Nouveautés en FA : aspects pratiques pour le neurologue

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DISCLOSURES

RESEARCH FUNDING

- Kathleen & Dr Henry Barnett Chair in Stroke Research
- Edward and Alma Saraydar Neurosciences Fund
- London Health Sciences Foundation
- Heart & Stroke Foundation (Canada)
- Brain Canada
- Canadian Stroke Consortium
- AMOSO Opportunities & Innovation Funds
- Western University grants
- Lawson Health Research Institute grants
- Department of Medicine Research Competition, Western U.
- Boehringer Ingelheim, Alexion, Genzyme, Medtronic

SPEAKER AND/OR CONSULTING HONORARIA

- Boehringer Ingelheim
- Pfizer
- Bayer
- β Innovation
- Gore

EDITORIAL ROLES

- STROKE: Editorial Board Member & Neurocardiology Section Editor
- JAHA: Editorial Board Member & Associate Editor
- NEUROLOGY: Editorial Board Member

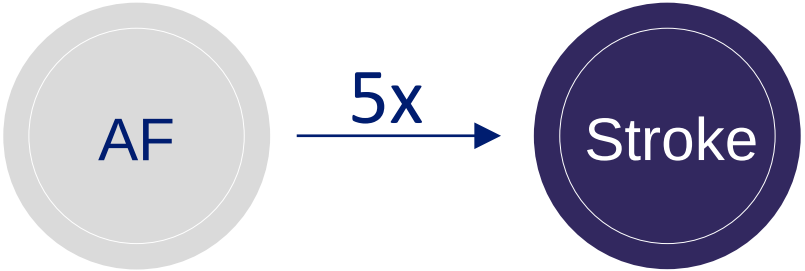
OVERVIEW

The Implications of Looking For and Finding AF in Stroke Patients

1. Device-detected AF in stroke patients (AFDAS) is a unique type of AF
2. Possible explanations
3. The role of anticoagulation

AFib is Bad

High-risk cardiac arrhythmia



Anticoagulants reduce stroke risk by 65%

Hart, Ann Intern Med 2007;146:857

Current Status of Cardiac Monitoring

Prolonged Cardiac Monitoring is the Key

CRYSTAL-AF EMBRACE 2014

Higher AF detection rates

International Guidelines

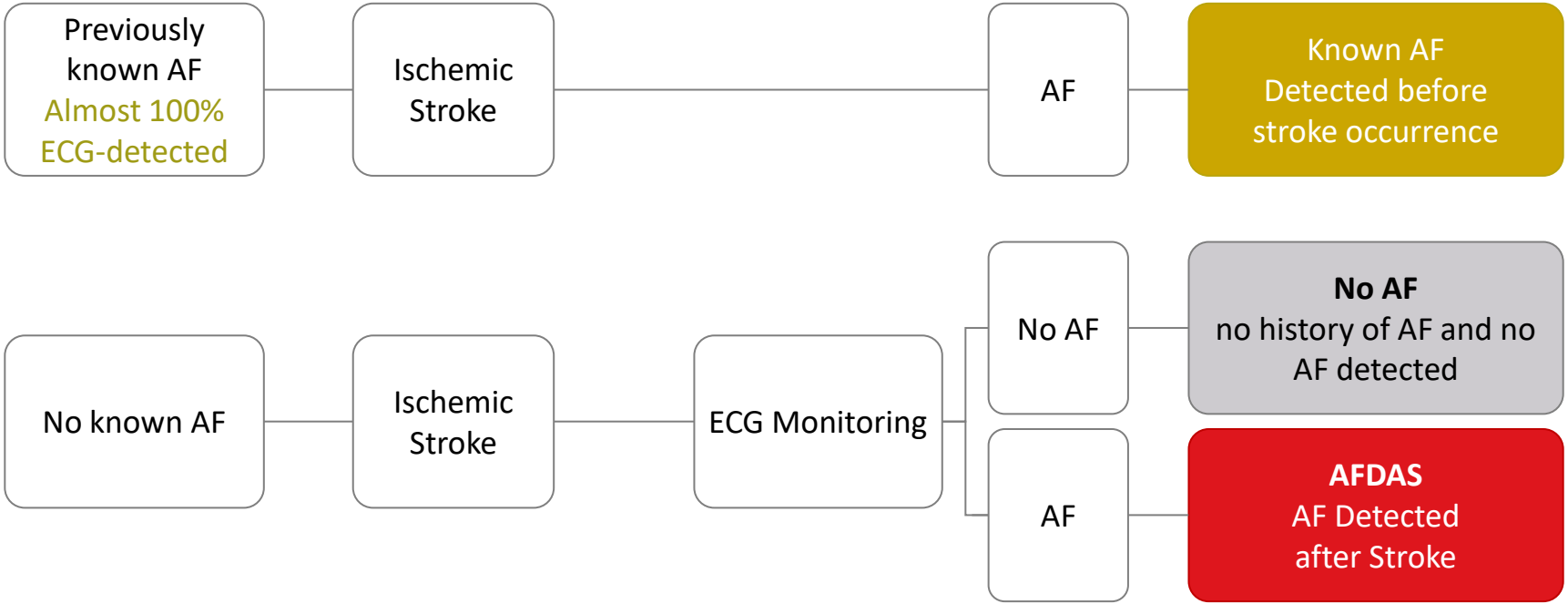
Recommending PCM

Real World Implementation

Generalized Uptake of PCM

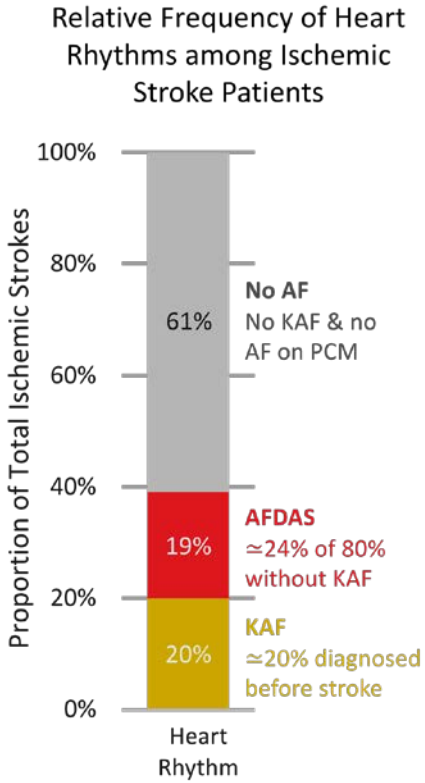
AF Detected After Stroke (AFDAS)

AF detected on Prolonged Cardiac Monitoring (PCM) post-stroke or TIA



AF Detection post-Stroke or TIA

If all Patients Received Prolonged Cardiac Monitoring



1.3 to **1.5** million

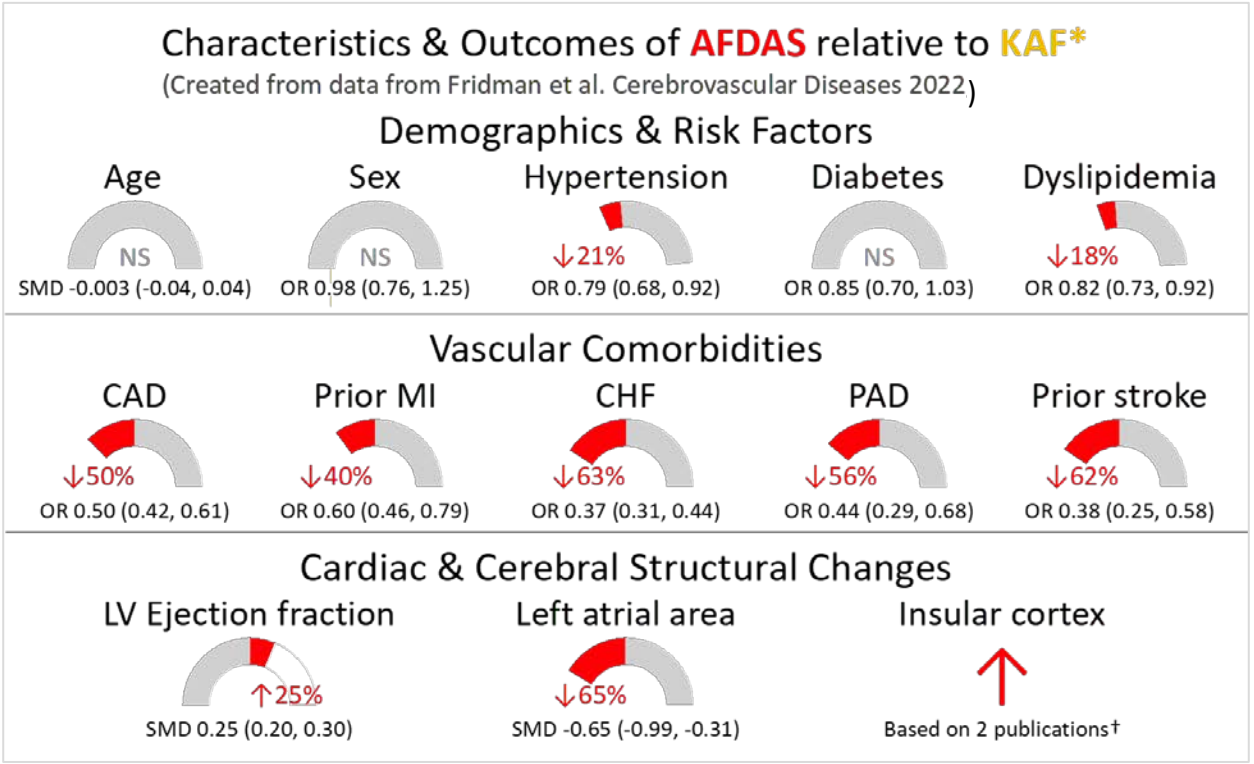
New AFDAS

each year

Sposato et al. Lancet Neurol 2015;14:377, Sposato et al. Stroke 2022;53:e94-e103.

New vs. Known AF in Stroke Patients

Lower burden of Risk Factors, Structural Heart Disease, and Risk Profile

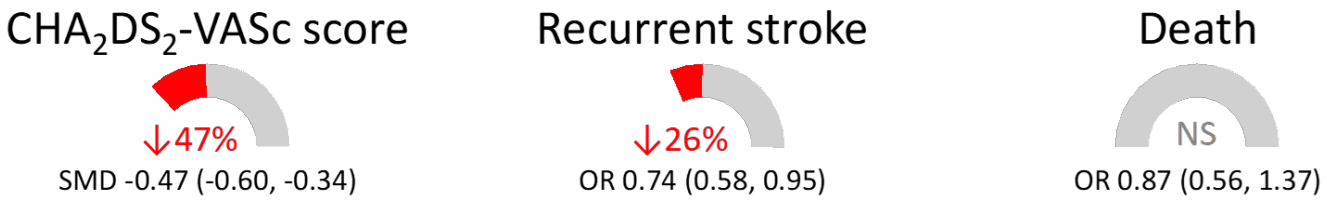


New vs. Known AF in Stroke Patients

Lower burden of Risk Factors, Structural Heart Disease, and Risk Profile

Characteristics & Outcomes of AFDAS relative to Known AF

(Created from data from Fridman et al. Cerebrovascular Diseases 2022)



SMD: standardized mean difference, OR: odds ratio

Observational studies with analyses adjusted for multiple variables, including the use of OACs

Conclusion #1

AFDAS and KAF are different

Risk factors

Cardiovascular comorbidities

Structural heart disease

Stroke recurrence risk

But why?

Why is AFDAS different from other AFs?

