Phlebolymphology

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.

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Editorial

Dear Readers,

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

There is significant variation in the treatment of combined truncal-vein reflux and symptomatic varicosities. **Nicholas OSBORNE** *and colleagues* **(USA)** *present the results of their study based on the Vascular Quality Initiative (VQI) / Varicose Vein Registry (VVR) in which they explored the contemporary real-world experience of combined ablation and phlebectomy versus ablation alone.*

Three-dimensional (3D) modeling of the venous system is often a great support to evaluate the patients with chronic venous disorders in the case of complex anatomy or recurrent varices after surgery (REVAS). **Jean-Francois UHL (France)** *explains how to build and print 3D models of the veins.*

Prasesh DHAKAL *and* **Robin Man KARMACHARYA** *and colleagues* **(Nepal)** *discuss the influence of age, gender, duration of illness and symptoms on pigmentation/ulceration in varicose veins of the great saphenous system based on their retrospective observational study results.*

Deep-vein thrombosis (DVT) along with superficial-vein thrombosis and pulmonary embolism constitute the group termed venous thromboembolism, which remains a significant medical and social problem. **Kirill LOBASTOV** *and colleagues* **(Russia)** *report the results of a pilot clinical study that aimed to assess the efficacy of the long-term use of micronized purified flavonoid fraction in adjunction to rivaroxaban for the treatment of popliteal-femoral DVT.*

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

Combination therapy in the treatment of varices

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Abstract

Background: There is significant variation in the treatment of combined truncal-vein reflux and symptomatic varicosities. We sought to use the Vascular Quality Initiative (VQI) Varicose Vein Registry (VVR) to explore the contemporary real-world experience of combined ablation and phlebectomy versus ablation alone. **Methods**: Using the VQI/VVR database, patients undergoing combined ablation and phlebectomy and ablation alone were identified between January 2015 and December 2018. Using propensity-score matching on age; gender; race; history of deep venous thrombosis (DVT); previous venous surgery; anticoagulation therapy; pre-op clinical, etiology, anatomy and pathophysiology (CEAP) classification; truncal-vein location; and surgical setting, patients undergoing combined treatment were matched with those undergoing truncal ablation alone. Univariate descriptive statistics of demographic and procedural data were performed before and after matching. Change in venous clinical severity score (VCSS), patient-reported outcomes (PROs), and complications were compared between groups after matching using logistic regression, and average treatment effects were reported. **Results:** 10 952 patients were identified on initial query of VQI/VVR, including 5979 patients who underwent combined ablation and phlebectomy and 4973 patients who underwent ablation alone. After matching, the cohort included 3348 combined-treatment patients and 3309 ablation-only patients. There were minimal differences in demographics or preoperative characteristics after matching. After matching, there were significantly greater improvements in both the VCSS (1.6 points greater improvement) and PROs for those receiving combined ablation and phlebectomy than with ablation alone. Systemic complications were rare. After matching, there were statistically higher rates of hematoma (0.9%) and paresthesias (2.1%) for combined treatment than with ablation alone. There was no statistically significant difference in the rates of DVT, bleeding, blistering, pigmentation, phlebitis, ulcer formation, wound infection, or endovenous heat-induced thrombosis (EHIT). **Conclusions:** Patients frequently undergo combined treatment of truncal reflux and varicosities. Combined treatment is associated with a significantly higher improvement in VCSS and PROs than ablation alone, even after matching for preoperative disease severity and risk factors. Combined procedures are associated with a slightly higher risk of post-op hematoma and paresthesias. These results suggest that combined treatment of reflux and varicosities may result in higher treatment satisfaction with minimal increased risk to patients than ablation alone.

Introduction

Varicose veins are a common manifestation of chronic venous insufficiency, affecting about 25% of adults in the Western hemisphere.[1,2] Superficial venous disease can present symptomatically as pain, itching, and irritation over the veins themselves, and be associated with heaviness, swelling, and achiness, leading to a diminished quality of life.[1] Conservative management, including exercise and the use of compression stockings, may provide symptomatic relief. However, definitive treatment involves not only the treatment of symptomatic varicose veins, but also the treatment of the underlying axial reflux. The treatment of combined axial reflux and symptomatic varicose veins can be approached with either a staged or combined approach (ablation and phlebectomy).

There is significant variation across venous practitioners' approach to patients with symptomatic varicose veins and axial reflux. Previous evidence has been limited to small clinical trials and case series with conflicting results. The four prospectively collected randomized clinical trials that have compared staged and combined ablation/phlebectomy enrolled less than 500 patients in total in all trials combined, often in single centers.[3-6] These trials all demonstrated significantly improved quality of life among patients undergoing combined treatment, and three demonstrated a significantly improved venous clinical severity score (VCSS).[3-5] Other data from nonrandomized studies, however, have suggested that patients treated with ablation may not necessarily go on to require phlebectomy.[7-9] Given the lack of clear evidence, guidelines have not definitively endorsed either strategy of combined or staged treatments. Recently, the Society for Vascular Surgery and American Venous Forum published Appropriate Use Criteria for venous disease and concluded that "Providing care for the diseased tributaries of an ablated saphenous vein either concomitantly or as a staged procedure is appropriate."[10]

Within this context, we sought to use the Vascular Quality Initiative (VQI) Varicose Vein Registry (VVR) to explore the contemporary real-world experience of combined ablation and phlebectomy versus ablation alone. We hypothesized that patients undergoing combined ablation and phlebectomy would have significantly greater improvements in VCSS and patient-reported outcomes (PROs) in the short term with minimal differences in complications compared with ablation alone.

Methods

Human subject protection

The Institutional Review Board for the Human Research Protection Program at the University of Michigan approved this retrospective study (HUM0114502) as exempt, and informed consent was waived.

Vascular Quality Initiative (VQI) Varicose Vein Registry (VVR)

The VQI VVR is a prospectively collected registry of patients treated surgically for superficial venous disease. Within this registry, trained staff at each center collect patient demographic, diagnostic, preoperative, intraoperative, and postoperative data prospectively.[11-14] This is a voluntary registry, and center participation is not required. To maintain consistent data integrity, several approaches are taken. Training webinars are used to educate data managers. There are accessible online support staff to answer questions. Data abstraction and all definitions are uniform across the database. An audit of hospital claims is used to ensure consecutive procedures are being entered by participating centers. All online VQI data forms have been augmented with error tracking software to avoid erroneous entry. Additionally, statistical tests are used to identify any data entry errors and these errors are manually reviewed with centers to ensure data integrity and accuracy.

Study cohort

The VQI VVR from January 2015 through December 2018 was queried specifically, identifying all patients who underwent treatment for venous insufficiency. Inclusion criteria included patients with symptomatic venous disease (C2-C5) who underwent procedures to ablate truncal veins (including the great saphenous vein, anterior accessory great saphenous vein, superficial accessory great saphenous vein, small saphenous vein, and other truncal vein) using either radiofrequency ablation or laser. We excluded patients who underwent procedures from 2014 because they had been entered into the registry retrospectively. To investigate the effect of combined ablation and phlebectomy, we excluded patients who underwent sclerotherapy to decrease confounding and selection bias. Follow-up within the registry occurred at an early (0-3 months) and late (>3 months) time period. Complications were analyzed at early follow-up, whereas outcomes (including VCSS, CEAP, and PROs) were analyzed at late follow-up (typically 3-12 months).

Patient-reported outcomes (PROs)

The VQI VVR includes not only the CEAP and VCSS score before surgery and post operatively, but also a detailed vein-specific quality of life survey (PRO score). This PRO score is based upon the previously validated Varicose Vein Symptom Questionnaire (VVSimQ)[15-16] with an expansion of measures to include the impact on work. This PRO score measures venous quality of life, specifically symptoms of i) heaviness, ii) achiness, iii) swelling, iv) throbbing, v) itching, vi) appearance, and vii) impact on work/activity. PROs are rated on a scale of 0-4 or 5 depending upon the variable. For the variables heaviness, achiness, swelling, throbbing, and itching, the scale was: 0, none of the time; 1, a little of the time; 2, some of the time; 3, a good bit of the time; 4, most of the time; and 5, all of the time. For appearance, the scale was: 0, not at all noticeable; 1, slightly noticeable; 2, moderately noticeable; 3, very noticeable; and 4, extremely noticeable. For impact on work/activity, the scale was: 0, none; 1, symptoms but full work/activity; 2, mildly reduced work/activity; 3, moderately reduced work/activity; 4, severely reduced work/activity; and 5, unable to do work/activity. The total PRO score could reach as high as 34.

Complications

Procedure-related complications are reported on the VQI VVR at initial (early) follow-up and include bleeding requiring re-intervention, skin blistering, deep venous thrombosis (DVT), proximal thrombus extension (endovenous heat-induced thrombosis, EHIT), hematoma, paresthesia, pigmentation, superficial phlebitis, ulceration, and infections. Systemic complications are also reported in the VQI VVR at early follow-up, including allergic reaction, migraine, visual disturbance, cough/chest tightness, systemic infection, pulmonary embolism, transient ischemic attack, stroke, and death.

Statistical analysis

Univariate analysis was used to evaluate patient demographics and procedural data using the Student t-test for continuous variables, X^2 for categorical variables, and Mann-Whitney for nonparametric measures. To better control for the differences in presentation, a propensity-score–matching strategy was employed. A propensity score was generated using age, gender, race, prior venous procedure, history of DVT, anticoagulation, truncal vein location, CEAP classification, and setting. Propensity-score matching was performed using STATA 14 *TEFFECTS PSMATCH* with a nearest neighbor 1:1 matching without replacement and a caliper of 0.05. After matching patients, the cohorts were compared on the basis of the standardized differences before and after matching to assess the adequacy of matching. Matching resulted in minimal differences between study populations (as shown in *Table I*). Next, the matched study cohorts were compared via logistic regression, and differences in outcomes between study cohorts were estimated on the basis of the average treatment effects. Average treatment effects represent a statistical test that is employed to compare the estimate effect of treatment on outcomes. Statistical significance was set at a *P*-value <0.05. We performed all statistical analyses with Stata version 15.0 software (StataCorp LP, College Station, Texas).

Results

Patient characteristics

A total of 10 952 patients were identified on initial query of VQI/VVR, including 5979 patients who underwent combined ablation and phlebectomy and 4973 patients who underwent ablation alone. After matching, the cohort included 3348 combined-treatment patients and 3309 ablation-only patients. Patient demographics and clinical characteristics are shown in *Table I*. After matching, patients were well-matched for all variables, except for surgical setting. Combined-treatment patients were more likely to be treated in an office-based setting as opposed to an ambulatory surgical center or outpatient hospital setting. Before matching, there were significant differences in the C classification among patients undergoing combined ablation and phlebectomy versus ablation alone; however, after matching, these differences were significantly attenuated.

Preoperative disease severity was also assessed using the VCSS and PROs (*Table II*). Before matching, the VCSS score was significantly higher among patients undergoing ablation alone than with combined ablation and phlebectomy. In contrast, there was slightly higher severity of patient-reported symptoms (PROs) among patients undergoing combined ablation and phlebectomy than with phlebectomy alone. Importantly, after matching, these differences persisted.

PRO scores and VCSS

There were significantly greater improvements in both the VCSS and PROs with combined ablation and phlebectomy than with ablation alone (*Table III*). Before matching, the change in VCSS was a median of 5 among patients undergoing combined ablation and phlebectomy compared with 3.5 among patients undergoing ablation

Characteristics	Ablation Only (n=5979), N. (%)	Ablation and Phlebectomy (n=4973), N. (%)	P-value	Standardized Difference Before Matching	Standardized Difference After Matching
Age, mean years (SD)	57.1 (13.7)	54.1 (13.7)	<0.001	-0.254	0.019
Gender			0,006		
Men	1938 (32.4)	1490 (30.0)		REF	REF
Women	4047 (67.6)	3485 (70.1)		0.038	0.006
Race (white)	4331 (88.0)	4267 (93.9)	<0.001	-0.234	0.018
Length of follow-up, days, median (IQR)	2267 (51-802)	561 (99-942)	<0.001	0.444	0.029
BMI, mean (SD)	30.7 (7.4)	29.2 (6.7)	<0.001	-0.278	0.008
Primary Location of Ablation			<0.001		
GSV, Thigh and Calf	1763 (29.6)	1744 (35.3)		REF	REF
GSV, Thigh	2792 (46.9)	1906 (38.6)		-0.058	0.030
GSV, Calf	504 (8.5)	531 (10.8)		0.045	-0.029
SAGSV, Thigh	18 (0.3)	14 (0.3)		0.005	0.005
AAGSV, Thigh	234 (3.9)	306 (6.2)		0.113	0.001
AAGSV, Calf	28 (0.5)	6 (0.1)		-0.094	0.002
SSV, Thigh Extension	17 (0.3)	22 (0.4)		0.009	-0.017
SSV, Calf	514 (8.6)	377 (7.6)		-0.043	-0.010
Other Truncal Vein	85 (1.4)	31 (0.6)		-0.130	-0.014
Previous VV Treatment	1287 (21.5)	1108 (22.3)	0.307	0.007	0.050
History of DVT	410 (6.9)	287 (5.8)	0.021	0.021	0.025
Surgical Setting			<0.001		
Office-Based	3281 (54.9)	3689 (74.2)		REF	REF
Ambulatory Surgical Center	950 (15.9)	439 (8.8)		0.030	0.032
Hospital, Outpatient	1744 (29.2)	838 (16.9)		-0.472	-0.041
Hospital, Inpatient	4 (0.1)	7 (0.1)		0.024	
Receiving Anticoagulation	605 (10.1)	361 (7.3)	<0.001	-0.102	-0.009
Preoperative C Classification			<0.001		
2	1336 (23.7)	1956 (41.4)		REF	REF
3	2370 (42.1)	1592 (33.7)		-0.267	0.043
4	1362 (24.2)	934 (19.8)		-0.163	0.036

Characteristics	Ablation Only (n=5979), N. (%)	Ablation and Phlebectomy (n=4973), N. (%)	*P*-value	Standardized Difference Before Matching	Standardized Difference After Matching
5	166 (2.95)	113 (2.4)		-0.032	-0.007
6	396 (7.0)	131 (2.8)		-0.209	-0.039
Year of Surgery			<0.001		
2015	1223 (20.4)	761 (15.3)		REF	REF
2016	1954 (32.7)	1744 (35.1)		0.077	0.010
2017	1446 (24.2)	1447 (29.1)		0.136	-0.034
2018	1362 (22.8)	1023 (20.6)		-0.134	0.015

AAGSV, anterior accessory great saphenous vein; BMI, body mass index; DVT, deep venous thrombosis; GSV, great saphenous vein; IQR, interquartile range; SAGSV, superficial accessory great saphenous vein; SD, standard deviation; SSV, small saphenous vein; REF, reference; VV, varicose vein.

Table I. Patient and procedure characteristics before and after matching.

	Before Matching			After Matching		
	Ablation and Phlebectomy	Ablation Alone	P-value	Ablation and Phlebectomy	Ablation Alone	*P*-value
VCSS Patient-Reported Outcomes	7 (5.5,9)	8 (6,10)	<0.001	7 (6,9)	8 (6,10)	<0.001
Total Symptoms	14.5 (10,19)	14 (10,19)	0.02	14 (10,19)	14 (10,19)	0.005
Heaviness, median (IQR)	2 (1,3)	2, (1,3)	0.017	2 (1,3)	2 (1,3)	0.018
Achiness, median (IQR)	3 (2,4)	2.5, (2,4)	<0.001	3 (2,4)	2.5 (2,4)	<0.001
Swelling, median (IQR)	2 (1,3.5)	2 (1,4)	<0.001	2 (1,3)	2 (1,4)	<0.001
Throbbing, median (IQR)	2 (0.5,3)	2 (0,3)	<0.001	2 (1,3)	2 (0,3)	0.001
Itching, median (IQR)	1 (0,2)	1 (0,2)	0.003	1 (0,2)	1 (0,2)	0.061
Appearance, median (IQR)	3 (2,3)	3 (2,3.5)	<0.001	3 (2,3)	2 (1,3)	<0.001
Pain, median (IQR)	2 (1,2)	2 (1,2)	0.002	2 (1,2)	2 (1,2)	0.108
Impact on Work, median (IQR)	2 (1,3)	2 (1,3)	<0.001	2 (1,3)	2 (1,3)	<0.001

IQR, interquartile range; VCSS, venous clinical severity score.

