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INVITED REVIEW
Arrhythmia and electrophysiology

Yield of diagnosis and risk of stroke with screening strategies for atrial fibrillation: a comprehensive review of current evidence

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Atrial fibrillation (AF) is the most prevalent arrhythmia worldwide. The presence of AF is associated with increased risk of systemic thromboembolism, but with the uptake of oral anticoagulant (OAC) and implementation of a holistic and integrated care management, this risk is substantially reduced. The diagnosis of AF requires a 30-s-long electrocardiographic (ECG) trace, irrespective of the presence of symptoms, which may represent the main indication for an ECG tracing. However, almost half patients are asymptomatic at the time of incidental AF diagnosis, with similar risk of stroke of those with clinical AF. This has led to a crucial role of screening for AF, to increase the diagnosis of population at risk of clinical events. The aim of this review is to give a comprehensive overview about the epidemiology of asymptomatic AF, the different screening technologies, the yield of diagnosis in asymptomatic population, and the benefit derived from screening in terms of reduction of clinical adverse events, such as stroke, cardiovascular, and all-cause death. We aim to underline the importance of implementing AF screening programmes and reporting about the debate between scientific societies' clinical guidelines recommendations and the concerns expressed by the regulatory authorities, which still do not recommend population-wide screening. This review summarizes data on the ongoing trials specifically designed to investigate the benefit of screening in terms of risk of adverse events which will further elucidate the importance of screening in reducing risk of outcomes and influence and inform clinical practice in the next future.

Keywords Atrial fibrillation • Screening strategies • Review • Stroke

Introduction

Atrial fibrillation (AF) is one of the most prevalent cardiovascular conditions, being present in more than 59 million people worldwide.[1] The presence of AF is associated with an increased risk of thromboembolic and clinical events, which has been mitigated by the broad use of oral anticoagulant (OAC), and by the implementation of holistic integrated care management.[2–4] Patients with AF may suffer of AF-related symptoms, including palpitations, chest pain, shortness of breath, and fatigue, and in these occasions, AF diagnosis could be documented through a

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30-second electrocardiography (ECG) tracing.[2] However, the diagnosis of clinical AF does not necessarily requires a symptomatic presentation; indeed, according to the 2020 European Society of Cardiology (ESC) guidelines for the management of AF, clinical AF is defined by ECG documentation (12-lead ECG recording or a single-lead ECG tracing of ≥30 seconds) irrespective of the presence of specific symptoms.[2]

Diagnosis of AF is crucial to implement strategies to reduce thromboembolic risk, particularly treatment with OAC. Many patients have no symptoms, and unrecognized AF becomes overt only when complications occur. The true proportion of patients with asymptomatic AF (AAF) is unknown; a meta-analysis including 81 462 patients provided a pooled estimate of 26%,[5] even though other studies reported higher prevalence, up to 45%.[6] The rationale for implementing screening for AF is based on data revealing that patients with AAF have similar risk of stroke compared to that of patients with clinical AF[7] and that at least half of AAF patients might be eligible for anticoagulation.[8]

Current AF guidelines recommend opportunistic screening for AF;[2] however, recently, several studies have focused on the potential role of the active screening. Indeed, the *eHealth-based Bavarian Alternative Detection of Atrial Fibrillation* (eBRAVE-AF) trial[9] showed a two-fold increase in the detection of AF requiring OAC, by using a smart device compared to usual screening.

The aim of this review is to provide a comprehensive summary of the evidence regarding epidemiology of AAF, impact of screening on its detection, the techniques and methods used to perform such screening, the association with risk of stroke and other adverse outcomes, and impact of OAC prescription according to AAF detection.

Epidemiology of asymptomatic atrial fibrillation and risk of outcomes

The analysis of the actual burden of AAF is challenging, and its prevalence may be largely underestimated. AAF is often diagnosed in specific clinical settings, including pre-surgical assessment, screening programmes, workup of cryptogenic strokes, and implantable devices interrogations.[10–14] Previous studies reported a prevalence of AAF ranging from 10% to 40% depending on several factors (e.g. study design, population studied, patient's risk profile, geographical differences, etc.).

The pathophysiological mechanisms underlying the different clinical manifestations in AF patients (i.e. asymptomatic vs. symptomatic) are not yet completely understood. A higher prevalence of AAF has been reported among males and elderly and in patients with a high burden of comorbidities. However, short AF episodes may also be detected in patients who have a relatively low burden of comorbidity and are in the early phase of the disease.[15]

The development of AF-related symptoms is largely due to haemodynamic impairment and fast, irregular ventricular response. However, other factors—such as younger age, female sex, and hypertension—may be associated with the development of symptoms in AF patients, as suggested by the *Canadian Registry of Atrial Fibrillation* (CARAF) study.[16] More recently, contemporary AF registries confirmed that almost one-third of AF patients are asymptomatic or present mild symptoms. In the *Prevention of Thromboembolic Events—European Registry in Atrial Fibrillation* (PREFER in AF) study, 8.1% of patients were classified as asymptomatic (EHRA I), and 37.9% were classified as having mild symptoms (EHRA II). Of note, the study found that there was a significantly lower proportion of females in the asymptomatic group (22.8% vs. 41.2%) compared to symptomatic patients.[17] In the *EURObservational Research Programme-Atrial Fibrillation* (EORP-AF) General Pilot Registry, approximately 40% of the AF cases enrolled were asymptomatic (EHRA I).[18] Male sex, older age, previous myocardial infarction, and limited physical activity were significantly associated with AAF; interestingly, permanent AF was three-fold more common among asymptomatic patients.[18] Similarly, the *Global Anticoagulant Registry in the Field-Atrial Fibrillation* (GARFIELD-AF) recently confirmed these findings, reporting that at presentation, 25.4% of patients were asymptomatic, with a higher prevalence of AAF among elderly and males.[7]

From a clinical perspective, it is crucial to determine if AAF patients have lower rates of adverse outcomes compared to symptomatic AF patients. A recent systematic review and meta-analysis,[5] including more than 80 000 patients, found that patients with AAF and symptomatic AF had the same thromboembolic risk and there were no differences in the risk of stroke and other major outcomes. Hence, the thromboembolic risk prevention should not be limited to symptomatic clinical AF.[7,19,20] In a recent paper published by Wallenhorst and colleagues, reporting data about more than 22 000 with incident AF, matched to non-AF controls, ambulatory AAF patients had similar risk of stroke than ambulatory patients with symptomatic AF as well as hospitalized AF patients, both having AF as primary and secondary diagnosis.[21] Conversely, risk of all-cause death was significantly higher in hospitalized patients, particularly those having AF as a secondary diagnosis, while it was similar between ambulatory symptomatic and asymptomatic ones.[21] Considering the high prevalence of AAF, underdiagnosis and undertreatment of these patients may expose them to a higher risk of adverse cardiovascular events. Therefore, it appears clear how the role of screening is increasingly important to identify AAF patients, especially in high-risk populations.[22]

