Clinical Trials That Have Influenced the Treatment of Venous Thromboembolism: A Historical Perspective

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In 1960, Barritt and Jordan performed the first randomized trial demonstrating the efficacy of anticoagulant therapy in the treatment of venous thromboembolism. Since then, important therapeutic advances have been made in the treatment of deep venous thrombosis and pulmonary embolism. This paper reviews the important clinical trials involving anticoagulant therapy and vena caval interruption. The studies are discussed from a historical perspective, and an attempt is made to analyze both the thought processes that prompted their design and the reasons why they changed practice.

Ann Intern Med. 2001;134:409-417. www.annals.org

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The first randomized trial of treatment of venous thromboembolism (deep venous thrombosis or pulmonary embolism) was done in 1960 (1). Since then, impressive gains have been made in placing treatment of venous thromboembolism on firm scientific footing. Pivotal clinical trials have studied the optimal therapeutic range and duration of anticoagulant therapy with heparin and warfarin (2, 3). Low-molecular-weight heparin (LMWH) has been introduced and has revolutionized venous thromboembolism therapy (3, 4). Several new anticoagulants with theoretical advantages over existing agents have entered phase III studies in patients with venous thrombosis. After years of descriptive studies, a randomized trial has identified some of the limitations and benefits of vena caval interruption (5). Because progress in the rational use of thrombolytic therapy and surgical interventions for the treatment of venous thromboembolism has lagged behind progress seen with anticoagulant therapy, we confine our discussion to anticoagulant therapy and vena caval interruption (**Table**).

In this paper, studies that have changed the treatment of venous thromboembolism are considered from a historical perspective, with emphasis on the thought processes that led to the studies' design and their impact on patient care. Studies are presented not in chronologic order but by treatment method: injectable and oral anticoagulants and vena caval interruption.

Injectable Anticoagulants

Heparin for Initial Venous Thromboembolism Therapy

Heparin had been used to treat venous thromboembolism for more than 20 years when Barritt and Jordan performed their seminal randomized trial involving 35 patients with symptoms of acute pulmonary embolism (1). Their dramatic results, which were published in 1960, showed that intravenous heparin given in combination with an oral vitamin K antagonist reduced death and recurrence compared with no anticoagulant therapy. In justifying their study, Barritt and Jordan stated that physicians were reluctant to use anticoagulants to treat patients with suspected pulmonary embolism because they feared hemorrhage. Although this position was defensible at the time, their trial was considered unethical by Hunter and Walker (6), who wrote a letter in response that stated, "The cause of clinical trials is a good one, in season, but we fear it may be damaged by such intemperate enthusiasm for it as has been shown in this instance by Dr. Barritt and Dr. Jordan."

The study by Barritt and Jordan had a major impact on clinical practice. The benefits of anticoagulants seen in pulmonary embolism were extrapolated to deep venous thrombosis. For both disorders, the standard of care became treatment with heparin during hospitalization and a vitamin K antagonist after discharge. A notable exception was found in the Netherlands, where family practitioners occasionally treated patients with venous thrombosis at home using vitamin K antagonists. Dr. Harry Büller, a native of Amsterdam who returned to his home city in 1989 after completing a research fellowship in Canada, challenged this approach. He designed a study evaluating the need for an initial course of heparin therapy in patients presenting with deep venous thrombosis. This study demonstrated that the combined use of heparin and oral anticoagulants is

Table. **Major Advances in the Treatment of Venous Thromboembolism**

1960s	Barritt and Jordan demonstrate that anticoagulant therapy reduces death and recurrent venous thromboembolism in patients with pulmonary embolism
	The Mobin–Uddin umbrella is introduced
1970s	Recurrent venous thromboembolism is found to occur more often in patients who have subtherapeutic activated partial thromboplastin times within the first 24 hours of treatment
	The Kimray–Greenfield filter is introduced
	Low-molecular-weight heparin is discovered
1980s	Lower-intensity oral anticoagulation is shown to be as effective as but safer than high-intensity regimens
	The international normalized ratio is introduced for oral anticoagulant monitoring
1990s	4 to 5 days of initial heparin therapy is found to be as effective as 10 days
	The combination of initial heparin therapy and oral anticoagulation is demonstrated to be more effective than oral anticoagulation alone in deep venous thrombosis
	Low-molecular-weight heparin is found to be as effective as intravenous unfractionated heparin in deep venous thrombosis and pulmonary embolism
	Outpatient treatment with low-molecular-weight heparin is shown to be safe and effective
	It is recognized that patients with idiopathic venous thromboembolism are at higher risk for recurrence than those with thrombosis secondary to transient risk factors
	A randomized trial demonstrates that inferior vena caval filters increase the long-term risk for recurrent venous thrombosis and do not reduce long-term mortality rates in patients who receive 3 months of anticoagulant therapy
2000	Designer anticoagulants are compared with established anticoagulants