Table II. Preoperative venous clinical severity score (VCSS) and patient-reported outcomes (PROs).

alone. Similarly, the total improvement in symptoms (PROs) was 12 among patients undergoing ablation as compared to 9 among patients undergoing ablation alone. The individual PROs are shown in *Table III*. After propensity-score matching, the differences between combined ablation and phlebectomy and ablation alone persisted for both VCSS improvement and improvement in PROs.

The average treatment effect of combined treatment was 1.6, meaning that combined ablation and phlebectomy results in a greater average improvement in VCSS of 1.6 points more than ablation alone. Similarly, among the total symptom score (PRO), the average improvement was 3.14 points after matching. This means that patients undergoing ablation and phlebectomy on average have a more

	Before Matching		After Matching	
	Combined Ablation and Phlebectomy	Ablation Alone	Average Treatment Effect of Combined vs Ablation Alone	P-value
Improvement in VCSS	5 (3.5,6.5)	3.5 (1,6)	1.60	<0.001
Change in Symptoms (Post-Pre)				
Total	12 (8,16)	9 (5,14)	3.14	<0.001
Heaviness, median (IQR)	2 (0,3)	2 (0,3)	0.44	<0.001
Achiness, median (IQR)	2 (1,3)	2 (1,3)	0.48	<0.001
Swelling, median (IQR)	2 (0.5,3)	1 (0,3)	0.33	<0.001
Throbbing, median (IQR)	2 (0,3)	1 (0,2)	0.39	<0.001
Itching, median (IQR)	0 (0,2)	0.5 (0,2)	0.2	<0.001
Appearance, median (IQR)	2 (1,3)	1 (0,2)	0.81	<0.001
Pain, median (IQR)	2 (1,2)	1 (0,2)	0.34	<0.001
Impact on Work, median (IQR)	2 (1,3)	1 (0,2)	0.48	<0.001

IQR, interquartile range; VCSS, venous clinical severity score.

Table III. Improvement in venous clinical severity score (VCSS) and patient-reported outcomes (PROs) after combined ablation and phlebectomy versus ablation alone.

than 3-point greater improvement in symptoms than with ablation alone. The individual improvements in the PROs are shown in *Table III*.

Complications

Complications after combined ablation and phlebectomy compared with ablation alone are shown in *Table IV*. Systemic complications in all groups were very rare. Within both the combined and ablation-only cohorts, the total incidence of systemic complications was 0.31% (34 patients) and no significant differences were detected (0.35% vs 0.26%; *P*=0.401). Of these complications, there was 1 systemic infection, 2 pulmonary embolisms (PEs), and no episodes of transient ischemic attack (TIA)/ stroke or death. Given the low frequency, no further comparisons were performed. Before matching, combined therapy compared with ablation-only treatment of venous insufficiency and varicose veins was associated with an increased incidence of hematoma (1.07% vs 0.22%; *P*<0.001), and paresthesias (3.05% vs 1.17%; *P*<0.001). Combined therapy was associated with a statistically significant decreased incidence of EHIT (1.24% vs 1.87%; *P*=0.038). Other factors, including bleeding, DVT, pigmentation, phlebitis, ulceration, and infection were not

statistically significantly different between the two groups (*Table IV*).

After propensity-score matching, the average treatment effect of combined ablation and phlebectomy was calculated for each outcome (*Table IV*). Comparing the effect of combined treatment with ablation alone, patients undergoing combined ablation and phlebectomy had a 0.9% increased rate of hematoma as compared with patients undergoing ablation alone (average treatment effect of 0.009). Similarly, after matching, the difference in paresthesias remained; the average treatment effect of combined ablation and phlebectomy was a 2.1% higher rate of paresthesias than in patients undergoing ablation alone. After propensity-score matching, there was no statistically significant difference in the rate of DVT, bleeding, blistering, pigmentation, phlebitis, ulcer formation, wound infection, or EHIT.

Discussion

There is a lack of consensus about the timing and approach to treating patients with axial reflux and symptomatic varicose veins. Our analysis, using the robust and large sample size of the VQI VVR, demonstrates that combined

	Before Matching		After Matching	
	Unadjusted Rates (n)		Average Treatment Effect of Combined vs Ablation Alone	P-value
	Combined Ablation and Phlebectomy	Ablation Alone		
Any Systemic Complication	0.26% (13)	0.35% (21)	0.001	0.806
Any Procedure-specific Complication	6.35% (316)	3.59% (215)	0.043	<0.001
Deep Venous Thrombosis	1.41% (49%)	0.83% (27)	0.005	0.416
Bleeding Requiring Intervention	0.06% (2)	0.06% (2)	0	0.786
Skin Blistering	0.63% (22)	0.25% (8)	0.002	0.388
Hematoma	1.07% (37)	0.22% (7)	0.009	<0.001
Paresthesia	3.05% (106)	1.17% (38)	0.021	0.007
Pigmentation	0.63% (22)	0.68% (22)	0.004	0.132
Superficial Phlebitis	0.81% (28)	1.29% (42)	-0.002	0.663
Induced Ulcer Requiring Intervention	0.14% (5)	0.03% (1)	0.002	0.059
Wound Infection	0.46% (16)	0.46% (15)	0.003	0.321
Proximal Thrombus Extension (EHIT)	1.24% (43)	1.87% (61)	-0.001	0.791

EHIT, endovenous heat-induced thrombus.

Table IV. Complications after ablation and phlebectomy versus ablation alone.

ablation and phlebectomy is associated with greater improvement in both VCSS and PROs, with low rates of complications. Importantly, although both combined-ablation-and-phlebectomy and ablation-alone patients experienced improvements in their symptoms (PROs), patients experienced greater improvements in all symptoms when undergoing a combined procedure as opposed to ablation alone. This analysis not only used the largest sample to compare these groups, but also employed propensity-score matching to minimize the confounding from measured covariates, including C classification (CEAP). This data supports the ongoing treatment of superficial venous disease with a combined approach.

Previous work has suggested the superiority of a combined approach. Hager et al,[17] in a recent review of the literature, identified the relative advantages of a combined approach, including a single anesthetic, fewer visits, and easier scheduling. There are several randomized controlled clinical trials that have been performed comparing combined and staged procedures for the treatment of venous disease. The AVULS trial (Ambulatory Varicosity Avulsion Later or

Synchronized) randomized 101 patients to either combined ablation and phlebectomy or delayed phlebectomy after ablation.[4] Importantly, this trial demonstrated no major differences in complications and significantly greater VCSS improvement and Aberdeen Varicose Vein Questionnaire score (AVVQ) improvement at early follow-up. Importantly, these differences in the PROs using the AVVQ were not significant in longer follow-up beyond 6 weeks (Lane et al[4] 2015). Similarly, El-Sheikha et al[5] randomized 50 patients to receive either combined ablation and phlebectomy or ablation and staged phlebectomy and followed outcomes for 5 years. Patients undergoing combined procedures had greater improvement in VCSS and AVVQ scores at 12 weeks. These differences converged by 1 year of follow-up and were no longer statistically significant.[5] Carradice et al,[3] in another small randomized controlled trial, compared combined endovenous laser therapy (EVLT) and phlebectomy with EVLT alone. This study also demonstrated a statistically significant improvement in VCSS and AVVQ at the early follow-up (3 months) that attenuated over time and was no longer significant by 1-year follow-up. The authors noted that two-thirds of the patients in the

EVLT-alone arm required staged phlebectomy in follow-up as compared with only one patient among the combined EVLT and phlebectomy group who required an additional procedure.[3] These small randomized clinical trials were limited by small sample size and the single-center design, limiting the generalizability of these trials. More recently, others have reported analyses of venous registries examining this question. In a recent analysis of the American Venous Forum Varicose Vein Module of the American Venous Registry, Conway and colleagues[18] compared combined ablation and phlebectomy with ablation alone. This analysis included a larger sample size of 526 patients over a 5-year period, of which more than 80% of patients had milder disease (C2). The authors reported that patients undergoing a combined procedure had a greater improvement in VCSS at both 1-month and 6-month follow-up.[18]

Our analysis adds to the body of literature supporting the use of combined ablation and phlebectomy as a safe and effective treatment strategy for symptomatic varicose veins. Importantly, when compared with ablation alone, we have demonstrated that patients undergoing combined procedures have a significantly greater improvement in both VCSS and PROs. We did not, however, directly compare patients undergoing combined ablation and phlebectomy with staged ablation and phlebectomy. Such an analysis is difficult in the current database construction of the VQI VVR. Additionally, several previous studies have raised the question of the necessity for phlebectomy after a successful ablation.[19] After ablation of the axial reflux, varicose veins have been shown to significantly improve with as much as 42% of varicosities resolving above the knee and 25% below the knee.[7] Importantly, our analysis was not designed to assess the long-term risk of reintervention for varicose veins in patients undergoing ablation alone.

Additionally, there are some important limitations inherent to the design of the study and database used. The VQI VVR is a voluntary registry that may not be representative of all practices and patient populations. The surgical approach, including ablation methods, and individual surgeon bias will influence the choice of procedure. Similarly, this study utilized a propensity-score analysis to adjust for measured confounders, but it cannot adjust for unmeasured confounder or bias. Additionally, the outcomes can be reported over a variable time frame of 3 to 12 months, and previous studies have shown that the effect of varicose vein treatment attenuates over time. Without a consistent time for measuring the PROs and VCSS, this may lead to an underestimation of the effect of both treatments. Nevertheless, this analysis supports our hypothesis that in patients with truncal superficial vein reflux and symptomatic varicose veins, combination ablation and phlebectomy results in improved provider-measured results and PROs, with minimal risk of complications.

Conclusion

The results of this study add to the body of evidence that combined ablation and phlebectomy is a safe and effective treatment strategy for patients suffering from axial reflux and symptomatic varicose veins. This real-world multicenter analysis demonstrates that combined treatment is associated with greater improvement in both VCSS and quality of life (PROs), while also experiencing remarkably low rates of complications. Additional work is necessary to compare the outcomes of combined ablation and phlebectomy with planned staged ablation and phlebectomy.

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Modeling and 3D printing of veins from CT venograms

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Keywords:

3D modeling; 3D printing; CT venography; digital anatomy; education; simulation; venous anatomy

Abstract

Digital anatomy has more and more applications in medicine and surgery, thanks to the progress in imaging and power of computer software. To evaluate patients with chronic venous disorders, in the case of complex anatomy or recurrent varices after surgery (REVAS), three-dimensional (3D) modeling of the venous system is often a great support. A global 3D depiction of the whole venous morphology will help the hemodynamical mapping achieved by color Duplex ultrasound. In addition to anatomical information, color Duplex ultrasound also provides essential hemodynamic data for the treatment of each particular patient. This paper explains how to build and print 3D models of the veins. Data are provided by computed tomographic (CT) venography. The 3D reconstruction is possible through use of three software freely available on the internet: Horos® (Mac computers only), Meshmixer®, and Cura®. The resulting 3D models are easily displayed and handled on a personal computer, tablet, or smartphone and could be shared within 3D-model communities on the web. In the field of anatomy and in surgical simulations, 3D modeling of the human body is revolutionary. The primary aim of the UNESCO Chair of Digital Anatomy (Paris University) is the dissemination and sharing of digital tools and models for educational anatomy (www.anatomieunesco.org).

Introduction

Venous anatomy is complex and highly variable. For this reason, before any decision or treatment, a complete check of venous morphology and hemodynamics should be done via mapping in all patients with chronic venous disorders (CVD).

Color Duplex ultrasound is an evaluation method that may be used daily and reliably for building a venous map of patients, always performed while the patient is in the standing position. But in some cases, more detailed information about the venous anatomy of the whole network is needed, in particular, for deep veins. Moreover, this in-depth investigation of the deep system could discover some abnormality[1] or anatomical variation that could be a cause of so-called "primary" CVD. In fact, we call it primary in most cases because we do not find any cause.

Materials and methods

Data are provided by CT venography

The technique of investigation and indications for computed tomographic (CT) venography are described with more detail in our previous publications.[2-5] Here, we provide a brief summary of the CT venography protocols (*Table I*) and the indications for CT venography for patients with CVD.

CT venography could be used for education and research, but in most cases, the aim is venous assessment of patients with CVD.

The result of CT venography is a set of axial slices in DICOM® format (Digital Imaging and Communications in Medicine standards). The DICOM is the international standard of medical imaging, universally used by radiologists and

Protocols	Acquisition	Reconstruction	Post processing	Contrast injection
16 detectors CT: 600 slices in 25 s	120 kV, 150 mAs, slice collimation: 16x1.5 mm field 512, FOV 380 mm	Slice width 2 mm, slice increment 1.5 mm, filter B30 matrix 512x512, zoom factor 1.7	1998-2012 VRT fast and automatic with tissue transparencies	Medrad MCT injector system Uniphasic injection 20 mL of iodine contrast medium in 180 mL of serum
64 detectors CT: 1000 slices in 20 s	120 kV, 150 mAs	Slice width 1 mm, slice increment 0.75 mm, matrix 512x512, zoom factor 1.7	VRT	Puncture of a vein of the dorsal foot or scarcely the varices of the thigh
128 detectors CT: 1000 slices in 10 s		Rotation time 300 ms using a continuous helical scan MinDose® technique pitch=0.16−0.22	VRT with PC using multiprocessors OsiriX using fast graphic card	Proximal injection and biphasic injection to visualize pelvic veins

CT, computed tomography; FOV, field of view; VRT, volume rendering technique; MDCT, multidetector computed tomography; MCT, multislice CT (MSCT)

Table I. Multislice spiral computed tomography (CT) protocols for CT venography.

practitioners for diagnostic purposes in radiology all over the world.[6] It contains both an image and a collection of data about the exam and the patient.

This file format could be visualized and manipulated by dedicated software called DICOM® browsers (*Table II*).

Indications[2] for CT venography are mainly patient assessment and anatomical studies useful for research and for learning of anatomy, as well as for use by surgeons to run a preoperative simulation or for planning (*Figure 1*).

Reference methodology for building and printing 3D models (*Figure 2 and Table III*)

3D models are reconstructed from DICOM slices produced by CT venography. Models are built in three steps, through use of the following available *free software*:

- Horos®[7] (only for Mac computers) is a DICOM® browser and provides a 3D reconstruction of the venous anatomy. It produces 3D vector models, also called 3D mesh, obtained by a segmentation process.
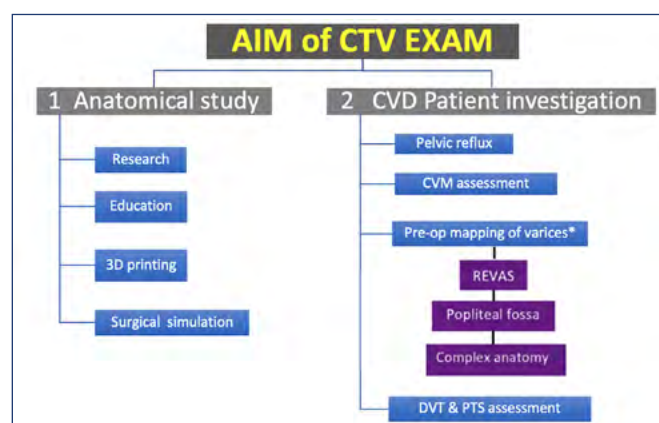

Figure 1. Indications of computed tomography (CT) venography.[2]

1) CT venography allows 3D interactive virtual dissection of the limb for education or simulation.

*2) CT venography provides pure morphological information; therefore, Doppler ultrasound is mandatory for hemodynamical assessment. *Particularly for recurrent varices after surgery (REVAS), complex cases, and popliteal fossa recurrence.*

Abbreviations: 3D, three-dimensional; CTV, computed tomographic venography; CVD, chronic venous disease; CVM, congenital venous malformations; DVT, deep-vein thrombosis; PTS, post-thrombotic syndrome.

Name	OS	Free	Website
Horos	Mac	YES	https://horosproject.org/
OsiriX	Mac		https://www.osirix-viewer.com
3DSLICER	Mac/PC		https://www.slicer.org
MicroDicom	PC	YES	http://www.microdicom.com/downloads.html
RadiAnt DICOM Viewer	PC		https://www.radiantviewer.com/
Philips DICOM Viewer	PC		https://philips-dicom-viewer-r3-0.software.informer.com/3.0/
Sante DICOM Viewer FREE	PC	YES	https://www.santesoft.com/win/sante-dicom-viewer-pro/download.html
ORS Visual Lite	PC		http://www.theobjects.com/orsvisual/index.html
Mango	Mac	NO	http://ric.uthscsa.edu/mango/mango.html
ORPALIS DICOM viewer	PC		https://www.orpalis.com/labs/dicom-viewer
Onis	PC	YES	http://www.onis-viewer.com/ProductInfo.aspx?id=19
MiViewer	PC		https://www.millensys.com/products/special/miviewer/index.html
Ginkgo CADx	PC		http://ginkgo-cadx.com/en/
MEDISP Lab DICOM Viewer	PC		http://www.bme.teiath.gr/medisp/downloadMEDISPDICOMViewer.htm
Weasis	PC	YES	https://sourceforge.net/projects/dcm4che/
YAKAMI DICOM	PC		https://www.kuhp.kyoto-u.ac.jp/~diag_rad/intro/tech/dicom_tools.html
DICOM Viewer 2.0	PC	YES	https://www.robomedical.com
Agnosco	PC	YES	http://www.e-dicom.com/

Table II. List of available DICOM (Digital Imaging and Communications in Medicine) viewer software.