The role of burden and vascular risk

AF-related Embolic Stroke risk = AF burden * vascular risk * structural heart disease

Maximum Daily AF Duration	CHA_2DS_2-VASc Score: 0 n=2922 (13.4%)	1 n=2151 (9.9%)	2 n=4554 (20.9%)	3-4 n=7164 (32.9%)	≥5 n=4977 (22.9%)
No AF n=16815 (77.2%)	0.33% 40 events	0.62% 46 events	0.70% 95 events	0.83% 139 events	1.79% 157 events
AF 6 min–23.5 h n=3381 (15.5%)	0.52% 11 events	0.32% 4 events	0.62% 17 events	1.28% 42 events	2.21% 36 events
AF >23.5h n=1572 (7.2%)	0.86% 4 events	0.50% 3 events	1.52% 19 events	1.77% 28 events	1.68% 13 events

21 768 nonanticoagulated patients with cardiovascular implantable electronic devices from the Optum electronic health record deidentified database (2007–2017) were linked to the Medtronic CareLink database

Kaplan et al. Circulation 2019;20:1639

Why is AFDAS different from other AFs?

The role of burden and vascular risk

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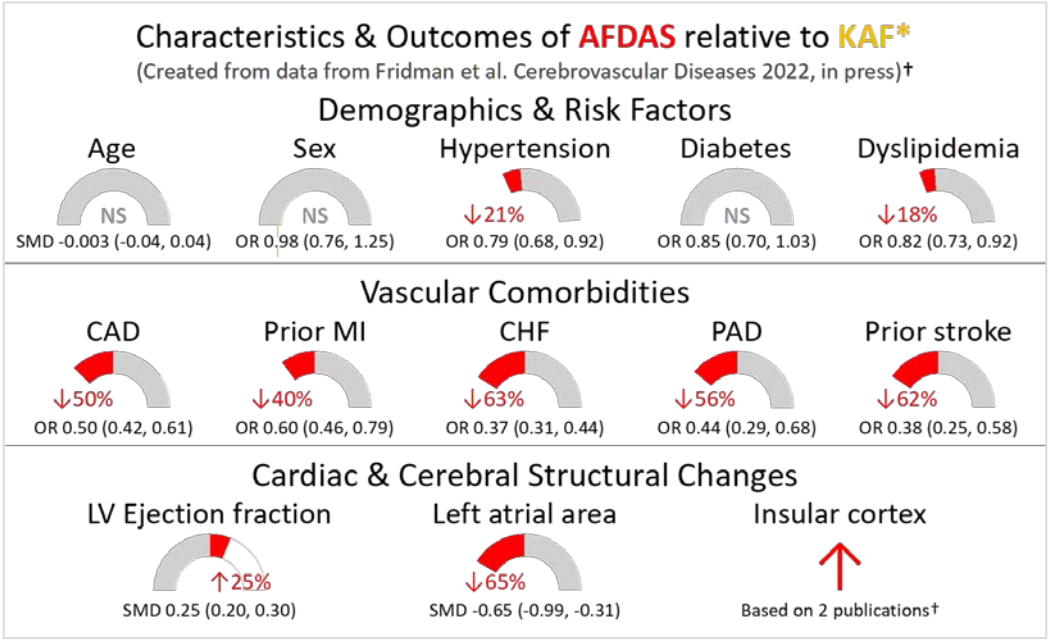

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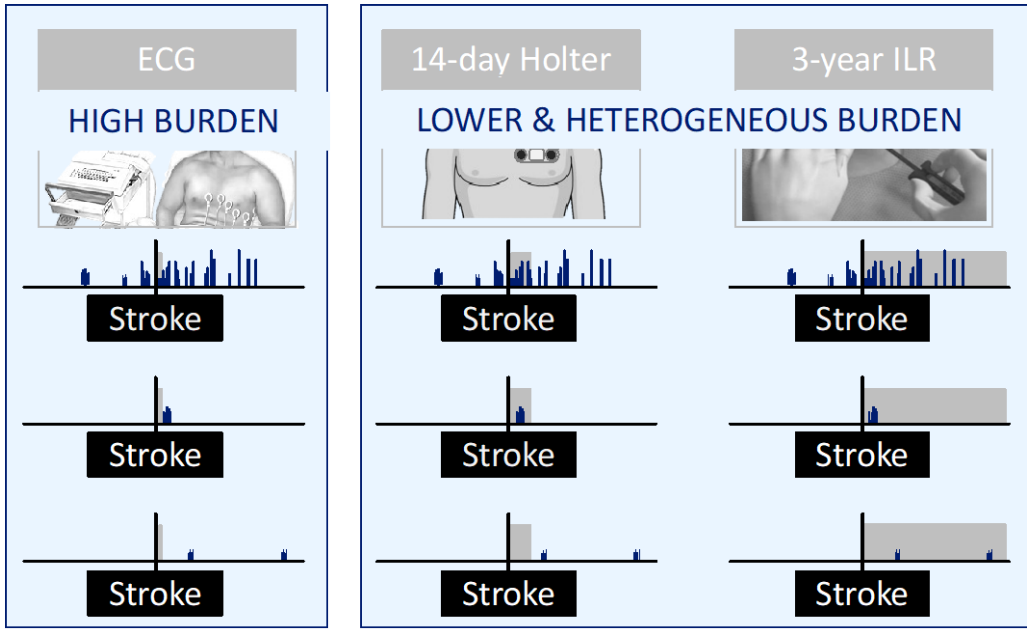
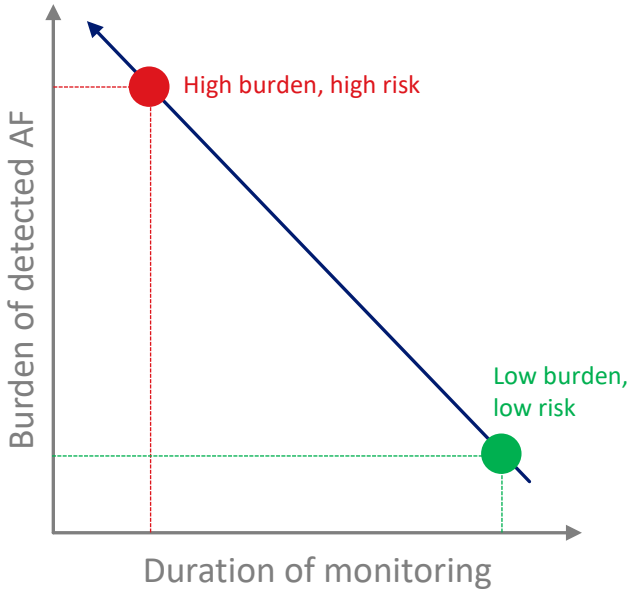
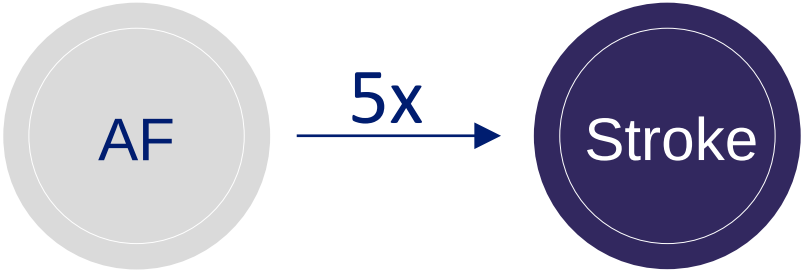




Sposato & Andrade. Neurology 2022; 98(19):781-783.

AFib is Bad

High-risk cardiac arrhythmia



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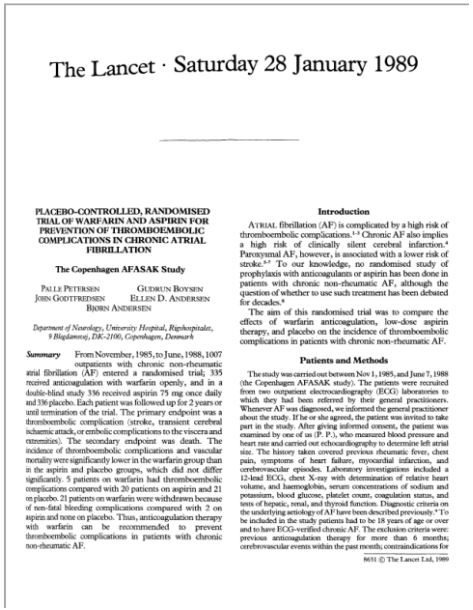
From ECG-based to PCM-based AF Diagnoses

Historical Understanding of Atrial Fibrillation Risk

AFASAK, 1989



The Lancet · Saturday 28 January 1989

PLACEBO-CONTROLLED, RANDOMISED TRIAL OF WARFARIN AND ASPIRIN FOR PREVENTION OF THROMBOEMBOLIC COMPLICATIONS IN CHRONIC ATRIAL FIBRILLATION

The Copenhagen AFASAK Study

PALLE PETERSEN, JØRN GODTFREDSEN, GUDRUN BOYSEN, ELLEN D. ANDERSEN, BJØRN ANDERSEN

Department of Neurology, University Hospital, Rigshospitalet, 9 Blegdamsvej, DK-2100, Copenhagen, Denmark

Summary From November, 1985, to June, 1988, 1007 outpatients with chronic non-rheumatic atrial fibrillation (AF) entered a randomised trial; 335 received anticoagulation with warfarin openly, and in a double-blind study 336 received aspirin 75 mg once daily and 336 placebo. Each patient was followed up for 2 years or until termination of the trial. The primary endpoint was a thromboembolic complication (stroke, transient cerebral ischaemic attack, or embolic complications to the viscera and extremities). The secondary endpoint was death. The incidence of thromboembolic complications and vascular mortality were significantly lower in the warfarin group than in the aspirin and placebo groups, which did not differ significantly. 5 patients on warfarin had thromboembolic complications compared with 20 patients on aspirin and 21 on placebo. 21 patients on warfarin were withdrawn because of non-fatal bleeding complications compared with 2 on aspirin and none on placebo. Thus, anticoagulation therapy with warfarin can be recommended to prevent thromboembolic complications in patients with chronic non-rheumatic AF.

Introduction

ATRIAL fibrillation (AF) is complicated by a high risk of thromboembolic complications.[1-3] Chronic AF also implies a high risk of clinically silent cerebral infarction.[4] Paroxysmal AF, however, is associated with a lower risk of stroke.[2,5] To our knowledge, no randomised study of prophylaxis with anticoagulants or aspirin has been done in patients with chronic non-rheumatic AF, although the question of whether to use such treatment has been debated for decades.[6]

The aim of this randomised trial was to compare the effects of warfarin anticoagulation, low-dose aspirin therapy, and placebo on the incidence of thromboembolic complications in patients with chronic non-rheumatic AF.

