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Atrial Fibrillation

Atrial Fibrillation Detection

Fishing for An Irregular Heartbeat Before and After Stroke

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Atrial fibrillation (AF) is present in ±3% of the general population above age 20, and its prevalence increases substantially in the ≥65-year-olds age group.[1] It is expected that AF prevalence will increase as populations get older. AF is asymptomatic in ≤40% of patients. Unfortunately, the absence of symptoms does not suggest a benign course.[2] The Framingham Heart Study found that stroke is the first manifestation of AF in at least 2% to 5% of AF patients.[3] In a hospital-based series, ≤20% of stroke patients had previously unidentified or unrecognized AF.[4] AF also increases the risk of cognitive impairment and dementia.[5] Identifying AF and reducing stroke risk in patients with AF before stroke occurs is, therefore, an important goal.

Should We Detect AF in the General Population Prior to Stroke?

Whether screening for AF in the general population is warranted is heavily debated. Opportunistic screening refers to screening offered to people as part of a routine medical checkup or when examined for another reason, whereas systematic screening entails screening in the general population (ie, mass screening) or a high-risk, target group (ie, patients with heart failure or diabetes mellitus). Opportunistic screening in patients aged >65 years with pulse palpation or ECG rhythm strip is the current recommended method by the European Society of Cardiology.[6] No recommendation is given in the US guidelines.[7] Pulse palpation is sensitive for detection of permanent AF (the sensitivity is 94%, and its specificity is 72%) but is not specific and requires confirmation with ECG. The equipment and time required to perform an ECG examination are a significant barrier to perform screening, but fortunately new methods for screening are being developed rapidly.[8] Proponents of screening cite the relatively high frequency of AF, the ease of detection and prevention of stroke with AF, and the high risk of stroke in patients with undetected AF as the main reasons for advocating systematic screening in the >65 years age group. The yield of single time-point screening for unknown AF is 1% (1.4% in those >65 years) and depends on the age and ethnicity and risk factor profile of the target population.[9] Only a minority of identified AF patients report symptoms. A significant proportion of patients with known AF who are undertreated are also identified.[10] The concerns with screening are the optimal method, frequency and setting of screenings, the lack of randomized evidence of whether screening will lead to measurable reductions in stroke incidence, and the questionable cost-efficacy of screening approaches. One randomized trial found no clear evidence of benefit of mass screening, but found opportunistic screening with pulse palpation, and found confirmation with 12-lead ECG to be probably cost-effective and superior to both mass screening and targeted screening.[11] However, this trial was performed in the warfarin era before non-vitamin K antagonists with an improved safety profile and reduced patient burden were available. Only half of the patients identified through mass screening attended a follow-up confirmation ECG.

Devices Used in Screening Programs

Technological advances have made screening without standard 12-lead ECG machines possible, removing at least one barrier to screening in high-risk populations. Low-cost devices attached to cell phones permitting single-lead ECG or dedicated screening devices are now available, which permit easy diagnosis of AF on the spot or allow wireless transmission to a cardiologist or technician for confirmation.[12–14] These devices provide single-lead ECGs of diagnostic quality. Studies comparing these devices head to head with standard 12-lead ECG report sensitivities of 90% to 100% and specificities between 90% and 97%.[8] Indirect methods include blood pressure measurement devices which permit simultaneous screening for AF and high BP and devices that analyze plethysmographic waveforms of cardiac activity attached to a smartphone camera with flash or a pulse oximeter.[15,16] False positives are possible with these indirect methods, and subsequent confirmation with ECG is still required.

These methods allow screening in primary-care doctor's offices, pharmacies, or other settings where screenings are performed, for example, during influenza vaccinations. The costs are also substantially less.

