

BMJ Open Design and rationale of DUTCH-AF: a prospective nationwide registry programme and observational study on long-term oral antithrombotic treatment in patients with atrial fibrillation

Gordon Chu ¹, Jaap Seelig,^{2,3} Emmy M Trinks-Roerdink ⁴, Anouk P van Alem,⁵ Marco Alings,⁶ Bart van den Bemt,^{7,8} Lucas VA Boersma,⁹ Marc A Brouwer,¹⁰ Suzanne C Cannegieter,¹¹ Hugo ten Cate,¹² Charles JHJ Kirchhof,¹³ Harry JGM Crijns ³, Ewoud J van Dijk,¹⁴ Arif Elvan,¹⁵ Isabelle C van Gelder,¹⁶ Joris R de Groot,¹⁷ Frank R den Hartog,¹⁸ Jonas SSG de Jong,¹⁹ Sylvie de Jong,²⁰ Frederikus A Klok,¹ Timo Lenderink,²¹ Justin G Luermans,²² Joan G Meeder,²³ Ron Pisters,² Peter Polak,²⁴ Michiel Rienstra,¹⁶ Frans Smeets,²⁵ Giovanni JM Tahapary,²⁶ Luc Theunissen,²⁷ Robert G Tieleman,²⁸ Serge A Trines ²⁹, Pepijn van der Voort,³⁰ Geert-Jan Geersing,⁴ Frans H Rutten,⁴ Martin EW Hemels,^{2,10} Menno V Huisman¹

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For numbered affiliations see end of article.

Correspondence to

Mr Gordon Chu;
k.g.chu@lumc.nl

ABSTRACT

Introduction Anticoagulation therapy is pivotal in the management of stroke prevention in atrial fibrillation (AF). Prospective registries, containing longitudinal data are lacking with detailed information on anticoagulant therapy, treatment adherence and AF-related adverse events in practice-based patient cohorts, in particular for non-vitamin K oral anticoagulants (NOAC). With the creation of DUTCH-AF, a nationwide longitudinal AF registry, we aim to provide clinical data and answer questions on the (anticoagulant) management over time and of the clinical course of patients with newly diagnosed AF in routine clinical care. Within DUTCH-AF, our current aim is to assess the effect of non-adherence and non-persistence of anticoagulation therapy on clinical adverse events (eg, bleeding and stroke), to determine predictors for such inadequate anticoagulant treatment, and to validate and refine bleeding prediction models. With DUTCH-AF, we provide the basis for a continuing nationwide AF registry, which will facilitate subsequent research, including future registry-based clinical trials.

Methods and analysis The DUTCH-AF registry is a nationwide, prospective registry of patients with newly diagnosed 'non-valvular' AF. Patients will be enrolled from primary, secondary and tertiary care practices across the Netherlands. A target of 6000 patients for this initial cohort will be followed for at least 2 years. Data on thromboembolic and bleeding events, changes in antithrombotic therapy and hospital admissions will be registered. Pharmacy-dispensing data will be obtained to calculate parameters of adherence and persistence to anticoagulant treatment, which will be linked to AF-related outcomes such as ischaemic stroke and major bleeding. In

Strengths and limitations of this study

- The DUTCH-AF registry will provide important insights into the effects of non-adherence and non-persistence of anticoagulation therapy on clinically adverse outcomes such as stroke and major bleeding. Moreover, it will also provide patient characteristics of non-adherent and non-persistent patients that could be targeted for adherence-improving interventions in the future.
- Patients are enrolled from all levels of care across the Netherlands including patients from general practices and thrombosis services, thereby increasing the generalisability of the study results.
- The registry will provide an essential framework for improving quality of care and for patient-centred research, including the opportunity for future registry-based randomised controlled trials or trials within cohort (TWiC) designs.
- Extrapolation and generalisability of this registry could be limited when patients are enrolled from primary or secondary/tertiary care disproportionately.

a subset of patients, anticoagulation adherence and beliefs about drugs will be assessed by questionnaire.

Ethics and dissemination This study protocol was approved as exempt for formal review according to Dutch law by the Medical Ethics Committee of the Leiden University Medical Centre, Leiden, the Netherlands. Results will be disseminated by publications in peer-reviewed journals and presentations at scientific congresses.

Trial registration number Trial NL7467, NTR7706 (<https://www.trialregister.nl/trial/7464>).