more effective than oral anticoagulants alone in patients with venous thrombosis (7).

Optimizing Heparin Therapy: Dose and Therapeutic Range

Substantial energy was expended throughout the 1970s, 1980s, and early 1990s to establish the starting dose and therapeutic range of heparin. Although both issues continue to be debated today, they are less important because LMWH is replacing heparin for the treatment of venous thromboembolism.

Two studies published 14 years apart, in 1972 (8) and 1986 (9), reported that risk for recurrence was higher in patients with activated partial thromboplastin times less than 1.5 times the control value early in treatment than in patients with activated partial thromboplastin times greater than 1.5 times the control value. These studies had only a modest impact on clinical practice, probably because the first was a cohort study and the second was a subgroup analysis of a randomized, controlled trial. It was not until 1993, when Raschke and colleagues published a randomized trial comparing their standard starting heparin infusion rate of 1000 U/h with a higher weight-adjusted dose (10), that the inadequacy of this rate was clearly demonstrated. The study by Raschke and colleagues showed that recurrent venous thromboembolism was less common in patients who received the higher heparin dose. The importance of achieving a therapeutic activated partial thromboplastin time within the first 48 hours has subsequently been called into question by the results of a meta-analysis (11).

Duration of Heparin Treatment

For many years, it was standard practice to delay the initiation of warfarin therapy for 3 or 4 days and to administer heparin for approximately 10 days. The rationale for this approach was based on an observation made in the 1950s. Wessler and associates noted that the antithrombotic effect of warfarin in a rabbit model of jugular venous thrombosis was delayed for 7 days after initiation of therapy (12). Because this approach often delayed hospital discharge and was supported by only meager evidence, two groups (one from McMaster University in Canada and the other from Flinders University in Australia) decided in the late 1980s to compare the standard duration of heparin treatment with a shorter course (13, 14). Both randomized studies reported that treatment with 4 to 5 days of heparin was as effective as the standard 9- to 10-day course. These findings had a marked impact on clinical practice. In addition to reducing the length of hospital stay, the shorter heparin course also led to a reduction in the risk for heparin-induced thrombocytopenia, a severe complication of heparin therapy that usually requires at least 5 days of heparin exposure to manifest (15).

LMWH Therapy

The introduction of LMWH in the 1980s revolutionized the early treatment of venous thromboembolism by simplifying dosing and administration. Like many other important discoveries in medical science, the early development of LMWH was prompted by observations that, in retrospect, contribute little to its advantages over heparin. The first observation, that LMWH has reduced anti-IIa activity relative to anti-Xa activity, was made by groups in the United Kingdom

and Sweden (16, 17). The second observation, that LMWH has a more favorable benefit-to-risk ratio than heparin in laboratory animals, was made at McMaster University (18, 19). We now know that LMWH has advantages over heparin mainly because it exhibits less nonspecific binding to cationic proteins and cell surfaces as a result of its lesser negative-charge density (20–23, Manson L, Rischke J, Weitz J, Young E, Hirsh J. Comparison of the effect of experimental endo toxaemia on the pharmacokinetics and pharmacodynamics of low-molecular-weight heparin with unfractionated heparin. In preparation). These reduced binding properties were identified more than 10 years after the anticoagulant was developed and had not been reported when clinical programs evaluating LMWH for prophylaxis of venous thromboembolism were well under way. However, they are responsible for LMWH's predictable dose–response relationship (4, 20, 22, 23), which obviates the need for laboratory monitoring (24, 25), and its longer plasma half-life, which allows once-daily administration by subcutaneous injection (26, 27). Compared with heparin, LMWH preparations are also associated with lower risks for heparin-induced thrombocytopenia (28) and heparin-induced osteoporosis (29); these properties probably reflect reduced binding of LMWH to platelet factor IV (30) and osteoclasts (31), respectively.

