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# Protocol for a randomized controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: The Danish Warfarin-Dialysis (DANWARD) trial



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# Protocol for a randomized controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: The Danish Warfarin-Dialysis (DANWARD) trial

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# ABSTRACT

## Introduction

Atrial fibrillation is highly prevalent in patients on chronic dialysis. It is unclear whether anticoagulant therapy for stroke prevention is beneficial in these patients. Vitamin K-antagonists (VKA) remain the predominant anticoagulant choice. Importantly, anticoagulation remains inconsistently used and a possible benefit remains untested in randomized clinical trials comparing oral anticoagulation with no treatment in patients on chronic dialysis. The Danish Warfarin-Dialysis (DANWARD) trial aims to investigate safety and efficacy of VKAs in patients with atrial fibrillation on chronic dialysis. The hypothesis is that VKA treatment compared with no treatment is associated with stroke risk reduction and overall benefit.

## Methods and analysis

The DANWARD trial is an investigator-initiated trial at 13 Danish dialysis centers. In an open-label randomized clinical trial study design, a total of 718 patients with atrial fibrillation on chronic dialysis will be randomized in a 1:1 ratio to receive either standard dose VKA targeting an international normalized ratio of 2.0 to 3.0 or no oral anticoagulation. Principal analyses will compare the risk of a primary efficacy endpoint, stroke or transient ischemic attack, and a primary safety endpoint, major bleeding, in patients allocated to VKA treatment and no treatment, respectively. The first patient was randomized in October 2019. Patients will be followed until one year after inclusion of the last patient.

## Ethics and dissemination

The study protocol was approved by the Regional Research Ethics Committee (journal number H-18050839) and the Danish Medicines Agency (case number 2018101877). The trial is conducted in accordance with the Helsinki Declaration and standards of Good Clinical Practice. Study results will be disseminated to participating sites, at research conferences, and in peer-reviewed journals.

## Trial registration numbers

NCT03862859, EUDRA-CT 2018-000484-86, and CTIS ID 2022-502500-75-00.

## Strengths and limitations of this study

- A national, multicenter, investigator-initiated randomized clinical trial with adequate power to investigate treatment effect on clinical outcomes
- First trial to investigate the efficacy and safety of vitamin K-antagonists compared with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis (hemo- and peritoneal dialysis)
- Intervention is congruent with general clinical practice
- Open-label design

## Abbreviations

AF: atrial fibrillation

DOAC: direct-acting oral anticoagulant

eGFR: estimated glomerular filtration rate

ESKD: end-stage kidney disease

INR: International normalized ratio

LAAO: Left atrial appendage occlusion

SAE: serious adverse event

SAR: serious adverse reaction

SUSAR: suspected unexpected serious adverse reactions

VKA: Vitamin K-antagonist

# INTRODUCTION

End-stage kidney disease (ESKD) is associated with substantial risk of cardiovascular disease and mortality.(1) Median survival following initiation of dialysis is 47-53 months(2) with an annual mortality of at least 20%.(3) Cardiovascular disease is the cause of death in >50% of these cases.(4)

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population with a global prevalence of approximately 0.5%(5) and is associated with a five-fold increase in risk of ischemic stroke.(6) The prevalence of AF is correlated with kidney dysfunction(7,8) and is found in >20% of patients with ESKD.(9–12). (9–12)

Net benefit of oral anticoagulation for stroke prevention in patients with AF has been carefully evaluated by weighing the reduced risk of stroke against the treatment-associated risk of bleeding.(13,14) In patients on chronic dialysis, the risk of stroke is increased two- to three-fold compared with the general population.(9) However, chronic dialysis is also associated with an increased risk of bleeding attributable to impaired platelet function and platelet-endothelial interactions(15,16), a high prevalence of antiplatelet drugs(17), and recurring exposure to low-molecular-weight heparin to minimize clotting of dialysis filters during hemodialysis treatment. This leads to possible moderation of the benefit demonstrated in multiple randomized clinical trials, where patients with advanced chronic kidney disease were excluded.(18–23)

Hence, in patients on chronic dialysis the benefit-to-risk ratio of oral anticoagulation compared with no treatment has not been investigated in a prospective trial and observational data remain divergent and inconclusive.(24–26) Consequently, guideline recommendations for anticoagulation in patients on chronic dialysis are ambiguous and based on low-level evidence.(13,14,27) Therefore, a prospective evaluation of the safety and efficacy of oral anticoagulation, i.e. warfarin, in these patients is warranted.

## Aims and objectives

The main objectives of the Danish Warfarin-Dialysis (DANWARD) trial are to investigate the benefit, tolerability, and safety of warfarin compared with no oral anticoagulation in patients with AF on chronic dialysis. The main hypothesis is that anticoagulation based on warfarin dosing targeting an international normalized ratio (INR) of 2.0 to 3.0 in patients with AF on chronic dialysis reduces the risk of stroke compared to no oral anticoagulation. Although the risk of major bleeding is increased in patients on chronic dialysis, we also hypothesize that warfarin is not associated with an increased risk of major bleeding as defined by the International Society on Thrombosis and Hemostasis compared with no oral anticoagulation.

# METHODS AND ANALYSIS

## Study design

The DANWARD trial is an investigator-initiated, prospective, open-label, parallel-group, randomized clinical trial. Patients ≥18 years with AF on chronic hemo- or peritoneal dialysis will be randomized to either oral anticoagulation with warfarin or no oral anticoagulation. Participants will be included from 13 centres across Denmark (supplementary Table S1) by site investigators who will obtain written informed consent. As warfarin

requires continued monitoring of INR, the study will be conducted open label, i.e. with no placebo study medication.

An overview of the study design, randomization of allocated treatment, and scheduled visits and examinations is provided in Figure 1. Details of inclusion and exclusion criteria are provided in Table 1. We used the SPIRIT checklist when writing our report.(28)

## Randomization

In accordance with a computer-generated allocation, participants are randomized 1:1 to either treatment with warfarin or no treatment via a secure web application. Allocation is stratified by center using permuted blocks of random sizes, with block size and allocation ratio concealed. Participants not receiving anticoagulation at inclusion are randomized to either initiation of oral anticoagulation or to continued non-treatment. Participants treated with anticoagulation at inclusion are randomized to either continued anticoagulation with warfarin or discontinuation of treatment.

The date of randomization defines treatment initiation and beginning of follow-up. All study participants are treated in accordance with the randomization for at least 12 months. Participants included early in the trial remain under allocated treatment throughout the study until one year after inclusion of the last participant. No specific recommendation regarding other medication, including antiplatelet agents, is given in the protocol. Except from INR measurements, patients in both allocation groups are monitored equally.

### Allocation to treatment with warfarin

Warfarin, a coumarin anticoagulant, inhibits vitamin K-reductase, leading to depletion of vitamin K-hydroquinone. This causes reduction in gamma-carboxylation and subsequent activation of vitamin K-dependent proteins involved in the synthesis of the vitamin-K-dependent coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S. Reduced availability of coagulation factors II, VII, IX and X results in reductions in prothrombin and thrombin levels leading to decreased clot formation.

Monitoring of warfarin treatment will be done in accordance with the local standard of care at the individual trial site following standard international guidelines for anticoagulation therapy(13,14), with dose-adjustments based on prothrombin time targeting an INR of 2.0 to 3.0.

All study medication will be provided free of charge.

### Allocation to no treatment

Participants randomized to no treatment will be monitored in accordance with the predefined monitoring plan (Figure 1) at monthly intervals.

### Departure from allocated treatment

Patients' departure from allocated treatment is registered throughout the trial to ensure correct identification of cross-over.

## End of trial

End of trial is defined by either the date of withdrawal of informed consent or the date of trial termination, which is set by the trial steering committee at least 12 months after inclusion of the last recruited patient (Figure 1).

## End of follow-up

End of follow-up for each participant is defined as six weeks after the end of trial (Figure 1).

## Study outcomes

### Primary outcomes

- Efficacy endpoint: Any fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke (Table 2).
- Safety endpoint: Major bleeding as defined by the International Society on Thrombosis and Hemostasis, i.e., major intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome, or gastrointestinal bleeding in non-surgical patients (Table 2).

### Secondary and tertiary outcomes

Table 2 displays outcomes.

### Adjudication of outcomes

Outcomes will be identified based on clinical registration in an electronic database and on registration of diagnosis codes in the comprehensive national administrative health registers(29–31) with subsequent adjudication of outcomes by an event committee.

## Statistical analysis

Treatment with warfarin will be compared with no treatment for all outcomes. Principal analyses will be performed based on the intention-to-treat population comparing the cumulative risk of the primary efficacy endpoint in patients allocated to warfarin treatment with no treatment, while accounting for competing risks. Gray's test will be employed. The null hypothesis is that warfarin is associated with equivalent risk of stroke or transient ischemic attack compared with no treatment. Hence, the alternative hypothesis is that warfarin is associated with a reduced risk of stroke or transient ischemic attack compared with no treatment.

Secondary analyses will evaluate the safety of warfarin compared with no treatment on risk of major bleeding based on a secondary hypothesis that although bleeding risk is increased in patients on chronic dialysis, warfarin is not associated with increased risk of major bleeding as defined by the International Society on Thrombosis and Hemostasis compared with no treatment.

Tertiary analyses will include 1) univariate and multiple cause-specific Cox regression models with stratification of treatment effect on predefined variables including, age, sex, comorbidity, trial site, dialysis modality (hemo- or peritoneal dialysis), AF class (prevalent or incident), prior anticoagulation treatment (no treatment or ongoing treatment), and concomitant platelet inhibitor treatment; 2) as-treated time-updated cause-specific Cox proportional hazards models permitting time-dependent assessment of treatment including time in therapeutic

range, dialysis modality, and risk covariates; and 3) on-treatment analyses with censoring of patients deviating from the allocated randomized treatment.

Subgroup analyses are planned for strata of age (<75 years and ≥75 years), sex (male/female), $CHA_2DS_2$-VASc score (2, 3-4, ≥5), antiplatelet treatment (yes/no), dialysis modality (hemodialysis/peritoneal dialysis), previous stroke (yes/no), and previous bleeding (yes/no).

For all analyses, statistical significance will be determined by a p-value ≤0.05. Determination of superiority will be based on the primary efficacy endpoint. A finalized statistical analysis plan will be prepared by the trial statistician and approved by the Trial Steering Committee prior to conclusion of randomization and initiation of data analyses.

### Sample size calculations

Prior to compiling this protocol, a retrospective study on Danish patients on chronic dialysis with incident AF diagnosed between 2002 and 2012 was made. During the study period, the incidence of AF increased from 4.0 (95% CI 3.8-4.2) per 100 person years to 7.8 (95% CI 6.8-9.0) per 100 person years.(32) Standardized one-year risks of stroke and major bleeding, respectively, were calculated as the average treatment effect using G-computation based on cause-specific Cox regression models.(33) This gave an absolute one-year risk of stroke of 1.7% (95% CI 0.1%-8.9%) and 6.1% (95% CI 4.2%-8.0%) in patients treated with and without warfarin, respectively (supplementary Figure S1A). The absolute one-year risk of major bleeding was 9.2% (95% CI 0.1%-20.8%) and 8.1% (95% CI 6.0%-10.0%) in patients with and without warfarin treatment, respectively (supplementary Figure S1B). Based on these results and the assumption of absence of a period effect, a sample size of n=299 per group is required to achieve a power of 1-β = 0.80 for a two-sided t-test with α=0.05. To compensate for ≤ 20% drop-out, 359 patients will be included in each group. A plot depicting sample size calculation is provided in supplementary Figure S2. Other trials investigating oral anticoagulation for patients with advanced chronic kidney disease and AF using a two-group study design include the RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban versus Warfarin in Atrial Fibrillation), the AXADIA-AFNET8 trial (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation an End-Stage Kidney Disease), the AVKDIAL trial (Oral Anticoagulation in Hemodialysis Patients), and the SACK trial (Stroke Prophylaxis with Apixaban in CKD5 Patients with Atrial Fibrillation). Planned enrollment in these trials was 762, 222, 855, and 1000-1400, respectively.

## Monitoring

### Data Safety Monitoring Committee

An independent Data Safety and Monitoring Committee has been established with the aim of safeguarding the interests of enrolled patients, assessing the safety and efficacy of the allocated treatment during the trial, and monitoring the overall conduct of the trial. The responsibilities of the Data Safety and Monitoring Committee have been described in a separate charter.

### Safety management

Serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the sponsor in accordance with the standards of Good Clinical Practice.(34) Harm will be adjudged based on the predefined safety endpoints pertaining to fatal or non-fatal major bleeding. Safety monitoring will be accomplished by tracing of SAEs, SARs, and SUSARs, safety and efficacy endpoints, and mortality. Registration of SAEs, SARs, and SUSARs for evaluation of potential late side effects will be continued until six weeks following end of trial irrespective of cause of discontinuation.

### Premature trial termination

The Data and Safety Monitoring Committee will have exclusive unblinded access to all data and may recommend discontinuation of the study to the Trial Steering Committee based on reviews of safety events. Throughout inclusion, interim analyses will be supplied in strict confidence for overview to the Data Safety Monitoring Committee. If results from the interim analyses provide sufficient evidence as to harm or benefit of the allocated treatments, the Data Safety Monitoring Committee will advise the Trial Steering Committee, thus enabling possible trial modifications or trial discontinuation.

### Trial auditing

Auditing of trial conduct will be performed by independent monitors from the regional Good Clinical Practice Units.

## ETHICS AND DISSEMINATION

The trial is to be conducted in accordance with the Helsinki Declaration and standards of Good Clinical Practice.(35,36) The trial is registered at www.clinicaltrials.gov (NCT03862859), EUDRA-CT number 2018-000484-86, and CTIS ID 2022-502500-75-00. The study protocol was approved by the Regional Research Ethics Committee on December 21, 2018 (journal number H-18050839), and by the Danish Medicines Agency on February 14, 2019 (case number 2018101877). The sponsor will release protocol amendments to the site investigators. Trial registration data set is provided in supplementary Table S2.

A trial steering committee (supplementary Table S3) has been involved in the study design and monitors the conduction of the study, analysis of study data, and publication of study results. The trial steering committee will have full access to all study data upon trial completion. The Vancouver recommendations will be used to access authorship eligibility. Data collection and management will be performed in accordance with the General Data Protection Regulations and all study-related material will be stored securely at the study site.

### Dissemination of results

Study results will be disseminated to participating sites, at research conferences, and in peer-reviewed journals.

### Patient and public involvement

Design and conduction of this study was performed without public or patient involvement. Conclusions from the study will be communicated as a newsletter in a relevant media.

## DISCUSSION

ESKD is a prothrombotic and prohemorrhagic condition. Patients on chronic dialysis were excluded from the six randomized controlled trials that demonstrated benefit of oral anticoagulation for stroke prevention in patients with AF.(18–23) Retrospective studies draw no clear picture of the benefit to harm-ratio.(9,17,37–44) Furthermore, benefit of oral anticoagulation in patients on chronic dialysis is also dependent on expected survival, given an annual mortality >20%(3), potential treatment-associated risk of accelerated vascular calcification through inhibition by carboxylation of Matrix Gla Protein(45,46), and induction of calciphylaxis.(47) Although apixaban and rivaroxaban have been approved by the US Food and Drug Administration based on data from pharmacokinetic studies(48,49), no direct-acting oral anticoagulants (DOACs) are approved for use in patients with ESKD by the European Medicines Agency(50–53), and VKAs continue to be widely used.(54,55) International guidelines give no clear recommendation for treatment strategy(13,14,27), and anticoagulation remains inconsistently prescribed with <50% of patients with incident AF on chronic dialysis initiating treatment.(39,41,56)

In patients without ESKD, DOACs have superseded VKAs as first-choice anticoagulants through the past 15 years as a result of the non-inferiority to warfarin with respect to efficacy and a lower bleeding risk demonstrated in randomized clinical trials.(57–60) However, anticoagulation with DOACs in patients with advanced kidney disease remains debated.(61) Recently, three trials comparing VKA and DOAC in patients with AF on chronic dialysis have been completed: the Valkyrie trial (n= 132, VKA vs. rivaroxaban)(62), the RENAL-AF trial (n=154, VKA vs. apixaban)(63), and the AXADIA-AFNET8 trial (n=97, VKA vs. apixaban)(64). All trials were underpowered for definite conclusions regarding safety and efficacy endpoints.

Optimal time-in-therapeutic range has proven difficult to achieve in both the landmark trials comparing VKA and DOACs in patients with preserved kidney function(57–60), and in the Valkyrie, RENAL-AF, and AXADIA-AFNET8 trials (ranging from 44 to 55%).(62–64) However, low proportions of time-in-therapeutic range could arguably be driven by episodic discontinuation and reintroduction of VKA treatment in connection with hospitalizations due to non-related causes such as issues with dialysis access, infections etc. These issues also apply for patients treated with DOACs, but treatment effect is only measured in patients treated with VKA.

Left atrial appendage occlusion (LAAO) has also been suggested as an alternative to prevent thromboembolic complications in patients with AF who are non-tolerant to anticoagulation.(13,14) Although non-inferiority of LAAO compared with warfarin was demonstrated in one of two randomized trials in patients with preserved renal function,(65,66) serious peri- and postprocedural complications were observed in >4% of patients, benefit on thromboembolic risk was not apparent until late during follow-up, and periodic post-procedural antithrombotic treatment was often required.(67) Considering the impact of early mortality and the limited evidence implicating thrombus formation in the left atrial appendage in patients on chronic dialysis, questions remain as to the overall benefit of LAAO in these patients.

For these reasons, the DANWARD study aims to address the essential question as to whether oral anticoagulation is indicated for stroke prevention in patients with AF on chronic dialysis.

A number of limitations apply. First, due to the requirement of INR monitoring in patients on warfarin, an open-label study design is employed. Although blinding of allocated treatment would be technically achievable, implementation would require fabrication of sham INR results, with possible implications for patient safety including unwarranted adjustments of dialysis-related anticoagulation. Furthermore, blinding of clinical trials on anticoagulants has previously been demonstrated to be difficult, in part due to the continued requirement of dose adjustments.(68) As such, use of an open-label study design seems reasonable, particularly in light of the predominant focus of the trial on objective measurable endpoints. Second, adherence to anticoagulation therapy in patients on dialysis is difficult, both in terms of subtherapeutic time in range(62–64) and treatment discontinuation.(38,69,70) Implementation of anticoagulation therapy in patients on chronic dialysis is complex, and intermittent discontinuation for elective procedures or medical complications may be unavoidable given the nature of chronic dialysis. Secondary analyses are planned to address this possible impact.

## CONCLUSION

The DANWARD trial will be the first trial to investigate the safety and efficacy of warfarin treatment compared with no oral anticoagulation in patients with AF on chronic dialysis.

Study results aim to provide evidence of initiating warfarin for stroke prevention with direct implications for clinical management and international guidelines concerning patients on chronic dialysis.

## AVAILABILITY OF DATA AND MATERIALS

A de-identified dataset will be uploaded to an appropriate data archive three years after collection of the one-year post-randomization results.

## AUTHOR CONTRIBUTIONS

Study conceptualization and design: AK, CB, CTP, DHA, ELFB, ELG, GG, JDJ, JO, LK, MH, MR, MS, NC, PC, TL

Statistical analysis plan: CTP, NC, TL

Acquisition, analysis and interpretation of data: ASN, CDP, DCN, DK, ELFB, FHM, FTN, IB, INT, JB, JDK, JKB, JMR, KL, LB, MCB, ML, NC, RB

Drafting of manuscript: ELFB, NC

Critical revision of manuscript and approval of final version: All authors

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## COMPETING INTERESTS

None related to the present study. The authors report the following general conflicts:

AK, ASN, CB, CTP, DCN, DK, FHM, FTN, GG, INT, JB, JDJ, JDK, JKB, JMR, KL, MCB, MR, MS, PC, TL report no conflicts of interest.

CDP has received speaker honoraria or consultancy fees from AstraZeneca and Astellas. Support for attending meetings and travel from Boehringer Ingelheim. CDP also has an ongoing collaboration with Vifor Pharma including donation of a research grant unrelated to this study.

DHA has received speaker and consultancy fees from AstraZeneca, GlaxoSmithKline, and UCB Nordic.

ELFB has received a donation of a research grant from AstraZeneca unrelated to this study.

ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Novo Nordisk, MSD, Lundbeck Pharma, and Organon. He is investigator in clinical studies sponsored by AstraZeneca, Idorsia, or Bayer and has received unrestricted research grants from Boehringer Ingelheim.

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RB has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, and Boehringer Ingelheim. She is investigator in clinical studies sponsored by Boehringer Ingelheim, AstraZeneca, or Bayer and has received unrestricted research grants from Boehringer Ingelheim.