Patients and Methods

The study was carried out between Nov 1, 1985, and June 7, 1988 (the Copenhagen AFASAK study). The patients were recruited from two outpatient electrocardiography (ECG) laboratories to which they had been referred by their general practitioners. Whenever AF was diagnosed, we informed the general practitioner about the study. If he or she agreed, the patient was invited to take part in the study. After giving informed consent, the patient was examined by one of us (P. P.), who measured blood pressure and heart rate and carried out echocardiography to determine left atrial size. The history taken covered previous rheumatic fever, chest pain, symptoms of heart failure, myocardial infarction, and cerebrovascular episodes. Laboratory investigations included a 12-lead ECG, chest X-ray with determination of relative heart volume, and haemoglobin, serum concentrations of sodium and potassium, blood glucose, platelet count, coagulation status, and tests of hepatic, renal, and thyroid function. Diagnostic criteria on the underlying aetiology of AF have been described previously.[6] To be included in the study patients had to be 18 years of age or over and to have ECG-verified chronic AF. The exclusion criteria were: previous anticoagulation therapy for more than 6 months; contraindications for cerebrovascular events within the past month; contraindications for

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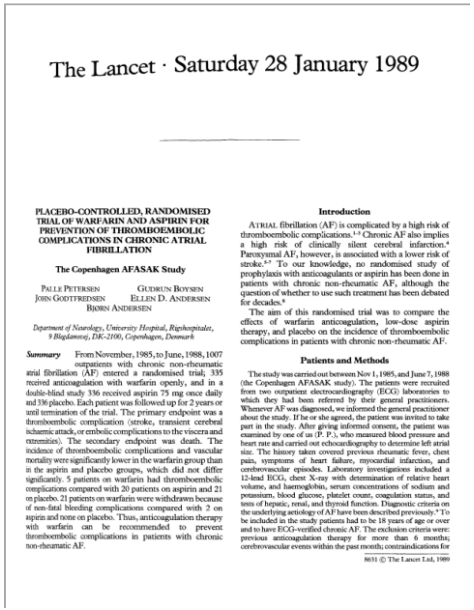
AFASAK, 1989



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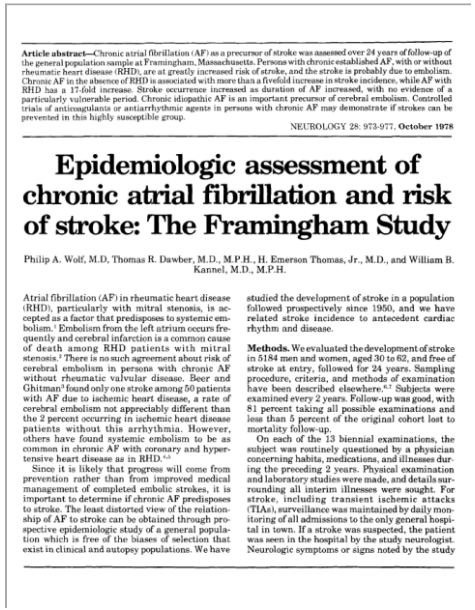
Framingham, 1978



Article abstract—Chronic atrial fibrillation (AF) as a precursor of stroke was assessed over 24 years of follow-up of the general population sample at Framingham, Massachusetts. Persons with chronic established AF, with or without rheumatic heart disease (RHD), are at greatly increased risk of stroke, and the stroke is probably due to embolism. Chronic AF in the absence of RHD is associated with more than a fivefold increase in stroke incidence, while AF with RHD has a 17-fold increase. Stroke occurrence increased as duration of AF increased, with no evidence of a particularly vulnerable period. Chronic idiopathic AF is an important precursor of cerebral embolism. Controlled trials of anticoagulants or antiarrhythmic agents in persons with chronic AF may demonstrate if strokes can be prevented in this highly susceptible group.

NEUROLOGY 28: 973-977, **October 1978**

Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: The Framingham Study

Philip A. Wolf, M.D, Thomas R. Dawber, M.D., M.P.H., H. Emerson Thomas, Jr., M.D., and William B. Kannel, M.D., M.P.H.

Atrial fibrillation (AF) in rheumatic heart disease (RHD), particularly with mitral stenosis, is accepted as a factor that predisposes to systemic embolism.[1] Embolism from the left atrium occurs frequently and cerebral infarction is a common cause of death among RHD patients with mitral stenosis.[2] There is no such agreement about risk of cerebral embolism in persons with chronic AF without rheumatic valvular disease. Beer and Ghitman[3] found only one stroke among 50 patients with AF due to ischemic heart disease, a rate of cerebral embolism not appreciably different than the 2 percent occurring in ischemic heart disease patients without this arrhythmia. However, others have found systemic embolism to be as common in chronic AF with coronary and hypertensive heart disease as in RHD.[4,5]

Since it is likely that progress will come from prevention rather than from improved medical management of completed embolic strokes, it is important to determine if chronic AF predisposes to stroke. The least distorted view of the relationship of AF to stroke can be obtained through prospective epidemiologic study of a general population which is free of the biases of selection that exist in clinical and autopsy populations. We have studied the development of stroke in a population followed prospectively since 1950, and we have related stroke incidence to antecedent cardiac rhythm and disease.

Methods. We evaluated the development of stroke in 5184 men and women, aged 30 to 62, and free of stroke at entry, followed for 24 years. Sampling procedure, criteria, and methods of examination have been described elsewhere.[6,7] Subjects were examined every 2 years. Follow-up was good, with 8.1 percent taking all possible examinations and less than 5 percent of the original cohort lost to mortality follow-up.

On each of the 13 biennial examinations, the subject was routinely questioned by a physician concerning habits, medications, and illnesses during the preceding 2 years. Physical examination and laboratory studies were made, and details surrounding all interim illnesses were sought. For stroke, including transient ischemic attacks (TIAs), surveillance was maintained by daily monitoring of all admissions to the only general hospital in town. If a stroke was suspected, the patient was seen in the hospital by the study neurologist. Neurologic symptoms or signs noted by the study

Framingham, 1991

Atrial Fibrillation as an Independent Risk Factor for Stroke: The Framingham Study

Philip A. Wolf, MD; Robert D. Abbott, PhD; and William B. Kannel, MD

The impact of nonrheumatic atrial fibrillation, hypertension, coronary heart disease, and cardiac failure on stroke incidence was examined in 5,070 participants in the Framingham Study after 34 years of follow-up. Compared with subjects free of these conditions, the age-adjusted incidence of stroke was more than doubled in the presence of coronary heart disease ($p < 0.001$) and more than trebled in the presence of hypertension ($p < 0.001$). There was a more than fourfold excess of stroke in subjects with cardiac failure ($p < 0.001$) and a near fivefold excess when atrial fibrillation was present ($p < 0.001$). In persons with coronary heart disease or cardiac failure, atrial fibrillation doubled the stroke risk in men and trebled the risk in women. With increasing age the effects of hypertension, coronary heart disease, and cardiac failure on the risk of stroke became progressively weaker ($p < 0.05$). Advancing age, however, did not reduce the significant impact of atrial fibrillation. For persons aged 80–89 years, atrial fibrillation was the sole cardiovascular condition to exert an independent effect on stroke incidence ($p < 0.001$). The attributable risk of stroke for all cardiovascular contributors decreased with age except for atrial fibrillation, for which the attributable risk increased significantly ($p < 0.01$), rising from 1.5% for those aged 50–59 years to 23.5% for those aged 80–89 years. While these findings highlight the impact of each cardiovascular condition on the risk of stroke, the data suggest that the elderly are particularly vulnerable to stroke when atrial fibrillation is present. The powerful independent effect of atrial fibrillation reported here is in accord with the findings of recent randomized clinical trials in which >50% of stroke events were prevented by warfarin anticoagulation. (*Stroke* 1991;22:983–988)

Although hypertension is the strongest risk factor for stroke, age and the presence of other risk factors may modify or enhance the effect of increased blood pressure on stroke occurrence.[1-4] Impaired cardiac function, overt or occult, increases stroke incidence at all levels of blood pressure. In hypertensive persons coronary heart disease, cardiac failure, and particularly atrial fibrillation are associated with increased stroke risk.[5-7]

Atrial fibrillation, which is frequently associated with hypertension, coronary heart disease, and cardiac failure, becomes increasingly prevalent among persons aged >70 years.[8] It has been suggested that atrial fibrillation is a risk "marker" for stroke and that the increased stroke incidence in persons with this arrhythmia is a result of age and associated cardiovascular abnormalities.[9,10] To help address this issue, we have extended our previous study and examined in detail the relative impacts of hypertension, coronary heart disease, cardiac failure, and atrial fibrillation on the incidence of stroke in the Framingham Study.[4] We took advantage of the 110 additional initial stroke events, and additional coronary heart disease and cardiac failure cases occurring during the 4 further years of follow-up, to enhance the analysis of the relative importance of each of the cardiovascular contributors to stroke with advancing age.

From the Department of Neurology (P.A.W.) and the Section of Preventive Medicine and Epidemiology, Evans Memorial Department of Clinical Research and Department of Medicine, University Hospital (P.A.W., W.B.K.), Boston University School of Medicine, Boston, Mass. and the Division of Biostatistics (R.D.A.), University of Virginia School of Medicine, Charlottesville, Va.

Supported in part by National Institute of Neurological Disorders and Stroke Grant 2-RO1-NS-17950 and National Heart, Lung, and Blood Institute Contract NIH-NOI-HC-38038.

Address for reprints: Philip A. Wolf, MD, Boston University School of Medicine, 80 East Concord Street, B608, Boston, MA 02118.

Received December 21, 1990; accepted April 23, 1991.

Subjects and Methods

Since 1948, the Framingham Study has biennially followed 5,209 men and women for the development of cardiovascular disease. For this report, 5,070 men and women free of cardiovascular disease (including atrial fibrillation) at study enrollment were examined every 2 years during a 34-year follow-up period. Sampling procedures, response rates and follow-up, and methods of examination have been described elsewhere.[11]

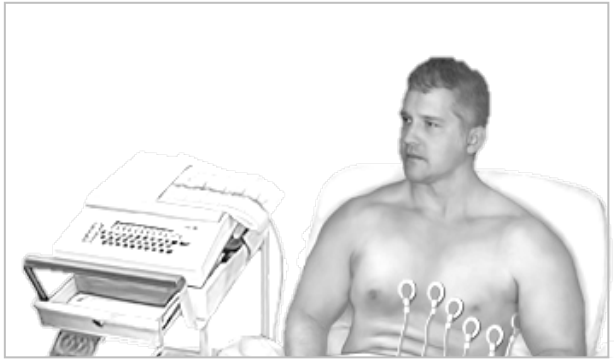
Wolf PA et al. Neurology 1978;28:973-977 | Wolf PA et al. Stroke 1991;22:983 | Petersen P et al. The Lancet 1989 ;1(8631):175-179 | Singer DA et al. New Eng J Med 1990; 29:1505-11

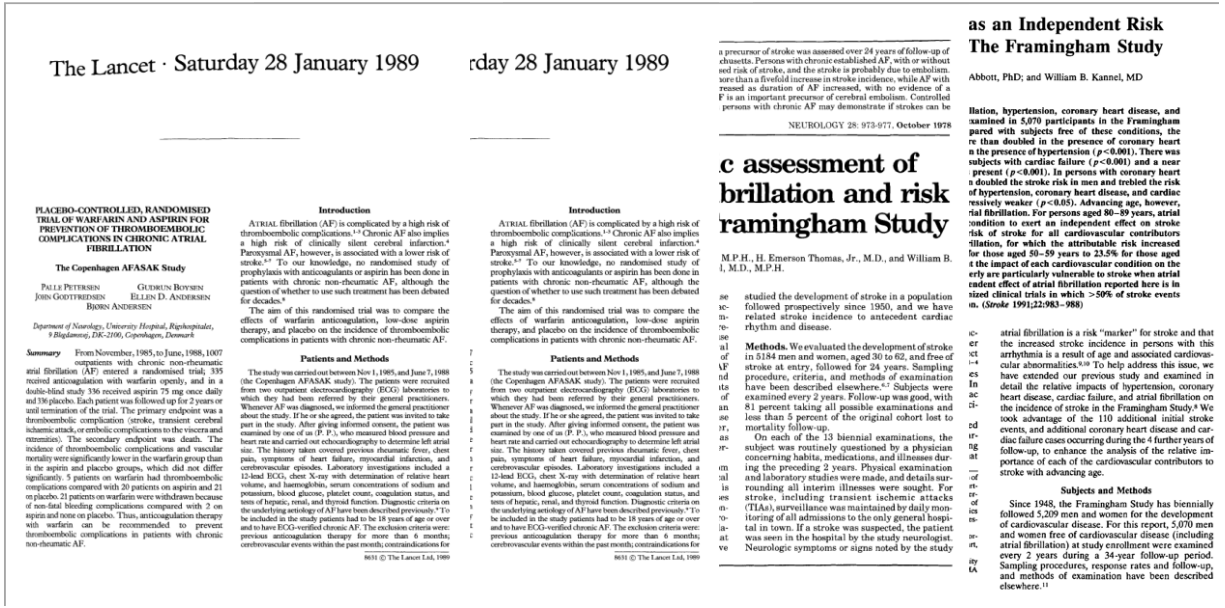
From ECG-based to PCM-based AF Diagnoses

