Non-interventional Post-Authorisation Safety Study (PASS) Protocol

Investigational Product(s):	Pradaxa, vitamin K antagonists, antiplatelet therapy	
Title:	PRODAST: **P**rospective **R**ecord **O**f the use of **D**abigatran in patients with **A**cute **S**troke or **T**IA	
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Status:	*Protocol final version*	
Version	**5.0**	**Date: September 24th, 2018**

SIGNATURES

The present study protocol was subject to critical review and has been approved in the present version by the undersigning persons.
Protocol Version: 5.0 final

Director of Investigation

04-Oct 2018 [redacted]
Date *Signature*

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DECLARATION OF INVESTIGATOR

I herewith certify that I agree to adhere to the observational plan and to all documents referenced in the observational plan.

Principal Investigator

Date *Signature*

Full name

Organization/Department

NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL SYNOPSIS

Title of study:	PRODAST: **P**rospective **R**ecord **O**f the use of **D**abigatran in patients with **A**cute **S**troke or **T**IA
Study site(s):	Overall up to about 100 hospitals with a neurological acute stroke unit
Objectives:	The main objectives are: To collect real-world data on major bleeding events under antithrombotic treatment for the early secondary prevention of stroke in patients with non-valvular atrial fibrillation (AF) who experienced an ischemic stroke or a TIA recently (≤ 1 week). • The primary objective is to assess if the 3-month major bleeding event rate following TIA or ischemic stroke in patients with AF is not significantly increased with dabigatran administrated early (≤ 7 days) compared with dabigatran treatment started after 7 days or with VKA started at any time. In addition, occurrences of major bleeding will be compared over time and the optimal time point for dabigatran administration will be determined. • To evaluate recurrent stroke rates under treatment with dabigatran, VKA, no anticoagulation or no oral antithrombotic treatment at all. Further objectives are described in Section 2.1.2
Methodology:	Multicenter, prospective, observational, non-interventional, post-authorisation safety study for patients with non-valvular atrial fibrillation and ischemic stroke. There will be a cross-sectional analysis at the patient's baseline visit for all patients and a follow-up 3 months after baseline for patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment and the assessment of vital status after 1 year.
No. of patients:	Enrolment of approximately 10.000 patients at baseline with follow-up of 6.000 patients is planned in total. Only patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment at all will be included in the follow-up of this study.
Diagnosis:	Patients with recent (≤ 1 week) ischemic stroke or TIA and confirmed non-valvular atrial fibrillation (permanent or paroxysmal).
Main criteria for inclusion:	Patients with non-valvular atrial fibrillation and recent (≤ 1 week) ischemic stroke or TIA, aged 18 years or older. Please note: More detailed information on inclusion and exclusion criteria can be found in section 3.3.
Duration of follow up:	3 months for patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment at all and the assessment of vital status after 1 year.

Outcomes*:*	Important clinical outcomes / endpoints for the PRODAST study are: Primary (Safety) Endpoint: • major bleeding events Secondary Endpoints: • stroke (hemorrhagic, ischemic or of uncertain classification) • transient ischemic attack (TIA) • systemic embolism • pulmonary embolism • myocardial infarction • life-threatening bleeding events • all cause of death (non-vascular, vascular or of unknown cause) • point in time and reason for withdrawal/change of medication Additional events of interest might be included as outcomes based on new information that could become available during the course of the study.
Other Criteria for safety:	Compliance with oral anticoagulant treatment, Adverse Events (AE) and Serious Adverse Events (SAE).
Statistical methods:	Descriptive statistics for patient characteristics and treatment patterns, creation of study specific propensity scores for type of treatment, time-to-event methodology, Cox regression models, risk curves, ROC curves

FLOW CHART

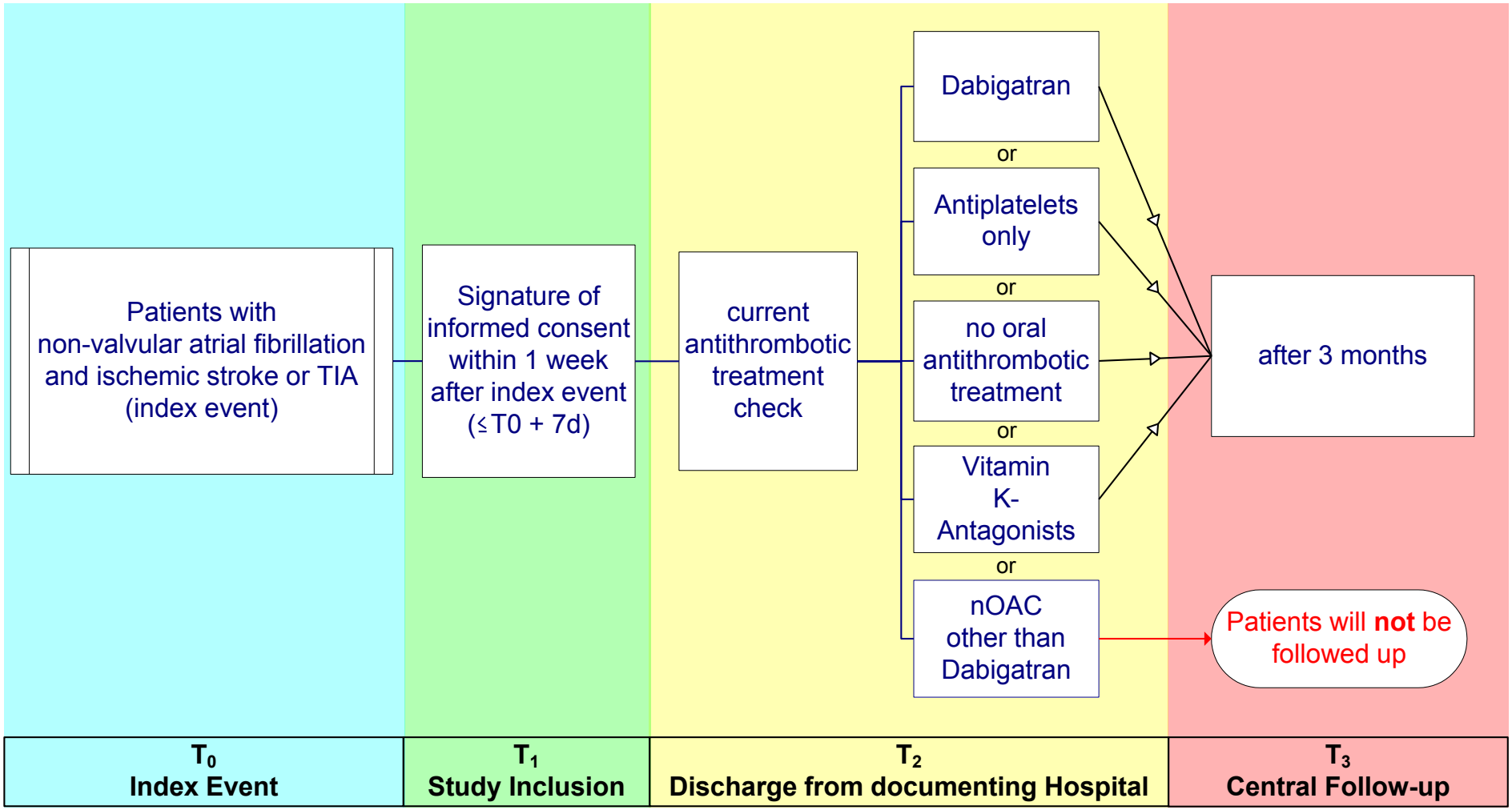

Fig. 1: Flow Chart according to the non-interventional study protocol of the PRODAST study.
10.000 patients with confirmed non-valvular atrial fibrillation who experienced a recent ischaemic stroke or TIA (➔ index event ≤ 1 week) will be enrolled at baseline for this study. It is planned to observe 6.000 patients in a period of 3 months who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment at all and the assessment of vital status after 1 year (T_4). Patients treated with nOAC other than dabigatran at discharge will not receive any follow-up. Data from this observation will be captured by a central follow-up after three months in the University Hospital of Essen.

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ABBREVIATIONS

AC	Anticoagulation
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
AMG	German Medicines Act
ATC	Anatomical Therapeutic Chemical (Classification System)
ASS	Acetylsalicid acid
BDSG	German Data Protection Law
BfArM	Federal Institute for Drugs and Medical Devices
BI	Boehringer Ingelheim
BID or b.i.d	*lat. bis in die* → twice per day
CAC	Clinical Adjudication Committee
CI	Confidence Interval
CRA	Clinical Research Associate
CRF	Case Report Form
DMP	Data Management Plan
EC	Ethics Committee
ECG	Electrocardiogram
EU	European Union
GCP	Good Clinical Practice
GPV	Good Pharmacovigilance Practice
ICU	Intensive care unit
IEC	Independent Ethics Committee
IMIBE	Institute for Medical Informatics, Biometry and Epidemiology
INR	International Normalized Ratio
ISF	Investigator Site File
LBBB	Left Bundle Branch Block
LV	Left Ventricular
MI	Myocardial Infarction
NVAF	Non-valvular atrial fibrillation
nOAC	Novel oral anticoagulant
OC	Operation Committee
PASS	Post-Authorisation Safety Study
PEI	Paul-Ehrlich-Institute
SAE	Serious Adverse Event
SC	Steering Committee
SEAP	Statistical and Epidemiological Analysis Plan
SmPC	Summary of Product Characteristics
TIA	Transient Ischemic Attack
VKA	Vitamin K Antagonist
ZKSE	Center for Clinical Trials in Essen

1. INTRODUCTION

1.1. MEDICAL BACKGROUND

Thromboembolic complications – particularly stroke – are a major cause of morbidity and mortality in patients with Atrial Fibrillation (AF). Most cases of stroke in patients with AF are the result of embolization of a left atrial thrombus, and particularly from the left atrial appendage. Patients with AF have a four to five fold higher risk for stroke than those without AF (31, 8). AF is detected in about 20-25% of all ischemic strokes (9) and an even larger percentage of patients with cryptogenic stroke are suspected to suffer from paroxysmal AF (26). Recurrent ischemic stroke and systemic embolism in AF patients can be effectively prevented by oral anticoagulation with VKAs and nOACs (11, 20).

However, VKAs have important limitations including a narrow therapeutic window, an unpredictable dose–response effect, numerous drug-drug and drug-food interactions, and a slow onset and offset of action. In a real-world setting, VKA treatment often results in INR values outside of the target therapeutic range (6, 13), leaving patients at increased risk of recurrent stroke or bleeding. As a result, many stroke patients with AF do not receive any effective oral anticoagulation (21, 30).

To address the many shortcomings of VKAs, several new oral anticoagulants have been developed including mainly direct thrombin inhibitors and factor Xa inhibitors. Dabigatran, a direct thrombin inhibitor, has recently been approved for the prevention of stroke and systemic embolism in patients with AF in many countries worldwide including the EU. In the RE-LY trial, a 18.113 randomized clinical patient study, dabigatran (150 mg b.i.d.) has been shown to significantly reduce the occurrence of stroke (both ischemic and hemorrhagic) and systemic embolism compared to warfarin while having a comparable rate of major bleeding (2). In the same trial dabigatran (110 mg b.i.d.) was demonstrated to be non-inferior to warfarin for the prevention of stroke and systemic embolism while resulting in statistically significantly fewer major bleeds in the same study. Importantly, both doses of dabigatran reduced the occurrence of intracranial hemorrhage in a statistically significant manner compared to warfarin. Of note, dabigatran has been taken up as adequate treatment alternative to VKAs in major treatment guidelines (e.g. USA, Canada, EU) during recent revisions. However, clinical trials cannot exactly simulate a real life scenario. Moreover, patients with recent TIA or ischemic stroke were excluded in the clinical trials investigating nOACs for stroke prevention in patients with atrial fibrillation. Although data on long-term effects of anticoagulation exist, there are no studies available that examined the long-term prognosis of stroke patients who underwent early anticoagulation with NOACs as compared to late anticoagulation. Long-term survival may differ between early (within first 14 days after stroke) and late anticoagulation. As PRODAST provides the unique opportunity to investigate not only short-term effects (3 months follow-up) but also long-term effects of early and late anticoagulation, assessment after one year will be performed. With this information overall and disease-specific survival will be analyzed. Therefore, natural history data on the relative frequency of recurrent ischemic events and bleeding complications under dabigatran in AF patients with recent ischemic stroke and TIA are needed.

With the approval of novel anticoagulants for stroke prevention in patients with AF, changes in antithrombotic treatment patterns will occur. The PRODAST study is designed to collect real-world data to assess these changes.

1.2. DRUG PROFILE

Dabigatran etexilate is the orally bioavailable prodrug of dabigatran, a direct thrombin inhibitor. The prodrug (dabigatran etexilate) does not have any antithrombin activity. Following oral administration, it is rapidly converted via esterases to the active moiety, dabigatran, which is a non-peptidic, potent, competitive, and reversible inhibitor of thrombin. For further information refer to the local approved label.

