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EHRA CONSENSUS DOCUMENT

Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

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Definitions, abbreviations and acronyms

Definitions

Atrial high rate event (AHRE): atrial high-rate episodes are defined as atrial tachyarrhythmia episodes with rate >190 beats/min detected by cardiac implantable electronic devices.

Subclinical atrial fibrillaton (AF): atrial high-rate episodes (>6 minutes and <24-hours) with lack of correlated symptoms in patients with cardiac implantable electronic devices, detected with continuous ECG monitoring (intracardiac) and without prior diagnosis (ECG or Holter monitoring) of AF.

Silent (asymptomatic) AF: documented AF in the absence of any symptoms or prior diagnosis often presenting with a complication related to AF e.g. stroke, heart failure, etc.

Excessive supraventricular ectopic activity (ESVEA): 30 premature supraventricular contractions (PSC) /hour (≥729 PCS /24 hours) or episode of PSC runs ≥20 beats.

Table 1 Scientific rationale of recommendations

Scientific evidence that a treatment or procedure is beneficial and effective. Requires at least one randomized trial, or is supported by strong observational evidence and authors' consensus.	Recommended/ indicated	
General agreement and/or scientific evidence favour the usefulness/efficacy of a treatment or procedure. May be supported by randomized trials that are, however, based on small number of patients to allow a green heart recommendation.	May be used or recommended	
Scientific evidence or general agreement not to use or recommend a treatment or procedure.	Should NOT be used or recommended	

This categorization for our consensus document should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I-III) and level of evidence (A, B, and C) to recommendations.

Abbreviations and acronyms

AF - atrial fibrillation

AHRE – atrial high rate episode

ASSERT – ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and atrial fibrillation Reduction atrial pacing Trial

AT – atrial tachyarrhythmia

AVB – atrioventricular block

BEATS – Balanced Evaluation of Atrial Tachyarrhythmias in Stimulated patients

$CHADS_2$ – Cardiac failure, Hypertension, Age, Diabetes, Stroke (doubled)

CHA_2DS_2-VASc – Congestive heart failure or left ventricular dysfunction, Hypertension, Age ≥75 (doubled), Diabetes, Stroke/ Transient Ischaemic Attack (doubled)-Vascular Disease, Age 65-74, Sex category (female)

CI – confidence interval

CIED – cardiac implantable electronic device

CRT – cardiac resynchronization therapy device

CRYSTAL – CRYptogenic STroke and underlying AtriaL fibrillation

ECG – electrocardiography

ELR – event loop recorder

ESVEA – excessive supraventricular ectopic activity

EMBRACE – 30-day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event

ESUS – embolic stroke of uncertain source

HAS-BLED – Hypertension (that is, uncontrolled blood pressure), Abnormal renal and liver function (1 point each), Stroke, Bleeding tendency or predisposition, Labile INR, elderly (>65 years, high frailty), Drugs (eg. concomitant aspirin or NSAIDs) and alcohol (1 point each)

HR – hazard ratio

ICD – implantable cardioverter-defibrillator

ILR – implantable/insertable loop recorder

IMPACT AF – Randomized trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation

INR – international normalised ratio

LA – left atrium

LAA – left atrial appendage

MDCT – multi-detector row computed tomography

MOST – MOde Selection Trial

MRI – magnetic resonance imaging

NOACs – non-vitamin K antagonist oral anticoagulants

OAC – oral anticoagulation

OR – odds ratio

PPM – permanent pacemaker

PSC – premature supraventricular contraction

RM – remote monitoring

RR – relative risk

SAF – silent/asymptomatic AF

SAMe-TT_2R_2 – Sex (female), Age (<60 years), Medical history, Treatment (interacting drugs, e.g. amiodarone for rhythm control), Tobacco use (within 2 years) (doubled), Race (non-Caucasian) (doubled)

SCAF – subclinical AF

SND – sinus node dysfunction

SOS AF – Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices

TE – thromboembolic / thromboembolism

TIA – transient ischaemic attack

TRENDS – The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke

TTR – time in the therapeutic range

VKA – vitamin K antagonist

Introduction

Among atrial tachyarrhythmias (AT), atrial fibrillation (AF) is the most common sustained arrhythmia. Many patients with AT have no symptoms during brief or even extended periods of the arrhythmia, making detection in patients at risk for stroke challenging. Subclinical atrial tachyarrhythmia and asymptomatic or silent atrial tachyarrhythmia often precede the development of clinical AF. Clinical AF and subclinical atrial fibrillation (SCAF) are associated with an increased risk of thromboembolism. Indeed, in many cases, SCAF is discovered only after complications such as ischaemic stroke or congestive heart failure have occurred.

Subclinical AT can be detected by various cardiac monitoring methods, including external surface monitoring (e.g. standard 12-lead electrocardiogram, ambulatory Holter monitors, event monitors) and by implantable cardiac devices (e.g. implantable cardiac loop recorders, dual-chamber permanent pacemakers (PPM), dual-chamber implantable cardioverter-defibrillators (ICD), cardiac resynchronization therapy (CRT) devices), many of which have remote monitoring capabilities.

Current guidelines do not address in detail management of SCAF.[1] There is therefore a need to provide expert recommendations for professionals participating in the care of such patients. To address this topic, a Task Force was convened by the European Heart Rhythm Association (EHRA), with representation from the Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS) and Sociedad LatinoAmericana de Estimulacion Cardiaca y Electrofisiologia (SOLEACE), with the remit to comprehensively review the published evidence available, and to publish a joint consensus document on the management of patients with subclinical AT, with up-to-date consensus recommendations for clinical practice. This consensus document will address definitions, clinical importance, implications and management of device-detected subclinical atrial tachyarrhythmias, as well as current developments in the field.

Evidence review

Consensus statements are evidence-based, and derived primarily from published data. In contrast with current systems of ranking level of evidence, EHRA has opted for a simpler, perhaps, more user-friendly system of ranking that should allow physicians to easily assess current status of evidence and consequent guidance (*Table 1*). Thus, a 'green heart' indicates a recommended statement or recommended/indicated treatment or procedure and is based on at least one randomized trial, or is supported by strong observational evidence that it is beneficial and effective. A 'yellow heart' indicates that general agreement and/or scientific evidence favouring a statement or the usefulness/efficacy of a treatment or procedure may be supported by randomized trials based on small number of patients or not widely applicable. Treatment strategies for which there has been scientific evidence that they are potentially harmful and should not be used are indicated by a 'red heart'. EHRA grading of consensus statements does not have separate definitions of Level of Evidence. The categorization used for consensus statements (used in consensus documents) should not be considered as being directly similar to that used for official society guideline recommendations which apply a classification (I–III) and level of evidence (A, B and C) to recommendations in official guidelines.

Relationships with industry and other conflicts

It is an EHRA/ESC policy to sponsor position papers and guidelines without commercial support, and all members volunteered their time. Thus, all members of the writing group as well as reviewers have disclosed any potential conflict of interest in detail, at the end of this document.

Incidence and predictors of device-detected subclinical atrial tachyarrhythmias

The reported incidence of subclinical AT varies with the study design (retrospective or prospective), underlying heart disease (sinus node dysfunction (SND), atrioventricular block (AVB), or heart failure), presence or absence of AF history, definition of atrial high rate episode (AHRE) duration, type of device detecting the AT, and the observation period.[2–7]

A retrospective study in SND/AVB patients without AF history reported that the incidence of pacemaker-detected AHRE ≥5 min was 29% (77/262 patients) at a mean follow-up of 596 days (24% at 1 year and 34% at 2 years); cumulative percentage of right ventricular pacing ≥50% was the only predictor of the occurrence of AHREs.[3] Another study reported that the incidence of pacemaker-detected AF was 51.8% (173/334 patients without AF history) over a mean follow-up of 52 months, and the patients with subclinical AF were older and more likely to have a history of clinical AF and larger left atrial volumes.[4] The atrial diagnostics ancillary study of the MOST (MOde Selection Trial) revealed that 160 (51.3%) of 312 patients with pacemakers implanted for sinus node disease had at least one AHRE lasting at least 5 min at a median follow-up of 27 months. Patients with AHREs were more likely to have a history of supraventricular arrhythmias, AVB, use of antiarrhythmic drug, and presence of heart failure than those without AHRE.[5]

Overall, the incidence of subclinical AT/AF is ~20% within 1 year of follow-up, but there have been no consistent predictors of SCAF in patients with PPMs and ICDs and without AF history.

Symptoms during atrial fibrillation episodes

Patient' perceptions of arrhythmia symptoms are highly variable: this includes individual awareness of on-going tachyarrhythmia. Among pacemaker patients who are known to experience symptoms due to AF only ~17–21% of symptoms were actually correlated with an episode of AF.[8,9] Asymptomatic AF is 12-fold more frequent than symptomatic AF in patients with paroxysmal AF, when evaluated by use of 5-day Holter monitoring[10]; only 10% of episodes give rise to symptoms. In pacemaker patients with known AF, asymptomatic AF comprises 38–81% of all AF episodes.[9,11] Among 114 patients with documented AF episodes 5% of patients had only asymptomatic AF episodes prior to pulmonary vein isolation on 7-day Holter monitoring whereas 37% of patients had only asymptomatic AF 6 months

Table 2 On-going studies on potentially subclinical and asymptomatic atrial fibrillation

Study	Study identifier	Inclusion criteria	Randomization/ Design	Size	Endpoint	Est. completion date
ARTESiA[13]	Clinicaltrials.gov NCT01938248	Permanent pacemaker, ICD or CRT CHA_2DS_2-VASc score of ≥ 4. Age ≥65 At least one episode of symptomatic AF ≥ 6 min (Atrial rate >175/min if an atrial lead is present), but no single episode >24 h in duration. Only patients without clinical AF	Randomized to: Apixaban 5 mg ×2 (or 2.5 mg ×2) vs. Aspirin 81 mg ×1 daily Randomized, double-blind, double-dummy.	4000 patients planned	1. Composite of ischemic stroke and systemic embolism 2. Major Bleeding	2019
NOAH AFNET 6[14]	Clinicaltrials.gov NCT02618577	Permanent pacemaker or defibrillator. Age ≥65+additional CHA_2DS_2-VASc score point of ≥ 2, i.e. CHA_2DS_2-VASc ≥3 At least one episode of AHRE ≥6 min (Atrial rate >180/min if an atrial lead is present), but no single episode >24 h in duration. Only patients without overt AF	Randomized to: Edoxaban 60 mg ×1 (or 30 mg if renal impairment) vs. Aspirin 100 mg ×1 daily or placebo[a] Randomized, double-blinded double dummy.	3400 patients planned	Composite of time to the first stroke, systemic embolism, or cardio-vascular death	2019
The (Danish) LOOP study[15]	Clinicaltrials.gov NCT02036450 www.loop-study.dk	Age >70 years and at least one of the following diseases: • Diabetes • Hypertension • Heart failure • Previous stroke	Randomization to receive an ILR or be treated as standard of care (ratio 1:3; i.e. 1500 randomized to ILR and 4500 randomized to standard care)	6000 patients planned	Composite of ischemic stroke and systemic embolism	2019

[a]The randomized therapy with aspirin or placebo.

AHRE, atrial high rate episode; CRT, cardiac resynchronization therapy device; ICD, implantable cardioverter-defibrillator; ILR, implantable loop recorder; ARTESiA, Apixaban for the Reduction of Thrombo-embolism in Patients with Device-detected Sub-clinical Atrial Fibrillation; ASSERT, ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and atrial fibrillation Reduction atrial pacing Trial; LOOP, Atrial fibrillation detected by continuous electro-cardiographic monitoring using implantable LOOP recorder to prevent stroke in individuals at risk; NOAH, Non-vitamin K Antagonist Oral Anticoagulants in Patients with Atrial High Rate Episodes.

after ablation, suggesting that the perception of symptoms changes after catheter ablation.[12]

There is no evidence that asymptomatic AF patients have a different risk profile compared with symptomatic AF. Several prospective trials are ongoing (*Table 2*).[13–15] The presence of symptoms will likely have little impact on clinical outcome, except that it increases the probability of earlier diagnosis and appropriate treatment.