Historical Understanding of Atrial Fibrillation Risk

Historical knowledge

ECG-based AF diagnosis





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Summary

Introduction

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Stroke. 1991;22:983-988

Abbott, PhD; and William B. Kannel, MD

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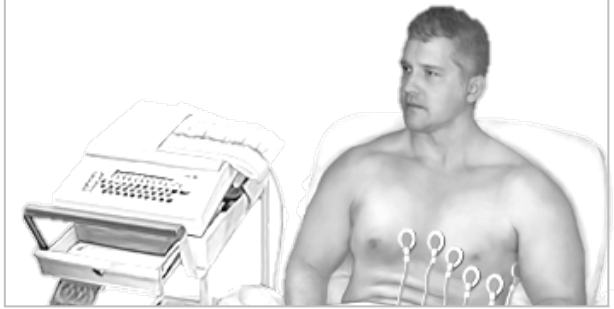
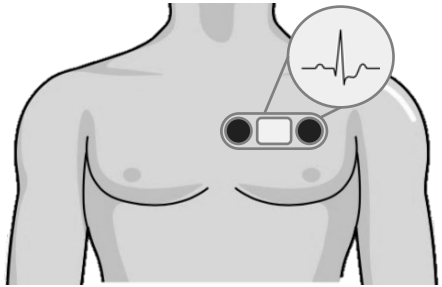
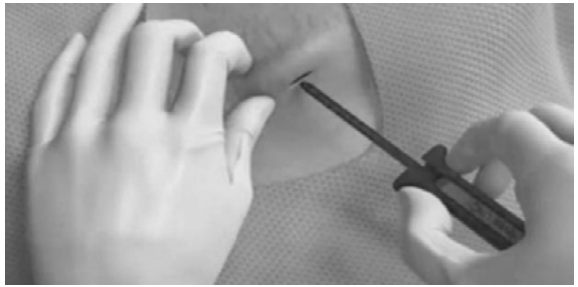
From ECG-based to PCM-based AF Diagnoses

Historical Understanding of Atrial Fibrillation Risk

Historical knowledge

Most of the new AFibs we currently deal with

ECG	14-day Holter	3- to 5-year ILR
		

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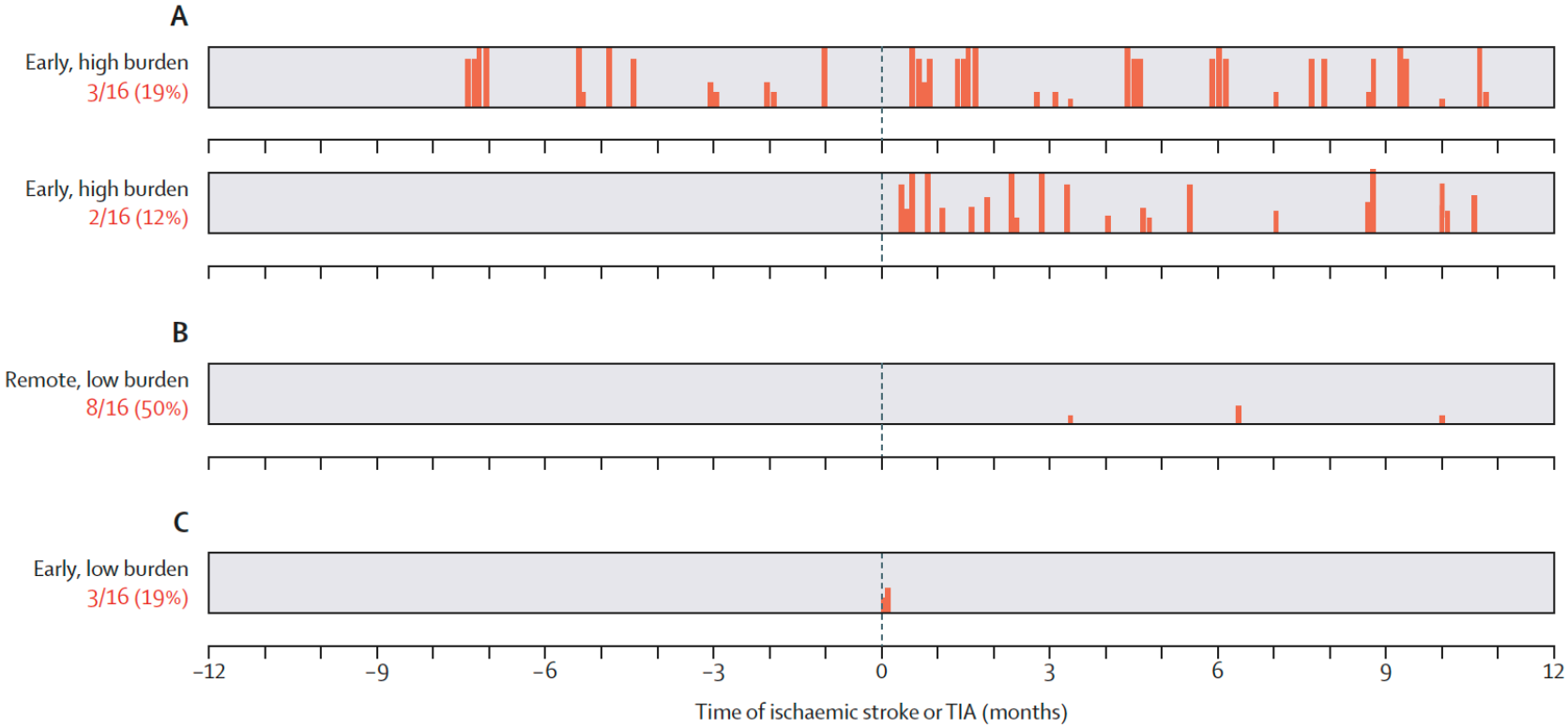
Subtypes of AFDAS

Based on Studies of Implantable Devices



Sposato, Field, Schnabel, Wachter, Andrade, Hill et al. Lancet Neurol 2023, published online on October 12, 2023

DELIMIT AF-STROKE

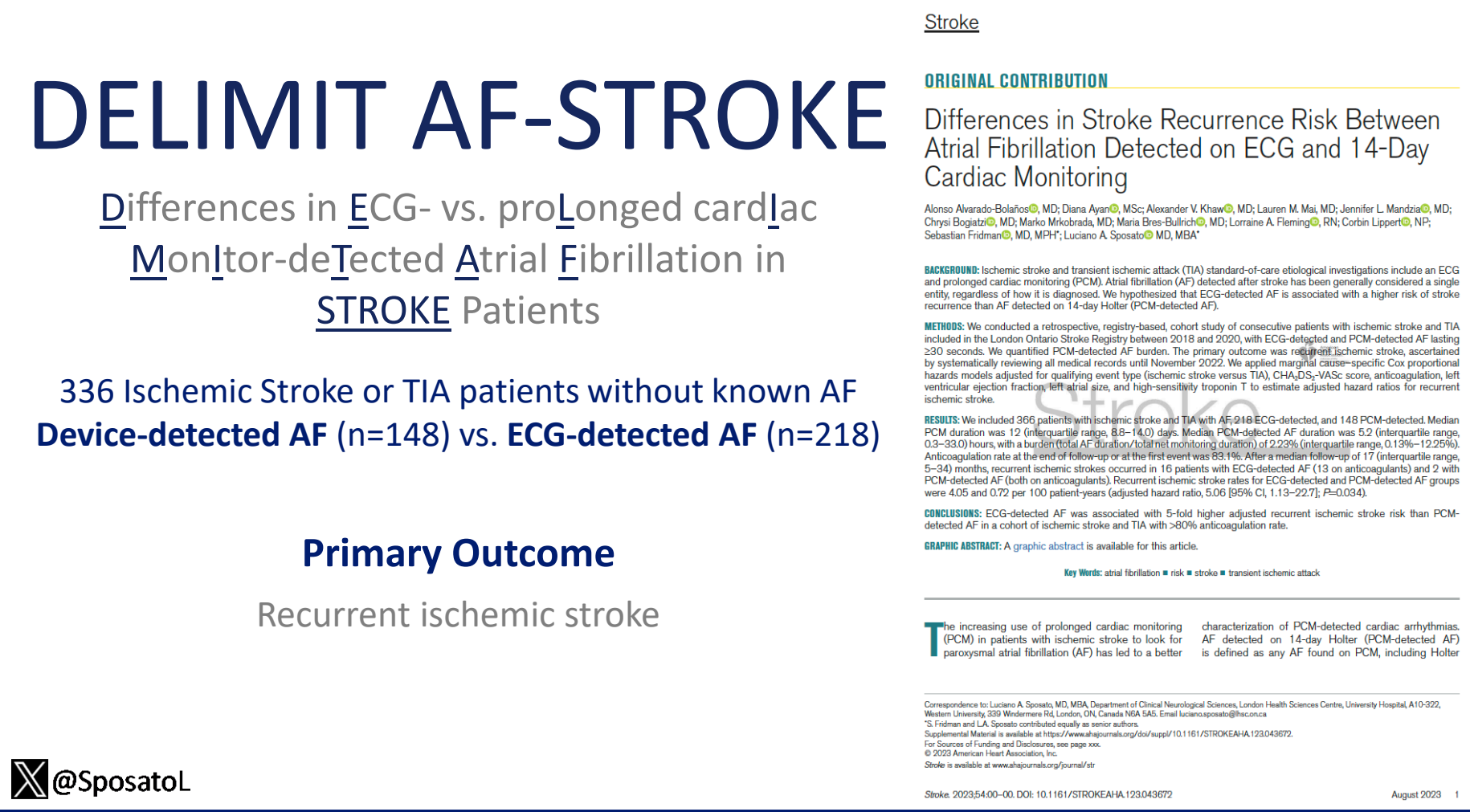
Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

336 Ischemic Stroke or TIA patients without known AF
Device-detected AF (n=148) vs. **ECG-detected AF** (n=218)

Primary Outcome

Recurrent ischemic stroke

@SposatoL



Stroke

ORIGINAL CONTRIBUTION

Differences in Stroke Recurrence Risk Between Atrial Fibrillation Detected on ECG and 14-Day Cardiac Monitoring

Alonso Alvarado-Bolaños, MD; Diana Ayan, MSc; Alexander V. Khaw, MD; Lauren M. Mai, MD; Jennifer L. Mandzia, MD; Chrysi Bogiatzi, MD; Marko Mrkobrada, MD; Maria Bres-Bullrich, MD; Lorraine A. Fleming, RN; Corbin Lippert, NP; Sebastian Fridman, MD, MPH*; Luciano A. Sposato MD, MBA*

BACKGROUND: Ischemic stroke and transient ischemic attack (TIA) standard-of-care etiological investigations include an ECG and prolonged cardiac monitoring (PCM). Atrial fibrillation (AF) detected after stroke has been generally considered a single entity, regardless of how it is diagnosed. We hypothesized that ECG-detected AF is associated with a higher risk of stroke recurrence than AF detected on 14-day Holter (PCM-detected AF).

METHODS: We conducted a retrospective, registry-based, cohort study of consecutive patients with ischemic stroke and TIA included in the London Ontario Stroke Registry between 2018 and 2020, with ECG-detected and PCM-detected AF lasting ≥30 seconds. We quantified PCM-detected AF burden. The primary outcome was recurrent ischemic stroke, ascertained by systematically reviewing all medical records until November 2022. We applied marginal cause–specific Cox proportional hazards models adjusted for qualifying event type (ischemic stroke versus TIA), CHA_2DS_2-VASc score, anticoagulation, left ventricular ejection fraction, left atrial size, and high-sensitivity troponin T to estimate adjusted hazard ratios for recurrent ischemic stroke.

