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Using virtual twin-based AI models to detect atrial fibrillation and improve stroke outcomes [TAILOR]: a multicentre prospective cohort study

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ABSTRACT

Introduction Atrial fibrillation (AF) is the leading cause of cardioembolic stroke and is associated with increased stroke severity and fatality. Early identification of AF is essential for adequate secondary prevention but remains challenging due to its often asymptomatic or paroxysmal occurrence. Artificial intelligence (AI) offers new possibilities by integrating biomarkers, clinical phenotypes, established risk factors and imaging features to define a personalised 'digital twin' model. The TAILOR study aims to (1) examine prospective detection of AF using monitoring devices, (2) investigate novel prognostic MRI markers in patients with an AF-related stroke (AFRS) and (3) validate AI-based models for outcome prediction in AFRS.

Methods and analysis This prospective multicentre observational cohort study includes patients aged 40 years and above, with neuroimaging-confirmed diagnosis of ischaemic stroke, recruited from two sites: Hospital del Mar Barcelona (Spain) and Radboud University Medical Centre (The Netherlands). For the first sub-study (n=300), patients will undergo clinical assessment at baseline, 3 months and 12 months, and patch-based or Holter cardiac monitoring. The second sub-study (n=200) involves repeated brain MRI and cognitive examination after AFRS. Finally, AI-driven 'digital twin' models developed on retrospective TARGET datasets will be prospectively evaluated in TAILOR using temporal and centre-stratified analyses for advanced predictive tools for AF and AFRS outcomes.

Ethics and dissemination The TAILOR study was approved by local ethics boards in Barcelona (CPMP/ICH/135/95) and Medical Research Ethics Committee Oost-Nederland (NL86346.091.24). Patients will be included after providing informed consent. Study results will be presented in peer-reviewed journals and at global conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ TAILOR investigates potential predictors of atrial fibrillation (AF) in a population of all strokes, not only those of undetermined aetiology.
⇒ TAILOR provides longitudinal multicentre neuroimaging and clinical follow-up data of patients after AF-related stroke.
⇒ TAILOR will evaluate the use of advanced digital twin-based AI models for i) improved detection of AF, ii) enhanced understanding of AFRS aetiology and iii) more accurate prediction of stroke outcomes (eg, at 3 months).

INTRODUCTION

Atrial fibrillation (AF) is the most frequent cause of cardioembolic stroke. Up to 25% of all ischaemic strokes can be attributed to AF, either previously known or detected during diagnostic workup after a stroke.[1] Few studies have estimated the percentages of 5–15% for the identification of AF after ischaemic stroke, with varying monitoring modalities.[2 3] In patients with no history of AF, it can be difficult to detect AF given its paroxysmal and asymptomatic occurrence. The Current European Stroke Organisation guideline recommends a minimum duration of 24 hours, although a longer duration of cardiac rhythmic monitoring is advised.[4 5] However, there are still many questions outstanding. First, the optimal maximal duration of monitoring for subclinical AF is uncertain. Second, many studies have focused on identifying subclinical AF in patients with a cryptogenic stroke, but not in patients with ischaemic stroke of presumed known cause, such as large artery disease and small vessel disease. These patients harbour the same risk factors for developing AF and a higher risk of recurrent stroke.[6] Therefore, searching for subclinical AF after any stroke is clinically relevant for optimising the treatment of stroke patients. Adequate identification of AF is essential as an anticoagulant treatment,

which is only given if AF is detected, and is highly effective for the prevention of ischaemic stroke recurrence.[4] This emphasises the need for adequate monitoring strategies for identification of AF to eventually reduce the incidence of AF-related stroke (AFRS) and stroke recurrence.

