Rivaroxaban for thrombosis prophylaxis in endovenous laser ablation with and without phlebectomy

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ABSTRACT

Objective: Endovenous heat-induced thrombosis (EHIT) is a well-described complication of endovenous laser ablation (EVLA). We report our centers' experience on the efficacy (EHIT level ≥2 according to the Kabnick classification) and safety (observed major and minor bleeding events) of rivaroxaban for EHIT prophylaxis in EVLA with and without concomitant phlebectomy.

Methods: Demographic, procedural, and outcome data of all patients with EVLA of the great, accessory, or small saphenous vein and EHIT prophylaxis with 10 mg/d rivaroxaban between 2012 and 2014 were reviewed and analyzed in this investigator-initiated multicenter retrospective observational single-arm study.

Results: During a median (interquartile range) follow-up duration of 51 (41-68) days, complete vein occlusion was achieved in 98.4% of 438 EVLA procedures in 306 patients. One patient had an EHIT level 2 (0.2%; 95% confidence interval, 0.006%-1.3%). No major bleedings (0%; 95% confidence interval, 0.0%-0.8%) and six minor bleedings (1.4%; 95% confidence interval, 0.5%-3%) were observed.

Conclusions: Rivaroxaban (10 mg/d) for 5 to 10 days seems to be an efficacious and safe alternative for EHIT prophylaxis in EVLA with or without phlebectomy. (J Vasc Surg: Venous and Lym Dis 2017;5:515-23.)

Because of its less invasive nature and comparable efficacy, the Society for Vascular Surgery, among others, now recommends thermal vein ablation rather than high ligation and stripping for treatment of superficial truncal vein incompetence.[1,2] Endovenous laser allows precise delivery of laser energy directly to the vein wall with subsequent vein occlusion as a result of the thermal destruction of the endothelium and breakdown of intramural collagen. Many studies have demonstrated the safety of thermal ablative techniques with low complications rates. However, proximal thrombus propagation from the treated superficial vein into the deep vein, causing deep venous thrombosis or pulmonary embolism, is a well-described complication and was subsequently termed endovenous heat-induced thrombosis (EHIT).[3] Whereas early publications report an EHIT incidence of up to 16% using first-generation ablation catheters, recent studies and meta-analyses report an incidence of EHIT after endovenous laser ablation (EVLA) between 0% and 6.4%.[4-10] There is no generally accepted standard for postprocedural care after EVLA to promote the vessel occlusion process and to decrease the incidence of EHIT. Graduated compression stockings or an elastic wrap is placed on the limb at the end of the procedure by most centers, and patients are instructed to ambulate regularly to promote flow in the nontreated venous segments. The role of pharmacologic prophylaxis is more controversial. Common regimens include peri-interventional prescription of aspirin, prophylactic dose of unfractionated or low-molecular-weight heparin, and no pharmacologic prophylaxis at all.[11-15]

Rivaroxaban, a novel direct factor Xa inhibitor that is administered orally, is approved in many countries for the prevention of venous thromboembolism in patients undergoing total knee and hip arthroplasty. Clinical evaluation in the setting of orthopedic surgery has shown that a once-daily dose of rivaroxaban (10 mg) provides superior prevention against thromboembolism compared with the low-molecular-weight heparin enoxaparin (40 mg once daily or 30 mg twice daily) without increasing the rate of bleeding.[16-18]

A regimen of EVLA EHIT prophylaxis using rivaroxaban may therefore offer several advantages; it can be easily administered orally, and it may provide superior venous thromboembolism prophylaxis without increasing bleeding complications. However, data on the use of rivaroxaban in this application are lacking.

Therefore, the primary and secondary aims of this observational study were to report our three-center

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experience on the efficacy (observed incidence of EHIT level 2-4) and safety (observed incidence of bleeding complications) of rivaroxaban for EHIT prophylaxis in EVLA with and without phlebectomy.

METHODS

The medical records of all patients with endovenous thermal vein ablations performed at three medical centers (University Hospital Basel, Limmattal Hospital, and Vascular Center Rapperswil) between 2012 and 2014 were reviewed in this retrospective data analysis study using the venous reporting standards guidelines.[19] The study follows the principles outlined in the Declaration of Helsinki and was approved by the local Ethics Committee.

All patients signed a written informed consent before an EVLA procedure, agreeing to use of their data anonymously for publication. A waiver for an additional formal informed consent was granted from the Ethics Committee to retrospectively review charts of subjects meeting inclusion criteria. All patients who had EVLA of the great saphenous vein (GSV), accessory saphenous vein (ASV), or small saphenous vein (SSV) using 1470-nm-wavelength radial laser (ELVeS; Biolitec, Vienna, Austria) were included in this analysis. Patients were not included in the analysis if they had an endovenous ablation technique other than EVLA; veins other than the GSV, ASV, or SSV treated with EVLA (ie, perforators); and postinterventional EHIT prophylaxis other than a prophylactic dose (10 mg/d) of rivaroxaban (Bayer AG, Zurich, Switzerland).

Demographic data, preoperative risk factors, vein characteristics, procedural data including concomitant phlebectomies, and outcome data including ultrasound findings and complications were assessed as defined later. All data were collected and entered by a dedicated study nurse or the study investigators.

EVLA procedure

The current standard practice of EVLA procedures in all three clinics and data acquisition are described in detail.