Appropriate early management of AAF patients has yet to be fully investigated and particularly in terms of rhythm or rate control management. The ongoing *Comparison Study of Drugs for Symptom Control and Complication Prevention of Atrial Fibrillation* (CODE-AF) prospective registry interestingly found that rhythm control was associated with a significant reduction in adverse cardiovascular events in AAF patients; these findings were confirmed also in patients with high thromboembolic risk (CHA_2DS_2-VASc score ≥3).[23] Recently, an *Early Treatment of Atrial Fibrillation for Stroke Prevention Trial* (EAST-AFNET 4) subanalysis[24] evaluated the effect of early rhythm control therapy in asymptomatic patients (EHRA I) compared to symptomatic patients. The results showed that the clinical benefit of early systematic rhythm control was similar between asymptomatic and symptomatic patients, suggesting that a rhythm control strategy may be beneficial also in AAF patients.

Strategies for atrial fibrillation screening

The need for an earlier AF detection and implementation of an integrated care management approach raises the urgency regarding the use of mobile health (mHealth) devices in cardiology that could facilitate detection and management of AF.[25–27] Traditional classification of mHealth devices identifies three groups, based on different technologies, namely, devices using photoplethysmography (PPG), pulse variability (PV), or ECG traces, based on mechanocardiography (MCG). All these mHealth solutions are also supported by systems which allow healthcare professionals' referral. However, the overall accuracy varies widely,[28,29] depending on the technology, the type of the devices (handheld vs. wearable), the study population (hospitalized vs. general population), and the AF detection monitoring method (intermittent vs. continuous monitoring).[30,31]

PPG devices implement an optical method, which identifies variations in peak-to-peak intervals and the pulse morphology of the illuminated microvascular blood to detect AF. Handled PPG-based devices like FibriCheck,[32] CardioRhythm,[33] and Preventicus[9,34] typically use

the smartphone camera flashlight as light source, with variable duration, and the accuracy of detecting AF is unaffected by the length of the recording.[29] The most promising mHealth devices are PPG-based wearable technology[35] which includes smartwatches (such as the Huawei Watch GT, Apple Watch, or Amazfit Health Band), wristbands (e.g. Samsung Simband, Fitbit devices), armbands, finger-bands, and earlobe sensor devices. To date, the sensitivity (Sn) and specificity (Sp) of validated wearable PPG devices vary from 67.7% to 100% and 60.7% to 100%, respectively.[36]

Those variations are the result of various reference tests and monitoring durations (*Table 1*).

The PV technology uses the variance of heartbeats detected by the arm cuff during at least three blood pressure measurements. Microlife BP and OMRON are the most extensively investigated sphygmomanometers and should be considered as a first-step AF screening strategy for hypertensive patients managed in dedicated clinics.[42]

The ECG-based devices may transmit and monitor an ECG trace, allowing a direct AF diagnosis.[2] Depending on the devices, they can record a single, 3-, 6-, or even 12-lead ECG trace for of at least 30 seconds. The most well known ECG-based handheld devices are MyDiagnostick and KardiaMobile, with similar Sn/Sp.[36]

The wearable ECG-based devices can be chest belts (e.g. Polar-H7, Zio XT) with short electrodes like the Rhythm Pad and smartwatches, with all similar accuracy.[36] The MCG-based devices, consisting of the accelerometers and gyroscopes placed in smartphones, have lesser evidence in screening scenarios (Sn 67%; Sp 99%).[59]

Combinations of various technologies appear the most useful in AF detection. Photoplethysmography signals appear to be more useful in general setting, due to the frequent coupling with smartphones and the consequent ubiquitous presence, and the ECG could be more effective in specific settings (e.g. post-stroke patients) thanks to their diagnostic accuracy. The Apple Heart Study[38] and the Fitbit Heart Study[41] utilized both PPG and ECG technologies; similarly, the eBRAVE-AF study,[9] comparing conventional and digital AF screening, showed that the most effective AF screening strategy was the digital one utilizing a combination of smartphone-based PPG signals validated by an external ECG loop recorder. Lastly, the most proficient systems to integrate AF screening with AF treatment and follow-up seem to be the mHealth tools that arrange an effective interaction between medical professionals and patients, making smoother and complete the chain of screening AF, as clearly shown in the Mobile Atrial Fibrillation Apps (mAFA) II trial.[26,60,61]

In summary, various mHealth tools are used in AF screening, and these are broadly regarded as reliable, thus being useful in the early detection of AF; moreover, the variety of tools available makes it easier to tailor the AF screening strategies even in populations difficult to reach. In any case, a standard ECG tracing recording AF $\geq$30 seconds is needed to make diagnosis.[2] In an EHRA consensus paper, the authors underlined how a significant gap in evidence exists regarding very short (<30 seconds) tachyarrhythmia episodes resembling AF, hence not fulfilling diagnostic criteria.[62] There is not a specified strategy for such situations, but we can consider that keeping monitoring could be reasonable to identify more structured arrhythmias.

Screening yield and risk for stroke and adverse outcomes

The increasing interest on AAF and the technological progresses described above, despite variable accuracy,[63] led to a significant development in the field of AF screening. Several studies explored so far the yield of new diagnosis of AF throughout screening programmes.

