Diagnostic and therapeutic management of venous and arterial disease

Bernardi, E.

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INTRODUCTION

Enrico Bernardi

From: Department of Emergency Medicine and Observation,
University Hospital of Padua, Italy

Deep-vein thrombosis (DVT) constitutes a challenge for the both the healthcare professionals and the society; because, when gone unnoticed, it may recur, cause permanent leg impairment (i.e. the post-thrombotic syndrome), or even death;\(^{1,5}\) while, if timely detected and properly treated, it is associated with a significantly lower morbidity,\(^{6-8}\) though the shortcomings of treatment, including (fatal) bleeding and thrombocytopenia, despite continuous improvements, cannot be completely eliminated.\(^{9-12}\)

The clinical course of subjects presenting with (or referred for) suspected DVT usually begins with a diagnostic phase, to confirm or rule out the disease. If DVT is adjudicated, then the patient will follow a typical pathway, encompassing initial treatment (either in hospital or at home); secondary prophylaxis (with various length, according to if the DVT episode is apparently unprompted, or associated with either continuous or temporary risk factors), and a period of monitoring with on-demand clinical evaluations, to ensure early detection of serious bleeding events (if still on anticoagulants), of recurrent venous thromboembolism, or other complications of DVT, including the post-thrombotic syndrome. If, otherwise, DVT is ruled out, he or she will be discharged, possibly with further indications to establish the likely cause of the initial complaints; including peripheral arterial disease of the lower extremities.

The material included this thesis spans about the last 10 years, and witnesses the scientific progresses achieved in the management of this disease; in particular with regard to: (a) the diagnostic approach to suspected DVT, either for the first time or in case of recurrent episodes (Chapters 1 to 4); (b) the treatment of established DVT (Chapters 5, 6); and, (c) the clinical course of DVT (Chapters 7, 8).

Thrombus formation constitutes a final common event triggered by the different (but also overlapping) risk factors for venous thromboembolic and atherosclerotic disease;\(^{13}\) and venous thromboembolism is associated with symptomatic peripheral arterial disease.\(^{14-16}\) Indeed, many drugs (heparin and deriva-
tives, vitamin K inhibitors, thrombolytics, statins, and even antiplatelet agents) are currently used for the initial treatment and the primary or secondary prophylaxis of both diseases. Notably, consensus on the efficacy of the various drugs commonly prescribed for conservative (non-surgical) management of patients with atherosclerosis of the lower extremities is still lacking. The last part of this work (Chapters 9, 10, and 11) systematically reviews the evidence supporting the state-of-the-art strategies for the conservative management of patients with peripheral arterial occlusive disease.

Diagnosis of deep-vein thrombosis

First episode of suspected DVT

The diagnosis of DVT was usually based on clinical grounds, until the validity of such an approach was questioned on a scientific basis; after that, “objective” methods (in contrast with the “subjectivity” of clinical diagnosis) would be used to rule in or exclude suspected DVT. Ascending contrast venography is generally accepted as the gold-standard, based on the fact that it allows for a direct visualisation of thrombi within the deep-vein system of the legs, either located in the proximal or in the distal veins. Furthermore, as venography allows a one-step diagnosis, all patients are usually managed on the same day of referral. Unfortunately, this technique has many drawbacks limiting its widespread application, including invasiveness, costs, discomfort for the patients, risk of serious adverse reactions to contrast dye, risk of post-phlebographic DVT, scarce availability outside research centres, and even a low diagnostic yield if not performed and interpreted by an experienced staff. Despite these considerations, venography is still employed; either in common practice, especially in the case of high-risk asymptomatic inpatients with suspected DVT; or in the research setting, as in the case of randomised trials investigating therapeutic and prophylactic strategies for DVT. Two non-invasive tests, impedance plethysmography (IPG) and compression ultrasonography (CUS), actually represent the commonest approaches to evaluate suspected DVT in symptomatic outpatients. Both tests, as compared with venography, are rapid and easy to perform, do not mandate the involvement of specialists or professionals, and are theoretically independent of time, place, and patients’ condition. However, due to their intrinsically low sensitivity to either non-occlusive (IPG) or isolated-calf DVT (CUS), both tests have to be performed in series, during the first 7- to 14-days period after referral. To reduce the number of (unnecessary) repeated testing, it was suggested that
baseline instrumental findings were to be coupled with the results of laboratory testing, or of standardised questionnaires assessing the pre-test clinical probability (PCP) of DVT.\textsuperscript{27,28} Among the various markers of blood coagulation and fibrinolysis (e.g. fibrin monomer, F\textsubscript{1+2}, TAT) that were investigated in this respect, D-dimer proved to possess a higher accuracy than the others.\textsuperscript{29} Several D-dimer assays are commercially available, that may differ in terms of outcomes (qualitative, semi-quantitative, or quantitative data), or in the way they are to be performed (manually or on automated coagulometers), or in the type of reaction involved (ELISA; latex, or red blood-cells agglutination).\textsuperscript{10}