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Follow-Up After Screening

For screening programs to be effective, adequate follow-up and institution of appropriate anticoagulant treatment is required. Most patients identified through screening seem to have at least a moderate to high risk of stroke and require treatment with an oral anticoagulant based on risk stratification according to guidelines. A systematic review found that ≈2/3 of identified cases were at high risk of stroke and would be eligible for oral anticoagulation.[9,17]

Single Time-Point Screening Versus Repeated Screening

As AF is not a permanent arrhythmia, one-time screening may miss nonpermanent forms of AF, especially paroxysmal AF. In a screening program of 75/76-year-olds in Sweden, involving twice daily screening over a period of 2 weeks, new AF was identified in 3% of 7173 respondents.[18] Surprisingly, AF was identified only in 17% on the first ECG, strongly suggesting that repeated screening is important to identify more AF. The yield of repeated screening increased to a 7% detection rate when analysis was restricted to patients with at least one stroke risk factor. Further screening programs, combining biomarkers and repeated, intermittent screening, are planned.[19]

Relevance of AF Identified Through Screening in Primary Prevention

The relevance of screening-detected AF has been questioned. The natural history of incidentally detected AF through screening has indeed not been studied in detail nor have randomized clinical trials been performed that found a decrease in vascular end points with widespread screening. However, the evidence from studies comparing asymptomatic AF with symptomatic AF does not show a lower risk of cardiovascular outcomes with asymptomatic status, and some studies even reported a worse prognosis.[20] There is growing consensus that screening-detected AF in primary prevention is associated with a high risk of stroke, and anticoagulation should be prescribed according to guidelines.[8]

Relevance of AF Identified in Patients With Pacemakers or Implantable Cardioverter-Defibrillator

Traditionally, the risk of stroke was thought to be similar in permanent and nonpermanent forms of AF. Therefore, none of the risk stratification schemes have incorporated the type of AF, and none of the guidelines have adopted a different stance toward recommending anticoagulation in patients with paroxysmal AF. A recent systematic review, however, found that nonpermanent forms of AF may have a 25% lower risk of stroke compared with permanent forms of AF.[21] Even though the risk of stroke may be reduced, post hoc analyses from the NOAC studies (Non-Vitamin K Oral Anticoagulant) report a similar efficacy and safety compared with warfarin in these patients.[22]

The relevance of AF is more contested when short episodes are identified, especially in patients who undergo continuous monitoring with pacemakers or implantable cardioverter-defibrillators.[23] These so-called atrial high-rate episodes may be because of various causes and require review before being labeled AF. They may occur in ≤30% to 60% of monitored patients. There is ongoing debate about the duration of AF required on these devices to increase the risk of stroke independently from the general cardiovascular risk profile. Reported studies cite an increase in risk from anywhere between 5 minutes and 24 hours. Moreover, it is unclear what the relationship is between device-detected AF and the type of AF that was studied in the trials that established superiority of anticoagulants over aspirin and placebo. In the clinical trials, for patients with paroxysmal AF to be enrolled, 2 episodes of AF lasting longer than 30 seconds had to be present on separate occasions, with at least one documented on ECG.

In ASSERT (Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the AF Reduction Atrial Pacing trial), a study that focused on patients without history of AF, the risk of stroke associated with episodes of device-detected atrial high-rate episodes was analyzed in 2580 patients. Episodes longer than 6 minutes were associated with a clinical diagnosis of AF and an increased risk of stroke or systemic embolism.[24] A post hoc analysis suggests that only episodes lasting longer than 24 hours are relevant and carry a 3-fold risk of future thromboembolism over the next 2.5 years.[25] It is probable that the length of the episode is not the only determinant of risk, and risk scores like the CHA_2D_2-VASC score or echocardiographic features or the burden of AF may have to be taken into account.

The relevance of these findings for patients without preexistent heart disease who are specifically monitored for subclinical AF is unclear. Three prospective studies have assessed the presence of AF in patients at high risk of stroke using an insertable cardiac monitor (ICM). The ASSERT-II study assessed the risk of AF using ICM in 273 high-risk patients with a CHA_2D_2-VASC score of ≥3, large left atria, elevated serum N-terminal pro-brain-type natriuretic peptide levels, or obstructive sleep apnea. Episodes lasting ≥5 minutes occurred in 34.4% of patients per year, with a higher risk in older patients and patients with heart failure. Episodes of subclinical AF were not related to stroke occurrence. In the PREDATE AF Study (Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events), 22.4% of 245 patients with a CHA_2D_2-VASC score of ≥2 were found to have AF episodes of >6 minutes on ICM during an average follow-up of 1.2 years.[26] In another study with similar inclusion criteria, the rate of AF was 29.3% at 18 months in 394 patients with ICM.[27] In none of these studies, an association was found with a prior history of stroke or transient ischemic attack (TIA), but details about the types of stroke patients included in these studies are scant and follow-up probably too short to reveal an association with stroke.

