EVENTOS CARDIOVASCULARES ADVERSOS MAYORES EN PACIENTES CON FIBRILACIÓN AURICULAR

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UNIVERSITAT ROVIRA i VIRGILI

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TESIS DOCTORAL

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Programa de Doctorado en Biomedicina

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Grado Universitario en Medicina por la Universidad Jaume I de Castellón, especialista en Medicina Familiar i Comunitaria, para optar al grado de Doctor en Biomedicina por la Universidad Rovira i Virgili.

Trabajo realizado bajo la supervisión y dirección de la Dra. Silvia Reverté Villarroya y el Dr. Josep Lluís Clua Espuny en el Programa de Doctorado en Biomedicina de la Facultad de Medicina y Ciencias de la Salud de la Universidad Rovira i Virgili.

Tortosa, 2024

UNIVERSITAT ROVIRA i VIRGILI

FAIG CONSTAR que aquest treball, titulat “Esdeveniments Cardiovasculars Adversos Majors en pacients amb Fibril·lació Auricular”, que presenta Pedro Moltó Balado per a l’obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Biomedicina d’aquesta universitat.

HAGO CONSTAR que el presente trabajo, titulado “Eventos Cardiovasculares Adversos Mayores en pacientes con Fibrilación Auricular”, que presenta Pedro Moltó Balado para la obtención del título de Doctor, ha sido realizado bajo mi dirección en el Departamento de Biomedicina de esta universidad.

I STATE that the present study, entitled “Major Adverse Cardiovascular Events in Atrial Fibrillation patients”, presented by Pedro Moltó Balado for the award of the degree of Doctor, has been carried out under my supervision at the Department of Biomedicine of this university.

Tortosa, 19 de Mayo de 2024,

El/s director/s de la tesi doctoral

El/los director/es de la tesis doctoral

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A Consu y la Domi, mis abuelas

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RESUMEN

Resumen

Introducción

La fibrilación auricular (FA) es una arritmia cardíaca que presenta un aumento de su prevalencia, de hecho se espera que los ictus relacionados con FA se triplicarán en 2060. Esta tendencia se asocia a un mayor riesgo de eventos cardiovasculares adversos mayores (MACE) que conllevará una de las principales cargas sanitarias y económicas. La asociación entre la FA y los MACE plantea retos en la identificación y el tratamiento precoces. En este trabajo se describe la incidencia de nueva FA asociada a ictus y mortalidad así como analizar los vínculos y asociaciones entre FA y MACE. Aunque los factores de riesgo existentes, los biomarcadores, las variantes genéticas y los parámetros de imagen predicen los MACE, los factores emergentes pueden ser más decisivos. Es por ello que el papel de la inteligencia artificial (IA) y las técnicas de *machine learning* (ML) ofrecen una vía prometedora para una predicción más eficaz del riesgo tromboembólico de la FA.

Objetivos

- Identificar la incidencia de FA y episodios de MACE
- Determinar las características de los pacientes con riesgo de presentar FA
- Definir los posibles factores predictores de MACE en los pacientes con nuevo diagnóstico de FA con IA

Metodología

Estudio multicéntrico, observacional, retrospectivo y comunitario de una cohorte (n = 40.297) de población general de 65-95 años, entre el 1 de enero de 2015 y el 31 de diciembre de 2021, sin diagnóstico previo de FA ni MACE en el ámbito de Atención Primaria (AP). Para la determinación de factores predictores de MACE en los pacientes con FA se desarrollaron cinco modelos ML. Dos tercios de los datos se utilizaron para el entrenamiento, empleando diversos enfoques y optimizando para minimizar los errores de predicción, mientras que el tercio restante se reservó para pruebas y validación.

Resultados

Un total de 2.574 personas (6,39 %) desarrollaron un primer episodio de FA con una incidencia global de 8,9/1.000 personas-año (IC 95 %: 8,6-9,2). La incidencia de MACE entre los pacientes con FA fue de 75,1/1.000 personas-año (IC 95%: 70,8-79,5), mientras que entre los pacientes sin FA fue de 20,6/1.000 personas-año (IC 95 %: 20,2-21,1), lo que dio lugar a una razón de tasas de 3,65 (IC 95%: 3,43-3,88; p<0,001). Además, la incidencia de insuficiencia cardiaca con FA fue de 40,1 personas-año (IC 95 % 37,1-43,2), mientras que en el grupo sin FA fue de 8,3 personas-año (IC 95 %: 7,9-8,6; p<0,001), con una razón de tasas de 4,85 (IC 95 %: 4,45-55,3; p<0,001). Antes del diagnóstico de FA, ya existe un mayor riesgo de enfermedad renal crónica, cardiopatía isquémica y arteriopatía

periférica. También se detectó un mayor riesgo de mal estado nutricional entre los pacientes con MACE (49,7 % frente a 26,6 %, p<0,001).

De los 5 modelos de ML generados, AdaBoost obtuvo el mejor rendimiento (accuracy: 0,9999; recall: 1; F1 score: 0,9997). Entre las características destacables que influyeron en las predicciones se incluyeron el índice de comorbilidad de Charlson (ICC), cáncer, diabetes mellitus, enfermedad pulmonar obstructiva crónica, deterioro cognitivo, enfermedad vascular, CHA_2DS_2-VASc y Wells, con asociaciones específicas identificadas. Se observó un riesgo elevado de MACE a partir de una puntuación ICC superior a 2,67 ± 1,31 (p<0,001), una puntuación CHA_2DS_2-VASc de 4,62 ± 1,02 (p<0,001) y una clasificación en la escala de Wells (riesgo intermedio).

Conclusión

Los pacientes estratificados dentro del 4º cuartil (Q4) con riesgo de desarrollar FA presentaban un mayor riesgo cardiovascular antes de ser diagnosticados de FA, especialmente en pacientes con enfermedad renal crónica, cardiopatía isquémica y arteriopatía periférica. El diagnóstico de FA multiplica por cuatro la incidencia de insuficiencia cardíaca y por ocho la incidencia de MACE. Las puntuaciones CHA_2DS_2-VASc, ICC y CONUT se identificaron como predictores independientes de FA relacionados con MACE. El modelo AdaBoost de ML ofrece un enfoque predictivo más preciso para facilitar la identificación precoz del riesgo de MACE en la evaluación de los pacientes con FA.

Sumary

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia with an increasing prevalence, in fact AF-related strokes are expected to triple by 2060. This trend is associated with an increased risk of major adverse cardiovascular events (MACE) that will lead to a major health and economic. The association between AF and MACE poses challenges for early identification and treatment. This paper describes the incidence of new AF associated with stroke and mortality and analyses the links and associations between AF and MACE. Although existing risk factors, biomarkers, genetic variants and imaging parameters predict MACE, emerging factors may be more decisive. Therefore, the role of artificial intelligence and machine learning (ML) techniques offers a promising avenue for more effective prediction of thromboembolic risk of AF.

Objectives

- Identify the incidence of AF and MACE events
- Determine the characteristics of patients at risk of developing AF
- Define possible predictors of MACE in patients with newly diagnosed AF and IA

Methodology

Multicentre, observational, retrospective, community-based, multicentre study of a cohort (n=40,297) of the general population aged 65-95 years between 1 January 2015 and 31 December 2021 with no previous diagnosis of AF or MACE in the Primary Care setting. Five ML models were developed to determine predictors of MACE in AF patients. Two-thirds of the data were used for training, employing various approaches and optimising to minimise prediction errors, while the remaining third was reserved for testing and validation.

Results

A total of 2.574 people (6,39 %) developed a first episode of AF with an overall incidence of 8.9/1,000 person-years (95 % CI: 8.6-9.2). The incidence of MACE among patients with AF was 75.1/1,000 person-years (95 % CI: 70.8-79.5), while among patients without AF it was 20.6/1,000 person-years (95 % CI: 20.2-21.1), resulting in a rate ratio of 3.65 (95 % CI: 3.43-3.88, p<0.001). In addition, the incidence of heart failure with AF was 40.1 person-years (95 % CI: 37.1-43.2), while in the AF-free group it was 8.3 person-years (95 % CI: 7.9-8.6; p<0.001), with a rate ratio of 4.85 (95 % CI: 4.45-55.3; p<0.001). Prior to AF diagnosis, there is already an increased risk of chronic kidney disease, ischaemic heart disease and peripheral arterial disease. A higher risk of poor nutritional status was also detected among patients with MACE (49.7 % vs. 26.6 %, p<0.001).

Of the 5 ML models generated, AdaBoost performed best (accuracy: 0.9999; recall: 1; F1 score: 0.9997). Notable characteristics that influenced predictions included Charlson Comorbidity Index (CCI), cancer, diabetes mellitus, chronic obstructive pulmonary disease, cognitive impairment, vascular disease, $_2$-VASc

and Wells, with specific associations identified. An elevated risk of MACE was observed for a CCI score greater than 2.67 ± 1.31 ($p<0.001$), a CHA_2DS_2-VASc score of 4.62 ± 1.02 ($p<0.001$) and a Wells scale (intermediate risk).

Conclusion

Patients stratified within the 4th quartile (Q4) at risk of developing AF had a higher cardiovascular risk before being diagnosed with AF, especially in patients with chronic kidney disease, ischemic heart disease and peripheral artery disease. A diagnosis of AF increases the incidence of heart failure fourfold and the incidence of MACE eightfold. CHA_2DS_2-VASc, ICC and CONUT scores were identified as independent predictors of AF related to MACE. The ML AdaBoost's model offers a more accurate predictive approach to facilitate early identification of MACE risk in the evaluation of AF patients.

ÍNDICE

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1. Listado de abreviaturas

Listado de abreviaturas

ABVD	Actividades Básicas de la Vida Diaria
AFRICAT	Atrial Fibrillation Research in Catalonia
AP	Atención Primaria
AUC	Área bajo la curva
CatSalut	Departamento de Salud de Cataluña
CIE-11	Clasificación Internacional de Enfermedades
CMBD-HA	Conjunto mínimo básico de datos al alta hospitalaria
CONUT	CONtrol NUTricional
DE	Desviación estándar
EAP	Equipo de Atención Primaria
E-CAP	Programa informático usado en Atención Primaria en Catalunya
ECG	Electrocardiograma
ERC	Enfermedad Renal Crónica
EPOC	Enfermedad Pulmonar Obstructiva Crónica
FA	Fibrilación Auricular
GMA	Grupos de Morbilidad Ajustados
HC3	Historia clínica compartida de Catalunya
HR	*Hazard ratio*
IA	Inteligencia Artificial
IC	Intervalo de Confianza
ICC	Índice de Comorbilidad de Charlson
ICS	Instituto Catalán de la Salud
IMC	Índice de Masa Corporal
INR	Índice Internacional Normalizado
MACE	Eventos cardiovasculares adversos mayores
ML	*Machine Learning*
NACO	Nuevos anticoagulantes orales
NNC	Número Necesario a Cribar
OD	*Odds ratio*
RIQ	Rango intercuartílico
SHAP	*SHapley Additive exPlanations*
RSTE	Región Sanitaria de Terres de l'Ebre
TEV	Tromboembolismo venoso

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2.1. Tablas

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3. Introducción

3.1. Antecedentes y estado actual del tema

La fibrilación auricular (FA) es una arritmia supraventricular con una activación eléctrica auricular descoordinada y, en consecuencia, una contracción auricular ineficaz. Es decir, las aurículas mandan señales eléctricas rápidas y desorganizadas originando contracciones muy rápidas e irregulares entre las aurículas y ventrículos[1].

Muchas personas con FA no presentan síntomas, lo que dificulta el diagnóstico. Sin embargo, los síntomas más comunes son: Palpitaciones, sensación de cansancio o fatiga, dificultad para respirar, mareos o aturdimiento. Para su diagnóstico se requiere el registro del ritmo en un electrocardiograma (ECG) que muestre FA al menos durante 30 segundos[2].

Las características electrocardiográficas de la FA incluyen[3]:

- Intervalos R-R irregularmente irregulares (cuando la conducción auriculoventricular no está alterada)
- Ausencia de ondas P repetitivas distintas
- Activaciones auriculares irregulares

La FA es la arritmia cardiaca más frecuente en el mundo y afecta entorno al 10% de la población mundial[1]. A principios del siglo XXI presentaba una tasa de mortalidad entorno al 50% a los 5 años de su diagnóstico entre los pacientes con FA respecto los que no la padecían[4] que con las mejoras en su detección y tratamiento ha disminuido notablemente dicha cifra aunque todavía queda trabajo por hacer. Se estima que entre 6 y 12 millones de personas sufrirán esta afección en 2050 en los EE. UU. y 17,9 millones de personas en Europa en 2060 debido al envejecimiento y el desarrollo de otras patologías[5], hecho que supone un gran desafío para los pacientes, la sociedad y la economía sanitaria[1].

La FA es una afección médica crónica que requiere el manejo no solo de las complicaciones agudas, sino también la modificación del proceso de la enfermedad y la trayectoria a largo plazo del paciente. A pesar de ser la arritmia cardíaca más prevalente, la identificación temprana, el diagnóstico y el tratamiento de la FA siguen siendo un desafío. La identificación de las personas con mayor riesgo de desarrollar FA podría facilitar la orientación de las intervenciones preventivas y los programas de cribado para su detección precoz[6].

El desarrollo y la progresión de la FA se asocia mayoritariamente con la edad pero también al tabaco, actividad física, obesidad, alcohol, peso, hipertensión arterial, diabetes, enfermedad renal crónica (ERC), sepsis, biomarcadores, alteraciones en el ECG, pruebas de imagen y genéticas[1,3]. Además, la FA aumenta el riesgo de accidente cerebrovascular isquémico[7], infarto de miocardio[8], insuficiencia cardíaca[9] y mortalidad[10,11]. Actualmente, estos cuatro factores se estudian de manera conjunta como eventos cardiovasculares adversos mayores (MACE)[12] siendo la FA un potente predictor de presentar un

MACE[11,13]. Se estima que los pacientes con FA e hipercolesterolemia presentan un 24,3 % riesgo de padecer un MACE a los 4 años[14].

En los últimos años ha crecido el interés por identificar nuevos factores predictivos de MACE en pacientes con FA[8]. Son bien conocidos aquellos factores de riesgo "tradicionales" como la edad, el sexo, la hipertensión, la diabetes, biomarcadores, variantes genéticas, parámetros de imagen y la función auricular izquierda[15,16] pero están cobrando fuerza otros como la obesidad, la enfermedad pulmonar obstructiva crónica (EPOC) o la ERC[17-19]; este enfoque novedoso se asocia a una reducción del riesgo de MACE, incluida la mortalidad y la tromboembolia[20]. Menos estudiados pero con previsiones alentadoras son el estado nutricional, la escala de Wells e ICC.

La escala del control nutricional (CONUT) permite de forma fácil, rápida y sencilla la valoración del estado nutricional de los pacientes con únicamente los valores del colesterol total, linfocitos y albumina de una analítica sanguínea[21]. Existen diferentes déficits nutricionales que están infradiagnosticados en los pacientes con FA[22]. También hay pocos datos sobre sujetos con FA desnutridos o sobre la relación entre la desnutrición y MACE a medio y largo plazo en la población con FA[23]. La malnutrición es un factor pronóstico desfavorable asociado al aumento de la mortalidad, número de estancias hospitalarias, reingresos y consumo de recursos que empieza a cobrar fuerza desde AP[24] ya que pueden reflejar necesidades sociales no halladas previamente[25].

Se ha estimado que las condiciones tromboembólicas fueron responsables de 1 de cada 4 muertes en todo el mundo en 2010 y, en conjunto, la trombosis, como mecanismo subyacente común de MACE y tromboembolia venosa (TEV)[26]. La escala de Wells se utiliza para estratificar el riesgo de sufrir una trombosis venosa profunda y embolia pulmonar[27]. La FA favorece un estado procoagulante que promueve el desarrollo de trombos en la aurícula izquierda provocando una alteración de la hemostasia, aumento del recambio de fibrina y la activación de plaquetas[28]. Aunque se ha observado que los pacientes con FA tienen un mayor riesgo de TEV durante los primeros 6 meses después del diagnóstico de FA[29], la puntuación de Wells no es aceptada como indicador de pronóstico de tromboembolia en pacientes con FA.

El ICC es una herramienta utilizada para medir la esperanza de vida a los diez años a partir de las comorbilidades de los pacientes[30]. Una puntuación más alta del ICC se correlaciona con un riesgo elevado de resultados adversos o mortalidad. Entre los pacientes con FA y un ICC elevado existe una mayor asociación más fuerte de MACE, hemorragias graves y hospitalización respecto aquellos pacientes sin diagnóstico de FA[31] pero esta relación todavía no se ha explorado de un forma exhaustiva.

Recientemente, se han realizado importantes progresos en la detección de la FA. La identificación de individuos con mayor riesgo de contraer FA podría facilitar la implementación de intervenciones preventivas y programas de cribado para la detección temprana de la FA, por ejemplo, en subgrupos con riesgo alto de ictus, introducción de anticoagulantes, optimización terapéutica, etc.

Recomendaciones actuales para el manejo de la FA[1] (destacados aquellos puntos relacionados entre FA y MACE):

Tabla 1. Recomendaciones sobre la FA de la *American College of Cardiology/American Heart Association (2023)*[1]

Recomendaciones	Clase de recomendación	Nivel de evidencia
Para pacientes con FA y un riesgo tromboembólico anual estimado de ≥2 % anual (por ejemplo, CHA_2DS_2-VASc de ≥2 en hombres y ≥3 en mujeres), se recomienda la anticoagulación para prevenir el ictus y la tromboembolia sistémica	I	A
En los pacientes con FA que no tienen antecedentes de estenosis mitral reumática de moderada a grave o una válvula cardíaca mecánica, y que son candidatos a la anticoagulación, se recomiendan los nuevos anticoagulantes orales (NACO) frente a la warfarina/acenocumarol para reducir el riesgo de mortalidad, ictus, embolia sistémica y hemorragia intracraneal	I	A
En los pacientes con FA que reciben warfarina/acenocumarol y desarrollan una hemorragia potencialmente mortal, se recomienda el tratamiento con concentrado de complejo de protrombina de 4 factores (si está disponible) además de vitamina K intravenosa para lograr rápidamente la corrección del índice internacional normalizado (INR) por encima del tratamiento con plasma fresco congelado y vitamina K intravenosa	I	A
Los pacientes con FA, independientemente de su sexo, diversidad de género, raza y etnia, o determinantes sociales de la salud (DSS) adversos, se les debe ofrecer de forma equitativa terapias de reducción del riesgo de ictus, así como estrategias de control de la frecuencia o el ritmo, estilo de vida y modificación de los factores de riesgo según esté indicado para mejorar la calidad de vida y prevenir resultados adversos	I	B
En pacientes con FA recién diagnosticada, se recomienda realizar un ecocardiograma transtorácico para evaluar la estructura cardíaca, pruebas de laboratorio que incluyan un hemograma completo, un panel metabólico y la función tiroidea cuando exista sospecha clínica, pruebas específicas para evaluar otras afecciones médicas asociadas a la FA, con el fin de determinar los factores de riesgo de ictus y hemorragia, así como las afecciones subyacentes que guiarán el tratamiento posterior	I	B
En pacientes con un dispositivo de ritmo intracardiaco capaz de diagnosticar FA, como el derivado de un marcapasos auricular, el diagnóstico de FA sólo debe hacerse después de confirmarlo visualmente mediante la revisión de los trazados intracardiacos para excluir artefactos de señal y otras arritmias	I	B

Los pacientes con FA deben ser evaluados para determinar su riesgo anual de eventos tromboembólicos, riesgo anual de tromboembolias mediante una puntuación de riesgo clínico, como CHA_2DS_2-VASc	I	B
Los pacientes con FA deben ser evaluados en busca de factores que indiquen específicamente un mayor riesgo de hemorragia, tanto previas y uso de fármacos que aumenten el riesgo, con el fin de identificar posibles intervenciones para prevenir hemorragias con anticoagulación	I	B
Entre los individuos sin antecedentes conocidos de FA, se recomienda que el diagnóstico inicial de FA lo realice un clínico mediante la interpretación visual de las señales electrocardiográficas, independientemente del tipo de ritmo o dispositivo de monitorización	I	B
Los pacientes con mayor riesgo de FA deben cambiar el estilo de vida y modificar los factores de riesgo abordando la FA, que aborde la obesidad, la inactividad física, el consumo de alcohol, el tabaquismo, la diabetes y la hipertensión	I	B
En los pacientes diagnosticados de FA que tienen un riesgo anual de ictus o eventos tromboembólicos ≥2 %, la selección del tratamiento para reducir el riesgo de ictus debe basarse en el riesgo de tromboembolia, independientemente de si el patrón de FA es paroxístico, persistente, persistente de larga evolución o permanente	I	B
En pacientes diagnosticados de FA con riesgo de ictus, se recomienda reevaluar periódicamente la necesidad y la elección del tratamiento para reducir el riesgo de ictus y hemorragia	I	B
En pacientes con FA que reciben dabigatrán y desarrollan una hemorragia potencialmente mortal, se recomienda el tratamiento con idarucizumab para revertir rápidamente el efecto anticoagulante del dabigatrán	I	B
Para los pacientes con FA que reciben warfarina/acenocumarol, se recomienda un INR objetivo entre 2 y 3, así como una gestión óptima de las interacciones entre fármacos, una ingesta dietética constante de vitamina K y una monitorización rutinaria del INR para mejorar el tiempo en el rango terapéutico y minimizar los riesgos de tromboembolismo evitable o hemorragia grave	I	B
En pacientes con FA que reciben inhibidores del factor Xa y presentan hemorragias potencialmente mortales, se recomienda el tratamiento con andexanet alfa (apixabán o rivaroxabán, edoxabán) o concentrado de complejo de protrombina de 4 factores para revertir rápidamente el efecto anticoagulante del inhibidor del factor Xa	I	B
En pacientes con función del ventrículo izquierdo reducida y FA, debe recomendarse el control del ritmo para evaluar si la FA está contribuyendo a la reducción de la función del ventrículo izquierdo	I	B

Para los pacientes con FA que reciben NACO, se recomienda una gestión óptima de las interacciones farmacológicas para aquellos que reciben tratamiento concomitante con fármacos interactuantes, especialmente inhibidores o inductores de CYP3A4 y/o p-glicoproteína	I	C
Para pacientes con FA y un riesgo tromboembólico anual estimado de ≥1 % pero <2 % anual (equivalente a una puntuación CHA_2DS_2-VASc de 1 en hombres y 2 en mujeres), la anticoagulación es razonable para prevenir el ictus y el tromboembolismo sistémico	IIa	A
Para los pacientes que han tenido un evento tromboembólico sistémico sin antecedentes conocidos de FA y en los que se busca la máxima sensibilidad para detectar la FA, se recomienda un monitor cardiaco implantable	IIa	B
Entre los pacientes con diagnóstico de FA, se debería inferir la frecuencia, duración y carga de la FA mediante algoritmos automatizados disponibles en monitores electrocardiográficos, monitores cardíacos implantables y dispositivos de ritmo cardíaco con derivación auricular con una revisión periódica para excluir otras arritmias	IIa	B
Entre los pacientes con FA en los que se aconseja la monitorización cardíaca, se recomienda el uso de un dispositivo electrocardiográfico que proporcione un trazado de alta calidad para detectar recurrencias	IIa	B
Pacientes con FA con riesgo anual intermedio de tromboembólicos según las puntuaciones de riesgo (p. ej., equivalente a una puntuación CHA_2DS_2-VASc de 1 en hombres o 2 en mujeres), que siguen teniendo dudas sobre el beneficio de la anticoagulación, podrían beneficiarse de la modificación de factores de riesgo de ictus para ayudar a fundamentar la decisión	IIa	B
En pacientes con ictus o accidente isquémico transitorio (AIT) de causa indeterminada, la monitorización cardíaca inicial, o si fuera necesaria la monitorización prolongada con un registrador de bucle implantable, son recomendables para mejorar la detección de la FA	IIa	B
En pacientes con FA sintomática, el control del ritmo puede ser útil para mejorar los síntomas	IIa	B
En pacientes con diagnóstico reciente de FA (<1 año), el control del ritmo puede ser útil para reducir las hospitalizaciones, el ictus y la mortalidad	IIa	B
En pacientes con FA e insuficiencia cardíaca, el control de ritmo puede ser útil para mejorar los síntomas y mejorar los resultados, como la mortalidad y las hospitalizaciones por insuficiencia cardíaca e isquemia	IIa	B
En pacientes con FA, las estrategias de control del ritmo pueden ser útiles para reducir la probabilidad de progresión de la FA	IIa	B

En los pacientes con FA que reciben dabigatrán y presentan hemorragia potencialmente mortal, el tratamiento con concentrado de complejo protrombínico activado es razonable para revertir el efecto anticoagulante de dabigatrán si no se dispone de idarucizumab	IIa	C
La toma de decisiones basadas en la evidencia podría ser útil para guiar las decisiones sobre el tratamiento de reducción del ictus a lo largo del curso de la enfermedad para mejorar el compromiso terapéutico, la calidad de la toma de decisiones y la satisfacción del paciente	IIb	B
En los pacientes con FA que desarrollan una hemorragia gastrointestinal grave, la reanudación del tratamiento anticoagulante oral puede ser razonable tras la corrección de las causas reversibles de la hemorragia y la reevaluación de sus beneficios y riesgos a largo plazo con un enfoque de equipo multidisciplinar	IIb	B
En pacientes con FA, las estrategias de control del ritmo pueden ser útiles para reducir la probabilidad de desarrollo de demencia o de empeoramiento de las anomalías estructurales cardíacas	IIb	B
En pacientes con FA que presenten síntomas asociados, un control del ritmo (p. ej., cardioversión o tratamiento farmacológico) puede ser útil para determinar qué síntomas son atribuibles a la FA	IIb	C
En pacientes con FA recién diagnosticada, no deben realizarse de forma rutinaria pruebas protocolizadas de isquemia, síndrome coronario agudo (SCA) y embolia pulmonar (EP) para evaluar la etiología de la FA, a menos que existan signos o síntomas adicionales que indiquen esos trastornos	III	B
En pacientes considerados de alto riesgo de ictus, las puntuaciones de riesgo de hemorragia no deben utilizarse de forma aislada para determinar la elegibilidad para la anticoagulación oral, sino para identificar y modificar los factores de riesgo de hemorragia y para informar la toma de decisiones médicas	III	B
En pacientes con FA candidatos a anticoagulación y sin indicación de tratamiento antiagregante plaquetario, no se recomienda el uso de ácido acetilsalicílico solo o en combinación con clopidogrel como alternativa a la anticoagulación para reducir el riesgo de ictus	III	B
En pacientes con FA sin factores de riesgo de ictus, la monoterapia con ácido acetilsalicílico para la prevención de episodios tromboembólicos no aporta ningún beneficio	III	B

El aumento de la prevalencia de la FA y la posibilidad de prevenir el ictus han impulsado iniciativas para implementar el cribado de la FA de rutina en aquellos pacientes con factores de riesgo mediante el electrocardiograma[1]. Generalmente, un cribado oportunista o sistemático en individuos a partir de ≥65 años o con otras características sugestivas de mayor riesgo de MACE siendo

Atención Primaria (AP) o el cribado comunitario un buen escenario para el cribado de la FA[32].

