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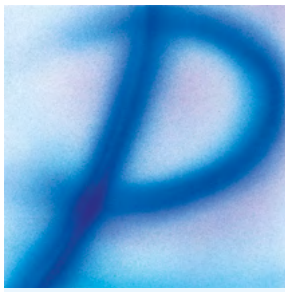

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Phlebolymphology

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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.

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Editorial

Dear Readers,

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

Congenital vascular malformations of the hand are variable and difficult to treat. ***R. E. MATTASSI*** *and* ***P. DI GIUSEPPE (Italy)*** *present a diagnostic approach for better management and report results from a group of patients with venous malformation who were treated by surgery.*

C. KARATHANOS *and* ***A. GIANNOUKAS (Greece)*** *provide an overview of the role of anticoagulant treatment in the prevention of post-thrombotic syndrome, which develops after deep vein thrombosis of the lower limbs and may affect up to 50% of patients after proximal deep vein thrombosis.*

The prevalence of calf vein thrombosis is between 5% and 33% of all cases of deep vein thrombosis detected by ultrasound. ***P. L. ANTIGNANI (Italy)*** *presents an update on calf vein thrombosis, including the epidemiology, risk factors, diagnostic approaches, and therapeutic management.*

Lastly, ***P. NEGLÉN (Cyprus)*** *and* ***B. EKLÖF (Sweden)*** *address the progress made over time in the management of patients with venous disease by describing their journey as physicians through these years, including experience with diagnosis, classification, and different treatment perspectives.*

Enjoy reading this issue!
Editorial Manager
Dr H. Pelin Yaltirik

Venous malformations of the hand: surgical treatment

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Keywords:

angiodysplasia, vascular malformation, venous anomaly, venous malformation.

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Abstract

Congenital vascular malformations (CVM) of the hand are extremely variable and difficult to treat. The correct approach first requires a complete, stepwise diagnostic procedure from clinical examination to echo Doppler (ECD) examination followed by magnetic resonance (MR) imaging, which can be performed without contrast if ECD demonstrated a slow-flow malformation. Treatment can be performed via sclerosis or surgery. Sclerosis has the advantage of being less invasive but the disadvantage of having a significant incidence of recurrence and the risk of nerve damage. Here, we report the results from a group of 115 patients with venous malformation (VM), all treated by surgery. The results were good for limited forms, with a high incidence of complete defect removal and healing (75% healed, 14% improved), and good improvement was observed for infiltrating forms (15% healed and 74% improved). Recurrence was 11% for limited forms and 10% for extended forms. Complications were few: 3 with temporary paresthesia and 2 with postoperative pain. Surgery is a good option in VM of the hand. However, experience with the surgical approach for the area and for VM is required. Teamwork between hand and vascular surgeons is a good option.

Introduction

Congenital vascular malformations (CVM) are inborn errors in the process of angiogenesis and vasculogenesis during fetal life. The result can be a defect in main vessels, such as the absence of (aplasia) vessels, reduction in lumen diameter (stenosis), dilatation (aneurysm), and remnants of embryonal, immature vascular masses in tissues.[1] The last type is by far the most common.

According to modern classification by the International Society for the Study of Vascular Anomalies (ISSVA), CVM can be of different types depending on the vessels involved. There are venous malformations (VMs), arteriovenous malformations (AVMs), lymphatic malformations (LMs), and a combination of these or a combination with other defects, which are called "syndromes."[2]

The most common type of CVM is the venous form, as shown in *Table I.*

Venous	918 (61%)
Arteriovenous	271 (18%)
Lymphatic	164 (11%)
Capillary	11 (7.5%)
Combined	26 (2%)
Arterial	7 (0.5%)
Total	1497

Table I. Distribution of vascular malformations. (Castellanza 2011-2017:1497 cases)

VM can be located in almost any part of the body and can differ in extension, infiltration of tissues, and involvement of other structures, making it an extremely variable disease to the point that it may be difficult to find 2 similar cases. That variability makes it difficult to have a clear understanding of any particular case and to choose the strategy for approach.

The hand is a very particular structure with complex anatomy in which many different tissues of high functional value (fine nerves, vessels, small muscles, tendons) are located within a small space. The hand is not rarely affected by VM, which may involve limited areas or infiltrate the entire hand even with extension to the wrist and forearm (*Figures 1-5*).

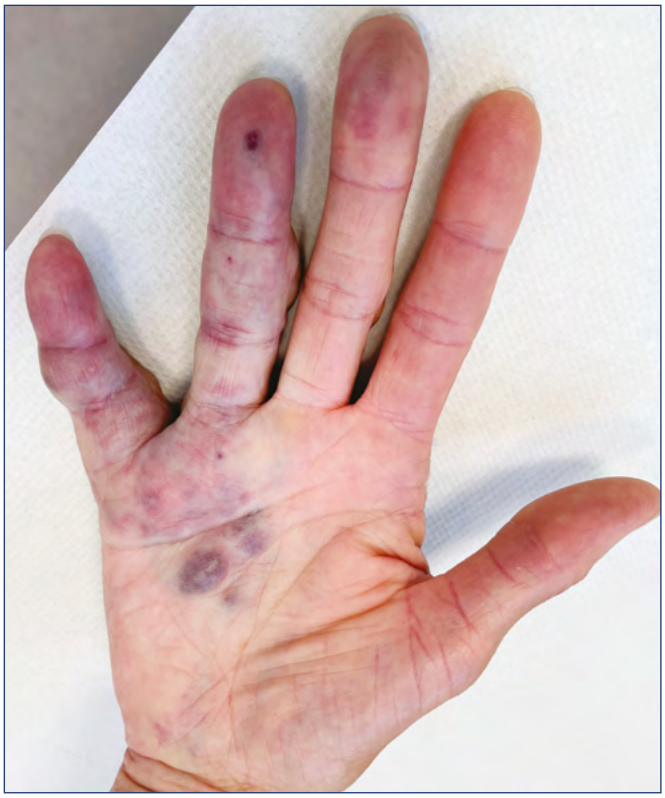

Figure 1. Venous malformation in fourth and fifth digits extended to the palm.

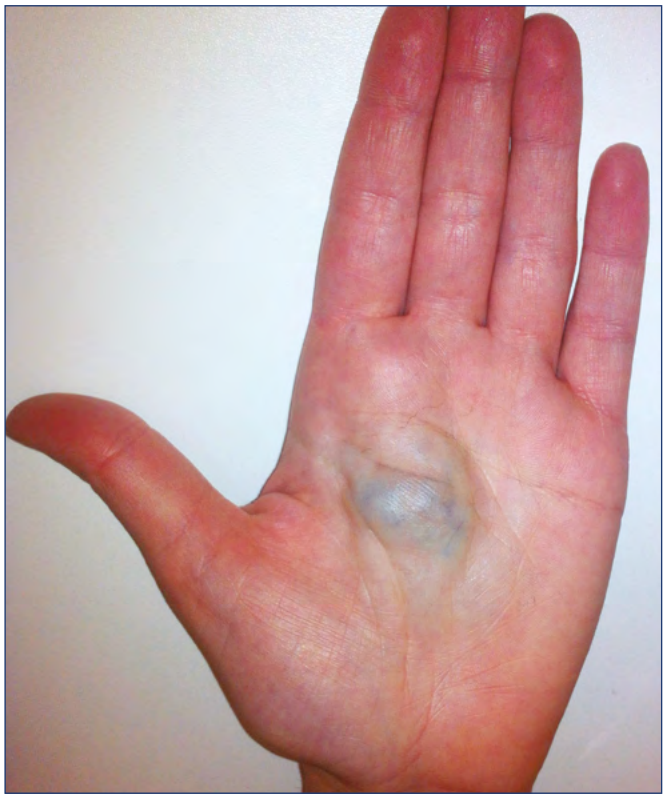

Figure 2. Palmar venous malformations.

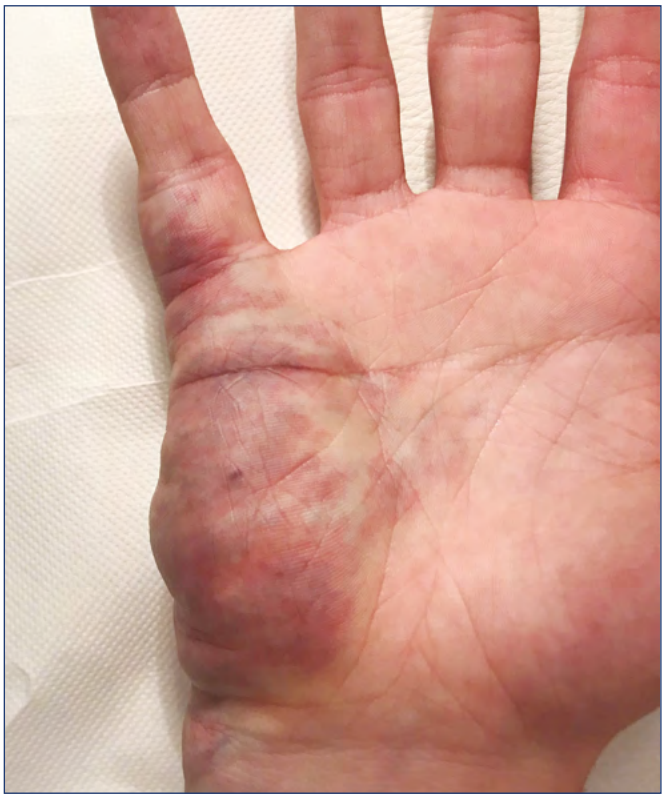

Figure 3. Hypothenar venous malformations.

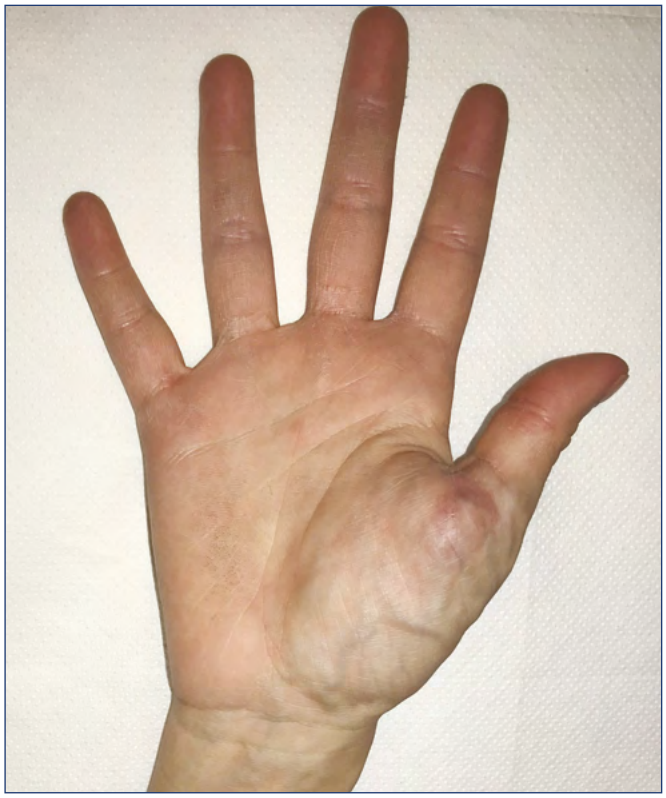

Figure 4. Thenar eminence venous malformations.

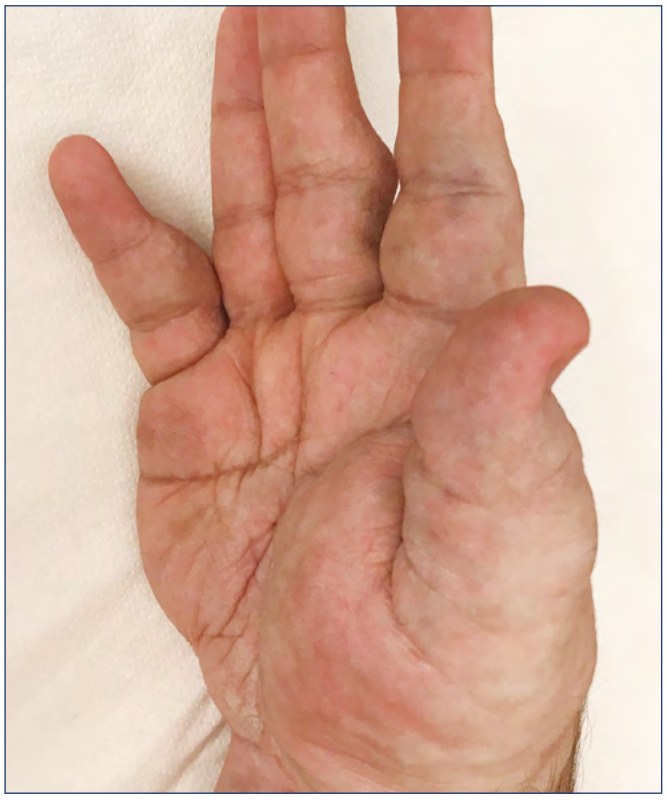

Figure 5. Extended venous malformations of the hand: the malformation extended to the wrist and forearm.

