

REVIEW

Systematic Review and Meta-Analysis of Iliofemoral Stenting for Post-thrombotic Syndrome

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WHAT THIS PAPER ADDS

Endovascular stenting is relevant to the management of post-thrombotic syndrome with chronic obstruction in iliofemoral venous segment. Although this systematic review demonstrates that the quality of evidence for iliofemoral stents is weak, venous stenting has the potential to be effective, with extremely rare occurrences of peri-operative complications. This review may assist in clinical decision making and guide future research.

Objective: Stent placements are considered as a treatment for post-thrombotic syndrome (PTS) with iliofemoral obstruction, but the application of these iliofemoral venous stents has also caused a lot of controversy. The purpose of this systematic review and meta-analysis was to summarise the efficacy and safety of venous stents in PTS with obstruction in iliofemoral venous segments.

Methods: MEDLINE, EMBASE, and the Cochrane Central Register for Controlled Trials databases and key references were searched up to 15 January 2018. The main relevant outcomes included technical success, peri-operative complications, symptom resolution, a change of symptom scores, and long-term patency of the stents.

Results: Overall, 504 limbs of 489 patients from seven studies were included in this study. A GRADE assessment showed the quality of the evidence was “very low” for 11 relevant outcomes. The technical success rate was 95%. The pooled rate of complications including 30 day thrombotic event, per-operative venous injury, and back pain was 3.4%, 18.14%, and 52%, respectively. The rates of ulcer healing, pain and oedema relief were 75.66%, 52%, and 42%, respectively. The primary, assisted primary and secondary patency rates were 83.36%, 90.59%, and 94.32%, respectively, at 12 months and 67.98%, 82.26%, and 86.10%, respectively, at 36 months.

Conclusions: Endovenous stenting has the potential to be effective and has a low risk of peri-operative complications. The quality of evidence to support this treatment is very low. Endovenous iliofemoral stenting should be considered a treatment option for PTS with iliofemoral obstruction.

Keywords: Post-thrombotic syndrome, Stents, Outcomes, Vascular patency, Systematic review, Meta-analysis

Article history: Received 28 January 2018, Accepted 20 September 2018, Available online 7 November 2018

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INTRODUCTION

Post-thrombotic syndrome (PTS) is the most common complication of deep vein thrombosis (DVT). The incidence of PTS ranges from 20% to 50% in DVT patients.^{1,2} The symptoms and clinical signs of PTS include chronic pain, intractable limb oedema, varicose veins, venous

claudication, hyperpigmentation, and venous ulcers.³ Conservative treatments, such as compression therapy, medication, and exercise training, can be considered first line treatments of PTS.^{4–8} Surgical treatment of PTS is attempted when conservative treatment fails. Open surgical techniques were used originally,^{9,10} however, in recent years, with advances in endovascular technology, many endovascular interventions have been attempted, especially stent placement, to reduce the symptoms of appropriately selected patients with PTS.

There have been some similar systematic reviews about iliofemoral stenting for chronic obstructive venous disease,^{11–13} however, the efficacy and safety of iliofemoral venous stents for PTS were not presented

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<https://doi.org/10.1016/j.ejvs.2018.09.022>

separately. Patients with May–Thurner syndrome have higher stent patency than patients with PTS.^{13–15} Therefore, outcomes of stenting may differ between thrombotic stenosis and non-thrombotic stenosis. Aiming to provide evidence supporting iliofemoral stent placement for PTS, a systematic review and meta-analysis of the literature on the efficacy and safety of these stents was performed.

METHODS

Search strategy

A search of the databases MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹⁶ The search was last conducted on January 15, 2018. No restrictions were placed on publication type, language or date. An electronic search, the details of which are available in the Supplementary material, was designed and conducted. After the initial search, the abstracts were assessed for inclusion in the study, and full text articles were subsequently reviewed for eligibility. The references of included studies and other important publications were manually searched for additional reports.

Eligibility criteria

Studies involving endovascular procedures in the treatment of PTS were selected, and these procedures included stent placement in the common femoral, external iliac, and/or common iliac vein, with or without concurrent venous procedures. Studies were excluded if they were narrative reviews, commentaries, letters, single case reports, or clearly irrelevant studies. Patients with acute DVT, non-thrombotic iliac vein lesions (NIVL) or May–Thurner syndrome or occlusion of the popliteal vein or inferior vena cava (IVC) were also excluded. In addition, articles with fewer than 20 stented limbs were removed. Studies written by the same author or those of colleagues using the same patient sample were also removed. However, if there was no overlap between two studies, they were both included.

Data extraction

Two independent authors (Q.P. and Z.B.) reviewed all records identified by the above mentioned search strategies. Discrepancies were adjudicated by a third reviewer (Z.X.). A standardised, pre-piloted form was used to extract data from the included studies for the assessment of study quality and for evidence synthesis. The following data were collected: study design, start and end years, demographics, number of patients and limbs, interval between DVT and procedure, procedural details, concomitant procedures, compression treatment, anti-thrombotic treatment, technical success rate, peri-operative complications, symptom resolution, and long-term patency.

