BMJ Open

Understanding the importance of social determinants and rurality for the long-term outcome after acute myocardial infarction: study protocol for a single-centre cohort study

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To cite: Sasko B, Jaehn P, Müller R, *et al*. Understanding the importance of social determinants and rurality for the long-term outcome after acute myocardial infarction: study protocol for a single-centre cohort study. *BMJ Open* 2022;**12**:e056888. doi:10.1136/bmjopen-2021-056888

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-056888).

Received 08 September 2021
Accepted 24 February 2022

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ABSTRACT

Introduction Acute myocardial infarction (AMI) is a major public health issue in Germany with considerable regional differences in morbidity and mortality. Possible reasons for regional differences include a higher prevalence of cardiovascular risk factors, infrastructural deficits, different levels of healthcare quality or social determinants. We aim to study associations of social determinants and of rural infrastructure with the quality of medical care (eg, time to reperfusion or medication adherence) and on the long-term outcome after myocardial infarction.

Methods and analysis We will employ a prospective cohort study design. Patients who are admitted with AMI will be invited to participate. We aim to recruit a total of 1000 participants over the course of 5 years. Information on outpatient care prior to AMI, acute healthcare of AMI, healthcare-related environmental factors and social determinants will be collected. Baseline data will be assessed in interviews and from the electronic data system of the hospital. Follow-up will be conducted after an observation period of 1 year via patient interviews. The outcomes of interest are cardiac and all-cause mortality, changes in quality of life, changes in health status of heart failure, major adverse cardiovascular events and participation in rehabilitation programmes.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee of Brandenburg Medical School (reference: E-01-20200923). Research findings will be disseminated and shared in different ways and include presenting at international and national conferences, publishing in peer-reviewed journals and facilitating dissemination workshops within local communities with patients and healthcare professionals.

Trials registration number DRKS00024463.

Strengths and limitations of this study

- ► It will be possible to study the interrelatedness of aspects of quality of care and social determinants of health.
- ► Standardised and validated instruments will be used for data collection.
- ► Data on multiple outcomes in terms of all-cause mortality, quality of life and cardiovascular adverse events will be available.
- ► Concerning the limitations, this is a single-centre study and the follow-up is restricted to 1 year. Results may not be generalisable to other areas.

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading cause of mortality worldwide.[1 2] Although data on the mortality due to coronary artery disease (CAD) and acute myocardial infarction (AMI) demonstrate decreasing trends in Germany,[3] both diseases still account for a major proportion of burden of disease. Simultaneously, CAD is the most common underlying cause of heart failure (HF) and accounts for 60%–70% of all HF cases.[4] There are considerable regional differences of CVD burden in Germany among the federal states and counties,[3 5 6] in the federal state of Bavaria, for example, the age-adjusted mortality rate of AMI in 2016 was 53 per 100 000, just below the national average of 55 per 100 000. In contrast, the mortality of AMI in the federal state of Brandenburg was 81 per 100 000.[3] During the last decades, these regional differences in mortality have persisted and could be observed at the level of federal states and counties.[3 7] Similar persisting regional differences have been observed for morbidity and mortality of CAD and HF.[5 8 9] The extent of the health and economic burden resulting from CVD is a complex public health problem. When challenging cardiovascular prevention and adopting therapeutic strategies, a more targeted approach might be necessary to fulfil the specific regional requirements for an optimal treatment.

There are several possible explanations of regional differences in cardiovascular health such as rurality or socioeconomic deprivation.[10] It is plausible to assume that acute and long-term healthcare for AMI is suboptimal in Brandenburg compared with other federal states, since the local mortality to incidence ratio of 0.30 exceeded the national average of 0.22 in 2016.[3] Residents living in Brandenburg, a federal state with rural characteristics, might face a number of barriers to receiving optimal treatment. It has been hypothesised that the quality of acute care for critically ill patients with AMI or trauma may be impaired due to the rural structure of a region.[11–14] Previous studies from the USA have observed a less sufficient management of AMI, HF and atrial fibrillation in rural hospitals compared with urban hospitals.[12 15 16] Furthermore, long distances to suppliers of acute healthcare may generally result in a treatment delay. It has been suggested that longer intervals from the first medical contact to revascularisation significantly enhanced the risk of death for patients with ST-elevation myocardial infarction (STEMI).[17] Beside barriers to receiving acute care, rurality might also be associated with poorer access to outpatient specialists, preventive healthcare services such as primary prevention in general practice or rehabilitation programmes. A previous study reported an association between low regional density of specialised cardiologists and high cardiovascular morbidity when comparing federal states in Germany.[18] Since density of cardiologists is low in Brandenburg, compared with the national average, it is conceivable that the majority of patients with AMI in Brandenburg may ultimately receive care from a general practitioner (GP) rather than from a specialist.[18]