Great variability in VM makes it difficult to approach those cases, as the malformation may involve fine structures that should be spared during treatment. Moreover, as these diseases are rare and as few centers are specialized in the approach for treatment of VM, few papers, mainly with limited numbers of cases, have been published.

A consensus and general guidelines about treatment of VM have been published.[3,4] However, due to the anatomical peculiarities of the hand, general principles need to be adapted for that specific location. Unfortunately, there is a lack of practical information in the literature about that topic.

With that in mind, here we discuss the diagnostic process and treatment of VM in the hand based on our experience from our VM-dedicated center. We also provide a retrospective analysis of the cases treated and the results of our approach.

Diagnosis

A complete diagnosis of VM in the hand is mandatory because of the variability of the disease and because precise data about VM location and extension are important in choosing treatment strategy.

The diagnostic process for this disease should progress in a stepwise manner, from the simplest test to the most invasive.[5] As a first step, clinical examination should determine the location of the disease and make the differential diagnosis with AVM and LM and the effects of the defect on hand function. Typically, VMs are masses that are not pulsating and that are compressible with slow refilling. By lifting the limb, an emptying effect is sometimes recognizable. Pressing the mass may be painful. Sometimes, solid masses may be perceptible in the context of the malformation: these are due to phleboliths, calcified areas, which are typical of VM.

The second step of the diagnostic process is an echo Doppler (ECD) examination, which can provide several main data and should not be ignored. Firstly, ECD shows the type of flow in the mass, allowing differential diagnosis with AVM (high flow) and LM (cysts with no flow); VM has a typical slow flow. Secondly, ECD provides information about the location, whether deep or superficial, and the involvement of tissues. By differentiating among an intramuscular, a superficial, and an interstitial form, ECD is useful for treatment planning (*Figure 6*). Phleboliths may be visible inside the malformation. Moreover, ECD may show whether the malformation is formed with venous lakes or with a more compact mass with small vessels: this difference is useful

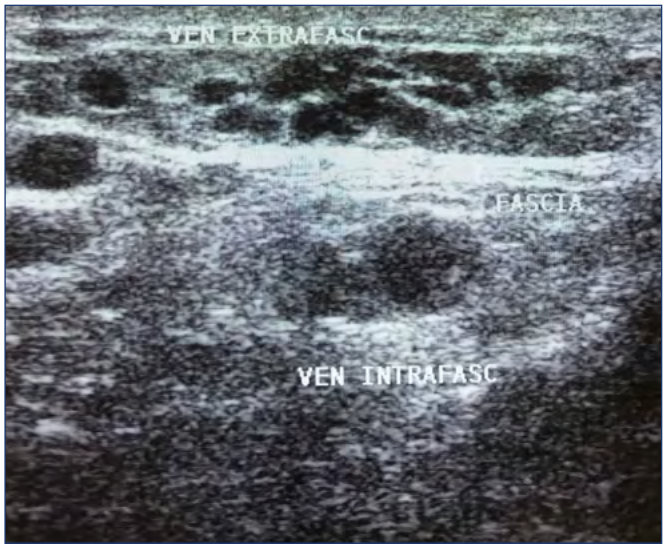

Figure 6. Echo Doppler of the palm of the hand in a case of venous malformation. Subcutaneous malformations are visible together with subfascial (intramuscular) forms.

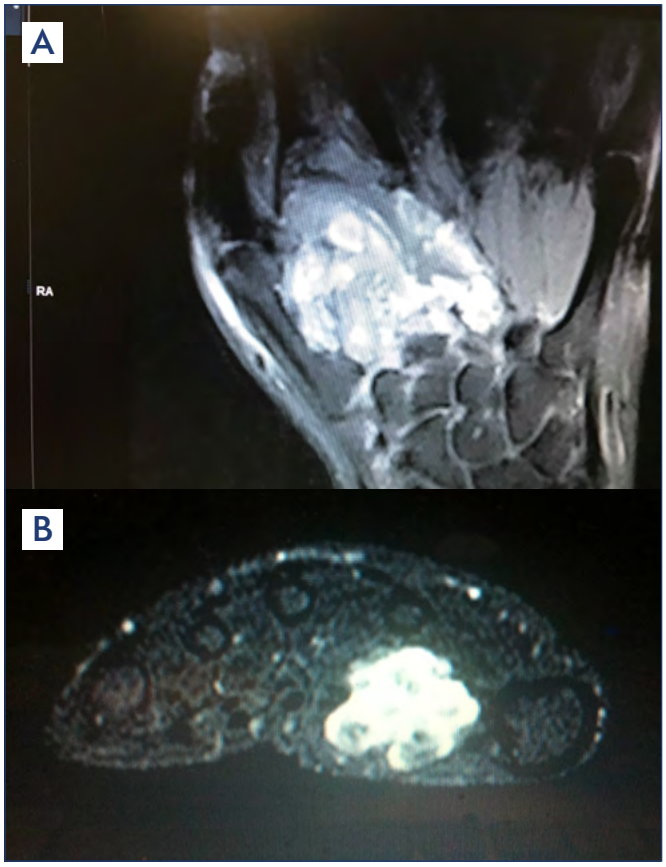

Figure 7. Magnetic resonance imaging in (A) frontal and (B) transversal views showing the location of venous malformations (bright areas).

for deciding whether to try sclerosis or not as in the second type (which is not uncommon) sclerosis is less effective.

The third step in the diagnostic process uses imaging procedures. Magnetic resonance (MR) imaging will clearly show the site and extension of the malformation. As VM has slow flow, recognized by the ECD performed before, contrast injection would not be necessary (*Figure 7*). Computed tomography (CT) with contrast may be useful; however, CT images are not as clear as those obtained by MR. Angio CT should be avoided because this test mainly shows the arterial tree, which is not pathologic or may show slight arteriovenous (AV) fistulas, whereas the VM is not as well shown as with MR.

Plain rx of the hand is an additional exam that is useful for recognizing bone involvement and showing phleboliths (*Figure 8*).[7]

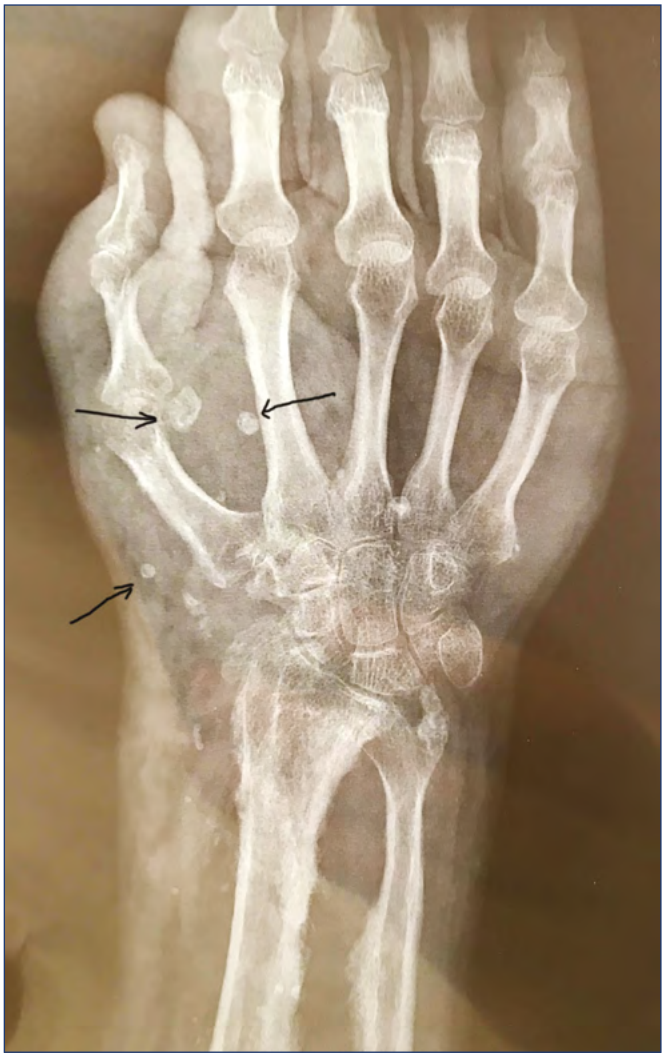

Figure 8. Plain rx of the hand in a case of extended vascular malformation: notice phleboliths (arrows).

Treatment

Treatment of VM is based on the following procedures: sclerosis, surgery, and laser.

Sclerosis is traditionally the first-line treatment for dilated veins, like in varicose veins. Several substances are available, such as polidocanol, sodium tetradecyl sulfate (TDSS) or ethanol, even in the form of ethanol gel.[8]

Sclerosis has been shown to be less effective for treatment of VM, with a high incidence of recurrence, except with the use of ethanol, pure or jellified.[4] Risks of sclerosis are skin necrosis, nerve damage (sometimes permanent), and muscle contracture.[9] An experimental study demonstrated that ethanol may exit the venous walls and cause damage in adjacent nerves, demonstrated by a reduction in nerve axons.[10] In small anatomic compartments, like the hand, the risk of alcohol migration outside the wall producing nerve damage is theoretically increased. Ethanol gel may have a lower incidence of complications.

The topic of risk for nerve damage is highly relevant with regard to the hand because finger sensibility is crucial for hand function: a loss of sensibility in the fingertips of the thumb or index finger is a main disability (blind finger). Some small case series studies report good results for sclerosis in treatment of VM in the hand,[11,12] but the topic of risk of complications remains open.

An alternative procedure is the surgical removal of the malformation. However, due to the peculiar anatomy of the hand, surgery requires specific experience in the approach for that area and in the management of its specific fine structures. Correct choice of skin incision, skin-sparing technique, tourniquet use, microscope use, and in how to handle the involved structures, such as bone, nerves, vessels, muscles, and tendons are all technical skills that may be crucial for a successful surgical treatment.[13] Unfortunately, reports of technical data from surgical treatment of VM in the hand are lacking in the literature. In the case of extended, infiltrating forms, a step-by-step procedure is indicated, in order to avoid long-duration surgery, which may lead to blood loss and poorer results. An approach by a multidisciplinary team may offer the best results.

Catheter embolization is not indicated in VM (unlike AVM), as that method can only occlude afferent arteries and is ineffective in reducing or occluding the vascular venous mass.[4] Unfortunately, even today, embolizations are sometimes performed in VM; the results are poor and may be dangerous if arteries of the fingers are occluded.

Laser treatment has a very limited application in this area because of the risk of structure damage.

Materials and methods

To obtain data about the characteristics of VM localized in the hand, the treatment performed, and the results, a group of patients treated in a single center were analyzed retrospectively.

In the period of 1986 to 2019, 115 patients with vascular malformation of the hand were treated. During the period of 1986 to 2010, they were treated in a vascular surgery division and from 2010 to 2019, in a center dedicated to vascular malformation.

Of the 115 patients, 74 (64%) were female and 41 (36%) were male. Mean age was 29.6 years and ages ranged from 5 to 70.

Extension of the lesions were recorded, dividing the cases into 2 groups: limited and extended forms. The extended forms included multiple-sited lesions and infiltrating forms of different areas of the hand. It was difficult to decide if limited lesions localized to 2 different areas, should be classified as "limited" or "extended." The decision was made to include these with multiple sites within the "extended" forms group because of the necessity to perform more operations.

All patients of this group were treated by surgery alone in a single operation or by 2 or more steps, according to the extension and to the symptoms. Nonsymptomatic areas were for the most part not treated. All operations were done in teamwork by the same vascular and hand surgeons.

