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EDITORIAL

This issue of *Phlebology* contains some excellent reviews on the management of venous thromboembolic disease.

Russell Hull, who is one of the leading clinical scientists in this field, together with his co-worker **Jeanne Sheldon**, presents proposals on how to conduct and report new drug trials, and gives an overview on the state of the art of how to treat patients with venous thromboembolism, based on recommendations from consensus papers.

Colleagues, who are planning randomized controlled trials, will find very important suggestions that will help to improve the quality of their studies.

An update on the use of factor Xa inhibitors for thrombosis prevention and treatment comes from **Joseph Caprini**, a top expert in the field of thromboprophylaxis. Until now, neither HIT (heparin-induced thrombopenia) nor osteoporosis has been observed after the administration of the factor Xa-inhibitor fondaparinux, which in various trials has achieved some of the lowest VTE rates ever observed following total hip or knee replacement, or hip fracture.

A well-balanced and critical analysis of the pharmacological treatment of chronic venous disorders is presented by **Michel Perrin** and **George Geroulakos**. Links between the pathophysiology of venous disorders, signs, and symptoms are discussed, and possible targets of phlebotropic drugs are outlined.

The paper of **René Milleret** points to a clinical problem that is probably underdiagnosed: popliteal vein entrapment syndrome. This condition may especially occur in connection with intensive sports training, or with recurrent sural vein thrombosis, but also after surgery of the small saphenous vein. Diagnostic tests are described and the outcome of surgery in 11 cases is reported.

A new feature of *Phlebology* is the **Book reviews**. Two new books on phlebology and on phlebology are reviewed by two leading authorities, **John Bergan** and **Michel Perrin**.

For future editions, the Editorial Board of Phlebology would like to encourage our readers to send in reviews of books or articles, together with their comments.

Enjoy your reading!

Hugo Partsch, MD



What have we learned from recent guidelines on the treatment of venous thromboembolism?

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ABSTRACT

Overwhelming evidence indicates that the quality of randomized, controlled trials reporting has been suboptimal. Accordingly, the extended CONSORT statement provides recommendations that will profoundly impact the design, conduct, and reporting of new drug trials. Additionally, registration of all trials in a public repository ensures that every trial becomes part of the public record, allowing clinicians to explore the full range of clinical evidence. Finally, QUORUM addresses standards for improving the quality of reporting meta-analyses of randomized, controlled, clinical trials. These improvements in the reporting of trials will strengthen evidence-based medicine guidelines. Evidence-based medicine guidelines have resulted in accepted standards of care for treating venous thromboembolism. Low-molecular-weight heparin is the initial treatment of choice for in-hospital and out-of-hospital therapy of deep vein thrombosis and, more recently, for submassive pulmonary embolism. A key uncertainty is the optimal duration of long-term treatment after a first episode or recurrent episodes of venous thrombosis.

BACKGROUND

Evidence-based medicine guidelines are critically dependent upon the quality of the evidence providing the basis for them. To improve the conduct and reporting of randomized clinical trials, standards have been set, which must be met for publication in high-impact journals.

These accepted standards focus on three areas:

- 1) the conduct and reporting of rigorous randomized trials, namely the Consolidated Standards of Reporting Trials (CONSORT) statements^{1,2}
- 2) avoiding a reporting bias in randomized trials by the requirement of mandatory clinical trial registration,³ and
- 3) the need to improve the quality of reporting of meta-analyses of randomized clinical trials, namely the QUORUM requirements.⁴ Many high-impact journals require mandatory compliance with these standards for reporting individual trial results or performing meta-analyses.

Keywords:

venous thromboembolism, pulmonary embolism, deep-vein thrombosis, treatment, evidence-based medicine, international guidelines.

Phlebology. 2007;14(1):3-16.

In more detail:

1) The CONSORT statements identify, “in response to overwhelming evidence and the consequences of poor quality reporting of randomized, controlled trials,” *the need for clear standards in the conduct and reporting of trials*.² “Many medical journals and editorial groups have now endorsed the CONSORT statement, a 22-item checklist and flow diagram” (Table I and Figure 1).² Recently, an extension of the CONSORT statement, the *Better Reporting of Harms in Randomized Trials* statement (Table II), provided upgraded guidelines that set the standard for the conduct and reporting of randomized clinical trials, including better reporting of benefits and harm.² Adherence to the CONSORT statement requirements is now widely accepted and will further strengthen the scientific validity of evidence-based guidelines for treatment of venous thromboembolism.

2) *Avoiding a reporting bias in the publication of data: the mandatory use of clinical trial registries*

Many high-impact journals now require mandatory prior registration of randomized clinical trials as a prerequisite for publication. The rationale behind move this was articulated clearly in a recent article setting this standard:³ “Altruism and trust lie at the heart of research on human subjects.” Selective reporting of trials distorts the body of evidence available for clinical decision-making. Mandatory registration of clinical trials reveals the existence of all clinical research, an important step in avoiding “selective reporting” of clinical trials.³ Public registration of all clinical trials at inception ensures that “every trial’s existence is part of the public record,” and enables clinicians to explore the aggregate of clinical evidence.³

3) *Improving the quality of reporting of meta-analyses (QUORUM)*

The QUORUM⁴ conference was convened to address standards for improving the quality of reporting of meta-analyses of randomized, controlled, clinical trials. The QUORUM checklist and flow diagram are available on *The Lancet’s* website (www.thelancet.com) (Table III and Figure 2). The authors state, “we hope that this document will generate further interest in the field of meta-analysis and that, like the CONSORT initiative, the QUORUM statement will become available in different languages and locations as it is disseminated.”⁴ Adherence to QUORUM recommendations is widely accepted.

EVIDENCE-BASED MEDICINE GUIDELINES

The ongoing use of the CONSORT statements, clinical trials registration, and the QUORUM requirements for meta-analyses as standards will substantially improve the quality of published evidence and provide clearer practical clinical recommendations. Two evidence-based medicine guidelines on the treatment of venous thromboembolism are widely accepted. These are *Prevention and Treatment of Venous Thromboembolism: International Consensus Statement*^{5,6} (Nicolaidis et al) and the *Seventh American College of Chest Physicians (ACCP) Conference on Antithrombotic and Thrombolytic Therapy*.⁷⁻⁹ Both international guidelines use an evidence-based approach.^{10,11} The use of evidence-based guidelines “reflects the emphasis on an evidence-based approach to making recommendations.” The development of evidence-based guidelines requires a clear and explicit definition of each question,¹² a definition that specifies eligibility criteria, including the relevant population, alternative management strategies, and the outcomes.⁷ Both consensus reports^{5,9} provide grades of recommendation based upon the methodological quality of the evidence underlying the recommendation.

The *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy* authors used the following grades of recommendation based on the methodologic quality of the evidence:⁸

- consistent results from randomized clinical trials generate Grade A recommendations;
- inconsistent results from randomized clinical trials generate Grade B recommendations;
- observational studies generate Grade C recommendations, or secure generalizations from randomized clinical trials.

In addition, the *Seventh ACCP Conference* uses the following grades of recommendation:

Grade 1) Experts are very certain that benefits do, or do not, outweigh risks, burdens, and costs, ie, a strong recommendation;

Grade 2) Experts are less certain of the magnitude of the benefits, risks, burdens, and costs, and thus of their relative impact, ie, a weaker recommendation.

It is evident that these expert opinions concerning Grade 1 and 2 recommendations may be affected by both national and regional differences in viewpoint. In addition, the use of costs to provide an expert grade of recommendation may confound the recommendations due to differing costs among health care systems. The use of costs would be better restricted to the national or local

Paper section and topic	Item number	Descriptor	Reported on page number
Title and abstract	1	How participants were allocated to interventions (eg, "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (eg, multiple observations, training of assessors).	
Sample size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules.	
Randomization			
Sequence generation	8	Method used to generate the random allocation sequence, including details of any restriction (eg, blocking, stratification).	
Allocation concealment	9	Method used to implement the random allocation sequence (eg, numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	
Implementation	10	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	
Blinding (masking)	11	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. If done, how the success of blinding was evaluated.	
Statistical methods	12	Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses, such as subgroup analyses and adjusted analyses.	
Results			
Participant flow	13	Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the number of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. Describe protocol deviations from study as planned, together with reasons.	
Recruitment	14	Dates defining the periods of recruitment and follow-up.	
Baseline data	15	Baseline demographic and clinical characteristics of each group.	
Numbers analyzed	16	Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat." State the results in absolute numbers when feasible (eg, 10/20, not 50%).	
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each group and the estimated effect size and its precision (eg, 95% confidence interval).	
Ancillary analyses	18	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	
Adverse events	19	All important adverse events or side effects in each intervention group.	
Discussion			
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	
Generalizability	21	Generalizability (external validity) of the trial findings.	
Overall evidence	22	General interpretation of the results in the context of current evidence.	

Table I. Checklist of items to include when reporting a randomized trial.² Reprinted with permission from *Annals of Internal Medicine*.

health care level in establishing grades of recommendation. Finally, the *Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy* consensus report^{8,13} has included values and preferences as part of their criteria for assigning grades of recommendation. The choice guiding the use of a particular therapeutic regimen may well be influenced by local values and preferences that are not shared internationally. Values and preferences, therefore, may be better used at the local rather than international level. An example of such a dichotomy is the widespread use of vitamin-K-antagonist prophylaxis in major orthopedic surgery in the United States and Canada based on a strong grade of recommendation, whereas low-molecular-weight heparin is the prophylaxis of choice in Western Europe.

Evidence-based grades based on the quality of the methodologic evidence are likely to be more consistent, unlike the grades of opinion. The authors of the *Prevention and Treatment of Venous Thromboembolism: International Consensus Statement*^{5,6} used similar grades of methodological evidence. Due to the potential variability amongst expert opinions based upon regional differences, the Grade 1 and Grade 2 criteria and values and preferences were not used.

Their levels of evidence include the following:

Grade A) level 1 evidence from multiple randomized trials with consistent results (eg, in systematic reviews), which are directly applicable to the target population;

Grade B) level 1 evidence from randomized trials with less consistent results, limited power, or other methodological problems;

Grade C) based on level 2 evidence from well-conducted observational studies with consistent results, directly applicable to the target population.

These two widely acknowledged consensus reports provide guidelines for the treatment of venous thromboembolism that are largely in harmony concerning the methodologic grades.^{5,8}

OVERVIEW OF THE TREATMENT OF VENOUS THROMBOEMBOLISM

Venous thromboembolism occurs not only as a complication in patients who are sick and hospitalized, but also in otherwise healthy ambulant individuals. Anticoagulant drugs—unfractionated heparin, low-

molecular-weight heparin, and vitamin K antagonists—are the mainstay of the management of venous thromboembolism. Low-molecular-weight heparin has replaced unfractionated heparin for many therapeutic indications. Unfractionated heparin, given by continuous intravenous infusion with laboratory monitoring using the activated partial thromboplastin time, in conjunction with warfarin starting on day 1 or day 2 and continued for three months or more, has historically been the standard treatment for established venous thromboembolism (deep vein thrombosis and pulmonary embolism). If unfractionated heparin is used initially, the therapeutic range must be reached within 24 hours.¹⁴ Over the past decade, low-molecular-weight heparin has supplanted unfractionated heparin and constitutes one of the most frequently used therapeutic regimens in the treatment of venous thromboembolism. Low-molecular-weight heparins have been evaluated against different treatments, including unfractionated heparin, for the prevention and treatment of venous thromboembolism. In many countries, the low-molecular-weight heparins have replaced unfractionated heparin for both the prevention and treatment of venous thromboembolism. Low-molecular-weight heparin therapy allows outpatient treatment of uncomplicated patients with deep vein thrombosis. For vitamin-K-antagonist therapy, the importance of maintaining a therapeutic international normalized ratio (INR) (2.0-3.0) is well documented; this requires frequent INR monitoring. The optimal duration of oral anticoagulant therapy, after initial or recurrent episodes of venous thromboembolism, is becoming better understood. For patients with cancer and venous thromboembolism, long-term treatment with low-molecular-weight heparin is preferred.^{15,16}

Initial antithrombotic therapies

Low-molecular-weight heparin:

For treating established venous thromboembolism, low-molecular-weight heparin, given by subcutaneous injection, has distinct advantages over continuous intravenous unfractionated heparin: once-daily (or twice-daily) subcutaneous administration and the antithrombotic response to low-molecular-weight heparin is highly correlated with body weight, permitting administration of a fixed-dose without laboratory monitoring. The use of low-molecular-weight heparin allows outpatient therapy in many patients with

