Evaluation of anticoagulant and antiplatelet therapy after iliocaval stenting: Factors associated with stent occlusion

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ABSTRACT

Objective: Iliocaval stenting has gained increased use over recent years for a variety of indications, including May-Thurner syndrome (MTS), post-thrombotic syndrome (PTS), and acute deep vein thrombosis (DVT).

Methods: A retrospective review of 155 patients undergoing iliocaval venous stenting at a large teaching hospital was performed. Clinical and procedural data, mode and duration of anticoagulation or antiplatelet therapy, and outcomes were recorded.

Results: Forty-five patients were treated for MTS, 49 for PTS. and 61 for acute DVT. The median follow-up was 19 months (interquartile range, 9-30 months). Primary patency rates were 97.8% in the MTS group, 85.7% in PTS, and 85.2% for the acute DVT group. Stent restenosis or occlusion occurred in one patient with MTS (2.2%), seven patients with PTS (14%), and nine patients with acute DVT (15%). An ipsilateral DVT recurred in 7 patients with PTS (14%) and 15 patients with acute DVT (25%). The stents that occluded had a tendency toward longer length (162.2 vs 125.2 mm; P = NS) and extension into the common femoral vein (18.8 vs 5.3%; P = NS). The patent stent group had statistically larger nominal diameter stents (P = .013). The duration of anticoagulation did not seem to be a significant factor in stent patency.

Conclusions: Stent diameter has a significant influence on iliocaval stent patency rates. (J Vasc Surg: Venous and Lym Dis 2019;7:527-34.)

Keywords: Post-thrombotic syndrome; May-Thurner syndrome; Iliac vein stent; Venous thrombosis

Iliocaval stenting has gained increased use over recent years for a variety of indications, including deep venous thrombosis (DVT) and May-Thurner Syndrome (MTS), among others.[1] Symptoms of venous outflow obstruction such as pain, edema, and ulceration have been shown to improve after iliac vein stenting, compared with medical therapy.[1,2] There is currently no consensus on the optimal medical therapy for patients after iliocaval stenting. Anticoagulant and antiplatelet agents have been used in varying dosages and durations. After implantation of an iliocaval stent, anticoagulant or antiplatelet therapy has been used to prevent thrombosis, restenosis, or occlusion. In a 2014 systematic review of venous stent placement trials after DVT, 86% of patients received anticoagulation and 33% received antiplatelet therapy.[3] In a series reported by Raju and Neglen,[4] only patients with thrombophilia received warfarin.

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METHODS

The authors retrospectively obtained all records of patients who underwent iliocaval venous stenting from January 2013 through September 2017 at Yale New Haven Hospital. Pharmacy records were collected. Clinical and procedural data, follow-up, and outcomes were obtained from the electronic medical records. All patients were symptomatic.

C classification of disease severity was recorded in the MTS and post-thrombotic syndrome (PTS) groups. Before the procedure all patients had at least one of ultrasound color duplex, computed tomography, or magnetic resonance venography. The procedure included venous access via the popliteal or common femoral vein (CFV). Venography was performed using iodinated contrast. The Volcano (Phillips, Amsterdam, the Netherlands) 0.35 system was used for intravascular ultrasound (IVUS). The self-expanding Wallstent endoprosthesis (Boston Scientific, Marlborough, Mass) was used in all cases of stenting. Intravenous heparin was administered for all interventions. All procedures were performed either in the operating room or a catheterization suite. In all, 17 operators from the three disciplines of vascular surgery, interventional cardiology, and radiology performed the procedures. The six operators with the highest volume performed more than 80% of the cases.

All patients were followed up clinically within at most 2 months of the index procedure. Follow-up color ultrasound studies were typically performed every 3 months

within the first year, although a minority of patients only had one follow-up study in the first 12 months. Patency was defined as an open vein. Restenosis was defined as at least a 50% decrease in the stent lumen area. Major bleeding was defined as bleeding resulting in hemodynamic compromise, hospitalization, death, intracranial bleeding, bleeding leading to a decrease in the hemoglobin of at least 2 g/dL, or bleeding requiring blood transfusion.