Preoperative evaluation. Patients with previously untreated symptomatic GSV, ASV, or SSV evaluated at the participating centers form the basis of this study. Standard preoperative evaluation included a duplex ultrasound examination performed on an iU21 ultrasound machine (Philips Healthcare, Andover, Mass) in the standing position under similar environmental conditions by an experienced vascular physician. A reflux of >0.5 second in the target vein and a Clinical, Etiology, Anatomy, and Pathophysiology (CEAP) C classification between 2 (varicose veins) and 6 (active venous ulcer) along with symptoms attributed to the venous disease (eg, heavy legs) assigned by the examining vascular specialist were required for endovenous therapy. The extent of reflux observed on the duplex ultrasound scan was documented and classified according to Hach: Hach I, reflux from the saphenofemoral junction (SFJ) to proximal thigh or saphenopopliteal junction (SPJ) to proximal calf; Hach II, SFJ to distal thigh or SPJ to midcalf; Hach III, SFJ to proximal calf or SPJ to distal calf ; and Hach IV, SFJ to distal calf. If significant reflux was manifested in more than one vein, it was our routine to ablate the GSV and the SSV or ASV in the same leg at the same sitting. If reflux existed in both legs, it was our routine to treat the more symptomatic leg first and to treat the other leg in a second sitting. However, it was at the discretion of the operator to treat both legs in the same sitting (eg, if requested by the patient).

In patients with superficial thrombophlebitis at the initial preoperative evaluation, depending on the extension and location of the thrombus, subtherapeutic anticoagulation was prescribed and the EVLA procedure was performed not earlier than 4 to 6 weeks later in an asymptomatic state.

EVLA procedure. Before the procedure, a written informed consent was obtained. All procedures were performed in an ambulatory office-based setting under local tumescent anesthesia. Patients were placed in the supine position for GSV or ASV treatment and in the prone position for SSV treatment. A 16-gauge intravenous catheter (if an ELVeS slim radial fiber was used) or a 6F vascular sheath (if an ELVeS radial fiber was used) was placed under ultrasound guidance at the distal extent of the reflux in the target vein (GVS, SSV, or ASV). For the GSV and ASV, the laser catheter was advanced distal to the origin of the superficial epigastric vein or 1.0 to 2.0 cm caudal to the SFJ; at the SSV, the catheter tip was placed 2 to 3 cm caudal to the SPJ. Tumescent local anesthetic solution (500 mg of prilocaine, 0.5 mg of epinephrine diluted in 500 mL of saline) was infiltrated along the whole length of the target vein using a 20-gauge (0.9- × 70-mm) needle under ultrasound guidance. After sonographic confirmation of the correct laser catheter tip position, laser energy was administered at 7 to 8 W power using a continuous setting, aiming for a linear energy delivery target of

ARTICLE HIGHLIGHTS

- **Type of Research:** Retrospective multicenter uncontrolled cohort study
- **Take Home Message:** In 438 EVLA procedures, a 10-day regimen of 10 mg of rivaroxaban daily resulted in one EHIT, no major bleeding complications, and six minor bleeding complications.
- **Recommendation:** The authors suggest that rivaroxaban can lower the incidence of EHIT in patients undergoing EVLA.

60 to 80 J/cm during slow pullback of the EVLA catheter. We did not measure the exact treatment length; however, in general, we ablated the refluxing vein segments completely; thus, we routinely ablated the GSV below the knee in patients with Hach III and IV reflux. In patients with varicose tributaries (clinically visible or >3 mm in diameter on ultrasound) or insufficient perforators (>3.5 mm in diameter on ultrasound), as a standard, concomitant phlebectomy was performed with 1- to 3-mm incisions over varicosities by using a hook (Oesch; Salzmann AG, St. Gallen, Switzerland) after laser ablation. Concomitant foam sclerotherapy was performed alone or in addition to phlebectomy using up to 10 mL of 1% to 3% aethoxysklerol mixed 1:4 with air in patients with neovascularization or tributaries of perforators (C2 or greater disease). An eccentric compression of the EVLA-treated vein and the phlebectomy incisions was applied by using sterile gauze rolls or foam pelottes (Toblero; 1a medical, Hettlingen, Switzerland) and a full-length graduated compression stocking class II (23 to 32 mm Hg; Salzmann Medico or Sigvaris, St. Gallen, Switzerland).[20]

As a standard, all EVLA patients were prescribed prophylactic-dose (10 mg/d) rivaroxaban unless the patient was already receiving therapeutic anticoagulation because of another medical condition (eg, patients taking phenprocoumon [Marcoumar] because of atrial fibrillation) or anticipated interactions with other drugs. Rivaroxaban was chosen as the standard antithrombotic drug for EHIT prophylaxis at our institutions as there is no other drug (ie, enoxaparin) formally approved for this indication, and rivaroxaban offers the convenience of oral administration along with a noninferior safety and efficacy profile as demonstrated in other settings. A dose of 10 mg/d was chosen as in the setting of orthopedic surgery, a once-daily dose of rivaroxaban (10 mg) was proven to be safe and effective for thrombosis prevention.[16,17] The first dose of rivaroxaban 10 mg was administered right after the procedure and prescribed for another 10 days once daily. Recognizing that so far no EHIT was recorded, one center reduced the duration of rivaroxaban to 5 days during the observed period. All patients were asked to walk immediately after the procedure and to return to normal activities as soon as they felt comfortable. A short course (2 days at least, up to 10 days as needed) of nonsteroidal anti-inflammatory drugs and a proton pump inhibitor (ie, pantoprazole 20 mg) were prescribed for all patients with no contraindications.

