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Protocol of the Berlin Long-term Observation of Vascular Events (BeLOVE): a prospective cohort study with deep phenotyping and long-term follow up of cardiovascular high-risk patients

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ABSTRACT

Introduction The Berlin Long-term Observation of Vascular Events is a prospective cohort study that aims to improve prediction and disease-overarching mechanistic understanding of cardiovascular (CV) disease progression by comprehensively investigating a high-risk patient population with different organ manifestations.

Methods and analysis A total of 8000 adult patients will be recruited who have either suffered an acute CV event (CVE) requiring hospitalisation or who have not experienced a recent acute CVE but are at high CV risk. An initial study examination is performed during the acute treatment phase of the index CVE or after inclusion into the chronic high risk arm. Deep phenotyping is then performed after ~90 days and includes assessments of the patient's medical history, health status and behaviour, cardiovascular, nutritional, metabolic, and anthropometric parameters, and patient-related outcome measures. Biospecimens are collected for analyses including 'OMICs' technologies (e.g., genomics, metabolomics, proteomics). Subcohorts undergo MRI of the brain, heart, lung and kidney, as well as more comprehensive metabolic, neurological and CV examinations. All participants are followed up for up to 10 years to assess clinical outcomes, primarily major adverse CVEs and patient-reported (value-based) outcomes. State-of-the-art clinical research methods, as well as emerging techniques from systems medicine and artificial intelligence, will be used to identify associations between patient characteristics, longitudinal changes and outcomes.

Ethics and dissemination The study was approved by the Charité—Universitätsmedizin Berlin ethics committee (EA1/066/17). The results of the study will be disseminated through international peer-reviewed publications and congress presentations.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The Berlin Long-term Observation of Vascular Events provides a unique opportunity to foster research on mechanisms that drive disease progression in a heterogeneous cardiovascular high-risk patient population with various organ-manifestations to develop disease-overarching personalised secondary prevention strategies.

⇒ The comprehensive collection of data and biospecimens at baseline, as well as during the 10 years follow-up programme, can be used as a platform to address multiple research questions.

⇒ Cooperation and data integration with other large ongoing cohorts is enabled by using similar phenotyping protocols (German National Cohort, NAKO); German National Pandemic Cohort Net (NAPKON).

⇒ A limitation is that due to the time-consuming deep phenotyping procedures (particularly during the day ~90 visit) the study participation might not be feasible for very severely ill patients resulting in a selection bias. Such a bias may additionally result from the necessity for participants to speak and comprehend German fluently which is required for multiple study measures.

⇒ Generalisability of the study population may also be limited by the recruitment setting in a major university hospital.

Study registration First study phase: Approved WHO primary register: German Clinical Trials Register: https://drks.de/search/de/trial/DRKS00016852; WHO International

Clinical Registry Platform: http://apps.who.int/trialsearch/Trial2.aspx?TrialID=DRKS00016852. Recruitment started on July 18, 2017. Second study phase: Approved WHO primary register: German Clinical Trials Register DRKS00023323, date of registration: November 4, 2020, URL: http://www.drks.de/ DRKS00023323. Recruitment started on January 1, 2021.

INTRODUCTION

Background and rationale

Despite advances in therapy and prevention,[1] cardiovascular disease (CVD) remains the leading cause of death and permanent disability worldwide.[2 3] Cardiovascular events (CVE), such as acute coronary syndrome (ACS), acute heart failure (AHF) or acute stroke, share multiple established risk factors,[4] including type 2 diabetes, hypertension, lipid disorders, obesity, smoking. In clinical practice, the individual risk factor profile is used in algorithms for CVE risk prediction and for prevention decisions.[5 6]Patients with a CVE are at very high risk for recurrent events and cardiovascular death.[6] However, individual risk varies substantially even when adhering to current standards of care.[7–9] Interactions between multiple aspects of health and disease are not fully understood. Interacting factors are, for example, cardiovascular and chronic cardiometabolic comorbidities,[10] behavioural and social factors, and the impact of treatment-related advances on long-term prognosis.[11] Furthermore, CVDs are systemic diseases that affect multiple organs.[12] Interorgan crosstalk is crucially involved in individual disease progression and outcome.

