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# Phlebolymphology



## Aims and Scope

***Phlebolymphology*** **is an international scientific journal entirely devoted to venous and lymphatic diseases.**

**The aim of *Phlebolymphology* is to provide doctors with updated information on phlebology and lymphology written by well-known international specialists.**

***Phlebolymphology*** **is scientifically supported by a prestigious editorial board.**

***Phlebolymphology*** **has been published four times per year since 1994, and, thanks to its high scientific level, is included in several databases.**

***Phlebolymphology*** **comprises an editorial, articles on phlebology and lymphology, reviews, and news.**

## Correspondence


**Editorial Manager**
**Hurrem Pelin YALTIRIK**
Servier Affaires Médicales
35, rue de Verdun,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 38 98
Email: hurrem-pelin.yaltirik@servier.com

**Publication Director**
**Christophe CHARPENTIER**
Suresnes, France

**Publisher**
**Les Laboratoires Servier**
50, rue Carnot,
92284 Suresnes Cedex, France
Tel: +33 (1) 55 72 60 00


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# Content

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# Editorial

**Dear Readers,**

In this new issue of *Phlebolymphology*, you will find the following articles:

**P. PRANDONI *(Italy)*** conveys important considerations regarding the risk of recurrent venous thromboembolism (VTE) after the interruption of anticoagulation, subsequent to an unprovoked or weakly provoked episode of VTE. The author suggests a risk stratification in order to identify those patients in whom anticoagulant therapy can be safely interrupted.

**A. N. NICOLAIDES *(Cyprus)*** draws attention to a frequent pathology: isolated deep venous thrombosis (DVT) of the calf. In these cases, routine anticoagulant therapy is controversial. The analysis of randomized clinical trials provides us with a clear indication for treatment with direct oral anticoagulants (DOACs).

The current possibility of recanalizing an iliocaval obstruction with a venoplasty-stenting technique is illustrated by **M. LUGLI *(Italy)*** who underlines the importance of carefully selecting patients to undergo this procedure. Deep vein obstruction is a primary cause of severe chronic venous insufficiency and impaired quality of life, especially in young patients affected by postthrombotic syndrome. Besides medical and compression therapies, which undoubtedly still represent the standard of care, an operative approach in selected cases should be considered today. Venoplasty and stenting for deep vein recanalization of the iliocaval segment have demonstrated efficacy, leading to satisfactory results with a low complication rate, thus suggesting an increasingly broad approach to this treatment.

Enjoy reading this issue!

*Editor in chief*
**Dr Oscar Maleti**

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# Extended treatment of venous thromboembolism

**Paolo Prandoni**, MD, PhD

Arianna Foundation on Anticoagulation, Bologna, Italy

## ABSTRACT

After discontinuing anticoagulation, the risk of recurrent venous thromboembolism (VTE) in patients suffering an episode of unprovoked or weakly provoked VTE ranges between 30% and 50%, the rate being higher in patients with primary deep venous thrombosis (DVT). Baseline parameters that increase this risk are male sex, obesity, carriership of thrombophilia, proximal location of DVT, and renal failure. While the latest international guidelines suggest indefinite anticoagulation for most such patients, new scenarios are being offered through the availability of risk stratification models that have the potential to identify patients in whom anticoagulation can be safely discontinued because of a low risk of recurrence, and those in whom extending anticoagulation is undesirable because of a high risk of bleeding. Low-dose apixaban and rivaroxaban are the mainstay of extended treatment of VTE in all patients, except those who are carriers of the antiphospholipid syndrome. As an alternative, low-dose aspirin and sulodexide have been reported to decrease the risk of recurrent events by 30% to 50% without increasing the bleeding risk.

**Keywords**

anticoagulation, aspirin, D-dimer, deep venous thrombosis, direct oral anticoagulants, pulmonary embolism, risk stratification models, sulodexide, venous thromboembolism, vitamin K antagonists

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# Clinical case

A 76-year-old male presented with unprovoked deep venous thrombosis (DVT) in his left leg, without symptoms of pulmonary embolism (PE). Compression ultrasonography confirmed DVT, showing incompressibility of the popliteal vein and of the distal segment of the superficial femoral vein. He had no personal or family history of venous thromboembolism (VTE), and tests for thrombophilia and occult malignancy were negative. He was treated with apixaban, starting with a loading dose of 10 mg twice daily for 1 week, followed by 5 mg twice daily for 6 months. Repeat ultrasonography showed recanalization of the previously affected veins. The question now is whether to discontinue anticoagulation, continue with the same dose, or switch to a low-dose regimen (2.5 mg twice daily) of apixaban.

# Rationale for extending anticoagulation in patients with unprovoked or weakly provoked venous thromboembolism

The optimal duration of anticoagulation in patients presenting with a first episode of proximal DVT and/or PE remains controversial. Historically, most patients with VTE (ie, all except those with major persistent risk factors, such as cancer) had their treatment discontinued after 3 months.[1] Recent evidence and new guidance suggest that this approach is overly simplistic, as it fails to consider patients with VTE that is either unprovoked or associated with minor (transient or persistent) risk factors, which are summarized in *Table I*.

The risk of recurrent VTE after discontinuing anticoagulation in patients with a first episode of unprovoked or weakly provoked VTE was assessed in a recent comprehensive meta-analysis of 18 studies.[2] Overall, the risk of recurrent VTE was found to be high, approaching 30% and 40% after 5 and 10 years, respectively, in men; 20% and 30%, respectively, in women. Besides male sex, factors that were found to be consistently associated with an increased risk of recurrent VTE were the proximal location of DVT, obesity, thrombophilia, and renal failure.[2] This risk is not impacted by the duration of anticoagulation prior to its discontinuation. Indeed, based on the analysis of individual participant data from 7 randomized clinical studies addressing different durations of anticoagulation, prolonging anticoagulation beyond the first 3 months up to 6, 12, or even 27 months was associated with a similarly high risk of recurrent VTE once anticoagulation was discontinued.[3] These findings have recently been confirmed by those of PADIS PE (Prolonged Anticoagulation During Eighteen Months vs Placebo After Initial Six-month Treatment for a First Episode of Idiopathic Pulmonary Embolism), a multicenter randomized clinical trial performed in France, where approximately 400 patients with unprovoked PE were randomized to receive either 6 or 18 months of anticoagulation.[4]

| Persistent risk factors | Transient risk factors |
|---|---|
| ***Major*** | ***Major*** |
| Active cancer | Major surgery or trauma |
| Major thrombophilias | Caesarean section |
| ***Minor*** | ***Minor*** |
| Intestinal inflammatory disease | Prolonged immobilization (>1 week) |
| Paralysis or paresis of a lower limb | Long trip (>8 hours) |
| Heart failure | Pregnancy or purperium |
| BMI >30 | Estrogen use |
| Creatinine clearance <50 mL/min | Leg trauma with reduced mobilization |
| Family history of VTE and/or minor thrombophilias | Knee arthroscopy |

*Table I.* Risk factors of venous thromboembolism.

**Abbreviations:** BMI, body mass index (calculated as weight in kg/height in m$^2$); VTE, venous thromboembolism.

Patients with a first symptomatic DVT are at higher risk of recurrent VTE than those with a first unprovoked PE.[5] In addition, patients with clinically symptomatic PE have consistently been found to be at a higher risk of recurrent PE than those with DVT alone. These findings have recently been confirmed by a patient-level meta-analysis.[6] According to the same meta-analysis, the clinical presentation with PE (alone or associated with DVT) increases by more than 3 times the risk of a new PE episode over the clinical presentation with isolated DVT.[6]

Unfortunately, prolonging anticoagulation beyond the first 3 to 6 months with the use of vitamin K antagonists (VKA) exposes to a high risk of unpredictable major bleeding complications.[7] In addition, whereas the expected rate of fatal bleeding during anticoagulation for 1000 patient-years

is comparable to that of fatal (recurrent) PE, the case-fatality rate of major bleeding complications (consistently around 10% to 12%) is considerably higher than that (3%-4%) for recurrent VTE events.[8]

Accordingly, administering for a fixed duration an anticoagulation therapy—except for patients at high risk of bleeding complications—and administering on a routine basis an indefinite treatment with VKA after a first episode of VTE that is either unprovoked or associated with weak risk factors of thrombosis should both be abandoned. An exception should be made for carriers of the antiphospholipid syndrome, as extended treatment with VKA has consistently been shown to be associated with the best benefit/risk profile.[9]

# Alternative scenarios

In a clinical trial that was published 20 years ago, administering after the first months of conventional treatment a low-intensity warfarin therapy (that is, a dose that produces an international normalized ratio ranging between 1.5 and 2.0) was found to be more effective than placebo, even when major bleeding complications occurring during warfarin anticoagulation were taken into account.[10] However, in a simultaneous head-to-head comparison, low-dose warfarin therapy was found to be significantly less effective than the conventional approach.[11] Accordingly, this strategy has virtually been abandoned.

