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Impact of a synchronous prophylactic treatment of the anterior accessory saphenous vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an insufficient great saphenous vein (SYNCHRONOUS-Study):
Study protocol for a prospective, multicentre, controlled observational study

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Impact of a synchronous prophylactic treatment of the anterior accessory saphenous vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an insufficient great saphenous vein (SYNCHRONOUS-Study): Study protocol for a prospective, multicentre, controlled observational study

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Keywords

Varicose veins, EVLA, Laser ablation, GSV, AASV, Efficacy, Safety, Outcome
Abstract

- **Introduction**: To date, there are no prospective studies evaluating the prevention of recurrent veins by the simultaneous treatment of a sufficient anterior accessory saphenous vein (AASV) in patients undergoing endovenous laser ablation (EVLA) of an insufficient great saphenous vein (GSV). This study will provide important information about the impact of the AASV in the development of recurrent veins after EVLA of the GSV. Additionally, it will be clarified whether patients benefit from a preventive ablation of a sufficient AASV.

- **Methods and analysis**: This is a multicenter, prospective, controlled, exploratory clinical study in 1150 patients with a medical indication for EVLA of a refluxing great saphenous vein. Within seven study visits, patients will be followed-up over a time period of five years. Primary study endpoint is the recurrence rate; secondary endpoints include inter alia, complication rate, post-operative pain intensity, quality of life and patient satisfaction.

- **Ethics and dissemination**: Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/).

**Strengths and limitations of this study**

- This exploratory study addresses this important open question for the first time in a prospective controlled setting under real-life clinical conditions based on a large sample size.

- Additionally, essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores.

- Limitations arise from the explorative study design which might limit the generalizability of the results. Nevertheless, data provided by this study makes it possible to plan and perform a randomized controlled future trial with a formal sample size calculation.


1. Introduction

Chronic venous insufficiency caused by varicose veins is a common disorder [1]. Approximately, 50% of the western adult population show stigmata of venous disease and 25% suffer from visible varicose veins [2,3]. Venous insufficiency is most often linked to reflux of the great saphenous vein (GSV) [4]. For a long time, high ligation and stripping (HLS) of the GSV was considered as a standard treatment for vein insufficiency [1,5]. Innovative endovenous methods such as endovenous laser ablation (EVLA) are being successfully applied worldwide for many years [4,5]. Several randomized controlled trials suggest that clinical results of EVLA and HLS are comparable [4,6-10]. Recurrent varicose veins are known to be a common problem after EVLA and HLS which is defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination [11,12]. One of the most important factors associated with recurrent veins includes a new secondary reflux of the anterior accessory saphenous vein (AASV) after GSV treatment [12-15]. The AASV is a tributary of the saphenofemoral junction and is located lateral to the GSV. In a study by Garner et al., patients were observed over a 3-year period after surgery. Out of 141 groin recurrences, 61 (43%) were due to a persistent AASV and, as such, was the commonest cause of recurrent varicose veins encountered in this study [13]. Within the REVATA-study a recurrence rate of 6.9% after endoluminal procedure was detected [14]. According to the authors every fourth recurrence was caused by a secondary incompetency of the AASV. One possible explanation of the authors is that once the GSV is ablated, the blood flow from the superficial epigastric vein and pudendal junctions is then directed into the AASV. Due to inherent defects in vein wall or valves, resultant insufficiency occurs. Prior to GSV ablation, refluxing flow preferentially follows the larger diameter of the GSV [14].

Hitherto, there is only little known about the possible prevention of recurrent veins by the simultaneous treatment of the sufficient AASV in patients undergoing EVLA of an insufficient GSV. Therefore, the preventive EVLA of AASV is currently a much discussed topic and is managed differently by phlebologists. Within this study, this issue will be evaluated for the first time in a prospective controlled setting.

2. Methods and analysis

2.1 Study design and Inclusion-/Exclusion criteria
This is a multicenter, prospective, controlled, exploratory clinical study in patients with a medical indication for elective thermal ablation of a refluxing GSV. 1150 Patients of at least 18 years of age and with a medical indication for elective thermal ablation of a refluxing GSV will be evaluated in this study. Patients with varicose veins and written informed consent will be included in the study. GSV incompetence is defined by a reflux time of > 0.5 sec on duplex imaging. Patients with an incompetent AASV, a tortuous GSV rendering the vein unsuitable for endovenous treatment, duplication of the saphenous trunk, deep venous incompetence/occlusion or patients that are not able to read, understand or sign the study specific informed consent form (e.g. impaired mental state, insufficient knowledge of the German language) or with expected lack of compliance will be excluded from this study. According to the standard procedure of the respective study center patients will be enrolled consecutively into two study groups (A/B). Half of the 8 study centers will enroll 575 patients into group A and will perform EVLA of the insufficient GSV only. The other half of the study centers will enroll 575 patients into Group B and will perform additional EVLA of the AASV (see Figure 1).

2.2 Study objectives
The primary objective of this study is to generate data to assess the impact of a synchronous treatment of the AASV for prevention of recurrent varicose veins in patients undergoing EVLA of an insufficient GSV. Recurrent varicose veins are defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination. Secondary objectives of this study are, inter alia, to address the complication rate, post-operative pain intensity, duration of absence from work and normal activity, health-related quality of life and disease-specific quality of life and patient satisfaction.

2.3 Endovenous laser ablation (EVLA)
According to the standard operating procedures of the respective study center the AASV will be treated simultaneously in patients undergoing EVLA of an insufficient GSV or not. When the AASV is treated simultaneously to the GSV, an explicit informed consent will be obtained concerning this procedure. In all study centres, EVLA is performed with a 1470nm two-ring radial laser fiber of the same manufacturer at 10 Watts (Biolitec®, Jena, Germany). Since it is known that a long residual saphenofemoral stump promotes recurrence, flush ablation of the junction is performed in all individuals in order to minimize stump length (endovenous crossectomy) [16,17]. In endovenous crossectomy the saphenofemoral junction with the
epigastric vein remains open or reopens postoperatively. All other junctional branches which flow into the femoral vein via GSV are immediately closed. AASV is closed via another puncture in a second step. In addition to EVLA, miniphlebectomies and sclerotherapy may be routinely performed in conjunction with EVLA if tributaries are present.

