ATRIAL FIBRILLATION
NETWORK

AXADIA - AFNET 8

STUDIENDESIGN

AXADIA – AFNET 8: Background

Atrial fibrillation is found in 10 – 30% of patients on chronic hemodialysis.

Patients with atrial fibrillation on hemodialysis are at very high risk of stroke and bleeding.

Drug excretion and metabolisation are disturbed in patients on hemodialysis. This alters plasma concentrations and can affect the safety and effectiveness of NOAC/DOAC therapy.

Vitamin K antagonists (VKA), in contrast, can be dose-adjusted based on INR measurements, but time in therapeutic range is often low in patients on hemodialysis treated with VKA (TTR 43-48%).

VKA may also accelerate vascular calcification in patients on hemodialysis.

Hemodialysis patients were not studied in the large NOAC/DOAC trials. Some observational data suggest relatively low stroke and bleeding rates in patients with AF on hemodialysis treated with NOACs/DOACs. Other data suggest a high risk of bleeding or death.

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AXADIA – AFNET 8: Hypothesis

Oral anticoagulation with apixaban 2.5 mg b.i.d. has non-inferior safety compared to to vitamin K antagonist therapy (target INR 2-3) in patients with atrial fibrillation on chronic hemodialysis

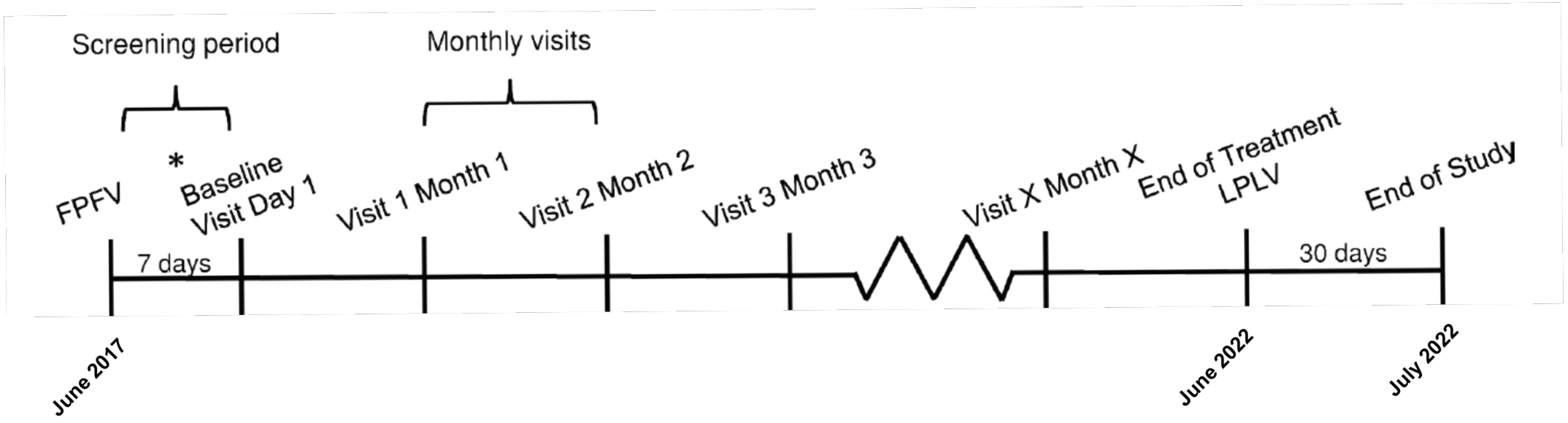
Reinecke H, et al. *BMJ Open* 8:e022690.(2018)

AXADIA – AFNET 8: Design

Prospective, randomized, open, blinded outcome assessment (PROBE) investigator-initiated trial.

Adult patients with atrial fibrillation documented on two ECGs on chronic hemodialysis and with an increased stroke risk (CHA_2DS_2-VASc score 2 or more, prior stroke if >3 months)

were randomized (1:1) to VKA (INR 2-3, phenprocoumon) or the NOAC apixaban 2.5 mg b.i.d



AXADIA-AFNET 8 study protocol and Reinecke H, et al. *BMJ Open* 8:e022690.(2018)

AXADIA – AFNET 8: Design

Primary (safety) outcome: composite of death, major bleeding, clinically relevant non-major bleeding based on the ISTH definition

Secondary (efficacy) outcome: composite of death, myocardial infarction, ischemic stroke, deep vein thrombosis, or pulmonary embolism

Event-driven trial with a fix end of follow-up in July 2022, started in June 2017

Sample size of N=108 calculated for non-inferiority, changed from superiority for bleeding in a major protocol amendment in Jan 2020 (requiring N=64 first primary outcome events)

Sponsor AFNET, funding from BMS/Pfizer

Modified from Reinecke H, et al. *BMJ Open* 8:e022690.(2018)

AXADIA – AFNET 8: Statistical analysis

Primary analysis population (mITT):

All randomized patients who received at least one dose of study drug
Kaplan-Meier estimates of the time-to-event outcome

Cox-Proportional hazard model to estimate the hazard ratio and its 95%CI

Test strategy (primary safety outcome):

1. $H_0^{\text{Non-Inferiority}}$: HR≥1.25 vs. $H_1^{\text{Non-Inferiority}}$: HR<1.25 (proof of non-inferiority of apixaban)
2. $H_0^{\text{Superiority}}$: HR≥1 vs. $H_1^{\text{Superiority}}$: HR<1 (proof of superiority of apixaban)

Sensitivity analysis was performed in the on treatment population, censoring patients at the time of study drug discontinuation, following the same analysis plan.

