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Multicentre and Prospective Approach to Early Diagnosis of Atrial Fibrillation, Silent Stroke, and Cognitive Impairment in High-Risk Patients: The PREFA-TE Trial.

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Complete List of Authors:	Hernández-Pinilla, Alba; Institut Catala de la Salut, Primary Health Care Centre Reus 2 (CAP Sant Pere), Primary Care Service Camp de Tarragona; Rovira i Virgili University, Biomedicine Doctoral Programme, Campus Tarragona Clua-Espuny, Jose-Luis; Institut Catala de la Salut Gerencia Territorial Terres de l'Ebre, Primary Health Care Centre Tortosa 1-Est; Institut de Recerca en Atenció Primària Jordi Gol, Unitat de Suport a la Recerca Terres de l'Ebre Satué-Gracia, EVA; Institut Catala De La Salut, Primary Care Service Camp de Tarragona; Institut de Recerca en Atenció Primària Jordi Gol, Unitat de Suport a la Recerca Camp de Tarragona-Reus Pallejà-Millán, Meritxell; Institut de Recerca en Atenció Primària Jordi Gol, Unitat de Suport a la Recerca Camp de Tarragona-Reus Martín-Luján, Francisco M.; Institut Catala de la Salut, Primary Care Service Camp de Tarragona; Institut de Recerca en Atenció Primària Jordi Gol, Unitat de Suport a la Recerca Camp de Tarragona-Reus PREFATE, study-group; Institut de Recerca en Atenció Primària Jordi Gol,
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ABSTRACT

Background: Atrial Fibrillation (AF) is the most common type of cardiac arrhythmia. Future estimations suggest an increase in the global burden of AF greater than 60% by 2050. Numerous studies provide growing evidence that AF is not only associated with stroke but also with cognitive impairment and dementia.

Aim: The main goal is to assess the impact of the combined use of cardiac rhythm monitoring devices, echocardiography, biomarkers, and neuroimaging on the early diagnosis of AF, silent strokes, and cognitive decline, in subjects at high–risk of developing AF.

Methods and analysis: Two-year follow-up of a cohort of individuals aged 65-85 years at high risk for AF, with no prior diagnosis of either stroke or dementia. The study involves baseline echocardiography, biomarkers, and neuroimaging, yearly cardiac monitoring, and semi-annual clinical assessments. Different parameters from these tests will be analysed as independent variables. Throughout the study period, primary outcomes: new diagnoses of AF, stroke, and cognitive impairment, as well as any clinical and therapeutic changes, will be registered. A first descriptive and bivariate statistical analysis, appropriate to the types of variables, will be done. The information obtained from the data analysis will encompass adjusted risk estimates along with 95% confidence intervals. Event risk predictions will rely on multivariate Cox proportional hazards regression models. The evaluation of predictive model performance will be conducted through the utilization of ROC curves for AUC calculation. Additionally, time-to-event analysis will be performed using Kaplan-Meier curves.

Ethics and dissemination: This study protocol has been reviewed and approved by the Independent Ethics Committee of the Foundation University Institute for Primary Health Care Research-IDIAP Jordi Gol(expedient file 22/090-P). The authors plan to disseminate the study results to the general public through various scientific events. Publication in open-access journals and presentations at scientific congresses, seminars, and meetings is also foresee.

Trial registration number: ClinicalTrials.gov Identifier: NCT05772806

Keywords: atrial fibrillation; arrhythmia; prevention; public health.

Strengths and limitations of this study

- This multicentre study contemplates the use of new technologies and criteria (and their combinations) in a primary care scenario. This innovative design could pose data acquisition challenges, and some participants may need the help of family or caregivers for proper monitoring.
- The longitudinal prospective nature of the study design will allow time-to-event analysis, in order to estimate more precisely the outcomes risk.
- The use of a novel algorithm will allow selecting a high-risk population to analyse sufficient events with a relatively small sample and follow-up period. However, for this reason, the applicability of the results to a lower-risk population cannot be guaranteed.
- Due to the outpatient setting, heterogeneity in monitoring adherence and proficiency in device usage is expected, as these factors will depend on patient engagement. Nevertheless, this variability will be taken into consideration during the analysis
- Few proportion of missing data and losses in follow-up are expected, like in all longitudinal studies; the use of data imputation methods at the analysis stage shall be considered.

