NEW PATHWAYS FOR EARLY IDENTIFICATION OF ATRIAL FIBRILLATION IN THE COMMUNITY

Juan Ballesta Ors

UNIVERSITAT ROVIRA i VIRGILI

2020

DOCTORAL THESIS

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Facultat de Medicina i Ciències de la Salut. Escola Doctorat

New pathways for early identification of atrial fibrillation in the community

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2020

Approved by CEIM IDIAP Jordi Gol
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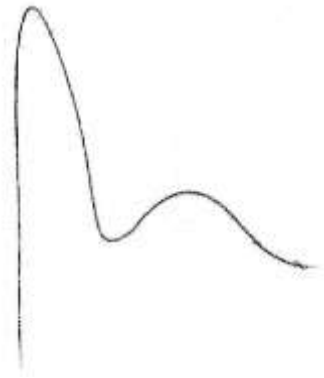
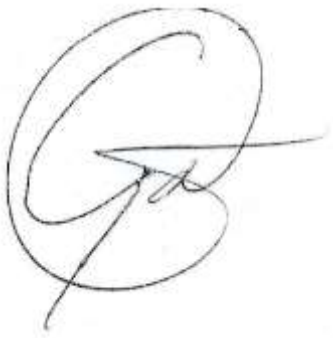
UNIVERSITAT ROVIRA i VIRGILI

WE STATE that the present study, entitled “New pathways for early identification of atrial fibrillation in the community”, presented by Juan Ballesta Ors for the award of the degree of Doctor, has been carried out under our supervision at the Department Biomedicine of this university.

Tortosa, 30/07/2020

Doctoral Thesis Supervisor/s

Josep Maria Alegret Colomé José Luís Clua Espuny Delicia Inés Gentille Lorente

Appreciations

To my mother and father, without whose constant support and unconditional love, I would never have become the person I am; to my brothers, who have encouraged me to continue all these years; to my girlfriend, for always trusting my decisions; and to my thesis supervisors, for the training they have given me, for their contributions to my improvement and for their qualitative monitoring, especially Dr. Clua, my Family Medicine mentor and without whose firm motivation I would not have considered this project.

To the inhabitants of Terres de l'Ebre, who will always have a place in my heart.

This doctoral thesis consists of a compendium of articles published in international journals with considerable impact factors and important quartiles. The first article was published in *Family Practice,* with an impact factor of 1.986 and a 2nd quartile, and the second article in *Frontiers in Neurology,* with an impact factor of 2.635 and a 1st quartile.

This thesis is also part of an Industrial Ph.D. grant (code Q9350003A by AGAUR [Agència de Gestió d'Ajuts Universitaris I de Recerca] in 2018). An Industrial Doctorate Plan is a strategy of the Government of the Generalitat of Catalonia, in collaboration with public and private universities, with the objectives of contributing to the competitiveness and internationalization of Catalan industries, retaining talent and placing doctoral students in positions to develop R + D + I projects in companies. It was developed at the Institut Català de la Salut, which is the largest provider of the Catalan Health Service, an insurer of universal health coverage in Catalonia.

AGAUR's report

Agència de Gestió d'Ajuts Universitaris i de Recerca
AGAUR

Primera Resolució parcial definitiva de la convocatòria de doctorats industrials (DI) 2018.

Fets

1. La Resolució EMC/307/2017, de 17 de febrer (DOGC núm. 7324 – 8.3.2017) aprova les bases reguladores de doctorats industrials (DI).

2. La Resolució EMC/591/2018, de 26 de març, modifica la Resolució EMC/307/2017, de 17 de febrer, per la qual es modifica la Resolució EMC/307/2017, de 17 de febrer, per la qual s'aproven les bases reguladores de doctorats industrials (DI).

3. La Resolució EMC/964/2018, d'11 de maig (DOGC núm. 7622 – 18.5.2018), obre la convocatòria de doctorats industrials (DI) 2018 (ref. BDNS 398838).

4. En data 25.6.2018 es publica al DOGC núm. 7649 la Correcció d'Errades a la Resolució EMC/964/2018, d'11 de maig.

5. El 17 de juliol de 2018 es reuneix la comissió de selecció de la convocatòria de doctorats industrials (DI) 2018.

Fonaments de dret

1. És d'aplicació la Llei 38/2003, de 17 de novembre, general de subvencions i el Reial decret 887/2006, de 21 de juliol pel qual s'aprova el Reglament de la Llei 38/2003, de 14 de novembre.

2. El capítol IX del Decret legislatiu 3/2002, de 24 de desembre, pel qual s'aprova el Text refós de la Llei de finances públiques de Catalunya, regula el règim jurídic de les subvencions i les transferències de la Generalitat de Catalunya.

3. La base 15.1 de la Resolució EMC/307/2017, de 17 de febrer, preveu que es podran dictar resolucions parcials definitives en les dates que es faran constar a la convocatòria corresponent.

4. L'article 5.2 de la Resolució EMC/964/2018, d'11 de maig, estableix el següent:

   " Es preveu dictar tres resolucions parcials definitives en les dates següents:

- Primera resolució parcial: primera quinzena de juliol de 2018.
  [...]"

5. La base 11 de la Resolució EMC/307/2017, de 17 de febrer, estableix que l'òrgan instructor dels expedients és el director executiu o directora executiva de l'AGAUR. La resolució de concessió correspon al Consell de Direcció de l'AGAUR i, per delegació, a la CEAR o la persona que n'ocupa la presidència, i a la CEAU o la

Agència de Gestió d'Ajuts Universitaris i de Recerca
AGAUR

persona que n'ocupa la presidència, segons l'acord del Consell de Direcció de 5 de desembre de 2002 (Resolució UNI/73/2003, de 14 de gener, DOGC núm. 3808, de 27.1.2003).

6. El president de la Comissió Executiva d'Ajuts Universitaris i el president de la comissió Executiva d'Ajuts de Recerca, en l'ús de les funcions que els han estat delegades pel Consell de Direcció de l'Agència, en sessió de 5 de desembre de 2002, i vista la proposta de resolució definitiva formulada pel director executiu de l'AGAUR de data 4 d'agost de 2018;

Resolen:

1. Concedir els ajuts que es detallen en el document adjunt: Sol·licituds Concedides, per un import de 1.493.088,00€ a càrrec de les partides 440.0001, 449.0001, 470.0001 i 482.0001 del pressupost de l'AGAUR per als anys 2018, 2019 i 2020, en el marc de la convocatòria de doctorats industrials (DI) 2018, en els termes que s'hi fan constar.

2. Sotmetre l'atorgament dels ajuts al compliment per part dels seus destinataris de les condicions i obligacions previstes a la Resolució EMC/307/2017, de 17 de febrer, per la qual s'aproven les bases reguladores de doctorats industrials (DI), a la Resolució EMC/591/2018, de 26 de març, que modifica la Resolució EMC/307/2017, de 17 de febrer, i a la Resolució EMC/964/2018, d'11 de maig per la qual s'obre la convocatòria de doctorats industrials (DI) 2018.

Contra aquesta resolució, que exhaureix la via administrativa, es pot interposar un recurs potestatiu de reposició davant el president de la Comissió Executiva d'Ajuts Universitaris i el president de la Comissió Executiva d'Ajuts de Recerca de l'AGAUR, en el termini d'un mes, a comptar des de l'endemà de la seva publicació al tauler electrònic de l'Administració de la Generalitat de Catalunya, o bé es pot interposar directament recurs contenciós administratiu davant el jutjat contenciós administratiu de Barcelona, en el termini de dos mesos, a comptar des de l'endemà de la seva publicació al tauler esmentat, de conformitat amb el que preveuen els articles 123 i 124 de la Llei 39/2015, d'1 d'octubre, del Procediment Administratiu Comú de les Administracions Públiques, i els articles 8, 14 i 46 de la Llei 29/1998, de 13 de juliol, reguladora de la jurisdicció contenciosa administrativa.

Signat a Barcelona.

P. d (Resolució UNI/73/2003, de 14 de gener, DOGC de 27.1.2003)

CPISR-1 C Josep Pallarès Marzal
Signat digitalment per CPISR-1 C Josep Pallarès Marzal
Ubicació: Barcelona
Data: 2018.09.12 10:55:11 +02'00'

El president de la Comissió Executiva d'Ajuts Universitaris
Josep Pallarès Marzal

Joan Gómez Pallarès
Barcelona
2018.09.10 12:59:37 +02'00'

El president de la Comissió Executiva d'Ajuts de Recerca
Joan Gómez Pallarès

Generalitat de Catalunya
Departament d'Empresa i Coneixement

ANNEX: Sol·licituds concedides

Núm. d'exp.	Empresa	CIF	Import atorgat empresa	Organisme de recerca	CIF	Import atorgat org. recerca	Identificació Candidat/a
2018 DI 001	Products & Technology S.L.	B65664013	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Flavio Palmieri
2018 DI 002	Cromogenia Units S.A.	A08012270		Universitat de Barcelona	Q0818001J	33.960,00 €	Sara Ruiz Castellar
2018 DI 003	Artificial Nature S.L.U.	B67067173	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Alfredo Martínez Cutillas
2018 DI 004	ORBITEL S.A.	A59361113		Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Jhoan Sebastián Rodrigues Tovar
2018 DI 005	Fundació Salut Empordà	G17029810	21.600,00 €	Universitat de Girona	Q6750002E	33.960,00 €	Álvaro Franquet Bonet
2018 DI 006	ITALSAN S.L.	B27492309		Universitat de Barcelona	Q0818001J	33.960,00 €	Josep Maria Ferrer Bruach
2018 DI 007	Espuña R&D, S.L.	B55222604		Institut de Recerca i Tecnologia Agroalimentàries	Q5455049B	33.960,00 €	Eva Ariadna Torres Baix
2018 DI 008	F. Iniciatives i+D+i	B62331160		Universitat Autònoma de Barcelona	Q0818002H	33.960,00 €	Rafael Gabriel Barahona
2018 DI 009	Institut Català de la Salut	Q5855029D		Universitat Rovira i Virgili	Q9150003A	8.472,00 €	Cristina Maria Martín Oriàe
2018 DI 010	Institut Català de la Salut	Q5855029D		Universitat Rovira i Virgili	Q9150003A	8.472,00 €	Jorgina Lucas Nell
2018 DI 011	Fundació el Solà	G43586262	21.600,00 €	Universitat Rovira i Virgili	Q9150003A	33.960,00 €	Cèlia Mallafré Balsells
2018 DI 012	Observatori del Tercer Sector i de la Societat Civil	G63349310		Universitat de Vic - Universitat Central de Catalunya	Q5802012H	8.472,00 €	Montserrat Fernández García
2018 DI 013	Biochemize S.L.	B65700163	21.600,00 €	Universitat Autònoma de Barcelona	Q0818002H	33.960,00 €	Miquel Canyelles Niño
2018 DI 014	Rhenus Logistics S.A.U.	A08213989	21.600,00 €	Universitat Oberta de Catalunya	G60667813	33.960,00 €	Sachin Tumkur Nataraj
2018 DI 015	Fundació Privada Educació Solidària Escola Pia	G61754362		Universitat Autònoma de Barcelona	Q0818002H	8.472,00 €	Mireia Gil Alcazar
2018 DI 016	Bio Sensing Solutions S.L.	B66508912	21.600,00 €	Universitat de Barcelona	Q0818001J	33.960,00 €	Jorge Verdú Añon
2018 DI 017	Institut Català de la Salut	Q5855029D		Universitat Rovira i Virgili	Q9150003A	8.472,00 €	Juan Ballesta Ors
2018 DI 018	3&Punt Solucions Informàtiques, SL	B63506869	21.600,00 €	Universitat Oberta de Catalunya	G60667813	33.960,00 €	Esa Pereira Gómez
2018 DI 019	Midtal Talentos SL	B55174205	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Carlos Andres Candelo Zuluaga
2018 DI 020	INTERQUIM S.A.	A08536476	21.600,00 €	Universitat Ramon Llull	G59069740	33.960,00 €	Álvaro Calviño Jiménez
2018 DI 021	RenAb Therapeutics, S.L.	B67210021	21.600,00 €	Universitat de Barcelona	Q0818001J	33.960,00 €	Sara Olivera Ardid
2018 DI 022	INDITEX	A15075062		Universitat Politècnica de Catalunya	Q0818003F	8.472,00 €	Francisco Beltagui Elder
2018 DI 023	AUDI Tooling Barcelona	B63243471	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Verónica Cabral Fernández
2018 DI 024	Isoquimen S.L.	B60640190		Universitat Autònoma de Barcelona	Q0818002H	8.472,00 €	Jose Antonio Badillo Vázquez
2018 DI 025	TALLERES A.R. S.A.	A58357104	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Lloreng Macià Cid
2018 DI 026	TAVIL-IND SAU	A17223116	21.600,00 €	Universitat de Girona	Q6750002E	33.960,00 €	Núria Barsà Paradell
2018 DI 027	Sedor Consulting, s.l.	B62076740		Universitat de Vic - Universitat Central de Catalunya	Q5802012H	8.472,00 €	David Reifs Jiménez
2018 DI 028	Instituto de Microcirugía Ocular IOS SL	B64261878		Universitat Oberta de Catalunya	G60667813	33.960,00 €	Silvia Herrera Hernández
2018 DI 029	Carethy E Commerce S.L.	B67129486	21.600,00 €	Universitat Oberta de Catalunya	G60667813	33.960,00 €	Francesc Font Cot
2018 DI 030	KOSTAL Elèctrica, S.A.	A58391822	21.600,00 €	Universitat Autònoma de Barcelona	Q0818002H	33.960,00 €	Byron Alexander Quezada Benalcázar
2018 DI 031	IED Europeo Di Barcelona S.L.	B80813959		Universitat Oberta de Catalunya	G60667813	33.960,00 €	Alessandro Marietti
2018 DI 032	Fundació Talela - VIOO Games Studio	G66065590		Universitat Oberta de Catalunya	G60667813	33.960,00 €	Carles Bonet Papell
2018 DI 033	Enlighting Technologies	B67033357	21.600,00 €	Universitat de Barcelona	Q0818001J	33.960,00 €	Adrià Huguet Ferran
2018 DI 034	CCE Montessori-Palau, S.A.	A17483653		Universitat de Vic - Universitat Central de Catalunya	Q5802012H	8.472,00 €	Aida Macià Gual
2018 DI 036	CONSELL COMARCAL DEL VALLÈS OCCIDENTAL	P5800007F	21.600,00 €	Universitat Autònoma de Barcelona	Q0818002H	33.960,00 €	Andrea Jover Pujol
2018 DI 037	Cromogenia Units S.A.	A08012270		Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Susana Torrelles Valle
2018 DI 038	SCYTL SECURE ELECTRONIC VOTING S.A.	A62604087	21.600,00 €	Universitat Politècnica de Catalunya	Q0818003F	33.960,00 €	Tamara Finogina
2018 DI 039	Abante & Pongkuppi SL	B62095914	21.600,00 €	Universitat de Barcelona	Q0818001J	33.960,00 €	Ander Sainz Loyola

Jordi Gol's ethical report

IDIAP Jordi Gol

INFORME DEL COMITÈ ÈTIC D'INVESTIGACIÓ CLÍNICA

Rosa Morros Pedrós, Presidenta del Comitè Ètic d'Investigació Clínica de l'IDIAP Jordi Gol.

CERTIFICA:

Que aquest Comitè en la reunió del dia 26/09/2018, ha avaluat el projecte ***Mejorando las estrategias para la prevención de impacto en la fibrilación auricular desconocida.*** amb el codi **P18/118** presentat per l' investigador/a **Josep Lluis Clua Espuny.**

Considera que respecta els requisits ètics de confidencialitat i de bona pràctica clínica vigents.

Barcelona, a 29/09/2018

0. Index

1. List of abbreviations

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AF: Atrial Fibrillation
CCP: Complex Chronic Patient
CI: Confidence interval
COPD: Chronic Obstructive Pulmonary Disease
CV: Cardiovascular
DOAC: Direct Oral Anticoagulants
EAP: Primary Care Team
ECAP: Computerized Clinical Record in Primary Care
ECG: Electrocardiogram
hAF: Holter monitoring
HF: Heart Failure
ICS: Catalan Health Institute
NCT: Number of Clinical Trial
NNS: Number Necessary to Screen
NT-proBNP: N-terminal pro hormone B-type natriuretic peptide
OAT: oral anticoagulant therapy
PC: Primary Care
uPAR: Urokinase Plasminogen Activator surface Receptor
vWF: Von Willebrand factor
WHO: World Health Organisation

2. List of tables and figures

2. List of tables and figures

Figures

Main text

Appendix

Tables

Appendix

3. Introduction

3. Magnitude of the problem:

3.1. Atrial Fibrillation Epidemiology

Atrial fibrillation (AF) is the most common sustained heart rhythm disorder [1]. It has become an epidemic condition that constitutes a serious public health problem with a heavy impact on sanitary costs. Its prevalence will increase in the coming decades due to an ageing population (in Europe, in the year 2060, it is estimated that the number of people suffering from AF will increase to 17.9 million) [1]. Both the population and proportion of older people are increasing: from 2012 to 2032, the populations of those 65–84 years old and over-85s are expected to increase by 39% and 106%, respectively. The risk of AF increases with age: about 1 in 200 people aged 50-59 have AF; this increases to almost 1 in 10 people over 80. However, evidence indicates that a large number of patients suffering from AF are being underdiagnosed and, thus, undertreated [2].

Accurate information on AF's prevalence in the general population is, therefore, not widely available. Some European countries have undertaken screening studies to estimate the proportion of the population affected. These studies reported rates in the general population ranging from 1.3% (UK, Italy) to 3.9% (Greece), with rates being highly dependent on age. Less data is available from Central and Eastern European countries. A pilot multicentric study (AFABE Study [3]) in the County of Terres de l'Ebre involved 1043 randomly selected patients older than 60 years of age. All of the patients underwent an ECG and different medical variables, such as $CHA_2DS_2VAS_C$ and HAS-BLED scores, international normalized ratio results and reasons for not receiving anticoagulant therapy, were observed and recorded. The study's various outcomes were: 1) the prevalence of AF increased with the patients' ages (1.2% in patients between 61 to 64 years old to 20.7% in those 85 years and older); 2) the prevalence of AF was higher in

male individuals (except in the group of 85 years and older); 3) the prevalence of hypertensive and diabetic patients was greater than that associated with other risk factors; the prevalence of AF indicated in the clinical history of the patients was 8.7%; 96.7% of the patients with a previous diagnose of AF had ≥2 $CHA_2DS_2VAS_C$ scores; 4) it was observed that the prevalence of previously undiagnosed AF was 2.2% (CI95% 1.3-3.1%); (5) and, among others, the percentage of patients diagnosed with AF that were not treated with anticoagulant therapy was 24.35% (mainly due to $CHA_2DS_2VAS_C$ scores <2 points, cognitive impairment and high risk of haemorrhaging). These results that were observed in our territory revealed the need to diagnose as many unknown AF cases as possible and treat those patients if indicated.

3.2. Risk of stroke and associated comorbidities

Evidence suggests that AF is one of the major causes of morbidity and cardiovascular mortality [4]. It increases death risk, congestive heart failure and the risk of systemic embolism, including stroke [5], and it is associated with a high risk of cognitive impairment, with or without a history of clinical stroke [6].

Studies in the general population [7] have also provided evidence that higher AF-risk is related to higher CHA_2DS_2VASc scores, higher stroke incidence and higher Pfeiffer scores, but the exact mechanisms are unclear. Structural and functional alterations of cerebral blood vessels have emerged as key correlates of conditions associated with cognitive impairment. In this way, targeting the stroke risk factors would not only reduce stroke, but also reduce cognitive impairment. Stroke and dementia are risk factors for each other and share some of the same, largely modifiable, risk and protective factors in asymptomatic individuals. Effective strategies for improvement in

the initial phases of the disease would have a massive beneficial impact on health care systems.

AF is often not diagnosed until after a stroke event and is not treated according to widely available, national, evidence-based guidelines. AF is estimated to increase the risk of stroke 3- to 5-fold and to be associated with around a quarter of all ischaemic strokes. Additionally, AF is associated with more severe strokes, leading to higher mortality and disability. AF is significantly more common in people who have had a stroke than in the general population. Reported prevalence rates are as high as 31-38%. Variation is also high both within countries and between studies with similar methodologies. Studies from Ireland[8], Iceland[9], Croatia[10] and Norway[11] reported that between a quarter to over half of AF diagnoses after stroke were unknown before. A recent meta-analysis also reported that 24% of stroke patients are newly diagnosed with AF after their strokes [11]. These reports again suggest a significant under-diagnosis of AF in the general population. Better detection rates of AF could lead to improved primary prevention. Over the last 25 years, the number of AF-related ischaemic strokes has trebled in adults over 80 years and is predicted to treble again by 2050.

Although the risk of AF-related stroke can be reduced by 64-70 % using oral anticoagulants [12], underutilization of this effective treatment and delayed diagnosis remain major obstacles. Around a quarter of patients have silent or asymptomatic AF [13] and up to 25% of patients with AF-related stroke only have this arrhythmia diagnosed at the time of the stroke. People with AF who suffer a stroke have greater mortality, more disability, more severe strokes, longer hospital stays and lower rates of discharge to their own homes compared to those without AF [14]. AF-related strokes are more likely to recur and fear of another stroke is likely to cause anxiety and affect quality of life (which cost 45 billion euros in 2015) [15]. Patients being newly admitted with stroke may

eventually lead to greater anguish for their families and larger health costs from extensive hospital assessment, including brain scans, admission to specialist stroke units and multidisciplinary specialist assessments from a range of healthcare professionals including physicians, physiotherapists, occupational therapists, clinical psychologists and speech and language therapists. Over time, patients are likely to require treatment for complications and rehabilitation therapy and have ongoing health and social care needs. Around 40% of discharged patients need help with daily activities. Nearly one-fifth had help solely from unpaid careers and approximately two-thirds from only paid careers, with the remainder receiving help from both. Eighteen percent needed three or more visits a day from social services. Eighty-five percent of patients required physiotherapy. Forty-eight percent required speech and language therapy. AF-related strokes are a great burden for patients. An important factor in the economic burden of AF relates to the detection of the condition. As noted earlier, AF is currently often only detected after a stroke; earlier AF detection and intervention to reduce stroke risk could reduce the occurrence of AF-related strokes and the associated economic burden.

The evidence suggests that AF is associated with a high risk of cognitive impairment as an independent risk factor with or without a history of clinical stroke. Fifteen to 20% of individuals aged over 65 years will suffer some degree of cognitive deterioration [6]. However, silent infarctions of the brain are even more frequent than symptomatic strokes [16]. Silent strokes remain undetected in most cases but can accumulate over time to cause or aggravate pre-existing cognitive impairment. In 2015, the estimated number of individuals with dementia in the world was 47.47 million, and this is expected to increase to 75.63 million by 2030 and 135.46 million by 2050 [17]. Therefore, the incidence of dementia will double every 5.9-years age increase, i.e., from 3.1/1000 person-years at age 60-64 to 175/1000 person-years at age ≥95.

Patients with AF and cognitive impairment [17] are more likely to be women, older and have a higher baseline burden of functional dependence in daily activities, higher cognitive impairment prevalence and higher mortality. In spite of preliminary reports indicating that anticoagulation can reduce the risk of cognitive impairment in patients with AF [18], AF is underdiagnosed [19]. Patients are undertreated with anticoagulation, with cognitive impairment being the main reason for not receiving oral anticoagulant therapy. Cognitive impairment was found to double mortality.

In our territory [20], patients with AF were on average older than patients without AF, a larger proportion was male and aged ≥80 years, they had a higher prevalence of heart failure (HF), higher Barthel scores and Charlson scores and a higher incidence of mortality than those without AF. Data from our primary care records [21] allowed us to uncover a major care gap in stroke prevention: the prevalence of undetected AF and its association with an increased risk of cognitive impairment, heart failure, sudden death and cardiovascular morbidity [22]. Despite progress in AF diagnosis and management [17], the prevention of stroke remains the cornerstone. In the group with known AF, 23.5% were not receiving oral anticoagulant therapy (OAT). The odds ratio for not being treated with OAT was 2.04 (95%CI 1.11-3.77) for women and 1.10 (95%CI 1.05-1.15) for more advanced age at diagnosis. Cognitive impairment (15.2%) was the main reason for not receiving OAT. Despite these challenges, interviewees from across countries and stakeholder types reported that policymaker awareness of AF is low and that AF is viewed as a medical issue rather than a public health issue.

3.3. Global burden of atrial fibrillation and economic cost

Due to demographic ageing, in Europe, the prevalence of AF is estimated to increase from 1.9% (2008) to 3.5% (2050) and the number of AF-related ischaemic strokes in people >80 years will triple (2010-2060). If we consider that more than 60% of

strokes occur in people older than 80 years of age, the proposed objective is extremely important. Approximately one-third of ischaemic strokes are related to the presence of unknown AF. In this case, strokes are more severe, more disabling, associated with cognitive decline and pose a higher risk of institutionalization than strokes from other causes [23].

Most patients with AF require long-term pharmacological treatment, often including warfarin or acenocoumarol. Monitoring anticoagulant treatment is expensive. AF also leads to hospitalization and is a cause of particularly costly cardiovascular morbidity—that is, stroke and heart failure. The number (and rate) of AF-related hospitalizations (both primary and secondary) has increased two-fold to three-fold in recent years. Consequently, AF is likely to impose a substantial and growing economic burden on health care systems.

In addition to the epidemiological predictions associated with demographic ageing, the greater cardiovascular comorbidity, frequency, average drug consumption, mortality and severity of the associated stroke would confirm the predicted increase in costs associated with the treatment of AF, especially in association with a stroke episode. Obviously, the impact will depend on both size and demographic composition. The presence of a progressive increase in the prevalence and severity of cognitive decline with the risk of AF increases the magnitude of the impact and reinforces the possible etiopathogenic interrelation between both processes in the general population, as well as the need to protocolize its detection. A model of comprehensive care for AF showed a 45% reduction in mortality from any cause [23], but its analysis is subsequent to the diagnosis of AF.

