusive DVT had CVI symptoms develop. On the contrary, only 6% of patients with INR levels within the desired range had CVI symptoms develop. Similar to other studies, we did not find an association between the location of the DVT on presentation and the subsequent development of CVI symptoms.[3,20] These results indicate that the degree of occlusion caused by the thrombi may have more influence on the long-term DVT outcomes than the location of the thrombi. This issue remains controversial because some authors have found a more benign outcome in DVT located distal to the knee,[6,15,27] whereas others have reported a correlation between patent and competent veins in the calf and favorable outcome.[1]

In conclusion, in this preliminary study, we have reported that two thirds of DVT resolve within 1 year of diagnosis and almost one third of the cases have symptoms develop that are suggestive of PTS. A number of factors, including vessel occlusion caused by thrombi and the level of oral anticoagulation therapy, have been found to be associated with DVT outcome 1 year after diagnosis. We agree with van Ramshorst et al[9] that serial duplex scanning has enormous potential for the assessment of DVT outcome, which may allow for the improved identification of patients with poor prognoses, a better definition of their clinical management, and a reduction in their risk of the development of CVI. Further studies with a larger number of patients and a longer period of follow-up examination are necessary to establish a stronger correlation between the level of oral anticoagulation therapy achieved 3 to 6 months after acute DVT and long-term outcomes, such as DVT resolution and the development of PTS.

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Submitted Feb 23, 1999; accepted Jun 3, 1999.

DISCUSSION

Dr D. Eugene Strandness, Jr (Seattle, Wash). I had the opportunity of reviewing this manuscript, and there are some interesting facts that have emerged from this study. We all recognize that different investigators in the past few years have shown us that there are issues that we should be dealing with in the long-term follow-up and treatment of patients with deep venous thrombosis. We know there is some element of lysis, fragmentation, and retraction of the thrombus that regularly occurs after an episode of deep vein thrombosis. The extent to which this occurs is variable and is influenced by factors that are not completely understood. What are some of these factors? The patient's own lytic system is obviously important. The extent of the thrombosis is obviously important. And, of course, the key point in this study is the level of anticoagulation attained with both heparin and warfarin therapy.

Our studies have shown that thrombus stability is clearly affected by the level of anticoagulation, particularly when heparin is used in the early phase of the therapy. In fact, we have a paper coming out in the Journal of Vascular Medicine that will show that a good share of the time with unfractionated heparin thrombus extension occurs even though you may think that your patient is adequately anticoagulated.

Warfarin therapy has shown, at least in our studies, that progression and extension of existing thrombi is not uncommon. However, we did not prospectively look at the international normalized ratio (INR) levels as was done in this study. It appears that this is a factor and further substantiates how important this management is in our patient follow-up. This study has shown that level of thrombus lysis is not only dependent on the level of the INR but also on the thrombus load. This would appear to make good sense, and I cannot see any major flaws in this study. The proportion of those patients with an INR between 2 and 3 was significant at only 1 month. However, even given these results, they were not predictive of clinical outcome, which is a bit disappointing. In other words, what is the relevance of the finding that was reported in this study?

As we suspect, the use of low–molecular weight heparin therapy may encourage thrombus stability during the acute phase of therapy. However, we have a drug now that appears to provide us with a stable thrombus in the first 5 days, but we have warfarin, which may not do as well in the long term. I frankly believe that warfarin therapy is equally as difficult as unfractionated heparin therapy, and I think that this study clearly has shown this.

I wonder if Dr Caprini would answer the following questions and perhaps speculate a bit on the future. Do you think that the failure to correlate outcome with INR is a matter of numbers? Do you think that a larger study is in order to examine this problem in some depth? I think this is probably realistic given the fact that we now realize that extension and rethrombosis may be a more common problem than we anticipated. Is it possible with the new interest in low–molecular weight heparin therapy that we will soon be looking at a new oral anticoagulant, an oral agent that may accomplish what we fail to do with warfarin? And then finally, what is the role perhaps of long-term therapy with low–molecular weight heparin if one were to discount the cost involved? I think Dr Hull suggested that there is a study going on in this country with low–molecular weight heparin therapy up to 10 months. I wonder, Dr Caprini, if you have any ideas how this might be implemented.

