Venous stenting for patients with outflow obstruction and leg ulcers: cost–effectiveness and budget impact analyses

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Aim: To perform cost–effectiveness analysis (CEA) and budget impact analysis (BIA) comparing stenting to standard medical treatment (SMT) for the management of deep venous outflow obstruction and leg ulcers from the Italian Healthcare Service perspective. **Materials & methods:** A Markov model was developed to project costs and quality-adjusted life-years (QALYs) over 3 years, based on data from literature combined with real-world data. Moreover, a BIA was performed comparing the current scenario (100% SMT) with increasing utilization rates of stenting over SMT from 0.5 to 5%, in the next 5 years. **Results:** Stenting is a cost-effective (incremental cost-utility ratio €12,388/QALY) or dominant option versus SMT, according to in-patient or day-hospital settings, respectively. Increasing use of stenting over SMT, in the next 5 years, is expected to yield additional costs of 39.5 million Euros (in-patient) or savings of 5.1 million Euros (day-hospital). **Conclusion:** Stenting is a cost-effective option compared with SMT for patients with deep vein occlusion and ulceration in Italy.

Deep vein outflow obstruction is a hemodynamic condition due to stenosis and/or occlusion of the cava and/or iliofemoral veins. It is mainly secondary, caused by post-thrombotic deep veins fibrosis and scarring, but it can be also primary, due to iliac vein nonthrombotic lesions such as compression.

Post-thrombotic syndrome (PTS) is a common long-term complication of deep vein thrombosis (DVT), which consists in chronic venous symptoms and/or signs. Among these, ulcer occurrence is the ultimate and most severe presentation of PTS. Peak prevalence of leg ulceration occurs in the age group 60–80 years and the prevalence rate is expected to increase as the population ages [1]. The disease severity is usually assessed using the Villalta score [2]. Post-thrombotic syndrome occurs in about 20–50% of patients with DVT. The variety of diagnostic scoring systems may be a cause of lack of precision in the reported epidemiological data related to this condition [3].

The mainstay of treatment for the prevention of PTS is elastic compression therapy. So far, few studies have assessed the value of this treatment starting in the acute or subacute phase after DVT, reporting divergent results [4–7]. Moreover, the best onset of compression therapy for the prevention of PTS is unwell defined and narrowly explored.

Compression therapy, with or without anticoagulants, is considered the standard conservative treatment modality [8] for patients with deep venous obstruction and venous ulceration.

In the last years, the endovascular approach to outflow obstruction treatment opened the way to minimally invasive recanalization of the obstructed vein through stent placement, thus drawing the attention on these

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therapeutic opportunities [9]. These procedures are safe and effective leading to alleviation of the symptoms in the lower extremities [10]. On the other hand, the evidences are derived mainly from retrospective studies conducted in single centers and with limited sample sizes.

The aim of the present study was to develop knowledge on the clinical and economic implications of both treatment strategies in order to support the stakeholders at national level in the management of patients with deep venous obstruction and leg ulcers. In particular, the main aim of the study was to perform a cost–effectiveness analysis comparing endovascular venous stenting procedure to standard medical treatment (SMT, compression therapy ± anticoagulation), from the Italian Healthcare System perspective. The second aim of the study was to assess the budget impact on the public healthcare expenditure of an increased diffusion of the endovascular treatment over SMT for patients with deep venous obstruction and leg ulcers.

In the preliminary phase of the study, a systematic literature review has been performed to derive the clinical evidences for the two options in order to populate the cost–effectiveness model, as better specified in the Methods section.

Methods

Literature review

A literature review has been conducted in order to retrieve clinical evidences on deep vein obstruction and presence of ulcers, and in particular rates of ulcers healing and recurrence for both stenting procedure and SMT. The search focused on studies published in the last ten years. A systematic literature search has been performed through Pubmed and Web of Science databases in July 2019. The search strategy and PRISMA diagrams are presented in Supplementary Material 1.

Studies were considered if published in English and if they referred to an adult population. Studies were included in case they provided data on clinical evidence for the use of the two treatment options. Both comparative and single-arm studies were considered. Editorials, case reports, letters and reviews were not considered.

The selection of abstracts and full-texts was conducted independently by two expert reviewers (CR, RT). In case of debate on eligibility, studies were verified in a collaborative way until a consensus was obtained. Through a customized template developed in Microsoft Excel, the following data were extracted from the retrieved studies: study features, participants' characteristics and clinical outcomes.

As much importance is given to the collection and analysis of real-world data for the evaluation of outcomes and costs of health technologies [11,12], clinical data on endovascular stenting, collected at Hesperia Hospital, which is the hospital in Italy presenting the largest case-series, have been retrieved in order to estimate rates of ulcers healing and recurrence in the clinical practice, to integrate the literature search.

Clinical data synthesis

Twenty-nine studies have been retrieved reporting data for stenting procedure, of which 19 reported data on ulcer healing rates and recurrence rates. Concerning standard medical therapy, eight studies with available data were extracted. Those studies considered different types of compression therapy, in particular stockings, bandages (with different number of layers: two, four, multi-layer) and Unna's boot.

Tables 1 & 2 show the study characteristics and retrieved data. Table 2 includes also the real-world data on stenting regarding 64 patients affected by primary obstruction, collected at Hesperia Hospital in Modena, Italy (study Lugli-Longhi-Maleti). These real-world data reported 11 active ulcers with 91% healing rate (mean healing time 3 months) and 0% of recurrences considering a follow-up of 24 months.

The evidences retrieved from the literature were retrospective or prospective studies presenting data on healing and recurrence rates. Evidence was neither available from head-to-head trials comparing the two options, nor from trials comparing each of the interventions of interest with the same comparator (e.g. placebo), so the method of indirect comparisons [38] was not applicable and, therefore, separate meta-analyses have been performed for stenting and SMT considering single arm data on percentage of ulcer healing and recurrence. In order to facilitate comparisons, for meta-analyses and CEA modeling, ulcers recurred have been reported as a percentage of the number of active ulcers.