Table 3 Fact box on clinical significance of subclinical and silent/asymptomatic atrial fibrillation

Facts	Supporting references
• Patients with symptoms have a higher probability of earlier diagnosis and thereby receive evaluation about relevant medical treatment compared with non-symptomatic patients	13–15
• The vast majority of AF episodes are asymptomatic	8–11
• At this time asymptomatic AF should be treated as symptomatic AF with regard to oral anticoagulation	13–15
• The thromboembolic risk related to different durations of AF episodes is incompletely understood	13–15

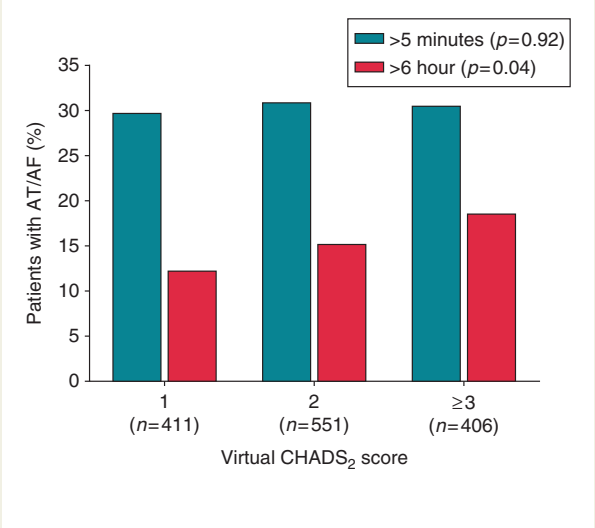

Figure 1 Incidence of newly detected atrial fibrillation (AHRE >5-min duration) in relation to the virtual $CHADS_2$ score. AHRE, atrial high rate episode; AF, atrial fibrillation; AT, atrial tachycardia. Reproduced from reference[5] with permission by Elsevier.

Detection and targeted screening for subclinical and silent (asymptomatic) atrial tachyarrhythmias in patients with CIEDs and higher risk populations

Detection of subclinical AF in patients with implanted permanent pacemakers, ICDs, and CRT devices

The term SCAF has been used to describe atrial arrhythmia episodes detected by cardiac implanted electronic devices (CIEDs). SCAF is usually discovered incidentally during a routine evaluation of the CIED, and has not caused any symptoms prompting the patient to seek medical attention. Patients with CIEDs have an advantage over cardiac patients who do not have a continuous arrhythmia monitor in place because clinically silent arrhythmias can be detected.

Current evidence suggests that the prevalence of SCAF is considerable among patients with implanted devices, and that the presence of subclinical AF increases the risk of thromboembolism (TE).[5–7] The minimum duration of AF (or minimum AF burden) which confers this increased TE risk is not precisely defined, but may be as brief as several minutes to several hours. The advent of non-vitamin K antagonist oral anticoagulants (NOACs), which offer the promise of improved efficacy and safety profiles, may further widen the indication for oral anticoagulation.[13,14]

Epidemiology of atrial fibrillation in patients with cardiac implantable electronic devices

The prevalence of AF in patients with CIEDs is reported to range from 30% to 60%.[4–7,16–21] In early 2000s, two studies of patients with pacemakers implanted for sinus node disease have reported atrial arrhythmias in 50–68% of patients.[5,16] More recently, Healey *et al.*[4] have shown similar results: AF was detected during follow-up in ~55% of unselected populations of patients with pacemakers which exactly reproduced earlier findings.[21]

Studies specifically designed to exclude subgroups of patients who may have had AF in the past (history of AF, history of oral anticoagulation use, history of anti-arrhythmic drug use), have found an incidence of newly detected SCAF in ~30% of device patients. For example, patients from the TRENDS (The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke) trial in 1368 patients who had no prior history of AF, no previous stroke or transient ischaemic attack (TIA) and no warfarin or antiarrhythmic drug use were analysed to look for newly detected AF.[6] Newly detected AF was defined as device-detected AHRE lasting at least 5 min. Thirty percent of patients (416 patients) experienced newly detected AF. The incidence of newly detected AF was consistent across patients with intermediate (virtual $CHADS_2$ score of 1) (30%), high (virtual $CHADS_2$ score of 2) (31%), and very high (virtual $CHADS_2$ score of ≥3) (31%) stroke risk factors ($P = 0.92$). (A virtual $CHADS_2$ score is calculated in a patient who has never previously had AF.) However, a significant increase was seen in the proportion of patients having days with >6 h of AT/AF as the virtual $CHADS_2$ score increased;

Table 4 Incidence of atrial fibrillation in the implanted device population

Year	Study	Device Indication	Clinical Profile of Patients	Follow-up	Incidence of AF
2002	Gillis *et al.*[16]	PPMs for sinus node disease	All	718±383 days	157/231 (68%)
2003	MOST[5]	PPMs for sinus node disease	All	median 27 months	156/312 (50%)
2006	BEATS[21]	PPMs for all indications	All	Prospective, 12 months	137/254 (54%)
2010	TRENDS[17]	PPMs and ICDs All indications	History of prior stroke No history of AF No OAC use ≥1 stroke risk factor	Mean 1.4 years	45/163 (28%)
2012	TRENDS[6]	PPMs and ICDs All indications	No history of prior stroke No history of AF No OAC use ≥1 stroke risk factor	1.1±0.7 years	416/1368 (30%)
2012	ASSERT[7]	PPMs and ICDs All indications	History of hypertension No history of AF No OAC use	2.5 years	895/2580 (34.7%)
2013	Healey *et al.*[4]	PPMs All indications	All	Single center retrospective	246/445 (55.3%)

AF, atrial fibrillation; ICD, implantable cardioverter-defibrillator; OAC, oral anticoagulation; PPM, permanent pacemaker; ASSERT, ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and atrial fibrillation Reduction atrial pacing Trial; BEATS, Balanced Evaluation of Atrial Tachyarrhythmias in Stimulated patients; MOST, MOde Selection Trial; TRENDS, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke.

Table 5 Summary of studies on atrial fibrillation detected by CIEDs and thromboembolic risk

Year	Trial	Number of patients	Duration of follow-up	Atrial rate cut-off	AF burden threshold	Hazard ratio for TE event	TE event rate (below vs. above AF burden threshold)
2003	Ancillary MOST[5]	312	27 months (median)	>220 bpm	5 min	6.7 (P=0.020)	3.2% overall (1.3% vs. 5%)
2005	Italian AT500 Registry[18]	725	22 months (median)	>174 bpm	24 h	3.1 (P=0.044)	1.2% annual rate
2009	Botto *et al.*[19]	568	1 year (mean)	>174 bpm	$CHADS_2$+AF burden	n/a	2.5% overall (0.8% vs. 5%)
2009	TRENDS[20]	2486	1.4 years (mean)	>175 bpm	5.5 h	2.2 (P=0.060)	1.2% overall (1.1% vs. 2.4%)
2012	Home Monitor CRT[22]	560	370 days (median)	>180 bpm	3.8 h	9.4 (P=0.006)	2.0% overall
2012	ASSERT[7]	2580	2.5 years (mean)	>190 bpm	6 min	2.5 (P=0.007)	(0.69% vs. 1.69%)
2014	SOS AF[23]	10016	2 years (median)	>175 bpm	1 h	2.11 (P=0.008)	0.39% per year Overall

AF, atrial fibrillation; bpm, beats per minute; CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; TE, thromboembolic; SOS AF, Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices. Other abbreviations as in *Table 4*.

12%, 15%, and 18% for intermediate, high, and very high risk, respectively; $P = 0.04$ (*Figure 1*).

In another analysis from the TRENDS trial, the incidence of newly detected AF was analysed in patients (319 patients) with a prior history of stroke or TIA.[17] Patients ($n = 156$) with a documented history of AF, warfarin use, or antiarrhythmic drug use were excluded from analysis. Newly detected AF (AHRE lasting at least 5 min) was identified by the implantable device in 45 of 163 patients (28%) over a mean follow-up of 1.1 years.

In the ASSERT (ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and atrial fibrillation Reduction atrial pacing Trial), a study of 2580 patients with a history of hypertension and no prior history of AF, SCAF (defined as lasting at least 6 min in duration) was detected at least once in 35% of the patients over a mean follow-up of 2.5 years.[7] Taken together, these two large studies show remarkably similar results: in patients with CIEDs, stroke risk factors, and no prior history of AF (regardless of TE history), SCAF can be identified in ~30% of patients. Selected trials that determined the incidence of device-detected AF are outlined in *Table 4*.

Thromboembolic risk of subclinical atrial fibrillation in the cardiac implantable electronic devices population

The major studies regarding the thromboembolic risk of sub-clinical device-detected AHRE in general populations of patients with

Table 6 Temporal relationship of device-detected atrial fibrillation to thromboembolic events

Year	Trial	Number of patients with TE event	Definition of AF episode	Any AF detected prior to TE event	AF detected only after TE event	No AF in 30 days prior to TE event	Any AF in 30 days prior to TE event
2011	TRENDS[24]	40	5 min	20/40 (50%)	6/40 (15%)	29/40 (73%)	11/40 (27%)
2014	ASSERT[25]	51	6 min	18/51 (35%)	8/51 (16%)	47/51 (92%)	4/51 (8%)
2014	IMPACT AF[26]	69	36/48 atrial beats ≥200 bpm	20/69 (29%)	9/69 (13%)	65/69 (94%)	4/69 (6%)

AF, atrial fibrillation; bpm, beats per minute; TE, thromboembolic; IMPACT AF, Randomized trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation. Other abbreviations as in *Table 4*.

Table 7 Causes for inappropriate atrial fibrillation detection and solutions by device programming[7,36,37]

False negative detection (AF not diagnosed by tde device)	
True atrial undersensing (AF not sensed due to small signals)	Increase atrial sensitivity (recommended setting: bipolar, 0.2–0.3 mV)
Functional atrial undersensing (AF potentials coincide with atrial blanking times)	Only important in atrial flutter; (i) limit upper tracking rate to ≤ 110 bpm if clinically feasible, (ii) activate specific atrial flutter detection algorithms
False positive detection (oversensed signals mistaken for AF)	
Ventricular farfield oversensing in the atrium	Prolong postventricular atrial blanking time (recommended: 100–150 ms)
Myopotential oversensing	Bipolar sensing setting; reduce sensitivity
Electromagnetic interference, lead failure	Activate noise reaction; lead revision
Ineffective atrial pacing (repetitive non-reentrant VA synchrony)	Reduce or deactivate sensor reactivity in rate-responsive pacing; shorten paced AV delay, activate non-competitive atrial pacing, inactivate AF suppression algorithm

Abbreviations. AF, atrial fibrillartion; AV, atrioventricular; VA ventriculoatrial.

Table 8 Recommendations and fact box for the management of device-detected atrial arrhythmias

Recommendations	Class	Supporting references
If available, review stored intracardiac electrograms to confirm diagnosis and exclude artifact or reduce the effect of oversensing/undersensing by automated algorithms is recommended; solutions to correct inappropriate AF detection are provided in *Table 7*		6, 36, 37
Facts		
The presence or absence of symptoms has no bearing on determining the need for anticoagulation.		13–15, 18–20, 22, 23

AF, atrial fibrillation.

implanted pacemakers, defibrillators, and CRT are summarized in *Table 5*.[5,7,18–20,22,23]. All show increases in stroke rate associated with device-detected AF episodes. A minimum of 5 min of AF was first found to have clinical relevance in 2003.[5] Alternative burden cut-points have been explored over the subsequent 10 years, ranging from 5 min to 24 h, coming back nearly full circle to the clinical significance of 6 min of AHRE burden in 2012.[7] In all of these studies, the AF threshold cut-points were either arbitrarily chosen, or were the results of the data itself (i.e. median values). Thus, there is still uncertainty regarding the minimum duration of device-detected AF that increases TE risk.

Temporal proximity of device-detected AF to stroke events

There does *not* seem to be a close temporal relationship of device-detected atrial arrhythmias to the occurrence of strokes, despite the fact that patients who have AHREs are at a significantly increased risk of stroke. Several studies have highlighted this point and are outlined in *Table 6*.[23–26] In the majority of patients (73–94%) there was no AF on the device recordings in the 30 days prior to the TE events. These data imply that, in the majority of device patients with AHREs and thromboembolic events, the mechanism of stroke may not be related to the AF episodes. It does not seem to matter if the AF episode is proximal to the stroke event,[23] and risk seems to be increased by relatively brief

Table 9 Recommendations for treatment of sub-clinical AF with oral anticoagulation

Recommendations	Class
Assessment of the patient's stroke risk using the CHA_2DS_2-VASc score is recommended	
No antithrombotic therapy for any patient with CHA_2DS_2-VASc score of 0 in males or 1 in females, irrespective of AHRE, is recommended	
For patients with two additional CHA_2DS_2-VASc risk factors (ie. ≥2 in males, ≥3 in females) oral anticoagulation is recommended for AF burden >5.5 h/day (if there are no contraindications). Lower duration may merit OAC if multiple risk factors are present.	
For effective stroke prevention in patients with CHA_2DS_2-VASc score ≥2, oral anticoagulation, whether with well controlled vitamin K antagonist (VKA) with a time in therapeutic range >70%, or with a non-VKA oral anticoagulant (NOAC, either dabigatran, rivaroxaban, apixaban or edoxaban) is recommended	
Consider oral anticoagulation for AF burden (longest total duration of AF on any given day) of > 5.5 h in patients with 1 additional CHA_2DS_2-VASc risk factor (ie. score=1 in males or = 2 in females)	
Recognize that the data suggests risk is similarly increased by a mere 5-min episode, but it is reasonable to see a patient with only a single 5-min episode again in follow-up to observe their AF burden over time before committing them to life-long oral anticoagulation.	
Bleeding risk should be assessed using validated scores, such as the HAS-BLED score. • Patients at high risk (score≥3) should be identified for more regular review and follow-up, and the reversible bleeding risk factors addressed. • A high HAS-BLED score is not a reason to withhold anticoagulation.	