1.3. PRODAST STUDY

The PRODAST study is an observational study focusing on safety assessment and will be performed in compliance with legal provisions for non-interventional post authorisation safety studies (= nicht-interventionelle Unbedenklichkeitsstudie). It is designed to characterize TIA and ischemic stroke patients with non-valvular atrial fibrillation treated in neurological strokes units and to describe current patterns of antithrombotic treatments selected at the patient's hospital stay. Patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only, or no oral antithrombotic treatment at all will be followed for 3 months and information such as change in antithrombotic medication since baseline including compliance and occurrence of any outcome or adverse events will be captured. In addition, survival up to one year will be assessed to explore the long-term effect of anticoagulation started at different points after ischemic stroke.

1.4. RATIONALE FOR THE PRODAST STUDY

When evaluating new drugs, the collection of real-world data is important for studying large patient numbers that include a broad spectrum of comorbidities and co-medication use with the use of the new drug. Observational studies can provide supplementary data compared to data collected in randomized clinical trials which generally have stricter inclusion criteria and structured monitoring schemes.

VKAs have been shown to be effective in preventing strokes and systemic embolism in controlled clinical trials, but despite this evidence, they are prescribed to less than 50% of the AF patients for whom they are indicated (5, 30). The approval of new antithrombotic agents for the prevention of stroke in AF patients is expected to alter the use of existing antithrombotic agents and there is consequently a need to understand how stroke or TIA patients with different characteristics are treated in the real-world.

Also, when evaluating the safety and outcome events associated with the use of new drugs, real-world data are important to accrue larger patient numbers and broader and more heterogeneous patient populations with respect to co-morbidities and co-medication use.

The here described study will provide information on the utilization of nOACs after approval and examine the early use and safety of dabigatran given after acute ischemic stroke and TIA.

2. OBJECTIVES AND BENEFIT-RISK ASSESSMENT

2.1. STUDY OBJECTIVES

2.1.1. Main Objective

The main objective is to collect real world data on important outcome events after initiation of antithrombotic treatments for the secondary prevention of stroke in AF patients. For the PRODAST study the following main objectives have been set (please note: a list of primary and secondary endpoints can be found in Section 6.1):

To collect real-world data on major bleeding events under antithrombotic treatment for the early secondary prevention of stroke in patients with non-valvular atrial fibrillation (AF) who experienced an ischemic stroke or a TIA recently (≤ 1 week).

- The primary objective is to assess if the 3-month major bleeding event rate following TIA or ischemic stroke in patients with AF is not significantly increased with dabigatran administrated early (≤ 7 days) compared with dabigatran treatment started after 7 days or with VKA started at any time.

- In addition, occurrences of major bleeding will be compared over time and the optimal time point for dabigatran administration will be determined.

- To evaluate recurrent stroke rates under treatment with dabigatran, VKA, antiplatelets only or no oral antithrombotic treatment at all.

2.1.2. Further Objectives

The following further objectives are:

- To assess different "real-world" safety and efficacy outcomes (cf. 'Outcomes' in synopsis; for a detailed definition of all primary and secondary endpoints please check Section 6.1).
- To investigate the patient characteristics influencing the choice of antithrombotic treatment for the secondary prevention of stroke in non-valvular AF patients.
- To investigate drug utilization (i.e. compliance and persistence) of oral anticoagulant treatments.
- To examine compliance with the dabigatran SmPC and VKA SmPC with regards to indication, posology, contraindications and warnings.
- To explore subgroups with different risk profiles impacting safety and effectiveness of dabigatran.
- To collect real-world data on potential side effects of antithrombotic treatments.
- To (develop and) validate a risk score for early bleeding complications.
- To investigate long term effects of anticoagulation after ischemic stroke.

2.2. BENEFIT RISK ASSESSMENT

As in any observational study, patients will be managed according to local medical practice. The choice of treatment is solely at the discretion of the participating physicians. This means that there are no additional risks to patients by participating in this study. No additional medical procedures are required, over and above those that the patient would receive if not enrolled.

Data from this study will contribute to the scientific knowledge regarding the management of cerebrovascular patients with atrial fibrillation.

3. DESCRIPTION OF DESIGN AND STUDY POPULATION

3.1. OVERALL DESIGN AND PLAN

The multi-center, prospective PRODAST study is investigating patients with TIA or ischemic stroke and non-valvular AF both with and without previous oral anticoagulation. It consists of a baseline visit and a 3 months central follow-up for patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only, or no oral antithrombotic treatment at all. Thus, data on the use of dabigatran and vitamin K antagonists in routine clinical practice will be collected to describe how dabigatran is prescribed and used in the population of AF patients with recent cerebrovascular events and how these factors influence important outcome and safety events. The utilization of dabigatran will be assessed with regards to treatment persistence, compliance, proportion of patients discontinuing treatment and reason for discontinuation as well clinical endpoints such as major bleeding, stroke or systemic embolism. Due to the fact that patients will be treated according to local medical practice it is possible that medication will be changed during the observation period. In the follow-up, the study will use data from the first as well as from the second prescribed medication. To explore a long-term effect of anticoagulation, survival up to one year will be assessed. Only those laboratory parameters will be documented which are collected routinely according to medical practice.

3.1.1. Study feasibility

The study described in this protocol will collect data in about 100 Stroke Units mainly in Germany, each treating minimum 50 stroke patients with AF per year. Each site should thus include at least 20 AF patients per year . To evaluate the study procedures, the PRODAST study will first start in Essen and then be gradually extended to 5 to 20 additional sites (pilot phase). If the implementation shows no critical issues, the study will be initiated in all remaining sites in the same way. If there are critical issues, changes will be implemented and then rolled out to all other sites. Overall it is planned to enroll approximately 10.000 patients over 3 years with a central follow-up after 3 months including about 6.000 patients. The remaining patients will not be included in the follow-up if they are discharged on a treatment with a new oral anticoagulant other than dabigatran (cf. Section 3.1 and Fig. 1).

For all patients who have been included in the PRODAST study, specific characteristics like year of birth, sex, time of admission in the hospital (month) will be recorded during baseline in a pseudonymized manner. This data will be used for statistical purposes independent of whether the patient will be followed up after 3 months or not.

The central follow-up will be performed at the university hospital of Essen.

Additional sites may be opened to accelerate or support recruitment. The site staff will be asked to provide data regarding site and physician characteristics, including:

- Number of ischemic stroke and TIA patients during the last 12 months
- Ability to recruit consecutive patients who meet entry criteria of this study to minimize selection bias at the patient level.

In case of lower than expected recruitment of sites, initiation of additional international sites in Austria is planned.

The start and end of data collection is from June 2015 to June 2021.

3.1.2. Administrative structure of the study

Steering Committee

A Steering Committee (SC) will provide scientific leadership for the planning and conduct of all phases of the study. It consists of members of all representatives involved in this study.

For more details regarding the SC please check Section 10.1.

3.2. DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

The study includes confirmed non-valvular atrial fibrillation patients with recent (≤ 1 week) stroke or TIA. The investigational group in this study consists of patients treated with dabigatran administered in the earlier period (≤ 7 days) or in the later period (> 7 days), while patients treated with VKA form the control group. The control group reflects standard treatment for patients with confirmed non-valvular atrial fibrillation. Thus, the design allows for direct comparison of treatment risks regarding major bleeding events using time-to-event methodology. Lack of exchangeability at baseline will be controlled for by either conventional multiple regression or by use of propensity scores (either as a PS-matched or PS-adjusted analysis). Propensity scores are superior to conventional multiple regression in terms of controlling for baseline covariates if and only if there are few events and a very large number of confounders. Based on the possibility to change medication during the observation period, analysis of primary and secondary time-to-event endpoints will be done with respect to each patient's person-time under treatment.

3.3. SELECTION OF POPULATION

3.3.1. Main diagnosis for study entry (source population)

Patients with recent (≤ 1 week from index) ischemic stroke or TIA and with confirmed non-valvular AF (documented by 12 lead ECG, ECG rhythm strip, pacemaker/ICD electrocardiogram, or Holter ECG) will be included.

3.3.2. Definition of study population

Only the following patients should be included in the study:

1. Age ≥18 years at enrollment
2. Male or female patient willing and able to provide written informed consent for data transmission. For patients who are not legally competent to sign this informed consent for data transmission exceptions/special cases are described in chapter 12.5.2.
3. Patient with ischemic stroke or TIA within the last 7 days.
4. Patient diagnosed with non-valvular AF. Documentation of AF by 12 lead ECG, ECG rhythm strip, monitor print-out, pacemaker/ICD electrocardiogram, Holter ECG (duration of AF episode at least 30 seconds) or written physician´s diagnosis prior to index event needed for all enrolled patients.

The following patients will not be entered in the study:

1. Presence of any mechanical heart valve, or valve disease that is expected to require valve replacement intervention (surgical or non-surgical) during the next 3 months.
2. Current participation in any randomized clinical trial of an experimental drug or device.
3. Women of childbearing age without anamnestic exclusion of pregnancy or not using an effective contraception or nursing mothers.

The following patients should be entered in the follow-up part of the study:

1. Patients treated with either dabigatran, VKA, antiplatelets only or no oral antithrombotic treatment at all.

The following patients will not be entered in the follow-up part of the study:

1. In case, it will be determined at baseline or at discharge that patients have been treated in deviation from the effective summary of product characteristics (SmPC) for dabigatran (Pradaxa), sect. 4.1 (field of application) and/or 4.3 (contraindication), those patients will not be included in the follow-up part of the study.

3.3.3. Removal of patients from study

A patient will be withdrawn from the study for the following reasons:

- A patient or legal representative withdraws consent (Details for data deletion see 12.5).
- A patient or legal representative disagrees with the declaration of the responsible medical investigator.
- The patient was erroneously included in the study (e.g. no AF).

3.3.4. Discontinuation of the study

The Director of Investigation reserves the right to discontinue the study overall (cf. Section 3.1) or at a particular study site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular study site,

2. Emergence of any efficacy/safety information that could significantly affect continuation of the study or any other administrative reasons,

3. Violation of GCP, the protocol, or the contract by a study site or investigator, disturbing the appropriate conduct of the study at this site.

4. TREATMENTS

4.1. PRESCRIBED TREATMENTS TO BE OBSERVED

In this observational (i.e. non-interventional) study no specific treatment is mandated and no treatment will be withheld from patients. The choice of antithrombotic agent and dosing should be performed according to local clinical practice and the SmPC and is at the discretion of the treating physician.

4.2. CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

All concomitant medications are prescribed based on the underlying medical condition and upon the discretion of the treating physician.

4.3. TREATMENT COMPLIANCE AND COMPLIANCE WITH DABIGATRAN AND VKA SMPC

Compliance with antithrombotic therapy for stroke prevention is evaluated at FU-Visit and will be assessed by derivation of the following variable on a patient-level:

- Proportion of days with compliant medication intake (based on reference period as specified in the CRF before planned follow-up visit, subjective measure: how many days during the past week have you not taken your medication as prescribed?)

Compliance with the SmPC of dabigatran and VKA will be evaluated by analysing different patient characteristics such as age, weight, hepatic disease, renal function, further stroke and bleeding risk factors and concomitant medications in relation to the prescription of dabigatran and VKA (including dose selection).

5. INVESTIGATIONAL PLAN

5.1. VISIT SCHEDULE

Recommended timing of assessments is presented in the Flow Chart of the observational period of this study (cf. Fig. 1) and summarized in Table 5.1.

The follow-up assessments are intended to be performed via telephone, under exceptional circumstances the family doctor/treating physician may answer a written questionnaire. The information given by telephone interview or written questionnaire should be entered by the interviewer as soon as possible into the eCRF after contact with the patient and/or family doctor/treating physician.

Table 5.1: Schedule of data collection

Data points	$\underline{T_0}$ index event	T_1 study inclusion	$\underline{T_2}$ discharge from documenting hospital	$\underline{T_3}$ 3 months from T1 (± 2 weeks) with central follow-up (interview[4])
	All patients			**Patients discharged with either dabigatran, VKA, antiplatelets only or no oral antithrombotic treatment at all**
Data points	$\underline{T_0}$ index event	T_1 study inclusion	$\underline{T_2}$ discharge from documenting hospital	$\underline{T_3}$ 3 months from T1 (± 2 weeks) with central follow-up (interview[4])
Data collection	patient file	entry in study database (also retrospective)		
Informed consent		**X**		
Selection of patients		**X**		
Demographics and Lifestyle factors	**X**			
Index event and neurological defects	**X**		**X**	
AF disease characteristics	**X**			
Medical history and Concomitant diseases	**X**			
Vital parameters			**X**	
Lab parameters[1]		**X**	**X**	
Antithrombotic treatment	**X**	**X**	**X**	**X**
Treatment compliance for antithrombotic treatment			**X**	**X (Patient interview only)**
Concomitant treatment			**X**	**X (only for patients with SAE or Outcome events)**
Outcome events (vascular and bleeding events)[2]		**X (starting at $\underline{T_0}$)**	**X**	**X**
Complications		**X (starting at $\underline{T_0}$)**		
Serious adverse events[3]			**X**	**X**
Non-serious adverse events			**X**	**X**
Vital status			**X**	**X (and 1 year after T_1)**

1. INR, serum creatinine, platelet count, bilirubin GOT, GPT (if routinely collected according to medical practice)

2. Includes outcome events defined in Section 6. Specific data of any outcome event has to be recorded in Section 6 "Endpoints" of the eCRF.
3. Serious adverse events (SAEs) irrespective of causal relationship with dabigatran or VKA or antiplatelets are to be recorded on SAE forms. Every SAE must be submitted within 24 h after becoming known to the Safety department of the University Hospital of Essen.
4. With patient/physician (for details see 5.2.1)

5.2. DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

5.2.1. ASSESSMENTS

The following data will be collected for all patients for the purpose of cross-sectional analyses. A central follow-up interview (orally or written) and the assessment of vital status after 1 year will be done in patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment at all. The baseline visit is defined as the physical visit when the informed consent is signed. During the baseline visit, data for the index-event (T0), and the hospitalization-time since signature of the informed consent (T1) will be collected. Time span between index-event (T0) and signature of the informed consent (T1) must not exceed 7 days (≤T0+7). The documentation in the eCRF can start only after the patient or the legal representative has signed the informed consent or the physician has assessed incapability.