For a more personalised risk stratification and more effective personalised interventions in patients with established CVD, a better understanding of the mechanistic involvement of systemic factors such as immunological processes,[13–15] metabolic parameters[12 16] or the gut microbiome[17] is needed. Characterisation of the long-term consequences of the interplay between organs[18–20] will help to understand the interindividual variability in disease progression and improve the development of interventions to reduce adverse CVD outcomes.

Objectives

The primary goal of the Berlin Long-term Observation of Vascular Events (BeLOVE) is to identify and to characterise risk factors for major adverse cardiovascular events (MACE) among patients at high CVD risk. Secondary objectives include the identification of characteristics and markers associated with mortality, and patient-reported outcomes. Also, BeLOVE aims to promote a cross-disease mechanistic understanding of CVD in high-risk patients to provide the basis for improved, individualised risk management. BeLOVE consists of a cohort of cardiovascular patients with different primary disease entities for comprehensive clinical, functional and molecular phenotyping with extensive collection of biospecimens. It will serve as a resource to identify and characterise novel risk factors in secondary prevention settings.

METHODS AND ANALYSIS

Study design

BeLOVE is a prospective cohort study of patients with either one of three recent acute index CVEs: (1) ACS, (2) AHF, (3) acute ischaemic stroke or transient ischaemic attack (TIA) or non-traumatic intracerebral haemorrhage or (4) patients who are at very high CV-risk as proposed by the European Society for Cardiology[21 22] but without a history of an acute CVE during the prior 12 months. The key study visits consist of initial phenotyping within 7 days after the acute CVE or within 14 days following study inclusion in the "chronic" CVD arm and comprehensive deep phenotyping after 90 (69–153) days. Participation in at least one of the two visits is a minimal requirement for study continuation. To measure longitudinal changes in exposures or phenotypes additional, more limited visits may be offered to a subset of the participants for up to every 2 years thereafter depending on the availability of additional funding.

The follow-up period will be up to 10 years for all participants for the incidence of MACE and secondary clinical outcomes, and is based on telephone interviews with participants and collection of clinical information from multiple sources (see under Collection of clinical data from medical records and additional sources).

BeLOVE is carried out at facilities of the Berlin Institute of Health (BIH), the Charité–Universitätsmedizin Berlin, and the Max Delbrück Center for Molecular Medicine in the Helmholtz Association, Berlin (MDC). The governance and management of the study and the institutions involved in the conduction of the study are described in online supplemental figure 1.

Recruitment

Patients are recruited at the Charité—Universitätsmedizin Berlin. The recruitment goal is 8000 participants by 2030. All patients who are admitted to the participating clinical departments of cardiology and neurology with an acute CVE are screened for eligibility to participate based on the criteria listed in table 1 (see online supplemental tables 1 and 2 for more details). Informed consent is obtained during the acute in-hospital phase. Patients who cannot or do not wish to participate in the inclusion visit (acute phenotyping) can postpone consent until the deep phenotyping visit at day ~90 (for details of the visit schedule see figure 1). Inclusion of patients in the chronic high-risk stratum can be initiated at any time. Candidates are approached and contacted (1) in outpatient clinics, (2) during hospitalisation for any reason and (3) by advertisement in Berlin public transport.

Research visits

The phenotyping of patients during the inclusion visit (see table 2) focuses on biosampling while day ~90 deep phenotyping additionally includes several technical examinations performed in the BeLOVE clinical unit, BCU (see table 3). Any deep phenotyping visit that is missed by a participant will be compensated for by an according

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Specification
Age ≥18 years and	
Provision of written informed consent and	
Willingness and ability to participate in the study and	
One of the four following conditions	Acute coronary syndrome*
	Acute cerebrovascular event*
	Acute heart failure*
	Very high-risk chronic cardiovascular conditions without an event in the past 12 months†, that are defined by (at least one of the following) ► A history of an acute cardiovascular or cerebrovascular event ≥12 months ago. ► Significant coronary, carotid or peripheral artery atherosclerosis. ► Severe kidney injury. ► The combination of diabetes mellitus type 2 and arterial hypertension and hypercholesterolemia. ► Diabetes mellitus type 2 with chronic kidney injury or/and with diabetic retinopathy or/and with diabetic neuropathy. ► Patients with a very high cardiovascular risk according to the European Society of Cardiology (ESC) SCORE2/SCORE2-OD.