RESULTS: We included 366 patients with ischemic stroke and TIA with AF, 218 ECG-detected, and 148 PCM-detected. Median PCM duration was 12 (interquartile range, 8.8–14.0) days. Median PCM-detected AF duration was 5.2 (interquartile range, 0.3–33.0) hours, with a burden (total AF duration/total net monitoring duration) of 2.23% (interquartile range, 0.13%–12.25%). Anticoagulation rate at the end of follow-up or at the first event was 83.1%. After a median follow-up of 17 (interquartile range, 5–34) months, recurrent ischemic strokes occurred in 16 patients with ECG-detected AF (13 on anticoagulants) and 2 with PCM-detected AF (both on anticoagulants). Recurrent ischemic stroke rates for ECG-detected and PCM-detected AF groups were 4.05 and 0.72 per 100 patient-years (adjusted hazard ratio, 5.06 [95% CI, 1.13–22.7]; P=0.034).

CONCLUSIONS: ECG-detected AF was associated with 5-fold higher adjusted recurrent ischemic stroke risk than PCM-detected AF in a cohort of ischemic stroke and TIA with >80% anticoagulation rate.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: atrial fibrillation ■ risk ■ stroke ■ transient ischemic attack

The increasing use of prolonged cardiac monitoring (PCM) in patients with ischemic stroke to look for paroxysmal atrial fibrillation (AF) has led to a better characterization of PCM-detected cardiac arrhythmias. AF detected on 14-day Holter (PCM-detected AF) is defined as any AF found on PCM, including Holter

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/STROKEAHA.123.043672.
For Sources of Funding and Disclosures, see page xxx.

Stroke is available at www.ahajournals.org/journal/str

Stroke. 2023;54:00–00. DOI: 10.1161/STROKEAHA.123.043672 August 2023 1

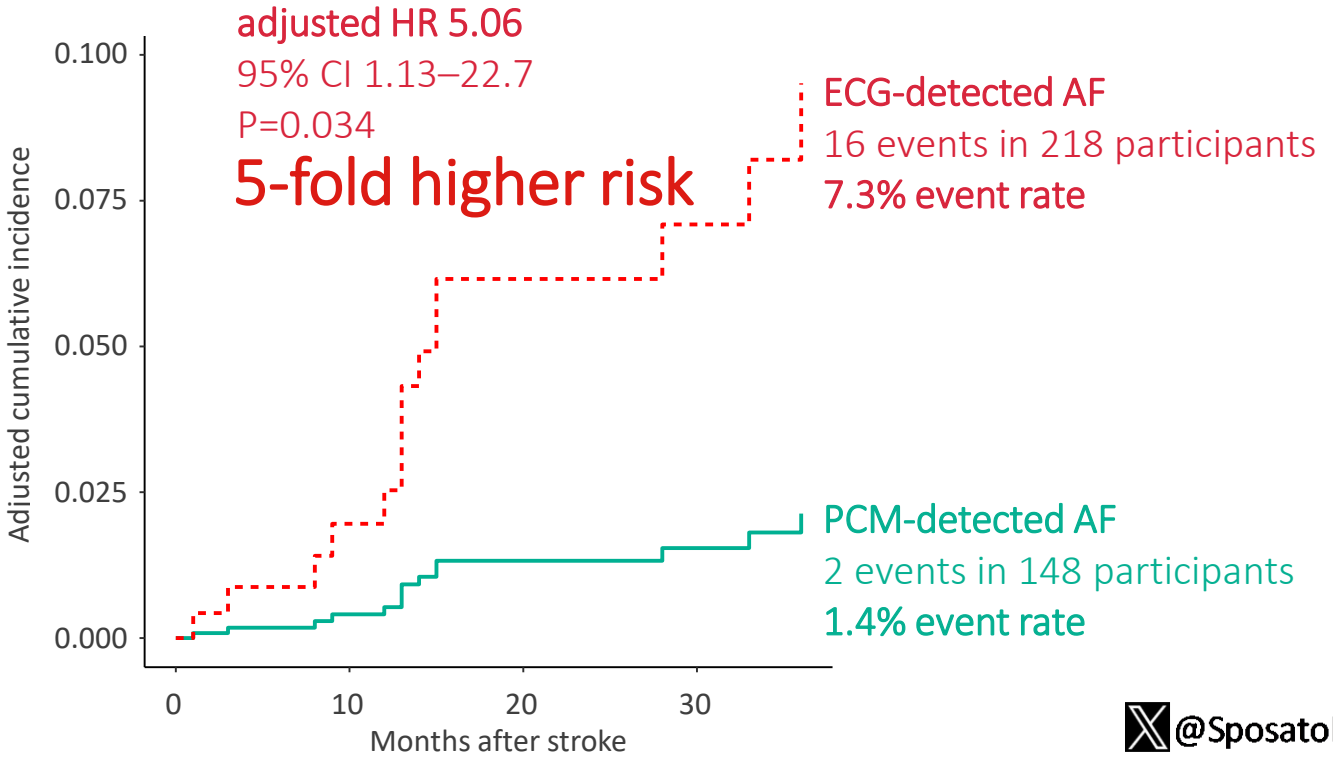
Alonso Alvarado Bolaños et al. Stroke 2023.

DELIMIT AF-STROKE
Results

Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

NCT05822791

Primary Outcome
Recurrent Ischemic Stroke



Median follow-up
17 [IQR 5-34] months

@SposatoL

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DELIMIT AF-STROKE

Results

Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

NCT05822791

DELIMIT AF-STROKE

Results

Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

NCT05822791

Time-varying Risk of Stroke Recurrence in Patients with ECG-AF compared to KAF

DELIMIT AF-STROKE

Results

Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

NCT05822791

AFDAS

OAC related intracranial hemorrhages **5** ⬅

➡ **5** recurrent ischemic strokes

median follow-up of 23.4 months (IQR 4.5-38.9)

DELIMIT AF-STROKE

Results

Differences in ECG- vs. proLonged cardIac MonItor-deTected Atrial Fibrillation in STROKE Patients

NCT05822791

Type of Event	Age	Sex	IS Mechanism ICH type	NIHSS	LVO MeVO	Anti-thrombotic	CHA_2DS_2-VASc score	AF recurrence post PCM	AF on ECG post AFDAS	Total AF duration	LAVI ml/m²	Death
Recurrent ischemic stroke												
Case 1	80-90	M	Polycythemia vera	2	No	Apixaban	6	No	0/8	4 min	29.7	No
Case 2	80-90	M	High-burden AFDAS*	1	No	Apixaban	7	Yes	12/14	>24 h	34.3	No
Case 3	70-80	F	LAD vs high-burden AFDAS	6	MeVO	Aspirin	6	Yes	5/11	>24 h	25.9	No
Case 4**	90-100	M	AF-related	6	MeVO	Aspirin	7	No	0/9	2.5 h	27.3	Yes
Case 5	70-80	M	Small vessel disease	1	No	Rivaroxaban	6	No	0/4	36 min	19.4	No
Intracranial hemorrhage												
Case 1	80-90	F	Deep, intracerebral	–	–	Rivaroxaban	6	No	0/5		26.0	Yes
Case 2	70-80	M	Subdural, traumatic	–	–	Apixaban	6	No	0/2	3 min	29.6	No
Case 3**	90-100	M	Subdural/Subarachnoid, traumatic	–	–	Apixaban	7	No	0/9	2.5 h	34.2	No
Case 4	80-90	F	Subdural, traumatic	–	–	Apixaban	8	Yes	14/34	1 min	36.3	No
Case 5	80-90	F	Deep, intracerebral	–	–	Apixaban	5	Yes	8/8	>24 h	39.4	Yes

IS: ischemic stroke. **ICH:** intracranial hemorrhage. **NIHSS:** National Institutes of Health Stroke Scale. **LVO:** large vessel occlusion. **MeVO:** medium vessel occlusion. **AF:** atrial fibrillation. **ECG:** 12-lead electrocardiogram **LAVI:** left atrial volume index. **M:** male. **F:** female. **AFDAS:** atrial fibrillation detected after stroke. Atrial fibrillation lasted >24 hours is considered large burden.

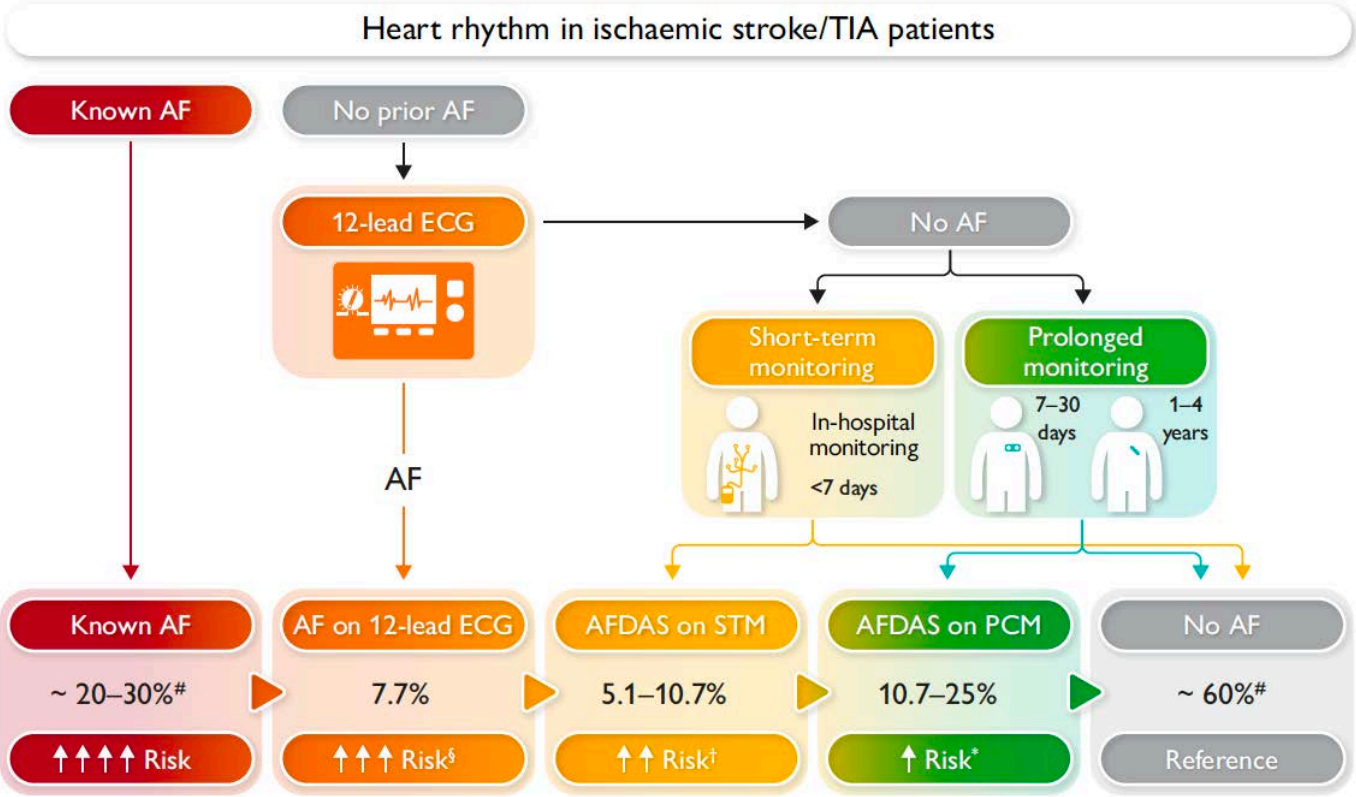
*Slow left atrial appendage flow identified on cardiac CT.

** Same patient. Apixaban was stopped after presenting with a subdural hematoma.

The Importance of Duration of Monitoring

The more we look, the less relevant AF?

