A randomised controlled trial comparing venous stenting with conservative treatment in patients with deep venous obstruction: research protocol

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ABSTRACT
Introduction Deep venous obstruction (DVO) has a great impact on quality of life (QoL) comparable to angina pectoris or chronic pulmonary disease. Post-thrombotic scar formation and May-Thurner syndrome (MTS) are the most common causes of DVO. Conventional treatment of DVO focuses on reducing pain or leg swelling by use of (pain) medication and therapeutic elastic stockings. In the past, a venous bypass was offered in severe post-thrombotic cases, but this procedure showed bad clinical and patency outcomes. With the introduction of percutaneous angioplasty and dedicated venous stents new opportunities were created. Deep venous stenting has been shown to be effective in retrospective case series. However, there is no prior research in which QoL after interventional treatment is compared with QoL after conventional treatment. Currently, there is a debate about the true additional value of interventional treatment. We investigate whether those patients who are treated with stenting experience a change in short form 36 (SF-36) and the Veines-QoL/Sym questionnaires compared with conventionally treated patients.

Methods and analysis This is a randomised trial comparing conservative deep venous management to interventional treatment. A total of 130 patients with post-thrombotic syndrome (PTS) or MTS, eligible for interventional percutaneous treatment, who did not have previous deep venous intervention will be included. Patients will be randomised to conservative treatment or venous stenting and stratified for the PTS or MTS subgroup. Conservative treatment consists of either one or a combination of pain medications, manual lymphatic drainage, compression stockings and regular post-thrombotic anticoagulant therapy. The primary outcome is the QoL change after 12 months compared with baseline QoL. Secondary outcomes are QoL changes at 6 weeks, clinical assessment of DVO, recurrence rate of deep venous thrombosis at 6 weeks and 12 months, and the total amount of working days lost. Intervention-specific outcomes include complications and patency.

Ethics and dissemination The protocol is approved by the Medical Ethics Committee of Academisch ziekenhuis Maastricht/Universiteit Maastricht, The Netherlands (protocol number NNL55641.068.15 / METC 161008). We aim to publish the results of this study in a peer reviewed journal and present our findings at national or international conferences.

Strengths and limitations of this study

- The quality of life (QoL) of patients with post-thrombotic syndrome (PTS) and May-Thurner syndrome (MTS) with or without a deep venous intervention has never been evaluated before.
- It’s a prospectively randomised designed trial.
- The outcomes of this study will make it possible to differentiate QoL outcomes between patients with PTS and MTS.
- Since this is a randomised trial, it is likely that there will be systematic difference between the patients who are willing to participate in this trial compared with those who are not.
- The investigated interventional therapy requires in-depth knowledge and related clinical skills which may interfere with the replication of the related outcomes.
- No haemodynamical data are available to indicate therapy. Therefore, the treatment is based on a combination of duplex ultrasound, magnetic resonance venography and phlebography showing a compression of >50% and apparent collaterals.

INTRODUCTION

Deep venous obstruction (DVO) is a condition caused by intraluminal or extraluminal obstructions of the veins.① In most cases, an intraluminal obstruction is related to a previous deep venous thrombosis (DVT). Annually, about 1–2 per 1000 people in Western European countries develop a DVT,② ③ in which 40% of cases affect the
For most patients, the physician selects one treatment or a combination of treatment modalities in an attempt to reduce the symptoms. However, the venous stasis component is not taken into account because until a few years ago no adequate therapy existed. The introduction of percutaneous angioplasty (PTA) and dedicated venous stents gave opportunities to treat this component. This procedure is already performed in various clinics around the world with good results, both on an individual basis as in case series. Although no comparative studies have been performed, guidelines recommend that PTA as a single treatment should not be offered to patients with DVOs but a combination with stent placement can be considered and may result in resolution of symptoms.

Since patients with established DVO can experience a significant impact on their quality of life (QoL) which is comparable to chronic pulmonary disease or angina pectoris this is an important issue to focus on. In the past, the effect of deep venous treatment on QoL has been investigated in small series. Furthermore, previous research has mainly focused on patency rates and complication outcomes after deep venous stenting. Unfortunately, the perceived QoL after interventional treatment has never been compared with this perception after conventional treatment. Currently, there is a debate about the true additional QoL value of this interventional treatment. The aim of this study is to analyse the perceived short form 36 (SF-36) and the Veines-QoL/Sym QoL in patients treated with stenting compared with conventionally treated patients.

