REVIEW

THE AMERICAN JOURNAL of MEDICINE®

# Long-Term Cardiac Monitoring After Embolic Stroke of Undetermined Source: Search Longer, Look Harder

**Dimitrios Sagris, MD,[a,b] Stephanie L. Harrison, PhD,[a,c] Benjamin J.R. Buckley, PhD,[a,c] George Ntaios, MD,[b] Gregory Y.H. Lip, MD[a,c,d]**

*[a]Liverpool Centre for Cardiovascular Science, University of Liverpool and Liverpool Heart & Chest Hospital, Liverpool, UK; [b]Department of Internal Medicine, School of Health Sciences, Faculty of Medicine, University of Thessaly, Larissa, Greece; [c]Department of Cardiovascular and Metabolic Medicine, Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK; [d]Department of Clinical Medicine, Aalborg University, Aalborg, Denmark.*

**ABSTRACT**

Embolic stroke of undetermined source (ESUS) represents a heterogeneous subgroup of patients with cryptogenic stroke, in which despite an extensive diagnostic workup the cause of stroke remains uncertain. Identifying covert atrial fibrillation among patients with ESUS remains challenging. The increasing use of cardiac implanted electronic devices (CIED), such as pacemakers, implantable defibrillators, and implantable loop recorders (ILR), has provided important information on the burden of subclinical atrial fibrillation. Accumulating evidence indicate that long-term continuous monitoring, especially in selected patients with ESUS, significantly increases the possibility of atrial fibrillation detection, suggesting it may be a cost-effective tool in secondary stroke prevention. This review summarizes available evidence related to the use of long-term cardiac monitoring and the use of implantable cardiac monitoring devices in patients with ESUS.

 *• The American Journal of Medicine (2022) 000:1−7*

**KEYWORDS:** Atrial fibrillation; Monitoring; Stroke; ESUS

## INTRODUCTION

Ischemic stroke is a heterogeneous syndrome that may result from several causes such as atherosclerosis, small vessel disease, and atrial fibrillation.[1] Despite an extensive diagnostic workup during the acute or chronic phase of the ischemic stroke, the cause of ischemic stroke remains unexplained for 20% of patients and is termed cryptogenic stroke.[2,3]

The term embolic stroke of undetermined source (ESUS) has been used to describe a subgroup of patients with cryptogenic stroke, in which, despite an extensive diagnostic workup, the cause of stroke remains uncertain.[4] ESUS comprises about 17% of all patients with ischemic stroke with a considerable risk for stroke recurrence and cardiovascular events.[2,5-8] ESUS represents a heterogeneous population of these patients in terms of the underlying cause of stroke. This may be due to atherosclerotic disease and low-degree stenosis, covert paroxysmal atrial fibrillation, patent foramen ovale, left ventricular disease, and others, which

**Funding:** This work is supported in part by an ESC Council on Stroke research fellowship awarded to DS, as well as an unrestricted educational grant from Medtronic. The funders had no role in the content or construct of this manuscript.

**Conflicts of Interest:** Dr. Sagris: nothing to declare; Dr. Harisson: nothing to declare; Dr. Buckley: nothing to declare; Dr. Ntaios: speaker fees/Advisory Boards/Research support from Amgen; Bayer; BMS/Pfizer; Boehringer-Ingelheim; Elpen; Galenica; Sanofi; Winmedica. All fees are paid to his institution (University of Thessaly); Dr. Lip: reports consultancy and speeker fees from BMS/Pfizer, Boehringerrr Ingelheim and Daiichi-Sankyo outside the submitted work. No fees received personally

**Authorship:** All authors had access to the data and a role in writing this manuscript.

Requests for reprints should be addressed to Gregory Y. H. Lip, MD, William Henry Duncan Building | 6 West Derby Street, Liverpool, L7 8TX, UK.

E-mail address: gregory.lip@liverpool.ac.uk


https://doi.org/10.1016/j.amjmed.2022.04.030

frequently overlap.[4,9,10] Among the diagnostic workup of potential causes of ESUS, identifying covert atrial fibrillation remains challenging.

The increasing use of cardiac implanted electronic devices (CIED), such as pacemakers, implantable defibrillators, and implantable loop recorders (ILR), has provided the ability to assess atrial arrhythmia burden. These devices can identify short episodes of subclinical atrial fibrillation and other atrial tachyarrhythmias, summarized under as atrial high-rate episodes (AHREs). Evidence suggests AHREs significantly increase the risk of stroke when present for >30 seconds in patients with CIEDs, and >2 minutes among patients with cryptogenic stroke and ILR.[11] However, it is unclear whether these patients would benefit from the use of oral anticoagulants to reduce their risk of stroke.[12]

Despite the results of several studies indicating the importance of atrial fibrillation detection by implantable monitoring devices, the use of ILRs remains underappreciated in clinical practice. This review summarizes available evidence related to the use of implantable devices in patients with ESUS.

