Study protocol PRAISE

Title:

PRediction of Acute coronary syndrome in acute Ischemic StrokE (PRAISE)

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Study type:
Multicenter observational prospective study with blinded endpoint evaluation

Background:
Cardiac troponins (i.e. I and T) are very sensitive and specific biomarkers used in clinical routine to detect cardiomyocyte damage. Elevation of cardiac troponins may indicate acute or chronic cardiomyocyte damage. An acute elevation of cardiac troponin with a dynamic change in serial measurements is often caused by an acute coronary syndrome due to a coronary culprit lesion[1]. Interestingly, many patients with acute ischemic stroke also have elevated troponin levels[2]. Depending on the assay and studied population, varying frequencies of elevated troponin levels in acute ischemic stroke patients have been reported in the literature. In acute ischemic stroke patients elevated troponin levels are associated with a higher rate of mortality and poor functional outcome[3,4].
This association is even more pronounced in patients with a dynamic change of troponin levels (so called “rise/fall pattern” indicating acute cardiomyocyte damage)[5]. Cardiac comorbidity is common in patients with cerebrovascular disease as both cardiac and cerebrovascular diseases share many common risk factors. Therefore, the current guideline of the American Heart Association (AHA) on the early management on acute ischemic stroke patients recommends routine measurement of troponin in patients with acute stroke[6].
Whether current algorithms for the diagnosis of acute coronary syndrome in patients with chest pain as described in the guideline of the European Society of Cardiology (ESC)[12] also apply to patients with acute ischemic stroke remains unclear. Additionally, the diagnostic value of noninvasive tests (e.g. ECG, echocardiography, GRACE-Score[13]) in patients with acute ischemic stroke and troponin elevation remains unclear.
Besides acute coronary syndrome, troponin elevation in acute ischemic stroke patients may also be caused by chronic cardiac diseases or even extracardiac diseases[5]. Additionally, some acute ischemic stroke patients, e.g. those with ischemic lesions located in the insula, may develop neurogenic myocardial injury with a phenotype similar to stress-induced cardiomyopathy[7]. The prospective TRELAS study showed that about 25% of ischemic stroke patients with a troponin elevation > 50 ng/l (hs-cTnT measured using the Roche Elecsys Assay)[8] have a coronary culprit lesion[9]. A prospective observational study by Amarenco et al showed that coronary culprit lesions significantly increase mortality in acute ischemic stroke patients[10]. Therefore, these lesions should be diagnosed and treated appropriately. Due to the neurological deficit, acute ischemic stroke patients with acute coronary syndrome often do not present with the typical symptom of chest pain. Thus, clinicians treating stroke patients are confronted with a diagnostic and therapeutic dilemma. On the one hand, coronary angiography is the diagnostic gold standard to detect coronary culprit lesions[11]. The detection and treatment of a culprit lesion – if present – would likely improve the patient’s prognosis. On the other hand, coronary angiography is an invasive procedure that often requires additional antithrombotic treatment[12]. In acute ischemic stroke patients, antithrombotic treatment may increase the risk of intracerebral hemorrhage, which is why clinicians are often hesitant to perform coronary angiography in these patients. Therefore, it is important to be able to select acute ischemic stroke patients with a high pre-test variability for a coronary culprit lesion. The results of the TRELAS study[9] suggest that a

coronary culprit lesion is more common in acute ischemic stroke patients with dynamic troponin elevation compared to patients with stable troponin elevation. However, the sample size of the TRELAS study was too small to develop a clinically useful algorithm or cut-off values for the detection of acute coronary syndrome.

In the general population, previous studies have found an association between higher troponin levels and poorer cognitive performance[14]. Higher troponin levels were especially associated with poorer executive function. Moreover, chronic heart failure is associated with cognitive decline[15]. This interaction between heart and brain has not been fully elucidated. In particular, it remains unclear whether a dynamic change of troponin levels is associated with poorer cognitive performance in patients with acute ischemic stroke.

Study aims:
The primary aim of the PRAISE study is to develop an algorithm for the prediction of acute coronary syndrome in acute ischemic stroke patients using non-invasive diagnostic tests. In order to improve prediction of acute coronary syndrome in patients with acute ischemic stroke, serial troponin measurements, ECG, echocardiography, GRACE score and clinical symptoms will be evaluated systematically and prospectively for the first time. Moreover, we aim to clarify whether a dynamic troponin elevation is associated with poor functional and cognitive outcome as well as higher mortality after stroke.