Actualmente, hay diferentes escalas para evaluar el riesgo de FA, pero ninguna ha sido trasladada a la práctica clínica habitual. A nivel del territorio de estudio, ha sido propuesta la escala de *risk*-FA como predictora de sufrir FA en los próximos 5 años[33]. Los avances de la tecnología harán posible que se pueda detectar la FA y evaluarla gracias a los nuevos dispositivos móviles[34-38] y aplicaciones[39].

Las patologías incluidas como MACE y sus factores de riesgo deberían ser tratados activamente para reducir la mortalidad relacionada. La FA es un potente predictor de MACE[11,13]. Estudios recientes también han demostrado el valor pronóstico de la puntuación CHA_2DS_2-VASc en varias enfermedades cardiovasculares y no cardiovasculares encontrando relación entre los MACE y el aumento del CHA_2DS_2-VASc, la presencia de puntuaciones elevadas se asocia con un mayor riesgo de sufrir un MACE[40,41].

Se han desarrollado diferentes esquemas de estratificación del riesgo de MACE, como CHA_2DS_2-VASc[1], la puntuación de Framingham[42], ATRIA[43], la puntuación CHARGE-AF[44,45] o Atrial Fibrillation Research in Catalonia (AFRICAT)[46]. Sin embargo, las puntuaciones de riesgo clínico siguen presentando dificultades y limitaciones que restringen su aplicabilidad a determinadas poblaciones. La capacidad discriminativa de las puntuaciones de riesgo clínico para predecir el riesgo de accidente cerebrovascular de un individuo es, en el mejor de los casos, moderada[47]. De ahí que la integración de factores de riesgo adicionales pueda ser un valioso complemento a los pronósticos existentes y ayudar a identificar a los pacientes de alto riesgo.

Considerando la enorme amenaza epidemiológica asociada con la FA y la disminución de MACE, los esfuerzos actuales ahora van más allá de la prevención primaria convencional basada en el tratamiento de los factores de riesgo a la llamada prevención "primordial", que significa la prevención del desarrollo de factores de riesgo en primer lugar[48]. Para conseguirlo hace falta la implementación de medidas preventivas, intervención temprana y programas de cribado en la población general. Este enfoque apunta a prevenir la aparición de factores de riesgo en la población a través, por ejemplo, de la mejora del comportamiento individual con la adopción de un estilo de vida saludable[48]. Una anamnesis y una exploración física específicas en la evaluación inicial y repetirse durante el seguimiento periódico, especialmente teniendo en cuenta el riesgo evolutivo de tromboembolia y la cadencia de los síntomas en respuesta al tratamiento[1,3]. El trabajo de un equipo multidisciplinar y una adecuada relación médico-paciente que fomente la confianza mutua es esencial para evaluar mejoras en el estilo de vida, identificar de forma temprana la FA y continuar monitoreando la evolución de los pacientes con el fin de evitar MACE.

La aparición de la IA pueden ser una prometedora vía para la detección, intervención y estratificación del riesgo de los pacientes con FA y reducir los MACE. Estos métodos proporcionan algoritmos precisos y eficientes para el

análisis de datos, mejorando la precisión de la predicción, la identificación y la automatización de tareas. Los algoritmos de IA se utilizan cada vez más en diversos escenarios relacionados con la FA, como el diagnóstico[49], la predicción de resultados[50], la caracterización de la enfermedad[49] y la evaluación de la eficacia del tratamiento[51].

El ML es una técnica de IA basada en algoritmos que mejoran automáticamente mediante un proceso iterativo de aprendizaje a partir de datos, identificación de patrones y toma de decisiones. Estos modelos de ML están obteniendo buenos resultados en pacientes con FA[52], ya que pueden integrar grandes cantidades de datos procedentes de múltiples fuentes e identificar patrones y correlaciones complejos que pueden no ser evidentes utilizando métodos estadísticos tradicionales[50,53] siendo una excelente oportunidad para los pacientes con FA y disminuir los MACE. Sin embargo, es importante tener en cuenta que el rendimiento y los enfoques de la IA y el ML pueden variar[54]. Los avances que proporcionan este tipo de modelos han hecho que se hayan establecido normas reguladoras para incluir enfoques y software de ML[55]. Las propuestas actuales están desarrollando métodos de regulación para la validación de los algoritmos, al tiempo que dejan margen para la flexibilidad y la innovación [55].

4. Hipótesis

4.1. Hipótesis

Hipótesis por cada objetivo principal:

- **Riesgo de FA**

H0: No existe mayor riesgo de incidencia en la población de un nuevo diagnóstico de FA.

H1: Existe mayor riesgo de incidencia en la población de un nuevo diagnóstico de FA.

- **Incidencia de FA y MACE**

H0: No existe mayor riesgo de incidencia de MACE en la población con nuevo diagnóstico de FA respecto a la que no desarrolla FA.

H1: Existe mayor riesgo de incidencia de MACE en la población con nuevo diagnóstico de FA respecto a la que no desarrolla FA.

- **Factores predictores de MACE en pacientes con FA**

H0: No existen factores predictores de MACE en los pacientes con nuevo diagnóstico de FA.

H1: Existen factores predictores de MACE en los pacientes con nuevo diagnóstico de FA.

4.2. Objetivos

Objetivos principales

- Identificar la incidencia de FA y el riesgo de MACE en la población con nuevo diagnóstico de FA
- Determinar las características de los pacientes con riesgo de presentar FA
- Definir los posibles factores predictores de MACE en los pacientes con nuevo diagnóstico de FA con IA

Objetivos secundarios

- Describir la incidencia de FA asociada al diagnóstico de ictus
- Identificar las características clínicas de los pacientes con FA y MACE
- Conocer las puntuaciones de las escalas CHA_2DS_2-VASc, Wells y CONUT
- Examinar el estado nutricional entre los pacientes con FA y el desarrollo de MACE
- Evaluar si el estado nutricional de los pacientes es un factor de riesgo de MACE en pacientes con FA

5. Materiales y métodos

5.1. Diseño, población de referencia y período de estudio

Para la consecución de los objetivos específicos propuestos, se diseñó el proyecto en tres fases:

a) Primera fase: diseño multicéntrico, observacional, retrospectivo y comunitario de una cohorte de pacientes (artículo 1) con el objetivo de determinar la incidencia de ictus y FA.

b) Segunda fase: diseño multicéntrico, observacional, retrospectivo y comunitario de una cohorte de pacientes (artículo 2) con el objetivo de describir las características de los pacientes con nuevo diagnóstico de FA y sus relaciones con los MACE.

c) Tercera fase: diseño multicéntrico, observacional, retrospectivo y comunitario de una cohorte de pacientes (artículo 3) con el objetivo de identificar factores pronósticos de MACE en pacientes nuevo diagnóstico de FA.

La población de referencia fue la población general de entre 65 y 95 años de la región sanitaria de Terres de l'Ebre (RSTE) entre el 01/01/2015 y el 31/12/2021 en el ámbito de AP.

5.2. Ámbito del estudio

El estudio se ha llevado a cabo en la RSTE (Figura **1**), situadas en la zona sur de Cataluña (España).

Figura 1. Mapa de Cataluña por regiones sanitarias. *Fuente: gencat.cat*

El territorio está compuesto por 4 comarcas, 11 Equipos de Atención Primaria (EAP), gestionados por el Instituto Catalán de la Salud (ICS), Departamento de Salud de Cataluña (CatSalut). La atención especializada se recibe en el hospital de referencia, Hospital de Tortosa Virgen de la Cinta, ubicado en Tortosa, que es gestionado públicamente por el ICS. Los EAP están organizados como equipos

clínicos funcionales independientes. La mayoría de la población censada en el territorio (98.2 %) cuenta con un Historial Compartido de Salud de Cataluña (HC3) activo y disponible digitalmente para el monitoreo continuo desde cualquier centro.

El territorio de TE presenta una población de 178.112 habitantes (49.6% mujeres) distribuidos en 54 municipios, con un promedio de 53.8 habitantes por km2, en comparación con los 241.8 habitantes por km2 en Cataluña[56]. Se puede constatar que el índice de envejecimiento de la población (159.5) es superior al de Cataluña (131.3) y España (118.4)[57]. Este índice se obtuvo mediante la relación entre la población mayor de 65 años y la población menor de 15 años por cada 100 habitantes. La población de 65 años o más representa el 31.1 % de la población total. La población del estudio tiene un ingreso promedio más bajo que la población general en Cataluña (77.4 % vs. 100 % per cápita)[58,59].

5.3. Recopilación de datos y fuentes de información

Los datos han sido obtenidos a partir de la historia clínica electrónica (programas E-CAP y SAP) gestionados por el ICS, que recopila la información de los centros de AP y hospitales de la región sanitaria de manera anónima y sin tener contacto con los casos incluidos.

El Departamento de las Tecnologías de la Información y Comunicaciones, a través del registro del conjunto mínimo básico de datos al alta hospitalaria (CMBD-HA), proporcionó retroactivamente una base de datos digitalizada y anonimizada con la historia clínica utilizando la Clasificación Internacional de Enfermedades (versión 11; CIE-11) al investigador principal en un formato totalmente anónimo.

Los conjuntos de datos utilizados para este proyecto fueron los siguientes:

1. El Instituto de Estadística de Cataluña recopiló datos sobre el índice de envejecimiento, la densidad de habitantes y la renta familiar bruta disponible por habitante para cada región de Cataluña.
2. El Plan de Salud de la Región Sanitaria de les TE 2021-2025 define los objetivos, prioridades y acciones sanitarias para la región.
3. El HC3 con la información demográfica y clínica sobre la atención hospitalaria y ambulatoria en los hospitales catalanes.
4. Las 11 EAP gestionadas por el ICS comparten una base de datos de información clínica de AP y de las interacciones hospitalarias, que incluye datos clínicos, diagnósticos, medicación, derivaciones y estado de los pacientes hasta el 31 de diciembre de 2021 (fecha fin del seguimiento).

5.4. Criterios de inclusión y exclusión

Inicialmente, el estudio incluyó a personas del territorio mayores de 65 años sin FA conocida o registrada ni MACE en su historial clínico, resultando en un total de 55.459 participantes. Se definieron los siguientes criterios:

- Criterios de inclusión: sujetos entre 65 y 95 años, sin diagnóstico de FA ni MACE previo, alto riesgo-FA, historia clínica activa en cualquiera de los centros de salud del territorio con información accesible a través de la HC3, residencia en el territorio y adscripción a alguno de los EAP del mismo. Se consideró motivo de exclusión la no disponibilidad o pérdida de información necesaria para el estudio.
- Criterios de exclusión: sujetos <65 o >95 años, diagnóstico previo de FA y/o MACE, población fuera de las TE, tratamiento con anticoagulantes, estado cognitivo incapacitante, Barthel <55, portador de marcapasos o desfibrilador.

5.5. Variables de estudio

La información sobre la FA y/o MACE así como las comorbilidades de riesgo cardiovascular se obtuvieron hasta la pérdida del seguimiento, la fecha de defunción o el 31 de diciembre de 2021, lo que ocurriera primero. Todos los diagnósticos de FA fueron verificados por dos médicos investigadores que desconocían el diagnóstico MEANS. En el caso de no existir un consenso en el diagnóstico de FA se consultó a un cardiólogo. Los pacientes se clasificaron según la presencia de FA. En los pacientes diagnosticados, durante el período de seguimiento, los datos se extrajeron en el momento del diagnóstico de FA o hasta el final del seguimiento. Las variables se incluyeron en el momento del diagnóstico de FA o MACE. En el resto de los casos, las variables se obtuvieron en el último año de seguimiento.

1. Variables sociodemográficas: edad, sexo, EAP y comarca.
2. Factores de riesgo cardiovascular y diagnósticos mediante prefijos de códigos específicos de la CIE-11 para hipertensión (I10-I15), hipercolesterolemia (E78), tabaquismo (F17.203, Z72), índice de masa corporal (IMC), diabetes mellitus (E10-E14), síndrome de apnea-hipopnea del sueño (G47.3), insuficiencia cardíaca (I50-51), cardiopatía isquémica (angina estable o inestable, intervención coronaria percutánea, *bypass* coronario o infarto de miocardio) (I20-I25), enfermedad renal crónica (ERC) (N18) y tasa de filtración glomerular estimada (TFGe ml/min/1.73 m2), enfermedad cerebrovascular (ictus isquémico o accidente isquémico transitorio) (I63, G45), EPOC, asma, bronquitis crónica (J40-J45), cáncer (C00-C96) y Covid (U07.1). La enfermedad coronaria se definió como antecedentes de infarto de miocardio, angioplastia coronaria transluminal percutánea y/o cirugía de injerto de derivación coronaria. Los datos sobre el Covid se recogieron desde el 15/03/2020 (primera oleada en España) hasta el 31/12/2021.

3. Puntuaciones clínicas: índice de riesgo de FA[33,46], riesgo de accidente cerebrovascular según la puntuación CHA_2DS_2-VASc, Índice de Barthel para Actividades Básicas de la Vida Diaria (ABVD), estado nutricional controlado (puntuación CONUT) y puntuación de Grupos de Morbilidad Ajustados (GMA) según las pautas actuales[1]. El modelo para categorizar el riesgo de sufrir fibrilación auricular en cinco años en personas de la comunidad ≥65 años fue publicado previamente[33,46]. Incluye las siguientes variables: sexo, edad, frecuencia cardíaca promedio, peso promedio y puntuación CHA_2DS_2-VASc. La fórmula matemática del modelo se aplicó a la población objetivo sin diagnóstico de FA y se definieron los cuartiles de la distribución de menor a mayor riesgo (Q1-Q4), siendo de interés el Q4 (alto riesgo). Se calculó la densidad de incidencia de fibrilación auricular/1000 personas-años (ID) para cada grupo, al igual que la incidencia de ictus, MACE y la prevalencia registrada de deterioro cognitivo.
4. Tratamiento farmacológico: antiagregantes plaquetarios, nuevos anticoagulantes y antivitamina K.
5. Estado final (muerte/vivo).

5.6. Análisis estadístico

Los datos basales se expresaron en diversos formatos: números, porcentajes, media, desviación estándar (DE), mediana y rango intercuartílico (RIQ), según se consideró apropiado. Para las variables cualitativas, se empleó la distribución chi-cuadrado para el análisis bivariante en los casos de distribuciones normales, mientras que las variables cuantitativas se evaluaron mediante la distribución t de Student para muestras independientes.

La tasa de incidencia se calculó considerando el tiempo total de observación de cada individuo de la población de estudio, que tiene en cuenta la duración tanto del riesgo de enfermedad como del seguimiento. Las variables con un valor p inferior a 0,05 se consideraron estadísticamente significativas en los análisis. Para evaluar el riesgo cardiovascular de los resultados asociados a la FA, se calcularon las *odds ratio* (OR) comparando la tasa de eventos en el grupo expuesto a la FA con la del grupo control o no expuesto. Los aumentos absolutos del riesgo se expresaron en eventos por 1.000 personas-año de seguimiento. Para la comparación de la incidencia de MACE entre los grupos con y sin FA, se empleó el análisis de regresión de Cox, mientras que la mortalidad se evaluó mediante curvas de Kaplan-Meier. También se calcularon *hazard ratio* (HR) utilizando el análisis de regresión de Cox proporcional. Las HR se ajustaron mediante la inclusión de variables de confusión significativas en el modelo de regresión. Cualquier variable que se encontrara con un valor p significativo ($p \leq 0.05$) y que no estuviera incluida en las puntuaciones utilizadas (CONUT y CHA_2DS_2-VASc) se consideró como posible factor de confusión.

El análisis estadístico y la gestión de los datos se realizaron con IBM SPSS Statistics versión 21.0.

5.6.1. Datos y algoritmos de *machine learning*

En este estudio, se utiliza la IA para analizar datos mediante la aplicación de técnicas de *machine learning* (ML). Se crearon diferentes modelos de ML. Estos se entrenaron con todas las características (variables) utilizadas en el estudio para predecir el desarrollo de MACE en el término de un año, así como la predicción del desarrollo de FA.

Una parte fundamental del estudio, previa a la construcción de los modelos de aprendizaje, consistió en la "Ingeniería de Características", que implica el análisis y selección de las variables, así como el procesamiento de los datos que contienen. Para ello, se eliminaron aquellas variables que solo aportaban ruido y/o estaban correlacionadas con otras que tenían mayor influencia en el objetivo que pretendíamos predecir.

Se seleccionaron aleatoriamente dos tercios de los datos para el entrenamiento y la construcción de los modelos con el fin de reducir el error de predicción. El tercio restante se utilizó para las pruebas finales y la validación de los modelos.

Los cálculos numéricos y el análisis de datos se realizaron utilizando Python versión 3, las bibliotecas SKLearn y TensorFlow debido a su versatilidad y facilidad de programación.

5.6.2. Análisis del rendimiento de los modelos

Se utilizaron diversas métricas para evaluar los algoritmos, incluyendo la robustez de la predicción, exhaustividad, sensibilidad, especificidad, precisión, *recall*, *accuracy* y F1 score (combinación de precisión y *recall*). La evaluación de estas métricas permitió el ajuste de los hiperparámetros del modelo. Después de evaluar el rendimiento de las diferentes plantillas mediante el valor medio del área bajo la curva ROC (AUC ROC), se eligió el modelo con el rendimiento más alto y robusto. También se tuvo en cuenta la DE de los resultados para evaluar la estabilidad, sensibilidad, especificidad y accuracy.

5.6.3. Interpretabilidad del modelo

Se utilizó el método de *SHapley Additive exPlanations* (SHAP) para analizar qué factores eran los más importantes y en qué medida contribuyen a las predicciones del modelo. Para permitir un análisis individual de cada paciente se creó un modelo individual de explicabilidad automática. Después de analizar las variables de un paciente, este último modelo permite explicar la probabilidad de que un paciente con FA tenga un MACE y qué factores y en qué medida contribuyen a esta predicción.

5.7. Aspectos éticos y protección de datos

Los protocolos de los estudios recibieron evaluación ética y aprobación del Comité Ético del Instituto Universitario de Investigación en Atención Primaria Jordi Gol con número de registro 22/243-P.

Los estudios se realizaron de acuerdo con las normas más relevantes en materia de tratamiento de datos, del contexto experimental con pacientes, ética y protección de datos y privacidad, siguiendo la Directiva 95/46/CE (protección de las personas físicas en lo que respecta al tratamiento de datos personales y a la libre circulación de dichos datos). Todos los datos fueron incluidos en un repositorio ad hoc, el cual fue entregado al investigador principal.

Todos los datos han sido considerados confidenciales y se han tratado acorde a la normativa actual relativa a la protección de datos personales de las personas físicas en el ámbito de la investigación en salud (Reglamento UE 2016/679 del Parlamento y Consejo Europeo, y la Ley Orgánica 3/2018). Según esta misma legislación, en estudios poblacionales y retrospectivos con extracción de datos anonimizados, no se requiere un permiso formal ni consentimiento informado del paciente antes de incluir sus datos médicos en estudios de investigación.

6. Resultados

6.1. Primer artículo

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Article

Early Diagnosis of Atrial Fibrillation and Stroke Incidence in Primary Care: Translating Measurements into Actions— A Retrospective Cohort Study

Clua-Espuny J-L, Molto-Balado P, Lucas-Noll J, Panisello-Tafalla A, Muria-Subirats E, Clua-Queralt J, Queralt-Tomas L, Reverté-Villarroya S, Investigators EBRICTUS Research. Early Diagnosis of Atrial Fibrillation and Stroke Incidence in Primary Care: Translating Measurements into Actions—A Retrospective Cohort Study. *Biomedicines*. 2023; 11(4):1116. https://doi.org/10.3390/biomedicines11041116

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- Q2: *Biochemistry & Molecular Biology* (92/285)
- Q2: *Medicine, Research & Experimental* (61/189)

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Josep-Lluis Clua-Espuny [1,2,*], Pedro Molto-Balado [3], Jorgina Lucas-Noll [4], Anna Panisello-Tafalla [1], Eulalia Muria-Subirats [5], Josep Clua-Queralt [2], Lluïsa Queralt-Tomas [6], Silvia Reverté-Villarroya [7,8,*] and Investigators EBRICTUS Research

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Abstract: (1) Background: AF-related strokes will triple by 2060, are associated with an increased risk of cognitive decline, and alone or in combination, will be one of the main health and economic burdens on the European population. The main goal of this paper is to describe the incidence of new AF associated with stroke, cognitive decline and mortality among people at high risk for AF. (2) Methods: Multicenter, observational, retrospective, community-based studies were conducted from 1 January 2015 to 31 December 2021. The setting was primary care centers. A total of 40,297 people aged ≥65 years without previous AF or stroke were stratified by AFrisk at 5 years. The main measurements were the overall incidence density/1000 person-years (CI95%) of AF and stroke, prevalence of cognitive decline, and Kaplan–Meier curve. (3) Results: In total, 46.4% women, 77.65 ± 8.46 years old on average showed anAF incidence of 9.9/10^3/year (CI95% 9.5–10.3), associated with a four-fold higher risk of stroke (CI95% 3.4–4.7), cognitive impairment(OR 1.34 (CI95% 1.1–1.5)), and all-cause mortality (OR 1.14 (CI95% 1.0–1.2)), but there was no significant difference in ischemic heart disease, chronic kidney disease, or peripheral arteriopathy. Unknown AF was diagnosed in 9.4% and of these patients, 21.1% were diagnosed with new stroke. (4) Conclusions: The patients at high AF risk (Q4th) already had an increased cardiovascular risk before they were diagnosed with AF.

