EAST - AFNET 4

Early treatment of Atrial fibrillation for Stroke prevention Trial

An Investigator-driven, **P**rospective, Parallel-group, **R**andomized, **O**pen, **B**linded Outcom**e** Assessment (PROBE-design), Multi-centre Trial for the Prevention of Stroke in High-risk Subjects with Atrial Fibrillation.

Investigational Medical Product (IMP):

Not applicable (proof-of-principal study)

Indication:
Atrial Fibrillation

Phase of the clinical trial:
IV

EudraCT-Number:
2010-021258-20

Register-Number:
NCT number: NCT01288352

ISRCTN04708680

Date: 19th February 2021
Version: final 1.0

SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
Kompetenznetz Vorhofflimmern e.V.
Atrial Fibrillation NETwork (AFNET)
Mendelstr. 11, 48149 Münster, Germany</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume: n.a.

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<tr><td>Name of Finished Product:
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<tr><td colspan="3">Title of Study: EAST - AFNET 4

Early treatment of Atrial fibrillation for Stroke prevention Trial

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<tr><td colspan="3">Investigators:
See Appendix 1</td></tr>
<tr><td colspan="3">Study centre(s):
See Appendix 1</td></tr>
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Publication (reference):

Early Rhythm-Control Therapy in Patients with Atrial Fibrillation
Paulus Kirchhof, A.John Camm, Andreas Goette, Axel Brandes, Lars Eckardt, Arif Elvan, Thomas Fetsch, Isabelle C. van Gelder, Doreen Haase, Laurent M. Haegeli, Frank Hamann, Hein Heidbuchel, Gerhard Hindricks, Josef Kautzner, Karl-Heinz Kuck, Luis Mont, G.Andre. Ng, Josef. Rekosz, Norbert Schoen, Ulrich Schotten, Anna Suling, Jens Taggeselle, Sakis Themistoclakis, Eik Vettorazzi, Panos Vardas, Karl Wegscheider, Stephan Willems, Harry.J.G.M. Crijns, and Günter Breithardt, for the EAST-AFNET 4 Trial Investigators
October 1, 2020 The New England Journal of Medicine 2020; 383:1305-1316.
DOI: 10.1056/NEJMoa2019422

Cabins, castles, and constant hearts: rhythm control therapy in patients with atrial fibrillation
Stephan Willems, Christian Meyer, Joseph de Bono, Axel Brandes, Lars Eckardt, Arif Elvan, Isabelle C. van Gelder, Andreas Goette, Michele Gulizia, Laurent M. Haegeli, Hein Heidbuchel, Karl Georg Haeusler, Josef Kautzner, Lluis Mont, G. Andre Ng, Lukasz Szumowski, Sakis Themistoclakis, Karl Wegscheider, and Paulus Kirchhof
November 22, 2019 European Heart Journal (2019) 0, 1–10.
DOI: 10.1093/eurheartj/ehz782

Improving outcomes in patients with atrial fibrillation: Rationale and design of the Early treatment of Atrial fibrillation for Stroke prevention Trial
Paulus Kirchhof, Günter Breithardt, A. John Camm, Harry J. Crijns, Karl-Heinz Kuck, Panos Vardas, and Karl Wegscheider
Sep 2013, American Heart Journal. 2013;166(3):442-8.
DOI: 10.1016/j.ahj.2013.05.015. Epub 2013 Jul 30

Multi-ethnic genome-wide association study for atrial fibrillation
Roselli C, Chaffin MD, Weng, LC et al.
June 11, 2018, Nature Genetics volume 50: pages1225–1233(2018).
DOI: 10.1038/s41588-018-0133-9

Studied period (years): (date of first enrolment) (date of last completed) FPI: 01.07.2011 LPO: 06.03.2020	Phase of development: IV

Objectives:

The objective of the trial was to test whether an early, comprehensive, rhythm control therapy can prevent outcomes in patients with atrial fibrillation (AF) compared to usual care.

Methodology:

In this international, investigator-initiated, parallel-group, open, blinded-outcome-assessment trial, we randomly assigned patients who had early AF (diagnosed ≤1 year before enrollment) and cardiovascular conditions to receive either early rhythm control or usual care.
In the **early therapy group**, patients received either catheter ablation (usually by pulmonary vein isolation), or adequate antiarrhythmic drug therapy at an early time point. The initial therapy was selected by the local investigator. Upon AF recurrence, both modalities were combined.
Usual care was conducted following the current European Society of Cardiology (ESC) guidelines for AF treatment. Early rhythm control therapy was guided by electrocardiogram (ECG) monitoring. Usual care limited rhythm control to the management of AF–related symptoms.
All patients received oral anticoagulation, rate control therapy, and therapy of concomitant cardiovascular conditions following existing evidence.
The first primary outcome was a composite of death from cardiovascular causes, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome; the second primary outcome was the number of nights spent in hospital per year. The primary safety outcome was a composite of death, stroke, or serious adverse events related to rhythm-control therapy. Secondary outcomes, including symptoms and left ventricular function, were also evaluated.

Number of patients (planned and analysed):

Planned:

- 2810 patients according to original protocol
- 2745 patients to be randomized according to protocol amendment 2019

Analysed:

- 2789 patients with early atrial fibrillation

The primary intention-to-treat population consisted of all 2789 patients.

Diagnosis and main criteria for inclusion:

We enrolled adults (≥18 years of age) who had early AF (defined as atrial fibrillation diagnosed ≤12 months before enrolment) and who were older than 75 years of age, have had a previous transient ischemic attack (TIA) or stroke, or met two of the following criteria: age greater than 65 years, female sex, heart failure, hypertension, diabetes mellitus, severe coronary artery disease, chronic kidney disease (Modification of Diet in Renal Disease stage 3 or 4 [glomerular filtration rate, 15 to 59 ml per minute per 1.73 m^2 of body-surface area]), and left ventricular hypertrophy (diastolic septal wall width >15 mm).

Test product, dose and mode of administration, batch number:

n.a., no specific IMP was tested in this trial, only treatment strategies were compared

Treatment of cardiovascular conditions, anticoagulation, and rate control were mandated in all patients, in accordance with guideline recommendations. Patients were randomly assigned in a 1:1 ratio to receive early rhythm control or usual care, with randomization stratified according to site and with variable block lengths used for concealment of assignments.

Early rhythm control required antiarrhythmic drugs or atrial fibrillation ablation, as well as cardioversion of persistent atrial fibrillation, to be initiated early after randomization. Local study teams chose the type of rhythm-control therapy independently to deliver this treatment, using protocol guidance based on current guidelines.

Patients who were randomly assigned to early rhythm-control therapy were asked to transmit a patient-operated single-lead ECG twice per week and when symptomatic. All abnormal ECG recordings were forwarded to the study site. Documentation of recurrent AF triggered an in-person visit from the site team to escalate rhythm-control therapy as clinically indicated.

Despite this proof-of-strategy character, some authorities had insisted that within this trial an investigational drug must be defined, partly based on formalities in the registration process. Thus, antiarrhythmic drugs to control heart rhythm have formally been defined as investigational drugs in some countries. Baseline drugs for therapy of AF which are recommended parts of background therapy in AF, e.g., anticoagulants or rate controlling agents cannot be considered investigational drugs. Most of the evidence has been reviewed and is outlined in the guidelines for the management of AF of the ESC (ESC, Camm AJ et al.: ESC Guidelines for the management of patients with atrial fibrillation; Eur Heart J 2012).

In Germany, Denmark, and Switzerland antiarrhythmic drugs (amiodarone, dronedarone, flecainide and propafenone) are considered investigational drugs whereas in the other countries these are not considered investigational drugs.

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Duration of treatment:

First-patient-in to last-patient-out: approx. 8 years

EAST-AFNET 4 was an event-driven trial designed to collect 685 first primary outcome events. The trial design included three planned interim analyses after accrual of 25%, 50%, and 75% of the outcome events. The trial was terminated due to efficacy at the third interim analysis. Including the overrun between the interim analysis and the end of observation period, the primary analysis was based on 565 first primary outcome events. A duration of the entire trial of around 8 years was expected. In-person follow-up visits were planned after 12 and 24 months in all patients. All patients were followed-up until the end of the trial with an average follow-up period of 5 years.

Reference therapy, dose and mode of administration, batch number:

Patients who were randomly assigned to usual care were initially treated with rate-control therapy without rhythm-control therapy. Rhythm-control therapy was only used to mitigate uncontrolled AF–related symptoms during adequate rate-control therapy (i.e., therapy that maintained the heart rate within guideline-recommended targets).

Standard management of AF:
All treatments applied within the trial were guideline-conform. The early therapy strategy differed in timing of rhythm control therapy only. Management of AF followed evidence-based therapy recommendations as summarized in the ESC guidelines for the management of AF. This standard management consisted of adequate antithrombotic therapy by either continuous therapy with vitamin K antagonists (achieving an International Normal Ratio (INR) of 2-3) or by approved non-vitamin K antagonist oral anticoagulants such as thrombin inhibitors or factor Xa inhibitors. The choice of agent and monitoring was to follow local routine.
In patients with AF, ventricular rate was to be well controlled. This was usually achieved by a resting heart rate of 80 – 100 beats per minute (bpm). An inadequately controlled ventricular rate was to be reduced by atrioventricular (AV) nodal slowing agents.

Furthermore, the recommendations regarding reduction of cardiovascular risk factors and treatment of concomitant cardiovascular conditions, like hypertension, diabetes mellitus, vascular heart disease, and heart failure were to be followed.

To ensure that rate and rhythm control therapy was applied safely, timely and within the current guidelines for AF management, a section of the study protocol details suggested procedures for antiarrhythmic drug therapy and for catheter ablation that are appropriate in the context of early therapy. This guidance was aligned with guideline recommendations. When these therapeutic modalities are applied in the conventional care group, the same recommendations apply.

Recommendations for usual care:
Usual care closely follows the suggestions laid out in the current guidelines for AF. In addition to the therapeutic modalities mentioned above, antithrombotic therapy and therapy of underlying heart disease, usual care usually consists of an initial attempt to control symptoms by rate control therapy. Rhythm control interventions are only indicated when symptoms cannot be controlled by optimal rate control therapy in the usual care group.

Criteria for evaluation:

Efficacy:

Primary outcome parameter
The two components of the multiple primary outcome parameter assess clinically relevant outcomes from the perspective of the patient (cardiovascular death, stroke, acute heart failure, acute coronary syndromes) and from the perspective of the health care system (nights spent in hospital).
The 1st primary outcome parameter is defined as the time to the first occurrence of a composite of

- cardiovascular death,
- stroke or TIA with matching lesion on imaging (ischemic stroke and hemorrhagic stroke, includes intracranial hemorrhage),
- worsening of heart failure, and
- acute coronary syndrome,

the latter two assessed by hospitalizations.

The second primary outcome parameter is nights spent in hospital per year. This parameter integrates a majority of health care expenditures and medical efforts in the management of the EAST-AFNET 4 trial population. Nights spent in hospital was chosen over other parameters because it is easily and objectively counted.

Secondary outcome parameters
The secondary outcome parameters are defined as

- all-cause death,
- AF-related death,
- time to the first occurrence of each of the components of the 1st primary outcome,
- time to recurrent AF (paroxysmal, persistent, long-lasting persistent, permanent),
- time to first therapy change,
- time to first cardiovascular hospitalization,
- number of cardiovascular hospitalizations (over-night stay),
- left ventricular function at 24 months (change as compared to baseline (continuous) as well as categorized <50 vs. ≥50),
- change in quality of life at 24 months compared to baseline (questionaires EQ-5D, SF-12),
- functional classification of AF at 12 and 24 months (European Heart Rhythm Association (EHRA) score)
- health-related cost calculation (volumes of medical data (e.g., nights spent in hospital, prescription of cardiovascular drugs)),
- change of cognitive function (Montreal Cognitive Assessment (MoCA)) at 24 months compared to baseline (continuous),
- cardiac rhythm (sinus rhythm and pacing vs. arrhythmia; at 12 and 24 months compared to baseline),
- time to first symptomatic AF recurrence,
- time to first progression of AF (from paroxysmal to persistent or long-lasting persistent or permanent and each of these components).

Some further outcome parameters will be investigated in sub-studies that will apply additional tests such as intensified ECG monitoring, advanced imaging techniques such as three-dimensional echocardiography, or cerebral magnetic resonance imaging, among others.

Safety:

Safety outcome parameters:
The **primary safety outcome parameter** is a composite of death including cardiovascular death, stroke/TIA, and serious adverse events of special interest related to rhythm control therapy
Secondary safety outcome parameters are the components of this composite, the number of serious adverse events of all types and of each type separately.