3.4. The need for screening/case finding

AF satisfies most of the *World Health Organization's* criteria for a disease suitable for screening (**Figure 1 Appendix**). Good AF management is essential to prevent stroke, but little has changed: guidelines are not fully implemented, many AF cases are not diagnosed before a stroke episode, patients are not given anticoagulants, many of those taking anticoagulants do not have quality criteria for good anticoagulation (TRT >60%) and there is postcode variation in the management and use of Direct Oral Anticoagulants (DOACs). Although many patients with AF develop symptoms that lead to appropriate diagnosis and management, the first manifestation may be a debilitating stroke or death. Finding AF before symptoms manifest could lead to the initiation of appropriate effective therapy to reduce stroke and death and potentially the initiation of risk-factor modifications to reduce complications from AF progression. A significant proportion of people with AF are diagnosed by chance during health assessments carried out for other reasons, or due to having a stroke. There may be multiple reasons for under-diagnosis, including the fact that AF can be asymptomatic and a lack of awareness about the condition and its symptoms.

The detection of AF can have important implications for reducing the risk of stroke and its large clinical and economic effects. Thus, different screening and case-finding strategies have been proposed and recommended by international organizations such as the European Society of Cardiology (ESC), Stroke Alliance for Europe (SAFE), National Institute for Health and Care Excellence (NICE), European Heart Rhythm Association (EHRA), World Health Care Forum (WHF), European Primary Care Cardiovascular Society (EPCCS) and others. Different organisations have different positions about whom to screen or to whom to aim case-finding [24-26]. For a screening program to be efficient, the screening technique must have a high positive predictive

value using a low-risk tool at low cost. Screening yield depends on disease prevalence and diagnostic test performance.

Opportunistic screening/case finding, where patients are checked for AF when they visit doctors for other reasons, is widely supported as a means to achieve higher rates of detection to enable early intervention. Primary care is an ideal setting: in addition to regular primary care physician visits, nursing support for screening is available and there is a direct link with the practitioner to prescribe OAC. Two challenges remain unsolved: 1) developing a sustainable strategy for detecting undiagnosed AF and 2) providing adequate treatment for patients with known or newly discovered AF because undertreatment is common. In primary care, regarding the methods of mass screening, handheld ECG devices have the advantage of providing a verifiable ECG trace that guidelines require for AF diagnosis and would, therefore, be preferred as screening tools. The AF diagnosis requires at least 30 s of absolutely irregular RR intervals and no discernible, distinct P waves on the electrocardiogram (ECG) [27]. Settings for screening include various venues in both the community and the clinic, but they must be linked to a pathway for appropriate diagnosis and management for screening to be effective **(Figure 2 Appendix)**. Opportunistic screening was tested against routine screening in the SAFE study, which found that opportunistic screening improved routine practice, whereas routine screening did not [1]. It can also be used in the community, in both high- and low-middle-income countries. In the clinic, it is usually performed by physicians or nurses, whereas in the community, non-physician health professionals and laypeople can be trained to detect pulse irregularity. Pulse checks, either done at home by the patients themselves or in GP surgeries or pharmacies, are a simple and effective way of checking for AF and should be used more.

Innovation in technology has produced new screening devices **(Figure 3 Appendix)** that improve the feasibility and cost-effectiveness of widespread screening and are easily available in primary care. These devices are recognized as valid for AF detection by the European Primary Care Cardiovascular Society and could be used to complement traditional screening by pulse palpation [28]. There are ongoing studies to determine the sensitivity and specificity of these new tools. Adding biomarkers (e.g. natriuretic peptides, high-sensitivity troponin) [29] to existing clinical predictors may improve the prediction of AF incidence. However, there are marginal improvements in model discrimination and reclassification. Continuous monitoring coupled with a diagnostic algorithm could detect paroxysmal AF more effectively than repeated patient-activated devices. Prolonged continuous ECG monitoring with external or subcutaneous recorders could diagnose more paroxysmal AF, but it requires further evaluation, so its cost-effectiveness is limited regarding the detection of AF with lower absolute stroke risk. Health resources are known to vary widely between countries and health systems, so the setting for AF screening should be both country- and health-system-specific. Improvement in the diagnosis and management of AF is needed, including systematic approaches to identifying and monitoring AF (**Figure 4 Appendix**). The effectiveness and cost-effectiveness of AF-screening policies of at-risk populations should be assessed in the respective health contexts of each country, as should new developments such as devices and apps for detecting AF, the self-monitoring of INR and new anti-coagulation therapies. A more systematic approach to monitoring guideline adherence (e.g. national or large regional audits), and possibly incentivising this adherence, might improve treatment rates [30].

3.5. Summary of Studies Regarding Screening for Atrial Fibrillation (Table 1 Appendix)

In the year 2017, the AF-SCREEN International Collaboration White Paper was published in *Circulation* [31]. It showed whom to screen, where to screen and how to screen for AF (**Figure 4 Appendix**). The preferred recommendations are to screen people aged >65 years or those patients with AF that are undertreated, to do so at Primary Care or Specialist clinics and for screening to be done first using opportunistic pulse palpation and then an ECG, or a single-lead ECG or to do so post-stroke.

Several prospective controlled and non-controlled studies have examined the effect of screening on the detection rate of previously undiagnosed AF, using a range of different screening programmes and target populations. These studies are summarized in **Table 1 of the Appendix (Table 12.2.1)**. Several in-progress trials may strengthen the evidence base for screening. The most common target population for screening was those aged ≥65 years in a primary care setting, with screening being carried out opportunistically at GP appointments or pharmacy visits or through invitation to an ECG. Many worldwide projects from various health collectives have been formed to try to screen as many populations as possible. One of the latest types of study to try to detect AF (due to the easy access of the population) are those initiated by pharmacies such as the PIAAF study in Canada [32], among others [33-35]. They agree on the same conclusion: opportunistic screening for AF in pharmacies is feasible and allows identifying people with previously unknown AF.

In order to improve the detection of silent AF, opportunistic screening for AF in all patients ≥65 years using the pulse has been recommended by ESC guidelines since 2012 [7] and is recommended by EHRA guidelines. Opportunistic screening by pulse-taking or ECG strip received a class I level of evidence B recommendation in the most

recent ECG guidelines. Yet, it may be questioned whether the yield of this opportunistic way of screening is sufficient in higher-risk patients and whether it should be extended to younger individuals. Further, systematic screening in higher risk groups may even be warranted. The first large-scale screening trial was the Screening for AF in the Elderly (SAFE) trial. The principal conclusion from the SAFE study was that active screening can identify an additional one-third of AF cases. Additional main studies on AF screening include the LOOP-Study, all of the PIAAF studies, the STROKESTOP Study and others (**Table 1 Appendix**). Opportunistic screening identified as many of these cases as systematic screening for considerably less effort, so it should be promoted in primary care as long as a high level of coverage can be maintained [8-9] (**Figure 5 Appendix**).

According to the evidence described above, it can be assumed that opportunistic screening is now recommended in patients ≥65 years. It may even be started at a lower age in the presence of a higher CHA2DS2-VASc score (CHA2DS2-VASc ≥2 in individuals ≥55 years). The need for systematic screening is still uncertain. So far, no clear advantage of systematic above opportunistic screening has been demonstrated.

AF is often asymptomatic and screening is not routinely undertaken in Europe. In most European countries, ESC guidelines have been assumed and are commonly used [36-38]. Although individuals with AF often have other diseases and disorders—including ischaemic heart disease, heart failure, hypertension, diabetes and hyperthyroidism—age has been identified as the strongest independent risk factor for AF. Screening studies also found that between 10% and 66% of people with AF were previously unknown cases (Belgium, Portugal, UK, Spain). This implies a significant under-diagnosis in Europe. A major screening study has been launched in Sweden to detect AF and to see whether screening reduces stroke incidence and is cost-effective [39].

The Belgian Heart Rhythm Association, with the contribution of two pharmaceutical industry sponsors, organizes the yearly Week of the Heart Rhythm [40], which involves free mass screening events and the distribution of information leaflets about self-administered pulse checks. A study on mass screenings, involving 69 hospitals that screened a total of 13,564 patients, found that these screenings are feasible and effective in detecting AF in approximately 2.2 per cent of the screened individuals. The French AVC Association launched a campaign to raise awareness about AF in reaction to a recent survey in France that showed that 87 per cent of people surveyed do not know what AF is. In 2013, the campaign covered 4,592 patients in 16 French cities by educating general practitioners on AF and modes of detection [41]. Five hundred and eighty-five patients (15.6%) were referred to cardiologists and 129 new AF cases were confirmed. The achievements of this campaign included increased awareness of cardiovascular disease (including AF and AF-related stroke), the integration of AF and AF-related stroke into a cardiovascular policy document and a call for increased political engagement on cardiovascular disease (including AF and AF-related stroke) as part of a broader commitment to public health. The German Stroke Foundation (Stiftung Deutsche Schlaganfall-Hilfe) sees regular pulse self-measurement as the best way to find irregularities in the heart rate and identify AF early [42]. The AF guidelines of the Italian Association for the Fight Against AF (ALFA 2014) note that patients who do not present symptoms are often not aware of their condition. The guidelines claim that if all individuals with AF were identified, the number of patients would double. The Association's patient information publication recommends that patients self-monitor their pulse at least once a week [43]. The Association created a campaign in 2014 to raise awareness of the importance of self-performed pulse checks.

A 2011 survey of NHS Primary Care Trusts (PCTs) found that while not compulsory, many encourage GPs to include pulse checks in their NHS Health Checks. NHS Health Checks are aimed at adults in England aged between 40 and 74 to help lower the risk of developing four common diseases: heart disease, stroke, diabetes and kidney disease. However, the 2011 survey also found that 26 per cent of NHS Health Checks did not include pulse checks. The 'Know Your Pulse' campaign, jointly launched by the AFA and Arrhythmia Alliance in 2019 [44], organises yearly awareness-raising campaigns on the risks of AF and stroke and offers guidance on pulse self-checks.

A survey completed by respondents from 33 European Heart Rhythm Association Research Network partners in 16 countries found that there is currently no consensus regarding the screening methods for asymptomatic AF. Opportunistic screening, in the form of a peripheral pulse check, should be carried out regularly for adults 65 years and older. Opportunistic screening in this group is recommended by the European Society of Cardiology and in the United Kingdom by the Royal College of Physicians of Edinburgh [45]. Indeed, opportunistic screening (compared to targeted screening) was the only strategy that improved on routine practice. A systematic review found that single time-point screening in adults 65 years or older identified previously unknown AF in 1.4 per cent of the screened population.

Case finding or primary screening, depending on the circumstances, is firmly recommended for diagnosing and treating as many patients as possible in different ambits and situations. It has been recommended as an easy manoeuvre to prevent stroke [46] and post-stroke [31] in the general population [47], in a population selected with a risk model [48], in metropolitan and rural areas by general practice [49] and in many other different populations and places. In our territory, Terres de l'Ebre (Tarragona, Spain), before 2012 there was no defined pathway for AF.

First, we evaluated the work done by the AFABE Study in the same territory, which had 48,336 patients. The new results show that a proper case finding for AF is feasible and is associated with an increase in the prevalence of AF. The same study also identified some of the real barriers that patients face in our health system regarding case finding for AF, which in our territory is guided mainly by GPs.

There remains little doubt that proper screening or case finding for AF is necessary. Many nuances are still not properly described: for example, different age ranges, which specialist should screen and many other variables. Nowadays, there is an important movement to screen high-risk patients for AF [48,11], as well as those with a heavy AF burden [50].

The AFRICAT Study (NCT 03188484) is another study on AF that was carried out in our territory. Its main hypothesis involved evaluating patients who had a high risk of developing AF to discover certain clinical characteristics that could be used to optimize screening strategies; as a second hypothesis, the study proposed that a combined approach integrating biological (blood biomarkers) and electrocardiographic information could achieve better accuracy than either of them separately. The global objective of the AFRICAT project was the development and validation of a multimodal sequential screening program for AF at primary care in high-risk individuals (patients with ages between 65 to 75 years with previous diagnoses of hypertension and diabetes). The main results were: first, the AFRICAT study shows ways to improve the diagnosis of AF in primary care; second, a 5-year predictive clinical model of AF in its population was validated in an independent sample; third, it found comparative results between different AF detection devices characterized by their high specificity; fourth, biomarkers could prove to be really useful in predicting AF risk, although the authors do not have cut-off points at different risk levels; finally, and probably most importantly, Holter monitoring

(for 30 days) in patients at high risk of AF could double the prevalence of previously known AF.

Various scales for measuring the risk of developing AF are being defined, which could ease the work of stratifying populations to screen. The most accepted and studied scale is the CHARGE-AF [51], which has been compared to the $CHA_2DS_2VAS_C$ score [52]. The CHARGE-AF scale has been proven to be the most suitable for primary screening.

With all this data, in our second study, taking into account the worldwide expert recommendations, the conclusions from the AFRICAT Study and different high-risk scales, we focused on more finely identifying those patients that could suffer from AF from the primary care point of view. In this second study, various biomarkers were analysed and compared to one-month Holter monitoring to find an accessible tool for GPs to use as a screening biomarker in a defined high-risk population.

There are some current studies evaluating various wrist devices for daily use. These studies are still very early and are being evaluated on a large scale, but the results are promising and could contribute to massive population screening in a few years, which, associated with predictive models of population risk, echocardiography criteria and specific biomarkers, may further help us to find unknown AF [53,54]. However, there is currently no evidence for their use in screening.

4. Hypothesis

4. Hypothesis

H0.1 (First article): Case finding strategy increases the detection of AF compared to the usual routine clinical practice.

H0.2 (Second article): The use of N-Terminal Pro B-Type Natriuretic Peptide makes a difference in the detection of unknown AF in asymptomatic high-risk populations in the context of a screening programme.

5. Objectives

5. Objectives

5.1. Primary objective/s

- To evaluate the effectiveness of AF case finding in the general population ≥ 60 years and older relative to usual clinical practice.
- To identify possible barriers to and enablers of opportunistic community AF case finding.
- To determine the usefulness of N-Terminal Pro B-Type Natriuretic Peptide's usefulness as a biomarker in asymptomatic high-risk populations for atrial fibrillation in the context of a screening programme.

5.2. Secondary objectives

- To propose an atrial fibrillation pathway, mainly from primary care, to establish early diagnosis.
- To target the most at-risk population to increase the screening's effectiveness.

This study, therefore, investigates possible social and clinical barriers to opportunistic community screening for AF and tries to target screening with a biomarker feasible for use in primary care to diagnose more AF.

6. Materials and methods

6. Material and methods

This study has two different phases focusing on different populations with different materials and methods, but these phases share the same purpose of finding a common AF pathway.

In 2015, the population from the County of Terres de l'Ebre, Tarragona, Spain, participated in a pilot study in collaboration with the Master Plan for Cerebral Vascular Malaltia / Agència de Qualitat i Avaluació Sanitàries de Catalunya (PDMVC) and the Estratègia d'Atention Integral a la Cronicitat for the design of an AF route with the general objectives of improving the care of people with AF, coordinating different levels of care, promoting excellent clinical practice and reducing AF-related morbidity and mortality, as well as health outcomes. For this reason, the initial objective was: "palpation of the arterial pulse and/or ECG and its registration in the electronic medical record (e-cap) to any citizen ≥60 years of age who contacted the health system, especially in care primary". For said registration, a specific variable (rhythmic/arrhythmic) was introduced in the e-cap, section on Prevention and Promotion of Health Activities, which appears in a different colour when the citizen belongs to the target group and has not carried out the activity.

The first part of this study was an observational, cross-sectional, multi-centric and non-interventional study in the context of ordinary primary care practice involving the population of the County of Terres de l'Ebre, Tarragona, Spain, ≥ 60 years of age (n = 51410) with an active clinical history (e-cap), of which 48,336 patients without known AF were included. The main variable was whether a patient's heartbeat is rhythmic or arrhythmic, as described in the record of the patient's medical history of case finding activity for AF during the period from 1 January 2016 to 31 December 2017, confirmed with a 12-lead ECG. Secondary variables were also studied and analysed, such as

sociodemographic variables, case identification code (the numbering of the Individual Health Card was used), age, sex and municipality of residence (>10,000 inhabitants, urban; 10,000-1000 inhabitants, semi-rural; <1,000 inhabitants, rural). Clinical relevant information and comorbidities were obtained from the coded diagnoses in the patients' medical histories in both primary and hospital care (the codes of the International Classification of Diseases version 10 used to select the different AF entities were I48 as the main diagnosis). The $CHA_2DS_2VAS_c$ scale was included. Cognitive impairment was evaluated by Pfeiffer scale (0-10): [0-2 errors] = normal; [≥ 3 errors] intermediate to severe involvement. The study recorded whether the patient was diagnosed as a Chronic Complex Patient [20]. Prescription information was recorded, including all drugs prescribed by any active diagnosis in an individual's medical history, with "poly medication" defined as the prescription of ≥5 different medications simultaneously. An evaluation of the use of direct anticoagulants and antivitamin K was carried out. Health service variables were considered, such as counting the number of visits to GPs and hospital doctors during each year and whether the patient had been institutionalized.

AF was detected either through direct AF case finding activity or without a direct AF screening procedure. Both were done by pulse palpation and/or registration of an ECG in an asymptomatic patient who was subsequently recorded in the e-cap program. This activity was performed either by consultation with a physician or nurse at the primary care centre or by a home visit. If a pulse palpation suggested an arrhythmia, it was immediately followed by an ECG. Thus, a twelve-lead ECG record verified by a physician was used to define AF.

A descriptive analysis of the sociodemographic and clinical variables was performed using the informatics programme SPSS 20.0, with the help of a statistician, to describe the frequency and percentage of the categorical variables and the mean and

standard deviation of the continuous variables. The adjusted prevalence and incidence of new AF were calculated, as was the number of screens required to diagnose new AF (NNS). This descriptive analysis was stratified according to whether the screening had been performed. To detect if there are statistically significant differences between these variables and the performance of the screening or not, the Chi-square independence test was performed on the variables; Crude and adjusted Odds ratios (multivariate model) were calculated to measure their associations with the performance of the screening using logistic regression. To calculate the goodness of fit of the multivariate model, a variable was created with the model's prediction probabilities and its ROC curve was calculated. A variable was created that included the factors associated with a significantly lower risk of performing opportunistic screening: <70 years of age, urban residence, institutionalization, Pfeiffer scale value ≥2 and number of visits to the primary care physician in 2017 ≤7. The adjusted odds ratio was calculated by logistic regression for all variables to measure the association of this variable with the screening.

The study's effectiveness was assessed based on changes observed in the prevalence of AF after two years of programme intervention and by comparing the incidence of newly diagnosed AF in the group with case finding as compared to the incidence in the control group (without AF case finding).

Following these findings, for the second phase of the AF study of Terres de l'Ebre's inhabitants, a population at risk for AF was defined. The intention of this part of the study was that, after demonstrating that performing atrial fibrillation screening and knowing what barriers we faced when carrying out case finding on patients, it was of great interest to apply a more complete study on subjects with high AF risk using clinical, biological and electrocardiographic registers to identify more AF cases. This second part of the study was an observational, multicentre, population-based study with the aim of

developing a screening programme to detect new cases of AF in high-risk individuals in primary care centres. It took place in the same County as in the first part of the study and involved randomly selecting 100 subjects aged 65–75 diagnosed with hypertension and diabetes from primary care between January 2016 and December 2017 out of a database consisting of 5,500 hypertensive and diabetic patients included in the AFRICAT project's database (NCT03188484).

The selected participants were ambulatory patients in a stable health situation (all individuals with chronic inflammatory diseases, cancer or dementia were excluded). The patients and their GPs arranged a visit to their primary care centre in which they received a comprehensive assessment consisting of clinical characteristics; an ECG was performed and a blood sample was extracted in EDTA and serum tubes to evaluate various blood markers (NT-proBNP, serum ApoC-III, plasma uPAR…) that could help predict AF. Patients were monitored with a Holter device for 4 weeks (trying to wear it for 23 hours every day and charging for 1 h) and the records were sent together with the ECG for blinded reading to the Rhythm Disorders Unit at the Cardiology Department of Hospital Virgen del Rocio in Seville to verify AF episodes. AF was defined following AHA guidelines as irregular R-R intervals without a P wave signal, lasting for more than 60 s.

Statistical analysis was also done using the informatics programme SPSS 20.0 with the help of a statistician. The sociodemographic and clinical variables were analysed to describe the frequency and percentage of the categorical variables and the mean and standard deviation of the continuous variables.

In the bivariate analysis of normal distributions, the T-test was used for independent samples in the case of quantitative variables and the Chi^2 test or Fisher's exact test in the case of categorical variables was performed to compare and study the population. ROC curves were obtained to calculate sensitivity, specificity and cut-off

values of NT-proBNP's discrimination power. In the multivariable test, given the characteristics of this pilot sample and the number of significant variables in the regression, if the p-value is below a specified level of significance (α) (generally 0.10, 0.05, or 0.01), the difference can be said to be statistically significant and reject the null hypothesis of the test. In this case, the value 0.09 was accepted as statistically significant due to the limitations of the pilot sample.

Different variables were analysed to avoid duplication. Three probability variables were used to identify possible duplication (date of birth, sex and Individual Health Card identification number) so that each individual in the numerator was only counted once. Reviews were carried out every six months to detect possible deviations and errors, missing values and extreme values and to obtain control of the state of the investigation.

The first part of this project was approved by the Ethics Committee for Scientific Research IDIAP Jordi Gol (code P18/118); for this type of study, formal consent is not required and the requirement for the informed consent of patients was waived prior to the inclusion of their medical data in this study. The protocol for the second part of the study was also approved by the clinical research ethics committee of IDIAP Jordi Gol (P15/047) and the Hospital Universitari Vall d'Hebron [PR (AG) 133-2015]; the formal consent of each patient was solicited and, if granted, the patients were included in the study. All data were included in an *ad hoc* repository, which was delivered to the main researcher in a completely anonymous format, supervised and assessed according to the General Data Protection Regulation of Spain/Europe of 1st February 2017.

7. Results

7. Results

For the main result derived from the first part of the study, more cases of AF were directly detected from the case finding of the general population older than sixty years. The population included 48,336 patients with a mean age of 75 years and 87% of the population had $CHA_2DS_2VAS_c$ scores ≥ 2; baseline characteristics are described in Table 1 and in the first article **(Appendix 12.3.1)**. Opportunistic AF case finding was performed in 61% of the population between 2016-2017. The average age was higher in the case finding group than in the control group, as was their associated comorbidity, $CHA_2DS_2VAS_c$ scores, proportion of urban residence and frequency of primary and hospital care. The detection of new AF cases was significantly higher in the case finding group for all age ranges. From the case finding for AF, two hundred and one new cases were directly diagnosed. The prevalence of stroke and the number of patients receiving anticoagulant therapy were significantly higher in the presence of AF than in the group without diagnosed AF ($p < 0.001$).

The prevalence of AF also increased through the end of the programme assessment (5.9% vs 7.7%, respectively; $p < 0.001$). Two hundred and one previously undiagnosed cases of AF were accounted for by AF case finding: 26.3% of all new AF cases diagnosed. Stroke was also proven to be significantly higher in the presence of AF compared to the group without diagnosed AF (4.4% vs 1.6%; $p < 0.001$).

The sociodemographic variables associated with the lack of performance of case finding were age < 70 years, urban residence, institutionalised status, Pfeiffer score ≥ 2 or a record of 'cognitive impairment', Charlson score ≤ 3 and a lower than average number of physician visits for the territory.

Table 1. Baseline characteristics of the population in the first part of the study

Variable	No case finding	Case finding	*P*	Total
Total *N* ≥ 60 years	19 320 (37.6%)	32 090 (62.4%)		51 410
Sex (%)				
Female	10 300 (53.3%)	17 230 (53.7%)	0.406	27 530
Male	9020 (46.7%)	14 860 (46.3%)		23 880
Average age	71.3 ± 9.9	75.12 ± 8.9	<0.001	73.68 ± 9.5
Residence (%)				
Urban	8370 (43.3%)	11 705 (36.5%)		20 075
Semi-urban	6643 (34.4%)	12 079 (37.6%)	<0.001	18 722
Rural	4307 (22.30%)	8306 (25.9%)		12 613
Institutionalization	806 (4.17%)	510 (1.59%)	<0.001	1316
Total *N* ≥ 60 years of age excluding known AF	**18 739 (38.76%)**	**29 597 (61.23%)**		**48 336**
New diagnosis of AF	129 (0.7%)	765 (2.6%)	<0.001	894
Total AF (%) at the end of the study	710 (3.7%)	3258 (10.1%)	<0.001	3968 (7.7%)
$CHA_2DS_2VAS_c$ score	2.12 ± 1.4	3.03 ± 1.31	<0.001	2.7 ± 1.41
Heart failure	703 (3.6%)	2687 (8.4%)	<0.001	3390
High blood pressure	7743 (40.1%)	21 390 (66.7%)	<0.001	29 133
Brain stroke/Transient Ischemic Attack	243 (1.2%)	689 (2.1%)	<0.001	932
Vascular disease	566 (2.9%)	1902 (5.9%)	<0.001	2468
Ischaemic cardiopathy	683 (3.5%)	2264 (7.1%)	<0.001	2947
Diabetes mellitus	2079 (10.8%)	8757 (27.3%)	<0.001	10 836
Impaired renal function (dialysis, renal transplantation or serum creatinine >200 µmol/l)	876 (4.5%)	3122 (9.7%)	<0.001	3998
Average glomerular filtrate (ml/min)	77.2 ± 19.9	74.3 ± 19.2	0.180	75.01 ± 19.4
Chronic liver disease or impaired hepatic function (bilirubin >2× or serum glutamic-pyruvic transaminase or serum glutamic-oxaloacetic transaminase or alkaline phosphatase >3× the normal limit)	26 (0.1%)	50 (0.2%)	0.633	76
COPD[a]	1469 (7.6%)	3517 (11.0%)	<0.001	4986
OSAS[b]	290 (1.5%)	767 (2.4%)	<0.001	1057
Anticoagulant treatment	550 (2.9%)	2759 (8.6%)	<0.001	(83.5%)
Anti-vitamin K	418 (2.2%)	2284 (7.1%)	<0.001	2702
NOACs[c]	132 (0.6%)	475 (1.5%)	<0.001	607
Statins	4471 (23.1%)	12 191 (38.0%)	<0.001	16 662
Cognitive impairment and/or Pfeiffer >2 score	963 (5.0%)	1691 (5.3%)	0.162	2654
Average Pfeiffer score	3.4 ± 3.3	2.3 ± 2.8	<0.001	2.58 ± 2.9
Number of CCP[d] criteria	0.3 ± 0.17	0.6 ± 0.23	<0.001	0.5 ± 0.21
Charlson Comorbidity Index	0.72 ± 1.06	1.15 ± 1.22	<0.001	0.99 ± 1.18
Number of drugs	3.66 ± 3.70	5.7 ± 3.77	0.007	4.93 ± 3.8
Average number of visits/year (PC[e])	9.15 ± 11.7	18.3 ± 15.5	<0.001	14.9 ±14.9
Median number of visits (PC)	6	14	<0.001	11
Average number of visits/year (HOSP[f])	0.17 ± 1.06	1.15 ± 1.22	<0.001	0.23 ± 0.88

[a]Chronic obstructive pulmonary disease.
[b]Obstructive sleep apnoea syndrome.
[c]Novel oral anticoagulants.
[d]Chronic complex patient.
[e]Primary care.
[f]Hospital.