Setting:
The study is financed by the German Center for Cardiovascular Research (DZHK) and the German Center for Neurodegenerative Diseases (DZNE). About 15 stroke centers in Germany will participate as recruiting study sites. The majority of recruiting study sites are university hospitals with both a neurology and a cardiology department. The PRAISE study is an observational study. Therefore, treatment of patients included in the PRAISE study will be at the discretion of the local treating physicians.

Hypotheses:
The **primary hypothesis** states that a dynamic change of troponin values > 50% after 3 hours[1] indicates acute coronary syndrome in patients with acute ischemic stroke. In patients with acute ischemic stroke, change of troponin values in serial measurements is helpful to identify patients with acute coronary syndrome.
Endpoint: diagnosis of acute coronary syndrome as established by an independent endpoint adjudication committee.

First secondary hypothesis:
Ischemic stroke patients with a dynamic change of troponin values have poorer functional outcome than patients with stable troponin values after three and twelve months.
Endpoint:
Functional outcome will be measured using the modified Rankin Scale (mRS) [16] as well as the Lawton Instrumental Activities of Daily Life Scale (IADL)[17] three and twelve months after the index event.

Second secondary hypothesis:
Ischemic stroke patients with a dynamic change of troponin values have poorer cognitive outcome than patients with stable troponin values three and twelve months after the index event.
Endpoint:

Cognitive outcome will be evaluated using the Montreal Cognitive Assessment (MoCA)[18] and the Telephone Interview for Cognitive Status (TICS)[19]

Third secondary hypothesis:
Ischemic stroke patients with a dynamic change of troponin values have an increased risk of recurrent cardiovascular events and mortality compared to patients with stable troponin values.
Endpoint:
Rates of recurrent ischemic strokes, TIA, myocardial infarction and mortality after three and twelve months.

Study population:
According to the sample size calculation, 251 stroke patients will be included prospectively. Both male and female patients will be included. Pregnant or breastfeeding patients will not be eligible for inclusion. The study will only recruit patients ≥ 18 years of age.

Inclusion criteria:
- age ≥ 18 years
- written informed consent
- diagnosis of ischemic stroke based on clinical symptoms and imaging (cranial CT or MRI) < 72 h after symptom onset
- troponin elevation:
    a) either highly abnormal initial troponin levels (Elecsys-Assay hs-cTnT > 52ng/l, Architect-Assay hs-cTnI > 52 ng/l[20], Dimension Vista Assay hs-cTnI > 107 ng/l[21])
    or
    b) dynamic troponin elevation with Δ change > 20% of the initial value after 3 hours and at least one value above the assay-specific upper reference limit according to ESC guidelines[12]
- diagnosis of transient ischemic attack, if the initial focal neurological deficit was objectified by a neurologist during clinical examination and the patient has an ABCD2-Score[22] ≥ 4 points
- patient willing to participate in follow-up via telephone interview

Exclusion criteria:
- renal insufficiency (i.e. estimated glomerular filtration rate (eGFR) < 30 ml/min/1,73 m²)[22]
- manifest hyperthyroidism
- cerebral infarct > 100 ml on diffusion weighted imaging (DWI-MRI) or on cranial CT (if performed > 24 hours after symptom onset) or ASPECTS-Score[23] < 7 (if cranial CT was performed within 24 hours of symptom onset)
- pregnancy or breast feeding
- relative contraindications for coronary angiography (e.g. acute renal failure, acute bleeding, known allergy to contrast agent, manifest hyperthyroidism, respiratory failure, hemodynamic instability not explained by acute coronary syndrome)[24]
- predmorbid Rankin score (mRS) > 3
- life expectancy < 1 year
- participation in an interventional study according to Medicinal Products Act (AMG) or Medical Devices Law (MPG)

Stopping rules

a) for the individual patient

Every patient has the right to withdraw their consent to participate in the study at any time and without the need to state a reason for their withdrawal of consent. The patient may communicate their withdrawal of consent in oral or written form.
If a study participant withdraws consent, any data that has been collected will be anonymized. In addition, every study participant has the right to demand that their personal data be deleted.
By withdrawing consent from participation in the PRAISE study, the participant also withdraws consent from participation in the DZHK biobanking (see below). Withdrawal of consent has to be reported to the Trusted Third Party (THS) of the DZHK. The THS will ensure that all data are anonymized by eliminating the link between the participant's pseudonym and their personal data. In addition, all collected biosamples will be destroyed.