Statistical methods:

The trial was designed as an event-driven trial. The first and second primary outcomes were tested independently for differences between the treatment groups at an overall two-sided type 1 error rate of 4% for the first primary outcome and 1% for the second primary outcome to reach an overall type 1 error rate of 5%. A between-group difference of 20% in the annual rate of the first primary outcome was deemed a clinically relevant difference. We calculated that 685 events would be needed to show a 20% difference in the event rate for the first primary outcome with a power of 80%.
Under the assumption of an event rate of 8% per year in the control group, a recruitment time of 48 months, a minimum follow-up time of 24 months, and a loss-to-follow-up of 5% of the observation time, a sample of 2810 patients was calculated to be needed. After a prespecified blinded interim analysis of pooled event data that was performed after 42 months of recruitment, follow-up time was increased to 30 months and the recruitment period to 65 months, resulting in a modified sample of 2745 patients without modifying the required number of events. Three unblinded interim analyses for early determination of significance were conducted by the data and safety monitoring board when 25%, 50%, and 75% of the required events of the first primary outcome had occurred.
The analyses of the primary outcomes included all patients who underwent randomization and at least one follow-up assessment. The analysis of the first primary outcome was a comparison of end-point review committee–adjudicated events between the treatment groups. The analysis followed a group-sequential design with three interim analyses with O'Brien–Fleming stopping boundaries and two-sided log-rank tests comparing early rhythm control with usual care. Deaths from non-cardiovascular causes were treated as censored. Additional events at the termination of the trial were included with the use of the inverse normal method. As the primary result of the trial, the two-sided P value based on Tsiatis, Rosner, and Mehta stagewise ordering, accompanied by the corresponding median unbiased estimate of the hazard ratio and 96% confidence interval, is given.
The second primary outcome was calculated as the observed sum of nights in hospital divided by the individual follow-up time (in days; in the case of a follow-up time of 0 days, 0.01 days of follow-up was assumed) and reported as annualized rates. The difference between the treatment groups was estimated as the arithmetic mean and t-based 99% confidence interval. For the primary analysis of the second primary outcome, a mixed negative binomial regression model was used.
Explanations of the sensitivity analyses and analyses of secondary outcomes and further statistical details are provided in the Appendix 4.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary Outcomes

The trial was stopped for efficacy at the third interim analysis after a median follow-up of 5.1 years per patient. A first-primary-outcome event occurred in 249 patients assigned to receive early rhythm control (3.9 per 100 person-years) and in 316 patients assigned to receive usual care (5.0 per 100 person-years) (Appendix 3: Table 2)
When the results were adjusted for the group-sequential design of the trial, a first-primary-outcome event was found to have occurred less often in patients assigned to early rhythm control than in patients assigned to usual care (hazard ratio, 0.79; 96% confidence interval [CI], 0.66 to 0.94; P = 0.005) (Appendix 3: Figure 2). The effects of early rhythm control on individual components of the first primary outcome were consistent with the overall result (Appendix 3: Table 2). The effect of early rhythm control on the first primary outcome remained stable after adjustment for relevant covariates (hazard ratio, 0.78; 95% CI, 0.66 to 0.92; P = 0.004) (Appendix 3: Figure 3). There was no significant difference in the mean (±SD) number of nights spent in the hospital between the treatment groups (early rhythm control, 5.8±21.9 days per year; usual care, 5.1±15.5 days per year; P = 0.23) (Appendix 3: Table 2).

Secondary Outcomes

Left ventricular function and cognitive function were stable at 2 years, with no evidence of significant differences between the treatment groups (Appendix 3: Table 2). Most patients in both groups were free from AF–related symptoms at 2 years, and the change from baseline in AF–related symptoms (EHRA score) and quality of life (EQ-5D score) did not differ significantly between the groups (Appendix 3: Table 2).

SAFETY RESULTS:

The numbers of patients with a primary-safety-outcome event did not differ significantly between the treatment groups (early rhythm control, 231 patients; usual care, 223 patients) (Appendix 3: Table 3 and Table S4). Numerically there were fewer deaths in the patients randomized to early rhythm control without significant differences to usual care. Stroke occurred less frequently among patients assigned to early rhythm control than among those assigned to usual care. Serious adverse events related to rhythm-control therapy were more common in the group assigned to early rhythm control but were infrequent; during the 5-year follow-up period, such events occurred in 68 patients (4.9%) assigned to early rhythm control and 19 patients (1.4%) assigned to usual care (Appendix 3: Table 3 and Table 4).

SUMMARY – CONCLUSIONS

Risk-Assessment regarding Covid-19-Pandemic:

Safety of patients:
Due to End of Observation being set to 06.03.2020 and to collection of last FU information via postal questionnaires (no personal visits), the safety of study participants was not affected by the current pandemic.

No IMP was in use.

Quality measures:
On site Monitoring was finalized before start of pandemic.

CONCLUSION:

Early initiation of rhythm control therapy reduced cardiovascular outcomes in patients with early AF and cardiovascular conditions without affecting nights spent in hospital.
As expected, the early rhythm control strategy was associated with more adverse events related to rhythm control therapy, but the overall safety of both treatment strategies was comparable.
These results have the potential to inform the future use of rhythm control therapy, further improving the care of patients with early AF.
Early rhythm control therapy should be offered to all patients with recently diagnosed AF and concomitant cardiovascular diseases in addition to oral anticoagulation, rate control, and therapy of concomitant cardiovascular conditions.

Date of the report:

19th February 2021

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Appendix:

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

EAST - AFNET 4

Early treatment of Atrial fibrillation for Stroke prevention Trial

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REPORT AUTHOR: Heidi Oellers-Smith, Atrial Fibrillation NETwork

Coordinating Chief Investigator: Prof. Dr. med. Paulus Kirchhof

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For sponsor: Dr. Doreen Haase - Managing Director Atrial Fibrillation NETwork -

Date/Signature: 19 Feb 2021 D. Haase _____

Statistician: Prof. Karl Wegscheider

Date/Signature: _____

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

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29 May 2020

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gb	Univ.-Hospital Manchester, GB	Dr. Neil Davidson
gb	Hospital Greater Manchester, GB	Dr. Mita Kale
gb	Hospital Bury Lancashire, GB	Dr. Mohammed Khalid
gb	Univ.-Hospital Basildon, GB	Dr. Stuart Harris
gb	Univ.-Hospital West Yorkshire, GB	Dr. Muzahir Tayebjee
it	Hospital Bari San Paolo, I	Dr. Pasquale Caldarola
it	Hospital Reggio Emilia, I	Dr. Nicola Bottoni
it	Univ.-Hospital Rome La Sapienza, I	Prof. Francesco Fedele
it	Univ.-Hospital Padova, I	Dr. Emanuele Bertaglia
it	Univ.-Hospital Varese, I	Prof. Dr. Roberto de Ponti
it	Hospital Mestre, I	Prof. Dr. Sakis Themistoclakis
it	Hospital Catania, I	Prof. Dr. Michele Gulizia
it	Hospital Cerignola, I	Dr. Michele Cannone
it	Hospital Acquaviva delle Fonti, I	Dr. Massimo Grimaldi
it	Hospital Castelnovo Ne Monti, I	Dr. Gianni Zobbi
it	Hospital Feltre, I	Dr. Aldo Bonso
it	Hospital Montecchio, I	Dr. Elisabetta Catellani
it	Hospital Guastalla, I	Dr. Alessandro Navazio
it	Hospital Pordenone, I	Dr. Ermanno Dametto
it	Hospital Rom, I	Dr. Leonardo Calò
it	Hospital Portogruaro, I	Dr. Francesco di Pede
nl	Hospital Zwolle, NL	Dr. Arif Elvan
nl	Hospital Zutphen, NL	Dr. Arthur Maas
nl	Hospital Haarlem, NL	Dr. R. Tukkie
nl	Univ.-Hospital Groningen, NL	Prof. Dr. Isabelle Van Gelder
nl	Univ.-Hospital Maastricht, NL	Dr. Carl Timmermans
nl	Hospital Harderwijk, NL	Dr. Eugène van Beek
nl	Hospital Leiderdorp, NL	Dr. Kjell Bogaard
nl	Hospital Den Haag, NL	Dr. Anouk van Alem
nl	Univ.-Hospital Leiden, NL	Prof. Dr. Katja Zeppenfeld
nl	Hospital Heerlen, NL	Dr. G.M.G. Paulussen
nl	Hospital Stadskanaal, NL	Dr. Arie Gerhard Vijn
nl	Hospital Schiedam, NL	Dr. Suzanne Valk
nl	Hospital Assen, NL	Dr. Martin de Leeuw
nl	Univ.-Hospital Rotterdam, NL	Dr. Rohit Ettyray Bhagwandien
nl	Hospital Roermond, NL	Dr. Patrick Peerenboom
pl	Hospital WSPRiTS Warsaw, PL	Dr. Jerzy Rekosz
pl	Hospital Institute of Cardiology Warsaw, PL	Prof. Dr. Lukasz Szumowski
pl	Hospital Warsaw Ministry of Interior Affairs, PL	Dr. Magdalena Sztechman-Czub
pl	Hospital Warsaw Nat. Inst. of Cardiology, PL	Dr. Piotr Michalek
pl	Hospital Warsaw, Nat. Inst. of Cardiology, valvular heart disease, PL	Prof. Dr. Tomasz Hryniewiecki
pl	Univ.-Hospital Katowice, PL	Dr. Anna-Maria Wnuk-Wojnar

Protocol History:

EAST: Early treatment of Atrial fibrillation for Stroke prevention Trial
An Investigator-driven, **P**rospective, Parallel-group, **R**andomized, **O**pen, **B**linded Outcom**e** Assessment (PROBE-design), Multi-centre Trial for the Prevention of Stroke in High-risk Subjects with Atrial Fibrillation.
EudraCT number: 2010-021258-20
ISRCTN04708680
ClinicalTrial.gov: NCT01288352
Sponsor: Atrial Fibrillation NETwork [AFNET]

Protocol
Version control:
Final, dated September 21st, 2010
Amended, dated December 10th, 2010
Amended, dated April 11th, 2011, Denmark only
Amended, dated October 11th, 2011, administrative
Amended, dated December 9th, 2011
Amended, dated May 10th, 2013, administrative
Amended, dated May 14th, 2015
Amended, dated August 12th, 2019, administrative

Amendment December 1 0 th , 2010
Essential changes:

….
6.2.3 Inclusion criteria
Old version (September 21 s t , 2010) :
….
• heart failure (stable NYHA II or LVEF <50%)
….
New version:
….
• stable heart failure (NYHA II or LVEF <50%)
….
Rationale:
Correction of wrong word order.
…

Further administrative changes

Amended, dated December 9th, 2011

See Attachment for essential changes

Further administrative changes

Amended, dated May 14th, 2015

See Attachment for essential changes

Further administrative changes

6.1 Informed Consent

Old version (Oct 11th, 2011):

A signed, ethics committee/IRB approved informed consent form (Appendix VIII), written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (Appendix XVI) and the applicable laws for research using medical devices and drugs, will be obtained from every patient prior to any study-related procedure. Screening assessment such as blood sampling or recording of a resting ECG is considered to be performed routinely during clinical routine and therefore is not considered to be part of study related procedures.

The investigator or responsible medical staff will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet (Appendix VIII). The patient will be given sufficient time to consider the study's implications before deciding whether to participate. ~~Should the investigator choose to produce his own information sheet, then the details provided by the study information sheet should be regarded as the minimum written explanation required. Information sheets of investigators must be version-tracked and approved by the responsible Ethics Committee / Institutional Review Board (IRB) before first use.~~

.....

New version:

A signed, ethics committee/IRB approved informed consent form (Appendix VIII), written in accordance with country-specific applicable data privacy acts, the Declaration of Helsinki (Appendix XVI) and the applicable laws for research using medical devices and drugs, will be obtained from every patient prior to any study-related procedure. Screening assessment such as blood sampling or recording of a resting ECG is considered to be performed routinely during clinical routine and therefore is not considered to be part of study related procedures.

The investigator or responsible medical staff (or other designated research staff if permitted by the relevant national regulations) will explain the nature, purpose and risks of the study and provide the patient with a copy of the patient information sheet (Appendix VIII). The patient will be given sufficient time to consider the study's implications before deciding whether to participate.

.....

Rationale:

Editorial change for reason of clarity:
a) According to ICH-GCP and the EU Directive 2001/20/EC also designated research staff may provide the patient with study information and
b) deletion of redundant information already provided in the first paragraph of this section.

6.2.2 Patient Screening and Screening Registry

Old version (Oct 11th, 2011):

All participating study sites cooperating with screening facilities will be equipped with patient-operated single-lead ECG devices. These will be used to screen for asymptomatic AF in patients at high risk for AF and for stroke. This screening will be performed in facilities where a population with a high risk for AF is expected, e.g. in neurology clinics and stroke units, in hypertension clinics etc. The screening is intended to facilitate early diagnosis of AF and to allow an early (timely) intervention within the protocol. The screening can be done by any of the study site team members (e.g. study nurses) and can be repeated as often as deemed necessary. ~~Screening activities are not part of the study procedures.~~

.....

New version:

All participating study sites cooperating with screening facilities will be equipped with patient-operated single-lead ECG devices. These will be used to screen for asymptomatic AF in patients at high risk for AF and for stroke. This screening will be performed in facilities where a population with a high risk for AF is expected, e.g. in neurology clinics and stroke units, in hypertension clinics etc. The screening is intended to facilitate early diagnosis of AF and to allow an early (timely) intervention within the protocol. The screening can be done by any of the study site team members (e.g. study nurses) and can be repeated as often as deemed necessary

.....