	Software	Function	Input format	Action	Output format
1	Horos®	DICOM browser	DICOM	Extracting a 3D mesh gross segmentation	obj
2	Meshmixer®	Modeler	obj	Refinement of segmentation Cleaning – mesh repair	obj/mix
3	Cura®	3D print	obj	Parameters for 3D printing	gcode

Table III. The three steps to build 3D printable mesh models from angio–computed tomography.

- Meshmixer®[8] is then used to clean, simplify, and repair the huge 3D mesh file produced by Horos®.
- Cura®[9] is finally used to build a "gcode" file. This will tell the 3D printer how to slice and print the 3D anatomical model.

More detailed, step-by-step methodology
Horos®
Two types of 3D reconstruction could be created by Horos® from the DICOM digital data as follows: i) volume rendering (VRT); and ii) surface rendering, also called vectorial modeling. In both cases, the main process is the "segmentation" of the anatomical data:

"Segmentation" means to outline and draw the boundaries of each anatomical structure. Each anatomical element (bone, skin, muscle, fat tissue) is automatically identified by its level of density (4096 levels of Hounsfield units in DICOM® slices). This operation on the image is named thresholding, which consists of a selection of a sample of densities that eliminates others. By this technique, one can erase some specific anatomical structures or make them transparent.
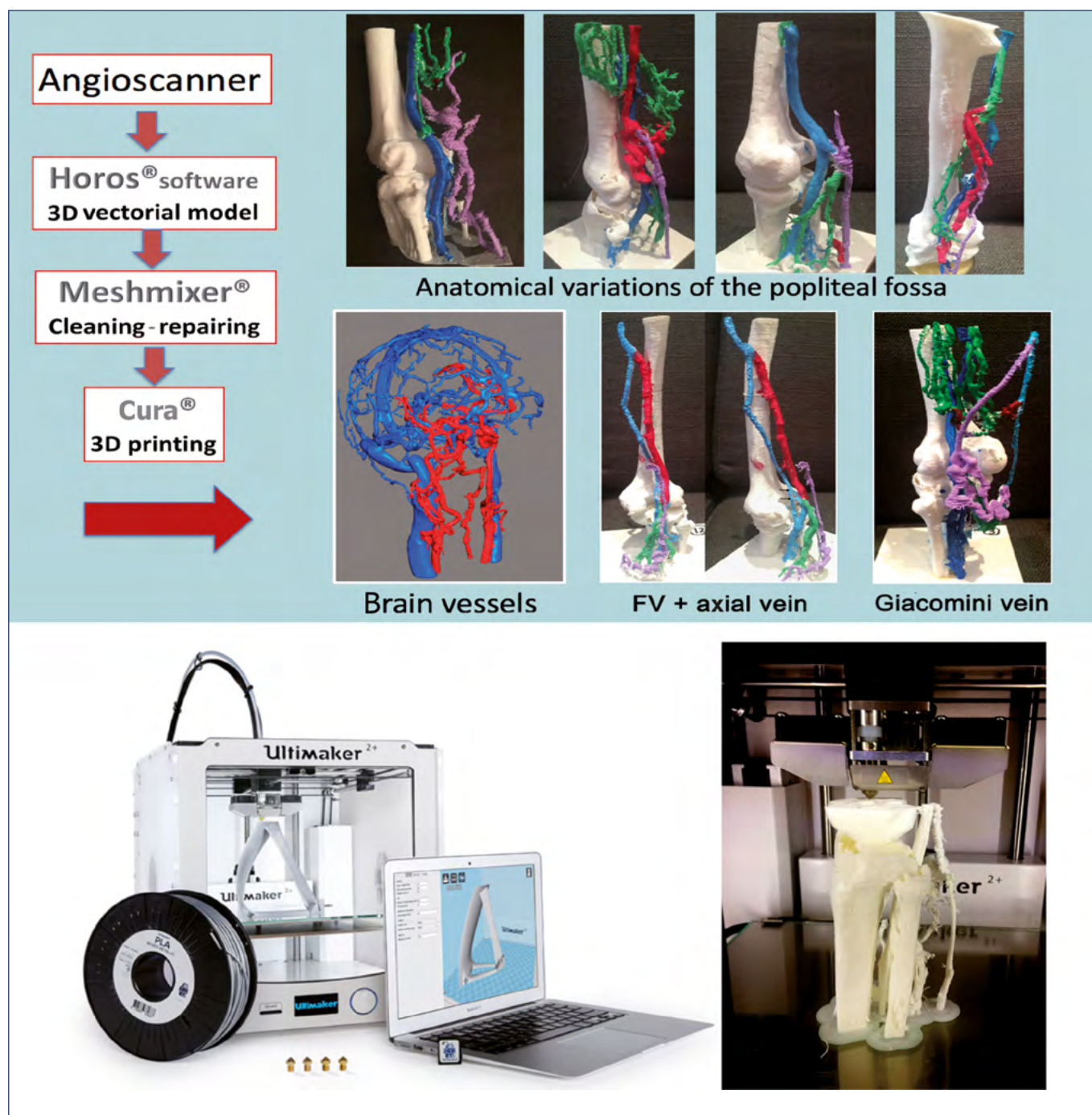
Figure 2. Methodology of 3D printing of educational models of venous anatomy. Workshop presented at Charing Cross 2019 and Krakow's 2019 International Union of Phlebology (UIP) Chapter meetings.

Abbreviation: FV, femoral vein.

Practical use of Horos®

After opening the list of the DICOM® exams, click to display the patient's file. This opens the 2D window showing the slices. Then choose a reconstruction protocol by clicking on the gray wheel located on the toolbar and selecting one of the seven 3D protocols listed in the menu (*Figure 3*). These seven are multiplanar reconstruction (MPR), curved MPR, orthogonal MPR, maximum intensity projection (MIP), volume rendering (VRT), surface rendering (SR), and virtual endoscopy.

The protocol for easy building of 3D vectorial models is 3D surface rendering. For this, we set up the parameters to obtain different segmentations of the tissues (*Figure 4*). In
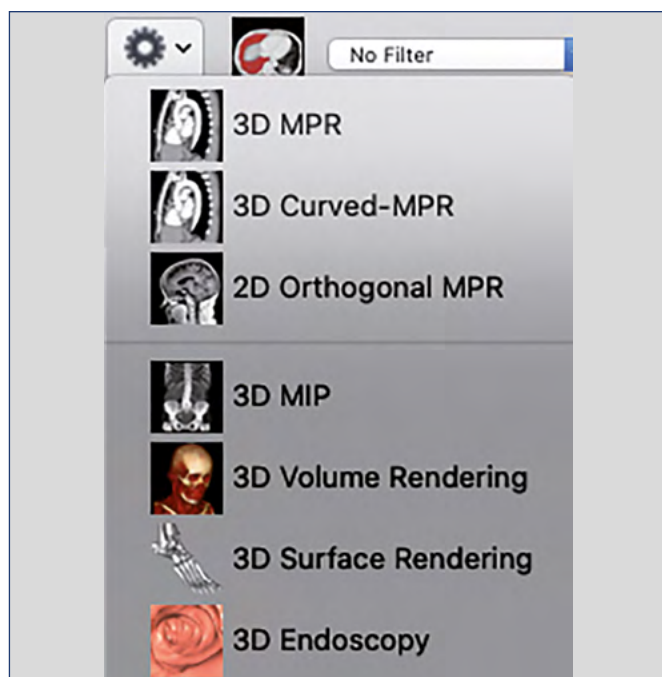
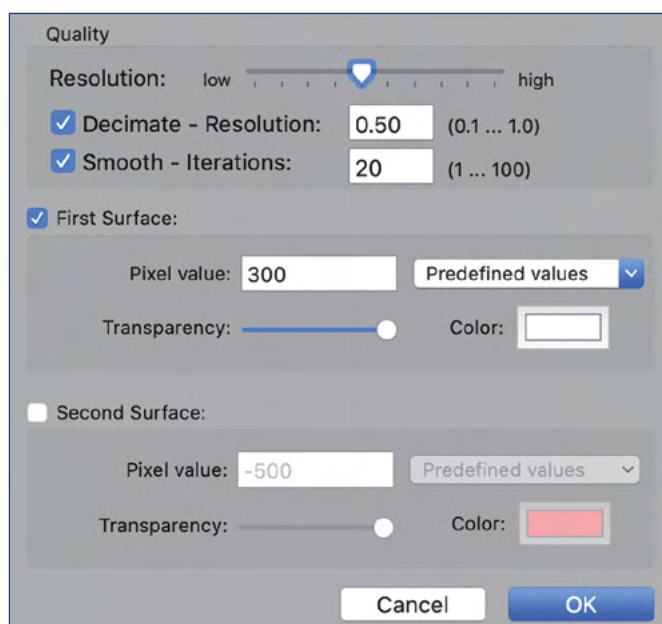Figure 3. Menu for choosing the 3D reconstruction protocol.

Figure 4. Setup of Horos® SR parameters to obtain different segmentations of the tissues.

most cases, the pixel value will be 100 and resolution, 90% to obtain a good segmentation of the bone and injected vessels. These parameters could be refined as necessary. The skin and lungs could also be segmented during the same process by choosing a second structure and choosing -300 as the pixel value of the second surface.

The huge 3D vectorial "mesh" model that is thus obtained has to be exported into "obj" or "STL" format. This could be done using the export menu (gray wheel on the toolbar).

Meshmixer®
We first open the obj file exported by Horos®. Manipulation of the mesh model is controlled through the right mouse button (3D move), through dragging the mouse wheel down (translation), and through wheel roll (zoom). The left mouse button is for selection of objects or menu options.

The aim of Meshmixer® is to clean the file by erasing the small isolated pieces, and to perform a further segmentation of its anatomical structures, mainly veins and bones. We use the following functions of Meshmixer® directly available through the following function keys: i) *E* extends the selection to all connected points; ii) *Y* separates the selection and creates a new layer; iii) *X* erases the selection; and iv) *I* inverts the selection. Several other functions are available, including color painting of the objects, sculpting the objects (inflate, smooth, flatten, etc) with brushes, and plane cutting to divide the mesh.

The main issue for segmentation is to separate the different structures by erasing their mesh connections. Further colorization of each anatomical element is possible to better visualize the 3D morphology and display animations.

The other main interest of Meshmixer® is to repair the 3D mesh and arrange it to be printable. The menu option "analysis" shows and repairs the holes, missing parts, or defects that could be removed for a better result of the 3D printed object.

The 3D file is then exported in obj format to be printed with Cura®.

Cura®
The aim of Cura® software is to divide the 3D anatomical mesh and compute it into thin slices to be added by the printer's head one by one onto the horizontal plate.

A number of parameters have to be set up according to the printer model, time, resolution, and quality of the printed model obtained.

We regularly organize courses and workshops with our partners to promote these new educational tools through the UNESCO Chair of Digital Anatomy[5] (Paris University). The goal is to learn more about the practical

use of these software in order to produce 3D anatomical models. Please visit our website for more information: www.anatomieunesco.org.

An educational video is also available on our YouTube TV channel at https://youtu.be/JmJ3yLcTUS0.

Results

Educational use of 3D modeling

- CT venography is both a great educational tool for learning venous anatomy and a powerful research tool for improving our understanding of the venous system.
- Through Horos® 3D animations, rotational models can be built and "journeys" taken inside the body.
- 3D modeling allows virtual dissection of the limb; it is a powerful teaching and learning tool for students of human anatomy in order to prepare for, not replace, cadaver dissection (see table of virtual dissection in reference 10; see *Figure 5*).
- 3D printing of anatomical models is a great tool to study anatomical variations, which are common in the venous network.
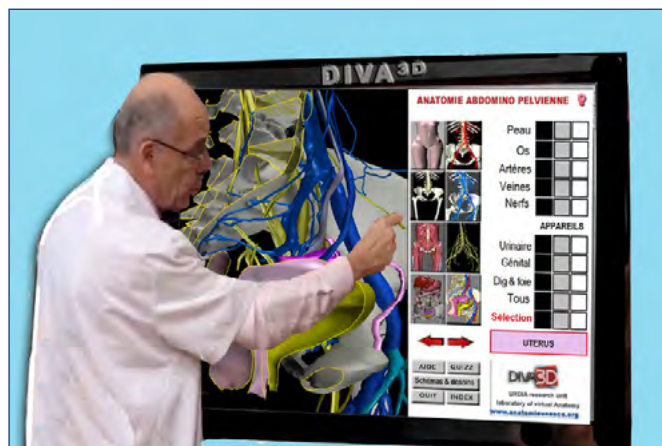

Figure 6. Colored vectorial 3D model (Meshmixer®) showing an aneurism of the saphenopopliteal junction (SPJ).

1, popliteal vein (PV) in dark blue; 2, lateral root of the PV; 3, medial root of the PV; 4, anterior tibial veins; 5, lateral gastrocnemial veins (in blue); 6, medial gastrocnemial veins (in green); 7, small saphenous vein (SSV) in purple; 8, aneurism of the SPJ; 9, thigh extension of the SSV (in red); 10, great saphenous vein (GSV; light blue); 11, oblique communicating vein.

Figure 5. Virtual dissection table[10] (Diva3D). The life-size anatomical model could be manipulated on a big touchscreen with only three fingers.

Examples of variations of the small saphenous vein (SSV) termination and the femoral vein variations are shown in *Figures 6 to 12*.

Web communities for sharing 3D anatomical models

For sharing 3D anatomical models, several websites are available. Some of them are totally free, and you can even download several printable 3D models. These sites include i) www.embodi3d.com (biomedical 3D printing), with
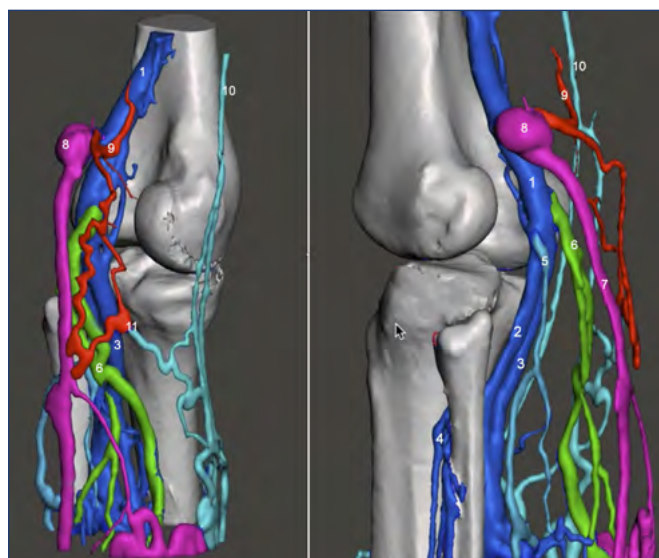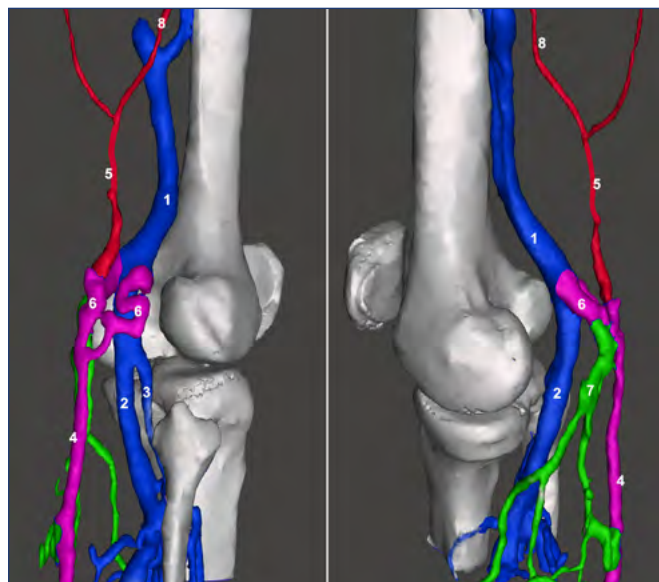