The analyses have been performed using Stata software (metaprop command). A random-effect model was applied assuming that the true effect size varies among the studies [39]. A test on the summary effect measure has been reported, as well as a test for heterogeneity quantified by I^2 (range 0%–100%, higher values representing higher heterogeneity among the studies) [40]. Figures 1 & 2 report the forest plots obtained. Studies concerning

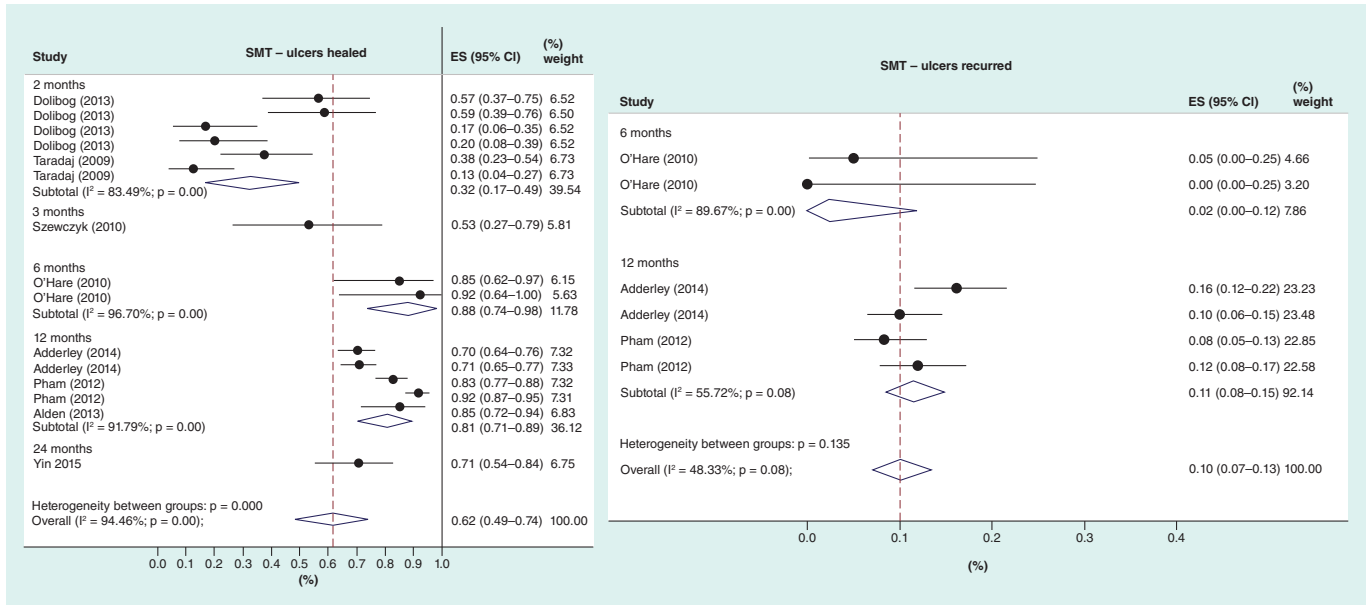**Figure 1.   Forest plots for % of ulcers healed and % of ulcers recurred for SMT.**
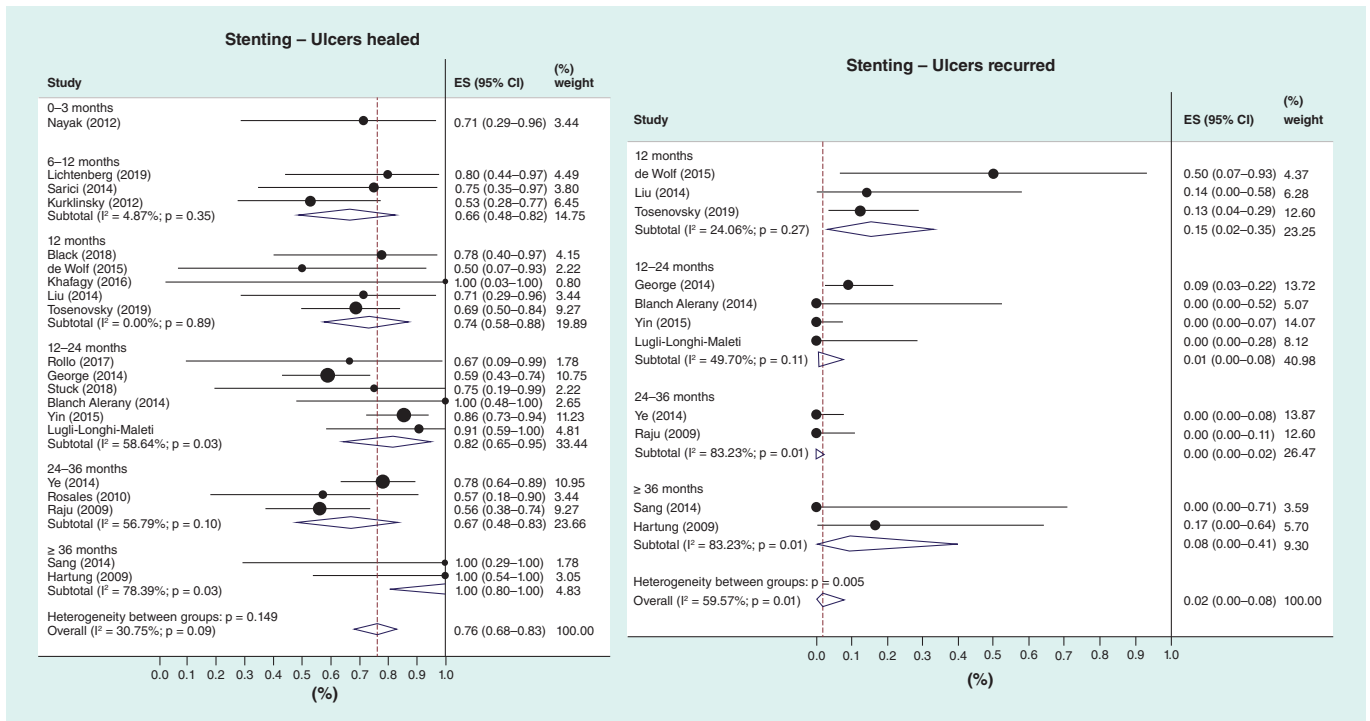ES: Effect size; SMT: Standard medical treatment.

Figure 2.   Forest plots for % of ulcers healed and % of ulcers recurred for endovascular treatment.

Table 1. Study characteristics for standard medical therapy.