Exclusion criteria	Specification
Inability to give informed consent	
Pregnancy or breastfeeding	
Lack of health insurance	
Reduced life expectancy (<6 months) due to a non-cardiovascular cause	
Active cancer	
A history of organ transplantation	

†More details and criteria to define the CVD inclusion criteria can be found in the online supplemental tables 1 and 2†.
CVD, cardiovascular disease.

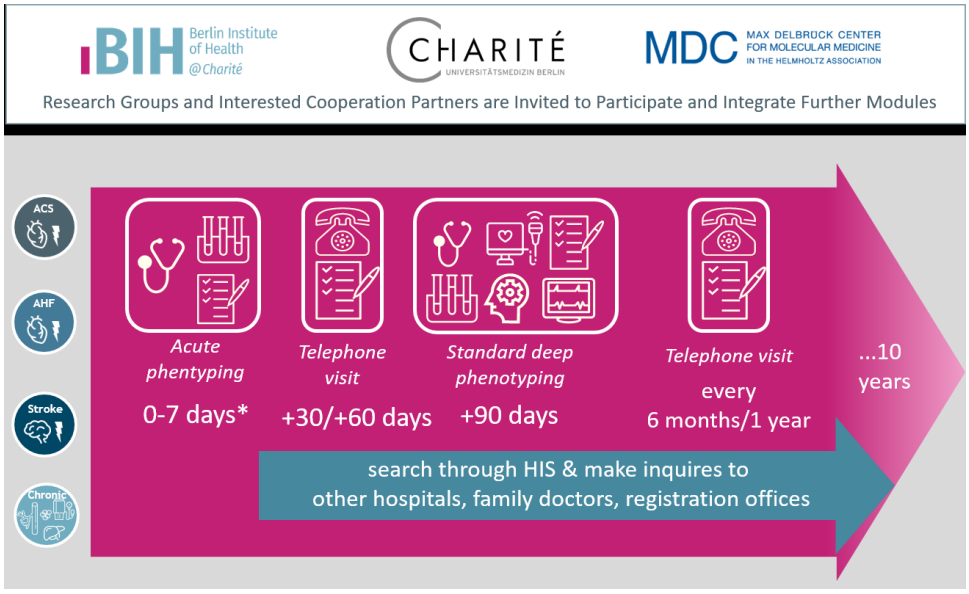

Figure 1 Overview of the study design. Time ranges given for all study procedures are after an acute event (ACS, AHF, stroke) or study inclusion in the chronic CV-risk arm (Chronic), respectively. Inclusion of patients with acute events is carried out during the acute phase of the event (days 0–7). Acute/initial phenotyping is performed within this period in the acute arms and *within 14 days after inclusion in the chronic CV risk arm. Note that phenotyping at day ~90 is much more comprehensive than at days 0–7. Information on new clinical events provides the source for endpoint adjudication and is captured by repeated search through the hospital information system (HIS) and inquiries to other hospitals, doctors and registration offices in all participants and additional interviews of participants joining the day ~90 and the telephone visits. ACS, acute coronary syndrome; AHF, acute heart failure; CV, cardiovascular; HIS, hospital information system.

Table 2 Overview of the initial phenotyping of the inclusion visit performed in participants within 7 days after an acute CVE or within 14 days after inclusion in the chronic CV risk arm respectively.