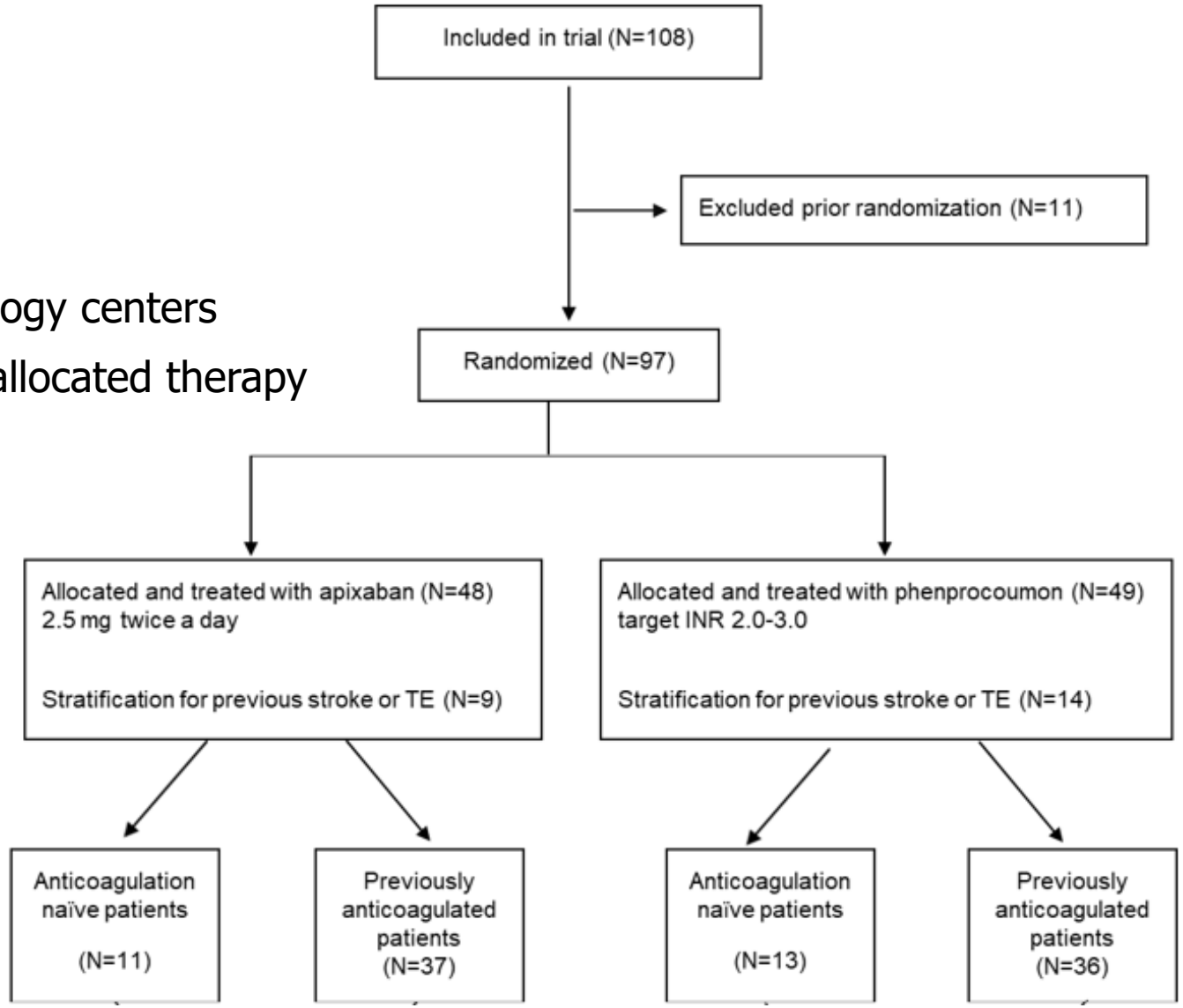
A statistical analysis plan was finalized before unblinding

AXADIA – AFNET 8: Enrolment and treatment allocation

39 sites in Germany:

36 hemodialysis centers, 3 cardiology centers

All randomized patients received allocated therapy



429 (range 37-1,370) days

506 (range 101-1,379) days, p=0.34