AF, atrial fibrillation; AHRE, atrial high rate episode; OAC, oral anticoagulation.

Table 10 Recommendations for treatment of subclinical atrial fibrillation with oral anticoagulation

CHA_2DS_2-VASc score	Duration of AHRE	Recommendation
≥2	>5.5 h (lower duration if multiple stroke risk factors are present)*	
1 (male) or 2 (female)	>5.5 h*	

*Data suggests risk is similarly increased by a mere 5 min.
AHRE, atrial high rate episode.

AF episodes.[27,28] What does seem to be consistent is the finding that the appearance of new AHREs increases thromboembolic event rates. Therefore, short episodes of newly detected AF may represent rather a marker for an ~2.5-fold risk of stroke but not the immediate cause of intracardiac thrombus formation and cardioembolic stroke.

Detection of atrial fibrillation in cardiac implantable electronic devices by remote monitoring

The capability of remote monitoring (RM) to detect AF has been consistently demonstrated by several observational[29,30] and randomized trials.[31,32] In the worldwide Home Monitoring database analysis,[33] 3 004 763 transmissions were sent by 11 624 patients with pacemakers, ICDs, and CRT devices. AF was responsible for >60% of alerts in pacemakers and CRT-D devices, and for nearly 10% of alerts in dual-chamber ICDs. The rate of false-positive alerts was low—86% were disease-related, 11%—system-related and 3%—device programming-related.

Approximately 90% of AF episodes triggering alerts are asymptomatic.[30] Even when an inductive remote monitoring system (without automatic alerts) is studied, RM performed better than standard follow-up in pacemaker patients for detection of AF.[34,35] Compared to standard scheduled follow-up, detection of AF occurs 1–5 months earlier with RM.

Device programming and choice of atrial lead for reliable atrial fibrillation detection

An implanted atrial lead is ideal to reliably detect AF, it is superior to the surface ECG that may mistake irregular RR intervals due to frequent premature atrial beats for AF, and unaffected by the regular RR intervals during AF in patients with AVB. However, even in automatic detection of AF by devices, the causes of false positive and false negative detections must be known to avoid misinterpretation of stored data (*Table 7*). For reliable AF detection by devices, a bipolar atrial lead (preferably with short bipole spacing) is required. A high atrial sensitivity is necessary to avoid intermittent undersensing of AF that can result in inappropriate detection of persistent AF as multiple short episodes. Ventricular farfield oversensing can be avoided by adjusting the postventricular atrial blanking time as shown in two randomized prospective trials.[7,36] Some specific forms of inappropriate AF detection by implantable devices with atrial leads should be known[37] to avoid misinterpretation and wrong treatment guided by device memory. It is also worth mentioning that cut-off values for AHRE rate and duration affects the false-positive results: longer duration of AHRE >190 beats/min >6 h reduces false-positive results as compared to >6-min duration.[38]

The presence of AF is associated with an almost five-fold increased risk of stroke.[39] However, the precise role that SCAF plays in raising the risk of stroke is less well understood. Further studies need to address whether AF is merely a marker for atrial fibrotic disease,[1] which predisposes a patient to an increased risk of stroke, or patient's risk of stroke increases primarily during and shortly following the

Table 11 Ambulatory Holter monitoring in evaluation of silent/asymptomatic atrial tachyarrhythmias in high-risk populations

Study	Design	Population	ECG monitoring types/duration	Follow-up	AF/ESVEA	Outcomes	Risk/Diagnostic value (95% CI)
Excessive supraventricular ectopic activity							
Binici *et al.*[48] Copenhagen Holter Study	Population cohort	678 healthy men and women without CVD, AF or stroke, 55–75 y	48 h HM ESVEA—≥30PCS/h or PSC runs >20 beats	6.3 y	ESVEA 70 episodes, PSC runs 42 episodes ESVEA(+) vs. ESVEA(-)	AF—12.8/1000 py vs. 4.3/1000 py, *P*=0.008 Stroke—18.8/1000 py vs. 4.9/1000 py, *P*=0.0002 Mortality—37.2/1000 py vs. 18.9/1000 py, *P*=0.005	Death or Stroke [a]HR 1.6 (1.03–2.06), *P*=0.036 Stroke admission [b]HR 2.37 (1.02–5.5), *P*=0.044 AF admissions– cHR 2.73 (1.07–6.96), *P*=0.035
Larsen *et al.*[43] Copenhagen Holter Study	Population cohort	678 healthy men and women w/o CVD, AF or stroke 55–75 y	48-h HM	14.4 y	ESVEA (+) 99 (14.6%) ESVEA (-) 579 (85.4%)	Excluding AF cases Ischemic stroke 19.9/1000 py vs. 7.2/1000 py, *P*=0.0001	Ischemic stroke [d]HR 1.96 (1.1–3.49), *P*=0.02 ESVEA(+) CHA_2DS_2-VASc ≥2 24.1% stroke events per 1000 py ESVEA(-) CHA_2DS_2-VASc ≥2 9.9% stroke events per 1000 py
Dewland *et al.*[48] Cardiovascular Health Study	Prospective cohort	1260 subjects w/o AF, >65 y	24 h HM	13 y	AF—27%	Risk—doubling of hourly PSC Incident AF—HR 1.17 (1.13–1.22), <0.001 Mortality—HR 1.06 (1.03–1.09), <0.001	
Engstrom *et al.*[50] 'Men born in 1914'	Prospective cohort	402 men 68 y w/o MI or stroke	24-h HM AF, PSC >218/h	14 y	Stroke: No PSC/No AF—11.6/1000 py, Frequent PSC—19.5/1000 py, AF—34.5/1000 py, *P*=0.007 Risk of stroke: Reference—No AF or PSC [e]PSC HR 1.9 (1.02–3.4), *P*=0.04		
Gladstone *et al.*[51] EMBRACE trial	RCT Intervention arm analysis	237 pts with CS or TIA w/o AF >55 y	Baseline 24-h HM 30-day ELR	2 y	PSC/24 h (IQR) AF—629 (142–1973) w/o AF—45 (14–250), *P*<0.001	SAF detection rate probability Reference 90-day AF—16% PSC 100/24 h—<9% PSC 100–499/24 h—9–24% PSC 500–999/24 h—25–37% PSC 1000–1499/24 h—37–40% PSC >1500/24 h—40%	

Continued

Table 11 *Continued*

Study	Design	Population	ECG monitoring types/duration	Follow-up	AF/ESVEA	Outcomes	Risk/Diagnostic value (95% CI)
Atrial fibrillation							
Salvatori *et al.*[52] Perugia General Practitioner Study	Prospective cohort	309 pts with HT >65 y 274—HM	48 h HM	SAF 10% (6.4–3.5%), ESVEA 20% (15.3–4.7%)		Risk factors for: SAF—age OR 1.12 (1.02–1.24), *P*=0.021 ESVEA—age OR-(1.02–1.12), *P*=0.009	
Marfella *et al.*[53]	Prospective case-controlled Cross-sectional arm	464 DM pts 240 healthy control subjects	48 h HM—quarterly AF < 48 h duration	37 m	Cross-sectional: DM vs. Controls SAF—11% vs. 1.6%, *P*<0.0001 Prospective: Stroke rate: SAF DM vs. DM: 1st y—3.8% vs. 1.4% 2nd y—6.2% vs. 2.2%		[f]SAF association: SCI OR 4.441 (2.418–8.157) LAD OR 2.667 (1.476–4.821) SBP OR 1.03 (1.010–1.050) DM duration OR 1.075 (1.002–1.154) Risk of stroke: SAF HR 4.6 (2.7–9.1) SBP HR 1.7 (1.02–2.92) SCI HR 3.1 (1.3–7.1)
Stamboul *et al.*[42]	Prospective cohort	737 MI pts	Continuous automated 48-h ECG mon. In-hospital	1 y	AF—14% SAF—4%	SAF vs. no AF HF hosp. 6.6% vs. 1.3%, *P*<0.001 CV death 5.7% vs. 2.0%, *P*<0.001	SAF vs. no AF CV death or HF hosp. OR 2.236 (95% CI 1.015–4.926) *P*=0.046
Stamboul *et al.*[54]	Prospective cohort	849 MI pts	Continuous automated 48-h ECG monitoring In-hospital	In-hospital	SAF—16%	SAF vs. No AF HF 41.8% vs. 21%, *P*<0.0001 Death 10.4% vs. 1.3%, *P*<0.0001	Predictors of mortality: SAF—OR 3.65 (1.44–9.23), *P*=0.006 Predictors of SAF History of AF OR 3.07 (1.38–6.82), *P*=0.006 Age, per/y 1.06 (1.04–1.07), *P*<0.001 LA area per cm^2/m^2 1.11 (1.04–1.18), *P*=0.002

Continued

Table 11 *Continued*

Study	Design	Population	ECG monitoring types/duration	Follow-up	AF/ESVEA	Outcomes	Risk/Diagnostic value (95% CI)
Grond *et al.*[56]	Prospective cohort study	1137 stroke TIA pts 67 y w/o known AF	24 h HM 72 h HM	SAF 24 h HM: 2.6% (1.5–3.7%) 72 h HM: 4.3% (3.4–5.2%)		Predictors of SAF: Advanced age OR 1.076 (1.042–1.111, *P*<0.0001) Mild-moderate vs. severe neurological deficit OR 0.261 (0.134–0.511) TIA pts: Presence of ischemic lesion on MRI OR 5.439 (1.276–23.1811)	
Hindricks *et al.*[12]	Prospective Cohort Study	114 pts Undergoing CA of AF	7-day HM Before CA After CA—3, 6, 12 m	12 m	Asymptomatic AF Before CA—5%, After CA—3 m—38%, *P*=0.021, 6 m—37%, *P*=0.021, 12 m—36%, *P*<0.05		
Choe *et al.*[57] CRYSTAL-AF	RCT	168 patients with CS or TIA	ICM and simulated monitoring Single HM: 24 h, 48 h, 7 days; Quarterly: 24 h, 48 h, 7 days; Monthly—24 h and 30 days EM		Sensitivity: Single HM vs. EM 24 h—1.3%, 30 days EM—22.8%, NPV—range 82.3–85.6% Periodical: Quarterly HM 24 h—3.1%, 7 days—20.8%, NPV—range 82.6–85.3%		
Dagres *et al.*[59]	Cohort	215 pts after CA of AF 56 y	7 days HM 6 m after CA of AF		Overall AF recurrence 7 days HM—64 pts (30%) Recurrence rates detected according to the length of recording: 24 h—59%, *P*<0.001, 48 h—67%, *P*<0.001, 72 h—80%, *P*<0.001, 4 days—91% *P*=0.041, 5 days—91% *P*=0.041, 6 days—95% *P*=0.242 of 100% 7 days HM		
Sposato *et al.*[63]	Meta-analysis 50 studies	11 658 pts with stroke or TIA with NDAF	Phases: (1) ER—ECG (2) In-hospital—serial ECG, CEM, TM, HM (3) 1st amb period—Ambulatory HM (4) 2nd amb period—Mobile outpatient TM, ELR, ILR		Phase 1: ECG in ER—7.7% Phase 2: serial ECG—5.6%, CEM—7.0%, TM—4.1%, HM—4.5%, overall phase 2–5.1% Phase 3: Ambulatory HM (1- to 7-day monitoring) 10.7%*,** Phase 4: mobile out-patient TM—15.3%, ELR—16.2%, ILR—16.9%, Overall phase 4—16.9%, Overall—23.7% (17.2–31.0) **P*=0.047 vs. phase 2 ***P*=0.037 vs. in-hospital HM		

AF, atrial fibrillation; AT, atrial tachycardia; BMI, body mass index; CEM, continuous stroke unit electrocardiographic monitoring; CRYSTAL, CRYptogenic STroke and underlying AtriaL fibrillation; CS, cryptogenic stroke; CV, cardiovascular; d, days; DBP, diastolic blood pressure; DM, diabetes; ECG, electrocardiogram; ELR, event loop recorder; EMBRACE, 30-day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event; ESVEA, excessive supraventricular ectopic activity; h, hours; HM, Holter monitoring; HR, hazard ratio; HT, hypertension; ILR, implantable/insertable loop recorder; IQR, interquartile range; MI, myocardial infarction; m, months; mon., monitoring; NDAF, newly diagnosed AF; NPV, negative predictive value; OR, odds ratio; PSC, premature supraventricular contraction; PPV, positive predictive value; RCT, randomized controlled study; SAF, silent AF; SBP, systolic blood pressure; SCI, silent cerebral infarct; TM, telemetry; y, years.

[a]Adjusted for smoking, SBP, DM, cholesterol, age and sex; [b]adjusted age, sex, SBP, BMI, DM and smoking; [c]adjusted for age and sex; [d]adjusted for age, sex, smoking, SBP, DM, BMI, cholesterol; [e]adjusted for SBP, DM, smoking, angina pectoris; [f]adjusted for sex, BMI, DBP, DM duration, Hb1Ac, hyperlipidemia.

