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Protocol for the Prospective Cohort Study for Varicose Veins Incidence and Natural Course (VINCI)

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ABSTRACT

Currently, there are no clear data on the incidence of varicose veins and other chronic venous diseases (CVD).

Objective. To assess the incidence, risk factors and natural course of CVD.

Material and methods. A prospective cohort study for VarIose veiNs inCIdence and natural course (VINCI) is designed for long-term follow-up of recruited patients with and without CVD at inclusion. Individuals to include are recruiters themselves and their close relatives. Researchers themselves and their close relatives are also included. The researchers are surgeons and vascular surgeons who regularly manage CVD patients. Patients with previous invasive treatment of CVD, as well as those with previous or ongoing venous thrombosis will not be included. Clinical examination and Doppler ultrasound will be performed annually. Data will be collected and carried out in a protected registry of the Russian Phlebology Association. Morbidity, absolute and relative risk will be calculated to estimate CVD progression. No personal data will be collected or stored.

Trial registration. ClinicalTrials.gov, ID: NCT04546750. Registered on 5 September 2020.

Keywords: *chronic venous disease, varicose veins, incidence, risk factors.*

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Introduction

CVD is one of the most prevalent vascular pathology. This is confirmed by a number of epidemiological studies conducted in different regions of the world [1—3]. Being extensively studied, CVD prevalence remains questionable nonetheless. This is due to many limitations of the studies where data on prevalence and risk factors of CVD were obtained. One of the most important limitation is examination of selected population rather than general. Besides, most epidemiological studies have been conducted a long ago, without using the CEAP classification. The fact that the available data are ambiguous is also indicated by a certain scatter of data on risk factors. Age, female sex, obesity, and heredity are generally accepted to be a CVD risk factors. Specific for female individuals' pregnancy, hormone therapy (estrogens, gestagens), menopause are reported [1, 4—7]. At the same time, not all studies confirm that gender is playing a significant role in CVD development [8, 9]. The role of pregnancy and childbirth in the genesis of varicose veins is evidenced by the data of many studies [7, 9, 10]. Overweight is considered one of the possible risk factors for CVD. However, a high body mass index (BMI) is associated with a higher number of pregnancies and childbirths in women cases [7, 11—14]. Heredity is also recognized as a risk factor for CVD [7, 15, 16]. Static loads, especially orthostatic ones, which are usually associated with working conditions are also considered risk factors, because they slow down the outflow of blood from the lower extremities. First of all, this happens as a result of insufficient calf muscle pump activity of the lower leg combined with a prolonged action of the gravity force. There is a list of occupancies, such as hairdressers, teachers, cooks, surgeons, and so on, whose work is believed to be connected with a higher risk of varicose veins. The data on that are contradictory as this connection was confirmed in some studies [15, 17, 18], while in others was not [7, 12].

Epidemiological data published up to now are inconsistent and based on results of a studies with questionable robustness [5, 9, 19—24]. Main disadvantages are related to relatively small number of subjects included and impossibility to follow participants for many

years. To include as many individuals as possible involvement of many doctors as recruiters is used. This may lead to another source of biases, because non-vascular specialists who do not have sufficient skills for correct diagnostics are often involved.

If the prevalence of CVD and varicose veins as well as the risk factors are more or less discovered the incidence seems to be unknown. The Tampere Varicose Veins Study with an included prospective cohort of 6,000 patients followed for over 5 years has probably the best data [25]. Varicose veins incidence was estimated by the subgroup of included adults at the time of enrollment (2400 patients) and was 14 per 1000 patient-years without considering family history and gender. This study had a number of significant limitations as the disease onset was estimated by patients themselves using a special questionnaire with only selective control by specialists. Another important disadvantage was age over 40 years at inclusion, although, the peak incidence of varicose is about 20—40 years.

Aim of this study is to assess an incidence and natural course of CVD based on a stable cohort of individuals followed by experienced vascular specialists.

Primary end-point:

— annual CVD incidence.

Secondary end-points:

— incidence of different C-classes (according to CEAP);
— CVD progression during follow up by registering changes of C-classes in individuals with manifested CVD;
— independent risk factors for CVD;
— independent risk factors for reticular veins/telangiectasias and for varicose veins;
— incidence of venous edema;
— incidence of trophic disorders;
— incidence of thrombotic complications of CVD;
— independent risk factors for CV1D complications.

Methods and analysis

Geographical context

Subjects will mainly represent a diverse population of Russian-speaking countries. It will be also possible to include individuals from other regions.

Study population

The population of prospective cohort study for VarIcose veins INCIdence and Natural Course (VINCI) will include recruiters themselves, i.e., phlebologists or other vascular specialists who decide to participate and their family members both male and female aged 10 years and more.

Inclusion criteria

— For the researcher:
  — daily practice in phlebology;
  — ability to perform duplex ultrasound him-/herself.
— As family members those are eligible:
  — spouse;
  — children;
  — brothers and sisters;
  — parents.
— Age 10 and more years.
— Family members must be available for annual physical examination and duplex ultrasound if it's needed.

