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Ana Teresa Melanda Alves

Patência a médio prazo do stent ilíaco venoso no síndrome de May-Thurner Não Trombótico: revisão sistemática com meta-análise

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"Mid-term patency of iliac venous stenting for Non-Thrombotic May-Thurner syndrome: a systematic review with meta-analysis."

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É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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Faculdade de Medicina da Universidade do Porto, 18 / 03 / 2021

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DEDICATÓRIA

Aos meus pais e irmã pelo apoio incondicional.

Ao Rúben pela força e dedicação.

À Anabela e ao Manuel António pelo carinho e apoio.

Mid-term patency of iliac venous stenting for Non-Thrombotic May-Thurner Syndrome: a systematic review with meta-analysis

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WHAT THIS PAPER ADDS

Iliac venous stenting has become a proeminent therapeutic choice for patients with symptomatic May-Thurner Syndrome (MTS), either as post-thrombotic syndrome or in its non-thrombotic form (NIVL). This systematic review evaluates long-term performance of venous stenting on NIVL.

Among eligible studies, very good patency rates at 36 months were found, with low associated complications rate. Additionally, a significant clinical improvement was registered since an important patients` proportion reported symptoms relief before and after iliac venous stenting.

This meta-analysis shows that iliac venous stenting may be a secure and durable technique for NIVL treatment, although more research is needed.

ABSTRACT

INTRODUCTION: May-Thurner syndrome (MTS) consists in a compression of the left common iliac vein by the right common iliac artery. Iliac venous stenting represents one of the landmark treatments for symptomatic Non-Thrombotic iliac vein lesion (NIVL). The aim of this systematic review is to evaluate the mid-term patency of iliac venous stenting and assess the symptomatic relief before and after stenting.

EVIDENCE ACQUISITION: Two databases were searched: Medline and Scopus. The last analysis was performed in September 2020. The articles were independently reviewed through their titles and abstracts. All studies that reported patients with NIVL submitted to iliac stenting were included.

EVIDENCE SYNTHESIS: Twelve articles were included in the analysis, totaling 1053 patients with NIVL submitted to iliac stenting, with a proportion of 95.2%. Among twelve articles, six reported primary stent patency after 12 months, with a combined proportion of 94.8%, and three studies evaluated the primary patency after 36 months reporting 96.8%. Four studies reported secondary patency, ranging from 100% to 91% during a follow-up of 18 months and 36 months respectively. Finally, some studies reported a clinical improvement, but only one of them quantified the global clinic improvement of 95.7% after endovascular treatment. Relatively to specific symptoms one study reported 58.5% of edema relief and other an edema cure rate over than 90% and an ulcer healing of 85.0%.

CONCLUSIONS: Iliac venous stenting is a safe and durable treatment in patients with NIVL, with a reduced rates of stent thrombosis and an important incidence of symptoms relief.

Key words: May-Thurner syndrome; Non-Thrombotic iliac vein lesions; stent; iliac vein

INTRODUCTION

May-Thurner syndrome (MTS) is a vascular condition in which the left common iliac vein is compressed by the right common iliac artery, occurring mostly on the left side due to iliac vein course [1, 2]. It presents itself in two major forms: thrombotic, also known as post-thrombotic syndrome, and non-thrombotic (NIVL). The exact prevalence and incidence of MTS are unknown since only a small percentage of patients develop symptoms [3]. It is estimated that 2-5% of acute lower venous disorders are caused by MTS and, according to Kibbe et al, 24% patients with more than 50% of left common iliac vein stenosis do not have symptoms [1, 4]. The progression of venous outflow obstruction with symptoms of chronic venous hypertension is possible with or without thrombosis, but in fact iliofemoral thrombosis increases the severity of the symptoms and the risk of post-thrombotic syndrome [5]. Clinical features of MTS include acute pain, asymmetric swelling, venous claudication and symptoms/signs of venous insufficiency, such as edema, skin hyperpigmentation and ulcers [6, 7].

Management of MTS has progressed through the years mainly due to the increased awareness of the disease and technological developments [8]. Nowadays, endovascular techniques are preferred over conservative treatment, targeting symptoms' relief, the recovery of venous flow and preventing post-thrombotic syndrome [9]. Iliocava stenting has been increasingly applied, however, there is still controversy regarding primary stenting in this cohort of patients [9, 10].

The aim of this study is to assess mid-term patency of venous iliac stenting for NIVL along with symptomatic improvement.

EVIDENCE ACQUISITION

Literature research

For the present study, a systematic review was performed in compliance with PRISMA Statement framework and focusing on Medline and Scopus databases. The databases were analyzed through the following queries:

- Medline: (((((stent[MeSH Terms]) OR (stent[MeSH Terms])) OR (Venous stent)) OR (Venous stenting) OR (Endovascular Procedures[MeSH Terms]) AND (((((May-Thurner Syndrome[MeSH Terms]) OR (Chronic venous insufficiency)) OR (iliac vein stenosis)) OR (iliac vein compression syndrome)) OR (non thrombotic iliac vein lesions))) AND ((((((vein[MeSH Terms]) OR (vein)) OR (venous[MeSH Terms])) OR (venous)) OR (iliac vein[MeSH Terms])) OR (iliac vein));
- Scopus: (ALL (iliac AND vein)) AND (ALL (may-thurner AND syndrome) OR ALL (nonthrombotic AND iliac AND vein AND lesions)) AND (ALL (venous AND stent) OR AND (venous AND stenting)).

The eligibility criteria for study selection were determined in advance. Inclusion criteria consisted of publications reporting iliac venous stenting for non-thrombotic iliac vein lesions subtype of MTS. Exclusion criteria were determined as following: articles published before 2000; reports in non-English languages; non-human studies; systematic reviews and meta-analysis; case reports with less than 10 patients; articles reporting iliac venous stenting after post-thrombotic syndrome; articles reporting MTS with thrombosis.

The last search for reports was performed on September 8, 2020. The articles' selection steps are shown in Figure 1, using the PRISMA flow diagram.

Study selection

All the collected articles were examined by two independent reviewers (TA and JOP), through the analysis of title and abstract and in agreement with the eligibility criteria. In case of disagreement between reviewers, the article in question would be reviewed by a third element (AM). In this initial process, all articles reporting NIVL submitted to iliac venous stenting were included. There were also no limitations on follow-up period, publication status or year of publication.

Data extraction

The two reviewers (TA and JOP) working independently determined each study's eligibility. After this initial process, the articles were further analyzed and the reviewers extracted descriptive, methodological data and results from each study. Disagreements were discussed with a third reviewer (AM), as stated in the "Study Selection" section.

The following data was extracted from each article: year of publication; number of patients with NIVL; number of stents in NIVL group; primary patency of the stent after 12 and/or 36 months; secondary patency of the stent; number of stent thrombosis; signs and symptoms relief after procedure; and procedural details as implanted device and anticoagulation protocol. When available, the demographic characteristics of patients were also collected: age, sex, clinical symptoms, prevalence of some major comorbidities (such as diabetes mellitus, hypertension and hypercoagulability state).

Quality assessment

Newcastle-Ottowa Quality Assessment Scale (NOS) was used to assess studies for their risk of bias. This scale evaluated all studies on three categories: patient selection method, comparability of the study group and evaluation of relevant outcomes. A score below 6 would classify the study with high chance of bias and less overall quality. (Table I).