Assessments at baseline after study inclusion (T0/T1):

- Date of hospitalization
- Informed consent and assessment if the patient is capable to give the informed consent
- Criteria determining if patients should be included in this study or not (check Section 3.3.2)
- Demographic data, including: birthday, gender, weight, height
- Date of cerebrovascular event
- Duration of neurological deficits (<1h, 1-24h, >24h)
- National Institutes of Health Stroke Scale (NIH-SS; rf. Table 12.1.5)
- Type and date of cerebral imaging
- Premorbid Modified Rankin Scale
- Information regarding AF
    - Type (paroxysmal, persistent, permanent)
    - Date of diagnosis of non-valvular AF
    - Previous cardioversion, ablation, pacemaker implantation, left atrial appendage occlusion and/or left atrial procedures
- INR, serum creatinine, platelet count, bilirubin, GOT, GPT (if routinely collected according to medical practice)
- History of antithrombotic treatment and stroke history
- Any antithrombotic treatment selected for secondary stroke prevention after index event including start and stop date.
- Medical history including current concomitant diseases
- complications during hospitalization
- Outcome events after index event as listed in Section 6.1

Assessments at discharge (T2):

- Date of discharge, kind of discharge (e.g. home, rehabilitation clinic, nursing home)
- Antithrombotic treatment (total daily dose, current, any change (start and stop dates), including compliance, reason for onset and change)
- Therapeutic/diagnostic interventions including interruptions of antithrombotic treatment
- Latest brain-imaging showing infarct-size of index-event (volume, site)
- Modified Rankin Scale
- Outcome events starting at study entry after index event as listed in Section 6.1.

- All (serious) adverse events after study inclusion (T1) judged as related or unrelated to dabigatran or VKA
- Vital status and in case of death, details for the cause of death
- Concomitant treatments (according to the medical report)
- Vital parameters
- INR, serum creatinine, bilirubin, platelet count, GOT, GPT (if routinely collected according to medical practice)

Assessments at the central follow-up interview (T3):

The follow-up will be performed centrally at the university hospital of Essen. A central follow-up is chosen to avoid loss to follow-up as much as possible and to reduce selection bias.

At first, an interview with the patient will be performed in order to detect any possible outcome events or SAEs which subsequently need to be validated with the family doctor or treating physician.

If the patient is not able to participate in the follow-up interview, the interview will be done either with close family members, the legal representative or nursing staff, if possible.

Questions (via telephone) to the patient, if possible, or to the legal representative, close family members or nursing staff:

- Antithrombotic treatment (current, any change (start and stop dates) including compliance, reason for change; including interruptions of antithrombotic treatment due to therapeutic/diagnostic interventions) including treatment compliance and bridging strategies
- Catheter ablation procedures or cardioversions
- Outcome events as listed in Section 6.1.
- All serious adverse events
- Pregnancy
- Selected concomitant treatment (current, any change) only for patients with outcome events and/or SAE to only assess the relationship

- Non-serious adverse events, vital status or cause of death
- INR-values according to the written documentation in patients taking VKA. The INR levels after 1 month of initiation of VKA will be used to define the quality of anticoagulation control. INRs during temporary or permanent discontinuation will be excluded.

A complete follow-up interview should be conducted even if the patient discontinues treatment with dabigatran/VKA or switches to another antithrombotic treatment. If a patient prematurely discontinues from the study, the following information should be collected at the time of study discontinuation if possible:

For early discontinuation:

- Date of study discontinuation
- Reason for study discontinuation
- Vital status

In a second step, the family doctor/treating physician should be contacted by telephone or in writing and be asked to confirm the occurrence and causal relationship of all outcome events and SAE, if he/she has detected additional outcome events, additional hospitalisations and further SAEs. If the

information about antithrombotic treatment by the patient is insufficient, detailed information will be collected from the family doctor/treating physician. Every outcome event or SAE which was reported by the family doctor/treating physician will be documented in the central follow-up unit. The family doctor/treating physician will also be asked for confirmation and relevant diagnostic findings. If no follow-up information by the patient/ legal representative /nurse or family doctor/treating physician can be obtained, even after repeated contact approaches, the local citizen registry will be contacted and queried about the vital status and current address of the patient.

Survival one year after study inclusion (T4)

The assessment of vital status will be performed centrally at the university hospital of Essen by queries to the local citizen registry. In a first step, the vital status of study participants will be requested from the local citizen registry. For patients who have died, in a second step, information on the cause of death will be collected from the family doctor or treating physician. In cases, where information on cause of death cannot be gained otherwise, civil registry offices and local health offices will be contacted in order to permit access to death certificates. The assessment after one year will not be performed if consent for study inclusion was exclusively given by the investigator, if death was already documented, or consent for participation in follow-up was withdrawn.

All patients lost to follow up will be characterized compared to the remaining patients and reason and time point of loss to follow up will be evaluated (cf. Section 7.4).

6. VARIABLES, DEFINITIONS AND THEIR ASSESSMENT

6.1. OUTCOMES

6.1.1. Outcome measures

Baseline characteristics including the antithrombotic treatment selected at the baseline visit will be captured.

During the follow-up of patients initially treated with dabigatran, vitamin K-antagonists or no oral anticoagulation, all antithrombotic treatments for the prevention of strokes and systemic embolism will be recorded. In addition, compliance at discharge with the dabigatran and VKA SmPC with regards to indication, posology, contraindications and warnings will be evaluated (cf. Section 4.3 for more information).

Recording of outcome events starts at index event (T0) and ends after 3 months. Participation of patients ends with the telephone interview 3 months after inclusion. Vital status will be assessed after 1 year by a query to the local citizen registry. In case of death, the cause of death will be assessed from an interview (orally or written) with the family doctor/ treating physician. Only in cases, where this information cannot be obtained, civil registry offices and local health offices will be contacted in order to permit access to death certificates.

Primary (Safety) Endpoint

The primary (safety) endpoint for the primary hypothesis is the major bleeding event rate within 3 months following the index event.

Secondary Endpoints

The endpoint for the secondary hypothesis is the rate of recurrent stroke (hemorrhagic, ischemic, uncertain classification) within 3 months following the index event.

The following events are also considered important clinical outcomes (definitions are provided in Section 6.1.2). Additional events of interest might be included based on new information that could become available during the course of the study and based on results obtained by the described main analysis:

- Stroke (hemorrhagic, ischemic, uncertain classification)
- Transient ischemic attack (TIA)
- Systemic embolism
- Pulmonary embolism
- Myocardial infarction
- Life-threatening bleeding events
- Gastrointestinal bleeding events
- Any cause of death
    - Non-vascular death
    - Vascular death
    - Death of unknown cause
- Point of time and reasons for withdrawal/change of medication
- Patient compliance and treatment persistence
- Complications during hospitalisation before study inclusion (= signature of informed consent)
- AE and SAE

In addition, the following composite endpoint will be analyzed:

- Stroke or
- systemic embolism or
- life-threatening bleeding events or
- death from any cause

6.1.2. Assessment of outcome measures

Patient Compliance

Detailed information regarding “Patient compliance” can be found in Section 4.3.

Treatment persistence

Treatment persistence will be assessed as time until permanent discontinuation of the treatment (start and end date). This information will be collected at discharge and during central follow-up by the University Hospital Essen. If the patient is insecure about the end date of the treatment / persistence, the University Hospital of Essen will contact the family doctor / treating physician to clarify this point.

Investigator Compliance with the SmPC (including dabigatran and VKA)

Compliance with the SmPC will be captured by collecting the appropriate variables, such as renal and liver function (e.g. by analyzing the Glomerular Filtration Rate (GFR) using the Creatinine Clearance; check also Section 12.2 “Chronic Kidney Disease”), stroke and bleeding risk factors, selected concomitant medications and diseases at discharge.

- Compliance with SmPC Indications: All patients included in the study are non-valvular atrial fibrillation (NVAF) patients at risk for stroke. The AF diagnosis and all risk factors for stroke will be collected at baseline, so that compliance with the SmPC indication can be analysed.
- Compliance with SmPC Contraindications: To investigate if any contraindication is present, such as severe renal or hepatic impairment, impairment of hemostasis and contraindicated concomitant medications, the respective variables will be recorded at baseline.
- Compliance with SmPC Posology: All factors relevant for dose selection, such as age, concomitant drugs and renal function (by computing the creatinine clearance based on collected serum creatinine, if a blood test was performed) will be analysed.

Compliance with SmPC Warnings: The treatment will be recorded at the follow-up visit including interruptions for outcome events (including major bleeds), procedures and other events which necessitate treatment interruptions (e.g. major trauma). If known by the investigator, also information on bridging strategies will be collected.

The following definitions apply and should be used as a guide when reporting a thrombotic event:

Newly occurring stroke:

Stroke is an acute onset of a focal neurological deficit of presumed vascular origin lasting for 24 hours or more or resulting in death. Stroke is also diagnosed if an acute infarction can be shown on cerebral imaging independently of duration of neurological symptoms. The stroke is categorized as ischemic or hemorrhagic (based on CT or MR scanning or autopsy) or uncertain origin. Fatal stroke is defined as death from any cause within 30 days of stroke. Severity of stroke will be assessed by modified Rankin scale (see Table 12.1.4) at discharge from hospital and/or at follow-up. Furthermore new and old strokes will be diagnosed by CT/MRT scanning.

Newly occurring Transient ischemic attack (TIA):

TIA is defined as a transient episode of neurological dysfunction lasting <24h caused by focal brain, spinal cord, or retinal ischemia without acute infarction (3).

Systemic embolism:

Systemic embolism is defined as an acute vascular occlusion of the extremities or any organ (kidneys, mesenteric arteries, spleen, retina or grafts), typically documented by angiography, surgery, scintigraphy, or autopsy.

Pulmonary embolism:

The criteria for diagnosis of pulmonary embolism were a new intraluminal filling defect on spiral CT or pulmonary angiography, a cutoff of a vessel of more than 2.5 mm in diameter on pulmonary angiography, a new perfusion defect of at least 75% of a segment with corresponding normal ventilation (high probability), a new non–high-probability perfusion defect associated with deep-veinthrombosis, as documented by ultrasonography or venography. Fatal pulmonary embolism was based on objective diagnostic testing, autopsy, or death which could not be attributed to a documented cause and for which pulmonary embolism could not be ruled out (unexplained death).

Myocardial infarction (MI) (29):

The term acute myocardial infarction (MI) should be used when there is evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia. Under these conditions any one of the following criteria meets the diagnosis for MI:

- Detection of a rise and/or fall of cardiac biomarker values [preferably cardiac troponin (cTn)] with at least one value above the 99th percentile upper reference limit (URL) and with at least one of the following:
  - Symptoms of myocardial ischemia.
  - New or presumed new significant ST-segment–T wave (ST–T) changes or new left bundle branch block (LBBB).
  - Development of pathological Q waves in the ECG.
  - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.
  - Identification of an intracoronary thrombus by angiography or autopsy.
- Cardiac death with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurred before cardiac biomarkers were obtained, or before cardiac biomarker values would be increased.
- Percutaneous coronary intervention (PCI) related MI is arbitrarily defined by elevation of cTn values (>5 x 99th percentile URL) in patients with normal baseline values (≤99th percentile URL) or a rise of cTn values >20% if the baseline values are elevated and are stable or falling. In addition, either (i) symptoms suggestive of myocardial ischemia or (ii) new ischemic ECG changes or (iii) angiographic findings consistent with a procedural complication or (iv) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality are required.
- Stent thrombosis associated with MI when detected by coronary angiography or autopsy in the setting of myocardial ischemia and with a rise and/or fall of cardiac biomarker values with at least one value above the 99th percentile URL.
- Coronary artery bypass grafting (CABG) related MI is arbitrarily defined by elevation of cardiac biomarker values (>10 X 99th percentile URL) in patients with normal baseline cTn values (≤99th percentile URL). In addition, either (i) new pathological Q waves or new LBBB, or (ii) angiographic documented new graft or new native coronary artery occlusion, or (iii) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.

Criteria for prior myocardial infarction

Any one of the following criteria meets the diagnosis for prior MI:

- Pathological Q waves with or without symptoms in the absence of non-ischemic causes.
- Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.
- Pathological findings of a prior MI.

<u>Major bleeding, defined as meeting one or more of the following criteria (25, 15, 35):</u>

Major bleeding is defined as a bleeding event that meets at least one of the following criteria:

- fatal bleeding
- critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, intraarticular or intramuscular with compartment syndrome)
- clinically overt bleeding associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-treatment level

- clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells
- clinically overt bleeding that necessitates surgical intervention.