b) for the entire study

The final decision for premature termination of the entire study lies with the Principal Investigators and the Steering Committee. The study's Data Safety Monitoring Board (DSMB) may recommend the premature termination of the study due to safety concerns. The DSMB will report to the Steering Committee on the study's safety after inclusion of 100 and 200 patients, respectively. All severe adverse events of special interest (SAESI, see below) will be collected and evaluated by a Critical Events Committee (CEC) and the results of the evaluation will be reported to the Data Safety Monitoring Board (DSMB). Possible reasons for premature termination of the entire study include

- Unexpectedly high rate of SAESI
- Unexpected SAESI that change benefit/risk assessment of the complete study
- Low rate of recruitment

c) for an individual study site

Possible reasons for early termination of the study at an individual study site include

- Repeated major protocol violations
- Continuously low rate of recruitment (< 5 patients/year for two years in a row)

The decision on early termination of the study at an individual study site is made by the principal investigators after consulting the Steering Committee. If an individual study site wishes to terminate their participation prematurely, they are required to notify the principal investigators in writing.

Study procedures:

Patients with acute ischemic stroke that undergo inpatient treatment at one of the PRAISE study sites may be included into the PRAISE study. Acute ischemic stroke will have to be diagnosed by an experienced neurologist at the recruiting study site. All patients will undergo cranial imaging (i.e. cCT or cMRI) as part of clinical routine before inclusion to rule out differential diagnoses to ischemic stroke. Patients will be eligible for inclusion within 72 hours after hospital admission. ECG, echocardiography and coronary angiography will have to be performed within 7 days after hospital admission.

Patient history and clinical examination:

Upon study inclusion (V1) the patient's clinical history will be taken and a clinical examination will be performed. The data will be collected in accordance with the DZHK basic data set (DZHK-SOP-K-02)[25]. In addition, we will gather data on current medication, premorbid mRS, the National Institutes of Health Stroke Scale (NIHSS)[26] on admission as well as the GRACE-Score. During the second study visit (V2, within 7 days after study inclusion), we will perform the NIHSS, mRS and perceived stress scale

(PSS). In addition, we will collect data on the patient's current medication. A 12-lead ECG will be taken at V1 and V2 according to DZHK-SOP-K-03[27].

Coronary angiography:

All patients included in the study will undergo coronary angiography, which is the gold standard to diagnose a coronary culprit lesion. The timing of coronary angiography will be determined according to the ESC guideline recommendations on risk stratification[28]. Coronary angiography will be performed according to a SOP. Treating cardiologists may choose the cardiac catheter for coronary angiography. We will collect data on duration of the procedure, amount of contrast agent given, puncture site (radial vs. femoral), periprocedural anticoagulation, balloon dilatation and stent angioplasty. In addition, we will collect data on periprocedural complications, e.g. dissections, arrhythmias, thrombus formation, perforation, cardiac tamponade and type 4a myocardial infarction. For central reading in the core laboratory, imaging data will be uploaded via the imaging data management system (BDMS) of the DZHK. Coronary lesions will be evaluated regarding their localization and morphology according to the AHA classification.

Echocardiography:

Transthoracic echocardiography (TTE) will be performed by a cardiologist at the participating study site according to DZHK-SOP-K-08[29]. For central reading in the core laboratory, imaging data will be uploaded via the imaging data management system (BDMS) of the DZHK.

Troponin:

Acute ischemic stroke patients with elevation of troponin values according to the inclusion criteria (see above) will be eligible for inclusion into the PRAISE study. Troponin will be measured on admission and after three hours during clinical routine in all recruiting study sites. A dynamic elevation of troponin is defined as a 20% change of troponin values in serial measurement with at least one value elevated above the assay-specific upper reference limit. Since not all recruiting study sites will use the same assay for measuring troponin in clinical routine, troponin will also be measured at a central core laboratory located at the University Hospital Hamburg-Eppendorf (Prof. Blankenberg). At the core laboratory, high-sensitivity (hs)-Troponin-T will be measured using the Roche Elecsys-Assay and hs-Troponin I will be measured using the Siemens Architect-Assay.