Quality assessment

The quality of the observational studies was assessed using the Newcastle–Ottawa Quality Assessment Scale (NOS)¹⁷ by two independent investigators (Q.P. and Z.Y.). This scale evaluates studies based on three domains: patient selection methods, comparability of the study group, and assessment of relevant outcomes. A score of fewer than 6 stars indicated a high chance of bias. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system was used to rate the quality of evidence and strength of each relevant outcome identified, and this was conducted using GradePro (www.gradepro.org).

Relevant outcomes

In this review, the main relevant outcomes included technical success, per-operative complications (30 day thrombotic event, per-operative venous injury, back pain, major bleeding, pulmonary embolism, peri-procedural mortality, stent migration, and stent fracture), symptom resolution from pain, venous claudication, oedema and ulcer, a change in symptom scores (clinical component of the clinical, aetiology, anatomy, and pathophysiology classification [C of CEAP],¹⁸ Venous Clinical Severity Score [VCSS],¹⁹ and Villalta score²⁰) and long-term patency of the stents (primary patency, assisted patency, and secondary patency).

Technical success was defined as successful recanalisation and stent deployment restoring patency to the target vessel with no major procedural complications. A 30 day thrombotic event was defined as restenosis or occlusion of the target lesion within 30 days of the procedure. Per-operative venous injury was defined as venous injury caused by the catheter or the guidewire during the procedure. Back pain was defined as lower back pain persisting after stent deployment. Primary patency was defined as confirmed patency with < 50% restenosis on follow up without any repeat intervention. Assisted primary patency was defined as secondary endovascular interventions to treat \geq 50% restenosis involving the originally treated venous segment. Secondary patency was defined as patency in the target lesion maintained by repeat intervention after occlusion of the treated venous segment.

Strategy for data synthesis

Depending on the data available, the main relevant outcomes were presented in different ways. Appropriate outcomes (technical success, 30 day thrombotic event, per-operative venous injury, back pain, symptom resolution from pain, oedema, and ulcer) were analysed by a separate meta-analysis. Study specific estimates of frequency were pooled and reported as event rates with corresponding 95% confidence intervals (95% CIs). The I^2 test was used to measure statistical heterogeneity. A fixed effects model was used when no significant heterogeneity ($I^2 < 50\%$) was detected among the studies. Otherwise, a random effects model was used.

Data on long-term patency (primary patency, assisted patency, and secondary patency) were provided by the text, life tables, and Kaplan–Meier curves in some studies. Two

independent authors (Q.P. and Z.B.) extracted numerical data from the provided graphical data by tracing via Engauge Digitizer 4.1 (open source, non-commercial product: <http://markummittchell.github.io/engaugedigitizer/>). These curves were then aggregated by fitting a Weibull model to the resultant data points, and a random effects framework allowed for inter-study heterogeneity in relevant outcomes.²¹ All data analyses were performed in R Version 3.4.3.

Some outcomes (major bleeding, pulmonary embolism, peri-procedural mortality, stent migration, stent fracture, and a change in symptom scores) that did not provide appropriate data for meta-analysis were shown narratively.

The study was registered with PROSPERO2015 (CRD42015030080). All analyses in this systematic review and meta-analysis were based on previous published studies that met ethical guidelines.

RESULTS

Study selection

The literature search yielded 1021 results. After duplicates were removed, 742 results remained for title and abstract screening, which resulted in the selection of 102 articles for full text assessment. Finally, seven articles met the defined inclusion criteria (Fig. 1).^{22–28}

Patient characteristics

Iliofemoral stents were deployed in 504 limbs of 489 patients in the seven studies. The median age of these

patients ranged from 41 to 58 years, and the female/male ratio was between 0.46 and 0.75. In five articles, the median time from acute DVT to the procedure ranged from five to 108 months.^{22,23,26–28} Five of seven studies provided the incidence of thrombophilia, and this ratio was between 5.97% and 50%.^{22–26} The mean follow up duration ranged from 1.5 months to 36.2 months. Patient characteristics are presented in Table 1.

Quality assessment of studies and grading of the evidence

All seven studies were observational. Only one study was a cohort study,²⁷ with a control group of patients treated conservatively by elastic compression stockings, while all the other studies were case series. Quality assessment of the included studies by NOS revealed one nine star study,²⁷ five six star studies,^{22–24,26,28} and one five star study²⁵ (Supplementary Table 1). Eleven relevant outcomes were analysed using the GRADE system. The quality of evidence was “very low” for all relevant outcomes (Table 2).