Clinical Studies

Although LMWH preparations had been shown to be effective for the prevention of venous thromboembolism, their most important advantage was not recognized until Scandinavian and French investigators (32, 33) took the bold step of evaluating weight-adjusted, fixed-dose LMWH for the treatment of venous thrombosis. The decision to dispense with laboratory monitoring was empirical because detailed pharmacodynamic studies had yet to demonstrate the predictable dose–response relationship of LMWH. These pilot studies prompted two large clinical trials, which demonstrated that weight-adjusted subcutaneous LMWH is at least as effective and safe as laboratory-monitored intravenous heparin in hospitalized patients with deep venous thrombosis (26, 34).

Capitalizing on the fact that laboratory monitoring was not needed, two randomized studies (one from Canada and the other from the Netherlands) (35, 36) demonstrated in the early 1990s that in patients with deep venous thrombosis, subcutaneous LMWH administered out-of-hospital without laboratory monitoring is as effective and safe as continuous infusions of heparin given in-hospital with laboratory monitoring. The effect of these clinical trials has been dramatic. An audit of the experience at two of the Canadian centers published 2 years after the randomized studies showed that approximately 90% of patients referred with venous thrombosis were being treated out-of-hospital (37). The experience was similar in the Netherlands, other European countries, and an increasing number of U.S. centers. Most patients prefer to be treated at home, and the savings to the health care system are substantial (38). The experience with unmonitored subcutaneous LMWH in venous thrombosis was soon duplicated in two studies that compared LMWH with heparin in patients with acute pulmonary embolism (27, 39).

Other studies comparing heparin and LMWH for the treatment of venous thromboembolism have since been performed. In addition, Gould and colleagues' meta-analysis of 11 randomized studies (40), published in 1999, showed that unmonitored subcutaneous LMWH is at least as effective and safe as heparin administered by continuous intravenous infusion with monitoring of activated partial thromboplastin time. Of interest, although LMWH preparations have a more predictable anticoagulant response than heparin, the dose–response relationship with weight-adjusted LMWH varies in patients with thrombosis (41). It is likely, therefore, that if careful pharmacodynamic studies had been performed with LMWHs before their clinical evaluation, they would now be administered with dose adjustment guided by anticoagulant monitoring; the main advantage of LMWH would have been lost. Furthermore, although LMWH has a longer plasma half-life than heparin, careful pharmacokinetic or pharmacodynamic studies would not have predicted the success of once-daily regimens. Therefore, we are fortunate that the development of LMWH proceeded along nontraditional lines.

Several unanswered questions remain regarding the optimal use of LMWH. It is uncertain whether a weight-adjusted dosing regimen without laboratory monitoring should be used in obese patients, pregnant women, or patients with renal insufficiency. Reversal of the anticoagulant effect of LMWH with protamine sulfate is limited to molecules larger than 4000 Da.

Because many LMWH chains are smaller than this (4, 20), clinicians are unsure about the effectiveness of protamine as an antidote for LMWH. Finally, there is uncertainty about whether the different LMWH preparations in use are clinically interchangeable. This uncertainty is likely to persist until the efficacy and safety of different LMWH preparations are directly compared.

ORAL ANTICOAGULANTS

In the 1970s, initial heparin therapy was usually followed by oral anticoagulation of varying duration. A common approach was to follow the initial course of heparin with a 3-month course of warfarin in doses sufficient to produce a prothrombin time of 1.5 to 2.0. We and others believed that warfarin treatment at this intensity was associated with a high rate of bleeding. Since low-dose heparin (5000 U subcutaneously twice daily) was being used successfully for primary thromboprophylaxis (42, 43), we performed a randomized study comparing a 3-month course of warfarin targeted to a prothrombin time of 1.5 to 2.0 with low-dose heparin (44). The results, which were reported in 1979, demonstrated that warfarin was much more effective than low-dose heparin (recurrence rate, 0% vs. 47%) but produced more bleeding (24% vs. 0%). We then performed a second randomized trial that compared a higher adjusted dose of subcutaneous heparin with warfarin (45). This study showed that although both treatments were equally effective, adjusted-dose heparin produced much less bleeding than "standard" warfarin.