Rationale:

Editorial change for the sake of clarity (capable of being misunderstood).

6.2.14 Exclusion criteria

Old version (Oct 11th, 2011):

....

E14. Severe renal dysfunction (stage V, requiring or almost requiring dialysis~~, glomerular filtration rate (GFR) < 10 ml/min~~).

.....

New version:

....

E14. Severe renal dysfunction (stage V, requiring or almost requiring dialysis).

.....

Rationale:

Editorial change for reason of clarity: According to KDOQI (Kidney Disease Outcome Quality Initiative), MDRD stage V is defined as GFR < 15 ml/min. By mistake, a different GFR value was initially mentioned within the protocol.

7.3.1 Antiarrhythmic rhythm control drug therapy

Old version (Oct 11th, 2011):

Antiarrhythmic drug therapy using ion channel blockers is an essential part of early and comprehensive rhythm control in EAST. Given the fact that recurrent AF may be caused by many different processes, antiarrhythmic drug therapy should not be modified upon the first or second AF recurrence, but should rather be considered a part of a long-term therapy concept. Important for the selection of an antiarrhythmic drug in EAST should be safety concerns. The following antiarrhythmic drugs are suggested for early and safe rhythm control therapy in EAST:

.....

New version:

Antiarrhythmic drug therapy using ion channel blockers is an essential part of early and comprehensive rhythm control in EAST and should be initiated within two weeks after randomisation latest. Given the fact that recurrent AF may be caused by many different processes, antiarrhythmic drug therapy should not be modified upon the first or second AF recurrence, but should rather be considered a part of a long-term therapy concept. Important for the selection of an antiarrhythmic drug in EAST should be safety concerns. The following antiarrhythmic drugs are suggested for early and safe rhythm control therapy in EAST:

.....

Rationale:

Editorial change: clarification in order to distinguish between early rhythm control by ablation (for reason of feasibility in clinical routine to be performed within two months after it's indication, i.e. after randomization) and early rhythm control by antiarrhythmic drug therapy that should be initiated earlier.

7.3.2 Rate control therapy

Old version (Oct 11th, 2011):

....

Table 3: Suggested daily doses for rate control agents. These drugs are readily available and used in all study sites. The aim of rate control is adequate control of ventricular rate during AF.

Metoprolol	100 – 200 mg/d (often 3 x 47.5 mg/d) po
Bisoprolol	5 – 10 mg/d po
Digoxin	0.2 mg/d maintenance dose, loading is usually required for 3-7 days
Digitoxin	0.07 mg/d po maintenance dose, loading is usually required for 3-7 days
Verapamil	3 x 80 mg/d po, no loading dose required

.....

New version:

....

Table 3: Suggested daily doses for rate control agents. These drugs are readily available and used in all study sites. The aim of rate control is adequate control of ventricular rate during AF.

Metoprolol	100 – 200 mg/d (often 3 x 47.5 mg/d) po
Bisoprolol	5 – 10 mg/d po
Digoxin	0.2 - 0,25 mg/d maintenance dose, loading is usually required for 3-7 days
Digitoxin	0.07 mg/d po maintenance dose, loading is usually required for 3-7 days
Verapamil	3 x 80 mg/d po, no loading dose required

.....

Rationale:

Editorial change, i.e. correction of daily dosage of Digoxin in accordance to daily routine.

7.4 Concomitant medication

Old version (Oct 11th, 2011):

.....
ß-adrenoreceptor blockers (ß-blockers) are permitted (except sotalol), but should be used with caution. Dronedarone, propafenone and amiodarone have AV-nodal slowing properties in addition to their antifibrillatory effects. Therefore, the ß-blocker dose should be adapted to achieve adequate rate during AF if given concomitantly with dronedarone, propafenone or amiodarone. Dronedarone may increase plasma levels of digoxin. Therefore, it should be expected that patients could require and tolerate lower doses of digoxin than usual.
.....

New version:

.....
ß-adrenoreceptor blockers (ß-blockers) are permitted (except sotalol that is not considered as ß-blocker but as antiarrhythmic drug), but should be used with caution. Dronedarone, propafenone and amiodarone have AV-nodal slowing properties in addition to their antifibrillatory effects. Therefore, the ß-blocker dose should be adapted to achieve adequate rate during AF if given concomitantly with dronedarone, propafenone or amiodarone. The dose of other rate-controlling agents should be adjusted if needed. Dronedarone may increase plasma levels of digoxin. Therefore, it should be expected that patients could require and tolerate lower doses of digoxin than usual.
.....

Rationale:

Editorial change, i.e. clarification of wording.

7.6 Ablation procedure

Old version (Oct 11th, 2011):

.....

Each ablation procedure should be performed not later than two months after its indication, i. e. two months after randomisation or two months after AF recurrence ~~outside of the therapy stabilization period.~~

7.6.1 Re-ablation with the aim to re-isolate the pulmonary veins

.....
Similar to the first procedure, re-ablation should be performed as early as possible, and no later than 2 months after documentation of recurrent arrhythmias.

New version:

.....

In patients of the early therapy group, each ablation procedure should be performed not later than two months after its indication, i. e. two months after randomisation or two months after AF recurrence requiring escalation of rhythm control therapy.

7.6.1 Re-ablation with the aim to re-isolate the pulmonary veins

.....
Similar to the first procedure, in patients of the early therapy group, re-ablation should be performed as early as possible, and no later than 2 months after documentation of recurrent arrhythmias.

Rationale:

Editorial change, i.e. specification necessary as the aim of an early ablation and re-ablation procedure applies to patients of the early therapy group, only.

8.2 Serious Adverse Events

Old version (Oct 11th, 2011):

(hospitalization for AF ablation not specified)

New version:

(added as last paragraph)

A catheter ablation for AF (if performed during a hospitalisation) is **not** considered as "hospitalisation" in the sense of the criteria for Serious Adverse Events as it is part of the therapy within the context of the EAST study. A catheter ablation for AF will be documented in the eCRF as extra "visit" but must not be documented as Serious Adverse Event unless any other criteria for seriousness is met.

Rationale:

Administrative change: Catheter ablation for AF usually is performed during a hospital stay and as part of the rhythm control therapy is an expected intervention within the context of the EAST study. Thus it is neither considered as adverse event nor fulfilling the criteria for seriousness.

8.3 Recording and Reporting Serious Adverse Events and Adverse Events of Special Interest (if serious)

Old version (Oct 11th, 2011):

.....
In the case of knowledge of a serious adverse event, the investigator must immediately (within one working day of being notified of the event):

- Fill out as a minimum the following items of the internet-based SAE report:
  - type of event,
  - description (if mandatory),
  - date of onset,

.....

New version:

.....
In the case of knowledge of a serious adverse event, the investigator must immediately (within one working day of being notified of the event):

- Fill out as a minimum the following items of the internet-based SAE report:
  - type of event,
  - description (if mandatory),
  - date of onset,
  - criteria for seriousness,
  - causal relationship to study therapy.

.....

Rationale:

Administrative change: Additional items are necessary to be completed by the investigator within the initial SAE reporting in order to enable the 2nd assessment of an SAE by the sponsor.

9.2 Baseline visit

Old version (Oct 11th, 2011):

.....
At the baseline visit, the investigator or designee will:

- .....
- Obtain a 12-lead ECG
- .....
- Perform a transthoracic echocardiography (a TTE performed within 4 weeks prior to randomisation might be used as baseline TTE ~~provided that the examination was performed at the study site~~)
- .....

New version:

.....
At the baseline visit, the investigator or designee will:

- .....
- Obtain a 12-lead ECG (an ECG performed within 14 days prior to randomisation might be used as baseline ECG)
- .....
- Perform a transthoracic echocardiography (a TTE performed within 4 weeks prior to randomisation might be used as baseline TTE)
- .....

Rationale:

Administrative change, i.e. modification for reason of feasibility in clinical routine.

9.3.3 Triggered Visits

Old version (Oct 11th, 2011):

In case AF recurrence is detected in an ECG ~~(i.e. patient-operated ECG device),~~ the investigator will schedule a triggered visit of the patient ~~within two weeks~~. During these triggered visits, the investigator or his designee will:

- Obtain a standard 12-lead ECG and evaluate AF and type of AF
- Assess for clinical events and AEs respectively SAEs occurred since the preceding visit / contact

New version:

In case AF recurrence is detected in an ECG and the decision is taken for an escalation in therapy, a triggered visit should be scheduled and therapeutic measures should be documented in the eCRF. Escalation in therapy does not include change of dosage or change of antiarrhythmic drug within the same substance class (e.g. flecainide to propafenone). During these triggered visits, the investigator or his designee will:

- Obtain a standard 12-lead ECG and evaluate AF and type of AF
- Assess for clinical events and AEs respectively SAEs occurred since the preceding visit / contact

Rationale:

Administrative change, i.e. adaptation in accordance to intended meaning and to feasibility in clinical routine.

9.7 Blood Samples

Old version (Oct 11th, 2011):

Routine laboratory parameters must be assessed within 7 days prior to planned inclusion in the study as part of the screening procedure in order to verify the enrolment criteria.

.....

New version:

Routine laboratory parameters will be assessed at baseline visit in order to determine the current laboratory status. If these parameters can be assessed from a blood sample not older than 7 days at the date of inclusion, the blood sampling does not have to be repeated.

.....

Rationale:

Administrative change for clarification: Enrolment criteria will not be assessed by a single laboratory value obtained at baseline but by taking into consideration the patient's history (e.g. a single pathological creatinine value or liver value is not a reliable predictor for renal insufficiency respectively liver disease).

Appendix X – Definitions of study assessments

Old version (Oct 11th, 2011):

Recurrent AF is any symptomatic or asymptomatic AF episode after index therapy that is documented in an ECG (longer than 30 seconds).
When AF is only documented by a single telemetric ECG, verification of the presence of AF by another technique (standard ECG, Holter ECG or implanted ECG) is required. Any documentation of AF in a standard ECG or Holter ECG constitutes an AF recurrence.

Persistent AF is present when an AF episode either lasts longer than 48 hours or is terminated by cardioversion (either with drugs or electrical shocks). Persistent AF also implies that a rhythm control therapy strategy is pursued. Persistent AF is discerned from long-lasting persistent AF by its duration and recurrence pattern.

Time to recurrent AF is defined as the time from initiation of index therapy to the first documented recurrent AF.

Time to recurrent symptomatic AF is defined as the time from initiation of index therapy to the first recurrent AF with accompanying AF-related symptoms.

New version:

Recurrent AF is any symptomatic or asymptomatic AF episode (clinically lasting longer than 30 seconds) after successful index therapy that is documented in an ECG.
When AF is only documented by a single telemetric ECG, verification of the presence of AF by another technique (standard ECG, Holter ECG or implanted ECG) is required. Any documentation of AF in a standard ECG or Holter ECG constitutes an AF recurrence.

Persistent AF is present when an AF episode either lasts longer than 7 days or is terminated by cardioversion (either with drugs or electrical shocks). Persistent AF also implies that a rhythm control therapy strategy is pursued. Persistent AF is discerned from long-lasting persistent AF by its duration and recurrence pattern.

Time to recurrent AF is defined as the time from first documented sinus rhythm after initiation of index therapy to the first documented recurrent AF of any type.

Time to recurrent symptomatic AF is defined as the time from first documented sinus rhythm after initiation of index therapy to the first recurrent AF with accompanying AF-related symptoms.

Rationale:

Editorial change, i.e. specification for the purpose of clarification.

Appendix XV – Description of ECG monitoring

Old version (Oct 11th, 2011):

Patients in the early therapy group will receive a patient-operated ECG monitoring device capable of transtelephonic transmission (Tele-ECG). This device will allow to detect asymptomatic AF recurrences. Every patient receives a personal credit card-sized, single-lead event recorder (Tele-EKG-Card 100 IR Vitaphone®, Germany) to record his ECG daily as well as to transmit the data via telephone. Several technical prerequisites had to be fulfilled: simple and safe handling by the patient, easy transtelephonic transmission of the ECG to the analysis centre, sufficient ECG quality to assess P waves, fully automatic ECG reception 24 hours a day and automated first-line rhythm analysis separating sinus rhythm ECGs from suspected rhythm disturbances. The transmitted ~~daily~~ Tele-ECG is the basis for early recognition of recurrent AF.

.....

All Tele-ECGs will be classified automatically as a) sinus rhythm, b) suspicious for rhythm disturbances or c) not valid for automated classification. In case of a), the ECG will be archived but not manually evaluated. In case of b), the ECG recording will be sent automatically as PDF to the corresponding study site for further evaluation. In case of c), the ECG will be manually classified by CRI into a) or b) or remain in c).

.....