AFRS is typically associated with a greater stroke severity and fatality.[7 8] Moreover, AF is associated with the increased risk of cognitive decline and dementia after stroke.[9] Disability and cognitive impairment lead to reduced quality of life, increased dependency and greater caregiver burden. While brain network damage has been observed across various ischaemic stroke subtypes, cardioembolic strokes are radiologically characterised by larger lesion volumes, frequent cortical involvement, multiple territory infarcts, more white matter abnormalities and possibly more frequent silent ischaemia, leading to disruption of networks such as the default mode network (DMN) and motor networks.[10–12]

Prognostic scores are typically based on statistical regression models. However, factors like complex interaction between variables, repeated measurements, missing data and small datasets can limit transferability across different clinical settings. Artificial Intelligence (AI) techniques can incorporate a larger number of predictors and perform better than traditional logistic regression models.[13] In the context of AF and AFRS, AI can optimise patient-specific risk stratification and clinical decision-making across disease progression stages. When combined with the digital twin technology, it can facilitate precision medicine approaches.[14] Digital twins, in the context of healthcare, serve as virtual representations of individual patients, integrating diverse data sources (including clinical, biological and behavioural data) to simulate patient-specific physiology and disease trajectories. Emerging AI methods, combining novel biomarkers, clinical phenotypes, established risk factors and radiological features, will serve to define a 'digital twin' of the patients.[15–18] This technique will enable the development of personalised risk and outcome prediction models.

As part of the EU project TARGET (Health virtual twins for the personalised management of stroke related to AF, grant agreement: 101136244),[19 20] the TAILOR clinical observational study aims to (1) identify individuals at risk of developing AF, and those at risk of complications such as AFRS, (2) improve diagnostic and treatment algorithms for AFRS, (3) prospectively evaluate the use of developed digital twin-based AI tools for AF and AFRS prognostication and risk stratification. AI model development is conducted on retrospective TARGET datasets, and TAILOR data are used exclusively for validation.

METHODS AND ANALYSIS

Project status

Patient inclusion started in September 2024 at Radboud University Medical Centre and in March 2025 at Hospital del Mar Barcelona.

Study design

TAILOR study is a prospective multicentre observational cohort study in patients with an ischaemic stroke with neuroimaging confirmed diagnosis. This study will be conducted at two sites: Hospital del Mar Barcelona (Spain) and Radboud University Medical Centre (The Netherlands). The Ethics Committees in Barcelona (CPMP/ICH/135/95) and region Arnhem-Nijmegen (NL86346.091.24) approved the study, and all participants will be requested to sign an informed consent before participation.

Objectives

This study has the following three primary objectives: (1) to detect AF using prospectively collected cardiac monitoring data, (2) to investigate novel MRI markers of stroke outcomes in patients with AFRS and (3) to validate digital twin-driven AI models developed as part of TARGET project predicting AFRS diagnosis and stroke outcomes.

Study population

For **sub-study 1**, all consecutive patients with an image-based acute ischaemic stroke admitted from 1/9/2024 to 31/12/2027 to the stroke unit or seen at the outpatient transient ischaemic attack (TIA) clinic will be asked to participate in the study. The inclusion criteria are individuals aged 40 years and above, with radiological evidence of cerebral ischaemia and sinus rhythm at the first ECG performed at emergency room arrival. Potential participants are excluded if they have previously known AF, mechanical valve prostheses or require anticoagulant use.

For **sub-study 2**, we will recruit patients with AFRS, defined as an ischaemic stroke occurring in the context of either previously known AF or new-onset AF diagnosed at the time of the index stroke event. The inclusion criteria are age 40 years and above, with radiological evidence of cerebral ischaemia due to a mild to moderate AFRS (at discharge: National Institutes of Health Stroke Scale (NIHSS) scores from 1 to 15, and pre-stroke modified Rankin score (mRS) 0–2). The exclusion criteria are life expectancy lower than 3 months due to other pathologies, presence of neurological diseases or technical artefacts that may interfere with the extraction of radiological features, and previous severe cognitive impairment or other neurological diseases, unwillingness to undergo MRI, or contra-indication for MRI (e.g. pacemaker, pregnancy).