2.4. Study visits
In total, there will be 7 study visits during the study. The patients will be examined at the time of recruitment (V1), at the day of the procedure/EVLA (V2), until 10 days after EVLA (V3), 6 months (±4 weeks; V4), 1 year (±8 weeks; V5), 3 years (±8 weeks; V6), and 5 years after EVLA (±8 weeks; V7). For evaluation of the primary endpoint, the rate of recurrent varicose veins in general and in particular recurrent veins caused by a new AASV reflux will be obtained after EVLA in V3-V7. The secondary endpoints will be obtained by documentation of the complication rate and duration of absence from work and normal activity after the procedure. The disease-specific quality of life, disease severity and outcome of therapy for venous disease, post-operative pain intensity and patient satisfaction will be evaluated by means of the respective questionnaire in V1-V7 (see Figure 1). The following data will be obtained during the respective study visit:

Visit 1 (preoperative baseline visit): assessment of exclusion/inclusion criteria, documentation of baseline characteristics and disease severity, performance of clinical and duplex examination (the patients are examined in the standing position and reflux >0.5 seconds is considered positive. Duration of reflux and the vein diameter (mm) of the GSV at the saphenofemoral junction (and 3/15 cm below) and the length of vein will be documented). Determination of disease severity and disease-specific quality of life.

Visit 2 (EVLA): Length of treated vein (GSV and AASV), intra-operative complications, postoperative anticoagulation, postoperative compression therapy.

Visit 3-7: Post-operative complications (e.g. the presence of ecchymosis, hyperpigmentation, necrosis/burns at the puncture site, deep vein thrombosis or endovenous heat induced thrombosis (EHIT)) and sensory disorders. Treatment success/failure (closed vein or no longer visible), recurrent varicose veins, post-operative pain intensity, duration of absence from work and normal activity, disease-specific quality of life, disease severity and outcome of therapy for venous disease, patient satisfaction.

2.5 Data assessment via patient questionnaires
The disease severity and outcome of therapy for venous disease are being assessed via validated Venous Clinical Severity Score (VCSS) [18]. Disease-specific quality of life is determined by means of the Aberdeen Varicose Vein Questionnaire (AVVQ) which is a validated 13-question survey addressing all elements of varicose vein disease [19]. Furthermore, each patient is required to evaluate patient satisfaction with the treatment on a scale of 1-5. By means of a pain intensity score, patients will be asked to evaluate the pain on a scale of one (no pain) to ten (severe pain): A: the greatest pain since the last visit, B: currently experienced pain in the area of the operated limb, C: the current pressure pain, D: the most severe pressure pain since the last visit.

2.6 Statistical analysis

As this is the first explorative study investigating the recurrence rate of varicose veins caused by a persistent AASV in patients with a treated refluxing GSV, a formal sample size calculation is neither applicable nor feasible. Nevertheless, a sample size of n = 1150 patients is planned to be included as this is feasible within a reasonable period of time. Assuming a drop-out rate of 30%, this leads to a sample size of 800 to be analyzed. The information on the rate of varicose veins in general varies strongly in the literature. However, in Group A, we expect to obtain a recurrent varicose vein rate of 20% after three years. With a sample size of 800 a reduction of 7.4% (from 20% to 12.6%) of recurrent varicose veins can still be detected with a power of 80% and a significance level of 5% using a chi-square test. The primary analysis will be adjusted for covariates (see section 2.5.2) which, in general, rather increases the power of the procedure. All endpoints and patient characteristics will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, either means, standard deviations, medians, and first and third quartiles, as well as minimum and maximum, or absolute and relative frequency will be reported. Descriptive p-values of t-tests and chi-square tests for continuous or categorical data will be given, respectively. Furthermore, the associated 95% confidence intervals of the means or rate differences will be provided. If appropriate, graphical methods will be used to visualize the findings. The primary null hypothesis of equal rates in the primary endpoint (varicose veins, yes/no per person) after three years (V6) in both groups will be tested using a logistic regression model. The group variable, age, BMI and gender will be included as predictors. For each factor, the odds ratio with 95% confidence intervals and p-values will be reported. Missing values will be imputed using a multiple imputation approach. A Fully Conditional Specification (FCS) method will be applied. This is a commonly used method and appropriate for an arbitrary structure of missing
values which is the most general form of a missing data pattern (see, for example, Berglund PA, 2015). All variables that are used in the primary model will be included in the imputation models. The same logistic regression model will be fit when analyzing the primary endpoint at the other time points (V3-V5 and V7). For all other endpoints, (generalized) regression models will be applied as appropriate including the same predictors as in the primary analysis. Furthermore, longitudinal (mixed) regression models for all endpoints will be applied including all time points into one model. A random intercept (for patients) will be included and different correlation structures will be applied (in particular, an unstructured covariance matrix and an auto-correlation structure). Again, the same predictors as before will be included as fixed factors and odds ratios with 95% confidence intervals and p-values will be reported.

2.7 Study organization and data management
Study coordination and data management is performed by the Department of Dermatology, University of Heidelberg. Data collection is done via case report forms (CRFs). Statistical analysis will be performed by the Institute of Medical Biometry. All study procedures will be done according to approved standard operating procedures (SOPs) which are based on ICH-GCP guidelines (E6), the German implementation of Good clinical practice (GCP) and the current laws.

2.8 Ethical considerations, dissemination plan and regulatory obligations
The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/).