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## TABLES AND FIGURES



## Supplemental material

**Table 1: Inclusion and exclusion criteria**

Inclusion criteria

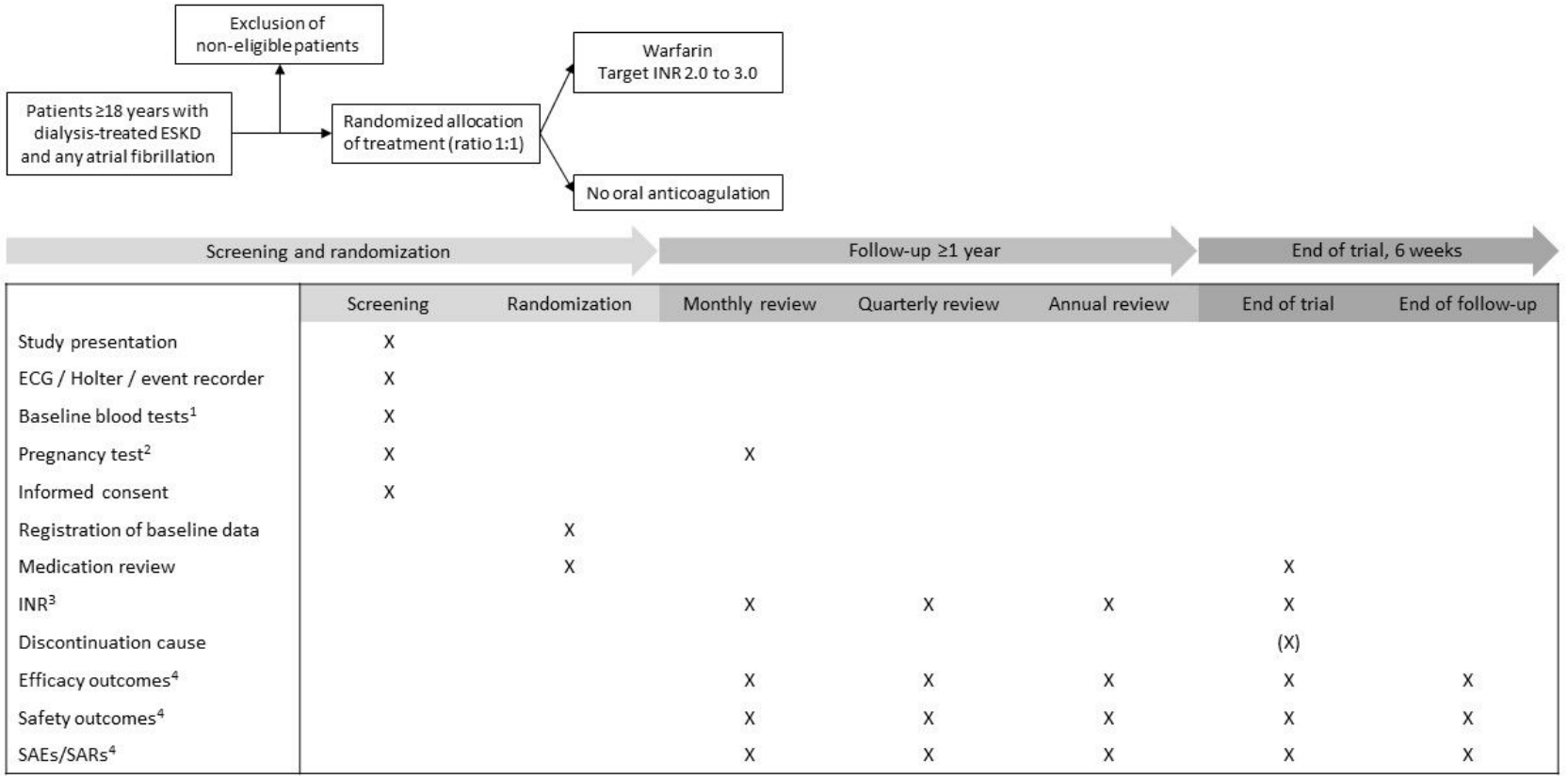
- Patients ≥18 years on chronic dialysis
- Any non-valvular paroxysmal, persistent, or permanent atrial fibrillation or flutter documented by an electrocardiogram, episode of ≥30 seconds on Holter monitor, or episode of ≥6 minutes on event recorder or any other recording device
- Competence to understand the study rationale, including potential risks and benefits associated with treatment, necessary for written informed consent

Exclusion criteria

- $CHA_2DS_2$-VASc Score ≤1
- Other indications for oral anticoagulation treatment (pulmonary embolism <6 months, deep vein thrombosis <3 months, mechanical heart valve prosthesis) - irrespective of whether treatment is implemented
- Ongoing dual antiplatelet treatment
- Malignancy (with exception of non-melanoma skin cancer) with recent (<1 year), ongoing or planned curative or palliative chemo-, radiation-, and/or surgical therapy
- Endoscopy with gastrointestinal ulcer <1 month
- Esophageal varices
- Autoimmune or genetic coagulation disorders
- Congenital alactasia, Lapp Lactase deficiency or glucose-galactose malabsorption
- Pending spinal tap
- Cerebrovascular malformations
- Arterial aneurisms
- Ulcers or wounds (Wagner grade >1)
- Bacterial endocarditis <3 months
- Active bleeding contraindicating anticoagulation
- Any non-elective and/or non-ambulant surgery <7 days
- Cerebral hemorrhage <4 weeks
- Thrombocytopenia (platelet count $<100 \times 10^9$/L) <30 days
- Severe liver insufficiency (spontaneous international normalized ratio >1.5) <30 days.
- Known intolerance to warfarin
- Use of hypericum perforatum/St. John's Wort
- Uncontrolled hypertension (repeated blood pressure >180/110 mmHg) <30 days
- Uncontrolled hyperthyroidism (thyroid-stimulating hormone <0.1 µIU/mL) <30 days
- Pregnancy or lactation
- Participation in other ongoing intervention trials adjudged to influence study outcomes

| Table 2: Primary, secondary, and tertiary outcomes |
|---|
| **Primary efficacy outcome** |
| Fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke |
| **Primary safety outcome** |
| Fatal or non-fatal major bleeding[1] |
| **Secondary outcomes** |
| Fatal or non-fatal ischemic or unspecified stroke[2] |
| Fatal or non-fatal ischemic stroke[2] |
| Fatal or non-fatal hemorrhagic stroke[2] |
| Fatal or non-fatal ischemic or hemorrhagic stroke[2] |
| All-cause mortality |
| Combination of any non-fatal stroke and all-cause mortality |
| Combination of any non-fatal stroke, any non-fatal major bleeding and all-cause mortality |
| **Tertiary outcomes** |
| Discontinuation of allocated randomized therapy |
| Calciphylaxis/calcific uremic arteriolopathy |
| Fatal or non-fatal acute myocardial infarction |
| Hospitalization due to left-sided heart failure |
| Peripheral artery disease |
| Thrombosis of arteriovenous fistula |
| Osteoporotic fractures including low energy fractures of the proximal femur, distal radius, humerus, pelvis, and vertebrae |
| [1]As defined by the International Society on Thrombosis and Hemostasis |
| [2]For patients who meet a primary outcome |

**Figure 1: Study design**



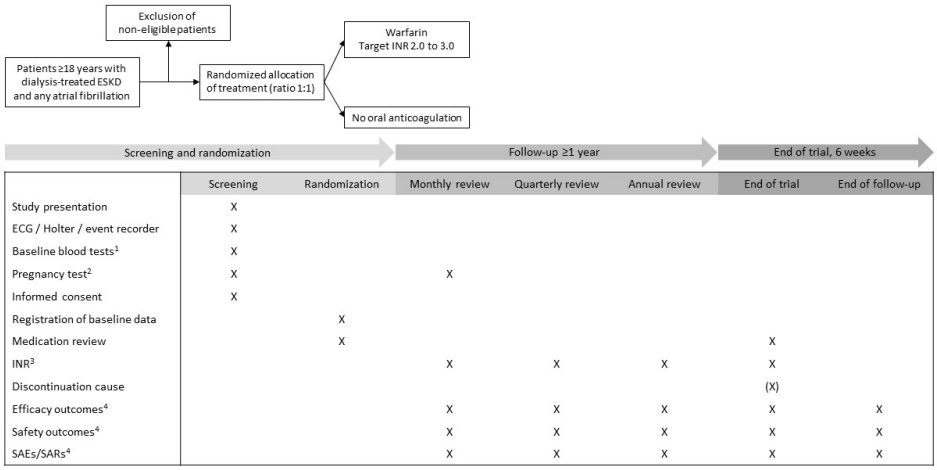

| | Screening | Randomization | Monthly review | Quarterly review | Annual review | End of trial | End of follow-up |
|---|---|---|---|---|---|---|---|
| Study presentation | X | | | | | | |
| ECG / Holter / event recorder | X | | | | | | |
| Baseline blood tests[1] | X | | | | | | |
| Pregnancy test[2] | X | | X | | | | |
| Informed consent | X | | | | | | |
| Registration of baseline data | | X | | | | | |
| Medication review | | X | | | | X | |
| INR[3] | | | X | X | X | X | |
| Discontinuation cause | | | | | | (X) | |
| Efficacy outcomes[4] | | | X | X | X | X | X |
| Safety outcomes[4] | | | X | X | X | X | X |
| SAEs/SARs[4] | | | X | X | X | X | X |

**Figure 1: Study design**
Eligibility is assessed in accordance with the inclusion and exclusion criteria.

Abbreviations: INR, international normalized ratio; ECG, electrocardiogram; SAE, serious adverse event; SAR, serious adverse reaction

[1]Plasma-hemoglobin, platelet count, albumin, phosphate, ionized calcium, parathyroid hormone, c-reactive protein, urea nitrogen, and creatinine
[2]Required in all women of childbearing potential at inclusion and monthly throughout the trial.
[3]Last recorded INR
[4]SAEs/SARs will be recorded continuously with reporting of SAEs/SARs to the study sponsor within 24 hours of identification for assessment. Efficacy and safety outcomes will be registered every month in an electronic database.

**Figure 1: Study design**




| | Screening | Randomization | Monthly review | Quarterly review | Annual review | End of trial | End of follow-up |
|---|---|---|---|---|---|---|---|
| Study presentation | X | | | | | | |
| ECG / Holter / event recorder | X | | | | | | |
| Baseline blood tests[1] | X | | | | | | |
| Pregnancy test[2] | X | | X | | | | |
| Informed consent | X | | | | | | |
| Registration of baseline data | | X | | | | | |
| Medication review | | X | | | | X | |
| INR[3] | | | X | X | X | X | |
| Discontinuation cause | | | | | | (X) | |
| Efficacy outcomes[4] | | | X | X | X | X | X |
| Safety outcomes[4] | | | X | X | X | X | X |
| SAEs/SARs[4] | | | X | X | X | X | X |

Figure 1: Study design
Eligibility is assessed in accordance with the inclusion and exclusion criteria.
Abbreviations: INR, international normalized ratio; ECG, electrocardiogram; SAE, serious adverse event; SAR, serious adverse reaction

1Plasma-hemoglobin, platelet count, albumin, phosphate, ionized calcium, parathyroid hormone, c-reactive protein, urea nitrogen, and creatinine
2Required in all women of childbearing potential at inclusion and monthly throughout the trial.
3Last recorded INR
4SAEs/SARs will be recorded continuously with reporting of SAEs/SARs to the study sponsor within 24 hours of identification for assessment. Efficacy and safety outcomes will be registered every month in an electronic database.

338x190mm (96 x 96 DPI)

# Supplemental material

Supplementary Table S1: Trial sites

Supplementary Table S2: Participants of the DANWARD study

Supplementary Table S3: Trial Registration Data Set

Supplementary Figure S1: 1-year standardized risk of A) stroke and B) major bleeding

Supplementary Figure S2: Sample size calculation

Supplementary Appendix 1: Protocol version 1.26, February 17, 2023

Supplementary Appendix 2: Informed consent materials (in Danish)

| **Supplementary Table S1: Trial sites** |
| --- |
| Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark |
| Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark |
| Esbjerg and Grindsted Hospital, Finsensgade 35, 6700 Esbjerg, Denmark |
| Herlev and Gentofte Hospital, Borgmester Ib Juuls Vej 1, 2730 Herlev, Denmark |
| Holbæk Hospital, Smedelundsgade 60, 4300 Holbæk, Denmark |
| Bornholm Hospital, Ullasvej 8, 3700 Rønne, Denmark |
| Hospital of Southern Jutland, Sydvang 1, 6400 Sønderborg, Denmark |
| Gødstrup Regional Hospital, Hospitalsparken 15, Herning, Denmark |
| Lillebælt Hospital, Sygehusvej 24, 6000 Kolding, Denmark |
| Copenhagen University Hospital – North Zealand, Dyrehavevej 29, 3400 Hillerød, Denmark |
| Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København, Denmark |
| Viborg Regional Hospital, Heibergs Alle 5A, 8800 Viborg, Denmark |
| Zealand University Hospital, Sygehusvej 10, 4000 Roskilde, Denmark |

| **Supplementary Table S2: Trial Registration Data Set** | |
|---|---|
| Data category | Information |
| Primary registry and trial identifying number | ClinicalTrials.gov: NCT03862859 |
| Date of registration in primary registry | February 22, 2019 |
| Secondary identifying numbers | EUDRA-CT 2018-000484-86, CTIS ID 2022-502500-75-00. |
| Source(s) of monetary or material support | The Danish Heart Foundation, the Augustinus Foundation |
| Primary sponsor | Nicholas Carlson, Dept. of Nephrology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark |
| Secondary sponsor(s) | None |
| Contact for public queries | NC, ELFB |
| Contact for scientific queries | NC, GG |
| Public title | The Danish Warfarin-Dialysis Study - Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis |
| Scientific title | The Danish Warfarin-Dialysis Study: Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis - A Nationwide Parallel-group Open Randomized Clinical Trial |
| Countries of recruitment | Denmark |
| Health condition(s) or problem(s) studied | Atrial fibrillation, stroke, major bleed, end-stage renal disease |
| Intervention(s) | Drug: Warfarin |
| Key inclusion and exclusion criteria | Inclusion criteria: Adult patient (≥18 years) with any atrial fibrillation on chronic dialysis<br>Exclusion criteria: $CHA_2DS_2$-VASc score ≤1, other indication for oral anticoagulation, contraindications for oral anticoagulation, participation in other intervention trials adjudged to influence outcomes |
| Study type | Interventional |
| Date of first enrolment | October 16, 2019 |
| Target sample size | 718 |
| Recruitment status | Recruiting |
| Primary outcome(s) | Primary efficacy outcome: Fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke<br>Primary safety outcome: Fatal or non-fatal major bleeding |
| Key secondary outcomes | All-cause mortality; combination of any non-fatal stroke and all-cause mortality; combination of any non-fatal stroke, any non-fatal major bleeding, and all-cause mortality |

**Supplementary Table S3: Participants of the DANWARD study**

**Trial Steering Committee**

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Lene Boesby, MD PhD, Department of Medicine, Zealand University Hospital, Denmark

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Marianne Rix, MD PhD, Department of Nephrology, Copenhagen University Hospital – Rigshospitalet, Denmark

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Nicholas Carlson MD PhD, Department of Nephrology, Copenhagen University Hospital – Rigshospitalet, Denmark
Rikke Borg, MD PhD Associate Professor, Department of Medicine, Zealand University Hospital, Denmark & Department of Clinical Medicine, University of Copenhagen, Denmark

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Theis Lange, PhD Professor, Department of Public Health, University of Copenhagen, Denmark

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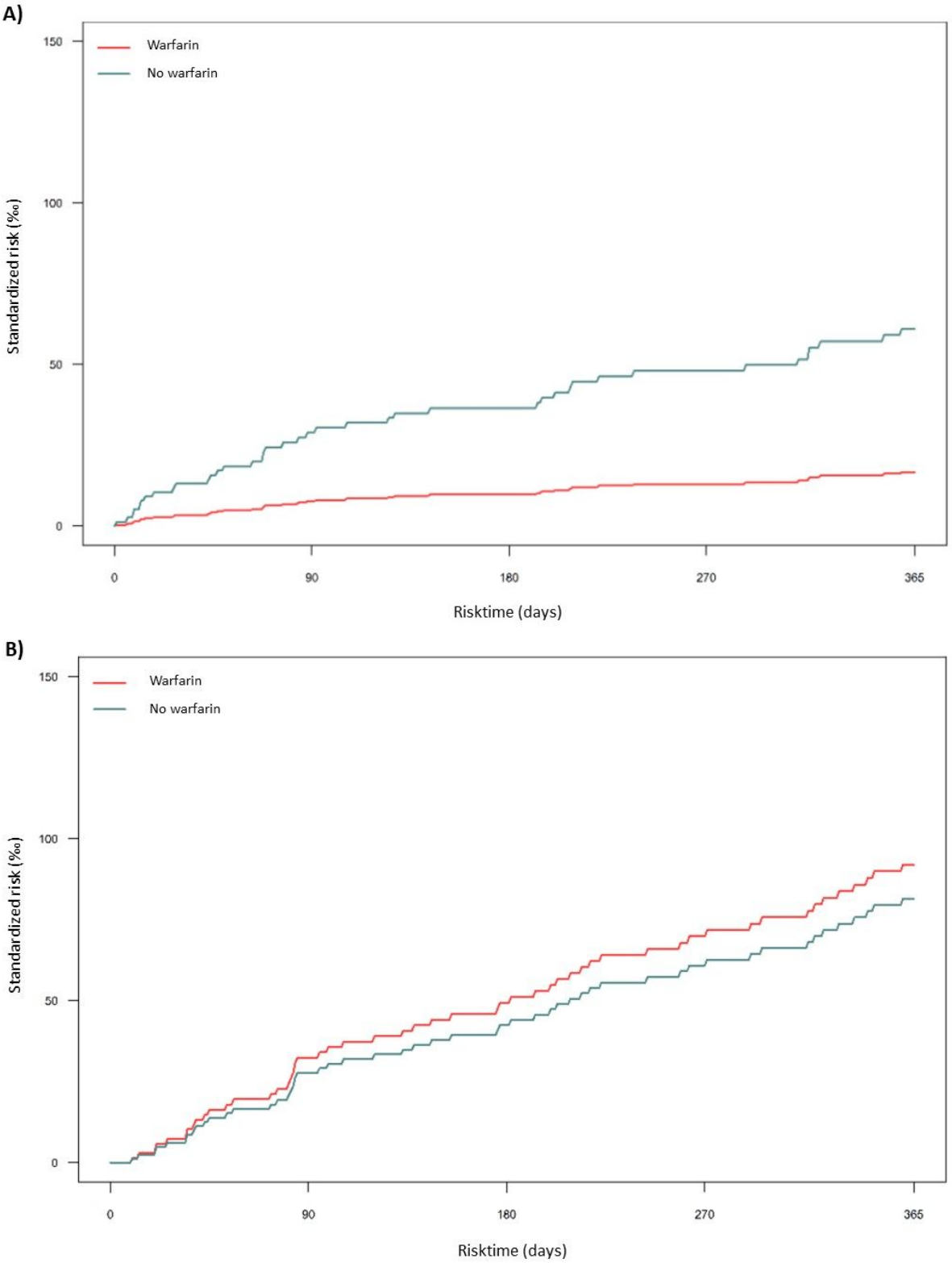
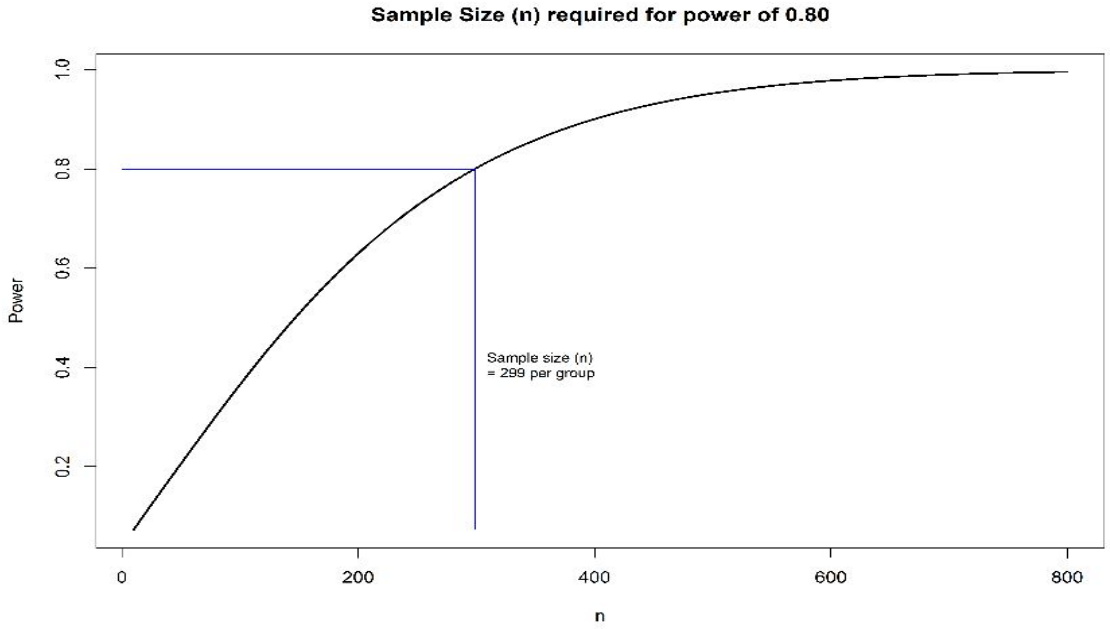
**Supplementary Figure 1:** 1-year standardized risk of A) stroke and B) major bleeding




Predicted 1-year standardized risk of stroke and major bleeding in Danish patients with end-stage kidney disease and atrial fibrillation based on hazards ascertained in multiple cause specific Cox regression.

**Supplementary Figure S2:** Sample size calculation




Sample size i.e. the number of patients (n) in each group is depicted with corresponding power, based on predicted one-year absolute risk of stroke.