Two studies addressed the efficacy of low-dose aspirin for prevention of recurrent VTE.[12,13] When data from these 2 trials are pooled, there is a 30% to 35% reduction in the rate of both recurrent VTE and major vascular events. Moreover, these benefits are achieved with a negligible risk of bleeding.[14] In addition, favorable results have been observed with the use of sulodexide in the SURVET study (Multicentre, Randomised, Double Blind, Placebo Controlled Study on Long-Term Treatment with Sulodexide for Prevention of Recurrent DVT in Patients with Venous Thromboembolism). In this double-blind study, approximately 600 patients with a first unprovoked VTE who had completed 3 to 12 months of oral anticoagulant treatment were randomly assigned to sulodexide (500 U twice daily) or placebo for 2 years. The rate of recurrent events was found to be twice lower in patients randomized to sulodexide than in those allocated to placebo. No major bleeding episodes occurred in either group.[15]

Hence, based on available evidence, aspirin in low doses and sulodexide may offer a safe and cost-effective option for the long-term prevention of recurrent VTE. However, the extent by which they reduce the rate of recurrent VTE (30%-50%) is remarkably lower than that achievable with the current anticoagulant drugs. Thus, they can only be considered in selected patients in whom old and novel anticoagulants are not accepted by patients or are contraindicated.

# Direct oral anticoagulants

In the AMPLIFY-EXT study (Efficacy and Safety Study of Apixaban for Extended Treatment of Deep Vein Thrombosis or Pulmonary Embolism), apixaban in low preventive doses (2.5 mg twice daily), administered for 1 year after the first 6 months of conventional anticoagulation in more than 2500 patients with unprovoked VTE, was found to be as effective as conventional doses (5 mg twice daily).[16] Each of the 2 apixaban doses reduced by almost 90% the risk of recurrent VTE over placebo. The bleeding risk was similarly low in all 3 study arms. Of interest, the rate of combined major and clinically relevant non-major bleeding did not differ between low-dose apixaban and placebo.[16]

In the EINSTEIN CHOICE study (Reduced-dose Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism), published a few years later, almost 3500 patients in whom there was uncertainty about the optimal long-term treatment (thus including a substantial proportion of patients with provoked VTE) were randomized to receive—after the first 6 months of conventional anticoagulation—20 mg of rivaroxaban, 10 mg of rivaroxaban, or low-dose aspirin for 1 year.[17] Each of the 2 rivaroxaban doses reduced by 70% the rate of recurrent VTE over aspirin, and the bleeding risk was similarly low in all 3 study groups. The results were, therefore, fully consistent with those shown for apixaban in the AMPLIFY-EXT study. Whereas no patients with VTE associated with major surgery or trauma developed recurrent events, in all other patient categories, the risk of VTE while on low-dose aspirin was substantial and was reduced by each of the 2 rivaroxaban doses.

These findings are consistent with those achieved in an analysis where the results of the EINSTEIN CHOICE study were combined with those of the EINSTEIN EXTENSION study (Once-daily Oral Direct Factor Xa Inhibitor Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism in Patients With Symptomatic Deep-vein Thrombosis or Pulmonary Embolism).[18] To this purpose, identifiable risk factors were stratified according to the classification indicated in *Table I*. In this combined analysis, once again, whereas in the patient category for VTE associated with major surgery or trauma no patients

developed recurrent events, in all other patient categories (including unprovoked VTE and VTE associated with minor risk factors) the risk of VTE while on low-dose aspirin and even more so on placebo was substantial and was reduced by each of the 2 rivaroxaban doses. However, whether administering low-dose direct oral anticoagulants (DOACs) in all patients with unprovoked or weakly provoked VTE is the most proper strategy is still a matter of debate.

# Risk stratification models

Several stratification models have been derived and validated, which have the potential to identify those patients in whom anticoagulation can be safely discontinued (*Table II*).[19-22] The most suitable is the Canadian model HERDOO2 (hyperpigmentation, edema, or redness in either leg; D-dimer level ≥250 µg/L; obesity with body mass index ≥30; or older age, ≥65 years). In the derivation study, women with idiopathic VTE and none or 1 of several parameters (including age older than 60, obesity, D-dimer >250 µg/L at time of discontinuing anticoagulation, and postthrombotic manifestations) exhibited a considerably low risk of recurrent VTE.[19] These findings have subsequently been confirmed by those of a validation study[23] and have found strong support in a recent subanalysis of the Canadian REVERSE study (REcurrent VEnous Thromboembolism Risk Stratification Evaluation) dealing with women with VTE associated with the use of contraceptive pills.[24]

The serial D-dimer approach, which had been shown in the DULCIS (D-dimer and ULtrasonography in Combination Italian Study) and MORGAGNI (Optimal Duration of Anticoagulation in Deep Venous Thrombosis) studies to identify patients in whom anticoagulation can be safely discontinued,[25,26] has surprisingly failed to confirm its value in the recently published APIDULCIS study (Apixaban for Extended Anticoagulation), a prospective cohort multicenter Italian study.[27] More than 800 patients with a first episode of unprovoked or weakly provoked VTE who had completed at least 12 months of anticoagulation had D-dimer measured at baseline and, if negative, 3 more times in the following 2 months. In patients with serially negative D-dimer, anticoagulation was permanently interrupted. All other patients were given low-dose apixaban (2.5 mg twice daily). All patients were followed-up for up to 18 months. Disappointingly, patients managed with the serial assessment of D-dimer experienced an unacceptably high rate of recurrent symptomatic VTE over the prespecified follow-up, whereas the rate of events in the group of patients (approximately 50% of all recruited patients) who had been administered low-dose apixaban was low. However, the results of the APIDULCIS study may have been impacted by the pandemic.[28] In addition, a

| | Men continue and HERDOO2[19] | Vienna prediction model[20] | DASH score[21] | DAMOVES score[22] |
|---|---|---|---|---|
| **Study design** | Prospective cohort | Prospective cohort | Meta-analysis | Prospective cohort |
| **Patients** | 646 | 929 | 1818 | 398 |
| **Parameters** | *Men:*<br>None<br>*Women:*<br>Age >60 years<br>PTS signs<br>BMI >30<br>D-dimer >250 µg/L during therapy | Sex<br>VTE location<br>D-dimer after stopping therapy | Abnormal D-dimer after stopping therapy<br>Age < 50 years<br>Male sex<br>Hormonal therapy | Age<br>Sex<br>Obesity<br>D-dimer during therapy<br>F VIII<br>Thrombophilia<br>Varicose veins |
| **Increase in the risk of recurrent VTE** | >1 point | >180 points (based on a nomogram) | >1 point | >11.5 (based on a nomogram) |
| **Risk of recurrence in low-risk patients** | 1.6% (95% CI, 0.3-4.6) | 4.4% (95% CI, 2.7-6.2) | 3.1% (95% CI, 2.3-3.9) | 2.9% (95% CI, 2.13-4.35) |

BMI, body mass index (calculated as weight in kg/height in $m^2$); DAMOVES, D-dimer, Age, Mutation, Obesity, Varicose veins, Eight, Sex); DASH score, D-dimer 1 month after stopping anticoagulation (score: +2 if positive), age (+1 if ≤50 years), sex (+1 if male) and use of hormonal therapy (−2); F VIII, Factor VIII (antihemophilic factor); HERDOO2, Hyperpigmentation, Edema, or Redness in either leg; D-dimer level ≥250 µg/L; Obesity with body mass index ≥30; or Older age, ≥65 years; PTS, postthrombotic syndrome; VTE, venous thromboembolism.