Whether anticoagulation is warranted in patients with device-detected AF is being further explored in the Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation study and the Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes study.[28,29]

Other High-Risk Groups for AF

AF is often diagnosed in the context of systemic conditions like pneumonia and thyroid disease or after cardiothoracic surgery.[30]

In these patients, anticoagulation is not typically considered because this type of AF was typically considered transient and benign. Recent data suggest that these patients are at high risk of recurrent AF and stroke.[30,31] In one study, the risk of developing AF was 6- to 8-fold with postoperative AF.[32] Whether patients with secondary AF will benefit from early anticoagulation or should undergo repeated screening for AF is currently unknown.[33]

AF Detection After TIA or Stroke?

The detection of AF after stroke is important because it provides clues to the mechanism of stroke and generally leads to a change in antithrombotic strategy from antiplatelets to anticoagulation. It is estimated that ≈25% of patients with stroke or TIA will be diagnosed with AF if systematic, long-term screening is performed.[34] After TIA or stroke, most guidelines, therefore, recommend screening patients for the presence of AF, with 12-lead ECG, Holter monitoring, telemetry, or monitoring devices, but the exact timing and duration of screening with these techniques are undefined. Table 1 describes the available methods for prolonged screening.

In the 2008 European Stroke Organisation guidelines, the recommended duration is a 12-lead ECG, continuous ECG monitoring for an undefined duration, and 24-hour Holter monitoring if no cause of stroke can be found.[41] In the 2013 and 2014 American Heart Association/American Stroke Association guidelines, cardiac monitoring is recommended for 24 hours, and prolonged rhythm monitoring for 30 days is considered reasonable in patients without an apparent cause.[42,43] According to the 2016 guidelines for the management of AF from the European Society of Cardiology more prolonged monitoring is warranted with 72 hour monitoring for all stroke patients and consideration should be made of long-term recordings in some patients.[6]

Four randomized trials have been performed that examined the yield of more intensive monitoring strategies after TIA or stroke. These trials generally show that more intensive monitoring detects more AF, but were underpowered to show a reduction in TIA, stroke, or systemic emboli. In a small trial (n=100), a 7-day continuous event-monitoring device detected AF in an additional 16% of patients compared with standard practice.[44] No difference in vascular events was identified (4 events in both study arms). In the EMBRACE trial (Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event), a 30-day external cardiac monitoring device was compared with an extra Holter testing in patients with stroke of unknown cause. AF was detected in 16.1% compared with 3.2% of patients in the control group. The vascular event rate was not reported.[45] In CRYSTAL AF (Cryptogenic Stroke and Underlying AF trial), an ICM detected AF at 6 months in 8.9% versus 1.4% of patients in the control group in patients who underwent extensive diagnostic testing prior to inclusion.[46] The control group underwent 6 monthly clinical follow-up that consisted of probing for symptoms of AF and ECG or Holter as per the investigator's discretion. A nonsignificant TIA or stroke event reduction was found at 1 year (5.2% in the ICM arm versus 8.2% in the control group). The FIND AF study randomized 398 patients with recent (<7 days) TIA or stroke who did not have carotid or intracranial artery stenosis to a strategy of enhanced monitoring or standard of care.[47] The enhanced monitoring strategy consisted of repeated 10-day monitoring at 3 months' intervals for 1 year. At 6 months, the intensive monitoring strategy detected AF in 14% of patients compared with 5% in the control group. At 1 year, the stroke rate was 3.7% with enhanced monitoring compared with 5.4% with standard monitoring.

Who to Screen After TIA or Stroke?

Indirect clues of the presence of AF can often be obtained from clinical information, biomarkers, or echocardiographic findings. These are summarized in Table 2.