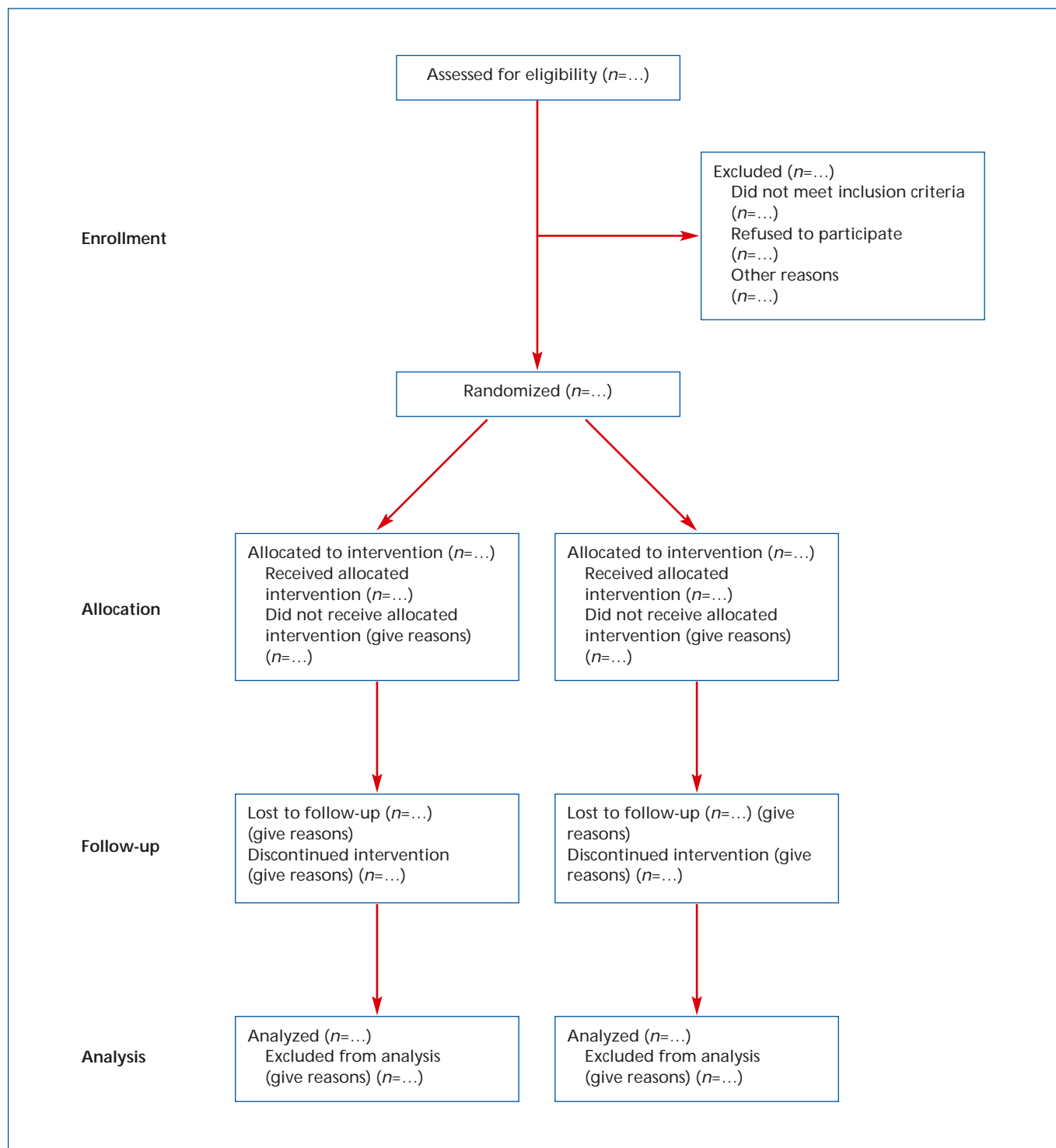


Figure 1. Revised template of the CONSORT (Consolidated Standards of Reporting Trials) diagram showing the flow of participants through each stage of a randomized trial.¹ Reprinted with permission from *Annals of Internal Medicine*.

uncomplicated deep vein thrombosis.⁹ As low-molecular-weight heparins have become widely available for treatment, they have replaced intravenous unfractionated heparin in the initial management of most patients with venous thromboembolism.

Evidence is accumulating that complications such as bleeding, osteoporosis, and heparin-induced thrombocytopenia are indeed less serious and less frequent with the use of low-molecular-weight heparin when compared with unfractionated heparin.^{9,17} The findings of a recent meta-analysis¹⁷ suggest that the frequency of heparin-induced thrombocytopenia with low-molecular-weight heparin is 0.2% whereas the risk is 2.6% with unfractionated heparin. The low-molecular-weight heparins all cross-react with unfractionated heparin and, therefore, cannot be used as an alternative therapy in patients who develop heparin-induced thrombocytopenia. Upon diagnosis of heparin-induced thrombocytopenia, low-molecular-weight heparin must be stopped immediately.¹⁸ In patients requiring ongoing anticoagulation, alternate therapy is required, for example argatroban.

Unfractionated heparin:

Classic anticoagulant therapy for venous thromboembolism involves a combination of continuous intravenous heparin using a heparin protocol¹⁹ and an oral vitamin K antagonist. Initial intravenous heparin therapy is administered for 5 days, or until the INR remains within the therapeutic range (2.0 to 3.0) for 2 consecutive days.⁹ Simultaneous use of initial heparin and warfarin has become clinical practice for all patients with venous thromboembolism who are medically stable.⁹

Clinical trials have established the need for initial heparin (or low-molecular-weight heparin) treatment in patients with venous thromboembolism.⁸ Randomized clinical trials have shown that achieving the lower limit of the therapeutic range within 24 hours is required to adequately prevent recurrent venous thromboembolism in patients receiving intravenous heparin.^{14,20} Anticoagulant monitoring of unfractionated heparin therapy is described elsewhere.¹⁹ In most patients with deep vein thrombosis and many patients with submassive pulmonary embolism, low-molecular-weight heparin has appropriately supplanted the use of unfractionated heparin, avoiding entirely the problems associated with anticoagulant monitoring.

The main adverse effects of heparin therapy include bleeding, thrombocytopenia, and osteoporosis.^{18,19,21} Patients at particular risk are those who have had recent surgery or trauma, or who have other clinical factors that predispose to bleeding when on heparin, such as peptic ulcer, occult malignancy, liver disease, hemostatic defects, weight, age >65 years, and female gender. The development of thrombocytopenia may be accompanied by arterial or venous thrombosis, which may lead to serious consequences such as death or limb amputation. Upon diagnosis of heparin-induced thrombocytopenia, heparin must be stopped immediately.¹⁸ In patients requiring ongoing anticoagulation, alternate therapy is required, for example argatroban. Osteoporosis has been reported in patients receiving unfractionated heparin for more than 6 months. Demineralization can progress to the fracture of vertebral bodies or long bones, and this defect may not be entirely reversible.¹⁹

Fondaparinux:

The synthetic pentasaccharide, fondaparinux, is effective at treating deep vein thrombosis and submassive pulmonary embolism.^{9,22,23} This new agent will become visible in the therapeutic arena, supported by future evidence-based medicine guidelines, once approval by the regulatory affairs agencies has been completed.

Thrombolytic therapy:

It is widely accepted that patients with acute massive pulmonary embolism may benefit from this adjunctive therapy.⁹ However, thrombolytic therapy remains controversial, particularly due to the risk of bleeding, and it is not indicated for the routine treatment of venous thromboembolism.

Long-term antithrombotic therapies

Vitamin-K-antagonist therapy:

The anticoagulant effect of vitamin-K-antagonist therapy is delayed until after the normal clotting factors have been cleared from the circulation, and the peak effect does not occur until 36 to 72 hours after drug administration.²⁴ The use of initial daily doses of 5 to 10 mg is the preferred approach for initiating vitamin-K-antagonist treatment; many clinicians advocate starting with 5 mg. The dose-response relationship to vitamin-K-antagonist therapy varies widely between individuals, therefore frequent monitoring of the INR is required, particularly initially, to establish therapeutic

Paper section and topic	Item number	Descriptor	Reported on page number
Title and abstract	1	If the study collected data on harms and benefits, the title or abstract should so state.	
Introduction			
Background	2	If the trial addresses both harms and benefits, the introduction should so state.	
Methods			
Participants	3	List addressed adverse events with definitions for each (with attention, when relevant, to grading, expected vs unexpected events, reference to standardized and validated definitions, and description of new definitions). Clarify how harms-related information was collected (mode of data collection, timing, attribution methods, intensity of ascertainment, and harms-related monitoring and stopping rules, if pertinent). Describe plans for presenting and analyzing information on harms (including coding, handling of recurrent events, specification of timing issues, handling of continuous measures, and any statistical analyses).	
Interventions	4		
Objectives	5		
Outcomes	6		
Sample size	7		
Randomization			
Sequence generation	8		
Allocation concealment	9		
Implementation	10		
Blinding (masking)	11		
Statistical methods	12		
Results			
Participant flow	13	Describe for each arm the participant withdrawals that are due to harms and their experiences with the allocated treatment.	
Recruitment	14	Provide the denominators for analyses on harms. Present the absolute risk per arm and per adverse event type, grade, and seriousness, and present appropriate metrics for recurrent events, continuous variables, and scale variables, whenever pertinent.† Describe any subgroup analyses and exploratory analyses for harms.‡	
Baseline data	15		
Numbers analyzed	16		
Outcomes and estimation	17		
Ancillary analyses	18		
Adverse events	19		
Discussion			
Interpretation	20	Provide a balanced discussion of benefits and harms	
Generalizability	21	with emphasis on study limitations, generalizability,	
Overall evidence	22	and other sources of information on harms.§	

* This proposed extension for harms includes 10 recommendations that correspond to the original CONSORT checklist.

† Descriptors refer to items 17, 18, and 19.

‡ Descriptors refer to items 20, 21, and 22.

Table II. Checklist of items to include when reporting harms in randomized trials.²⁸ Reprinted with permission from *Annals of Internal Medicine*.

anticoagulation.^{9,24} A number of factors influence the anticoagulant response of vitamin-K-antagonist therapy in individual patients, including dietary changes and drugs that interfere with the metabolism of vitamin K antagonist.²⁴ Heparin or low-molecular-weight heparin therapy is discontinued on the fifth day following initiation of vitamin-K-antagonist therapy, provided the INR remains in the recommended therapeutic range (INR 2.0 to 3.0) for at least two consecutive days.

Once the anticoagulant effect and the patient's warfarin dose requirements are stable, the INR should be monitored every 1 to 3 weeks throughout the course of warfarin therapy. However, if there are factors that may produce an unpredictable response to warfarin (eg, concomitant drug therapy), the INR should be monitored more frequently to minimize the risk of complications due to poor anticoagulant control.

To promote standardization of the prothrombin time for monitoring oral anticoagulant therapy, the World Health Organization (WHO) developed an international reference thromboplastin from human brain tissue and recommended that the prothrombin time ratio be expressed as the INR. The INR is the prothrombin time ratio obtained by testing a given sample using the WHO reference thromboplastin. For practical clinical purposes, the INR²⁴ for a given plasma sample is equivalent to the prothrombin time ratio obtained using a standardized human brain thromboplastin known as the Manchester Comparative Reagent, which has been widely used in the United Kingdom. In recent years, thromboplastins with a high sensitivity have been commonly used. In fact, many centers have been using the recombinant tissue factor, which has an ISI value between 0.9 and 1.0 giving an INR equivalent to the prothrombin time ratio.²⁴

The duration of anticoagulant therapy is influenced by the knowledge of multiple parameters: first episode versus recurrent episode of venous thromboembolism; transient, continuing, or unknown predisposing risk factors; and the risk of bleeding, to name some. There is increasing awareness that venous thromboembolism should be considered a chronic disease with a potential continued risk of venous thromboembolism often associated with minor provocation.²⁵

In many patients, there will be considerable uncertainty as to the duration of long-term anticoagulant therapy (see evidence-based guidelines for the long-term

treatment of patients with venous thromboembolism). For this reason, it is important to include patient preferences in the decision-making process concerning duration of anticoagulant therapy (*Figure 3*). In deep vein thrombosis or pulmonary embolism patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals. Where appropriate, the patient should be involved in the decision process.

Long-term low-molecular-weight heparin therapy:

Long-term low-molecular-weight heparin has been compared in randomized clinical trials^{15,16,26,27} against warfarin therapy in patients presenting with venous thromboembolism. Long-term low-molecular-weight heparin is a useful alternative to vitamin-K-antagonist therapy, and is the preferred therapy for up to 6 months or so in cancer patients with venous thromboembolism.^{15,16}

Adjunctive therapy

Inferior vena caval interruption:

To understand the role of the inferior vena cava filter in patients with venous thromboembolism, it is important to consider the natural history of venous thromboembolism. Patients with untreated proximal venous thrombosis, with or without pulmonary embolism, have a poor prognosis off therapy: intervention is required. What line of defence can be offered to the patient with proximal venous thrombosis or pulmonary embolism for whom immediate anticoagulant therapy is contraindicated due to hemorrhagic complications, or who have an unacceptable risk of bleeding? Since the early 1970s, the answer has been insertion of an inferior vena cava filter, the use of which is less harmful to the patient than inferior vena cava ligation. The clinical use of the inferior vena cava filter has markedly increased over the past two decades; indeed by the late 1990s at least 30 000 – 40 000 filters were inserted in patients annually in the United States.^{28,29} Retrievable filters represent a new generation of inferior vena cava filters with the potential for considerably less harm.³⁰ Retrieval of the filter may result in less thrombotic complications in the long term, which is a particular problem with permanent filters.³¹⁻³³ Due to the paucity of rigorous clinical trial data including randomized trials, it remains difficult to definitively

Heading	Subheading	Descriptor	Reported? (Y/N)	Page number
Title		Identify the report as a meta-analysis (or systematic review) of RCTs		
Abstract		Use a structured format		
	Objectives	Describe The clinical question explicitly		
	Data sources	The databases (ie, list) and other information sources		
	Review methods	The selection criteria (ie, population, intervention, outcome, and study design), methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses		
	Conclusion	The main results Describe		
Introduction		The explicit clinical problem, biological rationale for the intervention, and rationale for review		
Methods	Searching	The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication)		
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design)		
	Validity assessment	The criteria and process used (eg, masked conditions, quality assessment, and their findings)		
	Data abstraction	The process or processes used (eg, completed independently, in duplicate)		
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, etc., and how clinical heterogeneity was assessed		
	Quantitative data synthesis	The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any apriori sensitivity and subgroup analyses; and any assessment of publication bias		
Results	Trial flow	Provide a meta-analysis profile summarizing trial flow (see figure)		
	Study characteristics	Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period)		
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg, 2x2 tables of counts, means, and SDs, proportions)		
Discussion		Summarize key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda		

Table III. Quality of reporting of meta-analyses.⁴ Reprinted with permission from *The Lancet*.

assess the benefit-to-harm relationship, not only of permanent inferior vena cava filters, but also of their potential successor, the retrievable vena cava filter.