At the same time as the first part of the study, having identified the barriers of the population in the case finding and to improve the efficiency of the applied screening method, we proposed using different biomarkers and electrocardiography in a high-risk population for AF to help identify more patients at risk of suffering from AF.

One hundred individuals were randomly selected from 5,500 hypertensive and diabetic patients aged 65-75 years. The clinical characteristics of the population used in this second part of the study can be found in Table 2 and in the second article **(Appendix 12.3.2)**. These demonstrated that coronary heart disease, heart failure, valvular diseases

and the use of anticoagulants were more common in AF individuals; CHA2DS2-VASc scores were also higher in patients suffering AF.

Table 2. Baseline characteristics of the population in the second part of the study

	All patients (100)	AF (20)	No AF (80)	hAF (7)	*P*-value[a]	*P*-value[b]
Age	70 (68–73)	69 (66–71.5)	70 (68–73)	70 (65–72)	0.273	0.655
Sex (% female)	33 (33)	7 (35)	26 (32.5)	3 (42.9)	0.832	0.682
Tobacco	20 (20)	4 (20)	16 (20.3)	1 (14.3)	1.000	1.000
Alcohol	11 (11)	1 (5)	10 (12.5)	0 (0)	0.456	1.000
Dyslipidaemia	81 (81)	16 (80)	65 (81.3)	5 (71.4)	1.000	0.619
Coronary heart disease	18 (18)	8 (40)	10 (12.5)	3 (42.9)	0.008*	0.032*
Heart failure	3 (3)	3 (15)	0 (0)	0 (0)	0.007*	1.000
Valvular disease	4 (4)	3 (15)	1 (1.3)	0 (0)	0.024*	0.767
Previous stroke	6 (6)	2 (10)	4 (5)	0 (0)	0.597	1.000
Anticoagulation	9 (9)	8 (40)	1 (1.3)	0 (0)	0.000*	0.920
Antiplatelets	50 (50)	7 (35)	43 (53.8)	3 (42.9)	0.134	0.702
Familiar history FA	5 (5)	2 (10)	3 (3.9)	0 (0)	0.273	1.000
SBP, mm Hg	143.50 (134–153)	140.5 (127.5–162.5)	144 (134–151.75)	140 (124–168)	0.973	0.773
DBP, mm Hg	78.95 ± 10.09	80.95 ± 10.85	78.45 ± 9.90	79.14 ± 6.66	0.332	0.857
Heart rate	77.94 ± 15.70	77.25 ± 16.94	78.11 ± 15.48	73 ± 22.14	0.724	0.421
CHA_2DS_2-VASc	4 (3–4)	4 (3–4)	4 (3–5)	4 (3–5)	0.035*	0.284

[a]*P*-value comparison AF vs. no AF.
[b]*P*-value comparison hAF vs no AF.
*$P < 0.05$. AF, atrial fibrillation; DBP, diastolic blood pressure; hAF, Holter-detected atrial fibrillation; SBP, systolic blood pressure.

Out of the 100 individuals, 96 were monitored with an ECG Holter device, with a median monitoring time of 457 h. Few adverse events were described (mainly cutaneous rash). In 20 of these patients, AF was present (11 newly detected in the study). AF burden, defined as minutes being in AF divided by the total minutes of readable records, was calculated as a percentage. The median AF burden was of 10.35% (1.00-56.50).

In the biomarker analysis, NT-proBNP, ApoC-III, sUPAR, vWF and ADAMTS13 were analysed; inter- and intra-assay variation was acceptable, and thus all samples were included in the analysis.

Table 3. Biomarker levels and comparison between different groups in the second part of the study

	AF (20)	No AF (80)	hAF (7)	*P*-value[a]	*P*-value[b]
NT-proBNP (pg/ml)	643.65 (155.72–1339.25)	64.26 (37.08–133.10)	128.30 (97.69–191.8)	<0.0001*	0.03*
ApoC-III (ng/ml)	107,594 (92,501–129262.06)	104,450 (766,64–130,393)	105,352 (91,956–132,268)	0.496	0.574
ADAMTS13 (ng/ml)	1131.24 ± 471.419	1221.41 ± 459.80	1271.68 ± 561.01	0.437	0.796
vWF (ng/ml)	0.139 ± 0.052	0.139 ± 0.706	0.146 ± 0.060	0.987	0.802
uPA (std)[c]	2.01 (1.41–2.39)	1.60 (1.38–2.35)	1.68 (1.29–2.35)	0.720	0.868
uPAR (pg/ml)	2220.80 (557.74–2810.52)	2267.54 (1518.33–2763.05)	2246.12 (1926.03–259.23)	0.689	0.918

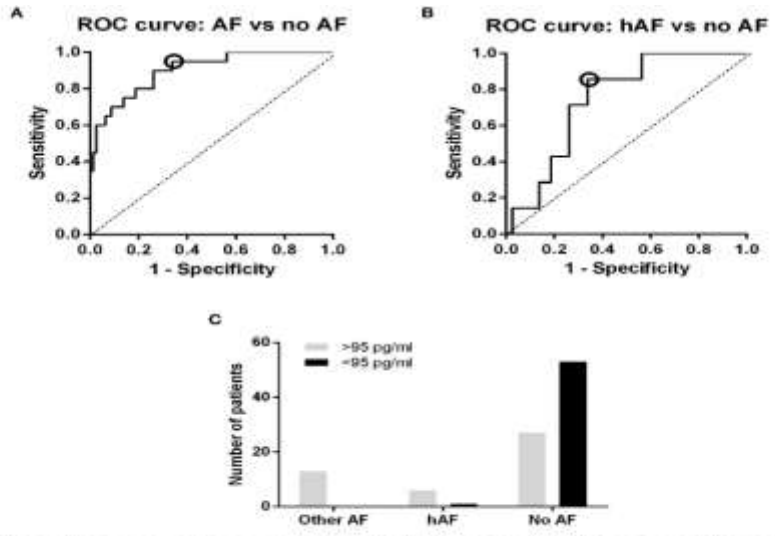
[a]*P*-value comparison AF vs. no AF.
[b]*P*-value comparison hAF vs. no AF.
[c]Ninety-one individuals included in the uPA analysis (73 no AF and 18 AF, of whom 6 were hAF).
*$P < 0.05$. AF, atrial fibrillation; ApoC-III, Apolipoprotein C-III; hAF, Holter-detected group; NT-proBNP, N-terminal pro B-type natriuretic peptide; vWF, von Willebrand factor; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator surface receptor.

Two subgroups were studied and compared: AF diagnosed patients vs patients not diagnosed with AF, and AF diagnosed by Holter devices (hAF) vs patients not diagnosed with AF.

In the first comparison, NT-proBNP was significantly higher in individuals with AF compared to no AF [643.65 pg/ml (IQR 155.72–1339.25) vs. 64.28 pg/ml (IQR 37.08–133.10), $p < 0.0001$], while the remaining biomarkers were not different between the two groups; also, the cut-off point of NT-proBNP of >95 pg/ml showed 95% sensitivity, 66.2% specificity, 41.3% positive predictive value (PPV) and 98.1% negative predictive value (NPV) for detecting any AF. It was also demonstrated that AF burden correlated with NT-ProBNP (r=0.597, p=0.024).

The second subgroup analysed, hAF vs No AF, showed that NT-proBNP levels varied between patients without AF (no AF) and those with AF diagnosed by Holter devices (hAF) [64.28 pg/ml (IQR 37.08–133.10) vs. 128.3 pg/ml (IQR 97.69–191.3), $p = 0.031$]. The rest of the biomarkers did not show notable differences. The cut-off point of NT-proBNP of >95 pg/ml had 85.7 % sensitivity, 66.2% specificity, 18.2% PPV and 98.1% NPV to detect hAF.

Figure 1. ROC Curve showing NT-proBNP discrimination power in the second part of the study



NT-proBNP discrimination power. **(A)** ROC curve: ability to discriminate between AF and no AF. **(B)** ROC curve, ability to discriminate between Holter-detected AF and no AF. The cut-off with the best specificity and sensitivity to detect hAF is marked with a circle in the two curves (95 pg/ml), as it is the cut-off value that was used to calculate sensitivity, specificity and predictive values. **(C)** Discrimination power of the NT-proBNP cut-off value of 95 pg/ml. All AF individuals had NT-proBNP plasma levels below the previous cut-off (except for a patient with paroxysmal AF), and the majority of no AF patients had values above the cut-off.

In the presence of AF, in addition to NT-proBNP, in the univariate analysis (Table 2.), ischaemic heart disease, heart failure, the presence of valvulopathy, anticoagulant treatment and CHA2DS2-VASc were found to be as significant variables. The results of the logistic regression (Table 4) were obtained from all the variables associated with AF and/or AF diagnosed by Holter registry in the univariate analysis (Table 2), thereby reducing the significant variables to anticoagulants (OR = 18.90; 95% CI, 2.10–169.83; p = 0.09) and NT-proBNP >95 pg/ml (OR = 22.42; 95% CI, 2.74–183.15; p=0.04) as the only independent predictors of AF in the logistic regression analysis performed in the whole cohort. CHA_2DS_2-VASc was an independent AF predictor when considered alone in the regression analysis (OR = 2.29; 95% CI 1.16–4.44; p = 0.017), but *P-value comparison hAF vs no AF* was not significant. A source for confusion is likely related to how the CHA2DS2VASc score is included in guideline recommendations: if the sum of points exceeds a certain threshold, a recommendation of treatment is triggered. This approach is great when making dichotomous decisions. There is previous evidence about the use of CHA2DS2VASc score in patients without atrial fibrillation. The Cox model was applied just on the variables included in CHADsVASc score as covariates in the regression analysis. Certainly, this could improve the creation of a model including CHA2DS2VASc only and allow comparing its performance to another model including CHA2DS2VASc and variables that are not included in CHA2DS2VASc score; calculating integrated discrimination improvement (IDI) and net reclassification index (NRI) could facilitate decisions of clinical usefulness in future studies.

Table 4. Comparison according to atrial fibrillation diagnosis.

	***Univariate analysis* *P*-value**	***Regression analysis* *P-value***
Coronary heart disease	0.008	0.247
Heart failure	0.007	0.870
Valvular disease	0.024	0.357
Anticoagulation	0.000	0.09
NT-proBNP >95	<0.0001	0.04
CHA_2DS_2-VASc	0.035	0.017*

* when considered alone in the regression analysis

As for the variable NT-proBNP> 95 pg/ml as a cut-off applicable to systematic AF screening, it is lower as a cut-off point here than in other studies [55,56] that place it at ≥125 ng/L as a negative predictive value to be screened among individuals with newly detected AF and CHA2DS2-VASc parameters do not differ significantly with those without AF, so the populations are not identical. However, the conclusions were similar: NT-proBNP increased in individuals with newly detected AF and future studies could clarify if NT-proBNP can be used to correctly select individuals that benefit most from AF screening.

The variable "Anticoagulation" should be interpreted as a discriminatory marker as soon as patients with diagnosed AF are anticoagulated. The global results reflect a significantly higher use of anticoagulants among those cases with AF in which opportunistic screening was performed.

Finally, the result for CHA2DS2-VASc as an independent AF predictor when considered alone in the regression analysis agrees with previous publications [57-60] that showed its possible predictive value in the stratification of the risk of suffering from AF and / or stroke and not only as an indicator of anticoagulant treatment.

8. Discussion

8. Discussion

Both parts of the study had the common goal of helping to establish a guided route for AF. As main results from this project, we established that a health program of case finding is a tool that increases the prevalence and incidence of AF, we revealed barriers for the case finding, and we identified that NT-proBNP is a marker that could be used in AF case finding.

In the first phase, 61% of over 48,000 patients aged 60 and older underwent case finding for AF, thereby tripling the incidence of new AF cases detected compared to the control group. Case finding or/and screening are extremely useful secondary prevention measures; its basic purpose is to decrease the incidence of complications derived from important pathologies that can lead to significant disability, decrease mortality, and/or increase the quality of life of people affected by certain pathologies [61,62]. The effectiveness of case finding, in this case, was conditioned by variables including age, residence, institutionalization and comorbidities. Before this study, previous papers mainly focused on treatment barriers [63, 64], but no study has focused before on "not so clinical" barriers such as the frequentation of health services, age, place of residence and other comorbidities. Considering these variables and the implementation of new digital technologies could improve the results of AF case finding, especially for populations at higher risk of AF. Remarkably, 87% of the new AF cases had $CHA_2DS_2VAS_c$ scores of ≥ 2.

The variables associated with the lack of AF case finding should be considered in the implementation of a healthcare program. The first variable was the place of residence; patients in urban zones were less likely to have case finding for AF performed. This could be attributed to many causes, but in our territory, it could be because there are no urban municipalities in the two districts with a higher demographic age. Another variable to

consider is the association of the number of visits to the patient's GP with the performance of opportunistic case finding. The study showed that if the number of visits increased, so did the possibility for performing case finding and thus detecting new AF cases. For this reason, the population could be encouraged to perform self-case finding [65] or we wait for that to happen [66] through pulse palpation and the use of new AF detection devices. Institutionalized patients were found to have less AF identified; we could explain this by the fact that these patients have fewer possibilities to access their GPs and have more comorbidities.

The results of the second phase of the study show that NT-proBNP could be used as a screening biomarker to detect even paroxysmal AF in asymptomatic, high-risk individuals. One of the main goals of this part of the study was to predict or diagnose paroxysmal AF through biomarkers and to use them as a first step in a screening workflow in an AF pathway. Our study differed from others [67,68] by not only classifying paroxysmal AF with a normal ECG, but by overcoming this limitation by recording the patients' cardiac records using a Holter monitor, thereby detecting more cases of paroxysmal AF. This is the longest period over which asymptomatic individuals have been monitored to detect AF in a biomarker study, if we exclude studies using pacemakers. The inclusion in the study was performed before any biomarker determination and 4-week Holter monitoring was used as the gold standard to assess the usefulness of blood-based biomarkers in AF screening. A limitation of this part of the study might be the small number of participants, but after validating these results with a larger cohort, NT-proBNP could be implemented as part of a case finding program for AF in a defined AF pathway.

A specific cut-off point for AF case finding was proposed for the first time. NT-proBNP with values > 95 pg/ml reached a high sensitivity in identifying AF (95%), even

in patients with paroxysmal AF (85.7%). Although NT-proBNP can be categorised as an unspecific biomarker for AF (it can be elevated in different chronic and acute diseases), high sensitivity is more useful than specificity for screening purposes. Although it might be suspected that elevated NT-proBNP levels were due to a higher burden of heart failure and other cardiovascular diseases in the AF subjects of our cohort, in the hAF group, there were few individuals with known comorbidities that could affect NT-proBNP levels. In fact, in this group, there were no cases of heart failure, and there were only differences in coronary heart disease when compared to individuals with no AF. In addition, the study was carried out at the outpatient clinic and, therefore, no patient was in a situation of acute decompensated heart failure. B-type natriuretic peptide (BNP) and the stable N-terminal portion of the prohormone NT-proBNP are peptides synthesized by myocytes, predominantly in the left ventricle, in response to elevated wall stress. High natriuretic peptide levels correlate positively with cardiac filling pressures, making them excellent markers for abnormal LV wall stress; patients' elevated NT-proBNP levels independently predict an increased risk of developing AF [69]. The other biomarkers studied in this phase were not useful for AF case finding. It is also remarkable that a higher level of NT-proBNP was associated with a higher AF burden (observed from continuous Holter monitoring).

On the one hand, the limitations of this study include its non-randomisation and its duration compared with the follow-up visits with the patients. It is limited by its duration to minimal follow-up regarding stroke incidence in the patients. On the other hand, the small sample size and the small number of patients with diagnosed AF suggest that these results should be interpreted as hypothesis-generating. Eventually, the burden of AF will be important to consider and reuse. It can be defined as the duration of AF episodes during a certain time (varies in different studies) [70, 71]. The duration of AF

episodes and number of times shown in the record have yet to be deeply investigated, but they are useful in assessing the risk of developing clinically significant AF and thus the need for anticoagulant treatment. Currently, the burden of AF necessary to indicate anticoagulation is a matter of debate.

It should be noted that this part presents the results of the pilot study of the AFRICAT project, which included only the first 100 patients as a prior evaluation of the methodological strategy and the detection of potential problems in the final inclusion phase, so it was not designed for multivariate analysis. However, it does highlight that, with due caution in interpreting the results, a cut-off point can be defined in a biomarker within the scope of routine care among primary care professionals; this biomarker can be used to increase the effectiveness of screening by identifying individuals at high risk of not only of AF, but also of strokes. The results of the AFRICAT study will confirm or modify this cut-off point, its ability to discriminate and the post-test probability in AF screening.

The main global objective of the two parts of the study was to define and create a precise route for the screening, diagnosis and treatment of AF and thus to avoid the obvious adverse effects derived from said pathology.

Our proposal is to aim case finding for AF to a general population sixty years or older excluding only those patients previously diagnosed with AF **(Figure 6 Appendix)**. The general practitioner should first account for the social, demographic and other barriers identified in the first paper to try to find as many cases as possible. Once identified, as doctors, we should consider whether the patient could be defined as having a high risk of suffering from AF, using different scores, such as $CHA_2DS_2VAS_C$ or the CHARGE-AF score, and with the aid of different devices such as Watch BP, Fibricheck, intelligent watches and wristbands, among others. If the patient is defined as having a

high risk of developing AF, we should investigate further and search for biological and or echocardiographic criteria for AF. In the case of this study, NT-proBNP >95 pg/ml proved to be elevated in patients with AF compared to the control patients. If any of the biological and/or echocardiographic criteria for AF are fulfilled, to confirm whether our patients suffer from AF, we should plan to use Holter monitoring. These two works should be considered together with the emerging evidence from other similar studies to have an accurate AF pathway for the detection of AF.

The results of both articles define a more effective methodology in the active screening for AF. AF is an independent predictor of heart failure and stroke. The number of AF-related incident ischaemic strokes at age ≥80 years has trebled over the last 25 years, despite the introduction of anticoagulants, and are projected to treble again by 2050, along with the number of systemic emboli. Improved prevention in older people with AF should be a major public health priority. Overall, this highlights the high costs associated with different cardiovascular factors in an ageing society and also the cost of previously unknown AF-associated strokes. These progressive increases in overall burden justify the investigation of methodologies and their cost-effectiveness ratios to better direct prevention and treatment strategies.

9. Conclusions

9. Conclusions

1) The performance of opportunistic case finding is associated with a significant increase in the recorded prevalence and incidence of AF. If proper and aimed case finding is eventually done in a high-risk population (defined and categorized by risk scales), the detection of new cases of AF will be significantly higher.

2) There is a relationship between the performance of opportunistic case finding and factors like the frequent use of health services, age, place of residence and comorbidities. These should be considered in an AF case finding pathway in primary care.

3) NT-proBNP may be useful as a screening biomarker for AF in asymptomatic high-risk populations with a promising cut-off point of 95 pg/ml, but this requires further validation.

10. Future research proposals

10. Future Research proposals

For future objectives, we should first try to better identify and categorize patients at high risk of AF with more accurate scales and try to break as many barriers to access as possible.

Our second and short-term objective is for NT-proBNP >95 pg/ml to have external validation with a larger cohort of patients to prove if it is still valid and establish a more accurate cut-off point. Also, more biomarkers should be identified and tested to find the most useful for the early diagnosis of AF.

The third objective is to establish the needed time for a Holter device to diagnose a patient with AF. Also, we should find more comfortable devices with higher battery capacity.

Future studies should further analyse and test different watches and or wristbands, which could allow us to screen a large population without creating additional cost or time burdens for GPs.

The last objective is to evaluate and test whether anticoagulation should be initiated before AF identification in certain patients with a very high risk of AF after an evaluation based on clinical, ECG, imaging and biological markers. The burden of AF should also be evaluated before deciding to anticoagulate.

Future research should focus on cost-utility analysis using a patient-level Markov decision analytic model with a lifetime horizon to determine lifetime costs, quality-adjusted life years and the incremental cost-effectiveness ratio of active screening for AF with new technologies and biomarkers, particularly in relation to routine care in patients at high risk of atrial fibrillation.

11. References

11. References

1. The burden of Stroke in Europe report. King's College London for the Stroke Alliance for Europe (SAFE). Brussels, May 11th 2017. Available in http://www.strokeeurope.eu/downloads/TheBurdenOfStrokeInEuropeReport.pdf (accessed 25/03/2018).

2. Turakhia MP, Shafrin J, Bognar K, Trocio J, Abdulsattar Y, Wiederkehr D, Goldman DP. Estimated prevalence of undiagnosed atrial fibrillation in the United States. PloS One 2018;13:e0195088.

3. Clua-Espuny JL, Muñoz Pérez MA, Bustamante-Rangel A, Montaner Villalonga J, Pedrote Martínez AA, et al. On behalf of the members of the AFRICAT Group. Stepwise High Risk Individuals Screening for Atrial Fibrillation Using Sequential Clinical-electro-biological Register: the AFRICAT Study (Atrial Fibrillation Research In Catalonia). ClinicalTrials.gov Identifier: NCT03188484

4. Melissa Leung MBBS, Philippe J. van Rosendael, Rachid Abou, Nina Ajmone Marsan, Dominic Y. Leung, Victoria Delgado, et al. The Impact of Atrial Fibrillation Clinical Subtype on Mortality. JACC Clin Electrophysiol. 2018 Feb;4(2):221-227. doi: 10.1016/j.jacep.2017.09.002. Epub 2017 Nov

5. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and Mechanisms of Stroke: Time for a New Model. *Stroke*. 2016;47(3):895–900. doi:10.1161/STROKEAHA.115.012004

6. Diener HC, Hart RG, Koudstaal PJ, Lane DA, Lip GYH. Atrial Fibrillation and Cognitive Function: JACC Review Topic of the Week. J Am Coll Cardiol. 2019 Feb 12;73(5):612-619. doi: 10.1016/j.jacc.2018.10.077

7. Saliba W, Gronich N, Barnett-Griness O, Rennert G. Usefulness of $CHA_2DS_2VAS_C$scores in the prediction of new-onset atrial fibrillation: a population-based study. Am J Med 2016;129:843-849

8. McElwaine, P, McCormack, J and Harbison, J. Irish Heart Foundation/HSE National Stroke Audit 2015. 2015.

9. Pikija, S., et al., A High Burden of Ischemic Stroke in Regions of Eastern/Central Europe is Largely Due to Modifiable Risk Factors. Curr Neurovasc Res, 2015. 12(4): p. 341-52.

10. Naess, H., et al.,[Patients with acute cerebral infarction admitted to stroke unit]. Tidsskr Nor Laegeforen, 2011. 131(8): p. 814-8.

11. Sposato, L.A., et al., Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol, 2015. 14(4): p. 377-87.

12. Lowres N, Giskes K, Hespe C, Freedman B. Reducing Stroke Risk in Atrial Fibrillation: Adherence to Guidelines Has Improved, but Patient Persistence with Anticoagulant Therapy Remains Suboptimal. *Korean Circ J*. 2019;49(10):883–907. doi:10.4070/kcj.2019.0234

13. Clua-Espuny JL, Lechuga-Duran I, Bosch-Princep R, Roso-Llorach A, Panisello-Tafalla A, Lucas-Noll J, et al. (2013) Prevalencia de la fibrilación auricular desconocida y la no tratada con anticoagulantes. Estudio AFABE. Rev Esp Cardiol. 2013;66 (7): 545-552. DOI: 10.1016/j.recesp.2013.03.006

14. Ali AN, Abdelhafiz A. Clinical and Economic Implications of AF Related Stroke. *J Atr Fibrillation*. 2016;8(5):1279. Published 2016 Feb 29. doi:10.4022/jafib.1279

15. Zungsontiporn N and Link MS. Newer technologies for detection of atrial fibrillation. BMJ. 2018 Oct 17;363:k3946. doi: https://doi.org/10.1136/bmj.k3946

16. Hahne K, Mönnig G, Samol A. Atrial fibrillation and silent stroke: links, risks, and challenges. *Vasc Health Risk Manag*. 2016;12:65–74. Published 2016 Mar 7. doi:10.2147/VHRM.S8180

17. https://www.who.int/health-topics/dementia Consulted on March 2020.

18. Leif Friberg, Mårten Rosenqvist, Less dementia with oral anticoagulation in atrial fibrillation, *European Heart Journal*, Volume 39, Issue 6, 07 February 2018, Pages 453–460, https://doi.org/10.1093/eurheartj/ehx579

19. Aldrugh S, Sardana M, Henninger N, Saczynski JS, McManus DD. Atrial fibrillation, cognition and dementia: A review. *J Cardiovasc Electrophysiol*. 2017;28(8):958–965. doi:10.1111/jce.13261

20. Queralt-Tomas ML, Panisello-Tafalla A, González-Henares A, Clua-Espuny JL, Campo-Tamayo W, et al. (2017) Complex Chronic Patients and Atrial Fibrillation: Association with Cognitive Deterioration and Heart Failure. J Clin Exp Res Cardiol 3(1): 104]

21. Clua-Espuny JL, Lechuga-Duran I, Bosch-Princep R, Roso-Llorach A, Panisello-Tafalla A, Lucas-Noll J. Prevalencia de la fibrilación auricular desconocida y la no tratada con anticoagulantes. Estudio AFABE. REC Publicatios. 2013;66(7):545-552. Published July 2013. DOI: 10.1016/j.recesp.2013.03.006

22. Chunyan Lei, Qionghua Deng, Haijiang Li, Lianmei Zhong. Association Between Silent Brain Infarcts and CognitiveFunction: A Systematic Review and Meta-Analysis. Journal of Stroke and Cerebrovascular Diseases, Vol. 28, No. 9 (September)

23. Chugh SS, Havmoeller R, Narayanan K, Singh D, Rienstra M, Benjamin EJ, et al. Circulation 2013 Dec 17;[EPub Ahead of Print].