Figure 7. Colored vectorial 3D model (Meshmixer®) showing a duplicated termination of the small saphenous vein (SSV). 1, popliteal vein (PV) in dark blue; 2, medial root of the PV; 3, lateral root of the PV; 4, SSV (in pink); 5, thigh extension of the SSV (in red); 6, ring-shaped termination of the SSV; 7, medial gastrocnemial veins (in green); 8, thigh perforator.
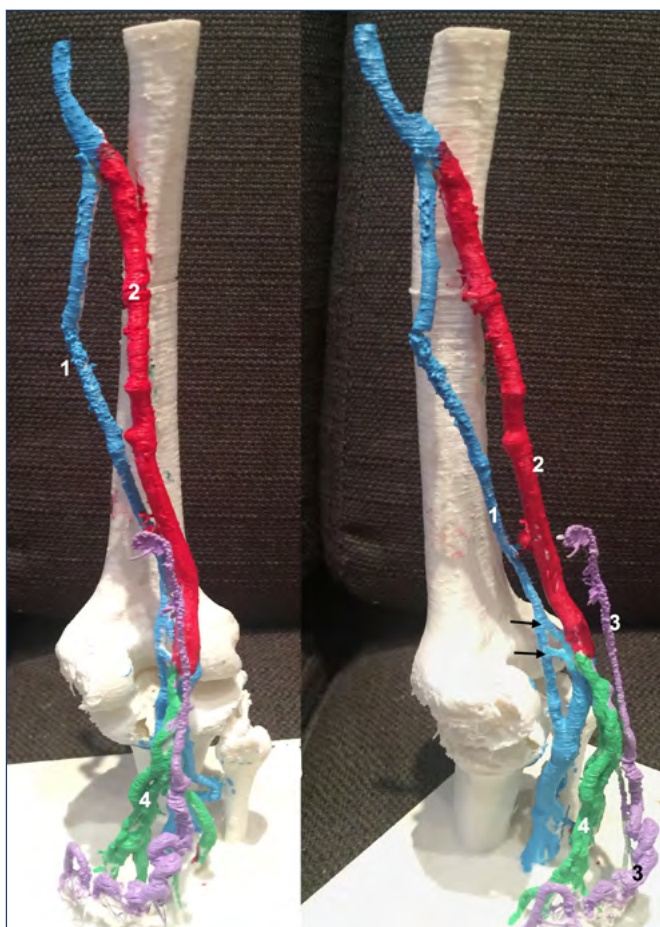
Figure 8. 3D printed model of a femoral vein duplication.

1, femoral vein in the Hunter canal (in blue); 2, axial vein along the sciatic nerve (in red); 3, small saphenous vein (SSV; in purple) dystrophic and dilated; 4, medial gastrocnemial veins (in green).
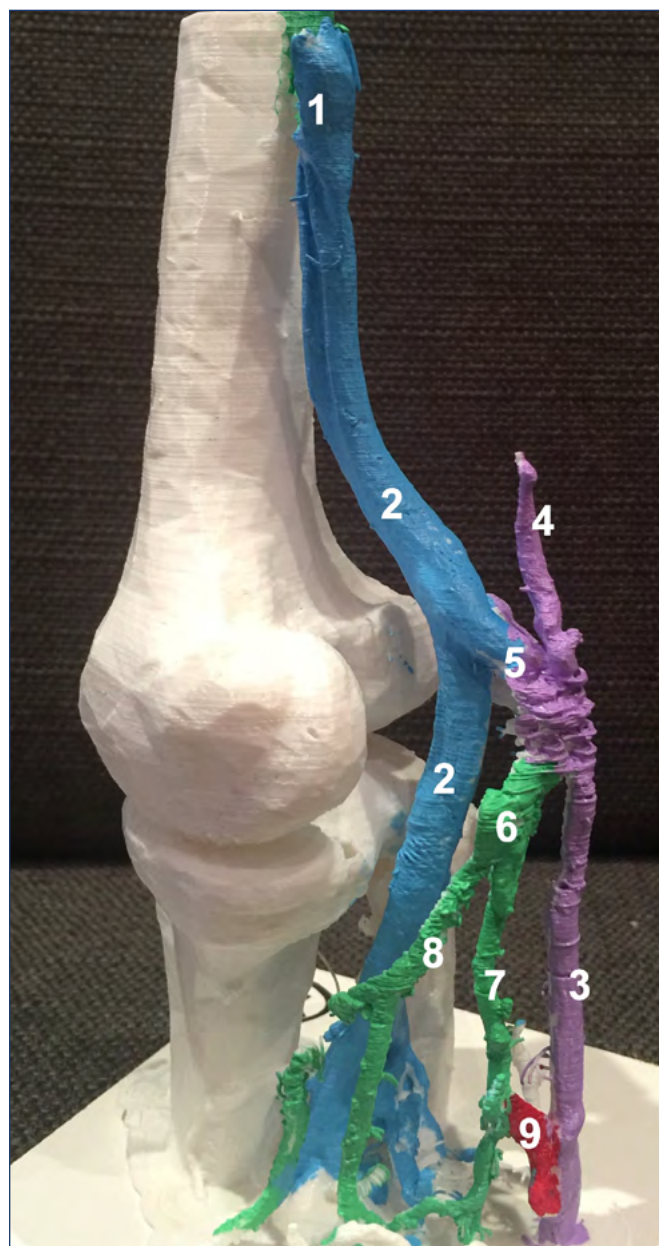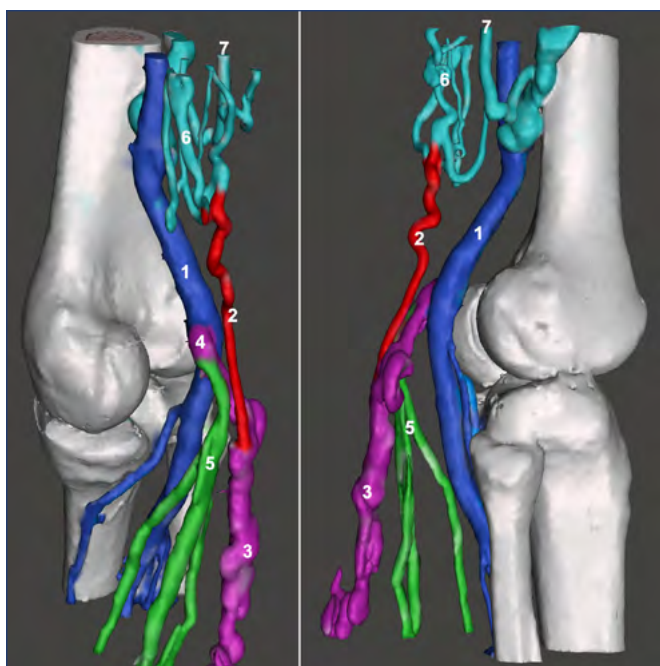

Figure 10. 3D printed model of a common trunk between the small saphenous vein (SSV) and the medial gastrocnemial vein (GV).

1, femoral vein (in blue); 2, popliteal vein (in blue); 3, SSV (in purple); 4, thigh extension of SSV (in purple); 5, common trunk SSV-GV; 6, trunk of medial GV (in green); 7, dorsolateral component of the medial GV; 8, ventromedial component of the MGV; 9, perforating vein of the calf (in red).

Figure 9. Colored vectorial 3D model (Meshmixer®) showing a common trunk between the small saphenous vein (SSV) and the medial gastrocnemial vein (GV) and a thigh extension of the SSV.

1, popliteal vein (PV) in dark blue; 2, thigh extension of SSV (in red); 3, small saphenous vein (SSV) in purple; 4, common trunk of the SSV with the medial GV (in purple); 5, medial GV veins (in green); 6, deep femoral vein; 7, venous arcades of the semimembranosus muscle.
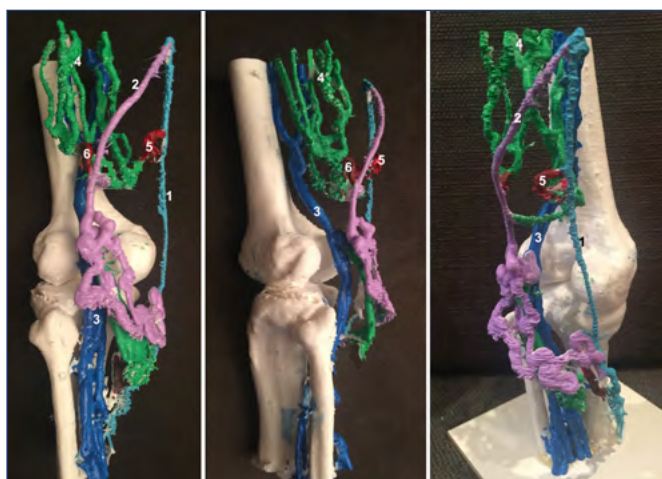
Figure 11. 3D printed model of a Giacomini vein.

From left to right posterior, lateral, and medial views.

1, great saphenous vein (GSV; in light blue); 2, Giacomini vein (in purple); 3, popliteal vein (in dark blue); 4, venous arcades of the semimembranous muscle (in green); 5, Hunterian perforator vein with GSV (in red); 6, thigh perforator with the Giacomini vein.

the possibility to automatically convert CT scans into 3D printable models for free with democratiz3D®; and ii) NIH 3Dmodels.com, which has a large collection of 3D models of vascular cardiac pathology.

Other web solutions propose to host your models; for example, Sketchfab® (www.sketchfab.com).[11] With such solutions, you subscribe to buy or sell your own collection of 3D models. You can include labels of the structures (*Figure 13*) and display the model in virtual reality (VR) mode (*Figure 14*).

Another interesting possibility is to display your own models on your tablet or smartphone (*Figure 15*). This is possible with the free software named *3D PDF reader*, available on the App Store or Google Play. The only limitation is the size of your 3D model (may not exceed 15 000 faces).

Using these different tools, educational anatomy is now entering a new era in which these 3D models are available for everyone willing to teach or learn human anatomy. They could also be used together with an e-learning platform like we do on the website of the UNESCO Chair of Digital Anatomy (www.anatomieunesco.org).

Surgical applications

The main example is the Visible Patient® software created by IRCAD (Research Institute Against Digestive Cancer) (*Figure 16*).[12] This makes possible the surgical use of
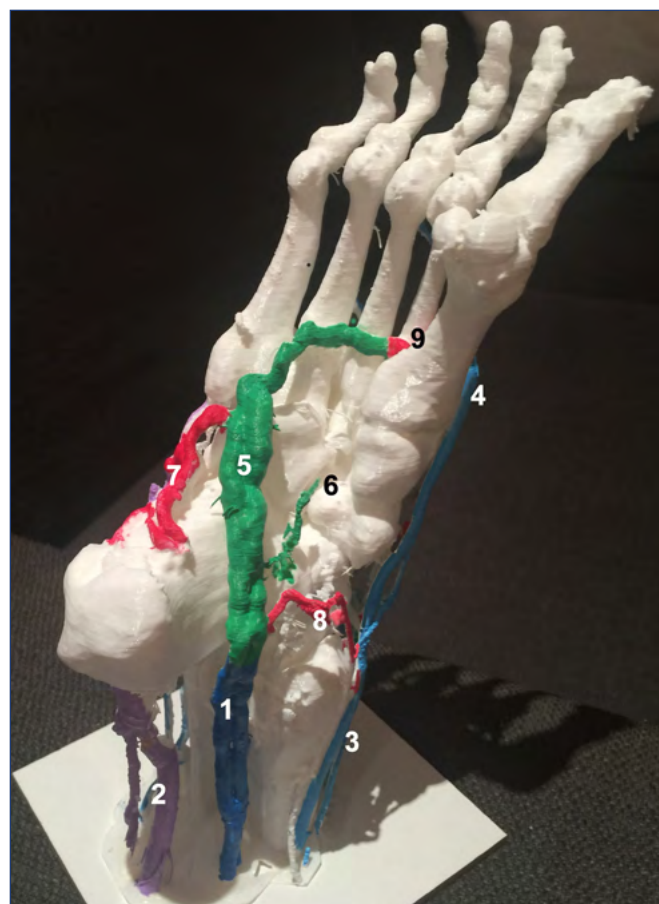

Figure 12. 3D printed model of the foot veins.

Medial view of the sole.

1, posterior tibial veins at the calcaneus convergence (in blue); 2, small saphenous vein (SSV; in purple, dilated); 3, great saphenous vein (GSV; in blue); 4, medial marginal vein; 5, lateral plantar veins (foot pump, in green); 6, medial plantar veins; 7, calcaneus perforator vein (in red); 8, inframalleolar perforator vein (PV); 9, PV of the first metatarsal interspace.

3D vascular models. Such models show the vascular segmentation of the main organs, which is necessary for making decisions and for good surgical planning. Its application would be useful in hepatic surgery (*Figure 17*), kidney surgery, lung surgery, orthopedics, dental implantology, and in neurosurgery.

The aim of these 3D anatomical models of the patients before surgery is to have an in-depth knowledge of the vascular anatomy. This makes it possible to simulate the operation according to the personal anatomy of the patient and the organ segmentation.

This makes possible the new world of image-guided surgery: mini-invasive, more controlled, more accurate, and safer because it avoids the main complications.

Figure 15. Use of educational models of anatomy on tablets, smartphones, and web communities of models.
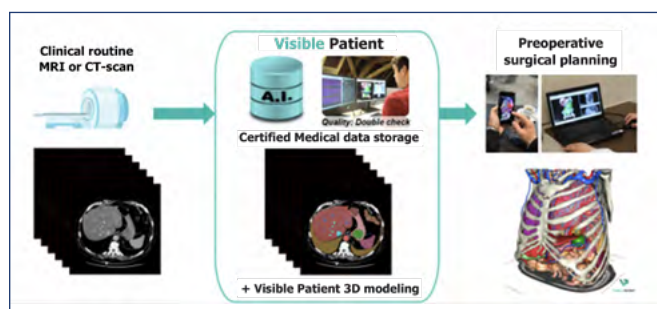
Figure 16. Visible Patient software™ is a company resulting from 15 years of research by the IRCAD R&D department in computer-assisted surgery. Visible Patient proposes a connected solution providing a 3D model of a patient from his/her medical image sent through a secured internet connection.

Abbreviations: 3D, three dimensional; AI, artificial intelligence; CT, computed tomography; MRI, magnetic resonance imaging.
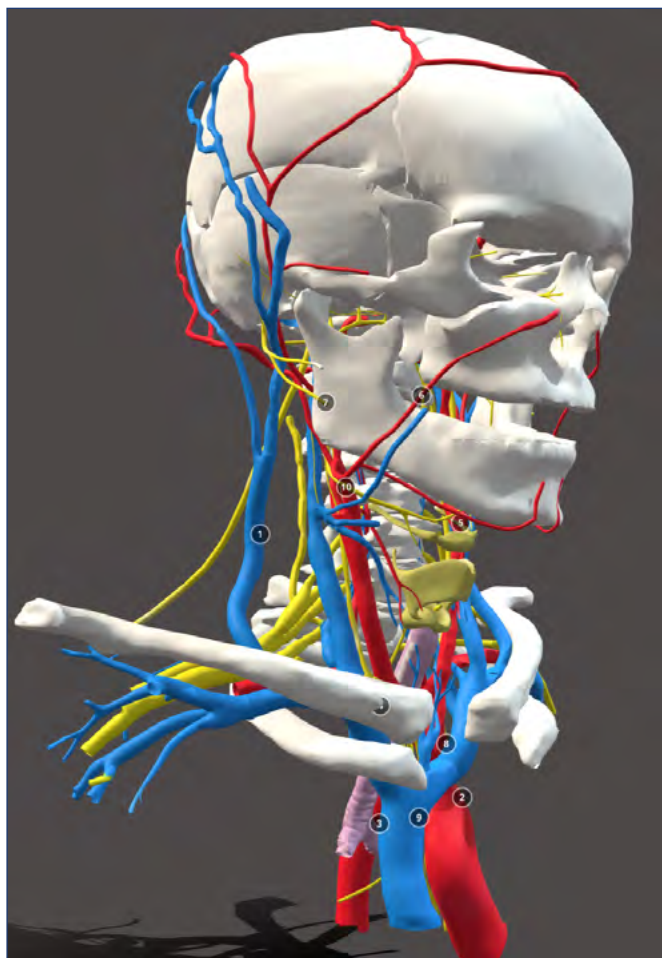

Figure 13. Display of the interactive 3D model of the head and neck with labels via Sketchfab®.
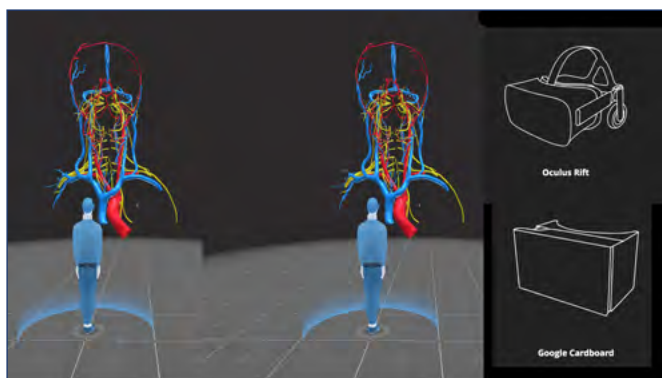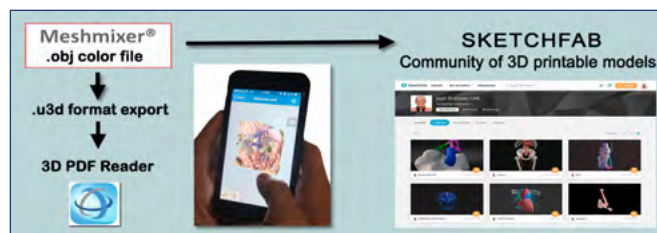

Figure 14. Display of the 3D model in virtual reality (VR) mode with labels via Sketchfab®.