Optimal Therapeutic Range for Warfarin

Since oral warfarin is more convenient than parenteral heparin for long-term use, there was an urgent need to improve the safety of warfarin therapy. In the early 1980s, the results of our previously discussed randomized studies (44, 45) were presented at a hematology conference in the United Kingdom. British hematologists reacted with disbelief because they had the strong impression that their warfarin-related bleeding rates were much lower than those in our trials. It was then discovered that although the prothrombin times used in the United Kingdom and North America were the same, the average dose of warfarin in our studies was approximately 20% higher. Using the same plasma samples, we subsequently compared the prothrombin times achieved with the thromboplastin reagent used at McMaster Hospital and the British thromboplastin (provided by Dr. Leon Poller). We found that a prothrombin time of 2.0 with our local thromboplastin reagent corresponded to a prothrombin time of 5.3 with the British thromboplastin; conversely, a prothrombin time of 2.0 with the British thromboplastin corresponded to a prothrombin time of 1.3 with our reagent. Thus, we discovered that the oral anticoagulation being used to treat patients in North America was considerably more intense than that used in the United Kingdom. Who was correct?

To resolve the issue, we performed a third randomized trial in which patients with venous thrombosis receiving warfarin were assigned to a target prothrombin time of 2.0 to 3.0 using either the British reagent or the commercial reagent used at McMaster Hospital (46). The mean warfarin dosage was 5.8 mg/d in patients assigned to the commercial North American reagent and 4.9 mg/d in those assigned to the British reagent. The incidence of recurrent thrombosis was approximately 2% in both groups, but bleeding rates were more than five times higher in patients assigned to the more intense regimen (22% vs. 4%).

How did these differences in the targeted intensities between British and North American practices occur? The explanation is simple but disturbing. In the first 15 years that prothrombin time was used to monitor coumarin therapy, most laboratories worldwide prepared their thromboplastins locally using similar methods. These local thromboplastin reagents were highly sensitive to the anticoagulant effect of coumarin. In the 1970s, laboratories in the United States and Canada began to purchase their thromboplastin reagents for prothrombin time monitoring from commercial sources. These commercial thromboplastins were much less sensitive than the locally prepared reagents to reductions in the vitamin K–dependent clotting factors. Because the target prothrombin time of 1.5 to 2.0 remained unchanged when the sensitive thromboplastins were replaced with insensitive commercial reagents, an unrecognized increase occurred in the warfarin doses used to treat patients with venous thromboembolism in North America (47). In contrast, no such increase occurred in the United Kingdom because most laboratories continued to use the sensitive Manchester reagent.

In 1992, Bussey and coworkers (48) performed a survey of U.S. hospitals and reported that many labora-

tories used thromboplastins with an international sensitivity index of 1.8 to 2.7. The more sensitive thromboplastin commonly used in the United Kingdom, however, had an international sensitivity index of 1.0. Fortuitously, the discovery that less intense anticoagulation is just as effective, but much safer, than high-intensity anticoagulation occurred at approximately the same time that European investigators identified the dangers of using prothrombin time reagents with variable sensitivities. This realization prompted the development of the international normalized ratio (INR) as a means of standardizing prothrombin time reporting.

In 1982, the World Health Organization recommended that laboratories adopt the INR method. The recommendation was accepted in Europe but was opposed by influential groups in North America. At McMaster University, we began reporting the prothrombin time as an INR in 1985. Although our unilateral decision initially caused confusion, it markedly accelerated the switch from prothrombin time to INR reporting in Canada. The problem of variable sensitivities of thromboplastin reagents was highlighted in the 1986 edition of the American College of Chest Physicians–National Heart, Lung, and Blood Institute National Conference on Antithrombotic Therapy (49), and by 1992 all recommendations on anticoagulant intensity were reported by using the INR (50). A survey by the College of American Pathologists reported that implementation of the INR standard in the United States increased from 21% in 1991 to 97% in 1997 (51). The adoption of moderate-intensity anticoagulation, the INR method of reporting, and the introduction of sensitive thromboplastins (international sensitivity ratio, 1.0 to 1.4) have had a huge impact on the safety and utility of warfarin therapy, not only in patients with venous thrombosis but also in those with atrial fibrillation and those with prosthetic heart valves.