Stenting procedure details

The most common access sites were the femoral vein, the popliteal vein and the internal jugular vein under local anaesthesia. The mean number of stents per limb ranged from 1.0 to 2.5. Wallstents were used in all six studies that mentioned the trade names of stents.^{22–24,26–28} Only one article did not mention the name of inserted stents.²⁵ In three articles,^{25,26,28} multiple stents were overlapping by at least 1 cm or 2 cm. Three studies reported the position of

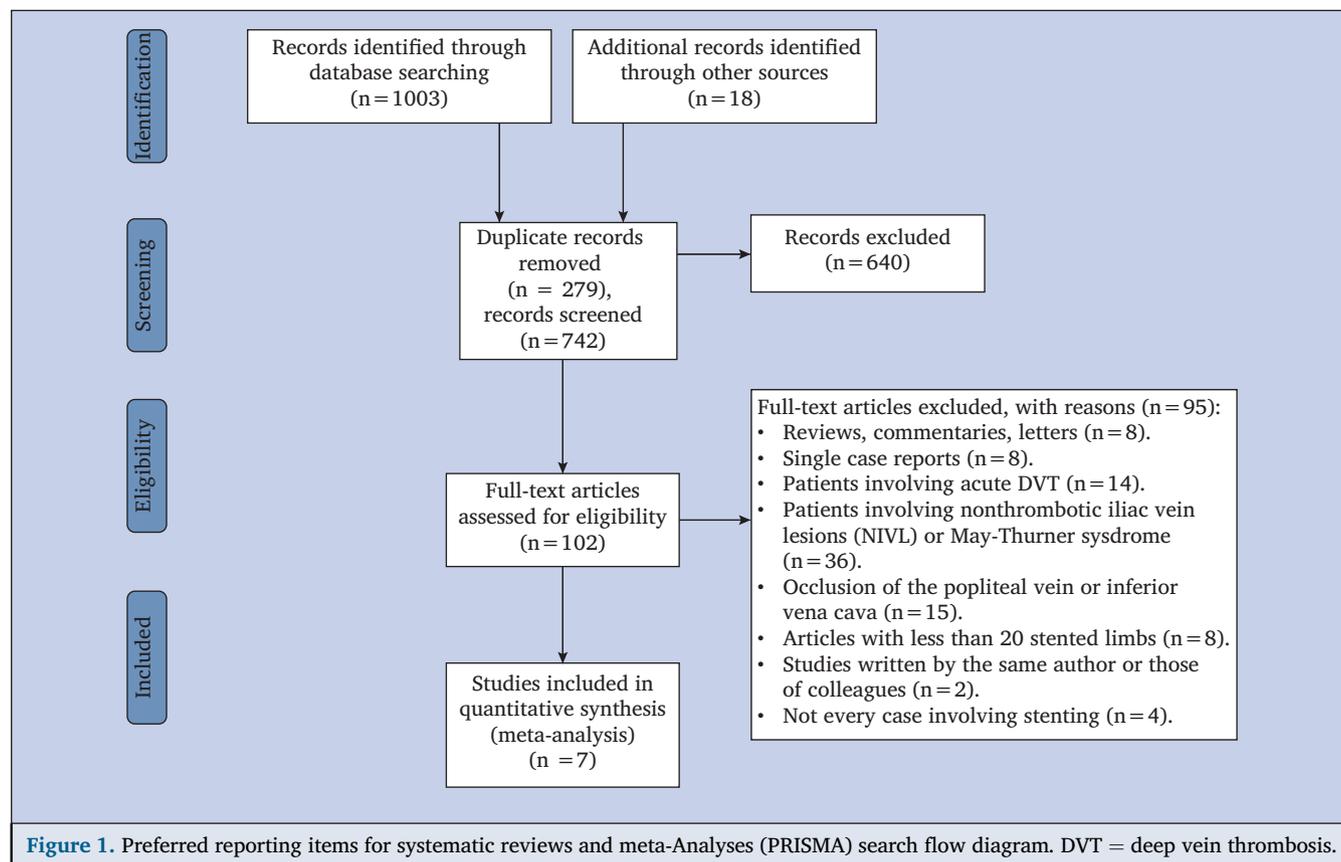


Figure 1. Preferred reporting items for systematic reviews and meta-Analyses (PRISMA) search flow diagram. DVT = deep vein thrombosis.

Table 1. Characteristics of included study populations

Study	Treatment period	No. of patients	Median age (range), years	Female	Limbs	Left limbs	Mean time from DVT to procedure (months)	Follow up duration
Rosales 2010 ²²	2000–2009	34	41 (15–63)	56% (19/34)	34	NA	108	Median 33 months (range, 1–96 months)
Kurklinsky 2012 ²⁴	2003–2008	89	46 (38–54)	70% (62/89)	91	81	NA	Median 11.3 months (range, 0.8–72.4 months)
Nayak 2012 ²³	2003–2009	44	42 (20–77)	55% (24/44)	50	10	60	Mean 44 days ± 24.5 (range, 16–145 days)
Sarici 2013 ²⁵	2011	52	58 (23–76)	75% (39/52)	59	NA	NA	≥6 months
Sang 2014 ²⁶	2005–2012	67	44 (24–72)	46% (31/67)	67	67	6–36	Mean 36.2 months (range, 1–84 months)
Yin 2015 ²⁷	2007–2012	122	46 (30–81)	61% (75/122)	122	19	9	Median 21 months (range, 3–58 months)
Ruihua 2017 ²⁸	2013–2014	81	57 (29–82)	54% (44/81)	81	65	93.6	Median 19 months (range, 1–38 months)

DVT = deep vein thrombosis; NA = information not available.

stents for venous obstructions adjacent to the IVC, and the length of extension into IVC suggested in these studies was < 0.5 cm,²⁶ approximately 1 cm,²⁴ and 1–2 cm.²² The detailed procedural information is presented in Table 3. As reported in six articles,^{22,23,25–28} the technical success rate was 95% (95% CI 91–98%, $I^2 = 59.3%$, $p = .031$) (Supplementary Table 2 and Table 4).