*Table II.* Risk stratification models for the assessment of the risk of recurrent venous thromboembolism in patients with unprovoked or weakly provoked venous thromboembolism.

successful management with the serial D-dimer approach could not be excluded in females.[27,28] These findings are consistent with those coming from a recent subanalysis of the Canadian REVERSE study[29] and suggest that, at least in males, the serial D-dimer approach should be abandoned and replaced by extended treatment with low-dose apixaban or rivaroxaban for the long-term management of patients with unprovoked or weakly provoked VTE.

# Assessing the bleeding risk

Before embarking on an indefinite treatment regime with low-dose DOACs, the bleeding risk should be carefully evaluated. Recently, results were published for a meta-analysis of 27 prospective cohort or randomized clinical trials that had addressed the long-term follow-up of patients with unprovoked VTE in the last 30 years.[30] According to the findings of this meta-analysis, the rate of major bleeding complications while on DOAC treatment (annual rate, 1.2%), although lower than that (2.0%) reported in patients managed with VKAs, was not negligible. In addition, the case-fatality rate of major bleeding complications did not differ between patients managed with VKA and DOAC. Factors that were found to be independently associated with the risk of major bleeding were elderly age, renal failure, history of bleeding, simultaneous antiplatelet therapy, and severe anemia.

Although accurate estimation of major bleeding risk is essential to help optimize the long-term management of patients with unprovoked VTE, the scientific community has remained without a valid tool until recently. As a result of a multicenter, international collaboration, a model has been developed and externally validated (the VTE-PREDICT risk score), which has the potential to help physicians establish both the risk of recurrent VTE (after discontinuing anticoagulation) and that of major bleeding (while on anticoagulation) following the initial treatment in all VTE patients free of cancer based on a few readily available patient characteristics, including several demographics and clinical parameters (age, sex, body mass index, blood pressure), nature of the thrombotic episode (primary DVT or PE), risk factors of thrombosis (surgery, trauma, immobilization, estrogen therapy), medical history (cancer, VTE, bleeding, stroke), laboratory values (hemoglobin) and comedications (nonsteroidal anti-inflammatory drugs).[31] The model can be freely retrieved (vtepredict.com). After including step-by-step requested information, physicians and patients are given the predicted risk of recurrent VTE (after discontinuing anticoagulation) and that of major bleeding (while on anticoagulation) over the following 5 years.

Finally, in a prospective multinational cohort study of patients with unprovoked (or weakly provoked) VTE receiving extended anticoagulation after completing at least 3 months of initial treatment, Wells and coworkers were able to identify and internally validate a novel model (the CHAP [creatinine, hemoglobin, age, and use of antiplatelet agent] model), which has the potential to accurately discriminate between patients at high and low risk of major bleeding, defined as higher and lower than 2.5 events per 100 patient-years, respectively.[32] This model includes only four easily retrievable parameters (creatinine, hemoglobin, age, and the concomitant use of an antiplatelet agent). The annual rate of major bleeding can be easily calculated on individual basis with the use of the following formula: 0.02 x [(creatinine in µmol/L x 0.0017) + (hemoglobin in g/L x -0.0127) + (age x 0.0251) + (1 x 0.8995 in case of antiplatelet use)]. The CHAP model was found to accurately discriminate between patients with unprovoked or weakly provoked VTE at high and low risk of major bleedings while on extended anticoagulation. Its value has recently been supported by a retrospective analysis of findings from the international RIETE registry (*Registro Informatizado de Enfermedad TromboEmbólica*).[33]

In a context dominated by uncertainty about the optimal management of patients with unprovoked VTE, pending the scarce reliability of available bleeding prediction models, the VTE-PREDICT and the CHAP models have the potential to provide clinicians with a useful tool to balance the thrombotic risk with the hemorrhagic risk when deciding the intensity and duration of anticoagulation, and they qualify as pivotal steps in the prognostic assessment of patients with unprovoked VTE.

# The role of age

Among factors that are expected to increase the risk of (major) bleeding complications is elderly age.[30] Not surprisingly, therefore, the prolongation of anticoagulation beyond the initial 3 to 6 months in patients over 75 years of age is generally discouraged.[34] However, this recommendation can only be justified if the risk of recurrent VTE in patients in whom anticoagulation is discontinued does not exceed that expected in younger individuals. The risk of recurrent VTE beyond the age of 75 has recently been assessed in the framework of the RIETE registry.[35] Almost 25 000 patients at their first episode of VTE, of whom approximately one-third were aged over 75, were followed-up for up to 3 years after discontinuing anticoagulation. After adjusting for the baseline characteristics, the hazard ratio of recurrent VTE showed

no difference between subjects older and younger than 75 (1.03; 95% CI, 0.92–1.17). These findings are consistent with those coming from the Asiatic COMMAND-VTE registry (multicenter registry enrolling 3027 consecutive patients with acute symptomatic VTE in Japan between January 2010 and August 2014).[36] Accordingly, elderly age, which is a well-known risk factor for venous thrombosis, does not seem to increase the risk of recurrent VTE in patients older than 75 who develop a first thromboembolic episode. As in these individuals the risk of bleeding complications while on anticoagulation exceeds that reported in younger people,[30] the decision about extending anticoagulant drugs after the first 3 to 6 months should be carefully balanced against the hemorrhagic risk with the help of the aforementioned risk assessment models.[31,32]

# Discussion of the clinical case

The development of an unprovoked episode of proximal DVT in a male individual is a strong indication for prolonging, indefinitely, anticoagulation with low-dose DOACs, provided there are no contraindications and risk assessment models indicate a favorable benefit/risk profile. Despite the patient's age, the risk models (VTE-PREDICT, CHAP) suggest continuing anticoagulation is appropriate. The patient agreed to prolong anticoagulation and to refer to the thrombosis center on an annual basis for periodic reassessments.

# Conclusions

In conclusion, in addition to carriers of cancer and those with major thrombophilias and other conditions requiring an indefinite anticoagulation therapy, extended treatment of VTE should be considered in males with a first episode of unprovoked or weakly provoked VTE, provided the hemorrhagic risk (as assessed with the CHAP or VTE-PREDICT model) is low. In women, the decision may be guided by a stratification model (HERD002 or serial D-dimer). This is especially valid for sex-related VTE (ie, VTE related to hormonal therapy, pregnancy, or delivery). The drugs to be favored are apixaban or rivaroxaban in preventive doses.

**CORRESPONDING AUTHOR**

**Dr Paolo Prandoni**

Arianna Foundation on Anticoagulation,
Via P. Fabbri 1/3 –
40138, Bologna, Italy

EMAIL: *prandonip@gmail.com*

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# Isolated calf deep vein thrombosis: to treat or not to treat

**Andrew N. Nicolaides**, MS, DSc, PhD, FRCS

Vascular Screening and Diagnostic Center, Nicosia, Cyprus; *and* Department of Vascular Surgery, Imperial College, London, United Kingdom; *and* Department of Basic and Clinical Science, University of Nicosia Medical School, Nicosia, Cyprus

## ABSTRACT

On the basis that in the presence of isolated calf deep venous thrombosis (DVT) fatal pulmonary emboli (PE) did not occur while the patient was in hospital, there was one school of thought that routine anticoagulation was unnecessary and that ultrasound surveillance would suffice, reserving anticoagulation for those in whom the thrombus extends into the popliteal or more proximal veins. However, another school of thought, based on the realization that local damage to the venous valves with the development of reflux and skin changes, and symptoms of persistent pain and edema in 10% to 23% of patients leading to CEAP C4-C6 classes and a DVT recurrence rate of up to 14%, believed anticoagulation should be routine in such patients unless there were serious contraindications. Recent evidence from randomized controlled trials and meta-analyses indicates that isolated calf DVT should be treated. A key message from studies addressing the comparison between direct oral anticoagulants (DOACs) and conventional therapy for the initial and short-term therapy (3-6 months) is that treatment of acute isolated calf DVT with DOACs is as effective as standard therapy; also, it's associated with a statistically significant reduction in the risk of major bleeding complications, clinically relevant as intracranial and fatal bleeding are the most reduced types.