**Chapter 1** is a diagnostic management study, in which the safety and feasibility of a novel compound diagnostic strategy, based on the results of CUS and of a D-dimer assay, is evaluated prospectively. Namely, all symptomatic outpatients with suspected DVT and a normal baseline CUS result underwent D-dimer (Instant I.A.) testing: if the latter was also normal, patients were not to receive treatment or further CUS testing; while, if D-dimer results were abnormal, patients were scheduled for repeat CUS evaluation at 1 week. A follow-up of 3 months was arranged for all patients with a normal diagnostic work-up, in order to detect thromboembolic complications. Similarly, in **Chapter 2**, another management study is described, in which the diagnostic value of combining CUS and D-dimer was evaluated in a cohort of symptomatic outpatients with suspected DVT. The approach used is identical to that described in Chapter 1, except for a different D-dimer assay (SimpliRED), a rapid whole-blood test, was used in combination with CUS. Additionally, a PCP assessment was prospectively obtained in all patients. As PCP scores were obtained for all patients at presentation, the potential value of combining this clinical information with D-dimer results could be addressed in a scenario analysis.

**Recurrent DVT**

A variable proportion (15 to 30%) of the subjects presenting with clinically suspected DVT will have abnormal findings on objective testing,\textsuperscript{31} during the subsequent course, some of these patients, irrespective of the treatment, will develop new or worsening leg symptoms, suggesting the presence of recurrent DVT. Whichever the case, clinicians will now be faced with a difficult task, as only one third, roughly, of patients with symptoms suggestive of recurrent DVT will indeed have the disease; implying that up to 70% of these patients would receive unnecessary (often lifelong) anticoagulant treatment if the diagnosis were based on clinical grounds only.\textsuperscript{32}
Symptomatic patients presenting with a first episode of suspected DVT are usually managed on the results of simple non-invasive diagnostic strategies. Conversely, there is no consensus on the preferred diagnostic procedure for recurrent DVT, as both invasive and non-invasive methods usually applied in the case of clinically suspected DVT are limited in this context.

Contrast venography is established as gold-standard for the diagnosis of recurrent DVT based on its ability to visualize the whole deep-vein system, as in the case of the first episode of suspected DVT, albeit no study ever evaluated venography with this indication. The interpretation of venography in case of suspected recurrence would require both a baseline venographic study, typically performed at the time of the first episode of DVT, and highly qualified personnel, as the deep-vein system usually undergoes significant rearrangement after the first thrombotic episode.

In this respect, as most of the patients with a first episode of suspected DVT are currently managed on the basis of non-invasive techniques (CUS or IPG), there is scarce availability of such baseline studies; and experienced radiologists, able to correctly interpret venograms even in case of suspected recurrent VTE, are even scarcer outside highly specialised research centers.

Based on these considerations, it is possible to affirm that, with this indication, venography is going to become somewhat obsolete. On the other hand, newer invasive imaging techniques, including contrast-enhanced three-dimensional magnetic resonance venography, and spiral-CT venography, albeit promising, deserve further evaluation.