However, the lack of optimal treatment may only partially account for the adverse outcomes. It has been suggested that social determinants of health (SDH) create healthy or unhealthy framework conditions.[19] Among others, SDH include such factors as education, unemployment, food insecurity, working conditions, built environment and access to health services. SDH play a critical role for individual and population health as they shape the surroundings of individuals at multiple levels and influence their health during the lifespan. For example, a precarious individual social and economic position is related to a poorer outcome after the first occurrence of AMI.[20 21] Furthermore, a low socioeconomic position is known to be associated with limited access to cardiac healthcare, as socially disadvantaged patients were less likely to use specialised medical care than socially privileged patients.[22] This might be explained by a certain lack of knowledge in socially disadvantaged patients concerning their disease itself and the disease management, such as the need of specialist care or the participation in cardiac rehabilitation.[23] Additionally, the patients perceived role in healthcare includes the tendency to delegate responsibility to healthcare professional, by that relying on third persons to coordinate their specialist care, possibly decreasing such care.[23] Moreover, socially disadvantaged patients show a less strict adherence to secondary prevention[24 25] and more frequently live an unhealthy lifestyle[26]—thus rendering suboptimal conditions for secondary prevention and treatment.

Furthermore, a large body of evidence showed associations of occupation, income, or socioeconomic deprivation with CVD risk factors, as well as cardiovascular morbidity and mortality.[27–31] For example, obesity, smoking, arterial hypertension and hypercholesterolaemia is more frequent among patients without a university education. In addition, females with university education or paid employment are less likely to have diabetes, while males with paid employment have lower prevalence rates for hypertension and smoking than unemployed males.[28] These results can be supported by a meta-analysis, which found significantly increased odds of CAD, hypertension, diabetes and dyslipidaemia in patients with lower subjective social status.[29]

Moreover, social support and integration in social networks is associated with the outcome after AMI.[32] For example, a study from Germany showed that being married is associated with a better survival after AMI among men.[33] Hence, sparse opportunities to participate in key social domains or active social exclusion might contribute to unhealthy living conditions and unfavourable prerequisites for successful cardiovascular healthcare among inhabitants of Brandenburg.[29 31 34 35] In sum, these considerations highlight the necessity of a comprehensive analysis of the importance of both SDH and rurality for healthcare and clinical outcomes among patients with AMI. In addition, research on specific aspects of healthcare is needed that might mediate social inequities of AMI outcomes.

Aims

We assume that there are environmental and social conditions in Brandenburg that might not be supportive for optimal cardiovascular care and survival after AMI. Recognising the importance of health-sustaining framework conditions, the aim of this study is to assess how SDH as well as rurality are related to suboptimal care and clinical outcomes of patients with AMI. Outcomes of interest are major adverse cardiovascular events (MACE), quality of life, health status of HF, use of rehabilitation services, cardiac mortality and all-cause mortality 1 year after AMI diagnosis. SDH of interest are social isolation, socioeconomic status, education, income, occupation, migration background and regional socioeconomic deprivation. Moreover, we aim to collect detailed information regarding the given infrastructure, which includes several aspects of rurality such as the distance to primary or specialist care, access to health services or response times in emergencies. Since both SDH and rurality might have considerable impact on the quality of healthcare, we aim to assess the patient's regular contact to primary physicians, adherence to preventative medication, adherence to lifestyle-related prevention (eg, physical activity, tobacco use) as possible mediating factors of the

Figure 1 Possible mediating factors of the exposure–outcome relationship. AMI, acute myocardial infarction.

exposure–outcome relationship (figure 1). In addition, we will evaluate processes during the acute care for AMI, with a focus on time patterns of emergency care (such as door-to-wire-time), or invasive and non-invasive interventions including drug therapy.