METHODS AND ANALYSIS

Study design

This prospective randomised controlled, single-blind study will be performed in the Maastricht University Medical Care Centre (MUMC). This hospital is a tertiary referral care centre for deep venous pathology situated in the Netherlands. Patients with PTS or MTS who are referred to the department of venous surgery at the MUMC will be recruited.

Study population

The study population includes all patients with PTS or MTS, called DVO, eligible for interventional percutaneous treatment, who did not undergo previous deep venous intervention, that visit the venous surgery department at the MUMC and are willing to participate. All patients have received conservative management for 1 year. Patients with a chronic non-ambulatory status are generally not eligible for interventional treatment. Before admission all patients will be screened for undersigned inclusion and exclusion criteria. Whenever these cannot be met, patients cannot be considered in this study.

INCLUSION CRITERIA

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age >18 years
Meet criteria for
- PTS (debilitating clinical symptoms) with iliofemoral obstruction on radiological workup expected to be treated solely percutaneous (without endophlebectomy and Ar fistula (AVF)) based on post-thrombotic changes till 1 cm above the femoral/profundal confluence
or
- MTS on additional imaging (duplex ultrasound (DUS)/magnetic resonance venography (MRV)/CT venography (CTV)) with clinical symptoms
- Life expectancy of more than 1 year
- DVT > 1 year
- Signed informed consent

EXCLUSION CRITERIA
A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Previous intervention of central veins (inferior vena cava, iliac veins, common femoral vein) on the affected limb
- Known pregnancy
- Inability to answer Dutch QoL questionnaires or limited communication in Dutch (spoken and written)
- Contraindication for prolonged anticoagulant therapy
- Recent, <1 year, DVT or pulmonary embolism
- Known contrast allergy
- Known dialysis or renal insufficiency needing additional preparation for injection of contrast
- Uncontrolled or active coagulopathy or known uncorrectable bleeding diathesis
- Hypersensitivity to nitinol or nickel
- Known to be, or suspected to be unable to comply with the study protocol (eg, no permanent address, known to be non-compliant or presenting with an unstable psychiatric history)
- Legal incapacity and/or other circumstances rendering the subject unable to understand the nature, scope and possible impact of the study
- Subjects in custody by juridical order
- Subjects who do not agree to the transmission of their pseudonymous data within the liability of documentation and notification
- Close affiliation with the investigational site: for example, close relative of the investigator or a possibly dependent person (eg, employee or student of investigational site)

Interventions
After inclusion, patients will be randomised between conventional therapy and interventional treatment. Randomisation will be stratified for the PTS or MTS group. Patients in the intervention group will be scheduled and treated with regular interventional deep venous stenting. When performing an interventional treatment, patients should be administered to the patient ward for at least 24 hours. The creatinine, haemoglobin and International Normalized Ratio (INR) levels will be checked before start of the procedure. INR levels above 4 should be treated with lowering the amount of used anticoagulant tablets and can result in postponement of the procedure until an INR level of <2.5 has been reached.

The procedure will be performed in an angiosuite after cleansing and sterile draping of the abdomen and leg. Patients with MTS will be treated with local anaesthesia (lidocaine, 1%) and patients with PTS will receive sedation. All patients will have an intravenous infusion and the sedated patients will receive a urinary tract catheter. Percutaneous venous access will be performed by sonographic guided puncture of the popliteal, femoral, common femoral or jugular vein. After puncture of the vein, a sheet is introduced with radiological and contrast agent assistance. Second, a guide wire is passed along the affected segment and this segment is dilated with a PTA balloon (with 2 mm overdilatation). During the intervention a bolus of 5000 IE of heparin will be administered. Afterwards, one or multiple dedicated venous stents (Optimed, GmbH, Germany) will be deployed in the vein and postdilatation with a PTA balloon will follow to optimise the geometry of the stent. Lastly, all patients need to lie down for at least 3 hours to ensure optimal closure of the percutaneous vessel puncture. Pneumatic stockings are used to increase the inflow when immobilised. All patients will receive therapeutic anticoagulation after stenting for a minimum of 6 months. In the bridging period low molecular weight heparins will be used until therapeutic anticoagulation levels are reached. After 6 months, the anticoagulation is continued if the patient was already on anticoagulation before the intervention. Also when stent related issues occur, the anticoagulation might be continued.