Among non-invasive methods, only serial IPG, alone or in combination with leg scanning and venography, and serial CUS were adequately investigated in the diagnostic approach to patients with suspected recurrent DVT.

The combined strategy of serial IPG, 125I-fibrinogen leg scanning and venography, albeit safe and effective for the management of patients with suspected recurrent DVT, is actually abandoned because of concerns regarding the biological safety of injecting patients with radio-labeled human fibrinogen. On the contrary, although IPG is declining as diagnostic test for patients with a first episode of suspected DVT (due to its reduced sensitivity in populations at lower pretest probability than the original validation cohorts, and possibly to the favourable results obtained with CUS), serial IPG is still recommended for the management of patients with recurrent DVT, albeit in a composite strategy including CUS, and venography.

At the moment, serial CUS (alone or in combination with PCP or D-Dimer) is the preferred management strategy for patients with a first episode of suspect-
ed DVT. However, if only the (qualitative) criterion of full vein compressibility were to be applied, CUS can only be employed in the evaluation of patients with recurrent symptoms with a normalised CUS. According to published studies, normalisation rate is around 50% during the first year after DVT; thus, current evidence indicates that serial CUS is of limited value for the diagnostic management of patients with suspected recurrent DVT.

Recently, a different (quantitative) conception of CUS gained popularity, based on the estimate of "thrombus thickness" (that is, a progressive reduction of the diameter of an incompressible vein under maximal compression due to either the anticoagulant treatment and spontaneous fibrinolysis after the initial thrombotic episode); specifically, up to a 50% reduction of the residual thrombus thickness, as compared with previous measurements, was observed after a 3-month follow-up in 2 separate studies.

Chapter 3 introduces a novel combined CUS method, based on two criteria: the vein incompressibility criterion (qualitative), and the thrombus thickness measurement (quantitative), the latter was validated using venography as the reference test. The study consisted of 2 steps, a cross-sectional survey and a prospective investigation: in both phases the normalisation rate of a previously abnormal CUS test was assessed; however, in the cross-sectional survey the combined CUS method was executed only once, whereas in the prospective phase it was performed repeatedly, at scheduled times (at 1, 3, 6, and 12 months) after the initial DVT episode. Moreover, during the prospective investigation, patients presenting with suspected DVT recurrence underwent repeat testing and results were compared to those available from the previous examination. Recurrent DVT was adjudicated if a previously normal or normalised venous segment had become non-compressible or if thrombus thickness was increased ≥2 mm as compared with the previous measurement. Confirmatory venography was mandatorily obtained within 24 hours, and the patients managed accordingly.

Recently, we validated the combined CUS method in a prospective cohort study. This investigation, described in Chapter 4, was principally designed to assess the safety of withholding anticoagulation from patients with a normal serial combined CUS work-up. Patients with baseline stable or improved CUS findings had 2 repeated ultrasound assessments within 1 week (at day 2 (±1) and 7 (±1), respectively). Patients with normal serial CUS results were not treated, and were followed-up for 6 months to determine the incidence of symptomatic recurrent thromboembolism. Furthermore, to assess the positive predictive value of the combined CUS method, all patients with abnormal results of
either the baseline test or the serial evaluation were also scheduled for confirmatory venography.

**Treatment of DVT**

Once a definite diagnosis of DVT has been accomplished, patients need to be treated in order to reduce the risk of (fatal) recurrent venous thromboembolism (VTE). Low-molecular-weight heparins (LMWHs), albeit equivalent to unfractionated heparin (UFH) in terms of safety and efficacy, are now established as the first therapeutic option for VTE especially because of some peculiar features, including the possibility of being administered once-daily on an outpatient basis, the lower incidence of type-2 heparin-induced thrombocytopenia, and the lower likelihood of osteoporosis after prolonged treatment periods. Nonetheless, UFH still remains the drug of choice for the initial treatment of acute venous thromboembolism in many countries, including the United States.