Outcome assessment

Following these initial steps, statistical analysis ensued. Combined proportion was used to calculate the percentage of patients with NIVL submitted to iliac venous stenting and to calculate the mid-term patency of the stent. The number of stent thrombosis was also evaluated by combined proportion.

Among twelve articles reporting patients with NIVL submitted to iliac venous stenting, six of them reported primary patency after 12 months and only three reported this outcome at 36 months. All studies with primary patency values were included in the meta-analysis, albeit only some of these had secondary patency and number of stent thrombosis.

Primary patency was defined as the permeability of the iliac vein after placement of a stent, assessed by duplex ultrasonography or venography; Secondary patency was defined as flow in the stent applied in the iliac vein after additional intervention due to previous stent occlusion.

To conclude this assessment, symptomatic relief reported by the selected studies was analyzed, both quantitative and qualitatively before and after the endovascular procedure or compared with NIVL treated with conservative measures.

Assessment of heterogeneity

Cochran's Q test and parameter I^2, retrieved from the Higgins and Thompson heterogeneity index (H), measure the impact of heterogeneity in meta-analysis. I^2 quantifies the proportion of the total variation in studies that is due to heterogeneity and not attributable to chance. Regarding the selection of I^2 value and the use of a fixed effects model, many authors consider that a low heterogeneity has its cut-off at 25%, with 50% considered as intermediate heterogeneity. In this meta-analysis, it was determined that if I^2 exceeded 50% a random effects model would be applied, otherwise a fixed effect model was to be used.

Missing data

In cases in which the required data from a study selected for this analysis was absent, contacts with the authors would ensue to obtain as much information as possible.

Following the reviewers' analysis, contact with the authors of one of the articles [16] was carried out to obtain the missing data pertaining to their study that was essential to the present analysis.

Statistical analysis

Jamovi® version 1.6.15 with metafor package software was used to analyze the collected data. All patients who had been implanted with a stent to treat NIVL were included in calculations. Primary patency as well as stent thrombosis were calculated in proportion and with 95% confidence intervals (CIs).

EVIDENCE SYNTHESIS

Research

In a first iteration, 1440 potentially relevant articles were found using the aforementioned methodology. However, after analyzing title and abstract, thirty-eight articles were read in full. Of these, twelve articles mentioned the incidence of treatment with stent in patients with NIVL (n=1053) but, only six reporting iliac stent primary patency at 12 months and three reporting this outcome at 36 months. These were considered eligible in the meta-analysis. The PRISMA flow diagram represented in Figure 1 shows the research progress.

Incidence

The number of patients with NIVL was 1144. Of these, 1053 were eligible to treated with iliac venous stenting [3, 11-21] with a proportion of 95.2% (95% CI 0.93; 0.98; I^2=88.00%) (Figure 2). Significance variance in reporting iliac venous stenting was observed, ranging between 56.3 [15] and 100% [11, 14, 16, 18, 21] (Table II). The remaining patients (n=91) were not treated with iliac venous stenting due to some reasons: refusal of endovascular treatment, eligibility for conservative treatment and technical impossibilities for stent placement.

Demographics and Characteristics

Among the selected articles, the mean age of patients ranged between 39.4 and 57 years (n = 811 [3, 11, 13-16, 20]). The percentage of female patients was 71% [range 54.1-83.9%] (n = 811[3, 11, 13-16, 20]). The average follow-up period obtained was 34.8 months (range 9.6 - 94 months) (n = 1053 [3, 11-21]). The number of patients with hypercoagulable states was reported in four studies (n = 298 [11, 14-16]). Although other risk factors have been mentioned in several studies, they did not refer to the group of patients studied in this systematic review and the comorbidities identified as relevant by the reviewers (as described in section “Data Extraction”), thenceforth they were not included in the demographic characteristics. The characteristics of the studies and patients are presented in Table III and IV.

The type and combination of implanted stents varied in each study. Twelve articles included in this systematic review referred to the intraprocedural and/or post-

procedural anticoagulation protocol with an average duration of 3-6 months. The procedural details are presented in Table V.

Primary Patency

Six studies [3, 11, 13-16] reported primary patency at 12 months. The pooled proportion for this outcome was 94.8% (95% CI 0.92; 0.98; I^2 = 64.56%) (Table VI, Figure 3).

Regarding the 36 months assessment only three articles [13, 14, 21] proceeded to evaluate primary patency. The combined proportion of stent patency was 96.8% (95% CI 0.95; 0.98; I^2 = 0.00%) (Table VI, Figure 4).

Secondary Patency

Four articles [11, 14-16] reported the secondary patency of the iliac venous stent. Due to the heterogeneity of the evaluation, it was not possible to carry out a statistical analysis. However, it was observed that secondary patency had ranged from 100% [11] to 91% [14] for 18 months and 36 months respectively.

Stent Thrombosis

Five articles [3, 11, 13, 14, 21] evaluated the incidence of stent thrombosis related to its failure, with a follow-up variation between 12 months and 62 months. The combined proportion obtained in the meta-analysis was 2.24% (95% CI 0.01; 0.03; I^2 = 44.75%) (Table VI, Figure 5)

Symptoms Relief

Eight [3, 12-17, 19] of the twelve selected studies reported a qualitative improvement in symptoms associated with NIVL, comparing before and after procedure evaluations. The most common symptoms associated with this condition are pain, edema, venous claudication and ulcers.

This outcome was reported quantitatively by four studies. Three of them compared the clinical improvement in NIVL before and after the endovascular procedure: all symptoms relief in 95.7% (Hager et al [14]), edema relief in 58.5% (Liu et al [3]), edema cure over 90% and ulcer healing of 85.0% (Meng et al [13]). The remainder study (Rollo et al [15]) reported the difference between stented and nonstented non-thrombotic patients, showing a clinical improvement of 94.0% vs 57.0%.

DISCUSSION

Iliac venous stenting is increasingly used to treat chronic venous disease including NIVL however, estimated mid term patency is a concern either for patients and interventionists [22]. The present review reports excellent mid-term patency of iliac venous stenting for treatment of NIVL, with low thrombosis stent rate along with a significant symptomatic improvement.

In the present meta-analysis, studies` primary 12 months patency ranged between 88.3% [16] and 100.0% [11, 15]. The lowest value was reported in patients with iliac vein stenosis ≥ 90% [16], whereas in studies with the highest patency the degree of stenosis were lower [11, 15].

Regarding primary patency at 36 months, only three studies with significantly different sample size reported outcomes: n=19 [14], n=177 [21] and n=272 [13].

Despite reported 36 months patency is above 12 month patency, this fact may be related to the paucity and difference in studies reporting such outcomes.

In 2013, Raju et al [23] showed a secondary patency between 90% and 100% during 4 to 7 years. In our work, secondary patency was between 91.0% and 100% during 18 months to 36 months, which is in accordance with previously described.