METHODS

Study design

To understand how SDH and rurality relate to suboptimal care after AMI, we chose a prospective single-centre observational cohort study design. It is planned to enrol participants in five consecutive years. The first participant will be enrolled in January 2021 and we expect the follow-up of the last enrolled participant to end in March 2026. For each patient, the follow-up period is 12 months, resulting in a total study duration of 6 years. The study design uses elements of the clinical MONICA/KORA AMI registry of Augsburg,[36] and combines it with items of the regional myocardial infarction registry of Saxony-Anhalt (RHESA),[37] to ensure data comparability and a high quality of measurement tools.

Study population

The University Hospital Brandenburg in the city of Brandenburg an der Havel is a tertiary teaching hospital of the Brandenburg Medical School and serves a population of approximately 150 000 with 30 000 visits in the emergency department per year. All patients ≥18 years of age hospitalised alive in the University Hospital Brandenburg due to a confirmed diagnosis of an AMI, defined according to the 'Fourth universal definition of myocardial infarction' by the European Society of Cardiology,[38] will be asked for written consent to participate in the study .

For participants presenting with STEMI, the recruitment process starts after referral to the catheter laboratory and revascularisation in order to avoid a treatment delay. Written informed consent is obtained following recovery from the percutaneous coronary intervention (PCI). In case of NSTEMI at admission, some patients will have other causes than myocardial ischaemia for elevated troponin levels. We identify patients with possible myocardial ischaemia by monitoring patients with elevated troponin levels until the definitive cause has been confirmed, which may last up to 48 hours. Accordingly, patients without myocardial ischaemia will be excluded from the study. Figure 2 illustrates the recruitment process.

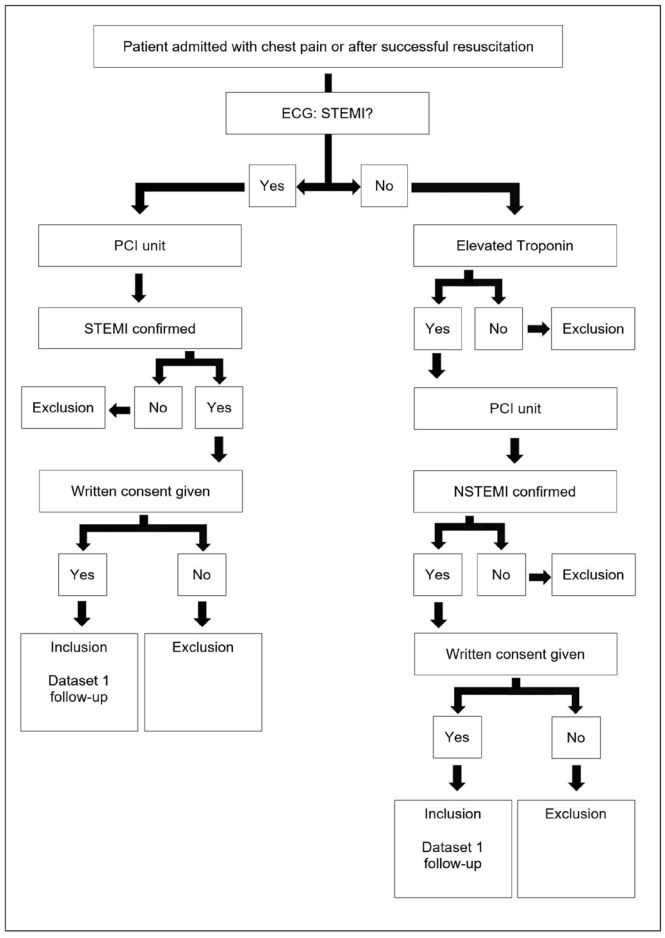

Figure 2 Summary of recruitment process. PCI, percutaneous coronary intervention; NSTEMI, non-STEMI; STEMI, ST-elevation myocardial infarction.

Exposures and confounders

Baseline data comprise demographics, healthcare quality, structural characteristics and social factors. Demographic data and data on acute treatment of myocardial infarction (box 1) are extracted from the hospital electronic data system. All baseline measures will be obtained by the study staff following a standardised protocol. The research staff conducts a structured bedside interview with participants to assess baseline clinical data and a detailed socialeconomic status. Among patients who were discharged before contact with the study team on site, these baseline data are collected in a structured phone interview.