You can visualize the model in stereovision with your smartphone inserted into a cardboard or an Oculus® mask.

Hepato-Pancreatico-Biliary surgery

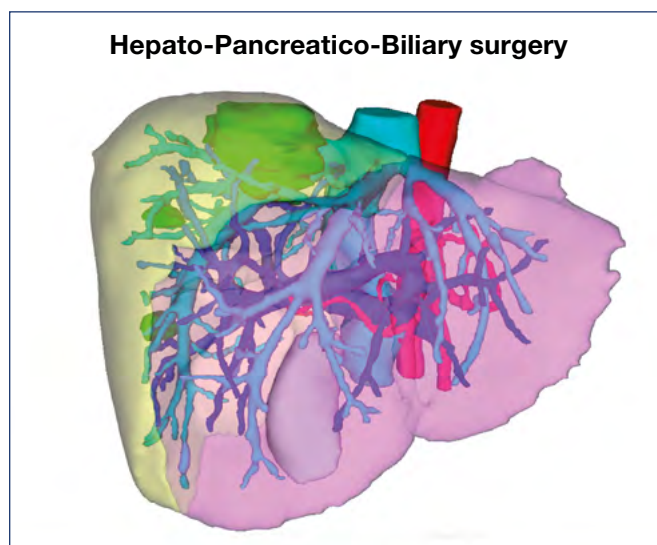Figure 17. Visible Patient software: planning for hepatic surgery.[12]

(By permission from Professor Luc Soler, IRCAD - Strasbourg.)

The 3D modeling of the vessels of the liver and of the segmentation makes it possible to make decisions about the type of excision (segmentectomy, partial hepatectomy) and the technique to be followed. Here, several liver metastases are all located in segment VIII.

Conclusion

The new tools of 3D modeling are revolutionary for educational anatomy and for clinical applications in the case of complex venous anatomy. It is also the future of surgery, providing accurate information about the vascular anatomy of each particular patient. Modern surgery has to be image-guided surgery for elective and more limited ablation of organs (segmentectomy).

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Influence of age, gender, duration of illness, and symptoms on pigmentation/ulceration in varicose veins of the great saphenous system

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great saphenous vein; pigmentation; ulceration; varicose veins

Abstract

Background: Venous pigmentation and ulceration in varicose veins pose significant financial and psychological burdens and affect quality of life. Not all varicose veins progress to this stage (C4-C6 in CEAP classification), and knowing the predictors for progressing to pigmentation/ulceration in varicose veins helps address high-risk patients early on. **Materials and methods:** This is a retrospective observational study done in patients diagnosed with varicose veins in the great saphenous system and subjected to radiofrequency ablation with or without any adjunct procedure during the time frame of January 1, 2018 to December 31, 2019. Using standardized questionnaires, physicians interviewing participants at the time of examination noted risk factors for pigmentation/ulceration in the form of age, gender, duration of illness, and symptoms. **Results:** Among 247 limbs with varicose veins that involved the great saphenous vein and were subjected for radiofrequency ablation, C3 stage was observed in the highest percentage of cases (44.5%) followed by C2 stage (27.9%). Pigmentation or ulceration were observed in 27.5% of cases. Duration of illness (longer duration), male gender, and age (higher age) were identified as predictors of pigmentation or ulceration. **Conclusion:** Large-scale studies to identify cutoff values for duration of illness and age would help clinicians in making treatment decisions.

Introduction

Varicose veins is a common chronic venous disease leading to life-limiting ulcerations and serious health risks such as deep-vein thrombosis.[1] Venous ulceration accounts for more than half of lower-limb ulcerations.[2] Venous pigmentation and chronic venous ulcer have heavy financial and psychological burdens, both to the individual and the health system, and significantly affect the quality of life.[2-6] The pathophysiological mechanism underlying formation of

venous pigmentation and ulceration has been attributed to macroscopic processes such as venous hypertension and destruction of venous wall architecture, which leads to chronic inflammatory processes that accumulate to form ulcers.[7] The National Institute for Health and Care Excellence (NICE) guideline states that approximately 3% to 6% of patients with this condition will develop venous ulcers in their lifetime.[8,9] In order to classify varicose veins, CEAP classification comprising clinical stage, etiology, anatomical location, and pathophysiology of varicose veins has been widely used since its introduction in 1994 by the American Venous Forum.[10] With the 2004 revision of the CEAP classification, the C4 stage includes pigmentation or eczema (C4a) and lipodermatosclerosis or atrophie blanche (C4b), whereas C5 and C6 stages include cases with healed and active ulceration respectively and are associated with significant morbidity and altered quality of life in patients with varicose veins.[11,12,13]

There are several hypotheses regarding the development of venous ulcers; however, the most common and held-to hypothesis is local venous hypertension, which leads to venous pooling and dilatation resulting in leukocyte trapping that ultimately leads to release of proteolytic enzymes and causes tissue damage.[14] Newer hypotheses on the cause of venous ulcers involve cytokines/growth factors, tumor necrosis factor α and transforming growth factor β.[15] Our series published in 2014 found venous ulcers to be prevalent in 3.9% of varicose vein cases and pigmentation in 33.3%.[16] Our case series published later involving 533 varicose vein cases found 13.1% of such cases had venous ulcers and 37.1% had pigmentation.[17]

In a cross sectional epidemiological survey–based study of 8000 people carried out in France, 51.3% of females and 30.2% of males had chronic venous disorder, among which 50.5% of women and 30.1% of men were in C2 stage (varicose vein), and skin trophic changes (pigmentation and/or ulcer) were seen in 2.8% of females and 5.4% of males. The information gathered from phone-based interviews in this study were later confirmed by clinical examination of patients with significant findings.[18] Investigation to elucidate predictive models for venous ulcers has found previous ulceration to be the most important predictor.[19] Not all cases of varicose vein progress to this stage, and the duration taken to reach this stage in untreated cases can vary. Also, research into the predictors of earlier progression to this stage is not extensive, although some proposed predictors include being overweight, duration of illness, age, and reflux velocity, among others.[12,20,21]

Methodology

This is a retrospective cross-sectional observational study carried out in the Cardiothoracic and Vascular Surgery Department of Dhulikhel Hospital in Nepal. All patients diagnosed with varicose veins in the great saphenous system and subjected to radiofrequency ablation with or without any adjunct procedure during the time frame of January 1, 2018 to December 2019 were included in the study. Ethical approval was obtained from the International Review Committee (IRC) of the Kathmandu University School of Medical Sciences (KUSMS).

Consent was obtained and a structured questionnaire filled in by the physician interviewing participants at the time of examination in the Vascular Surgery Outpatient Department, noting the clinical examination findings, risk factors for ulceration/pigmentation in terms of age, gender, symptoms, and duration of illness. Calculation of the duration of illness since the first bothering symptom is taken into account.

The data were analyzed using Statistical Package of Social Sciences (SPSS) version 19.0. If we consider the proportion of cases with pigmentation and/or ulceration as 20%, the sample size will be 1.96*1.96*0.2*0.8/(0.05*0.05), which is 246.[18] Continuous variables were expressed in the form of mean, standard deviation (SD), and range (minimum and maximum values). Nominal variables were expressed in the form of percentage. Means of the parametric variables were compared using the t-test (two variables) and the one-way analysis of variance (ANOVA) test (more than two variables). Frequency of nominal variables was compared using the Chi square test. P values of less than 0.05 were considered significant. Regression analysis was done to identify the predicting power of independent variables on dependent variables. Potential confounders were controlled in this study through a statistical approach, as regression analysis is able to control for the confounding variables and isolate the relationship of interest.[22]

Results

A total of 223 patients were enrolled over the study period. Among them, 24 had two limbs evaluated, 105 had only their left limb evaluated, and 94 had only their right limb evaluated. For ease of analysis, 247 limbs were considered as independent cases even if there was bilateral involvement within a single patient. Data pertaining to the right limb and that for left limb were entered separately.

Heading	Subheading	Number (limbs)/values	Percentage	Remarks
Gender	Male	147	59.5	male:female=1.47
	Female	100	40.5	
Age	Mean age	43.7, SD 13.4; Range (min-max), 18-71 y		P<0.05
	Male	41.8, SD 14.3; Range (min-max), 18-71 y		P<0.05
	Female	46.4, SD 11.9; Range (min-max), 22-68 y		
CEAP staging	C1	0	0.0	179 (C1 - C3) (72.5%)
	C2	69	27.9	
	C3	110	44.5	
	C4	48	19.4	68 (C4- C6) (27.5%)
	C5	10	4	
	C6	10	4	
Symptomatology	Asymptomatic	11	4.5	
	Pain	226	91.5	
	Prominent veins	205	83.0	
	Pigmentation	65	26.3	
	Itchiness	35	14.2	
	Ulceration	20	8.1	
	Feeling of heaviness	92	37.2	
Side	Right	118	47.8	Right only, 94 Left only, 105 Bilateral, 24
	Left	129	52.2	
Duration of illness	Mean	16.2 mo, SD 29.7; Range (min-max), 1-240 mo.		

CEAP, clinical, etiological, anatomical, pathophysiological classification; min-max, minimum to maximum; mo, months; SD, standard deviation; y, years.

Table I. Characteristics of the population.

In *Table I*, general parameters are shown. There were a higher number of male patients (male:female=1.47). The mean age was 43.7 years (SD, 13.4); in males, it was 41.8 years (SD, 14.3) and in females, 46.4 years (SD, 11.9).

The highest percentage of cases were classified as C3 stage (44.5%), followed by C2 stage (27.9%). There were no patients in C0 or C1 stage. There were 179 limbs (72.5%) without pigmentation or ulceration (C1-C3), whereas there were 68 (27.5%) with pigmentation and/or ulceration (C4-C6). The most common symptom was the perception of pain in 226 limbs (91.5%) followed by the presence of prominent veins in 205 limbs (83%). The mean duration of illness was 16.2 months (SD, 29.7).

Figure 1 shows a box plot of duration of illness in different C stages. There is a noticeable increase in duration of illness from C4 stage onwards.

In *Table II*, various predictors are shown. Duration of illness was significantly higher in the C4-C6 group (33.5 months) than in the C0-C3 group (9.6 months) with a *P* value less than 0.01. Mean age was higher in the C4-C6 group (47.8 years) than in the C0-C3 group (41.8 years) with a *P* value less than 0.01. Also, there was a higher percentage of limbs in C4-C6 stages in male patients than in female patients. No patients in the C4-C6 group were without pain. Pigmentation/ulceration was found in a higher percentage of limbs with itchiness than in those without. Among eight variables, significant differences were observed between
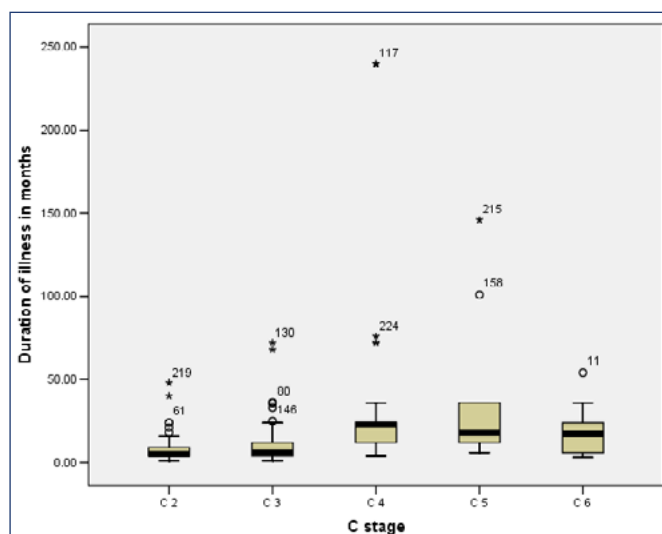
Figure 1. Duration of illness (months) according to different C-stages.

C0-C3 and C4-C6 groups for duration of illness, age, gender, perception of pain, and itchiness. *Table III* shows a comparison of symptoms between males and females. Pigmentation and ulceration were more prevalent in males than females; this was statistically significant.

Linear regression analysis was performed (*Table IV*). Four variables significantly predicted ulceration in varicose veins. Pain β=0.366, *P*<0.01), itchiness β=0.355, *P*<0.01), duration of illness (β=0.204, *P*<0.01), and male gender (β=0.196, *P*<0.01) were significant predictors. However, age was not a significant predictor of ulceration.

Variables	Subheading	C0-C3	C4-C6	*P* value
Duration of illness		9.6 mo, SD 10.3; Range (min-max) 1-72 mo	33.5 mo, SD 50.3; Range (min-max) 3-240 mo	**<0.01**
Age	Both male and female included	41.8 y, SD 13.8; Range (min-max) 18-71 y)	47.8 y, SD 11.6; Range (min-max) 23-69 y	**<0.01**
	Male	38.5 y, SD 14.7; Range (min-max) 18-71 y	46.3 y, SD 12.4; Range (min-max) 23-69 y	**<0.05**
	Female	44.9 y, SD 12.3; Range (min-max) 22-66 y	51.6 y, SD 8.9; Range (min-max) 36-68 y	**<0.05**
Gender	Male	96 (65.3%)	51 (34..6%)	**<0.01**
	Female	84 (84%)	16 (16%)	
Asymptomatic	Yes	10 (90.9%)	1 (9.1%)	0.16
	No	169 (71.61%)	67 (28.39%)	
Pain	Yes	158 (69.91%)	68 (30.09%)	**<0.01**
	No	21 (100%)	0 (0%)	
Prominent veins	Yes	152 (74.15%)	53 (25.85%)	0.19
	No	27 (51.92%)	15 (48.08%)	
Feeling of heaviness	Yes	68 (73.91%)	24 (26.09%)	0.40
	No	111 (71.61%)	44 (28.39%)	
Itchiness	Yes	8 (22.86%)	27 (77.14%)	**<0.01**
	No	171 (80.66%)	41 (19.34%)	

Min-max, minimum-maximum; mo, months; SD, standard deviation; y, years.

Table II. Analysis of different variables in two groups of clinical classification.

Variables	Results	Male	Female	*P* value
Asymptomatic	Yes	4 (36.36%)	7 (63.63%)	0.10
	No	143 (54.36%	93 (39.4%)	
Ulceration	Yes	16 (80%)	4 (20%)	**<0.05**
	No	131 (57.7%)	96 (42.29%)	
Prominent veins	Yes	124 (60.48%)	81 (39.51%)	0.30
	No	23 (54.76%)	19 (45.24%)	
Feeling of heaviness	Yes	54 (58.69%)	38 (41.3%)	0.47
	No	93 (60%)	62 (40%)	
Itchiness	Yes	21 (60%)	14 (40%)	0.55
	No	126 (59.43%)	86 (40.56%)	
Pigmentation	Yes	48 (73.84%)	17 (26.15%)	**<0.05**
	No	99 (54.39%)	83 (45.6%)	

Table III. Symptoms based upon gender.

Variable	Beta coefficient value	*P* value
Gender (male)	0.196	**<0.01**
Age	0.087	0.15
Itchiness	0.355	**<0.01**
Pain	0.366	**<0.01**
Duration of illness	0.204	**<0.01**

Table IV. Regression analysis on perception of pain, itchiness, gender, age, and duration of symptoms.