2.9 Patient and public involvement
No patient involved.

2.10 Recruitment and status of the study
Ethical approval was granted in October 2018. First enrollment was in February 2019. The estimated time required for recruitment is 48 months. The total duration of the study is expected to be 108 months, including statistical analysis.
3 Discussion
To date, there are no controlled prospective studies evaluating the impact of a simultaneous EVLA of AASV for prevention of a secondary reflux in patients undergoing EVLA of an insufficient GSV. Therefore, it remains unclear whether patients benefit from this procedure. This exploratory study addresses this important open question for the first time in a prospective controlled setting under real-life clinical conditions based on a relatively large sample size. Additionally, essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores. Limitations arise from the explorative study design which might limit the generalizability of the results. Nevertheless, data provided by this study makes it possible to plan and perform a randomized controlled future trial with a formal sample size calculation.

ABBREVIATIONS
EVLA Endovenous Laser Ablation
AASV Anterior Accessory Saphenous Vein
GSV Great Saphenous Vein
SFJ Sapheno-femoral junction
VCSS Venous Clinical Severity Score
AVVQ Aberdeen Varicose Vein Symptom Severity Score
ICH-GCP International Conference on Harmonization-Good Clinical Practice
CEAP Clinical, etiological, anatomical and pathological
SD Standard Deviation

DECLARATIONS
Ethics approval and consent to participate: before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018).
Consent for publication: not applicable

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors state “no conflict of interest”.

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Authors’ contributions

Conception and design: CF, KH, TH, TM, TW, MS, LU, TH

Analysis and interpretation: CF, CD, KH, TH, LU

Data collection: CF, CD, KH, TM, PZ, JV, TW, GL, LM, MS, LU, TH

Writing the article: CF, CD, KH, TM, PZ, JV, TW, GL, LM, MS, LU, TH

Critical revision of the article: CF, CD, KH, TM, PZ, JV, TW, GL, LM, MS, LU, TH

Final approval of the article: CF, CD, KH, TM, PZ, JV, TW, GL, LM, MS, LU, TH

Overall responsibility: CF, KH, LU, TH

All authors read and approved the final manuscript

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FIGURES

Figure 1  Flowchart of the study
Flowchart of the study

Patients meeting inclusion criteria with a medical indication EVLA of a refluxing GSV (n = 1150)

\[ \sim 50\% \]

\[ \sim 50\% \]

Group A
EVLA of the insufficient GSV only

Group B
EVLA of the insufficient GSV & preventive EVLA of AASV

- V1 (Baseline)
- V2 (EVLA)
- V3 (10 days after EVLA)
- V4 (6 months ±4 weeks) after EVLA)
- V5 (1 year ±8 weeks) after EVLA)
- V6 (3 year ±8 weeks) after EVLA)
- V7 (5 year ±8 weeks) after EVLA)

Analysis

Group A
n = 575

Drop out
30%

Group B
n = 575

Flowchart of the study

190x254mm (96 x 96 DPI)
| Section/item                  | Item No | Description                                                                                                                                 |
|------------------------------|---------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Administrative information   |         |                                                                                                                                            |
| Title                        | 1       | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym                                     |
| Trial registration           | 2a      | Trial identifier and registry name. If not yet registered, name of intended registry                                                     |
|                              | 2b      | All items from the World Health Organization Trial Registration Data Set                                                                   |
| Protocol version             | 3       | Date and version identifier                                                                                                               |
| Funding                      | 4       | Sources and types of financial, material, and other support                                                                               |
| Roles and responsibilities   | 5a      | Names, affiliations, and roles of protocol contributors                                                                                   |
|                              | 5b      | Name and contact information for the trial sponsor                                                                                        |
|                              | 5c      | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities |
|                              | 5d      | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) |
| Introduction                 |         |                                                                                                                                            |
| Background and rationale     | 6a      | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention |
|                              | 6b      | Explanation for choice of comparators                                                                                                     |
| Objectives                   | 7       | Specific objectives or hypotheses                                                                                                          |
| Trial design                 | 8       | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) |
Methods: Participants, interventions, and outcomes

Study setting 9 Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained

Eligibility criteria 10 Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)

Interventions 11a Interventions for each group with sufficient detail to allow replication, including how and when they will be administered

11b Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)

11c Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)

11d Relevant concomitant care and interventions that are permitted or prohibited during the trial

Outcomes 12 Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended

Participant timeline 13 Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)

Sample size 14 Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations

Recruitment 15 Strategies for achieving adequate participant enrolment to reach target sample size

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation 16a Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions
Allocation concealment mechanism 16b Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned

Implementation 16c Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions

Blinding (masking) 17a Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how

17b If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant’s allocated intervention during the trial

Methods: Data collection, management, and analysis

Data collection methods 18a Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol

18b Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols

Data management 19 Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

Statistical methods 20a Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol

20b Methods for any additional analyses (eg, subgroup and adjusted analyses)

20c Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)

Methods: Monitoring

Data monitoring 21a Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed
21b Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial

Harms 22 Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct

Auditing 23 Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor

**Ethics and dissemination**

Research ethics approval 24 Plans for seeking research ethics committee/institutional review board (REC/IRB) approval

Protocol amendments 25 Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)

Consent or assent 26a Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)

26b Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

Confidentiality 27 How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial

Declaration of interests 28 Financial and other competing interests for principal investigators for the overall trial and each study site

Access to data 29 Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators

Ancillary and post-trial care 30 Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation

Dissemination policy 31a Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions

31b Authorship eligibility guidelines and any intended use of professional writers

31c Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
Appendices

Informed consent
materials 32 Model consent form and other related documentation given to participants and authorised surrogates

Biological specimens 33 Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons “Attribution-NonCommercial-NoDerivs 3.0 Unported” license.
Impact of a synchronous prophylactic treatment of the anterior accessory saphenous vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an insufficient great saphenous vein (SYNCHRONOUS-Study): Study protocol for a prospective, multicentre, controlled observational study

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Impact of a synchronous prophylactic treatment of the anterior accessory saphenous vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an insufficient great saphenous vein (SYNCHRONOUS-Study): Study protocol for a prospective, multicentre, controlled observational study

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Keywords

Varicose veins, EVLA, Laser ablation, GSV, AASV, Efficacy, Safety, Outcome
Abstract

- **Introduction:** To date, there are no prospective studies evaluating the prevention of recurrent veins by the simultaneous treatment of a sufficient anterior accessory saphenous vein (AASV) in patients undergoing endovenous laser ablation (EVLA) of an insufficient great saphenous vein (GSV). This study will provide important information about the impact of the AASV in the development of recurrent veins after EVLA of the GSV. Additionally, it will be clarified whether patients benefit from a preventive ablation of a sufficient AASV.