Compression stockings were recommended for another 2 to 3 weeks, except during sleep and baths.

Follow-up. All patients were followed up on an outpatient basis for medical history, physical examination, and duplex ultrasound examination at day 1 and 4 to 6 weeks after the procedure; in one center, an additional examination was also performed regularly after 1 week. The eccentric compression dressing was removed, and the presence of hematoma, dysesthesia, and superficial thrombophlebitis were recorded. Duplex ultrasound of the superficial and deep venous system was performed in the supine position, assessing for successful saphenous vein ablation and deep venous thrombosis. If a saphenous vein segment was compressible and thus appeared nonoccluded, the segment was also examined in the standing position for any reflux.

Definition of outcome parameters

The primary and secondary aims of this observational study are efficacy (observed incidence of EHIT level 2-4) and safety (observed incidence of bleeding complications) of rivaroxaban 10 mg once daily for EHIT prophylaxis in EVLA with and without phlebectomy as specified later. All primary and secondary outcome events (EHIT > level 1 and any bleeding) as well as all adverse events as defined later were centrally adjudicated by two experienced vascular specialists at the University Hospital of Basel. In situations of disagreement about the adjudication of an event, cases were reviewed and adjudicated in conjunction with a third independent vascular specialist.

EHIT (efficacy end point). The distance of the occluded vein or thrombus in relation to the SFJ or SPJ recorded during the follow-up duplex ultrasound examinations was reviewed and classified according to an adjusted Kabnick classification (Fig 1).[3]

Bleeding events (safety end point). Major bleeding was defined as bleeding that was fatal, occurred in a critical organ (eg, retroperitoneal, intracranial, intraocular, and intraspinal bleeding), or required operation or extrasurgical site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g/dL or that required transfusion of 2 units or more of whole blood or packed cells.[16,17] Other safety outcomes included any nonmajor (minor) bleeding (ie, at least one episode of clinically apparent melena/hematemesis, spontaneous gingival bleeding or epistaxis lasting for >5 minutes) and hemorrhagic wound complications (excessive wound hematoma or wound hematoma leading to an unplanned consultation, hospitalization, or prolonged inability to work). Noteworthy, as a standard, all patients who contact our offices and complain about complications are asked to show up for a face-to-face consultation with the treating physician to ensure an optimal standard of care. Bleeding events that started after the first oral dose of rivaroxaban and were observed during the follow-up period were recorded.

Other adverse events. Medical records were reviewed for adverse events potentially related to rivaroxaban. An adverse event was defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the

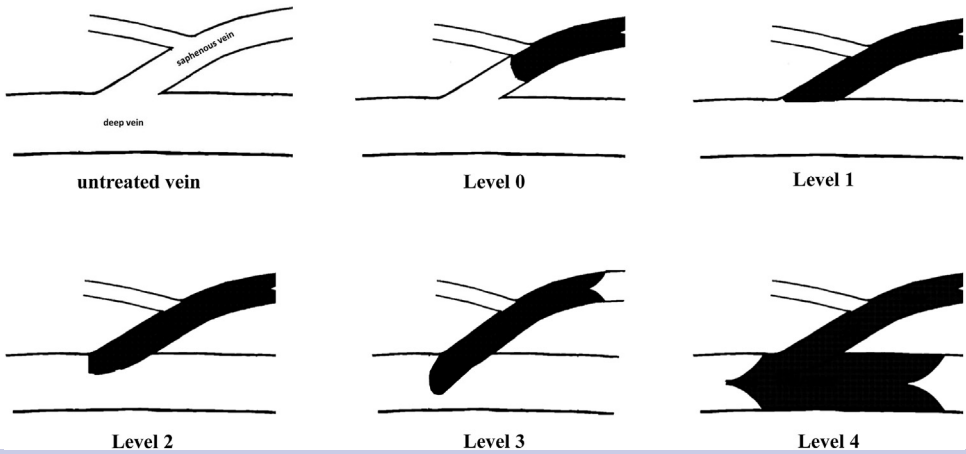

Fig 1. Endovenous heat-induced thrombosis (EHIT) classification (adjusted Kabnick classification). Level 0: venous thrombosis of the superficial vein, not extending to the saphenofemoral junction (SFJ) or saphenopopliteal junction (SPJ). Level 1: venous thrombosis to the SFJ or SPJ, not extending into the deep venous system. Level 2: nonocclusive venous thrombosis projecting to the deep venous system, whereby the cross-sectional area of thrombus in the deep vein is <50%. Level 3: as in level 2, but with cross-sectional area in the femoral vein of the thrombus >50%. Level 4: occlusive deep venous thrombosis.

use of rivaroxaban, whether or not it was considered related to rivaroxaban. The assessment of the relationship of an adverse event to the administration of rivaroxaban is a clinical decision based on all available information at the time of the completion of the study and was performed by two experienced vascular specialists as outlined before.

Statistical analysis

The distribution of summary demographic and clinical parameters was tested using the Shapiro-Wilks test and expressed as mean ± standard deviation or median ± interquartile range as appropriate. The incidence of each EHIT level and the incidence of all complications are reported in absolute and relative numbers including corresponding 95% confidence intervals. The χ^2 test, Fisher exact test, and Mann-Whitney *U* test were used for comparisons between the two rivaroxaban groups (5 and 10 days). Analyses were performed using SPSS version 22 software package (IBM Corp, Armonk, NY).