The study followed principles outlined in the Declaration of Helsinki. This retrospective study was approved by the institutional review board. Because the analysis was retrospective and anonymized, subject consent was not obtained.

The Student *t*-test or Mann-Whitney-Wilcoxon tests were used to compare differences between subjects with and without stent occlusion for continuous variables. The χ^2 test or Fisher's exact test was used to compare the frequencies of categorical variables. Multivariable logistic regression analysis was conducted to evaluate association between the minimum and maximum stent size and occlusion, adjusting for other covariates.

RESULTS

Data from 155 patients who underwent iliofemoral or caval stenting was evaluated (Table I). The study population was divided based on pathology and indication: MTS, PTS, or acute DVT. Patients were diagnosed with MTS based on symptoms plus IVUS, magnetic resonance or computed tomography venography diagnosis of at least 50% stenosis. Patients with history of DVT (of ≥3 months prior) and judged to have ongoing symptoms of PTS formed the PTS group. Patients presenting with acute DVT (<2 weeks since symptom onset) formed the DVT group.

Forty-five patients were treated for MTS, 49 for PTS, and 61 for acute DVT. Patient and procedural data are summarized in Table II. Anticoagulant and antiplatelet therapy, mode, and duration are summarized in Table III. The median follow-up was 19 months (interquartile range [IQR], 9-30 months). There were no periprocedural deaths, bleeding, or pulmonary embolism.

Procedural outcomes are summarized in Table IV. In the MTS group, at median follow-up of 18 months (IQR, 8-28 months), the primary patency was 97.8%, assisted-primary patency 100%, and secondary patency 100% (Fig 1). The PTS group had a primary patency of 85.7%, assisted-primary patency of 87.8%, and secondary patency of 91.8% at median follow-up of 19 months (IQR, 7-28 months; Fig 2) The DVT group had a primary patency of 85.2%, assisted-primary patency 85.2%, and secondary patency of 86.9% at median follow-up of 24 months (IQR, 9-37 months; Fig 3)

Fig 4 demonstrates the percentage of patients maintained on anticoagulation over time. In the MTS group, the single patient with stent occlusion was not on anticoagulant or antiplatelet therapy. In the PTS group, among those with reocclusion or severe restenosis of stent, five of seven (71%) were on anticoagulants at the time. In all seven cases of ipsilateral DVT, the patients were still on anticoagulants. In the seven restenosis/occlusions cases in the PTS group, five of the seven patients received anticoagulation for more than 6 months, and two of the seven for 6 months.

In the acute DVT group, thrombolysis in some form was used for 57 patients (93%). Nine received rheolytic thrombectomy only, 26 received ultrasonic thrombolysis, 7 received an intravenous infusion of tissue plasminogen activator, and 15 received a combination. After the procedure, all 61 patients were maintained on oral anticoagulants. At a median follow-up of 24 months, 15 patients (25%) had a recurrent ipsilateral DVT, 3 (5%) had a pulmonary embolism, and 9 (15%) a stent restenosis/occlusion (Table IV). The patients were on anticoagulant

ARTICLE HIGHLIGHTS

- **Type of Research:** Single-center retrospective cohort study
- **Key Findings:** There were 155 patients who underwent iliocaval stenting. In patients with acute deep vein thrombosis and post-thrombotic syndrome, there was a statistically significant larger stent diameter in those with patent stents. The majority of stent occlusion and restenosis cases occurred within the first 3 months, when most patients were still on anticoagulant therapy.
- **Take Home Message:** Larger diameter iliocaval vein stents are associated with improved patency rates.

