Intensive heart rhythm monitoring to decrease ischemic stroke and systemic embolism—the Find-AF 2 study—rationale and design

Tobias Uhe, MD[a,#], Katrin Wasser, MD[b,#], Mark Weber-Krüger, MD[c,#], Wolf-Rüdiger Schäbitz, MD[d], Martin Köhrmann, MD[e], Johannes Brachmann, MD[f], Ulrich Laufs, MD[a], Martin Dichgans, MD[g,h,i], Götz Gelbrich, PhD[j,k], David Petroff, PhD[l], Christiane Prettin, PhD[l], Dominik Michalski, MD[m], Andrea Kraft, MD[n], Thorleif Etgen, MD[o], Peter D. Schellinger, MD[p], Hassan Soda, MD[q], Florian Bethke, MD[r], Michael Ertl, MD[s], Bernd Kallmünzer, MD[t], Martin Grond, MD[u], Katharina Althaus, MD[v], Gerhard F. Hamann, MD[w], Meinhard Mende, PhD[l], Marcus Wagner, PhD[l], Sonja Gröschel, MD[x], Timo Uphaus, MD[x], Klaus Gröschel, MD[x,†], and Rolf Wachter, MD[a,y,z,†], on behalf of the Find-AF 2 study group

Göttingen, Germany; Essen, Germany; Coburg, Germany; Munich, Germany; Würzburg, Germany; Leipzig, Germany; Halle, Germany; Traunstein, Germany; Minden, Germany; Bad Neustadt, Germany; Ibbenbüren, Germany; Augsburg, Germany; Bielefeld, Germany

Background Atrial fibrillation (AF) is one of the most frequent causes of stroke. Several randomized trials have shown that prolonged monitoring increases the detection of AF, but the effect on reducing recurrent cardioembolism, ie, ischemic

From the [a]Department of Cardiology, University Hospital Leipzig, Leipzig, Germany, [b]Department of Neurology, University of Göttingen Medical Center, Göttingen, Germany, [c]Department of Palliative Medicine, University of Göttingen Medical Center, Göttingen, Germany, [d]Department of Neurology, EvKB-Bethel University Hospital, Bielefeld, Germany, [e]Department of Neurology, University of Essen, Essen, Germany, [f]Department of Cardiology, Klinikum Coburg, Coburg, Germany, [g]Institute for Stroke and Dementia Research (ISD), University Hospital, LMU Munich, Munich, Germany, [h]German Center for Neurodegenerative Diseases (DZNE, Munich), Munich, Germany, [i]Munich Cluster for Systems Neurology (SyNergy), Munich, Germany, [j]Institute for Clinical Epidemiology and Biometry, University of Würzburg, Würzburg, Germany, [k]Clinical Trial Center Würzburg, University Hospital Würzburg, Würzburg, Germany, [l]Clinical Trial Centre (ZKS) Leipzig, Leipzig University, Leipzig, Germany, [m]Department of Neurology, University Hospital Leipzig, Leipzig, Germany, [n]Department of Neurology, Hospital Martha-Maria, Halle, Germany, [o]Department of Neurology, Klinikum Traunstein, Traunstein, Germany, [p]Department of Neurology and Neurogeriatrics, University Hospital Minden, Minden, Germany, [q]Department of Neurology, Rhön Hospital, Bad Neustadt, Germany, [r]Department of Neurology, Ibbenbüren Hospital, Ibbenbüren, Germany, [s]Clinic for Neurology and Clinical Neurophysiology, University Hospital Augsburg, Augsburg, Germany, [t]Department of Neurology, University Hospital Erlangen, Erlangen, Germany, [u]Department of Neurology, Siegen Hospital, Siegen, Germany, [v]Department of Neurology, University Hospital Ulm, Ulm, Germany, [w]Clinic for Neurology and Neurorehabilitation, Bezirkskrankenhaus Günzburg, Günzburg, Germany, [x]Department of Neurology, University Medical Center of the Johannes Gutenberg University Mainz, Mainz, Germany, [y]Department of Cardiology and Pneumology, University of Göttingen Medical Center, Göttingen, Germany, [z]DZHK (German Center for Cardiovascular Research), partner site Göttingen, Göttingen, Germany

[#]Contributed equally and share first authorship.

[†]Contributed equally and share last authorship.