12-lead ECGs, echocardiography and coronary angiography will be evaluated by independent and blinded core laboratories (Uni.-Prof. Dr. med. Burkhard Pieske at Charité Campus Virchow Klinikum for echocardiography, Uni.-Prof. Dr. med. Wilhelm Haverkamp at Charité Campus Virchow Klinikum for ECG und Univ.-Prof. Dr. Ulf Landmesser at Charité Campus Benjamin Franklin for coronary angiography).

The diagnosis of „acute coronary syndrome" is the study's primary endpoint and will be established by an independent endpoint adjudication committee according to the ESC guidelines. The endpoint adjudication committee will take the results of coronary angiography, ECG and echocardiography as well as clinical symptoms into account. The endpoint adjudication committee will be blinded to patients' troponin levels.

DZHK Biobanking:

All patients included in the PRAISE study will be offered optional participation in the DZHK biobanking. If the patient agrees to participate in the DZHK biobanking, blood and urine samples will be taken during V2. The documentation process depends on whether the recruiting study site is also a DZHK site. The exact procedure is described in DZHK-SOP-B-01 and DZHK-SOP-B-02. Biosamples will be

stored at the participating study sites at -80°C. If a participant withdraws consent to participate in the DZHK biobanking, all collected biosamples will be destroyed. A withdrawal of consent to participate in the PRAISE study automatically includes withdrawal of consent to participate in the DZHK biobanking.

Cognition:
Cognitive performance will be assessed during V1 and V2 using the Montreal Cognitive Assessment (MoCA). In addition, cognitive performance will be assessed during follow-up visits using the Telephone Interview for Cognitive Status (TICS). At V1 the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE)[30] will be performed to assess cognitive decline prior to the index stroke. In order to differentiate between cognitive impairment and delirium, we will use the Delirium Rating Scale (DRS)[31] at V1.

Functional Outcome:
Functional outcome will be assessed using the modified Rankin Scale (mRS) and the Lawton Instrumental Activites of Daily Living Scale (IADL). mRS will be assessed at V1, V2 and both telephone follow-up visits (see below). IADL will be assessed during telephone follow-up visits. The secondary endpoints recurrent myocardial infarction, recurrent cerebral ischemia (ischemic stroke or TIA) and mortality will be assessed at V2 as well as both telephone follow-up visits.

Follow-up:
Follow-up will be performed three and twelve months (± 14 days) after the index stroke in form of telephone interviews. During the telephone interviews, cognitive outcome and functional outcome will be assessed as described above. In addition, patients will be questioned on recurrent cardiovascular events (i.e. myocardial infarction, stroke and TIA). Data on mortality will be acquired from local registration offices.

Data management:
Data for the PRAISE study will be collected at each individual study site using an eCRF (electronic case report form). The PRAISE study will use the scientific infrastructure of the DZHK for data collection and storage. Data will be collected and stores according to the requirements of the data protection policy of the DZHK[32] as well as Guidelines for Good Clinical Practice (GCP). Data will be stored using the webbased tool "secuTrial", which conforms with all regulatory standards of the FDA[32]. In case of participation in the DZHK biobanking, all biosamples will be stored locally in the recruiting study sites (see above).

The DZHK has a central data management (ZDM), which consists of three institutions

- Trusted third party (THS) at the Institute of Community Medicine, Greifswald
- Data repository (DH) at the Institute of Medical Informatics, Göttingen
- IT-administration at the DZHK main office

Medical data that are entered into the eCRF will be stored at the study database of the DH. The patients' personal data will be stored on the servers of the THS. Thus, the patients' personal data and the patients' medical data will be stored on separate servers provided by different organizations. Only the individual study sites will have access to both the patients' personal and medical data.

The THS will provide the eCRF for collection of patients' personal data via secuTrial. Thus, data will be stored directly on the servers of the THS. The signed informed consent (IC) form will be scanned and

sent to the THS electronically. Informed consent will also be documented electronically via a separate eCRF. The THS will subsequently generate the patient's pseudonym, which will be used to enter the patient's medical data. The patient's pseudonym will be available to the local staff at the study site. The DH will provide the eCRF for the collection of medical data. For central assessment of coronary angiography, transthoracic echocardiography (TTE) and ECG, imaging data will be uploaded using the image data management system (BDMS) of the DZHK. The respective core laboratories will have separate eCRFs in secuTrial to enter the results of imaging assessment.