**Keywords**

calf | controversy | deep vein thrombosis | treatment

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# Introduction

Relatively little was known about the true incidence of postoperative deep venous thrombosis (DVT) or its natural history prior to the 1960s, although by that time, it was established that the clinical diagnosis of DVT was unreliable because in the presence of symptoms and signs only 50% of the patients were found to have DVT on venography. In addition, leg veins were thought to be the common site for the origin of pulmonary emboli (PE).[1] The available knowledge on DVT at that time had been summarized as follows by Ian Aird in his classic monograph "*A Companion in Surgical Studies*" published in 1958[2]:

> **DVT occurs in 0.5%-1% of all hospital patients, in 3%-4% of surgical patients, more than 1% of obstetric patients and in less than 1% of patients treated in bed without operation... There is twice as much risk of thrombosis after laparotomy as there is after other operations... It is strange that thrombosis is twice as common after bilateral herniotomy, an observation which suggests that the main causative factor, whatever it is, in the production of thrombosis acts at the time of operation and varies directly with the time spent by the patient on the operating table.**

It was also stated that:

> **[PE] occurs in some 50%-60% of patients who have thrombosis after surgical operations, and PE kills 16%-20% of patients who have thrombosis. PE occurs in 20%-35% of obstetric patients who have thrombosis but kills only 3%-4% of them... The age of the patient is important. Surgical and medical patients who suffer from thrombosis are normally middle-aged or old... DVT is common in some families than in others. Other factors predisposing to thrombosis are cardiac infarction, extensive lower limb varicosities and low output cardiac insufficiency.**

In 1960, Hobbs and Davies argued that the largest specific component of the thrombus was the fibrin network, and as fibrinogen could be labeled with radioactive iodine, it should be incorporated in a forming thrombus and detected by an external scintillation counter. They demonstrated the feasibility of this in rabbits using $^{131}$I.[3,4]

In 1965, Atkins and Hawkins[5,6] working at Kings College Hospital Medical School, London, United Kingdom substituted the isotope $^{125}$I for $^{131}$I as the radioactive label because $^{125}$I had a longer half-life (60 days instead of 8 days) and a lower gamma radiation energy so that a lighter and more mobile apparatus could be used. The accuracy of the test was confirmed by venography,[7-9] and by using a ratemeter[9] it became a simple test suitable for the routine screening of a large numbers of patients.

# True incidence of DVT

Several studies using the $^{125}$I-fibrinogen test demonstrated that patients who undergo surgical procedures are at high risk of developing venous thrombus embolism (VTE). The findings of these early studies were summarized in a review by Hobbs and Nicolaides in 1971.[10] In the absence of prophylaxis, the risk of silent DVT was 30% in general surgery, 17% in gynecological surgery, 47% in patients with a fractured neck of femur, 30% in urological surgery, 34% in acute myocardial infarction, and 68% in medical patients in shock. It was found that the majority of the thrombi started during the operation and that 89% of thrombi started in the calf, 6.5% in the popliteal region, and 4% in the thigh.[11] Subsequent venographic studies demonstrated that in patients with fractured neck of femur and elective hip replacement, calf DVT that occurred in the first week after surgery was often followed by iliac vein thrombosis, which tended to occur *de novo* in the second week after operation.[12]

# Natural history of calf DVT

Of the thrombi that started in the calf, 20% lysed spontaneously. This was particularly so in patients who were ambulant. However, 25% of calf thrombi extended more proximally into the popliteal, femoral, or iliac veins. If the thrombosis was limited to the calf, the risk of serious PE during hospitalization was negligible, but if the popliteal and femoral veins became involved, the risk of PE rapidly increased, reaching 50% when the iliac veins were involved.[13]

During the 1970s, the $^{125}$I-fibrinogen test was used as a diagnostic tool in most randomized controlled trials (RCT) on the efficacy of different methods of prevention[14] and was the tool used in RCT that established the value of low-dose heparin, low-molecular-weight heparin (LMWH), elastic compression, electrical calf muscle stimulation, and intermittent pneumatic compression in the prevention of postoperative DVT. These RCTs eventually demonstrated that if a method prevents calf DVT, it also prevents proximal DVT, symptomatic DVT, PE, and fatal PE.[15,16] The $^{125}$I-fibrinogen test was eventually replaced by ultrasound, and with the appearance of AIDS in 1981 it became obsolete. However, its "legacy" and the problem of how to manage isolated calf DVT remained a controversial subject.

# Two schools of thought

The finding that in the presence of isolated calf DVT fatal PE did not occur while the patient was in hospital resulted in a school of thought that routine anticoagulation was unnecessary and that surveillance with ultrasound would suffice, reserving anticoagulation for those in whom the thrombus extends into the popliteal or more proximal veins. However, the realization that local damage to the venous valves with the development of reflux and skin changes, and symptoms of persistent pain and edema in 10% to 23% of patients leading to CEAP (clinical-etiological-anatomical-pathophysiological) C4-C6 classes and a DVT recurrence rate of up to 14%[17-19] led to the development of another school of thought that such patients should be routinely anticoagulated unless there were serious contraindications.

# DVT recurrence after isolated calf DVT

In 1984, a randomized study of 51 patients with symptomatic isolated calf DVT, of whom 23 received warfarin for 3 months and 28 did not, investigated the rate of recurrence.[20] Recurrences and their extent were confirmed with venography. Both groups received an initial course of heparin, and all patients wore compression stockings. During the first 3 months, recurrence occurred in 29% of patients in the non-warfarin group compared with none in the warfarin group ($P$<0.01). Five of these patients had a recurrence with proximal extension and 1 had a pulmonary embolus. At 1 year, 1 (4.3%) out of 23 patients in the warfarin group had a recurrence, compared with 19 (68%) out of 28 in the non-warfarin group (risk ratio [RR], 0.13; 95% CI, 0.02 to 0.99). The findings suggested that oral anticoagulants should be given to all patients with symptomatic isolated calf DVT and that 3 months seemed to be sufficient.

However, a study in 2016 (the CACTUS study, [Contention Alone Versus Anticoagulation for Symptomatic Calf Vein Thrombosis Diagnosed by Ultrasonography]) questioned these conclusions.[21] This was a double-blind, placebo-controlled RCT involving 259 low-risk outpatients (without active cancer or previous VTE) with a first acute symptomatic DVT in the calf who were assigned to receive either LMWH (nadroparin 171 UI/kg, subcutaneously, once daily) or placebo for 6 weeks. There was no significant difference between the groups in the composite primary outcome (a composite of extension of calf DVT to proximal veins, contralateral proximal DVT, and symptomatic PE), which occurred in 4 (3%) patients in the LMWH group and in 7 (5%) in the placebo group ($P$=0.54). Bleeding occurred in 5 patients (4%) in the LMWH group and no patients in the placebo group ($P$=0.03). It was concluded that nadroparin was not superior to placebo in reducing the risk of proximal extension or VTE events in low-risk outpatients with symptomatic calf DVT but did increase the risk of bleeding. Accordingly, in patients with acute isolated distal DVT of the leg and without severe symptoms or risk factors for extension, guidelines suggested serial imaging of the deep veins for 2 weeks over anticoagulation; by contrast, in patients with severe symptoms or risk factors for extension, anticoagulation was suggested over serial imaging of the deep veins.[22]

In the most recent double-blind RCT (RIDTS [Rivaroxaban for the treatment of symptomatic Isolated Distal deep vein Thrombosis]) addressing the optimal duration of anticoagulation in patients with symptomatic isolated calf DVT, the administration of therapeutic doses of rivaroxaban (20 mg once daily) for 3 months was found to reduce the incidence of recurrent VTE over a 2-year follow-up period compared with a shorter course (6 weeks) without increasing the hemorrhagic risk.[23] Indeed, among the 404 patients that were recruited, the primary efficacy outcome (composite of isolated distal DVT, recurrent isolated distal DVT, proximal DVT, symptomatic PE, or fatal PE) occurred in 23 (11%) patients in the rivaroxaban arm and 39 (19%) in the placebo arm (RR, 0.59; 95% CI, 0.36 to 0.95). No major bleeding events occurred.