Catheter interventions:

Catheter-tip devices for the extraction or the fragmentation of pulmonary embolism have the potential for producing immediate relief from massive pulmonary embolism. Catheter-tip interventions may have a role in patients in whom there is a contraindication for thrombolytic therapy.

Thrombectomy and embolectomy:

The routine use of venous thrombectomy and embolectomy is not recommended.

EVIDENCE-BASED GUIDELINES FOR TREATMENT OF VENOUS THROMBOEMBOLISM: GRADES OF RECOMMENDATION

The recommendations used in this document are consistent with and adapted from those reported in the *Seventh ACCP Conference on Antithrombotic Therapy and Thrombolytic Therapy*,⁹ and from those recently reported that are entirely consistent with the evidence. The international consensus guidelines are in press.⁵ With few exceptions, patients with deep vein thrombosis or pulmonary embolism are treated similarly.

Initial treatment of patients with venous thromboembolism

Initial regimen:

For patients with objectively confirmed deep vein thrombosis or pulmonary embolism, short-term treatment with subcutaneous low-molecular-weight heparin or intravenous unfractionated heparin is recommended (Grade A). Subcutaneous unfractionated heparin may be used in deep vein thrombosis patients (Grade A). For patients with a high clinical suspicion of deep vein thrombosis or pulmonary embolism, treatment with anticoagulants while awaiting the outcome of diagnostic tests is suggested (Grade C). In patients with deep vein thrombosis or acute nonmassive pulmonary embolism, low-molecular-weight heparin, instead of unfractionated heparin, is recommended

(Grade A). Uncomplicated deep vein thrombosis patients may be treated as outpatients (Grade C). In patients with acute deep vein thrombosis or nonmassive pulmonary embolism treated with low-molecular-weight heparin, routine monitoring with anti-factor Xa levels is not recommended (Grade A). In patients with severe renal failure, intravenous unfractionated heparin rather than low-molecular-weight heparin is suggested (Grade C).

Duration of initial treatment:

In acute deep vein thrombosis or pulmonary embolism, initial treatment with low-molecular-weight heparin or unfractionated heparin for at least 5 days is suggested (Grade C).

Commencing vitamin-K-antagonist therapy:

Initiation of vitamin K antagonist together with low-molecular-weight heparin or unfractionated heparin on the first treatment day and discontinuation of heparin when the INR is stable and >2.0 is recommended (Grade A).

Adjunctive initial therapy

Thrombolytic therapy:

In patients with deep vein thrombosis or pulmonary embolism, the routine use of systemic thrombolytic treatment is not recommended (Grade A). In selected deep vein thrombosis patients, such as those with massive iliofemoral deep vein thrombosis at risk of limb gangrene secondary to venous occlusion, intravenous thrombolysis is suggested (Grade C). In selected patients with pulmonary embolism, systemic administration of thrombolytic therapy is suggested (Grade B). For pulmonary embolism patients who are hemodynamically unstable, use of thrombolytic therapy is suggested (Grade B). For patients with pulmonary embolism who receive thrombolytic regimens, use of thrombolytic regimens with a short infusion time over those with prolonged infusion times is suggested (Grade C). In pulmonary embolism patients, it is suggested that local administration of thrombolytic therapy via a catheter should not be used (Grade C). In patients with deep vein thrombosis, the routine use of catheter-directed thrombolysis is not suggested (Grade C). In deep vein thrombosis patients, confining catheter-directed thrombolysis to selected patients such as those requiring limb salvage is suggested (Grade C).

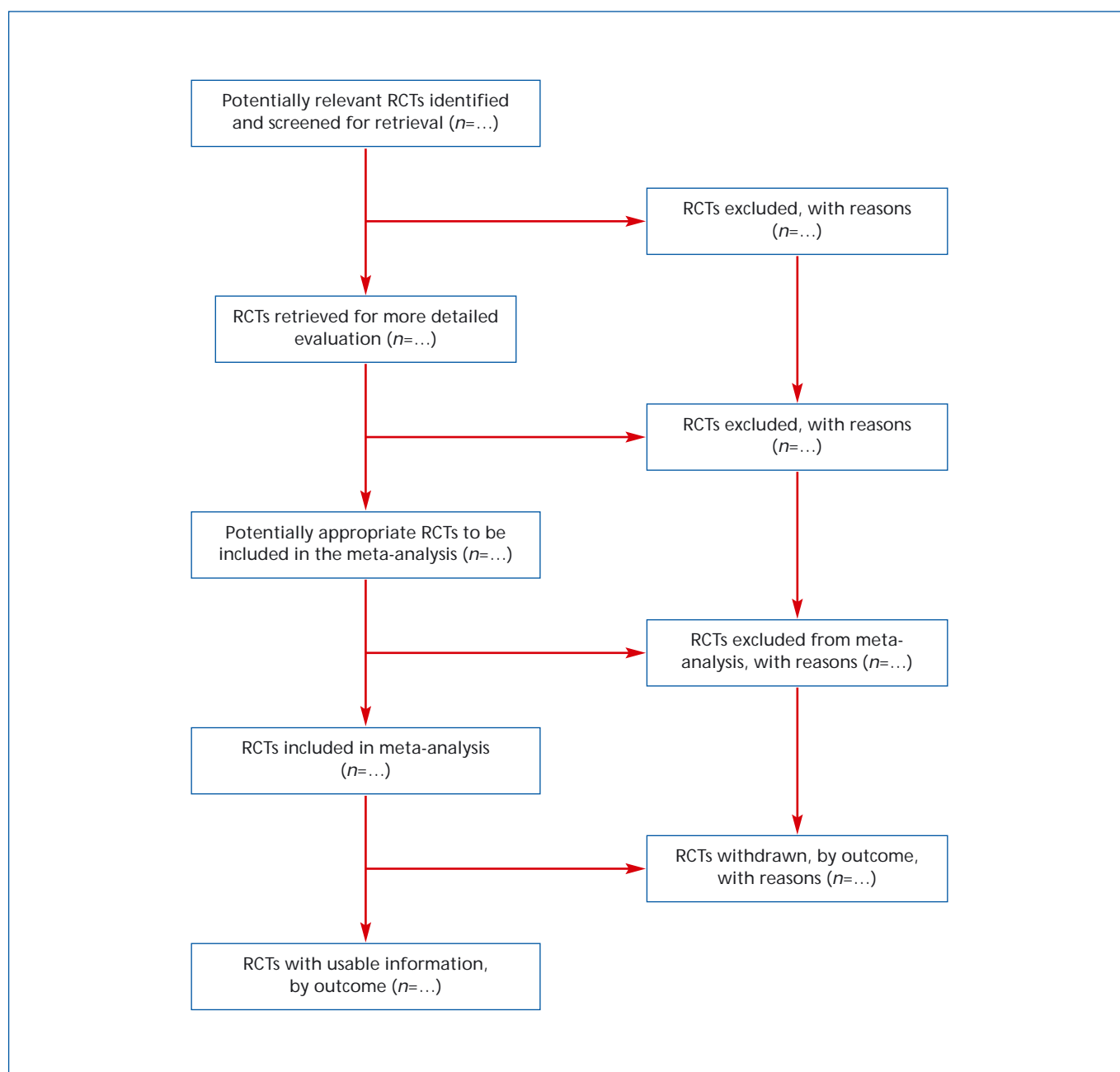


Figure 2. Progress through the stages of a meta-analysis for RCTs.⁴ Reprinted with permission from *The Lancet*.

Nonsteroidal anti-inflammatory agents:

For the initial treatment of deep vein thrombosis, the use of nonsteroidal anti-inflammatory agents is not recommended (Grade B).

Ambulation:

For deep vein thrombosis patients, it is recommended that these patients be permitted ambulation as tolerated (Grade B).

Long-term treatment of patients with venous thromboembolism

Intensity of long-term vitamin-K-antagonist therapy:

In patients with deep vein thrombosis or pulmonary embolism, adjusting the dose of vitamin K antagonist to maintain a target INR of 2.5 (range, 2.0 and 3.0) for all treatment durations is recommended (Grade A). High-intensity vitamin-K-antagonist therapy (INR range, 3.1 to 4.0) is not recommended (Grade A). Low-intensity

therapy (INR range, 1.5 to 1.9) compared with an INR range of 2.0 to 3.0 is not recommended (Grade A).

Long-term low-molecular-weight heparin treatment:

For most patients with deep vein thrombosis or pulmonary embolism and concurrent cancer, treatment with low-molecular-weight heparin for at least the first 3 to 6 months of long-term treatment is recommended (Grade A). For these patients, anticoagulant therapy, indefinitely or until the cancer is resolved, is suggested (Grade C).

Duration of long-term vitamin-K-antagonist therapy

Transient (reversible) risk factors:

For patients with a first episode of deep vein thrombosis or pulmonary embolism secondary to a transient (reversible) risk factor, long-term treatment with a vitamin K antagonist for at least 3 months over treatment for shorter periods is recommended (Grade A).

Idiopathic: For patients with a first episode of idiopathic deep vein thrombosis or pulmonary embolism, treatment with a vitamin K antagonist for at least 6 to 12 months is recommended (Grade A). Considering patients with first-episode idiopathic deep vein thrombosis or pulmonary embolism for indefinite anticoagulant therapy is suggested (Grade A).

Presence of a thrombophilia: For patients with a first episode of deep vein thrombosis or pulmonary embolism who have documented antiphospholipid antibodies or who have two or more thrombophilic conditions (eg, combined factor V Leiden and prothrombin 20210 gene mutations), treatment for 12 months is recommended (Grade C). Indefinite anticoagulant therapy in these patients is suggested (Grade C). For patients with a first episode of deep vein thrombosis or pulmonary embolism who have documented deficiency of antithrombin, deficiency of protein C or protein S, or the factor V Leiden or prothrombin 20210 gene mutation, homocysteinemia, or high factor VIII levels (>90th percentile of normal), treatment for 6 to 12 months is recommended (Grade A). Indefinite therapy as for patients with idiopathic thrombosis is suggested (Grade C).

Recurrent venous thromboembolism:

For patients with two or more episodes of objectively documented deep vein thrombosis or pulmonary embolism, indefinite treatment is recommended (Grade A).

Indefinite anticoagulant treatment:

In deep vein thrombosis or pulmonary embolism patients who receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals (Grade C).

Prognostic testing

In patients with deep vein thrombosis or pulmonary embolism, repeat testing with compression ultrasonography for the presence or absence of residual thrombosis or measurement of plasma d-dimer is suggested (Grade C).

Vena caval filter

For most patients with deep vein thrombosis, the routine use of a vena cava filter in addition to anticoagulants is not recommended (Grade A). In deep vein thrombosis or pulmonary embolism patients, the placement of an inferior vena caval filter in patients with a contraindication for, or a complication of, anticoagulant treatment is suggested (Grade C), as well as in those with recurrent thromboembolism despite adequate anticoagulation (Grade C).

Catheter interventions

For most patients with pulmonary embolism, use of mechanical approaches is not recommended (Grade C). In selected highly compromised patients who are unable to receive thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, use of mechanical approaches is suggested (Grade C).

Thrombectomy and embolectomy

In patients with deep vein thrombosis, the routine use of venous thrombectomy is not recommended (Grade C). In selected patients such as patients with massive iliofemoral deep vein thrombosis at risk of limb gangrene secondary to venous occlusion, venous thrombectomy is suggested (Grade C). For most patients with pulmonary embolism, pulmonary embolectomy is not recommended (Grade C). In selected highly compromised patients who are unable to receive

thrombolytic therapy or whose critical status does not allow sufficient time to infuse thrombolytic therapy, pulmonary embolectomy is suggested (Grade C).


Post-thrombotic syndrome (PTS)

The use of an elastic compression stocking with a pressure of 30 to 40 mm Hg at the ankle for a duration of 2 years after an episode of deep vein thrombosis is recommended (Grade A). A course of intermittent pneumatic compression for patients with severe edema of the leg due to PTS is suggested (Grade B). The use of elastic compression stockings for patients with mild

edema of the leg due to PTS is suggested (Grade C). In patients with mild edema due to PTS, administration of rutosides is suggested (Grade B).

In individual deep vein thrombosis or pulmonary embolism patients who, for example, receive indefinite anticoagulant treatment, the risk-benefit of continuing such treatment should be reassessed in the individual patient at periodic intervals. Where appropriate the patient should be involved in the decision process. The patient provides guidance in the assessment process by completing the Patient Planner prior to his or her review in our clinic (*Figure 3*).