The description of the severity (i.e.: life threatening versus non-life threatening major bleed), localisation (i.e.: intracranial, gastrointestinal, etc.) and temporal pattern (i.e.: time-to-event analysis) is encouraged.

Gastrointestinal Bleedings:

The following criteria refer to gastrointestinal bleedings and should be reported if the severity of the bleeding has been assessed as major by the investigator:

- vomit containing frank blood or coffee ground material which tests positive for blood
- Endoscopically confirmed bleeding
- Frank blood per rectum or melena stools
  (Exception: Bleedings caused by haemorrhoids must not be reported)

Life-threatening bleedings

In order to describe bleeding severity, major bleedings may be further sub-classified as life threatening if they meet at least one of the following criteria:

- Fatal, symptomatic intracranial bleed (see below);
- Reduction in haemoglobin of at least 5 g/dL;
- Transfusion of at least 4 units of blood or packed cells;
- Associated with substantial hypotension requiring the use of intravenous inotropic agents; or
- Necessitating surgical intervention.
- All the remaining major bleeds may be considered as non-life threatening major bleeds.

Symptomatic intracranial bleeding

- New intracranial bleeding as evidenced on CCT or MRI with worsening of neurological symptoms
- Major intracranial bleedings (haemorrhagic stroke/intracerebral haemorrhage, subdural or epidural haematoma/haemorrhage, or subarachnoid haemorrhage) comprise an important part of all major bleedings reported in this indication, and are associated to a higher risk of death or disability than major extracranial bleedings. Therefore, major bleedings should also be described by localisation (e.g.: intracranial and extra-cranial, separately) and outcome (e.g.: resulting in death; resulting in disability; recovered without sequels).

Previous major bleedings:

All major bleedings a patient experienced before the index event (ischemic stroke or TIA) have to be recorded in the patient file. Here again a description of the severity, localisation and temporal pattern should be enquired.

Deaths

- will be classified as being: vascular (including bleeding); non-vascular, due to other specified causes (e.g., malignancy), or unknown cause, when cause is not known.

All strokes and major bleeding events will be adjudicated blinded by an independent Clinical Adjudication Committee (CAC). The CAC will consist of 2 Neurologists, 1 Cardiologist and 1 Neuroradiologist who will be, depending on the endpoint, selected for adjudication as needed. For this procedure the CAC members will receive anonymized data from the CRF and relevant source documents from the patient's medical record (cf. Section 10.2).

Complications during hospitalization

Every complication (like pneumonia, fall, catheter induced inflammatory reaction) or other unfavourable signs –independent from the causal relationship with AF, stroke or TIA will be reported.

Any complication occurring before date of study entry (=time of informed consent) will be reported retrospectively in the eCRF including severity assessment (slight, moderate, strong, life-threatening).

Any complication occurring at study entry or later will be reported as an adverse event including severity assessment.

Further Confounders

Additional definitions of important confounders can be found in Section 12.3.

6.2. SAFETY AND PHARMACOVIGILANCE

6.2.1. Endpoint(s) of safety

Please refer to safety related outcome events as described in Section 6.1.

6.2.2. Assessment of adverse events

6.2.2.1. Definitions of adverse events

Adverse Event (AE):

An adverse event ("AE") shall mean any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient or clinical investigation subject administered a pharmaceutical product. The medical occurrence does not necessarily have a causal relationship with the treatment. An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (Guideline on good Pharmacovigilance practice, Annex I Definitions) including an exacerbation of a pre-existing condition, during the PASS.

Any AE which occurred prior to the date of study entry (=Date of informed consent) will be reported retrospectively as complication. If the patient is incapable to consent, the date of consent will be assumed 7 days after index event at the latest. Only after study entry it is allowed to start the AE/SAE documentation in the eCRF and to report serious adverse events (SAE) to the University Hospital of Essen.

Serious Adverse Event (SAE):

A serious adverse event is defined as any AE which

- results in death,
- is life-threatening,
- results in persistent or significant disability or incapacity,
- requires in-patient hospitalization, or
- prolongation of existing hospitalization, or
- is a congenital anomaly/birth defect.

Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

The basis for judging the causal relationship between the product of interest and the adverse event is described below.

A (Serious) Adverse Event can be an outcome/endpoint but is not necessarily one. Nevertheless each (S)AE is to be reported if above mentioned criteria are fulfilled.

(Serious) Adverse Drug Reaction ((S)ADR):

If an adverse event has been deemed by the investigator to have a reasonable causal relationship with a drug, it is regarded as an adverse drug reaction.

Causality assessment:

The expression “Reasonable causal relationship” is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship. Medical judgment should be used to determine the causal relationship, considering all relevant factors, including pattern of reaction, temporal relationship, positive de-challenge or re-challenge and/or confounding factors such as concomitant medication, concomitant diseases and relevant history.

6.2.2.2. Serious Adverse Event and (Serious) Adverse Reaction reporting

After study entry i.e. after signing the informed consent or 7 days after index event at the latest until up to follow-up interview, all SAEs (cf. Section 6) are to be collected, documented, and reported within 24 h after awareness by the Investigator or Interviewer (Follow-up visit after 3 months) to the Drug Safety Department of the University of Essen. If an Outcome event is also an SAE both must be reported.

For patients who will not participate in the follow-up, only events that occur after study entry until discharge from the documenting hospital need to be reported.

The investigator or interviewer has the obligation to report any SAE. The "Report Form for SAEs" has to be used for reporting which can be found in the eCRF (printable pdf-form for the investigator) and additionally in the Investigator Site File (ISF). After this form is filled out it has to be faxed to the Drug Safety Department of the University Hospital of Essen within 24 hours of becoming aware of the event to the following number:

+49 (0) 201 723 947 4134

In addition the correlating AE has to be documented on the "Adverse Events" form with the notification that this AE was declared as SAE.

All SAEs continuing after the end of the study need to be followed up until the patient recovered or the event is sufficiently followed up.

With receipt of any further information on any SAE or SADR, a follow-up report has to be completed immediately.

Reporting of drug exposure during pregnancy:

In rare cases pregnancy might occur. Any pregnancy and the outcome of pregnancy will be reported on the 'Report of a pregnancy: Meldung einer Schwangerschaft' form which can be found only in the ISF.

APPROPRIATENESS OF MEASUREMENTS

The measures conducted within this study reflect the current real-world approach regarding clinical practice.

All sites will be trained for this trial. The Clinical Adjudication Committee (CAC) is responsible for the final assessment of strokes and major bleedings.

AE and SAE in the follow-up will be systematically requested by the interviewer.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Details of all analyses will be provided in the statistical and epidemiological analysis plan (SEAP).

7.1. STATISTICAL DESIGN AND MODEL

This prospective, multi-center observational study consists of a collection of baseline data for non-valvular AF patients with ischemic stroke or TIA and a 3 months central follow-up period only in patients who were treated with dabigatran, vitamin K-antagonists, antiplatelets only or no oral antithrombotic treatment at all.

Analysis of the primary endpoint will be based on the number of major bleeding events within 3 months of follow-up with respect to person-time under medication. For the analysis time-to-event methodology, namely Cox proportional-hazards models, will be used. As change of therapy is allowed during the observation period, each patient can contribute person-time to more than one treatment. As this is the case and risk for major bleeding is assumed to be higher at the beginning of the observation period than at the end, treatment will be included in the regression model as time-dependent variable, i.e., using counting process syntax, for example described in Powell and Bagnell (24). To account for possible confounders of major bleeding, either conventional multiple regression or propensity scores (either as a PS-matched or PS-adjusted analysis) will be used. For a list of variables used to calculate the propensity score, see Section 7.4.2.

7.2. NULL AND ALTERNATIVE HYPOTHESES

In this observational post-authorisation study, we do not have formal primary null and alternative hypotheses. The primary objective is to compare 3 months major bleeding risk following TIA or ischemic stroke in patients with non-valvular AF under early dabigatran (initiated within 7 days) treatment with risk under late dabigatran (initiated later than 7 days) treatment and under VKA treatment, respectively. A further objective is to compare recurrent stroke risks for selected antithrombotic treatments including patients treated with no oral antithrombotics.

7.3. CALCULATION OF STATISTICAL POWER

It is planned to recruit approximately 10.000 patients in the study and thereof approximately 6.000 patients with follow-up as shown in Figure 1.

The number of patients included and the duration of enrolment are not driven by a formal sample size calculation, but are primarily dependent on the availability of eligible patients treated with dabigatran and on the presence of channeling bias (confounding by indication).

Several possible scenarios for patient proportions and major bleeding risks within the first three months following the index event are presented in the following table. For example, comparing the group with early dabigatran admission (600 patients) and the late dabigatran group (1800 patients) and assuming major bleeding risks of 1% and 2% for the groups respectively, a statistical power of 93.2% is obtained for detecting a significant difference between the two groups.

Power calculation for different scenarios of patient proportions and major bleeding risks within the first three months following the index event

	Group 1 (dabigatran early)	Group 2 (dabigatran late)	Group 3 (VKA)	Group 4 (no anti-coagulation)	Power G1-G2	Power G1-G3	Power G2-G3
Proportion	10%	30%	40%	20%			
Group size (N)	600	1800	2400	1200			
Cumulative risk within 3 months (major bleeding)							
Scenario 1	2%	3%	4%	5%	63.9%	98.9%	78.0%
Scenario 2	1%	2%	3%	4%	93.2%	>99.9%	93.8%
Scenario 3	0,5%	1%	2%	3%	84.4%	>99.9%	>99.9%

	Group 1 (dabigatran early)	Group 2 (dabigatran late)	Group 3 (VKA)	Group 4 (no anti-coagulation)	Power G1-G2	Power G1-G3	Power G2-G3
Proportion	15%	25%	35%	25%			
Group size (N)	900	1500	2100	1500			
Cumulative risk within 3 months (major bleeding)							
Scenario 1	2%	3%	4%	5%	73.5%	99.8%	71.3%
Scenario 2	1%	2%	3%	4%	97.1%	>99.9%	89.7%
Scenario 3	0,5%	1%	2%	3%	91.3%	>99.9%	99.8%

	Group 1 (dabigatran early)	Group 2 (dabigatran late)	Group 3 (VKA)	Group 4 (no anti-coagulation)	Power G1-G2	Power G1-G3	Power G2-G3
Proportion	5%	35%	35%	25%			
Group size (N)	300	2100	2100	1500			
Cumulative risk within 3 months (major bleeding)							
Scenario 1	2%	3%	4%	5%	42.4%	88.3%	78.9%
Scenario 2	1%	2%	3%	4%	75.2%	99.3%	94.2%
Scenario 3	0,5%	1%	2%	3%	62.2%	99.8%	>99.9%

	Group 1 (dabigatran early)	Group 2 (dabigatran late)	Group 3 (VKA)	Group 4 (no anti-coagulation)	Power G1-G2	Power G1-G3	Power G2-G3
Proportion	5%	10%	50%	35%			
Group size (N)	300	600	3000	2100			
Cumulative risk within 3 months (major bleeding)							
Scenario 1	2%	3%	4%	5%	33.9%	89.5%	47.9%
Scenario 2	1%	2%	3%	4%	63.3%	99.4%	68.5%
Scenario 3	0,5%	1%	2%	3%	50.8%	99.9%	95.4%

7.4. PLANNED ANALYSES

Analyses will be performed by the statistician of the Institute of Medical Informatics, Biometry and Epidemiology (IMIBE) in Essen and by the Department of Neurology, University Hospital of Essen. A final analysis and a report will be prepared once the data collection is completed, the data are cleaned, and the database is locked.

The analysis population will consist of all eligible patients (i.e. all patients fulfilling the population description of the study) and the analysis will focus on the antithrombotic treatment choice for stroke prevention.

The primary endpoint, major bleeding event rate within 3 months following the index event, will be examined using the model specified in Section 7.1. The decision will be based on the hazard ratios of early dabigatran treatment (compared with late dabigatran treatment and with VKA) and its respective 95% Wald confidence limits. In addition, hazard functions for major bleeding under different treatments will be compared. Furthermore, time-dependent ROC curve analysis will be performed to determine the optimal time point for administration of dabigatran. For this analysis all person-times corresponding to dabigatran treatment will be considered.

The secondary endpoints will be analyzed with the same Cox proportional-hazards approach as the primary endpoint as long as they are time-to-event endpoints (see 6.1.1).

The model assumptions of the proportional hazards models will be visually checked by Schoenfeld residuals. Summary statistics for continuous variables will include the N, mean, standard deviation, minimum, Q1 (lower quartile), median, Q3 (upper quartile), and maximum value.

Tabulations of categorical variables will present all possible categories and will display the number of observations per category as well as percentages. All estimates will be presented with 95% confidence intervals.

All these analyses can be accompanied by p-values of suitable statistical tests. All p-values and confidence intervals but the p-value of the primary hypothesis are descriptive in nature and used for explorative purposes only.

Demographics and baseline characteristics of the population will be analyzed descriptively.

Estimates and confidence intervals for event rates (interpreted on a descriptive level) will be computed. 95% confidence intervals will be calculated for several outcome events. Therefore, it can be expected that false positive significant differences may arise, i.e., a treatment regimen cohort may appear by chance with a lower or a higher event rate for specific outcome events or for the composite endpoint variable; consequently, results have to be interpreted with care.