No clear algorithm has been developed that reliably identifies patients in whom prolonged monitoring is required. Prolonged screening will lead to higher detection rates in patients with cryptogenic stroke or embolic stroke of unknown source, but the exact yield in other subtypes of stroke is not yet clear.[67] Patients with large vessel atherosclerotic disease and small vessel disease often have risk factors that contribute to AF development and atherosclerosis, and AF often coexists. A systematic review identified a rate of detection of 2.4% in small vessel disease and 2.2% with large vessel disease. This was generally lower than the 9.2% rate in studies that did not define subtype of the stroke.[68] No studies were found that performed longer monitoring than 7 days in the small/large vessel disease subtypes, except FIND AF, which did not find a difference in the rate of detection between cryptogenic stroke and noncryptogenic stroke (excluding large vessel disease). The yield

Table 1. Overview of Noninvasive Monitoring Techniques and Insertable Cardiac Monitoring Devices

Methods for Detecting Paroxysmal AF
Noninvasive screening for AF over the medium term is possible with traditional Holter monitors, wearable patches, or belts.[35–37] These provide recording periods of ≤2–4 wk. Real-time transmission and analysis is possible with the most sophisticated devices. Holters and some patches store the ECG information and only provide diagnosis in retrospect. Activity monitors (eg, Fitbit devices, smartwatches) used to track sports activities or walking also record heart rates, and are promising for detecting AF when supplemented with deep learning algorithms, but do not produce diagnostic ECG and when abnormalities are found require further confirmation with ECG. The indirect information provided by these devices, for example, sudden increases in heart rates, may, however, provide clues to the presence of AF. Other issues with many of the wearable, consumer-oriented technologies include the need for validation, the cost-effectiveness, data security, and privacy. Yet it is hoped that in the foreseeable future, relatively cheap wearables will become available that reliably track AF.
Insertable cardiac monitoring devices are slightly more invasive devices that store abnormal rhythm episodes in memory, which can be remotely analyzed after wireless transmission.[38–40] Confirmation of the nature of the episodes by a specialist is still required. The durability of these devices is restricted by battery life, which is generally ≤3 y. The devices are MRI compatible. Dependent on the device's algorithm and settings, the sensitivity and specificity compared with Holter is high.[39] Insertable cardiac monitoring devices cannot detect all types of atrial flutter and may miss brief episodes of AF.

MRI indicates magnetic resonance imaging.

Table 2. Clues From ECG, Echocardiography, and Blood Biomarkers That Suggest a Higher Risk of AF

Characteristic	Method of Detection	Threshold or Value	Comment	Reference
P-wave dispersion	ECG	≥40 ms	Defined as the difference between the longest and shortest P-wave duration from different surface ECG leads; reflects inhomogeneous intraatrial conduction	Dilaveris and Gialafos[48]
P-wave duration	ECG	Very long P-wave duration in the top fifth percentile associated with doubling of risk of AF		Guidera and Steinberg[49]; Magnani et al[50]
PR interval	ECG	Each 20 ms increases risk of AF with 20% in primary population	In cryptogenic stroke, 30% increase with 10 ms increase	Thijs et al[51]; Cheng et al[52]
			Influenced by cardiac and antihypertensive medication	
R-R variability analysis	Continuous cardiac monitoring	Requires special commercial software to postprocess continuous cardiac monitoring devices	Further studies are needed to assess yield of this method in patients with large R-R variability without AF	Duning et al[53]
Atrial premature beats (ABP)	Holter	Low (7%–9%) probability of AF with <100 ABP/24 h and high probability (>37%) with ≥1000 ABP/24 h	Validation of cutoff needed in separate population	Gladstone et al[54]
Supraventricular ectopic activity	Holter	Thirty supraventricular ectopic complexes per hour/any episode of run of ≥20 SV complexes	Increases risk of clinical AF diagnosis and AF in primary prevention population over 6 y	Binici et al[55]
Left atrial volume	Echocardiography	Risk of score increases 2.4× per 10 mm increase in LA volume	Echocardiographic features are not independent predictors in AF risk score after correction for other risk factors[56]	Benjamin et al[57]
Left atrial appendage velocity and spontaneous echo contrast	Echocardiography	Low velocities found in patients with paroxysmal AF		Kim et al[58]; Patti et al[59]
NT-proBNP	Laboratory	Variable	Promising factor, but variable cutoffs	Hijazi et al[60]; Patton et al[61]; Shibazaki et al[62]; Samuel et al[63]; Rodríguez-Yáñez et al[64]
TSH	Laboratory	30% increase of risk of AF in subclinical hyperthyroidism; high normal thyroid function 12% increase in risk of AF		Selmer et al[65]
Single nucleotide polymorphisms	Genetic testing	Increased burden of AF predisposing genes	Untested strategy	Lubitz et al[66]

AF indicates atrial fibrillation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; and TSH, thyroid stimulating hormone.

of AF detection in other stroke subtypes is further investigated in the STROKE-AF study (Stroke of Known Cause and Underlying AF), where 500 patients with stroke associated with large or small vessel disease will be randomized to an ICM or standard of care.[69] Similarly, TIA patients are often less intensively examined and monitored, and in some settings, even no cardiac monitoring is performed as patients are discharged home. A systematic review of the limited number of studies specifically assessing the yield of screening in TIA found a rate of detection of TIA in 4%.[70] Detection rates were higher with longer monitoring and in patients with unexplained TIA.