The **sub-study three** has been designed as a validation study. For this, we will retrospectively apply AI-based models to data from newly recruited patients to evaluate their performance for AF detection (same inclusion criteria as sub-study 1) and AFRS outcome prediction (same inclusion criteria as sub-study 2).

Sample size calculation

For **sub-study 1,** we plan to include 150 patients (50 patients/year) per centre, for a total of 300 patients (100 patients/year). Post-stroke AF prevalence is estimated

at 10–20% using different detection methods following stroke or TIA. Therefore, we anticipate including at least 30–60 stroke patients with AF, which will allow repeating the evaluation cycle of the digital twin-based AI models in case further optimisation is required to enhance their performance.

For **sub-study 2**, sample size calculations are based on fractional anisotropy (FA) values, a diffusion tensor imaging (DTI) parameter to evaluate the integrity of the white matter, derived from the FUTURE study.[21] The calculations were performed using G*Power, assuming a two-sided significance level of 5% and power of 95%. To detect a true difference in FA between patients with good and poor outcomes, we will need in total 100 patients per centre, which also includes accounting for attrition. This is based on the estimated effect size of 0.60 and allocation ratio of 3 (one poor outcome vs 2 good outcome patients). Patients will undergo at least two MRIs, resulting in a minimum of 400 neuroimaging studies.

For **sub-study 3**, we aim to recruit as many patients as possible during the development of AI-based models. Given the caseload at each centre, we anticipate including approximately 450 patients at each centre. We will design a survey and qualitative interviews addressed to health professionals and representatives of specific categories of patients to evaluate the applicability of the models and to design prospective randomised trials. In both cases, we will check the percentage of agreement between real and predicted stroke aetiology and outcome variables at the 3 month follow-up visit.

Measures

See figure 1 for an overview of all assessments per study visit.

Clinical assessment

Demographics, medical history, medication use, cardiovascular risk factors and clinical presentation are recorded based on electronic medical records and by interviewing participants at baseline. Height and weight are recorded to determine body mass index. Blood pressure is measured at baseline. Standard post-stroke diagnostics will be performed, including ECG at admission and blood sampling. The previous functional performance is measured using the mRS.[22] Acute stroke severity and symptoms are assessed with the NIHSS score.[23] The mRS will also be assessed during follow-up, preferably at 3 months and, if possible, repeated at 12 months. Secondary prevention treatment at discharge will be registered.

Cardiac analyses (sub-study 1)

If AF is not detected on admission, patients will undergo long-term cardiac monitoring using a portable patch-based monitoring system or a standard Holter. These devices will be placed either at the stroke unit admission or during follow-up and will be worn for 24 hours up to 7 days.

A standard echocardiogram will be performed, where applicable. Left ventricular function, left atrial dimensions and aortic valve function will be recorded.

Neuroimaging acquisition (sub-study 2)

- *Hospital del Mar Barcelona:* All images will be obtained in a 3T MRI machine (Philips Achieva 3.0T X-Series MRI System). We will obtain the following sequences: (1) 3D T1-weighted sequence; (2) 3D fluid-attenuated inversion recovery (FLAIR) sequence; (3) Axial T2-weighted sequence; (4) Axial T2* Gradient Echo sequence; (5) Susceptibility Weighted Imaging (SWI)