Technically, the resection was done with the aim of avoiding damage to vessels, nerves, and tendons. For this reason, in case of VM surrounding these structures, the surgeries were planned in detail and included use of magnifying glasses or a microscope to aid in separating the malformed tissue from the fine structures (*Figure 9*).[13]

All patients were controlled after treatment by clinical examination and by ECD performed by the same investigator.

Results were divided thusly: healed (no residual VM), improved (absence or significant reduction in symptoms, but with residual VM), and recurrence (new growth of malformation in the operated area), with distinction between limited and extended forms.

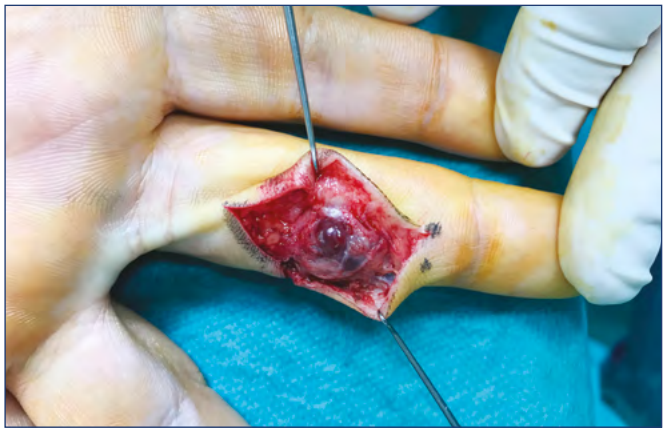

Figure 9. Removal of a limited venous malformation of a finger.

The label of "healed" in the extended group was given only in relation to the operated area and did not consider other involved areas that were not treated.

Results

Location of the malformations in the hand are shown in *Table II*; notice that the fingers were the most common site of VM. According to the extension of the defect, we registered 76 limited and 39 infiltrating cases. The number of operations for limited and extended forms are reported in *Table III*. Complications of surgery are shown in *Table IV*. The results of surgical treatment, divided by limited and extended forms, is shown in *Table V*.

Fingers	36
Hand and wrist	23
Hand and fingers	21
Palm	14
Thenar	12
Hypothenar	9
Total	**115**

Table II. Location of venous malformations in the hand

Operations	Limited	Extended
1	48	12
2	9	4
3	-	9
4	-	6
5	-	2

Table III. Number of operations for limited and extended forms.

	Limited	Extended
Hematoma	0	0
Skin necrosis	0	0
Nerve palsy	0	0
Temporary paresthesia	3	0
Postoperative temporary pain	0	2

Table IV. Complications of surgical treatment in 115 cases of vascular malformation in the hand.

Type of defect		
Result	**Limited**	**Extended**
Healed (no residual dysplasia	56 (74%)	6 (15.5%)
Improved (with residual dysplasia)	12 (16%)	29 (74.5%)
Recurrence	8 (10%)	4 (10%)
Total	**76**	**39**

Table V. Results of surgical treatment in limited and in extended forms: 115 operated cases.

Discussion

Analysis of these series demonstrated that VM may be located in various sites in the hand. The most common site is the fingers, which is also a location where surgery may be possible, whereas sclerosis has a higher probability of producing nerve damage (*Figure 10*). The distinction between limited and infiltrating forms is crucial, as the approach, the number of operations involved, and the results differ, as seen in *Tables III-V*.

The decision to operate in all cases here instead of choosing sclerosis was based on our former experience in which we noticed a significant recurrence or even no effect after sclerosis with classical substances, even using the foam technique. Over the years, we've had several other cases treated elsewhere via sclerosis, mainly with polidocanol or TDSS with very poor results, such as no effect or early recurrence. We have also tried ethanol sclerosis, which is known to be much more effective. However, we noticed some cases of nerve damage, even permanent damage, which discouraged us from continuing with this treatment.

For these reasons, we have chosen to approach VM of the hand mainly via surgery in teamwork.

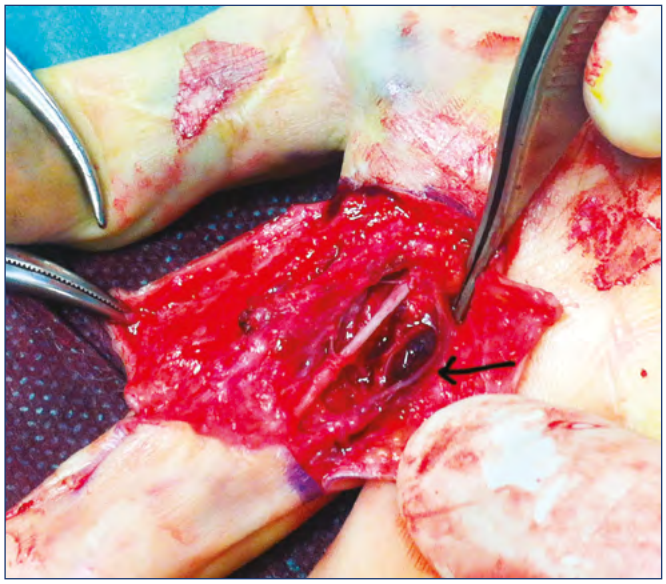

Figure 10. Surgical approach to a limited venous malformation of a finger: notice that nerve (front) and vessels (arrow) have been isolated before removing the malformation (dark area).

We are aware that some other groups have a preference for sclerosis. However, the lack of data about surgery and the good results we observed in our early experience encouraged us to continue with the surgical strategy.

During surgery, we have noticed that VMs often are not typical vessels but are blackberry-like, crumbly tissue, sometimes containing phleboliths (*Figures 11, 12, 13*). Moreover, these malformations may be irregular and infiltrate deeply into muscles or surrounding nerves, tendons, and vessels. These characteristics made us question whether such tissue could be successfully sclerosed. Regardless, we found that removal of limited malformations by surgery were mainly successful.

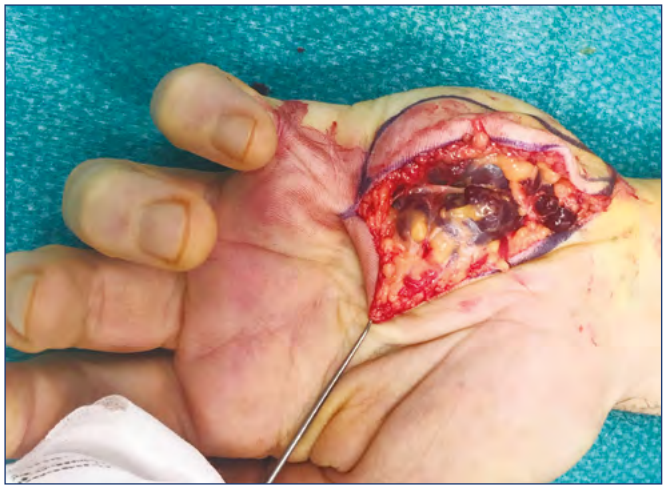

Figure 11. Removal of a venous dysplastic intramuscular mass in hypothenar area.

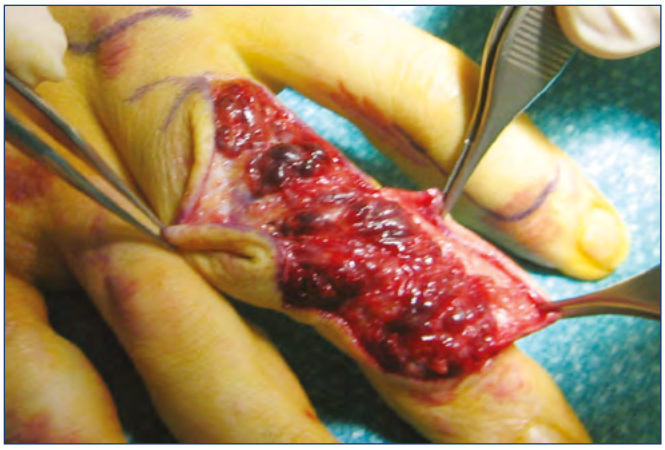

Figure 12. Resection of limited venous malformations of the dorsum of the finger: notice the aspect of several small, limited masses; sclerosis would probably be ineffective in this case.

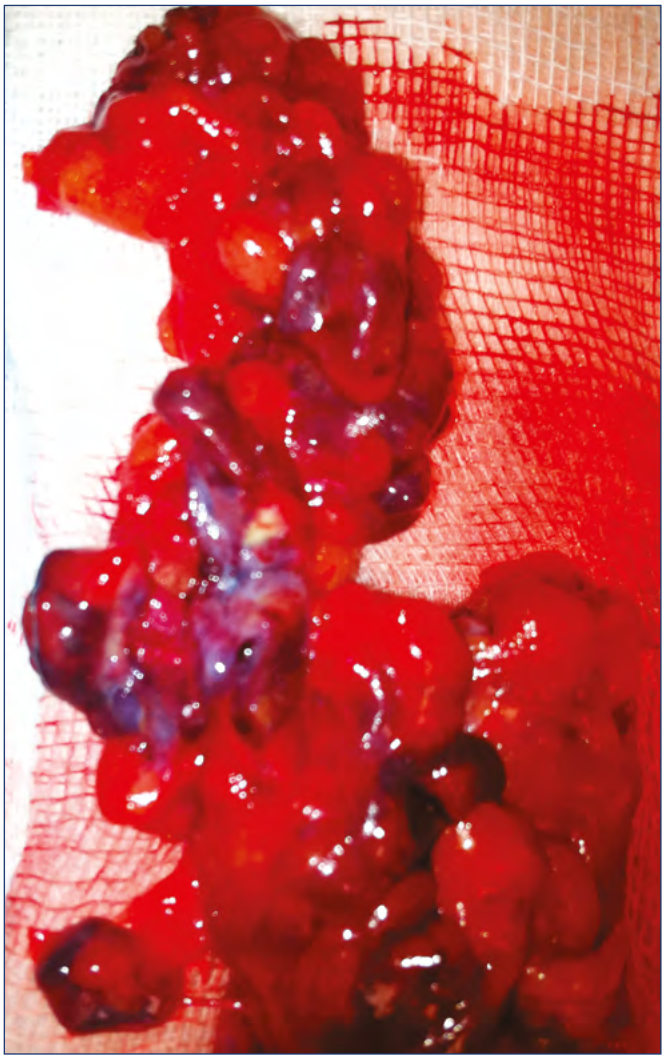

Figure 13. Tissue specimen of removed venous malformation: notice several blue masses mixed with normal fat. This patient is the same as for Figure 12. This is not the aspect in all cases: other (more common) forms arise mainly by a vascular mass without fat.

More difficult is the approach for infiltrating/extended cases. The aim for these was to reduce or eliminate symptoms, such as recurrent or continuous pain. The strategy in these cases was the tailored removal of the most symptomatic area of dysplastic vessels (*Figure 14*). In deep infiltrating forms, complete removal of the malformations located within the deep layers was not always possible. In many cases, several operations were required (*Table III*).

One main point is that VMs are often not only formed by vascular tissue: in many cases, fat hypertrophy was noticed, which is part of the mass effect and should be removed together with the malformation (*Figure 15*).

Complications were very few, as *Table IV* shows, even in the infiltrating group, and were even less than we expected. A main point here is that a stepwise strategy, splitting treatment into 2 or more surgical sessions rather than a single main session avoided significant blood loss, skin necrosis (except very limited necrosis of 1 edge of the wound, which healed spontaneously), complications of prolonged ischemia by tourniquet, and postoperative hematoma (we had not a single hematoma that required evacuation).

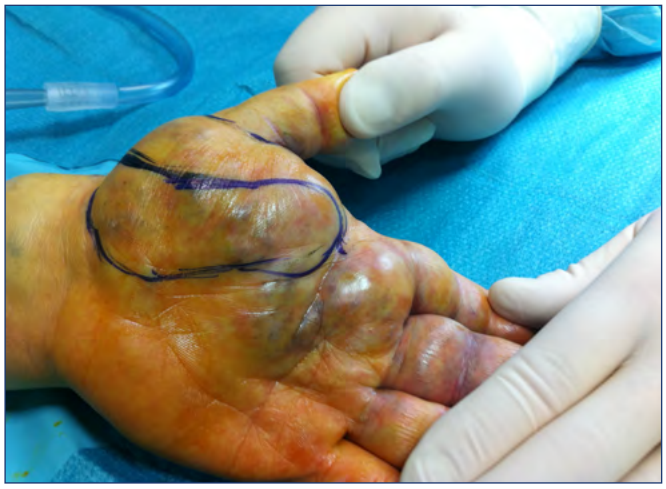

Figure 14. Incision planning in an extended form.