Conservative treatment consists of either one or a combination of the following items: pain medication, manual lymphatic drainage therapy, compression stockings and regular post-thrombotic anticoagulant therapy. The necessity of each therapy, except for therapeutic elastic stockings short (till knee) Class II, will be evaluated on an individual basis in interaction with both the patient as well as the treating physician.

In case of conservative management without any indications for prolonged anticoagulant therapy, this will not be started again.

Outcomes
Quality of life
QoL can be measured by numerous questionnaires, for example, with specifically general questionnaires and disease-specific questionnaires. The SF-36, is a widely used questionnaire to measure the general QoL.

This questionnaire is composed of eight dimensions and mainly focuses on the patients’ experiences in which a high score in all dimensions reflects a good QoL.24
The Veines-QoL/Sym questionnaire is a 100-point disease-specific scoring questionnaire which can be used to evaluate the psychometric properties of venous disease. This census paper is a valid and reliable instrument which has been used to evaluate outcomes in previous literature. 25 26

Both, the SF-36 and the Veines-QoL/Sym will be used to evaluate the effect of the treatment.

The primary outcome evaluated in this study, is the change in QoL measured by the Veines QoL/Sym score in patients with DVO. The scores will be evaluated at baseline and after 12 months of follow-up. A comparison will be made between the intervention (stenting) group and the conservative group (individually based management with short, class II elastic compression stockings, exercise, lymph drainage therapy and the use of (pain) medication).

Secondary outcomes will be QoL change evaluated by the SF-36, EuroQOL-5D, and Pain Disability Index in patients with DVO. Equal to the primary outcome, these scores will be evaluated at baseline and at 12 months follow-up. A comparison will be made between the intervention group and the conservative group.

**Patency**

The stent patency will be evaluated by DUS during every follow-up visit. Primary patency is defined as flow in the stent lumen without the need for additional interventional procedures due to stenosis or occlusion. Assisted primary patency is defined as flow in the stent lumen after additional stenting or PTA because of a stenosis with related clinical symptoms. Secondary patency is defined as flow in the stent lumen after additional thrombolysis, thrombectomy, creation of an AVF, re-stenting or PTA because of previous stent occlusion.

**Clinical outcomes**

Venous claudication will be scored positive whenever patients experience onset or worsening of pain during (mild) exercise, which subsides during rest, especially when sitting or lifting the leg.

The Venous Clinical Severity Score (VCSS) and the Villalta Score are clinical scores which have been validated for PTS. 27 Both scores will be analysed before and after treatment and changes will be compared between the intervention group and conservative group.

Since patients with MTS may have a higher chance of DVT, and patients with PTS have a higher chance of a recurrent DVT, due to the outflow obstruction, the DVT recurrences will be registered.

Lastly, it is important to analyse the burden of working loss, as DVO can cause invalidating symptoms in daily practice. For this reason, the number of working days lost will be registered for both treatment groups in every follow-up visit. Furthermore, modifications in the time and type of work will be evaluated.

All outcomes will be evaluated at baseline, at 6 weeks follow-up and at 12 months follow-up by an observer who is blinded to treatment assignment. In the intervention group, patency will be assessed at 2 weeks, 6 weeks, 6 months and 12 months. When a stenosis or occlusion of the stent is seen, the date is registered. Further treatment will be offered and dates of additional treatment will be recorded.

**Time line**

Like in regular workup for patients with deep venous pathology, all eligible patients will have imaging of the veins by DUS and MRV or CTV. Related to these radiographic images, the extent of the obstruction or occlusion of the veins will be assessed.

Eligible patients will be contacted and offered the opportunity to participate in the study. After gaining informed consent, patients will be randomised to either conservative treatment or stenting at a 1:2 ratio.

At baseline and during all follow-up visits, patients will have a full clinical examination to assess the extent of complaints and clinical manifestations of DVO. The severity of complaints is scored using VCSS, Venous Claudication Score, highest C of CEAP and the Villalta Scale.

To assess QoL, the SF-36 V2 will be used for generic QoL and the Veines-QoL/Sym will be used for the disease-specific QoL.