Patient Planner



What would you like to know by the end of your visit? Please list your three most important questions here.

1. _____

2. _____

3. _____

Is there anything in particular worrying you about your problem (complaints, symptoms, and feelings)?

How much control do you want to have in deciding which treatment options are best for you? Please number the following in order of preference.

A. ____ I prefer to make the decision about which treatment I will receive.

B. ____ I prefer to make the final decision about my treatment after seriously considering my doctor's opinion.

C. ____ I prefer that my doctor and I share responsibility for deciding which treatment is best for me.

D. ____ I prefer that my doctor makes the final decision about which treatment will be used, but seriously considers my opinion.

E. ____ I prefer to leave all decisions regarding treatment to my doctor.

Figure 3. Patient contracting. Reprinted with permission from Vascular Surgery.



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Update on anticoagulants: clinical support for the use of selective factor Xa inhibitors

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ABSTRACT

Over the past decade, a number of new anticoagulant compounds have been developed, including the low-molecular-weight heparins (LMWHs) and the factor Xa inhibitors fondaparinux and idraparinux. Factor Xa inhibitors are powerful anticoagulants that act by producing a reversible conformational change in the antithrombin III molecule. Unlike unfractionated heparin and warfarin, these new compounds, which have a linear pharmacokinetic profile, do not require frequent patient monitoring. Factor Xa inhibition has been studied in the prevention and treatment of venous thromboembolic problems in orthopedic, general surgical, and medical patients, and, more recently, in the reduction of thrombotic complications associated with acute coronary syndrome. At present, most of the randomized trial data pertain to fondaparinux, the first selective factor Xa inhibitor to become available for clinical use. The purpose of this review will be to present clinical support for the use of selective factor Xa inhibitors for thrombosis prevention and treatment.

INTRODUCTION

Since the 1960s, unfractionated heparin (UFH) has been the gold standard for the prophylaxis and treatment of venous thromboembolism (VTE).

Although this drug has an immediate onset of action, short half-life, and can easily be measured and reversed, there are a number of problems associated with its use. The effects of UFH on the clotting system are often unpredictable. In addition, quickly establishing a therapeutic level (within 12 to 24 hours) in patients with acute thrombosis can be challenging due to significant binding of nonclotting proteins. Finally, the incidence of heparin-induced thrombocytopenia (HIT) may be as high as 1% to 3% in patients receiving the drug. The emergence of the low-molecular-weight heparins (LMWHs) in the 1970s and 1980s represented a major breakthrough in the approach to thrombosis prophylaxis and treatment. These drugs have a greater bioavailability, longer half-lives, more predictable dose response, and are

Keywords:

thrombosis, anticoagulation, factor Xa inhibitor, fondaparinux, idraparinux.

associated with a lower incidence of HIT and heparin-induced osteoporosis. They also have a greater survival benefit in the patient with cancer.¹

Until recently, warfarin was the only available oral anticoagulant. It has been widely used for the prevention of secondary thrombosis, as well as for the treatment of acute VTE. This agent is relatively inexpensive and is reversible with vitamin K. Problems associated with this drug include a delayed onset and offset of action (36 to 72 hours to achieve an appropriate therapeutic effect), frequent food and drug interactions, and the need for careful monitoring and possible dose adjustment. In addition, warfarin actually suppresses the body's natural anticoagulants before achieving a full circulating anticoagulant effect in the patient. This is due to the order in which the clotting factor levels decline following warfarin administration. Factor VII is the first to decline and produces a prolonged prothrombin time and an increased international normalized ratio (INR). The patient is not therapeutically anticoagulated since the other vitamin K-dependent factors (factor II, factor IX, and factor X) have not yet been depleted. The intrinsic clotting pathway is intact, as can be measured by a normal activated partial thromboplastin time (aPTT) about 48 to 72 hours following the initiation of warfarin. At the same time, protein C and protein S, which are naturally occurring anticoagulants in the circulation, begin to decline because they are vitamin K-dependent. This results in hypercoagulability during the next 24 hours until levels of coagulation factors II, IX, and X in the plasma decline. These effects can sometimes produce skin necrosis or paradoxical thrombotic complications in patients with borderline or low levels of protein C or protein S. Finally, after a period of about 5 days, the patient is adequately anticoagulated with warfarin. If the patient is being treated for VTE with UFH or LMWH in an overlapping fashion, these drugs can be stopped after

the 5-day period.² The practice of using only warfarin for postoperative thrombosis prophylaxis can be risky in some cases, and can precipitate thrombosis as mentioned above.

Unlike warfarin, UFH, or LMWH, factor Xa inhibitors act on a single point in the coagulation schema. Factor Xa inhibitors are powerful anticoagulants that block activated factor Xa by producing a reversible conformational change in the antithrombin III molecule. Fondaparinux, a synthetic pentasaccharide, is a nonbiological compound that is administered subcutaneously once daily. It possesses a high bioavailability with a 17-hour half-life. Neither HIT nor heparin-induced osteoporosis has been an observed side effect. Idraparinux, a new, long-acting, synthetic pentasaccharide, has a half-life of approximately 4 days and can be administered subcutaneously once a week. Like other pentasaccharide formulations, it has a linear pharmacokinetic profile and does not require frequent patient monitoring. Although new data continue to emerge, at present, the bulk of the randomized trial data available for this review pertain to fondaparinux, which was the first factor Xa inhibitor to be approved for clinical use.

ORTHOPEDIC SURGERY

From a clinical perspective, some of the lowest VTE rates ever observed following total hip or knee replacement or hip fracture involved prophylaxis with the factor Xa inhibitor fondaparinux. Several studies have reported that this drug may be equal to, or better than, LMWH in hip replacement, knee replacement, and following hip fracture surgical repairs.³⁻⁶ More than 7300 patients were studied in four clinical trials, resulting in approval in the United States for these three indications. *Table I* outlines the results of the four studies, which use the LMWH

Type of procedure	Patients	Factor Xa inhibitor		LMWH	
		Total VTE	Proximal DVT	Total VTE	Proximal DVT
Hip fracture repair ⁴	1711	8.3%*	0.9%*	19.1%	4.3%
Total hip replacement ⁷	2309	4.0%*	0.7%†	8.8%	2.5%
Total hip replacement ⁵	2275	6.1%	1.7%	8.3%	1.2%
Total knee replacement ⁶	1034	12.5%*	2.4%	27.8%	5.4%

* $P < 0.001$; † $P = 0.0021$.

*Table I. Prophylaxis of venous thromboembolism following orthopedic procedures.*⁵⁻⁷

Abbreviations: DVT, deep venous thromboembolism; VTE, venous thromboembolism; LMWH, low-molecular-weight heparin.

enoxaparin as the comparator. No difference in clinically relevant bleeding was observed between factor Xa inhibitor and LMWH in any of these trials. In addition, no differences existed in any of the bleeding parameters between the two drugs in either of the hip replacement trials.^{4,5} However, minor bleeding was increased in the hip fracture study compared with LMWH.³ An increased incidence of major bleeding was observed in the knee trial, along with a positive bleeding index compared with LMWH, although 6 of the 9 patients with a positive bleeding index had the study drug continued by their surgeon.⁶

A post hoc analysis of these 4 studies revealed a statistically significant relationship between the timing of the first dose of factor Xa inhibitor and the incidence of major bleeding ($P=0.0075$), but not efficacy ($P=0.67$).⁷ An additional analysis found that major bleeding was significantly lower ($P=0.045$) in patients who received the first dose of factor Xa inhibitor ≥ 6 hours after surgery (as directed in the prescribing information), compared with those who received the first dose < 6 hours after surgery. There were no differences between factor Xa inhibitor and LMWH in pulmonary embolism (PE) and overall safety, which included wound infections and surgical site complications.³⁻⁶

The most successful prophylaxis trial to date involved extended VTE prophylaxis following hip fracture surgery. Patients who had previously received fondaparinux for 7 ± 1 days received fondaparinux (2.5 mg once daily) or placebo for an additional 3 weeks (± 2 days).⁸ Factor Xa inhibitor reduced the incidence of VTE from 35% (placebo) to 1.4% ($P < 0.001$), demonstrating a relative risk reduction of 96%. There were no differences between the groups in clinically relevant bleeding, although there was a trend toward more major bleeding in the factor Xa inhibitor group. One may conclude from these results that 30 days of therapy with the factor Xa inhibitor fondaparinux practically eliminates thromboembolism in patients with surgically repaired hip fractures. Another important observation can be made: in patients receiving factor Xa inhibitor for 7 ± 2 days, the incidence of VTE was 8.3% when the venogram was done at 11 days,³ but jumped to 35% when the venogram was done at 30 days.⁸ This would reinforce the concept that the majority of VTE cases following hip operations occur following hospital discharge.

Another important trial addressed the timing of the first dose of fondaparinux administered to patients undergoing major orthopedic surgery. The first dose of fondaparinux (2.5 mg) was administered either 8 ± 2 hours postoperatively or the following morning.⁹ No significant difference in the incidence of symptomatic VTE was observed between the groups (1.9% and 1.8%, respectively, $P=0.89$). Bleeding events were also similar between the groups. Together, this evidence suggests that delaying administration of factor Xa inhibitor could provide additional treatment flexibility without compromising safety or efficacy.

ACUTE TREATMENT OF DVT AND PE

Fondaparinux was also evaluated in a treatment trial conducted among 2200 patients with deep venous thrombosis (DVT) randomized to receive either enoxaparin (1 mg/kg) twice daily, or 7.5 mg fondaparinux once daily with transition to oral anticoagulation for 6 months in both groups.¹⁰ A second treatment trial compared UFH with 7.5 mg fondaparinux once daily in 2200 patients with PE with or without DVT.¹¹ Both trials showed factor Xa inhibitor to be as safe and effective as UFH or LMWH in treating these diseases. Rates of recurrent DVT, death from PE, and bleeding were not statistically significantly different among any of the groups studied.^{10,11} These studies have led to approval of fondaparinux in the United States for the treatment of acute DVT, and for the treatment of PE with or without DVT. The use of this drug in these trials was dose-adjusted; patients weighing < 50 kg received 5 mg daily, those weighing 50 to 100 kg received 7.5 mg daily, and those weighing > 100 kg received 10 mg daily. HIT has not been observed in any patients treated with factor Xa inhibitor, which is an advantage when patients have had or have been suspected of having HIT in the past. An important consideration when using this renally excreted drug is to know the creatinine clearance of the patient. Fondaparinux should not be used when the patient's creatinine clearance is less than 30 mL/min and should be used with caution when the creatinine clearance is between 30 and 50 mL/min.¹²

A phase 2 clinical trial, the PERSIST study, compared four different dose regimens of the factor Xa inhibitor idraparinux with warfarin for secondary prevention of DVT.¹³ This new drug has an 80-hour half-life and was given once a week by subcutaneous injection. This

preliminary study demonstrated that weekly administration of 2.5 mg of factor Xa inhibitor for 3 months was as safe and effective as warfarin administration when given for the same period of time.¹³ An analysis of liver enzymes in participants from this study also showed that factor Xa inhibitor administration did not increase plasma liver enzymes significantly.¹⁴

General surgery and medically ill in-patient therapy

Two important trials have been conducted to evaluate fondaparinux for VTE prophylaxis in general surgery patients. In the European trial, fondaparinux (2.5 mg), given once daily starting 6 hours after surgery, was compared with the LMWH dalteparin (2500 IU), given 2 hours before surgery and the evening of the same day, and once daily (5000 IU) thereafter.¹⁵ Both agents were given subcutaneously for 7±2 days. The incidence of any VTE event was 6.1% in the LMWH group and 4.6% in the factor Xa inhibitor group; these results were not significantly different. There were no differences of statistical significance in the clinical incidence of DVT and nonfatal or fatal PE. The VTE rates for patients with a median duration of surgery longer than 2.5 hours were 5.5% and 9.1% in the factor Xa inhibitor and LMWH groups, respectively. The VTE rates in patients with a median duration of surgery less than 2.5 hours were 3.7% and 2.8% in the factor Xa inhibitor and LMWH groups, respectively. There were no statistically significant differences in major or minor bleeding in either treatment group.

The second study in general surgery patients was done in the USA and compared the combined efficacy of fondaparinux and intermittent pneumatic compression (IPC) versus IPC alone for VTE prevention after major abdominal surgery.¹⁶ Patients in this trial were treated with IPC and either fondaparinux (2.5 mg) or placebo subcutaneously 6 to 8 hours after surgery, and then once daily for 7±2 days. Combined therapy significantly reduced the VTE rate from 5.3% (placebo + IPC) to 1.7% (factor Xa inhibitor + IPC; $P=0.004$). Rates of proximal DVT were also reduced in the factor Xa inhibitor + IPC group (0.2%) compared with IPC alone (1.7%; $P=0.037$). The incidence of major bleeding was 1.6% in the factor Xa inhibitor + IPC group versus 0.2% in the placebo + IPC group ($P=0.006$); however, no bleeding was fatal or involved critical organs. Although the bleeding risk was higher in patients treated with factor Xa inhibitor, this risk was low and consistent with that reported in other similar trials. Results from this trial

demonstrated that factor Xa inhibitor and IPC combination therapy was significantly more effective than IPC alone for VTE prevention after major abdominal surgery.