To assess exposures related to outpatient healthcare prior to AMI and acute healthcare of AMI we used tools as in the MONICA/KORA and RHESA study.[36 37] Bleeding complications are classified according to the International Society on Thrombosis and Haemostasis (ISTH) definition (Box 1).[39] Distances from patients' homes to the GP, cardiologist and PCI-unit were measured in Google Maps. The shortest driving distance by car was used. Rurality of the place of residency was classified according to the German Federal Institute for Research on Building, Urban Affairs and Spatial Development, which defines

Box 1 Measured variables

Social determinants and healthcare-related environmental factors

Healthcare-related environmental factors:
- Distance to general practitioner (GP), cardiologist and percutaneous coronary intervention unit.
- Rural or urban environment.

Social determinants of health:
- Education.
- Employment.
- Income.
- Social isolation.
- German Index of Socioeconomic Deprivation.
- Migration background.

Demographics:
- Age (year of birth).
- Sex.
- Place of residency.

Quality of care:

Outpatient care prior to acute myocardial infarction (AMI):
- Frequency and reasons for GP visit prior to the AMI.
- Prior outpatient treatment by a cardiologist.

Acute healthcare of myocardial infarction:
- Symptoms, time of symptom onset, time to first medical contact.
- Clinical status at admission and at discharge.
- Primary medical management of emergency services.
- Medical treatments and interventions during hospitalisation and at discharge.
- In-hospital process of care including benchmark time variables.
- Bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) definition. Major bleeding are defined as: fatal bleeding, symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular resulting in vision changes, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome), bleeding causing a fall in hemoglobin level of 2-g/dL or more, and/or bleeding leading to transfusion of two or more units of whole blood or red cells.

Compliance:
- Medication intake

Risk factors of cardiovascular disease:
- Medical risk factors (hypertension, diabetes, lipoproteins, lipids).
- Comorbidities and prior medication.
- Depression and addiction/substance abuse.
- Smoking.
- Body mass index.
- Self-reported physical activity.

rurality as a low population density combined with the lack of a regional centre.[2]

For a detailed assessment of social determinants, we developed a questionnaire in cooperation with the Robert Koch-Institute, Berlin, Germany, and the Brandenburg State Office for Occupational Safety, Consumer Protection and Health (Landesamt für Arbeitsschutz, Verbraucherschutz und Gesundheit). On the basis of the questionnaire used in the GEDA 2014/2015-European Health Interview Survey (EHIS) survey, we adopted ten questions regarding education, occupation and income.[40 41] Additionally, the German Index of Socioeconomic Deprivation (GISD) was determined for the area of residence of each patient. The GISD illustrates regional socioeconomic differences at various spatial levels and contributes to explaining regional health differences.[10] Furthermore, another 12 items addressing family structure, life circumstances and social isolation complete the assessment form. The city of Brandenburg an der Havel is suited to assess associations of SDH and rurality with outcomes of AMI, since it is an urban regional centre with a highly rural environment and additionally it displays considerable heterogeneity of socioeconomic deprivation. Exposures and confounders are summarised in box 1.

Demographic data and risk factors of CVDs are conceptualised as confounders of our main research question. Risk factors were measured as follows: a short questionnaire developed by a collaborating group of several German medical societies to assess tobacco use and exposure in epidemiological studies is used to determine possible smoking-related health effects.[42] The questionnaire was adopted on the basis of the first German National Health Survey (BGS98-Questionnaire) which was carried out from October 1997 to March 1999 in order to examine the general health status of the German population. To assess physical activity as one of the major health determinants, a modified shorter version of the EHIS-PAQ is used,[43] which itself is part of the GEDA 2014/2015-EHIS questionnaire.[40] The German Health Update (GEDA) and the EHIS are both health monitoring programmes which aim to obtain information on the population's health status, health inequalities, health determinants and healthcare utilisation on national and European level. The EHIS questionnaire was completely integrated in the latest GEDA survey.[40] The quality of life and health status of HF at baseline are further confounders. Their measurement is described in the outcomes section.

Table 1 Summary of outcome measures

Outcome	Measurement
Cardiac mortality (in-hospital)	Hospital records
Change in quality of life	EQ-5D-5L
Change in health status of heart failure	KCCQ-12
Major adverse cardiovascular events	Hospital records, follow-up at 12 months, GP interview, death registry
Participation in rehabilitation programmes	
Cardiac and all-cause mortality	

EQ-5D-5L, European Quality of Life 5 Dimensions 3 Level Version; GP, general practitioner; KCCQ-12, 12-item Kansas City Cardiomyopathy Questionnaire.