All source documents are stored in the Investigator Site File/Study Patient File. Source documents are stored locally at the recruiting study sites for 10 years.

Study variables:

Identifying data:

Name, patient number, sex, date of birth, age, address, telephone number

General examination:

DZHK basic data set
Current medication
NIHSS (0-42)
mRS (0-6)

laboratory diagnostics:

troponin value at admission (in ng/l)
troponin value after three hours (in ng/l)
clinical chemistry
DZHK-Biobanking (24 ml) (optional)

Study-specific examinations:

IADL (0-8)
MoCA (0-30)
TICS
IQCODE
GRACE-Score
Beck Depression Inventory (BDI) (0-63)[33]
DRS (0-39)
Perceived Stress Scale (0-40)
12-lead ECG (ACS-typical changes)
Transthoracic echocardiography (regional wall motion abnormalities, left-ventricular ejection fraction)
Coronary angiography (presence of coronary culprit lesion)

Communication of test results

If echocardiography or coronary angiography yield pathological findings, any decision on further diagnostic or therapeutic measures is at the discretion of the treating physicians at the study sites. Individual results of central imaging assessment in core laboratories will not be communicated with the participating sites or with patients.

	Screening (V1)	**Study-specific examinations (V2)**	**Follow-up 1**	**Follow-up 2**
	< 72 h after admission	< day 7 (+/- 1 day)	3 months (+/- 7 days)	12 months (+/- 7 days)
Study inclusion				
Inclusion/exclusion criteria	X			
Written informed consent	X			
General examination				
DZHK basic data set	X			
Premorbid mRS	X			
Current medication	X	X		
NIHSS	X	X		
mRS	X	X	X	X
Cognitive tests				
TICS			X	X
MoCA	X (Version A)	X (Version B)		
IQCODE		X		
BDI			X	X
DRS	X			
perceived stress scale		X		
Gender term (Sub-study)		X		
Laboratory diagnostics				
Troponin (0 und 3 h)	X			
Clinical chemistry	X			
DZHK-Biobanking (optional)		X		
Study-specific examinations				
GRACE-Score	X			
Adverse Events	X	X	X	X
ECG	X	X		
Echocardiography (TTE)		X		
Coronary angiography		X		
endpoints				
Acute coronary syndrome (ACS)		X		
Recurrent cerebral ischemia, myocardial infarction, mortality		X	X	X

Table 1: PRAISE study procedures

Statistical analysis:

Sample size calculation:

The sample size calculation of the PRAISE study is based on data from the TRELAS study (Troponin elevation in acute stroke)[9]. In the TRELAS study, 7/29 (24%) of ischemic stroke patients with troponin elevation had a coronary culprit lesion and 11/29 (38%) of patients had dynamic troponin elevation (i.e. Δ change > 50%). Of 11 patients with dynamic troponin elevation, 6 patients (54%) had a coronary culprit lesion. In patients without dynamic troponin elevation, only one patient (1/18=6%) had a coronary culprit lesion. Thus, the odds ratio of a dynamic troponin elevation for presence of a coronary culprit lesion was at 20.4. Due to the small sample size of the TRELAS study, we used the lower limit of the 80% confidence interval of the odds ratio (~4) to calculate the sample size for the PRAISE study. We assumed that the proportion of stroke patients with dynamic troponin elevation will be similar to the TRELAS study. Thus, 203 patients will have to be included to achieve a statistically significant result with a power of 80% (alpha=0.05). Since the TRELAS study only recruited patients with an initial hs-troponin T value > 50 ng/l (Roche Elecsys Assay), the proportion of patients with dynamic troponin elevation will likely be even higher in PRAISE. In order to compensate for cases of withdrawal of consent we plan to include 251 patients. The primary hypothesis will be tested using an intention-to-diagnose analysis by calculation of the odds ratio of acute coronary syndrome in patients with dynamic vs. stable troponin elevation. Secondary endpoints will be analyzed using the same statistical method.