An additional trial investigated fondaparinux VTE prophylaxis in acutely ill medical patients. In this trial, factor Xa inhibitor reduced the incidence of VTE to 5.6%, compared with 10.5% in the placebo group (relative risk reduction, 46.7%, $P=0.029$).¹⁷ No significant difference in bleeding risk was observed between the two groups. In addition, a reduction in mortality up to day 32 was observed in older medical patients (≥ 60 years) receiving factor Xa inhibitor compared with patients receiving placebo (3.3% versus 6%; $P=0.06$).

ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) refers to the full spectrum of coronary artery disease (CAD), including ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA).^{18,19} Atherosclerotic plaque formation, and disruption, and subsequent thrombus formation are characteristic of the pathophysiology that underlies ACS.^{18,19} Antithrombotic therapies, including anticoagulants and platelet inhibitors, are therefore mainstays of treatment for preventing thrombosis in these patients. Two recent, large, multicenter trials have evaluated the effects of fondaparinux in patients with ACS. The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-5) and Sixth Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS-6) studies compared fondaparinux with standard approaches in patients with UA/NSTEMI or STEMI, respectively.^{20,21}

OASIS-5 compared the anti-ischemic benefits and bleeding risk of factor Xa inhibitor versus the LMWH enoxaparin in patients with UA/NSTEMI.²⁰ Ischemic events (a composite of death, myocardial infarction, or refractory ischemia) occurred in 5.8% of patients assigned to factor Xa inhibitor, as compared with 5.7% of patients receiving LMWH, thus satisfying the prespecified criteria for noninferiority. The primary safety endpoint, the rate of major bleeding at 9 days, was reduced by about half with factor Xa inhibitor (2.2%) compared with LMWH (4.1%) ($P<0.001$), a difference

that persisted over time. In addition, factor Xa inhibitor was associated with significantly reduced mortality at 30 days (2.9% versus 3.5%; $P=0.02$) and at 6 months (5.8% versus 6.5%; $P=0.05$), and a significant reduction in the long-term risk of stroke (factor Xa inhibitor, 1.3% versus LMWH, 1.7%; $P=0.04$). In patients with UA/STEMI, factor Xa inhibitor provided similar short-term anti-ischemic benefits to LMWH, and improved long-term mortality and morbidity, thus demonstrating that factor Xa inhibitor is an attractive option for the treatment of patients with ACS.

OASIS-6 compared the effect of fondaparinux versus usual care (UFH or placebo in patients for whom UFH was not indicated) in patients with STEMI.²¹ The incidence of death or reinfarction at 30 days was significantly reduced from 11.2% in the control group to 9.7% in the factor Xa inhibitor group (hazard ratio [HR], 0.86; $P=0.008$). There was a consistent and significant reduction in death throughout the study with use of factor Xa inhibitor (7.8% versus 8.9% in controls; $P=0.03$); this reduction in mortality was due entirely to a reduction in cardiac deaths. A nonsignificant trend toward fewer severe bleeding episodes was observed with factor Xa inhibitor compared with the control group at day 9 (61 versus 79; $P=0.13$). In patients undergoing interventional procedures (percutaneous catheter intervention), treatment with factor Xa inhibitor was associated with a significantly higher incidence of guiding catheter thrombosis and coronary complications. Overall, OASIS-6 showed a significant reduction in mortality and reinfarction with use of factor Xa inhibitor, when compared with usual care. Notably, this reduction occurred without the increase in bleeding or hemorrhagic stroke observed with other antithrombotic and antiplatelet agents,²²⁻²⁴ and OASIS-6 is the only STEMI trial to date to demonstrate a mortality benefit without an increased risk of bleeding.

STROKE

Patients with atrial fibrillation are at risk for the formation of thrombi within the heart and subsequent vascular occlusive events as a result of embolization of these thrombi. A phase 3 study, AMADEUS (Atrial fibrillation trial of Monitored, Adjusted Dose vitamin k antagonist, comparing Efficacy and safety with Unadjusted SanOrg 34006/idraparinux), was initiated to evaluate idraparinux for the prevention of stroke in patients with atrial fibrillation.²⁵ The results of this study are not yet available.

CONCLUSION

The ideal thrombosis prophylaxis agent should be efficacious, inexpensive, easy to administer and monitor, and have no complications or side effects. Although we are still searching for the perfect thrombosis prophylaxis agent, the emergence of newer anticoagulant therapies such as LMWHs and the selective factor Xa inhibitors fondaparinux and idraparinux have brought us closer to this goal.



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Pharmacological treatment of chronic venous disorders

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The term chronic venous disorder (CVD) is used to denote all abnormal clinical changes that result from venous disease of the lower extremities, and that have a chronic course.¹ According to this definition, CVD includes patients who present with so-called symptoms and/or signs of venous disease that characterize each class of CVD in the Clinical, Etiological, Anatomical, Pathophysiological (CEAP) classification,² from class C0s to class C6.

A review of the literature³ shows that CVD is most commonly manifested by the following symptoms: heaviness in the legs, pain, a sensation of swelling, restless legs, paresthesia, nighttime cramps, tiredness, and itching.

It should be stated that none of these symptoms is specific to CVD, and even less so pathognomonic. Since it is not possible to confirm whether such symptoms are related to venous disease, it is important to characterize them using the following secondary criteria:

- **Variability with position or physical activity:** Symptoms generally occur after prolonged standing, at the end of the day, and do not exist, or are diminished, in the morning, in the supine position, or with the legs elevated;
- **Variability with temperature:** Symptoms are exacerbated by warmth, summer temperatures season, hot baths, hot waxing to remove body hair, floor-based heating systems, and regress; symptoms are diminished in winter and on exposure to low temperatures;
- **Variability with levels of circulating sex hormones:** Symptoms fluctuate with the menstrual cycle; they can occur with hormonal therapy (estrogens or estrogen-progestin), and disappear with discontinuation of such treatment.

The existence of at least two secondary criteria is necessary to confirm that symptoms are related to CVD, but the absence of such criteria does not rule out the possible venous-related origin of the symptoms.

Whatever the therapy used, the effect of treatment on symptoms is difficult to quantify because these symptoms are subjective. Therapeutic efficacy can be assessed more readily based on a certain number of signs, such as edema or venous ulcers.

Keywords:

chronic venous disease, flavonoids, phlebotropic drugs, pain, micronized purified flavonoid fraction (MPFF).

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CLASSIFICATION OF PHLEBOTROPIC DRUGS

Phlebotropic drugs belong to several different chemical families. The majority of them are plant-derived compounds. Some have been produced by chemical synthesis. The main phlebotropic drugs⁴ are summarized in *Table I*.

PATHOPHYSIOLOGICAL TARGETS OF PHLEBOTROPIC DRUGS

It is important to specifically identify the mode of action of phlebotropic drugs depending on the pathophysiological mechanisms that they aim to treat. Among such mechanisms, we can differentiate the following:

- those that are identified before microcirculatory disorders occur, consisting mainly of alterations in the venous wall; and
- those consisting of microcirculatory disorders.

Pharmacological targets before the occurrence of abnormal changes in the microcirculation

Two major mechanisms may be responsible for pain in the absence of trophic changes:

- first, venous wall tension, which results from dilation of the vein in a normal subject in the erect position, and the valvular incompetence during dynamic move-

ment in the erect position in a subject with valvular insufficiency; and

- second, hypoxia of the tunica media of the venous wall due to alteration of the vasa vasorum. Pain seems more related to hypoxia. In the early stages of CVD, superficial venous distensibility is slight, while pain is more severe than in the advanced stages of CVD where venous pressure is elevated, and venous wall pressure is therefore high.⁵ However, the venous remodeling phase that precedes the development of varicose veins, which is accompanied by the process of venous distention, hemorrhheological disturbances, and conditions of hypoxia can be painful.

Pain and heaviness in the legs

Phlebotropic drugs are intended to decrease sensation of heaviness in the legs, pain, and ankle edema at the end of the day. The first target of such therapy is increased venous wall pressure. Distensibility is increased by 10% to 50% in patients,⁶ and this is due to a decrease in venous tone. The second target is hypoxia of the tunica media which is related to disease of the vasa vasorum.⁵

Restless legs, nighttime cramps

These symptoms most often occur during the latter half of the night, but can also occur during prolonged sitting.

1. Benzopyrones

a) Alpha-benzopyrones

Coumarin (1,2-benzopyrone; 5,6-alpha-benzopyrone)

Dicoumarols (dimers of 4 hydroxycoumarins): oral anticoagulants

b) Chromenones (flavonoids)

Micronized purified flavonoid fraction (MPFF)

Diosmin, kacinpererol, diosmethin, quercetin, rutin and derivatives, O-(b-hydroxyethyl) rutosides (HR or oxerutins)

2. Saponins

Escin, horse-chestnut extracts

Extracts of ruscus, Centella asiatica

3. Other plant extracts

Anthocyanosides: blueberry extract (protoescigenin, barringtogenol, a-and b-escin, cryptoescin)

Proanthocyanidols: grape seed extracts

Ginkgo biloba

4. Synthetic products

Calcium dobesilate

Benzarone, naftazone

Table I. Classification of the main phlebotropic drugs.

Pathophysiology	Symptom	Sign
Leukocyte adhesion in subvalvular areas/areas of inflammation	Pain	Early valvular reflux
Valvular incompetence		Reflux
Venous hypertension and venous wall tension	Pain	Edema
Venous wall hypoxia	Pain	
Increased capillary pressure	Sensation of heavy legs and swelling	Edema
Hemorheological disorders and platelet hyperaggregability	Nighttime cramps Restless legs	

Table II. Possible links between pathophysiological variables, symptoms, and signs of chronic venous disorders.

They can also be related to hypoxia of the tunica media, but more specifically may be associated with hemorheological disorders.⁵ In fact, red blood cell hyperviscosity and hyperaggregation are constant findings in venous disease.^{7,8} It appears likely that hemorheological disorders worsen the circulation in the vasa vasorum. Hypoxia in the tunica media, in turn, induces deterioration of the venous wall. Hypoxia has a potent effect in inducing metabolic disorders: triggering of enzymatic activities, such as those of matrix metalloproteinases (MMP), and dedifferentiation, and migration of smooth muscle cells, which secrete growth factors. Fibrosis of the venous wall governs the development of the varicose vein. The diseased venous wall generates several metabolic disorders, including hypofibrinolysis due to elevated levels of plasminogen activating inhibitor (PAI-1). The links between pathophysiology, symptoms, and clinical signs of CVD are summarized in *Table II*.

Pharmacological targets related to microcirculatory disorders

The process of edema is manifestly due to increased capillary permeability related to permanent venous hypertension,⁵ whose mechanisms vary: reflux or obstruction. Two stages should be distinguished in the progression of capillary disorders as venous disease becomes progressively worse: a functional disorder, followed by development of a lesional disorder, which characterizes chronic venous insufficiency.

Capillary functional disorder

At a relatively early stage, capillary permeability is observed in patients, as assessed by ankle plethysmography, following proximal venous hypertension, with fluorescein capillary angioscopy, and the Gibbon-Landis radioisotope test. A second aspect is capillary fragility demonstrated by the suction cup test.

Traditionally, such disorders are taken as targets when studying the effects of phlebotropic drugs (*Table III*). However, it is not known whether they play a part in the development of lesional disorders. One argument in favor of their involvement is that they are accompanied by microedema and hemorheological disorders, which occur at an early stage of venous disease. And yet, it is known that red blood cell hyperaggregation promotes microcirculatory disorders.

Microvascular lesional disease

Alteration of the cutaneous microcirculation in the lower extremities is the long-term result of permanent venous hypertension, as the distal venous valves gradually become incompetent. The result is trophic changes whose incidence is proportional to the increase in ambulatory venous pressure.

Over the last few years, advances have been made in understanding the pathophysiology of events, allowing better identification of the structures targeted by phlebotropic drugs:

- Doppler-laser investigation has shown an increase in cutaneous blood flow at rest, related to increased con-

1. Analgesic, antiedema and capillary protection effects: *all products*
2. Effect on venous tone: *all products*
Ruscus: partial agonist action on venular alpha-1 adrenergic receptors (neutralized by NO on the arterial side)
3. Lymphotrophic effects: *Ruscus, coumarin, micronized purified flavonoid fraction*
4. Improvement of red blood cell rheology: *micronized purified flavonoid fraction, troxerutin, rutin*
5. Profibrinolytic action: *micronized purified flavonoid fraction, troxerutin, diosmins*
6. Anti-inflammatory action: *micronized purified flavonoid fraction, Gingko biloba, diosmins*
7. Decreased adhesive properties of neutrophils and monocytes: *micronized purified flavonoid fraction*
8. Protective effect on the venous valve: *micronized purified flavonoid fraction*
9. Protective effect on the venous wall
 - 9.1: inhibition of lysosomal enzymes: *melilot extract, rutins, pycnogenols*
 - 9.2: protection of fibrous proteins (collagen): *procyanidolic oligomers*
 - 9.3: anti-free radical properties: *micronized purified flavonoid fraction, Gingko biloba*
 - 9.4: normalization of the synthesis of prostaglandin E2 : *micronized purified flavonoid fraction*
 - 9.5: improvement of circulation in the vasa vasorum: *troxerutin*

Table III. Pharmacological targets of phlebotropic drugs.

centrations of circulating red blood cells. This involves impairment of blood distribution affecting the most superficial areas where hypoxia develops, while intra- and subcutaneous PO₂ concentrations are normal.⁹

- Hypofibrinolysis increases concomitantly with increasing severity of trophic changes, usually with very high levels of PAI-1.¹⁰
- The hemorheological disorder, in particular, red blood cell hyperaggregation, is exacerbated and correlated with the clinical severity of the disease.
- Hypoxia, and excess delivery of oxygenated free radicals in the most superficial capillaries promote endothelial and leukocyte activation.¹¹

Therefore, leukocyte accumulation and activation in dilated capillary loop worsen the condition, which is extensively involved in the pathogenesis of venous ulcer.¹¹

In summary, microcirculatory disorders progressively worsen with hemodynamic alterations. During this process, leukocyte adhesion to the vascular endothelium produces endothelial activation with release of proteolytic enzymes and free radicals in the tissues.¹² In addition, *in vitro* studies have demonstrated the release of prostaglandin (especially PGF₂) and basic fibroblast growth factor (bFGF), which may be directly involved in venous wall remodeling.¹³ These mediators are found in abnormal quantity in varicose veins.¹⁴ During this process, venous valves may be the first to be damaged.¹⁵

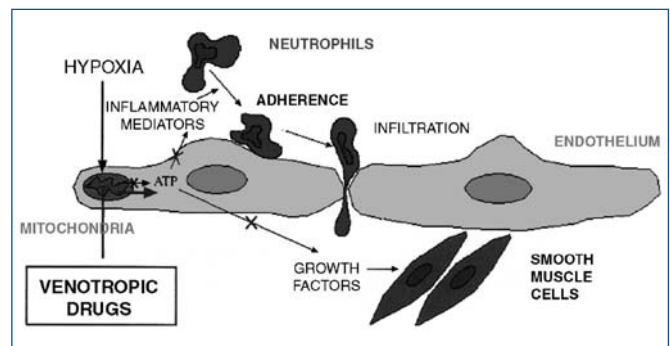


Figure 1. Possible protection of mechanism of endothelial cell by phlebotropic drugs.

