Statistical Analysis Plan

NOAH

Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes

ClinicalTrials.gov: NCT02618577, EudraCT number: 2015-003997-33, ISRCTN number: ISRCTN17309850

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Version history

Version	Date	Section number changed	Description/Changes made
1	15.10.2019		New version based on the of the former SAP prepared by Gregory Chlouverakis
2-6	29.10.2020	complete	Changes in Section 5 S,Sehner, A.Ozga • Censoring • Primary and secondary endpoint analyses • Missing data analyses • Sensitivity analyses • Per protocol analyses
7	04.05.2021	Minor things in some sections	5.4 deleted; 2.5. written in past tense; Reference section
8	06.09.2021	All	Cleaning
9	17.12.2021	2.6, 3.2, 5.7	• More description of timing of final analysis • Compliance changed to adherence • Adherence as subgroup
10	12.05.2022	3.2	Protocol deviations specified
Final Version	27.08.2022	All	Finalization
Final Version with Amendment, i.e version 2	17.10.2022	Amendment	Amendment added after first SAP version was signed (before unblinding)
Final Version with Amendment, i.e version 3	08.02.2023	Amendment	Further clarification of analysis (before unblinding), i.e. Analysis of: adherence, AHRE during the study duration, Baseline variables
Second Final Version	21.03.2023	Amendment	Finalization (typos)

Signature Page

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Abbreviations

ACS	Acute coronary syndrome
AF	Atrial fibrillation
AFNET	Kompetenznetz Vorhofflimmern e.V.
AHRE	Atrial high rate episodes
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Alanine aminotransferase
BMI	Body-mass-index
CABG	Coronary artery bypass graft
CONSORT	Consolidated standards of reporting trials
CRI	The Clinical Research Institute GmbH
DAPT	Dual antiplatelet therapy
DSMB	Data safety monitoring board
EC	Ethics committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EHRA	European heart rhythm association
ERC	Endpoint review committee
FMI	Fraction of missing information
GOT	Glutamic-oxaloacetic transaminase
GPT	Glutamic pyruvic transaminase
I/E criteria	Inclusion/exclusion criteria
ILR	Implantable loop recorder
IMP	Investigational medicinal product
INR	International normalized ratio
IQR	Inter-quartile range
IRB	Institutional Review Board
ISTH	International society on thrombosis and haemostasis
LLT	Lowest level terms
MACE(s)	Major adverse cardiac event(s)
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
MICE	Multivariate imputation by chained equations
mITT	Modified intention-to-treat
MoCA	Montreal cognitive assessment
NOAC(s)	Non-vitamin K antagonist Oral anticoagulant(s)
NOAH	Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate ^ Episodes
OD	Once daily
PCI	Percutaneous coronary intervention
PP	Per protocol
PROs	Patient-reported outcomes
PT	Preferred term
SAE(s)	Severe adverse event(s)
SAP	Statistical Analysis Plan
SC	Steering committee
SD	Standard deviation
SmPC	Summary of Product Characteristics
SOC	System organ class
TIA	Transient ischemic attack
UKE	University medical-center Hamburg-Eppendorf
VKA(s)	Vitamin K antagonist(s)

1 Introduction

This Statistical Analysis Plan (SAP) is based on the study protocol version 5.1 of October 1, 2020 and corresponding amendment no.5 and follows the guideline for statistical analysis plans (Gamble, et al., 2017). Some points of the statistical methods and of the study design are already described in the study protocol. This SAP aims to further specify the procedures and statistical methods applied during the final analysis of the study data.

1.1 Background and rationale

Atrial fibrillation (AF) is a common cause of stroke, especially ischemic stroke. So far, all available data that demonstrate a beneficial effect of oral anticoagulation for stroke prevention have been collected in populations with AF documented by conventional electrocardiogram (ECG) recordings. It is well established that a large proportion of AF episodes remain undiagnosed ("silent AF"), and many of these patients present with a stroke as the first clinical sign of AF. Earlier initiation of anticoagulation could prevent such events. Continuous monitoring of atrial rhythm by implanted devices could close this diagnostic gap. Pacemakers, defibrillators, and cardiac resynchronization devices already provide automated algorithms alerting to the occurrence of highly organized atrial tachyarrhythmia episodes, also called "subclinical atrial fibrillation" or, more commonly, "atrial high rate episodes" (AHRE). Data from large prospectively followed patient cohorts demonstrated that stroke rate is increased in patients with AHRE. A sizeable portion of these patients develops clinically detected AF over time. In these patients, AHRE can be considered as an early manifestation of paroxysmal AF. A few AHRE patients do not develop clinically overt AF, and the absolute stroke rates are lower in patients with AHRE when compared to stroke rates in patients with clinically diagnosed AF. In light of the bleeding complications associated with oral anticoagulant therapy, there is thus uncertainty about the optimal antithrombotic therapy in patients with AHREs.

The Non-vitamin K antagonist Oral anticoagulants (NOACs) provide similar or slightly better stroke prevention, and appear slightly safer compared to vitamin K antagonists (VKAs). In addition, no individual therapy adjustment of NOACs has to be performed. Edoxaban, a newly introduced NOAC, at a dose regime of 60 mg once daily (OD) has a favorable profile compared to dose-adjusted VKA therapy: In the ENGAGE-TIMI 48 trial (Giugliano, et al., 2013), edoxaban prevented strokes at least as effectively as VKA therapy but caused less major bleeding events than VKA therapy.

1.2 Objectives

To demonstrate that oral anticoagulation with the NOAC edoxaban is superior (test for difference) to current therapy (antiplatelet therapy or no therapy depending on cardio-vascular risk) to prevent stroke, systemic embolism, or cardiovascular death in patients with AHRE but

without overt AF and at least two stroke risk factors leading to a modified CHA_2DS_2VASc score of 2 or more.