RESULTS

A total of 513 EVLA interventions in 348 symptomatic patients were performed between January 2012 and December 2014. Fifteen patients (27 EVLA procedures) were receiving permanent therapeutic anticoagulation because of other medical conditions and received no additional EHIT prophylaxis, and 27 patients (48 EVLA procedures) received an EHIT prophylaxis other than rivaroxaban (45, low-molecular-weight heparin; 3, dual antiplatelet therapy) and were excluded from the present analysis, resulting in 438 EVLA procedures in 306 patients with rivaroxaban 10 mg EHIT prophylaxis included in this analysis. In 278 patients (402 EVLA procedures), the duration of rivaroxaban EHIT prophylaxis was 10 days; in 32 patients (36 procedures performed at one center between January 2014 and December 2014), the duration of rivaroxaban EHIT prophylaxis was 5 days (including four patients who had two interventions, receiving rivaroxaban for 10 days after the first intervention and for 5 days after the second one; Fig 2). Table I summarizes patients and procedure data, and Table II summarizes the main outcome data. In the same sitting, we ablated the GSV and SSV in 28 patients, the GSV of both sides in 7 cases, the GSV and ASV in 1 case, and the SSV of both sides in 1 case. As we did not record the exact treatment length, we cannot report on the minimum/maximum or average length of ablation; however, given the average treatment time and energy delivered, it is reasonable to speculate that the average treatment length was approximately 35 to 40 cm. An additional treatment of the tributaries was performed in 96.1% of the patients, concomitant phlebectomy in 79.2%, sclerotherapy in 5.7%, and a combination of phlebectomy and sclerotherapy in 11.2% of the patients. No additional staged procedures were performed within the follow-up period. Of note, the percentage of patients with a history of a previous deep venous thrombosis (5.9%) is higher in our cohort than in the general population, maybe reflecting that as our institutes are well-known regional centers, a selection bias for more complex venous patients might have occurred.

All patients had completed the first regular follow-up examination at the first postinterventional day; in all but four patients (four procedures [99.1%]), follow-up data including a dedicated ultrasound examination after

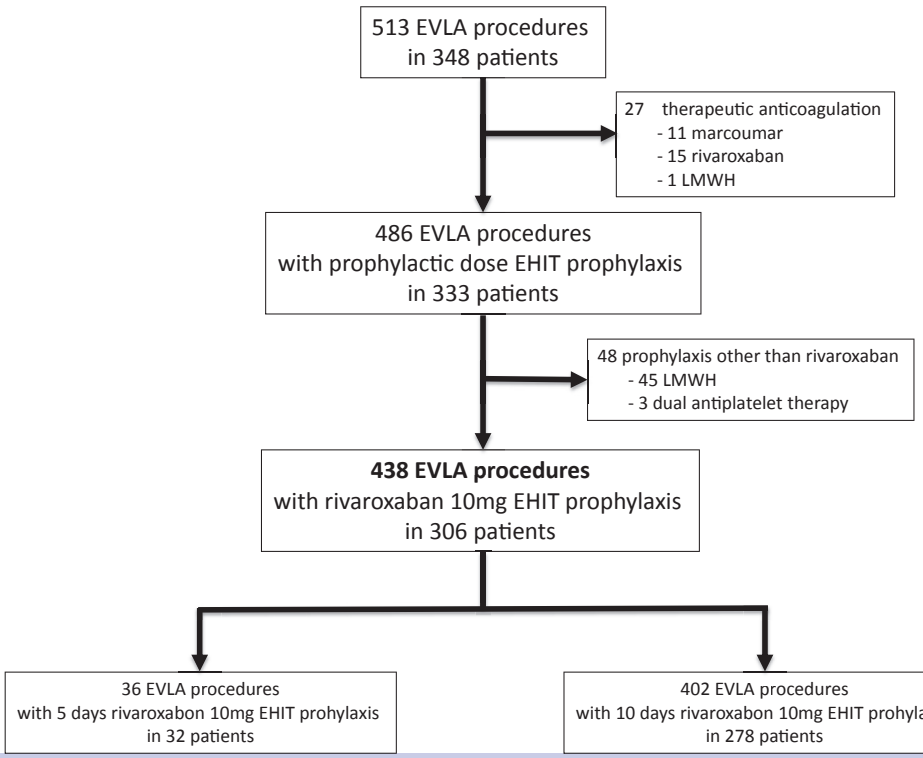

Fig 2. Study flow. *EHIT,* Endovenous heat-induced thrombosis; *EVLA,* endovenous laser ablation; *LMWH,* low-molecular-weight heparin.

a median of 51 days were available. One patient with EVLA of the SSV and concomitant phlebectomy had an asymptomatic EHIT level 2 diagnosed at the day 1 visit. In this patient, rivaroxaban 20 mg was prescribed for 6 weeks, with resolution of the thrombus at the 6-week follow-up duplex ultrasound scan and without any clinical symptoms of a pulmonary embolism; thus, rivaroxaban was stopped. No EHIT was observed in the 113 patients in whom an additional follow-up examination was performed after 1 week.