In order to assess other predictors of acute coronary syndrome we will use the Chi-Square-test for dichotomous variables and the Wilcoxon-Test for continuous variables.
In addition, we will perform univariable analyses and multivariable logistic regression analyses to calculate unadjusted and adjusted odds ratios for acute coronary syndrome. We will take a number of baseline regressors into account including age, sex, GRACE-Score, history of coronary heart disease, atrial fibrillation, heart failure, wall motion abnormalities on echocardiography and ACS-typical changes on ECG.
In an exploratory analysis, we will calculate an optimized multivariable logistic regression model using backward selection. In addition, we plan to calculate the best cut-off of troponin levels to predict acute coronary syndrome using the maximum area under the receiver operating characteristic (ROC) curve.
Subgroup analyses will be defined in the statistical analysis plan before the first endpoint analysis is performed.

Interim analyses

In order to assess safety of the study, we will perform an interim analysis of the occurrence of serious adverse events of special interest (SAESI, see below) after inclusion of 100 and 200 patients, respectively. This analysis will be used by the DSMB to consult the Steering Committee concerning the continuation or premature termination of the study due to safety concerns.

Methods against bias

PRAISE is a multicenter observational study. Recruiting sites are stroke centers in Germany. The diagnosis of “acute ischemic stroke” will be established by experienced neurologists. ECG, echocardiography and coronary angiography will be performed by experienced cardiologists according to SOPs. All study examinations will be re-assessed by blinded core laboratories (see above). Since troponin will be measured by the recruiting study sites before study inclusion using different assays, troponin will also be re-measured at a core laboratory (Prof. Blankenberg, UKE Hamburg) using the same biosamples. The primary endpoint will be adjudicated by an independent endpoint adjudication committee, which will be blinded to patients’ troponin levels. The assessment of functional and cognitive outcome will be performed using standardized scores (see above).
The primary hypothesis that has been described in this protocol will be tested in an intention-to-diagnose analysis in order to prevent possible selection bias. A per-protocol-analysis is planned as a secondary analysis.

Study timeline:

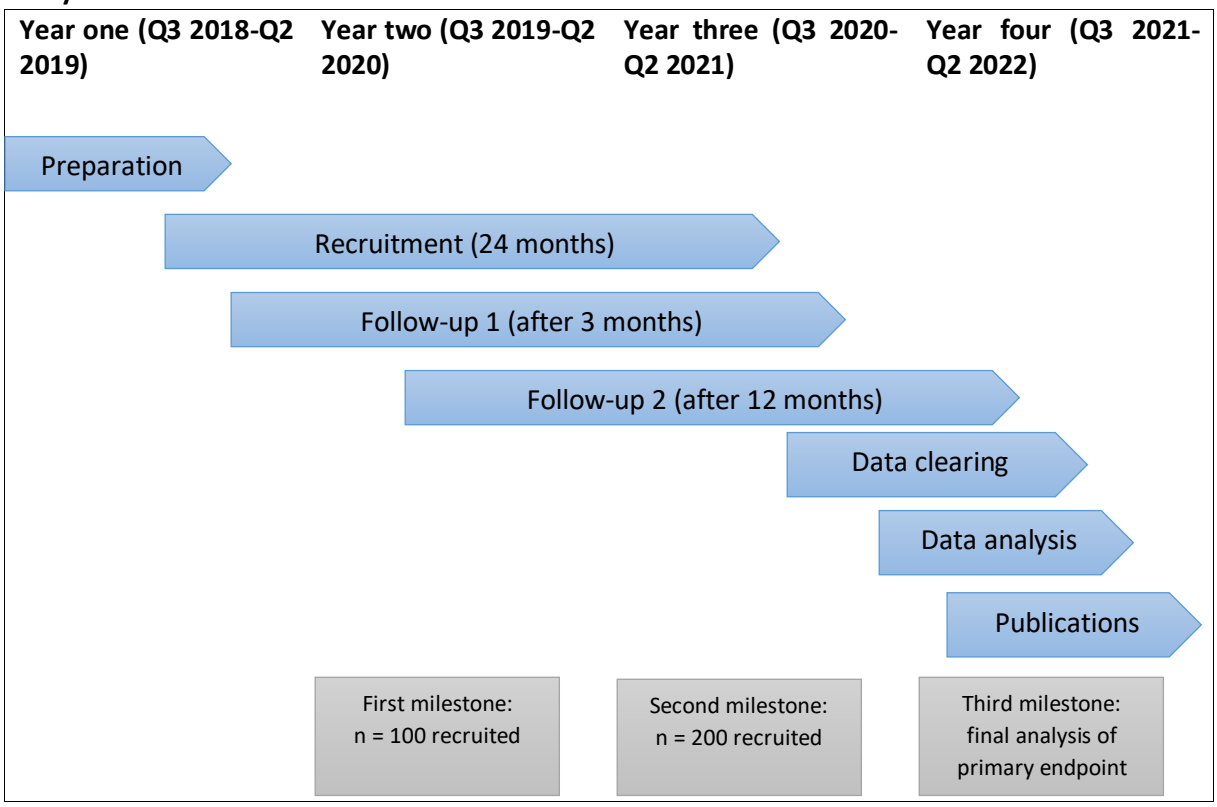

Fig. 1: study timeline

Ethical considerations:

The study will be conducted according to the Guidelines for Good Clinical Practice (ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996 Directive 91/507/EEC; D.M. 15.7.1997)[34] and the Declaration of Helsinki[35]. By signing the study contract, the study sites agree to conduct the study according to the study protocol. All examinations during the course of the study will be performed according to current guidelines of the European Society of Cardiology (ESC). Patients unable to provide informed consent may not be included in the study. For inclusion into the study, both the study physician and the patient have to sign the written informed consent form.

The study was approved by the Ethics Committee of Charité-Universitätsmedizin Berlin on March 29 2018.

Data protection:

The data will be collected and stored using the DZHK scientific infrastructure (see above). Therefore, our data protection policy builds on the DZHK data protection policy[32]. We will use the webbased tool secuTrial for data collection.

The servers of the THS and DH are protected by multi-stage firewall systems. The communication between server and clients is always encrypted. Communication with the THS is only possible with the client's pre-registered IP address and port. In addition, it is possible to define certain roles within secuTrial so that the access to the data may be adapted to different groups of study personnel. Each role is equipped with its own set of rights to access, enter and modify data.

During the process of data collection, data editing and query management, secuTrial creates an audit trail for every data point. The audit trail provides an overview of all changes that have been made and saved in an eCRF. Management of queries will also be realized via secuTrial and will only be accessible for registered users.

Data transfer:
Data collected during the course of the PRAISE study will be stored indefinitely within the DZHK infrastructure using a pseudonym. By providing informed consent, study participants will grant the DZHK unlimited right to use the stored data. In addition, study participants will agree to transfer the ownership right to their biosamples that have been collected during the DZHK biobanking to the DZHK. If external researchers wish to use data or biosamples collected in DZHK-funded studies, they may write a scientific project proposal to the DZHK. The DZHK may then grant the researchers non-exclusive, non-transferrable rights to use data for the purpose of the project for a limited time. Any research proposal sent to the DZHK will be evaluated by the DZHK Use and Access committee according to the DZHK use and access policy[36]. External researchers agree via contract that they will not try to re-identify patients, to copy data or biosamples or to forward them to any third party. After transfer of the data, the external researchers are required to delete the data within 5 years after the end of the contract period and to inform the DZHK accordingly.
The transfer of data to external researchers is only possible after a period of protection, which ends two years after the study has been completed. Within the period of protection, only the study's principal investigators have an unlimited right to use the data collected during the study.

Rights to publications:
The principal investigators of the PRAISE study plan to publish the main results of study together with the local investigators of all recruiting study sites. Before the publication of the study's main results, the investigators at recruiting study sites agree not to publish any of the data that have been collected at their respective study sites. If the principal investigators or financers of the study (i.e. the DZHK or DZNE) should intend to apply for intellectual property rights, the principal investigators will have the right to delay the publication of the study's main results. This is also applicable if the study should be terminated prematurely. The principal investigators will decide on the content of the publication. The investigators at recruiting study sites agree not to publish any confidential information. In any case, publications planned by investigators at recruiting study sites will have to be coordinated and agreed upon with the principal investigators (who may not deny the right to publication without reasonable arguments).

Patient treatment:
If the diagnosis of acute coronary syndrome cannot be confirmed, the choice of secondary stroke prevention will be at the discretion of the treating physicians. If a diagnosis of acute coronary syndrome is confirmed, the individual case will be discussed between the neurologists and cardiologists at the recruiting study sites in order to decide on further treatment. Treating physicians are encouraged to consult the ESC guidelines for appropriate treatment decisions. However, since PRAISE is an observational study, all treatment decisions lie with the treating physicians.