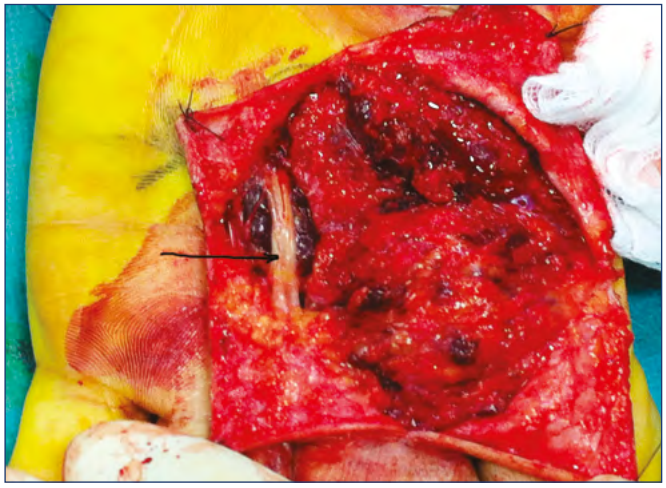

Figure 15. Surgery in a diffuse venous malformation of the hand. Fat overgrowth is combined with dysplastic venous tissue. Notice a nerve (arrow) isolated over a mass of dysplasias.

We saw good results for limited malformations, with a high incidence of healing without recurrence (*Figure 16*). The 75% of healed cases (no residual malformation) in the limited group indicates that surgery is likely to achieve a positive result in these cases. In our opinion, this is a better result than one would see with sclerosis, in which even occluded vessels may recur.

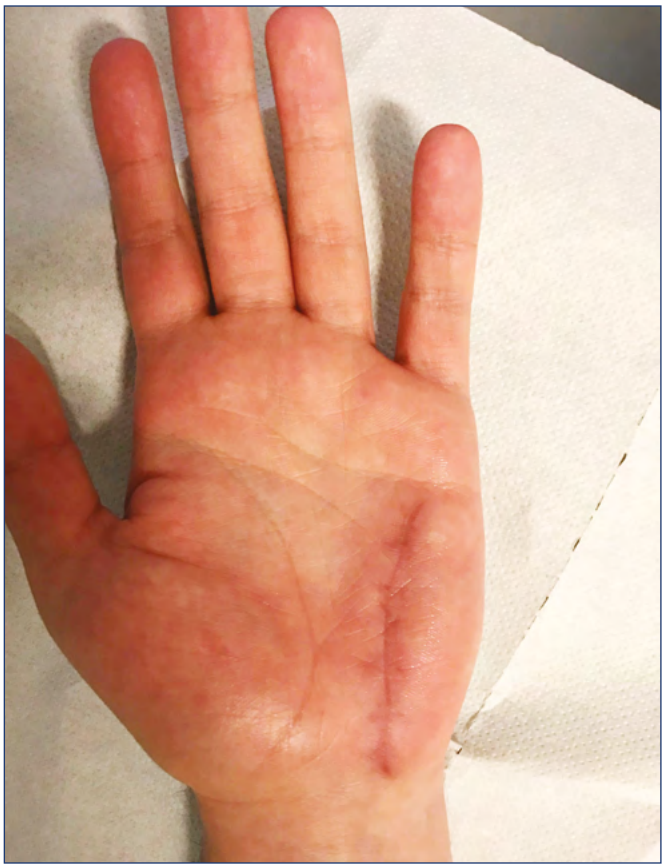

Figure 16. Postoperative control after removal of a venous malformation at hypothenar area: no residual malformation, confirmed by ultrasound exam. Same patient as for Figure 10.

In extended forms, we noticed that recurrence in the operated area was uncommon. We should point out that when speaking of "healing" and "recurrence" here, these refer to the operated area only. Even in these difficult cases, tailored surgery centered on the symptomatic points could improve patient condition (*Figure 17*).

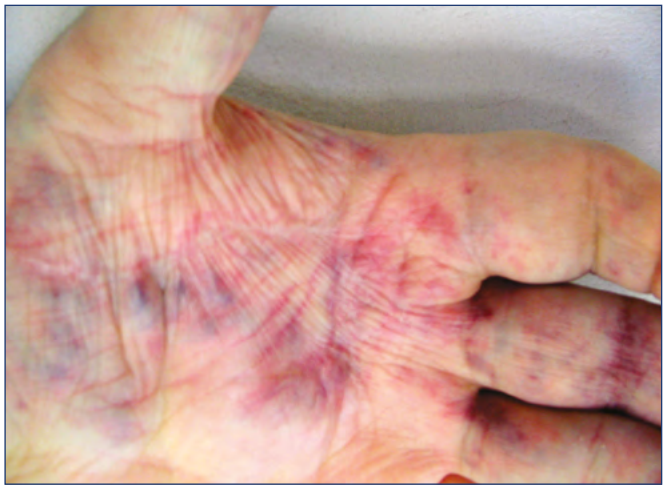

Figure 17. Postoperative result after successful tailored surgery in an extended venous malformation case. There is no mass recognizable in the operated area. Same patient as for Figure 14.

From our experience, we have learned several lessons. Firstly, VM can be removed successfully in many cases. Secondly, treatment should be chosen only after a complete diagnosis; for this, ECD was always very important for us. Thirdly, a team approach was crucial for us: the hand surgeon's skill in anatomical knowledge coupled with the vascular surgeon's skill in vessel management allowed us to successfully remove VM formerly considered inoperable.

Conclusion

Hand VM can be managed successfully by surgery if a careful and complete evaluation of the case is performed. Surgical treatment for hand VM is an effective and safe approach that reduces the incidence of recurrence. Complications are few if certain principles and techniques are followed.

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Role of anticoagulation treatment in the prevention of post-thrombotic syndrome

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anticoagulation, deep vein thrombosis, direct oral anticoagulants, low-molecular-weight heparins, post-thrombotic syndrome, warfarin.

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Abstract

Post-thrombotic syndrome (PTS) develops after deep vein thrombosis (DVT) of the lower limbs and may affect up to 50% of patients after proximal DVT. Prevention is of paramount importance as there is no gold standard for treatment of established PTS. Pharmacological or mechanical thromboprophylaxis is recommended to prevent PTS. Effective DVT treatment with vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), low-molecular-weight heparins (LMWHs), and fondaparinux are recommended as appropriate duration and intensity of anticoagulation therapy prevents DVT recurrence and PTS development. Rivaroxaban offers more favorable prognosis in terms of PTS development and severity than treatment with VKAs. LMWH have anti-inflammatory properties and may be superior to VKAs. Larger randomized controlled studies are needed to clarify optimal treatment for PTS prevention.

Introduction

Post-thrombotic syndrome (PTS) is a frequent complication of deep vein thrombosis (DVT) of the lower limbs.[1] PTS refers to chronic clinical manifestations of venous valvular dysfunction following proximal DVT, including various symptoms affecting a patient's quality of life (QOL).[2] It is also associated with a reduced ability to work, with considerable consequences for both the patient and heath care systems.[3] Almost half of the patients with DVT (20%-50%) will develop PTS within 2 years after the index event, despite conventional anticoagulation therapy.[4] Others reported that the incidence of PTS continues to increase up to 10 years after the initial diagnosis of DVT.[5,6]

Venous hypertension is the main pathophysiological factor for PTS development.[1] Outflow venous obstruction deriving from persistent residual vein thrombosis (RVT) and acute inflammatory response after venous thrombosis leads to valvular damage and reflux and occurrence of venous hypertension.[1] Another important factor for PTS development is the chronic inflammation affecting the venous wall and the microcirculation. Excessive capillary leakage and impairment of skin nutrition leads to skin changes and ulceration in more severe forms of PTS.[7] Inflammation also delays thrombus resolution and causes fibrosis in the vein wall.[8,9]

No standard criteria exist for diagnosis of PTS and thus its presence becomes evident when signs and symptoms of deep venous incompetence occurs after the acute episode of DVT has passed (after 6 months).[10] The signs and symptoms of PTS include limb edema, various degrees of pain, heaviness, cramps, fatigue, itching, venous claudication, varicose veins due to venous stasis, and skin changes.[11] Skin changes include hyperpigmentation, venous eczema, lipodermatosclerosis, and in more severe forms of PTS, venous ulceration (*Figures 1, 2*). Symptoms are provoked by standing position or walking and reduced by rest and elevation of the leg.

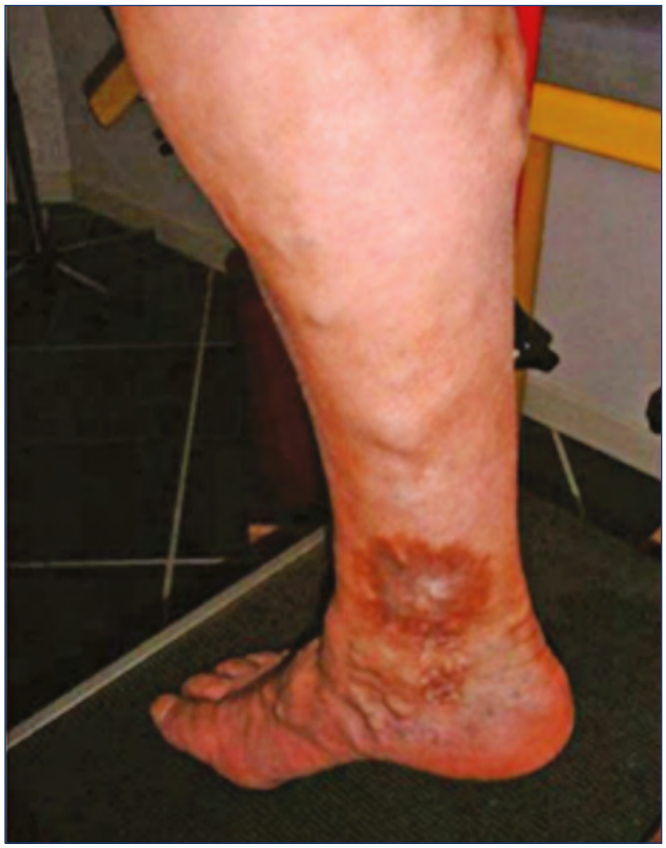

Figure 1. Post-thrombotic syndrome; healed ulcer with concomitant skin changes in the medial malleolus and varicose veins.

Photo provided courtesy of Department of Vascular Surgery, University Hospital of Larissa, Larissa, Greece.

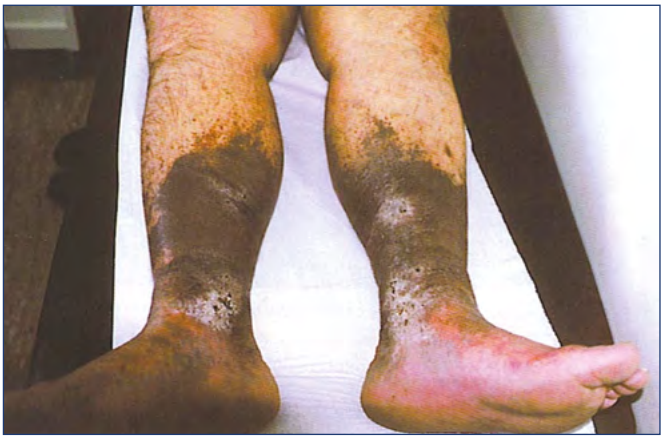

Figure 2. Post-thrombotic syndrome in both lower limbs with active ulcer and extensive concomitant skin changes in the gaiter area.

Photo provided courtesy of Department of Vascular Surgery, University Hospital of Larissa, Larissa, Greece.

Pharmacological or mechanical thromboprophylaxis is recommended to prevent PTS.[12] Appropriate duration and intensity of anticoagulation therapy prevents recurrent DVT and development of PTS.[13] Vitamin K antagonists (VKAs), direct oral anticoagulants (DOACs), low-molecular-weight heparins (LMWHs), and fondaparinux are recommended for treatment of DVT.[14] The latest PTS guidelines from the American Heart Association do not recommend a specific anticoagulant over another, although the quality and type of anticoagulation could affect the risk of PTS.[15] This review focuses on the role of conventional anticoagulation treatment in the prevention of PTS.