In all patients, a baseline as well as 12 months follow-up EDTA, serum and citrate blood sample (a total of 20 mL) will be requested. All of these blood samples will be taken by the diagnostic lab and sent to the Biobank in Maastricht. Blood samples will be frozen for 15 years in order to perform possible future examinations.

Questions about having a (paid) job will be asked and registered at baseline and follow-up visits. All patients will visit the outpatient clinic at 6 weeks and 12 months after enrolment into the study. The assessment of all clinical scorings and questionnaires will be accompanied by an independent investigator who is blinded for the type of intervention.

Patients in the conservative treatment group will be asked to take off the therapeutic elastic stockings to obtain the blinding.

The patients in the intervention group will have additional visits at 2 weeks, 12 weeks and 6 months to assess the patency of the stents by DUS. When a stenosis or occlusion of the stent is seen, further treatment will be offered. In case of an occlusion this additional treatment can consist of either ultrasound-enhanced catheter-directed thrombolysis or thrombectomy with or without endophlebectomy and the creation of an AVF. In case of a significant stenosis, a PTA with or without re-stenting can be performed. Lastly, in both cases a conservative treatment will be discussed whenever clinical complaints are absent or mild.

After 12 months, all patients in the intervention group will receive CTV to evaluate the stent patency and stent position.

Table 1. Timeline of stent group
Table 2. Timeline of conservative group
## WITHDRAWAL OF INDIVIDUAL SUBJECTS

Subjects can leave the study at any time for any reason if they wish to do so. This will not have any consequences for further treatment. The investigator can decide to withdraw a subject from the study for urgent medical reasons. In patients who withdraw from the trial, attempts will be made to retrieve data on the primary and secondary outcomes.

### Recruitment

All patients with PTS or MTS who are referred to the department of venous surgery at the MUMC and meet the inclusion criteria will be asked to participate.

The treating physician will inform potential candidates about this study during regular outpatient visits and will provide them with written study information. They will explicitly ask for the patient’s permission to pass the patient’s name, birth date, telephone number and address to the research physician. When interested, the patient is contacted and included by the research physician after 7–14 days. All questions will be answered and written informed consent will be obtained. A separate written consent for blood sample storage will be obtained. All participants will be provided with the contact information of the research physician, to enable contact if any study-related problems are encountered.

### Assignment of intervention

The randomisation between interventional and conservative management will be performed with random permuted blocks of 3–6 in a 2:1 ratio (2 stented versus 1 conservative). Randomisation will be stratified for MTS or PTS.

A web based randomisation programme will be used for randomisation (Alea, Release: V.2.2 build: 2070 | amc/ALEA). The randomisation will be performed by the research physician after obtaining the patient’s consent.

Because the treatment involves an invasive therapy, a sham operation would expose participants to unnecessary risks, and therefore the treatment allocation cannot be blinded. The independent researcher who performs the scoring at follow-up moments, will be blinded for treatment allocation.

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CTV, CT venography; DUS, duplex ultrasound; QoL, quality of life; VCSS, Venous Clinical Severity Score; venous claudication.

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<th>Conservative group</th>
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CTV, CT venography; DUS, DUS, duplex ultrasound; QoL, quality of life; VCSS, Venous Clinical Severity Score; VC: venous claudication.
Data collection, management and analysis

In accordance with section 10, subsection 4, of the Dutch law of medical research, the sponsor (MUMC) will suspend the study if there is sufficient ground to assume that continuation of the study will jeopardise the subject’s health or safety. The sponsor will notify the accredited Medical Ethical Committee (METC) without undue delay of a temporary halt including the reason for such an action. Subsequently, the study will be suspended pending a further positive decision by the accredited METC. The research physician will take care of informing the included subjects.

All adverse events related to the medical device and adverse events, reported spontaneously by the subject or observed by the research physician or his staff, will be recorded.

(Serious) adverse events ((S)AEs) (life-threatening or events leading to permanent impairment as well as inpatient hospitalisation or prolongation of existing hospitalisation, or medical or surgical intervention to prevent life-threatening illness) will be brought under the attention of the coordinating research physician and the head of the department. The research physician will report all SAEs to the sponsor without undue delay, but no later than 72 hours, after obtaining knowledge of the events. The following SAE is excluded for this reporting: persistent or significant disability or incapacity due to PTS when stents occlude or show a stenosis, since this is merely a risk of the treatment.