New version:

Patients in the early therapy group will receive a patient-operated ECG monitoring device capable of transtelephonic transmission (Tele-ECG). This device will allow to detect asymptomatic AF recurrences. Every patient receives a personal credit card-sized, single-lead event recorder (Tele-EKG-Card 100 IR Vitaphone®, Germany) to record his ECG 2-3 times per week as well as to transmit the data via telephone. Several technical prerequisites had to be fulfilled: simple and safe handling by the patient, easy transtelephonic transmission of the ECG to the analysis centre, sufficient ECG quality to assess P waves, fully automatic ECG reception 24 hours a day and automated first-line rhythm analysis separating sinus rhythm ECGs from suspected rhythm disturbances. The transmitted Tele-ECG is the basis for early recognition of recurrent AF.

.....

All Tele-ECGs will be classified automatically as a) sinus rhythm, b) suspicious for atrial fibrillation, c) suspicious for other rhythm disturbances or d) not valid for automated classification. In case of a), the ECG will be archived but not manually evaluated. In case of b) and c), the ECG recording will be sent automatically as PDF to the corresponding study site for further evaluation. In case of d), the ECG will be manually classified by CRI into a), b) or c), or remain in d).

.....

Rationale:

Editorial change: Adaption according to wording in the patient information, i.e. no daily ECG recording but 2-3 times per week, only, and specification of classification within the context of the automated analysis.

5 Study Design

Old version (10.05.2013):

....

Patient recruitment is expected to be completed after 48 months.

EAST is an event-driven trial with a planned number of randomised patients of n=2,810 and a fixed number of events (n=685). 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 projected rates. All patients will be followed until the end of the trial.

....

New version:

....

Patient recruitment is expected to be completed after 65 months.

EAST is an event-driven trial with a planned number of randomised patients of n=2,745 and a fixed number of events (n=685). 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 projected rates. All patients will be followed until the end of the trial.

...

Rationale:

Regulatory approval, initiation of countries and sites, and patient recruitment has been slower than initially planned. Therefore sample size estimation and estimated study duration was adapted to reflect the observed study activity. This adaptation of recruitment period and estimated study duration, based on pooled recruitment and event rates, was planned in the initial study design. The study statistician has presented a series of power-preserving blind sample size calculations with different scenarios regarding prolongation of recruitment period and/or follow-up period based on the observed enrolment and event rates. The executive Steering Committee has decided in favour of a slightly reduced target enrolment of 2,745 randomized patients, resulting in an estimated prolongation of recruitment until end of 2016 with a follow-up period of the last patient of 30 months, as this option seems to be a reasonable adaptation of the residual study duration to be expected. The decelerated and prolonged enrolment results in more observed follow-up years per patient on average. Hence, the new, smaller patient number will be sufficient to answer the study question.

This change is considered as a non-substantial modification.

5.1 Study Flow Chart

Old version (10.05.2013):

Study Procedures

.....

Outpatient FU at 12, 24, ~~36~~ months (both study groups)

....

New version:

.....

Outpatient FU at 12 and 24 months (both study groups)

.....

Rationale:

The clinical visit at month 36 will be replaced by a central follow-up visit to improve the collection of primary outcome events. Perception gained after 4 years of study conduct reveal that serious adverse events and primary endpoints are detected reliably via central FU questionnaires which trigger subsequent evaluation of detected events by the responsible study site. Importantly, all planned secondary outcomes will be analysed for the 2 year follow up (FU) time point. The protocol and analysis plan specified a comparison at this time point, where information from all patients will be available. Further, replacing the FU month 36 visit with a central follow-up visit results in less work load for study sites and will make the FU easier for patients, which will lead to improved compliance of sites during the prolonged duration of this long-term trail.

Replacing the in-person FU visit at month 36 with a central follow-up will not have impact on the safety of the patients because clinical events will be notified via central FU questionnaires and at regular clinical routine visits of the patients at which serious adverse events can be documented in the e-CRF at any time.

This change is considered as a non-substantial modification.

6.2.1 Number of patients

Old version (10.05.2013):

A total of 2,810 patients will be randomised. The sample size anticipates a loss-to-follow-up of 5% of the total observation time. The sample size may be adapted once in a blinded manner as described in the statistics section (section 12).

New version:

A total of 2,745 patients will be randomised. The sample size anticipates a loss-to-follow-up of 5% of the total observation time. The sample size may be adapted once in a blinded manner as described in the statistics section (section 12).

Rationale:

Regulatory approval, initiation of countries and sites, and patient recruitment has been slower than initially planned. Therefore sample size estimation and estimated study duration was adapted to reflect the observed study activity. This adaptation of recruitment period and estimated study duration, based on pooled recruitment and event rates, was planned in the initial study design. The study statistician has presented a blind sample size calculation with different scenarios regarding prolongation of recruitment period and/or follow-up period based on the observed enrolment and event rates. The executive Steering Committee has decided that a target enrolment of 2,745 randomized patients, resulting in an estimated prolongation of recruitment until end of 2016 with a follow-up period of the last patient of 30 months, seems a reasonable adaptation of the expected study duration. The slower enrolment results in more observed follow-up years per patient on average. Hence, the new, smaller patient number will be sufficient to answer the study question.

This change is considered as a non-substantial modification.

8.2. Serious Adverse Events

Old version (10.05.2013):

....

A catheter ablation for AF (if performed during a hospitalisation) is **not** considered as "hospitalisation" in the sense of the criteria for Serious Adverse Events as it is part of the therapy within the context of the EAST study. A catheter ablation for AF will be documented in the eCRF as extra "visit" but must not be documented as Serious Adverse Event unless any other criteria for seriousness is met.

New version:

....

A catheter ablation for AF (if performed during a hospitalisation) is **not** considered as "hospitalisation" in the sense of the criteria for Serious Adverse Events as it is part of the therapy within the context of the EAST study. A catheter ablation for AF will be documented in the eCRF as extra "visit" but needs not be documented as Serious Adverse Event unless any other criteria for seriousness is met.

Rationale:

Clarification of English wording (administrative change).

9.1 Visit schedule (Table 4)

Old version (10.05.2013):

Assessment	**Baseline Visit** Day 0	**Central FU*** Month 6	**Visit 1*** Month 12	**Central FU*** Month 18	**Visit 2*** Month 24	**Central FU*** Month 30	**Visit 3*** Month 36	**Central FU*** Month 42 [2]
Signed ICF (medical informed consent)	X							
Check inclusion & exclusion criteria	X							
Physical examination (PE)/ medical history	X		X		X		~~X~~	
12-lead ECG	X		X		X		~~X~~	
Laboratory parameters (blood sample)	X		X [3]		X		~~X~~ [3]	
Transthoracic echocardiography (TTE)	X				X			
Initiation of therapy (early rhythm control or usual care) [1]	X							
Karnofsky score	X		X		X		~~X~~	
MoCA	X				X			
Quality of Life (EQ-5D, SF-12)	X				X			
Adverse event/ serious adverse event		X	X	X	X	X	X	X

[1] In patients with persistent AF, an early cardioversion will be performed.

[2] Further central follow-up is planned in 6-monthly intervals until the end of the whole trial.

[3] Only INR / PT and alpha-PTT

* Time window +/- 2 month

New version:

Assessment	**Baseline Visit** Day 0	**Central FU*** Month 6	**Visit 1*** Month 12	**Central FU*** Month 18	**Visit 2*** Month 24	**Central FU*** Month 30	**Central FU*** Month 36	**Central FU*** Month 42 [2]
Signed ICF (medical informed consent)	X							
Check inclusion & exclusion criteria	X							
Physical examination (PE)/ medical history	X		X		X			
12-lead ECG	X		X		X			
Laboratory parameters (blood sample)	X		X [3]		X			
Transthoracic echocardiography (TTE)	X				X			
Initiation of therapy (early rhythm control or usual care) [1]	X							
Karnofsky score	X		X		X			
MoCA	X				X			
Quality of Life (EQ-5D, SF-12)	X				X			
Adverse event/ serious adverse event		X	X	X	X	X	X	X

[1] In patients with persistent AF, an early cardioversion will be performed.

[2] Further central follow-up is planned in 6-monthly intervals until the end of the whole trial.

[3] Only INR / PT and alpha-PTT

* Time window +/- 2 month

Rationale:

The clinical visit at month 36 will be replaced by a central follow-up visit to improve the collection of primary outcome events. Perception gained after 4 years of study conduct reveal that serious adverse events and primary endpoints are detected reliably via central FU questionnaires which trigger subsequent evaluation of detected events by the responsible study site. Importantly, all planned secondary outcomes will be analysed for the 2 year follow up (FU) time point. The protocol and analysis plan specified a comparison at this time point, where information from all patients will be available. Further, replacing the FU month 36 visit with a central follow-up visit results in less work load for study sites and will make the FU easier for patients, which will lead to improved compliance of sites during the prolonged duration of this long-term trail.

Replacing the in-person FU visit at month 36 with a central follow-up will not have impact on the safety of the patients because clinical events will be notified via central FU questionnaires and at regular clinical routine visits of the patients at which serious adverse events can be documented in the e-CRF at any time.

This change is considered as a non-substantial modification.

9.3 Follow-up

Old version (10.05.2013):

Information regarding study-relevant outcomes / events will be obtained by questionnaires in 6-monthly intervals, starting at month 6 until month 72 or longer if necessary (i.e. central follow-up). Personal follow-up visits will be performed at months 12, 24~~, and 36~~ only (instead of the central follow-up) as study-relevant technical measurements and health-economic information are expected to change only little in the long-term follow-up after three years.
All patients will be followed until completion of the total trial for outcome and safety. As some outcome events (e.g. stroke or myocardial infarction) are not directly related to the trial intervention, we encourage adherence to the assigned therapy group even after a primary outcome event occurred.
For all follow-up visits, a time window of +/- 2 months is allowed.

9.3.1 Clinical Visits (Months 12, ~~24, and 36, or longer if deemed necessary)~~

....

9.3.2 Central Follow-up ~~(Months 6, 18, 30, 42, 48, 54, 60, 66, 72 or longer if necessary)~~

....

New version:

Information regarding study-relevant outcomes / events will be obtained by questionnaires in 6-monthly intervals, starting at month 6 until month 90 or longer if necessary (i.e. central follow-up). Personal follow-up visits will be performed at months 12 and 24 only (instead of the central follow-up) as study-relevant technical measurements and health-economic information are expected to change only little in the long-term follow-up after three years.

All patients will be followed until completion of the total trial for outcome and safety. As some outcome events (e.g. stroke or myocardial infarction) are not directly related to the trial intervention, we encourage adherence to the assigned therapy group even after a primary outcome event occurred.
For all follow-up visits, a time window of +/- 2 months is allowed.

9.3.1 Clinical Visits (Months 12 and 24)

....

9.3.2 Central Follow-up

....

Rationale:

It was never planned to continue clinical visits at yearly intervals, whereas questionnaires within the context of the central follow-up will be continued in 6-monthly intervals after the last in person visit until the global end of the trial.

The clinical visit at month 36 will be replaced by a central follow-up visit to improve the collection of primary outcome events. Perception gained after 4 years of study conduct reveal that serious adverse events and primary endpoints are detected reliably via central FU questionnaires which trigger subsequent evaluation of detected events by the responsible study site. Importantly, all planned secondary outcomes will be analysed for the 2 year follow up (FU) time point. The protocol and analysis plan specified a comparison at this time point, where information from all patients will be available. Further, replacing the FU month 36 visit with a central follow-up visit results in less work

load for study sites and will make the FU easier for patients, which will lead to improved compliance of sites during the prolonged duration of this long-term trail.

Replacing the in-person FU visit at month 36 with a central follow-up will not have impact on the safety of the patients because clinical events will be notified via central FU questionnaires and at regular clinical routine visits of the patients at which serious adverse events can be documented in the e-CRF at any time.

This change is considered as a non-substantial modification.

10.1 Overall Duration of Study

Old version (10.05.2013):

With an expected screening and enrolment period of four years and a sliding initiation of sites over a period of 12 months, and a minimum follow-up period of another two years, overall study duration is calculated to be six years. The end of the study will be established, when the number of primary outcomes for final analysis has been reached (refer to section 12). This will be defined by the eSC based on the information provided by CRI and the study statistician. Final data cleaning will require presumably two more months after study closure.

New version:

With an expected screening and enrolment period of 65 months and a sliding initiation of sites over a period of about 18 months, and a minimum follow-up period of another 30 months, overall study duration is calculated to be approximately 8 years (95 months). The end of the study will be established, when the number of primary outcomes for final analysis has been reached (refer to section 12). This will be defined by the eSC based on the information provided by CRI and the study statistician. Final data cleaning will require presumably two more months after study closure.

Rationale:

Patient recruitment and the process of site initiation have been slower than initially planned. Therefore estimated study duration was adapted to reflect the observed study activity. Based on pooled recruitment and event rates the study statistician has presented a series of power-preserving blind sample size calculations with different scenarios regarding prolongation of recruitment period and/or follow-up period. The executive Steering Committee has decided that a fixed prolongation of recruitment until end of 2016 (i.e. overall 5 years and 5 months) with a follow-up period of the last patient of 30 months seems a reasonable estimate of study duration.