1.2.1 Primary outcome

The primary outcome parameter of NOAH is defined as the time from randomization to the first occurrence of a composite of ischemic stroke, systemic embolism or cardiovascular death.

1.2.2 Main secondary outcomes

The secondary outcome parameters are defined as

a) time from randomization to components of the primary outcome (time to first event, i.e. for the non-fatal events (ischemic stroke and systemic embolism) only the respective first event is used),
b) time from randomization to all-cause death,
c) time from randomization to first occurrence of Major Adverse Cardiac Events (MACEs: cardiovascular death, myocardial infarction, acute coronary syndrome (ACS); percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG)),
d) time from randomization to first occurrence of ischemic stroke or systemic arterial embolism (composite),
e) time to first occurrence of major bleeding event
f) number of major bleeding events according to the International Society on Thrombosis and Haemostasis (ISTH) definitions,
g) quality of life changes at 12 and 24 months compared to baseline (assessed by EQ-5D including its visual-analogue scale and by the Karnofsky scale (EuroQol Research Foundation, 2019), (van Hout & Janssen, 2012),
h) patient satisfaction changes at 12 and 24 months compared to baseline (assessed by modified EHRA score and PACT-Q2 (Prins, et al., 2009a), (Prins, et al., 2009b))
i) cognitive function changes (MoCA) at 12 and 24 months compared to baseline
j) changes of autonomy status only in patients with stroke during study participation, assessed at each clinical follow-up visit by modified Rankin scale; a maximum of 2 subsequent assessments in follow-up per patient with stroke should be performed.

1.2.3 Patient Reported Outcome (PRO)

Are captured in section 1.2.2 g), h).

1.2.4 Safety outcome parameters

Are captured in section 1.2.1 and 1.2.2 c), d), e), f).

Additionally the combined outcome of time from randomization to death or time from randomization to first occurrence of major bleeding (composite endpoint) will be analyzed.

2 Study Methods

2.1 Trial design

Investigator-initiated, prospective, parallel-group, randomized, controlled, double-blind, event-driven, multi-centre trial. Although it can be argued that the indication tested is within the registered label of edoxaban, NOAH will be conducted as a phase IIIb study.

2.2 Randomization and blinding

The randomization sequence was generated using STATA12 SE (StataCorp, 2011) with blocks of variable sizes of 4 to 8 entries to ensure allocation concealment could not be breached, by guessing the sequence at the end of each block. Patients were randomized in a 1:1 ratio to one of the two parallel groups NOAC or usual care arms, stratified by indication for ASA and study site.

The randomisation was performed with the integrated randomisation service in the web-based EDC system MARVIN used as eCRF. According to protocol, requirements and design of the eCRF, randomisation could only be performed after informed consent had been obtained and all in- and exclusion criteria had been confirmed by study site staff. Multiple randomisations or pseudo-randomisations of subjects are prevented by the integrated randomisation service. Details can be found in the study protocol, section 6.2.5.

Patients, all hospital personnel performing direct care and assessments of patients and the Endpoint Review Committee (ERC) will be blinded to randomized treatment assignments until the database is locked for the primary analysis. The DSMB will be unblinded to treatment assignment throughout the study.

In case of an event which threatens the patient's health without the knowledge of the study drug identity, investigator can unblind the subject's treatment group in the MARVIN e-CRF. The identity of the person having triggered the unblinding as well as date and time of unblinding, justification of unblinding and identity of random group are stored in the data base. From timepoint of unblinding, the subject is censored for analysis in the mITT (modified intention-to-treat; see Section 3.3.1) population.

2.3 Sample size

NOAH is an event-driven trial with a planned number of randomised and treated patients of n=2,538 and an anticipated number of primary endpoints of n=220. The protocol includes an

adjustment of the sample size based on an analysis of events after 1000 observed patient-years. Details of sample size calculation can be found in the study protocol, section 12.2.

2.4 Framework

NOAH intends to demonstrate that oral anticoagulation with the NOAC edoxaban differs to current therapy (antiplatelet therapy or no therapy depending on cardio-vascular risk) to prevent the occurrence of the primary endpoint defined as the time from randomization to the first occurrence of a composite of stroke, systemic embolism or cardiovascular death. For all other (secondary) endpoints a test for difference will also be used.

2.5 Statistical interim analyses and stopping guidance

The Steering Committee (SC) has assessed pooled event rates after about 1,000 patient-years of observation in the mITT (modified intention-to-treat; see Section 3.3.1) study population (without knowledge of study group assignment or study treatment). Alternatively the interim analysis could have been conducted after about 24 months after enrolment of the first patient (this was not the case). Sample size or inclusion criteria (e.g. enrichment for patients at higher risk for events should low event rates be observed, or adaptation of sample size based on observed event rates, or alternatively reduction of the number of patients needed based on observed events) were adapted to reflect the observed event rates.

The pooled event rate was calculated as the ratio of the sum of all observed primary events until the time point of interim analysis and corresponding person-years, defined as the sum of all observed follow-up times (in years) for each patient between randomization and the event date (patients with primary events), or the date of development of overt AF, date of unblinding, or the last documented follow-up information (all other patients). The corresponding 95%-confidence interval was estimated using the quadratic approximation to the Poisson log likelihood for the log-rate parameter.

The event rate of 4.4%, assumed for the sample size calculations, was not greater than the upper 95% limit. Adjustments in the sample size or in the inclusion criteria were discussed in the SC based on this result. No changes were decided.