The interaction between leukocyte and endothelium may be the key component in the pathogenesis of CVD and its complications, and may be an essential entity targeted by phlebotropic drugs.

Pharmacological action of phlebotropic drugs on these different targets

Remacle’s team has demonstrated the ability of phlebotropic drugs to inhibit the release of mediators of inflammation in endothelial cells placed under conditions of hypoxia (Figure 1).^{16,17}

A recent pharmacological study has demonstrated the ability of the micronized purified flavonoid fraction

(MPFF) to protect venous valves from destruction caused by venous hypertension.¹⁸ It is by inhibiting the expression of adhesion molecules on the surface of leukocytes and the endothelium that this phlebotropic drug limits leukocyte adhesion, and subsequently leukocyte infiltration into the valvular subendothelium, thereby limiting inflammatory events.¹⁸ This effect had been demonstrated previously with the same preparation in the microcirculation.¹⁹

CLINICAL TRIALS OF PHLEBOTROPIC DRUGS

Action on symptoms

Pain and heaviness in the legs are the two symptoms most commonly identified in studies on symptoms of venous disease.³

Symptoms and, in particular, pain, can be assessed with self-evaluation rating scales. Three types of scales have been validated:²⁰ the simple verbal scale, the numerical scale, and the visual analog scale. All these scales evaluate pain intensity but do not provide information on the nature of the pain. They can be used to compare intra-individual variations between groups of patients in evaluation studies, or longitudinal observational surveys.

Symptoms have an effect on the quality of life of patients with CVD. Overall assessment of quality of life allows quantification of the impact of symptoms on functional ability. Several quality-of-life questionnaires have been specifically adapted to CVD.²¹⁻²³

Evaluation of symptoms associated with venous disease, and of the expected benefit of therapy with phlebotropic drugs, is not easy because many intercurrent factors exist. However, many double-blind, placebo-controlled studies with a washout period have been conducted using measurable criteria for evaluation of pain and heaviness in the legs.

We will briefly summarize the studies conducted on calcium dobesilate,²⁴⁻²⁸ Horse chestnut extract,^{29,30} hydroxyrutin,³¹⁻³³ and micronized purified flavonoid fraction,³⁴⁻³⁷ and to which a few meta-analyses and reviews may be added.³⁸⁻⁴⁷ All these studies have confirmed the reduction in symptoms with all the different therapeutic agents. Quality of life was assessed during treatment with a phlebotropic drug. It markedly improved after 6 months of treatment, in particular in symptomatic patients, and was greater in patients in whom reflux had not been identified.⁴⁸

Action on edema

Several methods have been used to measure edema and study the efficacy of phlebotropic drugs on this sign.

The simplest method is measurement of ankle circumference, as done most often with a Leg-O-Meter®. This instrument, which has been validated,⁴⁹ takes into account the height at which the measurement is made. However, changes observed in ankle circumference are not always correlated with changes in volume of the lower limb. This is why methods to measure differences in leg volume are preferable. The most well-known is the volumetric method of fluid displacement,^{50,51} which has been validated.

Volumetric measurement has been used to show that the most painful legs are those affected by edema. Furthermore, the volumetric method has demonstrated that the standing position, or even prolonged sitting with no activity of the calf muscle pump system, produces an increase in leg volume. Moreover, such edema is correlated with the degree of venous insufficiency.⁵² Thus, this accounts for leg edema during long-distance airline travel. Other methods have been used to assess edema in CVD: the optoelectronic method,⁵³ the tomographic method,⁵⁴ high-resolution magnetic resonance imaging, and X-ray absorptiometry.⁵⁴

In the literature, randomized, controlled studies have demonstrated the efficacy of phlebotropic drugs on edema: Jaeger et al²⁵ and Casley-Smith²⁶ on calcium dobesilate, Vayssairat's study on naftazone,⁵⁵ Diehm's study on horse chestnut extract,⁵⁶ that of Blume on micronized purified flavonoid fraction,⁵⁷ and a study by Cesarone et al on the effect of hydroxyrutin^{58,59} on edema associated with long-distance airline travel. These studies have demonstrated a significant decrease in edema.

Action on chronic venous insufficiency: classes C4-C6

Few phlebotropic drugs have been studied in the treatment of chronic venous insufficiency. The phlebotropic drug most widely studied by far in venous ulcer and its complications is micronized purified flavonoid fraction.⁶⁰⁻⁶³ A recent meta-analysis of five clinical trials with this drug revealed its beneficial action on reduction of time needed for healing of venous ulcer.⁶⁴

Among phlebotropic drugs, horse chestnut seed extract,^{55,65} and hydroxyrutosides⁶⁶ reduce both edema and symptoms of chronic venous insufficiency, but are

not demonstrably better than compression in advanced chronic venous insufficiency,⁶⁵ or in preventing venous ulcer recurrence.⁶⁶ This may be because reduction in edema alone is insufficient to treat leg ulceration. Additional factors must be influenced in order to speed ulcer healing, which the micronized purified flavonoid fraction might be able to address. Recently, much attention has been focused on the involvement of growth factors,⁶⁷ and leukocytes in the development of venous ulceration.¹⁹ This has opened up new areas of investigation.

By reducing the likelihood of leukocyte adhesion, micronized purified flavonoid fraction presumably acts through an anti-inflammatory mechanism.¹⁹ Thus, among the many mechanisms at work in the pathogenesis of venous ulceration, the mechanism involving leukocyte activation and interaction with the endothelium seems at present to be the most responsive to pharmacological treatment.

ROLE OF PHLEBOTROPIC DRUGS IN THE TREATMENT OF CHRONIC VENOUS DISORDERS

Phlebotropic drugs have a well-established effect on edema. They also effectively decrease the so-called symptoms of venous disease, such as heaviness of the legs, pain, sensation of swelling, and nighttime cramps.

In both patients classified as having stage C0s disease, and in those classified as C1s and C2s for whom invasive therapy (sclerotherapy, surgery) does not appear warranted, phlebotropic drugs appear to be good first-line

treatment of chronic venous disorder, possibly in conjunction with compression therapy.

At more advanced disease stages, phlebotropic drugs have no demonstrable additional benefit over compression on improvement of skin changes, or in ulcer healing, except for micronized purified flavonoid fraction, which may be used in conjunction with sclerotherapy, surgery, and/or compression therapy, or as an alternative treatment when surgery is not indicated or is not feasible.⁴⁶



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Popliteal vein entrapment: an unrecognized cause of failure in surgery for superficial venous insufficiency

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SUMMARY

Positional compression of the popliteal vein syndrome, or popliteal vein entrapment, often goes unrecognized.

For the last 5 years, we have systematically sought to detect this condition in cases where clinical signs suggest its presence. These are: edema related to position, cramps associated with prolonged standing, exertional pain together with cramps and swelling of the calf muscle in athletes, and asymmetry of the circumference of the anterior and posterior tibialis muscles. The most frequent circumstances in which this condition is detected are:

- intensive muscle-building training in young women who practice high-risk sports;
- repeated recurrence of varicose veins in the area supplied by the short saphenous vein;
- recurrent sural vein thrombosis outside of any context of thrombophilia.

The diagnosis is confirmed by duplex scanning investigation with active and passive maneuvers, whose aim is to detect the position that triggers this condition. Imaging methods supplement the workup: dynamic venography, and dynamic MRI.

Surgery eliminates the compression at the cost of a relatively long incision to allow investigation of the vein along its entire length. A repeat check by perioperative maneuvers, possibly aided by electrical stimulation, confirms that the vein has been entirely freed in all positions. We operated on 11 patients, with immediate good results. In two patients, a supplementary aponeurotomy had to be performed.

Being aware of possible popliteal vein compression provides an effective solution to offer patients who are disappointed by the recurrence of their venous disorder.

INTRODUCTION

Although popliteal artery entrapment is a well-defined anatomic entity, whose treatment has received a broad consensus of approval, extrinsic compression of the popliteal vein syndrome, more recently recognized,¹ is rarely systematically sought.

Treatment of this condition is subject to differences in terms of methods and indications. Some authors have proposed the term “popliteal vein

Keywords:

popliteal vein, extrinsic compression, varicose vein recurrence, short saphenous vein.

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entrapment syndrome” to associate so-called “functional forms” and anatomical forms, observed more rarely.

We prefer to use the term “popliteal vein extrinsic positional obliteration syndrome” referring to the triggering position found in these two entities. We have observed this syndrome in young athletes. It then most often involves the effect of overly intensive or improperly balanced physical training.

However, the systematic search for positional compression, in certain cases of an incompetent short saphenous vein, has allowed us to diagnose popliteal vein compression as the origin of many varicose recurrences. These cases can help in providing relief to patients with a recurrence of varicose veins refractory to the usual therapies.

MATERIAL AND METHODS

Since 2001, the diagnosis of popliteal vein compression requiring surgical intervention has involved 11 patients in our center.

Variable circumstances of detection

- Repeated recurrence of varicose veins in the area supplied by the short saphenous vein: four cases;
- Rapid-onset edema or swelling of the calf muscle during exertion in a young athlete: three cases;
- Unilateral positional edema: two cases;
- Recurrent sural vein thrombosis without thrombocytopenia: two cases.

The patients’ ages ranged from 19 to 47 years: mean age = 28.4 years.

Eight out of the 11 patients were women.

The clinical examination consisted of the following

- A systematized interview to look for symptoms suggestive of this condition:
 - Exertional edema or after standing for a prolonged period;
 - Nighttime cramps or cramps occurring after prolonged sitting;
 - Lane’s sign: alternating weight-bearing of one lower limb on the other in the standing position;

- Calf pain after wearing shoes without heels;
- Heaviness in the legs without superficial or deep reflux.

- The examination measures the leg circumference to detect possible asymmetry found in 8 out of 11 cases (*Figure 1*). It records the existence of varices in the area supplied by the short saphenous vein.



Figure 1. Asymmetry of calf muscles: multiple varicose vein recurrence.

- Ultrasonographic hemodynamic examinations were performed with Esaote Partner duplex scanning and Hokanson continuous Doppler:
 - Duplex scanning of the popliteal vein is done in the standing position, with normal weight-bearing on the ball of the foot, with the knee locked in extension. The transducer is placed high on the popliteal vein to detect compression by the gastrocnemius muscle.
 - Duplex scanning of the popliteal vein with the patient in the prone position, with his or her feet extended over the examining table.
 - Morphological workup: to look for dilatation of the sural veins, in particular the posterior tibial veins, suggesting a soleus syndrome.
 - Looking for a decrease or abolition of the arterial signal of the posterior tibial artery at the ankle during forced flexion of the foot.
 - Passive maneuvers of the foot in flexion-extension, with the leg stretched against the thigh, with the transducer placed on the middle of the popliteal vein, and then on the upper part of the popliteal vein.

- Active maneuvers: of flexion of the foot against resistance to obtain optimum contraction of the calf muscles.
- Dynamic ascending venography was the main component of the diagnosis.
- Anterior and lateral views, with the leg at rest and then with flexion/extension of the foot; if necessary with the foot in weight-bearing position with the examining table tilted to 60, combined with varicography in cases of recurrent varicose veins. It was always performed in the surgeon's presence (Figures 2 and 3).
- We did not use modern imaging methods, ie, angio-scanning and angio-NMR, because venography confirmed the diagnosis.