Table I. Study population characteristics and comorbidities (N = 155)

Characteristic	
Age, years	51.9 ± 16.8
Male sex	63 (40.6)
BMI	31.1 ± 7.6
Cancer, past or current	34 (21.9)
Hypercoagulable syndrome	30 (19.3)
DM	11 (7.1)
HTN	34 (21.9)
CKD (stage ≥3)	8 (5.2)
PE	20 (12.9)
CAD	10 (6.4)
CHF	2 (1.3)
CVA	3 (1.9)

BMI, Body mass index; *CKD,* chronic kidney disease; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *CVA,* cerebrovascular accident; *DM,* diabetes mellitus; *HTN,* hypertension; *PE,* pulmonary embolism.
Values are presented as mean ± standard deviation or number (%).

Table II. Patient parameters and procedural details based on pathology (May-Thurner Syndrome [*MTS*], post-thrombotic syndrome [*PTS*] and deep vein thrombosis [*DVT*])

	MTS	PTS		DVT
Age, years	53.9 ± 17.9	51.4 ± 17.2	Age, years	51.0 ± 15.9
Sex	Male, 13 (28.9); female, 32 (71.1)	Male, 27 (55.1); female, 22 (44.9)	Sex	Male, 23 (37.7)
Laterality of symptoms	Left, 30 (66.7); right, 6 (13.3); bilateral, 9 (20)	Left, 33 (67.3); right 7 (14.3); bilateral 9 (18.4)	Laterality of symptoms	Left, 39 (64.0); right, 10 (16.3)
BMI	29.3 ± 6.8	32.5 ± 8.1	BMI	31.2 ± 7.6
C classification	3.2 ± 0.8	3.3	Phlegmasia	34 (55.7)
Cancer history	10 (22)	10 (20.4)	Cancer history	14 (22.9)
IVC filter	0	14 (28.6)	IVC filter	31 (50.8)
Hypercoagulable syndrome	1 (2.2)	8 (16.3)	Hypercoagulable syndrome	21 (34.4)
Procedural details			MTS diagnosed	23 (37.7)
IVUS use	26 (58)	37 (75.5)	Procedural details	
No. of stents, mean	1.6 ± 0.9	1.9 ± 1.1	Thrombolysis	56 (91.8)
Stent diameter, mm (minimum)	18.3 ± 2.9	15.6 ± 3.1	IVUS use	16 (26.2)
Stent diameter, mm (maximum)	18.9 ± 3.6	16.5 ± 3.0	No. of stents	1.7 ± 1.3
Stent length, mm	100 ± 56	133 ± 84	Stent diameter, mm (minimum)	15.7 ± 2.9
Stent location			Stent diameter, mm (maximum)	17.1 ± 3.1
CIV only	26	17	Stent length, mm	123.3 ± 85.2
CIV + EIV	9	16	Stent location	
CIV + EIV + CFV	3	2	CIV only	20
IVC only	4	4	CIV + EIV	21
IVC + CIV	2	3	CIV + EIV + CFV	3
IVC + CIV + EIV	1	6	IVC only	2
IVC + CIV + EIV + CFV	0	1	IVC + CIV	7
			IVC + CIV + EIV	8
			IVC + CIV + EIV + CFV	0

BMI, Body mass index; *CFV*, common femoral vein; *CIV*, common iliac vein; *EIV*, external iliac vein; *IVC*, inferior vena cava; *IVUS*, intravascular ultrasound. Values are presented as mean ± standard deviation or number (%) unless otherwise indicated.

therapy in 10 of the 15 cases (67%) of recurrent ipsilateral DVT and in 6 of the 9 cases (67%) of stent restenosis/occlusion. Among stent occluders, six of the nine patients received anticoagulation for more than 6 months, and three for less than 6 months.

Table V presents the combined data for the acute DVT and PTS groups with stent, procedural, and patient characteristics in those that occluded against those that remained patent. The stents that occluded had a tendency toward longer length, extension into the CFV and more hypercoagulable syndromes (P = NS). The patent stent group had statistically larger nominal diameter stents. This finding applied whether comparing the nominal diameter of the largest stent used in the case (17.1 mm vs 15.4 mm; $P = .048$) or the smallest diameter stent used (16 mm vs 14 mm; $P = .013$).