**CLINICAL SIGNIFICANCE**

- Identifying covert atrial fibrillation among patients with embolic stroke of undetermined source remains challenging.
- Some patients with embolic stroke of undetermined source may benefit from anticoagulation.
- Identifying patients with embolic stroke of undetermined source in higher risk of atrial fibrillation is essential.
- Long-term continuous monitoring in selected patients with embolic stroke of undetermined source increases the possibility of atrial fibrillation detection.

## CRYPTOGENIC STROKE AND ESUS, NOT JUST ANOTHER CARDIOEMBOLIC STROKE

In pursuit of reclassifying patients with cryptogenic stroke into a therapeutically relevant category, which may benefit from use of oral anticoagulation, the Cryptogenic Stroke/ESUS International Working Group introduced the term ESUS.[4] Two large randomized control trials, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE ESUS) and Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source (RESPECT ESUS), which compared rivaroxaban and dabigatran versus aspirin, respectively, showed that anticoagulation was not superior to aspirin for secondary stroke prevention in patients with ESUS.[13,14] These findings indicated that the use of oral anticoagulation for the unselected population with ESUS was not the optimal strategy and further suggested that the ESUS concept remains an etiologically heterogeneous entity. The failure of the RESPECT-ESUS and NAVIGATE-ESUS trials in demonstrating efficacy in the prevention of stroke recurrences in patients with ESUS may be partially attributed to the recent finding that the majority of patients with ESUS have more than 1 potential embolic source.[10] Despite the overlap, among all potential embolic sources, patients diagnosed with atrial fibrillation were identified with the highest risk of stroke recurrence.[10] Although a direct causative association between ESUS and atrial fibrillation episodes detected during follow-up is unclear, especially if the episodes occur late or are of short duration,[15] it is important that these episodes are detected because this may indicate the need for oral anticoagulation treatment to reduce the risk of recurrent stroke. Overall, available evidence suggests that not all patients with ESUS may benefit from anticoagulation, but a thorough investigation for atrial fibrillation following stroke and initiation of anticoagulation if atrial fibrillation is detected may be warranted in this population.

## FROM ELECTROCARDIOGRAPHY TO IMPLANTABLE CARDIAC MONITORS AFTER ESUS: SEARCH LONGER

Atrial fibrillation is a dynamic arrhythmia, and the ability to identify atrial fibrillation during follow-up is improved with an intensity of the diagnostic workup. Consecutive electrocardiography recordings identified atrial fibrillation in almost 1 in 20 patients with acute stroke.[16] Although other modalities such as telemetry and bedside monitoring during the acute stroke are highly sensitive, these approaches are associated with high false-positive rates and are not suitable for long-term monitoring.[17]

The Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) study, which included patients with cryptogenic stroke who were investigated for atrial fibrillation with wearable event recorders, showed that 30-day cardiac monitoring could significantly increase the identification of atrial fibrillation and the prescription of oral anticoagulants.[18] Similarly, wearable patches or mobile continuous outpatient telemetry devices significantly increase the possibility of atrial fibrillation identification compared to short-duration Holter.[19] Furthermore, in the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL-AF) study, patients underwent continuous monitoring with an insertable device for a 6-month period following ischemic stroke. The results showed that atrial fibrillation detection was significantly higher in the implantable cardiac monitoring (ICM) group compared to conventional follow-up (8.9% vs 1.4% respectively; hazard ratio [HR]: 6.4; 95% confidence interval [CI]:1.9 - 21.7),[20] while after 2 years of follow-up, 1 out of 5 patients with cryptogenic stroke were diagnosed with atrial fibrillation episodes >2 minutes, which

otherwise may have been missed by external recorders.[21] In the same study, among patients with ICM long-term continuous monitoring was found to be superior in detecting atrial fibrillation compared to several intermittent monitoring strategies.[22] A recent meta-analysis including 47 studies and 8,215 patients with cryptogenic or ESUS stroke using ICMs or noninvasive cardiac monitoring showed that the rate of atrial fibrillation detection by ICMs increased by the duration of follow-up (range from 2.0% [95% CI: 0.0-5.6, $I^2$: 52%] at 1 week to 28.5% [95% CI:17.6-39.3, $I^2$ 92%] at 36 months),[23] whereas age (odds ratio [OR]: 3.48, 95% CI: 2.50-4.84), female sex (OR: 1.35, 95% CI 1.04-1.74), left atrial dilatation >40 mm (OR: 1.55, 95%CI 1.08-2.23), and the congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack, vascular disease, and sex ($CHA_2DS_2VASc$) score (OR: 1.84, 95% CI: 1.00-3.38) were positively corelated to atrial fibrillation detection.[23]