Study (year)	Study type	Country	Type of therapy	FUP (months)	N pts	N ulcers	% healed	Healing time (days)	% recurrences[†]	Ref.
Adderley et al. (2014)	Multicenter randomized controlled trial	England and Northern Ireland	Bandages	12	224	224	70%	98	23%	[13]
			Stockings	12	230	230	71%	99	14%	
Alden et al. (2013)	Retrospective study	USA	Compression	12	47	47	85%	154	49%	[14]
Dolibog et al. (2013)	Prospective, randomized, comparative study	Poland	Stockings	2	30	30	57%	NA	NA	[15]
			Multi-layer short-stretch bandaging	2	29	29	59%	NA	NA	
			Two-layer short-stretch bandaging	2	30	30	17%	NA	NA	
			Unna's boot	2	30	30	20%	NA	NA	
O'Hare et al. (2010)	Randomized controlled trial	UK	Four-layer compression bandages	6	20	20	85%	NA	6%	[16]
			Four-layer compression bandages with additional foam sclerotherapy	6	13	13	92%	NA	0%	
Pham et al. (2012)	Randomized trial	Canada	Four-layer bandage	12	215	215	83%	62	10%	[17]
			Short-stretch bandage	12	209	209	92%	77	13%	
Szewczyk et al. (2010)	Randomized trial	Poland	Stockings	3	15	15	53%	NA	NA	[18]
Taradaj et al. (2009)	Prospective randomized clinical trial	Poland	Compression stockings and drug therapy	2	40	40	38%	NA	NA	[19]
			Short-stretch bandages and drug therapy	2	40	40	13%	NA	NA	
Yin et al. (2015)	Retrospective review	China	Stockings	24	94	41	71%	NA	NA	[20]

[†]Percentages are calculated on the number of healed ulcers.
FUP: Follow-up; NA: Not available; pts: Patients.

SMT and stenting considered a maximum follow-up of 24 and 36.2 months, respectively.

For SMT the percentage of ulcers healed was 62% (mean healing time 3 months), with 10% of recurrences, while for stenting those values were 76% (mean healing time 2.2 months) and 2%. The higher heterogeneity among studies was reported for ulcers healed with SMT.

The model

A CEA model has been developed with TreeAge Pro Software (TreeAge Software, Inc., MA, USA) in order to compare venous stenting with SMT from the National Healthcare Service perspective in Italy. The analysis was reported according to Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [41]. The CHEERS checklist is reported in Supplementary Material 2.

A Markov multistate model has been developed to estimate quality-adjusted life years (QALYs) and economic outcomes associated with stenting procedure and SMT in an adult population with deep venous outflow obstruction and leg ulcers. Markov models, which are frequently used in economic evaluations, allow to represent the possible consequences of the options of interest. The model has been informed by percentages of ulcers healed and recurred obtained from the meta-analyses. As the longest mean follow-up considered in the studies was about 36 months, this time horizon has been considered in the model. A discount rate of 3% has been applied to QALYs and costs [42] and 1-month Markov cycle length has been chosen.

The health states considered in the implemented model were: 'active ulcer', 'healed ulcer' and 'recurred ulcer'. Because in the literature there is insufficient evidence for an increased risk of mortality with venous leg ulcers [43],

Table 2. Study characteristics for endovascular treatment.

Study (year)	Study type	Country	FUP (months)	N pts	N stents	Procedural success	N ulcers	% ulcers healed	Mean healing time (months)	% recurrences[†]	Ref.
Black et al. (2018)	Retrospective single-center study	UK	12	88	101	NA	9	71%	NA	NA	[21]
Blanch Alerany et al. (2014)	Prospective study	Spain	21	36	41	95%	5	100%	NA	0%	[22]
de Wolf et al. (2015)	Prospective study	NA	5.4	40	40	100%	4	50%	NA	100%	[23]
George et al. (2014)	Retrospective review of a case series	India	15	38	44	NA	44	60%	1.5	14%	[24]
Hartung et al. (2009)	Prospective study	France	38	89	89	98%	6	100%	NA	17%	[25]
Khafagy et al. (2016)	Prospective study	Egypt	12	12	12	67%	1	100%	NA	NA	[26]
Kurklinsky et al. (2012)	Retrospective study	USA	11.3	89	91	100%	17	53%	NA	NA	[27]
Lichtenberg et al. (2019)	Prospective study	Germany	6	80	116	NA	10	80%	NA	NA	[28]
Liu et al. (2014)	Prospective cohort study	China	12	48	48	96%	7	71%	NA	29%	[29]
Lugli-Longhi-Maleti et al. (2019)[‡]	Real-world data	Italy	24	64	64	100%	11	91%	3	0%	
Nayak et al. (2012)	Retrospective study	USA	11.7	44	50	96%	7	71%	NA	NA	[30]
Raju et al. (2009)	Prospective study	USA	33	159	167	83%	32	56%	NA	0%	[31]
Rollo et al. (2017)	Retrospective study	USA	3	31	42	100%	3	67%	3	NA	[32]
Rosales et al. (2010)	Prospective study	Norway	33	34	34	94%	7	57%	3	NA	[33]
Sang et al. (2014)	Retrospective study	China	36.2	67	67	94%	3	100%	NA	0%	[10]
Sarici et al. (2014)	Prospective study	Turkey	6	52	59	100%	8	75%	NA	NA	[34]
Stuck et al. (2018)	Prospective study	Switzerland	21	64	64	98%	4	75%	NA	NA	[35]
Tosenovsky et al. (2019)	Prospective study	Australia	12	109	118	100%	32	53%	3	18%	[36]
Ye et al. (2014)	Retrospective study	China	25	110	118	95%	46	78%	NA	0%	[37]
Yin et al. (2015)	Retrospective study	China	24	122	122	95%	49	87%	NA	0%	[20]

[†] Percentages are calculated on the number of healed ulcers.
[‡] Real-world data from Hesperia Hospital, Modena, Italy.
FUP: Follow-up; NA: Not available; pts: Patients.

a death state has not been included in the model. No mortality has been shown also in Hesperia Hospital, which has the largest case-series on endovascular stenting in Italy for this kind of patients. In the view of the limited time horizon of the model and the mean age of the indicated population, also overall mortality has not been considered. Moreover, considering that no complications [32,36] or low rates of complications (2%) [35] are reported for stenting in more recent studies, also a complication health state has been excluded from the model.