Keywords: atrial fibrillation; stroke; neurocognitive impairment; risk management; screening

1. Introduction

Atrial fibrillation (AF) and stroke are two common conditions that disproportionately affect the elderly population. AF is expected to rise by 2.5 times in the next 50 years, is often asymptomatic, and has a recognized association with other comorbidities, which contribute to the increased risk of stroke and adverse events. A 34% increase in strokes related to AF is

predicted in the coming decades, the number of ischemic strokes recorded in people above 80 years of age will triple (2010–2060), and there will be an estimated 27% increase in stroke survivors who develop these diseases, alone or in combination. Therefore, AF will become one of the main health and economic burdens on the European population [1–7]. Both AF and stroke incidence rates will increase with age, and the aging of the global population has contributed to a rise in the prevalence of these conditions with multifactorial and complex causes. Age-related changes in the heart, such as fibrosis and decreased conductivity, can increase the risk of developing AF as well as other factors such as hypertension, diabetes, obesity, and a history of heart disease or heart failure. Similarly, stroke risk factors include hypertension, diabetes, atrial fibrillation, smoking and atherosclerosis.

Stroke is already one of the leading causes of death and long-term disability in developed countries and the second highest burden of disease in Europe due to its social and economic impacts [5,8]. One out of four strokes is recurrent, and secondary stroke carries a greater risk than first stroke of death and disability. A link was reported between silent cerebral infarction detected by MRI and atrial myopathy with an increased risk of developing cognitive impairment, dementia [9] and a range of different cardiovascular diseases referred to as major adverse cardiovascular events (MACEs) [10,11]. Ischemic stroke in people with AF [12–14] is characterized by greater severity and disability, increasing costs by up to 20%, and its incidence is 2.3-fold higher among people ≥75 yearsold. Moreover, up to 50% will suffer from residual disability, insufficient cognitive ability and/or poor mental health [15,16].

Given the prevalence of AF and the fact that its complications will increasein the coming decadesbecause of the aging population, itisaprioritytodevelop proposals aimed at improving diagnosis and treatment. Among these approaches, strategies for the opportunistic detection of AF are recommended by international organizations including the European Society of Cardiology (ESC), Stroke Alliance for Europe (SAFE), European Heart Rhythm Association (EHRA), Royal College of Physicians of Edinburg (RCPE), World Healthcare Forum (WHF), European Primary Care Cardiovascular Society (EPCCS), and Health Information and Quality Authority (HIQA). However, there is disagreement about whether opportunistic screening detects AF more effectively than the usual practice [17–19].

The Action Plan in Europe (2018–2030) [6] prioritizes the availability of detection and treatment programs in primary care to improve the diagnosis and monitoring of populations at risk of AF in the respective health contexts of each country, a lack of information prevails on whether an elevated risk exist for the correlation between AF and stroke before the diagnosis of AF. As a result, it remains paramount to identify patients at elevated risk of AF to determine who would benefit from risk factor control and treatment. Conventional practices involve the use of clinical risk scoring criteria to identify patients at risk, but these risk scores have modest discriminatory power. The past decade has seen substantial advances in the diagnostic and treatment options available to minimize the impact of acute ischemic stroke, new insights have been gained on the utility of biomarkers and imaging modalities, and there are emerging data on the importance of the identification of subclinical AF using wearable devices in primary care practice. The main goal of this study is to describe the incidence of new cases of AF associated with the diagnosis of stroke as well with cognitive decline and major adverse cardiovascular events among people at high risk of AF.

2. Materials and Methods

2.1. Study Design

This was an observational, retrospective, multicenter, and community-based study of a cohort of 40,297 of the general population aged 65 to 95 years between 1 January 2015 and 31 December 2021 without a prior diagnosis of atrial fibrillation or stroke. The protocol received ethics evaluation and approval from the Ethical Committee of Jordi Gol University Institute of Primary Care Research with registration number P15/047.

2.2. *Study Scope*

The study was conducted in the primary care setting of Terres de l'Ebre (Catalonia, Spain) (Appendix A). According to census data, the territory comprises 178,112 inhabitants (women, 49.6%), with a higher aging index (159.5) than Catalonia (131.3) and Spain (118.4) [20]. This is relevant to the demographics of the study because most of the cohort was made up of older individuals [21,22].

The public health service is made up of four counties with a total of 11 primary care teams (EAPs), all managed by the Catalan Health Institute, Department of Health (CatSalut). In total, 98.2% of the census population has an active clinical record in at least one of the EAPs and/or reference hospitals of the territory. This availability of digitalized clinical history allows for continuous follow-up care from any center.

2.3. *Data Collection and Information Sources*

The clinical background data were obtained retrospectively from a computerized database, provided to the principal investigator by the Information and Communication Technology Department from the minimum basic dataset at hospital discharge (CMBD-HA) register using the specific International Classification of Diseases (10th version; ICD-10) in a fully encrypted format. The particular datasets utilized for this project were as follows:

1. The "Health Plan of the *"Terres de l'Ebre"* region 2021–2025 [23]: a digital access platform used by the Department of Health.
2. The Institute of Statistics of Catalonia for each region of the territory: demographics, inhabitant density/km^2, and aging index vs. Catalonia (100%).
3. The HCC3 Patient Episode Dataset for Catalonia (CatSalut, Health Department), which includes demographic and clinical data on all daily inpatient and outpatient admissions in Catalonian hospitals.
4. The 11 EAPs (Catalonian Health Institute, Governmental agency) share a clinical information database for all general practice (E-cap, HC3) and hospital (E-sap) interactions, including clinical data, symptoms, investigations, diagnoses, comorbidities, prescribed medications, referrals to secondary and tertiary care, and status (alive/dead). Pharmacological variables were collected from the SIRE (Catalan acronym for Integrated Electronic Prescription System).

Data on these factors were collected automatically when possible, or manually otherwise.

2.4. *Study Population*

Initially, the study included people 65–95 years-old, resulting in a total of 55,459 patients. After applying inclusion criteria, 40,297 people without AF were included in the study. All the patients enrolled were followed up for the occurrence of atrial fibrillation after the inclusion. In this analysis, the primary outpoint was the outcome of ischemic stroke. Other secondary outcomes investigated cognitive impairment, cardiovascular outcomes (MACEs), and all-cause death. The hypothesis was that the incidence of stroke, cognitive impairment, and all-cause mortality would be higher in individuals at high risk for AF before its diagnosis.

2.5. *Inclusion and Exclusion Criteria*

2.5.1. Inclusion Criteria

Patients 65–95 years old with a high risk of AF [24], active medical records in any of the health centers with information accessible through the shared history (HCC3), without prior AF or stroke, residence in the territory, and assignment to any of the territory's primary are teams (EAP). The non-availability or loss of accessibility to the information necessary for the study was considered as a reason for exclusion.

2.5.2. Exclusion Criteria

Previous diagnosis of AF and/or stroke, non-availability of AF-index prognosis [25], pacemaker or defibrillator wearer, absence of or lack of access to individual or theirclinical records for any reason, difficulty in following the instructions, patient's non acceptance of conditions, and/or residence outside the Terres de l'Ebre.

2.6. Variables

The information on AF and co-morbidities relevant to cardiovascular risk were obtained until loss-to-follow-up, date of death, or 31 December 2021, whichever occurred first. Atrial fibrillation was diagnosed according to the guidelines of the European Society of Cardiology. All new AF diagnoses were verified by two research physicians blind to the MEANS diagnosis. A cardiologist was consulted when consensus was not reached. Patients were classified according to the presence of AF. In cases of AF diagnosed during the follow-up period, data were extracted at the time of AF diagnosis or until the end of follow-up. Data for patients who did not present AF during follow-up were obtained according to the mean during follow-up:

(1) Cardiovascular risk factors and diagnostics using specific International Classification of Diseases (ICD–10) code prefixes for cerebrovascular disease (ischemic stroke or transient ischemic attack, I63, G45), heart failure (I50-51), ischemic heart disease (stable or unstable angina, percutaneous coronary intervention, coronary artery bypass grafting or myocardial infarction) (I20-I25), hypertension (I10–I15), hypercholesterolemia (E78), diabetes mellitus (E10–E14), body mass index (BMI), chronic kidney disease (CKD) (N18) and estimated glomerular filtration rate (eGFR ml/min/1.73 m^2).
(2) Clinical scores: AF risk index, CHADsVASc score, Pfeiffer Short Mental Status Questionnaire (SPMSQ) score, NIHSS score, and modified Rankin scale (mRS) in case of stroke as recommended by current guidelines. The model to stratify the risk of suffering AF at five years among individuals aged ≥65 years was published previously [24,25].
(3) Antiplatelet and/oral anticoagulation (antivitaminK vs. NOACs).
(4) Vital status (dead/alive) at the end of the study. All participants were followed from 1 January 2015 to 31 December 2021, loss tofollow-up, or date of death, whichever occurred first.

According to the guidelines of the European Society of Cardiology, the performance of screening for AF registered in the electronic medical records (e-cap) of any citizen aged ≥65 yearswho contacted the health system during the study period was evaluated. Eventually, 359 randomized patients at high risk of AF received a wearable Holter device (Nuubo™) for 4 weeks. Expert cardiologists evaluated the anonymized Holter records to identify AF episodes. Full details on protocol and results of the AFRICAT study have been previously reported elsewhere [26] (AFRICAT: Atrial Fibrillation Research in CATalonia, NCT03188484).

2.7. Statistical Analysis

The characteristics of the population were defined through a descriptive statistical analysis. Baseline characteristics are presented as counts and percentages, mean and standard deviation (SD) for normally distributed continuous variables, or median and interquartile range (IQR) for non-normally distributed continuous variables, as appropriate. Quantitative variables were examined with Student's *t*-distribution for independent samples while qualitative variables were analyzed with the chi-square distribution according to bivariate analysis for normal distributions.

The mathematical formula of the model was applied to the target population, and the quartiles of the distribution from lowest to highest risk were defined (Q1st–Q4th), with the Q4th (high risk) being of interest. The AF incidence density/1000 people/year (ID), the incidence of MACEs, and the registered prevalence of cognitive decline were calculated for each group. The incidence rate was calculated in person-years, and the denominator

was the sum of the length of time for which each person was observed, totaled for all persons. This denominator represents the total time the population was at risk of and being monitored for disease. The odds ratio (OR) risk increase for each vascular outcome associated with atrial fibrillation was calculated by the event in the exposure group divided by the odds of the event in the control or non-exposure group. Absolute risk increases were expressed in events per 1000 people/year of follow-up. Kaplan–Meier curves were used for mortality assessment, to compare survival probabilities, and to identify any significant differences. Two-sided p-value <0.05 was considered statistically significant. All statistical analyses were conducted using IBM SPSS Statistics version 21.0.

3. Results

3.1. Baseline Characteristics

The patient's baseline characteristics according to study groups are shown in Table 1. In total, 40,297 people without a personal history of AF were included. The average age of the patients was 77.88 ± 8.47 years, 46.48% were women, and the follow-up time was 80.65 ± 9.5 months. There were significant differences between the AF patterns for all the risk factors of interest at baseline. In total, 18.15% died during follow-up. Those with AF were significantly older (81.22 ± 7.91 vs. 77.65 ± 8.46 years, $p < 0.001$), and the most prevalent cardiovascular risk factors were arterial hypertension (HTA) (75.5%), dyslipidemia (47.6%), and diabetes (29.8%).

Table 1. Baseline characteristics: no atrial fibrillation vs. newly diagnosed atrial fibrillation.

Variables	All	No AF	AF	*p*
All (*n*)	40,297	37,723	2574	
Female	18,878	17,535	1343	<0.001
Age average	77.88 ± 8.47	77.65 ± 8.46	81.22 ± 7.91	<0.001
Arterial hypertension	25,555	23,610	1945	<0.001
Diabetes mellitus	10,458	9689	769	<0.001
BMI (kg/m^2)	28.71 ± 5.16	28.66 ± 5.14	29.5 ± 5.38	<0.001
Dyslipidemia	19,129	17,913	1216	0.822
Active Smoking	838	809	29	0.854
Risky Alcohol	506	487	19	0.395
Ischemic cardiomyopathy	2915	2558	357	<0.001
Heart failure	2772	2096	676	<0.001
Stroke	885	698	187	<0.001
Peripheral vascular disease	2776	2431	345	<0.001
Dementia/cognitive impairment	3781	3471	310	<0.001
Antiplatelet therapy	6251	6110	141	<0,001
CHA_2DS_2-VASc	3.24 ± 1.16	3.20 ± 1.15	3.83 ± 1.2	<0.001
Anticoagulation	2981	987	1994	<0.001
AntivitaminK	1698	754	944	<0.001
NACO	1288	235	1053	<0.001
Death—all causes	7317	6799	518	0.008

3.2. Atrial Fibrillation Incidence

The AF incidence (ID) was 9.9/1000 people per year (CI95% 9.5–10.3) and increased in line with the AFrisk levels, reaching 17/1000 people-years (CI95% 16.1–18.1) among those at the highest risk of AF (Figure 1), with a significantly higher incidence among men (OR 1.23 (CI95% 1.14–1.33)) than women. However, in the fourth quartile, the incidence of AF was higher among women (OR 1.52 (CI95% 1.35–1.71)). The average age (81.22 ± 7.91) was significantly higher than that of the overall group.

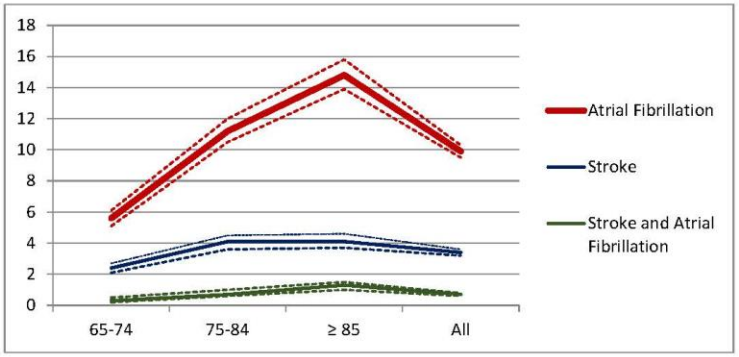

Figure 1. Atrial fibrillation and stroke incidence density rates for every 1000 people per year (CI95%), by age group.

3.3. Atrial Fibrillation and Stroke Incidence

In total, 885 stroke episodes were confirmed among the patients with a high risk of AF. The diagnosis of AF was found to be associated with a four-fold higher risk of stroke (OR 4.03 (CI95% 3.43–4.74)), and the highest stroke incidence was 11.1/1000 people/year (CI95% 9.6–12.8). The stroke incidence displayed a significant linear correlation with the Rankin scores ($p < 0.001$) and Pfeiffer scores ($p < 0.001$). In total, 187 of the strokes (21.12%) were associated with atrial fibrillation (Table 2). The factors associated with AF and strokes were different from those associated with atrial fibrillation alone. These factors included higher CHA_2DS_2-VASc and Charlson scores, higher MACE's incidence, higher rates of cognitive impairment, and higher rates of mortality than those without stroke.

Table 2. Characteristics of people with newly diagnosed AF with stroke and without stroke.

Variables	All	AF and Stroke	AF without Stroke	*p*
All (N)	2574	187	2387	<0.001
Women (*n*)	1343	112	1231	0.565
Men (*n*)	1231	97	1134	
Average age (years ± SD)	81.95 ± 8.46	82.91	81.87	0.899
Arterial hypertension (*n*)	2035	152	1883	0.667
Diabetes mellitus (*n*)	788	57	731	0.935
BMI (kg/m^2 average ± SD)	28.71 ± 5.16	28.62 ± 5.21	29.40 ± 5.37	0.052
Glomerular filtration rate (mL/min/1.73 m^2)	72.17 ± 18.89	65.92 ± 20.13	62.84 ± 20.43	0.069
Dyslipidemia (*n*)	1263	86	1177	0.374
Ischemic cardiomyopathy (*n*)	370	24	346	0.591
Heart failure	716	50	666	0.738
Peripheral vascular disease(*n*)	360	26	334	1.000
MACE (*n*)	1162	209	953	<0.001
CHA_2DS_2-VASc (average ± SD)	3.83 ± 1.19	4.76 ± 1.1	3.74 ± 1.17	<0.001
Anticoagulation (*n*)	2026	134	1892	0.016
Pfeiffer score (average ± SD)	3.02 ± 3.07	3.38 ± 2.91	2.98 ± 3.09	0.332
Dementia/cognitive impairment (*n*)	342	41	301	<0.001
Charlson score (average ± SD)	1.81 ± 1.43	2.60 ± 1.36	1.75 ± 1.42	<0.001
Statins treatment (*n*)	957	91	866	=0.001
Death—allcauses (*n*)	2574	137	2437	0.008

Most strokes (78.8%) occurred in people without AF, but 65.7% occurred in the Q4thrisk level, especially among women (88.17%). The stroke incidence increased in line with the AFrisk levels, reaching 6.8/1000 people-years (CI95% 6.2–7.5), and with the mean value ($p < 0.001$) on the Rankin scale. The incidence rate of stroke with AF was significantly higher (11.1/10^3-year, (CI95% 9.6–12.8, $p < 0.001$)) than among those without AF (2.7/10^3-year (CI95% 2.5–3.0, $p < 0.001$)). In total, 57.1% of patients with a simultaneous diagnosis of stroke and AF were in the Q4th group and displayed higher NIHSS scores (7.25 ± 8.62 vs. 4.55 ± 5.74, $p = 0.002$).

Screening for AF was reported in 74.5% of the population ≥65 years old. From the sample of 359 individuals, new AF was diagnosed in 34 subjects (9.47%) during the Holter monitoring period. Up to 82.35% of the cases of AF were recorded during the first 7 days and up to 88.23% during the first two weeks. The number of patients screened that was required to detect one new AF case in the study was 15. Unknown AF was diagnosed in 9.47% of people at high risk of AF, among whom 21.1% were diagnosed with new stroke.

3.4. Atrial Fibrillation and Cognitive Impairment

The 41.7% of cases with cognitive impairment were concentrated in the Q4th risk level, were older (84.84 ± 6.70 vs. 81.22 ± 7.91, $p < 0.001$), and already had a higher incidence of cognitive impairment and mortality before their diagnosis of AF.

The risk of cognitive impairment (OR 1.34 (CI95% 1.19–1.51, $p < 0.001$) was higher not only with a new diagnosis of AF, but also with the association between AF and stroke ($p = 0.001$). There was a progressive increase in prevalence (2.6% up to 15.3%), and there was an association of cognitive deterioration with AFrisk level as well as a significant linear correlation between AFrisk score and Rankin score (0.66 ± 1.15 vs. 2.27 ± 1.53, $p < 0.001$) and Pfeiffer score ((2.13 ± 3.06 vs. 3.86 ± 3.42, $p < 0.001$), but not with the NIHSS score ($p = 0.150$) after a stroke episode.

3.5. Atrial Fibrillation and Cardiovascular Comorbidities

Those with a new AF (Table 3) had a significantly high incidence of cardiovascular comorbidities and all-cause mortality. However, individuals in the Q4th quartile of AF risk had similar incidence rates of ischemic heart disease, chronic kidney disease, and peripheral arteriopathy prior to their AF diagnosis, as compared to those who were newly diagnosed with AF.

Table 3. Odds ratio of atrial fibrillation vs. no-atrial fibrillation vs. high AF risk (4th quartile).

	High AF Risk (Q4th)	New AF	No AF	OR AF/Q4 (CI95%)	OR AF/NoAF (CI95%)
N	10,072	2574	37,718		
AF all	1148	2574			
Incidence/1000 people per year (CI95%)	17.3 (16.3–18.3)	9.9 (9.5–10.3)	-		
Women *n* (%)	2876	1231			
Incidence/1000 people per year (CI95%)	22.8 (20.7–25.1)	8.9 (8.4–9.4)	-		
Men *n* (%)	7196	1343			
Incidence/1000 people per year (CI95%)	15.0 (13.9–16.1)	11.0 (10.4–11.6)	-		
Stroke/Transient ischemic attack	456	187	698	1.62 (1.37–1.92) $p < 0.001$	4.03 (3.43–4.74) $p < 0.001$
Incidence/1000 people per year (CI95%)	6.9 (6.2–7.5)	3.4 (3.2–3.6)	2.7 (2.5–3.0)		
Heart Failure	1.844	676	2.096	1.45 (1.33–1.6) $p < 0.001$	4.85 (4.5–5.3) $p < 0.001$
Incidence/1000 people per year (CI95%)	27.5 (26.3–28.8)	40.1 (37.1–43.2)	8.3 (7.9–8.6)		
Ischemic Heart Disease	1468	367	2558	0.99 (0.88–1.11) $p = 0.908$	2.16 (1.93–2.41) $p < 0.001$
Incidence/1000 people per year (CI95%)	22.0 (20.8–23.1)	21.8 (19.6–24.1)	10.1 (9.7–10.5)		

Table 3. *Cont.*

	High AF Risk (Q4th)	New AF	No AF	OR AF/Q4 (CI95%)	OR AF/NoAF (CI95%)
Major Cardiovascular Events	3791	1230	5352	1.29	3.52
Incidence/1000 people per year (CI95%)	56.3 (54.5–58.1)	73.0 (68.9–77.1)	21.1 (20.5–21.6)	(1.21–1.38) $p < 0.001$	(3.31–3.75) $p < 0.001$
Cognitive Impairment	1553	310	3471	0.78	1.34
Incidence/1000 people per year (CI95%)	23.3 (22.1–24.5)	18.4 (16.4–20.6)	13.7 (13.2–14.1)	(0.69–0.89) $p = 0.002$	(1.19–1.51) $p < 0.001$
Chronic Kidney Disease	2731	676	5158	0.98	1.97
Incidence/1000 people per year (CI95%)	40.8 (39.3–42.3)	40.1 (37.1–43.2)	20.3 (19.8–20.9)	(0.90–1.06) $p = 0.706$	(1.82–2.13) $p < 0.001$
Peripheral Arteriopathy	1.337	345	2.431	1.02	2.13
Incidence/1000 people per year (CI95%)	20.0 (18.9–21.1)	20.5 (18.4–22.7)	9.6 (9.2–10.0)	(0.90–1.15) $p = 0{,}724$	(1.90–2.4) $p < 0{,}001$
Death—allcauses	2822	518	6799	0.72	1.14
Incidence/1000 people per year (CI95%)	42.5 (40.9–44.0)	30.7 (28.1–33.5)	26.8 (26.1–27.4)	(0.65–0.79) $p < 0.001$	(1.04–1.25) $p = 0.027$

4. Discussion

In this large study of people at high AF risk, we present the results related to its incidence, unknown prevalence, and association with a higher risk of heart failure, ischemic heart disease, and stroke; along with the prevalence of cognitive impairment and all-cause mortality. Atrial fibrillation is considered a chronic and progressive disorder [7,10,27,28]. Cardiovascular risk is already higher before AF diagnosis, especially in the case of chronic kidney disease, ischemic heart disease and peripheral arterial disease. Moreover, aging is often associated with comorbidities, polypharmacy, and frailty, which can further increase the risk of AF and stroke, and patients who develop stroke while on antiplatelet therapy have a higher likelihood of developing atrial fibrillation after stroke [29]. The interplay between these factors is not yet fully understood, and further research is needed to better identify the causes. Nonetheless, it is necessary to translate all these measurements into early meaningful actions such as an early diagnosis, structured management, and optimization of cardiovascular risk factors and comorbidities to approaches in improving outcomes of AF patients.

Ninety percent of strokes are related to modifiable risk factors, and despite progress in the diagnosis and management of AF, the modification of these risk factors remains the cornerstone [7]. Several studies have noted that AF, HTA and diabetes mellitus are highly prevalent, frequently undiagnosed, and not optimally treated despite their high risk of stroke [4,6,7,30]. Furthermore, across Europe, primary and secondary prevention strategies do not appear to work well enough to control the major risk factors, and the proportion of people with a history of stroke with unhealthy lifestyle factors is increasing [31]. In addition, the results show an increasing incidence of AF and stroke from 65 years of age and onward, and the largest gap between the prevalence of AF and the estimated incidence occurred between 65 and 74 years of age, with a rate of undiagnosed AF of 2.2% (CI95% 1.3–3.1) [32].

Theuse ofpulse palpationin an ordinary visit has been recommended as the first step in screening to detect AF, but this has a lower sensitivity than other methodologies using devices [33–35], as screening studies have found a prevalence of unknown atrial fibrillation in 10–66% in patients with risk factors. There was no difference between systematic and opportunistic screening [36], and furthermore, screening did not reduce stroke incidence [37,38], although organization of the screening process can be more significant than the technical solutions used for assessing heart rhythm. This suggests that the success of screening programs may be influenced by various factors, such as the traits of the target population [39], the accessibility of resources, technology utilized, the involvement of healthcare professionals, and the level of community engagement and education [18].