Different factors may contribute to heterogeneity regarding patency rates among studies. Firstly, stenosis' degree: only Jayaraj et al [16] took into account this variable and reported a lower patency for the patients' subgroup diagnosed with more severe NIVL (stenosis ≥ 90%). Second, type of the implanted stent was different between studies, although is not clear if there can be established a relationship between stent's characteristics and its patency. Finally, the anticoagulation protocol. The absence of a standard protocol regarding anticoagulative and/or anti-aggregative therapeutics during and after the endovascular procedure could contribute to the discrepancies reported for stent's patency. According to the consensus, anticoagulation after procedure do not have clear evidence and the only recommendation is using low molecular weight heparin (LMWH) pre- and postprocedure and intraprocedure heparin [24].

Notwithstanding that most of the included articles in this meta-analysis did evaluate qualitatively the symptoms presented by patients with NIVL, a significant symptomatic improvement was uniform after treatment. Of these, two studies calculated the symptomatic relief before and after procedure, varying between 95.7% [14] and 94% [15]. Two studies specifically reported edema relief ranging between 58.5% [3] and over

90% [13] in patients diagnosed with NIVL. In the future, prospective studies comparing stenting efficacy in symptomatic improvement with conservative treatment is warranted.

Limitations of the study

Limitations can be associated with this systematic review that affect these conclusions. Firstly, only two databases were used which could have led to unnoticed data. Furthermore, only a small number of studies was eligible for the meta-analysis process, hindering all conclusions on the impact of the endovascular procedure in patients diagnosed with NIVL. Finally, only a restrict number of studies described the characteristics of patients diagnosed with NIVL and submitted to stent procedures. Due to these major limitations, heterogeneity can be high in the present study and could have increased the risk of potential bias in the review process.

Conclusion

In conclusion, iliac venous stenting can be considered safe and durable in mid-term treatment of patients with NIVL, reporting a low proportion of thrombosis and a significant improvement of clinical symptoms. Yet, larger studies with longer follow-up is required to ascertain procedural durability.

REFERENCES

1. Bondarev S, Keller EJ, Han T, Young VA, Gupta S, Vogelzang RL, et al. Predictors of Disease Recurrence after Venoplasty and Stent Placement for May–Thurner Syndrome. J Vasc Interv Radiol. 2019;30(10):1549-54.
2. Aldag M, Bademci MS, Kocaaslan C, Oztekin A, Aydin E. Clinical outcomes of pharmacomechanical thrombectomy and iliac venous stenting in iliac vein thrombosis with May-Thurner Syndrome. International Angiology. 2019;38(1):76-7.
3. Liu Z, Gao N, Shen L, Yang J, Zhu Y, Li Z, et al. Endovascular treatment for symptomatic iliac vein compression syndrome: A prospective consecutive series of 48 patients. Annals of Vascular Surgery. 2014;28(3):695-704.
4. Kibbe MR, Ujiki M, Goodwin AL, Eskandari M, Yao J, Matsumura J. Iliac vein compression in an asymptomatic patient population. J Vasc Surg. 2004;39(5):937-43.
5. Diniz J, Coelho A, Mansilha A. Endovascular treatment of iliofemoral deep venous thrombosis: is there enough evidence to support it? A systematic review with meta-analysis. Int Angiol. 2020;39(2):93-104.
6. Birn J, Vedantham S. May-Thurner syndrome and other obstructive iliac vein lesions: meaning, myth, and mystery. Vasc Med. 2015;20(1):74-83.
7. Guex JJ, Mariani F, Maleti O, Hamel-Desnos C, Vasdekis S, Staelens I, et al. European training requirements in phlebology. Int Angiol. 2019;38(5):345-64.
8. Oguzkurt L, Tercan F, Ozkan U, Gulcan O. Iliac vein compression syndrome: Outcome of endovascular treatment with long-term follow-up. European Journal of Radiology. 2008;68(3):487-92.
9. Mousa AY, AbuRahma AF. May-Thurner syndrome: update and review. Ann Vasc Surg. 2013;27(7):984-95.
10. Aboubakr A, Chait J, Lurie J, Schanzer HR, Marin ML, Faries PL, et al. Secondary interventions after iliac vein stenting for chronic proximal venous outflow obstruction. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019;7(5):670-6.
11. Attaran RR, Ozdemir D, Lin IH, Mena-Hurtado C, Lansky A. Evaluation of anticoagulant and antiplatelet therapy after iliocaval stenting: Factors associated with stent occlusion. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019;7(4):527-34.

12. Lou WS, Gu JP, He X, Chen L, Su HB, Chen GP, et al. Endovascular treatment for iliac vein compression syndrome: a comparison between the presence and absence of secondary thrombosis. Korean Journal of Radiology. 2009;10(2):135-43.
13. Meng QY, Li XQ, Qian AM, Sang HF, Rong JJ, Zhu LW. Endovascular treatment of iliac vein compression syndrome. Chinese Medical Journal. 2011;124(20):3281-4.
14. Hager ES, Yuo T, Tahara R, Dillavou E, Al-Khoury G, Marone L, et al. Outcomes of endovascular intervention for May-Thurner syndrome. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2013;1(3):270-5.
15. Rollo JC, Farley SM, Oskowitz AZ, Woo K, DeRubertis BG. Contemporary outcomes after venography-guided treatment of patients with May-Thurner syndrome. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2017;5(5):667-76.e1.
16. Jayaraj A, Buck W, Knight A, Johns B, Raju S. Impact of degree of stenosis in May-Thurner syndrome on iliac vein stenting. Journal of Vascular Surgery: Venous and Lymphatic Disorders. 2019;7(2):195-202.
17. Ahmed O, Ng J, Patel M, Ward TJ, Wang DS, Shah R, et al. Endovascular Stent Placement for May-Thurner Syndrome in the Absence of Acute Deep Vein Thrombosis. J Vasc Interv Radiol. 2016;27(2):167-73.
18. Shi WY, Gu JP, Liu CJ, He X, Lou WS. Endovascular treatment for iliac vein compression syndrome with or without lower extremity deep vein thrombosis: A retrospective study on mid-term in-stent patency from a single center. European Journal of Radiology. 2016;85(1):7-14.
19. Derubertis BG, Alktaifi A, Jimenez JC, Rigberg D, Gelabert H, Lawrence PF. Endovascular management of nonmalignant iliocaval venous lesions. Annals of Vascular Surgery. 2013;27(5):577-86.
20. Xu J, Liu Y, Zhou W. Mid-and long-term efficacy of endovascular-based procedures for Cockett syndrome. Scientific Reports. 2018;8(1).
21. Zhang X, Jing Y, Sang H, Chen Z, Sun Y, Li X. Long-term follow-up of the stenting across the iliocaval confluence in patients with iliac venous lesions. Journal of Thrombosis and Thrombolysis. 2019;47(1):134-9.
22. Seager MJ, Busuttil A, Dharmarajah B, Davies AH. Editor's Choice - A Systematic Review of Endovenous Stenting in Chronic Venous Disease Secondary to Iliac Vein Obstruction. European Journal of Vascular and Endovascular Surgery. 2016;51(1):100-20.

23. Raju S. Best management options for chronic iliac vein stenosis and occlusion. Journal of Vascular Surgery. 2013;57(4):1163-9.
24. Black SA, Alvi A, Baker SJ, Beckett D, Breen K, Burfitt NJ, et al. Management of acute and chronic iliofemoral venous outflow obstruction: a multidisciplinary team consensus. Int Angiol. 2020;39(1):3-16.