Concomitant procedures and conservative treatment

Percutaneous transluminal angioplasty (PTA) was performed in all seven studies. Four studies^{22,24,27,28} performed both pre- and post-dilatations. Two studies^{23,25} performed post-dilatations, and one study²⁶ performed only pre-dilatations. Three articles^{22,23,26} mentioned other concomitant procedures, including venous valve transplantation, construction of arteriovenous fistulae, endovenous laser ablation (EVLA), and ligation and stripping of the great saphenous vein. Compression treatments were used after

the endovascular procedure in six studies,^{22,23,25–28} and most of them used elastic compression stockings for from three months to two years. After the procedure, anticoagulants, which were reported in all articles, included 4000 U of low molecular weight heparin twice a day before using warfarin for two²⁴ or six months^{26–28} and/or a lifelong aspirin regimen. Information on concomitant procedures and conservative treatments is summarised in Table 5.

Peri-operative complications

Four studies reported 30 day thrombotic event rates, and the pooled proportion of this complication was 3.4% (95% CI 1.59–7.22%, $I^2 = 6%$, $p = .360$).^{22,24–26} Peri-operative venous injury was mentioned in four studies, with a pooled rate of 18.14% (95% CI 7.88–36.45%, $I^2 = 86.5%$, $p < .0001$).^{22,26–28} Back pain, the most common minor complication, was mentioned in two studies, and the rate was 52% (95% CI 45–59%, $I^2 = 26.8%$, $p = .242$).^{27,28} In

Table 2. GRADE assessment of main outcomes in 7 included studies

Outcome	No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
Technical success	6 ^{22,23,25–28}	Observational	Serious	Serious	No	No	Very low
30 day thrombotic event	4 ^{22,24–26}	Observational	Serious	No	No	Serious	Very low
Per-operative venous injury	4 ^{22,26–28}	Observational	Serious	Serious	No	No	Very low
Back pain	2 ^{27,28}	Observational	Serious	No	No	Serious	Very low
Pain relief	2 ^{23,24}	Observational	Serious	Serious	No	Serious	Very low
Oedema relief	2 ^{23,24}	Observational	Serious	No	No	Serious	Very low
Ulcer healing	7 ^{22–28}	Observational	Serious	No	No	No	Very low
Change of PTS scores	6 ^{22,23,25–28}	Observational	Serious	Serious	No	No	Very low
Primary patency	5 ^{22,24,26–28}	Observational	Serious	Serious	No	No	Very low
Assisted patency	4 ^{22,24,27,28}	Observational	Serious	Serious	No	No	Very low
Secondary patency	5 ^{22,24,26–28}	Observational	Serious	Serious	No	No	Very low

GRADE Working Group grades of evidence: high quality, further research is very unlikely to change our confidence in the estimate of effect; moderate quality, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; very low quality, we are very uncertain about the estimate. PTS = post-thrombotic syndrome.

Table 3. Procedural details in 7 included studies

Study	Access site	Type of anaesthesia	No. of stents per patient	Type of stent	Length of extension into IVC	Multiple stents	Imaging during the operation	Anticoagulation during procedure
Rosales 2010 ²²	Popliteal, femoral, jugular vein	General anaesthesia	NA	Wallstent (Boston)	1–2 cm	NA	Venography	NA
Kurklinsky 2012 ²⁴	Internal jugular, common femoral vein	Local anaesthesia	2.5	Wallstent (Boston), Protégé (ev3), S.M.A.R.T. (Cordis), Luminexx (Bard)	1 cm	NA	Venography	Heparin 5000 U
Nayak 2012 ²³	NA	Local anaesthesia	1.0	Wallstent (Boston), S.M.A.R.T. (Cordis)	NA	NA	Venography	NA
Sarici 2013 ²⁵	Femoral vein	Local anaesthesia	NA	Nitinol stent	NA	Overlap > 1 cm	Venography	Heparin 5000 U
Sang 2014 ²⁶	Common femoral, popliteal vein	Spinal or local anaesthesia	2.1	Wallstent (Boston), S.M.A.R.T. (Cordis), Luminexx (Bard)	< 0.5 cm	Overlap >1 cm	Venography	Heparin 100 units/kg
Yin 2015 ²⁷	Common femoral, popliteal vein	Local anaesthesia	2	Wallstent (Boston), EverFlex (ev3), LIFESTENT (BARD)	NA	NA	Venography	Heparin 80 units/kg
Ruihua 2017 ²⁸	Femoral, popliteal vein	Local anaesthesia	2.2	Wallstent (Boston), E-Luminexx (Bard)	NA	Overlap >2 cm; first: Wallstent in distal end, second: self expanding stent in proximal end	Venography	Heparin 80 units/kg

