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Screening for atrial fibrillation: the role of CHA_2DS_2-VASc and atrial fibrillation burden

Lucas Yixi Xing [1]*, Oliver B. Vad [1,2], Daniel Engler [3,4], Jesper H. Svendsen [1,5], and Søren Z. Diederichsen [1]

[1]Department of Cardiology, Heart Center, Copenhagen University Hospital—Rigshospitalet, Copenhagen, Denmark; [2]Department of Biomedical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark; [3]Department of Cardiology, University Heart and Vascular Center Hamburg Eppendorf, Hamburg, Germany; [4]German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; and [5]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

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Individuals with subclinical atrial fibrillation (AF) face an increased risk of thromboembolic events, which may potentially be mitigated through AF screening and subsequent anticoagulation. However, data from randomized clinical trials (RCTs) indicate a lower stroke risk in subclinical AF compared with the clinical phenotype. This—along with the inherent bleeding risk related to anticoagulation—seems to render the net clinical benefit of AF screening less evident. Further, current guidelines recommend consideration of CHA_2DS_2-VASc score and AF episode duration to guide screening and treatment. These recommendations, in general, lack support and seem questionable in view of the limited RCT data. More evidence is warranted to provide insights into the potential benefits of screening and treatment of screen-detected AF in specific population subgroups and AF phenotypes.

Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a rapidly increasing prevalence partly due to population aging.[1-3] In 2010, around 30 million people were estimated to live with AF globally and the number was increased to >50 million in 2021.[2,4] More importantly, AF is a major risk factor for mortality and morbidity, particularly stroke for which the risk is increased by up to two-fold in patients diagnosed with AF compared to without.[1,5,6] In this regard, guideline-directed treatment with oral anticoagulation appears useful for stroke prevention,[1,3] yielding a relative risk (RR) reduction of ~60% compared with placebo.[7] Due to advancements in implantable and wearable technologies for heart rhythm monitoring, AF screening has become a hot topic in recent years both in the clinical setting and outside it. Indeed, there is growing evidence that many AF episodes are unrelated to symptoms.[8,9] This primarily asymptomatic nature of AF may contribute to underdiagnosis and thereby also undertreatment, potentially predisposing these patients to a greater thromboembolic risk that could indeed be mitigated by anticoagulation. Various studies have been undertaken to assess the feasibility and yield of different AF screening approaches. However, as the bulk of our current evidence on benefits of anticoagulation is based on clinically documented AF, more data are needed from the subclinical or undiagnosed phenotypes to establish the potentially preventive effects of AF screening on clinical outcomes. This will help to inform AF screening strategies, both when it comes to selecting individuals

*Corresponding author. Tel: +45 3545 1442, Email: lucas.yixi.xing@regionh.dk

for screening and when it comes to the choice of screening methodology. In recent years, several randomized controlled trials (RCTs) have been launched—some already completed and some still ongoing—attempting to document the benefits of screening and treatment of subclinical AF. In this review, we will provide a narrative summary of the available evidence on the efficacy of AF screening and treatment on clinical outcomes, thereby highlighting the knowledge gaps that call for further investigation.

Subclinical atrial fibrillation

As per current guidelines, clinical AF is defined as AF (with or without symptoms) diagnosed by conventional 12-lead electrocardiogram (ECG) and lasting the entire 10 s or by a surface ECG tracing that documents AF lasting at least 30 s.[1,3] Subclinical AF refers to AF discovered during the interrogation of prolonged heart monitoring and is often asymptomatic. However, the distinction between clinical and subclinical AF is gradually being challenged by the technological advancement and increasing accessibility of especially consumer-directed wearables in the society.

Several studies have indicated a poor correlation between AF episodes and the presence of symptoms, with >90% of AF detected by implanted devices being asymptomatic.[8,9] Subclinical AF is particularly common in elderly individuals, with an incidence of >30% when monitoring with implantable loop recorder (ILR).[10,11] This subclinical type of AF further appears to confer an increased risk of developing clinical AF and ischaemic stroke.[8,12] The landmark AF study from 2012, *Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial* (ASSERT), examined 2580 AF-naïve patients aged ≥65 years, with hypertension and newly implanted cardiovascular implantable electronic device (CIED).[8] Besides an overall incidence of subclinical AF at 34.7% over a mean follow-up of 2.5 years, this study documented a more than five-fold increased risk of clinical AF {6.3%/year vs. 1.2%/year; hazard ratio [HR] 5.56 [95% confidence interval (CI): 3.78–8.17]} and a 2.5-fold increased risk of ischaemic stroke or systemic embolism [1.7%/year vs. 0.7%/year; HR 2.49 (95% CI: 1.28–4.85)] for patients with vs. without subclinical AF. These findings were further ascertained by a meta-analysis in 2018 reporting similar risk increases [odds ratio of 5.66 (95% CI: 4.02–7.97) for clinical AF and 2.41 (95% CI: 1.78–3.26) for stroke] across pacemaker cohorts.[12]