Method/measure	Description/content
History, sociodemographics and clinical course	
History and demographics	Medical, family and reproductional history; age, gender, ethnicity
Sociodemographics and health-related behaviour	Education, occupation, family status, household members, need for care, smoking, alcohol consumption, drugs, physical activity and sports
Concomitant medication	Prescribed and non-prescribed
Clinical scales and scores	
Gender questionnaire (modified from Gender index)[40]	Association of gender and cardiovascular disease
modified Rankin Scale[41]	Poststroke disability scale
New York Heart Association classification[42]	Heart failure
Rose dypnea scale[43]	Heart failure
Nutrition and metabolic function	
Glucose monitoring	Continuous 14 days glucose monitoring
Weight and height (BMI)	Self- reported by the participant
Patient reported (value-based) outcomes	
PROMIS-29,[44] EQ-5D-5L[45]	Generic health-related quality of life (QoL)
Stroke: SS-QoL[46]; AHF: MLHFQ,[47] KCCQ[48] ACS: Seattle Angina Questionnaire,[49] Diabetes: ADD-QoL[50]	Disease-specific QoL
Biosampling	
Blood sample (89,5 mL)	Directly analysed routine parameters, samples for biobanking (serum, plasma, EDTA, including aprotinin and FC mix, citrate), buffy coat and peripheral blood mononuclear cells, TempusTM for DNA and RNA extraction)
Urine	Creatinine, albumin

ACS, acute coronary syndrome; ADDQoL, Audit of Diabetes Dependent Quality of Life; AHF, acute heart failure; BeLOVE, Berlin Long-term Observation of Vascular Events; BMI, body mass index; CVE, cardiovascular event; EQ-5D-5L, EuroQol 5-Dimensions-5-Level; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; SS-QoL, Stroke-Specific QoL.

telephone visit. For more details of the visit schedule, refer to the supplement.

Inclusion visit

The inclusion visit (see table 2) contains assessment of the medical and family history as well as health-related behaviour, demographic data, socioeconomic status, gender aspects and several self-assessed measures for value-based outcomes, including Patient-Reported Outcomes Measurement Information System-29 (http://www.healthmeasures.net),[23] EuroQol 5-Dimensions-5-Level (http://www.euroqol.org)[24] and a set of disease-specific measures. A total volume of ~90 mL of blood is collected, an aliquot of which is analysed immediately (see online supplemental table 3). Biomaterials used for biobanking include the remaining venous blood and urine. After preanalytical processing and aliquotation these biosamples are stored in the appropriate medium, either at −80°C or in the vapour phase of liquid nitrogen in the central biobank (for details on biosample processing refer to the supplement). Continuous glucose monitoring for 14 days is initiated before discharge.[25]

Deep phenotyping visit

Deep phenotyping involves comprehensive examinations carried out in the BCU and the completion of questionnaires at home. All individuals participating in the 4.5 hour standard deep phenotyping are also asked to participate in additional phenotyping modules lasting an extra ~4 hours (see figure 2 and online supplemental table 4 for more information).

However, since a proportion of participants will not be able to join standard deep phenotyping (e.g., due to health-related issues) a reduced (~1 hour) basic deep phenotyping is offered for them (see figure 2 and table 3).

The collection of biological samples during standard deep phenotyping follows in principle the same protocol as for the inclusion visit, with additional collection of saliva and stool and a larger blood volume of ~190 mL. In addition to the collection of medical history, sociodemographics and clinical course as well as clinical scales and scores, phenotyping includes comprehensive cardiovascular and cardiopulmonary tests, assessment of anthropometry and vital signs, acquisition of nutrition and metabolic function, different tests of physical activity and neuromuscular function, retinal imaging, as well as cognitive function. Further, health-related patient-reported outcomes are measured. For details, refer to online supplemental table 5.