Members of the Find-AF 2 study group: Rolf Wachter, Klaus Gröschel, Katrin Wasser, Tobias Uhe, Wolf-Rüdiger Schäbitz, Martin Köhrmann, Martin Dichgans, Sonja Gröschel, Timo Uphaus, Marianne Hahn, Frederic Zuhorn, Leonard Wulff, Jorge Plümer, Lena Kok, Marcel Janz, Alkisti Kitsiou, Julian Gehmeyr, Alhuda Dabbagh, Charlotte Huber, Johann Pelz, Katja Wartenberg, Dominik Michalski, Mirko Seidel, Oscar Flissakowski, Anna Goschenhofer, Rabia-Basari Hussain, Ina Kim, Stephan Kinze, Christian Kroneberger, Michale Lingnau, Dennis Lischewski, Florian Muhn, Witold Rogge, Miriam Schieffer, Anuscheh Setayesh-Roonizi, Paul Sparenberg, Jill Marie Schertel, Peter Ringleb, Jan Purrucker, Anne Berberich, Miriam Heyse, Matthias Ungerer, Gregor Bauer, Christine Reichardt, Thorleif Etgen, Bernhard Ebel, Dragana Milanković-Eberl, Olav Schwarte, Constanze Höcherl, Eric-Manuel Asch, Luisa Bojtschuk, Maximilian Frey, Tomas Dlouhy, Michael Ertl, Philipp Patrick Zickler, Barbara Beier, Lino-Dominic Braadt, Inessa Gabrielyan, Pawel Kermer, Matthias Kaste, Ahmed Anter, Corina Stirbulescu, Nataliia Meleshchenco, Friederike Burgholte, Claus Lüers, Thorsten Steiner, Cierpinski, Lichti Mari-Carmen, Florian Bethke, Lars Bonowski, Hassan Abou Eid, Esteban Vajda-Medina, Mareike Probst, Hisham Essa, Benedikt Frank, Benjamin Stolte, Lennart Milles, Hassan Soda, Erich Hiermann, Renate Weinhardt Alexandra Rascher, Marius Stan, Stefan Kääb, Lars Kellert, Konstantinos Dimitriadis, Anna Kopczak, Bettina Küster, Moritz Sinner, Ignaz Steiger, Maria Kaffe, Sebastian Clauß, Daniel Janowitz, Raffael Thaler, Peter Schellinger, Jörg Glahn, Jan Schubert, Simone Jenniges, Silke Markmann-Boenke, Anne-Sophie Putzer, Michael Schwarze Vera Straeten, Marcus Wiemer, Bernd Kallmünzer, Kosmas Macha, David Haupenthal, Stefanie Balk, Clara-Sophie Kossel, Georg Häusler, Dominik Lehrieder, Peter Cidlinsky, Christian Hametner, Christine Vogl, Thomas Fischer, Moritz Huttelmaier, Octavian Maniuc Peter Nordbeck, Albrecht von Hardenberg, Martin Jünemann, Tobias Braun, Maxime Viard, Stefan Gerner, Omar AlHaj Omar, Sonja Genau, Linus Olbricht, Matthias Wassenberg, Niklas Langguth, Christian Fräbel, Romy Baumgart, Love-Preet Kalra, Norma Diel, Frank Hoffmann, Andrea Kraft, Bettine Schönmuth, Anja Giebler, Lorenz Weber, Martin Grond, Jan Birringer, Sandra Lichte-Schneider, Daniela Hütwohl, Lars Udo Krause, Martina Petersen, Katharina Althaus, Konstantin Kirchmeier, Liubov Novikova, Susanne Müller, Sebastian Schellong, Mirko Brudzinski, Ulrich Gerk, Holger Palisch, Frank R. Heinzel, Jana Fett, Avinash Suntha, Katja Burian, Bettina Schmitz, Anna Gutwinski, Veronika Angermüller, Tameem Alhammoud, Hüsniye Cakiroglu, Ullrich Bach, Darius Nabavi, Jens Offermann, Olaf Crome, Boris Dimitrijeski, Carsten Meincke, Gerhard Hamann, Burkhard Alber, Robert Müller, Lars-Peder Pallesen, Volker Pütz, Christian Hartmann, Jörg Berrouschot, Anett Stoll, Janina Keilitz, Dietrich Klunk, Roman Voigt, Andreas Kastrup, Andreas Schröter, Johannes Schmucker, Waltraud Pfeilschifter, Christoffer Krämer, Milena Wiemers, Micha Simon, Alexander Finke, Christian Weiß, Carsten Hobohm, Katrin Naupold, Karen Bley-Renning, Sabrina Winter, Sven Poli, Annerose Mengel, Khouloud Poli, Alexandra Gómez Expósito, Joshua Mbroh, Maria Tieck, Michael Rosenkranz, Stefan Boskamp, Nicolas Ritter, Lena Seibel, Christian Schöps, Rebecca Ketzler, Herbert Nägele, Karsten Sydow, Natalia Kurka, Jan Hendrik Schäfer, Daniel Charisse, Katharina Gruber, Konstantin Kohlhase, Franziska Lieschke, Felix Operhalski, Alexander Seiler, Gabor Petzold, Felix Jürgen Bode, Sebastian Stösser, Julius Meißner, Taraneh Ebrahimi, Julia Nordsiek, Niklas Beckonert, Karin Weissenborn, Gerrit Maximilian Große, Hans Worthmann, Ann-Katrin Hennemann, Svenja Jochmann, Julius Gründahl, Jana Al-Ayoubi, Johanna Ernst, Oliver Bähr, Herbert Gruber, Sonka Benesch, Thomas Pollinger, Nawar Alachkar, Sonia Busch, Steffi Butz, Mathias Forkmann, Christian Mahnkopf, Thomas Mischke, Steffen Schnupp, Götz Thomalla, Milani Deb-Chatterji, Bastian Cheng, Mathias Gelderblom, Julia Hoppe, Märit Jensen, Maximilian Schell, Eckhard Schlemm, Lars Marquardt, Haiko Kazarians, Pia Franziska Rheingans, Kai Hötzer, Dietmar Rose, Tobias Neumann-Haefelin, Jörg Berthel, Lirim Alijaj, Joachim Krug, Margit Niethammer,Géza-Attila Szöllösi, Marc Obermann, Nicoletta Adochitei, Herwig Strik, Arne Lenz, Frank Steigerwald, Jörg Müller, Martin Honermann, Marian Christoph Burgstaller, Rainer Kollmar, Maryam Rashid, Ahmad Ajaz Ganai, Ossendorf, Majda Saric, Karl-Heinz Tischer, Adela Toluli, Frank Arne Wollenweber, Laya Rahban, Thais Portugal Silva, Miri Lee, Matthias Julius Grosch, Jens Minnerup, Jan Liman, Martin Nückel, Magdalena Böhm.

Submitted May 19, 2023; accepted June 29, 2023

Reprint requests: *Rolf Wachter, MD, Department of Cardiology, University Hospital Leipzig, Liebigstraße 20, Haus 4, Leipzig 04103, Germany.*

E-mail address: rolf.wachter@medizin.uni-leipzig.de.

0002-8703

https://doi.org/10.1016/j.ahj.2023.06.016

stroke and systemic embolism, remains unknown. We aim to evaluate whether a risk-adapted, intensified heart rhythm monitoring with consequent guideline conform treatment, which implies initiation of oral anticoagulation (OAC), leads to a reduction of recurrent cardioembolism.

Methods Find-AF 2 is a randomized, controlled, open-label parallel multicenter trial with blinded endpoint assessment. 5,200 patients ≥ 60 years of age with symptomatic ischemic stroke within the last 30 days and without known AF will be included at 52 study centers with a specialized stroke unit in Germany. Patients without AF in an additional 24-hour Holter ECG after the qualifying event will be randomized in a 1:1 fashion to either enhanced, prolonged and intensified ECG-monitoring (intervention arm) or standard of care monitoring (control arm). In the intervention arm, patients with a high risk of underlying AF will receive continuous rhythm monitoring using an implantable cardiac monitor (ICM) whereas those without high risk of underlying AF will receive repeated 7-day Holter ECGs. The duration of rhythm monitoring within the control arm is up to the discretion of the participating centers and is allowed for up to 7 days. Patients will be followed for at least 24 months. The primary efficacy endpoint is the time until recurrent ischemic stroke or systemic embolism occur.