Introduction

In Europe, the number of ischemic strokes related to atrial fibrillation (AF) among people aged ≥80 years will triple (2010-2060). In addition to this increase in incidence, the socioeconomic gradient in both the age of diagnosis and the burden of comorbidity is widening [1-3]. Ischemic strokes and AF, which are interlinked and have common complex pathways, are becoming a double epidemic, especially among older persons, with significant health implications, increased disability, and a great socio-economic burden for society. Together with the well-established relationship among AF and ischemic strokes, there is growing evidence supporting the association between AF and cognitive impairment, and dementia [4-10]. Furthermore, in 24% of patients with a stroke episode, a previously unknown AF is detected [11], with a higher risk of new cognitive impairment diagnoses or worsening of pre-existing ones, heart failure, sudden death, and cardiovascular morbidity [12-14]. Early detection of AF is crucial because it enables healthcare providers to implement appropriate management strategies, such as anticoagulation therapy, to reduce the risk of recurrent strokes and other associated complications. However, despite this evidence, there is very limited research regarding intervention in high-risk individuals without a known diagnosis of AF.

Cardiac monitoring for early detection of AF

Various risk scales have been proposed to identify patients at high risk, for whom monitoring would facilitate early detection of AF [15-21]. The electrocardiogram (ECG) and machine learning classifiers provide valuable insights that can significantly enhance the identification of AF in patients with embolic stroke of undetermined source [22,23]. Prolonged monitoring using devices like Holter monitors, implantable loop recorders, or mobile cardiac telemetry can capture intermittent AF episodes that might go unnoticed during a brief in-office ECG [24]. Emerging screening tools, including smartphone apps and smartwatches, are rapidly advancing for the detection of AF, particularly in high-risk patients. These innovations hold the potential to enhance AF prediction and improve stroke prevention significantly [23-25].

Brain conditions and AF

Silent strokes are associated with the presence of AF irrespective of its subtype [26]; they are asymptomatic in the majority of cases but have been detected in up to 22% of studies employing computed tomography scans and as high as 44% using Magnetic Resonance

Imaging (MRI) [27]. It is possible to identify patterns in brain lesions among patients who have had an ischemic stroke and then utilise these patterns to predict the probability of experiencing a first episode of AF [28].

At the same time, silent brain infarcts have been associated with progressive cognitive dysfunction [29]. Cognitive impairment is notably higher in women [20], and the risk of Alzheimer's dementia is already elevated by 30% in individuals with AF [30].

The role of biomarkers

Several biomarkers have been associated with brain lesions [31]. In the case of dementia and cognitive impairment, various investigations are underway with the goal of identifying potential biomarker profiles for both early diagnosis and disease progression monitoring [32]. However, challenges persist in determining their cost-effectiveness and applicability in clinical practice [33]. A recent publication has demonstrated the cost-effectiveness of integrating biomarkers into stroke risk stratification scales for patients with AF [34]. Furthermore, combining parameters derived from images and biomarkers could improve the predictive value for identifying patients at risk of suffering a stroke or developing dementia. However, the current understanding of the predictive value and applicability, particularly in primary care, of combining plasma biomarkers and radio imaging patterns with clinical variables in the stratification of AF, stroke, or dementia remains unknown.

Echocardiography, AF, cerebrovascular disease and cognitive impairment

The echocardiographic features of AF have predictive value for cognitive assessment outcomes. Left atrial dysfunction, rather than its size, has shown correlations with the risk of dementia [35] and cerebrovascular ischemic events [34-39]

Although its suitability for clinical practice remains unproven, primarily due to the absence of prospective randomized studies, certain research indicates that incorporating parameters of atrial cardiopathy alongside conventional algorithms may potentially improve risk stratification for both ischemic stroke and AF [40].