Table 3 Overview of the standard deep phenotyping performed in participants ~90 days after an acute event or after inclusion in the chronic CV risk arm, respectively

Method/measure	Description/content
History,* sociodemographics* and clinical course*	Education, occupation, family status, household members, need for care, smoking, alcohol consumption, drugs, physical activity and sports; medication; newly made diagnosis or vaccination for COVID-19, newly made diagnosis of diabetes, arterial hypertension, hyperlipidaemia or terminal kidney disease, falls, disease specific symptoms or new treatments, etc.
Clinical scales and scores	modified Rankin Scale,[41] New York Heart Association classification, Rose dypnoea scale[43] National Institutes of Health Stroke Severity Scale,[51] Barthel-Index,[52] Canadian Cardiovascular Society Score,[53] St. Georges Respiratory Questionnaire,[54] Survey of Autonomic Symptoms,[55] painDETECT,[56] Michigan Neuropathy Screening Instrument.[57]
Athropometry, nutrition and metabolic function	Height, weight, temperature, blood pressure, pulse, heart frequency, hip-waist-ratio, Air displacement plethysmography (BodPod), Indirect Calorimetry, Metabolic challenge (performed in a subpopulation), Glucose monitoring, Nutrition questionnaire Weikert,* Three Factor Eating Questionnaire*,[58] Food Frequency Questionnaire*
CV and cardiopulmonary tests	ECG, pulse wave analysis (Sphygmocor), Ankle brachial index, two-dimensional echocardiography, spiroergometry (performed in a subpopulation), Body Plethysmography
Retinal imaging	Ocular fundus photography, ocular coherence tomography
Physical and neuromuscular function	Hand grip strength test (manual force), Five chair rise test (rising from sitting), Balance Test, 4 m gait speed test, 2 min walk test, Mobile accelerometry (ActiGraph), Physical Fatigue Severity Questionnaire,[59] Clinical Frailty Scale[60]
Cognition	MOntreal Cognitive Assessment,[61] Cambridge Neuropsychological Test Automated Battery,[62] Multi-Choice Vocabulary Intelligence Test, Version A (Mehrfachwahl-Wortschatz-Intelligenztest A),[63] Logic Thinking Subset-3 (Leistungspruefsyste-3)[64]
Biosampling	Venous Blood sample (~186.5 mL),* urine,* stool,* saliva sample*
Endpoint research	Structured interview concerning any new hospitalisations, any new myocardial infarction, new-onset angina pectoris, newly made diagnosis or of coronary artery disease, interventional treatment of coronary, carotid, or peripheral artery disease, acute heart failure, aortic dissection or aneurysm, new strokes or transient ischaemic attacks (TIAs), diagnosis or treatment for dementia, depression or anxiety, acute kidney injury or terminal kidney disease
Value-based outcomes	Generic QoL: PROMIS-29,[44] EQ-5D-5L,[45] SF-36[65]; Domain-specific QoL: PROMIS: physical function, sleep disturbance, pain behaviour, pain scale intensity, anxiety, depression[26]; PHQ-8[66]; Stroke-related QoL: SS-QoL[46]; AHF-related QoL: MLHFQ,[47] KCCQ[48]; ACS- related QoL: Seattle Angina Questionnaire[49]; Diabetes- related QoL: ADD-QoL[50]

*Measures that are also performed during ~1 hour of basic deep phenotyping.
†Patient-reported new events are only considered as endpoints if they can be validated by reviewing medical records (see the section Clinical Endpoints).
ACS, acute coronary syndrome; ADDQoL, Audit of Diabetes Dependent Quality of Life; AHF, acute heart failure; CV, cardiovascular; EQ-5D-5L, EuroQol 5-Dimensions-5-Level; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; PHQ8, Patient Health Questionnaire 8; PROMIS, Patient-Reported Outcomes Measurement Information System; SF-36, Short Form 36; SS-QoL, Stroke-Specific QoL .

BeLOVE also assesses the response to physiological challenges, including a meal challenge and an exercise challenge, to examine the individual metabolism in the postprandial and the exertional state. The nutritional challenge includes a standardised mixed meal (15% protein/45% fat/40% carbohydrates; 500 kcal) after 12 hours of fasting. The physical challenge includes a cardiopulmonary exercise test using a spiroergometry cycle device according to standard operating procedures (SOP) of the German Center for Cardiovascular Research (DZHK).[26] Venous blood samples are taken before and after both challenges.