Stroke risk assessment in atrial fibrillation

Over the last three decades, substantial efforts have been dedicated to identifying risk factors for thromboembolism in AF and devising effective risk stratification schemes to guide clinical decision regarding anticoagulation treatment for stroke prevention in patients with clinical AF. Several risk scores have been developed, with those based on clinical factors being particularly favoured due to their simplicity, practicality, and swift calculation. Here, the CHA_2DS_2-VASc score is considered as the most validated one and therefore widely used in both research and clinical settings.[1,3,13] The risk scheme provides a score from 0 to 9 based on age, sex, the clinical history of heart failure, hypertension, diabetes mellitus, stroke, and vascular disease (see *Table 1*), which are all well-established stroke risk factors in patients with clinical AF.[1,3,14,15] For risk classification, a CHA_2DS_2-VASc score of 0 for men and 1 for women indicates low risk, whereas 1 and ≥2 additional risk components are required to be categorized into intermediate (i.e. score 1 for men and 2 for women) and high-risk groups (i.e. score ≥2 for men and ≥3 for women), respectively. For stroke prevention, initiation of oral anticoagulation is recommended to patients with clinical AF in the high-risk group and should be considered for those with intermediate stroke risk.[1,3] Although data supporting the CHA_2DS_2-VASc scheme primarily stem from observational studies of clinical AF, it is intuitive to believe that these could be extrapolated to subclinical AF. Therefore, both European and American guidelines advocate its use in assessing stroke risk and guide screening and anticoagulation in the context of subclinical AF,[1,3] while all current RCTs of subclinical AF have consistently adopted this risk stratification algorithm for participant selection. However, it is important to note that despite the wide use and the simplicity of CHA_2DS_2-VASc score, it only demonstrates a modest ability for stroke prediction on individual level in previous studies.[1,16] Other prediction models, such as the ABC-Stroke score further incorporating cardiac biomarkers, appeared to outperform CHA_2DS_2-VASc score in predicting thromboembolic events.[17,18]

Table 1 CHA_2DS_2-VASc risk scheme

Components	Description	Points
C	A history of congestive heart failure	+1
H	Hypertension history or current antihypertensive pharmacological treatment	+1
A_2	Age ≥75 years	+2
D	A history of diabetes mellitus or treatment with antidiabetic drugs	+1
S_2	A history of ischaemic stroke, TIA, peripheral embolism, or pulmonary embolism	+2
V	A history of vascular disease defined as coronary artery disease, peripheral vascular disease, and/or aortic plaque	+1
A	Age 65–74 years	+1
Sc	Sex category as being female	+1

TIA, transient ischaemic attack.

Anticoagulation trials for subclinical atrial fibrillation

To date, only four completed RCTs have assessed subclinical AF for stroke prevention (see *Table 2*), including two recently reported trials focusing on anticoagulation of device-detected AF. The *Non-Vitamin K Antagonist Oral*

Table 2 Completed randomized controlled trials for subclinical atrial fibrillation