DISCUSSION

The intended purpose of venous stenting is a decrease in the peripheral venous pressure, so large-bore stents approximating normal venous anatomy are used for effective decompression.[5] A review of approximately 1500 iliac and IVC stent series found cumulative patency ranged from 90% to 100% and from 74% to 89% for non-thrombotic and post-thrombotic disease, respectively, at 3 to 5 years of follow-up.[1]

There is a paucity of evidence for the optimal mode of antiplatelet or anticoagulant therapy after iliocaval stenting. It has been suggested that, compared with anticoagulants, antiplatelet therapy may play a lesser role in the slow-flow low shear venous system, compared with the arterial system.[6,7] In a small animal study, peri-procedural administration of a direct factor Xa inhibitor

Table III. Breakdown of anticoagulant and/or antiplatelet therapy, duration pathology (May-Thurner Syndrome [*MTS*], post-thrombotic syndrome [*PTS*] and deep vein thrombosis [*DVT*])

	MTS	PTS	DVT
No.	45	49	61
No antiplatelet or anticoagulation therapy	9 (20)	0	0
ASA	1 (2.2)	0	0
Clopidogrel	9 (20)	2 (4.1)	0
ASA + clopidogrel	8 (17.8)	0	0
VKA	5 (11.1)	14 (28.6)	7 (11.7)
LMWH	3 (6.7)	6 (12.2)	13 (21.6)
LMWH then oral anticoagulation	0	8 (16.3)	18 (30)
DOAC	7 (15.6)	14 (28.6)	12 (20)
Anticoagulation + ASA/clopidogrel	3 (6.7)	5 (10.2)	10 (16.7)
Anticoagulation duration, mean ± SD weeks	15.1 ± 29.4	79 ± 68	78.9 ± 63.8

ASA, Aspirin; *DOAC*, direct-acting oral anticoagulant; *LMWH*, low-molecular-weight heparin; *VKA*, vitamin K antagonist (warfarin).
Values are presented as number (%) mean ± standard deviation unless otherwise indicated.

was superior to aspirin and/or clopidogrel in the prevention of in-stent thrombus formation.[8]

A systematic review of 14 venous stent studies after DVT (including those with PTS) conducted by Eijgenraam et al[3] in 2014 found no clear evidence that anticoagulant or antiplatelet therapy affects clinical outcomes. Most of the studies were prospective or retrospective cohort in design and most enrolled fewer than 100 patients. The incidence of recurrent ipsilateral thrombosis ranged from 5% to 25%.

The American College of Chest Physicians guidelines recommend at least 3 months of anticoagulation in the setting of iliac vein stenting and thrombolysis for DVT. No specific recommendations for post iliac stent anticoagulation for chronic obstruction (PTS) are made.[9]

The Cardiovascular and Interventional Radiological Society of Europe guidelines on iliocaval stenting strongly recommend postprocedural anticoagulation, although they acknowledge the lack of randomized, controlled trial evidence.[10] A survey of more than 100 venous experts from 28 countries showed marked diversity of approaches to anticoagulation or antiplatelet therapy after iliocaval stenting.[11] Nevertheless, anticoagulation was the preferred strategy in the first 6 to 12 months after stenting in the setting of acute DVT. Long-term and even lifelong anticoagulation was preferred in the setting of iliac stenting for post-thrombotic iliac vein occlusion. There was poor consensus on antiplatelet therapy.[11]

A number of small studies performing a similar analysis to this study have been published.[12] Hartung et al[13]

Table IV. Iliocaval stent outcomes (May-Thurner Syndrome [*MTS*], post-thrombotic syndrome [*PTS*] and deep vein thrombosis [*DVT*])