No anticoagulation was prescribed in the patients with EHIT level 1. No major and six minor bleedings were observed. One patient reported increased menorrhagia leading to inability to work for 3 days, three patients had an unplanned consultation because of painful hematoma at a phlebectomy site (treated with conservative measures only), one patient had an unplanned consultation because of persistent bleeding at a phlebectomy site 2 days after intervention (treated with a single ligature), and one patient had an infected hematoma at a phlebectomy site 1 week after intervention (treated with an incision and oral antibiotics). All bleeding events occurred in the rivaroxaban 10-day group and none in the 5-day group ($P = .355$). Based on the study population of 438 procedures, the incidence of EHIT level ≥2 was 0.2% (95% confidence interval, 0.006%-1.3%), and the incidence of major and minor bleedings was 0% (95% confidence interval, 0.0%-0.8%) and 1.4% (95% confidence interval 0.5%-3%), respectively.

No adverse events potentially attributed to rivaroxaban were documented in the medical records. Although there was no disagreement about the adjudication of the end points by the two vascular specialists, all patients with a potential bleeding end point (n = 9) were also reviewed by a third independent vascular specialist who also agreed to the adjudication.

DISCUSSION

This study reports on the efficacy and safety of orally administered rivaroxaban for EHIT prophylaxis after EVLA. It demonstrates in a multicenter setting including >400 interventions that a 10-day regimen of rivaroxaban 10 mg seems to be an efficient and safe option for EHIT prophylaxis in EVLA with and without phlebectomy. Results in a small subgroup of 36 patients suggest that rivaroxaban 10 mg/d for 5 days only may be as effective as 10 days in preventing EHIT.

Undoubtedly, since its introduction in the late 1990s, EVLA for treatment of varicose veins is a success story. EVLA procedures increased markedly in the last years, and nowadays EVLA represents one of the most common forms of intervention worldwide. However, EVLA gives rise to the possibility of EHIT, the extension of thrombus from the GSV or SSV into the deep venous system at a site of recent thermoablation. Fortunately, given

Table I. Patient and procedure data

	All	Rivaroxaban, 10 days	Rivaroxaban, 5 days	*P* value
EVLA procedures	438	402	36	
Patients	306	278	32	
Female	317 (72.4)	294 (73.1)	23 (63.9)	.235
Age, years	54 (41-66)	54 (41-66)	51 (40-63)	.540
Personal history of				
DVT/PE	26 (5.9)	25 (6.2)	1 (2.8)	.817
Superficial thrombophlebitis	44 (10.0)	41 (10.2)	3 (8.3)	.765
Intervention side right	222 (50.7)	201 (50.0)	21 (58.3)	.328
Treated vein				.234
GSV	343 (78.5)	318 (79.3)	25 (69.4)	
SSV	77 (17.6)	66 (16.5)	11 (30.6)	
Anterior ASV	13 (3.0)	13 (3.2)	0	
Posterior ASV	4 (1.0)	4 (1.0)	0	
Maximum vein diameter, mm	7 (5-9)	7 (5-9)	7 (5-9)	.987
Hach classification				.730
I	15 (3.7)	12 (3.2)	3 (8.3)	
II	99 (24.3)	92 (24.8)	7 (19.4)	
III	214 (52.6)	197 (53.1)	17 (47.2)	
IV	79 (19.4)	70 (18.9)	9 (25)	
CEAP clinical stage				.009
C2	228 (52.3)	218 (54.6)	10 (27.8)	
C3	122 (28.0)	108 (27.0)	14 (38.9)	
C4	73 (16.7)	62 (15.5)	11 (30.6)	
C5-6	13 (3.0)	12 (3.1)	1 (2.8)	
Applied energy, joules	2771 (1652-3550)	2785 (1688-3560)	2144 (1327-3041)	.048
Application time, seconds	356 (216-460)	356 (217-464)	315 (200-402)	.137
Concomitant phlebectomy	396 (90.4)	370 (92.1)	26 (72.2)	.051
Concomitant sclerotherapy	74 (16.9)	69 (17.2)	5 (13.9)	.052

ASV, Accessory saphenous vein; *CEAP,* Clinical, Etiology, Anatomy, and Pathophysiology class; *DVT,* deep venous thrombosis; *EVLA,* endovenous laser ablation; *GSV,* great saphenous vein; *SSV,* small saphenous vein; *PE,* pulmonary embolism.
Data indicate median (interquartile range) or number (%). *P* values indicate between-group differences.

the ongoing improvement of both technical equipment and operators' experience, the reported incidence of EHIT has substantially declined over time. EHIT incidence rates as low as 0% to 1% have been reported, questioning the need for any pharmacologic EHIT prophylaxis.[9,10,21] Recent publications, though, report EHIT incidence of 2.4% to 6% in series not using standard EHIT prophylaxis.[7,22,23] Treating otherwise, for the most part, healthy and highly demanding patients, these rates are unacceptably high.