	NOAH-AFNET 6[19]	ARTESiA[20]	STROKESTOP[24]	LOOP Study[10]
Sample size for the primary analysis	$n = 2536$	$n = 4012$	$n = 27\,975$	$n = 6004$
Main inclusion criteria	Age ≥65 years Subclinical AF episode ≥6 min ≥1 additional stroke risk factor[a]	Age ≥55 years Subclinical AF lasting 6 min to 24 h detected by implanted device CHA_2DS_2-VASc score ≥3 or previous stroke/TIA/ systemic embolism or age ≥75 years	Residents in Halland and Stockholm regions in Sweden Age 75–76 years	Age 70–90 years ≥1 of hypertension, diabetes, heart failure, and prior stroke
Main exclusion criteria	A history of AF documented on an ECG Contraindication or other indications for oral anticoagulation	Clinical AF documented by surface ECG Contraindication to apixaban or aspirin; other indication for oral anticoagulation.	None	Known AF Pacemaker or implantable cardioverter defibrillator Contraindication or other indications for oral anticoagulation
Intervention	Edoxaban	Apixaban	Invitation to intermittent screening with single-lead ECG device twice daily for 14 days among those without a history of AF	ILR screening and subsequent anticoagulation initiation upon detection of subclinical AF lasting ≥6 min
Comparator	Placebo	Aspirin	No invitation	Usual care
Randomization ratio	1:1	1:1	1:1	1:3
Baseline information[b]				
Duration of subclinical AF, h	2.8 [0.8, 9.4]	1.5 [0.2, 5.0]	–	–
Age, years	Mean, 77.5 ± 6.7	Mean, 76.8 ± 7.6	Median, 76.0 [75.5, 76.6]	Mean, 74.7 ± 4.1
Male sex	1587 (62.6)	2565 (63.9)	12 702 (45.4)	3167 (52.7)
Systolic blood pressure, mmHg	–	135.0 ± 18.8	–	150.0 ± 19.4
CHA_2DS_2-VASc	Median, 4 [3, 5]	Mean, 3.9 ± 1.1	Mean, 3.5 ± 1.3	Median, 4 [3, 4]
Heart failure	696 (27.4)	1137 (28.3)	2143 (7.7)	266 (4.4)
Hypertension	2205 (86.9)	3269 (81.5)	9943 (35.5)	5444 (90.7)
Diabetes	681 (26.9)	1167 (29.1)	4222 (15.1)	1710 (28.5)
Prior stroke or TIA	253 (10.0)	361 (9.0)	3070 (11.0)	1056 (17.6) with previous stroke
Ischaemic heart disease	669 (26.4)	1485 (37.0)	–	791 (13.2)
Peripheral artery disease	–	334.(3)	–	161 (2.7)
Clinical AF diagnosis	0 (0.0)	0 (0.0)	3485 (12.5)	0 (0.0)
Oral anticoagulant	0 (0.0)	0 (0.0)	2595 (9.2)	0 (0.0)
Aspirin	1367 (53.9)	2302 (57.4)	7227 (25.8)	–
Duration of follow-up, years	Median, 1.8	Mean, 3.5 ± 1.8	Median, 6.9 [6.5, 7.2]	Median, 5.4 [4.9, 5.8]
Event censoring for the primary analysis	AF documented on an ECG	Subclinical AF lasting ≥24 h or the development of clinical AF	Regular censoring	Regular censoring

Continued

Table 2 Continued

	NOAH-AFNET 6[19]	ARTESiA[20]	STROKESTOP[24]	LOOP Study[10]
The primary efficacy outcome	Cardiovascular death, stroke, or systemic embolism; 83 (3.2%/year) vs. 101 (4.0%/year) for edoxaban vs. placebo; HR 0.81 [0.60–1.08]	Stroke or systemic embolism; 55 (0.8%/year) vs. 86 (1.2%/year) for apixaban vs. aspirin; HR 0.63 [0.45–0.88]	Stroke, systemic embolism, hospitalization due to bleeding, or all-cause death; 4456 (5.5%/year) vs. 4616 (5.7%/year) for invitation vs. no invitation; HR 0.96 [0.92–1.00]	Stroke or systemic embolism; 67 (0.9%/year) vs. 251 (1.1%/year) for ILR screening vs. usual care; HR 0.80 [0.61–1.05]
Ischaemic stroke outcome	Ischaemic stroke; 22 (0.9%/year) vs. 27 (1.1%/year) for edoxaban vs. placebo; HR 0.79 [0.45–1.39]	Stroke of ischaemic or unknown type; 45 (0.6%/year) vs. 71 (1.0%/year) for apixaban vs. aspirin; HR 0.62 [0.43–0.91]	Ischaemic stroke; 766 (0.9%/year) vs. 830 (1.0%/year) for invitation vs. no invitation; HR 0.92 [0.83–1.01]	Ischaemic stroke; 55 (0.7%/year) vs. 220 (1.0%/year) for ILR screening vs. usual care; HR 0.75 [0.56–1.01]
The primary safety outcome	Major bleeding or all-cause death; 149 (5.9%/year) vs. 114 (4.5%/year) for edoxaban vs. placebo; HR 1.31 [1.02–1.67]	Major bleeding; 106 (1.5%/year) vs. 78 (1.1%/year) for apixaban vs. aspirin; HR 1.36 [1.01–2.82]	—	—
Bleeding outcome	Major bleeding; 53 (2.1%/year) vs. 25 (1.0%/year) for edoxaban vs. placebo; HR 2.10 [1.30–3.38]	—	Hospitalization for major bleeding; 1431 (1.71%/year) vs. 1448 (1.74%/year) for invitation vs. no invitation; HR 0.98 [0.91–1.06]	Major bleeding; 64 (0.9%/year) vs. 156 (0.7%/year) for ILR screening vs. usual care; HR 1.26 [0.95–1.69]