The need for an early diagnosis of AF

Currently, there is a lack of evidence regarding the outcomes associated with early diagnosis of AF and potential vascular comorbidities before its formal diagnosis. This

entails utilising a combination of high-risk clinical criteria, echocardiography, MRI, and monitoring in patients without a prior AF diagnosis.

Thus, the main objective of present study was to determine the impact of the combined use of cardiac rhythm monitoring devices, biomarkers, echocardiography, and MRI on the early detection of AF, silent strokes, and cognitive decline in subjects at high risk of developing atrial fibrillation.

Methods and analysis

Study design and setting

This is a multicentre, prospective study, which will follow a cohort of patients between 65-85 years old at high risk of AF for two years.

Participants will be recruited from the usual consultations in six primary healthcare (PHC) centres managed by the Catalan Health Institute, and located in Tarragona region (South Catalonia, Spain).

Study population

Persons assigned to any of the study PHC centres who meet the following conditions will be invited to participate (**eligibility criteria**):

- High risk of AF, according to the risk score validated in the AFRICAT study. This scale considers the following variables for risk calculation: sex, age, weight, cardiac rate, and CHA2DS2-VASc score [15],
- CHA_2DS_2-VASc score ≥ 2, and
- Ability to use a smart phone (or at least the caregiver).

Patients with the following conditions will be excluded (**exclusion criteria**):

- Previous diagnosis of AF,
- Previous diagnosis of stroke,
- Severe cognitive impairment, with a score on the Global Deterioration Scale (GDS) ≥ 3,
- Severe functional impairment, with a Barthel score ≤ 60, or modified Rankin score ≥ 4,
- Active Anticoagulant treatment at the inclusion,
- Vital prognosis less than one year, or
- Pacemaker carriers

Follow-up

A two-year follow-up after study starting (2023) is planned, and abandonment of the follow-up will occur in cases of death, transfer to another PHC centre, or upon the patient's expressed will.

Determinations (baseline and follow-up assessments)

Once during study period

At first, all included patients will undertake echocardiography, laboratory biomarkers, and cranial MRI. These tests will detect the main conditions associated with a major risk of presenting the primary outcomes of the study.

From the echocardiogram, signs of morphological or functional dysfunction of the left atrium will be recorded as predictors of AF, such as size and volume, strain, and ejection fraction of the left atrium, as well as valvular dysfunctions.

In the cranial MRI, signs of chronic ischemia or atrophy, likely related to cognitive impairment, will be examined for, including microinfarts, enlarged ventricles, white matter hyperintensities (along with Fazekas score), microbleeds, and perivascular dilations.

Specific biomarkers that will be determined are: N-terminal pro-brain natriuretic peptide (NT-proBNP), angiopoietin-2 (Ang2), fibroblast growth factor-23 (FGF-23), bone morphogenetic protein(BMP)-10, and troponin T. All of them are presumptive markers of cardiac or cerebral damage or dysfunction.

Every year

Cardiac monitoring (during 14 days) for active search of AF, with two different electronic devices: the FibriCheck App® [41] and the Fitbit® bracelet [42].will be performed at the beginning and one year after inclusion.

Every six-months

Electrocardiogram (ECG) and complete clinical assessment will be done to register risk factors and comorbidities, new cardiovascular events, cardiovascular parameters (arterial pressure, heart rate...), and scores at different tests related to functional status (Barthel or Rankin), cognitive function (GDS, Mini Mental State Examination, and AF/stroke risk

(CHA2DS2-VASc score). Changes in drug prescriptions (according to electronic registers) at baseline and changes during study period will be also recorded biannually.

Figure 1 shows an outline of the most important assessments during the baseline visit and study follow-up.

Data collection and management

Study data will be recorded from tests and evaluations performed on participants: anamnesis (including scales), physical examination, laboratory tests, and reports provided by specialists (available at computerised clinical records of hospital centres [e-SAP]). The echocardiogram and cranial MRI data will be recorded from the reports made by the specialists who will carry out the tests: a cardiologist and a radiologist. Data registered in the electronic PHC records (e-CAP) of participants will also be collected. Therapeutic (pharmacological) changes will be registered from the Integrated Electronic Prescription System (SIRE).