@Sposa



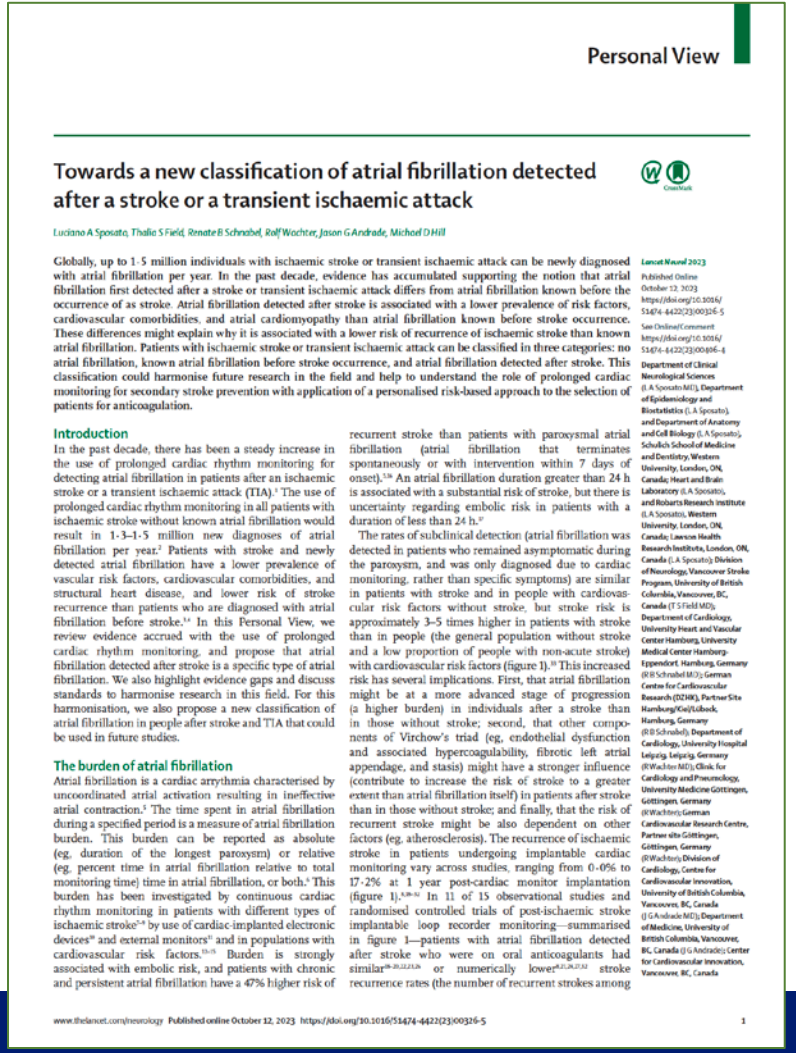
Sposato, Lip, Häusler. Eur Heart J 2024, published online

Conclusion #2

AF-related risk of stroke varies in relation to the timing of detection and duration of cardiac monitoring

Heart Rhythm Classification in Stroke & TIA

Definition, Proposed Research Standards, & Knowledge Gaps



Personal View

Towards a new classification of atrial fibrillation detected after a stroke or a transient ischaemic attack

Luciana A Sposato, Thalia S Field, Renate B Schnabel, Rolf Wachter, Jason G Andrade, Michael D Hill

Globally, up to 1·5 million individuals with ischaemic stroke or transient ischaemic attack can be newly diagnosed with atrial fibrillation per year. In the past decade, evidence has accumulated supporting the notion that atrial fibrillation first detected after a stroke or transient ischaemic attack differs from atrial fibrillation known before the occurrence of as stroke. Atrial fibrillation detected after stroke is associated with a lower prevalence of risk factors, cardiovascular comorbidities, and atrial cardiomyopathy than atrial fibrillation known before stroke occurrence. These differences might explain why it is associated with a lower risk of recurrence of ischaemic stroke than known atrial fibrillation. Patients with ischaemic stroke or transient ischaemic attack can be classified in three categories: no atrial fibrillation, known atrial fibrillation before stroke occurrence, and atrial fibrillation detected after stroke. This classification could harmonise future research in the field and help to understand the role of prolonged cardiac monitoring for secondary stroke prevention with application of a personalised risk-based approach to the selection of patients for anticoagulation.

Lancet Neurol 2023
Published Online October 12, 2023
https://doi.org/10.1016/S1474-4422(23)00326-5
See Online/Comment
https://doi.org/10.1016/S1474-4422(23)00696-4

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Introduction

In the past decade, there has been a steady increase in the use of prolonged cardiac rhythm monitoring for detecting atrial fibrillation in patients after an ischaemic stroke or a transient ischaemic attack (TIA).[1] The use of prolonged cardiac rhythm monitoring in all patients with ischaemic stroke without known atrial fibrillation would result in 1·3–1·5 million new diagnoses of atrial fibrillation per year.[2] Patients with stroke and newly detected atrial fibrillation have a lower prevalence of vascular risk factors, cardiovascular comorbidities, and structural heart disease, and lower risk of stroke recurrence than patients who are diagnosed with atrial fibrillation before stroke.[3,4] In this Personal View, we review evidence accrued with the use of prolonged cardiac rhythm monitoring, and propose that atrial fibrillation detected after stroke is a specific type of atrial fibrillation. We also highlight evidence gaps and discuss standards to harmonise research in this field. For this harmonisation, we also propose a new classification of atrial fibrillation in people after stroke and TIA that could be used in future studies.

The burden of atrial fibrillation

Atrial fibrillation is a cardiac arrythmia characterised by uncoordinated atrial activation resulting in ineffective atrial contraction.[5] The time spent in atrial fibrillation during a specified period is a measure of atrial fibrillation burden. This burden can be reported as absolute (eg, duration of the longest paroxysm) or relative (eg, percent time in atrial fibrillation relative to total monitoring time) time in atrial fibrillation, or both.[6] This burden has been investigated by continuous cardiac rhythm monitoring in patients with different types of ischaemic stroke[7–9] by use of cardiac-implanted electronic devices[10] and external monitors[11] and in populations with cardiovascular risk factors.[12–15] Burden is strongly associated with embolic risk, and patients with chronic and persistent atrial fibrillation have a 47% higher risk of recurrent stroke than patients with paroxysmal atrial fibrillation (atrial fibrillation that terminates spontaneously or with intervention within 7 days of onset).[3,16] An atrial fibrillation duration greater than 24 h is associated with a substantial risk of stroke, but there is uncertainty regarding embolic risk in patients with a duration of less than 24 h.[17]

The rates of subclinical detection (atrial fibrillation was detected in patients who remained asymptomatic during the paroxysm, and was only diagnosed due to cardiac monitoring, rather than specific symptoms) are similar in patients with stroke and in people with cardiovascular risk factors without stroke, but stroke risk is approximately 3–5 times higher in patients with stroke than in people (the general population without stroke and a low proportion of people with non-acute stroke) with cardiovascular risk factors (figure 1).[18] This increased risk has several implications. First, that atrial fibrillation might be at a more advanced stage of progression (a higher burden) in individuals after a stroke than in those without stroke; second, that other components of Virchow's triad (eg, endothelial dysfunction and associated hypercoagulability, fibrotic left atrial appendage, and stasis) might have a stronger influence (contribute to increase the risk of stroke to a greater extent than atrial fibrillation itself) in patients after stroke than in those without stroke; and finally, that the risk of recurrent stroke might be also dependent on other factors (eg, atherosclerosis). The recurrence of ischaemic stroke in patients undergoing implantable cardiac monitoring vary across studies, ranging from 0·0% to 17·2% at 1 year post-cardiac monitor implantation (figure 1).[8,19–32] In 11 of 15 observational studies and randomised controlled trials of post-ischaemic stroke implantable loop recorder monitoring—summarised in figure 1—patients with atrial fibrillation detected after stroke who were on oral anticoagulants had similar[20,21,24,27,32] or numerically lower[8,22,26,28,29,31] stroke recurrence rates (the number of recurrent strokes among

Sposato, Field, Schnabel, Wachter, Andrade, Hill.
Lancet Neurol 2024; 23: 110–22

Heart Rhythm Classification in Stroke & TIA

Definition, Proposed Research Standards, & Knowledge Gaps

Panel 1: **Atrial fibrillation detected after a stroke or transient ischaemic attack (TIA)**

All the following criteria should be fulfilled:

- Atrial fibrillation or atrial flutter diagnosed in patients with stroke (ischaemic or haemorrhagic) or TIA
- No history of atrial fibrillation
- No atrial fibrillation on ECG done after the stroke or TIA in people without known atrial fibrillation
- Atrial fibrillation detected on short-term cardiac monitoring (eg, 24 h or 48 h Holter) or prolonged cardiac monitoring (eg, ≥7 days)

Sposato, Field, Schnabel, Wachter, Andrade, Hill.
Lancet Neurol 2024; 23: 110–22

Duration, timing, and type of cardiac monitoring

- Intended duration of monitoring
- Net duration of monitoring
- Type of monitoring device
- Timing of monitoring initiation post stroke

Atrial fibrillation burden and timing

- Longest atrial fibrillation episode duration
- Otal atrial fibrillation duration
- Maximum atrial fibrillation duration in 24 h of recording
- Proportion of atrial fibrillation in relation to total monitoring time
- Percentage of patients with atrial fibrillation duration greater than 30 s, greater than 6 min, greater than 1 h, greater than 6 h, and greater than 24 h

Outcome events

- Stroke recurrence (ischaemic, haemorrhagic, and total), death, progression of atrial fibrillation, and major adverse cardiovascular events
- Stratification by variables known to influence outcomes risk§

*We recommend a definition of qualifying outcomes and study eligibility criteria. †Left atrial size should be ideally reported as left atrial volume index. ‡Valvular abnormalities of interest are moderate or severe mitral stenosis, a prosthetic mitral valve, or mechanical aortic valve replacement. §Outcome stratification should ideally be reported for sex, age, atrial fibrillation burden, atrial cardiopathy, and duration and initiation of monitoring.

Conclusion #3

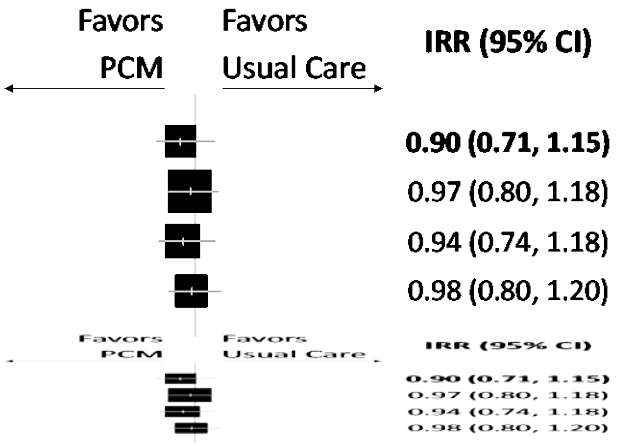
AF detected on an ECG post-stroke is a high-risk AF, probably pre-existing and should not be considered AFDAS

Should we anticoagulate patients with AFDAS?

No differences between PCM and Usual Care in Randomized Controlled Trials

PCM ➡↑ Anticoagulation➡ No ↓ Stroke Recurrence

OUTCOME	STUDIES (n)	FOLLOW-UP PERS-MONTH	IRR (95% CI)
Randomized controlled trials			
Recurrent ischemic stroke*	**4**	**52,332**	**0.90 (0.71, 1.15)**
Recurrent ischemic stroke or TIA	6	68,556	0.97 (0.80, 1.18)
Recurrent stroke (ischemic or hemorrhagic)	4	55,932	0.94 (0.74, 1.18)
Recurrent stroke (ischemic or hemorrhagic) or TIA	4	52,332	0.98 (0.80, 1.20)



None of these trials was designed to show a reduction in recurrent stroke risk

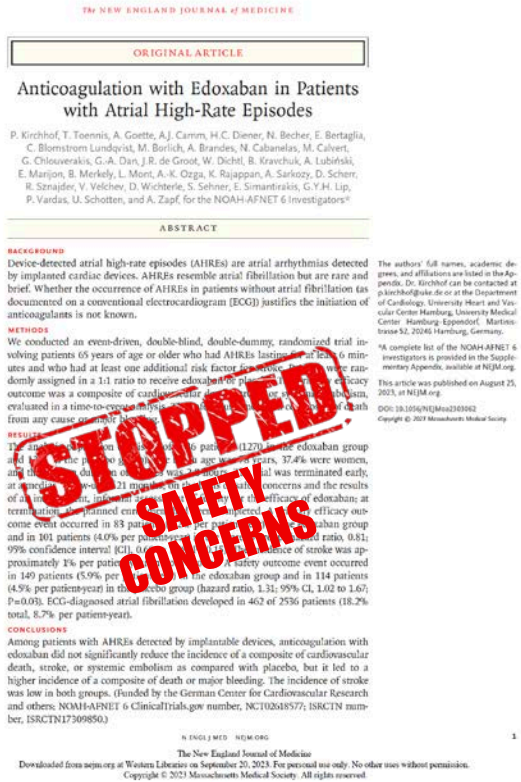
Minimum Device-detected AF duration of 2 min

Modified from Sposato et al. Stroke 2022;53:e94-e103.