Discussion

The study focused on whether gender, age, duration of illness, and symptoms such as perception of pain, skin discoloration, itchiness, ulceration, and feeling of heaviness were predictors of pigmentation/ulceration. The duration of illness, older age, male gender, and itchiness as a symptom were significantly longer, higher, or more common in limbs with pigmentation and/or ulceration. There were more male participants in our series. In a study by Nayak et al carried out in India, 82.5% of patients were male.[24] In our earlier published series, there was also a predominance of male study participants.[17] Differences in health-seeking behavior between males and females might be an underlying reason behind this.[24]

The mean age of 43.7 in our study is similar to that of other studies. For example, in a study by Maly in the Czech Republic, the mean age was also 44 years, almost the same as in our study.[25] However, in our study, the mean age in males was significantly lower than that in females.

In terms of CEAP staging, the most common C classification was C3 followed by C2. In contrast, in a study by Cassou et al in Brazil, C2 was more common (50.25%) followed by C3 (23.05%)[26]; likewise in a study by Maly, where the most common C classification was C2 (32.3% of cases).[25] The proportion of cases in C4-C6 stage (pigmentation/ulceration) in our study was 27.5%. Overall, there were 19.4% in C4, 4% in C5, and 4% in C6 groups. The mean age among males with C0-C3 was 38.5 years and in females was 44.9 years. Similarly, in the C4-C6 group, the mean age among males was 46.3 years and in females was 51.6 years. These findings suggest either that male patients consult early or the disease itself occurs early in males. Also, as it takes time for progression of clinical staging from C1 to C6, higher age as a predictor is considered for higher clinical staging.[27] In the study by Maly, the proportion of C4-C6 cases was 32.4%.[25] In the earlier mentioned study by Cassou, this was only 2.2%.[26] Being a tertiary care center and getting many referrals for late-stage varicose veins might be a reason behind the higher proportion of pigmentation/ulceration. In our earlier published study involving 533 limbs, the percentage of

pigmentation and ulceration was 50.2%.[17] Compared with patients from 2013-2018 in earlier-published work, the proportion observed with pigmentation/ulceration in our study has decreased (2018-2019).[17]

Mean duration of illness in our study was 16.2 months. The mean duration of illness in patients at stage C0-C3 was 9.6 months; for those at stage C4-C6, it was 33.5 months. In a study done by Liu et al to elucidate the factors related to venous ulcer size, the mean duration of symptoms in patients with venous ulcer was 25.7 months.[27]

Major predictors of pigmentation/ulceration in varicose veins were identified as duration of illness, gender (male), history of pain, and itchiness. The study by Liu et al also identified gender and duration of illness as predictors for increased size (diameter >2 cm) of venous leg ulcer.[27] Studies aiming to identify predictors of ulceration usually include analysis on the presence of deep-vein thrombosis, smoking, obesity, calf-muscle power, level of physical inactivity, etc. A study carried out in the UK suggested deep-vein thrombosis, smoking, obesity, restricted ankle movement, and calf-muscle-pump power predicted ulceration.[28] As the cases included in our study were those subjected to radiofrequency ablation of the great saphenous vein, there were no cases with deep-vein thrombosis, as radiofrequency ablation is usually not done in such cases. In a study by Abelyan et al, important risk factors for ulceration were found to be postthrombotic syndrome (odds ratio of 14.9), reflux in deep veins, history of leg injury, and physical inactivity. In that study, stages C1 to C4 were included in a control group and C5 and C6 were included in the case group.[2]

Large-scale studies to delineate other predictors of pigmentation/ulceration, such as familial/genetic causes, calf-muscle power, and range of ankle movement also need to be done.[28-30] Our study focused on identifying predictors in terms of symptomatology, duration of illness, gender, and age, which have not received much previous study.

Conclusion

In conclusion, we found duration of illness, gender and symptoms of pain and itchiness as predictors for pigmentation/ulceration in varicose vein patients. Larger studies are required to help know cutoff points for some predictors. Knowing high-risk groups helps in early intervention to prevent ulceration/pigmentation that will decrease the disease burden.

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Micronized purified flavonoid fraction in adjunction to rivaroxaban improves outcomes of popliteal-femoral deep-vein thrombosis at 12-month follow-up

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Keywords:

deep-vein thrombosis; inflammation; micronized purified flavonoid fraction; post-thrombotic syndrome; recanalization

Abstract

Aim: To assess the efficacy of the long-term use of micronized purified flavonoid fraction (MPFF) in the treatment of popliteal-femoral deep-vein thrombosis (DVT). **Methods:** In this pilot, comparative, open-label clinical study, patients with the first episode of popliteal-femoral DVT confirmed by duplex ultrasound scan (DUS) were allocated to two groups: the control group received standard treatment with rivaroxaban for 6 months and compression stockings for 12 months, and the MPFF group received adjunctive MPFF 1000 mg/day for 12 months. During the 12-month follow-up, the degree of recanalization was assessed bi-monthly by the DUS and Marder score. Finally, patients were evaluated for post-thrombotic syndrome (PTS) via the Villalta score (score of ≥5 defined PTS). **Results:** Sixty patients (40 males and 20 females; mean age 56.3±13.4 years) were allocated to the MPFF or control group (n=30 in each group) and followed-up for 12 months. The median Villalta score was significantly lower in the MPFF group than in the control group (1.9±2.0 vs 5.2±2.6; *P*<0.001) with a smaller number of verified PTS (10% vs 53%; *P*=0.001). In the MPFF group, a greater reduction in the Marder score and a faster recanalization of the popliteal and the femoral veins were observed. **Conclusion:** The results of this pilot study suggest that long-term use of MPFF is associated with a lower incidence of PTS at 12 months and a faster recanalization of the deep veins in patients with popliteal-femoral DVT treated with rivaroxaban. These findings should be confirmed in more powerful randomized clinical trials.

Introduction

Deep-vein thrombosis (DVT) along with superficial vein thrombosis and pulmonary embolism (PE) constitute the group termed venous thromboembolism (VTE), which remains a significant medical and social problem.[1,2] Standard treatment of DVT

consists of using parenteral and/or oral anticoagulants for at least 3 months, with a possible prolongation of therapy for an indefinitely long period.[3,4] The treatment is aimed at preventing the progression of thrombotic disease, reducing the risk of PE and fatal outcome. The introduction of direct oral anticoagulants (DOAC) has changed the paradigm of VTE treatment, making this process safer and more convenient for both the doctor and the patient. Treatment with DOACs compared with conventional therapy by low-molecular-weight heparin (LMWH) switched to vitamin K antagonists (VKA) was found to be not less effective, but safer.[5]

After eliminating the threat to life, the risk of developing long-term complications, in particular post-thrombotic syndrome (PTS), which significantly affects the quality of life and work capacity, comes to the fore. The prevalence of PTS in 10 to 15 years after the first thrombotic episode accounts for 19% to 42% with skin ulceration in 3% to 4% of patients.[6-9] The essential risk factors for PTS are as follows: proximal localization of the thrombus; ipsilateral DVT recurrence; preexisting chronic venous disease (CVD); insufficient vein recanalization and preservation of residual venous obstruction (RVO); elderly age; inadequate anticoagulant therapy; and intensive and prolonged inflammation in the thrombus and the adjacent venous wall.[10]

Inflammation is a crucial component of the initiation and propagation of the thrombotic process, along with other components including the venous wall and valve damage factor.[11-14] In parallel, the inflammatory response is vital for the release of the vessel lumen from thrombotic masses. Therefore, a significant suppression of its intensity may affect the recanalization.[15-17] Poor recanalization with the preservation of RVO increases the risk for PTS 1.6- to 2.1-fold.[18-22] We hypothesized that the pharmacological modulation of the inflammatory response could protect the venous wall from the excessive injury while retaining the fundamental role of immune cells in the recanalization process. Several drugs have potential properties for such modulation, and flavonoids are at the top of the list.

Anti-inflammatory and venoprotective actions of flavonoids are well studied, and these agents are widely used to relieve symptoms and signs of CVD.[23,24] Among all flavonoids, the micronized purified flavonoid fraction (MPFF) is the most established agent.[25] Previous experimental studies have shown endothelial protective properties in the settings of reperfusion injury and venous hypertension,[26-29] as well as suppression of the inflammatory response in patients with CVD,[30] including those after sclerotherapy.[31] Long-term intake of MPFF up to 12 months is associated with a low incidence of AEs, most of which are mild and do not affect health status.[23,24,32] Thus, the MPFF shows a favorable risk-benefit profile for long-term use as an adjunctive treatment for DVT.

This pilot study aimed to assess the efficacy of the long-term use of MPFF in addition to rivaroxaban for the treatment of popliteal-femoral DVT.

Methods

This study was a pilot, single-center, open-label, comparative clinical trial with a blinded assessment of efficacy outcomes. The detailed design and findings at the 6-month follow-up have been published previously.[33] Here, we present findings from the 12-month extended observation. The study protocol was approved by an Institutional Review Board of Clinical Hospital no.1 of the President's Administration of the Russian Federation, and all patients provided signed informed consent for participation. The protocol was not registered in any open registry of clinical trials because of its pilot nature, absence of funding, and local Institutional policy. The pilot nature of the study was dictated by the lack of any experimental or clinical data on the influence of MPFF on the course of DVT, as well as the inability to perform a sample size calculation.

The study enrolled patients at the age of >18 years with the first episode of provoked or unprovoked popliteal-femoral DVT, as confirmed by DUS, who signed informed consent. The exclusion criteria have been reported previously.

The study was conducted at Clinical Hospital no.1 of the President's Administration of the Russian Federation in 2017-2018. The pretest clinical probability by two-level Wells score[34] and D-dimer was utilized according to the Institutional protocol in all patients admitted to the emergency department with suspected DVT. Treatment with LMWH, followed by DUS, was initiated in subjects with a high clinical probability of DVT or low clinical probability in combination with positive D-dimer. As soon as DVT was confirmed by DUS, patients were assessed for eligibility and enrolled in the study after signing informed consent. The allocation to the experimental (MPFF) or control group was based on the number on the patient's medical record form. The general sequence of the diagnosis and treatment for DVT and enrollment in the study are represented in *Figure 1*.
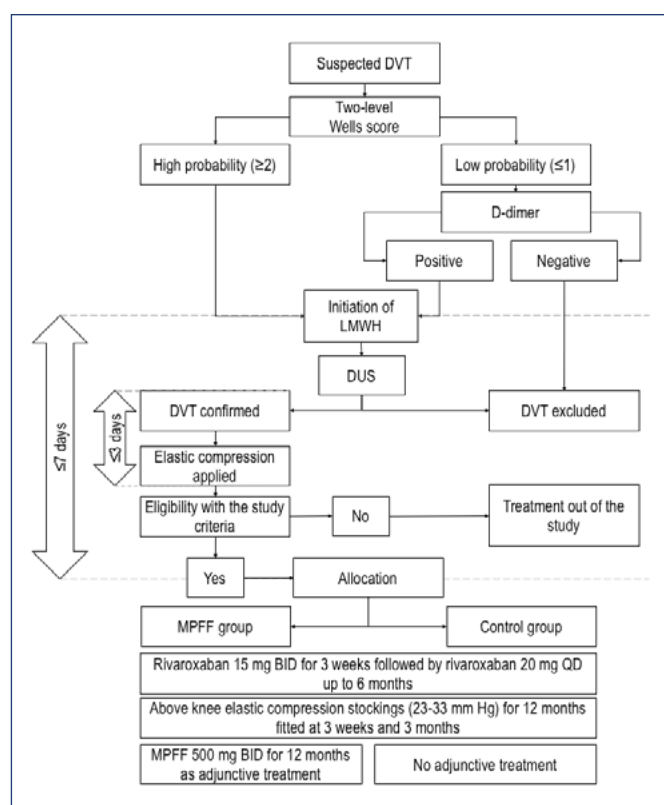
Figure 1. The general sequence of the diagnosis and treatment for deep-vein thrombosis and enrollment in the study.

Abbreviations: BID, twice a day; DVT, deep-vein thrombosis; DUS, duplex ultrasound; LMWH, low-molecular-weight heparin; MPFF, micronized purified flavonoid fraction; QD, once a day.

Patients were allowed to receive therapeutic doses of LMWH (enoxaparin 1 mg/kg twice daily) during the period from hospital admission to the allocation, but not more than 7 days. After the assignment, they switched to rivaroxaban 15 mg twice daily for up to 3 weeks, followed by 20 mg once daily for up to 6 months. Within the first 3 days after DVT confirmation, patients of both groups applied above-knee elastic compression stockings with a pressure of 23 to 32 mm Hg and were recommended to use it for 12 months. Fitting for size was obligatory at 3 weeks and 3 months after the index DVT. In the MPFF group, patients received MPFF 500 mg twice daily for 12 months in adjunction to standard treatment. The first dose of MPFF was administered immediately after treatment allocation and in parallel with rivaroxaban.

Patients were followed-up for 12 months with bimonthly clinical and ultrasound examinations. At baseline, the standard clinical data were evaluated, and the affected limb was assessed with CEAP classification (clinical, etiological, anatomical, pathophysiological classification;

2004 version)[35] for preexisting CVD by the methodology described previously.[36] At 6 and 12 months, the CEAP clinical class was reassessed in parallel with the evaluation of the Villalta score, venous clinical severity score (VCSS), and CIVIQ-20 score (20-item Chronic Venous disease quality-of-life Questionnaire). The final decision on the presence of PTS and the severity of CVD was made by an independent expert blinded to the patient's allocation to MPFF or control group.

A DUS was performed by use of the MyLab30 (Esaote, Italy) machine with a linear ultrasound transducer LA532 in the frequency range of 5 to 13 MHz. The common femoral vein (CFV) and femoral vein (FV) were assessed in the supine position, popliteal vein (PV) in the prone position, and calf veins in a sitting position. The whole-leg scan was performed at any time.

The criteria for DVT were incompressibility of the vein during compression by the ultrasound probe and the absence of blood flow on the color mapping mode with provocation maneuvers. A modified Marder score was used to assess the extension of the thrombotic lesion as described previously.[33,37] Briefly, occlusion of different venous segments was scored from 1 (calf veins) to 8 (iliac veins) with the maximal score of 34 for each limb. A higher score corresponds to a higher extension of the thrombotic lesion. The recanalization degree (RD; the inverse criteria of RVO) at the narrowest point of PV, FV, and CFV was calculated as previously described (*Figure 2*).[33,37] All ultrasound studies were performed by a specialist blinded to the patient's allocation to the MPFF or control group. The DUS could be performed in an unscheduled and urgent manner if any clinical suspicion for VTE recurrence arose.

The primary outcome of the extended study was the detection of PTS at 12 months. The PTS was diagnosed with the Villalta score by the blinded expert. The score of 0-4 defined the absence of disease; 5-9, mild disease; 10-14, moderate disease; and score of ≥15 or the presence of venous ulcer, severe disease.