Adult patients with deep venous outflow obstruction and leg ulcers enter the Markov model in the 'active ulcer' health state; they may stay in the 'active ulcer' state or, in case of healing, may move to the 'healed ulcer' state. In case of ulcer recurrence, patients will move from 'healed ulcer' to 'recurred ulcer' health state.
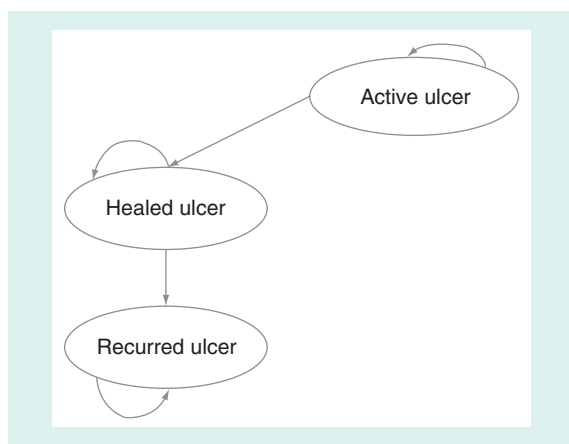
Figure 3.   Representation of the implemented model.

Table 3. Healthcare resource consumption and associated costs.		
Item	**Cost**	**Ref.**
Endovascular procedure (stenting)	€2258 (day-hospital setting for stenting) €4742 (regular hospital admission for stenting)	Diagnosis Related Group 479: Other vascular procedures without complications
Compression therapy and anticoagulants	€16.02 per week	[44]
Ulcer management	Healed ulcer €3450 Unhealed ulcer €15,574	[45]

Transition probabilities between health states for patients undergoing SMT or stenting have been estimated according to percentages of ulcers healed and recurred retrieved by the meta-analyses (Supplementary Table 1). Exponential functions have been considered leading to constant transition probabilities. For the health state 'healed ulcer' the model considers a healing time of 2 and 3 months for stenting and SMT, respectively, so transition probabilities for these states are set equal to 0 in the subsequent period. The model structure is presented in Figure 3, while Supplementary Figure 1 reports patients' distributions (Markov cohort analysis) over time among the health states for SMT and stenting.

Healthcare resource consumption & costs

The model included only direct healthcare resource consumption (direct costs; Eur, 2019). For the endovascular procedure two models of care were considered, in other words, regular hospital admission and day-hospital care. The Italian NHS uses the DRG system to remunerate hospital services. DRG 479 refers to vascular procedure but its tariff differs according to whether it is delivered in day-hospital (€2258) or through a regular admission (€4742).

The cost of compression therapy and anticoagulants has been estimated in €14.3 per week from [44] (€16.02 up-lifted to year 2019). Because compression therapy is often combined with endovascular treatment, this cost has been computed in both treatment strategies.

For both compared options, the management cost for a healed ulcer has been estimated in £2981 (€3450) per patient from a published study in the UK context [45]. The same study reported a mean cost per patient for unhealed ulcer of £13,455 (€15,574) that in the model has been considered for active ulcer and for ulcer recurrence. These costs include visits, exams, dressings and drugs (e.g., analgesics and anti-infectives) and cover a time horizon of 1 year.

Costs related to the healthcare resource consumption are summarized in Table 3.

Quality-of-life estimates

For the utility coefficients for the health states of the model we made reference to a published study [46] which collected health utility data from 200 people with venous leg ulcers using the standard gamble method. We considered 0.73 (range 0.70–0.76) for active ulcer, 0.64 for recurred ulcer (range 0.61–0.68) and 1 for healed ulcer.

Cost–effectiveness analysis

The incremental cost-utility ratio (ICUR) has been calculated as the difference in mean expected costs (i.e., incremental cost, ΔC) between endovascular treatment and SMT divided by the difference in mean expected outcomes (i.e., incremental QALYs, ΔE) between these strategies (ICUR = $\Delta C/\Delta E$).

Deterministic and probabilistic sensitivity analyses (PSA) have been performed in order to test the robustness of the model. Univariate analyses have been performed according to the monthly cost of compression and anticoagulants, the cost for the management of healed ulcer and unhealed ulcer, the cost for the endovascular procedure, utility coefficients for active ulcer, healed ulcer and recurred ulcer and discount rate. The discount rate has been varied between 0 and 10%, while the other parameters have been varied of ±20% of their baseline values. The results of the analyses have been reported as tornado diagrams for the ICUR according to both settings for stenting (regular hospital admission and day-hospital). The PSA has been conducted by assigning distributions to model parameters (beta for utilities and gamma for costs, with a standard deviation of 20% of the baseline value). In Monte Carlo simulations, all parameters were randomly sampled from their assigned distributions considering a cohort of 10,000 patients. Results have been presented graphically as scatterplots in the cost–effectiveness plane considering a cost–effectiveness threshold of 30,000€. Supplementary Table 2 reports the details on the parameters used in these analyses.

In absence of strong evidences that report lower recurrence rates for stenting than SMT, the structural uncertainty of the model has been explored by using one pooled estimate for this parameter for both strategies. Consequently, a meta-analysis has been performed on percentage of ulcers recurred by pooling the studies on SMT and stenting retrieved from the systematic literature search. This meta-analysis yielded a percentage of ulcers recurred equal to 4% (Supplementary Figure 2).

Another structural uncertainty has been evaluated by including a death state in the model representing overall mortality according to Italian life tables [47]. A population aged 60 years as evaluated by Cheng and colleagues [43] has been considered entering the model since vein obstruction and leg ulcers mainly affect the elderly population.

Budget impact analysis

A BIA has been developed based on the CEA model in order to estimate the expected changes in the next 5 years in the public healthcare expenditure for the Italian Healthcare Service in the hypothesis of an increased utilization of stenting over SMT for patients experiencing deep vein obstruction and ulceration. The analysis has been conducted in accordance with the ISPOR Principles of Good Practice for Budget Impact Analysis [48].

The model has been developed according to the following steps:

- Research and analysis of epidemiological data (i.e., incidence) relating to patients with deep vein obstruction and ulceration in Italy;
- Definition of the current scenario of distribution of patients among the two alternative options;
- Definition of future scenarios with appropriate increased use of stenting over SMT, considering different annual penetration rates.