The administration of therapeutic UFH doses is generally regarded as a cumbersome task, since, due to its pharmacokinetics, and unlike LMWHs, UFH cannot be given in fixed doses, and has to be targeted on the results of laboratory tests, usually the activated partial thromboplastin time (aPTT), to a predefined "therapeutic" range. Despite frequent aPTT determinations, it is very difficult to stick to the mentioned aPTT range, and often the patients' aPTT will remain well below or above it; in the former case the risk is that of under-treatment, and consequently, of a higher incidence of recurrent VTE; in the latter, the potential hazard is that of over-treatment, and thus of a higher frequency of (major) bleeding episodes. A UFH nomogram is standardised guideline which should potentially assure a timely achievement of therapeutic aPTT levels in most treated patients. Chapter 5 is a both a conventional and a quantitative review of the published clinical studies on the implementation and validation of UFH dosing nomograms. The use of such algorithms virtually assures that all treated patients will promptly achieve adequate levels of anticoagulation, thus decreasing the likelihood of recurrent venous thromboembolism without extra bleeding-risk.

Based on the observation coming from Chapter 5, and on the fact that LMWHs were still not licensed for therapeutic administration in Italy, we implemented a weight-based algorithm for treatment of DVT with subcutaneous UFH. In Chapter 6, a prospective cohort trial to test the usefulness of the mentioned nomogram is described. Symptomatic outpatients with a first episode of (CUS)
documented DVT were administered subcutaneous weight-adjusted UFH after a single intravenous UFH loading dose. We choose the intravenous route for the initial UFH bolus because of the poor bioavailability of subcutaneous UFH;\textsuperscript{49} while we selected the subcutaneous route since subcutaneous UFH is equivalent to intravenous UFH,\textsuperscript{54} but warrants some additional benefits, including a prompt mobilisation and, possibly, an early discharge of suitable patients; finally, we opted for a weight-based algorithm because weight is recognised as the single best predictor of individual heparin requirements.\textsuperscript{53} The study end points were: the proportion of patients achieving aPTT levels above the lower limit of the therapeutic range within 24 and 48 hours, and the number of patients with aPTTs above the upper limit of the range for >12 hours. Furthermore, we also assessed the rate of recurrent VTE during a 3-month follow-up and that of major bleeding occurring during heparin treatment and in the following 48 hours.

**Clinical course of DVT**

Long-term prospective follow-up studies of patients who suffered a single episode of documented DVT clearly demonstrated that VTE is a chronic disease, as the rate of recurrence continuously increases up to 10 years after the initial episode.\textsuperscript{8,54-56} Among recognised determinants of the incidence and time of onset of recurrence, idiopathic DVT, the presence of persisting risk factors (i.e., thrombophilia and cancer), the adequacy of initial heparin treatment, and the duration of secondary prophylaxis with oral anticoagulants are those supported by a more robust evidence.\textsuperscript{57} Nevertheless, VTE recurs even in patients with a low-risk profile, as those with removable risk factors (i.e., without cancer or coagulation abnormalities).\textsuperscript{38} Recent randomised trials indicate that, prolonging the duration of secondary prophylaxis with oral anticoagulants after a first episode of (idiopathic) VTE results in a significant (>90%) reduction of the recurrent VTE rate;\textsuperscript{59,60} and as long as anticoagulation is maintained, the incidence of recurrence is definitely low (<5%) albeit paid at the price of a higher risk of (major) bleeding.\textsuperscript{49} Among patients with a history of DVT, those affected by cancer appear to be at a higher risk for both recurrent VTE and bleeding while on anticoagulants;\textsuperscript{61-66} and in those patients a lifelong anticoagulation is usually indicated.\textsuperscript{49} Furthermore, is still uncertain whether this higher risk profile during anticoagulation applies to all cancer patients or depends on the tumor type or stage.