NA = information not available; IVC = inferior vena cava.

addition, the back pain was self limiting and relieved 1–3 days after the procedure without medical therapy. Six studies^{23,24,26–28} stated no major bleeding, four studies^{23,26–28} stated no pulmonary emboli, four studies^{25–28} stated no peri-procedural mortality, one study²³ stated no stent migration, and two studies stated no stent fracture.^{26,27} The reported peri-operative complications are shown in [Supplementary Table 2](#) and [Table 4](#).

Symptom relief

All studies reported data on ulcer healing, which had a high rate of 75.66% (95% CI 66.78–82.78%, $I^2 = 35%$, $p = .161$).

Data on pain and oedema relief were presented in two studies, and their rates were 52% (95% CI 32–72%, $I^2 = 26.8%$, $p = .058$) and 42% (95% CI 33–52%, $I^2 = 0%$, $p = .405$), respectively ([Tables 4 and 6](#)).^{23,24} Two other studies, which used scores to assess pain and oedema relief, showed post-treatment oedema and pain scores were significantly lower than pre-treatment.^{27,28} Only one study mentioned improvement of venous claudication, and the rate of improvement was 92.86% ([Table 6](#)).²⁶

Six articles used symptom measures to assess the changes in PTS severity.^{22,23,25–28} The median Villalta scores provided in three studies,^{25,27,28} the median VCSS scores reported in three studies,^{22,25,26} and the median CEAP

Table 4. Meta-analysis of main outcomes

Outcome	No. of studies	No. of limbs	Event rate		Heterogeneity among studies	
			Point estimate (%)	95% CI	I^2 (%)	p
Technical success	6 ^{22,23,25–28}	413	95	91–98	59.3	.031
30 day thrombotic event	4 ^{22,24–26}	251	3.4	1.59–7.22	6	.360
Per-operative venous injury	4 ^{22,26–28}	304	18.14	7.88–36.45	86.5	< .0001
Back pain	2 ^{27,28}	203	52	45–59	26.8	.242
Pain relief	2 ^{23,24}	81	52	32–72	72.1	.058
Oedema relief	2 ^{23,24}	99	42	33–52	0	.405
Ulcer healing	7 ^{22–28}	124	75.66	66.78–82.78	35.0	.161

Other main outcomes (as detailed in [Table 2](#)): Change of PTS scores is shown in [Table 8](#) (the duration of follow up for these scores and questionnaires was unclear; therefore no meta-analysis could be applied); primary patency, assisted patency, and secondary patency are presented in [Figs 2–4](#) (aggregated by fitting a Weibull model to the data points). The I^2 statistic is derived from the Q statistic $[(Q-df/Q) * 100]$, and I^2 was defined as low (<50%) or high ($\geq 50%$). CI = confidence intervals.

Table 5. Summary of concomitant procedures and conservative treatment

Study	Concomitant PTA	Other concomitant procedures	Compression treatment after stenting	Antithrombotic treatment
Rosales 2010 ²²	Pre-, post-	Venous valve transplantation, construction of an arteriovenous fistulae	Pneumatic sequential pumps	LMWH + warfarin
Kurklinsky 2012 ²⁴	Pre-, post-	–	–	LMWH + warfarin > 2 months
Nayak 2012 ²³	Post-	EVLA	Compression therapy	Aspirin
Sarici 2013 ²⁵	Post-	–	Class II below knee compression stocking	Lifelong aspirin + clopidogrel 2 months
Sang 2014 ²⁶	Post-	Ligation and stripping of great saphenous vein, temporary arteriovenous fistulas	Elastic compression stocking > 2 years	LMWH + warfarin > 6 months
Yin 2015 ²⁷	Pre-, post-	–	No ECS in moderate PTS, 30–40 mmHg in severe symptoms (1–3 months), prolonged ECS in unhealed ulcer > three months	Hadroparin + warfarin > 6 months
Ruihua 2017 ²⁸	Pre-, post-	–	Graduated compression stockings after the procedure (23–32 mmHg)	LMWH + warfarin for 6 months

Pre- = pre-dilatation; post- = post-dilatation; PTA = percutaneous transluminal angioplasty; EVLA = endovenous laser ablation; ECS = elastic compression stocking; LMWH = low molecular weight heparin; PTS = Post-thrombotic syndrome.