In view of EAST being an event-driven trial with a fixed number of events but an estimated overall duration and total number of patients, this change is considered non-substantial modification.

10.2 Individual duration of Study

Old version (10.05.2013):

According to the study protocol, follow-up is planned in 6-monthly intervals after enrolment until the end of the study. It is expected that the mean follow-up time will be about four years per patient with a minimum follow-up time of two years and a maximum follow-up time of presumably six years. Every patient will be followed-up until the end of the entire study.

New version:

According to the study protocol, follow-up is planned in 6-monthly intervals after enrolment until the end of the study. It is expected that the mean follow-up time will be about five years per patient with a minimum follow-up time of 30 months and a maximum follow-up time of presumably approximately 8 years (95 months). Every patient will be followed-up until the end of the entire study or death.

Rationale:

Patient recruitment and the process of site initiation have been slower than initially planned. Therefore estimated study duration was adapted to reflect the observed study activity. Based on pooled recruitment and event rates the study statistician has presented a series of power-preserving blind sample size calculations with different scenarios regarding prolongation of recruitment period and/or follow-up period. The executive Steering Committee has decided that a fixed prolongation of recruitment until end of 2016 (i.e. overall 5 years and 5 months) with a follow-up period of the last patient of 30 months seems a reasonable estimate of study duration.

In view of EAST being an event-driven trial with a fixed number of events but an estimated overall duration and total number of patients, this change is considered non-substantial modification.

12.2 Sample size calculation

Old version (10.05.2013):

....

Based on these assumptions and further assumptions on recruitment and on follow-up as defined before, a sample size calculation for a group sequential design with four stages was performed resulting in a required recruitment of 2,810 patients at a rate of 59 pts/month to compensate a loss-to-follow-up of 5% of the observation time to keep an overall alpha level of 5% two-sided and to reach a power of 80%. Details are given in Appendix XI.

....

New version:

....

Based on these assumptions and further assumptions on recruitment and on follow-up as defined before, a sample size calculation for a group sequential design with four stages was performed resulting in a required recruitment of 2,745 patients at a rate of 42 pts/month to compensate a loss-to-follow-up of 5% of the observation time to keep an overall alpha level of 5% two-sided and to reach a power of 80%. Details are given in Appendix XI.

....

Rationale:

Regulatory approval, initiation of countries and sites, and patient recruitment has been slower than initially planned. Therefore sample size estimation and estimated study duration was adapted to reflect the observed study activity. This adaptation of recruitment period and estimated study duration, based on pooled recruitment and event rates, was planned in the initial study design. The study statistician has presented a series of power-preserving blind sample size calculations with different scenarios regarding prolongation of recruitment period and/or follow-up period based on the observed enrolment and event rates. The executive Steering Committee has decided in favour of a slightly reduced target enrolment of 2,745 randomized patients, resulting in an estimated prolongation of recruitment until end of 2016 with a follow-up period of the last patient of 30 months, as this option seems to be a reasonable adaptation of the residual study duration to be expected. The decelerated and prolonged enrolment results in more observed follow-up years per patient on average. Hence, the new, smaller patient number will be sufficient to answer the study question.

This change is considered as a non-substantial modification.

15.1.4 Endpoint Review Committee

Old version (10.05.2013):

The Endpoint Review Committee (ERC) will centrally adjudicate all outcome events in EAST, i.e.:

- cardiovascular death,
- TIA or stroke,
- worsening of heart failure assessed by hospitalisation,
- acute coronary syndrome assessed by hospitalisation and
- cardiovascular hospitalisation

as well as any hospitalisation for other reason and any other SAE. Furthermore, cardiovascular deaths will be sub-classified as AF-related death or non AF-related deaths.

~~In addition, the ERC will determine the expectedness of an adverse reaction (details regarding this process will be described in the ERC charter).~~

The committee will be blinded to therapy group and will consist of experienced clinicians not related to the trial (refer to Appendix V).

New version:

The Endpoint Review Committee (ERC) will centrally adjudicate all outcome events in EAST, i.e.:

- cardiovascular death,
- TIA or stroke,
- worsening of heart failure assessed by hospitalisation,
- acute coronary syndrome assessed by hospitalisation and
- cardiovascular hospitalisation

as well as any hospitalisation for other reason and any other SAE. Furthermore, cardiovascular deaths will be sub-classified as AF-related death or non AF-related deaths.

The committee will be blinded to therapy group and will consist of experienced clinicians not related to the trial (refer to Appendix V).

Rationale:

According to current European Guidelines it is the sponsor's responsibility to assess the expectedness of an SAE. The sponsor has delegated this responsibility to CRI. Only in cases where the responsible person at CRI cannot judge an SAE, the ERC will provide support to identify possible suspected unexpected serious adverse reactions (SUSARs). This procedure is described in the ERC charter and implemented since study start.

Thus, this modification is considered administrative change.

15.1.6 Ablation Committee

Old version (10.05.2013):

A specific Ablation Committee consisting of experienced clinicians (refer to Appendix VII) will propose and update a list of suitable techniques, catheters, and devices for the ablation procedures performed within the EAST trial. The committee will limit that list to approved devices, used in-line, with proven efficacy, usual in at least one controlled study. Experimental and new devices should not be used for AF ablation within the EAST trial. If local routine is based on other devices and techniques than those listed in the aforementioned list, the ablation site in question will disclose the proposed procedure and its outcome to the Ablation Committee. The committee and the local study site will seek a consensus solution for safe and effective AF ablation therapy at that site.

New version:

(deleted)

Rationale:

Pulmonary vein isolation performed by catheter ablation for the treatment of atrial fibrillation has become a clinical routine procedure in recent years with clinically established routine processes and techniques. After four years of study conduct an ablation committee providing recommendations for suitable techniques, catheters, and devices for the ablation procedures reveals no longer necessary.

Omitting the ablation committee has neither impact on the scientific value nor on the safety of study patients. Thus, this modification is considered non-substantial.

Appendix VIII: Patient Information and Informed Consent

NOTE: The wording of the patient information / informed consent included in the protocol is an English master version, only. It does not correspond to the English version to be used in UK study sites.

Old version (protocol version 10.05.2013):

3. What are the procedures of this clinical trial and what do I have to bear in mind in case of participation?

....

Further study participation will depend on the result of this baseline examination. In case of participation three follow-up visits will take place at annual intervals (months 12, 24, 36) in the hospital/medical practice of your study doctor. In between these visits, you will receive, likewise at annual intervals (months 6, 18, 30) and thereafter in 6-monthly intervals (months 42, 48, 54, etc.), a questionnaire by mail to collect information about hospital stays and other important events during the past year respectively 6-month-period. The number of questionnaires will depend on the total duration of this clinical trial: in any case you will regularly be followed-up until the end of the entire study, with a minimum follow-up period of two years.

....

New version:

3. What are the procedures of this clinical trial and what do I have to bear in mind in case of participation?

....

Further study participation will depend on the result of this baseline examination. In case of participation two follow-up visits will take place at annual intervals (months 12 and 24) in the hospital/medical practice of your study doctor. In between these visits, you will receive, likewise at annual intervals (months 6, 18, 30) and thereafter in 6-monthly intervals (months 36, 42, 48, 54, etc.), a questionnaire by mail to collect information about hospital stays and other important events during the past year respectively 6-month-period. The number of questionnaires will depend on the total duration of this clinical trial: in any case you will regularly be followed-up until the end of the entire study, with a minimum follow-up period of two and a half years.

....

Rationale:

Omission of follow-up visit month 36 and replacement by a questionnaire as well as prolonged minimum follow-up-period are considered non-substantial changes.
For all patients included in the study until mid of 2016, the prolonged minimum follow-up-period has no effect because in anyway those patients are followed-up until the end of the entire study, i.e. longer than two years. Only those patients included in the last half year of recruitment period might have a prolonged minimum follow-up period of two and a half year. Thus, at the time of this protocol amendment, included study patients do not need to be informed retrospectively about the prolonged minimum follow-up.
Patients included in the study after implementation of this protocol amendment will be provided with an updated patient information and informed consent form which has been to be approved by the corresponding Ethics Committee on beforehand.

Appendix IX: Time Schedule

Old version (10.05.2013):

	Tasks	Date
Study planning	Draft Protocol, review and finalisation by Steering Committee	06/09-06/10
Study preparation	Set up of e-TMS (MARVIN), preparation of e-CRF; preparation of all other study relevant documentation	09/09-09/10
Study initiation	▪ Site selection, site contacts	10/09-12/10
	▪ Supply of the sites with study materials, initiation visits (country-wise)	03/11-12/11
	▪ Recruitment period (FPI to LPI)	04/11-03/15
	▪ Treatment / Follow-up of last patient (LPI to LPO)	04/15-03/17
Study duration	Mean follow-up period of all patients, assuming a linear patient recruitment	48 months
Interim analyses	▪ Blinded interim analysis for sample size recalculation	04/14 (or when 2,400 patients have been recruited)
	▪ 1st interim analysis (approx. 32 months after FPI	10/13
	▪ 2nd interim analysis (approx. 47 months after FPI)	approx. 03/15
	▪ 3rd interim analysis (approx. 59 months after FPI)	approx. 02/16
Study closure	Final data cleaning /study closure	04/17-05/17
Final analysis	Statistical analysis, incl. review by Steering Committee	06/17-08/17

6.2.1 Number of patients

Old version (10.05.2013):

A total of 2,810 patients will be randomised. The sample size anticipates a loss-to-follow-up of 5% of the total observation time. The sample size may be adapted once in a blinded manner as described in the statistics section (section 12).

New version:

A total of 2,745 patients will be randomised. The sample size anticipates a loss-to-follow-up of 5% of the total observation time. The sample size may be adapted once in a blinded manner as described in the statistics section (section 12).

Rationale:

Regulatory approval, initiation of countries and sites, and patient recruitment has been slower than initially planned. Therefore sample size estimation and estimated study duration was adapted to reflect the observed study activity. This adaptation of recruitment period and estimated study duration, based on pooled recruitment and event rates, was planned in the initial study design. The study statistician has presented a blind sample size calculation with different scenarios regarding prolongation of recruitment period and/or follow-up period based on the observed enrolment and event rates. The executive Steering Committee has decided that a target enrolment of 2,745 randomized patients, resulting in an estimated prolongation of recruitment until end of 2016 with a follow-up period of the last patient of 30 months, seems a reasonable adaptation of the expected study duration. The slower enrolment results in more observed follow-up years per patient on average. Hence, the new, smaller patient number will be sufficient to answer the study question.

This change is considered as a non-substantial modification.