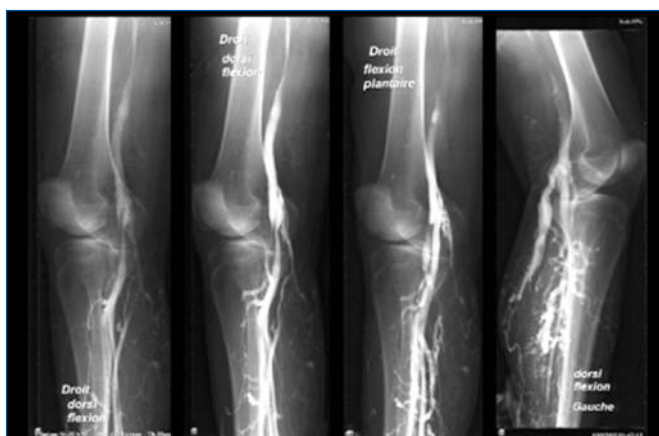


Figure 2. Preoperative venography: medial compression of the popliteal vein in varicose vein recurrence.



Figure 3. Preoperative venography: severe medial compression in a young athlete.

Surgery was performed under general anesthesia.

- The approach was as follows:
 - In three cases, internal approach to the ring of the soleus muscle in the case of low-situated compression (two cases), repeat procedure for four varicose vein recurrences (one case).
 - In 8 cases, posterior approach with a transverse incision 1 fingerbreadth from the point of flexion of the knee, and vertical or oblique extension as required during the dissection. Thus, the patient was installed in the prone position with his or her feet extended over the edge of the operating table to allow perioperative maneuvers.

A long vertical aponeurotomy provided the approach to the area. At the end of the procedure, it was converted into an aponeurectomy by resection of a triangular strip to prevent any compression upon closure.

In the case of varicose vein recurrence, an injection of sclerosing foam was administered, using a short 18 G catheter, at the periphery to limit additional phlebectomies and bleeding during the dissection. The sclerosing foam was obtained using Tessari's whirlpool method, with 1 part Lauromacrogol 1% and 4 parts air collected through a filter. The popliteal vein was located and progressively dissected. Small collateral vessels located on the lateral and posterior aspects were ligated with absorbable 3/0 suture thread. In the case of a neojunction, the latter was sectioned on a level even with the popliteal vein using sutures with 5/0 non-absorbable single suture thread. The perforating vessels in the popliteal fossa were treated in the same manner. By extending the dissection of the popliteal vein upwards, the anatomy of insertion of the gastrocnemius muscle was identified. In the case of abnormal insertion: three muscle heads, with lateral insertion, disinsertion was performed. Similarly, any muscular component crossing the vein (plantaris muscle) was sectioned. The vein was "cleaned" of all adventitial fibrous material. After releasing the venous axis, movements of flexion-extension of the foot were performed to aid in verifying the absence of compression by a muscular or residual fibrous component.

In the four patients who underwent surgery, a muscle stimulator was used to obtain active contractions, similar to the actual triggering clinical situation.

Drainage with a Redon drain was installed. Aponeurectomy was performed with closure of the skin. The patient was allowed to ambulate on the evening of

the day of the procedure and was discharged the next day, wearing an elastic compression stocking for 1 week. The following abnormalities were found:

- a third head of insertion of the gastrocnemius muscle: two cases;
- high and lateral insertion of this muscle: three cases;
- globular hypertrophy of the muscle: six cases;
- hypertrophy of the plantaris or popliteal muscle: four cases (*Figure 4*);
- perivenous fibrosis: seven cases;
- a fibrous strip crossing the vein: three cases;
- a postsurgical bend: three cases.

ie, a mean of about three abnormalities per patient.

Therefore, it is difficult to refer to a functional syndrome because surgery always revealed one or more anatomical causes of compression.

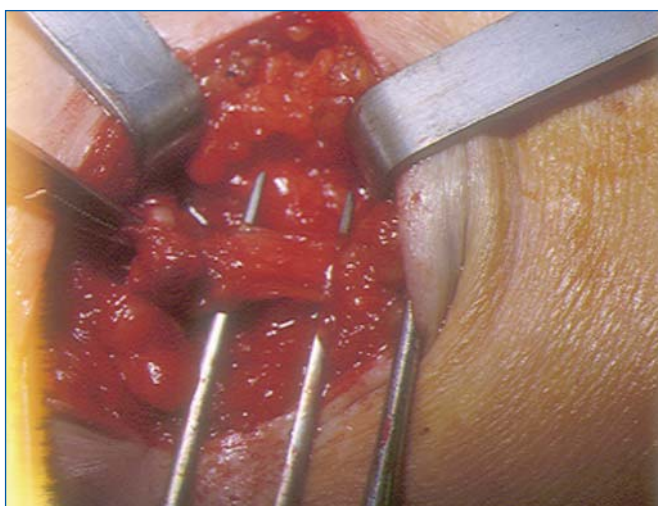


Figure 4. Perioperative view: hypertrophied popliteal muscle prior to sectioning.

RESULTS

Patients were seen again 1 month after the procedure, and then at repeat visits at 6 months and 1 year. Long-term monitoring was initiated with a hemodynamic evaluation every 2 years, except for patients with a varicose vein recurrence who were seen yearly. Symptoms improved in nine out of 11 patients. The two patients who remained symptomatic underwent repeat surgery for aponeurotomy of the tibialis muscle in the setting of a compartmental syndrome. Both of these patients were athletes who had resumed training during

the weeks following surgery. Heaviness in the calf muscle persisted in two patients, one of whom had sequelae of sural vein thrombosis.

The clinical signs, ie, positional edema, present prior to surgery in all of the patients, showed lasting improvement in eight: two presented with a recurrence on a more moderate level and did not undergo repeat surgery. In the two cases, edema was manifest in the seated position.

Calf circumference was increased by over 2 cm compared with the opposite calf in nine patients. It decreased by 1.5 cm on average in six, less than 1.5 cm in three, and was unchanged in two others.

In the last five patients who underwent surgery, an SF 12 Quality-of-Life questionnaire was filled out before the procedure, and at the first two repeat visits. It demonstrated a significant improvement with a mean of 34 before and 8 after surgery.

The four patients with repeated varicose vein recurrence who underwent surgery did not present any major recurrence during follow-up. Three of them underwent sclerosing therapy of collateral veins at the visits of 1 and 2 years.

The hemodynamic evaluation confirmed the elimination of extrinsic compression in the nine patients who underwent surgery.

The other two underwent repeat venography, which showed the persistence of a positional imprint that was less pronounced than preoperatively.

DISCUSSION

We diagnosed extrinsic compression of the popliteal vein in three different clinical situations:

- in active patients, often athletes, or patients whose occupation promoted hemodynamic decompensation;
- in patients who underwent surgery for an incompetent short saphenous vein;
- in the case of a recurrent sural vein thrombosis.

1/ Popliteal vein entrapment in athletes

By examining asymptomatic subjects, ie, medical students, Nicolaïdes² demonstrated the existence of postural impairment to emptying of the popliteal vein in 25% of cases.

Anatomical variations in the popliteal fossa are common, and bear witness embryonic development. Some variations consist of the existence of an additional bundle

for insertion of the gastrocnemius muscle, which becomes the artery, and the manifestation of ischemic disorders.

Other variations are less pathogenic: high, lateral insertion of this muscle, producing conditions favorable to venous compression in the case of an additional factor.

Currently, this factor is represented by athletic activity, especially in young women.

The practice of a sport that results in overdevelopment of the calf muscle, eg, weight lifting (bench press), is often a precipitating factor: we found this in 5 out of 7 subjects who underwent surgery.

In a series of 30 cases reported by Turnipseed,³ 27 were confirmed athletes whose mean age was 24 years.

Should these young women be subjected to surgery, which leaves a long scar, and whose cosmetic result cannot be guaranteed (frequent occurrence of keloids in this area)?

Raju and Neglen⁴ reported of 30 patients treated with surgery which can help to provide an answer. Their patients' mean age was clearly higher (49 years), 30% of them presented with advanced venous insufficiency with varicose ulcers. This internationally renowned team received patients considered as difficult cases, and thus there was a selection bias.

However, it is possible to consider that among subjects diagnosed at a young age, a significant percentage run the risk of progressing to chronic venous insufficiency if the obstacle to venous drainage is not removed. In addition, these subjects wish to resume their athletic activity: 24 of the 27 athletes operated on by Turnipseed resumed training under good conditions.

The surgical approach allows a less damaging procedure: Raju uses an internal approach, Turnipseed a short posterior medial approach focused on the insertion of the gastrocnemius. However, these limited approaches do not allow extended dissection of the popliteal vein, and thus run the risk of inadequate release with subsequent recurrence.

It may be useful to study a laparoscopic approach to the area in an effort to diminish the cost of a resultant scar.

Can the occurrence of this syndrome be prevented?

In an anatomically predisposed area, all subjects do not present with symptoms.

Nicolaïdes did not follow the long-term course and outcome of his medical students who had a hemodynamic obstacle: how many of them became symptomatic?

In the setting of sports medicine, it may be possible to consider having young women who engage in a "high-risk" sport answer a questionnaire aimed at screening to detect positional compression. In the case of replies suggesting this, a hemodynamic evaluation with duplex scanning would be ordered. The training program should then be adapted to take into account hemodynamic fragility, in particular avoiding contractions of the calf muscle in response to heavy loads, and by working more on elongation.

Another possibility would be perform an isolated aponeurectomy, which requires a small incision, but which could be sufficient to decrease the pressure exerted on the vein. The relationship found by some authors between popliteal vein entrapment and a compartmental syndrome encourages us to attempt this relatively noninvasive solution.

2/ Popliteal vein entrapment and varicose vein surgery

Four of our operated patients had undergone surgery for treatment of varices: one simultaneous resection of the long and short saphenous veins, three stripping of the short saphenous vein. All of them had presented with rapid-onset recurrence of varicose veins, 6 to 18 months after the first procedure. All of them had undergone repeat surgery at least once, and two had undergone three procedures!

The relationships between extrinsic compression of the popliteal vein and varices lie on several levels:

- Compression revealed by stripping

The saphenous veins are the main pathway of collateral circulation of obliteration of the popliteal vein in the case of a popliteal thrombosis. Acceleration of saphenous blood flow seen with Doppler scanning is a constant sign of this. Depending on the level of compression, the deep blood flow will be shunted either by the short or the long saphenous vein, as Gillot demonstrated in his venographic studies.⁵

Elimination of this collateral circulation can decompensate a fragile hemodynamic situation. The obstructive syndrome in the deep venous network then induces the recurrence of varices, which are accessory drainage veins. This process is explained, for example, by the secondary occurrence of reflux by the popliteal perforator vein following surgery of the short saphenous vein.

As long as the deep obstacle is not removed, varices recur, as was the case in our four patients.

- Compression induced by stripping

In a “borderline” anatomical situation, stripping can result in compression if the aponeurotomy of the saphenopopliteal junction is horizontal and if it is sutured at the end of the surgical procedure. This suture narrows the popliteal fossa and promotes postural compression.

Raju also believes that the stumps of a crossotomy can induce the formation of a fibrous tract that can produce a bend in the popliteal vein in some positions.

How to avoid these complication

In the preoperative assessment, it is important to detect popliteal vein entrapment, especially prior to surgery on the short saphenous vein.

Here too, as in athletes, the interview can provide pointers. A hemodynamic evaluation will be ordered. If positive, there should be no hesitation in ordering dynamic venography before performing an intervention. Prevention of an iatrogenic syndrome is based on making a vertical unsutured aponeurotomy at the end of the procedure. It is also necessary to ligate and section the collateral vessels, which can produce a bend in the popliteal vein. The operator should remember to perform dynamic maneuvers during the procedure.

3/ Recurrent sural vein thrombosis

Two of our patients presented with a sural vein thrombosis, which recurred during the months following the end of anticoagulant therapy. Laboratory tests did not reveal any coagulation abnormalities such as thrombophilia. Wakefield⁶ has described this possible etiology and the possible resultant sequelae.

This problem can be suspected based on clinical findings when calf edema persists in spite of deep repermeation,

and does not improve a few months after an acute episode. If the diagnosis is not established, these patients will be seen at the stage of chronic venous insufficiency, which was the case of Raju’s surgically treated patients. Our two patients with this disorder who underwent surgery have not had a recurrence 2 and 4 years after the procedure.

CONCLUSION

In the majority of cases, extrinsic compression of the popliteal vein is caused by hypertrophy of the gastrocnemius muscle when it is inserted higher than normal. Its clinical manifestation is often suggestive in young athletes. However, the examiner should be aware of this condition in the context of other presentations, in particular recurrent varicose veins in the area supplied by the short saphenous vein, or recurrent sural vein thrombosis. Surgical treatment is effective, at the cost of a scar, which is sometimes distressing for young women. In the future, endoscopic methods may provide a remedy for this shortcoming.



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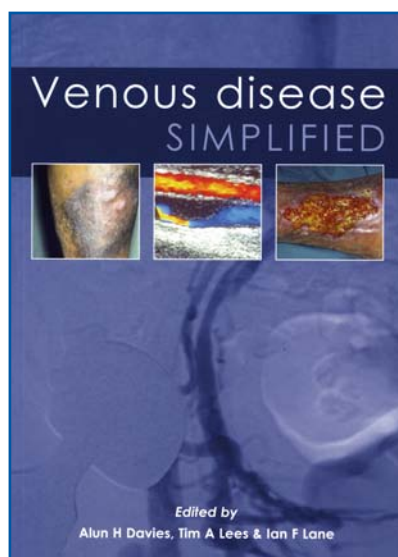
E-mail: rmilleret001@rss.fr

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Book review



Venous Disease Simplified

Editors:

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 2006, 240 pp.
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VENOUS DISEASE SIMPLIFIED

A review by John J. Bergan

In today's medical publishing, this book is unique. This is because it is almost entirely about venous insufficiency and venous reflux. Despite the fact that venous insufficiency is exceedingly common, no recent book deals exclusively with this subject.