# Reporting checklist for protocol of a clinical trial.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | Suppl. Table S3 |
| Protocol version | #3 | Date and version identifier | 1 |
| Funding | #4 | Sources and types of financial, material, and other support | 11 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 11 + Suppl. Table S2 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 1 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Suppl. Table S2 |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 5 |
| Objectives | #7 | Specific objectives or hypotheses | 5 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, | 5 |

| | | | |
|---|---|---|---|
| | | equivalence, non-inferiority, exploratory) | |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 + suppl. Table S1 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Table 1 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 6 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 6 + Figure 1 |

| | | | |
|---|---|---|---|
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7 + Table 2 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |

| | | | |
|---|---|---|---|
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 5 |
| **Methods: Data collection, management, and analysis** | | | |

| | | | |
|---|---|---|---|
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 7 + Figure 1 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 + Figure 1 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 7+9 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 7 + Table 2 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 7-8 |
| Statistics: analysis population and | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any | 7-8 |

| | | | |
|---|---|---|---|
| missing data | | statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 8 |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 8 |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8-9 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
| **Ethics and dissemination** | | | |

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|---|---|---|---|
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 9 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 9 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 9 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 12 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 9 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial | NA |

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| | | participation | |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 9 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 9 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 9 |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | Suppl. appendix 2 |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

Notes:

- 2b: Suppl. Table S3
- 5a: 11 + Suppl. Table S2
- 5d: Suppl. Table S2

- 9: 5 + suppl. Table S1
- 11c: 6 + Figure 1
- 12: 7 + Table 2
- 18a: 7 + Figure 1
- 18b: 7 + Figure 1
- 20a: 7 + Table 2
- 32: Suppl. appendix 2

BMJ Open

# Protocol for a randomized controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: The Danish Warfarin-Dialysis (DANWARD) trial



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| Primary Subject Heading: | Cardiovascular medicine |
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| Keywords: | Dialysis < NEPHROLOGY, End stage renal failure < NEPHROLOGY, Thromboembolism < CARDIOLOGY, Clinical Trial, Anticoagulation < HAEMATOLOGY |
| | |

# Protocol for a randomized controlled trial comparing warfarin with no oral anticoagulation in patients with atrial fibrillation on chronic dialysis: The Danish Warfarin-Dialysis (DANWARD) trial

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**Keywords**: DANWARD, End-stage kidney disease, atrial fibrillation, anticoagulation, thromboembolism, chronic dialysis, clinical trial, warfarin

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# ABSTRACT

## Introduction

Atrial fibrillation is highly prevalent in patients on chronic dialysis. It is unclear whether anticoagulant therapy for stroke prevention is beneficial in these patients. Vitamin K-antagonists (VKA) remain the predominant anticoagulant choice. Importantly, anticoagulation remains inconsistently used and a possible benefit remains untested in randomized clinical trials comparing oral anticoagulation with no treatment in patients on chronic dialysis. The Danish Warfarin-Dialysis (DANWARD) trial aims to investigate safety and efficacy of VKAs in patients with atrial fibrillation on chronic dialysis. The hypothesis is that VKA treatment compared with no treatment is associated with stroke risk reduction and overall benefit.

## Methods and analysis

The DANWARD trial is an investigator-initiated trial at 13 Danish dialysis centers. In an open-label randomized clinical trial study design, a total of 718 patients with atrial fibrillation on chronic dialysis will be randomized in a 1:1 ratio to receive either standard dose VKA targeting an international normalized ratio of 2.0 to 3.0 or no oral anticoagulation. Principal analyses will compare the risk of a primary efficacy endpoint, stroke or transient ischemic attack, and a primary safety endpoint, major bleeding, in patients allocated to VKA treatment and no treatment, respectively. The first patient was randomized in October 2019. Patients will be followed until one year after inclusion of the last patient.

## Ethics and dissemination

The study protocol was approved by the Regional Research Ethics Committee (journal number H-18050839) and the Danish Medicines Agency (case number 2018101877). The trial is conducted in accordance with the Helsinki Declaration and standards of Good Clinical Practice. Study results will be disseminated to participating sites, at research conferences, and in peer-reviewed journals.

## Trial registration numbers

NCT03862859, EUDRA-CT 2018-000484-86, and CTIS ID 2022-502500-75-00.

## Strengths and limitations of this study

- A national, multicenter, investigator-initiated, open-label randomized clinical trial congruent with general clinical practice
- Adequate power to investigate harm and benefit of warfarin treatment on risk of bleeding, thromboembolic outcomes, and death
- Pragmatic study design permitting broad inclusion of patients on chronic dialysis with both incident and prevalent atrial fibrillation
- Open-label design enabling non-protocolized INR-dependent dose adjustments and continuous evaluation of requirements for dialysis-related anticoagulation and antiplatelet treatment
- Trial limited to allocation of warfarin vs. no treatment due to non-approval of direct-acting oral anticoagulants in chronic dialysis by the European Medicines Agency

## Abbreviations

AF: atrial fibrillation

DOAC: direct-acting oral anticoagulant

eGFR: estimated glomerular filtration rate

ESKD: end-stage kidney disease

INR: International normalized ratio

LAAO: Left atrial appendage occlusion

SAE: serious adverse event

SAR: serious adverse reaction

SUSAR: suspected unexpected serious adverse reactions

VKA: Vitamin K-antagonist

# INTRODUCTION

End-stage kidney disease (ESKD) is associated with substantial risk of cardiovascular disease(1) accounting for >50% of deaths in the population.(2)

Atrial fibrillation (AF) is the most common sustained arrhythmia in the general population with a global prevalence of approximately 0.5%(3) and is associated with a five-fold increase in risk of ischemic stroke.(4) The prevalence of AF is correlated with kidney dysfunction(5,6) and is found in >20% of patients with ESKD.(7–10)

Net benefit of oral anticoagulation remains debated in ESKD. In patients on chronic dialysis, the risk of stroke is increased two- to three-fold compared with the general population.(7) However, chronic dialysis is also associated with an increased risk of bleeding attributable to impaired platelet function and platelet-endothelial interactions(11,12), a high prevalence of antiplatelet drugs(13), and recurring exposure to low-molecular-weight heparin to minimize clotting of dialysis filters during hemodialysis treatment. Furthermore, benefit is dependent on expected survival, given an annual mortality >20%(14), potential treatment-associated risk of accelerated vascular calcification through inhibition by carboxylation of Matrix Gla Protein(15,16), and induction of calciphylaxis.(17)

The benefit-to-risk ratio of vitamin K-antagonists (VKA) compared with no treatment remains untested in prospective trials in patients with advanced kidney disease, due to exclusion of patients on chronic dialysis from all six existing randomized controlled trials demonstrating benefit of VKA for stroke prevention in patients with AF. (18–23) Furthermore, data from retrospective studies remains inconclusive(7,13,24–31), and although direct-acting oral anticoagulants (DOAC) are advocated as first-line treatment in patients with preserved kidney function(32,33), the role of DOAC remains debated in ESKD(34), with inconclusive results reported in recent prospective trials comparing DOACs and VKAs.(35–37) Consequently, guideline recommendations for anticoagulation in patients on chronic dialysis are ambiguous and based on low-level evidence(32,33,38), and anticoagulation remains inconsistently prescribed with <50% of patients with incident AF initiating treatment.(26,28,39)

A prospective evaluation of the safety and efficacy of oral anticoagulation with warfarin in these patients is warranted.

## Aims and objectives

The main objectives of the Danish Warfarin-Dialysis (DANWARD) trial are to investigate the benefit, tolerability, and safety of warfarin compared with no oral anticoagulation in patients with AF on chronic dialysis. The main hypothesis is that anticoagulation based on warfarin dosing targeting an international normalized ratio (INR) of 2.0 to 3.0 in patients with AF on chronic dialysis reduces the risk of stroke compared to no oral anticoagulation. Although the risk of major bleeding is increased in patients on chronic dialysis, we also hypothesize that warfarin is not associated with an increased risk of major bleeding as defined by the International Society on Thrombosis and Hemostasis compared with no oral anticoagulation.

# METHODS AND ANALYSIS

## Study design

The DANWARD trial is an investigator-initiated, prospective, open-label, parallel-group, randomized clinical trial. Patients ≥18 years with AF on chronic hemo- or peritoneal dialysis will be randomized to either oral anticoagulation with warfarin or no oral anticoagulation. From October 1, 2019, to January 31, 2026, participants will be included from 13 centres across Denmark (supplementary Table S1) by site investigators who will obtain written informed consent. As warfarin requires continued monitoring of INR, the study will be conducted open label, i.e. with no placebo study medication.

An overview of the study design, randomization of allocated treatment, and scheduled visits and examinations is provided in Figure 1. Details of inclusion and exclusion criteria are provided in Table 1. We used the SPIRIT checklist when writing our report.(40) Study protocol and patient information material are provided in supplementary Appendix 1 and 2.

## Randomization

In accordance with a computer-generated allocation, participants are randomized 1:1 to either treatment with warfarin or no treatment via a secure web application. Allocation is stratified by center using permuted blocks of random sizes, with block size and allocation ratio concealed. Participants not receiving anticoagulation at inclusion are randomized to either initiation of oral anticoagulation or to continued non-treatment. Participants treated with anticoagulation at inclusion are randomized to either continued anticoagulation with warfarin or discontinuation of treatment.

The date of randomization defines treatment initiation and beginning of follow-up. All study participants are treated in accordance with the randomization for at least 12 months. Participants included early in the trial remain under allocated treatment throughout the study until one year after inclusion of the last participant. In accordance with the pragmatic nature of the trial, no specific recommendation regarding other medication, including dialysis-related anticoagulation and antiplatelet agents, is provided in the protocol. Except from INR measurements, patients in both allocation groups are monitored equally.

### Allocation to treatment with warfarin

Warfarin, a coumarin anticoagulant, inhibits vitamin K-reductase, leading to depletion of vitamin K-hydroquinone. This causes reduction in gamma-carboxylation and subsequent activation of vitamin K-dependent proteins involved in the synthesis of the vitamin-K-dependent coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S. Reduced availability of coagulation factors II, VII, IX and X results in reductions in prothrombin and thrombin levels leading to decreased clot formation.

Monitoring of warfarin treatment will be done in accordance with the local standard of care at the individual trial site following standard international guidelines for anticoagulation therapy(32,33), with dose-adjustments based on prothrombin time targeting an INR of 2.0 to 3.0.

All study medication will be provided free of charge.

### Allocation to no treatment

Participants randomized to no treatment will be monitored in accordance with the predefined monitoring plan (Figure 1) at monthly intervals.

### Departure from allocated treatment

Patients' departure from allocated treatment is registered throughout the trial to ensure correct identification of cross-over.

## End of trial

End of trial is defined by either the date of withdrawal of informed consent or the date of trial termination, which is set by the trial steering committee at least 12 months after inclusion of the last recruited patient (Figure 1).

## End of follow-up

End of follow-up for each participant is defined as six weeks after the end of trial (Figure 1).

## Study outcomes

### Primary outcomes

- Efficacy endpoint: Any fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke (Table 2).
- Safety endpoint: Major bleeding as defined by the International Society on Thrombosis and Hemostasis, i.e., major intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome, or gastrointestinal bleeding in non-surgical patients (Table 2).

### Secondary and tertiary outcomes

Table 2 displays outcomes.

### Adjudication of outcomes

Outcomes will be identified based on clinical registration in an electronic database and on registration of diagnosis codes in the comprehensive national administrative health registers(41–43) with subsequent adjudication of outcomes by an event committee.

## Statistical analysis

Treatment with warfarin will be compared with no treatment for all outcomes. Principal analyses will be performed based on the intention-to-treat population comparing the cumulative risk of the primary efficacy endpoint in patients allocated to warfarin treatment with no treatment, while accounting for competing risks. Gray's test will be employed. The null hypothesis is that warfarin is associated with equivalent risk of stroke or transient ischemic attack compared with no treatment. Hence, the alternative hypothesis is that warfarin is associated with a reduced risk of stroke or transient ischemic attack compared with no treatment.

Secondary analyses will evaluate the safety of warfarin compared with no treatment on risk of major bleeding based on a secondary hypothesis that although bleeding risk is increased in patients on chronic dialysis, warfarin

is not associated with increased risk of major bleeding as defined by the International Society on Thrombosis and Hemostasis compared with no treatment.

Tertiary analyses will include 1) univariate and multiple cause-specific Cox regression models with stratification of treatment effect on predefined variables including, age, sex, comorbidity, trial site, dialysis modality (hemo- or peritoneal dialysis), AF class (prevalent or incident), prior anticoagulation treatment (no treatment or ongoing treatment), and concomitant platelet inhibitor treatment; 2) as-treated time-updated cause-specific Cox proportional hazards models permitting time-dependent assessment of treatment including time in therapeutic range, dialysis modality, and risk covariates; and 3) on-treatment analyses with censoring of patients deviating from the allocated randomized treatment.

Subgroup analyses are planned for strata of age (<75 years and ≥75 years), sex (male/female), $CHA_2DS_2$-VASc score (2, 3-4, ≥5), antiplatelet treatment (yes/no), dialysis modality (hemodialysis/peritoneal dialysis), previous stroke (yes/no), and previous bleeding (yes/no).

For all analyses, statistical significance will be determined by a p-value ≤0.05. Determination of superiority will be based on the primary efficacy endpoint. A finalized statistical analysis plan will be prepared by the trial statistician and approved by the Trial Steering Committee prior to conclusion of randomization and initiation of data analyses.

### Sample size calculations

Prior to compiling this protocol, a retrospective study on Danish patients on chronic dialysis with incident AF diagnosed between 2002 and 2012 was made. During the study period, the incidence of AF increased from 4.0 (95% CI 3.8-4.2) per 100 person years to 7.8 (95% CI 6.8-9.0) per 100 person years.(44) Standardized one-year risks of stroke and major bleeding, respectively, were calculated as the average treatment effect using G-computation based on cause-specific Cox regression models.(45) This gave an absolute one-year risk of stroke of 1.7% (95% CI 0.1%-8.9%) and 6.1% (95% CI 4.2%-8.0%) in patients treated with and without warfarin, respectively (supplementary Figure S1A). The absolute one-year risk of major bleeding was 9.2% (95% CI 0.1%-20.8%) and 8.1% (95% CI 6.0%-10.0%) in patients with and without warfarin treatment, respectively (supplementary Figure S1B). Based on these results and the assumption of absence of a period effect, a sample size of n=299 per group is required to achieve a power of $1-\beta = 0.80$ for a two-sided t-test with $\alpha=0.05$. To compensate for ≤ 20% drop-out, 359 patients will be included in each group. A plot depicting sample size calculation is provided in supplementary Figure S2. Other trials investigating oral anticoagulation for patients with advanced chronic kidney disease and AF using a two-group study design include the RENAL-AF trial (Renal Hemodialysis Patients Allocated Apixaban versus Warfarin in Atrial Fibrillation), the AXADIA-AFNET8 trial (Compare Apixaban and Vitamin K Antagonists in Patients With Atrial Fibrillation an End-Stage Kidney Disease), the AVKDIAL trial (Oral Anticoagulation in Hemodialysis Patients), and the SACK trial (Stroke Prophylaxis with Apixaban in CKD5 Patients with Atrial Fibrillation). Planned enrollment in these trials was 762, 222, 855, and 1000-1400, respectively.

## Monitoring

### Data Safety Monitoring Committee

An independent Data Safety and Monitoring Committee has been established with the aim of safeguarding the interests of enrolled patients, assessing the safety and efficacy of the allocated treatment during the trial, and monitoring the overall conduct of the trial. The responsibilities of the Data Safety and Monitoring Committee have been described in a separate charter.

### Safety management

Serious adverse events (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) will be reported to the sponsor in accordance with the standards of Good Clinical Practice.(46) Harm will be adjudged based on the predefined safety endpoints pertaining to fatal or non-fatal major bleeding. Safety monitoring will be accomplished by tracing of SAEs, SARs, and SUSARs, safety and efficacy endpoints, and mortality. Registration of SAEs, SARs, and SUSARs for evaluation of potential late side effects will be continued until six weeks following end of trial irrespective of cause of discontinuation.

### Premature trial termination

The Data and Safety Monitoring Committee will have exclusive unblinded access to all data and may recommend discontinuation of the study to the Trial Steering Committee based on reviews of safety events. Throughout inclusion, interim analyses will be supplied in strict confidence for overview to the Data Safety Monitoring Committee. If results from the interim analyses provide sufficient evidence as to harm or benefit of the allocated treatments, the Data Safety Monitoring Committee will advise the Trial Steering Committee, thus enabling possible trial modifications or trial discontinuation.

### Trial auditing

Auditing of trial conduct will be performed by independent monitors from the regional Good Clinical Practice Units.

## Patient and public involvement

Design and conduction of this study was performed without public or patient involvement. Conclusions from the study will be communicated as a newsletter in a relevant media.

# ETHICS AND DISSEMINATION

The trial is to be conducted in accordance with the Helsinki Declaration and standards of Good Clinical Practice.(47,48) The trial is registered at www.clinicaltrials.gov (NCT03862859), EUDRA-CT number 2018-000484-86, and CTIS ID 2022-502500-75-00. The study protocol was approved by the Regional Research Ethics Committee on December 21, 2018 (journal number H-18050839), and by the Danish Medicines Agency on February 14, 2019 (case number 2018101877). The sponsor will release protocol amendments to the site investigators. Trial registration data set is provided in supplementary Table S2.

A trial steering committee (supplementary Table S3) has been involved in the study design and monitors the conduction of the study, analysis of study data, and publication of study results. The trial steering committee will have full access to all study data upon trial completion. The Vancouver recommendations will be used to access authorship eligibility. Data collection and management will be performed in accordance with the General Data Protection Regulations and all study-related material will be stored securely at the study site.

## Dissemination of results

Study results will be disseminated to participating sites, at research conferences, and in peer-reviewed journals.

## AVAILABILITY OF DATA AND MATERIALS

A de-identified dataset will be uploaded to an appropriate data archive three years after collection of the one-year post-randomization results.

## AUTHOR CONTRIBUTIONS

Study conceptualization and design: AK, CB, CTP, DHA, ELFB, ELG, GG, JDJ, JO, LK, MH, MR, MS, NC, PC, TL

Statistical analysis plan: CTP, NC, TL

Acquisition, analysis and interpretation of data: ASN, CDP, DCN, DK, ELFB, FHM, FTN, IB, INT, JB, JDK, JKB, JMR, KL, LB, MCB, ML, NC, RB

Drafting of manuscript: ELFB, NC

Critical revision of manuscript and approval of final version: All authors

## FUNDING STATEMENT

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## COMPETING INTERESTS

None related to the present study. The authors report the following general conflicts:

AK, ASN, CB, CTP, DCN, DK, FHM, FTN, GG, INT, JB, JDJ, JDK, JKB, JMR, KL, MCB, MR, MS, PC, TL report no conflicts of interest.

CDP has received speaker honoraria or consultancy fees from AstraZeneca and Astellas. Support for attending meetings and travel from Boehringer Ingelheim. CDP also has an ongoing collaboration with Vifor Pharma including donation of a research grant unrelated to this study.

DHA has received speaker and consultancy fees from AstraZeneca, GlaxoSmithKline, and UCB Nordic.

ELFB has received a donation of a research grant from AstraZeneca unrelated to this study.

ELG has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Novo Nordisk, MSD, Lundbeck Pharma, and Organon. He is investigator in clinical studies sponsored by AstraZeneca, Idorsia, or Bayer and has received unrestricted research grants from Boehringer Ingelheim.

IB has received speaker honoraria from Amgen and Bayer.

JO has received speaker honoraria or consultancy fees from Bayer, Bristol-Myers Squibb, Organon, and Pfizer.

LB has received consultancy fees from AstraZeneca, Astellas, Vifor Pharma, Pfizer, Novartis.

LK has received speaker honoraria from AstraZeneca, Bayer, Boehringer Ingelheim, Novartis, and Novo Nordisk.

MH has received speaker and consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Vifor, and GSK within the last 3 years.

ML has received speaker and consultancy fees from AstraZeneca, Bayer, Boehringer Ingelheim, Novo Nordisk, and GlaxoSmithKline.

NC has received speaker honoraria from AstraZeneca and Bristol-Myers Squibb

RB has received speaker honoraria or consultancy fees from AstraZeneca, Bayer, and Boehringer Ingelheim. She is investigator in clinical studies sponsored by Boehringer Ingelheim, AstraZeneca, or Bayer and has received unrestricted research grants from Boehringer Ingelheim.

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## TABLES AND FIGURES



## Supplemental material

# Figure legends

**Figure 1: Study design**
Eligibility is assessed in accordance with the inclusion and exclusion criteria.

Abbreviations: INR, international normalized ratio; ECG, electrocardiogram; SAE, serious adverse event; SAR, serious adverse reaction

[1]Plasma-hemoglobin, platelet count, albumin, phosphate, ionized calcium, parathyroid hormone, c-reactive protein, urea nitrogen, and creatinine
[2]Required in all women of childbearing potential at inclusion and monthly throughout the trial.
[3]Last recorded INR
[4]SAEs/SARs will be recorded continuously with reporting of SAEs/SARs to the study sponsor within 24 hours of identification for assessment. Efficacy and safety outcomes will be registered every month in an electronic database.