Table 2 summarizes the studies which explored screening AF strategies in asymptomatic population. In the eBRAVE-AF trial,[9] the screening yield was found to be two- to three-fold gain in detection rate of AF requiring OAC compared to conventional screening. Other studies reported the screening yield of AF: in the Belgian Heart Rhythm Week programme,[73] participants were screened for AF with single-lead ECG. The study showed that the AF prevalence was higher in males and in those aged $\geq$65. The most important aspect is that more than two-thirds of patients with AF had a CHA_2DS_2-VASc score $\geq$2, being eligible for OAC. A patient-level meta-analysis[74] confirmed that people with screen-detected AF have a high risk of stroke as they were above age 65 and more than two-thirds have an additional stroke risk factor other than age/sex. Moreover, it was found that the number needed to screen to identify one new treatable AF was inversely associated to increasing age. Conversely, the percentage of OAC prescription increased with age. Atrial fibrillation screening yield may also depend on risk stratification of screened populations. The STROKESTOP II study[72] used a 125 ng/L cut-off of N-terminal B-type natriuretic peptide for 75- to 76-year-old patients, to identify high-risk patients that were offered to prolong the screening and were found to have a higher rate of detected AF; in the lower-risk group, consistently, the study found a lower rate of detected AF. Nonetheless, two cluster randomized trials with single timepoint screening in patients $\geq$65 years failed to demonstrate a higher rate of AF detection. The VITAL-AF[71] study did not find differences between systematic screening and usual care arms in primary care patients; however, older age ($\geq$85 years old) was found at higher incidence of new AF. Moreover, general characteristics of the patients included showed a very high risk of AF, and the rate of AF diagnosis was significantly higher in the control arm, compared to previous studies.[71] Also, in the *Detecting and Diagnosing Atrial Fibrillation* (D2AF)[67] study, which tested an opportunistic screening approach in the context of primary care patients, no difference was found between the two arms of the study, even though in this case, the results were strongly affected by a low uptake of patients to the screening programme (~45% of the total assigned to screening). All these results underline how the identification of the targeted population performing the screening campaign and its success are essential to obtain a significant yield of screening.

So far, the research in this field showed that the AF screening is effective in detecting AF; however, assuming that patients with detected AF and moderate-high risk of stroke would be prescribed with OAC, whether the AF screening is also effective in reducing the risk of adverse events at follow-up remains unclear. Recently, several studies investigated the screening methods for AF and analysed the adverse outcomes at follow-up. The *Remote Heart Rhythm Sampling Using the AliveCor Heart Monitor to Screen for Atrial Fibrillation* (REHEARSE-AF)[66] study was one of the first to explore adverse outcomes. In 2017, this study randomized over 65-year-old patients with CHA_2DS_2-VASc $\geq$2 and no OAC prescription, to single-lead handheld ECG screening with the AliveCor Kardia monitor twice a week or standard care. The results showed a four-fold increase in AF detection in the active arm; however, there was no difference in the reduction of clinical events in the two groups at 1 year. The study had several limitations, including the relatively short length of follow-up, and the low rate of clinical events. In the LOOP Study,[69] patients $\geq$70-year-old were randomized to receive implantable loop recorder (ILR) monitoring or usual care; despite the introduction of OAC in those eligible, there was no significant difference in the risk of primary outcome of stroke/systemic embolism between the two groups. Afterwards, the STROKESTOP[64,65] study showed a lower risk of the primary composite outcome of stroke (ischaemic/haemorrhagic), systemic embolism, hospitalization for bleeding, and all-cause death in patients actively screened for AF compared to those allocated to usual care, even though survival curves start to diverge only after 4 years of follow-up {with a hazard ratio [HR] of 0.96 [95% confidence interval (CI) 0.92–1.00]}. Notwithstanding, the 'as-

Table 1 Studies investigating atrial fibrillation screening strategies

Study	Design	*N*	F (%)	Age[a]	Main characteristics	Country	Devices	Monitoring time	% AF	Sn (%)	Sp (%)	Reference test
PPG-handheld												
Yan *et al.*[33]	PSA	217	28.6	70.3	Hospitalized	China	CardioRhythm/ smartphone camera	20 s × 3 s.t.	34.6	95	96	12-l-ECG
Verbrugge *et al.*[32]	PSA	12 328	42	49	General	Belgium	FibriCheck/smartphone camera	7 d	0.01	—	—	—
Brasier *et al.*[34]	PSA	592	45.3	78	Hospitalized	Germany/Switzerland	Preventicus/smartphone camera	5 m s.t.	41.9	91.5	99.6	s-l-ECG
Rizas *et al.*[9]	RCT	5551	31	n.a.	>65 y.o.	Germany	Preventicus/smartphone camera	6 m	1.33	89.9	99.1	12-l-ECG Holter
PPG-wearable												
Guo *et al.*[26]	PSA	187 912	13.3	34.7	Amb.	China	HonorBand, Huawei Watch GT/wristband and wristwatch	60 s every 10 m for 14 d	87	n.a.	n.a.	12-l-ECG; 24-h-Holter
Zhang *et al.*[37]	PSA	361	49.3	50	Amb.	China	HonorBand, Huawei Watch GT/wristband and wristwatch	60–45 s every 10 m for 14 d	8.6	100	100	12-l-ECG
Perez *et al.*[38]	mPSA	419 297	42	41	General	USA	Apple Watch/ wristwatch (PPG)	117 d	0.52	—	—	—
Chen *et al.*[39]	PR	401	49.1	n.a.	Hosp./Amb.	China	Amazfit/Wristband	3 m	37	88	96.4	12-l-ECG
Nemati *et al.*[40]	RSA	46	n.a.	n.a.	Hospitalized	USA	Samsung Simband/ wristwatch	3.5–8.5 m	33	97	94	s-l-ECG
Lubitz *et al.*[41]	PSA	1057	n.a	n.a	≥22 y.o.	USA	Fitbit	122 d	32.2	67.6	98.4	ECG patch monitor
PV-based												
Marazzi *et al.*[42]	PSA	503	45.7	67	Hypertension	Italy	Microlife (1) and Omron (2)/ sphygmomanometer	3 s.t.	20	(1) 92 (2) 100	(1) 97 (2) 94	12-l-ECG
ECG-handheld												
Boriani *et al.*[22]	PSA	2814	55.5	66	General	Italy	MyDiagnostick/stick	1 m s.t.	2.0	98.2	23.6	12-l-ECG
Battipaglia *et al.*[43]	PSA	855	n.a.	n.a.	General	UK	MyDiagnostik/stick	15 s s.t.	0.8	100	100	e.d.
Desteghe *et al.*[44]	PTA	445	58.9	72.2	Hospitalized	Belgium	MyDiagnostick/stick	1 m s.t.	11.9–36	60.5–81.8	93.3–96.1	12-l-ECG
Kaasenbrood *et al.*[45]	PSA	3269	51	69.4	General	Netherlands	MyDiagnostick/stick	1 m s.t.	3.7	96	100	e.d.
Rivezzi *et al.*[46]	PSA	1820	53.4	≥65 yo	≥65 yo	Italy	MyDiagnostick/stick	1 m s.t.	5.5	94	100	12-l-ECG
Tavernier *et al.*[47]	PSA	214	61.7	84	Hospitalized	Belgium	MyDiagnostick/stick	1 m s.t.	33	88	97	12-l-ECG
Chan *et al.*[48]	PSA	1013	53.2	68.4	≥65 yo	China	KardiaMobile/plate	30 s s.t.	2.8	71.4	99.4	e.d.
Chan *et al.*[49]	PSA	2052	54.2	67.8	≥65 yo	China	KardiaMobile/plate	30 s s.t.	1.2	66.7	99.5	12-l-ECG
Chan *et al.*[50]	PTA	13 122	71.5	64.7	General	China	KardiaMobile/plate	30 s s.t.	1.8	98	29.2	e.d.
Desteghe *et al.*[44]	PTA	445	58.9	72.2	Hospitalized	Belgium	KardiaMobile/plate	30 s s.t.	11.9–36	36.8–72.7	96.1–98.1	12-l-ECG
Orchard *et al.*[51]	RCT	3103	36	75.1	≥65 yo	Australia	KardiaMobile/plate	30 s s.t.	1.2	97	92	12-l-ECG
Lowres *et al.*[52]	PSA	1000	56	76	≥65 yo	Australia	KardiaMobile/plate	30–60 s s.t.	6.7	98.5	91.4	12-l-ECG
Soni *et al.*[53]	PSA	2074	52.2	33.7% ≥66 yo	General	India	KardiaMobile/plate	30 s 2–3 t./5 d	1.6	38	n.a.	e.d.
Zaprutko *et al.*[54]	PSA	525	68.2	73.7	≥65 yo	Poland	KardiaMobile/plate	30 s s.t.	2.3	100	98.7	e.d.
ECG-wearable												
Lown *et al.*[55]	mPSA	418	n.a.	n.a.	≥65 yo	UK	Polar-H7/chest belt	45 s	19.6	96.3	98.2	12-l-ECG
Sabar *et al.*[56]	PSA	750	51	n.a.	High AF risk	UK	Rhythm Pad/patch	10 s	10	95.4	98.8	12-l-ECG
Lin *et al.*[57]	PSA	30	n.a.	n.a.	Hospitalized	China	Medi-Trace 200/wireless record	6 m	67	94.6	n.a.	12-l-ECG
Steinhubl *et al.*[58]	PR	2659	38.6	72.4	High AF risk	USA	Zio XT/patch	4 m	3.9	n.a.	n.a.	e.d.
Rizas *et al.*[9]	RCT	5551	31	n.a.	>65 yo	Germany	CardioMem/ECG loop	6 m	1.33	91	n.a.	12-l-ECG Holter
MCG-based												
Jaakkola *et al.*[59]	CC	300	44	74.8	General	Finland	MCG tech.	3 m s.t.	n.a.	95.3	96	Tele-ECG