Follow-up of adverse events

All (S)AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, the follow-up may require additional tests or medical procedures, and/or referral to a general physician or a medical specialist.

Handling and storage of data and documents

All study documents will be stored in locked cabinets in the University of Maastricht for a period of 15 years. Patients will have a unique trial number not related to their names or birth dates. Only the investigators will have an overview of the trial numbers and patient names. Digital data will be stored at a secure drive at MUMC. All clinical patient data, which are noted as usual in the electronic patient files, can only be viewed and held by authorised personnel of MUMC.

The handling of personal data complies with the Dutch Personal Data Protection Act.

All blood samples will be stored in the freezer of the Biobank Maastricht in a coded version. This code will be exactly the same as the code for other patient data. Only the investigators will have an overview of trial numbers and patient names. Blood samples will be frozen for 15 years in order to make future examinations in line with this research possible.

Monitoring and quality assurance

Data monitoring will be performed by members of the Clinical Trial Centre Maastricht (CTCM). CTCM will monitor the course of the trial and provide ongoing oversight of the data entry. CTCM is independent from the sponsor and does not recall any competing interests.

At 6 months after study initiation, all bleeding complications will be gathered and reviewed by an independent Data Safety Monitoring Board with the authority to interrupt the study prematurely, based on significant enhanced bleeding risk or excess morbidity/mortality in the intervention arm of the study population. Following the initial gathering, the safety monitoring board will review all incidences of bleeding on a regular base (at least once every 6 months). No interim analysis will be performed.

AMENDMENTS

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion. Whenever these amendments are substantial, trial participants and trial registries will be informed.

TEMPORARY HALT (AND PREMATURE) END OF STUDY REPORT

The sponsor (MUMC) will notify the accredited METC and the competent authority about the end of the study within a period of 8 weeks. The end of the study is defined as the last visit of the last patient.

The sponsor will notify the METC immediately in case of a temporary halt of the study, including the reason of such an action.

Whenever the study ends prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within 1 year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the competent authority.

STATISTICAL ANALYSIS AND POWER CALCULATION

The data will be analysed by an intention-to-treat analysis and per protocol analysis. Efforts will be made to minimise the number of missing values. In patients who withdraw from the trial, attempts will be made to retrieve data on at least the primary outcome by asking the subject to fill out the 12-month questionnaires.

Primary study parameter(s)

For evaluation of patency of stents a Kaplan-Meier survival analysis will be used.

The primary end point is the change in QoL at 12 months (on the disease-specific Veines QoL/Sym questionnaire) from baseline. Change in QoL from baseline between the randomised groups will be compared and tested for statistical significance using analysis of
covariance. The dependent variable will be the QoL end score and baseline QoL and group will be entered as covariates.

The comparability of baseline characteristics between groups will be evaluated. Nominal and categorical data will be presented as absolute numbers and percentages. Continuous data will be presented as mean values with SD or as median values with IQR, depending on normality of distribution. In case of imbalances, linear multivariate regression analysis will be used to adjust for baseline differences. For all analyses, a p value ≤0.05 is being used to indicate statistical significance.

Power calculation
The sample size calculation is based on the consideration that an improvement in QoL (from baseline to 12 months) of 14 points on the disease-specific Veines QoL/Sym questionnaire can be considered as minimally clinical relevant. To detect at least 14 points’ improvement (SD=22) with a power of 90% and two-sided α=5%, and a randomisation ratio of 2:1 (intervention: conservative), a total of 117 patients is required (78 in the intervention group vs 39 in the conservatively treated group). To account for loss to follow-up of ≥10% of patients, a total of 130 patients need to be included (86 in the intervention group vs 44 in the conservatively treated group). We will perform a subgroup analysis (PTS vs MTS) to evaluate consistency of the effect of intervention across subgroups.

DISCUSSION
Previous systematic reviews have shown low complication rates (0%–8.7%) and high technical successes (up to 98%) for deep venous stenting.14 16 Reviews also show a relief of oedema and pain in up to 64%–68% and, respectively, 82% of patients. Furthermore, primary patency rates between 32% and 98.7% and secondary patency rates of 66% to 96% are reported.14 Although these reviews show favourable results, the outcomes are mainly based on retrospective, single-centre, cohort trials. Besides this, the main important outcome for patients, that is the QoL they experience in relation to their complaints, is not continuously examined.