2.6 Timing of final analysis

NOAH is an event-driven trial with a planned number of randomised patients of n=2,538 and a fixed number of valid events (n=220). The total duration of the trial is an estimate based on observed outcome rates in other large trials with similar populations. The total number of events in the trial is depending on the time at risk that is the follow-up time of all patients. In practice, the event-driven design may result in slight variation of the expected trial duration and

of the total number of patients enrolled if observed event rates do not exactly match the assumed rates. All patients will be followed until the global end of the trial. Remaining medication will be collected at the final visit. As given in the study protocol following estimation for the study duration is made: Screening and enrolment of patients is expected to be accomplished after 71 months. Based on the sample size estimation, it is expected that the required number of adjudicated (verified primary outcome events) will be reached 12 months after enrolment of the last patient. Due to the time required to obtain follow-up information and to adjudicate events (about 3 months to perform a final study visit in all patients still in the trial plus 4 months for receiving adjudication by ERC to confirm that the required number of adjudicated endpoints have been reached), a total study duration of 71 + 12 + 3 + 4 = 90 months is expected. The total study duration of 90 months (about 7.5 years) was adapted based on an interim analysis. After that and data management the final analysis can be conducted.
Global end of study (EOS) is defined as the last Final Visit performed in a study patient. This date will be approved by the sponsor and announced by the CRI.
The global end of study will be announced by the CRI after all necessary primary endpoints have been reached.
This procedure can result in more than the anticipated primary events within the final analysis (depending on the amount of events that can be adjudicated).

The accrual time and hence the total study time was further adapted in 2022 due to loss of Ukrainian participants and the lower than expected event rate. The steering committee decided to censor all Ukrainian patients on the last documented contact before the 24th February 2022, the day of the outbreak of war in Ukraine, to protect the trial against unexpected changes in event rates due to the influence of war on Ukrainian patients.

3 Statistical Principles

3.1 Confidence intervals and *P* values

All applicable statistical tests will be two-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided. Analyses of secondary, safety and patient reported outcomes will be performed exploratory without adjustment for multiplicity.

3.2 Adherence and protocol deviations

Adherence with study drug is defined as following (percentages refer to the period between the last documented follow-up visit and the next, ideally 6 months):

- Non-adherence: Intake of study drugs < 80% of the number of daily dosages calculated for the corresponding time period.
- Acceptable adherence: Intake of study drugs 80% to < 90% of the number of daily dosages calculated for the corresponding time period.
- Good adherence: Intake of study drugs 90% or more of the number of daily dosages calculated for the corresponding time period.

Thereby, the duration of discontinuation is not considered.
In case of non-adherence the investigator has to instruct the patient about importance of regular drug intake.
Adherence is measured by count of remaining pills in each returned medication box by the site staff. The pill count entered into the eCRF system for each blister and medication box is confirmed by a second pill count performed by Monitors during Monitoring or Site Close-Out visits at end of study. Successful intake of one daily dosage is defined as the intake of one pill of product ASA (or placebo) and one pill of product edoxaban (or placebo). Blisters and medication boxes that were disposed by the patient as being confirmed completely used by the patient, are considered as intake of all contained daily dosages in a best-case scenario.

Permanent discontinuation of study medication is documented in the eCRF. A sensitivity analysis comparing the two randomised groups during exposure to study medication will be planned. For this analysis, all patients will be censored at the time of permanent discontinuation of study medication.

Major protocol violations are any unapproved changes in the research study design and/or procedures that are within the investigator's control and not in accordance with the IRB- or EC-approved protocol that may affect the participant's rights, safety or well-being, or the completeness, accuracy and reliability of the study data. Patients with major protocol violations will be excluded from the per protocol analysis. Some major protocol violations may be reported to regulatory authorities within defined time periods as mandated. Study specific definitions of major protocol violations will be given by the SC.
The type and reason of protocol violation will be documented in this study, and the summary of protocol violations will be reported in both arms.

Following protocol deviations were specified by the SC:

- deviation from inclusion criteria is a major protocol deviation, i.e. if the following is not fulfilled:
    - Pacemaker, defibrillator or insertable cardiac monitor implanted for any reason with feature of detection of AHRE, implanted at least 2 months prior to randomisation (not major for ILR (implantable loop recorder))
    - AHRE detection feature activated for adequate detection of AHRE (not major if AHRE episodes were reviewed by site and adequate criteria found)
    - AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration) documented by the implanted device via its atrial lead and stored digitally. Any AHRE episode recorded is potentially eligible, but AHRE episodes detected in the first 2 months after implantation of a new device involving placement or repositioning of atrial electrodes are not eligible. AHRE episodes recorded in the first two months after a simple “box change” operation, i.e. exchange of a pacemaker or defibrillator device without exchange or repositioning of atrial electrodes, are eligible.
    - modified CHA2DS2VASc score of 2 or more
- deviation from exclusion criteria is a major protocol deviation, i.e. if the following is observed:
    - Any disease that limits life expectancy to less than 1 year
    - Participation in another controlled clinical trial, either within the past two months or still ongoing.
    - Previous participation in the present trial NOAH - AFNET 6.
    - Drug abuse or clinically manifest alcohol abuse.
    - Any history of overt AF or atrial flutter
    - Indication for oral anticoagulation (e.g. deep venous thrombosis).
    - Contraindication for oral anticoagulation in general
    - Contraindication for edoxaban as stated in the current SmPC.
    - Indication for long-term antiplatelet therapy other than acetylsalicylic acid or a need for treatment with any antiplatelet agent in addition to edoxaban, especially dual antiplatelet therapy (DAPT). Patients with a transient requirement for DAPT (e.g. after receiving a stent) will be eligible when the need for DAPT is no longer present.
    - Acute coronary syndrome, coronary revascularisation (PCI or bypass surgery), or overt stroke within 30 days prior to randomisation.
    - End stage renal disease (creatinine clearance < 15 ml/min as calculated by the Cockcroft-Gault method).
    - All persons exempt from participation in a clinical trial by law.