The secondary efficacy outcomes were as follows: diagnosis of PTS at 6 months (the primary outcome of the previous report); diagnosis of severe PTS at 6 and 12 months; severity of PTS by the Villalta score at 6 and 12 months; symptomatic or asymptomatic DVT recurrence and symptomatic PE within the follow-up period; progression of CVD at 6 and 12 months by CEAP clinical class; severity of CVD by VCSS score at 6 and 12 months; quality of life
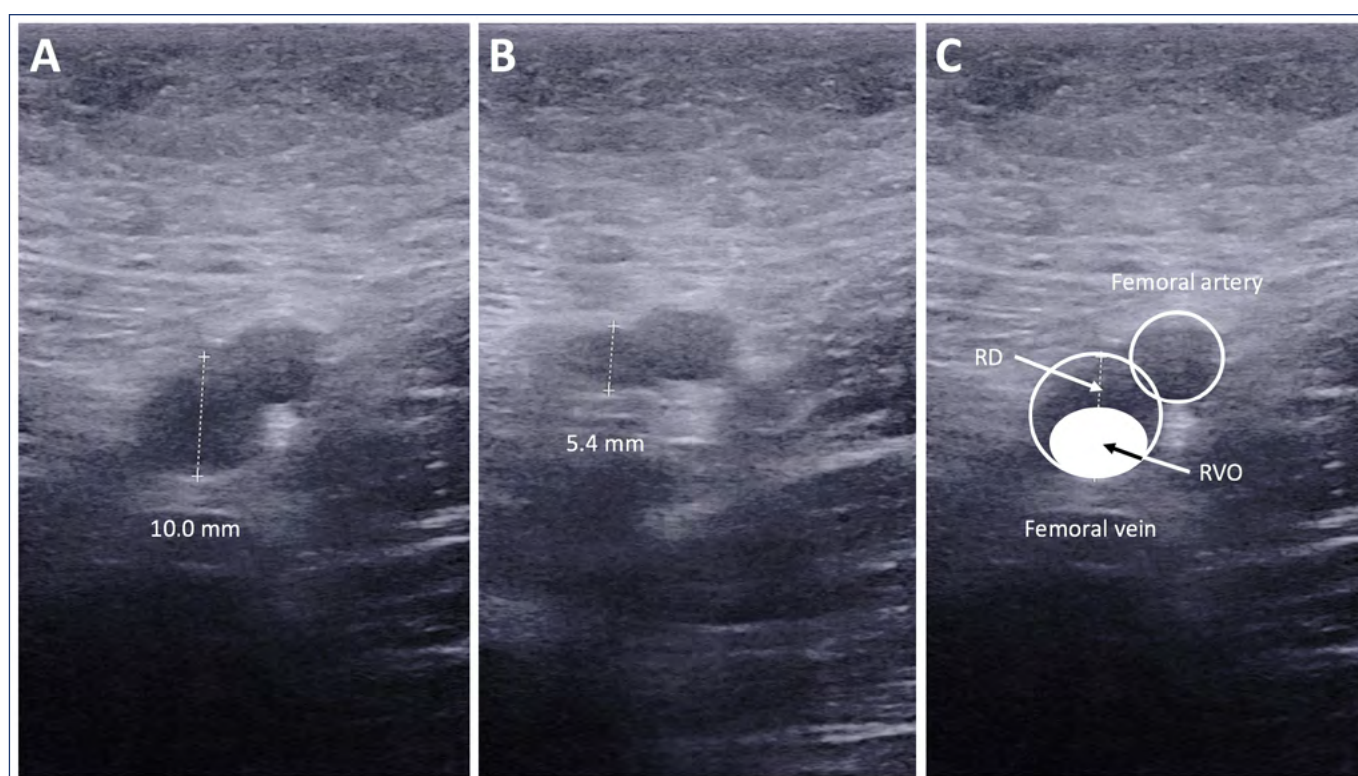
Figure 2. An example of the assessment for recanalization degree on the femoral vein.

A) The diameter of the vein without compression (10.0 mm). B) The diameter of the vein under maximal compression at the narrowest point (5.4 mm). C) The relationship between RVO and RD.

Residual venous obstruction (RVO) = d(under compression) / d(without compression) x 100% = 5.4/10.0 x 100% = 54%.

Recanalization degree (RD) = [d(without compression) − d(under compression)] / d(without compression) x 100% = (10.0-5.4)/10.0 x 100% = 46%.

RD = 100% - RVO = 100% - 54% = 46%.

by CIVIQ-20 questionnaire at 6 and 12 months; complete recanalization of the PV, FV, and CFV at 12 months; change in recanalization degree at the PV, FV, and CFV within the follow-up period; and change in thrombus burden by the Marder score within the follow-up period.

The symptomatic DVT recurrence was defined as an increase in edema, pain, or skin hyperemia of the affected limb, or the occurrence of the same signs in the intact leg. It had to be confirmed by the scheduled or unscheduled DUS. The asymptomatic DVT recurrence was defined as the occurrence of total occlusion in a previously recanalized venous segment or appearance of the new occlusion in the primary intact vein as detected by scheduled DUS. PE could be suspected in the presence of typical clinical signs (shortness of breath, chest pain, cough, increased heart rate, and decreased arterial blood pressure) and confirmed by appropriate imaging tests.[4] The progression of CVD was defined as a transition from a lower CEAP clinical class to a higher class, eg, C0 to C1 to C2 to C4. Complete vein

recanalization was suggested as clearance of thrombotic masses by 80% or more with RVO <20% or RD ≥80%.

The safety outcomes were represented by major or clinically relevant nonmajor (CRNM) bleeding, as defined by the International Society of Thrombosis and Hemostasis (ISTH),[36,38] or minor bleeding (any other hemorrhage not fulfilling the criteria of major or CRNM bleeding), and any other adverse event (AE), including serious adverse event (SAE). All safety outcomes were assessed by the three authors and two independent experts in vascular surgery and cardiology for the casual relationship with studied drugs. Bleeding events were considered as expected AEs related to rivaroxaban if they occurred within the period of anticoagulation treatment and 3 days after cessation and were analyzed as prespecified safety outcomes.

Specific measuring for compliance with MPFF, rivaroxaban, or compression stockings was not prespecified. Patients were asked to report any preliminary cessation of studied

drugs or elastic compression. The subjects with expected low adherence were not included according to the study design.

Statistical analysis

As this was a pilot study, the minimal sample size was not calculated. All absolute values are presented as the mean with the standard deviation (SD) and relative values, presented as percent with a 95% confidence interval (CI) as calculated by Wilson. The comparisons were performed using the t-test for continuous variables or the two-sided Fisher's exact test and a chi-square test for categorical variables. A comparison of mean values with time was performed by assessment of within- and between-subject effects, as well as their within-subject interaction via the general linear model for repeated measurements (GLM-RM), a kind of dispersion analysis (ANOVA). Time to event was represented by survival curves and compared via the Kaplan-Meier test. Statistical analysis was carried out using the IBM SPSS Statistics v.26 software package. The relative risk and its 95% CI were calculated with a free online calculator by MedCalc (https://www.medcalc.org). Differences were considered statistically significant if the *P*-value was less than 0.05.

Results

During the enrollment period, 132 patients with suspected DVT were admitted to the hospital, and the diagnosis was confirmed in 104 cases. Of these, 68 patients fulfilled the criteria of eligibility, and eight patients refused to participate. The remaining 60 patients were allocated to one of the two treatment groups (n=30 in each group), and all of them completed the 12-months follow-up (*Figure 3*).

The clinical characteristics of the enrolled patients are presented in *Table I*. Participants in the control group receiving a standard treatment had a higher prevalence of CVD prior to the DVT, in particular, the CEAP clinical classes of C2 to C4 (73% vs 50%; *P*=0.110). The prevalence of thrombotic occlusion in popliteal, femoral, and CFVs was comparable in both groups. However, the total thrombus extension by the Marder score was higher in the MPFF group due to the higher involvement of the calf veins. The other characteristics were comparable among participants in both groups.

The results for the primary and secondary outcomes are summarized in *Table II*. At 12 months, PTS was reported in 3 of 30 (10%; 95% CI, 3.5%-25.6%) patients who received adjunctive MPFF in comparison to 16 of 30 (53%; 95% CI, 35.8%-69.5%) who were treated only with rivaroxaban and compression stockings. Interestingly, when compared with the results obtained at 6 months, the number of established PTS at 12 months decreased from 20% to 10% (minus three patients) in the MPFF group and from 57% to 53% (minus one patient) in the control group. At the final assessment, most of the cases were classified as mild PTS. Only two patients in the control group had moderate disease, and none developed severe disease. The Villalta score was significantly lower in the MPFF group than in the control group (1.9±2.0 vs 5.2±2.6; *P*<0.001). These figures
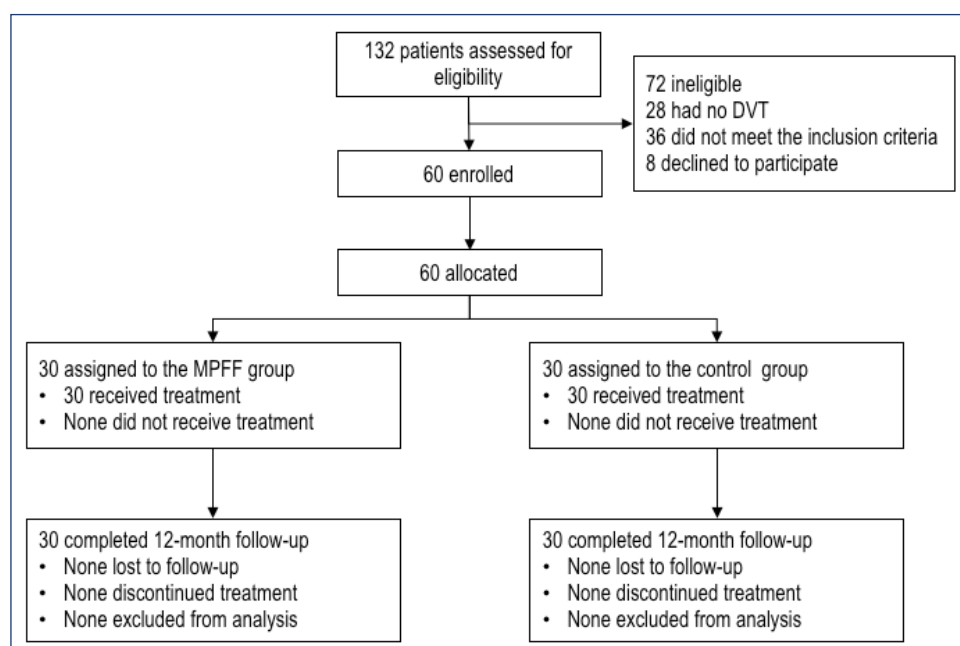

Figure 3. Trial profile (CONSORT flow diagram).

Abbreviation: DVT, deep-vein thrombosis; MPFF, purified flavonoid fraction.

Characteristic	MPFF group	Control group	P value
Age, years (mean ± SD)	55.2±14.9	57.5±11.9	0.518
Male, no./no. of the total (%)	17/30 (57%)	23/30 (77%)	0.170
Clinically unprovoked DVT, no./no. of the total (%)	17/30 (57%)	22/30 (73%)	0.279
Duration of symptoms, days (mean ± SD)	4.3±3.7	4.2±2.6	0.936
Time to allocation, days (mean ± SD)	3.9±1.2	3.9±1.7	0.931
Preexisting CVD, no./no. of the total (%)	15/30 (50%)	22/30 (73%)	0.110
CEAP clinical class of C0	7/30 (23%)	7/30 (23%)	0.014
CEAP clinical class of C1	8/30 (27%)	1/30 (3%)	
CEAP clinical class of C2	10/30 (33%)	14/30 (48%)	
CEAP clinical class of C3	5/30 (17%)	4/30 (13%)	
CEAP clinical class of C4	0/30 (0%)	4/30 (13%)	
CEAP clinical class of C5-6	0/30 (0%)	0/30 (0%)	
Left limb affected, no./no. of the total (%)	15/30 (50%)	12/30 (40%)	0.604
CFV affected, no./no. of the total (%)	13/30 (43%)	10/30 (33%)	0.596
FV affected, no./no. of the total (%)	25/30 (83%)	20/30 (67%)	0.233
PV affected, no./no. of the total (%)	30/30 (100%)	30/30 (100%)	1.000

CEAP, clinical, etiological, anatomical, pathophysiological classification; CFV, common femoral vein; CVD, chronic venous disease; DVT, deep-vein thrombosis; MPFF, micronized purified flavonoid fraction; FV, femoral vein; PV, popliteal vein; SD, standard deviation.

Table I. The clinical characteristics of patients enrolled in the study.

decreased during extended observation from 2.9±2.7 to 1.9±2.0 in the MPFF group and from 5.8±3.0 to 5.2±2.6 in the control group ($P<0.001$). Thereby, the addition of MPFF to the standard treatment of popliteal-femoral DVT significantly reduced the risk of PTS by 81% at 12 months.

The progression of CVD was observed in 1 of 30 (3%; 95% CI, 0.5%-16.2%) patients who received MPFF in comparison with 7 of 30 (23%; 95% CI, 11.6%-40.6%) patients who did not. In the MPFF group, the only subject who had preexisting untreated varicose veins (clinical class of C2) developed a disease progression to hyperpigmentation (clinical class of C4). In contrast, in the control group, two subjects with C0 progressed to C1 and C3, respectively, and five subjects with C2 progressed to C3 (n=4) or C4 (n=1). In total, CVD progression showed a significant association with the development of PTS. Only 11 of 52 (21%) patients without CVD progression were diagnosed with PTS in comparison to 8 of 8 (100%) subjects with CVD progression ($P<0.001$).
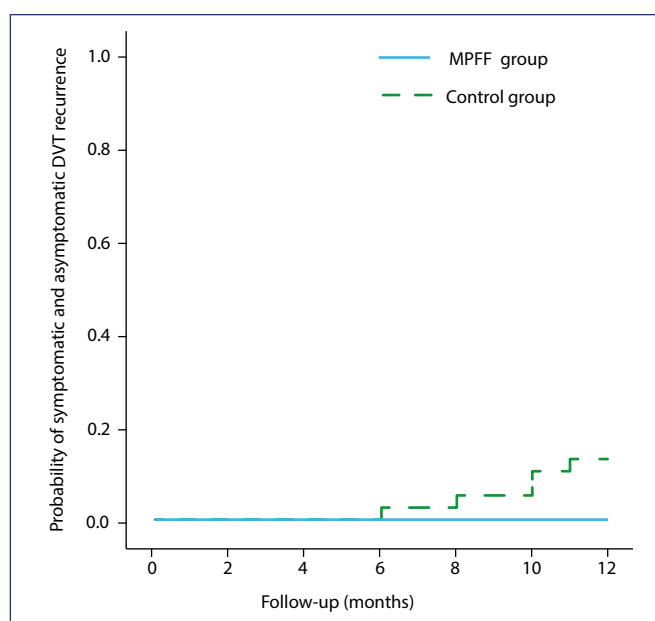

Figure 4. Probability of symptomatic and asymptomatic deep-vein thrombosis recurrence. Kaplan-Meier statistics and log-rank test (P=0.021).

Abbreviations: DVT, deep-vein thrombosis; MPFF, micronized purified flavonoid fraction.

Outcome	MPFF group	Control group	Relative risk (95% CI)	P value
Diagnosis of PTS at 12 months, no./no. of the total (%)	3/30 (10%)	16/30 (53%)	0.19 (0.06-0.56)	0.001
Diagnosis of mild PTS at 12 months, no./no. of the total (%)	3/30 (10%)	14/30 (47%)	0.21 (0.07-0.67)	0.003
Diagnosis of moderate PTS at 12 months, no./no. of the total (%)	0/30 (0%)	2/30 (7%)	0.20 (0.01-4.00)	0.492
Diagnosis of severe PTS at 12 months, no./no. of the total (%)	0/30 (0%)	0/30 (0%)	n/a	n/a
Diagnosis of PTS at 6 months, no./no. of the total (%)	6/30 (20%)	17/30 (57%)	0.35 (0.16-0.77)	0.007
Villalta score at 12 months (mean ± SD)	1.9±2.0	5.2±2.6	n/a	<0.001
Villalta score at 6 months (mean ± SD)	2.9±2.7	5.8±3.0	n/a	<0.001
VCSS score at 12 months (mean ± SD)	1.5±1.3	4.9±2.0	n/a	<0.001
VCSS score at 6 months (mean ± SD)	2.3±1.9	4.9±1.9	n/a	<0.001
CVD progression at 12 months, no./no. of the total (%)	1/30 (3%)	7/30 (23%)	0.14 (0.02-1.09)	0.052
CIVIQ-20 score at 12 months (mean ± SD)	21.6±2.1	30.0±8.3	n/a	<0.001
CIVIQ-20 score at 6 months (mean ± SD)	24.1±4.6	31.6±8.5	n/a	<0.001
VTE recurrence at 12 months, no./no. of the total (%)	0/30 (0%)	5/30 (17%)	0.09 (0.05-1.57)	0.492
Bleeding at 12 months, no./no. of the total (%)	2/30 (7%)	3/30 (10%)	0.67 (0.12-3.71)	0.999
Major bleeding, no./no. of the total (%)	0/30 (0%)	0/30 (0%)	n/a	n/a
CRNM bleeding, no./no. of the total (%)	1/30 (3%)	2/30 (7%)	0.50 (0.05-5.23)	0.999
Minor bleeding, no./no. of the total (%)	1/30 (3%)	1/30 (3%)	1.00 (0.67-15.26)	0.999
Other SAE related to MPFF, no./no. of the total (%)	0/30 (0%)	0/30 (0%)	n/a	n/a
Other AE related to MPFF, no./no. of the total (%)	3/30 (10%)	0/30 (0%)	7.00 (0.38-129.93)	0.999

AE, adverse event; CI, confidence interval; CIVIQ-20, 20-item ChronIc Venous dIsease quality-of-life Questionnaire; CRNM, clinically relevant non-major bleeding; CVD, chronic venous disease; MPFF, micronized purified flavonoid fraction; n/a, nonavailable; PTS, post-thrombotic syndrome; SAE, serious adverse event; SD, standard deviation; VTE, venous thromboembolic event

Table II. Primary and secondary outcomes in the MPFF and control groups.