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TABLES

Table I: Quality assessment employing the Newcastle-Ottowa Quality Assessment Scale (NOS)

Author	Year	Type of Study	n	Selection	Comparability	Outcome
Lou[12]	2009	Retrospective Study	38	3	1	2
Meng[13]	2011	Retrospective Study	272	3	0	3
Hager[14]	2013	Retrospective Multi Centre Study	19	3	0	3
DeRubertis[19]	2013	Retrospective analysis	7	3	0	2
Liu[3]	2014	Prospective Cohort Study	36	3	0	3
Rollo[15]	2015	Retrospective Study	18	3	1	3
Shi[18]	2016	Retrospective Case Series Study	66	3	0	3
Ahmed[17]	2016	Retrospective Single Centre Study	23	3	0	2
Jayaraj[16]	2018	Retrospective Study	202	3	0	3
Xu[20]	2018	Retrospective Single Centre Study	151	2	0	2
Attaran[11]	2019	Retrospective Single Centre Study	45	3	0	3
Zhang[21]	2019	Retrospective Multi Centre Study	177	3	0	3

Table II: Study characteristics and patients with NIVL submitted to stent.

Study	Year	No. patients with NIVL	Patients with NIVL submitted to stent	
			No.	%
Lou[12]	2009	39	38	97.4%
Meng[13]	2011	296	272	91.9%
Hager[14]	2012	19	19	100.0%
DeRubertis[19]	2013	11	7	63.6%
Liu[3]	2014	42	35	83.3%
Rollo[15]	2015	32	18	56.3%
Shi[18]	2016	66	66	100.0%
Ahmed[17]	2016	34	23	67.6%
Jayaraj ≤60%[16]	2018	55	55	100.0%
Jayaraj 61-89%[16]	2018	87	87	100.0%
Jayaraj ≥90% [16]	2018	60	60	100.0%
Xu[20]	2018	181	151	83.4%
Attaran[11]	2019	45	45	100.0%
Zhang[21]	2019	177	177	100.0%

Table III: Patient demographic characteristics.

Author	Year	Female Gender (%)	Mean Age (years)	Mean time of follow-up (months)	Clinical symptoms	
					Pain (%)	Swelling (%)
Lou[12]	2009	NR	NR	10.2	NR	NR
Meng[13]	2011	160/296 (54.1)	43	46	NR	98/296 (32.4)
Hager[14]	2013	14/19 (73.7)	52.8	22.4	NR	NR
DeRubertis[19]	2013	NR	NR	9.6	11/11 (100.0)	11/11 (100.0)
Liu[3]	2014	24/36 (66.7)	39.4	12	15/36 (41.7)	17/36 (47.2)
Rollo[15]	2015	24/32 (75.0)	46	24	25/32 (78.1)	32/32 (100.0)
Shi[18]	2016	NR	NR	72	NR	NR
Ahmed[17]	2016	NR	NR	21.3	NR	NR
Jayaraj ≤60%[16]	2018	46/55 (83.6)	57	94	NR	NR
Jayaraj 61-89%[16]		73/87 (83.9)	55		NR	NR
Jayaraj ≥90%[16]		46/60 (76.7)	54		NR	NR
Xu[20]	2018	100/181 (55.2)	44	26.4	NR	NR
Attaran[11]	2019	32/45 (71.1)	53.9	18	NR	NR
Zhang[21]	2019	NR	NR	62	NR	NR

NR: Non reported

Table IV: Patient demographic characteristics – continued.

Author	Diabetes Mellitus (%)	Hypertension (%)	Hypercoagulable state (%)
Lou[12]	NR	NR	NR
Meng[13]	NR	NR	NR
Hager[14]	3/19 (15.8)	7/19 (36.8)	0 (0.0)
DeRubertis[19]	NR	NR	NR
Liu[3]	NR	NR	NR
Rollo[15]	NR	NR	7/32 (31.8)
Shi[18]	NR	NR	NR
Ahmed[17]	NR	NR	NR
Jayaraj ≤60%[16]	NR	NR	20/55 (36.4)
Jayaraj 61-89%[16]	NR	NR	38/87 (43.7)
Jayaraj ≥90%[16]	NR	NR	31/60 (51.7)
Xu[20]	NR	NR	NR
Attaran[11]	NR	NR	1/45 (2.2)
Zhang[21]	NR	NR	NR

NR: Non reported

Table V: Procedural details.

Author	Device (stent)	Anticoagulation protocol
Lou[12]	Luminexx stent	LMWH 3-5 days + Warfarin 1-6 months
Meng[13]	NR	NR
Hager[14]	Protegè stent	Heparin bolus intraprocedure AAS + Clopidogrel 3 months + compression stockings
DeRubertis[19]	Protegè stent or Wallstent	Heparin intraprocedure + AAS+Clopidogrel 3 months + Strict compression therapy
Liu[3]	Wallstent	LMWH 4,000IU 12-12h 3 days + warfarin 6 months + compression stockings 3 months
Rollo[15]	Self-expanding stainless steel stents	LMWH intraoperative + AAS+Clopidogrel 3months
Shi[18]	Luminexx stent	LMWH initially + warfarin ≥6months + elastic stockings ≥1y
Ahmed[17]	S.M.A.R.T stent or Wallstent	LMWH before + enoxaparin 2x/d 14days + compression stockings
Jayaraj ≤60%[16]	Wallstent-Z stent +/- Cook Gianturco Z stent	Perioperative LMWH 40mg + Bivalirudina intraoperative + Oral anticoagulants ≥ 3 months + aspirin 81mg+cilostazol 50mg 2x/d ≥ 6 weeks
Jayaraj 61-89%[16]		
Jayaraj ≥90%[16]		
Xu[20]	COOK 1880 Z stent; Wallstent; Luminexx stent; Optimed sinus stent or Protegè stent	Warfarin 6-12 months + elastic stockings 6m-1y
Attaran[11]	Wallstent endoprothesis	Intravenous heparin during intervention Anticoagulation after procedure
Zhang[21]	Luminexx stent or Sinus XL stent	LMWH 5-7 days + Anticoagulation or anti-platelet + compression stockings

Table VI: Outcomes results.

Patency outcome	No. Of studies	No. of patients	Pooled proportion	95% CI	Heterogeneity I^2 (%)
Primary Patency at 12 months (3, 11, 13-16)	6	592	94.8%	0.92-0.98	64.56
Primary Patency at 36 months (13, 14, 21)	3	468	96.8%	0.95-0.98	0.00
Stent Thrombosis (3, 11, 13, 14, 21)	5	549	2.24%	0.01-0.03	44.68

TITLES OF FIGURES

Figure 1 - PRISMA flow diagram for systematic reviews and meta-analysis.

Figure 2 - Forest plot representing the pooled proportion of patients with NIVL submitted to liac venous stenting. A random effects model was used for meta-analysis.

Figure 3 - Forest plot representing the pooled proportion of Primary Patency after 12 months. A random effects model was used for meta-analysis.

Figure 4 - Forest plot representing the pooled proportion of Primary Patency after 36 months. A fixed effects model was used for meta-analysis.

Figure 5 - Forest plot representing the pooled proportion of Stent Thrombosis. A fixed effects model was used for meta-analysis.