- Deviation related to study therapy defined as major:
    - Intake of study drugs < 80% of the number of pills calculated for the corresponding time period
    - Permanent stop of IMP intake without indication or contraindication for oral anticoagulation
    - Measurement of creatinine value at baseline visit older 28 days if it is not measured within 6 months of therapy initiation
- Deviation related to study procedures defined as major:
    - No complete chain of medication supply if interruption is 20% or more of the planned treatment time (aligned with definition of adherence)
    - Simultaneous intake of study medication and other oral anticoagulation
    - Simultaneous intake of study medication and any antiplatelet agent

3.3 Analysis populations

3.3.1 Modified Intention to treat Population (mITT)

The modified intention to treat population (mITT) consists of all randomised patients with a qualifying AHRE and intake of at least one dose of study drug. The mITT doesn't include patients that were randomized but a) have AF onset before 1st dose of IMP, or b) die before 1st dose of IMP, c) withdrew their consent before 1st dose of IMP or d) are lost to follow up before 1st dose of the IMP.

3.3.2 Per Protocol population (PP)

The Per Protocol population consists of mITT populations patients who have no major protocol deviation. Definition of major protocol deviation are given is Section 3.2.

3.3.3 Safety Population

Safety data will be collected on all enrolled patients (i.e. all patients that signed informed consent) in this study.

4 Trial Population

4.1 Eligibility

The number of ineligible patients randomised, i.e. those randomised by not fulfilling the inclusion and exclusion criteria, will be reported, with reasons for ineligibility.

4.2 Recruitment

A CONSORT (Schulz, Altman, & Moher, 2010) flow diagram will be used to summarise the number of patients (per treatment group where appropriate) who were:

- enrolled (patients documented in MARVIN, numbers will be provided by CRI to IMBE for construction of CONSORT flow chart)
    - fulfilling I/E-Criteria at screening
    - not fulfilling I/E-Criteria at screening*
    - post-hoc violation of I/E-Criteria*
- randomised
- not randomised*
- received the randomised treatment
- did not receive the randomised treatment*
- lost to follow-up*
- randomised and included in the primary analysis
- randomised and excluded from the primary analysis*

*reasons will be provided

4.3 Withdrawal / follow-up

Information on the number and level of withdrawals/drop outs, number included in the analysis and the number died will be presented in CONSORT diagram format with numbers and reasons for withdrawal and/or exclusion from analysis given at each visit. Levels of withdrawal are defined as:

- Modification of consent (MOC):
  Patients who wish to withdraw from the study are asked to maintain consent for minimal effort follow-up, allowing to use their clinical data achieved at the clinically indicated visits. All available data will be used until the end of study (no drop out of patient).
- Withdrawal of consent (WOC):
  If patients withdraw consent to any further study participation, data will be used until time of withdrawal and censored afterwards.
- Complete withdrawal:
  Patient request deletion of all his/her data.
- Early withdrawal: Withdrawal of patient's consent (WOC) within the first month after study inclusion. Patients with early withdrawal will be included in primary analysis. Furthermore, a sensitivity analysis will be conducted without these patients.

4.4 Baseline patient characteristics (Definition of table 1)

Patients will be described with respect to age, gender, and clinical features, both overall and separately for the two randomised groups. A shell table is included in the appendix.

Categorical data will be summarised by numbers and percentages. Continuous data will be summarised by mean, SD, median, 1st and 3rd quartile, and minimum and maximum. Histograms and boxplots will be used to check the distribution and possible outliers for continuous variables. Number of available observations and number of missing observations will be presented for the treatment groups separately. Tests of statistical significance will not be undertaken for baseline characteristics; rather the clinical importance of any imbalance will be noted (Senn, 1994).

5 Analysis

5.1 Censoring and event definition

5.1.1 Trial specific censoring

Patients who develop overt AF during the trial period will be censored at that point in time but followed according to protocol until the global end of the trial.

From time point of unblinding, the subject is censored for analysis in the mITT population. Patients without an event at the end of follow-up will have their efficacy measure censored at the end of follow-up.

If a patient is lost to follow-up, the last time point of contact is used as censoring time point in case of no event, else the event time point is used for analysis.

If a patient withdraws his/her consent but accepts that data till this time point of withdrawal can be used, the time point of last contact is used as censoring time point in case of no event, else the event time point is used for analysis.

5.1.2 Event definition

No matter what, i.e. although events might occur in quick succession, the first event that was observed is used within analysis. Primary outcomes that occur within one day of unblinding will be counted as primary outcomes.

5.2 Primary endpoint analysis

The primary outcome analysis will be performed in the mITT population using the adjudicated endpoint data of the ERC. The primary endpoint is the time from randomisation to the first

occurrence of ischemic stroke, systemic embolism or cardiovascular death. Deaths of unknown cause will be classified as cardiovascular death (Hicks, et al., 2018) in all analyses.
All patients who will not reach the primary endpoint by the global end of the study will be censored at that time point.
Because all-cause death acts as a competing event for the primary endpoint the following methods will be applied:

- Primary analysis: Cause-specific Cox-proportional hazards model with frailty for centers and the fixed effects random group and ASA, i.e. an adjusted estimated (cause-specific) hazard ratio (hazard ratio of edoxaban vs usual care) with two-sided 95% confidence interval, and corresponding p-value will be provided.
- Graphical display of results: cumulative incidence curves (Aalen-Johansen estimates)

The proportional hazards assumption will be checked graphically (e.g. Schoenfeld residuals, -log-log-survival).

5.3 Secondary endpoints analysis

5.3.1 Time-to-event endpoints

The following secondary endpoints will be analysed in the same way as the primary endpoint:

a) time to components of primary outcome,
c) time to first occurrence of major adverse cardiac events,
d) time to first occurrence of stroke or arterial embolism,
e) time to first major bleeding events.

b) Time to all-cause death will be analysed using an adjusted Cox-proportional hazards model (hazard ratio of edoxaban vs usual care) with the fixed effects random group and ASA and a frailty term for study side.