INTRODUCTION

As a consequence of the increasing prevalence of atrial fibrillation (AF) in our ageing society, its associated adverse events and the overall societal healthcare burden, there is a need for optimisation of AF management.¹ Collecting data on case-mix, treatment and outcomes of AF patients has been shown to be valuable for improving the management of AF patients.²⁻⁴

DUTCH-AF is a nationwide, prospective registry designed to gather information on the (anticoagulation) management and clinical course of patients with newly diagnosed AF. Virtually all newly diagnosed AF patients in the Netherlands are eligible for this registry, and patients will be included throughout all levels of care. By collecting these data, DUTCH-AF will provide a base for future research (notably registry-based randomised trials) and will provide benchmark data for care providers. This will strengthen the cooperation between different care providers and improve quality of AF care and research.

Aside from collecting registry data, a prospective study assessing non-adherence and non-persistence to anticoagulation therapy in this AF population will be performed simultaneously, under the hypothesis that non-adherence and non-persistence to anticoagulation therapy increases the risk of AF-related and anticoagulant-related adverse events, such as stroke and bleeding. As a recent meta-analysis has shown, primary therapy non-adherence is frequently seen in common chronic diseases.⁵ For instance, in patients with therapy-resistant hypertension, non-adherence was seen in over two-thirds of patients.⁶ In line with these findings, multiple studies have shown in recent years that non-adherence and non-persistence to anticoagulation therapy occur frequently in AF patients as well, which subsequently affects safety and efficacy outcomes negatively.⁷⁻¹² Based on these findings, identifying predictors of non-adherence and non-persistence is highly needed, as these patients could be targeted for adherence-improving interventions in the future.

Furthermore, one important complication of anticoagulation therapy, which could also affect patient adherence and persistence, is bleeding. Identifying AF patients with high risk of bleeding could potentially help decision-making and follow-up strategies in anticoagulant management, in particular to flag or identify potentially modifiable risk factors for bleeding. Unfortunately, existing AF bleeding prediction models perform moderately well and have few clinical implications.^{3 13-16}

With this prospective study, DUTCH-AF aims to (i) determine the clinical impact of non-adherence and non-persistence to anticoagulation therapy in AF patients, (ii) identify predictors for non-adherence and non-persistence to oral anticoagulants (OAC) therapy, and (iii) validate and refine current bleeding prediction models.

By combining subsequent research with a quality registry, DUTCH-AF aims to provide important insights into contemporary (anticoagulation) management of

AF and the clinical impact of non-adherence and non-persistence to anticoagulation therapy.

METHODS

Design

DUTCH-AF is a prospective, observational, multicentre, nationwide study of a representative sample of Dutch patients with newly diagnosed AF. The registry started as of January 2018, with a planned 3 years of patient recruitment. The intended duration of patient follow-up will be at least 2 years.

DUTCH-AF is an integral part of a nationwide cardiovascular data registration strategy. The creation of this nationwide registry was conducted in collaboration with the Netherlands Society of Cardiology (NVVC), the Netherlands Association of Cardiothoracic Surgery (NVT), the Dutch College of General Practitioners (NHG), the Netherlands Heart Registry (NHR) and the Dutch Heart Foundation. Prior experience of the Netherlands Heart Network (NHN) was incorporated in the design as well.¹⁷ The data gathered in DUTCH-AF is managed by the NHR and will be the basis of a continuous, ongoing AF registry, enabling the possibility to conduct registry-based trials by applying the trials within cohort (TWiC) design.¹⁸⁻²⁰ This is done with the ambition to enhance scientific evaluation in AF research, and bring valuable, promising interventions easier and faster to patients at lower study costs and burden.

Study population

Investigators enrol consecutive patients aged ≥ 18 years with newly diagnosed non-valvular AF (initial AF diagnosis < 6 months before the inclusion date). Patients with valvular AF (ie, moderate-to-severe mitral stenosis or a mechanical heart valve), an anticipated life expectancy < 6 months or with documented AF developing within 14 days after cardiothoracic surgery will be excluded. AF following cardiothoracic surgery is an exclusion criterion for this registry due to its high incidence (in 20% to 40% of all surgeries) and its self-limiting nature (80% revert back to sinus rhythm within 24 hours).^{21 22} All patients are asked to provide written informed consent for participation and permission (i) to collect their baseline and predefined follow-up data, (ii) to be approached for future studies, for example, registry-based trials (TWiC design), and (iii) for participation in a paper survey on anticoagulation adherence and beliefs about drugs.