Table 12 Recommendations and fact box on use of Holter monitoring to detect atrial tachyarrhythmias

Recommendations	Class	Supporting references
Holter monitoring may be considered for detection of SAF in high-risk patients who has no CIEDs and has no indication for long-term event monitoring	IIb	51, 53, 56, 58, 59
Holter monitoring may be used as a step in screening strategy or in combination with other screening tools to improve detection of subclinical arrhythmia and to select candidates for long-term monitoring	IIb	51, 57, 60
Serial Holter monitoring may be considered if longer duration monitoring tools are not available	IIa	51, 53, 56, 57, 59
Fact		
ESVEA documented by Holter monitoring can be considered be a surrogate marker for paroxysmal AF		43, 48–51

AF, atrial fibrillation; ESVEA, excessive supraventricular ectopic activity; CIED, cardiac implantable electronic device; SAF, silent atrial fibrillation.

occurrence of AF; and whether a single episode of AF lasting 5 min is a sufficient indication for life-long anticoagulation. Until larger trials or registries are conducted, it is important to follow established treatment recommendations regarding oral anticoagulation (*Tables 9* and 10), given the risk of fatal or disabling strokes if left untreated.

Whether this suggested approach to therapy will have a net benefit in reducing TE events remains to be determined.

Ambulatory Holter monitoring to detect atrial tachyarrhythmias

Current evidence on the role of Holter monitoring in screening for subclinical arrhythmias is limited. Several observational cohort studies demonstrated an association of subclinical AT with increased risk of stroke and mortality in high-risk populations (*Table 11*).[7,40–43] The efficacy of detection of SCAF by monitoring devices depends on the duration and method of ECG monitoring: 24-h Holter monitoring has moderate sensitivity (44–66%) compared to event recorders and CIEDs (sensitivity—91%).[44] Current guidelines on management of patients with AF recommend Holter monitoring in cases when the arrhythmia type is unknown and for monitoring efficacy of rate control.[45,46] In clinical practice, Holter monitoring of variable duration of up to 7 days is also used for detection of asymptomatic AF in populations undergoing a rhythm control strategy, including post-ablation.[47]

Excessive supraventricular ectopic activity (ESVEA) is associated with risk of incident AF [≥30 premature supraventricular contractions (PSC)/hour or episode of PSC runs ≥20 beats),[48] stroke (≥729 PSC/24 h or episode of PSC runs ≥20 beats),[43] and mortality in selected populations depending on the frequency of PSC on Holter monitoring.[49–51] It was an independent predictor of stroke and incident AF admissions in a middle-aged population,[47] and in combination with CHA_2DS_2-VASc score ≥2 yielded 24.1% stroke events per 1000 patient years compared to 9.9% of stroke events per 1000 patient years in those CHA_2DS_2-VASc score ≥2 and without ESVEA.[43] Doubling of hourly rate of PSC increased the risk of subsequent AF, cardiovascular and overall mortality in elderly (>65 years old)[49] and frequent PSC doubled the risk of stroke in elderly men with or without hypertension.[50] In a substudy of the EMBRACE (30-day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event) trial,[51] ESVEA detected by 24-h Holter monitoring was a predictor of AF developing after cryptogenic stroke and predicted detection of AF by 30-day event monitor.

Silent AF (SAF) rates vary between 1.5% and 14% in high-risk populations, depending on type and duration of monitoring.[12,41,52–59] SAF was associated with older age and presence of ESVEA on 48-h Holter monitoring in patients with hypertension.[52] Patients with diabetes and SAF were more likely to have silent cerebral infarct (lacunar infarct of <15 mm on magnetic resonance imaging), dilatation of left atrium, high blood pressure and longer duration of disease than diabetics without SAF, and their risk of stroke during 3 years of follow-up was increased by factor of 4.6.[53] Detection of SAF on 72-h Holter monitoring showed an association with the presence of ischemic lesions on magnetic resonance imaging in patients with transient ischemic attack, and also with the severity of neurological deficit in patients with stroke.[56]

Longer duration of Holter monitoring (7-day monitoring) increases detection of SAF. The CRYSTAL-AF (CRYptogenic STroke and underlying AtriaL fibrillation) trial demonstrated that longer term monitoring had higher sensitivity in AF detection compared to 24-h Holter monitoring.[57] A recent meta-analysis showed that ≥7-day monitoring increase the detection of SAF in patients with cryptogenic stroke or TIA by factor of 7.6 as compared to <72-h Holter monitoring.[58] In a study of 7-day Holter monitoring in patients after catheter ablation for AF, authors analysed detection rates of AF recurrence according to the (7-day monitoring—100% of AF recurrence episodes), duration of monitoring and demonstrated stepwise increase in detection of AF recurrence with the extension of monitoring from 59%—24-h, 67%—48-h, 80%—72-h to 91% on days 4 and 5, and 95% on day 6.[59]

Comparison of AF screening strategies in patients with stroke revealed that stopping screening after ECG in emergency room (phase 1) and any in-hospital monitoring method (phase 2) would have resulted in detection of 50.2% and after out-of-hospital ambulatory Holter monitoring (1- to 7-day monitoring, phase)—81.9% of post-stroke AF diagnosed after phase 4 (mobile outpatients telemetry, implantable loop recorders [ILR] and external loop recorders [ELR]). There are several on-going trials testing AF screening strategies in high-risk populations[60–62] but more studies are needed to clarify the role of Holter monitoring alone or in combination with other tools in screening of subclinical tachyarrhythmias in high-risk populations.

Event recorders to detect sub-clinical and silent atrial fibrillation

The 24-h Holter monitor represents the most established, but, as outlined earlier, least sensitive device for continuous ECG monitoring

Table 13 Summary of key studies examining the utility of monitoring for the detection of previously undetected atrial fibrillation[a]

Study (Year)	Design (number)	Monitoring device	Population	Definition of AF	Prevalence of AF
EMBRACE[68] (2014)	RCT (286 with monitor vs. 285 with Holter)	Braemar ER910AF event monitor with dry electrode belt; automatic AF detection vs. 24-hr Holter	Cryptogenic Stroke	≥30 s Detected within 90 days	Monitor: 16.1% Holter 3.2
Grond *et al.*[56] (2013)	Cohort (1172)	72-hr Holter; Lifecard CF (Spacelabs)	Ischemic stroke or TIA	>30 s	4.3% after 72 hr 2.6% after 24 hr
Jabaudon *et al.*[69] (2004)	Cohort (149)	7-day; *R*-test Evolution II, (Novacor)	Stroke or TIA	Not stated	ECG: 2.7% 24-hr Holter: 5% ELR: 5.7%[b]
Tung *et al.*[64] (2014)	Cohort (1171)	14-day continuous ECG monitor (Ziopatch; iRhythm)	Stroke or TIA	>30 s	5%
ASSERT-III[67] (2015)	Cohort (100)	30-day event monitor; automatic AF detection (Vitaphone 3100), wireless central monitoring (m-Health Solutions)	Age≥80 years with hypertension and at least one additional AF risk factor)	≥6 min	15%
SCREEN-AF (NCT02392754)[70]	Ongoing Cohort (1800)	Two 14-day continuous ECG monitors (Ziopatch; iRhythm)	Age≥75 years without prior AF	≥5 min	Ongoing study

[a]All exclude patients with a prior diagnosis of AF.
[b]Tests done sequentially. ELR detected AF in 5.7% of patients with no AF on ECG or 24-hr Holter.
AF, atrial fibrillation; ECG, electrocardiogram; ELR, event loop recorder; hr, hour; RCT, randomized controlled trial;TIA, transient ischemic attack; ASSERT, ASymptomatic atrial fibrillation and Stroke Evaluation in pacemaker patients and atrial fibrillation Reduction atrial pacing Trial; EMBRACE, 30-day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event.

Table 14 Fact box on use of event recorders to detect subclinical and silent atrial fibrillation

Facts	Supporting references
A variety of technologies (continuous or intermittent ECG recording) now exist for prolonged ambulatory cardiac monitoring to detect SCAF and SAF	7, 56, 65, 68, 69, 70
Longer monitoring periods are associated with a greater rate of SCAF and SAF detection	7, 31, 66

SAF, silent atrial fibrillation; SCAF, sub-clinical atrial fibrillation; ECG, electrocardiography.

Table 15 Atrial fibrillation detection percentage in embolic stroke of uncertain source (ESUS)

Study	Year	Study Design	AF detection	AF (%)
Dahal *et al.*[72]	2015	Meta-analysis of RCT	Cardiac monitoring ≥7 days vs. ≤2 days	13.8% vs. 2.5% (P<0.001, total 1149 patients)
Li *et al.*[74]	2015	Population-based analysis	Paroxysmal AF % in cryptogenic stroke vs. large/small vessel disease	6% vs. 10% (P=0.17, total 2555 patients)

AF, atrial fibrillation; RCT, randomized controlled trial.

to detect silent AF, while implanted atrial-based PPMs and ICDs are the most sensitive methods in detection of SCAF.[7] Between these two extremes, there are a variety of technologies which either continuously record the heart rhythm, or make intermittent recordings.[44] The latter are either patient-activated, or have automatic AF detection algorithms which use the ventricular rate and/or regularity to define when AF is occurring. As SCAF is typically asymptomatic[7] devices with automatic AF-detection algorithms have an advantage; however, patient-activated devices may still be used by asking patients to make multiple random recordings while asymptomatic. Devices may use dry or adhesive electrodes; may come in the form of an adhesive patch,[64] or resemble a typical Holter monitor.

Table 16 Implantable loop recorders in detection of atrial fibrillation in cryptogenic stroke patients

Study (year)	Number of patients	AF detection criteria	AF yield	Mean/median time to detect (days)	Notes
Dion *et al.*[80] (2010)	24	N/A	4.2%	435	All patients were <75 years of age; EP testing of no value
Etgen *et al.*[81] (2013)	22	6 min	27.3%	365	
Rojo-Martinez *et al.*[82] (2013)	101	2 min	33.7%	102	
Cotter *et al.*[83] (2013)	51	2 min	25.5%		
SURPRISE[84] (2014)	85	2 min	16.1%		
CRYSTAL AF[41] (2014)	221	>30 s	12.4% (1 year) 30% (3 years)	41	Small number of patients followed for 3 years
Ziegler *et al.*[71] (2015)	1247		12.2%	182	
Afzal *et al.*[73] (2015)	1170		23.3%	365	
Bernstein *et al.*[75] Crystal AF Trial (2015)	212		20.9%	365	AF % in cryptogenic stroke with or without brain infarction, topography verification

AF, atrial fibrillation; CRYSTAL AF, CRYptogenic STroke and underlying AtriaL fibrillation; EP, electrohysiological; SURPRISE, Stroke Prior to Diagnosis of Atrial Fibrillation Using Long-term Observation with Implantable Cardiac Monitoring Apparatus Reveal. Modified from reference.[71]

Table 17 Predictors of atrial fibrillation in cryptogenic stroke population

Study	Predictors of atrial fibrillation
Cotter *et al.*[83] (2013)	Age Frequent atrial premature beats Inter-atrial conduction block Increased left atrial volume
CRYSTAL AF[41] (2014)	Age (U and M) $CHADS_2$ score (U) PR interval (U and M) Frequent atrial premature beats (U) Diabetes (U)

M, multivariate; U, univariate; CRYSTAL AF, CRYptogenic STroke and underlying AtriaL fibrillation.

Table 18 Recommendations on use of implantable loop recorders and anticoagulation in cryptogenic stroke

Recommendations	Class	Supporting references
Outside of the research context patients with cryptogenic stroke may not receive an ILR		26, 84, 85, 87
Patients with cryptogenic stroke may receive anticoagulation (based upon brain imaging) after a negative comprehensive cardiac and vascular investigation		26, 84, 85, 87

*The recommendations are based on the IMPACT trial data.[26]
See grading EHRA evidence grading for yellow heart—*Table 1*.
ILR, implantable loop recorder.

A systematic review of monitoring studies, mostly done in post-stroke populations, suggests that longer periods of monitoring are associated with a higher rates of SAF detection.[65] Technologies which continuously record the ECG (e.g. Holter, 14-day or longer term monitoring) have the advantage that they can calculate the frequency of premature atrial contractions and short runs of atrial tachycardia, which studies suggest are associated with an increased risk of AF and stroke.[48] Given the potentially prolonged periods of monitoring, wireless devices with central monitoring facilitate earlier physician recognition of SCAF.

Population screening studies have been done using single-point or intermittent ECG monitoring.[66] As monitoring technology has evolved, various continuous monitoring technologies have been used to study prevalence of undetected AF in patients without prior stroke (*Table 13*). In the ASSERT III study, for example, which monitored patients continuously for 30–60 days, 15% of patients 80 years or older had at least one episode of SCAF ≥ 6 min (*Table 13*).[67] Although continuous monitoring provides a higher rate of SCAF detection than that in studies using single-point and intermittent methods, it is more expensive. Ongoing research will define which technologies are the most cost-effective for SCAF/SAF detection and in which specific patient populations they should be applied.