[a]Mean age reported except where specified; AF, atrial fibrillation; Amb, ambulatory; CC, case-control; d, days; ECG, electrocardiography; ECV, electrical cardioversion; e.d., expert diagnosis; f, female; m, minutes; mPSA, multileft prospective single arm; n.a., not available; Mon., monitoring; PPG, photoplethysmography; PSA, prospective single arm; PR, prospective randomized; PTA, prospective two arms; pts, patients; PV, pulse variability; Ref. reference; RFs, risk factors; RSA, retrospective single arm; s, seconds; s-l-ECG, single-lead ECG; Sn, sensitivity; Sp, specificity; s.t., single time; tech, technology; y.o., years old; 12-l-ECG, 12 leads ECG.; MCG, mechanocardiography.

Table 2 Studies about atrial fibrillation screening strategies and risk of adverse outcomes

Study	Year	ToS	Location	Screened population	*n*	Modality	Screening period	Screening Yield—AF detection	Summary screening yield	FU	Outcomes	Results	Summary outcomes
STROKESTOP[64,65]	2015, 2021	RCT	Sweden	75–76	Screened ($n = 7173$) (For follow-up $n = 13\,979$)	12-ECG + handheld ECG for 2 weeks	14 days	3.0%	Intermittent ECGs increased new AF detection four-fold	5 years	Combined endpoint of ischaemic or haemorrhagic stroke, SE, hospitalization for bleeding, or death from any cause	HR: 0.96, 95% CI 0.92–1.00, $P = 0.045$	Subjects randomized to screening had a lower risk of the composite endpoint throughout the follow-up observation
					Control ($n = 14\,381$) (For Follow-up $n = 13\,996$)	Usual care	14 days	—					
REHEARSE-AF[66]	2017	RCT	The UK	>65 with CHA_2DS_2-VASc > 2 with no AF and no OAC or pacing	Screening ($n = 501$)	30 s single-lead handheld ECG twice weekly	1 year	3.7%	Almost four-fold increase in the diagnosis of AF in the screened population (HR 3.9, 95% CI 1.4–10.4, $P = 0.007$)	1 year	Stroke/TIA/SE	HR: 0.61 (95% CI 0.22–1.69; $P = 0.34$	No significant difference was found between the two groups
					No screening ($n = 500$)	—	—	1.0%					
D2AF[67]	2020	Cluster RCT	The Netherlands	≥65 with no AF in primary care	Screening ($n = 8874$)	Single-lead handheld ECG in primary care	1 y	1.62%	Opportunistic screening for atrial fibrillation in primary care patients did not increase the detection rate of AF			No FU	
					Usual care ($n = 9102$)	Usual care	1 year	1.53%					
mSToPS[58,68]	2018, 2021	NRCT	The USA	≥75 or males ≥55/females ≥65 with one risk factor/comorbidity	Immediate Screening ($n = 1366$)	Single-lead patch monitor for up to 14 days (screened period)	1 year	6.7 per 100 person-years	Volunteer monitored individuals, compared with nonmonitored matched controls, had higher rates of AF diagnosis	3 years	Combined endpoint of ischaemic stroke, systemic embolism, myocardial infarction all-cause death	8.4 vs. 13.8 per 100 person-years HR: 0.53, 95% CI: 0.40–0.78, $P < 0.01$	Subjects assigned to screening have a lower risk of the combined endpoint
					Delayed screening ($n = 1293$)	Single-lead patch monitor for up to 14 days (unscreened period)	1 year						
					Unmonitored ($n = 3476$)	—	1 y	2.6 per 100 person-years					
LOOP Study[69]	2021	RCT	Denmark	70–90 without AF, with at least one additional stroke risk factor	Screened ($n = 1501$)	ILR monitoring	4 years	8.04 per 100 person-years	Three times increase in detection of atrial fibrillation and concomitant anticoagulation in the screened population (HR: 3,17 (95% CI 2,81–3,59, $P < 0.00001$)	6 years	Stroke or systemic arterial embolism	0.88 vs. 1.09 events per 100 person-years HR: 0.80 (95% CI 0.61–1.05]; $P = 0.11$	No significant decrease in the risk of stroke or systemic arterial embolism
					Control ($n = 4503$)		4 years	2.48 per 100 person-years					
SCREEN-AF[70]	2021	RCT	Canada/Germany	≥75 without know AF	Screened ($n = 434$)	2-week ambulatory cECG patch monitor + automated home BP monitor with an	6 months	5.3%	10-fold increase of the AF detection in the screened population			No FU	