FIGURES

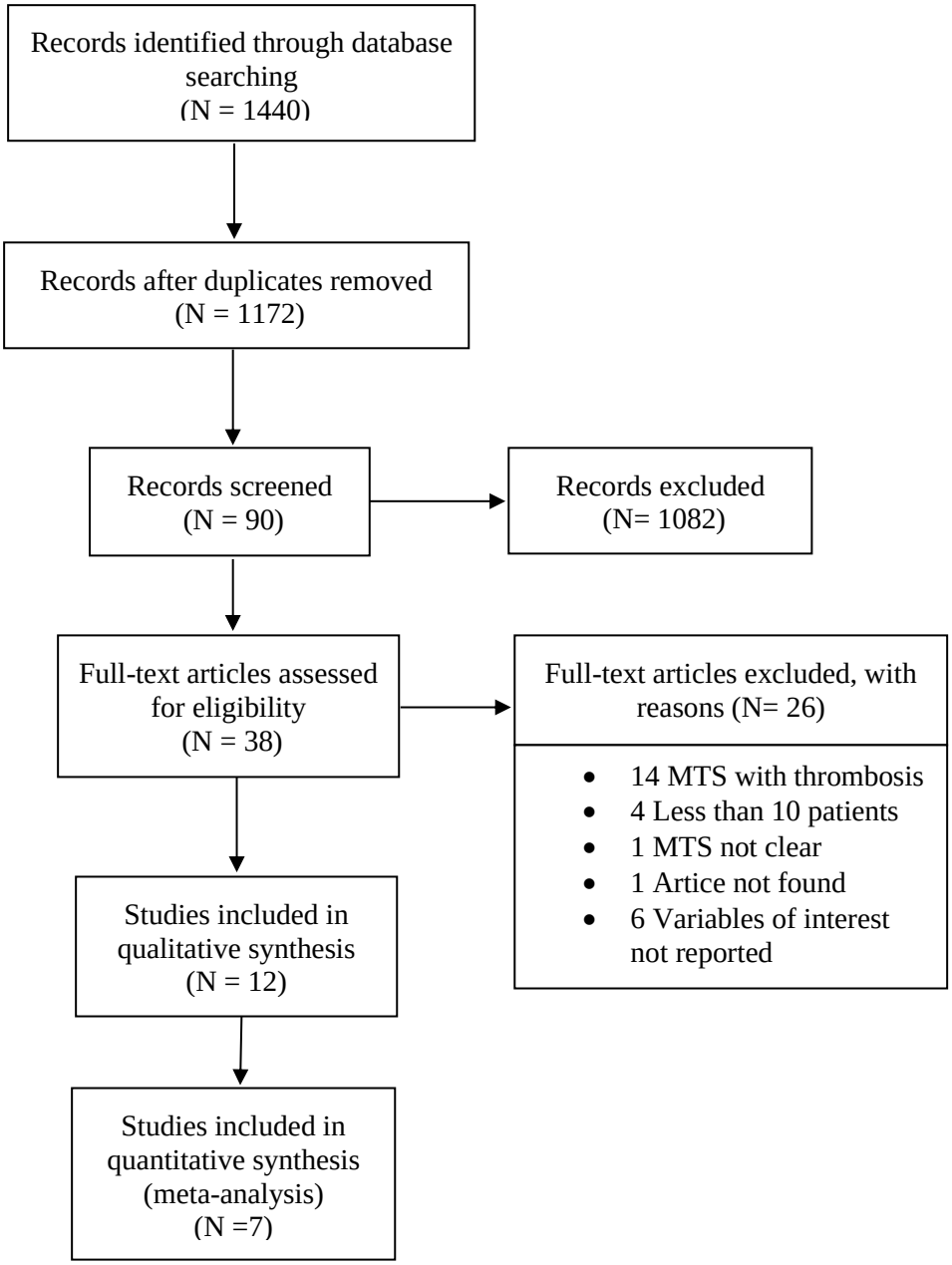
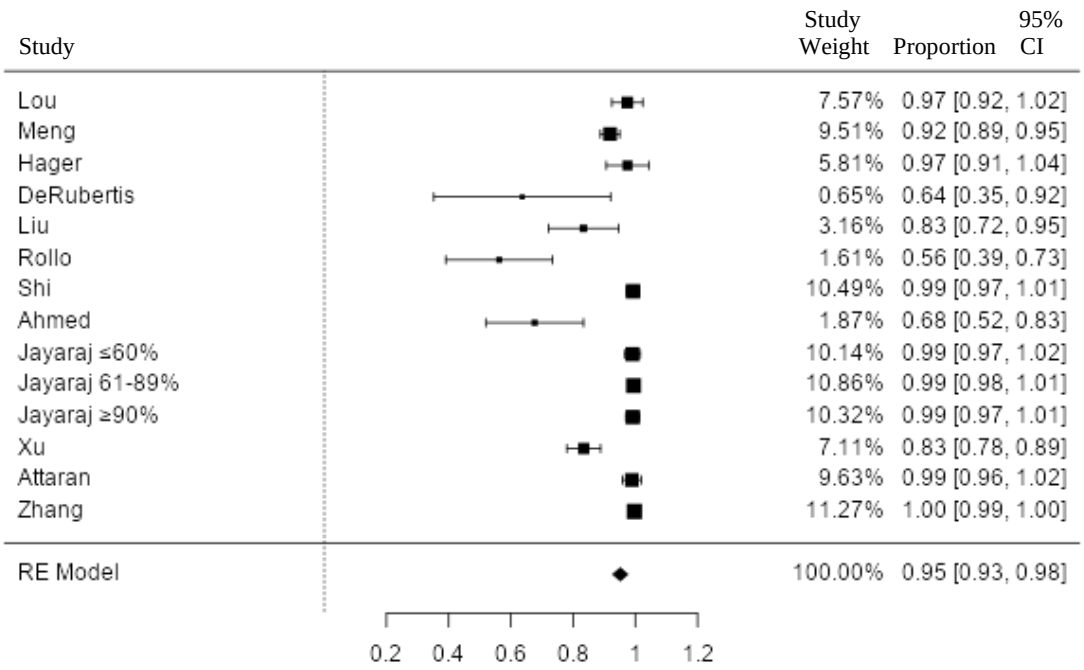
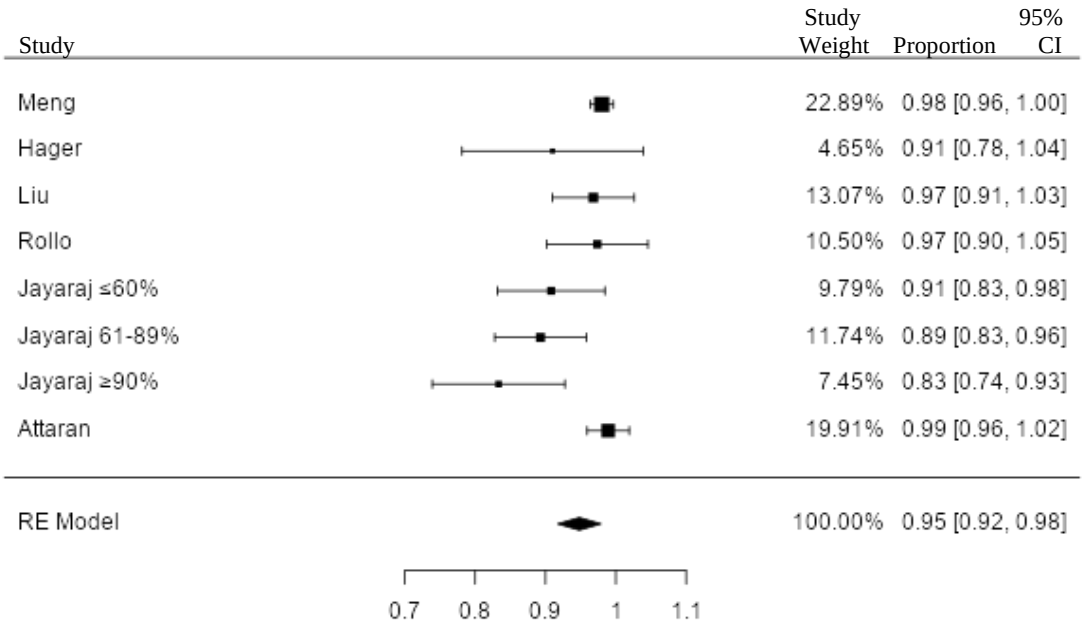