- **Methods and analysis:** This is a multicenter, prospective, controlled, exploratory clinical study in 1150 patients with a medical indication for EVLA of a refluxing great saphenous vein. Patients will be enrolled into two study groups: in half of the patients EVLA will be performed of the insufficient GSV only. In the other half of the patients EVLA will be performed of the insufficient GSV and additionally of the sufficient AASV. Within seven study visits, patients will be followed-up over a time period of five years. Primary study endpoint is the recurrence rate; secondary endpoints include inter alia, complication rate, post-operative pain intensity, quality of life and patient satisfaction.

- **Ethics and dissemination:** Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/). Research findings will be disseminated in a peer-reviewed journal and at relevant conferences.

Strengths and limitations of this study

- This exploratory study investigates the impact of the AASV in the development of recurrent veins in a prospective controlled setting.
- Patients will be assessed under real-life clinical conditions.
- Study results will be based on a large sample size with a long follow-up period of five years.
• Essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores.
• Limitations arise from the explorative study design which might limit the generalizability of the results.

1. Introduction

Chronic venous insufficiency caused by varicose veins is a common disorder [1]. Approximately, 50% of the western adult population show stigmata of venous disease and 25% suffer from visible varicose veins [2,3]. Venous insufficiency is most often linked to reflux of the great saphenous vein (GSV) [4]. For a long time, high ligation and stripping (HLS) of the GSV was considered as a standard treatment for vein insufficiency [1,5]. Innovative endovenous methods such as endovenous laser ablation (EVLA) are being successfully applied worldwide for many years [4,5]. Several randomized controlled trials suggest that clinical results of EVLA and HLS are comparable [4,6-10]. Recurrent varicose veins are known to be a common problem after EVLA and HLS which is defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination [11,12]. One of the most important factors associated with recurrent veins includes a new secondary reflux of the anterior accessory saphenous vein (AASV) after GSV treatment [12-15]. The AASV is a tributary of the saphenofemoral junction and is located lateral to the GSV. In a study by Garner et al., patients were observed over a 3-year period after surgery. Out of 141 groin recurrences, 61 (43%) were due to a persistent AASV and, as such, was the commonest cause of recurrent varicose veins encountered in this study [13]. Within the REVATA-study a recurrence rate of 6.9% after endoluminal procedure was detected [14]. According to the authors every fourth recurrence was caused by a secondary incompetency of the AASV. One possible explanation of the authors is that once the GSV is ablated, the blood flow from the superficial epigastric vein and pudendal junctions is then directed into the AASV. Due to inherent defects in vein wall or valves, resultant insufficiency occurs. Prior to GSV ablation, refluxing flow preferentially follows the larger diameter of the GSV [14].

Hitherto, there is only little known about the possible prevention of recurrent veins by the simultaneous treatment of the sufficient AASV in patients undergoing EVLA of an insufficient GSV [15]. Therefore, the preventive EVLA of AASV is currently a much discussed topic and
is managed differently by phlebologists. Within this study, this issue will be evaluated for the first time in a prospective controlled setting.

2. Methods and analysis

2.1 Study objectives

The primary objective of this study is to generate data to assess the impact of a synchronous treatment of the AASV for prevention of recurrent varicose veins in patients undergoing EVLA of an insufficient GSV. Recurrent varicose veins are defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination. Secondary objectives of this study are, inter alia, to address the complication rate, post-operative pain intensity, duration of absence from work and normal activity, health-related quality of life and disease-specific quality of life and patient satisfaction.

2.2 Study design and Inclusion-/Exclusion criteria

This is a multicenter, prospective, controlled, exploratory clinical study in patients with a medical indication for elective thermal ablation of a refluxing GSV. 1150 Patients of at least 18 years of age and with a medical indication for elective thermal ablation of a refluxing GSV will be evaluated in this study. Patients with varicose veins and written informed consent will be included in the study. GSV incompetence is defined by a reflux time of > 0.5 sec on duplex imaging. Patients with an incompetent AASV, a tortuous GSV rendering the vein unsuitable for endovenous treatment, duplication of the saphenous trunk, deep venous incompetence/occlusion or patients that are not able to read, understand or sign the study specific informed consent form (e.g. impaired mental state, insufficient knowledge of the German language) or with expected lack of compliance will be excluded from this study. Only study centers were selected that treat a high number of patients with the 1470nm two-ring radial laser fiber. All recruiting physicians work in a private practice located in Germany. Allocation of the study centers to the two treatment groups was based on the standard practices in each center for the treatment of refluxing GSV. According to the standard procedure of the respective study center patients will be enrolled consecutively into two study groups (A/B). Half of the 8 study centers will enroll 575 patients into group A and will perform EVLA of the insufficient GSV only. The other half of the study centers will enroll 575 patients into Group B and will perform additional EVLA of the AASV (see Figure 1).
2.3 Endovenous laser ablation (EVLA)

According to the standard operating procedures of the respective study center the AASV will be treated simultaneously in patients undergoing EVLA of an insufficient GSV or not. When the AASV is treated simultaneously to the GSV, an explicit informed consent will be obtained concerning this procedure. In all study centres, EVLA is performed with a 1470nm two-ring radial laser fiber of the same manufacturer at 10 Watts (Biolitec®, Jena, Germany). Since it is known that a long residual saphenofemoral stump promotes recurrence, flush ablation of the junction is performed in all individuals in order to minimize stump length (endovenous crossectomy) [16,17]. In endovenous crossectomy the saphenofemoral junction with the epigastric vein remains open or reopens postoperatively. All other junctional branches which flow into the femoral vein via GSV are immediately closed. AASV is closed via another puncture in a second step. In addition to EVLA, miniphlebectomies and sclerotherapy may be routinely performed in conjunction with EVLA if tributaries are present.