Table 6. Signs and symptoms healing outcomes

Study	Ulcer healing	Pain relief	Oedema relief	Venous claudication alleviation	Symptom measures
Rosales 2010 ²²	4/7 healing	–	–	–	VCSS: C III 9 (5–12) to 1 (0–11) ($p = .0001$), C IV 21 (18–29) to 7 (6–14) ($p = .002$)
Kurklinsky 2012 ²⁴	9/17 healing	18/43 relief	23/59 relief	–	–
Nayak 2012 ²³	5/7 complete healing, 1/7 partial healing, 1/7 none or minimal healing	24/38 complete relief, 5/38 partial relief, 9/38 none or minimal relief	19/40 complete relief, 5/38 partial relief, 9/38 none or minimal relief	–	Post-treatment CEAP scores were significantly lower than pre-treatment CEAP scores ($p < .01$)
Sarici 2013 ²⁵	6/8 healing (according to change in CEAP class)	–	–	–	VCSS: 14 (6–28) to 5 (5–17) in 6 months ($p < .001$) Villalta: 18 (7–30) to 8 (4–19) in 6 months ($p < .01$) CIVIQ–20: 64 (50–75) to 83 (65–92) in 6 months ($p < .001$)
Sang 2014 ²⁶	3/3 healing	–	–	39/42 alleviation	VCSS: 9.5 ± 1.4 to 5.8 ± 1.2 ($P < .001$)
Yin 2015 ²⁷	42/49 healing	Oedema score was 3 before treatment and 1 after treatment ($p < .01$)	Pain score was 7 before treatment and 3 after treatment ($p < .01$)	–	Villalta: 22 (11–33) to 8 (2–18) ($p < 0.01$)
Ruihua 2017 ²⁸	27/33 healing	Oedema score was 2.7 ± 1.5 before treatment and 1.1 ± 0.5 after treatment ($p < .01$)	Pain score was 7.4 ± 2.9 before treatment and 3.2 ± 1.9 after treatment ($p < .01$)	–	Villalta was 21.5 ± 3.7 before treatment and 11.0 ± 2.7 after treatment ($p < 0.01$)

CEAP = clinical, etiology, anatomical and pathophysiology - comprehensive classification system for chronic venous disorders; VCSS = venous clinical severity score; CIVIQ = chronic venous insufficiency quality of life questionnaire.

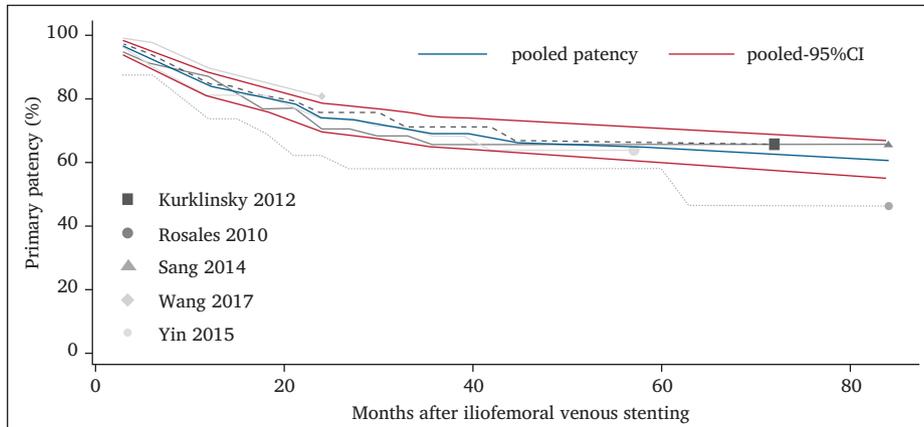


Figure 2. Kaplan–Meier pooled estimate of primary patency in aggregate model analysis. CI = confidence interval.

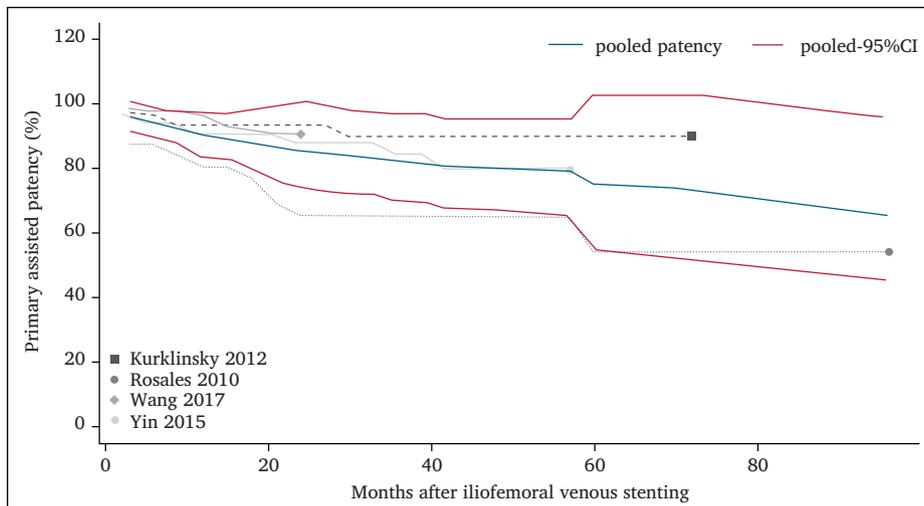


Figure 3. Kaplan–Meier pooled estimate of primary assisted patency in aggregate model analysis. CI = confidence interval.