AF, atrial fibrillation; ECG, electrocardiogram; HR, hazard ratio; ILR, implantable loop recorder; TIA, transient ischaemic attack.
[a]As defined by other components of the CHA_2DS_2-VASc.
[b]Presented as *n* (%), mean ± standard deviation, or median [interquartile range].

Anticoagulants in Patients with Atrial High Rate Episodes (NOAH-AFNET 6) study enrolled older patients with additional stroke risk factors and subclinical AF ≥6 min detected by CIED or ILR and randomized them to either anticoagulation treatment with edoxaban or placebo (or aspirin if otherwise indicated, which was the case for 54%).[19] Over a median follow-up of 1.8 years owing to early termination of this trial, edoxaban led to a non-significant reduction in the primary efficacy outcome of stroke, systemic embolism, or cardiovascular death [HR 0.81 (95% CI: 0.60–1.08)] and a significant increase in major bleeding [HR 2.10 (95% CI: 1.30–3.38)] as expected. The other anticoagulation trial, *Apixaban for the Reduction of Thrombo-Embolism in Patients with Device-detected Subclinical Atrial Fibrillation* (ARTESiA), examined the treatment effects of apixaban vs. aspirin in high-risk patients with device-detected AF but constrained to only those with subclinical AF lasting ≥6 min up to 24 h.[20] With a study population comparable to that of NOAH-AFNET 6 but a larger sample size (n = 4012) and a longer follow-up (mean 3.5 ± 1.8 years), this trial found a lower risk of stroke or systemic embolism for apixaban vs. aspirin [HR 0.63 (95% CI: 0.45–0.88)] and in turn also a higher risk of major bleeding [HR 1.36 (95% CI: 1.01–1.82)]. When considering event severity, apixaban appeared to reduce the risk of severe stroke (defined as score ≥3 on modified Rankin scale) as indicated by a HR of 0.51 (95% CI: 0.29–0.88), while there was no significant difference in fatal bleeding [HR 0.70 (95% CI: 0.31–1.57)]. A study-level meta-analysis of these two RCTs confirmed an overall 32% reduction in ischaemic stroke by anticoagulation treatment compared with placebo/aspirin [RR of 0.68 (95% CI: 0.50–0.92)], but at the expense of a 62% increase in major bleeding [RR of 1.62 (95% CI: 1.05–2.50)].[21] However, no significant differences were observed in fatal bleeding, cardiovascular death, or all-cause death between the anticoagulation and the control group. An important lesson from these two trials was the lower-than-expected risk of ischaemic stroke reported among the non-anticoagulated controls, with a crude event rate being only 1.0%/year. Not only was it low considering the baseline CHA_2DS_2-VASc score of ∼4 or when comparing with an incidence at 2.1%/year among the aspirin-treated patients with clinically diagnosed paroxysmal AF in the *Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events* (ACTIVE-A) and *Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment* (AVERROES) trials,[22] but the stroke rate was also lower than that found in the non-anticoagulated patients with device-detected AF from the ASSERT study (1.5%/year).[8] Indeed, an estimated annual thromboembolic risk of ≤1% is considered low and, in case of clinical AF, would not necessarily justify anticoagulation according to guidelines.[1,3] Possible explanations for this low risk may include the following: (i) the relatively low AF burden at baseline in these two trials and the self-limiting nature

of subclinical AF as described in a previous study by Diederichsen *et al.*[9]; (ii) the overall trend with improving patient care and risk factor management over time; (iii) risk dilution due to anticoagulation initiation upon ECG documentation of AF; and (iv) healthy user bias or health-seeking behaviour upon trial enrolment. A sub-study of NOAH-AFNET 6 found equally low stroke rates in the small subgroup of patients with subclinical AF episodes ≥24 h at baseline.[23] Hence, these findings suggest that initiating anticoagulation for accidentally detected subclinical AF could contribute to stroke prevention, but a more sophisticated approach to identify individuals at a truly high stroke risk might be essential for guiding clinical decision regarding oral anticoagulation to achieve a net clinical benefit.