2.4 Study visits

In total, there will be 7 study visits during the study. The patients will be examined at the time of recruitment (V1), at the day of the procedure/EVLA (V2), until 10 days after EVLA (V3), 6 months (±4 weeks; V4), 1 year (±8 weeks; V5), 3 years (±8 weeks; V6), and 5 years after EVLA (±8 weeks; V7). For evaluation of the primary endpoint, the rate of recurrent varicose veins in general and in particular recurrent veins caused by a new AASV reflux will be obtained after EVLA in V3-V7. The secondary endpoints will be obtained by documentation of the complication rate and duration of absence from work and normal activity after the procedure. The disease-specific quality of life, disease severity and outcome of therapy for venous disease, post-operative pain intensity and patient satisfaction will be evaluated by means of the respective questionnaire in V1-V7 (see Figure 1). The following data will be obtained during the respective study visit:

Visit 1 (preoperative baseline visit): assessment of exclusion/inclusion criteria, documentation of baseline characteristics and disease severity, performance of clinical and duplex examination (the patients are examined in the standing position and reflux >0.5 seconds is considered positive. Duration of reflux and the vein diameter (mm) of the GSV at the saphenofemoral junction (and 3/15 cm below) and the length of vein will be documented). Determination of disease severity and disease-specific quality of life.
Visit 2 (EVLA): Length of treated vein (GSV and AASV), intra-operative complications, post-operative anticoagulation, postoperative compression therapy.

Visit 3-7: Post-operative complications (e.g. the presence of ecchymosis, hyperpigmentation, necrosis/burns at the puncture site, deep vein thrombosis or endovenous heat induced thrombosis (EHIT)) and sensory disorders. Treatment success/failure (closed vein or no longer visible), recurrent varicose veins, post-operative pain intensity, duration of absence from work and normal activity, disease-specific quality of life, disease severity and outcome of therapy for venous disease, patient satisfaction.

2.5 Data assessment via patient questionnaires

The disease severity and outcome of therapy for venous disease are being assessed via validated Venous Clinical Severity Score (VCSS) [18]. Disease-specific quality of life is determined by means of the Aberdeen Varicose Vein Questionnaire (AVVQ) which is a validated 13-question survey addressing all elements of varicose vein disease [19]. Furthermore, each patient is required to evaluate patient satisfaction with the treatment on a scale of 1-5. By means of a pain intensity score, patients will be asked to evaluate the pain on a scale of one (no pain) to ten (severe pain): A: the greatest pain since the last visit, B: currently experienced pain in the area of the operated limb, C: the current pressure pain, D: the most severe pressure pain since the last visit.

2.6 Statistical analysis

As this is the first explorative study investigating the recurrence rate of varicose veins caused by a persistent AASV in patients with a treated refluxing GSV, a formal sample size calculation is neither applicable nor feasible. Nevertheless, a sample size of n = 1150 patients is planned to be included as this is feasible within a reasonable period of time. Assuming a drop-out rate of 30%, this leads to a sample size of 800 to be analyzed. The information on the rate of varicose veins in general varies strongly in the literature. However, in Group A, we expect to obtain a recurrent varicose vein rate of 20% after three years. With a sample size of 800 a reduction of 7.4% (from 20% to 12.6%) of recurrent varicose veins can still be detected with a power of 80% and a significance level of 5% using a chi-square test. The primary analysis will be adjusted for covariates (see section 2.5.2) which, in general, rather increases the power of the procedure. All endpoints and patient characteristics will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, either means, standard deviations, medians, and first and third quartiles, as well as minimum...
and maximum, or absolute and relative frequency will be reported. Descriptive p-values of t-tests and chi-square tests for continuous or categorical data will be given, respectively. Furthermore, the associated 95% confidence intervals of the means or rate differences will be provided. If appropriate, graphical methods will be used to visualize the findings. The primary null hypothesis of equal rates in the primary endpoint (varicose veins, yes/no per person) after three years (V6) in both groups will be tested using a logistic regression model. The group variable, age, BMI and gender will be included as predictors. For each factor, the odds ratio with 95% confidence intervals and p-values will be reported. Missing values will be imputed using a multiple imputation approach. A Fully Conditional Specification (FCS) method will be applied. This is a commonly used method and appropriate for an arbitrary structure of missing values which is the most general form of a missing data pattern (see, for example, Berglund PA, 2015). All variables that are used in the primary model will be included in the imputation models. The same logistic regression model will be fit when analyzing the primary endpoint at the other time points (V3-V5 and V7). For all other endpoints, (generalized) regression models will be applied as appropriate including the same predictors as in the primary analysis. Furthermore, longitudinal (mixed) regression models for all endpoints will be applied including all time points into one model. A random intercept (for patients) will be included and different correlation structures will be applied (in particular, an unstructured covariance matrix and an auto-correlation structure). Again, the same predictors as before will be included as fixed factors and odds ratios with 95% confidence intervals and p-values will be reported.

2.7 Study organization and data management
Study coordination and data management is performed by the Department of Dermatology, University of Heidelberg. Data collection is done via case report forms (CRFs). Statistical analysis will be performed by the Institute of Medical Biometry. All study procedures will be done according to approved standard operating procedures (SOPs) which are based on ICH-GCP guidelines (E6), the German implementation of Good clinical practice (GCP) and the current laws.

2.8 Ethical considerations, dissemination plan and regulatory obligations
The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics
approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/). Research findings will be disseminated in a peer-reviewed journal and at relevant conferences.

2.9 Patient and public involvement

No patient involved.

2.10 Recruitment and status of the study

Ethical approval was granted in October 2018. First enrollment was in February 2019. The estimated time required for recruitment is 48 months. The total duration of the study is expected to be 108 months, including statistical analysis.