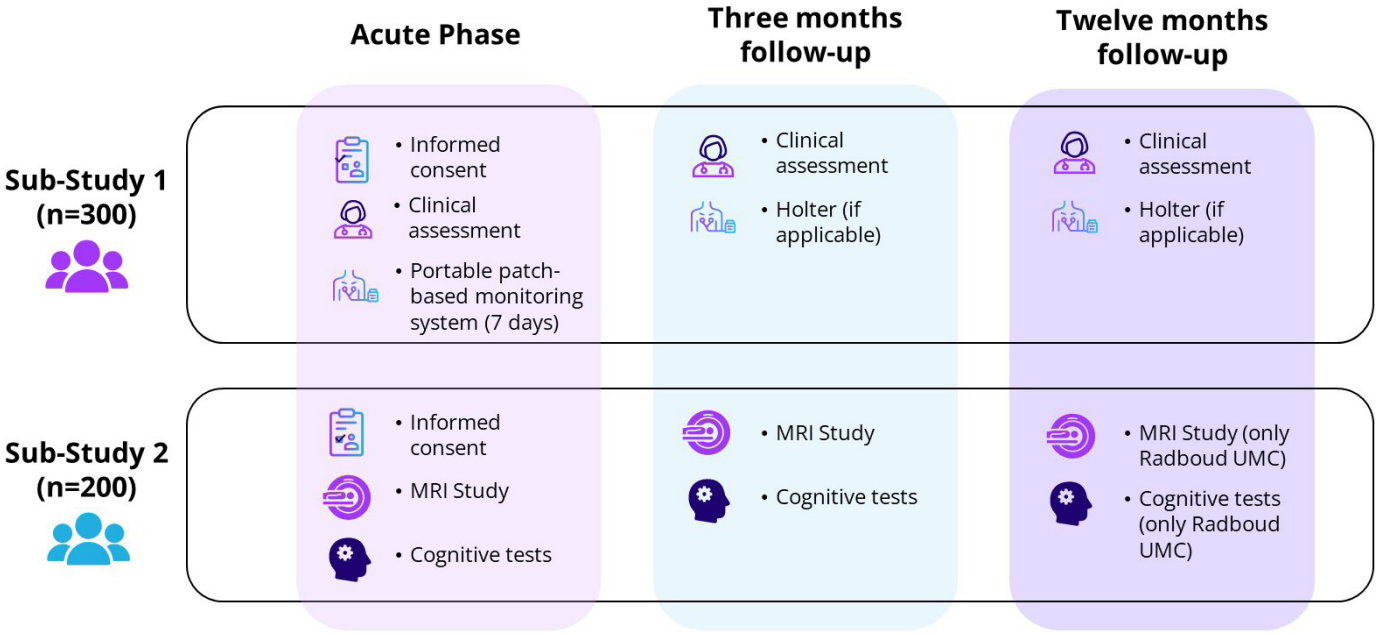

Figure 1 Study design. The figure represents the tests and modalities obtained at each visit.