The incidence of venous leg ulcers in Italy in people aged over 65 years accounts for about 0.76/100 person-years in men and 1.42/100 person-years in women [1], meaning that about 156,000 patients are affected each year.

As the use of stenting for deep vein obstruction and ulceration is an emerging technology in Italy, the current scenario of patients' distribution between the two alternative options considered 100% of use of SMT. For the same reason, future scenarios considered small increased proportions of stenting over SMT of 0.5, 1, 2, 3 and 5% for the following 5 years. However, additional scenario analyses have been performed by considering a more significant adoption of stenting in the next 5 years (scenario 1: 1, 2, 4, 6, 10%; scenario 2: 2, 4, 8, 12 and 20%).

The model applies the variations of the market share to the new incident cohorts (naive treatments). Constant yearly incident cohorts of 156,000 patients were considered in the analysis. The costs for current and future scenarios were estimated by multiplying yearly costs of each option by the proportion of the eligible population using that option and by the number of patients in the eligible population, taking into account subsequent yearly incident cohorts. As the focus was on the expected budget at each point in time, the financial streams were presented as undiscounted costs [48].

Table 4. Cost–effectiveness analysis results (stenting vs SMT, mean values and 95% credible intervals).

Scenario	Option	Costs	QALYs	Incremental cost	Incremental QALYs	ICUR
DH setting for stenting	Stenting	€8935 (7092; 11,010)	2.66 (2.30; 2.79)	-€631 (-2227; 906)	0.15 (0.03; 0.27)	Stenting dominant
	SMT	€9566 (6995; 12,601)	2.51 (2.06; 2.74)			
Regular hospital admission for stenting	Stenting	€11,419 (9300; 14,165)	2.66 (2.30; 2.79)	€1853 (-306; 4,219)	0.15 (0.03; 0.27)	€12,388/QALY
	SMT	€9566 (6995; 12,601)	2.51 (2.06; 2.74)			

DH: Day-hospital; ICUR: Incremental cost-utility ratio; QALY: Quality-adjusted life-years; SMT: Standard medical treatment.

Results

Cost–effectiveness analysis

Considering a time horizon of 3 years, the average estimated QALYs were 2.66 and 2.51 respectively for patients undergoing stenting and SMT regimens. For stenting, in the scenario considering the DH setting (tariff €2258), the estimated mean cost per patient was €8935, while considering the regular hospital admission the mean cost per patient was €11,419. The mean cost per patient for SMT was €9,566. The model results for the two scenarios are summarized in Table 4. When the DH setting for stenting was considered, stenting was the dominant strategy (lower cost and higher QALYs), while considering the regular hospital admission for stenting, the ICUR of stenting versus SMT was €12,388/QALY, highlighting the cost–effectiveness of the endovascular procedure (ICUR <€30,000).

Tornado diagrams for both scenarios (DH and regular hospital admission for stenting) reporting one-way sensitivity analyses for the ICUR, according to variations of the model parameters, are reported in Figure 4. Because stenting was the dominant option in the scenario considering the DH setting for the endovascular procedure, the represented ICUR is negative. We chose to represent the ICUR for both scenarios, instead of net monetary benefit [49], in order to present analyses on the same outcome considered in the CEA. The parameters for both scenarios reporting the greater variations on the ICUR were the costs for the endovascular procedure and for the management of an unhealed ulcer, and the utility coefficients for 'healed ulcer' and 'active ulcer' health states. For the scenario considering the DH tariff for stenting (A), an annual cost for the management of an unhealed ulcer lower than €12,487.6 lead stenting to loose dominance but it remains cost-effective compared with SMT (ICUR = €39 considering a management cost for unhealed ulcer of €12,459, see lower value in Supplementary Table 2).

Regarding PSA, the plots of incremental costs versus incremental QALYs obtained from the Monte Carlo simulations are shown in Figure 5 (A: DH setting for stenting; B: Regular hospital admission for stenting). Dotted lines represent a theoretical cost–effectiveness threshold of €30,000/QALY; 99.6% and 83.6% of points lie below this line for A and B scenarios, respectively. Table 4 reports 95% credible intervals for all relevant outcomes of the model according to PSA.

In order to explore the structural uncertainty of the model on the representation of ulcer recurrences, a scenario analysis has been evaluated by considering the same percentage of ulcers recurred, equal to 4% for both SMT and stenting strategies. In this setting, the ICUR of stenting versus SMT was €3544 and €26,012, for the scenario considering DH and DRG tariff for stenting, respectively, thus confirming the cost–effectiveness of the endovascular procedure (ICUR <€30,000). In this case the PSA showed the cost–effectiveness of stenting versus SMT in 92.4 and 47.6% of simulations for A and B scenarios, respectively.

The scenario analysis that considered the inclusion of a death state for overall mortality reported an ICUR of €15,295 of stenting versus SMT in case the DRG tariff for the endovascular procedure was applied, while stenting was the dominant option in case the DH tariff was considered instead. According to these scenarios, the PSA showed the cost–effectiveness of stenting versus SMT in 99.3 and 76.1% of simulations, respectively.