The recently published Post-Embolic Rhythm Detection With Implantable Versus External Monitoring (PER DIEM) randomized trial including 300 patients with cryptogenic stroke, confirmed that the detection of atrial fibrillation lasting >2 minutes was significantly higher in long-term monitoring with ILR compared with external loop recorders.[24] In this study, atrial fibrillation detection rate was 15.3% among patients with cryptogenic stroke followed with ILRs for 12 months compared with 4.7% in the group of external monitoring for 30 days (risk ratio [RR]: 3.29, 95% CI: 1.45-7.42).[24] Accordingly, the Atrial Fibrillation Detected by Continuous ECG Monitoring (LOOP) study showed that ILR screening among individuals with stroke risk factors resulted in a 3-fold increase in atrial fibrillation detection (HR: 3.17, 95% CI: 2.81-3.59).[25] Despite this high proportion of diagnosed atrial fibrillation, with a significant increase in the use of anticoagulation (HR: 2.72, 95% CI: 2.41-3.08), atrial fibrillation detection did not result in a significant reduction of stroke during follow-up (HR: 0.80, 95% CI: 0.61-1.05).[25] This finding may potentially be attributed to the short duration threshold of 6 minutes used in this study, which may have led to anticoagulation initiation in patients at low risk of future ischemic stroke.[25] Although ILR were found to be superior compared with external monitoring in atrial fibrillation identification, the combination of both external cardiac monitoring followed by an ICM may be a cost-effective way to identify more patients with ESUS with atrial fibrillation.[26] These data indicate that long-term continuous monitoring of patients with ESUS significantly increases the possibility of identifying atrial fibrillation during follow-up and demonstrates the need to optimize patient selection for long-term cardiac monitoring, including wearable and ICM devices, based on the risk of atrial fibrillation and stroke recurrence.

## CANDIDATES FOR LONG-TERM CARDIAC MONITORING: LOOK HARDER

Given the large prevalence of ESUS and the restricted resources for prolonged cardiac monitoring, which may not always be accessible to patients with ESUS, it is essential to stratify patients with ESUS based on the risk of incident atrial fibrillation. The $CHA_2DS_2$-VASc score, which was originally created to assess the risk of thromboembolism among patients with atrial fibrillation, was found to correlate with increased risk of stroke recurrence among patients with ESUS.[27] Accordingly in the CRYSTAL-AF study, atrial fibrillation was detected in almost half of the patients with ESUS with a $CHADS_2$ score ≥4.[28]

Several other atrial fibrillation risk stratification tools have been developed or validated among patients with cryptogenic stroke or ESUS (see Table).[29-36] The atrial fibrillation-embolic stroke of undetermined source (AF-ESUS) score, which was derived by a multicenter ESUS database, factoring for the coexistence of several potential causes of ESUS, showed high sensitivity and a high negative predictive value to identify patients with ESUS with a low probability of new atrial fibrillation (94.9%, 95% CI: 89.3-98.1% and 98.0%, 95% CI: 95.8-99.3%, respectively), suggesting that patients with ESUS with score of ≥1 may be better candidates for prolonged automated cardiac monitoring.[30] AF-ESUS was externally validated in patients with ESUS with ICM, showing that patients with AF-ESUS score ≤0 were unlikely to develop long lasting episodes of atrial fibrillation on follow-up.[37] The HAVOC score, which stands for hypertension, age, valvular heart disease, peripheral vascular disease, obesity, congestive heart failure, and coronary artery disease, and which was developed from and validated in the Stanford Translational Research Integrated Database Environment (STRIDE), in a cohort of patients with cryptogenic stroke or transient ischemic attack showed that patients with lower HAVOC scores had a lower risk of atrial fibrillation (area under the curve [AUC]: 0.77).[31] A recent analysis of the Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate Versus Acetylsalicylic Acid in Patients With Embolic Stroke of Undetermined Source (RE-SPECT ESUS) trial showed that a HAVOC score ≥3 was associated with a significantly higher possibility of incident atrial fibrillation compared with a score of 0 or 1 (HR: 2.68, 95% CI: 1.96-3.66).[38] Although an increase in the HAVOC score per 1 point was associated with an increased risk of atrial fibrillation (OR: 1.22, 95% CI:1.16-1.28), the score showed only modest ability to discriminate this risk (c-statistic: 0.62),[38] while the low rate of atrial fibrillation detection in patients with a low HAVOC score was not confirmed in external validation.[39] Similarly the recent Graz AF Risk Score developed among 150 patients with cryptogenic stroke showed good discriminating effect (AUC: 0.85, 95% CI 0.78-0.92).[32] Recently, the Re-CHARGE-AF (Re-Cohorts for Heart and Aging Research in Genomic Epidemiology for Atrial Fibrillation) score, which was developed based on the Cohorts for Heart and Aging Research in Genomic Epidemiology for Atrial Fibrillation (CHARGE-AF) score, was proposed to identify atrial fibrillation among patients with ischemic stroke, independently of the