Table 19 Fact box on use of hand-held ECG devices to detect silent atrial fibrillation in stroke patients

Facts	Supporting references
Hand-held electrocardiogram devices can be inexpensive, cost-effective, and non-invasive tools for screening of silent intermittent AF episodes, for example, in patients with ischemic stroke or TIA without a history of AF	90–93

AF, atrial fibrillation; ECG, electrocardiogram; TIA, transient ischamic attack.

Cryptogenic stroke and subclinical atrial tachyarrhythmias

Cryptogenic stroke is defined as an embolic (defined by brain imaging characteristics) cerebrovascular infarct for which no underlying cause can be identified after full cardiovascular evaluation including exclusion of intracranial shunts and carotid/vertebral arterial disease by appropriate imaging studies, and 'thrombogenic' arrhythmias such as AF, atrial flutter and, more recently, high frequency atrial premature beats by continuous electrocardiographic monitoring.

Large scale randomized trials and meta-analyses have shown that the prevalence of AF becomes higher as the monitoring periods are longer (*Tables 15* and *16*).[71–73] For example, continuous arrhythmia monitoring for periods up to 1 year in patients with cryptogenic stroke show an AF prevalence to be ~20%.[73] However, the topography (shape, size and location) of the cerebral ischemic infarction area is not related to AF prevalence.[74,75]

There is much similarity between the phenotype of cryptogenic stroke (embolic stroke of uncertain source [ESUS]) and AF-related stroke. Risk stratification of reccurent stroke can be performed in ESUS using the CHA_2DS_2-VASc score, as with AF-related stroke.[76] Also, stroke severity in ESUS was shown to be similar to AF-related strokes,[77] though in women AF–related stroke was accompanied by more disabling symptoms.[78]

Implantable loop recorders in patients with cryptogenic stroke

Several randomized studies have compared standard follow-up after cryptogenic stroke with implanted monitoring using remote data acquisition, while most studies were observational reporting findings in patients with stroke, who received monitor after full clinical evaluation.[79] Although in some cases the implanted device was not fully capable of automated detection of AF,[80] such devices are generally associated with more rapid identification of AF than less intensive routine follow-up. Recent meta-analysis of detection rates of new-onset AF after stroke or transient ischemic attack has demonstrated that the increase in monitoring time increases detection rates of the arrhythmia up to 16.9% with ILR, resulting in a cumulative detection rate of every 4th case of AF compared with ambulatory Holter monitoring (10.7%) and in-hospital monitoring (5.2%) (*Table 11*).[60]

Despite apparent discrepancies in detection rates which are likely related to patient selection factors and varying device characteristics/settings (*Table 16*), there are common findings with regard to predictors of AF (*Table 17*).[41,80–84]

With regard to trends over time, most studies have observed that detection rates of AF increase over time.[41] Although implantable monitors could be utilized for AF detection after cryptogenic stroke, this strategy has not been shown to have clinical utility in regard to future stroke prevention and its cost-effectiveness compared with an empiric anticoagulation strategy remains speculative given the substantial expense of the devices. In light of the IMPACT (Randomized trial to IMProve treatment with AntiCoagulanTs in patients with Atrial Fibrillation) primary prevention data[26] in which temporal dissociation of arrhythmia and embolic events was definitively demonstrated in a randomized trial where rapid anticoagulation after identification of AF had no effect upon stroke outcomes, we cannot justify an expensive monitoring strategy using implantable devices after embolic stroke unless this is part of an investigation in which empiric anticoagulation after cryptogenic stroke is the comparison group.

A rapidly evolving recent understanding of fibrotic pathology and the pro-thrombotic characteristics of blood sampled from the left atrium in patients with AF have led to a new paradigm of understanding the mechanism of stroke; AF in this framework is not directly causal, but is a marker and an amplifier of underlying atrial pathology in which the arrhythmia itself is not a necessary condition for thrombus formation.[85,86]

Hand-held ECG detection of silent atrial fibrillation in stroke patients

It has been shown that prolonged continuous monitoring detects increased number of undiagnosed episodes of AF in patients after ischaemic stroke.[87] However, prolonged continuous ECG monitoring can also be associated with poorer compliance and high costs.

Brief intermittent ECG monitoring over a long time period (30 days) is a low-cost non-invasive alternative method. Intermittent arrhythmia screening with handheld electrocardiogram (ECG) has shown to be significantly more sensitive in the detection of silent AF compared to conventional 24-h Holter-ECG[88,89] as well as in one study of patients who had suffered an ischaemic stroke/TIA. In that observational prospective controlled study, 249 consecutive patients with a recent stroke/TIA without a history of AF were recruited, within 14 days from the index event.[90] Those investigators performed an ambulatory continuous 24-h Holter-ECG recording before or within the first few days after hospital discharge. Simultaneously, patients were equipped with a handheld ECG recorder and instructed to perform 10 s rhythm recordings once in the morning and once in the evening for 30 days and in case of any arrhythmia symptoms. A total of 17 patients were diagnosed with AF. Intermittent handheld ECG recordings detected AF in 15 patients and 2 exclusively by 24 h continuous ECG. In three patients, AF was diagnosed by both methods. The ability to detect AF was significantly better for the handheld ECG compared with the Holter-ECG ($P = 0.013$). The total prevalence of AF was 6.8% and increased to 11.8% in patients ≥75 years. An economic evaluation estimated that

Table 20 Recommendations on stroke prevention in subclinical atrial tachyarrhythmias

Recommendations	Class	Supporting references
The presence of AHRE >5 min is associated with an increased risk of stroke/SE especially in the presence of ≥ 2 stroke risk factors using the CHA_2DS_2-VASc score. Thus, OAC should be considered in such patients, whether as a NOAC or well controlled VKA with TTR>70%.		5, 38

AHRE, atrial high rate episode; NOAC, non-vitamin K antagonist oral anticoagulant; OAC, oral anticoagulation; SE, systemic embolism; TTR, time in the therapeutic ranges; VKA, vitamin K antagonist.

silent AF screening by intermittent ECG recordings in 75-year-old patients with a recent ischaemic stroke is a cost-effective use of health care resources saving both costs and lives and improving the quality of life.[91]

Smartphone ECG application to detect silent atrial fibrillation

Recent studies indicate that it is technically feasible to identify AF automatically using a simple electrode attachment for a smartphone[92,93]; in addition, community based screening using such consumer technology has been shown to identify AF in 1.5% of a high-risk population attending retail pharmacies.[89] However, whether detection of truly silent AF is valuable at all is a question that remains unresolved: either there is a clinical concern regarding the relationship between non-specific symptoms and arrhythmia (in which case the AF is technically not silent), or the identification of truly silent AF raises complex questions for which no clear answers in relation to management are currently apparent.[94] While there is an established relationship in the pacemaker population between overall burden of AF and stroke, the similarly well-established temporal dissociation of arrhythmia episodes and stroke presents a paradox that will likely be clarified by ongoing prospective studies such as Tactic AF and REACT.COM study which use continuous monitoring to drive intermittent novel anticoagulant therapy.[95,96]

Role and limitations of imaging techniques in stroke prediction in silent atrial fibrillation

Although the CHA_2DS_2-VASc score is important in prediction of stroke risk in patients with AF, many patients with score 0–1 may still present with a stroke. Imaging techniques have focused on anatomical and functional properties of the left atrium (LA) as well as the left atrial appendage (LAA). Both LA/LAA enlargement and reduced function have been associated with AF and stroke.[85,97–99]

Various LAA variables have been independently associated with an increased risk of thromboembolic events. The LAA shape (an anatomical parameter), but also markers of reduced LAA function such as dense spontaneous echo contrast or thrombi, but also reduced flow have been independently associated with an increased risk of thromboembolic events.[85,97,98] Optimal assessment of LAA size and anatomy is obtained with 3-dimensional imaging techniques such as multi-detector row computed tomography (MDCT) or magnetic resonance imaging (MRI), whereas the different functional parameters are derived from transthoracic or transesophageal echocardiography.[100]

The LA variables that may be relevant for development of stroke, can also be divided into anatomical and functional parameters. LA size can be measured with echocardiography; historically, diameters have been used, but volumetric measures may be preferred. These can be obtained with 3-dimensional echocardiography, but also with MDCT or magnetic resonance imaging (MRI).[85,97,98] Another marker that appears relevant for the development of AF and has also been related to stroke, is the presence and extent of LA fibrosis.[85,97,98] This can roughly be estimated with transthoracic echocardiography using integrated back scatter, but is more precisely quantified with contrast-enhanced MRI.[101]

Functional parameters are derived mostly from echocardiography. For example, LA function consists of three parts, namely the reservoir function (filling of the LA during left ventricular systole), the conduit function (acting as a conduit between the pulmonary veins and the left ventricle during early diastole, reflected by the E-wave on Doppler echocardiography) and the active booster pump function (LA contraction, reflected by the A-wave on Doppler echocardiography).[98] Advanced measurement of these variables can be performed with 3-dimensional echocardiography. More recently, quantification of the active deformation (strain) of the LA has been demonstrated with echocardiography and MRI.[85,97,98]

Finally, there is a clear relation between the anatomical and functional LA parameters. LA dilatation is often associated with LA fibrosis, which in turn results in reduced LA function and specifically LA strain. An indirect marker of LA fibrosis is the assessment of the electro-mechanical delay or prolonged totalatrial activation time; this can be expressed by the time delay between the P-wave (on the ECG) and the mechanical activation of the LA (the so-called PA-TDI, as derived from echocardiographic tissue Doppler imaging).[98]

All of the aforementioned parameters are related to development of AF and subsequent stroke.

Stroke risk assessment and prevention strategies in subclinical atrial tachyarrhythmias

Arrhythmia burden whether assessed by all episodes, longest episodes or number of episodes all show a relationship to annual stroke/TE rates.[19] For example, the absolute rate of stroke in ASSERT increased with increasing $CHADS_2$ score, ranging from a stroke/TE rate of 0.56%/year at $CHADS_2$ score 1, to 1.29% at $CHADS_2$ score 2 and 3.78%/year with $CHADS_2$ score >2. Of note,

Table 21 Studies on cost-effectiveness of device-based screening for silent atrial fibrillation after ischemic stroke

Study (Year)	Type of Evaluation and Health Care System	Patients Population	Study Design	Main Study Findings
Kamel *et al.*[116] (2010)	A semi-Markov model to compare the cost and utility of warfarin vs. aspirin to prevent stroke in patients with AF under a US payer perspective.	Hypothetical cohort of 70-year-old AF patients with a prior ischemic stroke and no contraindication to warfarin	Meta-analysis was used to determine the yield of 7-days outpatient cardiac monitoring which could detect AF (5.9% detecting rate vs. 1.45% with standard care) and trigger the prescription of warfarin vs. standard care with aspirin and no monitoring after ischemic stroke.	Outpatient cardiac monitoring is cost-effective over a wide range of model inputs (cost-utility ratio of outpatient monitoring would be ~$13 000 per QALY gained), but the optimal duration and method of monitoring is unknown.
Levin *et al.*[91] (2015)	Markov model to estimate the cost and QALY of oral anticoagulants vs. no therapy to prevent stroke in patients with AF under a Sweden healthcare system.	Hypothetical cohort of 75-year-old AF patients with a recent ischemic stroke and followed for 20 years	A decision analytic model combining the use of an observational prospective controlled study and epidemiological data to determine the yield of intermittent ECG recording using a handheld device (6% detection of AF) and 24-h Holter monitoring (0.8% detection of AF) vs. no monitoring, which could detect AF and trigger the prescription of OAC.	Intermittent handheld ECG screening is cost-effective use of health care resources saving cost and lives, and improving quality of life (gain of 29 life-years or 23 QALYs, and cost saving of €55400 after 7 years, assuming that 85% of detected AF patients received lifetime OAC).
Diamantopoulos *et al.*[118] (2016)	Markov model to compare the cost and lifetime QALYs of NOAC vs. aspirin to prevent stroke in patients with AF under UK National Health Service perspective.	Hypothetical cohort of patients (mean age 62-year old) with a recent cryptogenic stroke or transient ischemic attack, allocated to receive either an ICM vs. standard of care as observed in the CRYSTAL-AF trial.	A deterministic analytic model combining the use of data from the CRYSTAL-AF and with models used in previous National Institute for Health and Care Excellence (NICE) assessments of AF treatments to determine the yield of ICM (8.9%, 12.4% and 30% detecting AF at 6, 12 and 36 months) vs. no monitoring which could detect AF and trigger the prescription of NOAC.	Implantable cardiac monitors are a cost-effective diagnostic tool for the prevention of recurrent stroke in cryptogenic stroke patients (cost per QALY gain was estimated to be £17 175 and £13 296 with the use of NOAC, and warfarin, respectively).