3 Discussion

To date, there are no controlled prospective studies evaluating the impact of a simultaneous EVLA of AASV for prevention of a secondary reflux in patients undergoing EVLA of an insufficient GSV. Therefore, it remains unclear whether patients benefit from this procedure. This exploratory study addresses this important open question for the first time in a prospective controlled setting under real-life clinical conditions based on a relatively large sample size. Additionally, essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores. Limitations arise from the explorative study design which might limit the generalizability of the results. Nevertheless, data provided by this study makes it possible to plan and perform a randomized controlled future trial with a formal sample size calculation.

ABBREVIATIONS

EVLA Endovenous Laser Ablation
AASV Anterior Accessory Saphenous Vein
GSV Great Saphenous Vein
SFJ Sapheno-femoral junction
VCSS Venous Clinical Severity Score
AVVQ Aberdeen Varicose Vein Symptom Severity Score
ICH-GCP International Conference on Harmonization-Good Clinical Practice
CEAP Clinical, etiological, anatomical and pathological
SD Standard Deviation

DECLARATIONS

Ethics approval and consent to participate: before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018).

Consent for publication: not applicable

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors state “no conflict of interest”.

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Authors’ contributions

Conception and design: CF, KH, TH, TM, HCW, TW, MS, FP, LU, TH

Analysis and interpretation: CF, CD, KH, TH, LU

Data collection: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, FP, LU, TH

Writing the article: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, LU, TH

Critical revision of the article: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, FP, LU, TH

Final approval of the article: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, FP, LU, TH

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FIGURES

Figure 1  Flowchart of the study
Patients meeting inclusion criteria with a medical indication EVLA of a refluxing GSV (n = 1150)

~ 50% ~ 50%

Group A
EVLA of the insufficient GSV only

Group B
EVLA of the insufficient GSV & preventative EVLA of AASV

\[ \bullet V1 \text{ (Baseline)} \]

\[ \bullet V2 \text{ (EVLA)} \]

\[ \bullet V3 \text{ (10 days after EVLA)} \]

\[ \bullet V4 \text{ (6 months (~4 weeks) after EVLA)} \]

\[ \bullet V5 \text{ (1 year (~8 weeks) after EVLA)} \]

\[ \bullet V6 \text{ (3 year (~8 weeks) after EVLA)} \]

\[ \bullet V7 \text{ (5 year (~8 weeks) after EVLA)} \]

Flowchart of the study

190x254mm (96 x 96 DPI)
Impact of a synchronous prophylactic treatment of the anterior accessory saphenous vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an insufficient great saphenous vein (SYNCHRONOUS-Study): Study protocol for a prospective, multicentre, controlled observational study

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Impact of a synchronous prophylactic treatment of the anterior accessory saphenous
vein on the recurrent varicose vein rate in patients undergoing thermal ablation of an
insufficient great saphenous vein (SYNCHRONOUS-Study): Study protocol for a
prospective, multicentre, controlled observational study

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Keywords

Varicose veins, EVLA, Laser ablation, GSV, AASV, Efficacy, Safety, Outcome
Abstract

- **Introduction:** To date, there are no prospective studies evaluating the prevention of recurrent veins by the simultaneous treatment of a sufficient anterior accessory saphenous vein (AASV) in patients undergoing endovenous laser ablation (EVLA) of an insufficient great saphenous vein (GSV). This study will provide important information about the impact of the AASV in the development of recurrent veins after EVLA of the GSV. Additionally, it will be clarified whether patients benefit from a preventive ablation of a sufficient AASV.

- **Methods and analysis:** This is a multicenter, prospective, controlled, exploratory clinical study in 1150 patients with a medical indication for EVLA of a refluxing great saphenous vein. Patients will be enrolled into two study groups: in half of the patients EVLA will be performed of the insufficient GSV only. In the other half of the patients EVLA will be performed of the insufficient GSV and additionally of the sufficient AASV. Within seven study visits, patients will be followed-up over a time period of five years. Primary study endpoint is the recurrence rate; secondary endpoints include inter alia, complication rate, post-operative pain intensity, quality of life and patient satisfaction.

- **Ethics and dissemination:** Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/). Research findings will be disseminated in a peer-reviewed journal and at relevant conferences.

Strengths and limitations of this study

- This exploratory study investigates the impact of the AASV in the development of recurrent veins in a prospective controlled setting.
- Patients will be assessed under real-life clinical conditions.
- Study results will be based on a large sample size with a long follow-up period of five years.
Essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores.

Limitations arise from the explorative study design which might limit the generalizability of the results.

1. Introduction

Chronic venous insufficiency caused by varicose veins is a common disorder [1]. Approximately, 50% of the western adult population show stigmata of venous disease and 25% suffer from visible varicose veins [2,3]. Venous insufficiency is most often linked to reflux of the great saphenous vein (GSV) [4]. For a long time, high ligation and stripping (HLS) of the GSV was considered as a standard treatment for vein insufficiency [1,5]. Innovative endovenous methods such as endovenous laser ablation (EVLA) are being successfully applied world-wide for many years [4,5]. Several randomized controlled trials suggest that clinical results of EVLA and HLS are comparable [4,6-10]. Recurrent varicose veins are known to be a common problem after EVLA and HLS which is defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination [11,12]. One of the most important factors associated with recurrent veins includes a new secondary reflux of the anterior accessory saphenous vein (AASV) after GSV treatment [12-15]. The AASV is a tributary of the saphenofemoral junction and is located lateral to the GSV. In a study by Garner et al., patients were observed over a 3-year period after surgery. Out of 141 groin recurrences, 61 (43%) were due to a persistent AASV and, as such, was the commonest cause of recurrent varicose veins encountered in this study [13]. Within the REVATA-study a recurrence rate of 6.9% after endoluminal procedure was detected [14]. According to the authors every fourth recurrence was caused by a secondary incompetency of the AASV. One possible explanation of the authors is that once the GSV is ablated, the blood flow from the superficial epigastric vein and pudendal junctions is then directed into the AASV. Due to inherent defects in vein wall or valves, resultant insufficiency occurs. Prior to GSV ablation, refluxing flow preferentially follows the larger diameter of the GSV [14].