Budget impact analysis

In the scenario with regular hospital admission for stenting, the mean cost (undiscounted) per patient was higher tha0n SMT, leading to higher costs for the NHS considering increased uses of the endovascular technology. Conversely, in the scenario with DH setting for stenting, this cost was lower than SMT, leading to budget
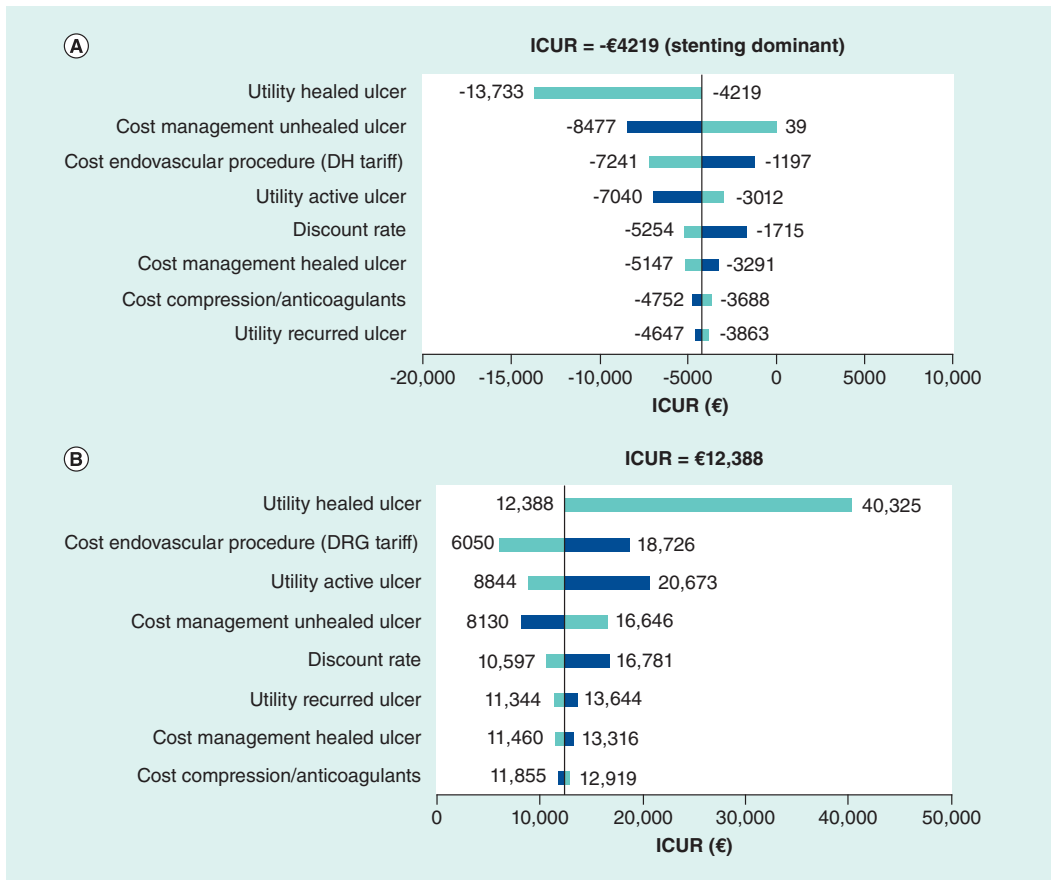
Figure 4.   Tornado diagram reporting one-way sensitivity analyses: (A) DH setting for stenting; (B) regular hospital admission for stenting. The vertical line in the middle represents the incremental value between the two strategies using the base-case value for each parameter. As the parameters deviate from their base-case values, the ICUR changes. A dark bar represents the variation of the ICUR when the parameter ranges from the base-case to the high uncertainty value, conversely, a light bar shows the ICUR variation when the parameter ranges from the low uncertainty value to the base-case value.
ICUR: Incremental cost-utility ratio; DH: Day-hospital; DRG: Diagnosis related group.

savings for the healthcare service. Yearly costs for the two options, obtained from the CEA model, are reported in Supplementary Table 3.

Compared with the current scenario (year 0), by progressively increasing the use of stenting for patients with deep vein obstruction and ulceration to 0.5, 1, 2, 3 and 5%, in the scenario which considers the regular hospital admission for stenting the incremental expenditure for the Italian Healthcare Service would be €39,458,060 over the next 5 years. If conversely the procedure is delivered in day-hospital, the increasing use of stenting would save to the Italian NHS €5,104,900 over the next 5 years (Table 5).

The scenarios which consider a more significant adoption of stenting showed incremental costs for the NHS of €78,916,119 (scenario 1: 1, 2, 4, 6 and 10%) and €157,832,239 (scenario 2: 2, 4, 8, 12 and 20%) when considering a full DRG tariff for stenting, while in the setting of DH possible savings were €10,209,801 (scenario 1) and €20,419,601 (scenario 2).

Discussion

Despite preventive strategies, deep vein outflow obstruction, primary or more frequently secondary, is a hemody-namic alteration leading to substantial morbidity. Although current epidemiological data are lacking, it is estimated that 1–2% of people over the age of 65 years suffer leg ulceration [50], one of the worst symptoms of PTS. Chronic wounds are more difficult to heal and the treatment of leg ulcers is associated with the use of considerable healthcare resources.
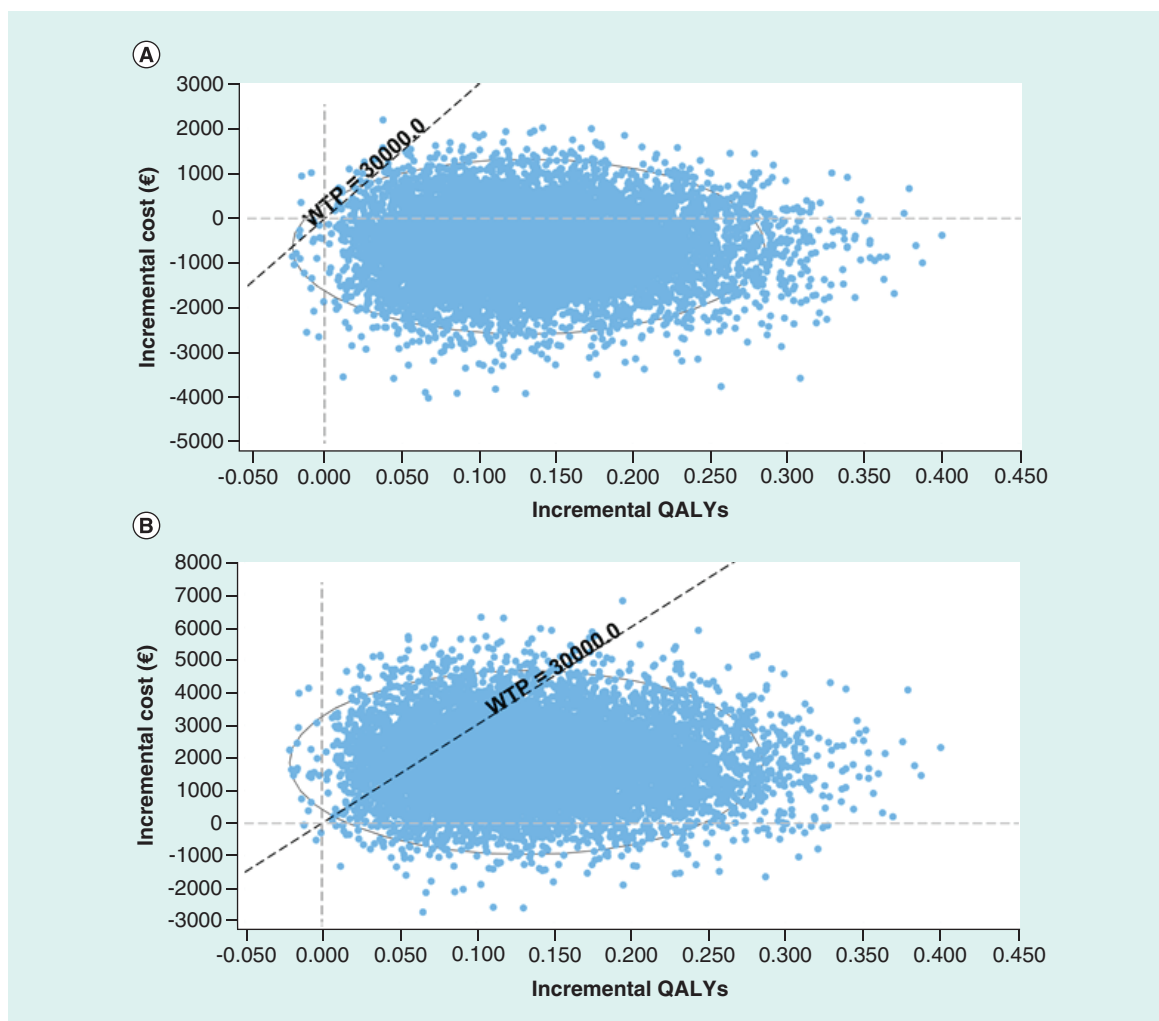
Figure 5.   Scatterplots of incremental costs versus incremental QALYs. (A) Day-hospital setting for stenting; **(B)** regular hospital admission for stenting.
QALY: Quality-adjusted life-years; WTP: Willingness To Pay.