In daily routine, several centers therefore use prophylactic-dose low-molecular-weight heparin as standard EHIT prophylaxis, but robust data showing the effectiveness of this approach are currently lacking. Furthermore, the injection of the low-molecular-weight heparin causes patients discomfort and is occasionally associated with local hematoma at the injection sites. Thus, the use of rivaroxaban for EHIT prophylaxis, a direct factor Xa inhibitor, may offer some advantages. First, it is administered orally, thus enhancing patients' comfort, which may finally lead to better adherence to the prescribed prophylaxis regimen. Second, clinical evaluation in the setting of orthopedic surgery indicated that rivaroxaban might be more effective for prevention against thromboembolism compared with the low-molecular-weight heparin enoxaparin without increasing the rate of bleeding.[16-18] Our multicenter experience presented in this study supports the hypothesis that rivaroxaban 10 mg/d is also effective and safe in patients with EVLA. However, because of the lack of a control arm, no reliable conclusion on the effectiveness compared with low-molecular-weight heparin or placebo can be drawn, and given the study size and low incidence rates, the precision of the reported estimation of incidence rates is limited. In this regard, we would like to emphasize that although we did not observe any major bleeding complication, our sample size is likely to be insufficient to truly characterize the

Table II. Outcome data

	All	Rivaroxaban, 10 days	Rivaroxaban, 5 days	*P* value
Follow-up duration, days	51 (41-68)	51 (41-69)	45 (43-55)	
EVLA-treated veins	438	402	36	.153
Complete occlusion	425 (98.4)	392 (98.7)	33 (94.3)	—
Partial occlusion	6 (1.4)	4 (1.0)	2 (5.6)	—
Complete recanalization	1 (0.2)	1 (0.3)	0	—
Highest EHIT level during follow-up[a]				.947
0	419 (95.7)	384 (95.6)	35 (97.2)	—
1	18 (4.1)	17 (4.2)	1 (2.8)	—
2	1 (0.2)[d]	1 (0.2)[d]	0	—
3	0	0	0	—
4	0	0	0	—
Major bleeding[b]	0	0	0	—
Minor bleeding[c]	6 (1.4)	6 (1.5)	0	.596
Superficial thrombophlebitis	15 (3.4)	13 (3.0)	2 (5.6)	.361
Inability to work, days				<.001
0-1	226 (51.6)	194 (48.3)	32 (88.9)	
2-3	105 (24.0)	103 (25.6)	2 (5.6)	
4-7	87 (19.9)	85 (21.1)	2 (5.6)	
>7	20 (4.6)	20 (5.0)	0 (0)	

EHIT, Endovenous heat-induced thrombosis; *EVLA*, endovenous laser ablation.
Data indicate median (interquartile range) or number (%). *P* values indicate between-group differences.
[a]Adjusted Kabnick classification.
[b]Bleeding that was fatal, occurred in a critical organ, or required operation or extrasurgical site bleeding that was clinically overt and was associated with a fall in the hemoglobin level of at least 2 g/dL or that required transfusion of 2 units or more of whole blood or packed cells.
[c]Any nonmajor (minor) bleeding leading to an unplanned consultation, hospitalization, or prolonged inability to work.
[d]One patient with EVLA of the small saphenous vein (SSV) and concomitant phlebectomy had an asymptomatic EHIT level 2 diagnosed at the day 1 visit.

potential for serious (ie, intracranial) or major retroperitoneal bleedings.

We cannot exclude that we might have missed EHIT events between our standard follow-up examinations at day 1 and week 4 to 6; however, no EHIT was discovered in the 113 patients in whom an additional examination at 1 week was performed. Furthermore, no symptomatic EHIT or thrombotic event was reported in our cohort, and any asymptomatic EHIT that has resolved and therefore been missed at the 4- to 6-week examination is likely to be of no clinical relevance. Variations in procedural factors that have been shown to influence the incidence of EHIT, including the distribution of CEAP class among the patients treated, the average vein diameter treated, the frequency of concomitant phlebectomy, and the frequency and timing of follow-up examinations, may explain, at least partially, differences in EHIT rates.[9,22,23] For example, a recent study by Ryer et al showed that a substantial portion (44%) of patients with EHIT would not have been identified with a single postoperative scan performed 24 hours after the intervention. Furthermore, the optimal distance of the fiber to the SFJ still has to be determined. Some data indicate that a distance of 2 to 3 cm might be beneficial to decrease the EHIT rate. However, in contrast to the first bare laser fibers used, latest-generation radial fibers nowadays allow precise and targeted ablation at the level of the SFJ. Indeed, many experienced operators now start the ablation directly at the SFJ to reduce varicose vein recurrences through tributaries at the level of the SFJ (ie, the anterior ASV). We used a treatment protocol with a distance of 1 to 2 cm to the SFJ, aiming to occlude the origin of the anterior and posterior saphenous vein in most cases. More data are needed to clarify this important issue.[24] The observed EHIT rate of 0.2% with a 95% confidence interval of 0.006% to 1.3% in our study along with the low rate of observed minor bleedings (1.4%) compares favorably with other reports. Including >400 EVLA procedures performed at three different centers with a high rate (>90%) of concomitant phlebectomy and a stringent standard follow-up resulting in at least two duplex ultrasound scans performed by experienced vascular physicians in 99% of the patients analyzed indicates a low likelihood of selection bias and high follow-up quality, ensuring the comparability of our results. Of course, owing to the retrospective, single-arm observational design of our study, selection and allocation bias as well as confounding cannot be excluded completely, and only descriptive analyses could be performed. Furthermore, although a standardized follow-up schema, including a thorough clinical

and duplex ultrasound examination by experienced vascular physicians at several time points, is institutionalized at our centers, we did not collect data on adverse events prospectively and thus cannot exclude underreporting of minor adverse events (eg, nausea). We also did not specifically record the amount of bruising in our patients, which may have caused increased discomfort or prolonged recovery times; however, the return to regular activities was likely shorter than the time to return to work.