Continued

Table 2 *Continued*

Study	Year	ToS	Location	Screened population	*n*	Modality	Screening period	Screening Yield—AF detection	Summary screening yield	FU	Outcomes	Results	Summary outcomes
						AF screening algorithm to be used twice daily during monitoring periods							
standard care			6 months	0.5%	Control ($n = 422$)								
VITAL-AF[71]	2022	Cluster RCT	The USA	General Population without AF	Screened ($n = 15$ 393)	Handheld single-lead ECG	1 year	1.72%	Screening for AF using a single-lead ECG at primary care visits did not affect new AF diagnoses among all individuals aged 65 years or older compared with usual care			No FU	
					Control ($n = 15$ 322)	Usual care	1 year	1.59%					
eBRAVE-AF[9]	2022	RCT	Germany	50–90 with a CHA2DS2-VASc score of ≥1 (men) or ≥2 (women), not known to have paroxysmal or persistent AF and not treated with OAC	Screened ($n = 2860$)	Digital screening	6 months	1.33%	Digital screening increases the detection rate of AF requiring OAC compared to routine symptom-based screening (OR 2.12, 95% CI, 1.19–3.76; $P = 0.010$) and AF Detection (OR 1.90, 95% CI 1.16–3.11, $P = 0.011$)	1 year	Stroke; Thromboembolic events; Major bleeding Death	Stroke: OR 1.03 (95% CI 0.45–2.33, $P = 0.950$ Thromboembolic events: OR 2.07 (95% CI 0.72–5.98, $P = 0.177$) Major bleeding: OR 1.01 (95% CI 0.49–2.09, $P = 983$) Death: OR 1.88 (95% CI 0.47–7.54, $P = 0.371$)	No statistical risk decrease for any of the secondary outcomes between the two groups
					Control ($n = 2691$)	Routine symptom-based screening	6 months	0.63%					
STROKESTOP II[72]	2020	RCT	Sweden	75–76	Screened with NT-proBNP ≥ 125 ($n = 3766$)	Handheld ECG monitoring intermittent for 2 weeks	14 days	4.4%	The screening procedure resulted in an absolute increase in AF prevalence from 8.1% to 10.5% among participants. All new AF diagnosed in the screening group were 2.6%, (95% CI 2.2–3.0%)			See *Table 3*.	
					Screened with NTproBNP < 125 ($n = 3766$)	Handheld ECG monitoring	One-time	0.04%					
					Control ($n = 14$ 356)	Usual care (for follow-up)	—	—					

Legend: AF, atrial fibrillation; CI, confidence interval; ECG, electrocardiogram; FU, follow-up; HR, hazard ratio; ILR, implanted loop recorded; OAC, oral anticoagulant; OR, odds ratio; NT-proBNP, *N*-terminal pro-B-terminal natriuretic peptide; NRCT, non-randomized clinical trial; RCT, randomized clinical trial; ToS, type of study.

treated' analysis, comparing subjects who actually participated to the screening programme to those randomized to control group, excluding those randomized but which never showed up ($n = 6814$, 48.7% of those invited), found that undergoing the screening programme was associated with a consistent reduction in the risk of the composite outcome (HR 0.76, 95% CI 0.67–0.85), which emerged since the very beginning of follow-up observation. Furthermore, the mSToPS,[58,68] using a patch system for AF screening, showed a prominent risk reduction of composite of death, stroke, systemic embolism, and myocardial infarction; however, this analysis was a post-hoc non-randomized comparison, with significant limitation of comparability between the propensity-matched controls and volunteer study group. Also, even in the control arm, after the initial phase of the study, screening patch was offered in the case they volunteered. These aspects need to be taken in mind when considering the follow-up phase results. Recently, a systematic review and meta-analysis collecting data about 35 386 subjects coming from 5 different screening studies showed that screening strategies were associated to a reduction in the risk of stroke (relative risk 0.91, 95% CI 0.84–0.99). Notwithstanding, the sequential trial analysis underlined how the number of patients needed to prove the benefit of screening in reducing the risk of thromboembolic events would slightly exceed the 100 000 subjects, in the light of the very low incidence of adverse events, underlining the need for new studies.[75]

The pre-mAFA trial[26] implemented an mHealth technology both for the AF screening and then for the management of general population-based patients with AF.[27] In this trial, at least 14-day monitoring with wristband has been proposed for a high-risk population (CHA_2DS_2-VASc ≥ 2). Subsequently, screened AF patients were cluster randomized to receive the structured care pathway (mAFA intervention) or the usual care in the mAFA II trial.[27] This study showed a significant reduction of the primary composite outcome of stroke, thromboembolism, death and rehospitalization. However, mAFA II trial also includes inpatients and outpatients with symptomatic AF and those results cannot be translated to all the AAF.