**Table 1: Inclusion and exclusion criteria**

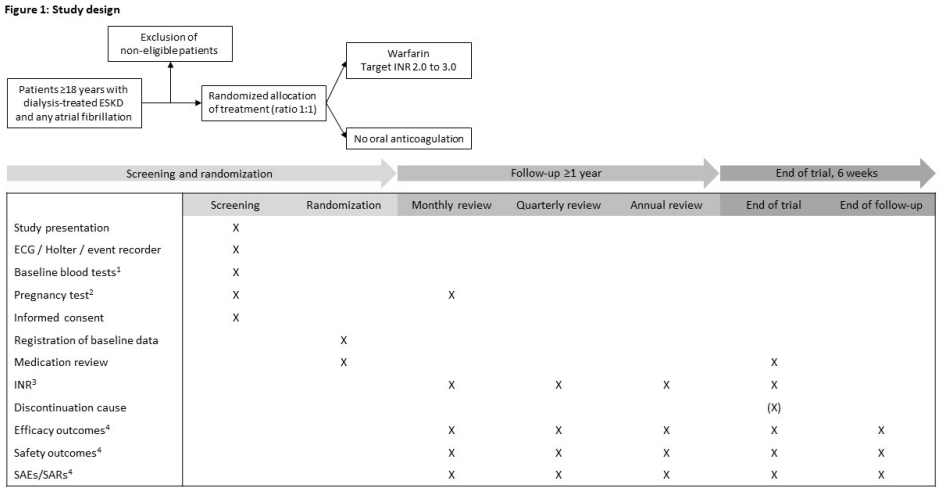
Inclusion criteria

- Patients ≥18 years on chronic dialysis
- Any non-valvular paroxysmal, persistent, or permanent atrial fibrillation or flutter documented by an electrocardiogram, episode of ≥30 seconds on Holter monitor, or episode of ≥6 minutes on event recorder or any other recording device
- Competence to understand the study rationale, including potential risks and benefits associated with treatment, necessary for written informed consent

Exclusion criteria

- $CHA_2DS_2$-VASc Score ≤1
- Other indications for oral anticoagulation treatment (pulmonary embolism <6 months, deep vein thrombosis <3 months, mechanical heart valve prosthesis) - irrespective of whether treatment is implemented
- Ongoing dual antiplatelet treatment
- Malignancy (with exception of non-melanoma skin cancer) with recent (<1 year), ongoing or planned curative or palliative chemo-, radiation-, and/or surgical therapy
- Endoscopy with gastrointestinal ulcer <1 month
- Esophageal varices
- Autoimmune or genetic coagulation disorders
- Congenital alactasia, Lapp Lactase deficiency or glucose-galactose malabsorption
- Pending spinal tap
- Cerebrovascular malformations
- Arterial aneurisms
- Ulcers or wounds (Wagner grade >1)
- Bacterial endocarditis <3 months
- Active bleeding contraindicating anticoagulation
- Any non-elective and/or non-ambulant surgery <7 days
- Cerebral hemorrhage <4 weeks
- Thrombocytopenia (platelet count $<100 \times 10^9$/L) <30 days
- Severe liver insufficiency (spontaneous international normalized ratio >1.5) <30 days.
- Known intolerance to warfarin
- Use of hypericum perforatum/St. John's Wort
- Uncontrolled hypertension (repeated blood pressure >180/110 mmHg) <30 days
- Uncontrolled hyperthyroidism (thyroid-stimulating hormone <0.1 µIU/mL) <30 days
- Pregnancy or lactation
- Participation in other ongoing intervention trials adjudged to influence study outcomes

| Table 2: Primary, secondary, and tertiary outcomes |
|---|
| **Primary efficacy outcome** |
| Fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke |
| **Primary safety outcome** |
| Fatal or non-fatal major bleeding[1] |
| **Secondary outcomes** |
| Fatal or non-fatal ischemic or unspecified stroke[2] |
| Fatal or non-fatal ischemic stroke[2] |
| Fatal or non-fatal hemorrhagic stroke[2] |
| Fatal or non-fatal ischemic or hemorrhagic stroke[2] |
| All-cause mortality |
| Combination of any non-fatal stroke and all-cause mortality |
| Combination of any non-fatal stroke, any non-fatal major bleeding and all-cause mortality |
| **Tertiary outcomes** |
| Discontinuation of allocated randomized therapy |
| Calciphylaxis/calcific uremic arteriolopathy |
| Fatal or non-fatal acute myocardial infarction |
| Hospitalization due to left-sided heart failure |
| Peripheral artery disease |
| Thrombosis of arteriovenous fistula |
| Osteoporotic fractures including low energy fractures of the proximal femur, distal radius, humerus, pelvis, and vertebrae |
| [1]As defined by the International Society on Thrombosis and Hemostasis |
| [2]For patients who meet a primary outcome |




| | Screening | Randomization | Monthly review | Quarterly review | Annual review | End of trial | End of follow-up |
|---|---|---|---|---|---|---|---|
| Study presentation | X | | | | | | |
| ECG / Holter / event recorder | X | | | | | | |
| Baseline blood tests[1] | X | | | | | | |
| Pregnancy test[2] | X | | X | | | | |
| Informed consent | X | | | | | | |
| Registration of baseline data | | X | | | | | |
| Medication review | | X | | | | X | |
| INR[3] | | | X | X | X | X | |
| Discontinuation cause | | | | | | (X) | |
| Efficacy outcomes[4] | | | X | X | X | X | X |
| Safety outcomes[4] | | | X | X | X | X | X |
| SAEs/SARs[4] | | | X | X | X | X | X |

Figure 1: Study design
Eligibility is assessed in accordance with the inclusion and exclusion criteria.
Abbreviations: INR, international normalized ratio; ECG, electrocardiogram; SAE, serious adverse event; SAR, serious adverse reaction

1Plasma-hemoglobin, platelet count, albumin, phosphate, ionized calcium, parathyroid hormone, c-reactive protein, urea nitrogen, and creatinine
2Required in all women of childbearing potential at inclusion and monthly throughout the trial.
3Last recorded INR
4SAEs/SARs will be recorded continuously with reporting of SAEs/SARs to the study sponsor within 24 hours of identification for assessment. Efficacy and safety outcomes will be registered every month in an electronic database.

338x190mm (96 x 96 DPI)

# Supplemental material

Supplementary Table S1: Trial sites

Supplementary Table S2: Participants of the DANWARD study

Supplementary Table S3: Trial Registration Data Set

Supplementary Figure S1: 1-year standardized risk of A) stroke and B) major bleeding

Supplementary Figure S2: Sample size calculation

Supplementary Appendix 1: Protocol version 1.26, February 17, 2023

Supplementary Appendix 2: Informed consent materials (in Danish)

| **Supplementary Table S1: Trial sites** |
| --- |
| Aalborg University Hospital, Mølleparkvej 4, 9000 Aalborg, Denmark |
| Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, 8200 Aarhus, Denmark |
| Esbjerg and Grindsted Hospital, Finsensgade 35, 6700 Esbjerg, Denmark |
| Herlev and Gentofte Hospital, Borgmester Ib Juuls Vej 1, 2730 Herlev, Denmark |
| Holbæk Hospital, Smedelundsgade 60, 4300 Holbæk, Denmark |
| Bornholm Hospital, Ullasvej 8, 3700 Rønne, Denmark |
| Hospital of Southern Jutland, Sydvang 1, 6400 Sønderborg, Denmark |
| Gødstrup Regional Hospital, Hospitalsparken 15, Herning, Denmark |
| Lillebælt Hospital, Sygehusvej 24, 6000 Kolding, Denmark |
| Copenhagen University Hospital – North Zealand, Dyrehavevej 29, 3400 Hillerød, Denmark |
| Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 København, Denmark |
| Viborg Regional Hospital, Heibergs Alle 5A, 8800 Viborg, Denmark |
| Zealand University Hospital, Sygehusvej 10, 4000 Roskilde, Denmark |

| **Supplementary Table S2: Trial Registration Data Set** | |
|---|---|
| Data category | Information |
| Primary registry and trial identifying number | ClinicalTrials.gov: NCT03862859 |
| Date of registration in primary registry | February 22, 2019 |
| Secondary identifying numbers | EUDRA-CT 2018-000484-86, CTIS ID 2022-502500-75-00. |
| Source(s) of monetary or material support | The Danish Heart Foundation, the Augustinus Foundation |
| Primary sponsor | Nicholas Carlson, Dept. of Nephrology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark |
| Secondary sponsor(s) | None |
| Contact for public queries | NC, ELFB |
| Contact for scientific queries | NC, GG |
| Public title | The Danish Warfarin-Dialysis Study - Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis |
| Scientific title | The Danish Warfarin-Dialysis Study: Safety and Efficacy of Warfarin in Patients With Atrial Fibrillation on Dialysis - A Nationwide Parallel-group Open Randomized Clinical Trial |
| Countries of recruitment | Denmark |
| Health condition(s) or problem(s) studied | Atrial fibrillation, stroke, major bleed, end-stage renal disease |
| Intervention(s) | Drug: Warfarin |
| Key inclusion and exclusion criteria | Inclusion criteria: Adult patient (≥18 years) with any atrial fibrillation on chronic dialysis<br>Exclusion criteria: $CHA_2DS_2$-VASc score ≤1, other indication for oral anticoagulation, contraindications for oral anticoagulation, participation in other intervention trials adjudged to influence outcomes |
| Study type | Interventional |
| Date of first enrolment | October 16, 2019 |
| Target sample size | 718 |
| Recruitment status | Recruiting |
| Primary outcome(s) | Primary efficacy outcome: Fatal or non-fatal transient ischemic attack, ischemic stroke, or unspecified stroke<br>Primary safety outcome: Fatal or non-fatal major bleeding |
| Key secondary outcomes | All-cause mortality; combination of any non-fatal stroke and all-cause mortality; combination of any non-fatal stroke, any non-fatal major bleeding, and all-cause mortality |

**Supplementary Table S3: Participants of the DANWARD study**

**Trial Steering Committee**

Alice S Nielsen, MD, Department of Medicine, Esbjerg Hospital, University Hospital of Southern Denmark, Denmark

Anne-Lise Kamper, MD DMSc, Department of Nephrology, Copenhagen University Hospital – Rigshospitalet, Denmark

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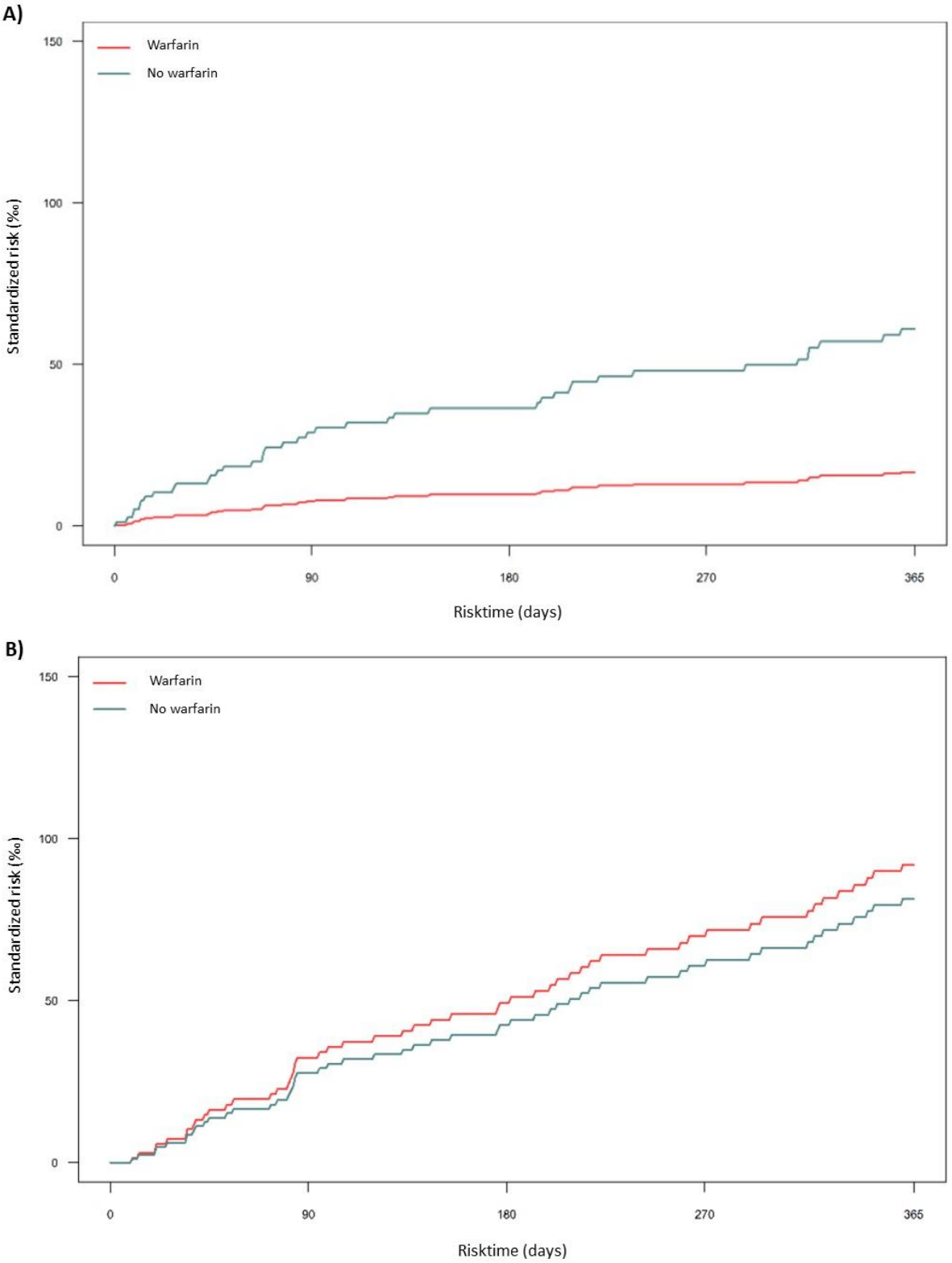
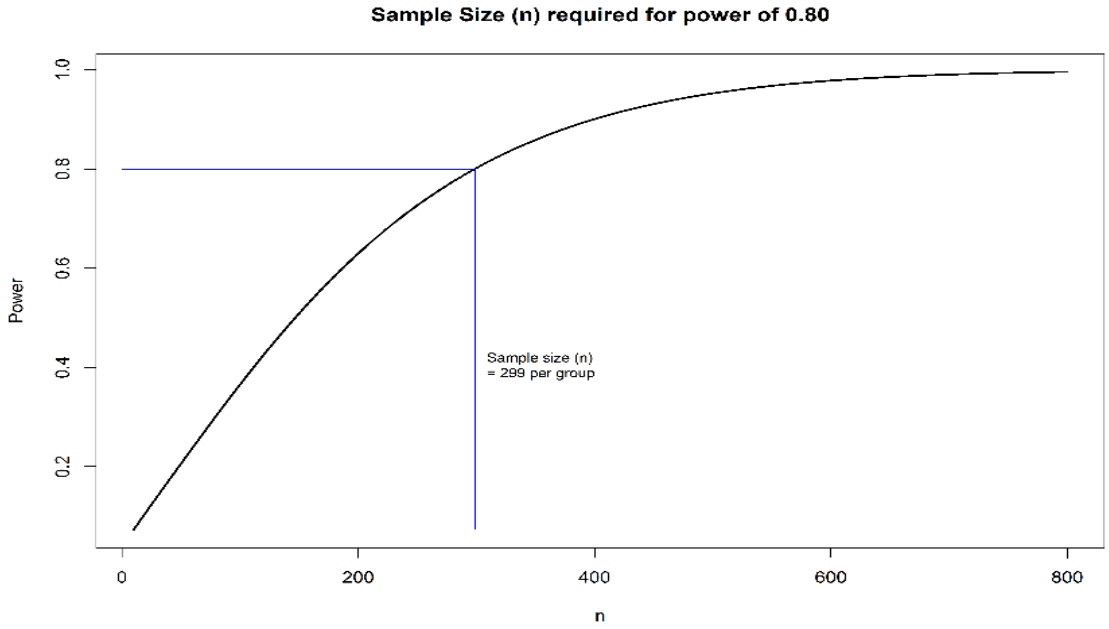
**Supplementary Figure 1:** 1-year standardized risk of A) stroke and B) major bleeding




Predicted 1-year standardized risk of stroke and major bleeding in Danish patients with end-stage kidney disease and atrial fibrillation based on hazards ascertained in multiple cause specific Cox regression.

**Supplementary Figure S2:** Sample size calculation




Sample size i.e. the number of patients (n) in each group is depicted with corresponding power, based on predicted one-year absolute risk of stroke.

# DAN-WAR-D

## Danish Warfarin-Dialysis Study

**Safety and efficacy of warfarin in patients with atrial fibrillation on dialysis -**

**A nationwide parallel-group open randomized clinical trial**



# Protocol

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# Table of Contents

# Introduction

Prevalence of dialysis-treated end-stage renal disease has remained stable at ~2.500 patients in Denmark throughout the past decade.[1] However, patients with end-stage renal disease continue to be at significantly increased risk of cardiovascular disease and mortality, and although cardiovascular outcomes have been observed to be improving in patients with end-stage renal disease, advances remains inferior to improvements observed in general populations.[2] As such, cardiovascular disease accounts for approximately 50% of mortalities in end-stage renal disease;[3] thereby contributing substantially to the observed annual mortality of >20% in the dialysis population.[4] Of note, incidence of myocardial infarction and stroke is 5- to 15-fold higher in dialysis-treated patients with end-stage renal disease,[5, 6] and cardiovascular mortality is 10- to 30-fold higher compared with general populations.[7]

## Atrial fibrillation in general populations

Atrial fibrillation continues to be the most common sustained arrhythmia in general populations,[8] with growth in both prevalence and incidence observed throughout the past decade.[9] Presence of atrial fibrillation is associated with a 5-fold increase in risk of ischemic stroke,[10] and development and subsequent embolization of atrial thrombi may occur with any form of atrial fibrillation. However, treatment with oral anticoagulation is associated with a ⅔ reduction in risk of stroke based on cumulated data from multiple randomized trials comprising ~28.000 patients.[11] Notably, the efficacy of oral anticoagulation in patients with end-stage renal disease on dialysis remains wholly untested in prospective studies due to systematic exclusion from existing trials.

The decision to prescribe oral anticoagulation in patients is based on clinical assessment of net benefit i.e. is treatment-associated increase in risk of bleeding offset by the benefit on risk of stroke. Currently, treatment benefit is assessed using the $CHA_2DS_2$-VASc and HAS-BLED algorithms (Supplemental Table S1).[12, 13] The 2014 American College of Cardiology/American Heart Association guideline for management of patients with atrial fibrillation advocates oral anticoagulation if the $CHA_2DS_2$-VASc score is ≥2.[14] Oral anticoagulation is essentially recommended in all patients irrespective of bleeding risk; however, a HAS-BLED score ≥3 indicates particular risk of bleeding obliging close monitoring of patients for risk mitigation, careful monitoring of international normalized ratios, and possibly individualized dosing of oral anticoagulation therapy. Similarly, the 2016 European Society of Cardiology guideline

and the 2018 European Heart Rhythm Association guideline for management of atrial fibrillation also advocate oral anticoagulation for all patients based on the $CHA_2DS_2$-VASc score; however, patients at increased risk of bleeding should be identified and modifiable risk factors addressed.[15, 16]

## Atrial fibrillation and end-stage renal disease

Prevalence of atrial fibrillation is inversely correlated with renal function, and incidence is markedly increased in patients with end-stage renal disease.[17-19] An estimated one in five patients on dialysis due to end-stage renal disease suffer from atrial fibrillation, with incidence of new-onset atrial fibrillation ranging from 25 to 150 per 1.000 person-years.[20-23] Additionally, atrial fibrillation in patients with end-stage renal disease is associated with increased mortality and a two- to three-fold increase in risk of stroke compared with general populations,[20] corresponding to an incidence of 60 to 150 per 1.000 person-years.[24-26]

Presence of end-stage renal disease is associated with increased risk of bleeding due to impairment of platelet function and possible abnormal platelet-endothelial interaction.[27, 28] Of note, levels of circulating coagulation factors remain normal or elevated, and no prolongation of prothrombin or partial thromboplastin times have been observed.[29] Additionally, vitamin K antagonism i.e. warfarin may accelerate vascular calcification through an inhibition of matrix Gla- (γ-carboxyglutamate) protein regulation of bone morphogenic protein-2 and -4.[30, 31] Although rare, warfarin may also be associated with induction of ectopic vascular calcification and possibly calciphylaxis / uremic calcific arteriolopahty characterized by dermal ulceration and necrosis with medial calcification and intimal proliferation of small vessels.[32] As such, uremia may moderate benefit of treatment with oral anticoagulation in patients with end-stage renal disease and atrial fibrillation;[24, 26] the issue however remains unresolved, and the efficacy and safety of oral anticoagulation i.e. warfarin in patients with end-stage renal disease and atrial fibrillation has remained untested in prospective studies.[33, 34]

A number of retrospective studies have evaluated the benefit and harm of oral anticoagulation in dialysis-treated patients with end-stage renal disease; results however remain divergent.[20, 24, 25, 33, 35-41] Specifically, observational cohorts comparing benefit of oral anticoagulation in end-stage renal disease and atrial fibrillation have reported treatment with warfarin to be associated with reduced risk of stroke,[24, 35, 38, 41] increased risk of stroke,[33, 39, 40] and

neither decreased nor increased risk of stroke.[22, 25, 36] Similarly, warfarin may also be associated with increase in risk of bleeding,[24, 25, 36, 37] or no increase in risk of bleeding.[35, 39, 41] Unsurprisingly, a recent meta-review comprising >50.000 patients with end-stage renal disease observed no definite warfarin-associated increase or decrease in risk of stroke, and no definite warfarin-associated increase or decrease in risk of major bleeding.[42]

Consequent to the discrepant results, guidelines pertaining to anticoagulation in end-stage renal disease remain ambiguous with regard to the benefit of treatment. As such, while the 2014 American College of Cardiology/American Heart Association guideline extends recommendations of treatment with oral anticoagulation to include patients with end-stage renal disease,[14] the Kidney Disease Improving Global Outcomes (KDIGO) guidelines caution that, given the lack of randomized clinical trials, the risk-to-benefit ratio of routine anticoagulation for primary or secondary prevention of stroke in end-stage renal disease remains uncertain.[43] No definitive recommendation is advocated with regard to oral anticoagulation in the 2016 European Society of Cardiology guideline and 2018 European Heart Rhythm Association guideline, both merely advocating further research.[15, 16]

Considering the deficient evidence pertaining to the safety and efficacy of oral anticoagulation in patients with end-stage renal disease and atrial fibrillation, equipoise currently exists among nephrologists regarding the benefit-to-risk ratio of anticoagulation for stroke risk reduction in the dialysis population.[44] Unsurprisingly, prescription of oral anticoagulation i.e. warfarin in patients with end-stage renal disease diagnosed with new-onset atrial fibrillation remains inconsistent, with <50% of patients initiating oral anticoagulation currently.[25, 36, 38] As such, a prospective evaluation of the safety and efficacy of oral anticoagulation i.e. warfarin in patients with end-stage renal disease and atrial fibrillation is warranted,[45] as results would expectantly provide essential insights with unequivocal implications for clinical practice.