Finally, heart rate monitoring data will be collected through the electronic devices' registers.

An ad hoc data collection questionnaire will be created to register and store all study variables. The electronic questionnaire will be available at a specific application, and only accessible from the corporate Intranet of the Catalan Health Institute. The data will remain stored for five years, and can only be recorded and accessed by study's researchers using personal passwords.

Primary outcomes

- Time to detection of AF. To diagnose the AF, confirmation by a 12-lead ECG or Holter will be required [43,44].
- Time to new stroke diagnosis. Confirmation through a neuroimaging test or neurologist assessment will be required.
- Time to new cognitive impairment or dementia diagnosis. Changes in cognitive function will be assessed through scores at the GDS. Dementia diagnosis will be established with scores ≥ 4. The diagnosis shall also be made if there is a suspicion confirmed by a neurologist's evaluation.

- Time to death (if it occurs).

Sample size calculation

To estimate the prevalence of atrial fibrillation observed with a difference of 0.1 units compared to the reference population (0.07), a sample of 148 individuals will be required. An alpha risk of 0.05 and a beta risk of 0.20 are accepted, and a loss rate of 15% has been estimated.

Statistical analysis

A descriptive analysis of the study variables will be carried out, providing absolute and relative frequencies for categorical variables and mean and standard deviation (or median and interquartile interval for variables with non-normal distributions, according to the Shapiro-Wilk test) for continuous variables. For bivariate analysis (comparing people with study outcomes with people without) the chi-square test, or exact Fisher test if applicable, will be used to compare categorical variables; the Student t test, ANOVA or Mann-Withney/kruskal-Wallis for non-normal distributions will be applied to compare two or more continuous variables.

The information extracted from data analysis will include adjusted risk estimates and 95% confidence intervals. The predictions of study outcomes risk will be based on multivariate Cox proportional hazards regression models. ROC curves and AUC (Area Under the Curve) will be used to evaluate the predictive power of the models. The analysis of time to event will be conducted using Kaplan-Meier curves.

The statistical package R (R Foundation for Statistical Computing, Vienna, Austria; version R 3.4.3 for Windows) will be used for all analyses. Statistical significance shall be established at p <0,05.

Ethics and dissemination

This study protocol has been reviewed and approved by the Independent Ethics Committee of the Foundation University Institute for Primary Health Care Research-IDIAP Jordi Gol, expedient file 22/090-P.

The authors plan to publish the results from this study in open access international and national journals as well as to present them at scientific congresses, seminars and

meetings. Additionally, it is planned to explain the results and their clinical applicability to the general public in different scientific dissemination events.

Discussion

There is a need for interventions that enable early diagnosis and management of AF to mitigate the social burden resulting from both the condition itself and its associated diseases or complications. These interventions should also take into account and aim to minimise inequities. It have been demonstrated that implementing interventions during the early stages of the condition with effective strategies could yield significant benefits for healthcare systems [3,45-47].

Numerous methods have been proposed for detecting undiagnosed AF. However, persistent barriers exist that go beyond individualised person-centered interventions and health promotion efforts [41-48].

The experts at the consensus conference recommend systematic screening for all individuals aged ≥75 years and suggest that systematic screening may also be considered for people aged 65-74 years who have additional risk factors, elevated biomarkers, or a positive alert from digital devices [43-44,49]. Furthermore, the first practical guide on the use of digital devices for monitoring heart rhythm and frequency provides clarification on which technologies to employ and under what circumstances [50]. Nevertheless, despite clear recommendations in the European Stroke Organisation-ESO Guidelines following a stroke episode, significant gaps in primary detection and ambulatory monitoring persist [51].

The results of this study could provide new information about the added benefits that the combination of different strategies, each of which has individually shown efficacy, can bring in the early diagnosis of AF. It is also expected that this early detection will be followed by appropriate therapeutic changes, resulting in a reduction in the incidence of both ischemic stroke and cognitive impairment or dementia.