Previously unknown AF was diagnosed in 9.4% of the monitored sample of individuals at high risk of AF, and a lower number of screened patients required to diagnose one case of AF was shown (NNS = 15) compared with the NNS of 147 required using the opportunistic detection method [26]. Furthermore, in primary care, the use of health technologiesfor heart rhythm monitoring may improve the detection of AF, especially among people at high risk.

Although the clinical benefits of early anticoagulation are widely recognized and safe, 26.9% did not achieve appropriate control objectives [18,38–43]. This fact increases the impact of the unknown AF (Table S1). The rate of ischemic stroke in patients with AF $\geq$ 75 years old was 2.3 times higher and was associated with greater severity and disability as well as a 20% increase in stroke-related costs [13,14]. For this reason, different international associations [41] have recently proposed extra cost associated with poor control and/or the non-use of oral anticoagulants to the total cost of stroke care. About one-third of the annual treatment cost of a patient with AF can be attributed to anticoagulation management [43,44]. With regard to other prevalent risk factors such as hypertension and diabetes, they are disproportionally affected by the risk of major outcomes, but only 40% of patients who have had a stroke episode are correctly treated. Given the frequent association with diabetes and hypertension in the populations with AF [43,45] and its use among the risk factors to stratify thromboembolic risk in AF patients, the importance of active AF screening among hypertensive and diabetic individuals is highlighted [24,25,46].

Despite the wide variability in the estimated degree of stroke preventability from the perspective of risk factor control [47,48], at least 1082 strokes/year (8.3–14.2% of all the strokes/year in Catalonia) associated with previously undiagnosed AF could be avoided (Table S1). Therefore, 5662 cases of unknown AF may be diagnosed through the device-based monitoring of people at high risk of AF. According to stroke costs [2], the estimated potential savings could be around EUR 260 million/year in a short time horizon, without including the costsaving associated with the prevention of long-term disability and the saving of lives. In addition to the epidemiological estimate associated with demographic aging, the greater cardiovascular comorbidity, frequency, average drug consumption, mortality and severity of stroke confirm the estimated increase in the costs associated with the treatment of stroke episodes associated with AF. The accuracy of screening is crucial, but the health outcomes resulting from screening compared to no screening have not been evaluated. Potential harms of screening includethe misinterpretation of records, which can lead to false reassurance or false alarms as well as to the possible initiation of unnecessary treatment or known risks of appropriate treatment [49].

The prevalence of cognitive disorder is higher in each quartile in relation to that in the general population [50]. Several studies [51–54] have reported echocardiographic criteria and several biomarkers as prognostic factors for the development of dementia and new AF, raising the possibility of a new approach to early detection. However, how this may affect prevalence seems to be unknown. The presence of a progressive increase in the prevalence and severity of cognitive impairment with the risk of AF would support a possible etiopathogenic interrelation between both processes in the general population [55], as well as the need to protocolize its detection [56].

A model of comprehensive care for AF showed a 45% reduction in mortality from any cause [27,28], but its analysis was subsequent to the diagnosis of AF. A pathway referred to as "Atrial fibrillation Better Care" (ABC) has been proposed to streamline a more holistic or integrated care approach to atrial fibrillation (AF) management and has been associated with a reduced risk of major adverse events, including mortality, thromboembolism, and MACE [27,54]. In the territory of study [23], cardiovascular diseases are the main causes of death, and stroke is the main etiology related to years of lives lost and disability among women. The results highlight that the highest incidence of AF, stroke, cognitive impairment, and mortality were concentrated among women in the fourth quartile. This may reflect inequality in health, and women in the fourth quartile should be a priority for AFscreening in primary care. In total, 23% of patients who have

suffered a stroke will suffer a second stroke, with higher rates of disability (36% to 51%) and increased mortality (20% to 34%) [4,6,7,16]. Secondary prevention measures have the potential to reduce the number of stroke survivors who suffer additional strokes by 80%. International best practice guidelines recommend a multifaceted approach to secondary stroke prevention and care [56–58] addressing both technological support for timely medical decisions and the effective provision of self-management tools and recommendations for stroke survivors and their careers.

Currently, biomarkers [26,59], electronic devices [60–63], and machine learning techniques [64,65] are new tools in AF screening and may improve its effectiveness [66]. The application of a clinical risk model (Figure S1) could optimize the selection of candidates for screening even further, and early anticoagulation and early treatments such as cryoablation or drug therapy [67] may modify the chronic progression of atrial fibrillation, lowering stroke risk rates. Around 80% of the participants diagnosed with AF in the United Kingdom population are eligible for early cardiac rhythm control [68], and the implementation of new digitalhealth technologieshas the potential to improve outcomes by facilitating self-management and by enabling earlier detection and intervention for adverse events [69–71]. Finally, the use of artificial intelligence (AI) approaches in stroke risk prediction showed a significant ability to predict the risk of stroke occurrence, but it did not significantly improve discriminative accuracy for new-onset stroke compared with pooled cohort equations [72].

As potential limitations of the study, the authors consider the following: the under-registration of diagnoses; the cross-sectional format used does not allow for the definition of causal relationships between AF, silent stroke and cognitive impairment even in the absence of stroke, and the fact that the results are limited to a generic AF and cognitive decline and do not account for differences in ages, type of AF and cognitive dysfunction. It must be considered that the estimates of mild cognitive impairment in general population studies include all cases, regardless of their likelihood of being detected in the health care system or the underlying disease etiology. The strengths of the study include the considerable number of cases, the long follow-up, and the fact that the study was conducted in the general population [24,25] using a validated statistical model that predicts the probability of suffering from AF based on their covariates prior to the inclusion of patients in order to reduce a possible bias. The target population for screening is yet to be established, particularly with regard to the impact of oral anticoagulation on cognitive outcomes. At present, ideal strategies for screening for AF remain to be defined. Future research will aim to focus on the interrelation of high-riskAF models, silent stroke, cognitive impairment and the cost-effectiveness analysis of a protocol that should include the systematic identification of patients along the AF risk scale, AF burden, type of cognitive disorder, modification of risk factors, use of echocardiographic and imaging criteria, biomarkers, and technological support tools, including electronic devicesand machine learning techniques. This may resolve the uncertainties related to the most effective type of monitoring and the question of whether to start anticoagulant treatment as well as supporting the definition of therapeutic strategies to prevent AF-related cognitive decline.

5. Conclusions

1. The individuals with the higher riskAF (Q4th) already had a similar risk to those with AF for ischemic heart disease, chronic kidney disease, or peripheral arteriopathy before their diagnosis of AF.
2. Unknown AF was diagnosed in 9.47% of patients at high risk of AF (Q4th) and among 21.1% of those with a new stroke. The NNS to detect one new case of AF was 15.
3. Individuals with prevalent AF had higher incidence of cardiovascular disease (MACE), four-fold higher risk of stroke, cognitive impairment (OR 1.34 (CI95% 1.1–1.5), and all-cause mortality (OR 1.14 (CI95% 1.0–1.2).
4. Stroke incidence increased progressively with AF risk levels. The 57.1% of simultaneous diagnoses of stroke and AF occurred in the Q4th risk level. The cardiovascular

profile of individuals with AF and stroke was found to be different from those with atrial fibrillation alone.

5. The 41.7% of cases with cognitive impairment were concentrated in the Q4th risk level, were older (84.84 ± 6.70 vs. 81.22 ± 7.91, $p < 0.001$), and already had a higher incidence of cognitive impairment and mortality before diagnosing AF and displayed higher NIHSS (7.25 ± 8.62 vs. 4.55 ± 5.74, $p = 0.002$) scores than those without AF.

6. Patents

Patent AFRICAT: Diagnosis markers for atrial fibrillation (EP19382321.8).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/biomedicines11041116/s1, Table S1: Estimated avoidable strokes by early diagnosis of atrial fibrillation (census Catalonia2020 [21]).

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Institutional Review Board Statement: Ethical review and approval were waived for this study prior to the inclusion of medical data since formal consent is not required for this type of study. The protocol received ethics evaluation and approval from the Ethical Committee of Jordi Gol University Institute of Primary Care Research with the registration number P15/047. Date of approval: 29 April 2015. The AFRICAT study was approved by the Ethics Committee of Research Institute IDIAP Jordi Gol (P15/047/2015) and by the Hospital Universitari Vall d'Hebron Clinical Research Ethics Committee (PR(AG)133-2015). The study was conducted in compliance with the Declaration of Helsinki. All participants received written information and subsequently signed their informed consent before inclusion. Fata collection was supervised and conducted in accordance with the most relevant standards regarding data handling, concerning the experimental context with patients, ethics, and data protection and privacy, following Directive 95/46/EC (protection of individuals with regard to the processing of personal data and on the free movement of such data). All of the data were included in an ad hoc repository, which was delivered to the main researcher.

Informed Consent Statement: The study protocol has been published elsewhere [26] (AFRICAT: Atrial Fibrillation Research in CATalonia, NCT03188484). Informed consent was obtained from all subjects involved in the study. 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).

Data Availability Statement: Datasets were deposited in a publicly available database (https://github.com/Hipocrates57/Atrial_fibrillation/blob/main/Base%2065_95_quartils_DATASET.sav, accessed on 14 February 2023) or (https://github.com/Hipocrates57/Atrial_fibrillation.git, accessed on 14 February 2023).

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Appendix A

Figure A1. The application of a clinical risk model.

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6.2. Segundo artículo

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Heart Failure and Major Adverse Cardiovascular Events in Atrial Fibrillation Patients: A Retrospective Primary Care Cohort Study

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Abstract: Background: Atrial fibrillation (AF) is a common cardiac arrhythmia that is associated with an increased risk of major adverse cardiovascular events (MACE). The main goal was to analyze the links and associations between AF and MACE. Methods: A multicenter, observational, retrospective, community-based study of a cohort (n = 40,297) of the general population aged 65–95 years between 1 January 2015 and 31 December 2021 without a previous diagnosis of AF or MACE in the Primary Care setting. Results: 2574 people (6.39%) developed a first AF event, resulting in an overall incidence of 8.9/1000 people-years [CI95% 8.6–9.2]. The incidence of MACE among those with AF was 75.1/1000 people-years [CI95% 70.8–79.5], whereas among those without AF, it was 20.6/1000 people-years [CI 95% 20.2–21.1], resulting in a rate ratio of 3.65 [CI 95% 3.43–3.88, $p < 0.001$]. Besides, the incidence of HF with AF was 40.1 people-years [CI 95% 37.1–43.2], while in the group without AF, it was 8.3 people-years [CI 95% 7.9–8.6, $p < 0.001$], with a rate ratio of 4.85 [CI 95% 4.45–55.3, $p < 0.001$]. Before an AF diagnosis, there is already a higher risk of chronic kidney disease, ischemic cardiopathy, and peripheral artery disease. A higher risk of poor nutritional status was detected among those with MACE (49.7% vs. 26.6%, $p < 0.001$). Conclusions: AF diagnosis increases the incidence of heart failure fourfold. Additional information is required to establish the connection between AF, major adverse cardiovascular events, and nutritional status.

Keywords: atrial fibrillation; risk-atrial fibrillation; heart failure; outcomes; major adverse cardiovascular events (MACE); major outcomes; vascular events; primary health care

1. Introduction

Major adverse cardiovascular events (MACE) [1] are known as the composite of total death, myocardial infarction, coronary revascularization, stroke, and heart failure (HF). These events contribute to significant all-cause morbidity and mortality, decreased

quality of life, and increased medical costs [2,3]. Heart failure (HF) is a growing global problem that is expected to increase in the coming years due to population aging, an increase in cardiovascular risk factors, and improvements in the management of acute cardiovascular events. On the one hand, it is the leading cause of hospitalization in patients over 65 years old and the third leading cause of cardiovascular mortality. On the other hand, HF can be caused by a variety of factors, including AF, which is a leading cause of morbidity and mortality, with an estimated five million incident cases globally. It is estimated that the prevalence of AF will increase from 1.9% (2008) to 3.5% (2050), and the number of AF-related ischemic strokes in people >80 years will triple (2010–2060) [4] in both developing and developed countries. AF occurs in more than half of individuals with HF, and HF occurs in more than one-third of individuals with AF [5]. The potential association between HF and AF makes them one of the chronic conditions with the greatest health and economic impact [6].

Other factors have been associated with an increased risk of MACE in patients with AF [1–3,7,8] as well as hypercholesterolemia [9], malnutrition [10,11], or an elevated CHA2DS2-VASc score [12,13], a commonly increased score in AF patients, but both HF and AF, along with factors associated with MACE, are frequently underdiagnosed. In the last three decades, new therapeutic targets have allowed for the modification of the natural history of heart failure, but mortality rates and recurrent hospitalizations remain very high in patients with HF, suggesting that additional measures are needed. Identifying high-risk populations for AF and detecting it early can help reduce the burden of MACE associated with heart failure and reduce their risk of serious complications. The European Action Plan (2018–2030) [14] considers the availability of screening and treatment programs for stroke risk factors in Europe to be important.

Traditional practice advocates the use of clinical risk score criteria to distinguish at-risk patients, but these risk scores have modest discriminatory power. New insights have been gained into the usefulness of biomarkers and imaging techniques, and data are emerging on the importance of subclinical device detection using portable devices to recognize cardiac arrhythmias in primary care practice. The main goal of this study was to compare the characteristics of patients developing their first episode of diagnosed AF during the follow-up period and analyze links and associations between AF and MACE.

2. Materials and Methods

2.1. Study Design

The study analyzes links and associations between AF and MACE among 40,297 people from the general population aged between 65 and 95 years old residing in the region of Ebre's lands, Catalonia, Spain. It was an observational, retrospective, and community-based study conducted between 1 January 2015, and 31 December 2021.

2.2. Study Scope

The study was carried out in Terres de l'Ebre (Health Region Terres de l'Ebre, Appendix A), located in the southern part of Catalonia (Spain).

The territory is made up of 4 counties with 11 primary care teams (EAPs), managed by the Catalan Health Institute (ICS), Department of Health (CatSalut). Specialized care is received at the reference hospital located in Tortosa, "Hospital Verge de la Cinta", which is publicly managed by the ICS. The EAPs are organized as independent clinical functional teams. The majority of the census population in the territory (98.2%) has an active Shared Health Record of Catalonia (HC3) available digitally for continuous care monitoring from any center.

2.3. Data Collection and Information Sources

Data for all participants were managed by ICS through the 11 EAPs. The Department of Information and Communication Technologies, through the registration of the minimum basic dataset at hospital discharge (CMBD-HA), retroactively provided an

anonymized computerized database with the clinical history using the specific International Classification of Diseases (10th version; ICD-10) to the principal investigator in a fully de-identified format.

The data sets utilized for this project were as follows:

1. The Institute of Statistics of Catalonia collected data on aging index, inhabitant density, and gross disposable household income per inhabitant for each region in Catalonia [14–17].
2. The Health Plan of the Terres de l'Ebre Healthcare Region 2021–2025 [14] outlines healthcare goals, priorities, and actions for the region.
3. The HC3 Patient Episode Dataset contains demographic and clinical information on inpatient and outpatient care in Catalan hospitals.
4. The 11 EAPs managed by the Catalonian Health Institute share a clinical information database for general practice and hospital interactions, including clinical data, diagnoses, medication, referrals, and patient status as of 31 December 2021.

2.4. Ethical Aspects and Data Protection

The data were analyzed and supervised according to the General Data Protection Regulation of Spain/Europe from 1 February 2017. The study was conducted in accordance with the most relevant standards regarding data handling, concerning the experimental context with patients, ethics, and data protection and privacy, following Directive 95/46/EC (protection of individuals with regard to the processing of personal data and on the free movement of such data). All of the data were included in an ad hoc repository, which was delivered to the main researcher. The study protocol received ethics evaluation and approval from the Ethical Committee of Jordi Gol University Institute of Primary Care Research with registration number 22/243-P.

2.5. Study Population

Initially, the study included individuals over 65 years old (n = 55,459) who did not have a history of AF or major adverse cardiovascular events in their medical records. The following criteria were defined:

1. Outcomes: The new diagnosis of AF was the primary outcome. Secondary outcomes were major adverse cardiovascular events, cognitive impairment, and all-cause mortality.
2. Inclusion criteria: Subjects 65–95 years of age who met the inclusion criteria: high-risk AF (according to the risk model and belonging to Q4) [18,19], active medical history in any of the health centers in the territory with information accessible through the shared history (HC3), without prior AF, residence in the territory, and assignment to any of the Primary Care Teams (EAP) of the same.
3. Exclusion criteria: Persons under 65 or over 95 years of age; population who are not from Terres de l'Ebre; patients without a previous diagnosis of AF; treatment with anticoagulants; impairment of cognitive status; Barthel score <55 points; pacemaker or defibrillator wearer. The non-availability or loss of accessibility to the information necessary for the study was considered a reason for exclusion.

After excluding patients because they did not fit the inclusion criteria or due to a lack of the appropriate variables to categorize the risk of AF, 40,297 people (Figure 1) joined the trial. All participants were monitored from the date of inclusion (1 January 2015) until 31 December 2021 loss-to-follow-up, or date of death, whichever happened first.

2.6. Variables

The data on AF and comorbidities for cardiovascular risk trajectories lasted until loss-to-follow-up, date of death, or 31 December 2021, whichever happened first. AF was diagnosed according to the guidelines of the European Society of Cardiology [19]. The diagnosis of AF was verified by two investigating physicians blinded to the diagnosis. When a consensus was not reached, a cardiologist was consulted. Patients were classified

according to the presence of AF. In the case of AF diagnosed during the follow-up period, data were collected at the time of AF diagnosis or until the end of the follow-up. MACE after AF diagnosis until the end of follow-up were analyzed. MACE prior to AF diagnosis were not analyzed. Data for patients who did not present with AF during follow-up were obtained in the last year of follow-up.

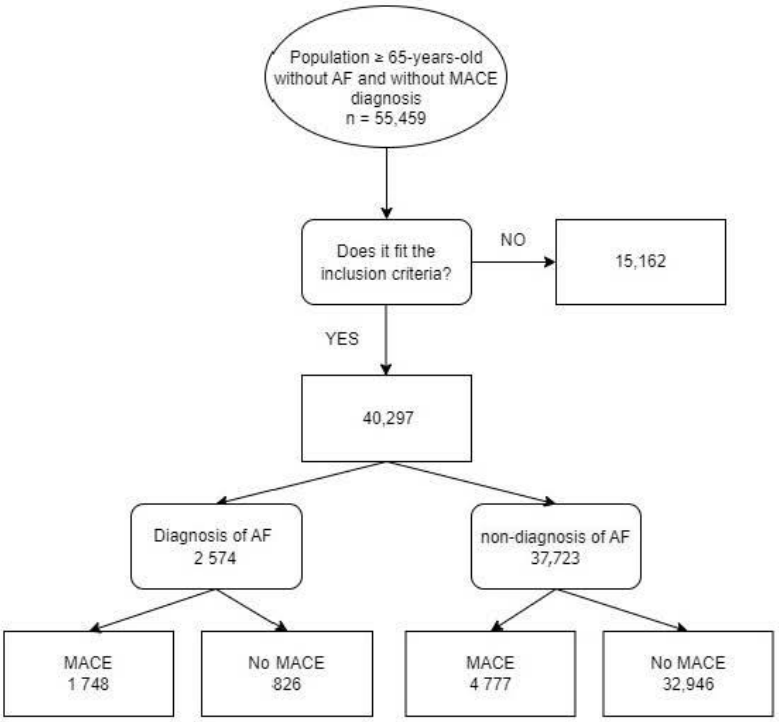

Figure 1. Flowchart of the selection process according to the inclusion and exclusion criteria. MACE: major adverse cardiovascular events; AF: atrial fibrillation.

1. Sociodemographic: age, sex, primary care team, and region.
2. Cardiovascular risk factors and diagnostics using specific ICD–10 code prefixes for hypertension (I10–I15), hypercholesterolemia (E78), smoking (F17.203, Z72), body mass index (BMI), diabetes mellitus (E10–E14), sleep apnea-hypopnea syndrome (G47.3), heart failure (I50-51), ischemic heart disease (myocardial infarction, percutaneous coronary intervention, stable or unstable angina or coronary artery bypass grafting) (I20–I25), chronic kidney disease (CKD) (N18), and estimated glomerular filtration rate (eGFR mL/min/1.73 m^2), cerebrovascular illness (transient ischemic attack or ischemic stroke) (I63, G45), COPD, asthma, chronic bronchitis (J40–J45), cancer (C00–C96), and COVID-19 (U07.1). Coronary artery disease was defined as either a history of myocardial infarction, coronary bypass graft surgery, and/or percutaneous transluminal coronary angioplasty. Data on COVID-19 was collected from 15 March 2020 (first wave in Spain) to 31 December 2021.
3. Clinical scores: risk-index AF [18,19], stroke risk by CHA_2DS_2-VASc score, Barthel Index for Activities of Daily Living (ADL), controlling nutritional status (CONUT) score, and Adjusted Morbidity Groups (GMA) score as recommended by current guidelines [20]. The model to categorize the risk of suffering AF at five years among community members ≥65 years old was previously published [18,19]. It includes the following variables: sex, age, average heart rate, average weight, and CHA_2DS_2VASc

score. The mathematical formula of the model was applied to the target population without a diagnosis of AF, and the quartiles of the distribution from lowest to highest risk were defined (Q1–Q4), with Q4 (high risk) being of interest, though the AF incidence density/1000 people-years (ID) was calculated for each group, as was the incidence of MACEs and the registered prevalence of cognitive decline.

4. Pharmacological treatment: antiplatelet agents, new anticoagulants, and antivitamin K.
5. Final status: dead/alive.

2.7. Statistical Analysis

The characteristics of the population were defined through a descriptive statistical analysis. Baseline data are presented as numbers and percentages, mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Qualitative variables were analyzed with the chi-square distribution according to bivariate analysis for normal distributions, while quantitative variables were examined with Student's t-distribution for independent samples. The calculation of the incidence rate took into account the total observation time for each person in the population, reflecting the duration of both disease risk and monitoring.

To assess the increased risk of vascular outcomes associated with AF, hazard ratios are calculated using Cox proportional hazards regression analysis. The hazard ratios were adjusted by including the significant confounding variables in the regression model. Any variables that were found to have a significant p-value ($\leq$0.05) and were not included in the scores used (CONUT and CHA_2DS_2-VASc) were considered potential confounding factors. Absolute risk increases were reported in terms of events per 1000 person-years of follow-up. Cox regression was utilized to compare MACE incidence between the AF and non-AF groups, while Kaplan–Meier curves were used to evaluate mortality. IBM SPSS Statistics version 21.0 was utilized for statistical analysis and data management.

3. Results

3.1. Baseline Characteristics

Patient baseline characteristics are shown in Table 1. A total of 40,297 people without a personal history of AF were included. The average follow-up time was 80.65 $\pm$ 9.5 months. The study population had an average age of 77.65 $\pm$ 8.46 years, with 46.48% being women who were significantly older than men (81.22 $\pm$ 7.91 vs. 77.65 $\pm$ 8.46 years, $p < 0.001$).

Table 1. Baseline characteristics of cases with AF vs. without AF.