## Drug information: warfarin

The coumarin anticoagulant, warfarin, is a racemate of two active isomers. Administration is oral, bioavailability is 79-100%, volume of distribution is 0.14l/kg, and 99% is albumin-bound. Warfarin is employed in the prevention and treatment of thromboembolic diseases including venous thrombosis, thromboembolism, pulmonary embolism, and

for the prevention of ischemic stroke in patients with atrial fibrillation. Warfarin inhibits vitamin K reductase leading to depletion of the reduced form of vitamin K (vitamin KH2). Vitamin K is a cofactor for the carboxylation of glutamate residues on the N-terminal regions of vitamin K-dependent proteins; as such the depletion of vitamin KH2 limits gamma-carboxylation and subsequent activation of the vitamin K-dependent coagulant proteins effects inhibited synthesis of the vitamin K-dependent coagulation factors II, VII, IX, and X, and the anticoagulant proteins C and S. Reduced availability of the vitamin K-dependent coagulation factors II, VII, and X results in decreases in prothrombin and thrombin levels leading to decreased clot thrombogenicity.

Elimination of warfarin is predominantly by hepatic metabolism, and renal clearance is limited. Metabolites are however principally excreted into the urine, and to a lesser extent into the bile. Warfarin is metabolized by stereo- and regio-selectively by hepatic microsomal enzymes including cytochrome P450, CYP1A1, 1A2, and 3A4 to yield hydroxylated metabolites. The biological half-life is 20-60 hours, and steady-state is usually realized within 2 days; however, therapeutic effects are delayed >48 hours as circulating coagulations factors remain unaffected by the drug. The effects of warfarin may be reversed with phytonadione (vitamin K1), fresh frozen plasma, or prothrombin complex concentrate.

Warfarin treatment is guided by monitoring of the prothrombin time as expressed in the international normalized ratio. The target international normalized ratio is dependent on the clinical situation; an international normalized ratio of 2-3 is indicated for prevention of ischemic stroke in patients with atrial fibrillation. Due to the common interaction of warfarin with nutrients and other medications, continuous adjustment of the warfarin dose in accordance with the international normalized ratio is indicated. Guidelines pertaining to warfarin therapy advocate initiation of treatment employing a daily dose of 5mg with dose-adjustment in accordance with a measured international normalized ratio on day 5,[46-48] with indefinite monitoring of international normalized ratios and adjustment of therapy.

The major complication associated with warfarin is bleeding. Generally, the risk of major bleeding is about 2 to 3% per year;[49, 50] however, risk of bleeding is individual and greatest during the first weeks following warfarin initiation, and during periods of illness.[51, 52] As such, in patients tolerating treatment for > 6 months, the risk of bleeding

decreases to < 1% per year,[52] and although the risk of major bleeding increases with rising international normalized ratios (particularly with international normalized ratios > 4), the 30-day risk of bleeding associated with a singular dysregulated international normalized ratio remains low <1%.[53-55] Other complications associated with warfarin including skin necrosis, hair loss, and calciphylaxis / calcific uremic arteriolopathy remain rare.

## Aims and objectives

Overall, data pertaining to the tolerability, safety, and benefit of initiating anticoagulation for stroke risk reduction in patients with end-stage renal disease and atrial fibrillation remains conflicting and insufficient. Patients on dialysis continue to be routinely excluded from randomized controlled trials, and evidence from observational studies is plausibly biased. The **main objective** of the following parallel-group open randomized clinical trial presents a nationwide study aimed at investigating the benefit, tolerability, and safety of initiating warfarin versus no treatment in patients with atrial fibrillation on dialysis. The **anticipated results** from this project will provide conclusive evidence as to the appropriateness of initiating oral anticoagulation for stroke risk reduction in dialysis populations with atrial fibrillation with direct effects on clinical management and international guidelines pertaining to these patients.

Based on the anticipated results, the study is initiated based on a **general hypothesis** theorizing that initiation of anticoagulation in dialysis-treated patients with end-stage renal disease and atrial fibrillation is associated with stroke risk reduction and benefit on survival. Explicitly, the **specific hypothesis** theorizes that anticoagulation based on warfarin dosing targeting an international normalized ratio of 2-3 is associated with net benefit as compared to no treatment in dialysis-treated patients with end-stage renal disease and atrial fibrillation.

## Methods

### Study participants

Prevalence and incidence of dialysis-treated patients with end-stage renal disease is approximately 2.500 and 600-700 per year in Denmark, respectively.[56] Incidence of de novo atrial fibrillation in dialysis-treated end-stage renal disease is approximately 150-300 per year (unpublished data based on data in the Danish National Patient Registry

2000-2012), and rising. Dialysis-treated patients with end-stage renal disease diagnosed with atrial fibrillation identified in the clinical setting will be recruited from all 14 existing dialysis centers (including satellites) in Denmark (overview provided as Supplemental Table S2).

Participants will be recruited in accordance with the listed inclusion and exclusion criteria.

## Inclusion criteria

1. Patients ≥18 years on chronic dialysis due to end-stage renal disease.
2. Any non-valvular paroxysmal, persistent or permanent atrial fibrillation or flutter documented by an electrocardiogram, episode of ≥30 seconds on Holter monitor, or episode of ≥6 minutes on event recorder or any other recording device
3. Competence to understand the study rationale, including potential risks and benefits associated with treatment, necessary for written informed consent.

## Exclusion criteria

1. $CHA_2DS_2$-VASc Score ≤1
2. Other indications for oral anticoagulation treatment (pulmonary embolism < 6months, deep vein thrombosis <3months, mechanical heart valve prosthesis) - irrespective of whether treatment is implemented
3. Ongoing dual antiplatelet treatment
4. Malignancy (with exception of non-melanoma skin cancer) with recent < 1 year, ongoing, or planned curative, or palliative chemo- , radiation-, and/or scheduled surgical therapy
5. Endoscopy with gastrointestinal ulcer <1 month
6. Esophageal varices
7. Autoimmune or genetic coagulation disorders
8. Congenital alactasia, Lapp Lactase deficiency or glucose-galactose malabsorption
9. Pending spinal tap
10. Cerebrovascular malformations
11. Arterial aneurisms

12. Ulcers or wounds (Wagner grad >1)
13. Bacterial endocarditis < 3 months
14. Active bleeding contraindicating anticoagulation
15. Any non-elective and/or non-ambulant surgery <7 days
16. Cerebral hemorrhage <4 weeks
17. Thrombocytopenia (platelet count $<100 \times 10^9$/L) <30 days.
18. Severe liver insufficiency (spontaneous international normalized ratio >1.5) <30 days.
19. Known intolerance to warfarin
20. Use of hypericum perforatum / St. John's Wort
21. Uncontrolled hypertension (repeat blood pressure >180/110mmhg) < 30 days
22. Uncontrolled hyperthyroidism (thyroid-stimulating hormone <0.1μIU/mL) <30 days
23. Pregnancy or lactation
24. Participation in other ongoing intervention trials adjudged to influence study outcomes

**Pregnancy and contraception**

A woman is considered of childbearing potential i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single measurement is considered insufficient.

All female study participants of childbearing potential will be required to use highly effective birth control methods throughout participation in the study until the end of systemic exposure. The end of systemic exposure is defined as the time point where the warfarin, including active or major metabolites, has decreased to a concentration no longer considered relevant for human teratogenicity / fetotoxicity i.e. a period extended 30 days beyond 5 half-lives (>6 weeks) to ensure against genotoxicity. Highly effective birth control methods are defined as methods able t can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly

effective birth control methods in accordance with the definition provided in the Heads of Medicine Agencies guideline.

Highly effective birth control methods:

1. Combined estrogen and progestogen hormonal contraception (oral, intravaginal, or transdermal)
2. Progestogen-only hormonal contraception (oral, injectable, or implantable)
3. Intrauterine device
4. Intrauterine hormone-releasing system
5. Bilateral tubal occlusion
6. Vasectomized partner
7. Sexual abstinence

A negative highly sensitive pregnancy test will be required for all women of childbearing potential at inclusion, with scheduled monthly pregnancy testing throughout the study period.

## Randomization of allocated treatment

Dialysis-treated patients with end-stage renal disease with diagnosis of paroxysmal, persistent, or permanent atrial fibrillation will be randomly allocated to either treatment with warfarin or no treatment. Hence, patients already receiving anticoagulation will be randomized to continue or discontinue their treatment. Participants will be assigned to either warfarin or no treatment with a 1:1 allocation as per a computer-generated randomization schedule based in REDCap stratified by center using permuted blocks of random sizes. Block size and allocation ratio will remain undisclosed to ensure concealment. All study participants will be allocated to receive treatment in accordance with the randomization for the full duration of the trial i.e. at a minimum one year following randomization. Allocated warfarin treatment will be prescribed by the recruiting nephrology departments. Patients will be considered enrolled in the study from the date of randomization.

A schematic overview of study design and randomization of allocated treatment is provided in **Figure 1**.

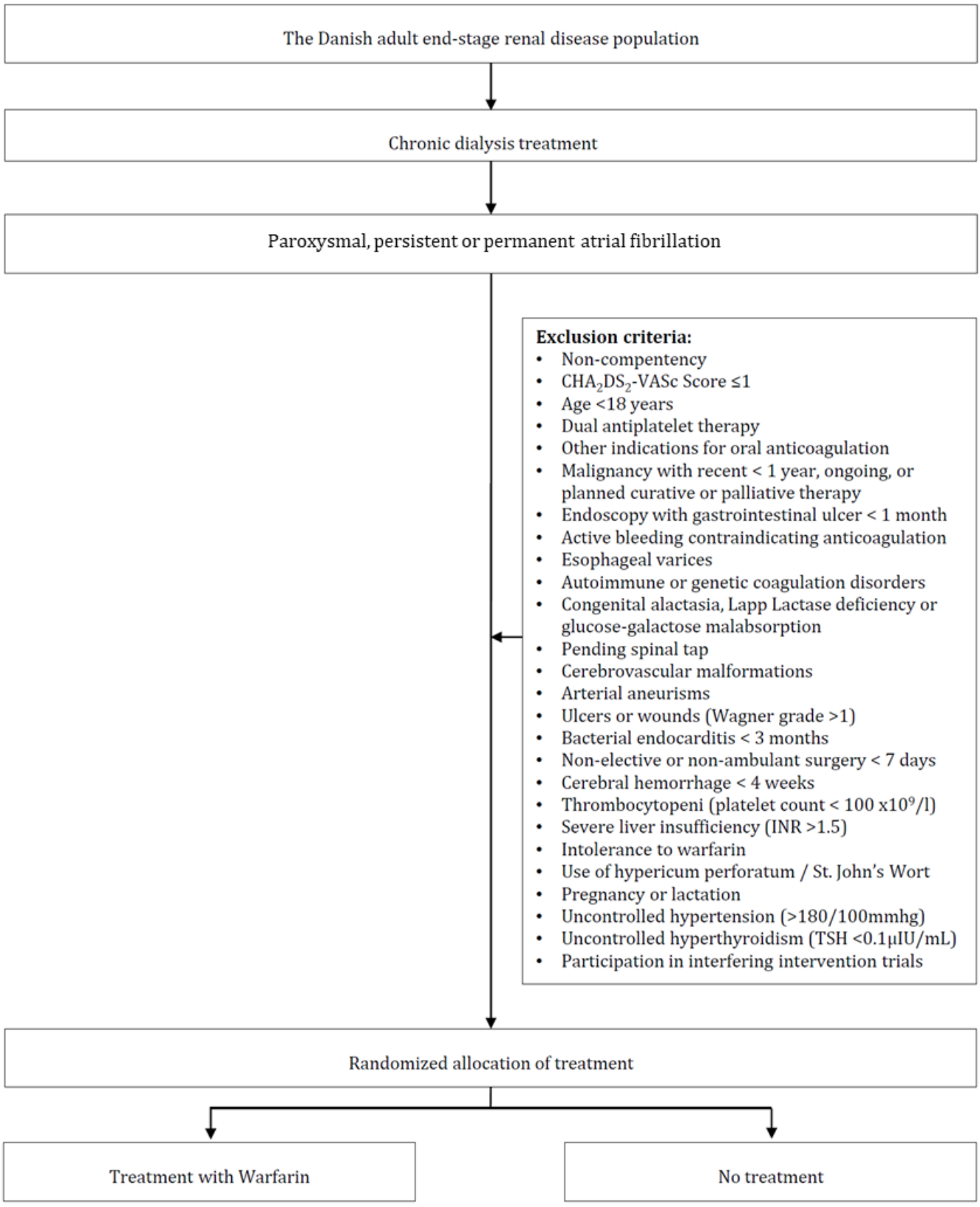

**Figure 1 Study design and allocation of randomized treatment**

Randomization of patients with end-stage renal disease on chronic dialysis with atrial fibrillation to either treatment with warfarin or no treatment.

Post-randomization discontinuation of the allocated treatment is indicated if oral anticoagulation is required due to other indications, if considerable and repeated side effects arise, or in any case where the attending physician or patient assesses that the allocated treatment should be discontinued pending deliberation of treatment appropriateness with the Study nucleus.

## Data sources

The study is planned as a multicentre, randomized, open label, parallel group study. Patients will be allocated to treatment with warfarin or no treatment. As indicated below, the study is planned to include 718 patients. The steering committee may review recruitment rate and overall event rate, blinded by treatment, and increase sample size until 1.436 patients pending approval of a substantial amendment of the protocol to relevant authorities. Study follow-up including study outcomes will be recorded in a central database by on-site investigators using the REDCap webapplication, with qualitative monitoring of registration based on data from national health care registers; importantly, dialysis-treated patients with end-stage renal disease require frequent and systematic follow-up in nephrology centres regardless of study inclusion. As such, any additional systematic follow-up solely directed by the trial is minimized. Overall, information including baseline data, data pertaining to trial adherence, and data pertaining to outcomes during follow-up will be recorded via registration in the REDCap webapplication by on-site investigators in the context of ambulant dialysis control and quarterly reviews, with qualitative monitoring of data registration based on data extraction from national health care registers.

### Monitoring via the Danish Health Care Registers

A qualitative assessment of study data recorded by on-site investigators will be performed based on data retrieved from national administrative and clinical databases. Numerous comprehensive and validated national registers exist in Denmark.[57-59] Information regarding hospitalization, medication, morbidity and mortality is recorded in national databases (i.e. the Danish National Patient Register, the Danish Registry of Medicinal Product Statistics, the Civil

Registration System, the National Laboratory database) under a unique individual central person register (CPR) number permitting cross-referencing of data between registers. Data procurement will be effectuated through the research service afforded under the Danish Health Authority permitting cross-referencing of data regarding morbidity, mortality, prescriptions, socioeconomic status, hospitalization and treatment. Information concerning mortality will be obtained from the Civil Registration System and information regarding cause of death from the National Register of Causes of deaths. Prescription data, including dosage and treatment changes, will be acquired from the national prescription database permitting assessment of compliance. Data relating international normalized ratios will be acquired from the national laboratory database permitting qualitative evaluation of the time in therapeutic range. Specific illness will be determined through the Danish National Patient Register, the Danish Stroke Register, and the Danish National Register on Regular Dialysis and Transplantation.[60]

## Study data

Civil registration number, patient age, gender, primary renal disease, dialysis modality and access type, dialysis longevity, prior renal transplantations, existing cardiovascular comorbidity (ischemic heart disease, prior revascularization, heart failure and left ventricular ejection fraction, hypertension, stroke, TCI, thromboembolic disease, peripheral vascular disease, prior lower extremity amputation) and non-cardiovascular comorbidity (hypo-/hyperthyroidism, chronic obstructive pulmonary disease, diabetes mellitus, liver disease, prior gastrointestinal bleed, prior malignancy, prior psychiatric disease), smoking status and alcohol consumption, medication, laboratory measurements relating the most recent hemoglobin level, platelet count, albumin level, phosphate level, ionized-calcium level, parathyroid hormone level, c-reactive protein level, blood urea nitrogen, HbA1c and creatinine level, and allocated treatment will be recorded by onsite investigators using the REDCap webapplication at the time of randomization. Baseline and follow-up data will procured based on registrations using the REDCap webapplication in a central database by on-site investigators; the quality of registration will additionally be monitored based on data retrieved from national health care registers. Adherence to the allocated treatment will be ascertained based on time in therapeutic range as defined by international normalized ratios relating time in therapeutic range (%) and patient reported non-adherence recorded by on-site investigators; registration by on-site investigators will be completed within the context of ambulant dialysis control and retrospectively within the context of quarterly reviews. Patients

will be considered enrolled in the study following randomization, and all patients enrolled will be accounted for in the study results.

## Follow-up

Monitoring and dosing of warfarin therapy will be conducted in accordance with national guidelines pertaining to anticoagulation therapy with warfarin as defined by the Danish Society of Cardiology (http://nbv.cardio.dk/ak#afs14_1) and the Danish Health Authority (Supplementary Figure S1). Monitoring of treatment and warfarin dosing will be performed within the context of ambulant dialysis controls in accordance with common practice. Patients with end-stage renal disease are continuously evaluated by nurses and physicians at nephrology departments while undergoing ambulant dialysis treatment with pre-scheduled non-trial related clinical and laboratory assessment in the majority of patients performed on a weekly basis. Patient assessment and monitoring will additionally be performed within the context of the study at a minimum by on-site investigators at scheduled monthly, quarterly, and annual assessments as defined in the study schedule of appointments (Supplementary Table S4). However, on-site investigators may schedule additional ambulatory control in patients where indicated. As defined in the national guidelines, warfarin therapy necessitates continuous evaluation and documentation of treatment quality, as defined by a time in therapeutic range ≥70%, i.e. an international normalized ratio of 2-3 more than 70% of the time as defined in national and international guidelines. Adherence and compliance will be monitored by on-site investigators based on recorded measurements relating therapeutic time in range (%) and patient-reported adherence to the allocated treatment at the scheduled quarterly ambulant controls; non-adherence will be defined as an time in therapeutic range <70% or patient-reported non-adherence. On-site investigators will at minimum register the latest international normalized ratio, the patient-reported adherence to allocated treatment, and data pertaining to outcomes of patients at scheduled quarterly reviews via the REDCap webapplication in accordance with the schedule of appointment, with supplementary monitoring of the latest international normalized ratios at monthly intervals.

Additionally, the study nucleus will perform annual qualitative assessment of registration practices based on data retrieval from national health care registers via the research service afforded under the Danish Health Authority (https://sundhedsdatastyrelsen.dk/da/forskerservice). The Danish Health Authority is a state-owned entity in

Denmark sorting under the Ministry of Health. Professors Christian Torp-Pedersen and Gunnar Gislason in collaboration with the coordinating investigator Nicholas Carlson will share responsibility for maintaining an updated database including patient identification and treatment allocation permitting monitoring of recruitment and outcomes by the Trial Steering Committee.

## Study end

Study end will be defined as one year after ultimate randomization. A preplanned analysis of outcome by allocated treatment is proposed at study end. Patients will be informed of study end by the local primary investigator within the context of a scheduled end of treatment control. All individuals will be followed a minimum of one year; however patients randomized early in the trial will be followed for the full four year duration of the trial. Following end of treatment, patients will be followed for an additional 6 weeks to ensure registration of delayed treatment effects. Patients may opt to discontinue the allocated treatment for any reason, and on-site physicians may opt to discontinue allocated treatment due to clinical necessity permitting deliberation of treatment appropriateness in the study nucleus. All patients discontinuing treatment will be assessed within the context of an end of treatment control with registration of reasons for discontinuation of treatment. As patients will be receiving warfarin therapy in accordance with the approved indication and the summary of product characteristics, no formal instructions on patient management beyond existing guidelines are proposed. Of note, the decision to continue or discontinue treatment with warfarin beyond study completion will be at the discretion of the onsite investigators.

## Study outcomes

The primary efficacy outcome of any transient ischemic attack, ischemic or unspecified stroke or death due to a transient ischemic attack, ischemic or unspecified stroke will be compared between patients allocated warfarin and no treatment. The primary safety outcome will be major bleeding defined in accordance with the International Society on Thrombosis and Hemostasis definition pertaining to major bleeding in non-surgical patients, i.e. major intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, intramuscular with compartment syndrome, or gastrointestinal bleeding.[61]

Secondary outcomes will include; non-fatal and fatal ischemic or unspecified stroke, non-fatal and fatal stroke, non-fatal and fatal haemorrhagic stroke, non-fatal and fatal ischemic or hemorrhagic stroke, all-cause mortality, and the combination of any non-fatal stroke and all-cause mortality, and the combination of any non-fatal stroke, any non-fatal major bleeding, and all-cause mortality as defined in table 2. Tertiary outcomes will include discontinuation of the allocated randomized therapy, calciphylaxis, arteriovenous fistula thrombosis, fatal or non-fatal acute myocardial infarction, hospitalization due to left-sided heart failure, peripheral artery disease, arteriovenous fistula thrombosis, osteoporotic fractures, alopecia, and dermal necrosis. Additionally, the time in therapeutic range adjudge by international normalized ratios will be evaluated amongst patients treated with warfarin.

All study outcomes will be at a minimum be registered by onsite investigators in the study database using the REDCap webapplication within the context of quarterly reviews and ambulant dialysis control.

To ensure accurate registration of study outcomes by onsite investigators, efficacy and safety outcomes will additionally be monitored qualitatively based on administrative billing codes recorded in the Danish National Patient Register or the Danish National Register of Causes of Death. End of trial will be defined as 6 weeks following end of treatment. The working definition of ischemic stroke is based on pre-existing validation studies pertaining to the employment of administrative billing codes for identification of ischemic stroke in the Danish National Patient Register.[62, 63] Administrative billing codes pertaining to the defined efficacy and safety outcomes are presented below in **Table 1**.