Although the prescription of rivaroxaban is associated with additional costs (currently approximately 46 CHF/53 USD for 10 days) in the beginning, one might argue that its effectiveness might allow further follow-up ultrasound scans to be omitted, thus saving even more money later on. However, because of the lack of a control arm, we also cannot report the number needed to treat with rivaroxaban to prevent one clinically significant EHIT or deep venous thrombosis and thus the cost-effectiveness of our approach. Although it is reasonable to believe that the major risk for significant thrombotic complications would be early after the procedure, particularly while the patient's level of ambulation and activity are decreased, we know from other clinical settings (hip and knee replacement) that the prothrombotic state after a procedure may last up to several weeks. As demonstrated by Ryer et al, a substantial portion (44%) of EHITs seem to develop between day 1 and the first week after ablation; thus, in our opinion, it is reasonable to believe that for effective EHIT prevention, a pharmacologic thromboembolism prophylaxis duration of at least several days is required. The smallest package of rivaroxaban 10 mg on the market contained 10 pills; thus, we initially decided somewhat arbitrarily to start with a standard EHIT prophylaxis for 10 days. Again, somewhat arbitrarily, the duration of EHIT prophylaxis was shortened from 10 to 5 days in one center, recognizing that so far no EHIT was recorded and a duration of 5 days might be even more cost-effective and may further reduce the risk of bleeding complications. Surely, this approach demands further scientific evaluation before it can be recommended, and better understanding of the timing, procedural risk factors, and significance of EHIT is needed to finally determine the optimal risk-benefit and cost-effective care for patients after EVLA for varicose veins.

Given the overall low incidence of EHIT observed in our study and other studies, we have no doubt that not all patients might require a pharmacologic EHIT prophylaxis. The Caprini risk score, used as an assessment tool for the occurrence of venous thromboembolism among general surgery patients, has been proposed to be used to identify patients at high risk, but preliminary data indicate that it might not perform well in the setting of EVLA.[25]

Undoubtedly, our study cannot provide final conclusions on the effectiveness and safety of rivaroxaban for EHIT prophylaxis, emphasizing that there is a strong clinical need for well-conducted, large-scale prospective randomized studies comparing different schemas of EHIT prophylaxis.

CONCLUSIONS

This study indicates that orally administered rivaroxaban (10 mg/d) for 10 days is an efficacious and safe option for EHIT prophylaxis in EVLA with and without phlebectomy and suggests that even 5 days of treatment could have the same efficacy.

AUTHOR CONTRIBUTIONS

Conception and design: HU, DH, PB, DS, LS
Analysis and interpretation: HU, DH, PB, DS, LS
Data collection: HU, DH, PB, DS, LS
Writing the article: HU
Critical revision of the article: DH, PB, DS, LS
Final approval of the article: HU, DH, PB, DS, LS
Statistical analysis: HU
Obtained funding: HU
Overall responsibility: HU

REFERENCES

1. Gloviczki P, Comerota AJ, Dalsing MC, Eklof BG, Gillespie DL, Gloviczki ML, et al. The care of patients with varicose veins and associated chronic venous diseases: clinical practice guidelines of the Society for Vascular Surgery and the American Venous Forum. J Vasc Surg 2011;53(Suppl):2S-48S.
2. Marsden G, Perry M, Kelley K, Davies AH. Guideline Development Group. Diagnosis and management of varicose veins in the legs: summary of NICE guidance. BMJ 2013;347:f4279.
3. Kabnick L, Agis H, Almeida J, Moritz M, Spreafico G, editors. Endovenous heat induced thrombus (EHIT) following endovenous vein obliteration: to treat or not to treat? A new thrombotic classification. Third International Vein Congress; Miami, Fla; April 14-16 2005.
4. Hingorani AP, Ascher E, Markevich N, Schutzer RW, Kallakuri S, Hou A, et al. Deep venous thrombosis after radiofrequency ablation of greater saphenous vein: a word of caution. J Vasc Surg 2004;40:500-4.
5. Marsh P, Price BA, Holdstock J, Harrison C, Whiteley MS. Deep vein thrombosis (DVT) after venous thermoablation techniques: rates of endovenous heat-induced thrombosis (EHIT) and classical DVT after radiofrequency and endovenous laser ablation in a single centre. Eur J Vasc Endovasc Surg 2010;40:521-7.
6. Rhee SJ, Cantelmo NL, Conrad MF, Stoughton J. Factors influencing the incidence of endovenous heat-induced thrombosis (EHIT). Vasc Endovascular Surg 2013;47:207-12.
7. Kane K, Fisher T, Bennett M, Shutze W, Hicks T, Grimsley B, et al. The incidence and outcome of endothermal heat-induced thrombosis after endovenous laser ablation. Ann Vasc Surg 2014;28:1744-50.
8. Nesbitt C, Bedenis R, Bhattacharya V, Stansby G. Endovenous ablation (radiofrequency and laser) and foam sclerotherapy versus open surgery for great saphenous vein varices. Cochrane Database Syst Rev 2014;7:CD005624.