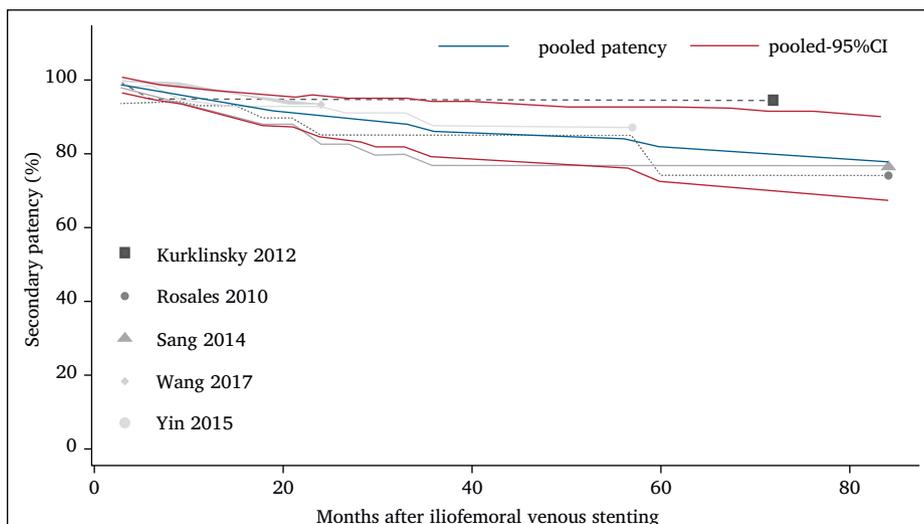


Figure 4. Kaplan–Meier pooled estimate of secondary patency in aggregate model analysis. CI = confidence interval.

scores mentioned in one study²³ all showed significant improvement after stenting. Two studies used CIVIQ to assess quality of life (QOL) among patients, and both showed significant improvement after stent placement (Table 6).^{25,28} However, the duration of follow up for these scores and questionnaires was unclear, and, therefore, these data could not be used in the meta-analysis.

Long-term patency

Five studies provided Kaplan–Meier curves of primary patency that allowed aggregate model analysis, which is illustrated in aggregated Kaplan–Meier curves (Fig. 2).^{22,24,26–28} The rate of primary patency was 83.36% (95% CI 78–89%) at one year, 67.98% (95% CI 61.40–75.26%) at three years, and 63.39% (95% CI 56.76–70.80%) at five years.

Kaplan–Meier curves of assisted patency were presented by four studies, which were synthesised by aggregate model analysis.^{22,24,27,28} The pooled data are shown in aggregated Kaplan–Meier curves (Fig. 3). The rate of assisted patency was 90.59% (95% CI 83.75–97.99%) at one year, 82.26% (95% CI 70.07–96.57%) at three years, and 75.09% (95% CI 54.77–102.95%) at five years.

Five studies reported Kaplan–Meier curves of secondary patency, allowing aggregate model analysis, which is shown in aggregated Kaplan–Meier curves (Fig. 4).^{22,24,26–28} The rate of secondary patency was 94.32% (95% CI 91.51–97.22%) at one year, 86.10% (95% CI 78.85–94.02%) at three years, and 81.90% (95% CI 72.4–92.65%) at five years.

DISCUSSION

Although there is no gold standard test to establish the diagnosis of PTS, this common, late complication of DVT can be diagnosed based on the presence of typical symptoms in a patient with previous DVT.³ Currently, various treatments, including compression, pharmacological agents, open venous surgery, and endovascular intervention, are relevant to the management of PTS. Endovascular interventions, especially stent placement, are considered by many vascular surgeons as a treatment for patients with obstructions in iliofemoral venous segments.^{5,24} Notably, patients with iliofemoral venous segments are also more likely to develop PTS than patients with thrombus in more distal locations,^{29,30} making endovascular interventions more practical. There have been some reviews of endovascular intervention for chronic iliofemoral venous obstructions, but most of them were narratives.^{31,32} Several similar systematic reviews on iliofemoral stenting for chronic obstructive venous disease mixed patients with primary (May–Thurner syndrome) and secondary (PTS) disease,^{11–13} and the efficacy and safety of the iliofemoral venous stents for PTS were not presented separately. Although these broad scope reviews can provide a comprehensive summary of evidence and assess the generalisability of findings across different types of patients, these patients with different pathological mechanisms may have different

outcomes. In addition, venous stents were also placed in the IVC to treat patients with chronic IVC obstruction in many studies, but the rate of primary patency of these stents is significantly lower than that of iliofemoral stents.³³ To the best of the authors knowledge, this was the first meta-analysis of stent placement for the treatment of PTS. In addition, this review may assist in clinical decision making and guide future research.