**Table 1 Administrative billing codes pertaining to the defined primary efficacy and safety outcomes**

| | |
|---|---|
| **Primary efficacy outcome** | |
| Any transient ischemic attack, fatal and non-fatal ischaemic or unspecific stroke | ICD-10: DG45 or DI63-64 |
| **Primary safety outcome** | |
| Fatal or non-fatal major bleeding | ICD-10: DI60-62, DK250, DK252, DK254, DK256, DK260, DK262, DK264, DK266, DK270, DK272, DK274, DK276, DK280, DK282, DK284, DK286, DK290, DK298A, DK920-922, DJ942, DN02, DR319A, DG951A, DD500, DD62, DS368D, DS064-66, and/or DR04 |

Qualitative monitoring of registration of secondary and tertiary outcomes will also be performed based on administrative billing codes recorded in the Danish National Patient Register or the Danish National Register of Causes of Death. Administrative billing codes pertaining to secondary and tertiary outcomes are provided below in **Table 2** and **Table 3**.

**Table 2 Administrative billing codes pertaining to the defined secondary outcomes**

| **Secondary outcomes** | |
|---|---|
| Fatal or non-fatal ischemic or unspecified stroke | ICD-10: DI63-64 |
| Fatal or non-fatal ischemic stroke | ICD-10: DI63 |
| Fatal or non-fatal haemorhagic stroke | ICD-10: DI60-62 |
| Fatal or non-fatal ischemic or haemorhagic stroke | ICD-10: DI60-64 |
| All-cause mortality | Registration of death in the civil registration system |
| Combination of any non-fatal stroke and all-cause mortality | ICD-10: DI60-64 or registration of death in the civil registration system |
| Combination of any non-fatal stroke, any non-fatal major bleeding, and all-cause mortality | ICD-10: DI61-64 or registration of death in the civil registration system or ICD-10: DI60, DK250-253, DK260-263, DK270-273, DK290, DK920-922, DK298A, DN02, DR319A, DG0951A, DD62, and/or DR04 |

**Table 3 Administrative billing codes pertaining to the defined tertiary outcomes**

| **Tertiary outcomes** | |
|---|---|
| Discontinuation of allocated randomized therapy | Non-redemption of prescriptions in the The Danish Registry of Medicinal Product Statistics |
| Calciphylaxis / calcific uremic arteriolopathy | ICD-10: DL942B |
| Fatal or non-fatal acute myocardial infarction | ICD-10: DI21 |
| Hospitalization due to left-sided heart failure | ICD-10: DI50 |
| Peripheral artery disease | ICD-10: DI70 and DI739 |
| Thrombosis of arteriovenous fistula | ICD-10: DI744 or KPBU |
| Osteoporotic fractures including low enery fractures of the proximal femur, distal radius, humerus, pelvis, and vertebrae | ICD-10: DM80, DS72, DS32, DS422-4, DS525, and DS22 |

## Statistical analyses

Treatment with warfarin will be compared with no treatment for all outcomes. A principal analysis will be performed based on an intention-to-treat model comparing cumulative risk of ischemic stroke in patients with end-stage renal disease and incident atrial fibrillation allocated warfarin treatment and no treatment, respectively. Gray's test will be employed to compare the weighted averages of the subdistribution hazards across allocated treatments for the event of interest. The null hypothesis is that warfarin is associated with equivalent or increased risk of ischemic stroke compared with no treatment. The alternative hypothesis that warfarin is associated with benefit on risk of ischemic or hemorrhagic stroke compared with no treatment.

Secondary analyses will evaluate whether warfarin is associated with benefit on risk of ischemic stroke greater than a specified superiority margin $\delta \leq 0.68$. The superiority margin is based on the risk reduction observed in existing placebo-controlled warfarin trials in patients with preserved renal function.[64] The defined superiority margin preserves 50% of the benefits of oral anticoagulating treatment compared to control therapy based on the upper boundary of the 95% confidence interval in patients with preserved renal function. Although the risk of major bleeding is increased in end-stage renal disease, we also hypothesize that warfarin is not associated with an increased risk of major bleeding compared with no treatment greater than the safety margin $\delta = 1.23$ corresponding to a harm-to-benefit ratio of 2.

A number of tertiary analyses will be performed employing multiple Cox regression models stratified according to gender, age, sex, prior anticoagulation treatment, comorbidity including stratification on prior stroke (ischemic or unspecified, or hemorrhagic), prior bleeding, atrial fibrillation heritage (incident or prevalent), dialysis center, and dialysis modality. Furthermore, time-to-event analyses based on as-treated time-updated models using Cox proportional hazards model permitting assessment of for time-dependent assessment of treatment including time in therapeutic range, dialysis modality, and risk covariates, and intention-to-treat analyses with censoring of patients deviating from the allocated randomized treatment will also be performed. For all analyses, significance will be determined by a p-value ≤0.05. Determination of superiority will be based on the primary efficacy endpoint.

## Pilot study

In a retrospective pilot study, patients with end-stage renal disease and incident atrial fibrillation between 2002 and 2012 were identified; incidence of new-onset atrial fibrillation increased continuously from 4.0 (95% CI 3.8 - 4.2) per 100 person years to 7.8 (95% CI 6.8 – 9.0) per 100 person years from 2002 to 2012.[65] Based on a multiple cause-specific Cox regression model, standardized one-year risks of stroke and major bleeding were calculated using the g-formula for warfarin and acetylsalicylic acid.[66] Absolute one-year risk of stroke was 1.7 (95% CI 0.1 - 8.9) per 100, and 6.1 (95% CI 4.2 - 8.0) per 100 in patients treated with warfarin and no treatment, respectively, and absolute one-year risk of major bleeding was 9.2 (95% CI 0.1 - 20.8) per 100, and 8.1 (95% CI 6.0 - 10.0) per 100, respectively. Standardized absolute one-year risks of stroke and major bleeding are illustrated in **Figures 2a** and **2b**. Benefit-to-harm ratios comparing numbers needed-to-treat and –harm for stroke and major bleeding, respectively are illustrated in **Figure 3**.

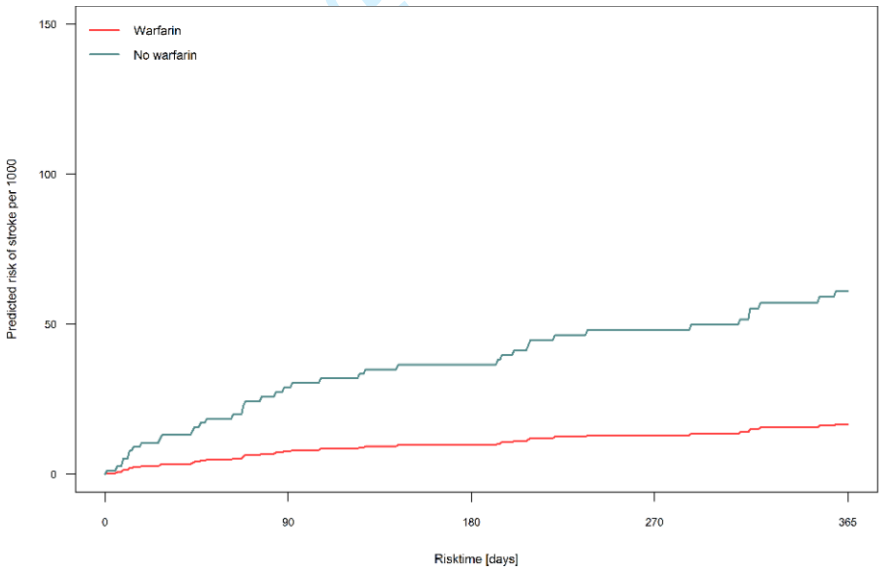


**Figure 2a One-year risk of stroke**

Predicted one-year risk of stroke in Danish patients with end-stage renal disease based on g-estimation modelled on cause-specific multiple cox regression

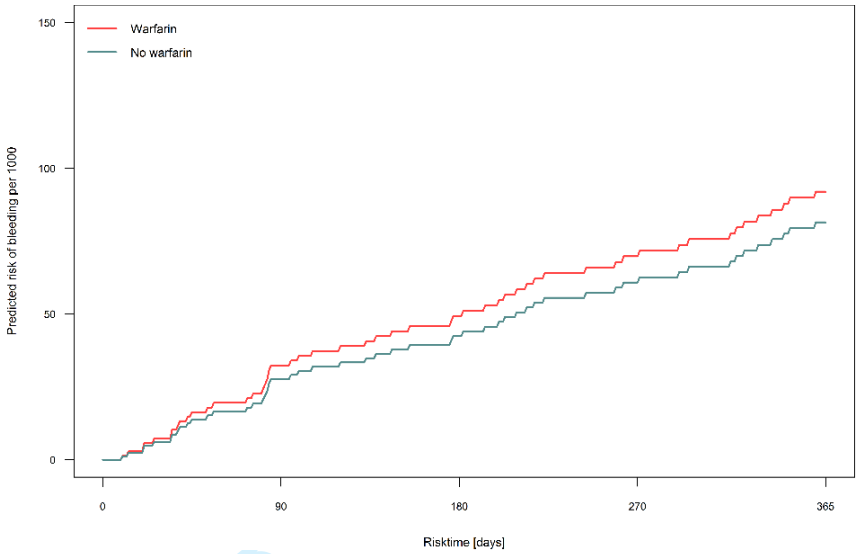


**Figure 2b One-year risk of major bleeding**

Predicted one-year risk of major bleeding in Danish patients with end-stage renal disease based on g-estimation of cause-specific multiple cox regression

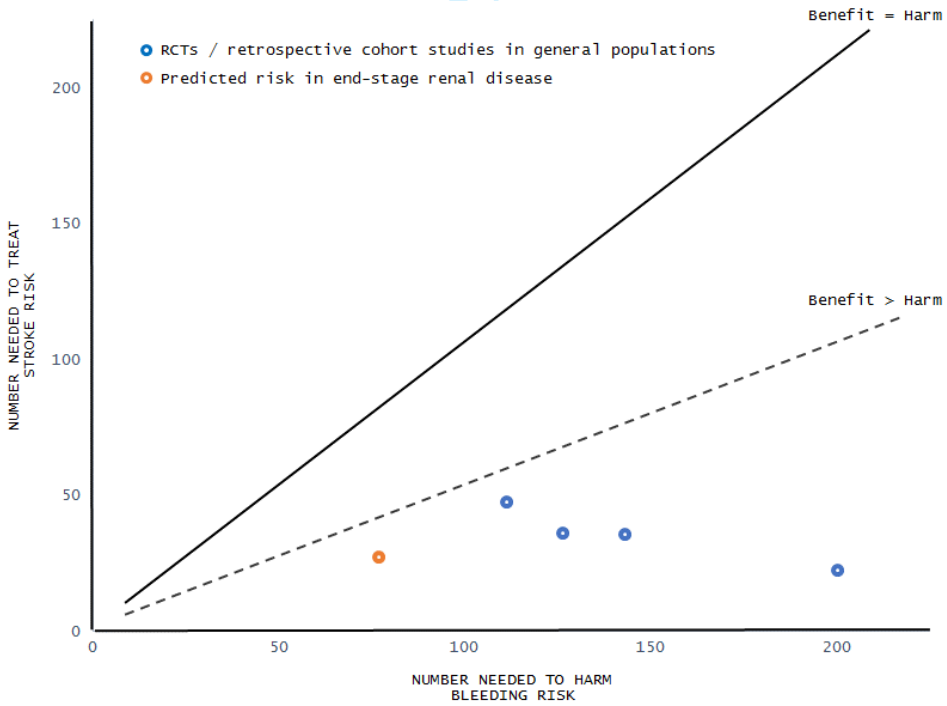


**Figure 3 Benefit-to-harm ratio**

Ratios of number needed-to-treat and -harm based on estimates of one year risk.[67-71] Non-dotted and dotted lines demarcate nondescript benefit-to-harm ratios of 1 and 2, respectively

### Sample size calculation

Sample size was determined based on an assumption of an absence of a period effect. In the pilot study, warfarin was associated with an absolute risk reduction of >4% with regards to the primary outcome of ischemic or hemorrhagic stroke, corresponding to a risk ratio of 0.27 i.e. within the specified superiority margin $\delta \leq 0.68$. Within this framework, a sample size of n=299 per group would be required to achieve a power of $1-\beta = 0.80$ for a two-sided t-test with $\alpha=0.05$.

Due to the employment of validated national registers, drop-out rates due to loss to follow-up are expected to be minimal; nonetheless, to compensate for ≤20% drop-out, 359 patients will be included in each group. A plot depicting sample size calculation is provided in **Figure 4**.

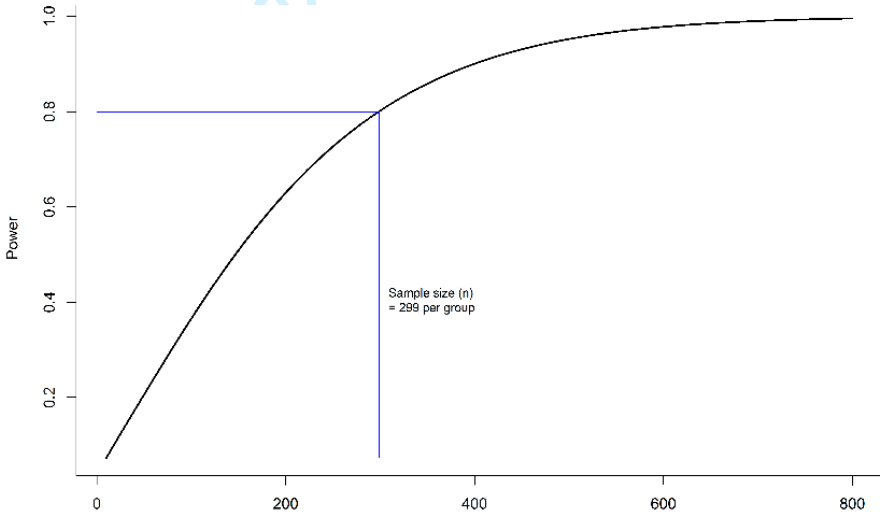


**Figure 4 Sample size calculation**

Based on predicted one-year absolute risk stroke, sample size i.e. the number of patients (n) in each group is depicted with corresponding power

## Ethics

### Data Safety Monitoring Committee

Prior to the initiation of the study, an independent Data Safety Monitoring Committee will be established. The Data Safety and Monitoring Committee will be formed with the aim of safeguarding the interests of enrolled patients,

assessing the safety and efficacy of the allocated treatment during the trial, and monitoring the overall conduct of the trial. The Data Safety Monitoring Board will consist of three members; one expert in the field (Peter Clausen MD PhD Consultant, Department of Nephrology, Rigshospitalet), one biostatistician (Theis Lange, Associate Professor, Section of Biostatistics, Department of Public Health, University of Copenhagen), and one investigator with knowledge of trial conduct and methodology otherwise uninvolved in the study (Lars Valeur Køber, MD Professor DMSc, Department of Cardiology, Rigshospitalet). The responsibilities of the Data Safety and Monitoring Committee will include; interim and cumulative evaluation of study-related adverse events, interim and cumulative evaluation of treatment efficacy, evaluation and confirmation of data quality, completeness and timeliness, and evaluation of participant adherence to the study protocol.

## Premature trial termination

The Data Safety Monitoring Committee will at minimum review the safety endpoints every six months. The Data and Safety Monitoring Committee will have exclusive unblinded access to all data, and may recommend discontinuation of the study to the Trial Steering Committee based on reviews of safety events; however, no formalized interim analyses are preplanned. Throughout inclusion, interim analyses will be supplied in strict confidence for overview to the Data Safety Monitoring Committee. If results from the interim analyses provide sufficient evidence as to harm or benefit of the allocated treatments, the Data Safety Monitoring Committee will advise the Trial Steering Committee, thus enabling possible trial modifications or trial discontinuation. Premature trial termination will be communicated to study participants by on-site study investigators

## Safety Management

The Data Safety Monitoring Committee will adhere to the Data Safety Monitoring Committee Charter. Harm will be adjudged based on the predefined safety endpoints pertaining to fatal or non-fatal major bleeding. Safety monitoring will be accomplished by tracing of serious adverse events and reactions (SAEs and SARs), safety and efficacy endpoints and mortality in the continuously updated database registering adverse endpoints and outcomes recorded by on-site investigators via the REDCap webapplication in a central databank independent of data extraction from administrative health care registers. SAEs and SARs will be defined in accordance with the Danish Medicines Agency

guideline as any serious event or reaction resulting in death, a life-threatening event, hospitalization or prolongation of a hospital stay, significant or lasting disability or work incapacity, or congenital anomalies or malformations. Retrospective registration of endpoints in the webapplication REDCap will at minimum be performed within the context of the monthly reviews. SAEs will be assessed for causality by the study investigators and reported to the study sponsor for further assessment of causality and expectedness within 24 hours when a SAR is suspected or when the SAE is not pre-specified in the following list of a priori anticipated SAEs. Registration of the anticipated list of SAEs will nonetheless at minimum require registration in the REDCap webapplication within the context of the scheduled monthly reviews.

<u>Anticipated SAEs exempt from requirement of reporting within 24 hours for assessment of causality</u>

- Any transient ischemic attack, or ischaemic or unspecific stroke
- Any myocardial infarction
- Any hospitalization due to left-sided heart failure
- Any diagnosis of peripheral artery disease
- Any hospitalization due to complications of arteriovenous fistula
- Any osteoporotic fractures
- Any hospitalization due to infection
- Any hospitalization due to dialysis catheter dysfunction
- Any hospitalization due to electrolyte imbalance
- Any hospitalization due to overhydration
- Any hospitalization due to hypotension
- Any hospitalization due to hypertension
- Any hospitalization due to diabetes including ketoacidosis
- Any hospitalization due to heart arrhythmia
- Any hospitalization due to muscle- or joint pains

Treatment with warfarin will be implemented in accordance with common practice and the summary of product characteristics. Adverse effects of warfarin are well-known, the drug has been on approved for medical use since the 1950's, and is on the World Health Organization list of essential medications. Adjudication of adverse events and reactions will be based on the chapter 4.8 in the product resume for Warfarin. In addition to the continuous monitoring of safety by the Data Safety Monitoring Committee, SAEs, SARs, safety and efficacy endpoints, and mortalities will be reported as summary results to the Danish Medicines agency annually throughout the duration of the study for assessment of safety. The Data Safety Monitoring Committee will evaluate safety based on SAEs, SARs, defined safety and efficacy endpoints including all-cause mortality.

**Suspected Unexpected Serious Adverse Reactions**

All clinicians engaging with patients included in the trial will be required to report any serious and/or unexpected adverse events / reactions (SUSARs) potentially related to allocated treatment to the study investigators. The product resume for Warfarin will be employed as a reference document for assessment of the expected / unexpected nature of serious adverse events. In accordance with the legal requirements pertaining to SUSARs, all relevant information related to the life-threatening or lethal SUSARS will be reported to the Danish Medicines Agency by the study sponsor within 7 days of notification, and recorded in the dedicated safety databank. All non-life-threatening or non-lethal SUSARS will be reported to the Danish Medicines Agency by the study sponsor within 15 days. The product resume for Warfarin will be used as the reference document for evaluation and adjudication of adverse events and reactions including SUSARs. All SUSARs will be reported using the Danish Medicines Agency's e-form.

No pre-specified directives governing the management of treatment-specific side effects have been determined for the trial. As such, on-site physicians may discontinue the allocated treatment if major bleeding is observed or otherwise indicated.

## Study implementation

The proposed randomized clinical trial will be implemented in a nationwide collaboration between the Trial Steering Committee, Trial Management Committee, site-specific lead investigators, a data manager, and dialysis centers (including satellite units). The Trial Steering Committee represents an established research environment, and

previous collaborations have yielded a number of internationally acclaimed epidemiological and clinical research projects. An overview of the Trial Steering Committee is provided in Supplementary Table S4. An existing collaboration with Statistics Denmark permits access to all necessary registers, and databases with relevant data from the national registers will be made available. Furthermore, a formalized partnership with the Biostatistics Department at Copenhagen University already exists. The study nucleus is wholly responsible for initiation of the proposed randomized clinical trial; no commercial sponsors are involved or planned for involvement in the study. Funding for wages to the principal investigator has been provided by The Danish Heart Foundation.

Study results are to be published in international peer-reviewed medical journals regardless of outcome, and study conclusions are to be publicised in press releases to national media.

The study is proposed to initiate September 1st 2019 and end one year after ultimate randomization.

## Initiation and maintenance of warfarin treatment

Introduction of warfarin treatment in patients with chronic kidney disease has been observed to be associated with marked increase in risk of adverse hemorrhagic events < 90 days;[33, 52, 72] plausibly due to initial overdosing.[51] Additionally, a 2016 Cochrane review comparing initial warfarin dose of 10mg versus 5mg observed no benefit in patients initiating with more aggressive dosing.[73] Existing guidelines advocate an initial dosing strategy of 5-10mg of warfarin daily in patients with renal competency. Of note, the British Committee for Standards in Hematology guideline pertaining to oral anticoagulation with warfarin specifically notes the possible appropriateness of a reduction in initial dose of warfarin < 5mg daily in elderly patients.[46] Similarly, the Danish Health Authority guideline governing anticoagulation with warfarin advocates dose reduction of 25-50% in patients > 80 years,[47] and the Danish Cardiology Society guideline also recommends tapering of dosing in elderly / frail patients.[48]

All patients allocated to oral anticoagulation will initiate treatment with warfarin in accordance with the existing Danish Health Authority guideline (Supplemental Figure S1). Monitoring and dosing will be performed by onsite investigators in accordance with common clinical practice. Patients allocated to oral anticoagulation will be required discontinuation of antiplatelet drugs (i.e. aspirin or Adenosine diphosphate receptor inhibitors) unless specifically contraindicated.

Treatment with warfarin is non-expensive (<5 Danish kroner per day), and warfarin will be prescribed in accordance with common practice and the summary of product characteristics. Importantly, noncompliance and –adherence remains substantial in patients with end-stage renal disease on dialysis; an estimated ½ to ⅓ of patients are noncompliant with regard to treatment.[74] Objectives predominating management of patients with end-stage renal disease include management of common complications including hypertension, hyperphosphatemia, and anemia while mitigating risks associated with prevalent comorbidities i.e. diabetes and coronary heart disease. Therapeutic goals are however unreachable without imparting a substantial pharmaceutical burden. Patients with end-stage renal disease remain amongst the group of patients with greatest daily pill burden. Reportedly, end-stage renal disease patients are prescribed ~20 medications, with a quarter of patients taking >25 pills daily.[75] Unsurprisingly, the significant pill burden is known to be closely associated with issues related to adherence and compliance.