Site selection

Sites from all over the Netherlands participate in this registry, consisting of but not limited to a broad mix of hospitals (secondary and tertiary centres), anticoagulation clinics and general practitioner (GP) practices. All Dutch centres treating AF patients are encouraged to join the registry. Centres are informed on the registry through symposia, newsletters, mailings and word of mouth with the help of the Dutch Federation of Anticoagulation

Clinics (FNT), NVVC, NHR, general practitioner networks and NVVC Connect-AF. In this way, we aim to enrol a representative sample of all Dutch newly diagnosed AF patients, minimising selection and allowing for a broad generalisability of findings.

Data collection and follow-up

Data will be primarily collected from electronic medical records of the enrolled patients, and will mainly consist of routine care data. At baseline, data will be collected on patient demographics, pattern of AF, date and location of the initial AF diagnosis, secondary causes of AF, European Heart Rhythm Association (EHRA) classification, relevant medical history with items that contribute to the CHA₂DS₂-VASc score (Congestive heart failure, Hypertension, Age ≥75, Diabetes mellitus, Stroke/TIA/thromboembolism, Vascular disease, Age 65-74, Sex category (ie, female sex)) and bleeding risk assessment, and the (cardiovascular) medical treatment.²³ Follow-up is scheduled at 12 and 24 months after inclusion. At follow-up, data will be collected from electronic medical records, accompanied by telephone interviews. Follow-up data will be complemented with pharmacy dispensing data from the Foundation for Pharmaceutical Statistics (SFK).²⁴ **Box 1** provides an overview of the data collected during baseline and follow-up. **Table 1** provides an overview of the causes of secondary AF.²³

Outcomes

The following clinical outcomes will be registered during follow-up: (i) thromboembolic adverse events (ie, transient ischaemic attack, ischaemic stroke, arterial thrombotic event and myocardial infarction), (ii) bleeding (ie, major, clinically relevant non-major bleeding (CRNMB) and minor bleeding), (iii) AF-related visits to the emergency department or hospital admissions, (iv) all changes in antithrombotic therapy, (v) adherence to antithrombotic therapy, and (vi) all-cause mortality. Outcome definitions of all major cardiovascular and bleeding endpoints will be assessed as stated in online supplementary table 1.^{16 25 26} Thromboembolic adverse events, clinically relevant bleeding and myocardial infarction will be judged by a blinded, independent adjudication committee, consisting of a neurologist, a cardiologist and a vascular internist.

Data on adherence and persistence to OAC will be acquired in two ways. First, the SFK, which has a coverage of >95% of all community pharmacies, will provide medication dispensing data of all included patients.²⁴ Adherence and persistence rates to OAC will be calculated using these data. The various measures are explained in the Statistical Analysis section. Second, a subset of patients will be sent a composite questionnaire regarding anticoagulation adherence and beliefs about drugs at one point in time. The composite questionnaire consists of the Beliefs about Medicines Questionnaire (BMQ), the Medication Adherence Report Scale (MARS-5) and the Dutch General Self-Efficacy Scale (DGSS).²⁷⁻³⁰ The composite

Box 1 Overview of baseline and follow-up variables

Baseline

Demographics: gender, age and ethnicity
 Weight, height and blood pressure
 Recent haemoglobin and kidney function
 Medical history: all parameters included in CHA₂DS₂-VASc, sleep apnoea, chronic lung disease, malignancy and prior bleeding history
 Date of AF diagnosis
 Location of AF diagnosis: primary or specialist care
 Complaints of AF: EHRA symptom classification
 Pattern: paroxysmal or persistent AF
 Treatment: none, rhythm or rate control
 Secondary causes of AF: infection/inflammation, non-cardiothoracic surgery, MI, alcohol consumption, thyrotoxicosis, pericardial and myocardial disease and acute pulmonary embolism
 Anticoagulation prior to AF diagnosis: none, antiplatelet agents, VKA and/or NOAC
 Anticoagulation after AF diagnosis: none, antiplatelet agents, VKA and/or NOAC

Follow-up

Weight and blood pressure
 Recent haemoglobin and kidney function
 Pattern: paroxysmal, persistent, long-standing persistent and permanent AF
 Occurrence of bleeding events:

- ▶ Severity: MB, CRNMB
- ▶ Location: intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, intramuscular, gastrointestinal, urogenital, nasal and pulmonary.