Conclusions The Find-AF 2 trial aims to demonstrate that enhanced, prolonged and intensified rhythm monitoring results in a more effective prevention of recurrent ischemic stroke and systemic embolism compared to usual care. (Am Heart J 2023;265:66–76.)

Background and rationale

Stroke is the leading cause of disability and the second most common cause of death worldwide.[1,2] A high proportion of strokes is attributable to atrial fibrillation (AF).[3] In patients with an established diagnosis of AF, anticoagulation reduces the risk of cardioembolism (ie, ischemic stroke or systemic embolism) by 64%.[4] However, in its paroxysmal form (pAF), it often escapes routine diagnostics because episodes occur unpredictably, persist for short durations and are often asymptomatic.

Cryptogenic strokes are frequent and often presumed to result from cardiac emboli, eg, due to undetected AF. But neither warfarin[5] nor rivaroxaban,[6] dabigatran,[7] or apixaban[8] have shown a benefit in patients with cryptogenic stroke or embolic stroke of unknown source.

An alternative approach would be to search thoroughly for AF in stroke patients and only switch secondary prevention from antiplatelets to oral anticoagulation (OAC) once AF is detected. Six randomized trials showed that different types of prolonged heart rhythm monitoring increased the AF detection rate after stroke nearly threefold.[9–14]

However, whether this translates into a risk reduction of recurrent ischemic stroke by a higher anticoagulation rate is currently unknown. In a meta-analysis including 2,188 patients, prolonged AF-monitoring was associated with a trend towards a reduced risk of recurrent stroke after initiation of OAC, but due to a relatively short follow-up with a resulting low event rate, this meta-analysis was not powered to provide a clear answer to this question.[15]

The duration and intensity of ECG monitoring should ideally be stratified by the individual patient's risk of AF,[16] since thorough analysis of ECG-monitoring data is personnel-intensive, time-consuming and thus associated with high costs. Excessive supraventricular ectopy (ESVEA) has been identified as a strong predictor of both AF and ischemic stroke in the population based Copenhagen Holter Study[17] and may be used to identify patients with an increased risk of undiscovered AF, which has recently been shown in stroke patients.[18–20] Based on unpublished data from the forerunner trial Find-AF$_{\text{RANDOMISED}}$, the prevalence of excessive supraventricular activity (ESVEA) according to the definition of Binici et al. (ie, either >30 premature atrial contractions/recorded hour or at least 1 atrial run >20 beats during the 24-hour Holter ECG) in patients with ischemic stroke is about 25%.[17]

Find-AF 2 is an investigator initiated and publicly funded randomized, controlled trial investigating whether enhanced, prolonged and intensified ECG monitoring in patients with recent ischemic stroke reduces the rate of recurrent ischemic stroke or systemic embolism in comparison to usual care.

Methods

Study design

Find-AF 2 (NCT04371055, registered at clinicaltrials.gov) is a randomized, controlled prospective open-label multicenter trial with blinded endpoint assessment (PROBE).

Find-AF 2 has a clinically relevant primary endpoint (time to ischemic stroke or systemic embolism) and will evaluate whether a practicable, risk-adapted and patient individualized strategy of enhanced, prolonged and intensified ECG monitoring to identify underlying pAF reduces recurrent ischemic strokes and systemic embolism compared with usual care AF-detection strategies. Usual care is defined by current stroke guidelines and includes

Table I. Inclusion and exclusion criteria.

Inclusion criteria	
1.	Recent symptomatic ischemic stroke within the last 30 d (sudden focal neurologic deficit lasting > 24 h consistent with the territory of a cerebral artery). If the neurologic deficit lasted < 24 h a corresponding lesion on brain imaging is needed, ie, an acute lesion on diffusion-weighted magnetic resonance imaging, native CT or CT perfusion imaging or a recent occlusion or intravascular thrombus on angiography (CTA, MRA, DSA).
2.	Age ≥ 60 y.
3.	Patient without or with only slight disability (modified Rankin Scale score ≤ 2) before onset of stroke-related symptoms.
4.	Written informed consent.
Exclusion criteria	
1.	Known history of atrial fibrillation/flutter or atrial fibrillation/flutter on admission ECG.
2.	Current indication or contraindication for OAC at randomization.
3.	Intracerebral bleeding in medical history
4.	Patient scheduled for ECG-monitoring lasting > 7 d (Holter ECG, ICM, etc.).
5.	Implanted pacemaker device, cardioverter/defibrillator or ICM.
6.	Patient not willing to be treated with oral anticoagulants.
7.	Carotid artery stenosis ipsilateral to the current ischemic stroke needing operation or intervention.
8.	History of carotid endarterectomy or percutaneous stent intervention of cerebral or cervical artery within the last 30 d.
9.	Life expectancy <1 y for reasons other than stroke (eg, metastatic cancer).
10.	Patients under legal supervision or guardianship.
11.	Psychological/mental or other inabilities to supply required information (eg, fill out the questionnaire due to dementia, language difficulties, ...) or participate in the required tests.
12.	Participation in other randomized interventional trials.
13.	Suspected lack of compliance.

CT, computed tomography; CTA, computed tomography angiography; DSA, digital subtraction angiography; ECG, electrocardiogram; ICM, implantable cardiac monitor; MRA, magnetic resonance angiography; OAC, oral anticoagulation.

a standard Holter ECG of at least 24 hours' duration and additional AF-monitoring according to local practice of the study centers, eg, usually telemetry for 72 hours.[21]

Inclusion and exclusion criteria

Patients ≥ 60 years of age with recent (≤ 30 days) ischemic strokes according to the AHA/ASA definition will be screened for eligibility.[22] Detailed inclusion and exclusion criteria are listed in Table I.