Currently, four randomized trials are ongoing to further examine the effectiveness of screening strategies in reducing stroke occurrence. All these studies (*Table 3*) were specifically designed and powered to investigate the risk of stroke and other adverse outcomes. Indeed, *Screening for Atrial Fibrillation with ECG to Reduce stroke* (SAFER) trial,[76] the five years follow-up of STROKESTOP II,[77] the *ReducinG stroke by screening for UndiAgnosed atRial fibrillation in elderly inDividuals* (GUARD-AF) (NCT04126486), and the HEARTLINE (NCT04276441) will generate data on more than 200 thousand patients, likely providing definitive evidence regarding the implementation of screening strategies to reduce the occurrence of stroke and other adverse outcomes in AAF subjects. Furthermore, the European Union's Horizon 2020 programme recently funded a project, the *Digital, Risk-Based Screening for Atrial Fibrillation in the European Community* (AFFECT-EU, http://affect-eu.eu), which aims to develop a specific algorithm to implement a risk-based screening approach, identifying those populations at higher risk of AF in which develop specific screening programmes, and also includes a progressive patient-level data meta-analysis of all randomized studies.[78]

Current guideline recommendations

The screening for AF aims at early arrhythmia detection, possibly leading to a better prevention of thromboembolic events. Despite the increasing interest in this field promoted by new AF screening tools/devices, not all international guidelines recommend AF screening. Indeed, recommendations in each guideline can be conditioned by

Table 3 Ongoing randomized studies about atrial fibrillation screening strategies and risk of adverse outcomes

Ongoing studies						
Study	**Year**	**Study design**	***N***	**Follow-up**	**Outcomes**	**Trial registration**
SAFER[76]	2017	≥70-year-old subjects from a primary care unit network randomized to receive screening through a single-lead handheld ECG four times daily for 3 weeks; the study comprises two feasibility phases and one large interventional trial	126 000	5 years	Ischaemic and haemorrhagic stroke	ISRCTN: ISRCTN72104369
GUARD-AF	2019	≥70-year-old subjects from a primary care unit network randomized to receive screening through an ECG skin patch with no AF and no OAC	52 000	2 years	Stroke leading to hospitalization and bleeding leading to hospitalization	ClinicalTrials.gov: NCT04126486
HEARTLINE	2020	≥65-year-old subjects randomized to receive screening through a smart watch device and a healthy heart engagement program	150 000	3 years	Composite of cerebrovascular events and all-cause death	ClinicalTrials.gov: NCT04276441
STROKESTOP II	2017	75–76-year-old Stockholm region inhabitants, randomized to receive screening procedure or usual care; subjects randomized to screening were assigned to handheld ECG monitoring either intermittent for 2 weeks or one-stop screening according to NT-proBNP levels	6868	5 years	Primary outcome: stroke or systemic embolism; secondary outcome: bleeding stroke, systemic embolism, or all-cause death	ClinicalTrials.gov: NCT02743416

ECG, electrocardiography; OAC, oral anticoagulant; NT-proBNP, *N*-terminal pro-B-terminal natriuretic peptide.

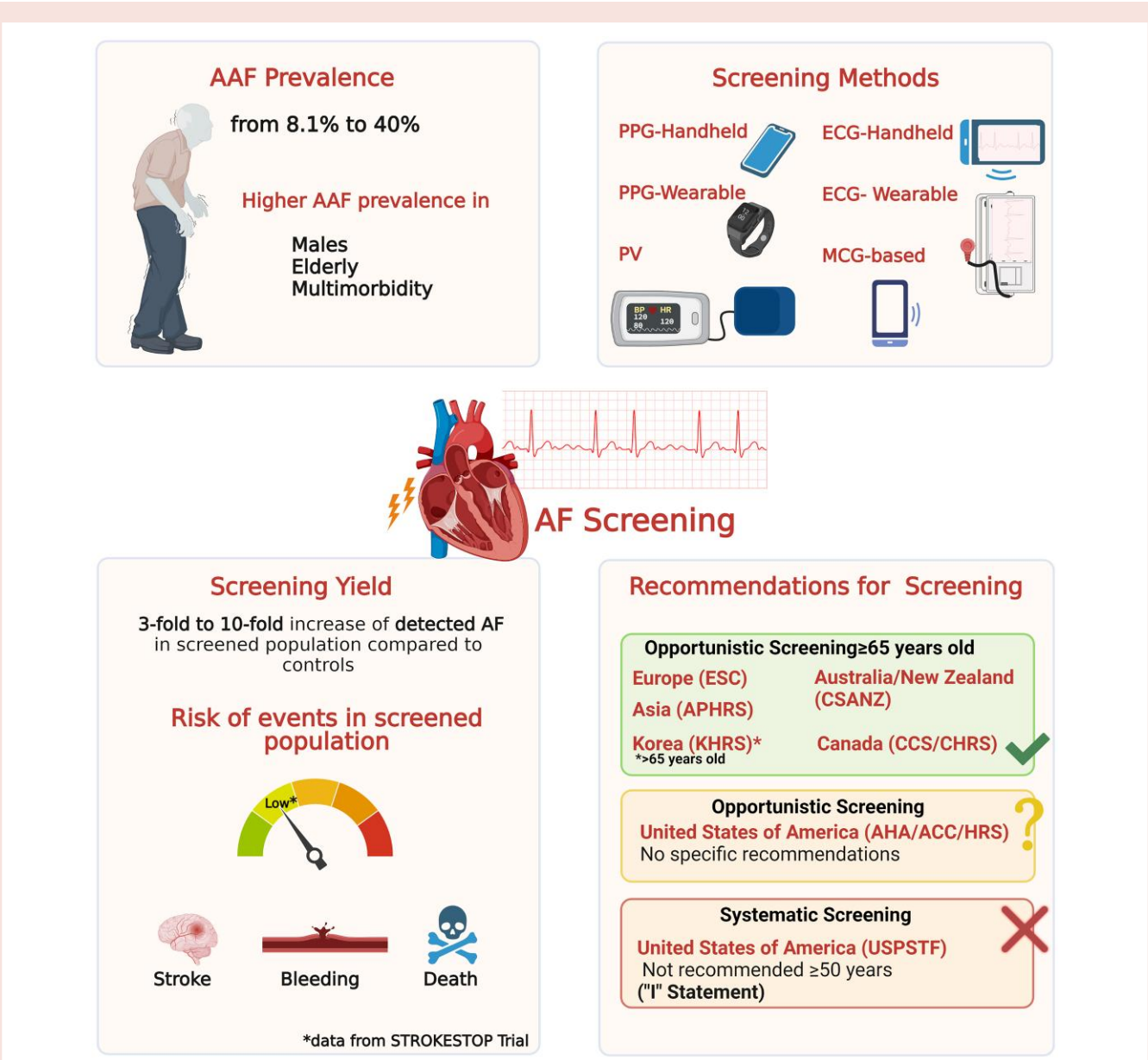

Figure 1 AAF, asymptomatic atrial fibrillation; AF, Atrial Fibrillation; APHRS, Asia Pacific Heart Rhythm Society; AHA/ACC/HRS, American Heart Association/American College of Cardiology/ Heart Rhythm Society; CSANZ: Cardiac Society of Australia and New Zealand; CCS/CHRS, Canadian Cardiovascular Society/Canadian Heart Rhythm Society; ECG, electrocardiography; PPG, photoplethysmography; PV, pulse variability; MCG, mechanocardiography; KHRS, Korean Heart Rhythm Society; USPSTF, United States Preventive Services Task Force. (Created with Biorender.com).

different regional epidemiological features of AF and availability of new mHealth devices. Similarly, the perception of AF screening utility by the treating physicians may vary according to patient symptoms, being underused in asymptomatic patients.