Variables	No AF	(%)	AF	(%)	*p*	ALL
All (*n* %)	37,723	93.6%	2,574	6.4%	-	40,297
Women	17,535	46.5%	1343	3.3%	<0.001	18,878
Age average	77.6 ± 8.7		81.2 ± 7.9		<0.001	77.9 ± 8.5
CHA_2DS_2-VASc	3.2 ± 1.1		3.8 ± 1.2		<0.001	3.2 ± 1.2
Hypertension arterial	23,610	62.6%	1945	75.6%	<0.001	25,555
Diabetes mellitus	9689	25.7%	769	30%	<0.001	10,458
Dyslipidemia	17,913	47.5%	1216	47.3%	0.822	19,129
BMI [1] (kg/m^2)	28.7 ± 5.1		29.5 ± 5.4		<0.001	28.7 ± 5.2
Ischemic cardiomyopathy	2558	6.8%	357	13.9%	<0.001	2915
Heart failure	2096	5.6%	676	26..%	<0.001	2772
Stroke/TIA	698	1.9%	187	7.3%	<0.001	885
Vascular peripheral disease	2431	6.4%	345	13.4%	<0.001	2776
Dementia/cognitive impairment	3471	9.2%	310	12.1%	<0.001	3781
Liver disease	72	0.2%	10	0.4%	0.04	82
Chronic kidney disease	5158	13.7%	676	26.3%	<0.001	5834
Glomerular filtration rate ($mL/min/1.73\ m^2$)	72.9 ± 18.6		63.5 ± 20.4		<0.001	72.2 ± 19
Thyroid disease	2613	6.9%	215	8.3%	0.047	2828
OSAHS [2]	1022	2.7%	126	4.9%	<0.001	1148
COPD [3]/asthma/bronchitis	4591	12.2%	447	17.4%	<0.001	5038
CONUT	0.8 ± 1.3		1.3 ± 1.5		<0.001	0.8 ± 1.3
Serum albumin (g/dL)	5.5 ± 10.5		5 ± 10.7		0.029	5.5 ± 10.4

Table 1. *Cont.*

Variables	No AF	(%)	AF	(%)	*p*	ALL
Lymphocytes ($\times 10^3/\mu L$)	2.4 ± 17.5		2.1 ± 1.3		0.312	2.4 ± 16.8
Statins	11,806	31.3%	945	36.7%	<0.001	12,751
Antiaggregants	6110	16.2%	141	5.5%	<0.001	6251
Anticoagulation	987	2.6%	1994	77.5%	<0.001	2981
VKA [4]	754	2%	944	36.7%	<0.001	1698
NOAC [5]	235	0.6%	1053	40.9%	<0.001	1288
CHARLSON	1.3 ± 1.3		1.8 ± 1.4		<0.001	1.3 ± 1.3
Average follow-up time	80.8 ± 9.3		78.6 ± 12.1		<0.001	80.7 ± 9.5
COVID-19	2931	7.8%	260	10.1%	<0.001	3191

[1] BMI: body mass index; [2] OSAHS: obstructive sleep apnea-hypopnea syndrome; [3] COPD: chronic obstructive pulmonary disease; [4] VKA: vitamin K antagonist; [5] NOAC: non-vitamin K antagonist oral anticoagulant.

3.2. AF Incidence

A total of 2574 people (6.39%) developed a first AF event after a median follow-up time of 78.6 ± 12.1 months. The overall incidence was 8.9/1000 people-years [CI 95% 8.6–9.2], significantly higher among men [9.8/1000 people-years, CI95% 9.3–10.3 vs. 8.1/1000 people-years, CI95% 7.7–8.5; $p < 0.001$]. There were significant differences between the AF patterns for all risk factors of interest at baseline (Table 1). The average age of 81.2 ± 7.9 was significantly higher than the average age of the overall study population.

Participants with AF had a significantly higher prevalence of major adverse cardiovascular events (MACE) compared to those without AF (40.7% vs. 12.7%, $p < 0.001$). Additionally, they had higher average scores ($p < 0.001$) on the CHA_2DS_2-VASc and CONUT scales, as well as higher overall mortality rates (18.02% vs. 20.12%, $p < 0.001$).

3.3. MACE Incidence among AF vs. No-AF Patients

During 15,779 patient-years of follow-up, we observed a total of 2574 AF new diagnoses and 1748 episodes of MACE (Table 2). The overall incidence rate of MACE in the group with AF was 73.0/1000 people-years [CI95% 68.9–77.1], while in the group without AF, it was 21.1/1000 people-years [IC95% 20.5–21.6, $p < 0.001$], with a rate ratio of 3.52 [CI95% 3.31–3.75, $p < 0.001$]. The overall incidence rate of HF in the group with AF was 40.1 people-years [CI95% 37.1–43.2], while in the group without AF, it was 8.3 people-years [IC95% 7.9–8.6, $p < 0.001$], with a rate ratio of 4.85 [CI95% 4.45–55.3, $p < 0.001$] (Figure 2).

Table 2. Association between AF diagnosis and MACE according to risk quartile.

	Q4	No-AF	New AF	HR AF/Q4	HR AF/No-AF
N	10,239	37,723	2574		
Age (average ± SD)	84.8 ± 6.7	77.65 ± 8.4	81.2 ± 7.9		
AF (n) Incidence/1000 people-years [CI95%]	1148 17 [16.1–18.1]	-	2574 8.9 [8.6–9.2]		
Chronic kidney disease (n %) Incidence/1000 people-years [CI95%]	2748 (26.83%) 40.8 [39.3–42.3]	5158 (13.67%) 20.3 [19.8–20.9]	676 (26.26%) 40.1 [37.1–43.2]	0.98 [0.90–1.06] $p = 0.706$	1.97 [1.82–2.13] $p < 0.001$
Cognitive impairment (n %) Incidence/1000 people-years [CI95%]	1569 (15.32%) 23.3 [22.1–24.5]	3471 (9.2%) 13.7 [13.2–14.1]	310 (12.04%) 18.4 [16.4–20.6]	0.78 [0.69–0.89] $p = 0.002$	1.34 [1.2–1.51] $p < 0.001$
Heart failure (n %) Incidence/1000 people-years [CI95%]	1853 (18.1%) 27.5 [26.3–28.8]	2096 (5.56%) 8.3 [7.9–8.6]	676 (26.26%) 40.1 [37.1–43.2]	1.45 [1.33–1.6] $p < 0.0001$	4.85 [4.5–5.3] $p < 0.0001$

Table 2. *Cont.*

	Q4	No-AF	New AF	HR AF/Q4	HR AF/No-AF
Ischemic heart disease (n %) Incidence/1000 people-years [CI95%]	1479 (14.44%) 22.0 [20.8–23.1]	2558 (6.78%) 10.1 [9.7–10.5]	367 (14.26%) 21.8 [19.6–24.1]	0.99 [0.88–1.11] $p = 0.908$	2.16 [1.93–2.41] $p < 0.001$
Stroke/transient ischemic attack (n %) Incidence/1000 people-years [CI95%]	459 (4.48%) 6.8 [6.2–7.5]	698 (1.85%) 2.7 [2.5–3.0]	187 (7.26%) 11.1 [9.6–12.8]	1.62 [1.37–1.92] $p < 0.001$	4.03 [3.43–4.74] $p < 0.001$
Peripheral arteriopathy (n %) Incidence/1000 people-years [CI95%]	1347 (13.15%) 20.0 [18.9–21.1]	2431 (6.44%) 9.6 [9.2–10.0]	345 (13.4%) 20.5 [18.4–22.7]	1.02 [0.90–1.15] $p = 0.724$	2.13 [1.90–2.4] $p < 0.001$
Death (n %) Incidence/1000 people-years [CI95%]	2861 (27.94%) 42.5 [40.9–44.0]	6799 (18.02%) 26.8 [26.1–27.4]	518 (20.12%) 30.7 [28.1–33.5]	0.72 [0.65–0.79] $p < 0.001$	1.14 [1.04–1.25] $p = 0.027$
Total MACE (n%) Incidence/1000 people-years [CI95%]	3791 (37.02%) 56.3 [54.5–58.1]	5352 (14.11%) 21.1 [20.5–21.6]	1748 (67.9%) 73.0 [68.9–77.1]	1.29 [1.21–1.38] $p < 0.001$	3.52 [3.31–3.75] $p < 0.001$

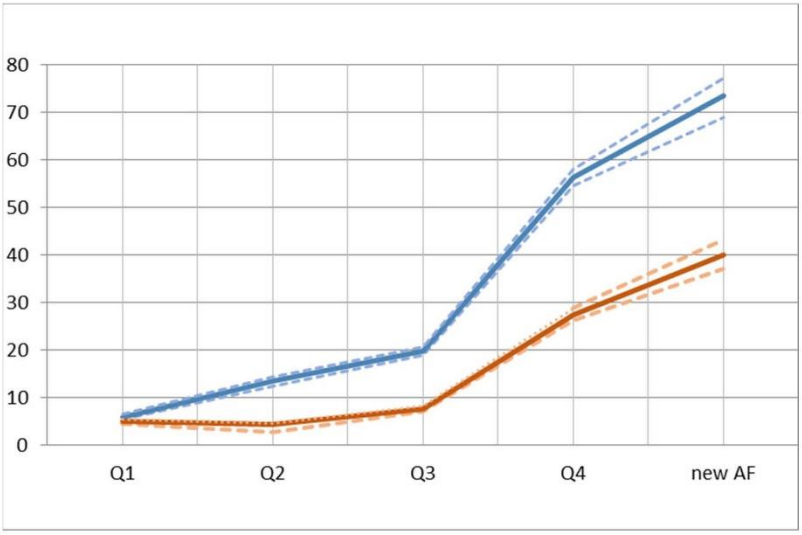

Figure 2. Major adverse cardiovascular events (MACE) and heart failure (HF) incidence density rates for every 1000 people-years (IC95%) by risk quartiles vs. new atrial fibrillation. The thick line indicates the CI and the dashed lines show the confidence intervals.

In this comprehensive review of the association between AF and the risk of MACE, various results were observed (Table 2), including a 3.65-fold increased risk of a major cardiovascular event, a 2.38-fold increased risk of ischemic heart disease, a 4.97-fold increased risk of congestive heart failure, a 5.04-fold increased risk of ischemic stroke, and a 2.57-fold increased risk of all-cause mortality.

Eventually, among patients diagnosed with AF, 718 (27.9%) were not treated with anticoagulants (NOAC or vitamin K antagonist). A total of 392 (25.7%) in the AF+MACE- group and 326 (31.1%) in the AF+MACE+ group were on anticoagulant treatment. On the

other hand, out of the 1220 (2.3%) patients without a diagnosis of AF, 899 (1.7%) in the AF-MACE- group and 321 (0.6%) in the AF-MACE+ group were treated with anticoagulants.

As the risk of AF increased from Q1 to Q4, there was a corresponding increase in the incidence of MACE. In fact, being in Q4 doubled the risk of most vascular events included in the study (Table 2). The results showed a significantly increased risk ($p < 0.001$) of heart failure, stroke, and MACE among individuals newly diagnosed with AF. However, there were no significant differences in the incidence of peripheral artery disease ($p = 0.724$), ischemic cardiomyopathy ($p = 0.908$), or chronic kidney disease ($p = 0.706$). Furthermore, AF was found to be associated with a 1.34-fold increased risk of cognitive impairment ($p < 0.001$), and the overall mortality rate was higher among individuals in the fourth quartile.

3.4. Nutritional Status Assessed by CONUT Score

Using the CONUT scale (Table 3), 49.7% of patients with AF were detected to have malnutrition ($p < 0.001$). The presence of MACE doubles the risk of malnutrition ($p < 0.001$).

Table 3. Nutritional status and prevalent AF with MACE.

CONUT Risk (n)	[AF + MACE+] 1748	[AF+ MACE−] 826
Normal (1–2)	879 (50.3%)	606 (73.4%)
Light (2–4)	671 (38.4%)	187 (22.7%)
Moderate (5–8)	137 (7.8%)	31 (3.7%)
Severe (9–12)	61 (3.5%)	2 (0.2%)

3.5. Regression Cox Model

After adjusting for age, genre, BMI, cardiovascular risk factors, antiaggregants, and anticoagulants, only the CHA_2DS_2-VASc, Charlson score, and CONUT scores were retained as independent prognostic factors (Table 4) for major adverse cardiovascular events among individuals with a new diagnosis of AF.

Table 4. Prognostic independent factors of MACE incidence among AF people.

Variables	Hazard Ratio	CI95%	*p*
CHA_2DS_2-VASc score	2.50	2.41–2.57	<0.001
CONUT score	1.06	1.04–1.08	<0.001
Charlson score	1.24	1.21–1.27	<0.001

4. Discussion

In this large study, the incidence of AF was associated with a higher incidence of MACE (heart failure, ischemic heart disease, stroke, and mortality), CKD, and cognitive impairment. The relative and absolute risk increase associated with many of these events is higher than that of those subjects without AF. Several studies have reported similar findings regarding the increased risk of most major cardiovascular events in individuals diagnosed with AF [1,5,6]. Specifically, AF has been associated with a higher prevalence of heart failure, particularly in older adults and those with pre-existing cardiovascular disease. Moreover, the study findings highlight that the risk of cardiovascular events is already elevated prior to the diagnosis of AF, particularly in patients with CKD, ischemic cardiopathy, and peripheral artery disease who are classified as high-risk for developing AF.

AF is not only frequently undiagnosed but also commonly left untreated and unmanaged [21–24]. Moreover, AF and heart failure often coexist and can worsen each other's impact. Anticoagulation therapy has been shown to improve outcomes in patients with HF and AF, particularly by reducing the risk of stroke and other thromboembolic events, which can cause further damage to the heart and worsen HF [25,26]. Additionally, some

studies have suggested that anticoagulation therapy may have direct anti-inflammatory effects on the heart, which can help improve heart function and reduce HF symptoms [27]. The increase in risk for most major cardiovascular events associated with a diagnosis of AF is higher than those described in other studies [6,8]. In general, the risk of MACE in patients with AF is estimated to be approximately double that of those without AF, and its magnitude varies according to the studied population, individual risk factors, and the control of risk factors, especially the indication of anticoagulant treatment and, in the case of using a vitamin K antagonist, achieving the goals within the therapeutic range. These indicators were shown to be deficient in previous research [28].

Moreover, the undiagnosed and poor control of cardiovascular risk factors associated with AF [1] is known from common evidence, and its incidence may be higher than previously thought. It is uncertain how exactly AF contributes to an increased risk of various cardiovascular diseases, but it is possible that AF may serve as an indicator of common underlying risk factors for cardiovascular disease. These risk factors may include hypertension, which is present in as many as 90% of AF patients, as well as obesity, diabetes, obstructive sleep apnea [29], and the CHA_2DS_2-VASc score. However, it is important to note that AF is a treatable condition, and effective management of AF can help reduce the risk of heart failure and mortality [8]. Close monitoring and management of underlying cardiovascular risk factors can also be helpful in reducing the risk of complications associated with AF.

The CHA_2DS_2-VASc score is a widely used tool for assessing the risk of stroke in patients with AF. It takes into account several risk factors that are associated with both AF and heart failure, such as age, hypertension, diabetes, and previous cardiovascular disease. A higher CHA_2DS_2-VASc score is associated with an increased risk of developing heart failure and an increased risk of MACCEs [29] in patients with AF [30]. Therefore, the CHA_2DS_2-VASc score can be a useful tool for identifying patients with AF who are at high risk of developing heart failure and who may benefit from more aggressive management of their cardiovascular risk factors. It may also have beneficial effects on heart failure outcomes.

Women are often older at the time of diagnosis and have a higher prevalence of hypertension and valvular heart disease [31], and AF is a stronger risk factor for cardiovascular disease and death in women compared with men [32]. Although decisive evidence is pending, it is suggested that the structural development of AF differs, with women tending to have more atrial fibrosis and different patterns of electrical function. This may imply differences in the underlying pathophysiology between men and women. In this study, women had a higher prevalence of AF and a higher age average at diagnosis than men, according to current evidence [21,32]. Perhaps the subgroup of women in Q4 should be considered for both AF screening and close monitoring of modifiable risk factors, given their higher incidence of comorbidities, stroke, and severe disability [14,19,32]. Consequently, clinicians should be aware of the importance of detecting and providing appropriate therapies for MACE prophylaxis, as well as the downstream economic burden on an increasingly aging population with an increased incidence of AF [6,21].

Several nutritional alterations have been described and underdiagnosed in AF patients [33], but little is known about the nutritional status of AF patients and the relationship between malnutrition and mid- and long-term mortality. The study highlighted that patients with AF and MACE had a higher prevalence of some degree of malnutrition, which is consistent with the results of previous studies [10,34–36]. This fact may reflect the social needs and social determinants of health (SDOH) leading to poorer health outcomes [37,38]. Therefore, healthcare providers should address social needs and SDOH in their patient care to reduce prevalent healthcare disparities. Further information is needed to determine the relationship between AF, MACE, and nutritional status. Likewise, the detection of nutritional alterations in individuals with cardiovascular risk should be evaluated as a target subgroup for AF screening and MACE.

The statement highlights an important finding from a study that suggests that certain conditions such as chronic kidney disease, ischemic cardiopathy, and peripheral artery disease may increase the risk of developing AF and heart failure. The study further suggests that this risk may be present even before the diagnosis of AF is made, especially among individuals in the fourth quartile. Subclinical AF has been associated with an increased risk of stroke [39], but there is limited understanding of their temporal relationship. Individuals with chronic kidney disease are at a higher risk of developing AF and heart failure. This may be due to the fact that chronic kidney disease can lead to changes in the structure and function of the heart, which can increase the likelihood of developing AF and HF [38]. Similarly, ischemic cardiopathy and peripheral artery disease can also lead to changes in the heart that increase the risk of developing AF and MACE [29,40]. These conditions can lead to changes in the structure and function of the heart, which could also increase the likelihood of developing AF [41,42] and emphasize the importance of managing these risk factors in patients at risk of AF. However, it should be noted that individuals with prevalent AF are more likely to develop these conditions. Therefore, more aggressive monitoring and treatment of this high-risk population may improve outcomes.

Additionally, it should be pointed out that there was a significant increase in the incidence of cognitive impairment and mortality from the 4th quartile group (Q4) to the group with newly diagnosed AF. A high incidence of silent cerebral infarction detected by MRI and AF-induced cognitive dysfunction related to silent cerebral infarction has been reported [43]. It has been suggested that AF ablation may also reduce the risk of MACE in selected patients [44], such as those with heart failure and left ventricular dysfunction. However, further studies are needed to confirm these findings and determine which patients may benefit most from AF ablation in terms of reducing the risk of MACE.

The prevalence of sleep apnea recorded in the study was 4.9%, which is higher than the published prevalence [45,46]. It would be interesting to examine the characteristics of AF patients with a high probability of sleep apnea, such as males, smokers, and individuals with an increased BMI [47]. Additionally, the interaction between clinical risk factors remains uncertain, and several combinations of risk factors may carry a higher risk when examined together compared to other combinations. Additionally, the role of AF burden in patients with subclinical paroxysmal AF is still under debate [48].

The Charlson comorbidity index is a tool used to measure the severity and impact of multiple comorbid conditions on a patient's health status. Both AF and heart failure are common comorbidities that may increase a patient's Charlson score, which was associated with a higher risk of developing AF independent of other risk factors [49], a greater risk of mortality in patients with HF [50], and an increased risk of hospitalization and mortality [51]. Emphasizing the impact of the association between AF and cardiovascular comorbidities across a wide spectrum raises an important point about the "chicken and egg" relationship between AF and cardiovascular disease. Its temporal relationships have not yet been fully explored, though it has been described as having a lower risk for ischemic stroke in prevalent HF than in incident HF and higher mortality and a higher risk of re-hospitalization for HF among patients in whom HF preceded AF [52]. This approach offers several advantages, including a more comprehensive understanding of the disease, facilitation of holistic patient care, improvement in risk assessment, enablement of targeted interventions, and promotion of further advancements in research and innovation.

Given that the COVID-19 pandemic occurred during the study period and contracting the disease was associated [53,54] with an increased risk of thromboembolism and a higher risk of mortality, it was included as a baseline variable. Several studies [55–58] have suggested that there may be a relationship between COVID-19 and an increased risk of developing MACE, HF, and AF, particularly in patients with pre-existing cardiovascular disease. Given that the exact mechanisms by which COVID-19 may increase the risk of MACE, heart failure, and AF are not fully understood, more evidence from ongoing clinical studies is necessary to identify possible criteria for developing MACE and the impact of thromboprophylaxis, as well as outcome factors on MACEs.

One of the key strengths of this study is the large sample size because several populations require special assessment when considering individualized risk stratification, and these populations are poorly represented in the original derivation cohorts for clinical risk scores; as such, the applicability of such scores is limited. On the other hand, some potential limitations need to be taken into account in the interpretation of our results. Thromboembolic and AF risk scores are highly effective in determining the risk of the population, but they are often misleading when applied to individuals. This is especially true for low-risk patients. Due to the observational study design, we are not able to prove causality, and residual confounding may persist despite comprehensive multivariable adjustment.

The project will continue by utilizing a matching learning methodology (artificial intelligence) to discover patterns and correlations between various variables and develop predictive models. It may be the case that some variables with the potential to impact outcomes have not been recorded, and there is a chance that little details may not be accurately recorded. The authors used registered cohorts in all of their analyses, which is an approach that helps to overcome comparability limitations that arise due to the heterogeneity of the available data. However, it should be noted that the use of the registration system and territorial organization as the basis for this approach can be considered a common limitation. The study design does not allow for an answer to this limitation.

5. Conclusions

Patients with atrial fibrillation have a significantly higher incidence of heart failure, with a four-fold increase in risk. Additionally, both the CHA_2DS_2-VASc, Charlson, and CONUT scores have been identified as independent prognostic factors for MACE-related AF. The risk of developing heart failure is already elevated prior to AF diagnosis, especially in patients with chronic kidney disease, ischemic cardiopathy, and peripheral artery disease in the fourth quartile. To identify modifiable predictors of MACE, it may be useful to explore various tools for detecting AF and implement preventive interventions in primary care.

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Informed Consent Statement: Patient consent was waived prior to the inclusion of medical data since formal consent is not required for this type of study.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author (S.R.-V. and J.L.C.-E.) upon reasonable request.

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Appendix A

Figure A1. Spanish map and the territory of Terres de l'Ebre by regions where the study was made.

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6.3. Tercer artículo

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Machine Learning Approaches to Predict Major Adverse Cardiovascular Events in Atrial Fibrillation

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Abstract: The increasing prevalence of atrial fibrillation (AF) and its association with Major Adverse Cardiovascular Events (MACE) presents challenges in early identification and treatment. Although existing risk factors, biomarkers, genetic variants, and imaging parameters predict MACE, emerging factors may be more decisive. Artificial intelligence and machine learning techniques (ML) offer a promising avenue for more effective AF evolution prediction. Five ML models were developed to obtain predictors of MACE in AF patients. Two-thirds of the data were used for training, employing diverse approaches and optimizing to minimize prediction errors, while the remaining third was reserved for testing and validation. AdaBoost emerged as the top-performing model (accuracy: 0.9999; recall: 1; F1 score: 0.9997). Noteworthy features influencing predictions included the Charlson Comorbidity Index (CCI), diabetes mellitus, cancer, the Wells scale, and CHA_2DS_2-VASc, with specific associations identified. Elevated MACE risk was observed, with a CCI score exceeding 2.67 ± 1.31 ($p < 0.001$), CHA2DS2-VASc score of 4.62 ± 1.02 ($p < 0.001$), and an intermediate-risk Wells scale classification. Overall, the AdaBoost ML offers an alternative predictive approach to facilitate the early identification of MACE risk in the assessment of patients with AF.

Keywords: atrial fibrillation; major adverse cardiovascular events (MACE); machine learning; artificial intelligence

1. Introduction

Despite being the most prevalent cardiac arrhythmia, the early identification, diagnosis, and treatment of atrial fibrillation (AF) remain challenging. AF affects millions of individuals globally and is linked to a heightened risk of stroke, heart failure, and mortality [1–4]. These medical conditions collectively fall under the term Major Adverse Cardiovascular Events (MACE) and are subject to extensive research [5]. The diagnosis of AF is associated with a fourfold increase in heart failure incidence and an eightfold increase in MACE occurrence [6].

Risk factors for MACE in AF patients have been identified as age, gender, hypertension, diabetes (known as "traditional"), biomarkers, genetic variants, imaging parameters, and left atrial function [7–10]. In recent years, there has been growing interest in identifying new

predictors of MACE in AF patients [11] beyond traditional ones such as obesity, chronic obstructive pulmonary disease (COPD), or chronic renal failure [7,8,12]; this novel approach is associated with a reduced risk of MACE, including mortality and thromboembolism [13].

Several proposals for stroke risk assessment in AF have been developed, such as CHA_2DS_2-VASc [14], the Framingham score [15], Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) [16], Cohorts for Heart and Aging Research in Genomic Epidemiology for Atrial Fibrillation (CHARGE-AF) [17,18], and Atrial Fibrillation Research In CATalonia (AFRICAT) [19]. However, there are still challenges and limitations with clinical risk scores that restrict their applicability to certain populations. Moreover, the discriminatory ability of clinical risk scores in predicting stroke risk for an individual is at best moderate [20]. For MACE risk specifically, some studies [21,22] have proposed additional scoring systems or modifications to existing scores to better predict cardiovascular events in patients with AF. Leveraging artificial intelligence (AI) and machine learning (ML) techniques on electronic health record (EHR) data offers a potential avenue to further refine these risk prediction models. However, it is important to note that the extent of performance improvement achieved through AI and ML approaches can vary [23,24].