Figure 1 - PRISMA flow diagram for systematic review and meta-analysis.



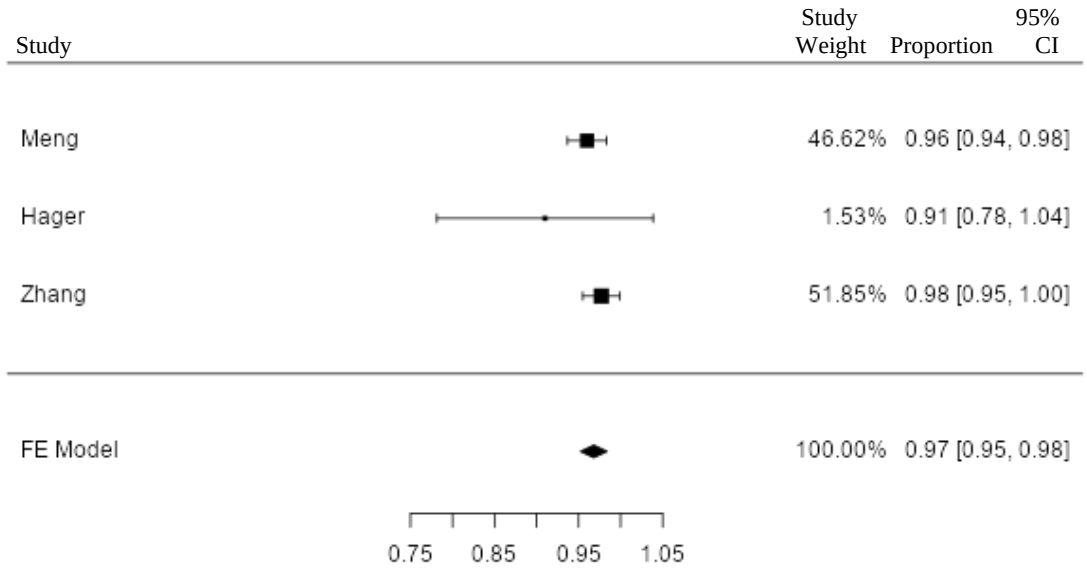
Heterogeneity: I^2=88.00; Q=108.32; p<0.001

Figure 2 - Forest plot representing the pooled proportion of patients with NIVL submitted to iliac venous stenting. A random effects model was used for meta-analysis.



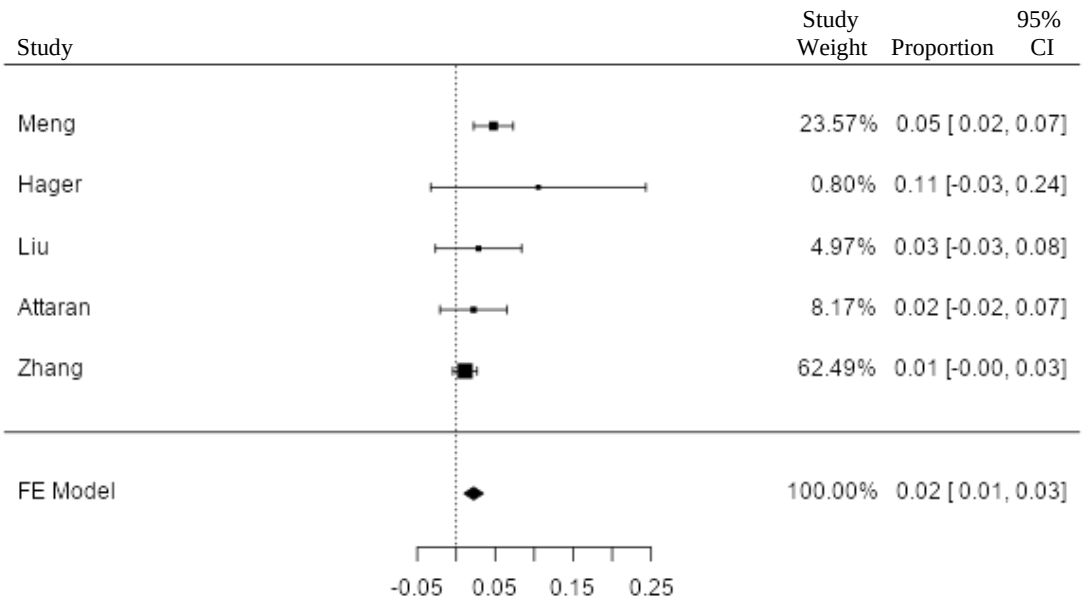
Heterogeneity: I^2=64.56%; Q=19.75; p=0.006

Figure 3 - Forest plot representing the pooled proportion of Primary Patency after 12 months. A random effects model was used for meta-analysis.



Heterogeneity: I^2=0.00%; Q=1.87; p=0.392

Figure 4 - Forest plot representing the pooled proportion of Primary Patency after 36 months. A fixed effects model was used for meta-analysis.



Heterogeneity: I^2=44.75%; Q=7.24; p=0.124

Figure 5 - Forest plot representing the pooled proportion of Stent Thrombosis. A fixed effects model was used for meta-analysis.

AGRADECIMENTOS

Esta importante jornada da minha vida termina para dar lugar a outra que espero que seja recheada de vitórias e muitas alegrias. Contudo, nada teria sido possível sem um conjunto de pessoas:

Ao Professor Doutor Armando Mansilha pela disponibilidade em aceitar ser meu tutor na tese final.

Ao Professor José Pedro Pinto pela co-orientação, por ter estado sempre disponível para me auxiliar na elaboração deste trabalho e por ter esclarecido sempre as minhas dúvidas.

Por fim, à minha família e ao meu namorado por terem estado sempre disponíveis para me ouvir e por contribuírem ativamente na minha vida académica. Sem eles esta longa jornada teria sido muito mais difícil. Aos meus pais e irmã que mesmo longe todos os dias me davam força e ânimo para ultrapassar as adversidades. Ao Rúben Calaia por ser um “porto seguro”.

ANEXOS

Anexo I - PRISMA Statement - Checklist of items that should be included in systematic review and meta-analysis.