**Table** Atrial Fibrillation Prediction Scores Developed or Validated in Patients with ESUS or Cryptogenic Stroke

| NDAF[29] | HAVOC[31] | AF-ESUS[30] | Graz AF[32] | Brown ESUS-AF score[33] | STAF score[34] | ACTEL score[35] | Decryptoring score[36] |
|---|---|---|---|---|---|---|---|
| Age | Age | Age | Age | Age | Age | Age | Age |
| Coronary artery disease or stroke | Congestive heart failure | Hypertension | NT-proBNP | Left atrial enlargement | NIHSS | Hypercholesterolemia | Hypertension |
| Left atrial area | Hypertension | Left ventricle hypertrophy | Brain imaging | | Left atrial dilatation | Tricuspid regurgitation | Troponin T |
| | Valvular disease | Left atrial diameter | ECG/monitoring | | Vascular etiology | Left ventricular end-diastolic volume | NT-proBNP |
| | Coronary artery disease | LVEF <35% | Echocardiography | | | Left atrium | Left atrial strain reservoir |
| | Peripheral artery disease | Supraventricular extra-systole on ECG | | | | | Left atrial strain conduct |
| | BMI | Subcortical infarct | | | | | |
| | | Nonstenotic carotid plaques | | | | | |

ACTEL = Age ≥ 75 years; hyperCholesterolemia; Tricuspid regurgitation ≥ mild-to-moderate; left ventricular End-diastolic volume <65 mL; Left atrium ≥4 cm; AF-ESUS = atrial fibrillation-embolic stroke of undetermined source; BMI = body mass index; ECG = electrocardiogram; ESUS-AF = embolic stroke of undetermined source-atrial fibrillation; ; HAVOC = hypertension, age, valvular heart disease, peripheral vascular disease, obesity, congestive heart failure, coronary artery disease; LVEF = left ventricle ejection fraction; NDAF = newly diagnosed atrial fibrillation; NIHSS = National Institute of Health Stroke Scale; NT-proBNP = N-terminal pro-brain natriuretic peptide; STAF = Score for the Targeting of Atrial Fibrillation.

ischemic stroke etiology, with improved discrimination capacity [C-statistic, 0.74 (95% CI: 0.68-0.79)].[40]

Several other tools that have been developed in the non-stroke population have been proposed to evaluate the risk of atrial fibrillation in patients with ischemic stroke, including the Coronary, Heart failure, Age, stroke SEverity,-LipidEmia, Sugar, prior Stroke (CHASE-LESS),[41] the Coronary Artery Disease or Chronic Obstructive Pulmonary Disease; Hypertension; Elderly; Systolic Heart Failure; Thyroid Disease ($C_2$HEST),[42] the Age: 0.76 points/year, Stroke Severity NIHSS ≤5 = 9 points, NIHSS >5 = 21 points; to Find AF (AS5F),[43] and the $CHA_2DS_2$-VASc score (even though the latter was designed as a stroke risk stratification score and not to predict incident atrial fibrillation).[27] Therefore, the accuracy of clinical tools to predict risk of atrial fibrillation in patients with ESUS may warrant further investigation. The recent focus on multimorbidity, the challenges of dynamic risk stratification (with aging and incident comorbidities), and the opportunities from artificial intelligence and machine learning may improve our approach to risk stratification.[44,45]

In summary, the use of atrial fibrillation risk stratification tools in patients with ESUS has the potential to improve the distribution of resources by targeting long-term monitoring and ICM to the highest-risk patients. The increasing use of mHealth technologies and machine learning approaches are increasing in this rapidly evolving arena.