Hitherto, there is only little known about the possible prevention of recurrent veins by the simultaneous treatment of the sufficient AASV in patients undergoing EVLA of an insufficient GSV [15]. Therefore, the preventive EVLA of AASV is currently a much discussed topic and
is managed differently by phlebologists. Within this study, this issue will be evaluated for the first time in a prospective controlled setting.

2. Methods and analysis

2.1 Study objectives

The primary objective of this study is to generate data to assess the impact of a synchronous treatment of the AASV for prevention of recurrent varicose veins in patients undergoing EVLA of an insufficient GSV. Recurrent varicose veins are defined as a reflux in the treated groin area with or without a persistent GSV stump in duplex examination. Secondary objectives of this study are, inter alia, to address the complication rate, post-operative pain intensity, duration of absence from work and normal activity, health-related quality of life and disease-specific quality of life and patient satisfaction.

2.2 Study design and Inclusion-/Exclusion criteria

This is a multicenter, prospective, controlled, exploratory clinical study in patients with a medical indication for elective thermal ablation of a refluxing GSV. 1150 Patients of at least 18 years of age and with a medical indication for elective thermal ablation of a refluxing GSV will be evaluated in this study. Patients with varicose veins and written informed consent will be included in the study. GSV incompetence is defined by a reflux time of > 0.5 sec on duplex imaging. Patients with an incompetent AASV, a tortuous GSV rendering the vein unsuitable for endovenous treatment, duplication of the saphenous trunk, deep venous incompetence/occlusion or patients that are not able to read, understand or sign the study specific informed consent form (e.g. impaired mental state, insufficient knowledge of the German language) or with expected lack of compliance will be excluded from this study. Only study centers were selected that treat a high number of patients with the 1470nm two-ring radial laser fiber. All recruiting physicians work in a private practice located in Germany. Allocation of the study centers to the two treatment groups was based on the standard practices in each center for the treatment of refluxing GSV. According to the standard procedure of the respective study center patients will be enrolled consecutively into two study groups (A/B). Half of the 8 study centers will enroll 575 patients into Group A and will perform EVLA of the insufficient GSV only. The other half of the study centers will enroll 575 patients into Group B and will perform additional EVLA of the AASV (see Figure 1).
2.3 Endovenous laser ablation (EVLA)

According to the standard operating procedures of the respective study center the AASV will be treated simultaneously in patients undergoing EVLA of an insufficient GSV or not. When the AASV is treated simultaneously to the GSV, an explicit informed consent will be obtained concerning this procedure. In all study centres, EVLA is performed with a 1470nm two-ring radial laser fiber of the same manufacturer at 10 Watts (Biolitec®, Jena, Germany). Since it is known that a long residual saphenofemoral stump promotes recurrence, flush ablation of the junction is performed in all individuals in order to minimize stump length (endovenous crossectomy) [16,17]. In endovenous crossectomy the saphenofemoral junction with the epigastric vein remains open or reopens postoperatively. All other junctional branches which flow into the femoral vein via GSV are immediately closed. AASV is closed via another puncture in a second step. In addition to EVLA, miniphlebectomies and sclerotherapy may be routinely performed in conjunction with EVLA if tributaries are present.

2.4 Study visits

In total, there will be 7 study visits during the study. The patients will be examined at the time of recruitment (V1), at the day of the procedure/EVLA (V2), until 10 days after EVLA (V3), 6 months (±4 weeks; V4), 1 year (±8 weeks; V5), 3 years (±8 weeks; V6), and 5 years after EVLA (±8 weeks; V7). For evaluation of the primary endpoint, the rate of recurrent varicose veins in general and in particular recurrent veins caused by a new AASV reflux will be obtained after EVLA in V3-V7. The secondary endpoints will be obtained by documentation of the complication rate and duration of absence from work and normal activity after the procedure. The disease-specific quality of life, disease severity and outcome of therapy for venous disease, post-operative pain intensity and patient satisfaction will be evaluated by means of the respective questionnaire in V1-V7 (see Figure 1). The following data will be obtained during the respective study visit:

Visit 1 (preoperative baseline visit): assessment of exclusion/inclusion criteria, documentation of baseline characteristics and disease severity, performance of clinical and duplex examination (the patients are examined in the standing position and reflux >0.5 seconds is considered positive. Duration of reflux and the vein diameter (mm) of the GSV at the saphenofemoral junction (and 3/15 cm below) and the length of vein will be documented). Determination of disease severity and disease-specific quality of life.
Visit 2 (EVLA): Length of treated vein (GSV and AASV), intra-operative complications, post-operative anticoagulation, postoperative compression therapy.

Visit 3-7: Post-operative complications (e.g. the presence of ecchymosis, hyperpigmentation, necrosis/burns at the puncture site, deep vein thrombosis or endovenous heat induced thrombosis (EHIT) and sensory disorders. Treatment success/failure (closed vein or no longer visible), recurrent varicose veins, post-operative pain intensity, duration of absence from work and normal activity, disease-specific quality of life, disease severity and outcome of therapy for venous disease, patient satisfaction.

2.5 Data assessment via patient questionnaires

The disease severity and outcome of therapy for venous disease are being assessed via validated Venous Clinical Severity Score (VCSS) [18]. Disease-specific quality of life is determined by means of the Aberdeen Varicose Vein Questionnaire (AVVQ) which is a validated 13-question survey addressing all elements of varicose vein disease [19]. Furthermore, each patient is required to evaluate patient satisfaction with the treatment on a scale of 1-5. By means of a pain intensity score, patients will be asked to evaluate the pain on a scale of one (no pain) to ten (severe pain): A: the greatest pain since the last visit, B: currently experienced pain in the area of the operated limb, C: the current pressure pain, D: the most severe pressure pain since the last visit.