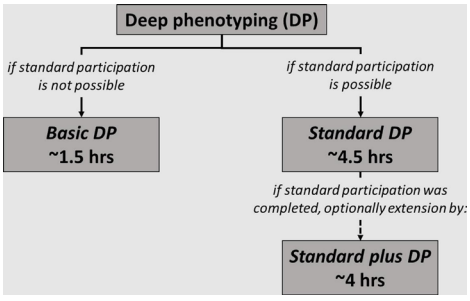

Figure 2 Options for participation in the deep phenotyping (DP) visit ~90 days after the index event. Basic DP is usually reserved for participants with health-related inabilities to join standard DP. The measures of standard and basic DP are enlisted in table 3. Standard plus phenotyping (see supp. table 4) can be joined by all participants of standard deep phenotyping and is performed on a second day.

Optional additional phenotyping ('standard plus') is offered to all participants of the standard deep phenotyping (see figure 2). These additional measures are (refer to online supplemental table 4 for more details): (1) a 1-hour disease-specific set of exams that allow for more sophisticated testing for disease-specific aspects; (2) a 1-hour disease-overarching set of exams with additional specific tests of interest for all disease entities that cannot be implemented within the 4-hour deep phenotyping module due to high expenditure of time and/or financial limitations and (3) MRI, including cardiac, cerebral, pulmonary, kidney and 'metabolic' imaging.

Telephone visits

Follow-up is carried out by telephone calls at ~day 30, ~day 60 and then biannually for all participants, and includes assessment of clinical endpoints as well as patient-reported outcomes (table 4).

Collection of clinical data from medical records and additional sources

In addition to visit-related data, BeLOVE is integrating health-related information from the clinical context of the acute phase that is available in the Charité hospital information system. Data from medical records are also

Table 4 Interviews and questionnaires evaluated by annual telephone interviews

Method/measure	Description/content
History, sociodemographics and clinical course	
Sociodemographics and behaviour	See table 2
Concomitant medication	See table 2
Clinical course	See table 3
Clinical scales and scores	
Gender questionnaire (modified from Gender index)[40]	See table 2
Modified Rankin Scale[41]	See table 2
Barthel Index[52]	See table 3
Canadian Cardiovascular Society Score (CCS)[53]	See table 3
New York Heart Association classification (NYHA)	See table 2
Rose Dyspnoea Scale[43]	See table 2
Cognition	
MOntreal Cognitive Assessment (MoCA)[61]	See table 2
Endpoint interview	
Clinical events interview*	See table 3
Value-based (patient-reported) outcomes	
PROMIS-29,[44] EQ-5D-5L[45]	See table 2
Stroke: SS-QoL[46]; AHF: MLHFQ,[47] KCCQ[48]; ACS: Seattle Angina Questionnaire[49]; Diabetes: ADD-QoL[50]	See table 2

*Interviews for new clinical events (endpoints) are additionally carried out at additional telephone calls every 6 months. Patient-reported events are only considered as endpoints if they can be validated by reviewing medical records (see section on Clinical endpoints adjudication).
ACS, acute coronary syndrome; ADD-QoL, Audit of Diabetes Dependent QoL; AHF, acute heart failure; KCCQ, Kansas City Cardiomyopathy Questionnaire; MLHFQ, Minnesota Living with Heart Failure Questionnaire; PROMIS, Patient-Reported Outcomes Measurement Information System; SS-QoL, Stroke-Specific QoL .

used to validate self-reported history as far as possible (see online supplemental table 5 for more details).

Further, repeated collection of information on new clinical events every 6 months is the basis for endpoint adjudication and uses several sources as described in the supplement (see also online supplemental figure 2).

Clinical endpoints adjudication

Clinical outcomes (endpoints) are assigned by a clearly defined procedure. A specialised team and endpoint committee adjudicates endpoints based on the clinical information gathered as described above. The primary clinical outcome is a composite of MACE defined as non-fatal acute myocardial infarction, non-fatal acute ischaemic or haemorrhagic stroke, hospitalisation for non-fatal AHF, or vascular death (see online supplemental table 6 for more details).