24. Jones NR, Taylor CJ, Richard Hobbs FD, Bowman L, Casadei B. Screening for atrial fibrillation: a call for evidence, *European Heart Journal*, Volume 41, Issue 10, 7 March 2020, Pages 1075–1085, https://doi.org/10.1093/eurheartj/ehz834

25. Joung B, Lee JM, Lee KH, et al. 2018 Korean Guideline of Atrial Fibrillation Management. *Korean Circ J*. 2018;48(12):1033–1080. doi:10.4070/kcj.2018.0339

26. Freedman B, Camm J, Cakins H, Healey JS, Rosenqvist M, Wang J, et al. Screening for Atrial Fibrillation. A Report of the AF-SCREEN International Collaboration. Circulation.2017;135:1851-1867. https://doi.org/10.1161/CIRCULATIONAHA.116.026693

27. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESCGuidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78.

28. Hijazi Z, Oldgren J, Lindbäck J, Alexander JH, Connolly SJ, Eikelboom JW. The novel biomarker-based ABC (age, biomarkers, clinical history)-bleeding risk score for patients with atrial fibrillation: a derivation and validation study. Lancet. 2016 Jun 4;387(10035):2302-11. doi: 10.1016/S0140-6736(16)00741-8.

29. Chang KW, Hsu JC, Toomu A, Fox S, Maisel AS. Clinical Applications of Biomarkers in Atrial Fibrillation. Am J Med. 2017 Dec;130(12):1351-1357. doi: 10.1016/j.amjmed.2017.08.003. Epub 2017 Aug 16.

30. https://strokeeurope.eu/ Consulted in March 2020.

31. Renate B. Schnabel, Karl Georg Haeusler, Jeffrey S. Healey, Ben Freedman, et al. Searching for Atrial Fibrillation Poststroke. A White Paper of the AF-SCREEN International Collaboration. Circulation. 2019;140:1834-1850. DOI: https://doi.org/10.1161/CIRCULATIONAHA.119.040267

32. www.cspin.ca/studies/piaaf/piaaf-pharmacy/ Consulted in March 2020

33. Caley M. Kroop, Nichelle L. Huber, David Sager, Murrium Sadaf, J.PaulMounsey, Samuel F. Sears. Mobile-ECG screning in rural pharmacies: rates of atrial fibrillation and associated risk factors. Heart & Lung. DOI: https://doi.org/10.1016/j.hrtlng.2020.01.004

34. Bacchini, M, Bonometti, S, Del Zotti, F, et al. Opportunistic Screening for Atrial Fibrillation in the Pharmacies: A Population-Based Cross-Sectional Study. High Blood Press Cardiovasc Prev 26, 339-344 (2019). https://doi.org/10.1007/s40292.019-00334-4

35. Da Costa FA, Mala-Ladova K, Lee V, Tous S, Papastergiou J, Griffiths D. Awareness campaigns of atrial fibrillaion as an opportunity for early detection by pharmacist: an international cross-sectional study. J Thromb Thrombolysis. 2019 Nov 28. DOI: https://doi.org/10.1007/s11239-019-02000-x

36. A. John Camm, Gregory Y.H. Lip, Raffaele De Caterina, Irene Savelieva, Dan Atar, Stefan H. Hohnloser, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: An update of the 2010 ESC Guidelines for the management of atrial fibrillation Developed with the special contribution of the European Heart Rhythm Association, *European Heart Journal*, Volume 33, Issue 21, November 2012, Pages 2719–2747, https://doi.org/10.1093/eurheartj/ehs253

37. Fabienne Midy , Véronique Raimond , Clémence Thébaut , Cléa Sambuc y Catherine Rumeau-Pichon. Haute Autorite de sante opinion on cost-effectiveness of health products: results and perspectives.Sante Publique. 2015 Sep-Oct;27(5):691-700.

38. Ermini G, Perrone V, Veronesi C, Degli Esposti L, Di Pasquale G. Antithrombotic prophylaxis of atrial fibrillation in an Italian real-world setting: a retrospective

study. *Vasc Health Risk Manag*. 2017;13:239–246. Published 2017 Jul 5. doi:10.2147/VHRM.S136009

39. Kemp Gudmundsdottir K, Fredriksson T, Svennberg E, et al. Stepwise mass screening for atrial fibrillation using N-terminal B-type natriuretic peptide: the STROKESTOP II study. *Europace*. 2020;22(1):24–32. doi:10.1093/europace/euz255

40. Marco Proietti, Georges H. Mairesse, Peter Goethals, Christophe Scavee, Johan Vijgen, Ivan Blankoff, Yves Vandekerckhove, Gregory Y.H. Lip, on behalf of Belgian Heart Rhythm Week Investigators, A population screening programme for atrial fibrillation: a report from the Belgian Heart Rhythm Week screening programme, *EP Europace*, Volume 18, Issue 12, December 2016, Pages 1779–1786, https://doi.org/10.1093/europace/euw069

41. Lévy S, Maarek M, Coumel P, Guize L, Lekieffre J, Medvedowsky JL, Sebaoun A.Characterization of different subsets of atrial fibrillation in general practice in France: the ALFA study. The College of French Cardiologists. *Circulation. 1999 Jun 15; 99(23):3028-35*

42. Hillmann S, Wiedmann S, Rücker V, et al. Stroke unit care in germany: the german stroke registers study group (ADSR). *BMC Neurol*. 2017;17(1):49. Published 2017 Mar 9. doi:10.1186/s12883-017-0819-0

43. http://www.alleanzalfa.org/news.htm Accessed March 2020

44. https://heartrhythmalliance.org/afa/uk/global-af-aware-week-uk-2019 Accessed March 2020

45. Fay Matthew, Ditzmaurice David, Freedman Ben. Screening of older patients for atrial fibrillation in general practice: Current evidence and its implications for future practice. European Journal of General Practice. Pages 246-253 | Received 03 Nov

2016, Accepted 15 Aug 2017, Published online: 16 Oct 2017. DOI: https://doi.org/10.1080/13814788.2017.1374366

46. Freedman B, Schnabel R, Calkins H. Opportunistic Electrocardiogram Screening for Atrial Fibrillation to Prevent Stroke. JAMA Cardiol. 2019; 4(2):91-92. doi:10.1001/jamacardio.2018.4335

47. Welton NJ, McAleenan A, Thorm HH, Davies P, Higgins JP, Okoli G, et al. Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. Health Technology Assessment. Volume: 21, Issue: 29, Published May 2017. DOI: https://doi.org/10.3310/hta21290

48. Linker DT, Murphy TB, Mokdad AH. Selective screening for atrial fibrillation using multivariable risk models. Heart. 2018 Sep;104(18):1492-1499. DOI: https://doi.org/10.1136/heartjnl-2017-312686

49. Orchad J, Li J, Gallagher R, Freedman B, Lowres N, Neubeck L. BMC Family Practice. 2019; 20:170. DOI: https://doi.org/10.1186/s12875-019-1058-9

50. Chan NY. Systematic Screening for Atrial Fibrillation in the Community Evidence and Obstacles. Arrhythm Electrophysiol Rev. 2018;7(1):39-42. DOI: https://doi.org/10.15420/aer.2017.47.2

51. Himmelreich JCL, Veelers L, Lucassen WAM, Schnabel RB, Rienstra M, van Weert HCPM, et al. Prediction models for atrial fibrillation applicable in the community: a systematic review and meta-analysis. EP Europace. 2020 Feb 3. DOI: https://doi.org/10.1093/europace/euaa005

52. Ingrid E, Christophersen MD, Xiaoyan Yin, Martin G. Larson, Steven A. Lubitz, Jared W. Magnani, et al. A comparison of the CHARGE-AF and the $CHA_2DS_2VAS_C$risk scores for prediction of atrial fibrillation in the Framingham Heart Study. Am Heart J. 2016;178:45-54. DOI: https://doi.org/10.1016/j.ahj.2016.05.004

53. Winnie Chua, Yanish Purmah, Victor R Cardoso, Georgios V Gkoutos, Samantha P Tull, Georgiana Neculau, et al. Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation, *European Heart Journal*, Volume 40, Issue 16, 21 April 2019, Pages 1268–1276, https://doi.org/10.1093/eurheartj/ehy815

54. Ghazal F, Theobald H, Rosenqvist M, Al-Khalili F (2019) Assessment of N-terminal pro-B-type natriuretic peptide level in screening for atrial fibrillation in primary health care. PLOS ONE 14(2): e0212974. https://doi.org/10.1371/journal.pone.0212974

55. Emma Svennberg, Peter Henriksson , Johan Engdahl, Ziad Hijazi Faris Al-Khalili , Leif Friberg , Viveka Frykman. N-terminal pro B-type natriuretic peptide in systematic screening for atrial fibrillation. Heart. 2017 Aug;103(16):1271-1277. doi: 10.1136/heartjnl-2016-310236.

56. Magnussen, C.; Niiranen, T.; Ojeda, F.M.; Gianfagna, F.; Blankenberg, S.; Njølstad, I.; Vartiainen, E.; Sans, S.; Pasterkamp, G.; Hughes, M.; et al. Sex Differences and Similarities in Atrial Fibrillation Epidemiology, Risk Factors, and Mortality in Community Cohorts: Results From the BiomarCaRE Consortium (Biomarker for Cardiovascular Risk Assessment in Europe). Circulation2017, 136, 1588–1597, doi:10.1161/CIRCULATIONAHA.117.028981.

57. Muria-Subirats E, Clua-Espuny JL, Ballesta-Ors J, et al. Incidence and Risk Assessment for Atrial Fibrillation at 5 Years: Hypertensive Diabetic Retrospective Cohort. Int J Environ Res Public Health. 2020;17(10):3491. Published 2020 May 16. doi:10.3390/ijerph17103491.

58. Saliba, W.; Gronich, N.; Barnett-Griness, O.; Rennert, G. Usefulness of CHADS2 and CHA2DS2-VASc Scores in the Prediction of New-Onset Atrial Fibrillation: A

Population-Based Study. Am. J. Med.2016, 129, 843–849, doi:10.1016/j.amjmed.2016.02.029.

59. Kaplan, R.M.; Koehler, J.; Ziegler, P.D.; Sarkar, S.; Zweibel, S.; Passman, R.S. Stroke Risk as a Function of Atrial Fibrillation Duration and CHA 2 DS 2 -VASc Score. Circulation2019, 140, 1639–1646, doi:10.1161/circulationaha.119.041303.

60. Morillas P, Pallares V, Rubio LF, Llisterri JL, Sebastián ME, Gómez M, et all. La puntuación CHADS2 como predictor de riesgo de ictus en ausencia de fibrilación auricular en pacientes hipertensos de 65 o más años. Rev. Española de Cardiol. 2015, 68, 485–491, doi:10.1016/j.recesp.2014.06.028.

61. Crossan C, Lord J, Ryan R, Nherera L, Marshall T. Cost effectiveness of case-finding strategies for primary prevention of cardiovascular disease: a modelling study. *Br J Gen Pract*. 2017;67(654):e67-e77. doi:10.3399/bjgp16X687973

62. Ascunce Elizaga, N. Screening: why and how. *SCIELO* Anales Sis San Navarra vol.38 n.1 Pamplona Jan./Apr. 2015. http://dx.doi.org/10.4321/S1137-66272015000100001

63. Verdino RJ. Untreated atrial fibrillation in the United States of America: Understanding the barriers and treatment options. *J Saudi Heart Assoc*. 2015;27(1):44-49. doi:10.1016/j.jsha.2014.09.003

64. Barra S, Fynn S. Untreated atrial fibrillation in the United Kingdom: Understanding the barriers and treatment options. *J Saudi Heart Assoc*. 2015;27(1):31-43. doi:10.1016/j.jsha.2014.08.002

65. Jaakkola J, Vasankari T, Virtanen R, Juhani Airaksinen KE. Reliability of pulse palpation in the detection of atrial fibrillation in an elderly population. *Scand J Prim Health Care*. 2017;35(3):293-298. doi:10.1080/02813432.2017.1358858

66. Rahimi K, Kirchhof P. Self-palpation for detection of paroxysmal atrial fibrillation: Much noise with little signal. *PLoS Med* 17(3): e1003098. https://doi.org/10.1371/journal.pmed.1003098

67. Turagam MK, Mirza M, Werner PH, et al. Circulating Biomarkers Predictive of Postoperative Atrial Fibrillation. *Cardiol Rev*. 2016;24(2):76-87. doi:10.1097/CRD.0000000000000059

68. Hijazi Z, Oldgren J, Siegbahn A, Granger CB, Wallentin L. Biomarkers in atrial fibrillation: a clinical review. *Eur Heart J*. 2013;34(20):1475-1480. doi:10.1093/eurheartj/eht024

69. Víchez JA, Roldan V, Hernández-romero D, Valdés M, et al. Biomarkers in atrial fibrillation: an overview, *The International Journal of Clinical Practice*, Volume 68, Issue 4, April 2014, Pages 434-443, https://doi.org/10.1111/ijcp.12304

70. Bayés-de-Luna A, Martínez-Sellés M, Elosua R, Bayés-Genís A, Mendieta G, Baranchuk A, et al. Relation of Advanced Interatrial Block to Risk of Atrial Fibrillation and Stroke. *Am J Cardiol*. 2020 Mar 16. pii: S0002-9149(20)30208-3. doi: 10.1016/j.amjcard.2020.02.034

71. Lin Y. Chen, Mina K. Chung, Larry A. Allen, Michael Ezekowitz, Karen L. Furie, Pamela McCabe, et al. Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. *Circulation*. 2018;137:e623-e644. https://doi.org/10.1161/CIR.0000000000000568

12. Appendix

12.1. Figures

12.1.1. Figure 1. WHO attributes of a good screening program.

1. Important health program
2. Available treatment
3. Facilities for diagnosis and treatment
4. Asymptomatic phase of disease
5. The test should be acceptable to the population
6. There should be a test for the condition
7. Natural history understood; agreement on policy
8. There should be an agreed policy on whom to treat
9. Cost of case finding balanced with overall costs
10. Tests should be sensitive
11. Screening should be a continuous process

12.1.2. Figure 2. Screening tools. EHRA consensus document.

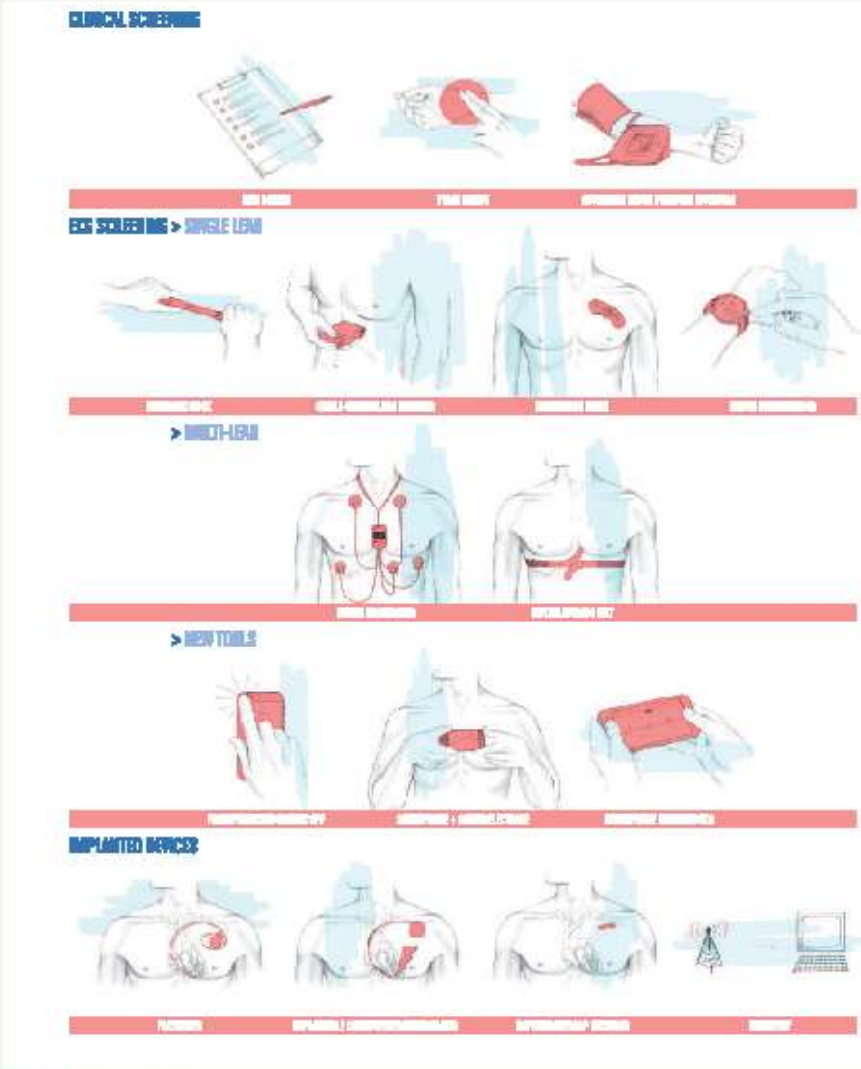


Figure 2 Screening tools.

12.1.3. Figure 3. New screening devices.

Table 5 | Sensitivity and specificity of newer intermittent ECG recording devices

Study	Study design	Population	AF detection methods	Sensitivity	Specificity	Remarks
Standalone handheld devices						
Tavernier R et al. 2018[31]	Cross sectional analysis of prospective cohort study	1402 single lead ECG recordings from prospective cohort study of patients admitted to department of geriatric medicine	MyDiagnostick automated algorithm	88%	97%	Reference diagnosis: MyDiagnostick single lead ECG interpreted by panel of three blinded electrophysiologists
Desteghe L et al. 2017[27]	Cross sectional observational study	265 patients without pacemaker/ICD admitted to cardiology ward	MyDiagnostick automated algorithm (A); MyDiagnostick single lead ECG interpreted by blinded electrophysiologists (EP1 and EP2)	82% (A); 77% (EP1); 73% (EP2)	94% (A); 93% (EP1); 96% (EP2)	Reference diagnosis: 12 lead ECG interpreted by two blinded electrophysiologists
		113 patients without pacemaker/ICD admitted to geriatric ward	MyDiagnostick automated algorithm (A); MyDiagnostick single-lead ECG interpreted by blinded electrophysiologists (EP1 and EP2)	90% (A); 100.0% (EP1); 95% (EP2)	96% (A); 84% (EP1); 90% (EP2)	Reference diagnosis: 6 lead ECG interpreted by two blinded electrophysiologists
Tieleman RG et al. 2014[28]	Cross sectional observational study	192 patients from outpatient cardiology/ specialised AF outpatient clinic (mean age 69.4 (SD 12.6) years; 48% male)	MyDiagnostick automated algorithm	100%	96%	Reference diagnosis: 12 lead ECG interpreted by blinded cardiologist
		676 patients attending for influenza vaccination (mean age 74 (SD 7.1) years)	MyDiagnostick automated algorithm	100%	99%	Reference diagnosis: MyDiagnostick single lead ECG interpreted by blinded cardiologist
Vaes B et al. 2014[29]	Cross sectional observational study	181 selected patients with and without history of AF and without active cardiac pacing recruited in primary care setting (mean age 74.6 (SD 9.7) years; 52% male)	MyDiagnostick automated algorithm	94%	93%	Reference diagnosis: 12 lead ECG interpreted by blinded cardiologist
Svennberg E et al. 2017[30]	Retrospective analysis	80 149 ECG recordings from 3209 participants in randomized controlled trial of AF screening strategy	Zenicor-ECG automated algorithm	97.8%	88.2%	Reference diagnosis: Zenicor-ECG single lead ECG interpreted by specially trained nurses + physicians
Doliwa PS et al. 2009[32]	Cross sectional observational study	100 patients with AF, atrial flutter, or sinus rhythm from cardiology outpatient clinic	Zenicor-ECG single lead ECG interpreted by blinded cardiologist	96%	92%	Reference diagnosis: 12 lead ECG interpreted by blinded cardiologist
Kearley K et al. 2014[33]	Cross sectional observational study	999 patients aged ≥75 recruited from primary care practices (mean age 79.7 (range 75.1-99.8) years; 49.3% male)	Omron monitor (model HCG-801, Omron Healthcare Europe, Netherlands) autoanalysis (A); Omron monitor single lead ECG interpreted by blinded cardiologists (meta-analysis of 4) (C)	98.7% (A); 94.4% (C)	76.2% (A); 94.6% (C)	Reference diagnosis: interpretation of 12 lead ECG by two blinded cardiologists. AF was found in 7.9% of study population
			Merlin ECG event recorder (Meditech Ltd, Hungary) single lead ECG interpreted by blinded cardiologists (meta-analysis of 4)	93.9%	90.1%	
Smartphone based device						
Chan PH et al. 2017[35]	Cross sectional observational study	2052 patients aged ≥65 with hypertension or diabetes mellitus without pacemaker or defibrillator attending primary care clinic (mean age 67.8 (SD 10.6) years; 45.8% male)	AliveECG App version 2.2.2	66.7%	99.5%	Reference diagnosis: interpretation of single lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. AF was found in 1.2% of study population
Desteghe L et al. 2017[27]	Cross sectional observational study	265 patients without pacemaker/ICD admitted to cardiology ward	AliveECG App version 2.1.2 (A) (recalled)[34]; interpretation of AliveCor single lead I ECG by blinded electrophysiologists (EP1 and EP2)	55% (A); 91% (EP1); 91% (EP2)	98% (A); 95% (EP1); 96% (EP2)	Reference diagnosis: 12 lead ECG interpreted by two blinded electrophysiologists
		113 patients without pacemaker/ICD admitted to geriatric ward	AliveECG App version 2.1.2 (A) (recalled)[34] interpretation of AliveCor single lead I ECG by blinded electrophysiologists (EP1 and EP2)	79% (A); 95% (EP1); 95% (EP2)	98% (A); 87% (EP1); 88% (EP2)	Reference diagnosis: 6 lead ECG interpreted by two blinded electrophysiologists
Chan PH et al. 2016[37]	Cross sectional observational study	1013 patients with hypertension, diabetes mellitus, or age ≥65 years, without pacemaker or defibrillator, attending primary care clinic (mean age 68.4 (SD 12.2) years; 46.8% male)	AliveECG App version 2.2.2	71.4%	99.4%	Reference diagnosis: interpretation of single-lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. AF was diagnosed in 2.8% of study population
Orchard J et al. 2016[47]	Cross sectional observational study	973 patients aged ≥65 years attending for influenza vaccination	AliveCor KardiaMobile optimized research algorithm[34]	95%	99%	Reference diagnosis: interpretation of single-lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. Newly identified AF was found in 8/973 (0.8%) patients
Taraka KG et al. 2015[48]	Prospective cohort study	55 patients with AF undergoing ablation who had iPhones (mean age 60 (SD 12) years; 78% male)	AliveCor single lead I ECG (interpreted by blinded electrophysiologist) at least once/week and as needed for symptoms during 3 month follow-up period	100%	97%	Reference diagnosis: concurrent traditional transtelephonic monitor tracing interpreted by blinded electrophysiologist

Study	Study design	Population	AF detection methods	Sensitivity	Specificity	Remarks
Lowres N et al. 2014[36]	Retrospective analysis	996 ECGs from pharmacy customers aged ≥65 without paced rhythm (n=1000, mean age 76 (SD 7) years; 44% male)	AliveCor KardiaMobile optimized research algorithm[34]	98.5%	91.4%	Reference diagnosis: AliveCor KardiaMobile single lead ECG interpreted by cardiologist
Lau JK et al. 2013[49]	Cross sectional observational study	109 recruited patients (39 in AF)	AliveCor KardiaMobile original research algorithm (A)[34]; interpretation of AliveCor single lead I ECG by blinded cardiologists (C1 and C2)	87% (A); 100% (C1); 95% (C2)	97% (A); 90% (C1); 94% (C2)	Reference diagnosis: 12 lead ECG interpreted by blinded cardiologist
		204 recruited patients (48 in AF)	AliveCor KardiaMobile optimized research algorithm[34]	98%	97%	Reference diagnosis: 12 lead ECG interpreted by blinded cardiologist
Smartwatch based device						
Bumgarner JM et al. 2018[50]	Cross sectional observational study	112 single lead ECGs from 100 patients with AF undergoing cardioversion (mean age 68 (SD 11) years; 83% male)	Kardia Band automated algorithm	93%	84%	Reference diagnosis: 12 lead ECG interpreted by two blinded electrophysiologists. 57/169 single lead ECGs were uninterpretable and were excluded from analysis

AF=atrial fibrillation; ECG=electrocardiography; ICD=implantable cardioverter-defibrillator.