All results will be reported within tables with estimated hazard ratios, corresponding confidence intervals, and p-values and visualized by cumulative incidence curves (Aalen-Johansen estimates in case of the competing event all-cause death; for all-cause death Kaplan-Meier type estimates).

5.3.2 Continuous endpoints

The following continuous secondary endpoints:

g) change in quality of life (EQ-5D and Karnofsky score),

h) patient satisfaction (PACT-Q2, EHRA),
i) cognitive function (MoCA),
at 12 and 24 months will be analysed using the difference to baseline as outcome in the following model:
- baseline and randomization strata (ASA) adjusted linear mixed effects regression,
- with a time (12 and 24 months) by treatment interaction if interaction p-value <0.05; else only both main effects
- the dependency structure of the time points will be modelled by including the study side as random effect (independent identically distributed) and patient nested within study side, with an unstructured variance covariance matrix of the residuals matrix (time points).

Normal distributed residuals will be checked graphically via histogram of residuals.

Adjusted mean values and adjusted effect estimators (mean differences) with corresponding confidence intervals and p-values will be given.

f) Number of major bleeding events according to ISTH: randomization strata adjusted mixed negative binomial regression with the individual observational time as offset.

5.3.3 Change in autonomy status.

Changes in autonomy status will be quantified by comparing modified Rankin scales over time after a stroke using a shift analysis (Ganesh, Luengo-Fernandez, Wharton, & Rothwell, 2018). For this, a cumulative ordinal regression is used with random group and ASA as fixed effects and center as random effect. The joint adjusted odds ratio (OR) with two-sided 95% confidence interval, and corresponding p-value will be provided.

5.4 Missing data analysis

For the primary outcome the worst case scenario will be used for missing values, i.e. deaths of unknown cause will be classified as CVD (Hicks, et al., 2018) in all analyses.
No other imputation will be conducted for primary endpoint analysis.

Missing values for continuous secondary outcomes will be imputed using chained equations (MICE) with of at least 20 imputations (M) if the assumption of M=100**FMI* (Largest Fraction of Missing Information) is fulfilled (White & Royston, 2009). The imputation model includes simultaneously all above described variables at all measured time points and the following

clinical relevant predictors at all measured time points: age, sex, body mass index, NYHA class, documentation of overt atrial fibrillation, left ventricular ejection fraction, eligibility for aspirin therapy, estimated creatinine clearance.

If possible we will use a parametric approach depending on the measurement level of the variable, otherwise predictive mean matching with the ten nearest neighbors will be used. Imputation will be performed stratified by treatment.

If possible sum-scores will be imputed on item level. If, due to complexity of the model, the imputation on item level is not possible the sum-score will be used.

This imputation model will be used if estimateable, else a further reduction of the complexity of the model will be performed. The results of the imputed data will be primarily reported.

For outcome g) death can be imputed (with 0), but for others outcomes which are no time to event endpoints this is not possible and hence information on these patients remains missing.

5.5 Sensitivity analyses

For sensitivity analyses for the primary endpoint will be estimated:

- using the per-protocol population,
- using the mITT population with censoring of patients at the time of discontinuation of IMP (“on treatment analysis”)
- without censoring for overt AF or for unblinding,
- using the Fine-and-Gray model with random group and ASA as fixed effects but without a frailty for study site,
- without patients who withdrew their consent (early or late and early only, i.e. <1 month),

For further sensitivity analyses for secondary continuous outcomes complete case analysis will be conducted, i.e. analysis without imputed data.

5.6 Per protocol analyses

The primary endpoint will be evaluated in the PP population as a sensitivity analysis in the same manner as described in Section 5.2.

5.7 Subgroup analyses

Explorative subgroup analyses with respect to the primary outcome that allow identifying determinants of treatment success will be performed by the appropriate interaction tests for each subgroup separately. Each test will be performed at a significance level of alpha=5% and within the mITT population.

Predefined subgroups are:

- Sex
- Age groups split by median as well as ≥75 years
- Maximal duration of AHRE episodes (≥24 hours vs other)
- Maximal AHRE duration split by median
- Stratified by CHA_2DS_2VASc score / factors
    - congestive heart failure history
    - hypertension history
    - diabetes history
    - Stroke/TIA/thromboembolism history
    - Vascular disease history (prior MI, peripheral artery disease, or aortic plaque)
- high comorbidity burden (CHA_2DS_2VASc score ≥5 and CHA_2DS_2VASc score > median)
- Adherence:
    - Non-adherence: Intake of study drugs < 80% of the number of daily dosages calculated for the corresponding time period.
    - Acceptable adherence: Intake of study drugs 80% to < 90% of the number of daily dosages calculated for the corresponding time period.
    - Good adherence: Intake of study drugs 90% or more of the number of daily dosages calculated for the corresponding time period.
- Patients without any AHRE during the study duration

5.8 Additional analyses

A more detailed extended analysis of the primary outcome will be performed in the mITT population after global end of the study by statistical model building based on cause-specific Cox proportional hazard models with fixed effects for random group and ASA and a frailty for study site and the inclusion of several covariates. In particular variables that differ clinically relevant between the random groups at baseline will be determined with respect to the primary outcome. In addition to clinical predictors available in the locked data base, further analyses will determine potential genetic and biomolecule-based predictors of outcomes.