Therefore, more comprehensive risk prediction models incorporating a wider range of predictors or with more prognostic value are needed. Such models can be achieved using ML algorithms, which offer a promising approach in AF patients [2], as they can integrate large amounts of data from multiple sources and identify complex patterns and correlations that may not be evident using traditional statistical methods.

The heterogeneous mechanisms and risk factors associated with AF make it necessary to target personalized treatment approaches, requiring extensive patient data to identify specific patterns. AI algorithms are particularly suitable for handling high-dimensional data, predicting outcomes, and ultimately optimizing strategies for patient management [25]. Recent advances in ML have resulted in great success and have also been utilized to analyze electrocardiogram (ECG) data and predict the future occurrence of arrhythmias. Future Innovations in Novel Detection for Atrial Fibrillation (FIND-AF), an extensively scalable ML algorithm, is capable of analyzing routinely collected primary care data to identify individuals with an elevated risk of short-term AF [26]. Other studies have demonstrated the utility of machine learning-based models in AF for real-time identification of a variety of rhythms using 12-lead or single-lead ECG recordings, as well as for diagnosis, outcome prediction, disease characterization, and treatment assessment [2,27–33]. However, they do not address the discrimination of cardioembolic from noncardioembolic stroke among individuals with AF with high accuracy and surpassing traditional risk scores. These methods provide precise and efficient algorithms for data analysis, improving prediction accuracy, pattern identification, and task automation. If patients at higher risk of MACE could be identified, treatment strategies could be developed to potentially reduce incidence and associated complications.

The primary objectives of this study encompassed the identification of noteworthy clinical indicators associated with MACE in patients with new AF. It further aimed to assess the prognostic impact of these predictors within a community cohort, aged 65–95 years, tracked from 2015 to 2021.

2. Materials and Methods

2.1. Study Design

This was an observational study, and the data were retrospectively collected where possible, or manually collected otherwise. The specific codes of the International Classification of Diseases (ICD-10) were used. The project encompassed the broader demographic of individuals aged 65–95 years ($n = 40{,}297$) who did not have AF as part of their inclusion criteria and was conducted within the Primary Care facilities of Terres de l'Ebre, located in Catalonia, Spain, during the period spanning from 1 January 2015 to 31 December 2021.

The data were available from the electronic medical datasets (E-CAP and SAP) managed by the Catalan Health Institute (ICS), which collect information from primary care

centers and hospitals in the health region anonymously and without contact with the cases included, as follows:

1. The Health Plan [33] outlines healthcare priorities in the "Terres de l'Ebre" Healthcare Region (Catalonia, Spain) from 2021 to 2025.
2. The HC3 Patient Episode Dataset provides clinical information of care on inpatient and outpatient care in Catalan hospitals.
3. The clinical database of 11 primary care teams includes comprehensive health data for 97.7% of residents, covering symptoms, tests, diagnoses, comorbidities, prescribed medication, and referrals.
4. The Integrated System of Electronic Prescription (SIRE) captures information on prescribed medications.
5. The Statistics Institute of Catalonia includes demographic information [34–36].

The datasets generated, used, and analyzed during the current study are available from the corresponding author on reasonable request.

2.2. *Eligibility Criteria*

All patients over 65 years of age from Terres de l'Ebre (N 55,459) without AF or MACE in their clinical history were considered, and the following criteria were defined:

1. Outcomes: AF patients who had a MACE.
2. Inclusion criteria: Subjects aged 65–95 years who met the inclusion criteria: high risk-AF (according to the risk model and belonging to Q4) [19], active clinical history in any of the health centers of the territory with information accessible through the shared history (HC3), without previous AF or MACE, residing in the territory, and attached to any of the Primary Care Teams (EAP) of the territory.
3. Exclusion criteria: under 65 years of age or over 95 years of age, living outside Terres de l'Ebre, a previous diagnosis of AF, treatment with anticoagulants, impaired cognitive status, Barthel score < 55 points, or pacemaker or defibrillator wearer. Non-availability or loss of accessibility to the information necessary for the study was considered a reason for exclusion.

2.3. *Data and Preprocessing*

The overall composition of the dataset for MACE prediction is given in Table 1 Numerical calculations and data analysis were performed using Python library version 3. Code and models used for the analysis are available online (https://github.com/vmalonsobarberan/MACE) (accessed on 15 December 2023).

Table 1. Comparison of the performance of different models.

Machine Learning Model	Accuracy	Precision	Recall	F1 Score	Sensitivity	Specificity	PPV	NPV	AUC
Random Forest	96.78%	0.8456	0.9263	0.8841	0.9885	0.8456	0.9741	0.9263	96.78%
Extra Trees	98.82%	0.9641	0.9554	0.9597	0.9923	0.9641	0.9938	0.9554	98.82%
AdaBoost	99.99%	0.9994	1	0.9997	1	0.9994	0.9999	1	99.99%
XGBoost	99.95%	1	0.9971	0.9985	0.9995	1	1	0.997	99.95%
LightGBM	99.96%	1	0.9977	0.9988	0.9996	1	1	0.9977	99.96%

2.4. *Model Development*

To develop ML models for estimation, we took features of the individuals with newly diagnosed AF who developed MACE, following the eligibility criteria. ML model development was performed using the SKLearn and TensorFlow libraries due to their versatility and ease of programming. For each fold, hyperparameters were tuned on training data using a randomized search after the determination of a candidate hyperparameter set. Evaluation of validation data was performed using the metrics described in the next section.

Five different ML models were implemented based on the following algorithms: Random Forest, Extra Trees, AdaBoost, XGBoost, and LightGBM. They were trained on all the features (variables) used in the study to predict the development of MACE within one year as well as to predict the development of AF.

A fundamental part of the study, prior to the construction of the learning models, consisted of "Feature Engineering", which consists of the analysis and selection of the variables, as well as the processing of the data they contain. To this end, those that only contribute noise and/or are correlated with others that have a greater influence on the objective we aimed to predict were eliminated.

The performance of MACE prediction was quantified using the following metrics: precision, recall, accuracy, and F1 score (combination of precision and recall). Two thirds of the data (36,973) were randomly selected for training and model building using different approaches and optimized to reduce the prediction error. The remaining 1/3 (18,486) was used for testing and validation. The models underwent testing using this separate test data to assess their performance on data that had not been utilized during the training phase. This evaluation aimed to determine whether the models could effectively generalize and make accurate predictions on unseen data.

2.5. Model Performance Analysis

Several metrics were used to evaluate the algorithms, including prediction robustness, completeness, sensitivity, specificity, precision, recall, accuracy, and F1 score (combination of precision and recall). Evaluation of these metrics allowed us to adjust the hyperparameters of the model to improve the most desirable aspect of the model. The model with the highest and most robust performance was chosen after evaluating the performance of the different models using the mean value of the area under the ROC curve. The assessment of our models included consideration of the standard deviation of the results to evaluate their stability, along with an analysis of sensitivity, specificity, and accuracy. After fitting and evaluating different models, the best model was selected, and the hyperparameters were adjusted to obtain the optimal results.

2.6. Model Interpretability

The Shapley Additive exPlanations (SHAP) method was used to analyze which factors were the most important and to what extent they contribute to the model's predictions. An individual automatic explainability model was also created to allow an analysis to be made for each individual patient. The latter allows, after analyzing a patient's variables, to explain how likely a patient with AF is to have a MACE and which factors contribute to this prediction and to what extent.

2.7. Statistical Analysis

The traditional statistical analysis of the baseline data was previously documented [6].

3. Results

3.1. Study Population Patient Characteristics

The study encompassed a cohort of 2574 individuals devoid of prior MACE incidents, with a mean age of 81.22 $\pm$ 7.91 years and a gender distribution of 52.01% women. A detailed analysis of baseline characteristics, as outlined previously [6], revealed notable distinctions among the study groups. Notably, women who experienced MACE exhibited a higher mean age (82.23 $\pm$ 7.59 years, compared to 80.53 $\pm$ 8.05 years for males, $p < 0.001$) and a higher prevalence of cardiovascular risk factors and comorbidities. Refer to Table 2 for a comprehensive overview of the selected variables instrumental in model construction.

Table 2. Distribution of AF patients according to the presence of MACE.

Variables	No MACE	(%)	MACE	(%)	*p*	All
All	1527	59.32%	1047	40.68%		2574
Woman	785	51.41%	558	53.30%	0.356	1343
Age average	80.53 ± 8.05		82.23 ± 7.59		<0.001	81.22 ± 7.91
Hypertension, arterial	1112	72.82%	833	79.56%	<0.001	1945
Diabetes mellitus	406	26.59%	363	34.67%	<0.001	769
Dyslipemia	692	45.32%	524	50.05%	0.020	1216
Vascular disease	59	3.86%	286	27.32%	<0.001	345
Dementia/cognitive impairment	174	11.39%	136	12.99%	<0.001	310
Liver disease	6	0.39%	4	0.38%	1.000	10
Renal failure	339	22.20%	337	32.19%	<0.001	676
Cancer	516	33.79%	340	32.47%	0.496	856
Thyroid disease	109	7.14%	106	10.12%	0.018	215
OSAHS [1]	60	3.93%	66	6.30%	0.007	126
COPD [2]	225	14.73%	222	21.20%	<0.001	447
Inflammatory disease (Crohn's and Colitis)	9	0.59%	7	0.67%	0.804	16
Deep vein thrombosis	20	1.31%	17	1.62%	0.506	37
Weight (kg)	77.47 ± 5.7		78.03 ± 16.51		0.038	77.69 ± 16.04
BMI [3]	29.32 ± 5.28		29.75 ± 5.51		0.041	29.49 ± 5.38
Heart rate/min	76.05 ± 1847		75.71 ± 18.47		0.625	75.91 ± 18.47
Cholesterol mg/dL	184.23 ± 38.07		164.98 ± 38.14		<0.001	176.4 ± 39.24
ProBNP (pg/mL)	1550		3301.75 ± 2882.7		0.625	2951.4 ± 2616.52
Dimer D (ng/mL)	1753.59 ± 2714.47		1319.72 ± 2954.13		0.337	1532.56 ± 2838.47
Glomerular filtration rate (mL/min/1.73 m^2)	66.11 ± 19.8		59.85 ± 20.74		<0.001	63.48 ± 20.43
Serum albumin (g/dL)	4.94 ± 5.43		5.04 ± 14.85		0.835	4.98 ± 10.68
Lymphocytes ($\times 10^3/\mu L$)	2.12 ± 1.11		2.02 ± 1.62		0.072	2.08 ± 1.34
Statins	505	33.07%	607	57.98%	<0.001	945
Anticoagulation	1207	79.04%	787	75.16%	0.021	1994
Antivitamin-K	613	40.14%	331	31.61%	<0.001	944
NOAC [4]	595	38.96%	458	43.74%	0.015	1053
Anti-aggregants	67	4.38%	74	7.06%	0.003	141
Pfeiffer score ± SD	2.91 ± 3.1		2.61 ± 2.8		0.218	2.75 ± 2.94
CHA_2DS_2-VASc ± SD	3.26 ± 0.95		4.62 ± 1.02		<0.001	3.81 ± 1.20
CCI [5] ± SD	1.24 ± 1.19		2.67 ± 1.31		<0.001	1.82 ± 1.43
CONUT score ± SD	1.31 ± 0.54		1.48 ± 0.61		<0.001	1.38 ± 0.58
Wells score ± SD	1.35 ± 0.48		1.33 ± 0.47		0.415	1.34 ± 0.47
COVID-19	150	9.82%	110	10.51%	0.573	260
Death	1279	83.76%	777	74.21%	<0.001	2056

[1]. OSAHS: obstructive sleep apnea-hypopnea syndrome; [2]. COPD: chronic obstructive pulmonary disease; [3]. BMI: Body Mass Index; [4]. NOAC: new oral anticoagulants; [5]. CCI: Charlson Comorbidity Index.

3.2. Machine Learning Model

3.2.1. Comparison between the Different Models

In the comparative analysis of various pre-trained models, AdaBoost emerged as the top-performing model, showcasing exceptional metrics, with an accuracy of 0.9999, recall of 1, and an F1 score of 0.9997. This marked superiority was evident, making AdaBoost the optimal choice, balancing both sensitivity and specificity (Figure 1).

Following closely behind, XGBoost (accuracy: 0.9995; recall: 0.9971; F1: 0.9985) and LightGBM (accuracy: 0.9996; recall: 0.9977; F1: 0.9988) emerged as the second-best models in our evaluation (Table 1). Notably, Random Forest and Extra Trees, while achieving commendable Area Under the Curve values (Figure 2), did not match the performance levels achieved by AdaBoost.

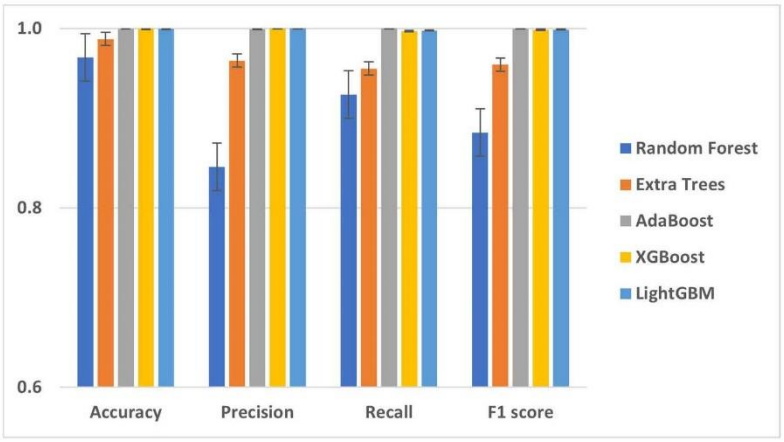

Figure 1. Comparison of the performance of different models.

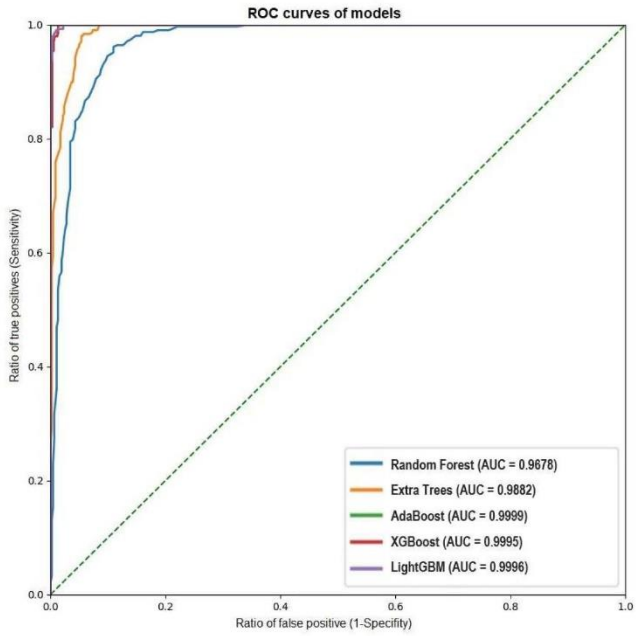

Figure 2. Comparison of AUC results between the machine learning models.

The confusion matrices of the different models and cross-validation were calculated. Each model has a confusion matrix. The models were ranked by true positive rates (Table 2).

3.2.2. Predictors by Outcomes

Figure 3 shows the main prognostic factors for MACE in AF patients. From most to least important were an elevated CCI, cancer, diabetes mellitus, COPD/asthma/bronchitis, cognitive impairment, vascular disease, high values of the CHA_2DS_2-VASc, and Wells scale.

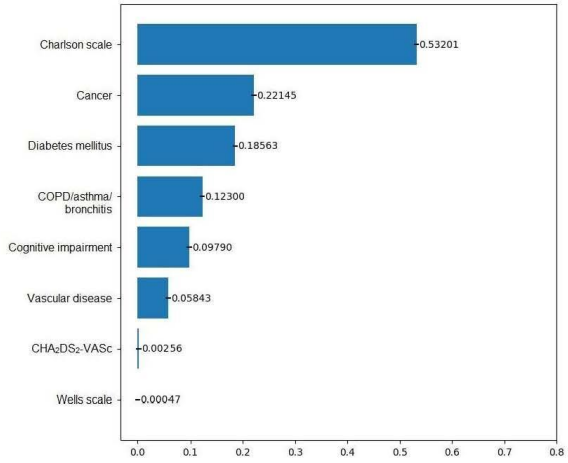

Figure 3. Strength of the main prognostic factors for MACE.

3.2.3. Model Interpretation

Figure 4 encapsulates a comprehensive overview of the feature contributions within the optimal model, AdaBoost. The SHAP (SHapley Additive exPlanations) summary chart delineates the significance of various characteristics, with the following five features emerging as the most influential: CCI, diabetes mellitus, cancer, Wells scale, and CHA_2DS_2-VASc. This SHAP summary chart not only identifies the primary features impacting the prediction but also quantifies their respective magnitudes through the SHAP values. The figures provide valuable insights into the relative importance of each feature, aiding in a nuanced understanding of the predictive dynamics within the AdaBoost model.

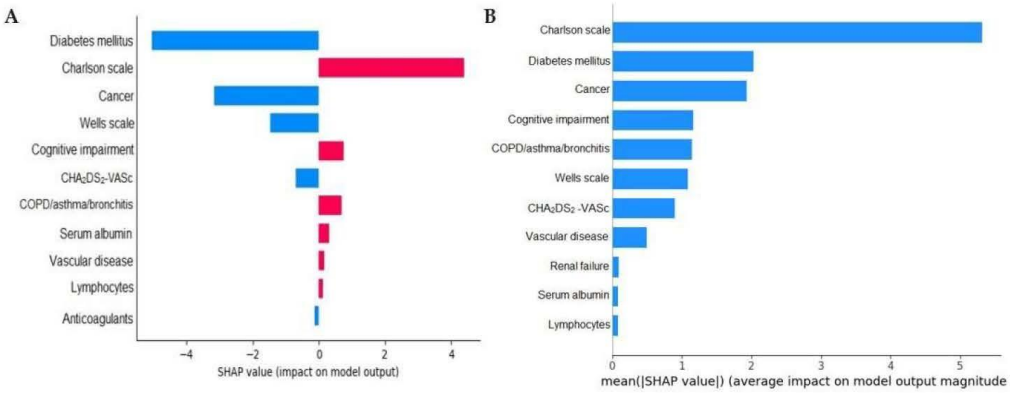

Figure 4. SHAP summary plot of optimum model. (**A**) The warm SHAP plot shows the distribution of SHAP values for each characteristic. (**B**) Bar chart according to feature importance.

Figure 5, the SHAP bar plot, serves as a visual representation elucidating the overall significance of each feature in predicting the occurrence of MACE. The height of the bars directly correlates with the importance of each feature to the model—higher bars denote greater importance. This graphical representation offers a clear and straightforward depiction of the overall magnitude and relevance of individual features in influencing the predictive outcome of MACE within the model. The visual emphasis on bar height

facilitates an immediate understanding of the relative contributions of different features, enhancing the interpretability of the model's decision-making process.

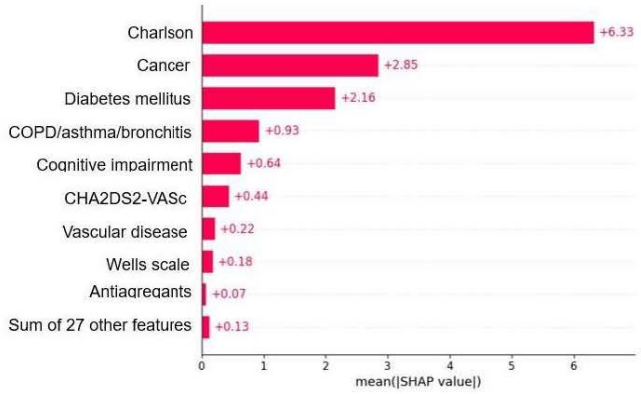

Figure 5. SHAP bar plot showing the overall magnitude and importance of the features.

The analysis delved into the influence of specific diseases, as outlined in the model, as predictors of MACE in AF patients. A CCI score exceeding 2.67 ± 1.31 ($p < 0.001$), a CHA_2DS_2-VASc score of 4.62 ± 1.02 ($p < 0.001$), and an intermediate-risk classification in the Wells scale were all observed to significantly elevate the risk of MACE. These findings underscore the nuanced interplay of individual patient characteristics, providing valuable insights into the factors contributing to the heightened risk of MACE in AF patients.

In Figure 6, the force chart dynamically illustrates the contributions of each feature in directing the model prediction from the base value to the ultimate result. The length of the colored bars within the chart serves as a visual indicator of the magnitude of each feature's contribution. This graphical representation offers a dynamic and insightful portrayal of how individual features influence the model's predictions, emphasizing the varying degrees of impact that contribute to the final outcome. The length of each bar provides a quick and intuitive assessment of the relative importance of each feature in shaping the model's decision-making process.

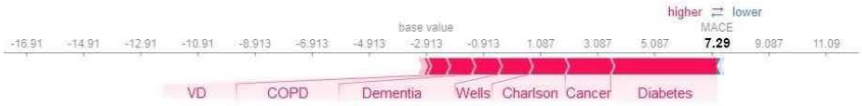

Figure 6. Dynamic force chart.

4. Discussion

The study identified AdaBoost as the best-performing model for MACE prediction in AF patients. Additionally, the CCI, concurrent cancer diagnosis, diabetes mellitus, and Wells and CHA_2DS_2-VASc scores emerged as primary predictors of MACE among patients newly diagnosed with AF. In a previous investigation [6], subsequent adjustments for age, gender, body mass index, cardiovascular risk factors, antiplatelets, and anticoagulants revealed that only the CHA_2DS_2-VASc, CCI, and CONUT scores remained as independent prognostic factors for MACE in individuals with a recent diagnosis of AF [6].

The various potential benefits of the results can be described in the different sections included in the flowchart for the approach and treatment of AF [14] as risk stratification, the prevention of thromboembolism among patients with silent AF and stroke without a previous diagnosis of AF, and for specific comorbidities such as chronic coronary disease, peripheral artery disease, heart failure, chronic kidney disease, and cognitive impairment.

AF almost quintuples the risk of MACE [6], especially ischemic stroke and heart failure. The 23.5% with known AF were not receiving oral anticoagulant therapy [37]. The AF was associated with more severity, disability, and a 20% increase in stroke-related costs. The clinical benefits of appropriate anticoagulation are widely recognized, and clinicians should be aware of the importance of anticoagulation therapies in stroke prophylaxis, the occurrence of stroke, and the downstream economic burden on an increasingly aging population [38]. Patients with AF may benefit from evaluating factors such as the AdaBoost model. This information can assist in making informed decisions about treatment.

The decision to prescribe oral anticoagulants for preventing MACE in patients with intermediate annual risk of thromboembolic events, as determined by classic risk scores like CHA_2DS_2-VASc or an equivalent, and who are uncertain about the benefits of anticoagulation, may require additional discussion. This is due to the diverse magnitude of risk associated with each factor across different populations. Managing specific patient groups, particularly those with risk factors for MACE, can improve risk discrimination by incorporating additional factors, as seen with the AdaBoost model.

Moreover, it addresses the optimization of treatment decisions concerning the burden of AF in relation to the associated risks of thromboembolism and ischemic stroke. This involves assessing the need for anticoagulant treatment decisions in individuals experiencing either paroxysmal or persistent AF because of the predictive significance of the AF burden [39,40]. A pioneering aspect of this approach involves the comprehensive analysis of large patient cohorts and the integration of diverse data sources, including blood biomarkers, electrical signals, and medical images [41]. The significance of this research extends into the domain of Personalized Risk Assessment, providing a promising approach for the early non-invasive detection of AF. This extends to optimizing treatment approaches and anticipating long-term clinical trajectories.

The algorithm emphasizes the CCI as the primary predictor, a widely utilized tool in the medical field for predicting the risk of mortality linked to chronic health conditions. It encompasses various factors such as heart disease, diabetes, and cancer and assigns specific weights to each based on their impact on mortality. The cumulative score is then employed to estimate an individual's overall health status and prognosis. A higher CCI score correlates with an elevated risk of adverse outcomes or mortality. Remarkably, until now, the CCI has not been previously associated with the risk of thromboembolism in patients recently diagnosed with AF. Notably, there have been instances where the use of anticoagulant therapy was linked to a lower CCI score [42]. While the CCI has undergone extensive validation and widespread use in predicting outcomes across various medical contexts, its application in specific situations, such as predicting outcomes in patients with AF [6], may not have been as comprehensively explored.