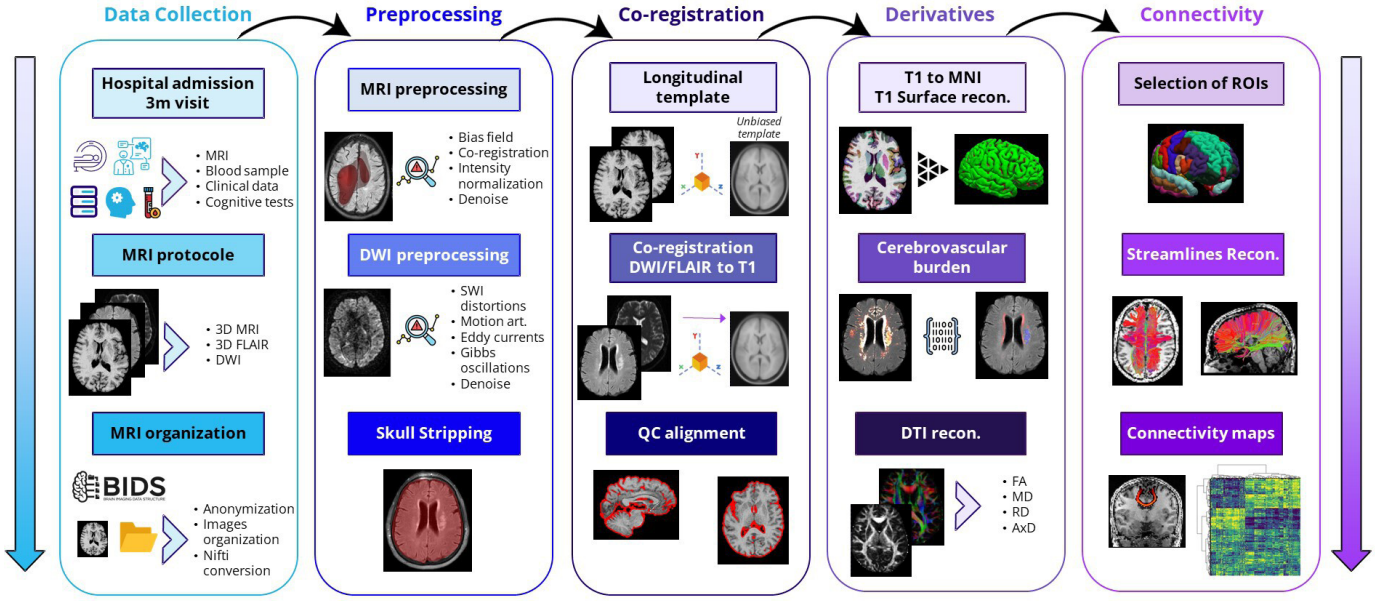

Figure 2 Neuroimaging protocol. Parts from this figure contain icons made by photo3idea_studio, kmg design, HAJICON, prettycons and Freepik from www.flaticon.com. AxD, axial diffusivity; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; FLAIR, 3D fluid-attenuated inversion recovery; MD, mean diffusivity; MNI, Montreal Neurological Institute; RD, radial diffusivity; ROI, region of interest; SWI, susceptibility weighted imaging.

and (6) Multi-Shell Diffusion-Weighted Imaging (DWI).

- *Radboud University Medical Centre:* All images will be obtained in a 3T MRI machine (Siemens Magnetom Trio, Erlangen, Germany). The imaging protocol includes: (1) 3D T1-weighted sequence (MP2RAGE); (2) 3D FLAIR sequence; (3) T2-weighted sequence; (4) Quantitative Susceptibility Mapping (QSM) and (5) Multi-shell DWI.

For a more detailed MRI protocol, see online supplemental material.

Neuroimaging protocol (sub-study 2)

Neuroimaging data will be acquired at hospital admission and at the 3 month follow-up. Additionally, in Radboudumc, imaging will also be performed at 12 months. All images will be anonymised and organised according to the BIDS (Brain Imaging Data Structure) standard.

The neuroimaging protocol is summarised in figure 2. In brief, structural T1-weighted and FLAIR images will undergo bias-field correction, spatial normalisation and co-registration. DWI data will be pre-processed to remove noise and correct for biases such as eddy currents and head motion. All imaging sequences will be co-registered to T1 space. At each time point, we will extract the following structural metrics: cortical thickness and white matter hyperintensity (WMH) burden. To assess brain connectivity, DTI will be reconstructed to derive median values of mean diffusivity (MD), FA and radial diffusivity (RD). Additionally, connectivity maps will be generated at both baseline and follow-up, enabling longitudinal analysis of brain network changes.

Neuropsychological assessment (sub-study 2)

Extensive neuropsychological assessment will be performed at acute phase, 3 months follow-up (at Hospital del Mar Barcelona and Radboud University Medical Centre) and 12 months follow-up (at Radboud University Medical Centre).

Hospital del Mar Barcelona:

1. Cognitive outcome: Montreal Cognitive Assessment (MOCA)[24]
2. Psychological outcome: ESD-SODS[25]
3. Functional outcome: Barthel Index and Quality of Life test (EQ-5D).[26 27]

Radboud University Medical Centre:

1. Cognitive outcome: MOCA, Rey Auditory Verbal Learning Test, Stroop Test, Rey Complex Figure Test, Brixton Spatial Anticipation Test, Symbol Digit Modalities Test, Fluency Test, Star Cancellation Test, Short Token Test, Digit Span (WAIS-IV) and Emotion Recognition Test.[24 28–37]
2. Psychological outcome: Hospital Anxiety and Depression scale (HADS), Subjective Memory Complaints, Apathy Motivation Index, CIS20R and SF-12.[38–42]
3. Functional outcome: IADL, EQ-5D and SIS 3.0.[27 43 44]

Validation of digital twins

As part of the data analysis strategy in TAILOR, we will evaluate the performance and clinical relevance of digital twin-based AI models developed within the TARGET project. These patient-specific computational models are designed to support predictive, personalised medicine by simulating individual health trajectories and informing clinical decision-making beyond current standards of care. The digital twins developed in TARGET are multi-organ

and multi-scale, integrating data across various biological and temporal dimensions. These include the genomic layer (eg, genetic predispositions), cellular layer (eg, cardiac electrophysiology), organ level (eg, heart and brain function) and exposomic factors (e.g. lifestyle, treatments and physical activity). By combining these layers, the models allow in-silico exploration of disease mechanisms, risk stratification, therapy planning and outcome prediction.

Within TARGET, model development is performed exclusively on retrospective datasets held by the consortium partners; TAILOR data are not used for model training. In TAILOR, we will assess and validate these TARGET-developed models using clinical outcomes collected during the study, focusing on AF detection (sub-study 1) and prognosis after AFRS (sub-study 2); sub-study three is explicitly designed as a validation study applying the AI models to newly recruited patients. Validation analyses will be conducted using temporal and centre-stratified splits to examine performance and transportability across settings.

The planned sample for sub-study 1 (n=300 across two centres) is expected to yield approximately 10 to 20 per cent AF detection (about 30 to 60 AF positive cases). This event count supports repeated validation cycles, for example, an initial temporal split followed by confirmatory temporal and centre stratified analyses. If optimisation is indicated, parameters will be updated only on retrospective TARGET datasets, and the updated model will then be revalidated on a fresh TAILOR split, which preserves independence and prevents data leakage.

In TARGET, the data-driven digital twins will be used to develop causal AI-based models, which will be assessed and validated in TAILOR using clinical outcomes collected during the study. Specifically, we will examine their predictive performance in relation to AF detection, AFRS aetiology and stroke prognosis. This evaluation will provide critical insight into the utility of digital twin technologies in real-world clinical settings and their potential to enhance decision-making and enable more personalised, effective care for patients along the AFRS pathway.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting or dissemination plans of this study due to its early, infrastructure-focused nature. However, as part of TARGET, a dedicated work package has been established for stakeholder engagement, ensuring that patients and healthcare professionals will be actively involved in the development of decision support tools in future stages.

ETHICS AND DISSEMINATION

Ethical approval has been obtained from the local ethics boards in Barcelona (CPMP/ICH/135/95) and Medical Research Ethics Committee Oost-Nederland (NL86346.091.24). The study will be conducted in accordance with the principles of the Declaration of Helsinki, the conditions and principles of Good Clinical Practice and the applicable local regulatory requirements and laws. Data curation and management will be conducted in compliance with local protection laws. Data will be stored on secure, access-controlled servers, and will be pseudonymised to ensure confidentiality. Access to the data will be restricted to authorised study personnel only. Results of the study will be disseminated through publication in peer-reviewed scientific journals and presentation at international conferences.

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Collaborators TARGET Consortium.

Contributors EGS, JJ-B, JJ-C, APG, AT, EJvK and TJFtC set up the study at Hospital del Mar Barcelona (Spain) and Radboud University Medical Centre (The Netherlands) respectively, coordinated recruitment and data collection, and drafted the manuscript. TJFtC provided expertise in cardiology. FJAM and BBM provided expertise in neuroimaging. SOM provided expertise in artificial intelligence and development of digital twin modelling. AT and EGS are the principal investigators. AT is the guarantor of this study at both sites. All authors reviewed and revised the manuscript for intellectual content and approved the final manuscript.

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