5.9 Safety analyses (SAE)

Safety analyses will be performed based on the data of the safety population following the ITT principle. The primary safety outcome in this study is a composite of cardiovascular death, ischemic stroke, and systemic embolism, which will be analysed using time-to-event methodology, as described for the primary outcome analysis. Time to first occurrence of Major

Adverse Cardiac Events, time to first occurrence of stroke or systemic arterial embolism, and time to first occurrence of major bleeding event are also considered as safety outcomes and already captured in secondary endpoint analysis. Additionally the composite of time to death or time to first occurrence of major bleeding event will be analysed in the same cause-specific time-to-event manner.

SAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 19.1) dictionary in its actual version at the start of the study by Lowest Level Terms (LLT). Treatment related SAEs will be summarized under each treatment group, by system organ class (SOC) and preferred term (PT). SAEs will be summarized by severity and relation to study treatment received.

5.10 Harms

The investigational medicinal product (edoxaban) has a known safety profile and is approved for use in patients with atrial fibrillation. Knowing that the administration of edoxaban in AHRE patients without overt non-valvular AF is not in-line with the approved label, adverse events are expected to occur in similar clinical manifestations and at a comparable rate as the known adverse events of the approved therapies applied in the trial (i.e. “low risk trial”). The safety profile includes major bleeding events. As stated in Section 5.9 we will therefore compare the secondary outcome time to first occurrence of major bleeding and a combined outcome of time to death or time to first major bleeding between the random groups.

5.11 Statistical software

- STATA 17 or newer
- R 3.4.1 or newer
- SPSS 22.0 or newer
- SAS 9.4 or newer

6 Database Sources

6.1 Source data and documents

Source data are defined as all information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents.

Source documents are defined as original documents, data and records (e.g. hospital records, clinical and office charts, electronic patient records, laboratory notes, memoranda, patient diaries or evaluation check lists, pharmacy dispensing records, recorded data from automated

instruments, copies or transcriptions, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, records kept at pharmacy, at the laboratories and at medico technical departments) involved in this clinical study.
In case of data that are result of patient reporting and will not be documented in clinical routine, the e-CRF is the source document, if the patients answer is documented there without prior documentation on paper.

6.2 Direct access to data

Direct access is defined as the permission to examine, analyze, verify and reproduce any records and reports that are important to evaluation of a clinical study. Any party with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirements to maintain the confidentiality of patient identities and sponsor proprietary information.

6.3 Storage, transformation of data and preparation for analysis

All study data, administrative data and relevant metadata are collected, stored and secured against deletion or unnoticed manipulation according to current regulatory requirements for electronic data capture in clinical trials. The data of the e-CRF database are extracted and transformed to structured data sets for analysis in a validated process. All structured data are prepared for statistical analysis with the statistical software package R using validated functions and scripts.

7 Amendment

On 2 September 2022, the NOAH-AFNET6 sponsor, the Atrial Fibrillation NETwork (AFNET), decided to terminate the NOAH-AFNET6 study prematurely. This decision follows a unanimous recommendation by the Data and Safety Monitoring Board (DSMB) on 26 August 2022 to terminate the study and a unanimous vote by the study's Steering Committee on 2 September 2022 to follow this recommendation.
As reasons for its recommendation to terminate NOAH-AFNET6 the DSMB cited an observed trend towards futility of efficacy combined with safety concerns.
Furthermore, on the basis of a unanimous vote of the Steering Committee, the decision was taken by the sponsor to orderly terminate the trial, i.e., the final patient visit should be performed for each patient still in follow-up as soon as possible, and all patients still taking Investigational medicinal product (IMP) should conduct a regular final visit at the study site at which the IMP intake ends.

Due to the premature study termination some changes have to be made to the first version of the signed SAP. These are described in this chapter.

7.1 Changes in chapter *1.2.2. Main secondary outcomes*

g) EQ-5D-5L: The index analysis based on the values of United Kingdom will be primarily reported. The index analysis based on the German values or values of the Netherlands as well as the analysis of the visual-analogue scale will be reported as additional analysis.

For outcome

j) changes of autonomy status only in patients with stroke during study participation, assessed at each clinical follow-up visit by modified Rankin scale; a maximum of 2 subsequent assessments in follow-up per patient with stroke should be performed

the following is added/changed:

A maximum of two assessments for patients with stroke during study participation is foreseen by Rankin Score. This information is only captured in patients with a stroke. First and last assessment will be evaluated in the analysis.

Also, the EQ-5D has been renamed EQ-5D-5L in all subsequent chapters.

7.2 Changes in chapter *2.6 Timing of final analysis*

Added information on Ukraine:

All collected data until the 23rd of February 2022 (war started in the early hours on 24th of February) will be evaluated. All outcome events occurring on or prior to 23 February will be counted in the primary analysis. Patients are lost to follow up if there is no final visit done or any contact to the patient. SC will finally decide how to handle special cases.

The SC decided on December 19, 2022 to end the study on December 31, 2022. The date is equal to end of observation.

7.3 Changes in chapter *3.3.2 Per Protocol population (PP)*

If possible patients with major protocol deviation are censored at the time of a major protocol deviation for the per protocol population. The censoring time of the major protocol deviation will be used if it occurs before a primary event or other censoring was observed.

7.4 Changes in chapter *4.2 Recruitment*

The following is added:

Lost to follow up: This will be explained if possible, e.g. withdrawn consent, including “no known reason” where this is the case. This information will be captured in the CONSORT diagram.