	MTS	PTS	DVT
No.	45	49	61
Follow-up, months, median (IQR)	18 (8-28)	19 (7-28)	24 (9-37)
DVT, overall	0	7	15
≤30 days	0	4	4
>30 days	0	3	11
PE	0	0	3 (4.9%)
Bleeding, major	0	4 (8.1%)	9 (14.8%)
Re-stenosis/occlusion	1 (2.2%)	7 (14.2%)	9 (14.8%)
Death			
Malignancy	3	1	3
Sepsis	–	1	1
Primary patency	97.8%	85.7%	85.2%
Assisted primary patency	100%	87.8%	85.2%
Secondary patency	100%	91.8%	86.9%

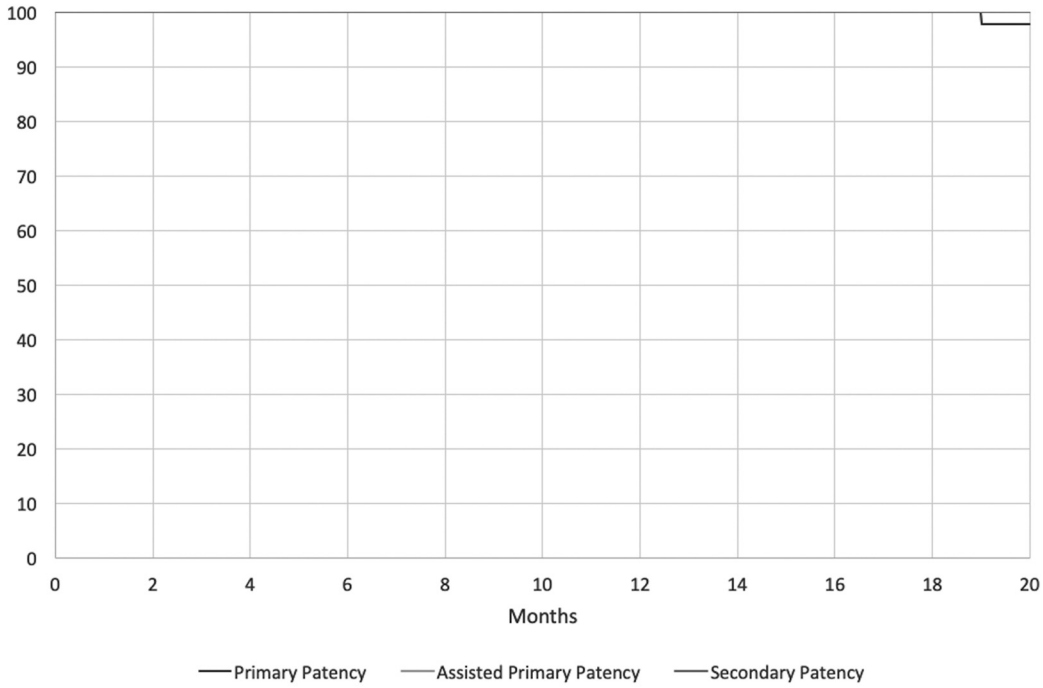

Fig 1. Stent patency (%) in the May-Thurner syndrome (MTS) group (months).

published their experience on 89 patients who underwent iliocaval stenting. Most patients (n = 52) had a primary etiology (MTS) and 35 had secondary iliac obstruction (30 PTS, 5 retroperitoneal fibrosis). Forty-four patients (49%) had a history of venous thromboembolism. Most patients (n = 52) were discharged on 6 months of oral anticoagulants. At a median follow-up of 38 months, stent thrombosis occurred in 6% and restenosis in 7%. There were some notable differences in the study population compared with our series.