## THE PATHWAY TOWARD IMPROVING ATRIAL FIBRILLATION DETECTION

Searching harder and longer for atrial fibrillation in patients with ESUS will give the opportunity of an individualized and holistic approach to the thromboembolic risk assessment and reduction of future stroke risk.[46] This is important given that asymptomatic atrial fibrillation episodes may be associated with poor outcomes post stroke.[47,48]

Although it is important to identify patients with ESUS who will most likely benefit from long-term rhythm monitoring, a standardized pathway may further improve the quality of secondary stroke prevention management for patients with ESUS, decreasing the future burden of atrial fibrillation related to ischemic stroke (Figure). The increasing use of ICM in patients with ESUS and the available evidence from randomized and observational studies suggest that it may be a cost-effective diagnostic modality that may benefit an important proportion of patients with ESUS.[49,50]

However, despite the evident efficacy of ICMs to identify atrial fibrillation in patients with ESUS, its efficacy related to recurrent major cardiovascular outcomes and whether short subclinical atrial fibrillation episodes identified by ICMs merit anticoagulation remains unclear. The ongoing Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) and Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes (NOAH-AFNET) trials in patients with CIEDs, may

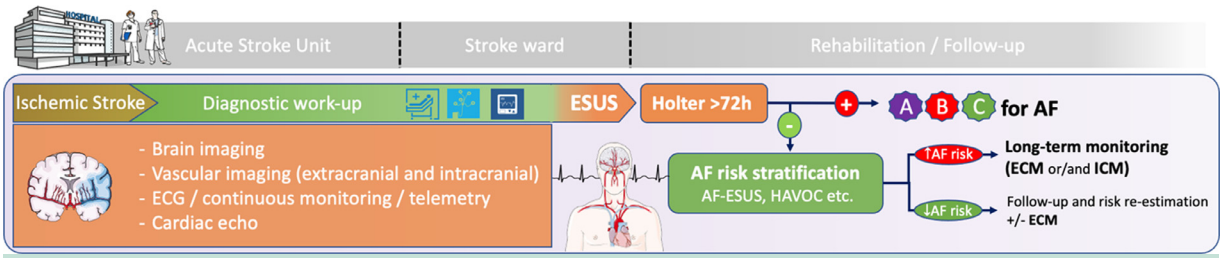


**Figure** The pathway toward more AF detection. AF = atrial fibrillation; ECG = electrocardiogram; ECM = external continuous monitoring (wearable patches, mobile cardiac outpatient telemetry, etc.); ESUS = embolic stroke of undetermined source; ICM = implantable continuous monitoring. Servier Medical Art images were used for this figure (https://smart.servier.com)

provide essential information on the use of anticoagulation in patients with subclinical atrial fibrillation.[51,52] These data may highlight the importance of new randomized cardiovascular outcome trials assessing the efficacy and safety of anticoagulation therapy in patients with ESUS with ICM.

Nonetheless, on detection and confirmation of atrial fibrillation in patients after sustaining a stroke, appropriate stroke prevention with anticoagulation can be initiated, but it should be remembered that stroke prevention is only one part of the appropriate characterization[53] and the holistic management approach to atrial fibrillation care.[54] Adherence to such an integrated care approach has been associated with improved clinical outcomes in patients with atrial fibrillation.[55,56] Indeed, an integrated care approach has also been proposed for patients of stroke and other chronic conditions.[57-59]

In conclusion, not only do we look harder and look longer for atrial fibrillation, this should lead into a holistic, integrated patient pathway for comprehensive atrial fibrillation detection and confirmation of the diagnosis; characterization and evaluation of the patient; and an integrated care approach to its management.