All eligible patients will receive a 24-hour Holter ECG prior to randomization. This will serve 4 purposes: First, the guideline compliant minimum of 24 hours of ECG-monitoring will be guaranteed in the control arm. Second, patients with easily detectable AF will be identified and excluded from the trial. Third, the initial ECG will serve to stratify the risk of underlying or developing AF in the intervention arm depending on the occurrence of ESVEA (defined as either >30 premature atrial contractions/hour × recorded hours or at least 1 atrial run >20 beats during the 24-hour Holter ECG). Finally, it is a compliance test ensuring that patients accept at least 24 hours of Holter ECG.

After the initial 24-hour Holter ECG, patients without observed AF and at least 18 hours of evaluable ECG data will be randomized 1:1 to the control group and the intervention group. Patients in the intervention group with ESVEA have a high risk of underlying/developing pAF and will receive an implantable cardiac monitor (ICM, Reveal LINQ, Medtronic, Minneapolis, MN) within 7 days. Those without ESVEA will receive a 7-day Holter ECG immediately after randomization, which will be repeated after 3 months, 12 months and annually thereafter.

The primary endpoint is the time until a recurrent ischemic stroke or systemic embolism occurs. The primary safety endpoint is the occurrence of hemorrhagic stroke. Life threatening and major bleedings are the secondary safety endpoints. Endpoints will be assessed and classified by independent blinded expert adjudication committees. An overview of the trial design is shown in the Study flow chart (Figure 1).

Ethical conduct

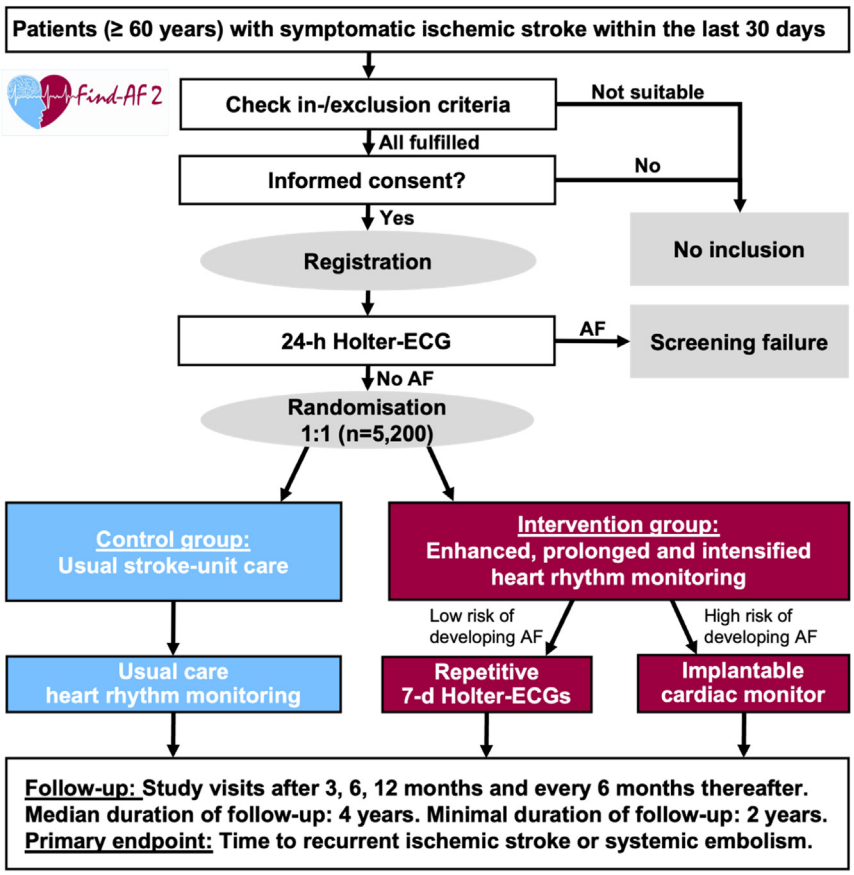
All persons participating in the conduct of the trial commit themselves to observe the latest issues of the Declaration of Helsinki, the ICH guidelines for Good Clinical Practice (GCP) and CPMP/ICH/135/95, as well as all pertinent national laws. All participating study sites will contact their local ethics committee to obtain approval.

An informed consent form must be signed by the patient before performing any study related procedures.

Although it is the clear aim of the trial to initiate secondary preventive OAC in all patients with an episode of AF (as defined by the current AF-guideline, including only episodes ≥ 30 seconds[23]), the study team will only advise the treating physicians on this matter. The final decision on secondary preventive treatment lies in the responsibility of the treating physicians.

Study devices have a CE mark and are used according to licensed indications.

Figure 1



Study flow chart.

Conduct and funding

Find-AF 2 is an investigator-initiated trial and Leipzig University, Germany, acts as the sponsor. The trial is supported by an unrestricted grant from the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG, grant number 426336050) after a peer-reviewed application process. ICMs are provided by Medtronic (Minneapolis, MN) free of charge. All data are documented in a secure eCRF database, which is provided, managed and secured by the Clinical Trial Centre (ZKS), Leipzig University, Germany. The authors are responsible for the design and conduct of this study, the drafting and editing of the paper and its final contents. The study is led by a steering committee.