This book brings under one cover the opinions of 25 physicians, most of whom have published heavily in British and international journals. Collectively, they have contributed clearly formulated chapters on primary varicose veins, management of recurrent varicose veins, quality of life, in addition to essays on symptomatology, history, and epidemiology. Altogether, very good and complete coverage of a very important subject.

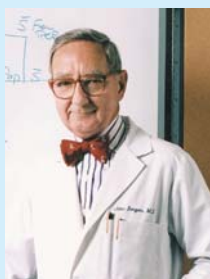
A single American surgeon, Joseph Caprini of Northwestern University, enters this august company. He has contributed the only chapter on venous thrombosis in an entire volume devoted to venous insufficiency. His chapter on thromboprophylaxis is the longest in this slim volume.

The most innovative chapter in what proves to be a very well written volume is by Linda de Cossart of Chester, UK. She emphasizes: "getting it right before patients get to the operating theatre," and provides a long and detailed checklist of how to do so. Example: "On reading the referral letter and meeting the patient, look up and greet the patient." Equally detailed is her list of what to do in the operating room. For example, when "performing the strip, you should be thinking: How do I get the stripper out of the limb with the best cosmetic results?"

As expected in this new century, new methods of vein ablation are included, but are not as dominant as might be expected. Mark Whiteley, a very experienced British surgeon, covers these in a single chapter. Philip Coleridge-Smith, whose chapter is so complete and informative that he includes a key reference from 1956 in the German language, fortunately counters Whiteley's brief views of foam chemical ablation of veins. His is perhaps the most forward-looking chapter in the entire book.

Venous reconstruction carries the imprint of Kevin Burnand, and a unique series of chapters have to do with nurse-led clinics, venous leg ulcer services, and quality of life in patients with varicose veins, and those with leg ulcers.

It's all here. From stripping to subfascial endoscopic perforator vein surgery (SEPS), and even beyond to recurrent varicose veins. This is a most



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informative book covering the important subject of venous insufficiency in a very condensed fashion. It is thoroughly up-to-date and modern, and should be in the library of every physician who has the slightest interest in venous disorders.

A review by Michel Perrin

This book, written mainly by physicians in the United Kingdom, with just about one exception, aims to provide an update on acute and chronic venous diseases of the lower limbs through a simplified presentation, as its title suggests. It is intended for general practitioners, specialist physicians not specializing in venous disease, angiologists, phlebologists, as well as vascular surgeons. But the latter will not find a detailed description of methods of investigation or surgical procedures.

The book is divided into 17 chapters, each of which ends with a descriptive insert clearly and precisely summarizing the main points of the chapter. Readers will notice the unfortunate absence of a chapter on anatomy, physiology, and pathophysiology.

After the usual historical review, epidemiological data are analyzed by the epidemiologist in the group who produced the Edinburgh survey. He clearly differentiates the classes of the CEAP classification, and, in particular, reminds the reader that the term chronic venous insufficiency should be reserved for the C3-C6 classes of disease. In the following chapter, the signs and symptoms of chronic venous disease are reviewed, as well as the manner in which the interview and physical examination should be conducted since, depending on the findings that they provide, instrumental investigations will be decided. Classically, these findings will be classified according to the anatomical and functional information they provide. Quality of life of patients who present with varicose veins or a skin ulcer is analyzed in two separate chapters, and the results of surgical treatment are objectively reviewed, in particular, the cost-to-efficacy ratio. It is emphasized that surgery for treatment of varices improves quality of life and symptoms, in spite of a recurrence rate of about 25% at 10 years.

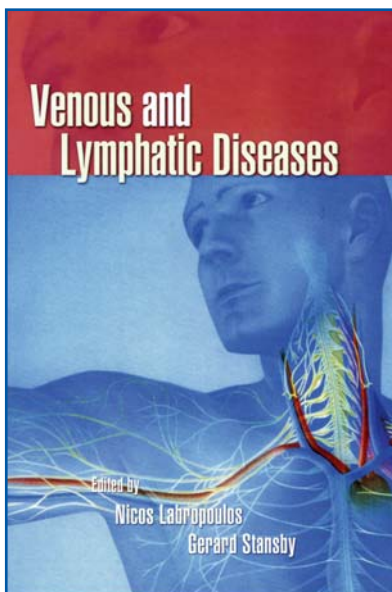
One of the three chapters devoted to varices is especially original: it describes advice that circumvents peri- and post-operative complications, and possible disappointment or complaints by patients treated with surgery. But the reader with a Cartesian mindset may be surprised by the fact that the indications for treatment are not the subject of recommendations.

On the other hand, the management of skin ulcers as performed in the United Kingdom, by nurses and physicians in specialized centers, deserves careful analysis and reflection. It shows an outstanding pragmatic approach.

Venous compression therapy and pharmacological treatments of chronic venous disease are not discussed. Sclerotherapy of venules, telangiectasias, and foam sclerotherapy are discussed in 2 separate, well-documented chapters. Thromboembolic disease is very well detailed with over 100 references and is

supplemented by a chapter on possible travel-related risks. Reconstructive deep vein surgery is discussed briefly.

Of course, as is true for all works written by several authors (25 in this book), contradictory opinions are voiced on certain points, but the overall presentation remains very consistent and of high quality. Some chapters are traditional, while others are truly original in format and content. References appear throughout the body of the text, and Internet web sites are listed. A limited number of black and white photographs are included.



Venous and Lymphatic Diseases

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VENOUS AND LYMPHATIC DISEASES

A review by John J. Bergan

This book is deceptive. Sitting on the desk it looks like a small novel. However, a glance at the Table of Contents reveals otherwise. Few books attempt to cover all of the problems of venous disorders, as well as those affecting the lymphatic systems of the extremities. This book does this task and does it exceedingly well.

There are six sections, which treat venous disorders, and an additional section, which deals with lymphatic disorders.

On the venous side, one of the strengths is the contribution by Alberto Caggiati, who provides an interesting and novel historical background, and then turns to another subject and provides a chapter on venous and lymphatic anatomy. He is, after all, Professor of Anatomy at the University of Rome. Professor Caggiati has been a part of the movement towards standardizing nomenclature of the veins. He includes the new terms in his chapter, also providing a very clear diagram of the saphenous compartment and its companion accessory saphenous veins.

Physiology of the veins and lymphatics is explained by Philip Coleridge-Smith, and no one can do it better.

Other chapters in this first section include epidemiology of venous disorders, health economics, and quality of life, as well as classification of chronic venous disease and outcome assessment.

The following sections are testimony to the authors' interest in providing a mixture of North American and European contributors. Junior authors are listed, but the chapters have the imprint of each of the senior contributors. There are chapters on clinical assessment, noninvasive evaluation, and invasive tests. A section follows the chapter on diagnosis of deep vein thrombosis. Because of the importance of this subject, its diagnosis,

epidemiology, treatment, relationship to malignant disease, and thrombolysis occupy the next seven chapters, each representing an authoritative opinion of an internationally well-known author.

The authors have not given short shrift to the subject of varicose veins. Here, there are eight chapters, including an interesting diversion into medical-legal aspects of treatment of varicose veins. It is appropriate that most of the authors in this section are from Europe and the United Kingdom.

Superficial venous surgery appears again in the section on chronic venous insufficiency, simply because the majority of patients with chronic leg ulcer have only superficial incompetence, with or without perforator incompetence.

Illustrating the fact that this is a complete book is the final venous section, which covers the subjects of upper extremity venous thrombosis, mesenteric and portal vein thrombosis, as well as superior vena cava obstruction and congenital venous abnormalities.

Reflecting their recent experience, the authors of the chapter on venous trauma are from Belfast, and cover their subject exceedingly well in very few pages.

Physicians and surgeons interested in venous disorders inevitably see a great number of patients with lymphedema. Only two chapters are devoted to this subject, but they are thorough, discuss clinical features, investigations, the role of conservative, medical, and surgical treatments, and the management of the very difficult problems of chylous ascites and chylothorax.

This is an excellent book on many important topics and could be a farewell gift to a good vascular trainee. It also belongs in the libraries of every teaching vascular service, both in America and abroad.

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*E-mail: francoise.pitsch@netgrs.com



Congress and conference calendar

■ SYMPOSIUM THERAPEUTIC APPROACHES TO VASCULAR DISEASE

This congress will be held in Maui (Hawaii) from January 15 to 19, 2007.

• *For further information, please contact:*

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Organizing secretariat:
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Web site: www.strandness-symposium.com

■ INTERNATIONAL FRENCH LANGUAGE ANGIOLOGY CONGRESS

This congress will be held in Paris (France) from February 2 to 3, 2007.

• *For further information, please contact:*

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Dr Michèle Cazaubon
145, rue de la Pompe
75 116 Paris, France

Tel: +33 1 47 27 10 63
Fax: +33 1 47 27 21 47

E-mail: micazang@noos.fr
Web site: www.sfa-online.com

■ CONTROVERSIES AND UPDATES IN VASCULAR SURGERY

This congress will be held in Paris (France) from January 19 to 20, 2007.

• *For further information, please contact:*

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E-mail: nfontant@aphenix.com
Web site: www.aphenix.com / www.cacvs.org

■ SIXTH ANNUAL MEETING OF THE AMERICAN VENOUS FORUM

This congress will be held in Rancho Bernardo Inn, San Diego (California, USA) from February 14 to 17, 2007.

• *For further information, please contact:*

President: Dr Michael C. Dalsing

Organizing secretariat:
203 Washington St
PMB 311
Salem, MA 01970, USA

Tel: +1 978 744 5005
Fax: +1 978 744 5029

E-mail: venous-info@administrare.com
Web site: www.venous-info.org

■ XXXIIND 2007 INTERNATIONAL ANGIOLOGY CONGRESS

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• *For further information, please contact:*

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118 01 Praha, Czech Republic

Tel: +420 257 007 629
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E-mail: uhrova@amca.cz
Web site: www.angiologie.cz

■ XLIST CONGRESS OF THE FRENCH COLLEGE OF VASCULAR PATHOLOGY

This congress will be held in Paris (France) in March 2007.

• *For further information, please contact:*

President: C. Olivier

Organizing secretariat:
Dr Pascal Priollet
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75 007 Paris, France

Tel: +33 1 55 04 82 13
Fax: +33 1 55 04 82 17

E-mail: cfpv-jmv@wanadoo.fr

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• *For further information, please contact:*

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92 100 Boulogne Billancourt, France

Tel: +33 1 46 43 33 00
Fax: +33 1 46 43 33 34

E-mail: congres@nex-com.com
Web site: www-palaisdescongres-versailles.com

■ XVIIITH CONGRESS OF THE EUROPEAN CHAPTER OF THE INTERNATIONAL UNION OF ANGIOLOGY (EUROCHAP) – A SOCIETY FOR VASCULAR MEDICINE AND SURGERY AND VASCULAR INTERVENTIONS

This congress will be held in Lefkosia (Cyprus) from April 26 to 29, 2007.

• *For further information, please contact:*

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■ **VITH NORTH SEA CONGRESS ON
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YOUNG AND VERY OLD PATIENTS**

This congress will be held in Amstelveen (the Netherlands) from May 11 to 12, 2007.

• *For further information, please contact:*

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This congress will be held in Praha (Czech Republic) from May 12 to 13, 2007.

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E-mail: meet@meetandwork.com
munerett@med.unibs.it
Web site: www.meetandwork.com
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■ **THE ASIAN CHAPTER MEETING OF THE
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This congress will be held in Kyoto (Japan) from June 18 to 20, 2007.

• *For further information, please contact:*

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■ VIIIITH MEETING OF THE EUROPEAN VENOUS FORUM

This congress will be held in Istanbul - Marmara Hotel, Taksim square (Turkey) from June 29 to July 1, 2007.

• *For further information, please contact:*

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Organizing secretariat:

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Web site: www.evf2007istanbul.org

■ FRENCH SOCIETY OF VASCULAR MEDICINE

This congress will be held in Brest (France) in September 2007.

• *For further information, please contact:*

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Organizing secretariat:

Alexandra Leclerc - Elizabeth Negre

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■ XXXVIITH BRAZILIAN CONGRESS OF ANGIOLOGY

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Web site: www.sbacv.org.br

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President: Prof Salvatore Novo

Organizing secretariat:

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Fax: +1 510 832 7300

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■ **XVITH WORLD MEETING OF THE UNION INTERNATIONALE DE PHLEBOLOGIE (UIP)**

This congress will be held in the principality of Monaco from August 31 to September 4, 2009.

• *For further information, please contact:*

Chairman of scientific committee:

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■ **XXIVTH WORLD CONGRESS OF THE INTERNATIONAL UNION OF ANGIOLOGY (IUA)**

This congress will be held in Buenos Aires (Argentina) from April 21 to 25, 2010.

• *For further information, please contact:*

President: Prof Salvatore Novo

Organizing secretariat:

Ana Juan Congresos

Malasia 884 (C1426BNB)

Buenos Aires, Argentina

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Web site: www.iua2010.com.ar (available from October 2006)

More information on Venous or Lymphatic Diseases ?



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