AF, atrial fibrillation; CUR, cost-utility ratio; ECG, electrocardiogram; ICM, implantable cardiac monitoring; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulants; QALY, quality adjusted life-year.

the event rates at $CHADS_2$ 0 and 1 were lower than those seen for corresponding $CHADS_2$ score event rates seen in the general AF population. Until more evidence is forthcoming, stroke(and bleeding risk in such patients should be assessed according to established risk assessment tools, such as the CHA_2DS_2-VASc (for stroke) and the HAS-BLED (for bleeding) risk scores.[102,103] A high HAS-BLED score is not a reason to withhold OAC, but to indicate the patient potentially at risk of bleeding for more regular review and follow-up, assess changes in the score over time, and to address the potentially reversible bleeding risk factors.[104]

Given that all clinical risk scores have only modest predictive value for precise risk assessment, the initial step should be the identification of 'low risk' patients (CHA_2DS_2-VASc score 0 in males, 1 in females) who do not need any antithrombotic therapy; the subsequent step is to consider stroke prevention (which is OAC) in patients with ≥1 stroke risk factors, with a clear recommendation for OAC in those with CHA_2DS_2-VASc score ≥2. OAC refers to a NOAC or well controlled VKA, with time in the therapeutic range (TTR) >70%, given that the net clinical benefit for treatment is evident even with one stroke risk factor.[105] Most guidelines give a preference for the NOACs over VKA, given the efficacy, safety and convenience of the latter[1,106] as evident from randomized trials and increasing 'real world' evidence.[107–109]

A TTR of >70% is associated with the best efficacy and safety of the VKAs, and a good TTR can be predicted by various clinical risk factors encompassed within the SAMe-TT_2R_2 score.[110] The latter score is a simple clinical score that includes the common factors associated with

Table 22 Major knowledge gaps regarding device-detected atrial tachyarrhythmias

- Pathophysiologic link between device-detected atrial tachyarrhythmias and stroke. Are subclinical tachyarrhythmias the cause or just a marker of increased stroke risk? Type of strokes: embolic or ischemic?
- Is there a threshold of tachyarrhythmia duration leading to an elevated stroke risk?
- Can oral anticoagulation reduce stroke risk in patients with subclinical device-detected atrial tachyarrhythmias? Is there a threshold of tachyarrhythmia duration for a beneficial effect of oral anticoagulation? Do usual schemes for stroke risk stratification (e.g. CHA_2DS_2-VASc) apply in this setting equally well as in patient with overt atrial fibrillation?
- Potential role of different remote monitoring modalities: can it be help for management of these patients and how?

good international normalized ratio (INR) control, such that a score of 0–2 is associated with a good TTR, while a patient with a score of >2 is less likely to achieve a good TTR, such that more regular review and INR checks, as well as education and counselling are needed if a VKA is used—or to use a NOAC instead (rather than impose a 'trial of VKA' which can be associated with an excess of thromboembolism while the INR control is suboptimal.[111,112]

Other uncertainties remain. Although AHRE was associated with an increased risk of ischemic stroke and systemic embolism, there was a lack of a distinct temporal association between AHRE and the actual event.[24–26] Thus, AHRE could simply be a risk marker for stroke, or reflect an indirect mechanism related to multiple comorbidities associated with stroke. For example, in patients with a high CHA_2DS_2-VASc score, ischaemic stroke, thromboembolism and mortality rates with or without AF are broadly similar.[113,114]

One possible explanation may be that not all AHRE episodes are definitely AF. In an ancillary analysis from the ASSERT study,[38] for example, when using a cutoff of >6 min and >190 beats/min, the rate of false-positive AHREs was 17.3%, making a review of device electrograms necessary. However, for AHREs that are lasting >6 h, the rate of false positives was much lower, at 3.3%. Hence, rather than referring to these as AHRE, there is a suggestion to (as described earlier) use the term 'subclinical atrial tachyarrhythmias' given the lower events rates seen compared to 'conventional' ECG-defined AF and the false positive electrograms.

What is less clear is the required 'burden' of the arrhythmia (that is, AF episodes and duration) necessary for precipitating stroke and TE. Recent results of ASSERT trial, demonstrated that only episodes longer than 24 h of duration were associated with three-fold increase in stroke rate as compared to episodes of shorter duration.[115] Also, the number of AHRE episodes per day—as well as AF burden (whether quantified by duration or number of AHRE)—can vary greatly, and the paroxysms of AF are frequently asymptomatic.

Ongoing studies (see relevant section below) will address the impact of OAC on reducing stroke/TE in patients with AHRE detected on devices. As mentioned earlier, there is a positive net clinical benefit for OAC in overt AF with the presence of ≥1 stroke risk factors;[105] however, this benefit is less clear for AHRE, especially where arrhythmia burden is low.

Cost-effectiveness of screening for silent AF after ischemic stroke

The improvement of the sensitivity and specificity for AF detection using different device-based methods, such as handheld ECG device,[91] external[68] or implantable cardiac recorders[41] as compared to surface ECG or 24-h Holter monitoring have the potential to increase the yield to identify silent AF as aetiology for ischemic stroke. The cost-effectiveness of different mobile devices for screening of AF in the primary care setting have been evaluated by the National Institute for Health and Care Excellence (NICE) of UK. Both the WatchBP Home A (https://www.nice.org.uk/guidance/mtg13/chapter/5-Cost-considerations) and AliveCor Heart Monitor device (https://www.nice.org.uk/advice/mib35/chapter/Evidence-review) are more cost-effective than portable ECG device in detecting silent AF and preventing stroke in primary care setting. Nevertheless, there are only limited cost-effectiveness analyses to determine whether these screening methods should be implemented for screening for silent AF after ischemic stroke in whom no aetiology can be determined (i.e. cryptogenic stroke) (*Table 21*).

In a meta-analysis, Kamel *et al.*[116] have demonstrated that 1 week of outpatient cardiac monitoring for screening of silent AF after cryptogenic stroke is cost-effective compared with no monitoring in a US-based health care system. Based on a Swedish cohort, Levin *et al.*[91] have shown that brief, intermittent long-term ECG recording with a handheld ECG device for screening of silent AF in cryptogenic stroke is also more cost-effective compared to no screening or 24-h Holter monitoring, and even cost-saving after 7 years of implementation. Recently, Diamantopoulos *et al.*[117] performed a cost-effectiveness analysis using data from the CRYSTAL-AF trial from a UK-based health care system, and revealed that ILRs were a cost-effective screening method for prevention of recurrent stroke in cryptogenic stroke. While all these studies[91,116,117] demonstrate that device-based screening methods for silent AF after cryptogenic stroke are cost-effective, several assumptions are included in these models, including that the use of screening for AF in elderly high risk populations (aged > 70 or 75 years old), and treatment with OAC are highly effective for recurrent stroke prevention. Indeed, the efficacy of OAC for prevention of recurrent stroke in cryptogenic stroke will be addressed by two ongoing clinical trials.[118,119] Moreover, direct comparisons between these different devices on the cost-effectiveness of screening for silent AF in cryptogenic stroke also require future investigation.

Current research gaps, ongoing trials and future directions

There are convincing data that subclinical atrial tachyarrhythmias detected by cardiovascular electronic devices in patients without clinically overt AF are associated with an increased risk of stroke. However, several major aspects of this association remain unclear, as summarized in *Table 22*.

In particular, the pathophysiologic link between subclinical AF and stroke is still obscure.[28] The simple explanation of thrombus formation during subclinical tachyarrhythmic episodes followed by embolization is challenged by the lack of a temporal relation between the tachyarrhythmic episodes and the strokes as suggested in the ASSERT and TRENDS studies,[24,26] and confirmed by the IMPACT trial.[26] Thus, subclinical AF may rather be a marker of increased stroke risk rather than a direct cause of thromboembolism. We also do not know whether a certain duration of such episodes needs to be exceeded before an elevation of stroke risk is apparent. Respective data are contradictory. For example, in the TRENDS study, tachyarrhythmic episodes <5.5 h were not associated with an increased thromboembolic risk[20] whereas in the ASSERT study, episodes ≥6 min already led to a higher embolic risk,[7] and in the Copenhagen Holter Study even ESVEA was associated with a higher risk of stroke.[47] Most importantly, the benefit of oral anticoagulation based solely on device-detected subclinical atrial tachyarrhythmias for reducing the stroke risk has not yet been examined. Prospective clinical trials are ongoing,[13,14] and results are expected in 2019 (*Table 2*).

Consensus statements

	Consensus statements	Class
1.	Incidence of subclinical AT/AF varies depending on the clinical characteristics of the population studied.	
2.	• The vast majority of AF episodes are asymptomatic. • Symptoms do not affect long-term prognosis, but they do increase the probability of making a correct diagnosis and offering proper treatment.	
3.	• The likelihood of detecting subclinical AT/AF increases as the duration of monitoring lengthens. • A variety of technologies, both non-invasive and invasive now exist for prolonged cardiac monitoring to detect subclinical AT/AF.	
4.	• The appearance of subclinical AT/AF predisposes to thromboembolic events. • The minimum duration of AT/AF episode or AT/AF burden which confers increased thromboembolic risk is not precisely defined, but may be as brief as several minutes to several hours. • There is no established cut-point for increase in risk, and NO minimum duration that is without risk.	
5.	• There does not seem to be a close temporal relationship of device-detected atrial arrhythmias to the occurrence of strokes. • This implies that, in the majority of device patients with AHREs and thromboembolic events, the mechanism of stroke may not be related to the AF episodes.	
6.	If available, review of stored intracardiac electrograms to confirm diagnosis and exclude artifact or reduce the effect of oversensing/undersensing by automated algorithms is recommended	
7.	The presence or absence of symptoms has no bearing on determining the need for anticoagulation	
8.	Consider no antithrombotic therapy for any patient with CHA_2DS_2-VASc score of 0 in males or 1 in females, irrespective of AHRE	
9.	Consider oral anticoagulation for AF burden (longest total duration of AF on any given day) of > 5.5 h in patients with one additional CHA_2DS_2-VASc risk factor (i.e. score=1 in males or = 2 in females)	
10.	For patients with two additional CHA_2DS_2-VASc risk factors (ie. ≥2 in males, ≥3 in females) oral anticoagulation is recommended for AF burden >5.5 h/day (if there are no contraindications). Lower duration may merit OAC if multiple risk factors are present.	
11.	• Novel user-friendly external devices for AF detection have the potential to increase the	

Continued

Continued

Continued

Consensus statements	Class
yield of identifying silent AF as an aetiology for ischemic stroke. • However, comparative effectiveness studies on these various external devices and cost-effectiveness analyses on the use of these devices still need to be done.	
12. Remote monitoring may be used for detection of AF: • Even when an inductive remote monitoring system (without automatic alerts) is studied, RM performs better than standard follow-up in pacemaker patients for detection of AF. • Compared to standard scheduled follow-up, detection of AF occurs 1–5 months earlier with remote monitoring.	
13. • There is a positive net clinical benefit for oral anticoagulants in overt AF with the presence of ≥ 1 stroke risk factors. • This benefit is less clear for AHRE, especially where arrhythmia burden is low.	
14. Whether oral anticoagulation will have a net benefit in reducing TE events for SCAF remains to be determined. Until larger trials or registries are conducted, it is important to consider following established guidelines regarding anticoagulation (See above).	
15. ESVEA documented by Holter monitoring can be considered as a surrogate marker for paroxysmal AF.	