Table 6 | Sensitivity and specificity of non-ECG devices

Study	Study design	Population	AF detection methods	Sensitivity	Specificity	Remarks
Automatic oscillometric blood pressure monitors with AF detection algorithm						
Chan PH et al. 2017[78]	Cross sectional observational study	5969 patients with hypertension, diabetes mellitus, or age ≥65 without pacemaker or defibrillator attending primary care clinic (mean age 67.2 (SD 11.0) years; 46.1% male)	Microlife WatchBP Home A (three measurements performed)	80.6%	98.7%	Reference diagnosis: interpretation of single-lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. AF was found in 1.2% of study population
Chan PH et al. 2017[77]	Cross sectional observational study	2052 patients aged ≥65 with hypertension or diabetes mellitus without pacemaker or defibrillator attending primary care clinic (mean age 67.8 (SD 10.6) years; 45.8% male)	Microlife WatchBP Office AFIB	83.3%	98.7%	Reference diagnosis: interpretation of single lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. AF was found in 1.2% of study population
Gandolfo C et al. 2015[71]	Cross sectional observational study	207 patients in stroke unit with unselected recent stroke or TIA without pacemaker or defibrillator (mean age 77.7 (SD 11.3) years; 50% male)	Microlife AFib model BP3MQ1-2D (three measurements performed)	90%	99%	Reference diagnosis: interpretation of 12 lead ECG by blinded cardiologist. AF was found in 18% of study population
Wiesel J et al. 2014[72]	Cross sectional observational study	183 patients aged ≥50 without pacemaker or defibrillator in two outpatient cardiology clinics (mean age 74 (range 50-100) years; 59% male; 71% white)	Microlife BP A 200 (rhythm considered to be AF on basis of ≥2/3 measurements)	100%	92%	Reference diagnosis: interpretation of 12 lead ECG by blinded cardiologist. AF was found in 16% of study population
			Omron M6 Comfort (Omron Healthcare, Kyoto, Japan) (rhythm considered to be AF on basis of one measurement)	30%	97%	
Kearley K et al. 2014[45]	Cross sectional observational study	999 patients aged ≥75 without pacemaker or defibrillator recruited from primary care practices (mean age 79.7 (range 75.1-99.8) years; 49.3% male)	Microlife WatchBP	94.9%	89.7%	Reference diagnosis: interpretation of 12 lead ECG by two blinded cardiologists. AF was found in 7.9% (1.2% new) of study population
Marazzi G et al. 2012[73]	Cross sectional observational study	503 patients without pacemaker or defibrillator referred to hypertension clinic (mean age 67.0 (SD 10.5) years; 54.3% male)	Microlife BP A 200 Plus (rhythm considered to be AF on basis of ≥2/3 measurements)	92%	97%	Reference diagnosis: interpretation of 12 lead ECG by blinded cardiologists. AF was found in 20% (new 9.3%) of study population
			Omron M6 (rhythm considered to be AF on basis of one measurement)	100%	94%	
Stergiou GS et al. 2009[74]	Cross sectional observational study	73 patients with known sustained AF, other non-AF arrhythmias, and sinus rhythm without pacemaker or defibrillator (mean age 70.5 (SD 10.6) years; 66% male)	Microlife BPA 100 Plus (rhythm considered to be AF on basis of ≥2/3 measurements)	100%	89%	Reference diagnosis: ECG interpreted by one investigator and verified by expert cardiologist
Wiesel J et al. 2009[75]	Cross-sectional observational study	405 unselected outpatients without pacemaker or defibrillator seen in two cardiology clinics (mean age 73 (range 34-98) years; 51% male)	Microlife BP3MQ1-2D (rhythm considered to be AF on basis of ≥2/3 measurements)	97%	88%	Reference diagnosis: interpretation of 12 lead ECG by blinded cardiologists. AF was found in 23% of study population
Smartphone based PPG with automated algorithms						
Rozen G et al. 2018[79]	Cross sectional observational study	191 pulse recordings from 98 patients undergoing cardioversion for AF (mean age 67.7 (SD 10.5) years; 76% male; 92% white)	iPhone based PPG with Cardio Rhythm Mobile Application which analyzes degree of self similarity of PPG waveform over time to find repeating patterns (rhythm classified as AF if ≥2/3 recordings were irregular	93%	91%	Reference diagnosis: interpretation of 12 lead or single lead ECG by two blinded cardiologists
Chan PH et al. 2016[37]	Cross sectional observational study	1013 patients with hypertension, diabetes mellitus, or age ≥65 without pacemaker or defibrillator attending primary care clinic (mean age 68.4 (SD 12.2) years; 46.8% male)	iPhone based PPG with Cardio Rhythm Mobile Application which analyzes degree of self similarity of PPG waveform over time to find repeating patterns (rhythm classified as AF if ≥2/3 recordings were irregular	92.9%	97.7%	Reference diagnosis: interpretation of single lead I ECG tracing recorded by AliveCor device by two blinded cardiologists. AF was diagnosed in 2.8% (0.5% new) of study population
McManus DD et al. 2016[77]	Cross sectional observational study	219 pulse recordings from 121 selected participants with AF, PACs, and PVCs (mean age 66 years; 82% male; 93% white)	iPhone based PPG with automated algorithm that performs beat-to-beat rhythm analysis using three validated statistical techniques	97%	93.5%	Reference diagnosis: interpretation of 12 lead ECG or 3 lead telemetry by physicians

AF=atrial fibrillation; ECG=electrocardiography; ICD=implantable cardioverter-defibrillator; PAC=premature atrial contraction; PPG=photoplethysmography; PVD=premature ventricular contraction; TIA=transient ischemic attack.

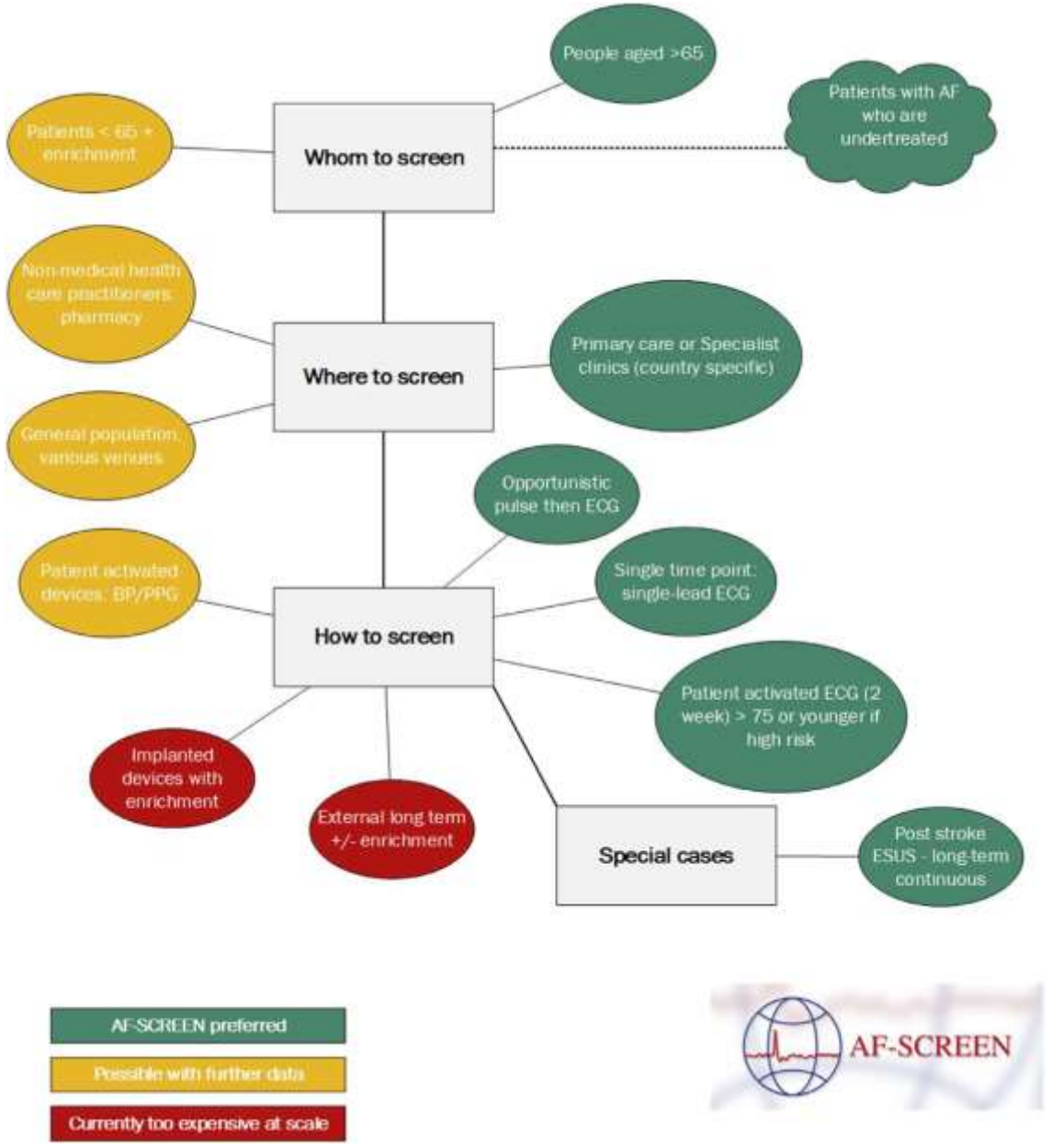
Table 7 | Sensitivity and specificity of implantable loop recorders (ILRs)

Study	Study design	Population	AF detection methods	Sensitivity	Specificity	Remarks
Ciconte G et al. 2017[106]	Prospective cohort study	63 patients with ILRs at risk of AF episodes (mean age 60.4 (SD 9.4) years; 86% male)	BioMonitor (Biotronik, Berlin, Germany) (3 ECG vectors) automatic AF detection algorithm	100% (per patient analysis; ≥1 episode of AF ≥2 min)	67% (per patient analysis; ≥1 episode of AF ≥2 min)	Reference diagnosis: simultaneous 48 h Holter monitor interpreted by blinded cardiologists. Correlation coefficient of AF burden by both devices=0.90
Nolker G et al. 2016[93]	Prospective cohort study	79 patients with ILRs and suspected or known paroxysmal AF (mean age 66.1 (SD 9.3) years; 58% male)	SJM Confirm Model DM2102 (St Jude Medical, St Paul, MN; now Abbott) automatic AF detection algorithm	100% (per patient analysis; ≥1 episode of AF ≥2 min). 84% (AF burden analysis)	86% (per patient analysis; ≥1 episode of AF ≥2 min). 99% (AF burden analysis)	Reference diagnosis: simultaneous 4 day Holter monitor interpreted by blinded electrophysiologist. Correlation coefficient of AF burden by both devices=0.959
Sanders P et al. 2016[97]	Prospective cohort study	138 patients with ILRs (>80% with history of AF) (mean age 56.6 (SD 12.1) years; 67% male)	Reveal LINQ (Medtronic, Minneapolis, MN) automatic AF detection algorithm	97% (per patient analysis; ≥1 episode of AF ≥2 min). 98% (AF burden analysis)	97% (per patient analysis; ≥1 episode of AF ≥2 min). 100% (AF burden analysis)	Reference diagnosis: simultaneous 24 h Holter monitor interpreted by blinded reviewers. Correlation coefficient of AF burden by both devices=0.995
Hindricks G et al. 2010[95]	Prospective cohort study	206 patients with ILRs who were likely to present with paroxysmal AF (mean age 57 (SD 10) years; 67% male)	Reveal XT (Medtronic, Minneapolis, MN) automatic AF detection algorithm	96% (per patient analysis; ≥1 episode of AF ≥2 min). 98% (AF burden analysis)	85% (per patient analysis; ≥1 episode of AF ≥2 min). 99% (AF burden analysis)	Reference diagnosis: simultaneous 46 h Holter monitor interpreted by blinded cardiologists. Correlation coefficient of AF burden by both devices=0.976

AF=atrial fibrillation.

Zungsontiporn Nath, Link Mark S. Newer technologies for detection of atrial fibrillation *BMJ* 2018; 363 :k3946

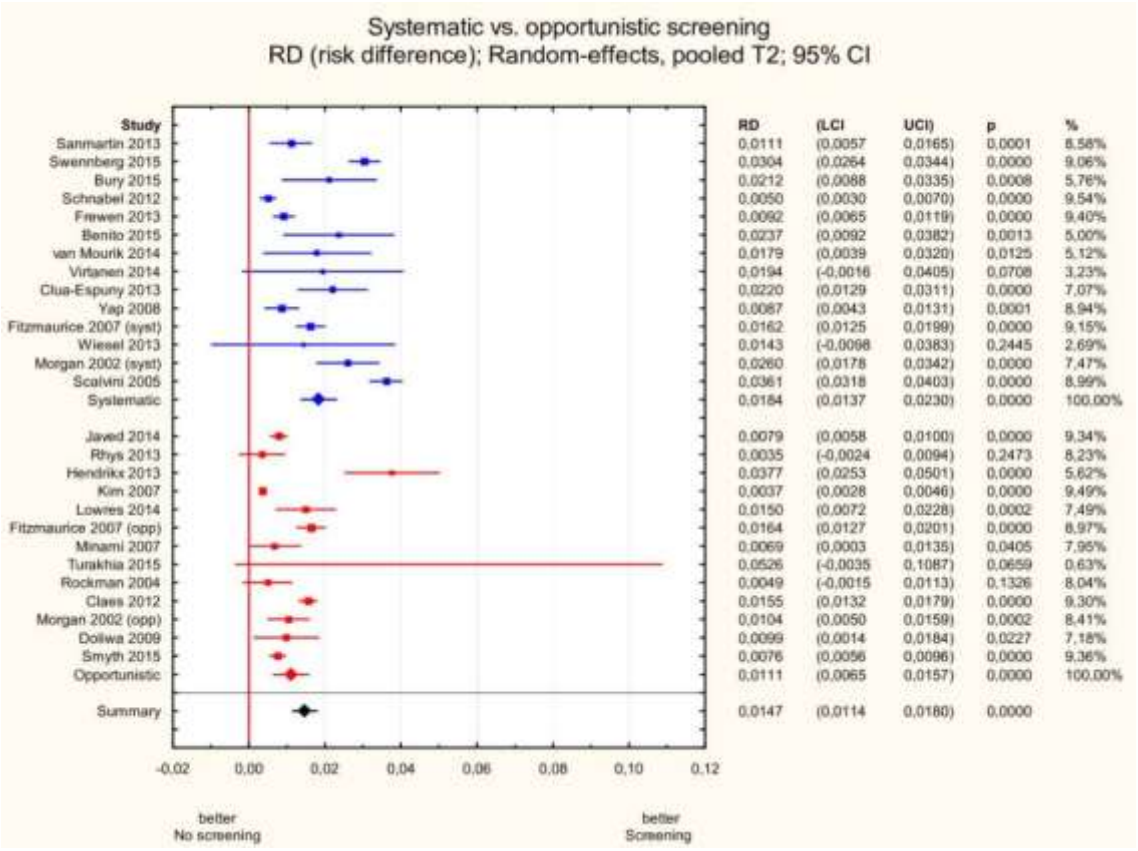
12.1.4. Figure 4. Current guidelines in Primary Care.



Freedman at al. *Circulation.* 2017;135:1851–1867. DOI: 10.1161/CIRCULATIONAHA.116.026693

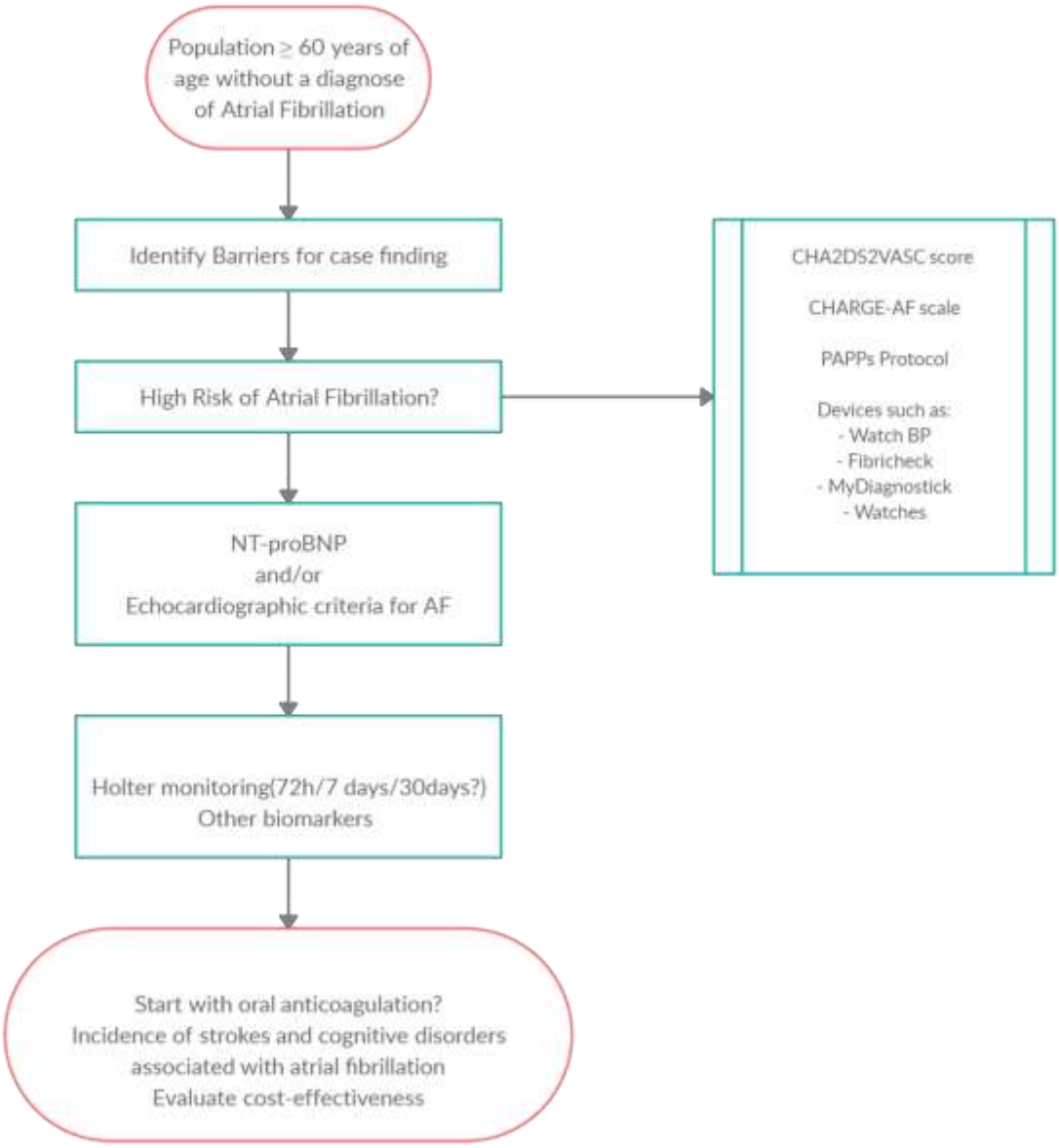
Visit www.afscreen.org for more information.

12.1.5. Figure 5. Systematic vs opportunistic screening for AF.



Petryszyn P, Niewinski P, Staniak A, et al. Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis. *PLoS One*. 2019;14(3):e0213198. Published 2019 Mar 20. doi:10.1371/journal.pone.0213198

12.1.6. Figure 6. Atrial fibrillation Pathway (AFOSS Study, 2020).



12.2. Table

12.2.1. Table 1. Summary of Studies Regarding Screening for Atrial Fibrillation (≥2015).

Name of Study **Year** **Number of participants** **Clinical Trial**	**Main objective**	**Target Population**	**Conclusions**
LOOP-Study 2015 N 6000 NCT02036450	Screening for AF episodes lasting ≥6 minutes (AF) with implantable loop recorder for 40 months of continuous monitoring randomized 3:1 to control (n=4500)	≥70 years old and have ≥1 stroke risk factors	AF was detected in 209 (35%) of the patients
PIAAF-FP 2015 N 2174 NCT02262351	Pulse palpation vs BPM vs ECG. Screening	<90 years	No Results Posted
PIAAF-HOME 2015 N 856 NCT02392754	AF screening in primary care patients using the ZIO XT Patch, a wearable adhesive patch monitor that provides continuous ECG recording for up to 14 days,	>75 years	ECG patch monitor is superior to standard care for AF detection

Incident AF – PREVEND 2015 N 8265	9.7 ± 2.3 years of follow-up for all inhabitants of the city of Groningen, the Netherlands Baseline screening program	28 to 75 years old	The overall incidence rate of AF was 3.3 per 1,000 person-years
D2AF 2015 N 19200 NTR 4914	Pulse palpation vs BPM vs ECG. Screening	>65 years	No Results Posted
ASSERT III 2015 N 129 NCT02401854	Determine the incidence of sub-clinical (silent) atrial fibrillation (AF) among elderly patients with hypertension and at least one other risk factor for AF. Wireless external loop monitor for 30 to 60 days	80 Years and older	Monitoring will detect AF in at least 10% of patients who would be potential candidates for anticoagulant therapy
STROKESTOP Study 2015 N 7173 NCT01593553	Define the prevalence of untreated atrial fibrillation (AF) in a systematic screening intermittent ECG recordings	75-76 years	A previous diagnosis of AF was known in 9.3%. Total AF prevalence in the screened population was 12.3%
Taggar et al. 2015 N 15129	Systematic review and meta-analysis		Blood pressure monitors and 12-lead ECG have the most accuracy

mSToPS 2015 N 2274	Identify a high-risk cohort suitable for screening for asymptomatic atrial fibrillation at the end of the 4-month monitoring period in a mobile health technology-enabled home monitoring program.	55 Years and older	No Results Posted
Area rural (Ireland) 2016 N 7262	Opportunistic screening. Over 6 months, subjects were screened by local General Practitioners using radial pulse palpation confirmed by 12 lead Electrocardiogram.	65 years and older	735 (10.1%) had known AF and 55 (0.76%) had newly detected AF
DOFA_AP 2017 N 5465	Opportunistic vs symptomatic patients	>65 years	No differences
AFFORD 2017 N 970	Opportunistic; Denmark	>65 years	Detection of new AF-patients
Akershus Cardiac Examination 1950 study 2017 N 1510	Screening for atrial fibrillation 2-week intermittent ECG screening	>65 years CHA_2DS_2-VASc score ≥2 for men or ≥ 3 for women	Identified undiagnosed AF in 0.9%. The total prevalence of AF was 7.6%
Petryszyn 2019 N 88786	Meta-analysis about the effectiveness of screening for AF		Active screening for AF is effective beginning from 40 years of age. Systematic screening seems more effective than opportunistic

Screening for Actionable Atrial Fibrillation During Preoperative Consultation With the MyDiagnostick 2016 N 505 NCT02960334	Presence of AF pre-operatory	65 Years and older	Analysed the rhythm for the presence of AF and distinguished AF from normal cardiac rhythms by measuring RR-irregularity
Opportunistic Screening in Pharmacies for Atrial Fibrillation in Seniors (AF-Stroke) 2016 N 7606 NCT03004859	Whether an opportunistic AF screening with a hand-held diagnostic tool in a German pharmacy setting is useful for detecting unknown AF among people aged 65 and older	(>65 Years)	No Results Posted
Systematic Screening for Atrial Fibrillation-potential Patients to Increase AF Detection Rate (SCAN-AF) 2017 N 1316 NCT03313167	Number of subjects screened with AF identified at Index Visit (4 weeks)	Individuals 65 years of age or older with moderate-to-high risk of stroke	No Results Posted
Atrial Fibrillation Screening in Nursing Homes 2019 N 245 NCT03860246	Number of participants with atrial fibrillation on any of four rhythm recordings	Age ≥75 years	No Results Posted

Home-Based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older (SCREEN-AF) 2015 N 856 NCT02392754	Detection of new atrial fibrillation or flutter	Age ≥75 years	No Results Posted
Screening for Atrial Fibrillation (AF)-Potential Patients to Increase AF Detection Rate 2017 N 1316 NCT03313167	Number of subjects screened with AF identified at Index Visit [Time Frame: Up to 4 weeks]	65 Years and older	No Results Posted
Novel Methods for Arrhythmia Detection: Preliminary Study 2018 N 220 NCT03721601	Chest strap and PPG-device data quality	All	No Results Posted

A Digital Non-interventional Atrial Fibrillation (AF) Screening Study With Commercial Pulse Detection Systems 2017 N 165 NCT02875106	The rate of correctly detected sinus rhythm signals by CPDS in reference to ECG (sensitivity of CPDS).	Not posted	No Results Posted
Opportunistic Screening in Pharmacies for Atrial Fibrillation in Seniors (>65 Years) 2017 N 7606 NCT03004859	· Number of newly detected atrial fibrillation in adults from the age of 65 by means of an opportunistic screening with an ECG hand-held diagnostic tool in a pharmacy setting · The subject's behaviour change regarding diagnosis and therapy from the ECG measurement at a pharmacy at 8 weeks and 12 months. · Identification and description of new therapeutic measures.	65 Years and older	No Results Posted
Program for the Identification of "Actionable" Atrial Fibrillation in the Family Practice Setting 2015 N 2174 NCT02262351	· Performance of screening tests · Cost of each method per case of actionable AF detected · Cost-effectiveness measures based on each screening test and their potential impact on stroke and other clinical endpoints	65 Years and older	No Results Posted

Screening for Atrial Fibrillation in Native AmeRicans Using iPhone ECG 2018 N 1500 NCT03740477	· Incidence of newly diagnosed atrial fibrillation · Prevalence of guideline-directed anticoagulant use among participants who were found to have atrial fibrillation	50 Years to 100 Years	No Results Posted
Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics 2018 N 35308 NCT03515057	· Incident AF during the study period · Incident AF associated with a primary care encounter during the study period · New oral anticoagulation prescription during the study period	65 Years and older	No Results Posted
Risk-Based Screening for the Evaluation of Atrial Fibrillation Trial 2018 N 755 NCT03911986	· New detected (and centrally confirmed) cases of atrial fibrillation/flutter > 2 minutes · Initiation of oral anticoagulation	55 Years and older	No Results Posted

Systematic Screening With Electrocardiogram for Unknown Atrial Fibrillation in 65 Years Old and Above People in Nursing Home 2015 N 287 NCT02892578	· Presence of atrial fibrillation on electrocardiogram · Presence of irregular pulse	65 Years and older	No Results Posted
Silent Atrial Fibrillation - Screening of High-risk Groups for Atrial Fibrillation (The Silence Study) 2016 N 1622 NCT02893215	· Number of participants with silent atrial fibrillation as assessed by handheld ECG measurements in high-risk heart failure patients · Number of participants with silent atrial fibrillation as assessed by handheld ECG measurements in high-risk type 2 diabetes patients · Number of participants with supraventricular ectopic activity	65 Years and older	No Results Posted
Hong Kong Outpatient AF Screening Using Single-lead ECG Device 2015 N 500 NCT02409654	· Utilization rates of evidence-based stroke prevention therapy · Rates of newly diagnosed atrial fibrillation in elderly >65 years of age · Clinical outcomes including death, stroke and bleeding	65 Years and older	No Results Posted

mHealth Screening to Prevent Strokes 2015 N 2274 NCT02506244	· Incidence of newly diagnosed AF · Prevalence of atrial fibrillation · Time to first event of the combined endpoint of stroke, systemic emboli or MI in patients diagnosed with AF in monitored vs. control cohorts. · Difference in total healthcare costs in AF cohorts of monitored and controls	55 Years and older	No Results Posted
Screening for Sleep Apnea in Patients Undergoing Atrial Fibrillation Ablation 2015 N 100 NCT02332096	· Prevalence of sleep apnea in patients with atrial fibrillation · Arrhythmia recurrence · Need for antiarrhythmic medications · CPAP compliance when prescribed	18 Years and older	No Results Posted
Stepwise Screening for Silent Atrial Fibrillation After Stroke 2018 N 300 NCT03570060	Diagnosis of atrial fibrillation during continuous monitoring in a Stroke unit within six months of stroke	18 Years and older	No Results Posted