## Systematic reviews and meta-analyses

A systematic literature review and meta-analysis of 24 studies on the duration of anticoagulant therapy in patients with isolated calf DVT, involving 2936 patients, was published in 2016.[24] Of these, 5 studies were RCTs, 7 were prospective cohort studies, 7 were retrospective studies, and 1 was a combined

prospective and retrospective cohort study. Four additional studies compared different durations of anticoagulation. Recurrent VTE (proximal propagation, recurrence of DVT or PE) was reduced from 11.1% in patients not on anticoagulation to 6.5% in patients on anticoagulation (odds ratio [OR], 0.50; 95% CI, 0.15 to 0.73) without increase in major bleeding. Recurrent DVT was reduced from 6.5% to 1.5% (OR, 0.23; 95% CI, 0.08 to 0.65), and PE was reduced from 2.4% to 1.4% (OR, 0.48; 95% CI, 0.25-0.91). The recurrence rate of VTE was reduced from 10.7% in those receiving anticoagulation for less than 6 weeks to 3.2% in those receiving anticoagulation for more than 6 weeks (OR, 0.39; 95% CI, 0.17 to 0.90). The authors concluded that in patients with isolated calf DVT, anticoagulation reduces the incidence of PE and recurrent DVT without increased risk of major bleeding. Although most patients on anticoagulants in the studies included in the meta-analysis were receiving vitamin K antagonists (VKA), the authors suggested that direct oral anticoagulants (DOACs) should be considered for treatment of isolated calf DVT, given their improved efficacy-to-safety profile.

The most recent Cochrane systematic review and meta-analysis[25] published in 2020 identified 8 RCTs involving 1239 patients with isolated calf DVT. In 5 trials, anticoagulation therapy was used up to 3 months; and in 3 trials, anticoagulation of different periods was used. Recurrence of VTE was reduced from 9.1% in the placebo/no intervention group to 2.9% in the VKA group (RR, 0.34; 95% CI, 0.15 to 0.77). There was no significant difference in the risk of PE, but the risk of DVT recurrence was reduced from 7.9% to 1.65% (RR, 0.25; 95% CI, 0.10 to 0.67). There was no significant increase in major bleeding, but there was an increase in clinically relevant non-major bleeding from 1.8% to 7.0% (RR, 3.34; 95% CI, 1.07 to 10.46). In 3 RCTs comparing treatment with VKA for 3 or more months with treatment for 6 weeks, treatment for 3 months or more reduced the incidence of VTE from 13.9% in the 6-week group to 5.8% in the 3-or-more-months group (RR, 0.42; 95% CI, 0.26 to 0.68). The risk of recurrent DVT was also reduced from 14.4% to 4.8% (RR, 0.32; 95% CI, 0.16 to 0.64).

# The end of the debate

The evidence from the RCTs and meta-analyses has now resulted in resolution of the debate on whether isolated calf DVT should be treated or not. These data indicate that isolated calf DVT should be treated.[26-28] A key message from the above systematic reviews and meta-analyses addressing the comparison between DOACs and conventional therapy for the initial and short-term therapy (3-6 months) is the following: treatment of acute isolated calf DVT with DOACs is as effective as standard therapy and is associated with a reduction in the risk of major bleeding complications that is not only statistically significant but also clinically relevant, as intracranial and fatal bleeding are the most reduced types.[24,25,29]

### Current recommendations by the European Society for Vascular Surgery (ESVS) 2021 clinical practice guidelines on the management of venous thrombosis

In view of the high risk of recurrence, proximal extension, and subsequent PE in patients with isolated calf DVT in the absence of anticoagulation and in view of the efficacy of anticoagulation demonstrated by RCTs, the recommendations in the 2021 guidelines of the ESVS are as follows:

> ''For patients with symptomatic calf DVT..., 3 months therapy is recommended over shorter durations'' (Class 1, Level A).[27]

> In patients in whom anticoagulation is contraindicated, ''...clinical reassessment and repeat whole leg ultrasound after 1 week is recommended'' (Class 1, Level B).[27]

> For patients with symptomatic calf DVT in the presence of active cancer, ''anticoagulation beyond 3 months should be considered'' (Class IIa, Level C).[27]

The value of DOACs in patients with isolated calf DVT has not yet been investigated. However, in view of their improved efficacy and reduced incidence of bleeding demonstrated by RCT in patients with proximal DVT or PE compared with VKA they should be considered as preferable to VKA. Thus, the following additional recommendation is made: For patients with calf DVT requiring anticoagulation, ''[DOACs] are recommended over [LMWH] followed by [VKA]'' (Class1, Level C).[27]

## Current recommendations by the International Consensus Statement (Guidelines according to scientific evidence) on the prevention and management of venous thromboembolism

"Isolated symptomatic calf DVT should be treated for 3 months (Level of evidence high, recommendation strong) or followed by serial ultrasonography on 2 occasions if anticoagulation is contraindicated due to high bleed risk or other factors (Level of evidence moderate, recommendation moderate)."[28]

"For patients with calf DVT requiring anticoagulation, rivaroxaban is recommended over LMWH followed by VKA (Level of evidence moderate, recommendation strong)." [28]

CORRESPONDING AUTHOR

**Professor Andrew Nicolaides**

2 Kyriacou Matsi Street, Ayios Dhometios, 2368 Nicosia, Cyprus

EMAIL: *anicolaides1@gmail.com*

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# Treatment of vena cava obstruction and occlusion

**Marzia Lugli**, MD

Department of Cardiovascular Surgery, Hesperia Hospital, Modena, Italy

## ABSTRACT

Obstruction of the inferior vena cava (IVC) is a significant contributor to chronic venous insufficiency (CVI). Patients may present with a wide range of symptoms, from being asymptomatic to suffering from severely debilitating conditions.

The causes of IVC obstruction can be congenital, related to malignancies, or nonmalignant. Among these, nonmalignant causes are the most common.

The protocol for selecting patients for cava recanalization and stenting must be strict. The clinical basis should guide the procedural approach for inferior cava obstruction.

The endovascular technique for addressing proximal deep vein obstruction is now well standardized. Special care should be taken to reconstruct the confluence when applied in the IVC.

Considering the low complication rates, satisfactory patency rates, and symptom improvement, the endovascular approach is worth considering to enhance the quality of life for these patients. Although additional high-quality evidence is needed, the benefits outweigh the drawbacks for cava recanalization in selected individuals.

**Keywords**

cava obstruction | chronic venous insufficiency | postthrombotic syndrome | vein stenting

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# Introduction

Inferior vena cava (IVC) obstruction, associated or not with iliofemoral obstruction, is an important cause of chronic venous insufficiency (CVI). The clinical presentation may vary from asymptomatic patients to those with severe debilitating disease, leading to a dramatic compromise in the quality of life. There are several possible causes, primarily thrombotic events, neoplastic compression, surgical or traumatic interruptions, and congenital defects. Regardless of the cause of the obstruction, conservative treatments, such as anticoagulation and compression therapy, have long been the only therapeutic options due to the significant complication rates associated with open surgery for correcting cava obstruction. Nowadays, the endovascular technique for IVC obstruction management is the first-line procedural approach. There is undoubtedly a widespread and increasing tendency to treat cava obstruction utilizing recanalization/stenting, supported by good clinical results and a low complication rate.[1]

# Inferior cava obstruction

The IVC obstruction etiology can be congenital, malignant related, or nonmalignant. The nonmalignant etiology is the most frequent one, due to thrombotic events involving the cava and frequently iliac/femoral segments *(Figure 1)*.[2] Frequently, these events occur in young patients (eg, thrombosis caused by coagulation defects or trauma), leading to severe symptoms and signs such as disabling leg edema, venous claudication, and ulcers, as well as the whole spectrum of CVI manifestations. Even if cava obstruction may be well compensated at the beginning, usually over time the quality of life for these patients deteriorates progressively. In malignant-related obstruction, cava compression usually needs to be managed, even in compassionate situations for patients with a short life expectancy. Open surgical cava replacement may, in some cases, be considered when the vein wall is involved in tumoral infiltration *(Figure 2)*. Cava congenital anomalies are quite rare. Cava duplication *(Figure 3)*, as the result of abnormal persistence of the left supracardinal vein, and the left-sided cava *(Figure 4)* are not so infrequent and can be recanalized if needed. The cava interruption, due mainly to the failure of the right subcardinal vein to anastomose with the vitelline vein, is on the other hand difficult to manage given the absence of axiality *(Figure 5)*.[3]