Overall, European approach to AF screening appears substantially different as compared to United States. In the latest ESC guidelines,[2] the section on AF screening is extensively represented, discussing in detail all digital devices for AF screening and indicating the most reliable strategies. Recommendations are stratified by patient age, with a Class I recommendation (level of evidence B) for opportunistic screening in patients ≥65 years and Class IIa (level of evidence B) for systematic screening in individuals aged ≥75. In the recent European Heart Rhythm Association (EHRA) practical guide on how to use digital devices to detect and manage arrhythmias,[79] the proposed organization of AF screening depends mainly on its opportunistic/systematic nature. Age (<65, 65–75, ≥ 75 years), number of comorbidities (0, 1, ≥ 2), digital literacy (a continuum from limited to complete), and use of PPG vs. ECG devices drive the choice between these two different screening types. In patients aged ≥65 years, PPG devices (confirmed by an ECG) are proposed in the opportunistic setting for less comorbid patients with limited digital skills. On the other hand, ECG devices are proposed in systematic AF screening setting for patients aged ≥75 years, those with multimorbidity, and fully digital skilled. For younger, non-comorbid, and symptomatic patients, ECG devices are recommended. No screening is suggested for asymptomatic, non-comorbid, young patients.

Also, the National Institute for Health and Care Excellence (NICE) guidelines support the opportunistic screening using WatchBP Home during blood pressure measurement by primary care professionals,[80] even though the UK National Screening Committee recommends against screening for AF.[81]

The 2018 Heart Foundation and Cardiac Society of Australia and New Zealand (CSANZ) guidelines[82] include a recommendation for opportunistic screening in the clinic or community in people ≥65 years, suggesting pulse palpation and single-lead handheld ECG devices as screening strategie. On the same side, also the 2020 Canadian Cardiovascular Society/Canadian Heart Rhythm Society (CCS/CHRS) guidelines recommend opportunistic screening for patients ≥65 years by pulse-based screening (pulse palpation, BP monitors, plethysmograph) or single-lead ECG devices.[83] Similarly, the Asia Pacific Heart Rhythm Society (APHRS)[84] suggests an opportunistic screening in people aged ≥65 years and a systematic screening in people aged ≥75 years with high-risk factors for AF development (e.g. post-stroke patients). The 2018 Korean Heart Rhythm Society (KHRS) AF guidelines[85] recommend the opportunistic screening for >65 years by pulse taking or ECG strip (Class I, level of evidence B); systematic screening may also be considered in patients >75 years or at high stroke risk (Class IIa, level of evidence B). On the contrary, the 2014 American Heart Association/American College of Cardiology/Heart Rhythm Society (AHA/ACC/HRS) AF guidelines[86] make no specific recommendation for AF screening. The subsequent AHA/ACC/HRS focused update published on 2019[87] introduced a possible role for screening of silent AF with a remote ECG acquisition by smartwatches or handheld ECG devices.

Recently, the United States Preventive Services Task Force (USPSTF)[88] published the 2022 updated version of their document dedicated to AF screening, still highlighting their concern about the lack of effectiveness of an AF screening structured pathway as compared to usual care opposed to some risk of adverse events, as anxiety, excessive testing, and overtreatment. Thus, given that current evidence is deemed insufficient to assess the balance of benefits and harms of screening for AF, the agency has expressed against the implementation of screening in asymptomatic adults aged ≥50 years.

Summary and discussion

In this review about AF screening strategies, we presented an extensive overview of evidence, which allows us to make some important assumptions: (i) AAF is common among the overall population of AF patients, not differing significantly from symptomatic AF in terms of thromboembolic risk and of occurrence of stroke and other adverse outcomes (*Figure 1*); (ii) nowadays the technological advances and the widespread diffusion of mobile health/wearables devices allows to implement AF screening strategies which are more suitable to each specific setting, with all screening methods recognizing super-imposable performances in terms of sensitivity and specificity; (iii) epidemiological evidence underline how, irrespective of the method, screening strategies provide a significant yield of AF diagnosis, identifying large proportions of patients with AAF worth to be prescribed with OAC due to a high thromboembolic risk; (iv) the studies published so far, even though with some limitations due to low sample size and other several bias, seem to suggest that implementation of screening strategies to identify AAF, with a subsequent prescription of OAC, appears to reduce the risk of outcomes over follow-up, even though further studies properly powered are still needed to fully clarify these observations; and (v) most of the current clinical guidelines recommend the implementation of opportunistic/systematic screening strategies based on chronological age and baseline thromboembolic risk; nonetheless health agencies currently do not recommend the large scale implementation of AF screening due to the lack of solid evidence regarding the reduction of stroke and other adverse outcomes.

Our review suggests how screening can identify from 3 to 10 times more AF. This variability is directly linked to inter- and intra-individual variability, related to the presence of mild subjective symptoms, as well as the potential temporal distance between AF and symptoms onset. Maximization of the yield of screening could depend on the duration of the monitoring, as reported by a recent position paper of EHRA,[62] which suggests a monitoring time lasting 2 weeks or longer. The different screening yield of AF screening could be due to the different screened population. Most of the studies were conducted in population aged ≥ 65 years old, others targeted to an older population (≥75 years old) and at higher risk to develop AF.[65,72] Notwithstanding these differences, the detection of AF allows to identify patients who need OAC. Two large Canadian studies confirmed the need for AF screening, pointing out the existence of a consistent proportion of patients with unknown AF who need to be prescribed with appropriate anticoagulant treatment.[89,90] Similarly, stronger data were shown in the eBRAVE-AF trial[9] demonstrating two-fold increase in the AF detection in screened population requiring OAC [odds ratio (OR) 2.12, 95% CI, 1.19–3.76]. If the large diffusion of wearables can represent a positive factor, the increasing request for clinical referral related to the consumer-led screening still poses questions and represents a critical issue in terms of appropriateness, privacy, and risk of excessive medicalization of patients for which it is substantially useless. New care and management pathways are needed to manage those subjects and avoid mass request for inappropriate medical checks.[91]

It can be possible that mass screening for AF puts patients at greater risk of overdiagnosis, anxiety, misinterpretation of the ECG, and, eventually, unnecessary additional tests. This could be a reason to refuse the enrolment in a screening programme, reflecting the failure of some trials in demonstrating the benefit of AF screening. Even the STROKESTOP study, which showed a reduction of adverse events in the screened population compared to controls in secondary analysis, was affected by the declination of half of participants invited to screen.[64,65] Also, the results coming from the mSToPS, again coming from a secondary analysis, are reassuring in terms of adverse events reduction in patients undergoing screening.