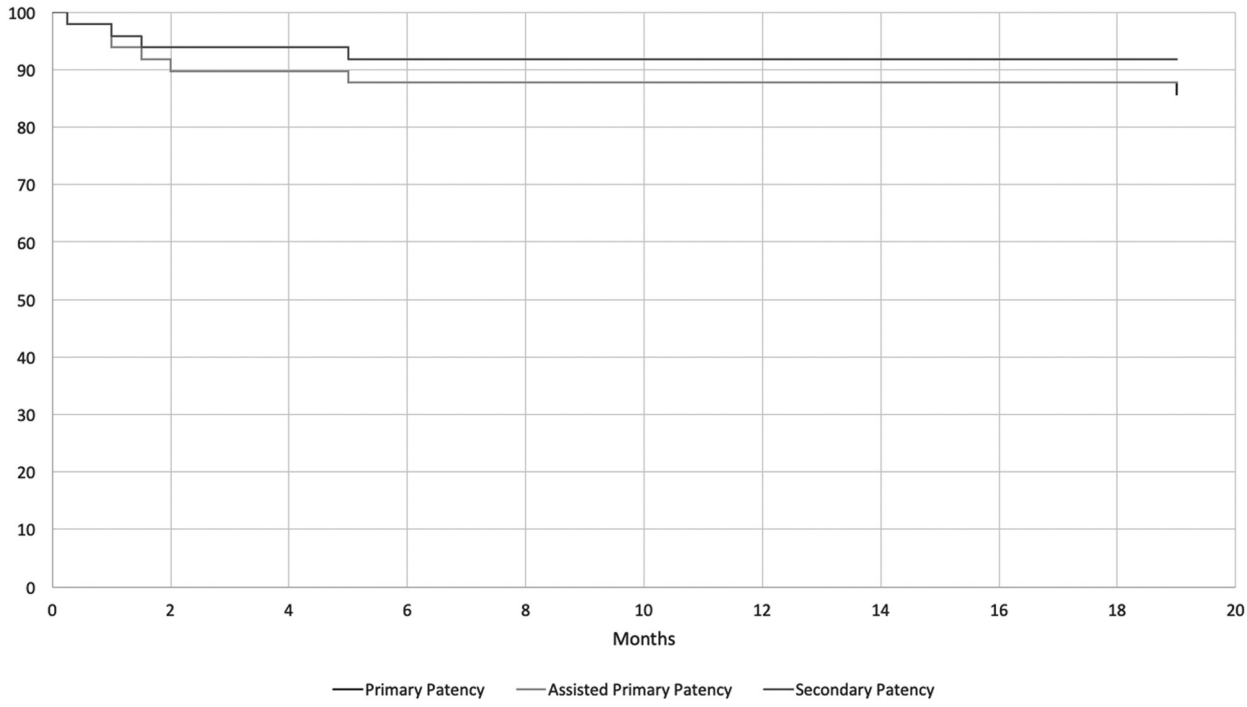

Fig 2. Stent patency (%) in the post-thrombotic syndrome (PTS) group (months).

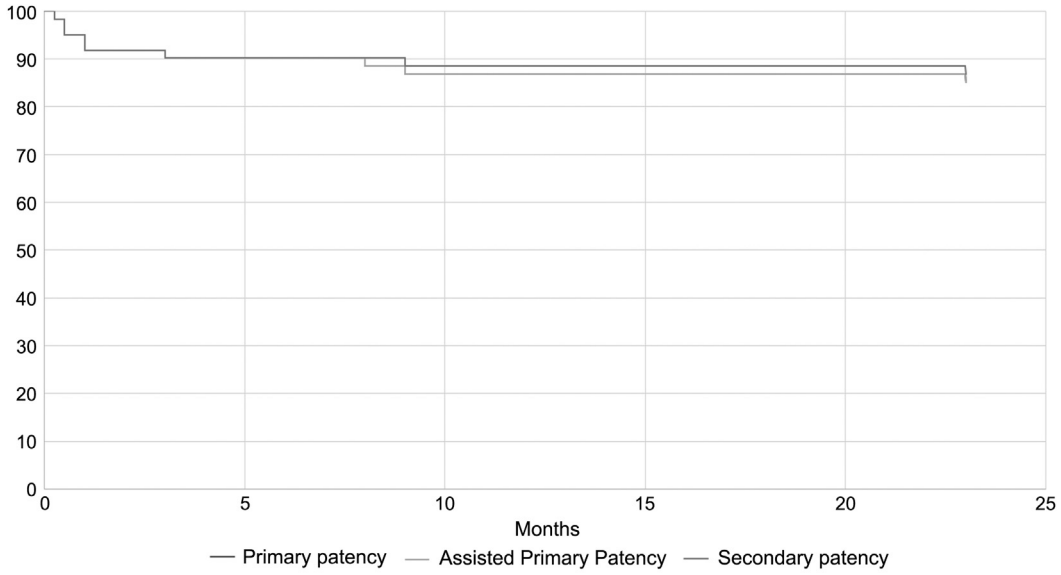

Fig 3. Stent patency (%) in the deep vein thrombosis (DVT) group.