Exclusion criteria:

— previous invasive treatment for CVD;
— history of DVT/PE or DVT/PE at inclusion.

Researchers

As researchers, phlebologists, vascular specialists, surgeons who are managing venous patients on a daily basis will be invited. Every researcher will include family members to follow. This will guarantee correct diagnostics of CVD in accordance with recent guidelines.

Study design

This protocol is designed for a longitudinal cohort study with a prospective component. The methodology for cohort building and the following of recruited subjects is presented in **Fig. 1**.

Cohort formation will start within 6 months from the start of the study. The inclusion of new researchers or new subjects is possible during the entire study. In the last quarter of every year researchers will have to examine all subjects they follow.

The cohort will be divided into two subgroups. The first subgroup will include individuals with no CVD at inclusion. CVD incidence assessment will be the main outcome to measure in this sub-group. Regardless of when subjects enter the subgroup, they will be followed prospectively every 12 months or until CVD development. When this happens, individuals are moved to the second subgroup. The second subgroup will include also subjects with CVD at inclusion. The subjects from the second subgroup will be followed every 12 months as well.

Data collection and management

Patient's family and medical history, descriptive data, medical data obtained from physical examination and duplex ultrasound of lower limbs venous system will be reported. Data on specific variables of interest will be ascertained from each source as outlined in **Table.**

All data will be entered and stored in the database «Registry for Chronic Venous Disease Incidence and Natural Course (RRCVD)», which is designed for this study and registered at ClinicalTrials.gov, ID NCT04487314 as non-interventional patient register [26]. This register is a component of the Russian Phlebological Association Register System and facilitates creation and management of data collection instruments, monitoring of data quality and statistical analysis of data.

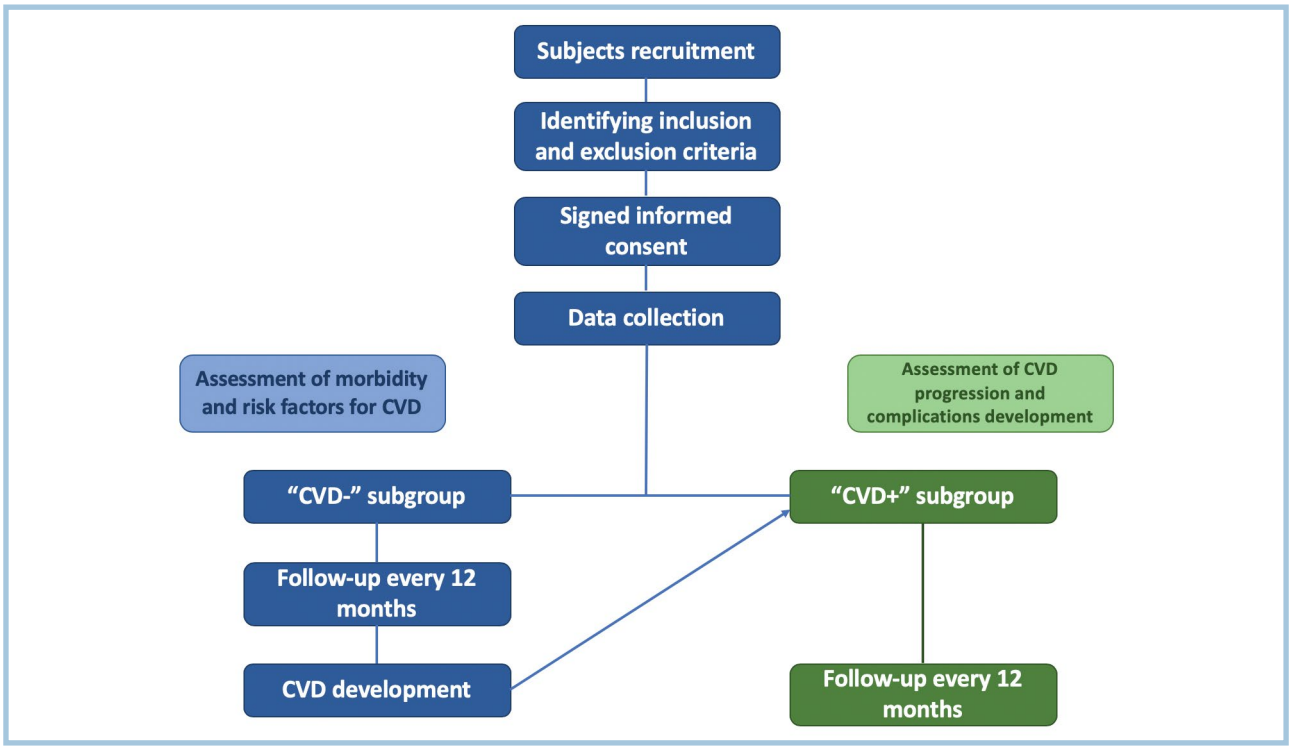

Fig. 1. **Flowchart of patient inclusion and their subsequent follow-up.**
CVD — Chronic Venous Disease; CVD− — absence of CVD; CVD+ — presence of CVD.