Optimal Duration of Anticoagulant Therapy after Initial Therapy

For years, it was conventional to continue anticoagulant therapy in patients with venous thromboembolism for approximately 3 months. Some clinicians preferred 6 weeks of treatment, while others favored 6 months. Patients with recurrent venous thrombosis or those with inherited or acquired thrombophilia were treated for longer periods. Early attempts to determine the optimal duration of treatment were unsuccessful because of methodologic problems (52), including inadequate sample size (53, 54), failure to use objective methods to confirm suspected recurrence (55–57), and lack of blinded outcome assessment (53–58). The results of these early studies suggested that the risk for recurrence after discontinuation of anticoagulant therapy was lower if the initial episode was associated with a reversible cause (for example, postoperative deep venous thrombosis) than if it was idiopathic (55, 59) or associated with continuing risk factors, such as malignancy (59).

In 1995, a Swedish group headed by Dr. Sam Schulman performed the first rigorously designed study addressing optimal duration of anticoagulant therapy in patients with venous thrombosis (60). Patients were randomly assigned to 6 weeks or 6 months of oral anticoagulant therapy and were followed for recurrence. The primary analysis showed that the incidence of recurrence was significantly lower in the 6-month group. A secondary subgroup analysis demonstrated that patients with reversible risk factors had a lower risk for recurrence than those with idiopathic venous thrombosis, confirming the results of previous studies. Subsequently, Kearon and coworkers (61) performed a multicenter, double-blind, randomized trial in which patients with idiopathic venous thrombosis were assigned to 3 months or 2 years of treatment with warfarin. The annual incidence of recurrence was 27% after 3 months of anticoagulant therapy and only 2% in patients who continued treatment. Although the risk for recurrence after 3 months of treatment was much higher than the 9% risk after 6 months of treatment reported by Schulman and colleagues (60), the incidence of thrombosis in both studies was reduced by more than 90% in patients assigned to long-term treatment with warfarin. The benefits of long-term treatment in both studies were offset by major bleeding rates of 3% to 4% per year, which are likely to be higher in elderly patients with several risk factors (62).

Approximately 20% of major bleeding episodes (61, 63) and 5% of recurrences (64) are fatal. Therefore, patients who have a 10% estimated annual risk for recurrence and consequently a greater than 0.5% annual risk for fatal pulmonary embolism (for example, those with an idiopathic event and those with ongoing risk factors) in association with a low risk for bleeding

should be considered for indefinite anticoagulation. In contrast, those with a very high risk for bleeding should receive anticoagulation for a limited period.

New Oral Anticoagulants

For the past 50 years, only one class of oral anticoagulant has been available for clinical use. Now, new oral thrombin inhibitors and factor Xa inhibitors have been developed, as have novel approaches to render heparin orally active. An oral thrombin inhibitor is being compared with warfarin in phase III trials in patients with venous thromboembolism. This agent is being administered in a fixed dose without laboratory monitoring, an approach that, if effective and safe, could revolutionize the way we treat patients with venous thromboembolism.

Inferior Vena Caval Interruption

Vena caval ligation was popularized by Ochsner in the 1950s. In a review published in 1960 (65), he stated that after he performed the procedure on Ben Hogan, the famous golfer went on to win tournaments. When it became clear that caval ligation is often complicated by leg swelling, the procedure was replaced by a variety of caval plications or clips designed to intercept large emboli but allow blood to flow through small channels. The modern era of percutaneous devices for caval interruption began with the introduction of the Mobin–Uddin umbrella in 1968 (66). However, the umbrella was thrombogenic, and concomitant anticoagulant therapy was required. The umbrella was replaced by the Kimray–Greenfield filter in 1973 (67). Further refinements were introduced, and Greenfield and colleagues reported low rates of pulmonary embolism or caval thrombosis in several follow-up case series (68–70). The development of the filter was an important advance because it provided a much less invasive alternative to caval plication for patients with venous thromboembolism in whom anticoagulants were contraindicated (71–73). However, the filter was sometimes overused (74). In 1998, Decousus and coworkers (5) performed the first randomized trial of vena caval interruption in 400 patients with proximal thrombosis, all of whom received anticoagulants for 3 months. Filter placement significantly reduced new pulmonary embolism by day 12; however, it was associated with a doubled risk for recurrent venous thrombosis at 2 years, indicating thrombogenicity. Thus, although caval filters can save lives, they should be used selectively because they increase risk for recurrent venous thromboembolism.