Follow-up and outcomes

A summary of outcome measures is displayed in table 1. One short-term outcome (in-hospital cardiovascular mortality) and five outcomes after 12 months of follow-up will be assessed. To measure early occurring in-hospital deaths, fatal events were classified according to the WHO/MONICA project as 'definite', 'possible', 'unclassifiable' due to insufficient data and 'no myocardial infarction or coronary death'.[44] Information about the cause of death will be obtained from chart review and by interviewing the last treating physician and nurse.

A follow-up interview by phone is planned to be conducted 12 months after AMI to update information about incident MACE, the quality of life, the health status of HF and the participation in rehabilitation programmes after an AMI event. MACE are defined as non-fatal reinfarction, HF, recurrent angina pain, rehospitalisation for cardiovascular-related illness, repeated PCI, coronary artery bypass grafting, stroke and all-cause mortality. To conduct the follow-up interview, the research staff will attempt to contact the patient by phone up to four times at different days and day times. If no contact can be made, the GP will be contacted and asked for the survival of the patient. In case of no further information by the GP, the resident registration office of the council taht is in charge for death certificates will be contacted by the staff and asked to check the death registry. By that, a possible lost to follow-up is minimised.

At the time of inclusion, a phone number will be provided to offer the patient an option of contacting the research staff.

We use the EQ-5D-5L as a two-part instrument (EQ-5D and EQ Visual Analogue Scale (VAS)) for the assessment of the change of quality of life between the baseline and the follow-up after 12 months.[45] The EQ VAS describes the self-related health on a quantitative measure and reflects the patient's own health perception. The EQ-5D-5L is available as a self-complete form on paper or as an interviewer administered version, either in face-to-face or telephone interviews (eg, for follow-up interviews). The 12-item Kansas City Cardiomyopathy Questionnaire is used to assess the change in health status of HF.[46] It is a validated measurement tool to detect clinical changes, physical and social limitations due to HF symptoms and by that a quality of life impairment. These outcome measures will not be further pooled in a composite endpoint and each outcome will be analysed separately.

Statistical analyses and power

We aim to estimate associations of exposures with any outcome after 12 months of observation. Where possible, time-to-event analysis will be conducted using Kaplan-Meier estimators. Differences in means will be calculated to assess the change of quality of life and the health status of HF. Multivariable logistic regression in case of binary outcomes, Cox regression in case of time-to-event analyses, and linear regression in case of continuous outcome measures will be applied to adjust associations for confounding and to assess the role of mediating factors. In a pilot study, we were able to include 200 participants with AMI within 1 year. In conclusion, we estimate that recruiting 1000 participants is feasible during the study period of 5 years. Moreover, we expect a lost to follow-up of 20%. Power was calculated assuming a total of 800 observations for the final analysis, a level of α=5% and a risk of death due to any cause of 8% after 12 months among unexposed.[47] To detect a risk ratio of 1.8, there is a power of 82% for exposures with a prevalence of 50%, and a power of 68% for exposures with a prevalence of 20%.

Quality assurance

To guarantee the quality and validity of data, we developed appropriate quality assurance plans for the study. To reduce variability in data collection, all questionnaires are filled in according to standard operating procedures (SOPs) by the research staff. Furthermore, data handling and data analysis are also performed according to SOPs. In order to ensure quality to a level sufficient for the intended purposes, a 7-item set of quality indicators will be established (lost to follow-up, missing data, missing mandatory data, duplicates, recruitment rate, data completeness, data consistency). All records are automatically checked for errors, validity and inconsistencies when entered in the electronic case report form (eCRF) (commercial EDC-system SecuTrial, interActive Systems GmbH, Glogauer Str. 19, 10999 Berlin, Germany). All electronic systems for data collection are conform with Good Clinical Practice (GCP) guidelines and certified according to DEKRA and ISO 9001. An internal audit will be carried out by the supervising investigators, including the principal investigator (PI) and co-PI (co-PI). A statistician will check the data quality and validity on an annual basis. Additionally, the recruitment process, data handling, data security and the effectiveness of the SOPs will be reviewed and supervised in a joint evaluation by the PI, co-PI and statistician. On the basis of these results, measures to assure data quality will be initiated.