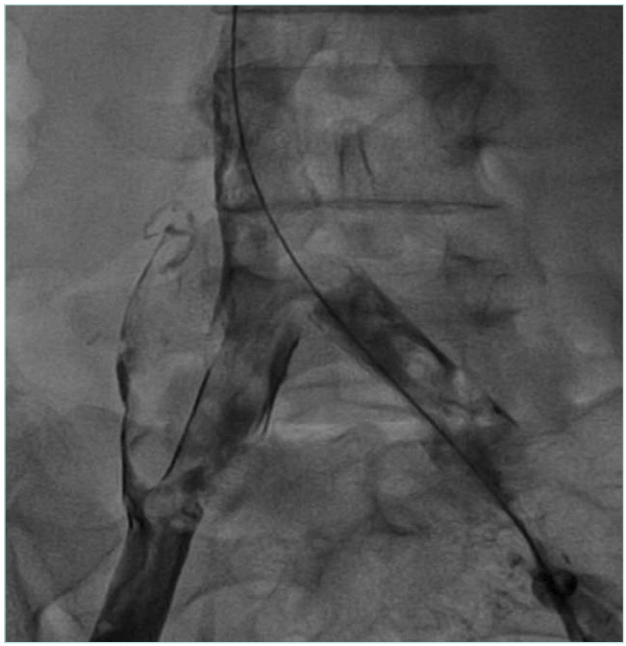

*Figure 1.* Extensive acute iliocaval thrombosis. Clots are clearly visible inside iliac veins and the inferior vena cava.

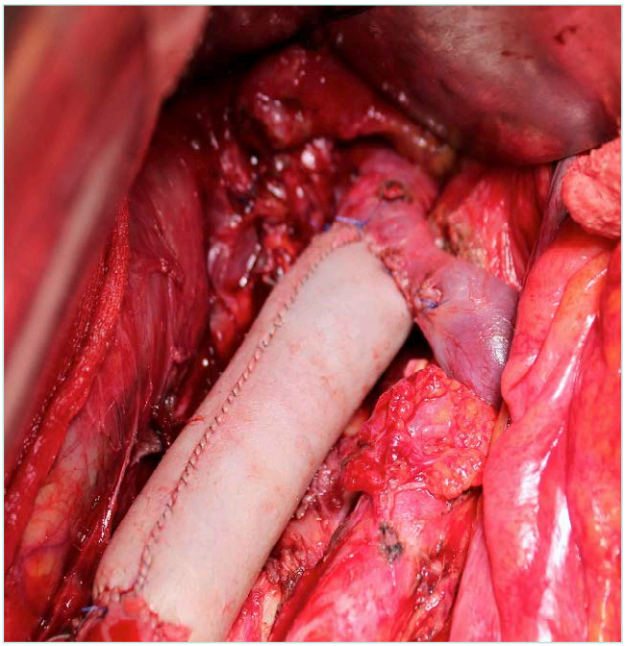

*Figure 2.* Cava bypass for right renal tumor vein wall infiltration. The cava has been harvested, and a bovine pericardium bypass has been constructed from the left renal vein down to the confluence of the iliac veins.

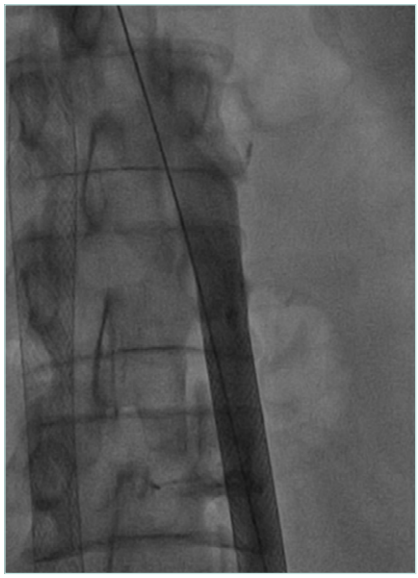

*Figure 3.* Inferior cava duplication: both cava segments have been stented.

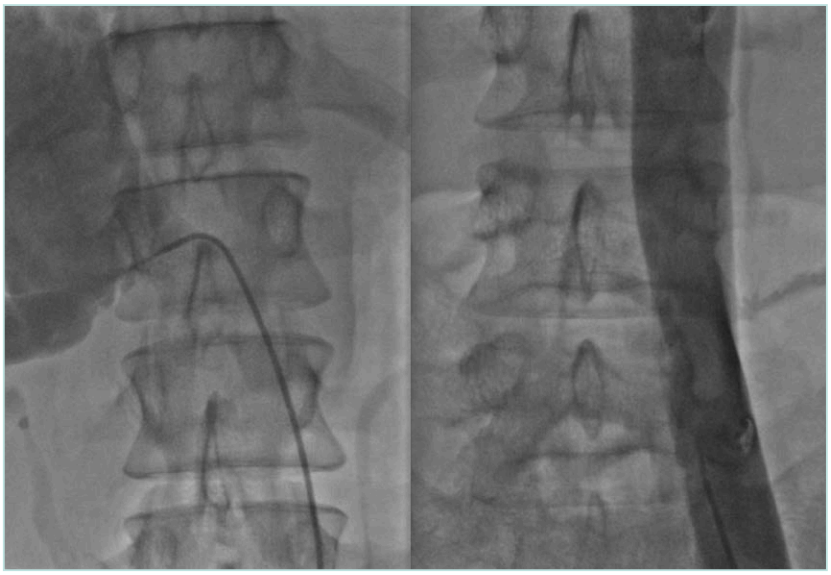

*Figure 4.* Left-sided cava.

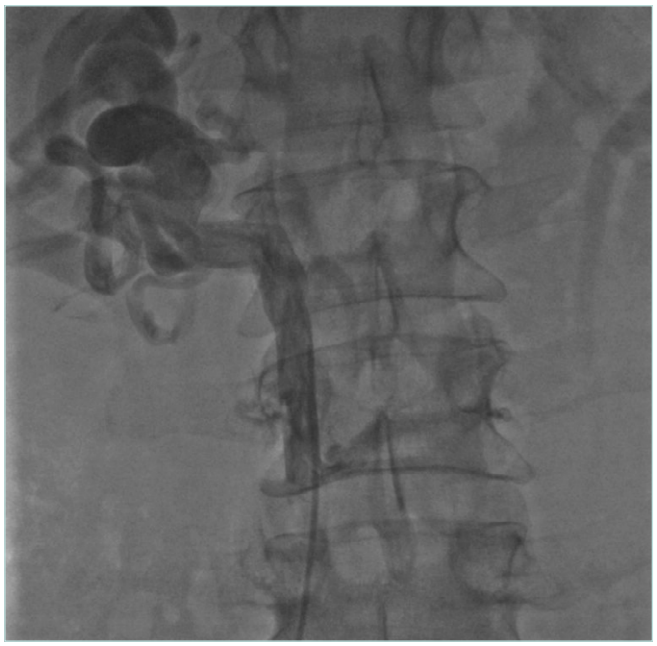

*Figure 5.* Congenital cava interruption. The cava (postthrombotic damage inside the vein) is stopped at the confluence of suprahepatic veins, visible on the left. There is no continuity with the right atrium.