Atrial fibrillation screening trials

Looking at AF screening as opposed to the treatment of incidentally diagnosed subclinical AF, two RCTs have reported long-term clinical outcomes. The *Systematic ECG Screening for Atrial Fibrillation among 75-year-old Subjects in the Region of Stockholm and Halland, Sweden* (STROKESTOP) study randomized 75- and 76-year-old residents in Sweden to invitation for intermittent AF screening with handheld single-lead ECG device twice daily for two weeks.[24] In this elderly population-based cohort with an overall better cardiovascular risk profile and a slightly lower CHA_2DS_2-VASc (3.5 ± 1.3), intermittent ECG screening managed to increase AF detection by 1.9% (baseline 12.1% vs. post-screening 14.0%). Further, over a median follow-up of 6.9 [interquartile range (IQR): 6.5, 7.2] years, a marginal but statistically significant net clinical benefit—as indicated by a HR of 0.96 (95% CI: 0.92–1.00) for the composite endpoint of stroke, systemic embolism, bleeding requiring hospitalization, or all-cause death (*P*-value 0.045)—was obtained by the screening compared with usual care. The annualized incidence of ischaemic stroke was 0.9%/year in the invited-to-screening group vs. 1.0%/year in the control group [HR 0.92 (95% CI: 0.83–1.01)]. On the other hand, the *Atrial Fibrillation Detected by Continuous Electrocardiogram Monitoring using Implantable Loop Recorder to Prevent Stroke in High-Risk Individuals* (LOOP) study examined a more intensive AF screening approach with long-term continuous ECG monitoring and subsequent anticoagulation initiation for AF ≥6 min in 70–90-year-old individuals with additional stroke risk factors recruited from the general population.[10] By using ILR, the study detected more than three times as much AF as with usual care [8.0%/year vs. 2.5%/year; HR 3.17 (95% CI: 2.81–3.59)], albeit a remarkably higher rate of clinical AF shown in the control group than 0.6%/year as reported by the *Cryptogenic Stroke and Underlying AF* (CRYSTAL-AF) trial.[25] Over a median follow-up of 5.4 (IQR: 4.9–5.8) years, the LOOP study found a 20% non-significant reduction in stroke or systemic embolism [HR 0.80 (95% CI: 0.61–1.05)] by ILR screening but also a 26% non-significant increase in major bleeding, while the bleeding risk was doubled after anticoagulation initiation compared with before.[26]

Additionally, some of the completed AF screening RCTs that aimed to evaluate the screening yield and subsequent anticoagulation uptake also provided limited data on clinical outcomes. One of these trials, *Remote HEArt Rhythm Sampling using the AliveCor heart monitor to scrEen for Atrial Fibrillation* (REHEARSE-AF), randomized individuals aged ≥65 years with CHA_2DS_2-VASc ≥2 to intermittent screening with single-lead ECG device twice weekly or usual care.[27] At 12-month follow-up, the incidence of AF detection was increased by nearly four-fold for screening vs. usual care [HR 3.90 (95% CI: 1.40–10.4)], whereas a numerically lower number of stroke and transient ischaemic attack (TIA) events were demonstrated in the screening group (6 of 500) compared with the control group (10 of 501), although not statistically significant [HR 0.61 (95% CI: 0.22–1.69)]. The *Home-based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older* (SCREEN-AF) study assessed the short-term continuous AF screening with wearable ECG patch for a total of four weeks in patients aged ≥75 years with hypertension.[28] For a 6-month follow-up, this continuous screening approach resulted in a substantial increase in AF detection compared with usual care [RR 11.2 (95% CI: 2.7–47.1)]. But for clinical endpoints, very few events were reported (one death in the control group vs. two ischaemic strokes and one TIA in the screening group). However, by combining these four AF screening RCTs—i.e. STROKESTOP, LOOP, REHEARSE-AF, and SCREEN-AF—for a meta-analysis at the study level, McIntyre *et al.*[29] stated a favourable effect on stroke prevention for screening vs. no screening [RR 0.91 (95% CI: 0.84–0.99)]. Likewise, the *mHealth Screening to Prevent Strokes* (mSToPS) study—comprising a RCT to evaluate the immediate vs. the delayed continuous AF screening with an ECG patch for four weeks and then an observational study to compare the screened participants with a matched cohort[30]—also demonstrated a lower risk of stroke in the screening group relative to the matched controls at 3-year follow-up [1.7%/year vs. 2.2%/year; HR 0.75 (95% CI: 0.57–0.99)].[31]