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References

1. Kirchof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B *et al.* 2016 ESC guidelines for management of atrial fibrillation developed in collaboration with EACTS. *Europace* 2016;**18**:1609–78.
2. Chen-Scarabelli C, Scarabelli TM, Ellenbogen KA, Halperin JL. Device-detected atrial fibrillation. What to do with asymptomatic patients? *J Am Coll Cardiol* 2015;**65**:281–94.
3. Cheung JW, Keating RJ, Stein KM, Markowitz SM, Iwai S, Shah BK *et al.* Newly detected atrial fibrillation following dual chamber pacemaker implantation. *J Cardiovasc Electrophysiol* 2006;**17**:1323–8.
4. Healey JS, Martin JL, Duncan A, Connolly SJ, Ha AH, Morillo CA *et al.* Pacemaker-detected atrial fibrillation in patients with pacemakers: prevalence, predictors, and current use of oral anticoagulation. *Can J Cardiol* 2013;**29**:224–8.
5. Glotzer TV, Hellkamp AS, Zimmerman J, Sweeney MO, Yee R, Marinchak R, MOST Investigators *et al.* Atrial high rate episodes detected by pacemaker diagnostics predict death and stroke: report of the Atrial Diagnostics Ancillary Study of the MOde Selection Trial (MOST). *Circulation* 2003;**107**:1614–9.
6. Ziegler PD, Glotzer TV, Daoud EG, Singer DE, Ezekowitz MD, Hoyt RH *et al.* Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. *Am J Cardiol* 2012;**110**:1309–14.
7. Healey JS, Connolly SJ, Gold MR, Israel CW, Van Gelder IC, Capucci A, ASSERT Investigators *et al.* Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;**366**:120–9.
8. Strickberger SA, Ip J, Saksena S, Curry K, Bahnson TD, Ziegler PD. Relationship between atrial tachyarrhythmias and symptoms. *Heart Rhythm* 2005;**2**:125–31.
9. Quirino G, Giammaria M, Corbucci G, Pistelli P, Turri E, Mazza A *et al.* Diagnosis of paroxysmal atrial fibrillation in patients with implanted pacemakers: relationship to symptoms and other variables. *Pacing Clin Electrophysiol* 2009;**32**:91–8.
10. Page RL, Wilkinson WE, Clair WK, McCarthy EA, Pritchett EL. Asymptomatic arrhythmias in patients with symptomatic paroxysmal atrial fibrillation and paroxysmal supraventricular tachycardia. *Circulation* 1994;**89**:224–7.
11. Israel CW, Grönefeld G, Ehrlich JR, Li YG, Hohnloser SH. Long-term risk of recurrent atrial fibrillation as documented by an implantable monitoring device: implications for optimal patient care. *J Am Coll Cardiol* 2004;**43**:47–52.
12. Hindricks G, Piorkowski C, Tanner H, Kobza R, Gerds-Li JH, Carbucicchio C *et al.* Perception of atrial fibrillation before and after radiofrequency catheter ablation: relevance of asymptomatic arrhythmia recurrence. *Circulation* 2005;**112**:307–13.
13. Population Health Research Institute. Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA). https://clinicaltrials.gov/ct2/show/study/NCT01938248 (16 January 2016, date last accessed).
14. German Atrial Fibrillation Network Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH). https://clinicaltrials.gov/ct2/show/NCT02618577 (16 January 2016, date last accessed).
15. Rigshospitalet. Atrial Fibrillation Detected by Continuous ECG Monitoring (LOOP). https://clinicaltrials.gov/ct2/show/NCT02036450 (21 April 2016, date last accessed).
16. Gillis AM, Morck M. Atrial fibrillation after DDDR pacemaker implantation. *J Cardiovasc Electrophysiol* 2002;**13**:542–7.
17. Ziegler PD, Glotzer TV, Daoud EG, Wyse DG, Ezekowitz MD, Singer DE *et al.* Incidence of newly detected atrial arrhythmias via implantable devices in patients with a prior history of thromboembolic events. *Stroke* 2010;**41**:256–60.
18. Capucci A, Santini M, Padeletti L, Gulizia M, Botto G, Boriani G *et al.* Monitored atrial fibrillation duration predicts arterial embolic events in patients suffering from bradycardia and atrial fibrillation implanted with antitachycardia pacemakers. *J Am Coll Cardiol* 2005;**46**:1913–20.
19. Botto GL, Padeletti L, Santini M, Cappucci A, Pulizia M, Zolezzi F *et al.* Presence and duration of atrial fibrillation detected by continuous monitoring: crucial implications for the risk of thromboembolic events. *J Cardiovasc Electrophysiol* 2009;**20**:241–8.
20. Glotzer TV, Daoud EG, Wyse DG, Singer DE, Ezekowitz MD, Hilker C *et al.* The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. *Circ Arrhythm Electrophysiol* 2009;**2**:474–80.
21. Israel CW, Neubauer H, Olbrich HG, Hartung W, Treusch S, Hohnloser SH. Incidence of atrial tachyarrhythmias in pacemaker patients: results from the Balanced Evaluation of Atrial Tachyarrhythmias in Stimulated patients (BEATS) study. *Pacing Clin Electrophysiol* 2006;**29**:582–8.

22. Shanmugam N, Boerdlein A, Proff J, Ong P, Valencia O, Maier SK *et al*. Detection of atrial high-rate events by continuous home monitoring: clinical significance in the heart failure-cardiac resynchronization therapy population. *Europace* 2012;**14**:230–7.
23. Boriani G, Glotzer TV, Santini M, West TM, De Melis M, Sepsi M *et al*. Device-detected atrial fibrillation and risk for stroke: an analysis of > 10,000 patients from the SOS AF project (Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices). *Eur Heart J* 2014;**35**:508–16.
24. Daoud EG, Glotzer TV, Wyse DG, Ezekowitz MD, Hilker C, Koehler J, TRENDS Investigators *et al*. Temporal relationship of atrial tachyarrhythmias, cerebrovascular events, and systemic emboli based on stored device data: a subgroup analysis of TRENDS. *Heart Rhythm* 2011;**8**:1416–23.
25. Brambatti M, Connolly SJ, Gold MR, Morillo CA, Capucci A, Muto C, ASSERT Investigators *et al*. Temporal relationship between subclinical atrial fibrillation and embolic events. *Circulation* 2014;**129**:2094–9.
26. Martin DT, Bersohn B, Waldo AL, Wathen MS, Choucair WK, Lip GY *et al*. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and resynchronization devices. *Eur Heart J* 2015;**36**:1660–8.
27. Camm AJ, Simantrakis E, Goette A, Lip GYH, Vardas P, Calvart M *et al*. Atrial high-rate episodes and stroke prevention. *Europace* 2017;**19**:169–79.
28. Benezet-Mazuecos J, Rubio JM, Cortés M, Iglesias JA, Calle S, de la Vieja JJ *et al*. Silent ischaemic brain lesions related to atrial high rate episodes in patients with cardiac implantable electronic devices. *Europace* 2015;**17**:364–9.
29. Varma N, Stambler B, Chung S. Detection of atrial fibrillation by implanted devices with wireless data transmission capability. *Pacing Clin Electrophysiol* 2005;**28**:S133–6.
30. Ricci RP, Morichelli L, Santini M. Remote control of implanted devices through Home Monitoring technology improves detection and clinical management of atrial fibrillation. *Europace* 2009;**11**:54–61.
31. Varma N, Epstein A, Irimpen A, Schweikert R, Shah J, Love CJ. Trust trial Investigators. Efficacy and safety of automatic remote monitoring for ICD Follow-Up: the TRUST trial. *Circulation* 2010;**122**:325–32.
32. Crossley G, Boyle A, Vitense H, Chang Y, Mead RH. The clinical evaluation of remote notification to reduce time to clinical decision (CONNECT) trial: the value of wireless remote monitoring with automatic clinician alerts. *J Am Coll Cardiol* 2011;**57**:1181–9.
33. Lazarus A. Remote, wireless, ambulatory monitoring of implantable pacemakers, cardioverter defibrillators, and cardiac resynchronization therapy systems: analysis of a worldwide database. *Pacing Clin Electrophysiol* 2007;**30**:S2–12.
34. Crossley GH, Chen J, Choucair W, Cohen TJ, Gohn DC, Johnson WB *et al*. Clinical benefits of remote versus transtelephonic monitoring of implanted pacemakers. *J Am Coll Cardiol* 2009;**54**:2012–9.
35. Dubner S, Auricchio A, Steinberg JS, Vardas P, Stone P, Brugada J *et al*. ISHNE/EHRA expert consensus on remote monitoring of cardiovascular implantable electronic devices (CIEDs). *Europace* 2012;**14**:278–93.
36. Kolb C, Wille B, Maurer D, Schuchert A, Weber R, Schibgilla V *et al*. Management of far-field R wave sensing for the avoidance of inappropriate mode switch in dual chamber pacemakers: results of the FFS-test study. *J Cardiovasc Electrophysiol* 2006;**17**:992–7.
37. Barold SS, Levine PA. Pacemaker repetitive nonreentrant ventriculoatrial synchronous rhythm. A review. *J Interv Card Electrophysiol* 2001;**5**:45–58.
38. Kaufman ES, Israel CW, Nair GM, Armaganijan L, Divakaramenon S, Mairesse GH *et al*. Positive predictive value of device-detected atrial high-rate episodes at different rates and durations: an analysis from ASSERT. *Heart Rhythm* 2012;**9**:1241–6.
39. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;**22**:983–8.
40. Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH *et al*. Asymptomatic atrial fibrillation: clinical correlates, management, and outcomes in the EORP-AF pilot general registry. *Am J Med* 2015;**128**:509–18.
41. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, CRYSTAL AF Investigators *et al*. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;**370**:2478–86.
42. Stamboul K, Zeller M, Fauchier L, Gudjoncik A, Buffet P, Garnier F *et al*. Prognosis of silent atrial fibrillation after acute myocardial infarction at 1-year follow-up. *Heart* 2015;**101**:864–9.
43. Larsen BS, Kumarathurai P, Falkenberg J, Nielsen OW, Sajadieh A. Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident atrial fibrillation. *J Am Coll Cardiol* 2015;**66**:232–41.
44. Roseroa SZ, Kutyifa V, Olshansky B, Zareba W. Ambulatory ECG monitoring in atrial fibrillation management. *Prog Cardiovasc Dis* 2013;**56**:143–52.
45. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, ESC Committee for Practice Guidelines *et al*. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). European Heart Rhythm Association; European Association for Cardio-Thoracic Surgery. *Europace* 2010;**12**:1360–420.
46. January CT, Wann SL, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC. ACC guidelines AF 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Developed in Collaboration with the Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014;**64**:e1–76.
47. Dobreanu D, Svendsen JH, Lewalter T, Hernández-Madrid A, Lip GY, Blomström-Lundqvist C. Scientific Initiatives Committee, European Heart Rhythm Association. Current practice for diagnosis and management of silent atrial fibrillation: results of the European Heart Rhythm Association survey. *Europace* 2013;**15**:135–40.
48. Binici Z, Intzilakis T, Nielsen OW, Køber L, Sajadieh A. Excessive supraventricular ectopic activity and increased risk of atrial fibrillation and stroke. *Circulation* 2010;**121**:1904–11.
49. Dewland TA, Vittinghoff E, Mandyam MC, Heckbert SR, Siscovick DS, Stein PK *et al*. Atrial ectopy as a predictor of incident atrial fibrillation: a cohort study. *Ann Intern Med* 2013;**159**:721–8.
50. Engström G, Hedblad B, Juul-Möller S, Tydén P, Janzon L. Cardiac arrhythmias and stroke increased risk in men with high frequency of atrial ectopic beats. *Stroke* 2000;**31**:2925–9.
51. Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS *et al*. EMBRACE Steering Committee and Investigators. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the EMBRACE trial. *Stroke* 2015;**46**:936–41.
52. Salvatori V, Becatini C, Laureti S, Baglioni G, Germini F, Grilli P *et al*. Holter monitoring to detect silent atrial fibrillation in high-risk subjects. *Intern Emerg Med* 2015;**10**:595–601.
53. Marfella R, Sasso FC, Siniscalchi M, Cirillo M, Paolisso P, Sardu C *et al*. Brief episodes of silent atrial fibrillation predict clinical vascular brain disease in type 2 diabetic patients. *J Am Coll Cardiol* 2013;**62**:525–30.
54. Stamboul K, Zeller M, Fauchier L, Gudjoncik A, Buffet P, Garnier F *et al*. Incidence and prognostic significance of silent atrial fibrillation in acute myocardial infarction. *Int J Cardiol* 2014;**174**:611–7.
55. Turakhia MP, Ullal AJ, Hoang DD, Than CT, Miller JD, Friday KJ *et al*. Feasibility of extended ambulatory electrocardiogram monitoring to identify silent atrial fibrillation in high-risk patients: the Screening Study for Undiagnosed Atrial Fibrillation (STUDY-AF). *Clin Cardiol* 2015;**38**:285–92.
56. Grond M, Jauss M, Hamann G, Stark E, Veltkamp R, Nabavi D *et al*. Improved detection of silent atrial fibrillation using 72-hour Holter ECG in patients with ischemic stroke. a prospective multicenter cohort study. *Stroke* 2013;**44**:3357–64.
57. Choe WC, Passman RS, Brachmann J, Morillo CA, Sanna T, Bernstein RA, for the CRYSTAL AF Investigators *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**:889–93.
58. Dussault C, Toeg H, Nathan M, Wang ZJ, Roux JF, Secemsky E. Electrocardiographic monitoring for detecting atrial fibrillation after ischemic stroke or transient ischemic attack: systematic review and meta-analysis. *Circ Arrhythm Electrophysiol* 2015;**8**:263–9.
59. Dagres N, Kottkamp H, Piorkowski C, Weis S, Arya A, Sommer P *et al*. Influence of the duration of Holter monitoring on the detection of arrhythmia recurrences after catheter ablation of atrial fibrillation: implications for patient follow-up. *Int J Cardiol* 2010;**139**:305–6.
60. Uittenbogaart SB, Verbiest-van Gurp N, Erkens PMG, Lucassen WMA, Knottnerus JA, Winkens B *et al*. Detecting and Diagnosing Atrial Fibrillation (D2AF): study protocol for a cluster randomized controlled trial. *Trials* 2015;**16**:478.
61. Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LÅ, Rosenqvist M. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace* 2013;**15**:5–6.
62. Weber-Kruger M, Gelbrich G, Stahrenberg R, Liman J, Kermer P, Hamann GF *et al*. Find-AF (RANDOMISED) investigators. Finding atrial fibrillation in stroke patients: randomized evaluation of enhanced and prolonged Holter monitoring–Find-AF(RANDOMISED) – rationale and design. *Am Heart J* 2014;**168**:438–45.
63. Sposato LA, Cipriano LE, Saposnik G, Ruíz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol* 2015;**14**:377–87.
64. Tung CE, Su D, Turakhia MP, Lansberg MG. Diagnostic yield of extended cardiac patch monitoring in patients with stroke or TIA. *Front Neurol* 2015;**5**:266.
65. 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**:2935–40.