 Occurrence of ischaemic events: TIA, ischaemic stroke, ATE and MI
 Healthcare utilisation: emergency department visits or hospital admission for AF treatment
 Side effects to antiarrhythmic treatment
 Changes in anticoagulation treatment and CHA₂DS₂-VASc
 Prescription data from SFK:

- ▶ Dispensing data (type and dosage)
- ▶ Concomitant medical therapy

 Adherence and persistence
 In a subset of patients: MARS-5/BMQ/DGSS questionnaires

ATE, arterial thrombotic event; BMQ, Beliefs about Medicines Questionnaire; CRNMB, clinically relevant non-major bleeding; DGSS, Dutch General Self-Efficacy Scale; EHRA, European Heart Rhythm Association; MARS-5, Medication Adherence Report Scale; MB, major bleeding; MI, myocardial infarction; NOAC, non-vitamin K oral anticoagulants; SFK, Foundation of Pharmaceutical Statistics; TIA, transient ischaemic attack; VKA, vitamin K antagonist.

questionnaire is sent randomly after 1, 6, 12 or 24 months after inclusion if patients (1) agreed to participate when consulted at inclusion, and (2) used antithrombotic therapy within 1 month after inclusion. **Table 2** provides an overview of the various items asked in the questionnaires.^{27-29 31}

Data management

All clinical data are accumulated using a web-based Electronic Data Capture System and are registered in electronic case report forms (e-CRF). All e-CRF records will be pseudonymised and patients are assigned a unique study identifier. Personal data of all included patients will be collected to send the composite questionnaire on

Table 1 Definition of secondary AF used in the DUTCH-AF registry

Secondary AF	AF that is triggered within 14 days after (1) infection or inflammation, (2) non-cardiothoracic surgery, (3) myocardial infarction, (4) pericarditis/myocarditis, (5) exacerbation chronic pulmonary disease, (6) hyperthyroidism, (7) pulmonary embolism, (8) cardiac tamponade or (9) acute alcohol intoxication. If AF was triggered by any amount of alcohol use, as stated in the medical records by the treating physician, this was also scored as 'acute alcohol intoxication'.
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AF, atrial fibrillation.

medication adherence and beliefs about drugs, for linkage with the SFK and for approach of the patients for future research. All personal data will be handled according to the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the GDPR, and will be stored separately from the e-CRF. By using an application for the storage of personal data, the risk of including the same patient twice is negligible. Data monitoring will be performed by the coordinating researchers to ascertain completeness and accuracy of the entered data. Source data verification will be undertaken in 1% to 10% of all cases. A comprehensive plan has been developed to monitor the quality of data entered into the electronic database during the course of the programme. Linkage of the pharmacy dispensing data with the corresponding study participants will be performed by a trusted third party using pseudonymised data.

Statistical analysis

Research aim 1: association between OAC adherence/persistence, dosage and clinical outcomes

To evaluate adherence and persistence of non-vitamin K oral anticoagulants (NOACs), subsequent dispensing of NOACs will be assessed. If the prior prescription ended prior to the subsequent dispensing date, it would be considered a gap. The length of the gap will be measured in days. To improve the accuracy of our adherence assessment, we will correct for patients stacking their medication at home, and account for the carry-over of oversupply. Patient adherence to NOAC will be expressed through the medication possession rate (MPR) and the proportion of days covered (PDC). The PDC is obtained by dividing the number of daily doses dispensed from the first prescription until, but not including, the last refill with the number of days in that interval and expressed as a percentage. Patients will be classified as adherent or non-adherent dependent on various PDC cut-off points, including the PDC >80%, in line with previous publications.³² Other measures of patient adherence will be assessed, including the gap length and the total gap days. As a proxy of patient adherence to vitamin K antagonist (VKA), patient adherence to VKA will be expressed through the time in therapeutic range (TTR) of international normalized ratio (INR). Patients will be classified as adherent dependent on various TTR cut-off points. The TTR will be calculated with the Rosendaal method.³³

Persistence will be defined as the time, in days, between the first dispensation and until the day of treatment

discontinuation. As patients can switch to another anti-coagulant therapy, we will assess persistence to the prescribed anticoagulant in particular and to anticoagulant therapy in general as well. Persistence rates for both VKA and NOACs will be calculated for various time intervals. Kaplan-Meier curves will be used to graphically display persistence over time.