## References

1. Ntaios G, Hart RG. Embolic stroke. *Circulation* 2017;136(25):2403–5. https://doi.org/10.1161/CIRCULATIONAHA.117.030509.
2. Hart RG, Catanese L, Perera KS, Ntaios G, Connolly SJ. Embolic stroke of undetermined source: a systematic review and clinical update. *Stroke* 2017;48(4):867–72. https://doi.org/10.1161/strokeaha.116.016414.
3. Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis. *Stroke* 2015;46(1):176–81. https://doi.org/10.1161/strokeaha.114.007240.
4. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13(4):429–38. https://doi.org/10.1016/S1474-4422(13)70310-7.
5. Ntaios G, Papavasileiou V, Milionis H, et al. Embolic strokes of undetermined source in the Athens stroke registry: an outcome analysis. *Stroke* 2015;46(8):2087–93. https://doi.org/10.1161/strokeaha.115.009334.
6. Ntaios G, Lip GYH, Vemmos K, et al. Age- and sex-specific analysis of patients with embolic stroke of undetermined source. *Neurology* 2017;89(6):532–9. https://doi.org/10.1212/wnl.0000000000004199.
7. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;378(23):2191–201. https://doi.org/10.1056/NEJMoa1802686.
8. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;380(20):1906–17. https://doi.org/10.1056/NEJMoa1813959.
9. Ntaios G. Embolic stroke of undetermined source: JACC review topic of the week. *J Am Coll Cardiol* 2020;75(3):333–40. https://doi.org/10.1016/j.jacc.2019.11.024.
10. Ntaios G, Perlepe K, Lambrou D, et al. Prevalence and overlap of potential embolic sources in patients with embolic stroke of undetermined source. *J Am Heart Assoc* 2019;8(15):e012858. https://doi.org/10.1161/JAHA.119.012858.
11. Sagris D, Georgiopoulos G, Pateras K, et al. Atrial high-rate episode duration thresholds and thromboembolic risk: a systematic review and meta-analysis. *J Am Heart Assoc* 2021;10(22):e022487. https://doi.org/10.1161/jaha.121.022487.
12. Schnabel RB, Haeusler KG, Healey JS, et al. Searching for atrial fibrillation poststroke. *Circulation* 2019;140(22):1834–50. https://doi.org/10.1161/CIRCULATIONAHA.119.040267.
13. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. *N Engl J Med* 2018;378(23):2191–201. https://doi.org/10.1056/NEJMoa1802686.
14. Diener H-C, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. *N Engl J Med* 2019;380(20):1906–17. https://doi.org/10.1056/NEJMoa1813959.
15. Ntaios G, Papavasileiou V, Lip GY, et al. Embolic stroke of undetermined source and detection of atrial fibrillation on follow-up: how much causality is there? *J Stroke Cerebrovasc Dis* 2016;25(12):2975–80. https://doi.org/10.1016/j.jstrokecerebrovasdis.2016.08.015.
16. Liao J, Khalid Z, Scallan C, Morillo C, O'Donnell M. Noninvasive cardiac monitoring for detecting paroxysmal atrial fibrillation or flutter after acute ischemic stroke: a systematic review. *Stroke* 2007;38(11):2935–40. https://doi.org/10.1161/strokeaha.106.478685.
17. Kurka N, Bobinger T, Kallmünzer B, et al. Reliability and limitations of automated arrhythmia detection in telemetric monitoring after stroke. *Stroke* 2015;46(2):560–3. https://doi.org/10.1161/STROKEAHA.114.007892.
18. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370(26):2467–77. https://doi.org/10.1056/NEJMoa1311376.
19. Kaura A, Sztriha L, Chan FK, et al. Early prolonged ambulatory cardiac monitoring in stroke (EPACS): an open-label randomised controlled trial. *Eur J Med Res* 2019;24(1):25. https://doi.org/10.1186/s40001-019-0383-8.
20. Sanna T, Diener H-C, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370(26):2478–86. https://doi.org/10.1056/NEJMoa1313600.
21. Ziegler PD, Rogers JD, Ferreira SW, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world