7.4.1. Secondary efficacy analyses

A) Patient characteristics influencing choice of antithrombotic treatment for stroke prevention at baseline

Demographics and baseline characteristics (including specifically stroke/bleeding risk scores ($CHADS_2$, CHA_2DS_2-VASc and HAS-BLED, see Appendix 12.1)) will be summarized descriptively for all eligible patients by antithrombotic treatment choice for stroke prevention at the baseline visit.

The antithrombotic treatment choice for secondary stroke prevention at discharge visit will be described.

Potential channeling bias between patients initiating dabigatran, other nOACs and VKA at discharge will be explored using comparisons of important baseline characteristics such as stroke or bleeding risk factors. A precise description can be found in the Statistical and Epidemiological Analysis Plan.

B) Important outcome events

Incidence rates and cumulative risks over time since initiation with 95%-confidence intervals for important outcome events (see Section 6.1) will be calculated within the different antithrombotic treatments and no treatment cohorts. The analysis will be based on all eligible patients initiating dabigatran or VKA for stroke prevention. Patients who discontinue dabigatran or VKA treatment for stroke prevention permanently or switch to a different treatment without experiencing the respective important outcome event will be censored at date of last drug intake.

In order to explore which factors potentially modify the effect of different antithrombotic treatments vs. no anticoagulation in terms of occurrence of important outcome events, the incidence rates for the dabigatran and VKA groups by subgroup variables will be calculated for at least the following subgroups: age, gender, CHADS2, CHA2DS2-VASc and HAS-BLED risk scores.

As a sensitivity analysis, incidence rates for important outcome by antithrombotic treatment will be calculated without censoring at permanent discontinuation of an antithrombotic treatment.

C) Analysis of composite endpoint of stroke, vascular death, MI, life-threatening bleeds

Incidence rates and cumulative risks with 95%-confidence intervals for the composite endpoint and for the individual components of the composite endpoint will be calculated. In addition these analyses will be done stratified by antithrombotic treatment for indication other than AF. This analysis will be repeated within subgroups. Subgroup variables are, e.g., age, gender, stroke and bleeding risk factors.

The analysis will be based on antithrombotic treatment choice prescribed for secondary prevention and all eligible patients. Patients who discontinue antithrombotic treatment for stroke prevention permanently or switch to a different treatment without experiencing one of the composite endpoint defining outcome events will be censored at date of last drug.

As a sensitivity analysis, incidence for the composite endpoint by antithrombotic treatment will be calculated without censoring at permanent discontinuation of an antithrombotic treatment

7.4.2. Potential for bias and confounding

Selection bias

Selection bias may occur on two different levels: The site level and the patient level. If sites where dabigatran is most used differ systematically with respect to patients or routine procedures from sites in which it is less used, the between-site difference would lead to non-comparability between dabigatran patients and others, even if no clinician accounted for patient characteristics in his or her decision to use the product.

Loss to follow up

All efforts will be made to minimize loss to follow up in patients with a pre-planned follow up (e.g. contact with family members, family doctor/treating physician, local citizen registry, legal representatives, geriatric nurses), particularly for the assessment of vital status.

Channeling bias (confounding by indication)

Channeling bias can occur due to preferential prescribing in relation to different risks for the events of interest, e.g., if dabigatran was more often prescribed to patients at higher risk of bleeding compared to other treatments, higher incidences of outcome events would then be expected in the dabigatran group. The potential for channeling bias will be controlled via including propensity scores in the respective regression model. In order to control for potential channeling, regular assessments will be conducted, i.e., patients initiating antithrombotic treatments will be assessed regarding the comparability of important patient baseline characteristics (e.g., age, sex, comorbidities, stroke and bleeding risk scores, concomitant medications). Further comparisons of other nOACs may be added. Details of the propensity score can be found at the end of this section. Furthermore, a subgroup analysis will be undertaken that compares patients with first-time strokes and patients with recurrent strokes.

Depletion of susceptibles and healthy user / adherence bias

Depletion of susceptibles occurs, when persons most at risk for an event suffer the event early on in therapy, so that cohorts ascertained later during therapy have a lower prevalence of such at risk patients. In the absence of a direct measure of susceptibility, depletion of susceptibles manifests itself as an apparently declining risk with the passage of time. Other common reasons for a risk that declines with time elapsed since initiation of therapy include metabolic adaptations that diminish the effect of the product (tachyphylaxis) and the prescriber's acquisition of skill in managing the drug for a particular patient. Whatever the origin, when the risk of an outcome varies over time especially when the risk is higher just after initiating therapy and declines thereafter, the comparison of prevalent users and incident (new) users will be biased, because long-time users will be less likely to manifest the outcome of interest. In addition, there is a potential healthy user / adherence bias, i.e. patients who use a drug or are adherent with treatment are more likely to be healthier in general (e.g. have other healthy behaviors) than patients who are non-user/non-adherent. The effects of changes in risk with time and adherence will be reduced through inclusion within 1 week after ischemic stroke or TIA. To account for time-varying risks, estimates of cumulative risks will be calculated. Due to the possibility that medication may change during the observation period, time-varying risks may bias medication effects if one treatment is, on average, initiated at a later point in time than another. To account for this, medication will be modeled as a time-dependent variable in the Cox regression, i.e., using the counting process syntax described in Powell and Bagnell (24) as mentioned at the beginning of this section.

Information and recall bias

Information bias can e.g. occur due to selective under-reporting of already established and known adverse effects for a known product (e.g. VKA) as compared to a new product (e.g. dabigatran), or vice versa. A standardized data collection form will be used for assessing exposure and AEs (see Section 6). Medical charts at hospital will also be reviewed by site staff and during CRA monitoring visits. These standardized procedures for data collection are intended to minimize such biases. Recall bias may be caused, e.g., if visits are separated by long time intervals and patients forget certain information (e.g., use of over-the-counter medications). It can be reduced by associating questions with specified time intervals (e.g. how often did you take this co-medication during the last 5 days?).

Confounding

The distribution of known prognostic factors for major bleeding events will be studied across therapeutic subgroups (e.g. early/late dabigatran, VKA) and factors that lack unequal distributions across subgroups will be adjusted for by either conventional multiple regression analysis or by propensity score analysis (either adjusted or matched). Propensity scores are superior to conventional multiple regression in terms of controlling for baseline covariates if and only if there are few events and a very large number of confounders. The following baseline information will be included in either case: previous major bleedings (intracranial or gastrointestinal), prior treatment with VKA and unstable INR, risk of tripping/falling, renal and/or liver insufficiency, age, treatment with thrombolysis or thrombectomy for index event and treatment with valproate.

7.4.3. Treatment related analyses

A) Drug utilisation (i.e. treatment compliance and persistence)

Characteristics of the drug exposure and utilization will be analysed descriptively for patients receiving antithrombotic therapies. This includes choice of dosage (for selected treatment regimens

only), treatment persistence in terms of duration of therapy and compliance in terms of accordance with the prescribed medication regimen.

B) Investigator compliance with the SmPC

Compliance with the antithrombotic treatment SmPC with regards to indication, posology, contraindications and warnings will be evaluated by conducting the following analyses:

- Percentage and characterization (if feasible based on patient number) of dabigatran and VKA initiators outside the SmPC indication,
- Percentage and characterization (if feasible based on patient number) of dabigatran and VKA initiators with contraindications (overall and per contraindication captured),
- Percentage and characterization of dabigatran and VKA initiators with relevant co-medications that should be used with caution,
- Percentage and characterization (if feasible based on patient number) of dabigatran and VKA initiators without assessment of renal function (no Serum Creatinine Concentration reported) or liver function prior to treatment initiation,
- Percentage and characterization (if feasible based on patient number) of dabigatran initiators receiving dose which are not recommended according to SmPC,
- Percentage and characterization (if feasible based on patient number) of dabigatran initiators receiving 150 mg BID although 110 mg BID is recommended according to SmPC (e.g. patients > 80 years or patients with high bleeding risk),
- Percentage and characterization (if feasible based on patient number) of dabigatran and VKA initiators without an interruption of dabigatran due to outcome events (including major bleeds), procedures and other events which necessitate treatment interruptions (e.g. major trauma).

These analyses will be based on the treatment choice; therefore only eligible patients receiving dabigatran and VKA treatment for secondary prevention at the starting point of treatment will be included.

C) Treatment strategies in patients with important outcome events

The number and percentage of patients switching their antithrombotic treatment for stroke prevention for the first, second, third time and so on will be calculated based on the subgroup of the eligible patients who experience an important outcome event under their antithrombotic treatment regimen. The number and percentage of patients discontinuing their treatment will be broken down by subsequent treatment choice. This analysis will be performed overall and by current antithrombotic treatment for stroke prevention.

Additionally, analysis of site characteristics will be performed; demographics and patients` baseline characteristics will be summarized by further subgroup variables. Additional analyses including the analysis of possible further outcomes or of further subgroups may be performed based on new information that might become available during the course of the study and based on results obtained by the described analyses. These analyses will be described in the SEAP.

7.4.4. Safety analyses

The safety analyses will include all patients enrolled with planned follow up (i.e. only patients who were discharged with dabigatran, vitamin K-antagonists, antiplatelets only, or no oral antithrombotic treatment at all). Statistical analysis and reporting of ADRs will be descriptive in nature. No hypothesis testing is planned.

Occurrences of ADRs will be analyzed relative to the number of patients treated and additionally relative to observed patient-years (i.e. time at risk). The safety analysis will be based on the concept of treatment emergent adverse events. Patients will be analyzed according to the antithrombotic treatment for stroke prevention they have received at the time of the event. Adverse events that deteriorate under treatment will also be considered as 'treatment emergent'. The safety analyses will include the following parameters:

- AE
- ADRs (related to antithrombotic therapy for stroke prevention)
- AE leading to discontinuation of antithrombotic treatment
- SAEs
- SARs (related to any antithrombotic therapy for stroke prevention)
- Deaths

Systematic follow-up of vital signs and laboratory parameters is not planned.

7.4.5. Continuous Safety Monitoring

Analysis of safety parameters will be performed during the conduct of the study on a regular basis. If periodic reports on drugs are required, they will be sent to the competent authority and the leading ethics committee.

7.4.6. Interim analyses

There are no interim analyses planned in this study.

7.5. HANDLING OF MISSING DATA

In order to assess the effects of loss to follow-up, patients, percentages of dropouts and reason for loss to follow-up will be summarized in patients with a pre-planned follow up (such as patients initiating defined antithrombotic treatments or no anticoagulation). In addition baseline characteristics of patients who were lost to follow-up in comparison to patients with a complete follow-up will be described.

Any reasonable attempt will be undertaken to ensure completeness of data collection in this study (see also Section 9.4). Imputation might be performed dependent on amount and distribution of missing values.

7.6. RANDOMISATION

Not applicable.

8. DATA PROTECTION

The European General Data Protection Regulation (GDPR) (EU)2016/679, as effective from 25th May 2018, which has replaced the European Data Protection Directive 95/46/EC, and is legally binding immediately in every European member state, forms the legal background for the protection of individuals with regard to the processing of personal data and on the free movement of such data in the European Union. Especially in Germany, the informational self-determination is regarded as a basic right, which has to be considered in the context of data collection, transmission, evaluation and storing. Generally, the handling of personal data is only allowed after the person concerned has been properly informed about all aspects of the data collection and has given his/her written consent, Art. 6 (1) a) GDPR (cf. Fig. 2). But there are also other justifications for the legality of data processing in the GDPR, Art. 6 (1) b) – f).

For all stroke units, where patients are treated in the context of the PRODAST study, it can be proven that data collection is done in order to fulfill a specific research purpose by carefully describing the scientific question to be answered answer and the purpose for data evaluation. Generally, a medical research project, that observes the safety aspects of medicinal products, will be of potential necessity for public interest. Above all, scientific research must be an independent process free from external influence, but is not hindered to be financed by third-party funding. Data that has originally been collected by the general practitioners, hospitals or health care facilities for the purpose of therapy, will be transmitted and evaluated for another purpose, namely scientific research. This is allowed, in cases where the scientific interest for performing the research project prevails the interest of the patient for keeping the purpose limited to therapy. Additionally, it needs to be shown, that the research purpose cannot be fulfilled at all or only with disproportional effort in another way.

In PRODAST, the research purpose can only be fulfilled by also using data of participants who cannot consent themselves or when informed consent is given by a legal representative. The necessity can be shown in a relation of expenditure of time, costs and manpower to the value of the data. In PRODAST, most stroke patients will be at least temporarily incapable of giving an informed consent and might not have a legal representative (appointed by court) or proxy agent, but their data is extremely necessary for the evidence of the study. If the PRODAST study would only be performed with data of patients having the full legal capacity to consent to data transmission, there might be a lack of evidence for the whole study. A careful description of the research purpose and its scientific value will enable justification of the transmission of additional data from sources outside of stroke units. Only this might outweigh the high-ranking right of the patients to informational self-determination.