Conclusions

The practice of medicine has changed dramatically in the 41 years since Barritt and Jordan published the first randomized clinical trial involving the treatment of pulmonary embolism. Physicians are prepared to change their practice, but only when the recommended changes are based on properly designed clinical trials using clinically relevant end points. Arguably, the two most important advances in the treatment of venous thromboembolism have been the development of LMWH and the establishment of an optimal intensity for warfarin therapy. The first has increased the convenience of initial treatment and has reduced the risk for some side effects of heparin. The second has improved the safety of warfarin, thereby broadening its clinical use and benefiting many patients. Anticoagulants designed to target specific coagulation enzymes are being evaluated in clinical trials. However, if these new anticoagulants are to replace the very effective agents that are currently available, they will have to be more convenient, cost-effective, and safe.

Despite the progress that has been made, several issues have yet to be resolved. The optimal duration of anticoagulation in various subgroups of patients with venous thrombosis has not been determined. It is not known whether less intense warfarin therapy, which would cause less bleeding, is effective in preventing recurrent venous thromboembolism. Much also remains unknown about optimal treatment of venous thromboembolism in pregnant women, patients with cancer, and patients with antiphospholipid antibodies.

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Acknowledgment: The authors thank Drs. J.S. Lawsen, J.I. Weitz, and M. Levine for critically reviewing the manuscript.

Disclaimer: Dr. Hirsh has received honoraria as a speaker and as a member or chairman of speaker panels for continuing medical education events from Aventis, Astra-Zeneca, Sanofi, Leo, Pharmacia & Upjohn, and DuPont; has received consulting fees from Conceptis, Aventis, and Astra-Zeneca; and owns stock in Glycodesign, a public glycobiology company. However, no Glycodesign product was mentioned in this paper. Dr. Bates has received honoraria as a speaker from Pharmacia & Upjohn.

Grant Support: Dr. Bates is the recipient of a Heart and Stroke Foundation of Ontario Research Fellowship.

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His preoccupation lasted all the way across the sodden vegetable patch until they arrived in greenhouse three, but here he was distracted by Professor Sprout showing the class the ugliest plants Harry had ever seen. Indeed, they looked less like plants than thick, black, giant slugs, protruding vertically out of the soil. Each was squirming slightly and had a number of large, shiny swellings upon it, which appeared to be full of liquid.

"Bubotubers," Professor Sprout told them briskly. "They need squeezing. You will collect the pus–"

"The *what*?" said Seamus Finnigan, sounding revolted.

"Pus, Finnigan, pus," said Professor Sprout, "and it's extremely valuable, so don't waste it. You will collect the pus, I say, in these bottles. Wear your dragon-hide gloves; it can do funny things to the skin when undiluted, bubotuber pus."

Squeezing the bubotubers was disgusting, but oddly satisfying. As each swelling was popped, a large amount of thick yellowish-green liquid burst forth, which smelled strongly of petrol. They caught it in the bottles as Professor Sprout had indicated, and by the end of the lesson had collected several pints.

"This'll keep Madam Pomfrey happy," said Professor Sprout, stoppering the last bottle with a cork. "An excellent remedy for the more stubborn forms of acne, bubotuber pus. Should stop students resorting to desperate measures to rid themselves of pimples."

"Like poor Eloise Midgen," said Hannah Abbott, a Hufflepuff, in a hushed voice. "She tried to curse hers off."

"Silly girl." said Professor Sprout, shaking her head. "But Madam Pomfrey fixed her nose back on in the end."

J.K. Rowling
Harry Potter and the Goblet of Fire
New York: Arthur A. Levine Books, Scholastic Press; 2000:194-5

Submitted by:
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