Figure 1

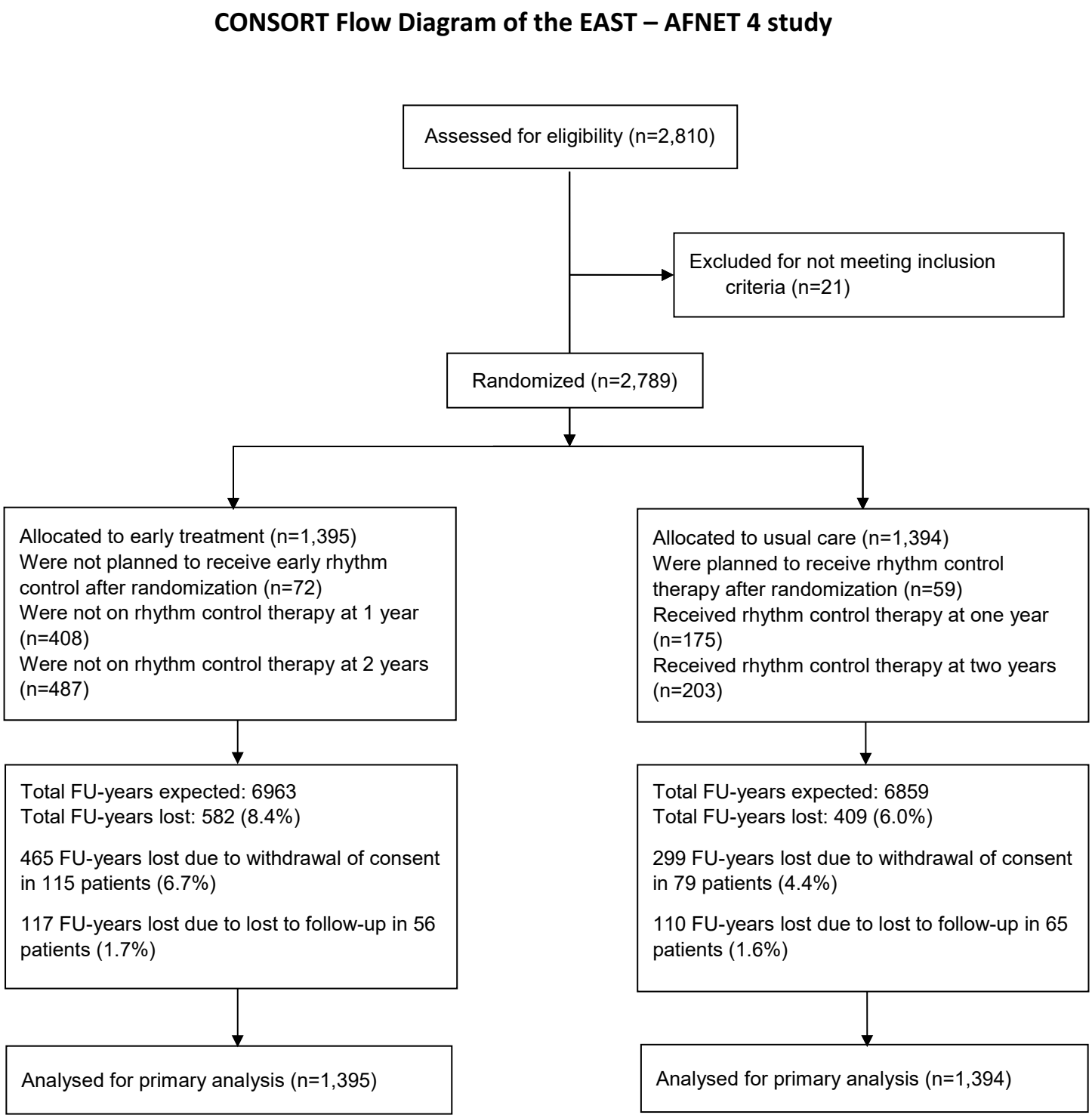

CONSORT Flow Diagram of the EAST – AFNET 4 study
Assessed for eligibility (n=2,810)
Excluded for not meeting inclusion criteria (n=21)
Randomized (n=2,789)
Allocated to early treatment (n=1,395)
Were not planned to receive early rhythm control after randomization (n=72)
Were not on rhythm control therapy at 1 year (n=408)
Were not on rhythm control therapy at 2 years (n=487)
Allocated to usual care (n=1,394)
Were planned to receive rhythm control therapy after randomization (n=59)
Received rhythm control therapy at one year (n=175)
Received rhythm control therapy at two years (n=203)
Total FU-years expected: 6963
Total FU-years lost: 582 (8.4%)
465 FU-years lost due to withdrawal of consent in 115 patients (6.7%)
117 FU-years lost due to lost to follow-up in 56 patients (1.7%)
Total FU-years expected: 6859
Total FU-years lost: 409 (6.0%)
299 FU-years lost due to withdrawal of consent in 79 patients (4.4%)
110 FU-years lost due to lost to follow-up in 65 patients (1.6%)
Analysed for primary analysis (n=1,395)
Analysed for primary analysis (n=1,394)

Table 1: Clinical characteristics

Baseline demographic, clinical characteristics and medications at discharge from the baseline visit by randomized group and the overall trial population. This table provides a longer list of clinical characteristics than the table published in the main paper.

		Randomized group		
		Early rhythm control (N=1395)	Usual care (N=1394)	Total (N=2789)
Age	Mean ± SD	70.2 ± 8.4	70.4 ± 8.2	70.3 ± 8.3
	Median [IQR]	71.0 [65.0;76.0]	71.0 [66.0;76.0]	71.0 [66.0;76.0]
	Range	39.0-94.0	34.0-91.0	34.0-94.0
Age ≥ 75 years		403 (28.9%)	409 (29.3%)	812 (29.1%)
Sex (Male)		750 (53.8%)	746 (53.5%)	1496 (53.6%)
Weight [kg] [N=2777]	Mean ± SD	85.0 ± 18.4	85.0 ± 18.2	85.0 ± 18.3
	Median [IQR]	82.0 [72.0;95.0]	84.0 [72.5;95.0]	83.0 [72.2;95.0]
	Range	42.0-180.0	42.0-190.0	42.0-190.0
Body Mass Index [N=2776]	Mean ± SD	29.2 ± 5.4	29.3 ± 5.4	29.3 ± 5.4
	Median [IQR]	28.4 [25.5; 32.0]	28.7 [25.4; 32.3]	28.6 [25.5; 32.1]
	Range	16.6 - 58.2	15.9 - 56.7	15.9 - 58.2
AF Characteristics				
Type of AF	First episode	528/1391 (38.0%)	520/1394 (37.3%)	1048/2785 (37.6%)
	Paroxysmal	501/1391 (36.0%)	493/1394 (35.4%)	994/2785 (35.7%)
	Persistent	362/1391 (26.0%)	381/1394 (27.3%)	743/2785 (26.7%)
Heart rhythm at baseline	Atrial fibrillation or atrial flutter	627/1389 (45.1%)	650/1393 (46.7%)	1277/2782 (45.9%)
	Sinus rhythm	762/1389 (54.9%)	743/1393 (53.3%)	1505/2782 (54.1%)
Duration of AF history at baseline (days) [N=2786]	Mean ± SD	81.5 ± 172.5	85.5 ± 185.1	83.5 ± 178.9
	Median [IQR]	36.0 [6.0;114.0]	36.0 [6.0;112.0]	36.0 [6.0;112.0]
	Range	0.0-4586.0	0.0-4109.0	0.0-4586.0
Overall symptom score (EHRA score)	EHRA I (asymptomatic)	395/1305 (30.3%)	406/1328 (30.6%)	801/2633 (30.4%)
	EHRA II	666/1305 (51.0%)	692/1328 (52.1%)	1358/2633 (51.6%)
	EHRA III	230/1305 (17.6%)	217/1328 (16.3%)	447/2633 (17.0%)
	EHRA IV	14/1305 (1.1%)	13/1328 (1.0%)	27/2633 (1.0%)
AF therapy	Previous cardioversion	546/1364 (40.0%)	543/1389 (39.1%)	1089/2753 (39.6%)

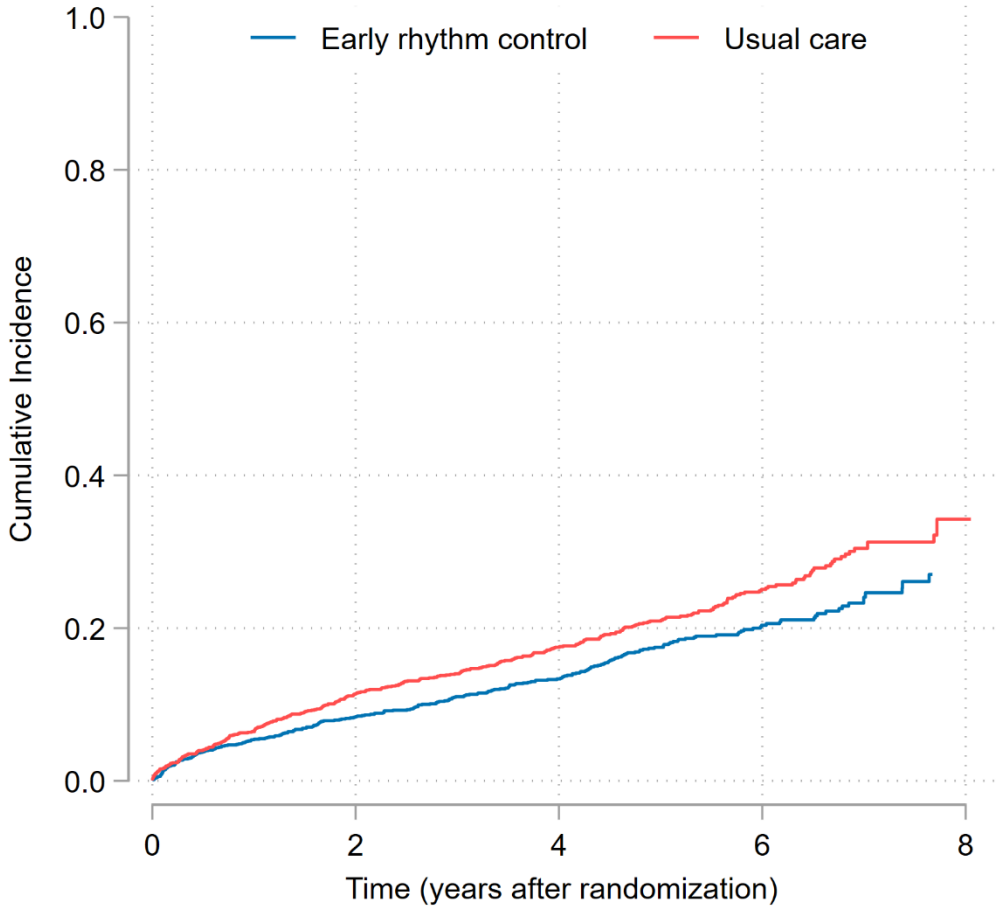
Table 2: First primary endpoint and components, incidences and test results between randomized groups (N=2789).*****

	Events		Person-years		Incidence		HR [95% CI]	p-value Cox	p-value log-rank	PH-test
	ERC	**UC**	**ERC**	**UC**	**ERC**	**UC**				
First primary outcome	249	316	6399.1	6332.2	0.039	0.050	0.782 [0.662-0.923]	0.004	0.004	0.824
Cardio-vascular death	67	94	6915.4	6987.8	0.010	0.013	0.718 [0.525-0.983]	0.039	0.040	0.942
Stroke	40	62	6812.8	6855.9	0.006	0.009	0.652 [0.438-0.97]	0.035	0.034	0.856
Worsening of heart failure	139	169	6620.3	6557.5	0.021	0.026	0.814 [0.65-1.02]	0.073	0.076	0.784
Acute coronary syndrome	53	65	6762.0	6816.2	0.008	0.010	0.828 [0.576-1.191]	0.309	0.308	0.814

*****Cox-regression including randomized group as fixed factor and site as random effect.

ERC Early rhythm control, HR hazard ratio, PH proportional hazards, UC Usual care.

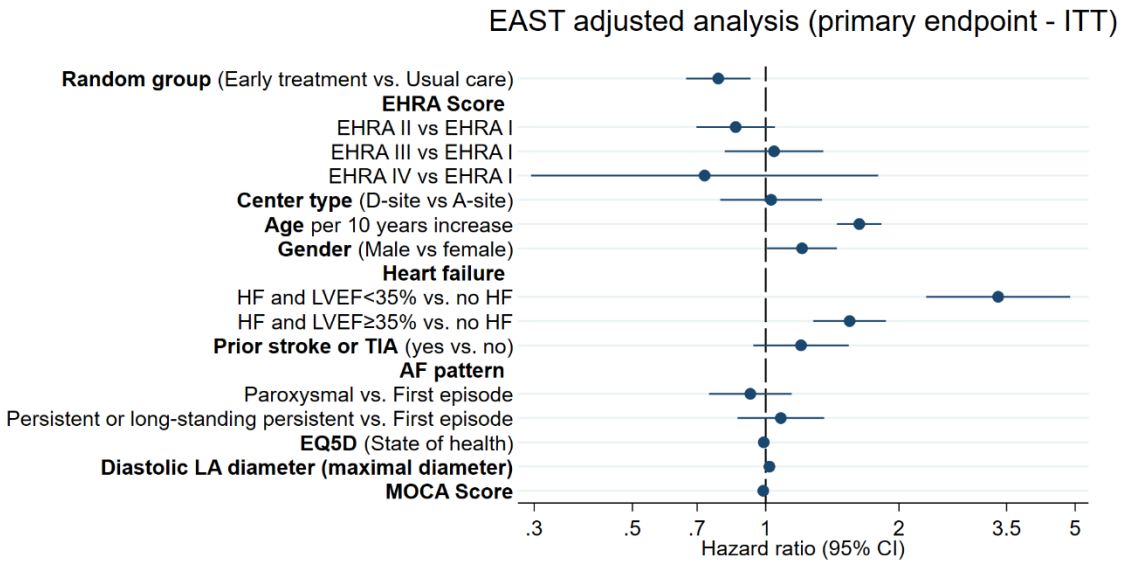
Figure 2: Cumulative incidence curves (Aalen-Johansen) of first occurrence of cardiovascular death, stroke, or hospitalization with worsening of heart failure or acute coronary syndrome (first primary outcome parameter) by randomized group.



Patients at risk

Early rhythm control	1395	1193	913	404	26
Usual care	1394	1169	888	405	34

Figure 3: List of covariates for the adjusted analysis of the first primary outcome.



This figure highlights covariates that influenced the occurrence of first primary outcome events in the EAST–AFNET 4 population. These covariates were identified prior to unblinding without consideration of the randomized group. The presented hazard ratios with 95% confidence intervals result from a multiple Cox-regression including a pre-specified list of covariates as fixed effects and site as random effect. Intention to treat (ITT) population (n=2789, events=565) using multiply imputed dataset.

Table 3. Safety outcomes.