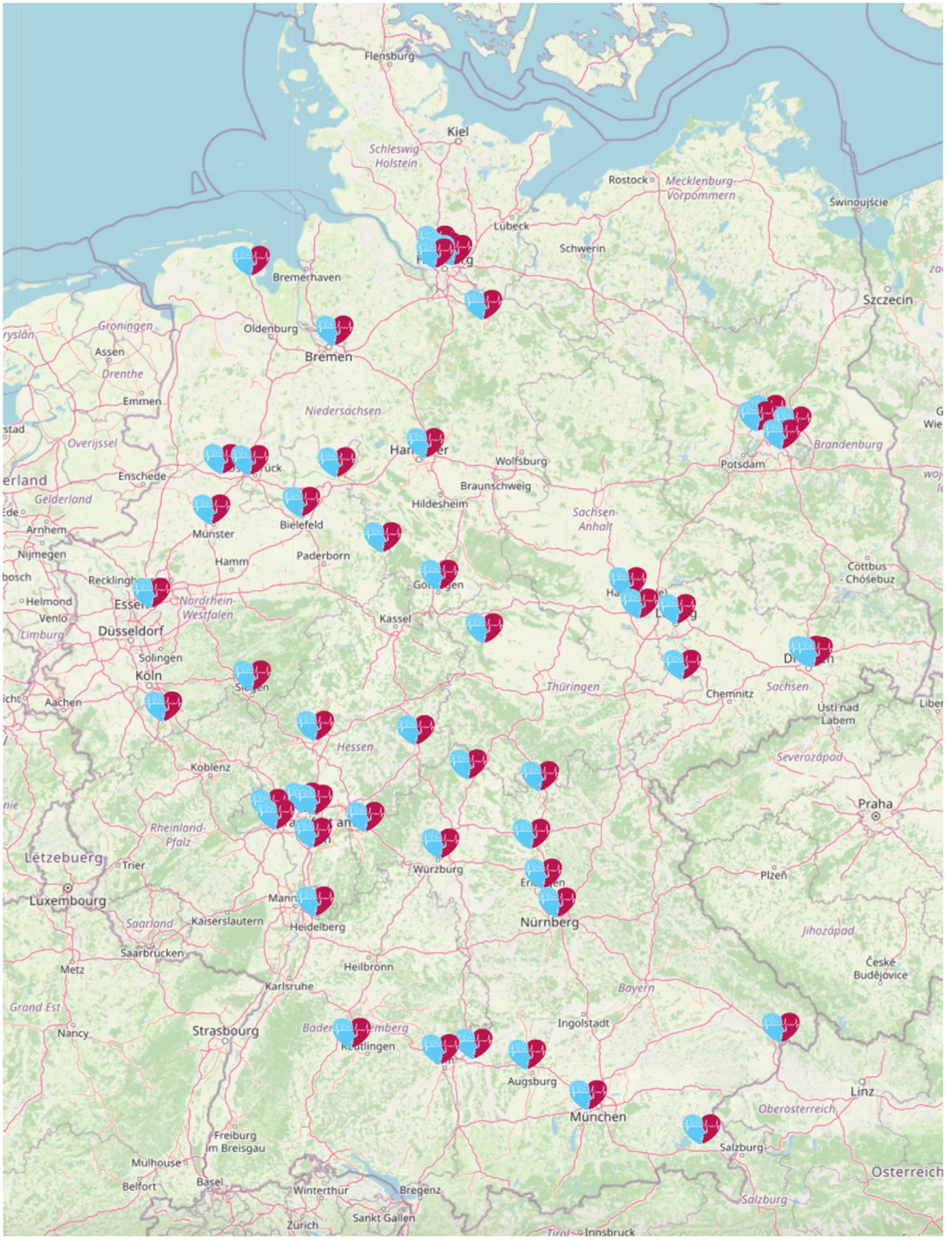
Study centers

Patients will be randomized in 52 study centers in Germany, representing university hospitals as well as hospitals in urban and rural areas with a specialized stroke unit. Study sites treat at least 500 patients with cerebral ischemia per year and have a cardiology department or established partnership with 1 or more cardiologists to perform transthoracic/transesophageal echocardiography. Furthermore, infrastructure for ICM implantation and study conduct is available. Figure 2 shows the geographical distribution of study centers within Germany.

Twenty-four hour Holter ECG monitoring

A 24-hour Holter ECG will be obtained from all enrolled patients before randomization using a commercially available 5-lead device (SEER 1000, GETEMED, Teltow, Germany). The data will be uploaded to a central server and the ECG core laboratory, located at Leipzig University, will analyze the uploaded data within 1 workday, using a dedicated analysis software (CardioDay, GETEMED, Teltow, Germany) and following a predefined standard operation procedure. The analysis will focus on the detection of atrial fibrillation/flutter $\geq$ 30 seconds and the extent of ESVEA (number of premature atrial complex and the longest SV-run). Study centers receive an electronic report of the screening 24-hour Holter ECG

Figure 2



Geographical distribution of Find-AF 2 study centers in Germany (source of image: www.find-af2.com; ZKS Leipzig / Leaflet | OpenStreetMap contributors).

comparable to a routine Holter ECG report specifying heart rhythm, heart rate and arrhythmias, usually within 2 hours after data upload. Patients with AF during the 24-hour screening Holter ECG will be documented as screening failures and those without observed AF and at least 18 hours of evaluable ECG data can be randomized.

Randomization

Patients will be randomized in a 1:1 ratio to either "enhanced, prolonged and intensified ECG-monitoring" or "standard of care". Randomization will be performed centrally by a secure web-based-tool, provided by Clinical Trial Centre (ZKS), Leipzig. Allocation uses a block randomization procedure with computer-generated blocks of variable length. Randomization is stratified by center, AF risk category (low/high) and lacunar/nonlacunar stroke.

Enhanced, prolonged, and intensified ECG-monitoring

The term "*enhanced* monitoring" refers to the analysis of all ECG-data at a central core laboratory by specially trained personnel working under the supervision of expert physicians in the field of ECG-analysis (TU, RW).

All patients in the intervention group will receive *prolonged* heart rhythm monitoring. Patients in the "low risk of developing AF" subgroup will receive a 7-day Holter ECG (SEER 1000, GETEMED, Teltow, Germany) immediately after randomization. The Holter examination will be repeated after 3 months, after 1 year and then annually. Patients will be advised on how to change the ECG electrodes and will be instructed to return the device via mail as soon as the monitoring episode is over.

Patients in the "high risk of developing AF" subgroup of the intervention arm will receive *intensified* heart rhythm monitoring by means of an ICM (Reveal LINQ, Medtronic, Minneapolis, MN) implanted at the study site within at most 7 days. ICM settings will be programmed as described previously.[14] Continuous remote monitoring will be performed using automatic data transmission via the Medtronic CareLink Network. In case of suspected AF or missing transmission for 1 week, patients are asked to initiate the transmission manually.

If AF occurs in the intervention group outside the study interventions, study centers are asked to provide ECG documentation of this episode. The ECG core lab will adjudicate all episodes suspicious of AF. If the core lab classifies an episode as AF in the "low risk of developing AF" group, no further 7-day Holter ECGs are necessary. Study centers will receive quarterly reports of ECG analysis for patients with ICMs, even after detection of a first episode of AF.