OAC adherence and persistence will be linked to risks of both thromboembolic and bleeding outcomes. First, patients with such occurrences will be matched with patients without occurrences on time, since start of follow-up. We will classify adherence and persistence measures as described above. ORs with 95% CI will be calculated using conditional multivariate logistic regression to assess the association between adherence and persistence to the anticoagulation therapy and the risk of event.

Research aim 2: predictors of NOAC non-adherence/non-persistence

NOAC non-adherence will first be defined as a PDC below 80%, similarly as above. Next, using this binary outcome, a logistic model is fitted to quantify correlations of clinical variables with NOAC non-adherence. From the collected data, the following variables are considered, based on clinical likeliness to be correlated with NOAC-adherence: age, sex, comorbidity and comedication.³⁴ This list of variables that potentially correlate with NOAC adherence will continuously be expanded based on the latest publications regarding this subject. As clinical outcomes, such as bleeding or thromboembolism, may affect adherence and persistence afterwards, secondary analyses will be performed in which the impact of such clinical outcomes on adherence and persistence measures will be assessed. Furthermore, we will assess whether the predictors of non-adherence prior to or after an event differ. If the impact of such clinical outcomes on adherence are of relevance, we will perform similar prediction analyses considering only the PDC measures prior to or without an event. Missing values are imputed using existing multiple imputation techniques and subsequently pooled using Rubin's rule, assuming that the missing at random assumption is met. Using backward selection, variables are eliminated from the list of potential predictors if they do not have independent predictive ability in the model (criterion $p < 0.15$). To prevent overfitting, we will apply bootstrapping techniques. Model performance is subsequently assessed by estimations of the discriminative power of

Table 2 Questionnaires for the assessment of patients' beliefs, attitudes and behaviour regarding anticoagulants in English and Dutch language

Beliefs about Medicine Questionnaire specific (BMQ-S)

This 11-item scale asks the patient to rate their beliefs regarding anticoagulation therapy. Respondents indicate their degree of agreement with each statement on a 5-point Likert scale, ranging from 1=strongly disagree to 5=strongly agree. Scores obtained for individual items are summed and divided by the total number of items in the scale to give a scale score of 1 to 5. Higher scores indicate stronger beliefs.

1. My health at present depends on my anticoagulation therapy
In Dutch: Op het moment hangt mijn gezondheid af van mijn bloedverdunders
2. Having to take anticoagulants worries me.
In Dutch: Ik maak me zorgen over het feit dat ik bloedverdunders moet nemen.
3. My life would be impossible without anticoagulants
In Dutch: Mijn leven zou erg moeilijk zijn zonder bloedverdunders
4. I sometimes worry about the long-term effects of anticoagulation therapy
In Dutch: Soms maak ik me zorgen over de effecten die mijn bloedverdunders op de lange termijn kunne hebben
5. Without anticoagulation therapy, I would be very ill
In Dutch: Zonder mijn bloedverdunders zou ik heel ziek zijn
6. My anticoagulation therapy is a mystery to me
In Dutch: Ik ben onvoldoende op de hoogte van wat mijn bloedverdunders doen
7. My health in the future depends on anticoagulation therapy
In Dutch: Mijn toekomstige gezondheid hangt af van mijn bloedverdunders
8. My anticoagulation therapy disrupts my life
In Dutch: Mijn bloedverdunders ontwrichten mijn leven
9. I sometimes worry about becoming too dependent on anticoagulants
In Dutch: Soms ben ik bang dat ik te afhankelijk zal worden van mijn bloedverdunders
10. Anticoagulation therapy protects me from becoming worse
In Dutch: Mijn bloedverdunders voorkomen dat ik verder achteruit ga
11. This anticoagulation therapy cause me unpleasant side effects
In Dutch: Deze bloedverdunders hebben onplezierige bijwerkingen

Medication Adherence Report Scale, 5-item (MARS-5)

This 5-item scale asks the patient to rate the frequency with which he/she engages in each of the five aspects of non-adherent behaviour. Each item is rated on a 5-point Likert scale, where 1=always to 5=never. Score for each of the five items are summed and divided by five to give a scale score of 1 to 5, where higher scores indicate higher levels of reported adherence.