The issue is particularly pertinent with regard to warfarin as bleeding risk is particularly pronounced in patients in the early phase of anticoagulant therapy, and unsurprisingly in patients with poor anticoagulation control.[55, 76] As such, risk of bleeding in patients with end-stage renal disease taking warfarin could quite plausibly be correlated with non-adherence and shifting compliance. Consequently, the study will investigate adherence and compliance as independent endpoints.

Warfarin will be provided free of charge to patients randomized to treatment in the study. Study medicine will be prepared and packaged by the hospital pharmacy in accordance with the rules governing Good Manufacturing Practices Annex 13 with appropriate labeling detailing the study identification number, the name of the study investigator, and the notification 'For clinical trial'. A labelling example is provided in the appendices (Supplementary Figure S2). In the event of death or discontinuation of anticoagulation treatment discontinuation, disposal of study medication will be completed without requirement of specific documentation by study investigators in accordance with common practice for prescription medication in general.

Study investigators will register treatment adherence / compliance and latest international normalized ratios at monthly intervals and scheduled quarterly safety reviews.

## Research ethics approval

The trial is a multicenter parallel-group open randomized controlled trial which is conducted according to the Declaration of Helsinki. The protocol and the template informed consent forms, participant information and recruitment materials, and other documents – and any subsequent modifications – contained in the appendix have been approved by the Regional Committee on Health Research Ethics (Journal no.:H-18050839) and the Danish Medicines Agency (Case no. 2018101877) with respect to scientific content and compliance with applicable research regulations. The protocol has been registered with the European Clinical Trials database (EudraCT number 2018-000484-86), Clinical Trials Information System (CTIS ID 2022-502500-75-00) and clinicaltrials.gov (ID NCT03862859). No patients will be included until all relevant authorizations have been attained. The investigators have no conflicts of interest to report.

## Funding

The trial is an investigator-initiated study. The study is however supported by a research grant of 990.000 DDK from the Danish Heart Foundation covering preliminary database and project development. The research grant is administered by the research department at the Danish Heart Foundation. All participating investigators are independent of financial interest in the study results.

## Modifications to the protocol

Any modification of the protocol with potential impact on the conduct of the study, patient benefit or harm, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by Trial Steering Committee, and be submitted for approval by the Regional Committee on Health Research Ethics prior to implementation in accordance with existing regulations. Administrative changes of the protocol defined as minor corrections and/or clarifications that have no effect on the way the conduct of the study will be agreed upon by the Trial Steering Committee, and will be documented in a memorandum. The Regional Committee on Health Research Ethics may be notified of administrative changes at the discretion of Trial Steering Committee.

## Recruitment and informed consent

Recruitment will adhere to all relevant provisions of the Research Ethics Committee pertaining to informed consent. Patients will be recruited by on-site physicians under guidance by the lead investigator at each distinct dialysis centre. Recruiting physicians will inform potential participants of their entitlement to guidance and council by a patient assessor prior to being informed on the study, and aid in securing council for the informed consent if so indicated. Recruiting physicians will introduce the trial to patients and provide information sheets, thus enabling an informed discussion of potential benefits and harms. Participants will be informed on the globally strict data confidentiality pertaining to personal data in Denmark, and on the employment of register-based follow-up by authorized persons in the study. Recruiting physicians will obtain oral and written consent from patients willing to participate in the trial. Recruitment and informed consent will be attained with consideration for disturbances and patient deliberation. Appropriate emphasis will be placed on the non-compulsory nature of study participation, with particular emphasis placed on the non-consequential significance of non-participation on treatments beyond the trial.

Recruitment of patients to the study entails screening and randomization. At screening, patients will be approached by on-site physicians upon verification of atrial fibrillation or flutter by electrocardiogram, typically while receiving ambulatory dialysis treatment. Patients will initially receive a short oral presentation of the study by the on-site physician as previously described. Following the oral presentation, patients will receive written information pertaining to the study with allowance for a minimum of one hour delay to permit comprehension. Patients may opt for additional time. Following the delay, the patient will be approached by study personnel who will provide oral information and answers to trial-related questions. As part of the screening procedure, the on-site physician will secure relevant laboratory testing to ensure against inclusion of patients meeting exclusion criteria as defined in the study schedule of appointments. All such study-related procedures will however not be performed until signing of the written informed consent.

Randomization will be performed upon signing of the written informed consent. The written informed consent must be signed <7 days of being approached for trial inclusion. Patients may waive their right to delay between screening and randomization.

Oral and written presentation of the trial will be effectuated within the context of quiet and undisturbed surroundings. Patients will be informed of their right to outside council during presentation of the trial. Furthermore, patients will be informed of their entitlement to delay between oral and written presentation and authorizing of the written informed consent. All patients will be unambiguously informed as to the non-binding nature of the informed consent; specifically, patients will be informed as to the non-restricted right to 'voluntary withdrawal of consent' i.e. the non-restricted right of patients to withdraw from the study at any time and for any reason, or no reason at all without risk of retribution. Of note, female patients with childbearing potential will be informed of the requirement of the use of highly effective prevention 6 weeks beyond the end of the trial. On-site investigators will register baseline data and perform review of study patients medication at the time of randomization.

## Ethical considerations

The trial will be conducted in adherence to the Helsinki Declaration and to the standards of Good Clinical Practice.[77, 78] Currently, there is no conclusive evidence from randomized clinical trials on the potential benefit or harm of warfarin in dialysis-treated patients with end-stage renal disease and atrial fibrillation. Warfarin is widely but non-systematically used for stroke risk reduction in dialysis-treated patients with end-stage renal disease and atrial fibrillation, and the indications employed for inclusion in the present trial are consistent with observed clinical practice and the summary of product characteristics as defined by the Danish Medicines Agency. As such, trial participants will not be exposed to unknown risk. Warfarin is associated with both specific benefit and harm; benefit in terms of substantial stroke risk reduction, and harm in terms of increase risk of bleeding and possibly accelerated arteriosclerosis. The research question is however undeniably in the interest of the general public – specifically the patients planned for inclusion in the study -, and the trial design will provide meaningful data with potential for statistical significance leading to an acceptance or rejection of the null hypothesis with direct clinical implications.

## Data confidentiality

All study-related information will be stored securely at the study site. Administrative forms will be stored in locked file cabinets in areas with limited access. All data recorded will be secured in a central database using the REDCap webapplication. Data management will be administered via the Danish in accordance with governing rules and regulations. Participant information will not be released outside of the study. The Trial Steering Committee will be given access to distilled de-identified data sets within the framework of Statistics Denmark.

## Data sharing statement

No later than 3 years after the collection of the one-year post-randomization results, a completely de-identified dataset will be delivered to an appropriate data archive for sharing purposes.

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# Appendix

**Supplementary table S1 Overview of the CHA2DS2-VASc and HAS-BLED algorithms**

| **CHA2DS2-VASc risk factors** | **Score** |
|---|---|
| C: Congestive heart failure / Left ventricular dysfunction | 1 |
| H: Hypertension | 1 |
| A: Age ≥75 years | 2 |
| D: Diabetes | 1 |
| S: Prior stroke, transiet ischemic attack, and/or systemic embolism | 2 |
| V: Prior myocardial infarction or peripheral vascular disease | 1 |
| A: Age 65-74 years | 1 |
| Sc: Gender female | 1 |
| **HAS-BLED risk factors** | |
| H: Hypertension | 1 |
| A: Abnormal renal or liver function | 1 or 2 |
| S: Prior stroke | 1 |
| B: Prior major bleeding | 1 |
| L: Labile INR (Time in therapeutic interval < 60%) | 1 |
| E: Elderly (age > 65 years) | 1 |
| D: Drug or alcohol abuse | 1 or 2 |

**Supplementary table S2 Dialysis centers (including satellite units) in Denmark**

| | Dialysis Center (with satellite units) |
|---|---|
| 1. | Aalborg University Hospital (including satellite unit at Vendsyssel and Thy-Mors Hospitals) |
| 2. | Aarhus University Hospital (including satellite unit at Horsens and Randers Hospital) |
| 3- | Herlev Hospital (including satellite unit at Hvidovre Hospital) |
| 4. | Holbæk Hospital (including satellite unit at Slagelse Hospital) |
| 5. | Holstebro Regional Hospital |
| 6. | Hospital Lillebaelt |
| 7. | Hospital of Bornholm |
| 8. | Hospital of Southern Jutland |
| 9.. | Hospital South West Jutland |
| 10. | North Zealand Hospital |
| 11. | Odense University Hospital (including satellite unit at Svendborg Hospital) |
| 12. | Rigshospitalet (including satellite unit at Frederiksberg Hospital) |
| 13. | Viborg Regional Hospital |
| 14. | Zealand University Hospital Roskilde (including satellite unit at Nykøbing-Falster Hospital) |

**Supplementary table S3 Trial Steering Committee**

- Nicholas Carlson MD PhD, Staff specialist at the Department of Nephrology, Copenhagen University Hospital Rigshospitalet
- Professor Gunnar Gislason, MD PhD FESC FACC FAHA, Chief Physician at the Department of Cardiology, Copenhagen University Hospital Gentofte & Director of Research, The Danish Heart Foundation
- Professor Christian Torp-Pedersen, MD DMSc FACC FESC, Chief Physician at the Department of Cardiology, North Zealand Hospital, Hillerød
- Anne-Lise Kamper. MD DMSc, Chief Physician at the Department of Nephrology, Copenhagen University Hospital Rigshospitalet
- Jonas Bjerring Olesen, MD PhD, Staff specialist at the Department of Cardiology, Copenhagen University Hospital Gentofte
- Associate professor Casper Bang, MD PhD. Chief Physician at the Department of Cardiology, Frederiksberg and Bispebjerg Hospital, Copenhagen
- Professor Thomas Alexander Gerds, the Danish Heart Foundation, Vognmagergade 7, 3. 1120 Copenhagen, Denmark, and Section of Biostatistics, University of Copenhagen
- Ditte Hansen, MD PhD, Chief Physician at the Department of Nephrology, Copenhagen University Hospital Herlev
- Professor, Morten Schou, MD PhD, Chief Physician at the Department of Cardiology, Copenhagen University Hospital Herlev
- Professor Mads Hornum, MD PhD, Chief Physician at the Department of Nephrology, Copenhagen University Hospital Rigshospitalet
- Associate professor Erik Grove, MD PhD, Chief Physician at the Department of Cardiology, Aarhus University Hospital
- Associate professor Jens Dam Jensen, MD PhD, Chief Physician at the Department of Nephrology, Aarhus University Hospital

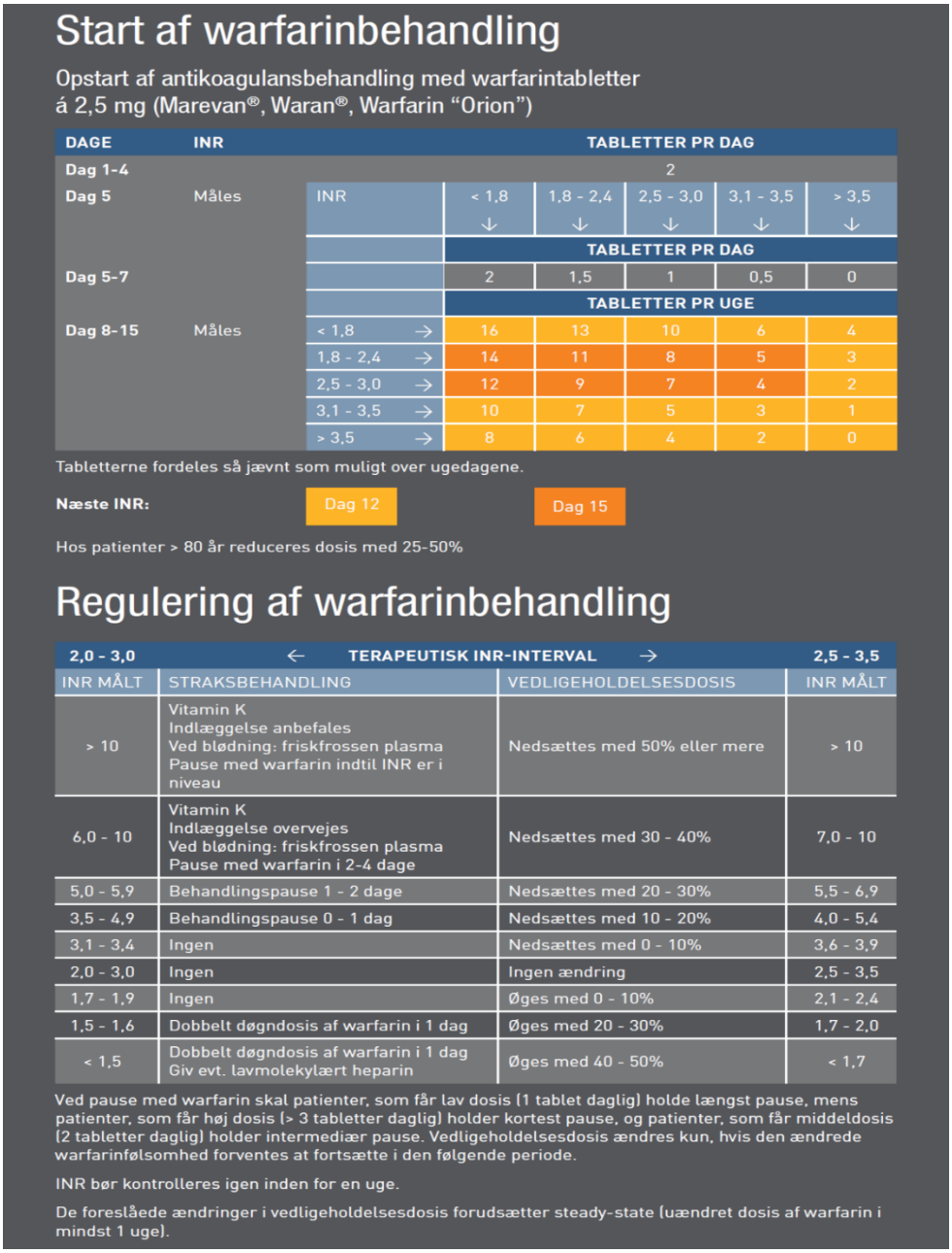
- Ellen Linnea Freese Ballegaard, MD, PhD-student at the Department of Nephrology, Copenhagen University Hospital Rigshospitalet

**Supplementary table S4 Study schedule of appointments**

| | **Screening** | **Randomization** | **Montly review** 1 month intervals (+/- 1 weeks) | **Quarterly review** 3 month intervals (+/- 1 weeks) | **Annual review** (+/- 1 month) | **End of Treatment** | **Termination of followup** End of treatment +6 weeks |
|---|---|---|---|---|---|---|---|
| Study presentation | • | | | | | | |
| ECG / Holter / Event recorder | • | | | | | | |
| Baseline blood tests[1] | • | | | | | | |
| Pregnancy test[2] | • | | • | | | | |
| Informed consent | • | | | | | | |
| Registration of baseline data | | • | | | | | |
| Medication review | | • | | | | • | |
| International normalized ratio[3] | | | • | • | • | • | |
| Patient-reported adherence[4] | | | | • | • | • | |
| Discontinuation cause | | | | | | (•) | |
| Efficacy outcomes[5] | | | • | • | • | • | • |
| Safety outcomes[5] | | | • | • | • | • | • |
| SAEs / SARs[5] | | | • | • | • | • | • |

1. Plasma-hemoglobin, platelet count, albumin, phosphate, ionized-calcium, parathyroid hormone, c-reactive protein, urea nitrogen, and creatinine.
2. Required in all women of childbearing potential at inclusion and monthly througout the trial. Women of non-childbearing potential are defined as having no uterus, ligation of the fallopian tubes, permanent cessation of ovarian function due to ovarian failure or surgical removal of the ovaries, or infertility due to natural causes i.e. amenorrhia >12 months or an FSH >40 IU/L
3. Last recorded international normalized ratio
4. Patient-reported adherence: As defined by informed non-adherence > 1 week.
5. Safety and efficacy outcomes, SAEs/SARs will be recorded continously with reporting of SAEs/SARs to the study sponsor within 24 hours of identification for assesment. Restrospective registration of endpoints in the webapplication REDCap will at minimum be performed within the context of the quarterly reviews.

**Supplementary Figure S1 Guideline pertaining to warfarin treatment from the Danish Health Authority**



## Start af warfarinbehandling

Opstart af antikoagulansbehandling med warfarintabletter
á 2,5 mg (Marevan®, Waran®, Warfarin "Orion")

| DAGE | INR | | TABLETTER PR DAG | | | | |
|---|---|---|---|---|---|---|---|
| Dag 1-4 | | | 2 | | | | |
| Dag 5 | Måles | INR | < 1,8 ↓ | 1,8 - 2,4 ↓ | 2,5 - 3,0 ↓ | 3,1 - 3,5 ↓ | > 3,5 ↓ |
| | | | TABLETTER PR DAG | | | | |
| Dag 5-7 | | | 2 | 1,5 | 1 | 0,5 | 0 |
| | | | TABLETTER PR UGE | | | | |
| Dag 8-15 | Måles | < 1,8 → | 16 | 13 | 10 | 6 | 4 |
| | | 1,8 - 2,4 → | 14 | 11 | 8 | 5 | 3 |
| | | 2,5 - 3,0 → | 12 | 9 | 7 | 4 | 2 |
| | | 3,1 - 3,5 → | 10 | 7 | 5 | 3 | 1 |
| | | > 3,5 → | 8 | 6 | 4 | 2 | 0 |

Tabletterne fordeles så jævnt som muligt over ugedagene.

**Næste INR:** Dag 12 Dag 15

Hos patienter > 80 år reduceres dosis med 25-50%

## Regulering af warfarinbehandling

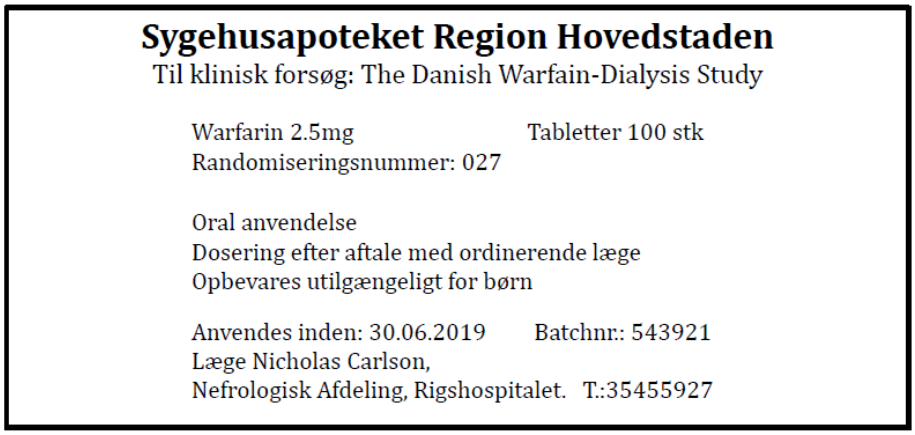
| 2,0 - 3,0 | ← TERAPEUTISK INR-INTERVAL → | | 2,5 - 3,5 |
|---|---|---|---|
| INR MÅLT | STRAKSBEHANDLING | VEDLIGEHOLDELSESDOSIS | INR MÅLT |
| > 10 | Vitamin K<br>Indlæggelse anbefales<br>Ved blødning: friskfrossen plasma<br>Pause med warfarin indtil INR er i niveau | Nedsættes med 50% eller mere | > 10 |
| 6,0 - 10 | Vitamin K<br>Indlæggelse overvejes<br>Ved blødning: friskfrossen plasma<br>Pause med warfarin i 2-4 dage | Nedsættes med 30 - 40% | 7,0 - 10 |
| 5,0 - 5,9 | Behandlingspause 1 - 2 dage | Nedsættes med 20 - 30% | 5,5 - 6,9 |
| 3,5 - 4,9 | Behandlingspause 0 - 1 dag | Nedsættes med 10 - 20% | 4,0 - 5,4 |
| 3,1 - 3,4 | Ingen | Nedsættes med 0 - 10% | 3,6 - 3,9 |
| 2,0 - 3,0 | Ingen | Ingen ændring | 2,5 - 3,5 |
| 1,7 - 1,9 | Ingen | Øges med 0 - 10% | 2,1 - 2,4 |
| 1,5 - 1,6 | Dobbelt døgndosis af warfarin i 1 dag | Øges med 20 - 30% | 1,7 - 2,0 |
| < 1,5 | Dobbelt døgndosis af warfarin i 1 dag<br>Giv evt. lavmolekylært heparin | Øges med 40 - 50% | < 1,7 |

Ved pause med warfarin skal patienter, som får lav dosis (1 tablet daglig) holde længst pause, mens patienter, som får høj dosis (> 3 tabletter daglig) holder kortest pause, og patienter, som får middeldosis (2 tabletter daglig) holder intermediær pause. Vedligeholdelsesdosis ændres kun, hvis den ændrede warfarinfølsomhed forventes at fortsætte i den følgende periode.

INR bør kontrolleres igen inden for en uge.

De foreslåede ændringer i vedligeholdelsesdosis forudsætter steady-state (uændret dosis af warfarin i mindst 1 uge).