cryptogenic stroke population. *Int J Cardiol* 2017;244:175–9. https://doi.org/10.1016/j.ijcard.2017.06.039.
22. Choe WC, Passman RS, Brachmann J, et al. A comparison of atrial fibrillation monitoring strategies after cryptogenic stroke (from the cryptogenic stroke and underlying AF trial). *Am J Cardiol* 2015;116(6):889–93. https://doi.org/10.1016/j.amjcard.2015.06.012.
23. Noubiap JJ, Agbaedeng TA, Kamtchum-Tatuene J, et al. Rhythm monitoring strategies for atrial fibrillation detection in patients with cryptogenic stroke: a systematic review and meta-analysis. *Int J Cardiol Heart Vasc* 2021;34:100780. https://doi.org/10.1016/j.ijcha.2021.100780.
24. Buck BH, Hill MD, Quinn FR, et al. Effect of implantable vs prolonged external electrocardiographic monitoring on atrial fibrillation detection in patients with ischemic stroke: the PER DIEM randomized clinical trial. *JAMA* 2021;325(21):2160–8. https://doi.org/10.1001/jama.2021.6128.
25. Svendsen JH, Diederichsen SZ, Højberg S, et al. Implantable loop recorder detection of atrial fibrillation to prevent stroke (The LOOP Study): a randomised controlled trial. Lancet. 2021;398(10310):1507-1516. https://doi.org/10.1016/S0140-6736(21)01698-6
26. Medic G, Kotsopoulos N, Connolly MP, et al. Mobile cardiac outpatient telemetry patch vs implantable loop recorder in cryptogenic stroke patients in the us - cost-minimization model. *Med Devices (Auckl)* 2021;14:445–58. https://doi.org/10.2147/mder.S337142.
27. Ntaios G, Vemmos K, Lip GY, et al. Risk stratification for recurrence and mortality in embolic stroke of undetermined source. *Stroke* 2016;47(9):2278–85. https://doi.org/10.1161/strokeaha.116.013713.
28. Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: Insights from insertable cardiac monitors. *Int J Stroke* 2019;14(2):146–53. https://doi.org/10.1177/1747493018798554.
29. Bugnicourt JM, Flament M, Guillaumont MP, et al. Predictors of newly diagnosed atrial fibrillation in cryptogenic stroke: a cohort study. *Eur J Neurol* 2013;20(10):1352–9. https://doi.org/10.1111/ene.12017.
30. Ntaios G, Perlepe K, Lambrou D, et al. Identification of patients with embolic stroke of undetermined source and low risk of new incident atrial fibrillation: the AF-ESUS score. *Int J Stroke* 2021;16(1):29–38. https://doi.org/10.1177/1747493020925281.
31. Kwong C, Ling AY, Crawford MH, Zhao SX, Shah NH. A clinical score for predicting atrial fibrillation in patients with cryptogenic stroke or transient ischemic attack. *Cardiology* 2017;138(3):133–40. https://doi.org/10.1159/000476030.
32. Kneihsl M, Bisping E, Scherr D, et al. Predicting atrial fibrillation after cryptogenic stroke via a clinical risk score-a prospective observational study. *Eur J Neurol* 2022;29(1):149–57. https://doi.org/10.1111/ene.15102.
33. Ricci B, Chang AD, Hemendinger M, et al. A simple score that predicts paroxysmal atrial fibrillation on outpatient cardiac monitoring after embolic stroke of unknown source. *J Stroke Cerebrovasc Dis* 2018;27(6):1692–6. https://doi.org/10.1016/j.jstrokecerebrovasdis.2018.01.028.
34. Göksu E, Yüksel B, Esin M, et al. The value of STAF (score for the targeting of atrial fibrillation) in patients with cryptogenic embolic stroke. Noro Psikiyatr Ars. 2019;56(2):119-122. doi:10.5152/npa.2017.19348
35. Muscari A, Barone P, Faccioli L, et al. Usefulness of the ACTEL score to predict atrial fibrillation in patients with cryptogenic stroke. *Cardiology* 2020;145(3):168–77. https://doi.org/10.1159/000505262.
36. Vera A, Cecconi A, Ximénez-Carrillo Á, et al. A comprehensive model to predict atrial fibrillation in cryptogenic stroke: the Decryptoring Score. *J Stroke Cerebrovasc Dis* 2022;31(1):106161. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106161.
37. Kitsiou A, Sagris D, Schäbitz W-R, Ntaios G. Validation of the AF-ESUS score to identify patients with embolic stroke of undetermined source and low risk of device-detected atrial fibrillation. *Eur J Intern Med* 2021;89:135–6. https://doi.org/10.1016/j.ejim.2021.04.003.
38. Bahit MC, Sacco RL, Easton JD, et al. Predictors of atrial fibrillation development in patients with embolic stroke of undetermined source: an analysis of the RE-SPECT ESUS trial. *Circulation* 2021;144(22):1738–46. https://doi.org/10.1161/CIRCULATIONAHA.121.055176.
39. Ntaios G, Perlepe K, Lambrou D, et al. External performance of the HAVOC score for the prediction of new incident atrial fibrillation. *Stroke* 2020;51(2):457–61. https://doi.org/10.1161/STROKEAHA.119.027990.
40. Ashburner JM, Wang X, Li X, et al. Re−CHARGE−AF: recalibration of the CHARGE−AF model for atrial fibrillation risk prediction in patients with acute stroke. *J Am Heart Assoc* 2021;10(21):e022363. https://doi.org/10.1161/JAHA.121.022363.
41. Hsieh C-Y, Lee C-H, Sung S-F. Development of a novel score to predict newly diagnosed atrial fibrillation after ischemic stroke: the CHASE-LESS score. *Atherosclerosis* 2020;295:1–7. https://doi.org/10.1016/j.atherosclerosis.2020.01.003.
42. Li YG, Bisson A, Bodin A, et al. $C_{(2)}$HEST score and prediction of incident atrial fibrillation in poststroke patients: a French nationwide study. *J Am Heart Assoc* 2019;8(13):e012546. https://doi.org/10.1161/jaha.119.012546.
43. Uphaus T, Weber-Krüger M, Grond M, et al. Development and validation of a score to detect paroxysmal atrial fibrillation after stroke. *Neurology* 2019;92(2):e115–24. https://doi.org/10.1212/wnl.0000000000006727.
44. Guo Y. A new paradigm of "real-time" stroke risk prediction and integrated care management in the digital health era: innovations using machine learning and artificial intelligence approaches. *Thromb Haemost* 2022;122(1):5–7. https://doi.org/10.1055/a-1508-7980.
45. Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C, Sloop S. Improving stroke risk prediction in the general population: a comparative assessment of common clinical rules, a new multimorbid index, and machine-learning-based algorithms. *Thromb Haemost* 2022;122(1):142–50. https://doi.org/10.1055/a-1467-2993.
46. Kitsiou A, Rogalewski A, Kalyani M, et al. Atrial fibrillation in patients with embolic stroke of undetermined source during 3 years of prolonged monitoring with an implantable loop recorder. *Thromb Haemost* 2021;121(6):826–33. https://doi.org/10.1055/a-1346-2899.
47. Sun W, Freedman B, Martinez C, Wallenhorst C, Yan BP. Atrial fibrillation detected by single time-point handheld electrocardiogram screening and the risk of ischemic stroke. *Thromb Haemost* 2022;122(2):286–94. https://doi.org/10.1055/a-1588-8867.
48. Proietti M, Boriani G. Screening for atrial fibrillation in relation to stroke and mortality risk. *Thromb Haemost* 2022;122(2):171–5. https://doi.org/10.1055/a-1562-0747.
49. Thijs V, Witte KK, Guarnieri C, et al. Cost-effectiveness of insertable cardiac monitors for diagnosis of atrial fibrillation in cryptogenic stroke in Australia. *J Arrhythm* 2021;37(4):1077–85. https://doi.org/10.1002/joa3.12586.
50. Rinciog CI, Sawyer LM, Diamantopoulos A, et al. Cost-effectiveness of an insertable cardiac monitor in a high-risk population in the UK. *Open Heart* 2019;6(1):e001037. https://doi.org/10.1136/openhrt-2019-001037.
51. Lopes RD, Alings M, Connolly SJ, et al. Rationale and design of the apixaban for the reduction of thrombo-embolism in patients with device-detected sub-clinical atrial fibrillation (ARTESiA) trial. *Am Heart J* 2017;189:137–45. https://doi.org/10.1016/j.ahj.2017.04.008.
52. Kirchhof P, Blank BF, Calvert M, et al. Probing oral anticoagulation in patients with atrial high rate episodes: rationale and design of the non-vitamin k antagonist oral anticoagulants in patients with atrial high rate episodes (NOAH-AFNET 6) trial. *Am Heart J* 2017;190:12–8. https://doi.org/10.1016/j.ahj.2017.04.015.
53. Potpara TS, Lip GYH, Blomstrom-Lundqvist C, et al. The 4S-AF Scheme (stroke risk; symptoms; severity of burden; substrate): a novel approach to in-depth characterization (rather than classification) of atrial fibrillation. *Thromb Haemost* 2021;121(3):270–8. https://doi.org/10.1055/s-0040-1716408.