Secondary endpoints include, for example, recurrent myocardial infarction, stroke or heart failure, TIA, any hospitalisation for any reason and all-cause mortality. Definitions and the adjudication process of endpoints are described in more detail in online supplemental figures 3,4 and table 6.

Patient-reported outcomes

Value-based outcomes are patient-reported outcomes measured during study inclusion and ~day 90 deep phenotyping visits as well as telephone visits once a year. Generic health-related, as well as domain-specific and disease-specific quality of life, is measured by multiple established questionnaires (see online supplemental table 6 for more details).

Incidental findings management

Since the deep phenotyping protocol is expected to produce incidental findings with clinical relevance to the participants BeLOVE has established a standardised findings management. Based on ethical guidelines,[27–29] evidence-based recommendations from specific medical guidelines, procedures of other studies[30 31] and our own experience from the first study phase, a standardised operating procedure was developed that defines specific results and their urgency to be communicated and acted on. The concept and first data of incidental findings management will be published separately.

Retention strategy

BeLOVE employs several strategies to improve study adherence and retention, which have been proven to be effective in combination[32] (see online supplemental file for more details).

Data management, quality assurance and quality control

Data management and quality assurance/quality control are conducted by a professional data management team and in cooperation with the Clinical Study Center of the

Charité. These fully established structures and processes are described in detail in the supplement.

Statistical methods

Sample size and effect size estimation

BeLOVE is an observational study that aims to address different research questions (see online supplemental table 7). The primary research aim is to identify risk factors for MACE using a comprehensive set of biomarkers and variables from various time points and to develop a prediction model for MACE.

It is assumed that within the 1-year follow-up 8%–12% of the patients experience a new CVE of any type.[33–35] For a two-sided significance level of 5%, a power of 80%, and no correlation between the predictors and an annual event proportion of 8%, the minimal detectable effect in 7000 participants is HR 1.13, which is lowered to HR 1.10 when a 12% annual incidence of outcome is assumed. A more detailed sample size justification is depicted in the supplement. Since we assume a drop-out rate of around 12%, 8000 patients should be included (see online supplemental figures 5 and 6) for more details).

Statistical analyses

Before analysing the primary and secondary outcomes, detailed statistical analyses plans will be provided. In general, for independent and for outcome variables, depending on their scaling, descriptive measures, such as means, SD, medians, IQRs or absolute and relative frequencies will be reported. Kaplan-Meier survival curves and estimates will be used as descriptive measures for time-to-event data. Analyses will be stratified by index disease entity.

Cox proportional hazards regression,[36] adjusted for potential confounders, will be used for the primary analysis to model the association between the exposure variables of interest and the major endpoint (MACE). Time from inclusion into the study (acute event) will be used to calculate person-time at risk until the occurrence of MACE or censoring. Among others, we will use directed acyclic graphs to model the path from exposure to event, and to identify potential confounding or intermediary variables.

Additionally, statistical regression models for recurrent or competing events and structural equation models for time-to-event data will be used to analyse more thoroughly the relations of different markers and characteristics to the outcomes. Continuous outcomes (eg, plasma levels of biomarkers), binary endpoints or ordinal endpoints will be analysed using linear, generalised linear, binary logistic or ordinal regression models. Analyses will be stratified by disease entity of the index event/disease.

Effect estimates and corresponding CIs will be reported where possible and appropriate, instead of reporting 'statistical significance', as is recommended by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline for the reporting of observational studies.[37] More details on the planned statistical analyses methods can be found in online supplemental file 1.

Patient and public involvement

The general concepts, overall research question and the study design were developed without patient involvement. However, all patients will be interviewed about their motivation to participate in the study during the inclusion visit; reasons for study participation and patient's motivation will be used to improve processes serving to inform and retain patient's participation. Patients are also informed about clinically relevant findings within the framework of incidental findings management. Furthermore, patients' representative involvement is planned as part of the data and sample use process. We will develop further patient participation strategies in close cooperation with BIH-QUEST (BIH Center for Transforming Biomedical Research).