**Supplementary Figure S2 Labelling example for study medicine**



# D A N - W A R - D

# Danish Warfarin-Dialysis Study

**Blodfortyndende behandling til forebyggelse af slagtilfælde hos patienter med dialysekrævende kronisk nyresvigt og forkammerflimren:**

**Et nationalt lodtrækningsforsøg**

# Information til patienter om deltagelse i et forskningsprojekt

**(indeholder samtykke erklæring)**

## Forespørgsel om deltagelse

Hermed ønsker vi at spørge, om du vil deltage i et videnskabeligt forsøg vedrørende blodfortyndende behandling. Forsøget udgår fra Nefrologisk afdeling på Rigshospitalet og er etableret i et samarbejde med Hjerteforeningen. Førend du beslutter dig, om du vil deltage i forsøget, er det nødvendigt, at du fuldt ud forstår forsøgets formål og begrundelse. Vi vil derfor bede dig læse følgende deltagerinformation grundigt, hvorefter du vil blive inviteret til en samtale om forsøget, hvori denne deltagerinformation vil blive uddybet, og du vil få mulighed til at stille spørgsmål til forsøget. Du er i forbindelse med denne samtale velkommen til at tage et familiemedlem, en ven eller en bekendt med. Såfremt du beslutter dig for at deltage i forsøget, vil vi bede dig underskrive en samtykkeerklæring. Vær opmærksom på, at du har ret til betænkningstid, før du beslutter, om du vil underskrive samtykkeerklæringen. Det er helt frivilligt at deltage i forsøget, og du kan når som helst og uden yderligere begrundelse trække dit samtykke tilbage, uden at det vil få konsekvenser for din videre behandling i øvrigt.

## Indledning

Forkammerflimren er en hyppigt forekommende hjerterytmeforstyrrelse. Ubehandlet indebærer tilstanden en øget risiko for slagtilfælde og død. Patienter med kronisk nyresvigt er særligt disponerede for forkammerflimren og er ydermere i særlig risiko for slagtilfælde som følge af forkammerflimren. Forebyggende behandling med blodfortyndende medicin som f.eks. Warfarin anbefales utvetydigt til patienter med bevaret nyrefunktion, idet behandling mere end halverer risikoen for et slagtilfælde. Blodfortyndende behandling forebygger slagtilfælde og blodpropsdannelse ved at hæmme blodets størkningsevne. Patienter med kronisk nyresvigt i dialyse er dog i udgangspunktet særligt disponerede for blødningskomplikationer, hvorfor behandlingen ikke benyttes systematisk hos patienter med kronisk nyresvigt i dialyse og forkammerflimren i Danmark.

## Formål og metode

Undersøgelsens hovedformål er at undersøge betydningen af forebyggende behandling med den blodfortyndende medicin Warfarin på risikoen for slagtilfælde og død hos patienter med kronisk nyresvigt i dialyse og forkammerflimren. Undersøgelsen gennemføres som et nationalt lodtrækningsforsøg med deltagerrekruttering fra alle danske dialyseafdelinger. Deltagende patienter tildeles ved lodtrækning enten behandling med den blodfortyndende medicin Warfarin eller ingen behandling. Warfarin doseres i tabletform. Behandlingen varetages i henhold til gældende behandlingsvejledninger af hospitalslæger på de respektive dialyseafdelinger. Behandling doseres på baggrund af en blodprøve, der tages i forbindelse med dialysebehandlingen, og indebærer forventeligt indtag af 5-10 tabletter ugentligt i hele forsøgets forløb. Behandlingens effekt følges indtil studiets afslutning gennem indberetninger fra deltagende afdelinger. Ved undersøgelsens afslutning sammenlignes forekomsten af slagtilfælde, blødninger og dødsfald mellem deltagere behandlet med den blodfortyndende medicin Warfarin og deltagere, der ikke har modtaget behandling. Forsøget tilsigter at kunne rekruttere omtrent 700 patienter mellem 2019 og 2025.

## Undersøgelsens nytte

Den forebyggende virkning af blodfortyndende behandling med Warfarin er fortsat usikker hos patienter med dialysekrævende nyresvigt og forkammerflimren. Undersøgelsen vil være medvirkende til entydigt at afklare, hvorvidt behandling med den blodfortyndende medicin Warfarin bør tilbydes patienter med dialysekrævende

nyresvigt og forkammerflimren. Behandlingen kan potentielt medvirke til at reducere antallet af slagtilfælde og dødsfald.

Deltagelse i forsøget vil for den enkelte forsøgsdeltager medføre mere deltaljeret kontrol af dialysebehandlingen, herunder blødningstallene. Herved tilsigtes en mindskelse af risikoen for blødningskomplikationer. Det er ikke sikkert, at den enkelte forsøgsdeltager selv vil få direkte gavn af undersøgelsen, men resultaterne fra undersøgelsen vil medvirke til at hjælpe andre patienter i fremtiden.

Overordnet forventes forsøgets resultater at få afgørende betydning for behandlingen af patienter med dialysekrævende nyresvigt og forkammerflimren i fremtiden, og såfremt forsøgets resultater kan dokumentere en behandlingsgevinst, vil forsøget på direkte vis kunne medvirke til at reducere antallet af slagtilfælde og dødfald hos patienter med dialysekrævende nyresvigt. Undersøgelsens endelige svar vil først være tilgængelige, når resultaterne er gjort op. Informationer om resultaterne forventes tilgængelige 1 år efter, sidste patient er inkluderet i forsøget.

## Bivirkninger, risici og ulemper

Den blodfortyndende medicin, Warfarin, er godkendt af Sundhedsstyrelsen til forebyggelse af slagtilfælde og blodpropsdannelse hos patienter med forkammerflimren hos alle patienter uanset nyrefunktion, og behandlingen anvendes allerede i begrænset omfang blandt patienter med dialysekrævende nyresvigt. Behandling med den blodfortyndende medicin, Warfarin, er forbundet med visse ulemper. Lægemidlet vil blive udskrevet i henhold til gældende behandlingsvejledninger. Deltagelse i studiet vil dog ikke indebære økonomisk ulempe, idet den blodfortyndende behandling, Warfarin, vil blive udleveret gratis til deltagende patienter. Dosisjustering af Warfarin foretages løbende på baggrund af en blodprøve. Deltagelse vil derfor fordre hyppigere blodprøvekontrol. Blodprøvekontrol og dosisjustering vil dog for størstedelen af deltagende patienter kunne gennemføres i forbindelse med den vanlige dialysebehandling, hvorved ulempen minimeres.

Behandling med den blodfortyndende medicin, Warfarin, er forbundet med en række beskrevne bivirkninger og risici, herunder øget blødningstendens og overfølsomhedsreaktioner. Særligt fokus vil tillægges blødningskomplikationer. Sjældne bivirkninger indbefatter hudirritation med vævstab, karbetændelse, hårtab og blødninger fra mave-tarm-kanalen.

## Graviditet og svangerskabsforebyggelse

Er du gravid kan du ikke deltage i denne undersøgelse. Deltagelse i undersøgelsen forudsætter, at kvinder i den fødedygtige alder anvender et effektivt svangerskabsforebyggende middel såsom p-piller eller spiral indtil 6 uger efter undersøgelsens afslutning. Forsøgsdeltagere i den fødedygtige alder vil i tillæg blive graviditetstestet før inklusion i undersøgelsen, samt en gang hver måned så længe undersøgelsen varer.

## Hvis undersøgelsen indstilles før planlagt

Lægen kan lade dig udgå af undersøgelsen såfremt det skønnes, at det er til dit eget bedste. Dette gælder også på trods af, om det skulle være mod din vilje. Endvidere har forskningsgruppen og/eller myndighederne bemyndigelse til at afslutte undersøgelsen før det planlagte tidspunkt under forudsætning af, at du bliver informeret om årsagen herfor.

## Hvis du ikke ønsker at deltage i undersøgelsen

Deltagelse i studiet er fuldstændigt frivilligt, og du kan på ethvert tidspunkt vælge at træde ud af forsøget, uden at det vil influere på dit forhold til afdelingen. Ønsker du ikke at deltage i undersøgelsen, vil du tilbydes det sædvanlige behandlingstilbud i henhold til afdelingens almindelige retningslinjer.

## Anvendelse af persondata i undersøgelsen

Hvis du medvirker i undersøgelsen, vil din læge sende informationer om dig og dit helbred og om forløbet af din sygdom til en central database hos Rigshospitalets Nefrologiske afdeling. Informationerne vil her blive opbevaret og analyseret. Alle informationer vil blive opbevaret sikkert og behandlet strengt fortroligt.

Under forsøget kan hospitalslæger og undersøgelsens hovedansvarlige læge (eller dennes repræsentant) få adgang til din sundhedsjournal med henblik på at indhente nødvendige oplysninger om dit helbred og behandling til brug i analyser af forsøget resultater. Bemyndigede personer fra sundhedsmyndigheder og lægemiddelstyrelse kan endvidere også tilgå din sundhedsjournal for at kontrollere, om forsøget bliver udført retvist.

I tillæg vil der ved samtykke til deltagelse i studiet indhentes specifikke informationer vedrørende tidligere og pågående dialysebehandling, receptpligtig medicin, laboratoriesvar og sygehistorik. Alle oplysninger bliver

registreret og anvendt i en videnskabelig opgørelse. Dine personlige data vil blive behandlet strengt fortroligt, og ingen oplysninger, som kan henføres til dig personligt, vil blive udleveret til personer uden for den videnskabelige undersøgelsesgruppe. Alt personale involveret i forsøget har tavshedspligt. Hvis du vælger at trække dit informerede samtykke tilbage, vil ingen nye data blive indsamlet og registreret. Imidlertid tillader lovgivningen, at data indsamlet, inden du trækker dit samtykke tilbage, stadig indgår i forsøgets datamateriale. Oplysningerne vil blive registreret og opbevaret i 15 år efter forsøgets afslutning, og de vil blive anvendt i en videnskabelig opgørelse.

## Økonomi

Undersøgelsen udgår fra Nefrologisk Klinik på Rigshospitalet og gennemføres i samarbejde med deltagende dialyseafdelinger. Projektet er støttet af Hjerteforeningens forskningsfond. Udgifter forbundet med rekruttering og behandlingsmonitorering afholdes af den respektive behandlende afdeling. Undersøgelsen er udelukkende videnskabelig med henblik på at forbedre den forebyggende behandling hos patienter med kronisk nyresvigt og forkammerflimren. Ingen af de involverede læger har økonomisk gevinst af undersøgelsen. Du modtager som forsøgsdeltager intet vederlag. Eventuelle ekstraordinære besøg i afdelingen, som forsøget måtte kræve, honoreres efter regler for offentlig transport.

## Deltagelse i undersøgelsen

Det er frivilligt at deltage i undersøgelsen. Meningen med denne skriftlige information er at give dig mulighed for at overveje din deltagelse, herunder at drøfte den med dine nærmest. Det er suverænt din beslutning, om du ønsker at deltage i undersøgelsen. Vælger du at deltage, kan du på et hvilket som helst tidspunkt uden begrundelse trække dig fra undersøgelsen. Vi opfordrer dig og dine nærmeste til at læse vedhæftede folder "Forsøgspersoners rettigheder i et sundhedsvidenskabelig forskningsprojekt". Uanset om du svarer ja, nej eller fortryder på et senere tidspunkt, vil vi fortsat tilbyde dig den bedst mulige behandling af din sygdom. Beslutter du dig for at deltage i undersøgelsen, kræver dansk lov at du bekræfter dette ved at underskrive vedlagte samtykke og fuldmagt.

Efter forsøgets afslutning kan du kontakte din læge, hvis du ønsker at få informationer om resultaterne.

Med venlig hilsen,

DAN-WAR-D studiet

Hvis du har spørgsmål vedrørende forsøget, er du naturligvis velkommen til at kontakte

**Kontaktlæge:** .....

**E-mail:** .....

**Telefon:** .....

lokale protokolansvarlige investigator

## Koordinerende protokolansvarlige læge

Nicholas Carlson, læge, seniorforsker

Nefrologisk Klinik P, Rigshospitalet

Opgang 2 og 3, 13. sal, Inge Lehmanns Vej 5 og 7

2100 København Ø

telefon 35455927 / mail: Nicholas.carlson.01@regionh.dk

## Forsøgspersoners rettigheder i et sundhedsvidenskabeligt forskningsprojekt

Som deltager i et sundhedsvidenskabeligt forskningsprojekt skal du vide, at:

- din deltagelse i forskningsprojektet er helt frivillig og kun kan ske efter, at du har fået både skriftlig og mundtlig information om forskningsprojektet og underskrevet samtykkeerklæringen.
- du til enhver tid mundtligt, skriftligt eller ved anden klar tilkendegivelse kan trække dit samtykke til deltagelse tilbage og udtræde af forskningsprojektet. Såfremt du trækker dit samtykke tilbage påvirker dette ikke din ret til nuværende eller fremtidig behandling eller andre rettigheder, som du måtte have.
- du har ret til at tage et familiemedlem, en ven eller en bekendt med til informationssamtalen.
- du har ret til betænkningstid, før du underskriver samtykkeerklæringen.
- oplysninger om dine helbredsforhold, øvrige rent private forhold og andre fortrolige oplysninger om dig, som fremkommer i forbindelse med forskningsprojektet, er omfattet af tavshedspligt.
- behandling af oplysninger om dig, herunder oplysninger i dine blodprøver og væv, sker efter reglerne i databeskyttelsesforordningen, databeskyttelsesloven samt sundhedsloven. Den dataansvarlige i forsøget skal orientere dig nærmere om dine rettigheder efter databeskyttelsesreglerne.
- der er mulighed for at få aktindsigt i forsøgsprotokoller efter offentlighedslovens bestemmelser. Det vil sige, at du kan få adgang til at se alle papirer vedrørende forsøgets tilrettelæggelse, bortset fra de dele, som indeholder forretningshemmeligheder eller fortrolige oplysninger om andre.
- der er mulighed for at klage og få erstatning efter reglerne i lov om klage- og erstatningsadgang inden for sundhedsvæsenet. Hvis der under forsøget skulle opstå en skade kan du henvende dig til Patienterstatningen, se nærmere på www.patienterstatningen.dk

**De Videnskabsetiske Komiteer for Region Hovedstaden (6 komiteer)**
Tlf.: +45 38 66 63 95
E-mail: vek@regionh.dk
Hjemmeside:
https://www.regionh.dk/til-fagfolk/Forskning-og-innovation/Kliniske-test-og-forsoeg/Sider/De-Videnskabsetiske-Komitéer.aspx

**De Videnskabsetiske Komiteer for Region Syddanmark (2 komiteer)**
Tlf.: + 45 76 63 82 21
E-mail: komite@rsyd.dk
Hjemmeside:
https://komite.regionsyddanmark.dk/wm258128

**Den Videnskabsetiske Komité for Region Nordjylland** Tlf.: +45 97 64 84 40
E-mail: vek@rn.dk
Hjemmeside:
http://www.rn.dk/vek

**Den Videnskabsetiske Komité for Region Sjælland**
Tlf.: +45 93 56 60 00
E-mail: RVK-sjaelland@regionsjaelland.dk
Hjemmeside:
https://www.regionsjaelland.dk/sundhed/forskning/forfagfolk/videnskabsetisk-komite/Sider/default.aspx

**De Videnskabsetiske Komiteer for Region Midtjylland (2 komiteer)**
Tlf.: +45 78 41 01 83 / +45 78 41 01 82 / +45 78 41 01 81
E-mail: komite@rm.dk
Hjemmeside:
http://www.komite.rm.dk

**National Videnskabsetisk Komité**
Tlf.: +45 72 21 68 55
E-mail: kontakt@nvk.dk
Hjemmeside: http://www.nvk.dk

*Dette tillæg er udarbejdet af det videnskabsetiske komitésystem og kan vedhæftes den skriftlige information om det sundhedsvidenskabelige forskningsprojekt. Spørgsmål til et konkret projekt skal rettes til projektets forsøgsansvarlige. Generelle spørgsmål til forsøgspersoners rettigheder kan rettes til den komité, som har godkendt projektet.*

Revideret 21. september 2019

[Patient-label]

# D A N - W A R - D

**Danish Warfarin-Dialysis Study:**

Blodfortyndende behandling til forebyggelse af slagtilfælde hos patienter med dialysekrævende kronisk nyresvigt og forkammerflimren: Et nationalt lodtrækningsforsøg

**Samtykkeerklæring fra forsøgsdeltageren:**

Jeg bekræfter hermed, at jeg efter at have modtaget information om ovenstående forskningsprojekt, såvel mundtligt som skriftligt, indvilliger i at deltage i den beskrevne undersøgelse. Jeg er vidende om, at deltagelse heri er frivilligt, og at jeg på et hvilket som helst tidspunkt og uden begrundelse kan trække mit tilsagn om deltagelse tilbage.

**Udfyldes af forsøgsdeltageren:**

Dato: _____ Patientnavn: _____
Blokbogstaver

Patientunderskrift: _____

Såfremt der tilstøder nye væsentlige helbredsoplysninger om dig i forbindelse med forskningsprojektet vil du blive informeret. Vil du **frabede** dig information om nye væsentlige helbredsoplysninger fremkommet som led i forskningsprojektet, bedes du markere her: _____ (sæt x)

Ønsker du at informeres om forskningsprojektets resultater samt eventuelle konsekvenser for dig?:

Ja _____ (sæt x) Nej _____ (sæt x)

**Erklæring fra den læge der indhenter informeret samtykke:**

Jeg erklærer, at forsøgsdeltageren har modtaget mundtlig og skriftlig information om undersøgelsen, heriblandt at denne har haft mulighed for at stille spørgsmål til mig. Det er derfor min overbevisning at der er givet tilstrækkelig information til, det der kan træffes beslutning om deltagelse i forsøget.

**Udfyldes af lægen:**

Dato: _____ Lægenavn: _____
Blokbogstaver

Lægeunderskrift: _____

Samtykke og erklæring underskrives i **2 eksemplarer** (et til forsøgsdeltagere, og et til afdelingens projektmappe)

# Reporting checklist for protocol of a clinical trial.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | #1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | #2a | Trial identifier and registry name. If not yet registered, name of intended registry | 2 |
| Trial registration: data set | #2b | All items from the World Health Organization Trial Registration Data Set | Suppl. Table S3 |
| Protocol version | #3 | Date and version identifier | 1 |
| Funding | #4 | Sources and types of financial, material, and other support | 11 |
| Roles and responsibilities: contributorship | #5a | Names, affiliations, and roles of protocol contributors | 11 + Suppl. Table S2 |
| Roles and responsibilities: sponsor contact information | #5b | Name and contact information for the trial sponsor | 1 |

| | | | |
|---|---|---|---|
| Roles and responsibilities: sponsor and funder | #5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | NA |
| Roles and responsibilities: committees | #5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | Suppl. Table S2 |
| **Introduction** | | | |
| Background and rationale | #6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5 |
| Background and rationale: choice of comparators | #6b | Explanation for choice of comparators | 5 |
| Objectives | #7 | Specific objectives or hypotheses | 5 |
| Trial design | #8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, | 5 |

| | | | |
|---|---|---|---|
| | | equivalence, non-inferiority, exploratory) | |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | #9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 5 + suppl. Table S1 |
| Eligibility criteria | #10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | Table 1 |
| Interventions: description | #11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 6 |
| Interventions: modifications | #11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease) | 6 |
| Interventions: adherance | #11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests) | 6 + Figure 1 |

| | | | |
|---|---|---|---|
| Interventions: concomitant care | #11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 6 |
| Outcomes | #12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 7 + Table 2 |
| Participant timeline | #13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| Sample size | #14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 8 |
| Recruitment | #15 | Strategies for achieving adequate participant enrolment to reach target sample size | 5 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |

| | | | |
|---|---|---|---|
| Allocation: sequence generation | #16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | 6 |
| Allocation concealment mechanism | #16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | 6 |
| Allocation: implementation | #16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | 6 |
| Blinding (masking) | #17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | 5 |
| Blinding (masking): emergency unblinding | #17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | 5 |
| **Methods: Data collection, management, and analysis** | | | |

| | | | |
|---|---|---|---|
| Data collection plan | #18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 7 + Figure 1 |
| Data collection plan: retention | #18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 7 + Figure 1 |
| Data management | #19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 7+9 |
| Statistics: outcomes | #20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 7 + Table 2 |
| Statistics: additional analyses | #20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | 7-8 |
| Statistics: analysis population and | #20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any | 7-8 |

| | | | |
|---|---|---|---|
| missing data | | statistical methods to handle missing data (eg, multiple imputation) | |
| **Methods: Monitoring** | | | |
| Data monitoring: formal committee | #21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | 8 |
| Data monitoring: interim analysis | #21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | 8 |
| Harms | #22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 8-9 |
| Auditing | #23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | 9 |
| **Ethics and dissemination** | | | |

| | | | |
|---|---|---|---|
| Research ethics approval | #24 | Plans for seeking research ethics committee / institutional review board (REC / IRB) approval | 9 |
| Protocol amendments | #25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators) | 9 |
| Consent or assent | #26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | 5 |
| Consent or assent: ancillary studies | #26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | NA |
| Confidentiality | #27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | 9 |
| Declaration of interests | #28 | Financial and other competing interests for principal investigators for the overall trial and each study site | 12 |
| Data access | #29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | 9 |
| Ancillary and post trial care | #30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial | NA |

| | | | |
|---|---|---|---|
| | | participation | |
| Dissemination policy: trial results | #31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | 9 |
| Dissemination policy: authorship | #31b | Authorship eligibility guidelines and any intended use of professional writers | 9 |
| Dissemination policy: reproducible research | #31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | 9 |
| **Appendices** | | | |
| Informed consent materials | #32 | Model consent form and other related documentation given to participants and authorised surrogates | Suppl. appendix 2 |
| Biological specimens | #33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | NA |

Notes:

- 2b: Suppl. Table S3
- 5a: 11 + Suppl. Table S2
- 5d: Suppl. Table S2

- 9: 5 + suppl. Table S1
- 11c: 6 + Figure 1
- 12: 7 + Table 2
- 18a: 7 + Figure 1
- 18b: 7 + Figure 1
- 20a: 7 + Table 2
- 32: Suppl. appendix 2