Definition of atrial fibrillation/flutter

AF and atrial flutter are defined according to current guidelines, ie, AF is a supraventricular tachyarrhythmia with uncoordinated atrial electrical activation and consequently ineffective atrial contraction. Electrocardiographic characteristics of AF include irregular R-R intervals (when atrioventricular conduction is not impaired), absence of distinct repeating P waves, and irregular atrial activations. The minimum duration of an ECG tracing of AF required to establish the diagnosis of clinical AF is at least 30 seconds, or an entire 12-lead ECG.[23]

Recurrent stroke adjudication

All qualifying strokes will be classified according to the TOAST and ESUS classification by the study centers.[24,25] All recurrent transient ischemic attacks (TIA), as well as ischemic and hemorrhagic strokes will be adjudicated independently by 2 blinded experts. If their assessments yield identical results, adjudication of that case is complete. Otherwise, a third blinded expert will be consulted and the majority opinion will define the result. If no decision can be reached in this way, the case will be discussed in the entire endpoint committee. These experts will classify all recurrent strokes according to the TOAST and ESUS classification[24,25] based on pseudonymized data. These include results of clinical examinations and diagnostic test results (eg, brain and vascular imaging).

Bleeding adjudication

Bleeding events will be evaluated and classified by a blinded endpoint adjudication committee of bleeding experts. In case of different expert opinions, the adjudication pathway is identical to that noted in 2.9. Bleedings will be grouped as life-threatening or fatal bleeding, clinically relevant nonmajor bleeding, and intracranial hemorrhage according to the criteria of the International Society of Thrombosis and Hemostasis (ISTH), TIMI and BARC.[26-28]

Study visits

Table II gives an overview of study visits. At the screening visit V0, patients receive a 24-hour Holter ECG after giving written informed consent. Visit V1 usually takes place the following day and patients will be randomized if they meet all inclusion and exclusion criteria (including absence of AF within the 24-hour Holter ECG). Patients randomized to 7-day Holter ECG will receive the first 7-day monitoring immediately after randomization (V1). Those randomized to an ICM will receive the device within 7 days after randomization (V1b). At discharge, medication and adverse events will be documented (V1e). After 3 months (V2), patients will be seen at the study center again and those in the intervention arm at low risk for developing AF will receive another 7-day Holter ECG. An optional biospecimen sampling study will be performed at V1 and V2. Thereafter, telephone visits will take place after 6, 18, 30, and 42 months. In-person visits at the study center will be attended after 12

Table II. Study schedule.

Visit	Scr/ V0	V1	V1b[1]	V1e	V2	V3	V4	V5	V6	V7	V8	V9	V10	V99
Time (months)		0	0	0	3±0.5	6±1	12±1	18±1	24±1	30±1	36±1	42±1	48±1	Final
	🏠	🏠	🏠	🏠	🏠	☎	🏠	☎	🏠	☎	🏠	☎	🏠	🏠
Inclusion / exclusion criteria	X	X												
Informed consent	X													
Randomization		X												
Medical history	X	X			X	X	X	X	X	X	X	X	X	X
Medication	X	X		X	X	X	X	X	X	X	X	X	X	X
Quality of life (HADS, SIS-16, EQ-5D)		X			X		X		X		X		X	X
Morbidity/mortality/EP	X	X		X	X	X	X	X	X	X	X	X	X	X
Holter ECG (days)	1	7[2]			7[2]		7[2]		7[2]		7[2]		7[2]	
ICM implantation			X[1]											
Adverse events		X	X	X	X		X		X		X		X	X
mRS		X			X	X	X	X	X	X	X	X	X	X
NIHSS	X				X									
Cognition: IQCODE		X												
Cognition: MoCA,		X			X		X		X		X		X	X
Cognition: IADL					X		X		X		X		X	X
Biobanking		X			X									
Brain imaging[4]	X													
Vascular imaging[4]	X													
12-lead-ECG		X												X
Laboratory testing[3]	X													
Echocardiography[4]		X												

[1] = V1b only for patients in the intervention arm with high risk of developing AF receiving ICM.
[2] = only in patients in the intervention group with low AF risk not receiving ICM.
[3] = standard laboratory test (eg, cholesterol, HbA1c, creatinine) will be obtained according to local standard.
[4] = according to local standard, ☎ = telephone visit, 🏠 = study center visit.

ECG, electrocardiogram; EP, endpoint; IADL, Instrumental Activities of Daily Living; ICM, implantable cardiac monitor; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly; MoCA, Montreal Cognitive Assessment; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale.

months and annually thereafter. Visits proceed according to this schedule until 24 months after last-patient-in.

An overview of all study procedures is shown in Table II.

Study outcomes

The primary outcome of the study is the time until a recurrent ischemic stroke or systemic embolic event occurs. Secondary endpoints include (1) all-cause mortality, (2) ischemic, hemorrhagic or unspecified stroke, (3) myocardial infarction, (4) a combination of stroke, myocardial infarction or cardiovascular death, (5) new onset of AF/atrial flutter, and (6) quality of life based on the Stroke Impact Scale (SIS-16), the EuroQol-5D (EQ-5D) and the Hospital Anxiety and Depression Scale (HADS). A substudy focusses on dementia using the Instrumental Activities of Daily Living (IADL) and Montreal Cognitive Assessment (MoCA) tests.

The main safety endpoint will be the occurrence of hemorrhagic stroke. Life-threatening or major bleeding will be reported as a secondary safety endpoint.

Statistical analysis

The primary hypothesis is that prolonged, enhanced and intensified rhythm monitoring in patients with recent ischemic stroke reduces the hazard of recurrent ischemic strokes or systemic embolisms by identifying AF more frequently and earlier, thereby changing the secondary prevention therapy from antiplatelets to OAC. The analysis will follow the intention-to-treat principle. The primary analysis will use a Cox regression model treating recurrent ischemic stroke (fatal and nonfatal) and systemic embolism as a combined endpoint. The predictor variable is the diagnostic approach, defined by randomization. Age, qualifying-stroke severity, the randomization strata lacunar/nonlacunar stroke and high/low AF-risk as well as the baseline $CHADS_2$-Score will be included as covariates. Patients lost to follow-up, with nonstroke-related death or death of unknown cause will be censored. Continuous statistical monitoring will be performed in order to assure data quality and completeness.