In **Chapter 7** we analysed data from consecutive patients with symptomatic DVT to evaluate if, during anticoagulant treatment, patients with cancer are
exposed to a higher risk for recurrent VTE and major bleeding than those without. As short-term mortality is usually high in this population we restricted the follow-up analysis to a maximum of 1 year.

Following DVT, a number of patients will complain new or worsening leg symptoms, including pain and swelling, suggesting recurrent DVT; however, in only 30% of them, roughly, recurrence will be objectively confirmed; while, the rest will be labelled as “not having” the disease. Such a “negative” diagnosis, though satisfying for the clinician, is quite often frustrating for the patients, as they, indeed, are facing a new or worsened situation, both troublesome and invalidating. Verily, some of these subjects are being affected by a complication of DVT, the post-thrombotic syndrome (PTS). The clinical presentation of PTS may vary between a mild form, characterised by swelling, pain, skin changes, and dilated superficial veins, to severe manifestations such as chronic pain, pitting oedema, and even leg ulcer. **Chapter 8** provides an outline of various aspects of PTS, including incidence, pathophysiology, diagnosis, treatment and prognosis.

**Treatment of peripheral arterial disease**

Peripheral arterial disease (PAD) is a common disease in Western countries, as its incidence reaches 1% per year after the age of 65. It is most frequently related to atherosclerotic narrowing of the arteries of the ilio-femoral district, often in combination with similar lesions in the more distal arteries of the leg. The clinical picture is characterised by the appearance of sharp pain at the calf, the thigh, or the buttocks during exercise (stage II, according to Fontaine’s classification), or at rest (Fontaine’s stage III); on top of pain at rest, some patients (Fontaine’s stage IV) even experience the appearance of skin ulcers and gangrene (usually of the foot).

Intermittent claudication (Fontaine’s stage II), the commonest form of PAD with an estimated prevalence around 5% in males over 50 years, is associated with generalized atherosclerosis, responsible for a 2-fold increased death rate in these patients, largely from myocardial infarction and stroke, as compared to individuals without intermittent claudication. Follow-up studies have shown that intermittent claudication improves spontaneously in 40% of the patients, and worsens in only 10-20% (leading to amputation in 7% within 5 years). Many treatment modalities for intermittent claudication are available, either active or just symptomatic, including conservative strategies (physical, pharmacological), and surgical procedures (revascularisation), and the relative value of these treatment modalities is controversial.
In Chapter 9 and 10 the current options for the conservative treatment of patients with intermittent claudication are reviewed. Chapter 9 attempts to critically evaluate the evidence supporting the recommendation of the more commonly prescribed strategies for this disease (physical training, smoking cessation, pentoxifylline, and nafronyl); whereas Chapter 10 reviews the potential usefulness of antiplatelet drugs (aspirin and dipyridamole, ticlopidine, clopidogrel, sulocitil, picotamide, indobufen) and anticoagulant drugs (e.g., LMWHs, vitamin K inhibitors, defibrotide) in the conservative management of intermittent claudication.

Up to 25% of patients with PAD, regardless the Fontaine's stage, will undergo revascularisation procedures (i.e., bypass grafting, PTCA, endoarterectomy) within 10 years from the onset of symptoms, and, lacking additional treatment, reocclusion will occur in 20-60% of cases within 5 years from the intervention. As re-thrombosis and neointimal fibrous hyperplasia are certainly involved in reocclusion, the use of anticoagulant or antiplatelet agents seems a rational approach to improve the long-term patency of re-opened vessels. Moreover, these patients have a higher mortality rate than the general population, mainly related to myocardial infarction and stroke, and antithrombotic agents may improve their survival by reducing the incidence of such cardiovascular end-points. However, their effectiveness, both for maintaining patency and preventing death in this patients group, is still controversial. A systematic review (meta-analysis) of the available evidence related to the use of antiplatelet therapy (aspirin, ticlopidine), and other interventions (vitamin K inhibitors) after revascularisation procedures in patients with PAD is provided in Chapter 11.

References


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