At the same time, all possible measures to reduce data volume and personal reference will be taken. Commercial reasons for research are suspended. The use of personal data has a high potential of disadvantages for the person concerned depending on the research purpose and the number of persons involved in the data processing, which might increase the risk of unauthorized access. In order to protect the data of patients, strict rules for the technical and organizational handling of the data, especially pseudonymization, will be put in place. As in the PRODAST study re-identification is important for re-contacting the study participants in the follow-up phase, anonymization of the data would be inefficient. As, on the other hand, pseudonymization allows the allocation of personal references and medical data, only a special user group responsible for the data monitoring in the PRODAST study at the University Hospital Essen shall have knowledge of this correlation. Subject to a special data protection concept is the separated storage of personal reference and medical data in different databases. The data which identifies the study participants (IDAT) will only be used to approach the participants for the telephone interview during the follow-up phase. The medical data (MDAT) collected during hospital stay and follow-up phase will be stored in a separate database as pseudonymized data by using a patient identification number (PAT-ID).

Special caution has to be exercised in cases of data transmission from other sources like general practitioners, hospitals or health care facilities, as it is planned in the PRODAST study in the phase of central follow-up. There are two general principles in data protection law, which have to be followed with the exception of special circumstances: Generally, the data shall be collected under participation and with knowledge of the person concerned. Therefore, the patient interview shall take precedence over the data submission from other sources. In the case of a patient, who is permanently incapable of giving consent and data collection in direct contact with the patient would be impossible, it could be regarded as an exceptional circumstance under which data transmission from other sources would be possible. It is important to assure that predominant interests of the patient will not be harmed.

The second principle points to purpose limitation of data collection, transmission and evaluation: If an entity of the public sector, e.g. the University Hospital Essen, asks for transmission of data from another source, this entity has to prove the legitimacy of data transmission. In this context, medical confidentiality (as stated in § 203 (1) No. 1 of the German Penal Code, StGB) is an important point to consider: In principle, a patient has to release his medical practitioner from confidentiality before medical data may be submitted. An exception can be made, as the University Hospital Essen is able to prove that it is also legally bound to keep all data confidential by performance of its duties as a research institution, according to § 203 (2) No. 6 StGB (German Penal Code).

Specifications about the patient information and the informed consent, especially for above mentioned exceptional cases, are described in Sections 9.1 and 12.5.

A detailed description of the legal background regarding data protection can be found in Section 12.4.

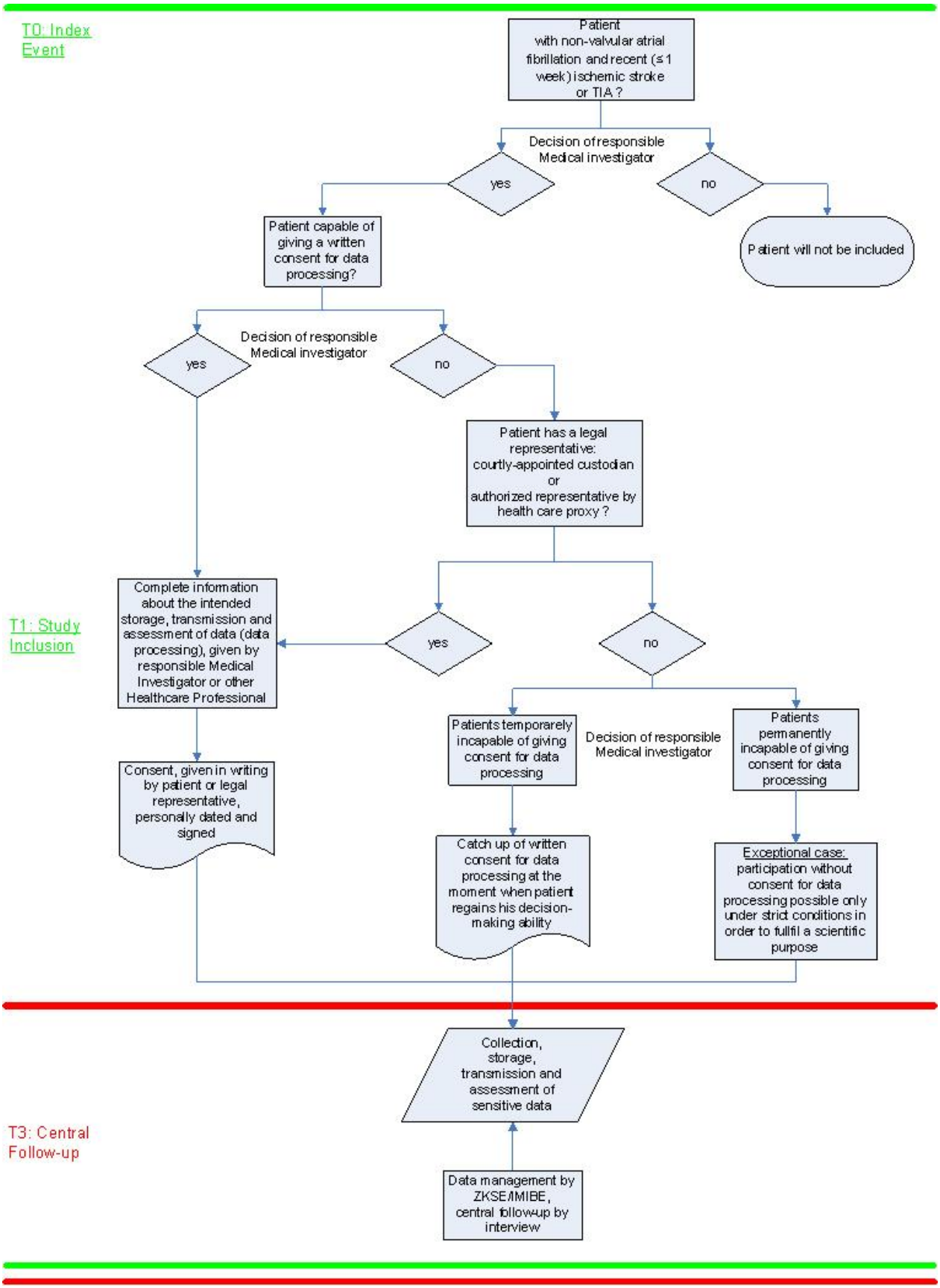

Fig. 2: Illustration of the context of data protection and informed consent with regard to the inclusion of patients found eligible and willing to participate in the PRODAST study. The exceptional case for patients who die before informed consent is given personally is described in chapter12.5.3.

As a general rule, it shall be forbidden to process special categories of data, e.g. health data, Art. 9 (1) GDPR. An exemption can be made, e.g. in cases of an informed consent given by the affected person, Art 9 (2) a) GDPR. Another important exemption in data protection law in the field of medical and scientific research is offered by Art. 9 (2) j) GDPR. This example for the possibility to use data without the prior informed consent of the affected person is shown in Fig. 2. . It is especially important in order to allow the participation of patients who are incapable to give consent due to a medical condition (e.g. stroke) which is to be studied in the research project. Within the different types of research projects, a non-interventional study which aims to observe the routine use of medicinal products has to be regarded differently from a clinical study with a medicinal product in consideration of vital interests of the study participants. According to Art. 9 (2) j) GDPR, the processing of personal data, e.g. concerning health, shall be allowed in cases where it is necessary for reasons of scientific research purposes and if the data processing is proportionate in relation to the targeted goal, the person's rights regarding data protection are preserved and appropriate and specific measures are taken in order to protect the basic rights and interests of the affected person. More details regarding guarantees and exemptions for the data processing for scientific research purposes can be found in Art. 89 GDPR. Recital No. 156 of the Directive points out that important reasons of public interest, that justify the derogation from the prohibition on processing sensitive categories of data, can be seen in areas such as public health and scientific research.

A detailed description of the legal background regarding data protection can be found in Section 12.4.

Specifications about the patient information and the informed consent, especially for above mentioned exceptional cases, are described in Section 9 and Section 12.5.

9. INFORMED CONSENT, STUDY RECORDS

9.1. STUDY APPROVAL AND INFORMED CONSENT

According to the legal requirements of § 67 (6) of the German Medicine Act, a notification will be send to the competent authority (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM), "Kassenärztliche Bundesvereinigung", „Spitzenverband Bund der Krankenkassen" and „Verband der Privaten Krankenversicherung e.V." with the start of the PRODAST study. The Director of Investigation will provide the competent authority with the PRODAST protocol and progress reports when requested. Also a favourable vote of the leading IEC will be requested prior initiation of this study. Although, according to German law, a favourable vote of an IEC is not mandatory for the performance of non-interventional, observational studies, the prior consultation of an Ethics Committee is recommended by the German competent authorities (BfArM, PEI) in order to avoid conflicting interests concerning data protection, patient protection, protection and liability of medical personnel and interests of the Director of Investigation. Furthermore, most of the Medical Association's Professional Codes of Conduct in the German federal states indicate a consultation of an IEC as a requirement for all research projects, including epidemiological studies, especially concerning patient protection, protection of informational self-determination and risk-benefit balance.

Prior to patient participation in the PRODAST study, written informed consent for collection, transmission, evaluation and storing of sensitive personal data must be obtained from each patient (or the patient's legal representative) according to the regulatory and legal requirements of the participating country. The patient should be given appropriate time to consider if he/she accepts to participate in the PRODAST study. In exceptional cases and under strict conditions, national regulations might allow the participation of patients without written informed consent (for details

see Sections 8 and 12.5). In this case the investigator must sign and date on special informed consent forms that the patient is incapable.

Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study.

A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legal representative.

Furthermore the patients must be informed that the study-related data/information obtained within the framework of this study will be recorded and forwarded without disclosing any names (pseudonymized) to the Centre for Clinical Trials in Essen (ZKSE).

Patients must also be informed that a delegated and authorized person such as a monitor (Clinical Research Associate, CRA) or auditor, who is obliged to secrecy, and the competent national and international supervisory and regulatory authorities may review the personal medical records kept by the investigator.

9.2. INSPECTIONS / AUDITS

A quality assurance audit of the PRODAST study may be conducted by an IEC or the Director of Investigation of the study or his designees. The quality assurance auditor must be provided access to all medical records, the investigator's study-related files and correspondence, and the informed consent documentation that is relevant to this study.

9.3. STUDY RECORDS AND REPORTING

All of the clinical data and site/investigator characteristics will be captured in electronic Case Report Forms (eCRFs) using a web-based electronic data capture (EDC) system with secure access features (username, password and secure identification – an electronic password system). The software will comply with GCP and international standards for capturing study data.

The data will be entered into the eCRF online via internet by the central follow-up staff and the responsible investigator at the study site soon after measurement. Entering data may be delegated to members of the site's study team. The eCRF has to be signed electronically by the investigator to confirm the correctness of captured data.

Data entry into the eCRF is allowed only after informed consent.

All data in the eCRF will be identified only by a patient identification number (patient ID) allocated from informed consent. The date of birth shall be documented in the eCRF only by year, not the day or month. The investigator stores a separate confidential record of these details in the investigator site file (ISF) to permit identification of all patients enrolled in the study.

Name and contact details of patients and their family doctors/treating physicians will further be stored in a separate database, with secure access only by people who perform the central follow-up. For this a copy with the required details from the informed consent will be faxed to the central office in Essen.

The investigator will be responsible for retaining all records pertaining to the study as specified in the appropriate contract.

9.3.1. Source documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. A template to support source data documentation is available in the ISF. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available. For the eCRFs all data must be derived from source documents.

9.3.2. Direct access to source data and documents

The investigator / institution will permit study-related monitoring and audits providing direct access to all related source data / documents. CRFs and all source documents, including progress notes and medical test results must be available at all times for review by the Director of Investigation and his designee(s) and auditors. The Clinical Research Associate (CRA) / auditor may review all CRFs and signed informed consent forms. The accuracy of the data will be verified by reviewing the documents described in Section 9.3.1 and in the Monitoring Plan.

9.4. DATA MANAGEMENT / CENTRAL MONITORING

A data management plan (DMP) will be created to describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will be reviewed if data is missing, out of range, inconsistent or potentially erroneous. For this, simple checks such as range validation, date inconsistency or presence/absence of data, or complex cross-form verifications such as date deviations across visits will be carried out. Many plausibility checks are run automatically during data entry in the eCRF, thereby detecting many discrepancies immediately. The CRA and data management will conduct further manual checks for completeness and plausibility and will clarify any questions with the study sites electronically via the EDC software and these queries are followed up for resolution. A responsible investigator will be obliged to either correct the implausible data or to confirm its authenticity and to give appropriate explanations.

Further in depth checks for plausibility, consistency and completeness of the data will be performed after completion of the study. If no further corrections are to be made, the database will be declared closed and be used for the statistical analysis.

Further details will be described in the Monitoring Plan and DMP.

MedDRA (Medical Dictionary for Drug Regulatory Activities) will be used for coding of AEs and SAEs, diseases (medical history and concomitant diseases) and concomitant therapies will be coded using the ATC classification system.

A source data quality audit may be initiated to ensure that the data recorded in the database are accurate. Source data verification (SDV) will be performed at sites identified by a risk-based approach outlined in the monitoring plan.

9.4.1. Storage and archiving of data and study-related documents

The eCRF database uses an automatic data backup system.

All study-related documents and pseudonymized data will be deleted 10 years after study closure. Study sites are also obliged to archive all study-related data.

Personal contact information of participating patients, stored in separate database, will be permanently deleted within 3 months after the last study related assessment.