NOAH-AFNET 6

Device detected AF

Edoxaban vs. double dummy placebo (Aspirin if indicated or placebo if no indication for Aspirin) in ≥ 65-year-old patients with no history of AF, with AHRE ≥6 min on implanted devices and ≥1 additional risk factor for stroke.



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Anticoagulation with Edoxaban in Patients with Atrial High-Rate Episodes

P. Kirchhof, T. Toennis, A. Goette, A.J. Camm, H.C. Diener, N. Becher, E. Bertaglia, C. Blomstrom Lundqvist, M. Borlich, A. Brandes, N. Cabanelas, M. Calvert, G. Chlouverakis, G.-A. Dan, J.R. de Groot, W. Dichtl, B. Kravchuk, A. Lubiński, E. Marijon, B. Merkely, L. Mont, A.-K. Ozga, K. Rajappan, A. Sarkozy, D. Scherr, R. Szrajder, V. Velchev, D. Wichterle, S. Sehner, E. Simantirakis, G.Y.H. Lip, P. Vardas, U. Schotten, and A. Zapf, for the NOAH-AFNET 6 Investigators*

ABSTRACT

BACKGROUND

Device-detected atrial high-rate episodes (AHREs) are atrial arrhythmias detected by implanted cardiac devices. AHREs resemble atrial fibrillation but are rare and brief. Whether the occurrence of AHREs in patients without atrial fibrillation (as documented on a conventional electrocardiogram [ECG]) justifies the initiation of anticoagulants is not known.

METHODS

We conducted an event-driven, double-blind, double-dummy, randomized trial involving patients 65 years of age or older who had AHREs lasting for at least 6 minutes and who had at least one additional risk factor for stroke. [illegible] were randomly assigned in a 1:1 ratio to receive edoxaban 60 mg [illegible] efficacy outcome was a composite of cardiovascular death, stroke, or systemic embolism, evaluated in a time-to-event analysis. [illegible] of death from any cause or major bleeding.

RESULTS

[illegible] patients (1270 in the edoxaban group and [illegible] in the placebo group) [illegible] age was 74 years, 37.4% were women, and the [illegible] was 2.9 years. [illegible] was terminated early, at a median follow-up of 2.1 months, [illegible] safety concerns and the results of an [illegible] efficacy of edoxaban; at termination, the planned enrollment [illegible] efficacy outcome event occurred in 83 patients (6.5% per patient-year) in the edoxaban group and in 101 patients (8.0% per patient-year) in the placebo group (hazard ratio, 0.81; 95% confidence interval [CI], [illegible]; P=0.08). The incidence of stroke was approximately 1% per patient-year in each group. A safety outcome event occurred in 149 patients (5.9% per patient-year) in the edoxaban group and in 114 patients (4.5% per patient-year) in the placebo group (hazard ratio, 1.31; 95% CI, 1.02 to 1.67; P=0.03). ECG-diagnosed atrial fibrillation developed in 462 of 2536 patients (18.2% total, 8.7% per patient-year).

CONCLUSIONS

Among patients with AHREs detected by implantable devices, anticoagulation with edoxaban did not significantly reduce the incidence of a composite of cardiovascular death, stroke, or systemic embolism as compared with placebo, but it led to a higher incidence of a composite of death or major bleeding. The incidence of stroke was low in both groups. (Funded by the German Center for Cardiovascular Research and others; NOAH-AFNET 6 ClinicalTrials.gov number, NCT02618577; ISRCTN number, ISRCTN17309850.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Kirchhof can be contacted at p.kirchhof@uke.de or at the Department of Cardiology, University Heart and Vascular Center Hamburg, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany.

*A complete list of the NOAH-AFNET 6 investigators is provided in the Supplementary Appendix, available at NEJM.org.

This article was published on August 25, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2310062

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STOPPED SAFETY CONCERNS

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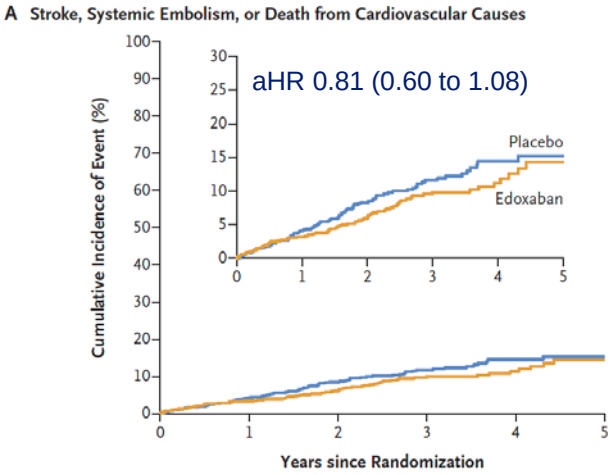
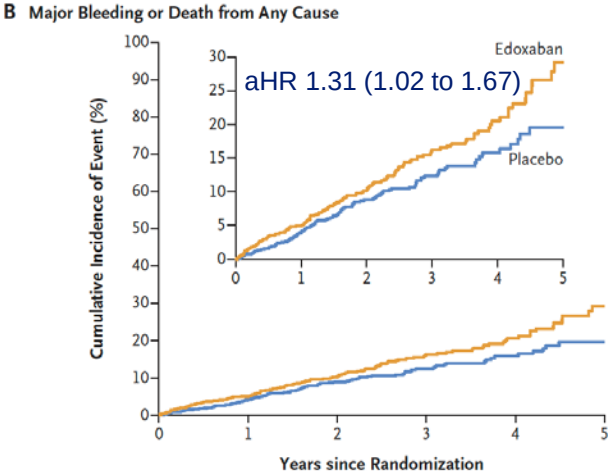
Primary Efficacy Outcome



Primary Safety Outcome



Outcome	Edoxaban (N=1270)	Placebo (N=1266)	Adjusted Hazard Ratio (95% CI)
	no. of patients with event/patient-yr (% per patient-yr)		
Ischemic stroke	22/2573 (0.9)	27/2519 (1.1)	0.79 (0.45 to 1.39)

Kirchhof et al. New Eng J Med; August 25, 2023

NOAH-AFNET 6

Device detected AF

Edoxaban vs. double dummy placebo (Aspirin if indicated or placebo if no indication for Aspirin) in ≥ 65-year-old patients with no history of AF, with AHRE ≥6 min on implanted devices and ≥1 additional risk factor for stroke.

Subanalysis in Patients with a Previous Stroke or TIA

Outcome	No prior stroke or TIA			Prior stroke or TIA			*P*-interaction value
	Edoxaban	Placebo	Edoxaban vs placebo	Edoxaban	Placebo	Edoxaban vs placebo	
	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	
Primary efficacy outcome	69/2310 (3.0)	85/2240 (3.8)	0.8 (0.6–1.1)	14/246 (5.7)	16/254 (6.3)	0.9 (0.4–1.8)	0.76
Secondary efficacy outcomes							
Ischemic stroke	18/2323 (0.8)	21/2263 (0.9)	0.8 (0.4–1.6)	4/250 (1.6)	6/255 (2.3)	0.7 (0.2–2.4)	0.82
Systemic embolism	12/2324 (0.5)	25/2255 (1.1)	0.5[†] (0.2–1.0)	2/254 (0.8)	3/259 (1.2)	0.7 (0.1–4.1)	0.71
Myocardial infarction	9/2321 (0.4)	14/2262 (0.6)		1/257 (0.4)	2/259 (0.8)		
Peripheral limb	0/2337	3/2274 (0.1)		1/254 (0.4)	0/260		
Abdominal embolism	0/2337	1/2278 (0.0)		0/257	0/260		
Stroke or systemic arterial embolism	21/2316 (0.9)	31/2253 (1.4)	0.7 (0.4–1.2)	4/250 (1.6)	7/255 (2.7)	0.6 (0.2–2.0)	0.89
Post hoc outcome stroke and systemic embolism[*]	59/2323 (2.5)	68/2258 (3.0)	0.8 (0.6–1.2)	13/246 (5.3)	13/255 (5.1)	1.0 (0.5–2.2)	0.64
Cardiovascular death	44/2337 (1.9)	49/2278 (2.2)	0.9 (0.6–1.3)	8/257 (3.1)	8/260 (3.1)	1.0 (0.4–2.7)	0.78

Median time between stroke occurrence and randomization 5 to 6 years

Kirchhof et al. JAHA 2024;13:e036429.

NOAH-AFNET 6

Device detected AF

Edoxaban vs. double dummy placebo (Aspirin if indicated or placebo if no indication for Aspirin) in ≥ 65-year-old patients with no history of AF, with AHRE ≥6 min on implanted devices and ≥1 additional risk factor for stroke.

Secondary Analysis in Patients with a Previous Stroke or TIA

Outcome	No prior stroke or TIA			Prior stroke or TIA			*P*-interaction value
	Edoxaban	Placebo	Edoxaban vs Placebo	Edoxaban	Placebo	Edoxaban vs placebo	
	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	No. of patients with event per patient-y (% per patient-y)		Adjusted HR (95% CI)	
Safety outcomes							
All-cause death	94/2337 (4.0)	81/2278 (3.6)	1.1 (0.8, 1.5)	17/257 (6.6)	13/260 (5.0)	1.3 (0.6, 2.7)	0.69
Major bleeding (ISTH)	45/2285 (2.0)	23/2249 (1.0)	1.9* (1.2, 3.2)	8/248 (3.2)	2/259 (0.8)	4.3† (0.9, 20.1)	0.34
Hemorrhagic Stroke	6/2285 (0.3)	7/2249 (0.3)		0/248	0/259		
All-cause death and major bleeding	125/2285 (5.5)	99/2249 (4.4)	1.3‡ (1.0, 1.6)	24/248 (9.7)	15/259 (5.8)	1.7 (0.9, 3.2)	0.40

ARTESIA

Device detected AF

Apixaban vs. double dummy Aspirin 81 mg in patients with subclinical AF lasting between 6 minutes and 24 hours detected on implantable devices.

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
Stroke or systemic embolism	55	0.78	86	1.24	0.63 (0.45–0.88)	0.007
Stroke	55	0.78	84	1.21	0.64 (0.46–0.90)	
Ischemic or unknown type†	45	0.64	71	1.02	0.62 (0.43–0.91)	
Hemorrhagic	10	0.14	13	0.18	0.76 (0.33–1.73)	
Severity according to score on modified Rankin scale‡						
0–2	31	0.44	45	0.65	0.68 (0.43–1.07)	
3–6	19	0.27	37	0.53	0.51 (0.29–0.88)	
Missing data	5	0.07	2	0.03	2.48 (0.48–12.80)	
Systemic embolism	0		2	0.03	NA	
Stroke, TIA, or systemic embolism§	82	1.17	107	1.56	0.75 (0.56–1.00)	
Stroke, systemic embolism, or death from cardiovascular causes	148	2.10	171	2.47	0.85 (0.68–1.06)	
Stroke, myocardial infarction, systemic embolism, or death	419	6.01	418	6.10	0.98 (0.86–1.12)	
Myocardial infarction	37	0.52	41	0.59	0.89 (0.57–1.40)	
Death	362	5.06	341	4.82	1.04 (0.90–1.21)	
Death from cardiovascular causes	105	1.47	108	1.53	0.96 (0.73–1.25)	

Healey J et al. New Eng J Med 2023

ARTESIA
Device detected AF

Apixaban vs. double dummy Aspirin 81 mg in patients with subclinical AF lasting between 6 minutes and 24 hours detected on implantable devices.