Risks for study participants:
Coronary angiography will only be performed in a study patient after thorough information on potential risks and benefits and if the patient provides informed consent. Coronary angiography will be performed according to ESC guideline recommendations. In order to avoid risks related to the application of contrast agent, patients with renal insufficiency (eGFR < 30 ml/min), manifest hyperthyroidism and allergy to contrast agent may not be included. In addition, patients who are hemodynamically unstable with their condition not being sufficiently explainable by acute coronary syndrome, are not eligible for inclusion. In order to reduce the risk for intracerebral hemorrhage related to periprocedural antithrombotic treatment, patients with very large ischemic lesions may not be included (see exclusion criteria).

Quality control:

The THS and DH of the DZHK offer web-based seminars to any initiator of a DZHK study. During the course of the webinar, the technical processes are explained and issues may be solved before study initiation. After initiation of several study sites there will be a quality training to educate study personnel, e.g. on the correct data collection process. Investigators at recruiting study sites will ensure that their staff is trained adequately.

Before the start of recruitment at any study site, there will be a site initiation visit by the study coordinators. During the recruitment period, we plan two monitoring visits at each study sites. During the course of monitoring visits, all informed consent forms will be checked. In addition, all further source data will be checked in at least 10% of patients per study site. Before recruitment for the PRAISE study commences, study-specific quality control measures will be determined in a monitoring manual. In addition to in-person monitoring, all data entered into the study database will be subjected to a review process. After the data for a study visit has been entered into the eCRFs, the investigator at the recruiting study site will have to assign the "Review A" status to the respective eCRFs. The "Review A" status signifies that the data entry is complete so that quality control measures including remote monitoring can be performed. Quality control measures include remote monitoring by a study nurse from the study's main office as well as automated quality control by the DH. After completion of quality control measures including query management, the study's main office will assign the "Review B" status to the eCRFs. After the „Review B" status has been set, data cannot be entered, modified or deleted anymore. Only data that have been assigned the "Review B" status may be forwarded to external researches according to the DZHK Use and Access Policy.

Safety, SAESI:

A „Serious Adverse Event of special interest" (SAESI) is an event, which may cause prolongation of the in-hospital treatment, renewed admission to hospital, functional impairment or death of the study participant. SAESI are defined to include potential complications of coronary angiography.

In the PRAISE study, the following events are defined as SAESI:

- Ischemic stroke[37]
- Transient ischemic attack (defined as focal neurological deficit lasting for < 24 hours)
- Intracerebral hemorrhage[38,39]
- Subarachnoid hemorrhage[39]
- Severe hemorrhage (defined as hemorrhage type 3-5 according to the BARC classification)[40]
- Type 4 myocardial infarction[1]
- Peripheral arterial occlusion
- Anaphylactic shock[41]
- Renewed coronary revascularization during the in-hospital stay
- death

All SAESI will be documented by the study personnel on the appropriate eCRF in secuTrial within three work days. The study coordinators will be informed automatically if a new SAESI is reported. Study sites are required to evaluate all SAESI regarding their severity and potential causal relationship with coronary angiography.

All reported SAESI will be evaluated by the Critical Events Committee (CEC) regarding their classification, relevance and causal relationship with coronary angiography. All CEC meetings have to be attended by at least one neurologist and one cardiologist. The adjudicating members of the CEC may not be involved in the treatment of study patients whom they are evaluating. The adjudication will be carried by vote of majority. The adjudication of the CEC will be documented on a separate eCRF

in secuTrial. The DSMB is required to write a report on their assessment of the study's safety after inclusion of 100 and 200 patients, respectively. The DSMB will consult the Steering Committee regarding its recommendation of study continuation or premature termination due to safety concerns.

Financial compensation:
Study participants will not receive financial compensation.

Insurance:
Study participants from all study sites will be insured via study insurance provided by Newline Insurance Company Limited.

Berlin, 19.06.2018 Dr. Matthias Endres

Digital unterschrieben von Dr. Matthias Endres
Datum: 2024.10.24 16:46:27 +02'00'

(Prof. Dr. med. Matthias Endres)
Principal Investigator

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