The data entry interface has been made as simple and clear as possible. Entering data is carried out by setting checkboxes or by choosing options in the drop-down list. Register consists of patient's profiles with the raw data page and the follow-up visits pages linked to profile **(Fig. 2)**. The raw data page consists of patient's demographic, family and medical history, physical activity, medical status, obstetric and gynecological history (for women), CVD description based on CEAP classification (type, localization), venous duplex ultrasound results, invasive and non-invasive CVD treatment data, CVD symptoms description.

The follow-up visit pages are used for registering changes in life circumstances, general health conditions, changes in CVD status, including recent duplex ultrasound.

Statistical analysis

Data to be analyzed will be exported from RRCVD into Microsoft Excel tables. In order to estimate the time from the beginning of supervision to the development of CVD and CVD complications, Kaplan—Meyer survival curves will be constructed.

The main statistical parameters for the occurrence of CVD or appearance of CVD complications are incidence, absolute and relative risk. It is possible to use additional statistical parameters for progression estimating such as attributive risk, risk difference, etiological fraction (EF), additional population risk, internal reliability of the study.

Considering the long duration of the study and the expected non-simultaneous dropouts of participants as well as the possibility of adding new ones, the person-time incidence rate will be used in the study process.

Variables of interest with corresponding data source

Anamnestic data	Patient description	Description of CVD
Family history	Demographic data	CVD description based on CEAP classification, version 2020
Medical history	Physical activity	Venous ultrasound data registration (based on CEAP-classification 2020)
Obstetric and gynecological history (for women)	Medical status (including presence of diseases, medications taken)	The non-invasive treatment of CVD
	Pregnancy, hormone therapy (for women)	The invasive treatment of CVD
		CVD symptoms recording

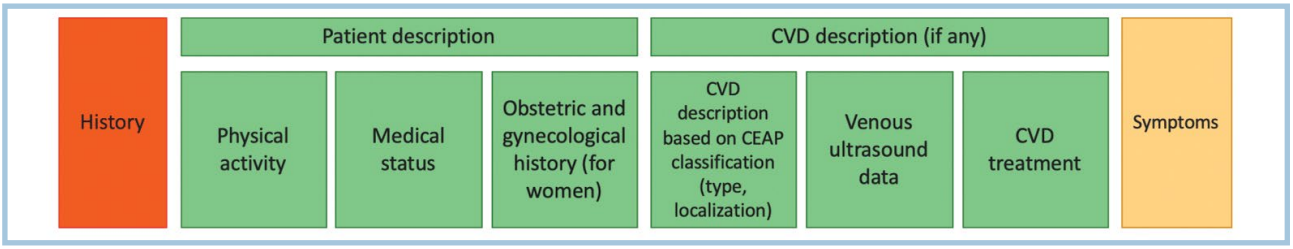

Fig. 2. **Data page structure.**

Discussion

This study is designed to assess the incidence of CVD. We are going to form cohort of individuals both with and without CVD at inclusion. For every relatively large cohort study with a long follow up period there are two main disadvantages that may influence the data quality. At first, to include many individuals in a short time period it needs to invite many physicians as recruiters. For this purpose, not only vascular specialists are invited to participate, but also others like general practitioners, internists etc [9]. This may significantly impact on the data quality as recruiters like those usually don't have enough skills to effectively diagnose CVD, which leads often to overestimation of the symptoms and signs. Another problem of longitudinal studies is high drop-out rates related to difficulties with repetitive contacts with patients during follow up. To overcome both problems we decided to form the study population from the recruiters themselves and from theirs close relatives. As we are going to invite as recruiters only specialists with regular practice in phlebology, we may guarantee correct estimation of venous status. On the other hand, inclusion of members recruiters' families allows us to effectively decrease drop-out during follow up.

Dividing population onto two sub-cohorts will allow us to observe both incidence of CVD following those with no disease at inclusion and progression of CVD by following CVD positive individuals. We also hope to reveal independent risk factors for CVD development to confirm the data previously found in different epidemiological studies. By identifying particular risk factors, it will be possible to develop a predictive model with risk scores for the likelihood of CVD development within a certain period of time. In addition, CVD incidence data collected from the cohort will be robust, as data will be obtained continuously through regular examinations of the subjects from the stable cohort. Of note, this study will also allow to determine the time of thrombotic and non-thrombotic CVD complications and their frequency.

The study is planned as open-ended.

Ethics and dissemination

The primary investigators have extensive training and experience in clinical research and bioethics. The researchers' team will include vascular specialists that have qualifications and experience to conduct the study. There are no anticipated physical, social, legal or economic risks associated with the study.

The design of the study was approved by Ethics Committee of Pavlov Ryazan State Medical University.

Data protection

No personal data except medical will be collected. All subject-specific data will be entered and be kept confidential on the protected web-site of RRCVD that can be accessed by recruiters only. All records containing personal health information will not be made publicly available. Deidentified collected data may be used for future analysis and publication.

We hope to present the results of this study to the scientific community at conferences and in peer-reviewed journals.

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The authors declare no conflict of interest.

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