9. Sufian S, Arnez A, Labropoulos N, Lakhanpal S. Endovenous heat-induced thrombosis after ablation with 1470 nm laser: incidence, progression, and risk factors. Phlebology 2015;30:325-30.
10. Dermody M, Schul MW, O'Donnell TF. Thromboembolic complications of endovenous thermal ablation and foam sclerotherapy in the treatment of great saphenous vein insufficiency. Phlebology 2015;30:357-64.
11. Knipp BS, Blackburn SA, Bloom JR, Fellows E, Laforge W, Pfeifer JR, et al. Endovenous laser ablation: venous outcomes and thrombotic complications are independent of the presence of deep venous insufficiency. J Vasc Surg 2008;48:1538-45.
12. Proebstle TM, Gül D, Lehr HA, Kargl A, Knop J. Infrequent early recanalization of greater saphenous vein after endovenous laser treatment. J Vasc Surg 2003;38:511-6.
13. Harlander-Locke M, Jimenez JC, Lawrence PF, Derubertis BG, Rigberg DA, Gelabert HA, et al. Management of endovenous heat-induced thrombus using a classification system and treatment algorithm following segmental thermal ablation of the small saphenous vein. J Vasc Surg 2013;58:427-31.
14. Haqqani OP, Vasiliu C, O'Donnell TF, Iafrati MD. Great saphenous vein patency and endovenous heat-induced thrombosis after endovenous thermal ablation with modified catheter tip positioning. J Vasc Surg 2011;54(Suppl):10S-7S.
15. Hamel-Desnos C, Desnos P, Allaert FA, Kern P. "Thermal group" for the French Society of Phlebology and the Swiss Society of Phlebology. Thermal ablation of saphenous veins is feasible and safe in patients older than 75 years: a prospective study (EVTA study). Phlebology 2015;30:525-32.
16. Eriksson BI, Borris LC, Friedman RJ, Haas S, Huisman MV, Kakkar AK, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after hip arthroplasty. N Engl J Med 2008;358:2765-75.
17. Lassen MR, Ageno W, Borris LC, Lieberman JR, Rosencher N, Bandel TJ, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty. N Engl J Med 2008;358:2776-86.
18. Turpie AG, Lassen MR, Davidson BL, Bauer KA, Gent M, Kwong LM, et al. Rivaroxaban versus enoxaparin for thromboprophylaxis after total knee arthroplasty (RECORD4): a randomised trial. Lancet 2009;373:1673-80.
19. Porter JM, Moneta GL. Reporting standards in venous disease: an update. International Consensus Committee on Chronic Venous Disease. J Vasc Surg 1995;21:635-45.
20. Bakker NA, Schieven LW, Bruins RM, van den Berg M, Hissink RJ. Compression stockings after endovenous laser ablation of the great saphenous vein: a prospective randomized controlled trial. Eur J Vasc Endovasc Surg 2013;46:588-92.
21. Jones RT, Kabnick LS. Perioperative duplex ultrasound following endothermal ablation of the saphenous vein: is it worthless? J Invasive Cardiol 2014;26:548-50.
22. Ryer EJ, Elmore JR, Garvin RP, Cindric MC, Dove JT, Kekulawela S, et al. Value of delayed duplex ultrasound assessment after endothermal ablation of the great saphenous vein. J Vasc Surg 2016;64:446-51.e1.
23. Shutze WP, Kane K, Fisher T, Doud Y, Lassiter G, Leuking R, et al. The effect of wavelength on endothermal heat-induced thrombosis incidence after endovenous laser ablation. J Vasc Surg Venous Lymphat Disord 2016;4:36-44.
24. Nelzén O. Reconsidering the endovenous revolution. Br J Surg 2016;103:939-40.
25. Wagstaff A, Goodyear S, Nyamekye I. Risk adjusted DVT prophylaxis for ambulatory varicose vein procedures: how useful is the Caprini risk assessment model? Seventeenth Annual Meeting of the European Venous Forum; London; July 7-9, 2016.

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INVITED COMMENTARY

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This study raises an important question about endovenous laser therapy for superficial venous disease. Do the benefits of treatment with an anticoagulant outweigh the risk of bleeding complications or exceed (or mitigate) the risk of endovenous heat-induced thrombosis (EHIT)? This manuscript does not have me convinced that it does.

Most relevant is the lack of a control arm for comparison of outcomes as far as EHIT and technical success. The authors cite six studies, half of which demonstrate a relatively low EHIT rate of 0% to 2% (see references 9, 10, 21) and the other half of which demonstrate EHIT rates between 2% and 5% (see references 7, 22, 23). None of them conform to the methods or structure of the present study (eg, one includes the use of foam sclerotherapy, another uses different ablation modalities), and all of their follow-up protocols are different. In some cases, it is hard to distinguish the level of EHIT to exclude EHIT <2 for comparison. Hence, in the context of this analysis and in the absence of a control arm, there is little to truly understand the risk of no prophylaxis.

The data are confounded by the inclusion of myriad treatment algorithms that may influence outcome and end point. The ablation of both legs simultaneously in some cases, the anticoagulant treatment of patients with thrombophlebitis preoperatively, the use of up to 10 mL of foam sclerotherapy, and, most relevant, that the treatment protocol changed in one center from 10 to 5 days make the data less compelling. Six percent of patients had a prior deep venous thrombosis, higher because of referral patterns, yet reflective of some differences compared with the population at large.

Last, the occurrence of several complications that the authors deem inconsequential should be lent greater scrutiny. The loss of work days, the presence of painful