7.5 Changes in chapter *4.4 Baseline patient characteristics (Definition of table 1) and correction of Appendix A*

Added information on characteristics of interest, i.e. the following patients’ characteristics will be given in this table (also correction of Appendix A):

- Age (years)
- Sex (female, male)
- Weight (kg)
- BMI (body-mass-index)
- AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration) (yes, no)
- CHA2DS2VASc score
- Older than 75 years (yes, no)
- Symptomatic Heart failure (yes, no)
- Hypertension (yes, no)
- Diabetes mellitus (yes, no)
- Stroke or TIA (yes, no)
- Vascular disease (yes, no)
- Indication for ASA (yes, no)
- Unstable angina pectoris (yes, no)
- Acute myocardial infarction (yes, no)
- Prevention of re-infarction (yes, no)
- After arterial vascular or general surgical interventions (e.g. after CABG or after PTCA) (yes, no)
- For prevention of transitory ischaemic attacks (TIA) and strokes (yes, no)
- Patient currently has a contraindication for ASA (yes, no)
- Hypertension (yes, no)
- NYHA (No heart failure, I, II, III, IV)
- Cardiomyopathy (No, Hypertrophic cardiomyopathy, Dilatative cardiomyopathy, Arrhythmogenic right ventricular cardiomyopathy, Other cardiomyopathy)
- Valvular heart disease (yes, no)
- Confirmed Coronary Artery Disease (yes, no)
- Confirmed carotid stenosis (>50% lumen reduction) (None, left side, right side, both sides)
- Arterial hypertension (yes, no)

- Diabetes mellitus (No, oral antidiabetics, insulin therapy, oral antidiabetics and insulin therapy)
- Hypercholesterinaemia (yes, no)
- Peripheral arterial vascular disease (yes, no)
- Overall heart rhythm (Sinus rhythm prevails, Atrial fibrillation prevails, Pacing prevails, Pacing and AF, Other)
- Heart rate
- QRS interval
- PR interval
- QT duration
- QT duration calculated
- Amiodarone (yes, no)
- Dronedarone (yes, no)
- Flecainide (yes, no)
- Ibutilide (yes, no)
- Propafenone (yes, no)
- Digoxin or Digitoxin (yes, no)
- Antiarrhythmic drugs (yes, no)
- Antianginal drugs (yes, no)
- Potassium channel inhibitor (yes, no)
- Sodium channel inhibitor (yes, no)
- Diuretics (yes, no)
- Loop diuretics (yes, no)
- Mineralocorticoid receptor antagonist (yes, no)
- Beta blockers (yes, no)
- Calcium channel antagonists (yes, no)
- Rate controlling calcium channel antagonist (yes, no)
- ACE inhibitors or angiotensin II receptor blocker (yes, no)
- Renin inhibitor (yes, no)
- Imidazole and triazole derivatives (yes, no)
- Non-Steroidal Anti-Inflammatory Drugs (yes, no)
- Intravenous anticoagulant (yes, no)
- NOAC (yes, no)
- Platelet inhibitors (yes, no)
- Vitamin K antagonists (yes, no)
- Insulin (yes, no)
- Oral antidiabetics (yes, no)

- SGLT2 inhibitors (yes, no)
- Statins (yes, no)
- Serum creatinine value (mg/dl)
- Creatinine clearance
- Haemoglobin (g/l)
- Hematocrit
- Red blood cells
- Leucocytes
- Thrombocytes
- INR (international normalized ratio)
- aPTT (activated partial thromboplastin time)
- ALT (alanine aminotransferase) (GPT; glutamic pyruvic transaminase) (U/l)
- AST (aspartate aminotransferase) (GOT; glutamic-oxaloacetic transaminase) (U/l)
- Total bilirubin (µmol/l)
- Cholesterol (mmol/l)
- Karnofsky score
- Atrial fibrillation symptom score (EHRA) (EHRA I, EHRA IIa, EHRA IIb, EHRA III, EHRA IV, unknown)
- Cognitive function at baseline (MoCA)
- ≤ 12 years formal education (yes, no)
- MoCA (<26) (Cognitive impairment: yes, no)
- EQ-5D-5L: Mobility
- EQ-5D-5L: Self-Care
- EQ-5D-5L: Usual Activities
- EQ-5D-5L: Pain/Discomfort:
- EQ-5D-5L: Anxiety/Depression:
- EQ-5D: State of health rate on a scale of 1 (very poor) to 100 (very good)
- EQ-5D total score

7.6 Changes in chapter *5.1.2 Event definition*

The following is added: All potential outcome events will be adjudicated by the endpoint review committee. That definition defines the nature of each event.

7.7 Changes in chapter *5.4 Missing data analysis*

No imputation for missing values for secondary endpoints will be conducted. Due to the premature termination of the trial, not all patients will be followed up until 12 months. Currently

60-65% of the patients have undergone or are scheduled to undergo a 12 months visit (n=1.680) and for less than 50% after 24 months (n=1.100). This means information is missing for the outcomes of interest. The expected number of missing values (ca 1/3) is too large to perform reliable imputation. Clinically relevant changes in quality of life can be expected to be detectable in ca 1600 patients as well.

Hence, data analysis will be done for those patients where regular 12 and/or 24 months visits and assessments have been done. Patients without 12 and 24 months follow up data (roundabout 30%) will not be included in the statistical analysis of the following secondary outcomes:

- change in quality of life (EQ-5D-5L and Karnofsky score),
- patient satisfaction (PACT-Q2, EHRA),
- cognitive function (MoCA),
- changes of autonomy status.

7.8 Changes in chapter *5.5. Sensitivity Analyses*

The point

- using the mITT population with censoring of patients at the time of discontinuation of IMP (“on treatment analysis”)

changes to

- using the mITT population with censoring of patients at the time of permanent discontinuation of IMP (kind of censoring)

(which is not exactly an “on treatment analysis” but a specific kind of censoring)

7.9 Changes in chapter *5.7. Subgroup Analyses*

The cut-off for CHA2DS2VASc score is changed to ≥5.

Furthermore, the section is divided into two parts:

- Baseline subgroups, i.e. subgroups specified before randomization and which do not change over time
- Subgroups that occur over time, i.e. are not defined by data collected at baseline but by data collected after randomization during the course of the study

The subgroups that are defined by data collected during the course of the study are “Patients without any AHRE during the study duration” and “Adherence”. All other subgroups are baseline subgroups.