9.5. STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient confidentiality will be ensured by using patient identification code numbers and a specific patient's ID-list. Only the staff of the centre conducting the central follow-up has further access to the patient's contact details via a secured database. Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians, by the Institutional Review Board / IEC competent health authorities and the Director of Investigation and/or its representatives and/or designees.

The data collected in the eCRFs will be transferred to the database via the Internet through secure web-sites. Details are described in the ISF and the DMP.

9.6. COMPLETION OF STUDY

A report will be sent to the competent authority in Germany according to legal requirements within one year after the end or early termination of the study.

9.7. PUBLICATION POLICY

It is the joint task of the Operations and the Steering Committee to facilitate publications and/or presentations of data from this study. Authorship will be determined jointly by the SC, the Director of Investigation and ZKSE / ZKE / IMIBE. The rights of the Operations Committee, of the Investigators and of the Director of Investigation with regards to publication of the result of this study are described in the individual contracts and in the SC and OC charters. Any publication of this study though must be guided by the current version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors (ICMJE).

10.STUDY ADMINISTRATION

All persons responsible for the study are listed in the investigator site file including name, address, phone and email.
In order to monitor specific aspects of the current study, the following Reference Committees will be established: Steering Committee (SC), Operations Committee (OC) and a Clinical Adjudication Committee (CAC). The work of these committees will be based on the 'Guideline on Data Monitoring Committees' EMEA/CHMP/EWP/5872/03.

10.1. STEERING COMMITTEE (SC) AND OPERATIONS COMMITTEE (OC)

A Steering Committee (SC) will provide scientific leadership for the planning and conduct of all phases of the study. It will be composed of experts in neurology and epidemiology with one Chair and Co-Chair. A charter describing the tasks and responsibility of the committee will be developed. Membership in the Steering Committee may change over time for various reasons. The SC will meet regularly, based upon the volume of work. Meetings will generally be by teleconference or web-conference. Face-to-face meetings may occasionally be held if there is a necessity.

An Operations Committee (OC) consisting of a Boehringer Ingelheim (BI) representative, a statistician, as well as the study coordinators in Essen will monitor the study preparation and will report the study progress to the SC.

10.2. CLINICAL ADJUDICATION COMMITTEE (CAC)

A blinded (without information about the stroke prevention) Clinical Adjudication Committee will confirm all strokes and major bleeding events and it will make the final decision on whether a patient had any of these events. For this purpose the eCRF and, if necessary, additional information of the patient concerned will be examined by the members of this committee. The committee can also request additional ancillary information from an individual study investigator to assist their review. The CAC will also confirm the type (e.g. ischemic, hemorrhagic) and localization of each stroke or cause of death.

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12. APPENDICES

12.1. SCORES FOR AF PATIENTS

Data collected at the baseline visit will be used to generate the following scores for use in the respective analysis:

Table 12.1.1: $CHADS_2$ Stroke Risk Score

CHADS2 components	**Points**
Congestive heart failure	1
Hypertension	1
Age 75 years or older	1
Diabetes mellitus	1
Prior cerebral ischemia (i.e., stroke, TIA)	2
Maximum score	**6**

$CHADS_2$ score is based on a point system in which 2 points are assigned for a history of stroke or transient ischemic attack and 1 point each is assigned for age 75 years or older, hypertension, diabetes, or clinical heart failure or impaired left ventricular systolic function (generally interpreted as an ejection fraction $\leq 40\%$). A $CHADS_2$ score of 0 identifies patients at low stroke risk, a score of 1 to 2 identifies patients at moderate stroke risk, and a score greater than 2 identifies patients at high stroke risk (5).

Table 12.1.2: CHA_2DS_2-VASc Stroke Risk Score

$CHA_2DS_2VAS_c$ score	
Risk factors for stroke and thrombo-embolism in non-valvular AF	
Major risk factors	**Clinically relevant non-major risk factors**
Previous stroke, TIA, or systemic embolism Age ≥ 75 years	Heart failure or moderate to severe LV systolic dysfunction (e.g. LV Ejection Fraction ≤40 %) Hypertension - Diabetes mellitus Female sex - Age 65-74 years Vascular disease
Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VAS_c (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/systemic embolism	2
Vascular disease*	1
Age 65-74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

* myocardial infarction, complex aortic plaque and Peripheral Artery Disease (PAD)

The CHA_2DS_2-VASc risk score is based on a point system in which 2 points are assigned for a history of stroke or TIA, or age ≥75; and 1 point each is assigned for age 65–74 years, a hypertension, diabetes, cardiac failure, vascular disease and female sex. On the basis of the risk strata defined in previous guidelines, a CHA_2DS_2-VASc score of 0 corresponds to "low risk", a score of 1 corresponds to "intermediate risk", and a score of 2 or more corresponds to "high risk" (16).

Table 12.1.3: HAS-BLED Bleeding Risk SCORE

Clinical characteristics comprising the HAS-BLED bleeding risk score		
Letter	**Clinical characteristic**	**Points awarded**
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
Maximum score		**9**

Hypertension is defined as systolic blood pressure >160 mmHg. 'Abnormal renal function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 μmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g. <60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. If a patient is not on VKA the value for 'labile INRs' will not be assessed. Further details will be given in the SEAP.

A HAS-BLED score of ≥3 indicates 'high risk' for AF patients to develop a bleed and some caution and regular review of the patient is needed following the initiation of antithrombotic therapy, whether with VKA or aspirin (22).

Table 12.1.4: Modified Rankin Scale (mRS)
Definition of disabling stroke by modified Rankin Scale:

Grade 0: no symptoms at all

Grade 1: no significant disability despite symptoms;
able to carry out all usual duties and activities

Grade 2: slight disability:
unable to carry out all previous activities but able to look after own affairs without assistance

Grade 3: moderate disability:
requiring some help but able to walk without assistance

Grade 4: moderate severe disability:
unable to walk without assistance and unable to attend to own bodily needs without assistance

Grade 5: severe disability:
bedridden, incontinent, and requiring constant nursing care and attention.

Grade 6: dead

Table 12.1.5: National Institutes of Health Stroke Scale (NIH-SS)

NATIONAL INSTITUTES OF HEALTH STROKE SCALE (NIHSS)

ITEM	SCORE
Level of consciousness	
Alert	0 points
Drowsy	1 point
Stupor	2 points
Coma	3 points
Response to 2 questions (orientation)	
Know age and current month	0 points
Answers 1 question correctly	1 point
Cannot answer either question correctly	2 points
Response to 2 commands	
Follows 2 commands correctly	0 points
Follows 1 command	1 point
Cannot follow either command	2 points
Best gaze (movement of eyes to left or right)	
Normal eye movements	0 points
Partial gaze paresis to one side	1 point
Forced gaze palsy to one side	2 points
Visual fields	
No visual loss	0 points
Partial homonymous hemianopia	1 point
Complete homonymous hemianopia	2 points
Bilateral visual loss	3 points
Facial motor function	
No facial weakness	0 points
Minor unilateral facial weakness	1 point
Partial unilateral facial weakness	2 points
Complete paralysis of 1 or both sides	3 points
Upper-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of upper extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Lower-extremity motor function (right and left scored independently 0 – 8 points)	
Normal movement	0 points
Drift of lower extremity	1 point
Some effort against gravity	2 points
No effort against gravity but moves	3 points
No movement	4 points
Limb ataxia (cannot be tested in presence of paresis)	
No limb ataxia	0 points
Ataxia present in 1 limb	1 point
Ataxia present in 2 limbs	2 points
Sensory function	
No sensory loss	0 points
Mild-to-moderate sensory loss	1 point
Severe-to-total sensory loss	2 points
Language	
Normal language	0 points
Mild-to-moderate aphasia	1 point
Severe aphasia	2 points
Mute	3 points
Articulation	
Normal articulation	0 points
Mild-to-moderate dysarthria	1 point
Severe dysarthria	2 points
Extinction or inattention (neglect)	
No neglect or extinction	0 points
Visual or sensory inattention or extinction	1 point
Profound inattention to visual and sensation	2 points

12.2. CREATININE CLEARANCE

The serum creatinine clearance will be calculated according to Cockroft-Gault:

$$Cl_{cr}\ (ml/min) = \frac{(140 - age) * weight\ (kg) * GF}{72 * Scr\ (mg/dL)}$$

Cl_{cr} = Creatinine clearance

$S_{cr}Cr_s$ = Serum creatinine

(when serum creatinine is given in µmol/L, divide the value by 88.4)

GF = Gender correction factor (0.85 for women and 1.00 for men)

12.3. CONFOUNDERS

Specific definitions for the assessment of outcome measures and important confounders are described in Section 6.1.2. A few additional definitions of confounders are presented below. More details regarding confounding can be found in Section 7.4.2.

Prior treatment with VKA and unstable INR:

It is important to know if a patient was treated with VKA in the past (VKA-experienced patient) or not (VKA- naïve patients). Whatever condition is present it should be recorded in the CRF. Furthermore it should be known if the INR was stable in VKA patients or not by checking if the INR was in the recommended therapeutic range as indicated in the SmPC for the VKA (cf. German SmPC :"Fachinformation: Marcumar MEDA Pharma").
The information of prior treatment with VKA may contribute to the choice of future anticoagulation compared to patients who never have been treated with a VKA (VKA-naïve patients). Furthermore a Danish study had shown that the adjusted risk of thromboembolism was higher among users of dabigatran as compared to warfarin, although when stratified by previous use of VKA, the increased risk of thromboembolism was only seen among previous VKA users (for both 110 and 150 mg). The adjusted risk of bleeding was increased among patients treated with dabigatran (110 mg) as compared to warfarin, which only persisted in previous users of VKA after stratification. Bleeding risk was increased in previous VKA users receiving dabigatran 110 mg, but not in patients with 150 mg dabigatran, nor in the VKA naïve users (28).

Age:

According to the AFFIRM trial the risk of major bleeding increases by 5% per year of age in elderly patients when comparing 70-74 year old patients with >85 year old ones.

Moreover renal function is reduced with aging (17) and renal insufficiency is connected with a higher risk for bleeding. Renal function testing is therefore necessary in elderly patients and treatment with dabigatran should be adjusted in these patients (s. BfArM "Hinweise zum Umgang mit Blutungen unter Dabigatran (Pradaxa®)").

Furthermore it is also very important to know the exact age of each patient because it will contribute in the determination of different scores as the Stroke Risk and Major Bleeding Scores (CHADS2, CHA2DS2-VASc, HAS-BLED, cf. Section 12.1 et seqq.).

In addition patients of older age can be affected of a higher risk of tripping or falling (see below). The tendency of tripping or falling can be higher in elderly patients but there is no scientific evidence that it can influence the choice of medication especially for patients with atrial fibrillation indicated for treatment with anticoagulants.

Concomitant Medication:

Concomitant medications are known to have adverse effects in combination with anticoagulants (see below). It is therefore very important to record the patients' concomitant medication but also his medical history. Therefore all concomitant medication will be recorded at discharge. After discharge concomitant medication will be only recorded for patients experiencing a serious adverse event or outcome event. In the following are some examples of adverse effects described for specific drugs/agents in combination with anticoagulants:

- Antiplatelet drugs:

VKAs combined with e.g. ASS have a higher risk for major bleeding (11) especially for upper gastro-intestinal bleeding in combined VKA and ASS/Clopidogrel therapy (10, 27).

- Non-steroidal anti-inflammatory drugs (NSAIDs):

  NSAIDs are associated with a higher risk of gastro-intestinal bleedings. In combination with VKAs this risk is increased 11-fold (18, 1).

- Valproate:

  Valproate (or valproic acid) is used (among other things) as an anti-epileptic drug. Important to know is that valproate has an anticoagulant effect and moreover is known to interact with the VKA warfarin by displacing it from the protein binding sites resulting in significant INR changes (33).

Comorbidities: Chronic kidney disease and chronic liver insufficiency

Chronic kidney disease and chronic liver insufficiency are known to increase significantly the risk of bleeding (14). Therefore it is important to know the renal and hepatic condition of all patients not only for the bleeding risk issue but also because drugs as e.g. anticoagulants are specifically eliminated by the liver and/or the kidney. So impairment of the kidney and/or liver can cause heterogeneous side effects.

- Definition of Chronic Kidney Disease (CKD):

  CKD is defined as abnormalities of kidney structure or function, present for > 3 months, with implications for health and CKD is classified based on cause and GFR category. The glomerular filtration rate (GFR) is the flow rate of fluid filtered by the kidney and can be determined by calculating the creatinine clearance using the Cockroft-Gault formula. A GFR of <30 ml/min is an indicator for an insufficient kidney function which is important to know because treatment with dabigatran is contraindicated in patients with a GFR of < 30 ml/min. For more details please check “The Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease” (40).

- Definition of Chronic liver insufficiency:

  Abnormal liver function is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin > 2x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/ alkaline phosphatase >3x upper limit normal, and so forth) (22). A treatment with dabigatran or vitamin K-antagonists is contraindicated in patients with chronic liver insufficiency.

12.4. LEGAL BACKGROUND: DATA PROTECTION

Legal Background

The Data Protection Directive 95/46/EC has been repealed by European General Data Protection Regulation (GDPR) (EU) 2016/679 , as of 27th April 2016, which has already entered into force and is effective in all EU Member States from 25th May 2018.