2.6 Statistical analysis

As this is the first explorative study investigating the recurrence rate of varicose veins caused by a persistent AASV in patients with a treated refluxing GSV, a formal sample size calculation is neither applicable nor feasible. Nevertheless, a sample size of n = 1150 patients is planned to be included as this is feasible within a reasonable period of time. Assuming a drop-out rate of 30%, this leads to a sample size of 800 to be analyzed. The information on the rate of varicose veins in general varies strongly in the literature. However, in Group A, we expect to obtain a recurrent varicose vein rate of 20% after three years. With a sample size of 800, a reduction of 7.4% (from 20% to 12.6%) of recurrent varicose veins can still be detected with a power of 80% and a significance level of 5% using a chi-square test. The primary analysis will be adjusted for covariates (see section 2.5.2) which, in general, rather increases the power of the procedure. All endpoints and patient characteristics will be analyzed descriptively by tabulation of the measures of the empirical distributions. Depending on the scale level of the variables, either means, standard deviations, medians, and first and third quartiles, as well as minimum
and maximum, or absolute and relative frequency will be reported. Descriptive p-values of t-tests and chi-square tests for continuous or categorical data will be given, respectively. Furthermore, the associated 95% confidence intervals of the means or rate differences will be provided. If appropriate, graphical methods will be used to visualize the findings. The primary null hypothesis of equal rates in the primary endpoint (varicose veins, yes/no per person) after three years (V6) in both groups will be tested using a logistic regression model. The group variable, age, BMI and gender will be included as predictors. For each factor, the odds ratio with 95% confidence intervals and p-values will be reported. Missing values will be imputed using a multiple imputation approach. A Fully Conditional Specification (FCS) method will be applied. This is a commonly used method and appropriate for an arbitrary structure of missing values which is the most general form of a missing data pattern (see, for example, Berglund PA, 2015). All variables that are used in the primary model will be included in the imputation models. The same logistic regression model will be fit when analyzing the primary endpoint at the other time points (V3-V5 and V7). For all other endpoints, (generalized) regression models will be applied as appropriate including the same predictors as in the primary analysis. Furthermore, longitudinal (mixed) regression models for all endpoints will be applied including all time points into one model. A random intercept (for patients) will be included and different correlation structures will be applied (in particular, an unstructured covariance matrix and an auto-correlation structure). Again, the same predictors as before will be included as fixed factors and odds ratios with 95% confidence intervals and p-values will be reported.

2.7 Study organization and data management

Study coordination and data management is performed by the Department of Dermatology, University of Heidelberg. Data collection is done via case report forms (CRFs). Statistical analysis will be performed by the Institute of Medical Biometry. All study procedures will be done according to approved standard operating procedures (SOPs) which are based on ICH-GCP guidelines (E6), the German implementation of Good clinical practice (GCP) and the current laws.

2.8 Ethical considerations, dissemination plan and regulatory obligations

The study is conducted in accordance with the Declaration of Helsinki principles (2013), applicable local government regulations, and independent Ethics Committee policies and procedures. Before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics
approval number S-596/2018). This study was prospectively registered at the German Clinical Trial Register (DRKS): DRKS00015486 (https://www.germanctr.de/). Research findings will be disseminated in a peer-reviewed journal and at relevant conferences.

2.9 Patient and public involvement

No patient involved.

2.10 Recruitment and status of the study

Ethical approval was granted in October 2018. First enrollment was in February 2019. The estimated time required for recruitment is 48 months. The total duration of the study is expected to be 108 months, including statistical analysis.

3 Discussion

To date, there are no controlled prospective studies evaluating the impact of a simultaneous EVLA of AASV for prevention of a secondary reflux in patients undergoing EVLA of an insufficient GSV. Therefore, it remains unclear whether patients benefit from this procedure. This exploratory study addresses this important open question for the first time in a prospective controlled setting under real-life clinical conditions based on a relatively large sample size. Additionally, essential patient related outcome measures (e.g. quality of life and response to therapy) are being assessed by validated scores. Limitations arise from the explorative study design which might limit the generalizability of the results. Nevertheless, data provided by this study makes it possible to plan and perform a randomized controlled future trial with a formal sample size calculation.

ABBREVIATIONS

EVLA Endovenous Laser Ablation
AASV Anterior Accessory Saphenous Vein
GSV Great Saphenous Vein
SFJ Sapheno-femoral junction
VCSS Venous Clinical Severity Score
AVVQ Aberdeen Varicose Vein Symptom Severity Score
ICH-GCP International Conference on Harmonization-Good Clinical Practice
CEAP Clinical, etiological, anatomical and pathological
SD Standard Deviation

DECLARATIONS

Ethics approval and consent to participate: before initiation of the study, the protocol was presented and approved by the independent ethics committee of the medical faculty of the University of Heidelberg (Ethics approval number S-596/2018).

Consent for publication: not applicable

Availability of data and materials: the datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: All authors state “no conflict of interest”.

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Authors’ contributions

Conception and design: CF, KH, TH, TM, HCW, TW, MS, FP, LU, TH

Analysis and interpretation: CF, CD, KH, TH, LU

Data collection: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, FP, LU, TH

Writing the article: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, LU, TH

Critical revision of the article: CF, CD, KH, TM, HCW, PZ, JV, TW, GL, LM, MS, FP, LU, TH

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FIGURES

Figure 1 Flowchart of the study
Patients meeting inclusion criteria with a medical indication EVLA of a refluxing GSV (n = 1150)

~ 50 %

Group A
EVLA of the insufficient GSV only

~ 50 %

Group B
EVLA of the insufficient GSV & preventive EVLA of AASV

- V1 (Baseline)
- V2 (EVLA)
- V3 (10 days after EVLA)
- V4 (6 months ±4 weeks) after EVLA
- V5 (1 year ±8 weeks) after EVLA
- V6 (3 year ±8 weeks) after EVLA
- V7 (5 year ±8 weeks) after EVLA

Flowchart of the study

190x254mm (96 x 96 DPI)