Trial registration number

ClinicalTrials.gov Identifier: NCT05772806

Funding statement

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(expedient file SLT/21/000027). The study protocol has undergone full external peer review by the funding body as part of the peer review process. This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Patient and public involvement

The research team have not considered patient or public involvement in the design of the present protocol. However, it is planned to share the main results and, in particular, their possible applicability with patient associations and elderly representatives to define the best strategy for disseminating and transferring to clinical practice these results.

Competing interests statement

All authors declare no competing interest.

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Author's contributions:

J-L.C-E. conceived the study and got the funding; J-L.C-E., F.M-L., E.S-G. and M.P-M. provided the methodology; A.H-P. wrote and prepared the original draft; J-L.C-E., E.S-G. and F.M-L. reviewed and edited the writing. All authors have read and approved the final manuscript.

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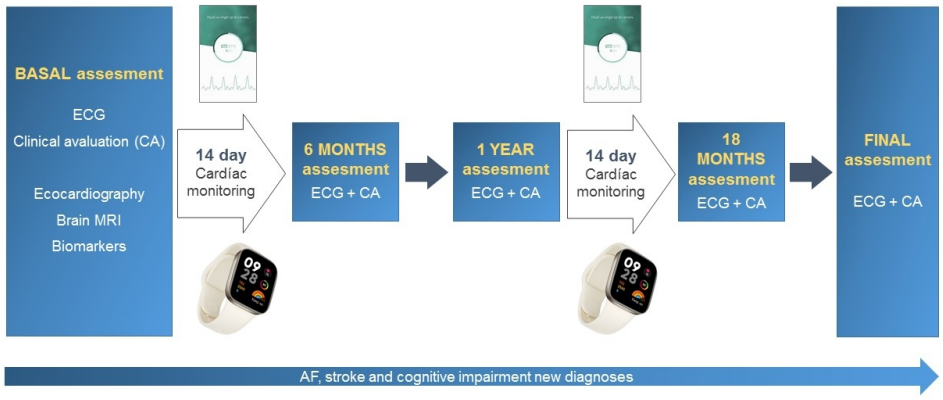
Figure 1. Main evaluations during study follow-up



ABBREVIATIONS. ECG: Electrocardiogram; MRI: Magnetic Resonance Imaging; CA: Clinical assessment.
Cardiac monitoring is performed using two heart-monitoring devices: the FibriCheck App® [reference 42] and the Fitbit® bracelet [reference 43].

FIGURE 1

338x190mm (96 x 96 DPI)

PREFA-TE study investigators

A.Panisello-Tafalla, J. Clua-Queralt (*Primary Health* Care [PHC} Centre Tortosa est); A. Grau-Roche , T. Forcadell-Arenas, KV. Yañez-Cabrera (PHC Centre Tortosa oest); E. Muria-Subirats , EM. Lloren-Insa ; MJ. Forcadell-Peris (PHC Centre Amposta); G. Batll-Escolies (PHC Centre L'Aldea); S. Sancho-Maigi (PHC Centre Camarles); T. Miralles-Saura (PHC Centre L'Ampolla); A. Quilez-Recio, G. Lucas-Noll, C. Calduch-Noll (PHC Centre La Rapita); C. de Diego-Cabanes, A. Diaz-Vilarasau (PHC Centre Salou); D. Ribas-Seguí, C. Rojas-Molins (PHC Centre Sant Pere i Sant Pau); D. Gentille-Lorente, I. Lechuga-Duran (*Cardiology Department; Verge de la Cinta Hospital* , Tortosa); M. Guillen-Marzo, LA. Anmad-Shihadeh, A. Bardají-Ruiz (Cardiology Department*, Joan XXIII Hospital.* Tarragona)*;* JA. Izuel-Navarro, AM. Viveros-Castaño (*Institute of Diagnostic Imaging* [IDI} Terres de l'Ebre); M. Rovira-Beltran, E. Salvado-Geli, A. Samitier-Pastor (IDI Camp de Tarragona); P. Delgado-Martínez, A Penalba-Morenilla (VHIR, Barcelona).