Generally, the processing of personal data, e.g. concerning health, shall be prohibited according to Art. 9 (1), with given exemptions such as Art. 9 (2) j, in cases where processing is necessary for scientific research. The data processing shall be allowed if it is proportionate in relation to the targeted goal, the person's rights regarding data protection are preserved and appropriate and specific measures are taken in order to protect the basic rights and interests of the affected person. Recital No. 53 points out that the processing of personal data for health related reasons may be performed if it is necessary in the interest of single natural persons or of the society as a whole. This is relevant especially for scientific research purposes, relying on legal provisions of the EU or a European member state, which serve as a goal of public interest and for studies which are performed in the public interest in the field of public health.

The Regulation clarifies that personal data may be processed for scientific research purposes and, according to Art. 89 (2), Union or Member State law may provide for derogations from the subjects' rights referred to in Art. 15, 16, 18 and 21 – rights for access, rectification, restriction of processing and objection – in so far as such rights are likely to render impossible or seriously impair the achievement of the research purposes. The processing of personal data for scientific research purposes, according to recital No. 156, can be interpreted in a broad manner including studies conducted in the public interest in the area of public health, also privately funded. To meet the specificities of processing personal data for scientific research purposes, specific conditions, regarding publication or otherwise disclosure of personal data, shall be applied. Safeguards for the rights and freedoms of the persons affected, such as technical and organisational measures, including pseudonymisation, ensure respect for the principle of data minimization, Art. 89 (2).

Generally, the handling of personal data is only allowed after the person concerned has been properly informed about all aspects of the data collection and has given his/her written consent, Art. 6 (1) a) GDPR, or another justifications for the legality of data processing in the GDPR must be applicable, Art. 6 (1) b) – f). According to recital No. 50, the processing of personal data for purposes other than those for which the personal data were initially collected should be allowed only where the processing is compatible with the purposes for which the personal data were initially collected. In particular, processing for scientific purposes will be considered to be compatible lawful processing operations, as specified in Art. 5 (1) a). In such cases, no legal basis different from that which allowed the collection of the personal data shall be required. This applies especially for data which has been collected during routine examinations as part of the patient record and which is intended to be assessed retrospectively. The principles of data protection shall apply for all information relating to identified or identifiable individuals, according to recital No. 26. This also applies to pseudonymized personal data, but not to anonymized information.

As accompanying Member State law, Germany has prepared a completely new version of the German Data Protection Law (GDPL), which has also become effective on 25th May 2018.

According to § 27 (1) GDPL, the processing of certain categories of personal data, e.g. health data, is possible for scientific research purposes without prior consent of the subject concerned, provided that the processing is required to fulfill this purpose and if the interest of

the responsible person regarding the processing substantially prevails the interest of the affected person to suspend the data processing. In order to make use of the privilege for research purposes, a reasonable weighing of interests needs to be performed and justified. For the data processing, § 27 (1) assumes that a legal basis according to Art. 6 GDPR exists, e.g. Art. 6 (1) f): legitimate interest of the responsible person (necessity), as long as no prevailing fundamental right or freedom of the affected person regarding protection of personal data exists. Additionally, the responsible person must foresee appropriate and specific measurements for the protection of interests of the affected person. Examples for those measurements can be found in Art. 22 (2) 2, No. 1 to 10 GDPR, including pseudonymization, encryption etc. Those exceptions are especially important in the field of medical and scientific research in order to allow the participation of patients who are incapable to give consent due to a medical condition (e.g. stroke) which is to be studied in the research project. Within the different types of research projects, a non-interventional study which aims to observe the routine use of medicinal products has to be regarded differently from a clinical study with a medicinal product in consideration of vital interests of the study participants.

Like Art. 89 (2) GDPR, § 27 (2) GDPL points out that the subjects' rights referred to in Art. 15, 16, 18 and 21 may be restricted in case those rights will presumably preclude or severely affect the realization of research purposes and the restriction is considered necessary to enable the scientific research. According to § 27 (3) GDPL, personal data shall be anonymized as soon as it is permitted by the scientific purpose, except opposed by reasonable interest of the affected person. Unless anonymization is possible, those characteristics, which enable the correlation of personal information to individual persons, must be retained separately and may only be consolidated for the scientific purpose.

It has to be kept in mind, that the GDPL will be complemented by German federal state law, which could possibly install differentiating or more strict regulations.

12.5. PATIENT INFORMATION AND INFORMED CONSENT

The PRODAST study will be conducted in accordance with the protocol, the principles of Good Clinical Practice (GCP), the Declaration of Helsinki as of October 2013 (2013WMA 2013), the Data Protection Directive 95/46/EC, guidelines for Good Epidemiological Practice (38), Good Pharmacoepidemiologic Practice (39), Good Pharmacovigilance Practices (36) Module VIII – Post-authorisation safety studies, GPV Module VIII Addendum I – Member States' requirements for transmission of information on non-interventional post-authorisation safety studies, GPV Module VI – Management and reporting of adverse reactions to medicinal products, "Registries for Evaluating Patient Outcomes: A User's Guide" (7), and local regulations, especially concerning data protection.

According to § 2 (34) of the German Medicine Act (AMG), the safety assessment of a medicinal product intended for human use is any trial with an authorized medicinal product that will be performed in order to evaluate, describe or quantify a safety risk, to confirm the safety profile of the medicinal product or to measure the efficiency of risk management systems. On the European level, safety assessment trials of medicinal products with a granted marketing authorisation are called Post-Authorisation Safety Studies (PASS) and the legal background can be found in the Guidelines of Good Pharmacovigilance Practices (GPV), which were implemented by the new pharmacovigilance legislation (Regulation (EU) 1235/2010 and Directive 2010/84/EU), and in the Good Pharmacovigilance Practice (GPV) Module V on Risk management systems and Module VIII on PASS, basing on Art. 108a of Directive 2010/84/EU. In Art. 1 Nr. 15 of Directive 2001/83/EC a PASS is defined as "a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard relating to an authorized medicinal product". A fundamental distinction has to be made between interventional PASS, which are regarded as clinical studies, and non-interventional (observational) PASS. In context of a non-interventional PASS, methods such as interviews, questionnaires and blood samples may be considered as normal clinical practice.

In Germany, safety assessment trials are primarily initialized in order to address safety issues of a medicinal product. Generally, a PASS will be mentioned as an additional pharmacovigilance measure in the risk management plan (RMP) of the medicinal product. For non-interventional safety assessment trials, which will be performed on own initiative of the marketing authorisation holder, the notification obligation of § 63 f AMG applies. A safety assessment trial, that will be performed independently from the marketing authorisation holder, has to be notified to the competent authority by the initiator, according to the general notification obligations for observational studies in § 67 (6) AMG.

Information, surveillance plans and final reports on safety assessment trials shall be published in the EU-PAS registry (http://www.encepp.eu/) appropriate to the specifications of GPV Module VIII.

The investigator should inform the Director of Investigation immediately of any urgent safety measures taken to protect the study subjects against any immediate hazard, and also of any serious breaches of the observational protocol / ICH GCP (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) / Declaration of Helsinki.

12.5.1. Patients who are capable of giving their written informed consent or have a legal representative

The responsible medical investigator shall decide at baseline (between time point T0 and T1) if the stroke patient is capable to give consent by assessing the capacity of discernment and ability to judge. The treating physician will confirm in writing, on the informed consent form, his positive assessment about the decision-making ability of the patient and capability to give informed consent. In case of incapability to consent, all measures shall be taken in order to find out about the existence of a legal representative, who can be either a courtly-appointed custodian or an authorized representative by health care proxy. It has to be kept in mind, that a custodian or proxy agent shall arrange the affairs only for the well-being of the person incapable to consent. Therefore it is prohibited to give consent for data processing in a research other than for the benefit of the person concerned. The patient or his legal representative shall be informed, preferably in advance of the medical treatment and data collection, about the intended storage, transmission and assessment of data: The patient or his legal representative shall receive complete information about the kind and content of data to be collected, especially that sensitive personal and medical data will be used, the reason for the data collection in context of the PRODAST study, the performance of data assessment and evaluation and the personal involved, the duration of data assessment and storage and when the data will be deleted, name and address of the person or institution responsible for the research project, the group of people that will be involved in the study and get knowledge about the data and all safety measures that will be taken in order to protect the patient data. Besides the data collected in the stroke unit, the patient or his legal representative shall be informed about a second phase of the study, when more data is going to be collected in a central follow-up: Therefore, the patient or his legal representative will be asked to give consent to requests by University Hospital Essen, Department of Neurology for additional data from general practitioners, hospitals or health care facilities. The patient or his legal representative needs to give an authorisation to release from medical confidentiality. Furthermore, the patient or his legal representative shall be informed that it is possible to withdraw the informed consent at any time without any justification and that neither the withdrawal of consent nor the refusal to consent will have any impact on the medical treatment. Data handling in case of withdrawal will be performed as described in Section 12.5.4. The patient or legal representative shall be given enough time for consideration and give the consent in writing, personally dated and signed.

The patient will be informed about the intended storage, transmission and assessment of data collected in this non-interventional study either by a treating physician or a trained staff member familiar with the study.

12.5.2. Patients who are incapable of giving their written informed consent at time of study inclusion (T1) and have no legal representative

Some medical conditions, such as stroke, could result in incapacity of giving an informed consent. It is the professional responsibility of the medical investigator to assess the medical condition and decision-making ability of the patient. In cases, where it is impossible to obtain the informed consent before the start of data collection (time point T1) due to the medical condition of the patient who has no legal representative, the medical investigator decides about study inclusion. As described in Section 8, the participation and data collection of persons incapable of giving consent shall be possible under strict conditions in order to fulfil a scientific purpose. Points which have been considered are the scientific question to be answered and the purpose of data evaluation: Without participation of patients who are incapable of giving an informed consent, data collection would suffer from bias and the study would not succeed to display real-life data. It has been evaluated that, for this study, the public interest to use the personal data of those patients for scientific research prevails the

interest of the person concerned to keep his data confidential. In order to protect the data of patients, strict rules for the technical and organizational handling of the data are put in place.

The responsible medical investigator will assess the medical condition and decision-making ability of the patient and will document in writing the diagnosis of incapability to give informed consent and the scientific medical justification for participation in the study. As soon as the patient regains his decision-making ability before discharge from hospital, he/she will be asked to give additional consent to the data collection, storage, transmission and assessment and to release his medical practitioner from confidentiality. Data will be collected, stored, transmitted and assessed also for those patients who are still incapable of giving consent for data processing at the time of discharge from hospital. In order to perform the follow-up interview, the investigators at University Hospital Essen will make all reasonable efforts to obtain informed consent from the patient himself, in case of capability regained after discharge, or from a legal representative appointed in the meantime.

A detailed procedure for this case is part of the ISF and has been presented to the Ethics Committee: It includes additional informed consent forms to be signed and returned to the University Hospital Essen (Follow-up centre) as well as prepared self-addressed envelopes which will be given to a patient's close relative/family member. The relative/family member will be informed about the study process and involved to support the procedure of obtaining the informed consent.

In case consent in written form is not available by the time of the follow up interview, oral consent from the patient or legal representative will be obtained, including detailed documentation of the process in accordance with existing standard operating procedures.

12.5.3. Patients who die during hospital stay or after discharge

It has to be distinguished between different situations when the patient might die.

Death during stay in hospital

1) In some cases the patient possibly dies before he/she or his/her legal representative can give the informed consent or the responsible medical investigator can draw the diagnosis for the patient being incapable to give an informed consent. In this situation, the patient has not been included as a study participant, so there will be no reason and justification to collect, store, transmit or evaluate any medical data for study purposes.

2) If the patient dies during the stay in hospital and he/she or the legal representative has given informed consent before or the responsible medical investigator has declared the patient to be incapable to give an informed consent, all medical data collected up to this point will be stored, transmitted and evaluated. No personal data will be forwarded to the University Hospital Essen. If personal data has already been sent to the University Hospital of Essen, this data will be deleted.

Death after discharge

3) If the patient dies after discharge and he/she or the legal representative has given informed consent before or the responsible medical investigator has declared the patient to be incapable to give an informed consent, all medical data collected up to this point will be stored, transmitted and evaluated.
a) Informed consent by patient or legal representative covers also the follow-up interview, which can be performed with legal representatives and/or family doctors/treating physicians.

Vital status (time and place of death) will be requested at the local citizen registry. In case of death, details of cause of death after discharge will be requested from the family doctor or treating physician. In cases, where information on cause of death cannot be gained otherwise, civil registry offices and local health offices will be contacted in order to permit access to death certificates.
b) In cases where the responsible medical investigator has declared incapability of the patient, all data collected after the moment of death shall be subject to medical confidentiality and no follow-up interview shall be performed. Vital status information will also be requested at local citizen registry, but no information on cause of death due to lack of informed consent.

12.5.4. Withdrawal of informed consent

The patient or his/her legal representative may withdraw a given informed consent at any time. This withdrawal can refer either to personal data or to medical data or to all data. In case that withdrawal is restricted to personal data, this data will be deleted, but pseudonymized medical data will be used for evaluation. In case that withdrawal is restricted to medical data, all medical data collected will be blocked in the database und will not be used for evaluation. In case that the informed consent is withdrawn completely, all personal data will be deleted and all medical data collected will be blocked in the database und will not be used for evaluation.
The patient may restrict the use of personal or medical data in advance by cancelling parts of the informed consent.