RedStroke - Reducing Europe's Stroke Incidence 2019 N 2100 NCT04108884	· Prevalence of Atrial Fibrillation · Costs related to the AF screening · Compliance of patients using the app	All ages	No Results Posted
Prevention of Postop Atrial Fibrillation Through Intraoperative Inducibility of Atrial Fibrillation and Amiodarone Treatment 2017 N 600 NCT03868150	Decreasing the incidence of Post-Operative Atrial Fibrillation for Cardiac Surgery Patients	18 Years and older	No Results Posted
A Study to Determine if Identification of Undiagnosed Atrial Fibrillation in People at Least 70 Years of Age Reduces the Risk of Stroke 2019 N 52000 NCT04126486	· Occurrence of all strokes leading to hospitalization · Occurrence of bleeding leading to hospitalization	70 Years and older	No Results Posted

Sleep Apnea and Atrial Fibrillation Recurrence 2017 N 280 NCT02906839	· Time to recurrence of AF after AF ablation · Cost-utility analysis of SAS screening by reporting health resource utilization · Measure of health status EQ-5D	18 Years to 79 Years	No Results Posted
Atrial Fibrillation Research In CATalonia (AFRICAT) 2016 N 500 NCT03188484	Atrial fibrillation (AF) diagnosis	65 Years to 75 Years	No Results Posted
Handheld ECG Tracking of In-hOspital Atrial Fibrillation 2018 N 804 NCT03197090	Newly detected in-hospital AF	All ages	No Results Posted

Program for the Identification of "Actionable" Atrial Fibrillation in the Family Practice Setting 2015 N 2174 NCT02262351	· Performance of screening tests · Cost of each method per case of actionable AF detected · Cost-effectiveness measures based on each screening test and their potential impact on stroke and other clinical endpoints	65 Years and older	No Results Posted
Implementing Digital Health in a Learning Health System 2018 N 500 NCT03713333	· Patient-Reported Outcome Measures · Patient-Reported Experience Measures · Health Economic Outcomes	18 Years and older	No Results Posted
AFOSS 2017 N 46374 NCT03589170	Atrial fibrillation	60 Years and older	Case finding is associated with a significant increase in the prevalence and incidence of AF. There is a relationship between the performance of opportunistic case finding and factors like the frequent use of health services, age, place of residence and comorbidities NT-proBNP may be useful as a screening biomarker in AF A screening strategy based on NT-proBNP, alone or in combination with other biomarkers, might be of interest for the early initiation of anticoagulants, which could reduce cardioembolic stroke consequences

12.3 Articles

12.3.1 First article

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Health Service Research

Results, barriers and enablers in atrial fibrillation case finding: barriers in opportunistic atrial fibrillation case finding—a cross-sectional study

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Abstract

Background: Atrial fibrillation (AF) is often asymptomatic, and screening is not routinely undertaken.
Objective: Evaluate the feasibility and effectiveness of a population-based case finding program and to identify the enablers of and/or barriers to its implementation.
Methods: We conducted a cross-sectional study of a health care case finding program for AF from 1 January 2016, to 31 December 2017, that included 48 336 people ≥60 years of age in the region of Terresde l'Ebre (Catalonia, Spain). We analysed the effect on the prevalence of AF and, stratified by age, on the incidence of new diagnoses of AF. We assessed the sociodemographic and clinical variables related to the realization of a case finding.
Results: A total of 32 090 (62.4%) people were screened for AF. We observed a significant increase in the AF prevalence after 2 years of program intervention (5.9–7.7%; $P < 0.001$). The detection of new AF cases was significantly higher in the case finding group across the whole of the age range, and 765 (2.6%) new AF cases were diagnosed using case finding. The factors that were significantly associated with an underuse of case finding were: age <70 years, urban residence, institutionalized status, Pfeiffer score ≥2, Charlson score >3 and number of visits <7/year.
Conclusions: A health care program of case finding is feasible and is associated with a significant increase in the prevalence and incidence of AF. The results depend on factors such as the ease of access to health care, age, place of residence and comorbidities.

Key words: Anticoagulants, atrial fibrillation, case finding, patient, prevention, stroke

Key Messages

- Case finding was associated to increased diagnosis of new AF.
- Age, residence, institutionalization and comorbidity might condition the case finding.
- The screened population is treated more with anticoagulants (84.7% versus 77.4%).

Introduction

Atrial fibrillation (AF) is estimated to increase the risk of experiencing a stroke by a factor of three to five. AF, along with high blood pressure, is a risk factor for ischaemic stroke that is insufficiently detected and treated (1–4) in the general population and which has been previously unknown in 24–31% of patients who have experienced at least one stroke (1,2). The prevalence of AF and its complications will increase in the coming decades because of the ageing population (5), so developing proposals aimed at improving diagnosis and treatment is a priority. Population strategies for the opportunistic detection of AF are recommended by international organizations including the European Society of Cardiology (ESC), the Stroke Alliance for Europe (SAFE) (1), the European Heart Rhythm Association (EHRA), the Royal College of Physicians of Edinburgh (RCPE), the World Healthcare Forum (WHF), the European Primary Care Cardiovascular Society (EPCCS) and the Health Information and Quality Authority (HIQA). Disagreement remains, however, over whether case finding detects more AF than do standard practices (6).

Numerous studies have been initiated (7–10) with the objective of evaluating different strategies for AF detection. We can differentiate between those studies aimed at opportunistically diagnosing AF in binary form (11–14) and those using real-time monitoring technologies and/or biomarkers (15–18) to diagnose AF early, especially in subjects with high cardiovascular risk (19–21).

Based on previous results (4,22,23), a pilot project was developed in the region of Terres de l'Ebre (in Catalonia, an autonomous region of Spain) that had among its main objectives the implementation of a binary opportunistic case finding programme for AF in the population ≥60 years of age. The study aimed to evaluate the effectiveness of AF case finding in the general population ≥60 years of age relative to usual clinical practice and to identify possible factors in and barriers to AF case finding.

Methods

In 2015, the region of Terres de l'Ebre participated in a pilot project in collaboration with the Pla Director Malaltia Vascular/Agència de Quality i Avaluació Sanitàries de Catalunya (PDMVC) and the Estratègia d'Atención Integral a la Cronicitat (PPAC) to design a programme for AF detection. The PDMVC aims to embrace a comprehensive approach to cardiovascular diseases, from promotion and prevention to rehabilitation, taking into account the principles of equity and the reduction of inequalities. The purpose of the PPAC is to provide a new model of social and health care for all residents of Catalonia to use in responding to the challenge of chronicity and dependence, promoting health and preventing the risk factors of chronic diseases of highest impact, with attention paid from the very first phases to those of greatest complexity. As initial objectives, the project involved palpating the arterial pulse, registering an electrocardiogram and recording the results in the electronic medical records (e-cap) of any citizen ≥60 years of age who contacted the health system, especially a primary care provider. To register patients, a specific variable (A/AR) was introduced in the e-cap program, which was coded in a different colour when the citizen belonged to the target group but assessment had not been undertaken.

Territorial scope

Terres de l'Ebre is a territory comprising the four southernmost regions of Catalonia: Baix Ebre, Montsià, Terra Alta and Ribera d'Ebre. The area, which encompasses 3329 km², has a population of 191 791 in 52 municipalities with an average of 58 inhabitants/km². The bulk of the population is concentrated in the regions of Baix Ebre and Montsià, which constitute 81% of the region's population. A total of 7.46% of the population lives in municipalities with less than 1000 inhabitants (coded as rural in the software), 47.66% in those between 1000 and 10 000 inhabitants (coded as semi-rural in the software) and 44.87% in those of greater than 10 000 inhabitants (coded as urban in the software). The two counties with the oldest average population (Terra Alta and Ribera d'Ebre) contain no urban municipalities. The active ageing index [the ratio of the number of elderly persons (aged 65 and over) to the number of young persons (aged 0–14)] of these areas is 151.5, which is higher than that of both Catalonia (112.06) and Spain (118.43) as a whole. With regard to the health care system, the territory has a general hospital for the area as well as 11 primary care teams, all managed by the Institut Català de la Salut, a governmental agency, which holds the medical histories of 97.78% of the residents of the area who appeared in the official census of the territory between 1 January 2016 and 31 December 2017.

Type of study and description of the general and target populations

This was an observational, cross-sectional, multi-centric and non-interventional study in the context of ordinary primary care practice involving the population ≥60 years of age (n = 51 410) with an active clinical history (e-cap). A total of 48 336 patients without known AF were included in the study.

Variables

The main variable is whether a patient's heartbeat is rhythmic or arrhythmic, as described in the record of the patient's medical history of case finding activity for AF during the period from 1 January 2016 to 31 December 2017. The patient's record indicated whether case finding was performed. Case finding or screening for AF is defined as pulse palpation during routine general practitioner consultations at least once a year, together with a 12-lead ECG confirmation of an irregular or regular pulse (11)—for instance, during an annual cardiac disease review, with the result recorded as either 'rhythmic' (R) or 'arrhythmic' (AR). Patients with a previous record of AF were excluded (n=3074/51 410, 5.97%). Thus, new cases of AF were classified according to their relationship to the case finding:

a) AF was detected by means of direct AF case finding activity, which occurred by palpation of the pulse and/or registration of an ECG in asymptomatic patients for the purpose of detecting

an AF, which was subsequently recorded in the e-cap program (ICD code I48). Either in an office consultation or at home, a physician or referring nurse performed palpation and/or an ECG as a routine procedure, mainly to monitor chronic cardiovascular conditions (hypertension, diabetes, ischaemic heart disease and heart failure). A suspected arrhythmia via palpation was always followed by an ECG. The medical practitioner recorded any co-incidental clinical findings of the case finding, ECG and new AF diagnosis.

b) The detection of AF was made without a direct AF screening procedure. In these patients, AF was newly diagnosed within the context of decisions rendered in clinical practice from the presentation of symptoms or exploration of other comorbidities in any medical centre or at home, but not those taken as result of a case finding activity. The clinical findings of the case finding and/or ECG and the unintended new FA diagnosis were recorded.

The following secondary variables were defined:

- Sociodemographic: Age, gender and municipality of residence (>10 000 inhabitants, urban; 1000–10 000 inhabitants, semi-rural and <1000 inhabitants, rural).
- Clinical information: Comorbidities were obtained from the codes of the International Classification of Diseases, version 10 (ICD-10) in each patient's clinical history, both in primary and inpatient care settings. I48 was the code used to select the different entities of AF as the main diagnosis. The conditions of the $CHA_2DS_2VAS_c$ score were included. Cognitive impairment was unspecified and registered without noting its subtype or severity and evaluated using the Pfeiffer score (0–10), with 0–2 errors = normal and ≥3 errors = intermediate-to-severe affectation.
- Cognitive impairment was also used as a criterion in the diagnosis of a complex chronic patient (CCP), a variable assigned according to specific criteria, such as multi-morbidity, single severe or progressive chronic pathology, a high probability of suffering decompensations, intense and refractory persistent symptoms, dynamic evolution requiring continuous monitoring, the high use of health services, polymedication, severity, geriatric syndromes and extreme age.
- Prescription information: All medication prescribed for any active diagnosis in the individual's medical history was included. We define 'polymedication' as the prescription of ≥5 different medications simultaneously.
- Health services variables: The frequency or average number of visits recorded in a primary care setting and/or at a referral hospital over 1 year (i.e. separately for 2016 and 2017). We quantified the registered clinical visits for every medical condition, regardless of the area of speciality. The median and average annual attendance (family medicine plus nursing visits) were used as a reference.
- Long-stay institutionalized patients: Those patients in nursing homes for the elderly, under either private or public management, under the care of specific primary care teams from the territory. Patients residing in such homes have an active medical history with a specific coding due to their condition.

Goals

The study's objectives were to evaluate the feasibility and effectiveness of a population-based case finding programme and to identify the factors associated with them.

Statistics

A descriptive analysis of the sociodemographic and clinical variables was performed, describing the frequency and percentage of the categorical variables and the mean and standard deviation for the continuous variables. We compared these variables according to whether case finding was performed. Chi-square tests were used to compare the categorical variables' means, and unpaired Student's *t*-tests were used to compare the continuous variables. The prevalence and adjusted incidence by age at new AF per 1000 people were calculated, as well as the number of necessary case finding incidents to diagnose a new AF case (NNS). To measure the association of these variables with the detection of AF after case finding, we calculated the crude odds ratio and adjusted the multivariate model value using logistic regression. With those variables that were statistically significant, another logistic regression model was created that included factors associated with a significant inferior probability of having AF case finding performed, such as the following: <70 years of age, urban residence, institutionalization, Pfeiffer scale value ≥2 and ≤7 visits in 2017 to the patient's primary care physician. Through logistic regression, the odds ratio adjusted for all variables was calculated to measure the association of this created variable with the fulfilment of the case finding. Quality control was carried out through programmes that allowed for the basic detection of errors of two types: purely transcription errors and inconsistency between the values of the variables collected. Audits were carried out to detect possible deviations and errors and lost values and to determine the status of the investigation. Data analysis was performed using the statistical package SPSS 20.0.

Quality control

The identity of the participants was kept strictly confidential, and their anonymity was guaranteed at all times. The clinical application, including the cases, was subject to the current regulations for the protection of personal data (Ley Orgánica 15/1999; BOE-A-1999-23750 30/07/2018). The project was approved by the Ethics Committee for Scientific Research IDIAP Jordi Gol, protocol number P18/118. For this type of study formal consent is not required, as it was approved by the Ethics Committee, and the requirement of the informed consent of patients was waived prior to the inclusion of their medical data in this study. It has been registered at clinicaltrials.gov (identifier: NCT03589170).

Three probability variables were used to identify possible duplications (a patient's date of birth, sex and identification number on his or her individual health card) and ensure that each individual in the numerator was counted only once. Reviews were undertaken every 6 months to detect possible deviations, errors, lost values and extreme values, as well as to assess the status of the investigation.

The study's effectiveness was assessed based on changes observed in the prevalence of AF after 2 years of programme intervention and by comparing the incidence of newly diagnosed AF in the group with case finding as compared with the incidence in the control group.

Results

The population included 48 336 patients, whose baseline characteristics are described in Table 1. The mean age was 75 years, and 87% of the population had a $CHA_2DS_2VAS_c$ score of ≥2. Opportunistic AF case finding was performed in 61% of the population during the study period (2016–17) (Fig. 1). The average age was higher in the case finding group than the control group, as was their associated comorbidity, $CHA_2DS_2VAS_c$ score (24), proportion of urban

Table 1. Baseline characteristics of the population ≥60 years (Terres de l'Ebre, Catalonia) comparing case finding for AF versus no case finding (2016–17)

Variable	No case finding	Case finding	*P*	Total
Total *N* ≥ 60 years	19 320 (37.6%)	32 090 (62.4%)		51 410
Sex (%)				
Female	10 300 (53.3%)	17 230 (53.7%)	0.406	27 530
Male	9020 (46.7%)	14 860 (46.3%)		23 880
Average age	71.3 ± 9.9	75.12 ± 8.9	<0.001	73.68 ± 9.5
Residence (%)				
Urban	8370 (43.3%)	11 705 (36.5%)		20 075
Semi-urban	6643 (34.4%)	12 079 (37.6%)	<0.001	18 722
Rural	4307 (22.30%)	8306 (25.9%)		12 613
Institutionalization	806 (4.17%)	510 (1.59%)	<0.001	1316
Total *N* ≥ 60 years of age excluding known AF	**18 739 (38.76%)**	**29 597 (61.23%)**		**48 336**
New diagnosis of AF	129 (0.7%)	765 (2.6%)	<0.001	894
Total AF (%) at the end of the study	710 (3.7%)	3258 (10.1%)	<0.001	3968 (7.7%)
$CHA_2DS_2VAS_c$ score	2.12 ± 1.4	3.03 ± 1.31	<0.001	2.7 ± 1.41
Heart failure	703 (3.6%)	2687 (8.4%)	<0.001	3390
High blood pressure	7743 (40.1%)	21 390 (66.7%)	<0.001	29 133
Brain stroke/Transient Ischemic Attack	243 (1.2%)	689 (2.1%)	<0.001	932
Vascular disease	566 (2.9%)	1902 (5.9%)	<0.001	2468
Ischaemic cardiopathy	683 (3.5%)	2264 (7.1%)	<0.001	2947
Diabetes mellitus	2079 (10.8%)	8757 (27.3%)	<0.001	10 836
Impaired renal function (dialysis, renal transplantation or serum creatinine >200 μmol/l)	876 (4.5%)	3122 (9.7%)	<0.001	3998
Average glomerular filtrate (ml/min)	77.2 ± 19.9	74.3 ± 19.2	0.180	75.01 ± 19.4
Chronic liver disease or impaired hepatic function (bilirubin >2× or serum glutamic-pyruvic transaminase or serum glutamic-oxaloacetic transaminase or alkaline phosphatase >3× the normal limit)	26 (0.1%)	50 (0.2%)	0.633	76
COPD[a]	1469 (7.6%)	3517 (11.0%)	<0.001	4986
OSAS[b]	290 (1.5%)	767 (2.4%)	<0.001	1057
Anticoagulant treatment	550 (2.9%)	2759 (8.6%)	<0.001	(83.5%)
Anti-vitamin K	418 (2.2%)	2284 (7.1%)	<0.001	2702
NOACs[c]	132 (0.6%)	475 (1.5%)	<0.001	607
Statins	4471 (23.1%)	12 191 (38.0%)	<0.001	16 662
Cognitive impairment and/or Pfeiffer >2 score	963 (5.0%)	1691 (5.3%)	0.162	2654
Average Pfeiffer score	3.4 ± 3.3	2.3 ± 2.8	<0.001	2.58 ± 2.9
Number of CCI[d] criteria	0.3 ± 0.17	0.6 ± 0.23	<0.001	0.5 ± 0.21
Charlson Comorbidity Index	0.72 ± 1.06	1.15 ± 1.22	<0.001	0.99 ± 1.18
Number of drugs	3.66 ± 3.70	5.7 ± 3.77	0.007	4.93 ± 3.8
Average number of visits/year (PC[e])	9.15 ± 11.7	18.3 ± 15.5	<0.001	14.9 ±14.9
Median number of visits (PC)	6	14	<0.001	11
Average number of visits/year (HOSP[f])	0.17 ± 1.06	1.15 ± 1.22	<0.001	0.23 ± 0.88

[a]Chronic obstructive pulmonary disease.
[b]Obstructive sleep apnoea syndrome.
[c]Novel oral anticoagulants.
[d]Chronic complex patient.
[e]Primary care.
[f]Hospital.

residence and frequency of their primary and hospital care (Table 2). By contrast, the mean score on the Pfeiffer test for the case finding group was significantly lower than that of the control group. The number of patients receiving anticoagulant treatment (84.7%) was significantly higher ($P < 0.001$) in the case finding group than in the control group (77.4%).

A significant increase in the prevalence of AF was observed between the beginning and end of the programme assessment (5.9% versus 7.7%, respectively; $P < 0.001$). The detection of new AF cases was significantly higher in the case finding group for the full age range (Table 3). Two hundred and one new AF cases were detected by performing case finding, accounting for 0.6% of all people screened and 26.3% of all new AF cases diagnosed in this group. The number of case finding incidents (NNS) required for a new AF diagnosis using the opportunistic detection procedure was 147, which decreased progressively with age.

The prevalence of a stroke was significantly higher in the presence of AF than in the group without diagnosed AF (4.4% versus 1.6%; $P < 0.001$). The number of patients prescribed anticoagulant treatment was significantly higher in the group with a case finding of AF than in the control group (84.7% versus 77.4%; $P < 0.001$). The treatment with direct anticoagulant in the non-case finding group was higher (18.7% versus 14.6%; $P = 0.001$) than in the control group.

We analysed those variables related to the lack of performance in case finding. After adjusting for all variables, we obtained those

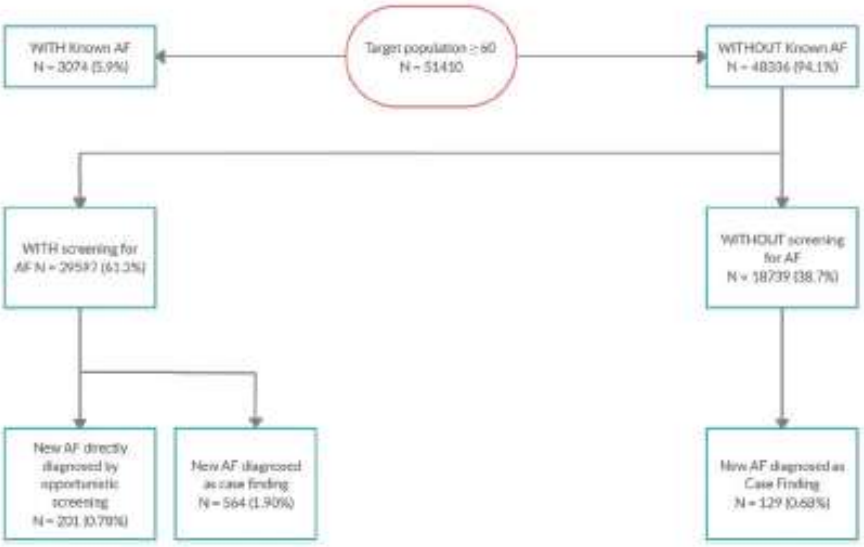

Figure 1. Flowchart of AF case finding in population ≥60 years (Terres de l'Ebre, Catalonia, 2016–17).

Table 2. Factors associated with the realization of AF case finding in people ≥60 years (Terres de l'Ebre, Catalonia, 2016–17

	OR	[a]CI95%	*P*	[b]ORaj	[a]CI95%	*P*
Sex						
Female	1			1		
Male	0.98	(0.95–1.02)	0.403	1.08	(0.93–1.26)	0.292
Age (years)						
60–69	1					
70–79	2.47	(2.36–2.58)	<0.001	1.73	(1.32–2.27)	<0.001
80–89	2.79	(2.65–2.93)	<0.001	1.69	(1.32–2.17)	<0.001
≥90	1.74	(1.61–1.88)	<0.001	1.33	(1.02–1.73)	0.032
Residence						
Urban	1					
Semi-urban	1.30	(1.25–1.35)	<0.001	1.37	(1.16–1.61)	<0.001
Rural	1.38	(1.25–1.44)	<0.001	1.02	(0.86–1.21)	0.833
Institutionalized						
No	1					
Yes	0.37	(0.33–0.41)	<0.001	0.38	(0.31–0.47)	<0.001
Pfeiffer score						
≤2	1					
>2	0.51	(0.45–0.59)	<0.001	0.59	(0.51–0.69)	<0.001
Charlson's Comorbidity Score						
0	1					
1	2.43	(2.32–2.56)	<0.001	1.36	(1.11–1.65)	0.002
2	1.81	(1.73–1.90)	<0.001	1.27	(1.04–1.56)	0.018
3	2.97	(2.75–3.19)	<0.001	1.22	(0.98–1.53)	0.079
4	3.74	(3.26–4.29)	<0.001	1.51	(1.11–2.03)	0.008
5	3.29	(2.57–4.20)	<0.001	1.02	(0.67–1.55)	0.937
6	2.51	(1.46–4.31)	0.010	0.68	(0.31–1.52)	0.349
Number of visits to PC in 2017	1.07	(1.07–1.08)	<0.001	1.02	(1.01–1.03)	<0.001

[a]95% confidence interval.
[b]Odd ratio adjusted for all variables (multivariate model).

Table 3. Adjusted incidence of new diagnosed AF in people ≥60 years (Terres de l'Ebre, Catalonia) by age (2016–17)

Age (years)	Total *N*	Total new AF cases (2016–17)	Population without case finding			Population with case finding			*P*
			N	Total new AF cases (2016–17)	Incidence of new AF cases/1000/year (CI95%)	*N*	Total new AF cases (2016–17)	Incidence of new AF cases/1000/year (CI95%)	
60–69	19 958	129	10 164	24	1.2 (0.7–1.7)	9794	105	5.3 (4.4–6.5)	<0.001
70–79	15 408	286	4624	35	3.8 (2.7–5.7)	10 784	251	11.6 (10.2–13.1)	<0.001
80–89	10 181	345	2878	46	8 (5.8–10.6)	7303	299	20.4 (18.2–22.9)	<0.001
≥90	2789	134	1073	24	11.2 (7.1–16.6)	1710	110	32 (26.3–33.6)	<0.001
Total	48 336	894	18 739	129	3.4 (2.8–4.1)	29 597	765	12.9 (12–13.6)	<0.001

identified as statistically significant (Table 2) and associated with not having opportunistic case finding for AF: age <70 years, urban residence, institutionalized status, Pfeiffer score ≥2 or a record of 'cognitive impairment', a Charlson score ≤3 and a lower than average number of physician visits for the territory. We identified no differences associated with sex.

Discussion

In this study of over 48 000 patients aged 60 and older in one region of Spain, 61% of the eligible population underwent case finding for AF over a period of 2 years, and the incidence of new AF cases detected was three times higher in the case finding population than the control group. A relationship between the performance of opportunistic case finding and its possible factors was also found.

The results of the study cannot prove causality but are nonetheless useful in the assessment of some barriers to and factors associated with a lower probability of performing case finding, which could improve its implementation in primary care and lead to more effective results. The results show an association of case finding with an increased diagnosis of AF, and the effectiveness of case finding was conditioned by variables including age, residence, institutionalization and comorbidities under usual conditions of care after a pilot health project was applied (4). Moreover, case finding was credited with detecting around one quarter of undiagnosed AF cases.