Vitamin K antagonists (VKAs)

For more than half a century, VKAs have been recommended as the standard treatment for DVT.[13] VKAs, such as warfarin, acenocoumarol, and phenprocoumon, are administered orally and inhibit the γ-carboxylation of coagulation factors II, VII, IX, and X, and also the functional activity of the coagulation inhibitor proteins C and S.

Numerous studies have documented that the quality of VKA treatment plays an important role in PTS development.[16,17] The Einstein DVT trial, a randomized controlled study (RCT) that compared the efficacy and safety of rivaroxaban with subcutaneous enoxaparin followed by a VKA in 3449 patients with acute DVT, demonstrated that 21% of patients treated with VKA were below the therapeutic international normalized ratio (INR) levels.[18] A large Danish survey including 310 300 patients being treated with VKA reported that around 70% of patients were in therapeutic range, whereas another study from the United States (US) showed that only 54% of the patients had achieved continuing target levels of INR.[19,20] A meta-analysis by Erkens et al[21] reported that patients treated with VKAs are at the target level of anticoagulation (INR 2-3) for only about 50% of their treatment time, with a strong tendency toward subtherapeutic INR (42% in 0-1 month of treatment, 35% in 1-3 months, and 24.1% in 1-6 months).

Subtherapeutic anticoagulation with VKAs has been related to a 3-fold higher risk of PTS in patients who had an INR less than 2.0 for more than 50% of the treatment duration.[16,17] About 30% of the patients, especially in the first weeks of treatment have subtherapeutic INR.[16,17,21] In this period, delayed clot lysis and stimulated connective tissue growth due to thrombin generation may cause permanent fibrosis and venous damage.[22] Therefore, it is crucial that patients treated with VKAs have adequate INR control during the first weeks of therapy for prevention of PTS.

Direct oral anticoagulants (DOACS)

DOACs have become over the last years the new standard of treatment for venous thromboembolism (VTE).[14] DOACs can be given in fixed doses without routine monitoring. The following DOACs are licensed for VTE treatment: dabigatran, which inhibits thrombin, and rivaroxaban, edoxaban, and apixaban, which inhibits factor Xa (FXa). The latest guidelines by the European Society for Vascular Surgery (ESVS) recommend DOACs over VKAs for the treatment of VTE (grade 1A) in patients without cancer.[14] Theoretically, DOACs may also reduce the incidence of PTS compared with VKA, due to their more reliable dosing and predictable pharmacodynamics. It remains unknown whether DOACs are equivalent to LMWH with respect to PTS prevention.

Several studies have suggested that rivaroxaban, compared with warfarin, reduces the risk of PTS after DVT, although only a few of these studies were randomized and the incidence of PTS was the primary outcome.[19,20,23-28] Two registries have also concluded a benefit of rivaroxaban, compared with warfarin, regarding the PTS prevalence.[19,20] In the Danish registry, rivaroxaban was associated with decreased risk of PTS compared with warfarin within the 3-year follow-up (0.53 per 100 per year vs 0.55 per 100 per year, respectively).[20] In a multicenter retrospective study from Norway, the risk of PTS development was lower after 2 years among patients treated with rivaroxaban than in warfarin-treated patients (odds ratio [OR], 0.5; 95% confidence interval [CI], 0.3 to 0.8; *P*=0.01).[24] Another retrospective multicenter study by Ferreira and colleagues also reported a benefit of rivaroxaban over warfarin after 15 months among 127 patients with DVT (50.7% vs 69%; *P*=0.002).[25] Prandoni and colleagues investigated the prevalence of PTS at 3 years in a prospective cohort study of 309 patients treated with rivaroxaban, apixaban, or dabigatran, compared with a historical cohort of 1036 patients treated with warfarin.[26] Although the majority of the patients in the DOAC cohort were treated with rivaroxaban (84%), the risk of PTS in the DOAC-treated patients was reduced by 54% in comparison with patients treated with warfarin (OR, 0.46; 95% CI, 0.33 to 0.63).[26] In a post hoc subgroup analysis of 336 patients previously included in the Einstein DVT trial, in which 48% were treated with rivaroxaban and 52% with warfarin, the prevalence of PTS 60 months after the acute DVT was numerically lower in the rivaroxaban group than in the warfarin group although statistically nonsignificant after adjustment for possible confounders (29% vs 40%; *P*=0.18).[27] In a small RCT by de Athayde Soares and colleagues, rivaroxaban-treated patients had lower incidences of PTS and better total vein recanalization rates at 1-year follow-up than warfarin-treated patients.[28] Finally, 2 recent meta-analyses found that the use of rivaroxaban for the treatment of DVT was associated with a roughly 50% reduction in PTS risk compared with warfarin.[29,30]

In a post hoc subgroup analysis of patients who participated in the RE-COVER studies, the long-term prevalence of PTS (mean time from the index event, 8.7 ± 1.4 years) was investigated.[31] The RE-COVER studies randomized 5109 patients with DVT and/or pulmonary embolism (PE) to receive 6 months of treatment with either dabigatran (150 mg twice a day) or warfarin in double-blind design.[32,33] After the completion of the studies, patient-reported Villalta and health-related QOL (HRQOL) questionnaires were sent by mail to the patients who agreed to participate. In total, 349 patients were included, of which 166 (48%) were treated with dabigatran and 183 (52%) with warfarin. PTS was diagnosed in 63% of patients with DVT and in 46% of patients with PE only and did not differ between the treatment groups; the crude odds ratio for PTS in patients treated with dabigatran compared with warfarin was 1.1 (95% CI, 0.6 to 1.8) after DVT and 1.2 (95% CI, 0.5 to 2.6) after PE only. It is possible that the higher quality of warfarin anticoagulation achieved in clinical trials than in clinical practice can partially explain why PTS prevalence did not differ between groups in the RE-COVER and Einstein DVT post hoc subgroup analyses.

In a recent published meta-analysis, 1894 patients were analyzed regarding the severity of PTS.[30] Severe PTS was less common in patients treated with rivaroxaban, according to Villalta score, than in patients treated with warfarin (3.7% vs 6.4%) (OR, 0.55; 95% CI, 0.36 to 0.85; *P*=0.024).[30] Furthermore, in another meta-analysis by Li and colleagues, rivaroxaban therapy was found to be associated with a reduced risk of mild PTS (OR, 0.64; 95% CI, 0.50 to 0.82; *P*=0.0005), moderate PTS (OR, 0.64; 95% CI, 0.45 to 0.91; *P*=0.01), and severe PTS (OR, 0.52; 95% CI, 0.33 to 0.82; *P*=0.005).[29]

DOACs may produce an earlier reduction in the RVT detected on duplex ultrasound and consequently an earlier

vein recanalization. Prandoni and colleagues reported that the degree of RVT in the patients treated with rivaroxaban decreased from 50% to 40% at 3 months and continued to decrease even to 20% at 6 months after the episode of DVT.[34] The study concluded that vein recanalization progressively increases over time in patients treated with DOACs in contrast with those treated with warfarin.[34] Ferreira and colleagues[25] demonstrated a significantly lower rate of RVT in patients treated with rivaroxaban (24.4%) than in patients treated with VKAs (64.6%). Others reported that the incidence of total recanalization 1 year after the episode was significantly higher in the rivaroxaban group than in the warfarin group, whereas partial or no venous recanalization was higher in the warfarin group.[28]

Low-molecular-weight heparins (LMWHs)

LMWHs are polysulfated glycosaminoglycans derived from unfractionated heparin by enzymatic or chemical depolymerization. The molecular weight is on average 4-5 kDa (range 2-9 kDa) and inhibits FXa over thrombin.[35,36] LMWHs have anticoagulant and anti-inflammatory properties.[37-39] Experimental studies have shown that LMWHs reduce venous wall inflammation,[37] enhance endothelization,[38] and reduce fibrosis,[39] and it is probable that these anti-inflammatory properties could have a role in preventing PTS.

A systematic review by Hull and colleagues[40] compared long-term LMWH (≥3 months) with VKAs for DVT treatment and showed a more favorable recanalization rate and lower incidence of venous ulceration with LMWHs. Another study that compared tinzaparin with VKAs showed a 23% reduction in signs and symptoms of PTS at 3 months with tinzaparin.[41] In a subgroup analysis of 480 patients included in the home-LITE study, the prevalence of PTS was lower in the tinzaparin-treated patients than in warfarin-treated patients regardless of DVT location (iliac/noniliac).[42] Patients with iliac DVT had an overall odds ratio of 0.53 (95% CI, 0.33 to 0.83; *P*=0.0079) for PTS, and patients with noniliac DVT had an odds ratio of 0.79 (95% CI, 0.67 to 0.93; *P*=0.0046), both in favor of tinzaparin. The study concluded that LMWH may be a suitable alternative for the prevention of PTS in patients with iliac DVT who are unlikely to undergo invasive thrombolysis.[42]

Conclusions

Anticoagulation remains the fundamental therapy for VTE, and in terms of PTS prevention, the quality of anticoagulation is particularly important. Rivaroxaban offers a more favorable prognosis in terms of PTS development and severity than treatment with VKAs. Careful INR monitoring remains critical for the outcome in case of VKA treatment. LMWH have anti-inflammatory properties in addition to anticoagulation and may provide a more favorable outcome. In future, more research is needed with large RCTs to better define the role of different DOACs compared with warfarin as well as LMWH and fondaparinux in the prevention of PTS.

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Update on calf vein thrombosis

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Abstract

Calf deep vein thrombosis, defined as thrombosis confined to the calf veins of the lower limbs, is a frequent finding in symptomatic outpatients and inpatients when the ultrasound examination is extended to the deep veins of the whole leg. The prevalence of the disease is between 5% and 33% of all deep vein thrombosis (DVT) cases detected by ultrasound, low in symptomatic patients and higher in asymptomatic patients at high risk of DVT. Thrombi in the calf veins can extend to proximal veins, lyse spontaneously, or recanalize over several weeks or months. Focusing on the embolic risk, data are heterogeneous: the rates of propagation to proximal veins and pulmonary embolism (PE) during surveillance have been reported to range from 0% to 35% and from 0% to 5.8% respectively, whereas the prevalence of silent PE was 13%. There are different diagnostic approaches: the preference for a proximal rather than a complete ultrasound approach could be safely guided by the presence of symptoms in the calf. Therapeutic anticoagulation in patients with isolated calf DVTs may be warranted to reduce the risk for proximal venous thromboembolism. However, randomized studies are needed to draw firmer conclusions. Because the benefits of anticoagulation seem unclear, it is important to evaluate the risk for bleeding when determining whether anticoagulation is appropriate.

Keywords:

anticoagulant, calf vein system, duplex ultrasound, vein thrombosis

Introduction

Clinical relevance and treatment of calf vein thrombosis are controversial because thrombosis can propagate to the proximal deep vein with possible pulmonary embolism (PE).

Calf vein thrombosis is defined as any clot involving the deep veins of the calf that did not extend into the popliteal vein. The calf veins are 3 paired veins, posterior tibial, fibular (also known as peroneal), anterior tibial, and 2 nonpaired muscular veins, soleal and gastrocnemial. Usually, the most common veins involved are the peroneal veins.[1] The following terms should be used in clinical practice to identify thrombosis of the calf according to the nomenclature: isolated calf muscle vein thrombosis (ICMVT) for a thrombosis confined to the muscle veins only; deep calf vein thrombosis (DCVT) for a thrombosis present in the paired calf veins; isolated distal deep vein thrombosis (IDDVT) for the composite of ICMVT and DCVT, occurring either in isolation or in combination.[2]

The confluent segment that joins axial veins to the popliteal vein, called the "trifurcation area," is often considered as proximal.

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Anterior tibial vein thromboses are uncommon, so these veins are generally excluded from ultrasound investigation. When specifically assessed during venous duplex ultrasound (DUS), IDDVTs account for approximately half of all DVTs.[3]

Prevalence, incidence, and distribution

The prevalence of calf vein thrombosis is between 5% and 33% of all DVT cases detected by ultrasound[3]; prevalence is low in symptomatic patients and higher in asymptomatic patients at high risk of DVT: 15% after knee or hip surgery, and 45% after coronary artery bypass surgery.[4]

In 2007, a study from Nord-Trøndelag, Norway, based on all residents aged ≥20 years (n=94 194), identified the incidence of venous thromboembolism (VTE) between 1995 and 2001 from diagnosis characteristics retrieved from medical records.[5] A total of 740 patients with a first-time VTE event were identified (incidence rate, 1.43 per 1000 person-years), with a DVT incidence rate of 0.93 per 1000 person-years. Proximal DVT was 3-fold more frequent than was distal DVT, and it was mostly located on the left side. The incidence increased exponentially with age and was higher in cancer patients.