The severity of CVD assessed by the VCSS score was significantly lower in patients who received MPFF: 1.5±1.3 vs 4.9±2.0 (*P*<0.001). A similar tendency in score reduction from 6 to 12 months was observed only in the MPFF group (*P*<0.001). The CIVIQ-20 score was significantly lower in the MPFF group, corresponding with better quality of life: 21.6±2.1 vs 30.0±8.3 (*P*<0.001). A further reduction in the score in both groups after 6 months was observed as well (*P*<0.001).

No episode of symptomatic PE was detected. The recurrence of DVT was found in none of the patients in the MPFF group (0%; 95% CI, 0.0%-11.4%) compared with 5 (17%, 95% CI, 7.6%-33.9%) patients in the control group. The time-to-event is represented in *Figure 4*. Four of five recurrences

were observed after cessation of anticoagulation at 8 to 11 months. Only two episodes were symptomatic, and scheduled DUS revealed the other three. The contralateral DVT represented three cases; the reocclusion of the previously recanalized vein, the only case; and the new occlusion of the previously unaffected ipsilateral vein, the last case. In four patients, anticoagulation treatment was reinitiated if it had been previously stopped. The only patient who developed recurrence within the period of oral anticoagulation was switched to LMWH. All these patients were analyzed for clinical outcomes with the exclusion of the new ipsilateral venous lesions from the analysis of ultrasound end points. The appearance of recurrent DVT significantly affected the risk of PTS development. Four of five (80%) subjects with recurrent thrombosis developed

PTS in comparison with only 15 of 55 (27%) patients free of recurrence (*P*=0.031).

No new safety outcome besides that previously published was reported beyond 6 months of observation. One CRNM and one minor rectal bleeding incident were detected in the MPFF group. Two CRNM macrohematuria and one minor epistaxis were observed in the control group. No SAE related to MPFF was identified. Three patients in the MPFF group reported a mild dyspeptic disorder, which appeared within the first month of therapy, did not require treatment discontinuation, and was relieved by changing the time of MPFF intake with the consumption of food. All these events were classified as AE certainly related to MPFF.
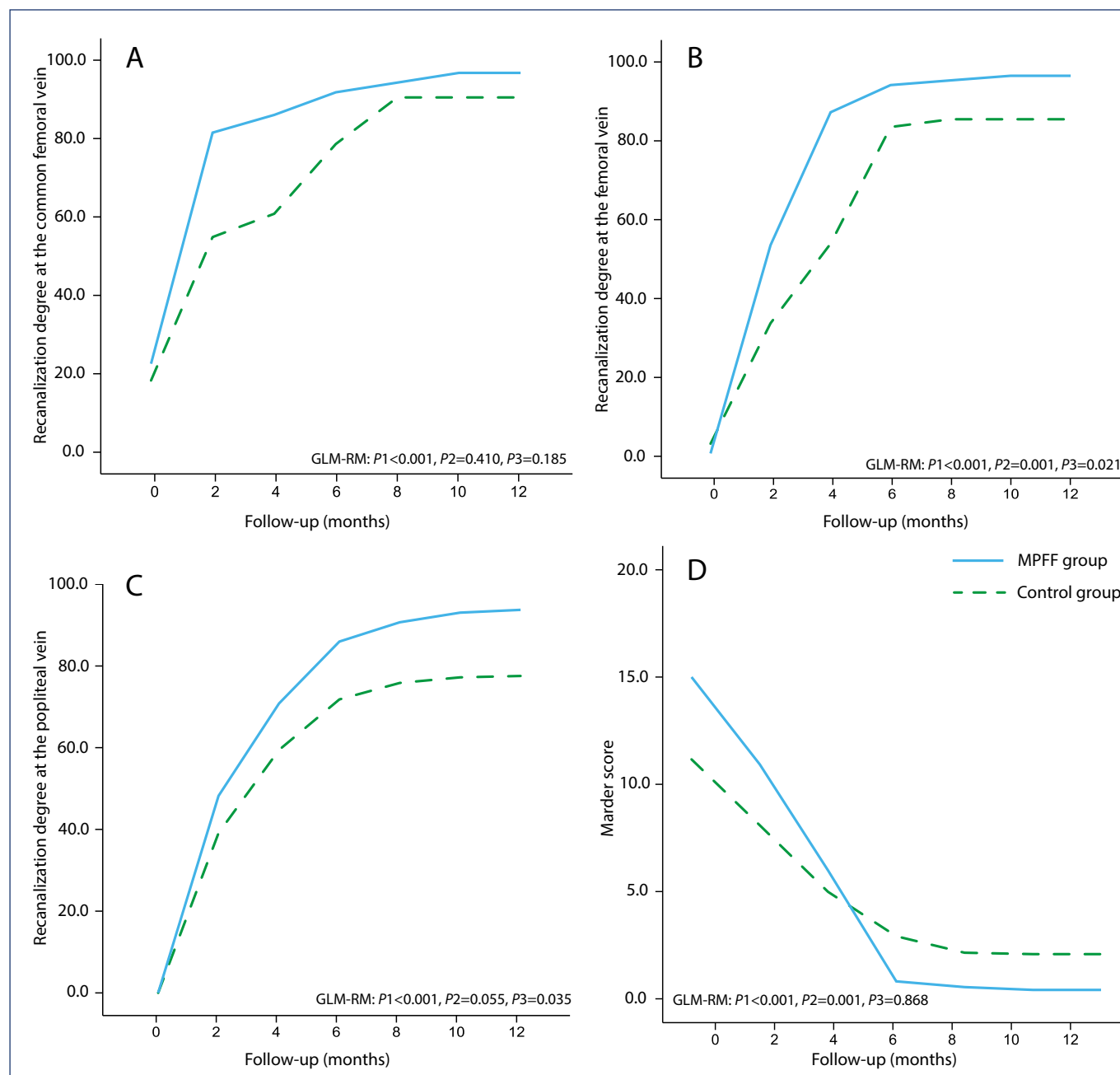
Figure 5. The recanalization of the main venous segments and thrombotic burden. Changes in recanalization degree at the (A) common femoral vein, (B) femoral vein, and (C) popliteal vein; (D) dynamics of the Marder score. GLM-RP (generalized linear model repeated measures): P1, within-subject effect "time" (P<0.05 interpreted as significant changes over time in both groups); P2, within-subject interaction "time x group" (P<0.05 interpreted as a significant difference in the slope of curves related to faster recanalization); P3, between-subject effect "group" (P<0.05 interpreted as a significant deviation of the curves related to complete recanalization).

Outcome	MPFF group	Control group	P value
Thrombus extension by the Marder score (mean ± SD)			
Baseline	15.0±4.8	11.1±4.3	0.002
2 months	10.9±4.0	8.1±3.1	0.003
4 months	6.0±1.9	5.0±2.8	0.114
6 months	0.8±1.6	2.8±3.5	0.006
8 months	0.5±1.3	2.1±2.6	0.004
10 months	0.4±1.2	2.1±2.3	0.003
12 months	0.4±1.2	2.1±2.6	0.003
Recanalization degree (mean ± SD)			
Common femoral vein	n=13	n=10	
Baseline	23.3±30.3	19.0±30.7	0.744
2 months	82.9±31.7	56.0±34.1	0.072
4 months	87.5±29.3	62.0±33.9	0.073
6 months	93.3±23.1	80.0±35.0	0.296
8 months	95.8±14.3	92.0±25.3	0.660
10 months	98.3±5.8	92.0±25.3	0.408
12 months	98.3±5.8	92.0±25.3	0.408
Femoral vein	n=25	n=20	
Baseline	0.0	2.5±11.1	0.330
2 months	53.6±34.7	33.5±34.1	0.058
4 months	87.8±27.1	54.0±34.4	0.001
6 months	94.8±20.6	84.0±26.0	0.28
8 months	96.0±20.0	86.0±26.4	0.170
10 months	97.2±14.0	86.0±26.4	0.098
12 months	97.2±14.0	86.0±26.4	0.098
Popliteal vein	n=30	n=30	
Baseline	0.0	0.0	-
2 months	47.7±31.1	38.7±27.6	0.241
4 months	70.0±32.8	58.8±29.5	0.168
6 months	85.0±29.7	71.0±29.5	0.072
8 months	89.6±23.4	75.0±25.6	0.026
10 months	92.0±21.9	76.3±24.2	0.011
12 months	92.7±20.8	76.7±24.0	0.008

MPFF, micronized purified flavonoid fraction; SD, standard deviation.

Table III. Ultrasound outcomes in the experimental and control groups.

The ultrasound outcomes are represented in *Table III* and *Figure 5*. A significant trend toward the progressive clearance of thrombotic masses from the vessel lumen was observed on PV, FV, and CFV in both groups. No difference in the intensity of recanalization was found on the CFV. Complete recanalization was seen on all of 13 (100%) veins in the MPFF group and on 9 of 10 (90%) veins in the control group (*P*=0.434). In contrast, the speed of recanalization on FV and PV was higher in the MPFF group. At the end of the observation period, complete recanalization on FV was identified in 24 of 25 (95%) patients in the MPFF group compared with 15 of 20 (75%) patients in the control group (*P*=0.074). As for the PV, the adjunctive use of MPFF led to an increase in complete recanalization from 60% to 90% (*P*=0.015).

The reduction in thrombotic burden as assessed by the Marder score was more intensive with the adjunctive use of MPFF (*Figure 5*). At baseline, the thrombus extension in the MPFF group was significantly higher than in the control group (15.0±4.8 vs 11.1±4.3, respectively; *P*=0.002), but after 12 months of therapy, it was significantly lower (0.4±1.2 vs 2.1±2.6, respectively; *P*=0.003).

The specific measure for compliance with MPFF, rivaroxaban, and elastic compression stockings was not prespecified. However, none of the enrolled patients reported preliminary cessation of study drugs or elastic compression.

Discussion

Here, we present the findings of extended follow-up on 60 patients who were treated for popliteal-femoral DVT. The results obtained at 6 months have already shown a significant decrease in PTS by long-term use of MPFF.[33] Surprisingly, the cumulative incidence of PTS did not increase during the extended follow-up. In contrast, three patients received MPFF plus compression stockings, and one patient who used compression stockings alone dropped out of the criteria for PTS. That shows the high efficacy of conservative therapy to control the symptoms and signs of CVD.

Preexisting CVD is a well-established predisposing factor that increases the risk of PTS 1.5- to 3.2-fold.[10] This fact may be related to misdiagnosis of PTS by the Villalta score, for example, when preexisting CVD is considered a new PTS even without worsening of symptoms and signs,[39] or to true disease progression. In the current study, we encountered a higher prevalence of preexisting CVD in the control patients. This fact could affect the results, providing a higher

incidence of PTS in the control group. However, preexisting CVD did not increase the risk of PTS in this study: 35% of patients with CVD compared with 27% of patients without CVD were diagnosed with PTS (*P*=0.581). In contrast, CVD progression was strongly associated with PTS, and treatment with MPFF slowed this progression. Our data support the previous experimental findings on MPFF treatment reducing venous disease development and progression.[28,29]

The important findings from the extended follow-up concern the rate of DVT recurrence. Four new thrombotic events were observed after cessation of anticoagulation in control patients only. The significant trend for reduction in the recurrence rate with MPFF treatment was observed. These data should be interpreted with caution and be confirmed in more powerful trials. However, they may suggest some slight protective effects of MPFF on recurrent DVT owing to its anti-inflammatory action similar to statins.[40]

In comparison with ultrasound outcomes obtained at 6 months, no further significant recanalization was found. Thus, the most intensive process of thrombus clearance was observed within the first half-year. Treatment with MPFF improved deep-vein recanalization, probably due to its anti-inflammatory actions. This idea should be confirmed in future trials assessing inflammatory biomarkers. The most appropriate candidates are interleukin-6, intercellular adhesion molecule 1, soluble P-selectin, matrix metalloproteinase-9, and C-reactive protein.[14,41]

It is an essential finding that continuous treatment with MPFF was safe. No new AEs were reported after the first 6 months. This study is one of the few[20] that confirms the possibility of long-term treatment with MPFF without serious consequences.

The limitations of the study are related to its pilot and open design, small sample size, absence of placebo, and appropriate randomization. However, this study is the first to provide information on the influence of MPFF on the course of DVT and the size of this effect. That will allow making appropriate sample size calculations for further randomized controlled trials that should overcome the limitations of the current one. A new study evaluating the level of biomarkers is suggested.

Conclusion

The results of this pilot study suggest that long-term treatment with MPFF can increase the speed of deep-

vein recanalization and reduce the incidence of PTS at 12 months in patients with popliteal-femoral DVT treated with rivaroxaban. Continued MPFF intake may have an influence on DVT recurrence after cessation of anticoagulation treatment. These findings should be confirmed in more powerful randomized clinical trials.

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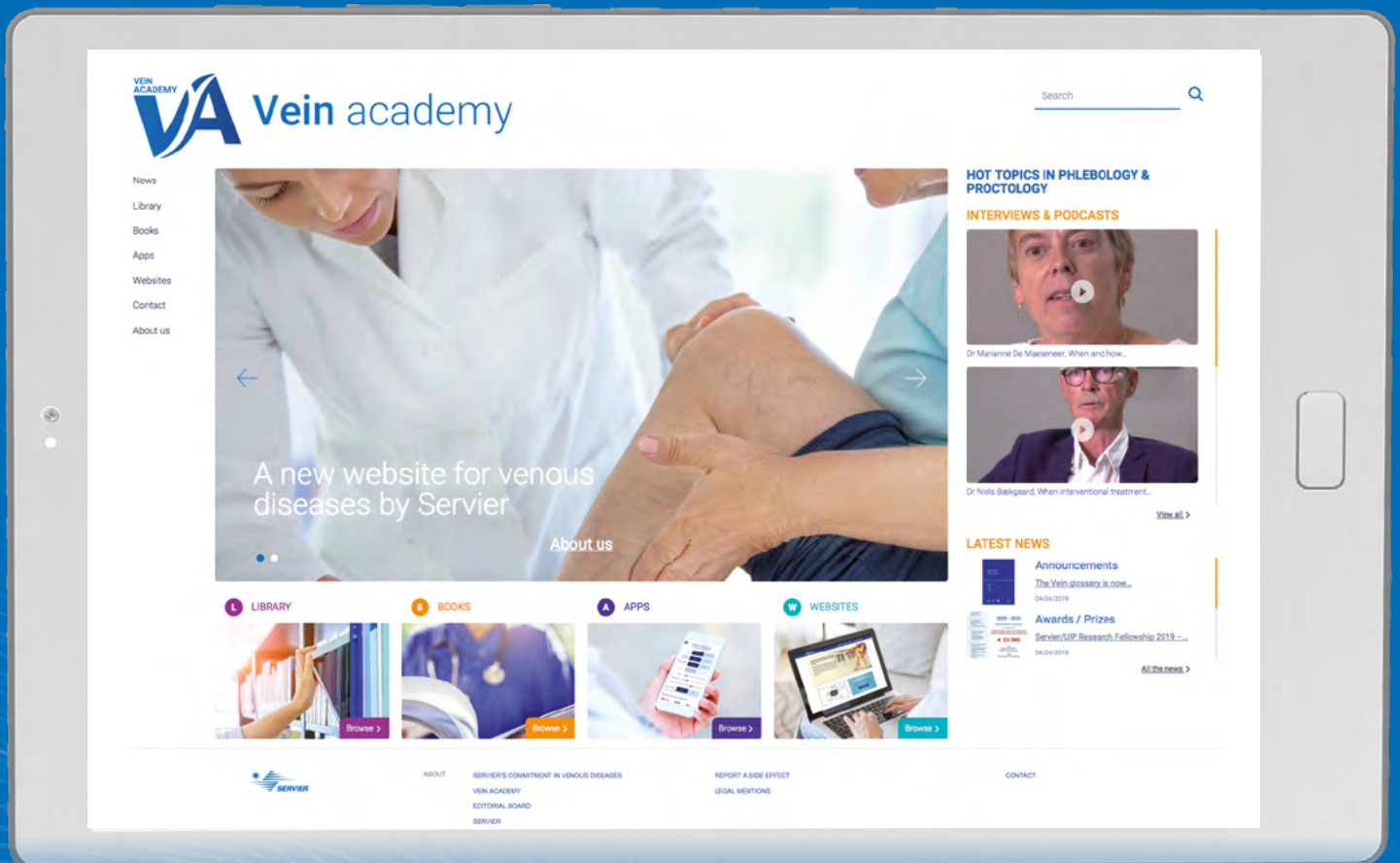
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For any information, please contact:

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