Other ongoing studies on case finding focus mainly on the effectiveness of different types of strategies (6) and on different devices and their sensitivity (17,18), but there remain no studies that have described possible barriers to AF case finding. The use of pulse palpation (either manual or automatic for 30 seconds during an ordinary visit) has been recommended as the first step in case finding for detecting AF (22), but it is still necessary to confirm the diagnosis by a register (such as a Holter device) (23). Previous other studies using this method in different populations worldwide have produced contradictory results regarding its effectiveness (6,25,26). Nevertheless, this methodology could have lower sensitivity (27) for detecting AF (17) when compared with other methodologies using technology (16,21,28). The implementation of new digital technologies could improve the results of AF case finding, especially for populations at higher risk of AF (16).

In our study, opportunistic case finding facilitated the diagnosis of new AF in patients with a high risk of embolism; 87% of the new AF cases had a $CHA_2DS_2VAS_c$ score of ≥2. This was consistent with the results of other studies (24). Consequently, anticoagulant treatment was used significantly more in this subgroup (77.4% versus 84.7%; $P < 0.001$). The low incidence of strokes during this period and the cross-sectional nature of the study prevented a conclusion about the usefulness of this method in reducing the incidence of strokes in the population.

In addition to determining the effectiveness of a health care programme, another important aspect of implementing it is to identify the difficulties of carrying out case finding for AF. We have identified some variables related to the underuse of opportunistic case finding for AF by pulse palpation that had not previously been identified and should be taken into account in the implementation of a health care program. The first variable was the patients' place of residence; those living in an urban zone were less likely to receive case finding for AF. One possible explanation for this could be that there are no urban municipalities in the two districts with higher demographic ageing where the study took place. The significant association of the number of physician visits with the performance of opportunistic case finding has positive implications for the accessibility and performance of an AF management pathway in primary care (24,26). If the number of visits increases, so does the probability of case finding and detecting new AF; thus, it would be justifiable to evaluate case finding strategies, such as the performance of self-monitoring of the patient by self-palpation (27,21) or the use of technological devices (14,18,27,21,30) and the participation of other centres of health care, such as pharmacies (31,32). The low percentage of AF identified among institutionalized patients—a subgroup with higher CV factors, a very high embolic risk due to habitual bedding and pluripathology and, usually, the typical conditions described for CCPs—should prompt the inclusion of opportunistic or systematic case finding in this population. The fact that institutionalized patients have less AF identified, can also be explained by the difficulties these patients have in accessing their GPs more frequently because of their fragile health. A Pfeiffer score of ≥2 or a determination of 'cognitive impairment' could be associated with a greater probability of institutionalization for these patients and therefore may limit their access to health services. Similarly, the presence of few comorbidities and a Charlson score of ≤3 could be associated with fewer medical visits and therefore with less case finding in these patients.

The limitations of this study include its non-randomization and its duration compared with the follow-up visits with these patients. It benefits from being performed under the usual circumstances of clinical practice, and it fulfils most conditions of a quasi-experimental study. It is limited by its duration to minimal follow-up regarding stroke incidence in these patients.

Conclusions

The performance of opportunistic case finding is associated with a significant increase in the recorded prevalence and incidence of AF.

There is a relationship between the performance of opportunistic case finding and factors like the frequent use of health services, age, place of residence and comorbidities. These should be considered in an AF case finding pathway in primary care.

Declaration

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Ethical approval: The project was approved by the Ethics Committee for Scientific Research IDIAP Jordi Gol, protocol number P18/118.
Conflict of interest: none.

References

1. The burden of Stroke in Europe report. *King's College London for the Stroke Alliance for Europe (SAFE)*. Brussels, 2017. http://www.strokeeurope.eu/downloads/TheBurdenOfStrokeInEuropeReport.pdf (accessed on 25 March 2018).
2. Clua-Espuny JL, Piñol-Moreso JL, Gil-Guillén VF *et al.* [Primary and secondary cardiovascular prevention results in patients with stroke: relapse risk and associated survival (Ebrictus study)]. *Rev Neurol* 2012; 54 (2): 81–92.
3. Sposato, LA, Cipriano LE, Saposnik G *et al.* Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015; 14 (4): 377–87.
4. Clua-Espuny JL, Lechuga-Duran I, Bosch-Princep R *et al.* Prevalence of undiagnosed atrial fibrillation and of that not being treated with anticoagulant drugs: the AFABE study. *Rev Esp Cardiol (Engl Ed)* 2013; 66: 545–52.
5. Proietti M, Laroche C, Opolski G *et al.* Real-word' atrial fibrillation management in Europe: observations from the 2-year-follow-up of the EURO Observational Research Programme-Atrial Fibrillation General Registry Pilot Phase. *Europace* 2017; 19 (5): 722–33.
6. Health Technology Assessment (HTA) of a National Screening Programme for Atrial Fibrillation in Primary Care. Health Information and Quality Authority, 2015. https://www.hiqa.ie/sites/default/files/2017-02/HTA-of-Screening-for-Atrial-Fibrillation.pdf (accessed on December 2017).
7. Jonas DE, Kahwati LC, Yun JDY *et al.* Screening for atrial fibrillation with electrocardiography evidence report and systematic review for the US preventive services task force. *JAMA* 2018; 320 (5): 485–98.
8. Quinn FR, Gladstone DJ, Ivers NM *et al.* Diagnostic accuracy and yield of screening tests for atrial fibrillation in the family practice setting: a multicentre cohort study. *CMAJ Open* 2018; 6 (3): E308–15. Published 2018 Aug 2. doi:10.9778/cmajo.20180001
9. Smyth B, Marsden P, Corcoran R *et al.* Opportunistic screening for atrial fibrillation in a rural area. *QJM* 2016; 109 (8): 539–43.
10. Moran PS, Flattery MJ, Teljeur C *et al.* Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev* 2013; (4): CD009586. doi:10.1002/14651858.CD009586.pub2
11. Uittenbogaart SB, Verbiest-van Gurp N, Erkens PMG *et al.* Detecting and Diagnosing Atrial Fibrillation (D2AF): study protocol for a cluster randomised controlled trial. *Trials* 2015; 16: 478.
12. Hobbs FDR, Taylor CJ, Geersing GJ *et al.* European Primary Care Cardiovascular Society (EPCCS) consensus guidance on stroke prevention in atrial fibrillation (SPAF) in primary care. *Eur J Prev Cardiol* 2016; 23 (5): 460–73.
13. Sanmartin M, Fraguela Fraga F, Martín-Santos A *et al.* Campaign for information and diagnosis of atrial fibrillation: 'Pulse Week'. *Rev Esp Cardiol* 2013; 66 (1): 34–8.
14. Camm, JA, Lobban T, Knight E *et al.* 2014. *The Route Map for Change in the European Atlas on the Prevention of AF-Related Stroke.* http://www.anticoagulationeurope.org/files/files/Interactive%20Route%20Map%20for%20 Change%2011Nov14%20final.pdf (Accessed on May 2018).
15. Svennberg E, Engdahl J, Al-Khalili F *et al.* Mass screening for untreated atrial fibrillation. The STROKESTOP Study. *Circulation* 2015; 131: 2176–84.
16. Reiffel J, Verma A, Halperin JL *et al.* Rationale and design of REVEAL AF: a prospective study of previously undiagnosed atrial fibrillation as documented by an insertable cardiac monitor in high-risk patients. *Am Heart J* 2014; 167: 22–7.
17. Palà E, Bustamante A, Clúa-Espuny JL *et al.* N-terminal pro b-type natriuretic peptide's usefulness for paroxysmal atrial fibrillation detection among populations carrying cardiovascular risk factors *Front Neurol.* 2019; 10: 1226. Published 2019 Nov 29. doi:10.3389/fneur.2019.01226
18. Hess PL, Healey JS, Granger CB *et al.* The role of cardiovascular implantable electronic devices in the detection and treatment of subclinical atrial fibrillation: a review. *JAMA Cardiol* 2017; 2 (3): 324–31.
19. Bumgarner JM, Lambert CT, Hussein AA *et al.* Smartwatch algorithm for automated detection of atrial fibrillation. *J Am Coll Cardiol* 2018; 71: 2381–8.
20. Chen LY, Chung Mk, Allen LA *et al.* Atrial fibrillation burden: moving beyond atrial fibrillation as a binary entity: a scientific statement from the American Heart Association. *Circulation* 2018; 137: e623–44.
21. Welton NJ, McAleenan A, Thom HH *et al.* Screening strategies for atrial fibrillation: a systematic review and cost-effectiveness analysis. *Health Technol Assess* 2017; 21 (29): 1–236.
22. Fay MR, Fitzmaurice DA, Freedman B. Screening of older patients for atrial fibrillation in general practice: current evidence and its implications for future practice. *Eur J Gen Pract* 2017; 23 (1): 246–53.
23. Freedman B, Camm J, Calkins H *et al.* Screening for atrial fibrillation: a report of the AF-SCREEN International Collaboration. *Circulation* 2017; 135 (19): 1851–67.
24. Saliba W, Gronich N, Barnett-Griness O *et al.* Usefulness of $CHADS_2$ and CHA_2DS_2-VAS_c scores in the prediction of new-onset atrial fibrillation: a population-based study. *Am J Med* 2016; 129: 843–9.
25. Petryszyn P, Niewinski P, Staniak A *et al.* Effectiveness of screening for atrial fibrillation and its determinants. A meta-analysis. *PLoS ONE* 2019; 14 (3): e0213198.
26. Chan NY. Systematic screening for atrial fibrillation in the community: evidence and obstacles. *Arrhythm Electrophysiol Rev* 2018; 7 (1): 39–42.
27. Taggar JS, Coleman T, Lewis S *et al.* Accuracy of methods for detecting an irregular pulse and suspected atrial fibrillation: a systematic review and meta-analysis. *Eur J Prev Cardiol* 2016; 23 (12): 1330–8.
28. Mortelmans C. Results of the Diagnostic Accuracy of FibriCheck in a Screening Setting Presented as a Best Poster Presentation at the ESC Conference in Munich. August 28th 14:00, Best Poster Screen, Poster Area, 2018.
29. Jacobs MS, Kaasenbrood F, Postma MJ *et al.* Cost-effectiveness of screening for atrial fibrillation in primary care with handheld, single lead electrocardiogram device in the Netherlands. *Europace* 2018; 20 (1): 12–8.
30. Jaakkola J, Jaakkola S, Lahdenoja O *et al.* Mobile phone detection of atrial fibrillation with mechanocardiography: the MODE-AF Study (Mobile Phone Detection of Atrial Fibrillation). *Circulation* 2018; 137: 1524–7.
31. Tison GH, Sanchez JM, Ballinger B. Passive detection of atrial fibrillation using a commercially available smartwatch. *JAMA Cardiol* 2018; 3: 409–16.
32. Tarride JE, Dolovich L, Blackhouse G *et al.* Screening for atrial fibrillation in Canadian pharmacies: an economic evaluation. *CMAJ Open.* 2017;5(3):E653–E661. doi:10.9778/cmajo0.20170042

12.3.2. Second article

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N-Terminal Pro B-Type Natriuretic Peptide's Usefulness for Paroxysmal Atrial Fibrillation Detection Among Populations Carrying Cardiovascular Risk Factors

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Background: Atrial fibrillation (AF) systematic screening studies have not shown a clear usefulness in stroke prevention, as AF might present as paroxysmal and asymptomatic. This study aims to determine the usefulness of some blood-biomarkers to identify paroxysmal atrial fibrillation in the context of a screening programme.

Methods: A total of 100 subjects aged 65–75 years with hypertension and diabetes were randomly selected. AF was assessed by conventional electrocardiogram (ECG) and 4 weeks monitoring with a wearable Holter device (Nuubo^{TM}). N-terminal pro B-type natriuretic peptide (NT-proBNP), apolipoprotein CIII (ApoC-III), von Willebrand factor (vWF), ADAMTS13, urokinase plasminogen activator surface receptor (uPAR), and urokinase plasminogen activator (uPA) were determined in serum/plasma samples and the levels were compared depending on AF presence and mode of detection.

Results: The AF prevalence in the studied population was found to be 20%. In seven subjects, AF was only detected after 1 month of Holter monitoring (hAF group). NT-proBNP levels were higher in subjects with AF compared with subjects with no AF ($p < 0.0001$), even when only taking into account the hAF group ($p = 0.031$). No significant differences were found in the other biomarkers. The NT-proBNP >95 pg/ml cut-off showed high sensitivity and specificity to detect AF (95%, 66.2%) or hAF (85.72%, 66.2%) and was found to be an independent predictor of AF and hAF in a logistic regression analysis. NT-proBNP correlated with AF burden ($r = 0.597$, $p = 0.024$).

Conclusion: NT-proBNP was elevated in AF cases not identified by ECG; thus, it may be used as a screening biomarker in asymptomatic high-risk populations, with a promising cut-off point of 95 pg/ml that requires further validation.

Keywords: stroke, atrial fibrillation, biomarker, screening, NT-proBNP

INTRODUCTION

Atrial fibrillation (AF) is one of the fastest-growing cardiovascular epidemics of the twenty-first century (1). This heart rhythm disorder multiplies by five the risk of ischemic stroke (2), and its prevalence in the population over 60 years has been quantified at 10.9% (3). Anticoagulation may reduce stroke risk in AF individuals by ~60% (4), but unfortunately, given its paroxysmal and asymptomatic nature at earlier stages, AF is often undiagnosed and/or undertreated when stroke occurs. In a previous study, the absolute prevalence of undiagnosed AF in individuals over 60 years was 3.4%, representing up to 31% of the overall AF prevalence in our area (5, 6). International collaborations (7, 8) recommend opportunistic screening for AF in patients >65 years as a strategy to reduce stroke and death, but systematic screening programmes have failed to show a clear benefit and those strategies are lacking in high-risk populations (9–11).

Blood biomarkers might represent an alternative tool for AF screening, because some of them might have elevated circulating levels after AF paroxysms, a kind of "biological memory" offering a temporal advantage over electrical detection of the paroxysm itself. N-terminal pro B-type natriuretic peptide (NT-proBNP) has been found to be elevated in cardioembolic (CE) stroke (12) and to be associated with AF (13–16). Von Willebrand factor (vWF) was found to be elevated in non-valvular AF (17) and, together with apolipoprotein CIII (ApoC-III), was found to be predictor of stroke CE etiology [unpublished results from the Stroke-Chip study (18)]. ADAMTS-13 is the key regulator of vWF, and it has been associated with AF recurrence after cardioversion (19). Urokinase plasminogen activator surface receptor (uPAR) has been associated with AF prevalence (20) while its ligand, urokinase plasminogen activator (uPA), has not been studied in AF patients.

This study aims to determine the usefulness of the aforementioned biomarkers to identify AF individuals in the context of a screening programme, especially in cases of paroxysmal AF that would not be detected using a regular 12-lead ECG.

MATERIALS AND METHODS

Patients and Protocol

AFRICAT (Atrial Fibrillation Research in CATalonia; NCT03188484) is an observational, multicenter, population-based study with the aim of developing a screening programme to detect new cases of AF in high-risk individuals in primary care centers. In Phase I of the project, 100 subjects aged 65–75 with hypertension and diabetes were selected from primary care registers (e-cap), which include the clinical records from most Catalonia inhabitants between January 2016 and December 2017. In two different health service areas, Servei d'Atenció Primària (SAP) Muntanya and SAP Terres de l'Ebre, patients fulfilling the inclusion criteria were identified in primary care centers from each catchment [Centre d'Atenció Primària (CAP) Sant Rafael and CAP Trinitat Vella in SAP Muntanya; Equip d'Atenció Primària (EAP) Tortosa Est and EAP Tortosa Oest in SAP Terres de l'Ebre]. Physicians from these primary care centers were informed about the study protocol, and patients were invited by them to participate in the study until 50 patients were recruited in each catchment. Participants were ambulatory patients in a basal situation, meaning they were contacted at home to arrange a visit in their primary care center specifically for the study. During the appointments, patients received a comprehensive assessment consisting of clinical characteristics (demographic factors, vascular risk factors, medications, comorbidities, and vitals), electrographic assessment and a blood sample collection. Comorbid conditions were defined using standard outpatient and inpatient ICD-10 codes by electronic data capture, including pharmacy records, laboratory data, and emergency room and hospitalization diagnoses across all primary care centers and hospitals.

Individuals with chronic inflammatory diseases, cancer or dementia were excluded. AF was assessed by conventional electrocardiogram (ECG). Moreover, patients were monitored for 4 weeks with a wearable Holter device (Nuubo™) as described previously (21). The Holter device was composed of a sensor that captured the electrocardiographic signal by non-invasive textile electrodes and a recorder of the signal that stored the information for subsequent detailed analysis. Participants were instructed by local trained researchers to wear the Holter for 23 h and recharge it for 1 h daily. After 4 weeks, individuals brought the Holter to their primary care center, and data were collected. Holter records, anonymized and encrypted, were sent together with the ECG for blinded reading to the Rhythm Disorders Unit at the Cardiology Department of Hospital Virgen del Rocio in Seville, to verify AF episodes. AF was defined following AHA guidelines as irregular R-R intervals without a P wave signal, lasting for more than 60 s (22). Individuals with previous AF were not excluded at this step, but Holter monitoring was optional in this subgroup.

Patients were classified and compared in five groups defined by past medical history (PMH) for AF, ECG findings and Holter AF detection as follows: no AF, PMH-ECG-Holter+ [Holter-detected AF (hAF)], PMH-ECG+, PMH+ECG-, and PMH+ECG+. Specific comparisons were done between the hAF and no AF groups.

The AFRICAT study protocol was approved by the clinical research ethics committees of IDIAP Jordi Gol (P15/047) and Hospital Universitari Vall d'Hebron [PR (AG) 133-2015]. All participants signed informed consent before inclusion. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Biomarker Measurement

Blood was collected into EDTA and serum tubes at the time of inclusion. After centrifugation at 1,500 g and 4°C for 15 min, plasma and serum aliquots were frozen at −80°C until biomarker determination.

Plasma NT-proBNP levels were determined by automated immunoassay in a COBAS c8000 (Roche Diagnostics); serum ApoC-III, plasma uPAR and plasma uPA by ELISA (Abnova, R&D Systems, and Cloud-Clone); and plasma vWF and ADAMTS13 by a magnetic Luminex® assay (R&D Systems).

All assays were performed blinded to clinical information and according to the manufacturer's instructions. All samples were tested in duplicate and inter-assay variation was determined by a commercial control (Human Serum, male AB, USA origin from clotted, SIGMA, ref number H16914; Human plasma K2 EDTA, Innovative Research, ref number IPLA-N) tested in duplicate in each plate. When inter-assay variation was >20% biomarker levels were standardized using the Z-score.

Statistical Analysis

Statistical analysis was conducted with SPSS version 20. Graphs were elaborated with GraphPad Prism 6. Data are expressed as number (%) for categorical variables and as mean ± SD or median (interquartile range) for continuous variables, depending on the data distribution. For univariate analysis, the Mann–Whitney *U*-test or Student's *t*-test was used for continuous variables, and the χ^2 test was used for categorical variables. ANOVA or the Kruskal–Wallis test was used to compare >2 variables depending on variable distribution. Receiver operator characteristic (ROC) curves were configured to calculate sensitivity, specificity, and cut-off values. The Spearman test was used for correlations. Comparisons were first performed between AF patients and no AF patients and second between hAF and no AF patients (excluding other subtypes of AF). Binary logistic regression analysis was performed including variables associated with AF or hAF in univariate analysis.

RESULTS

Patient Characteristics and AF Detection

Clinical characteristics of the cohort can be found in **Table 1**. Coronary heart disease ($p = 0.008$), heart failure ($p = 0.007$), valvular diseases ($p = 0.024$), and use of anticoagulants ($p < 0.0001$) were more common in AF individuals. Of the 9 anticoagulated individuals, only one was anticoagulated for reasons other than AF (ischemic cardiopathy and deep venous thrombosis). The CHA2DS2-VASc score was higher in AF individuals ($p = 0.035$). Coronary heart disease ischemia was more common in hAF individuals compared to no AF ($p = 0.032$). No cases of heart failure, valvular disease or anticoagulation were present in this subgroup.

Of the included 100 individuals, 96 were monitored with ECG Holter. All patients with negative ECG were monitored. Median monitoring time was 457 h. Six cutaneous adverse events related to wearing the Holter were noted; these consisted of a rash that normally disappeared with topical steroids. However, in two subjects, these adverse events prevented the monitoring being continued.

Of the 100 selected subjects, AF was present in 20 (11 newly detected within the present study) classified as follows: 7 PMH-ECG-Holter+ (hAF), 4 PMH-ECG+, 2 PMH+ECG-, and 7 PMH+ECG+ (**Figure 1**).

In 14 individuals (11 newly detected and 3 PMH+ECG+ were monitored), AF was detected during Holter monitoring and AF burden was calculated. AF burden was defined as minutes being in AF divided by the total minutes of readable records and is expressed as a percentage. The median AF burden was 10.35% (1.00–56.50).

Biomarker Analysis

NT-proBNP, ApoC-III, sUPAR, vWF, and ADAMTS13 inter- and intra-assay variation was acceptable (coefficient of variation<20); hence, all the samples were included in the analysis. uPA levels were standardized because the inter-assay variation was higher than 20%, and 9 samples were eliminated from statistical analysis

TABLE 1 | Clinical characteristics of the cohort and comparison according to atrial fibrillation diagnosis.

	All patients (100)	AF (20)	No AF (80)	hAF (7)	*P*-value[a]	*P*-value[b]
Age	70 (68–73)	69 (66–71.5)	70 (68–73)	70 (65–72)	0.273	0.655
Sex (% female)	33 (33)	7 (35)	26 (32.5)	3 (42.9)	0.832	0.682
Tobacco	20 (20)	4 (20)	16 (20.3)	1 (14.3)	1.000	1.000
Alcohol	11 (11)	1 (5)	10 (12.5)	0 (0)	0.456	1.000
Dyslipidaemia	81 (81)	16 (80)	65 (81.3)	5 (71.4)	1.000	0.619
Coronary heart disease	18 (18)	8 (40)	10 (12.5)	3 (42.9)	0.008*	0.032*
Heart failure	3 (3)	3 (15)	0 (0)	0 (0)	0.007*	1.000
Valvular disease	4 (4)	3 (15)	1 (1.3)	0 (0)	0.024*	0.767
Previous stroke	6 (6)	2 (10)	4 (5)	0 (0)	0.597	1.000
Anticoagulation	9 (9)	8 (40)	1 (1.3)	0 (0)	0.000*	0.920
Antiplatelets	50 (50)	7 (35)	43 (53.8)	3 (42.9)	0.134	0.702
Familiar history FA	5 (5)	2 (10)	3 (3.9)	0 (0)	0.273	1.000
SBP, mm Hg	143.50 (134–153)	140.5 (127.5–162.5)	144 (134–151.75)	140 (124–168)	0.973	0.773
DBP, mm Hg	78.95 ± 10.09	80.95 ± 10.85	78.45 ± 9.90	79.14 ± 6.66	0.332	0.857
Heart rate	77.94 ± 15.70	77.25 ± 16.94	78.11 ± 15.48	73 ± 22.14	0.724	0.421
CHA_2DS_2-VASc	4 (3–4)	4 (3–4)	4 (3–5)	4 (3–5)	0.035*	0.284

[a]*P-value comparison AF vs. no AF.*
[b]*P-value comparison hAF vs no AF.*
**P < 0.05. AF, atrial fibrillation; DBP, diastolic blood pressure; hAF, Holter-detected atrial fibrillation; SBP, systolic blood pressure.*

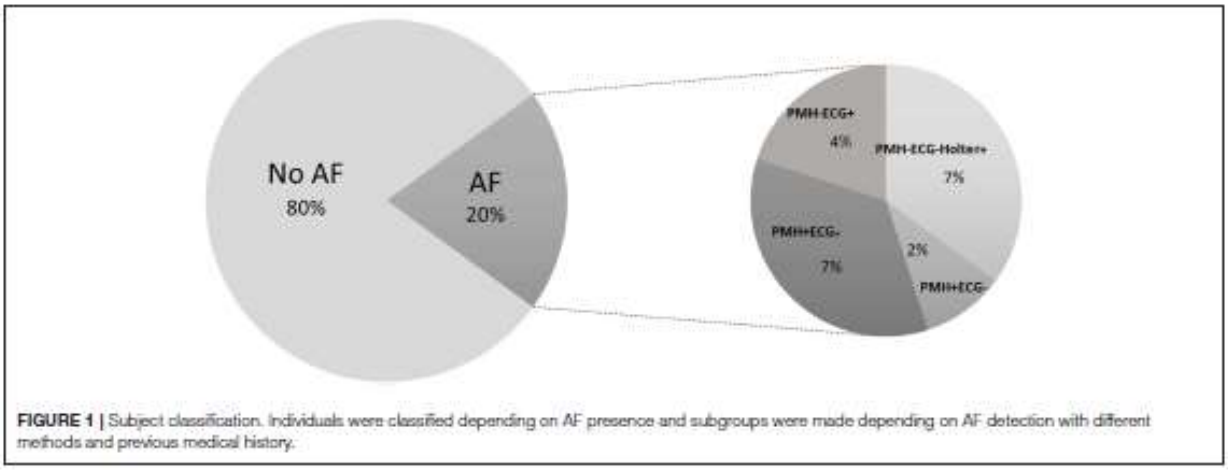

FIGURE 1 | Subject classification. Individuals were classified depending on AF presence and subgroups were made depending on AF detection with different methods and previous medical history.

TABLE 2 | Biomarker levels and comparisons between different groups.