Study implementation, results and modifications to the protocol

Recruitment into the BeLOVE study started on18 July 2017, with an implementation phase, which lasted until 31 December 2020. In this phase, 1939 patients were included (see recruitment, retention and baseline characteristic in online supplemental figure 7 and table 8). During recruitment, it became evident that the study protocol needed to be adapted for logistic and budgetary reasons and the adjustments made are described in detail in online supplemental table 8 and figures 8,9.

The main study phase started on 1 January 2021. By 1 March 2023, 3465 patients have been recruited into the study during all phases combined.

DISCUSSION

BeLOVE is characterised by the following features: (1) inclusion of patients in the acute phase after CVE, (2) long-term follow-up, (3) harmonised application of comprehensive deep phenotyping and (4) acquisition of clinically collected data in a study population that includes both patients after a CVE as well as patients at chronic high risk for a CVE. This approach will enable the identification of risk predictors and pathomechanisms, providing the basis for further investigation and development of personalised strategies for secondary prevention using systemic medicine approaches.

Data collection is largely standardised by using common data elements (CDEs) to allow comparison and combination of BeLOVE with other cohorts (www.nlm.nih.gov/cde). The selection of phenotyping methods not mapped by CDE is the result of scientific exchange and personnel communication with several cardiovascular and population-based studies, such as the population-based Framingham Heart Study[38] and the German National Cohort (GNC) study.[39] A subset of 'CVD-free' participants of the GNC, with no or very few cardiovascular risk factors may serve as a control group for comparison with

the BeLOVE cohort. In addition, standardised processes used for cardiovascular phenotyping were adapted to the SOPs used in clinical studies of the DZHK.[26]

BeLOVE provides the opportunity to study the short-term and long-term outcomes of patients with high cardiovascular risk. The standardised phenotyping protocol allows to study disease-overarching research questions and thus better understand 'crossover risk', as well as the similarities and differences between the different clinical phenotypes. The unique design to follow patients without prior CVE as well as patients in the acute and chronic phase after a CVE allows us to understand and ameliorate potential biases.

ETHICS AND DISSEMINATION

Ethics approval

The BeLOVE study has been approved by the responsible local Ethics Committee of the Charité University Medicine (Charité Campus Mitte; Berlin/Germany; no.EA1/066/17, decision of October 22, 2020). For any changes to the study protocol, we will seek approval by the ethics committee before implementation. The study is conducted in accordance with the Declaration of Helsinki in its current version, Good Epidemiological Practice (GEP) and the applicable German laws. Where applicable, guidelines of the International Conference on Harmonisation of Good Clinical Practice are adhered to.

Informed consent

All study participants are informed comprehensively and with sufficient time for them to reflect on the nature and scope of the study. Written informed consent is obtained from all participants prior to all study-related procedures. Informed consent to participate includes permission to analyse data and samples and to publish all results, at least by the BeLOVE Group.

Data statement

The BeLOVE consortium aims to ensure that the collected data and sample material will be used for the greatest possible benefit to health-related research, in particular cardiovascular research. Researchers interested in the data of BeLOVE may apply for data access through our use and access committee, as long as one member of the project team is part of the BIH research community to support the research process. The use and access committee evaluates the merits and technical feasibility of the project proposal and assesses potential overlap with ongoing projects and analyses. Data transfer will be performed according to established General Data Protection Regulation (GDPR) data sharing guidelines.

Dissemination

We aim to make BeLOVE publications open access to the scientific community, preferably through publication in peer-reviewed open access journals (or the open access option within subscription journals, golden route to open access), or alternatively by depositing the final accepted version (postprint, maximal 3 months after publication) in the institutional repository of the Freie Universität Berlin (https://refubium.fu-berlin.de/) or the Max Delbrück Center (https://edoc.mdc-berlin.de/) if possible, as well a conference presentations.

Code availability

Not applicable.

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