A new, retrospective, single-center study on ultrasound-verified DVT has illustrated the large diversity of thrombus distribution.[6,7] The analysis concerned patients >18 years old presenting with unilateral DVT who were referred to 1 hospital in Antwerp between 1994 and 2012 (n=1338). Calf-vein DVT (distal DVT) occurred in 28% of the cohort; femoropopliteal DVT, in 33%; and iliofemoral DVT (proximal DVT), in 38%.

Calf thrombosis can be asymptomatic or symptomatic: thrombi in the first case are smaller and with fewer complications. Seinturier et al[8] studied 1913 patients with vein thrombosis of the lower limbs for 2 years: they found that at 2 years, survival rate was 80% in patients with unilateral distal thrombosis, and 67% for bilateral-distal, 72% for unilateral proximal, and 65% for bilateral-proximal thrombosis. Thromboembolic disease was present in 7.7% of patients with unilateral-distal thrombosis, and 13.3% with bilateral-distal, 14% with unilateral proximal, and 13.2% with bilateral-proximal thrombosis.

Evolution of calf vein thrombosis

Thrombi in the calf veins can extend to proximal veins, lyse spontaneously, or recanalize over several weeks or months. The evolution of untreated IDDVT in symptomatic outpatients was well-reported in the CALTHRO (CALf deep vein THROmbosis) study.[9] This study suggests that IDDVT can be diagnosed in about 15% of high-risk symptomatic outpatients. Proximal extension within 5–7 days occurs in about 3% of patients, whereas over 90% have complete resolution without anticoagulant treatment.

The balance between clot-propagating risk factors and counteracting repair mechanisms in IDDVT is different than in proximal DVT or PE, and therefore IDDVT might be regarded as a distinct disease entity, even if it needs to be confirmed in other cohorts.[10] This disease has a prognosis similar to proximal thrombosis, probably due to a more intense thrombophilic status. Patients with bilateral distal vein thrombosis are older, suffer heart failure or respiratory failure, cancer, bed rest, venous insufficiency, recurrence of thrombosis, and higher mortality.

In a systematic review, proximal extension was reported in 10% of non-anticoagulated patients.[10] In the CALTHRO study, propagation into the popliteal vein 5–7 days after the first compression ultrasound (CUS) was observed in 3.1% of 64 untreated high-risk outpatients.[9]

This result is consistent with findings reported by MacDonald and colleagues in patients with untreated muscular IDDVT (3%), and with studies that evaluated serial proximal CUS (1% to 5.7%).[11]

Risk of embolism

Focusing on the embolic potential, data are heterogeneous, as in recent systematic reviews, the rate of propagation to proximal veins and PE during surveillance have been reported to range from 0% to 35% and from 0% to 5.8% respectively, whereas the prevalence of silent PE was 13%.[12,13]

In our study, the extension to the proximal veins greatly increases the risk of PE: 4 of 34 patients (11.7%) with calf DVT who developed proximal DVT detected by color-flow duplex scanning (CFDS) and phlebography had a subsequent symptomatic PE.[14]

Risk of recurrence or death

Regarding the late complication, in a study that involved 154 patients with unprovoked IDDVT, the cumulative risk of recurrence was 17% and 30%, respectively, 10 and 20 years after the diagnosis.[15]

Cancer was the main independent predictive factor of death: patients with cancer-related IDDVT had a 9 times higher long-

term risk of death than subjects without cancer (3.5% versus 38.3%).[16]

More recently, observations from the GARFIELD-VTE Registry confirmed that DVT location was a less important prognostic factor for recurrence and death in patients with cancer or unprovoked IDDVT.[17]

Risk of post-thrombotic syndrome

Post-thrombotic syndrome is not a usual complication after distal vein thrombosis: Masuda et al[18] showed complete lysis of thrombi at 3 months in 88% of distal vein thrombosis studied and, at 3 years, only 5% of patients had hyperpigmentation and varicose vein development. The post-thrombotic syndrome is not correlated to the venous segment involved, and symptoms are very few.

Finally, the risk of post-thrombotic syndrome was 2.3-fold higher in proximal DVT (PDVT) patients than in patients affected by IDDVT.[19,20]

Diagnostic approaches

The introduction of the CFDS brought advantages in the diagnosis of DVT.[21] More recently, a meta-analysis revealed that a CFDS examination is more sensitive for distal veins (75% vs 59%) and slightly less specific (94% vs 98%) than with CUS only.[22]

Schellong[17] affirms that the distal ultrasound, using a well-structured protocol of examination, is a valid 4-minute procedure that can easily be added to the examination of proximal veins.

Two ultrasonographic approaches, both based on vein compression, are validated: the whole-leg ultrasound, consisting of CUS that may be helped by color flow and spectral Doppler, and the proximal CUS, confining the examination up to the trifurcation area, without detecting calf veins. The latter approach, when negative, has to be repeated after 1 week to exclude proximal extension of a calf thrombosis, assuming that IDDVT may cause complications only in this case, and is seldom occurring, generally within the first 2 weeks after the onset of symptoms. However, as suggested by the American College of Chest Physicians (ACCP), and more recently by the American Society of Hematology (ASH) guidelines, assessment of pretest probability (PTP) and D-dimer measurement significantly reduced the number of repeated ultrasounds.[23,24] Hence, whereas these algorithms have been widely validated for the diagnosis of PDVT, their accuracy in patients with suspected IDDVT is not well-defined.

The preference for a proximal rather than a complete ultrasound approach could be safely guided by the presence of symptoms in the calf.[25,26]

In the PALLADIO study (Simplification of the Diagnosis of Deep Vein Thrombosis), which enrolled 1162 symptomatic outpatients with suspected DVT, both ultrasound strategies were incorporated, restricting the use of the whole-leg CUS to patients with both a likely PTP and positive D-dimer levels. Safety of the algorithm was demonstrated by the 3-month low incidence of events in untreated patients (0.87%), which nevertheless reached 1.49% (95% CI 0.51–4.27) in the highest risk group.[27]

Doubts concerning the safety of a single complete ultrasound in high-risk patients emerged in other studies and are also raised in the ASH 2018 guidelines for diagnosis of VTE[24] and in the recommendations of the Society of Radiologists in Ultrasound Consensus Conference.[28] The Consensus Conference took a net position, suggesting the use of the complete DUS as the safest strategy, with CUS at 2-cm intervals from the inguinal ligament to the ankle, spectral Doppler analysis in common femoral and popliteal veins, and color Doppler images. The expert panel emphasized the importance of examining calf veins regardless of the therapeutic strategy.

However, this choice could virtually lead to an increased diagnosis of IDDVT, exposing patients to the risk of overtreatment. In this regard, neither Consensus Conference nor ASH guidelines addressed the screening use of ultrasound in subgroups of asymptomatic high-risk trauma/intensive care patients. This growing practice, which varies among clinicians and hospitals, leads to a higher detection of IDDVT that is difficult to date and of questionable relevance.

A contribution to correctly differentiate between an acute and a chronic thrombosis could possibly be provided by a novel technique, ultrasound elastography, based on evaluation of tissue elasticity. Preliminary results with this technique are encouraging but need to be confirmed in prospective research.[29]

Therapeutic approaches

The therapeutic approach to IDDVT is a relevant challenge and varies among centers and clinicians.[30]

Few small randomized controlled trials (RCTs) and numerous observational studies, which differed by clinical setting and IDDVT definition (not all authors classified the trifurcation area as proximal, other authors enrolled only patients with clot diameter >5 mm), have analyzed the need for anticoagulation and have compared intensity and duration of different regimens, with discordant results. Since no strategy has been evaluated in the context of sufficiently powered RCTs, guideline recommendations are weak and not based on solid evidence.[31]

In the treatment of IDDVT, Pinede et al[32] randomized about 200 patients with IDDVT to receive low-molecular-weight heparin (LMWH) followed by oral anticoagulants for 12 weeks or for 6 weeks; the incidence of the thromboembolic events was 3.4% and 2%, respectively, in both groups. The authors concluded that a treatment of 6 weeks was adequate.

In another study,[33] the efficacy of a treatment with LMWH was evaluated in patients with isolated thrombosis of the muscular veins of the calf. Patients allocated in the treatment group received subcutaneous full-dose, weight-adjusted LMWH, whereas patients allocated in the control group received only graduated compression stockings and clinical surveillance.

Patients belonging to the first group showed no progression to the proximal deep venous system, whereas in the control group, 25% of patients showed an extension of IDDVT in the proximal veins.

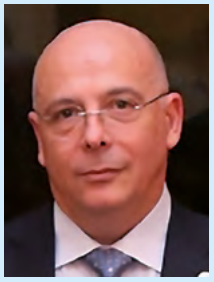
Many, but not all,[20,34,35] of the available observational studies have underlined the dangers of conservative management; others have reported an increased risk of major bleeding during anticoagulation. Conversely, in some research, the use of reduced therapeutic regimens resulted in a safe strategy, and authoritative experts have also suggested it when limited to carefully selected patients.[34,35] As commented by Sartori et al, both in the CALTHRO and in the CACTUS (anticoagulant therapy for symptomatic calf deep vein thrombosis) studies, a 3-month event rate of 8% and 11%, respectively, in untreated patients was not negligible. Instead, in their recent observational study, lower doses of LMWH seemed to be safe, with a low VTE event rate, except for cancer patients.[36,37]

In recent years, systematic reviews and meta-analyses have been published with the aim of finding stronger evidence from the literature. Many of these have showed that an anticoagulant treatment, even at reduced doses, was safer than a conservative management, whereas others underlined the lack of solid evidence clearly supporting one strategy instead of another.[38-40] The 2 most recent meta-analyses showed a significant advantage of anticoagulation versus no anticoagulation, suggesting that a treatment >6 weeks should be preferred over a shorter duration, as a longer course was associated with a lower rate of recurrent VTE and proximal extension. However, caution is suggested in interpreting these results, as only a few studies have been included in the analysis.[39,40]

According to the 2016 update of the ACCP guideline, it is probable that not all IDDVTs deserve an anticoagulant treatment; patients at high bleeding risk are more likely to benefit from ultrasound surveillance; serial imaging of calf veins for 2 weeks is suggested over anticoagulation (grade 2C) in patients without severe symptoms or risk factors for extension; otherwise, the treatment is suggested (grade 2C) "using the same anticoagulation as for PDVT" (grade 1B).[41]

Conclusion

Whether all IDDVTs require an anticoagulant treatment, and what the optimal intensity and duration may be, is currently a gray area and one of the most difficult challenges for clinicians. Whereas in the ACCP guidelines,[41] both 3 months of therapy and 2 weeks ultrasound surveillance are suggested, the International Consensus Statement on Prevention and Treatment of VTE affirmed that 3 months of oral anticoagulant therapy should be prescribed to all patients with symptomatic IDDVT.[42] As advised by expert opinion, once diagnosed, IDDVT should receive an anticoagulant treatment, for which dose and duration should be reasonably modulated based on the patient's overall risk profile.



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Progress in the management of venous disease during our five decades as surgeons

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Abstract

The authors' experience spans 5 decades of development in the management of venous disease. They describe their journey through the open surgery era; the transforming introduction of duplex ultrasound scanning; the establishment of consensus-driven classification, terminology, and investigatory planning, hugely important for research and patient care; and the emergence of minimally invasive endovascular procedures during the 21st century with greater acceptability by patients, minimal morbidity/mortality, and wider application than open surgery. The management of patients with venous disease has progressed immensely since the 1960s.