1. I forget to take my anticoagulants
Ik vergeet mijn bloedverdunders in te nemen
2. I modify the doses of my anticoagulants
Ik wijzig de dosering van mijn bloedverdunders
3. I stop taking medications during a certain period
Ik stop een tijdje met bloedverdunders te nemen
4. I decide to miss a dose
Ik besluit een dosering over te slaan
5. I take less than what is prescribed
Ik neem minder dan is voorgeschreven

Dutch General Self-efficacy Scale (DGSS)

The DGSS is a 10-item Likert-type scale, where 1=is not true at all to 4=exactly true, that assesses general self-efficacy. Higher scores represent higher levels of general self-efficacy

1. I can always manage to solve difficult problems if I try hard enough
Het lukt me altijd om moeilijke problemen op te lossen, als ik er genoeg moeite voor doe
2. If someone opposes me, I can find the means and ways to get what I want
Als iemand mij tegenwerkt, vind ik toch manieren om te krijgen wat ik wil
3. It is easy for me to stick to my aims and accomplish my goals
Het is voor mij makkelijk om vast te houden aan mijn plannen en mijn doel te bereiken
4. I am confident that I could deal efficiently with unexpected events
Ik vertrouw erop dat ik onverwachte gebeurtenissen doeltreffend aanpak
5. Thanks to my resourcefulness, I know how to handle unforeseen situations
Dankzij mijn vindingrijkheid weet ik hoe ik in onvoorziene situaties moet handelen
6. I can solve most problems if I invest the necessary effort
Ik kan de meeste problemen oplossen als ik er de nodige moeite voor doe
7. I can remain calm when facing difficulties because I can rely on my coping abilities
Ik blijf kalm als ik voor moeilijkheden kom te staan omdat ik vertrouw op mijn vermogen om problemen op te lossen
8. When I am confronted with a problem, I can usually find several solutions
Als ik geconfronteerd word met een probleem, heb ik meestal meerdere oplossingen
9. If I am in trouble, I can usually think of a solution
Als ik in een benarde situatie zit, weet ik meestal wat ik moet doen
10. I can usually handle whatever comes my way
Wat er ook gebeurt, ik kom er wel uit

the model (Harrell's C-statistic, graphically illustrated in receiver operating characteristic (ROC) space) and its calibration, illustrated in a calibration plot (predicted against observed risk).

Research aim 3: validation of bleeding models

All variables of active cancer, male gender with uncontrolled hypertension, anaemia, history of bleeding, age ≥ 60 years and renal dysfunction (VTE-BLEED) will be included in the study database in accordance with the definitions used in the derivation study.³⁵ Next, for each individual patient, predicted risk of the VTE-BLEED model will be calculated using the intercept and beta's from the original derivation study. Subsequently, as mentioned previously, model performance of VTE-BLEED is assessed by quantifying its discriminative power (Harrell's C-statistic, graphically illustrated in ROC space) and its calibration, illustrated in a calibration plot (predicted against observed risks). Finally, to quantify the ability to predict the risk of major bleeding, we will run univariate logistic regression models with major bleeding as binary outcome. Hereto, ORs and 95% CI are obtained for the VTE-BLEED high-risk score class (threshold >2) versus low-risk class serving as the reference group.

Should model performance of VTE-BLEED be disappointing (given that VTE-BLEED models was originally derived to predict bleeding complications in patients with venous thromboembolism, this may occur), simple updating techniques will be applied to optimise model performance for use in AF patients (rather than developing a new model). This may include, with increasing complexity, an adjustment of the intercept of the model, re-estimating the beta's for the variables from the original regression model or including novel variables if needed.

Study size

The registry has a target enrolment of 6000 patients with a follow-up of at least 2 years. We expect 5500 NOAC users. Based on a 1 year non-persistence in one-third of the NOAC users, 1815 patients on NOACs will be non-persistent.³⁶ If we assume a 50% increased risk of ischaemic stroke/systemic embolism in these patients, we can expect on average a 3% yearly risk compared with the 2% in the 3685 patients who will continue to use their drug.⁷ During 2-year follow-up, we expect 250 patients will develop ischaemic stroke/systemic embolism.