Furthermore, LOOP Study did not show any significant difference in the reduction of stroke or systemic arterial embolism; this was probably due to the ability of ILR, used as screening method, to pick up very short episode of AF, whereas in STROKESTOP, intermittent ECG were more likely to identify individual with clinically meaningful AF. Moreover, in the same study, there was a higher-than-expected rate of AF detection in the control group. Moreover, LOOP Study was also affected by a higher rate of early discontinuation of ILR monitoring.[13] These data underline an important aspect of the research studies involving this topic so far, which were mostly underpowered and methodologically not suitable to verify the studies hypotheses, as already pointed out.[75]

Other relevant aspects of performing AF screening are related to the identification of specific subjects' subsets in which the procedure is implemented. A subgroup analysis of LOOP trial suggested that screening reduced the risk of stroke and systemic embolism only in patients with the highest systolic blood pressure, underlining the idea that screening strategies could be targeted towards specific populations with a higher likelihood of presenting AF with a higher risk of stroke and other clinical outcomes, and, in general, underlies the need to better identify the population worth to screen.[69] In this regard, stratification of the population, by biomarkers (e.g. NT-pro-BNP in STROKESTOP II[72]) or by one of the validated scores, such as C_2HEST risk score,[92] could identify people at risk to develop AF and, therefore, the best candidates for active screening. The importance of this aspect emerges also from the fact

Table 4 Learning points: the '6 Ws' about AF screening strategies

Learning points: the '6 Ws' about the AF screening strategies	
Why to screen for AF?	AAF is highly prevalent (8–40%) and patients with AAF has the **same risk to develop adverse events** compared to those symptomatic
Where to screen?	Structured programmes in **targeted high-risk population** irrespective of their clinical setting
What to use to screen?	PPG, PV, and MCG technologies or ECG trace
Who we need to screen?	**a. Opportunistic screening** in patients **≥65** (Class I)* **b. Systematic screening** in individuals aged **≥75** (Class IIa)*
What do to if screening if positive?	**a. Check** the need of confirmation with 30 s ECG trace (if non-ECG technologies were used) **b. Assess** thromboembolic risk (CHA_2DS_2VASc score) **c. Decide** the need to start oral anticoagulation **d. Optimize treatment** of AF through implementation of ABC Pathway for Integrated Care
What to do if a AAF patient has no need for anticoagulation?	**Regular follow-up** and **re-assessment** of thromboembolic risk over time

AAF, asymptomatic atrial fibrillation; ECG, electrocardiography; PPG, photoplethysmography; PV, pulse variability; MCG, mechanocardiography.*From 2020 ESC AF guidelines.

that European Union, by funding the AFFECT-EU project,[78] has considered relevant to invest a considerable amount of funds to develop a more refined screening strategy, which could allow a higher yield of screening and the identification of patients at an even higher risk of adverse outcomes.

The 'debate' between scientific societies' clinical guidelines and the USPSTF again strengthens the need for further research. Several guidelines worldwide generally agree on recommending an opportunistic screening strategy for patients ≥65 years old,[2,82–85] with some of them also suggesting systematic screening in those over 75 years old.[2,84,85] If from a scientific point of view appears justified to suggest the implementation of screening strategies (which are indeed recommended with an overall low level of evidence), it may be understandable that from a regulatory point of view, stronger evidence is required.

Also, data coming from cost-effectiveness analyses are reassuring regarding the implementation of screening studies which generate significant yield of diagnosis and reduction of events at reasonable willingness-to-pay thresholds.[93–96] However, these studies weren't designed and powered to detect differences in clinical outcomes but rely mostly on statistical modelling.[93–96] Recently, a cost-effectiveness analysis derived from the follow-up phase of STROKESTOP study demonstrated an improvement in cost-effectiveness which also increases with a progressively higher participation to the screening programme.[97] Moreover, a study based on UK population shows how implementation of a screening strategy in targeted population at risk of AF would substantially reduce healthcare costs of AF-related stroke.[98]

The ongoing studies (e.g. SAFER,[76] GUARD-AF, HEARTLINE, and the 5-year follow-up of STROKESTOP II), which will be specifically powered to detect differences in incidence of stroke and other adverse clinical outcomes, will certainly provide consistent evidence able to confirm and hopefully extend the current evidence which strongly point out to a beneficial effect of the screening strategies, informing the guidelines' authors more properly and strengthening the recommendations in the next years.

Learning points

In this comprehensive narrative review, we summarized all the major evidence regarding the relevance, feasibility, and effectiveness of AF screening strategies in both identifying new AAF patients worth to be treated and reducing the occurrence of stroke and major adverse events (*Table 4*). This issue remains one of the most interesting in the field of AF clinical research. Epidemiological data indicate how AAF represents a big healthcare issue, with high prevalence of patients unaware of the increased risk of developing major adverse events. Screening strategies are feasible and effective, with high yields of diagnosis and large widespread among the general population. While caution is still needed for the consumer-led screening, it is clear how their implementation can identify patients requiring treatment. Moreover, performing AF screening do not recognize clear contraindications, while some caution is needed regarding possible adverse effects such stress/anxiety or overdiagnosis/overtreatment.[88] The main point of debate is still related to their effectiveness in reducing risk of stroke and other adverse events. Despite some methodological and contextual limitations of the studies performed so far, the evidence strongly suggests that AF screening strategies are associated with a significant reduction of adverse outcomes. Future studies will hopefully elucidate more strongly and solidly, even for the regulatory authorities, the actual impact of screening strategies, influencing the clinical practice in the next decades.

Lead author biography

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Data availability

No new data were generated in support of the article.

Author contributions

M.P. contributed to the conception and the design of the work. B.C. and M.P. wrote the first draft and finalized the final version of the manuscript. N.B., J.F.I., G.F.R., M.V., and L.A. contributed to draft the manuscript; S.B., B.F., T.S.P., G.B., and G.Y.H.L. critically revised the manuscript and gave relevant intellectual contributions. All authors approved the last version of the manuscript.

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