Keywords:

DVT, progress, reflux, treatment, varicose veins, venous disease, venous obstruction

Introduction

At the 12th annual meeting of the American Venous Forum in Phoenix, Arizona, year 2000, Professor Norman Browse gave the keynote lecture, in his provocative way questioning if anything was new in phlebology since the time of Hippocrates. His presentation was delivered right at the tipping point of the advancement of research and treatment of venous disease. Today in 2022, we can clearly state that much is new since ancient times. The authors' decades-long journey in venous disease management and their contributions are described here. It is the personal experience of two vascular surgeons with a life-long interest in the diagnosis and treatment of venous disease, who also for several years were fortunate and privileged to closely collaborate with two pioneers in venous disease, Bob Kistner (with Bo Eklöf) and Seshadri Raju (with Peter Neglén). This presentation should not be viewed as a well-referenced comprehensive review and does not lay claim to be an accurate or objective account of the evolution of modern phlebology. It is a subjective record of the events that affected us.

1960-1990: era of open surgery

In the 1960s and 1970s, early in our careers, the prevalent misconceptions of phlebology were that venous disease equated to varicose veins, that it involved the science of reflux alone, and the belief that surgery cannot be performed in

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the deep system. Only a few general and vascular surgeons were interested in venous disease worldwide, especially in the United States.

Contrarily, the Scandinavians performed basic research in its diagnosis and management at that time.[1] The percutaneous ultrasound was not available, and investigations were made by venography and invasive flow measurements. It was in that inherited tradition that our interest in venous disease was nurtured. At that time, invasive surgical treatment of varicose veins was predominant. The technique was refined over time. The radical operations with large incisions under general anesthesia and several days in hospital evolved to minimally invasive techniques (great saphenous vein [GSV] stripping with local avulsions) as an outpatient procedure performed under regional or local anesthesia. Present-day surgery is further advanced with ultrasound guidance and minute stab avulsions. Liquid sclerotherapy was used alone or in combination with high ligation of the GSV with variable results, but it was still inferior to the minimally invasive open surgery.[2]

Already in 1968, Bob Kistner described the first successful repair of a deep venous valve, an internal valvuloplasty, and the results in 17 patients were later presented in 1975.[3,4] He proceeded to perform transposition (1975) and external valvuloplasty (1991) as an alternative to treat deep venous reflux. Although the internal valvuloplasty was not initially recognized as a breakthrough, it was an extraordinary feat. Generally, it showed that surgery of the deep venous system did not invariably lead to thrombosis, as was the predominant belief, and, specifically, that it was possible to repair the delicate venous valve leaflets. It rekindled interest in deep venous disease, especially deep venous reflux, and the treatment of extensive deep venous thrombosis (DVT).

Several alternative approaches to direct valvuloplasty have since been described. Alternative external methods to control deep reflux were already introduced in 1972, so called "cuffing" by Hallberg. In the absence of valve leaflets, such as in postthrombotic disease, a transplantation of a valve-carrying axillary vein segment to the femoral or popliteal veins was described in 1982 by Taheri. Angioscopy-assisted valvuloplasty was used in 1991. As late as 2007, Maleti developed a unique "neovalve" reconstruction by skillful dissection of the vein wall to build at least 1 valve leaflet. Valvuloplasty in patients with primary vein reflux has been shown to have a sustained cumulative clinical improvement and valve competence long term (around 75%), whereas competency in postthrombotic patients steadily deteriorates over the years to a low rate of 25% after 8 years. Under the best circumstances, these patients can be offered an ulcer-recurrence–free interval of 60% for 6 years.[5,6] The valve repair in the most common postthrombotic group is nowadays therefore considered a "last ditch" attempt in patients with severe chronic venous insufficiency (CVI). Open deep repair was never popularized; Drs Kistner, Raju, and Sotturai were most active in the United States, and Dr Perrin had the largest experience in Europe.[7] The necessary skill set, the careful selection of patients, and the variable long-term durability have today limited its use to a few interested venous surgeons. However, there is no doubt that relief of an axial deep reflux leads to dramatic clinical improvement with 95% of primary healing of venous ulcers. One-third of patients have complete relief of symptoms with no compressive stockings for more than 10 years.[5]

In Europe and Scandinavia, a few enthusiastic surgeons started early to explore flow-directed or systemic deep thrombolysis with streptokinase to treat acute DVT. It never caught on because the complications frequently were severe. Open femoro-ilio-caval thrombectomy was popularized in some centers in Europe. During the 1970s and 1980s, the technique was advanced using contrast-dye–filled venous Fogarty balloons, more efficient distal clearance, temporary arteriovenous fistulae, percutaneous closure of the arteriovenous fistulae, and percutaneous balloon dilation of any residual stenosis.[8] We also started to better understand the hematological contributing factors to acute DVT as multiple types of thrombophilia were discovered. Our collected experience for 3 decades working in Sweden, Kuwait, and Hawaii includes over 200 treated patients. The long-term outcome has been favorable in pooled large series (465 patients) with a 73% patency rate, femoro-popliteal patency/competence in 44%, and symptom-free lower limb in 63% of operated patients. Despite positive results, no properly powered randomized study has ever been performed.

The basic experiences gathered from this "open surgery era" thrombectomy were important for facilitating the later introduction of percutaneous removal of thrombus. Although clinical and physiological improvements were shown with open thrombectomy, the Achilles' heel was the inability to treat the frequently revealed underlying venous stenosis and to achieve a satisfying clearance of the femoral-popliteal segment. It was not until percutaneous catheter-directed urokinase infusion and venous stenting were introduced in the 1990s[9,10] that the treatment paradigm of iliofemoral DVT shifted and early thrombus removal was popularized.

Chronic venous obstruction was, during the "open surgery era," treated like arterial obstruction with bypass surgery. The Palma procedure (suprapubic transposition of the GSV;

a "cross-over by-pass") was already introduced in 1960.[11] When a suitable GSV was unavailable, a 10-12-mm ringed polytetrafluoroethylene (PTFE) graft was later used, but with a much inferior patency rate. Using artificial grafts for venous bypass surgery was frowned upon in the 1980s due to the high failure rate. Short and long iliac, ilio-caval, and femoro-ilio-caval occlusions were, however, treated by in-line ringed PTFE grafts. Open surgical venous reconstructions were and are still challenging and demand life-long anticoagulation, and patency is affected by the type of conduit, graft material, low venous pressure, and the presence of thrombophilia. Open venous bypass surgery was only considered in select patients, those fit for surgery and with severely symptomatic, preferably short chronic venous obstruction. With correct selection of patients, Palma vein and iliofemoral/ilio-caval PTFE bypasses have been shown to have excellent cumulative secondary patency rates (70%-83% patency at 3-6 years and 85% at 10 years; respectively) with good symptomatic relief.[12,13] With later introduction of percutaneous venous stenting this treatment paradigm changed.

1990: era of diagnosis and classification

The authors worked together from 1971 to 1990. In the early 1990s, we were privileged to start working with pioneers in venous surgery both in research and practical management. Bo Eklöf joined Bob Kistner in Hawaii in 1991, and Peter Neglén moved to Mississippi to share practice with Seshadri Raju in 1997 after a stint as Visiting Professor at the University of Mississippi in 1990-1991 (*Figure 1*).

Figure 1. The 3 venous musketeers and D'Artagnan (from left to right, Bob Kistner, Peter Neglén, Seshadri Raju, and Bo Eklöf).

Photo provided courtesy of Peter Neglén.

During the late 1980s, real-time and duplex ultrasound scanning (DUS) arrived. It revolutionized venous investigations as it opened the venous system for noninvasive studies in acute and chronic disease. It was now possible to separate venous segments in the deep and superficial systems. The definition of valve function was changed as the duration of retrograde flow could be quantified (1989).[14] Multi-segment reflux scores were shown to correlate to clinical severity. Morphological segmental venous obstruction could be visualized confidently. Several studies showed in 1992-1993 that DUS was superior to ascending and descending venography as a diagnostic tool and replaced it as the main morphological investigation. Thus, the availability of DUS changed the whole paradigm of diagnosis. The ongoing controversy whether venous ulcer would only develop in the presence of deep venous reflux was quickly laid to rest. It was shown that superficial reflux alone can result in ulcer formation. The dispute whether descending venography was to be performed in supine or semi-erect position was buried. DUS quickly made the continuous wave Doppler (CWD) obsolete in most countries, and venography became largely a preoperative investigation. Air plethysmography was first presented in 1987.[15] It was rapidly accepted as a good research and teaching tool on global venous hemodynamics. It was possible to differentiate between reflux (venous filling index was validated to reflect global reflux) and calf muscle pump function (ejection fraction). Initially, it was thought that residual volume fraction correlated linearly to ambulatory venous pressure, but several reports subsequently showed this not to be true.

An advanced vascular laboratory using noninvasive investigations including DUS and invasive pressure measurements was established in Mississippi in the early 1990s. It was the foundation for basic venous physiological research and assessment of results of surgery, resulting in numerous publications.[16] The factors involved in the development of CVI proved to be multiple, involving parallel systems with reflux and/or obstruction and microvascular events (*Figure 2*).

Despite comprehensive investigations, the results of preoperative investigation did not always correctly reflect the severity of disease in individual patients, and clinical improvement was not necessarily resulting in physiological improvement post intervention. Although correlations were found in groups of patients, the tests were unable to place a patient in a specific class. This was very disappointing. The challenge was and still is to be able to identify and quantify the presence of

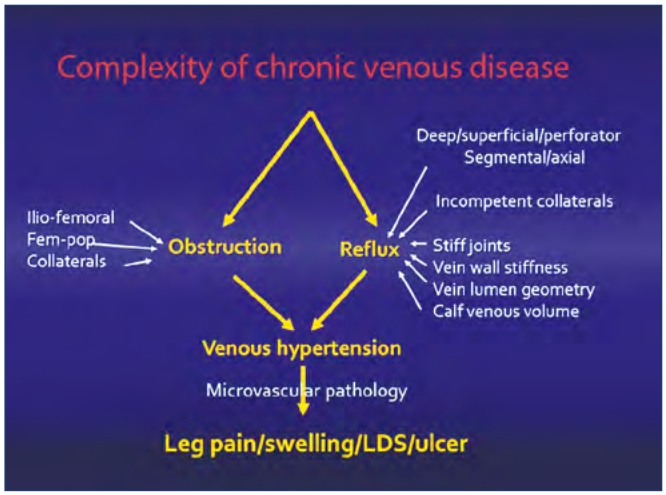

Figure 2. The complexity of the pathology of chronic venous disease is schematically outlined. Axial or segmental reflux may occur in 3 parallel axial systems: the profunda, femoro-popliteal, and saphenous systems. The contribution of obstruction depends on which segment(s) is involved in the popliteo-femoro-ilio-caval outflow. The calf muscle pump may compensate for reflux or malfunction, increasing the venous pressure. The microvascular pathology induced by hypertension finally results in venous signs and symptoms.

Abbreviations: Fem-pop, femoro-popliteal; LDS, lipodermatosclerosis.

reflux and obstruction in each vein segment and to assess the contribution of each individual or groups of segments to the global hemodynamics. If so, we would be able to direct the treatment to the dominant contributor in a complex multisystem disease. It would be immensely helpful because it has been clearly shown that the clinical condition is improved by partial correction of the pathology. The difficulty to assess physiological outcome led to the introduction and popularization of clinical severity scores and quality-of-life (QOL) assessments.

Several organizations with specific interest in venous disease were established. In 1989, the American Venous Forum was founded by 20 members of the Society for Vascular Surgery. The first president was John J. Bergan. Initially, its membership was select and academic, but later it has substantially widened. Now, 33 years later, it is the leading phlebological society in the world with 800 members and a strong influence on the management of venous and lymphatic disease through its publication, *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, and important consensus work. In the United States, the American College of Phlebology (now renamed American Vein & Lymphatic Society) had a profound impact, especially on the treatment of varicose veins and other superficial venous disorders. Although the European national phlebological societies had been active since the 1970s, the increased interest for phlebology resulted in the founding of the European Venous Forum in 2000. During the same period, the Asian Venous Forum, the Latin American Venous Forum, and the Australian and New Zealand Society of Phlebology were established.

Importantly, all this interest and societal activity saw the beginning of consensus work on classification, terminology, and investigatory planning, which continues today. An accurate classification system in venous disease is fundamental to understanding the clinical disease processes and to facilitate communication. In 1994, the American Venous Forum convened a consensus committee that created the CEAP (Clinical, Etiology, Anatomy, Pathology) classification (revised in 2004 and 2020),[17] which provided a snapshot description of each individual patient. The classification made an appropriate comparison of patient cohorts possible, hugely important for venous research. "Basic" CEAP is also very useful to guide diagnosis and workup in daily practice. It is an instrument to make a correct diagnosis and to guide appropriate treatment. As CEAP was not intended to be used for linear follow-up, the American Venous Forum created the VCSS (Venous Clinical Severity Score) for this assessment. The difficulty to assess physiological outcomes led to the popularization of QOL assessments, both generic and venous disease–specific tools.