Moreover, the population-based *Danish Cardiovascular Screening* (DANCAVAS) trial evaluated a comprehensive screening programme for subclinical cardiovascular diseases (CVDs)—including ECG-gated cardiac and truncal computed tomography with telemetry monitoring, measurement of branchial and ankle blood pressure, and plasma glucose and cholesterol measurement—in men aged 65–74 years.[32] At 5-year follow-up, a significant reduction in ischaemic stroke was observed in the invited-to-screening group (0.9%/year) relative to no screening [1.0%/year; HR 0.89 (95% CI: 0.81–0.96)]. However, it is uncertain how much of this screening benefit was attributable to early AF detection by continuous ECG monitoring during the scanning. Indeed, the study reported a screening yield of only 0.5% for AF, while there was no obvious difference in anticoagulation initiation between the screening and the control groups [1.3%/year vs. 1.3%/year; HR 1.00 (95% CI: 0.93–1.08)].

Taken together, the available evidence from RCTs consistently indicates that subclinical AF does carry a risk for stroke that could be mitigated by oral anticoagulation. But the lower stroke risk relative to clinical AF, along with the inherent bleeding risk related

to anticoagulation therapy, seems to render the net clinical benefit of AF screening less evident. Thus, further insights into subclinical AF are needed to identify high-risk patient groups who may benefit the most from early AF detection and treatment, thereby balancing the bleeding risk and optimizing the net benefits.

Screening effects according to traditional risk factors

According to the 2020 AF guidelines from the European Society of Cardiology, a thromboembolic risk assessment with CHA_2DS_2-VASc is recommended to patients with subclinical AF detected by CIED or ILR, and of note, it is further proposed to consider initiation of anticoagulation in the presence of device-detected AF duration exceeding 24 h and an estimated high stroke risk.[1] The recent American guidelines from 2023 have taken a step further and issued a Class IIa recommendation supporting the use of anticoagulation in patients with subclinical AF ≥24 h and CHA_2DS_2-VASc ≥2 as well as in those with shorter episodes lasting down to 5 min and CHA_2DS_2-VASc ≥3.[3] Moreover, both guidelines advocate considering extended long-term continuous screening for AF, in addition to the routine cardiac monitoring of 24-72 h, in the context of stroke of undetermined cause, with a Class IIa recommendation.[1,3] However, as mentioned above, clear evidence has yet to be established to justify these recommendations.