The presence of cancer emerges as the second-ranking predictor of MACE. While the algorithm does not specify the type of cancer, numerous studies have explored the connection between cancer and thromboembolism in patients with AF. Some of these studies not only identify cancer as a significant predictor of MACE, encompassing thromboembolic events [43], but also suggest that the onset of new AF is associated with an elevated risk of developing cancer [44,45]. These findings underscore the intricate interplay between AF, cancer, and thromboembolic complications, as well as the importance of considering both conditions in clinical assessment and management [46].

The Wells score has not been widely recognized as a prognostic factor for thromboembolism among patients with AF; it is typically used to assess the likelihood of deep vein thrombosis and pulmonary embolism. AF and venous thromboembolism share several common risk factors. Moreover, the presence of AF may be linked to a higher risk of developing VTE, and individuals with a high risk of experiencing VTE may also face an elevated risk of developing AF [47]. This bidirectional association highlights the potential interplay between these two conditions, suggesting that they may influence each other's occurrence and progression. Further research is warranted to fully understand the com-

plex relationship between AF and VTE and its implications for clinical management and preventive strategies.

Diabetes mellitus and peripheral artery disease play an important role as a predictor of MACE [7,48]. Although they are also variables included in the CHA_2DS_2-VAS_c and CCI scales, they alone are also an important variable for the development of MACE, and the significance of CHA_2DS_2-VAS_c is widely recognized among patients with nonvalvular AF receiving oral anticoagulants [6,14,49,50]. In a recent study [51], machine learning models demonstrated satisfactory performance in forecasting MACE among patients with Type 2 diabetes mellitus. Notably, these models exhibited a higher accuracy in predicting strokes than myocardial infarction and heart failure.

Eventually, the study shed light on the significant role of COPD in the development of MACE among patients with AF, in alignment with existing evidence [8,12,50,52]. Prolonged P-wave duration acts as a potent precursor to AF, a condition that may be triggered by obstructive sleep apnea [53]. The presence of COPD in AF patients may contribute to an increased risk of MACE, emphasizing the importance of considering and managing this comorbidity when evaluating cardiovascular outcomes in this patient population.

While simpler models, such as logistic regression and decision trees, are more straightforward to interpret, they frequently exhibit inferior predictive performance compared to more sophisticated algorithms, including ensembles of decision trees like XGBoost and random forests [54]. Harnessing ML [53] algorithms facilitates the early identification of subtle indicators of thromboembolism risk from intricate datasets, thereby uncovering latent relationships among the risk factors associated with AF. The LightGBM model revealed associations between ischemic stroke and various peripheral blood biomarkers (such as creatinine, glycated hemoglobin, and monocytes) not considered by CHA_2DS_2-VASc and demonstrated significance in predicting ischemic stroke among AF patients [55,56]. These algorithms not only facilitate the analysis and correction of potential confounding factors but also serve as powerful tools to identify and mitigate bias in the AI system. Continuous monitoring using ML algorithms offers ongoing assessment of thromboembolic risk among AF patients, contributing to the tracking of disease progression, monitoring treatment response, and promptly detecting any sudden changes in health status. Additionally, by enhancing follow-up through the prediction of patient-specific risks, these algorithms can prioritize follow-up visits and interventions, ultimately leading to improved patient outcomes.

Using the Deep Learning methodology, the results were slightly inferior to those achieved with Machine Learning (accuracy of 0.9678). The primary reason for this discrepancy may be the fact that neural networks demand a substantial amount of data to effectively learn. They are characterized by an abundance of parameters that require tuning, allowing them to grasp intricate, high-dimensional patterns. However, this proves to be a disadvantage when the dataset is limited. In instances of small datasets, these models become prone to overfitting, essentially 'memorizing' the training data rather than 'learning' the underlying pattern. Consequently, this results in suboptimal generalization performance when applied to unseen data.

The strengths of the study include the models of prediction, the high-quality datasets, and strict adherence to data privacy regulations, as well as clinical context and domain knowledge, making it easy to interpret the reasons behind their predictions. In summary, incorporating machine learning algorithms into the clinical management of individuals at high risk of AF and those with AF yields potential benefits, including personalized risk assessment, data-driven decision support, and improved patient care. However, further validation in independent studies is required.

Some limitations should be considered, as external validation is essential before effectively adopting and integrating AI systems into patient care. One crucial factor that largely determines the efficiency and accuracy of these models is the quantity of data available. For small datasets, like in our case, traditional machine learning models tend to outperform their deep learning counterparts, contrary to popular belief. AI models trained

on specific datasets might not generalize well to different populations or healthcare settings, and overfitting could limit their applicability. Additionally, it is important to note that correlation does not necessarily imply causation. Establishing causal relationships between risk factors for AF and thromboembolism requires further research and experimentation. By addressing these limitations and maintaining responsible and effective AI use, we can enhance our understanding beyond not only the early detection of AF but also the risk associated with the incidence of MACE, providing opportunities to intervene in modifiable risk factors, and including aspects such as monitoring methods, detection technologies, and biomarkers linked to the association between AF and thromboembolism, ultimately leading to enhanced patient care outcomes.

Artificial intelligence-based clinical decision support systems may improve the outcomes among patients who have AF, but the efficacy of the tool in the real world is seldom reported. Future research could explore additional advantages, such as personalized risk assessment. By analyzing extensive datasets, including social determinants of health [18,57,58], biomarkers [59], multimodality imaging parameters [60,61], and nutritional status associated with AF risk [57,62], a comprehensive assessment can be made. This integration facilitates a more comprehensive and personalized risk assessment for each individual, allowing the identification of distinctive patterns and factors specific to the patient. This approach leads to more accurate risk predictions compared to traditional statistical models [6,23,63] and, consequently, may improve treatment decision making.

5. Conclusions

The application of Machine Learning, employing multiple models, indicates that the AdaBoost model is the most effective in predicting MACE in patients with newly diagnosed AF, with an accuracy of 0.9999, recall of 1, and an F1 score of 0.9997. The primary prognostic factors identified included an elevated Charlson Comorbidity Index, cancer, diabetes mellitus, COPD, cognitive impairment, vascular disease, and high values on the CHA_2DS_2-VASc and Wells scale. This finding contributes to the optimization of treatment decisions concerning the burden of AF in relation to the associated risks of thromboembolism and ischemic events.

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Institutional Review Board Statement: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Approval was obtained from the Ethics Committee of the Institut Universitari d'Investigació en Atenció Primària Jordi Gol with the registration number 22/243-P (30 November 2022). Registry information was collected from the government-run healthcare provider responsible for all inpatient care in the county, without contact with participants, in order to gather data from the study. The manuscript does not contain clinical studies or patient data that might disclose the identity of the people under study.

Informed Consent Statement: Not applicable. 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.

Data Availability Statement: Numerical calculations and data analysis were performed using Python library version 3. The code and models used for the analysis are available online (https://github.com/

vmalonsobarberan/MACE) (15 December 2023). The datasets generated, used, and analyzed during the current study are available from the corresponding author (P.M.-B.) upon reasonable request.

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Conflicts of Interest: The authors declare no conflict of interest.

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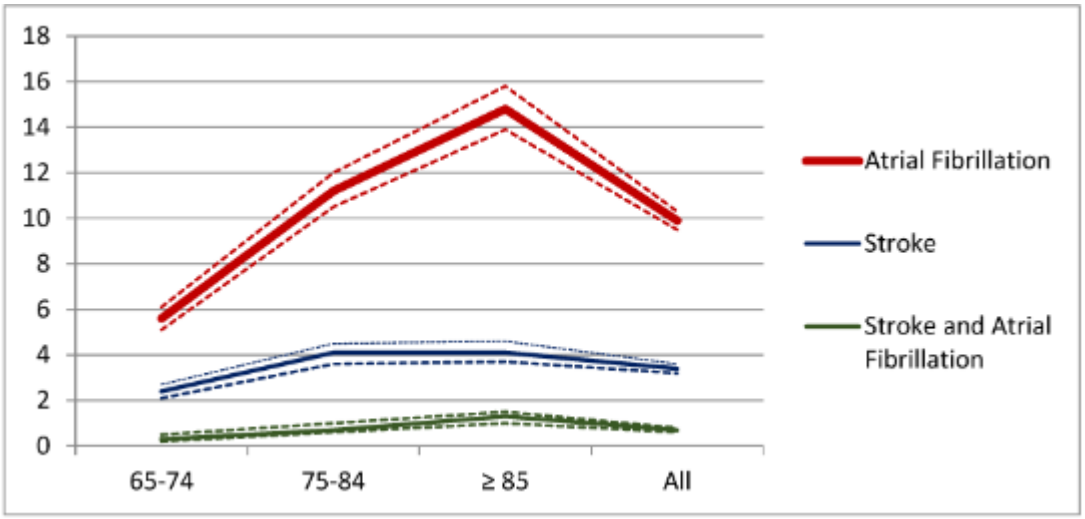
6.4. Resumen de los resultados

En el primer artículo se incluyeron un total de 40.297 personas sin antecedentes personales de FA ni de ictus con el objetivo de determinar la incidencia de ictus y FA. El tiempo medio de seguimiento fue de 80,65 ± 9,5 meses. La población de estudio tuvo una edad promedio de 77,65 ± 8,46 años, siendo el 46,48 % mujeres significativamente mayores que los hombres (81,22 ± 7,91 vs. 77,65 ± 8,46 años, p<0,001).

La incidencia de FA fue de 9,9/1000 personas-año (IC 95 %: 9,5-10,3) y aumentó en línea con los niveles de riesgo de FA, alcanzando 17/1000 personas-año (IC 95 %: 16,1-18,1) entre aquellos con mayor riesgo de FA (Figura **2**).

Figura 2. Tasas de densidad de incidencia de FA e ictus por cada 1000 personas-año por grupo de edad.



Se confirmaron 885 episodios de ictus entre los pacientes con alto riesgo de FA (Q4). Encontrando que en el diagnóstico de FA había un riesgo cuatro veces mayor de accidente cerebrovascular [OR 4,03 (IC 95 %: 3,43–4,74)] y la incidencia más alta de accidente cerebrovascular fue de 11,1/1.000 personas-año (IC 95 %: 9,6–12,8). En total, 187 de los ictus (21,12 %) se asociaron con FA. Los pacientes con FA que desarrollaron un ictus tenían puntuaciones más altas de CHA_2DS_2-VASc, ICC, mayor incidencia de MACE, tasas más altas de deterioro cognitivo y tasas más altas de mortalidad que aquellos sin accidente cerebrovascular.

La incidencia de ictus aumentó en consonancia con los niveles de riesgo de FA, alcanzando 6,8/1.000 personas-año (IC 95 %: 6,2-7,5). Se diagnosticó FA desconocida en el 9,47 % de las personas con alto riesgo de FA, entre las cuales al 21,1 % se le diagnosticó un nuevo accidente cerebrovascular. El 41,7 % de los casos con deterioro cognitivo se concentraron en el nivel de riesgo Q4 con una mayor incidencia de deterioro cognitivo y mortalidad antes de su diagnóstico de FA.

En el segundo artículo, un total de 2.574 personas (6,39 %) desarrollaron FA después de una mediana de seguimiento de 78,6 ± 12,1 meses. La incidencia

general fue de 8,9/1.000 personas-año (IC 95%: 8,6–9,2), significativamente mayor entre los hombres [9,8/1.000 personas-año (IC 95 %: 9,3–10,3) vs. 8,1/1.000 personas-año (IC 95 %: 7,7–8,5); p<0,001]. Hubo diferencias significativas entre los patrones de FA para todos los factores de riesgo de interés al inicio del estudio.

Los participantes con FA tuvieron una prevalencia significativamente mayor de MACE en comparación con aquellos sin FA (40,7 % frente a 12,7 %, p<0,001). Además, tuvieron puntuaciones promedio más altas (p<0,001) en las escalas CHA_2DS_2-VASc y CONUT, así como tasas de mortalidad general más altas (18,02 % vs. 20,12 %, p<0,001).

Se observaron 1.748 episodios de MACE entre los pacientes con FA. La tasa de incidencia global de MACE en el grupo con FA fue de 73,0/1000 personas-año (IC 95 % 68,9-77,1), mientras que en el grupo sin FA fue de 21,1/1000 personas-año (IC 95 % 20,5-21,6; p<0,001), con una razón de tasas de 3,52 (IC 95 % 3,31–3,75; p<0,001). La tasa de incidencia global de insuficiencia cardíaca en el grupo con FA fue de 40,1 personas-año (IC 95 % 37,1-43,2), mientras que en el grupo sin FA fue de 8,3 personas-año (IC 95 % 7,9-8,6; p<0,001), con un ratio de tasas de 4,85 (IC 95 % 4,45–55,3; p<0,001) (Figura **3**).

Figura 3. Asociación entre el diagnóstico de FA y los MACE según el cuartil de riesgo riesgo de desarrollar FA.

	Q4	No-AF	New AF	HR AF/Q4	HR AF/No-AF
N	10,239	37,723	2574		
Age (average ± SD)	84.8 ± 6.7	77.65 ± 8.4	81.2 ± 7.9		
AF (n) Incidence/1000 people-years [CI95%]	1148 17 [16.1–18.1]	-	2574 8.9 [8.6–9.2]		
Chronic kidney disease (n %) Incidence/1000 people-years [CI95%]	2748 (26.83%) 40.8 [39.3–42.3]	5158 (13.67%) 20.3 [19.8–20.9]	676 (26.26%) 40.1 [37.1–43.2]	0.98 [0.90–1.06] $p = 0.706$	1.97 [1.82–2.13] $p < 0.001$
Cognitive impairment (n %) Incidence/1000 people-years [CI95%]	1569 (15.32%) 23.3 [22.1–24.5]	3471 (9.2%) 13.7 [13.2–14.1]	310 (12.04%) 18.4 [16.4–20.6]	0.78 [0.69–0.89] $p = 0.002$	1.34 [1.2–1.51] $p < 0.001$
Heart failure (n %) Incidence/1000 people-years [CI95%]	1853 (18.1%) 27.5 [26.3–28.8]	2096 (5.56%) 8.3 [7.9–8.6]	676 (26.26%) 40.1 [37.1–43.2]	1.45 [1.33–1.6] $p < 0.0001$	4.85 [4.5–5.3] $p < 0.0001$
Ischemic heart disease (n %) Incidence/1000 people-years [CI95%]	1479 (14.44%) 22.0 [20.8–23.1]	2558 (6.78%) 10.1 [9.7–10.5]	367 (14.26%) 21.8 [19.6–24.1]	0.99 [0.88–1.11] $p = 0.908$	2.16 [1.93–2.41] $p < 0.001$
Stroke/transient ischemic attack (n %) Incidence/1000 people-years [CI95%]	459 (4.48%) 6.8 [6.2–7.5]	698 (1.85%) 2.7 [2.5–3.0]	187 (7.26%) 11.1 [9.6–12.8]	1.62 [1.37–1.92] $p < 0.001$	4.03 [3.43–4.74] $p < 0.001$
Peripheral arteriopathy (n %) Incidence/1000 people-years [CI95%]	1347 (13.15%) 20.0 [18.9–21.1]	2431 (6.44%) 9.6 [9.2–10.0]	345 (13.4%) 20.5 [18.4–22.7]	1.02 [0.90–1.15] $p = 0.724$	2.13 [1.90–2.4] $p < 0.001$
Death (n %) Incidence/1000 people-years [CI95%]	2861 (27.94%) 42.5 [40.9–44.0]	6799 (18.02%) 26.8 [26.1–27.4]	518 (20.12%) 30.7 [28.1–33.5]	0.72 [0.65–0.79] $p < 0.001$	1.14 [1.04–1.25] $p = 0.027$
Total MACE (n%) Incidence/1000 people-years [CI95%]	3791 (37.02%) 56.3 [54.5–58.1]	5352 (14.11%) 21.1 [20.5–21.6]	1748 (67.9%) 73.0 [68.9–77.1]	1.29 [1.21–1.38] $p < 0.001$	3.52 [3.31–3.75] $p < 0.001$

La escala CONUT se consagró como un factor pronóstico independiente de MACE (HR 1,24 IC 95 % 1,21-1,27; p<0,001). Se detectó desnutrición en el 49,7 % de los pacientes con FA (p<0,001) y la presencia de MACE duplicaba el riesgo de desnutrición (p<0,001) (Tabla **2**).

Tabla 2. Estado nutricional de los pacientes FA dependiendo del desarrollo de MACE.

CONUT Risk (n)	[AF + MACE+] 1,047	[AF+ MACE-] 1,527
Normal (1-2)	610 (58.26%)	1,121 (73.41%)
Leve (2-4)	375 (35.82%)	346 (22.66%)
Moderado (5-8)	61 (5.83%)	57 (3.74%)
Severo (9-12)	1 (0.09%)	3 (0.19%)

El tercer artículo continuó el trabajo iniciado examinando los MACE. Un análisis detallado de las características basales, reveló notables diferencias entre los grupos del estudio. En particular, las mujeres que sufrieron MACE presentaban una media de edad más elevada (82,23 ± 7,59 años frente a 80,53 ± 8,05 años, p<0,001) y una mayor prevalencia de factores de riesgo cardiovascular y comorbilidades.

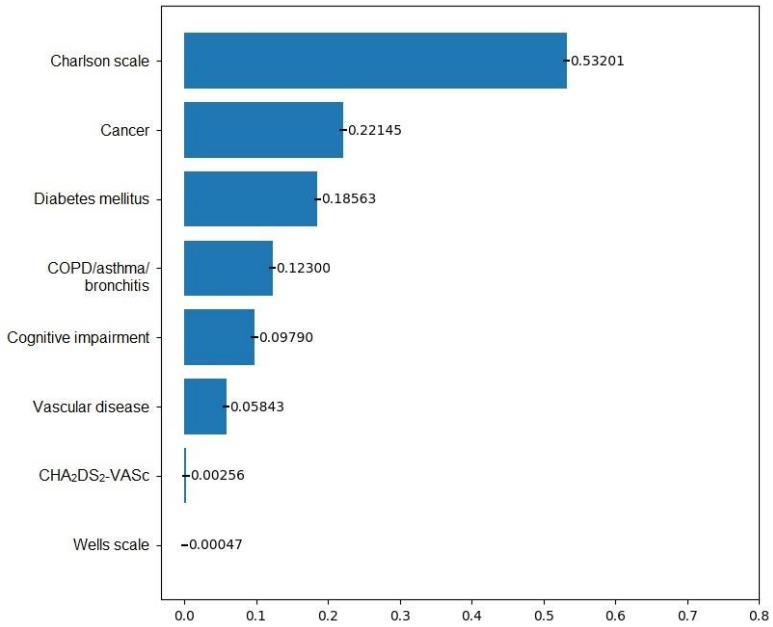
En el análisis comparativo de varios modelos preentrenados, AdaBoost resultó ser el modelo de mejor rendimiento, mostrando unas métricas excepcionales con una accuracy de 0,9999, una recall de 1 y una F1 score de 0,9997 (Tabla **3**).

Tabla 3. Comparación del rendimiento de distintos modelos.

Modelos de Machine Learning	Accuracy	Precision	Recall	F1 score	Sensibilidad	Especificidad	PPV	NPV	AUC
Random Forest	96.78%	0.8456	0.9263	0.8841	0.9885	0.8456	0.9741	0.9263	96.78%
Extra Trees	98.82%	0.9641	0.9554	0.9597	0.9923	0.9641	0.9938	0.9554	98.82%
AdaBoost	99.99%	0.9994	1	0.9997	1	0.9994	0.9999	1	99.99%
XGBoost	99.95%	1	0.9971	0.9985	0.9995	1	1	0.997	99.95%
LightGBM	99.96%	1	0.9977	0.9988	0.9996	1	1	0.9977	99.96%

El modelo AdaBoost determinó los principales factores pronósticos de MACE en pacientes con FA (Figura **4**), de mayor a menor importancia: ICC (≥2,67 ± 1,31; p<0,001), cáncer, diabetes mellitus, EPOC, deterioro cognitivo, enfermedad vascular, CHA_2DS_2-VASc (≥4,62 ± 1,02; p<0,001) y escala de Wells (riesgo intermedio y alto).

Figura 4. Principales factores pronósticos de MACE en pacientes con FA.



7. Discusión

Este trabajo culmina el proyecto de tesis doctoral referente a los MACE en los pacientes con FA constituido por 3 estudios con el objetivo de evaluar la asociación de incidencia de FA y episodios de MACE así como sus factores pronósticos.

En el primer estudio, se pone de manifiesto que la FA es un trastorno crónico y progresivo[12,60], siendo el riesgo cardiovascular mayor antes del diagnóstico de FA, especialmente en el caso de la ERC, la cardiopatía isquémica y la arteriopatía periférica.

El 90 % de los ictus están relacionados con factores de riesgo modificables y, a pesar de los avances en el diagnóstico y el tratamiento de la FA, la modificación de estos factores sigue siendo la piedra angular[61]. Además, en toda Europa, las estrategias de prevención primaria y secundaria no parecen funcionar lo suficientemente bien como para controlar los principales factores de riesgo y la proporción de personas con antecedentes de ictus con factores de estilo de vida poco saludables está aumentando[62]. Los resultados muestran una incidencia creciente de FA e ictus a partir de los 65 años, y la mayor diferencia entre la prevalencia de FA y la incidencia estimada se produjo entre los 65 y los 74 años, con una tasa de FA no diagnosticada del 2,2 % (IC95 %: 1,3-3,1)[7].

Se diagnosticó FA previamente desconocida en el 9,4 % de la muestra monitorizada de individuos con alto riesgo de FA, y se demostró un menor número de pacientes cribados necesarios para diagnosticar un caso de FA (NNC = 15) en comparación con el NNC de 147 necesario utilizando el método de detección oportunista[46].

La prevalencia de trastorno cognitivo es mayor en cada cuartil en relación con la de la población general[63]. Varios estudios[64,65] han informado de criterios ecocardiográficos y diferentes biomarcadores como factores pronósticos para el desarrollo de demencia y nueva FA, lo que plantea la posibilidad de un nuevo enfoque para la detección precoz. Sin embargo, parece desconocerse cómo puede afectar esto a la prevalencia. La presencia de un aumento progresivo de la prevalencia y gravedad del deterioro cognitivo con el riesgo de FA apoyaría una posible interrelación etiopatogénica entre ambos procesos en la población general[66]. Se ha propuesto una vía denominada "Atrial fibrillation Better Care" (ABC) para racionalizar un enfoque asistencial más holístico o integrado del tratamiento de la FA que se ha asociado a una reducción del riesgo de eventos adversos mayores, como mortalidad, tromboembolia y MACE[65,67].

En el segundo estudio se continuó con la línea del primero obteniendo más datos sobre la evolución de la FA. Los resultados demostraron que la incidencia de FA estaba asociada a una mayor incidencia de MACE, ERC y deterioro cognitivo. El aumento del riesgo relativo y absoluto asociado a muchos de estos eventos es superior al de los sujetos sin FA. Varios estudios han comunicado resultados similares en relación con el aumento del riesgo de la mayoría de los principales episodios cardiovasculares en individuos diagnosticados de FA[12,68]. Se tuvo en cuenta la mayor prevalencia entre insuficiencia cardíaca y FA, sobre todo en adultos mayores y en personas con enfermedades cardiovasculares

preexistentes. Los pacientes con FA tienen una incidencia significativamente mayor de insuficiencia cardíaca, con un riesgo cuatro veces mayor. La FA y la insuficiencia cardíaca coexisten a menudo y pueden agravarse mutuamente. Se ha demostrado que el tratamiento anticoagulante mejora la evolución de los pacientes con insuficiencia cardíaca y FA, sobre todo al reducir el riesgo de ictus y otros episodios tromboembólicos, que pueden causar más daño al corazón y empeorar la insuficiencia cardíaca[69].

Los resultados muestran que el riesgo de MACE ya es elevado antes del diagnóstico de FA, sobre todo en pacientes con ERC, cardiopatía isquémica y/o arteriopatía periférica clasificados como de alto riesgo para desarrollar FA. Además, debe señalarse que hubo un aumento significativo de la incidencia de deterioro cognitivo y mortalidad desde el Q1-Q4 hasta el grupo con FA recién diagnosticada. Las puntuaciones CHA_2DS_2-VASc, Charlson y CONUT se identificaron como factores pronósticos independientes para la FA relacionada con MACE.