54. Chao TF, Joung B, Takahashi Y, et al. 2021 focused update consensus guidelines of the Asia Pacific Heart Rhythm Society on Stroke Prevention in Atrial Fibrillation: executive summary. *Thromb Haemost* 2022;122(1):20–47. https://doi.org/10.1055/s-0041-1739411.
55. Romiti GF, Pastori D, Rivera-Caravaca JM, et al. Adherence to the 'atrial fibrillation better care' pathway in patients with atrial fibrillation: impact on clinical outcomes-a systematic review and meta-analysis of 285,000 patients. *Thromb Haemost* 2022;122(3):406–14. https://doi.org/10.1055/a-1515-9630.
56. Yoon M, Yang PS, Jang E, et al. Improved population-based clinical outcomes of patients with atrial fibrillation by compliance with the simple abc (atrial fibrillation better care) pathway for integrated care management: a nationwide cohort study. *Thromb Haemost* 2019;119(10):1695–703. https://doi.org/10.1055/s-0039-1693516.
57. Guo Y, Zhang J, Lip GYH. Embolic stroke of undetermined source: the need for an integrated and holistic approach to care. *Thromb Haemost* 2021;121(3):251–4. https://doi.org/10.1055/a-1336-0576.
58. Lip GYH, Ntaios G. Novel clinical concepts in thrombosis: integrated care for stroke management-easy as ABC. *Thromb Haemost* 2022;122(3):316–9. https://doi.org/10.1055/a-1632-1777.
59. Field M, Kuduvalli M, Torella F, McKay V, Khalatbari A, Lip GYH. Integrated care systems and the aortovascular hub. *Thromb Haemost* 2022;122(2):177–80. https://doi.org/10.1055/a-1591-8033.