Sample size discussion

Details of the sample size considerations can be found in the Supplement.

The primary endpoint is based on a time-to-event analysis. Consequently, the sample size calculation determines the number of events required to achieve the desired power. Based on assumptions about (1) the progress of enrolment, (2) the amount of theoretically detectable AF in the study population, (3) the AF detection probability, (4) the rate of adequate OAC treatment admitted to patients with detected AF, and (5) the stroke recurrence rate, we derive a hazard ratio (HR), which can be converted into a number of events and a corresponding sample size by standard calculations.

The original trial protocol found a HR of 0.770 and arrived at a sample size of 5,200 patients to achieve 80% power assuming a recruitment period of 2 years and a drop-out rate of 16%. This calculation was accepted by the funder (German Research Foundation) and Ethics Committees. Questions about the complex original calculation, which can be found in the trial protocol (see Supplement), led us to recalculate with slightly modified assumptions. Based on the true progress of the trial, we now allow for 4 years of recruitment and believe that the drop-out rate will be lower than 10%. With the newly calculated HR of 0.798, we find a sample size of 4,413 patients to achieve 80% power, without dropout. Details of the calculation are given in the supplement. We confirm the original sample size of 5,200 patients, allowing for a conservative 15% dropout. Notably that the primary analysis is based on a Cox regression model and not a log-rank test, meaning we expect slightly higher power in the final analysis.

Interim analyses and data safety and monitoring board

The above sample size calculation takes into account 2 planned interim analyses after 50% and 75% of the expected number of events have been adjudicated. Termination for effectiveness is foreseen if the p-value is below 0.003, 0.018 (first and second interim analyses) or 0.044 (final analysis) based on the O'Brien-Fleming α-spending function. A Data Safety and Monitoring Board (DSMB) consisting of a neurologist, cardiologist and medical statistician meet at regular intervals to monitor safety and data quality. They make recommendations regarding continuation or termination of the trial. Criteria for stopping for futility are not foreseen since precise estimates of the hazard ratio are desirable even if the intervention should turn out not to be effective.

Study progress

On April 1, 2020 the responsible ethics committee of Leipzig, Germany approved Find-AF 2. Due to the restrictions of the COVID-19 pandemic, the first study center was initiated in June 2020 and the first patient was randomized on July 7, 2020. By July 23, 2023, 3867 patients (74 % of recruitment target) have been randomized in 51 active centers. We expect the recruitment phase to be closed by mid of 2024. The last patient's final visit will take place in 2026. First study results can be expected in late 2026/early 2027.

Discussion

Find-AF 2 is the first adequately powered randomized multicenter trial to investigate whether heart rhythm monitoring for AF reduces cardioembolism by advanced

AF detection and consequent prescription of OAC in unselected ischemic stroke patients aged 60 years and above.

Inclusion and exclusion criteria

In Find-AF 2, patients ≥ 60 years of age will be included after suffering from a recent ischemic stroke of any etiology. In the past, monitoring was mostly confined to patients with cryptogenic strokes because AF was assumed to be most prevalent if no other potential cause of stroke was identified.[9,10] However, monitoring trials in broader stroke populations (eg, Find-AF$_{\text{RANDOMISED}}$ and MondAFIS) and patients with large artery atherosclerosis and small vessel disease have depicted that the detection rate for AF is similar in all stroke subtypes.[11-13] We decided to include stroke patients with different potential etiologies, because the occurrence of stroke itself is often associated with an increased cardiovascular risk implying a high risk of underlying AF, as AF shares several intersecting risk factors with atherosclerosis. Moreover, the presumed etiology of a recurrent stroke event changes in up to 45% of cases compared with the initial event, making it reasonable to screen for AF in any stroke patients irrespective of initially suspected etiology.[29] Although patients with internal carotid artery stenosis share the same risk factors with AF patients, we decided to exclude patients with an surgery or intervention of the stenotic artery within thirty days of our trial, because the periprocedural stroke risk could possibly dilute the effect of our intervention on the primary outcome.[22]

Risk-adapted diagnostic approach

In contrast to other ongoing and completed trials addressing AF detection in ischemic stroke patients, Find-AF 2 has a novel feature of an individualized risk-adapted AF detection approach, which was adapted from pharmacological intervention trials: Usually those with the highest absolute risk require the most intensive treatment. Therefore, those with a high risk of underlying or developing AF should receive continuous ECG monitoring by ICM, while patients with lower risk receive repeated 7 days Holter ECG monitoring. This approach is supported by recent publications of post-hoc analyses of major ECG monitoring trials: In EMBRACE, patients with > 1,500 atrial premature beats within 24 hours had a > 40% risk of AF compared to < 9% in those with < 100 atrial premature beats.[18] Similarly, patients with ESVEA in Find-AF had an increased risk of AF during Holter ECG monitoring in the following 7 days[19] as well as developing recurrent ischemic strokes during 3 years of follow-up.[20]

Follow-up duration

In comparison to previous trials, Find-AF 2 will provide the most extended follow-up data in a stroke cohort screened for AF. Previous trials were hampered by a median follow-up period of 3,[10] 12[14] and 19 months,[30] respectively. Thirty-six months follow-up data were reported in Find-AF$_{\text{RANDOMISED}}$[31] and Stroke-AF.[32] The median follow-up duration in Find-AF 2 will be 4 years, but all patients will be followed until the end of the trial, which means we will have a maximum follow-up duration of approximately 6 years.