En este trabajo, las mujeres presentan una mayor prevalencia de FA y una media de edad en el momento del diagnóstico superior a la de los hombres, de acuerdo con la evidencia actual[10,70]. Quizá el subgrupo de mujeres del Q4 deba ser considerado tanto para el cribado de FA como para un seguimiento estrecho de los factores de riesgo modificables, dada su mayor incidencia de comorbilidades, ictus y discapacidad grave[10,16]. Aunque los beneficios clínicos de la anticoagulación precoz son ampliamente reconocidos y seguros, el 25,4 % de los pacientes con FA no estaban correctamente anticoagulados, cifra similar a las ya conocidas[71,72].

La prevalencia de apnea del sueño registrada en el estudio fue del 4,9 %, superior a la publicada[73]. Sería interesante examinar las características de los pacientes con FA con una alta probabilidad de apnea del sueño, como los varones, los fumadores y los individuos con un IMC elevado[74]. Además, la interacción entre los factores de riesgo clínicos sigue siendo incierta, y varias combinaciones de variables pueden conllevar un mayor riesgo cuando se examinan conjuntamente en comparación con otras combinaciones.

Se sabe poco sobre el estado nutricional de los pacientes con FA y la relación entre malnutrición y mortalidad a medio y largo plazo. Pero queda de manifiesto que los pacientes con FA y MACE presentaban una mayor prevalencia de algún grado de desnutrición, lo que concuerda con los resultados de estudios previos[75,76]. Este hecho puede reflejar las necesidades sociales y los determinantes sociales de la salud. Se necesita más información para determinar la relación entre FA, MACE y estado nutricional. Asimismo, debería evaluarse la detección de alteraciones nutricionales en individuos con riesgo cardiovascular como subgrupo diana para el cribado de la FA y los MACE.

El tercer estudio mostró que el uso de IA para descubrir patrones y correlaciones entre diversas variables y desarrollar modelos predictivos de MACE en pacientes con FA mediante ML. El estudio identificó AdaBoost como el modelo de mejor rendimiento para la predicción de MACE en pacientes con FA. Siendo el ICC, el

cáncer, la diabetes mellitus, el EPOC, el deterioro cognitivo, la enfermedad vascular, la escala CHA_2DS_2-VASc y Wells surgieron como predictores primarios de MACE entre los pacientes con diagnóstico reciente de FA. En el segundo estudio se culmina con 3 factores pronósticos mediante la estadística tradicional (CONUT, ICC y CHA_2DS_2-VASc)[77]. Sin embargo, con IA se obtuvieron más predictores de MACE en individuos con diagnóstico reciente de FA con mayor precisión.

Un aspecto pionero de este enfoque del estudio es el análisis exhaustivo de una gran cohorte de pacientes y la integración de diversas fuentes de datos[78]. La importancia de esta investigación se extiende al ámbito de la evaluación personalizada del riesgo, proporcionando un enfoque prometedor para la detección precoz no invasiva de la FA.

El modelo generado hace hincapié en el ICC como principal predictor, una herramienta ampliamente utilizada en el ámbito médico para predecir el riesgo de mortalidad vinculado a enfermedades crónicas. Abarca diversos factores, como las cardiopatías, la diabetes y el cáncer, y asigna pesos específicos a cada uno de ellos en función de su impacto en la mortalidad. Una puntuación más alta del ICC se correlaciona con un riesgo elevado de resultados adversos o mortalidad. Sorprendentemente, hasta ahora no se había asociado el ICC con el riesgo de tromboembolia en pacientes con diagnóstico reciente de FA. Se asoció con un mayor riesgo de desarrollar FA independientemente de otros factores de riesgo[79], un mayor riesgo de mortalidad en pacientes con insuficiencia cardíaca[80] y un mayor riesgo de hospitalización y mortalidad[81]. Aunque el ICC ha sido ampliamente validado y utilizado para predecir resultados en diversos contextos médicos, es posible que su aplicación en situaciones específicas, como la predicción de resultados en pacientes con FA[77], no se haya explorado de forma tan exhaustiva.

La presencia de cáncer es el segundo factor predictivo de MACE. Aunque no se especifica el tipo, numerosos estudios han explorado la conexión entre cáncer y tromboembolia en pacientes con FA. Otros estudios no sólo le identifican como un factor predictivo significativo de MACE, que incluye los episodios tromboembólicos[82], sino que también sugieren que la aparición de una nueva FA se asocia a un riesgo elevado de desarrollar cáncer[83,84]. Estos hallazgos subrayan la interacción entre FA, complicaciones tromboembólicas y cáncer, así como la importancia de tener en cuenta ambas afecciones en la evaluación y el tratamiento clínicos[85].

La puntuación CHA_2DS_2-VASc es una herramienta ampliamente utilizada para evaluar el riesgo de ictus en pacientes con FA. Una puntuación CHA_2DS_2-VASc más alta se asocia con un mayor riesgo de desarrollar insuficiencia cardíaca y un mayor riesgo de MACE[86] en pacientes con FA[87].

La diabetes mellitus y la arteriopatía periférica desempeñan un papel importante como factores predictivos de MACE[18,88]. Aunque también son variables incluidas en la escala CHA_2DS_2-VASc y el ICC, por sí solas también son una variable importante para el desarrollo de MACE. En un estudio reciente[89], los modelos de

ML demostraron un rendimiento satisfactorio en la predicción de los MACE entre los pacientes con diabetes mellitus de tipo 2. En particular, estos modelos mostraron una mayor precisión en la predicción de accidentes cerebrovasculares que en infarto de miocardio e insuficiencia cardíaca.

Hay que destacar el importante papel de la EPOC en el desarrollo de MACE entre los pacientes con FA, en consonancia con la evidencia existente[19,90]. La presencia de EPOC en pacientes con FA puede contribuir a aumentar el riesgo de MACE, lo que subraya la importancia de tener en cuenta y tratar esta comorbilidad al evaluar los resultados cardiovasculares en esta población de pacientes.

La puntuación de Wells no ha sido ampliamente reconocida como factor pronóstico de tromboembolia entre los pacientes con FA. Normalmente se utiliza para evaluar la probabilidad de trombosis venosa profunda y embolia pulmonar. La FA y la TEV comparten varios factores de riesgo comunes. La presencia de FA puede estar relacionada con un mayor riesgo de padecer un TEV al igual que las personas con alto riesgo de un TEV también pueden tener un riesgo elevado de padecer FA[91]. Esta asociación bidireccional pone de relieve la posible interacción entre estas dos enfermedades, lo que sugiere que pueden influirse mutuamente en su aparición y progresión. Es necesario seguir investigando para comprender plenamente la compleja relación entre FA y TEV y sus implicaciones para el tratamiento clínico y las estrategias preventivas.

El aprovechamiento de los algoritmos ML[92] facilita la identificación precoz de indicadores sutiles de riesgo de tromboembolia a partir de conjuntos de datos intrincados, descubriendo así relaciones latentes entre los factores de riesgo asociados a la FA. El modelo LightGBM reveló asociaciones entre el ictus isquémico y varios biomarcadores de sangre periférica (como la creatinina, la hemoglobina glicosilada y los monocitos) no considerados por el CHA_2DS_2-VASc y demostró su importancia en la predicción del ictus isquémico entre los pacientes con FA[92,93]. Estos algoritmos no sólo facilitan el análisis y la corrección de posibles factores de confusión, sino que también sirven como potentes herramientas para identificar y mitigar el sesgo en el sistema de IA. La monitorización continua mediante algoritmos de ML ofrece una evaluación continua del riesgo tromboembólico entre los pacientes con FA, contribuyendo al seguimiento de la progresión de la enfermedad, monitorizando la respuesta al tratamiento y detectando con antelación cualquier cambio repentino en el estado de salud. Además, al mejorar el seguimiento mediante la predicción de los riesgos específicos del paciente, estos algoritmos pueden priorizar las visitas de seguimiento y las intervenciones, lo que en última instancia conduce a mejores resultados para los pacientes.

Como posibles limitaciones de este proyecto destaca el subregistro de diagnósticos, ya que, al tratarse de una extracción retrospectiva de variables, existe la posibilidad de un infradiagnóstico registrado, aun así, las variables fueron recogidas mediante la clasificación CIE-11, dando homogeneidad a los datos incluidos y analizados. Los autores utilizaron cohortes registradas en todos

sus análisis, que es un enfoque que ayuda a superar las limitaciones de comparabilidad que surgen debido a la heterogeneidad de los datos disponibles. Sin embargo, cabe señalar que el uso del sistema de registro y la organización territorial como base de este enfoque puede considerarse una limitación común. El diseño del estudio no permite responder a esta limitación. Las puntuaciones de riesgo tromboembólico y de FA son muy eficaces para determinar el riesgo de la población, pero suelen ser engañosas cuando se aplican a individuos. Esto es especialmente cierto en el caso de los pacientes de bajo riesgo. Debido al diseño observacional del estudio, no podemos demostrar la causalidad, y es posible que persistan factores de confusión residuales a pesar de un ajuste multivariable exhaustivo. En cuanto al uso de IA, es esencial la validación externa antes de adoptar e integrar eficazmente los sistemas de IA en la atención al paciente. Los modelos de IA entrenados en conjuntos de datos específicos podrían no generalizarse bien a diferentes poblaciones o entornos sanitarios, y el sobreajuste podría limitar su aplicabilidad. Además, es importante tener en cuenta que la correlación no implica necesariamente causalidad. El establecimiento de relaciones causales entre los factores de riesgo de FA y tromboembolia requiere más investigación y experimentación.

Los puntos fuertes del estudio incluyen el considerable número de casos, el largo seguimiento y el hecho de que el proyecto se realizó en población general utilizando un modelo estadístico validado que predice la probabilidad de padecer FA en función de sus covariables antes de la inclusión de los pacientes, con el fin de reducir un posible sesgo. También se incluyen los modelos de predicción, los conjuntos de datos de alta calidad y el estricto cumplimiento de las normas de privacidad de datos, así como el contexto clínico y el conocimiento del dominio, lo que facilita la interpretación de las razones que subyacen a sus predicciones. La incorporación de algoritmos de ML en el tratamiento clínico de las personas con alto riesgo y/o diagnóstico de FA aportan beneficios potenciales, como la evaluación personalizada del riesgo, el apoyo a la toma de decisiones y la mejora de la atención al paciente basándose en datos.

Esta tesis doctoral es de especial interés dados los distintos beneficios potenciales de los resultados que se han descrito en las diferentes secciones para el abordaje y el tratamiento de la FA como la estratificación del riesgo, la prevención de MACE y tromboembolismo. Es necesario traducir todas estas mediciones en acciones tempranas significativas, como un diagnóstico precoz, un tratamiento estructurado y la optimización de los factores de riesgo cardiovascular y las comorbilidades, para abordar la mejora de los resultados de los pacientes con FA. En AP, el uso de tecnologías sanitarias puede mejorar la detección de la FA evitando MACE especialmente entre las personas de alto riesgo.

8. Conclusiones

Conclusiones principales

1. Los individuos con mayor riesgo (Q4) de presentar FA tienen un riesgo similar al de los individuos con FA de padecer cardiopatía isquémica, ERC o arteriopatía periférica antes de su diagnóstico de FA.
2. La FA de nueva aparición se asocia a una mayor incidencia de MACE, ERC, deterioro cognitivo y mortalidad.
3. AdaBoost es el modelo más robusto para predecir MACE en pacientes con FA.
4. Los principales factores pronósticos de MACE son: índex de Charlson, cáncer, diabetes mellitus, EPOC, deterioro cognitivo, enfermedad vascular, CHA_2DS_2-VASc, Wells y CONUT.

Conclusiones secundarias

1. El NNC para detectar un nuevo caso de FA fue de 15.
2. El sexo femenino presenta más enfermedades de riesgo cardiovascular y comorbilidades.
3. El sexo femenino con nuevo diagnóstico de FA presenta mayor incidencia de MACE.
4. El 25,4 % de los pacientes con FA no está anticoagulado.
5. El riesgo de desnutrición es el doble entre los pacientes con FA y/o MACE.
6. La IA aporta más información sobre los MACE y mayor precisión respecto a la estadística tradicional.
7. La IA permite la optimización de decisiones y prevención de MACE en pacientes con FA.

9. Futuras líneas de investigación

La presente tesis doctoral pone en evidencia diferentes aspectos e intereses sobre los cuales se podrían seguir investigando.

Ante los resultados obtenidos, se podría considerar la creación de un nuevo *score* para la evaluación del riesgo trombótico en alto riesgo de FA y prevención de MACE. La aparición de nuevos factores de riesgo y su relevancia, hace plantearse este supuesto dado que la mayoría de los *score* existentes no consideran algunas de las variables obtenidas en este trabajo como el EPOC.

Para mejorar y optimizar los resultados de la IA sería conveniente obtener un conjunto de datos más diverso que incluya diferentes poblaciones de estudio, lo que permitiría la obtención de resultados mucho más eficaces y precisos. Teniendo en cuenta que la IA aprende con los algoritmos y variables será capaz de evaluar que parámetros serán más adecuados y más eficaces en la determinación MACE en pacientes con FA.

El papel que están teniendo a nivel mundial las nuevas tecnologías y la IA sugiere explorar y explotar más su cribage y detección precoz de FA (*smartwatch,* dispositivos manuales, parches cutáneos…) así como también en la prevención de MACE.

En pacientes con FA y/o MACE debería considerarse el cribado del estado nutricional como indicador de alarma sociosanitaria, ya que las dos etiologías son prevalentes en las personas ≥65 años y constituyen un factor de riesgo de MACE. Su detección puede prevenir situaciones de vulnerabilidad, carencia de soporte familiar y falta de recursos económicos. La creación de estrategias de trabajo conjunto entre trabajo social, nutrición y AP puede favorecer su detección temprana así como mejorar la calidad de vida de los pacientes.

10. Bibliografía

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11. Anexos

Anexo 1. Certificado comité de ética IDIAP

INFORME DEL COMITÈ D'ÈTICA D'INVESTIGACIÓ AMB MEDICAMENTS

Rosa Morros Pedrós, Presidenta del Comitè Ètic d'Investigació amb medicaments (CEIm) de l'IDIAP Jordi Gol.

CERTIFICA

Que aquest Comitè en la reunió del dia 30/11/2022, ha avaluat el projecte:

Codi CEIm: 22/243-P
Investigador IDIAP: Pedro Moltó **Investigador Principal:** Pedro Moltó Balado
Títol: Risc d'esdeveniments cardiovasculars adversos majors (MACE) en pacients amb fibril·lació auricular: Estudi retrospectiu en Atenció Primària

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Revisat i debatut el protocol per a realitzar l'estudi esmentat, considera que:

1. L'estudi avaluat compleix amb tots els requeriments metodològics i tècnics
2. Les competències i habilitats dels investigadors i els medis disponibles són els adequats per a realitzar l'estudi
3. L'estudi compleix amb els principis de la Declaració de Helsinki i els requeriments reglamentaris aplicables en aspectes ètics i de protecció de dades

El Comitè d'Ètica d'Investigació amb medicaments de l'IDIAPJGol considera el següent dictamen: **Aprovat**.

El CEIm de l'IDIAPJGol compleix amb les normes de BPC (CHMP/ICH/135/95) i amb la legislació vigent que regula el seu funcionament, i podeu consultar la composició dels seus membres en el següent enllaç: https://www.idiapjgol.org/index.php/ca/presentacio

Rosa Morros Pedrós
Presidenta
Comitè Ètic d'Investigació amb Medicaments
IDIAP Jordi Gol

Barcelona, 12/12/2022

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MORROS PEDRÓS

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Anexo 2. Comunicaciones orales y posters generados durante el trabajo

1. Título del trabajo: Aplicació d'Intel·ligència Artificial en la predicció d'Events Cardiovasculars Adversos Majors en Pacients amb Fibril·lació Auricular
   Nombre del congreso: 40º Jornades Mèdiques i de la Salut de les Terres de l'Ebre
   Ciudad de celebración: Tortosa
   Fecha de celebración: 22-23 de febrero de 2023
   Entidad organizadora: Acadèmia de Ciències Mèdiques de les Terres de l'Ebre
   Autores: Moltó Balado P, Reverté Villarroya S, Alonso Barberán V, Balado Albiol MT, Monclús Arasa C, Clua Espuny JL.
2. Título del trabajo: Relación de la insuficiencia cardíaca y los eventos cardiovasculares adversos mayores en los pacientes con fibrilación auricular
   Nombre del congreso: 45º Congreso Nacional SEMERGEN
   Ciudad de celebración: Valencia
   Fecha de celebración: 18-21 de octubre de 2023
   Entidad organizadora: Sociedad Española de Médicos de Atención Primaria (SEMERGEN)
   Autores: Moltó Balado P, Clua Espuny JL, Esteller Gimeno M, Pellicer Martínez S, Cervera Aparicio S, Reverté Villarroya S.
3. Título del trabajo: Estado de malnutrición como factor pronóstico de eventos cardiovasculares adversos mayores (MACE) en los pacientes con fibrilación auricular
   Nombre del congreso: 45º Congreso Nacional SEMERGEN
   Ciudad de celebración: Valencia
   Fecha de celebración: 18-21 de octubre de 2023
   Entidad organizadora: Sociedad Española de Médicos de Atención Primaria (SEMERGEN)
   Autores: Moltó Balado P, Clua Espuny JL, Monclús Arasa C, Balado Albiol MT, Reverté Villarroya S.
4. Título del trabajo: Combined Major Adverse Cardiovascular Events (MACE) and Atrial Fibrillation: a Retrospective Primary Care Cohort Study.
   Nombre del congreso: 28 th WONCA Europe Conference
   Ciudad de celebración: Bruselas, Bélgica
   Fecha de celebración: 7 - 10 de junio de 2023
   Entidad organizadora: World Organization of Family Doctors (WONCA)
   Autores: Molto Balado P, Clua Espuny JL, Hernandez Pinilla A, Reverte Vilarroya S, Monclus Arasa C, Satue Gracia E.M., Lucas Noll J, Martín Lujan F, on behalf EBRICTUS Group Collaborators.
5. Título del trabajo: The stroke care in outpatient settings: translating research into meaningful actions. Systematic review.
   Nombre del congreso: 28 th WONCA Europe Conference
   Ciudad de celebración: Bruselas, Bélgica

Fecha de celebración: 7 - 10 de junio de 2023
Entidad organizadora: World Organization of Family Doctors (WONCA)
Autores: Clua Espuny JL, Lucas Noll J, Panisello Tafalla A, Hernandez Pinilla A, Satue Gracia EM, Molto Balado P, Reverte Villarroya S, Martin Lujan FM, Lleixà Fortuño MM, Carles Làvila M, on behalf PREFATE Project Investigators.

6. Título del trabajo: Atrial fibrillation, stroke incidence and cognitive decline: a multicenter, retrospective Primary Care Cohort Study.
   Nombre del congreso: 28 th WONCA Europe Conference
   Ciudad de celebración: Bruselas, Bélgica
   Fecha de celebración: 7 - 10 de junio de 2023
   Entidad organizadora: World Organization of Family Doctors (WONCA)
   Autores: Hernandez-Pinilla A, Clua Espuny JL, Satue Gracia EM, Molto Balado P, Reverte Villarroya S, Lucas Noll J, Martin Lujan FM, on behalf PREFATE Project Investigators.
7. Título del trabajo: Proyecto PREFATE: Diagnóstico precoz de fibrilación auricular, ictus silente y deterioro cognitivo en personas de alto riesgo.
   Nombre del congreso: XLIII Congreso de la semFYC
   Ciudad de celebración: Donostia
   Fecha de celebración: 11-13 de mayo de 2023
   Entidad organizadora: Sociedad Española de Medicina de Familia y Comunitaria (semFYC)
   Autores: Hernandez Pinilla A, Clua Espuny JL, Satué Gracia EM, Martín Luján F, Lucas Noll J, Moltó Balado P.
8. Título del trabajo: Los eventos adversos cardiovasculares mayores (MACE) y la fibrilación auricular: estudio retrospectivo de cohorte en atención primaria.
   Nombre del congreso: XLIII Congreso de la semFYC
   Ciudad de celebración: Donostia
   Fecha de celebración: 11-13 de mayo de 2023
   Entidad organizadora: Sociedad Española de Medicina de Familia y Comunitaria (semFYC)
   Autores: Moltó Balado P, Clua Espuny JL, Monclús Arasa C, Hernandez Pinilla A, Reverté Villarroya S, Grupo de Investigación Ebrictus (AGAUR).
9. Título del trabajo: Combinació d'esdeveniments cardiovasculars adversos majors i fibril·lació auricular: Estudi retrospectiu de cohorts d'atenció primària
   Nombre del congreso: 39º Jornades Mèdiques i de la Salut de les Terres de l'Ebre
   Ciudad de celebración: Tortosa
   Fecha de celebración: 2-3 de marzo de 2023
   Entidad organizadora: Acadèmia de Ciències Mèdiques de les Terres de l'Ebre
   Autores: Moltó Balado P, Reverté Villarroya S, Monclús Arasa C, Balado Albiol MT, Carot Domènech J, Clua Espuny JL.

Anexo 3. Premios

Mejor proyecto de investigación en ciencias de la salud 39º Jornadas Médicas de les Terres de l'Ebre

Filial de Tortosa i Terres de L'Ebre

L'Acadèmia de Ciències Mèdiques de les Terres de l'Ebre

de l'Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears

Certifica que:

Moltó Balado, P.; Reverté Villarroya, S.; Monclús Arasa, C.; Balado Albiol, M.T.; Carot Domènech, J. i Clua Espuny, J.L.

han estat guardonats amb el premi al millor projecte d'investigació en Ciències de la Salut en l'àmbit de les Terres de l'Ebre amb:

Combinació d'esdeveniments cardiovasculars adversos majors i fibril·lació auricular: Estudi retrospectiu de cohorts d'atenció primària

presentat a les 39 Jornades Mèdiques i de la Salut de les Terres de l'Ebre, celebrat a Tortosa, els dies 2 i 3 de març de 2023.

Tortosa, 3 de març de 2023.

Dr. Pau Margalef Benaiges.
President Filial de Tortosa i Terres de l'Ebre.
Acadèmia Ciències Mèdiques i de la Salut de Catalunya i de Balears.

L'Acadèmia. Major de Can Caralleu, 1-7. 08017 – Barcelona. Tel. 93 203 10 50 – Fax 93 212 35 69 – www.academia.cat

5º Premio al Mejor Trabajo de Investigación Original de residentes

"SEMERGEN, contigo 50 años más"
45 Congreso Nacional SEMERGEN
Palacio de Congresos de VALENCIA del 18 al 21 de Octubre 2023
SEMERGEN 50 AÑOS CONTIGO 1973 - 2023
SEMERGEN AP

CERTIFICADO DE PREMIO

Residente
5º Premio al Mejor Trabajo de Investigación Original

Título:

"ESTADO DE MALNUTRICIÓN COMO FACTOR PRONÓSTICO DE EVENTOS CARDIOVASCULARES ADVERSOS MAYORES (MACE) EN LOS PACIENTES CON FIBRILACIÓN AURICULAR"

del/de los autor/es:

P. Moltó Balado, J. Clua Espuny, C. Monclús Arasa, M. Balado Albiol, S. Reverté Villarroya

presentado en el

45º Congreso Nacional SEMERGEN

celebrado del 18 de octubre al 21 de octubre de 2023

Valencia, 21 de Octubre de 2023

Dr. D. José Polo García
Presidente de SEMERGEN

Mejor proyecto de investigación en ciencias de la salud 40º Jornadas Médicas de les Terres de l'Ebre

Filial de Tortosa i Terres de L'Ebre

L'Acadèmia de Ciències Mèdiques de les Terres de l'Ebre

de l'Acadèmia de Ciències Mèdiques i de la Salut de Catalunya i de Balears

Certifica que:

Moltó Balado, P. ; Reverté Villarroya, S. ; AlonsoBarberán, V. ; Balado Albiol, M.T. ; Monclús Arasa, C. ; Clua Espuny, J.L.

han estat guardonats amb el premi al millor projecte d'investigació en Ciències de la Salut en l'àmbit de les Terres de l'Ebre amb:

Aplicació d'Intel·ligència Artificial en la predicció d'Esdeveniments Cardiovasculars Adversos Majors en Pacients amb Fibril·lació Auricular.

presentat a les 40 Jornades Mèdiques i de la Salut de les Terres de l'Ebre, celebrat a Tortosa, els dies 22 i 23 de febrer de 2024.

Tortosa, 23 de febrer de 2024.

Dr. Pau Margalef Benaiges.
President Filial de Tortosa i Terres de l'Ebre.
Acadèmia Ciències Mèdiques i de la Salut de Catalunya i de Balears.

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