If we assume 30% of the remaining NOAC users to be non-adherent, we can expect 1105 non-adherent NOAC users. With an expected yearly risk of 3.5% major bleeding in adherent patients and a 2.5% for non-adherent patients, we expect 176 major bleeding events annually.^{37–39} For cardiovascular death, we expect a risk of about 1.5% in all NOAC users, leading to 135 deaths in 2 years. Therefore, we expect a total of about 600 patients meeting one of our pre-specified major cardiovascular endpoints consisting of ischaemic stroke/systemic embolism, major bleeding including intracranial bleeds and all-cause mortality. These numbers will be sufficient to

(i) determine risk groups, (ii) construct a prediction model for non-adherence, and (iii) validate and develop bleeding risk scores.

Administrative structure

A steering committee (SC), comprised of experts in cardiology, vascular medicine, pharmaceuticals and medication adherence, neurology, general practice and epidemiology, is responsible for the study design and study conduct. A user committee, together with the NHR and the SC, evaluates and oversees the inclusion of patients and follow-up within the registry.

Patient and public involvement

Two patient advisory groups are involved in DUTCH-AF. Harteraad was involved in the grant application process for funding from The Netherlands Organisation for Health Research and Development (ZonMw). The Cliëntenraad Nederlandse Trombosediensten (CTDN) has joined the SC of DUTCH-AF. At the end of the study, the patient advisory groups will be involved to present the results to their peers and patient groups.

ETHICS AND DISSEMINATION

The Medical Ethics Review Committee of Leiden University Medical Centre approved this study and concluded that the (Dutch) Medical Research Involving Human Research Act (WMO) does not apply, as strictly speaking, no experimental interventions are studied or imposed on patients. The study is conducted in accordance with the Declaration of Helsinki, the Guideline for Good Clinical Practice and local regulatory requirements. All patients provide written consent to participate after being informed about the study. Participants are free to withdraw at any time. This study is registered in the Netherlands Trial Register (Trial NL7467, NTR7706). Results of the study will be disseminated to healthcare professionals and to the scientific community, through publications in peer-reviewed journals as well as presentations at scientific congresses.

DISCUSSION

In the DUTCH-AF registry, baseline characteristics, current anticoagulant treatment practices, medication adherence and clinical outcome of real-life AF patients in the Netherlands will be described. Data are collected from newly diagnosed patients with AF. Patients will be represented across all levels of care in the Netherlands, irrespective of treatment strategies.

In cooperation with the NHR, this registry constitutes an essential framework for improving the quality of care and for patient-centred research, including the opportunity of registry-based randomised controlled trials (RCT). Participating centres can continuously evaluate and benchmark their current practice on guideline implementation and guideline non-adherence. The minimal

data set has been designed to minimise registration burden, but will be sufficient for answering important current and future research questions. In the near future, our minimal data set will be implemented in Dutch electronic medical records to minimise double-registration. This will improve the quality of the continuing quality registry, as the data set will be entered by healthcare professionals, instead of using traditional methods with disease or treatment codes. The incorporation of the DUTCH-AF registry within the centralised network structure of the NHR will allow for cross-talk between registries through data linkage and through the adoption of a standardised set of definitions. Data collected for the AF registry could provide valuable information for other registries in which a patient is enrolled, without the need for additional follow-up.

A strong feature of this registry includes the inclusion of patients from all levels of care across the Netherlands, including patients from general practices. In the Netherlands, most AF patients will be referred back to the GP after the initial management by a cardiologist. The GP will have the responsibility for further AF care, including routine monitoring of anticoagulant adherence, kidney function and side effects, to ensure safe continuation of anticoagulation therapy. The participation of general practices will provide further information on patients who are never referred to specialist care, which are presumably more 'frail' and at an increased risk of stroke and bleeding.

The registry will also provide insights into the effects of (non-)adherence and persistence of the anticoagulant therapy on clinical adverse outcomes such as stroke and major bleeding. Current guidelines on NOACs are predominantly based on the NOAC RCTs, which showed high discontinuation rates despite stringent monitoring.^{40–43} Recent observational data showed similar or higher rates of discontinuation.^{44–45} Due to the short half-life of NOACs, interruptions are suggested to increase the risk for strokes, as was seen in historical VKA studies.^{46–49} However, long-term prospective studies assessing the effects of non-adherence to NOACs on adverse outcomes are lacking. Hence, DUTCH-AF is essential for providing patient-based information on adherence/persistence and dosage of anticoagulant treatment with NOACs in daily practice.