Outcome	Apixaban (N=2015)		Aspirin (N=1997)		Hazard Ratio (95% CI)	P Value
	no. of patients with event	*%/patient-yr*	*no. of patients with event*	*%/patient-yr*		
INTENTION TO TREAT						
Major bleeding¶	106	1.53	78	1.12	1.36 (1.01–1.82)	0.04
Fatal bleeding	10	0.14	14	0.20	0.70 (0.31–1.57)	
Symptomatic intracranial hemorrhage	17	0.24	23	0.33	0.73 (0.39–1.36)	
Gastrointestinal bleeding	55	0.78	31	0.44	1.76 (1.13–2.74)	
Transfusion performed	35	0.49	31	0.44	1.11 (0.68–1.80)	
ON TREATMENT						
Major bleeding§	86	1.71	47	0.94	1.80 (1.26–2.57)	0.001
Fatal bleeding	5	0.10	8	0.16	0.63 (0.20–1.91)	
Symptomatic intracranial hemorrhage	12	0.24	15	0.30	0.77 (0.36–1.64)	
Gastrointestinal bleeding	45	0.89	20	0.40	2.23 (1.32–3.78)	
Transfusion performed	26	0.51	18	0.36	1.43 (0.78–2.61)	

Healey J et al. New Eng J Med 2023

ARTESIA

Device detected AF

Apixaban vs. double dummy Aspirin 81 mg in patients with subclinical AF lasting between 6 minutes and 24 hours detected on implantable devices.

Secondary Analysis in Patients with a Previous Stroke or TIA

Primary Outcome: Stroke or SE (3.5 years follow-up)

ARTESIA

Device detected AF

Apixaban vs. double dummy Aspirin 81 mg in patients with subclinical AF lasting between 6 minutes and 24 hours detected on implantable devices.

Secondary Analysis in Patients with a Previous Stroke or TIA

Endpoint	Apixaban events (rate)	Aspirin events (rate)	HR (95% CI)	Interaction p-value	Absolute risk reduction (Apixaban - Aspirin)	Interaction p-value
Stroke				0.21		0.03
Previous stroke or TIA	7 (4.1)	18 (10.3)	0.40 (0.17-0.95)		0.07 (0.02-0.12)	
No Previous stroke or TIA	48 (2.6)	66 (3.6)	0.71 (0.49-1.03)		0.01 (-0.00-0.03)	
Ischaemic stroke or unknown stroke				0.43		0.02
Previous stroke or TIA	7 (4.1)	15 (8.6)	0.47 (0.19-1.16)		0.06 (0.01-0.11)	
No Previous stroke or TIA	40 (2.2)	57 (3.1)	0.69 (0.46-1.03)		0.01 (-0.00-0.02)	
Disabling or fatal stroke (mRS 3-6)				0.22		0.02
Previous stroke or TIA	3 (1.7)	12(6.9)	0.26 (0.07-0.93)		0.05 (0.01-0.09)	
No Previous stroke or TIA	16(0.9)	25(1.4)	0.63 (0.33-1.17)		0.01 (0.00-0.01)	

Shoamanesh et al. Presented at ESOC 2024

Conclusion #4

Patients with AFDAS should receive anticoagulants

BUT

A personalized approach is recommended based on

AF detection method and its duration

Risk factors, burden of cardiovascular comorbidities, and structural heart disease

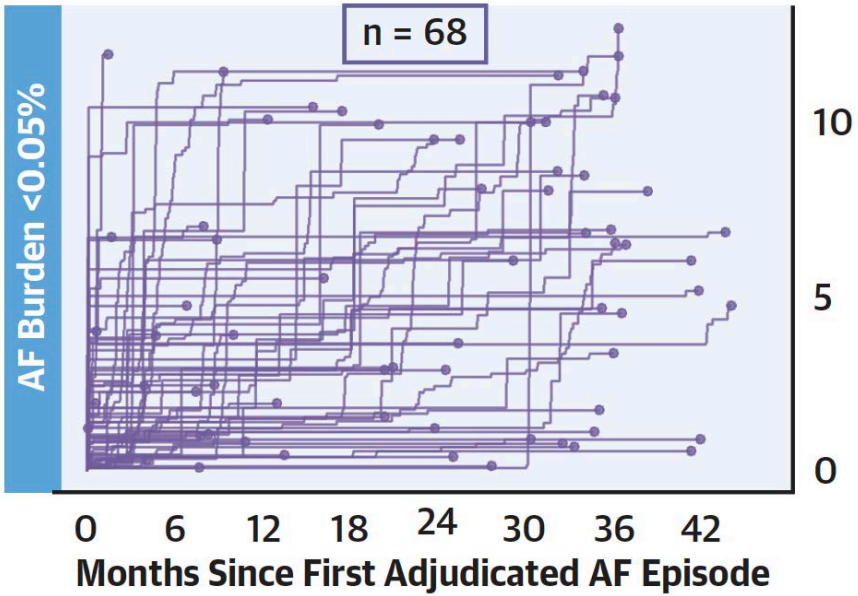
Personalized estimate of bleeding risk

Patients’ preferences

Natural History of Device-detected AF

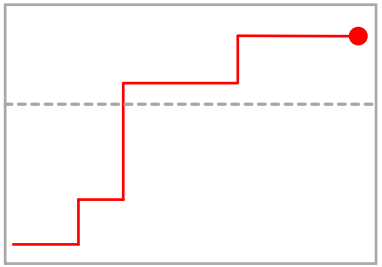
Longitudinal Data from the LOOP Study: AF as a progressive disease

Adjudicated AF episodes lasting >6 min

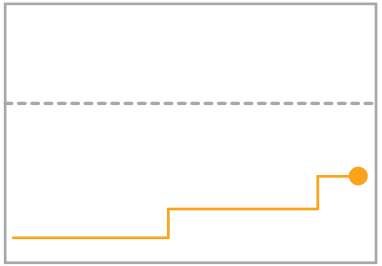


@SposatoL

16%
Progression to high burden (>24h)



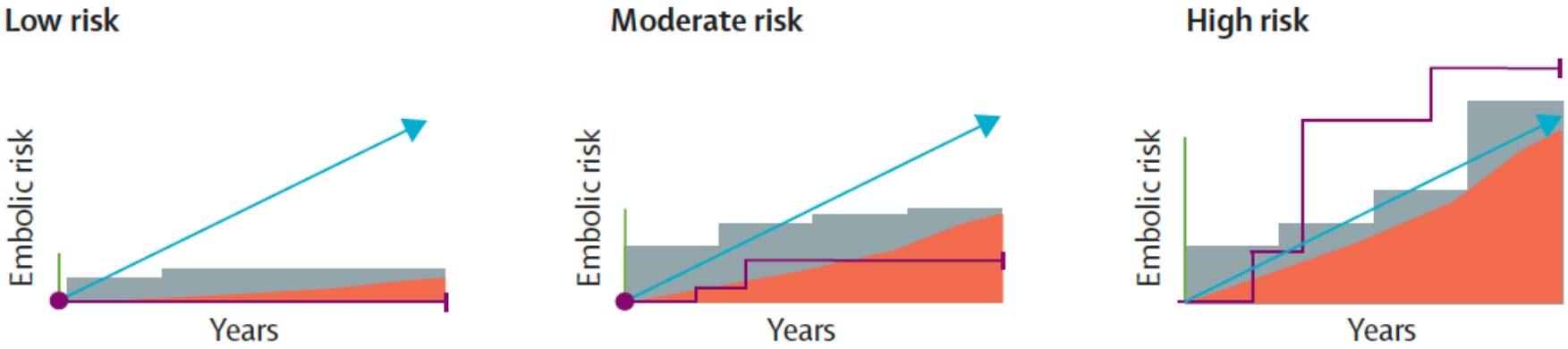
62%
Recurrent AF but no progression to high-burden



22%
Complete remission: no recurrent AF episodes

Personalizing AF Management

Concept of Evolving Risk

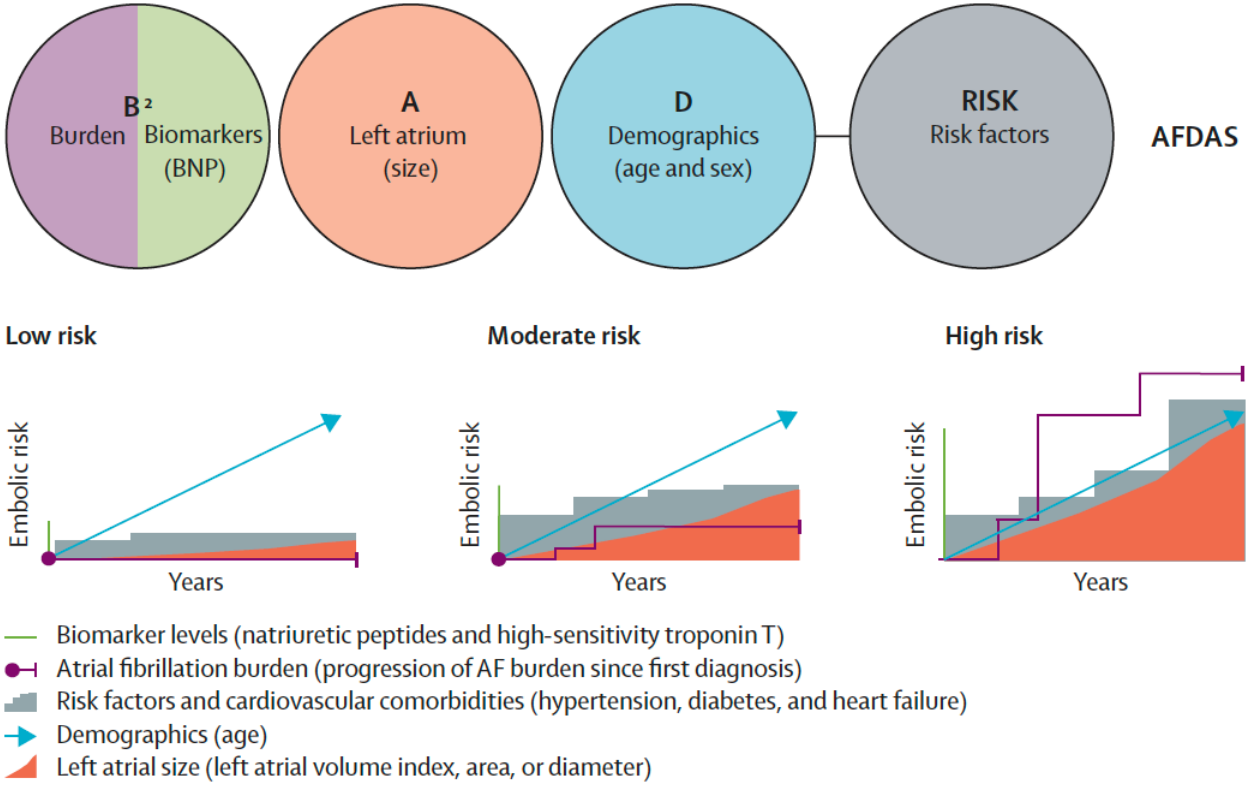


@SposatoL

Sposato, Field, Schnabel, Wachter, Andrade, Hill et al. Lancet Neurol 2024; 23: 110–22

Personalizing AF Management

BAD-RISK AFDAS Approach



@SposatoL

Sposato, Field, Schnabel, Wachter, Andrade, Hill et al. Lancet Neurol 2024; 23: 110–22

Conclusion #5

We can do better!