66. Engdahl J, Andersson L, Mirskaya M, Rosenqvist M. Stepwise screening of atrial fibrillation in a 75-year-old population: implications for stroke prevention. *Circulation* 2013;**127**:930–7.
67. Healey JS, Connolly SJ, Manja V, Liu Y, Simek KD, Quinn R *et al*. Sub-clinical atrial fibrillation in elderly primary care patients without clinical atrial fibrillation. *Circulation* 2015;**132**(Suppl 3):A14972.
68. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, EMBRACE Investigators and Coordinators *et al*. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;**370**:2467–77.
69. Jaboudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischmic attack. *Stroke* 2004;**35**:1647–51.
70. Population Health Institute. Home-based Screening for Early Detection of Atrial Fibrillation in Primary Care Patients Aged 75 Years and Older. (SCREEN-AF) https://clinicaltrials.gov/ct2/show/NCT02392754 (3 June 2016, date last accessed).
71. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Sarkar S, Koehler JL *et al*. Real-world experience with insertable cardiac monitors to find atrial fibrillation in cryptogenic stroke. *Cerebrovasc Dis* 2015;**40**:175–81.
72. Dahal K, Chapagain B, Maharjan R, Farah HW, Nazeer A, Lootens RJ *et al*. Prolonged cardiac monitoring to detect atrial fibrillation after cryptogenic stroke or transient ischemic attack: a meta-analysis of randomized controlled trials. *Ann Noninvasive Electrocardiol* 2016;**21**: 382–8.
73. Afzal MR, Gunda S, Waheed S, Sehar N, Maybrook RJ, Dawn B *et al*. Role of outpatient cardiac rhythm monitoring in cryptogenic stroke: a systematic review and meta-analysis. *Pacing Clin Electrophysiol* 2015;**38**:1236–45.
74. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, Oxford Vascular Study *et al*. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015;**14**:903–13.
75. Bernstein RA, Di Lazzaro V, Rymer MM, Passman RS, Brachmann J, Morillo CA *et al*. Infarct topography and detection of atrial fibrillation in cryptogenic stroke: results from CRYSTAL AF. *Cerebrovasc Dis* 2015;**40**:91–6.
76. Ntaios G, Vemmos K, Lip GY, Koroboki E, Manios E, Vemmou A *et al*. Risk Stratification for recurrence and mortality in embolic stroke of undetermined source. *Stroke* 2016;**47**:2278–85.
77. Ntaios G, Papavasileiou V, Lip GY, Milionis H, Makaritsis K, Vemmou A *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;**pii**:S1052-3057(16)30287-7.
78. Martin RC, Burgin WS, Schabath MB, Kirby B, Chae SH, Fradley MC *et al*. Gender-specific differences for risk disability and death in atrial fibrillation-related stroke. *Am J Cardiol* 2017;**119**:256–61.
79. Glotzer TV, Ziegler PD. Cryptogenic stroke: is silent atrial fibrillation the culprit?. *Heart Rhythm* 2015;**12**:234–41.
80. Dion F, Saudeau D, Bonnaud I, Friocourt P, Bonneau A, Poret P *et al*. Unexpected low prevalence of atrial fibrillation in cryptogenic ischemic stroke: a prospective study. *J Interv Card Electrophysiol* 2010;**28**:101–7.
81. Etgen T, Hochreiter M, Mundel M, Freudenberger T. Insertable cardiac event recorder in detection of atrial fibrillation after cryptogenic stroke: an audit report. *Stroke* 2013;**44**:2007–9.
82. Rojo-Martinez E, Sandín-Fuentes M, Calleja-Sanz AI, Cortijo-García E, García-Bermejo P, Ruiz-Piñero M *et al*. [High performance of an implantable Holter monitor in the detection of concealed paroxysmal atrial fibrillation in patients with cryptogenic stroke and a suspected embolic mechanism]. *Rev Neurol* 2013;**57**:251–7.
83. Cotter PE, Martin PJ, Ring L, Warburton EA, Belham M, Pugh PJ. Incidence of atrial fibrillation detected by implantable loop recorders in unexplained stroke. *Neurology* 2013;**80**:1546–50.
84. Christensen LM, Krieger DW, Højberg S, Pedersen OD, Karlsen FM, Jacobsen MD *et al*. Paroxysmal atrial fibrillation occurs often in cryptogenic ischaemic stroke. Final results from the SURPRISE study. *Eur J Neurol* 2014;**21**:884–9.
85. Hirsh BJ, Copeland-Halperin RS, Halperin JL. Fibrotic atrial cardiomyopathy, atrial fibrillation, and thromboembolism: mechanistic links and clinical inferences. *J Am Coll Cardiol* 2015;**65**:2239–51.
86. Kamel H, Okin PM, Elkind MS, Iadecola C. Atrial Fibrillation and mechanisms of stroke: time for a new model. *Stroke* 2016;**47**:895–900.
87. Roche F, Gaspoz JM, Da Costa A, Isaaz K, Duverney D, Pichot V *et al*. Frequent and prolonged asymptomatic episodes of paroxysmal atrial fibrillation revealed by automatic long-term event recorders in patients with a negative 24-hour Holter. *Pacing Clin Electrophysiol* 2002;**25**:1587–93.
88. Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J *et al*. Feasibility and cost effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost* 2014;**11**:1167–76.
89. Doliwa PS, Rosenqvist M, Frykman V. Paroxysmal atrial fibrillation with silent episodes: intermittent versus continuous monitoring. *Scand Cardiovasc J* 2012;**46**:144–8.
90. Sobocinski PD, Rooth EA, Kull VF, von Arbin M, Wallén H, Rosenqvist M. Improved screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2012;**14**:1112–6.
91. Levin LA, Husberg M, Sobocinski PD, Kull VF, Friberg L, Rosenqvist M *et al*. A cost-effectiveness analysis of screening for silent atrial fibrillation after ischaemic stroke. *Europace* 2015;**17**:207–14.
92. McManus DD, Lee J, Maitas O, Esa N, Pidikiti R, Carlucci A *et al*. A novel application for the detection of an irregular pulse using an iPhone 4S in patients with atrial fibrillation. *Heart Rhythm* 2013;**10**:315–9.
93. Lau JK, Lowres N, Neubeck L, Brieger DB, Sy RW, Galloway CD *et al*. iPhone ECG application for community screening to detect silent atrial fibrillation: a novel technology to prevent stroke. *Int J Cardiol* 2013;**165**:193–4.
94. Zimetbaum P, Waks JW, Ellis ER, Glotzer TV, Passman RS. Role of atrial fibrillation burden in assessing thromboembolic risk. *Circ Arrhythm Electrophysiol* 2014;**7**:1223–9.
95. Passman R, Leong-Sit P, Andrei AC, Huskin A, Tomson TT, Bernstein R *et al*. Targeted anticoagulation for atrial fibrillation guided by continuous rhythm assessment with an insertable cardiac monitor: the Rhythm Evaluation for Anticoagulation with Continuous Monitoring (REACT.COM) Pilot Study. *J Cardiovasc Electrophysiol* 2015;27-264-70.
96. St Jude Medical. Clinical trials. Safety Study on Stopping Anticoagulation Medication in Patients With a History of Atrial Fibrillation (TACTIC AF). https://clinicaltrials.gov/show/NCT01650298 (10 January 2016, date last accessed).
97. Siontis KC, Geske JB, Gersh BJ. Atrial fibrillation pathophysiology and prognosis: insights from cardiovascular imaging. *Circ Cardiovasc Imaging* 2015;**8**:pii: e003020.
98. Bax JJ, Marsan NA, Delgado V. Non-invasive imaging in atrial fibrillation: focus on prognosis and catheter ablation. *Heart* 2015;**101**:94–100.
99. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M *et al*. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging* 2016;**17**:355–83.
100. Beigel R, Wunderlich NC, Ho SY, Arsanjani R, Siegel RJ. The left atrial appendage: anatomy, function, and noninvasive evaluation. *JACC Cardiovasc Imaging* 2014;**7**:1251–65.
101. Gal P, Marrouche NF. Magnetic resonance imaging of atrial fibrosis: redefining atrial fibrillation to a syndrome. *Eur Heart J* 2017;**38**:14–9.
102. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart survey on atrial fibrillation. *Chest* 2010;**137**:263–72.
103. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess one-year risk of major bleeding in atrial fibrillation patients: the Euro Heart survey. *Chest* 2010;**138**:1093–100.
104. Lip GY, Lane DA. Bleeding risk assessment in atrial fibrillation: observations on the use and misuse of bleeding risk scores. *J Thromb Haemost* 2016;**14**:1711–4.
105. Lip GY, Skjoth F, Nielsen PB, Larsen TB. Non-valvular atrial fibrillation patients with none or one additional risk factor of the CHA_2DS_2-VASc score. A comprehensive net clinical benefit analysis for warfarin, aspirin, or no therapy. *Thromb Haemost* 2015;**114**:826–34.
106. Macle L, Cairns J, Leblanc K, Tsnag T, Skanes A, Cox JL *et al*. 2016 focused update of the Canadian Cardiovascular Society Guidelines for the management of atrial fibrillation. Can. *J Cardiol* 2016;**32**:1170–85.
107. Carmo J, Moscoso Costa F, Ferreira J, Mendes M. Dabigatran in real-world atrial fibrillation. Meta-analysis of observational comparison studies with vitamin K antagonists. *Thromb Haemost* 2016;**116**:754–63.
108. Freedman B, Lip GY. "Unreal world" or "real world" data in oral anticoagulant treatment of atrial fibrillation. *Thromb Haemost* 2016;**116**:587–9.
109. Bai Y, Deng H, Shantsila A, Lip GY. Rivaroxaban versus dabigatran or warfarin in real-world studies of stroke prevention in atrial fibrillation: systematic review and meta-analysis. *Stroke* 2017;**48**:970–6.
110. Apostolakis S, Sullivan RM, Olshansky B, Lip GY. Factors affecting quality of anticoagulation control among patients with atrial fibrillation on warfarin: the SAMe-TT(2)R(2) score. *Chest* 2013;**144**:1555–63.
111. Proietti M, Lip GY. Simple decision-making between a vitamin K antagonist and a non-vitamin K antagonist oral anticoagulant: using the SAMe-TT2R2 score. *Eur Heart J Cardiovasc Pharmacother* 2015;**1**:150–2.
112. Esteve-Pastor MA, Roldán V, Valdés M, Lip GY, Marín F. The SAMe-TT2R2 score and decision-making between a vitamin K antagonist or a non-vitamin K antagonist oral anticoagulant in patients with atrial fibrillation. *Expert Rev Cardiovasc Ther* 2016;**14**:177–87.
113. Melgaard L, Gorst-Rasmussen A, Lane DA, Rasmussen LH, Larsen TB, Lip GY. Assessment of the CHA_2DS_2-VASc score in predicting ischemic stroke,

thromboembolism, and death in patients with heart failure with and without atrial fibrillation. *JAMA* 2015;**314**:1030–8.
114. Guo Y, Wang H, Tian Y, Wang Y, Lip GY. Multiple risk factors and ischaemic stroke in the elderly Asian population with and without atrial fibrillation. An analysis of 425,600 Chinese individuals without prior stroke. *Thromb Haemost* 2015;**115**:184–92.
115. Van Gelder IC, Healey JS, Crijns HJCM, Wang J, Hohnloser SH, Gold MR *et al*. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. *Eur Heart J* 2017. doi:10.1093/eurheartj/ehx042.
116. Kamel H, Hegde M, Johnson DR, Gage BF, Johnston SC. Cost-effectiveness of outpatient cardiac monitoring to detect atrial fibrillation after ischemic stroke. *Stroke* 2010;**41**:1514–20.
117. Diamantopoulos A, Sawyer LM, Lip GY, Witte KK, Reynolds MR, Fauchier L *et al*. Cost-effectiveness of an insertable cardiac monitor to detect atrial fibrillation in patients with cryptogenic stroke. *Int J Stroke* 2016;**11**:302–12.
118. Bayer. Rivaroxaban versus aspirin in secondary prevention of stroke and prevention of systemic embolism in patients with recent embolic stroke of undetermined source (ESUS) (NAVIGATE ESUS). ClinicalTrials.gov, NLM Identifier: NCT02313909. https://clinicaltrials.gov/ct2/show/NCT02313909 (19 November 2015, date last accessed).
119. Boehringer Ingelheim. Dabigatran Etexilate for secondary stroke prevention in patients with embolic stroke of undetermined source (RE-SPECT ESUS). ClinicalTrials.gov., NLM Identifier: NCT02239120. https://clinicaltrials.gov/ct2/show/NCT02239120 (19 November 2015, date last accessed).