Their study population was younger (mean age, 43 years vs 52 years), with more females (81% vs 60%), and had more left-sided disease (89% vs 66%). Also, they only included patients with an at least 5-year life expectancy. They recorded number and length of stents used (slightly lower than in our patients), but not their diameter. No IVUS was used. They also reported CFV disease to be a significant factor in lower primary patency.

Neglen et al[14] also published their large series (n = 982) of iliocaval stenting. Primary patency at 72 months was 79% in nonthrombotic disease and 57% in thrombotic disease. Stent occlusion was primarily seen in post-thrombotic patients. Thrombophilia alone was not a risk factor. A more recent retrospective analysis of 31 post-thrombotic iliocaval occlusive lesions that underwent stenting showed primary 1-year patency of 66%.[15]

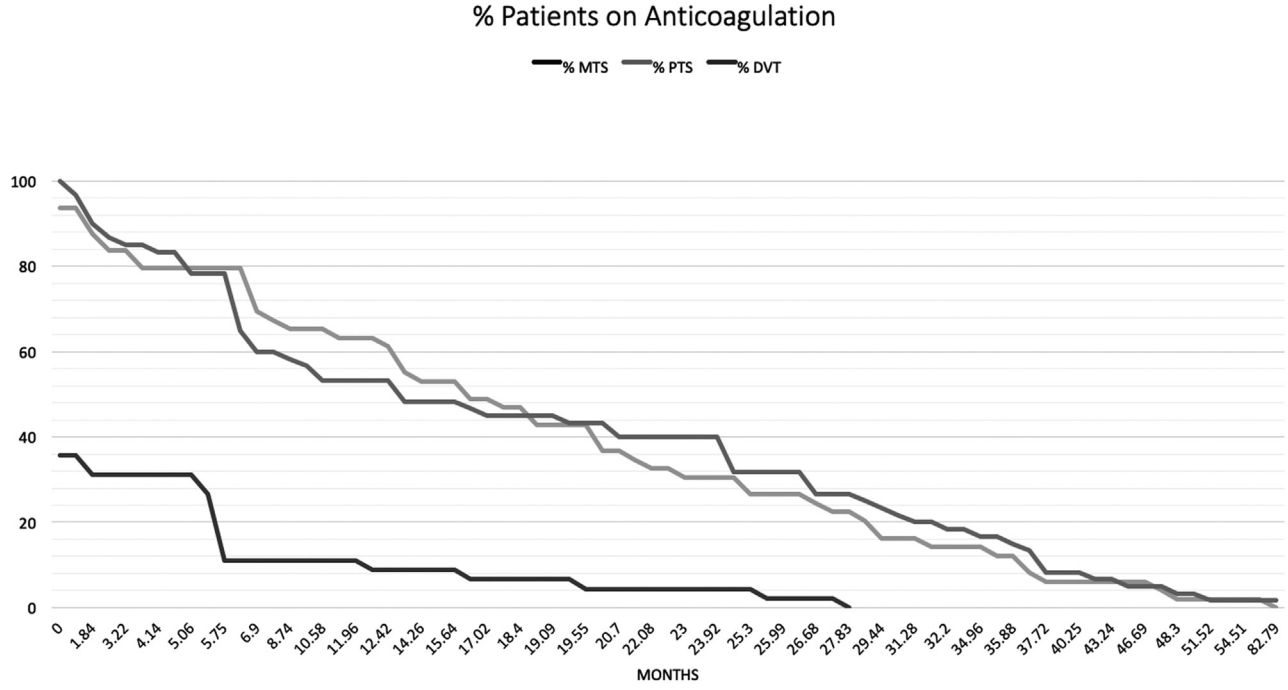

Fig 4. Percentage of patients maintained on anticoagulation over time (months) based on pathology: deep vein thrombosis (*DVT*), May-Thurner syndrome (*MTS*), and post-thrombotic syndrome (*PTS*).