Therefore, this research focuses on the reported QoL of patients with PTS and MTS. Moreover, the prospectively randomised design underlines the strength of this study. The outcomes of this study will clarify if the QoL in DVO will improve and to which extent it will change. Furthermore, this study will show if the QoL outcomes are comparable for both interventional treatment and conservative management. Additionally, it is possible to differentiate between outcomes in PTS and MTS. Since PTS and MTS are different entities, this study will focus on the effect in both patient groups and show the difference in QoL. We hypothesise that the change in QoL in patients with MTS will be different from patients with PTS since PTS causes DVO as well as venous insufficiency. With deep venous stenting, complaints related to valve reflux will not be treated and thus not all complaints will resolve.

Limitations
Since this is a randomised trial, it is likely that there will be systematic difference between the patients who are willing to participate in this trial compared with those who are not. This can eventually lead to an outcome that cannot be translated to all patients with DVO. On the contrary, the patients who are not willing to participate in this study, may not experience the symptoms in a way that their daily activities are affected and so will not opt for interventional treatment at all.

Second, MUMC is the most experienced centre in deep venous stenting in the Netherlands. The investigated interventional therapy requires in-depth knowledge and related clinical skills. This may interfere with the replication of the interventional treatment and specifically the related outcomes across other institutions.

If a similar randomized controlled trial would be performed in other countries, it would be beneficial to pool all data and perform a meta-analysis. However, the treatment diagnostics and definition of an MTS should be standardised to compare actual outcomes. Especially, the definition of MTS may alter the decision to perform a deep venous intervention.28 In our centre, treatment is based on a combination of DUS, MRV and phlebography showing a compression of >50% and apparent collaterals. Other countries may use an intravascular ultrasound to plan their treatment decisions. The pooling of these data in a meta-analysis may be a challenge.

Ethics and dissemination
This study is financially supported by Optimed GmbH, Ettringen, Germany, unrestricted grant number 155025 (CTCM). The study sponsor and funders play no role in study design, collection, management, analysis, and interpretation of data or writing of the report. All patients will be asked to provide written informed consent and will be informed about the voluntary participation. Ultimately, it is our aim to publish the results of this study in a peer reviewed journal (be they positive or negative). Moreover, it is our intention to present the findings at national or international conferences. The protocol (protocol number NL 555641.086.15 / METC 161008) is approved by the Medical Ethics Committee of Academisch ziekenhuis Maastricht/Universiteit Maastricht, The Netherlands. The study protocol was registered at www.clinicaltrials.gov (registration number: NCT03026049) on 17 January 2017.

Contributors TMAJvV, conception and design of study, developed the Research Application, acquisition of data, drafting of manuscript, writing manuscript. MvG, conception and design of study, critical revision of manuscript. JHHvL, developed the Research Application, drafting of manuscript, critical revision of manuscript. PJN, conception and design of study, drafting of statistical analysis, critical revision of manuscript. RdG, developed the Research Application, conception and design of study, acquisition of data, drafting of manuscript, critical revision of manuscript. CHAW, developed the Research Application, conception and design of study.

acquisition of data, drafting of manuscript, critical revision of manuscript. All authors read and approved the final manuscript.

**Funding** This study is financially supported by Optimed GmbH, Ettingen, Germany, unrestricted grant number 155025 (CTCM). The study sponsor and funders play no role in study design, collection, management, analysis, and interpretation of data or writing of the report.

**Competing interests** RdG has consultancy agreement with BARD GmbH / Angiomed; consultancy agreement with Optimed GmbH. CHAW has consultancy agreement with Angiocard; consultancy agreement with BoMedical; consultancy agreement with Medi; consultancy agreement with Optimed; consultancy agreement with Vascular Insights; research funds from BTG; research funds from EKOS; research funds from Vascular Insights; research funds from Medtronic; research funds from Angiocare, research funds from Bayer, research funds from Medtronic; research funds from Optimed, research funds from Firstkind Medical, research funds from Bard, research funds from Venilii.

**Patient consent** Obtained.

**Ethics approval** METC AzM/UM referencenumber NL55641.068.15 / METC 161008.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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**REFERENCES**