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. - **MANDATÓRIO**	Page 1: "Mid-term patency of iliac venous stenting for Non-Thrombotic May-Thurner Syndrome: a systematic review with meta-analysis"
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Page 3: "**INTRODUCTION:** May-Thurner syndrome (MTS) consists in a compression of the left common iliac vein by the right common iliac artery. Iliac venous stenting represents one of the landmark treatments for symptomatic Non-Thrombotic iliac vein lesion (NIVL). The aim of this systematic review is to evaluate the mid-term patency of iliac venous stenting and assess the symptomatic relief before and after stenting. **EVIDENCE ACQUISITION:** Two databases were searched: Medline and SCOPUS. The last analysis was performed in September 2020. The articles were independently reviewed through their titles and abstracts. All studies that reported patients with NIVL submitted to iliac stenting were included. **EVIDENCE SYNTHESIS:** Twelve articles were included in the analysis, totaling 1053 patients with NIVL submitted to iliac stenting, with a proportion of 95.2%. Among twelve articles, six reported primary stent patency after 12 months, with a combined proportion of 94.8%, and three studies evaluated the primary patency after 36 months reporting 96.8%. Four studies reported secondary patency, ranging from 100% to 91% during a follow-up of 18 months and 36 months respectively. Finally, some studies reported a clinical improvement, but only one of them quantified the global clinic improvement of 95.7% after endovascular treatment. Relatively to specific symptoms one study reported 58.5% of edema relief and other an edema cure rate over than 90% and an ulcer healing of 85.0%.

			CONCLUSIONS: Iliac venous stenting is a safe and durable treatment in patients with (NIVL), with a reduced rates of stent thrombosis and an important incidence of symptoms relief.”
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Page 4: “Iliocava stenting has been increasingly applied, however, there is still controversy regarding primary stenting in this cohort of patients.”
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Page 4: “The aim of this study is to assess mid-term patency of venous iliac stenting for NIVL along with symptomatic improvement.”
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	NA
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	Page 5: “The eligibility criteria for study selection were determined in advance. Inclusion criteria consisted of publications reporting iliac venous stenting for Non-Thrombotic iliac vein lesions (NIVL) subtype of MTS. Exclusion criteria were determined as following: articles published before 2000; reports in non-English languages; non-human studies; systematic reviews and meta-analysis; case reports with less than 10 patients; articles reporting iliac venous stenting after post-thrombotic syndrome; articles reporting MTS with thrombosis.”
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.***	Page 5: “…a systematic review was performed in compliance with PRISMA Statement framework and focusing on Medline and Scopus databases.”, “…last search for reports was performed on September 8, 2020.”

		Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	Page 5: "Medline: (((((stent[MeSH Terms]) OR (stent[MeSH Terms])) OR (Venous stent)) OR (Venous stenting) OR (Endovascular Procedures[MeSH Terms]) AND (((((May-Thurner Syndrome[MeSH Terms]) OR (Chronic venous insufficiency)) OR (iliac vein stenosis)) OR (iliac vein compression syndrome)) OR (non thrombotic iliac vein lesions))) AND ((((((vein[MeSH Terms]) OR (vein)) OR (venous[MeSH Terms])) OR (venous)) OR (iliac vein[MeSH Terms])) OR (iliac vein)); - Scopus: (ALL (iliac AND vein)) AND (ALL (may-thurner AND syndrome) OR ALL (nonthrombotic AND iliac AND vein AND lesions)) AND (ALL (venous AND stent) OR AND (venous AND stenting)).”
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Figure 1 Page 5: “The eligibility criteria for study selection were determined in advance. Inclusion criteria consisted of publications reporting iliac venous stenting for Non-Thrombotic iliac vein lesions (NIVL) subtype of MTS.”
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Page 6: “The two reviewers (TA and JOP) working independently determined each study’s eligibility. After this initial process, the articles were further analyzed and the reviewers extracted descriptive, methodological data and results from each study. Disagreements were discussed with a third reviewer (AM), as stated in the “Study Selection” section.”
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Page 6: “…year of publication; number of patients with NIVL; number of stents in NIVL group; primary patency of the stent after 12 and/or 36 months; secondary patency of the stent; number of stent thrombosis; signs and symptoms relief after procedure; and procedural details as implanted device and anticoagulation protocol. When available, the demographic

			characteristics of patients were also collected…
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	Page 6: "Newcastle-Ottowa Quality Assessment Scale (NOS) was used to assess studies for their risk of bias."
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Page 6: "Combined proportion was used to calculate the percentage of patients with NIVL submitted to iliac venous stenting and to calculate the mid-term patency of the stent. The number of stent thrombosis was also evaluated by combined proportion."
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	Page 7: "In this meta-analysis, it was determined that if I^2 exceeded 50% a random effects model would be applied, otherwise a fixed effect model was to be used."
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	NA
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	Figure 1 Page 8: "The PRISMA flow diagram represented in Figure 1 shows the research progress."

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	Tables III, IV and V. Page 8: "The characteristics of the studies and patients are presented in Table III and IV. The type and combination of implanted stents varied in each study. Twelve articles included in this systematic review referred to the intraprocedural and/or post-procedural anticoagulation protocol with an average duration of 3-6 months. The procedural details are presented in Table V."
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Table I: "Quality assessment employing the Newcastle-Ottowa Quality Assessment Scale (NOS)" Page 6: "Newcastle-Ottowa Quality Assessment Scale (NOS) was used to assess studies for their risk of bias. This scale evaluated all studies on three categories: patient selection method, comparability of the study group and evaluation of relevant outcomes."
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	Figures 2, 3, 4 and 5.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	Page 9: "…pooled proportion for this outcome was 94.8% (95% CI 0.92; 0.98; $I^2 = 64.56\%$)…"; "…combined proportion of stent patency was 96.8% (95% CI 0.95; 0.98; $I^2 = 0.00\%$)…"; "…combined proportion obtained in the meta-analysis was 2.24% (95% CI 0.01; 0.03; $I^2 = 44.75\%$)…"
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	Page 10: "The present review reports excellent mid-term patency of iliac venous stenting for treatment of NIVL, with low thrombosis stent rate along with a significant symptomatic improvement."
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	Page 11: "Limitations can be associated with this systematic review that affect these conclusions. Firstly, only two databases were used which could have led to unnoticed data. Furthermore, only a small number of studies was eligible for the meta-analysis process, hindering all conclusions on the impact of the endovascular procedure in patients diagnosed with NIVL. Finally, only a restrict number of studies described the characteristics of

			patients diagnosed with NIVL and submitted to stent procedures. Due to these major limitations, heterogeneity can be high in the present study and could have increased the risk of potential bias in the review process."
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	Page 11: "In conclusion, iliac venous stenting can be considered safe and durable in mid-term treatment of patients with NIVL, reporting a low proportion of thrombosis and the significant improvement of clinical symptoms. Yet, larger studies with longer follow-up is required to ascertain procedural durability."
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Page 15: "*Funding*. - The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work."

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Legend: NA – Not applicable

Anexo II: International Angiology instructions for manuscript formatting.

INSTRUCTIONS FOR MANUSCRIPT FORMATTING

- Insert the text in the relevant sections according to the instructions you will find in the boxes and then remove all boxes (including this one)
- Submit the file as plain unformatted text; use the same font all over the manuscript: Times New Roman 12, 1.5 line spacing
- Do not insert line numbers, page numbers, headings or footnotes
- Figures should not be included in the manuscript file – please upload them as separate files from the text at the online submission system
- Insert references as plain text without using footnotes and endnotes of Word
- Active hyperlinks should not be included in the text or in the references.