# Patient selection

The investigation protocol for selecting patients for cava recanalization/stenting should be rigorous. The procedural approach to inferior cava obstruction should be indicated on a clinical basis. The detection of a stenotic/occlusive image at diagnostic investigation does not represent an indication for treatment as underlined in the recent European Guidelines. In fact, the "Clinical Practice Guidelines on the Management of Chronic Venous Disease of the Lower Limbs" of the European Society for Vascular Surgery (ESVS) has given a recommendation IIa, level B in this direction.[4] In patients affected by CVI or by disabling venous claudication, the history of a previous episode of acute thrombosis suggests the screening for proximal obstruction. Ultrasound (US) investigation is the first-line examination to be performed; in the larger part of cases, US provides information about postthrombotic damage in the inferior cava system, flow spectrum alteration (ie, breath nonphasic flow), and rough cava alterations. Whenever a procedural approach is advisable, computed tomography venography (CTV), magnetic resonance venography (MRV), or phlebography are mandatory. Intravascular US (IVUS) is the gold standard for vein obstruction detection; so during the recanalization, its application is strongly recommended.[5]

Contraindications to cava recanalization are represented by

the presence of uncorrectable coagulation alterations, as well as the impossibility to apply anticoagulation therapy. Moreover, the decision-making process should take into account the likelihood of a low benefit with intervention: patients with ineffective muscular pump function or patients that are nonambulatory typically do not improve significantly after recanalization. To this end, the preoperative plethysmographic assessment of the ejection fraction (EF) is an essential parameter, given that it can provide information about the calf pump function.[6]

# Cava recanalization: the procedure

In cava obstruction recanalization, a multiple vein access procedure is usually required. There are several options for the access site (femoral vein, popliteal vein, internal jugular vein); the choice is led by the extent and localization of the steno-obstructive lesions to be treated, considering that cava postthrombotic obstruction is usually associated with iliac and common femoral damage *(Figure 6)*. The most frequent choice is bilateral femoral half-thigh access combined with jugular access. Ultrasound-assisted catheterization is mandatory to avoid or reduce complications.

Venous angioplasty or stenting is a painful procedure. In the event of complex iliocaval obstruction, general anesthesia should be considered, both for pain occurrence and the possible long duration of the procedure.[7,8]

Once the sheath has been placed, a multiplanar venography is performed to assess the extent and characteristics of the lesions. It is important to understand if the cava is occluded or stenotic: this will make a strong difference in the aggressiveness of the procedure (eg, in occluded cases, it is a stronger approach) and will affect outcomes. Systemic anticoagulation with 100 units/kg of unfractionated heparin is undertaken and the activated clotting time during the procedure is monitored.

The obstructive lesions are crossed by means of different types of wires and supporting catheters; telescopic techniques and specific devices for crossing occlusions are usually considered. Predilatation is performed with progressive large-diameter balloons.

The diagnostic assessment before stenting should be carried out by IVUS. The IVUS probe is directed over the atrial confluence of the IVC, and the scanning is recorded with a pullback technique. A precise assessment of residual stenosis, lesion extent, and stent size requirement, and a decision about landing zones are undertaken.

The stent choice, from among those available on the market, depends on the specific characteristics of the clinical situation. The most used stent sizes are 20 to 24 mm for the IVC, 14 to 16 mm for the iliac veins, and 12 to 14 mm for extension into the common femoral vein (CFV). Balloon postdilation is recommended.

How to reconstruct the cava confluence via stenting is an essential point. Different strategies may be applied, depending on local anatomy, inflow issues, and device availability. The main problem is how the iliac stents should converge into the cava stent. It is possible to infold them into the cava stent, thus requiring appropriate sizing; a carina Y-stent configuration can be used with the drawback of residual gaps. A double-barrel stent can also be used, which may behave as a flow diverter. There is no data to help select the best configuration. Thus, the choice mainly depends on each individual case.[9-11] *(Figures 7 to 11)*

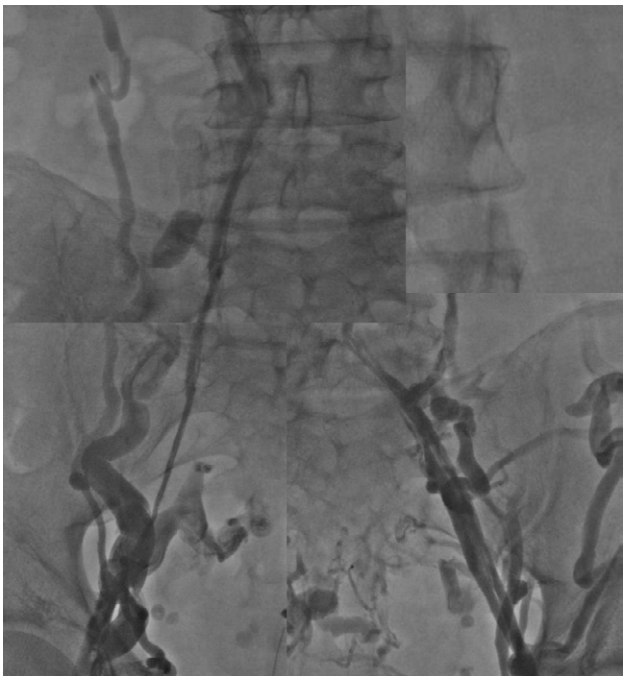

*Figure 6.* Extensive cava and iliofemoral postthrombotic obstruction. A cava filter is placed in the inferior vena cava.

A final check by IVUS and a completion venography are performed. Possible residual stenosis, adequate collapse of the collateral pathways, and adequate inflow are essential parameters to be assessed as predictors for patency.

At the end of the procedure, the venous access sheaths are removed, and an eccentric compression is performed. Elastic stockings are placed on, and intermittent pneumatic compression is applied until active ambulation.

Full anticoagulation is carried out; the anticoagulant agent and duration depend on the patient's characteristics (ie, presence of an anticoagulation defect, the persistent risk of deep venous thrombosis).

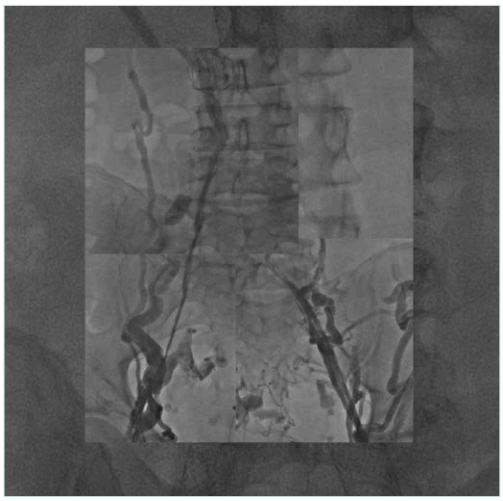

*Figure 7.* Possible cava confluence configuration: stent apposition.

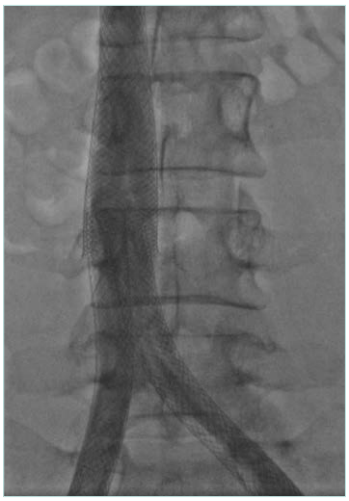

*Figure 8.* Possible cava confluence configuration: stent infolding.

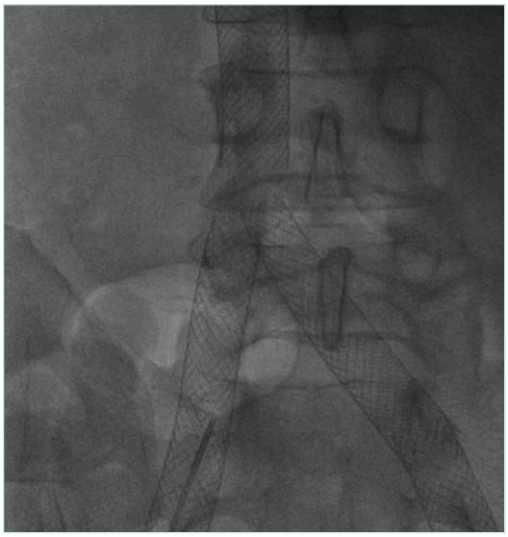

*Figure 9.* Possible cava confluence configuration: separate stent with gap at confluence.

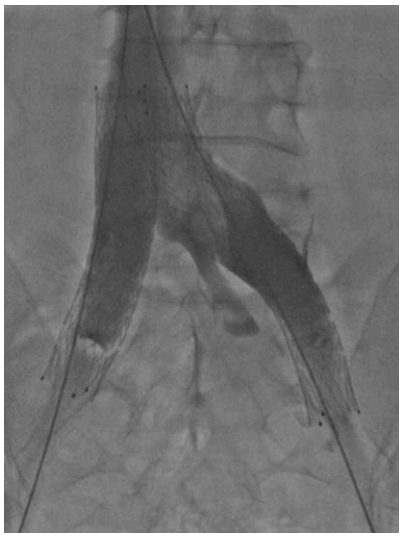

*Figure 10.* Possible cava confluence configuration: double barrel.