There are inherent limitations to this registry due to its design. First, the minimal data set of this registry is designed to specifically answer the predefined research aims regarding dosing, adherence and persistence of anticoagulants. To minimise registration burden, concise echocardiographic data were for example not registered. Furthermore, interpreting differences in outcome between hospitals or between the different (anticoagulant) treatment modalities must be done with caution. Confounding by indication cannot be entirely captured in the minimal data sheet. Also, recall bias can occur during the telephone conversation with the patient as part of follow-up. Besides, there is a risk of misclassification

(this risk will, however, be minimised by monitoring of the data as prescribed before). Another potential pitfall could occur when patients are not equally enrolled from primary and secondary/tertiary care, which could limit the extrapolation and generalisability of this registry.

The feasibility to derive a prediction model for VKA non-adherence will be determined by the number of novel AF patients treated with VKA. In the Netherlands, NOACs have overtaken VKA as the primary anticoagulant, with the number of starters on VKA decreasing rapidly.³⁷ Hence, deriving a prediction model for VKA non-adherence was not stated as a research aim; the feasibility of such an analysis will have to be assessed in the future.

Finally, as no other study uses the same methods to assess dosing, adherence and persistence of anticoagulants in AF patients, future external validation could, for example, be performed in patients included after the required 6000 patients. Options for external validation in other studies or registries will have to be assessed in the future, based on the comparability between study designs and aims.

Author affiliations

¹Department of Thrombosis and Hemostasis, Leiden University Medical Centre, Leiden, The Netherlands

²Department of Cardiology, Rijnstate, Arnhem, The Netherlands

³Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, Netherlands

⁴Department of General Practice, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht University, Utrecht, The Netherlands

⁵Department of Cardiology, Haaglanden Medical Centre, The Hague, The Netherlands

⁶Department of Cardiology, Amphia Hospital, Breda, The Netherlands

⁷Department of Pharmacy, Sint Maartenskliniek, Nijmegen, The Netherlands

⁸Department of Pharmacy, Radboud University Medical Centre, Nijmegen, The Netherlands

⁹Department of Cardiology, St. Antonius Hospital, Nieuwegein, The Netherlands

¹⁰Department of Cardiology, Radboud University Medical Centre, Nijmegen, The Netherlands

¹¹Department of Clinical Epidemiology, Leiden University Medical Centre, Leiden, The Netherlands

¹²Thrombosis Expert Centre, Maastricht University Medical Centre, Maastricht, The Netherlands

¹³Department of Cardiology, Alrijne Hospital, Leiderdorp, Netherlands

¹⁴Department of Neurology, Radboud University Medical Centre, Nijmegen, Netherlands

¹⁵Department of Cardiology, Isala Heart Centre, Isala Hospitals, Zwolle, Netherlands

¹⁶Department of Cardiology, University Medical Centre Groningen, Groningen, Netherlands

¹⁷Department of Cardiology, Heart Centre, Amsterdam University Medical Centre/ University of Amsterdam, Amsterdam, Netherlands

¹⁸Department of Cardiology, Gelderse Vallei Hospital, Ede, Netherlands

¹⁹Department of Cardiology, Heart Centre, OLVG, Amsterdam, Netherlands

²⁰Department of Cardiology, Elkerliek Hospital, Helmond, Netherlands

²¹Department of Cardiology, Zuyderland Medical Centre, Heerlen, Netherlands

²²Department of Cardiology, Maastricht University Medical Centre+, Maastricht, Netherlands

²³Department of Cardiology, VieCuri Medical Centre Noord-Limburg, Venlo, Netherlands

²⁴Department of Cardiology, St. Anna Hospital, Geldrop, Netherlands

²⁵Department of Cardiology, Hospital Bernhoven, Uden, Netherlands

²⁶Department of Cardiology, North West Hospital Group, Alkmaar, Netherlands

²⁷Department of Cardiology, Maxima Medical Centre, Eindhoven, Netherlands

²⁸Department of Cardiology, Martini Hospital, Groningen, Netherlands

²⁹Department of Cardiology, Heart-Lung Centre, Leiden University Medical Centre, Leiden, Netherlands

³⁰Department of Cardiology, Catharina Hospital, Eindhoven, Netherlands

Twitter Geert-Jan Geersing @gjeersing

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ORCID iDs

Gordon Chu <http://orcid.org/0000-0001-5466-3094>

Emmy M Trinks-Roerdink <http://orcid.org/0000-0002-0535-9253>

Harry JGM Crijns <http://orcid.org/0000-0003-1073-5337>

Serge A Trines <http://orcid.org/0000-0001-7715-9536>

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