		Randomized group		Total (N=2789)	p-value
		Early rhythm control (N=1395)	Usual care (N=1394)		
Occurrence of a primary safety outcome		231 (16.6%)	223 (16.0%)	454 (16.3%)	0.698
Occurrence of stroke		40 (2.9%)	62 (4.4%)	102 (3.7%)	0.027
Occurrence of cardiovascular death		67 (4.8%)	94 (6.7%)	161 (5.8%)	0.028
Occurrence of a serious adverse event of special interest (related to rhythm control therapy, detailed listing of events given in lines below)		68 (4.9%)	19 (1.4%)	87 (3.1%)	<0.001
AV block		2 (0.1%)	0 (0.0%)	2 (0.1%)	
Bleeding related to AF ablation, major		6 (0.4%)	0 (0.0%)	6 (0.2%)	
Bleeding related to AF ablation, non major		1 (0.1%)	2 (0.1%)	3 (0.1%)	
Blood pressure related (hypotension, hypertension; except syncope)		1 (0.1%)	0 (0.0%)	1 (0.0%)	
Drug toxicity of AF-related drug therapy		10 (0.7%)	3 (0.2%)	13 (0.5%)	
Drug-induced bradycardia		14 (1.0%)	5 (0.4%)	19 (0.7%)	
Hospitalization for AF		11 (0.8%)	3 (0.2%)	14 (0.5%)	
Implantation of a pacemaker, defibrillator, cardiac resynchronization device, or any other cardiac device		8 (0.6%)	4 (0.3%)	12 (0.4%)	
Non-fatal cardiac arrest		1 (0.1%)	1 (0.1%)	2 (0.1%)	
Other cardiovascular event		5 (0.4%)	1 (0.1%)	6 (0.2%)	
Other event		1 (0.1%)	3 (0.2%)	4 (0.1%)	
Pericardial tamponade		3 (0.2%)	0 (0.0%)	3 (0.1%)	
Syncope		4 (0.3%)	1 (0.1%)	5 (0.2%)	
Torsade de Pointes tachycardia		1 (0.1%)	0 (0.0%)	1 (0.0%)	
Worsening of heart failure, decompensated		3 (0.2%)	0 (0.0%)	3 (0.1%)	
Number of serious adverse events of all types	Mean ± SD	2.4 ± 3.0	2.5 ± 3.0	2.4 ± 3.0	0.590
	Median [IQR]	1.0 [0.0;3.0]	1.0 [0.0;3.0]	1.0 [0.0;3.0]	
	Range	0.0-24.0	0.0-24.0	0.0-24.0	
Occurrence of death		138 (9.9%)	164 (11.8%)	302 (10.8%)	0.105

*****For dichotomous outcomes mixed logistic regression models with a random effect for center were used for comparison of random groups. For number of serious adverse event of special interest mixed negative binomial regression models with a random effect for center were used for comparison of random groups.

AF atrial fibrillation, AV atrioventricular, IQR inter quartile range, SD standard deviation.

	AF ablation	0/1390 (0.0%)	0/1394 (0.0%)	0/2784 (0.0%)
	Surgical treatment of AF	0/1390 (0.0%)	1/1394 (0.1%)	1/2784 (0.0%)
Diastolic LA diameter [mm] [N=2407]	Mean ± SD	43.8 ± 8.4	44.0 ± 8.6	43.9 ± 8.5
	Median [IQR]	43.0 [38.0;48.0]	43.0 [39.0;48.0]	43.0 [38.0;48.0]
	Range	23.0-86.0	19.0-85.0	19.0-86.0
Concomitant conditions				
Prior stroke or transient ischemic attack		175 (12.5%)	153 (11.0%)	328 (11.8%)
MoCA total score [N=2667]	Mean ± SD	25.5 ± 3.7	25.5 ± 3.8	25.5 ± 3.8
	Median [IQR]	26.0 [23.0;28.0]	26.0 [23.0;28.0]	26.0 [23.0;28.0]
	Range	6.0-30.0	4.0-30.0	4.0-30.0
At least mild cognitive impairment (MoCA < 26)		582/1326 (43.9%)	584/1341 (43.5%)	1166/2667 (43.7%)
Arterial hypertension		1230 (88.2%)	1220 (87.5%)	2450 (87.8%)
Systolic blood pressure [mmHg] [N=2776]	Mean ± SD	136.5 ± 19.4	137.5 ± 19.3	137.0 ± 19.3
	Median [IQR]	135.0 [122.0;150.0]	136.0 [123.0;150.0]	135.0 [123.0;150.0]
	Range	85.0-240.0	90.0-230.0	85.0-240.0
Diastolic blood pressure [mmHg] [N=2776]	Mean ± SD	80.9 ± 12.1	81.3 ± 12.0	81.1 ± 12.0
	Median [IQR]	80.0 [73.0;90.0]	80.0 [74.0;90.0]	80.0 [73.0;90.0]
	Range	42.0-126.0	40.0-126.0	40.0-126.0
Stable heart failure (NYHA stage II or LVEF < 50%)		396 (28.4%)	402 (28.8%)	798 (28.6%)
Heart failure symptoms (NYHA classification)	No heart failure	905/1390 (65.1%)	914/1394 (65.6%)	1819/2784 (65.3%)
	I	165/1390 (11.9%)	166/1394 (11.9%)	331/2784 (11.9%)
	II	255/1390 (18.3%)	259/1394 (18.6%)	514/2784 (18.5%)
	III	65/1390 (4.7%)	55/1394 (3.9%)	120/2784 (4.3%)
Severe coronary artery disease (previous myocardial infarction, CABG or PCI)		243 (17.4%)	236 (16.9%)	479 (17.2%)
Peripheral artery disease		63 (4.5%)	59 (4.2%)	122 (4.4%)
Diabetes		351/1390 (25.3%)	343/1394 (24.6%)	694/2784 (24.9%)
History of valve replacement		11/1390 (0.8%)	12/1394 (0.9%)	23/2784 (0.8%)
CHA_2DS_2-VASc Score [N=2784]	Mean ± SD	3.4 ± 1.3	3.3 ± 1.3	3.3 ± 1.3
	Median [IQR]	3.0 [2.0;4.0]	3.0 [2.0;4.0]	3.0 [2.0;4.0]
	Range	1.0-8.0	1.0-9.0	1.0-9.0
Left ventricular hypertrophy		65 (4.7%)	67 (4.8%)	132 (4.7%)
Valvular heart disease		609/1389 (43.8%)	642/1391 (46.2%)	1251/2780 (45.0%)

Table 4. All adjudicated SAE per patient.

	Early Rhythm Control (N=1395)	Usual Care (N=1394)
SAE of special interest		
1 - Transient ischemic attack (TIA)	23 (1.6%)	23 (1.6%)
2 - Ischemic stroke (including transient events with matching lesion on cerebral imaging)	34 (2.4%)	51 (3.7%)
3 - Hemorrhagic stroke	8 (0.6%)	12 (0.9%)
4 - Stroke, other cause	0 (0.0%)	0 (0.0%)
5 - Stroke, unknown cause	0 (0.0%)	0 (0.0%)
6 - STEMI	11 (0.8%)	9 (0.6%)
9 - NSTEMI	26 (1.9%)	44 (3.2%)
10 - Unstable AP	16 (1.1%)	15 (1.1%)
11 - Stable AP or atypical chest pain	65 (4.7%)	39 (2.8%)
12 - Worsening of heart failure, decompensated	134 (9.6%)	165 (11.8%)
13 - Worsening of heart failure, not decompensated	10 (0.7%)	12 (0.9%)
14 - Torsade de Pointes tachycardia	1 (0.1%)	0 (0.0%)
15 - Ventricular tachycardia	4 (0.3%)	4 (0.3%)
16 - Ventricular fibrillation	3 (0.2%)	3 (0.2%)
17 - Drug-induced bradycardia	34 (2.4%)	22 (1.6%)
18 - AV nodal block	5 (0.4%)	3 (0.2%)
19 - Ablation-induced or drug-induced atrial flutter / atrial tachycardia	4 (0.3%)	1 (0.1%)
20 - Syncope	55 (3.9%)	44 (3.2%)
21 - Bleeding caused by catheter intervention or antithrombotic therapy	53 (3.8%)	59 (4.2%)
22 - Pulmonary vein stenosis	0 (0.0%)	0 (0.0%)
23 - Pericardial tamponade	6 (0.4%)	2 (0.1%)
24 - Atrio-esophageal fistula	0 (0.0%)	0 (0.0%)
25 - Drug toxicity of AF-related drug therapy	17 (1.2%)	8 (0.6%)
26 - Non-fatal cardiac arrest	10 (0.7%)	4 (0.3%)
27 - Cardiac transplantation	0 (0.0%)	0 (0.0%)
28 - Any type of cardiovascular surgery	57 (4.1%)	57 (4.1%)
29 - Implantation of a pacemaker, ICD, CRT or any other cardiac device	98 (7.0%)	103 (7.4%)
30 - Percutaneous coronary (e.g. PCI), cerebrovascular or peripheral procedure	81 (5.8%)	79 (5.7%)
31 - Blood pressure related (hypotension, hypertension; except syncope)	47 (3.4%)	53 (3.8%)
32 - Cardiovascular infection (e.g. endocarditis, pericarditis, infectious myocarditis)	5 (0.4%)	3 (0.2%)
33 - Major bleeding	104 (7.5%)	88 (6.3%)
34 - Pulmonary embolism or deep vein thrombosis	15 (1.1%)	12 (0.9%)
35 - Hospitalization for AF	306 (21.9%)	297 (21.3%)
36 - Other cardiovascular event	99 (7.1%)	91 (6.5%)
37 - Other event	654 (46.9%)	686 (49.2%)
38 - Death as primary event (sudden death)	66 (4.7%)	72 (5.2%)
MedDRA Primary System Organ Class of all SAE		
Blood and lymphatic system disorders	21 (1.5%)	22 (1.6%)
Cardiac disorders	526 (37.7%)	527 (37.8%)
Congenital, familial and genetic disorders	3 (0.2%)	4 (0.3%)
Ear and labyrinth disorders	19 (1.4%)	11 (0.8%)
Endocrine disorders	13 (0.9%)	5 (0.4%)
Eye disorders	7 (0.5%)	5 (0.4%)

	Early Rhythm Control (N=1395)	Usual Care (N=1394)
Gastrointestinal disorders	107 (7.7%)	103 (7.4%)
General disorders and administration site conditions	179 (12.8%)	185 (13.3%)
Hepatobiliary disorders	17 (1.2%)	22 (1.6%)
Immune system disorders	3 (0.2%)	4 (0.3%)
Infections and infestations	187 (13.4%)	201 (14.4%)
Injury, poisoning and procedural complications	208 (14.9%)	227 (16.3%)
Investigations	54 (3.9%)	43 (3.1%)
Metabolism and nutrition disorders	19 (1.4%)	27 (1.9%)
Musculoskeletal and connective tissue disorders	63 (4.5%)	54 (3.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	133 (9.5%)	130 (9.3%)
Nervous system disorders	165 (11.8%)	164 (11.8%)
Product issues	4 (0.3%)	7 (0.5%)
Psychiatric disorders	8 (0.6%)	13 (0.9%)
Renal and urinary disorders	46 (3.3%)	46 (3.3%)
Reproductive system and breast disorders	6 (0.4%)	8 (0.6%)
Respiratory, thoracic and mediastinal disorders	75 (5.4%)	75 (5.4%)
Skin and subcutaneous tissue disorders	9 (0.6%)	15 (1.1%)
Surgical and medical procedures	571 (40.9%)	584 (41.9%)
Vascular disorders	135 (9.7%)	153 (11.0%)
MedDRA Primary System Organ Class of non-cardiovascular SAE		
Blood and lymphatic system disorders	14 (1.0%)	17 (1.2%)
Cardiac disorders	5 (0.4%)	6 (0.4%)
Congenital, familial and genetic disorders	2 (0.1%)	4 (0.3%)
Ear and labyrinth disorders	19 (1.4%)	10 (0.7%)
Endocrine disorders	8 (0.6%)	5 (0.4%)
Eye disorders	4 (0.3%)	4 (0.3%)
Gastrointestinal disorders	72 (5.2%)	73 (5.2%)
General disorders and administration site conditions	79 (5.7%)	86 (6.2%)
Hepatobiliary disorders	17 (1.2%)	20 (1.4%)
Immune system disorders	3 (0.2%)	3 (0.2%)
Infections and infestations	181 (13.0%)	199 (14.3%)
Injury, poisoning and procedural complications	108 (7.7%)	147 (10.5%)
Investigations	11 (0.8%)	18 (1.3%)
Metabolism and nutrition disorders	17 (1.2%)	25 (1.8%)
Musculoskeletal and connective tissue disorders	62 (4.4%)	54 (3.9%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	129 (9.2%)	130 (9.3%)
Nervous system disorders	50 (3.6%)	38 (2.7%)
Product issues	0 (0.0%)	1 (0.1%)
Psychiatric disorders	7 (0.5%)	13 (0.9%)
Renal and urinary disorders	44 (3.2%)	37 (2.7%)
Reproductive system and breast disorders	6 (0.4%)	8 (0.6%)
Respiratory, thoracic and mediastinal disorders	43 (3.1%)	46 (3.3%)
Skin and subcutaneous tissue disorders	9 (0.6%)	14 (1.0%)
Surgical and medical procedures	270 (19.4%)	288 (20.7%)
Vascular disorders	4 (0.3%)	4 (0.3%)

AF atrial fibrillation, AP angina pectoris, AV atrioventricular, CRT cardiac resynchronization therapy, ICD implantable cardioverter-defibrillator, MedDRA Medical Dictionary for Regulatory Activities, NSTEMI non-ST elevation myocardial infarction, PCI percutaneous coronary intervention, SAE serious adverse event(s), STEMI ST elevation myocardial infarction.