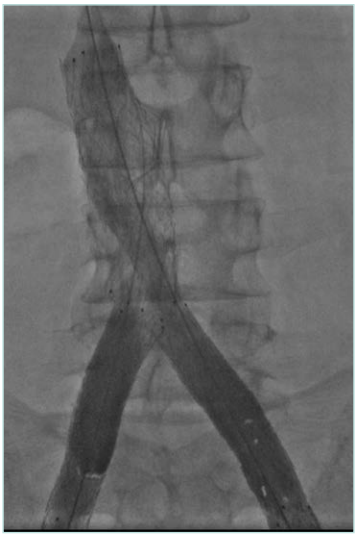

*Figure 11.* Possible cava confluence configuration: Y-stenting technique.

# Complications

Recanalization/stenting of venous obstruction is to be considered a safe procedure. Pulmonary embolism rate, bleeding from access points, stent migration, and infections are negligible. Stent restenosis and recurrent thrombosis are the essential issues to be considered and monitored attentively during follow-up in order to provide adjunctive maneuvers *(Figure 12)*.[12]

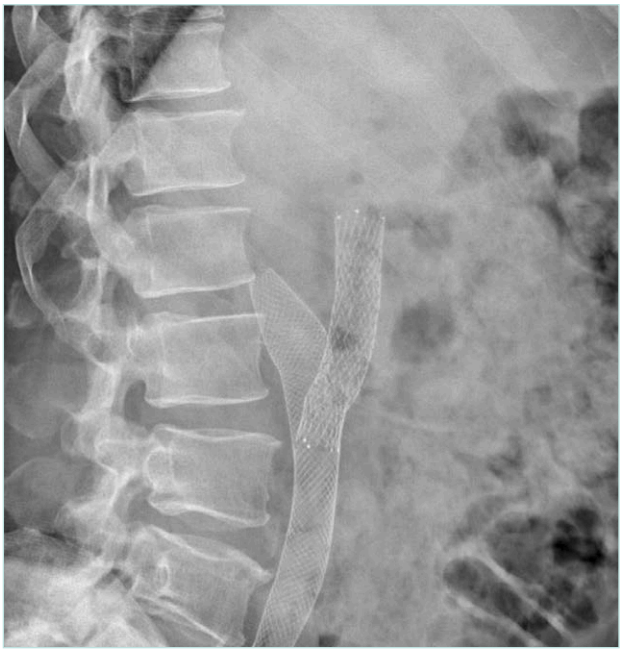

*Figure 12.* Proximal stent realignment for segmental occlusion. The cranial part of the original stent was occluded and a second one has been placed by means of fenestration.

# Results

Analyzing results from deep venous obstruction recanalization reveals several notable issues. Firstly, there is a lack of uniformity in how the treated population is described, scored, and classified. Additionally, the definitions for measuring outcomes require improvement. Furthermore, the duration of follow-up remains relatively brief. Nevertheless, the complication rate is low, and the technical success is relatively high.

Regarding stent patency, primary obstruction presents better results compared with postthrombotic syndrome patients in all available meta-analyses. In a review by Williams and Dillavou,[12] the 1-year primary patency rate for iliocaval cases is 79%. Recently, Morris et al reported primary patency rates of 75% (38% to 98%) and secondary patency rates of 91.5% (77% to 100%).[13] Clinical outcomes are variable due to the heterogenicity of the population, ranging from a 64% to 82% improvement. It is important to highlight that iliocaval recanalization is cost-effective compared with conservative therapy alone.[14]

# Conclusions

Inferior cava obstruction is a cause of severe CVI. Given the low rate of complications, satisfying patency rates, and improved symptoms, the endovascular approach should be considered to improve the quality of life in these patients. Even if more high-quality evidence is required, the ratio of pros and cons favors cava recanalization in selected patients.

**CORRESPONDING AUTHOR**

**Dr Marzia Lugli**,

Department of Cardiovascular Surgery, Hesperia Hospital, Via Arquà 80/A, 41125 – Modena, Italy

EMAIL:
*lugli@chirurgiavascoalremodena.com*

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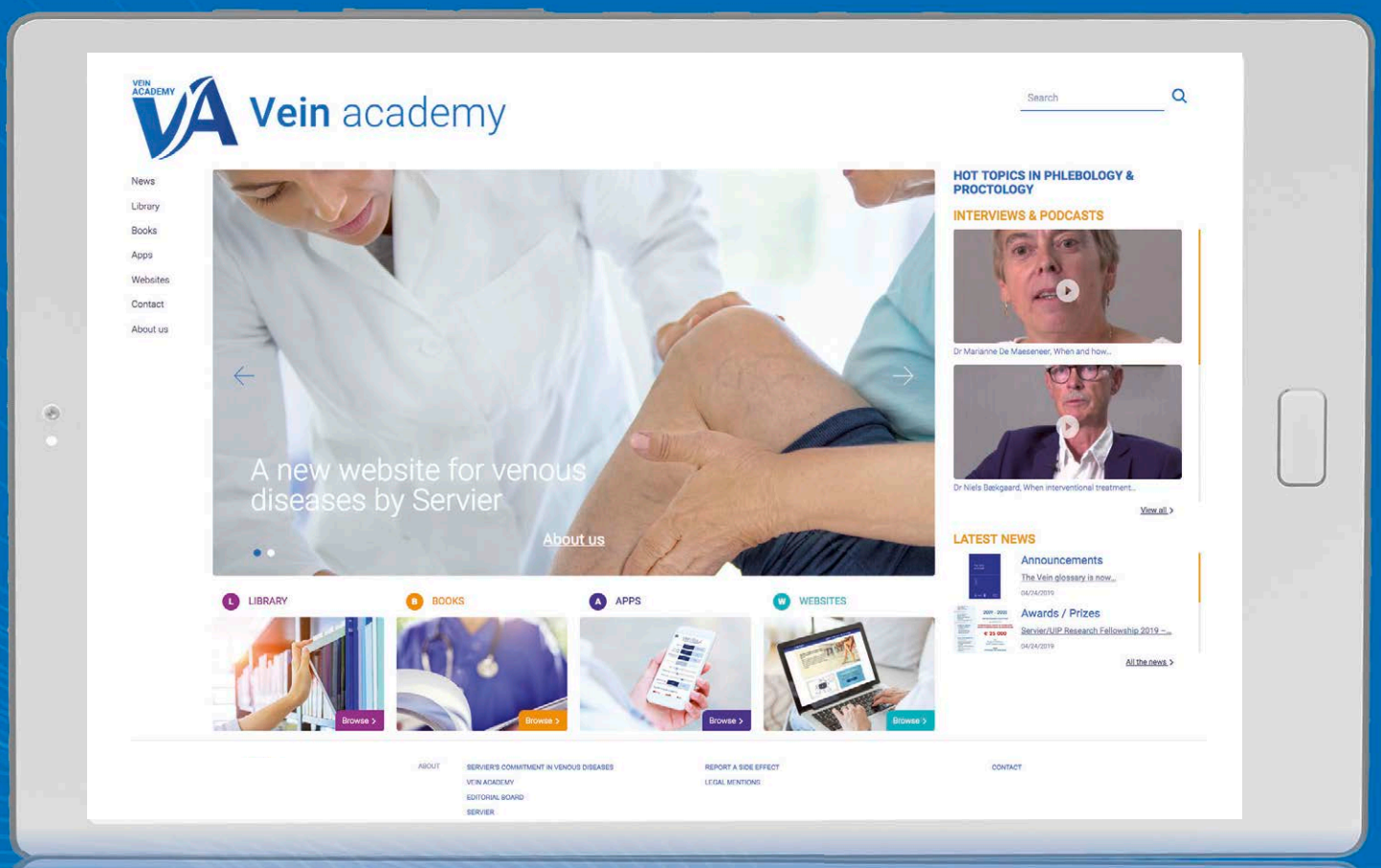


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