Besides the standard conservative treatment performed with compression items, the endovascular approach through stenting has become a broadly accepted treatment strategy in chronic venous obstruction reporting minimal complications, high technical success rates and short hospital stay [51].

The literature reports studies evaluating the cost–effectiveness of different types of compression therapy for the treatment of venous leg ulcers [17,52,53] but to our knowledge only one abstract published a cost-benefit analysis comparing stenting versus compression therapy for patients with chronic total venous occlusion in USA [54]. This study, although performed on a limited number of patients (9 stenting+compression, 17 compression alone), analyzed the actual costs from the hospital perspective and quality of life data for the two treatment strategies and showed that iliac stenting for venous leg ulcers resulted in less cost (US$1913 per patient) and increase in quality of life (0.01 QALYs) compared with compression alone, over a time horizon of 3 years.

The present study showed that, according to different models of care (i.e., regular admission and day-hospital), stenting procedure for the treatment of deep vein occlusion and ulceration may be a cost-effective or cost-saving option in comparison to SMT. The clinical effectiveness for stenting and SMT was derived by meta-analyses starting from data reported in the literature and the robustness of the results has been shown through one-way and probabilistic sensitivity analyses. Uncertainty on rates of recurred ulcers has been explored, as well. The BIA clearly highlighted that the endovascular procedure delivered in a day-hospital setting would save public healthcare expenditure of nearly 5 million Euros in the next 5 years. Given that day hospital regime seems to be as safe as

Table 5. Budget impact analysis for patients with deep vein obstruction and ulceration.

Scenario considering regular hospital admission for stenting

Current scenario

Year	SMT			Stenting			
	Market share	Users cohort	Cost	Market share	Users cohort	Cost	Total budget impact
0	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
1	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
2	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
3	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
4	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
5	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553

Future scenario

Year	SMT			Stenting				Incremental expenses in comparison to current scenario
	Market share	Users cohort	Cost	Market share	Users cohort	Cost	Total budget impact	
0	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553	€0
1	99.5%	155,220	€1,604,658,535	0.5%	780	€8,915,593	€1,613,574,128	€2,039,574
2	99%	154,440	€1,597,191,966	1%	1,560	€18,048,060	€1,615,240,026	€3,705,472
3	98%	152,880	€1,582,258,274	2%	3,120	€36,316,601	€1,618,574,876	€7,040,322
4	97%	151,320	€1,566,734,033	3%	4,680	€54,802,016	€1,621,536,049	€10,001,496
5	95%	148,200	€1,536,866,650	5%	7,800	€91,339,099	€1,628,205,749	€16,671,195
Total incremental expenditure								€39,458,060

Scenario considering day-hospital setting for stenting

Current scenario

Year	SMT			Stenting			
	Market share	Users cohort	Cost	Market share	Users cohort	Cost	Total budget impact
0	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
1	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
2	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
3	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
4	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553
5	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553

Future scenario

Year	SMT			Stenting				Incremental expenses in comparison to current scenario
	Market share	Users cohort	Cost	Market share	Users cohort	Cost	Total budget impact	
0	100%	156,000	€1,611,534,553	0%	0	€0	€1,611,534,553	€0
1	99.5%	155,220	€1,604,658,535	0.5%	780	€6,978,073	€1,611,636,608	€102,054
2	99%	154,440	€1,597,191,966	1%	1,560	€14,173,020	€1,611,364,986	-€169,568
3	98%	152,880	€1,582,258,274	2%	3,120	€28,566,521	€1,610,824,796	-€709,758
4	97%	151,320	€1,566,734,033	3%	4,680	€43,176,896	€1,609,910,929	-€1,623,624
5	95%	148,200	€1,536,866,650	5%	7,800	€71,963,899	€1,608,830,549	-€2,704,005
Total savings								€5,104,900

SMT: Standard medical treatment.

regular hospital admissions, our recommendation is to adopt this treatment option in order to provide patients with a more effective treatment and the Italian NHS with a cost-saving strategy. The present study raises considerations about the setting of applicability of DRG tariffs for stenting. The vast majority of countries are trying to reduce as much as they can the number of hospital beds (e.g. in Italy from 4.7/1000 inhabitants in 2000 to 3.2/1000 inhabitants in 2017 [55]) in order to contain costs and improve patients' experience outcomes and quality of life. In this way, they carry out a progressive shift of services from in-patient assistance to outpatient and territorial care. In

this context if from one hand the in-patient assistance may be appropriate for stenting procedure at the beginning, when this new technology is first introduced in the clinical practice, needing more time to supervise the patients, from the other hand, once clinicians have completely learned the endovascular technique and how to manage the patients, the day-hospital may be the adequate setting for this procedure, being consistent with the strategy of healthcare systems to apply care also economically sustainable.