Limitations

Some limitations have to be considered:

(1) Find-AF 2 only includes patients aged 60 years and above, thus its results may not apply to younger patients. However, AF is much less likely below 60 years and the benefit of heart rhythm monitoring is likely to be smaller.[33]
(2) By design, we do not compare different rhythm monitoring modalities in a randomized mode. Continuous monitoring detects AF at an earlier stage than repeated 7-day Holter ECG and hence the response to anticoagulation may be different to AF detected by intermittent monitoring. The stratification into high risk and low risk for developing AF will facilitate sub-group analyses, but a direct comparison of repeated 7-day Holter ECG and continuous monitoring will not be possible.
(3) The effect of anticoagulation will not be assessed directly, as this is a diagnostic study. Yet based on previous data, there will be a high correlation between patients diagnosed with AF and anticoagulation. As there are no other reasons why rhythm monitoring should reduce cardioembolism, any effect on rates of recurrent ischemic stroke or systemic embolism is likely to be attributable to anticoagulation.
(4) In stroke patients, any duration of AF usually leads to a switch from antiplatelet to anticoagulation therapy. It is unknown whether the efficacy of anticoagulation in patients with subclinical AF detected by an ICM (duration less than 24 hours) is similar to the efficacy in patients with Holter ECG detected AF. Find-AF 2 will provide important data regarding these patient groups, but a lower efficacy of anticoagulation in subclinical AF detected by an ICM might dilute the potential benefit of anticoagulation in Find-AF 2.

Conclusions

Find-AF 2 is the first adequately powered, randomized controlled prospective multicenter trial to evaluate whether enhanced, prolonged and intensified ECG-monitoring in stroke patients leads to a lower hazard for cardioembolism (recurrent ischemic stroke or systemic embolism) by increasing and advancing detection and

consequent guideline compliant initiation of OAC in patients with underlying paroxysmal AF and thereby has the potential of improving secondary stroke prevention in a more individualized, risk-adapted way.

Funding

Find-AF 2 is funded by grants from Deutsche Forschungsgemeinschaft (DFG, grant number 426336050) and Medtronic Plc, Minneapolis.

Disclosures

None reported.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ahj.2023.06.016.

References

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation. 2018;137:e67–e492. doi:10.1161/CIR.0000000000000558.
2. Feigin VL, Stark BA, Johnson CO, et al. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Neurol 2021;20:795–820.
3. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. Stroke 1991;22:983–8.
4. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857.
5. Mohr JP, Thompson JLP, Lazar RM, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444–51.
6. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191–201.
7. Diener HC, Sacco RL, Easton JD, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906–17.
8. Poli S, Meisner C, Poli K, et al. Apixaban for treatment of embolic stroke of undetermined source - ATTICUS randomized trial. European Stroke Organisation Conference; 2022.
9. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478–86.
10. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med 2014;370:2467–77.
11. Wachter R, Gröschel K, Gelbrich G, et al. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AF RANDOMISED): an open-label randomised controlled trial. Lancet Neurol 2017;16:282–90.
12. Haeusler KG, Kirchhof P, Kunze C, et al. Systematic monitoring for detection of atrial fibrillation in patients with acute ischaemic stroke (MonDAFIS): a randomised, open-label, multicentre study. Lancet Neurol 2021;20:426–36.
13. Bernstein RA, Kamel H, Granger CB, et al. Effect of long-term continuous cardiac monitoring vs usual care on detection of atrial fibrillation in patients with stroke attributed to large- or small-vessel disease: the STROKE-AF randomized clinical trial. JAMA 2021;325:2169.
14. 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;325:2160.
15. Tsivgoulis G, Triantafyllou S, Palaiodimou L, et al. Prolonged cardiac monitoring and stroke recurrence: a meta-analysis. Neurology 2022;98:e1942–52.
16. Haeusler KG, Gröschel K, Köhrmann M, et al. Expert opinion paper on atrial fibrillation detection after ischemic stroke. Clin Res Cardiol 2018;107:871–80.
17. Binici Z, Intzilakis T, Nielsen OW, et al. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. Circulation 2010;121:1904–11.
18. Gladstone DJ, Dorian P, Spring M, et al. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial. Stroke 2015;46:936–41.
19. Weber-Krüger M, Gröschel K, Mende M, et al. Excessive supraventricular ectopic activity is indicative of paroxysmal atrial fibrillation in patients with cerebral ischemia. PLoS One 2013;8:e67602.
20. Weber-Krüger M, Lutz C, Zapf A, et al. Relevance of supraventricular runs detected after cerebral ischemia. Neurology 2017;89:1545–52.
21. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/American Stroke Association. Stroke 2021;52:e364–467. doi:10.1161/STR.0000000000000375.
22. Sacco RL, Kasner SE, Broderick JP, et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:2064–89.
23. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2021;42:373–498.
24. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. Lancet Neurol. 2014;13:429–38.
25. Adams HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in acute stroke treatment. Stroke 1993;24:35–41.
26. Schulman S, Kearon Cthe SUBCOMMITTEE ON CONTROL OF ANTICOAGULATION OF THE SCIENTIFIC AND STANDARDIZATION COMMITTEE OF THE INTERNATIONAL SOCIETY ON THROMBOSIS AND HAEMOSTASIS. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients: definitions of major bleeding in clinical studies. J Thromb Haemost 2005;3:692–4.
27. Rao AK, Pratt C, Berke A, et al. Thrombolysis in myocardial infarction (TIMI) trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. J Am Coll Cardiol 1988;11:1–11.
28. Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding

definitions for cardiovascular clinical trials: a consensus report from the bleeding academic research consortium. Circulation 2011;123:2736–47.

29. Hillen T, Coshall C, Tilling K, et al. Cause of stroke recurrence is multifactorial: patterns, risk factors, and outcomes of stroke recurrence in the South London stroke register. Stroke 2003;34:1457–63.
30. Brachmann J, Morillo CA, Sanna T, et al. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the cryptogenic stroke and underlying atrial fibrillation trial. Circ Arrhythm Electrophysiol 2016;9:e003333. doi:10.1161/CIRCEP.115.003333.
31. Wachter R, Weber-Krüger M, Hamann GF, et al. Long-term follow-up of enhanced holter-electrocardiography monitoring in acute ischemic stroke. J Stroke 2022;24:98–107. doi:10.5853/jos.2021.01207.
32. Schwamm LH, et al. 3-year results from the STROKE AF randomized trial. International Stroke Conference; 2023.
33. Wachter R, Weber-Krüger M, Seegers J, et al. Age-dependent yield of screening for undetected atrial fibrillation in stroke patients: the Find-AF study. J Neurol 2013;260:2042–5.