Besides the thromboembolic events, the components of CHA_2DS_2-VASc have also been linked to an increased occurrence of AF and therefore a greater screening yield.[1,9,11,13,33-40] A STROKESTOP sub-study identified heart failure, diabetes, and a history of stroke/TIA as independent predictors of screen-detected AF.[36] In the *Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor* (ASSERT-II) study, advanced age and higher systolic blood pressure (SBP) were independently associated with a higher risk of subclinical AF as detected by ILR.[11] Further, the randomized *Screening for Atrial Fibrillation Among Older Patients in Primary Care Clinics* (VITAL-AF) trial showed a similar rate of new-onset AF diagnosis at 1 year for single-timepoint screening with single-lead ECG device vs. usual care among individuals aged ≥65 years in primary care practices [1.72% vs. 1.59%; risk difference 0.13% (95% CI: −0.16-0.42)], but a significantly higher AF incidence in the screening group than the control group when considering only those older than 85 years [5.56% vs. 3.76%; risk difference 1.80% (95% CI: 0.18-3.30)].[38] However, a higher screening yield may not necessarily translate into greater clinical benefits. Indeed, an important takeaway from the LOOP Study may be that not all AF is worth screening for or should merit oral anticoagulation. It is crucial to differentiate between clinically relevant and irrelevant AF phenotypes, as subclinical AF could be aside to cardiovascular morbidities rather than being a truly causal risk factor for stroke—or may arise even as part of normal physiology or aging. Supporting this notion is the apparent lack of correlation between CHA_2DS_2-VASc score and the screening effects on stroke prevention, as observed in the primary reporting of the LOOP Study.[10] Neither were there any noticeable interactions with traditional risk factors including age, sex, and clinical history, in the pre-specified subgroup analyses. In addition, surprisingly, a subsequent explorative analysis of the LOOP Study assessing screening effects according to the presence/absence of CVD—as defined by ischaemic heart disease, heart failure, prior stroke, valvular heart disease, or peripheral artery disease—revealed that the stroke preventive effects of ILR screening vs. usual care were mainly upheld by the healthier participants (without pre-existing CVD), although the rate of AF detection was lowest in this subgroup.[34] The HR for screening effects was 0.64 (95% CI: 0.44-0.93) vs. 1.13 (95% CI: 0.76-1.68) for without vs. with CVD ($P_{interaction} = 0.041$). A possible explanation may involve the complex interplay between stroke pathogenesis and cardiovascular comorbidities in patients with CVD. Besides, it could be speculated that the already comprehensive patient care and monitoring in these CVD patients would have led to the detection of the most clinically relevant AF as well as an optimal management of risk factors by usual care during study follow-up, thereby minimizing the potential benefits of additional AF screening. In line herewith, another LOOP sub-study focusing on stroke severity and aetiology also showed a significant reduction in severe/fatal cardioembolic stroke or embolic stroke of undetermined source for ILR screening vs. usual care among participants without prior stroke but not among those who had a stroke history [HR 0.46 (95% CI: 0.22-0.97) and 1.49 (95% CI: 0.64-3.45), respectively; $P_{interaction} = 0.04$].[41] Again, competing risk factors in patients with complicated health conditions seemed to diminish the efficacy of screening for, and treatment of, less clinically evident disease. This further corroborates findings from three previous RCTs. The German trials, *Finding Atrial Fibrillation in Stroke—Evaluation of Enhanced and Prolonged Holter Monitoring* (Find-$AF_{RANDOMISED}$) and *Impact of standardized MONitoring for Detection of Atrial Fibrillation in Ischemic Stroke* (MonDAFIS), compared additional continuous AF screening with Holter device to usual care with conventional rhythm monitoring of ≥24 h in patients with acute ischaemic stroke.[39,42] No significant difference in recurrent ischaemic stroke was observed between the randomization groups in either of the studies. On the other hand, the Canadian *Post-Embolic Rhythm Detection with Implantable* vs. *External Monitoring* (PERDIEM) trial evaluated the effects of prolonged ECG monitoring with ILR for 12 months vs. external recorder for four weeks in patients who suffered from an acute ischaemic stroke within the last 6 months.[40] At 12-month follow-up, similar rates of recurrent ischaemic stroke were reported across randomization groups, despite a clearly higher AF detection in the ILR group. Hence, these RCT data do not appear to support the otherwise guideline-recommended extended continuous AF screening beyond routine rhythm monitoring in a post-stroke regimen.[1,3] Some have even raised arguments that AF detected after stroke is less clinically relevant than AF diagnosed before stroke, due to a potentially lower AF burden.[43,44]

Looking at other variables to potentially refine screening targets, a *post hoc* analysis of 5997 participants with available baseline SBP measurements

in the LOOP Study demonstrated an increasing screening benefit with higher SBP from 150 mmHg.[33] Compared with usual care, ILR screening led to a significant stroke reduction only among participants with SBP ≥150 mmHg [HR 0.55 (95% CI: 0.37–0.82)] but not those with lower blood pressure [HR 1.18 (95% CI: 0.82–1.71); $P_{interaction}$ = 0.0061]. Nevertheless, relying solely on SBP to guide clinical decisions regarding AF screening may be controversial, given the diurnal and context-dependent measurement variability as well as the modifiable nature of blood pressure. Rather, more attention should be paid on better monitoring and management of risk factors to mitigate the health risks related to subclinical AF.