During the 1990s, open surgery for valve repair continued and was continuously refined as described above. A game changer would have been an off-the-shelf durable artificial valve that could be placed percutaneously. During the last decades, we have seen many artificial valves pass our eyes. Millions of dollars have been invested by companies to develop this "Holy Grail." Although several devices have had initial promising results in vitro or in animals, ultimately all of them have thrombosed or failed when placed in humans so far.

During the 1990s, the utilization of venous DUS increased exponentially. Multiple endovascular devices for percutaneous arterial interventions were developed. Simultaneously, interest in percutaneous procedures on the venous system emerged. When the first generation of radiofrequency and laser obliteration of saphenous veins was introduced in 1999-2000, interest in venous disease skyrocketed.

The 21st century: tipping point and era of endovenous interventions

The VEITH symposium continues to be the largest vascular meeting in the United States. In 2002, 7 papers were presented in a venous session on late Friday afternoon, when most

delegates vanished to enjoy the Big Apple. Eleven years later, in 2013, 175 papers on venous disease were given during 17 sessions over 3 days, sometimes with simultaneous sessions. What had happened? Was it progress?

We believe that several factors converged during the first decade of the new century. A major reason was that endovascular procedures largely started to replace open surgery (except for valve repair) (*Figure 3*). After the initial introduction of saphenous vein closure, improvements and novel methods were approved, which used various laser frequencies, steam, glue, foam sclerosants, etc. Numerous prospective randomized studies have been performed comparing treatment modalities. All methods were shown to be efficacious and resulted in a similar improvement in VCSS and QOL.[18] However, recanalization of the saphenous veins and repeated treatment were more frequent after foam sclerotherapy. The differences between modern open surgery and the endovenous procedures are insignificant in this aspect. No treatment modality can be recommended as superior to another. Modern open surgery is still the leading procedure in the world except for the United States and some European countries where endovenous procedures have taken over completely. This is probably due to the relatively high device costs or reimbursement issues.

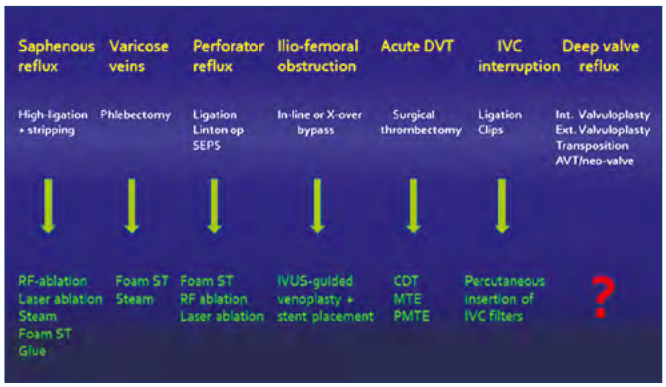

Figure 3. Open surgery is being replaced by minimally invasive endovenous procedures.

Abbreviations: AVT, axillary vein transposition; CDT, catheter-directed thrombolysis; DVT, deep venous thrombosis; IVC, inferior vena cava; IVUS, intravascular ultrasound; MTE, mechanical thrombectomy; PMTE, pharmacomechanical thrombectomy; RF, radiofrequency; SEPS, subfascial endoscopic perforator surgery; ST, sclerotherapy.

Percutaneous placement of inferior vena cava (IVC) filters increased, and after a peak of generous usage, now have a defined, more restricted, temporary application. In 1995, the first cases of early clot removal for acute iliofemoral DVT were reported using catheter-directed urokinase and later recombinant tissue plasminogen activator (rt-PA) infusion, largely replacing the open thrombectomy.[9] Mechanical devices with or without concomitant lysis were later developed. In the majority of cases, an underlying stenosis was revealed and treated in the same session with stent placement. The ultimate treatment would be to remove the blood clot, stent the causative stenosis, and have the patients return home within 24 hours. Much hope was tied to the ATTRACT study (Acute venous Thrombosis: Thrombus Removal with Adjunctive Catheter-directed Thrombolysis) in 2017, a randomized study of anticoagulation and various clot removal methods, to once and for all ensure efficacy of early iliofemoral clot removal and stenting.[19] Due to design and other issues, unfortunately, no dedicated conclusions could be made in this aspect.

Studies also emerged at that time showing that venous disease had a major impact on QOL and loss of work, although rarely being life or limb threatening. Long ignored, a large population had been underserved, and there was a present need of care. Campaigns by various organizations educated and made the population increasingly aware of the possible downsides of acute thromboembolism, postthrombotic disease, and varicose veins, and it wanted treatment. The novel minimally invasive procedures with low morbidity and rare mortality were certainly more readily accepted than the previous open surgery.

A major driver for the development was economy-based. As the procedures were attractively reimbursed (privately paid or by insurers), money could be made. With the evolution toward percutaneous therapy, not only surgeons but other specialties with catheter skills such as cardiologists and interventional radiologists were building venous therapy within their practices. Weekend-trained therapists with "hole-in-the wall" establishments jumped on the varicose vein treatment train. The medical device companies realized the emergence of a lucrative market in creating new technologies. Industry placed their commercial resources behind the surge, especially in the field of saphenous vein obliteration. Investors supported many start-ups with novel ideas.

Was the economy-based development unfavorable? A money-driven system will always be flawed by a potential widening of indications or an unnecessary use of a treatment modality, especially if the therapists poorly understand the disease and are not properly certified. This abuse was and still is observed (*Figure 4*). On the other hand, the high frequency of treatment stimulated novel studies on multiple aspects of venous disease. The science and research then drove additional innovation and progress. There is no doubt that the endovenous treatments

have substantially improved QOL for most patients, and without industry support, this would not have happened.

Figure 4. Professor Bo Eklöf lamenting the overuse of endovenous procedures in his signature way by singing a song (Blowing in the Wind) at an American Venous Forum gala:

How many stents must a doctor insert?

Before you call him a crook?

Wrong indication, the patient is hurt

The doctor should be on the hook!

How many veins should be burned or be cooked when reasons are overlooked?

The answer my friend is blowin' in the wind. The answer is blowin' in the wind.

Photo provided courtesy of Peter Neglén.

Little attention was given to chronic pelvic outflow obstruction until the mid-1990s because of the limitations of invasive open surgery. DUS was rarely carried out above the groin. With the comprehensive workup performed in Mississippi, Peter Neglén and Seshadri Raju became interested in the frequently observed stenoses or occlusions in the outflow tract of the limb in patients with CVI. The prevailing thought was that stenting in the venous system would invariably result in thrombosis due to low phasic flow and pressure. They started iliofemoral venous stenting in earnest in 1997 (*Figure 5*). The favorable outcomes of the first 92 stented patients were reported in 2000.[10,20] Already in 1999, clinical and investigatory follow-up started to be prospectively entered into a time-stamped standardized electronic medical records program, allowing ideal retrospective analysis. In 2007, the Mississippi experience reported cumulative analysis at 6 years of stent-related outcome and clinical and hemodynamic results in 982 patients stented for chronic obstructive lesions of the femoro-ilio-caval vein under intravascular ultrasound (IVUS) guidance.[21] It showed

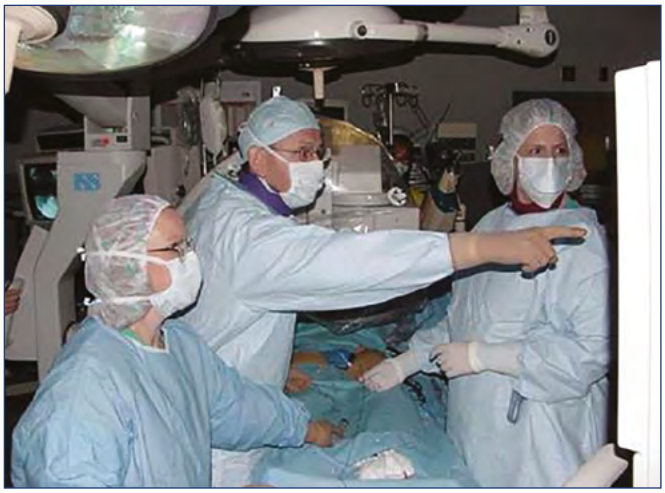

Figure 5. Early venous stenting in a dedicated interventional room in the operating theater of River Oaks Hospital, Mississippi, a rarity anywhere in 1997. Dr Neglén, seemingly excited, pointing at a venous outflow stenosis on the screen.

Photo provided courtesy of Peter Neglén.

that venous stenting could be performed with low morbidity and mortality, a long-term high patency rate, and a low rate of in-stent restenosis. It resulted in major symptom relief in patients with chronic venous disease. However, this was not consistently reflected in any substantial hemodynamic improvement by conventional measurements. The beneficial clinical outcome occurred regardless of presence of remaining reflux, adjunct saphenous procedures, or etiology of obstruction. These results have been reproduced by numerous single cohort studies since then.

Nowadays, a thorough assessment of the ilio-caval venous outflow tract is mandatory in the workup of a patient with CVI. IVUS-guided stenting of the chronic venous femoro-ilio-caval outflow has largely replaced open surgery and widened the strict indications for open surgery. Bypass surgery should nowadays not be performed unless a recanalization and stenting has been attempted or failed. In the 2010s, industry was convinced of the importance of venous stenting and the market opportunity. Several venous-dedicated stents have been developed and approved.

The unsatisfying aspect of diagnosis of obstruction is the lack of a validated hemodynamic test. The indication for placing a stent is a combination of symptoms and morphological measurement, arbitrarily shown to be more than 50% to 60% stenosis as detected by IVUS. As previously noted, it is not possible to detect the dominant pathology in a complex venous pathology. Therefore, our therapeutical approach is essentially blind. An initial treatment alternative is chosen

because of its simplicity, minimal invasiveness, low mortality/morbidity, and favorable clinical outcome in most patients. Therefore, venous stenting of the outflow of the limb and control of superficial reflux by minimally invasive methods are primary interventions in these patients. Compression therapy and local ulcer treatment is performed simultaneously (*Figure 6*). It is of paramount importance not to rely on these conservative measures alone, but to initially perform a proper investigation of the entire venous system of the lower limb and its outflow.

Figure 6. The champion of bandaging, Professor Hugo Partsch placing a compression bandage on the champion of deep valve repair, Dr Bob Kistner.

This illustrates the new mantra that the cornerstone for management of chronic venous disease is not compression therapy, but an accurate diagnosis and classification of the underlying venous problem to direct appropriate treatment, be it conservative and/or interventional.

Photo provided courtesy of Bo Eklöf.

To conclude, we can firmly state that the 21st century has seen a major emergence of successful treatment alternatives for venous disease. The DUS has been a pivotal tool for progress in understanding the venous circulation. Our main disappointment is that despite studies of the venous pathophysiology, we are still unable to build an adequate model of the venous circulation. In the future, we need to have a better understanding of venous physiology and develop accurate tests for obstruction and reflux to guide treatment. No doubt novel devices to treat venous disease minimally will be developed; perhaps the endovascular valve replacement will see daylight. New anticoagulants and agents targeting venous thrombus inflammation better preventing postthrombotic syndrome are on the horizon.

Our hope is that interest in venous disease will be less driven by monetary gain and more a requirement for proper education and certification of venous therapists. This would no doubt improve outcome and decrease any abuse. Teaching is provided by many societies and organizations such as the American Venous Forum with its fellows and attending courses and the European Venous Forum (EVF) with its EVF Hands-on Workshop (EVF HOW) and EVF HOW Plus courses (*Figure 7*). Certification is given by the American Vein & Lymphatic Society (AVLS) in the United States and a recently established European Board of Phlebology.

Figure 7. The authors (Peter Neglén left) visiting the operating theaters in Ankara during a meeting arranged by the Turkish Vascular Society in 2006.

Photo provided courtesy of Peter Neglén.

The future advances will probably be made in adequate venous centers where both of us were privileged to work, where various specialties such as vascular surgeons, hematologists, vascular medicine specialists, and interventional radiologists cooperate. Each type of physician will bring their unique expertise to the table to ensure the best coordinated care and outcome possible.

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