The baseline subgroups are analyzed as described in Chapter 5.7.

For the subgroup “Patients without any AHRE during the study duration” a causal mediation analysis will be conducted. Thereby, the variables described in chapter 7.10. will be considered in the model as potential confounders.
“Adherence” as a post randomization event will be analysed as time-dependent covariate and interactor for the treatment effect with censoring at study drug discontinuation.

7.10 Changes in chapter *5.8. Additional Analyses*

Potential genetic and biomolecule-based predictors of outcomes will not be part of the current SAP analyses but part of secondary subsequent analyses. A dedicated biomolecule SAP will be written when they are quantified.
For the multiple cause-specific Cox proportional hazard models with fixed effects for random group and ASA and a frailty for study site and the inclusion of several covariates, the additional covariates were chosen by the SC and include:

- age
- sex
- congestive heart failure history
- hypertension history
- diabetes history
- stroke/TIA/thromboembolism history
- vascular disease history (prior MI, peripheral artery disease, or aortic plaque)
- aspirin intake at baseline
- Non-Steroidal Anti-Inflammatory Drugs

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9 Appendix

Appendix A:

Shell table showing clinical characteristics.

Table 1
Baseline Characteristics and Demographics
(mITT Population)

Characteristics	Edoxaban (N = xxx)	SOC (N = xxx)	All subjects (N = xxx)
Age (yrs.)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)

Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Sex			
Female	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Male	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Weight (kg)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
BMI			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
AHRE (≥ 170 bpm atrial rate and ≥ 6 min duration)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
$CHA_2DS2VASc$			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Older than 75 years	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Sympt. Heart failure	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Hypertension	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Diabetes mellitus	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Stroke or trans. isch. attack	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Vascular disease	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Indication for ASA	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Unstable angina pectoris	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Acute myocardial infarction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Prevention of re-infarction	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
After arterial vascular or general surgical interventions (e.g. after CABG or after PTCA)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
For prevention of transitory ischaemic attacks (TIA) and strokes	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Coronary artery disease			
Other indication			
Patient currently has a contraindication for ASA	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Hypertension	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
NYHA			
I	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
II	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
III	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
IV	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)

Cardiomyopathy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
No	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Hypertrophic cardiomyopathy ∇	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Dilatative cardiomyopathy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Arrhythmogenic right ventricular cardiomyopathy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Other cardiomyopathy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Valvular heart disease	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Confirmed Coronary Artery Disease	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Confirmed carotid stenosis (>50% lumen reduction)			
None	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
left side	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
right side	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
both sides	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Arterial hypertension	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Diabetes mellitus	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
No	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
oral antidiabetics	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
insulin therapy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
oral antidiabetics and insulin therapy	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Hypercholesterinaemia	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Peripheral arterial vascular disease	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Overall heart rhythm			
Sinus rhythm	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Atrial fibrillation	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Pacing	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Pacing and AF	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Other	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Heart rate			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
QRS interval			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
PR interval			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
QT duration			

N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
QTc (calculated)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Serum creatinine value (mg/dl)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Estimated creatinine clearance			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Haemoglobin (converted to "g/l")			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Hematocrit			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Red blood cells			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Leucocytes			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Thrombocytes			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
INR			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Min, Max	xx, xx	xx, xx	xx, xx
aPTT			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
ALT (GPT) (converted to "U/l")			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
AST (GOT) (converted to "U/l")			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Total bilirubin (converted to "µmol/l")			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Cholesterol (converted to "mmol/l")			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
Amiodarone	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Dronedarone	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Flecainide	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Ibutilide	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Propafenone	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Digoxin or Digitoxin	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Antiarrhythmic drugs	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Antianginal drugs	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Potassium channel inhibitor	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Sodium channel inhibitor	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Diuretics	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Loop diuretics	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mineralocorticoid receptor antagonist	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Beta blockers	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Calcium channel antagonists	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Rate controlling calcium channel antagonist	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)

ACE inhibitors or angiotensin II receptor blocker	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Renin inhibitor	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Imidazole and triazole derivatives	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Non-Steroidal Anti-Inflammatory Drugs	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Intravenous anticoagulant	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
NOAC	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Platelet inhibitors	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Vitamin K antagonists	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Insulin	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Oral antidiabetics	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
SGLT2 inhibitors	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Statins	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Atrial fibrillation symptom score (EHRA)			
EHRA I	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
EHRA IIa	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
EHRA IIb	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
EHRA III	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
EHRA IV	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
unknown	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)	xxx/xxx (xx.x%)
Cognitive function at baseline (MoCA)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25^{th}, 75^{th})	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
≤ 12 years formal education	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Cognitive impairment (<26)	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
EQ-5D-5L responses at baseline			
EQ-5D-5L: Mobility	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
N			
Mean (SD)			
Median (25th, 75th)			
Min, Max			
EQ-5D-5L: Self-Care			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
EQ-5D-5L: Usual Activities			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)

Min, Max	xx, xx	xx, xx	xx, xx
EQ-5D-5L: Pain/Discomfort			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
EQ-5D-5L: Anxiety/Depression	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
N	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Mean (SD)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Median (25th, 75th)	xx, xx	xx, xx	xx, xx
Min, Max			
EQ-5D: State of health rate on a scale of 1 (very poor) to 100 (very good)			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx
EQ-5D total score			
N	xxx (xx.x%)	xxx (xx.x%)	xxx (xx.x%)
Mean (SD)	xx.x (xx.x)	xx.x (xx.x)	xx.x (xx.x)
Median (25th, 75th)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)	xx.x (xx.x, xx.x)
Min, Max	xx, xx	xx, xx	xx, xx