TITLE
Short title, with no abbreviations, in lowercase upright letters.

Manuscript title

RUNNING TITLE
A shortened version of the title, in lowercase upright letters.

Running title

AUTHORS
Authors must meet the criteria for authorship established by the Uniform Requirements for Manuscripts Submitted to Biomedical Editors by the International Committee of Medical Journal Editors (ICJME).
Author's name must be written in full, middle name's initial in capital letters and surname.
Names must be separated by a comma. Superscribe the Arabic numeral referring to the author's institution. Numbering should begin with the name of the first author. Please mark the corresponding author with an asterisk. A collective author can be added as last author.

ALL AUTHORS ARE INDIVIDUAL AUTHORS CASE 1

Name M. SURNAME [1] *, Name M. SURNAME [2], Name M. SURNAME [3]

COLLECTIVE AUTHOR – CASE 2
All individual authors named in the byline are also part of the Group Name on behalf of which they have prepared the manuscript. All members of the collective author, including the manuscript's authors, may be listed at the end of the manuscript under the Group Name (see Notes section at the end of the template) and will appear in PubMed as Collaborators. In this case individual authors will redundantly be included both as authors and as Collaborators.

Name M. SURNAME [1] *, Name M. SURNAME [2], Name M. SURNAME [3] on behalf of/ for Group Name ‡

‡Members are listed at the end of the paper (optional)

COLLECTIVE AUTHOR – CASE 3
Some of the individual authors named in the byline are also part of the Group Name. All members of the collective author, including some of the manuscript's authors, may be listed at the end of the manuscript under the Group Name (see Notes section at the end of the template). All members of the collective author will appear in PubMed as Collaborators. In this case some individual authors will redundantly be included both as authors and as Collaborators.

Name M. SURNAME [1] *, Name M. SURNAME [2], Name M. SURNAME [3], Group Name ‡

‡Members are listed at the end of the paper (optional)

COLLECTIVE AUTHOR – CASE 4
None of the individual authors named in the byline is part of the Group Name. All members of the collective author may be listed at the end of the manuscript under the Group Name (see Notes section at the end of the template). All members of the collective author will appear in PubMed as Collaborators.

Name M. SURNAME [1] *, Name M. SURNAME [2], Name M. SURNAME [3], Group Name ‡

‡Members are listed at the end of the paper (optional)

[1]Section, Department, Institution, Town, Country; [2]Section, Department, Institution, Town, Country; [3] Section, Department, Institution, Town, Country

AFFILIATIONS
Every entry must be accompanied by the superscribed Arabic numeral of the author in question and must be complete (Section, Department, Institution…). Affiliations should be separated by a semicolon without any line break.

*Corresponding author: Name M. Surname, Section, Department, Institution, Address, Zip Code, Town, Country. E-mail:

CORRESPONDING AUTHOR
Name, address, e-mail of the corresponding author preceded by "*Corresponding author:"

ABSTRACT
Articles should include an abstract of between 200 and 250 words. For systematic reviews and meta-analyses, the abstract should be structured as follows: introduction, evidence acquisition, evidence synthesis, conclusions. Insert the text in the related sections; typeset subtitles in upright non-italicized uppercase text followed by a colon.

INTRODUCTION:

EVIDENCE ACQUISITION:

EVIDENCE SYNTHESIS:

CONCLUSIONS:

Key words:

KEY WORDS:
Key words should refer to the terms from Medical Subject Headings (MeSH) of the Index Medicus and should include at least three items.

TEXT

Review articles. These articles are commissioned by the Editor in Chief or the Managing Editor. They should discuss a topic of current interest, outline current knowledge of the subject, analyze different opinions regarding the problem discussed, be up-to-date on the latest data in the literature. Systematic reviews and meta-analyses must be subdivided into the following sections: introduction, evidence acquisition, evidence synthesis, conclusions. For systematic reviews and meta-analyses it is suggested to the authors to follow the guidelines reported by the PRISMA statement (http://www.prisma-statement.org). The text should be 6000-12000 words (17 to 34 typed, double-spaced pages) not including references, tables, figures. No more than 100 references will be accepted.

Insert the text here.

REFERENCES

It is expected that all cited references will have been read by the authors. The references must contain only the authors cited in the text, be numbered in Arabic numerals and consecutively as they are cited. Bibliographical entries in the text should be quoted using superscripted Arabic numerals. References must be set out in the standard format approved by the International Committee of Medical Journal Editors (http://www.icmje.org).

JOURNALS

Each entry must specify the author's surname and initials (list all authors when there are six or fewer; when there are seven or more, list only the first six and then "et al."), the article's original title, the name of the Journal (according to the abbreviations used by MEDLINE/PubMed), the year of publication, the volume number and the number of the first and last pages. When citing references, please follow the rules for international standard punctuation carefully.

- Standard article

Liu H, Li J, Du L, Yang M, Yang D, Li J, *et al.* Short-term effects of core stability training on the balance and ambulation function of individuals with chronic spinal cord injury: a pilot randomized controlled trial. Minerva Med 2019;110:216-23.

- Both individual authors and organization as author

Castelli E, Fazzi E; SIMFER-SINPIA Intersociety Commission. Recommendations for the rehabilitation of children with cerebral palsy. Eur J Phys Rehabil Med 2016;52:691-703.

- Issue with supplement

Lacarrubba F, Musumeci ML, Martorell A, Palmucci S, Petrillo G, Micali G. Role of the Imaging Techniques in the Diagnosis and Staging of Hidradenitis Suppurativa. G Ital Dermatol Venereol 2018;153 (3 Suppl 2): 20-5.

BOOKS AND MONOGRAPHS

For occasional publications, the names of authors, title, edition, place, publisher and year of publication must be given.

- Books by one or more authors

Rossi G. Manual of Otorhinolaryngology. Turin: Edizioni Minerva Medica; 1987.

- Chapter from book

Donas K, Torsello G. Management of restenosis after carotid artery stenting and carotid endarterectomy. In: Jacobs M (editor). Prevention and management of vascular complications. Turin: Edizioni Minerva Medica; 2011. p.17-20.

- Congress proceedings

Novo S, Angelides N, Fletcher J, Roztocil K, editors. A multidisciplinary approach to cardiovascular diseases. Proceedings of the 1st Meeting of the Multidisciplinary Chapter of the International Union of Angiology (IUA); 2014 Oct 2-5; Palermo, Italy. Turin: Edizioni Minerva Medica; 2016.

ELECTRONIC MATERIAL

- Standard journal article on the Internet

Williams JS, Brown SM, Conlin PR. Videos in clinical medicine. Blood-pressure measurement. N Engl J Med. 2009 Jan 29;360(5):e6.

- Article published electronically ahead of the print version

Di Pierro F, Bertuccioli A, Cavecchia I, Possible therapeutic role of a highly standardized mixture of active compounds derived from cultured Lentinula edodes mycelia (AHCC) in patients infected with 2019 novel coronavirus. Minerva Gastroenterol Dietol 2020. [Epub ahead of print]

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