	AF (20)	No AF (80)	hAF (7)	*P*-value[a]	*P*-value[b]
NT-proBNP (pg/ml)	643.65 (155.72–1339.25)	64.28 (37.08–133.10)	128.30 (97.69–191.8)	<0.0001*	0.03*
ApoC-III (ng/ml)	107,594 (82,501–129262.06)	104,450 (766,64–130,393)	105,352 (91,966–132,268)	0.496	0.574
ADAMTS13 (ng/ml)	1131.24 ± 471.419	1221.41 ± 459.80	1271.68 ± 561.01	0.437	0.786
vWF (ng/ml)	0.139 ± 0.062	0.139 ± 0.706	0.146 ± 0.060	0.987	0.802
uPA (std)F	2.01 (1.41–2.39)	1.60 (1.38–2.35)	1.68 (1.29–2.35)	0.720	0.868
uPAR (pg/ml)	2220.80 (557.74–2810.52)	2267.54 (1518.33–2763.06)	2246.12 (1926.03–259.23)	0.689	0.918

[a]*P-value comparison AF vs. no AF.*
[b]*P-value comparison hAF vs. no AF.*
[c]*Ninety-one individuals included in the uPA analysis (73 no AF and 18 AF, of whom 6 were hAF).*
**P < 0.05. AF, atrial fibrillation; ApoC-III, Apolipoprotein C-III; hAF, Holter-detected group; NT-proBNP, N-terminal pro B-type natriuretic peptide; vWF, von Willebrand factor; uPA, urokinase plasminogen activator; uPAR, urokinase plasminogen activator surface receptor.*

because their duplicates showed CV > 20%. Median levels and comparisons are shown in **Table 2**.

AF vs. No AF

NT-proBNP was significantly higher in individuals with AF compared with no AF [643.65 pg/ml (IQR 155.72–1339.25) vs. 64.28 pg/ml (IQR 37.08–133.10), $p < 0.0001$; **Figure 2A**], while the remaining biomarkers were not different between the two groups (**Supplementary Figures 1**, **2**). The NT-proBNP distribution across the different subgroups is shown in **Figure 2B**. In addition, AF burden was correlated with NT-proBNP ($r = 0.597$, $p = 0.024$; **Figure 2D**). The discriminating ability (area under the ROC curve) of NT-proBNP was 0.900 (95% CI, 0.8274–0.9726, $p < 0.0001$) to detect any AF (**Figure 3A**). The cut-off point of NT-proBNP of >95 pg/ml showed 95% sensitivity, 66.2% specificity, 41.3% positive predictive value (PPV), and 98.1% negative predictive value (NPV) to detect any AF (**Figure 3C**).

Anticoagulants (OR = 18.90; 95% CI, 2.10–169.83; $p = 0.09$) and NT-proBNP >95 pg/ml (OR = 22.42; 95% CI, 2.74–183.15; $p = 0.04$) were the only independent predictors of AF in the logistic regression analysis performed in the whole cohort. CHA2DS2-VASc was an independent AF predictor when considered alone in the regression analysis (OR = 2.29; 95% CI 1.16–4.44; $p = 0.017$). However, after the addition of NT-proBNP>95 pg/ml, CHA2DS2-VASc was not significant in the model.

Alternatively, the cut-off point of NT-proBNP of >125 pg/ml, which is recommended for heart failure diagnosis in the non-acute setting, showed 85% sensitivity and 73.8% specificity, 44.7% PPV and 95.2% NPV. NT-proBNP>125 pg/ml was also an independent predictor of AF (OR = 8.85; 95% CI, 2.17–35.95; $p = 0.017$).

Sensitivity analysis was performed while excluding the patient who was anticoagulated for reasons other than AF, and the results were similar.

hAF vs. No AF

NT-proBNP levels were different between no AF and hAF [64.28 pg/ml (IQR 37.08–133.10) vs. 128.3 pg/ml (IQR 97.69–191.3), $p = 0.031$; **Figure 2C**] while other biomarkers did not show differences (**Supplementary Figures 1**, **2**). Patients without AF

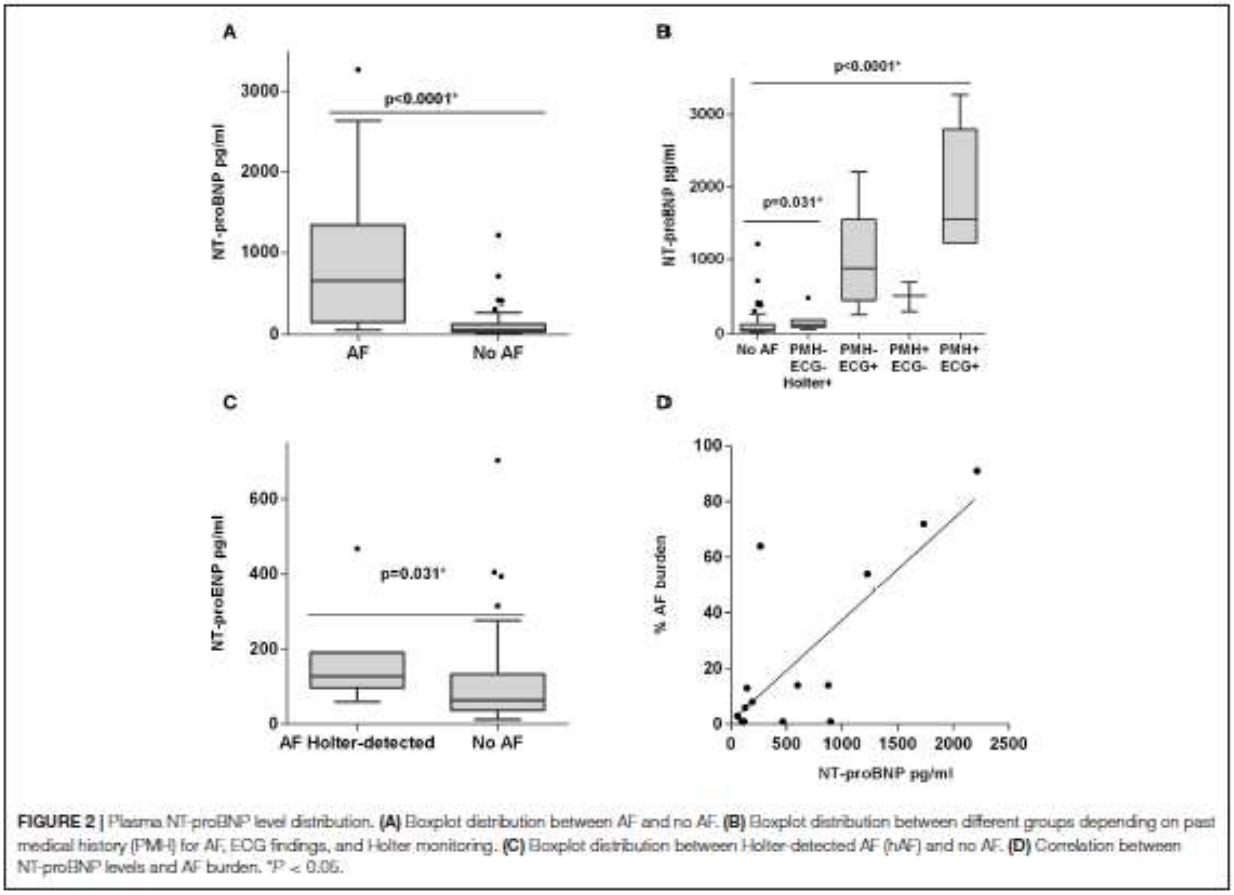

FIGURE 2 | Plasma NT-proBNP level distribution. **(A)** Boxplot distribution between AF and no AF. **(B)** Boxplot distribution between different groups depending on past medical history (PMH) for AF, ECG findings, and Holter monitoring. **(C)** Boxplot distribution between Holter-detected AF (hAF) and no AF. **(D)** Correlation between NT-proBNP levels and AF burden. *P < 0.05.

and with a Holter monitoring time below the median (457 h) were removed and all aforementioned comparisons were tested again, with similar results (data not shown). The discriminating ability (area under the ROC curve) of NT-proBNP was 0.7464 (95% CI 0.6087–0.8841, $p = 0.031$) to detect hAF (**Figure 3B**). The cut-off point of NT-proBNP of >95 pg/ml showed 85.7 % sensitivity, 66.2% specificity, 18.2% PPV, and 98.1% NPV to detect hAF (**Figure 3C**).

The logistic regression analysis performed on this subgroup confirmed that NT-proBNP ≥95 pg/ml was an independent predictor of Holter-detected atrial fibrillation (OR, 11.778; 95% CI, 1.35–102.85; $p = 0.026$). No clinical variable was an independent predictor of AF detection.

Alternatively, the cut-off point of NT-proBNP of >125 pg/ml showed 55.1% sensitivity, 73.8% specificity, 16% PPV, and 95.2% NPV. NT-proBNP >125 pg/ml also was an independent predictor of AF (OR = 8.85; 95% CI 2.17–35.95; $p = 0.017$). NT-proBNP >125 pg/ml was not an independent predictor of hAF.

DISCUSSION

The prevalence of AF in our population was 20%, of which 55% were newly detected AF individuals. This prevalence is higher than reported in previous screening studies (from 2.3 to 12.3%) (10, 11). Most such studies have only used ECG or pulse devices instead of long-term monitoring, so they have missed cases of paroxysmal AF. Moreover, we used a targeted screening approach, focussing on a high-risk population with advanced age and other conditions related to AF, such as hypertension and diabetes, who should present a higher AF prevalence (23). Longer monitoring in a high-risk population might therefore be a good strategy to further explore in larger cohorts. Other studies using long-term monitoring with insertable cardiac devices or pacemakers in patients without prior history of AF have also shown a higher prevalence of AF (24). In fact, in the recent REVEAL AF trial, detection rates of AF rose with the monitoring time (25). Moreover, in patients with cryptogenic stroke, long-term monitoring was found to be associated with higher rates of AF detection, with a significant impact in secondary prevention (26). However, although it could become the gold standard for AF detection, long-term monitoring devices are expensive and unsuitable for application in primary care. In that sense, biomarkers might be used as cost-effective alternatives for AF systematic screening.

The present study suggests that NT-proBNP might be used as a screening biomarker to detect even paroxysmal AF in

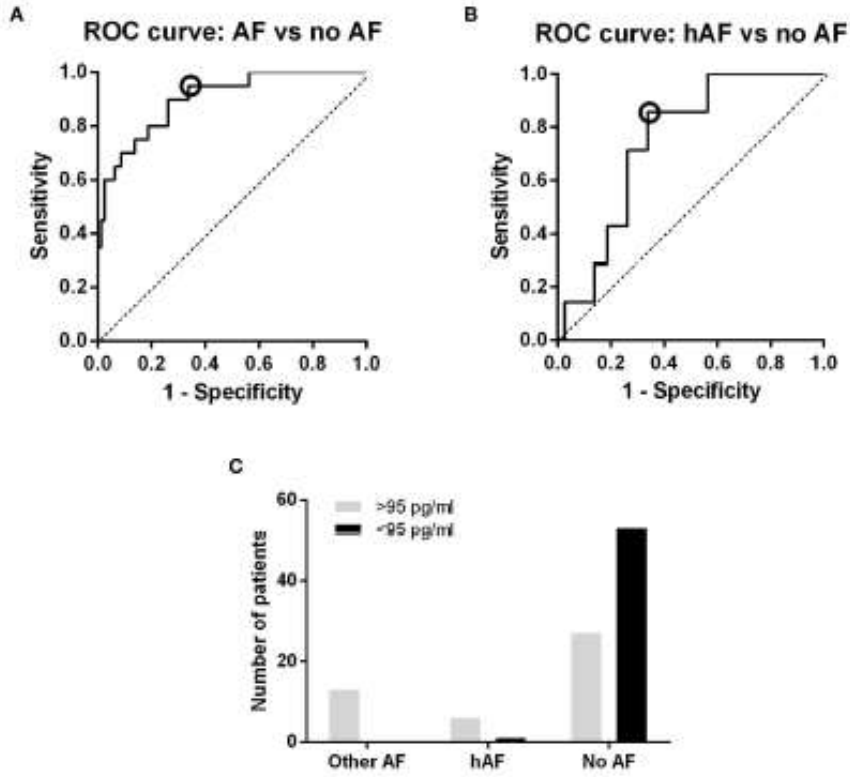

FIGURE 3 | NT-proBNP discrimination power. **(A)** ROC curve: ability to discriminate between AF and no AF. **(B)** ROC curve, ability to discriminate between Holter-detected AF and no AF. The cut-off with the best specificity and sensitivity to detect hAF is marked with a circle in the two curves (95 pg/ml), as it is the cut-off value that was used to calculate sensitivity, specificity and predictive values. **(C)** Discrimination power of the NT-proBNP cut-off value of 95 pg/ml. All AF individuals had NT-proBNP plasma levels below the previous cut-off (except for a patient with paroxysmal AF), and the majority of no AF patients had values above the cut-off.

asymptomatic, high-risk individuals. The focus of the present study was to assess the predictive ability of NT-proBNP and other biomarkers to diagnose paroxysmal atrial fibrillation and be used as the first step of a screening workflow. In fact, the best screening biomarker in this context would be able to detect those cases impossible to notice with other available tools, such opportunistic ECG or hand-held ECG devices. It should be mentioned that paroxysmal AF (pAF) patients also can have increased risk of stroke (27, 28). Moreover, pAF may progress to permanent AF within a year in almost 20% of cases in the aging population (29, 30).

Previous studies have suggested NT-proBNP as a screening tool (14–16), but a limited length of monitoring might have misclassified some cases of paroxysmal atrial fibrillation. Our study overcame this limitation by recording patient's heart rhythm continuously for 30 days using a Holter monitor, allowing us to detect more AF cases. This is to our knowledge the longest period over which asymptomatic individuals have been monitored to detect atrial fibrillation in a biomarker study, if we exclude studies using pacemakers (13). The limitation of pacemakers is that their use is restricted to very specific populations with cardiac diseases that could affect some biomarker levels.

In the pilot study of Seegers et al. (14), in addition to a limited 7-day Holter ECG for the evaluation of paroxysmal AF, patients were preselected as those with lowest and highest NT-proBNP quartiles, overestimating the discriminatory value of the biomarker. In our study, inclusion was performed before any biomarker determination, and 4-week Holter monitoring was used as the gold standard to assess the usefulness of blood-based biomarkers in AF screening. Although individuals with AF detected by other methods were not excluded from the whole study, to increase the statistical power, specific comparisons were performed while excluding these patients and only taking into account AF cases detected with long-term monitoring, i.e., cases with neither previous AF history nor detection during electrocardiographic assessment. Even though few patients were part of this group, specific comparisons showed the usefulness of NT-proBNP to identify those patients outside AF paroxysms. After validating those results with a larger cohort, NT-proBNP could be implemented as part

of a screening programme to indicate long-term monitoring in patients with a risk biological profile. Such a protocol would identify patients at risk of AF who would benefit from anticoagulation, thereby improving primary stroke prevention by preventing cardioembolic stroke, which is associated with the poorest disability and mortality rates among stroke etiologies (31).

Additionally, we proposed for the first time a specific cut-off point for atrial fibrillation screening. Seegers et al. (14) suggested that NT-proBNP could be used for stroke prevention after finding increased values in AF individuals, without indicating any cut-off. Svenberg et al. (15) and Ghazal et al. (16) proposed a cut-off point of NT-proBNP >125 pg/ml, which is the recommended for heart failure in the non-acute setting (32). Here, NT-proBNP >95 pg/ml reached high sensitivity (95%) even to detect paroxysmal AF individuals (85.7%). In fact, in our cohort, this cut-off point only misclassified one paroxysmal AF individual. Although the NT-proBNP biomarker is not specific for AF and might be elevated in other cardiac diseases and renal dysfunction (33), a high sensitivity is more useful than specificity for screening purposes. NT-proBNP might be rapid and easy to use to identify all patients who need follow-up Holter monitoring since it is already widely employed as a point-of-care analysis tool for heart failure.

Although it might be suspected that elevated NT-proBNP levels were due to a higher burden of heart failure and other cardiovascular diseases in the atrial fibrillation subjects of our cohort, in the hAF group, there were few individuals with known comorbidities that could affect NT-proBNP levels. In fact, in this group, there were no cases of heart failure, and there were only differences in coronary heart disease when compared to no AF individuals. In addition, the study was carried out at the outpatient clinic, and therefore, no patient was in a situation of acute decompensated heart failure. This, combined with multivariate analysis, confirmed the independent value of NT-proBNP in diagnosing paroxysmal atrial fibrillation.

ApoC-III, vWF, ADAMTS13, uPAR, and uPA were not elevated in AF individuals in the present study. Although associated with cardioembolic stroke or AF recurrence, these biomarkers might not be useful in the context of AF screening. However, it would be interesting to perform further discovery studies to find new biomarkers that might be used in combination with NT-proBNP, increasing its specificity and sensitivity.

Interestingly, the present study showed that a higher level of NT-proBNP was correlated with higher AF burden, a conclusion based on continuous Holter monitoring. This tendency was also reflected in the distribution of NT-proBNP levels between the groups, with higher levels in individuals with a previous medical history of AF compared with individuals with hAF, as shown in **Figure 1B**. In fact, some studies have suggested that AF burden is related to higher stroke risk (34), and other biomarker-based models have confirmed NT-proBNP as a stroke risk surrogate (35).

Although the present study was performed in asymptomatic patients, NT-proBNP might also be useful for detecting cryptogenic stroke patients with occult AF. Recently, the negative results from clinical trials of embolic strokes of undetermined source (ESUS) patients receiving non-vitamin K antagonists (NOACs) (36, 37) indicate that this is a heterogeneous group of patients who need different management, only a minority of whom have undetected paroxysmal AF (38). In fact, the ongoing ARCADIA trial (39) will test the use of anticoagulants in ESUS patients with atrial cardiopathy using high NT-proBNP (>250 pg/ml) as one of the inclusion criteria.

Our study has some limitations. First, the participant selection was not randomized and might have suffered some selection bias: the high rates of AF might not be attributed only to the selection of high-risk patients and long-term monitoring but also to patients with more cardiac comorbidities being more prone to participate. The small sample size and the small number of patients with AF suggest that these results should be interpreted as hypothesis-generating. The protocol of the study did not include an echocardiography, missing the opportunity to establish correlations between biomarkers and left atrial diameter. Finally, the included population presented specific risk factors, and the results may not be directly applicable to populations with other combinations of risk factors. Further validation studies in larger cohorts are needed.

CONCLUSIONS

NT-proBNP was found to be elevated in AF individuals compared to controls. This biomarker also detected cases of AF not previously known or detected by ECG. NT-proBNP may be useful as a screening biomarker in asymptomatic high-risk populations with a promising cut-off point of 95 pg/ml that requires further validation. A screening strategy based on NT-proBNP, alone or in combination with other biomarkers, might be of interest for the early initiation of anticoagulants, which could reduce cardioembolic stroke consequences.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of Research Institute IDIAP Jordi Gol (P15/047/2015) and Hospital Universitari Vall d'Hebron Clinical Research Ethics Committee [PR(AG)133-2015]. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AB, JC-E, FG-L, JB-O, and MM recruited patients. JA and AP read Holter-ECG to verify AF episodes. EP, NG, and AC performed biomarker measurements. AB, JC-E, JP, MM, and JM planned the whole project and drafted the study protocol. EP

performed statistical analysis and drafted the manuscript. All authors have critically reviewed the manuscript and approved the final article version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.01226/full#supplementary-material

REFERENCES

1. Stevens E, Emmett E, Wang Y, McKevitt C, DA Wolfe C. *The Burden of Stroke in Europe Report*. King's College London for the Stroke Alliance for Europe (SAFE), Brussels (2017).
2. Wolf P, Dawber T, Thomas HJ, Kannel W. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology*. (1978) 28:973–7. doi: 10.1212/WNL.28.10.973
3. Roso-llorach A, Clua-espuny JL, Panisello-tafalla A, Lucas-noll J, Lo C, Galliofre M, et al. Prevalence of undiagnosed atrial fibrillation and of that not being treated with anticoagulant drugs : the AFABE study. *Rev Esp Cardiol*. (2013) 66:545–52. doi: 10.1016/j.rec.2013.03.003
4. Hart RG, Pearce LA, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. (2007) 146:857–67. doi: 10.7326/0003-4819-146-12-200706190-00007
5. Panisello-tafalla A, Clua-espuny JL, Gil-guillen VF, González-henares A, Queralt-tomas ML, López-pablo C, et al. Results from the registry of atrial fibrillation (AFABE): gap between undiagnosed and registered atrial fibrillation in adults — ineffectiveness of oral anticoagulation treatment with VKA. *Biomed Res Int*. (2015) 2015:134756. doi: 10.1155/2015/134756
6. Morillas P, Pallarés V, Llisterri L, Sanchis C, Sánchez T. Prevalence of atrial fibrillation and use of antithrombotics in hypertensive patients aged ≥ 65 years. The FAPRES Trial. *Rev Esp Cardiol*. (2010) 63:943–50. doi: 10.1016/S1885-5857(10)70188-2
7. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Rev Esp Cardiol*. (2017) 70:50. doi: 10.1016/j.rec.2016.11.033
8. Freedman B. Screening for atrial fibrillation: a report of the AF-SCREEN international collaboration. *Circulation*. (2017) 135:1851–67. doi: 10.1161/CIRCULATIONAHA.116.026693
9. Moran PS, Teljeur C, Ryan M, Smith SM. Systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev*. (2016) 2016:CD009586. doi: 10.1002/14651858.CD009586.pub3
10. Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass screening for untreated atrial fibrillation the STROKESTOP study. *Circulation*. (2015) 131:2176–84. doi: 10.1161/CIRCULATIONAHA.114.014343
11. Lowres N, Neubeck L, Redfern J, Ben Freedman S. Screening to identify unknown atrial fibrillation: a systematic review. *Thromb Haemost*. (2013) 110:213–22. doi: 10.1160/TH13-02-0165
12. Llombart V, Antolin-Fontes A, Bustamante A, Giralt D, Rost NS, Furie K, et al. B-type natriuretic peptides help in cardioembolic stroke diagnosis. *Stroke*. (2015) 46:1187–95. doi: 10.1161/STROKEAHA.114.008311
13. Wakula P, Neumann B, Kienemund J, Thon-Gutschi E, Stojakovic T, Manninger M, et al. CHA2DS2-VASc score and blood biomarkers to identify patients with atrial high-rate episodes and paroxysmal atrial fibrillation. *Europace*. (2017) 19:544–51. doi: 10.1093/europace/euw101
14. Seegers J, Zabel M, Grüter T, Ammermann A, Weber-Krüger M, Edelmann F, et al. Natriuretic peptides for the detection of paroxysmal atrial fibrillation. *Open Hear*. (2015) 2:e000182. doi: 10.1136/openhrt-2014-000182
15. Svennberg E, Henriksson P, Engdahl J, Hijazi Z, Al-Khalili F, Friberg L, et al. N-terminal pro B-type natriuretic peptide in systematic screening for atrial fibrillation. *Heart*. (2017) 103:1271–7. doi: 10.1136/heartjnl-2016-310236
16. Ghazal F, Theobald H, Rosenqvist M, Al-Khalili F. Assessment of N-terminal pro-brain natriuretic peptide level in the screening for atrial fibrillation in the primary health care. *PLoS ONE*. (2019) 14:e0212974. doi: 10.1371/journal.pone.0212974
17. Muñoz-Cortés G, Viveros-Sandoval ME, Areán-Martínez C, Vega-Gómez HE, López-Castañeda SE, et al. Von Willebrand factor plasma levels variability in nonvalvular atrial fibrillation. *J Atr Fibrillation*. (2014) 7:1124. doi: 10.4022/jafib.1124
18. Bustamante A, López-Cancio E, Pich S, Penalba A, Giralt D, García-Berrocoso T, et al. Blood biomarkers for the early diagnosis of stroke: the stroke-chip study. *Stroke*. (2017) 48:2419–25. doi: 10.1161/STROKEAHA.117.017076
19. Freynhofer MK, Bruno V, Jarai R, Gruber S, Höchtl T, Brozovic I, et al. Levels of von Willebrand factor and ADAMTS13 determine clinical outcome after cardioversion for atrial fibrillation. *Thromb Haemost*. (2011) 105:435–43. doi: 10.1160/TH10-09-0615
20. Ichihara N, Miyamura M, Maeda D, Fujisaka T, Fujita SI, Morita H, et al. Association between serum soluble urokinase-type plasminogen activator receptor and atrial fibrillation. *J Arrhythmia*. (2017) 33:469–74. doi: 10.1016/j.joa.2017.05.003
21. Pagola J, Juega J, Francisco-Pascual J, Moya A, Sanchis M, Bustamante A, et al. Yield of atrial fibrillation detection with Textile Wearable Holter from the acute phase of stroke: pilot study of Crypto-AF registry. *Int J Cardiol*. (2018) 251:45–50. doi: 10.1016/j.ijcard.2017.10.063
22. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. (2014) 130:2071–04. doi: 10.1161/CIR.0000000000000040
23. Lau DH, Nattel S, Kalman JM, Sanders P. Modifiable risk factors and atrial fibrillation. *Circulation*. (2017) 136:583–96. doi: 10.1161/CIRCULATIONAHA.116.023163
24. Van Gelder IC, Healey JS, Crijns HJGM, Wang J, Hohnloser SH, Gold MR, et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J*. (2017) 38:1339–44. doi: 10.1093/eurheartj/ehx042
25. Reiffel JA, Verma A, Kowey PR, Halperin JL, Gersh BJ, Wachter R, et al. Incidence of previously undiagnosed atrial fibrillation using insertable cardiac monitors in a high-risk population: the REVEAL AF study. *JAMA Cardiol*. (2017) 2:1120–7. doi: 10.1001/jamacardio.2017.3180
26. Tsivgoulis G, Katsanos AH, Mac GB, Köhrmann M, Ricci BA, Tsioufis K, et al. Prolonged cardiac rhythm monitoring and secondary stroke prevention in patients with cryptogenic cerebral ischemia. *Stroke*. (2019) 50:2175–80. doi: 10.1161/STROKEAHA.119.025169
27. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. *Eur Heart J*. (2010) 31:967–75. doi: 10.1093/eurheartj/ehn599
28. Lilli A, Di Cori A, Zacà V. Thromboembolic risk and effect of oral anticoagulation according to atrial fibrillation patterns: a systematic review and meta-analysis. *Clin Cardiol*. (2017) 40:641–7. doi: 10.1002/clc.22701
29. Proietti R, Hadjis A, Alturki A, Thanassoulis G, Roux JF, Verma A, et al. A systematic review on the progression of paroxysmal to persistent atrial