In the analysis, recanalizing thrombosed iliofemoral veins enjoyed high success rates, with up to 95% technical success, 83.36% primary patency and 94.32% secondary patency at one year. The proper application of endovascular technology may play an important role in the high patency rate from iliofemoral stent placement for PTS. In the endovascular procedure for treating PTS, there are two acknowledged difficulties. First, for stent placement, crossing the inguinal ligament is necessary for venous occlusions beneath it. However, stents extending below the inguinal ligament are the major risk factors for in-stent restenosis in patients with PTS.³⁴ Sang et al.²⁶ showed that the Wallstent could cross the inguinal ligament with high primary stent patency and did not report cases of stent fracture.²⁶ Although data on the long-term results of iliofemoral stents that cross the inguinal ligament are lacking, stents with good flexibility have the potential to be safe. Second, for venous obstructions adjacent to the IVC, it is difficult to select the site at which to deploy the stent where it can both avoid coverage of the contralateral iliac vein ostium and secure adequate outflow. In this review, the length of extension into IVC mentioned in three articles ranged from 0.5 cm to 2 cm. However, studies on outcomes of different extension length are lacking.

Importantly, not all symptoms of PTS are ameliorated by satisfactory patency rates, and only half of the patients reported pain and oedema relief. Without control groups, whether these results are part of the natural evolution of PTS remains unknown. The reason for the low symptom relief rate may be attributable to the following reasons. First, venous stent implantation cannot improve all haemodynamic parameters in PTS. The development of symptoms may be due to two pathological mechanisms: persistent venous obstruction and valvular reflux.³⁵ Recanalisation of thrombosed veins by stent placement can also minimise outflow obstruction, which can reduce venous pressure and relieve venous ulceration. In contrast, it is difficult to improve symptoms such as limb swelling, which is the result of valvular insufficiency, while maintaining anatomical patency by stent placement alone.¹¹ Second, the rates of restenosis and reocclusion were high in these studies, and these recurrent thrombotic events are likely to result in symptom recurrence. Although assisted and secondary patency enjoyed high technical success rates, these re-interventions may not be as effective as primary interventions. Third, it is difficult to establish adequate inflow for endovascular recanalisation of the common femoral vein, even if the profunda vein or great saphenous vein is chosen as the inflow. In PTS patients, blood flow occurs through multiple small channels between synechia. On

expansion of the stent between these synechiae, collateral and profunda vein outflow could be occluded by the compression of multiple intraluminal synechiae.³⁶ Previous endovascular surgeons have performed concomitant procedures to address the aforementioned phenomenon, but there is no evidence that these hybrid techniques can achieve better symptomatic relief.^{22–24}

In this review, the ulcer healing rate was high at 75.66%. Compression methods, including stockings and bandages, are considered the standard first line treatment for venous ulceration, with an ulcer healing rate ranging from 31.7% to 86%.^{37–40} In this review, the only study with a control group of patients who were treated conservatively with elastic compression stockings illustrated a significantly higher ulcer healing rate in the stenting group than in the control group (86.6% vs. 70.6%, $p < .01$).²⁷ In some studies, endovascular procedures were performed when PTS ulcers failed to heal with conservative treatment.^{26,28} Therefore, iliofemoral stenting should be an effective therapy for PTS ulcers.

Even though the efficacy of stenting for PTS remains uncertain, it has the potential to be safe. There were no major complications in any of the seven studies involving more than 500 limbs. Minor complications were reported at low rates, with the most frequent complication being back pain followed by per-operative venous injury and 30 day thrombotic events. Although major complications were also rare in open surgical treatment of PTS, the rates of wound infection and haematoma/seroma formation were much higher than in endovascular therapy.^{41–43}

Several limitations of this review should be considered. First, the quality of evidence in this review is weak, mostly because of a lack of control groups. It is difficult to conclude whether these results are truly the effects of stenting or alternatively, a reflection of the natural process of PTS or the influence of other concomitant treatments. Second, since there is no gold standard for PTS diagnosis, personal characteristics of the participants and various symptoms may have affected the outcomes of stenting, and may diminish the interpretability of this review. At the same time, the variation in the standards used for assessing outcomes and the different follow up periods in these studies also increase the risk of potential bias in the review process. Third, an enhanced secondary analysis was used which is a reliable tool for the meta-analysis of studies reporting time to event data, a method that attempts to present long-term aggregated data and perform a meta-analysis of main relevant outcomes. However, as a systematic review, the analysis was not without selection, publication and reporting biases. It is hoped that data derived from the randomised controlled trial (a randomised controlled trial comparing venous stenting with conservative treatment in patients with deep venous obstruction) will further clarify the efficacy and safety of venous stents in PTS.⁴⁴ An ideal comparison between stenting and other treatments for PTS would include a multicentre, prospective, randomised controlled trial with long-term follow up and outcome measures that include validated PTS measures and QOL scores.

CONCLUSION

Endovenous iliofemoral stenting should be considered a treatment option for PTS with iliofemoral obstruction. The quality of evidence to support this treatment is very low. Endovenous stenting has the potential to be effective and has a low risk of peri-operative complications. However, further research with stricter methodology is needed to evaluate the potential role of endovenous stenting for the treatment of PTS.

CONFLICT OF INTEREST

None.

FUNDING

None.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ejvs.2018.09.022>.

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