Using a simple, validated risk scheme based solely on clinical variables—such as the CHA_2DS_2-VASc score—might seem to be an appealing and straightforward approach for risk stratification and selection to AF screening in clinical practice. However, as indicated by the data from randomized trials presented above, patients deemed to have a high risk of AF and stroke by the presence of traditional cardiovascular risk factors do not necessarily benefit from screening. Adding to the complexity of this matter is partly the already enhanced patient management by contemporary standard care, along with the seemingly intricate and not yet fully understood interrelation between the pathophysiological mechanisms of stroke and cardiovascular risk profiles, in patients with subclinical AF. Thus, more data from RCTs are warranted to elucidate the risk stratification of subclinical AF with respect to the potential benefits of early detection, thereby informing AF screening strategies. In this context, biological surrogate markers may hold potential in enabling more precise risk estimation, as these are speculated to be more sensitive and better reflect preclinical cardiac disease states. It is worth noting that various biomarkers from imaging, ECG, and blood tests have already been linked to subclinical AF and stroke in previous research,[9,17,45–53] although their clinical utility for AF screening is less established. However, a recent secondary analysis of the LOOP Study demonstrated N-terminal pro-B-type natriuretic peptide (NT-proBNP) being a promising tool to identify patients more likely to benefit from AF screening, as the stroke preventive screening effects seemed to increase with higher NT-proBNP levels.[53] Additionally, the ongoing *Systematic NT-proBNP and ECG screening for Atrial Fibrillation Among 75 Year Olds in the Region of Stockholm, Sweden* (STROKESTOP II) trial is currently evaluating the effects of a stratified AF screening strategy based on NT-proBNP vs. usual care in an older general population and may help to provide further insights into the potential role of this cardiac biomarker in screening.[54]

The burden of subclinical atrial fibrillation

In addition to the cardiovascular risk profile, the thromboembolic risk associated with subclinical AF is believed to increase with its burden.[1,3,8,12,13,55–57] Although cardiac monitoring has enabled characterizing subclinical AF burden in different ways and further investigating for the related stroke risk, clear evidence on the most appropriate burden threshold for initiating anticoagulation is still lacking. Nonetheless, in contemporary practice, there is a common consensus that subclinical AF episodes exceeding 24 h should prompt consideration for oral anticoagulation.[1,3] This was originally based on findings from a secondary analysis of the landmark ASSERT trial, where Van Gelder *et al.*[55] showed the increased stroke risk in patients with CIED-detected AF to be primarily upheld by longer episodes lasting ≥24 h. Subsequently, an American retrospective cohort study of data from the Veterans Health Administration examined the use of oral anticoagulation for stroke in patients with device-detected AF.[56] The study demonstrated that compared to no anticoagulation prescription, the use of oral anticoagulation was associated with a remarkably reduced stroke risk only among those with an episode duration ≥24 h. However, the observational nature of these studies inherently limited their ability to infer causality. In view of the recently reported ARTESiA trial, oral anticoagulation appeared to protect against strokes also in device-detected AF with an episode duration shorter than 24 h, albeit no clear net benefits observed.[20] Future explorative analyses from ARTESiA may help to shed light on the optimal burden threshold for meriting oral anticoagulation in the context of subclinical AF.

To date, only one study had reported on the effects of oral anticoagulation for subclinical AF according to the episode duration using randomized trial data. In a pre-specified analysis of the NOAH-AFNET 6 trial, Becher *et al.*[23] stated no significant interactions between baseline AF duration and the effects of edoxaban vs. placebo. For ischaemic stroke, the anticoagulation therapy did not significantly reduce the outcome among patients with baseline AF duration ≥24 h [0.95%/year vs. 0.97%/year for edoxaban vs. placebo; HR 1.03 (95% CI: 0.14–7.32)] or those with shorter duration [0.90%/year vs. 0.96%/year; HR 0.92 (95% CI: 0.50–1.70); $P_{interaction}$ = 0.89]. The lack of a differential effect across AF burden could be potentially explained by (i) the limited power due to early trial termination and (ii) the possible dilution of treatment effects by open-label anticoagulation upon ECG documentation of AF, which occurred more frequently among those with baseline AF duration ≥24 h.[23] Nevertheless, their findings are arguably in alignment with those reported by the above-mentioned LOOP sub-study evaluating the impact of preexisting CVD on screening effects. Indeed, although patients with CVD were at markedly higher risk of developing AF episodes ≥24 h as detected by ILR [HR 1.64 (95% CI: 1.05–2.56)], a significant screening benefit for ILR vs. usual care was found only among those without CVD at baseline.[34] Thus, these RCT data appear to raise questions about the justification of using episode duration as a proxy for the clinical relevance of subclinical AF and call for further investigation on the association between arrhythmia burden and the potential benefits of subclinical AF detection and treatment.

Conclusions

Atrial fibrillation is often asymptomatic but still associated with increased stroke risk, which could be mitigated by early detection and treatment. Current

guidelines recommend consideration of concomitant risk factors to guide screening and AF episode duration to guide treatment, which seems questionable in view of the limited data. More evidence is warranted to provide insights into the potential benefits of screening and treatment of screen-detected AF in specific population subgroups and AF phenotypes.

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Data availability

No new data were generated or analysed in support of this research.

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