Our study has a number of limitations. First of all, the model did not consider possible complications due to the endovascular procedure. Although studies reported very high frequencies of technical success for stenting, in case of complications the management cost may increase, potentially compromising the cost–effectiveness results. This concept is related also to the experience of the operators who perform the interventions; it has been demonstrated that clinical outcomes and resource consumption related to patients managed with new technologies, such as stenting, may be strongly influenced by the underlying learning curve of operators. Continuous data collecting and monitoring could provide more robust data also for the evaluation of this aspect.

Second, in the base-case model we did not consider patients' mortality as in the literature there is lack of evidence reporting an increased risk of death in patients with venous leg ulcers [43]; however, the analysis of a scenario including all-causes mortality confirmed the cost–effectiveness of stenting compared with SMT. Third, In the cost–effectiveness analysis we used a relatively short time horizon based on the follow-up from studies retrieved by the systematic literature search; a similar approach has been followed also by other published studies that evaluated the cost–effectiveness of different technologies or models of care for the treatment of venous leg ulcers. They considered a time horizon for the analyses ranging from 4 to 12 months [17,46,52,53,56] according to the follow-up of studies providing input data for the model. A longer time horizon, equal to 5 years, has been considered in the study by Cheng and colleagues [43]; nevertheless the authors recognized to have assumed a constant risk of recurrence over time in the absence of long-term follow-up data, and to have limited the time horizon to 5 years in order to avoid events overestimation. In light of these considerations, economic evaluations or budget impact analyses have the primary objective to support the policy makers in the healthcare resource allocation process; although decision makers recognize the value of models to obtain cost projections, they require that these models are populated with solid clinical evidence. In the context of medical devices, where innovation is often stepwise, short-term analyses based on the available clinical data may be more relevant and useful to support the decision process [57]. Fourth, the considered studies often did not distinguish the type of vein occlusion, thus if it was a primary (May-Thurner) or a secondary disease (PTS). Subgroup analysis considering different disease causes might have provided more precise results, likely with better clinical outcomes and less costs for patients with primary disease. Another point relates to the treatment's indications. Although the model compares SMT and stenting, these options may not be indicated for the same population. Compression therapy is considered the mainstay of the treatment approach for venous ulcers, while invasive treatments can be considered generally in the failure of compression therapy; nevertheless, the available evidence-based scientific literature reports heterogeneity whenever comparing different treatment guidelines of different countries and sometimes even of different institutions in the same nation [58]. In this context, the definition of the best target population for SMT and stenting may be very challenging and a comprehensive evaluation of the patient and ulcer is required to determine etiology and to frame an appropriate management strategy [59]. Finally, data on patients' quality of life were derived from a study [46] conducted in UK and the transferability of the retrieved utility values to an Italian context was not considered.

Our findings showed that stenting for the management of deep vein obstruction and ulceration may be a cost-effective option compared with SMT. An additional treatment option is therefore now available to clinicians who may offer an appropriate and individualized management plan for the patients in a view to improve their health. For now, decision-makers may use the preliminary results of the present study in order to support stenting procedure in defined target patient populations. Future studies comparing SMT to stenting will be able to increase the clinical body of evidence in order to confirm or reject the validity of this preliminary evaluation.

Future perspective

Venous ulceration is a common devastating problem that is often the result of obstruction of the iliac veins and inferior vena cava. Venous ulceration is associated with substantial pain, morbidity and cost. Intervention on veins with subsequent stenting has proven to be a low-risk procedure effective in alleviating symptoms and in healing ulcers. However, the widespread use of venous stents without defining exactly which patients may benefit most from the therapy may be problematic. Future research should focus on the development of efficient diagnostic therapeutic pathways in order to offer patients an early diagnosis and timely appropriate treatment interventions. Any potential

sign and symptom of venous disorder should be identified early so that an appropriate management can be started as soon as possible. Moreover, the patient should be assessed holistically, preferably with a multidisciplinary team, taking into account all patient-related factors, such as lifestyle, quality of life and overall health factors, including his/her medical history.

Executive summary

- Post-thrombotic syndrome (PTS) is a common long-term complication of deep vein thrombosis, which consists in chronic venous symptoms and/or signs. Among these, ulcer occurrence is the ultimate and most severe presentation of PTS.
- Compression therapy, with or without anticoagulants, is considered the standard medical treatment (SMT) modality for patients with deep venous obstruction and venous ulceration. In the last years, the endovascular approach to outflow obstruction treatment opened the way to minimally invasive recanalization of the obstructed vein through stent placement, thus drawing the attention on this therapeutic opportunity.
- In this study, we performed a cost–effectiveness analysis comparing endovascular venous stenting procedure to SMT for patients with deep venous obstruction and leg ulcers from the Italian Healthcare Service perspective. Moreover, a BIA was undertaken considering different scenarios of increased utilization rates of venous stenting over SMT.
- A Markov model was developed to project costs and QALYs associated to the considered strategies over 3 years. Proportions of ulcers healed and recurred were derived from published literature and combined with real-world data, while the consumption of healthcare resources was monetized through DRG tariffs or published figures.
- According to in-patient or day-hospital (DH) settings, respectively, endovascular stenting can be considered a cost-effective (ICUR €12,388/QALY) or dominant option in comparison to SMT for the management of patients with deep venous obstruction and venous ulceration, over a time horizon of 3 years.
- Compared with the current SMT scenario, increasing utilization rates of stenting over SMT from 0.5 to 5%, in the next 5 years, is expected to increase the total budget of about 39.5 million Euros in the scenario considering the in-patient setting for stenting. In case the DH setting is considered instead, the increasing use of stenting would allow savings of about 5.1 million Euros in the same period. The scenarios considering a more significant adoption of stenting (10 or 20% at 5 years) showed incremental costs for the NHS of 78.9–157.8 million Euros (in-patient setting for stenting), or savings of 10.2–20.4 million Euros (DH setting for stenting).
- The present study supports the use of venous stenting in patients with deep venous obstruction and venous ulceration. Future studies comparing SMT to stenting will be able to increase the clinical body of evidence to confirm these conclusions.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Open access

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