I want to thank the Society for the privilege of addressing this paper. It was well done. Thank you very much.

Dr Joseph A. Caprini. Thank you very much, Dr Strandness. It was an honor to have you comment on this paper, and I am happy I am still standing.

First of all, for your findings as far as thrombus extension, we have seen that as well. I think that it indicates there are some shortcomings with monitoring unfractionated heparin that result in thrombus extension.

As far as clinical outcomes, the study is too small. I really think that this should be just a stimulus to all of us, and I also agree that warfarin has shortcomings. I think we all need to get some of the finest vascular laboratories, of which you are an excellent example, to pool their results in a prospective analysis of this problem with significant numbers. Is this really true? Is it not really true? It looks like it is worth trying to do in any event.

Low–molecular weight heparin, a very interesting compound, as you know, not only has a specificity for factor X_{19}/antithrombin-3 complex, but it has been shown to decrease the von Willebrand factor. Heparins stimulate the fibrinolytic system. They have an affect on IIB/IIIa, a step in platelet aggregation that provides anticoagulant therapy. And, if you take a look at the trials, total hips, total knees, where warfarin or oral anticoagulants have been pitted against low–molecular weight heparin, in every single case, low–molecular weight heparin has come out statistically significantly better.

The only question is whether those clots that they are preventing are really important long term. So, my point is that I agree with you 100%. I think that now that we have low–molecular weight heparin, we have to establish what is going on with the standard warfarin therapy, but we need a prospective randomized trial in which we use it initially and convert to warfarin and we also use it completely for the entire treatment period. It is my bias on the basis of some of those hematologic things that I have said. There are a number of heparins that have shown promise in the cancer patient, and I think this is worth a full and complete trial.

Dr John J. Ricotta (Stony Brook, NY). Dr Caprini, I enjoyed your presentation. You associated two factors with good long-term results. One was incomplete occlusion of the vein wall, and the other was the INR. Was the INR association independent of the complete versus incomplete thrombosis, or were your numbers too small to tell?

Dr Caprini. That is an excellent question. I think, as Dr Strandness pointed out, that the outcomes are related to the clot load—there is no question about that—and I think the outcomes are also related to the level of anticoagulation. Now we do not have enough numbers to know whether they are independent, but my bias is that warfarin therapy is inferior for this. One of the reasons for this may even be that, as physicians, we all tend to underdose our patients. I do not say that without a tremendous respect. I know that for years I have been treating lots of patients and really sort of poo-pooing the bleeding problem. Then, within 1 month, I had two deaths with perfect INRs, everything followed to the letter, so that I think it is a very dangerous situation here with this drug and it is a very complex interrelationship between those two factors. I think it would take a bigger study to sort it out, but I think that the question you ask must be answered.

Dr Ricotta. The second question I have is: if you go ahead with a larger study, would you anticipate doing any sort of screening for coagulation disorders or fibrinolytic disorders? If so, what would you plan to look at in these patients?

Dr Caprini. Another wonderful question that brings up a whole host of other issues. First of all, if I were designing the study, I would do their leiden status, prothrombin 2021A, and homocystinemia because they are three congenital defects and when the one is positive the other two may be positive. As you know, with the leiden defect, 20% of people with a history of thrombosis will test positive, so it is well worth doing. So, I would do that, but I think I would blind it because we do not know what to do with leiden-positive patients. So, I would not muddy the waters with that.

To answer the second part of your question, we had presented for this society previously that there was a fibrinolytic shutdown in certain patients that we could document on the 1-day blood draw that we could correlate with nonresolution at 1 year. In future studies, I would do a more extensive analysis of the fibrinolytic system, and blind those data until 1 year to see what those data would show in terms of the eventual outcome of the thrombus.

Dr David S. Sumner (Springfield, Ill). Instead of taking resolved clots and telling what the average INR was, could you turn the data around the other way and tell us what proportion of clots resolved when the INR was greater than 2 versus what proportion of clots resolved when it was less than 2? In other words, look at the data in the opposite direction.

Dr Caprini. I am going to have to think about that. I am not sure that I know my numbers perfectly. My bias is that the INRs are much better when the clots resolve, but I would have to think about that question.