Table V. Comparison of patient, stent and procedural characteristics in those that occluded/restenosed against those remaining patent

	Patent (n = 94)	Occluded/restenosed (n = 16)	*P* value
Stent diameter, mm (minimum)	16.0 ± 3	14 ± 2.1	.013[a]
Stent diameter, mm (maximum)	17.1 ± 3	15.4 ± 3.3	.048[a]
Stent length, mm	125.2 ± 90.7	162.2 ± 76.1	.13
IVC stented	27.7	31.3	.77
CFV stented	5.3	18.8	.06
No. of stents	1.8 ± 1.3	2.2 ± 1.1	.13
MTS	45.7	37.5	.54
IVUS use	46.8	56.3	.48
Age, years	50.6 ± 16.7	54.1 ± 14.2	.43
BMI	31.9 ± 8	30.6 ± 6.3	.53
Cancer	21.3	18.8	.82
Hypercoagulable state	23.4	37.5	.23
IVC filter	41.5	37.5	.76
IVC filter removed	25.6	0	.28
Anticoagulation duration, weeks	76 ± 59	95.9 ± 94.5	.42

BMI, Body mass index; *CFV,* common femoral vein; *IVC,* inferior vena cava; *IVUS,* intravascular ultrasound; *MTS,* May-Thurner syndrome.
Values are presented as mean ± standard deviation or percent.
[a]Statistically significant.

The current study's observation of 98% stent patency in the MTS group regardless of the mode of postprocedural therapy mirrors other studies. The stent occlusion/restenosis rates were similar when comparing the PTS and acute DVT groups at 14.2% and 14.8%, respectively. The majority of reocclusions occurred within the first 3 months, when most patients were still on anticoagulant therapy.

In the PTS and acute DVT groups, those with stent occlusion were more likely to have longer stents and stent extension into the CFV (P = NS). There was a statistically significant difference in nominal stent diameters when comparing those that remained patent versus those that restenosed or occluded. The use of a smaller diameter stent is a plausible mechanism for reocclusion. However, the use of a longer stent and stent extension into the CFV may merely reflect more extensive disease, which also likely increases the risk of reocclusion.

This study's findings suggest that, within the PTS group, remaining on anticoagulation did not seem to lower the stent occlusion rates, in that 71% were still on anticoagulants at the time. The same supposition may also be made about the acute DVT group where 67% of stent occluders were on anticoagulants at the time of occlusion/restenosis.

The limitations of this trial include its retrospective nature and small sample size. The overall higher prevalence of hypercoagulable syndrome in the acute DVT group may be a function of more testing in that group. Other limitations include the low rates of IVUS use in the DVT group which could imply that the observed iliac vein compression (MTS) rates of 37.7% may be an underestimate.

CONCLUSIONS

These findings suggest that larger stent diameter has a significant positive influence on iliocaval stent patency rates. There may be an association between stent extension into the CFV and stent occlusion, although this factor may represent burden of disease. Stent patency rates were similar among patients with acute DVT and those with PTS. The efficacy of mode and duration of anticoagulant therapy in the maintenance of stent patency is less clear.

AUTHOR CONTRIBUTIONS

Conception and design: RA
Analysis and interpretation: RA, IL, CMH, AL
Data collection: RA, DO
Writing the article: RA, DO, IL, CMH
Critical revision of the article: CMH, AL
Final approval of the article: RA, DO, IL, CMH, AL
Statistical analysis: IL
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Overall responsibility: RA

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