Statistical analysis - details

Database for the current analysis

On 17 February 2020 a meeting of the Data Safety Monitoring Board (DSMB) of EAST–AFNET 4 took place at which the 3rd planned interim analysis was discussed, including safety data until 15 January 2020 and more than 514 first primary outcome events. Following the closed session, the DSMB recommended to the executive Steering Committee (eSC) to stop the trial for effectiveness as the 3rd interim analysis showed a positive effect regarding the first primary outcome parameter which reached the pre-defined significance level given for the 3rd interim analysis in Appendix XI of the study protocol and in the DSMB charter. This recommendation was formalized in a letter to the eSC on 5 March 2020. In its meeting on 6 March 2020, the eSC of the EAST-AFNET 4 trial unanimously agreed to follow the statement of the DSMB and to recommend to end the observation period for all patients on the day of the meeting and to subsequently terminate the total trial. The sponsor followed this recommendation on 6 March 2020 which then became the end of observation (EOO).

To obtain complete follow-up information on all patients with the best achievable precision, all centers were asked to contact their study patients to enable a rapid collection of data on events that occurred up to the date of trial termination (final assessment). This final assessment followed the same procedures as the follow-up questionnaires described above. The end of study date was set to 31 May 2020, the last event was adjudicated by the Endpoint Review Committee on 12 June 2020, and the final database was locked on 29 June 2020. The final database included the overrun of events occurring between 15 January 2020 (status of data base for the 3rd interim analysis) and 6 March 2020 (EOO). This database was used for the analyses presented here.

Consideration of site effects

In EAST-AFNET 4, the recruitment of centers was performed in a two-step procedure. First, centers that were able to perform ablation procedures were selected (A sites). These ablation centers selected smaller hospitals or office-based cardiologists, that operated as full study sites (D sites) and executed all study procedures with the exception of AF ablation, which, when needed, was performed in the ablation site of that cluster[1]. With this recruitment strategy, a special cluster structure results of D sites nested in A sites, reflecting potential differences between A sites and D sites due to differences in patient populations and medical standards. This cluster structure had to be taken into account for the randomization procedure as well as for the statistical analysis. Therefore, the randomization was stratified by D sites. In the statistical analysis, potential site effects were taken into account by adding two nested random terms for D sites within A sites to the statistical models. However, during the statistical analysis it turned out that the contribution of A sites to the cluster effect was marginal while the contribution of D sites was substantial. We thus decided to model a common cluster effect for A and D sites to increase model stability. Cluster effects were taken into regard in almost all statistical models, denoted by the term 'mixed' in the model descriptions. The only exceptions were the interim analyses during the running study after adjudication of 25%, 50%, and 75% of the first primary outcome events, and the primary analysis of the first primary outcome that took the interim analysis into account.

The described models take into regard the cluster effect due to site differences in patients and medical standard. They do not take into account whether the treatment effect of early rhythm-control differs between sites. The subgroup analysis in **Figure S5** only distinguishes between A sites without nested D sites (sites that perform atrial fibrillation (AF) ablation themselves and D sites nested in A sites (sites that only offer antiarrhythmic drug therapy themselves and refer patients for AF ablation to an A site), but not between individual D sites. The question of whether early rhythm therapy works independently of the site will be

answered in the context of more sophisticated analyses of the treatment effects which will be published at a later point in time.

Consideration of competing events

The first primary outcome parameter does not include non-cardiovascular death. Further, withdrawals may have compromised the time-to-event analyses. Both event types, non-cardiovascular death and withdrawal may not occur independently of the composite outcome parameter. Thus, it is not sufficient to model these events as censored, as it is frequently done. Instead, they should be considered as competing events in the time-to-event analysis. For this purpose, we abstained to present Kaplan-Meier curves in this paper as these curves may be biased in the presence of competing events.[2] Instead, we present Aalen-Johansen cumulative incidence curves throughout which are not biased in the presence of competing risks.[3] Further, we fitted Cox proportional hazards models for the first primary outcome (sensitivity analyses) as well as its components which allow the bias-free estimation of cause-specific hazard ratios even in the presence of competing risks.[2,4] As a sensitivity analysis we further fitted Fine and Gray models[5] to the data which explicitly include the competing events and report the results of Gray's test[6] for differences between treatments (see below in chapter 'sensitivity analyses').

Handling of missing data

To set up a proper imputation model, we followed the recommendations of White, Royston and Wood[7]. Our imputation model consisted of three "types" of variables: 1. Outcome parameter variables, which are to be imputed. These were left ventricular ejection fraction (LVEF), EQ-5D visual analogue scale (VAS), SF-12 Mental and Physical Score and Montreal Cognitive Assessment (MoCA)) (at 24 months and to optimize prediction baseline values were also included in the multiple imputation model) as well as sinus rhythm and EHRA score (at baseline, 12 and 24 months). 2. Outcome parameter variables, which do not need to be imputed, but will be used in the final regression. These were the number of nights spent in hospital as well as the primary outcome parameter (represented by the Nelson-Aalen

estimator of the cumulative hazard function and the censoring indicator). 3. Further adjusting variables, which were planned to be included in the adjusted analysis of primary outcome parameter. These were center type (A vs. D-Site), age, gender, stroke, atrial fibrillation pattern, diabetes mellitus, chronic obstructive pulmonary disease (COPD), kidney disease, diastolic left atrial diameter as well as heart failure (NYHA classification at baseline, 12 and 24 months).

Considering all those variables in all time points, we found missing values in at least one variable in 58.6% of patients. Following the rule of thumb by White, Royston & Wood[7] we decided to conduct a multiple imputation procedure with 60 repetitions. While for the EQ5D visual analogue scale it was decided in the Statistical Analysis Plan to replace the score with zero for deceased patients, for all other variables not mentioned above we did not replace missing values.

Statistical analysis of the second primary outcome parameter

Based on a blind review of the pooled database before code break, it was decided to use a zero-inflated mixed negative binomial model for the analysis of the nights spent in hospital[8]. These models combine a binomial model for hospitalization (yes/no) with a count model for the nights in hospital if hospitalized and allow to distinguish between the treatment effect on the likelihood to be hospitalized at all during the study and the treatment effect on the number of hospital nights once a patient was hospitalized. The log (years in follow-up) was used as offset for both components while a random intercept modeling site effects was only fitted to the count model.

Using this model, the odds ratio for the zero-inflated part was estimated to be 1.69, 95% CI 0.77-3.72, p=0.192, indicating a lower likelihood for hospitalization for the early rhythm-control group, while the incidence rate ratio for nights spent in hospital was estimated to 1.09, 95% CI 1.00-1.20, p=0.049, indicating a trend for a higher number of hospital nights in the early treated patients once they were hospitalized. However, both effects were not

significant as the alpha level for the second primary outcome parameter was set to 0.01. The two non-significant trends have different directions. Patients in the early rhythm-control group tended to be less frequent in hospital but to stay longer in hospital after admission. Since both effects were not significant, we simplified the model by omitting the term measuring the zero inflation, ending up with a simpler mixed negative binomial model for the counts of the hospital nights. With this model, the incidence rate ratio was estimated to be 1.08, 95% CI 0.95-1.23, p=0.226, indicating that there was no significant increase in the number of hospital nights in patents with early rhythm-control . Sensitivity analyses supported this result (see below in chapter 'sensitivity analyses').

Statistical analysis of secondary outcome parameters

Secondary outcome parameters were analyzed according to the type of scale: time-to-event outcome parameters (components of the first primary outcome: cardiovascular death, stroke, worsening of heart failure, and acute coronary syndrome) were analyzed without adjustment for group-sequential design by use of Cox-proportional hazards models with a frailty term for sites to estimate the (cause-specific) hazard ratio of early intervention compared to usual care. Proportional hazards assumption was assessed by visual inspection of log-log-plots and tested using the log hazard-ratio function (PH test). Aalen-Johansen cumulative incidence curves that take into account non-cardiovascular death as competing event were computed for visualization. Change from baseline to 24 months in continuous outcome parameters (LVEF, EQ-5D VAS, SF-12 Mental and Physical Score and MoCA) was analyzed after multiple imputation of missing values in survivors using mixed linear regression models adjusting for baseline measurement and site effect (random effect). Categorical variables determined at 24 months (patients in sinus rhythm and asymptomatic patients (EHRA I)) were analyzed using baseline-adjusted mixed logistic regression models with a random term for site after multiple imputation of missing values in survivors. For

dichotomous safety outcomes mixed logistic regression models with a random effect for site were used for comparison of random groups.

Sensitivity analyses

The presented primary analysis of the first primary endpoint takes the interim analyses during the running study into account. However, this analysis does not take potential site effects or the influence of the competing event 'non-cardiac death' into account. As a sensitivity analysis, we therefore calculated a Cox proportional hazards model with a frailty term for site effects added to the data. The resulting cause-specific hazard ratio was estimated to 0.78, 95% confidence interval [0.66- 0.92], p=0.004. The proportional hazards test was not significant. This result is almost identical to the result of the primary analysis. Additionally, we performed a Gray's test[6] that directly compares the group-specific Aalen-Johansen cumulative incidence curves[3] shown in **Figure 2** (and in **Figure S4** for the components) that take the non-cardiac death as competing event into account. This analysis was pre-specified in the Statistical Analysis Plan as a sensitivity analysis. The corresponding p-value for the primary outcome was 0.003 and again very similar to the p-value of the primary analysis. This analysis shows that the consideration of non-cardiac death as competing event does not change the conclusions of the study. Furthermore, we analyzed whether adjustment for baseline imbalances would change the estimate of the hazard ratio of the primary analysis. The forest plot[9] of the corresponding Cox regression analysis is shown in **Figure S1**. The adjusted hazard ratio of treatment was only marginally different from the estimate of the primary analysis.

For sensitivity analysis of the second primary outcome parameter, a two-sample permutation test (Fisher-Pitman[10]) was pre-specified in the Statistical Analysis Plan to compare the yearly averages of nights spent in hospital between groups. The corresponding p-value of the Fisher-Pitman-Test was 0.808. Additionally, a Mann-Whitney-U test was applied to the same data, yielding a p-value of 0.725. These results support the conclusion of non-significance in the main paper.

An additional sensitivity analysis was added post-hoc in reaction to the observation of group differences in the withdrawal rates, see below in the chapter '*Post-hoc analysis of withdrawals*'.

Post-hoc analysis of withdrawals

Surprisingly, when the data set was analyzed, it turned out that the withdrawal rates were significantly different between random groups (**Figure S2**). Differential withdrawal rates have the potential to bias a study. Since this effect was not anticipated, there was no provision for this case in the Statistical Analysis Plan. We thus performed an additional sensitivity analysis for a better understanding of the potential contribution of withdrawals to the main study results.

We first performed a cause-specific Cox regression analysis of the time to withdrawal, based on the same baseline covariates used for adjustment when analyzing the clinical outcome parameters. For this purpose, we fitted a Cox proportional hazards regression model on time to withdrawal using the imputed dataset that was used for the first primary outcome parameter. However, the covariates did not fully explain the differences between the random groups. We then added interaction terms of all adjusting variables with randomized group to the model in order to identify variables that might explain the differential withdrawal rates. After a backward selection procedure, the difference between A sites (without nested D sites) and D sites (nested in A sites) was the only variable that could explain the differential withdrawals, indicating that the excess of withdrawals in the treatment group was mainly located in A sites (p=0.012). This means that withdrawals occurred predominantly in ablation centers without supporting D sites.

Secondly, we repeated the sensitivity analysis of the first primary outcome parameter by adding withdrawal as second competing event (in addition to non-cardiac death) to the competing event model. The resulting sub-distribution hazard ratio[2] was 0.76, 95% CI 0.65-0.90, p=0.002. The resulting figures are almost identical to the figures resulting if no

correction for withdrawals is performed, indicating that the reported treatment effect is not caused by group differences in non-cardiac deaths or differential withdrawal rates.

Deviations of the published analysis from study protocol and Statistical Analysis Plan, post-hoc analyses

The analyses followed the Statistical Analysis Plan in almost all details. Small deviations and additions in the statistical methodology are described in detail above. However, not all analyses provided in the study protocol or in the Statistical Analysis Plan could be presented in this paper. A list of secondary outcomes not presented here or not analyzed yet is included in **Table S4**. AF including the best estimate of AF burden is adequately represented by the secondary outcome “cardiac rhythm (sinus rhythm and pacing vs. arrhythmia; at 12 and 24 months compared to baseline)”. The analysis of AF burden, proposed in the study protocol, is captured by the analysis of this outcome. Therefore, the planned analysis will be dropped as the number of available ECGs does not allow to meaningfully express AF burden according to its definition in the study protocol. Post-hoc a detailed sensitivity analysis of the withdrawals was added that was not pre-specified since the observation of differences in the withdrawal rates was not anticipated. This analysis is likewise documented in this statistical supplement.