Data protection and ethics

All data derived for this study is entered into an eCRF that was designed using the commercial electronic data capture system SecuTrial. For each patient entered in the eCRF, a pseudonym will be automatically created. The corresponding personal data and the pseudonym are stored and locked in the research facility, no personal data are stored in the data capture system. Access to personal data is only granted to the research staff who have specific responsibilities related to the specific information (eg, conducting follow-up interviews). Collaborating scientists will only receive anonymised data for scientific purposes, therefore, the data which will be released to investigators outside the research facility do not include any identifying information. This study is conducted on the basis of the principles of GCP and according to International Conference on Harmonisation guidelines. Ethics approval was

granted by the ethics committee of Brandenburg Medical School (E-01-20200923).

Patient and public involvement

No patient involved

DISCUSSION

Burden due to AMI remains an important public health issue with regional differences as far as incidence and mortality are concerned. Especially the combination of high socioeconomic deprivation and the rural character of a region are possible drivers of both CVD incidence and the quality of care after diagnosis of AMI. Incidence and survival after diagnoses may ultimately contribute to the high burden of AMI mortality in the federal state of Brandenburg.

General recommendations and guidelines for secondary prevention are still the guiding principle in the treatment process of CVD,[48] but their realisation might be hindered due to multiple possible reasons such as suboptimal quality of care, unsupportive built environment, time famine resulting from socioeconomic stress due to inflexible working hours or low social integration at the local level.

Improving the quality of care typically aims at improving acute care, secondary or tertiary prevention. Although deficits in the quality of care only account for a part of adverse outcomes, healthcare interventions frequently focus on optimising the medical treatment and by that improving the outcome. SDH, on the other hand, are non-medical factors, which play a critical role for individual health as they shape the framework conditions for healthy living and healthcare.

In consequence, we conduct a cohort study which aims to investigate two important influences on health outcome in CVD on a local level: first, the quality of care in a socioeconomically deprived rural area and second, the relationship of selected SDH with adverse outcomes after AMI diagnosis. Our approach includes individual patient factors, quality of care, sociobehavioural and environmental factors and it therefore reflects the multiple dimensions of social inclusion, which are part of the SDH. This study has some limitations. Since this study is planned as a single centre study in Eastern Germany, our results may not be transferable to other regions. Furthermore, a follow-up will be limited to 12 months and long-term effects beyond that period will not be collected.

This study protocol offers an opportunity for analysing SDH and aspects of rurality in care of AMI with a strong emphasis on the socioeconomic situation on the one side and the built environment on the other side. To enable the development of healthcare interventions that address the suboptimal aftercare of AMI patients, a much better understanding of why people do not adhere to recommendations is needed. This assessment of social, infrastructural and healthcare-related aspects among a rural and socioeconomically deprived population will allow the development of such customised and targeted healthcare interventions on a local level, by giving a detailed information regarding barriers to healthcare. In addition, theorising factors such as employment, education and social networks as facets of social inclusion and exclusion may contribute to direct the attention to underlying modifiable social processes and, hence, enable policy to build more health sustaining social environments.[49] By that, this study will contribute to greater evidence about targeted entry points for intervention to improve secondary prevention strategies and to adopt them to the specific regional conditions and prerequisites. We aspire to contribute to the evidence base about protective conditions of inclusive societies for the outcome after AMI.

ETHICS AND DISSEMINATION

The study will be conducted according to the ethical principles of the Declaration of Helsinki, GCP guidelines, local regulations and after approval from the local ethics committee of the Brandenburg Medical School (E-01-20200923). Any planned protocol modification or amendment will be submitted to the local ethic committee for approval. All patients are required to provide written informed consent to the investigator.

Findings of the study will be communicated using different forms of dissemination on a national and international level. This includes publishing in peer-reviewed journals and presenting results at national and international conferences and making announcements on the study group's website (https://herz-brandenburg.de/).

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Contributors BS and NP had the original idea of the study, were responsible for designing the protocol. OR, PJ and CH helped to develop the protocol and supervised the process. BS, PJ and RM had the lead for writing. PJ drafted the statistical section. HA, SM and RM significantly contributed to the development of the study method. All authors revised the manuscript and provided critical feedback.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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