The yield of monitoring is probably the highest early after the cerebral ischemic event, but late detection of AF is also common. The earliest opportunity for detection is in the prehospital setting; however, most episodes will be detected during the in-hospital stay.[71]

At the time of stroke unit admission or in intensive care unit, telemetry or continuous electrocardiographic monitoring is performed.[72,73] Cardiac monitoring devices require special software to detect and record AF. In the absence of such dedicated software, irregular heart rhythms must be detected and recorded by stroke unit nurses. Post hoc analysis of recordings of telemetry devices is possible using RR interval analysis performed off-line. This approach has been shown to increase the detection rate compared with standard stroke unit care.[72] In the FIND AF study, 2/3 of the AF events were detected with the first 10-day Holter monitor. In EMBRACE, half of the AF events were detected in the first week of monitoring, but patients were enrolled 2.5 months after the ischemic event. Similarly, in CRYSTAL AF, half of the events detected within 6 months occurred within 42 days of monitoring. This suggests that the yield of AF detection is highest in the first weeks to months after the cerebral ischemic event. Nevertheless,

30-day monitoring would miss a relevant number of AF episodes. For instance, in CRYSTAL AF, AF was detected by 3 years in ≤30% of these patients (compared with 8.9% at 6 months).[46] Simulations from CRYSTAL AF suggest that any intermittent method of screening AF, be it 30-day monitoring or repeating annual monitoring, would have a limited sensitivity of only ≤22.8% and a negative predictive value of 85.7%.[74]

After stroke or TIA, it seems that the highest yield for detecting AF is early after symptom onset, in patients with ischemic stroke (as opposed to TIA), and in patients with cryptogenic stroke. However, significant gaps remain, in our knowledge, on the yield of screening after TIA and stroke, and none of the current screening strategies are fully satisfactory. A commonly performed strategy consists of of stepwise screening with ECG, continuous inpatient electrocardiographic monitoring followed by prolonged monitoring for up to 30 days, after which ICM is considered in patients with unexplained stroke.[54] Further selection to proceed with AF may be based on indirect markers (see Table 2). Sequential testing and analysis are, however, cumbersome and require multiple visits and close collaboration with cardiologists. Forgoing the prolonged monitoring and immediate ICM use at discharge is a sensitive strategy, but its cost-efficacy and budget impact remain to be determined in various healthcare settings.[75] The anticoagulation trials in patients with embolic stroke of unknown source will also shed new light on the importance of prolonged screening after stroke and will have to be compared with screening strategies.

Conclusions

AF detection is important in primary prevention and secondary prevention after stroke. A plethora of screening devices is now available that allow reliable detection of AF, but a cheap, noninvasive way of detecting AF over extended periods of time is still missing. The implications of AF that is detected with the new technologies on anticoagulant management are not always clear. Screening for AF in selected populations in primary prevention and prolonged screening after cryptogenic stroke is recommended.

Disclosures

Dr Thijs reports receiving consulting fees from Medtronic. Dr Thijs is on the steering committee of the DIAGNOSE-AF (Detection in Transient Ischemic Attack Patients Using Continous monitoring vs Standard Evaluation for Atrial Fibrillation) and REACT AF (Rhythm Evaluation for Anticoagulation With Continuous Monitoring of Atrial Fibrillation Clinical Trial) clinical trials sponsored by Medtronic. Dr Thijs reports speaker and consulting fees and travel support by Boehringer Ingelheim, Pfizer/BMS, Daichi Sankyo, and Bayer.

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KEY WORDS: atrial fibrillation ■ cardioembolic stroke ■ cryptogenic stroke ■ embolic stroke of unknown source ■ screening ■ stroke